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MASS SPECTROMETRY STUDIES OF FISCHER
CARBENES AND TRACELESS STEREOINDUCTION FOR
THE FORMATION OF HEXAHYDRODIBENZOPYRANS:
THE USE OF THE CHROMIUM TRICARBONYL GROUP AS
A STEREOCONTROL ELEMENT

presented by

Keith A. Korthals

has been accepted towards fulfillment
of the requirements for the

Doctoral degree in Chemistry

James D. Long
Major Professor's Signature

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**MASS SPECTROMETRY STUDIES OF FISCHER CARBENES AND
TRACELESS STEREOINDUCTION FOR THE FORMATION OF
HEXAHYDRODIBENZOPYRANS: THE USE OF THE CHROMIUM
TRICARBONYL GROUP AS A STEREOCONTROL ELEMENT**

VOLUME 1

By

Keith A. Korthals

A DISSERTATION

**Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of**

DOCTOR OF PHILOSOPHY

Department of Chemistry

2007

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ABSTRACT

MASS SPECTROMETRY STUDIES OF FISCHER CARBENES AND TRACELESS STEREOINDUCTION FOR THE FORMATION OF HEXAHYDRODIBENZOPYRANS: THE USE OF THE CHROMIUM TRICARBONYL GROUP AS A STEREOCONTROL ELEMENT

By

Keith A. Korthals

The axial-planar interactions of the Wulff-Dötz reaction with propargyl amines has been explored. These initial results showed good diastereoselectivity ($\geq 94 : 6$) for the resulting chromium tricarbonyl arenes. The initial optimization has been done toward improve yields.

The Diels-Alder reaction in tandem with the Wulff-Dötz reaction has been done in a "traceless manner" where "no trace" of the initial stereochemical element is present in the final product for the formation of hexahydrodibenzopyrans. The yields were up to 58 %, and the enantiomeric excess of up to 94 % were obtainable. Also the initial studies of the Wulff-Dötz reaction with a tandem electrocyclization reaction have been explored.

The mechanistic studies of ionization were explored for Fischer carbene complexes under conditions of electrospray ionization (ESI). For alkenyl Fischer carbene complexes, the major pathway of ionization proceeded through the allene organometallic **5-26**. For alkynyl carbene complexes, the major pathway proceeded through the McLafferty type rearrangement to also form an allene organometallic complex.

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The formation of allyl amines from aziridines was investigated using dimethylsulfonium methylide. The yields for opening an aziridine to give an allyl amine were up to 92 % and the substrate scope was investigated.

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To my family.....

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ACKNOWLEDGMENT

I would like to thank my adviser Dr. William D. Wulff for his assistance and patience during the course of my studies. Dr. Wulff allowed me to go in my own direction despite some of the silly experiments that I conducted and insane laboratory behavior. Dr. Wulff also provided a multitude of good stories and excellent wine. I would like to thank Dr. Babak Borhan for the large numbers of chemicals that I took from his laboratory and for being a technical resource. I would like to thank Dr. Baker for his patience sitting through long committee meetings and providing interesting comments. I would like to thank Dr. Smith for likewise sitting through extended committee meetings and being a source of inorganic knowledge to myself and many students throughout the department.

I would like to thank the NMRs anubis, hathor, imseti, khufu, maat, mut, ra, and isis for providing support for two and half years of my graduate experience. I would like to especially thank Kermit Johnson and Dan Holmes for the patience to answer my questions, assistance for NMR, and not becoming upset when yet another instrument went down. I would like to thank the department for supporting me through my graduate career and also tolerating my eccentric behavior.

It was my privilege to be lab mates with Cory Newman, Vijay Gopalsamuthiram, Yiqian Lian, Aman Desai, and Zhensheng Ding. I thank them for all their help and discussions. I would like to especially thank my very good

friend Jennifer

but her help

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friend Jennifer Schomaker who provided interesting discussions and whom with out her help and moral support I would not have made it through graduate school. It was my privilege to work with her on a collaborative project with Babak Borhan. I would like to thank Richard Hsung for providing a tome for a thesis that was a treasure trove of experimental procedures. I would like to thank the janitorial staff for providing services and clean up for my laboratory and for also providing a sense of security for those late nights in the lab. Many of the people that I have run across at Michigan State University are simply brilliant, and I have been humbled meeting them. Best of luck to all of those that I have encounter at Michigan State University over the years!

I would like to thank my parents William Korthals and Dorothy Korthals for financial support while an undergraduate. My father William remains morally and ethically the most outstanding person among all the people I have ever met. My mother has provided moral support and kindness beyond what I disserve. I would like to thank Helen Effrim for contributions to my educational fund though my parents. I would also like to thank my brother Scott Korthals who supplied a computer to me while I was an undergraduate student (my debt that still remains unpaid). Scott is truly an American hero; very deserving of the honors bestowed upon him by the Joint Chiefs of Staff of the United States. I would like to thank Lori (sister-in-law) who has provided much comic relief and who keeps my brother under control.

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Ac

Ar

Bn

Bz

CAN

mCPBA

DBU

DIBAL

DMF

DMSO

ESI

HMPA

hv

HQ

LDA

Ip

L-Selectride

MOM

MS

MsCl

NMO

KEY TO ABBREVIATIONS AND SYMBOLS

Ac	Acetyl
Ar	Aryl
Bn	Benzyl
Bz	Benzoyl
CAN	Ceric Ammonium Nitrate
<i>m</i> CPBA	<i>meta</i> -Chloroperoxybenzoic Acid
DBU	1,8-Diazabicyclo[5.4.0]undec-7-ene
DIBAL	Diisobutylaluminum Hydride
DMF	Dimethylformamide
DMSO	Dimethyl Sulfoxide
ESI	Electrospray Ionization
HMPA	Hexamethyl phosphoramide
<i>hν</i>	Irradiation with Light
HQ	Hydroquinone
LDA	Lithium Diisopropylamide
lp	Lone Pair
L-Selctride	Lithium Tri- <i>sec</i> -butylborohydride
MOM	Methoxymethyl
MS	Mass Spectra
MsCl	Methanesulfonyl Chloride
NMO	N-Methylmorpholin N-Oxide

o-QM

PFB

PMB

p-QM

Red-Al

TBAF

TBS

TCNQ

TIPS

THF

TMEDA

TMS

Tr

Troc

Ts

TTF

QM

<i>o</i>-QM	<i>ortho</i> -Quinone Methide
PFB	<i>p</i> -Fluorobenzene
PMB	<i>p</i> -Methoxybenzene
<i>p</i>-QM	<i>para</i> -Quinone Methide
Red-Al	Sodium Dihydrobis(2-methoxyethoxy)-aluminate
TBAF	Tetra- <i>n</i> -butylammonium Fluoroborate
TBS	<i>Tert</i> -butyldimethyl silyl (TBDMS)
TCNQ	Tetracyano- <i>p</i> -Benzoquinone
TIPS	Triisopropyl silyl
THF	Tetrahydrofuran
TMEDA	Tetramethylethylenediamine
TMS	Trimethylsilyl
Tr	Triphenyl methane
Troc	β,β,β -Trichloroethoxycarbonyl (Tcec)
Ts	<i>p</i> -Toluenesulfonyl
TTF	Tetrathiafulvalene
QM	Quinone Methide

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CHAPTER ONE

INTRODUCTION TO CHROMIUM AND METAL ARENES

The metal chromium is a d^6 metal occupying group six, period four of the periodic table. The metal chromium has important industrial applications including stainless steel, which is used for corrosion resistant applications in industry and in the home. Highly corrosion-resistant stainless steel is composed of 10 to 15 percent chromium, 2 - 10 percent nickel, 1 - 2 percent carbon, and 1 - 2 percent molybdenum. When chromium trichloride is exposed to carbon monoxide under 70 atmospheres of pressure in ether with phenyl magnesium bromide, it forms the six coordinate compound chromium hexacarbonyl which can be purified by sublimation under vacuum at 80 to 100 °C.¹ Chromium hexacarbonyl may also be crystallized from ether or dichloroethane.² The metals molybdenum and tungsten also form six coordinate metal hexacarbonyls. The metal carbonyls can be somewhat hazardous due to the fact that they sublime and can deposit in lung tissue, but as long as the metal carbonyls are stored in sealed containers in well ventilated rooms these hazards are minimal. Metal hexacarbonyl compounds are required to make metal arene complexes.

Chromium and metal arenes are a versatile chemical motif possessing interesting synthetic applications. The first report of chromium and molybdenum complexed with an aromatic ring system came in 1956 by Fischer and these

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a year later

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were dibenzene metal compounds.³ The first true metal carbonyls were reported a year later in 1957 also by Fischer, and dubbed " π -bonded to a metal" complexes or "half sandwich complexes."⁴ Chromium tricarbonyls can be chiral and used as chiral control elements. Chirality originates from a pseudo planar motif about the arene of a metal tricarbonyl arene.⁵ The absolute CIP (Cahn, Ingold, Prelog) designation (*R* or *S*) shown in Figure 1.1 can be applied to the chiral center in compound 1-1.⁶ The alternate representation is shown as compound 1-2.

In compound 1-3a to assign chirality, a plane must be chosen which includes the "locus of chirality." In compound 1-3a, this must include atoms a, b, and c which have higher priorities than any other choices. Compounds officially designated as having planar chirality are assigned via designating a "pilot atom" as marked with an arrow in compound 1-3a. The "pilot atom" must be outside the plane of chirality and the atom "nearest" to the "locus of chirality." The atoms a, b, c are chosen sequentially by priority. The atoms a and b are determined by connectivity from the pilot atom in this case, and atom c is determined by the usual CIP system of priority.⁶ The terms *pS* refer to "planar *S*" and the term *M* refers to the helix nomenclature in this case being a counter clockwise rotation observing above the "pilot atom." The concomitant term *P* refers to clockwise helical rotation.⁷

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For compound **1-3b**, the plane of chirality is first determined which contains as many atoms as possible which contains atoms a, b, and c. Next the "pilot atom" is determined which resides outside the plane and which is as directly as possible connected to the "locus of chirality." The "locus of chirality" is atoms a, b, and c. The assignment is made by observing down the bond between the "pilot atom" and atom a. Pseudo-rotation from a to b to c proceeds in a clockwise manner and is assigned *R* or *P* (helix nomenclature).

For compound **1-3c**, again a plane is chosen to include as many atoms as possible which includes the "locus of chirality" which is atoms a, b, and c. Next a pilot atom is chosen outside the plane which is directly connected to the "locus of chirality." Finally, pseudo-rotation from a to b to c is in a clockwise manner which is assigned *R* by the CIP rules. This would be *P* by the helix nomenclature.

Fig



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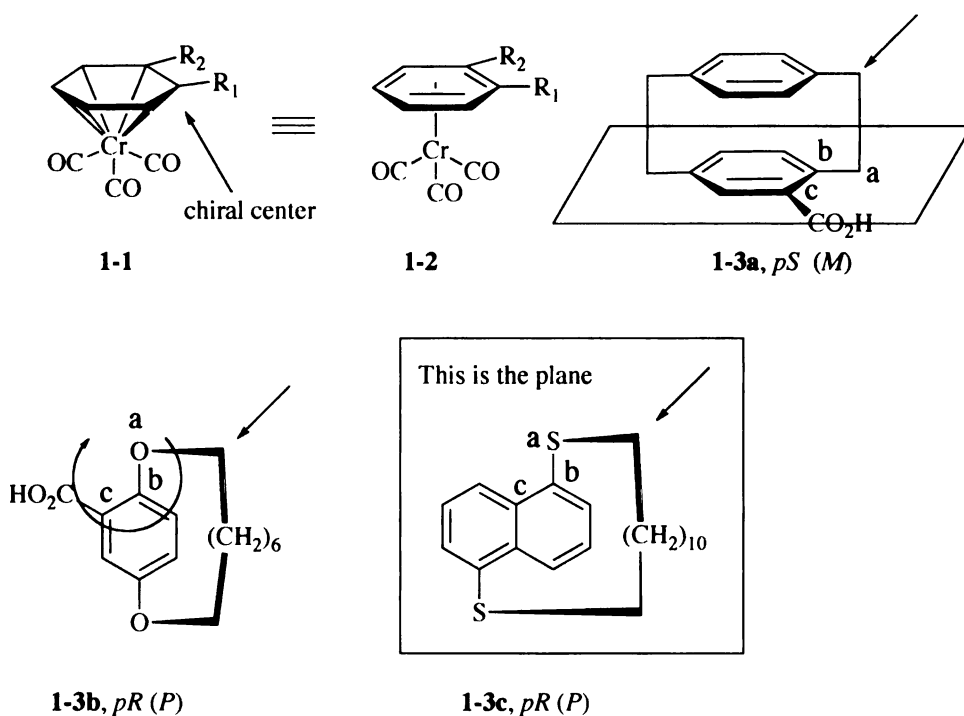
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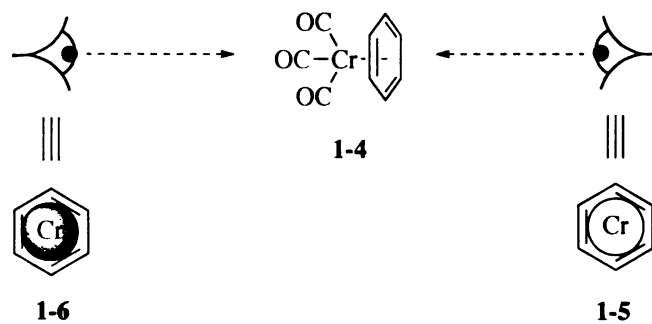
Fig

Figure 1.1. Interpretation of Planar Chirality



In Figure 1.2, the relative perspectives are shown for a pair of chromium tricarbonyl arenes. One can view the arene from over head represented by compound 1-5. The metal tricarbonyl can also be observed viewing the tricarbonyl moiety towards the observer as represented by compound 1-6. These representations shown in Figure 1.2 will be used throughout these discussions of metal tricarbonyl arenes for depicting chiral compounds.

Figure 1.2. Perspective and Drawing Definition



1.1 Method

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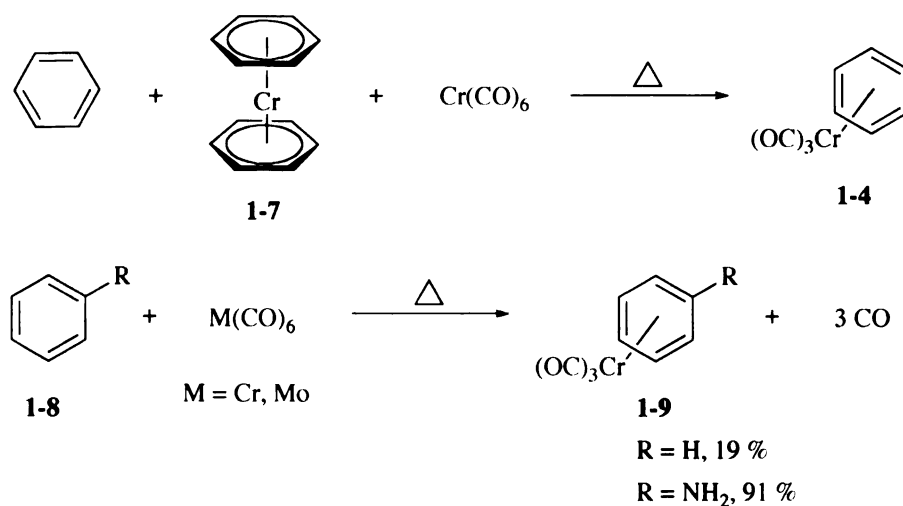
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1.1 Methods of Preparing Chromium Tricarbonyls

The first preparation done by Fischer involves the heating of chromium hexacarbonyl and dibenzene-chromium (**1-7**) in benzene to give a 27 % yield of benzene chromium tricarbonyl (**1-4**).^{3, 4} A simpler and more direct route was reported by Nicholls and Whiting, which simply involves refluxing of the organic aromatic (**1-8**) with chromium or molybdenum hexacarbonyl at temperatures of 100 to 210 °C (Scheme 1.1). The yields of compound **1-9** were 19 % for benzene and up to 91 % yield with the more electron rich aniline.⁸

Scheme 1.1. Arene and Chromium Hexacarbonyl Reaction

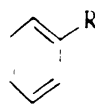


An alternate method involves the use of labile ligands on chromium to facilitate exchange with the arene as shown in Scheme 1.2. These methods involve the use of acetonitrile or ammonia ligand (**1-10**).^{9, 10} Pyridine has been used as a ligand on chromium (**1-11**) and in the presence of $\text{BF}_3 \cdot \text{OEt}_2$, the chromium arene (**1-9**) is formed.^{9, 11} Naphthalene chromium tricarbonyl complex

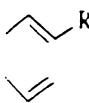
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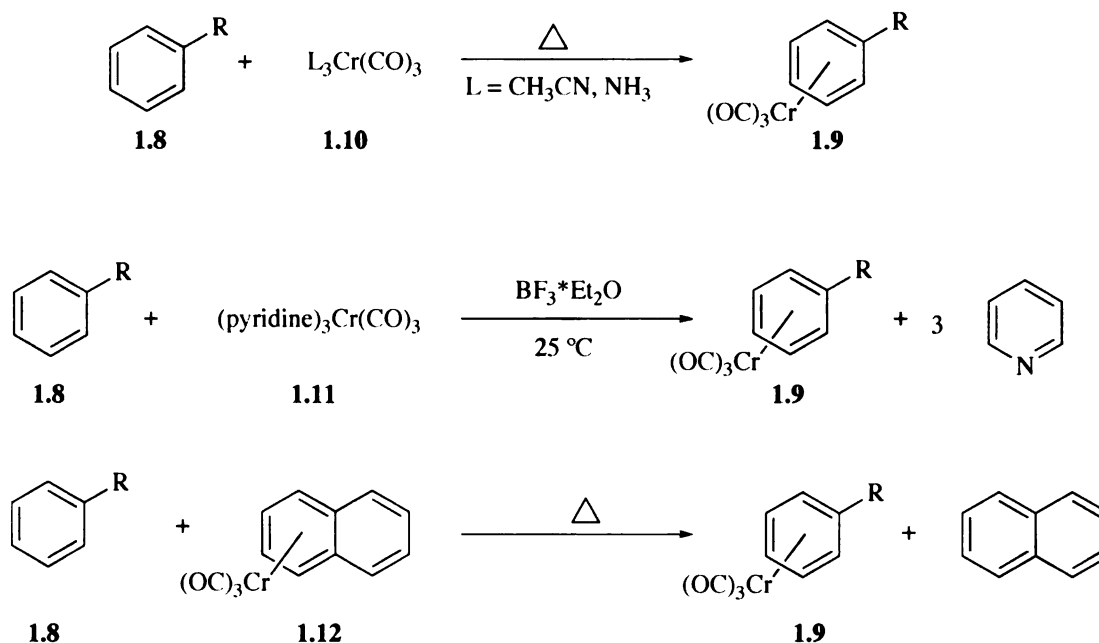
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reaction ca

(1-12) has also been used to transfer chromium tricarbonyl to an alternate aromatic ring (1-8) making a new chromium tricarbonyl arene (1-9).⁹

Scheme 1.2. Ligand Methods of Preparing Chromium Tricarbonyl Arenes



The formation of chromium tricarbonyl fluorobenzene can be difficult due to the electron withdrawing nature of fluorine, however it is one of the most synthetically useful metal complexed arenes. A special and well-developed procedure has been developed by Widdowson in which a Strohmeier apparatus was used without cooling water in di-*n*-butyl ether and THF.¹² This procedure has general application for other substrates.¹³

Light has been used to generate chromium and metal arenes (1-9) from chromium hexacarbonyl and arene 1-8. The advantage of this method is that the reaction can be done at room temperature as shown in Scheme 1.3.¹⁴

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1.5. Up

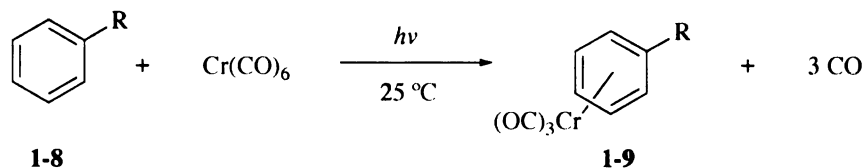
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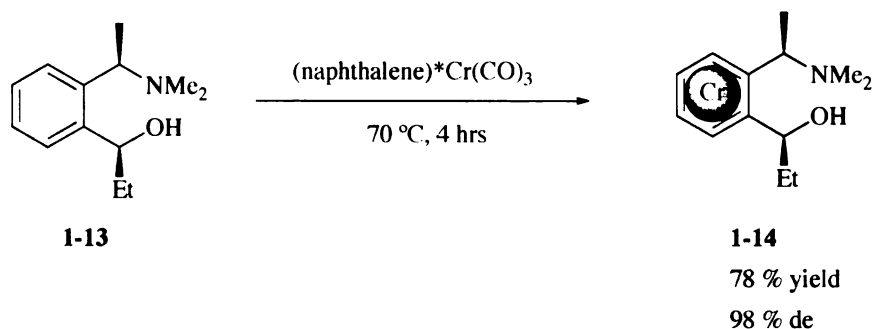
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Scheme 1.3. Light Induced Formation of Chromium Tricarbonyl Arenes



The chromium tricarbonyl motif can be added in a diastereoselective manner from a diastERICALLY pure aryl aminol complex (compound **1-14**) shown in Scheme 1.4.¹⁵ The treatment of the aminol (**1-13**) with naphthalene chromium tricarbonyl gives the chromium tricarbonyl arene (**1-14**) in 78 % yield with a dr of 98 %. The disadvantage of this method is that there must be an existing stereocenter in the starting material (**1-13**).¹⁶

Scheme 1.4. Chiral Chromium Tricarbonyl Arenes from Chiral Aromatics



Some aryl substrates give low yields such as the one shown in Scheme 1.5. Upon heating the aldehyde **1-15** in the presence of chromium hexacarbonyl in *n*-butyl ether and tetrahydrofuran at reflux for five hours only 5 % yield of compound **1-16** was obtained.¹⁷ Some chromium arenes such as substituted nitro or nitrile arenes are unknown because they cannot be formed. Presumably the electron withdrawing nature of the nitro or nitrile retards their formation.¹⁷

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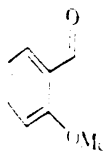
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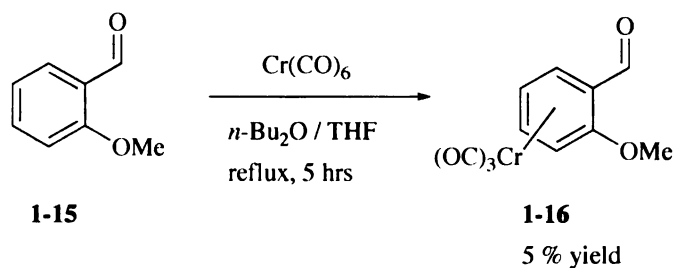
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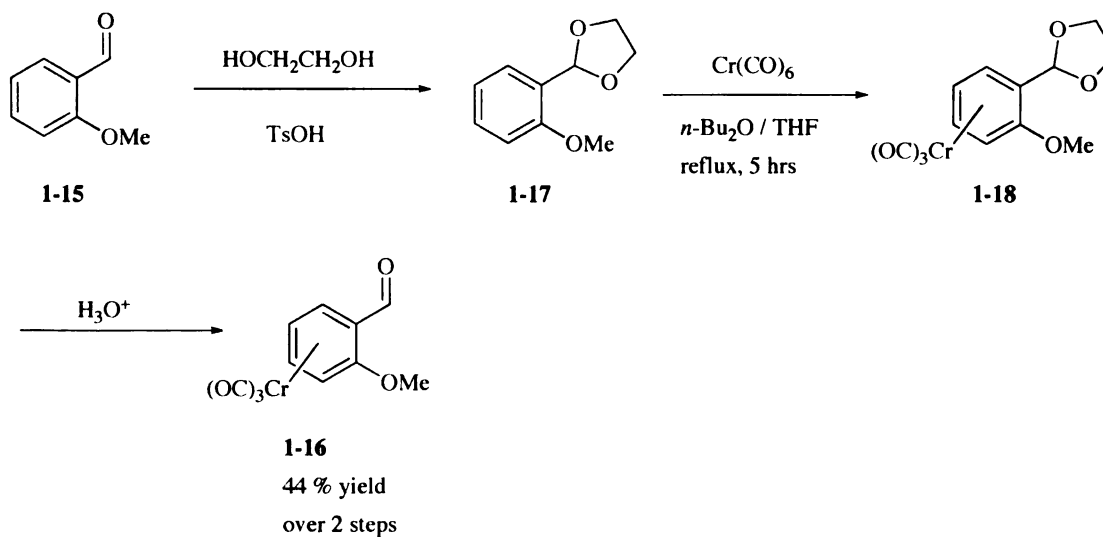
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Scheme 1.5. Formation of Chromium Tricarbonyl Arenes Containing Aldehydes



An alternative indirect route to arene complexes bearing aldehyde groups is shown in Scheme 1.6 in which the substrate aldehyde (**1-15**) is first protected as an acetal giving compound **1-17**.¹⁷ This acetal is then treated in refluxing n -butyl ether and tetrahydrofuran to give the chromium tricarbonyl arene complex (**1-18**) in the presence of chromium hexacarbonyl. The acetal could be converted to the aldehyde with acid in 44 percent yield over two steps giving compound **1-16**.¹⁷

Scheme 1.6. A Protection Scheme to Increase Yields for Aldehydes



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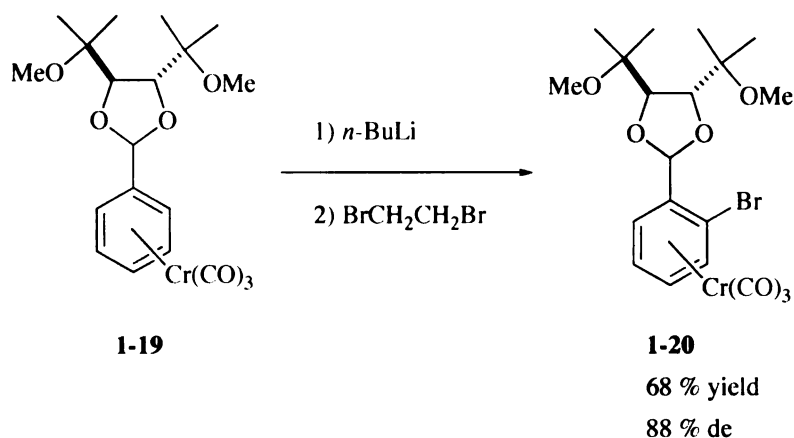
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Another approach to produce a chiral metal arene is to make a chiral acetal and subsequently perform selective *ortho*-lithiation and quench with a brominating agent.¹⁸ Shown in Scheme 1.7, the chromium arene was treated with *n*-butyl lithium which selectively deprotonated *ortho* to the acetal. The *ortho*-lithiated chromium tricarbonyl was then brominated with 1,2-dibromoethane to give a bromo chromium arene in 68 % yield (compound **1-20**) and 88 % de. The acetal could be deprotected with a dilute solution of acid and the arene could be further functionalized with coupling reactions such as Stille, Suzuki, Buchwald-Hartwig, and Sonogashira.¹⁸

Scheme 1.7. Diastereocontrol of a Chromium Tricarbonyl Arene

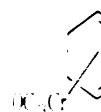


Kinetic resolution of metal tricarbonyl arenes is possible. One approach is to use bakers yeast to resolve chromium arene aldehydes as shown in Scheme 1.8 for compound **1-21**.¹⁹ Up to 96 % ee was obtained of the resulting alcohol of the enantiomer shown as compound **1-22** from the reduction of aldehyde **1-21**. The remaining aldehyde **1-23** was 100 % ee. A limitation of the approach shown

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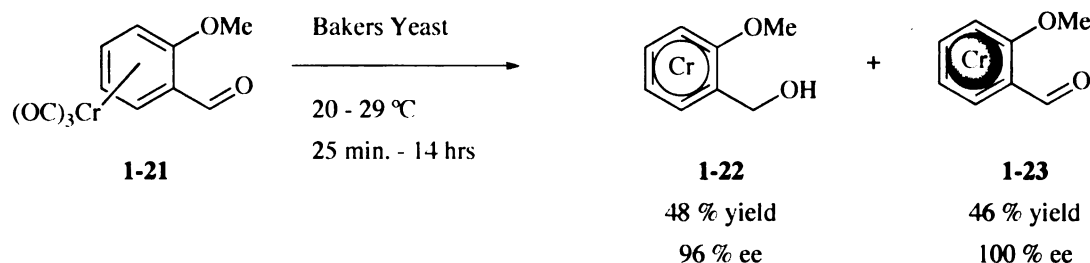
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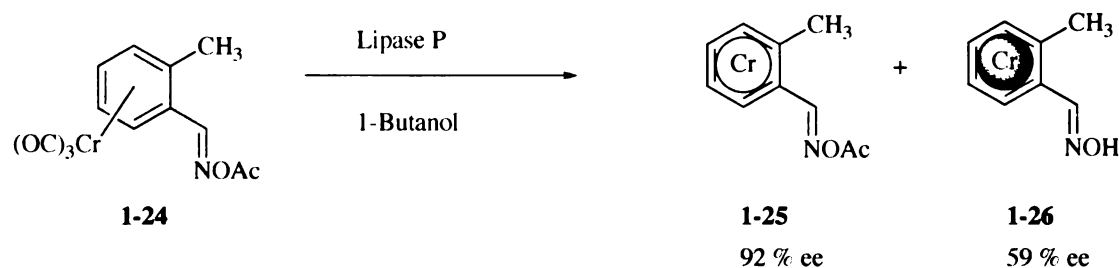
here is the poor solubility of the arene complex in the aqueous conditions required by the yeast-mediated resolution.¹⁹

Scheme 1.8. Baker's Yeast to Make Chiral Chromium Tricarbonyl Arenes



In Scheme 1.9, the enzyme Lipase P was used to resolve the enantiomers of an oxime ester (compound **1-24**).²⁰ The acetate of one of the enantiomers for the oxime ester was removed giving compound **1-26**. The ee's of the protected oxime ester (**1-25**) was 92 % ee and the ee of the oxime (**1-26**) was 59 %.²⁰

Scheme 1.9. Lipase P for Chiral Chromium Tricarbonyl Formation



In Scheme 1.10, a chiral hydrazone (**1-27**) was treated with a lithium nucleophile followed by treatment with Ph_3CPF_6 .²¹ The compound was then treated with dilute sulfuric acid to give the desired chromium tricarbonyl arene (**1-28**) in 55 % yield and > 97 % ee.²¹

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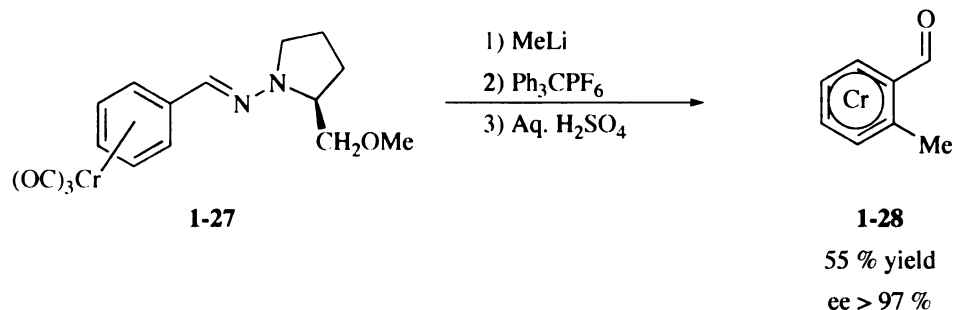
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Scheme 1.10. A Hydrazone for Chiral Chromium Tricarbonyl Arenes



Initial reports of an asymmetric desymmetrization for the formation of chiral chromium tricarbonyl have been reported by Uemura and coworkers.²² The reaction starts from compound **1-29** using Pd₂(dba)₃ and ligand **1-30** proceeding via a Mizoroki-Heck reaction followed by a Suzuki-Miyaura cross coupling.²² The yield of compound **1-31** was 54 % with a modest enantiomeric excess of 68 %. The reaction also provided compound **1-32** as a byproduct in 13 % yield and the ee was not reported.²²

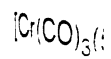
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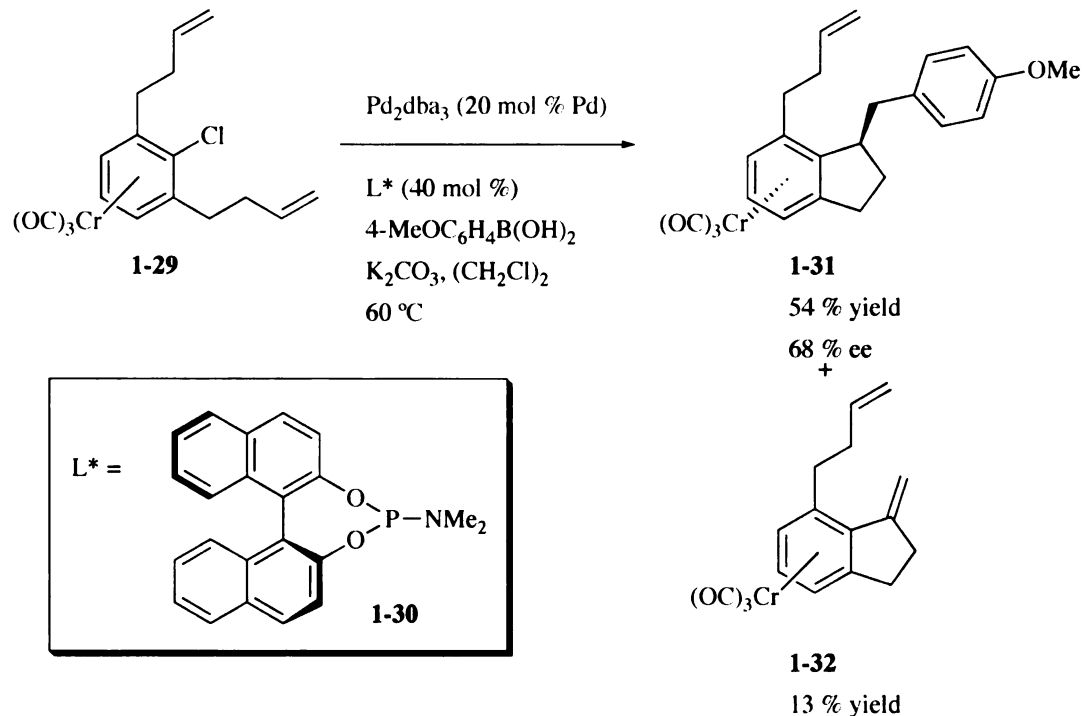
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Scheme 1.11. Catalytic Asymmetric Induction of Planar Chirality



The catalytic enantioselective hydrogenolysis of racemic $[\text{Cr}(\text{CO})_3(5,8\text{-dibromonaphthalene})]$ shown as compound **1-33** has been carried out to give $[\text{Cr}(\text{CO})_3(5\text{-bromonaphthalene})]$ shown as compound **1-34** in yields up to 80 % and enantiomeric excesses up to 97 %.²³ Also found was 8 - 15 % of compound **1-35**. The chiral ligand for this transformation was compound **1-36**. This provides a method to prepare a chiral aryl bromide complex by an asymmetric desymmetrization for further functionalization via well established coupling reactions of aryl bromides.

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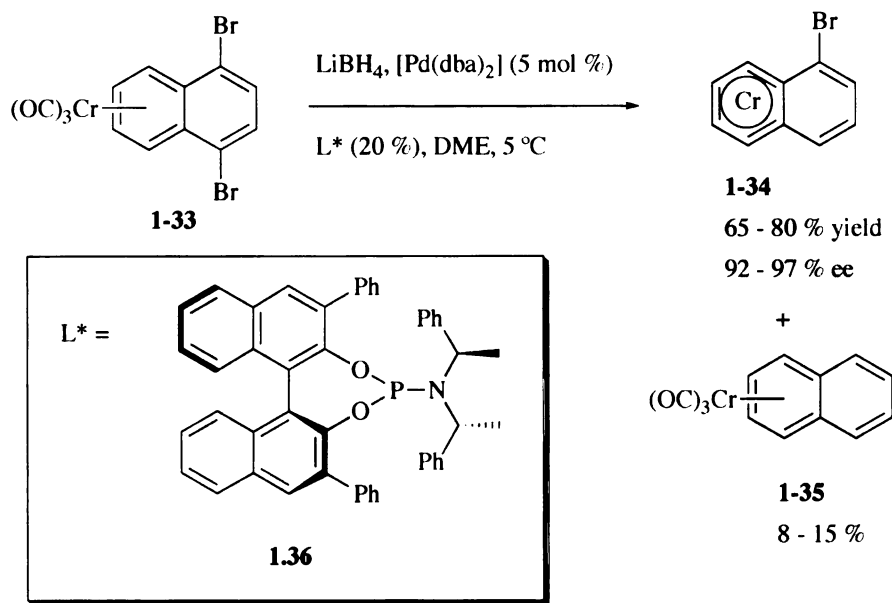
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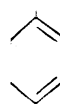
Scheme 1.12. Hydrogenolysis of $[\text{Cr}(\text{CO})_3(5,8\text{-dibromonaphthalene)]$



Well-developed methods for preparing other metal arenes complexes have been reported as shown in Scheme 1.13. The synthesis of $[(\text{arene})\text{FeCp}]^+$ shown as compound **1-37** can be accomplished with ferrocene compound **1-36**, AlCl_3 and aluminum metal as shown in Scheme 1.13.²⁴ The resulting iron arene cationic complex is extremely stable to air and heat.²⁵ Also, compound **1-38** in the presence of arene **1-8** forms a manganese tricarbonyl arene complex (**1-39**).

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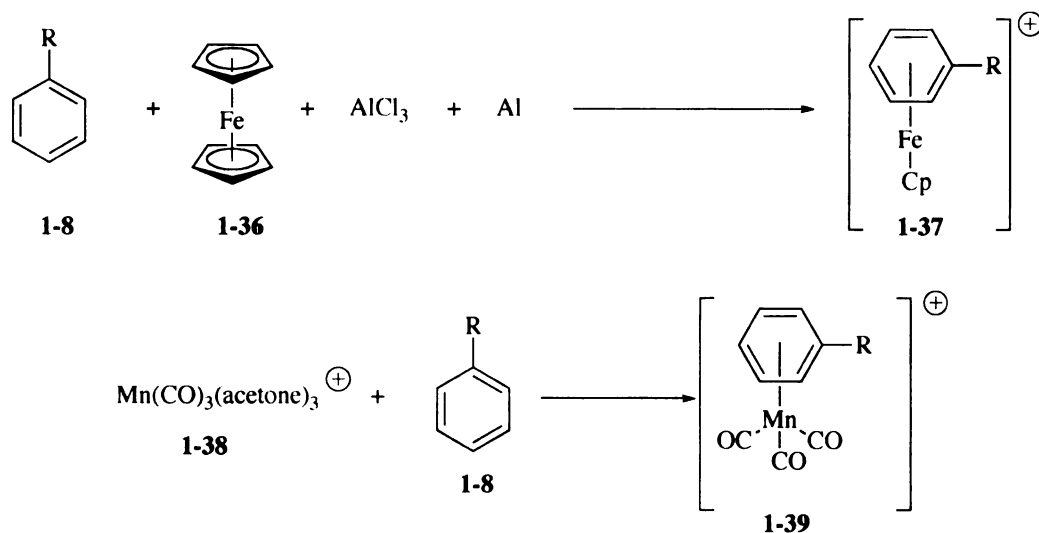
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Scheme 1.13. Formation of Iron and Manganese Arenes



1.2 Methods for Removing Metal Coordinated to Arenes

The removal of chromium tricarbonyl can be accomplished in several ways as shown in Scheme 14.²⁶ One such method is oxidation with air and light, however sometimes chromium tricarbonyl arene complexes can be robust and more aggressive methods are required. Excess iodine in dichloromethane provides a convenient method for the removal of $\text{Cr}(\text{CO})_3$. With iodine, the reaction is generally done in 15 to 30 minutes and the yields are generally 80 to 100 percent.²⁷ Another convenient reagent for the removal of chromium tricarbonyl is $\text{FeCl}_3 \cdot \text{DMF}$ complex shown in Scheme 1.14 and Scheme 1.15. Although the exact structure of $\text{FeCl}_3 \cdot \text{DMF}$ remains controversial, it can be prepared²⁸ by stirring iron trichloride in neat DMF and the resulting solution can be used directly for oxidations of metal tricarbonyls followed by the addition of

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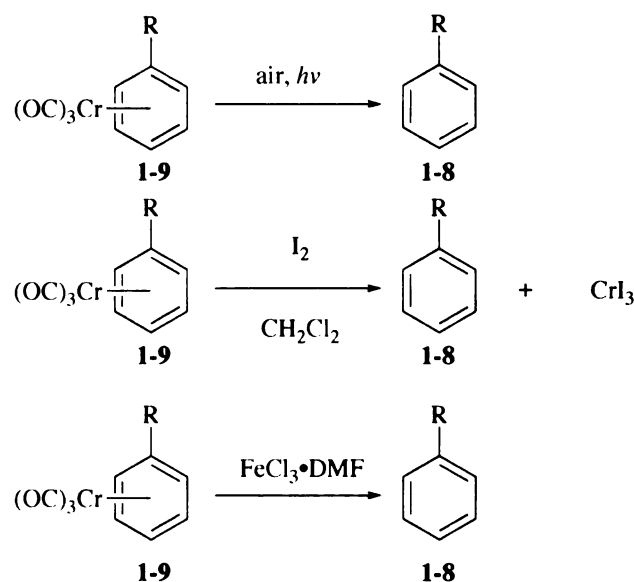
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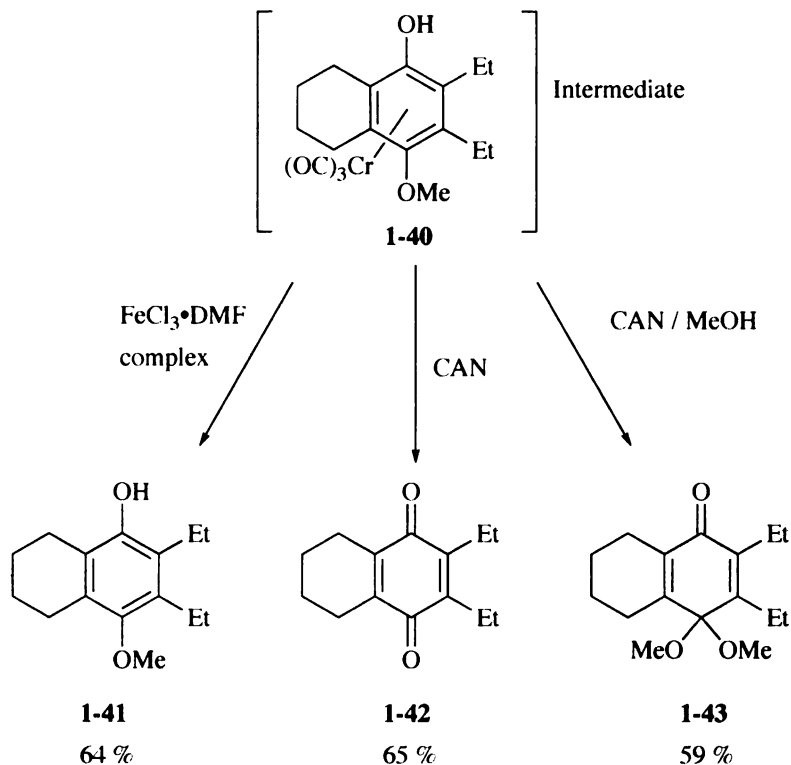
water.²⁹ The yields are generally high ranging from 60 to 100 percent. The reagent $\text{FeCl}_3 \cdot \text{DMF}$ has an additional advantage in that it will not oxidize *para* ether substituted phenols. In contrast, the metal is removed from naphthol chromium tricarbonyl complexes and the arene is oxidized to naphthoquinone.²⁹

Scheme 1.14. Methods for Removing Chromium Tricarbonyl from Arenes



Other methods exist for the oxidation of *para* substituted ether phenols such as compound **1-40** to quinones (Scheme 1.15).²⁹ The usual oxidant for this purpose is cerium ammonium nitrate (CAN) which gives compound **1-42**. When the reaction is done in methanol the product is the quinone mono-acetal (**1-43**).²⁹

Scheme 1.15. CAN Oxidants for the Removal of Chromium Tricarbonyl



Other oxidants that have been used include lead oxide,³⁰ nitric acid,³¹ and silver oxide.³² Lead oxide was used on a ferrocene containing compound resulting from a Wulff-Dötz benzannulation which gave a 71 % yield of compound **1-45** over two steps. Nitric acid was used to oxidize a phenol to the quinone **1-47** after the removal of the chromium tricarbonyl with carbon monoxide. Silver oxide has successfully been used for the oxidation of a chromium tricarbonyl arene in ether which gave a yield of 70 % of the quinone **1-47**.

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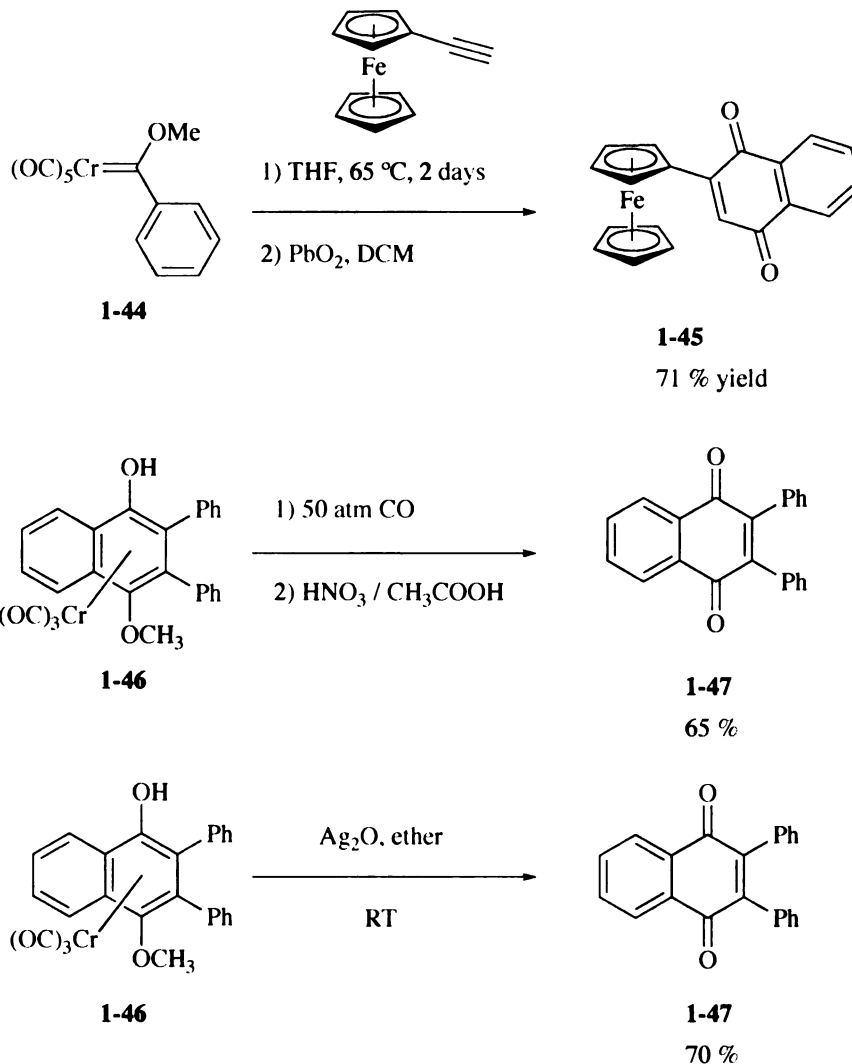
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Scheme 1.16. Lead Oxide, Nitric Acid, and Silver Oxide Oxidants



Pyridine *N*-oxide has also been used for the purpose of oxidative removal of a $\text{Cr}(\text{CO})_3$ group with 1.6 equivalents in dichloromethane as shown in Scheme 1.17.³³ In this reaction, a benzannulation from carbene complex **1-48** and alkyne **1-49** followed by oxidation with pyridine *N*-oxide then cyclization with Cs_2CO_3 gave compound **1-50** in 26 % yield.³³

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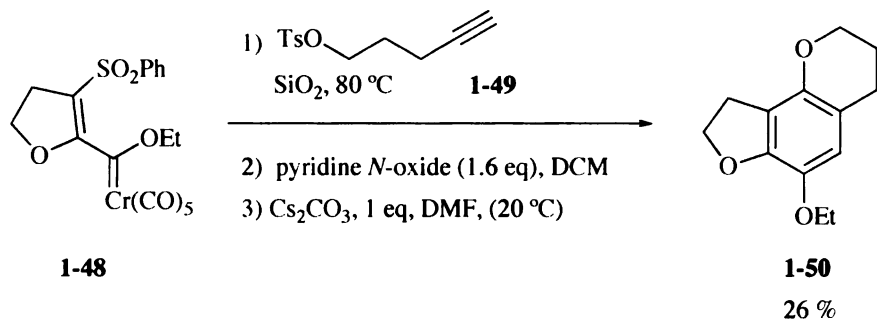
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Scheme 1.17. Pyridine N-Oxide as an Oxidant



Carbon monoxide can also be used to remove chromium tricarbonyl from an arene ring as shown in Scheme 1.18. Under these conditions, in a Paar bomb with 50 atmospheres of carbon monoxide, good yields of the demetalated phenol **1-53** are obtained.³⁴ In an ether solution, the resulting chromium hexacarbonyl is almost insoluble and simple filtration provides the free arene. The simple heating of the chromium tricarbonyl compound **1-51** at 70 °C results in migration of $\text{Cr}(\text{CO})_3$ to form compound **1-52**.

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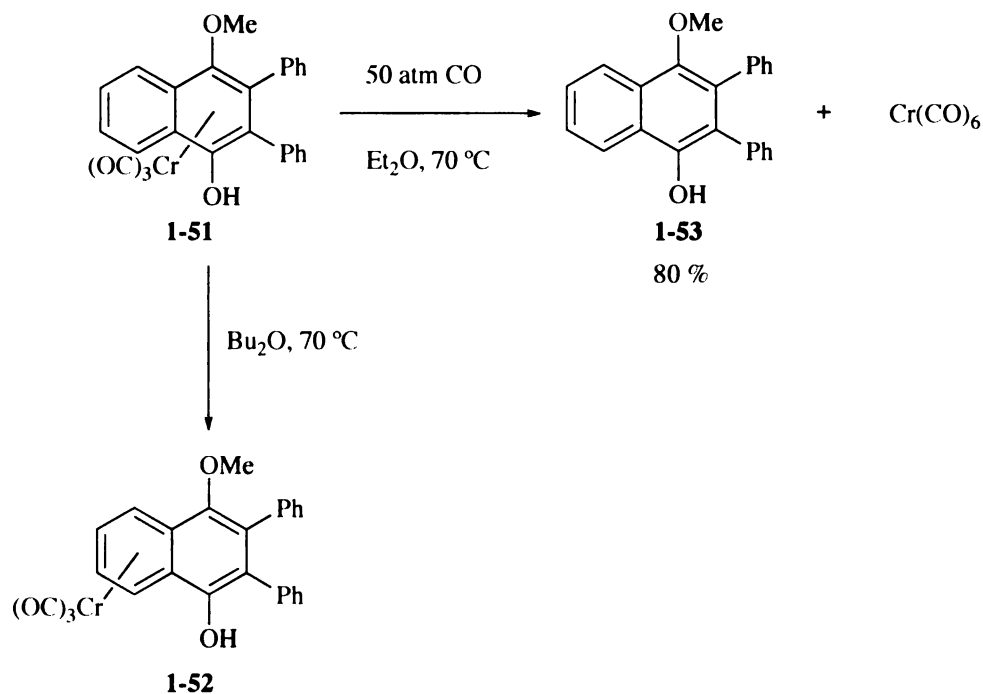
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Scheme 1.18. Carbon Monoxide for $\text{Cr}(\text{CO})_3$ Removal



Some metal arenes can be difficult to demetallate. For example, FeCp complexes are notoriously stable to air and high temperatures are required for demetalation such as compound **1-54** shown in Scheme 1.19.³⁵ The high temperatures can be detrimental to many functional groups. Also manganese complexes are stable and require Jones reagent to liberate the arene from the magnesium tricarbonyl complex, which of course can destroy any acid sensitive functionality such as acetals or oxidize alcohol-containing substituents.

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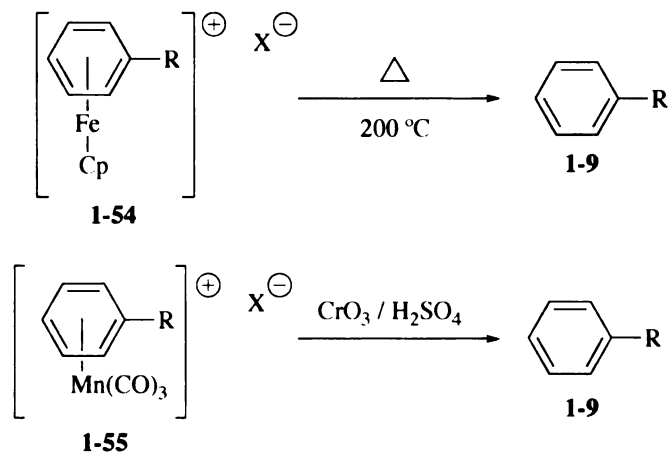
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Scheme 1.19. Thermal and Oxidative Removal of FeCp and Mn(CO)₃



1.3 General Properties of Chromium and Metal Tricarbonyls

Chromium and metal arenes shown in Figure 1.3 have fascinating properties regarding their reactivity.⁹ The arene has enhanced acidity. They can be chiral. Metal arenes have been used as substrates for nucleophilic substitution reactions, and the arene provides stability both for benzylic carbocations as well as anions. The metal carbonyl can provide steric hindrance for stereoselective reactions.⁹

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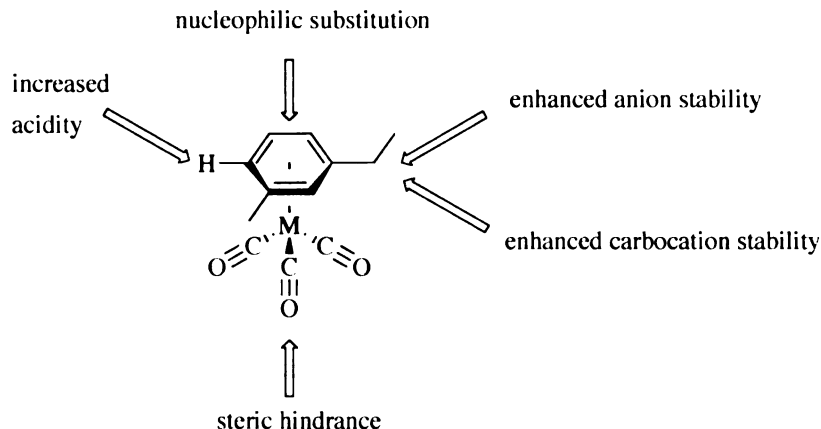
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Figure 1.3. General Reactivity of Chromium Tricarbonyl Arenes



The infrared bands of the C-H and C-C stretching vibrations show altered properties as would be expected. The spectra of the chromium tricarbonyl arenes show lower intensities for the C-H stretching band. For toluene, the apparent molar absorptivity at 3100 cm^{-1} is 22 and for the chromium tricarbonyl arene the molar absorptivity is 9 which is a decrease of 60 %.³⁶ In the carbon-carbon stretching region ($1650 - 1450\text{ cm}^{-1}$) the intensity of the band is virtually unaffected however the band is shifted to lower wavenumbers and subsequently lower energy showing weaker bonding between the carbons. The shifts for toluene between the free arene and the chromium tricarbonyl π -bonded complex is 1610 to 1540 cm^{-1} which is a shift of 70 wavenumbers.³⁶

The out-of-plane vibrations (850 to 670 cm^{-1}) for chromium tricarbonyls in general show an increase in wavenumbers.³⁶ For example, toluene has an out-of-plane vibration at 725 cm^{-1} , but for toluene chromium tricarbonyl complex, the

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band occurs at 805 cm^{-1} . The intensity of these bands are weakened by an order of magnitude comparing free aryls with metal coordinated arenes.

The most apparent infrared spectral feature of metal tricarbonyl complexes are the intense terminal carbonyl stretches occurring in the region $2000\text{ to }1800\text{ cm}^{-1}$ as shown in Table 1.1. The vibrational stretches of the terminal carbonyl groups in the IR occur in the active bands according to C_{3v} local symmetry.^{37, 38} The electron density of the arene is depleted by the metal tricarbonyl motif. This effect is observable in the IR through the CO active stretching band. When electron-withdrawing groups are attached to the arene (entry 1, Table 1), electron density is removed from the metal center. The metal no longer has as much electron density to donate into the anti-bonding orbital of the $C\equiv O$ bond. Therefore when the arene is substituted with electron withdrawing groups, the energy of the $C\equiv O$ bond increases (i.e. larger wavenumbers). The reverse is also true. When electron-donating groups such as OMe are attached to the arene, the bond strength of the $C\equiv O$ bond is decreased so the wavenumbers decrease.³⁹

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Table 1.1. ν_{CO} of $\text{RC}_6\text{H}_5\cdot\text{Cr}(\text{CO})_3$ ³⁹

entry	R	A ₁ (cm ⁻¹)	E (cm ⁻¹)	Solvent
1	CO ₂ Me	1992	1930	Isooctane
2	Cl	1992	1931	Cyclohexane
3	H	1987	1918	Cyclohexane
4	CH ₃	1983	1914	Cyclohexane
5	OMe	1975	1903	CCl ₄
6	OMe	1983	1914	Cyclohexane

The dipole moments for metal tricarbonyl complexes are large. They range from 3.5 to 6.3 D measured in benzene as shown in Table 1.2.³⁹ Electron donating substituents such as in entry 2 and 3 increase the dipole moment. Electron withdrawing groups deplete the electron density in the ring and subsequently affect the dipole moment.

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Table 1.2. Dipole Moments of Chromium Tricarbonyl Arenes³⁹

Entry	Ligand	Dipole Moment (D)
1	C ₆ H ₆	4.81
		4.92
		5.08
		5.03
2	<i>p</i> -Me ₂ C ₆ H ₄	5.39
		5.52
		5.41
3	<i>p</i> -(NH ₂) ₂ C ₆ H ₄	5.52
4	<i>p</i> -(CO ₂ Me) ₂ C ₆ H ₄	3.52

The pK_a values for chromium tricarbonyl complexes of benzoic acids are shown in Table 1.3.³⁹ A chromium tricarbonyl exerts about the same electron withdrawing effect as a nitro substituent comparing entries 2 and 3, however the nitro has an extra capacity to stabilize negative charges. Comparing entries 5 and 6, the pK_a values are about the same between a chromium tricarbonyl arene and a *para*-substituted nitro compound.³⁹

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Table 1.3. The pK_a Values of Chromium Tricarbonyl Arenes³⁹

Entry	Compound	pK _a
1	C ₆ H ₅ -CO ₂ H	5.68
2	[C ₆ H ₅ -CO ₂ H]Cr(CO) ₃	4.77
3	<i>p</i> -NO ₂ -C ₆ H ₄ -CO ₂ H	4.48
4	C ₆ H ₅ -CH ₂ CO ₂ H	5.64
5	[C ₆ H ₅ -CH ₂ CO ₂ H]Cr(CO) ₃	5.02
6	<i>p</i> -NO ₂ -C ₆ H ₄ -CH ₂ CO ₂ H	5.01

In the ¹H NMR, chromium arenes are shielded compared to their uncomplexed counterparts.³⁹ It has been proposed that the anisotropy of the CO ligands in the chromium tricarbonyl group alters the environment around the aromatic protons.⁴⁰ The proposal that the ring current is disrupted has been refuted by testing this with compounds **1-56** and **1-57**. The chemical shifts of H_a are almost identical between the free aromatic and the arene chromium tricarbonyl arene **1-57**. Therefore, alterations in the ring current of the aromatic cannot be responsible for the altered chemical shifts of the arene hydrogens in a chromium tricarbonyl complex.³⁹



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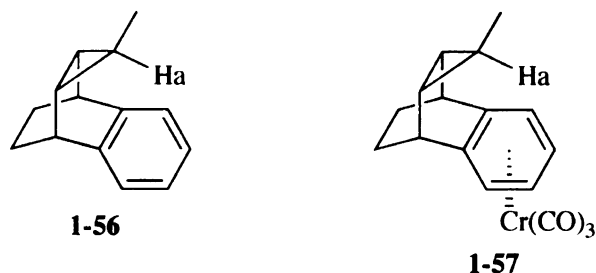
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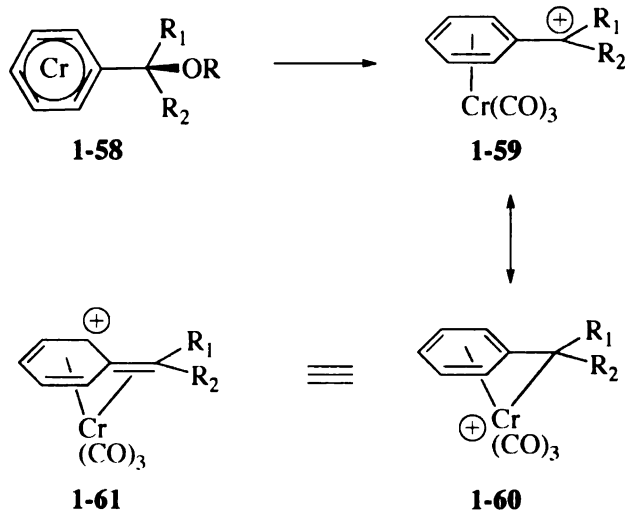
Figure 1.4. Ring Current Relationship to Chemical Shifts



1.4 Stabilization of Carbocations

A remarkable and important property of metal tricarbonyl arenes are their ability to stabilize carbocations (shown as compound **1-59**) on substituents attached to the arene.⁴¹ When a carbocation is formed, it can be stabilized by the chromium or metal tricarbonyl motif shown as structures **1-60** and **1-61**.

Scheme 1.20. Carbocation Stabilization of a Chromium Tricarbonyl Arene



The solvolysis reaction of benzyl chloride has been observed to be 10^5 times faster for a chromium tricarbonyl arene in water and acetone as shown in Scheme 1.21.⁴¹ This suggests the chromium is stabilizing the formation of the intermediate carbocation producing a faster rate.

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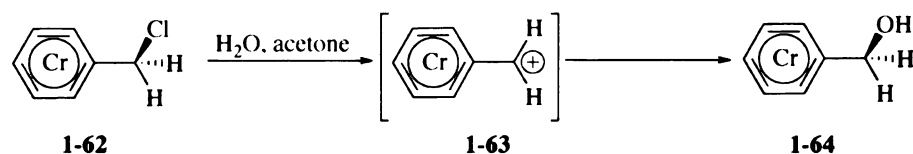
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Scheme 1.21. Solvolysis of Benzyl Chloride Chromium Tricarbonyl Complex



The rates of solvolysis have been studied on cumyl chloride as shown in Table 1.4. The rate for the CrCO₃ containing compound was $360 \times 10^5 \text{ s}^{-1}$ (entry 1) and was 13 s^{-1} (entry 2) for the free arene.⁴¹ This gives a ratio of $k_{\text{complex}}/k_{\text{free}}$ of 28 demonstrating the stabilization of the carbocation intermediate. For the biphenyl derivative shown in entries 3 and 4, the $k_{\text{complex}} / k_{\text{free}}$ ratio was 0.4 demonstrating the electron withdrawing nature of the chromium tricarbonyl unit. By placing the chromium tricarbonyl on an adjacent ring, the electron density of the parent ring is reduced, decreasing its ability to stabilize a partial positive charge during a solvolysis reaction.

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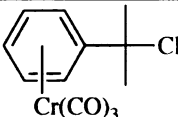
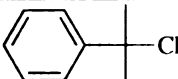
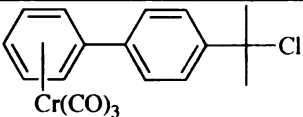
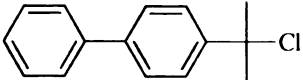
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Table 1.4. Solvolysis Rates for Cumyl Chloride Derivatives

Entry	Compound	$10^5 k$ (s ⁻¹)	Temperature (°C)	Relative rate
1	 Cr(CO) ₃	360	25	1
2		13	25	28
3	 Cr(CO) ₃	33.4	25	1
4		83.3	25	0.4

The stabilization of carbocations by the chromium tricarbonyl group enables diastereoselective reactions with the chromium tricarbonyl unit as a placeholder for the alcohol. Treatment of the chromium arene **1-65** in Scheme 1.22 with trimethyl aluminum gave the methyl substituted product **1-67** in 80 % yield.⁴¹ The diastereomeric excess was 99 %. This reaction is proposed to proceed through a chromium-stabilized carbocation to give compound **1-67**.

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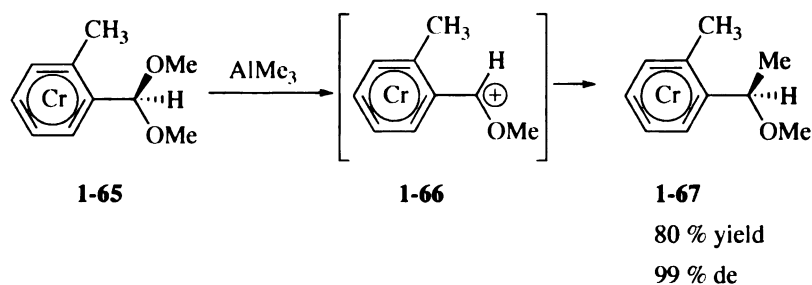
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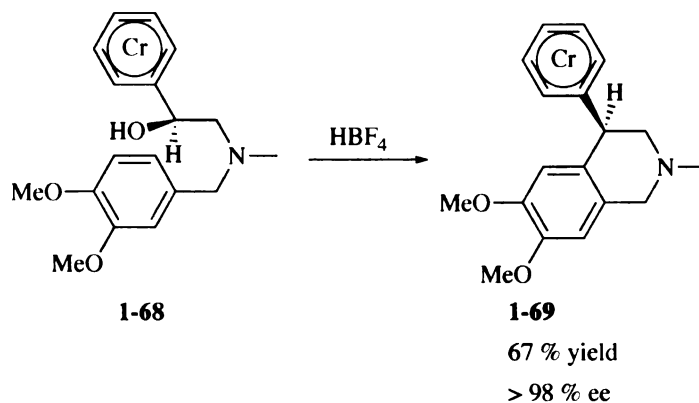
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Scheme 1.22. Substitution of Chromium Tricarbonyl Arenes



A chromium tricarbonyl was used as a placeholder for the alcohol during a Friedel-Crafts reaction involving the elimination of water from compound **1-68**. The yield of compound **1-69** was 67 % and the enantiomeric excess was > 98 %.⁴² This was an interesting example because the compound was not chiral at chromium but used the enantiomerically pure alcohol to produce a chiral cation that was stabilized by chromium tricarbonyl.⁴³

Scheme 1.23. A Chiral Friedel-Crafts Reaction Using a Non-Chiral Chromium Tricarbonyl Arene



A migration event is observed in Scheme 1.24 when compound **1-70** undergoes acetolysis.³⁹ This involves the stabilization of a cation at a β -position

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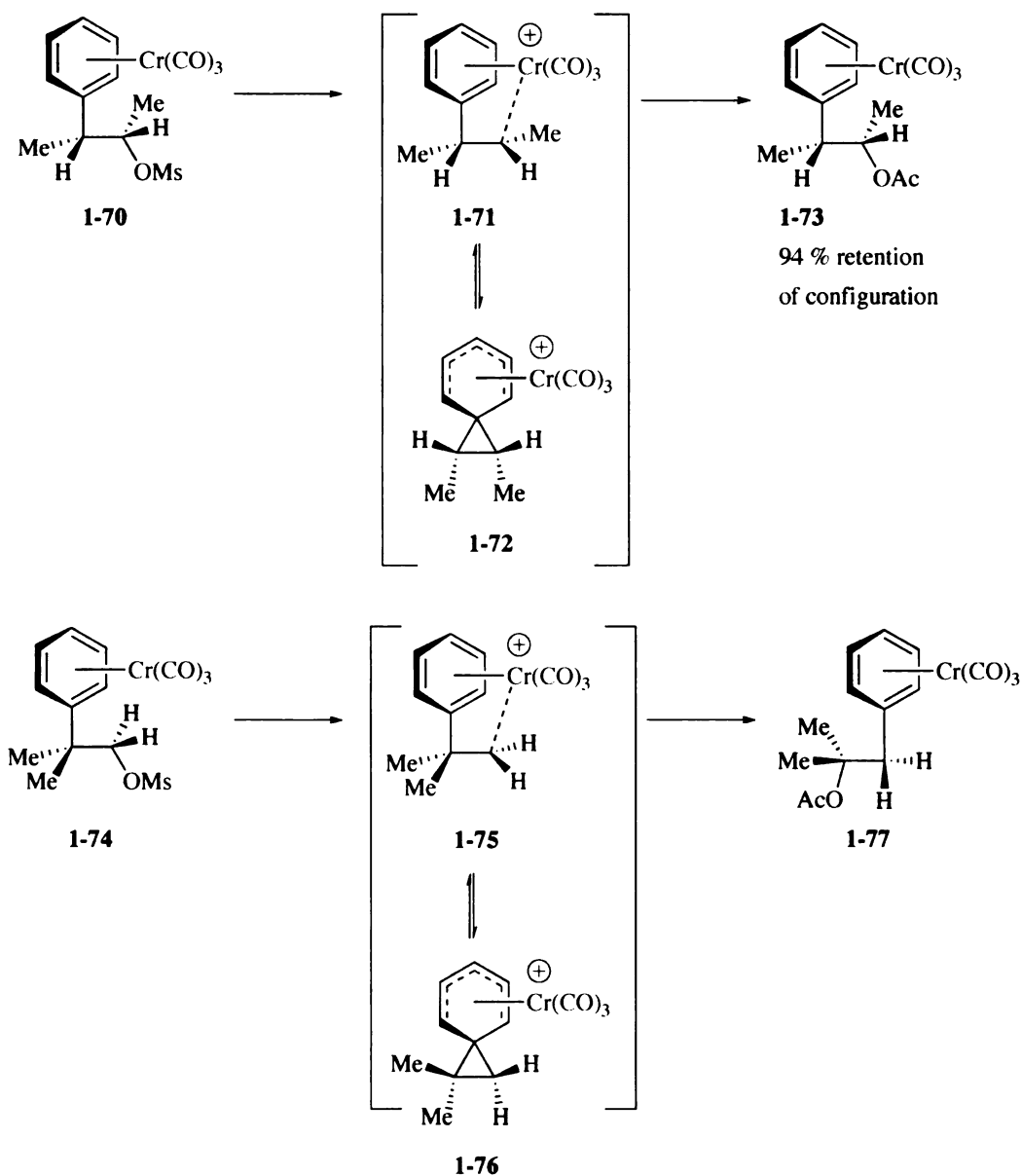
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with chromium tricarbonyl possibly through intermediate **1-71** or **1-72**. When compound **1-74** is subjected to acetolysis, compound **1-77** is formed suggesting intermediate **1-76** is involved. This in turn suggests that intermediate **1-72** is involved in the formation of **1-73**.

Scheme 1.24. Stabilization of a Carbocation at a β -Carbon



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1.5 Rate Enhancement of Elimination Reactions.

The rate enhancement of elimination in a chromium tricarbonyl has been attributed to the stabilization of the developing negative charge at the α -carbon during elimination. The chromium tricarbonyl removes electron density from the arene which can subsequently stabilize a negative charge at a benzyl position. The relative rates are $k_{\text{Cr(CO)}_3}/k_{\text{H}} = 148$ for OTs and 37 for Br (data not shown).⁴⁴ If these relative rates of formation are considered for the elimination of compound **1-78** shown in Table 1.5, it is observed that the effect of Cr(CO)_3 is considerable.⁴⁴ The relative difference between OTs and Br most likely is due to differences in negative charge density in the transition state on the α -carbon. If one considers NO_2 , the effects are $k_{\text{NO}_2}/k_{\text{H}} = 4020$ for OTs and 1975 for Br.⁴⁴ The stabilization effects of NO_2 are due to the direct resonance effects through the σ -framework rather than the π -cloud. The rates are shown in Table 1.5 for E2 reactions of compound **1-78**.⁴⁴

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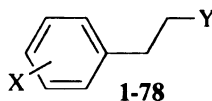
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Table 1.5. E2 Elimination of Substituted Ethylbenzenes



X	Y	Temp. (°C)	10 ³ k _{el.}
H	Br	40	1.20
<i>p</i> -NO ₂	Br	40	2370
π -Cr(CO) ₃	Br	96	290
H	OTs	40	0.16
<i>p</i> -NO ₂	OTs	40	643
π -Cr(CO) ₃	OTs	42	29.1

The ability of chromium tricarbonyl compounds to stabilize negatively charged substituents at the α -carbon has been applied to 4-aryl hydroisoquinolines such as compound **1-79**.⁴¹ In the first step, *ortho*-lithiation produces compound **1-80**, and in step two with the possibility of *ortho*-methylation eliminated, subsequent treatment with *n*-butyl lithium gave compound **1-81**. The methyl substituent was added on the opposite face to the chromium tricarbonyl. It is important to notice that the methyl substituent's relative stereochemistry of the methyl group is a result of the chromium

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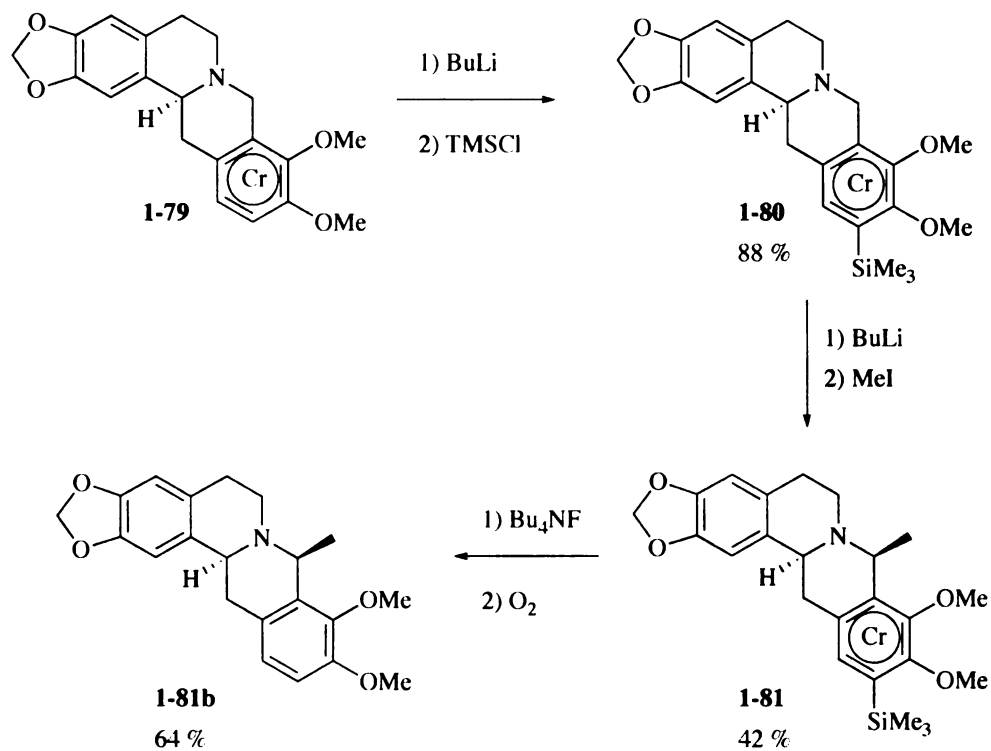
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tricarbonyl. The silyl group was removed with tetrabutyl ammonium fluoride and the chromium tricarbonyl was removed with oxidation to give compound **1-81b**.⁴¹

Scheme 1.25. A Chromium Tricarbonyl Group Used to Stabilize an Anionic Charge



1.6 Metalation Reactions (*ortho*-Lithiation)

Under mild conditions, alkyl lithiums can deprotonate aromatic protons on chromium tricarbonyl arene compounds. The selectivity is high in the case of metalation *ortho* to OMe, F, Cl, and "large" nitrogen substituents. For substituent attached to the arene such as Me, Et, *t*-Bu, and "small" substituted amines, there is little selectivity. The lithiation generally occurs at the less hindered of two

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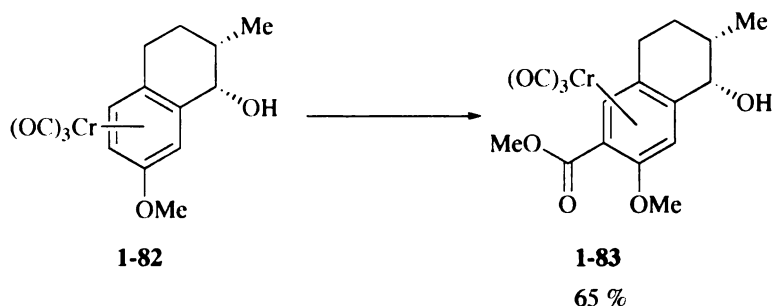
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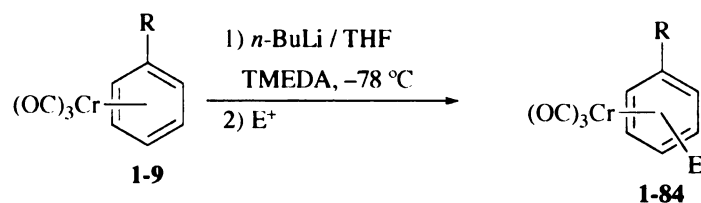
ortho-positions as shown in Scheme 1.26 where compound **1-82** was deprotonated with butyl lithium and acylated in 65 % to give compound **1-83**.⁴⁵

Scheme 1.26. Lithiation at the Less Hindered *Ortho*-Position



In Table 1.6, the lithiation of the substituted chromium tricarbonyl arenes (**1-9**) followed by quenching with an electrophile to give compound **1-84** is shown.⁹ In entries 1 - 3, with OMe the lithiation proceeds exclusively to the *ortho*-position. In entries 4 and 5 with F, the yields are higher compared to methoxy. In entry 7, a "large" amino substituent gives mostly *meta*-substitution and in entry 8 with a "small" amino substituent poor selectivity is observed. In entries 9 - 11, poor selectivity is observed for alkyl substituents.⁴⁶

Table 1.6. Lithiation of Substituted Chromium Tricarbonyl Arenes



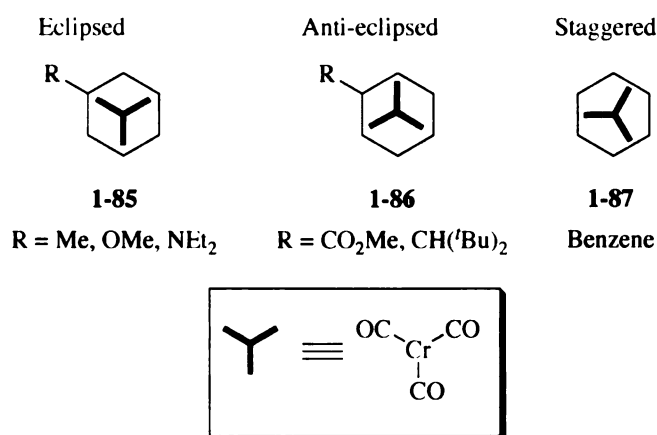
Entry	R	E ⁺	<i>Ortho</i> Yield	<i>Meta</i> Yield	<i>Para</i> Yield
1	OMe	CO ₂	86	-	-
2	OMe	Mel	14	-	-
3	OMe	TMSCI	70	-	-
4	F	CO ₂	99	-	-
5	F	Mel	71	-	-
6	Cl	CO ₂	98	-	-
7	N(Me)Si(Me) ₂ <i>t</i> -Bu	Mel	-	63	10
8	NMe ₂	Mel	19	32	11
9	Me	Mel	6	41	22
10	Et	Mel	5	49	26
11	<i>t</i> -Bu	Mel	-	32	22

1.7 Conformation of the Chromium Tricarbonyl Tripod

The conformation of chromium tricarbonyl tripod has been determined from analysis of a number of x-ray crystal structures.⁴⁷ The electronic and steric

effects of the arene substituents control the orientation of the tripod as shown in Figure 1.5. In the case where the substituent R is Me, OMe, or NEt₂ such as structure **1-85**, the eclipsed conformation predominates for mono-substituted arenes.⁴⁸ This is due to the electron donating effect of the substituents. The π -back bonding of the metal orients the carbon monoxide eclipsed to the electron-donating group due to d-orbital interactions to maximize orbital overlap. When R is CO₂Me or CH(*t*-Bu)₂ in structure **1-86**, the anti-eclipsed conformation is observed. This is due to the sterics of the bulkier groups and because of disfavored d-orbital overlap (CO orients eclipsing to the most electron dense carbon on the arene). In the case where there are no substituents the tripod resides in a staggered conformation as in structure **1-87**.⁴⁸

Figure 1.5. Conformations of Chromium Tricarbonyl Tripod (Mono-Substituted)



The tripod in disubstituted as well as mono-substituted chromium tricarbonyl complexes can be related to the electron-donating nature of the

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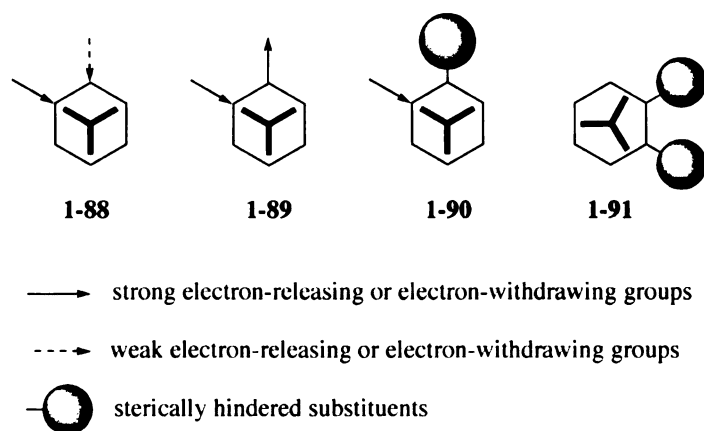
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substituents as shown in Figure 1.6.⁴⁹ The eclipsed tripod conformation is favored for a strong electron-donating substituent for structure **1-88**. In structure **1-89**, the orientation for a strong electron releasing group and a strong electron-withdrawing group is shown. In structure **1-90**, an electron-donating group with a bulky substituent is shown with the CO of the tripod aligning with the electron-donating group. Two bulky substituents twist the chromium tricarbonyl tripod as shown in structure **1-91**. The order of substituents to favor the eclipsed tripod configuration shown in structure **1-88** is as follows: $\text{N}(\text{Me})_2, \text{NHR}, \text{NH}_2 > \text{OMe} \gg \text{Me} \gg t\text{-Bu} \sim \text{CO}_2\text{Me} > \text{CHO}$.³⁹

Figure 1.6. Disubstituted Chromium Tricarbonyl Arene Complexes



The metal tripod rotation can be slowed on the NMR time scale at low temperature.⁵⁰ In the case of hexaethylbenzene chromium tricarbonyl, two observable aromatic carbons are observed (see section 1.8). In the case of (hexaethylbenzene) $\text{Cr}(\text{CO})_2\text{CS}$ (**1-92**), four none equivalent aromatic carbons are observed. For $[(\text{hexaethylbenzene})\text{Cr}(\text{CO})_2\text{NO}]^+$ (**1-93**), four aromatic

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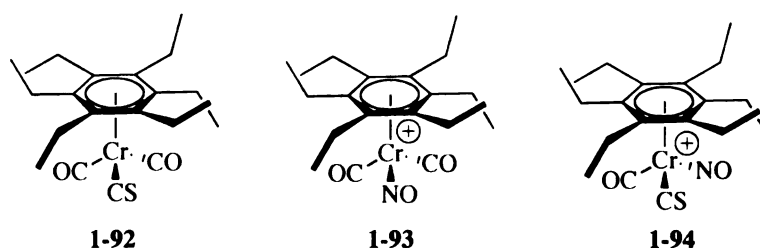
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carbons are observed, and for $[(\text{hexaethylbenzene})\text{Cr}(\text{CO})(\text{NO})(\text{CS})]^+$ (**1-94**), six aromatic carbons are observed.⁵⁰ The ^{13}C NMR results show that the chromium tripod rotation can be slowed on the NMR time scale resulting in the case of $[(\text{hexaethylbenzene})\text{Cr}(\text{CO})(\text{NO})(\text{CS})]^+$ (**1-94**) showing non-equivalency of the aromatic carbons.⁵⁰

Figure 1.7. Restricted Rotation of a Chromium Tripod



Metal complexes of benzene tend to have low barriers to tripodal rotation (< 0.3 kcal/mol).⁵¹ The rotational barrier for the metal complexes of compound **1-95** shown below is calculated to be 11 kcal/mol for chromium and up to 15 kcal/mol for molybdenum.⁵¹ The average bond length for the carbon-carbon bonds directly attached to the metal of the arene defined in structure **1-95** increases.⁵² The bond length of specific bonds has been determined by x-ray crystal structure of compound **1-96**.⁵³ For "cis" double bonds in benzene chromium tricarbonyl shown as structure **1-96**, the length is 1.423 Å, and for "trans" double bonds, the bond length is 1.406 Å. The aromatic C=C bond

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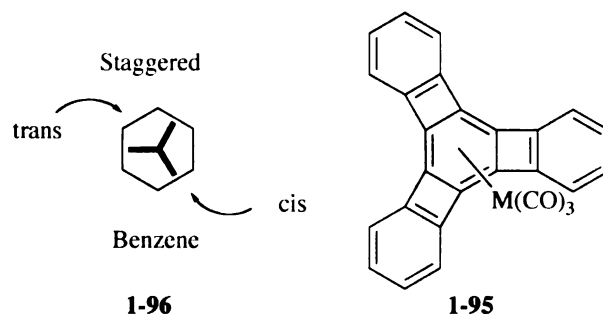
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lengths can vary between a C-C bond of 1.5 Å and an unconjugated C=C of 1.3 Å.⁵¹

Figure 1.8. Trans and Cis Bonding / Tripod Rotation Energy



The question arises from the distortion of the bond lengths, "Is the arene portion more aromatic or less aromatic?" This has been debated in the literature for some time.^{54, 55} Simion and Sorensen state that chromium tricarbonyl complexes should be regarded as anti-aromatic based on diamagnetic susceptibility.⁵⁶ Experimental evidence for aromaticity of a chromium tricarbonyl arene comes from evidence from bond lengths and coupling constants analysis. It is established that when two $[4n + 2\pi]$ -annulenes are fused as in naphthalene then the C2 - C3 bond of 1-97 is shorter and has a larger coupling constant than that of the C3 - C4 bond.⁵⁷ In biphenylene shown as structure 1-98, the bond C2 - C3 of this anti-aromatic system is longer than C3 - C4.⁵⁷ Also established is that for an $[4n\pi]$ -annulene such as biphenylene the C2 - C3 bond is longer and has a smaller coupling constant than that of the C3 -C4 bond.⁵⁷ These concepts

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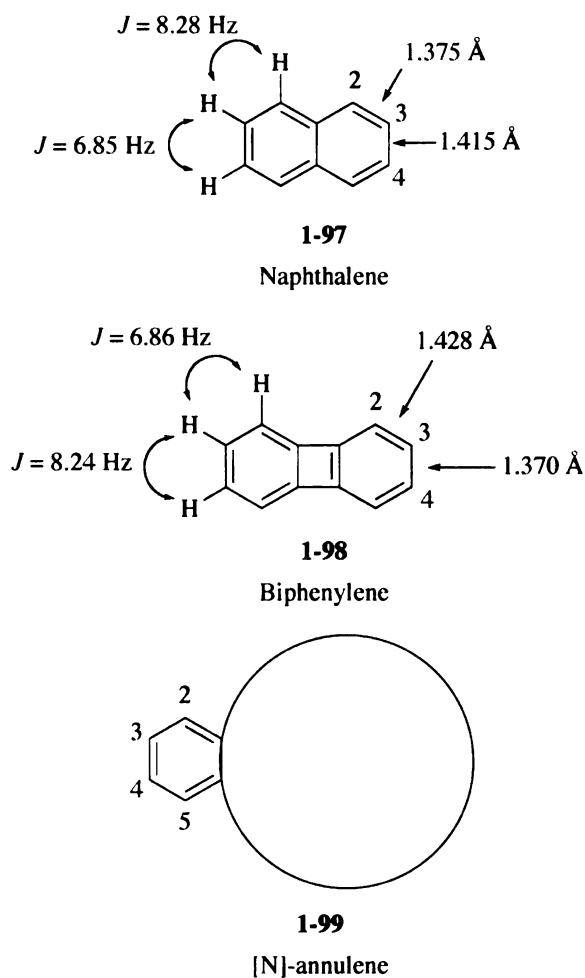
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of bond length and coupling constants can be used to determine aromaticity in [N]-annulene such as structure **1-99**.⁵⁴

Figure 1.9. Bond Length and Coupling Constants for Naphthalene and Biphenylene



These annulene arguments concerning aromatic and anti-aromatic systems can be extended to chromium tricarbonyl arenes. Shown in Figure 1.10 are the coupling constants and bond lengths of large annulene systems which will be used to determine if chromium tricarbonyl contributes to the aromatic

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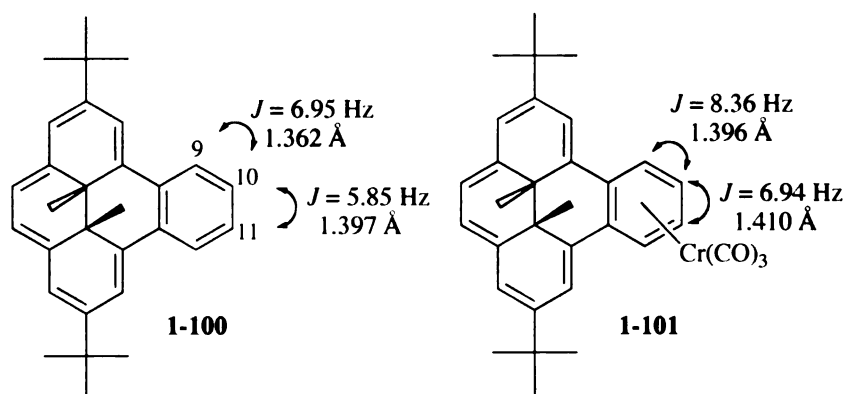
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nature of an annulene. The bond length for the C9 - C10 uncomplexed aromatic system (**1-100**) is 1.362 Å with a hydrogen coupling constant of 6.95.⁵⁴ This bond length is longer and the coupling constant smaller for the C10 and C11 bond (1.397 Å and 5.85 Hz) for the uncomplexed compound. For the annulene containing a chromium tricarbonyl motif (**1-101**), the coupling constants for hydrogen 9 and 10 is larger than for hydrogens 10 and 11.⁵⁴ The bond length for carbons 9 and 10 is shorter than carbons 10 and 11. The trend between compounds **1-100** and **1-101** are identical. For the uncomplexed compound **1-100** the difference between the hydrogens 9 to 10 and 10 to 11 is 1.1 Hz but for the chromium complex is 1.42 Hz. This suggests that both compounds are aromatic with the compound with the chromium tricarbonyl (**1-101**) having greater aromatic character due to the larger difference between the hydrogen coupling constants.^{54, 58}

Figure 1.10. Bond Length and Coupling Constant Evidence in Annulenes



1.8 Conformation of Substituents

In the case of anisole chromium tricarbonyl arenes, the methoxy group (C-O bond) stays in the plane of the arene ring. The C-O bond length is 1.33 Å, having some double bond character (the typical bond length of a C-O bond is 1.42 Å, and the typical bond length of a C=O bond is 1.22 Å).⁵⁹

When substituted with ethyl substituents such as in the case of hexaethylbenzene metal tricarbonyl complexes (**1-102**), the alkyl substituents are oriented alternately up and down around the ring perimeter as shown by x-ray crystal data. The calculated energy cost to flip one ethyl to the other side is 3.5 kcal/mol for either molybdenum or chromium. To have all the ethyl substituents on one side the energy would be 11.5 kcal/mol higher in energy.^{50, 60} The energy for tripodal rotation is estimated to be 9 kcal/mol in this system shown in Figure 1.11. The conformation of the substituents tend to alternate when attached to a metal tricarbonyl arene.

The metal tripod is preferentially in a staggered form in the crystal structure of **1-102**. This conformer under normal conditions in solution is > 99 % of the mixture at equilibrium as shown in Figure 1.11.

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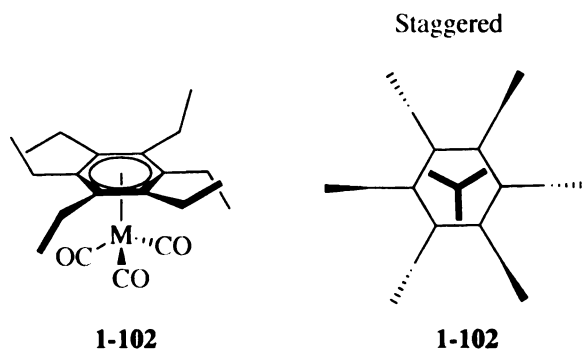
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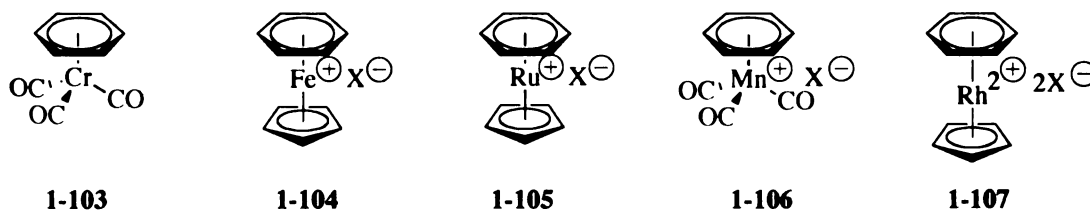
Figure 1.11. Hexaethylbenzene Metal Tricarbonyl Complex



1.9 Nucleophilic Reactions

Nicholls and Whiting in 1958 reported the first nucleophilic substitutions on chromium tricarbonyl arene complexes.⁶¹ This was the reaction of sodium methylate with chlorobenzene tricarbonyl chromium reacting at the *ipso* carbon to give anisole tricarbonyl chromium.⁶² Since then the reaction has been expanded to many other nucleophiles, leaving groups, and metals. There are five types of arene π -complexes that have been used in aromatic nucleophilic substitution reactions or S_NAr .⁶³ These are neutral η^6 -arene- $Cr(CO)_3$,⁶³ cationic (η^6 -arene)(η^5 -cyclopentadienyl)Fe(II)⁶⁴ and (η^6 -arene)(η^5 -cyclopentadienyl)Ru(II),⁶⁵ cationic η^6 -arene- $Mn(CO)_3$,⁶⁶ and dicationic (η^6 -arene)(η^5 -ethyltetramethylcyclopentadienyl)Rh(III)⁶⁷ complexes shown in Figure 1.12.

Figure 1.12. Complexes Used in Aromatic Nucleophilic Substitution



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Generally *ortho*-lithiation reactions use *n*-BuLi, MeLi, or *s*-BuLi. For nucleophilic aromatic substitution reactions, alkyl lithiums such as $\text{LiCH}_2\text{CO}_2t\text{-Bu}$, LiCH_2CN , 2-Li-1,3-dithiane, LiCH=CH_2 , or LiPh have been used successfully. Nucleophiles that fail for nucleophilic aromatic substitution are $\text{LiCH}(\text{CO}_2\text{Me})_2$, $\text{LiCH}_2\text{CO}t\text{-Bu}$, MeMgBr, *t*-BuMgBr, Me_2CuLi , and $\text{LiC}(\text{CN})(\text{Ph})(\text{OR})$.

The equilibration possibilities in nucleophilic substitution of compound **1-108** are shown in Scheme 1.27 when X = a halogen. There are several types of carbanions: (**type A**) these are the stabilized carbanions from carbon acids with $\text{pK}_a < \text{ca. } 18$ which easily rearrange, (**type B**) $\text{pK}_a > 20$ which at low temperature (-78°C) do not rearrange, and (**type C**) with $\text{pK}_a > 30$ that do not rearrange. In type A carbanions, the anion adds reversibly and unfavorably to the chromium tricarbonyl arene. Eventually the carbanion finds itself at the *ipso*-position in intermediate **1-109** then with irreversible loss of X the substituted product is formed (**1-110**). Quenching with iodine removes the chromium tricarbonyl. In type B, the initial reaction is over quickly with addition to the chromium tricarbonyl arene complex. If the reaction is quenched, mixtures of *ortho* (**1-112**) and *meta* (**1-114**) substituted products would be obtained. If the reaction is warmed to room temperature and stirred for several hours, the carbanion can rearrange to the *ipso* position (**1-109**) and with subsequent elimination of X give the substituted product (**1-110**). Quenching with iodine removes the chromium tricarbonyl. For type C, these carbanions add to the

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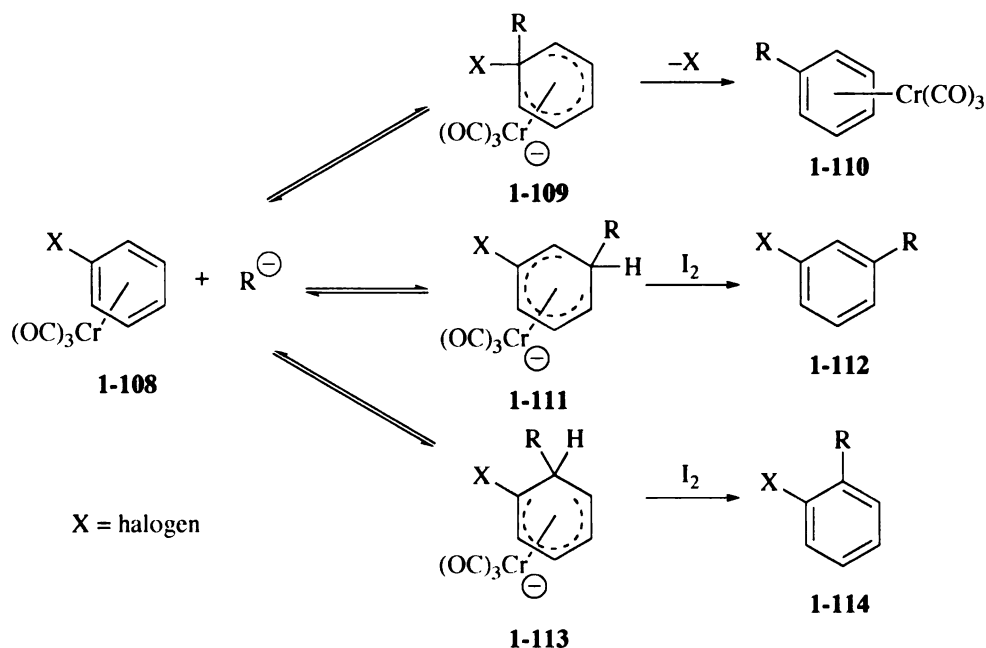
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arene and do not rearrange giving mixtures mostly having *ortho* and *meta* substitution. When quenched with iodine even after stirring for long periods of time at room temperature, the major product is the formal substitution of hydrogen at the *ortho* and *meta* positions giving compounds mainly **1-112** and **1-114** when X = Cl.

Scheme 1.27. Possibilities in Nucleophilic Additions to Chromium Tricarbonyl Arenes



Another mechanism is possible for nucleophilic substitution on arene complexes, and this mechanism involves *tele*-substitution.⁴⁸ This mechanism involves the hydride migration to a *meta*-position. If a nucleophile is added at room temperature to compound **1-115**, compound **1-116** is obtained, however at $-78\text{ }^\circ\text{C}$ a formal deuteride / hydride migration occurs giving intermediate **1-118**.

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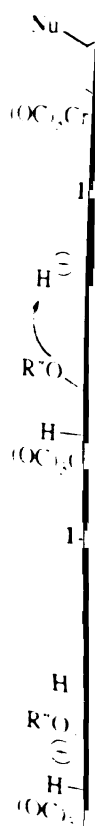
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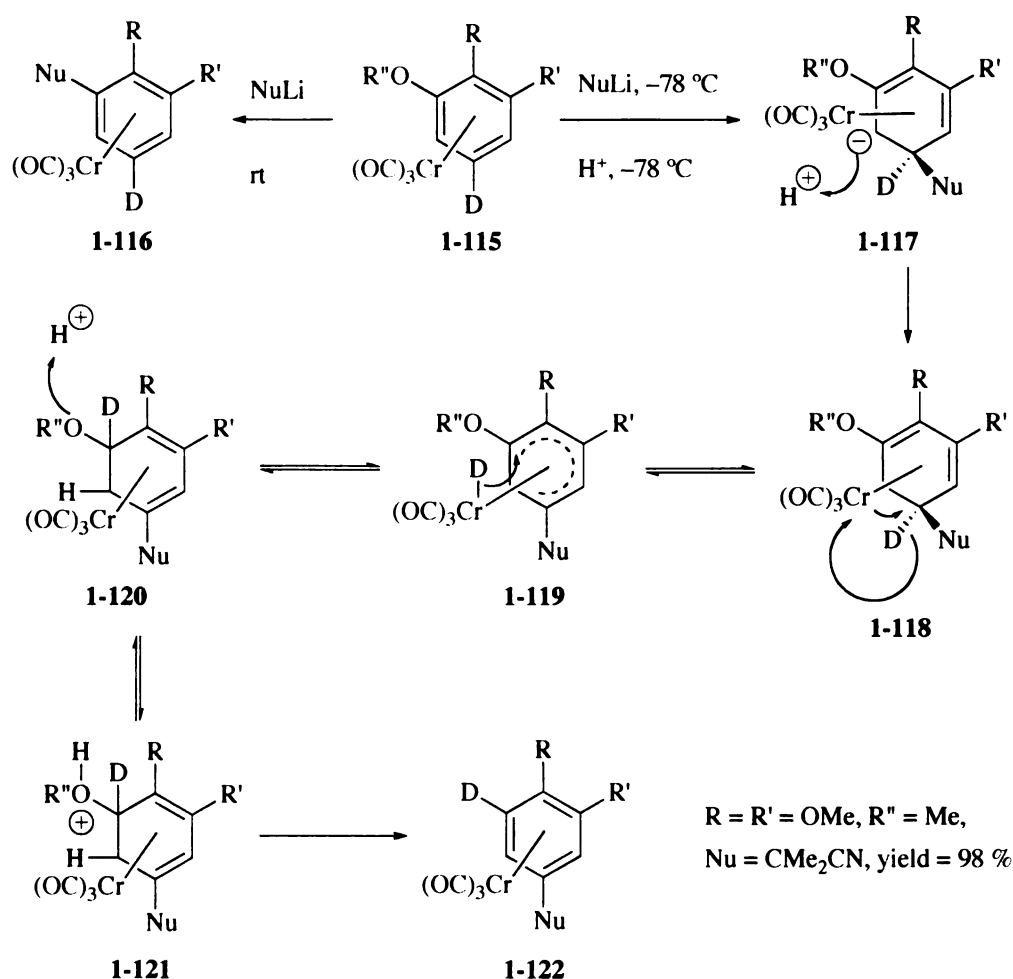
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Intermediate **1-118** can undergo β -hydride elimination to give metal hydride **1-119** which can undergo addition of the hydride *ipso* to the ether linkage to give intermediate **1-120**, and with elimination, compound **1-122** is formed through protonated species **1-121**. These yields are up to 98 % for the *tele-meta* substitution reaction which has been used for the synthesis of dopamine.⁶⁸

Scheme 1.28. *Ips*o and *Tele-meta* Nucleophilic Aromatic Substitution



When adding nucleophiles such as those in Table 1.7 followed by oxidation with I_2 , the addition is mostly *meta*-oriented (**1-112**) to the substituent as shown in entries 1 and 2. The selectivity was poor (10:90:0) with 2-lithio-1,3-

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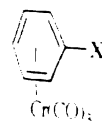
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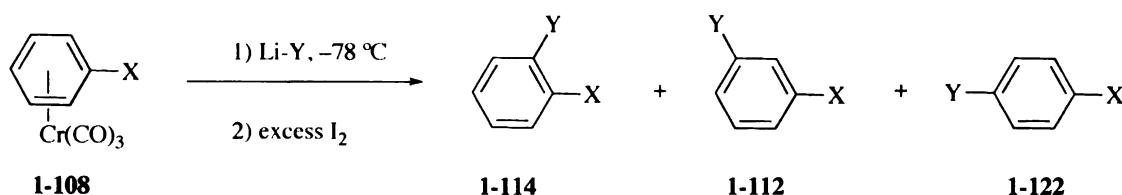
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dithiane (entry 3, 8, and 9). In entries 11 - 14, the effect of sterics can be observed; as the substituent X is changed from Me to *t*-Bu, a concomitant increase of the *para*-product (1-122) and a decrease in the amount of the *meta*-product (1-114) is observed.⁶³

Table 1.7. Addition and Oxidation of Substituted Benzene Chromium Tricarbonyl Complexes



Entry	X	LiY	Ratio (o:m:p)	Yield %
1	OMe	LiCH ₂ CN	3:97:0	38
2	OMe	LiC(Me) ₂ CN	3:97:0	93
3	OMe	2-Li-1,3-dithiane	10:90:0	35
4	NMe ₂	LiC(Me) ₂ CN	1:99:0	92
5	F	LiC(Me) ₂ CN	2:98:0	84
6	Me	LiCH ₂ CN	35:63:2	88
7	Me	Li(Me) ₂ CN(−78 °C)	1:97:2	86
8	Me	2-Li-1,3-dithiane	52:46:2	94
9	Cl	2-Li-1,3-dithiane	46:53:1	56
10	SiMe ₃	LiC(Me) ₂ CN	0:2:98	65
11	Me	LiC(OR)MeCN ^a	0:96:4	75
12	Et	LiC(OR)MeCN ^a	0:96:4	89
13	<i>i</i> -Pr	LiC(OR)MeCN ^a	0:80:20	88
14	<i>t</i> -Bu	LiC(OR)MeCN ^a	0:35:65	86

a. R = C(Me)OEt

The general rules for nucleophilic substitution on chromium tricarbonyl arenes are based on the electron donating or releasing nature of substituents. In

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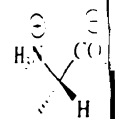
these nucleophilic additions, electron-donating substituents are deactivating and subsequently are *meta* directing. Electron-withdrawing substituents are *ortho/para* directing and also activating. A list of *meta* directors and *ortho / para* directors is listed in Table 1.8.^{39, 48, 63}

Table 1.8. List of *Meta* and *Ortho / Para* Directing Substituents

↑	<i>Meta</i> directors (Deactivating)	<i>Ortho / Para</i> Directors (Activating)	↓
	NH ₂	C(O)R	
	OH	CO ₂ R	
	OR	SO ₃ H	
	NHCO ₂ R	C(O)H	
	Ar	CO ₂ H	
	Me	CN	
	Halide	NO ₂	
		NR ₃ ⁺	

Other metals for nucleophilic substitution have been used such as (PhF)FeCp⁺ shown in Scheme 1.29.⁶⁴ Silylated amino acids such as **1-123** have sufficient reactivity with triethyl amine to give good yields of the arylated product (**1-124**) however removing the FeCp group gave low yields of the substituted aniline (**1-125**).

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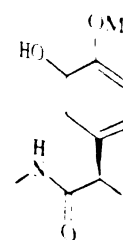
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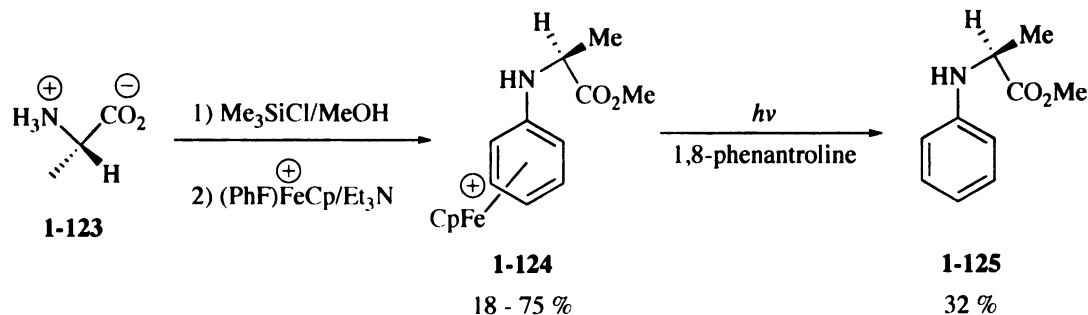


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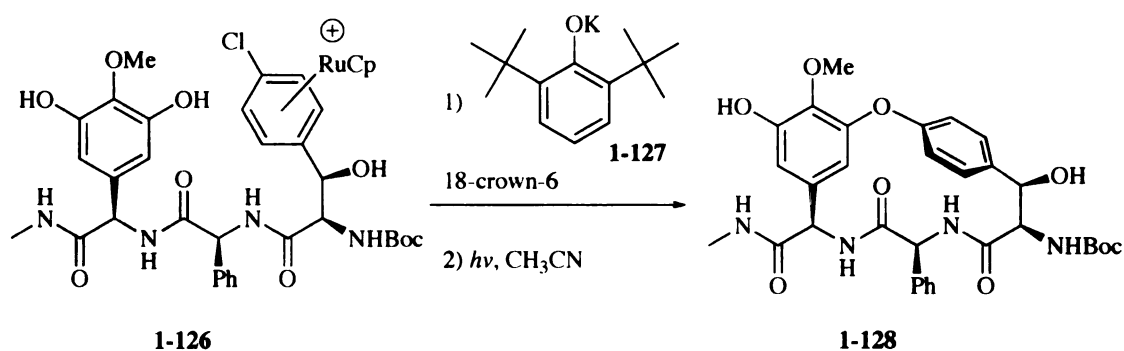
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Scheme 1.29. The Arylation of an Amino Acid



Halobenzene rhodium complexes such as **1-126** have been used in the synthesis of vancomycin related compounds such as **1-128**.⁶⁹ The RuCp^+ complexes are less electrophilic than FeCp^+ and RuCp^+ and have the advantage in that the decomplexation can be accomplished under mild conditions in acetonitrile.⁶⁵

Scheme 1.30. $\text{S}_{\text{N}}\text{Ar}$ Cyclization of a Vancomycin Related Compound



In Scheme 1.31, the use of chlorobenzene $\text{Mn}(\text{CO})_3^+$ (compound **1-129**) for substitution reactions is depicted with amine **1-130**.⁶³ Compound **1-131** would then be treated with a nucleophile to give compound **1-132**. The direct

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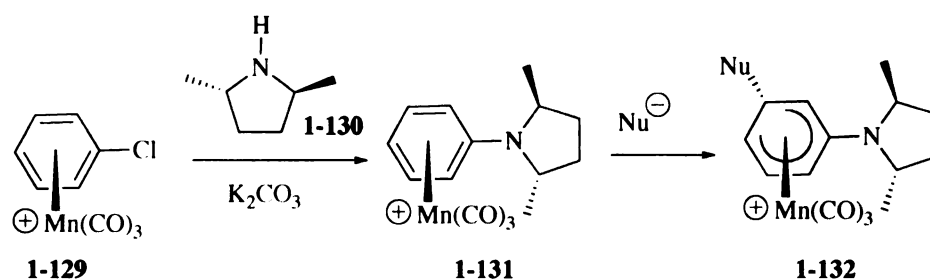
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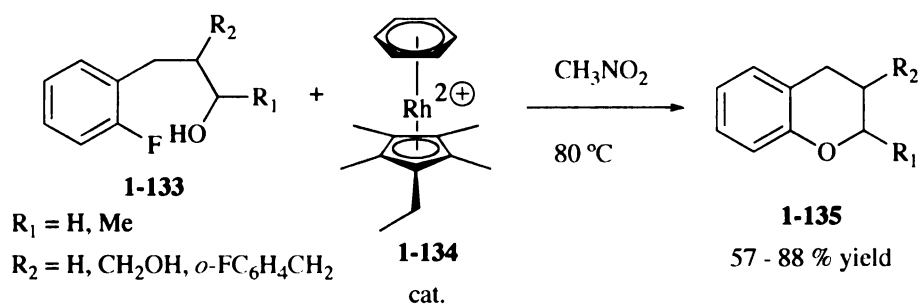
substitution of the halogen with alkoxy, phenoxy, thiolate, amine, and azide nucleophiles occurs.⁷⁰ The (fluorobenzene) $\text{Mn}(\text{CO})_3^+$ complex is so reactive that it solvolyzes rapidly during purification.⁶⁶ The selection for diastereotopic *meta* positions is possible using a chiral amine substituent.⁷¹

Scheme 1.31. Substitution of Chlorobenzene Manganese Tricarbonyl Cation



Rhodium (III) complexes such as **1-134** can be used catalytically for $\text{S}_{\text{N}}\text{Ar}$ reactions.⁶⁷ The rhodium complexes are so reactive that an alcohol nucleophile substitutes without base as shown in Figure 1.32 from compound **1-133**. Product **1-135** is formed in 57 to 88 % yield.

Scheme 1.32. Catalytic Rhodium (III) Arene



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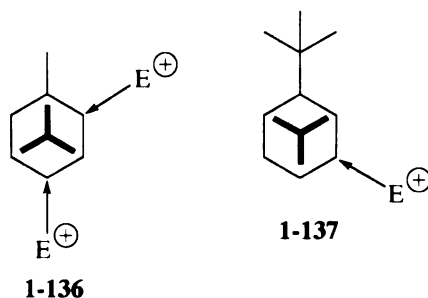
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1.10 Electrophilic Reactions

The electrophilic substitution of chromium tricarbonyl arenes has been investigated in the literature. The conformation of the chromium tripod influences the addition of the electrophile as shown in Figure 1.13. These results are predicted by Albright and Carpenter.⁷² An electron donating substituent orients the chromium tripod as in structure **1-136** for electrophilic addition as shown. A bulky substituent is oriented as in structure **1-137** for electrophilic addition as indicated.

Figure 1.13. Electrophilic Addition to Methyl and *t*-Butyl Benzene



Experimental results by Jackson and Jennings demonstrated the effects of the chromium tripod as shown in Table 1.9.⁷³ Jackson and Jennings noted that the chromium tricarbonyl arene complexes reacted more slowly than the free arenes toward Friedel-Crafts acetylation under conditions of the Perrier procedure.⁷⁴ In entries 1 and 2, toluene is investigated for acetylation reactivity. With toluene the preference is strongly for *para* product formation however with tricarbonyl(toluene)chromium the outcome changes to a nearly 1 : 1 mixture of *ortho* and *para* products. This preference has been attributed to the

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conformation of the chromium tripod as previously explained in Figure 1.13. Similar results are shown in entries 3 and 4 involving ethylbenzene. The most dramatic change was for *t*-butyl benzene (entry 5 and 6). The selectivity for *t*-butyl benzene was for the *para*-position 22 to 1 (*p* : *m*), but with the tricarbonyl-(*t*-butylbenzene) chromium, the selectivity was 7 to 1 (*m* : *p*) in favor of the *meta*-position (reversal in selectivity). This suggests a conformational preference of the chromium tripod in *t*-butyl benzene as shown in structure 1-137.

Table 1.9. Experimental Results of Electrophilic Acetylations

Entry	Compound	<i>ortho</i>	<i>meta</i>	<i>para</i>
1	Toluene	1.2	2	96.8
2	Tricarbonyl(toluene)chromium	43	17	40
3	Ethylbenzene	0.4	2.9	96.7
4	Tricarbonyl(ethylbenzene)chromium	24	33	43
5	<i>t</i> -Butylbenzene	0	4.3	95.7
6	Tricarbonyl-(<i>t</i> -butylbenzene) chromium	0	87	13

1.11 Complexation Site and Haptotropic Metal Migration of Chromium Tricarbonyl

The complexation site in diaromatic imines has been studied via procedures similar to that shown in Scheme 1.1.³⁹ It is known that the formation of chromium tricarbonyl arene complexes is favored for electron-donating substituents.⁶¹ The aromatic ring A in structure 1-138 is electron-rich from the η -

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π interaction and ring B with the π - π interaction is electron deficient. In the absence of substituents on the aromatic rings, a chromium tricarbonyl group will selectively complex to ring B giving a single mono-complex which is accompanied with some bis-complexed material.⁷⁵ Therefore, electron density is not a singular determining factor. The substituents and sterics have a large effect on the site of complexation of chromium tricarbonyl.

Figure 1.14. Complexation in Diaromatic Imines

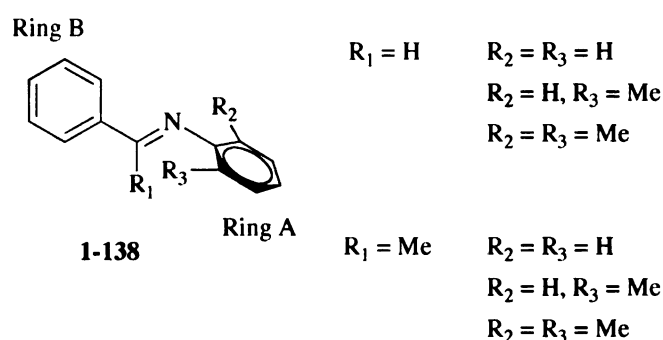


Table 1.10. Diaromatic Imine Complexation Sites

		$R_1 = H$			$R_1 = Me$	
	$R_2 = H$ $R_3 = H$	H Me	Me Me	$R_2 = H$ $R_3 = H$	H Me	Me Me
Global Yield	28	58	45	68	43	83
Unreacted imine	70	—	55	32	57	—
Complex On Ring A	0	81	100	8	38	100
On Ring B	0*	10	0	81	0	0
Dicomplexed	100	9	0	11	62	0

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The biaryls shown in Table 1.11 provide models for the effects of substituents.³⁹ The electron-donating substituents promote complexation and the electron withdrawing substituents disfavor complexation of chromium tricarbonyl. The substituent OMe is not sufficiently electron donating to favor complexation. Aryl compounds containing OMe disfavor complexation such that OMe acts like a weak electron withdrawing group. An amine substituent promotes complexation and so does OH. However in the case when R = OH, the chromium tricarbonyl complexes are unstable to air oxidation, and the ratio of products may not be a measure of the equilibrium between the ring A and ring B complexation sites. The complexation to ring A when R = OH may be unstable and the chromium tricarbonyl group migrates to ring B due to this instability. Also the yields are lower for R = OH as shown in Table 1.11. A ketone disfavors complexation of a chromium tricarbonyl group; the chromium tricarbonyl tends to migrate to the aromatic ring with the most electron density. The results shown in Table 1.19 are in agreement with a σ -bond contribution to the complexation of chromium tricarbonyl meaning oxygen is more electronegative than nitrogen therefore the chromium tricarbonyl group goes to the most electron rich ring.

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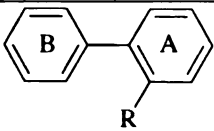
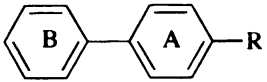
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Table 1.11. Site of Complexation on Biphenyl Compounds

		-----Complex on Ring (%)-----				
		R	A	B	AB	Yield (%)
	NH ₂		84	10	6	69
	OMe		15	81	4	78
	OH		0	100	0	58
	COMe		8	92	0	63
	NH ₂		93	7	0	47
	OMe		35	56	9	52
	OH		61	39	0	38
	COMe		37	63	0	45

The migration of chromium tricarbonyls on aromatic rings have been investigated. This process has been referred to as "haptotropic rearrangement" or "haptotropic migration." It differs in regard to the complexation site in the fact that the metal tricarbonyl motif migrates from one η^6 site to a new and none equivalent η^6 site, also called $\eta^6 - \eta^6$ metal shifts.⁷⁶

Shown in Scheme 1.33 is the Dötz benzannulation of carbene complexes **1-141** and **1-143** to give new polyaromatic systems **1-142** and **1-144** with selective metalation to the indicated arenes.⁷⁷

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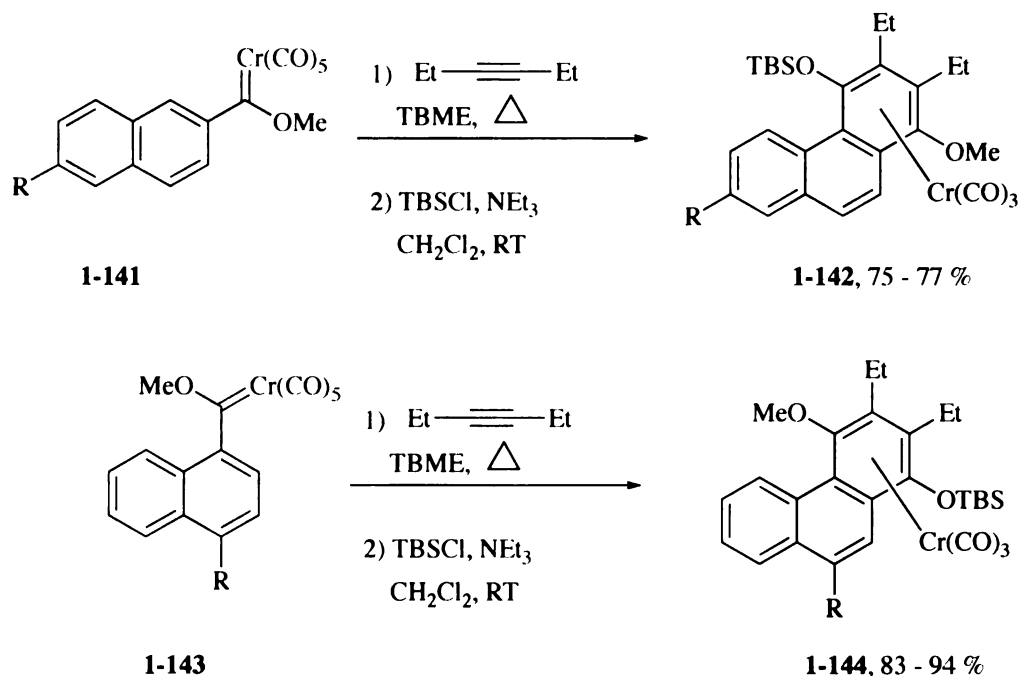
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Scheme 1.33. Benzannulation to Generate Selective Metalated Arenes



In Table 1.12, the migration of chromium tricarbonyl from ring A in compound **1-145** to ring C in compound **1-146** is induced with *n*-butyl ether or hexafluorobenzene.⁷⁷ In entry 1 with $\text{R}_1 = \text{Me}$ and $\text{R}_2 = \text{TBS}$ the yields were much lower than in entry 5 where $\text{R}_1 = \text{TBS}$ and $\text{R}_2 = \text{Me}$ giving 19 and 90 percent respectively. The x-ray crystal data suggests that the increased helical distortion caused by the substituents on ring A hampers the rearrangement in the case of entry 1. Decomplexation was the major byproduct in entry 1 (yield not reported).⁷⁸ The steric interactions between the chromium tricarbonyl group and the substituents on ring A promote the migration to ring C. Electron donating substituents favored the less substituted (ring C) as shown in entry 2. The addition of halogens decreased the yield as shown in entries 4, 8, 9, and 10. The

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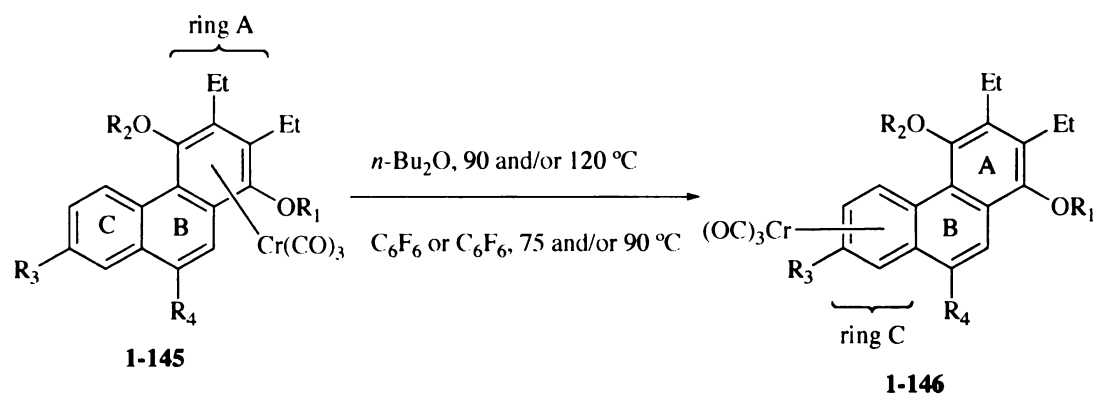
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reduction in yield was much pronounced in the case of entry 10 for fluorine. Having the halogen on the target arene (ring C) for the migration of chromium tricarbonyl group created the greatest hindrance for migration as demonstrated in entry 4 versus 9. The yield was 19 percent when R₃ was bromine (entry 4) but was 40 percent when R₄ (entry 9) was bromine. Therefore, the yield was lower when the halogen was on ring C as compared to having the bromine at the intermediate arene (ring B).⁷⁷

Table 1.12. Migration of Chromium Tricarbonyl Groups at Elevated Temperature



entry	R ₁	R ₂	R ₃	R ₄	temp. (°C)	time (hrs)	yield
1	Me	TBS	H	H	90	7	19
2	Me	TBS	OMe	H	90	6	70
3	"	"	"	"	120	1.5	75
4	Me	TBS	Br	H	120	1	19
5	TBS	Me	H	H	90	13	90
6	"	"	"	"	120	4	70
7	TBS	Me	H	Me	120	1	80
8	TBS	Me	H	Br	90	3.5	7
9	"	"	"	"	120	1.75	40
10	TBS	Me	H	F	90	5	5

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CHAPTER TWO

AXIAL AND PLANAR INTERACTIONS IN RELATION TO THE WULFF-DÖTZ BENZANNULATION REACTION

We are interested in the construction of axial and planar diastereomers such as those shown in Scheme 2.8. In this effort, the use of Fischer carbene complexes and alkynes were under examination for this purpose. To understand this topic, it is necessary to understand the general mechanism of the Wulff-Dötz reaction.

2.1 Mechanism of the Wulff-Dötz Benzannulation Reaction

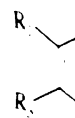
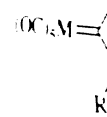
The exact details of the Wulff-Dötz reaction are still debated. The mechanism outlined in Scheme 2.1 shows the generally accepted intermediates.⁷⁹ The first step of the reaction involves the loss of carbon monoxide from carbene complex **2-1** to give intermediate **2-2**. The loss of CO is rate limiting making the investigation of this reaction mechanism difficult. The alkyne **2-3** then coordinates to the metal center which has been calculated to be either barrierless or a low-energy barrier process with a $\Delta E^\ddagger$ of 3.5 or 5 kcal/mol.⁸⁰ This means that the alkyne metal coordinated complex immediately rearranges to intermediate **2-4**. The η^1, η^3 -complex shown as **2-4** subsequently

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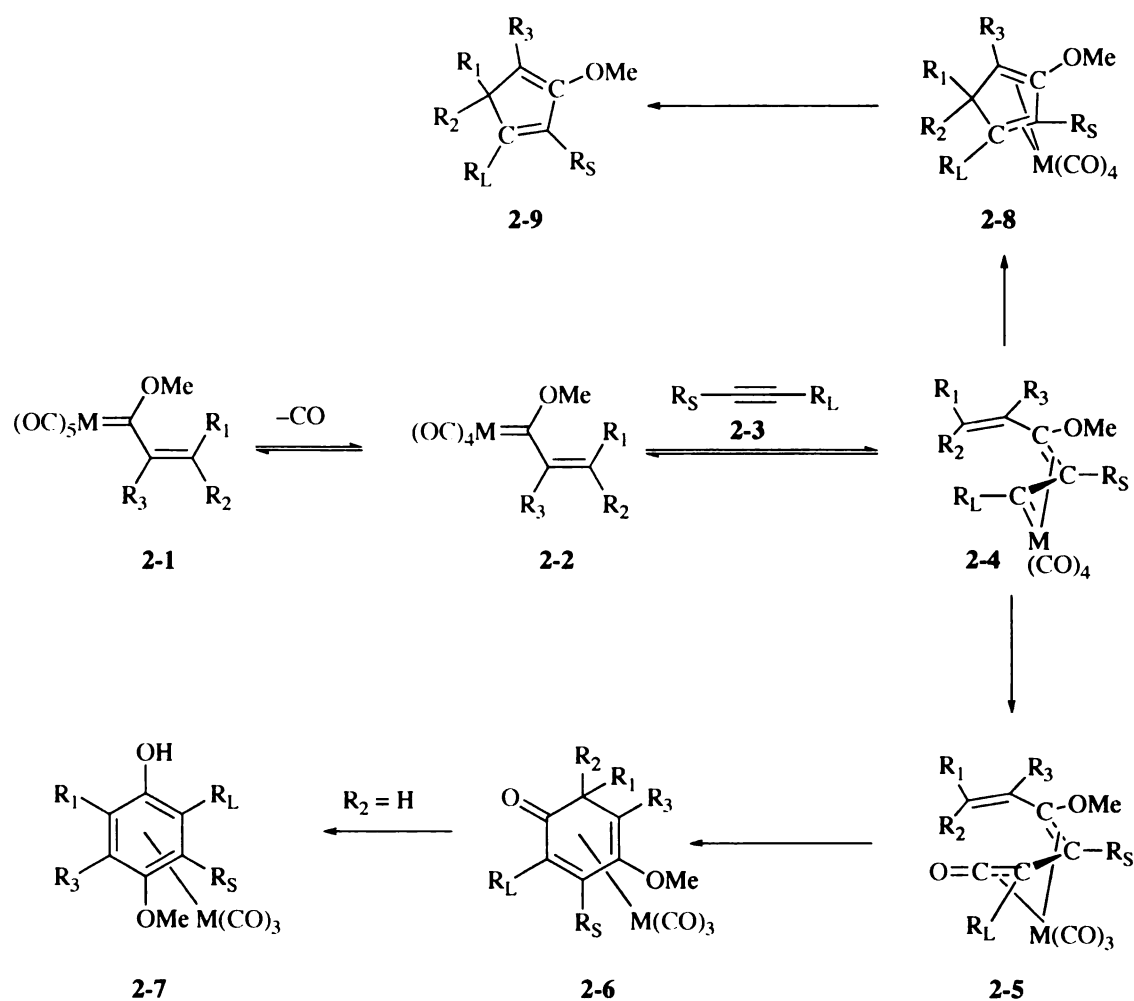
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undergoes CO insertion to give the η^4 -vinylketene complex **2-5** which undergoes electrocyclization to give intermediate **2-6**. When R_2 is hydrogen, intermediate **2-6** is short lived and proceeds to metal tricarbonyl arene complex **2-7**.⁸¹

Scheme 2.1. Mechanism of the Wulff-Dötz Benzannulation



Calculations done by Solà and coworkers suggest the intermediate shown in Figure 2.1 (structure **2-10**) as a low energy intermediate.⁷⁹ This suggestion has been supported by experimental evidence from Barluenga et al. where a

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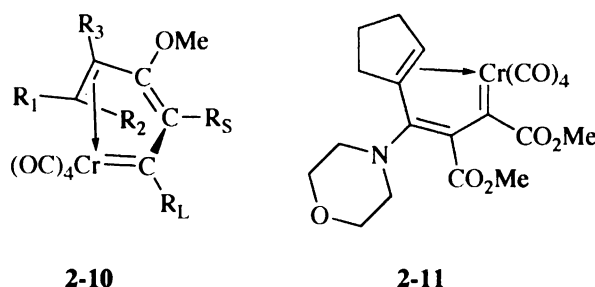
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chromahexatriene complex **2-11** was isolated and characterized by ^1H and ^{13}C NMR. The ^{13}C NMR clearly shows four signals for the carbon monoxide ligands for compound **2-11** and carbons for the complexed olefin at $\delta = 93.8$ (CH) and 102.1 (C) ppm versus $\delta = 130.7$ (C) and 157.9 (C) for the uncomplexed olefin.⁸² No single reaction has been successfully followed experimentally completely through the intermediates shown in Scheme 2.1 and therefore the mechanism may be highly substrate dependant (the intermediates change).

Figure 2.1. Calculated and Experimental Intermediates of the Wulff-Dötz Reaction



2.2 Overview of Previous Methods for Planar Chiral Construction

Several approaches are known for the formation of chiral axial units in organic synthesis besides the use of Fischer carbene complexes.^{83, 84} An advanced approach is the construction of a chiral linker between two aromatic units such as compound **2-12** which can then be intramolecularly coupled to give the axial chiral compound **2-13**.⁸⁵ When X is iodine in compound **2-12** and the linker is derived from 1,4-di-*O*-benzyl-*D*-threitol, nickel based coupling reactions give compounds like **2-13**.⁸⁶ Also used are compounds where X = OTf and the

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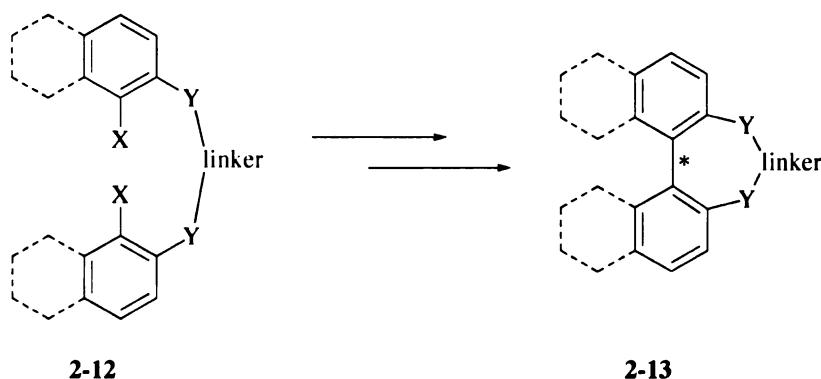
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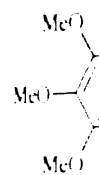
linker is a chiral amine using a variant of the Stille coupling reaction.⁸⁷ In general, a variety of coupling approaches have been used successfully with the "tether-controlled atroposelection."⁸⁸

Scheme 2.2. Tether-Controlled Atroposelection



It has been determined by Meyers that under their given reaction conditions a methoxy group of a 2-(2-methoxyaryl)oxazoline **2-14** could be displaced by nucleophilic aromatic substitution with Grignard reagent such as compound **2-15**. The chirality of the axial element is determined by the chirality of oxazoline. The aryl magnesium bromide attacks from the adjacent side of the isopropyl on the oxazoline. In the case shown in Scheme 2.3, the reaction of **2-14** and **2-15** gave the biaryl **2-16** in 90 % yield and 96 % de.

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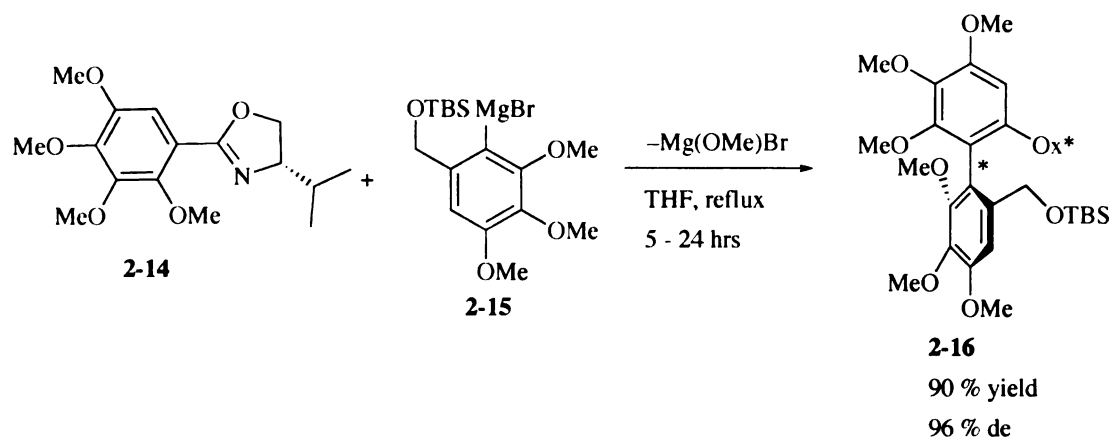
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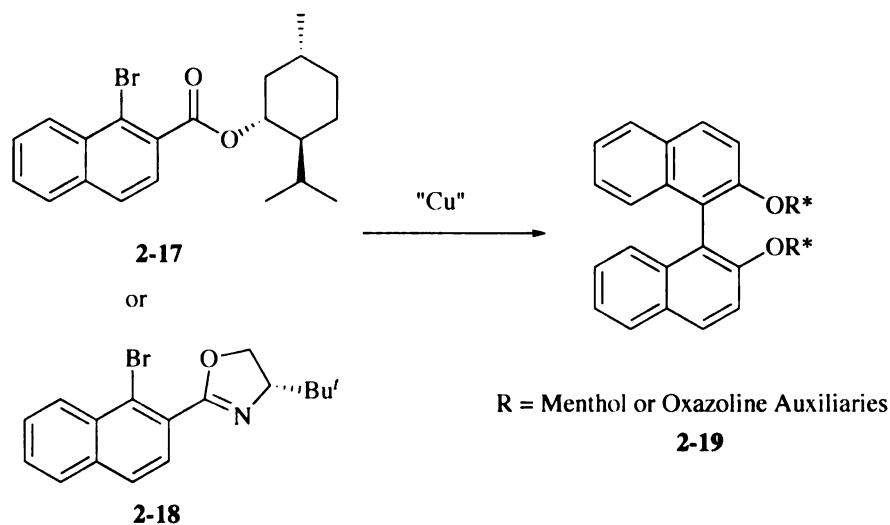
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Scheme 2.3. Meyer's Chiral Oxazoline to Form Biaryls



Atroposelection in the copper catalyzed Ullmann coupling was first done by Miyano and coworkers using menthol derivatives as chiral auxiliaries such as compound **2-17** which gave 13 % de for compound **2-19**.⁸⁹ Meyers and coworkers modified the original approach by using oxazoline auxiliaries such as compound **2-18** derived from chiral amino alcohols which gave 94 % de of compound **2-19**.⁹⁰

Scheme 2.4. Copper Catalyzed Ullmann Coupling



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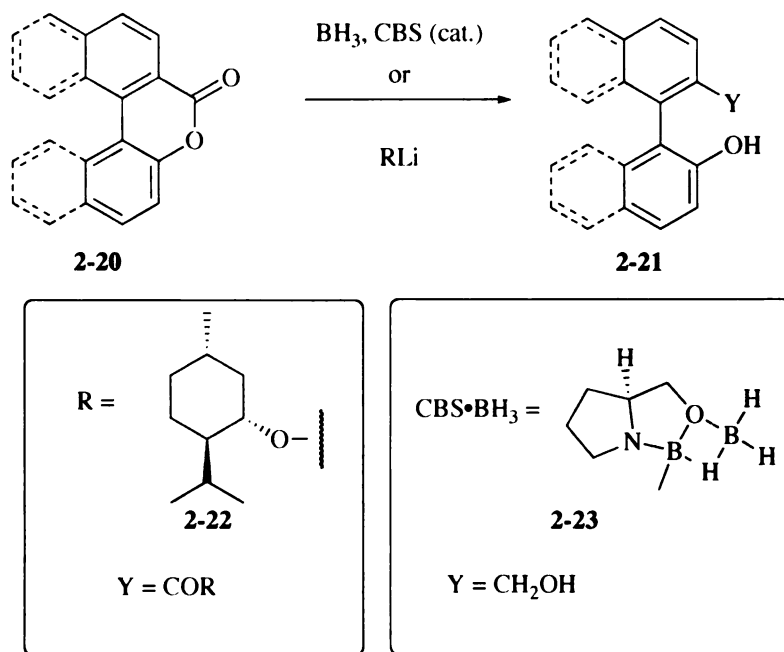
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The reduction of compounds like **2-20** can be done in an enantioselective manner using Corey's oxazaborolidine-borane reagent (CBS, **2-23**) shown in Scheme 2.5. The biaryl lactone **2-20** is not configurationally stable; the compound **2-20** exists as rapidly interconverting axial stereoisomers. The catalytic reduction reduces only one axial stereoisomer to give compound **2-21** as a single axial isomer.⁹¹ The yields are typically > 80 % and enantiomeric excesses of up to 97 % are achievable.

The other approach used for the selection of one enantiomer over another from compound **2-20**⁹² is to use a chiral nucleophile such as (+)-mentholate (**2-22**) which gives an atropoisomer ratio of up to 81 : 19 for compound **2-21**.⁹³

Scheme 2.5. Reductive and Nucleophilic Attack of an Ester to Produce an Axial Chiral Biaryl



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The method by Uemura uses a Suzuki-Miyaura coupling to produce an axial chiral compound shown in Scheme 2.6.⁹⁴ In this approach, the chromium tricarbonyl arene complex **2-24** was coupled with the boronic acid **2-25** resulting in compound **2-26** and / or compound **2-27**. When $R_2 = \text{Me}$, the major product formed was compound **2-26** with the methyl substituent oriented towards the chromium (*syn*). The intermediate **2-28** with the *cis* disposition of two aryl ligands on palladium has been proposed. When reductive elimination occurs to form the product, the substituent R_2 turns toward the chromium tricarbonyl group from the side of the small substituent (S) to avoid the triphenyl phosphine ligands. When R_2 is an aldehyde, the same intermediate has been proposed however the aryl aldehyde rotates after the initial formation of compound **2-26** to form compound **2-27**. The aryl aldehyde has a low barrier to rotation at elevated temperatures converting from compound **2-26** to compound **2-27**.

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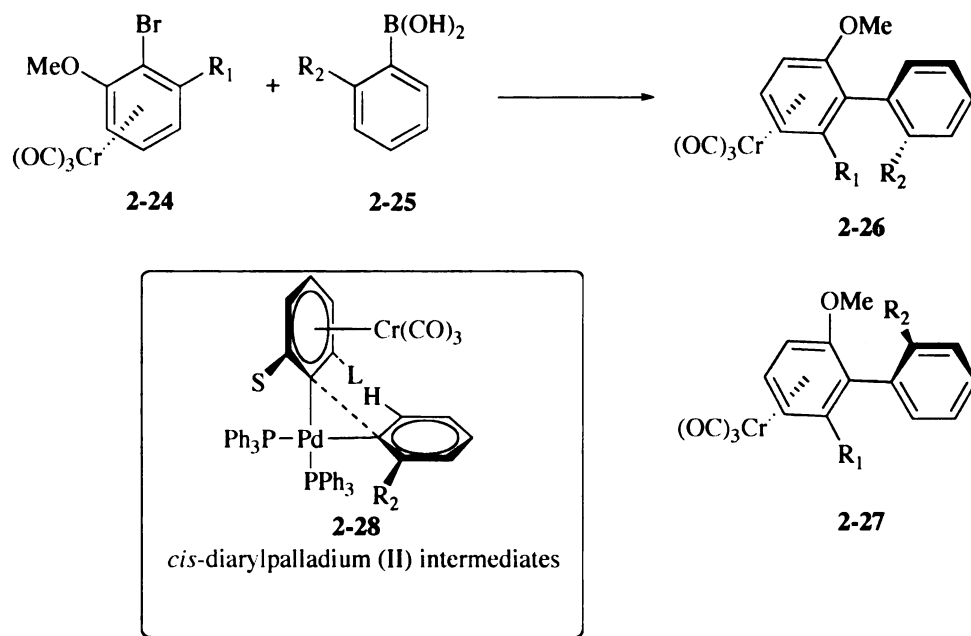
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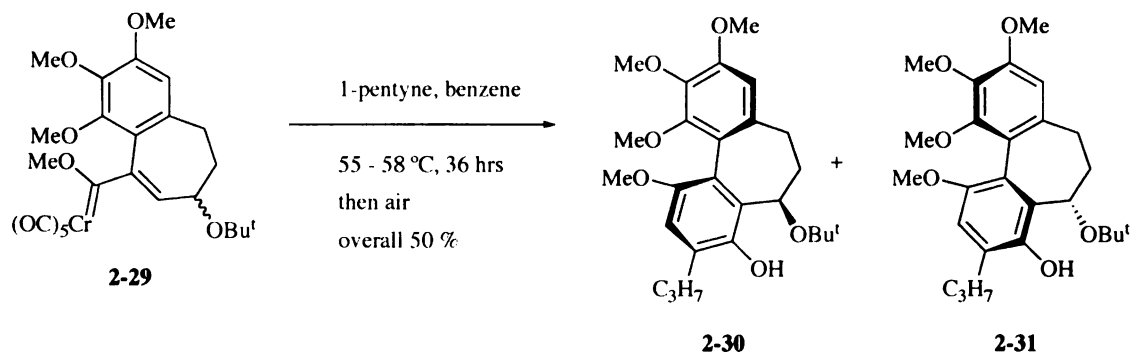
Scheme 2.6. Suzuki-Miyaura Coupling Method of Forming Biaryls



Syntheses of allocolchicinoids have been achieved via a central-to-axial chirality transfer benzannulation reaction by Vorogushin in this research group.⁹⁵ In Scheme 2.7, the benzannulation of carbene complex **2-29** with pentyne gave exclusively the pair of enantiomers **2-30** and **2-31**.

Scheme 2.7. Synthesis of Allocolchicinoids via Central-to-Axial Chirality

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2.3 Simultaneous Construction of Axial and Planar Chirality via a Benzannulation Reaction

The benzannulation reaction can be used to construct axial and planar centers in one step from carbene complex **2-32** and alkyne **2-33** as shown in Scheme 2.8.⁹⁶ This work was developed by the Wulff research group.⁹⁷ The substituent R_4 may point towards the chromium tricarbonyl (*syn*, complex **2-35**) or away from the chromium tricarbonyl (*anti*, complex **2-37**). Two methods were developed for controlling the *syn* and *anti* ratios.⁹⁷ In method A, the reaction is performed in the presence of 3 eq. of TBSCl (or an appropriate electrophile) and 5 eq. of Hunig's base for 24 hours. This traps the phenol complex **2-34** as the kinetic product and gives compound **2-35**. The relative stereochemistry is shown in Scheme 2.8. The absolute stereochemistry could not be controlled by this method. In method B, the reaction is performed devoid of TBSCl for the first 24 hours, and then TBSCl and Hunig's base is added and heated for an additional 24 hours. This traps the phenol **2-36** as compound **2-37** which is the thermodynamic product.⁹⁸

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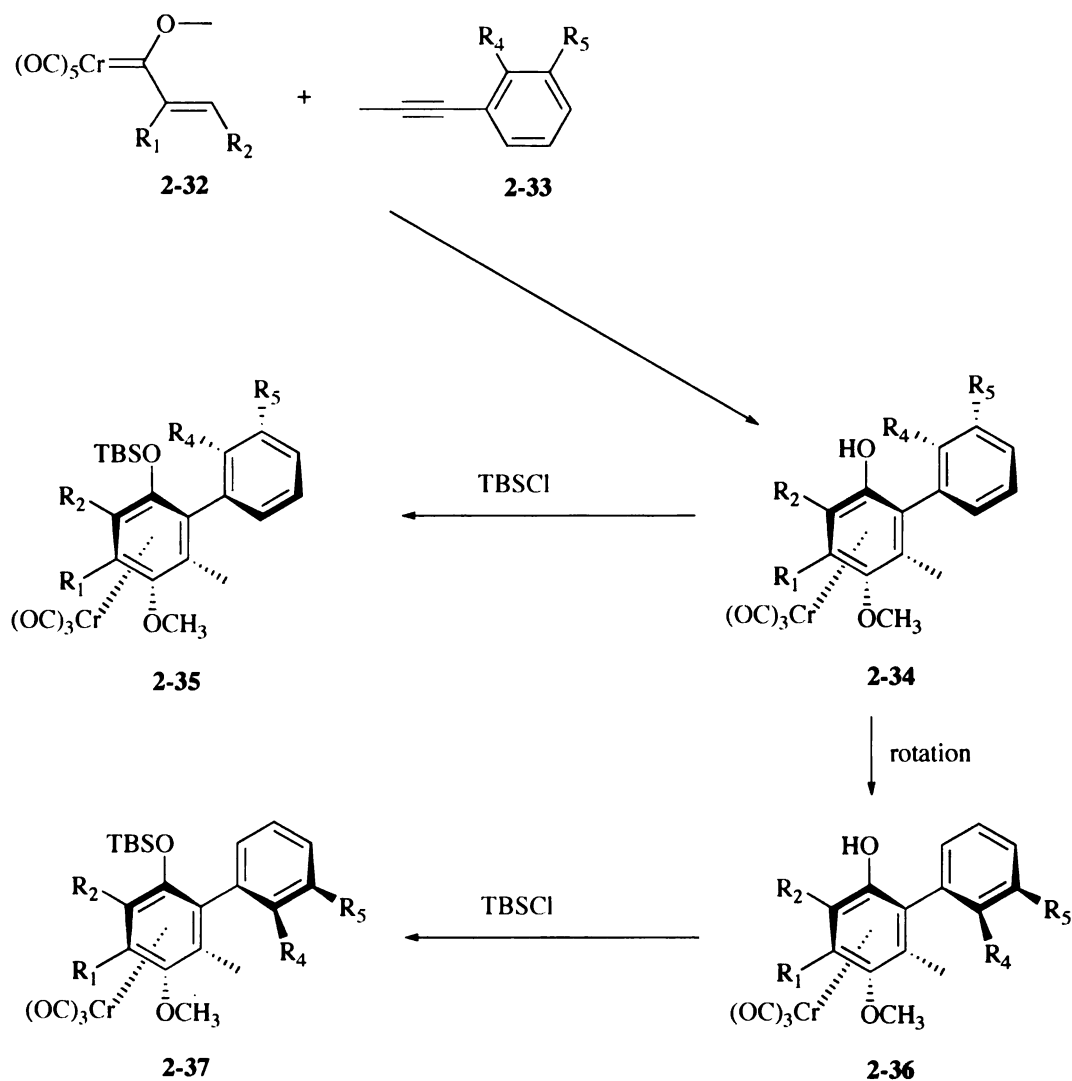
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Scheme 2.8. Axial-Planar Chirality via Benzannulation



A model to account for the selectivity in this reaction is shown in Scheme 2.9. The benzannulation occurs giving the η^1, η^3 -complexes **2-39** or **2-41**. It is thought that the reaction initially gives the kinetic product **2-42** via intermediate **2-41**. In intermediate **2-39**, the R_4 substituent on the phenyl ring will have close contacts with η^1, η^3 -ligand since the angle α is much larger than β . Thus **2-39**

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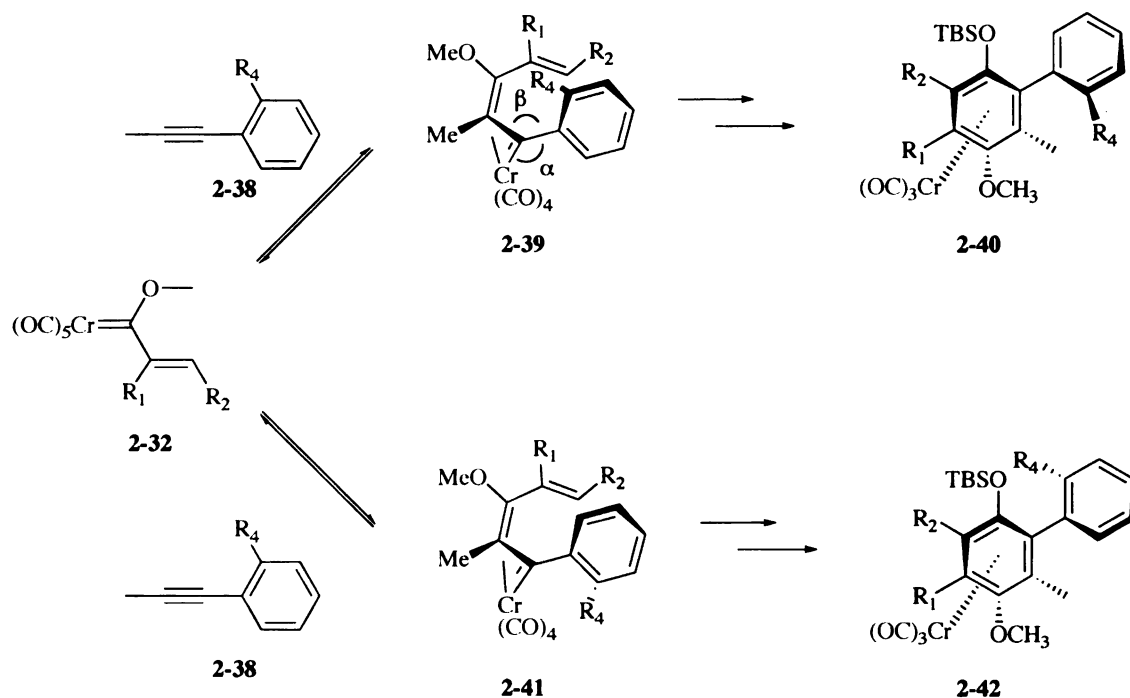
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should have a higher energy than **2-41**, and this would disfavor the formation of compound **2-40**.⁹⁹

Scheme 2.9. Mechanistic Model for the Origin of Diastereoselectivity



In Table 2.1, selected experimental data is presented from the published work by Fogel in our group.^{97, 98} The kinetic conditions for entry 1 gave a ratio of 89 : 11 for compound **2-42** as the major product. Under the thermodynamic condition in entry 2, the ratio was 3 : 97 with the major product being compound **2-40**. When a methyl substituent was in the R_1 position such as in entries 3 and 4, the selectivity was 22 : 78 and 2 : 98 respectively.⁹⁹

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Table 2.1. Diastereoselectivity in Benzannulation for the Formation of Chromium Tricarbonyl Arenes

entry	R ₁	R ₂	R ₄	method	time (hrs)	temp (°C)	yield 2-40 + 2-42	ratio 2-42 : 2-40
1	H	Me	Me	A	24	50	63	89:11
2	H	Me	Me	B	24, 24	80	62	3:97
3	Me	H	Me	A	3	50	61	22:78
4	Me	H	Me	B	24, 24	120	63	2:98
5	-(CH ₂) ₄ -		Me	A	24	50	77	21:79
6	-(CH ₂) ₄ -		Me	B	24, 24	50	75	14:86

Method A: The reaction was performed in the presence of 3 eq. of TBSCl and 5 eq. of Hunig's base. Method B: The reaction was performed for the indicated time then 3 eq. of TBSCl and 5 eq. of Hunig's base were added.

2.4 Aryl Carbene Complex As the Origin of the Axial Motif

An approach to the simultaneous generation of axial and planar centers of chirality that has not been previously investigated involves complex **2-43** which has an *ortho*-substituted phenyl group on the carbene complex.

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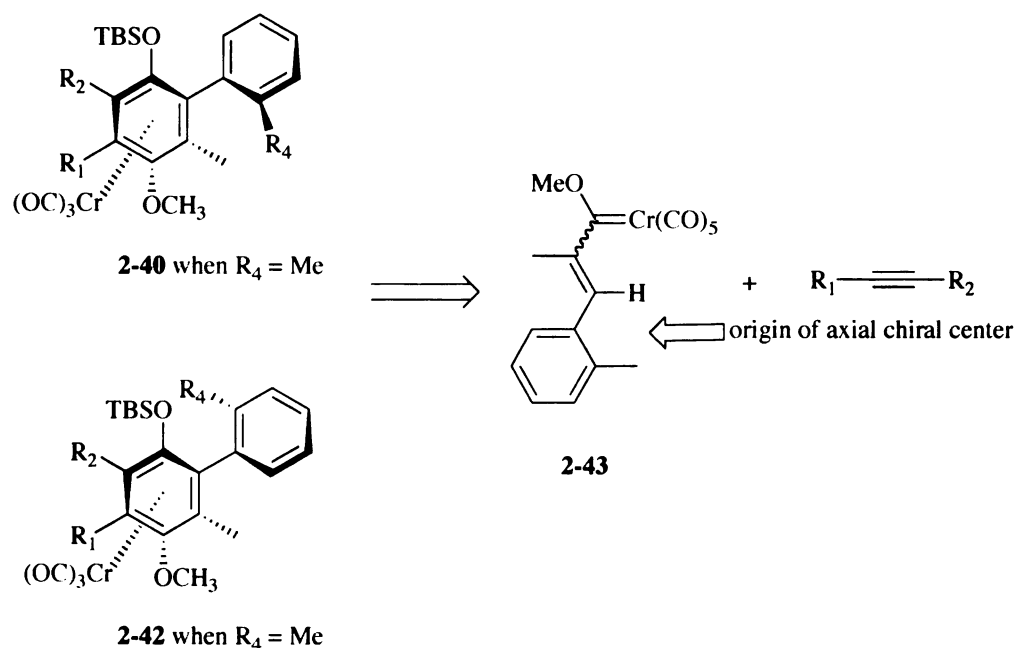
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Figure 2.2. The Carbene Under Study for Potential Axial Chirality



As a prelude to the preparation of carbene complex **2-43**, vinyl iodide **2-46** was prepared as shown in Table 2.2 via a Wittig reaction¹⁰⁰ with aldehyde **2-45** and the salt **2-44** according to the procedure shown in Table 2.2.¹⁰¹ In entry 1, the result is shown for the addition of the aldehyde **2-45** at room temperature which gave a selectivity ratio of 2.1 to 1 (Z : E) in favor of Z.¹⁰² When the temperature was lowered to $-18\text{ }^{\circ}\text{C}$ as shown in entry 2, the selectivity increased to 4.8 to 1. Decreasing the temperature even further as indicated in entries 3 and 4 gave increased selectivities of 20 : 1 and 24 : 1, respectively, for the vinyl iodide **2-46**.¹⁰³

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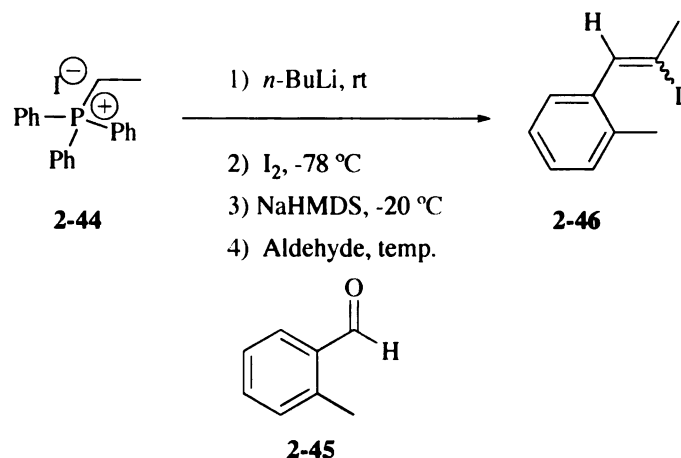
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Table 2.2. Formation of a Vinyl Iodide



entry	Temp. of Aldehyde Addition	Z : E Selectivity	Yield (%)
1	22 °C	2.1 : 1 (GC / MS) 2.9 : 1 (GC / FID)	14
2	-18 °C	4.8 : 1 (GC / FID) 4.4 : 1 (NMR)	54
3	-78 °C	20 : 1 (GC / MS) 18 : 1 (GC / FID)	n/d
4	-131 °C	24 : 1 (GC / FID)	72

The conversion of vinyl iodide **2-46** to carbene complex **2-47** proved to be problematic as shown in Scheme 2.10. Lithium halogen exchange with *t*-butyl lithium followed by treatment with chromium hexacarbonyl and then methylation with methyl triflate gave only 4 % yield of the carbene complex when starting from a 24 to 1 mixture of the *Z* and *E* vinyl iodide **2-46**. When the reaction was done with a 5 : 1 mixture of *Z* and *E* vinyl iodide **2-46**, the yield was 10 %. It is interesting to note that the yield increased for the 5 : 1 mixture of isomers to 10 %

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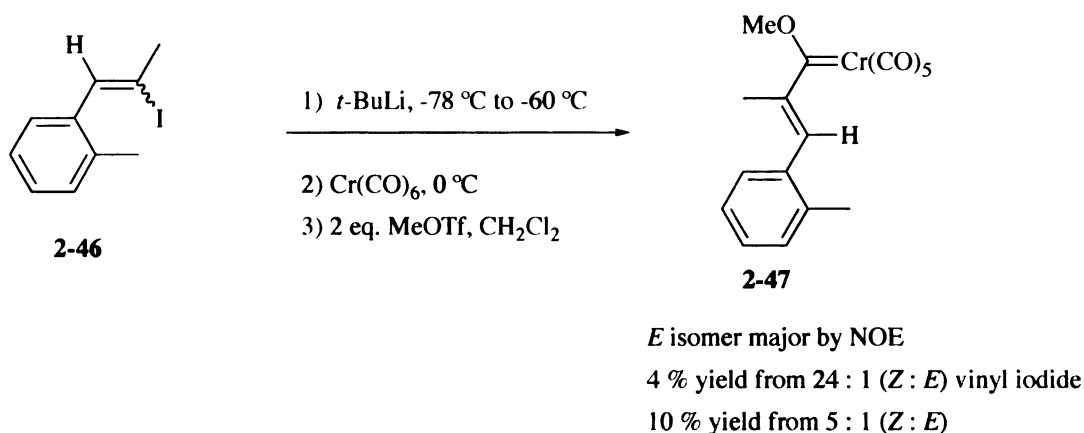
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from 4 % for the 24 : 1 mixture of isomers. The nOe evidence obtained from the product of this reaction (**2-47**) suggests that the carbene complex has *E* geometry and it is one compound. There was a strong nOe between the methyl at the α carbon in compound **2-47** and the aromatic ring.

Scheme 2.10. Formation of a Carbene Complex



The reason for the failure of the conversion of vinyl iodide **2-46** to carbene complex **2-47** is not understood. This may be related to problems in the metal / halogen exchange step.

The mechanism of lithium halogen exchange has been investigated and presents interesting considerations for synthetic or methodology applications. The general reaction mechanism involves SET (single electron transfer) reactions.¹⁰⁴ This is illustrated in Scheme 2.11. This mechanism probably is operative for alkyl halides such as alkyl bromides and perhaps to some extent for alkyl iodides. The reaction proceeds from the reacting lithium species **2-48** and halogenated species **2-49**. These undergo SET to form intermediates **2-50** and **2-51** which can form the solvent cage species **2-52**. From the solvent cage **2-52**,

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free radicals can be formed such as **2-53** and **2-54** which can undergo disproportionation and recombination reactions. Also disproportionation and recombination can occur directly from the solvent caged species. The radicals **2-53** and **2-54** can also abstract hydrogen radicals to form **2-56** and **2-57**. These radicals can undergo skeletal rearrangement to give radicals **2-58** and **2-59**. These can further extract protons from the solvent to give compounds **2-60** and **2-61**. Also, further electron transfer reactions can give anions **2-64** and **2-65** which upon work-up would give compounds **2-60** and **2-61**. Single electron transfer reactions of radicals **2-53** and **2-54** can give anions **2-62** and **2-63** which upon workup would give **2-56** and **2-57**. These side reactions give complex product distributions and are not generally useful. These problems generally involve alkyl bromides and chlorides.¹⁰⁴

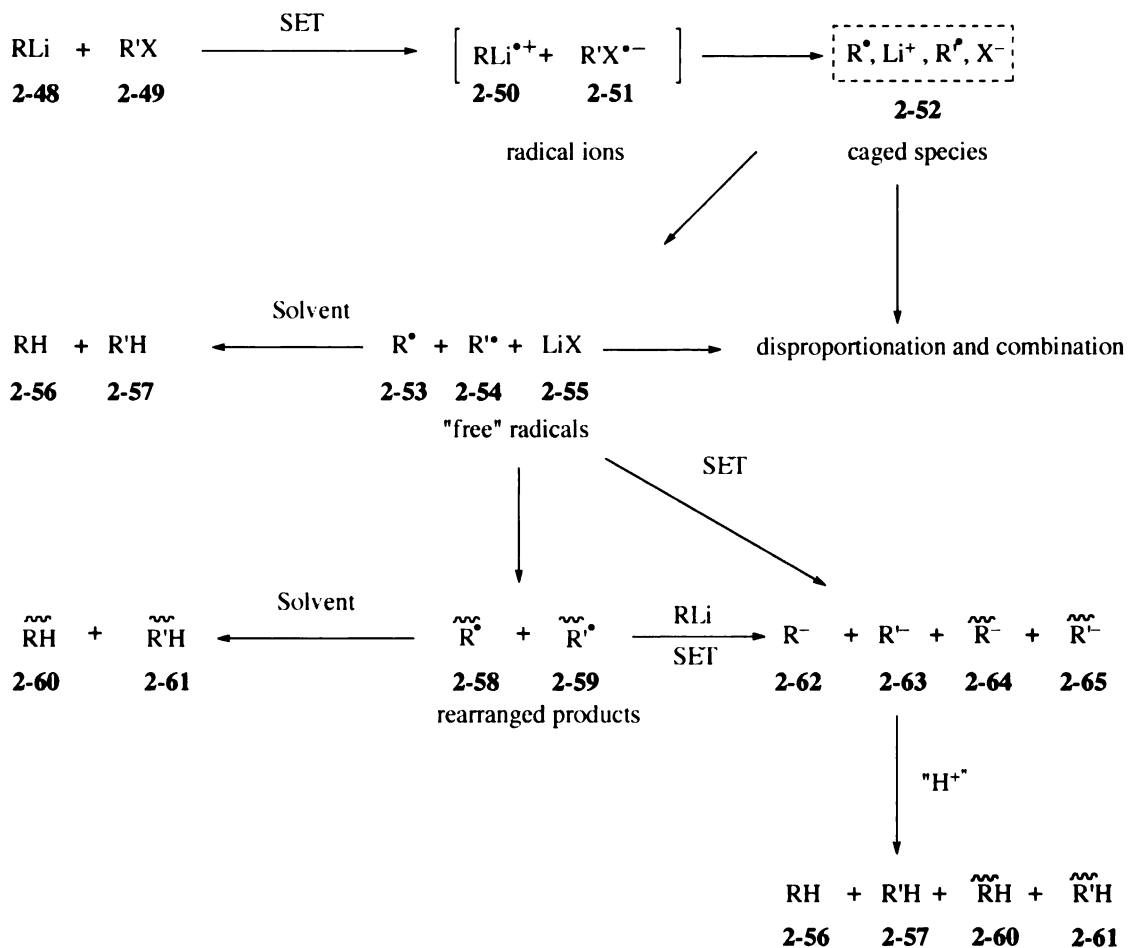
RLi +
2-48

RH +
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Scheme 2.11. Single Electron Transfer Reactions of Metal Halogen Exchange



Another mechanistic consideration is of the formation of "ate-complexes" shown in Scheme 2.12. When phenyl lithium **2-66** and phenyl iodide **2-67** are mixed, an intermediate "ate-complex" (**2-68**) has been suggested via kinetic and spectroscopic evidence.¹⁰⁴ Also an x-ray crystal structure for compound **2-69** has been obtained.¹⁰⁴ This mechanism may be operating for lithium halogen

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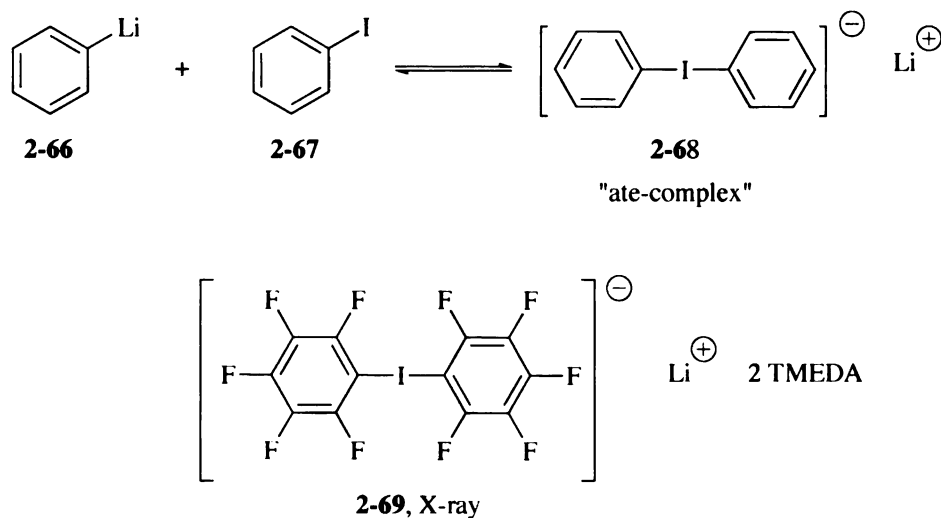
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exchange of aryl iodides, vinyl iodides, vinyl bromides, and possibly alkyl iodides.¹⁰⁴

Scheme 2.12. Formation of an "Ate-Complex" Depicted



The concluding remarks for the mechanism of the lithium halogen exchange shown in Scheme 2.10 are that the reaction possibly proceeds through an "ate" type intermediate. The formation of radicals should be suppressed because iodine is involved rather than a bromine or chlorine. Rather than a low yield resulting from free radical interactions, the *Z* geometry of the intermediate organolithium species originating from **2-46** possibly hinders attack on chromium hexacarbonyl. The *E* geometry of the resulting carbene complex **2-47** originates from the minor *E*-vinyl iodide.

The benzannulation shown in Scheme 2.13 is of the *E*-isomer from carbene complex **2-47** and alkyne **2-48** under kinetic conditions. The yield of the benzannulated product is 39 % with an 83 : 17 ratio of the diastereomeric complexes **2-49** and **2-50**. The diastereomeric ratios were determined by ¹H

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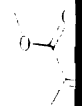
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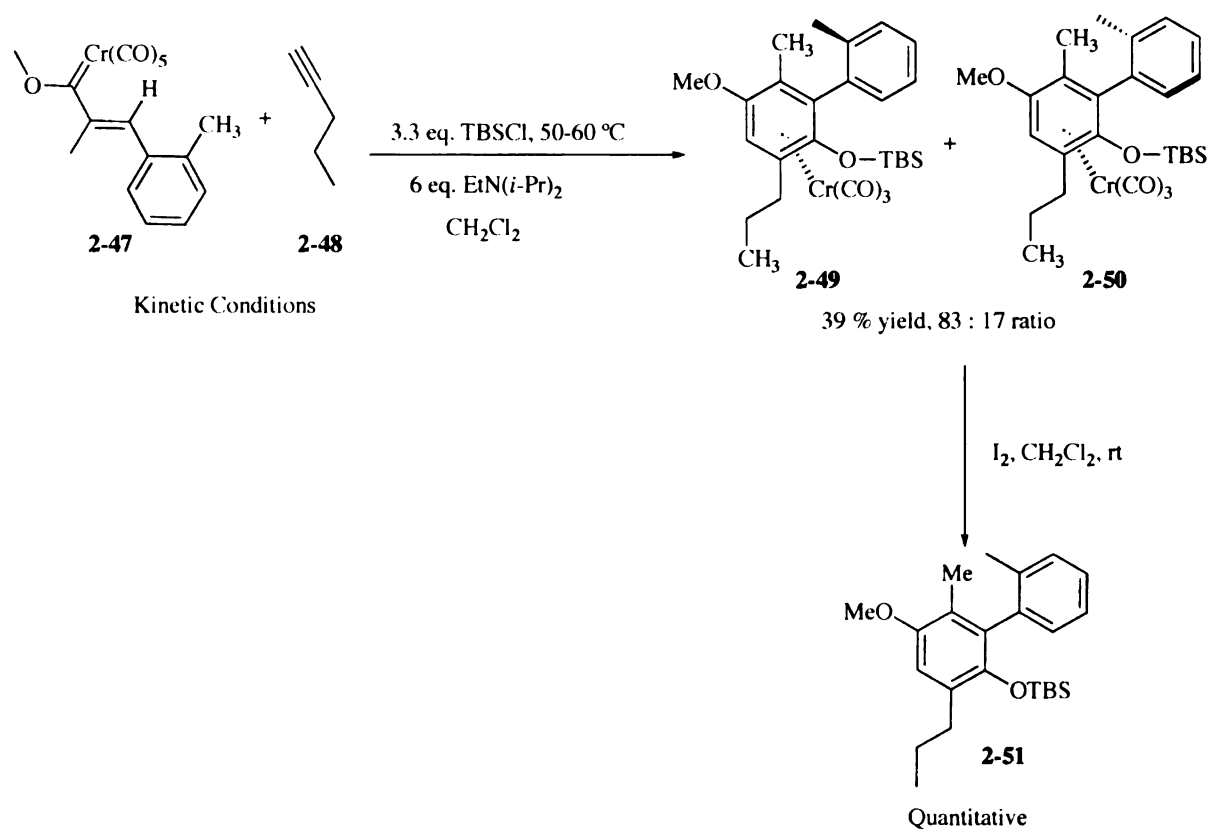
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NMR correlating with known compounds of the type shown in Scheme 2.13 whose stereochemistry has been determined by x-ray crystallography. The result presented in Scheme 2.13 give the *anti*-product in contrast to the substrates presented in Table 2.1. The chromium tricarbonyl arene complexes **2-49** and **2-50** can be demetalated to give compound **2-51** in quantitative yield. These results are intriguing and suggest additional investigation and may supply additional insights into the mechanism of the Wulff-Dötz reaction.

Scheme 2.13. Diastereoselectivity of Benzannulation



The model to explain the selectivity from the reaction of **2-47** is shown in Scheme 2.13. The carbene complex **2-47** undergoes the benzannulation reaction with the alkyne **2-48** giving intermediates **2-52** and **2-53**. The major product proceeds through intermediate **2-52** because of steric interactions

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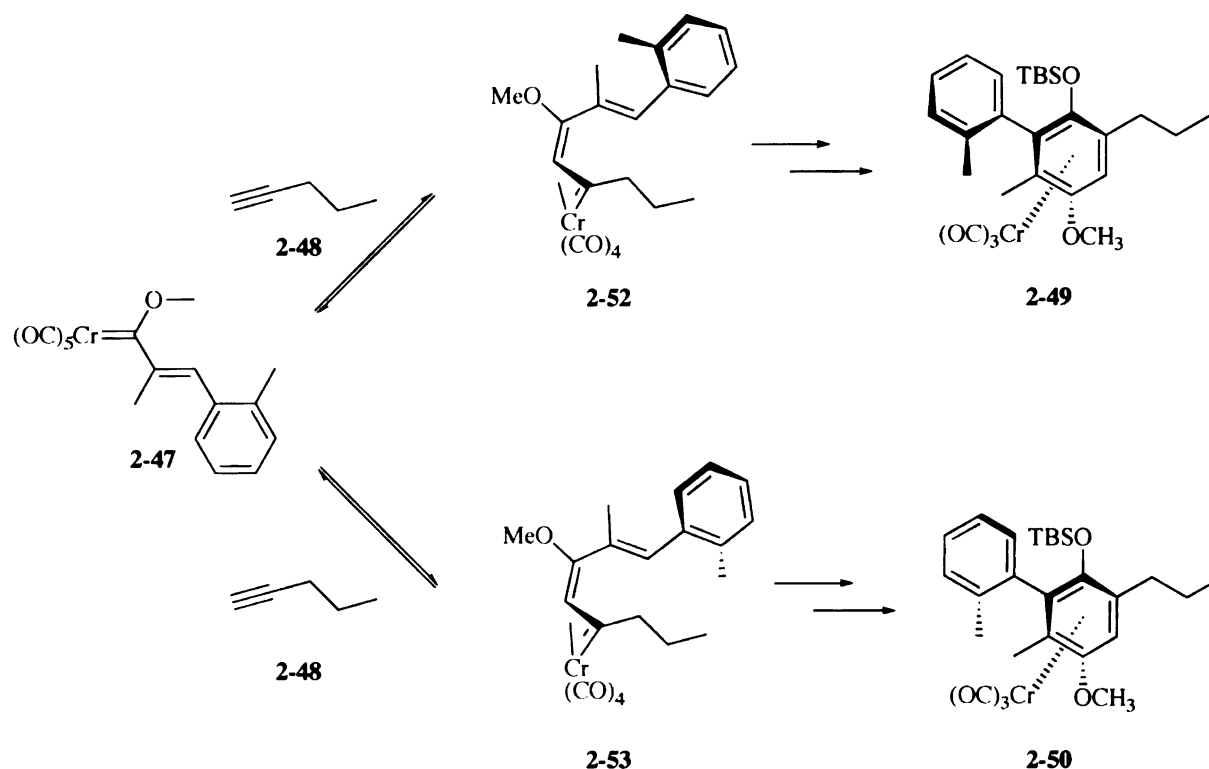
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between the aryl methyl and the bottom face of the molecule containing the chromium tricarbonyl unit and thus compound **2-49** is obtained as the major product.

Scheme 2.14. The Model for Diastereoselectivity of Axial-Planar Systems for the Wulff-Dötz Reaction



2.5 Attempts at Bis-Axial Chiral Compounds

In Scheme 2.15, the formation of an alkyne for generating a bis-axial system such as compound **2-54** from a benzannulation reaction is shown. In the first step, a Sonogashira coupling gives compound **2-57** in quantitative yield from iodotoluene (**2-55**) and TMS acetylene (**2-56**).¹⁰⁵ The deprotection of the TMS acetylene with sodium hydroxide and methanol gave 67 % yield of alkyne **2-58**.

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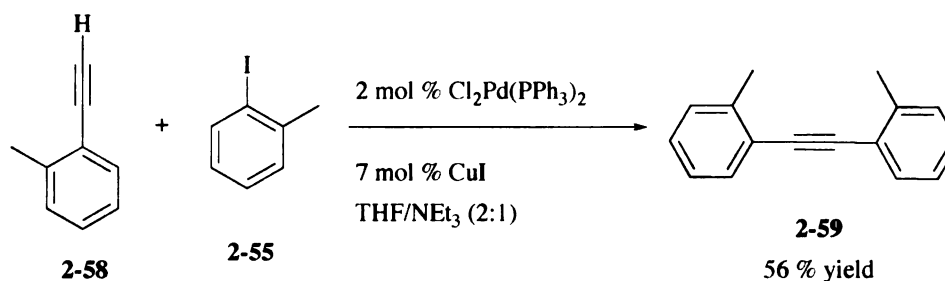
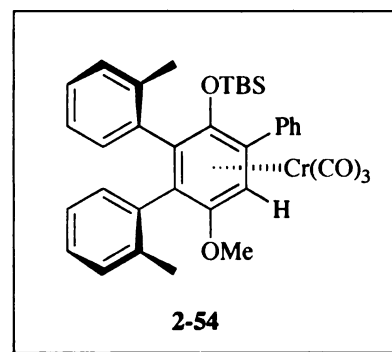
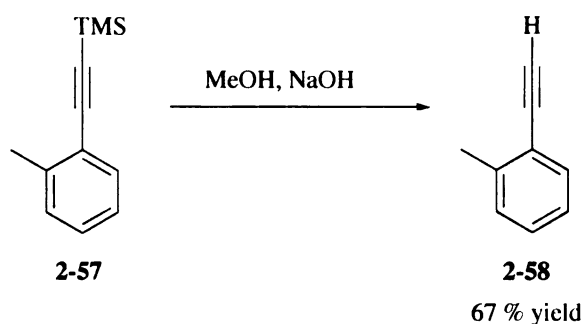
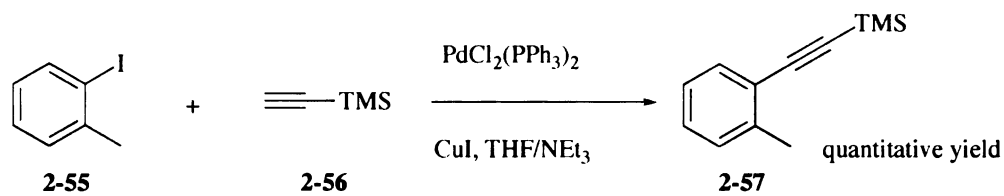
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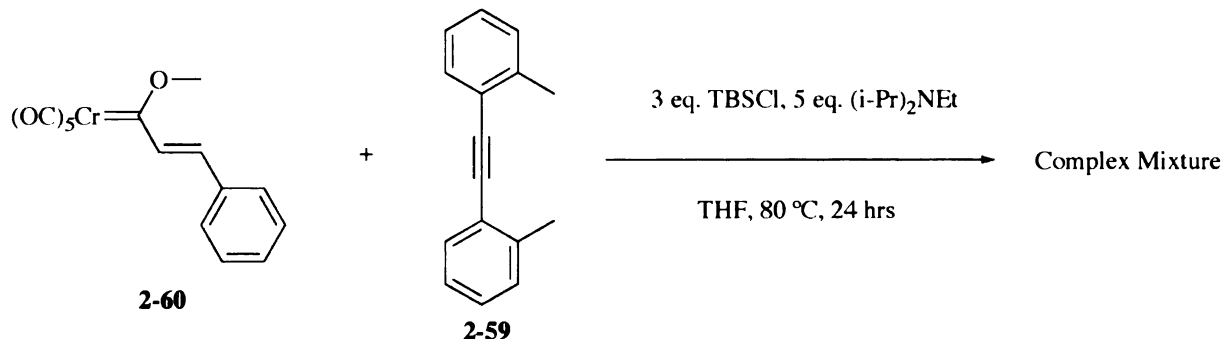
Another Sonogashira coupling yielded the alkyne interrupted biaryl **2-59** in 56 % yield.

Scheme 2.15. Formation of a Biaryl Alkyne



This approach of a bi-axial chiral chromium arene complex failed to give desirable results from carbene complex **2-60** and alkyne **2-59**. It yielded a complex mixture of inseparable compounds that contained a mixture of axial chiral compounds.

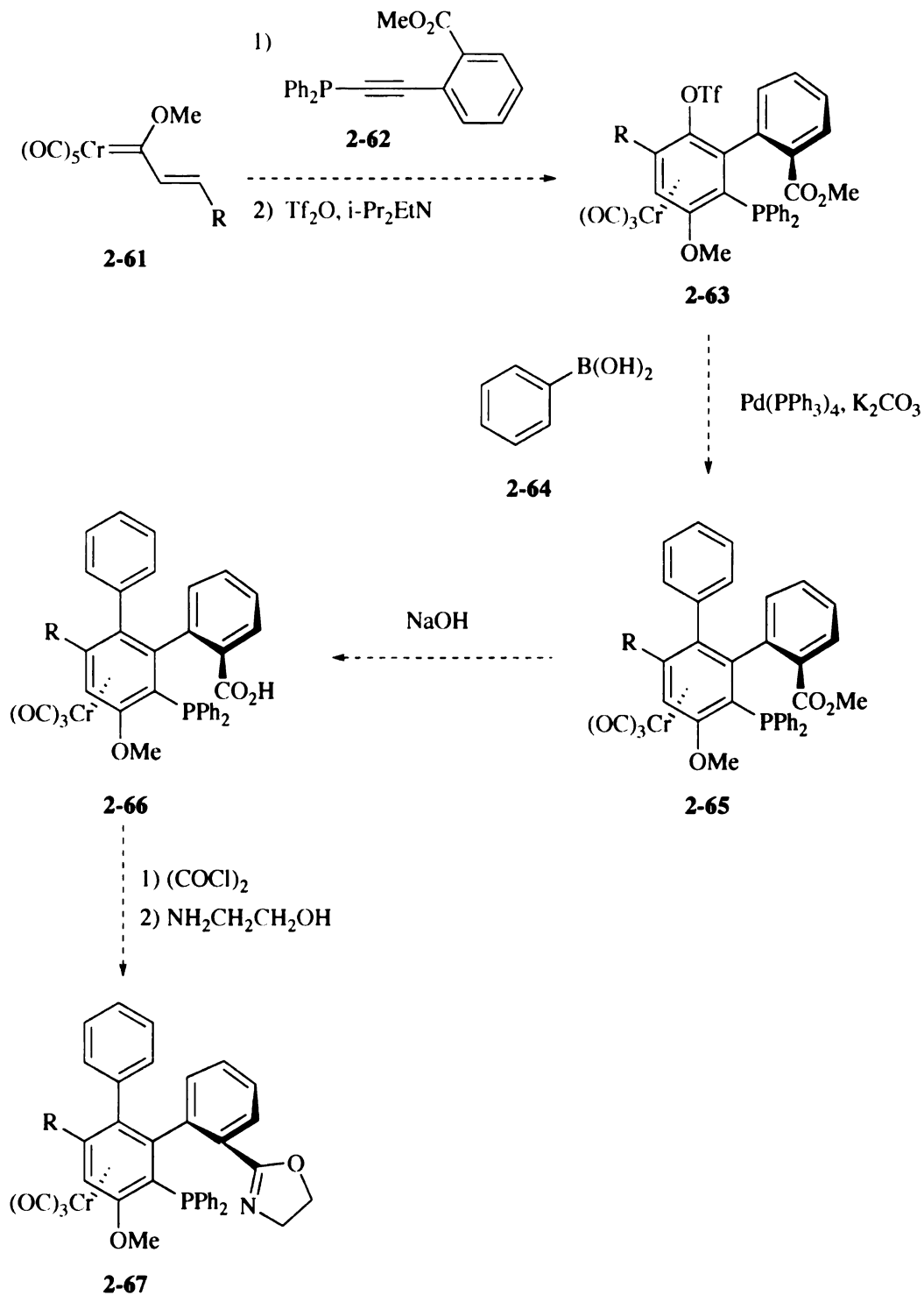
Scheme 2.16. Bi-axial Chirality Attempt



2.6 Benzannulation Attempts with Ethynylphosphines

It would be desirable to use ethynylphosphines for benzannulation reactions to construct ligands. Shown in Scheme 2.17 is the proposed formation of compound **2-63** from a benzannulation of carbene complex **2-61** and alkyne **2-62**. Further elaboration could be possible at the triflate and ester functionalities to form more complex ligands. A Suzuki coupling for example could form compound **2-65** and further treatment with NaOH could give compound **2-66**. Treatment with oxalyl chloride and then 2-aminoethanol could give the 4,5-dihydro-oxazole containing compound **2-67**. Compound **2-67** may have utility as a ligand however an additional resolution step would be required for chiral applications.

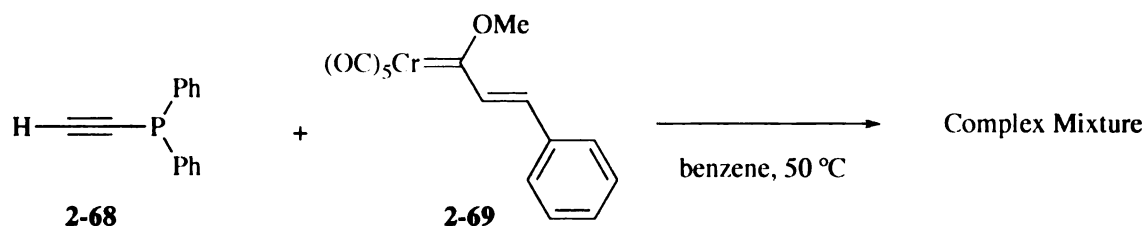
Scheme 2.17. Proposed Phosphine Containing Ligand



A phosphine does not work for benzannulation under the conditions employed between carbene complex **2-68** and ethylenephosphine **2-69**.¹⁰⁶ The

only report in the literature of benzannulation reaction of this type was involving an ethynylbis[diphenylphosphine].¹⁰⁷

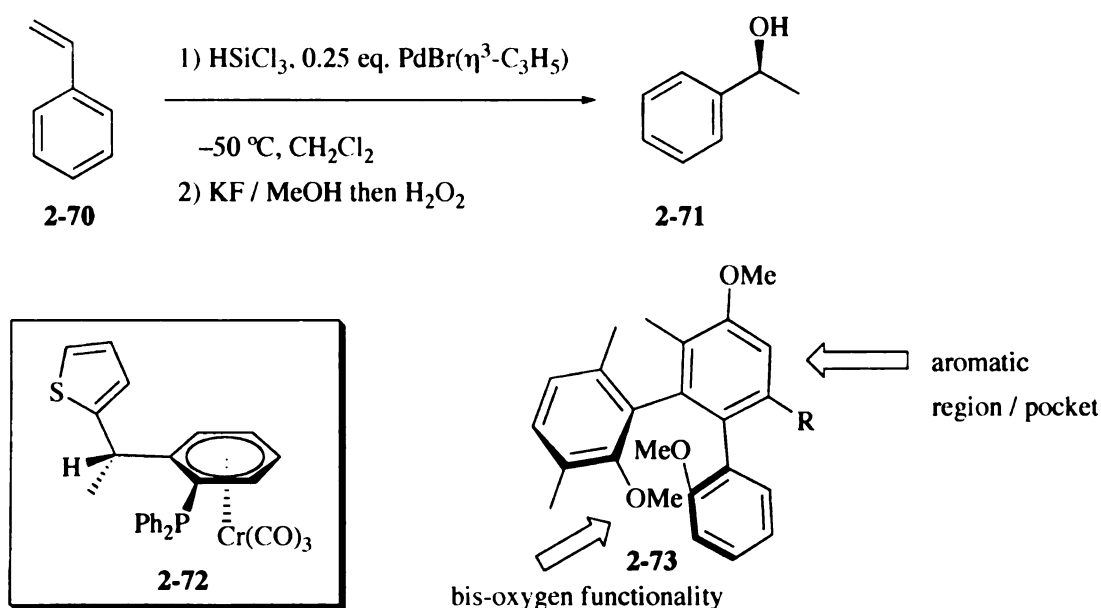
Scheme 2.18. Attempted Benzannulation with Ethynyl Phosphines



2.7 Future Work for Axial-Planar Chirality

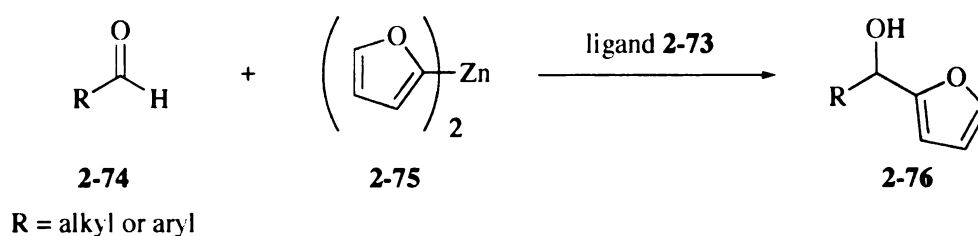
An application for the ligand development could be the hydrosilylation reaction. Catalyst **2-72** containing a chromium tricarbonyl motif has been used for this purpose.¹⁰⁸ An interesting new ligand to consider is compound **2-73**. This ligand possesses a bis-oxygen functionality to coordinate a metal center shown in Scheme 2.19. It also possesses an interesting aromatic pocket for either π -stacking or T-type aromatic interactions.¹⁰⁹

Scheme 2.19. Hydrosilylation with a Proposed Ligand



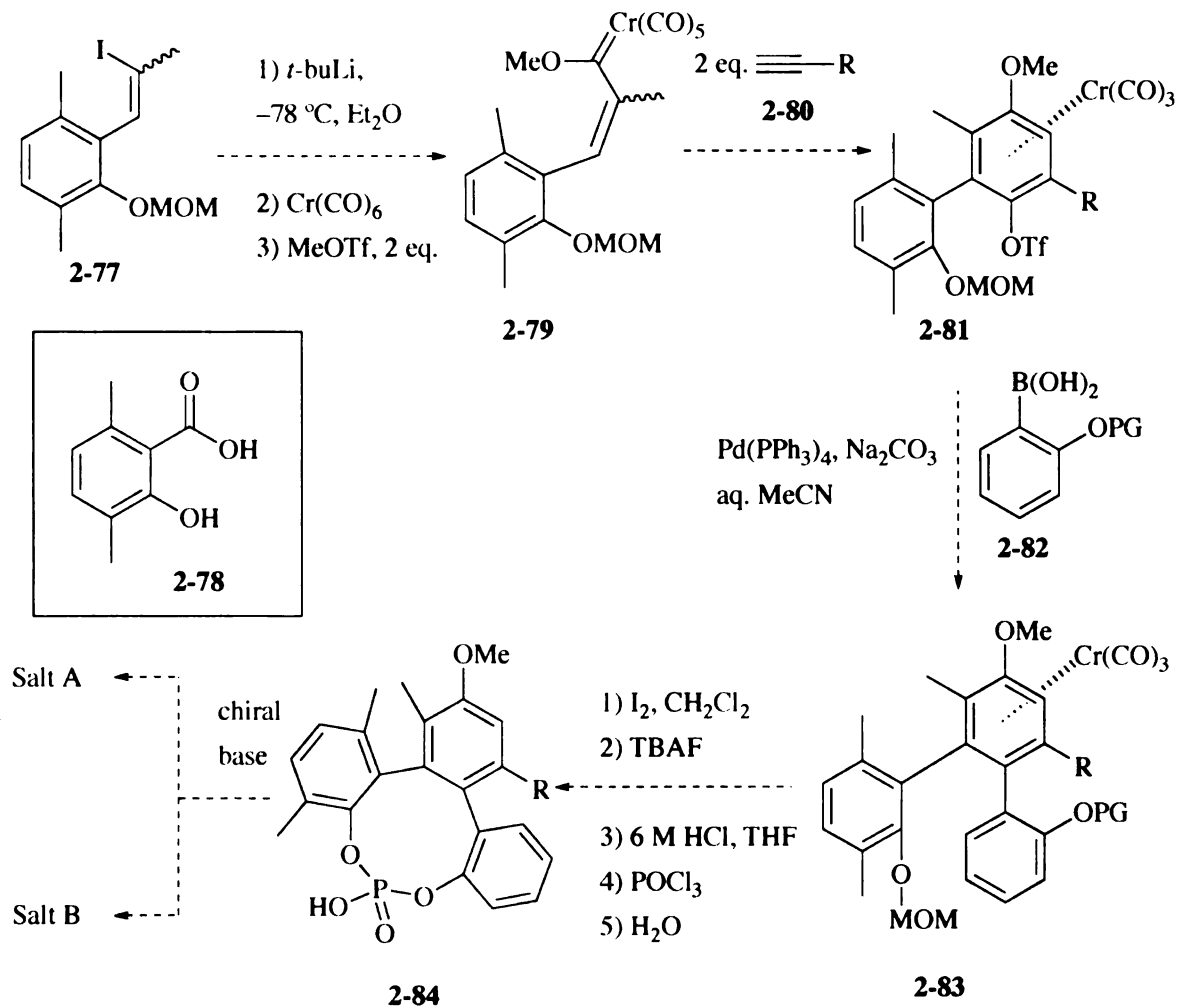
Another application for zinc in addition to the multitude of those already reported in the literature¹¹⁰ is the addition of furyl groups to aldehydes and specifically the furylation reaction between compounds **2-74** and **2-75** in Scheme 2.20. A search of the literature revealed limited attempts and the enantiomeric excesses therein are in the mid 70's.¹¹¹ Ligands **2-73** and **2-86** could be applied toward the addition of furyl zincs (**2-75**) to aldehydes (**2-74**).¹¹²

Scheme 2.20. Furyl Zinc Addition to Aldehydes



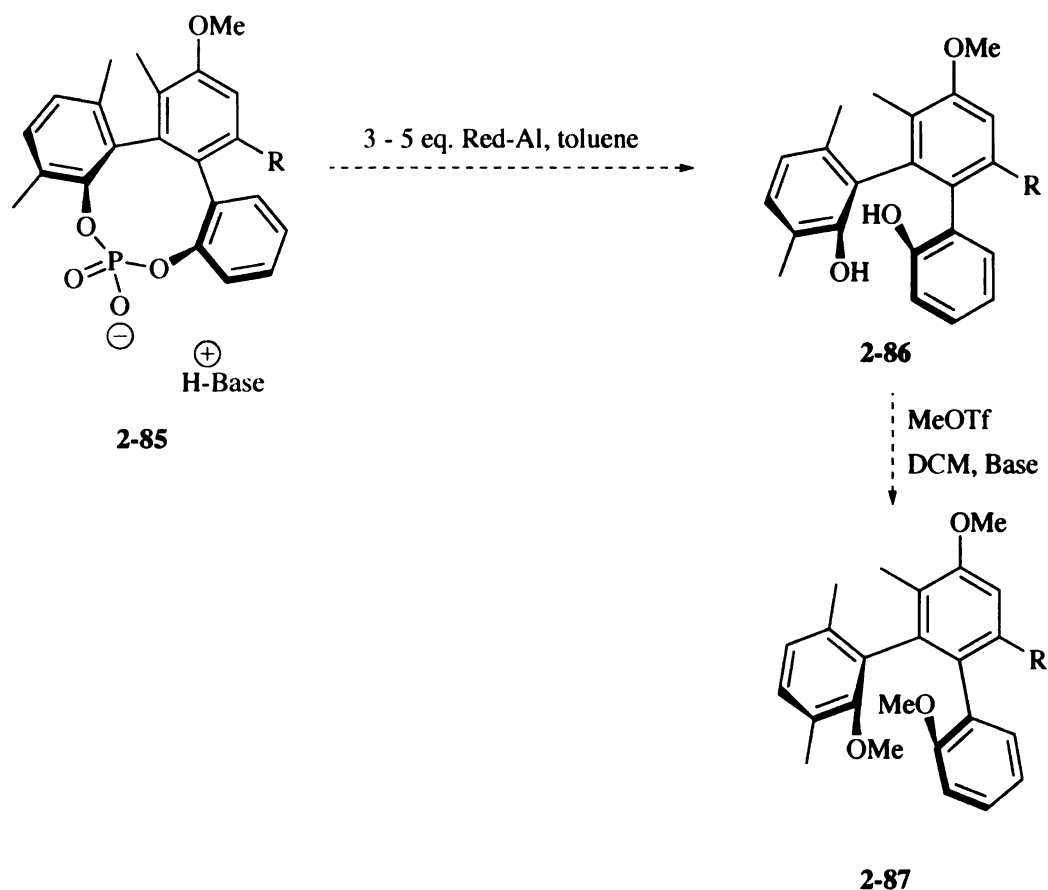
The proposed synthesis of the axial chiral ligand **2-73** is shown in Scheme 2.21. The synthesis of the ligand would begin from commercially available carboxylic acid **2-78** and through standard reduction, oxidation, and Wittig chemistry already discussed, compound **2-77** would be formed. With lithium halogen exchange, treatment with chromium hexacarbonyl and methyl triflate, compound **2-79** could be formed. With the Dötz reaction compound **2-81** could be formed. The axial planar selectivity is currently unknown for the formation of compounds like **2-81** and most likely would be a mixture. Suzuki coupling with a silyl protected boronic acid such as **2-82** should give compound **2-83**. The formation of the phosphoric acid shown as compound **2-84** could be performed. The treatment with a chiral base such as (–)-cinchonidine should provide separable salts by forming A and B salts of compound **2-84**.

Scheme 2.21. Proposed Synthesis of a Bi-Axial Planar Ligand



Having resolved Salt A and Salt B, the complex can be broken up and the phosphoric acid reduced with Red-Al as shown in Scheme 2.22 to give compound **2-86**. Treatment with methyl triflate would give ligand **2-87**.

Scheme 2.22. Formation of a Free Ligand and Methylation



2.8 Benzannulation for the Stereoselective Syntheses of Arene Chromium Tricarbonyl Complexes

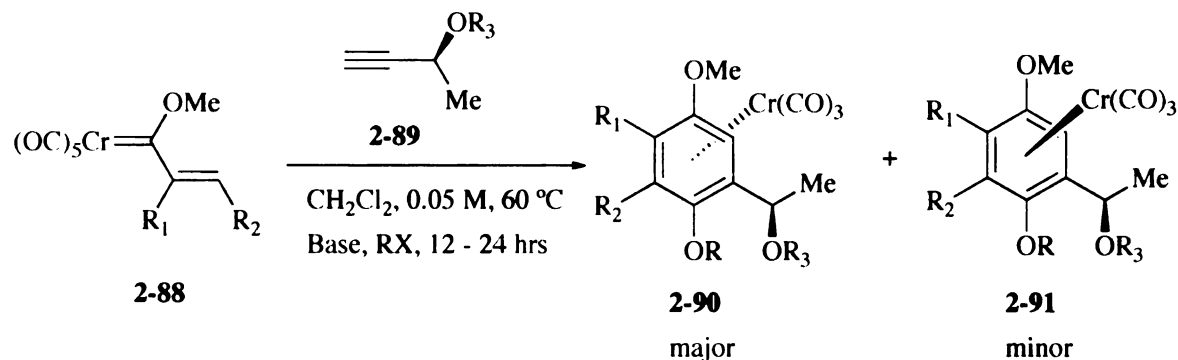
Selected results of the benzannulation reaction of propargyl alcohols such as compound **2-89** with carbene complexes such as compound **2-88** is shown in Table 2.3. This data is taken from the work of Richard Hsung while in the Wulff group⁹⁹ with the exception of entry 9 which comes from the present work. It can be observed in entry 1 with $R_3 = \text{Me}$ that the selectivity was 85 : 15 for compounds **2-90** and **2-91** respectively. As the substituent on R_3 is changed from methyl to TBS in entry 3 the selectivity improved to 91 : 9, and with TIPS in

entry 4 the selectivity is 95 : 5. Finally with trityl the reaction gave greater than 96 : 4 selectivity in entry 5. When the methyl substituent was moved from R_2 to R_1 , the selectivity was 55 : 45 as shown in entry 6. In entries 7 and 8 an electronic effect has been demonstrated. In entry 7 the selectivity was 85 : 15 for a relatively electron rich protecting group for R_3 however for entry 8 the selectivity was 62 : 38 with an electron deficient protecting group for R_3 . In entry 9, the styryl carbene complex was investigated which gave 93 % yield and $\geq 96 : 4$ diastereoselectivity.

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Table 2.3. Asymmetric Induction in the Benzannulation Reaction

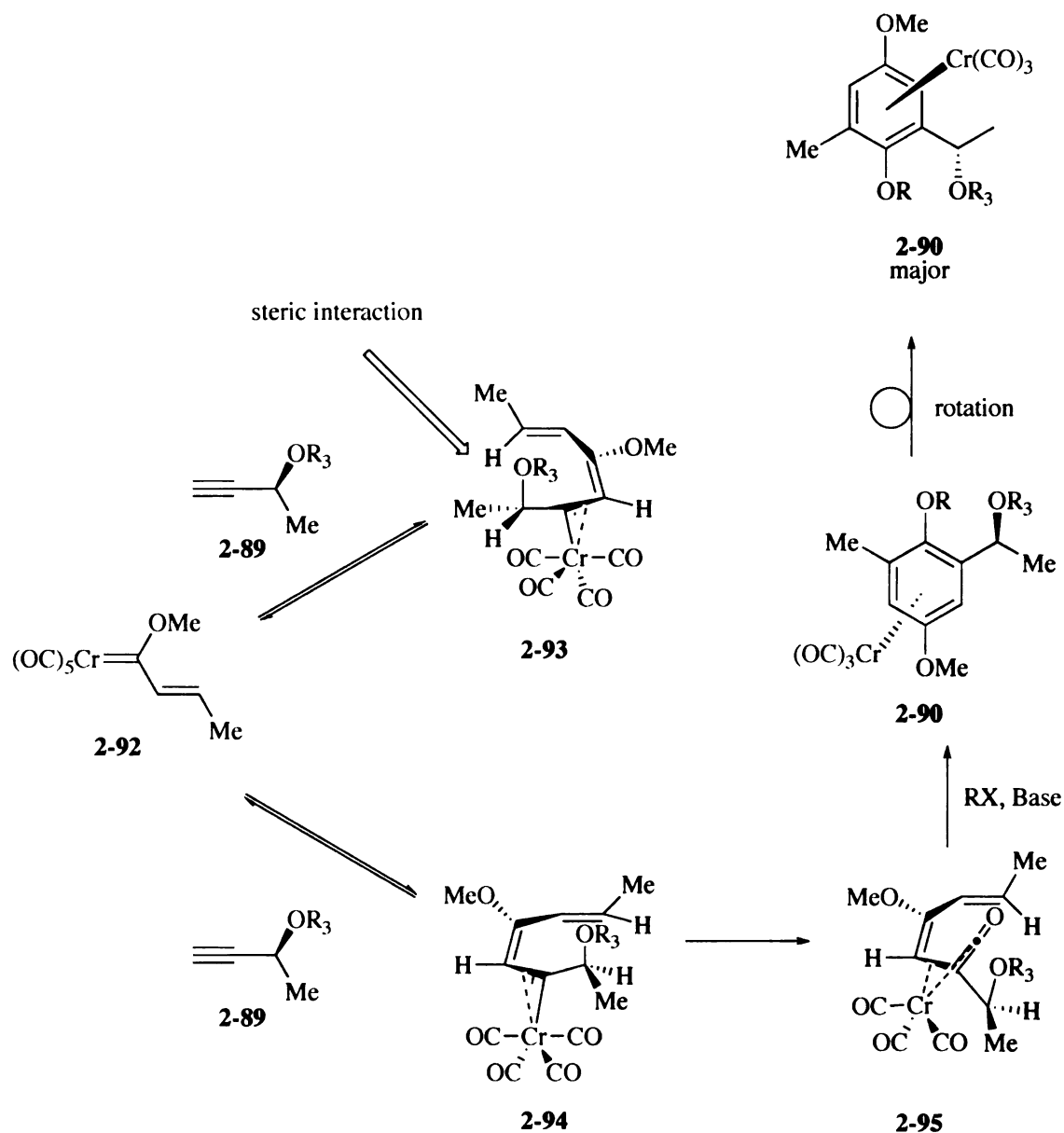


entry	R ₁	R ₂	R ₃	yield (%)	dr
1	H	Me	Me	82	85:15
2	H	Me	TMS	75	90:10
3	H	Me	TBS	70	91:9
4	H	Me	TIPS	87	95:5
5	H	Me	Tr	68	≥96:4
6	Me	H	Tr	89	55:45
7	H	Me	SiMe ₂ Ph	40	85:15
8	H	Me	SiMe ₂ C ₆ F ₅	32	62:38
9	H	Ph	Tr	93	≥96:4

In Scheme 2.23, the proposed mechanism to account for the selectivities shown in Table 2.3 is presented. From carbene complex **2-92** and alkyne **2-89**, the initial steps of benzannulation give intermediate **2-93** or intermediate **2-94**. In intermediate **2-93** there is a large steric interaction, whereas in drawing **2-94**

there are limited steric interactions. It is believed that the reaction proceeds through intermediate **2-94** involving ketene **2-95** then to product **2-90** due to the lower steric interactions involved in **2-94**.

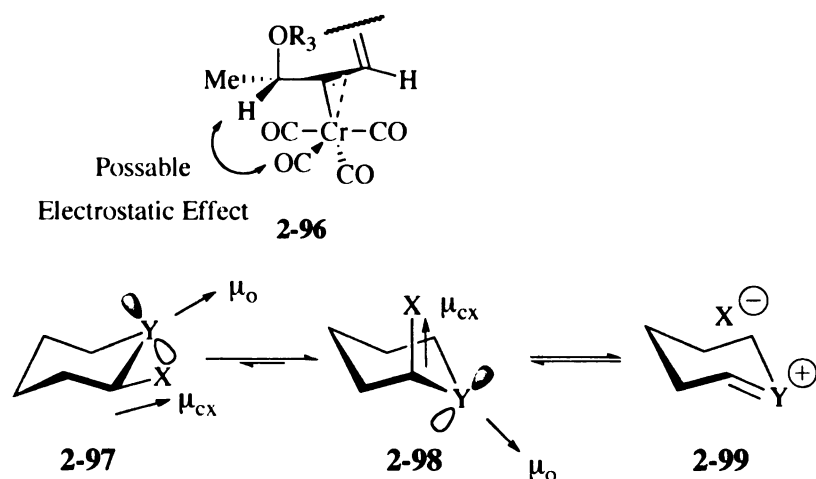
Scheme 2.23. Mechanism of Central-to-Planar Chirality Transfer



In compound **2-96**, oxygen and the chromium are oriented anti to each other as shown in Scheme 2.24. We have not performed calculations to account for this effect. Possible explanations include the arguments attributed to the

anomeric effect. Two explanations have been made for the anomeric effect; electrostatic interactions and molecular orbital interactions. We would like to invoke the dipole argument / electrostatic interactions concerning the anomeric effect.¹¹³ In compound **2-97**, **2-98**, and **2-99**, X and Y are heteroatoms. In conformer **2-97**, the dipole moments are oriented in the same direction. This is considered a destabilizing effect. In **2-98**, the dipole moments are oriented opposing each other or as near as possible and this effect is considered more stabilizing.¹¹⁴ The stabilizing effect for a C-O-C system is 5 - 10 kJ / mol. Steric interactions between $\text{Cr}(\text{CO})_4$ and OR_3 also occur. In summary, the orientation of the chromium and OR_3 may originate from the stereoelectronic effect of which both are important.¹¹⁵

Scheme 2.24. The Proposed Anti-orientation of Chromium and Oxygen



This back ground on the stereoselectivity of the benzannulations sets the stage for the studies of propargyl amines in the benzannulation reaction as a means to generate central-planar chiral chromium tricarbonyl arenes.

CHAPTER THREE

THE INITIAL STUDIES OF THE BENZANNULATION OF PROPARGYL AMINES

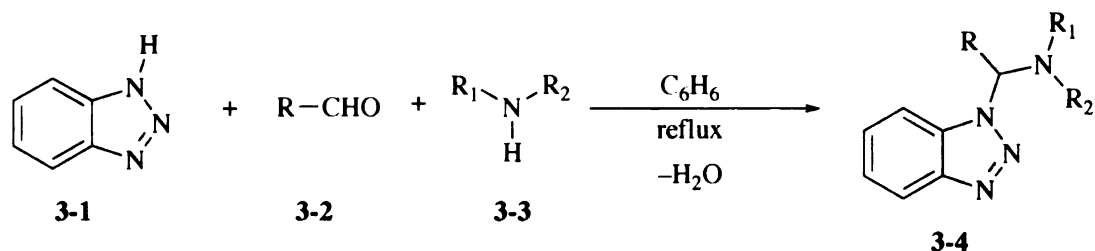
3.1 Mini-Review of Propargyl Amines

Propargyl amines are useful and dynamic building blocks for synthesis, and many examples are known in the literature.¹¹⁶ Also propargyl amines have been used directly without further elaboration as drugs. Specifically propargyl amines have biological activity toward the treatment of Parkinson's disease.¹¹⁷ A key goal of the present work is an exploration of propargyl amines as starting materials in the Wulff-Dötz benzannulation along the lines of the reactions with propargyl ethers previously discussed in chapter two of this thesis.¹¹⁸

3.1.1. Nucleophilic Substitution Reactions for the Formation of Propargyl Amines

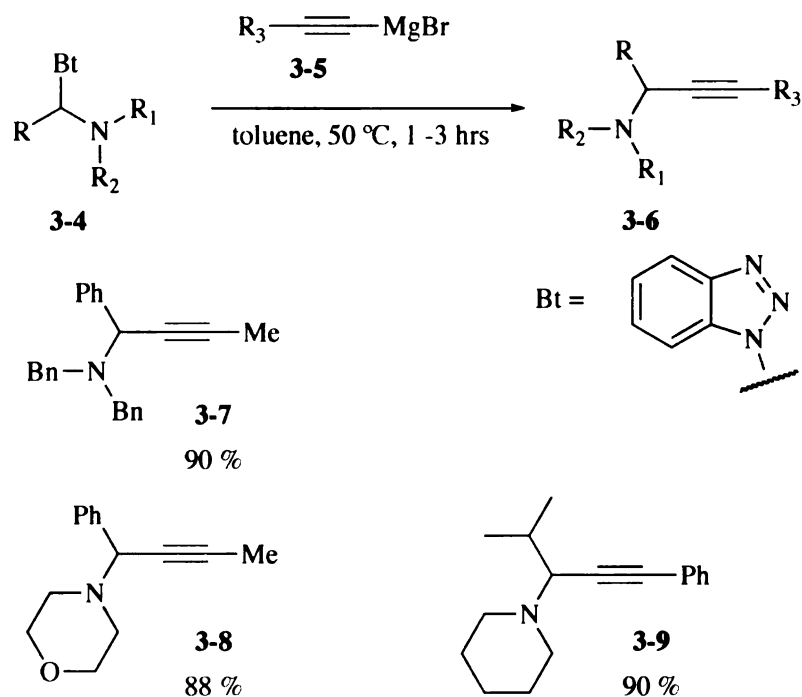
In Scheme 3.1, the synthesis of benzotriazole containing amines is presented.¹¹⁹ In this synthesis, a flask is charged with compounds **3-1**, **3-2**, and **3-3** in refluxing benzene to give compound **3-4**. Triazoles such as compound **3-1** can be used as leaving groups for the synthesis of propargyl amines.¹¹⁹

Scheme 3.1. The Synthesis of 1-(1-Dialkylaminoalkyl)benzotriazoles



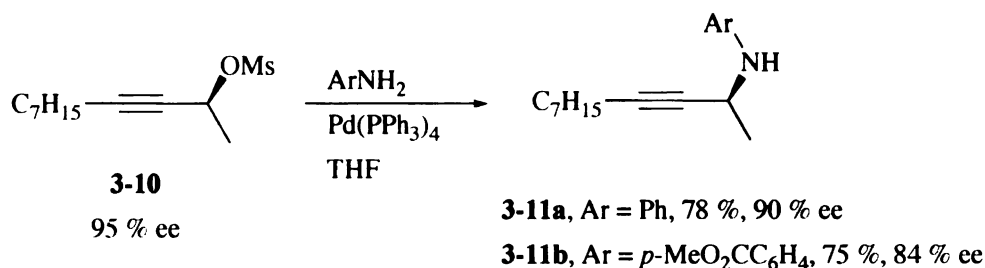
The use of triazole leaving groups is shown in Scheme 3.2. In this example a benzotriazole (Bt) derivative is used in toluene at 50 °C.¹²⁰ The propargyl amine **3-6** could be formed from amine **3-4** with acetylide **3-5** in good yields.¹²¹ The yield for compound **3-7** was 90 % using this method, and the yield for compound **3-8** was 88 %.¹²⁰ The yield for compound **3-9** was 90 %. Changes in electronics were well tolerated.¹²⁰

Scheme 3.2. The Use of Triazole Leaving Groups to Form Propargyl Amines



Shown in Scheme 3.3 is the substitution reaction with palladium tetrakis(triphenylphosphine).¹²² The reaction gives retention of stereochemistry with some loss in the enantiomeric excess as demonstrated for the conversion of compound **3-10** to the propargyl amine **3-11**.¹²³ For electronically neutral or electronically donating substituents, the ee loss was about 5 percent. For electron withdrawing groups such as esters the ee loss was greater (about 11 percent) for the formation of compound **3-11b**.¹²³

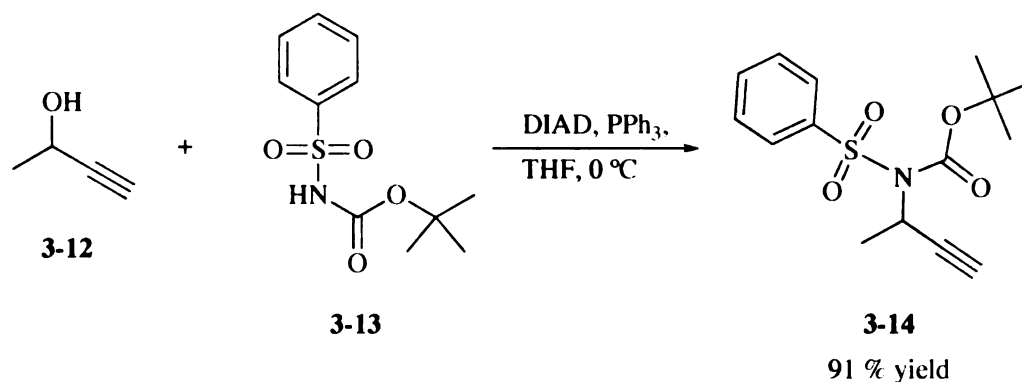
Scheme 3.3. Propargyl Amines by Palladium Mediated Substitution



3.1.2 Mitsunobu-Type Formation of Propargyl Amines

The Mitsunobu reaction has been done on 2-but-3-ynol (**3-12**) with *N*-t-butoxycarbonyl-*p*-toluenesulfonamide (**3-13**) to give the propargyl amine **3-14** in 91 % after recrystallization as shown in Scheme 3.4.¹²⁴ Electron withdrawing groups are important on the nitrogen to promote deprotonation of the nitrogen during the course of the reaction.¹²⁵

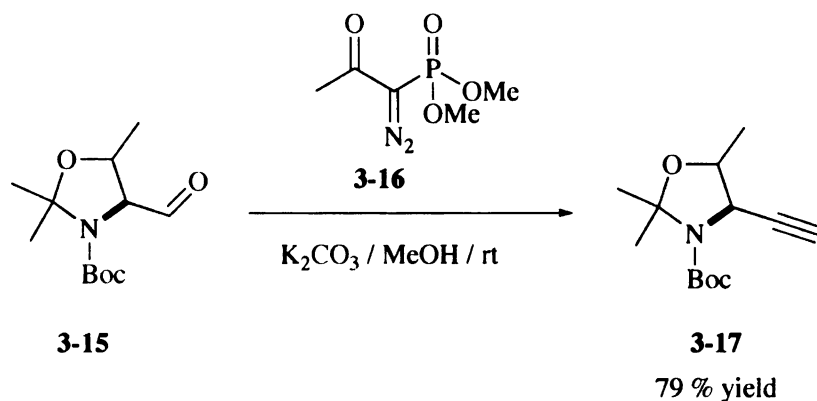
Scheme 3.4. A Mitsunobu Reaction to Form Propargyl Amines



3.1.3 Gilbert Seyferth Reagent

The Gilbert / Seyferth¹²⁶ reagent derivative **3-16** which has been called Ohira-Bestmann reagent¹²⁷ can be used to make propargyl amines as shown in Scheme 3.5.¹²⁸ This reagent can be used with mild bases such as potassium carbonate in methanol. In the example shown in Scheme 3.5, compound **3-15** was converted with **3-16** to compound **3-17** in 79 % yield. A mild base such as potassium carbonate was used. This can be useful when base sensitive functionality is present.^{126, 128} Methods such as the Corey-Fuchs require strong bases such as *n*-butyl lithium or sodium hexamethyldisilide.¹²⁹

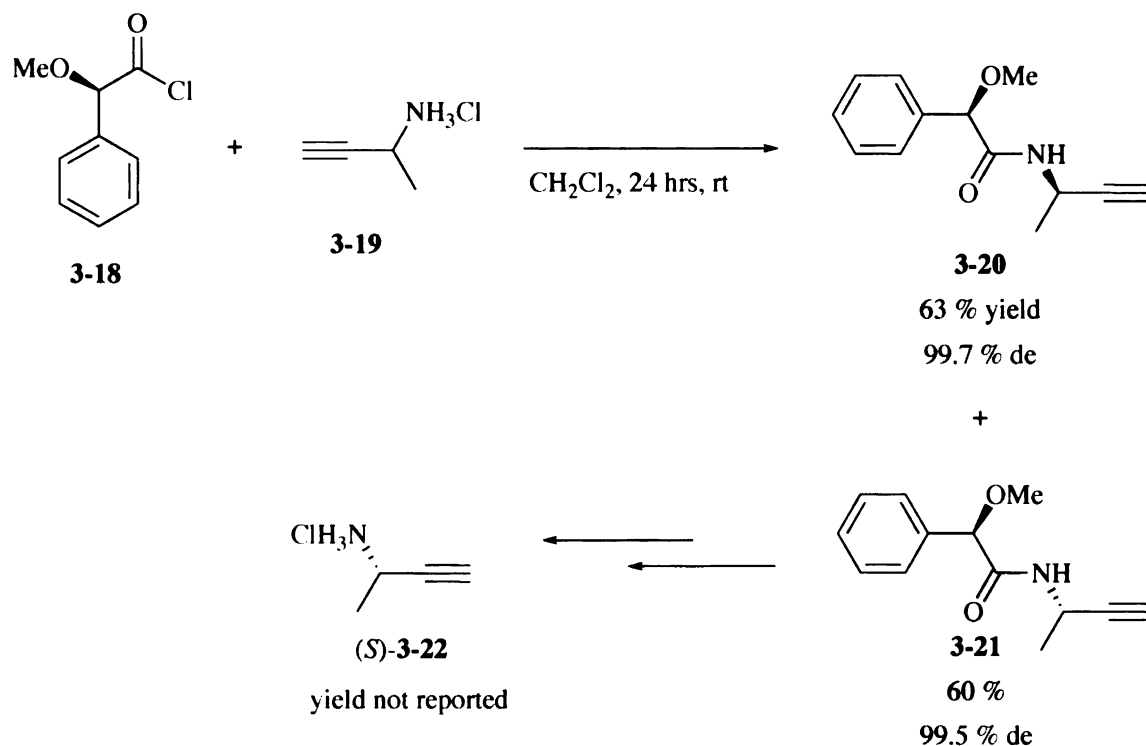
Scheme 3.5. The Formation of (*R*)-(-)-2,2-dimethyl-3-*t*-butoxycarbonyl-4-ethynyloxazolidine



3.1.4 Resolution

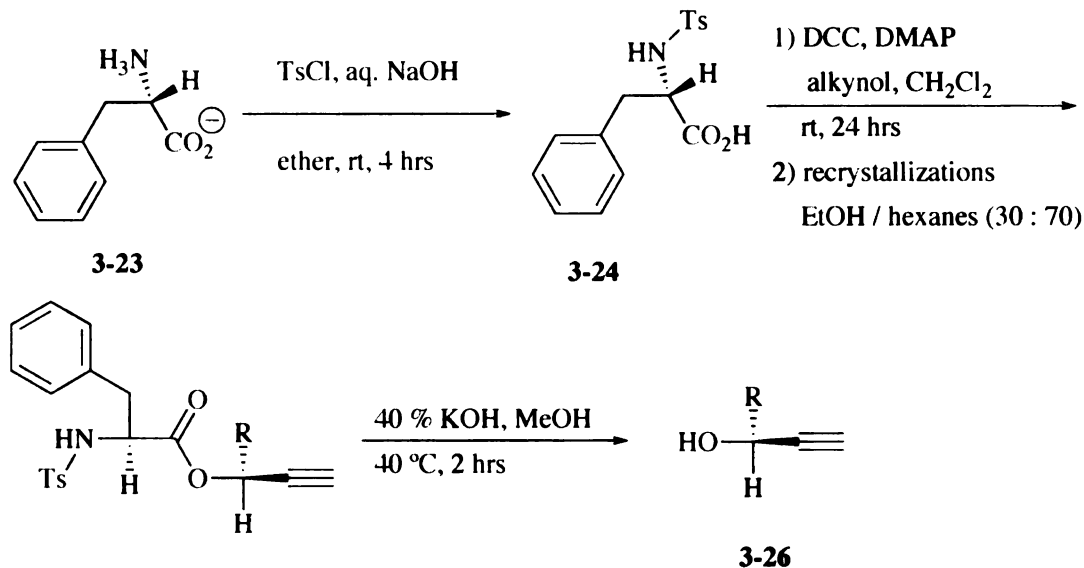
Although resolution is not as desirable as having an easy catalytic asymmetric approach, it can be efficient on a large scale and is sometimes required.¹³⁰ Shown in Scheme 3.6 is the resolution of 1-methyl-2-propynylamine **3-19**. The acid chloride of *o*-methylmandelic acid **3-18** is used to generate a mixture of diastereomers after charging compound **3-18** and compound **3-19** in a flask at room temperature for 24 hours.¹³⁰ Diastereomers **3-20** and **3-21** could be separated by column chromatography with ether and light petroleum (1:1). The unprotected optically active propargyl amine **3-22** could be obtained from compound **3-21** after protection / deprotection with di-*tert*-butyl dicarbonate followed by treatment with trifluoroacetic acid. The yield for the final two steps was not reported.¹³⁰ The yields in Scheme 3.6 were based on one diastereomer resulting from the reaction therefore the yields exceed 100%. This reaction was not diastereoselective.

Scheme 3.6. Resolution of 1-Methyl-2-Propynylamine



The resolution of propargyl alcohols is depicted in Scheme 3.7. Propargyl alcohols can be converted to propargyl amines via a Mitsunobu reaction.¹³¹ The tosylation of (*L*)-phenylalanine **3-23** gives compound **3-24**.¹³¹ The DCC (*N,N*-dicyclohexylcarbodiimide) coupling gives the ester **3-25** followed by recrystallization at least three times to obtain one diastereomer. The yields were modest in the upper 20's to low 30's. The ester functionality could be cleaved with potassium hydroxide in methanol to give compound **3-26** for which the yields were not reported. This method is suitable to large-scale applications despite the low yields.¹³¹

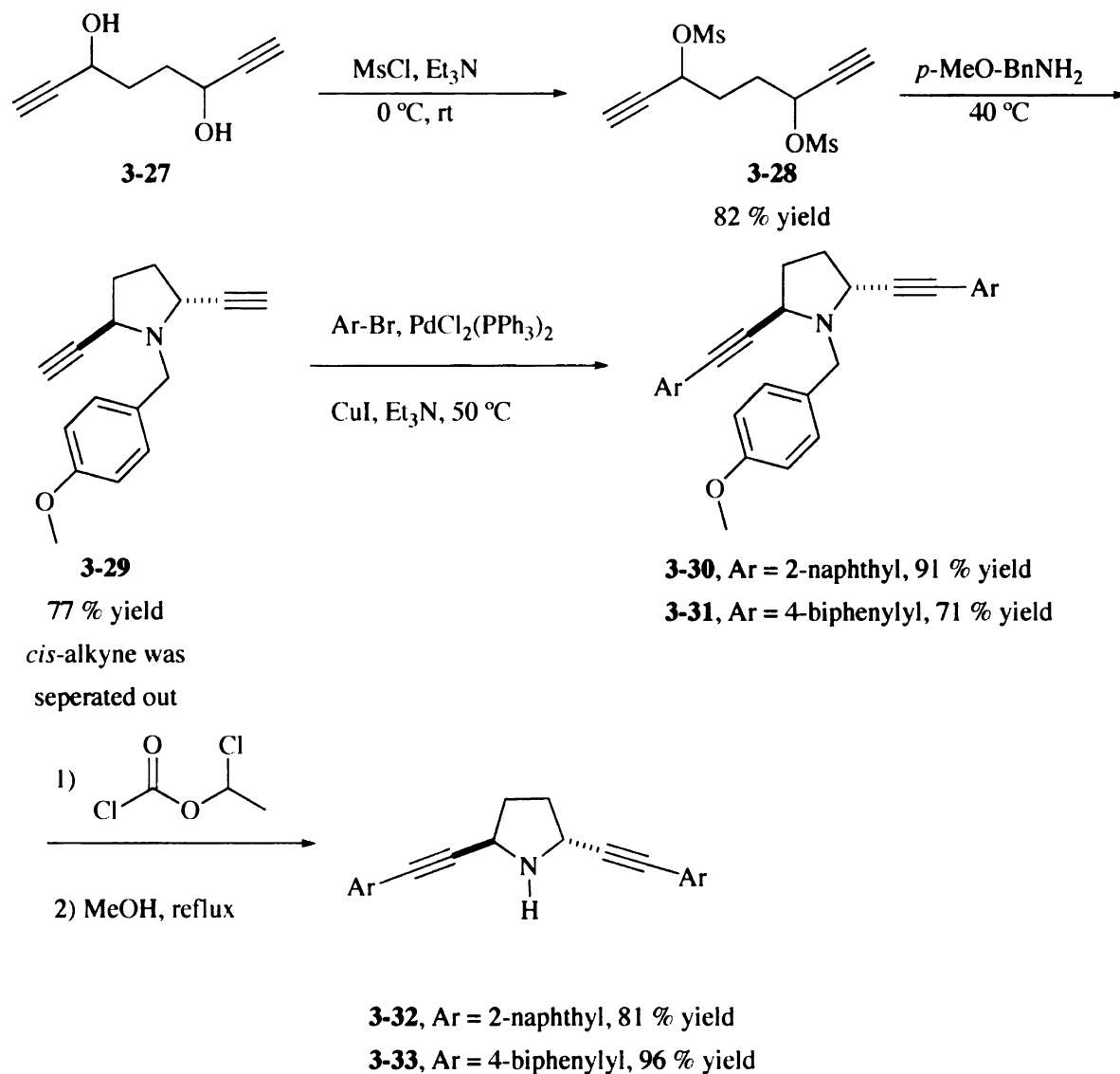
Scheme 3.7. The Resolution of Propargyl Alcohols



yields not reported

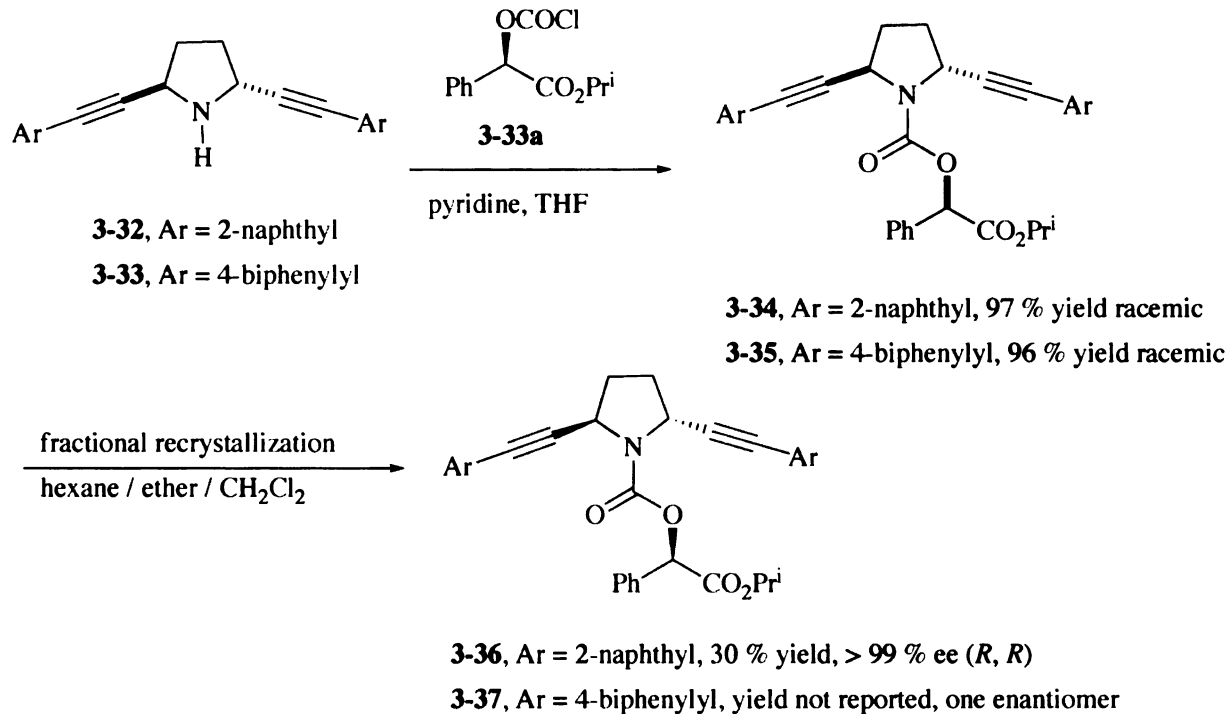
The synthesis of bis-propargyl amines is shown in Scheme 3.8. The mesylation proceeded by literature methods to give compound **3-28** in 82 % from compound **3-27**.¹³² The diol **3-27** was rich in the *dl*-isomer due to the fact that the *meso* compound precipitated out of the oil and was removed by filtration. The *dl* : *meso* ratio was 9 : 1 for compound **3-27**. The reaction with 4-methoxybenzylamine gave compound **3-29** in 77 % yield with the *trans* compound predominating because of the enhanced *dl* : *meso* ratio.¹³² The Sonogashira coupling¹³³ gave a 91 % yield of compound **3-30** and a 71 % yield of compound **3-31**. Deprotection via Olofson's protocol¹³⁴ gave 81 % yield of compound **3-32** and a 96 % yield of compound **3-33**.¹³²

Scheme 3.8. The Formation of Bis-Alkyne



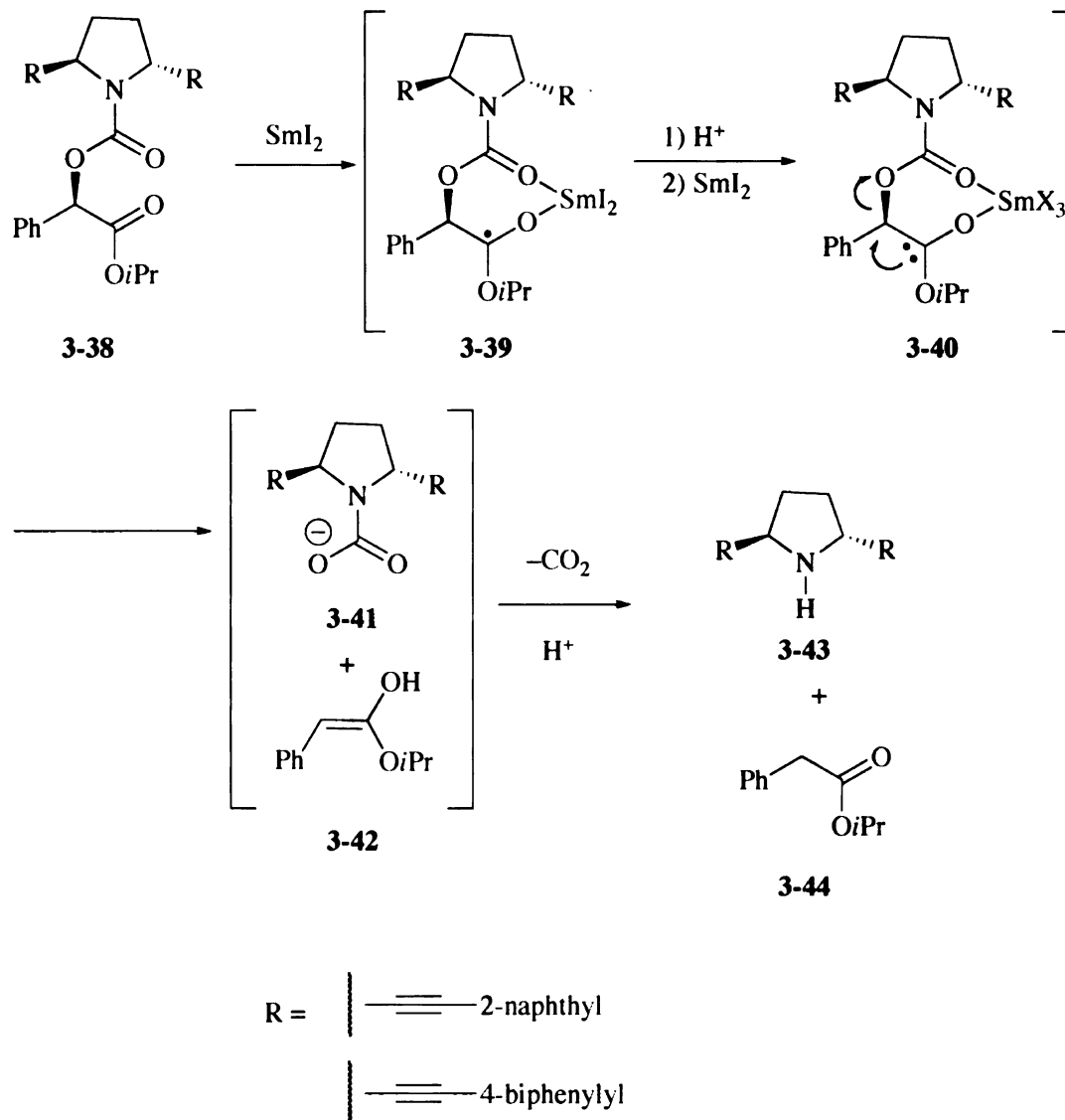
The resolution of compounds **3-32** and **3-33** is presented in Scheme 3.9. The use of chiral chloroformate **3-33a** gave compound **3-34** in 97 % yield and compound **3-35** in 96 % yield as mixtures of diastereomers (racemic at the alkyne stereocenters). Recrystallization with hexane, ether, and dichloromethane gave 30 % yield of compound **3-36** with > 99 % enantiomeric excess. Compound **3-37** was reported to give one enantiomer after deprotection and the yield was not reported.¹³²

Scheme 3.9. The Resolution of a Bis-Alkyne



The proposed mechanism for the deprotection of mandelyloxycarbonyl **3-38** is presented in Scheme 3.10.¹³² Samarium iodide is used first to coordinate then to transfer electrons to the carbonyl as shown in intermediate **3-39**. The reaction proceeds to anion **3-40** which can collapse to compounds **3-41** and **3-42**. With loss of CO₂ compounds **3-43** and **3-44** are formed. The yield of **3-43** was 92 % when R was alkynyl 2-naphthyl and when R was alkynyl 4-biphenyl, the yield was 96 %. The enantiomeric excess was > 99 % for both compounds.¹³²

Scheme 3.10. Deprotection of Mandelyloxycarbonyl



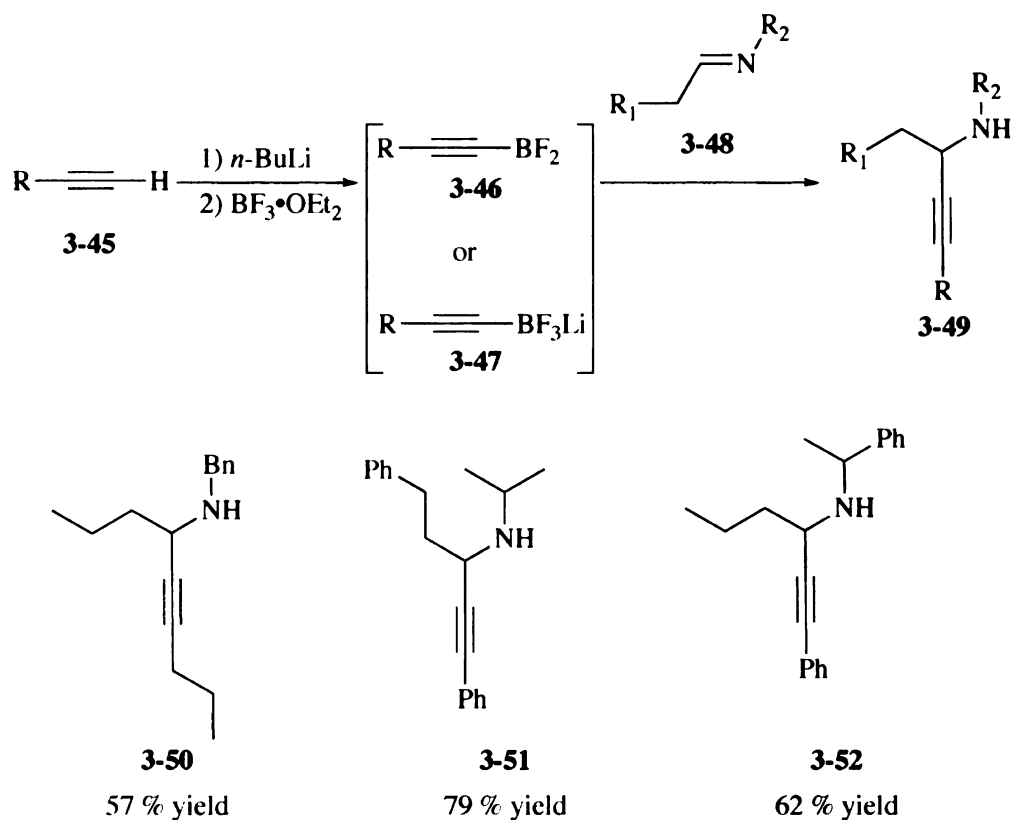
3.1.5 Addition to Imines

Shown in Scheme 3.11 is the addition of alkynylboranes to imines.¹³⁵ In this approach, an alkyne **3-45** is deprotonated with *n*-butyl lithium followed by treatment with $\text{BF}_3 \cdot \text{OEt}_2$ which gives compound **3-46** or **3-47**.¹³⁵ Two equivalents of the alkynylborane intermediate **3-46** or **3-47**¹³⁶ is usually used. The imine is then added. The reaction is usually done at -78°C . The yield of

compound **3-50** was 57 %. The yield of compound **3-51** was 79 %, and the yield of compound **3-52** was 62 %.¹³⁵

Scheme 3.11. Alkynyl Anion Addition to Aldimines to Form Propargyl

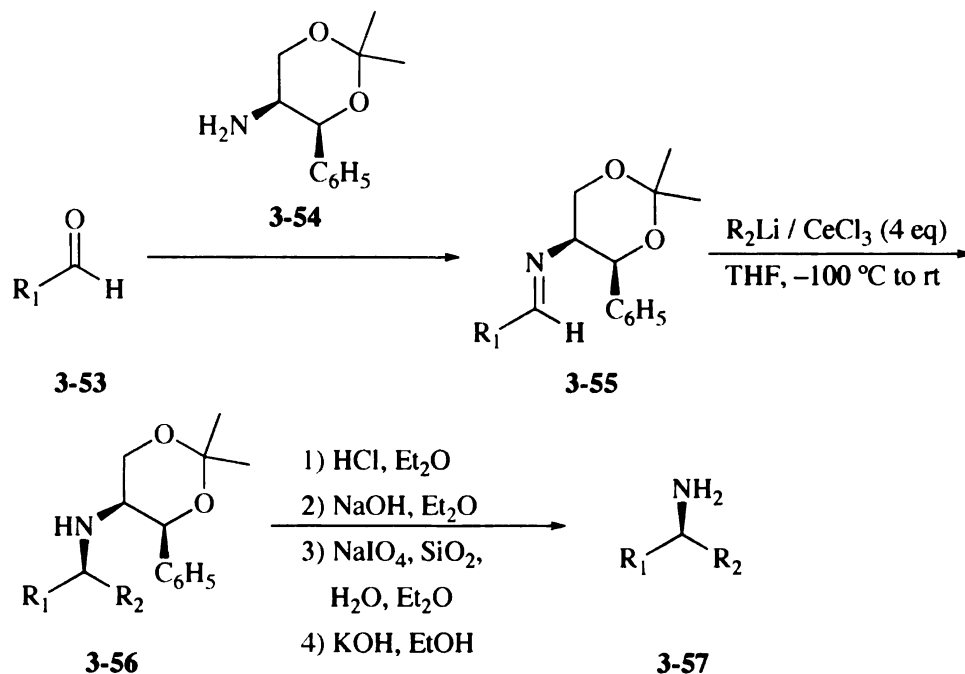
Amines



Shown in Scheme 3.12 is the addition of organocerium reagents to aldimines.¹³⁷ The imine **3-55** can be made from aldehyde **3-53** with amine **3-54**. When the imine **3-55** is treated with an organolithium nucleophile in the presence of cerium trichloride, compound **3-56** is obtained.¹³⁷ Compound **3-56** can be deprotected under the conditions shown to give compound **3-57**. When $R_1 =$

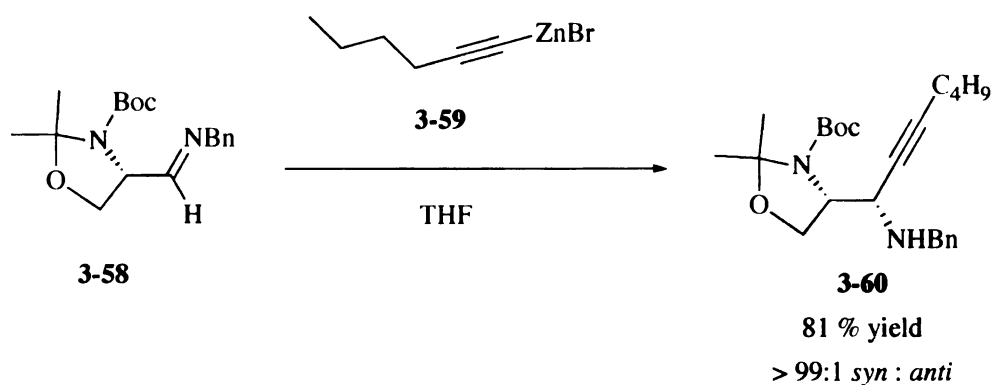
$C\equiv CPh$ and $R_2 = Me$, the overall yield was 37 % over all steps, and the enantiomeric excess was $\geq 98\%$ (*S*).¹³⁷

Scheme 3.12. Organocerium Reagent Addition to Aldimines to Form Propargyl Amines



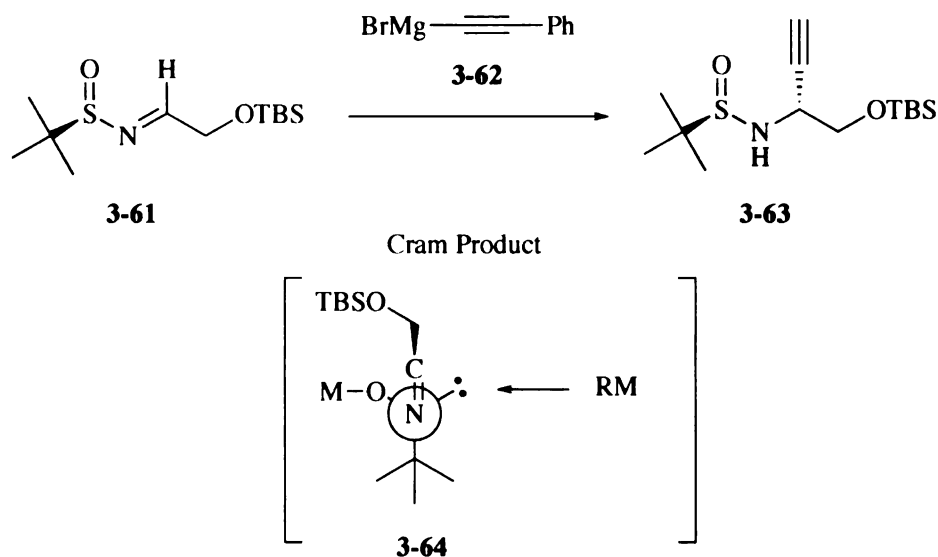
The addition of zinc acetylide **3-59** to imines such as **3-58** is shown in Scheme 3.13.¹³⁸ The yield was 81 % for compound **3-60** and the diastereoselectivity was $> 99 : 1$. The zinc acetylide **3-59** was made by first deprotonation with *n*-butyl lithium and then transmetalation (metal-metal exchange) with $ZnBr_2$.¹³⁸ The yields are generally lower for the addition of lithium acetylide however, with an electron-withdrawing group on nitrogen such as tosyl the yields are in the 70's.¹³⁹

Scheme 3.13. Addition Zinc Acetylide to Schiff Bases



Shown in Scheme 3.14 is chemistry developed by Ellman and coworkers.¹⁴⁰ In the example shown in Scheme 3.14, the reaction from the aldimine **3-61** with acetylide **3-62** gives compound **3-63**. The product follows the Cram rule as shown in the proposed preferred conformation **3-64**.¹⁴⁰

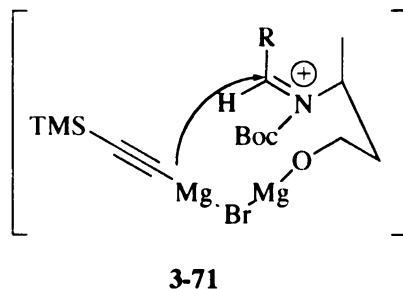
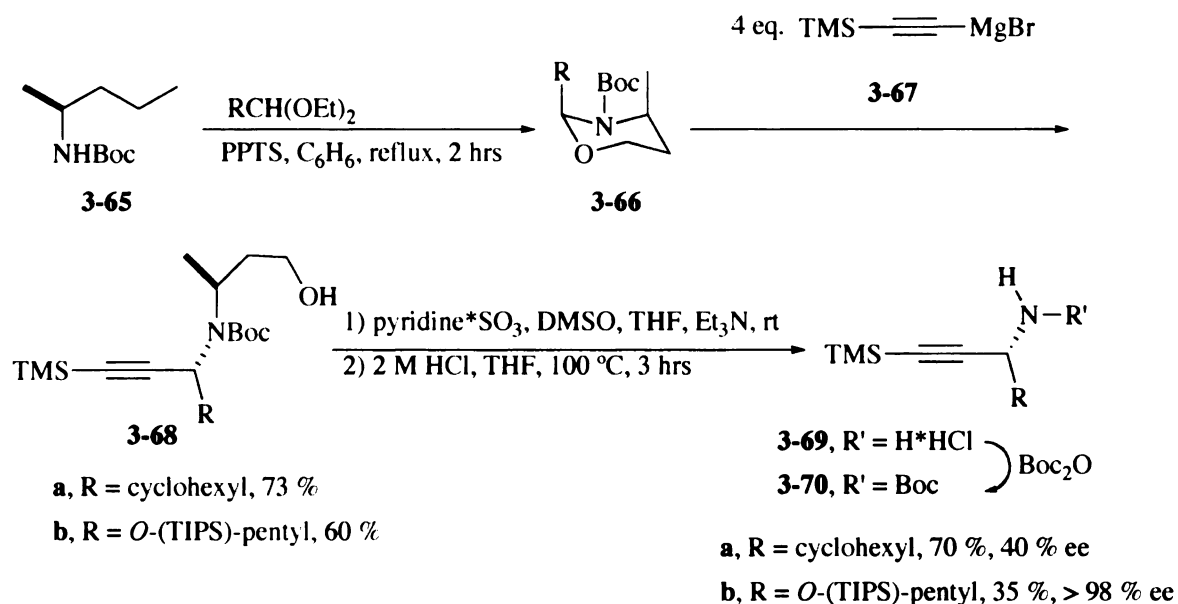
Scheme 3.14. *tert*-Butanesulfinyl Aldimines for Selective Addition of Acetylide



Shown in Scheme 3.15, the indirect formation of chiral propargyl amines is depicted.¹⁴¹ When compound **3-65** was treated with an acetal, compound **3-66**

was formed, and treatment of compound **3-66** with magnesium bromide acetylide **3-67** gave compound **3-68**.¹⁴¹ When R = cyclohexyl, the yield for this sequence was 73 % of compound **3-68a**. When R = *O*-(TIPS)-pentyl, the yield was 60 % for this sequence giving compound **3-68b**.¹⁴¹ Oxidation with pyridine•SO₃¹⁴² followed by treatment with acid at 100 °C gave compound **3-69**. Protection of the amine with a Boc group gave compound **3-70**. The yield when R = cyclohexyl was 70 % and the enantiomeric excess was 40 % for this sequence for compound **3-70a**. The yield when R = *O*-(TIPS)-pentyl was 35 % and enantiomeric excess was > 98 % for this sequence for compound **3-70b**.¹⁴¹ The proposed key mechanistic intermediate is shown as compound **3-71**. This key intermediate **3-71** is an iminium cation with magnesium coordination to oxygen; the acetylide is delivered to the electrophilic carbon.¹⁴¹

Scheme 3.15. Synthesis of Propargyl Amines from Tetrahydro-1,3-Oxazines

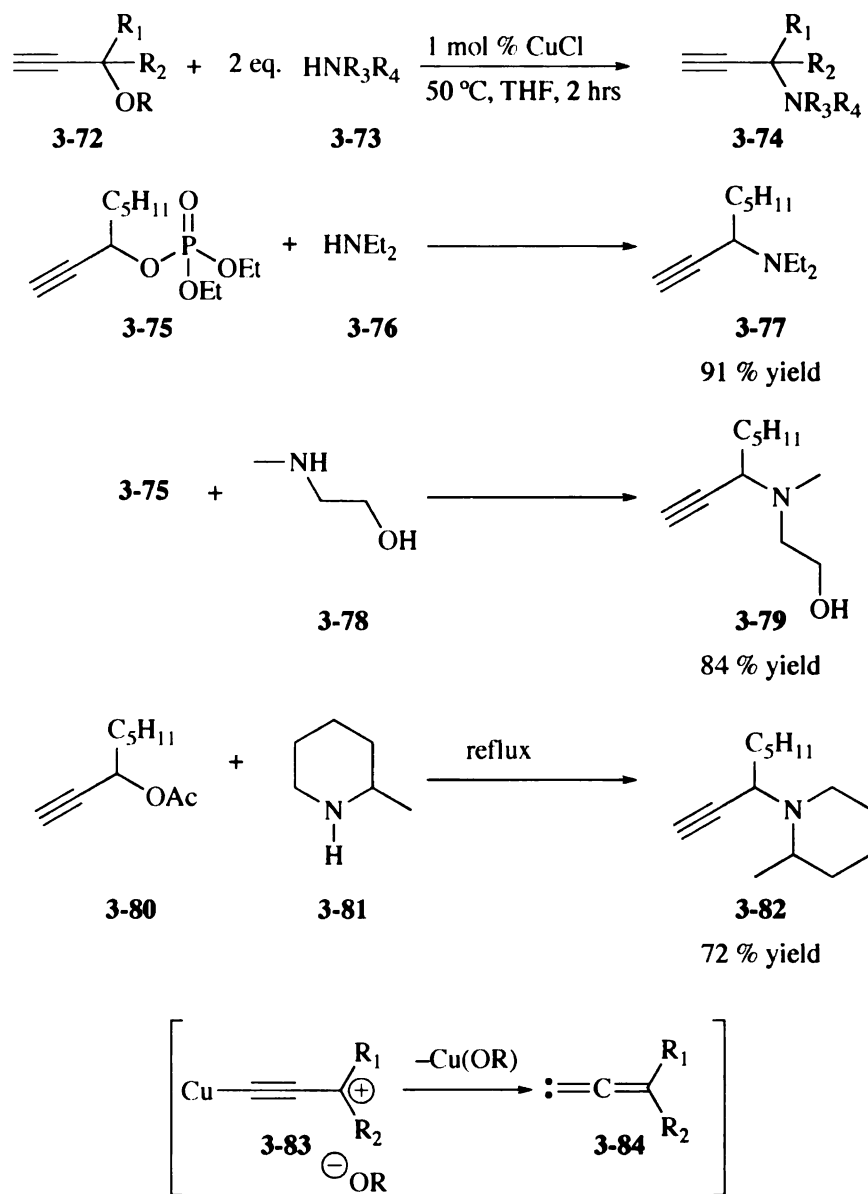


3.1.6 Copper Catalysis for the Formation of Propargyl Amines

Shown in Scheme 3.16 is a substitution involving the propargyl alcohol **3-72** with 2 equivalents of amine **3-73** in the presence of copper chloride to give the propargyl amine **3-74**.¹⁴³ The presence of a terminal acetylenic proton is required. The yield of compound **3-77** from propargyl phosphate **3-75** and amine **3-76** was 91 %. With amine **3-78**, the yield was 84 % to compound **3-79**. With propargyl acetate **3-80** and amine **3-81**, the yield was 72 % of compound **3-**

82.¹⁴⁴ The racemization of chiral starting material was noted. This racemization was explained by proposed intermediates **3-83** or **3-84** followed by the attack of the amine.

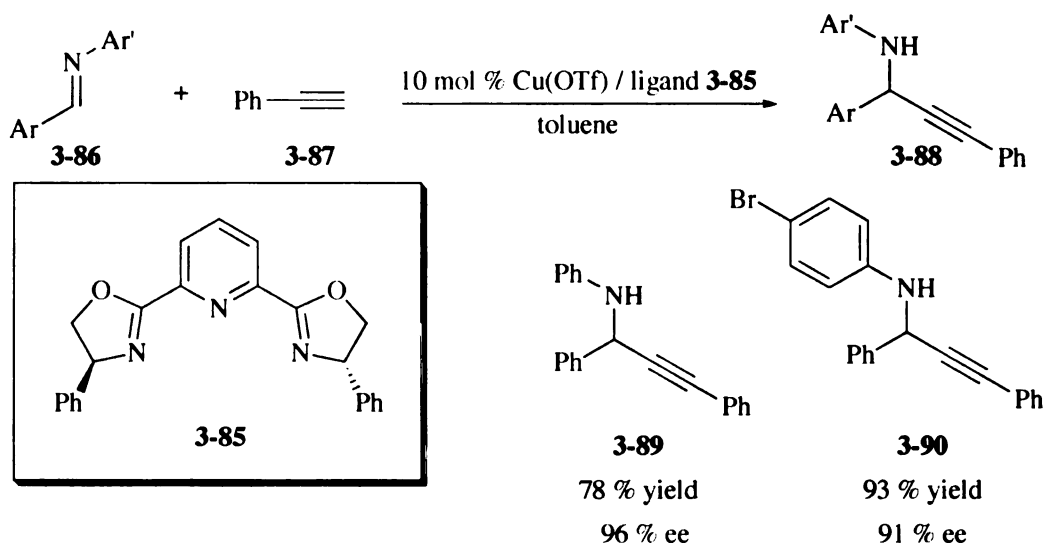
Scheme 3.16. Copper Mediated Amination of Propargyl Esters



Shown in Scheme 3.17 is the use of ligand **3-85** with CuOTf for the asymmetric formation of propargyl amines.¹⁴⁵ From imine **3-86** and alkyne **3-87**, the propargyl amine **3-88** is generated. The yield of compound **3-89** was 78 %

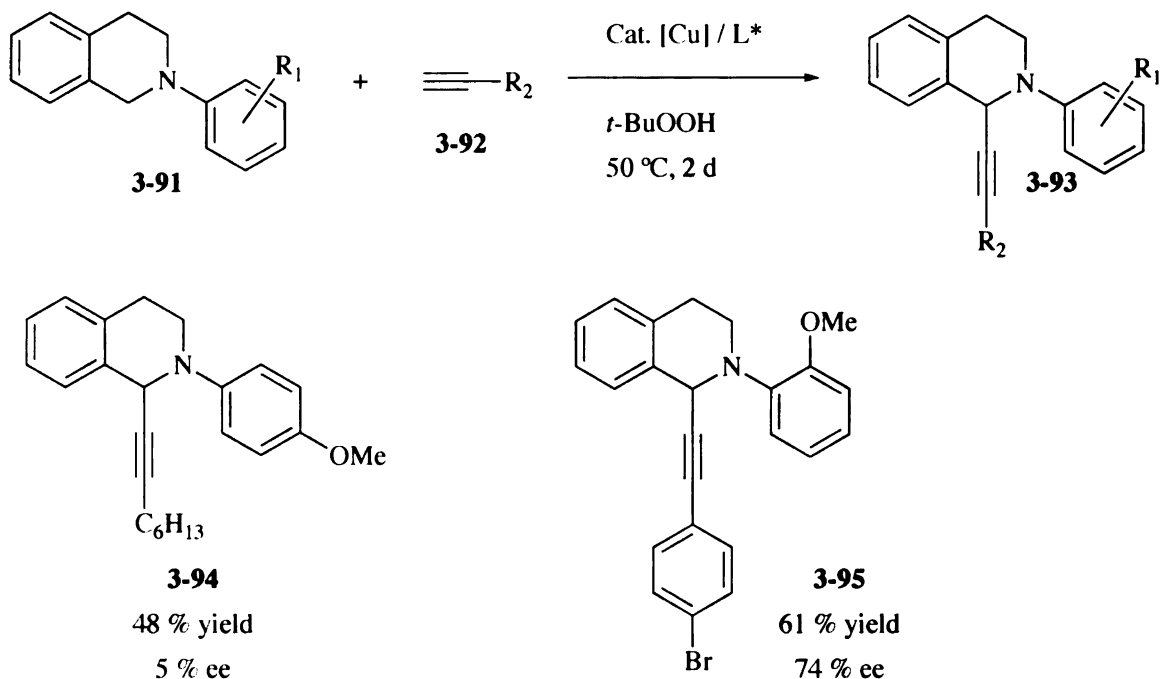
with an enantiomeric excess of 96 % ee. The yield of compound **3-90** was 93 % with an ee of 91 %. Enantiomeric excess of > 90 % required the use of phenyl acetylene.¹⁴⁵

Scheme 3.17. Phenyl Acetylene Addition to Imines



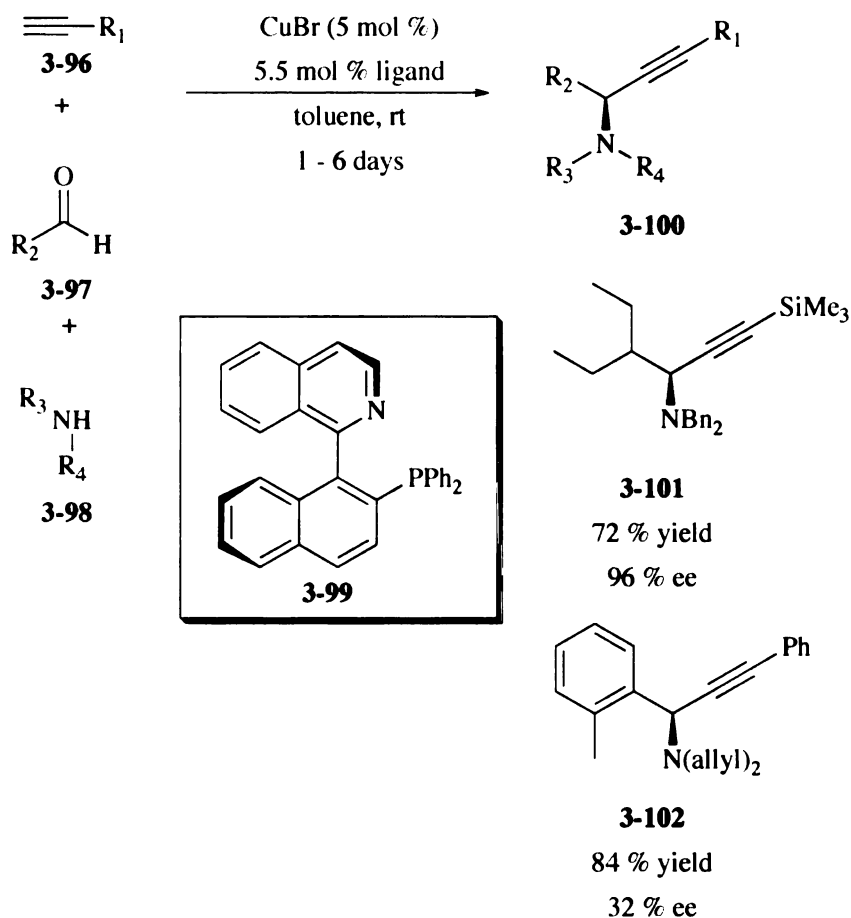
Using the same ligand **3-85** as in Scheme 3.17 above, a peroxide induced formation of a propargyl amine **3-93** from compound **3-91** and **3-92** has been accomplished.¹⁴⁶ With 1-octyne shown in Scheme 3.18, the yield of compound **3-94** was 48 % and 5 % ee.^{146, 147} With 4-bromophenylacetylene, the yield of compound **3-95** was 61 % and 74 % ee.^{146, 147} Phenylacetylenes gave higher enantiomeric excesses in general for this reaction.¹⁴⁷

Scheme 3.18. The Peroxide Induced Formation of Propargylamines



A copper(I)-catalyzed three-component reaction is shown in Scheme 3.19.¹⁴⁸ The reaction involves the use of an alkyne **3-96**, aldehyde **3-97**, and an amine **3-98**.¹⁴⁸ With copper bromide and ligand **3-99**, compound **3-100** was formed. For compound **3-101** the yield was 72 % with an enantiomeric excess of 96 %. The yield for compound **3-102** was 84 % with an ee of 32 %.¹⁴⁸ A microwave-promoted three-component coupling is known however it has not been applied in an asymmetric fashion.¹⁴⁹

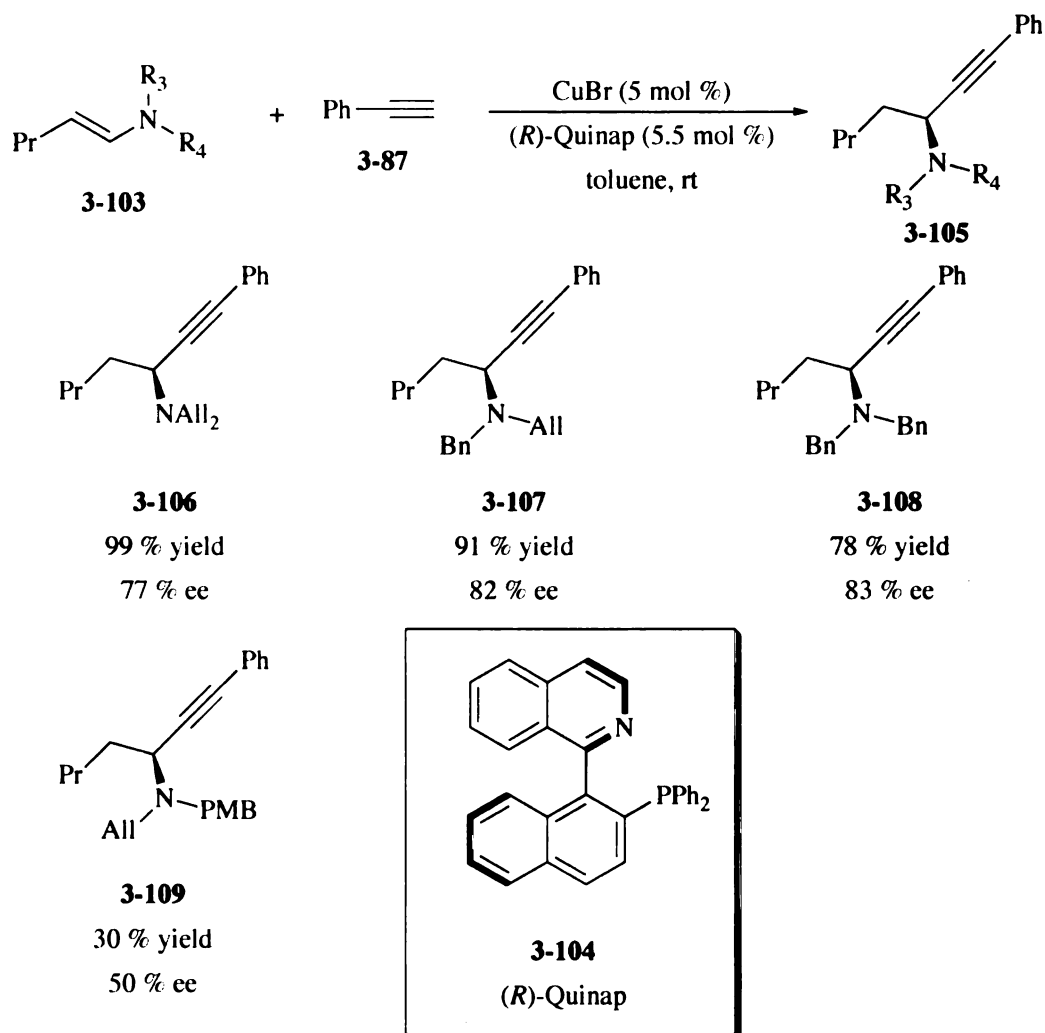
Scheme 3.19. Enantioselective, Copper(I)-Catalyzed Three Component Reaction for the Preparation of Propargylamines



Shown in Scheme 3.20 is the synthesis of enantiomerically enriched propargylamines. The enamine **3-103**¹⁵⁰ with phenyl acetylene **3-87** gives compound **3-105** with 5 mol % copper bromide and 5.5 mol % (*R*)-quinap (**3-104**) at room temperature.¹⁵¹ The yield of compound **3-106** was 99 % with an enantiomeric excess of 77 %. The yield of compound **3-107** was 91 % with an ee of 82 %.¹⁵¹ For compound **3-108**, the yield was 78 % with an ee of 83 %. Lastly, the yield of compound **3-109** was 30 % with an enantiomeric excess of 50 %. It is interesting to note that compound **3-109** was the only example with a

PMB (*para*-methoxybenzyl) group, and the yield and enantiomeric excess were the lowest of the examples shown.¹⁵¹

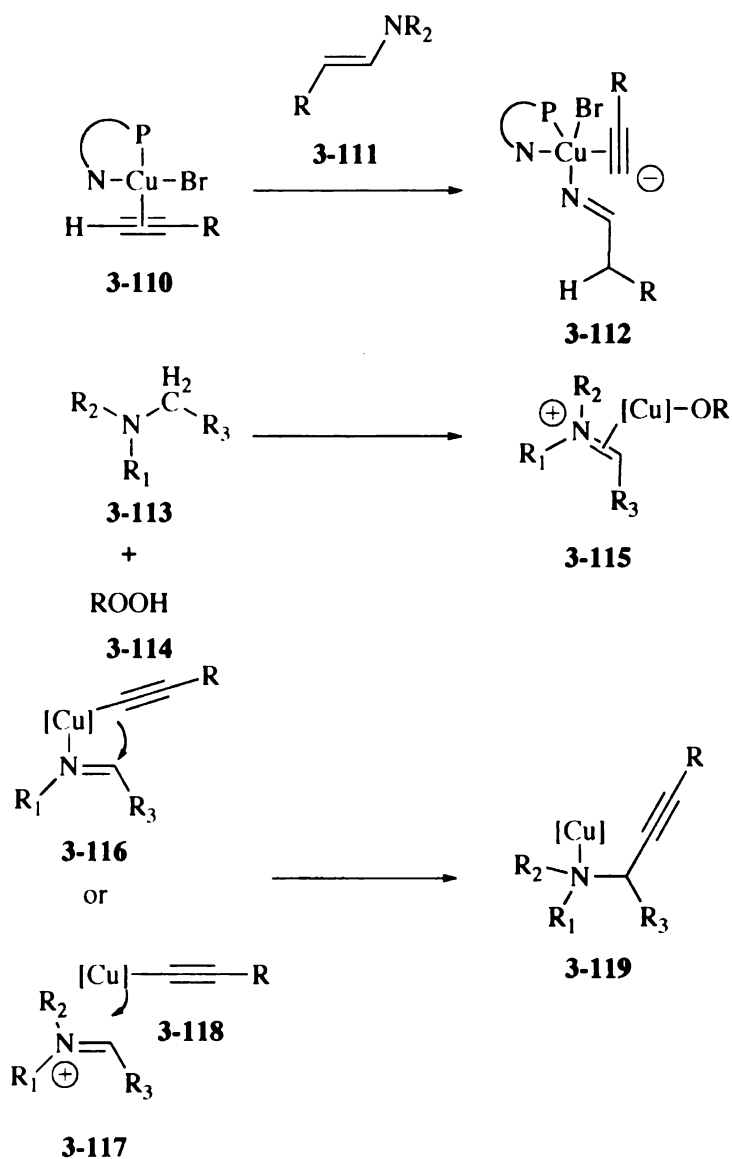
Scheme 3.20. Copper-Catalyzed Addition of Alkynes to Enamines



The hybrid mechanism for these copper mediated coupling reactions were taken from several sources and are presented in Scheme 3.21.^{146, 148, 149, 151} In the first reaction, the conversion of the enamine **3-111** to the imine **3-112** is depicted in the presence of a chiral copper catalyst complex **3-110**. This shows the formation of the acetylide which proceeds via the coordination of the copper

catalyst to the alkyne shown as compound **3-112**.¹⁴³ In the second reaction, the formation of an iminium **3-115** is shown originating from an amine **3-113** and peroxide **3-114** in the presence of a copper catalyst.¹⁴⁵ The addition of the copper acetylide is shown from compound **3-116** to compound **3-119**.¹⁴⁶ Alternatively, the addition could occur via compound **3-117** then form compound **3-119**.¹⁴⁸

Scheme 3.21. Various Mechanisms of Copper Catalyzed Alkyne Addition to Imines

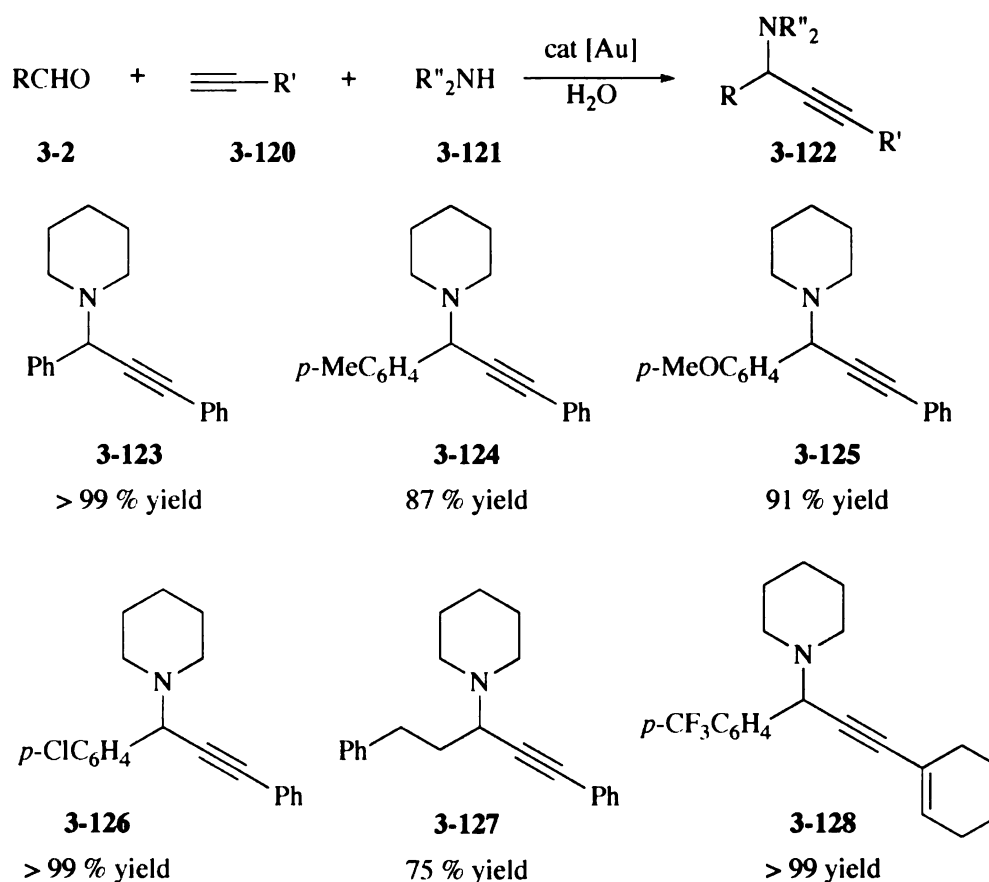


3.1.7 Miscellaneous Metals For the Formation of Propargyl Amines

The three-component coupling of aldehydes, alkynes, and amines is shown in Scheme 3.22.¹⁵² The reaction proceeds with aldehyde **3-2** and alkyne **3-120** and amine **3-121** in the presence of a gold catalyst. Several gold reagents were evaluated, and the best was gold tribromide.¹⁵² The best solvent in terms

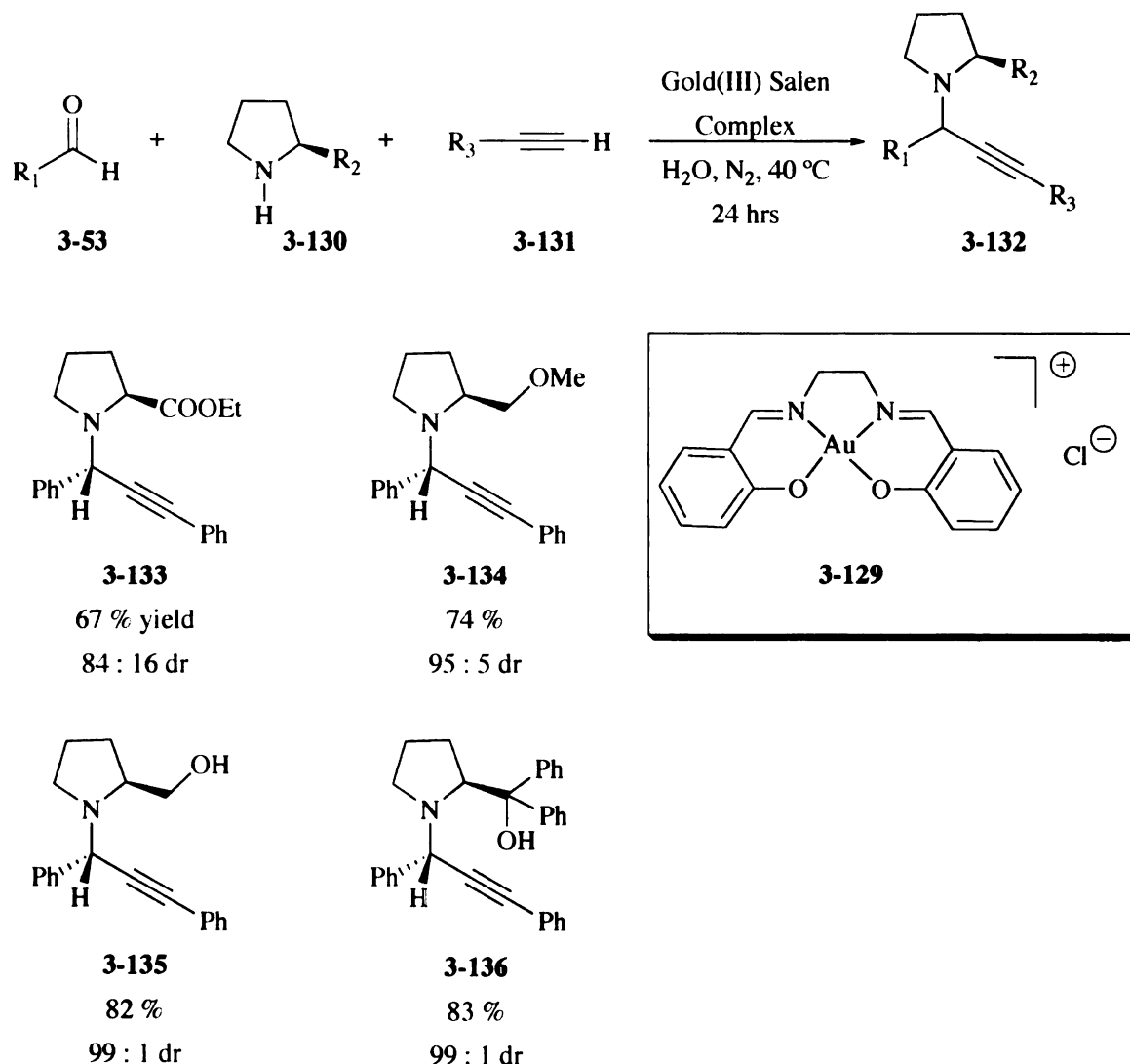
of yield was water which was better than toluene and THF. The yield of compound **3-123** was > 99 %. A more electron donating substrate gave an 87 % yield of compound **3-124**, and a *p*-methoxy containing substrate gave 91 % yield of compound **3-125**.¹⁵² A *p*-chloro containing substrate gave > 99 % yield of compound **3-126**, and the yield of compound **3-127** was 75 %. A *p*-trifluoromethane containing substrate gave a yield of > 99 % for compound **3-128**. The reaction time was generally 5 hours.¹⁵²

Scheme 3.22. Three-Component Coupling of Aldehydes, Alkynes, and Amines via C-H Activation Catalyzed by Gold in Water



The gold catalyzed reaction has been done with chiral ligands. Gold(III) salen complexes have been used for this purpose.¹⁵³ In Scheme 3.23, this reaction is presented with proline derivatives using salen **3-129** as a catalyst.¹⁵⁴ The reaction involves aldehyde **3-53**, amine **3-130**, and alkyne **3-131**. The conditions of the reaction involved water as solvent at 40 °C for 24 hours. The yield for compound **3-133** was 67 % and the diastereomeric ratio was 84 : 16. An improvement in the diastereomeric ratio to 95 : 5 (75 % yield) can be observed for compound **3-134**.¹⁵⁴ A further improvement was made with compound **3-135** having a yield of 82 % with a dr of 99 to 1. Compound **3-136** had a yield of 83 % and a dr of also 99 : 1.¹⁵⁴

Scheme 3.23. Gold(III) Salen Complexes For the Synthesis of Chiral Propargyl Amines

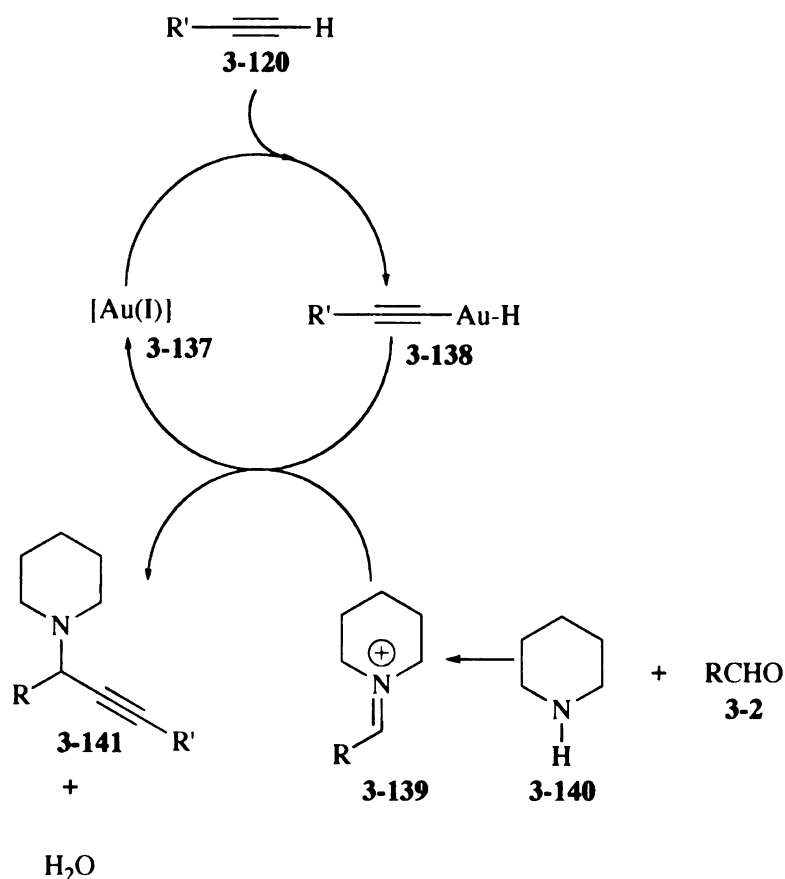


The mechanism of this catalytic reaction can be seen in Scheme 3.24.¹⁵²

From alkyne **3-120**, gold(I) **3-137** goes to the proposed metal alkynyl complex **3-138**.¹⁵⁴ From there, the organometallic intermediate **3-138** adds to the *in situ* generated iminium compound **3-139** to give the propargyl amine **3-141**.¹⁵⁵ The mechanism for the removal of the hydrogen from the gold complex **3-138** was not described in the reference¹⁵⁴ however Au(I) regeneration presumable involves

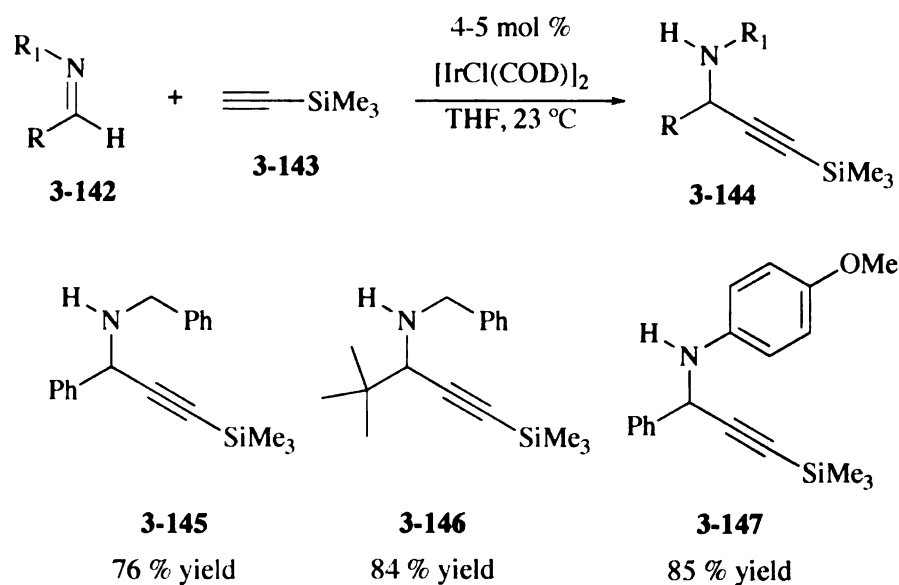
the removal of the hydrogen by a base which may simply be water or the generated propargyl amine.

Scheme 3.24. Tentative Mechanism for the Gold-Catalyzed Reaction in Water



The use of iridium for the formation of propargyl amines has been reported by Carreira.¹⁵⁶ In this reaction an imine **3-142** and TMS acetylene **3-143** with 4 - 5 mol % of $[\text{IrCl}(\text{COD})]_2$ gave the propargyl amine **3-144**.¹⁵⁶ The yield for compound **3-145** was 76 %, and the yield for compound **3-146** was 84 %. The yield for compound **3-147** was 85 %.¹⁵⁶

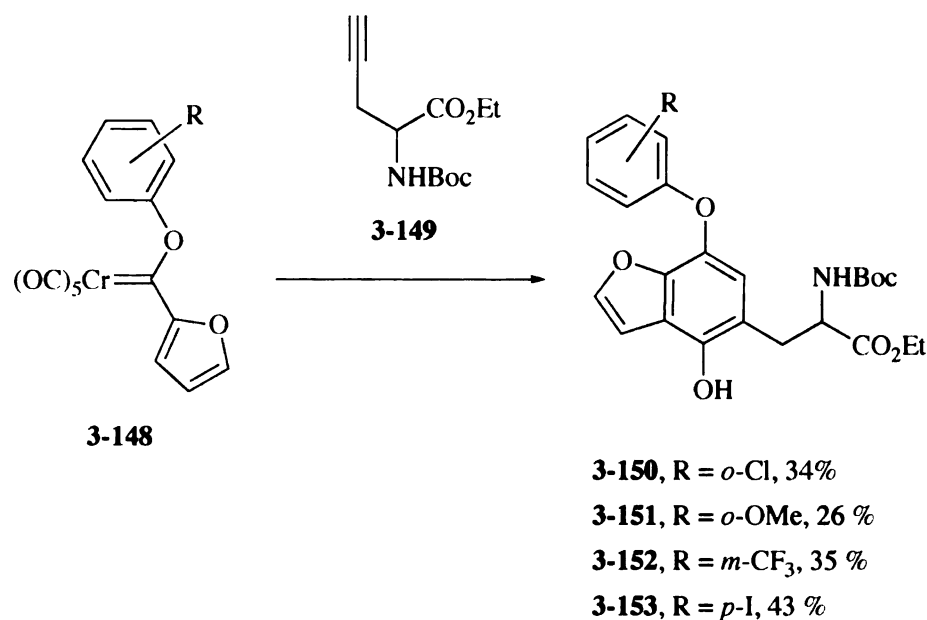
Scheme 3.25. The Use of Iridium For the Formation of Propargyl Amines



3.2 Related Reactions to the Benzannulation of Propargyl Amines

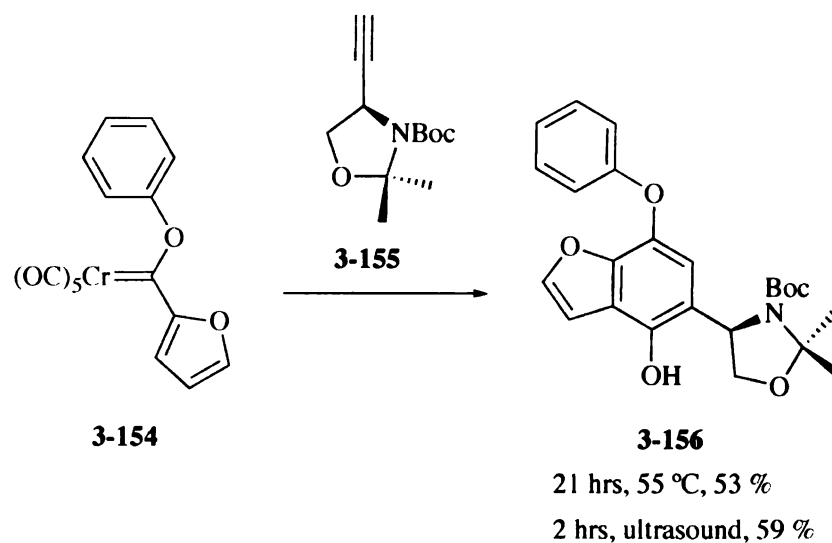
A reaction related to propargyl amines is the reaction of propargylglycinate¹⁵⁷ **3-149** with carbene complex **3-148** reported by Pulley and coworkers is shown in Scheme 3.26. This reaction has been investigated with several substituents. The yields were between 26 to 43 %.¹⁵⁸

Scheme 3.26. Benzannulation of Propargylglycinate



In Scheme 3.27, the benzannulation of carbene complex **3-154** with alkyne **3-155** has been investigated.¹⁵⁸ The effects of ultrasound were evaluated. With 21 hours of heating at 55 °C the yield was 53 % of compound **3-156**. With ultrasound the reaction was done in two hours with a yield of 59 %.¹⁵⁸

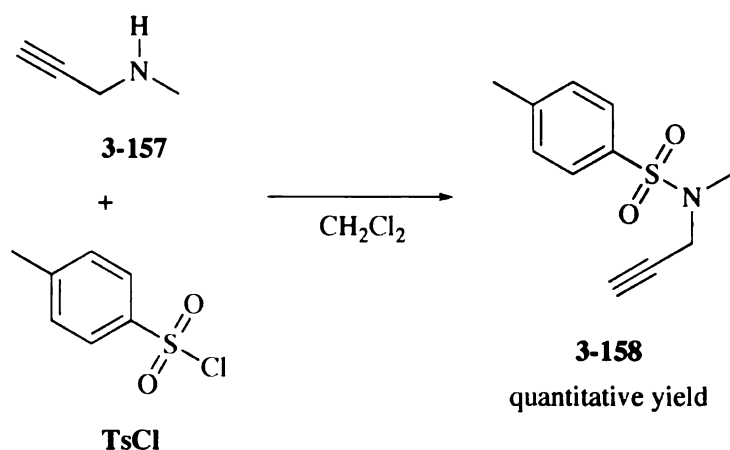
Scheme 3.27. Reported Benzannulation with Propargyl Amines



3.3 Our Explorations into the Benzannulation of Propargyl Amines.

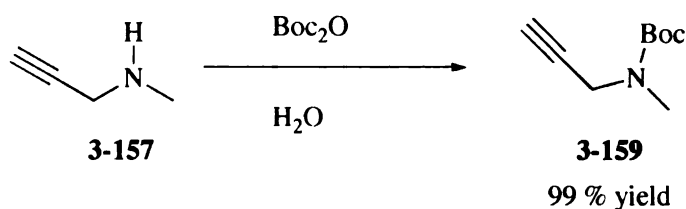
In order to study the initial requirements of the reaction between a propargyl amine and a carbene complex, we decided to construct some non-chiral propargyl amines. The tosyl protected propargyl amine **3-158** was made from commercially available N-methyl-2-propyne **3-157** in quantitative yield as a white solid. This compound has previously been reported in the literature.¹⁵⁹

Scheme 3.28. Tosylation of a Propargyl Amine



The Boc protected propargyl amine could also be constructed easily from the N-methyl-2-propyne **3-157**. This also proceeded in good yields to compound **3-159**. This compound has previously been reported in the literature.¹⁶⁰

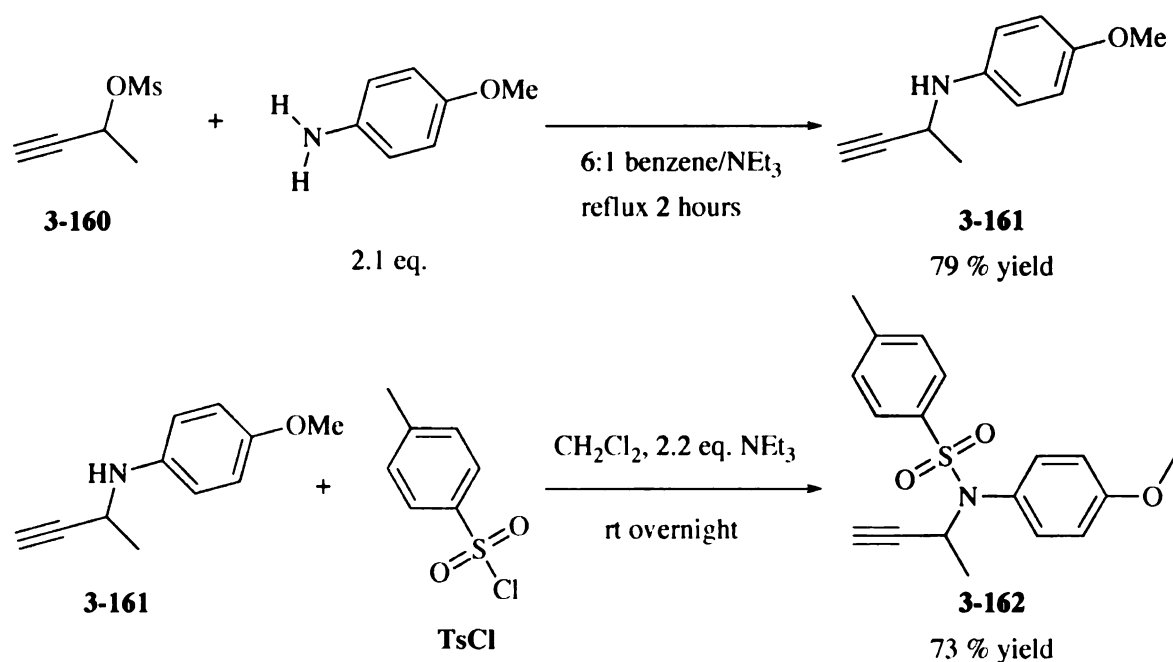
Scheme 3.29. Boc Protection of a Propargyl Amine



Attention was then turned to making propargyl amines with chiral centers. One of these could be made by the treatment of a commercially available

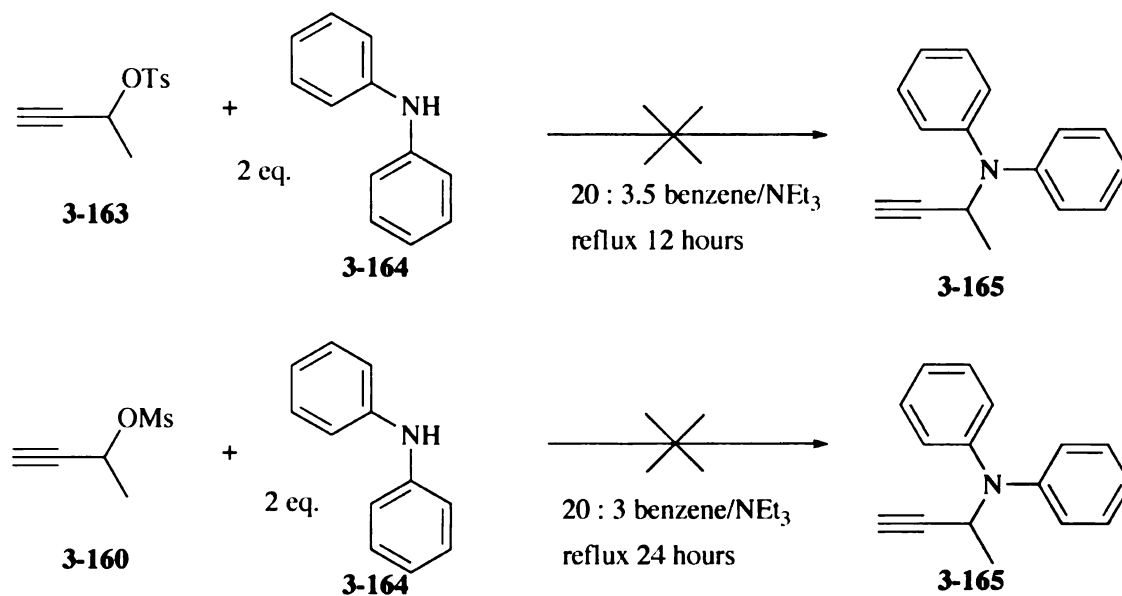
propargyl alcohol with mesyl chloride. The mesylate **3-160** could then be treated with anisidine to make the propargyl amine **3-161**. The S_N2 is known to proceed with inversion. The propargyl amine **3-161** could in turn be treated with tosyl chloride to give the desired propargyl amine **3-162**.¹⁶¹

Scheme 3.30. Synthesis of a Racemic Propargyl Amine



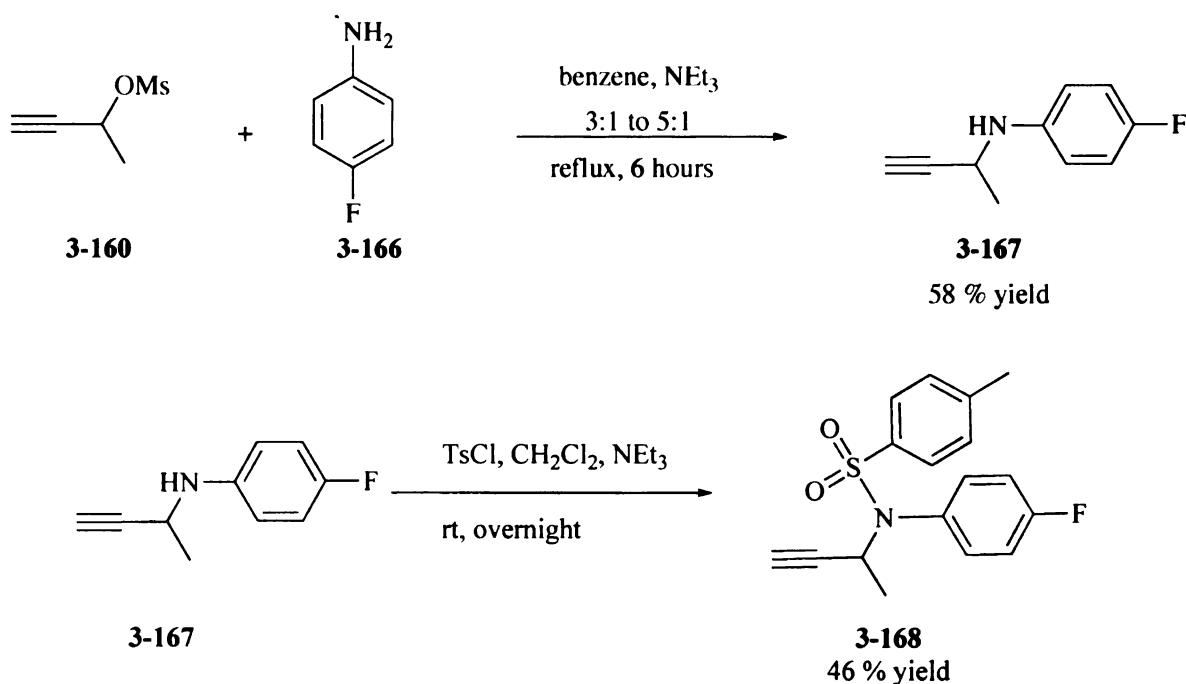
Attempts to form *N,N*-diphenyl-2-amino-3-butyne **3-165** failed via a simple S_N2 reaction between compound **3-163** and compound **3-164**. In a similar fashion, the mesylate **3-160** failed to give the desired compound **3-165**. This was most likely due to steric interactions during the S_N2 reaction from the bulky benzene rings which made diphenylamine **3-164** less nucleophilic.

Scheme 3.31. Attempted Formation of Propargyl Amine from Diphenyl Amine



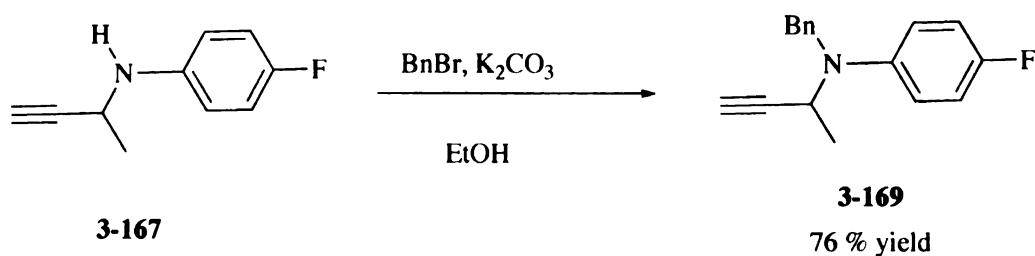
Derivatives of the propargyl amines can be made with mono-aryl anilines. In this case, 4-fluoroaniline **3-166** was treated with the mesylate **3-160**. The yield was 58 % for the S_N2 reaction giving compound **3-167**, and the tosylation proceeded in 46 % yield giving compound **3-168**.¹³¹

Scheme 3.32. An S_N2 Reaction with 4-Fluoroaniline



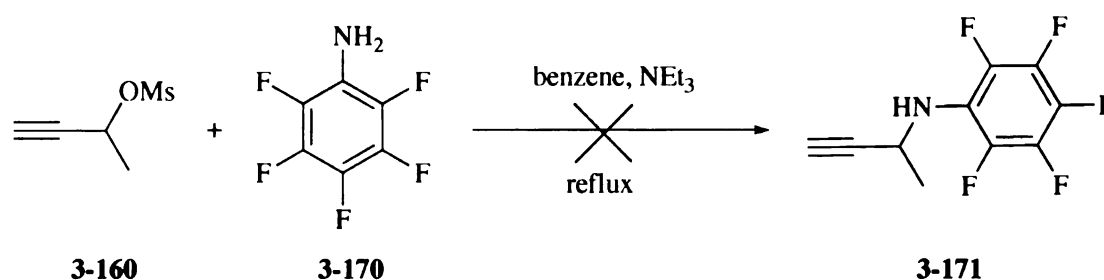
The benzylation of compound **3-167** proceeded in a yield of 76 % for compound **3-169** shown in Scheme 3.33. However, the benzannulation only gave a 23 % yield and diastereoselectivity of 70 : 30 shown in Table 3.1. The benzannulation will be discussed in greater detail in relation to Scheme 3.1. A better yield was anticipated because the eliminated product should have been disfavored due to the eliminated anion not being stabilized.

Scheme 3.33. Benzyl Protection of a Propargylamine



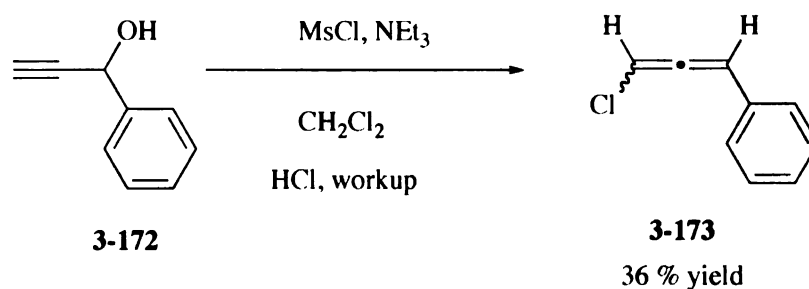
A substrate that did not give a propargyl amine is shown in Scheme 3.34. The aniline **3-170** was simply too electron withdrawing to undergo an S_N2 reaction to give compound **3-171**.

Scheme 3.34. Attempted Formation of Penta-Fluorobenzene Containing Propargyl Amine



Another substrate that failed to give propargyl amine via a mesylation procedure was the alcohol **3-172**. Attempted formation of the mesylate resulted in the formation of allene **3-173**.¹⁶²

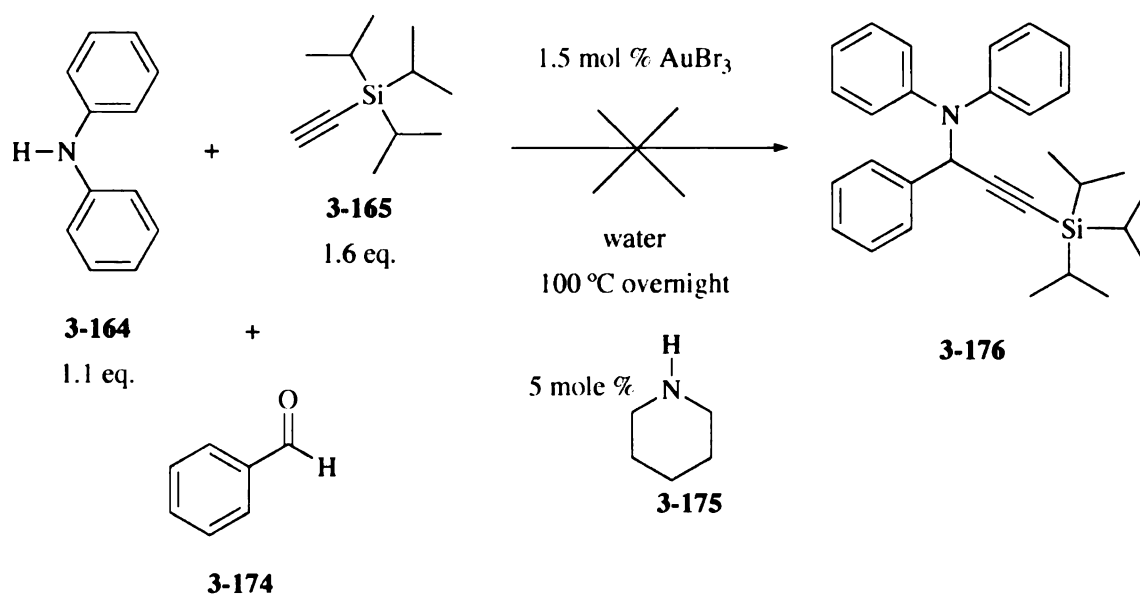
Scheme 3.35. Allene Formation



Gold catalyzed formation of propargyl amines also was tried for the formation of *N,N*-diphenyl propargyl amines such as compound **3-176**.¹⁵² A flask was charged with compounds **3-174**, **3-164**, and **3-165** with AuBr₃ and piperidine and heated overnight at 100 °C.¹⁵² This did not work for these substrates even

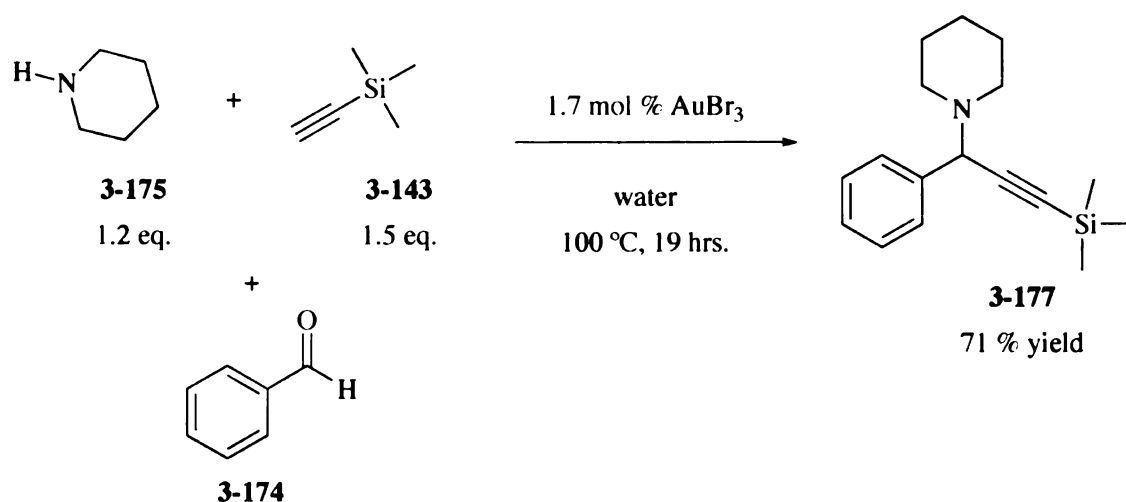
when catalytic amounts of piperidine **3-175** were added as shown in Scheme 3.36. It has been reported in the literature that this type of reaction fails with diphenylamine.¹⁵²

Scheme 3.36. Attempted Formation of Propargyl Amine From Diphenyl Amine



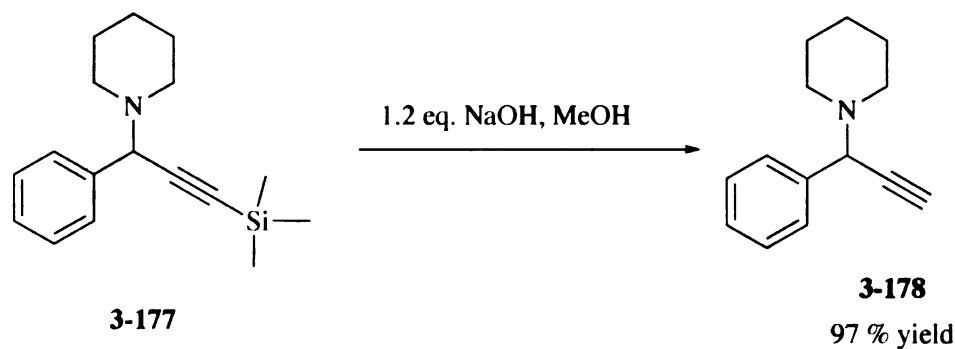
When piperidine was used as a substrate, the reaction proceeded in good yield to give compound **3-177**. This reaction is shown in Scheme 3.37 involving **3-157**, **3-143**, and **3-174**.

Scheme 3.37. Three Component Coupling to Form Propargyl Amines



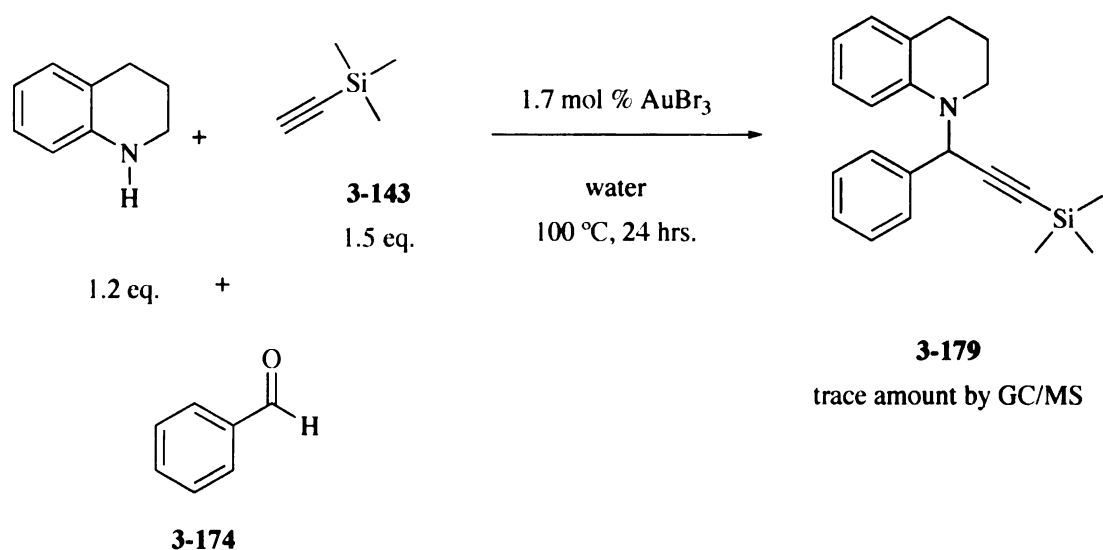
The TMS acetylene **3-177** could be easily deprotected with sodium hydroxide in methanol. The yield of the yellow oil shown as compound **3-178** was 97 %.

Scheme 3.38. Deprotection of Silyl Protected Alkyne



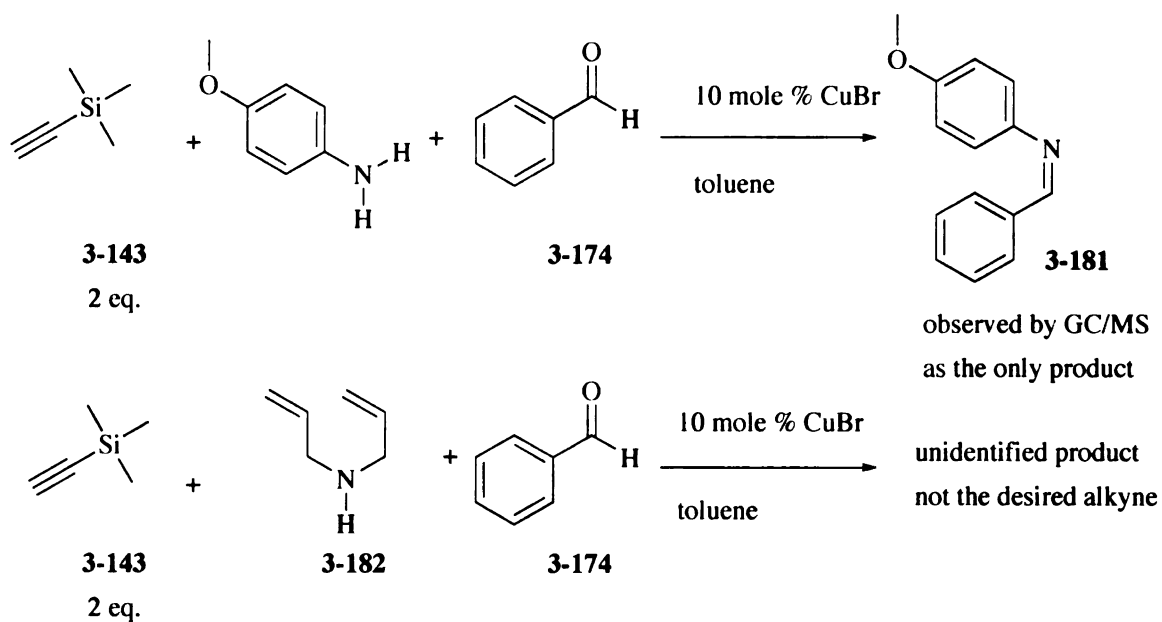
Unfortunately the reaction with gold tribromide appears to have limited scope. The application to more sterically hindered substrates such as tetrahydroquinoline, benzaldehyde, and TMS acetylene in Scheme 3.39 gave low yields of the desired propargyl amine **3-179**.

Scheme 3.39. Attempted Three Component Coupling



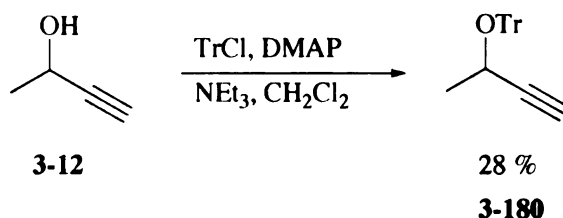
The copper bromide catalysis was pursued as shown in Scheme 3.40. However for the amines anisidine and **3-182** with alkyne **3-143** and aldehyde **3-174**, no product formation was detected by GC/MS or NMR. Only a compound that corresponded to **3-181** was found by GC/MS.

Scheme 3.40. Other Failed Three Component Couplings



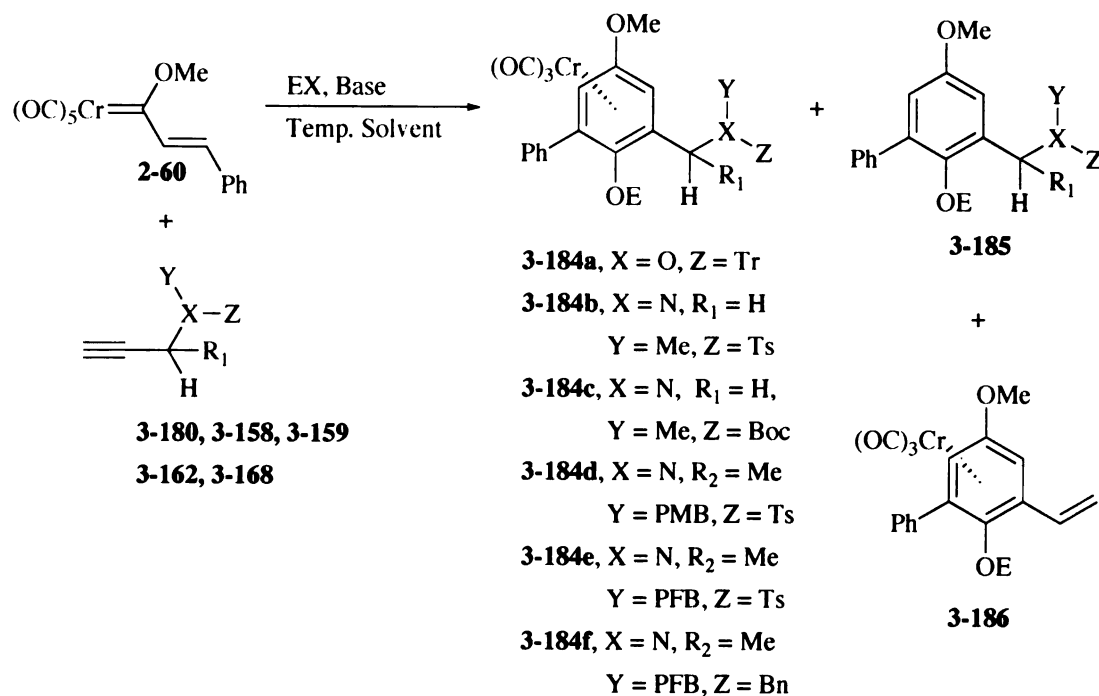
The tritylether **3-180** was prepared for purposes of providing a control experiment for the benzannulation of propargyl amines. The alkyne **3-12** was treated with trityl chloride and base to give compound **3-180** in 28 % yield.

Scheme 3.41. Trityl Protection of a Propargyl Alcohol



Shown in Table 3.1 are the results of the benzannulation reactions between carbene complex **2-60** and propargyl alcohols and amines. These reactions produced the chromium tricarbonyl arene complexes **3-184**. Compounds **3-184a** through **3-184g** were moderately unstable and did not lend themselves well to characterization.¹⁶³ The yield for compound **3-184a** in entry 1 was 93 % from the propargyl alcohol **3-180**. The yield for compound **3-184b** shown in entry 2 was 87 % from compound **3-158**. In entry 3, the yield was 60 % for compound **3-184c**. The yield for compound **3-184d** was 31 % with a dr of 74 : 26 in toluene. The yield and dr could be improved in dichloromethane for entries 5 - 7 for compound **3-184d**. In entry 8 and 9, the alkyne **3-168** was explored for the benzannulation giving **3-184e** with yields of 17 %. When the less electron withdrawing substituent benzyl replaced tosylate, the apparent diastereomeric ratio dropped to 70 : 30 by NMR (entries 9 and 10).¹⁶⁴

Table 3.1. Benzannulation of Propargyl Amines



entry ^a	R ₁	X	Y	Z	Comp.	Temp.	Time.	Solv.	Yield 3-184 % ^b	dr
1	Me	O	Ip	Trityl	3-180	60	12	DCM	93	94:6
2	H	N	Me	Ts	3-158	80	3	toluene	87	n/a
3	H	N	Me	Boc	3-159	80-105	0.75	toluene	60	n/a
4	Me	N	PMB	Ts	3-162	60	24	toluene	31	74:26
5	Me	N	PMB	Ts	3-162	60	24	DCM	24	≥ 96:4

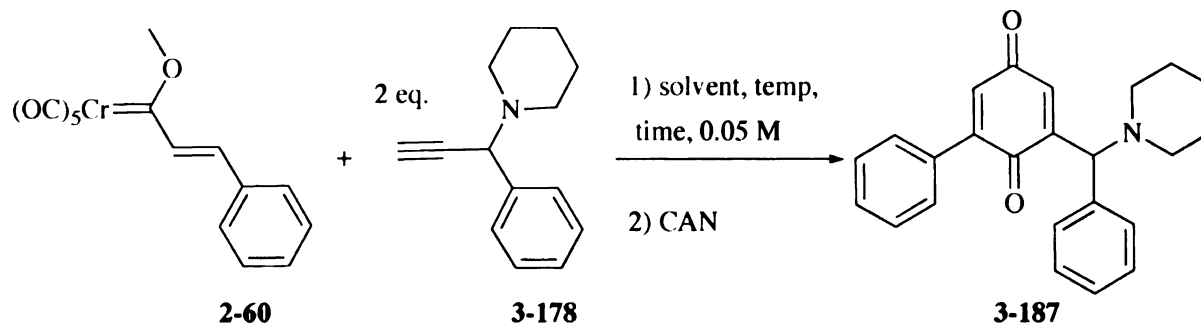
Table 3.1 (cont'd)

6 ^c	Me	N	PMB	Ts	3-162	60	16	DCM	13	≥ 96:4
7 ^d	Me	N	PMB	Ts	3-162	60	14	DCM	35 ^e	93:7
8	Me	N	PFB	Ts	3-168	50	12	DCM	17 ^f	≥ 96:4
9	Me	N	PFB	Ts	3-168	50	26	DCM	17 ^g	≥ 96:4
10	Me	N	PFB	Bn	3-169	60	13	DCM	23 ^h	70:30

lp = lone pair. PMB = *p*-methoxybenzene. PFB = *p*-fluorobenzene a. Typical reaction conditions were 3 eq. TBSCl, 5 eq., Hunig's base, and 0.03 M in carbene complex. b. Demetalated material **3-185** was found in 1 to 10 % yield. c. TBSCl (3 eq.) and Hunig's Base 1.1 eq. d. Used 1.5 eq. TBSOTf and 1.5 eq. lutidine. e. In addition, a 14 % yield of compound **3-186** was found. f. In addition, a 21 % of yield of compound **3-186** was found. g. In addition, a 48 % yield of compound **3-186** was found. h. A 38 % yield of compound **3-186** was found.

In Table 3.2, the results of the optimization experiments are shown for the reaction of carbene complex **2-60** and propargyl amine **3-178** giving the product **3-187**. In entry 1, the best yield of compound **3-187** was obtained and was 62 %.¹⁶⁵ In entries 2 and 3, the yields were 51 % for 1,2-dichloroethane and 60 % yield in toluene. The yields drop off at 80 °C in entries 4 and 5 into the low 30's. At 60 °C in entries 6 and 7, the yields are 29 and 22 for 1,2-dichloroethane and toluene respectively. In entries 8 and 9, the yield for dichloromethane was 22 %, and under a carbon monoxide atmosphere, the yield was 17 % of compound **3-187**.

Table 3.2. Optimization of Benzannulation of Propargyl Amines



entry	Solvent	Temperature, °C	Time	yield, % ^a
1	toluene	100	13 min.	62
2	1,2-dichloroethane	90	20 min.	51
3	toluene	90	20 min.	60
4	1,2-dichloroethane	80	1 hr	34
5	toluene	80	1 hr	32
6	1,2-dichloroethane	60	12 hrs	29
7	toluene	60	12 hrs	22
8	CH ₂ Cl ₂	60	12 hrs	22
9	CH ₂ Cl ₂ (1 atm CO)	60	12 hrs	17

a. Trace amounts of phenol were detected.

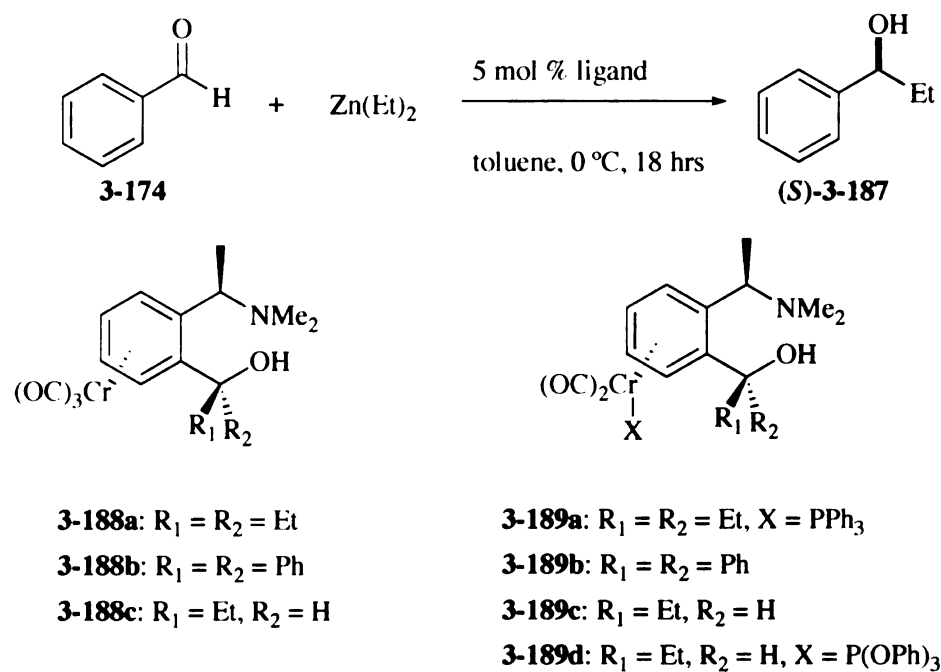
In conclusion, good diastereoselectivities (up to 96 : 4) could be obtained from propargyl amines to form chromium tricarbonyl arene complexes. Electron-donating substituents on nitrogen resulting in lower yields of the chromium tricarbonyl arene complex and lower diastereoselectivity. Elimination of the amine motif to form olefin **3-186** was problematic. This elimination process will be discussed further in chapter four. Further work is required to optimize the reaction conditions.

3.4 Future Work

It is known from the work of Uemura and coworkers¹⁶⁶ that the use of chiral chromium tricarbonyl arenes as ligands for the addition of diethyl zinc to benzaldehyde proceeds in high yield and good enantioselectivity as shown in Table 3.3. When R_1 and R_2 were hydrogen for the chromium tricarbonyl complex **3-188**, the yield was 70 % and the enantiomeric excess was 15 %.¹⁶⁶ The yields shown in entries 1 - 7 were 83 to 99 percent and the enantiomeric excesses were 93 to 97 %. The configuration was *S* for compound **3-187**.¹⁶⁶

Table 3.3. Chiral (η^6 -Arene)chromium Complexes For Diethyl Zinc

Addition to Benzaldehyde

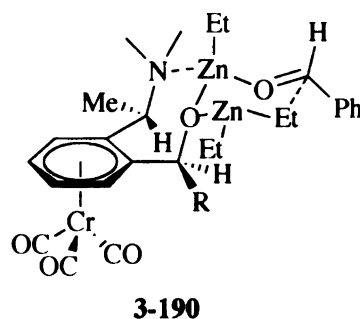


entry	catalyst	yield (%)	ee (%)
1	3-188a	89	95
2	3-188b	83	93
3	3-188c	87	93
4	3-189a	99	97
5	3-189b	99	94
6	3-189c	96	97
7	3-189d	97	96

In Figure 3.1, the proposed transition state for the addition of diethyl zinc to benzaldehyde is shown as compound **3-190**.¹⁶⁶ The proposed mechanism is

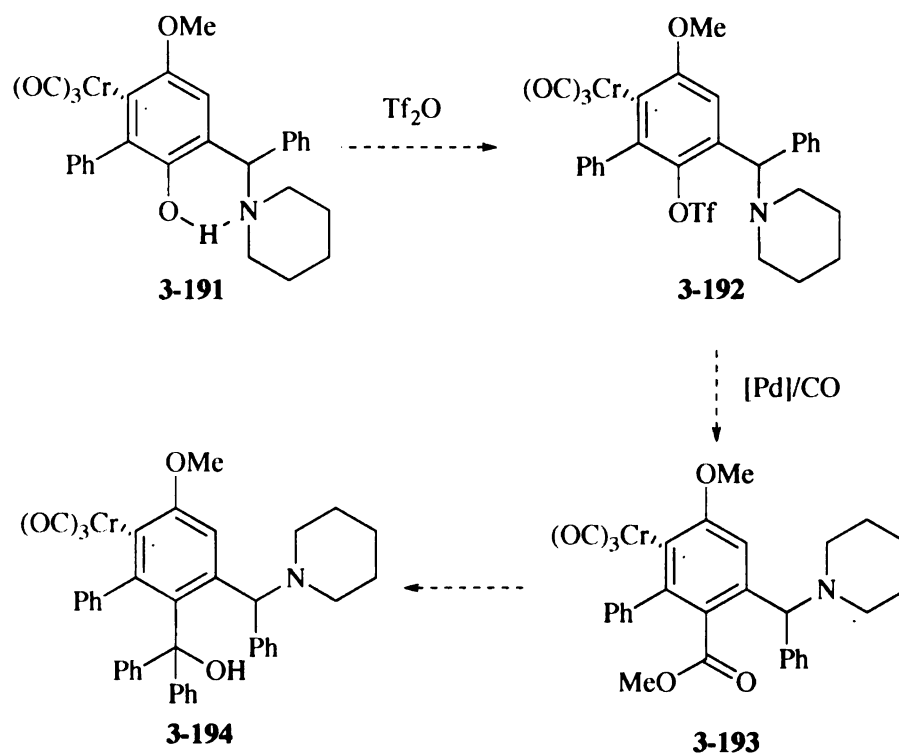
bimolecular in zinc, and the nitrogen and oxygen are oriented exo to the chromium tricarbonyl. The addition of the ethyl group proceeds through a chair like transition state.¹⁶⁶

Figure 3.1. Proposed Transition State for Ethyl Zinc Adding to Benzaldehyde



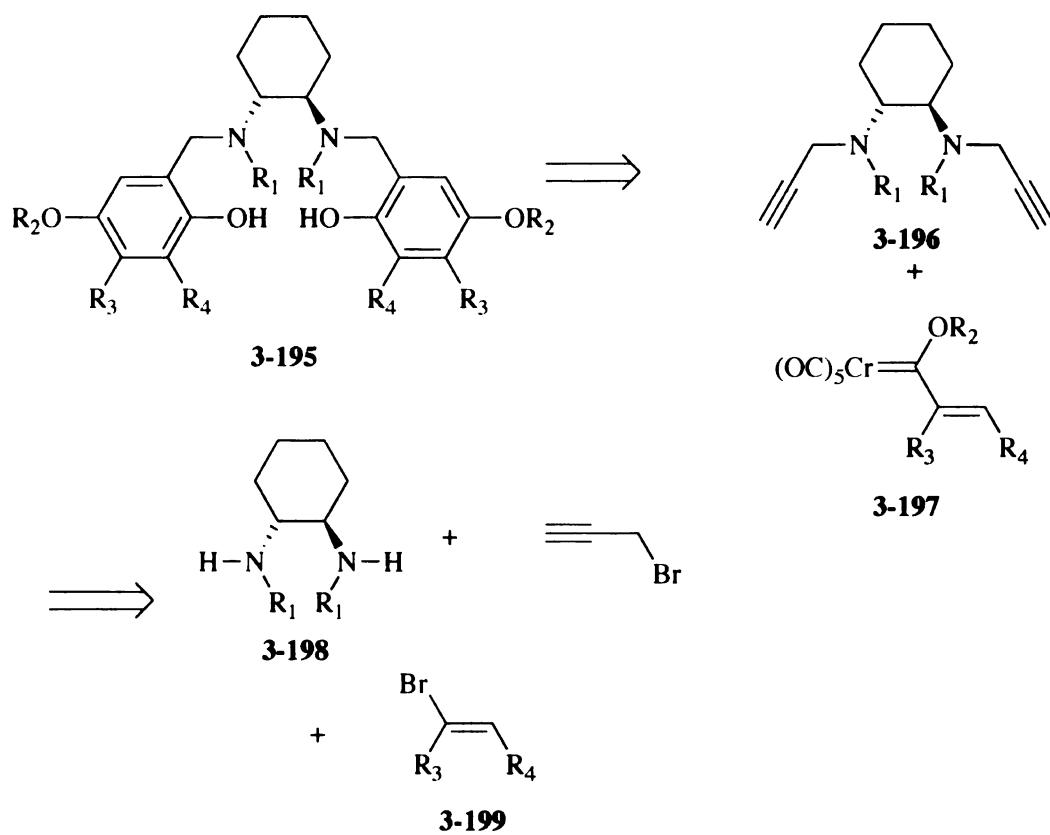
With the reactions shown in Table 3.1, the construction of similar ligands from compound **3-194** or compound **3-191** could be imagined directly as shown in Scheme 3.42.¹⁶⁷ With triflation, compound **3-192** could be obtained. Palladium carbonylation would give compound **3-193**.¹⁶⁸ Addition of a nucleophile such as phenyl magnesium bromide or phenyl lithium would give compound **3-194**.¹⁶⁶ These ligands could then be applied to furyl zinc addition or tested with diethyl zinc. This would be a convenient test case because we have the starting materials in hand to test the coupling reactions and the Grignard addition.¹⁶⁹ One problem with the proposed ligand **3-194** is that currently for the shown substituents there does not exist good methodology for the preparation of the concomitant chiral propargyl amines.¹⁷⁰

Scheme 3.42. Proposed Synthesis of a Ligand Resulting from a Benzannulation



One also could construct ligands of the type shown in Scheme 3.43.¹⁷¹ These would be mimics of the salen type ligands which have been used for the addition of organozincs to aldehydes.¹⁷² Compound **3-195** could be derived from the bis-propargyl amine **3-196** and carbene complex **3-197**. The bis-propargyl amine **3-196** could be derived from the commercially available diamine **3-198** and propargyl bromide,¹⁷³ and the carbene complex **3-197** could be derived from the vinyl bromide **3-199**.¹⁷⁴ A drawback to proposed ligand **3-195** would be the potential β -hydride elimination α to the nitrogen however with alkyl zincs this has not been reported as a problem.

Scheme 3.43. Ligand Formation Derived from Diamines



CHAPTER FOUR

DIELS-ALDER AND ELECTROCYCLIZATION REACTIONS IN TANDEM WITH THE BENZANNULATION REACTION

4.1. Antimalarial Aspects

In the world, 2.7 million will die this year (2007) alone from malaria.¹⁷⁵ Malaria is an infectious disease with 400 to 900 million new cases a year worldwide, and most of these cases are in the developing world. An average of one thousand cases annually are reported in the United States. A female mosquito of the genus *Anopheles* transmits the disease.¹⁷⁶ The disease is caused by the one-celled parasite of the genus *Plasmodium* which has hundreds of species infecting many host organisms.¹⁷⁷ Four species of *Plasmodium* infect humans: *Plasmodium vivax*, *Plasmodium falciparum*, *Plasmodium malariae*, and *Plasmodium ovale*. The symptoms include sweating, fever, chills accompanied by headache, and nausea. The attacks may reoccur on a regular basis.¹⁷⁷

The most prevalent form (*Plasmodium vivax*) causes the mildest form called tertian malaria. Every second day a fever reoccurs. The incubation period is two weeks.¹⁷⁷ *Plasmodium falciparum* is responsible for "jungle fever" (malignant tertian malaria) and it is responsible for the majority of deaths.¹⁷⁷ The

mortality rate is 25 to 50 % if untreated and death usually results in 24 to 72 hours. The usual victims are children under the age of ten.¹⁷⁷ The mechanism of the induction of fever, convulsions, and "drunk like state" is not entirely understood.¹⁷⁷ Two hypotheses have been proposed. The first being the mechanical hypothesis which states the interactions of *P. falciparum* (or infected red blood cells) and endothelial cells reduces macrovascular blood flow in the brain. This hypothesis has been substantiated by observation of restricted blood flow and congestion of red blood cells in the macrovascular regions of the brain. This theory is further substantiated by the recent discovery that West Africans with the variant hemoglobin C are protected from severe malaria.¹⁷⁸ It is believed that hemoglobin C prevents the expression of the protein PfEMP-1 on the cell surface of the host blood cells. Therefore, hemoglobin C can suppress the development of severe malaria by as much as 80 %.¹⁷⁸

However, this hypothesis does not explain why damage to the brain is not permanent.¹⁷⁷ Hypoxia resulting from this hypothesis should cause long lasting damage to the brain, however patients fully recover even from deep coma resulting from malaria.¹⁷⁸ A second hypothesis states the "malarial toxins" promotes the release of cytokines which induce the uncontrolled production of nitric oxide that has the same effects as anesthesia or ethanol.¹⁷⁹

Plasmodium malariae causes quartan malaria with attacks reoccurring every third day. The incubation period is 18 to 40 days. The rarest form of malaria, similar to the benign tertian malaria form, is caused by *Plasmodium ovale*.¹⁷⁷

There are many phases to the life cycle of the malaria parasite. When a form of the parasite enters a female mosquito, the first cycle of the life of the parasite begins. The parasite matures in the midgut of the mosquito. An adapted form of the parasite enters the body cavity of the mosquito. These forms of the parasite work their way to the salivary glands and ultimately into the saliva of the mosquito making it infectious to humans.

A vertebrate organism is bitten by a mosquito. Through this bit the sporozoites of malaria enter the circulatory system. The organism takes up habitation in a host's tissue, where it develops within a single host cell.¹⁷⁹ The type of cells in which this occurs depends on the type of malaria. The parasite transforms from one that lives in a poikilothermic (cold-blooded) insect into one that lives in a warm-blooded vertebrate during its life cycle.¹⁷⁹

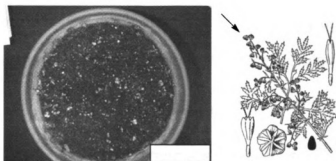
The parasite *Plasmodium* takes up habitation in the lymphoid macrophage system. It is ironic that this is the same system responsible for the removal of parasites. The host is unable to detect the infection and therefore not able to defend against it.¹⁷⁹

A patient's travel history is used to diagnose the disease. The identification of the parasite is confirmed by blood smears.¹⁷⁷

Chloroquine has been the staple treatment of malaria. The parasite has become resistant to chloroquine, which has presented serious problems. In Thailand, the resistant strains were first detected in 1957 and then moved through India in the 70's.¹⁷⁵ They were found to have moved north into the Mediterranean in the 80's and from Thailand through Southeast Asia. The resistant strain moved from India to east Africa in 1978 and then on to North Africa in the 80's. Resistant strains of Plasmodium have been found in Latin America and South America. Genetic mapping has confirmed the origins of the resistant Plasmodium.¹⁸⁰

The current recommended method of treatment is with artemisinin-based combination therapy (ACT).¹⁸¹ Usually this is a mixture of an artemisinin derivative and lumefantrine. The concentration of artemisinin based compounds decrease to almost zero after one hour in the body therefore a second drug is combined with these artemisinin compounds.¹⁸² The source of artemisinin can be grown in the United States and the plant is *Artemisia annua* which is shown in Figure 4.1.

Figure 4.1. *Artemisia annua* or Sweet Wormwood Grown in Dr. Wulff's Laboratories



4.2. Antibiotics Discussion

With the growing threat of drug resistant organisms, new antibiotics would be desirable.¹⁸³

It is a balancing act creating new antibiotics.¹⁸⁴ One must target specific chemoreceptors in parasites where the chemical agent must bond. Several compounds have this binding effect but the substance must also possess a group that destroys the bacteria or parasite.¹⁸³ Obviously the compound must not destroy the infected host. This depends on whether the compound is more toxic to the parasite or the host. If the chemical is too toxic to the host, the host perishes. The infection is not cured if the chemical is not potent enough to the parasites.¹⁸³

Another criteria for a good drug are both water and fat solubility because the drug needs to pass through cell membranes and intestinal linings. A drug candidate needs to be water-soluble because blood and intracellular fluid transports it to the target site or target organism. A parameter called partition

coefficient (log P) between octanol and water can be estimated for molecules by calculation.¹⁸⁵ The Lipinski's rule¹⁸⁶ of five for drug likeness state (1) a drug should not have more than five hydrogen bond donors, (2) a drug should not have more than ten hydrogen bond acceptors, (3) the molecular weight should not be greater than 500, and (4) the Log P_{oct/water} should not be greater than 5. The substructures usually have known pharmaceutical activity.¹⁸⁷ Of course the drug should be a stable compound with good shelf life preferable in perpetuity at room temperature.

Five actions of antibiotics are known. These disinfectants effect (1) metabolism, (2) protein synthesis, (3) bacterial membranes or membrane synthesis, (4) nucleic acid metabolism, and (5) peptidoglycan synthesis. If any processes needed for the functioning of the parasite is disrupted, the parasite will expire.

4.3. Historical Background of Malaria

The disease malaria has been with mankind since at least the time of the Roman Empire. The armies of Rome were devastated by malaria. The Italians associated the symptoms of this condition with "mal aria" or bad air commonly found around areas such as marshes and swamps. In 1880, the *Plasmodium* parasite was discovered which in turn was linked with malaria. It took 18 more years to identify the *Anopheles* mosquito as the transmitter of the disease. The United States has had no escape from malaria. As late as 1914, it is estimated that 600,000 cases of malaria still occurred within the U.S. borders.¹⁷⁹ In every

great war the United States was involved, malaria played an important factor. It has been stated that during World War II and the Vietnam war more time was lost to malaria than to bullets.

From the year 1970 to 1997 the infection rates in sub-Saharan Africa have increased by 40 percent.¹⁸⁸ In south-east Asia the cases of malaria have also increased in the last decade.¹⁸⁹ With global warming, this is likely to continue to increase unless significant resources become available to disaffect this increase. This has been due to the resistance of the mosquito population to insecticides and the resistance of the *Plasmodium* parasite to chloroquine, which has been the mainstay drug for the treatment of malaria.¹⁷⁹

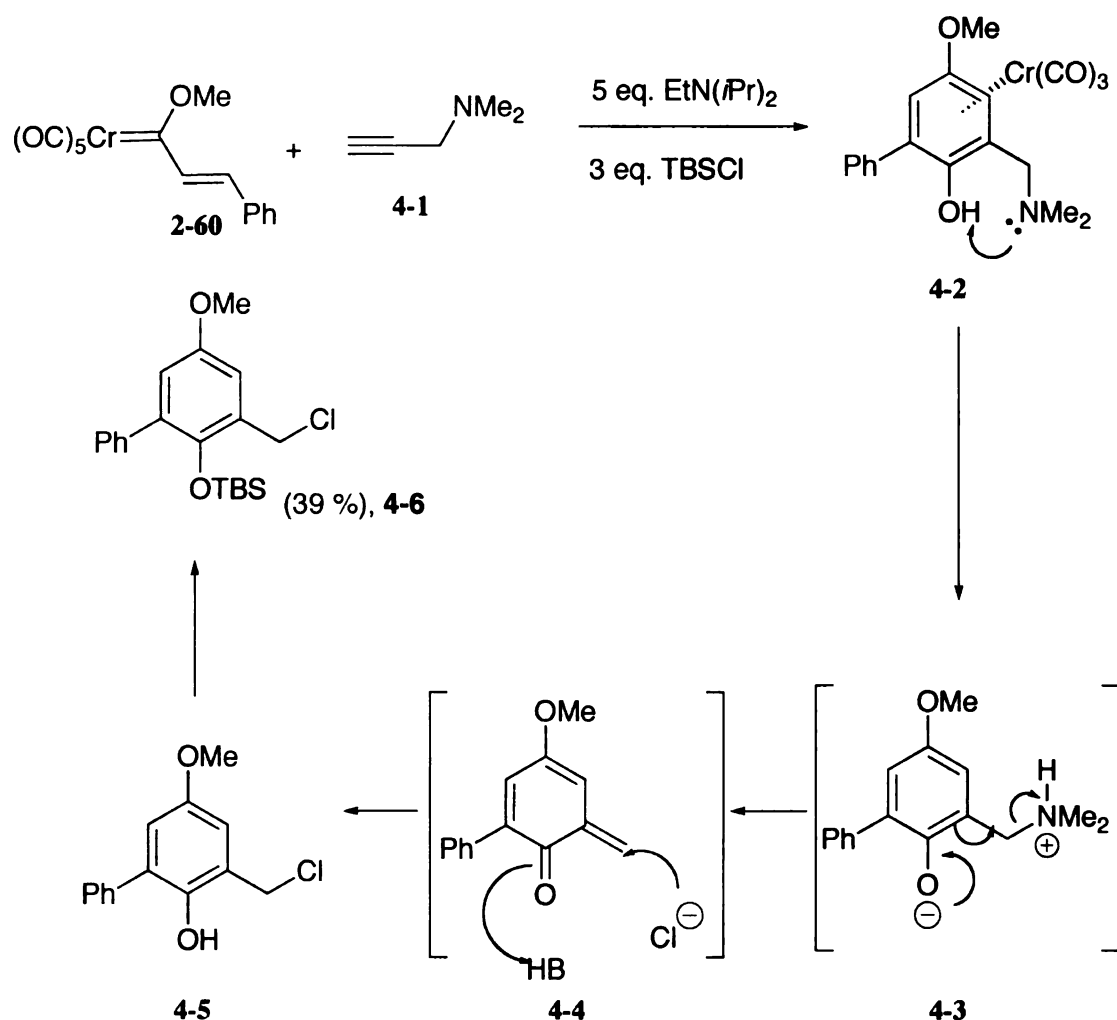
We recently discovered a unique reaction involving the formation of an α -quinone methide. We were looking for ways to utilize this reaction, and we discovered compounds, which were screened against a malaria parasite, containing a 6-6-6-member ring system that we could access with our methodology. In this context, synthetic approaches of compounds toward the treatment of malaria was begun.

4.4 Initial Studies of *Ortho*-Quinone Methides

An unexpected result from the studies of the benzannulation of the propargyl amines was the formation of the chlorinated phenol **4-6** obtained during the course of the study of the reaction shown in Scheme 4.1. The formation of **4-6** is proposed to proceed by the benzannulation reaction to give compound **4-2**, which in the presence of base forms the *ortho*-quinone methide **4-4** through

intermediate **4-3**.¹⁹⁰ Chloride then nucleophilically attacks the vinyl carbon with concomitant rearomatization via phenoxide formation to give **4-5**. The resulting phenol is then protected by *t*-butyldimethylsilyl chloride to form the indicated silyl ether in 39 % yield (**4-6**).¹⁹¹ The chromium tricarbonyl motif is lost during the reaction however it remains unclear at what step in the mechanism this occurs.

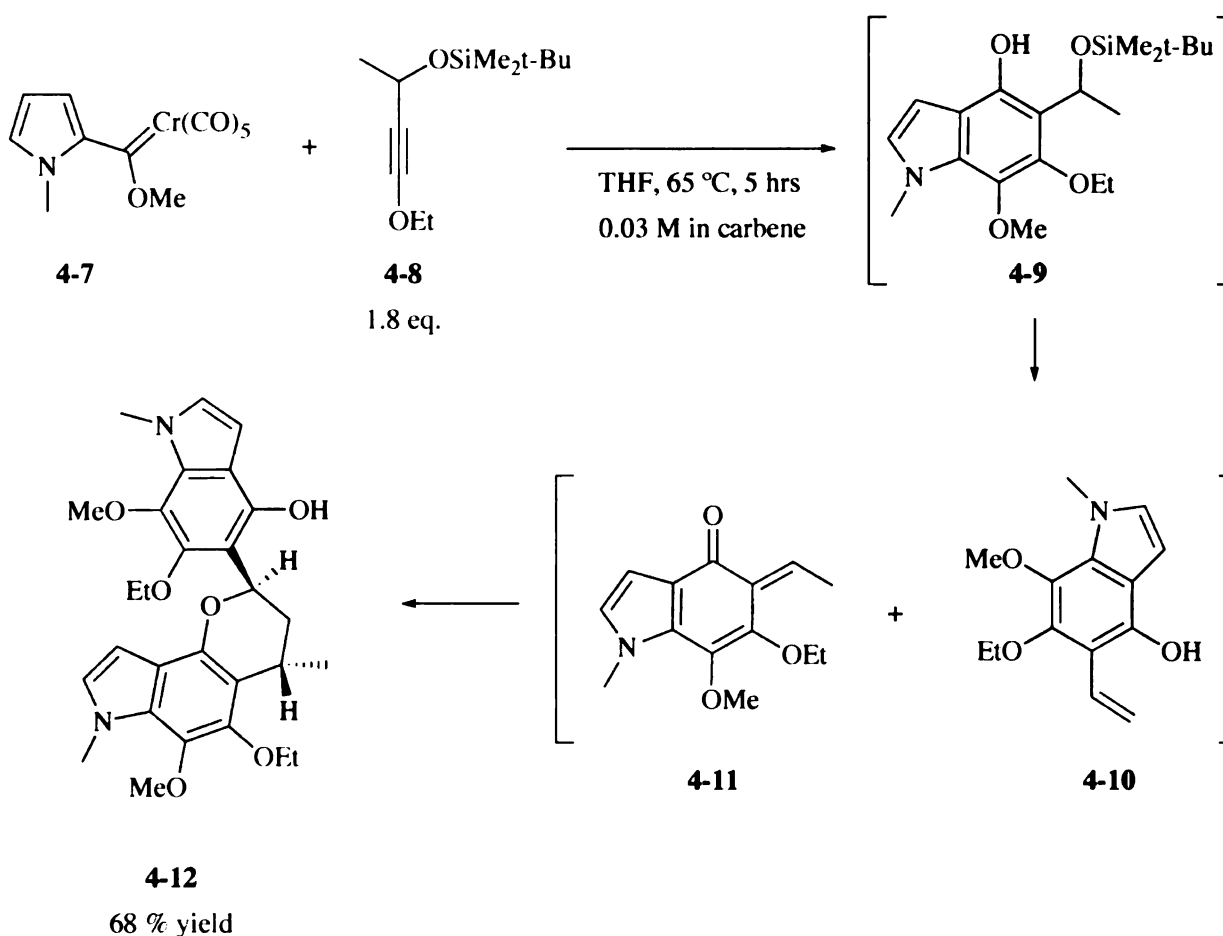
Scheme 4.1. Proposed Mechanism of the Formation of Chlorinated Silyl Protected Phenol



The only report of the formation of an *ortho*-quinone methide from the reaction of a carbene complex and an alkyne was by Yamashita.¹⁹² Shown in

Scheme 4.2 is the benzannulation between compound **4-7** and compound **4-8**. This forms the phenol **4-9** which undergoes elimination to form intermediates **4-10** and **4-11**.¹⁹² Intermediates **4-10** and **4-11** then undergo a Diels-Alder reaction to form compound **4-12**.¹⁹²

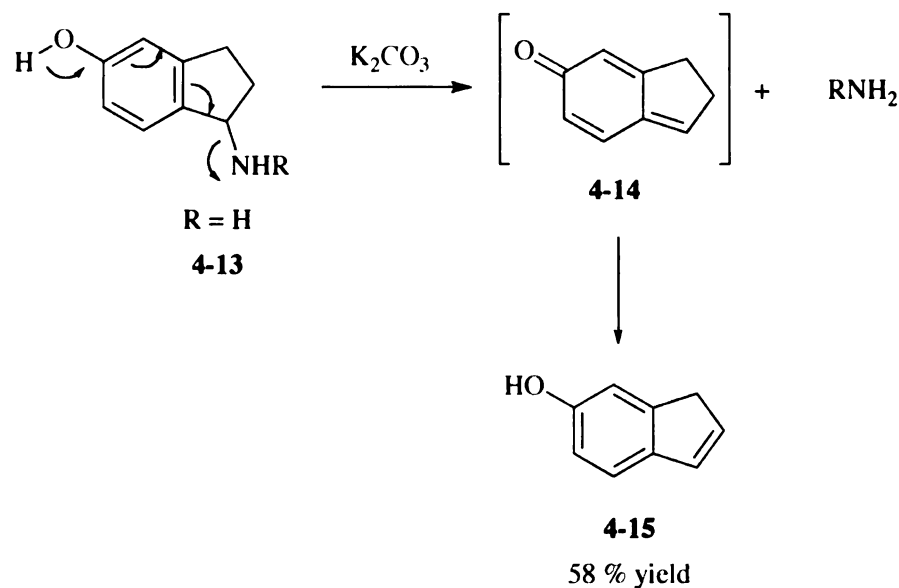
Scheme 4.2. Formation of *o*-Quinone Methides From a Benzannulation Reaction



Other unexpected formations of quinone methides have been reported from the loss of an amine group.¹⁹⁰ Shown in Scheme 4.3, the treatment of compound **4-13** with potassium carbonate gives the intermediate **4-14** with

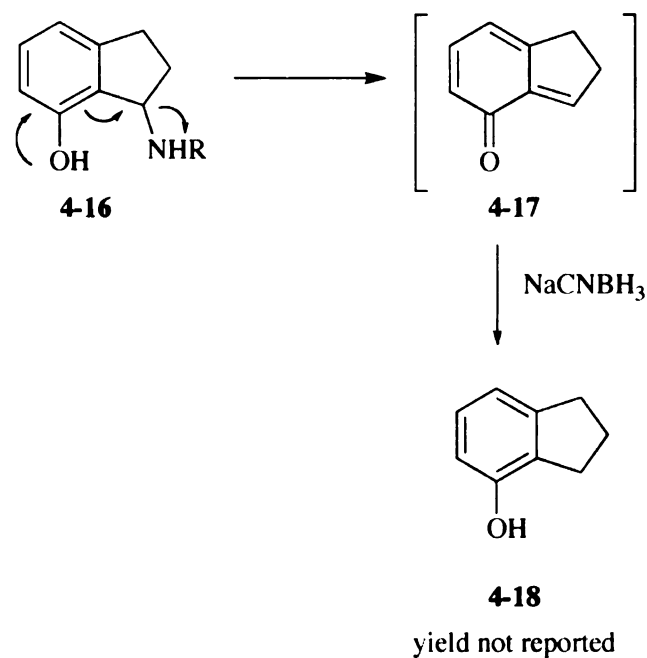
expulsion of RNH_2 and with rearrangement, compound **4-15** is obtained in 58 % yield.¹⁹⁰

Scheme 4.3. Formation and Rearrangement of *Para*-Quinone Methide



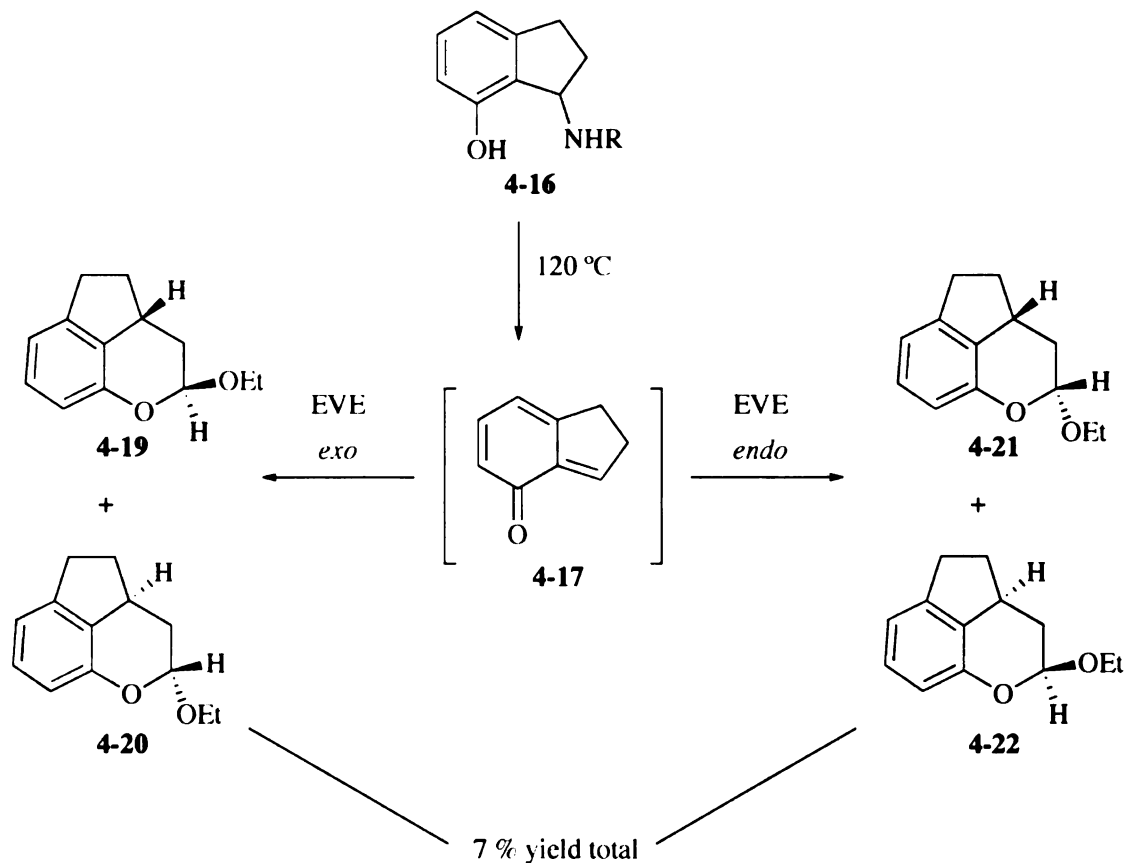
The formation of *ortho*-quinone methides by amine loss have also been observed.¹⁹⁰ From compound **4-16** (7-hydroxy-1-aminoindans), the intermediate **4-17** could be reduced with NaCNBH_3 to compound **4-18** as shown in Scheme 4.4. The yield was not reported.

Scheme 4.4. Formation and Reduction of *Ortho*-Quinone Methide.



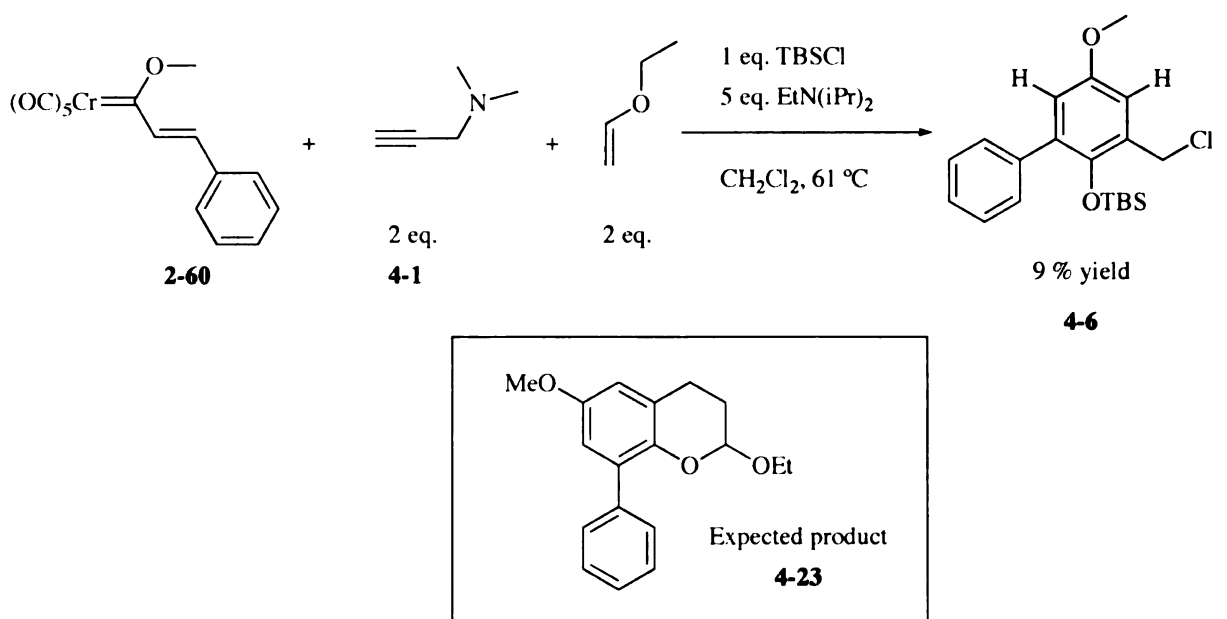
Shown in Scheme 4.5, compound **4-16** could be heated at $120\text{ }^{\circ}\text{C}$ to give intermediate **4-17** which could be trapped by ethyl vinyl ether (EVE) in 7 % yield to give compounds **4-19**, **4-20**, **4-21**, and **4-22** which were isolated as a mixture. Compounds **4-19** and **4-20** are from the *exo* approach of ethyl vinyl ether, whereas compounds **4-21** and **4-22** are from the *endo* approach. Compounds **4-19** and **4-20** are enantiomers as are compounds **4-21** and **4-22**.

Scheme 4.5. Trapping of an *Ortho*-Quinone Methide with Ethyl Vinyl Ether



As a follow up to the reaction Shown in Scheme 4.1 an attempt was made to trap the *ortho*-quinone methide **4-4** from the reaction of carbene **2-60**, propargyl amine **4-1**, and the dienophile ethyl vinyl ether in a Diels-Alder reaction but this was not successful as shown in Scheme 4.6. The reaction was carried out with 2 equivalents of the alkyne **4-1** and ethyl vinyl ether at 61 °C. The only product resolved from the complex mixture of products was **4-6**.¹⁹³

Scheme 4.6. Intermediate *o*-QM Trapping Experiment

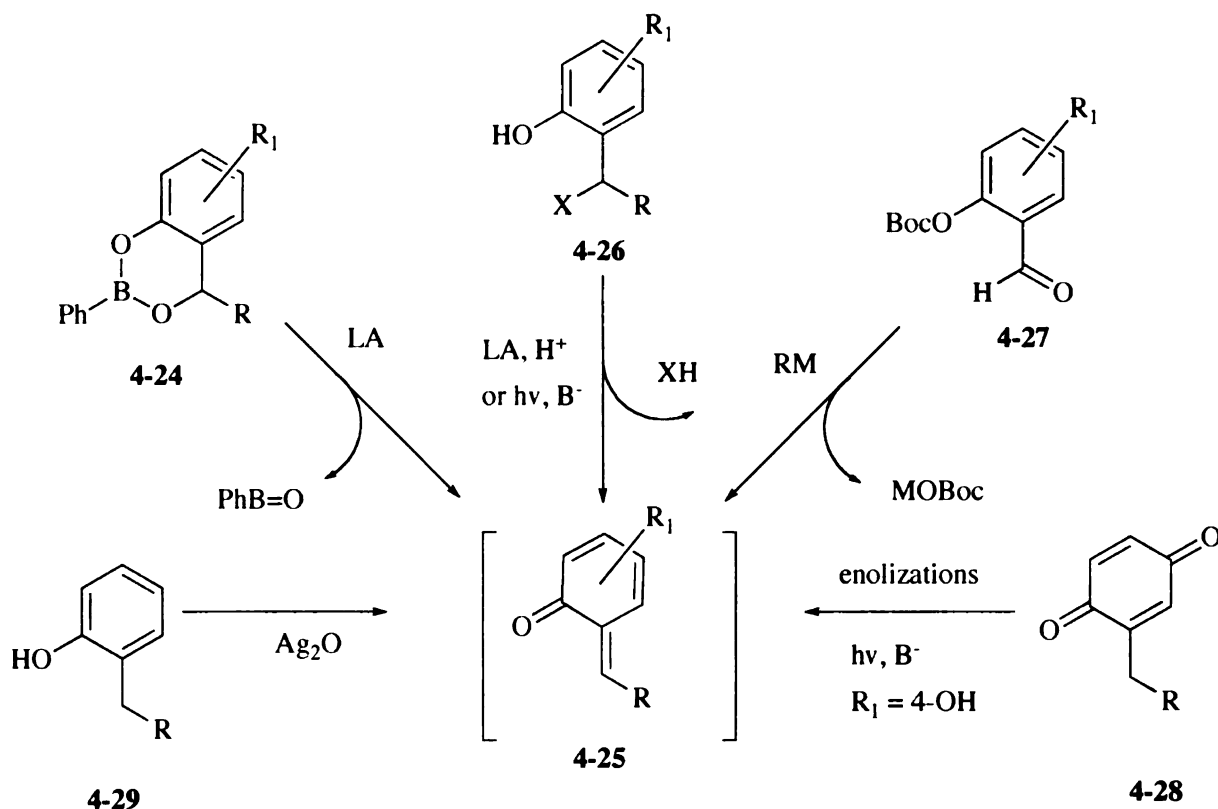


4.5 Mini-Review of *Ortho*-Quinone Methides

Ortho-Quinone methides (or *o*-QM) have been generated in situ and consumed in subsequent reactions.¹⁹⁴ They have been employed for sophisticated chemical synthesis. They are used for defense and regulation by some plants and insects by alkylating essential enzymes and DNA.¹⁹⁴ The bark and leaves of the willow tree contains salicortin which inactivates β -glucosidase enzymes of infesting organism via a quinone methide.¹⁹⁵ *Ortho*-quinone methide generation is usually the rate-determining step in the reaction.¹⁹⁶ Electron-rich dienophiles are required since *o*-QM most readily participates in inverse electron demand Diels-Alder reaction.¹⁹⁷ In 1907, the first report of the generation of an *o*-QM was made to explain the formation of dimers and trimers of *o*-QM.¹⁹⁸ Various strategies for *o*-QM generation are shown in Scheme 4.7. From

benzodioxaborins **4-24**, the *o*-QM **4-25** could be formed with a Lewis acid and heat.¹⁹⁹ In the next strategy, a leaving group such as X = OH, NR₂, Cl, or Br is used to generate the *o*-QM **4-25** from compound **4-26** either in the presence of a Lewis acid or by photolysis.^{200, 201} From *o*-Boc-salicylaldehydes **4-27**, an *o*-quinone methide **4-25** was generated by reaction with an organometallic such as a Grignard reagent.²⁰² The enolization of benzoquinone **4-28** can also form an *o*-QM **4-25**.²⁰³ The oxidation *o*-alkyl phenols **4-29** with silver oxide can also form an *o*-QM **4-25**.²⁰⁴

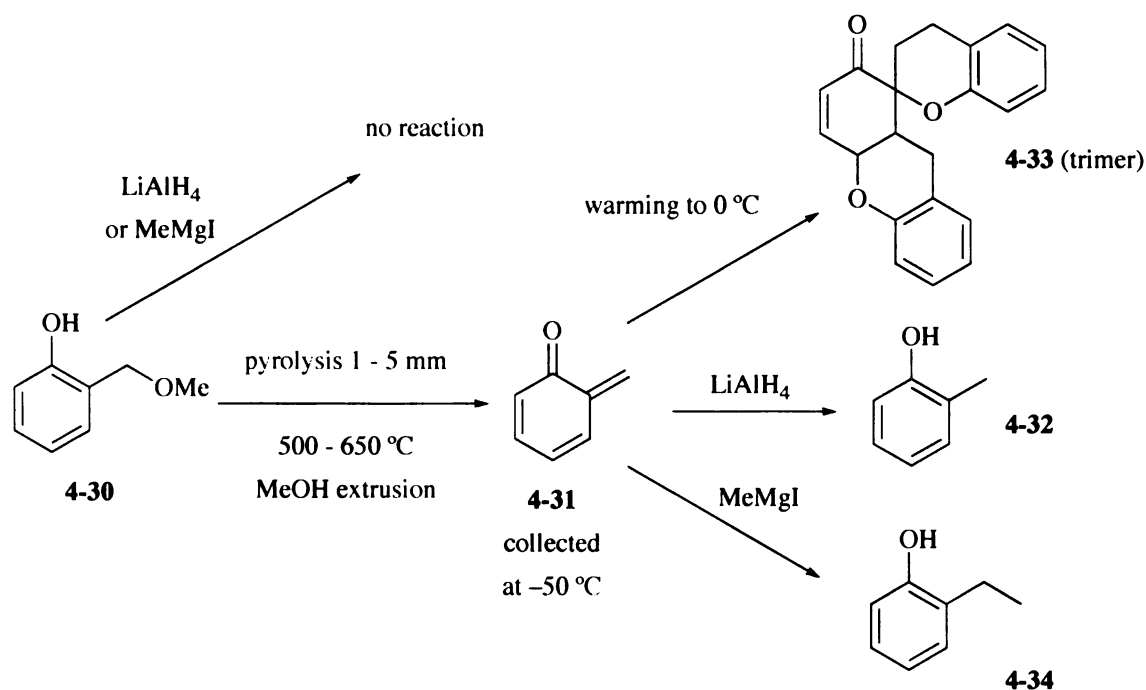
Scheme 4.7. General Methods for the Formation of *o*-Quinone Methides



One of the first controlled accounts of *o*-QM formation involves pyrolysis of compound **4-30** to give the *o*-quinone methide **4-31** as shown in Scheme 4.8.²⁰⁵

With compound **4-30** and lithium aluminum hydride, no reaction occurred. Only when the intermediate **4-31** was exposed to lithium aluminum hydride was compound **4-32** isolated. When the intermediate *o*-QM **4-31** was warmed to 0 °C, the trimer **4-33** was isolated in 70 % yield. Treatment of intermediate **4-31** with MeMgI gave compound **4-34**.¹⁹⁴

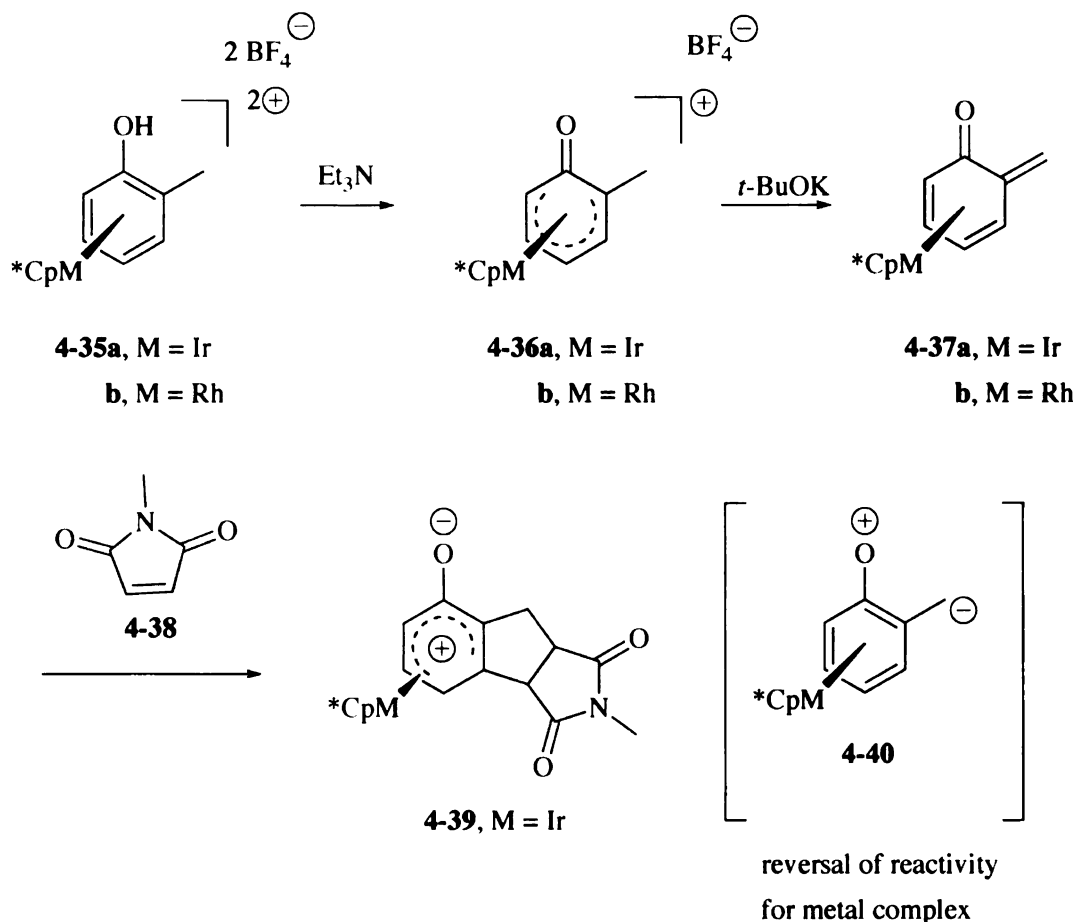
Scheme 4.8. Reaction and Formation of an *o*-Quinone Methide



Recently the isolation of *o*-QM has been accomplished via complexes with iridium and rhodium.^{194, 206} These organometallic species can be formed from compound **4-35** with triethyl amine followed by *t*-BuOK to give compound **4-37** via intermediate **4-36**.²⁰⁷ The x-ray crystal structure of both compounds involving iridium **4-37a** and rhodium **4-37b** derivatives have been reported.²⁰⁸ When compound **4-37a** was treated with **4-38**, compound **4-39** was formed. This

represents a reversal of reactivity of an *o*-QM species to one that has a nucleophilic carbon such as that indicated in intermediate **4-40** (Scheme 4.9).²⁰⁸

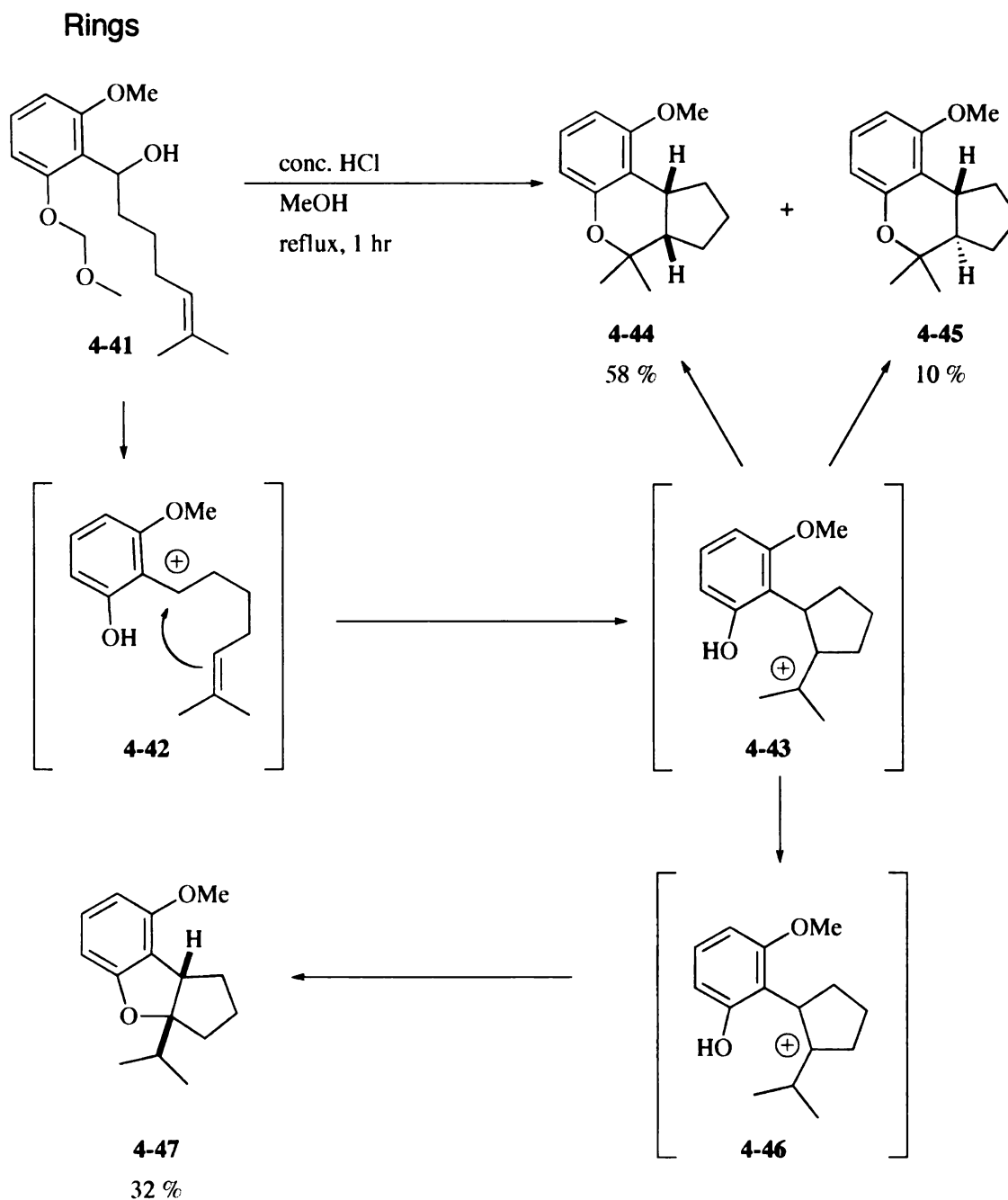
Scheme 4.9. Iridium and Rhodium Stabilized *o*-QM



Shown in Scheme 4.10 is the formation of a 6-6-5-tricyclic system. The proposed mechanism from compound **4-41** involves the intermediate carbocation **4-42** and not an *o*-QM because the resulting stereochemistry was *cis* for the bridgehead hydrogens.²⁰⁹ Also the isopropyl containing 6-5-5-tricyclic system **4-47** was isolated and the Diels-Alder reaction should give *trans* at the bridgehead.¹⁹⁴ A rearrangement of the carbocation **4-42** can give carbocation **4-43**. The charge could be quenched giving directly compound **4-44** or **4-45**.

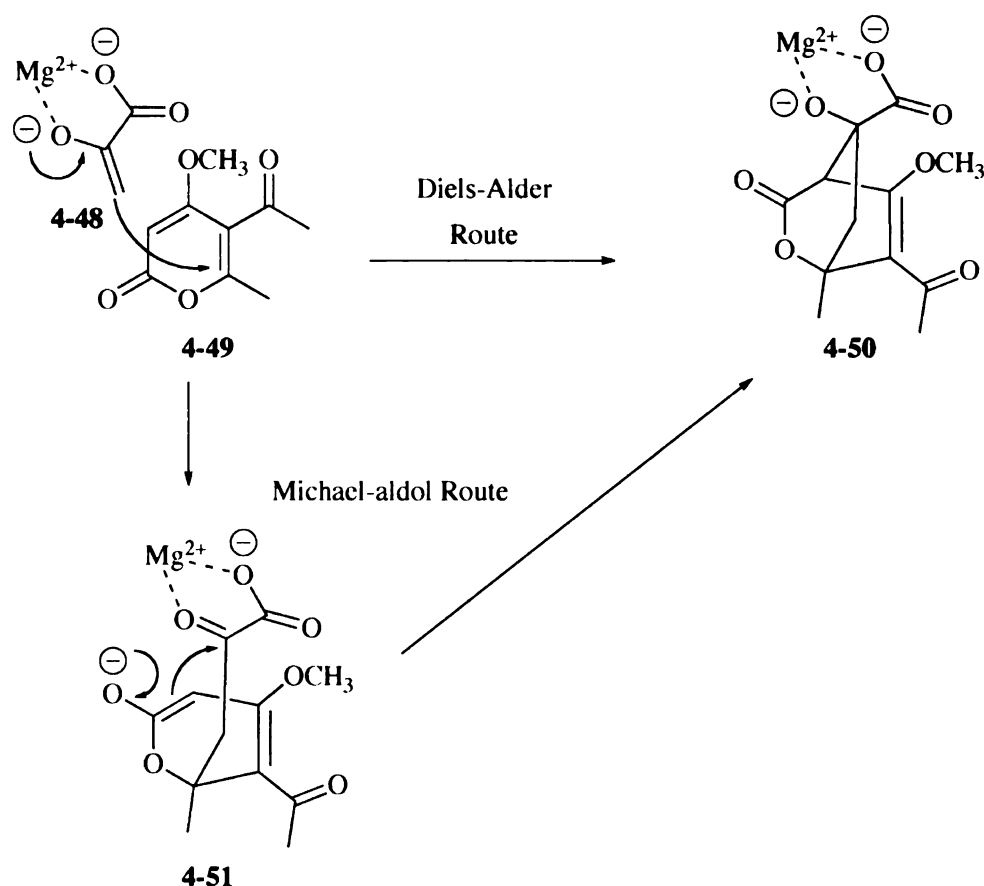
Further rearrangement could give cation **4-46** followed by phenol quenching of the carbocation to give compound **4-47**.²¹⁰ The energy barrier is stated to be < 5 kcal/mol for this hydride migration²¹¹ and "cationic rearrangements include 1,2-hydride shifts, 1,2-alkyl shifts, and 1,2-aryl shifts, all occur with great facility."²¹²

Scheme 4.10. Mechanistic Insight Into the Generation of 6-6-5-Member



The mechanistic proposal given above prompts the discussion of Diels-Alderases in nature. Does the 79-year old Diels-Alder reaction which is one of the most powerful synthetic reactions occur in nature? These questions are debated in the literature.²¹³ The Diels-Alder reaction has been proposed to occur in nature.²¹⁴ However recent calculations suggest a stepwise mechanism via a Michael-aldol route.²¹⁵ The Diels-Alder approach is shown for the conversion of compound **4-48** and **4-49** to compound **4-50**. The intermediate **4-51** in the Michael-aldol route is shown for the conversion of compound **4-49**.

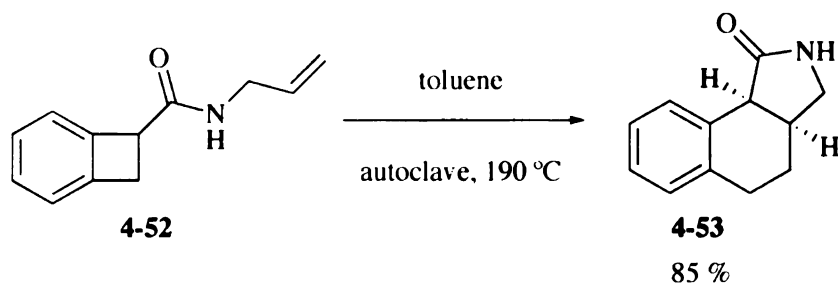
Scheme 4.11. A Diels-Alder or a Michael Route in Nature



Shown in Scheme 4.12 is the formation of a 6-6-5-member ring.²¹⁶ Although this is not an *ortho*-quinone methide (it is an *ortho*-quinodimethane), it

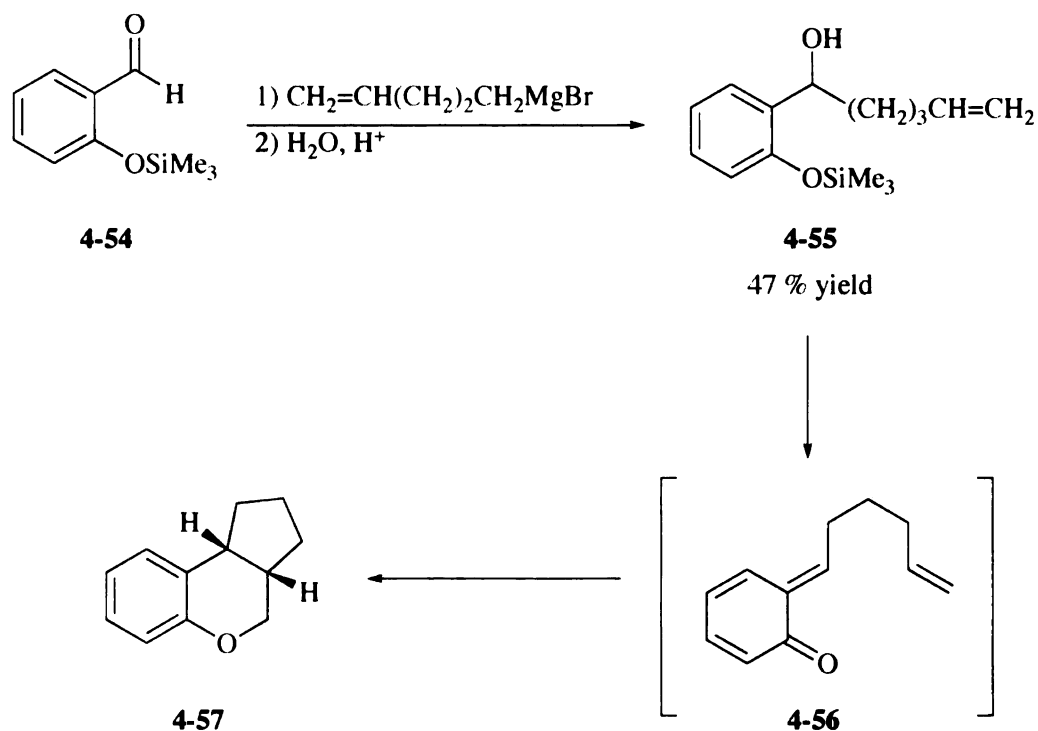
shows the *cis* geometry obtained from compound **4-52** which was obtained by heated at 190 °C in an autoclave giving compound **4-53**.²¹⁶ The authors did not specify whether the autoclave was a wet (steam) or a dry autoclave.²¹⁷

Scheme 4.12. Intramolecular Cycloadditions to Form *o*-Quinodimethanes



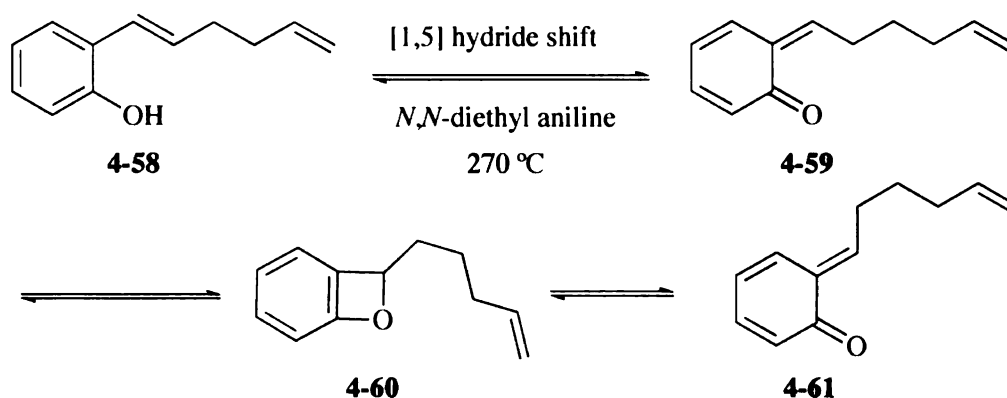
Compound **4-54** could be treated with 4-pentenylmagnesium bromide to give compound **4-55** in 47 % yield as shown in Scheme 4.13.²¹⁸ Compound **4-55** could then be subjected to pyrolysis at 700 °C under 0.01 mm of Hg pressure to give compound **4-57** in 12 % yield.²¹⁸ The conversion of compound **4-54** to compound **4-57** presumable goes through *o*-QM **4-56**. The resulting stereochemistry of compound **4-56** was *cis* at the bridgehead.²¹⁸

Scheme 4.13. Pyrolysis at 700 °C to Form 6-6-5-Member Rings



Shown in Scheme 4.14 is the 1,5 hydride shift from compound **4-58** giving the *o*-QM **4-59**.²¹⁹ The *o*-QM **4-59** has been proposed to be in equilibrium with intermediate **4-60** and **4-61**.²¹⁹

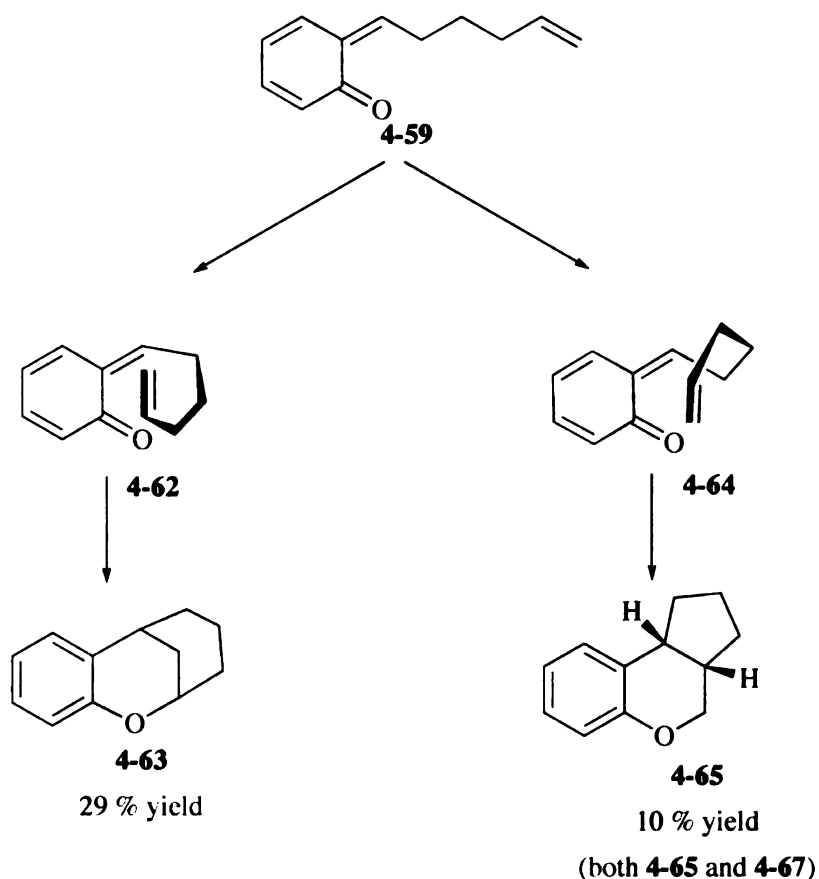
Scheme 4.14. Equilibrium of a Styryl Compound



The Diels-Alder reaction of the *Z*-*o*-QM **4-59** is presented in Scheme 4.15, which is a continuation of the discussion for Scheme 4.14.²¹⁹ The reaction

conditions are those in Scheme 4.14. In the first approach shown as structure **4-62**, the unexpected product **4-63** was formed which is a 6-6-6-ring system.²¹⁹ In structure **4-64**, the approach of the dienophile is shown giving compound **4-65** as a 6-6-5-ring system, which has a *cis* bridgehead.²²⁰ The yield of compound **4-65** for this reaction was 10 % while the yield for compound **4-63** was 29 %.²¹⁹

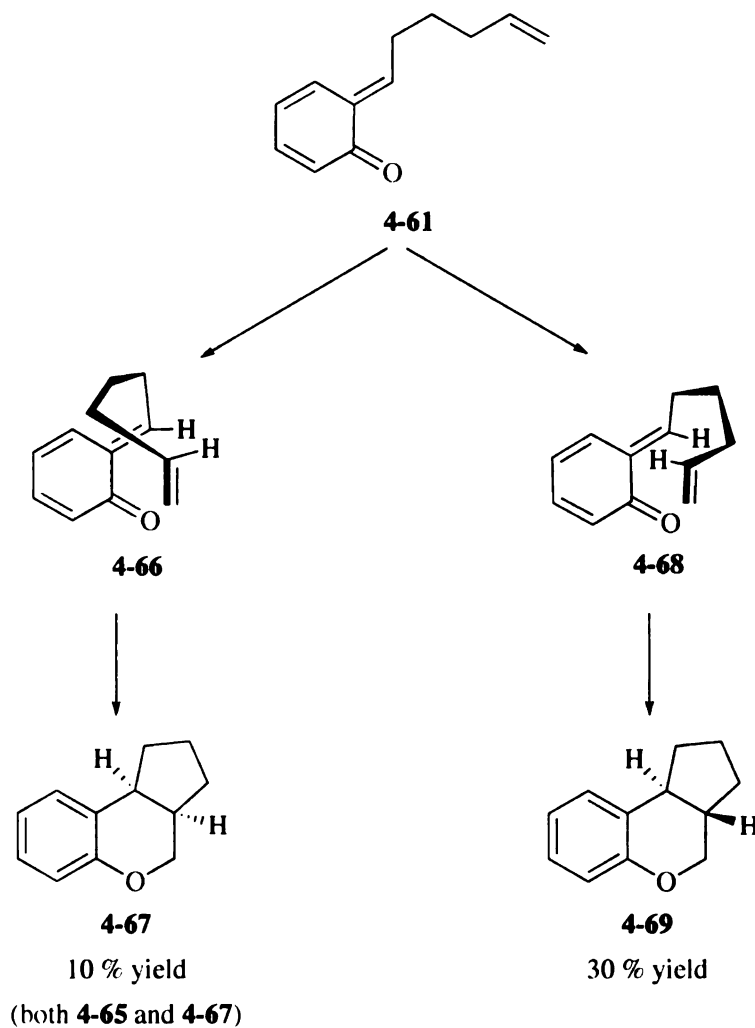
Scheme 4.15. Diels-Alder Reactions of *cis*-*o*-QM



In Scheme 4.16, the reaction of the (*E*)-*o*-QM **4-61** is depicted.²¹⁹ The reaction conditions are those in Scheme 4.14. In structure **4-66**, the *endo* approach is shown giving the *cis*-bridgehead compound **4-67**. The yield for the enantiomers **4-65** and **4-67** was 10 %.²¹⁹ In structure **4-68**, the *exo* approach

is shown giving compound **4-69**, which has the trans bridgehead. The yield for compound **4-69** was 30 %.²¹⁹

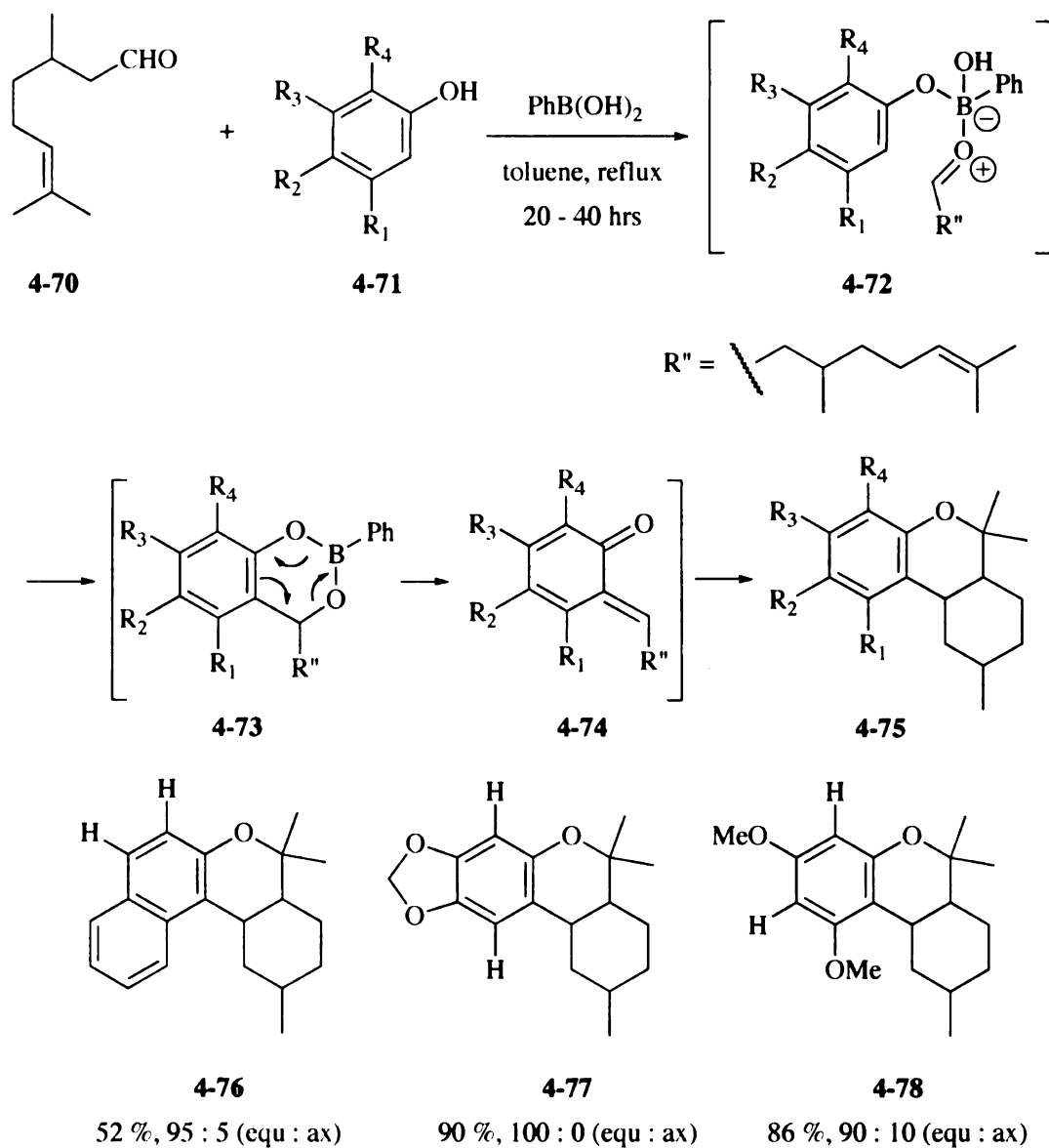
Scheme 4.16. *Endo* and *Exo* Approach for a Diels-Alder Reaction



Shown in Scheme 4.17 is the phenylboronic acid catalyzed formation of hexahydrocannabinoids.^{194, 199} The reaction begins with citronellal **4-70** and phenol **4-71** and proceeds through intermediate **4-72** followed by a [3,3]-sigmatropic rearrangement to give intermediate **4-73**, which forms the σ -QM **4-74**.^{194, 199} An intramolecular Diels-Alder reaction with the tethered olefin gives

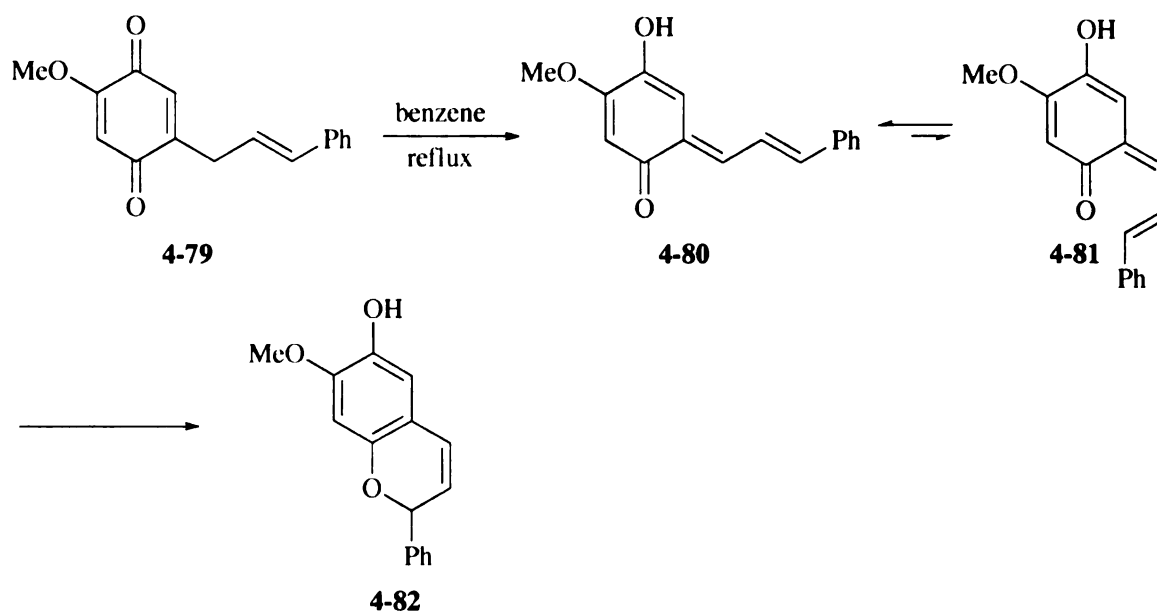
compound **4-75**. The overall yield of this strategy for compound **476** was 52 %, and the yield for compound **4-77** was 90 %.^{194, 199} The yield for compound **4-78** was 86 %.^{194, 199} The equatorial and axial (equ : ax) ratios of the products are reported in Scheme 4.17. Usually the equatorial to axial ratios of are > 95 : 5, and a detailed explanation will follow.¹⁹⁹

Scheme 4.17. Hexahydrocannabinoids with Phenylboronic Acid



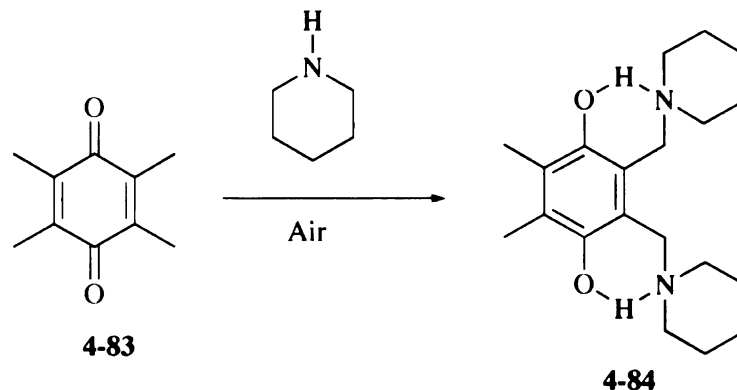
The thermal enolization to form an *o*-QM is shown in Scheme 4.18. Enolization of compound **4-79** generates compound **4-80**, which is in equilibrium with compound **4-81**. The equilibrium lies on the side of compound **4-80**. Electrocyclization gives compound **4-82**.

Scheme 4.18. Heat Induced Quinone Enolization



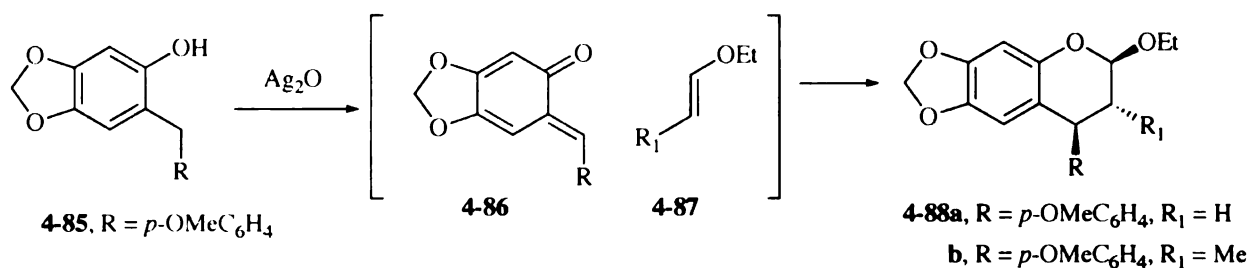
An interesting example of the formation of bis-amines **4-84** from the quinone **4-83** is related to the chemistry presented in chapter three of this dissertation (Scheme 4.19).²²¹ The bis-hydrogen bonds exist between the nitrogen and the oxygen shown as compound **4-84**.¹⁹⁴

Scheme 4.19. The Formation of a Bis-Amine by an Quinone Methide.



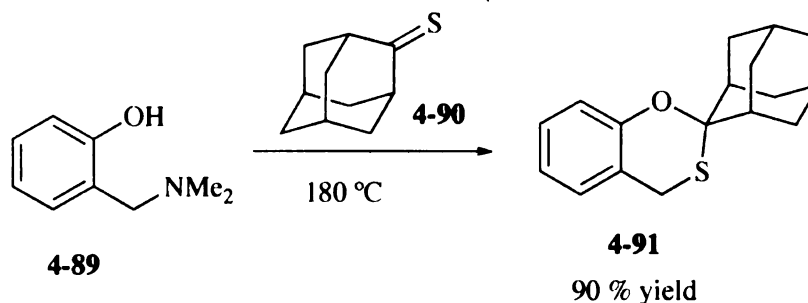
In Scheme 4.20, the treatment of compound **4-85** with silver oxide gives the intermediate *ortho*-quinone methide **4-86**.²²² In the presence of a vinyl ether **4-87**, compound **4-88** is formed.²²³

Scheme 4.20. Silver Oxide Oxidation for the Formation of *o*-QMs



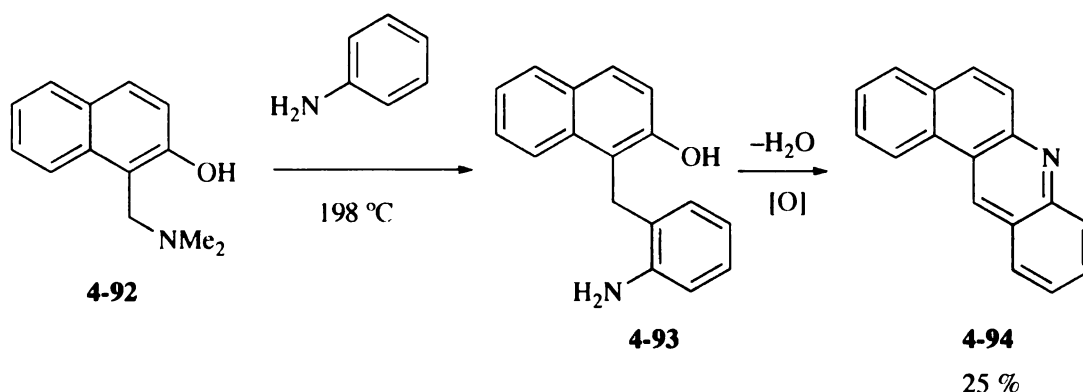
The thermal elimination of an amine is shown in Scheme 4.21. Heating compound **4-89** at 180 °C in the presence of compound **4-90**, led to the formation of compound **4-91** in 90 % yield.¹⁹⁴

Scheme 4.21. Thermal Elimination with Substitution



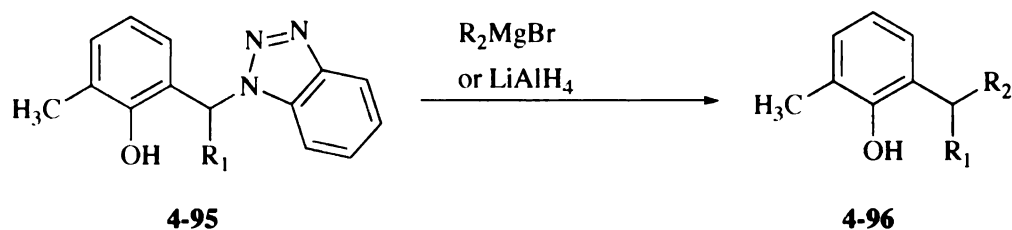
The formation of heterocyclic compound **4-93** can be accomplished by heating compound **4-92** with distilled aniline at 198 °C for 4 hours.¹⁹⁴ The expulsion of water and oxidation with $K_2Cr_2O_7$ gives compound **4-94** in 25 % yield.¹⁹⁴

Scheme 4.22. Heterocyclic Formation with an *o*-QM



Shown in Table 4.1 is the result of the substitution reaction of compound **4-95** with Grignard reagents and aluminum hydride to give compound **4-96**.¹⁹⁴ In entry 1, the yield was 45 %, and for entry 2, the yield was 29 %. The yield was lower for alkyl Grignards than for aryl Grignards. For entry 3, the yield was 80 %, and for entry 4, the yield was 66 %. For lithium aluminum hydride, the yield was 59 % for entry 5 and 62 % for entry 6.¹⁹⁴

Table 4.1. Basic Conditions For Formation of *o*-QM



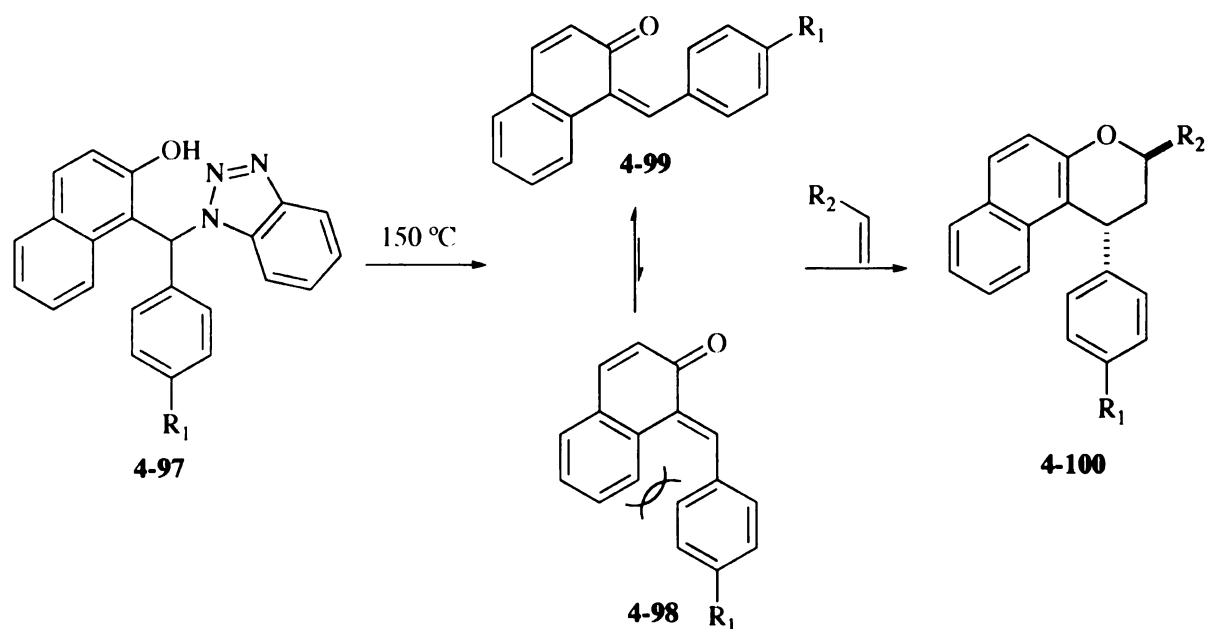
Entry	R ₁	R ₂	Reagent	Time, hrs	Yield (%)
1	H	Ph	PhMgBr	72	45
2	H	Bu	<i>n</i> -BuMgBr	24	29
3	Me	Ph	PhMgBr	17	80
4	Me	PhCH ₂	PhCH ₂ MgBr	12	66
5	Me	H	LiAlH ₄	48	59
6	Bu	H	LiAlH ₄	48	62

The thermal reaction shown in Scheme 4.2 generates *o*-QMs of 1-[α -(benzotriazol-1-yl)alkyl]-2-naphthols **4-97** such as intermediate **4-98** and **4-99**.²²⁴

The *o*-QM exists mainly as the *Z*-configuration **4-99**.²²⁵ In the *E*-configuration the strong H-H bumping prevents coplanarity of the naphthol and phenyl rings.

Less electron-rich olefins like styrene don't react under these conditions.²²⁴

Table 4.2. Cycloaddition With Dienophiles



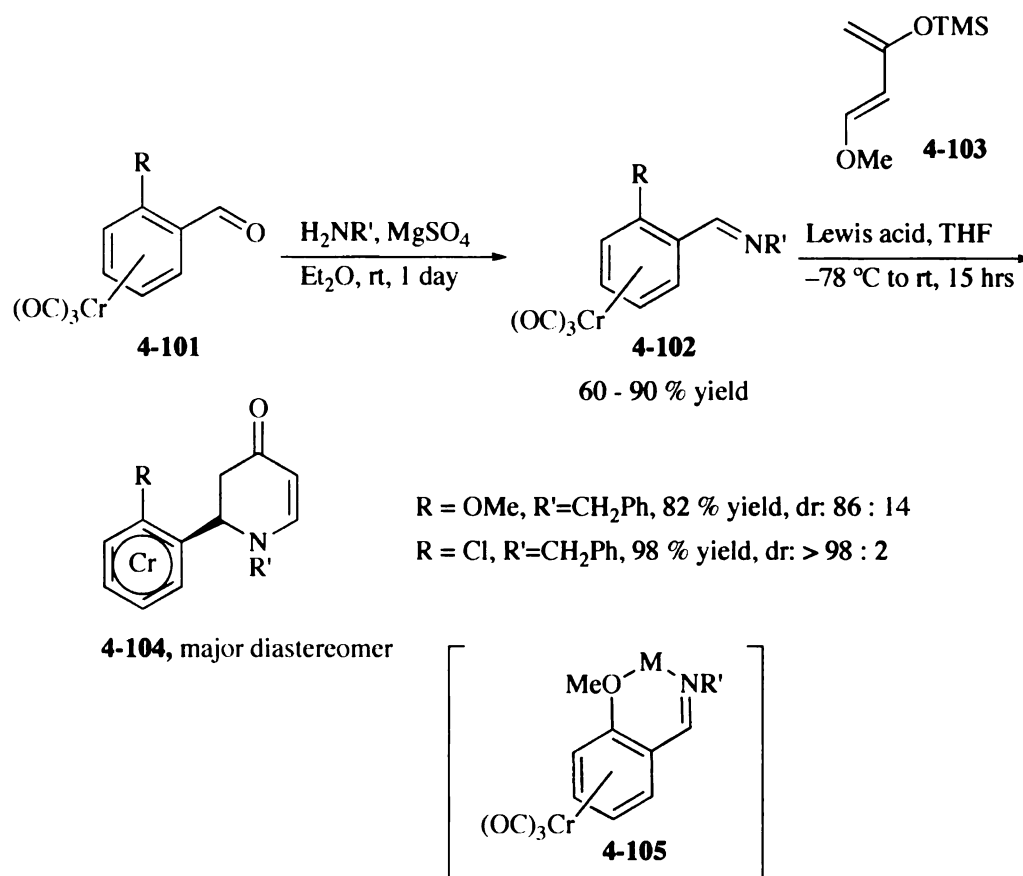
entry	R ₁	R ₂	Time (hrs)	dr (trans : cis)	Yield %
1	H	OEt	5	2.75 : 1	92
2	H	pyrr ^a	3	n/a	82
3	NMe ₂	OEt	5	2 : 1	49 (92) ^b
4	NMe ₂	pyrr ^a	3	n/a	27 (87) ^b

a. pyrrolidin-2-one b. total yield of products including mixtures

An asymmetric aza-Diels-Alder reaction is shown in Scheme 4.23.²²⁶ The Diels-Alder reaction begins with **4-101** and the formation of imine **4-102** in 60 to 90 % yield. The Diels-Alder step involves imine **4-102** and the diene **4-103**. The yield of **4-104** when R = OMe and R' = CH₂Ph was 82 %, and the diastereomeric ratio of 86 : 14.²²⁷ The yield was 98 % when R = Cl and R' = CH₂Ph, and the

diastereomeric ratio was > 98 : 2. The low diastereomeric ratio for compound **4-104** was proposed to be due to chelation as shown in intermediate **4-105**, which interferes with the approach of the diene **4-103**.²²⁷

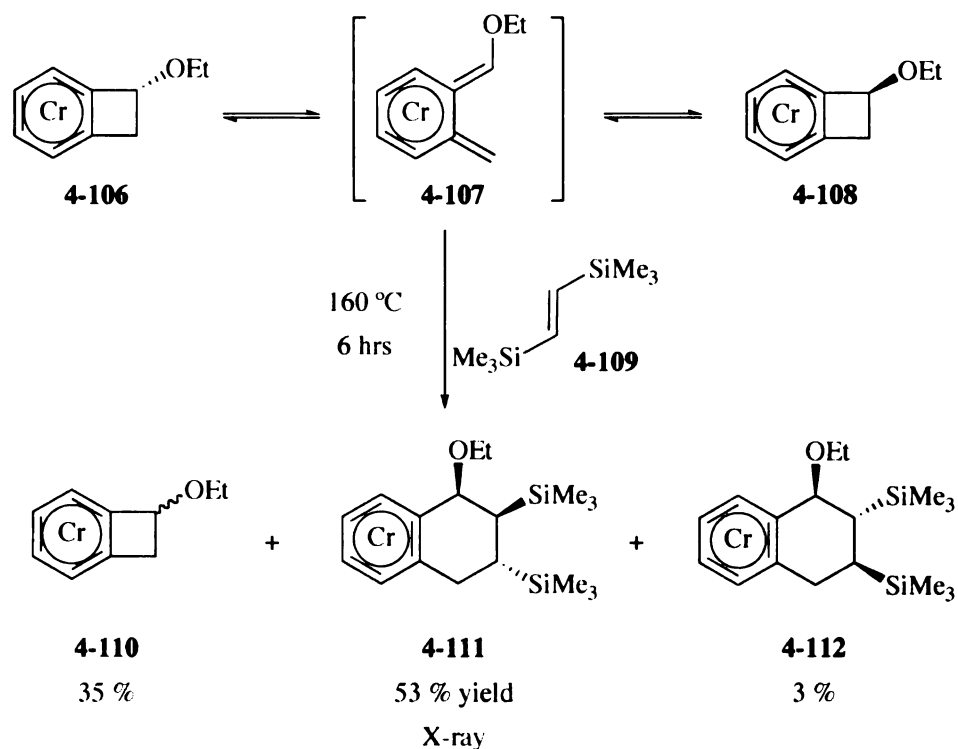
Scheme 4.23. Asymmetric Aza-Diels-Alder Reaction



Shown in Scheme 4.24 is the trapping of the intermediate *o*-quinodimethane **4-107** at 160 °C from compound **4-106**.²²⁸ The yield of compound **4-111** was 53 % as the major stereoisomer. The yield of the minor stereoisomer **4-112** was 3 %. An equilibrium is believed to exist between compound **4-106** and compound **4-108**.²²⁸ The recovery of compound **4-110**

was 35 % as a mixture of *syn* and *anti* with respect to the chromium tricarbonyl group and the ethyl ether.

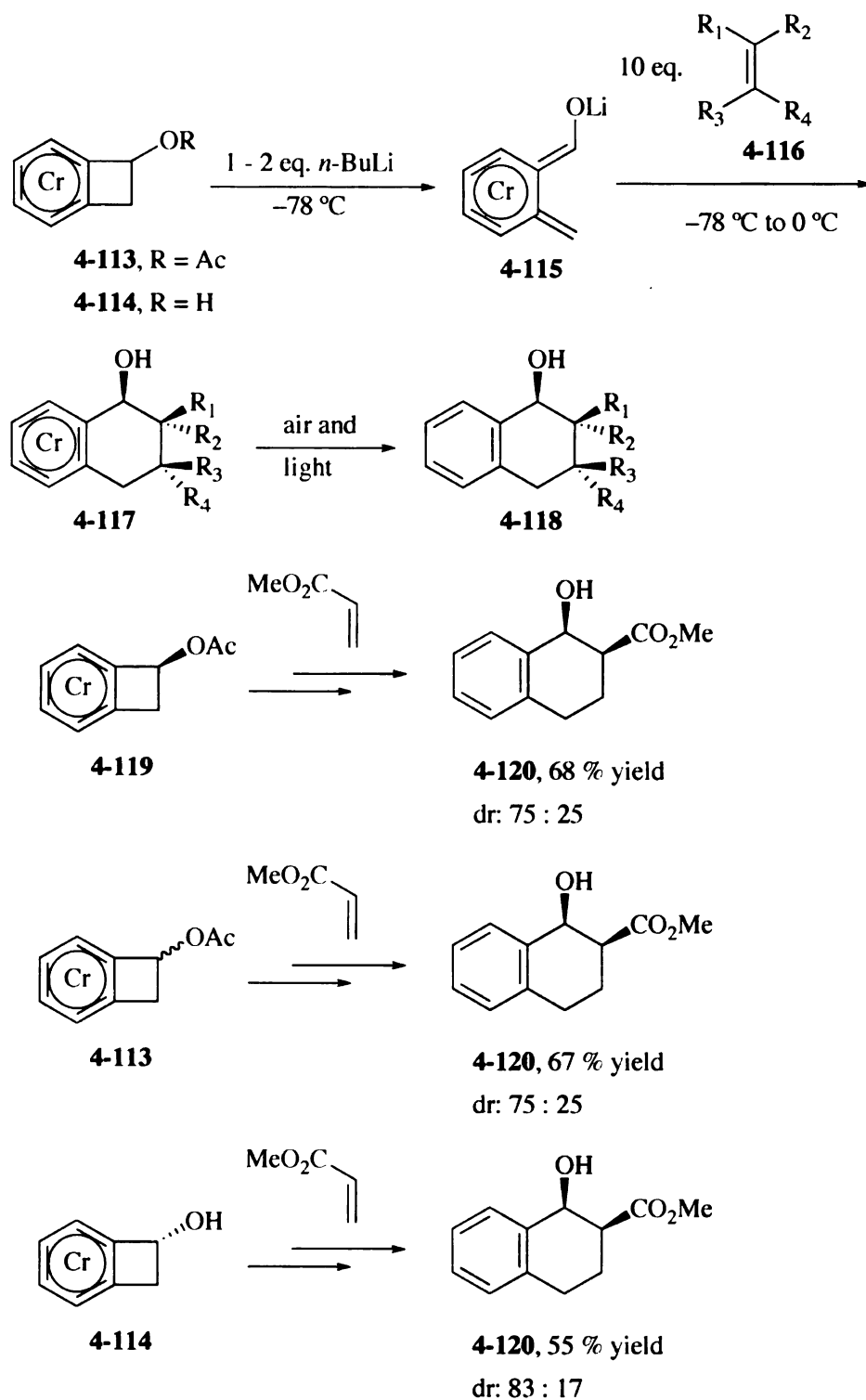
Scheme 4.24. A Trapped *o*-Quinodimethane



The anionic acceleration of the Diels-Alder reactions of the type show in Scheme 4.24 has previously been reported by Choy and Yang.²²⁹ This anionic rate acceleration experiment was attempted on chromium tricarbonyl arenes shown in Scheme 4.25 to promote selectivity by avoiding high temperatures.²²⁸ Compounds **4-113** and **4-114** can be treated with *n*-butyl lithium to give intermediate **4-115**, which will react with dienophile **4-116** to give compound **4-117**. Air and light can be used to remove the chromium tricarbonyl group (see chapter one) to give compound **4-118**.²²⁸ For compound **4-119**, the yield was 68 % yield with selectivities of 75 : 25 favoring the *syn*. The yield for compound **4-**

120 was 67 % and the selectivity was also 75 : 25 from compound **4-113** (mixture of *syn* and *anti* respectively).²²⁸ Compound **4-119** was one diastereomer and compound **4-113** was a 50 : 50 mixture; both compound **4-119** and **4-113** gave the same ratio of diastereomers for the product **4-120**. From alcohol **4-114**, the yield of compound **4-120** was 55 % and the diastereomeric ratio was 83 : 17.²²⁸

Scheme 4.25. Cationic Promotion of *o*-Quinodimethane Formation with the Chromium Tricarbonyl Group

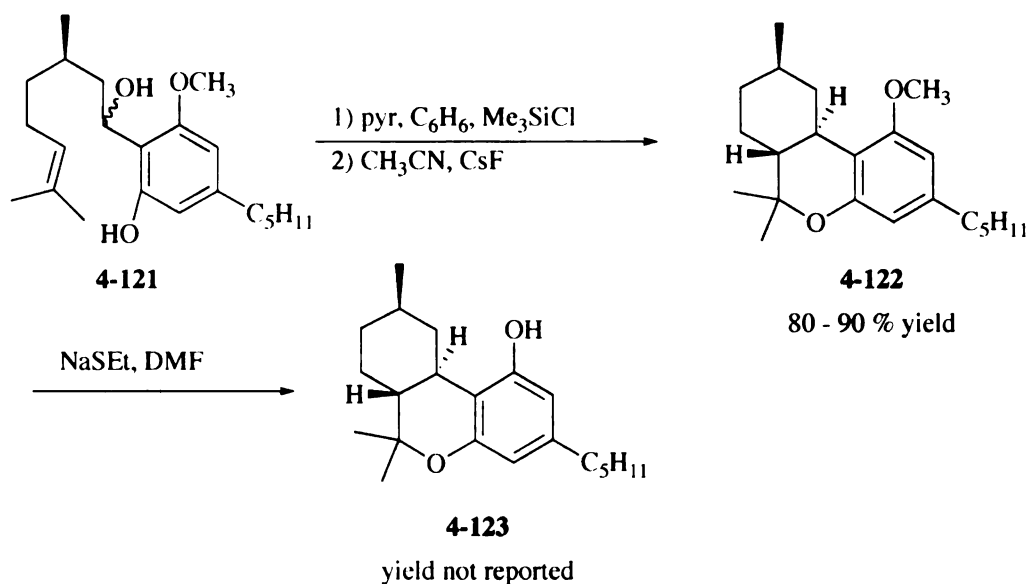


4.6 Diels-Alder Approach Toward Cannabinoid and Derivatives

Shown in Scheme 4.26 is the formation of (–)-hexahydrocannabinol.^{220,}

²³⁰ The first step is the silylation of the phenol from compound **4-121** followed by treatment with CsF. Compound **4-122** was formed in 80 to 90 % yield from **4-121**.²⁰⁶ The demethylation of compound **4-122** could be done with sodium ethyl thiolate but the yield for compound **4-123** was not reported.²³⁰

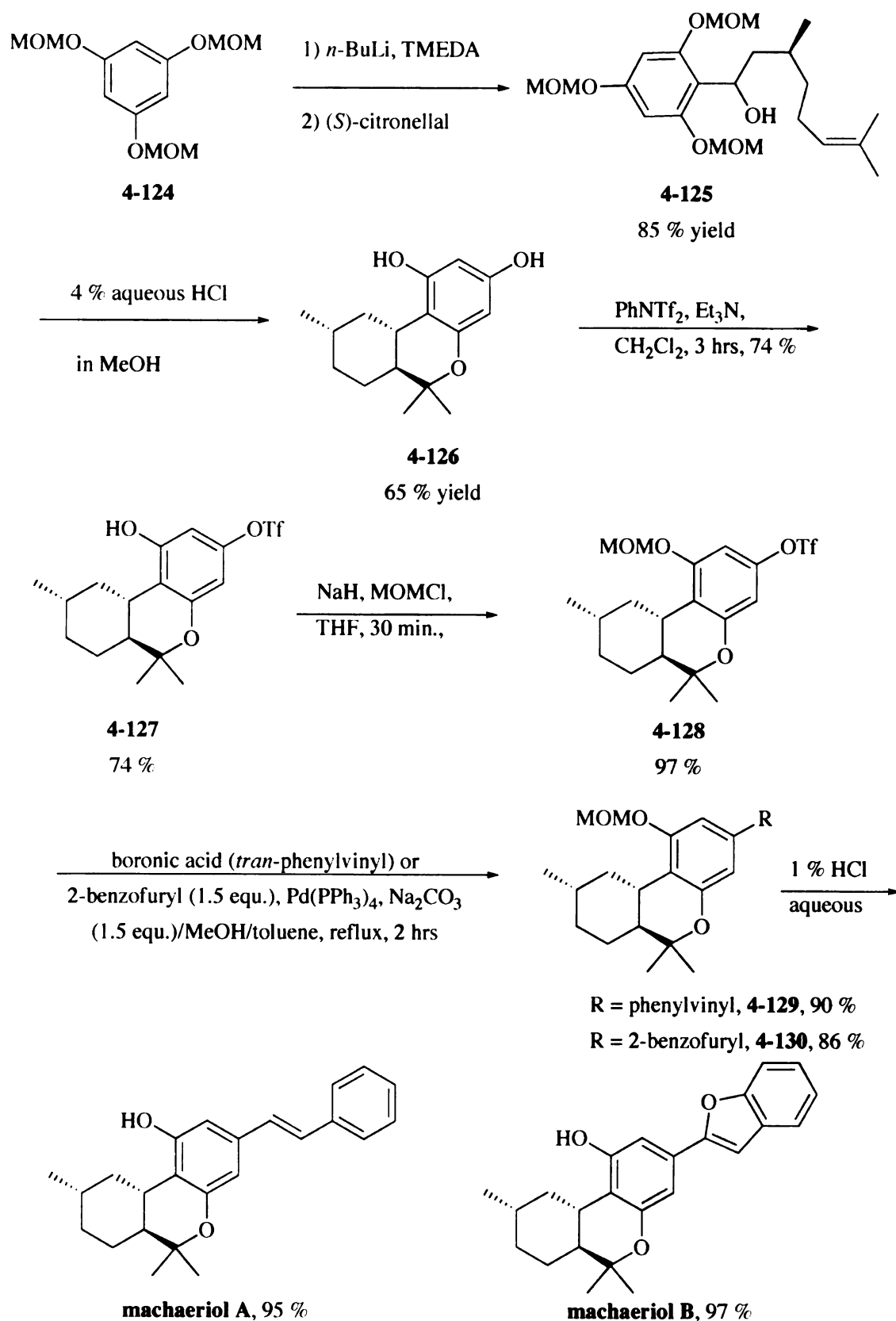
Scheme 4.26. Synthesis of Hexahydrocannabinol



The synthesis of the machaeriols A and B²³¹ are presented in Scheme 4.27.^{230, 232} Treatment of compound **4-124** with *n*-butyl lithium and TMEDA followed by citronellal gave compound **4-125** in 85 % yield. The deprotection of the MOM groups and cyclization was accomplished in 4 % aqueous HCl to give compound **4-126**. This step to form compound **4-126** presumably involves the elimination of the unprotected alcohol to give the *o*-QM followed by an

intramolecular Diels-Alder reaction.²⁰⁶ The triflation of the most sterically accessible hydroxyl group gave compound **4-127** in 74 % yield. The protection of the remaining hydroxyl group gave compound **4-128** in 97 % yield. The Suzuki coupling with either *trans*-phenylvinyl boronic acid or 2-benzylfuryl boronic acid gave compounds **4-129** and **4-130** with yields of 90 and 86 %, respectively. The deprotection of the MOM group with 1 % HCl aqueous solution gave machaeriol A and B with yields of 95 and 97 %.²³³

Scheme 4.27. Previous Synthesis of Machaeriols A and B



4.7 Traceless Stereoinduction for the Formation of Hexahydrodibenzopyrans

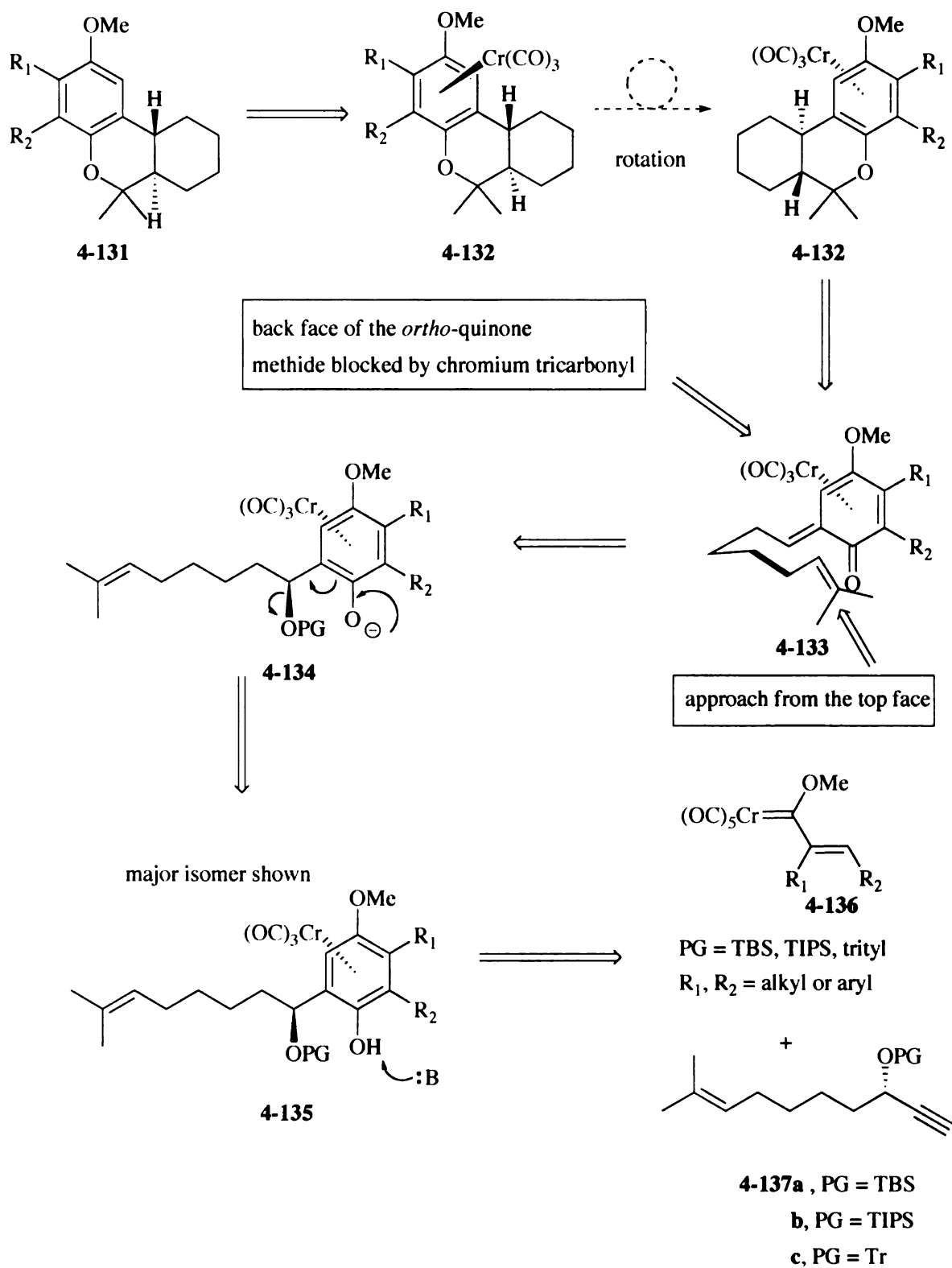
Our retrosynthetic approach for the formation of hexahydrodibenzopyrans such as compound **4-131** is shown in Scheme 4.28. Target molecule **4-131** could be derived from the chromium tricarbonyl arene **4-132**.²³⁴ With rotation one can see that compound **4-132** could originate from a Diels-Alder reaction from intermediate **4-133**. The back face of compound **4-133** is blocked by the chromium tricarbonyl group and thus should force the intramolecular Diels-Alder reaction to occur from the top face.²²⁷ The *ortho*-quinone methide **4-133** could originate from anion **4-134** by the elimination of a protected ether.²³⁵ To generate anion **4-134** from the phenol **4-135**, base would be required. A Wulff-Dötz benzannulation of compounds **4-136** and **4-137** should stereoselectively give compound **4-135**.²³⁶

As can be observed in Scheme 4.28, compounds such as **4-131** can be quickly assembled using the traceless stereoinduction approach which was called "traceless" because no "trace" of the stereocontrol element in alkyne **4-137** is present in the final product. The substituents at positions R₁ and R₂ can easily be varied by changing the Fischer carbene complex and the functionality of the alkyne could also be quickly changed. This method should provide for quick assembly of molecules of this type and possibly make new

hexahydrodibenzopyrans with greater biological activity than the machaeriols

(Scheme 4.27).

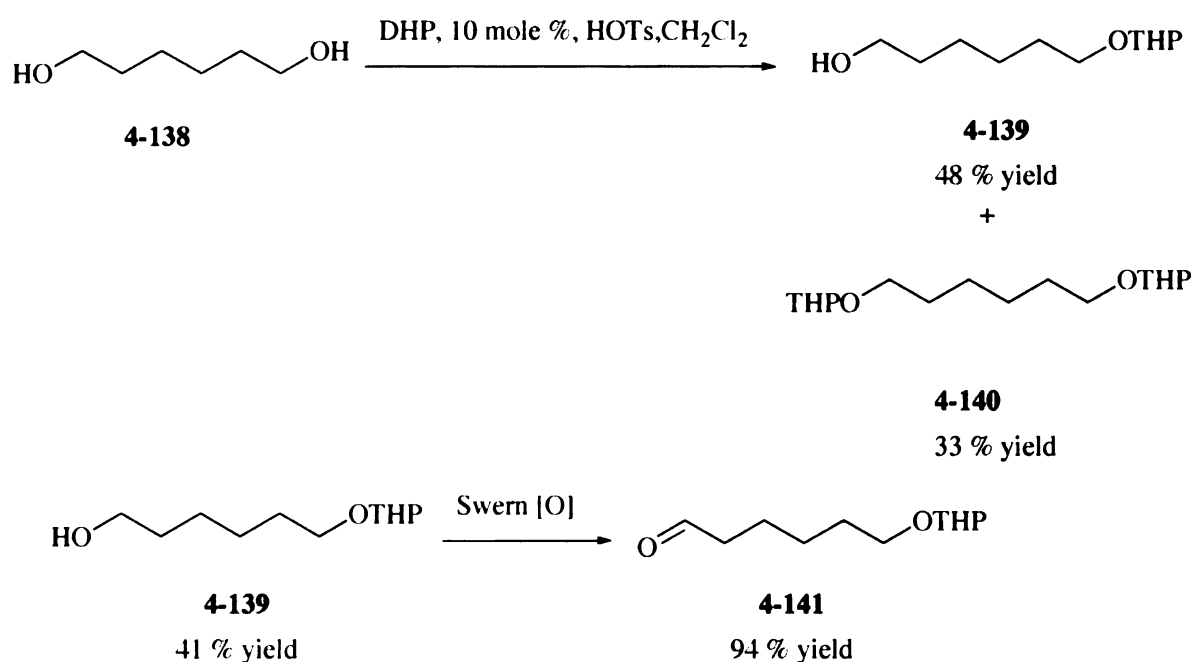
Scheme 4.28. Proposed Mechanism of Traceless Stereoinduction



4.7.1 The Formation of Starting Materials

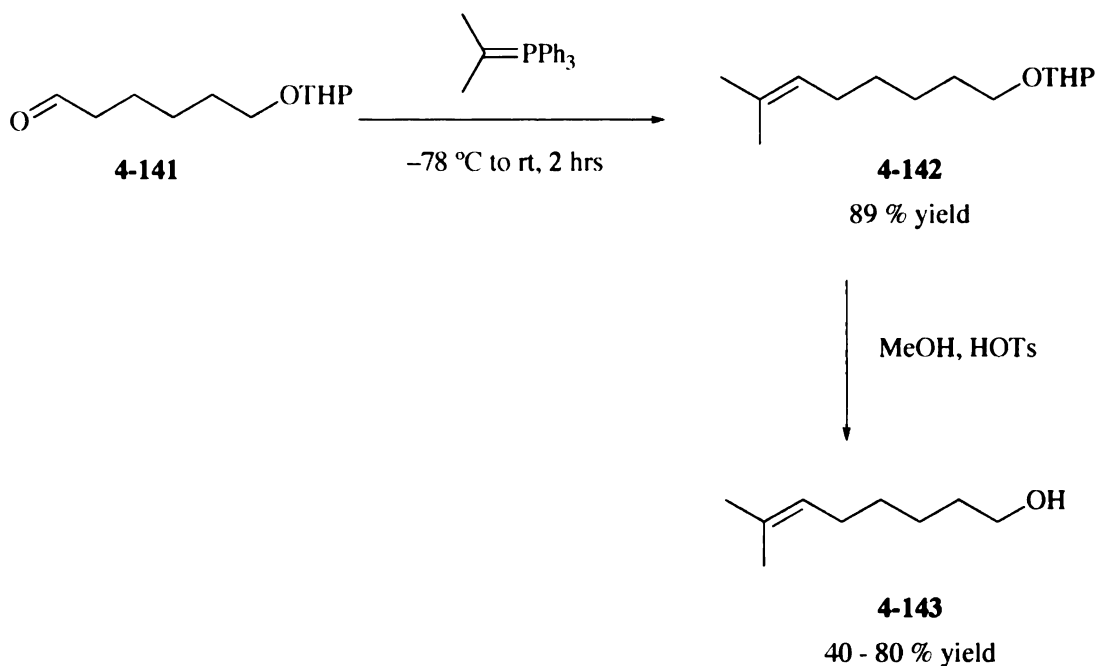
The synthesis of alkyne **4-137** begins with the mono-THP protection of compound **4-138** to give the protected alcohol **4-139** in 48 % yield along with the bis-THP compound **4-140** as a byproduct. Swern oxidation of compound **4-139** gives compound **4-141** in 94 % yield.²³⁷

Scheme 4.29. Synthesis of a THP Protected Aldehyde



The synthesis of alkyne **4-137** continues with the Wittig olefination to give compound **4-142** in 89 % yield.²³⁸ The deprotection of the THP protecting group with tosic acid gives compound **4-143** in 40 to 80 % yield.²³⁹

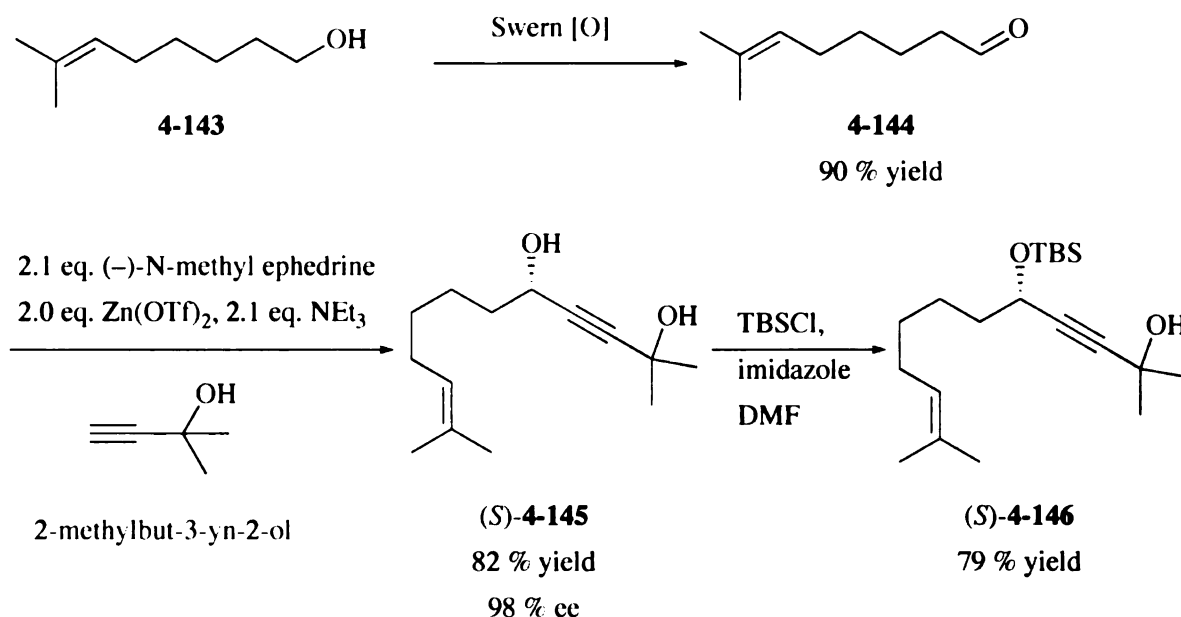
Scheme 4.30. A Wittig Reaction and THP Deprotection



Shown in Scheme 4.31 is the oxidation of alcohol **4-143** to give aldehyde **4-144** with a 90 % yield.^{240, 241} Using Carreira's chemistry, an asymmetric addition of 3-methyl-3-butynol to **4-144** was achieved to give (*S*)-**4-145** in 82 % yield and 98 % enantiomeric excess.²⁴² The absolute stereochemistry was determined by analogy / comparison with the published methods.²⁴² The determination of the enantiomeric excess was performed by chiral GC on alcohol (*S*)-**4-150** shown in Scheme 4.36. The alcohol (*S*)-**4-150** was formed from TBAF deprotection of silyl ether (*S*)-**4-137a**. The application of Carreira chemistry with TMS acetylene failed²⁴³ to give the desired product under the same conditions despite the report of its success in the literature.²⁴² The high asymmetric induction observed here is consistent with the report that alkyl aldehydes such as

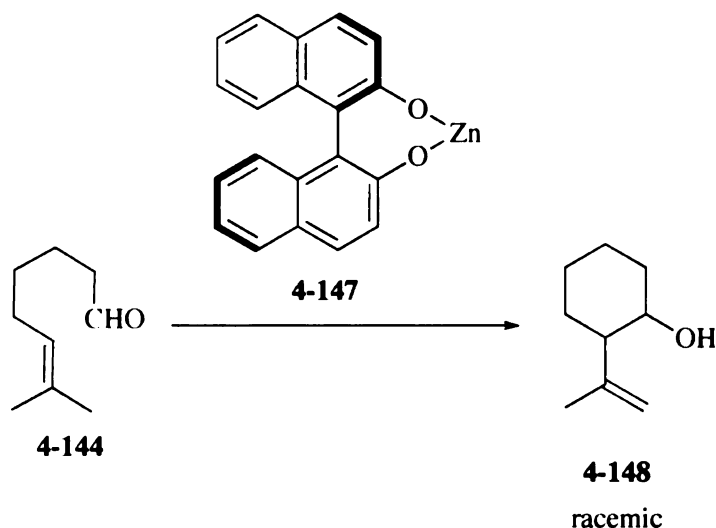
compound **4-144** give good enantiomeric excesses.²⁴² Protection with TBS gave a 79 % yield of compound (*S*)-**4-146**.

Scheme 4.31. Oxidation and Carreira Chemistry to Form Alkynes



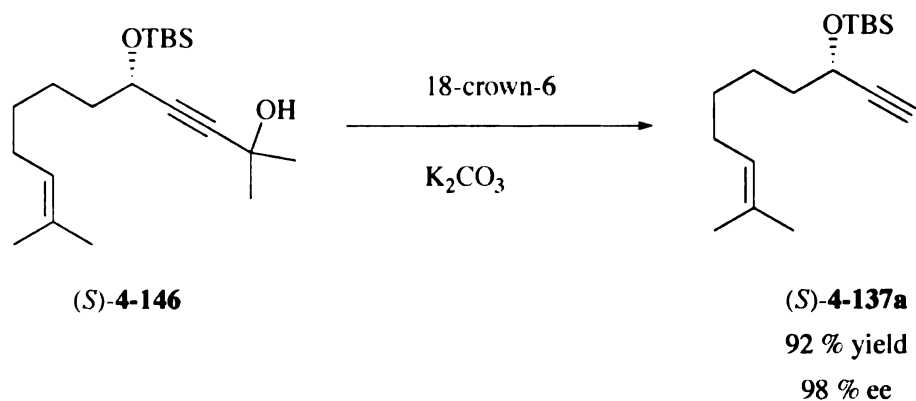
A potential side product of the zinc promoted addition of alkyne is shown in Scheme 4.32.²⁴⁴ From aldehyde **4-144** with the zinc catalyst **4-147**, compound **4-148** had been obtained. The zinc BINOL catalyst **4-147** was made from diethyl zinc and BINOL. The product **4-148** from this reaction was completely racemic.²⁴⁴ This zinc cyclization may explain reduced yields (30 to 50 %) when the addition of the aldehyde to $\text{Zn}(\text{OTf})_2$ and *N*-methyl ephedrine was not carried out slowly with syringe pump addition. It may be interesting to look at VAPOL and VANOL for this zinc catalyzed cyclization reaction shown in Scheme 4.32.

Scheme 4.32. Zinc Catalysis of Cyclization of Unsaturated Aldehydes



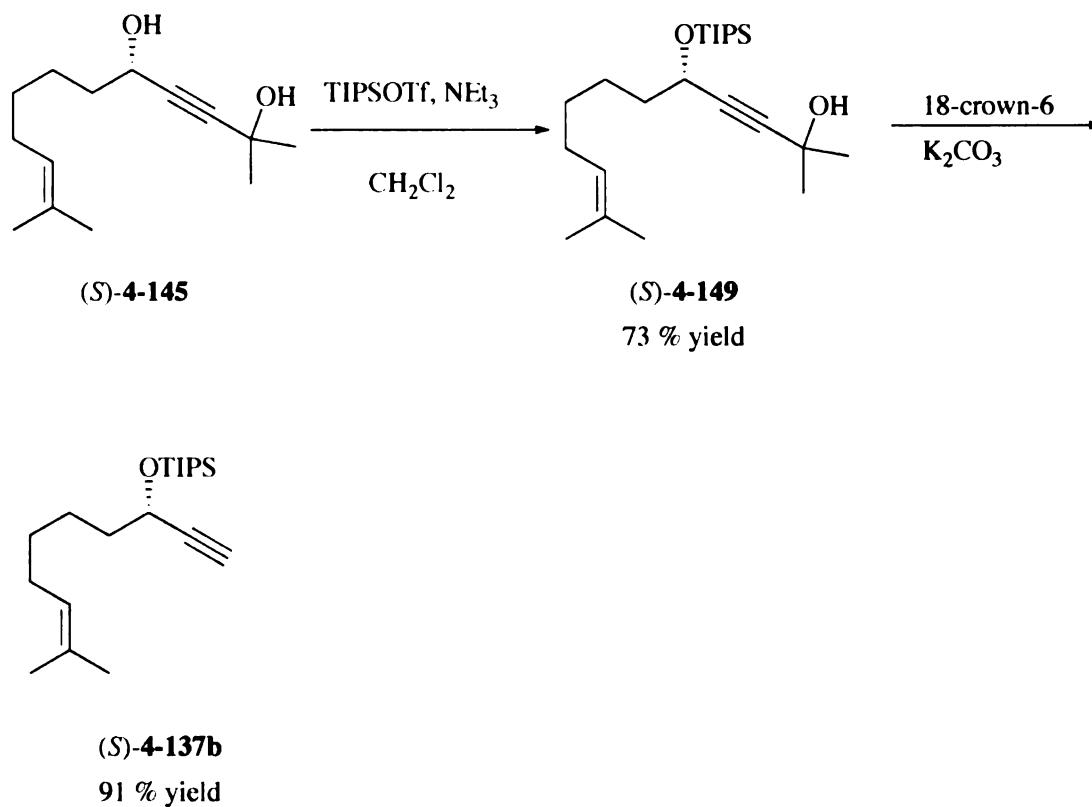
Shown in Scheme 4.33, the deprotection of the acetylene (*S*)-**4-146** with potassium carbonate and 18-crown-6 gives the desired terminal acetylene (*S*)-**4-137a** in 92 % yield (98 % ee).²⁴² The analysis of the enantiomeric excess was conducted on compound (*S*)-**4-150** by chiral GC. The minor enantiomer was not detectable by the conditions used for chiral GC. It was found to be critical for this deprotection that a "goodly flow"²⁴⁵ of nitrogen through the condenser be sustained to remove the resulting acetone to drive the equilibrium toward the terminal acetylene (*S*)-**4-137a**. Carreira has demonstrated that ≥ 99 % enantiomeric excess can be achieved for straight alkyl chained aliphatic aldehydes.²⁴²

Scheme 4.33. Deprotection to Form Terminal Acetylene



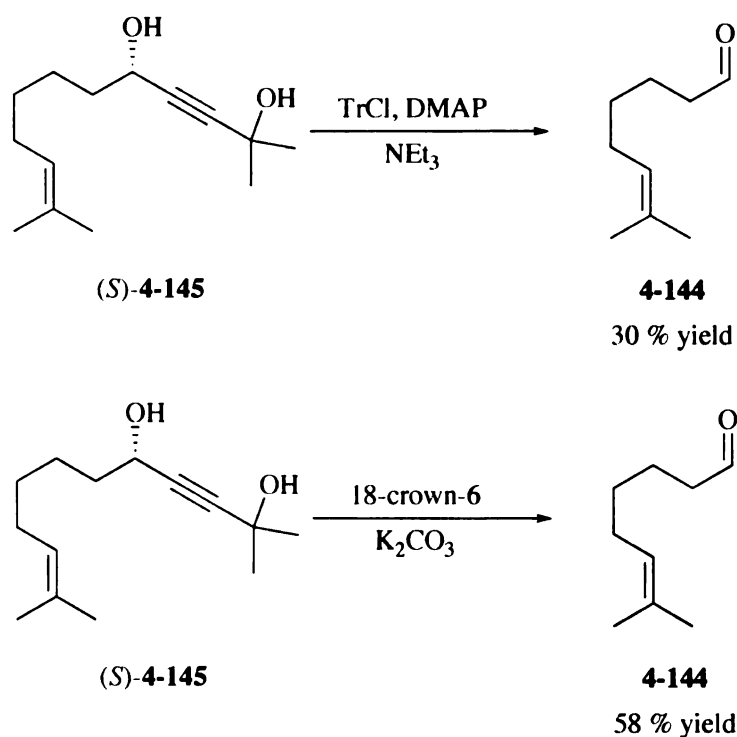
Likewise the formation of the TIPS protected alkyne **(S)-4-137b** was done in the same manner as is shown in Scheme 4.34. The protection of diol **(S)-4-145** gave an 73 % yield of compound **(S)-4-149**. Treatment of compound **(S)-4-149** with 18-crown-6 and potassium carbonate gave compound **(S)-4-137b** in 91 % yield.

Scheme 4.34. Formation of a TIPS Protected Alkyne



The treatment of the diol (*S*)-**4-145** with triphenylmethyl chloride in the presence of DMAP and triethyl amine gave the aldehyde **4-144**. Also the treatment of compound (*S*)-**4-145** with 18-crown-6 and potassium carbonate gave a 58 % yield of compound **4-144**. This was the retroaddition of alkyne shown in Scheme 4.35.

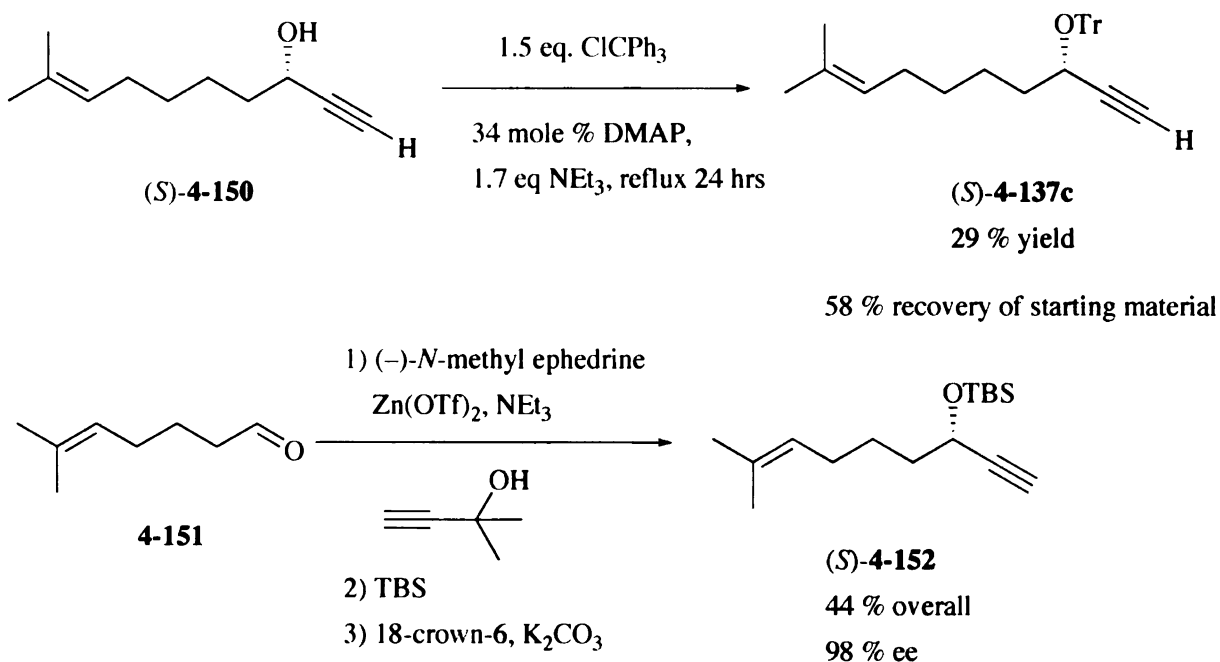
Scheme 4.35. Unexpected Formation of an Aldehyde



The removal of the silyl protecting group on the silylpropargyl ether **4-137a** could be done with TBAF to give compound **4-150**. The use of alcohol **4-150** was required for the formation of compound **4-137c** because the protection of diol **4-145** failed as shown above in Scheme 4.35. The yield was 29 % of compound **4-137c** with a recovery 58 % of the starting material **4-150**. The formation of compound (*S*)-**4-152** was done in 44 % overall yield over three steps

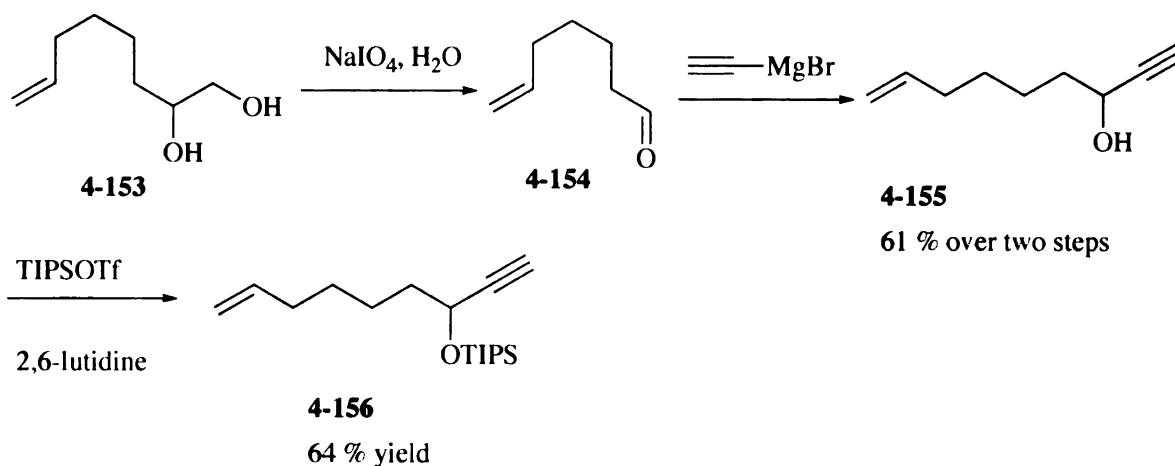
from aldehyde **4-151**. The enantiomeric excess was determined to be 98 % by TBAF deprotection of the silyl ether (*S*)-**4-152** by the application of chiral HPLC.

Scheme 4.36. Protection of the Propargyl Alcohol with TrCl and the Formation of Other Starting Materials



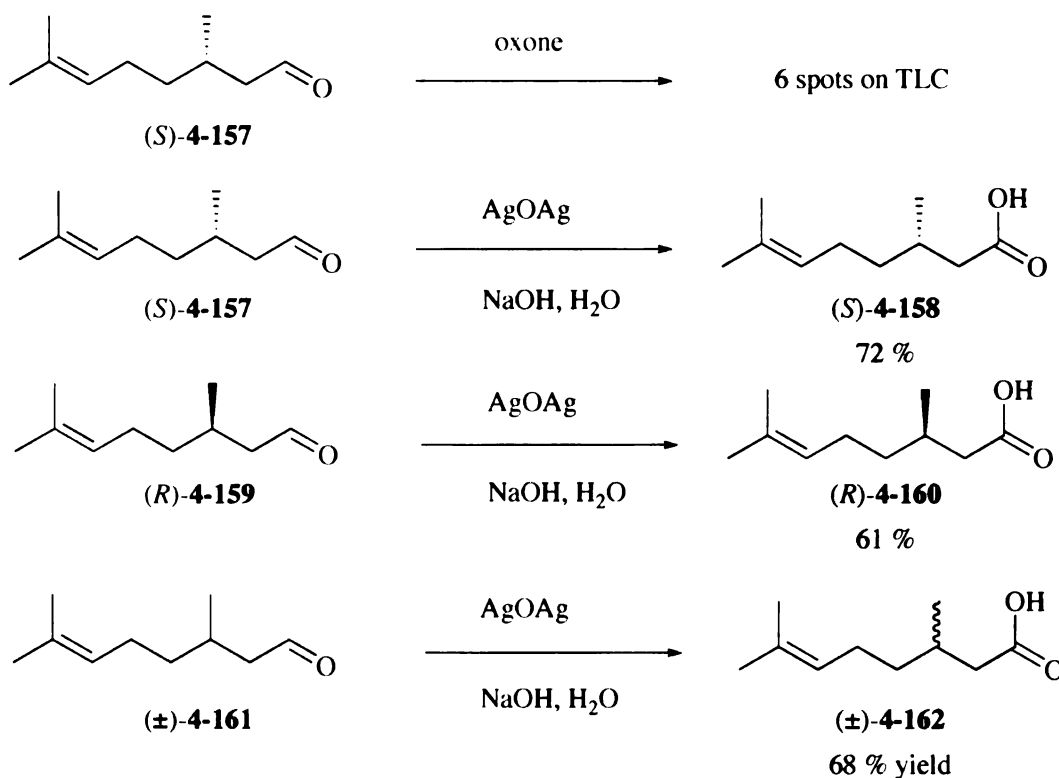
We also wished to explore chemistry with compound **4-156** in the benzannulation reaction which needed to be made. The formation of compound **4-155** was done in 61 % yield over two steps. Compound **4-154** is a known compound.²⁴⁶ The TIPS protection of compound **4-155** gave compound **4-156** in 64 % yield.

Scheme 4.37. Formation of Triisopropyl(non-8-en-1-yn-3-yloxy)silane



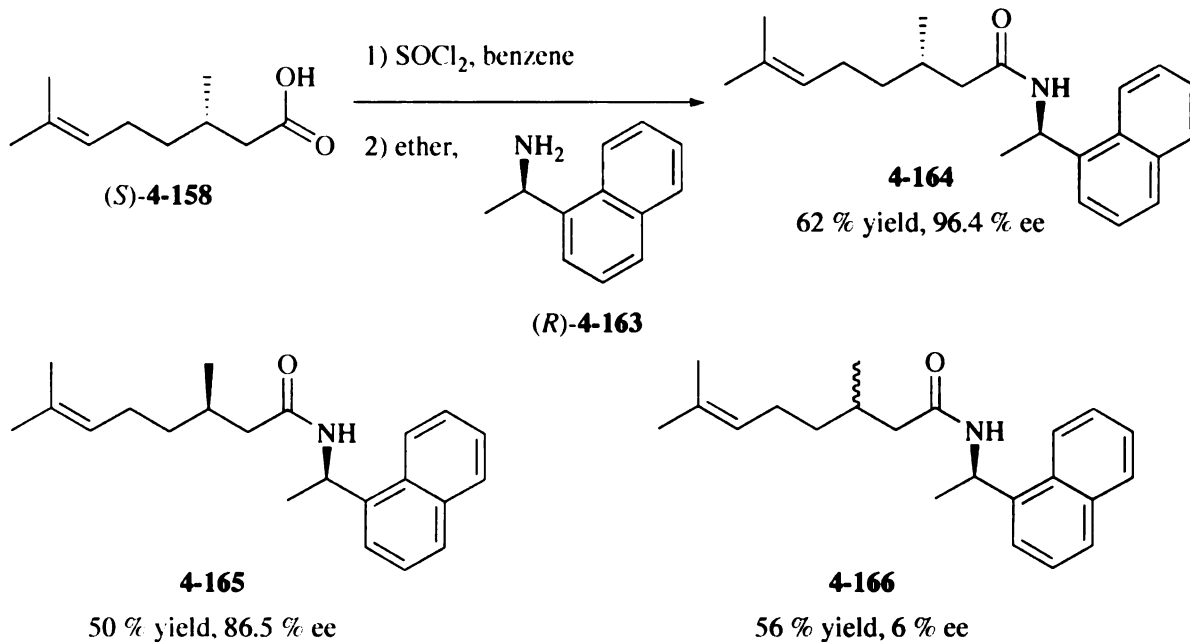
We wished to use citronellal as a starting material for the study of the Wulff-Dötz benzannulation with a tandem Diels-Alder reaction shown in Scheme 4.38. During the course of using citronellal, the enantiomeric excess needed to be determined. The oxidation of aldehyde (*S*)-4-157 was performed with oxone giving six spots on the TLC.²⁴⁷ Noting this result, the literature procedure for the formation of compound (*S*)-4-158 was followed with silver oxide.²⁴⁸ The yield for this reaction was between 61 - 72 % for the oxidation of *R* and *S*-citronellal (*R*)-4-157 and (*S*)-4-159, respectively.

Scheme 4.38. Oxidation of Citronellal



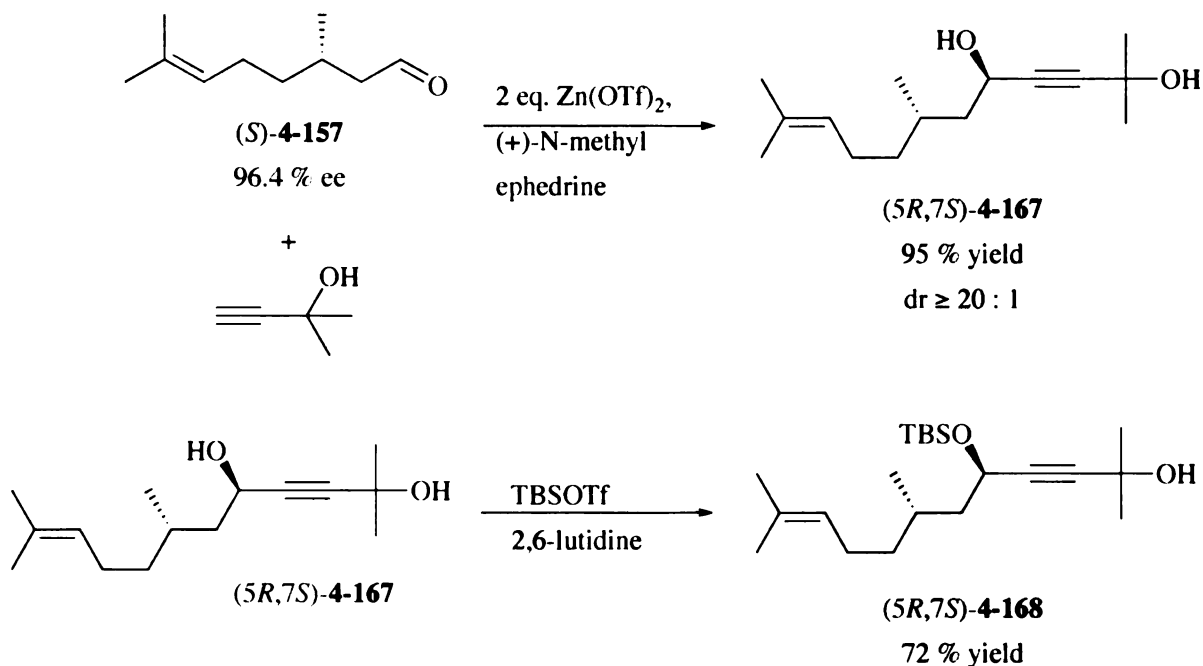
The formation of the amide shown in Scheme 4.39 that was required for the determination of the enantiomeric excess. The carboxylic acid **(S)-4-158** was treated with thionyl chloride followed by the amine **(R)-4-163**. The yields were 50 to 62 % of compound **4-164**. The reaction was carefully followed by TLC to insure the consumption of the starting material. The *(S)*-citronellal shown as compound **(S)-4-157** gave an enantiomeric excess of 96.4 %. The *(R)*-citronellal shown as compound **(R)-4-159** gave an enantiomeric excess of only 86.5 %. The enantiomeric excess was measured by HPLC with a silica column.²⁴⁹ We choose to work with the *(S)*-citronellal shown as compound **(S)-4-157** for the remainder of the experiments due to its high enantiomeric excess available directly out of the bottle from Aldrich chemical company.²⁵⁰

Scheme 4.39. Amide Formation Initially from Citronellal



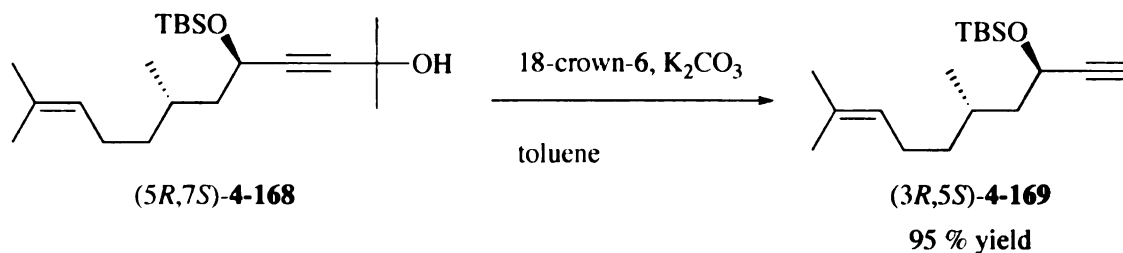
In Scheme 4.40 is depicted Carreira's chemistry for the formation of compound **(5R,7S)-4-167** from compound **(S)-4-157**. The yield was 95 % for the formation of compound **(5R,7S)-4-167**. The diastereomeric ratio was > 20 : 1 as determined by NMR. The TBS protection of the secondary alcohol gave compound **(5R,7S)-4-168** in 72 % yield using TBSOTf and 2,6-lutidine.

Scheme 4.40. Carreira's Chemistry Using Citronellal and Protection of the Resulting Alcohol



The deprotection of compound (5R,7S)-4-168 under basic conditions gave a 95 % yield of compound (3R,5S)-4-169 which is shown in Scheme 4.41. During this reaction a steady flow of nitrogen was maintained to expedite the removal of acetone to move the equilibrium forward.

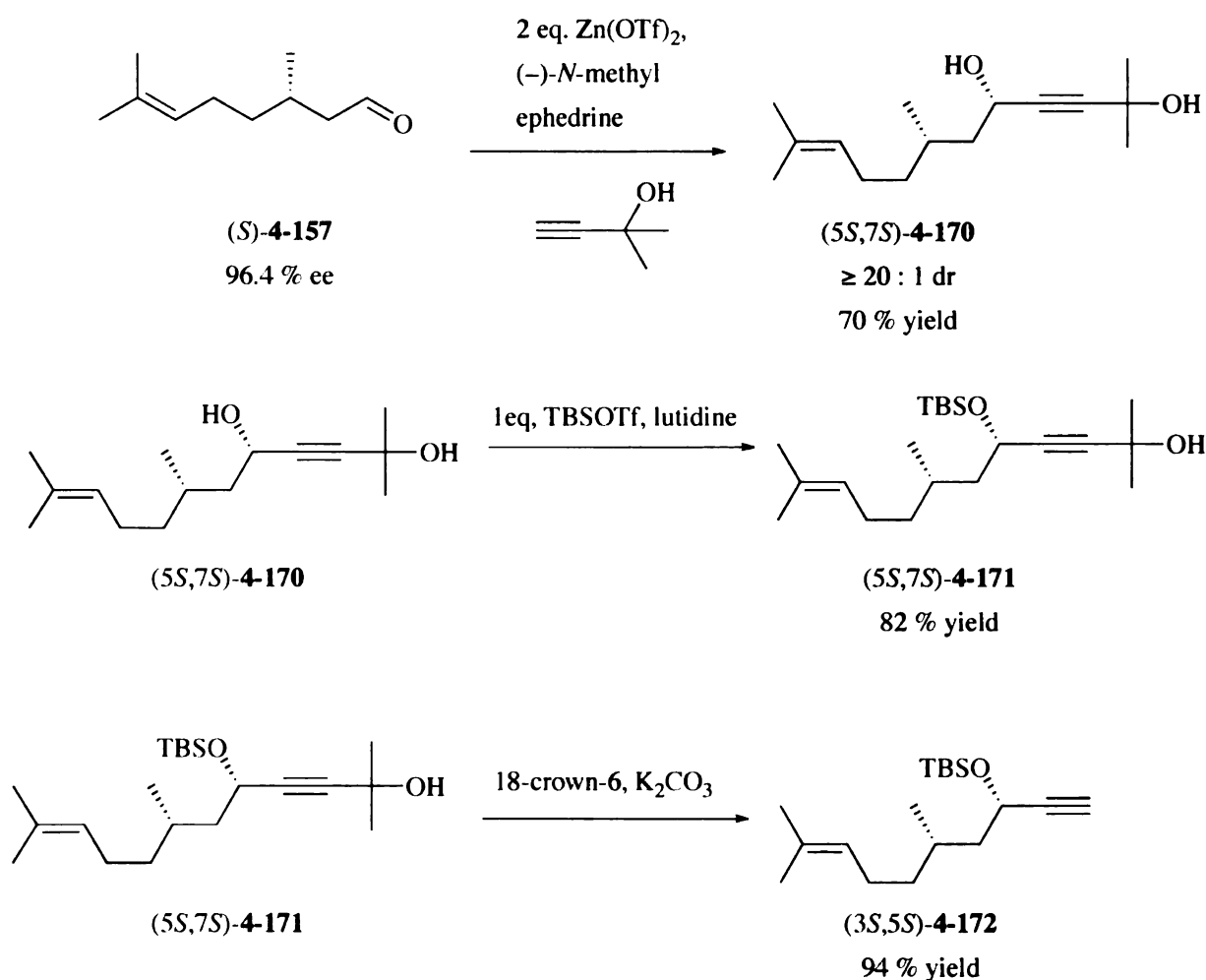
Scheme 4.41. Deprotection to a Terminal Alkyne



The formation of the alkyne to study the mismatched Diels-Alder reaction is shown in Scheme 4.42. From (S)-citronellal (S)-4-157, using Carreira chemistry,²⁴² compound (5S,7S)-4-170 was formed with a yield of 70 % and a

diastereomeric ratio of $> 20 : 1$ that was determined by NMR. With TBSOTf and lutidine, compound (5*S*,7*S*)-**4-171** could be formed in 82 % yield. The deprotection of alkyne (5*S*,7*S*)-**4-171** could be done with 18-crown-6 and K_2CO_3 in quantitative yield to compound (3*S*,5*S*)-**4-172**.

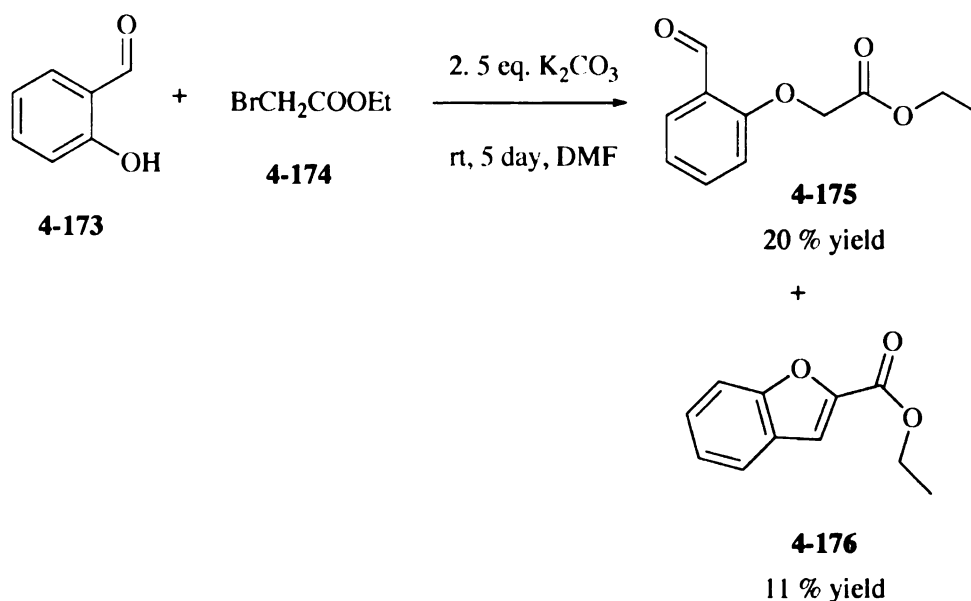
Scheme 4.42. Formation of an Alkyne for Testing the Mismatched System



Next, the synthesis of the non-routine carbene complexes were pursued. For the synthesis of carbene complex **4-180** (Scheme 4.47), the ester **4-176** was required. The alkylation and cyclization of compound **4-173** with compound **4-**

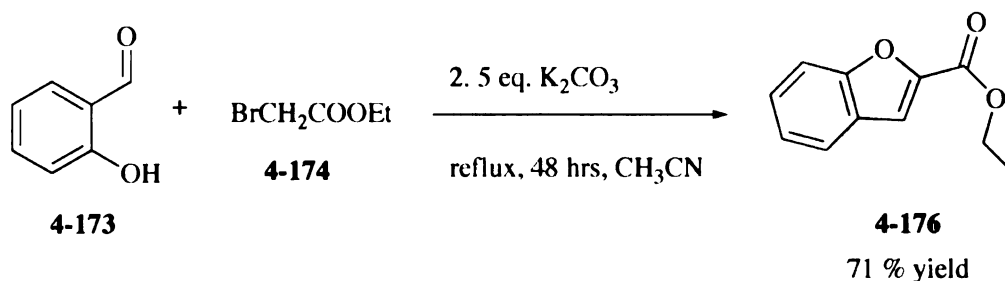
174 is shown in Scheme 4.43.²⁵¹ The yield of compound **4-175** was 20 % and the yield of the desired compound **4-176** was 11 %.²⁵¹

Scheme 4.43. The Alkylation of Salicylaldehyde



However, when the solvent was switched to acetonitrile, the yield of compound **4-176** was 71 % as shown in Scheme 4.44.²⁵¹ This was a significant improvement in yield.

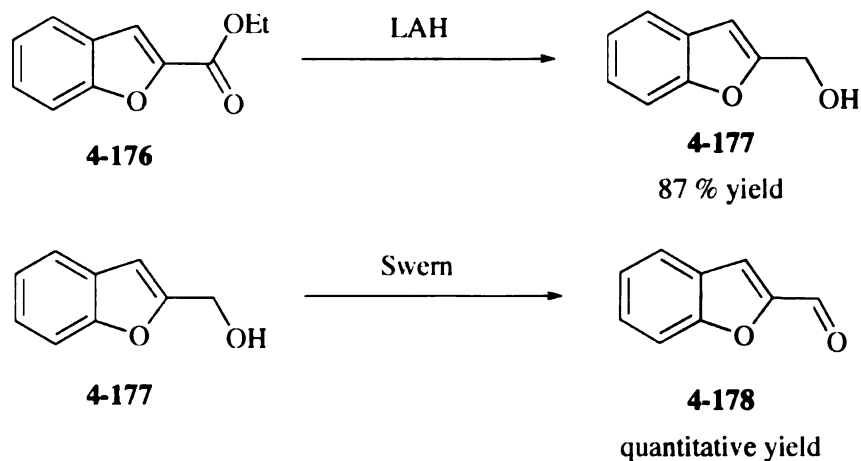
Scheme 4.44. Improved Alkylation of Salicylaldehyde



The lithium aluminum hydride reduction of compound **4-176** is presented in Scheme 4.45.²⁵¹ The yield from compound **4-176** to compound **4-177** was 87

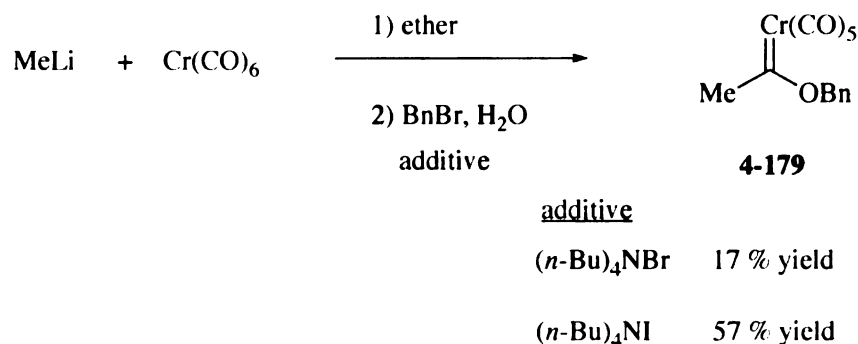
%. The oxidation of compound **4-177** gave a quantitative yield of compound **4-178**.²⁵¹

Scheme 4.45. Lithium Aluminum Reduction with Oxidation to the Aldehyde



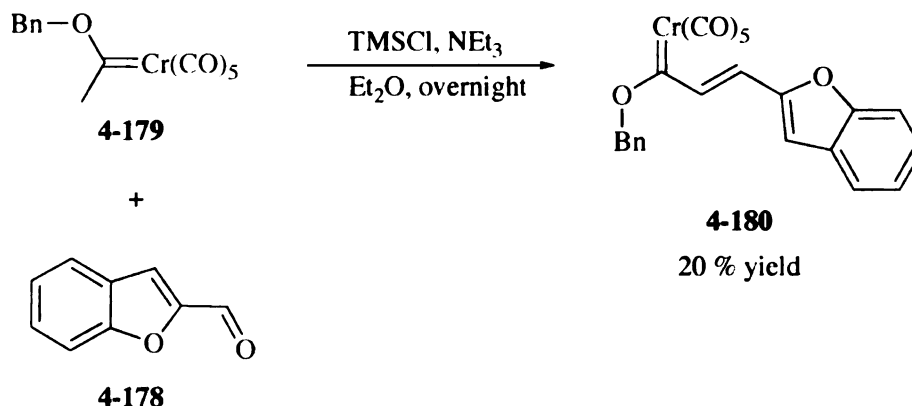
In preparation for the synthesis of carbene complex **4-180** by an aldol reaction, the carbene complex **4-179** was required. The action of methyl lithium on chromium hexacarbonyl as shown in Scheme 4.42 followed by benzyl protection gave complex **4-179**.²⁵² The literature procedure with tetrabutylammonium bromide was followed giving a yield of 17 % compound **4-179**.²⁵² A modified procedure with tetrabutylammonium iodide gave a yield of 57 % of compound **4-179**.²⁵²

Scheme 4.46. Formation of a Benzoxyethyl Carbene Complex



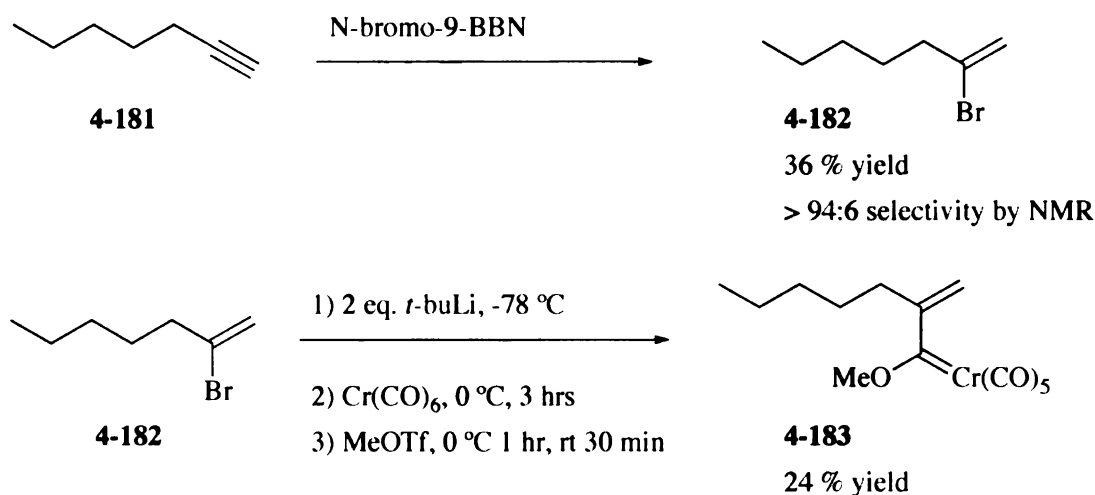
The aldol condensation of aldehyde **4-178** and carbene complex **4-179** gave a yield of 20 % for the carbene complex **4-180**. The silyl agent TMSCl and the base triethyl amine in ether are used to promote the reaction shown in Scheme 4.47.²⁵³ This gave a starting material for the Wulff-Dötz benzannulation reaction with a tandem Diels-Alder reaction.

Scheme 4.47. Aldol Condensation Forming a Carbene Complex



In Scheme 4.44, the bromoborylation of alkyne **4-181** is shown.²⁵⁴ This preliminary study gave a yield of 36 % for compound **4-182** with the selectivity of 94 to 6. Compound **4-182** was treated with *t*-butyl lithium, chromium hexacarbonyl, and finally methyl triflate. The yield for compound **4-183** was 24 %.

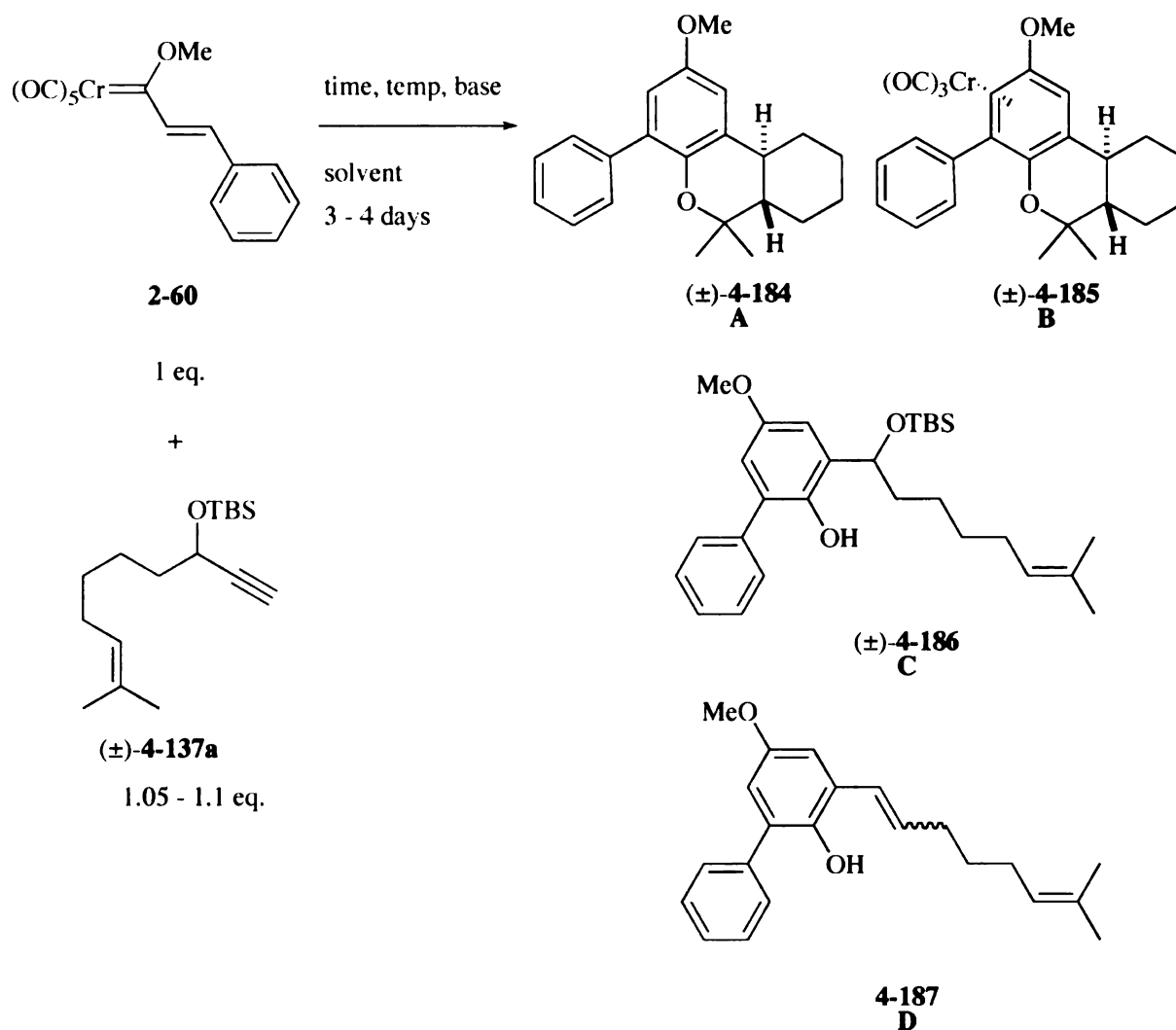
Scheme 4.48. Formation of an Alkyl Carbene Complex



4.7.2 Initial Optimization

Shown in Scheme 4.49 is the optimization of the Wulff-Dötz benzannulation reaction for the formation of the cyclized products (±)-**4-184** and (±)-**4-185**. Demetalation of the chromium tricarbonyl complex was noted during the optimization experiments giving compound (±)-**4-184**. The chromium tricarbonyl complex (±)-**4-185** was isolated during these experiments. Also observed during these experiments was the formation of phenol (±)-**4-186**. The elimination of the silyl ether has also been observed to give the olefin **4-187**. The elimination has been previously observed in chapter three with the propargyl amines of this work and it has been observed by Hsung.²⁵⁵

Scheme 4.49. Optimization of the Tandem Wulff-Dötz Reaction / Diels-Alder Reaction



The results of the preliminary optimization are shown in Table 4.3 for the reaction shown in Scheme 4.49. We varied the base from organic to inorganic. The solvent was changed including dichloromethane and toluene. The general conclusions from these experiments are that dichloromethane did not work well for the formation of the Diels-Alder products ($\pm$)-4-184 (A) and ($\pm$)-4-185 (B) as shown in entries 1 and 2. The major product was compound ($\pm$)-4-186 (C) in entry 1 and this yield was not reproducible. The highest yield was obtained in

entry 3 giving a 60 % yield of (±)-**4-184** and 18 % yield of (±)-**4-185**. The irreversible base sodium hydride was used in entry 10 with only a low yield of cyclized products. The inorganic base potassium carbonate did not produce high yields of the cyclized products in entry 11. The bases giving good yields of cyclized products were Hunig's base ($\text{EtN}i\text{Pr}_2$) in entry 3 or proton sponge (p.s.) in entry 7. We chose entry 3 with the TBS as a protecting group for compound (±)-**4-137** and Hunig's base as a starting point for the optimizations of the traceless stereinduction methodology.

Table 4.3. Results of the Optimization of the Tandem Wulff-Dötz Reaction
/ Diels-Alder Reaction

entry ^a	R ₁	Base	solvent	temp	A ^b	B	C ^b	D ^b	Total
1	TBS	None	DCM	60	-	-	66		
2 ^c	TBS	$\text{EtN}(i\text{Pr})_2$	DCM	80	10	17	49	trace	76
3	TBS	$\text{EtN}(i\text{Pr})_2$	toluene	80	60	18	8	3	89
4 ^c	TBS	$\text{EtN}(i\text{Pr})_2$	toluene	90	20	36	11	12	79
5	TBS	DABCO	toluene	90	nd	nd	36	nd	36
6 ^d	TBS	p.s. 2 eq.	toluene	90	35	42	10	8	95
7	TBS	p.s. 5 eq.	toluene	90	46	24	20	4	94

Table 4.3. (cont'd)

entry ^a	R ₁	Base	solvent	temp	A ^b	B	C ^b	D ^b	Total
8	TBS	TMP	toluene	90	<2	18	32	27	79
9	TBS	sparteine	toluene	90	10	9	27	15	61
10	TBS	NaH	toluene	90	11	trace	40	7	58
11	TBS	K ₂ CO ₃	toluene	90	-	-	46	nd	46
12	TBS	EtN(iPr) ₂	toluene	100	49	18	21	trace	88
13	TBS	EtN(iPr) ₂	toluene	120	58	20	<2	10	90
14	TBS	quinoline	toluene	120	57	11	13	trace	81

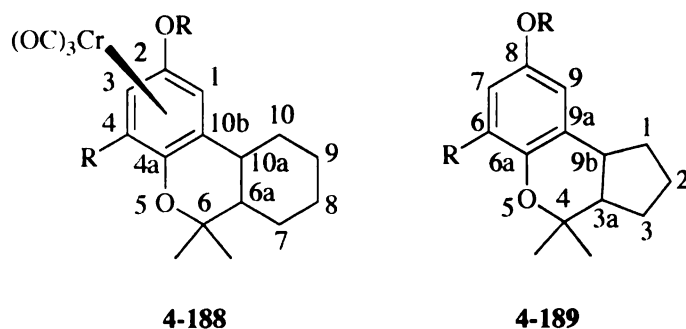
a. Typical conditions: 0.03 M in carbene, 5 eq. base, temperature control ± 0.5 °C. Air oxidation for 3 - 4 days in DCM/toluene. b. Compounds A, C, D were isolated as a mixture and yields were calculated via NMR. c. Two day oxidation. d. acetonitrile as solvent for oxidation.

4.7.3 Nomenclature

Before the discussions of our results continues, some nomenclature regarding the 6-6-6 and the 6-6-5 ring systems generated during these studies of traceless stereoinduction need to be presented. Shown in Figure 4.2 is the numbering system of two ring systems.²⁵⁶ The numbering systems differ substantially between the 6-6-6-ring system shown as illustration **4-188** or hexahydrodibenzopyran and the 6-6-5-ring system²⁵⁷ shown as illustration **4-189** which is self evident as shown in Figure 4.2. We have chosen to assign the chirality of the chromium tricarbonyl group at the ether linkage at carbon 4a in

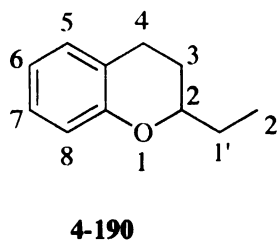
illustration **4-188**, which happens to have the highest priority atom (oxygen) attached to the chromium tricarbonyl arene.²⁵⁸

Figure 4.2. The Numbering System of 6-6-6 and 6-6-5 Ring Systems



The numbering system of chromans is shown in Figure 4.3. These numbers again substantially differ from those previously shown.²⁵⁹ The numbering sequence begins at oxygen 1 and proceeds around the ring shown as illustration **4-190**. A side chain attached at carbon 2 is numbered beginning with 1'.²⁶⁰

Figure 4.3. Numbering System of Chromans



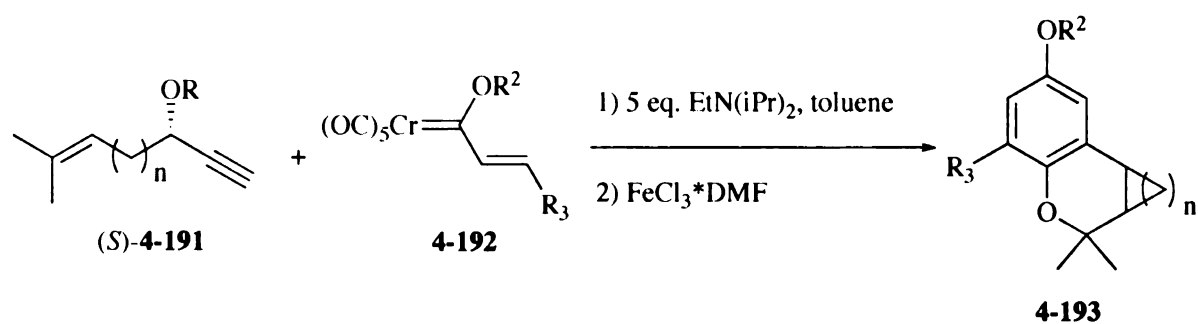
4.7.4 Experimental Results of the Traceless Stereoinduction Methodology

With the preliminary background discussions completed, the serious discussions of traceless stereochemistry can begin. Shown in Table 4.3 are the results of the traceless stereoinduction for the formation of

hexahydrodibenzopyrans. The benzannulation with a tandem Diels-Alder reaction is shown between compound (S)-4-191 and 4-192 to give compound 4-193. For compound (S)-4-191, when R is TIPS, the yield of compound (6a*R*,10a*R*)-4-194 is 42 % and 94 % ee. The yield was 60 % at 100 °C and the enantiomeric excess dropped slightly to 90 % of compound (6a*R*,10a*R*)-4-194. The yield of (6a*R*,10a*R*)-4-194 at 110 °C was 48 % with 92 % ee. The TBS ether of (S)-4-191 reacted at 90 °C to give a 39 % yield of (6a*R*,10a*R*)-4-194 with 94 % ee and the same results were observed at 100 °C. When the reaction time increased to 48 hours, the yield increased to 51 % without significant loss of ee. At 110 °C, the yield of compound (6a*R*,10a*R*)-4-194 was 58 % and the ee was 88 %. With a bulkier protecting group such as compound (S)-4-151c, the yield was 45 % and the ee was 86 %. Replacing the methoxy group on the carbene complex with a benzyloxy group gave compound (6a*R*,10a*R*)-4-195 in 48 % yield and 93 % ee. For the 6-6-5-member (3a*R*,9b*R*)-4-196, the yield was 50 % and the ee could not be determined due to decomposition of the compound during deprotection of the methyl ether. Compound (3a*R*,9b*R*)-4-197 was made with a benzyl-protecting group, and the yield was 43 % and ee was 94 %. Note that the compounds in Table 4.3 contained about 5 % of the *cis*-compound. This was accurately determined for compound 4-194 by GC/FID, and for the remainder of the compounds, the ratio was determined by NMR. The enantiomeric excess for the compounds in Table 4.3 were determined by removal of the either the benzyl-protecting group or the methyl protecting group. The demethylation will be

discussed later in this chapter. The absolute stereochemistry will be discussed in detail later but was assigned by stereochemical arguments from the work of Hsung.²⁶¹

Table 4.4. Results from Traceless Stereoinduction Methodology



Product	R	Temperature	Time (hrs)	Yield %	ee %
4-194 (6a<i>R</i>, 10a<i>R</i>)	TIPS	90	24	42	94
	TIPS	100	48	60 (2 runs)	90
	TIPS	110	24	48	92
	TBS	90	24	39	94
	TBS	100	24	39	94
	TBS	100	48	51	92
	TBS	110	24	58	88
	Tr	100	48	45 (2 runs)	86
4-195 (6a<i>R</i>, 10a<i>R</i>)	TIPS	100	48	48	93

Table 4.4. (cont'd)

Product	R	Temperature	Time (hrs)	Yield %	ee %
 4-196 (3 <i>aR</i> ,9 <i>bR</i>)	TBS	110	24	50	n/a
 4-197 (3 <i>aR</i> ,9 <i>bR</i>)	TBS	100	48	43	94

For compound (6*aR*,10*aR*)-**4-198** shown in Table 4.5, the yield was 40 % and the ee was 91 %. For compound *rel*-(2*R*,3*R*,4*S*)-**4-199** the yield was 23 % and ee was not determined. Compound *rel*-(2*R*,3*R*,4*S*)-**4-199** was a dimer from this reaction suggesting that the electron density of the olefin is critical to obtain the intramolecular Diels-Alder product. For compound (6*aR*,10*aR*)-**4-200**, the compound was unstable to silica gel resulting in a lower yield of 18 % with a dr of 9 : 1 (*trans* : *cis*). For the formation of compound **4-201**, it was found that the resulting product was a complex mixture that could not be characterized by the methods employed. Note that the compounds in Table 4.5 generally contained 5 % of the *cis*-compound unless otherwise noted.

Table 4.5. Additional Results of Traceless Stereoinduction

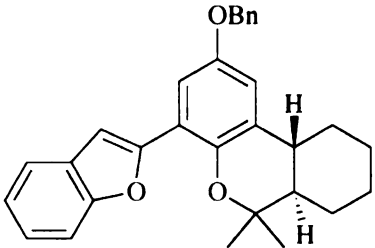
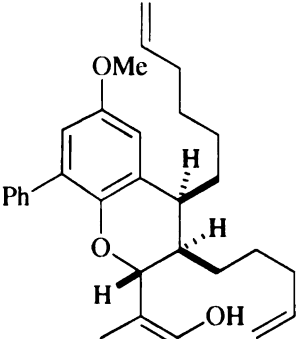
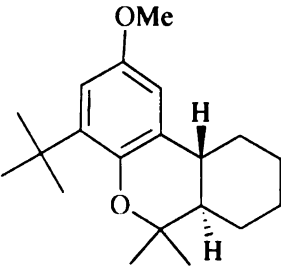
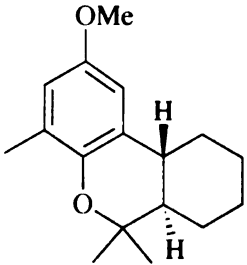
Product	R	Temperature	Time (hrs)	Yield %	ee %
 4-198 (6a<i>R</i>,10a<i>R</i>)	TIPS	100	48	40	91
 4-199 <i>rel</i>-(2<i>R</i>,3<i>R</i>,4<i>S</i>)	TIPS	100	48	23	n/a

Table 4.5. (cont'd)

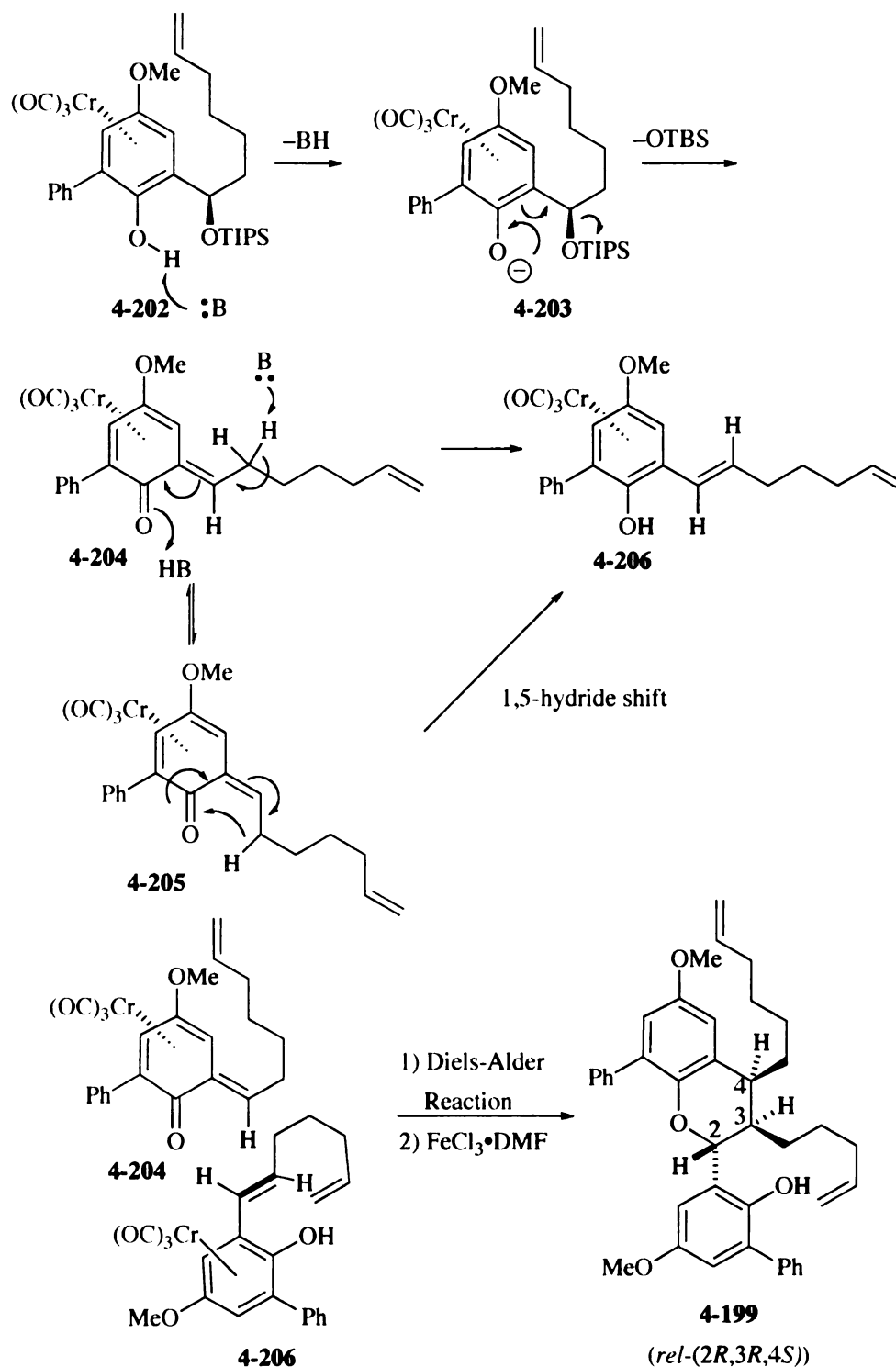
Product	R	Temperature	Time (hrs)	Yield %	ee %
 4-200 (6aR,10aR)	TIPS	100	48	18 dr: 9:1	n/a
 4-201 (6aR,10aR)	TIPS	100	48	complex mixture	n/a

The formation of dimer as compound *rel*-(2*R*,3*R*,4*S*)-**4-199** needs to be discussed. The mechanism of this formation is shown in Scheme 4.50. Compound **4-202** would be formed from a benzannulation reaction. In the presence of base, the anion **4-203** would be formed. An *o*-QM may then be formed shown as intermediate **4-204**. There may be an equilibrium between **4-204** and **4-205**. Intermediate **4-204** may undergo elimination with base to form olefin **4-206**. Alternatively intermediate **4-205** may undergo a 1,5-hydride migration to give olefin **4-206**. A Diels-Alder reaction between *o*-QM **4-204** and olefin **4-206** followed by oxidation with FeCl₃•DMF per the reaction procedure

gives compound *rel*-(2*R*,3*R*,4*S*)-**4-199**. The coupling constants obtained by ^1H

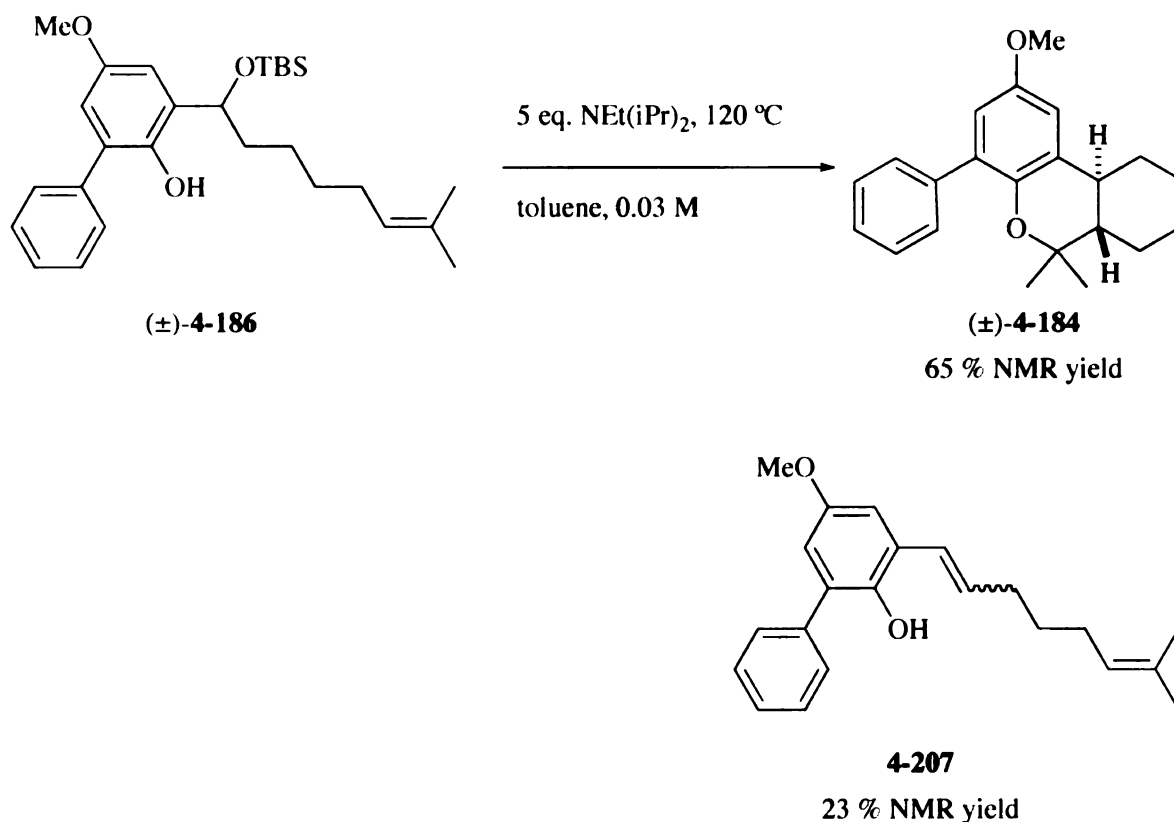
NMR of the product *rel*-(2*R*,3*R*,4*S*)-**4-199** will be discussed later.

Scheme 4.50. Elimination with a Concomitant Diels-Alder Reaction



The intramolecular Diels-Alder reaction was also carried out without chromium tricarbonyl complexed to the phenol as shown in Scheme 4.51. Compound ($\pm$)-**4-186** was made using the conditions shown in Table 4.3 entry 1. Racemic ($\pm$)-**4-186** is converted to the Diels-Alder product ($\pm$)-**4-184** with compound **4-207** as a byproduct. These results were determined by NMR and GC/FID. The stereochemistry at the bridgehead of compound ($\pm$)-**4-184** was *trans* for the major product with the minor (< 6 %) being the *cis*.

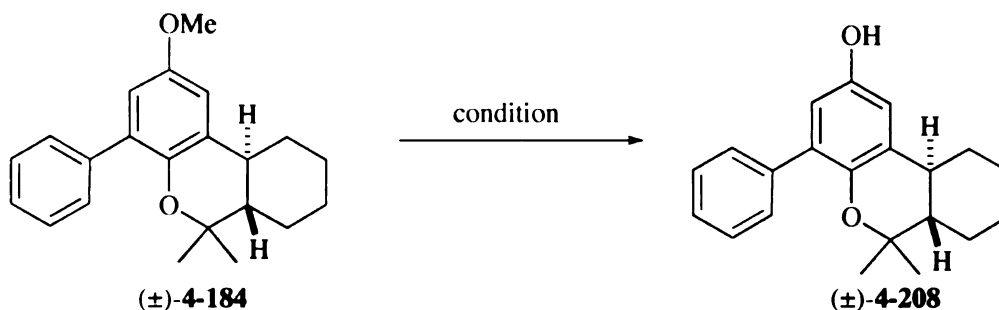
Scheme 4.51. Diels-Alder Reaction Without Chromium Tricarbonyl



Shown in Table 4.6 are the results for the determination of a procedure for the demethylation of compound ($\pm$)-**4-184** to give the phenol ($\pm$)-**4-208**. In entry 1, LiPPh₂ was employed without success.²⁶² In entry 2, sodium cyanide in DMSO failed to give any desired product as well.²⁶³ The use of CAN resulted in

complete decomposition of the starting material (entry 3).²⁶⁴ In entry 4, the use of superhydride also failed.²⁶⁵ In entry 5, the first success was obtained with AlCl_3 and propane thiol with a 35 % conversion.²⁶⁶ The use of AlBr_3 and propane thiol gave complete conversion by TLC in entry 6.²⁶⁷ The 6-6-5-member ring (3a*R*,9b*R*)-4-196 decomposed using AlBr_3 and propane thiol. Therefore compound (3a*R*,9b*R*)-4-197 was prepared and deprotected with Pd/C and hydrogen gas.

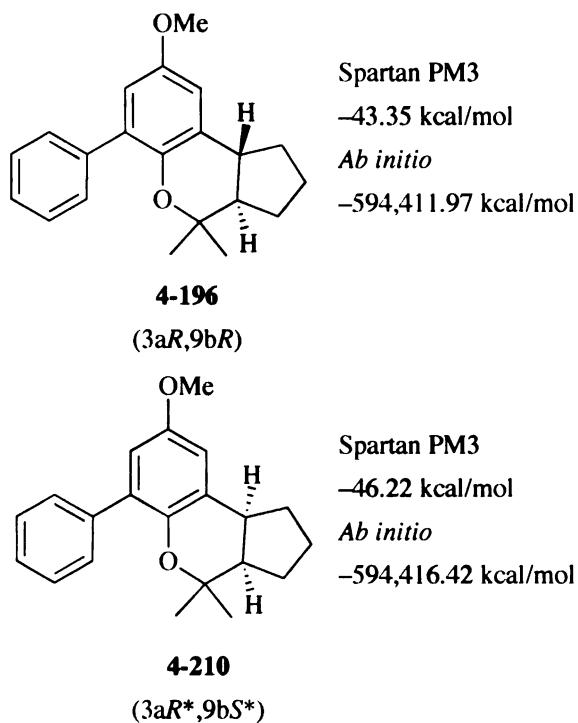
Table 4.6. Demethylation of Hexahydrodibenzopyrans



entry	Condition	Result
1	LiPPh_2 , THF 65 °C, 24 hrs	57 % recovery, no product
2	NaCN , DMSO	82 % recovery, no product
3	CAN solution, CH_2Cl_2	complete decomposition
4	Superhydride	no product by TLC
5	<i>n</i> -PrSH / AlCl_3 , 18 hrs	35 % conversion by NMR
6	<i>n</i> -PrSH / AlBr_3 , 5 - 10 minutes	70 % yield

Shown in Figure 4.4 are the energy calculations of the *cis* and *trans* isomers of the 6-6-5-ring system. The energy for compound (3a*R*,9b*R*)-4-196 was −43.35 kcal / mol and the energy for compound (3a*R*^{*},9b*S*^{*})-4-210 was −46.22 kcal / mol for PM3 spartan energy calculations. The energy difference was 2.87 kcal / mol. The energy difference between compound (3a*R*,9b*R*)-4-196 and compound (3a*R*^{*},9b*S*^{*})-4-210 for the *ab initio* calculations was 4.45 kcal / mol. The *ab initio* calculation were done at the STO-3G level of theory. This explains why the *cis* predominates under acidic conditions as shown in Scheme 4.10 without other controlling factors however the calculated energies seem high for the *ab initio* calculation. To explain the meaning of the term high, the value of 4.5 kcal / mol for a cyclohexane ring system gives equatorial / axial ratios of > 99 : 1. For the system depicted in Scheme 4.10, the ratio is 85 to 15 for the *cis* versus the *trans* with the calculated energy being 4.5 kcal / mol, the ratio should be > 99 to 1.²⁶⁸

Figure 4.4. Energy Differences Between *Cis* and *Trans* Products

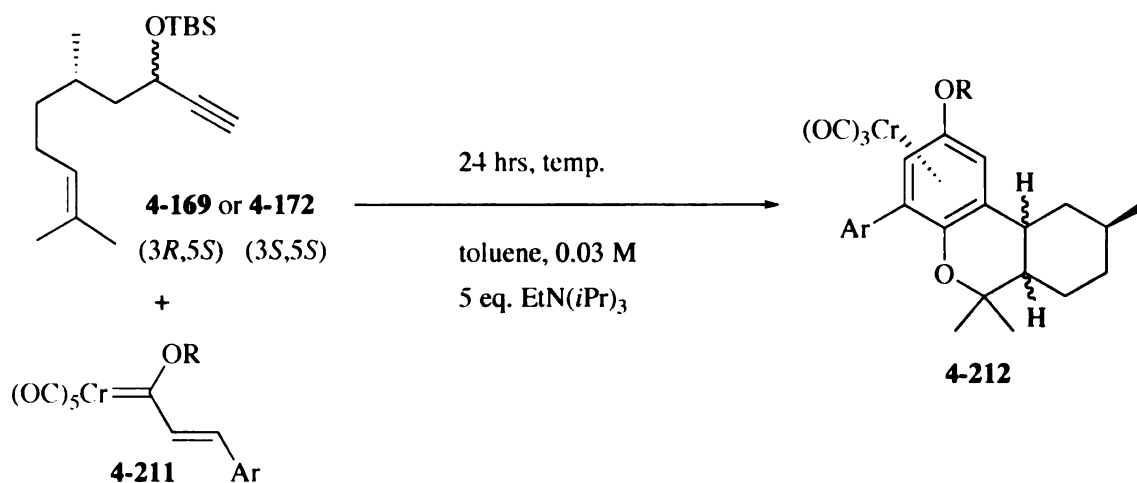


4.7.5 A Matched and Mismatched Case Study of the Tandem Wulff-Dötz / Diels-Alder Reaction

In Table 4.7, the benzannulation with a tandem Diels-Alder reaction matched-mismatched case study is presented. In this study compound (3*R*,5*S*)-**4-169** and carbene complex **2-60** are charged into a flask and heated for the specified time. In entry 1, the matched case is presented. Essentially one diastereomer was present in entry 1. The ratios presented in Table 4.7 were determined by NMR integration of peaks at and around 3.8 ppm. These integrations were substantiated by the GC/FID integrations after demetalation of the complex. Likewise compound (3*S*,5*S*)-**4-172** and carbene complex **2-60** was added to a flask for entry 2, the yield of **4-214** for the reaction was 34 % at 80 °C.

At 90 °C, the yield was 65 %. The diastereomeric ratio was 100 : 65 at 80 °C and 100 : 36 at 90 °C. The diastereomers obtained in entry 2 will be discussed later.

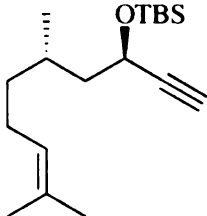
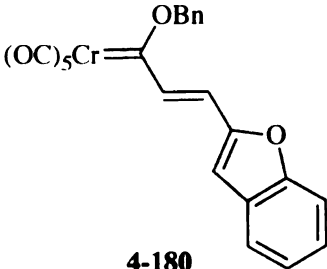
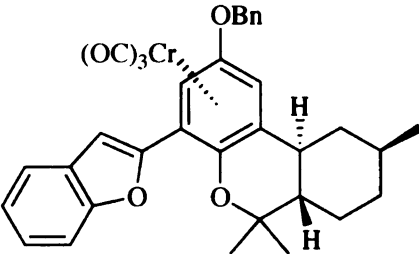
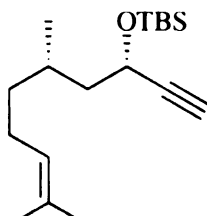
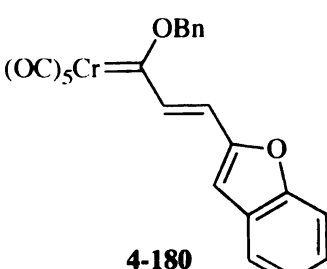
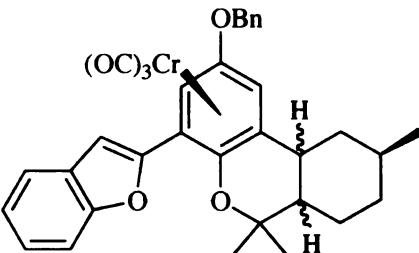
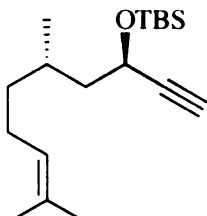
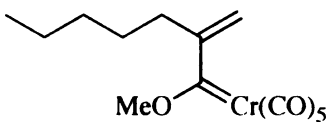
Table 4.7. Matched and Mismatched Case Study



Entry	Akyne	Carbene Complex	Chromium arene
1	(3<i>R</i>,5<i>S</i>)-4-169	2-60	4-213 (4<i>aS</i>,6<i>aS</i>,9<i>S</i>,10<i>aS</i>) 56 % yield, dr: ≤ 5 : ≤ 2 : 100, 80 °C
2	(3<i>S</i>,5<i>S</i>)-4-172	2-60	4-214a, 4-214b, and 4-214c 34 %, dr: 100 : 65 : 5, 80 °C 65 %, dr: 100 : 36 : 15, 90 °C

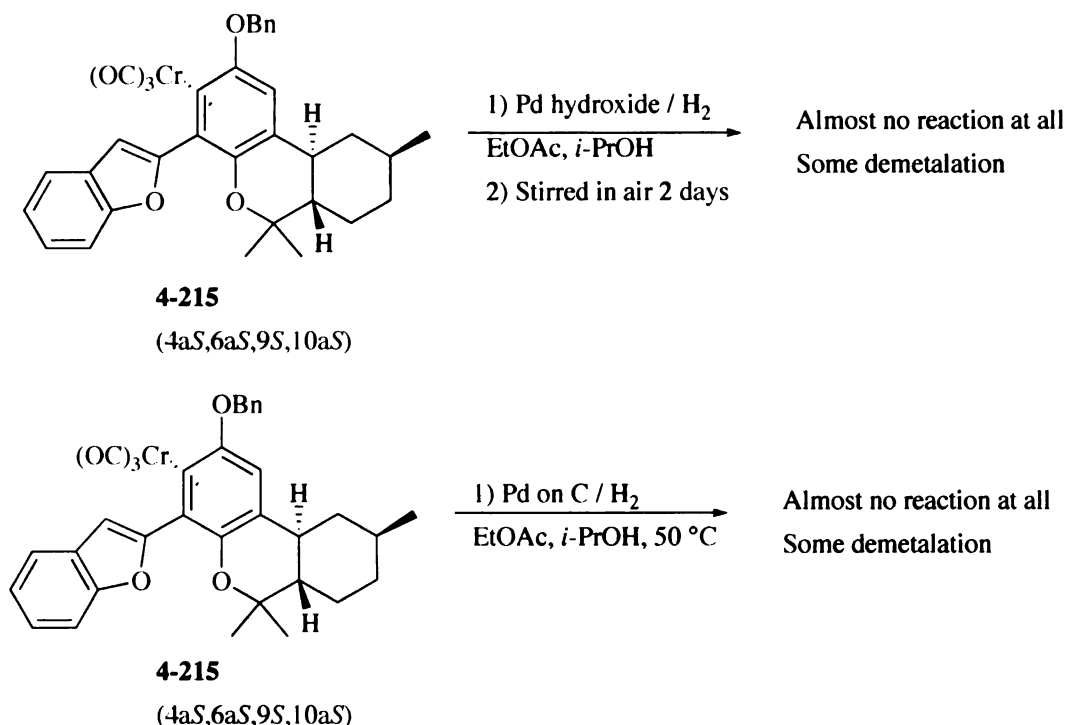
In entry 1 of Table 4.7, for the benzofuryl carbene complex **4-180**, the yield of **4-215** was 47 % with essentially one diastereomer. In entry 2, the mismatched system gives a diastereomeric ratio of 100 : 44 for compound **4-216**. In entry 3, the evaluation of carbene complex **4-183** resulted in a complex mixture. The diastereomers obtained in entry 2 will be discussed later.

Table 4.8. Matched and Mismatch Case Study

Entry	Alkyne	Carbene complex	Chromium arene
1	 (3R,5S)-4-169	 4-180	 4-215 (4aS,6aS,9S,10aS) 47 % yield, dr: ≤ 5 : ≤ 5 : 100, 80 °C
2	 (3S,5S)-4-172	 4-180	 4-216a , 4-216b, and 4-216c 39 % yield, dr: 100 : 44 : 10, 80 °C
3	 (3R,5S)-4-169	 4-183	Complex Mixture

Even more interesting, the presence of chromium tricarbonyl prevented the benzyl deprotection even at elevated temperatures. Shown in Scheme 4.52, the deprotection was attempted with compound **4-215**.

Scheme 4.52. Attempted Debenzylation of a Chromium Tricarbonyl Arene

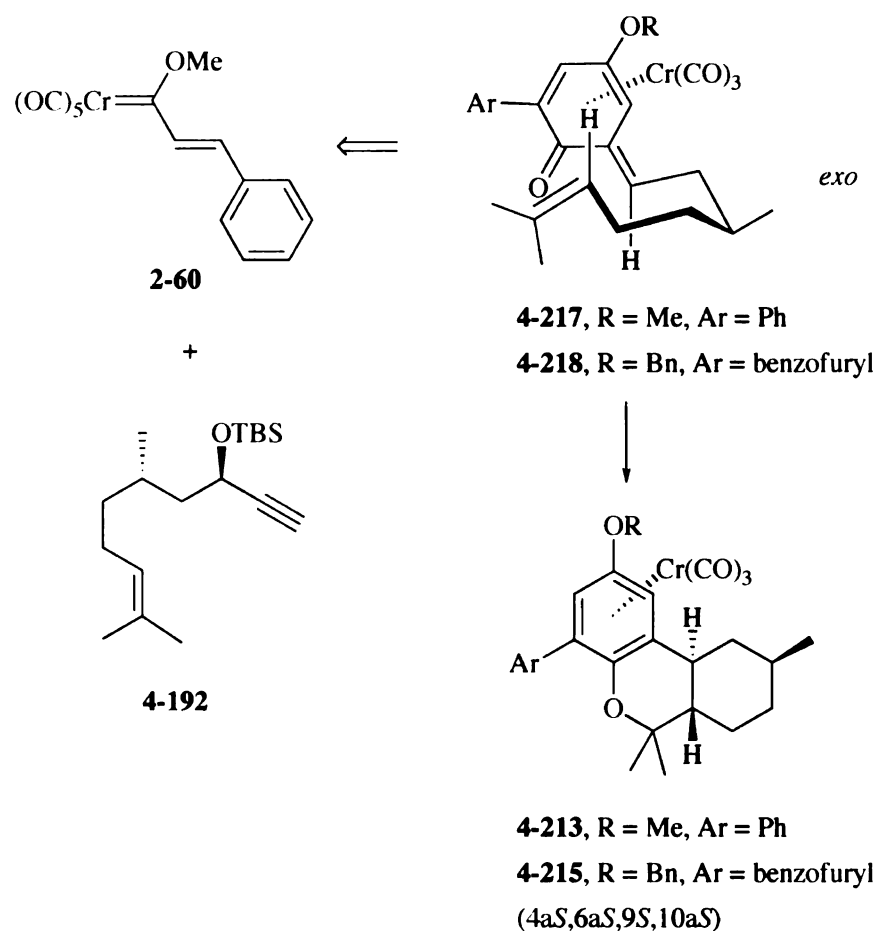


4.7.6 Proposed Stereochemical Origins of the Matched and Mismatched Studies

From compound **2-60** and **4-169**, intermediate **4-217** could form which can undergo the Diels-Alder reaction to give compound **4-213** and **4-215**. This has been evaluated in Tables 4.7 and 4.8. This system is the matched case because the equatorial methyl and the chromium tricarbonyl group cooperated to give one compound. The chromium tricarbonyl motif blocks the back face of the heterodiene in **4-217** and **4-218**. Compounds **4-213** and **4-215** show a *trans*-coupling constant and the nOe experiments also suggest compounds **4-213** and

4-215 along with the literature precedent²³⁰ for the chair transition state (*exo* approach) shown in Scheme 4.53 giving the 4a*S*,6a*S*,9*S*,10a*S* stereochemistry.

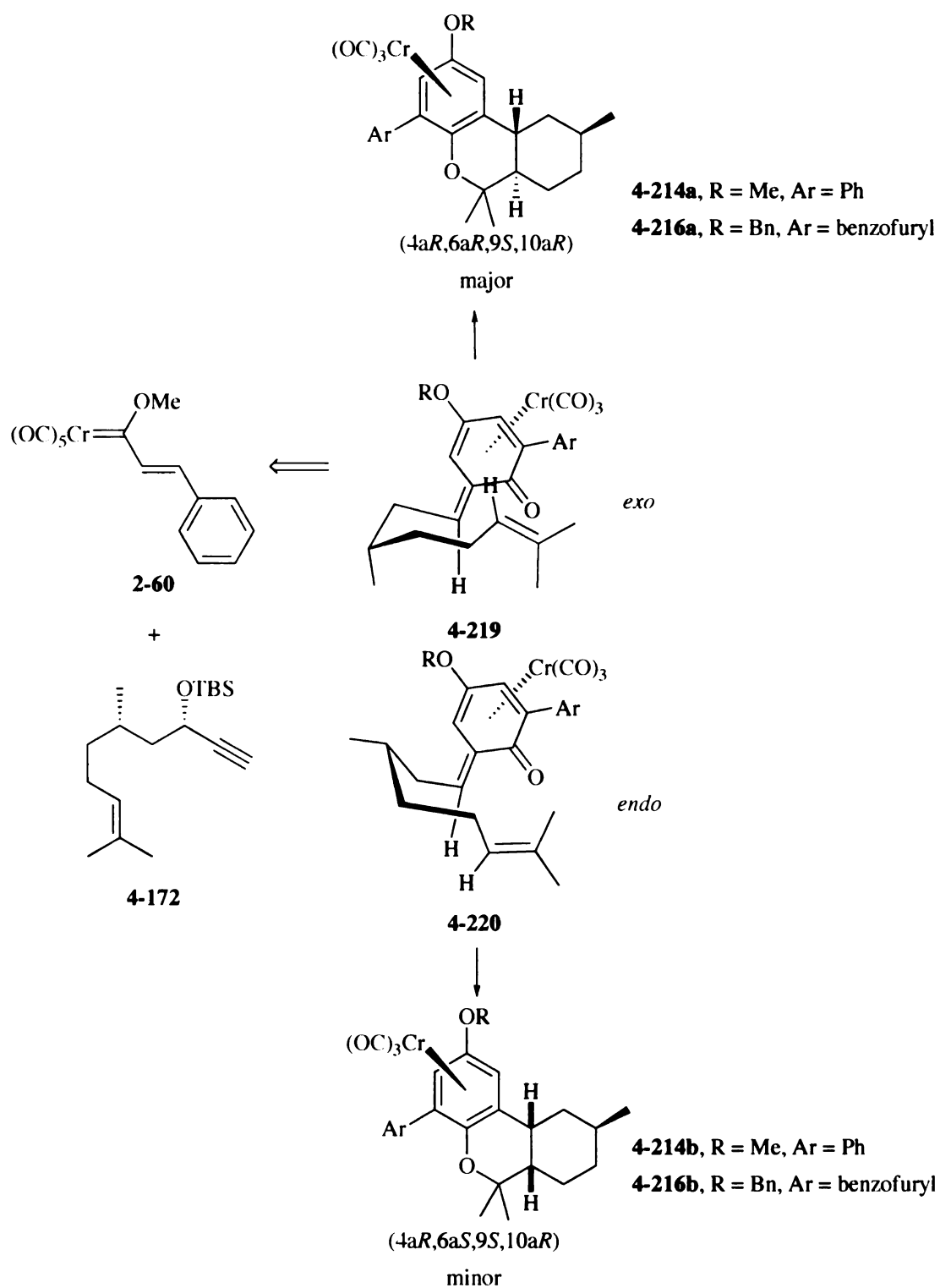
Scheme 4.53. Proposed Chair Conformation Preceding the Diels-Alder Reaction



Shown in Scheme 4.54 is the mismatched case. It is mismatched because the substituent methyl and the chromium tricarbonyl group do not cooperate to give one compound. Intermediate **4-219** could originate from compounds **2-60** and **4-172** with axial methyl giving compounds **4-214a** or **4-216a** as the major product. Alternately, conformation **4-220** could be formed

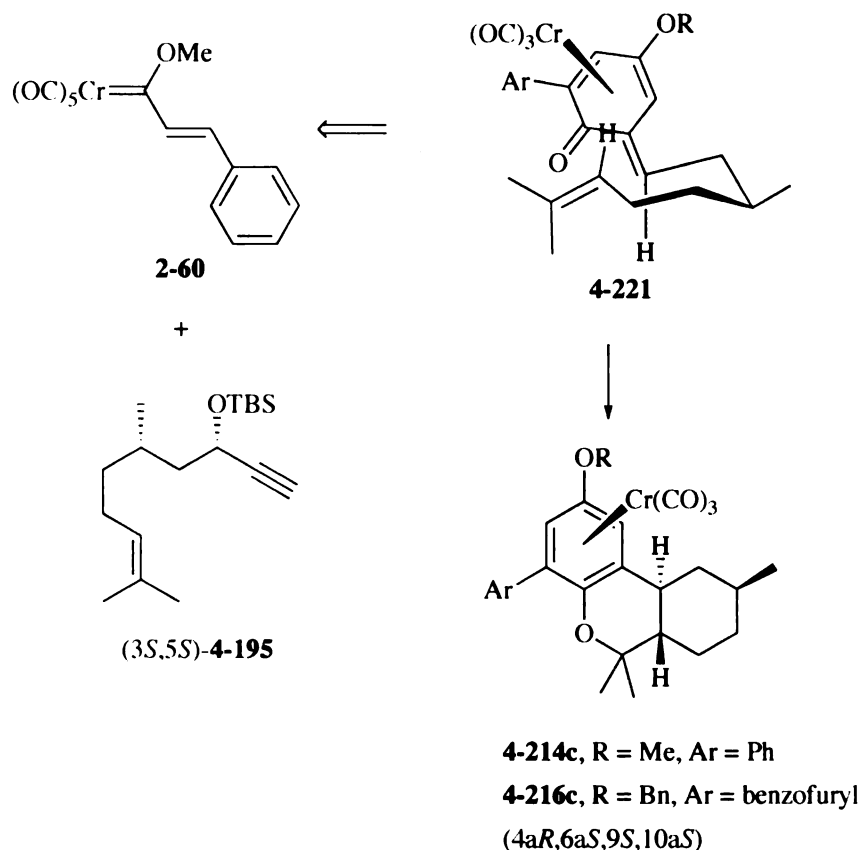
giving compounds **4-214b** or **4-216b** with the *cis*-bridgehead. Conformations **4-219** and **4-220** could interconvert.

Scheme 4.54. Proposed Conformation for the Mismatched Diastereomer System



Another alternative that we have ignored up to this point is the possibility that the olefin may approach the *o*-QM from the same face as the chromium tricarbonyl group. Shown in Scheme 4.55 is what we have previously called the "mismatched" case. Shown is the approach of the dieneophile *syn* to the chromium tricarbonyl group. This would result in the same carbon skeletal diastereomer (6a*S*,9*S*,10a*S*) as is formed in the "matched case" shown in Scheme 4.51 only differing by the configuration of the chromium at carbon 4a. If compound **4-214c** or **4-216c** were the major products, this would contradict the examples shown by Kündig which have previously been published that demonstrate the *anti* approach of the dieneophile to the chromium tricarbonyl group.²²⁸ This system shown in Scheme 4.55 should also only give one isomer if the *syn* approach to the chromium tricarbonyl was preferred and that is not the case. Three diastereomers are actually observed for this system. The dominant approach of the dieneophile in the cases discussed so far is *anti* to the chromium tricarbonyl group as initially proposed. The approach shown in Scheme 4.55 does account for the formation of the minor diastereomers shown as compound **4-214c** and **4-216c** with the *trans* orientation.

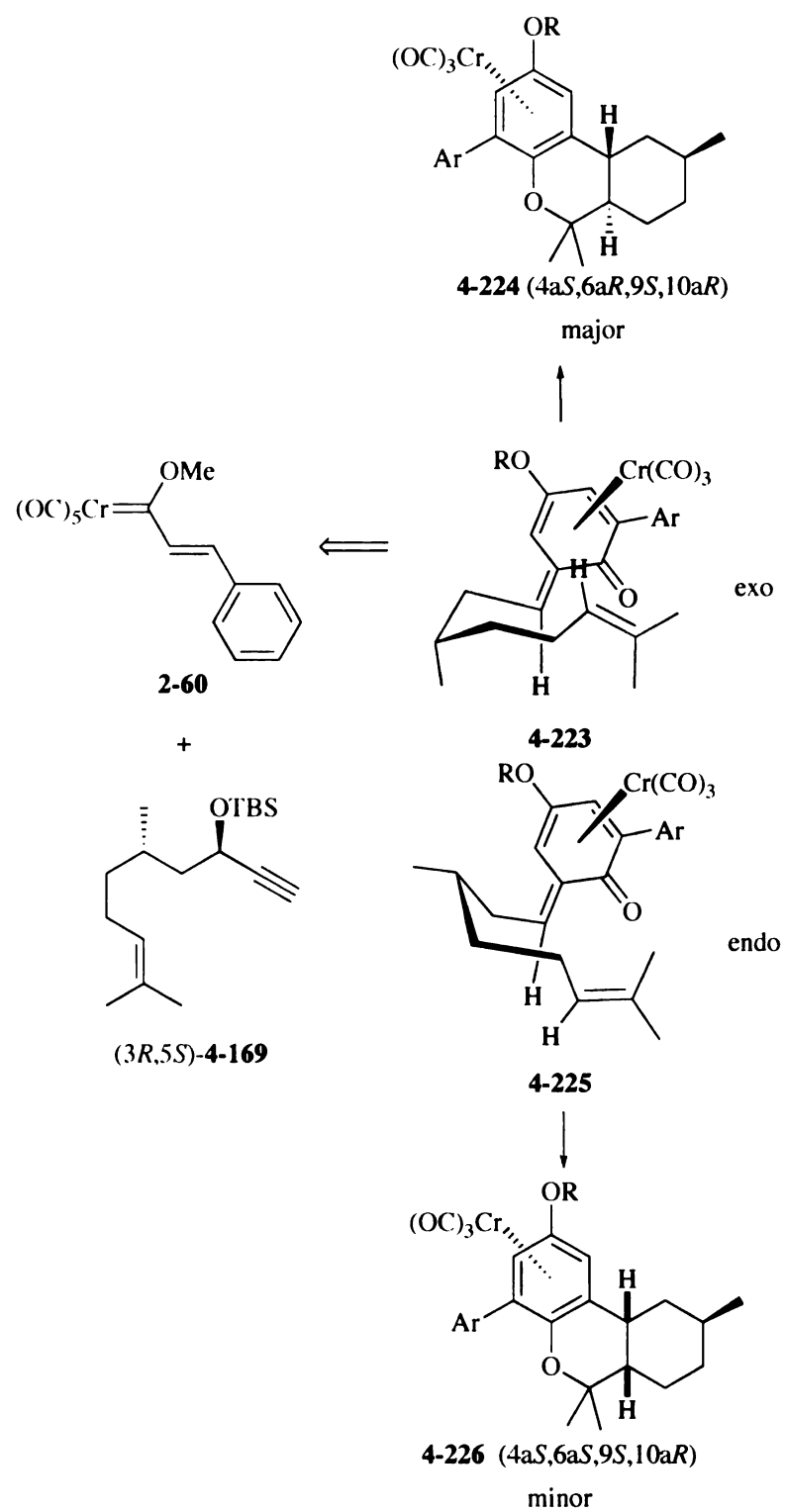
Scheme 4.55. Dieneophile Approaching *Syn* to the Chromium Tricarbonyl Group



To provide a complete discussion shown in Scheme 4.56 is the *syn* approach of the dieneophile to the chromium tricarbonyl for the previously termed "matched case." Again this violates chemical common sense by having the approach of a dieneophile from the most sterically congested pathway shown as conformations **4-223** and **4-225**. The *exo* approach is shown as conformation **4-223**. The *endo* approach is shown as conformation **4-225**. This approaching pathway *syn* to the chromium tricarbonyl group also would contradict the literature concerning Diels-Alder reactions involving the chromium tricarbonyl group by Kündig.²²⁸ Also with compound (3*R*,5*S*)-**4-169**, this reaction does not

give the two compounds proposed (**4-224** or **4-226**). One compound is essentially formed when (*3R,5S*)-**4-169** is used for this reaction. It was found that the coupling constants associated with (*6aS,9S,10aR*)-**4-226** results from the use of alkyne (*3S,5S*)-**4-172** (not (*3R,5S*)-**4-169**) which contradicts the proposal shown below in Scheme 4.56. The coupling constants of compound (*4aR,6aS,9S,10aR*)-**4-216b** are 7.4 and 3.8 Hz for the hydrogen on carbon 10a corresponding to the *cis* compound which originates from (*3S,5S*)-**4-172**. The coupling constants will be discussed in more detail in section 4.7.7.

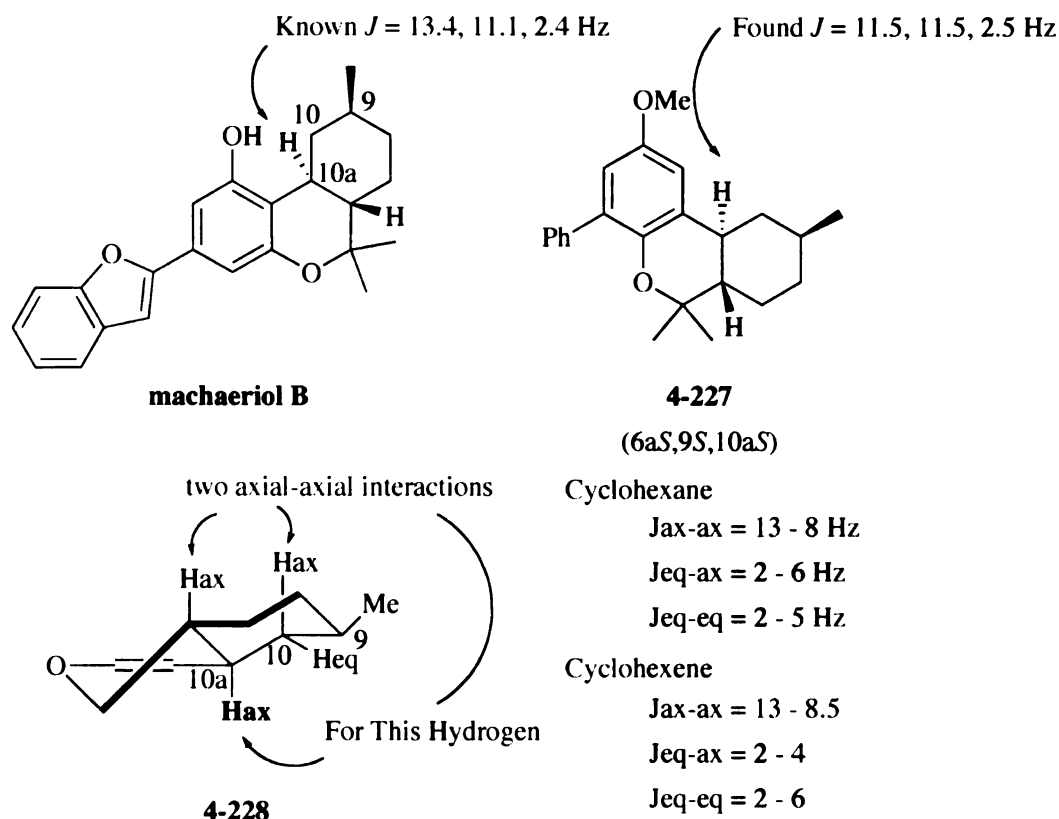
Scheme 4.56. Dieneophile Approaching *Syn* to the Chromium Tricarbonyl Group (Revisited)



4.7.7 Discussions of Coupling Constants for Structural Determinations

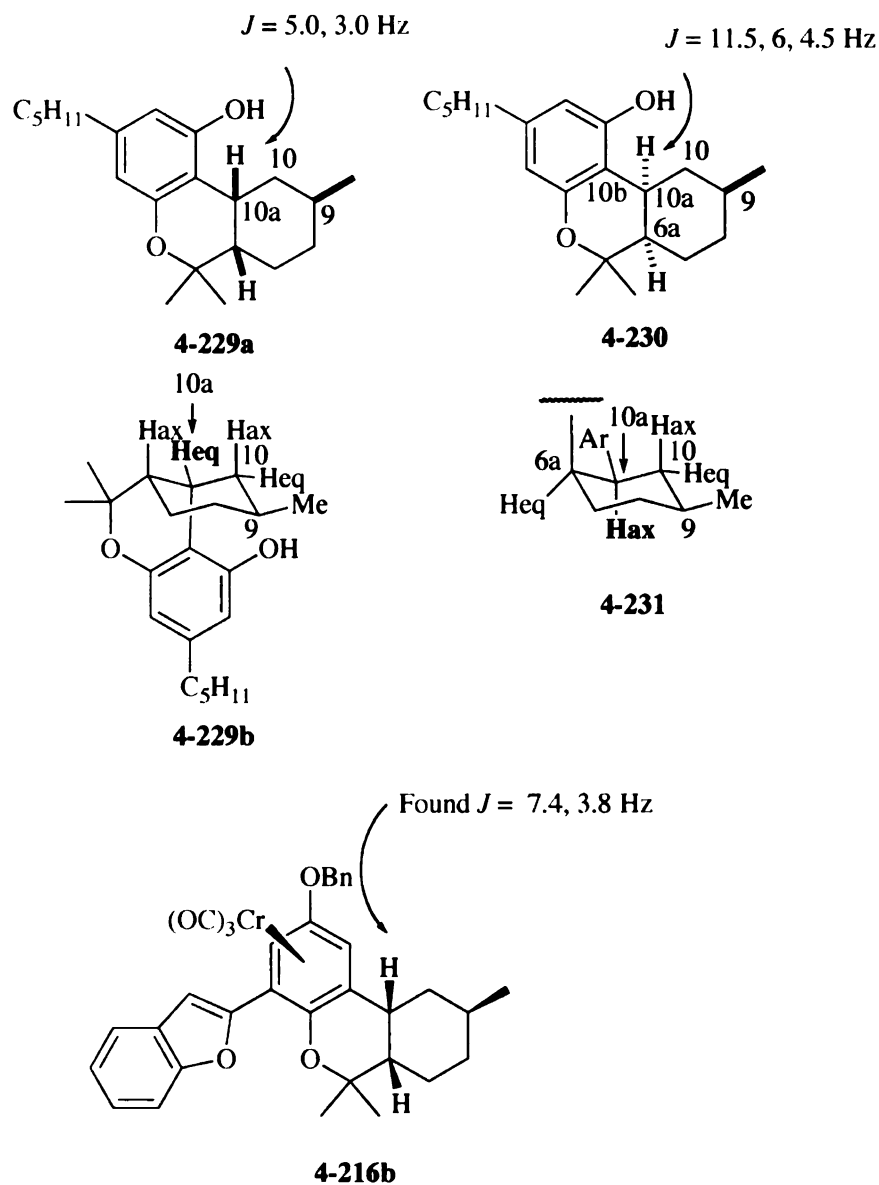
Figure 4.5 shows the coupling constants from machaeriol B²³¹ compared to compound **4-227**. The coupling constants in machaeriol B are $J = 13.4, 11.1,$ and 2.4 Hz. In compound **4-227**, a similar coupling constants are observed of $J = 11.5, 11.5,$ and 2.5 Hz for the proton on carbon 10a. These coupling constant patterns are consistent with two axial-axial interactions and one axial-equatorial interaction as shown in illustration **4-228**. The typical coupling constants of cyclohexanes and cyclohexenes²⁶⁹ are also presented in Figure 4.5, and they are consistent with proposed structure **4-227**.

Figure 4.5. Coupling Constants of Hexahydrodibenzopyrans (6-6-6 Ring Systems)



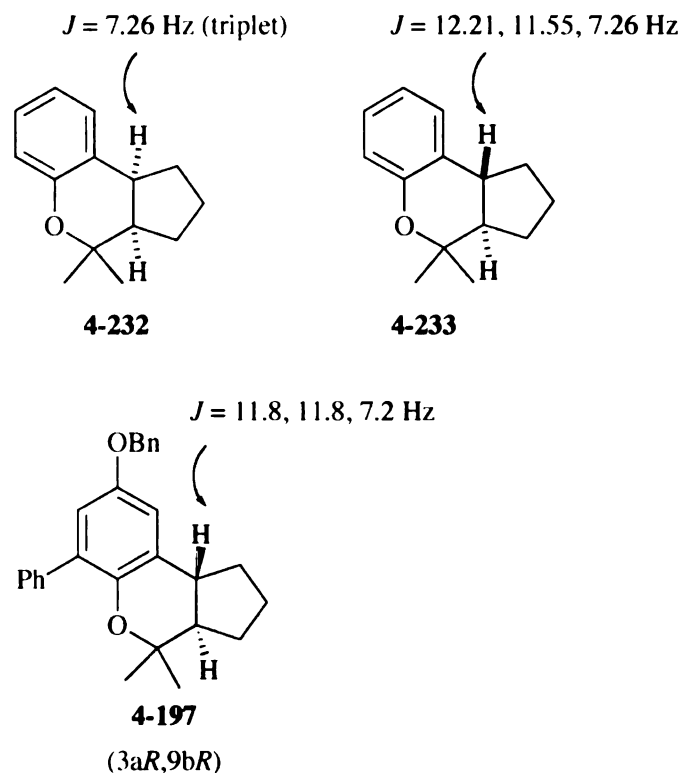
The minor isomer can be determined in the mismatched case as shown in Figure 4.6. The relative stereochemistry of *cis* and *trans* hexahydrodibenzopyrans has been determined from the cannabinol family.²⁷⁰ In compound **4-229a**, the hydrogens on carbon 10a and 6a are *cis* with the methyl on carbon 9. The coupling constants for the all *cis* compound is $J = 5.0$ and 3.0 Hz. This can be rationalized by two equatorial-axial couplings and one equatorial-equatorial coupling both < 8 Hz as shown in illustration **4-229b**. In compound **4-230**, the hydrogens on carbons 10a and 6a are *cis* to each other but *trans* to the methyl on carbon 9. The coupling constants for compound **4-230** are $J = 11.6$, 6 , and 4.5 Hz. This can be rationalized by one axial-axial coupling between hydrogen 10a and hydrogen 10 and two axial-equatorial couplings as shown in illustration **4-231**. For the compounds in our work where the coupling constant could be determined such as compound **4-216b**, the couplings were < 8 Hz with the all *cis* compound **4-216b** being consistent with the coupling reported for compound **4-229a**.²⁷⁰

Figure 4.6. Coupling Constants of Hexahydrodibenzopyrans



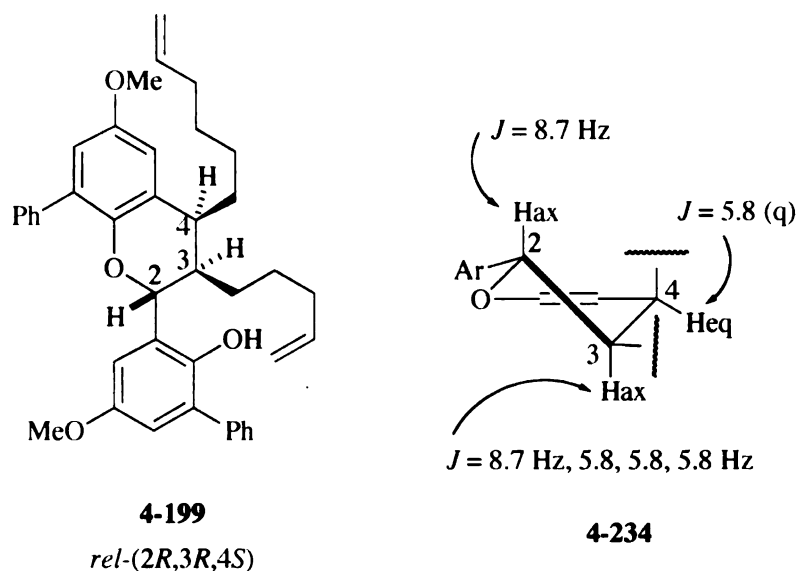
For the 6-6-5 ring system, the *cis* compound **4-232** shows a triplet with $J = 7.26 \text{ Hz}$ coupling constant at 3.26 ppm. For the *trans* compound **4-233**, a double of doublets of doublets is observed with coupling constants of $J = 12.21, 11.55,$ and 7.26 Hz .²⁰⁹ The coupling constants found in the current work are shown for compound (3a*R*,9b*R*)-**4-197** and are $J = 11.8, 11.8,$ and 7.2 Hz .

Figure 4.7. Coupling Constants of the 6-6-5 Member Rings



The relative stereochemistry of compound **4-199** was determined by the use of coupling constants. An apparent axial-axial coupling was observed for the proton on carbon 2 of 8.7 Hz as shown in illustration **4-234**. The coupling could be determined for the proton on carbon 3 via a gCOSY NMR experiment and a concomitant coupling constant of 8.7 Hz that was observed for this proton, which is also an apparent axial-axial coupling. The proton on carbon 4 has a small coupling constant of 5.8 suggesting an axial-equatorial or an equatorial-equatorial relationship between the hydrogen atoms.

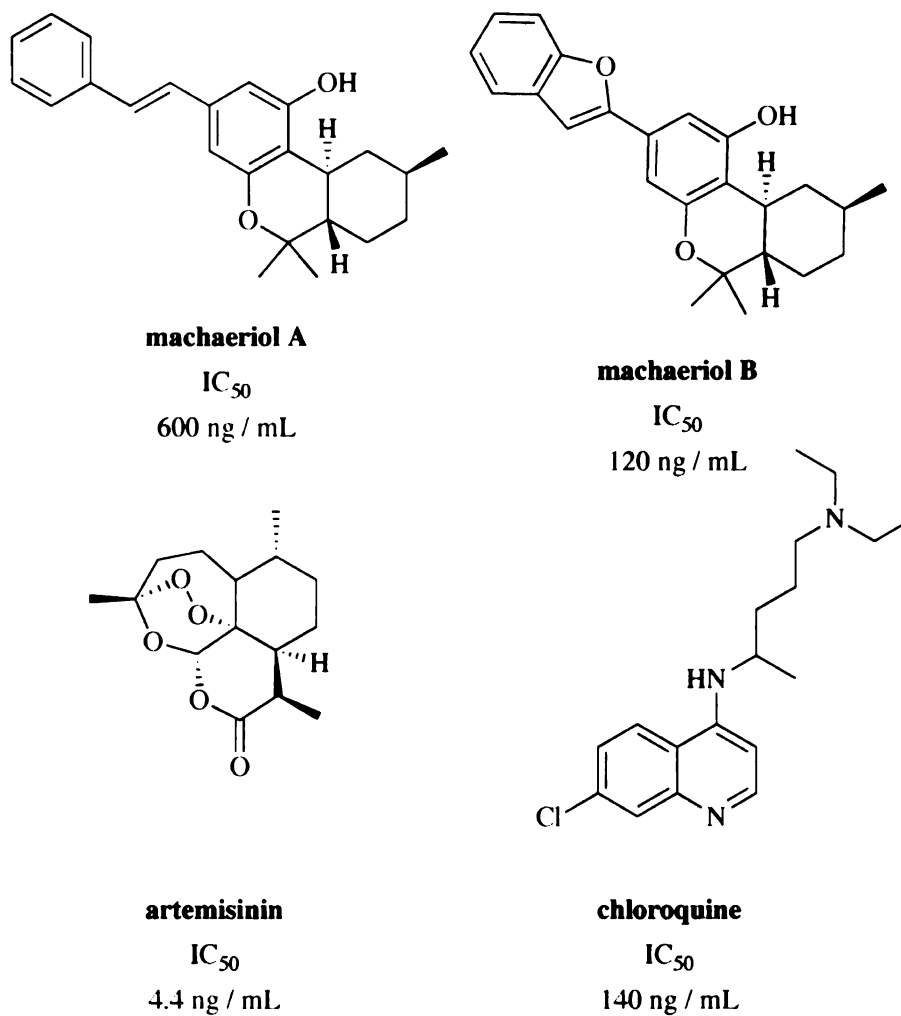
Figure 4.8. Coupling Constants for the Dimer Derived from Traceless Stereoinduction



4.8 A Brief Discussion of Biological Activity of Hexahydrodibenzopyrans Toward the Treatment of Malaria.

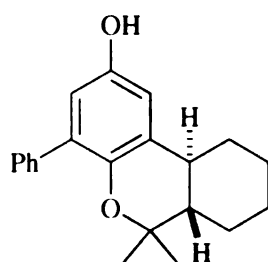
Biological testing was performed on some of the compounds made in our laboratory. The biological testing was performed in the laboratories of Dr. Ilias Muhammad at the University of Mississippi. The W-2 clones came from Africa and the D-6 clones came from East Asia. For the machaeriols,²⁷¹ the IC_{50} was 120 ng / mL for machaeriol B and machaeriol A the IC_{50} was 600 ng / mL which compares to the state of art compound artemisinin with a much lower IC_{50} value of 4.4 ng / mL (lower is better).²⁷¹ Chloroquine has an IC_{50} of 140 ng / mL which malaria has become resistant to, and the W-2 is a resistant strain.²⁷¹

Figure 4.9. Antimalarial Activity Against W-2 Malaria Parasite Clones



Shown in Figure 4.10 is the biological testing of some of our compounds. Testing was performed with the D-6 clones, W-2 clones, and a vero strain. For compound **4-235** the IC₅₀ was 3700 ng / mL. The remainder of the compounds were unfortunately above the testing threshold.

Figure 4.10. Biological Testing Results



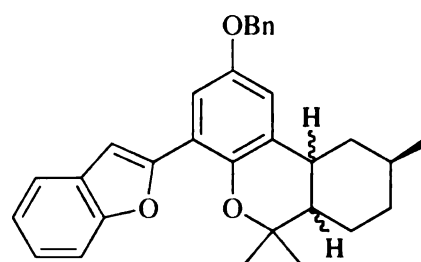
(6a*S,6a*S**)-4-235**

IC₅₀

D6 4700 ng / mL

W2 3700 ng / mL

Vero 15000 ng / mL



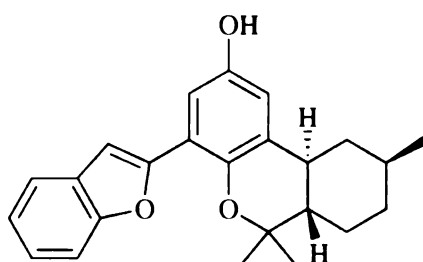
4-236 mismatched mixture

IC₅₀

D6 > 4760 ng / mL

W2 > 4760 ng / mL

Vero > 23800 ng / mL



4-237

(6a*S*,9*S*,10a*S*)

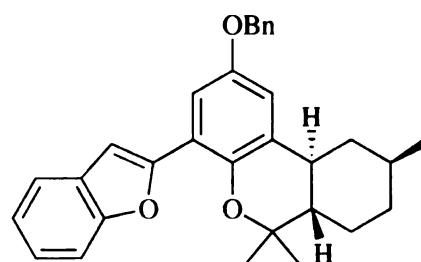
IC₅₀

one enantiomer

D6 > 4760 ng / mL

W2 > 4760 ng / mL

Vero > 23800 ng / mL



4-238

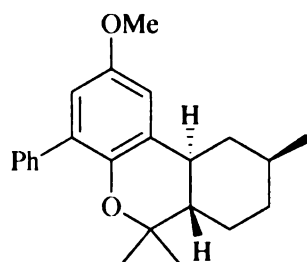
(6a*S*,9*S*,10a*S*)

IC₅₀

D6 > 4760 ng / mL

W2 > 4760 ng / mL

Vero > 23800 ng / mL



4-227

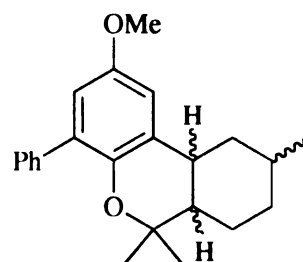
(6a*S*,9*S*,10a*S*)

IC₅₀

D6 > 4760 ng / mL

W2 > 4760 ng / mL

Vero > 23800 ng / mL



4-239 mixture

IC₅₀

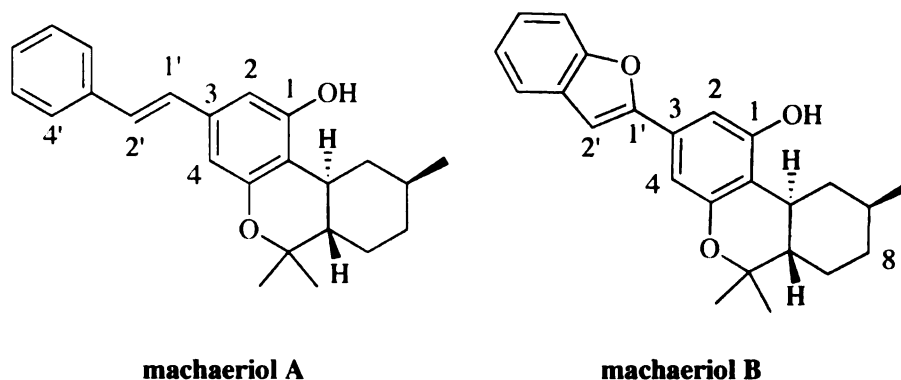
D6 > 4760 ng / mL

W2 > 4760 ng / mL

Vero > 23800 ng / mL

The C-1 free hydroxyl group appears to be essential for biological activity against malaria as demonstrated by the test results shown in Figure 4.10 that possessed a C-2 hydroxyl group had almost no activity.²⁷¹ It is also proposed the *trans*-hexahydrodibenzopyran is also indispensable.²⁷² The lipophilic nature of the compounds has been suggested as important and further hydroxylation may decrease their activity.²⁷² The substitution with an additional hydroxyl group at the C-4' for machaeriol A or at the C-8 for machaeriol B diminished the antimalarial activity.^{271, 272}

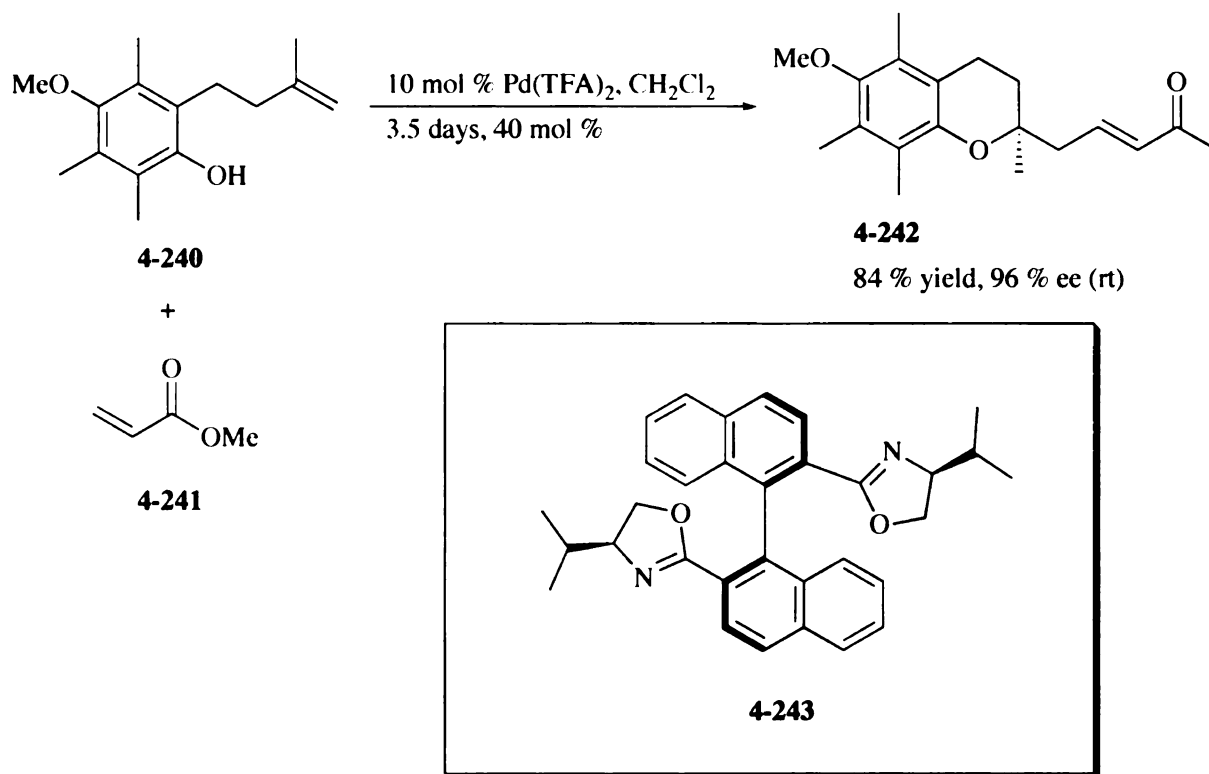
Figure 4.11. Biologically Active Compounds



4.9 Reactions Toward the Total Synthesis of Vitamin E

Shown in Scheme 4.57^{273, 274, 275} is the enantioselective synthesis of a chroman ring done by laboratories of Dr. Tietze. The yield from compounds **4-240** and **4-241** was 84 % to compound **4-242** with 96 % ee at room temperature. The catalyst that was used was compound **4-243**.²⁷³

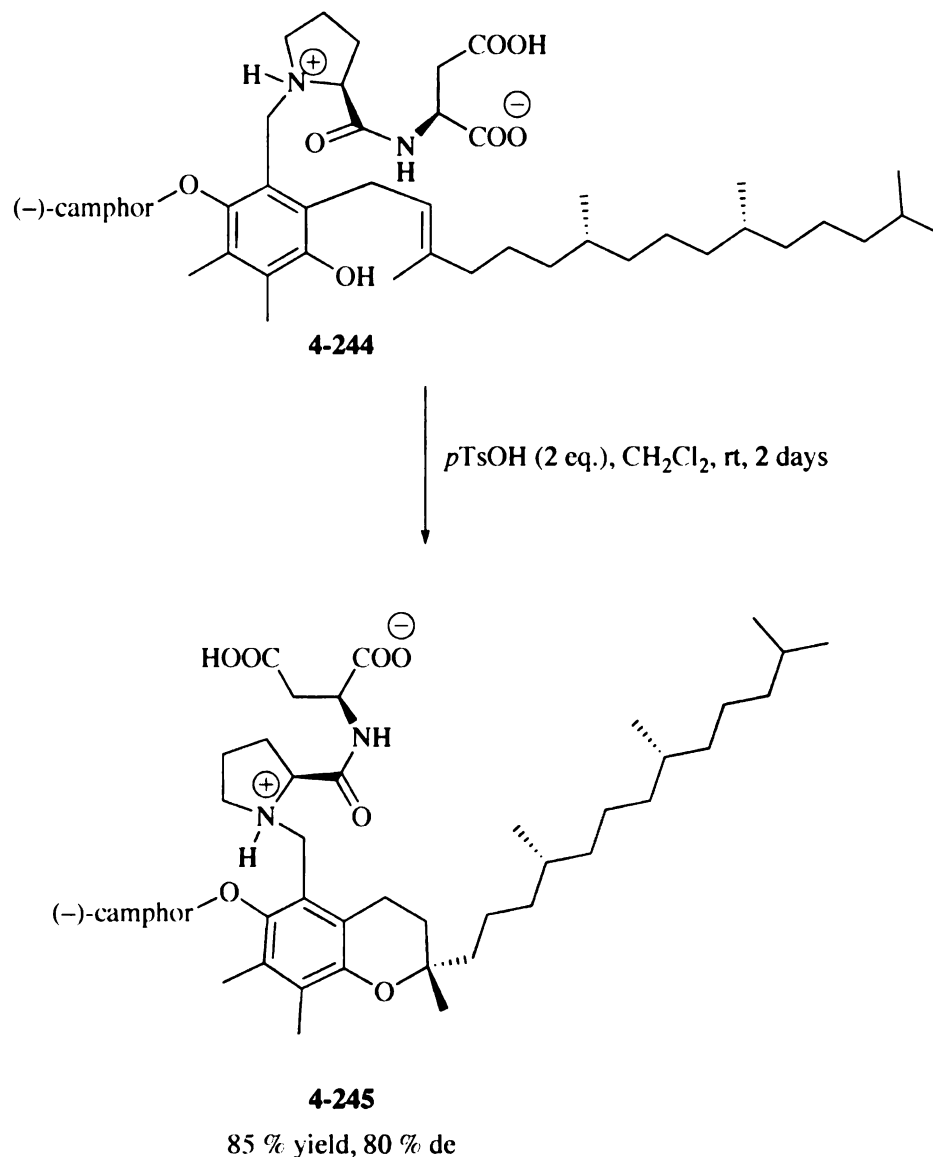
Scheme 4.57. Cyclization Toward Vitamin E



Shown in Scheme 4.58 the biomimic synthesis is presented.^{276, 277, 278,}

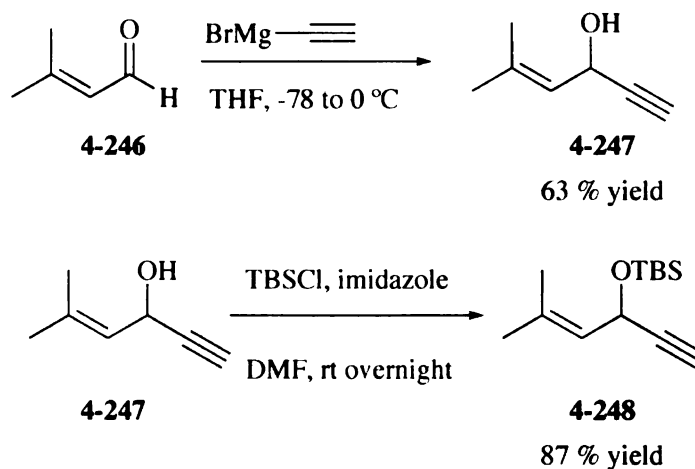
²⁷⁹ In the later step of this synthesis the treatment with *p*TsOH converts compound **4-244** to **4-245**. This cyclization of compound **4-244** gives 85 % yield and an 80 % diastereomeric excess.²⁷⁶

Scheme 4.58. The Key Step of a Biomimic Synthesis of Vitamin E



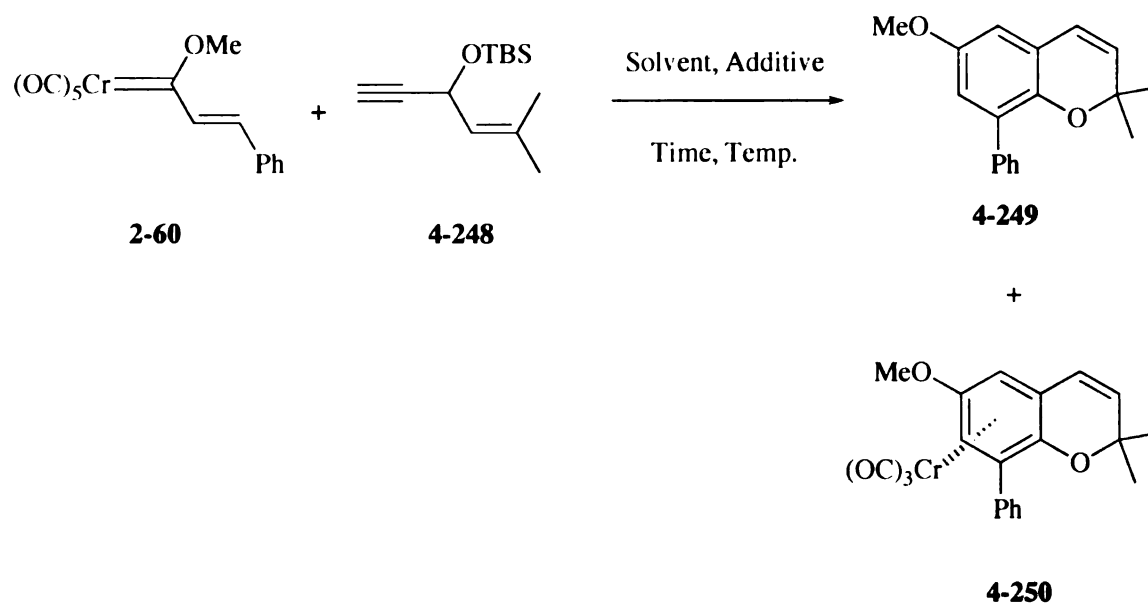
We began our studies with the formation of a test substrate for the Wulff-Dötz reaction with tandem electrocyclization. We treated compound **4-246** with ethynylmagnesium bromide to give compound **4-247** in 63 % yield. The protection of compound **4-247** with TBSCl and imidazole proceeded with 87 % yield to give compound **4-248**.

Scheme 4.59. Formation of Starting Material For Tests of
Electrocyclization Toward Vitamin E



With the starting material in hand, we tried the tandem Diels-Alder electrocyclization as shown in Table 4.9. In entry 1, in dichloromethane with no additives the yield was 46 % for compound **4-249** and 29 % for compound **4-250**. In entry 2 with Hunig's base, the yield was 10 % for compound **4-250**. In entry 3, in toluene and 5 eq. of Hunig's base, the yield was 16 % of compound **4-250** at 80 °C. In entry 4, in toluene and 5 eq. of Hunig's base at 100 °C, the yield was 16 % of compound **4-250**. Also found for entries 2, 3, and 4 were fractions that were complex mixtures by NMR.

Table 4.9. Electrocyclization Reaction

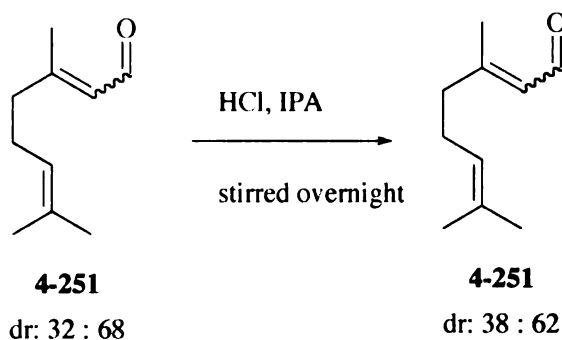


entry	Solvent	Additive	Temp. (°C)	Time (hrs)	Yield 4-249 (%)	Yield 4-250 (%)
1	CH ₂ Cl ₂	None	60	24	46	29
2	CH ₂ Cl ₂	2 eq. NEt(<i>i</i> Pr) ₂	60	12	Complex mixture	10
3	toluene	5 eq. NEt(<i>i</i> Pr) ₂	80	24	Complex mixture	16
4	toluene	5 eq. NEt(<i>i</i> Pr) ₂	100	24	Complex mixture	16

We were interested in extending our methodology to form chiral substrates. We chose compound **4-251** as a convenient starting material for our model studies toward Vitamin E. Shown in Scheme 4.55 is the isomerization attempt of compound **4-251** with HCl and isopropanol.²⁸⁰ With no significant

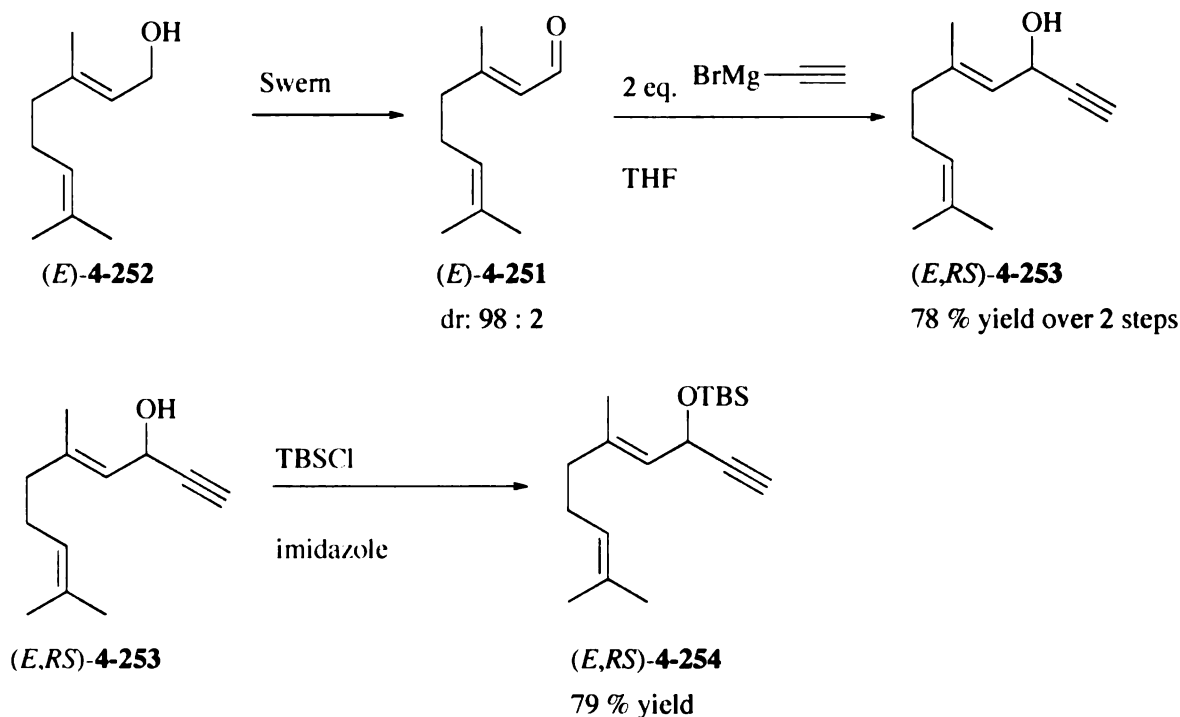
change in the isomer ratio, the pursuit of this approach was turned toward geranol.

Scheme 4.60. Isomerization Attempt



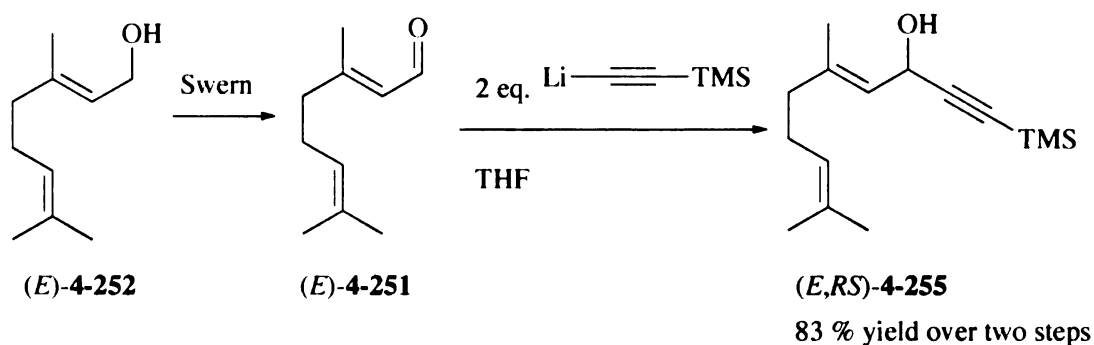
The alternate approach starts from geranol shown as compound **4-252**. A Swern oxidation gave aldehyde **4-251** with a dr of 98 to 2. This compound could be converted to alkyne (*E,RS*)-**4-253** with an overall yield of 78 %. Protection of the propargyl alcohol with TBSCl / imidazole gave compound **4-254** in 79 % yield.

Scheme 4.61. The Synthesis of Mostly Z-Alkyne



In an effort to prepare the optically active enyne (*E,3S*)-4-231 (Scheme 4.60), a Swern oxidation gave the α,β -unsaturated aldehyde (*E*)-4-251 and subsequent addition of lithium TMS acetylide, the propargyl alcohol (*E,RS*)-4-255 was formed in 83 % yield.

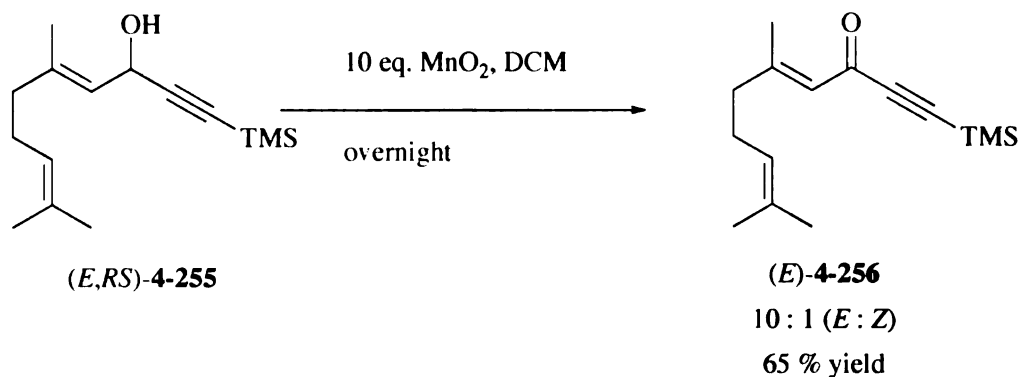
Scheme 4.62. Formation of a Propargyl Alcohol



The oxidation of propargyl alcohol (*E,RS*)-4-255 gave a 65 % yield of compound (*E*)-4-256. Compound (*E*)-4-256 had an E to Z ratio of 10 to 1

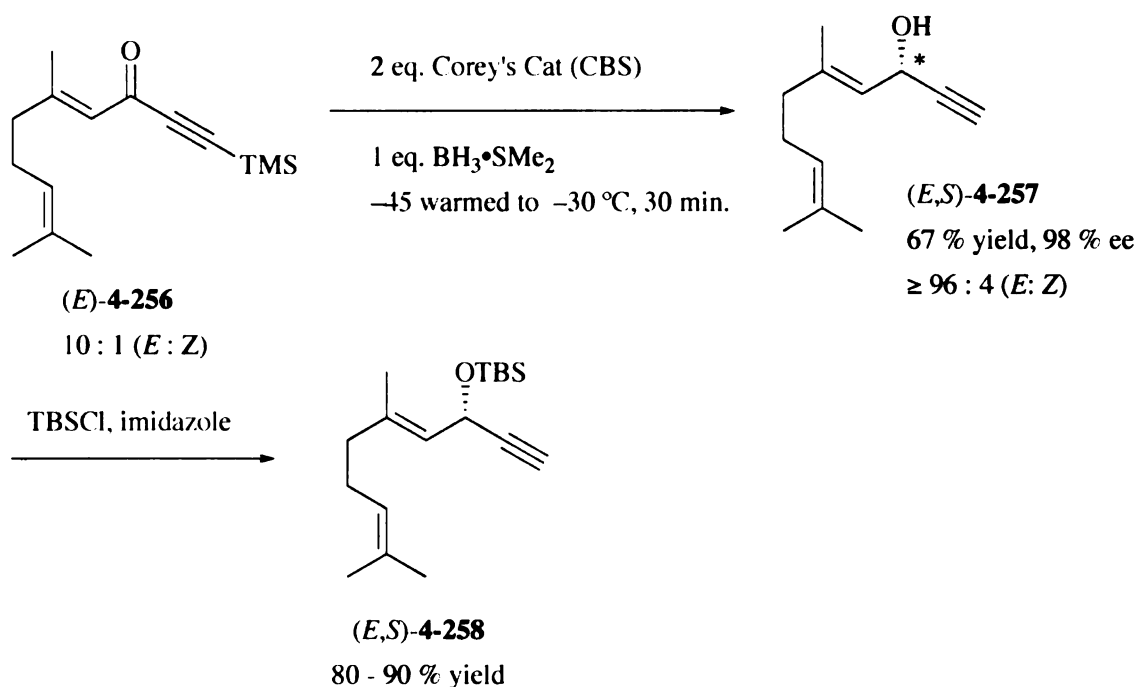
measured by NMR. The use of 10 equivalents of manganese dioxide was required.²⁸¹

Scheme 4.63. Oxidation of a Propargyl Alcohol



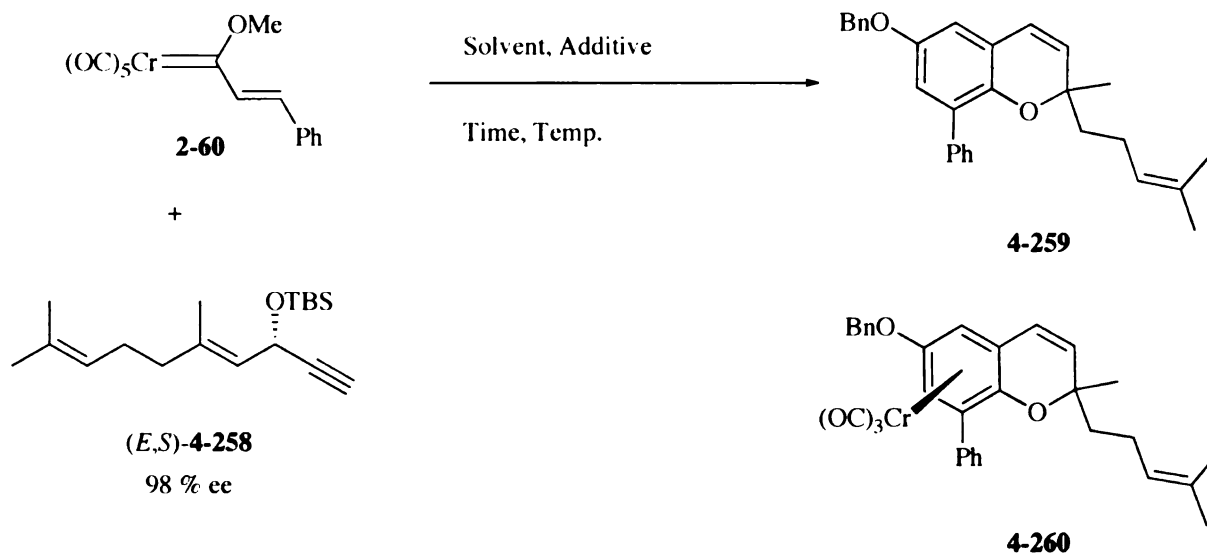
The use of 2 eq. of CBS with borane acting on compound **(E)-4-256** gave the chiral alcohol **(E,S)-4-257** in 67 % yield and 98 % ee.²⁸² The enantiomeric excess was determined by chiral GC on compound **(E,S)-4-257**. The *E* to *Z* ratio was greater than $\geq 96 : 4$ as determined by ^1H NMR of compound **(E,S)-4-257**. The TMS protecting group was removed during work-up. The protection of the alcohol with TBSCl and imidazole gave 80 to 90 % yield of compound **(E,S)-4-258**.

Scheme 4.64. CBS-Borane Reduction for the Formation of a Chiral Propargyl Alcohol with TBS protection



The results of the benzannulation between compound **(E,S)-4-232** and carbene complex **2-60** are shown in Table 4.9. In entry 1, the yield of compound **4-259** was 37 % and compound **4-260** was 21 %. The yield of compound **4-259** was 38 % and compound **4-260** was 22 % for entry 2. The yield in entry 3 was 53 % for compound **4-259** and 3 % for compound **4-260** in DCE (1,2-dichloroethane). In entry 4 the use of Hunig's base gave a yield of 9 % for compound **4-259** and 25 % for compound **4-260**. Entries 1 - 3 showed < 1 % enantiomeric excess. The overall enantiomeric excess for entry 4 was 74 % (both compounds **4-259** and **4-260**). The enantiomeric excess was measured by chiral HPLC following the removal of the chromium tricarbonyl group and the benzyl group. Although 74 % ee does not seem impressive, however this was for the differentiation between a methyl and an alkyl chain which can be difficult.

Table 4.10. Enantioselective Electrocyclization



entry	Solvent	Additive	Temp.	Time (hrs)	Yield 4-259 (%)	Yield 4-260 (%)
1	toluene	none	80 °C	24	37	21
2	toluene	none	90 °C	24	38	22
3	DCE	none	80 °C	24	53	3
4	DCE	5 eq. NEt(<i>i</i> Pr) ₂	80 °C	24	9 (74 % ee)	25 (74 % ee)

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**MASS SPECTROSCOPY STUDIES OF FISCHER CARBENES AND
TRACELESS STEREOINDUCTION FOR THE FORMATION OF
HEXAHYDRODIBENZOPYRANS: THE USE OF THE CHROMIUM
TRICARBONYL GROUP AS A STEREOCONTROL ELEMENT**

VOLUME 2

By

Keith A. Korthals

A DISSERTATION

**Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of**

DOCTOR OF PHILOSOPHY

Department of Chemistry

2007

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CHAPTER FIVE

MASS SPECTROMETRY IONIZATION MECHANISMS OF FISCHER CARBENE COMPLEXES

5.1 Background in Electrospray Ionization

The method of electrospray ionization (ESI) is a soft ionization method for solutions of organic, inorganic, and bioorganic molecules.²⁸³ High molecular weights can be analyzed by this method. The method of ESI involves electron transfer processes. Electron transfer reactions are essential processes for life that include photosynthesis and respiration.²⁸⁴

The basic concepts of soft ionization techniques such as ESI include a solution, usually aqueous, including nonvolatile, thermally labile compounds. Under these conditions thermal, pneumatic, or electrical forces are used to nebulize and ionize the sample for analysis.²⁸⁵ Ideally the matrix is the solvent, and in the case of ESI, field evaporation and coulomb explosions give rise to ionization. The molecular ions are usually multiples of $(M + H_n)^{n+}$ or $(M - H_n)^{n-}$. The mass range is up to 10^5 Da. The sensitivity is in the range of pg/ μ L.

A capillary nebulizes the solution to form droplets. The droplets are exposed to vacuum, and these droplets yield microdroplets. The surface tends to accumulate the charge. At some point the charge density causes the droplet to become unstable and explode (coulombic explosion). The charge / droplet

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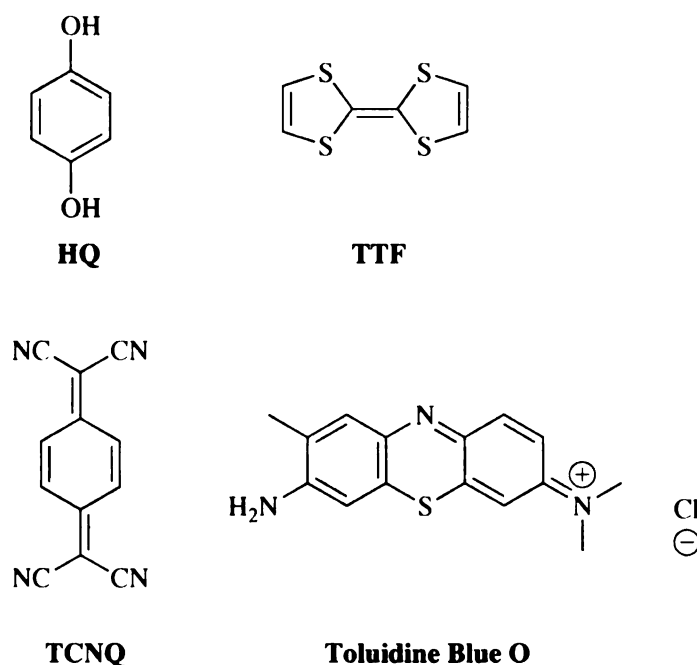
ES. y

size is limited by what is called the Rayleigh limit which depends on the electric field, vacuum, solvent, nature of the molecule, and number of charges on the molecule and / or droplet. The processes of ionization in ESI are not well understood.²⁸⁵

5.2 Previous Results of Electrospray Ionization

Previously reported was the use of electron transfer reagents for the ESI-MS of carbene compounds.²⁸⁶ The electron-donators that have been studied include hydroquinone (HQ) and tetrathiafulvalene (TTF). These compounds are electron-donators in the sense that they can transfer electrons to the molecule of interest. The electron-acceptors were also evaluated, which include tetracyano-*p*-benzoquinone (TCNQ) and toluidine Blue O shown in Figure 5.1.

Figure 5.1. Electron-Donor and Electron-Acceptor Compounds For ESI/MS



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The carbene complexes shown in Figure 5.2 were subjected to ESI/MS, and the quasimolecular ions were not observed without additives.²⁸⁶ In fact, no useful peaks were observed in the ESI/MS either in positive mode or in negative mode. The resulting spectrum only represented noise.²⁸⁶ When the electron-donators such as hydroquinone and tetrathiafulvalene were used as additives to solutions containing carbene complexes, some quasimolecular ions were noted resulting from the ionization of the carbene complexes. For Fischer carbene complexes **5-1** and **5-2**, no quasimolecular ions, with or without any additive, could be detected (compound **5-2**).²⁸⁶ For Fischer carbene complex **5-3**, the quasimolecular ion 483 *m/z* corresponding to $[M - H]^-$ was observed. For complex **5-4**, the ion 351 *m/z* corresponding to $[M - H]^-$ was observed. For carbene complex **5-5**, the ion 341 *m/z* corresponding to $[M - H]^-$ was observed, and for compound **5-6**, the ion 357 *m/z* corresponding to $[M - H]^-$ was observed. For the alkynyl carbene complex **5-7**, the quasimolecular ion 321 *m/z* corresponding to $[M - H - CO]^-$ was observed in our work.²⁸⁶

Figure

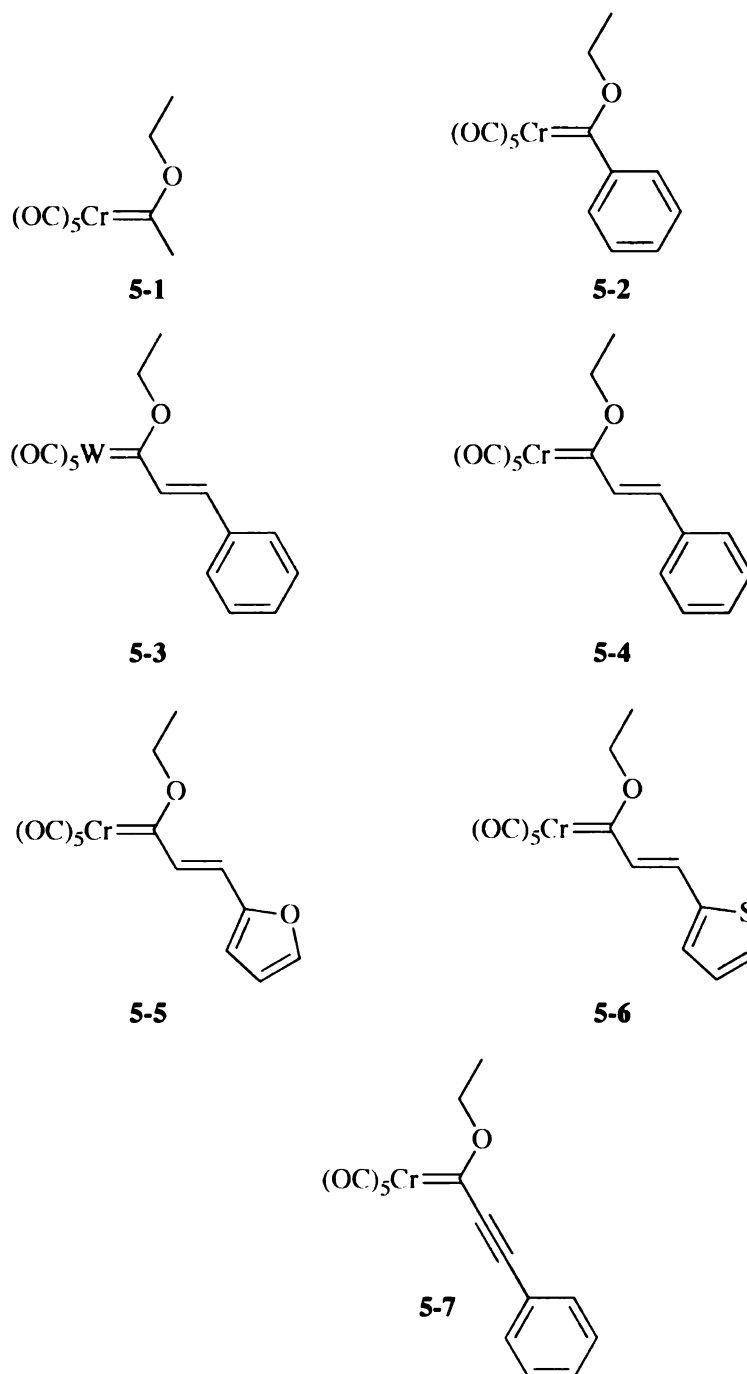
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Figure 5.2. Chromium Containing Fischer Carbene Complexes for ESI/MS



In Table 5.1, the redox potentials of Fischer carbenes and additives are presented. In cyclic voltammetry, a potential is applied to the system, and the faradaic current response is measured starting at the initial value and continuing

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until a predefined upper limit. At this point the potential is reversed thus the term "cyclic." The compounds that were first oxidized in the first (forward) scan can now be reduced in the second (reverse) scan if the reaction is reversible. The value E_{pa} (electrical potential at the anode) is for the forward oxidative process.

The value E_{pc} (electrical potential at the cathode) is for the reductive process.²⁸⁷

The values in parentheses are for the redox processes back to the neutral forms.

The oxidative process in terms of a chemical reaction has not been identified by the authors of the paper. The E_{pa} and E_{pc} are not necessarily the reversal of each other (reversal of the same redox reaction) in the examples shown in Table

5.1.²⁸⁸

Table

Compound

5-1

5-2

5-3

5-7

Hydroquinone
(HQ)

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Table 5.1. Redox Potentials (Volts) of Fischer Carbenes and Additives^a

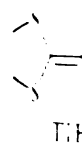
Compound	E_{pa}^1 oxidation	E_{pc}^1 reduction	E_{pa}^2 oxidation	E_{pc}^2 reduction
5-1	0.90	−1.78	-	-
5-2	1.07	−1.45	-	-
5-3	1.16	−1.25	-	-
5-7	1.17	−1.18	-	-
Hydroquinone (HQ)	1.17 (0.32)	−1.18	-	-
TTF	0.51 (0.28)	-	0.97 (0.65)	-
TCNQ	-	0.28 (0.36)	-	−0.44 (−0.23)
Toluidine Blue Q	-	−0.94 (−0.19)	-	−0.78 (−0.91)

a. BAS MF-2063 Ag/AgCl reference electrode and Pt wire and a Metrohm 6.0805.010 conventional glassy carbon electrode (3 mm o.d.) as the working electrode.

Under ESI conditions it has been proposed that hydroquinone goes to the radical anion **5-8**.²⁸⁶ Also under ESI conditions, tetrathiafulvalene (TTF) goes to the radical anion **5-9**. The radicals were anions such as **5-8** or **5-9**.²⁸⁶ In the presence of a metal complex M, an electron is transferred via a single electron transfer reaction giving the metal radical anion **5-10**. Also detected during ESI/MS are *m/z* 109 shown as anion **5-11** or *m/z* 204 corresponding to the radical anion **5-12**.²⁸⁶

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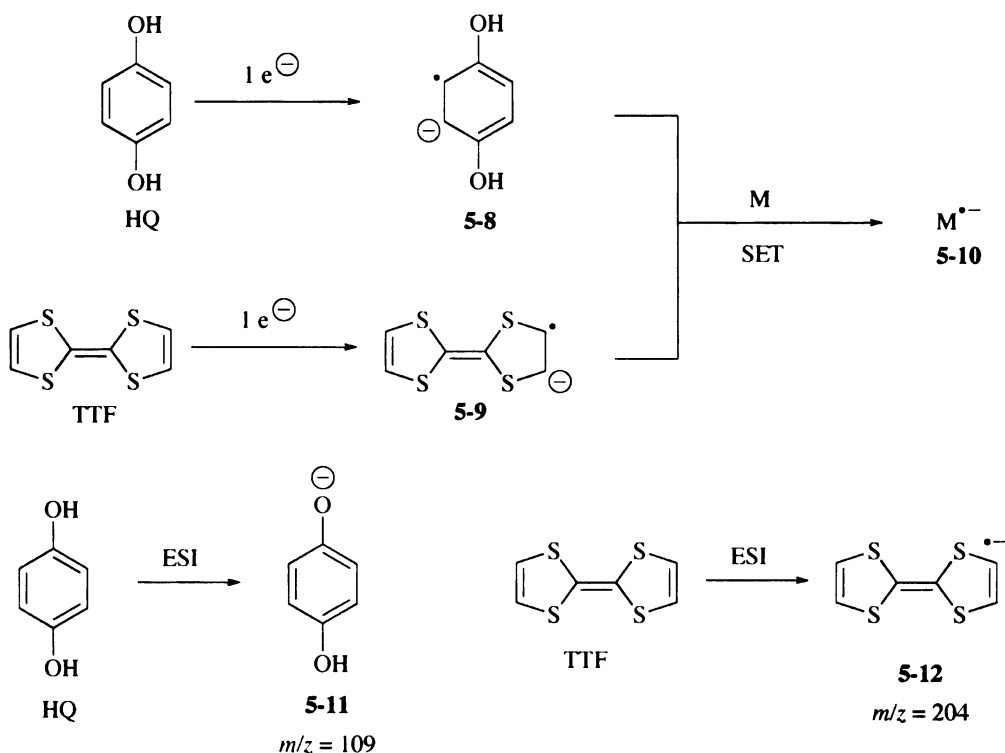
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Scheme 5.1. HQ and TTF Mechanism of Electron Transfer in the
Ionization of Carbenes



When the ferrocenyl carbene complexes **5-13** and **5-14** were subjected to ESI conditions, without any additives, the quasimolecular ions $[M - H]^-$ were 459 and 429 m/z respectively. It was proposed that ferrocene was a good electron-donor representing an *internal electron carrier* that makes the direct formation of the carbene radical anion possible in the ESI source. The ionization of compounds **5-15a** and **5-15b** with hydroquinone was observed giving $[M - H]^-$ as 405 and 537 m/z respectively and hydroquinone was required. This is a dramatic change in the ionization because (pentacarbonyl)[ethoxy](phenyl)carbene chromium(0) cannot be observed in the

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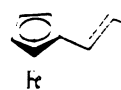
without in

observed

ESI/MS even with hydroquinone. For the bis-carbene complexes **5-16** and **5-17**, there were no special ionization properties. They both required the presence of hydroquinone for the observation of the quasimolecular ion of $[(M - H) - CO]^-$ as 857 and 593 m/z respectively.²⁸⁶ For tungsten-chromium carbene complex **5-18**, the quasimolecular ion of $[(M + MeOH - H) - 2 CO]^-$ was registered with hydroquinone as 729 m/z .

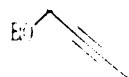
The compounds **5-19** and **5-20** possessing an alkynyl cobalt complex did not produce a detectable quasimolecular ion. The quasimolecular ion could not be detected with or without additives (ESI source only).²⁸⁶ It has been proposed that this is because the $Co_2(CO)_6$ moiety acts as an *electron-sink* that inhibits the electron transfer to the chromium fragment.²⁸⁶ It is likely that $Co_2(CO)_6$ is initially reduced by the ESI source or an interaction with $HQ^{\bullet-}$, and then it is oxidized without interacting with the Cr-C bond. Evidence for this effect has been observed in the ESI/MS corresponding to $Co(CO)_4^{\bullet-}$ as 171 m/z .²⁸⁶

Figure 5.3



5-13

$W(O)_2$

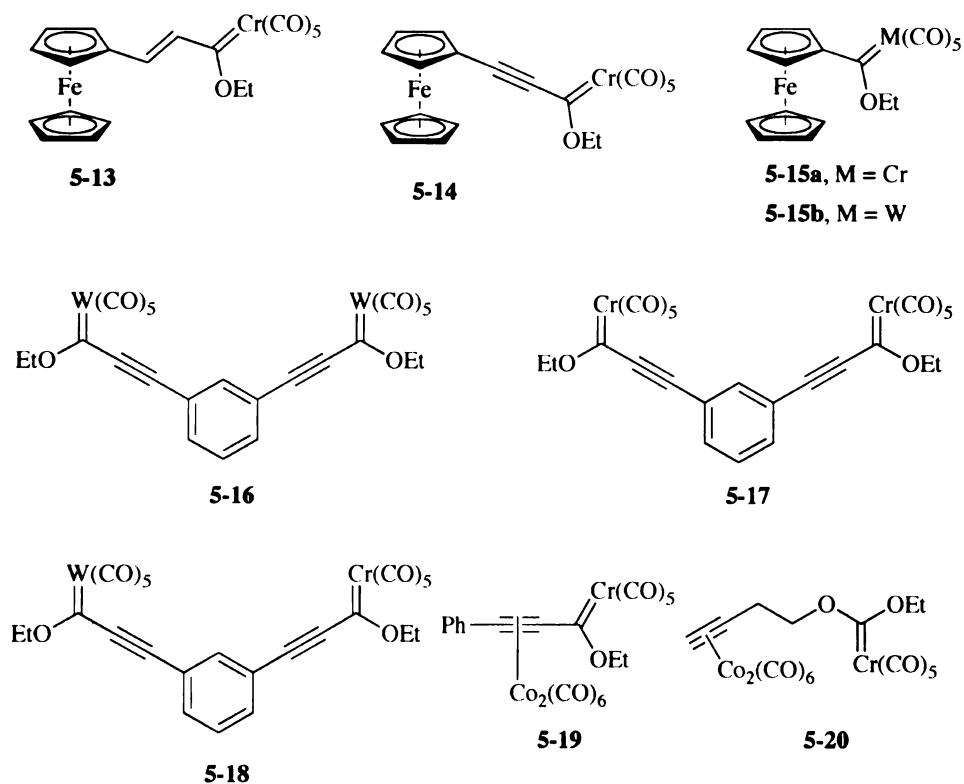


$W(O)_2$



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Figure 5.3. More Carbene Complexes Explored with ESI-MS



The cyclic voltammograms of carbene complexes **5-7** and **5-19** are presented in Table 5.2.²⁸⁹ It can be observed that the "reduction" of carbene complex **5-7** requires a negative potential of -1.15 volts relative to the standard electrode, but $\text{Co}_2(\text{CO})_8$ requires only -0.47 volts. Therefore $\text{Co}_2(\text{CO})_8$ has insufficient potential to "reduce" carbene complex **5-7** and $\text{Co}_2(\text{CO})_8$ does not make a good electron carrier.

Table 5.2.

Compound

5-7

$\text{Co}_2(\text{CO})_8$

5-19

5-7 with
 $\text{Co}_2(\text{CO})_8$

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Scheme 5

ionization



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5-1

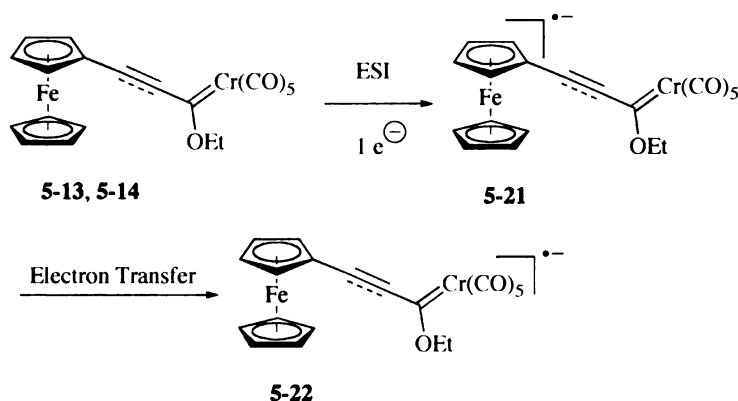
Fig.

Table 5.2. Cyclic Voltammograms of Carbene Complexes with $\text{Co}_2(\text{CO})_8$

Compound	E_{pc}^1 reduction	E_{pc}^2 reduction	E_{pa}^1 oxidation	E_{pa}^2 oxidation
5-7	-1.15	-	-	-
$\text{Co}_2(\text{CO})_8$	-0.47	-	0.14	1.26
5-19	-0.79	-	0.11	1.16
5-7 with $\text{Co}_2(\text{CO})_8$	-0.51	-1.17	0.12	1.24

For compounds **5-13** and **5-14** in Scheme 5.2, it has been proposed²⁸⁶ **that** during ESI, an electron is initially transferred to the ferrocenyl motif to give **reactive** species **5-21**. Then, an electron transfer event occurs that transfers the **electron** to the metal carbene complex giving the anion **5-22**.²⁸⁶

Scheme 5.2. Formation and Electron Transfer During Electrospray Ionization



5.3 Electrospray

Considerations

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5.3 Electrospray Ionization of Group 6 (Fischer) Carbenes with Mechanistic Considerations

A recent publication by Sierra and coworkers described the electrospray mass spectrum of some carbene compounds.²⁸⁶ In this publication, a mechanism was proposed that described the formation of a carbene anion in the presence of hydroquinone. As shown in Scheme 5.3, there are a number of possibilities for the formation of ion 357 m/z in the case where Ar = thiophene and M = Cr such as compound 5-23. In pathway A, the α -hydrogen to the metal is eliminated leading to the allene species 5-26 in the presence of 5-24 or 5-8. In pathway B, the β -hydrogen to the metal is eliminated giving the carbene-anion species 5-27 as the literature suggests.²⁸⁶ There also exists a possibility of a McLafferty rearrangement process as shown in pathway C via intermediate 5-29 with hydrogen radical loss to give 5-30.²⁹⁰

In order to discriminate between processes A, B, or C, we decided to construct a number of carbene complexes the first being one with the β -hydrogen to chromium deuterated.²⁹¹ If the pathway is through process B, then the mass of the resulting species should always have mass 357 m/z due to the loss of the β -hydrogen or β -deuterium. If the pathway is through process A or C, then the mass of the resulting species should be 358 m/z with the deuterated species and 357 m/z with the non-deuterated species.²⁹¹

When the

mass of anion 5

shown in Scheme

mass of 5-27 sho

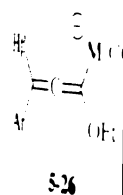
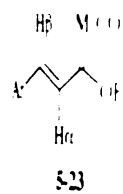
compound 5-23

positions.²⁹

When the α -hydrogen is deuterium for the ESI of compound **5-23**, the mass of anion **5-26** should be 357 m/z if the mechanism is by pathway A as shown in Scheme 5.3. If pathway B predominates for the ionization of **5-23**, the mass of **5-27** should be 358 m/z . If pathway C predominates for the ionization of compound **5-23**, the mass should be independent of deuteration at the α or β positions.²⁹¹

Scheme

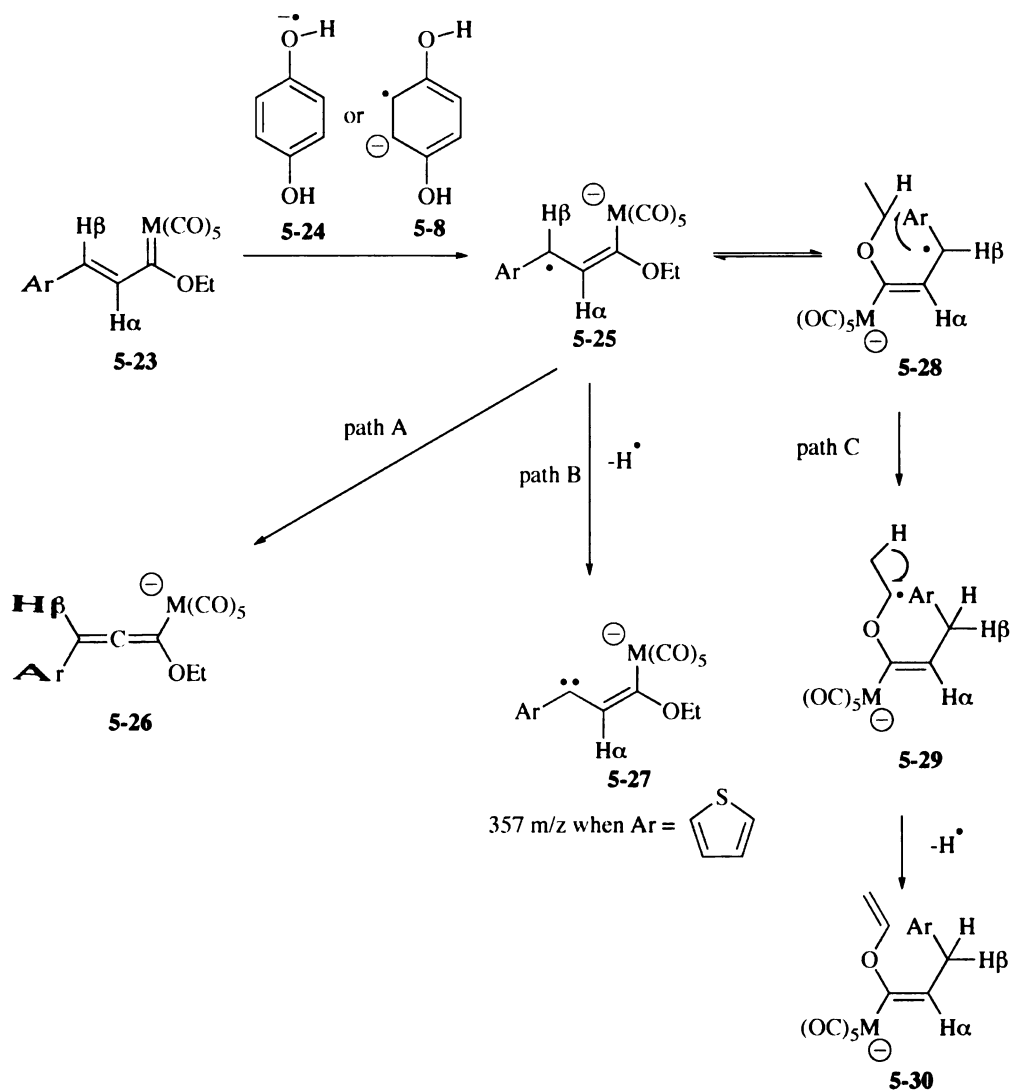
Complex



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Scheme 5.3. Possible Mechanisms of Ionization of Fischer Carbene Complexes

Complexes



In order to construct a deuterated carbene for this study, we required the **deuterated** aldehyde **5-35**. We started our synthesis from the commercially **available** 2-thiophenecarbonyl chloride **5-31**. The compound 2-**thiophenecarbonyl** chloride was reduced with Super-deuteride to give the alcohol

5-32. Depend

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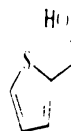
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Scheme

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5-31



5-32

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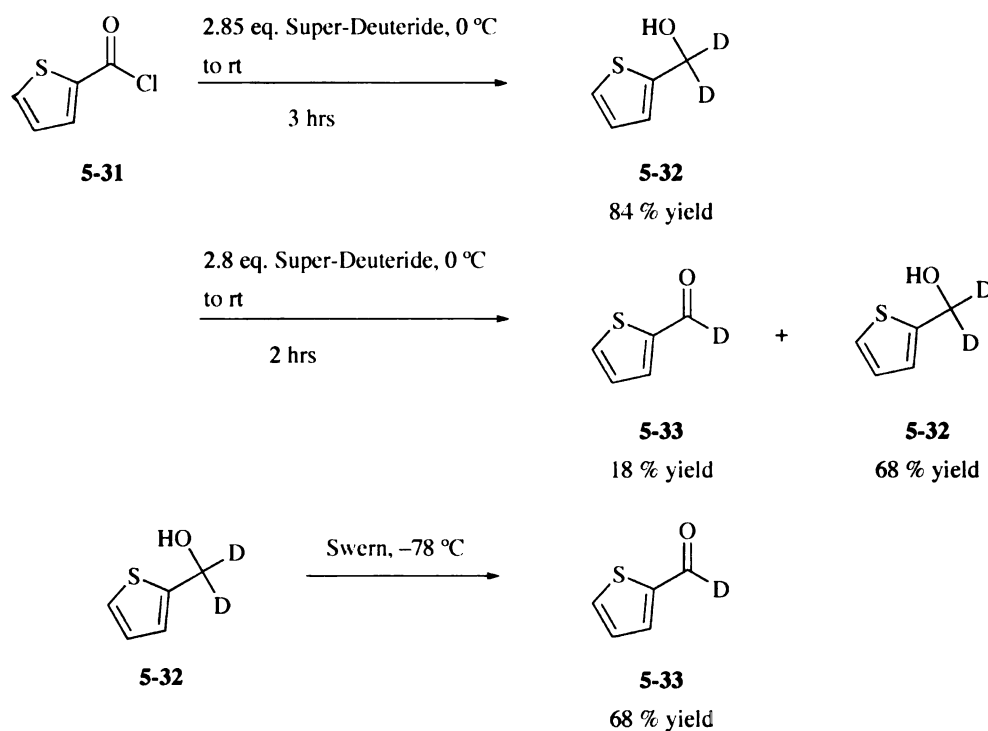
complex 5-37

shown.²⁹ The

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5-32. Depending on the conditions, only the alcohol **5-32** or both the alcohol **5-32** and the aldehyde **5-33** could be made. The resulting alcohol could be oxidized to the corresponding aldehyde **5-33** via a Swern oxidation in 68 % yield.

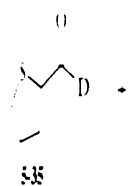
Scheme 5.4. The Formation of the Deuterated Aldehyde



Having the deuterated aldehyde **5-35** in hand, the desired carbene complex **5-37** was prepared in a 49 % yield using literature methods as shown.²⁹¹ The initial methyl ethoxy carbene complex **5-1** was prepared by literature methods.²⁹¹

Scheme

Position



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55 was 35 % ²⁹

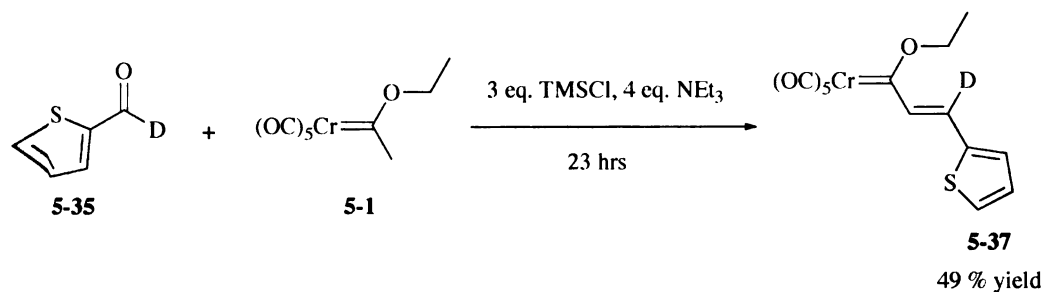
Scheme 5

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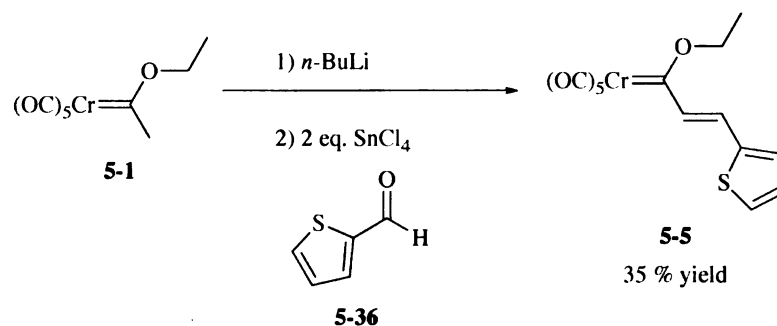
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Scheme 5.5. Formation of Deuterated Carbene Complex at the Beta-Position



We decided to try the aldol condensation approach for the formation of the **non**-deuterated carbene complex **5-5** from compound **5-1**.²⁹² The intermediate **alcohol** eliminated under the conditions employed without the use of the Burgess **reagent** or conversion to a more labile leaving group.²⁹² The yield for compound **5-5** was 35 %.²⁹¹

Scheme 5.6. Formation of Carbene **5-5** Under Lewis Acid Conditions



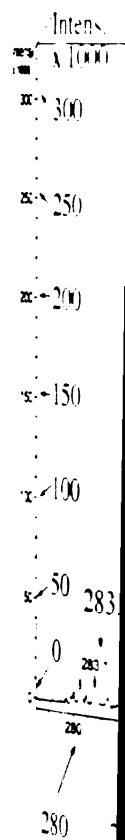
The ESI-MS of compound **5-37** is presented in Figure 5.4. The mass **includes** the deuterium. The ESI-MS of compound **5-5** was identical in all regard

complex 5-37

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Figure 5.

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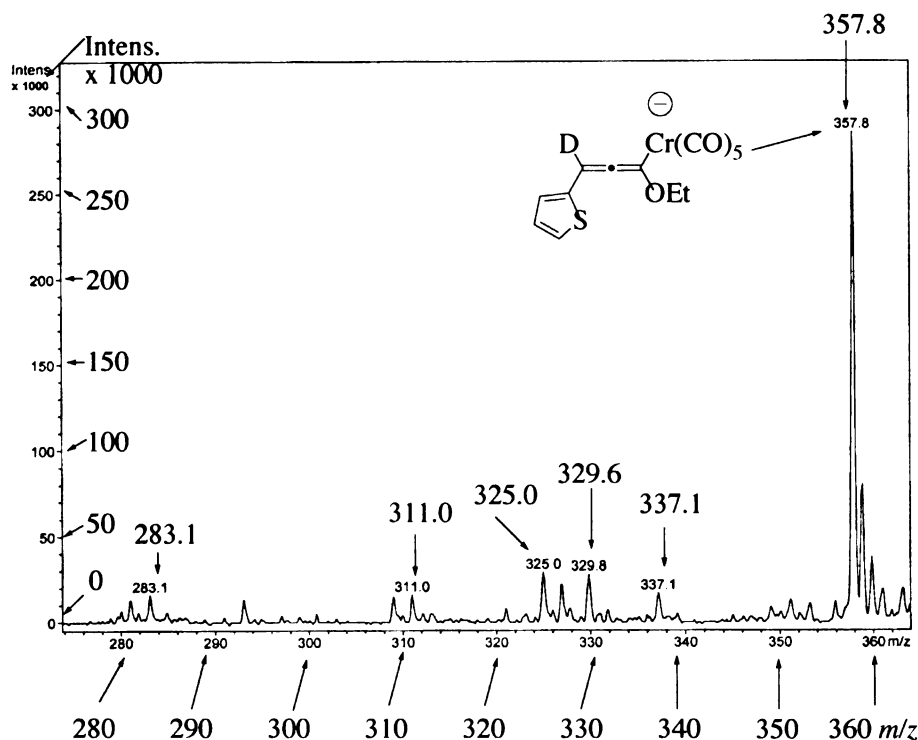
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to complex **5-37** except that the ion was $357\ m/z$.²⁹¹ The explanation of the results will be discussed later in the chapter.

Figure 5.4. ESI Mass Spectrum of Compound **5-37** in Negative mode
Showing the Pseudomolecular Ion $[M - H]^-$ at m/z 358



Other carbenes that were useful for this project were prepared by the standard route shown in Scheme 5.7.²⁹¹ The carbene complex **5-38** was prepared in a seven step process to give a 49 % yield overall.²⁹³ Compound **5-38** was subsequently treated with *n*-butyl lithium and two equivalents of 2-thiophenecarboxaldehyde **5-36**, followed by treatment with deuterated acetic acid

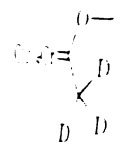
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96.7% deuterium

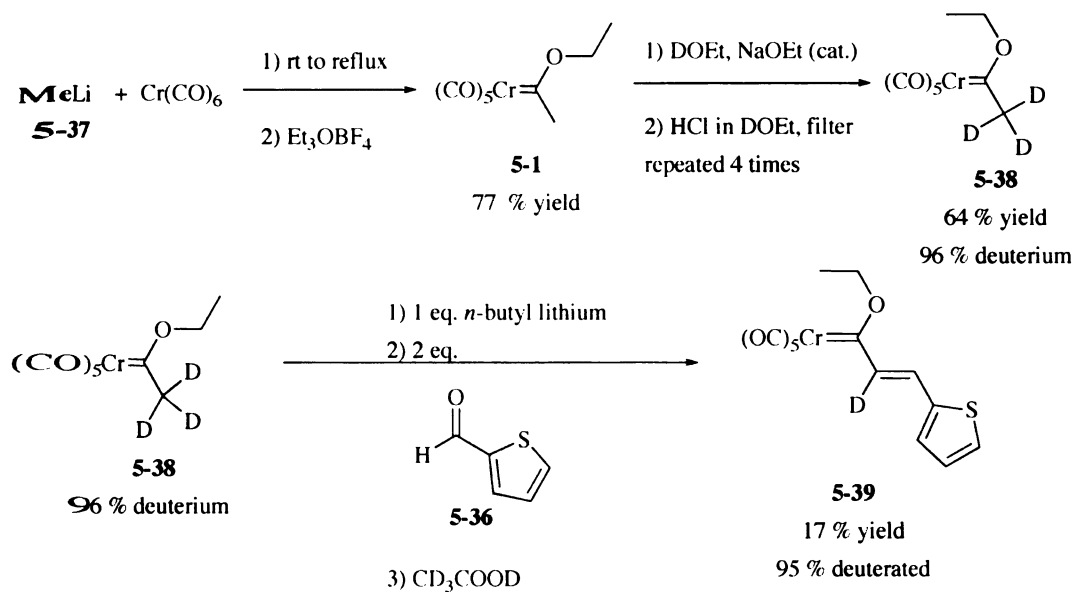
Compound

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was not detected

to give compound **5-39**. The Auman procedure for the formation of carbene **5-39** resulted in the loss of deuterium incorporation.²⁹⁴

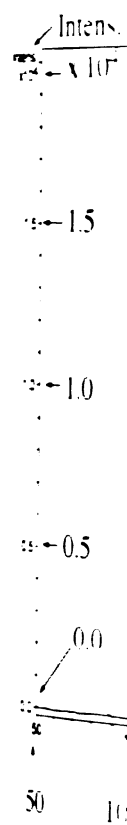
Scheme 5.7. Formation of α -Deuterated Carbene Complex



Compound **5-39** was subjected to negative mode electrospray ionization with mass spectrometry. The ion detected was $[\text{M}^+-1]$ at 356.9 m/z. The ion 358 was not detected as a major peak therefore the deuterium was lost.

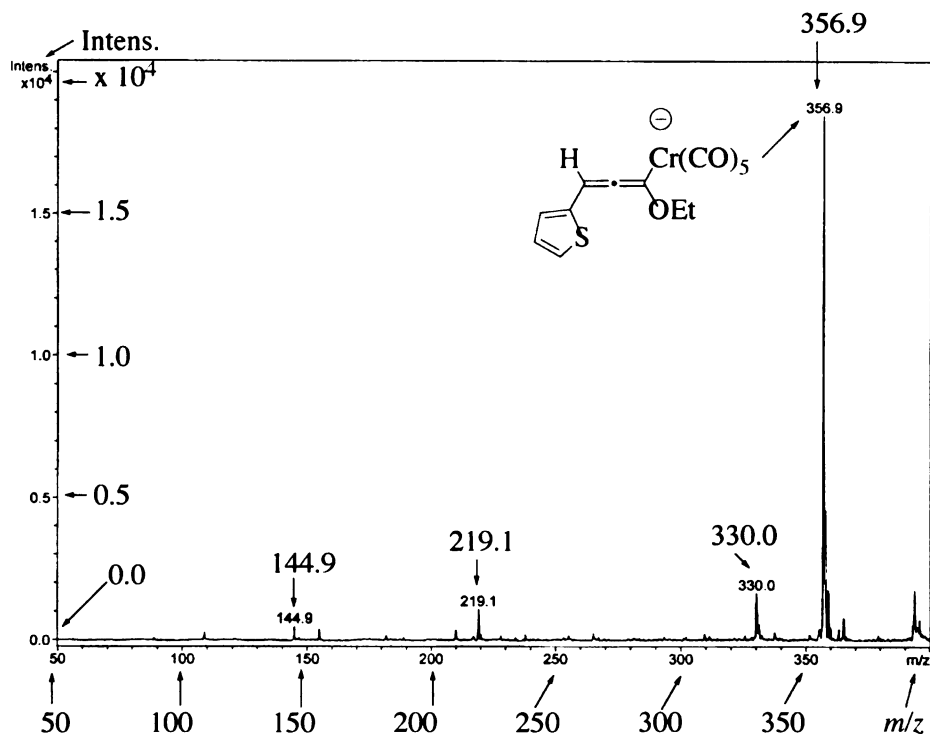
Figure

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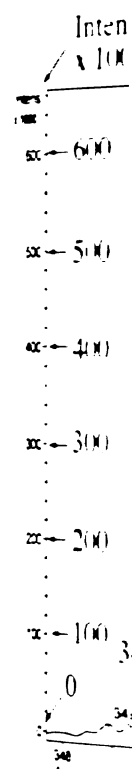
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Figure 5.5. ESI Spectrum of Complex **5-39** Showing the Pseudomolecular Ion $[M - D]^-$ at m/z 357



A deuterium cross over experiment was conducted to determine if intermolecular exchange of deuterium was possible. The Fischer carbene complexes **5-4** and **5-39** were co-injected showing masses of 351 and 357 m/z respectively. This spectrum is shown in Figure 5.6. The isotopic ratios did not change compared to the individually injected compounds.

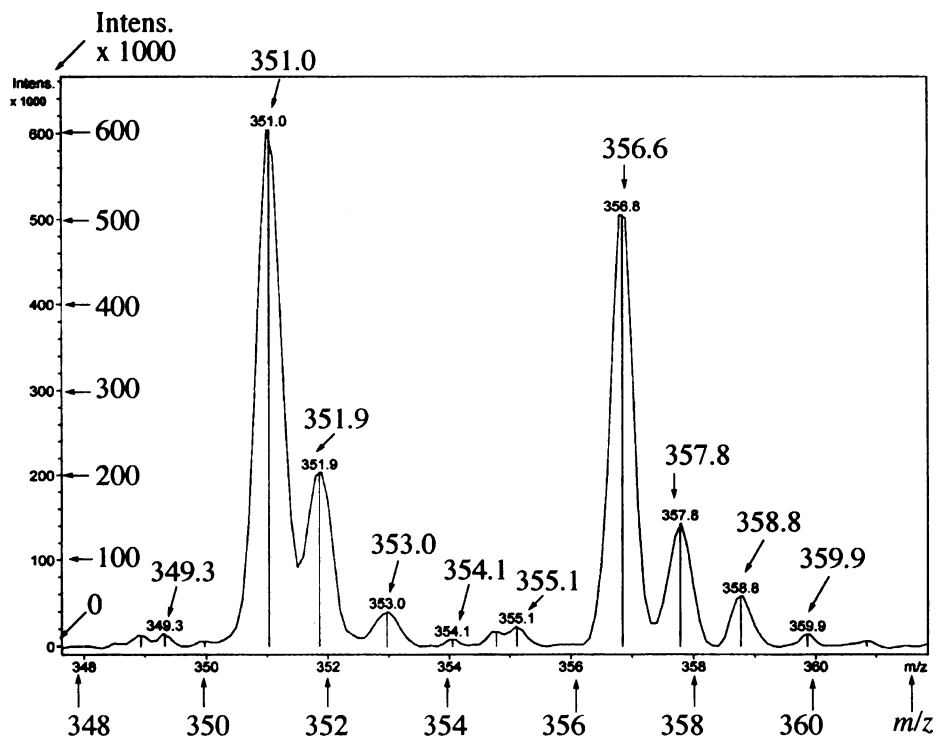
Figure



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Figure 5.6. Deuterium Crossover Experiment



In this experiment, we observed 357.22 m/z for the non-deuterated species (5-6) and 358.36 m/z for the deuterated species (5-37). With this result, we can exclude pathway B as the predominant mechanistic path. Pathway C may also be excluded because compound 5-39 clearly showed the loss of deuterium. Also, the β -deuterated carbene 5-37 was subjected to the ESI conditions with deuterated methanol and hydroquinone and no detectable additional deuterium incorporation was noted. This excludes the possibility of hydrogen exchange at the α -position so the α -deuterated carbene complex did not simply lose deuterium via solvent exchange under the ESI conditions then proceed through an alternate mechanism shown in Scheme 5.3. The

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Scheme



5-40

Compound

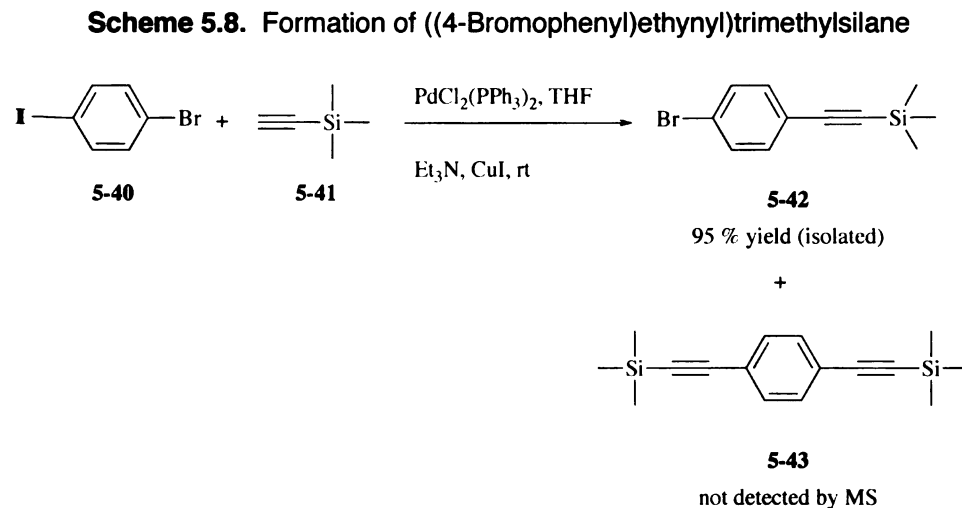
yield of 87 % for

group could be

yield of 2 - 5 %

mechanism of formation of the observed molecular ion most likely is through pathway A for carbene complexes of the type shown in Scheme 5.3.

It is of interest to study compounds like **5-7** to discover their fragmentation processes. In this effort, we treated compound **5-40** with acetylene **5-41** to give compound **5-42** as shown in Scheme 5.8. This proceeded in 95 % yield via a Sonogashira coupling with $\text{PdCl}_2(\text{PPh}_3)_2$, triethyl amine, and copper iodide. By this procedure, compound **5-43** was not detected by GC/MS with careful control of the stoichiometry of reagents.

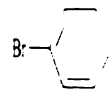


Compound **5-43a** could be prepared by lithium halogen exchange giving a **yield** of 87 % from compound **5-42** shown in Scheme 5.9.²⁹¹ The silyl protecting **group** could be removed with sodium hydroxide to give compound **5-44** in a low **yield** of 2 - 5 %. With effort to limit temperature during the removal of the solvent,

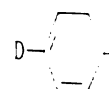
compound 5-4

Compound 5-4

Scheme



5



5

A low yield

step-one pot

optimization.

intermediate 5-

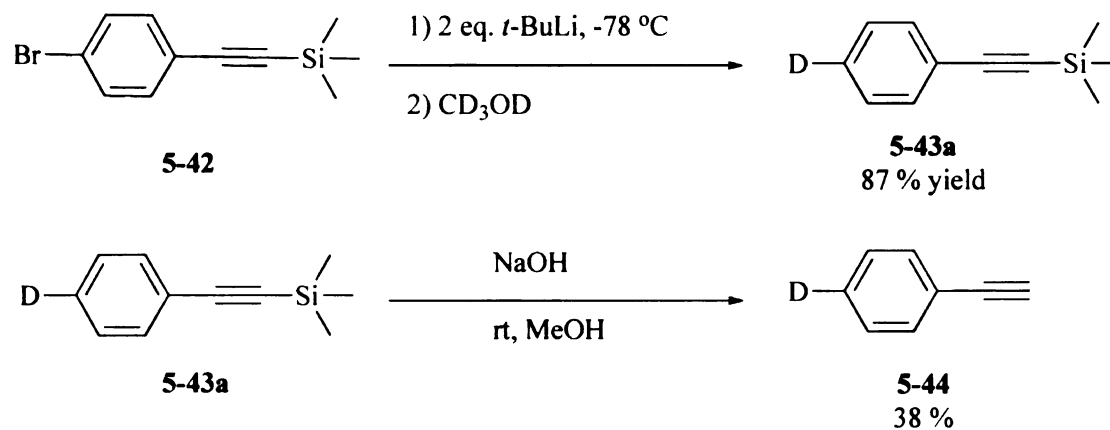
45 with chromi

low yield of 0.1

compound **5-44** could be isolated with trace amounts of solvent in 38 % yield.²⁹¹

Compound **5-44** was somewhat volatile.

Scheme 5.9. Formation of *p*-Deutero-ethynylbenzene



A low yield of the carbene complex **5-46** could be achieved in the two **step**-one pot procedure shown in Scheme 5.10. The reaction requires **optimization**. From compound **5-43a**, the formation of the alkynyl lithium **intermediate 5-45** could be formed.²⁹⁵ Subsequent treatment of intermediate **5-45** with chromium hexacarbonyl and Et₃OBF₄ gave carbene complex **5-46** in a **low** yield of 0.1 %.²⁹⁶

Scheme

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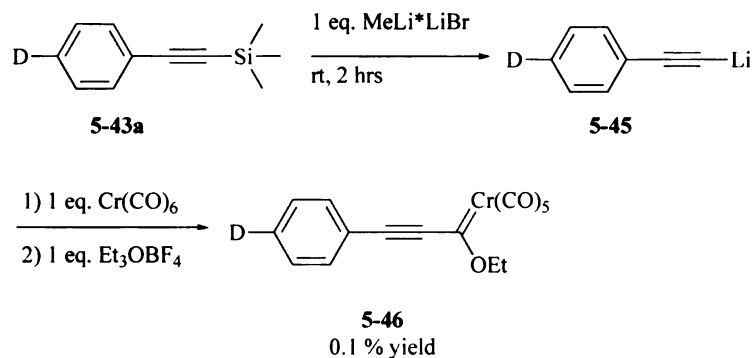
S-4



S-4

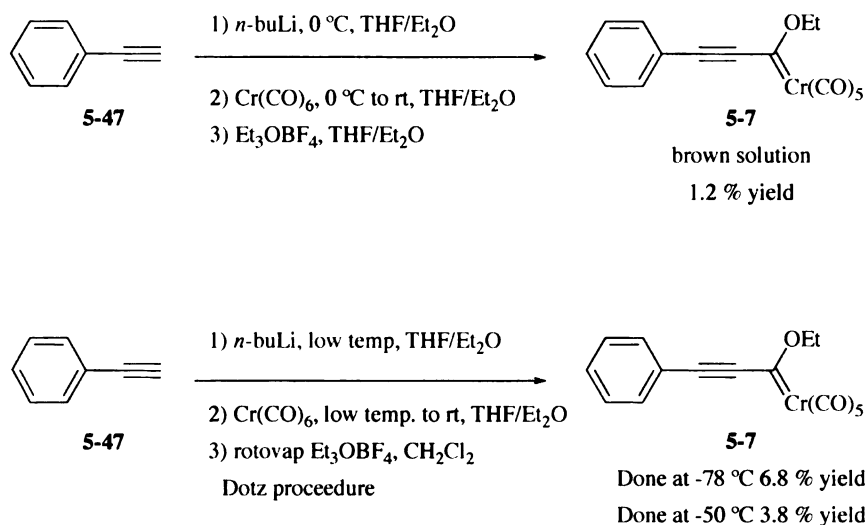
Scheme 5.10. Formation of Deuterated Alkynyl Fischer Carbene Complex via a One Pot Procedure

Complex via a One Pot Procedure



To optimize the formation of the carbene complex, phenyl acetylene **5-47** was employed as shown in Scheme 5.11. From the experiments to generate carbene complex **5-7**, it is clear that the problem lies with the last step which is the nucleophilic addition of the lithium anion to chromium hexacarbonyl and the subsequent alkylation with triethyloxonium tetrafluoroborate.²⁹⁷

Scheme 5.11. Formation of Alkynyl Fischer Carbene Complex



In Scheme 5, the reaction of 1,4-dideutero-2,5-bis(trimethylsilyl)benzene (1) with TTF and TBAF was shown. The deuterium label was retained in the product, indicating that the lithium followed the deuterium. This result was chosen to support the proposed mechanism with 98 % deuterium retention.

Scheme 5

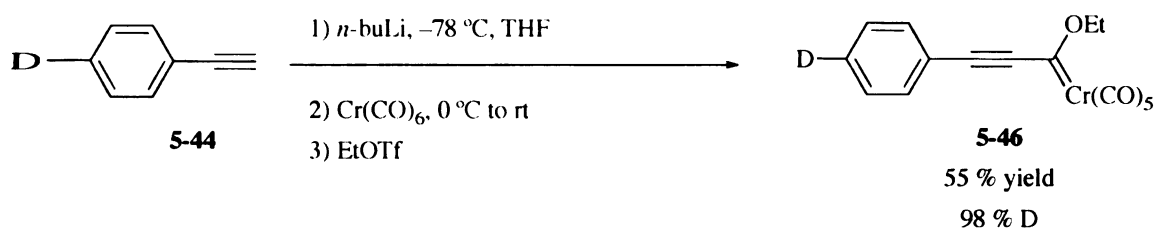


5-44

As shown in Scheme 5, the reaction of 1,4-dideutero-2,5-bis(trimethylsilyl)benzene (1) with TTF and TBAF was shown. The deuterium label was retained in the product, indicating that the lithium followed the deuterium. This result was chosen to support the proposed mechanism with 98 % deuterium retention. The deuterium label was retained in the product, indicating that the lithium followed the deuterium. This result was chosen to support the proposed mechanism with 98 % deuterium retention. The deuterium label was retained in the product, indicating that the lithium followed the deuterium. This result was chosen to support the proposed mechanism with 98 % deuterium retention.

In Scheme 5.12, the synthesis of the deuterocarbene complex **5-46** is shown. The deprotonation of the acetylene **5-44** was performed with *n*-butyllithium followed by treatment with chromium hexacarbonyl. The alkylating agent was chosen to be ethyl triflate instead of Et₃OBF₄. The overall yield was 55 % with 98 % deuterium incorporation.²⁹⁸

Scheme 5.12. Synthesis of Deuterocarbene Complex



As shown in Figure 5.7, we checked for the possible proton interchange using TTF and MeOH(D). Under these conditions, no exchange was observed by ESI/MS. In Figure 5.6a, the spectrum is presented for TTF with methanol, and in Figure 5.6b, the spectrum is presented for TTF with CD₃OD. There are no differences in the pseudomolecular peak. This experiment was done also with the deuterio complex **5-46** and no deuterium loss was noted.

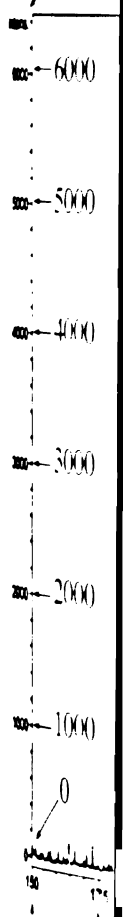
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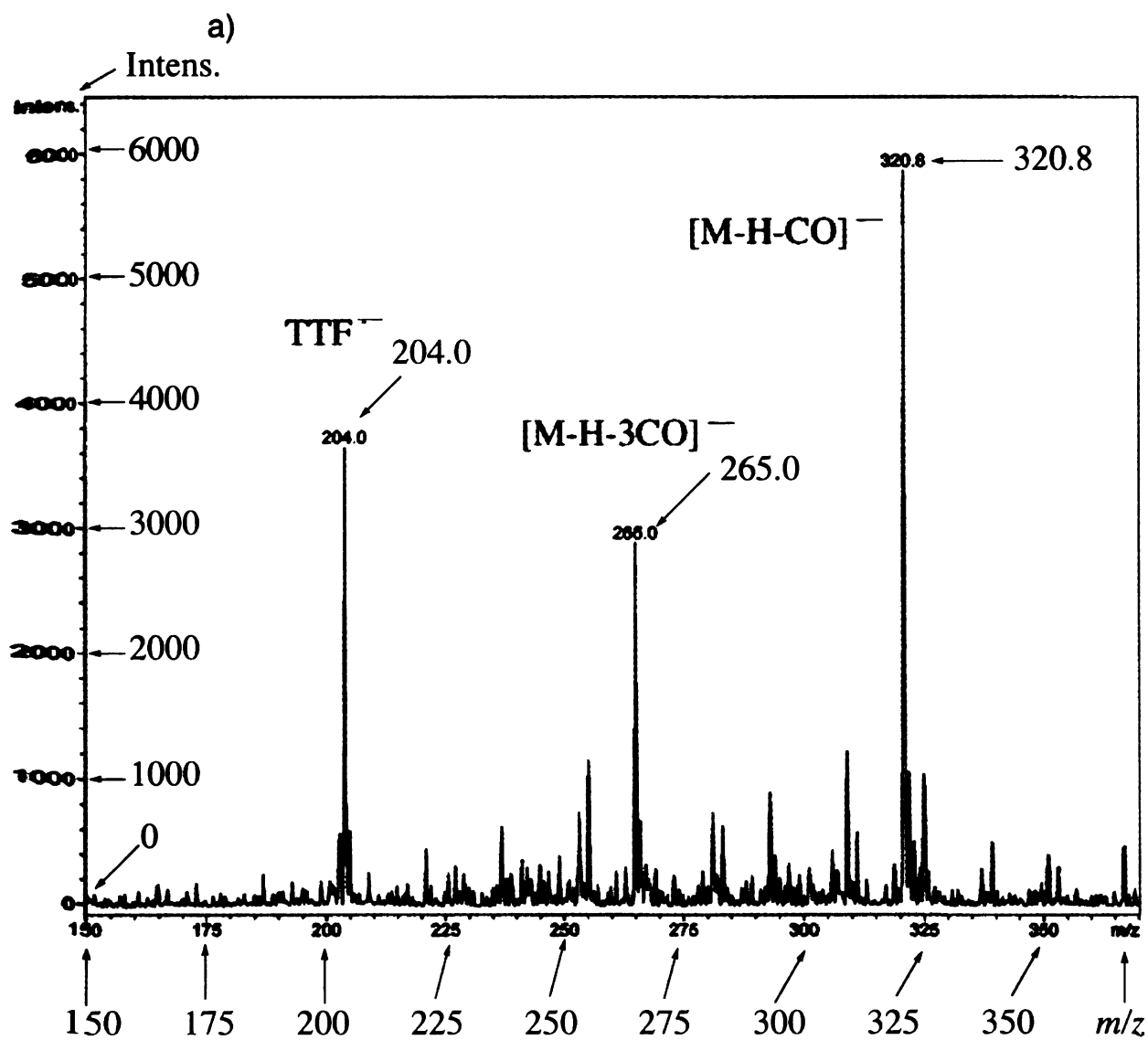
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Figure 5.7. a) ESI Mass Spectrum of Alkynyl Carbene Complex **5-7** With TTF and MeOH. b) ESI Mass Spectrum of Complex **5-7** with TTF and CD₃OD



Figure



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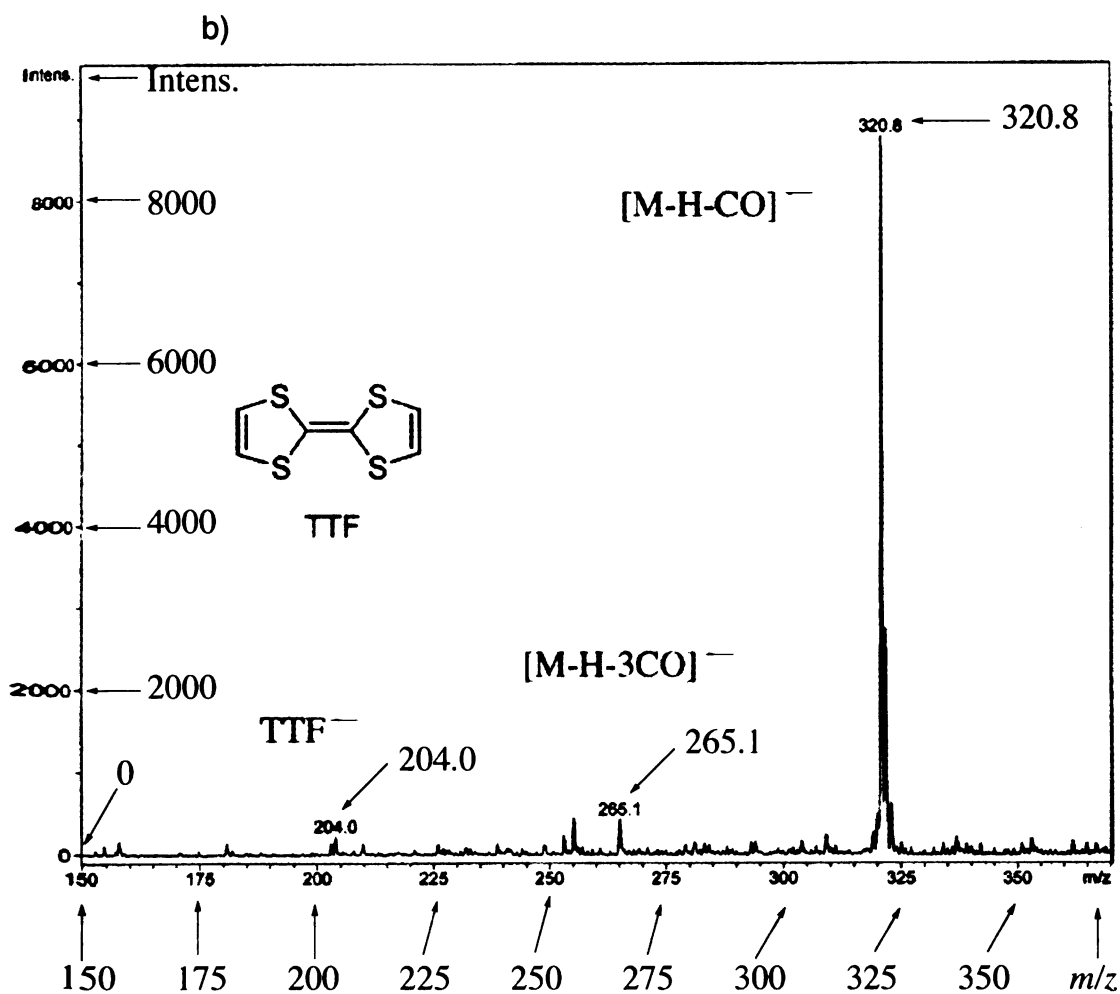
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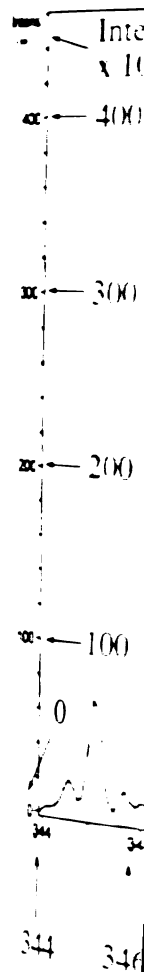
Figure 5.7 (cont'd)



In Figure 5.8, the peak region of the ESI-MS of compound 5-7 is presented using hydroquinone- d_6 and CD_3OD . The isotopic cluster of the pseudomolecular ion presented in Figure 5.7 can only be explained by the interchange of hydrogens of the aromatic ring shown as 351, 352, and 353 m/z . We did not continue work with carbene complex 5-7, HQ, and methanol.

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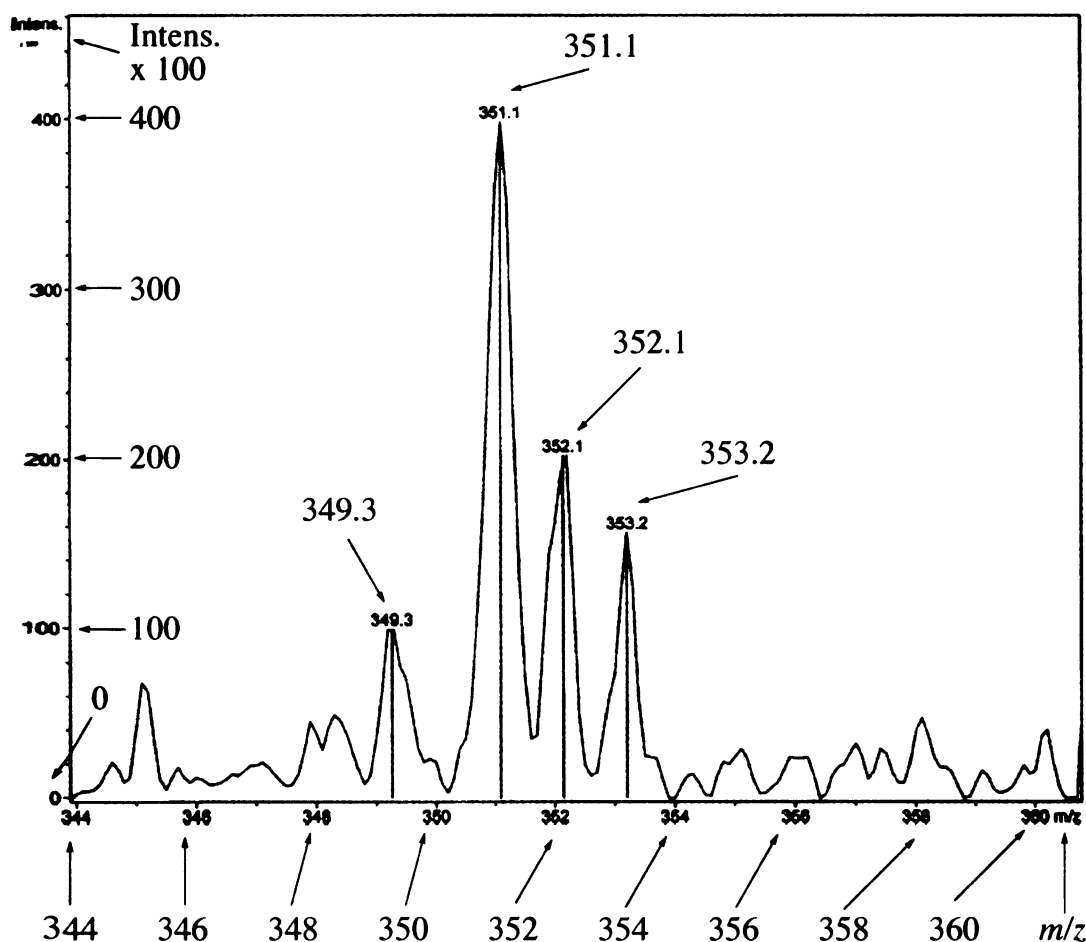
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Figure 5.8. Pseudomolecular Peaks for the ESI-MS of Compound **5-7**
with HQ- d_6 and CD_3OD



The proposed mechanism of the formation of the pseudomolecular ion is presented in Scheme 5.13. From compound **5-7**, an electron is transferred giving the intermediate **5-48**.²⁸⁶ Following pathway A, the elimination of hydrogen α gives carbene anion **5-49**. In pathway B a McLafferty type rearrangement gives compound **5-50**.²⁹⁰ With loss of a hydrogen radical, the pseudomolecular ion **5-51** would be formed (loss of CO was also observed in the

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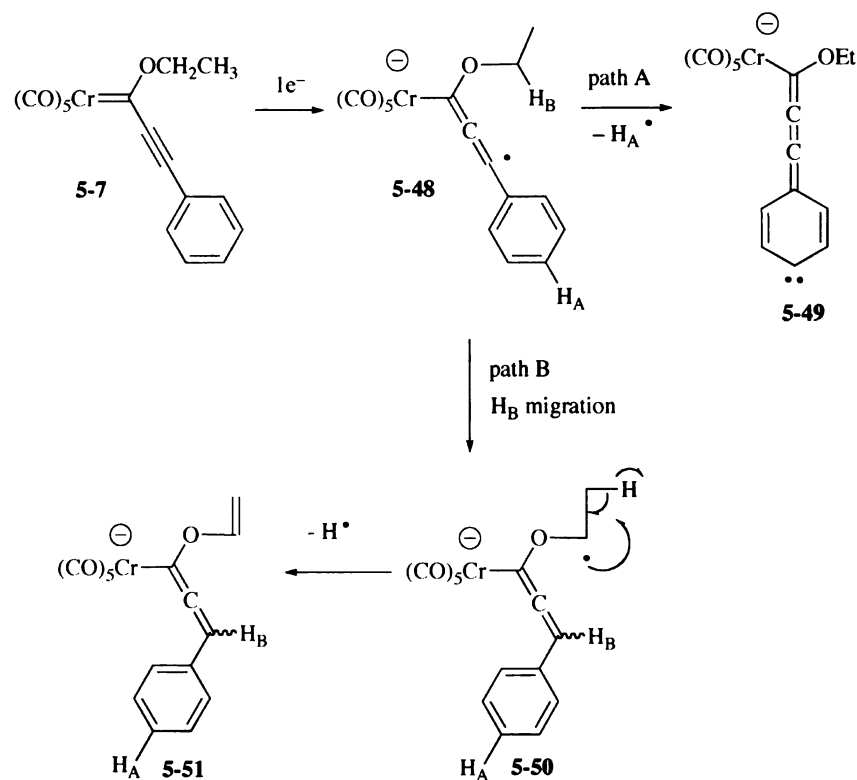
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ESI-MS). When ESI-MS was performed with CD₃OD under conditions to prevent deuterium scrambling²⁹¹ with H α = deuterium, the deuterium remained within the molecule with *m/z* of 322 for C₁₅H₈DCrO₅ [M – H – CO].[–]

Scheme 5.13. Formation of Alkynyl Carbene Complex

Pseudomolecular Ion



In Figure 5.9, the H α breakage in the ionization process has been rationalized by performing DFT calculations on a model system [(CO)₅Cr(OMe)CH=CH₂] shown as compound 5-52.²⁹⁹ The stability of the anions from the breakage of the H α and H β shown as compounds 5-53 and 5-54

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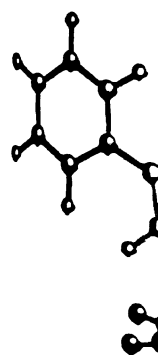
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are compared. Intermediates **5-52**, **5-53**, and **5-54** were optimized at the B3LYP/LANL2DZ&6-31G(d) level of theory. These results showed that the allenyl anion **5-53** was considerably more stable by 42.02 kcal/mol than carbene anion **5-54**. Additional calculations were done with complex **5-55** with an aromatic substituent $[(\text{CO})_5\text{Cr}(\text{OMe})\text{CH}=\text{CHPh}]$. The allenyl anion **5-57** resulted in the more stable intermediate than the carbene anion **5-56** by 34.05 kcal/mol. The difference in energy between the two species is high. The value 34.05 kcal/mol is an estimate of the allenyl-metal species stabilization energy compared to a vinyl-metal species. The charges on the metal in species **5-53** and **5-54** are almost identical which points to the small effect of the metal in the stability of the radical anion formed after the initial electron transfer reaction.

Figure 5

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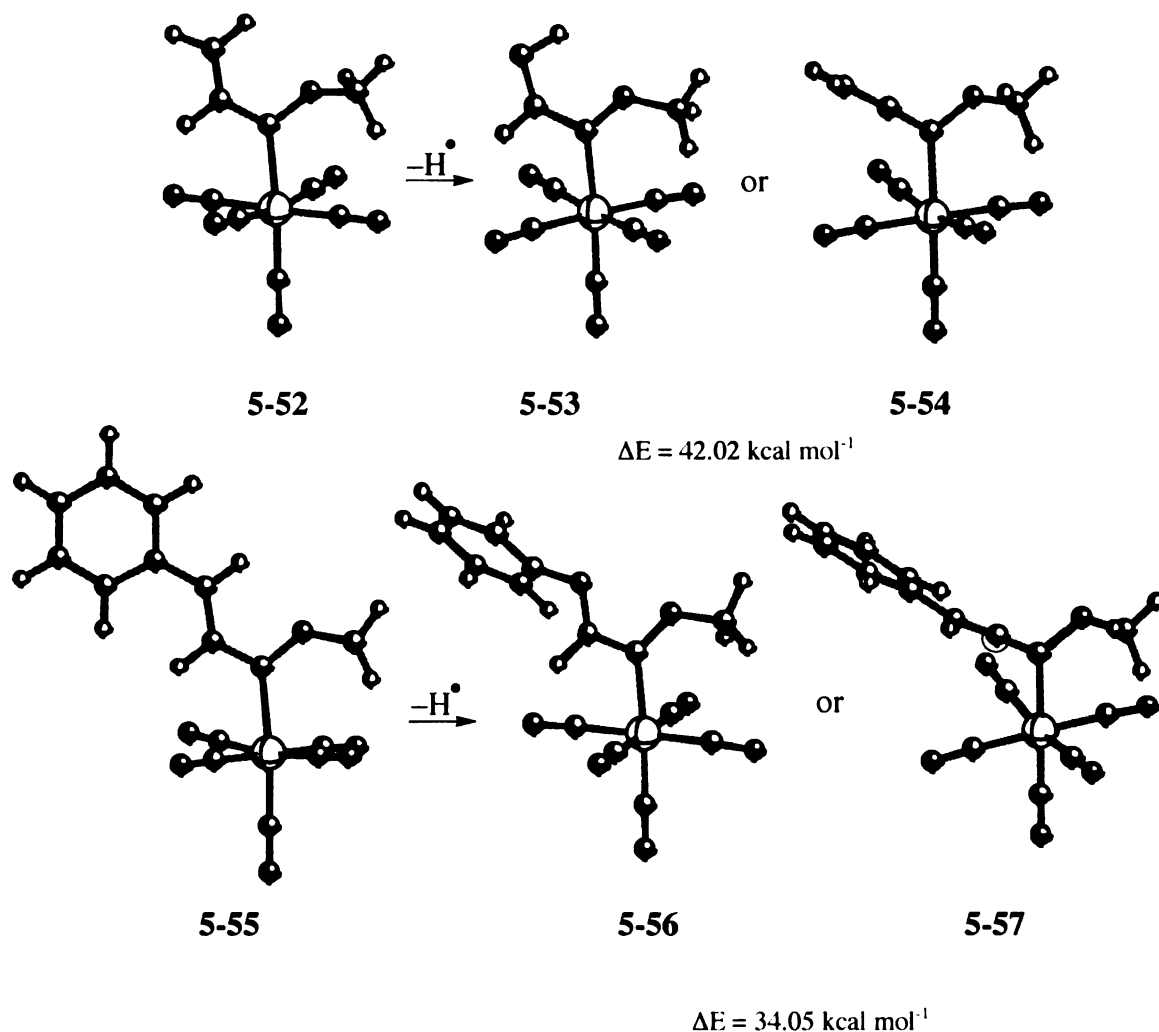
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Figure 5.9. The Optimized S0 Geometries (B3LYP/LANL2DZ&6-31+G(d))
of Radical Anions



5.4 Future Work with Fischer Carbenes and ESI-MS

It would be interesting to investigate the mechanism of the α,β -unsaturated ferrocenyl Fischer carbene complex and determine the mechanism shown in Scheme 5.14.²⁸⁶ The mechanism of the formation of the quasimolecular ion may proceed from compound **5-14** to intermediate **5-58** which could form intermediate **5-59** with an electron transfer from the ferrocene to the

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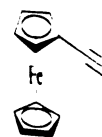
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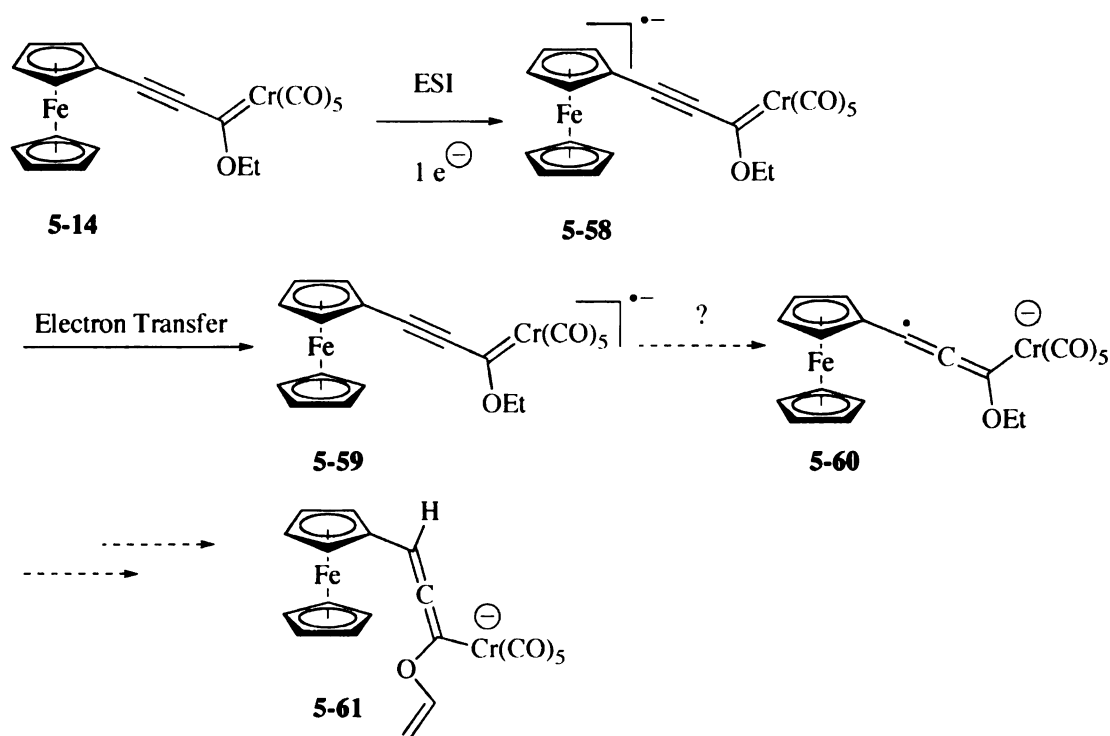
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chromium tricarbonyl motif.²⁹¹ The radical anion **5-60** may be formed. The gas phase reaction may give compound **5-14** as the final product from a McLafferty type rearrangement.²⁹⁰ It would be desirable to demonstrate the electron transfer within a carbene complex such as **5-14**.

Scheme 5.14. Proposed Mechanism of the Formation of a Quasimolecular Ion



It would be desirable to apply electrospray ionization / mass spectrometry toward applications of high resolution ESI-MS. The method of ESI may provide high-resolution mass spectroscopy via Q-Tof at a low price, which is an additional motivation for our group.

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CHAPTER SIX

FORMATION OF ALLYL AMINES FROM AZIRIDINES AND AZIRIDINES IN BRIEF

In collaboration with the Borhan laboratory especially with Jennifer Schomaker, the formation of allyl amines from aziridines was investigated. We were interested in the opening of aziridines for a variety of reasons, which include the possible use of aziridines as starting materials for the formation of propargyl amines and also to use sulfur-containing nucleophiles such as dimethylsulfonium methylide to open aziridines generated in the Wulff laboratory by our azirdination chemistry.³⁰⁰ Allyl amines are an important building block in organic chemistry and several reviews have been published on this topic alone.³⁰¹ They have been used for the formation of α -³⁰² and β -amino acids,³⁰³ alkaloids, and carbohydrate derivatives.³⁰⁴

6.1 Methods for Forming Allyl Amines

The formation of allylic amines is a broad topic and it encompasses tomes of literature. It is difficult to do the topic justice in one chapter of a dissertation however an overview of the various methods for the formation of allylic amines will be attempted. The formation of allyl amines has been accomplished from aziridines via the thermal method shown in Scheme 6.1. The aziridine (**6-1**) was refluxed neat giving compound **6-2** in 93 % yield.³⁰⁵

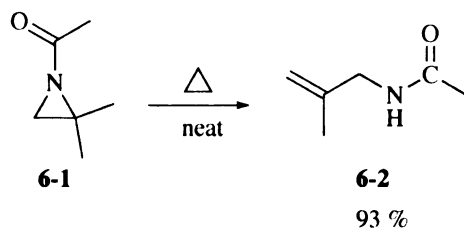
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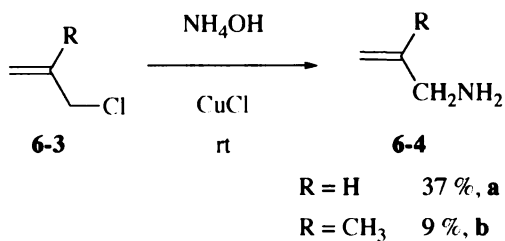
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Scheme 6.1. Thermal Formation of Allyl Amines



Shown in Scheme 6.2, the direct formation of allyl amines are depicted via substitution from the allylic chloride **6-3** mediated by copper. When the substituent R was hydrogen, the yield was 37 % for compound **6-4a**, but the yield was only 9 % when R = Me giving compound **6-4b**.³⁰⁶

Scheme 6.2. A Copper Mediated S_N2 Reaction



Phthalatide (**6-6**) has traditionally (Gabriel synthesis³⁰⁷) been used for the formation of allylic amines as shown in Scheme 6.3. In the example shown, allylic bromide (**6-5**) was used as an alkylating agent to form compound **6-7** in 87 % yield in ethanol.³⁰⁸

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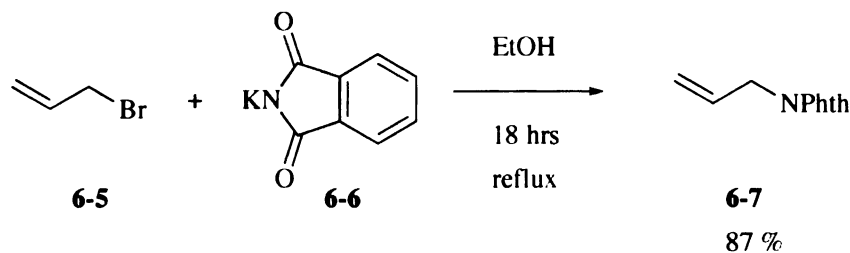
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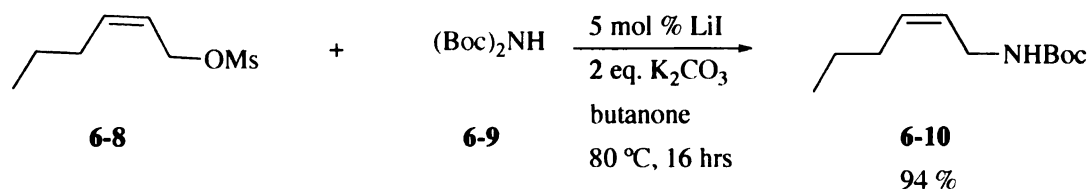
yield of 77 %.

Scheme 6.3. The Use of S_N2 Reactions for the Formation of Allyl Amines



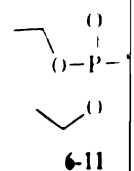
Also used for the formation of allylic amines such as **6-10** are mesylates (**6-8**) shown in Scheme 6.4. In the example shown, the yield was 94 % using catalytic lithium iodide and potassium carbonate from the amine **6-9**.^{306, 309} The reaction was done in butanone at 80 °C for 16 hours.

Scheme 6.4. The Use of S_N2 Reactions Involving Mesylates



When *N*-trimethylsilylphosphoramidate **6-11** was treated with sodium hydride and then alkylated with allyl bromide (**6-5**), compound **6-12** was formed after an ethanol quench in 95 % yield. Deprotection of compound **6-12** with HCl gave compound **6-13** in 89 % yield. The hydrogen chloride salt was not volatile. The two-step sequence from compound **6-11** to compound **6-13** gave an overall yield of 77 %.

Scheme



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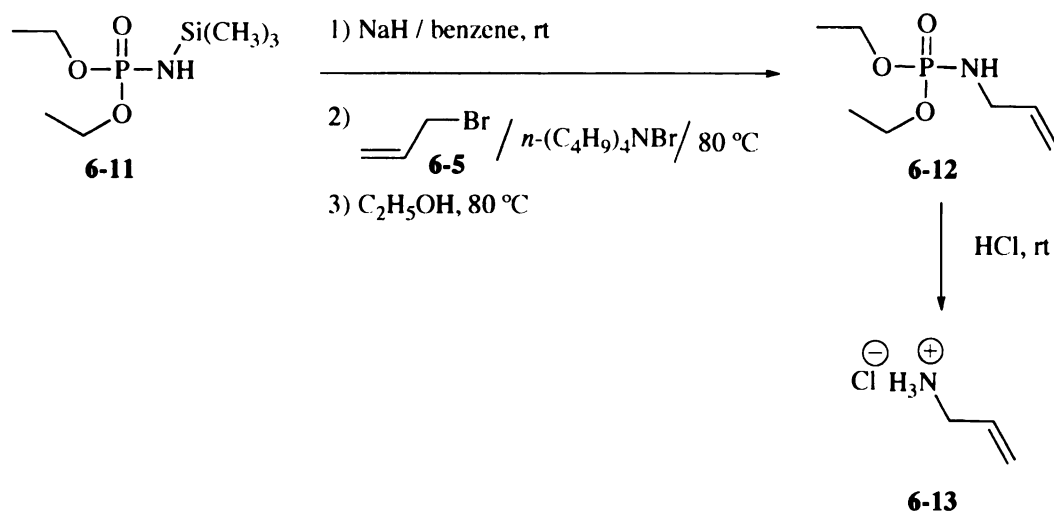
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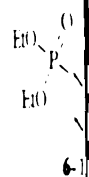
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Scheme 6.5. Diethyl *N*-[trimethylsilyl]phosphoramidate Alkylation



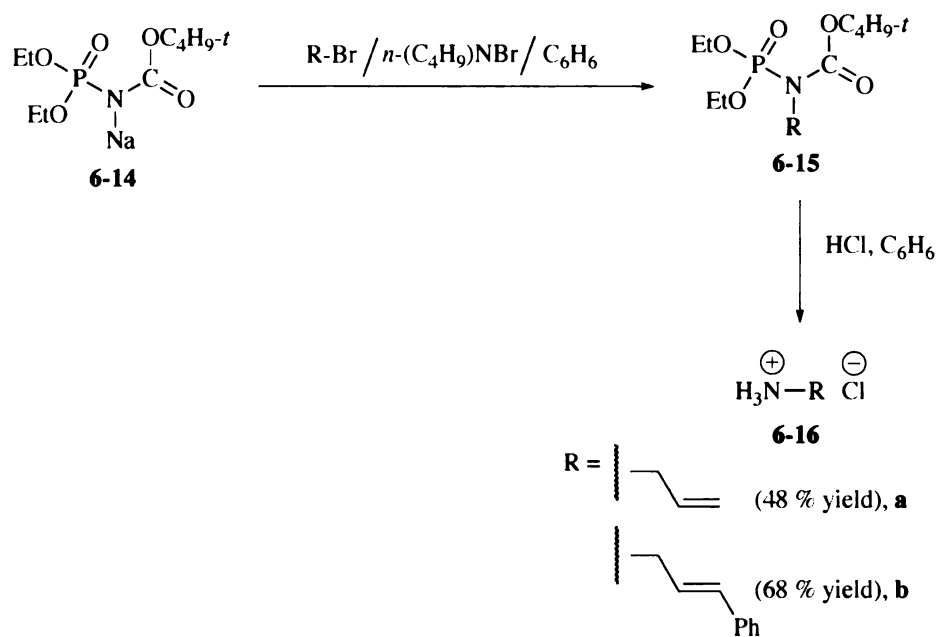
Compound **6-14** displays a superior reactivity for the formation of allylic amines compared to compound **6-11** shown in Scheme 6.6.³¹⁰ The alkylation proceeds in the presence of an ammonium salt in benzene from an allylic bromide. The yield for compound **6-16a** was 48 % from the diethyl *N*-sodio-*N*-[*t*-butoxycarbonyl]phosphoramidate (**6-14**). The yield for compound **6-16b** was 68 %.

Scheme



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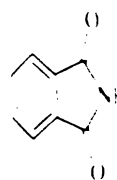
Scheme 6.6. Diethyl *N*-sodio-*N*-[*t*-butoxycarbonyl]phosphoramidate



The reaction of vinyl-tri-(*n*-butyl)phosphonium salt **6-18** with sodium phthalide (from **6-17**) forms intermediate **6-19**, and with an aldehyde gave the allylic imide **6-20** in 83 to 95 % yield as shown in Scheme 6.7.³¹¹ The *E* / *Z* ratios are generally greater than 4 to 1. Cleavage to the allylic amine **6-20** can be accomplished with hydrazine or sodium sulfide to give compound **6-21** in yields of 83 to 92 %.³⁰⁴

Scheme

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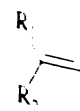
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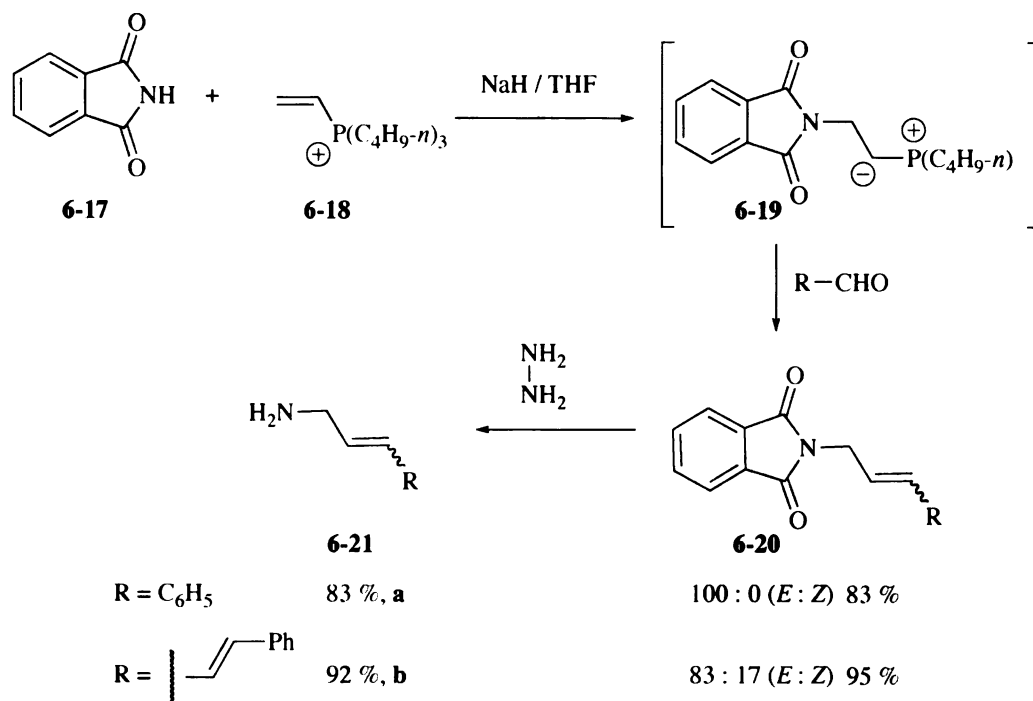
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Scheme 6.7. The Formation of Phosphonium Salts and the Wittig

Reaction for the Formation of Allyl Amines

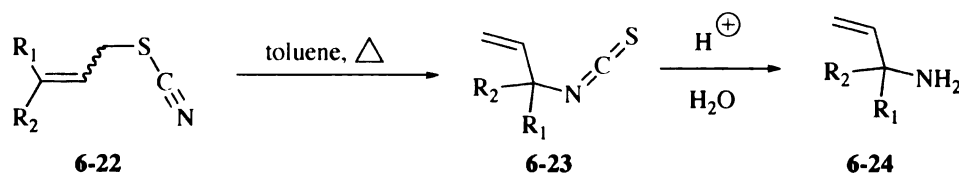


In Scheme 6.8, the use of thiocyanates is depicted.³⁰⁶ The thiocyanate

6-22 with reflux in toluene undergoes rearrangement to give compound **6-23**, and which upon treatment with acid, compound **6-24** is formed.

Scheme 6.8. Allylic Thiocyanates with Thermal Rearrangement to Form

Allylic Amines



In Scheme 6.9, the acid induced formation of allylic amines is shown. The

reaction yielded *E*-compound **6-26** in H_2SO_4 in 85 % yield.³⁰¹

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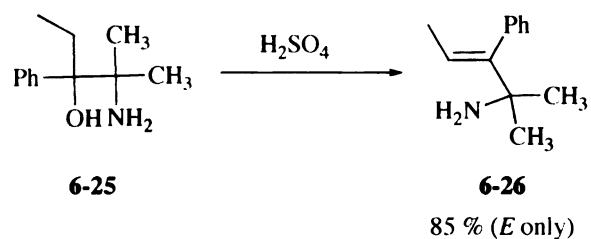
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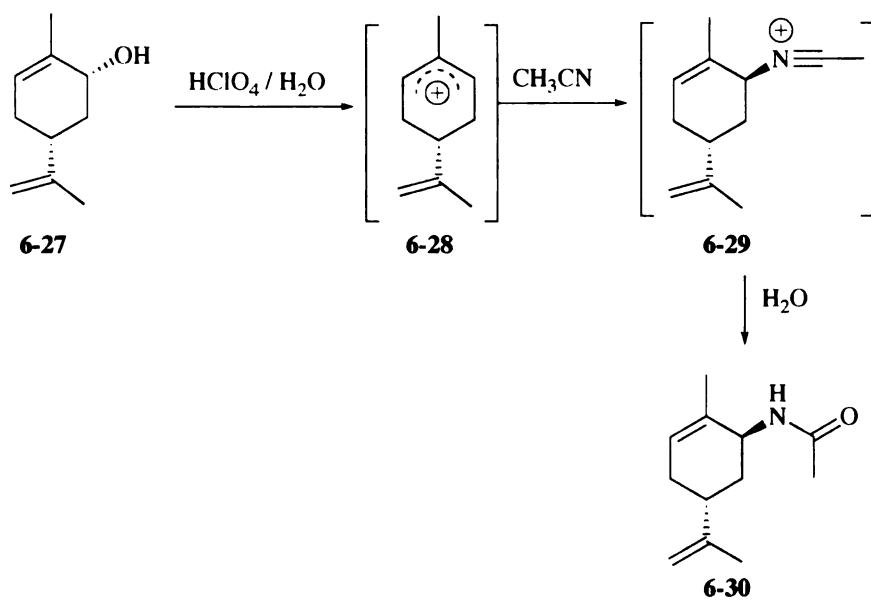


Scheme 6.9. Acid Rearrangement to Form Allylic Amines



The Ritter reaction shown in Scheme 6.10 can produce an allylic acetamide (**6-30**).³¹² In this reaction, the use of perchloric acid gives intermediate **6-28**, and in the presence of acetonitrile, the intermediate cation **6-29** is formed. When water is added, product **6-30** can be furnished. As can be observed, the Ritter reaction employs harsh conditions and this significantly limits its practical applications.³⁰⁴

Scheme 6.10. The Ritter Reaction Used for the Construction of Allylic Amines



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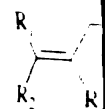
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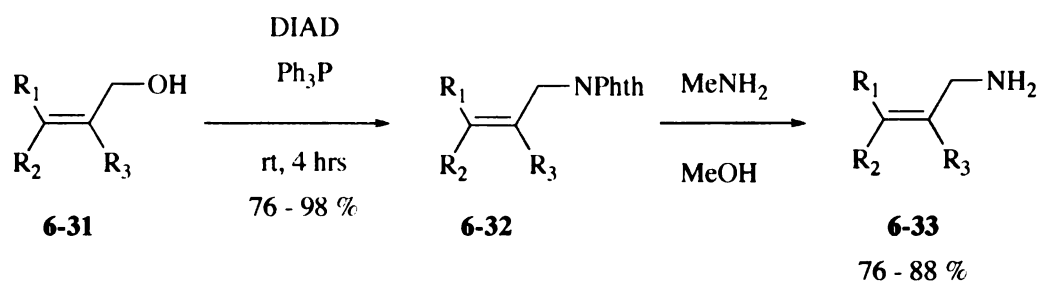
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The Mitsunobu reaction³¹³ is shown in Scheme 6.11 for the formation of allylic amines in which DIAD and triphenyl phosphine are used to substitute the alcohol functionality of compound **6-31** with phthalimide giving compound **6-32**.³⁰⁴ The phthalimide **6-32** can be converted to the primary allylic amine **6-33** in the presence of methylamine in 76 to 88 % yield.³¹⁴

Scheme 6.11. Mitsunobu Reaction Used for Allylic Amines



The synthetic manipulation of protection groups is shown in Scheme 6.12. Compound **6-34** could be protected by Boc giving amine **6-35** with subsequent treatment under the dissolved metal reducing condition with sodium and ammonia, the tosyl protecting group could be removed in 51 % yield with no loss of enantiomeric excess giving compound **6-36**.³⁰⁴ Compound **6-38** could be formed from the epoxide **6-37** in 37 % yield with 81 % ee. A Mitsunobu reaction³¹³ formed compound **6-35** in 95 % yield however when the Boc protecting group was removed forming compound **6-39**, the enantiomeric excess was only 18 %. This loss of ee has been attributed to the Mitsunobu reaction

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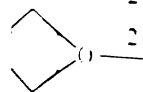
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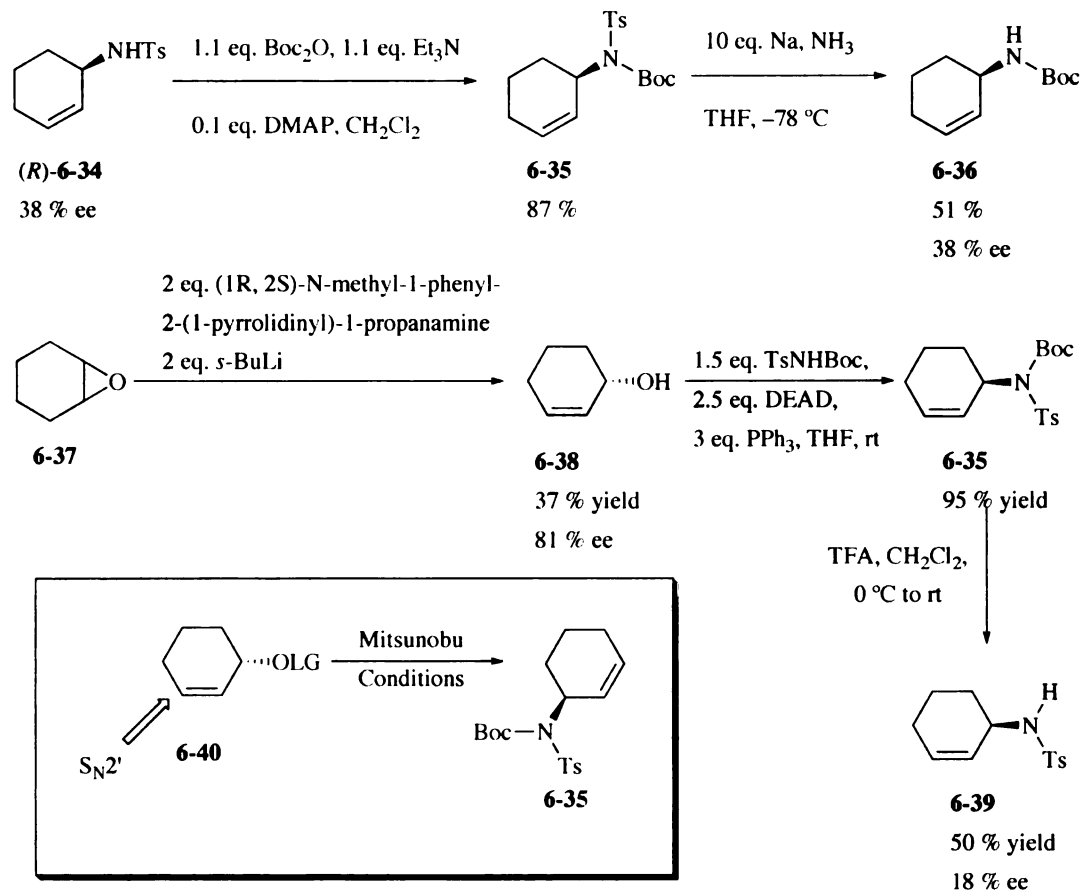
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Scheme 6.12. Synthetic Manipulation of Aziridine Protecting Groups



The deprotection of a tosyl protecting group can be higher in yield. In Scheme 6.13, the use of sodium / naphthalene to deprotect the tosyl protecting group is shown. The yield was an excellent 98 % from compound **6-41** giving compound **6-42**.

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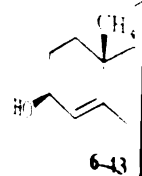
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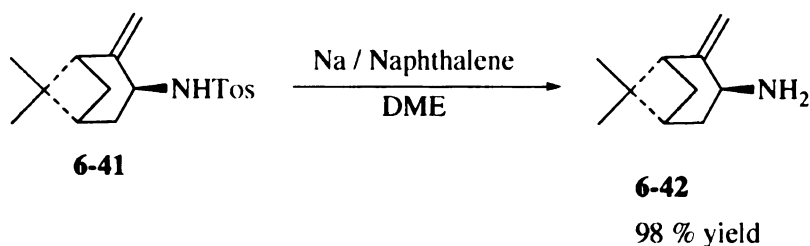
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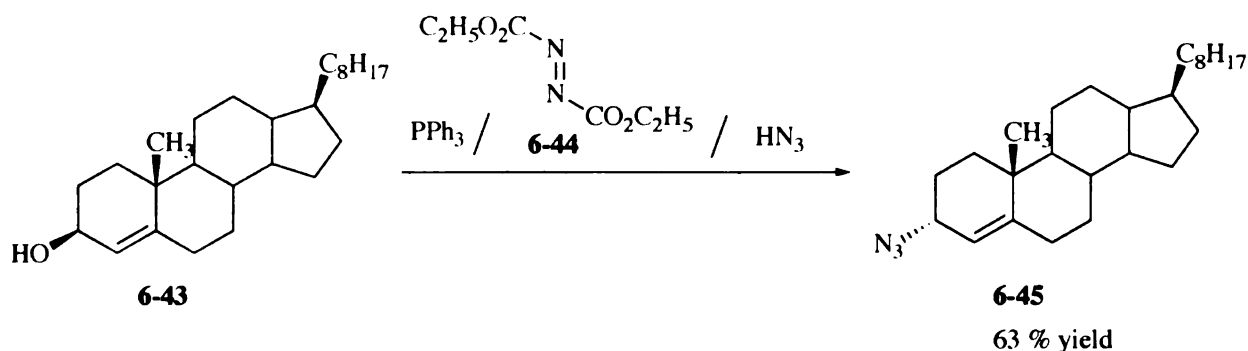
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Scheme 6.13. The Deprotection of Tosyl Amines



In Scheme 6.14, another application of the Mitsunobu reaction has been depicted.³¹⁵ In this example, alcohol **6-43** was treated with hydrogen azide giving a 63 % yield of compound **6-45**.³¹⁶ The enantiomeric purity was not reported however Mitsunobu reactions usual occur with complete inversion of the stereocenter.³¹³ This compound could easily be reduced with lithium aluminum hydride to give the corresponding primary allylic amine if needed.³¹⁷

Scheme 6.14. A Mitsunobu Reaction for the Substitution With an Azide

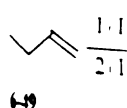
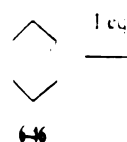


In Scheme 6.15, the use of DEAD is shown for the formation allyl amines from olefins. Compound **6-46** was converted to compound **6-47** followed by lithium ammonia reduction gave compound **6-48**. Other substrates like compound **6-49** forming compound **6-50**, the yield was 86 % with a ratio of *E* : *Z*

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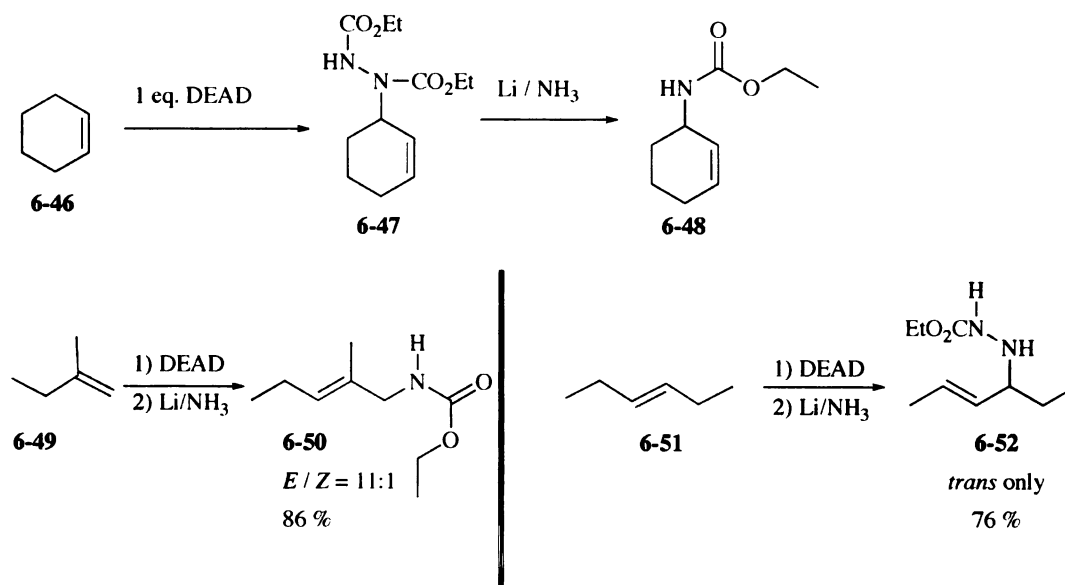


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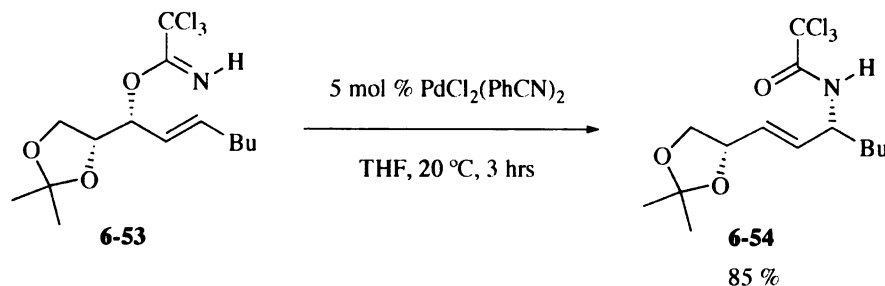
of 11 : 1. For compound **6-51** forming compound **6-52**, the yield was 76 % with only the *trans* (*E*) product found.

Scheme 6.15. DEAD Used for the Formation of Allyl Amines



In Scheme 6.16, the palladium-catalyzed rearrangement is shown for the chiral allyl *N*-phenyl imidate (**6-53**).³⁰¹ This reaction proceeds in the presence of palladium(II) in THF yielding protected amide **6-54** in 85 % yield.³¹⁸

Scheme 6.16. The Use of π -Allyl Complexes to Generate Allyl Amines



In Scheme 6.17, the use of allylic carbonates and palladium(0) fosters the formation of an π -allylpalladium intermediate. The use of *trans*-alkenes results in

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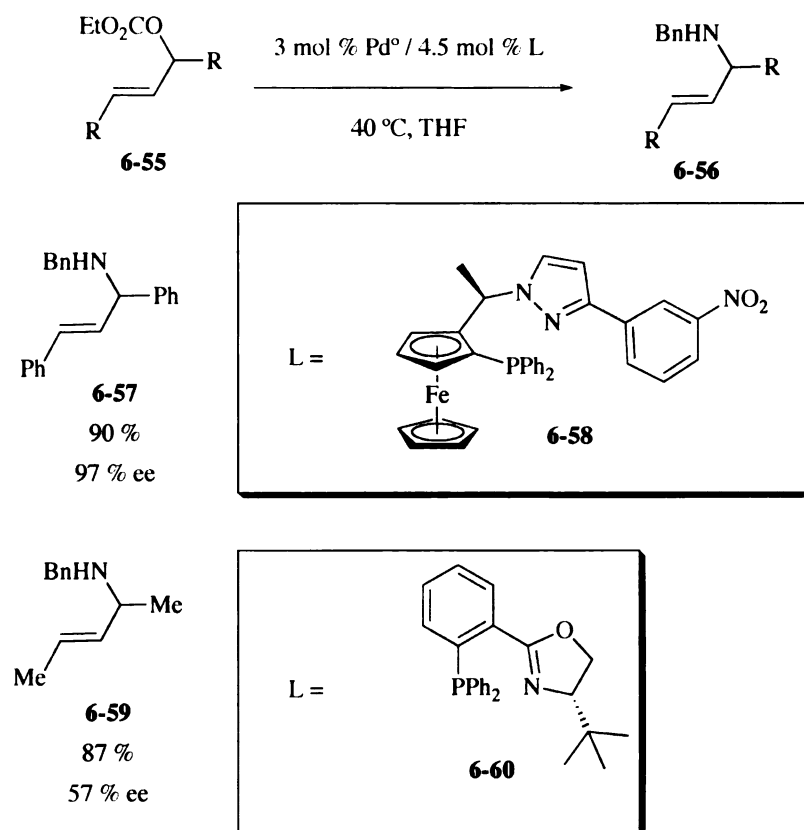
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the preservation of the stereochemistry about the double bond however the use of *cis*-alkenes has been limited.³⁰¹ The reaction has been performed with 3 mol % palladium(0) and 4.5 mol % of ligand (**6-58**) from compound **6-55** to allyl amine **6-56**. The yield for product **6-57** from the concomitant starting material was 90 % and 97 % ee. For product **6-59**, the yield was 87 % and the ee was 57 % using ligand **6-60**.³¹⁹

Scheme 6.17. The Use of π -Allyl Complexes for the Formation of Chiral Allyl Amines



Shown in Scheme 6.18 is the formation of chiral allylic amines using a sequential palladium catalyzed rearrangement from compound **6-61** to **6-62**

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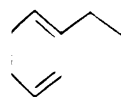
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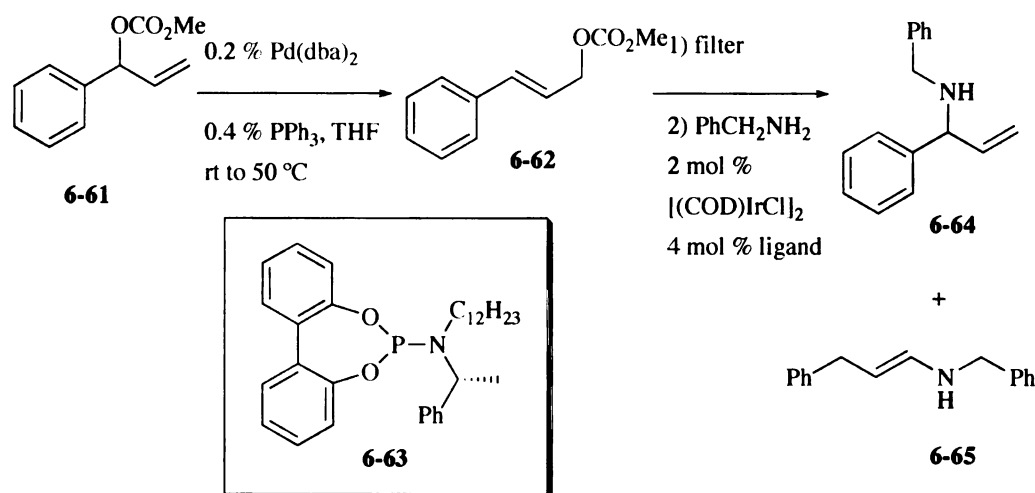
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followed by the use of ligand **6-63** (4 mol %) with iridium to give compound **6-64**. For the reaction shown, the yield was 76 % with 93 % ee, and the ratio between **6-64** and **6-65** was 98 to 2. The reaction was limited to aromatic substrates to obtain good enantiomeric excesses.³²⁰

Scheme 6.18. Sequential Catalytic Isomerization and Allylic Substitution



In Scheme 6.19, the four-component formation of allylic amines is shown.³²¹ The allenylboronate **6-66** and aryl iodide **6-67** were treated with $\text{Pd}_2(\text{dba})_3$ to give the proposed complex **6-68**. In the presence of a secondary amine, compound **6-70** was formed. On other substrates, the yield for compound **6-72** was 73 %, and for compound **6-73** the yield was 80%. The yield for compound **6-74** was 52 %.³²²

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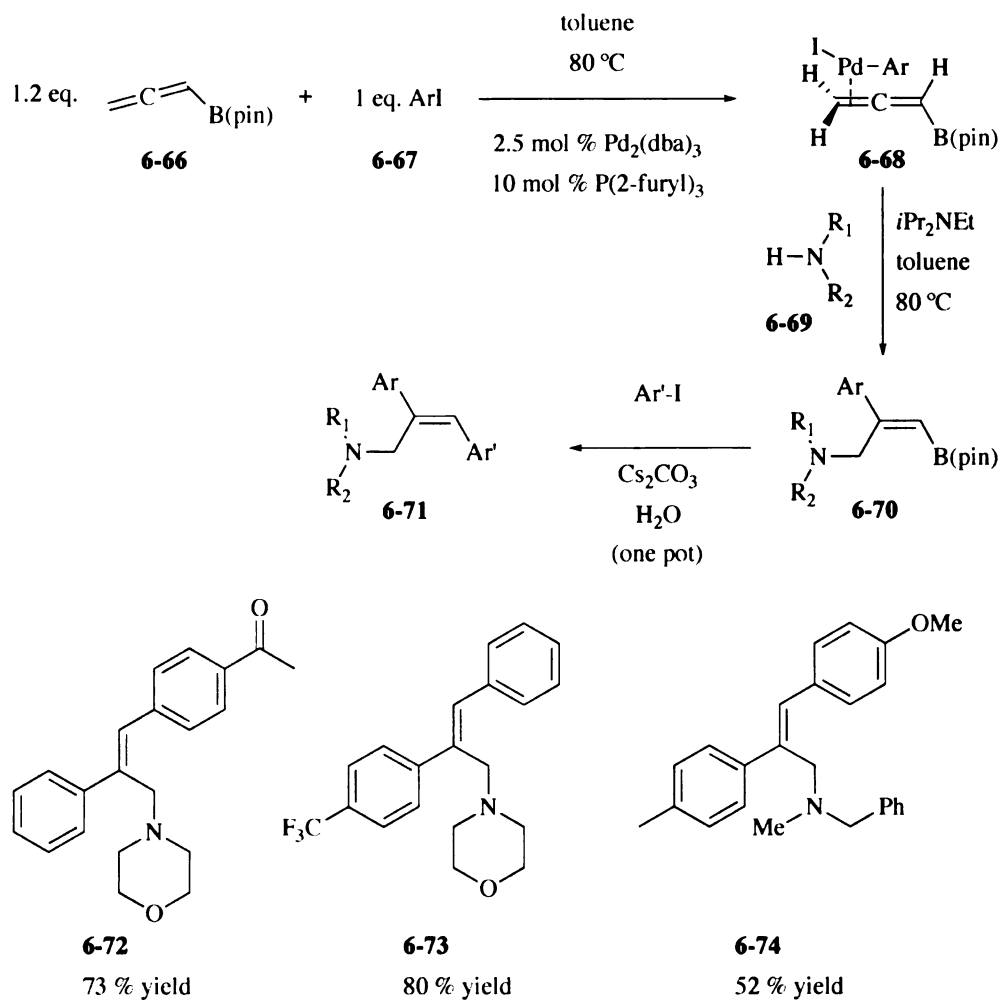
imines is de

Ni(cod)_2 cat

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Scheme 6.19. Catalytic Four-Component Assembly Based on

Allenylboronates



In Scheme 6.20, the catalytic coupling of organoboranes, alkynes, and imines is depicted between imine **6-75**, alkyne **6-76**, and triethyl borane with $\text{Ni}(\text{cod})_2$ catalyst. This reaction gives compound **6-77** with ligand **6-78**. For product **6-79**, the yield was 85 % with enantiomeric excesses of 89 %.

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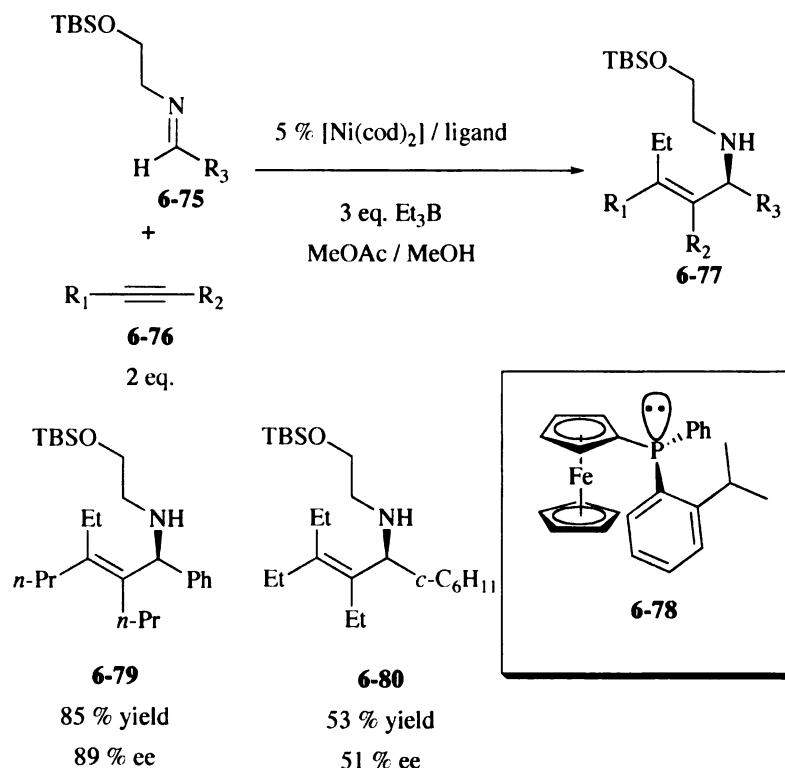
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product **6-80**, the yield was 53 % with enantiomeric excesses of 51 %.³²³ The reaction works best when R_3 is an aromatic substituent.³²⁴

Scheme 6.20. Catalytic Coupling of Organoboranes, Alkynes, and Imines



The three component coupling reaction shown in Scheme 6.21 has an interesting reaction mechanism. The proposed mechanism is shown.³²³ The nickel catalyst complexes to the olefin giving compound **6-81**. In the presence of triethyl borane compound **6-83** is formed. Alkyl transfer to the nickel metal center gives compound **6-84**, and in the presence of methanol, intermediate **6-85** is formed. Compound **6-85** is the methanol-nickel bound complex, and with reductive elimination with the associated transfer of the ethyl group from nickel to

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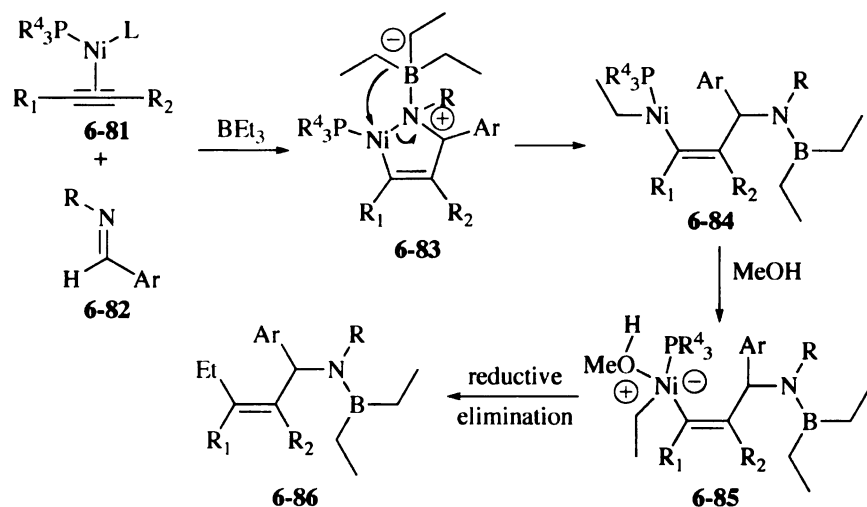
51 % for the

yield was 6

amine 6-94

the sp^2 carbon, compound **6-86** is formed. After hydrolysis, products that have been shown in Scheme 6.20 are formed with high enantiomeric excesses.³²⁵

Scheme 6.21. Proposed Mechanism of the Three-Component Coupling Reaction Between Organoboranes, Alkynes, and Imines



Odom and coworkers have developed a titanium-based system for the formation allylic amines.³²⁶ The reaction involves the use of $Ti(NMe_2)_4$ (**6-87**) and an allylic alcohol (**6-88**) with 3 eq. of an amine to give an allylic amine (**6-89**). The reaction is heated at 160 °C for 8 to 24 hours and then quenched with water. For aniline **6-90** with allylic alcohol **6-91** the yield was 78 % for the GC yield and 51 % for the isolated yield to allylic amine **6-92**. For cyclohexyl amine **6-92**, the yield was 63 % for the GC yield and 30 % for the isolated yield to the allylic amine **6-94**.³²⁶

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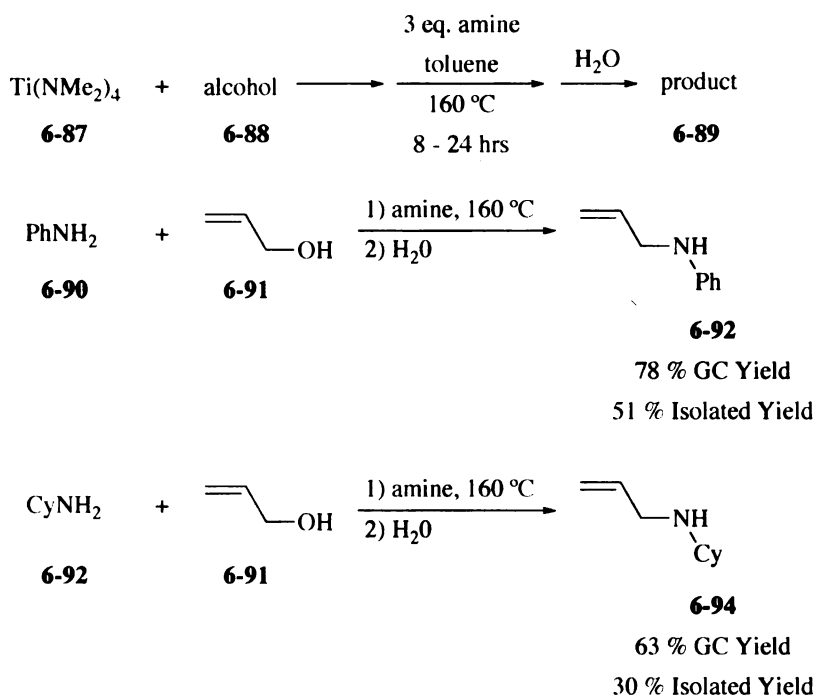
compound

retro-[2+2]

compound

98. Hydroly

Scheme 6.22. Results of Titanium-Mediated Transfer of Alkenyl Groups
from Alcohols



The proposed mechanism of the reaction proceeds from the titanium species **6-95** and allylic alcohol **6-91** to form the titanium allylic alcohol adduct **6-96**. In the presence of a primary amine **6-97**, the intermediate imido alkoxide compound **6-98** is formed. A [2+2] cycloaddition gives compound **6-100** and a retro-[2+2] cycloaddition gives compound **6-99**. The most direct access to compound **6-99** is through a [3,3]-sigmatropic rearrangement from compound **6-98**. Hydrolysis gives the allylic amine **6-101**.³²⁷

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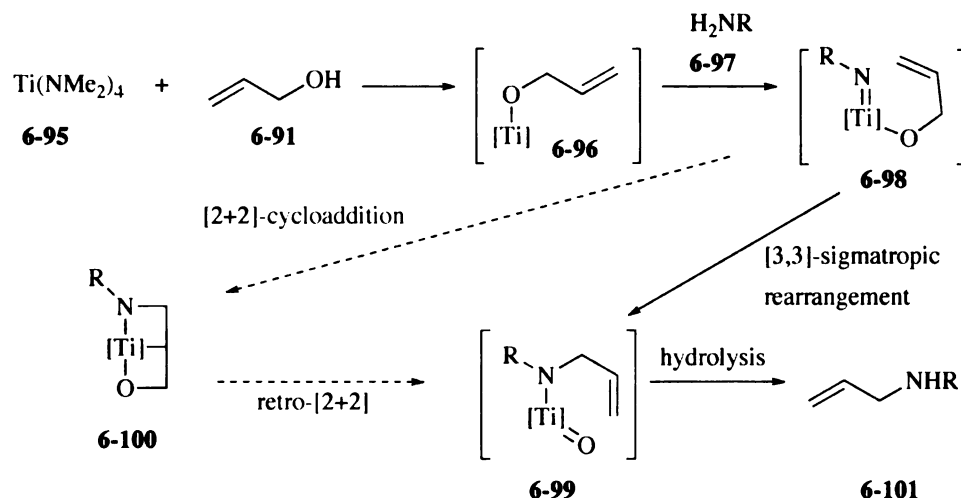
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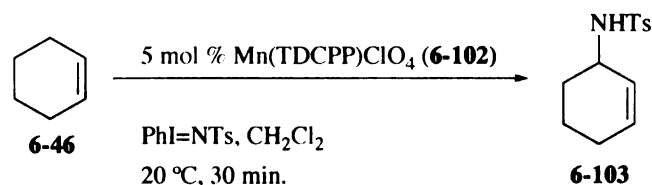
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Scheme 6.23. Mechanism of Titanium-Mediated Transfer of Alkenyl Groups from Alcohols



Shown in Scheme 6.24, the use of manganese for the formation of allylic amines. Generally manganese catalysts give allylic amines whereas copper catalysts give the aziridine products. For $\text{Mn}(\text{TDCPP})\text{ClO}_4$ (**6-102**), the selectivity for straight chain alkyl substrates is poor. Compound **6-103** is formed from **6-46**.

Scheme 6.24. Manganese for the Formation of Allyl Amines



In Table 6.1, the ene reaction is shown for the formation of allylic amines. From the olefin **6-104**, compound **6-105** can be formed.³⁰⁴ The allylic amine **6-106** can be formed with potassium hydroxide. In entry 1, the yield for the ene

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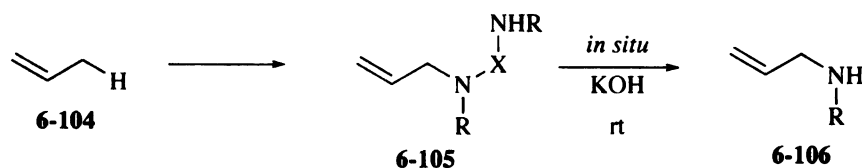
reaction from reagent **6-107** was 45 % and 54 % from reagent **6-109**. The yield for reagent **6-110** was 51 %. In entry 2, the selectivity was for the internal position (a) of compound **6-112** for all reagents shown in Table 6.1. In entry 3 for methylcyclohexene **6-113**, the selectivity was in favor of the internal position, however this selectivity was only slight. In entry 4, compound **6-46**, the yield was 70 % for reagent **6-107** and 51 % for reagent **6-108**. The yield was 45 % for reagent **6-109**.

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Table 6.1. Ene Reactions and Reagents for the Formation of Allyl Amines



Entry	Substrate	 6-107	 6-108	 6-109	 6-110
1	 6-111	45	–	54	51
2	 6-112	a / b 56 / 3	a 53	a / b 51 / 11	–
3	 6-113	a / b 38 / 33	–	a / b 35 / 20	–
4	 6-46	70	51	45	–

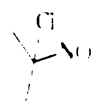
In Scheme 6.25, the use of α -chloro nitroso compound **6-115** for formation of allylic amines is depicted.³²⁸ In the example shown between compound **6-115** and pentene **6-116** for three days gives the proposed intermediate **6-117** which

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6-115

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Treatment

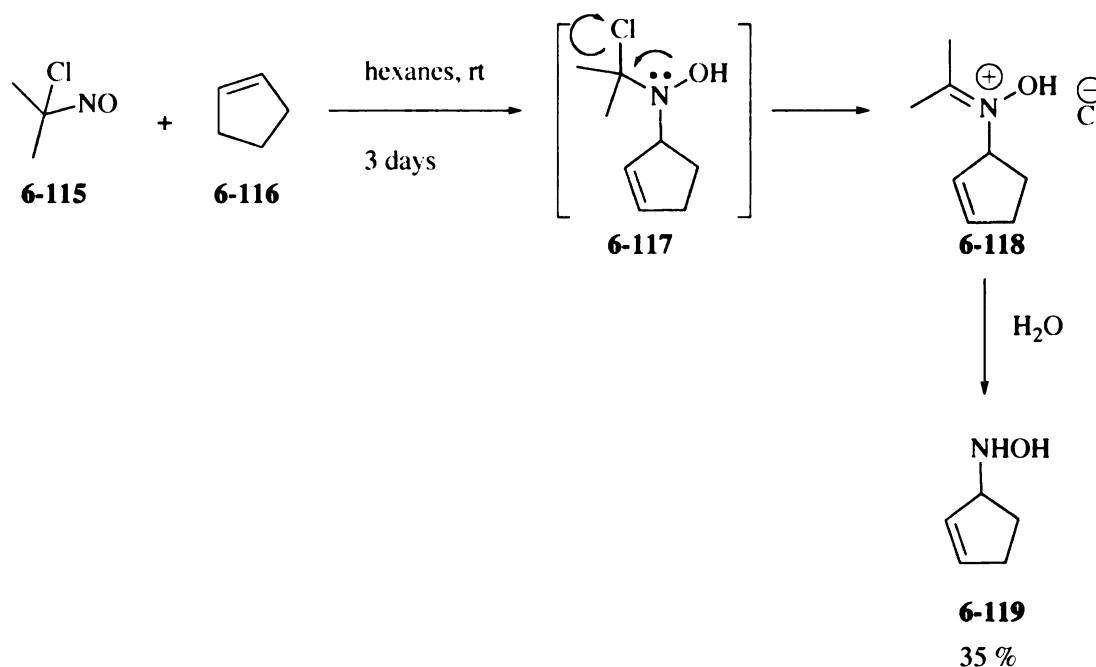
olefin 6-12

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eliminates chlorine to give intermediate **6-118**. The yield was 35 % of the allylic hydroxyamine **6-119** after hydrolysis.

Scheme 6.25. The Use of α -Chloro Nitroso Compounds for the Formation of Allylic Amines



The use of NNB (**6-120**, nitronitrosobenzene) is shown in Scheme 6.26. Treatment of olefin **6-121** with NNB (**6-120**) gave the product **6-122**.³²⁹ For olefin **6-123**, the allylic amine **6-124** was formed. The reaction is believed to proceed through the formation of the aziridine *N*-oxide **6-125** which induces intramolecular deprotonation to give allylic amines.³²⁹

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6-121

OH



6-123

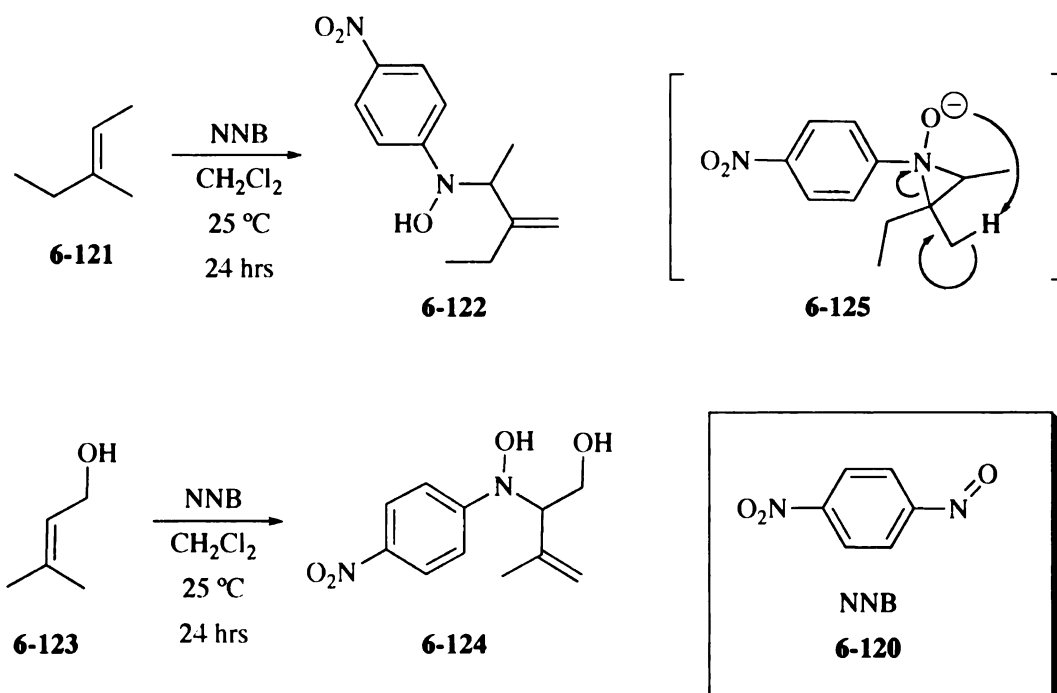
The

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Scheme 6.26. The Use of NNB for the Formation of Allyl Amines



The reaction of organometallic **6-126** with compound **6-127** gave compound **6-128**³³⁰ which was made in the hope of developing a new aziridination catalyst. This did not give the aziridine when treating olefin **6-129**, however the allylamine **6-130** was isolated in its stead with a yield of 57 %.³³⁰

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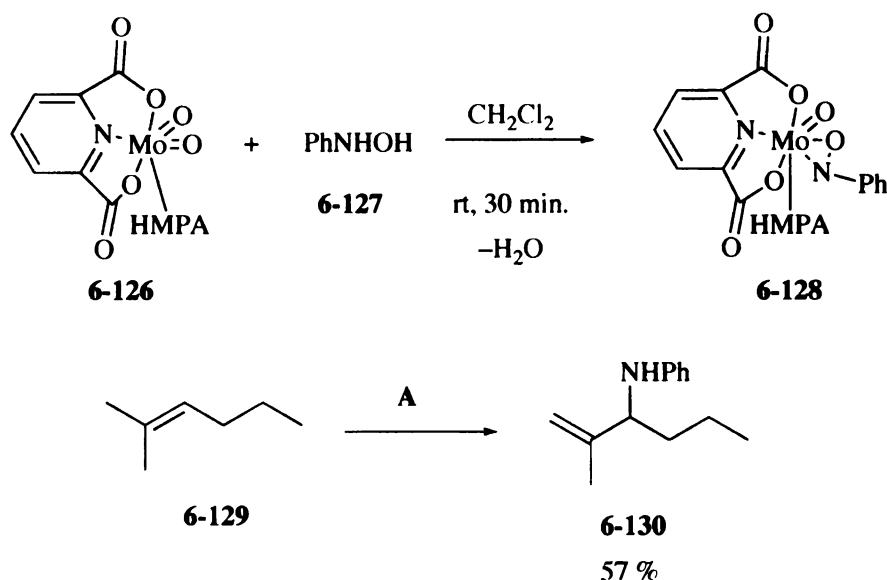
13 % for th

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Scheme 6.27. The Use of Molybdenaoxaziridine for the Formation of Allyl Amines



In Table 6.2, the reaction involving iron and molybdenum complexes to form allyl amines is depicted. The overall reaction involves the alkene **6-131** with the hydroxy amine **6-127** to give the allylic amine **6-132**. In entry 1, the iron porphyrin **6-133** gave a yield of 76 % and the mixture of FeCl_2 and FeCl_3 yielded 41 %. The molybdenum complex **6-128** yielded 42 % for entry 1.^{304, 331} In entry 2, the iron mixture gave a yield of 72 % and the iron complex **6-134** gave a yield of 88 %.^{304, 331} The yield in entry 3 was 22 % with the iron porphyrin **6-133** and 13 % for the iron mixture.^{304, 331} In the final entry, the yield was 30 % for the iron porphyrin **6-133** and 22 % for the iron chloride mixture.^{304, 331} The yield in entry 4 was 11 % for the molybdenum complex **6-128**.^{304, 331} These reactions were done in dioxane or toluene at 101 to 110 °C for 5 to 8 hours. All the reactions of

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Table

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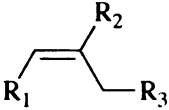
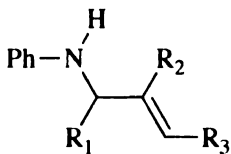
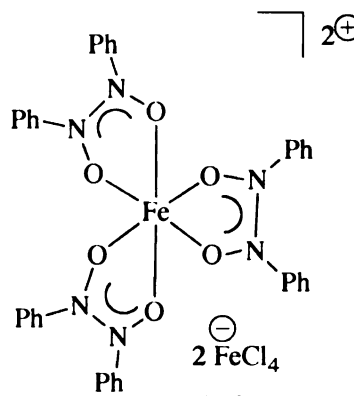
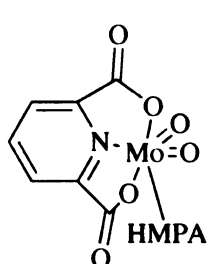
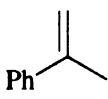
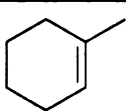
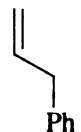
2
6

3
6

4
6

the reagents shown in Table 6.2 proceeded through an "ene like" transposition of the double bond.^{304, 331}

Table 6.2. Selectivity with Iron and Molybdenum for the Formation of Allyl Amines

 6-131 + PhNHOH 6-127 10 mol % cat. dioxane or toluene 101 - 110 °C 5 - 8 hrs  6-132					
entry	Substrate	Fe(porphyrin) 6-133	FeCl ₂ + FeCl ₃ (9 : 1)	 6-134	 6-128
1	 6-135	76	41	-	42
2	 6-136	-	72	88	52
3	 6-137	22	13	-	-
4	 6-138	30	22	-	11

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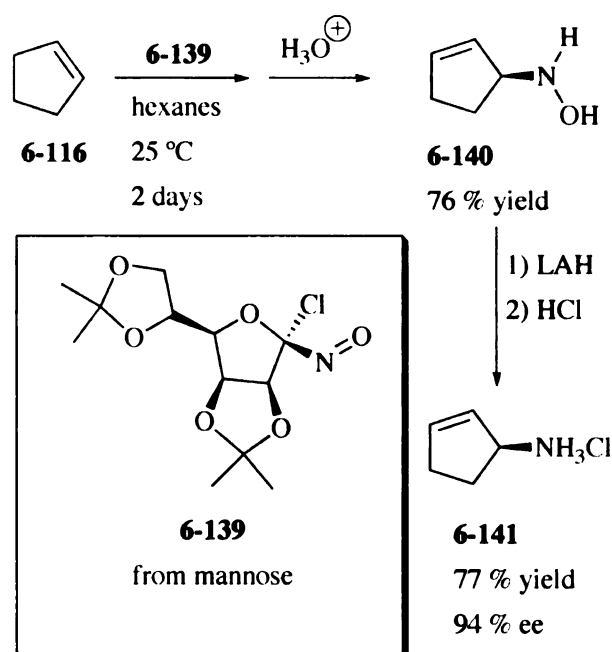
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In Scheme 6.28, the use of a nitroso sugar compound **6-139** for the formation of chiral allylic amines is shown. When cyclopentene **6-116** was used with compound **6-139** followed by acid hydrolysis, compound **6-140** was formed in 76 % yield. The reaction involves an ene type reaction with subsequent displacement of the chloride to form an iminium cation that undergoes hydrolysis to form compound **6-140**. Reduction of compound **6-140** followed by acid workup gave compound **6-141** in 77 % yield with 94 % ee.³⁰⁴

Scheme 6.28. The Use of Nitroso Sugar from Mannose for the Formation of Allyl Amines



In Scheme 6.29, an aziridine is opened via deprotonation at α -position to form an allylic amine. With *s*-butyl lithium and (–)-sparteine, the yield from a five-member ring **6-142** was 39 % with and 65 % ee shown as compound **6-144**. For a six member, ring such as compound **6-146**, the yield was 67 % with 38 % ee to allylic amine **6-149**. The mechanism is proposed as shown in Scheme 6.29 with

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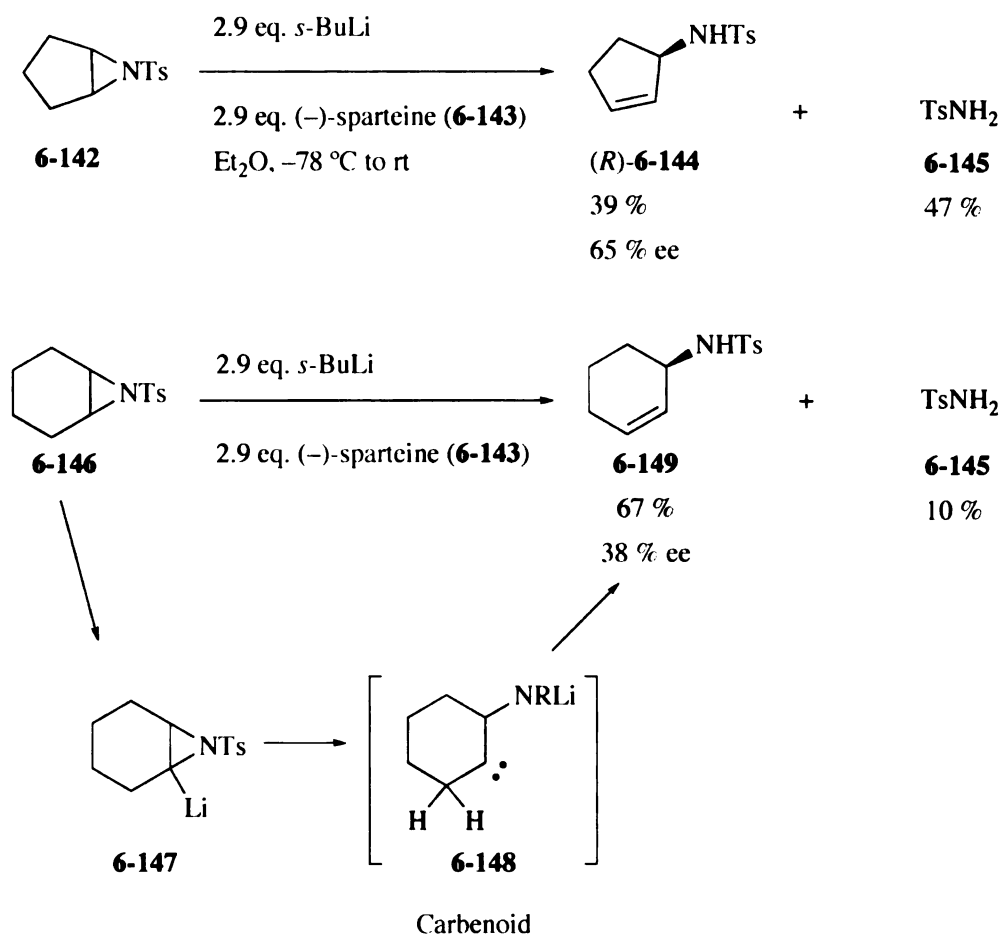
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the first step being a deprotonation shown as compound **6-147**. Compound **6-147** then forms a carbenoid **6-148** which proceeds to product **6-149**.³³²

Scheme 6.29. Alkyl Lithium to Deprotonate and Open Aziridines



In Scheme 6.30, the reductions of compound **6-150** with borane followed by a basic workup gives compound **6-151** in 51 % yield (*Z* isomer). The reduction is proposed to go through intermediate **6-152** with the borane coordinated to the nitrogen proceeded by the hydride delivery to the terminal olefin giving compound **6-151**. For compound **6-154a**, the yield was 75 % and for compound **6-154b** the yield was 79 %.³⁰⁶

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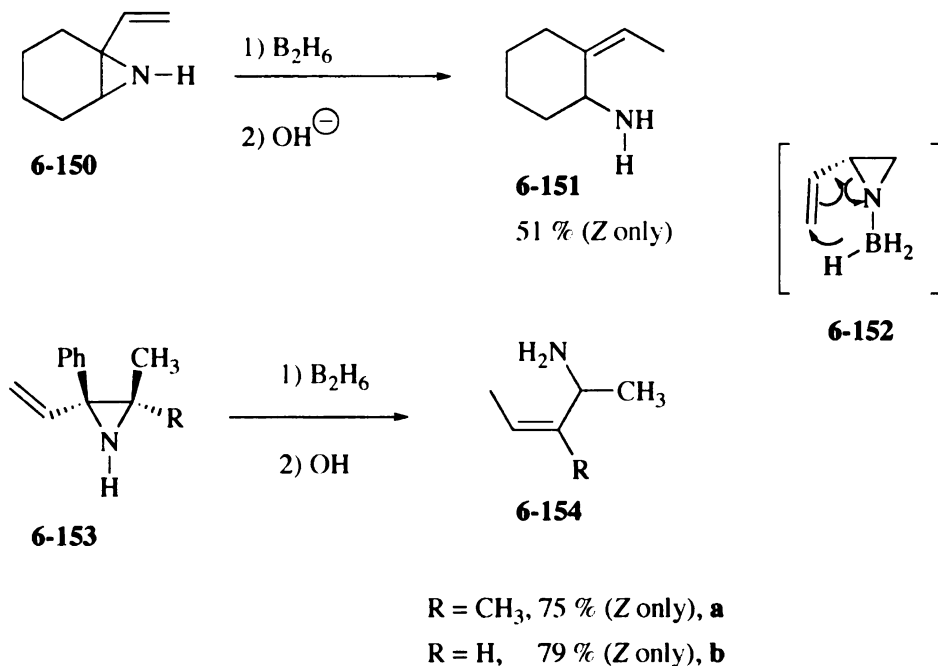
the yield w

compound

6-163, lea

95 % and

Scheme 6.30. Reduction of Aziridines



6.2 Methods of Aziridination

During the course of this work, the formation of aziridines were required and several methods for forming aziridines are known.³³³ These include the methods of Evans, Jacobsen, Wulff, and Sharpless. Shown in Scheme 6.31 is the formation aziridines with lead(IV) acetate via aminonitrenes.³³⁴ From hydrazine **6-155**, the intermediate nitrene **6-156** could be formed with olefin **6-157**, which could be transformed to the aziridine **6-158**. For compound **6-159**, the yield was 42 %, and for compound **6-160**, the yield was 73 %. The yield for compound **6-161** was 100 %. For compound **6-162**, the use of 1.6 eq. of ligand **6-163**, lead acetate (1.6 eq.), and *N*-aminophthalimide (1.5 eq.) gave a yield of 95 % and an enantiomeric excess of 90 %.

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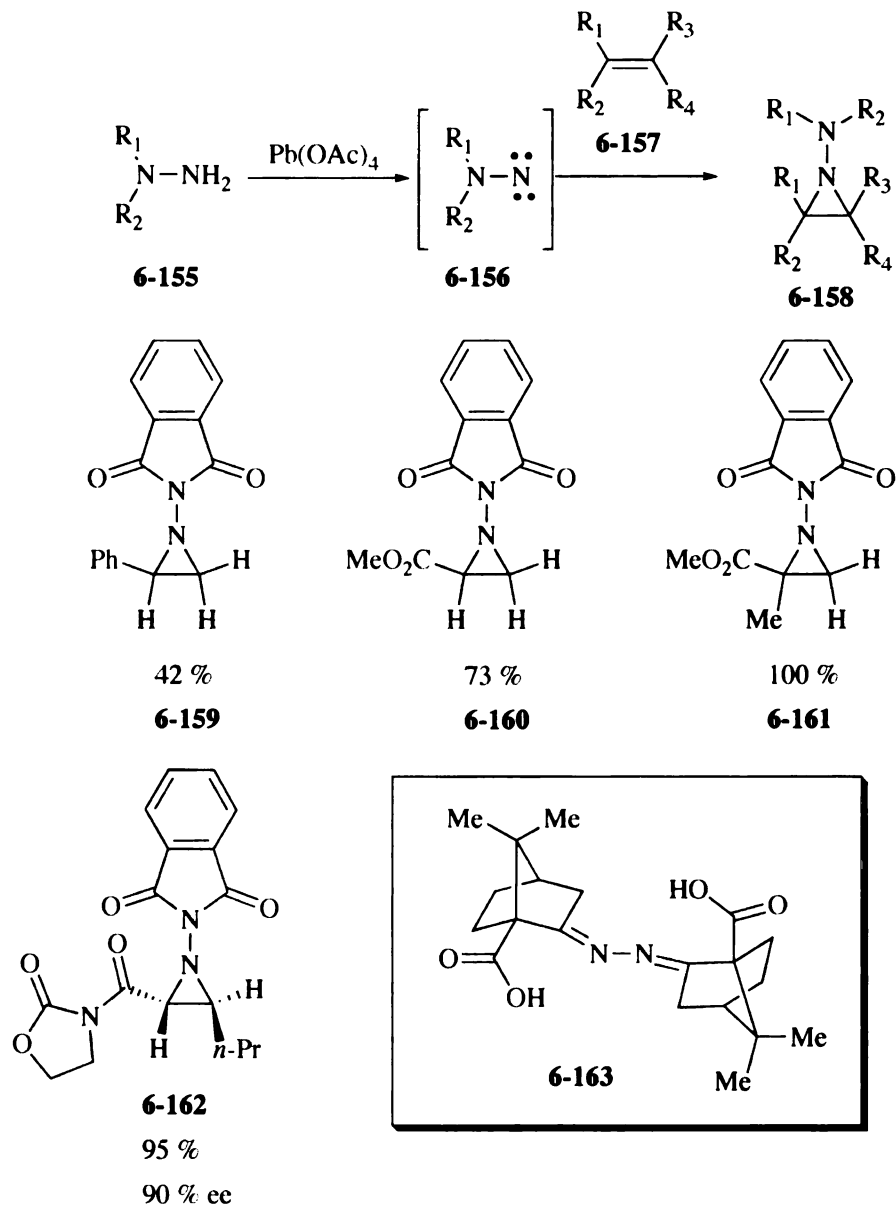
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Scheme 6.31. Lead Acetate with *N*-Amino-Phthalimide



Evans reported that the olefin **6-164** and $\text{PhI}=\text{NTs}$ when treated with the catalyst $\text{Cu}(\text{I})\text{OTf}$ (5 mol %) with 6 mol % of the chiral ligand **6-166** gave compound **6-167**.³³⁵ The reaction proceeds through an intermediate copper nitrene. This method worked best on aromatic substituents with electron withdrawing esters as represented by compound **6-164**. The yield was 64 % with an ee of 97 % for compound **6-167**.³³⁵

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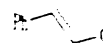
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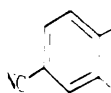
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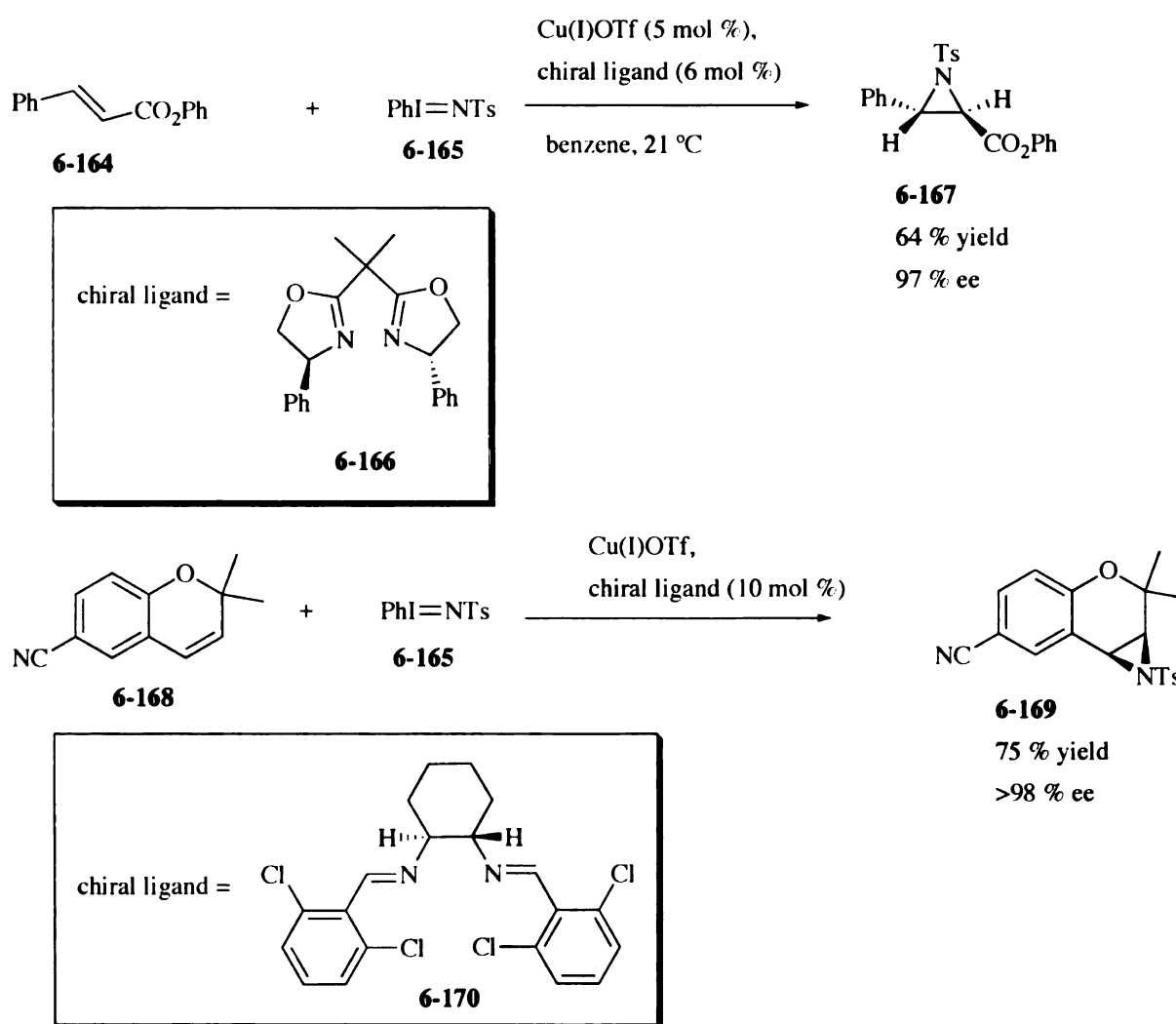
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The next shown is Jacobsen's work. In this approach salen ligands such as compound **6-170** were used. The substrate scope is limited from these types of ligands with the best results shown for compound **6-168** giving compound **6-169** in 75 % yield and > 98 % ee. When small changes in electronic of compound **6-168** are made, the enantiomeric excess drops to 10 % to 50 %.

Scheme 6.32. Evan's and Jacobsen's Aziridination Reactions



In Scheme 6.33, the copper(II) catalyzed racemic synthesis of aziridines done by Vedernikov is shown.³³⁶ This method again involves the use of PhINTs

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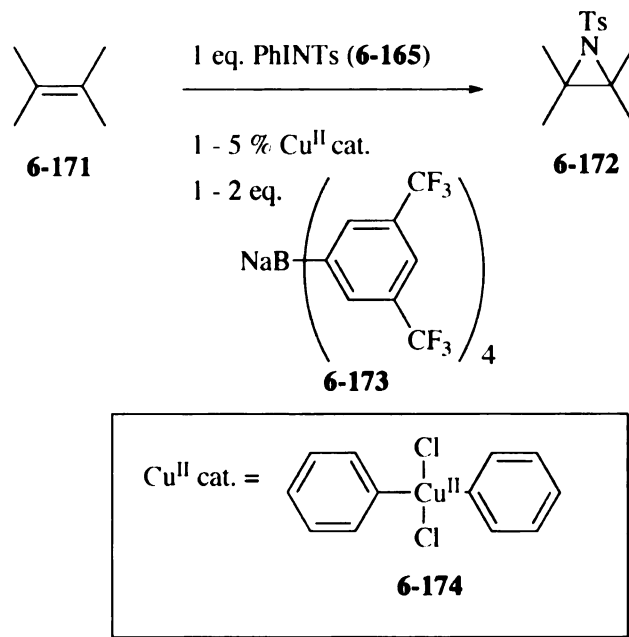
6-176 is fo

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172 with re

with an olefin **6-171**. The typical yields are 68 to 94 % to an aziridine **6-172**. The reaction involves the use of compound **6-173** and the copper source **6-174**.³³⁶

Scheme 6.33. Fast and General Non-Chiral Aziridination by Vedernikov



In Scheme 6.34, the mechanism of the copper(II) catalyzed aziridination reaction is shown.³³⁷ In the first step, copper(II) complexes (**6-173**) with PhINTS (**6-165**) to form intermediate **6-174**. With loss of PhI (**6-175**), the copper nitrene **6-176** is formed.³³⁷ The nitrene **6-176** maybe in resonance with the copper(III) compound **6-177**. The addition of the nitrene to olefin **6-172** gives aziridine **6-172** with regeneration of the copper catalyst **6-173**.³³⁷

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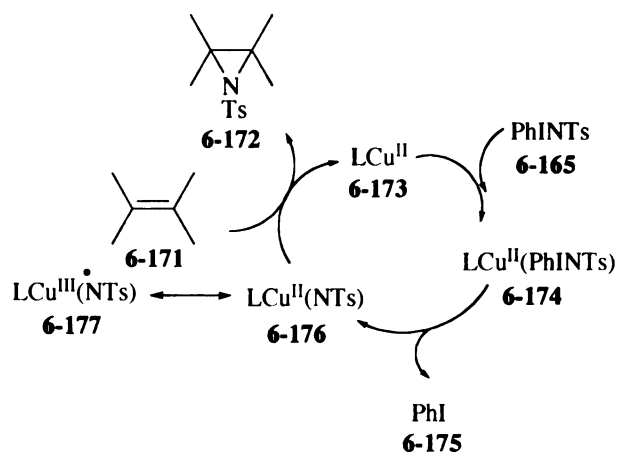
by heating

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Scheme 6.34. The Mechanism of Copper Catalyzed Formation of

Aziridines



In Scheme 6.35, the Wulff aziridination is shown.³⁰⁰ In the published version of the reaction, imine **6-178** and diazoethyl acetate **6-179** are treated with the catalyst overnight followed by chromatography to give aziridine **6-180** in 85 % yield and up to 92 % ee.³³⁸ The catalyst in the published procedure is prepared by heating VAPOL (**6-181**) and triphenyl borate in dichloromethane at 55 °C for one hour and then vacuum at 55 °C for 30 minutes. The catalyst is then transferred to the reaction flask with solvent.³³⁹

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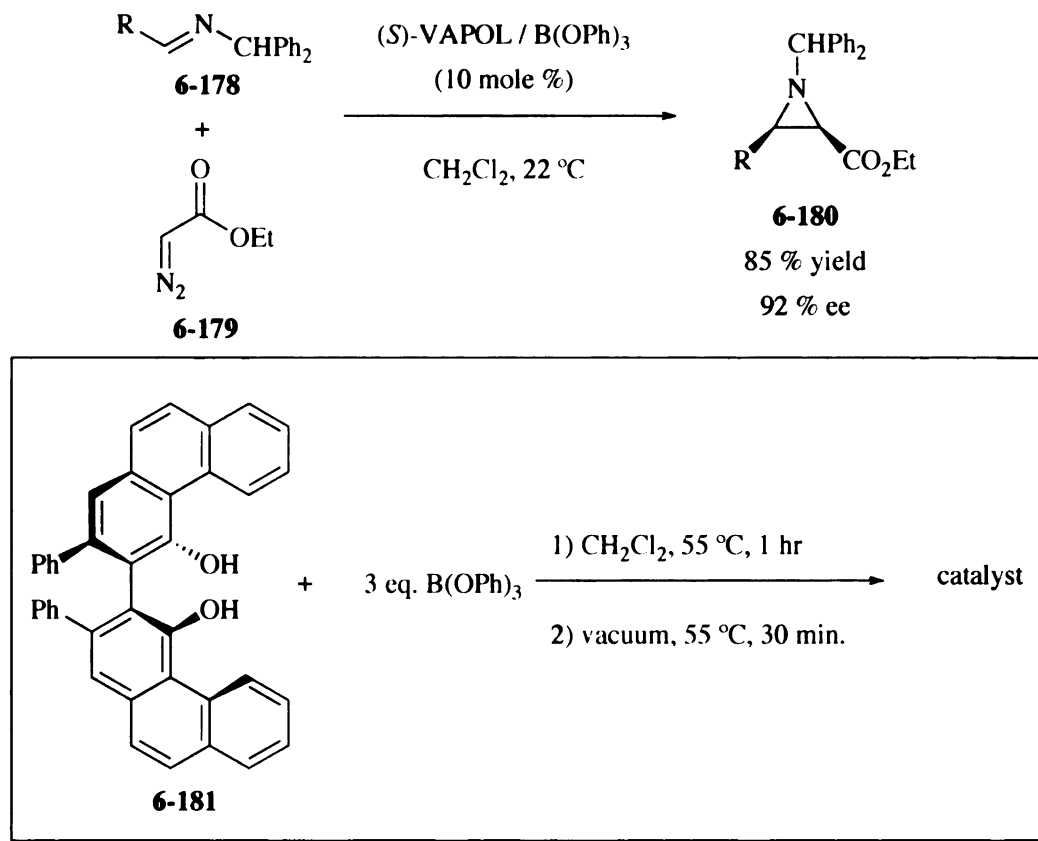
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Scheme 6.35. Wulff's Aziridination Reaction



In Scheme 6.36 is shown the proposed mechanism of Chloroamine T (6-182) formation of aziridines.³⁴⁰ In the first step, chloroamine T (6-182) abstracts a bromine atom from NBS to form intermediate 6-184. The bromination of the olefin 6-185 gives the bromonium 6-186 releasing compound 6-187.³⁴⁰ The bromonium is then opened with the nucleophilic nitrogen 6-187 to form compound 6-188, and the chlorine is then abstracted by succinate or bromine to form the aziridine 6-189 with nucleophilic ring closure with displacement of bromine. Chloroamine T (6-182) can abstract the bromine from compound 6-188 to restart the catalytic cycle.³⁴⁰

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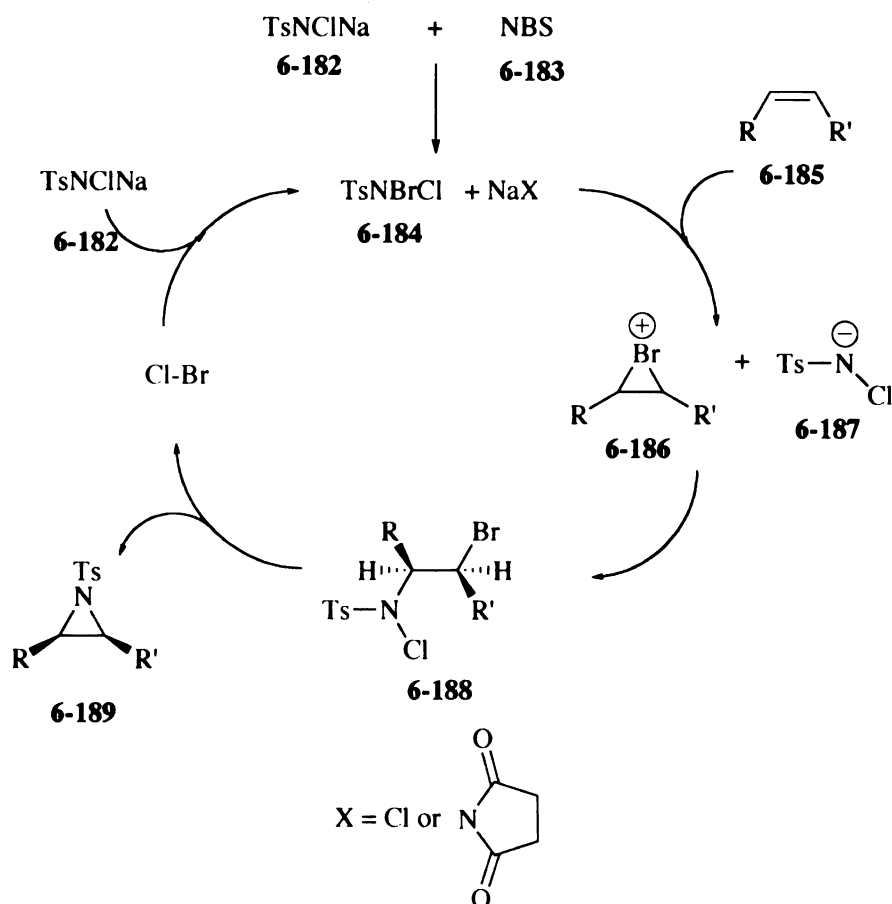
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Scheme 6.36. Mechanism of Chloramine T Aziridination



In Scheme 6.27, the synthesis of *t*-butylsulfonamide and its chloramine salt are shown.³⁴¹ The *t*-butylsulfonamide chloramine salt **6-191** can also be used to form aziridines by a similar mechanism as previously shown³⁴⁰ from olefin **6-190** to give the aziridine **6-192**. From the bis-*tert*-butyl disulfide **6-193**, *t*-butyl-*tert*-butanethiosulfinate **6-194** was formed with peroxide or VO(acac)₂ in 95 % yield.³⁴¹ Treatment of the resulting compound **6-194** with sulfuryl chloride gave *t*-butylsulfinyl chloride **6-195** in 70 % yield after distillation which contained minor impurities. The standard preparation through intermediate **6-196** of *t*-butyl

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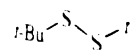
equivalent of

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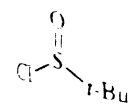
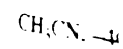
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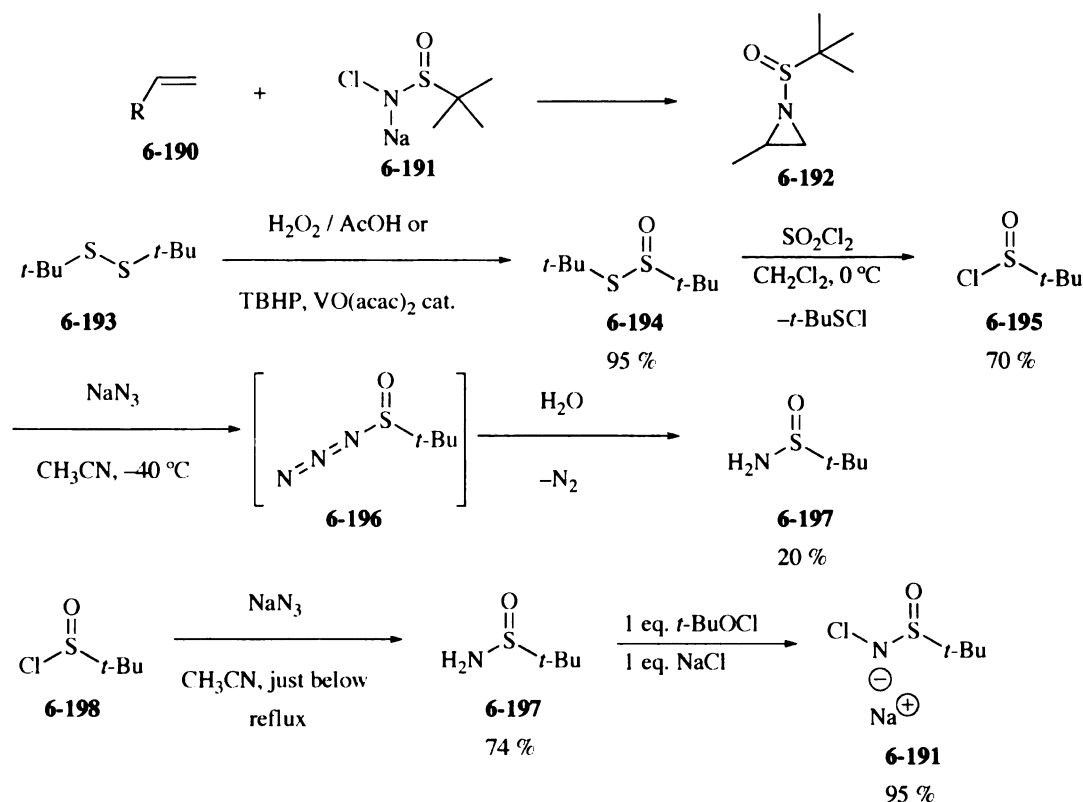
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sulfonamide **6-197** at $-40\text{ }^{\circ}\text{C}$ gave a low yield of 20 % of compound **6-197**.³⁴¹ A modified procedure with the reaction being just below reflux gave 75 % of the desired *t*-butyl sulfonamide **6-197**. The chloramine salt **6-191** could be prepared in 95 % yield by the reaction of *t*-butyl sulfonamide (**6-197**) with one equivalent of sodium hydroxide and *t*-butyl hypochlorite made from bleach and *t*-butyl alcohol.³⁴¹

Scheme 6.37. Synthesis of *tert*-Butylsulfonamide and Its Chloramine Salt



In Scheme 6.38, attempts were made to prepare the associated aziridine from the olefin shown using a literature method.³⁴⁰ These attempts were not successful and resulted in complex mixtures of products. In compound **6-199** (3-

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6.3 Opening

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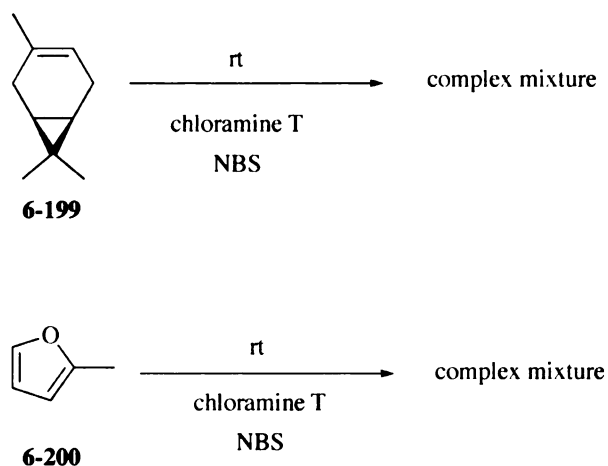
react.³⁴² For

epoxide 6-20

was 71 %.³⁴²

carene), we hoped to obtain diastereoselectivity however only a complex mixture was found. In compound **6-200**, the attempt to form an aziridine also failed.

Scheme 6.38. Failed Chloramine T Reactions



6.3 Opening Aziridines

In Scheme 6.39, the opening of epoxides such as compound **6-201** gave allylic alcohols such as **6-203**, which provides inspiration for the opening of aziridine rings.³⁴² It is known that under these conditions that only *cis*-epoxides react.³⁴² For compound **6-204**, the yield was 91 %, and for the five-member epoxide **6-205** ring the yield was also 91 %. For a compound **6-206**, the yield was 71 %.³⁴²

Schem

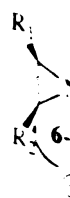
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6.40, the op

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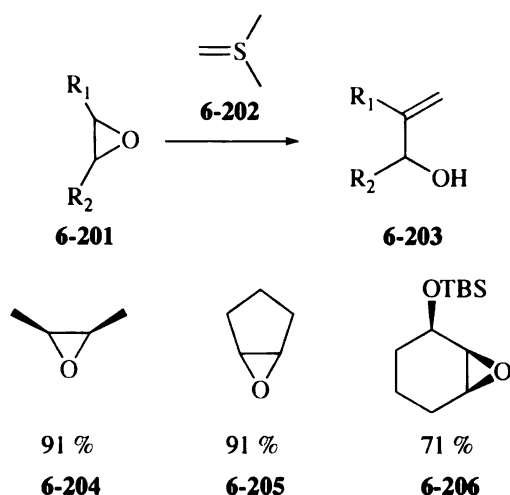
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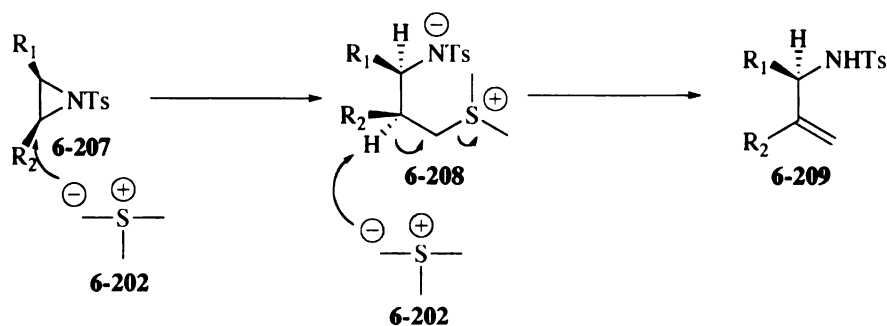
excess base

Scheme 6.39. Opening of Epoxides with Dimethylsulfonium Methylide



We opened aziridines in the same manner as epoxides.³⁴² In Scheme 6.40, the opening of an aziridine (6-207) is shown with dimethylsulfonium methylide (6-202) to give intermediate 6-208. With elimination, compound 6-209 is formed.

Scheme 6.40. Allyl Amines Via Dimethylsulfonium Methylide



Explored in the Borhan laboratory was the aza-Payne rearrangement shown in Scheme 6.41.³⁴³ From compound 6-210 with base, compound 6-211 is formed. Compound 6-211 then undergoes aza-Payne rearrangement with excess base to form the epoxide 6-212. With the nucleophilic ring opening of the

epoxide with

elimination, a

Schen

Ts-N

OH

6-210

Other

in Scheme 6

N-piperidine

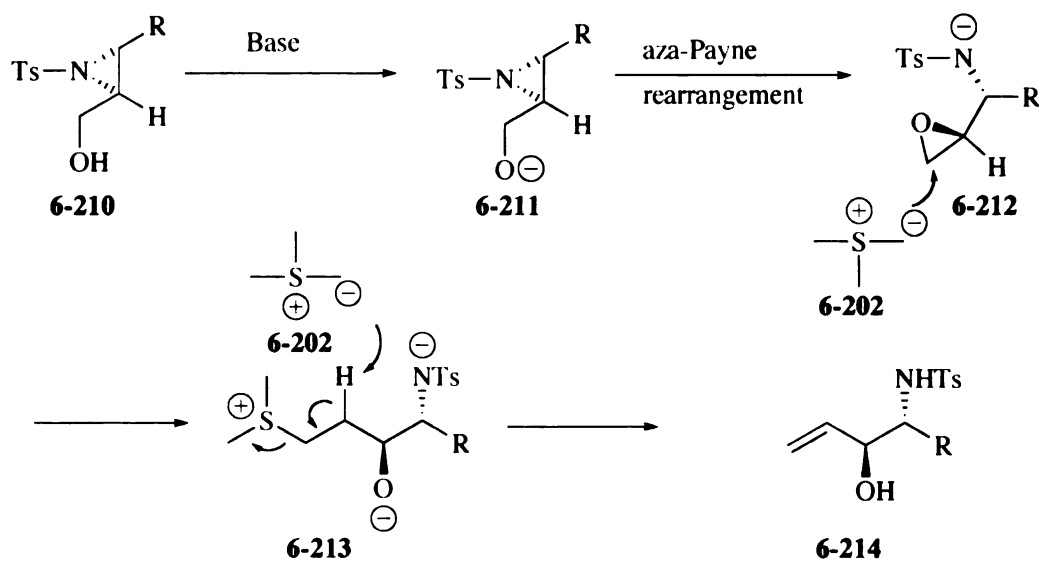
amine **6-217**

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6-

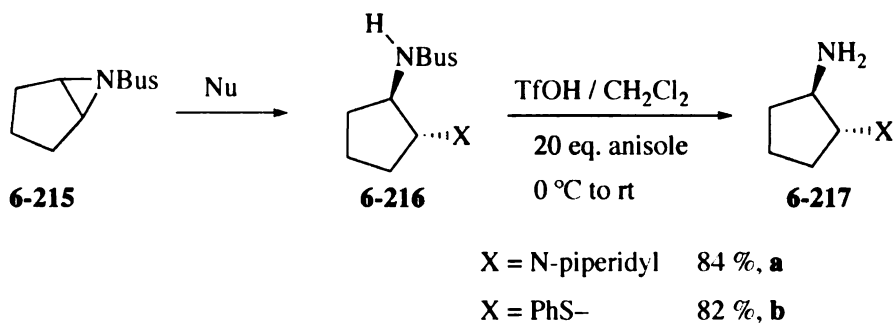
epoxide with dimethylsulfonium methylide, intermediate **6-213** is formed, and with elimination, allylic alcohol **6-214** is formed.³⁴³

Scheme 6.41. 1,2-Amino Alcohols via Aza-Payne Rearrangement



Other examples of the opening of aziridines with nucleophiles are shown in Scheme 6.42.³⁴¹ Aziridine **6-215** (Bus = *t*-butylsulfonyl) could be opened with *N*-piperidine or PhSH to give compound **6-216**. With treatment with triflic acid, amine **6-217** was obtained in moderate yields.³³⁹

Scheme 6.42. Bus Protected Aziridine Ring Opening and Deprotection



Based

epoxides with

aziridine ring

our first attempt

the formation

6-220 gave a

of **6-223**, and

6-225. For the

6 the yields

respectively.

opening at the

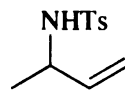
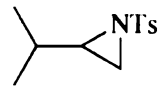
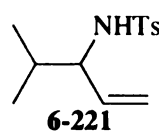
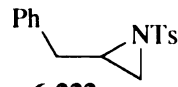
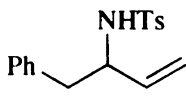
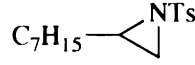
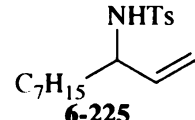
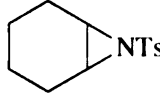
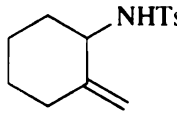
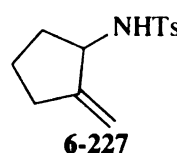
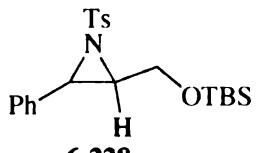
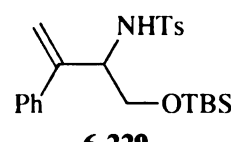
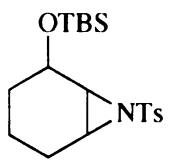
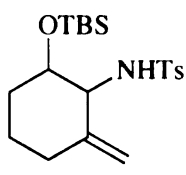
yield was 58

Based on previous reports by Alcaraz and coworkers³⁴² of opening epoxides with dimethylsulfonium methylide, we decided to attempt opening aziridine rings under similar conditions as shown in Table 6.3. Shown in entry 1, our first attempt yielded success from compound **6-218** with a yield of 92 % for the formation of compound **6-219**. In entry 2, an isopropyl substituted aziridine **6-220** gave a yield of 76 %. In entry 3 for compound **6-222**, the yield was 78 % of **6-223**, and for entry 4 from compound **6-224** the yield was 87 % of compound **6-225**. For the cyclic aziridines from compounds **6-146** and **6-142**, entries 5 and 6 the yields were 74 % to compound **6-226** and 79 % to compound **6-227**, respectively. In entry 7, the yield was 79 % from compound **6-228** to **6-229** opening at the phenyl substituent. For the cyclic aziridine **6-230** in entry 8, the yield was 58 % to the allylic amine **6-231**.³⁴⁴

Table

Dimeth

Table 6.3. Formation of Allyl Amines from Aziridines via Dimethylsulfonium Methylide

entry	aziridine	allylic amine	yield
1	 6-218	 6-219	92 %
2	 6-220	 6-221	76 % ^a
3	 6-222	 6-223	78 % ^a
4	 6-224	 6-225	87 %
5	 6-146	 6-226	84 %
6	 6-142	 6-227	70 % 79 % ^b
7	 6-228	 6-229	79 % ^a
8	 6-230	 6-231	58 % ^a

a. Results taken from J. Schomaker's Dissertation b. Using Me₃SOTf

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such as 6-23
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deprotonation

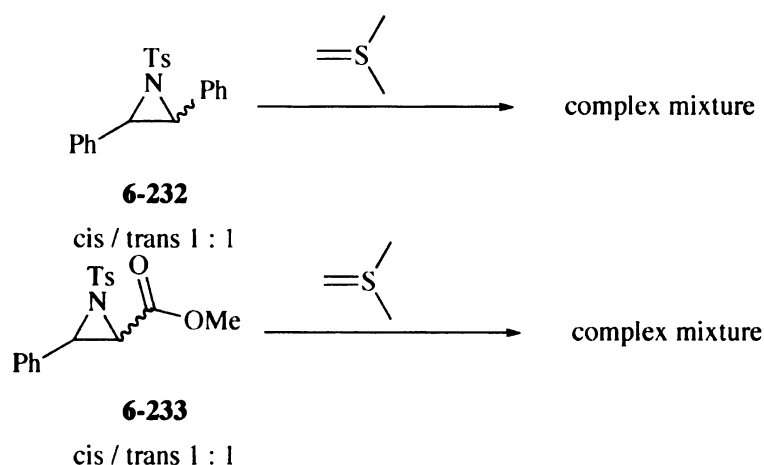
Schen

6.4 Future V

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sulfur ylides
of aziridine
Aziridine 6-
trifluoroacet
those genera
the alcohol

In Scheme 6.43, the unsuccessful attempts to open some aziridines are shown. The exact reason why complex mixtures were obtained remains unclear however a possible reason includes potential oligomerization for compounds such as **6-232**.³⁴² For compounds such as **6-233**, the sulfur ylide may have added to the ester or opened the aziridine creating a complex mixture. Also deprotonation at the α -carbon of the ester may have initiated oligomerization.

Scheme 6.43. Unsuccessful Examples of Allyl Amine Formation



6.4 Future Work with Aziridines

In Scheme 6.44, the proposed merger of allylic amine formation using sulfur ylides with the Wulff-aziridination methodology is proposed. The formation of aziridine **6-234** has been done with the Wulff-aziridination methodology.³⁰⁰ Aziridine **6-234** could be deprotected using strong acids such as triflic or trifluoroacetic acid also ozone has been used to deprotect aziridines such as those generated in the Wulff group.³⁴⁵ Reduction of compound **6-235** would give the alcohol **6-236**,³⁴⁶ and protection of the alcohol with TBSCl / imidazole could

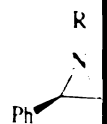
give compound

238.³⁴⁸ Treat

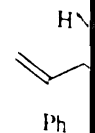
give compound

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Aziridin



6-2



6-2

Show

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treatment of

aziridine 6-24

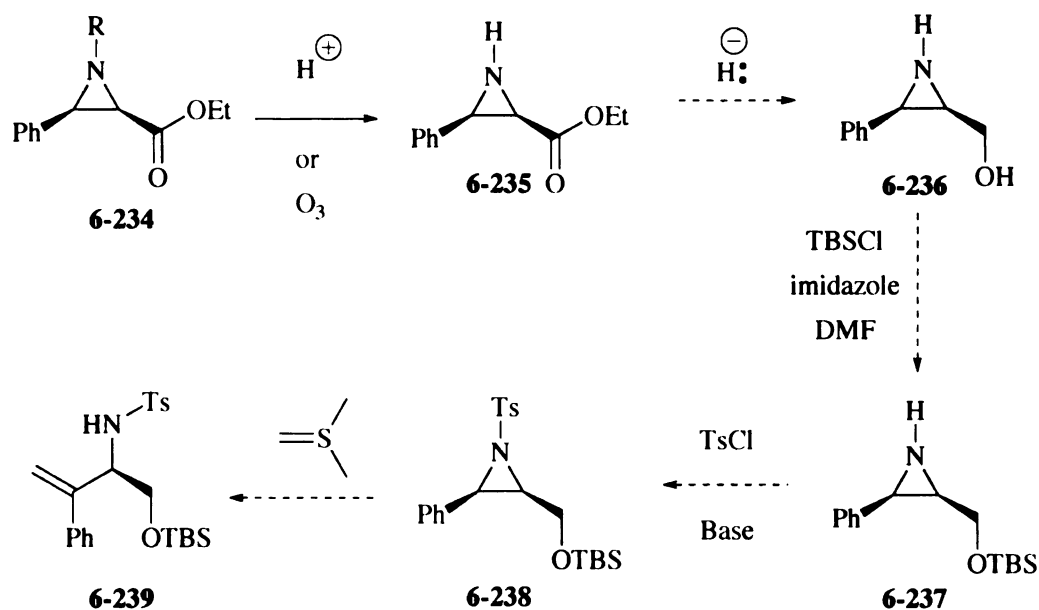
Borhan labo

with for exam

give compound **6-237**.³⁴⁷ Tosylation of the nitrogen would give compound **6-238**.³⁴⁸ Treatment of compound **6-238** with dimethylsulfonium methylide would give compound **6-239**.³⁴⁴

Scheme 6.44. Proposed Merging of Allyl Amine Formation with Wulff-

Aziridination



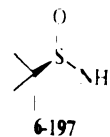
Shown in Scheme 6.25 is the proposed synthesis of propargyl amines using this methodology for the formation of allylic amines. This method would be chiral using the chiral *t*-butane sulfinamide **6-197**.³⁴⁹ With aldehyde **6-240**, compound **6-241** has been formed using titanium ethoxide in 60 % yield. The treatment of compound **2-241** with the resulting sulfur ylide **2-242** gives the aziridine **6-243** in 47 % with > 95 % de.³⁴⁹ Using the chemistry developed in the Borhan laboratory compound **6-244** could be formed. Protection of the amine with for example a benzyl group or possibly an *in situ* formed trimethyl silyl amine

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Sche

Alcoh

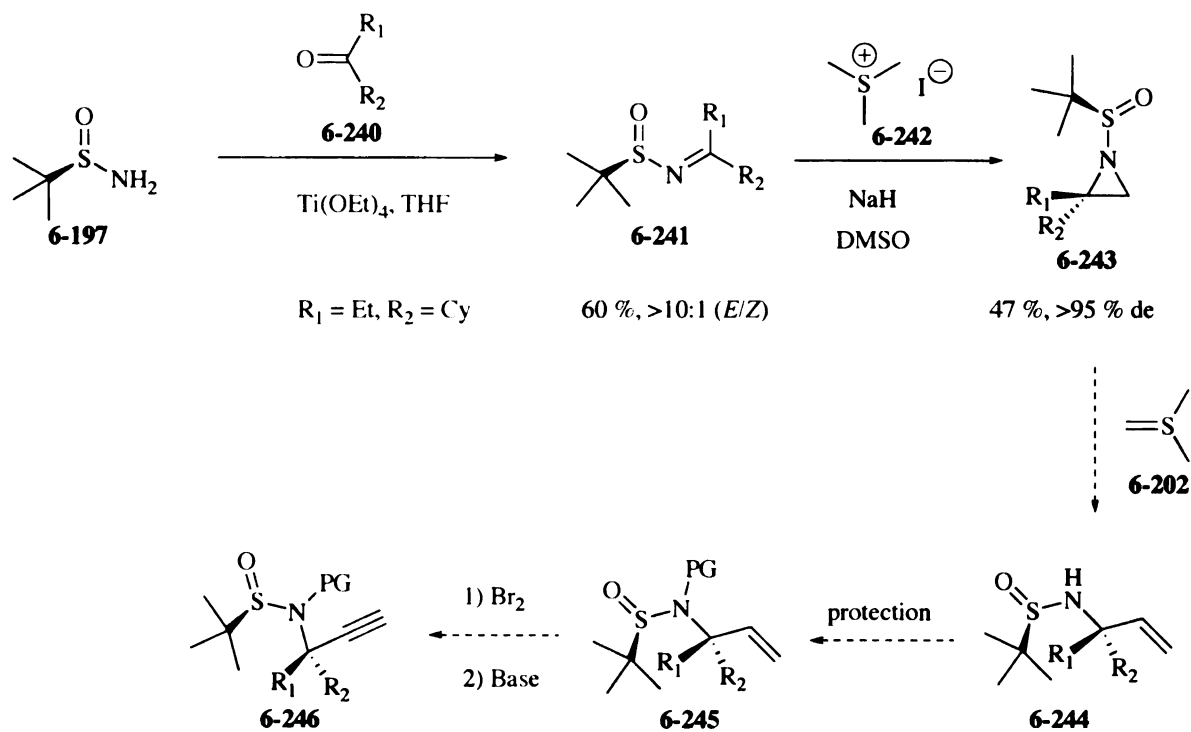


6-197

would give compound **6-245**. Treatment with bromine and base would give the propargyl amine **6-246**.³⁴⁹

Scheme 6.45. Proposed Method for the Formation of Chiral Propargyl

Alcohols



7.1 General

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CHAPTER SEVEN

EXPERIMENTAL PROCEDURES

7.1 General Procedures

Diethyl ether and tetrahydrofuran were distilled from sodium and benzophenone. Dimethyl sulphoxide (DMSO) was purified by standing overnight with CaH_2 and distillation over fresh CaH_2 at ~ 10 mm of Hg. DMSO was stored over 4 Å molecular sieves. The silica gel used was purchased from Sorbent Technology; 40 - 63 μm (230 x 400 mesh); 500 - 600 m^2/g ; pH 6.5 - 7.5. Spectroscopic data were acquired on Varian equipment for 300 and 500 MHz NMR. Infrared spectra were acquired on a Nicolet IR/42 spectrometer. EI-Mass spectroscopy of the volatile organic compounds were conducted on a Varian Chrompack Saturn 2000R 3800 Gas Chromatograph/MS with a CP Sil 8 CB low bleed/MS column. Gas chromatograms were conducted on Varian 3800 instrument using Econo-Cap capillary column (SE-54, 30 meters, 0.32 mm ID, 0.25 μM film thickness) using splitless conditions with an FID detector. Gas chromatography flow rates were determined directly with a Varian intelligent digital flowmeter. Reactions were conducted under a nitrogen or argon atmosphere unless otherwise stated. All glassware was either dried in an oven for at least 30 to 60 minutes or flame dried under high vacuum (< 3 mm Hg). Freeze thaw degassing was done when noted in the following manner: (1) the

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contents of the flask were solidified in liquid nitrogen; (2) the contents of the flask were exposed to high vacuum (< 3 mm Hg) for 30 seconds to one minute while the flask was in the liquid nitrogen bath; (3) the valve to the high vacuum line was closed and the reaction was allowed to warm up for 1-2 minutes; (4) the flask was placed into a warm water bath until the solidified solvent melted and the frost on the outside of the flask dissipated; (5) the contents of the flask were again pressurized to one atmosphere of argon; (6) this cycle was generally repeated three times unless otherwise noted. The following procedure was used for the removal of solvent under reduced pressure: (1) a water bath on a Büchi rotovapor R-114 was heated sufficiently to remove the solvent of the flask containing the solvent; (2) the compound was re-dissolved in hexane and solvent was removed on the rotovapor R-114; (3) the contents of the flask were put under high vacuum (< 3 mm Hg) to remove the last traces of solvent.

Temperature controller calibration was done. A temperature controller was purchased from ACE Glass model J/TC Econo Temp Controller. The device uses a Love 32A series 1/32 DIN microprocessor based PID (proportional-integral-derivative) controller. This device was evaluated and used for thermal control in all reactions. A second temperature controller was constructed using a solid-state relay DC to AC (250 V @ 50 A) using Barber-Colman 7SD PID (DIN 1/16). The controller was set to 80 °C and the temperature was evaluated. The temperature controller was set to 100 °C and the temperature was evaluated as shown below of the oil bath. Both temperature controllers gave similar

performance

Figure 7.1

Measureme

1

performance as shown below.

Figure 7.1. Thermal Controller Set at 80.0 °C (Typical Performance / Measurement of the Oil Bath Temperature)

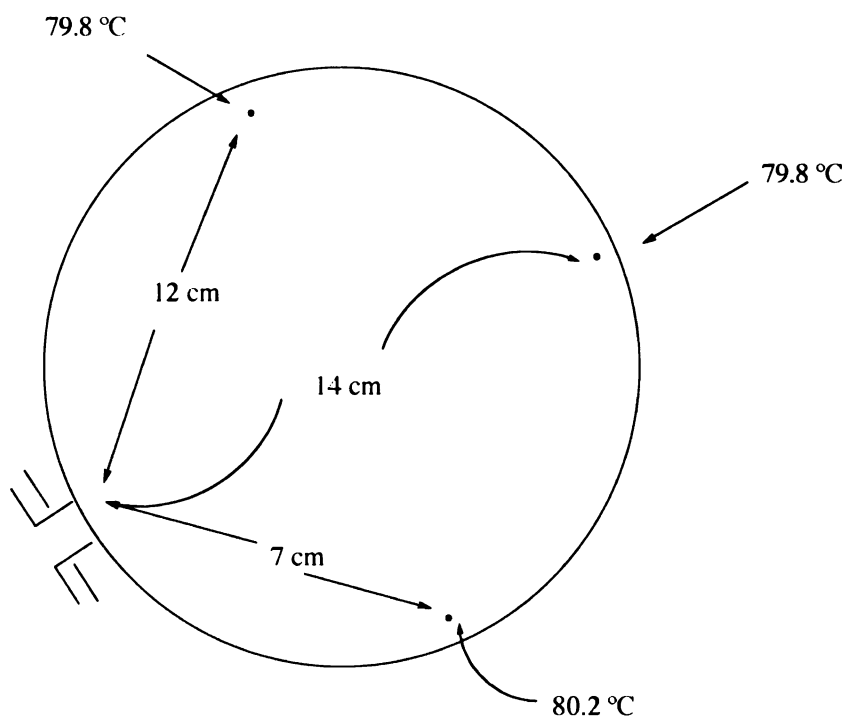
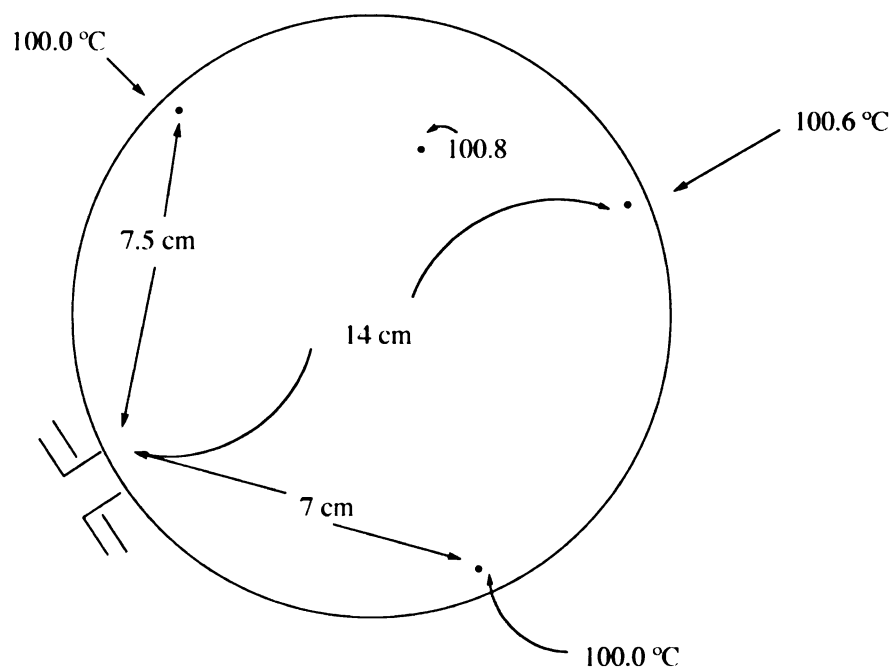


Figure 7.1

Measurements

1

Figure 7.2. Temperature Controller Set at 100 °C (Typical Performance / Measurement of the Oil Bath Temperature)



Compound



Triphenylphosphine

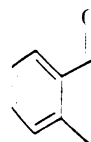
and THF (

sealed with

The solution

46.9 mmol)

Compound



2-45

To

mmol) in 1

19.8 mmol

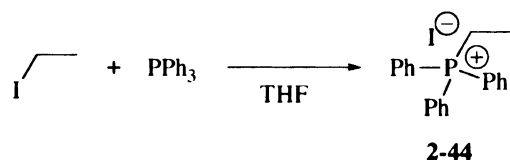
cannula to

The solution

19.5 mmol

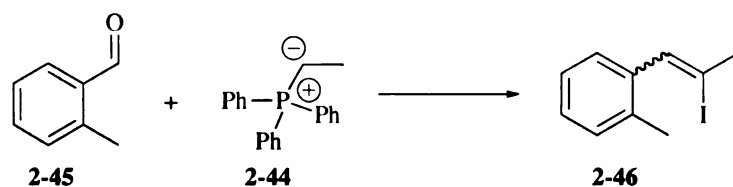
7.2 Chapter Two Experimental

Compound 2-44, Ethyltriphenylphosphonium iodide



Triphenylphosphine (20.2 g, 76.9 mmol), iodoethane (16.0 g, 103 mmol), and THF (20.0 mL) were charged into a flask. This was sparged with argon, sealed with a rubber septa which was wired on, and allowed to stir for 2 days. The solution was filtered and washed with ethyl ether yielding 19.7 g (61 % yield, 46.9 mmol). m.p. 153 - 155 °C (lit. 156 °C).³⁵⁰

Compound 2-46



To a solution of (ethyl)triphenylphosphonium iodide **2-44** (8.33g, 19.9 mmol) in 100 mL of THF, was added *n*-butyl lithium (12.4 mL, 1.6 M in hexanes, 19.8 mmol) dropwise at room temperature. This solution was transferred via cannula to a solution of iodine (5.10 g, 20.0 mmol) in 150 mL of THF at -78 °C. The solution was warmed to -20 °C and NaHMDS (1 M solution in THF, 19.5 mL, 19.5 mmol) was added dropwise. The solution was cooled to -130 °C and *o*-

methylbenz

was allowed

filtered thro

(28 cm x

mmol). GC

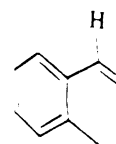
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¹H NMR

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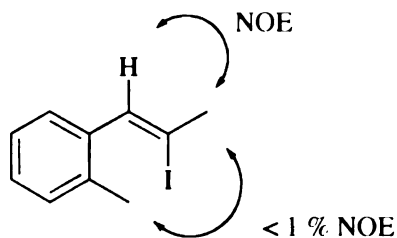
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1483 m,

intensity)

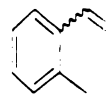
(6), 91 (5

methylbenzaldehyde (2.30 mL, 19.9 mmol) was added dropwise. The solution was allowed to warm to room temperature over several hours. The solution was filtered through Celite-503 and reduced under vacuum. Column chromatograph (28 cm x 3.5 cm, silica) with 100 % hexanes gave 3.63 g (72 % yield, 14.3 mmol). GC analysis showed retention times of 11.67 minutes for the *Z* and 11.94 minutes for the *E* with a ratio of 24.3 to 1. The GC oven was ramped from 80 °C to 230 °C at 10 °C / minute under the general conditions discussed above for GC analysis. At 22 °C, the ratio was 2.9 to 1 (*Z* : *E*, GC / FID) with 14 % yield on a 4.3 mmol scale. At –18 °C, the ratio was 4.4 to 1 (*Z* : *E*) with 54 % yield on a 4.3 mmol scale. At –78 °C, the ratio was 18 : 1 (*Z* : *E*) on a 19.9 mmol scale.



^1H NMR (CDCl_3): δ : 2.21 (s, 3 H), 2.71 (d, 3 H, $J = 1.7$ Hz), 6.59 (s, 1 H), 7.1 - 7.3 (m, 4 H); ^{13}C NMR (CDCl_3) δ : 19.86, 34.42, 102.75, 125.44, 127.62, 129.10, 129.64, 134.68, 135.79, 139.14; IR (thin film): 3065 w, 3019 w, 2959 s, 2913 s, 1483 m, 1456 m, 1426 m, 1078 s, 744 s cm^{-1} ; mass spectrum (EI), m/z (rel intensity): 259 $[\text{M}+1]^+$ (7), 258 M^+ (100), 257 $[\text{M}-1]^+$ (28), 131 (78), 115 (48), 103 (6), 91 (59). Yellow oil, $R_f = 0.60$ (hexane).

Compound



2-46

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^1H NMR (C

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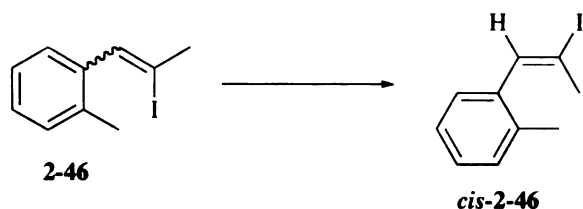
135.68, 13

1480 m, 1

244 (10),

(hexane).

Compound *cis*-2-46



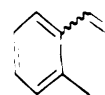
To a solution of 1-(2-iodoprop-1-enyl)-2-methylbenzene with a ratio of 4.4 to 1 (4.51 g, 17.5 mmol) in 50 mL of methanol, was added sodium hydroxide (1.0619 g, 26.5 mmol). The initial *Z* to *E* ratio was 4.8 : 1 determined by GC. GC analysis showed retention times of 11.7 minutes for the *Z* and 11.9 minutes for the *E*. The oven was ramped from 80 °C (1 minute hold at 80 °C) to 230 °C at 10 °C / minute under the general conditions discussed above. After 95 hours the ratio was 1 to 40.1 (*Z* : *E*) analyzed by GC (FID). A partial Kugelrohr distillation was done to remove the alkyne that was formed followed by column chromatography (23 cm x 3 cm, silica gel) with 100 % hexane. This gave 0.40 g of product (43 % recovery, 7.53 mmol).

^1H NMR (CDCl_3) δ : 2.21 (s, 3 H), 2.43 (d, 3 H, $J = 1.6$ Hz), 7.00 - 7.25 (m, 5 H);

^{13}C NMR (CDCl_3) δ : 19.69, 28.94, 98.15, 125.50, 127.43, 128.53, 129.90, 135.68, 136.63, 140.09; IR (thin film): 3061 s, 3019 s, 2948 s, 1913 s, 1624 m, 1480 m, 1431 m, 744 s cm^{-1} ; mass spectrum m/z (% rel intensity) 258 M^+ (100), 244 (10), 141 (12), 131 (66), 127 (18), 115 (54), 91 (46). Yellow oil, $R_f = 0.55$ (hexane).

Compound

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2-46

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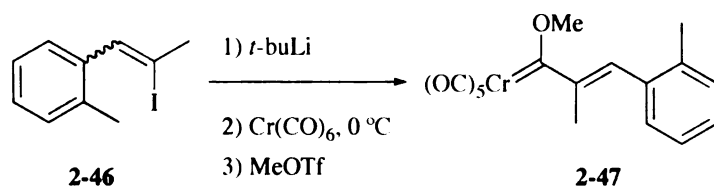
column w

0.16 g (10

scale. A

4.30 mmol

Compound 2-47, Carbene complex of 1-[(1*Z* and 1*E*)-2-iodoprop-1-enyl]-2-methylbenzene



To a solution of 1-[(1*Z* and 1*E*)-2-iodoprop-1-enyl]-2-methylbenzene **4-46** (1.11 g, 4.30 mmol) in diethyl ether (50 mL) at $-78\text{ }^\circ\text{C}$, *t*-butyl lithium (5.1 mL, 1.7 M solution, 8.67 mmol) was added dropwise. The contents of the flask were then allowed to warm to $-60\text{ }^\circ\text{C}$ over 45 minutes. The solution was transferred via cannula over 10 minutes to a suspension of sublimed Cr(CO)_6 (0.96 g, 4.370 mmol) in diethyl ether (90 mL) at $0\text{ }^\circ\text{C}$. The combined solution was allowed to stir for 6 hours at $0\text{ }^\circ\text{C}$. The diethyl ether was removed under reduced pressure and dichloromethane (60 mL) was added. The dichloromethane solution was cooled to $0\text{ }^\circ\text{C}$ and methyl triflate was added dropwise. The contents of the flask were allowed to stir for 20 minutes at $0\text{ }^\circ\text{C}$ and the flask was allowed to warm to room temperature. A gradient silica column from 100 % hexane to 5 % ethyl acetate: hexane gave no separation of two red spots but 1-[2-methylprop-1-enyl]-2-methylbenzene was isolated giving 0.033 g (6 % yield, 0.26 mmol). A second column with 100 % hexane gave good separations of the red products yielding 0.16 g (10 % yield, 0.43 mmol) of the desired carbene complex on a 4.30 mmol scale. A 4 % yield was obtained from a 24 to 1 (*Z* : *E*) mixture of vinyl iodide on a 4.30 mmol scale. The carbene complex was used without further purification and

was mo

Carbene

(s. 3 H).

31.2, 68

0.15 (10

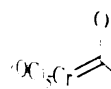
1-[2-meth

and 1.89

6.09 (octe

-7.40 (m,

Compound



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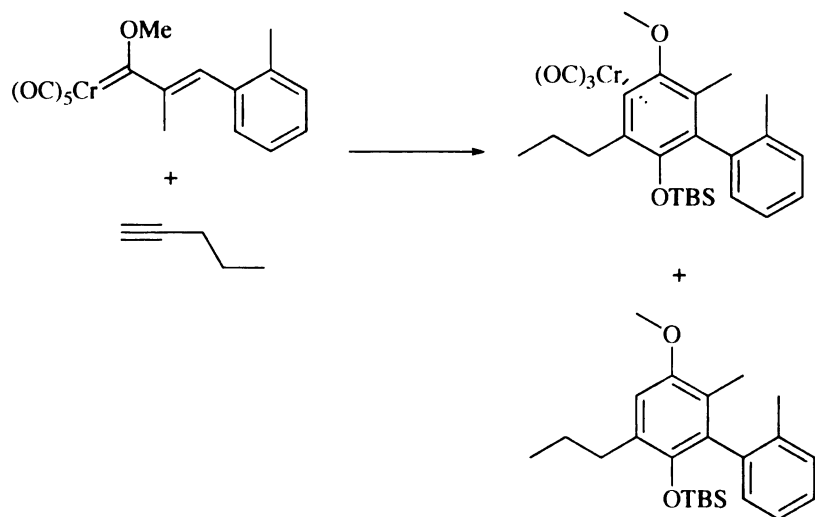
with a hig

was moderately unstable to air.

Carbene complex: ^1H NMR (CDCl_3 , 300 MHz): δ : 1.88 (d, 3 H, $J = 1.5$ Hz), 2.32 (s, 3 H), 4.64 (s, 3 H), 6.61 (1 H), 7.22 (4 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 20.0, 31.2, 68.5, 126.0, 128.2, 128.5, 129.1, 130.3, 135.1, 137.7, 217.0, 223.4; $R_f = 0.15$ (100 % hexane).

1-[2-methylprop-1-enyl]-2-methylbenzene: ^1H NMR (CDCl_3 , 300 MHz): δ : 1.73 and 1.89 (q, $J = 1.7$ Hz, $J = 6.6$ Hz, 3H), 2.07 (acetone), 2.31 and 2.40 (s, 3 H), 6.09 (octet, $J = 6.6$ Hz, $J = 15.6$ Hz, 1 H), 6.60 (q, $J = 1.7$, $J = 15.6$ Hz, 1 H), 7.00 - 7.40 (m, 4 H); $R_f = 0.61$ and 0.51 (100 % hexane).

Compound 2-49 and 2-50



To a single necked flask which had the standard tapered-joint replaced with a high vacuum Teflon threaded valve, carbene complex of 1-[(1*Z* and 1*E*)-2-

iodoprop

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^1H NMR

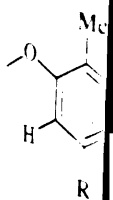
0.08 (s).

(s). 2.05 (

(s). 5.44 (

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Table 7.1.



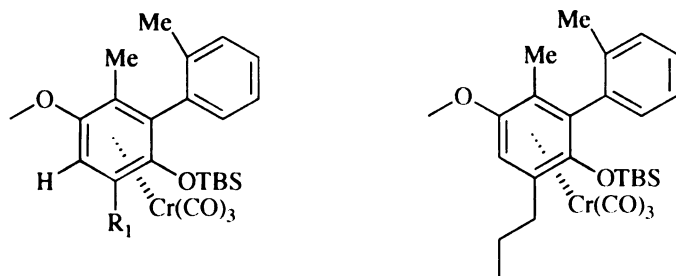
Fogel³⁵¹

This work

iodoprop-1-enyl]-2-methylbenzene **2-47** (0.0732 g, 0.2 mmol), 1-pentyne (40 μ L, 0.40 moles), TBSCl (0.100 g, 0.665 mmol), *N*-ethyl-*N,N*-diisopropylamine (0.148 g, 1.15 mmol), and 5 mL of dichloromethane. Three freeze thaw cycles were done replacing the atmosphere with argon each time. The contents of the flask were heated 24 hours at 50 to 60 $^{\circ}$ C. The flask was stored over night in a freezer. Column chromatography was performed with 30 % dichloromethane and 70 % hexane giving 0.040 g (39 % yield, 0.078 mmol). The compound was unstable and only the ^1H NMR was obtained.

^1H NMR (CDCl_3 , 300 MHz): δ : -0.49 (s), -0.43(s), -0.39 (s), -0.23 (s), -0.17 (s), 0.08 (s), 0.15 (s), 0.77 (s), 0.84 (s), 1.032 (m), 1.26 (s), 1.66 (d), 1.82 (s), 1.92 (s), 2.05 (s), 2.10 (s), 2.26 (m), 2.65 (m), 2.72 (s), 3.75 (s), 3.84 (s), 4.18 (s), 5.23 (s), 5.44 (s), 6.67 (s), 6.70 (s), 7.00 - 7.65 (m). Yellow paste (hexane), R_f = 0.35 (30 % dichloromethane: 70 % hexane).

Table 7.1. Chemical Shifts of Methoxys



	R_1	Syn OMe ppm	Anti, OMe ppm
Fogel ³⁵¹	Me	3.80	3.75
This work	$(\text{CH}_2)_2\text{CH}_3$	3.84	3.75

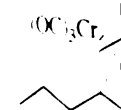
Table 7.2.

Fogel³⁵¹
This work

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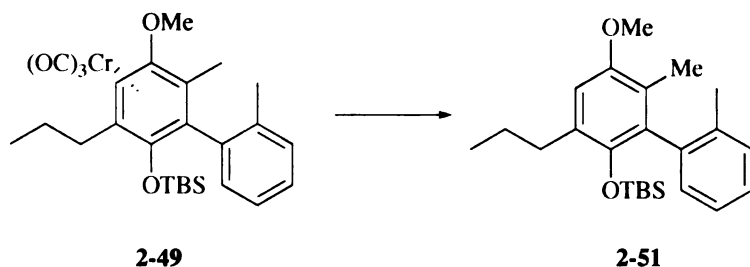
H), 3.83 (

Table 7.2. Chemical Shifts of Methyls

	R ₁	Syn, Me ppm	Anti, Me ppm
Fogel ³⁵¹	Me	2.72	2.12
This work	(CH ₂) ₂ CH ₃	2.72	2.10

From the integration for the ¹H NMR assignments for the methoxy chemical shifts, the distribution is 72 % anti and 28 % syn.

Compound 2-51



Chromium arene complex **2-49** (0.0401g, 0.077 mmol) was added to 5 mL of dichloromethane. One crystal of iodine was added and the mixture was stirred for 15 minutes. The dichloromethane layer was extracted with saturated sodium sulfite (2 x 3 mL) and then brine (10 mL). The dichloromethane layer was dried with sodium sulfate and the solvent removed under reduced pressure. Column chromatography with 30 % dichloromethane and hexane gave 0.030 g of oil (100 % yield, 0.077 mmol).

¹H NMR (CDCl₃, 300 MHz): -0.44 (s, 3 H), -0.24 (3 H), 0.78 (s, 9 H), 0.95 (t, 3H), 1.60 (sext, 2 H), 1.82 (s, 3H), 2.04 (s, 3 H), 2.46 (pent, 1 H), 2.72 (pent, 1 H), 3.83 (3 H), 6.66 (1 H), 7.2 - 7.3 (m, 4 H); ¹³C NMR (CDCl₃, 75 MHz) δ: -4.0,

-3.95, 13.

129.8, 13

(EI), m/z (

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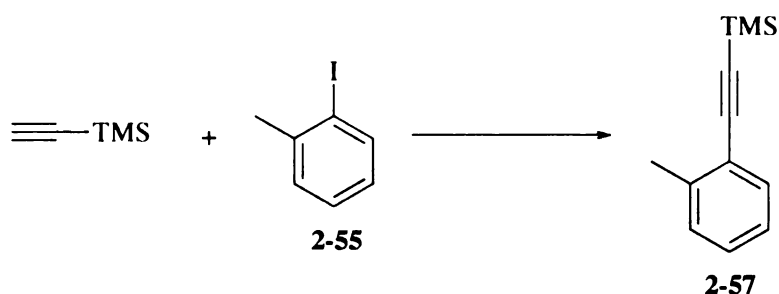
with 100 °

spectrosc

^1H NMR

–3.95, 13.5, 13.9, 18.5, 19.7, 23.9, 26.0, 33.1, 55.7, 110.7, 123.2, 125.0, 127.0, 129.8, 130.5, 131.7, 133.9, 137.6, 138.2, 144.3, 152.1, 162.9; mass spectrum (EI), m/z (% rel intensity): 385 (M^+ , 15), 384 (50, M^+-1), 369 (3), 328 (100), 286 (5), 270 (6), 254 (2), 228 (1), 193 (1), 180 (1), 165 (1), 115 (1), 91 (1), 73(2), 57 (1). Colorless oil, R_f = 0.59 (30 % CH_2Cl_2 / hexane).

Compound 2-57



To a single necked flask which had the standard tapered-joint replaced with a high vacuum Teflon threaded valve, 2-iodotoluene **2-55** (3.75 g, 17.3 mmol), trimethylsilyl acetylene (4.8 mL, 33.9 mmol), THF (19.5 mL), triethyl amine (7.0 mL), bis(triphenylphosphine) palladium (II) chloride (0.26 g, 0.38 mmol), and copper iodide (0.25 g, 1.30 mmol) were added. Three freeze thaw cycles were done replacing the atmosphere with argon each time. The flask was sealed and allowed to stir for 3 days at room temperature. The contents of the flask were filtered through Celite-503. Column chromatography (27 cm x 5.5 cm) with 100 % hexane gave 3.25 g or a quantitative percent yield (17.3 mmol). The spectroscopic properties were identical with those previously reported.³⁵²

¹H NMR (CDCl₃): δ: 0.25 (s, 9 H), 2.41 (s, 3 H), 7.0-7.3 (m, 4 H); ¹³C NMR

(CDCl₃)

140.59; 1

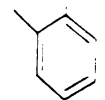
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2-57

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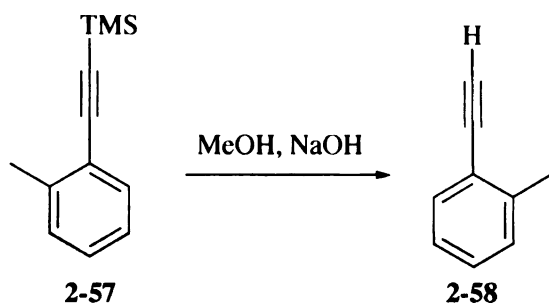
previously

¹H NMR (

= 7.6 Hz

(CDCl₃) δ : 0.06, 20.61, 98.18, 104.01, 122.90, 125.39, 128.43, 129.32, 132.09, 140.59; IR (thin film): 3063 m, 3023 m, 2961 s, 2923 m, 2899 m, 2157 s, 1483 s, 1250 s, 872 s, 755 m cm⁻¹; mass spectrum m/z (% rel intensity) 187 M⁺-1 (10), 173 (100), 128 (8), 115 (20), 105 (7), 61 (22); Light-yellow oil, R_f = 0.45 (100 % hexane).

Compound 2-58

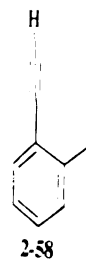


To a round bottom flask, trimethyl(2-*o*-tolylethynyl)silane **2-57** (3.26 g, 17.3 mmol), sodium hydroxide (0.8833 g, 22.1 mmol), and methanol were added. The solution was stirred under nitrogen for 2 hours. The contents of the flask were taken up in 100 mL of hexane and extracted with 70 mL of water. The organic layer was dried with Na₂SO₄ and concentrated under reduced pressure. This compound was used without further purification. This yielded 1.40 g (67 % yield, 11.6 mmol). The spectroscopic properties were identical to those previously reported.³⁵³

¹H NMR (CDCl₃) δ : 2.45 (s, 3 H), 3.26 (s, 1 H), 7.1 - 7.23 (m, 3 H), 7.46 (d, 1 H, J = 7.6 Hz); ¹³C NMR (CDCl₃) δ : 20.54, 80.90, 82.50, 121.91, 125.48, 128.70,

129.41, 1

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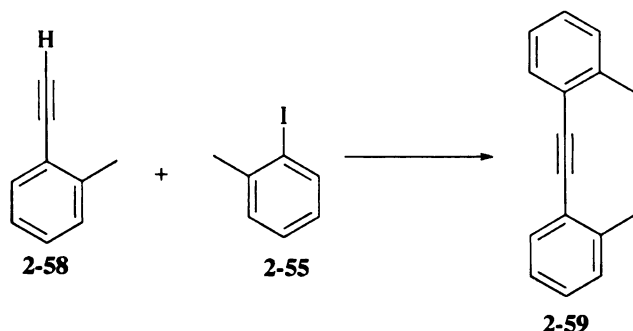
^1H NMR

20.80, 9

$\text{C}_{16}\text{H}_{14}$:

129.41, 132.49, 140.72. Yellow oil (hexane), $R_f = 0.56$ (hexane).

Compound 2-59



In a round bottom flask where the glass joint was replaced with a Teflon valve, THF (10 mL), triethyl amine (6 mL), 1-ethynyl-2-methylbenzene **2-58** (0.2869 g, 2.5 mmol), *o*-iodotoluene **2-55** (0.491 g, 2.3 mmol), trans-dichlorobis(triphenyl phosphine) palladium (II) (0.0332 g, 0.05 mmol, 2.1 mole %), and copper iodide (0.0305 g, 0.16 mmol, 7.1 mole %) were added. Three freeze thaw cycles were done replacing the atmosphere with argon each time. The contents of the flask were stirred for three days. The contents of the flask were taken up in hexanes and filtered through Celite-503. Column chromatography (20 cm x 3 cm, silica) with 100 % hexanes gave 0.26 g (57 % yield, 1.31 mmol). The spectroscopic properties were identical with those reported.³⁵⁴

^1H NMR (CDCl_3) δ : 2.38 (s, 6 H), 7.00 - 7.42 (m, 8 H); ^{13}C NMR (CDCl_3) δ : 20.80, 92.48, 123.44, 125.26, 128.00, 129.47, 131.49, 140.13; Anal calcd for $\text{C}_{16}\text{H}_{14}$: C, 93.20; H, 6.80. Found; C, 92.77; H, 7.26. Orange oil, $R_f = 0.33$

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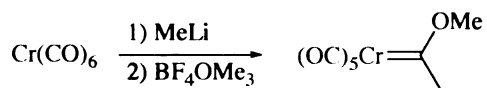
Compou

$(\text{OC})_5\text{Cr}=\text{CH}_2$

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(hexane).

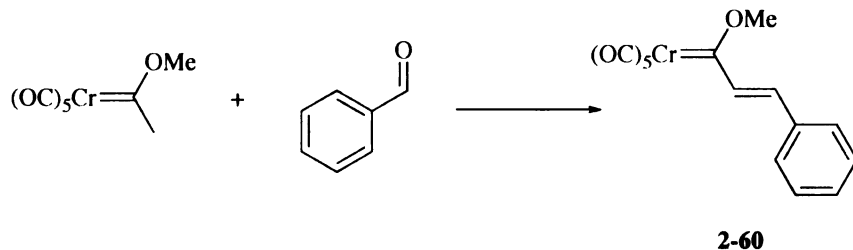
[Methylmethoxycarbenepentacarbonyl] chromium (0)



To a slurry of chromium hexacarbonyl (2.26 g, 10.3 mmol) in a flask equipped with a stirring bar and gas inlet for argon, methyl lithium (6.8 mL, 1.6 M solution) was added dropwise. The contents of the flask were heated for 2.5 hours at 30 to 35 °C in a warm water bath. Water (10 mL, nitrogen sparged) was added along with trimethyloxonium tetrafluoroborate (1.60 g, 10.8 mmol). The contents of the flask were stirred for 30 minutes. The mixture was then extracted with cold nitrogen sparged pentane (3 x 50 mL). The pentane layer was collected and the pentane was removed under vacuum yielding 1.96 g (76 %, 7.86 mmol). The spectroscopic properties were identical to that previously reported.³⁵⁵

¹H NMR (CDCl₃, 300 MHz) δ: 2.95 (s, 3 H), 4.71 (s, 3 H); ¹³C NMR (CDCl₃, 75 MHz) δ: 49.1, 68.0, 216.4, 223.3, 360.5.

Compound 2-60



[Methylmethoxycarbenepentacarbonyl] chromium (0) (0.496 g, 2.50 mmol)

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was added to a single necked 25 mL flask which had the standard tapered-joint replaced with a high vacuum Teflon threaded valve. Also added were diethyl ether 15 mL, benzaldehyde (0.271 g, 2.55 mmol), triethyl amine (1.60 mL, 11.4 mmol), and TMS chloride (1.0 mL, 7.8 mmol). Three freeze thaw cycles were done replacing the atmosphere of the flask with argon. The reaction was stirred for three days giving an isolated yield of 0.364 g (43 %, 1.08 mmol) after gradient column chromatography with hexane to 10 : 100 (ethyl acetate: hexane).

Burgess Reagent was used to prepare this compound.³⁵⁶ To [methoxymethyl] chromium (0) (1.13 g, 4.6 mmol) was added one equivalent of *n*-BuLi in 100 mL of ether at -78°C . In another flask was prepared a solution of benzaldehyde (0.92 mL, 9.1 mmol) and tin tetrachloride (9.1 mL, 9.1 mmol) in dichloromethane. The solution containing deprotonated [methoxymethyl] chromium was added via cannula to the solution containing the benzaldehyde at -78°C . To the solution was added 50 mL of water and the layers separated. The organic solvent was removed under reduced pressure. The resulting compound was put into a flask and freeze thaw degassed once then 1.15 g (4.8 mmol) of the Burgess reagent was added. Another cycle of freeze thaw degas was done. Column chromatography with 100 % hexane to 5 % ethyl acetate / hexane resulted in 0.86 g of product (67 % yield, 3.08 mmol). The spectroscopic properties were identical to that previously reported.³⁵⁷

^1H NMR (CDCl_3 , 300 MHz): δ : 4.83 (s, 3 H), 6.98 (d, 1 H), 7.40 (m, 3 H), 7.60 (m,

2 H), 7.

129.4, 1

(100 % h

2 H), 7.97 (d, 1 H); ^{13}C NMR (CDCl_3 , 75 MHz) δ : 66.4, 128.3, 128.9, 129.1, 129.4, 129.7, 130.8, 134.5, 139.6, 216.7, 224.3, 333.8. Dark solid, $R_f = 0.23$ (100 % hexane).

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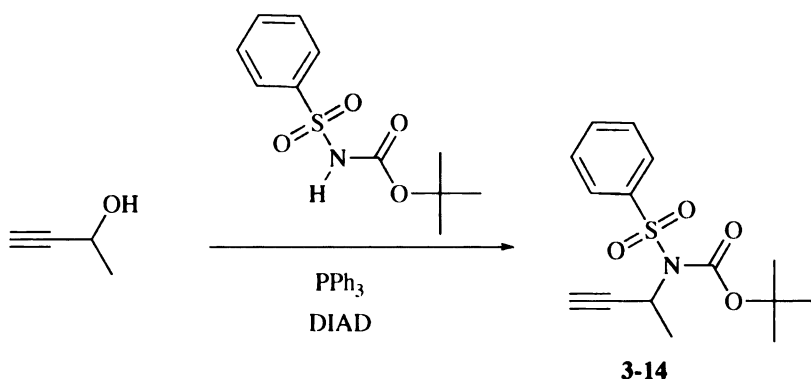
gel) with

g (97 %

¹H NMR

7.3 Chapter Three Experimental

Compound 3-14



To a racemic mixture of 3-butyn-2-ol (0.5 mL, 6.4 mmol), *t*-butyloxycarbonylphenylsulphonate (1.66 g, 6.5 mmol), and triphenylphosine (1.73 g, 6.6 mmol) in THF (15 mL) was added DIAD (1.5 mL, 7.7 mmol) at 0 °C over 5 minutes. The solution was stirred for 1 hour at 0 °C and 1 hour at room temperature. The contents of the flask were removed under reduced pressure. The remaining solvent removed under high vacuum for 2 hours. To the resulting oil was added 100 mL of ether and the solution was stirred until solid precipitated. To this solution was added hexane (100 mL), and the solution was passed through Celite-503 to remove the solid. The Celite-503 was washed with 200 mL of ether / hexane (1:1). Column chromatography (24 cm x 2.8 cm, silica gel) with 20 % ethyl acetate / hexane then 30 % ethyl acetate / hexane gave 1.90 g (97 % yield, 6.2 mmol).

$^1\text{H NMR}$ (CDCl_3) δ : 1.30 (s, 9 H), 1.72 (d, 3 H, $J = 7.1$ Hz), 2.37 (d, 1 H, $J = 2.7$

Hz), 5.4

(CDCl₃)

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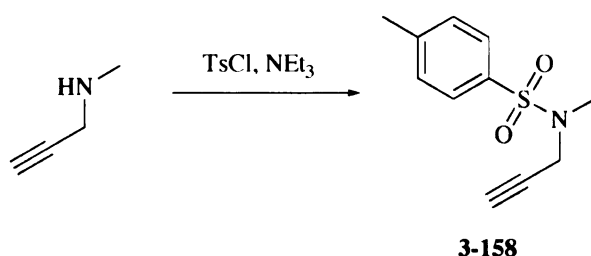
20 cm)

CH₂Cl₂

product

Hz), 5.44 – 5.47 (m, 1 H), 7.45 – 7.60 (m, 3 H), 7.92 – 7.95 (m, 2 H); ^{13}C NMR (CDCl_3) δ : 21.84, 27.75, 45.10, 71.46, 82.13, 84.95, 127.55, 128.64, 133.18, 140.15, 149.75; IR (thin film): 3283 s, 2984 s, 2940 w, 1478 w, 1449 m cm^{-1} ; mass spectrum m/z (% rel intensity) 286 (32), 234 (11), 210 (100), 158 (2), 145 (4), 130 (5), 118 (3); Yellow oil, R_f = 0.53 (50 % ethyl acetate / hexane).

Compound 3-158



To a solution of N-methyl propargylamine (0.973 g, 14.1 mmol) in 15 mL of dichloromethane and 4.0 mL of triethyl amine, *p*-toluenesulfonyl chloride (3.3047 g, 17.3 mmol) was added proportion-wise. The addition was done at room temperature and the reaction was exothermic. The solution was allowed to stir overnight. The organic layer was taken up in 40 mL of additional dichloromethane and extracted with 20 mL of water. The organic layer was dried with magnesium sulfate and gravity filtered. The organic layer was concentrated under reduced pressure. Column chromatography (silica gel column, 2.5 cm X 20 cm) was performed on the sample eluting from 100 % hexane to 50 % CH_2Cl_2 : hexane. This procedure yielded 3.13 g (99 % yield, 13.9 mmol) of product. The spectroscopic properties were identical to those previously

reported

^1H NMR

H, $J = 2$

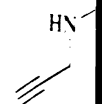
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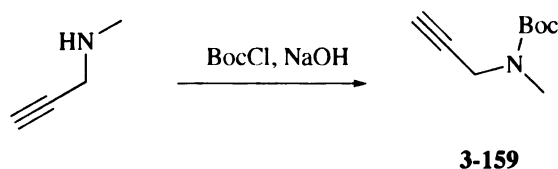
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those p

reported.³⁵⁸

¹H NMR (CDCl₃) δ: 2.08 (t, 1 H, *J* = 2.5 Hz), 2.43 (s, 3 H), 2.82 (s, 3 H), 4.02 (d, 2 H, *J* = 2.5 Hz), 7.30 – 7.35 (m, 2 H), 7.70 – 7.72 (m, 2 H); ¹³C NMR (CDCl₃) δ: 21.49, 34.25, 39.72, 73.93, 76.35, 127.89, 129.50, 134.21, 143.66; mass spectrum *m/z* (% rel intensity) 223 M⁺ (10), 155 (12), 139 (9), 116 (5), 92 (28), 91 (100), 68 (78), 65 (25). Colorless needles, mp 90 - 91 °C, R_f = 0.08 (30 % CH₂Cl₂ / hexane).

Compound 3-159



To a solution of *N*-methyl propyne amine (1.01 g, 14.7 mmol) in 25 ml of water, was added sodium hydroxide (0.61 g, 15.2 mmol). To this solution was added di-*tert*-butyl dicarbonate (3.89 g, 17.8 mmol). The solution was stirred at room temperature for 2.5 hours. The solution was extracted with dichloromethane (50 mL x 2), and the organic layer was washed with water (20 mL). Column chromatography (2.5 x 20 cm, silica) was performed on the sample eluding with 38 % ethyl acetate : hexane. This yielded 2.46 g of compound **3-159** (99 % yield, 14.55 mmol). The spectroscopic properties were identical to those previously reported.³⁵⁹

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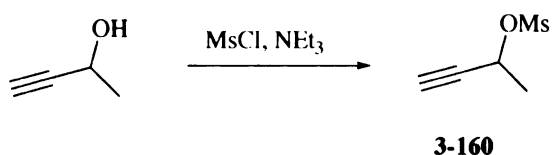
$^1\text{H NMR}$

3H), 5

oil, R_f

^1H NMR (CDCl_3) δ : 1.46 (s, 9 H), 2.21 (t, 1 H, $J = 2.5$ Hz), 2.91 (s, 3 H), 4.03 (bs, 2 H); ^{13}C NMR (CDCl_3) δ : 28.14, 33.20, 37.78, 71.46, 78.99, 79.86, 154.99.; mass spectrum m/z (% rel intensity) 196 M^+ (1), 164 (4), 126 (14), 114 (90), 96 (21), 57 (100). Yellow oil, $R_f = 0.59$ (40 % CH_2Cl_2 / hexane)

Compound 3-160



To a 50 mL round bottom flask 3-butyn-2-ol (1.08 g, 15.4 mmol), DCM (20 mL), mesyl chloride (1.3 mL, 17.0 mmol), and triethyl amine (3.0 mL, 17.0 mmol) were added. The triethyl amine was added last at 0 °C. The reaction was allowed to warm to room temperature and stirred for three hours. The solution was then extracted with 50 mL of 1 M HCl, saturated brine (50 mL) and dried over MgSO_4 . Each extract was back extracted with 50 x 2 mL of DCM. The solvent was removed under reduced pressure. Column chromatography (20 cm x 4 cm, silica gel) with 50 % ethyl acetate gave 2.08 g (91 % yield, 14.0 mmol). The spectroscopic properties were identical to that previously reported.³⁶⁰

^1H NMR (CDCl_3) δ : 1.61 (d, 3 H, $J = 6.7$ Hz), 2.68 (d, 1 H, $J = 2.0$ Hz), 3.08 (s, 3H), 5.25 (m, 1 H); ^{13}C NMR (CDCl_3) δ : 22.34, 39.04, 67.40, 76.24, 80.09; yellow oil, $R_f = 0.48$ (hexane).

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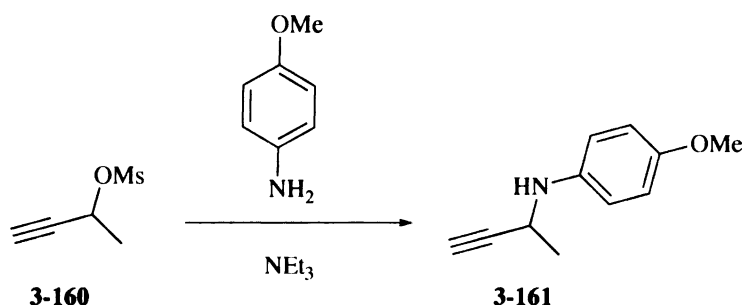
^1H NMR

4.12 (q

(CDCl₃)

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Compound 3-161



To a solution of **3-160** (1.53 g, 10.3 mmol) in 30 mL of benzene and 5 mL of triethyl amine, was added anisidine (2.61 g, 21.2 mmol). The solution was refluxed for three hours and cooled to room temperature. The contents of the flask were extracted with 20 mL of 3 M NaOH and water. Back extracting each aqueous layer with 3 x 20 mL of benzene. The organic layers were combined and dried over magnesium sulfate. The solution was gravity filtered and the organic solvent was removed under reduced pressure. Column chromatography (23 cm x 4 cm, silica) with 30 % ethyl acetate gave 1.43 g (79 % yield, 8.14 mmol) of **3-161** which was one of three spots by TLC. The spectroscopic properties were identical to that previously reported.³⁶¹

^1H NMR (CDCl_3) δ : 1.51 (d, 3 H, $J = 6.9$), 2.20 (d, 1 H, $J = 2.0$ Hz), 3.75 (s, 3 H), 4.12 (q, 1 H, $J = 1.5$), 6.68 (d, 2 H, $J = 9.1$), 6.80 (d, 2 H, $J = 9.1$ Hz); ^{13}C NMR (CDCl_3) δ : 22.42, 41.92, 55.70, 70.00, 85.91, 114.78, 115.88, 140.56, 153.02;

Yellow oil (hexane), $R_f = 0.53$ (3:7 ethyl acetate / hexane).

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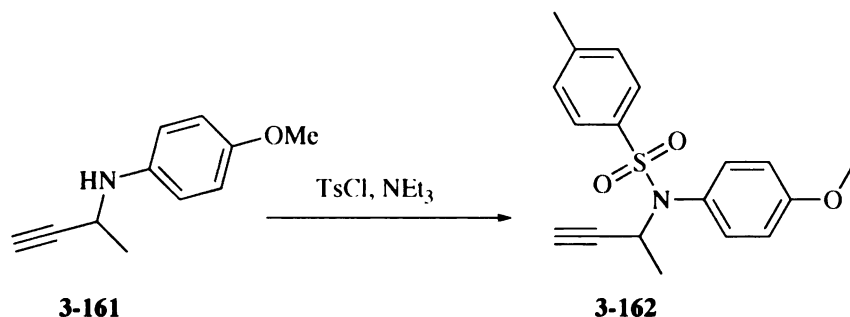
7.10 (d

(CDCl₃)

129.10

acetate

Compound 3-162



In a 100 mL round bottom flask was added **3-161** (0.28 g, 1.6 mmol), tosyl chloride (0.36 g, 1.9 mmol), triethyl amine (0.5 mL, 3.6 mmol), and 10 mL of DCM. The reaction was stirred overnight. The solution was extracted with 25 mL water, and the aqueous layer was back extracted with 2 x 20 mL DCM. The organic layers was dried over magnesium sulfate. The solvent was removed under reduced pressure. Column chromatography (21 cm x 2.2 cm, silica gel) with 10 % ethyl acetate / hexane lead to 0.39 g (73 % yield, 1.17 mmol) which was one of two spots by TLC.

One peak by HPLC silica column (90:10 hexane / isopropanol 2 mL/min retention time 1.85 min).

¹H NMR (CDCl₃) δ: 1.28 (d, 3 H, *J* = 7.0), 2.20 (d, 1 H, *J* = 2.5 Hz), 2.42 (s, 3 H), 3.80 (s, 3 H), 5.30 (dq, 1 H, *J* = 2.3 Hz, *J* = 7.0 Hz), 6.82 (d, 2 H, *J* = 9.1 Hz), 7.10 (d, 2 H, *J* = 9.2 Hz), 7.22 - 7.27 (m, 2 H), 7.59 - 7.63 (m, 2 H); ¹³C NMR (CDCl₃) δ: 21.53, 21.68, 46.35, 55.33, 73.28, 82.87, 113.89, 127.83, 128.10, 129.10, 132.78, 136.66, 143.25, 159.72; Beige powder (1:1 hexane/ethyl acetate), *R*_f = 0.63 (1:1 hexane/ethyl acetate).

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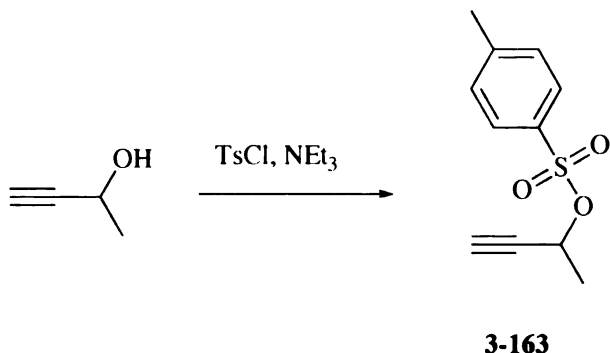
5.17 (dd

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Compound 3-163



The compound 3-butyn-2-ol was added to a 50 mL round bottom flask. The solvent DCM (30 mL) was added along with tosyl chloride (2.82 g, 14.8 mmol) and triethyl amine (4.00 mL, 28.7 mmol) at 0 °C. The solution was warmed to room temperature and stirred overnight. Column chromatography (20 cm x 4 cm, silica) with 10 % ethyl acetate to 20 % ethyl acetate / hexane gave 2.32 g (72 % yield, 10.7 mmol). The spectroscopic properties were identical to that previously reported.³⁶²

¹H NMR (CDCl₃) δ: 1.56 (d, 3 H, *J* = 6.6 Hz), 2.42 (d, 1 H, *J* = 2.2), 2.45 (s, 3 H), 5.17 (dq, 1 H, *J* = 2.0 Hz, *J* = 6.6 Hz), 7.33 (d, 2 H, *J* = 8.5), 7.81 (d, 2 H, *J* = 8.3 Hz); ¹³C NMR (CDCl₃) δ: 21.61, 22.53, 67.35, 75.51, 79.85, 127.98, 129.66, 133.82, 144.83; White solid (4:1 hexane / ethyl acetate), *R*_f = 0.68 (1:1 ethyl acetate / hexane).

Compound



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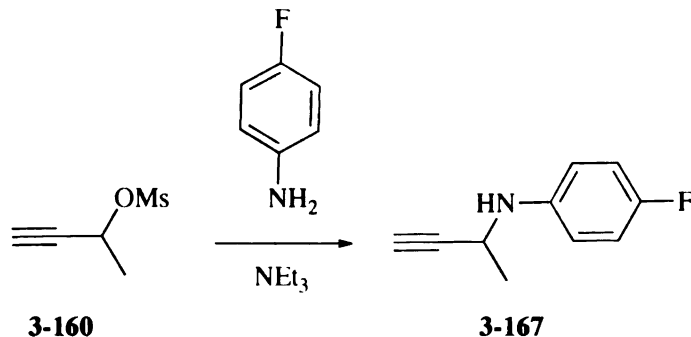
¹³C NMR

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[M+1]⁺

Compound 3-167



A flask was charged with **3-160** (2.62 g, 17.7 mmol), 4-fluoroaniline (4.05 g, 35.4 mmol), benzene (50 mL), and triethyl amine (10 mL). The solution was refluxed for 7 hours. The contents of the flask were extracted with 40 mL of 3 N NaOH, 50 mL water. The aqueous layers were back extracted with 25 mL x 3. The organic layers were combined and dried over sodium sulfate, filtered, and the solvent removed at reduced pressure. Column chromatography (30 cm x 5.8 cm, silica gel) with 5 % ethyl acetate to 10 % ethyl acetate / hexane gave 1.67 g (58 % yield, 2.35 mmol). Isolated one of three spots on TLC. This compound solidified in a -20 °C freezer.

¹H NMR (CDCl₃) δ: 1.52 (d, 3 H, *J* = 6.9 Hz), 2.20 (d, 1 H, *J* = 2.2 Hz), 3.7 (br s, 1 H), 4.12 (dq, 1 H, *J* = 2.2 Hz, *J* = 6.9 Hz), 6.62 - 6.7 (m, 2 H), 6.85 - 6.9 (m, 2 H);

¹³C NMR (CDCl₃) δ: 22.23, 41.44, 70.08, 85.35, 115.15, 115.21, 115.53, 115.70;

IR (thin film) 3401 m, 3299 s, 3040 w, 2982 m, 2934 m, 1615 w, 1510 s, 1308 m, 1221 s, 1167 s, 822 s, 650 s cm⁻¹; mass spectrum *m/z* (% rel intensity) 164

[*M*+1]⁺ (3), 163 *M*⁺ (28), 148 (100, 122 (3), 111 (7), 101 (8), 83 (10); mp 33 - 35

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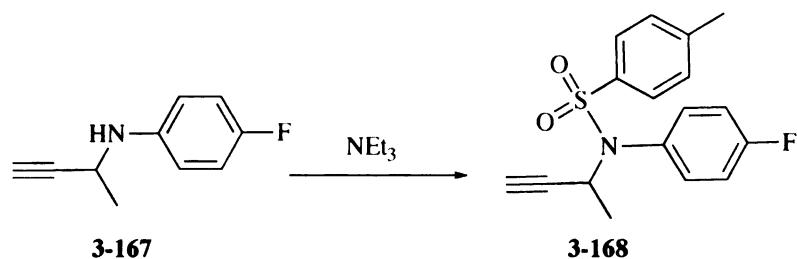
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°C. Clear oil which solidified to a beige solid, $R_f = 0.62$ (50 % ethyl acetate / hexane).

Compound 3-168



A flask was charged with compound **3-167** (0.30 g, 1.9 mmol), tosyl chloride (0.49 g, 2.6 mmol), CH_2Cl_2 (10 mL), and triethyl amine (0.5 mL, 3.6 mmol). The contents of the flask were stirred overnight at room temperature. The contents of the flask were extracted with water and the water was back extracted with 4 x 30 mL the DCM. The organic layer was dried over magnesium sulfate, filtered, and the solvent removed at reduced pressure. Column chromatography (2.8 cm x 30 cm, silica) was done with 30 % DCM to 67 % DCM / hexane. Isolated 0.28 g of product giving a yield of 46 % (0.87 mmol). Two additional spots were observed on the TLC plate which were not isolated.

^1H NMR (CDCl_3) δ : 1.22 (d, 3 H, $J = 7.2$), 2.15 (d, 1 H, $J = 2.0$ Hz), 2.36 (s, 3 H), 5.21 (dq, 1 H, $J = 2.4$ Hz, $J = 7.3$), 6.90 - 6.96 (m, 2 H), 7.10 - 7.20 (m, 4 H), 7.52 (d, 2 H, $J = 8.3$); ^{13}C NMR (CDCl_3) δ : 21.56, 21.67, 46.36, 73.64, 82.57, 115.56, 115.86, 128.10, 129.19, 131.36, 131.41, 133.36, 133.48, 136.27, 143.57, 160.99, 164.30; IR (thin film) 3278 s, 2928 w, 1730 w, 1597 w, 1505 m, 1354 m, 1337 m,

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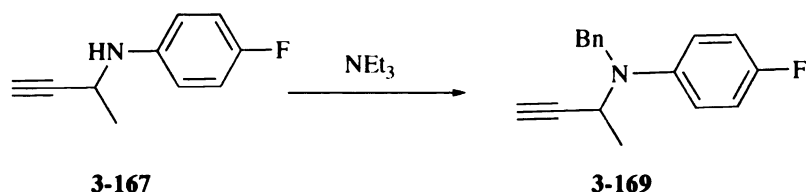
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1165 s, 1102 s, 1040 s cm^{-1} ; mass spectrum m/z (% rel intensity) 317 M^+ (13), 302 (17), 265 (6), 200 (11), 185 (6), 162 (33), 161 (25), 155 (41), 110 (25), 95 (34), 91 (100), 75 (12), 65 (19); White solid (50 % DCM / hexane), mp 111 – 113.5 $^{\circ}\text{C}$, R_f = 0.11 (7:1 hexane / DCM).

Compound 3-169



To a solution of **3-167** (0.49 g, 3.0 mmol) in 20 mL of ethanol was added benzyl bromide (0.40 mL, 3.4 mmol) and potassium carbonate. The solution was stirred for 7 days at room temperature. The contents of the flask were extracted with 50 mL of water, 20 mL brine, and all aqueous portions were back extracted with 3 x 20 mL with ethyl acetate. The organic layers were combined and dried over sodium sulfate, filtered, and the solvent removed under reduced pressure. Column chromatography (27 cm x 2.8 cm, silica gel) with 10 % ethyl acetate to 20 % ethyl acetate / hexane gave 0.58 g (76 % yield, 2.28 mmol). A second spot was observed on TLC with a mass of 0.1 g which was not identified.

^1H NMR (CDCl_3) δ : 1.41 (d, 3 H, J = 7.0 Hz), 2.30 (d, 1 H, J = 2 H), 4.42 - 4.51 (m, 3 H), 6.86 - 6.92 (m, 4 H) 7.20 - 7.36 (m, 5 H); ^{13}C NMR (CDCl_3) δ : 20.48, 47.68, 53.29, 71.85, 83.70, 115.19, 118.81, 126.77, 126.94, 128.42, 139.87; IR (thin film): 3299 m, 3031 w, 2984 w, 2934 w, 1604 w, 1509 s, 1231 s, 1167 s cm^{-1}

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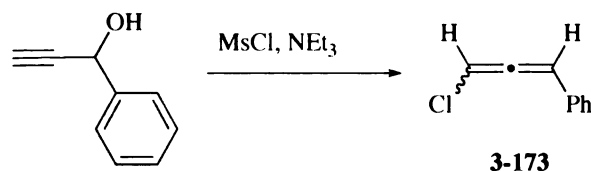
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¹; mass spectrum *m/z* (% rel intensity) 253 M⁺ (45), 238 (53), 198 (35), 161 (21), 122 (16), 95 (25), 91 (100), 77 (15), 75 (12), 65 (14), 57 (3), 51 (10); Yellow oil, R_f = 0.59 (7:3 hexane / ethyl acetate).

Compound 3-173



A flask was charged with 1-phenyl-2-propyn-1-ol (1.01 g, 7.70 mmol), mesyl chloride (0.60 mL, 7.8 mmol), triethyl amine (1.10 mL, 7.90 mmol), and DCM (20 mL). The triethyl amine was added last. The reaction was stirred for 1.5 days at room temperature. The contents of the flask were extracted with 50 mL of 1 M HCl, and 50 mL sat. sodium bicarbonate. Each water layer was back extracted with 2 x 50 mL. The organic layers were combined and dried over sodium sulfate. The solvent was removed under reduced pressure. Column chromatography (26 cm x 2.8 cm, silica) with 5 % ethyl acetate to 10 % ethyl acetate / hexane gave 0.42 g (36 % yield, 2.77 mmol). The spectroscopic properties were identical to those in the literature.³⁶³

¹H NMR (CDCl₃) δ: 6.42 (d, 1 H, *J* = 5.9 Hz), 6.55 (d, 1 H, *J* = 5.9 Hz), 7.24 - 7.36 (m, 5 H); ¹³C NMR (CDCl₃) δ: 91.33, 103.79, 127.90, 128.63, 128.81, 132.11, 203.41; Clear oil, R_f = 0.61 (9:1 hexane / ethyl acetate).

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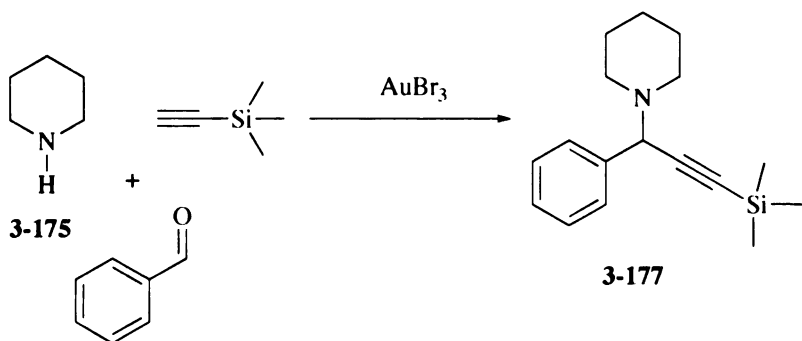
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Compound 3-177



A magnetic stirring bar was placed into a flame-dried single neck flask that had been modified by replacement of the joint with a threaded high vacuum Teflon valve. This flask was charged with benzaldehyde (1.50 mL, 14.8 mmol), piperidine (1.60 mL, 16.2 mmol), gold tribromide (0.067 g, 1.0 mole %), water (12 mL), and TMS acetylene (3.50 mL, 24.8 mmol). The flask was heated at 102 °C for 20 hours. After heating, 50 mL of water was added to the flask. The contents of the flask were extracted with 20 mL x 3 DCM. The organic layer was dried over sodium sulfate and filtered. The solvent was removed under reduced pressure. Column chromatography (29 cm x 3.8 cm, silica gel) with 100 % hexane and then 10 % ethyl acetate / hexane gave 2.86 g (71 % yield, 10.5 mmol).

¹H NMR (CDCl₃) δ: 0.30 (s, 9 H), 1.48 (m, 2 H), 1.61 (m, 4 H), 2.51 (t, 4 H, *J* = 5.3 Hz), 4.64 (s, 1 H), 7.30 - 7.42 (m, 3 H), 7.60 - 7.67 (m, 2 H); ¹³C NMR (CDCl₃) δ: 0.23, 24.48, 26.15, 50.42, 62.47, 92.10, 102.09, 127.30, 127.92, 128.40, 138.35; mass spectrum *m/z* (% rel intensity) 271 M⁺ (6), 270 (21), 194

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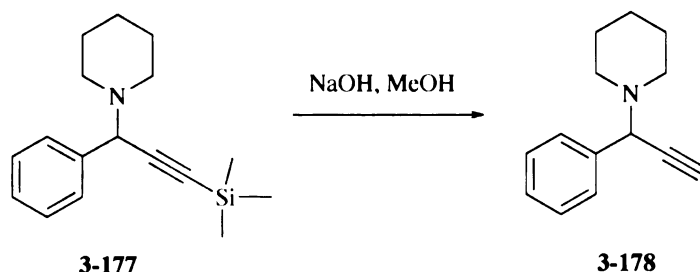
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(100), 174 (8), 159 (19), 84 (30). Yellow oil (hexane), $R_f = 0.40$ (10 % ethyl acetate / hexane).

Compound 3-178



To a solution of compound **3-177** (2.08 g, 7.7 mmol) in methanol was added sodium hydroxide (0.38 g, 9.4 mmol). The solution was stirred for 3.5 hours at room temperature. Water (50 mL) was added and the solution was extracted with 2 x 100 mL of dichloromethane. The organic layers were combined and extracted with brine (50 mL). The aqueous layer was extracted with 2 x 20 mL of dichloromethane. The organic layer was dried over sodium sulfate. Column chromatography with 100 % hexane then 5 % ethyl acetate / hexane (23 cm x 3.4 cm, silica gel) gave 1.48 g (97 % yield, 7.5 mmol). This compound was previously reported in the literature.³⁶⁴

^1H NMR (CDCl_3) δ : 1.43 (m, 2 H), 1.56 (m, 4 H), 2.47 (m, 4 H, 5.4 Hz), 2.52 (d, 1 H, $J = 2.3$ Hz), 4.59 (d, 1 H, $J = 2.2$ Hz), 7.2 - 7.4 (m, 3 H), 7.4 - 7.6 (m, 2 H); ^{13}C NMR (CDCl_3) δ : 24.37, 26.11, 50.41, 61.67, 75.32, 79.99, 127.45, 128.01, 128.30, 138.08; IR (thin film): 3303 s, 3060 w, 3030 w, 2936 s, 2855 m, 2809 m,

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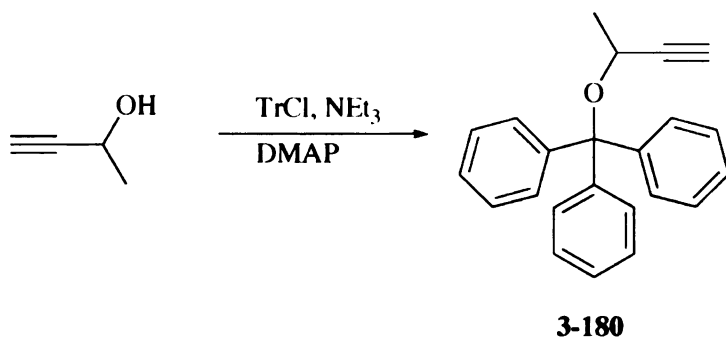
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2751, 1493, 1451, 1317, 1269, 1156, 993, 733, 642 cm^{-1} ; mass spectrum m/z (% rel intensity) 199 M^+ (9), 198 M^+-1 (35), 122 (100), 115 (74), 84 (25). Yellow oil (hexane) at room temperature, yellow solid at $-20\text{ }^{\circ}\text{C}$, $R_f = 0.37$ (10 % ethyl acetate / hexane).

Compound 3-180



A round bottom flask where the glass joint was replaced with a Teflon valve was charged with 3-butyn-2-ol (0.700 g, 10.0 mmol), triethyl amine (2.6 mL), DMAP (0.08 g, 0.70 mmol), trityl chloride (2.81 g, 10.0 mmol), and DCM (14 mL). The contents of the flask were heated at $50\text{ }^{\circ}\text{C}$ for 48 hours. The contents of the flask were poured over 10 mL of silica and the solvent removed under reduced pressure. Column chromatography (24 cm x 2.8 cm, silica gel) gave 0.86 g (28 % yield, 2.8 mmol). The spectroscopic properties were identical to those previously reported.³⁶⁵

$^1\text{H NMR}$ (CDCl_3) δ : 1.19 (d, 3 H, $J = 6.3$ Hz), 2.09 (d, 1 H, $J = 1.9$ Hz), 4.20 (m, 1 H), 7.20 - 7.55 (m, 15 H); Off white powder, $R_f = 0.81$ (30 % ethyl acetate / hexane).

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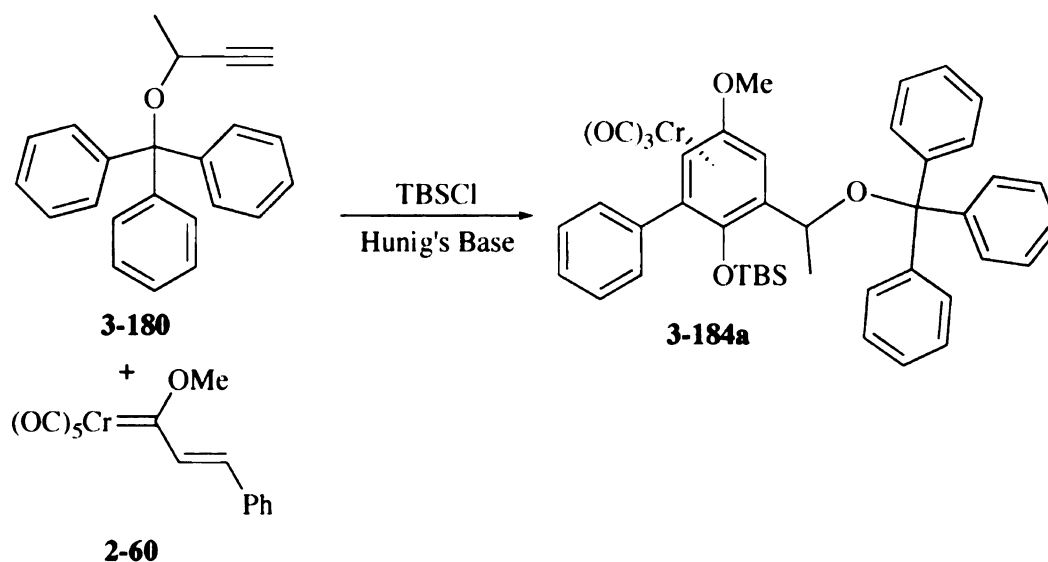
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Compound 3-184a



A magnetic stirring bar was placed into a flame-dried single neck flask that had been modified by replacement of the joint with a threaded high vacuum Teflon valve. To this flask was added styryl carbene complex **2-60** (0.103 g, 0.30 mmol), DCM (6 mL), compound **3-180** (0.183 g, 0.59 mmol), TBSCl (0.139 g, 0.92 mmol), and N,N-diisopropylethylamine (0.26 mL). Three freeze thaw cycles were done to degas the solvent. The contents of the flask were heated at 60 ± 1 °C for 12 hours. The contents of the flask were then poured onto silica (about 3 mL) and the solvent removed under reduced pressure. Column chromatography (25 cm x 2.2 cm, silica) from 100 % hexane to 10 % ethyl acetate hexane gave 0.208 g of **3-184a** (93 % yield, 0.28 mmol).

^1H NMR (CDCl_3) δ : -0.67 (s, 3 H), -0.19 (s, 3 H), 0.61 (s, 9 H), 1.52 (d, 3 H, $J = 6.2$ Hz), 3.56 (s, 3 H), 4.90 (q, 1 H, $J = 6.3$ Hz), 5.30 (d, 1 H, $J = 2.6$ Hz), 5.90 (d, 1 H, $J = 2.6$ Hz), 7.18 - 7.63 (m, 20 H); ^{13}C NMR (CD_2Cl_2) δ : -4.16, -3.44, 18.82, 25.96, 28.54, 56.67, 66.57, 83.76, 88.43, 103.22, 111.04, 127.72, 128.34,

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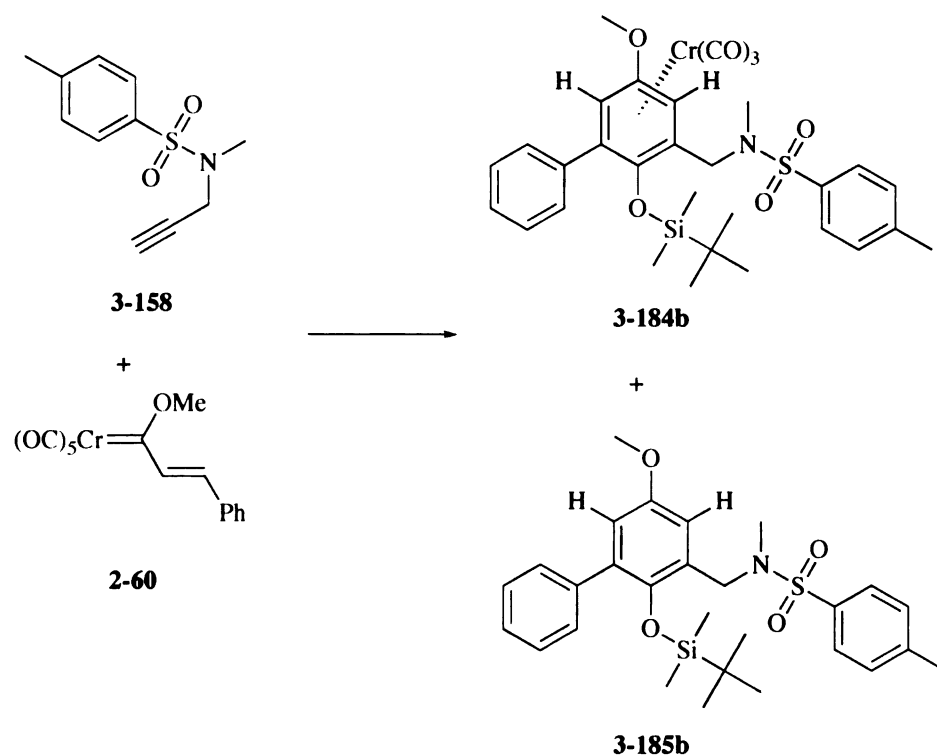
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128.67, 129.16, 131.74, 132.42, 135.85, 144.77, 234.92; IR (thin film) 2934.10 m, 1954.14 vs, 1869.26 vs, 1419.79m, 1369.63m, 1257.75m, 1217.24m, 1026.26m, 702.18m cm^{-1} ; mass spectrum m/z (% rel intensity, FAB^+) 736.2 M^+ (6), 652.3 (64), 243.2 (100), 165.1 (35), 73.1 (34); HRMS calcd for $\text{C}_{43}\text{H}_{44}\text{CrO}_6\text{Si}$ m/z 736.2312, meas 736.2309. Yellow solid (hexane).

Compound 3-184b



A magnetic stirring bar was placed into a flame-dried single neck flask that had been modified by replacement of the joint with a threaded high vacuum Teflon valve. To this flask was added styrene carbene complex **2-60** (0.106 g, 0.31 mmol), toluene (12 mL), compound **3-158** (0.086 g, 0.39 mmol), TBSCl (0.1517 g, 1.00 mmol), and *N,N*-diisopropyl ethylamine (0.30 mL). Three freeze

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thaw cycles were done to degas the solvent. The contents of the flask were heated at 80 ± 1 °C for 3 hours. The contents of the flask were then poured onto silica gel (about 3 mL) and the solvent removed under reduced pressure. The silica gel was dry loaded onto a column. Column chromatography (25 cm x 2.2 cm, silica) from 100 % hexane to 20 % ethyl acetate hexane gave 0.205 g of product. This gave a mixture of compounds. After analysis by ^1H NMR integrating the hydrogens on the newly formed aromatic ring and the N-methyl, the yield of chromium tricarbonyl product (**3-184b**) was 87 % (0.27 mmol). The yield of the biaryl product was 4.4 % (**3-185b**, 0.012 mmol), and the recovery of compound **3-158** was 25 % (0.11 mmol).

Mixture of starting alkyne and product was obtained and the peaks for the chromium tricarbonyl arene were extracted from the mixed NMR which are reported below.

Chromium tricarbonyl compound:

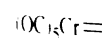
^1H NMR (CDCl_3) δ : -0.49 (s, 3 H), -0.36 (s, 3 H), 0.69 (s, 9 H), 2.39 (s, 3 H), 2.90 (s, 3 H), 3.64 (s, 3 H), 3.94 (d, 1 H, $J = 15.7$ Hz), 4.34 (d, 1 H, $J = 15.8$ Hz), 5.28 (d, 1 H, $J = 2.7$ Hz), 5.67 (d, 1 H, $J = 5.67$), 7.21 - 7.75 (m, 9 H); ^{13}C NMR (CDCl_3) δ : -4.83, -4.08, 18.30, 21.65, 25.78, 35.94, 48.87, 56.20, 79.01, 82.15, 98.14, 105.54, 127.43, 127.94, 128.43, 129.54, 129.89, 130.92, 133.87, 134.77, 137.01, 144.13, 233.54. Yellow solid, $R_f = 0.54$ (45 % ethyl acetate : hexane).

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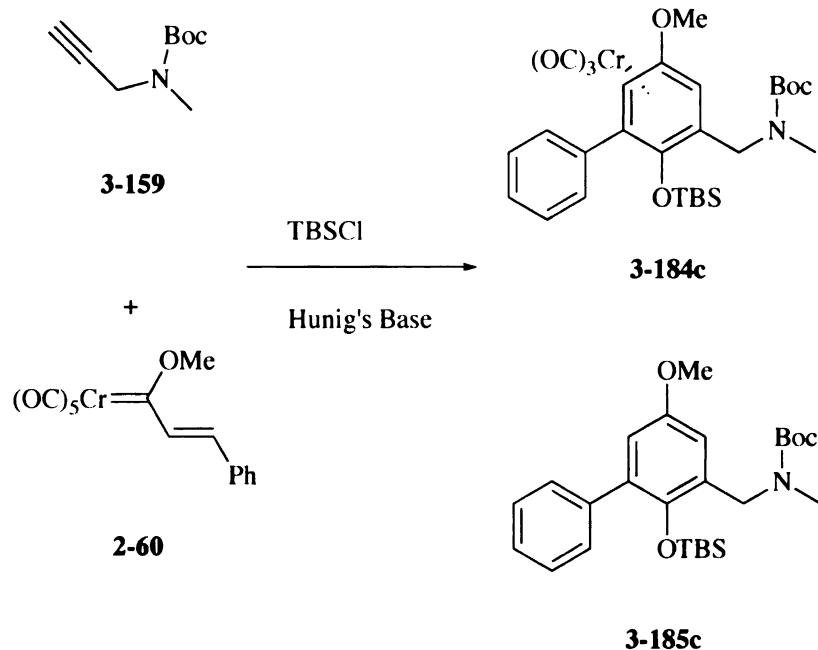
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Compound 3-184c



A magnetic stirring bar was placed into a flame-dried single neck flask that had been modified by replacement of the joint with a threaded high vacuum Teflon valve. To this flask was added styrene carbene complex **2-60** (0.11 g, 0.31 mmol), toluene (10 mL), compound **3-159** (0.072 g, 0.43 mmol), TBSCl (0.1489 g, 1.00 mmol), and N,N-diisopropylethylamine (0.30 mL, 1.73 mmol). Three freeze thaw cycles were done to remove the oxygen. The solution was heated for 45 minutes at 80 to 105 °C. The contents of the flask were stirred overnight at room temperature. The contents of the flask were poured onto silica, and the solvent was removed under reduced pressure to give a yellow solid. Column chromatography (25 cm x 2.3 cm, silica gel) with hexane to 20 % ethyl acetate : hexane gave 0.140 g. This procedure gave a yield of chromium tricarbonyl compound **3-184c** of 60.0 % (0.19 mmol, NMR calculated) and a yield of biaryl compound **3-185c** of 20 % (0.061 mmol).

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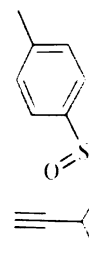
Chromium tricarbonyl species:

^1H NMR (CDCl_3) δ : -0.48 and -0.39 (s, 3 H), -0.23 and -0.14 (s, 3 H), 0.90 (s, 9H), 1.51 and 1.45 (s, 9 H), 3.10 (s, 3 H), 3.64 (s, 3 H), $4.00 - 4.95$ (m, 2 H), 5.32 (s, 1 H), 5.36 (s, 1 H), $7.27 - 7.47$ (m, 3 H), $7.48 - 7.65$ (m, 2 H).

Mixture of chromium tricarbonyl and biaryl:

^{13}C NMR (CDCl_3) δ : -5.20 , -4.59 , 18.53 , 25.90 , 28.38 , 47.74 (br), 56.13 , 78.82 (br), 79.90 (br), 80.42 (br), 81.18 (br), 81.88 (br), 99.48 , 104.74 , 128.09 , 128.29 , 128.84 (br), 129.42 (br), 130.90 , 131.11 , 135.11 , 233.53 , 233.90 . Yellow oily solid, $R_f = 0.55$ (30 % ethyl acetate / hexane).

Compo



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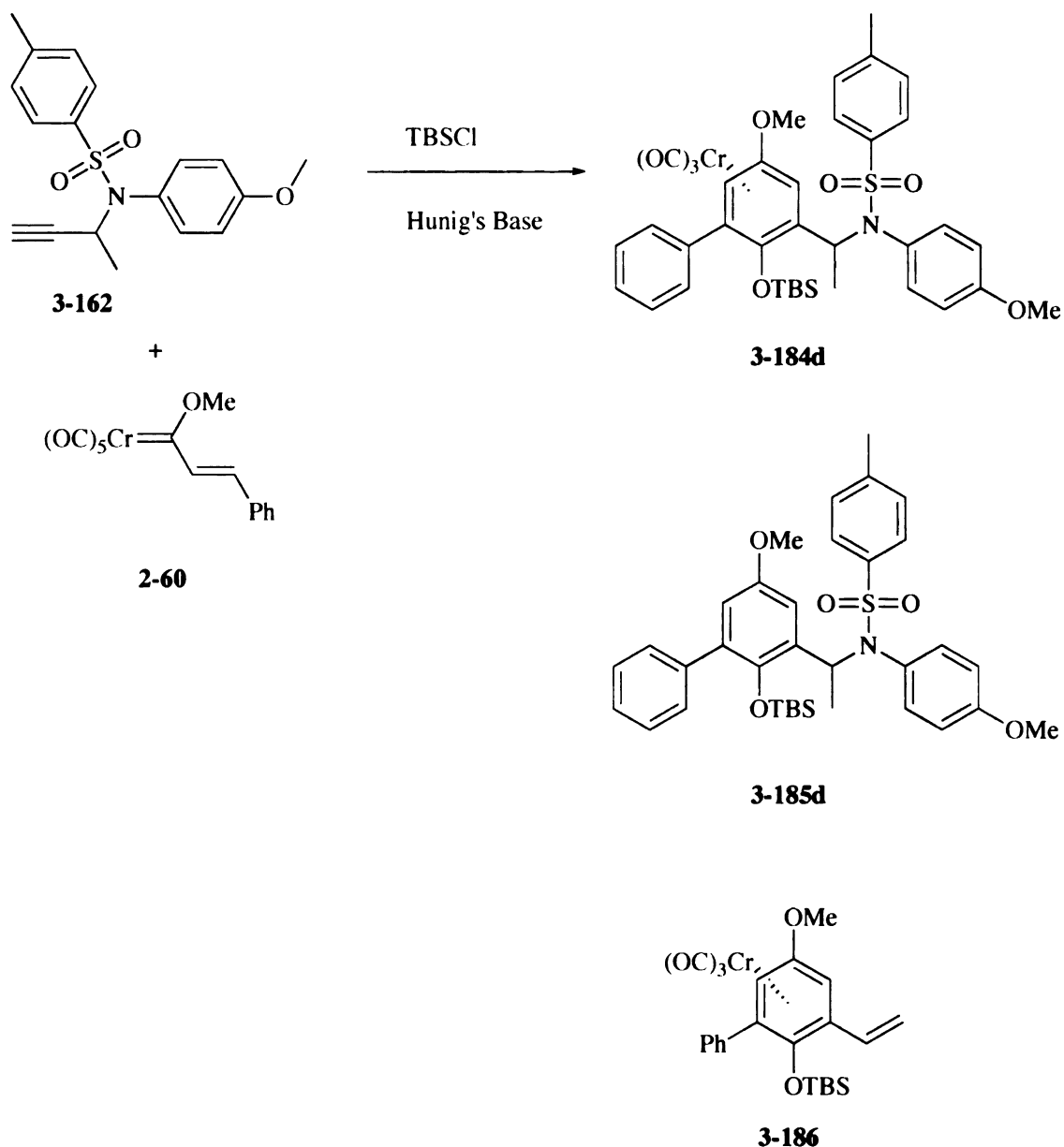
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Compound 3-184d



Typical procedure 3A:

A magnetic stirring bar was placed into a flame-dried single neck flask that had been modified by replacement of the joint with a threaded high vacuum Teflon valve. To this flask was added, styrene carbene complex **2-60** (0.107 g, 0.32 mmol), compound **3-162** (0.126 g, 0.38 mmol), TBSCl (0.18 g, 1.2 mmol), Hunig's base (0.27 mL, 1.5 mmol), and 6 mL of toluene (or DCM). Three freeze

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thaw cycles were done. The reaction flask was heated for 24 hours at 60 °C or other temperature specified in a table. Column chromatography (2.8 cm x 20 cm, silica gel) with 5 % DCM to 30 % DCM / hexane. This gave 0.064 g of product in two fractions (31 % yield, 74 : 26 dr) with a trace amount of demetalated compound.

At 60 °C for 24 hours in dichloromethane, the yield was 24 % ($\geq$ 96 : 4) along with 5 % of demetalated compound **3-185d**. When the reaction was done with 1.1 equivalents of Hunig's base the yield dropped to 13 %.

At 60 °C for 24 hours in dichloromethane with TBSOTf (3 eq.) and lutidine (1.5 eq.), the yield was 35 % with 4 % demetalated compound **3-185d**. Also found under this condition was a 14 % yield of the eliminated compound **3-186**. Isolated one spot of five spots by TLC when done in toluene. In DCM, there are only two spots by TLC.

Inseparable mixture of diastereomers:

Diastereomer A (minor): ^1H NMR (CD_2Cl_2) δ : -0.54 (s, 3 H), 0.10 (s, 3 H), 0.91 (s, 9 H), 1.64 (d, 3 H, 7.0 Hz), 2.42 (s, 3 H), 3.45 (s, 3 H), 3.82 (s, 3 H), 5.10 (d, 1 H, J = 2.8 Hz), 5.30 (d, 1 H, J = 2.6 Hz), 5.63 (q, 1 H, J = 7.2), 6.66 - 6.90 (m, 4 H), 7.24 - 7.63 (m, 9 H).

Diastereomer B (major): ^1H NMR (CD_2Cl_2) δ : -0.24 (s, 3 H), 0.14 (s, 3 H), 0.92 (s, 9 H), 1.64 (d, 3 H, 7.0 Hz), 2.42 (s, 3 H), 3.47 (s, 3 H), 3.77 (s, 3 H), 5.10 (d, 1 H, J = 2.8 Hz), 5.30 (d, 1 H, J = 2.6 Hz), 5.81 (q, 1 H, J = 7.0), 6.66 - 6.90 (m, 4 H), 7.24 - 7.63 (m, 9 H).

Mixtur

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128.19

134.10

160.37

$[\text{M}+\text{K}]^+$

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Mixture, the individual contributions could not be distinguished therefore too many carbons:

^{13}C NMR (CD_2Cl_2) δ : -4.10, -3.90, -3.61, -3.19, 21.38, 21.64, 26.25, 26.80, 31.96, 56.30, 56.42, 78.00, 81.77, 83.64, 84.78, 105.98, 106.77, 110.03, 114.39, 128.19, 128.48, 128.77, 128.86, 129.10, 129.15, 129.63, 129.70, 131.25, 131.31, 134.10, 134.51, 135.07, 135.94, 136.00, 136.65, 137.98, 144.05, 144.18, 160.25, 160.37, 234.18, 234.34; mass spectrum m/z (% rel intensity, MALDI) 792.7 $[\text{M}+\text{K}]^+$, 776.69 $[\text{M}+\text{Na}]^+$, 734.86 $[\text{M}-t\text{-Bu}]^+$, 669.99 $[\text{M}-3\text{CO}]^+$, 641.58, 640.76; HRMS calcd for $\text{C}_{38}\text{H}_{43}\text{CrNO}_8\text{SSi}$ m/z 753.1884, meas 753.1887. Yellow-oily solid (hexane), R_f = 0.5 and 0.4 (50 % ethyl acetate / hexane).

Compo



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compound

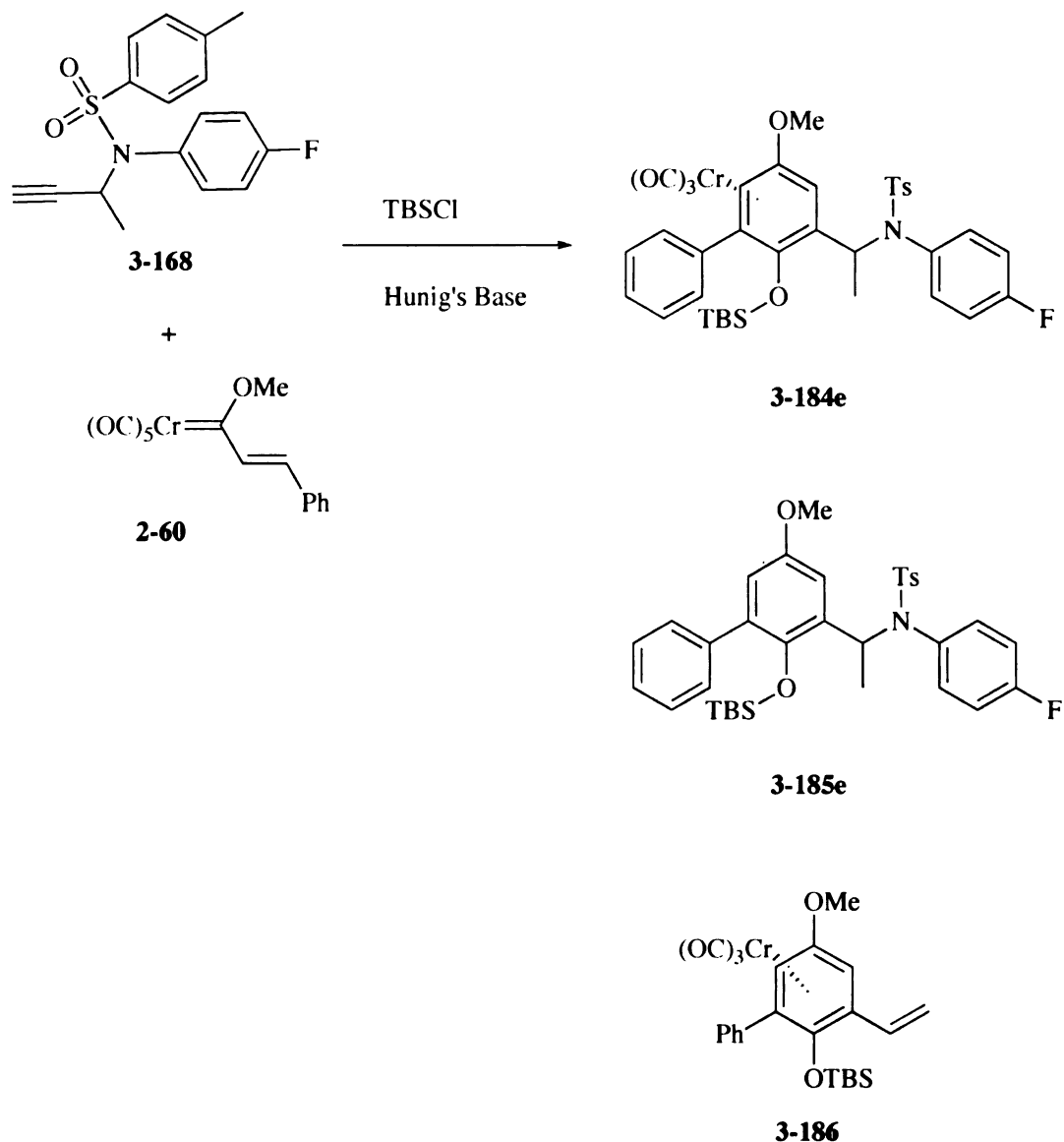
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compound

Compound 3-184e



Compound **3-184e** was prepared following the typical procedure for compound **3-184d** (procedure 3A) on a 0.31 mmol scale identical to that previously reported. Under the standard conditions at 50 °C for 12 hours, a yield of 17 % (**3-184e**) was obtained along with 4 % yield of the demetalated compound **3-185e**. Also found was a 21 % (0.07 mmo) of the eliminated compound **3-186**.

compo

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6.5 Hz)

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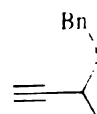
yellow so

At 50 °C for 26 hours a yield of 17 % was obtained with 4 % demetalated compound mixed in. Also found was a yield of 48 % of compound **3-186**.

This compound decomposed upon storage under argon in the freezer.

^1H NMR (CDCl_3) δ : -0.25 (s, 3 H), 0.17 (s, 3 H), 0.92 (s, 9 H), 1.67 (d, 3 H, $J = 6.5$ Hz), 2.41 (s, 3 H), 3.49 (s, 3 H), 5.04 (s, 1 H), 5.22 (s, 1 H), 5.82 (q, 1 H, $J = 6.5$ Hz), 6.80 - 8.60 (m, 13 H); ^{13}C NMR (too many carbons, CDCl_3) δ : -3.81, -3.29, 14.11, 18.78, 20.99, 21.55, 22.64, 35.4, 26.63, 31.58, 53.88, 56.00, 80.89, 83.71, 105.22, 105.48, 115.77, 116.07, 127.90, 128.19, 128.26, 128.55, 128.76, 129.05, 129.38, 130.05, 130.78, 132.21, 132.26, 134.48, 134.65, 134.76, 135.01, 135.14, 135.25, 135.48, 137.27, 143.66, 153.09, 160.95, 164.28, 233.59; bright yellow solid, $R_f = 0.16$ (7:3 hexane / ethyl acetate).

Compo



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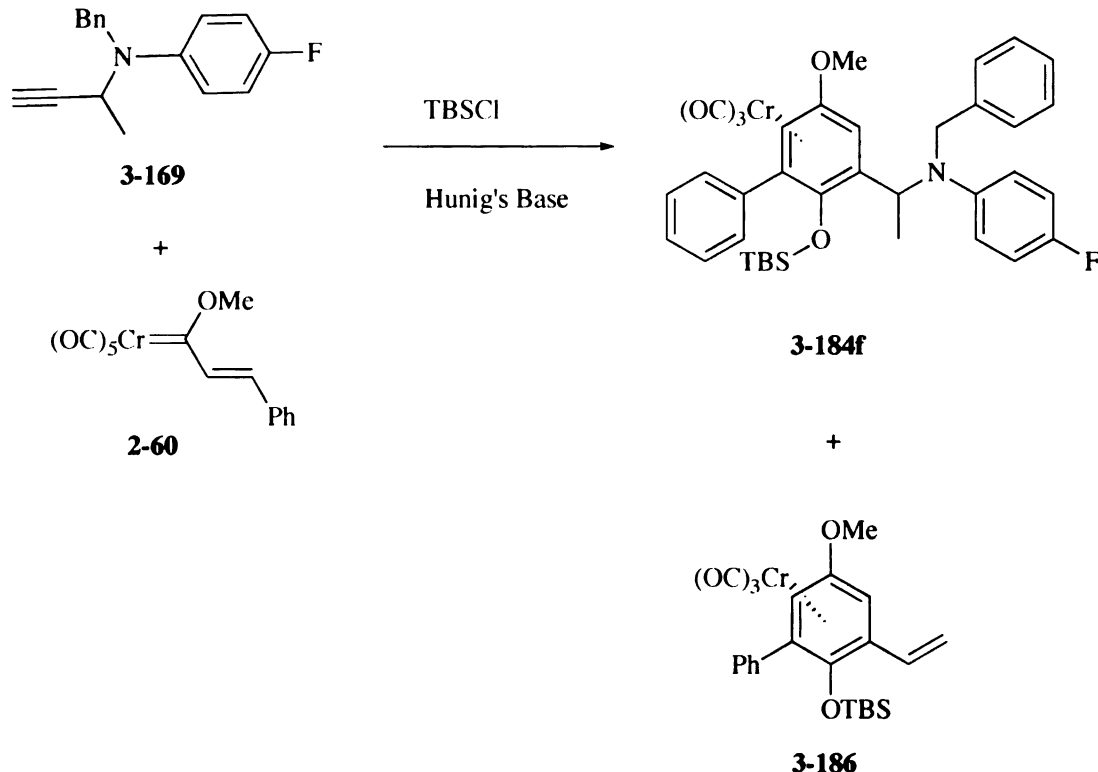
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Compound 3-184f (2-278)



A magnetic stirring bar was placed into a flame-dried single neck flask that had been modified by replacement of the joint with a threaded high vacuum Teflon valve. The flask was charged with styrene carbene complex **2-60** (0.098 g, 0.29 mmol), compound **3-169** (0.11 g, 0.44 mmol), TBSCl (0.14 g, 0.9 mmol), Hunig's base (0.25 mL, 1.4 mmol), and DCM. Three freeze thaw cycles were done. The flask was heated at 60 °C for 13 hours. The flask was cooled and extracted with 50 mL water, and the water was back extracted with 3 x 28 mL of DCM. The organic layers were combined and filtered. The solvent was removed under reduced pressure. Column chromatography (40 cm x 1.8 cm, silica) with 5 % ethyl acetate to 10 % ethyl acetate / hexane. Isolated three spots of three spots on TLC. The first spot was not identified (0.033 g). The yield of compound

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Mixture

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157.16.

3-184f was 23 % (0.067 mmol). The yield of compound **3-186** was 38 % (0.11 mmol). Compound **3-184f** decomposed on storage under argon in the freezer. Good NMR was not possible.

Mixture of diastereomers:

Diastereomer A (major):

^1H NMR (CDCl_3) δ : -0.41 (s, 3 H), 0.00 (s, 3 H), 0.72 (s, 9 H), 1.70 (d, 9 H, J = 6.4 Hz), 3.59 (s, 3 H), 4.60 (m, 2 H), 5.18 (m, 2 H), 5.4 (s, 1 H), 6.70 - 6.93 (m, 5 H), 7.18 - 7.52 (m, 9 H). Yellow solid, R_f = 0.47 (7:3 hexane / ethyl acetate).

Diastereomer B (minor):

^1H NMR (CDCl_3) δ : -0.35 (s, 3 H), -0.31 (s, 3 H), 0.89 (s, 3 H), 1.54 (d, 3 H, J = 6.6 Hz), 3.72 (s, 3 H), 4.60 (m, 2 H), 5.18 (m, 2 H), 5.4 (s, 1 H), 6.70 - 6.93 (m, 5 H), 7.18 - 7.52 (m, 9 H). Yellow solid, R_f = 0.47 (7:3 hexane / ethyl acetate).

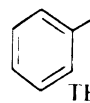
Mixture of Diastereomers:

^{13}C NMR (CDCl_3) δ : -3.82, -3.29, 17.10, 18.62, 26.12, 51.93, 56.19, 81.28, 82.95, 105.40, 106.23, 115.46, 115.46, 115.64, 115.88, 115.93, 117.64, 126.28, 126.75, 128.34, 129.07, 130.81, 135.44, 135.50, 139.95, 145.57, 153.84, 155.28, 157.16, 234.02.

Comp

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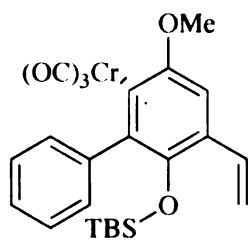
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HRMS

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Compound 3-186 This compound was formed from procedures described above.



3-186

^1H NMR (CDCl_3) δ : -0.54 (s, 3 H), -0.19 (s, 3 H), 0.88 (s, 9 H), 3.72 (s, 3 H), 5.37 (d, 1 H, $J = 11.0$), 5.44 (d, 1 H, $J = 2.8$), 5.59 (d, 1 H, $J = 2.4$), 5.65 (d, 1 H, $J = 17.3$), 6.89 (dd, 1 H, $J = 10.9$, $J = 17.8$), 7.30 - 7.46 (m, 3 H), 7.55 - 7.66 (m, 2 H); ^{13}C NMR (CDCl_3) δ : -4.75, -3.88, 18.37, 25.75, 56.29, 76.21, 80.82, 97.72, 104.64, 115.67, 128.10, 128.82, 131.00, 131.52, 135.15, 137.02, 233.90; IR (thin film) cm^{-1} 2931 s, 2856 m, 1958 vs, 1879 vs, 1653 m, 1541 m, 1408 m; mass spectrum m/z (% rel intensity) 476 M^+ (37), 392 (100), 283 (17), 126 (6), 73 (12); HRMS calcd for $\text{C}_{24}\text{H}_{28}\text{CrO}_5\text{Si}$ m/z 476.1111, meas 476.1110. Yellow-orange solid, mp 150 - 152 $^\circ\text{C}$, $R_f = 0.27$ (7:3 hexane / ethyl acetate).

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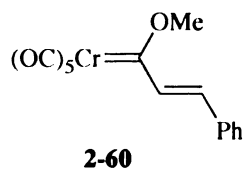
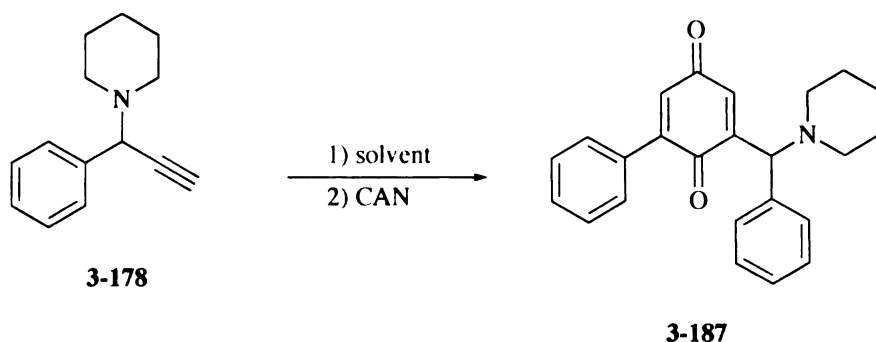
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Compound 3-187



Typical procedure: The alkyne **3-178** (0.13 g, 0.65 mmol), 6.8 mL of solvent, and carbene **2-60** (0.11 g, 0.33 mmol) were added to a 50 mL round bottom flask where the 14/20 glass joint was replaced with a threaded high-vacuum Teflon valve. To the flask was added 6.2 mL of dichloromethane. Three freeze thaw cycles were done to remove oxygen and the reaction was heated for the indicated time which in this example was 12 hours at 60 °C. The contents of the reaction were cooled to room temperature and 10 mL of dichloromethane and 10 mL ether were added. To this solution in air was added 6 mL of 0.5 M CAN and the reaction was stirred for 1 to 1.5 hours. The oxidation was complete at 1.5 hours. After 1 hour, some unoxidized phenol remained. The reaction was worked up by separating the aqueous layer from the organic. The aqueous layer was quenched with 10 mL of 3 M NaOH and then 20 mL of saturated bicarbonate solution. The aqueous layer was extracted with 3 x 20 mL ether. This organic layer was extracted with 50 mL of saturated sodium bicarbonate solution, 50 mL

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of brine, and dried over sodium sulfate. Each aqueous layer was back extracted with 3 x 20 mL of ether. Column chromatography (30 cm x 1.8 cm, silica gel) with 5 % ethyl acetate to 10 % ethyl acetate / hexane gave a yield of 22 % (0.026 g, 0.073 mmol). The yellow-orange band was isolated. The crude product also had minor spots on the TLC at $R_f = 0.32$ and two minor spots at $R_f = 0.14$ and 0.05 (10 % ethyl acetate / hexane). This compound **3-187** decomposes even when stored at $-20\text{ }^{\circ}\text{C}$. Unidentified blue and red bands appear during column chromatography after storage for one day.

Following the exact procedure from above with 0.65 mmol of **3-178** and 0.33 mmol of **2-60** at $60\text{ }^{\circ}\text{C}$ for 12 hours in dichloromethane replacing the volume of gas in the flask with CO on the last freeze thaw cycle, the yield was 17 %. At 60 ° for 12 hours in 1,2-dichloroethane under argon the yield was 29 %. At $60\text{ }^{\circ}\text{C}$ for 12 hours in toluene under argon the yield was 22 %. At $80\text{ }^{\circ}\text{C}$ for one hour in 1,2-dichloroethane, the yield was 34 %. At $80\text{ }^{\circ}\text{C}$ for one hour in toluene, the yield was 32 %. At $90\text{ }^{\circ}\text{C}$ for 20 minutes in 1,2-dichloroethane, the yield was 51 %. At $90\text{ }^{\circ}\text{C}$ for 20 minutes in toluene, the yield was 60 %. At $100\text{ }^{\circ}\text{C}$ for 13 minutes in toluene, the yield was 62 %.

^1H NMR (CDCl_3) δ : 1.4 - 1.5 (m, 6 H), 2.2 - 2.6 (m, 4 H), 4.56 (s, 1 H), 6.76 (d, 1 H, $J = 2.8\text{ Hz}$), 7.1 - 7.6 (m, 11 H); ^{13}C NMR (CDCl_3) δ : 24.54, 26.17, 53.09, 67.57, 127.61, 128.32, 128.55, 128.85, 129.23, 129.84, 131.71, 132.34, 132.94, 139.00, 146.17, 149.69, 186.24, 188.39; IR (thin film): 2934 m, 2851 w, 2801 w,

1651 :

(13), 2

77 (19

1651 s, 1597 w, 1298 m, 698 m; mass spectrum m/z (% rel intensity) 357 M^+
(13), 290 (6), 274 (28), 273 (42), 215 (8), 174 (17), 115 (32), 86 (62), 84 (100),
77 (19 Yellow oily solid (hexane), $R_f = 0.25$ (10 % ethyl acetate / hexane).

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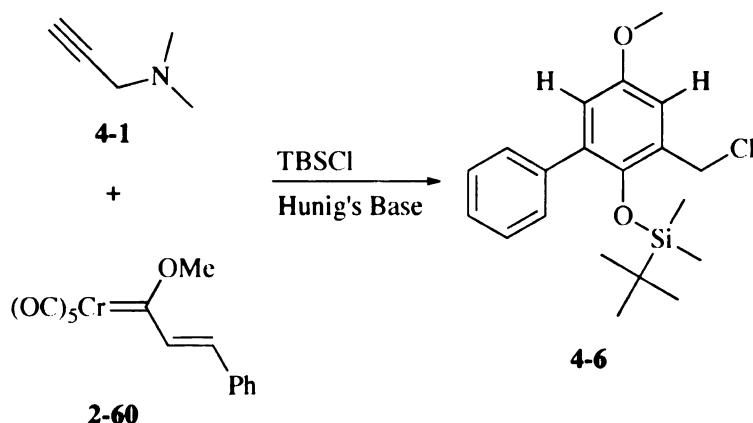
dichloro

mmol, 2

25.5 h

7.4 Chapter Four Experimental

Preparation of Compound 4-6



A magnetic stirring bar was placed into a flame-dried single neck flask that had been modified by replacement of the joint with a threaded high vacuum Teflon valve. To this flask was added styrene carbene complex **2-60** (0.2042 g, 0.604 mmol), dichloromethane (20 mL), TBSCl (0.30 g, 2.00 mmol), N,N-diisopropylethylamine (0.50 mL, 2.87 mmol), and N, N-dimethylpropargyl amine (0.0546 g, 0.66 mmol). Three freeze thaw cycles were done to remove oxygen from the solvent. The solution was heated at 80 °C for 2.5 hours. The reaction mixture was stirred over night at room temperature. The contents of the flask were poured onto about 3 cc of silica gel. The solvent was removed under reduced pressure. Column chromatograph (21.5 cm x 2 cm, silica gel) with 10 % dichloromethane : hexane to 20 % dichloromethane : hexane gave 0.049 g (0.13 mmol, 22 % yield) of **4-6**. Reaction under identical conditions at 61 ± 1 °C for 25.5 hours gave a yield of 39 % yield (0.24 mmol) of **4-6**.

$^1\text{H NMR}$

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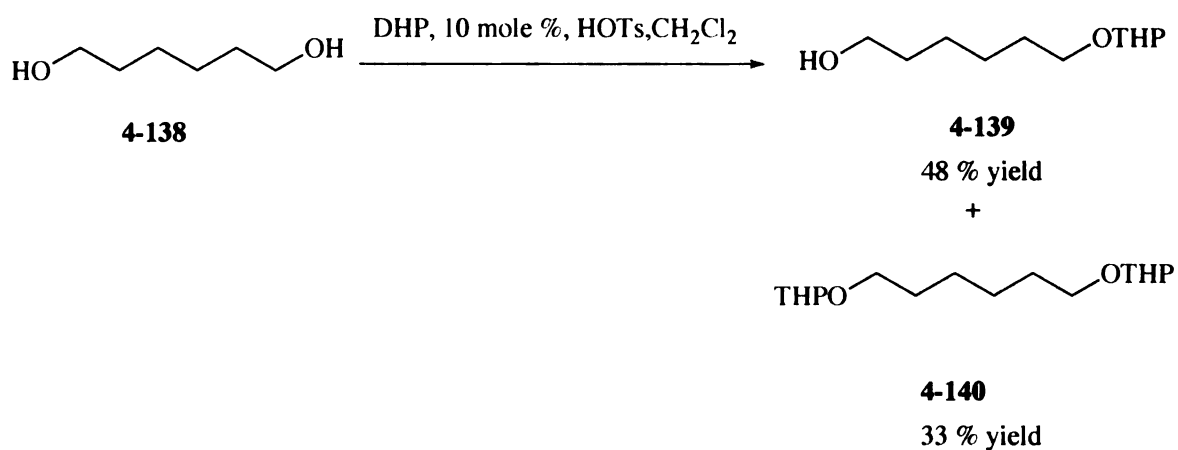
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^1H NMR (CDCl_3) δ : -0.39 (s, 6 H), 0.90 (s, 9 H), 3.79 (s, 3 H), 4.65 (s, 2 H), 6.81 (d, 1 H, J = 3.4 Hz), 6.96 (d, 1 H, J = 3.3 Hz), 7.28 - 7.38 (m, 3 H), 7.47 - 7.50 (m, 2 H); ^{13}C NMR (CDCl_3) δ : -4.64, 18.36, 25.90, 41.96, 55.66, 114.58, 117.08, 127.22, 128.13, 129.96, 129.99, 134.78, 139.44, 143.79, 154.10; IR (thin film) cm^{-1} 2928 s, 2855 s, 1607 w, 1466 s, 1437 m, 1258 m, 1204 m, 1055 m, 893 m, 839 m; mass spectrum m/z (% rel intensity) 364 M^+ (1, ^{37}Cl), 362 (1, ^{35}Cl), 328 (4), 327 (4), 269 (59), 255 (15), 241 (13), 291 (7), 181 (4), 169 (4), 165 (4), 115 (6), 93 (10). Yellow solid (hexane), mp 55 - 57 °C, R_f = 0.64 (30 % ethyl acetate : hexane).

Compounds 4-139 and 4-140



In a 500 mL round bottom flask was added 240 mL of dichloromethane, 1,6-hexanediol **4-138** (4.14 g, 35 mmol), THP (3.17 mL, 34 mmol), and tosylic acid (0.70 g, 3.7 moles). The reaction was monitored by TLC, and the reaction was complete in 1.5 hours. Column chromatography (24 cm x 4 cm, silica gel) with 20 % ethyl acetate / 2 % triethyl amine / hexane gave 3.28 g (33 %, 11.6

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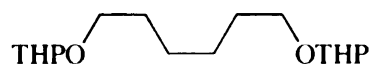
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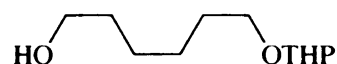
mmol) of **4-140** and 3.37 g (48 %, 16.8 mmol) of **4-139**. The spectroscopic information was identical to that reported in the literature.³⁶⁶

Compound 4-140



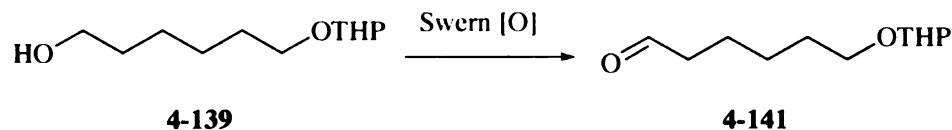
^1H NMR (CDCl_3) δ : 1.2 - 1.9 (m, 20 H), 3.3 - 3.6 (m, 4 H), 3.15 - 3.9 (m, 4 H), 4.52 (t, 2 H, $J = 4.0$ Hz); ^{13}C NMR (CDCl_3) δ : 19.43, 25.31, 25.91, 29.49, 30.56, 62.00, 67.28, 98.55; Yellow oil, $R_f = 0.65$ (50 % ethyl acetate / hexane).

Compound 4-139



^1H NMR (CDCl_3) δ : 1.2 - 1.9 (m, 15 H), 3.2 - 3.8 (m, 6 H), 4.54 (t, 1 H, 2.7 Hz); ^{13}C NMR (CDCl_3) δ : 19.41, 25.24, 25.39, 25.81, 29.44, 30.50, 32.41, 62.08, 62.28, 67.31, 98.62; Yellow oil, $R_f = 0.29$ (50 % ethyl acetate / hexane).

Compound 4-141



A 250 mL round bottom flask was charged with 64 mL of CH_2Cl_2 and DMSO (1.05 mL, 14.7 mmol). The contents of the flask were cooled to -78°C . To this solution was added oxalyl chloride (0.45 mL, 5.2 mmol) dropwise. Bubbling was noted. The contents of the flask were stirred for 15 minutes then

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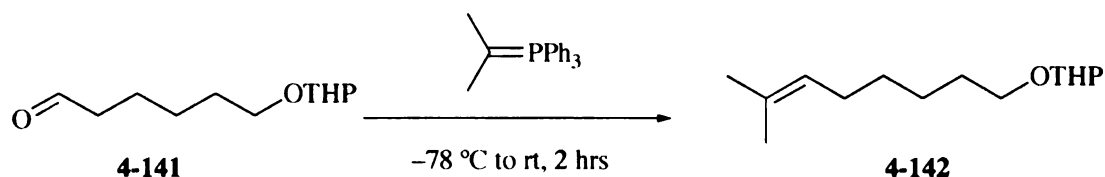
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alcohol **4-139** (1.03 g, 5.1 mmol) was added in a dropwise manner at $-78\text{ }^{\circ}\text{C}$. The solution was cloudy when the addition was completed. The solution was stirred for 20 minutes at $-78\text{ }^{\circ}\text{C}$ then 5 mL (36 mmol) of triethyl amine was added. The solution was allowed to warm to room temperature for one hour. The contents of the flask were poured into 100 mL of water (no acid was used in workup). The organic phase was washed with 100 mL of saturated bicarbonate. Each aqueous phase was back extracted with 3 x 15 mL of CH_2Cl_2 . The organic layers were combined and dried over magnesium sulfate and filtered. The organic solvent was removed under reduced pressure. Column chromatography (21 x 2.8 cm, silica gel) with 20 % ethyl acetate / hexane then 30 % ethyl acetate / hexane gave 0.95 g (4.79 mmol) of **4-141** (94 % yield). On a 9.8 g (49 mmol) scale the yield was 87 %. The spectroscopic characterization of this compound was identical to that previously reported.³⁶⁶

Compound 4-142



A 500 mL round bottom flask was charged with isopropyltriphenylphosphonium iodide (12.5 g, 28.8 mmol) and 250 mL of THF. The contents of the flask were cooled to $0\text{ }^{\circ}\text{C}$ and *n*-butyl lithium (1.6 M) in hexanes (16.1 mL, 25.8 mmol) was added dropwise. The reaction was allowed to warm to room temperature and stirred for three hours. The contents of the

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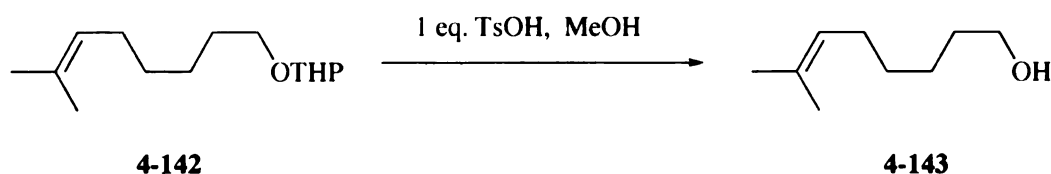
were

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500 mL round bottom flask were cooled to $-78\text{ }^{\circ}\text{C}$ and the aldehyde **4-141** (4.73 g, 23.6 mmol) was added dropwise quickly. The contents of the flask were poured into an equal volume of hexane and the organic portion filtered through Celite-503. Column chromatography (25 cm x 5.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 4.78 g (89 % yield, 23.0 mmol). Spectroscopic properties were identical to that previously reported.³⁶⁶

^1H NMR (CDCl_3) δ : 1.27 (qt, 5 H, $J = 3.8\text{ Hz}$), 1.39 - 1.54 (m, 6 H), 1.51 (s, 3 H), 1.56 - 1.63 (m, 1 H), 1.60 (d, 3 H, $J = 0.9\text{ Hz}$), 1.65 - 1.79 (m, 2 H), 1.89 (dd, 2 H, $J = 13.6, 6.6\text{ Hz}$), 3.24 - 3.34 (m, 1 H), 3.41 (dt, 1 H, $J = 11.0, 5.1\text{ Hz}$), 3.60 - 3.70 (m, 1 H), 3.74 - 3.84 (m, 1 H), 4.49 (t, 1 H, $J = 3.0\text{ Hz}$), 5.03 (tt, 1 H, $J = 7.2, 1.4\text{ Hz}$); ^{13}C NMR (CDCl_3) δ : 17.54, 19.58, 25.45, 25.61, 25.83, 27.89, 29.60, 29.64, 30.69, 62.14, 67.51, 98.69, 124.63, 131.11. Clear oil (hexane), $R_f = 0.62$ (30 % ethyl acetate / hexane).

Compound 4-143



A 500 mL flask was charged with methanol (200 mL), compound **4-142** (4.78 g, 21.1 mmol), and TsOH (2.05 g, 10.8 mmol). The contents of the flask were stirred for 6 hours at room temperature. The reaction mixture was extracted with 500 mL x 3 ethyl acetate and dried over magnesium sulfate. The

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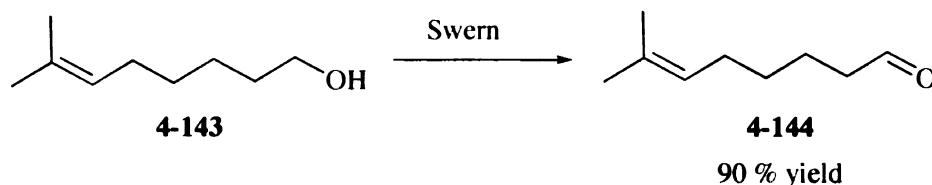
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resulting alcohol **4-143** was used without further purification. The yield of **4-143** was 80 % (2.40 g, 16.9 mmol). The yield varied from 40 - 80 %. High vacuum was avoided because the compound was slightly volatile. The spectroscopic properties were identical to those previously reported.³⁶⁶

¹H NMR (CDCl₃) δ : 1.25 - 1.36 (m, 4 H), 1.44 - 1.53 (m, 1 H), 1.55 (s, 3 H), 1.63 (d, 3 H, J = 1.0 Hz), 1.81 - 2.04 (m, 3 H), 3.57 (t, 2 H, J = 6.7 Hz), 5.06 (br t, 1 H, J = 7.2 Hz); ¹³C NMR (CDCl₃) δ : 17.58, 25.35, 25.64, 27.91, 29.61, 32.63, 62.74, 124.53, 131.31; Yellow oil (hexane), R_f = 0.28 (30 % ethyl acetate / hexane).

Compound 4-144



A flask was charged with dichloromethane (500 mL) and DMSO (11.6 g, 10.5 mL, 147 mmol). The contents of the flask were cooled to -78 °C. To this solution was added oxalyl chloride (6.7 g, 4.6 mL, 53 mmol) in a dropwise manner. The release of bubbles was noted. The solution was stirred for 15 minutes. The alcohol **4-143** (6.83 g, 48 mmol) was added in a dropwise manner. The solution was stirred for 30 minutes and it was noted that the solution turned cloudy upon completion of the addition of the alcohol. Triethyl amine (47 mL, 336 mmol) was added quickly. The solution was allowed to warm to room temperature for an hour. The contents of the flask were poured into an extraction

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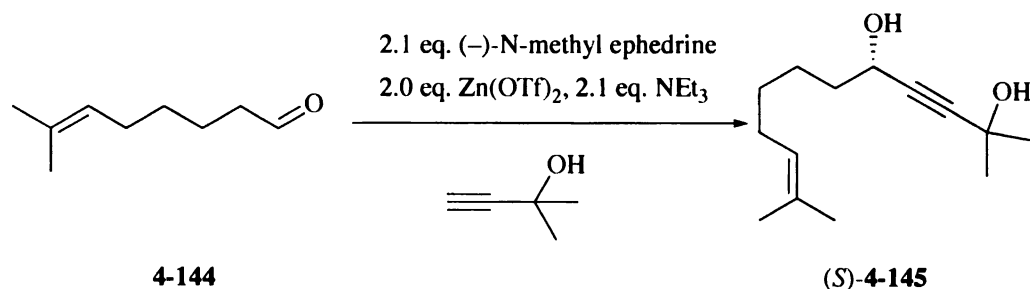
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funnel and washed with 250 mL of saturated ammonium chloride solution. The organic layer was collected and the ammonium chloride solution was extracted with DCM (50 mL x 2). The organic layers were combined and washed with brine and the brine solution was extracted with DCM (30 mL x 2). The organic layers were combined and dried over sodium bicarbonate and magnesium sulfate. The organic solvent was removed under reduced pressure. The exposure of **4-144** to high vacuum was limited due to the fact that it was volatile. Column chromatography with 5 % ethyl acetate / hexane gave 6 g (43.2 mmol) of **4-144** (90 % yield,) as an oil. This compound had spectroscopic properties identical to those previously reported.³⁶⁶

Preparation of (*S*)-**4-145**



A flask was charged with Zn(OTf)_2 (4.54 g, 12.5 mmol), (–)-N-methyl ephedrine (2.35 g, 13.1 mmol), triethyl amine (1.8 mL, 12.9 mmol), and 13 mL of toluene. This produced a cloudy suspension. The suspension was stirred rapidly for two hours at room temperature. The compound 2-methylbut-3-yn-2-ol (1.26 mL, 13.0 mmol) was added by rapid dropwise addition. The solution was stirred for 15 minutes then a 0.4 M solution of the aldehyde **4-144** (0.86 g, 6.2 mmol) was added dropwise via syringe pump over 4 hours. The solution was

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stirred 30 to 60 minutes after the addition of the aldehyde **4-144**. The reaction mixture was poured into 50 mL of saturated NH_4Cl . This was back extracted with 50 mL, 2 x 20 mL of ethyl acetate. The organics were combined and extracted with 20 mL of brine solution. The aqueous layer was back extracted with 3 x 20 mL of ethyl acetate. The organic layers were combined and dried over magnesium sulfate and sodium bicarbonate. Column chromatography (25 x 3.8 cm, silica gel) with 30 % ethyl acetate / hexane then 50 % ethyl acetate / hexane gave 1.15 g (82 % yield, 5.08 mmol) of (*S*)-**4-145**. On a 12.5 mmole scale the yield was 74 % following an identical procedure. The ee was determined to be 98 % after conversion to alcohol (*S*)-**4-150** over the following steps.

^1H NMR (CDCl_3) δ : 1.34 (q, 2 H, $J = 7.3$ Hz), 1.37 - 1.45 (m, 2 H), 1.49 (s, 6 H), 1.57 (s, 3 H), 1.60 - 1.72 (m, 2 H), 1.66 (s, 3 H), 1.96 (q, 2 H, $J = 7.1$ Hz), 2.37 (br s, 2 H), 4.35 (t, 1 H, $J = 6.64$ Hz), 5.08 (t, 1 H, $J = 7.1$ Hz); ^{13}C NMR (CDCl_3) δ : 17.66, 24.82, 25.67, 27.86, 29.44, 31.35, 37.69, 62.36, 65.10, 83.16, 89.55, 124.45, 131.49; IR (thin film): 3341 br s, 2931 s, 2932 s, 2859 s, 1456 m, 1377 m, 1237 m, 1167 m, 1026 w, 953 w cm^{-1} ; mass spectrum m/z (% rel intensity) 224 M^+ (10), 207 (38), 193 (14), 191 (19), 189 (21), 173 (35), 163 (17), 149 (17), 145 (39), 131 (32), 121 (22), 117 (25), 105 (78), 95 (100), 81 (96), 65 (41); Clear oil (hexane), $R_f = 0.1$ (30 % ethyl acetate / hexane). $[\alpha]_D^{22} +3.5^\circ$ (c 1.33, CH_2Cl_2).

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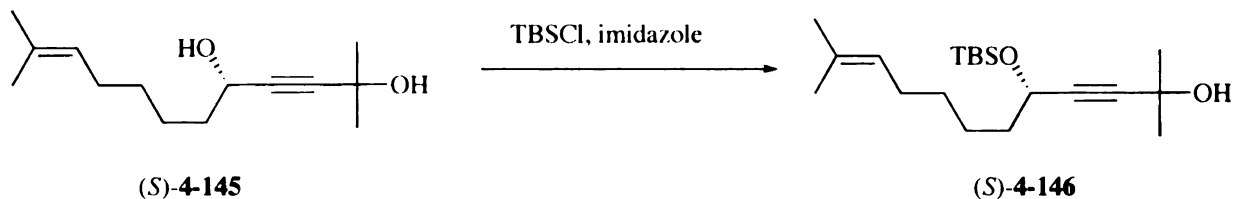
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Preparation of (S)-4-146



A 100 mL round bottom flask was charged with diol (S)-4-145 (0.87 g, 3.9 mmol, 98 % ee), imidazole (0.31 g, 4.5 mmol), TBSCl (0.59 g, 3.9 mmol), and 50 mL of DMF. The reaction mixture was stirred for 12 to 24 hours at room temperature. The contents of the flask were poured into 30 mL of saturated NH_4Cl and back extracted with 3 x 30 mL of CH_2Cl_2 . The organic layers were combined and dried over sodium bicarbonate and magnesium sulfate and filtered. The organic solvent was removed under reduced pressure. Column chromatography (25 x 3.0 cm, silica gel) with hexane then 5 % ethyl acetate / hexane then 10 % ethyl acetate / hexane gave 1.03 g (3.08 mmol) of (S)-4-146 (79 % yield, 3.08 mmol).

Compound (S)-4-145 (0.14 g, 0.63 mmol, 98 % ee) was added to a 25 mL flask along with 10 mL of CH_2Cl_2 . The contents of the flask were cooled to 0 °C, and 2,6-lutidine (0.15 mL, 1.3 mmol) was added; lutidine must be added before the triflate or decomposition occurred. To this flask at 0 °C was added TBSOTf (0.15 mL, 0.65 mmol) and the reaction was stirred for 15 minutes at 0 °C and the reaction was allowed to warm to room temperature over 45 minutes. The reaction was quenched by pouring it into 10 mL of saturated NH_4Cl . The

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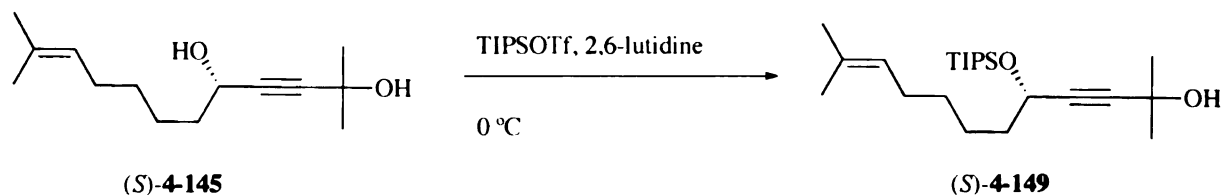
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aqueous layer was extracted with 3 x 10 mL of CH₂Cl₂. The organic layers were combined and dried over sodium bicarbonate and magnesium sulfate. The liquid was filtered through filter paper, and the solvent was removed under reduced pressure. Column chromatography (26 x 1.8 cm, silica gel) with hexane then 5 % ethyl acetate / hexane then 10 % ethyl acetate / hexane gave 0.16 g (67 %, 0.42 mmol) of (*S*)-**4-146**.

¹H NMR (CDCl₃) δ: 0.07 (s, 3 H), 0.10 (s, 3 H), 0.87 (s, 9 H), 1.24 - 1.43 (m, 5 H), 1.47 (s, 6 H), 1.52 - 1.65 (m, 1 H), 1.57 (s, 3 H), 1.65 (s, 3 H), 1.91 - 2.04 (m, 3 H), 4.31 (t, 1 H, *J* = 6.25 Hz), 5.07 (t, 1 H, *J* = 7.12 Hz); ¹³C NMR (CDCl₃) δ: -4.99, -4.48, 17.64, 18.22, 24.93, 25.69, 25.77, 27.88, 29.88, 31.29, 31.36, 38.49, 62.81, 65.06, 83.94, 88.44, 124.57, 131.32; IR (thin film): 3372 br s, 2932 s, 2859 m, 1474 w, 1364 w, 1254 w, 1165 w, 839 m cm⁻¹; mass spectrum *m/z* (% rel intensity) M⁺ (Not found), 281 M⁺-58 (1, loss of acetone), 223 (4), 181 (10), 167 (7), 149 (21), 147 (31), 139 (20), 133 (46), 120 (13), 105 (29), 95 (45), 75 (100), 67 (31), 55 (15); Clear thick oil (hexane), R_f = 0.45 (30 % ethyl acetate / hexane). [α]_D²² -35.5° (c 1.17, CH₂Cl₂) at 98 % ee.

Compound 4-149



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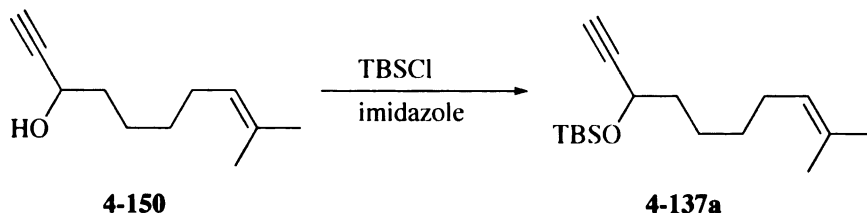
69 (55

A 100 mL flask was charged with compound (S)-4-145 (1.68 g, 7.5 mmol, 98 % ee), DCM, and 2,6-lutidine (1.3 mL, 11.2 mmol, must be added before the triflate). The reaction mixture was cooled to 0 °C. The TIPSOTf (2.0 mL, 7.5 mmol) was added dropwise and the solution was allowed to warm to room temperature over 1 hour. The reaction mixture was poured into 50 mL of saturated ammonium chloride and the organic layers separated from the aqueous. The aqueous layer was back extracted with 3 x 50 mL of DCM. The organic layers were combined and dried over sodium bicarbonate and magnesium sulfate and the solution was filtered through filter paper. The organic solvent was removed under reduced pressure. Column chromatography (25 cm x 3.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 2.08 g (73 %, 5.48 mmol) of (S)-4-149.

^1H NMR (CDCl_3) δ : 1.00 - 1.10 (m, 21 H), 1.32 (p, 2 H, J = 7.2 Hz), 1.42 (p, 2 H, J = 7.4 Hz), 1.47 (s, 6 H), 1.58 (s, 3 H), 1.62 - 1.72 (m, 2 H), 1.66 (s, 3 H), 1.96 (q, 2 H, J = 7.2 Hz), 4.45 (t, 1 H, J = 6.4 Hz), 5.09 (t, 1 H, J = 7.1 Hz); ^{13}C NMR (CDCl_3) δ : 12.27, 17.67, 18.04, 24.74, 25.69, 27.93, 29.55, 31.30, 38.79, 62.95, 65.16, 84.12, 88.41, 124.66, 131.33; IR (thin film): 3360 br m, 2944 s, 2867 s, 1464 m, 1377 w, 1100 w, 884 w, 679 w cm^{-1} ; mass spectrum m/z (% rel intensity) 337 $\text{M}^+ - 43$ (1), 321 (1), 279 (3), 267 (1), 253 (6), 215 (1), 189 (7), 169 (5), 147 (16), 131 (58), 123 (11), 119 (14), 111 (11), 103 (84), 95 (71), 75 (100), 69 (55), 61 (45); Clear thick oil (hexane), R_f = 0.46 (30 % ethyl acetate / hexane).

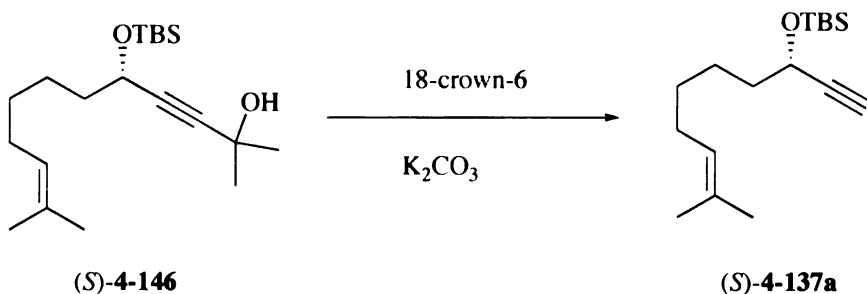
$[\alpha]_D^{22} -15.3^\circ$ (c 0.935, CH_2Cl_2) at 98 % ee.

Preparation of Racemic Compound 4-137a



The alcohol **4-150** (2.32 g, 13.9 mmol) was treated with TBSCl (2.4 g, 15.9 mmol) and imidazole (1.08 g, 15.9 mmol) in DMF (150 mL). The reaction was stirred for 18 to 24 hours at room temperature. The contents of the flask were poured onto 400 mL of water and the water layer was back extracted with ether 4 x 200 mL. The ether layers were combined and dried with magnesium sulfate. Column chromatography (25 x 3.8 cm, silica gel) with hexane, 10 % ethyl acetate / hexane, and 20 % ethyl acetate / hexane gave 3.11 g (80 % yield, 11.1 mmol) of racemic **4-137a** after the removal of the solvent under reduced pressure. The spectral data can be found below for the preparation of (*S*)-**4-137a**.

Preparation of (*S*)-4-137a



A 50 ml round bottom flask was charged with alkyne (*S*)-**4-146** (0.48 g, 1.4 mmol, 98 % ee), 18-crown-6 (0.45 g, 1.7 mmol), K_2CO_3 (0.20 g, 1.4 mmol), and

20 mL of toluene. The contents of the flask were brought to reflux under a rapidly flowing stream of nitrogen. A straight condenser was used (a coiled condenser does not work). Additional K_2CO_3 (0.11 g, 0.8 mmol) was added after one day of reflux. The reaction was refluxed an additional day. The toluene was removed under reduced pressure. Column chromatography (15 cm x 3.8 cm, silica gel) with hexanes then with 5 % ethyl acetate / hexane and finally with 10 % ethyl acetate / hexane gave 0.37 g of (*S*)-**4-137a** (92 % yield, 1.29 mmol).

^1H NMR (CDCl_3) δ : 0.09 (s, 3 H), 0.11 (s, 3 H), 0.89 (s, 9 H), 1.21 - 1.51 (m, 4 H), 1.58 (s, 3 H), 1.61 - 1.70 (m, 2 H), 1.66 (s, 3 H), 1.95 (q, 2 H, $J = 7.1$ Hz), 2.34 (d, 1 H, $J = 2.2$ Hz), 4.30 (dt, 1 H, $J = 2.0$ Hz, $J = 6.5$ Hz), 5.09 (bt, 1 H, $J = 7.3$ Hz);

^{13}C NMR (CDCl_3) δ : -5.23, -4.70, 17.56, 18.17, 24.74, 25.71, 25.77, 27.79, 29.32, 38.51, 62.56, 71.84, 85.65, 124.57, 131.32; IR (thin film): 3312 m, 2930 s, 2054 s, 1472 w, 1404 w, 1252 m, 1098 m, 837 s, 777 s cm^{-1} ; mass spectrum m/z

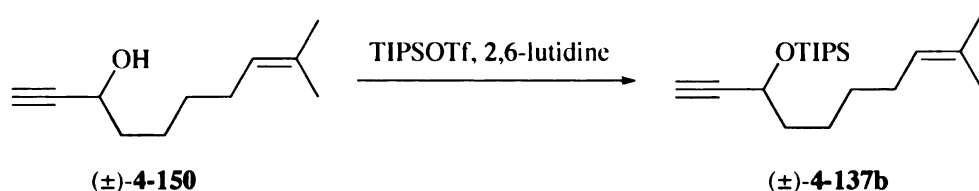
(% rel intensity) 280 M^+ (1), 224 (1), 203 (1), 181 (3), 169 (3), 167 (3); Anal calcd

for $\text{C}_{17}\text{H}_{32}\text{OSi}$: C, 72.79; H, 11.50. Found; C, 72.61; H, 11.68. Clear oil

(hexane), $R_f = 0.69$ (10 % ethyl acetate / hexane). For optically active material,

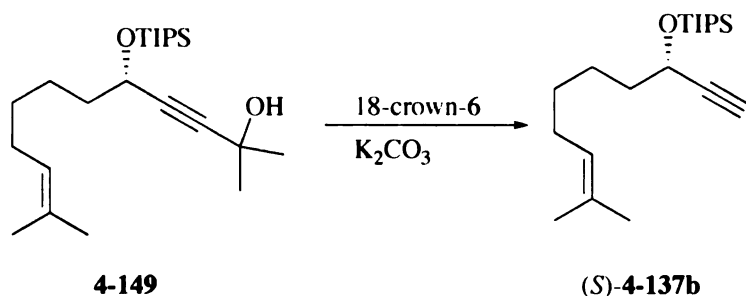
$[\alpha]_D^{20} -34.6^\circ$ (c 0.49, CH_2Cl_2) at 98 % ee.

Preparation of Racemic 4-137b



A 50 mL flask was charged with compound **(±)-4-150** (0.36 g, 2.2 mmol), dichloromethane (20 mL), and 2,6-lutidine (0.28 mL, 2.4 mmol). The contents of the flask were cooled to 0 °C and TIPSOTf (0.65 mL, 2.4 mmol) was added dropwise. The reaction mixture was stirred for 30 minutes. The layers separated. Saturated ammonium chloride (15 mL) was added to the stirring solution. The organic layer was back extracted with dichloromethane (20 mL x 3). The organic layers were combined and solid sodium bicarbonate was added until no bubbles were noted and the solution dried over magnesium sulfate. The solution was then gravity filtered. Column chromatography (20 x 3.2 cm, silica gel) with 5 % ethyl acetate / hexane then 10 % ethyl acetate / hexane gave 0.59 g (84 %, 1.84 mmol). The spectroscopic properties are shown below for **(S)-4-137b**.

Preparation of (S)-4-137b

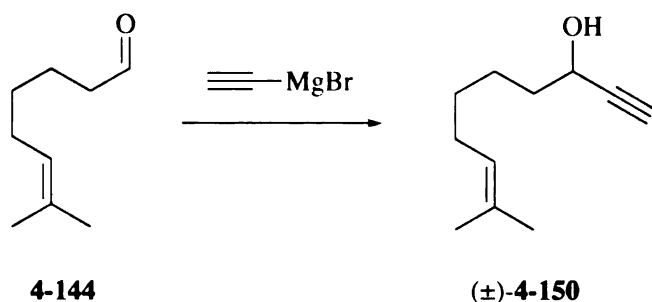


A 100 mL round bottom flask was charged with alkyne **(S)-4-149** (2.08 g,

5.5 mmol, 98 % ee), K_2CO_3 (0.76 g, 5.5 mmol), 18-crown-6 (1.47 g, 5.5 mmol), and 55 mL of toluene. The contents of the flask were brought to reflux with a rapid nitrogen flow across the top of the straight condenser (a coiled condenser does not work). The contents of the flask were refluxed for 48 hours. The solvent was removed under reduced pressure. Column chromatography (20 x 5.8 cm, silica gel) with hexane then 5 % ethyl acetate / hexane gave 1.60 g (91 % yield, 5.0 mmol) of (*S*)-**4-137b**.

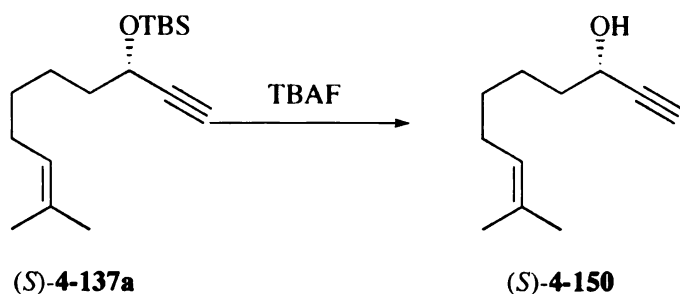
^1H NMR (CDCl_3) δ : 1.04 - 1.12 (m, 3 H), 1.06 (d, 18 H), 1.26 - 1.40 (m, 2 H), 1.41 - 1.53 (m, 2 H), 1.57 (s, 3 H), 1.65 - 1.72 (m, 2 H), 1.66 (s, 3 H), 1.97 (q, 2 H, J = 7.1 Hz), 2.35 (d, 1 H, J = 2.0 Hz), 4.44 (dt, 1 H, J = 2.1, 6.3 Hz), 5.09 (bt, 1 H, J = 7.1 Hz); ^{13}C NMR (CDCl_3) δ : 12.24, 17.66, 18.01, 24.57, 25.70, 27.95, 29.58, 38.74, 62.89, 71.91, 85.78, 124.61, 131.35; IR (thin film): 3312 m, 2944 m, 2867 s, 1462 w, 1101 m cm^{-1} ; mass spectrum m/z (% rel intensity) 323 M^+ +1 (6), 322 M^+ (8), 321 (12), 279 (100), 237 (19), 209 (10), 195 (25), 169 (30), 157 (10), 147 (38), 131 (61), 103 (54), 95 (82); Anal calcd for $\text{C}_{20}\text{H}_{38}\text{OSi}$: C, 74.46; H, 11.87. Found; C, 74.14; H, 11.81. Clear oil (hexane), R_f = 0.75 (30 % ethyl acetate / hexane). For optically active material $[\alpha]_D^{22}$ -17.8° (c 1.62, CH_2Cl_2) at 98 % ee.

Preparation of Racemic ($\pm$)-4-150



In a 500 mL round bottom flask charged with aldehyde **4-144** (3.32 g, 23.7 mmol) at 0 °C was added ethynyl magnesium bromide (0.5 M) in THF (95 mL, 47.5 mmol). The reaction was warmed to room temperature and the contents of the flask were stirred for 3 hours. The contents of the flask were poured into 200 mL of water. The water layer was back extracted with 50 mL x 3 of ethyl acetate. The organic layer was washed with brine 20 mL and the brine layer was extracted with 20 mL x 2 ethyl acetate. The organic layers were combined and dried with magnesium sulfate. The organic layer was removed under reduced pressure. Column chromatography (25 x 5.8 cm, silica gel) with 10 % ethyl acetate / hexane, 20 % ethyl acetate / hexane, and 30 % ethyl acetate / hexane which resulted in 2.41 g (61 % yield, 14.5 mmol).

Formation of (*S*)-4-150



Compound (*S*)-**4-137a** (0.045 g, 0.16 mmol, 98 % ee) and THF (2 mL)

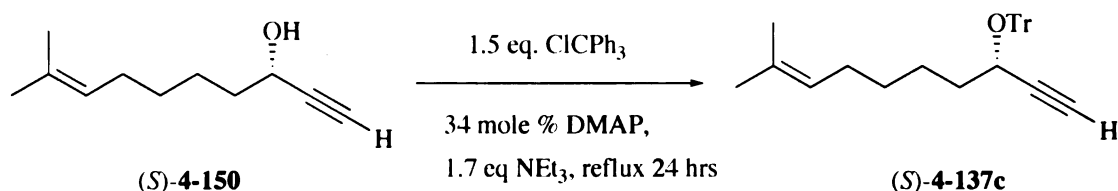
was placed into a 10 mL round bottom flask. The contents of the flask were cooled to 0 °C and TBAF (0.17 mL, 0.17 mmol) was added dropwise. The reaction was stirred until it was complete by TLC, which was about 30 minutes. The contents of the flask were poured into 5 mL of water, which was extracted, with 3 x 20 mL of CH₂Cl₂. The solution was dried over magnesium sulfate and sodium bicarbonate. The solution was filtered and the solvent removed under reduced pressure. This gave 0.025 g (93 % yield, 0.15 mmol).

This compound was analyzed by chiral GC with a Chiraldex B-MB, 30 m x 0.25 mm column. The column was at 110 °C with no split and 1 mL/min flow rate. The chiral compound was compared to the racemate (98 % ee). The retention times were 43.64 minutes (major) and 45.30 minutes (minor).

¹H NMR (CDCl₃) δ: 1.28 - 1.51 (m, 4 H), 1.58 (s, 3 H), 1.66 (s, 3 H), 1.68 - 1.75 (m, 2 H), 1.81 (br s, 1 H), 1.97 (q, 2 H, *J* = 7.2 Hz), 2.44 (d, 1 H, *J* = 2.1 Hz), 4.34 (qd, 1 H, *J* = 6.1 Hz, 2.0 Hz), 5.09 (t, 1 H, *J* = 7.2 Hz); ¹³C NMR (CDCl₃) δ: 17.60, 24.66, 25.63, 27.82, 29.40, 37.48, 62.14, 72.73, 85.00, 124.38, 131.42; IR (thin film): 3353 bm, 3306 s, 2930 s, 2859 s, 1455 w, 1377 w, 1078 w, 1019 w cm⁻¹; mass spectrum *m/z* (% rel intensity) 166 M⁺ (4), 165 (24), 151 (15), 147 (17), 137 (22), 133 (19), 123 (31), 111 (100), 97 (52), 95 (58), 81 (37), 67 (34), 55 (28); Anal calcd for C₁₁H₁₈O: C, 79.46; H, 10.91. Found; C, 79.51; H, 10.96. Clear oil (hexane), R_f = 0.43 (30 % ethyl acetate / hexane). [α]_D²² -2.0° (c 1.27,

CH₂Cl₂) at 98 % ee. $[\alpha]_D^{22} -1.0^\circ$ (c 0.61, CH₂Cl₂) at 98 % ee.

Compound 4-137c

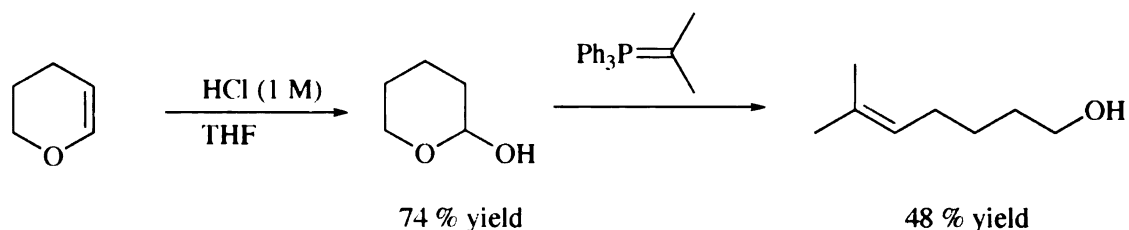


A flask was charged with compound (S)-4-150 (0.35 g, 2.1 mmol, 98 % ee), trityl chloride (0.89 g, 3.2 mmol), triethyl amine (0.3 mL, 2.2 mmol), DMAP (0.09 g, 0.7 mmol), and DCM (25 mL). The contents of the flask were refluxed for 72 hours and the reaction was followed by TLC (KMnO₄ stain). When the TLC did not indicate further conversion the solution was concentrated under reduced pressure, and the residue was subjected to column chromatography (5 % ethyl acetate / hexane and then with 10 % ethyl acetate / hexane on 25 x 3.1 cm of silica gel). This gave 0.25 g (0.61 mmol) of product of (S)-4-137c (29 % yield) and 0.21 g of starting material (58 % recovery).

¹H NMR (CDCl₃) δ: 1.10 - 1.23 (m, 2 H), 1.24 - 1.38 (m, 2 H), 1.38 - 1.50 (m, 2 H), 1.56 (s, 3 H), 1.67 (d, 3 H, *J* = 1.0 Hz), 1.88 (q, 2 H, *J* = 7.2 Hz), 2.11 (d, 1 H, *J* = 2.1 Hz), 3.99 (m, 1 H), 5.05 (br t, 1 H, *J* = 7.1 Hz), 7.20 - 7.32 (m, 9 H), 7.51 - 7.55 (m, 6 H); ¹³C NMR (CDCl₃) δ: 17.66, 24.44, 25.68, 27.85, 29.48, 36.24, 64.46, 72.86, 84.22, 87.82, 124.63, 127.04, 127.65, 129.05, 131.24, 144.45; IR (thin film): 3303 m, 3059 w, 2961 s, 2926 s, 2853 m, 1449 m, 1262 s, 1127 s, 1026 s cm⁻¹; mass spectrum *m/z* (% rel intensity) 408 M⁺ (<1), 243 (100, CPh₃),

184 (5), 165 (12), 91 (1), 77 (6); Clear thick oil (hexane), $R_f = 0.69$ (30 % ethyl acetate / hexane). $[\alpha]_D^{22} -45.8^\circ$ (c 0.85, CH_2CH_2) at 98 % ee.

Formation of 6-Methylhept-5-en-1-ol

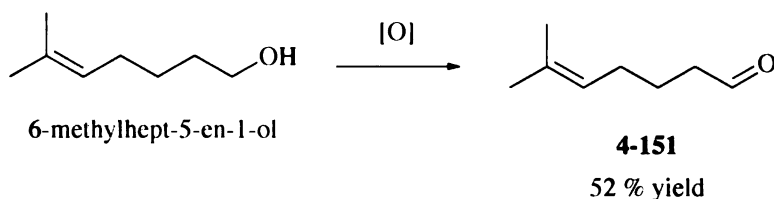


Following a known literature preparation,³⁶⁷ a 500 mL round bottom flask was charged with 3,4-dihydro-2*H*-pyran (20 mL, 21.9 mmol), THF (200 mL), and 1 M HCl (40 mL) at 0 °C. The contents of the flask were allowed to warm to room temperature and stirred for 4 hours. The solution was neutralized to pH ~7 with 3 M NaOH and extracted with 100 mL x 3 of ether. The ether layers were combined and extracted with 150 mL of brine, and the brine was back extracted with 50 mL of ether. The organic layers were combined. The solvent was dried with magnesium sulfate and filtered through Celite. The solvent was removed under reduced pressure. Kugelrohr distillation at 10 mm Hg and 120 - 160 °C gave 16.7 g (16.3 mmol, 74 % yield) of tetrahydro-2-hydroxy-2*H*-pyran as a clear oil. This compound was used without further purification. The spectroscopic properties were identical to that previously reported.³⁶⁷ This procedure was done twice to obtain enough tetrahydro-2-hydroxy-2*H*-pyran for the next step.

A 2 L three neck round bottom was charged with isopropyltriphenylphosphonium iodide (95 g, 22.0 mmol), THF (1 L), potassium

hydride (30 g, 22.4 mmol), and lastly tetrahydro-2-hydroxy-2*H*-pyran (22.3 g, 21 mmol) was added dropwise. The flask was equipped with a water-cooled reflux condenser. The unused necks of the flask were sealed with rubber septa. The contents of the flask were brought to reflux for three hours. The reaction mixture was cooled and poured into 100 mL of water and extracted with ether (50 mL x 3). The ether layers were combined and extracted with brine. The brine was extracted with 50 mL x 2 of ether. The ether layers were combined and dried with magnesium sulfate and filtered through Celite. The solvent was removed under reduced pressure. Column chromatography (30 cm x 4 cm, silica gel) with 30 % ethyl acetate / hexane gave 1.26 g (0.98 mmol, 48 % yield) of 6-methylhept-5-en-1-ol. This compound was used without further purification and the spectroscopic properties were identical to those previously reported.³⁶⁷

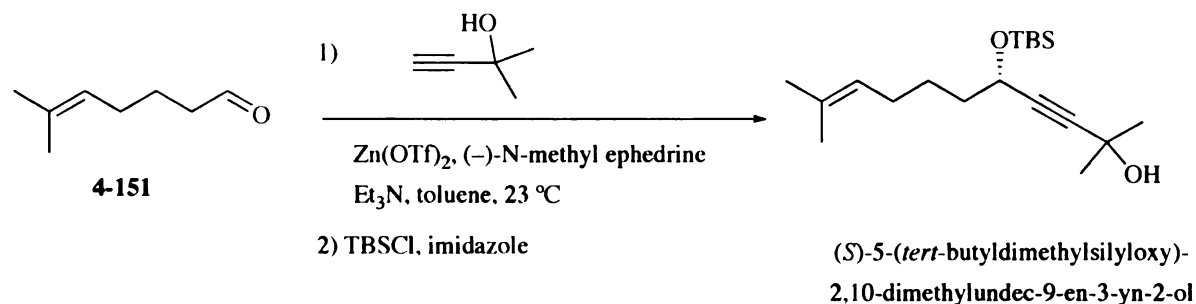
Compound 4-151



A 500 mL round bottom flask was charged with DMSO (3.5 mL, 49.3 mmol) and dichloromethane. The contents of the flask were cooled to $-78\text{ }^{\circ}\text{C}$ and oxalyl chloride (1.6 mL, 18.2 mmol) was added dropwise. The solution was stirred for 10 minutes while a gas was observed to evolve. The compound 6-methylhept-5-en-1-ol (2.1 g, 16.5 mmol) was added dropwise to the flask. The contents of the flask were allowed to stir at $-78\text{ }^{\circ}\text{C}$ for 20 minutes. Triethyl amine

(11.6 g, 115 mmol) was then added. The reaction was stirred and warmed to room temperature over an hour. The contents of the reaction were poured into 300 mL of 1 M HCl and extracted. The layers were separated and the aqueous layer was extracted with 50 mL x 3 of dichloromethane. The organic layers were combined and extracted with brine. The brine layer was back extracted with 50 mL x 2 of dichloromethane. The organic layers were combined and dried over magnesium sulfate and sodium bicarbonate. The solution was filtered through Celite. Column chromatography (23 x 4.3 cm, silica gel) of the residue with 10 % ethyl acetate / hexane gave 1.09 g (52 % yield, 8.7 mmol) as a yellow oil. The spectroscopic properties were identical to those previously reported.³⁶⁷

Preparation of (*S*)-5-(*tert*-butyldimethylsilyloxy)-2,10-dimethylundec-9-en-3-yn-2-ol



A flask was charged with zinc triflate (5.45 g, 15.0 mmol), (–)-*N*-methyl ephedrine (2.846 g, 15.8 mmol), toluene (41 mL), and triethyl amine (2.2 mL, 15.8 mmol). This suspension was stirred for 2 hours at room temperature and 3-methyl-1-butyn-3-ol (1.5 mL, 15.5 mmol) was added. The reaction mixture was stirred for 15 minutes. The compound 2-methyl-2-hepten-7-al **4-151** (0.95 g, 7.5 mmol) was added as a 0.4 M solution in toluene over 4 hours via a syringe pump.

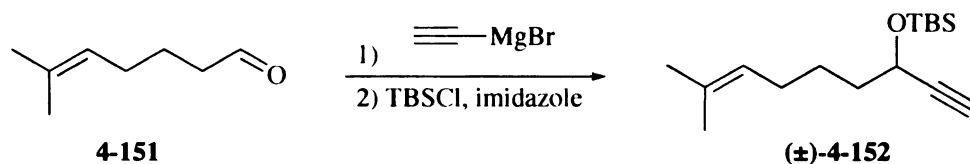
After the addition, the solution was stirred an addition 30 to 45 minutes. The TLC was checked for completion of the reaction. The contents of the flask were poured into 100 mL of saturated ammonium chloride solution. The layers were separated and the organic layer collected. The aqueous layer was back extracted with 3 x 100 mL of DCM (ethyl acetate gave higher yields). The organic layers were combined and dried over solid sodium bicarbonate and magnesium sulfate. The solvent was filtered and removed under reduced pressure. Column chromatography (15 cm x 3.8 cm, silica gel) with 30 % ethyl acetate / hexane then 50 % ethyl acetate / hexane gave 1.04 g (66 % yield, 4.95 mmol). This was not elementally pure and significant impurities were noted in the NMR. The compound was used without further purification to be cleaned-up in the next synthetic transformation.

A flask was charged with the diol, DMF (50 mL), imidazole (0.43 g, 6.2 mmol), and TBSCl (0.76 g, 5.03 mmol). The reaction mixture was stirred overnight at room temperature. The contents of the flask were poured into 100 mL of saturated ammonium chloride and back extracted with 3 x 50 mL DCM. The organic layers were combined and dried over sodium bicarbonate and magnesium sulfate. Column chromatography (25 cm x 4.3 cm, silica gel) with 5 % ethyl acetate / hexane gave 1.055 g (45 % yield over two steps, 3.38 mmol). The enantiomeric excess was 98 % determined on non-8-en-1-yn-3-ol.

$^1\text{H NMR}$ (CDCl_3) δ : 0.08 (s, 3 H), 0.10 (s, 3 H), 0.88 (s, 9 H), 1.32 - 1.45 (m, 2 H), 1.47 (s, 6 H), 1.55 - 1.68 (m, 2 H), 1.57 (s, 3 H), 1.66 (d, 3 H, $J = 1.0$ Hz), 1.86 (br

s, 1 H), 1.96 (q, 2 H, $J = 7.2$ Hz), 4.32 (t, 1 H, $J = 6.3$ Hz), 5.08 (br t, 1 H, $J = 7.1$ Hz); ^{13}C NMR (CDCl_3) δ : -4.95, -4.45, 17.67, 18.23, 25.52, 25.68, 25.80, 27.57, 31.33, 31.39, 38.22, 62.83, 65.10, 83.97, 88.50, 124.42, 131.59; IR (thin film): 3355 m, 2930 s, 2859 s, 1473 m, 1362 m, 1256 m, 1167 m, 1096 m, 837 m, 777 m cm^{-1} ; mass spectrum m/z (% rel intensity) 227 $\text{M}^+ - 97$ (5), 224 (7), 210 (4), 207 (6), 185 (86), 167 (30), 157 (10), 149 (8), 143 (3), 123 (42), 99 (74), 75 (100), 67 (12), 59 (15); HRMS (Q-ToF) calcd for $\text{C}_{19}\text{H}_{40}\text{NO}_2\text{Si}$ ($+\text{NH}_4$) m/z 342.2828, meas 342.2818. Clear oil (hexane), $R_f = 0.51$ (30 % ethyl acetate / hexane). $[\alpha]_D^{20} -2.0^\circ$ (c 0.505, CH_2Cl_2).

Preparation of racemic ($\pm$)-4-152

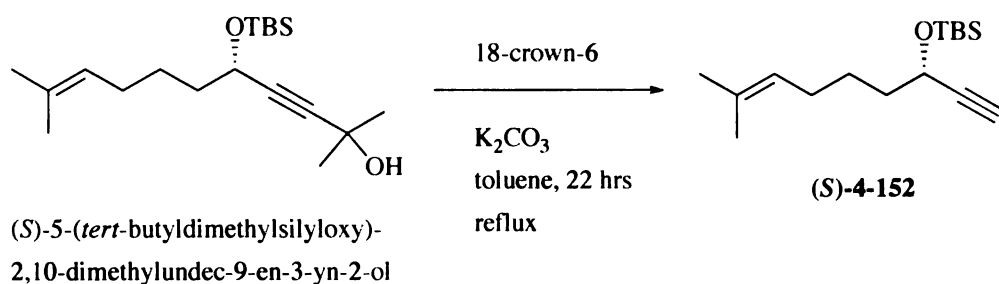


For racemic material, aldehyde **4-151** (0.45 g, 3.6 mmol) in THF (25 mL) was treated with ethynyl magnesium bromide (14 mL, 7.0 mmol) at -78°C and allowed to warm to 0°C . The reaction mixture was stirred at 0°C for 1 hour. The reaction mixture was poured into 50 mL of saturated ammonium chloride and back extracted with ether (2 x 50 mL), brine (100 mL), ether (3 x 50 mL), and the organic layers were combined. The solvent was dried over solid sodium bicarbonate and magnesium sulfate. The solvent was removed under reduced pressure and the resulting propargyl alcohol was used without further purification.

The spectroscopic properties of 8-methylnon-7-en-1-yn-3-ol were identical to that previously reported.³⁶⁸

A 100 mL flask was charged with the residue from the above reaction (3.6 mmol) along with DMF (40 mL), imidazole (0.27 g, 4.0 mmol), and TBSCl (0.55 g, 3.6 mmol). The reaction mixture was stirred overnight at room temperature. The reaction mixture was poured into 20 mL of water and back extracted with ethyl acetate (10 mL x 3). The organic layers were combined and dried over solid sodium bicarbonate and magnesium sulfate. The solution was then filtered through fluted filter paper and the remaining solvent was removed under reduced pressure. Column chromatography (20 x 2.8 cm, silica gel) with 10 % ethyl acetate / hexane gave 0.69 g (72 %, 2.6 mmol). The spectroscopic properties are reported below.

Preparation of (S)-4-152

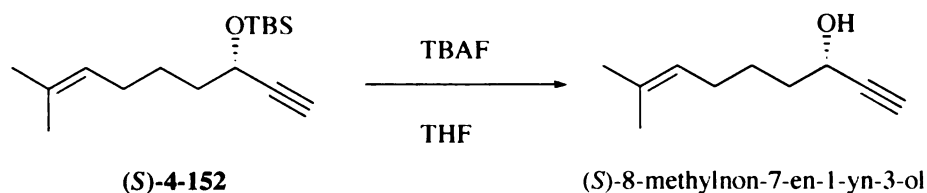


For the optically active material, a flask was charged with (S)-5-(*tert*-butyldimethylsilyloxy)-2,10-dimethylundec-9-en-3-yn-2-ol (0.85 g, 2.6 mmol), toluene (30 mL), 18-crown-6 (0.81 g, 3.1 mmol), and potassium carbonate (0.41 g, 2.9 mmol). The reaction mixture was refluxed for 2 days under a constant and health stream of nitrogen gas. The reaction mixture was cooled and filtered

through Celite. Column chromatography (25 x 4.4 cm, silica gel) with hexanes then 5 % ethyl acetate / hexane gave 0.68 g (97 %, 2.52 mmol). The enantiomeric excess was determined on non-8-en-1-yn-3-ol which was 98 % ee.

^1H NMR (CDCl_3) δ : 0.09 (s, 3 H), 0.11 (s, 3 H), 0.88 (s, 9H), 1.35 - 1.49 (m, 2 H), 1.58 (s, 3 H), 1.60 - 1.71 (m, 2 H), 1.67 (s, 3 H), 1.98 (q, 2 H, $J = 7.2$ Hz), 2.35 (d, 1 H, $J = 2.1$ Hz), 4.31 (td, 1 H, $J = 6.5, 2.1$ Hz), 5.09 (t, 1 H, $J = 7.1$ Hz); ^{13}C NMR (CDCl_3) δ : -5.07, -4.58, 17.69, 18.22, 25.36, 25.70, 25.78, 27.58, 38.17, 62.71, 71.88, 85.74, 124.37, 131.66; IR (thin film): 3312 m, 2932 s, 2859 s, 1474 m, 1252 m, 1098 s, 839 m cm^{-1} ; mass spectrum m/z (% rel intensity) 266 M^+ (5), 265 $\text{M}^+ - 1$ (12), 251 (15), 209 (46), 173 (22), 167 (17), 135 (100), 107 (15), 93 (15); Clear oil (hexane), $R_f = 0.25$ (100 % hexane), $R_f = 0.75$ (30 % ethyl acetate / hexane). $[\alpha]_{\text{D}}^{22} -34.7^\circ$ (c 0.825, CH_2Cl_2) at 98 % ee.

Formation of (S)-8-methylnon-7-en-1-yn-3-ol



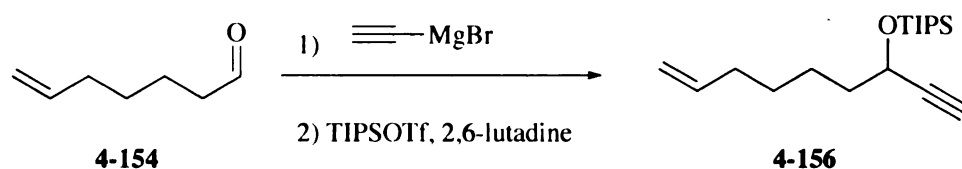
A 25 mL round bottom flask was charged with compound (S)-4-152 (0.157 g, 0.587 mmol) and THF (5 mL). The contents of the flask were cooled to 0 °C and TBAF (1 M, 0.65 mL, 0.65 mmol). The flask was warmed to room temperature, and the reaction mixture was stirred for one hour. To the flask was

added 20 mL of dichloromethane, and the solution was poured into 30 mL of water. The layers were separated, and the aqueous layer was extracted with 20 mL x 2 of dichloromethane. The organic layers were combined and extracted with 20 mL of brine. The aqueous layer was back extracted with 20 mL x 2 of dichloromethane. All the organic layers were combined, and they were dried over magnesium sulfate and sodium bicarbonate. The solution was filtered through fluted filter paper. The solvent was removed under reduced pressure. Column chromatography (17 x 2.4 cm, silica gel) with 10 % ethyl acetate / hexane then 20 % ethyl acetate / hexane gave 0.804 g (90 %, 0.528 mmol). The spectroscopic properties of 8-methylnon-7-en-1-yn-3-ol were identical to that previously reported.³⁶⁸

The enantiomeric excess was determined by chiral HPLC with a Chiralcel OJ-H column with 99.5 to 0.5 ratio of *n*-heptane and isopropanol respectively. The retention times were 34.4 minutes (major) and 39.0 minutes (minor). The enantiomeric excess was 98 %. The minor enantiomer was not detected.

¹H NMR (CDCl₃) δ : 1.40 - 1.92 (m, 5 H), 1.57 (s, 3 H), 1.66 (s, 3 H), 1.99 (q, 2 H), $J = 7.4$ Hz), 2.44 (dd, 1 H, $J = 2.1, 0.5$ Hz), 4.34 (br s, 1 H), 5.09 (t, 1 H, $J = 8.8$ Hz), $R_f = 0.38$ (30 % ethyl acetate / hexane); $[\alpha]_D^{22} -1.70^\circ$ (c 5.55, CH₂Cl₂) at 98 % ee; $[\alpha]_D -32.2^\circ$ (c 2.0, CHCl₃),³⁶⁸ the ee was not reported in the literature.

Compound 4-156



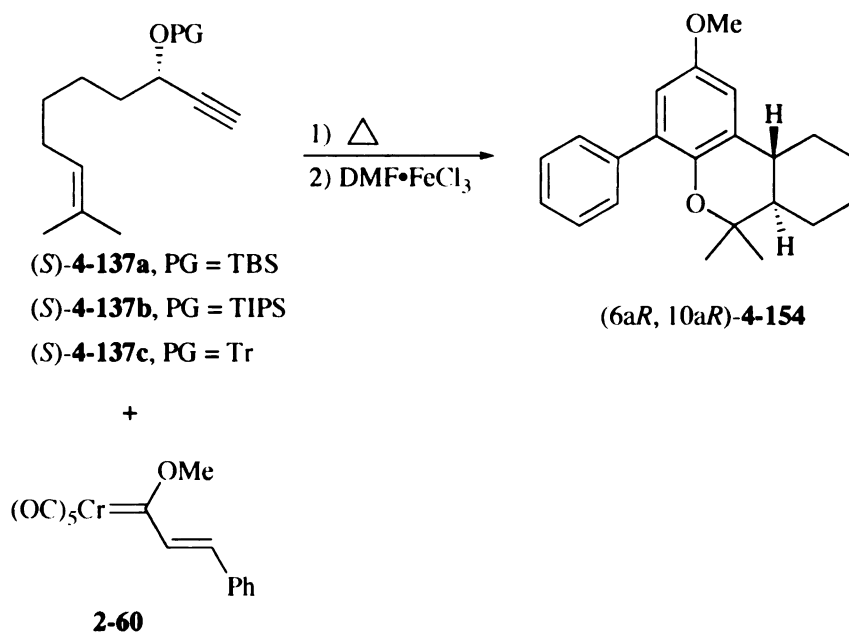
To a solution of aldehyde **4-154** (1.66 g, 14.8 mmol), prepared by literature methods,³⁶⁹ in 100 mL of THF was added ethyl magnesium bromide (50 mL, 1.8 eq., 0.5 M in THF) at 0 °C in a 250 mL flask. The contents of the flask were stirred for 3 hours at 0 °C. The contents of the flask were poured onto 100 mL of saturated ammonium chloride. The organic layer was separated and the ammonium chloride solution and extracted with 20 mL x 3 of ether. The organic layers were combined and extracted with brine (200 mL). The brine layer was extracted with ether (3 x 20 mL). The organic layers were combined and dried / neutralized with sodium bicarbonate and magnesium sulfate. The solution was filtered through fluted filter paper and the solvent was removed under reduced pressure. Column chromatography (20 x 2.8 cm, silica gel) with 20 % ethyl acetate / hexane gave 1.24 g of non-8-en-1-yn-3-ol ($R_f = 0.13$ with 10 % ethyl acetate / hexane). The clear oil was used without further purification. The alcohol (non-8-en-1-yn-3-ol) is known in the literature.³⁶⁹

A 100 mL round bottom flask was charged with non-8-en-1-yn-3-ol (1.24 g, 9 mmol), dichloromethane (50 mL), and 2,6-lutidine (1.6 mL, 13.7 mmol). The contents of the flask were cooled to 0 °C and TIPSOTf (2.4 mL, 9 mmol) was added dropwise. The reaction mixture was warmed to room temperature. The

contents of the flask were extracted with saturated ammonium chloride (25 mL) and brine. Each layer was back extracted with 3 x 20 mL of dichloromethane. The organic layers were combined and dried / neutralized over sodium bicarbonate and magnesium sulfate. The solution was filtered and the solvent removed under reduced pressure. Column chromatography (20 x 3.8 cm, silica gel) with 100 % hexanes gave 1.70 g (39 % yield over two steps, 5.85 mmol).

^1H NMR (CDCl_3) δ : 1.00 - 1.17 (m, 21 H), 1.31 - 1.57 (m, 4 H), 1.63 - 1.76 (m, 2 H), 2.05 (q, 2 H, $J = 7.1$ Hz), 2.35 (d, 1 H, $J = 2.1$ Hz), 4.45 (td, 1 H, $J = 6.2$ Hz, 2.1 Hz), 4.88 - 5.08 (m, 2 H), 5.80 (dddd, 370 1 H, $J = 17.0, 10.2, 6.7, 6.7$ Hz); ^{13}C NMR (CDCl_3) δ : 12.25, 18.00, 24.37, 28.67, 33.68, 38.62, 62.88, 71.97, 85.73, 114.33, 138.85; IR (thin film): 3312 m, 2944 s, 2869 s, 1464 w, 1101 m, 884 w cm^{-1} ; mass spectrum m/z (% rel intensity) 293 $\text{M}^+ - 1$ (1), 251 (63), 209 (64), 169 (14), 131 (37), 103 (46), 75 (100); Clear oil (hexane), $R_f = 0.16$ (100 % hexane).

Compound 4-154



Procedure 4A: To a 50 mL flask, where the standard 14/20 tapered joint was replaced with a threaded high vacuum Teflon valve, toluene (8 mL), styryl carbene complex **2-60** (82 mg, 0.24 mmol), alkyne (0.28 mmol), and Hunig's base (0.21 mL, 5 eq.) were added. Three freeze thaw cycles were done. The contents of the flask were heated for 24 hours at 110 °C. The solvent was removed by reduced pressure. The contents of the flask were taken up in 2 to 3 aliquots of 2 - 3 mL of DMF and transferred to a 20 mL vial. To this vial was added a solution of $\text{DMF} \cdot \text{FeCl}_3$ complex (freshly made by adding 250 mg of $\text{FeCl}_3 \cdot 6\text{H}_2\text{O}$ to 4 mL of DMF and stirred for 30 minutes) and the solution stirred until the TLC indicated that the yellow chromium tricarbonyl arene complex was gone; note that the TLC streaked from the FeCl_3 which could be substantially reduced by quenching the aliquot with water prior to running the TLC. The

oxidation with DMF•FeCl₃ general took about 30 minutes. To this solution was then added 10 to 15 mL of water and the solution was stirred 30 minutes. The solution was then extracted with CH₂Cl₂. Filtration through a 12 x 4.5 cm column of silica gel with 20 % ethyl acetate / hexane was followed by the solvent removal under reduced pressure. Preparative TLC on 1000 μm silica gel with fluorescent indicator was done with 20 % chloroform / hexane. The TLC plate was developed three times. The band that contained the product was scrapped from the TLC plate and stirred with 15 mL of methanol. The solution was filtered through a glass-fritted funnel with Celite eluting with methanol and then CH₂Cl₂. The solvent was removed under reduced pressure. The remaining residual was taken up in CH₂Cl₂ and filtered through a glass-fritted funnel with Celite and the resulting solvent was again removed under reduced pressure. This gave 0.045 g (58 %, 0.14 mmol) of product. Also found by scraping the remainder of the TLC plate and washing the silica with methanol as above was 0.045 g of a complex mixture.

To make the system "one-pot" the DMF•FeCl₃ solution could be added directly to the reaction flask either with the toluene present or after it was removed under reduced pressure. With the toluene present, the reaction took 3 to 4 hours.

The enantiomeric excess was measured by demethylation or debenzylation and running HPLC as described for compound **4-208**. The

absolute stereochemistry was assigned by a mechanistic argument based on the stereochemistry previously obtained for similar systems in the literature.³⁷¹

Other results of PG = TBS were performed. At 90 °C with PG = TBS for 24 hours, the yield was 39 % with an ee of 94 %. At 100 °C with PG = TBS for 24 hours, the yield was 39 % with an ee of 94 %. At 100 °C for 48 hours, the yield was 51 % with 92 % ee. At 110 °C with PG = TBS for 24 hours, the yield was 58 % with 88 % ee.

A similar procedure was followed for the TIPS and Tr versions under identical conditions. At 90 °C with PG = TIPS for 24 hours, the yield was 42 % with an ee of 94 %. At 100 °C with PG = TIPS for 48 hours, the yield was 60 (average of two runs) with an ee of 90 %. At 110 °C with PG = TIPS for 24 hours, the yield was 48 % with an ee of 92 %. At 100 °C with PG = Tr for 48 hours, the yield was 45 % (average of two runs) with 86 % ee (average of two runs).

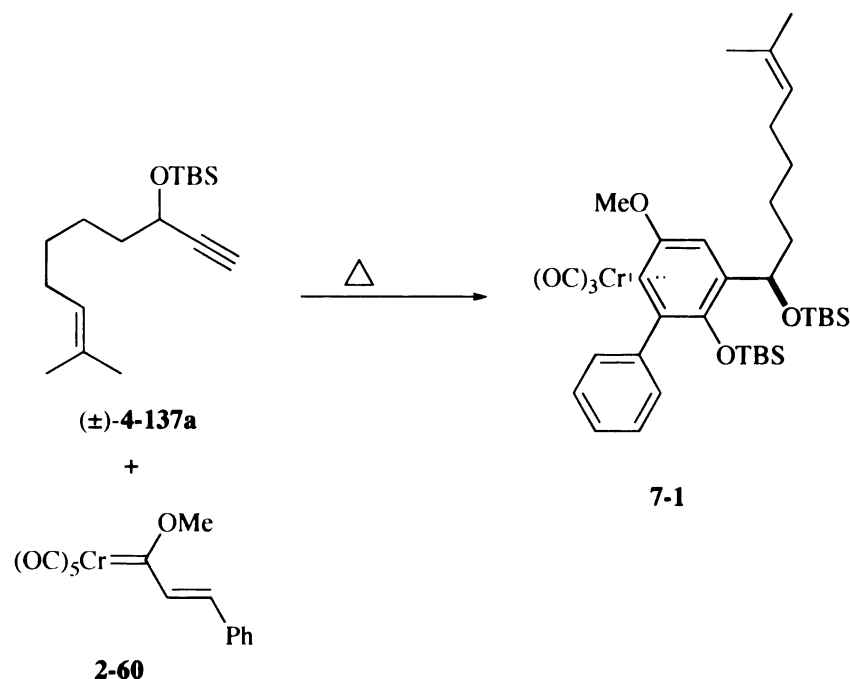
The diastereomeric ratio could be determined using GC/FID. With a reaction temperature of 110 °C or below the amount of the cis diastereomer was < 5 %. The retention time was 7.0 minutes for the minor and 8.8 minutes for the major. The temperature program was 80 °C for 1 minute then ramped to 230 °C at 10 °C / minute using an Alltech Econo-Cap SE54 column (30 m x 0.32 mm x 1.2 µm) with a 5 mL/min flow rate (no split).

The retention time for GC/MS was 21.6 minutes (minor) and 22.7 minutes. The temperature program was 60 °C for 2 minutes then ramped to 260 °C at 10

°C / minute using a CP-SIL 8 low bleed column (30 m x 0.25 mm) with a 5 mL/min flow rate (1/20 split ratio). The integration between the MS and FID were identical.

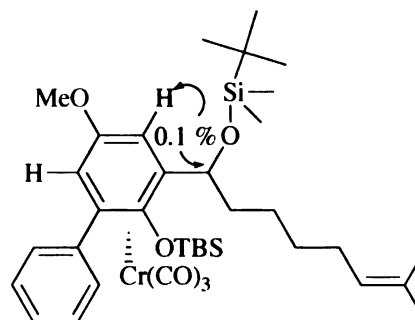
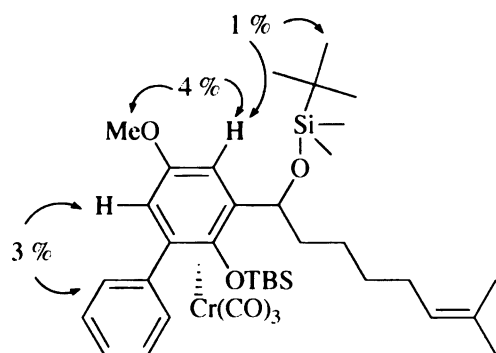
^1H NMR (CDCl_3) δ : 1.00 – 1.11 (m, 1 H), 1.15 (s, 3 H), 1.20 – 1.72 (m, 4 H), 1.30 (s, 3 H), 1.87 (m, 3 H), 2.37 – 2.47 (m, 2 H), 3.82 (s, 3 H), 6.75 (d, 1 H, $J = 3$ Hz), 6.80 (d, 1 H, $J = 3.0$ Hz), 7.20 – 7.60 (m, 5 H); ^{13}C NMR (CDCl_3) δ : 20.06, 26.19, 26.36, 27.69, 27.76, 31.44, 36.79, 47.27, 55.79, 76.81, 111.00, 114.25, 126.43, 126.87, 127.69, 129.78, 130.33, 139.0, 144.25, 152.60; IR (thin film): 2926 s, 2853 m, 1464 m cm^{-1} ; mass spectrum m/z (% rel intensity) 323 $[\text{M}+1]^+$ (26), 322 M^+ (100), 280 (47), 238 (4), 215 (s); Anal calcd for $\text{C}_{22}\text{H}_{26}\text{O}_2$: C, 81.95; H, 8.13. Found; C, 81.61; H, 8.34. Yellow solid (hexane), mp 92 - 95 °C, $R_f = 0.66$ (30 % ethyl acetate / hexane). For optically active material, $[\alpha]_D^{22} +12.0^\circ$ (c 0.11, CH_2Cl_2) at 94 % ee.

Compound 7-1



In a 50 mL round bottom were the standard tapered joint was replaced with a threaded high vacuum Teflon valve was added styryl carbene complex **2-60** (97 mg, 0.34 mmol), DCM (5 mL), racemic alkyne (±)-**4-137a** (97 mg, 0.34 mmol), Hunig's base (0.3 mL), and TBSCl (154 mg, 1.0 mmol). The flask was freeze thaw degassed three times. The reaction was heated at 60 °C for 17 hours. The contents of the flask were poured onto silica (2 cc) and the solvent removed under reduced pressure. Column chromatography (26 cm x 1.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 187 mg of compound **7-1** as a yellow-orange oil (82 % yield, 0.28 mmol). The other diastereomer was not observable for the proton at 5.13 ppm therefore $\geq 96 : 4$ dr. Two other compounds were observed by TLC but they were not isolated.

Homonuclear nOe ^1H - ^1H



Nuclei Irradiated

Enhanced Nuclei

5.77

5.49 (0.1 %)

4.76 (4 %)

0.90 or 0.91 (1 %)

5.49

4 (3 %)

5.77 (0.2 %)

4.76

5.77 (0.1 %)

1.8 – 2.1 (9 %)

0.90 or 0.91 (2 %)

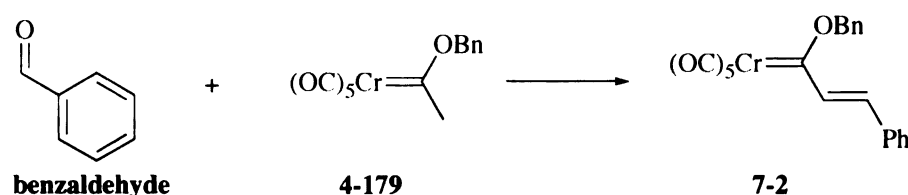
1.61 and 1.69

5.13 (1 %)

^1H NMR (CDCl_3) δ : -0.41 (s, 3 H), -0.14 (s, 3 H), -0.07 (s, 3 H), 0.07 (s, 3 H), 0.90 (s, 9 H), 0.91 (s, 9 H), $1.2 - 1.44$ (m, 4 H), 1.61 (s, 3 H), 1.69 (s, 3 H), $1.8 - 2.1$ (m, 4 H), 3.65 (s, 3 H), 4.76 (d, 1 H, $J = 9.8$ Hz), 5.13 (m, 1 H), 5.49 (d, 1 H, $J = 2.4$ Hz), 5.77 (d, 1 H, $J = 2.4$ Hz), $7.24 - 7.54$ (m, 5 H); ^{13}C NMR (CDCl_3) δ :

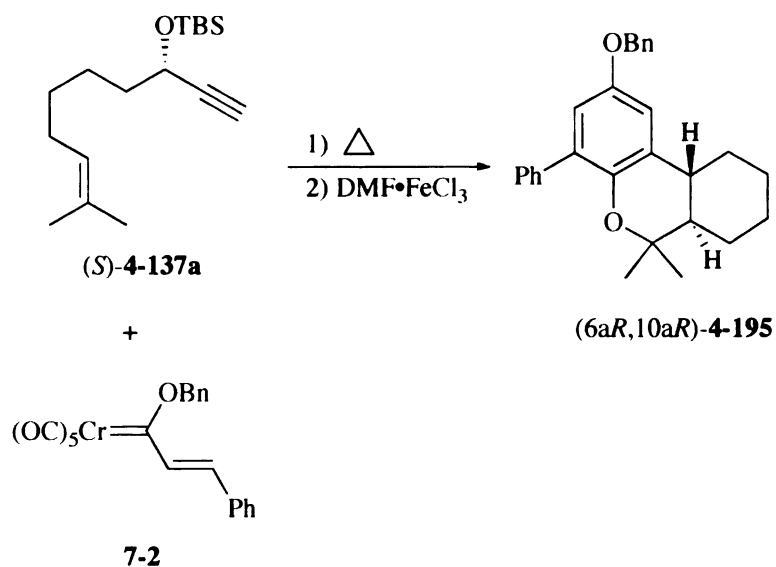
−4.65, −4.35, −4.23, −4.01, 17.64, 18.01, 18.64, 25.68, 26.00, 26.76, 27.87, 29.52, 41.30, 56.33, 68.07, 81.41, 86.96, 103.75, 110.21, 124.60, 128.25, 128.53, 128.60, 128.78, 130.13, 130.98, 131.38, 132.66, 132.81, 133.39, 135.40, 233.99; Yellow-orange oil (hexane), $R_f = 0.59$ (30 % ethyl acetate / hexane).

Compound 7-2



Compound **4-179** (2.53 g, 7.76 mmol), ether (30 mL), benzaldehyde (0.80 mL, 7.87 mmol), triethyl amine (4.3 mL, 30.8 mmol), and then TMSCl (3 mL, 23.7 mmol) were charged into a single neck flask that had been modified by replacement of the joint with a threaded high vacuum valve. Three freeze thaw cycles were done. The reaction mixture was stirred for 2 days at room temperature. The solvent was removed under reduced pressure. Column chromatography (20 cm x 3.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 1.96 g (4.73 mmol) of a dark oily solid of compound **7-2**. This solid was further purified by trituration with pentane three times. This gave 0.80 g (25 % yield, 1.94 mmol) of a dark solid. This compound had spectroscopic properties identical with those previously reported.³⁷²

Compound 4-195

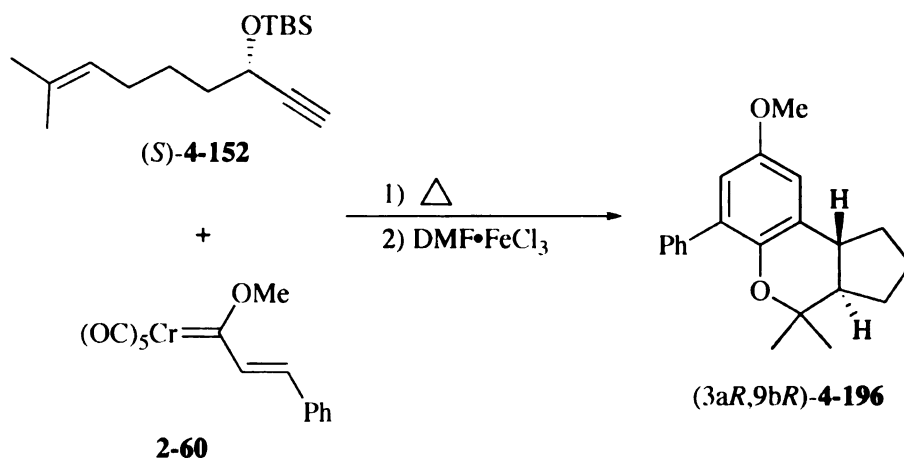


Following procedure 4A described above for compound **4-194** at 100 °C and 48 hours using carbene **7-2** (0.075 g, 0.18 mmol) and alkyne **4-137b** (0.066 g, 0.206 mmol), a yield of 48 % (0.034g, 0.085 mmol) and 93 % ee was obtained. The enantiomeric excess was obtained as described for compound **4-208** after debenzoylation on the phenol. The trans to cis ratio was greater $\geq 96 : 4$ as determined by NMR.

^1H NMR (CDCl_3) δ : 1.00 - 1.10 (m, 2 H), 1.11 (s, 3 H), 1.18 - 1.51 (m, 3 H), 1.27 (s, 3 H), 1.75 - 1.97 (m, 3 H), 2.34 - 2.50 m, 2 H), 4.98 (s, 2 H), 6.78 (d, 1 H, $J = 2.9$ Hz), 6.85 (d, 1 H, $J = 2.8$ Hz), 7.18 - 7.49 (m, 8 H), 7.54 (d, 2 H, $J = 7.1$ Hz); ^{13}C NMR (CDCl_3) δ : 20.03, 26.13, 26.28, 27.70, 27.78, 31.33, 36.68, 47.13, 70.74, 76.82, 112.128, 115.28, 126.50, 126.86, 127.58, 127.64, 127.81, 128.50, 129.64, 130.33, 137.49, 138.96, 144.48, 151.85; IR (thin film): 3030 w, 2928 s, 2857 s, 1576 w, 1458 m, 1144 m cm^{-1} ; mass spectrum m/z (% rel intensity) 398

M⁺ (35), 307 (81), 289 (15), 279 (1), 274 (1), 265 (6), 251 (11), 239 (11), 221 (3), 198 (33), 187 (5), 165 (10), 152 (5), 103 (16), 91 (100), 79 (11; Beige solid (hexane), mp 84 - 86 °C, R_f = 0.55 (30 % ethyl acetate / hexane). [α]_D²² -32.5° (c 2.44, CH₂Cl₂) at 93 % ee.

Compound 4-196

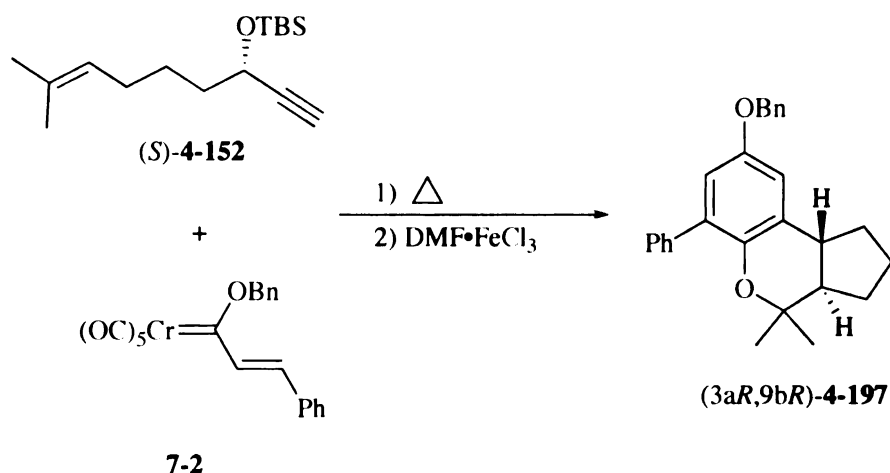


Compound (S)-4-152 (0.078 g, 0.29 mmol, 98 % ee), styryl carbene complex 2-60 (0.089 g, 0.26 mmol), Hunig's base (0.22 mL, 1.3 mmol), and toluene (9 mL) were charged into a single neck flask that had been modified by replacement of the joint with a threaded Teflon high vacuum valve. Three freeze thaw cycles were done. The flask was stirred and heated at 100 °C for 24 hrs. The contents of the flask were transferred to a 250 mL single neck round bottom flask the solvent was removed under reduced pressure. The residue was added to a solution of FeCl₃ (0.1 to 0.2 g) in DMF that was stirred for 30 minutes to 60 minutes. The reaction was monitored until the yellow spot was gone (note: there was some yellow streaking from the FeCl₃ which could be reduced by quenching

an aliquot with water prior to TLC). Preparative TLC on Silica Gel GF 1000 microns plates developing three times with 20 % chloroform / hexane gave 64 mg (50 % yield, 0.13 mmol). The ring generation was assigned as trans on the bases of the results obtained for compound **4-197** below where the coupling constant for hydrogen on carbon 9b was clearly observable. The % ee was not determined of **4-196** since the molecule decomposed upon attempted demethylation with AlBr₃ and propane thiol.

¹H NMR (CDCl₃) δ: 1.22 (s, 3 H), 1.25 - 1.37 (m, 2 H), 1.34 (s, 3 H), 1.46 - 1.60 (m, 2 H), 1.65 - 1.75 (m, 1 H), 1.76 - 1.83 (m, 1 H), 1.85 - 1.94 (m, 2 H), 3.78 (s, 3 H), 6.64 (dd, 1 H, *J* = 3.1, 1.1 Hz), 6.75 (dd, 1 H, *J* = 3.2, 0.67 Hz), 7.26 - 7.31 (m, 1 H), 7.36 - 7.40 (m, 2 H), 7.55 - 7.58 (m, 2 H); ¹³C NMR (CDCl₃) δ: 20.77, 22.92, 25.71, 25.89, 28.67, 29.14, 39.60, 51.33, 55.79, 78.82, 111.76, 114.04, 126.51, 127.65, 127.71, 128.10, 129.59, 139.19, 144.79, 152.33; IR (thin film): 2961 m, 2873 m, 1480 m, 1420 m, 1200 m, 1051 m cm⁻¹; mass spectrum *m/z* (% rel intensity) 310 [M+2]⁺ (14), 308 M⁺ (100), 293 (15), 265 (40), 239 (20), 223 (16), 213 (24), 178 (15), 164 (11), 152 (10); HRMS (Q-Tof) calcd for C₂₁H₂₅O₂ (+H) *m/z* 309.1855, meas 309.1864. Anal calcd for C₂₁H₂₄O₂: C, 81.78; H, 7.84. Found; C, 81.50; H, 7.94. Colorless solid (hexane), mp 115 - 117 °C, R_f = 0.60 (30 % ethyl acetate / hexane).

Compound 4-157

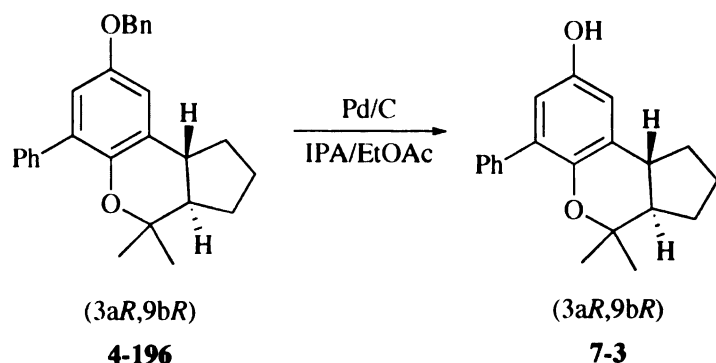


Following procedure 4A, the reaction of carbene complex 7-2 (0.079 g, 0.192 mmol) with alkyne (S)-4-152 (0.060 g, 0.225 mmol) at 100 °C and 48 hours, the yield was 43 % (0.0315 g, 0.0819 mmol) and the ee was 94 %. The trans ratio was 93 : 7. The % ee and trans ratio were determined after debenzylation as described for compound 7-3 below.

¹H NMR (CDCl₃) δ : 1.22 (s, 3 H), 1.25 - 1.31 (m, 1 H), 1.39 (s, 3 H), 1.48 - 1.60 (m, 1 H), 1.64 - 1.75 (m, 1 H), 1.76 - 1.84 (m, 1 H), 1.85 - 1.96 (m, 1 H), 2.32 (dddd, 1 H, J = 11.3, 7.3, 7.3, 3.5 Hz), 2.63 (ddd, 1 H, J = 11.8, 11.8, 7.2), 5.02 (s, 3 H), 6.73 (d, 1 H, J = 3.6 Hz), 6.85 (d, 1 H, J = 3.1 Hz), 7.25 - 7.34 (m, 2 H), 7.35 - 7.41 (m, 4 H), 7.42 - 7.47 (m, 2 H), 7.54 - 7.60 (m, 2 H); ¹³C NMR (CDCl₃) δ : 20.81, 22.95, 25.91, 28.67, 29.16, 39.62, 51.35, 70.80, 78.89, 112.90, 115.16, 126.47, 127.58, 127.63, 127.80, 128.11, 128.49, 129.58, 137.51, 139.17, 145.05, 151.65 (one carbon missing); IR (thin film): 3032 w, 2965 s, 2872 s, 1601 m, 1456 s, 1422 m cm⁻¹; mass spectrum m/z (% rel intensity) 385 [M+1]⁺ (40), 293

(81), 275 (5), 251 (9), 237 (13), 199 (23), 181 (4), 152 (5), 91 (100); Beige solid (hexane), mp 108 - 112 °C, $R_f = 0.60$ (30 % ethyl acetate / hexane). $[\alpha]_D^{22} -21.5^\circ$ (c 1.39, CH_2Cl_2) at 94 % ee.

Compound 7-3



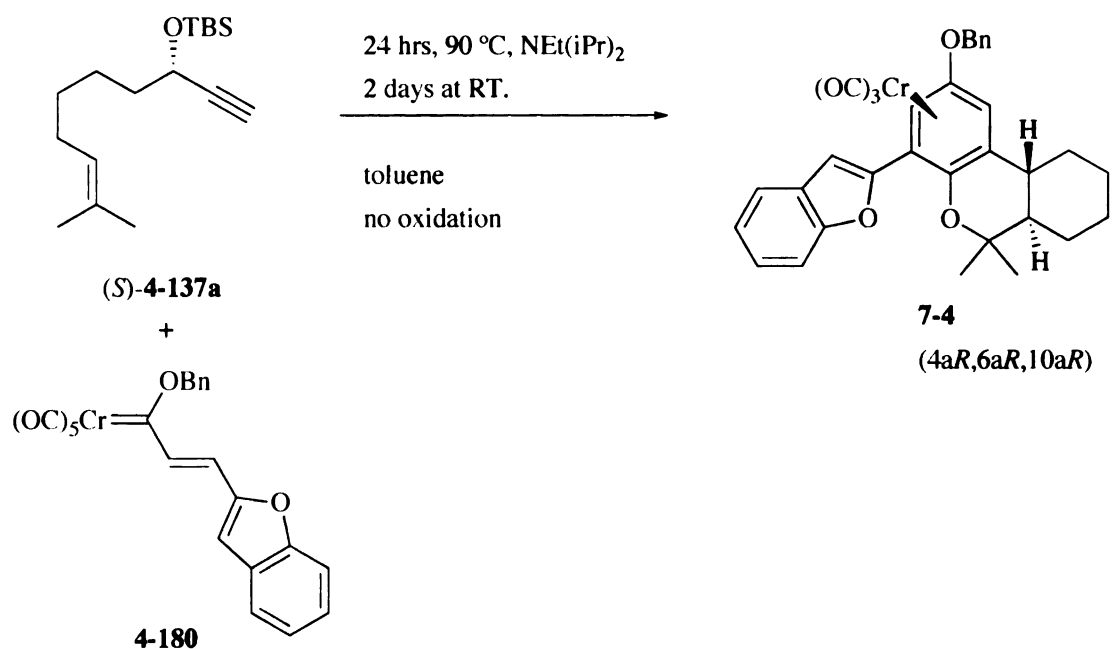
A 10 mL flask was charged with 29 mg of compound **4-156** (0.08 mmol), 50 mg of 10 % Pd on carbon, 2 mL of isopropanol, and 2 mL of ethyl acetate. The atmosphere was replaced with hydrogen and the reaction mixture was stirred for 2 hours at room temperature. The carbon was removed by filtering through a Celite. This gave 0.016 g (0.053 mmol, 70 % yield) of compound **7-3**. This contained 7 % of the cis compound (93 : 7 dr) determined by integrating the peak at 6.7 ppm and 6.6 ppm in the ^1H NMR. The enantiomeric excess was 94 %.

The enantiomeric excess was determined using HPLC with a Chiralpak AD column with retention times of 43 (major) and 51 minutes (minor) with a 98 : 2 hexane / isopropanol solvent mixture. With 99 : 1 hexane / isopropanol solvent mixture, the retention times were 100 minutes for the major peak and 122

minutes for minor peak.

^1H NMR (CDCl_3) δ : 1.20 (s, 3 H), 1.23 - 1.30 (m, 1 H, overlapping), 1.32 (s, 3 H), 1.49 (sex, 1 H, $J = 10.7$ Hz), 1.69 (sex, 1 H, $J = 5.9$ Hz), 1.83 - 1.94 (m, 2 H), 2.25 - 2.33 (m, 2 H), 2.59 (ddd, 1 H, $J = 11.8, 11.8, 7.1$ Hz), 4.35 (s, 1 H), 6.56 (d, 1 H, $J = 3.1$ Hz, sometimes appeared as a broad singlet), 6.66 (d, 1 H, $J = 3.1$ Hz, sometimes appeared as a broad singlet), 7.23 - 7.30 (m, 1 H), 7.32 - 7.38 (m, 2 H), 7.51 - 7.57 (m, 2 H); ^{13}C NMR (CDCl_3) δ : 20.79, 22.94, 25.90, 28.64, 29.15, 39.52, 51.31, 78.87, 112.68, 115.58, 126.57, 127.67, 128.32, 129.56, 129.82, 138.87, 144.79, 147.95; IR (thin film): 3343 m, 2959 s, 2926 s, 2872 s, 1603 w, 1454 m, 1417 m cm^{-1} ; mass spectrum m/z (% rel intensity) 294 M^+ (98), 279 (18), 251 (40), 225 (21), 212 (13), 209 (11), 199 (27), 181 (11), 177 (26), 165 (18); Beige oily solid (hexane), $R_f = 0.1$ (10 % ethyl acetate / hexane), $R_f = 0.35$ (30 % ethyl acetate / hexane). $[\alpha]_D^{22} -15^\circ$ (c 0.095, CH_2Cl_2) at 94 % ee.

Compound 7-4

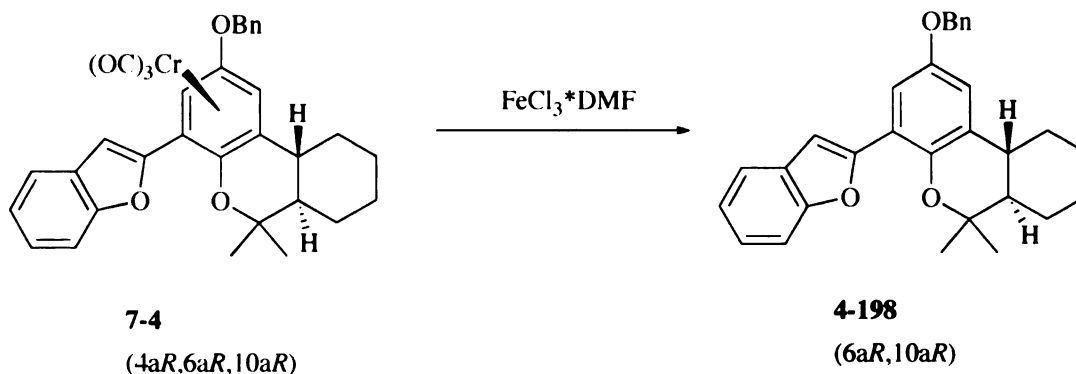


A magnetic stirring bar was placed into a flame-dried single neck flask that had been modified by replacement of the joint with a threaded high vacuum Teflon valve. The flask was charged with alkyne **(S)-4-137a** (0.070 g, 0.25 mmol, 98 % ee), carbene complex **4-180** (0.105 g, 0.23 mmol), Hunig's base (0.2 mL, 1.1 mmol), and toluene (6 mL). Three freeze thaw cycles were done. The reaction was heated 24 hours at 90 °C and stirred two days at room temperature. The contents of the flask were taken up onto silica gel and the solvent removed under reduced pressure. Column chromatography (20 x 2.2 cm, silica gel) with 5 % ethyl acetate / hexane gave 0.046 g (35 % yield, 0.088 mmol) of compound **7-4** which was a bright yellow solid.

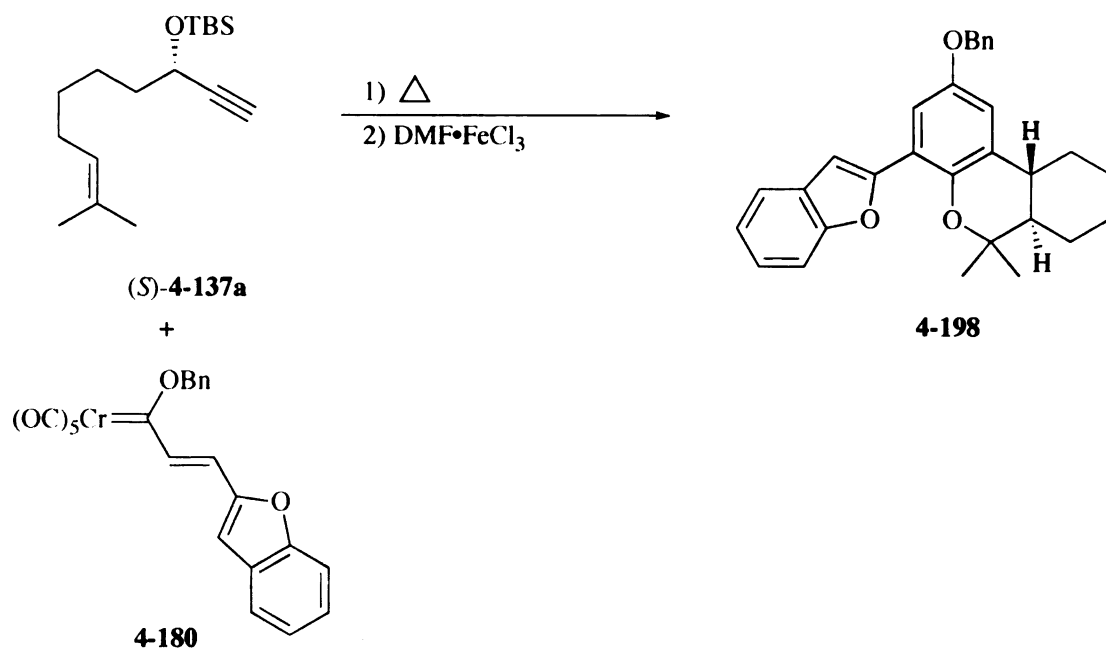
¹H NMR (CDCl₃) δ: 1.01 - 1.13 (m, 1 H), 1.20 (s, 3 H), 1.21 - 1.27 (m, 2 H), 1.28 - 1.32 (m, 2 H), 1.56 (s, 3 H), 1.84 - 1.90 (m, 3 H), 2.35 - 2.48 (m, 2 H), 5.09 (s, 2 H), 6.89 (d, 1 H, *J* = 2.4 Hz), 7.17 - 7.28 (m, 2 H), 7.32 - 7.24 (m, 4 H), 7.43 -

7.50 (m, 3 H), 7.57 - 7.60 (m, 2 H); ^{13}C NMR (CDCl_3) δ : 19.65, 25.59, 25.64, 27.34, 28.38, 30.76, 34.87, 46.71, 71.54, 76.22, 79.21, 81.17, 88.66, 94.95, 108.70, 111.07, 121.54, 123.07, 125.12, 126.78, 128.21, 128.62, 128.73, 129.00, 134.95, 135.23, 149.09, 154.01, 234.56; IR (thin film): 2973 m, 2930 s, 2857 m, 1458 s, 1144 m, 739 w cm^{-1} ; mass spectrum m/z (% rel intensity, +FAB) 574 M^+ (23), 438 $\text{M}^+ - \text{Cr}(\text{CO})_3$ (9), 399 (11), 347 (3), 329 (3), 303 (2); HRMS calcd for $\text{C}_{33}\text{H}_{30}\text{CrO}_6$ m/z 574.1445, meas 574.1444. Orange solid (hexane), mp 55 - 60 (dec.) $^\circ\text{C}$, R_f = 0.62 (30 % ethyl acetate / hexane). $[\alpha]_{\text{D}}^{22} -477^\circ$ (c 0.055, CH_2Cl_2) at 91 % ee.

Compound 4-198



Procedure One. A vial was charged with compound **7-4** (0.019 g, 0.033 mmol) and 2 mL of DMF. To this solution was added 0.2 g of FeCl_3 in 3 mL of DMF; this $\text{DMF} \cdot \text{FeCl}_3$ solution was stirred for 30 minutes before the addition. Column chromatography (1.8 x 15 cm, silica gel) with 5 % ethyl acetate / hexane gave 0.0116 g (80 % yield, 0.026 mmol) of **4-198**.

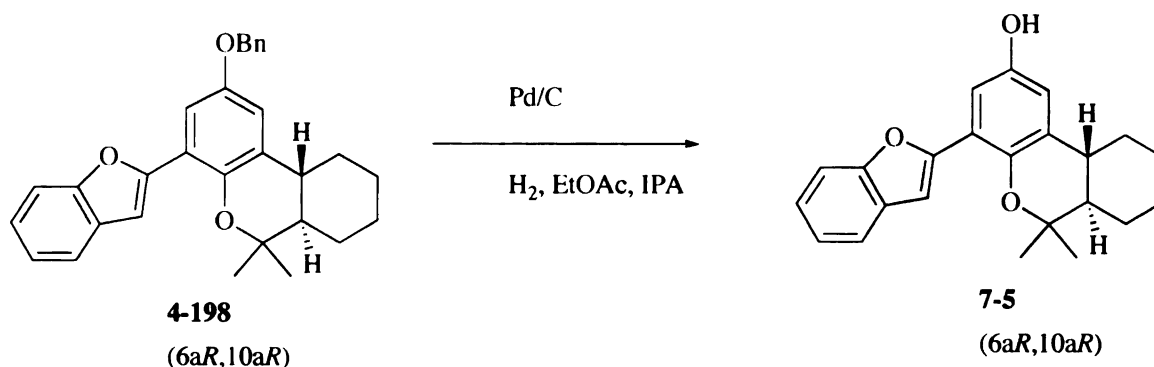


Procedure Two. Following the general procedure 4A with alkyne **(S)-4-137b** (0.066 g, 0.205 mmol, 98 % ee) at 100 °C for 48 hours, a yield of 48 % (0.0375 g, 0.098 mmol, 48 % yield) was obtained with 93 % ee. The % ee was obtained after debenzylation on the phenol **7-5**.

^1H NMR (CDCl_3) δ : 0.96 - 1.16 (m, 1 H), 1.15 - 1.37 (m, 2 H), 1.20 (s, 3 H), 1.42 - 1.54 (m, 3 H), 1.55 (s, 3 H), 1.86 - 1.94 (m, 2 H), 2.35 - 2.52 (m, 2 H), 5.09 (s, 2 H), 6.89 (d, 1 H), 7.14 - 7.30 (m, 2 H), 7.31 - 7.44 (m, 4 H), 7.45 - 7.55 (m, 3 H), 7.56 - 7.77 (m, 2 H); ^{13}C NMR (CDCl_3) δ : 20.48, 26.09, 26.21, 27.67, 28.01, 31.22, 36.43, 46.92, 70.83, 77.89, 106.28, 110.54, 110.74, 113.77, 119.00, 120.99, 122.54, 123.92, 127.01, 127.71, 127.88, 128.52, 129.93, 137.43, 145.14, 151.89, 152.65, 153.74; IR (thin film): 2973 w, 2930 s, 2857 m, 1684 w, 1653 w, 1566 w, 1458 s, 1262 m, 1144 m, 1042 m, 739 m cm^{-1} ; mass spectrum m/z (% rel intensity, ESI^-) 438 M^+ (62), 293 (72), 265 (100), 194 (54); Yellow solid

(hexane), mp 62 - 64 °C, $R_f = 0.62$ (30 % ethyl acetate / hexane). For chiral material, $[\alpha]_D^{22} -33.8^\circ$ (c 1.405, CH_2Cl_2), $[\alpha]_D^{22} -28.5^\circ$ (c 1.24, CH_2Cl_2).

Compound 7-5

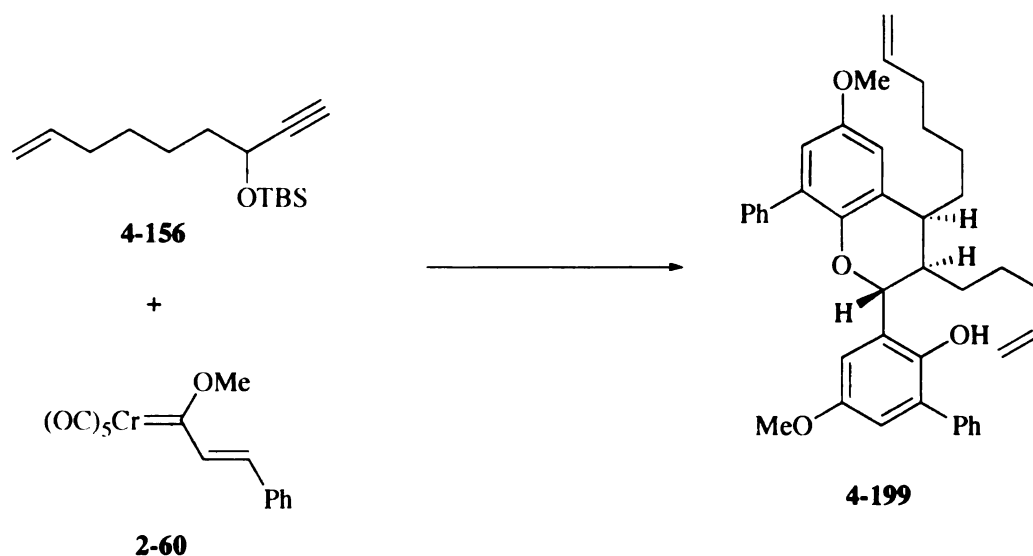


A 10 mL flask was charged with (6a*R*,10a*R*)-**4-198** (12.3 mg, 0.026 mmol), 2 mL of ethyl acetate, 2 mL of isopropanol, and 40 mg of 10 % Pd on carbon. The atmosphere was removed and replaced with hydrogen by first pulling a vacuum for less than a second and then introducing a hydrogen filled balloon. The reaction was stirred for two hours until the reaction mixture was complete by TLC. The reaction mixture was filtered through Celite and the organic solvent was removed under reduced pressure. Preparative TLC with 5 % ethyl acetate / hexane developed three times gave 9.7 mg of compound **7-5** (99 % yield, 12.2 mmol, 91 % ee) as a beige solid. The enantiomeric excess was determined with 97 : 3 (hexane / isopropanol) with a Chiralpak AD. The retention times were 59 minutes (minor) and 70 minutes (major).

^1H NMR (CDCl_3) δ : 1.00 - 1.59 (m, 5 H), 1.19 (s, 3 H), 1.54 (s, 3 H), 1.81 - 1.95 (m, 3 H), 2.32 - 2.48 (m, 2 H), 4.46 (br s, 1 H), 6.74 (d, 1 H, $J = 2.6$ Hz), 7.13 -

7.28 (m, 2 H), 7.37 - 7.42 (m, 2 H), 7.43 - 7.49 (m, 1 H), 7.56 - 7.61 (m, 1 H); ^{13}C NMR (CDCl_3) δ : 20.42, 26.07, 26.19, 27.65, 27.99, 31.21, 36.37, 46.89, 77.85, 106.38, 110.69, 111.34, 113.10, 119.18, 121.02, 122.55, 123.98, 127.20, 129.86, 144.85, 148.22, 152.38, 153.72; IR (thin film): 3364 br m, 2928 s, 2857 m, 1456 s, 1262 m, 1142 m, 939 m cm^{-1} ; mass spectrum m/z (% rel intensity) 348 M^+ (11), 305 (7), 263 (2), 252 (1), 239 (4), 223 (2), 211 (1), 205 (2), 193 (2), 181 (2), 170 (6), 164 (2), 153 (2), 149 (5), 141 (8), 131 (6), 97 (10), 84 (12), 71 (17), 56 (52), 44 (100). Beige solid (hexane), mp 58 - 62 $^\circ\text{C}$, R_f = 0.41 (hexane). $[\alpha]_D^{22}$ -57.1° (c 0.40, CH_2Cl_2) at 91 % ee.

Compound 4-199

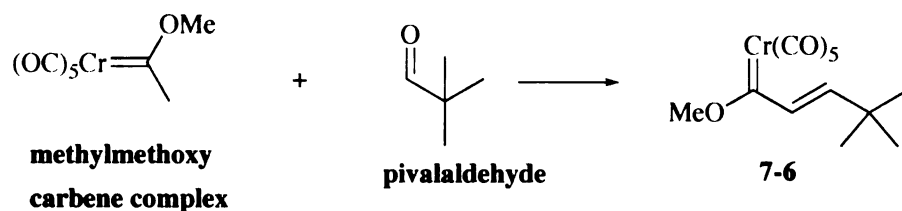


Following procedure 4A with carbene **2-60** (0.0931 g, 0.275 mmol) and alkyne **4-156** (0.0915 g, 0.311 mmol) at 100 $^\circ\text{C}$ for 48 hours, a yield of 23 % (0.0372 g, 23 % yield) was obtained. A brown spot on the base line of the prep. TLC plate was also found which had a mass of 0.25 g which was presumable

residual iron complex from the oxidation step. The enantiomeric excess was not determined.

^1H NMR (CDCl_3) δ : 1.10 - 1.57 (m, 8 H), 1.57 - 1.79 (m, 3 H), 1.87 - 2.10 (m, 4 H), 2.38 (dddd, 1 H, $J = 8.7^{373, 374}$, 5.8, 5.8, 5.8 Hz), 2.79 (q, 1 H, $J = 5.8$ Hz), 3.71 (s, 3 H), 3.80 (s, 3 H), 4.79 (d, 1 H, $J = 8.7$ Hz), 4.74 - 5.10 (m, 4 H), 5.60 - 5.85 (m, 2 H), 6.14 (s, 1 H), 6.68 (d, 1 H, $J = 3$ Hz), 6.71 (d, 1 H, $J = 2.9$ Hz), 6.75 (d, 1 H, $J = 3.1$ Hz), 6.77 (d, 1 H, $J = 3$ Hz), 7.22 - 7.60 (m, 10 H); ^{13}C NMR (CDCl_3) δ : 25.28, 25.89, 29.12, 31.93, 33.58, 33.91, 35.74, 40.75, 40.89, 55.67, 55.72, 82.08, 113.45, 113.49, 113.67, 114.30, 114.56, 114.77, 126.99, 127.21, 127.52, 128.02, 128.63, 129.27, 129.35, 129.75, 129.89, 130.99, 137.68, 137.92, 138.54, 138.87, 144.93, 145.87, 152.71, 154.01; IR (thin film): 3428 m, 2928 s, 2861 m, 1488 m, 1437 m, 1202 m cm^{-1} ; mass spectrum m/z (% rel intensity) 588 M^+ (28), 517 (4), 503 (3), 319 (2), 305 (12), 294 (70), 285 (4), 282 (8), 263 (11), 251 (15), 237 (42), 226 (48), 213 (100), 197 (47), 181 (26), 164 (18), 152 (14), 116 (12), 106 (10), 92 (12), 81 (12), 55 (27); Yellow oil (hexane), $R_f = 0.43$ (30 % ethyl acetate / hexane).

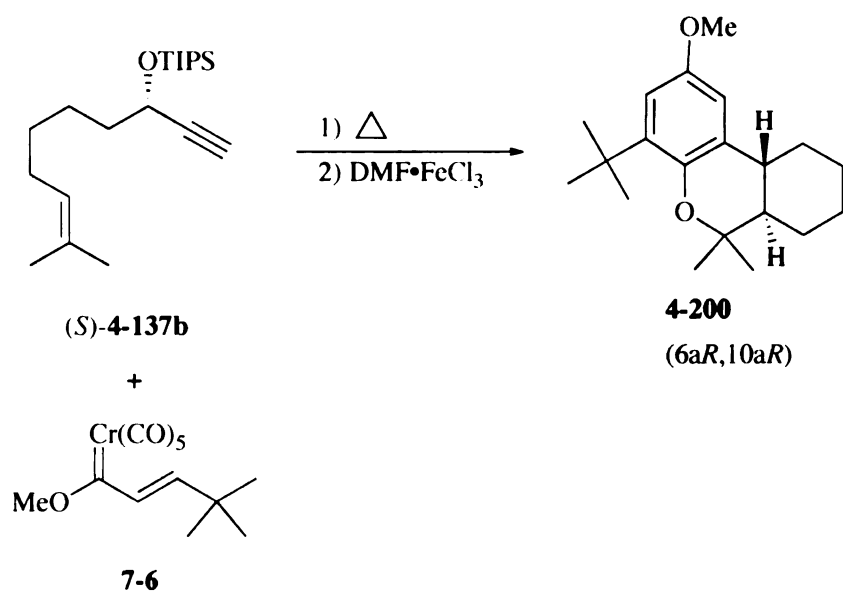
Compound 7-6



This compound was made by literature methods.³⁷⁵ Methyl methoxy carbene complex (0.502 g, 2.00 mmol) in ether (60 mL) was cooled to $-78\text{ }^{\circ}\text{C}$ in 100 mL round bottom flask. To this solution was added *n*-butyl lithium (1.3 mL, 1.6 M in hexane, 2.08 mmol) dropwise. The solution was stirred for 30 minutes and pivalaldehyde (0.22 mL, 2.0 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for two hours. The solution was poured into water (20 mL) and the layers were separated. The aqueous layer was extracted with 3 x 20 mL of ether. The organic layers were combined and dried over magnesium sulfate and sodium bicarbonate. The solution was filtered through a fluted paper funnel and the solvent was removed under reduced pressure. Column chromatography (20 x 2.8 cm, silica gel) with 100 % hexane gave a 40 % yield (0.25 g, 0.8 mmol) of compound 7-6. The spectroscopic properties were identical to that previously reported.³⁷⁵

^1H NMR (CDCl_3) δ : 1.10 (s, 9 H), 4.73 (s, 3 H), 6.29 (d, 1 H, $J = 9.0\text{ Hz}$), 7.20 (d, 1 H, $J = 9.0\text{ Hz}$); ^{13}C NMR (CDCl_3) δ : 28.72, 33.64, 66.31, 139.74, 146.70, 216.83, 224.02, 337.48; Dark solid (hexane).

Compound 4-200

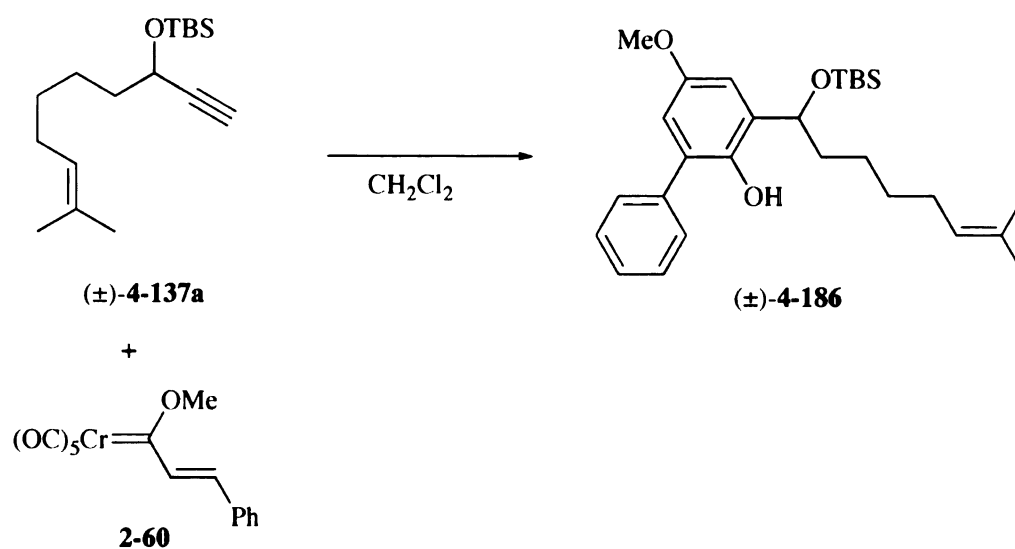


Following procedure 4A with alkyne **4-137b** (0.0797 g, 0.250 mmol) and carbene **7-6** (0.0863 g, 0.267 mmol) at 100 °C and 48 hours, a yield of 18 % (0.014 g, 0.045 mmol) was obtained of compound **4-200**. This compound decomposed on silica gel to multiple products and the NMR always had small amount of decomposition products.³⁷⁶ A second preparatory TLC only gave 25 % recovery of starting material. Satisfactory proof of purity could not be obtained. The diastereomeric ratio was 9 : 1 measuring the integration of the methoxy group at 3.74 (major) and 3.76 (minor).

¹H NMR (CDCl₃) δ: 0.95 - 1.07 (m, 1 H), 1.10 (s, 3 H), 1.17 - 1.48 (m, 4 H), 1.35 (s, 9 H), 1.40 (s, 3 H), 1.42 - 1.50 (m, 1 H), 1.80 - 1.92 (m, 3 H), 2.36 (q, 1 H, *J* = 2.4 Hz), 3.74 (s, 3 H), 6.63 (d, 1 H, *J* = 2.6 Hz), 6.73 (d, 1 H, *J* = 2.7 Hz); ¹³C NMR (CDCl₃) δ: 17.81, 19.67, 26.20, 26.42, 27.66, 28.03, 29.65, 31.57, 34.98, 36.99, 47.21, 55.58, 107.94, 111.87, 125.80, 138.87, 145.88, 152.01; IR (thin

film): 2939 s, 2855 s, 1605 w, 1464 m, 1429 m, 1213 m, 1148 m, 1069 m cm^{-1} ;
 mass spectrum m/z (% rel intensity) 302 M^+ (100), 287 (14), 259 (32), 203 (40),
 164 (3), 149 (3), 135 (2), 128 (2), 91 (4), 67 (3); Beige solid (hexane), mp 100 -
 107 °C, R_f = 0.75 (30 % ethyl acetate / hexane). $[\alpha]_D^{22} +1^\circ$ (c 0.235, CH_2Cl_2) at
 9 to 1 dr.

Compound 4-162

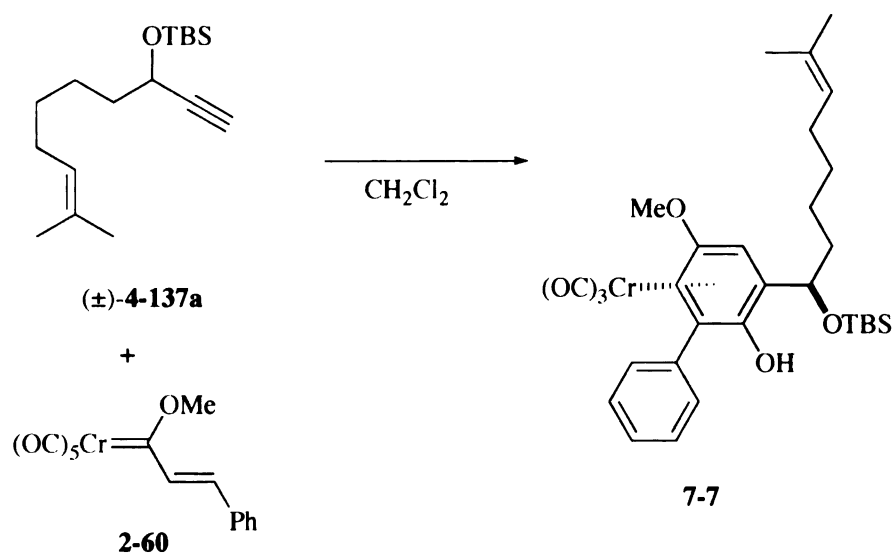


To a 50 mL flask, where the standard 14/20 tapered joint was replaced with a threaded high vacuum Teflon valve, styryl carbene complex **2-60** (104.3 mg, 0.31 mmol), alkyne (84.2 mg, 0.30 mmol), and DCM (5 mL) were added. Three standard freeze thaw cycles were done. The contents of the flask were heated at 60 °C for 18 hours. The contents of the reaction flask were stirred open to the air for 24 hours. Column chromatography (25 cm x 1.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 87.1 mg of compound (±)-**4-186** (62 % yield, 0.186 mmol). Alternatively, the chromium tricarbonyl arene complex could

first be isolated in 48 % yield without doing the air oxidation (chromium arene was too unstable to fully characterize) and then the chromium arene complex could be air oxidized to the free phenol in 14 % yield by stirring in air for 2 days in acetonitrile.

^1H NMR (CDCl_3) δ : 0.01 (s, 3 H), 0.12 (s, 3 H), 0.88 (s, 9 H), 1.10 - 1.48 (m, 4 H), 1.56 (s, 3 H), 1.65 (s, 3 H), 1.66 - 2.00 (m, 4 H), 3.76 (s, 3 H), 4.68 (t, 1 H, $J = 6.0$ Hz), 5.06 (t, 1 H, $J = 7.1$ Hz), 6.46 (d, 1 H, $J = 3.0$ Hz), 6.75 (d, 1 H, $J = 3.0$ Hz), 7.27 - 7.28 (m, 1 H), 7.29 - 7.40 (m, 2 H), 7.54- 7.57 (m, 2 H), 7.86 (s, 1 H); ^{13}C NMR (CDCl_3) δ : -5.06, 17.65, 18.15, 25.52, 25.71, 27.87, 29.58, 38.17, 55.74, 77.71, 112.35, 114.22, 124.51, 126.96, 128.09, 129.37, 129.44, 130.10, 131.43, 138.46, 146.41, 152.31; IR (thin film): 3359 m, 2932 s, 2857 s, 1601 w, 1466 m, 1424 m, 1256 w, 1049 w, 837 w cm^{-1} ; mass spectrum m/z (% rel intensity) 455 $[\text{M}+1]^+$ (0.08), 454 M^+ (0.3), 379 (0.6), 322 (20), 314 (2), 279 (21), 251 (5), 237 (9), 226 (10), 213 (30), 109 (15), 75 (100); Yellow oil (hexane), $R_f = 0.63$ (30 % ethyl acetate/ hexane).

Compound 7-7 (4-144)



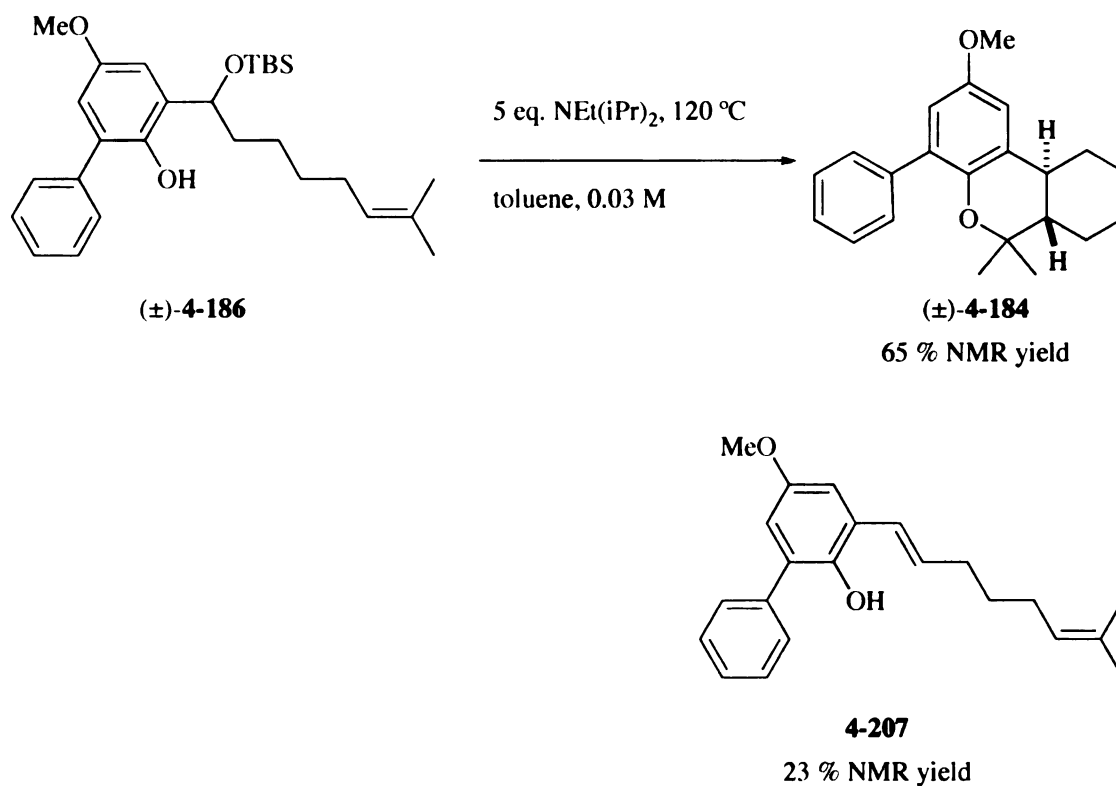
A magnetic stirring bar was placed into a flame-dried single neck flask that had been modified by replacement of the joint with a threaded high vacuum Teflon valve. To this flask was added styryl carbene complex **2-60** (0.107 g, 0.32 mmol), alkyne (±)-**4-137a** (0.095 g, 0.33 mmol), Hunig's base (0.3 mL, 1.8 mmol), and 10 mL of toluene. The contents of the flask were heated at 80 °C for 24 hours. The solvent was removed under reduced pressure and column chromatography (20 x 1.8 cm, silica gel) was done with 5 % ethyl acetate / hexane. This gave 0.075 g (40 % yield, 0.128 mmol) of a yellow unstable compound tentatively identified as **7-7**. Only one diastereomer was observed. Also found was 0.027 g of another chromium tricarbonyl arene complex (18 % yield) which upon air oxidation for 5 days in CH_2Cl_2 gave a compound that had identical spectroscopic properties to compound **4-154**.

The compound **7-7** was unstable and only ^1H NMR and IR could be

obtained.

^1H NMR (CDCl_3) δ : 0.23 (br s, 3 H), 0.33 (br s, 3 H), 0.93 (br s, 9 H), 1.24 (br m, 4 H), 1.56 (br s, 3 H), 1.65 (br s, 3 H), 1.94 (br m, 4 H), 3.62 (br s, 3 H), 4.70 (br s, 1 H), 5.08 (br s, 2 H), 5.69 (br s, 1 H), 7.38 (br s, 3 H), 7.63 (br s, 2 H), 8.81 (br s, 1 H); ^{13}C NMR (CDCl_3) δ : could not be obtained due to the instability of the compound; IR (thin film): 3379 m, 2923 m, 2853 m, 1958 vs, 1877 vs cm^{-1} ; Yellow oily solid (hexane), $R_f = 0.40$ (30 % ethyl acetate / hexane).

Compound 4-163

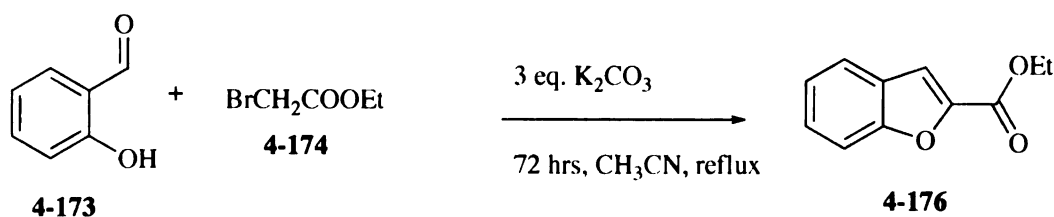


A magnetic stirring bar was placed into a flame-dried single neck flask that had been modified by replacement of the joint with a threaded high vacuum Teflon valve. To this flask was added phenol **(±)-4-186** (0.052 g, 0.11 mmol),

chromatography (15 x 1.8 cm, silica gel) with 10 % ethyl acetate / hexane gave 0.022 g (70 %, 0.119 mmol) of (6a*R*,10a*R*)-**4-208**. The enantiomeric excess was determined to be 94 % ee for compound (6a*R*,10a*R*)-**4-208**. The enantiomeric excess could be determined by HPLC with Chiralpac AD column with 98 : 2 (hexane to isopropanol) with retention times of 42.3 minutes for the minor and 48.01 minutes for the major.

^1H NMR (CDCl_3) δ : 0.94 - 1.11 (m, 1 H), 1.11 (s, 3 H), 1.14 - 1.20 (m, 1 H), 1.21 - 1.47 (m, 3 H), 1.26 (s, 3 H), 1.73 - 1.93 (m, 3 H), 2.30 - 2.44 (m, 2 H), 4.70 (br s, 1 H), 5.26 (s, 2 H), 6.65 (d, 1 H, $J = 2.8$ Hz), 6.69 (d, 1 H, $J = 2.8$ Hz), 7.20 - 7.28 (m, 1 H), 7.29 - 7.38 (m, 2 H), 7.49 - 7.54 (m, 2 H); ^{13}C NMR (CDCl_3) δ : 19.97, 26.12, 26.28, 27.67, 27.76, 31.30, 36.59, 47.08, 76.80, 111.92, 115.70, 126.56, 127.06, 127.66, 129.60, 130.55, 138.66, 144.19, 148.18; IR (thin film): 3362 m, 2930 s, 2857 m, 1456 m, 1429 m, 1262 m, 1144 m cm^{-1} ; mass spectrum m/z (% rel intensity) 308 $[\text{M}+1]^+$ (84), 265 (100), 237 (21), 223 (24), 212 (14), 199 (60), 183 (24), 165 (13), 153 (14), 109 (67), 77 (60), 42 (95); Beige solid (hexane), mp 46 - 48 °C, $R_f = 0.48$ (30 % ethyl acetate / hexane). $[\alpha]_{20}^{\text{D}} -28.5^\circ$ (c 0.745, CH_2Cl_2) at 88 % ee.

Compound 4-176



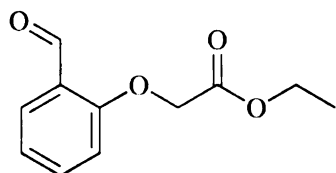
Procedure One. The following is a modified procedures from the literature.³⁷⁷ A flask was charged with salicylaldehyde **4-173** (3.67 g, 30 mmol), ethyl bromoacetate **4-174** (4.0 mL, 36.2 mmol), potassium carbonate (12.3 g, 89.0 mmol), and acetonitrile (250 mL). The contents of the flask were refluxed for 72 hours. The contents of the flask were poured into 200 mL of water and back extracted with 100 mL x 3 of ethyl acetate. Column chromatography (23 x 3.8 cm, silica gel) with 10 % ethyl acetate / hexane gave 5.27 g (92 % yield, 27.6 mmol) of compound **4-176** as a yellow oil. This solidified upon standing into a beige solid.

Procedure Two. A 1 L flask was charged with salicylaldehyde **4-173** (10.34 g, 84.7 mmol), ethyl bromoacetate **4-174** (10 mL, 90.4 mmol), potassium carbonate (29.2 g, 211.3 mmol), and 500 mL of DMF. The contents of the flask were stirred for 5 days at room temperature. The contents of the flask were poured into a mixture of 200 mL of water and 100 mL of 1 M HCl. The water layer was extracted with 100 mL x 3 of ethyl acetate. The organic fractions were combined and washed with brine (100 mL), and the brine was extracted with 100 mL x 3 of ethyl acetate. This resulted in 28.23 g of a yellow oil. Column chromatography (30 cm x 6 cm, silica gel) with 57 % of the material from extraction with 10 %

ethyl acetate / hexane, 20 % ethyl acetate / hexane, and 30 % ethyl acetate / hexane gave 1.024 g (11 % yield) of the desired compound **4-176** and also 2.0488 g (20 %) of **4-175**. The yields took into account that only 57 % of the mass of the product was separated. The spectroscopic properties were identical with those previously reported.³⁷⁷

¹H NMR (CDCl₃) δ: 1.46 (t, 3 H, *J* = 7.1 Hz), 4.48 (q, 2 H, *J* = 7.1 Hz), 7.32 (t, 1 H, 7.3 Hz), 7.47 (t, 1 H, 7.2 Hz), 7.55 (s, 1 H), 7.62 (d, 1 H, 8.2 Hz), 7.70 (d, 1 H, 7.8 Hz); ¹³C NMR (CDCl₃) δ: 14.12, 61.28, 112.11, 113.55, 122.58, 123.54, 126.62, 127.34, 145.50, 155.47, 159.35; Yellow oil (hexane), beige crystalline solid after standing overnight, *R*_f = 0.45 (30 % ethyl acetate / hexane).

Compound 4-175

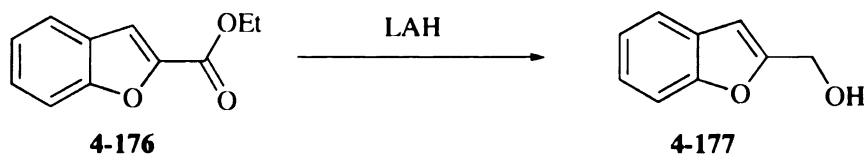


The spectroscopic properties were identical to that previously reported.³⁷⁷

¹H NMR (CDCl₃) δ: 1.22 (t, 3 H, *J* = 7.1 Hz), 4.19 (q, 2 H, *J* = 7.1 Hz), 4.68 (s, 2 H), 6.80 (d, 1 H, *J* = 8.4 Hz), 7.00 (br t, 1 H, *J* = 7.5 Hz), 7.46 (td, 1 H, *J* = 8.3 Hz, *J* = 1.8 Hz), 7.78 (dd, 1 H, *J* = 7.7 Hz, 1.6 Hz), 10.49 (d, 1 H, *J* = 0.75 Hz); ¹³C NMR (CDCl₃) δ: 13.92, 61.38, 65.41, 112.46, 121.59, 125.16, 128.26, 135.57, 159.94, 167.97, 189.33. Yellow solid (hexane), *R*_f = 0.30 (30 % ethyl acetate /

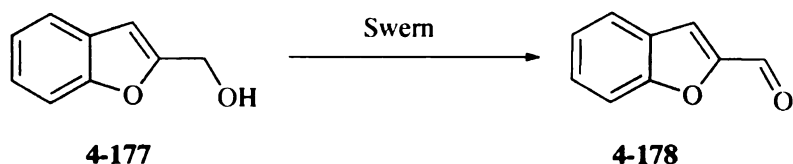
hexane).

Compound 4-177



Compound **4-177** was prepared by a modified procedure from the literature.^{377, 378} A flask was charged with LAH (0.78 g, 20.6 mmol) and THF (175 mL). The ester compound **4-176** (3.84 g, 20.2 mmol) was added in 50 mL of THF dropwise at room temperature. The contents of the flask were brought to reflux and heated for 3 hours. To this flask was added 300 mL of saturated potassium carbonate and the contents of the flask were stirred for 15 minutes. The contents of the flask were poured into 200 mL of ethyl acetate and stirred for 15 minutes. The aqueous layer was separated and it was extracted with 200 mL, 100 mL, and 50 mL of ethyl acetate. Column chromatography (25 x 3.5 cm, silica gel) with 30 % ethyl acetate / hexane gave 2.60 g (87 % yield, 17.6 mmol) of compound **4-177**. The spectroscopic properties were identical to those previously reported.^{377, 378}

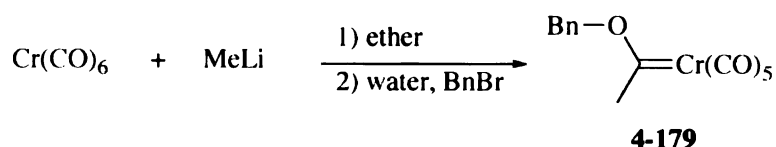
Compound 4-178



A 250 mL round bottom flask was charged with DMSO (4.5 mL, 63.4

mmol) and dichloromethane (125 mL) and the contents of the flask were cooled to $-78\text{ }^{\circ}\text{C}$. Oxalyl chloride (6.1 mL, 70.0 mmol) was added dropwise. The solution was stirred for 10 minutes then compound **4-178** (3.00 g, 20.5 mmol) was added dropwise and the solution was stirred for 15 minutes. Triethyl amine (20 mL) was added. The solution was warmed at room temperature for 1 hour. Extraction with 100 mL of 1 M HCl, saturated bicarbonate solution, and brine was done. Each aqueous layer was back extracted with 100 mL of ethyl acetate x 3. Column chromatography (24 x 3.8 cm, silica gel) with 5 % ethyl acetate / hexane then 10 % ethyl acetate / hexane was done giving 2.44 g (81 %, 16.61 mmol). The spectroscopic properties were identical to that previously reported.³⁷⁹

Compound 4-179



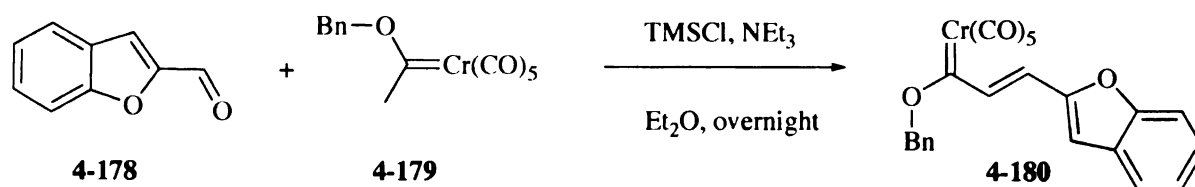
This experiment was done following an adapted literature procedure by Hoye and coworkers.³⁸⁰ Chromium hexacarbonyl (3.07 g, 13.9 mmol), methyl lithium (10 mL, 1.4 mol/L in hexanes, 14 mmol), and ether (150 mL) were added to a 250 mL round bottom flask. This was stirred at reflux for 1.5 hours. The solvent was removed under reduced pressure. A flask was charged with this residue along with 150 mL of water, (*n*-Bu)₄NBr (1 g, 3.1 mmol), and benzyl bromide (3.3 mL, 27.8 mmol). The solution was heated at $70\text{ }^{\circ}\text{C}$ for three hours. The flask was cooled to room temperature. It was extracted with 3 x 200 mL of

pentane. The organic layers were combined and dried over magnesium sulfate. The solvent was removed under reduced pressure. Column chromatography (15 x 5.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 0.76 g (17 % yield, 2.36 mmol) of carbene complex **4-179**.

A reaction that was setup side by side with the above reaction except using (*n*-Bu)₄NI which gave a 57 % yield.

The spectroscopic properties were identical to that reported in the literature.³⁸⁰

Compound 4-180



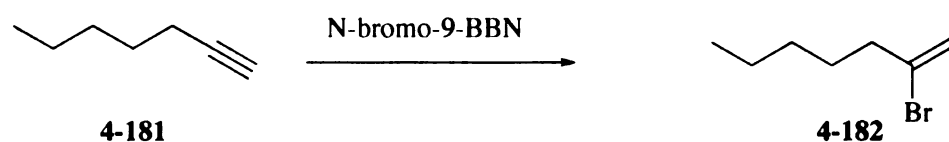
A magnetic stirring bar was placed into a flame-dried single neck flask (50 mL) that had been modified by replacement of the joint with a threaded high vacuum Teflon valve. The flask was charged with aldehyde **4-178** (0.11 g, 0.8 mmol), carbene complex **4-179** (0.23 g, 0.7 mmol), ether (10 mL), TMSCl (0.4 mL, 3.2 mmol), and triethyl amine (0.3 mL, 2.2 mmol). Three freeze thaw cycles were done. The solution turned red in color in 10 minutes after the triethyl amine was added. The reaction was stirred overnight and was blood red the next day. The contents of the flask were poured onto 5 cc of silica gel and the solvent was removed under reduced pressure. Column chromatography (25 x 2.8 cm, silica gel) with 10 % ethyl acetate / hexane gave a red oil. A second column (10 cm x

2.8 cm, silica gel) was done with hexane until the yellow band came off the column then 5 % ethyl acetate / hexane was used to isolate the red band by elution. This gave 0.11 g of a red oil which solidified upon standing. The resulting solid was triturated with hexanes and the hexanes were decanted. The remaining solid was used without further purification. The yield was 20 % (0.064 g, 0.14 mmol) after the trituration of carbene complex **4-180**.

^1H NMR (CD_2Cl_2) δ : 6.11 (s, 2 H), 6.83 (d, 1 H, $J = 15.1$ Hz), 7.14 - 7.64 (m, 10 H), 8.11 (d, 1 H, $J = 15.0$ Hz); ^{13}C NMR (CDCl_3) δ : 82.30, 111.87, 115.98, 116.56, 122.13, 123.90, 127.62, 128.81, 129.06, 129.28, 129.37, 135.37, 138.80, 152.94, 156.50, 217.10, 225.16, 330.34; IR (thin film): 2921 w, 2858 w, 2056 m, 1931 s cm^{-1} ; mass spectrum m/z (% rel intensity) 454 M^+ (5), 370 (20), 307 (51), 289 (22), 136 (74); HRMS calcd for $\text{C}_{23}\text{H}_{14}\text{CrO}_7$ m/z 454.0145, meas 454.0142.

Dark solid (hexane), mp 114 - 120 °C, $R_f = 0.55$ (30 % ethyl acetate / hexane).

Compound 4-178

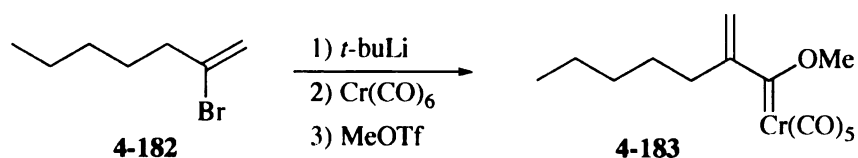


A 500 mL flask was charged with 1-heptyne (2.8 mL, 21.4 mmol) and 200 mL of CH_2Cl_2 . The flask was cooled to 0° C and a 1 M solution of Br-BBN (25 mL, 25.0 mmol) in CH_2Cl_2 was added dropwise. The contents of the flask were stirred for 3 hours. Acetic acid (11.4 mL, 20 mmol) was added dropwise at 0 °C.

The reaction was worked up with 3 N NaOH (150 mL) and 25 mL of hydrogen peroxide which was stirred for 30 minutes at room temperature. The contents of the flask were poured into 400 mL of hexane and the contents of the flask were extracted. The organic layer was extracted with saturated sodium bicarbonate, water, and each aqueous layer was back extracted with 2 x 50 mL of hexane. The organic layers were combined and filtered. Column chromatography (35 x 4.1 cm, silica gel) with 100 % hexane gave 1.37 g (36 %, 7.70 mmol) of vinyl bromide **4-182** with a regioselectivity of $\geq 96 : 4$ determined by ^1H NMR. The spectroscopic properties were identical to that previously reported.³⁸¹

^1H NMR (CDCl_3) δ : 0.88 (t, 3 H, $J = 6.8$ Hz), 1.29 (m, 4 H), 1.54 (sex, 2 H, $J = 7.2$ Hz), 2.39 (t, 2 H, $J = 7.3$ Hz), 5.36 (d, 1 H, $J = 1.6$ Hz), 5.53 (dd, 1 H, $J = 2.6, 1.2$ Hz); ^{13}C NMR (CDCl_3) δ : 13.96, 22.36, 27.57, 30.58, 41.39, 116.18, 134.95; IR (thin film): 2963 m, 2932 s, 2861 m, 1653 w, 1630 m, 1458 w, 1159 w, 884 w cm^{-1} ; mass spectrum m/z (% rel intensity) 177 $\text{M}^+ - 1$ (15, ^{81}Br), 175 $\text{M}^+ - 1$ (14, ^{79}Br), 120 (27), 95 (50), 89 (100), 81 (49), 55 (61); Clear oil (hexane), $R_f = 0.64$ (100 % hexane).

Compound 4-179



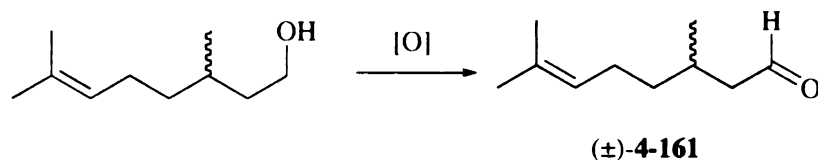
A 100 mL flask was charged with bromoalkene **4-178** (0.65 g, 3.7 mmol)

and 35 mL of ether. The contents of the flask were cooled to $-78\text{ }^{\circ}\text{C}$ and t-butyl lithium (4.5 mL, 7.7 mmol) was added. The contents of the flask were stirred for 30 minutes. To the flask was added chromium hexacarbonyl (0.85 g, 3.9 mmol) under a stream of argon gas, and the contents of the flask were warmed to $0\text{ }^{\circ}\text{C}$. The reaction mixture was stirred for 3 hours at $0\text{ }^{\circ}\text{C}$. The ether was removed under reduced pressure. To the flask was added 30 mL of CH_2Cl_2 and the contents of the flask were cooled to $0\text{ }^{\circ}\text{C}$. Then, MeOTf (0.84 mL, 7.4 mmol) was added to the flask and the contents of the flask were stirred for 1.5 hour. The contents of the flask were poured into 50 mL of water (emulsified, not the best way). The layers were separated (this was slow). The organic layer was extracted with brine (50 mL) and back extracted with 2 x 20 mL CH_2Cl_2 . The organic layers were combined and dried over magnesium sulfate. The solution was filtered and the solvent was removed under reduced pressure. Column chromatography (20 x 2.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 0.29 g (24 % yield, 0.89 mmol) of **4-183** as a red oil. Complete decomposition of this compound occurred when stored at $-20\text{ }^{\circ}\text{C}$ under argon for four days.

^1H NMR (CDCl_3) δ : 0.89 (br t, 3 H, $J = 6.7\text{ Hz}$), 1.20 - 1.35 (br m, 4 H), 1.36 - 1.51 (br m, 2 H), 2.17 (br t, 2 H, $J = 7.5\text{ Hz}$), 4.56 (br s, 3 H), 4.92 (br s, 1 H), 5.04 (br s, 1 H); ^{13}C NMR (CDCl_3) δ : 13.80, 22.38, 27.16, 31.57, 32.70, 66.03, 110.64, 163.12, 216.32, 223.85, 357.37; IR (thin film): 2958 s, 2932 s, 2863 s, 2084 s, 1943vs, 1454 m, 1235 m, 1148 m, 990 cm^{-1} ; mass spectrum m/z (% rel

intensity, FAB⁺) 332 M⁺ (55), 304 M⁺-CO (86), 276 M⁺-2 CO (14); Red oil (hexane), R_f = 0.64 (30 % ethyl acetate / hexane).

Formation of (±)-4-161

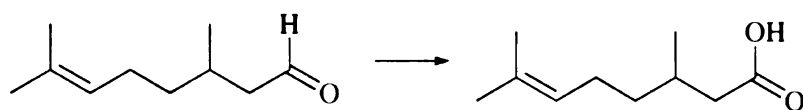


(±)-3,7-dimethyloct-6-en-1-ol

(±)-4-161

To a solution of DMSO (1.4 mL, 19.7 mmol) and dichloromethane (50 mL) at -78 °C was added oxalyl chloride (0.6 mL, 6.87 mmol) in a 250 mL round bottom flask. This was stirred for 15 minutes then 3,7-dimethyloct-6-en-1-ol ($[\alpha]_D^{22} = 0.00$ (neat), 1.00 g, 6.4 mmol) was added dropwise and the solution was stirred for 20 minutes at -78 °C. Triethyl amine (6.24 mL, 44.8 mmol) was added. The reaction mixture was warmed to room temperature for 1 hour. Column chromatography (20 x 2.8 cm, silica gel) with 10 % ethyl acetate / hexane gave 0.82 g (83 % yield, 5.33 mmol). The spectroscopic properties were identical with material from Aldrich.

Compounds 4-164 through 4-166



(*S*)-4-157

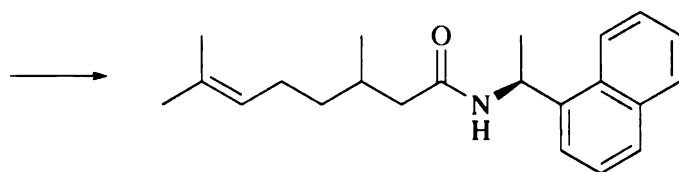
(*R*)-4-159

(±)-4-161

(*S*)-4-158

(*R*)-4-160

(±)-4-162



4-164

4-165

4-166

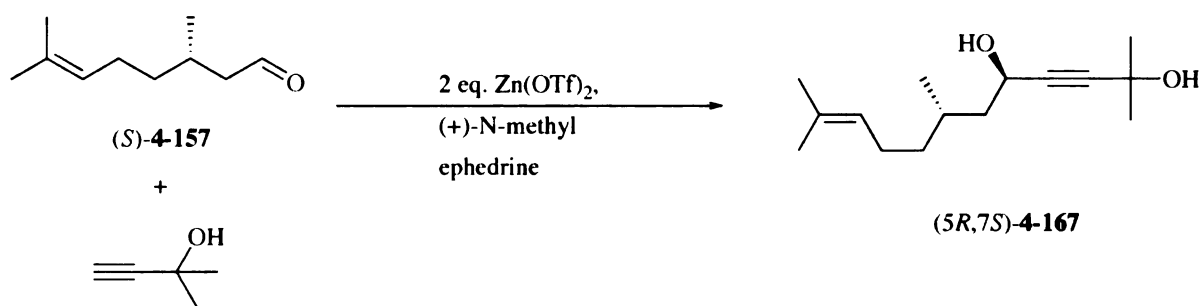
The analysis of citronellal was conducted using known literature methods.³⁸² A 25 mL round bottom flask open to the air was charged with (*S*)-4-157 (citronellal, 0.1 mL, 0.55 mmol) obtained from Aldrich, water (6 mL), Ag₂O (0.13 g, 0.556 mmol), and NaOH (0.10 g, 2.51 mmol). The reaction mixture was heated at 70 °C for 30 to 45 minutes. The solution was then cooled to room temperature and acidified with concentrated HCl the saturated sodium bicarbonate was added until no further gas generation was noted. No further purification was done. This yielded 0.068 g (72 % yield, 0.40 mmol) of (*S*)-3,7-dimethyloct-6-enoic acid.

The compound (*S*)-3,7-dimethyloct-6-enoic acid (0.068 g, 0.40 mmol) in 5 mL of benzene was treated with 0.088 mL (0.144 g, 1.2 mmol) of thionyl chloride in a 10 mL round bottom flask. The reaction mixture was stirred for 30 minutes

then the solvent was removed under reduced pressure. Then 5 mL of ether was added to the residue and cooled to 0 °C. Then (*R*)-naphthyl ethyl amine (**4-163**, 99.9 % ee, 0.13 mL, 0.81 mmol) was added. The mixture was stirred for one hour at 0 °C. The mixture was diluted with 100 mL of ether and washed successively with 1 M HCl (50 mL), saturated sodium bicarbonate (20 mL), water (10 mL), and dried over magnesium sulfate. The solvent was removed under reduced pressure. The resulting product was analyzed without further purification according to a literature procedure.³⁸³ This gave a yield of 62 % (0.24 g, 0.74 mmol) for compound **4-164**. The enantiomeric excess was determined to be 96.4 % using HPLC with a Microsorb-MV 100 Å column. The solvent system was 97 % hexane and 3 % isopropanol. The retention times were 14.02 minute for the minor compound and 15.36 minutes for the major compound. The retention times were compared to racemic ($\pm$)-**4-166** and were identical.

An identical procedure was followed for (*R*)-**4-159** obtained from Aldrich which gave an ee of 86.5 % measured on compound **4-165**. The yield of (*R*)-**4-160** was 61 % and the yield of **4-165** was 50 %. The yield of racemic ($\pm$)-**4-161** was 68 % and the yield of **4-166** was 56 %. The retention times were compared to **4-166** from racemic compound ($\pm$)-**4-161** and were identical.

Compound (5*R*,7*S*)-4-167



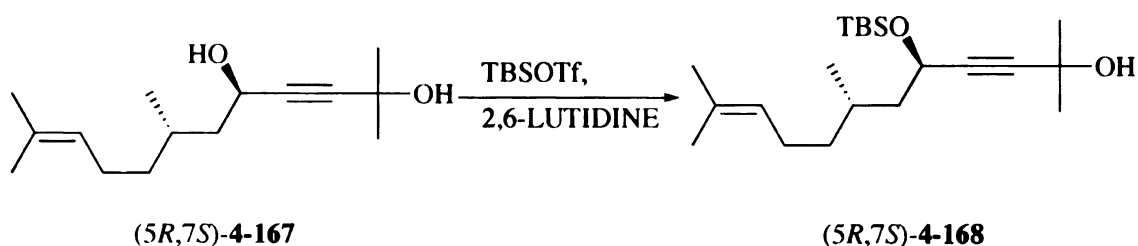
A 100 mL round bottom flask was charged with Zn(OTf)₂ (6.57 g, 18.1 mmol), N-methyl ephedrine (3.58 g, 20.0 mmol), toluene (50 mL), and triethyl amine (2.51 mL, 18.0 mmol). The reaction mixture was stirred for 2 hours at room temperature and 2-methyl-3-butyn-2-ol (1.8 mL, 18.6 mmol) that had been previously distilled over calcium hydride was added. The solution was stirred for 20 minutes. Citronellal (S)-4-157 (1.6 mL, 8.8 mmol, 96.4 % ee) was added via syringe pump over 4 hours in 5 mL of toluene and the reaction mixture was stirred overnight. Column chromatography (30 x 3.5 cm, silica gel) with 30 % ethyl acetate / hexane to 50 % ethyl acetate / hexane gave 1.99 g (95 % yield, 8.36 mmol) of compound (5*R*,7*S*)-4-167. The ratio of diastereomers was $\geq 20 : 1$ as determined by ¹H NMR.

¹H NMR (CDCl₃) δ : 0.90 (d, 3 H, $J = 6.7$ Hz), 1.10 - 1.18 (m, 1 H), 1.27 - 1.37 (m, 1 H), 1.40 - 1.48 (m, 1 H), 1.48 (s, 6 H), 1.56 (s, 3 H), 1.63 - 1.76 (m, 2 H), 1.64 (s, 3 H), 1.88 - 2.01 (m, 2 H), 2.97 (br s, 2 H), 4.41 (dd, 1 H, $J = 5.8$ Hz, 7.8 Hz), 5.06 (br t, 1 H, $J = 7.1$ Hz); ¹³C NMR (CDCl₃) δ : 17.59, 19.22, 25.30, 26.64, 28.91, 31.29, 37.00, 45.04, 60.33, 64.93, 83.58, 89.32, 124.55, 131.18; IR (thin

film): 3330 br s, 2969 s, 2926 s, 1456 m, 1377 m, 1237 w, 1165 m cm^{-1} ; mass spectrum m/z (% rel intensity) 223 (0.1), 220 $\text{M}^+ - 18$ (1), 205 (9), 187 (9), 177 (12), 163 (9), 145 (15), 135 (34), 121 (25), 107 (59), 95 (73), 82 (27), 67 (57), 56 (36), 42 (100); Thick clear oil (hexane), $R_f = 0.13$ (30 % ethyl acetate / hexane).

$[\alpha]_D^{22} +10.3^\circ$ (c 1.13, CH_2Cl_2) with $> 20 : 1$ dr.

Compound 4-168

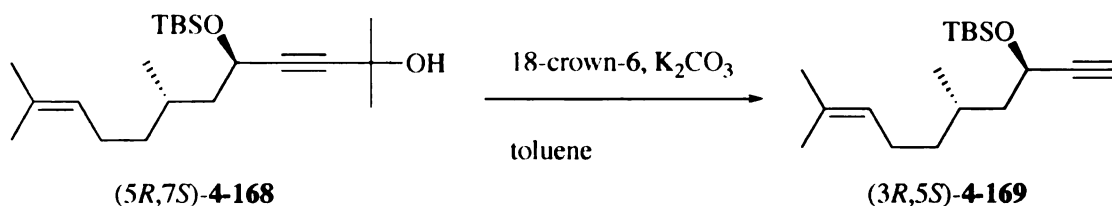


A 100 mL round bottom was charged with dichloromethane (30 mL), compound **4-167** (1.0 g, 4.2 mmol), and 2,6-lutidine (0.58 mL, 5 mmol). The reaction mixture was cooled to 0 °C and TBSOTf (0.95 mL, 4.1 mmol) was added dropwise. The reaction mixture was stirred for 3 hours at 0 °C and 20 mL of saturated ammonium chloride was added. The reaction was extracted with dichloromethane, 10 mL of saturated bicarbonate with back extraction of 10 mL x 3, and the organic layers were dried over magnesium sulfate. Column chromatography (22 x 4.1 cm, silica gel) with hexane then 5 % ethyl acetate / hexane and then 10 % ethyl acetate / hexane gave 1.05 g (72 % yield, 3.00 mmol). The diastereomeric ratio was $\geq 96 : 4$ as determined by ^1H NMR.

^1H NMR (CDCl_3) δ : 0.08 (s, 3 H), 0.11 (s, 3 H), 0.84 (d, 3 H, peak overlap), 0.87

(s, 9 H), 1.06 - 1.39 (m, 4 H), 1.47 (s, 6 H), 1.56 (s, 3 H), 1.65 (s, 3 H), 1.66 - 1.77 (m, 1 H), 1.95 (q, 2 H, $J = 5.2$ Hz), 2.18 (br s, 1 H), 4.40 (dd, 1 H, $J = 8.4$, 5.0 Hz), 5.06 (t, 1 H, $J = 7.0$ Hz); ^{13}C NMR (CDCl_3) δ : -5.07, -4.31, 17.64, 18.17, 19.11, 25.34, 25.69, 25.76, 28.47, 31.29, 31.35, 37.27, 45.83, 60.85, 65.07, 84.30, 88.33, 124.69, 131.15; IR (thin film): 3353 bm, 2957 s, 2930 m, 2857 s, 1472 w, 1464 w, 1377 w, 1362 w, 1252 m, 1167 s, 1088 s cm^{-1} ; mass spectrum m/z (% rel intensity) 337 (1), 293 (1), 267 (5), 227 (5), 177 (8), 147 (12), 119 (16), 109 (30), 75 (100), 73 (42), 68 (36); Anal calcd for $\text{C}_{21}\text{H}_{40}\text{O}_2\text{Si}$: C, 71.53; H, 11.43. Found; C, 71.35; H, 11.51. Clear oil (hexane), $R_f = 0.52$ (30 % ethyl acetate / hexane). $[\alpha]_D^{22} +48.3^\circ$ (c 0.553, CH_2Cl_2) with $> 20 : 1$ dr.

Compound (3*R*,5*S*)-4-169

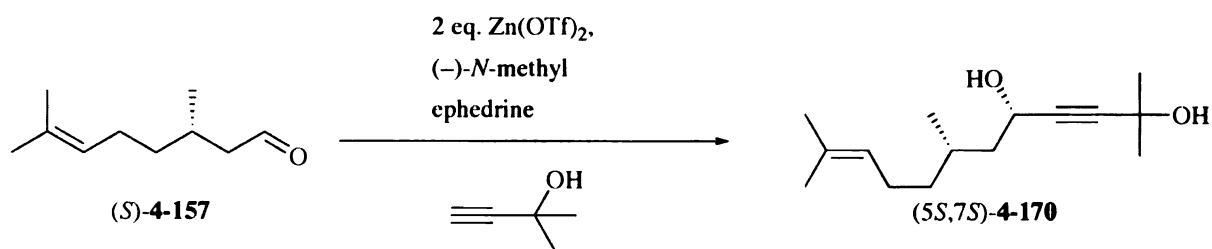


A 50 mL flask was charged with alkyne (5*R*,7*S*)-4-168 (0.99 g, 2.8 mmol), 18-crown-6 (0.77 g, 2.9 mmol), potassium carbonate (0.40 g, 2.9 mmol), and toluene (30 mL). The contents of the flask were refluxed for 18 to 24 hours under a stream of nitrogen gas. The nitrogen gas was allowed to pass out of the flask to remove any volatiles formed during the reaction. The solvent was removed under reduced pressure and directly taken on to column chromatography. Column chromatography (35 x 3.8 cm, silica gel) with 5 % ethyl acetate / hexane

gave 0.78 g (95 %, 2.66 mmol) of (3*R*,5*S*)-**4-169**. The diastereomeric ratio was $\geq$ 96 : 4 as determined by ^1H NMR.

^1H NMR (CDCl_3) δ : 0.09 (s, 3 H), 0.13 (s, 3 H), 0.88 (m, 12 H), 1.05 - 1.80 (m, 4 H), 1.58 (s, 3 H), 1.65 (s, 3 H), 1.66 - 1.80 (m, 1 H), 1.96 (q, 2 H, $J = 7.5$ Hz), 2.35 (d, 1 H, $J = 2.0$ Hz), 4.38 (ddd, 1 H, $J = 13.5, 4.8, 2.0$ Hz), 5.07 (t, 1 H, $J = 7.1$ Hz); ^{13}C NMR (CDCl_3) δ : -5.18, -4.45, 17.64, 18.16, 19.14, 25.33, 25.69, 25.74, 28.46, 37.18, 45.78, 60.78, 71.78, 86.12, 124.68, 131.19; IR (thin film): 3312 m, 2957 s, 2930 s, 2859 s, 1464 m, 1379 w, 1252 m, 1090 m cm^{-1} ; mass spectrum m/z (% rel intensity) 293 $\text{M}^+ - 1$ (2), 194 (35), 193 (42), 169 (8), 149 (12), 127 (25), 109 (100), 83 (95); Clear oil (hexane), $R_f = 0.74$ (30 % ethyl acetate / hexane). $[\alpha]_D^{22} +27.0^\circ$ (c 0.414, CH_2Cl_2).

Compound 4-170

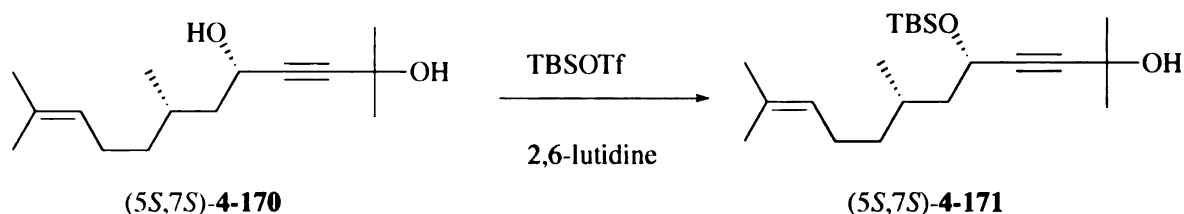


A 100 mL round bottom flask was charged with zinc triflate (4.20 g, 11.6 mmol), (-)-methyl ephedrine (2.21 g, 12.3 mmol), toluene (31 mL), and triethyl amine (1.6 mL, 11.5 mmol). This mixture was stirred for two hours at room temperature. To this solution was added 2-methylbut-3-yn-2-ol (1.1 mL, 11.4

mmol) and the reaction was stirred for 15 minutes. Over four hours, (–)-citronellal (*S*)-**4-156** (1 mL, 5.5 mmol, 96.4 % ee) was added by syringe pump. The reaction mixture was allowed to stir overnight. The contents of the flask were poured into 40 mL of saturated ammonium hydroxide. The aqueous layer was back extracted with 20 mL x 3 of ethyl acetate. The organic layers were combined and neutralized with solid sodium bicarbonate. To this solution was added magnesium sulfate as a drying agent. The organic fraction was filtered through fluted filter paper, and the solvent was removed under reduced pressure. Column chromatography (25 x 4 cm, silica gel) with 30 % ethyl acetate / hexane gave 0.92 g (70 % yield, 3.85 mmol) of (*5S,7S*)-**170**.

^1H NMR (CDCl_3) δ : 0.90 (d, 3 H, $J = 6.5$ Hz), 1.14 - 1.25 (m, 1 H), 1.31 - 1.40 (m, 1 H), 1.49 (s, 6 H), 1.51 - 1.56 (m, 1 H), 1.59 (s, 3 H), 1.62 - 1.67 (m, 2 H), 1.66 (s, 3 H), 1.93 - 2.03 (m, 4 H), 4.43 (t, 1 H, $J = 6.7$ Hz), 5.08 (br t, 1 H, $J = 7.1$ Hz); ^{13}C NMR (CDCl_3) δ : 17.65, 19.67, 25.28, 25.69, 29.35, 31.34, 36.88, 45.05, 60.99, 65.08, 83.21, 89.63, 124.56, 131.36; IR (thin film): 3339 s, 2967 s, 2926 s, 1456 w, 1377 m, 1165 m cm^{-1} ; mass spectrum m/z (% rel intensity) 220 M^+ -18 (1), 205 (4), 187 (9), 177 (12), 163 (9), 145 (16), 135 (29), 121 (25), 107 (54), 93 (25), 81 (33), 69 (91), 41 (100); Yellow oil (hexane), $R_f = 0.11$ (30 % ethyl acetate / hexane). $[\alpha]_D^{22} -15^\circ$ (c 0.025, CH_2Cl_2) with $> 20 : 1$ dr

Compound (5*S*,7*S*)-4-171

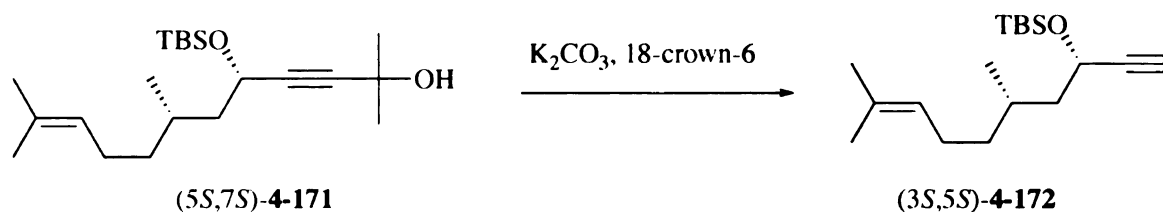


A 100 mL round bottom flask was charged with compound (5*S*,7*S*)-4-170 (0.92 g, 3.9 mmol), dichloromethane (50 mL), 2,6-lutidine (0.45 mL, 3.9 mmol), and the flask was cooled to 0 °C. To the pre-cooled flask was added TBSOTf (0.9 mL, 3.9 mmol) in a dropwise manor. The solution was stirred for 30 minutes at 0 °C. Column chromatography (30 x 4 cm, silica gel) with 10 % ethyl acetate / hexane gave 1.12 g (82 % yield, 3.20 mmol) of (5*S*,7*S*)-4-171.

^1H NMR (CDCl_3) δ : 0.087 (s, 3 H), 0.11 (s, 3 H), 0.83 - 0.91 (m, 12 H, overlapped s and d), 1.05 - 1.15 (m, 1 H), 1.31 - 1.38 (m, 1 H), 1.47 (s, 6 H), 1.474 - 1.54 (m, 1 H), 1.57 - 1.68 (m, 2 H), 1.58 (s, 3 H), 1.65 (s, 3 H), 1.85 (br s, 1 H), 1.90 - 2.02 (m, 2 H), 4.41 (t, 1 H, $J = 6.9$ Hz), 5.07 (br t, 1 H, $J = 6.6$ Hz); ^{13}C NMR (CDCl_3) δ : -4.92, -4.43, 17.63, 18.19, 19.93, 25.29, 25.71, 25.80, 28.91, 31.29, 31.34, 36.63, 45.84, 61.30, 65.12, 83.98, 88.58, 124.68, 131.14; IR (thin film): 3418 br m, 2959 s, 2936 m, 2190 w, 1653 m cm^{-1} ; mass spectrum m/z (% rel intensity) 335 $\text{M}^+ - 17$ (3), 295 (5), 266 (6), 239 (6), 211 (8), 197 (4), 187 (23), 177 (19), 169 (9), 161 (26), 159 (22), 135 (14), 133 (26), 119 (35), 109 (58), 105 (38), 75 (100), 69 (40); Clear oil, $R_f = 0.5$ (30 % ethyl acetate / hexane). $[\alpha]_D^{22} -6.0^\circ$ (c 0.17,

CH₂Cl₂).

Compound (3*S*,5*S*)-4-172

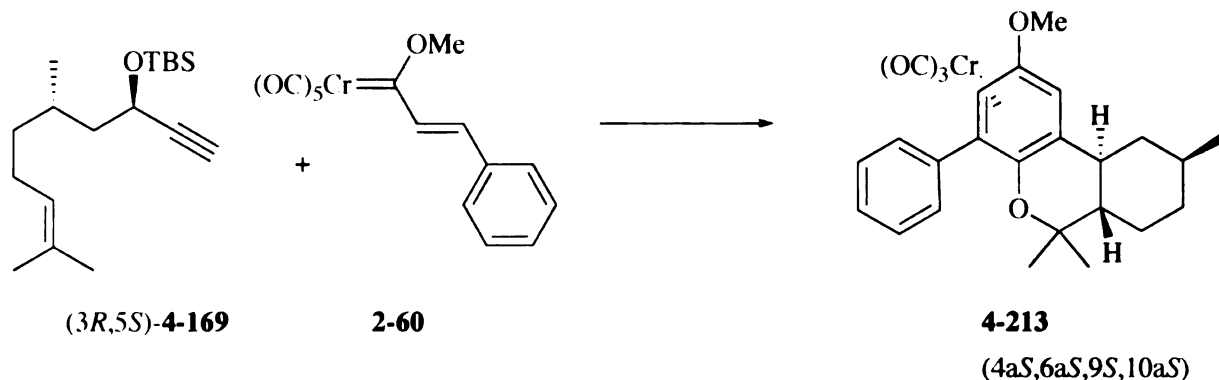


A 100 mL round bottom flask was charged with compound **(5*S*,7*S*)-4-171** (1.10 g, 3.1 mmol), 18-crown-6 (0.96, 3.6 mmol), potassium carbonate (0.48 g, 3.5 mmol), and toluene (30 mL). The contents of the flask were heated at 120 °C overnight under a moderate stream of nitrogen. The solvent was removed under reduced pressure. Column chromatography with 5 % ethyl acetate / hexane (30 cm x 4 cm, silica gel) gave 0.92 g (94 % yield, 2.91 mmol) of **(5*S*,7*S*)-4-172**. This compound is known in the literature.³⁸⁵

¹H NMR (CDCl₃) δ: 0.10 (s, 3 H), 0.12 (s, 3 H), 0.89 (s, 9H), 0.88 - 0.90 (d, 3 H, doublet obscured), 1.09 - 1.30 (m, 1 H), 1.31 - 1.40 (m, 1 H), 1.48 - 1.55 (m, 1 H), 1.58 (s, 3 H), 1.64 - 1.71 (m, 2 H), 1.66 (s, 3 H), 1.88 - 2.05 (m, 2 H), 2.35 (d, 1 H, *J* = 2.2), 4.39 (td, 1 H, *J* = 7.1, 2.02 Hz), 5.08 (br t, 1 H, *J* = 7.1 Hz); ¹³C NMR (CDCl₃) δ: -5.01, -4.51, 17.62, 18.19, 19.79, 25.34, 25.69, 25.79, 28.97, 36.83, 45.84, 61.35, 72.00, 85.79, 124.74, 131.12; IR (thin film): 3312 s, 2930 s, 2857 s, 1474 w, 1258 w, 1082 w cm⁻¹; mass spectrum *m/z* (% rel intensity) 293 M⁺-1 (0.25), 185 (1), 169 (5), 109 (32), 105 (15), 75 (100); Clear oil (hexane), R_f = 0.74

(30 % ethyl acetate / hexane). $[\alpha]_D^{22} -23.3^\circ$ (c 0.434, CH_2Cl_2) with $> 20 : 1$ dr.

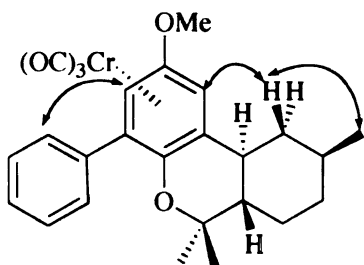
Compound 4-213



Procedure 4B. In a 50 mL round bottom were the standard tapered joint was replaced with a threaded high vacuum Teflon valve was added styryl carbene complex **2-60** (0.108 g, 0.32 mmol), alkyne (3*R*,5*S*)-**4-169** (0.108 g, 0.32 mmol), Hunig's base (0.30 mL, 1.7 mmol), and toluene 10 mL. The order of addition was carbene complex, toluene (5 mL), alkyne in toluene (5 mL), and Hunig's base. Three freeze thaw cycles were done. The reaction was heated at 80 °C for 24 hours. The reaction mixture was poured onto about 2 - 5 cc of silica gel and the solvent removed under reduced pressure and the silica loaded onto the top of the column. Column chromatography (30 cm x 1.8 cm, silica gel) with hexane then 5 % ethyl acetate / hexane gave 0.0846 g (56 % yield, 0.179 mmol) of **4-213**. The *trans* : *cis* ratio was found to be $\geq 95 : 5$ in all cases analyzed on compound **4-227**.

Table 7.3. Yields of **4-213**

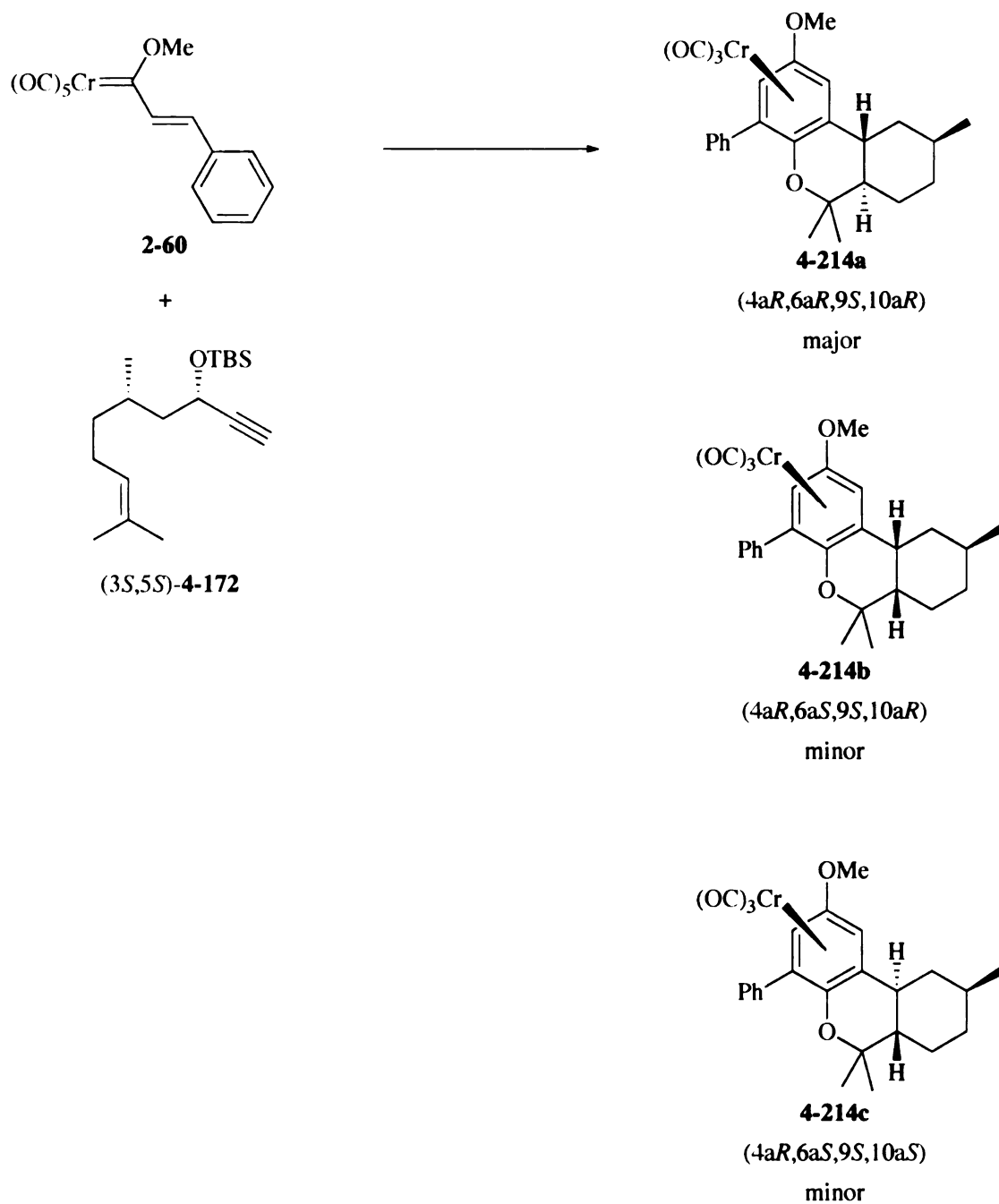
entry	solvent (M, carbene)	base	time	temp	yield 4-199
1	toluene (0.015)	N(iPr) ₂ Et 5 eq.	24 hrs	80	39
2	toluene (0.032)	N(iPr) ₂ Et 5 eq.	24 hrs	80	56
3	toluene (0.042)	none	24 hrs	80	34
4	toluene (0.046)	N(iPr) ₂ Et 5 eq.	13 hrs 11 hrs	60 80	27
5	toluene (0.073)	N(iPr) ₂ Et 5 eq.	13 hrs 11 hrs	60 80	26

Compound 4-213 Homonuclear nOe ¹H-¹H

¹H NMR (CDCl₃) δ: 0.84 - 1.00 (m, 2 H), 1.02 (d, 3 H, *J* = 6.6 Hz), 1.06 - 1.14 (m, 1 H), 1.25 (s, 3 H), 1.27 - 1.30 (m, 1 H), 1.34 (s, 3 H), 1.60 - 1.69 (m, 1 H), 1.78 (ddd, 1 H, *J* = 12.6, 6.3, 3.1 Hz), 1.84 (br d, 1 H, *J* = 13.0 Hz), 2.31 (br d, 1 H, *J* = 12.5 Hz), 2.63 (td, 1 H, *J* = 11.7, 3.8 Hz), 3.69 (s, 3 H), 5.32 (d, 1 H, *J* = 2.5 Hz), 5.45 (d, 1 H, *J* = 2.5 Hz), 7.32 - 7.42 (m, 3 H), 7.60 - 7.65 (m, 2 H); ¹³C NMR (CDCl₃) δ: 19.24, 22.36, 27.25, 28.18, 32.15, 34.17, 34.74, 39.20, 46.62, 56.08, 75.63, 80.33, 84.49, 94.49, 102.19, 127.77, 128.18, 128.31, 130.31, 134.47, 135.66, 234.66; IR (thin film): 2924 w, 2853 w, 1952 s, 1867 s, 1541 w, 1459 w,

1420 m cm^{-1} ; mass spectrum m/z (% rel intensity, FAD^+) 472 M^+ (52), 388 (100), 336.2 (24); HRMS calcd for $\text{C}_{26}\text{H}_{28}\text{CrO}_5$ m/z 472.1342, meas 472.1343. Yellow needle (hexane), mp 178 - 180 °C (dec.), $R_f = 0.56$ (30 % ethyl acetate / hexane). $[\alpha]_D^{22} +21.5^\circ$ (c 0.27, CH_2Cl_2) with > 20 : 1 dr.

Compound 4-214a, 4-214b, and 4-214c



This compound was made by following procedure 4B with carbene complex **2-60** (0.1039 g, 0.31 mmol) and alkyne **(3*S*,5*S*)-4-172** (0.107 g, 0.37 mmol) in 10 mL of toluene at 80 °C for 24 hours. This gave a total yield of 34 % (0.0498 g, 0.105 mmol) as a mixture. This material was isolated as a mixture

giving a ratio of 100 : 65 : 5 (**4-214a** : **4-214b** : **4-214c**) which could not be separated.

Following procedure 4B with carbene complex **2-60** (0.1011 g, 0.30 mmol), alkyne (3*S*,5*S*)-**4-172** (0.093 g, 0.32 mmol), and 10 mL of toluene at 90 °C for 24 hours. This gave a yield of 65 % (0.092 g, 0.193 mmol). This material was isolated as a mixture in a ratio of 100 : 36 : 15 (**4-214a** : **4-214b** : **4-214c**). The NMR data was obtained on the mixture and it was reported separately for clarity. The two different ratios containing 100 : 65 : 5 (**4-214a** : **4-214b** : **4-214c**) and 100 : 36 : 15 (**4-214a** : **4-214b** : **4-214c**) could be used to elucidate the different chemical shifts of protons.

Diastereomer A Corresponding to **4-214a** (major, extracted from mixed NMR):

¹H NMR (CDCl₃) δ: 0.81 - 0.98 (m, 2 H), 1.13 (d, 3 H, *J* = 7.2 Hz), 1.24 (s, 3 H), 1.36 (s, 3 H), 1.00 - 1.77 (m, 3 H), 2.09 - 2.31 (m, 3 H), 2.85 (td, 1 H, *J* = 11.5, *J* = 3.1 Hz), 3.69 (s, 3 H), 5.26 (d, 1 H, *J* = 1.8 Hz), 5.44 (d, 1 H, *J* = 1.8 Hz), 7.30 - 7.45 (m, 3 H), 7.57 - 7.69 (m, 2 H).

Diastereomer B Corresponding to **4-214b** (minor, extracted from mixed NMR):

¹H NMR (CDCl₃) δ: 0.81 - 0.98 (m, 2 H), 0.93 (d, 3 H, *J* = 6.0 Hz), 1.23 (s, 3 H), 1.00 - 1.77 (m, 3 H), 1.48 (s, 3 H), 2.09 - 2.31 (m, 2 H), 2.56 - 2.65 (m, 1 H), 3.47 (br s, 1 H), 3.70 (s, 3 H), 5.34 (d, 1 H, *J* = 1.7 Hz), 5.46 (d, 1 H, *J* = 1.9 Hz), 7.30 - 7.45 (m, 3 H), 7.57 - 7.69 (m, 2 H).

Diastereomer C Corresponding to **4-214c** (minor, extracted from mixed NMR, partial identification):

The identification of all peaks was not possible due to overlaps.

^1H NMR (CDCl_3) δ : 2.64 (br t, 1 H, $J = 12.2$ Hz), 5.15 (br s, 1 H), 5.23 (br s, 1 H).

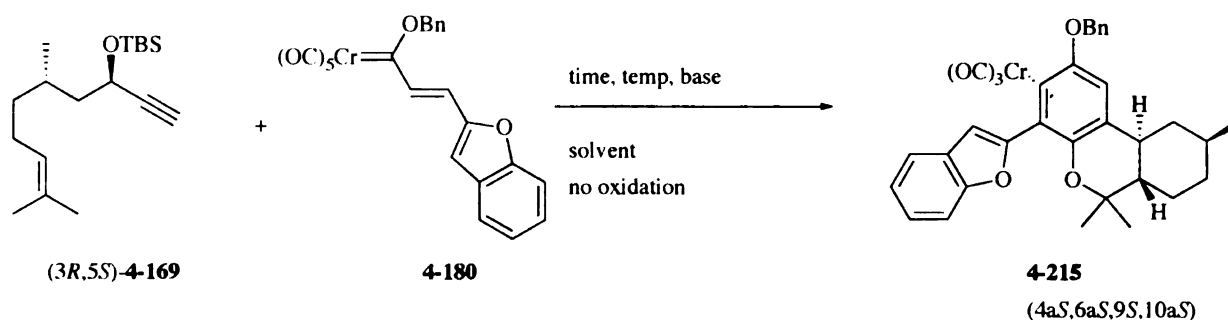
IR on the mixture (thin film): 2936 s, 2855 m, 1950 vs, 1867 vs, 1543 m, 1458 m, 1420 s, 1199 m, 1144 m cm^{-1} ; mass spectrum m/z (% rel intensity, FAB+) 472

M^+ (56), 388 $\text{M}^+ - 3\text{CO}$ (100), 336 (38); HRMS calcd for $\text{C}_{26}\text{H}_{28}\text{CrO}_5$ m/z 472.1342, meas 472.1340.

Mixture of diastereomers:

^{13}C NMR (CDCl_3) δ : 14.10, 18.01, 19.29, 21.68, 22.63, 24.93, 26.23, 26.46, 27.42, 28.01, 29.10, 30.92, 31.26, 31.57, 34.27, 34.64, 36.47, 37.04, 40.26, 47.28, 56.06, 56.09, 75.50, 76.86, 79.16, 80.20, 84.32, 84.34, 91.84, 92.08, 94.64, 102.02, 102.27, 127.77, 127.79, 128.31, 128.33, 130.26, 130.33, 134.48, 134.50, 135.75, 234.72, 234.61.

Compound 4-215



Following procedure 4B, the following results were obtained with carbene complex 4-180 (0.104 g, 0.23 mmol), alkyne (3*R*,5*S*)-4-169 (0.078 g, 0.27 mmol), and 5 mL of toluene. The reaction mixture was heated 24 hours at 80 °C. The yield was 47 % of (4*aS*,6*aS*,9*S*,10*aS*)-4-215. The trans to cis ratio was $\geq 96 : 4$

integrating 6.23 (minor) and 6.19 ppm (major). Typically also recovered 49 % of the mass as a mixture of unidentified and inseparable products ($R_f = 0.64$, 30 % ethyl acetate / hexane) under the conditions employed.

Table 7.4. Additional Results

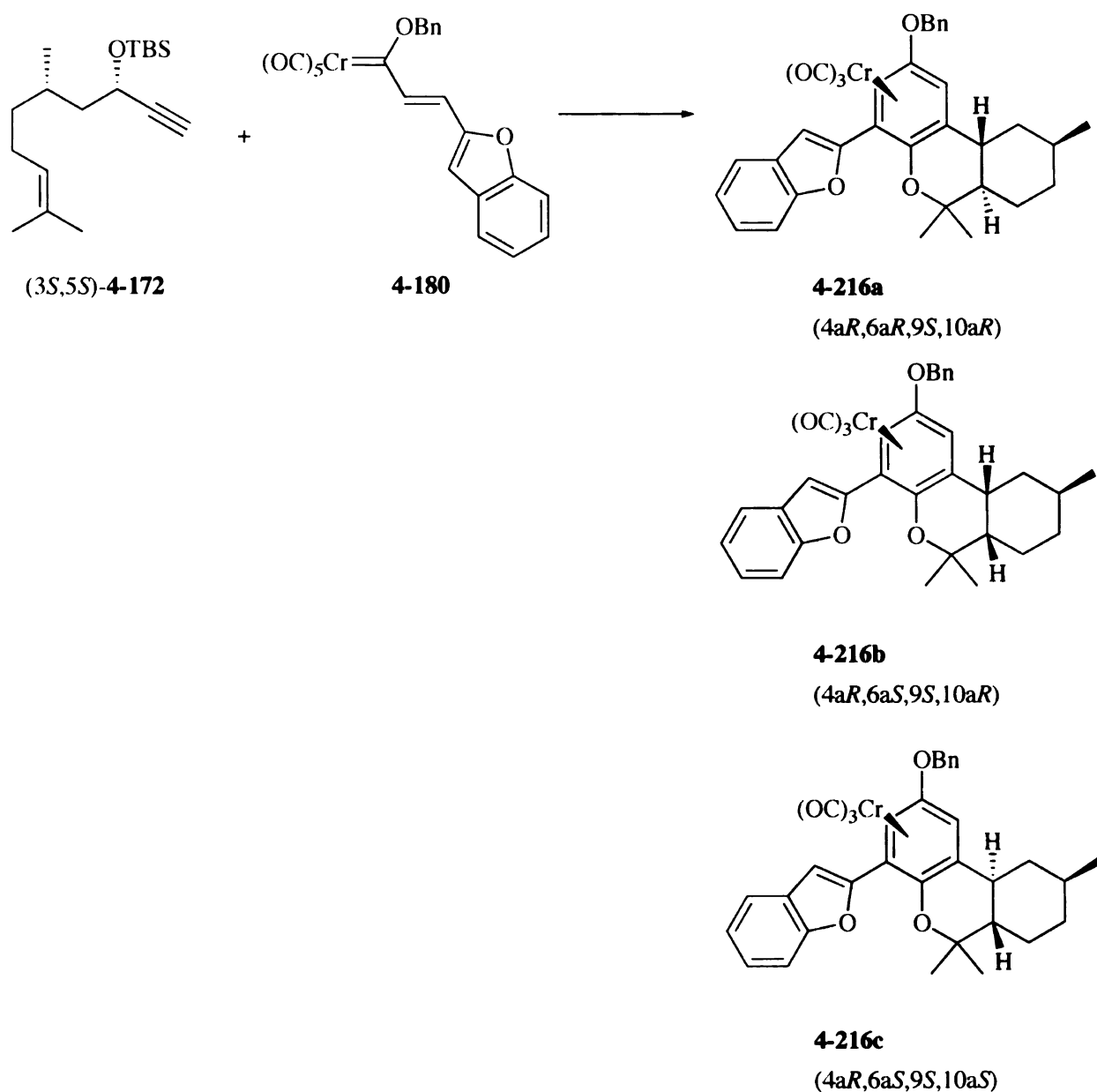
entry	solvent (M, carbene)	base (M)	time	temp	yield 4-222
1	toluene (0.01)	N(iPr) ₂ Et (0.43)	24 hrs	80	38
2	toluene (0.028)	N(iPr) ₂ Et (0.14)	24 hrs	80	44
3	toluene (0.04)	N(iPr) ₂ Et (0.22)	24 hrs	80	47
4	toluene (0.11)	N(iPr) ₂ Et (0.52)	24 hrs	80	43

Compound 4-215

¹H NMR (CDCl₃) δ : 0.77 - 0.86 (m, 2 H), 0.93 (d, 3 H, $J = 6.5$ Hz), 1.02 - 1.12 (m, 1 H), 1.23 - 1.32 (td, 1 H, $J = 11.7, 2.3$ Hz), 1.38 (s, 3 H), 1.43 (s, 3 H), 1.49 - 1.62 (m, 1 H), 1.77 (t, 2 H, $J = 12.3$), 2.18 (d, 1 H, $J = 12.9$), 2.59 (td, 1 H, $J = 11.6, 3.6$ Hz), 4.86 (d, 1 H, $J = 10.6$ Hz), 4.90 (d, 1 H, $J = 10.5$ Hz), 5.32 (d, 1 H, $J = 2.3$ Hz), 6.19 (d, 1 H, $J = 2.3$ Hz), 7.13 - 7.19 (m, 1 H), 7.23 (t, 1 H, $J = 7.8$ Hz), 7.27 - 7.35 (m, 4 H), 7.37 - 7.44 (m, 3 H), 7.53 (d, 1 H, $J = 7.7$ Hz); ¹³C NMR (CDCl₃) δ : 19.62, 22.39, 27.22, 28.51, 32.05, 34.13, 34.58, 39.18, 46.45, 71.58, 76.28, 79.17, 81.25, 88.59, 95.02, 108.69, 111.03, 121.52, 123.07, 125.10, 126.83, 128.21, 128.60, 128.72, 128.99, 134.92, 135.24, 149.06, 153.98, 234.54; IR (thin film): 2922 w, 2851 w, 1950 s, 1869 s, 1535 w, 1455 w, 1157 w, 1145 w

cm⁻¹; mass spectrum *m/z* (% rel intensity, FAB+) 588.4 M⁺ (24), 504.4 (100), 452.4 (6), 413.2 (9), 91 (54); HRMS calcd for C₃₄H₃₂CrO₆ *m/z* 588.1604, meas 588.1610. Yellow-orange solid (hexane), mp 72 - 75 °C (dec.), R_f = 0.56 (30 % ethyl acetate / hexane). [α]_D²² -237.3° (c 0.566, CH₂Cl₂).

Compound 4-216a, 4-216b, 4-216c



Following procedure 4B, alkyne (3S,5S)-4-172 (0.070 g, 0.24 mmol),

carbene complex **4-180** (0.097 g, 0.21 mmol), and 4.5 mL of toluene were heated at 80 °C for 30 hours. The yield was 39 % (0.049 g, 0.083 mmol) of a 100 : 40 : 10 mixture of **4-216a**, **4-216b**, and **4-216c** respectively. The ratio was determined by ^1H NMR integrating the multiplets at 2.35, 2.90, and 3.49 ppm.

Diastereomer A Corresponding to **4-216a** (major, extracted from mixed NMR):

^1H NMR (CDCl_3) δ : 0.92 - 1.08 (m, 1 H), 1.14 (d, 3 H, $J = 7.26$ Hz), 1.22 - 1.41 (m, 2 H), 1.484 (s, 3 H), 1.51 (s, 3 H), 1.54 - 1.76 (m, 3 H), 2.06 - 2.29 (m, 2 H), 2.90 (td, 1 H, $J = 11.8, 3.7$ Hz), 4.92 (d, 1 H, $J = 12.0$ Hz), 4.97 (d, 1 H, $J = 12.0$ Hz), 5.35 (d, 1 H, $J = 2.54$ Hz), 6.26 (d, 1 H, $J = 2.57$ Hz), 7.20 - 7.26 (m, 1 H), 7.29 - 7.33 (m, 1 H), 7.35 - 7.43 (m, 4 H), 7.43 - 7.52 (m, 3 H), 7.60 (d, 1 H, $J = 7.8$ Hz)

Diastereomer B Corresponding to **4-216b** (minor, extracted from mixed NMR):

^1H NMR (CDCl_3) δ : 0.84 (d, 3 H, $J = 6.0$ Hz), 0.92 - 1.08 (m, 1 H), 1.22 - 1.41 (m, 2 H), 1.475 (s, 3 H), 1.54 - 1.76 (m, 3 H), 1.58 (s, 3 H), 2.06 - 2.29 (m, 1 H), 2.61 - 2.73 (m, 1 H), 3.49 (br dd, 1 H, $J = 7.4, 3.8$ Hz), 4.97 (d, 1 H, $J = 11.0$ Hz), 5.01 (d, 1 H, $J = 11.0$ Hz), 5.36 (d, 1 H, $J = 2.54$ Hz), 6.31 (d, 1 H, $J = 2.57$ Hz), 7.20 - 7.26 (m, 1 H), 7.29 - 7.33 (m, 1 H), 7.35 - 7.43 (m, 4 H), 7.43 - 7.52 (m, 3 H), 7.60 (d, 1 H, $J = 7.8$ Hz).

Diastereomer C Corresponding to **4-216c** (minor, extracted from mixed NMR, partially reported):

The identification of all peaks was not possible due to overlaps.

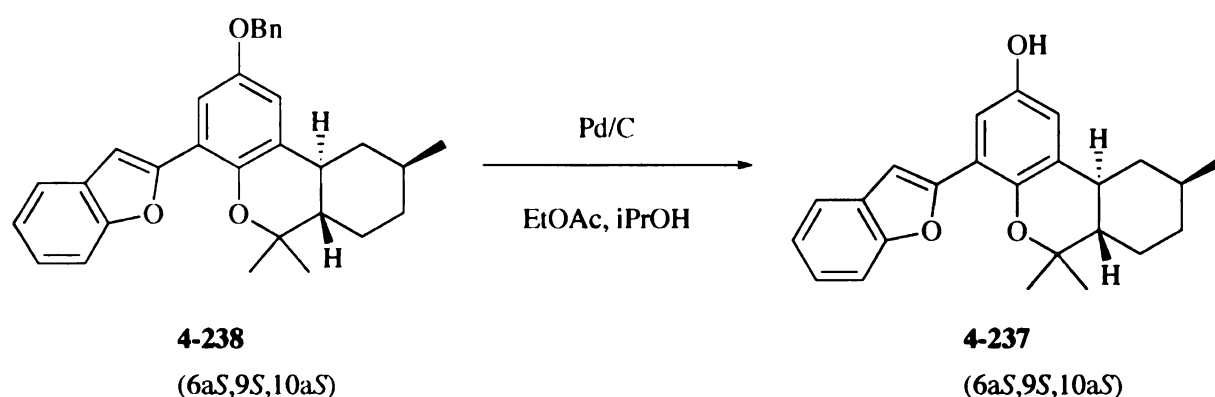
^1H NMR (CDCl_3) δ : 2.35 (br t, 1 H, $J = 13.0$ Hz), 5.09 (d, 1 H, $J = 10.0$ Hz, distorted), 5.12 (d, 1 H, $J = 10.0$ Hz, distorted), 5.39 (d, 1 H, $J = 2.55$ Hz), 6.27 (d, 1 H, $J = 2.57$ Hz).

Mixture of Diastereomers:

^{13}C NMR (CDCl_3) δ : 14.10, 17.98, 19.72, 21.64, 22.22, 22.29, 22.63, 25.27, 26.10, 26.80, 27.35, 28.35, 29.10, 29.68, 30.85, 31.25, 31.57, 34.19, 36.38, 36.94, 40.36, 47.12, 71.55, 71.64, 76.06, 77.32, 79.00, 79.47, 80.02, 81.15, 88.54, 88.75, 92.35, 95.18, 108.74, 108.87, 111.07, 121.54, 123.08, 125.12, 125.15, 126.98, 127.34, 127.71, 127.89, 128.25, 128.51, 128.61, 128.72, 128.82, 129.02, 135.06, 135.17, 135.24, 135.46, 149.04, 149.14, 154.04, 234.52, 234.63;

$R_f = 0.35$ (30 % ethyl acetate / hexane).

Compound 4-237

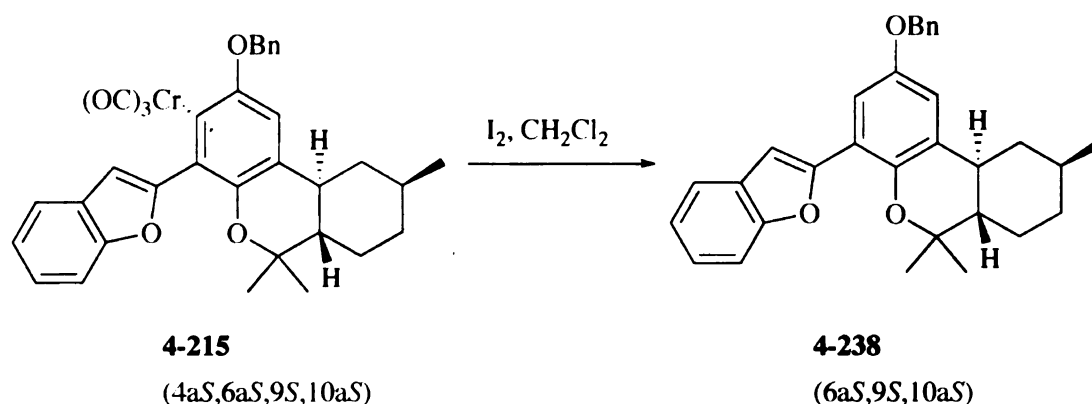


A 10 mL round bottom flask was charged with compound (6a*S*,9*S*,10a*S*)-**4-238** (0.0080 g, 0.018 mmol), 10 % Pd on carbon (0.0025 g), ethyl acetate (1 mL), isopropanol (1 mL). The contents of the flask were briefly exposed to

vacuum and the atmosphere was replaced with hydrogen. The mixture was stirred for 10 hours at room temperature. The mixture was filtered through Celite giving a yield of 6 mg (0.017 mmol) or 92 % of (6a*S*,9*S*,10a*S*)-**4-237**.

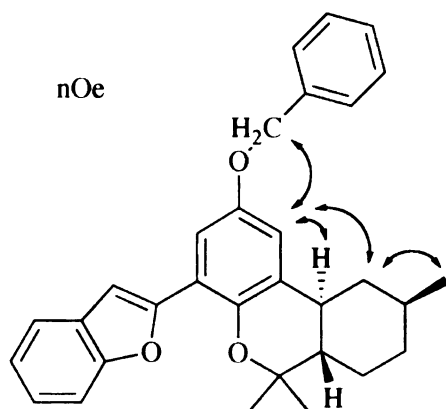
^1H NMR (CDCl_3) δ : 0.82 - 0.99 (m, 2 H), 1.00 (d, 3 H, $J = 6.6$ Hz), 1.05 - 1.17 (m, 2 H), 1.20 (s, 3 H), 1.21 - 1.36 (m, 1 H), 1.48 (td, 2 H, $J = 11.5, 2.7$ Hz), 1.57 (s, 3 H), 1.81 - 1.95 (m, 2 H), 2.27 (br d, 1 H, $J = 12.5$ Hz), 2.48 (td, 1 H, $J = 11.5, 3.5$ Hz), 4.45 (br s, 1 H), 6.78 (dd, 1 H, $J = 3.0, 1.0$ Hz), 7.15 - 7.31 (m, 1 H), 7.38 - 7.66 (m, 3 H); ^{13}C NMR (CDCl_3) δ : 20.72, 22.83, 27.72, 28.37, 32.81, 34.88, 36.21, 39.98, 46.81, 78.22, 106.58, 110.93, 111.56, 113.27, 119.40, 121.33, 122.81, 124.24, 127.40, 130.11, 145.08, 148.48, 152.72, 154.01.

Compound 4-212



A 10 mL round bottom was charged with compound **4-215** (0.049 g, 0.081 mmol), dichloromethane (2 mL), and one piece of iodine. The contents of the flask were stirred in air for 30 minutes. The contents of the flask were treated with 8 mL of saturated sodium sulfate for 15 minutes. Extracted with brine. Each aqueous layer was extracted with 3 mL x 3 of dichloromethane. Column

chromatography (35 cm x 2 cm, silica gel) with 5 % ethyl acetate / hexane gave an oily solid (0.026 g, 0.057 mmol, 70 %) of (6a*S*,9*S*,10a*S*)-**4-238**.

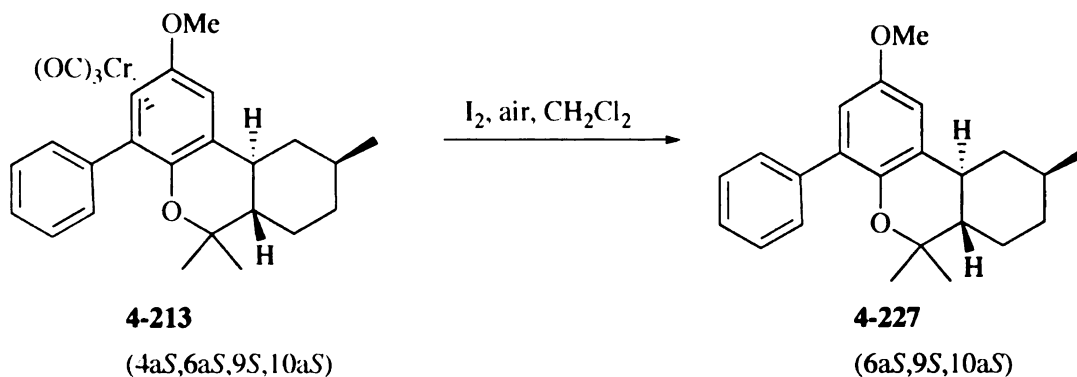


^1H NMR (CDCl_3) δ : 0.84 - 0.97 (m, 2 H), 0.99 (d, 3 H, $J = 6.6$ Hz), 1.04 - 1.16 (m, 2 H), 1.20 (s, 3 H), 1.25 - 1.65 (m, 2 H), 1.48 (td, 1 H, $J = 11.6, 2.7$ Hz), 1.57 (s, 3 H), 1.86 (br t, 2 H, $J = 10.5$ Hz), 2.36 (br d, 1 H, $J = 12.7$ Hz), 2.48 (td, 1 H, $J = 11.3, 3.3$ Hz), 5.10 (s, 2 H), 6.91 (d, 1 H), 7.17 - 7.29 (m, 2 H), 7.30 - 7.36 (m, 1 H), 7.37 - 7.42 (m, 2 H), 7.47 - 7.53 (m, 2 H), 7.57 - 7.63 (m, 2 H); ^{13}C NMR (CDCl_3) δ : 20.49, 22.56, 27.50, 28.09, 32.49, 34.66, 36.04, 39.75, 46.50, 70.80, 77.99, 106.25, 110.44, 110.74, 113.73, 118.92, 120.96, 122.51, 123.90, 126.95, 127.67, 127.84, 128.48, 129.90, 137.38, 145.13, 151.86, 152.63, 153.70; IR (thin film): 2924 m, 2867 m, 1566 m, 1456 m, 1262 w, 1157 w, 1144 m, 1044 w, 938 w, 739 w cm^{-1} ; mass spectrum m/z (% rel intensity) 452.3 M^+ (1), 361 (35), 343 (12), 319 (3), 315 (5), 305 (9), 287 (3), 263 (7), 239 (25), 129 (11), 91 (100), 69 (39); HRMS (Q-ToF) calcd for $\text{C}_{31}\text{H}_{33}\text{O}_3$ $[\text{M}+1]^+$ m/z 453.2424, meas 453.2430.

Beige solid (hexane), mp 134 - 137 $^\circ\text{C}$ (one isomer), $R_f = 0.61$ (30 % ethyl

acetate / hexane). $[\alpha]_D^{20} +18^\circ$ (c 0.16, CH₂Cl₂).

Compound 4-227



Compound **4-213** (0.023 g, 0.05 mmol) was added to a solution of dichloromethane (5 mL) and one piece of iodine. The solution was stirred for 15 minutes. The solution was treated with saturated sodium sulfite and stirred for 15 minutes. The organic and aqueous layers were separated. The aqueous layer was extracted with 5 mL x 3 of dichloromethane. The organic layers were combined and extracted with saturated brine and the aqueous layer was back extracted with 5 mL x 3 of dichloromethane. The organic layers were combined and dried over magnesium sulfate. The solvent was filtered through fluted filter paper and the solvent removed under reduced pressure. Column chromatography with 5 % ethyl acetate / hexane gave 0.01 g (54 % yield, 0.027 mmol). The isomer ratio was 98 : 2 (trans : cis) determined by GC/FID on a Alltech Econo-Cap SE-54 (30 m x 0.32 mm x 1.2 μ m) with a temperature program of 80 $^\circ$ C hold for 1 minute and 10 $^\circ$ C / minute until 230 $^\circ$ C. The flow rate was 5 cc / minute directly determined with a flow meter with a splitless injector. The retention times were 12.1 minutes for the minor and 16.7 minutes for the

major.

The retention time for GC/MS was 21.6 minutes (minor) and 22.7 minutes (major). The temperature program was 60 °C for 2 minutes then ramped to 260 °C at 10 °C / minute using a CP-SIL 8 low bleed column (30 m x 0.25 mm) with a 5 mL/min flow rate (1/20 split ratio). The integration between the MS and FID were identical.

Major Isomer:

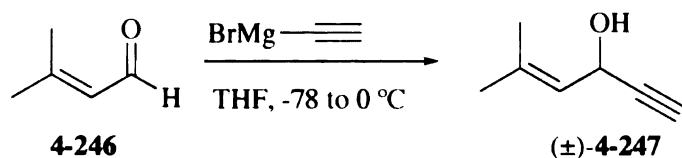
^1H NMR (CDCl_3) δ : 0.77 - 0.92 (m, 1 H), 0.94 - 1.11 (m, 2 H), 1.00 (d, 3 H, J = 6.5 Hz), 1.14 (s, 3 H), 1.20 - 1.28 (m, 1 H), 1.31 (s, 3 H), 1.53 - 1.70 (m, 1 H), 1.77 - 1.89 (m, 2 H), 2.40 (d, 1 H, J = 12.6 Hz), 2.47 (td, 1 H, J = 11.5, 2.5 Hz), 3.79 (s, 3 H), 6.75 (d, 1 H, J = 3.0 Hz), 6.81 (d, 1 H, J = 3.0 Hz), 7.27 - 7.32 (m, 1 H), 7.34 - 7.41 (m, 2 H), 7.53 - 7.59 (m, 2 H); ^{13}C NMR (CDCl_3) δ : 20.02, 22.62, 27.54, 27.92, 32.62, 34.75, 36.34, 39.89, 46.81, 55.75, 76.87, 110.89, 114.17, 126.50, 126.77, 127.65, 129.64, 130.32, 139.00, 144.18, 152.52; IR (thin film): 2927 s, 2860 m, 1464 s, 1200 m, 1055 m, 698 m cm^{-1} ; mass spectrum m/z (% rel intensity) 336 M^+ (100), 293 (61), 251 (11), 213 (13); Clear oil (hexane), R_f = 0.58 (30 % ethyl acetate / hexane). $[\alpha]_D^{22} +14.9^\circ$ (c 1.17, CH_2Cl_2) with > 20 : 1 dr.

Minor Isomer:

Mass spectrum m/z (% rel intensity) 336 M^+ (100), 293 (23), 254 (6), 251 (3), 213

(11).

Compound (±)-4-247

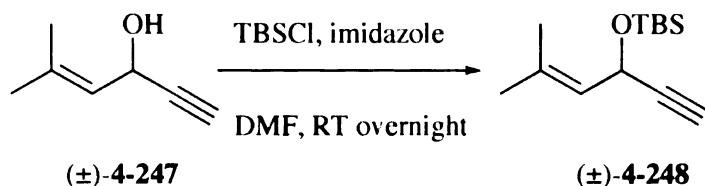


The compound was prepared following known literature methods and spectroscopic properties were identical to those previously reported.³⁸⁶ To a solution of 3-methylbut-2-enal (2.0 mL, 20.7 mmol) in 50 mL of THF at -78 °C was added ethynylmagnesium bromide (0.5 M in THF, 50 mL, 25.0 mmol). The reaction mixture was stirred for 3 hours at -78 °C and warmed to room temperature. The reaction mixture was monitored by TLC. The reaction mixture was then poured into 20 mL of saturated ammonium chloride solution. The aqueous layer was separated and extracted with 3 x 20 mL of ethyl acetate. The organic layers were combined and dried over magnesium sulfate and sodium bicarbonate. The solution was filtered through fluted filter paper and the solvent was removed under reduced pressure. Column chromatography (30 x 4.2 cm, silica gel) with 10 % ethyl acetate / hexane gave 1.43 g (63 % yield, 13.0 mmol, (±)-4-247) as a clear oil. The spectroscopic properties were identical to those previously reported.³⁸⁶

¹H NMR (CDCl₃) δ: 1.70 (d, 3 H, *J* = 1.3 Hz), 1.73 (s, 3 H, *J* = 1.3 Hz), 1.95 - 2.04 (m, 1 H), 2.47 (d, 1 H, *J* = 2.2 Hz), 4.98 - 5.10 (m, 1 H), 5.35 (d pentet, 1 H, *J* = 8.6, 1.4 Hz); ¹³C NMR (CDCl₃) δ: 17.99, 25.33, 58.99, 72.32, 84.62, 124.58,

137.31; IR (thin film): 3293 br s (overlap of two peaks), 2977 m, 2917 s, 1447 w, 1377 w, 1013 m, 924 w cm^{-1} ; mass spectrum m/z (% rel intensity) 111 $[\text{M}+1]^+$ (17), 110 M^+ (13), 96 (100), 91 (34), 77 (43), 65 (14), 55 (10), 53 (21); Clear oil (hexane), $R_f = 0.35$ (30 % ethyl acetate / hexane).

Compound (±)-4-248

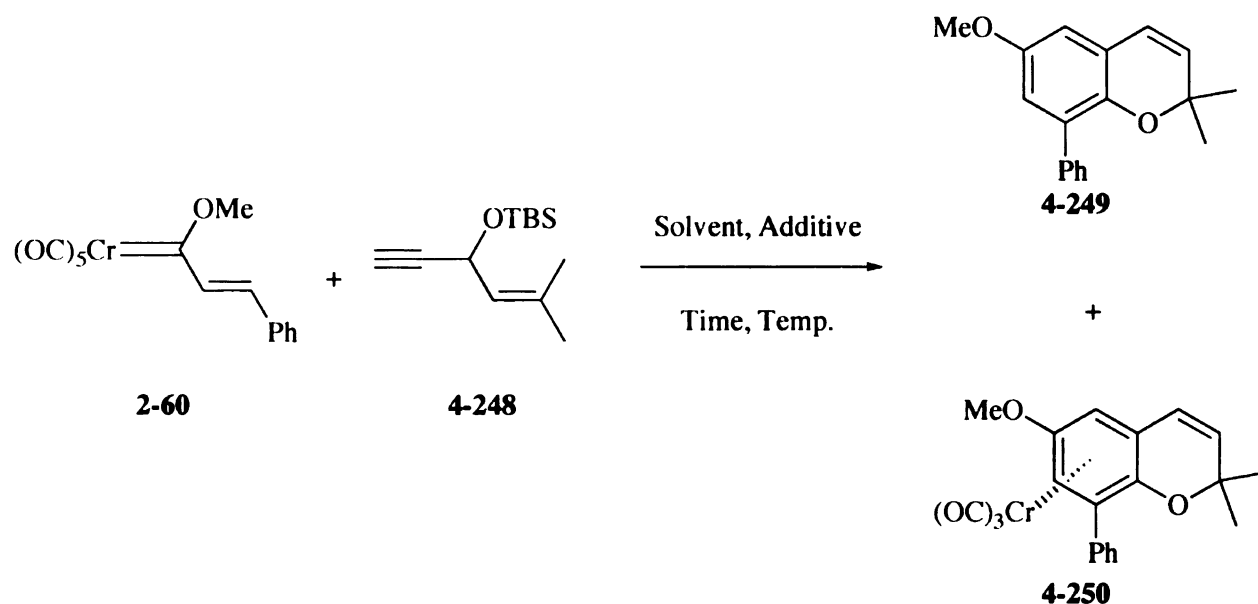


A 100 mL single neck round bottom flask was charged with compound (±)-4-247 (1.28 g, 11.6 mmol), imidazole (1.25 g, 18.4 mmol), TBSCl (1.91 g, 12.7 mmol), and DMF (50 mL). The mixture was stirred overnight. The solution was extracted with ether (50 mL x 2), ammonium chloride saturated solution (50 mL), water (100 mL), and back extracting each aqueous layer with ether (30 mL x 3). The organic layers were combined and dried over magnesium sulfate and sodium bicarbonate (neutralize any remaining acid). Column chromatography (27 x 3.8 cm, silica gel) with hexane, 5 % ethyl acetate / hexane, and then 10 % ethyl acetate / hexane gave 2.26 g (87 % yield, 10.09 mmol) of compound (±)-4-248. This was used without further purification. With further purification by distillation at 0.2 mm Hg and 45 °C, a 50 % yield was obtained that was elementally pure.

$^1\text{H NMR}$ (CDCl_3) δ : 0.09 (s, 3 H), 0.11 (s, 3 H), 0.88 (s, 9 H), 1.66 (d, 3 H, $J = 1.3$

Hz), 1.71 (d, 3 H, $J = 1.3$ Hz), 2.41 (d, 1 H, $J = 2.2$ Hz), 5.03 (dd, 1 H, $J = 8.4, 2.1$ Hz), 5.31 (dqt, 1 H, $J = 8.4, 1.4$ Hz); ^{13}C NMR (CDCl_3) δ : -4.68, -4.53, 18.09, 18.22, 25.54, 25.77, 59.85, 71.60, 85.11, 125.65, 134.25; IR (thin film): 3314 m, 2959 s, 2932 s, 2859 s, 1474 w, 1252 w, 1069 w, 837 m cm^{-1} ; mass spectrum m/z (% rel intensity) 225 $[\text{M}+1]^+$ (0.03), 224 M^+ (0.1), 209 (2), 167 (47), 91 (23), 83 (17), 75 (100), 61 (15); Anal calcd for $\text{C}_{13}\text{H}_{24}\text{OSi}$: C, 69.58; H, 10.78. Found: C, 69.38; H, 10.92. Clear oil (hexane), $R_f = 0.82$ (30 % ethyl acetate / hexane).

Compound 4-250



Typical procedure: Styryl carbene complex **2-60** (0.089 g, 0.26 mmol), compound **4-248** (0.071 g, 0.32 mmol), and dichloromethane (8.0 mL) were added to a single neck flask that had been modified by replacement of the joint with a threaded high vacuum Teflon valve. The reaction mixture was stirred and heated at 60 °C for 24 hours. The reaction mixture was taken up on 2 - 3 cc of silica gel.

The silica gel was loaded onto a chromatography column. Column chromatography (30 x 1.8 cm, silica gel) gave two fractions. The first fraction was 0.032 g (46 % yield, 0.12 mmol) of compound **4-249**. The second fraction gave a yield of 29 % (0.030 g, 0.075 mmol) for the metalated compound **4-250**.

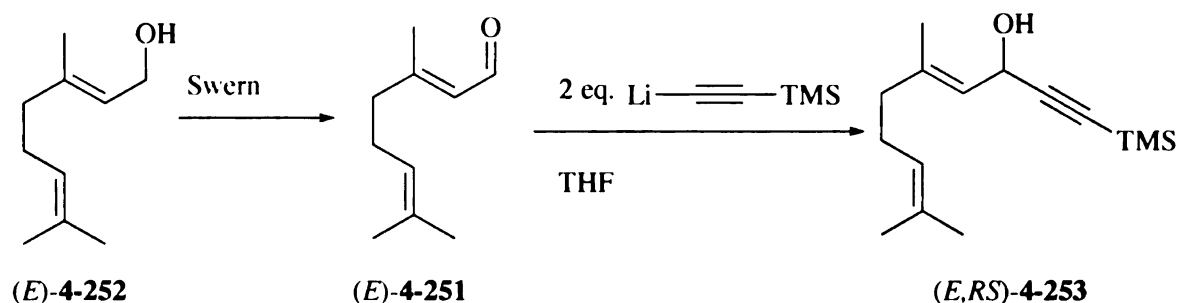
Compound **4-249**:

Adequate characterization is not available. $R_f = 0.45$ (30 % ethyl acetate / hexane).

Compound **4-250**:

$^1\text{H NMR}$ (CDCl_3) δ : 1.32 (s, 3 H), 1.49 (s, 3 H), 3.67 (s, 3 H), 5.21 (d, 1 H, $J = 2.5$ Hz), 5.41 (d, 1 H, $J = 2.5$ Hz), 5.73 (d, 1 H, $J = 10$ Hz), 6.12 (d, 1 H, $J = 10$ Hz), 7.32 - 7.44 (m, 3 H), 7.57 - 7.66 (m, 2 H); $^{13}\text{C NMR}$ (CDCl_3) δ : 26.59, 29.30, 56.73, 78.47, 79.26, 82.12, 88.95, 100.61, 120.48, 128.35, 128.47, 128.93, 130.59, 133.51, 134.30, 136.48, 235.07; IR (thin film): 2919 s, 2850 m, 1954 vs, 1871 vs, 1426 w cm^{-1} ; mass spectrum m/z (FAB^+ , % rel intensity) 402 M^+ (59), 318 (100), 267 (23), 251 (21); HRMS calcd for $\text{C}_{21}\text{H}_{18}\text{CrO}_5$ m/z 402.0559, meas 402.0561. Yellow-orange solid (hexane), mp 144 - 148 °C, $R_f = 0.35$ (30 % ethyl acetate / hexane).

Compound (*E,RS*)-4-253



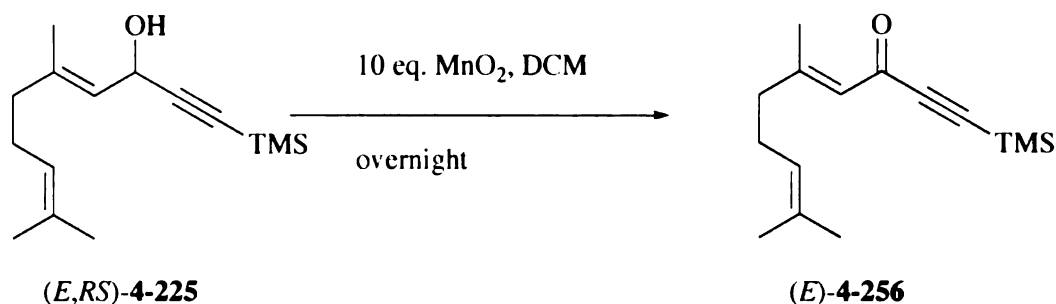
In dichloromethane (250 mL), DMSO (5.5 mL, 77.5 mmol) was treated with oxalyl chloride (2.5 mL, 28.5 mmol, 1.1 eq.) at $-78\text{ }^{\circ}\text{C}$ for 5 minutes then geraniol (*E*)-4-252 (4.5 mL, 25.9 mmol) was added and the reaction mixture was stirred for 15 minutes. Triethyl amine (25.3 mL, 181.0 mmol, 7 eq.) was added. The reaction was warmed to room temperature over an hour. The solution was poured into 200 mL of 1 M HCl. The solution was extracted with ethyl acetate (3 x 200 mL). The organic layers were combined and washed with brine (100 mL). The brine layer was back extracted with 3 x 50 mL of ethyl acetate. The organic layers were combined and dried over and neutralized over solid sodium bicarbonate and magnesium sulfate. The solvent was removed under reduced pressure and the crude aldehyde (*E*)-4-251 used without further purification. The ratio of *E/Z* was 98:2 as determined by GC/FID. The spectroscopic properties were identical with that previously reported in the literature.³⁸⁷

In diethyl ether (250 mL), TMS acetylene (3.06 g, 31.1 mmol) was deprotonated with *n*-butyl lithium (12.5 mL, 20.0 mmol) at $-78\text{ }^{\circ}\text{C}$. The solution was allowed to warm to room temperature over one hour. The solution was recooled to $-78\text{ }^{\circ}\text{C}$ and the aldehyde (*E*)-4-251 prepared above was added

dropwise. The solution was warmed to 0°C and stirred 40 minutes. The solution was then warmed to room temperature. The solution was poured into 100 mL of saturated ammonium chloride and back extracted with ether (3 x 100 mL). The organic layer was dried over magnesium sulfate, filtered through Celite, and the solvent removed under reduced pressure. Column chromatography (22 x 5.9 cm, silica gel) with 10 % ethyl acetate / hexane gave 5.39 g (83 % yield over two steps, 21.5 mmol).

^1H NMR (CDCl_3) δ : 0.12 (s, 9 H), 1.56 (s, 3 H), 1.64 (s, 3 H), 1.67 (d, 3 H, $J = 1.3$ Hz), 1.95 - 2.15 (m, 5 H), 4.99 - 5.09 (m, 2 H), 5.27 - 5.35 (ddd, 1 H, $J = 8.5, 2.5, 1.2$ Hz); ^{13}C NMR (CDCl_3) δ : -0.27, 16.53, 17.58, 25.52, 26.13, 39.16, 59.34, 88.82, 106.16, 123.57, 124.36, 131.77, 140.43; IR (thin film): 3331 br s, 2965 s, 2921 s, 2854 m, 2172 m, 1447 m, 1377 m, 1250 s, 1030 s, 840 s cm^{-1} ; mass spectrum m/z (% rel intensity) 249 $\text{M}^+ - 1$ (0.1), 235 (3), 219 (2), 207 (6), 192 (16), 177 (10), 163 (14), 149 (46), 123 (67), 109 (10), 96 (15), 81 (15), 73 (90), 69 (100), 59 (12); Anal calcd for $\text{C}_{15}\text{H}_{26}\text{OSi}$: C, 71.93; H, 10.46. Found; C, 71.52; H, 10.76. Yellow oil (hexane), $R_f = 0.41$ (30 % ethyl acetate / hexane).

Compound (E)-4-256

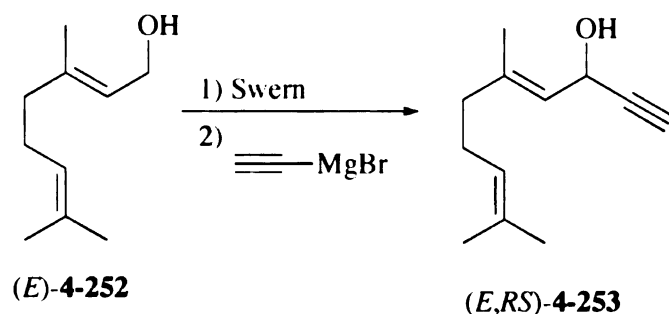


A 500 mL round bottom flask was charged with compound (E,RS)-4-225 (5.16 g, 20.6 mmol), DCM (250 mL), and MnO₂ (17.43 g, 200.4 mmol). The contents of the flask were stirred overnight and filtered through Celite washing with DCM to remove the MnO₂. Column chromatography with 10 % ethyl acetate / hexane (20 x 5.8 cm, silica gel) gave 3.89 g (76 % yield, 15.7 mmol) of (E)-4-256. The *E* to *Z* ratio was 90 to 10 as measure by ¹H NMR of the peaks at 6.11 (major) and 6.13 (minor).

¹H NMR (CDCl₃) δ: 0.20 (s, 9 H), 1.57 (s, 3 H), 1.65 (s, 3 H), 2.15 (m, 4 H), 2.17 (d, 3 H, *J* = 2.2 Hz), 5.03 (br s, 1 H), 6.11 (s, 1 H); ¹³C NMR (CDCl₃) δ: -0.79, 17.63, 20.03, 25.58, 41.35, 76.55, 95.74, 104.63, 122.68, 125.26, 132.67, 161.71, 176.28; IR (thin film): 2967 s, 2920 s, 2860 w, 1050 s, 1009 s, 1449 w, 1254 m, 1210 w, 1123 m, 851 s cm⁻¹; mass spectrum *m/z* (% rel intensity) 248 M⁺ (68), 233 (100), 217 (9), 205 (38), 191 (10), 177 (20), 165 (74), 149 (18), 123 (56), 105 (27), 91 (8), 68 (35); HRMS (Q-ToF) calcd for C₁₅H₂₅OSi *m/z* 249.1675 [M+1]⁺, meas 249.1682. Yellow oil (hexane), R_f = 0.68 (30 % ethyl acetate /

hexane).

Compound (*E,RS*)-4-253

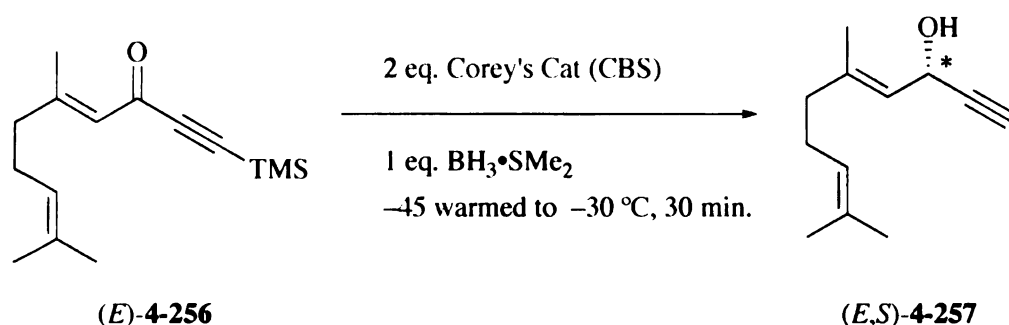


To a solution of DMSO (5.5 mL, 77.5 mmol) in 200 mL of DCM was added oxalyl chloride (2.62 mL, 30.0 mmol) at $-78\text{ }^{\circ}\text{C}$ which was stirred for 10 minutes. Geraniol (*E*)-4-252 (4.5 mL, 25.9 mmol) was added dropwise quickly to the solution. The reaction mixture was then stirred for 20 minutes and triethyl amine (25 mL) was added. The solution was allowed to warm to room temperature. The solution was poured into an extraction funnel and extracted with 200 mL of 1 M HCl and 200 mL brine with back extraction with 30 mL x 3 of DCM. The organic layers were combined and dried over a mixture of potassium bicarbonate and magnesium sulfate. The solution was filtered through fluted filter paper. The solvent was removed under reduced pressure. The aldehyde was used without further purification for the next step. The isomer ratio was 98 : 2 determined by GC/FID on a Alltech Econo-Cap SE-54 (30 m x 0.32 mm x 1.2 μm) with a temperature program of $80\text{ }^{\circ}\text{C}$ hold for 1 minute and $10\text{ }^{\circ}\text{C}$ / minute until $230\text{ }^{\circ}\text{C}$. The flow rate was 5 cc / minute directly determined with a flow meter with a splitless injector. The retention times were 6.53 minutes (minor) and 6.97 minutes (major) and the retention times were confirmed using a 68 : 32 ratio of

citral purchased from Aldrich chemical company.

To the aldehyde was added ethynyl magnesium bromide (90 mL, 0.5 M in THF) over 10 minutes in 250 mL of THF at $-78\text{ }^{\circ}\text{C}$. The solution was warmed to $0\text{ }^{\circ}\text{C}$ and stirred for 1 hour. The reaction mixture was poured into 200 mL of saturated ammonium chloride and back extracted with 3 x 50 mL of DCM. The resulting organic layers were combined and dried over sodium bicarbonate and magnesium sulfate. The solution was filtered through fluted filter paper and the solvent removed under reduced pressure. Column chromatography (28 x 3.8 cm, silica gel) with 10 % ethyl acetate / hexane gave 3.62 g (78 % yield over two steps, 20.2 mmol) of racemic (*E,RS*)-**4-253** as a yellow oil. The spectroscopic properties were identical with those previously reported³⁸⁸ and were identical to those reported for (*E,S*)-**4-257**.

Formation of Chiral (*E,S*)-**4-257**



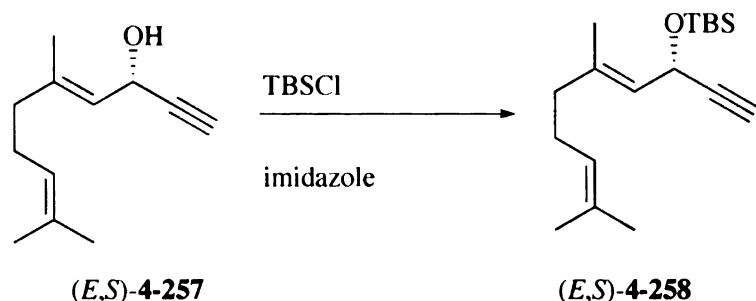
To a solution of (*S*)-(-)-2-methyl-CBS-oxazaborolidine (2.21 g, 7.9 mmol) and compound (*E*)-**4-256** (0.97 g, 3.9 mmol) at $-45\text{ }^{\circ}\text{C}$ in 40 mL of THF was added dropwise slowly $\text{BH}_3\cdot\text{SMe}_2$ (2 mL of a 2 M solution in THF, 4.0 mmol). The solution was warmed to $-30\text{ }^{\circ}\text{C}$ over 30 minutes. The TLC was checked to insure the reaction was complete. To the stirring solution was added methanol

(20 mL) via syringe. The solution was added to a 1:1 mixture of 3 M NaOH and saturated bicarbonate solution. The aqueous layers were back extracted with ether (3 x 50 mL). The organic layers were combined and the solvent was removed under reduced pressure. To the resulting oil was added 20 mL of ether and saturated HCl / MeOH solution was added dropwise with stirring until the solution was acidic to pH paper. The pH paper was wetted with water to insure the correct measure of pH i.e. the measurement of pH must be in an aqueous media. A solid formed and the organic layer was dried over sodium bicarbonate and magnesium sulfate. Column chromatography (20 x 2.8 cm, silica gel) with 10 % ethyl acetate / hexane gave 0.47 g (67 % yield with loss of TMS, 2.61 mmol, 98 % ee). The spectroscopic properties were identical with those previously reported for the racemate.³⁸⁸ The ee was determined by chiral GC with an Astec ChiralDEX B-MB column (30 m x 0.25 mm) with retention times of 23.55 minutes (minor) and 25.80 minutes (major). The temperature program was 50 °C hold for 1 minute then 5 °C/min to 150 °C. The flow rate was 5 cc / minute directly determined with a flow meter. The split ratio was 1 to 2.

¹H NMR (CDCl₃) δ: 1.56 (s, 3 H), 1.64 (s, 3 H), 1.68 (d, 3 H, *J* = 1.3 Hz), 1.93 - 2.13 (m, 4 H), 2.44 (d, 1 H, *J* = 2.2 Hz), 5.01 - 5.08 (m, 2 H), 5.34 (dq, 1 H, *J* = 8.4, 1.3 Hz); ¹³C NMR (CDCl₃) δ: 16.43, 17.56, 25.46, 26.08, 39.16, 58.85, 72.19, 84.39, 123.53, 123.98, 131.80, 140.59; IR (thin film): 3359 br s, 3306 s, 2968 m, 2921 s, 2851 m, 1667 w, 1445 w, 1377 w cm⁻¹; mass spectrum *m/z* (%)

rel intensity) 177 $M^{+}-1$ (0.2), 163 (3), 145 (16), 135 (10), 123 (48), 107 (15), 91 (78), 79 (27), 69 (100), 53 (50); Yellow oil (hexane), $R_f = 0.37$ (30 % ethyl acetate / hexane). $[\alpha]_D^{22} +66.0^\circ$ (c 0.37, CH_2Cl_2) at 98 % ee.

Compound (*E,S*)-4-258

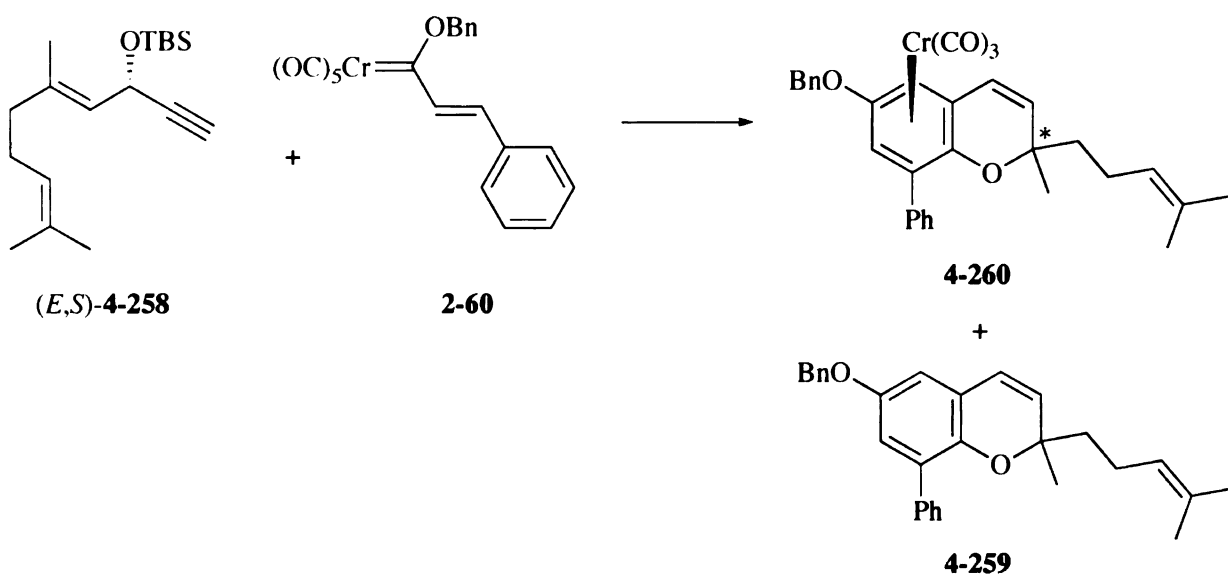


To a solution of compound (*E,S*)-4-257 (0.47 g, 2.6 mmol, 98 % ee) in DMF (30 mL) was added imidazole (0.27 g, 4.0 mmol) and TBSCl (0.44 g, 2.9 mmol). The reaction mixture was stirred over night. The solution was quenched with 30 mL of saturated ammonium chloride and the aqueous layer was back extracted with ethyl acetate (2 x 30 mL). The organic layers were combined and dried over magnesium sulfate. The solution was filtered through fluted filter paper and then the solvent was removed under reduced pressure. Column chromatography (23 x 3.3 cm, silica gel) with 5 % ethyl acetate / hexane gave 0.68 g (89 %, 2.31 mmol) of (*E,S*)-4-258.

1H NMR ($CDCl_3$) δ : 0.09 (s, 3 H), 0.1 (s, 3 H), 0.87 (s, 9H), 1.57 (s, 3 H), 1.65 (s, 6 H), 1.94 - 2.5 (m, 4 H), 2.40 (d, 1 H, $J = 2.1$ Hz), 5.00 - 5.12 (m, 2 H), 5.31 (dd, 1 H, $J = 8.2, 1.2$ Hz); ^{13}C NMR ($CDCl_3$) δ : -4.69, -4.54, 16.45, 17.63, 18.18, 25.63, 25.75, 26.07, 39.20, 59.87, 71.56, 85.03, 123.77, 125.71, 131.60, 137.42;

IR (thin film): 3314 m, 2955 m, 2928 s, 2859 m, 1462 w, 1252 w, 1065 w cm^{-1} ;
 mass spectrum m/z (% rel intensity) 293 $[\text{M}+1]^+$ (0.2), 292 M^+ (1), 277 (3), 235
 (13), 173 (14), 159 (26), 145 (49), 141 (34), 135 (11), 123 (67), 105 (18), 91 (51),
 70 (100); Clear oil (hexane), $R_f = 0.78$ (30 % ethyl acetate / hexane). $[\alpha]_D^{22}$
 $+24.4^\circ$ (c 0.499, CH_2Cl_2).

Compound 4-259 and 4-260



To a 25 mL single neck flask that had been modified by replacement of the joint with a threaded high vacuum Teflon valve was added styryl carbene complex **2-60** (0.086 g, 0.21 mmol), alkyne $(E,S)\text{-4-258}$ (0.069 g, 0.24 mmol, 98 % ee), and 1,2-dichloroethane (8 mL). The contents of the flask were heated for 24 hours at 80 $^\circ\text{C}$. The contents of the flask were taken up onto silica gel (~2 cc). Column chromatography (20 x 1.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 0.045 g (53 % yield, 0.11 mmol, NMR calculated) of **4-259** which was mixed with 0.029 g (0.10 mmol) of alkyne $(E,S)\text{-4-258}$ and 0.003 g (3 %

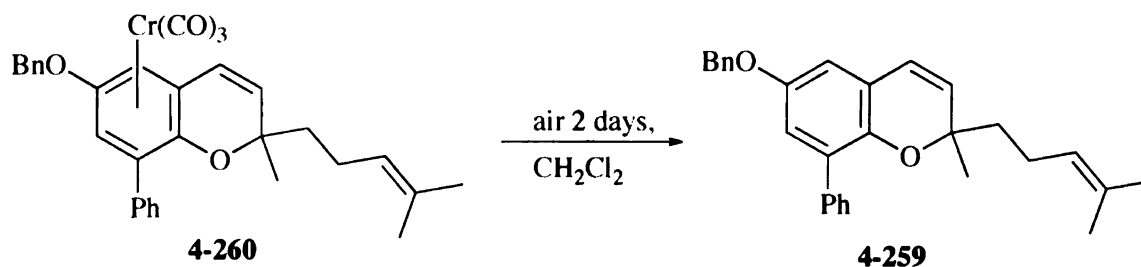
yield, 0.048 mmol, isolated) of **4-260**.

Compound **4-260**: ^1H NMR (CDCl_3) δ : 1.25 (s, 3 H), 1.58 (s, 3 H), 1.65 - 1.77 (m, 2 H), 1.66 (s, 3 H), 1.92 - 2.26 (m, 2 H), 4.84 (br s, 2 H), 5.08 (br s, 1 H), 5.35 (br s, 1 H), 5.51 (br s, 1 H), 5.72 (d, 1 H, $J = 9.8$ Hz), 6.19 (d, 1 H, $J = 9.8$ Hz), 7.39 (br s, 8 H), 7.61 (br d, 2 H, $J = 6.2$ Hz); ^{13}C NMR (CDCl_3) δ : 17.55, 22.74, 25.63, 26.78, 40.31, 71.75, 78.98, 80.89, 81.85, 89.20, 99.42, 121.40, 123.55, 127.87, 128.05, 128.43, 128.60, 128.73, 128.80, 130.18, 131.48, 132.23, 133.79, 134.60, 135.15, 234.71; IR (thin film): 2965 w, 2919 w, 2854 w, 1952 s, 1875 s, 1541 w, 1459 w, 1428 w cm^{-1} ; mass spectrum m/z (% rel intensity) 547 $[\text{M}+1]^+$ (43), 546 M^+ (72), 462 (100), 460 (17), 394 (32), 327 (29), 302 (16), 288 (16), 91 (33), 69 (17), 52 (19) ; HRMS calcd for $\text{C}_{32}\text{H}_{30}\text{CrO}_5$ m/z 546.1498, meas 546.1501.

Yellow solid (hexane), mp 112 - 116 $^\circ\text{C}$, $R_f = 0.50$ (30 % ethyl acetate / hexane).

The reaction in 1,2-dichloroethane without base or other additives done identically as above gave **4-260** which had 6 % ee determined from the demetalation / debenzylated phenol shown below, $[\alpha]_{\text{D}}^{22} +30.0^\circ$ (c 0.031, CH_2Cl_2) on **4-260**.

Compound 4-259

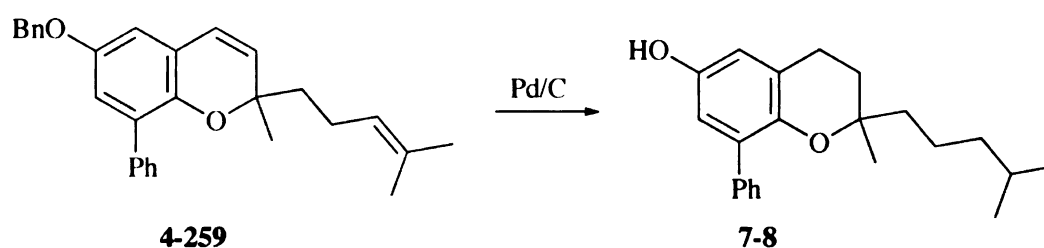


A vial was charged with 0.0069 g (0.0126 mmol) of compound **4-260** and 20 mL of CH_2Cl_2 . This was stirred for four days open to air and the CH_2Cl_2 was replenished during the process. The yellow solution turned green over four days. The solvent was removed under reduced pressure. Column chromatography (10 x 1.8 cm, silica gel) with 5 % ethyl acetate / hexane gave 0.0051 g (98 %, 0.012 mmol). The application HPLC with Chrialcel OC column using 99 : 1 hexane / isopropanol gave retention times of 12.8 and 15.6 minutes for the two enantiomers. The retention times were compared to racemic material and the retention times were identical. This was only a partial separation however it was good enough to determine that material was racemic.

$^1\text{H NMR}$ (CDCl_3) δ : 1.33 (s, 3 H), 1.49 (s, 3 H), 1.59 - 1.74 (m, 2 H), 1.63 (s, 3 H), 1.93 - 2.12 (m, 2 H), 5.02 (s, 3 H), 5.62 (d, 1 H, $J = 9.8$ Hz), 6.34 (d, 1 H, $J = 9.8$ Hz), 6.62 (d, 1 H, $J = 3.0$ Hz), 6.85 (d, 1 H, $J = 3.0$ Hz), 7.25 - 7.47 (m, 8 H), 7.52 - 7.63 (m, 2 H); IR (thin film): 2966 m, 2923 s, 2855 m, 1480 s, 1175 m cm^{-1} ; mass spectrum m/z (% rel intensity) 411 $[\text{M}+1]^+$ (1), 410 M^+ (4), 328 (18), 327 (83), 263 (2), 237 (5), 208 (41), 165 (8), 91 (2), 69 (85); Yellow thick oil (hexane),

$R_f = 0.59$ (30 % ethyl acetate / hexane).

Compound 7-8



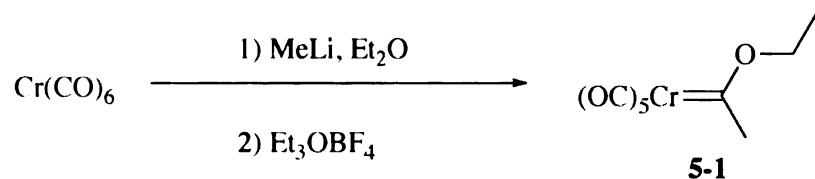
A flask was charged with compound **4-259** (0.060 g, 0.15 mmol), ethyl acetate (2 mL), isopropanol (2 mL), and 10 % Pd on carbon (31.9 mg). The atmosphere of the flask was removed and filled with hydrogen gas with a balloon. The solution was stirred for 4 hours at room temperature. The solution was filtered through Celite. Column chromatography (25 cm x 2 cm, silica gel) with 5 % ethyl acetate / hexane gave 0.034 g (0.105 mmol, 70 - 90 % yield typically, 75 % ee) of compound **7-8**. Chiral HPLC with 98 : 2 (hexane / IPA) and with a Chiralcel OD column which had retention times of 49.1 minutes for the minor and 55.05 minutes for the major.

^1H NMR (CDCl_3) δ : 0.81 (d, 6 H, $J = 6.5$ Hz), 1.11 (t, 2 H, $J = 7.1$ Hz), 1.20 (s, 3 H), 1.26 - 1.38 (m, 3 H), 1.44 - 1.57 (m, 2 H), 1.55 (s, water), 1.66 - 1.84 (m, 2 H), 2.65 - 2.87 (m, 2 H), 4.36 (s, 1 H), 6.53 (d, 1 H, $J = 3.0$ Hz), 6.65 (d, 1 H, $J = 3.2$ Hz), 7.21 - 7.29 (m, 1 H), 7.30 - 7.38 (m, 2 H), 7.48 - 7.55 (m, 2H); ^{13}C NMR (CDCl_3) δ : 21.25, 22.43, 22.60, 22.81, 23.20, 27.84, 31.17, 39.33, 40.53, 76.01, 114.75, 115.64, 122.66, 126.57, 127.60, 129.56, 130.86, 138.40, 144.89, 148.03;

IR (thin film): 3316 br m, 2951 s, 2868 m, 1450 , 1429 cm^{-1} ; mass spectrum m/z
(% rel intensity) 324 M^+ (27), 239 (27), 199 (100), 184 (21), 100 (13), 115 (12),
77 (10), 69 (22), 55 (24), 43 (34); $R_f = 0.45$ (30 % ethyl acetate / hexane).

7.5 Chapter Five Experimental

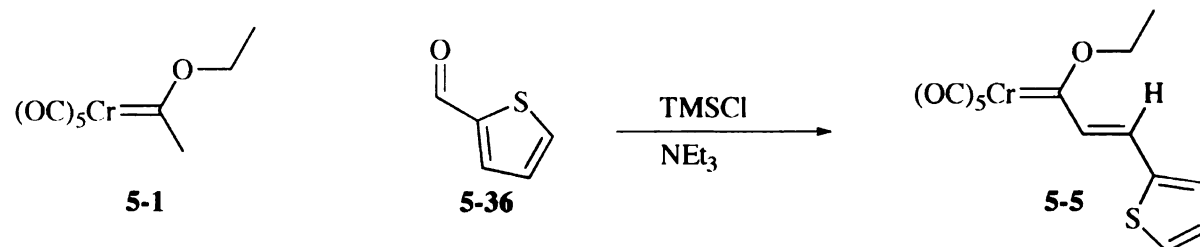
Compound 5-1



Compound **5-5** was prepared by well known literature methods in 81 % yield. The only deviation from the literature was purification by column chromatography on silica gel (10 % dichloromethane/hexane). The spectral data were consistent with the known literature compound.³⁸⁹ The characterizing data were identical to that previously reported.³⁸⁹

¹H NMR (CDCl₃) δ : 1.62 (t, 3 H, J = 7.1 Hz), 2.92 (s, 3 H), 4.99 (bs, 2 H), orange-oil at room temperature, yellow solid at -20 °C, R_f = 0.40 (9:1 hexane / EtOAc).

Compound 5-5

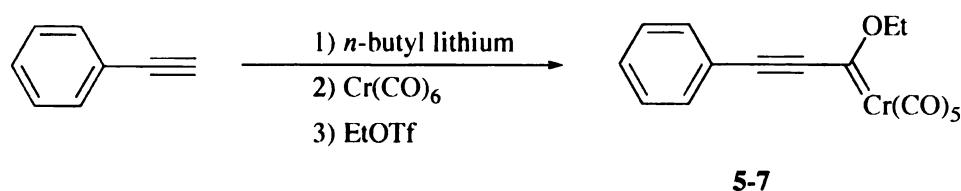


The literature compound **5-5** was made in the following way. Methyl ethoxy carbene complex **5-1** (0.555 g, 2.10 mmol) in diethyl ether at -78 °C was treated with *n*-butyl lithium (1.3 mL, 2.08 mmol, 1.6 M solution in hexane). This

solution was transferred via cannula to a solution of 2-thiophenecarboxaldehyde **5-36** (0.38 mL, 4.14 mmol) and SnCl_4 (4.2 mL, 4.2 mmol) in dichloromethane, which was also at -78°C . The solution was stirred for 2 hours at -78°C . After which, 50 mL of water was added. The water layer was extracted with 20 mL of dichloromethane and the organic layer was dried with sodium sulfate. Column chromatograph (22 cm x 3 cm, silica gel) with hexane to 10 % dichloromethane : hexane gave 0.477 g (35 % yield, 0.74 mmol). The spectroscopic properties were identical to that reported in the literature.³⁹⁰

$^1\text{H NMR}$ (CDCl_3) δ : 1.66 (t, 3 H, $J = 7.1$), 5.07 (q, 2 H, $J = 7.1$ Hz), 7.10 - 7.47 (m, 4 H), 7.72 (d, 1 H, $J = 15.1$ Hz); $^{13}\text{C NMR}$ (CDCl_3) δ : 15.12, 75.84, 123.35, 128.72, 130.46, 133.64, 138.39, 139.96, 216.78, 224.39, 328.41.

Compound 5-7 (3-40)



Procedure 1: Phenyl acetylene (1.1 mL, 10 mmol) was dissolved in 50 mL of diethyl ether and 20 mL of THF at 0°C . To this solution was added 6.3 mL (10 mmol) of *n*-butyl lithium. The reaction mixture was stirred 10 minutes and chromium hexacarbonyl (2.23 g, 10.1 mmol) was added. The reaction was stirred for two hours at room temperature and triethyl oxonium tetrafluoroborate (1.90 g, 10 mmol) was added. The reaction was stirred for one hour. The contents of the flask were taken up on silica by removing the solvent with a

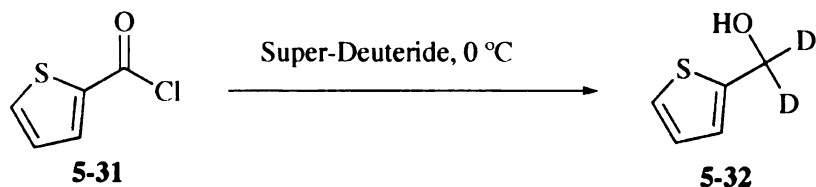
rotavap. Column chromatography (2.8 cm x 30 cm, silica) with hexane to 5 % DCM / hexane gave 0.041 g (1.2 % yield, 0.12 mmol).

Procedure 2: Phenyl acetylene (1.1 mL, 10 mmol) was dissolved in 20 mL of diethyl ether and 10 mL of THF and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. To this solution was added *n*-butyl lithium (6.4 mL, 10 mmol) in a dropwise manner. After 15 to 20 minutes chromium hexacarbonyl (2.24 g, 10.1 mmol) was added at $-78\text{ }^{\circ}\text{C}$ and allowed to warm to room temperature. After two hours the solvent was removed with a rotavap. and replaced with DCM. Triethyloxonium tetrafluoroborate (1.90 g, 10 mmol) was added at $-78\text{ }^{\circ}\text{C}$ to the solution. This reaction was warmed to room temperature over an hour. The contents of the flask were taken up on silica by removing the solvent with a rotavap. Column chromatography (2.8 cm x 30 cm, silica) with hexane to 10 % DCM / hexane gave 0.2379 g (6.8 % yield, 0.68 mmol).

Procedure 3: This was identical to procedure 2 except that the reaction was carried out at $-50\text{ }^{\circ}\text{C}$ instead of $-78\text{ }^{\circ}\text{C}$. This resulted in 0.1340 g (3.8 % yield, 0.38 mmol).

The spectroscopic properties were identical to that reported in the literature.³⁹¹

Compound 5-32

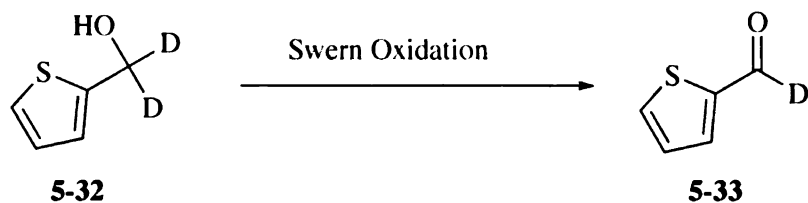


To a solution of 2-thiophenecarbonyl chloride **5-31** (1.03 g, 7.00 mmol) in

5 mL of diethyl ether, Super deuteride (20 mL, 20.0 moles, 1 M solution) was added dropwise at 0 °C. The contents of the flask were warmed to room temperature over 3 hours. Column chromatography (26 cm x 3 cm, silica gel) with 30 % ethyl acetate / hexane gave 0.68 g (84 % yield, 98 % deuterium incorporation, 5.88 mmol) of alcohol **5-32**. If the reaction was warmed over 2 hours, this gave a yield of 68 % of alcohol **5-32** and 18 % yield of aldehyde **5-33**. The deuterium incorporation was measured by comparing the area of the peak at 4.78 to 6.90 - 7.05 (m). The product **5-32** had spectral data identical with that previously reported for this compound.³⁹²

¹H NMR (CDCl₃) δ: 2.66 (s, 1 H), 6.90 - 7.05 (m, 2 H), 7.22 - 7.30 (m, 1 H); ¹³C NMR (CDCl₃) δ: 124.99, 125.39, 126.49, 126.73 (one carbon missing due to the relaxation of C-D bond); mass spectrum *m/z* (% rel intensity): 116 M⁺ (53), 115 (19), 99 (100), 86 (13), 83 (18) 55 (5), yellow oil, R_f = 0.31 (30 % EtOAc/hexane).

Compound 5-33

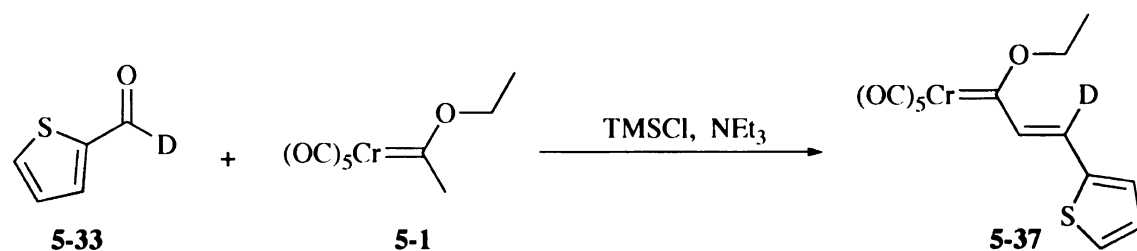


To a solution of DMSO (2.20, 41.7 mmol) in 175 mL of dichloromethane, oxalyl chloride (1.30 mL, 14.6 mmol) was added dropwise. The solution was stirred 10 minutes, and **5-32** (1.70 g, 14.60 mmol) in 20 mL of dichloromethane was added dropwise. Column chromatography (21 cm x 3 cm, silica gel) with 60

% dichloromethane/hexane gave 1.12 g (68 % yield, 99 % deuterium incorporation, 9.92 mmol) of aldehyde **5-33**. The deuterium incorporation was measured by comparing a small peak at 9.84 (s) to the 7.73 - 7.84 (m). The spectral data were identical to that previously reported for this compound.³⁹²

¹H NMR (CDCl₃) δ : 7.21 (t, 1 H, J = 4.3 Hz), 7.73 - 7.84 (m, 2 H); ¹³C NMR (CDCl₃) δ : 128.08, 134.82, 136.16, 143.54 (t, due to C-C-D coupling, ² J = 5.1 Hz), 182.45 (t, due to C-D coupling, ¹ J = 26.8 Hz); yellow oil, R_f = 0.36 (60 % CH₂Cl₂/hexane).

5-37

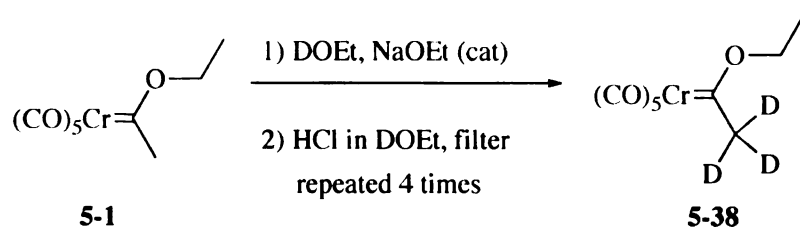


In a 50 mL round bottom flask where the 14/20 glass joint was replaced with a threaded high-vacuum Teflon valve, 30 mL of diethyl ether, compound **5-33** (0.59 g, 5.22 mmol), methyl ethoxy carbene complex **5-1** (1.35 g, 5.11 mmol), triethyl amine (3.0 mL, 21.5 mmol), TMSCl (2.0 mL, 15.8 mmol) were added. Three freeze thaw cycles were done to remove oxygen. The solution was stirred 23 hours at room temperature and then stored 24 hours at -20 °C. The contents of the flask were poured onto silica gel (~ 2 mL) and the solvent removed under reduced pressure. Column chromatography (24.5 cm x 4 cm, silica gel) with 30

% dichloromethane/hexane gave 0.89 g (49 % yield, 2.50 mmol, 97 % deuterium incorporation) of **5-37** along with 0.44 g (33 % recovery) of recovered carbene complex **5-1**. The yield of **5-37** was 72 % based on unrecovered **5-1**. The deuterium incorporation was calculated based on the integration of a small peak at 7.16 (d) compared to 7.08 (dd).

^1H NMR (CDCl_3) δ : 1.67 (t, 3 H, $J = 7.1$ Hz), 5.07 (q, 2 H, $J = 7.1$ Hz), 7.08 (dd, 1 H, $J = 3.7$, $J = 5.1$ Hz), 7.38 (dd, 1 H, $J = 1.0$, $J = 3.7$ Hz), 7.47 (dd, $J = 1$, $J = 4.9$ Hz); ^{13}C NMR (CDCl_3) δ : 15.15, 75.85, 123.49 (t, $^1J = 22.5$ Hz, very weak) 128.73, 130.45, 133.54, 138.35, 139.93, 216.80, 224.38, 328.60; IR (thin film) 3080 w, 3026 w, 2963 m, 2901 w, 2108 s, 1480 m cm^{-1} ; Anal calcd for $\text{C}_{14}\text{H}_9\text{DCrO}_6\text{S}$: C, 46.80; H, 3.09. Found; C, 46.72; H, 2.81. Black solid (30 % CH_2Cl_2 : hexane), mp 86 - 87 °C, $R_f = 0.51$ (30 % CH_2Cl_2 /hexane).

Compound 5-38

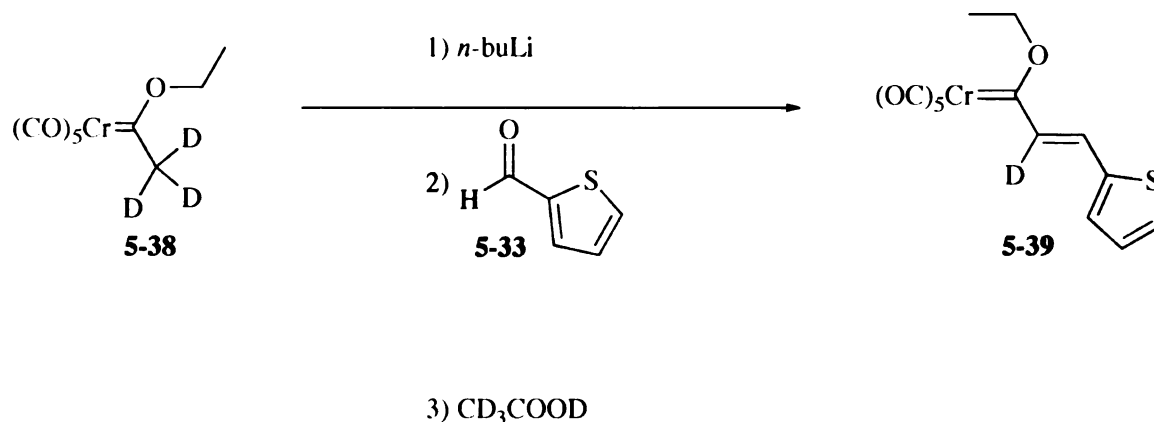


To methylethoxy carbene complex **5-1** (4.57 g, 17.3 mmol) was added 10 mL of ethanol- d_4 with pre-dissolved sodium metal < 4 mg. The solution was stirred for 15 minutes and acidified with 1:3 by volume of conc. HCl / ethanol- d_4 to a pH < 7. The solution was then taken up in ether and filtered through Celite-

503. The organic solvent was removed under reduced pressure. This procedure was repeated four times. This resulted in 2.94 g (64 % yield, 11.1 mmol, 96 % deuterium incorporation). The spectral data was consistent with the known literature compound.³⁹³ The deuterium incorporation was measured by the integration of the peak at 2.88 and 1.65 ppm.

¹H NMR (CDCl₃) δ: 1.64 (t, 3 H, *J* = 7.1 Hz), 2.88 (br s, 0.15 H, from undeuterated compound), 5.01 (bs, 2 H); ¹³C NMR (CDCl₃) δ: 14.93, 49.27 (broad and weak), 216.49, 223.40, 357.81 (deuterated carbon missing due to the relaxation time of C-D); IR (thin film) 2992 m, 2946 m, 2906 w, 2064 vs, 1918 vs, 1470 m, 1368 s, 1250 vs, 1129 s, 1030 s, 978 s 812 m, 640 vs cm⁻¹; orange oil at room temperature, yellow solid at -20 °C, *R*_f = 0.42 (9:1 hexane/EtOAc).

Compound 5-39

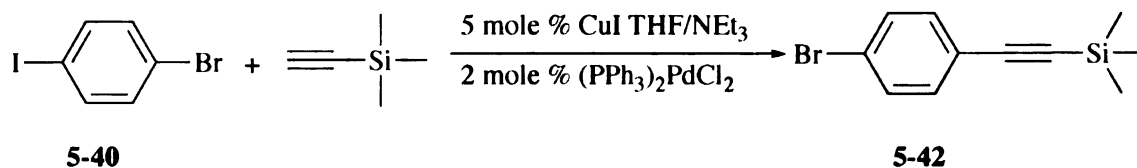


To a solution of **5-38** (1.0 g, 3.8 mmol) in ether (25 mL) at -78 °C was added 2.4 mL (1.6 M in hexanes, 3.8 mmol) of *n*-butyl lithium. The solution was stirred for 20 minutes and then 2-thiophenecarboxaldehyde **5-33** (0.7 mL, 7.7

mmol) was added at $-78\text{ }^{\circ}\text{C}$. The solution was stirred for 45 minutes at $-78\text{ }^{\circ}\text{C}$. The solution was warmed to room temperature and stirred for four hours. The solution was extracted with 10 mL of D_2O and the D_2O layer was adjusted to an apparent pH of < 7 with acetic acid- d_4 . The D_2O layer was extracted with DCM (3 x 50 mL). The organic layers were combined and dried over sodium sulfate. The solvent was removed under reduced pressure. Column chromatography (2.8 cm x 26 cm, silica gel) with 5 % DCM to 10 % DCM / hexane gave 0.24 g (17 % yield, 0.65 mmol, 95 % deuterium incorporation). The deuterium incorporation was determined by integrating the peak at 7.70 (d) and 7.36 (d) and comparing the area.

^1H NMR (CDCl_3) δ : 1.66 (t, 3 H, $J = 7.0\text{ Hz}$), 5.04 (q, 1 H, $J = 7.2\text{ Hz}$), 7.08 (dd, 1 H, $J = 3.8, J = 5.0\text{ Hz}$), 7.11 (s, 1 H), 7.36 (d, 1 H, $J = 3.8\text{ Hz}$), 7.47 (d, 1 H, $J = 5.0\text{ Hz}$), 7.70 (d, 0.05 H, $J = 15.0\text{ Hz}$, from undeuterated compound); ^{13}C NMR (CDCl_3) δ : 15.19, 75.86, 123.03, 128.74, 130.49, 133.64, 137.90 (t, $^1J = 23.7\text{ Hz}$, weak), 139.94, 216.78, 224.39, 328.33; IR (thin film) 3112 w, 2994 m, 2056 s, 1916 s 1561 s cm^{-1} ; Anal calcd for $\text{C}_{14}\text{H}_9\text{DCrO}_6\text{S}$: C, 46.80; H, 3.09. Found; C, 46.86; H, 2.82. Red solid, mp $86 - 88\text{ }^{\circ}\text{C}$, $R_f = 0.30$ (hexane).

Compound 5-42



The following procedure is adapted from one that has been reported for this compound. A magnetic stirring bar was placed into a flame-dried single neck 50 mL flask that had been modified by replacement of the 14/20 joint with a threaded high vacuum Teflon valve. The flask was charged with 1-bromo-4-iodobenzene **5-40** (4.05 g, 14.3 mmol), TMS acetylene **11** (2.0 mL, 14.2 mmol), THF (25 mL), triethyl amine (8 mL), dichloropalladium (II) bis(triphenylphosphine) (0.20 g, 2.0 mole %), and copper (I) iodide (0.14 g, 5 mole %). Three freeze thaw cycles were performed to remove oxygen. The contents of the flask were stirred for three days at room temperature under Argon. The contents of the flask were filtered through silica gel with ethyl acetate (3 x 170 mL). The ethyl acetate was removed under reduced pressure. The filtration procedure through silica gel was repeated once after the solvent was removed. Column chromatography (20 cm x 3.8 cm, silica gel) with 100 % hexane gave 3.44 g (95 % yield, 13.8 mmol) as a white solid. Spectral data were identical to that previously reported.³⁹⁴

¹H NMR (CDCl₃) δ: 0.25 (s, 9 H), 7.31 (d, 2 H, *J* = 8.6 Hz), 7.42 (d, 2 H, *J* = 8.6

Hz); ¹³C NMR (CDCl₃) δ: -0.15, 95.53, 103.81, 122.00, 122.72, 131.42, 133.35;

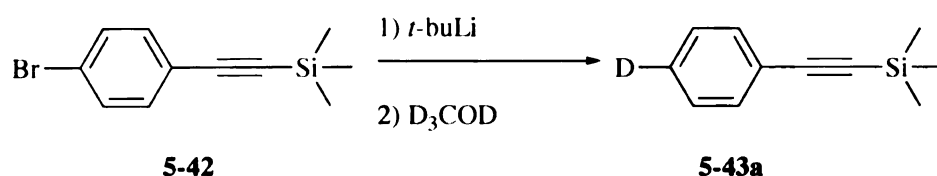
mass spectrum *m/z* (% rel intensity) 254 M⁺ (96, ⁸¹Br), 252 M⁺ (100, ⁷⁹Br), 240

(21), 239 (19, ^{81}Br), 238 (18), 237 (17, ^{79}Br), 144 (25), 129 (16), 115 (35), 75

(25); Anal calcd for $\text{C}_{11}\text{H}_{13}\text{BrSi}$: C, 52.18; H, 5.17. Found; C, 52.18; H, 5.34.

White solid (hexane), mp 60 - 61 °C, R_f = 0.50 (hexane).

Compound 5-43a

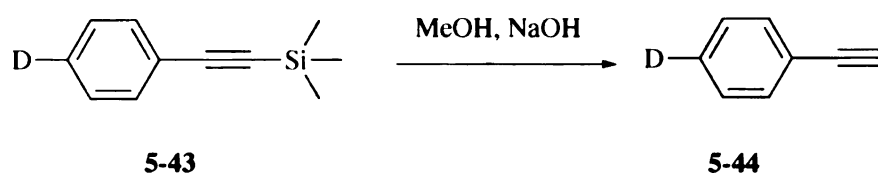


The following procedure is adapted from one that has been reported for this compound. To a solution of **5-42** (3.44 g, 13.5 mmol) in 100 mL ether at -78 °C was added *t*-butyl lithium (1.7 M in pentane, 16.4 mL, 27.9 mmol). The solution was stirred for 25 minutes after adding *t*-butyl lithium at -78 °C. Then, methanol- d_4 (1.2 mL, 29.6 mmol) was added at -78 °C. The solution was allowed to warm over four hours to room temperature. A cloudy white solution resulted. The solution was extracted with 50 mL of water and the water layer was back extracted with 3 x 50 mL ether. The organic layers were combined and dried over sodium sulfate. The solution was filtered and the solvent removed under reduced pressure. This gave a quantitative yield of **5-43a**, 2.36 g (> 99 %, 13.5 mmol, 98 % deuterium incorporation). The deuterium incorporation was measured by comparing the integration of 0.25 (set to 9) to 7.28 and 7.28 ppm. Spectral data were identical to that previously reported.³⁹⁵

^1H NMR (CDCl_3) δ : 0.25 (s, 9 H), 7.28 (d, 2 H, J = 8.0 Hz), 7.47 (d, 2 H, J = 8.0

Hz); ^{13}C NMR (CDCl_3) δ : -0.03, 94.04, 105.12, 123.13, 128.06, 128.17 (t, $^1J = 25.6$ Hz), 131.94; IR (thin film) 3079 s, 3029 s, 2961 vs, 2899 s, 2101 vs, 1595 m, 1480 m, 1406 m, 1250 m, 1219 m, 841 s cm^{-1} ; mass spectrum m/z (% rel intensity) 175 M^+ (3), 174 (11), 161 (20), 160 (100), 144 (5), 103 (4), 89 (8), 61 (21); Anal calcd for $\text{C}_{11}\text{H}_{13}\text{DSi}$: C, 75.36; H, 8.62. Found; C, 75.32; H, 8.54. Clear oil, $R_f = 0.38$ (hexane).

Compound 5-44



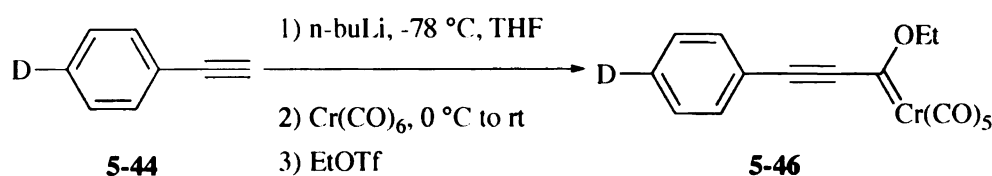
The following procedure is adapted from one that has been reported for this compound. Compound **5-43** (6.07 g, 34.6 mmol) was dissolved in methanol (20 mL). Sodium hydroxide (1.51 g, 37.8 mmol) was added. The reaction was stirred for three hours at room temperature. The solution was extracted with water and the water was back extracted with 3 x 50 mL of hexane. The organic layers were combined and dried over sodium sulfate. The volume of solvent was reduced to 35 mL under reduced pressure in a rotovap and the remaining solvent was removed by distillation leaving 1.35 g (38 % yield, 13.1 mmol, ≥ 98 % deuterium incorporation). There remained residual solvent that could not be removed without significant loss of product, and thus, this was taken directly to the next step. The deuterium incorporation was measured by setting the region of

integration of 7.50 (d) to 2 and noting the difference of the integration of the region of 7.31 (d). This difference was calibrated to the undeuterated compound.

Spectral data were identical to that previously reported.³⁹⁶

¹H NMR (CDCl₃) δ: 3.07 (s, 1 H), 7.31 (d, 2 H, *J* = 7.6 Hz), 7.50 (d, 2 H, *J* = 8.0 Hz); mass spectrum *m/z* (% rel intensity) 103 M⁺ (100), 88 (5), 77 (16), 61 (11), 50 (14).

Compound 5-46



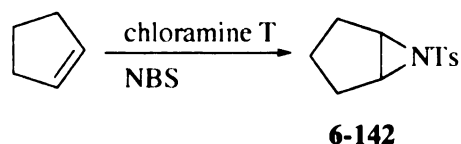
To a solution of **5-44** (0.37 g, 3.6 mmol) at -78 °C in 20 mL THF was added *n*-butyl lithium (1.6 M in pentane, 2.25 mL, 3.6 mmol). The solution was warmed to 0 °C and stirred for 45 minutes which gave a yellow-brown solution. At this point, chromium hexacarbonyl (0.80 g, 3.6 mmol) was added at 0 °C and the orange solution was allowed to warm to room temperature over 45 minutes. The solution was cooled to 0 °C and ethyl triflate (0.94 mL, 7.3 mmol) was added. The solution was stirred for 35 minutes which resulted in a blood-red solution. The contents of the flask were poured onto brine (50 mL) and extracted with three portions of ether (20 mL, 2 x 75 mL). The organic layers were combined and dried with sodium sulfate. The solvent was removed under reduced pressure with care taken to maintain a temperature of 0 to 10 °C for the water bath. Column chromatography (30 cm x 3.8 cm, silica gel) first with

hexane and then with 5 % ethyl acetate / hexane resulted in 0.69 g (55 % yield, 1.98 mmol, ≥ 98 % deuterium incorporation). Again, care was taken to maintain a temperature of 0 to 10 °C of the water bath when the solvent was removed. The deuterium incorporation was measured by setting the region of integration of 7.58 (d) to 2 and noting the difference of the integration of the region of 7.45 (d). This difference was calibrated to the undeuterated compound.

^1H NMR (CDCl_3) δ : 1.58 (t, 3 H, $J = 7.1$ Hz), 4.74 (q, 2 H, $J = 6.9$ Hz), 7.45 (d, 2 H, $J = 7.8$ Hz), 7.58 (d, 2 H, $J = 7.3$ Hz); ^{13}C NMR (CDCl_3) δ : 14.97, 75.83, 91.78, 121.02, 128.80, 131.32 (t, $^1J = 22.8$ Hz, weak), 132.67, 135.67 (weak), 216.30, 225.71, 313.84; IR (thin film) 2999 wb, 2155 m, 2060 s, 1935 s, 1294 m, 1196 m, 1146 w, 1109 w, 1036 m, 862 m, 681 m, 650 m, 608 m, 594 m cm^{-1} ; Anal calcd for $\text{C}_{16}\text{H}_9\text{DCrO}_6$: C, 54.71; H, 3.16. Found; C, 54.40; H, 3.00, Black solid (hexane), mp 61 - 63 °C, $R_f = 0.18$ (hexane), $R_f = 0.34$ (5 % EtOAc/hexane). Attempts to make compound 15 from compound 13 through the anion via treatment of compound 13 with MeLi-LiBr complex failed to give yields greater than 0.1 % for compound 15.

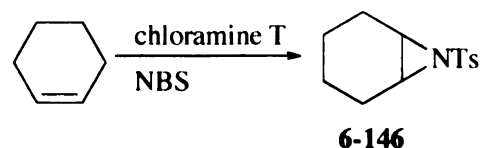
7.6 Chapter Six Experimental

Compound 6-142



This compound was prepared by literature methods.³⁹⁷ The following procedure came from Jenifer Schomaker: "Cyclopentene (2.5 g, 36.7 mmol, 1.0 eq) was combined with 180 mL of dry acetonitrile at rt. Chloramine T (8.8 g, 38.5 mmol, 1.05 eq) and NBS (1.3 g, 7.3 mmol, 0.2 eq) were added and the flask was covered with aluminum foil. The light yellow suspension was stirred overnight at rt. Extractive workup followed by purification by column chromatography gave the desired aziridine in 67% yield (24.6 mmol). The spectroscopic data matched those reported in the literature."^{397, 398} ¹H NMR (300 MHz, CDCl₃) δ 7.78 (d, 2 H, *J* = 8.1 Hz), 7.24 (d, 2 H, *J* = 7.8 Hz), 3.23 (s, 2 H), 2.38 (s, 3 H), 1.93-1.8 (m, 2 H), 1.62 - 1.2 (m, 4 H); ¹³C NMR (CDCl₃) δ: 19.3, 21.4, 26.7, 46.5, 127.4, 129.4, 135.8, 143.9."

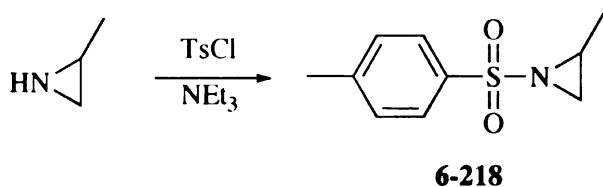
Compound 6-146



This compound was prepared by literature methods.³⁹⁸ The following

procedure was taken directly from the work of Jennifer Schomaker: "Cyclohexene (2.0 g, 24.3 mmol, 1.0 eq) was combined with 120 mL of dry acetonitrile at rt. Chloramine T (5.8 g, 25.6 mmol, 1.05 eq) and NBS (1.0 g, 4.9 mmol, 0.2 eq) were added and the flask covered with aluminum foil. The light yellow suspension was stirred overnight at rt. Extractive workup followed by purification by column chromatography gave the desired aziridine in 77% yield (18.7 mmol). The spectroscopic properties were identical to that reported in the literature."³⁹⁸ ¹H NMR (300 MHz, CDCl₃) δ 7.78 (d, 2 H, *J* = 8.1 Hz), 7.24 (d, 2 H, *J* = 8.1 Hz), 2.91 (s, 2 H), 2.39 (s, 3 H), 1.8 - 1.69 (m, 4 H), 1.4 - 1.28 (m, 2 H), 1.21 - 1.10 (m, 2 H); ¹³C NMR (75 MHz, CDCl₃) δ: 19.3, 21.5, 22.6, 39.6, 127.5, 129.5, 135.7, 143.9.

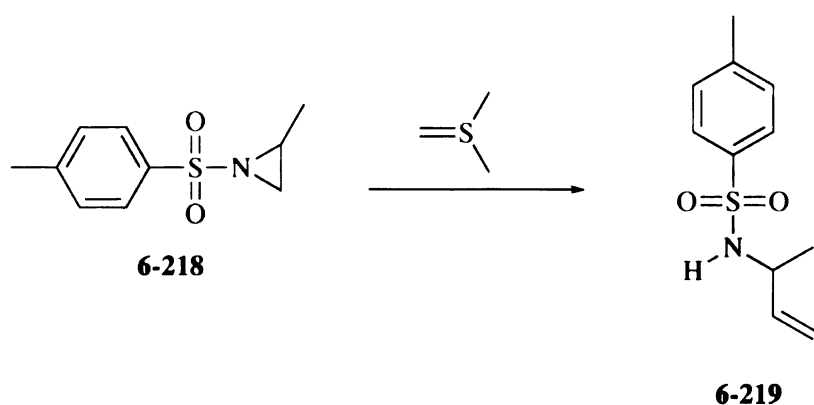
Compound 6-218



A solution of 2-methyl aziridine (0.40 g, 7.10 mmol) and TsCl (1.62 g, 8.5 mmol) in 20 mL of dichloromethane was cooled to 0 °C. To the reaction mixture was added triethyl amine (1.3 mL, 9.3 mmol) and the reaction mixture was noted to be warm to the touch. The reaction mixture was stirred overnight. The reaction mixture was poured into 30 mL of water. The layers were separated and the aqueous layer was back extracted with 20 mL x 2 of dichloromethane. The organic layers were combined and dried over magnesium sulfate. The solution

was filtered through fluted filter paper. The solvent was removed under reduced pressure. Column chromatography (22 x 2.8 cm, silica gel) with 100 % hexane then 25 % ethyl acetate / hexane gave a 92 % yield (1.38 g, 6.5 mmol). This compound was prepared by literature methods and the spectroscopic properties were identical with that previously reported.³⁹⁹

Compound 6-219

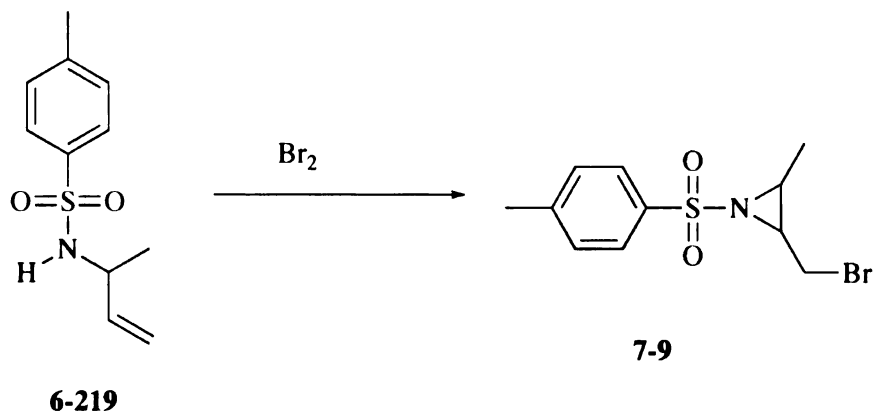


To a suspension of trimethylsulfur iodide (1.95 g, 9.5 mmol) in 35 mL of THF was added *n*-butyl lithium in hexane (5.5 mL, 8.8 mmol) at -10 °C. The suspension was stirred for 30 minutes. The aziridine (0.52g, 2.5 mmol) was added in 6 mL of THF in a dropwise manner. The reaction was warmed to 0 °C over one hour. The solution was observed to turn cloudy as it was warmed to 0 °C. The reaction was stirred for one hour at room temperature. Column chromatography (33 cm x 1.8 cm, silica) with 20 % ethyl acetate / hexane gave 0.44 g (80 % yield, 2.0 mmol). The spectroscopic properties were identical to that previously reported.⁴⁰⁰

¹H NMR (CDCl₃) δ: 1.34 (d, 3 H, *J* = 7.1 Hz), 2.37 (s, 3 H), 3.91 (m, 1 H), 4.34

(m, 2 H), 5.62 (m, 1 H), 7.20 - 7.41 (m, 3 H), 7.64 - 7.87 (m, 2 H); ^{13}C NMR (CDCl_3) δ : 21.49, 51.55, 115.11, 127.14, 129.59, 138.0, 138.95, 143.28. Clear oil, R_f = 0.29 (3:1 hexane/ethyl acetate).

Compound 7-9 (2-244)



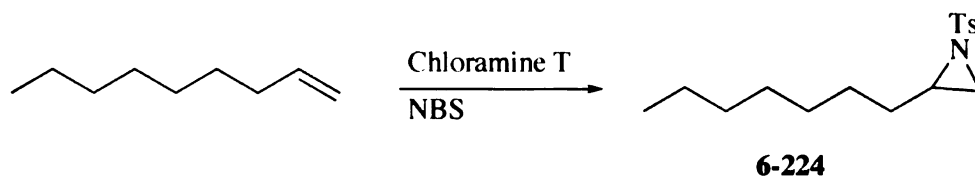
To a solutions of **6-219** (0.17 g, 0.7 mmol) in 10 mL DCM at $-40\text{ }^{\circ}\text{C}$, bromine (0.04 mL, 0.7 mmol) was added dropwise. The solution was stirred for 1 hour then NaHMDS (1.6 mL, 1.6 mmol) was added at $-40\text{ }^{\circ}\text{C}$. The solution was warmed to room temperature. The solution was extracted with 100 mL of water. The water layer was back extracted with 3 x 50 mL of DCM. The organic layers were combined and dried over sodium sulfate. Column chromatography with 30 % ethyl acetate / hexane gave 0.15 g (67 % yield, 0.46 mmol). The *cis* to *trans* ratio was 2 to 1 determined by ^1H NMR intergrating the peaks at 1.22 and 1.46 ppm.⁴⁰¹ This compound has been reported in the literature.⁴⁰²

Mixture of diastereomers:

^1H NMR (CDCl_3) δ : 1.22 (*cis*) and 1.46 (*trans*)⁴⁰¹ (d, 3 H), 2.18 (s, 3H), 2.65 -

3.20 (m, 2 H), 3.38 (m, 1 H), 7.20 - 7.35 (m, 2 H), 7.65 - 7.82 (m, 2 H); ^{13}C NMR (CDCl_3) δ : 11.50, 14.43, 16.67, 21.54, 26.93, 30.25, 34.63, 35.76, 40.88, 43.91, 46.51, 48.27, 126.90, 127.52, 127.69, 127.92, 129.44, 129.63, 129.81, 134.64, 137.18, 144.20, 144.32, 144.64; mass spectrum m/z (% rel intensity) 305 (M^+ , ^{81}Br), 303 (M^+ , ^{79}Br), 224 (97), 155 (19), 150 (97, ^{81}Br), 148 (100, ^{79}Br), 91 (44), 69 (56), 65 (24), 54 (17); Yellow oil, R_f = 0.40 and 0.33 (7:3 hexane / ethyl acetate).

Compound 6-224

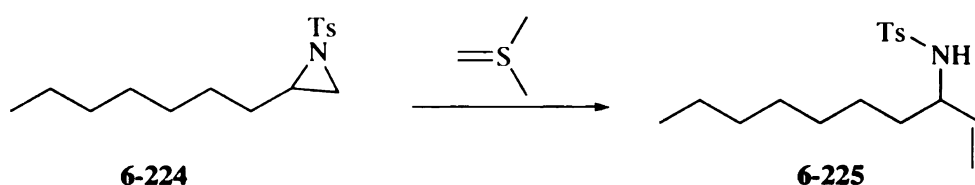


A flask was charged with nonene (365 mg, 2.90 mmol), chloramine T (665.6 mg, 2.92 mmol), NBS (103.6 mg, 0.58 mmol), and acetonitrile (20 mL). The atmosphere within the flask was replaced with argon and the reaction was stirred for 2 days. The contents of the flask were poured into 100 mL of water and extracted with ethyl acetate (50 mL x 3). The organic phases were collected and dried over sodium sulfate and the solvent removed under reduced pressure. Column chromatography with 10 % ethyl acetate / hexane gave 286 mg or 34 % yield (0.99 mmol). The spectroscopic properties were identical to that previously reported.⁴⁰³

^1H NMR (CDCl_3) δ : 0.83 (t, 3 H, J = 6.7 Hz), 1.07 – 1.36 (m, 12 H), 1.41 – 1.58

(m, 1 H), 2.02 (d, 1 H, $J = 4.6$ Hz), 2.40 (s, 3 H), 2.56 – 2.72 (m, 2 H), 7.30 (d, 2 H, $J = 8.1$ Hz), 7.79 (d, 2 H, $J = 8.1$ Hz); ^{13}C NMR (CDCl_3) δ : 13.87, 21.51, 22.51, 26.67, 28.97, 31.20, 31.52, 33.67, 40.40, 127.88, 129.50, 135.00, 144.30; IR (thin film): 1955 s, 2926 s, 2857 s, 1597 w, 1458 w, 1325 m, 1161 s, 1094 cm^{-1} ; Clear oil.

Compound 6-225

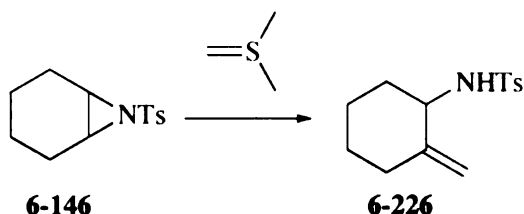


Procedure A. To a solution of trimethylsulfonium iodine (0.38 g, 1.9 mmol) in THF was added *n*-butyl lithium (1.1 mL, 1.8 mmol) at -18 °C. Compound **3-245** (0.14 g, 0.47 mmol) was added in 5 mL of THF (the solution turned yellow-green) after 30 minutes at -18 °C and the solution was stirred at 0 °C for 1 hour and 1.5 hours at room temperature. The solution was poured into 25 mL of water, back extracted with 30 x 3 mL of ethyl acetate. The organic layers were combined and extracted with 100 mL of saturated brine. The aqueous layer was back extracted with ethyl acetate (2 x 50 mL), and the organic layers were combined and dried with sodium sulfate. Column chromatography (30 cm x 2.8 cm, silica gel) with 20 % ethyl acetate / hexane gave 0.125 g (87 % yield, 0.41 mmol). One of two spots isolated by column chromatography. The spectroscopic properties were identical with the literature.⁴⁰⁴

^1H NMR (CDCl_3) δ : 0.79 (t, 3 H, $J = 6.9$ Hz), 1.00 – 1.25 (m, 10 H), 2.34 (s, 3 H),

3.65 (qt, 1 H, $J = 7.1$ Hz), 4.49 (bs, 1 H), 4.86 – 4.94 (m, 2 H), 5.42 – 5.53 (m, 1 H), 7.20 (d, 2 H, $J = 8.0$ Hz), 7.67 (d, 2 H, $J = 8.2$ Hz); IR (thin film): 3277 m, 2928 s, 2857 m, 1497 w, 1329 m, 1161 s, 1096 m, 922 w, 814 w cm^{-1} ; mass spectrum m/z (% rel intensity) 424 (15), 310 M^+ (12), 309 (38), 296 (35), 282 (58), 266 (35), 253 (54); Anal calcd for $\text{C}_{17}\text{H}_{27}\text{NO}_2\text{S}$: C, 65.98; H, 8.79; N, 4.53. Found; C, 65.72; H, 8.70; N, 4.36. Clear oil, $R_f = 0.38$ (30 % ethyl acetate / hexane).

Compound 6-226

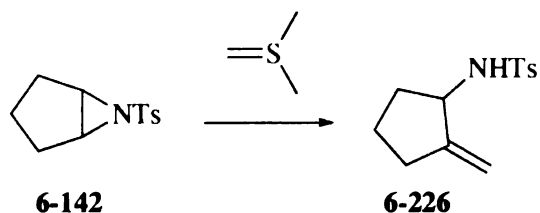


Procedure B: To a suspension of trimethylsulfonium iodide (922.3 mg, 4.52 mmol) in THF (5 mL) was added *n*-butyl lithium (2.7 mL, 4.3 mmol) at -18 °C. After 30 minutes, compound **6-146** (0.142 g, 0.567 mmol) was added in 3 mL of THF with 1 mL x 2 rinses. The reaction was stirred at -18 to -10 °C for 2 hours. The contents of the flask were then warmed to 0 °C and stirred for 1 hour. The contents of the reaction were allowed to warm to room temperature and stirred for one hour. To the contents of the flask were added 50 mL of water and the water layer was extracted with 50 mL, 30 mL x 3 of ethyl acetate. The organic layers were combined and dried with sodium sulfate. The organic layer was filtered and the solvent removed under reduced pressure. Column

chromatography (22 cm x 2.2 cm, silica gel) with 10 % ethyl acetate / hexane then eluding with 20 % ethyl acetate / hexane gave 126 mg (84 % yield, 0.48 mmol) of a white solid. The spectroscopic properties were identical with that previously reported.⁴⁰⁵

¹H NMR (CDCl₃) δ: 1.18 – 1.38 (m, 3 H), 1.47 – 1.72 (m, 3 H), 1.84 – 1.93 (m, 1 H), 2.16 -2.24 (m, 1 H), 2.34 (s, 3 H), 3.64 – 3.70 (m, 1 H), 4.59 (s, 1 H), 4.66 (s, 1 H), 4.83 (bs, 1 H), 7.21 (d, 2 H, *J* = 8.0 Hz), 7.70 (d, 2 H, *J* = 8.2 Hz); ¹³C NMR (CDCl₃) δ: 21.47, 24.14, 27.22, 33.88, 35.55, 56.13, 107.64, 126.98, 129.48, 138.06, 143.08, 147.45; IR (thin film): 3281 s, 2936 s, 2859 m, 1653 w, 1599 w, 1447 m, 1327 m, 1163 s, 1094 m, 903 w, 814 m, 666 m cm⁻¹; mass spectrum *m/z* (% rel intensity) 265 M⁺ (23), 227 (4), 184 (7), 184 (6), 156 (12), 155 (26), 139 (18), 104 (100), 91 (100), 65 (50); Anal calcd for C₁₄H₁₉NO₂S: C, 63.36; H, 7.22; N, 5.28. Found; C, 63.33; H, 7.21; N, 5.14. White solid (hexane), mp 79 - 81 °C, *R*_f = 0.32 (30 % ethyl acetate / hexane).

Compound 6-227



Procedure B was followed for compound **6-142** (0.138 g, 0.58 mmol) which gave a yield of 70 % (0.103 g, 0.41 mmol).

When Me₃SOTf (1.17 g, 5.4 mmol) was used instead of trimethylsulfonium iodide with compound **6-142** (0.154 g, 0.65 mmol) under identical conditions as procedure B, the yield was 79 % (0.128 g, 0.51 mmol) of **6-226**.

The spectroscopic properties were identical with that previously reported.⁴⁰⁵

¹H NMR (CDCl₃) δ: 1.23 – 1.58 (m, 2 H), 1.60 – 1.75 (m, 1 H), 1.81 – 1.88 (m, 1 H), 2.26 (t, 2 H, *J* = 6.3 Hz), 2.40 (s, 3H), 3.93 (q, 1 H, *J* = 8.2 Hz), 4.63 (bs, 1H), 4.86 (d, 1 H, *J* = 2.2 Hz), 4.90 (d, 1 H, *J* = 2.2 Hz), 7.27 (d, 2 H, *J* = 8.2 Hz), 7.76 (d, 2 H, *J* = 8.2 Hz); ¹³C NMR (CDCl₃) δ: 21.48, 21.92, 30.25, 34.38, 57.35, 100.49, 108.00, 127.02, 129.62, 137.95, 143.25, 151.35; IR (thin film): 3277 s, 2963 m, 2870 w, 1659 w, 1599 w, 1495 w, 1435 m, 1321 m, 1161 s, 1094 m, 899 , 816, 666 cm⁻¹; mass spectrum *m/z* (% rel intensity) 251 M+ (8), 186 (9), 155 (18), 96 (100), 91 (80), 79 (25), 65 (23), 41 (17); Anal calcd for C₁₃H₁₇NO₂S: C, 62.12; H, 6.82; N, 5.57. Found; C, 62.43; H, 6.89; N, 5.41. Clear oil that solidified on standing for 48 hours into a white solid, mp 69 - 70 °C, R_f = 0.37 (30 % ethyl acetate / hexane).

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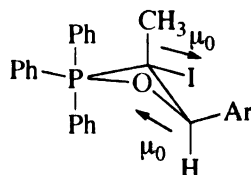
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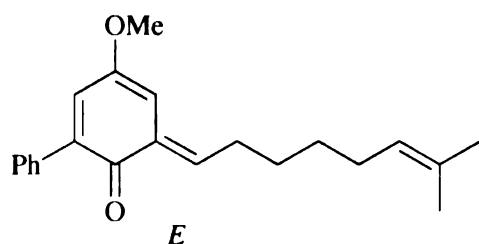
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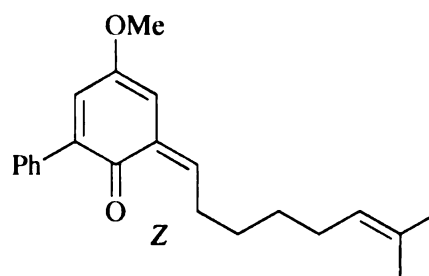
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-570080.69 kcal/mol

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said to originate from the Phoenicians which was learned by Thales. The arabian astronomers called the star *Al Kaukab al Shamaliyy* or the "Star of the North." The star has been referenced in great literature such as Bryant, Wordsworth, and Shakespeare. Ancient China described a concept of "cosmic mountain" refering to Polaris under the name *T' ai Chi* which literally means "The Axis of the Universe." Of couse Polaris is only the axis of the universe for a short time. All things must change. (b) For a detailed account see: Burnham, R. *Burnham's Celestial Handbook*; Dover Publication, Inc.: New York, 1978.

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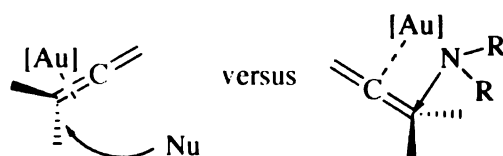
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