THE SYNTHETIC UTILITY OF ENOL BENZOATES AND THE DIRECTED ARYLTITANATION OF HOMOALLYLIC AND ALLYLIC ALCOHOLS

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DEDICATION

To my wonderful husband and parents for all their encouragement and support

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THE SYNTHETIC UTILITY OF ENOL DERIVATIVES AND THE DIRECTED ARYLTITANATION OF HOMOALLYLIC AND ALLYLIC ALCOHOLS

by

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ABSTRACT

THE SYNTHETIC UTILITY OF ENOL DERIVATIVES AND THE DIRECTED ARYLTITANATION OF HOMOALLYLIC AND ALLYLIC ALCOHOLS

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This dissertation is organized in three parts. First, enol derivatives represent important building blocks for organic synthesis. Often their olefin geometry directly translates into product diastero- and enantioselectivity. Thus, stereodefined enol benzoates are subjected to the Sharpless Asymmetric Dihydroxylation to form enantiomerically enriched α-hydroxy aldehydes. Due to their instability, these α-hydroxy aldehydes are further transformed *in situ* to demonstrate their utility in organic synthesis.

The second and third parts address the carbometalation of two types of alkenes. While the carbometalation of alkynes is a widely used transformation, the corresponding transformation for alkenes is less developed. Directing groups, such as homoallylic and allylic alcohols, may help overcome the poor reactivity of alkenes towards carbometalation. Herein the alcohols direct a highly diastereoselective aryltitanation to the proximal C–C double bond. Reactions with homoallylic alcohols result in stereospecific aryl incorporation at the terminal carbon of the double bond while the reactions with the allylic alcohol incorporate the aryl group proximal to the alcohol and generate two new sp^3 centers.

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PRIOR PUBLICATIONS

Lee, K.S.; Ready, J.M. "Titanium-Mediated Oxidative Arylation of Homoallylic Alcohols." *Angew. Chem. Int. Ed.* **2011**, *50*, 2111-2114.

DeBergh, J.R.; Spivey, K.M.; Ready, J.M. "Preparation of Substituted Enol Derivatives from Terminal Alkynes and Their Synthetic Utility." *J. Am. Chem. Soc.* **2008**, *130*, 7828-7829.

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Å	angstrom
Ac	acetyl
acac	acetylacetonyl
AD	asymmetric dihydroxylation
anhyd.	anhydrous
app	apparent
aq.	aqueous
Ar	aryl (substituted aromatic ring)
BBN (9-BBN)	9-borabicyclo[3.3.1]nonane
Bn	benzyl
Boc	*tert*-butyoxycarbonyl
BQ	benzoquinone
br	broad
^{t}Bu	*tert*-butyl
BuLi	butyl lithium
Bz	benzoyl
calc'd	calculated
cat.	catalytic
° C	degrees Celsius
conc.	concentrated
Cp	cyclopentadienyl
Cp*	pentamethyl cyclopentadienyl

Cy	cyclohexyl
δ	chemical shift downfield from $(CH_3)_4Si$
d	doublet
dba	dibenzylideneacetone
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCM	dichloromethane
DCE	1,2-dichloroethane
dd	doublet of doublets
ddd	doublet of doublet of doublets
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DET	diethyl tartrate
DHQ	dihydroquinine
DHQD	dihydroquinidine
DIBAL	diisobutylaluminum hydride
DMDO	dimethyldioxirane
DMAP	*N*,*N*-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMP	Dess-Martin periodinane
dmphen	2,9-dimethyl-1,10-phenanthroline
DMSO	dimethylsulfoxide
DMS	dimethylsulfide
DMT	dimethyl tartrate

dppf	bis(diphenylphosphino)ferrocene
dr	diastereomeric ratio
dt	doublet of triplets
ee	enantiomeric excess
EBTHI	ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)
EI	electron impact ionization
El^+	generic electrophile
ent-	enantiomer
eq.	equation
equiv	equivalent
ES	electrospray ionization
Et	ethyl
Et_3N	triethylamine
Et_2O	diethyl ether
EtOAc	ethyl acetate
g	gram
GC	gas chromatography
h	hour
[H]	reductant
Hg mm	millimeter of mercury (760 Hg mm = 1 atm = 760 Torr)
HMPA	hexamethylphosphoramide
HPLC	high-performance liquid chromatography
HRMS	high-resonance mass spectrometry

$h\nu$	light
Hz	hertz
IND	indolinyl carbamoyl
IPA	isopropyl alcohol
I^iPr	1,3-bis(2,6-diisopropylphenyl)imidazol-2-ylidene
IR	infrared
J	coupling constant
L	ligand
LA	Lewis acid
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LHMDS	lithium bis(trimethylsilyl)amide
liq.	liquid
M	molar
m	multiplet or medium
m-	meta
*m*CPBA	*m*-chloroperoxybenzoic acid
Me	methyl
MeCN	acetonitrile
MEM	(2-methoxy)ethoxymethyl
Mes	mesityl
mg	milligram
MHz	megahertz

min	minutes
mL	milliliter
mmol	millimole
MOM	methoxymethyl
m/*z*	mass/charge
Ms	methanesulfonyl
MS	molecular sieves
N	normal
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide
NIS	*N*-iodosuccinimide
NMI	neomenthylindenyl
NMO	*N*-methylmorpholine oxide
NMR	nuclear magnetic resonance
^{n}Pr	propyl
Nu	generic nucleophile
o-	ortho
[O]	oxidant
OAc	acetate
OMs	mesylate
OTf	triflate
*o*Tol	*ortho*-tolyl
p-	para

PCC	pyridinium chlorochromate
Ph	phenyl
PHAL	phthalazine
PhH	benzene
PhMe	toluene
piv	pivaloyl
PMB	*para*-methoxybenzoyl
PPh_3	triphenylphosphine
ppm	parts per million
PPTS	pyridinium *p*-toluenesulfonate
^{i}Pr	isopropyl
PYR	diphenylpyrimidine
pyr	pyridine
q	quartet
rac	racemic
R_f	retention factor in chromatography
rt	room temperature
s	singlet or strong
SDS	sodium dodecyl sulfate
t	triplet
TBAF	tetrabutylammonium fluoride
TBDPS	*tert*-butyldiphenylsilyl
TBS	*tert*-butyldimethylsilyl

^{t}BuOH	*tert*-butanol
TES	triethylsilyl
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPS	triisopropylsilyl
TLC	thin layer chromatography
TMEDA	*N,N,N',N'*-tetramethylenediamine
TMS	trimethylsilyl
tol	toluene
T_r	retention time
*p*TsOH	*p*-toluenesulfonic acid
Ts	toluenesulfonyl
w	weak
y	yield
Δ	heat at reflux

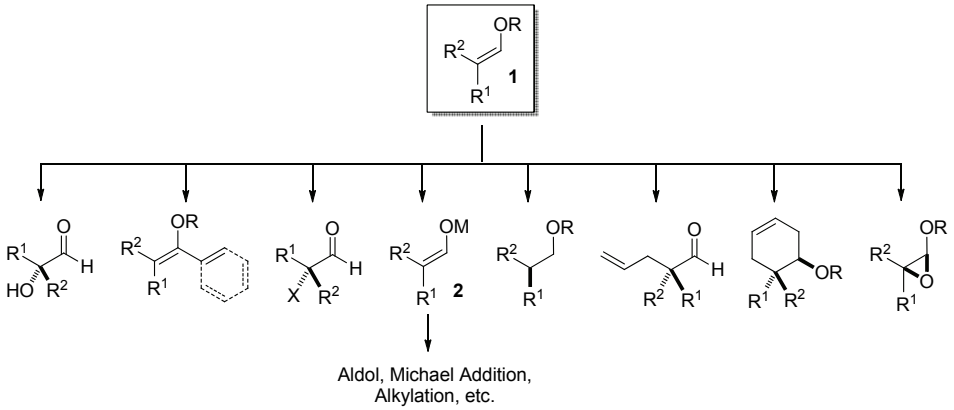
1. CHAPTER ONE

THE SYNTHETIC UTILITY OF ENOL BENZOATES

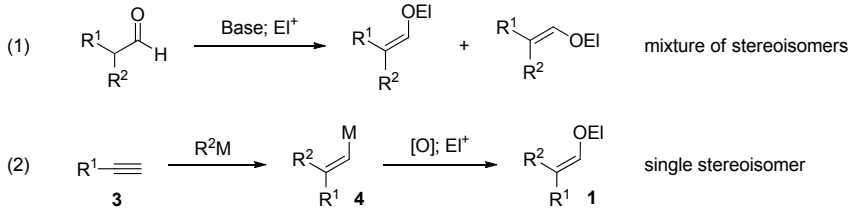
1.1. Introduction

Enol derivatives **1** are electron-rich functional groups capable of a wide range of transformations which result in the formation of a variety of new carbon-carbon or carbon-heteroatom bonds (Figure 1.1). Furthermore, the reactive enolate **2**, generated from an enol derivative,[1, 2] participates in other transformations such as aldol chemistry and conjugate additions. For those reactions which generate one or more new sp^3 stereocenters, control over the stereochemistry of the enol derivative is essential as mixtures of *E*- and *Z*-olefins lead to mixtures of diastereomeric products. While formation of stereodefined enolates *via* deprotonation of ketones has been thoroughly studied, access to single *aldehyde* enolate isomers is much less straightforward (Scheme 1.1, eq. 1).[3]

Figure 1.1. Synthetic utility of enol derivatives

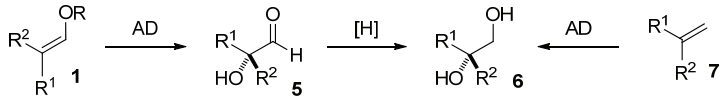


Scheme 1.1. Two approaches to trisubstituted enol derivatives



To address this gap in synthetic capabilities, the Ready Laboratory recently reported a new entry to stereodefined trisubstituted enol derivatives **1** involving a tandem carbometalation/oxidation of terminal alkynes (Scheme 1.1, eq. 2).[4, 5] Thus with access to these previously inaccessible structures, we wished to explore their synthetic utility in reactions which would benefit from the geometric purity. The Sharpless Asymmetric Dihydroxylation (AD) was chosen to demonstrate the utility of stereodefined enol derivatives because its substrate scope and mechanism have been thoroughly examined.[6] 1,1-Disubstituted alkenes **7** typically perform poorly in the AD compared with other classes of alkenes. The AD of the enol derivatives should provide access to the same 1,2-diols **6** after reduction of the α-hydroxy aldehyde products **5**.

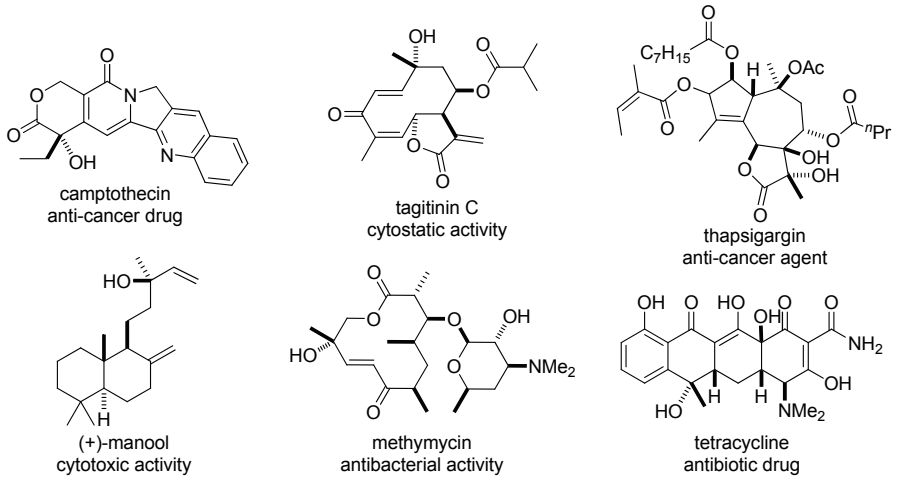
Scheme 1.2. Asymmetric Dihydroxylation of enol derivatives



Tertiary alcohols are present in a number of biologically active small molecules such as those shown in Figure 1.2. α-Hydroxy aldehydes present a convenient handle to construct small molecules containing 3° alcohols, which are often difficult to prepare. Optically active α-hydroxy aldehydes, however, are also difficult structures to access. Existing approaches require chiral auxiliaries,[7] transformations of optically active starting materials,[8] and, more recently, chiral transition metal catalysts.[9] Herein I describe in

further detail the importance of the stereochemistry of the enol derivative to forming enantioenriched α-hydroxy aldehydes and conversion of these aldehydes into propargylic alcohols, amino alcohols, α,β-unsaturated esters, and α-hydroxy esters.

Figure 1.2. Natural products containing 3° alcohols

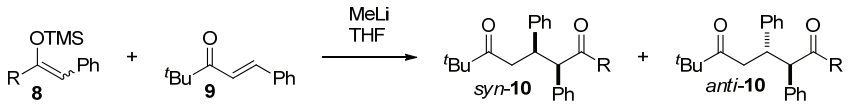


1.2. Background

1.2.1. Stereodefined Enol Derivatives

Enol structures have found wide use in synthetic chemistry, due, in large part, to the ability to control the geometry of ketone enolates. Stereoselective enol formation is often crucial to achieving high levels of product diastereoselectivity in reactions such as aldol and Michael reactions.[10-13] For example, the conjugate addition of *E*-enolates predominantly leads to *syn* products; alternatively, *Z*-enolates stereoselectively provide *anti* addition products (Table 1.1).[14] In each case, the *E*:*Z* ratio of the starting enolate directly translates to the *syn*:*anti* ratio of the Michael product. A similar effect can be

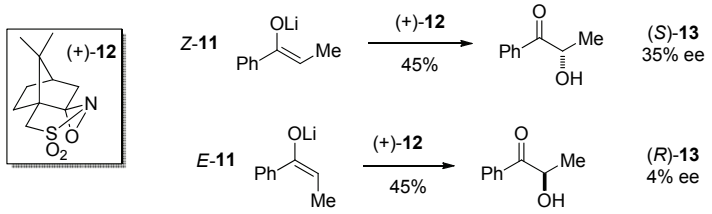
Table 1.1. Michael addition of *E*- and *Z*-enolates



Entry	R	*E*:*Z*	Yield	*syn*:*anti*
1	^{i}Pr	4:96	88	5:95
2	^{i}Pr	90:10	87	90:10
3	Ph	2:98	78	2:98
4	Ph	87:13	66	83:17

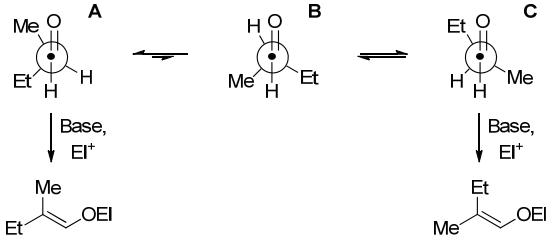
observed in the enantioselective oxidation of enolates **11** using Davis oxaziridine **12**.[15] A 97:3 mixture of *Z*:*E* enolates provides (*S*)-**13** whereas the predominantly *E* enolate (93:7 *E*:*Z*) slightly favors the *R* enantiomer. Thus enolate geometry impacts both product diastereo- and enantioselectivity.

Scheme 1.3. Davis oxaziridine oxidation of ketone enolates



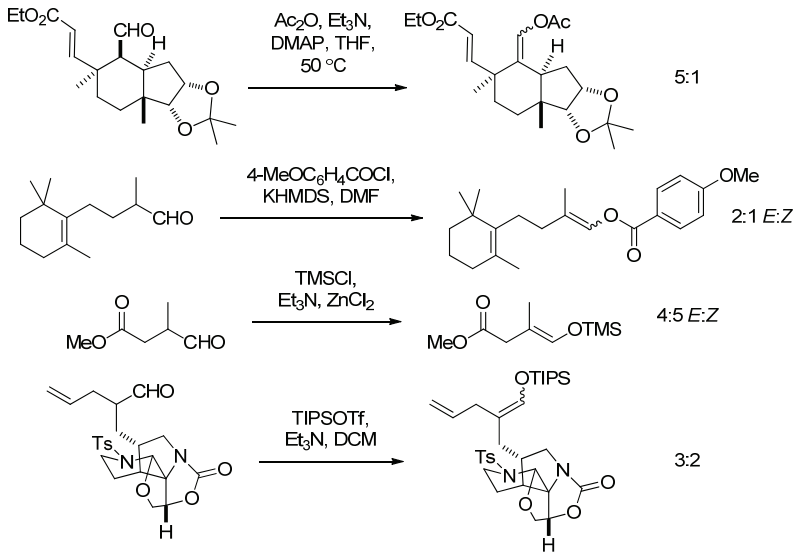
Although the geometry of ketone enolates may be controlled by varying the choice and stoichiometry of the base, the geometry of *aldehyde* enolates is much less predictable.[16] Indeed, the traditional methods of forming enolates typically generate mixtures of *E* and *Z* olefins when applied to aldehydes.[3, 17] This poor selectivity may be attributed to the facile interconversion of the various conformers of the aldehyde. For example, structures **A**-**C** represent the most energetically favored conformers of 2-methylbutanal (Figure 1.3).[18] Conformers **B** and **C** are energetically equivalent while **A** is slightly more stable by approximately 0.2 kcal/mol. Enolization of **A** leads to the *E* olefin isomer whereas enolization of **C** provides the *Z* isomer. The small energy difference in **A**

Figure 1.3. Conformations of α-methyl substituted aldehdyes



and **C** is reflected in the low *E*:*Z* selectivity of the newly formed enol derivatives. Scheme 1.4 shows a few representative examples of the mixtures of isomers obtained from the traditional enolization of aldehydes.[19-22] For these enol derivatives to be more synthetically useful, new methods are needed to achieve higher levels of control over their olefin geometry.

Scheme 1.4. Enol derivatives of aldehydes

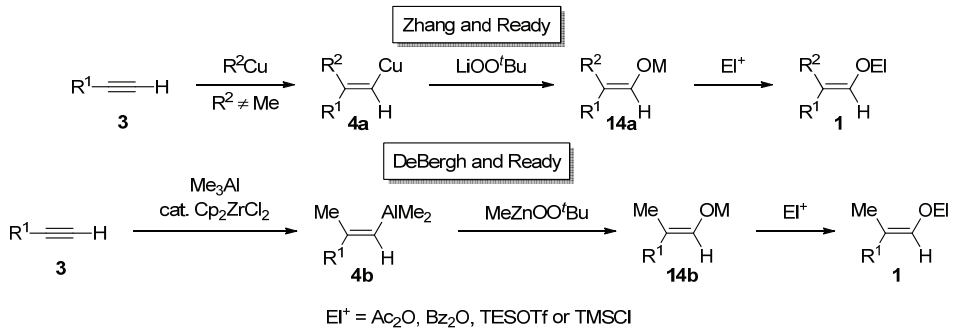


Previous work with terminal alkynes in the Ready Laboratory resulted in a new approach to forming stereodefined enol derivatives of aldehydes (Scheme 1.5).[4, 5] The new entry begins with the carbometalation of a terminal alkyne. The first report utilized a variety of organocopper reagents but was unsuccessful at incorporating methyl

substituents, prompting the development of the zirconium-catalyzed methylalumination procedure. The vinyl metal intermediate **4** is then oxygenated with a metal peroxide to form the stereodefined metal enolate **14**. Quenching with a proton source at this stage would provide access to racemic α-branched aldehydes. However, the geometry of the enolate may be preserved by trapping it with different electrophiles such as carboxylic anhydrides or silylating reagents to provide enol esters and silyl enol ethers, respectively, as single stereoisomers.

The approach takes advantage of the stereospecificity of alkyne carbometalation reactions to define the enol geometry. Both carbocupration and methylalumination occur with *syn* addition to the alkyne, favoring metalation at the less sterically hindered position.[23, 24] With the new access to stereodefined enol derivatives **1**, we wished to demonstrate their synthetic utility as substrates for asymmetric transformations. In particular, we believed these enol derivatives could provide access to enantioenriched α-hydroxy aldehydes.

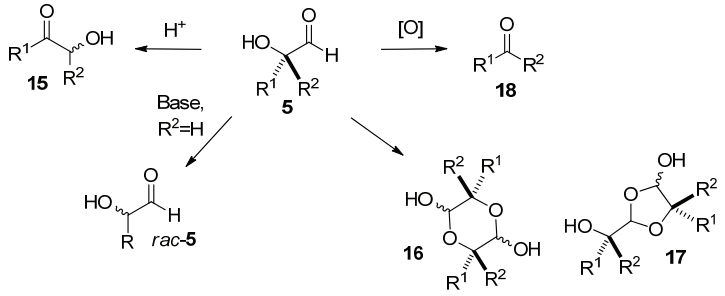
Scheme 1.5. Ready approach to stereodefined enol derivatives



1.2.2. α-Hydroxy Aldehydes

α-Hydroxy aldehydes have been used in a number of total syntheses because they offer two handles for functionalization that participate in a wide variety of transformations: the hydroxyl group and the aldehyde. Despite their utility, α-hydroxy aldehydes present a number of challenges due to their moderate stability (Figure 1.4).

Figure 1.4. Instability of α-hydroxy aldehydes



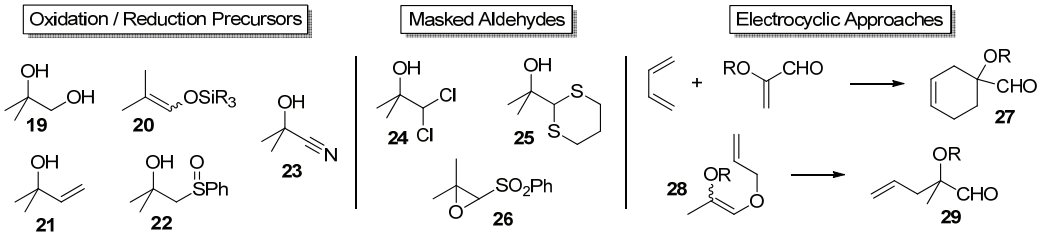
Under acidic conditions, α substituents are liable to undergo migration, resulting in isomerization to the α-hydroxy ketone **15**.[25] Under basic conditions, enantioenriched secondary alcohols are susceptible to epimerization. Furthermore, purification of the α-hydroxy aldehydes is often complicated by dimerization to 1,4- and 1,3-dioxolanes (**16** and **17**)[26, 27] or by oxidation to the ketone **18** with loss of formaldehyde.[25, 28]

1.2.2.1. Previous Syntheses

Previous syntheses of α-hydroxy aldehydes can be categorized into three main groups: 1) transformation of existing functional groups, 2) use of a chiral auxiliary, and 3) transition metal catalysis. By far, the most common approach involves the transformation of existing functional groups to install either the aldehyde or the alcohol (Figure 1.5). For example, 1,2-diols **19**,[29-33] silyl enol ethers **20**,[34, 35] allylic alcohols **21**,[36] and β-hydroxy sulfoxides **22**[35] all react under different oxidizing conditions to furnish α-

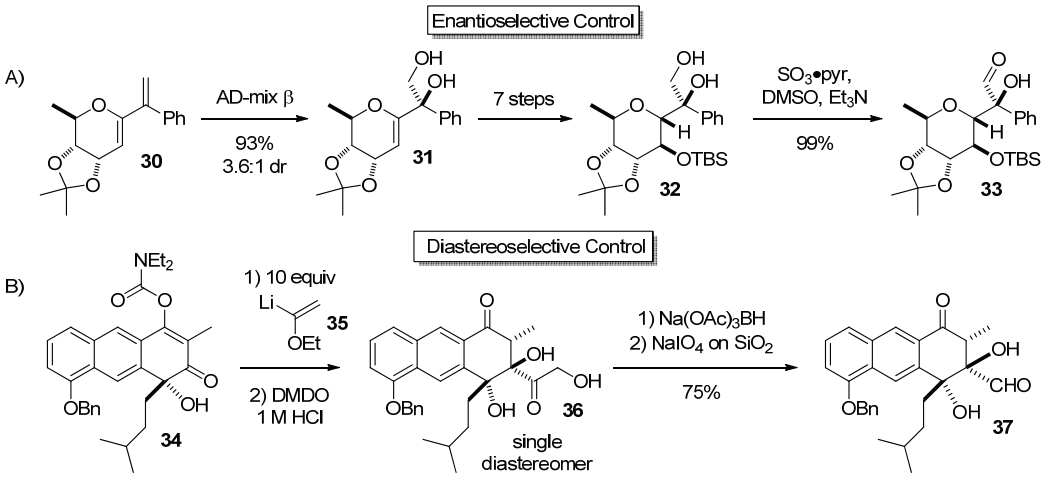
hydroxy aldehydes. Examples of reductions are mainly limited to α-siloxy nitriles **23**.[27] Alternatively, dichloromethylcarbinols **24**,[26] α-hydroxy dithioacetals **25**,[37] and epoxysulfones **26**[8] reveal aldehydes under hydrolysis conditions. α-Hydroxy aldehydes have also been prepared by electrocyclic reactions including Diels-Alder reactions[35] and Claisen rearrangements.[38]

Figure 1.5. Functional group precursors to α-hydroxy aldehydes



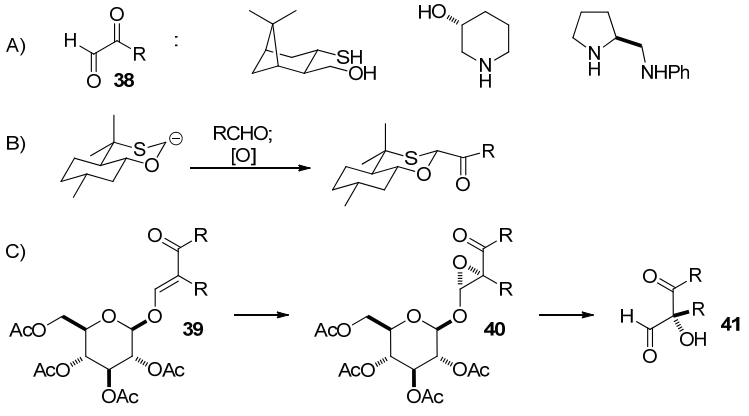
With a few rare exceptions, access to enantioenriched α-hydroxy aldehydes through the transformation of existing functional groups requires enantioenriched starting materials. Thus there must be either earlier asymmetric reactions in the synthesis to install those stereocenters or adjacent stereocenters to promote diastereocontrol.[8] For example, Koo and McDonald attempt a Sharpless AD to asymmetrically install the 3° diol from a 1,1-disubstituted alkene (Figure 1.6A).[30] Unfortunately, they only achieve a 3.6:1 selectivity with AD-mix β. In contrast, Pettus's route to (+)-rishirilide B begins with optically active starting materials (Figure 1.6B). He later takes advantage of an adjacent alkoxide to direct the addition of vinyl lithium **35** to ketone **34** with excellent diastereoselectivity.[39] The α-hydroxy aldehyde **37** is produced after a series of oxidations and reductions.

Figure 1.6. Enantio- and diastereoselective routes to 3° alcohols



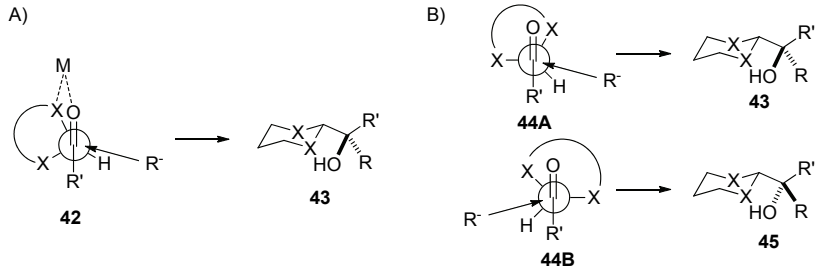
The use of chiral auxiliaries is significantly less prevalent in total syntheses than the previous approach. Chiral auxiliaries are typically attached to α-keto aldehyde starting materials **38** through acetal-like linkages (Figure 1.7A).[7, 40-42] Alternatively, the auxiliary homologates a starting aldehyde; oxidation of the alcohol intermediate provides access to the same acetal-like protection (Figure 1.7B).[28] This homologation approach has also been utilized with achiral 1,3-dithianes.[37, 43] The auxiliary may also be sugar-derived (**39**) and connect to the aldehyde oxygen as an enol ether (Figure 1.7C).[44]

Figure 1.7. Chiral auxiliaries for optically active α-hydroxy aldehydes



In general, the stereochemical induction is determined by two factors: the diastereoselectivity of the acetal formation and the diastereoselectivity of alkyl metal addition to the aldehyde.[45] Thermodynamics control the formation of the acetal; ligations of the chiral auxiliaries shown in Figure 1.7 are highly selective for a single diastereomer. The diastereoselectivity of alkylation is then controlled by either the steric hindrance of or chelation to the carbonyl (Figure 1.8). For example, when Grignard reagents are used (**42**, M=Mg), the magnesium chelates with the carbonyl and a heteroatom from the auxiliary to provide the diastereomer predicted by the Cram chelation model.[28, 40, 42] Alternatively, when alkyl lithium reagents are used, the steric environment becomes the dominating factor and provides the opposite diastereomer **45**.[41, 46] Removal of the auxiliary then reveals the enantioenriched 3° α-hydroxy aldehydes.

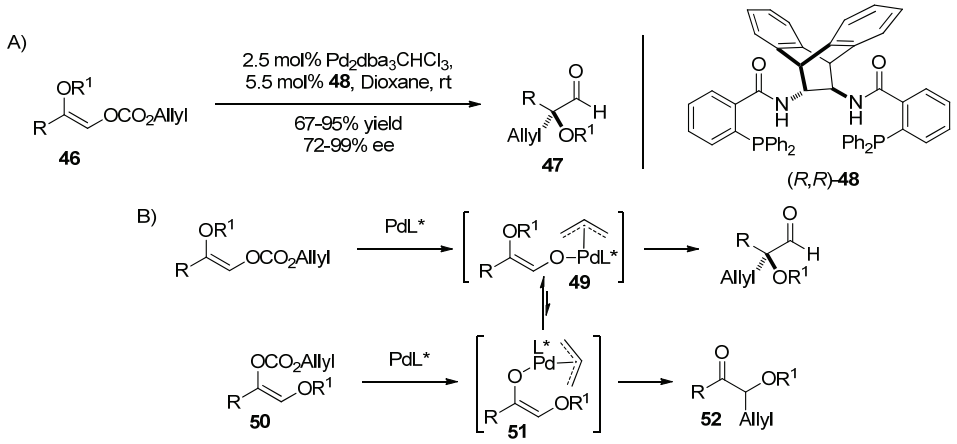
Figure 1.8. Chelation and sterics control diastereoselectivity



The first example of the third approach to α-hydroxy aldehydes, transition metal catalysis, was only recently described by Trost and coworkers.[9] They used catalytic amounts of Pd^0 with a chiral bisphosphine ligand **48** to form 3° α-hydroxy aldehydes with good enantioselectivity from enolates of α-hydroxy ketones. Both enol carbonates **46** and **50** provide the protected α-hydroxy aldehyde **47** with appropriate migrating groups (R^1=TBS, TMS, TIPS, Bz, piv, CO_2Me). The reaction takes advantage of the equilibrium

between the two enolate intermediates; enol **49** is favored sterically and electronically. Because allylation of **51** is slower than the equilibration, **49** is allylated preferentially. Alternatively, when the chiral ligand is exchanged for 1,2-bis(diphenylphosphino)ethane or when R^1 is acetyl, ketone **52** is preferentially formed because the rate of allylation of

Scheme 1.6. Palladium-catalyzed asymmetric allylation of enol derivatives

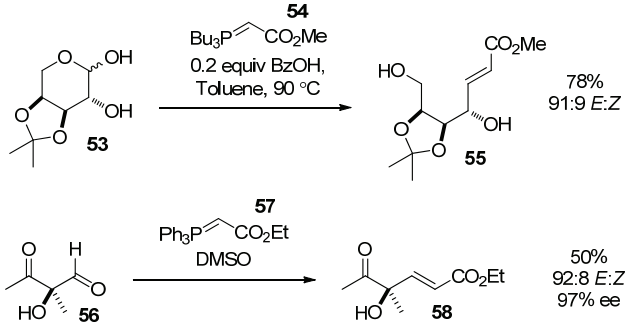


51 is faster than the equilibration of the enolates. Although this method proceeds with good yields and enantioselectivities, it has not been employed in a total synthesis to the best of our knowledge.

1.2.2.2. Functionalization of the aldehyde

Because of the instability of many α-hydroxy aldehydes,[8, 27] some researchers forego isolation of the aldehydes and transform them *in situ* to less problematic functional groups such as 1,2-diols, acids, esters, or olefins.[26, 28, 43, 47] Indeed these are only a few of the functional groups that may be produced from the α-hydroxy aldehydes.

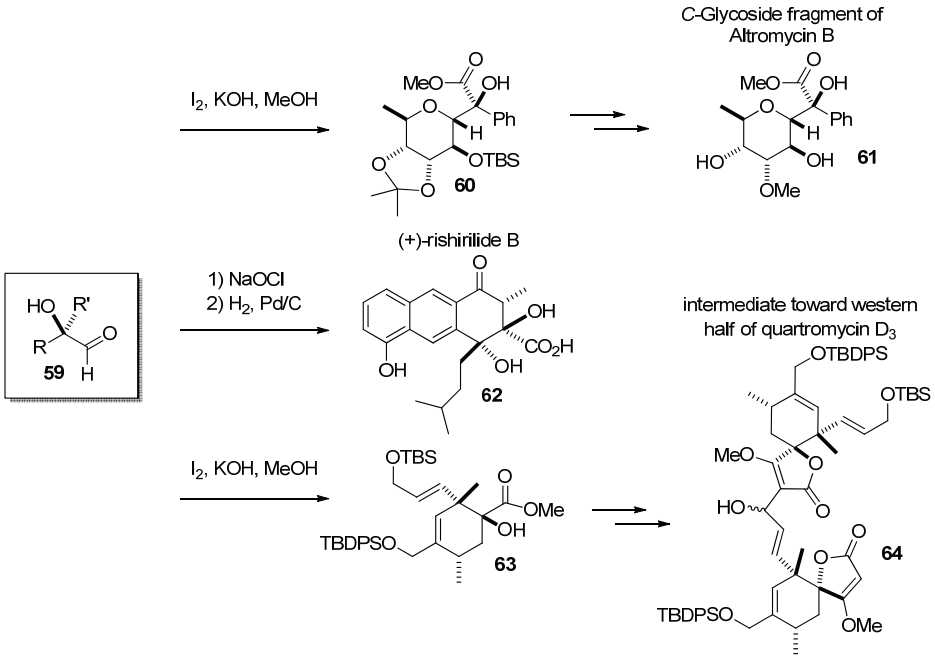
Scheme 1.7. α-Hydroxy aldehydes in Wittig olefinations



First, the Wittig olefination is a common transformation of aldehydes. The *E*:*Z* selectivity of the Wittig reaction has been the subject of numerous studies, providing the following generalizations: 1) stabilized ylides, which have strongly conjugating substituents, generate *E* olefins; 2) semi-stabilized ylides, which have only mildly conjugating substituents, generate mixtures of olefins; 3) non-stabilized ylides preferentially form *Z* olefins.[48] Wittig olefination of α-hydroxy aldehydes provides access to enantioenriched allylic alcohols. The presence of α-oxygenation may favorably influence olefin geometry; α-hydroxy ketones react faster and with higher *E*-selectivity than other ketones, presumably due to directing effects of the hydroxyl group.[49] Reactions of α-hydroxy aldehydes are known to proceed with up to 92:8 *E*:*Z* ratios (Scheme 1.7).[44, 50]

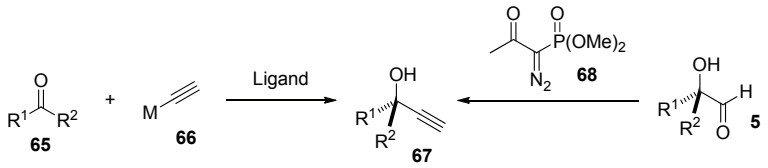
Second, the aldehyde may be oxidized to the corresponding acid or ester. These transformations have completed the total synthesis of (+)-rishirilide B **62**[39] and provided intermediates toward the syntheses of altromycin B[30] and quartromicins A_3 and D_3 (Figure 1.9).[34, 35] The 3° α-hydroxy ester is also present in camptothecin (Figure 1.2), an indole alkaloid with anti-cancer activity,[51] and thapsigargin, a sesquiterpene calcium uptake inhibitor.[52]

Figure 1.9. α-Hydroxy acid derivatives in total syntheses



Third, homologation of the aldehyde provides 3° propargylic alcohols. Although the addition of alkynyl Grignards or lithium to ketones **65** represents a direct method for the preparation of propargylic alcohols **67**, alkynyl metal species are less reactive than other organometallics, and the basicity of the alkynyl metal species can compete with its nucleophilicity to form enolates or aldol products.[53] Furthermore, stereoselective additions to carbonyls are very difficult to control. Several groups have developed methods involving less basic organometallic reagents (M = Zn, Cu, Ti, Al) and a variety of chiral ligands to promote addition and induce asymmetry with varying success.[54] Alternatively, homologation of enantioenriched 3° α-hydroxy aldehydes **5** provides access to the same enantioenriched addition products **67**. The Ohira-Bestmann homologation offers a mild procedure for such a transformation.[55, 56]

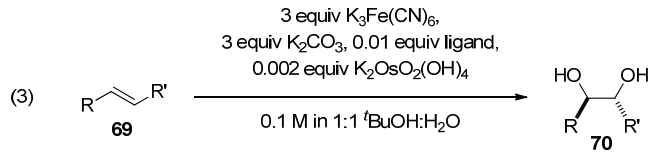
Scheme 1.8. Formation of enantioenriched 3° propargylic alcohols



Finally, the aldehyde may undergo reductive amination to generate 1,2-amino alcohols. Not only are amino alcohols present in natural products but also they have been used in a variety of transformations to induce asymmetry as chiral auxiliaries.[57] In addition, amino alcohols and their heterocyclic derivatives serve as chiral ligands in both metal-catalyzed and -mediated reactions.[58-60]

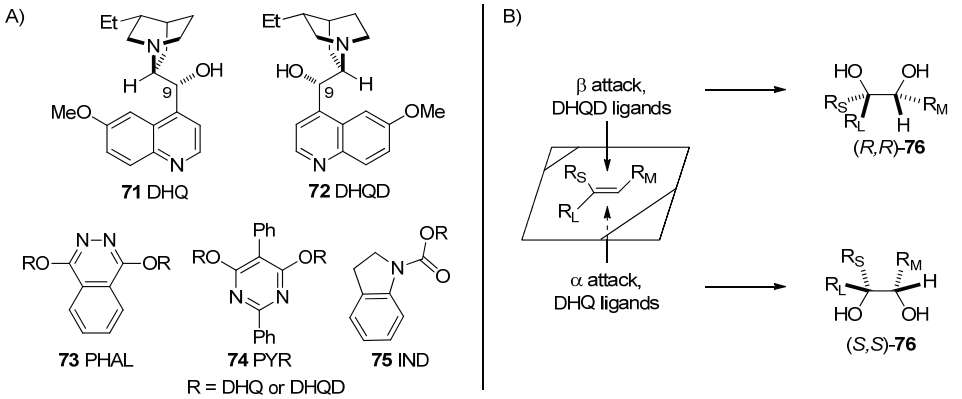
1.2.3. Asymmetric Dihydroxylation

Another entry to enantioenriched α-hydroxy aldehydes was envisioned *via* asymmetric dihydroxylation of stereodefined enol benzoates using Sharpless' conditions. The Sharpless AD has had a significant impact on synthetic organic chemistry since its discovery in the 1980s.[61] The reaction employs catalytic amounts of osmium tetroxide and stoichiometric $K_3Fe(CN)_6$ to add two hydroxyl groups to alkenes in the presence of chiral cinchona alkaloid-based ligands under basic biphasic conditions (eq. 3).[62] The reaction's widespread popularity can be attributed to several salient features of the AD. The mild reaction conditions tolerate a wide range of functional groups.[6] The commercial availability of the premixed components as AD-mix α and β greatly simplifies the reaction setup.[63] Special precautions for excluding air and water are unnecessary as the osmium catalyst is not susceptible to aerobic oxidation and the AD is performed in a 1:1 biphasic solution of ^{t}BuOH and water.



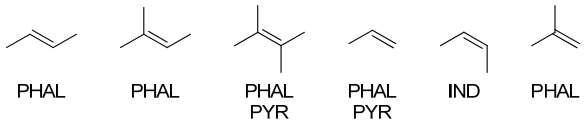
Systematic investigations into the structure of the chiral ligand have led to highly optimized ligand systems and a stereochemical model for predicting the enantiofacial selectivity of the dihydroxylation.[64] In the optimized ligands, two cinchona alkaloids are connected through a phthalazine (PHAL, **73**) or diphenylpyrimidine (PYR, **74**) at the alkaloid C9 position and form a C2-symmetrical enzyme-like binding pocket for the olefin (Figure 1.10A). Three structural features favorably influence the interaction of the alkene and the ligand: the ethyl substituent, the quinoline, and the aromatic linker. The large, flat aromatic area of quinoline also helps to increase the reaction rate and is aided by the methoxy substituent. In addition, the presence of the two ethers aids in binding of the ligand with the osmium; replacing the C9 ether with carbon inhibits coordination of the osmium. In addition, the *erythro* configuration of the quinuclidine and the C9 oxygen is very important for both the reaction rate and substrate binding.

Figure 1.10. AD ligands and mnemonic device for predicting enantiofacial attack



Just as enzymes provide steric environments which control the binding of substrates, the enzyme-like binding pocket of the cinchona alkaloid dictates how the olefin binds with the ligand.[65] The mnemonic device shown in Figure 1.10B may be used to predict the facial selectivity and thus the configuration of the resulting 1,2-diol **76**.[63, 64] The lower right quadrant is the most sterically congested position of the four, while the upper left quadrant is also limited to smaller substituents. The upper right and lower left quadrants, however, are less sterically hindered and accommodate the larger olefin substituents better. The lower left quadrant also provides attractive interactions for substituents. In the PHAL ligands, this position is "magnetic" for flat aromatic substituents; PYR ligands prefer to fill the same position with aliphatic groups.[66] When the olefin is oriented within this model, the dihydroxylation occurs with predictable enantiofacial control depending on which ligand is present within the reaction mixture. Dihydroquinidine (DHQD) derivatives, present as $(DHQD)_2$-PHAL in AD-mix β, prefer oxidation from the top face. Dihydroquinine (DHQ) derivatives, in AD-mix α as $(DHQ)_2$-PHAL, allow oxidation from the bottom face giving rise to the enantiomeric diol **76**.

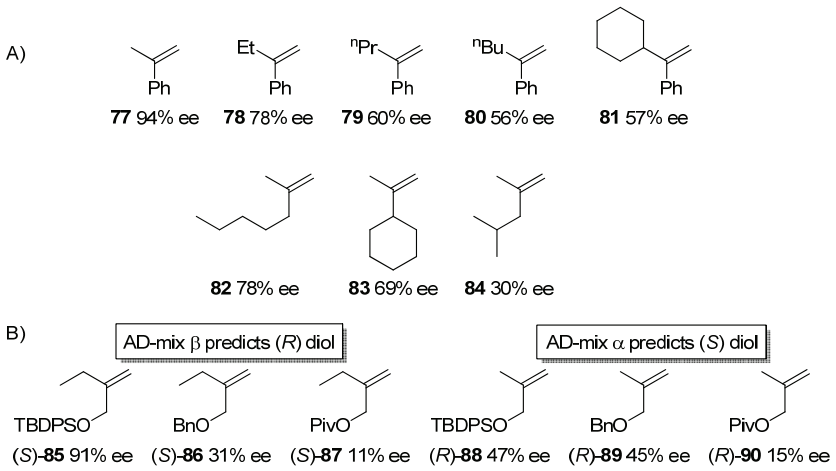
Figure 1.11. Optimal ligand class for each olefin type



Each of the six classes of olefins has been subjected to the Sharpless AD. The commercially available AD-mixes (containing PHAL derivatives) achieve high levels of enantioselectivity when the substrate fits the mnemonic model well. *trans*-Disubstituted olefins consistently achieve high enantioselectivities with the AD-mix ligands.[63, 67] Trisubstituted alkenes are also excellent substrates in the AD with the PHAL-based

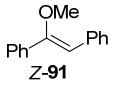
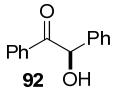
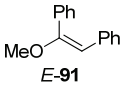
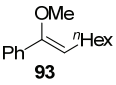
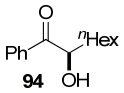
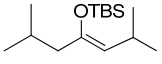
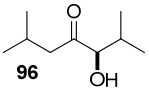
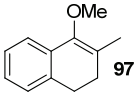
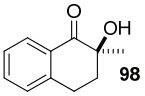
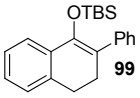
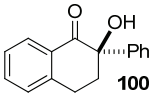
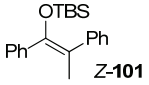
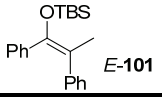
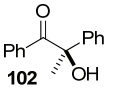
ligands.[6] The success of tetrasubstituted olefins varies widely in part because of the steric hindrance of the lower right quadrant, but enantioselectivities up to 89% are possible with the PYR-based ligands.[68] These three classes of olefins benefit from the addition of an equivalent of methanesulfonamide, which increases the reaction rate by facilitating the hydrolysis of an osmate ester intermediate.[63] Monosubstituted olefins are also capable of achieving high enantioselectivities, both with the PHAL- and PYR-based ligands.[69]

Figure 1.12. 1,1-Disubstituted alkenes in the Sharpless AD



The AD of the final two classes of olefins generally provides lower selectivities. *cis*-Disubstituted olefins are poor substrates with the AD-mix ligands but perform better with the indolinylcarbamoyl (IND, **75**) class of ligands (up to 80% ee).[70] Similarly, enantioselectivities of diols obtained from 1,1-disubstituted olefin are often highly variable, decreasing as the two substituents approach equal sizes (Figure 1.12A).[66] In some cases the model predicts the facial selectivity opposite to that which is observed; when one of the alkene substituents is a bulky allyloxy, the smaller hydrocarbon group preferentially fills the open lower left quadrant (Figure 1.12B).[66, 71]

Table 1.2. Asymmetric dihydroxylation of enol ethers

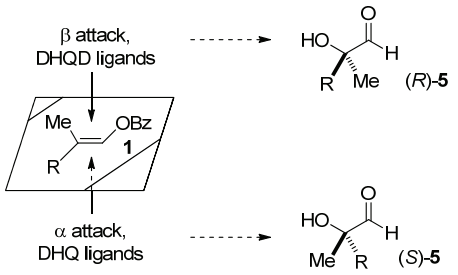
Entry	Alkene[a]	*E*:*Z*	Product	% ee
1	 *Z*-**91**	1:>99	 **92**	99
2	 *E*-**91**	>99:1		90
3	 **93**	33:67	 **94**	94
4	 **95**	12:88	 **96**	79
5	 **97**	-	 **98**	64
6	 **99**	-	 **100**	93
7	 *Z*-**101**	*b*		75
8	 *E*-**101**	*b*	 **102**	53

[a]Reactions performed on 1 mmol substrate with 1.4 g AD-mix β and 1 equiv $MeSO_2NH_2$. [b]*E*:*Z* ratios not reported.

Enol derivatives are also suitable substrates for the AD and provide enantioenriched α-hydroxy ketones (Table 1.2).[72] Sharpless reported 79-99% ee's for trisubstituted enol ethers. Interestingly, they also reported that high *E*:*Z* ratios are not essential for good enantioselectivities because both isomers provide the same enantiomer albeit with lower selectivity for the *E* olefin. As with their all-carbon counterparts, tetrasubstituted enol derivatives show a wider range of enantioselectivities.[68] Again, both olefin geometric isomers lead to the same enantiomer of α-hydroxy ketone (Table 1.2, entries 7 and 8). Most likely the controlling factor is the positioning of the smallest alkene substituent (methyl for *E*-**101** and *Z*-**101**) into the most sterically hindered region

of the ligand binding pocket when possible. The facial attack of the oxygenated alkene terminus is unimportant as that carbon does not become sp^3 hybridized. To the best of our knowledge, enol derivatives of aldehydes had not been reported as substrates in the Sharpless AD prior to this study.

Figure 1.13. Aldehyde enol benzoates as substrates for the AD



The new access to stereodefined methyl-substituted enol benzoates provides the opportunity to prepare enantioenriched α-hydroxy aldehydes with the Sharpless AD. These enol benzoates should be excellent substrates for the AD because their substituents align well within the mnemonic device (Figure 1.13). Both of the sterically congested quadrants are filled with the smallest of the alkene substituents while the more open quadrants are appropriately placed for the larger substituents R and OBz. In addition, benzoyl esters are known to interact favorably with the AD ligands to enhance enantioselectivity.[65, 73]

1.3. Asymmetric Dihydroxylation of Methyl-Substituted Enol Benzoates

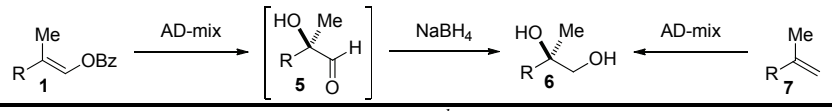
Several methyl-substituted enol benzoates were prepared with complete *E* selectivity from terminal alkynes using the tandem methylalumination-oxidation sequence (Scheme 1.5) developed by John R. DeBergh, a then-senior graduate student in

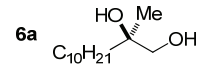
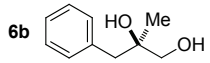
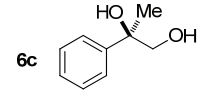
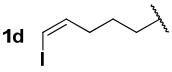
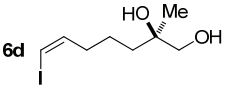
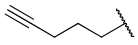
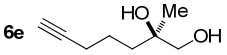
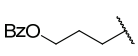
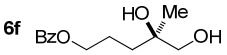
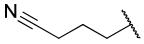
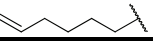
the Ready Laboratory. These stereodefined enol benzoates were subjected to the standard Sharpless AD reaction conditions using AD-mix β. Each 1.4 g of AD-mix necessary for oxidizing 1 mmol of substrate contains 0.98 g of $K_3Fe(CN)_6$ (3 equiv), 0.41 g of K_2CO_3 (3 equiv), 7.8 mg of $(DHQD)_2$-PHAL (0.01 equiv), and 0.74 mg of $K_2OsO_2(OH)_4$ (0.002 equiv).[72]

Isolation of the α-hydroxy aldehydes **5** proved difficult as concentration of purified aldehydes resulted in mixtures of the aldehyde, its hydrate, and dimers. This problem was circumvented by reducing the aldehydes *in situ* simply by adding an excess of sodium borohydride to the AD reaction mixture upon complete consumption of **1**. The enantiomeric excess (ee) of the 3° alcohol should be preserved during the reduction with sodium borohydride as the tertiary center is not susceptible to epimerization. Also, because reduction does not introduce any new stereocenters to the molecule, epimeric 3° alcohols cannot be distributed between diastereomeric products. Thus the ee of the diol is a reliable measure of ee for the α-hydroxy aldehyde.

Isolation of the diols proceeded smoothly, and their yields from the starting enol benzoate are listed in Table 1.3. Two substrates were not amenable to the dihydroxylation. The diol of nitrile **1g** was unstable and could not be isolated (entry 10), and terminal alkene **1h** suffered from poor mass balance (entry 11). Possibly the terminal alkene also undergoes dihydroxylation to form mixtures of the desired diol, the diol of the terminal olefin, and the tetrol. The *cis*-alkene **1d** most likely does not undergo competitive dihydroxylation because *cis*-alkenes are poor substrates for the AD with PHAL-based ligands and because the alkene is deactivated by the iodide (entry 7).

Table 1.3. AD of methyl-substituted enol benzoates



Entry [a]	R	ee (%) from [b] **1**	ee (%) from [b] **7**	Product	Yield (%) [c]
1	**1a** $^{n}C_{10}H_{21}$ (all *E*)	96	78	 **6a**	78
2	$^{n}C_{10}H_{21}$ (9:1 *E*:*Z*)	81			*e*
3	**1b** Bn	94		 **6b**	84
4		-86 [d]			*e*
5	**1c** Ph	95	94	 **6c**	75
6		-93 [d]			*e*
7	 **1d**	96		 **6d**	59
8	 **1e**	95	32	 **6e**	75 [f]
9	 **1f**	96		 **6f**	87
10	 **1g**	*e*		unstable	*e*
11	 **1h**	*e*		low mass balance	*e*

[a] Unless noted,1.4 g AD-mix β per 1 mmol alkene. [b]ee values determined by chiral HPLC. [c]Isolated yields from OBz. [d]Reaction performed with AD-mix α. [e]Not determined. [f]1 equiv $MeSO_2NH_2$ added to reaction.

In each case, the geometrically pure enol benzoates converted to diols **6** with greater than 94% ee using AD-mix β. The AD of the enol benzoates achieved higher enantioselectivities than the AD of the terminal alkenes **7** leading to the same diols (Table 1.3, entries 1, 5, and 7). Significantly, loss of geometric purity of the starting enol benzoate greatly affects the enantioselectivity of the dihydroxylation. A 9:1 mixture of *E*- and *Z*-isomers of **1a** was converted to **6a** in 81% ee, only slightly better than starting with terminal alkene **7a** (entry 2). The enantiomeric diols were obtained by subjecting the enol benzoates to the AD using AD-mix α (entries 4 and 6).

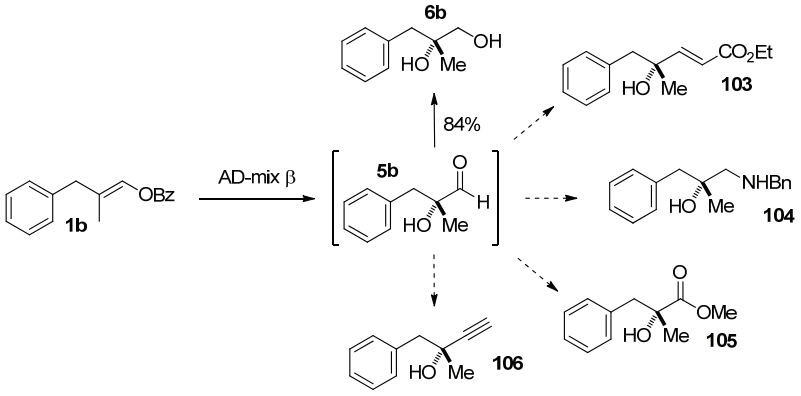
Therefore stereodefined enol benzoates are excellent substrates for the asymmetric dihydroxylation, providing better enantioselectivities than the corresponding

terminal alkenes. Deterioration of enol geometry purity greatly decreases the enantioselectivity of the AD.

1.4. Functionalization of α-Hydroxy Aldehydes

Thus far, I have demonstrated the reduction of the enantioenriched α-hydroxy aldehydes. However, aldehydes and alcohols both participate in a wide variety of transformations. Further functionalization of the aldehyde would provide access to

Scheme 1.9. Possible transformations of enantioenriched α-hydroxy aldehydes



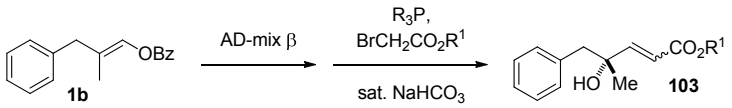
diverse enantioenriched 3° alcohols. Due to the instability of the aldehydes toward concentration,[43, 47, 74] transformations were purposefully selected for this study for either their biphasic conditions or tolerance to small amounts of air and water.

1.4.1. Wittig Reaction

Although traditionally performed in organic solvents, the Wittig reaction is capable of achieving good yields and selectivities in aqueous conditions with stabilized ylides.[75] Intrigued by the possibility of a one-pot procedure for forming α,β-unsaturated

esters **103** from the enol derivatives, I began to explore biphasic conditions for the Wittig reaction (Table 1.4). After completion of the asymmetric dihydroxylation, the crude reaction mixture was added to a suspension of phosphine and bromoester in water saturated with sodium bicarbonate. Unfortunately, both *cis*- and *trans*-alkenes were formed with very poor selectivity. A significant increase in selectivity for the *trans* adduct was observed upon exchanging the triphenylphosphine for tri-*n*-butylphosphine

Table 1.4. Tandem AD/Wittig under biphasic conditions



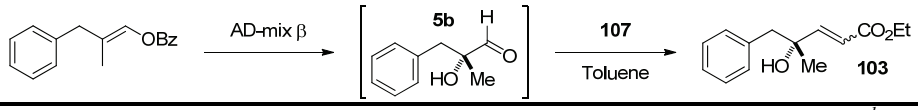
Entry[a]	R_3P	R^1	Temp (°C)	Additive	*E*:*Z*[b]
1	Ph_3P	^{t}Bu	rt	-	56:44
2	$^n Bu_3P$	Et	rt	-	81:19
3	$^n Bu_3P$	Et	90	-	87:13
4	$^n Bu_3P$	Et	rt	5 mol% DMSO	82:18
5	$^n Bu_3P$	Et	rt	2 equiv LiBr then 2.1 equiv HCl 2.3 equiv KO^{t}Bu	82:18
6	**107** $^n Bu_3P$=CO$_2$Et		rt	-	N.R.[c]

[a]Crude AD reactions added to 1.5 equiv R_3P and 1.8 equiv bromoester in sat. $NaHCO_3$. [b]Ratios determined by ^{1}H NMR of crude product. [c]AD reaction added to preformed **107** in deionized water.

(entry 2).[50, 76] The selectivity was further increased upon heating the biphasic Wittig reaction to 90 °C (entry 3).[77] Under these conditions, **103** was isolated in only 50% yield. Hoping to achieve complete selectivity for the *E*-alkene, I examined the effect of various additives. The addition of 5 mol% DMSO, which has increased *E*:*Z* ratios in both aqueous and nonaqueous conditions, resulted in no change (entry 2 vs. 4).[44, 78] Similarly, the Schlosser modification, which reverses the selectivity of nonstabilized ylides to favor *trans*-olefins,[79] provided no change compared with the additive-free conditions (entry 5). Finally, addition of the AD reaction mixture to a preformed ylide in deionized water

resulted in recovery of the aldehyde. The one-pot reactions often suffered from incomplete conversion from the aldehyde.

Table 1.5. Sequential AD/Wittig with solvent exchange



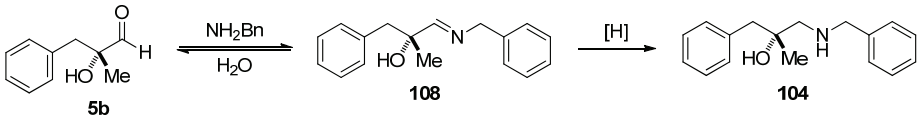
Entry[a]	Equiv **107**	Temp	Conversion	*E*:*Z*[b]
1	1.25	90→rt	incomplete	85:15
2	1.5	rt	incomplete	92:8
3	2.0	90→rt	incomplete	86:13
4	3.5	90	incomplete	90:10
5	1.5 x 2	90	complete	91:9

[a]AD reactions extracted with Et_2O, diluted with toluene, and partially concentrated to remove Et_2O. Then added freshly prepared ylide **107** in toluene.
[b]Ratios determined by ^1H NMR of crude product.

Thus more traditional procedures involving organic solvents were screened in the hopes of increasing both the yield and the *E*:*Z* selectivity. Although aqueous olefinations are typically faster, organic solvents generally provide higher *E*-selectivity.[78, 80] For these reactions, the aqueous phase of the AD reaction was extracted twice with diethyl ether, which was then azeotropically removed with toluene. The solution was never taken to dryness in order to avoid troublesome dimerization of the α-hydroxy aldehyde. Freshly prepared ylide **107** was added to the toluene solution, and the reaction was allowed to stir overnight. The unsaturated ester **103** was obtained with approximately the same conversion and *E*:*Z* ratios observed with the aqueous conditions. Increasing the equivalents of ylide did not provide complete conversion until a portionwise addition was attempted (entry 5). With these optimized conditions, *trans*-alkene **103** was isolated in 68% yield from the enol benzoate **1b**. These observed ratios equal the best ratios observed for α-oxygenated aldehydes.[44, 50]

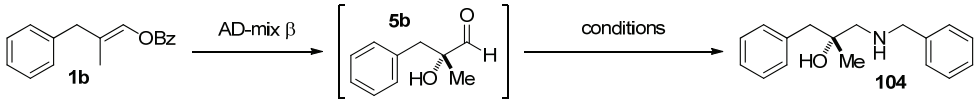
1.4.2. Reductive Amination

The ability to exchange the AD alcoholic solvent allowed us to consider transformations which would be disfavored under aqueous conditions. One such transformation is the reductive amination to form a 1,2-amino alcohol **104**, which involves the condensation of an amine with the α-hydroxy aldehyde and concommitant loss of water (eq. 4). This reversible condensation is facilitated by the removal of water from the reaction mixture. Therefore I sought amination conditions to form **104**.

(4) 

As in the Wittig olefination, the crude AD reaction mixture was extracted without workup using Et_2O. Our initial investigations into the amination required a solvent exchange for acetonitrile. Imine formation was facilitated by $ZnCl_2$ as a desiccant and preceded reduction with sodium triacetoxyborohydride (Scheme 1.10, condition A).[81] The desired amino alcohol was isolated in up to 59% yield, but results varied greatly, ranging from poor mass balance to no desired product. In addition, several side products were observed by ^1H NMR.

Scheme 1.10. Conditions for reductive amination



A) 3 equiv NH_2Bn, xs $ZnCl_2$, MeCN;
then 3 equiv $NaBH_3CN$, AcOH

B) 4 Å MS, 1.5 equiv NH_2Bn, Toluene, 105 °C;
then 15 equiv $NaBH_4$, MeOH, 0 °C, 84% yield of **104**

I then explored alternate conditions for the imine formation and reduction. First, the extracted AD reaction organic phase was azeotropically distilled with toluene before

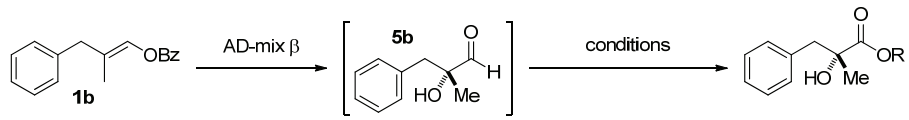
the addition of benzylamine and 4 Å molecular sieves.[82] The mixture was heated at 105 °C overnight, assisting the molecular sieves in the removal of water. Crude imine **108** was concentrated, diluted with methanol, and reduced with sodium borohydride at 0 °C. These conditions proved reproducible in terms of crude mass balance and yield with fewer side products than the $ZnCl_2$ procedure. However, difficulties were encountered during attempts to isolate the amine. Purification by flash SiO_2 column chromatography resulted in decomposition even when buffered with Et_3N. Attempts at forming the ammonium chloride provided a brown paste instead of a crystalline salt. Ultimately, the amine **104** was successfully isolated in 84% yield by first performing an acidic aqueous extraction and then an organic extraction from the basified aqueous solution.

1.4.3. Oxidation and Homologation

Finally, two more reactions which can occur in alcoholic solvents were examined: oxidation to either the ester or carboxylic acid and homologation to the propargylic alcohol. Among the various known conditions for the oxidation of aldehydes, the Pinnick Oxidation appeared well suited for use in tandem with the asymmetric dihydroxylation because both reactions are biphasic in ^{t}BuOH and water (Scheme 1.11, condition A).[83] Initially the oxidation components were added directly to the completed AD reaction. However, only benzoic acid was recovered. Most likely, the poor result stemmed from the decomposition of the chlorite by any remaining potassium ferricyanide, the reoxidant component of the AD-mix.[84] In order to remove the residual iron from the oxidation step and facilitate formation of carboxylic acid **109**, the aldehyde was extracted from the biphasic AD reaction. Unfortunately, the Pinnick Oxidation

suffered from incomplete conversion even when a large excess of oxidant was added either at the beginning of the oxidation or portionwise.

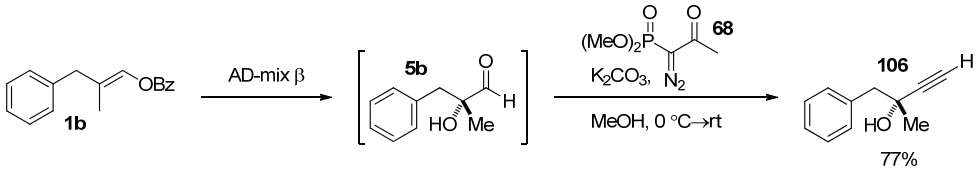
Scheme 1.11. Conditions for oxidation of aldehyde



A) $NaClO_2$, 2-methyl-2-butene, NaH_2PO_4, ^tBuOH, H_2O
R = OH, **109**
B) Br_2, $NaHCO_3$, MeOH
R = Me, **105** (30% yield)
C) I_2, KOH, MeOH
R = Me, **105** (92% yield)

Other oxidants were then examined. Specifically, molecular halogens are capable of converting aldehydes to esters in alcoholic solvents (Scheme 1.11, conditions B and C).[85] After exchanging the butanol from the AD for methanol, bromine-mediated oxidation provided methyl ester **105** in up to 30% yield along with numerous side products. Ultimately, Mr. DeBergh was able to successfully oxidize the aldehyde to **105** in 92% yield using iodine in methanol.[86] Homologation of the aldehyde to the enantioenriched 3° propargylic alcohol **106** also proceeded smoothly for Mr. DeBergh under the Ohira-Bestmann protocol (Scheme 1.12).[87]

Scheme 1.12. Ohira-Bestmann homologation to propargylic alcohol



1.5. Summary

In conclusion, the importance of controlling enol stereochemistry was illustrated by subjecting stereodefined enol benzoates to the Sharpless Asymmetric Dihydroxylation. The corresponding 3° α-hydroxy aldehydes were produced with ≥94% ee for every substrate tested. In contrast, a 9:1 mixture of *E*- and *Z*-enol benzoates resulted in a significant decrease in enantioselectivity. Reduction *in situ* provides 1,2-diols, which may also be accessed (albeit with lower enantioselectivities) by AD of the corresponding 1,1-disubstituted alkenes.

The synthetic utility of the enantioenriched α-hydroxy aldehydes was further demonstrated by transformation of the aldehyde. Optically active 3° propargylic alcohols, α,β-unsaturated esters, α-hydroxy esters, and 1,2-amino alcohols were prepared in good yields. The success of these transformations relied in large part on the ability to exchange the solvent of the crude asymmetric dihydroxylation reaction for other alcoholic or higher boiling solvents without concentration of the aldehyde intermediate. Thus use of stereodefined enol benzoates in the Sharpless AD should greatly facilitate the total syntheses of biologically active small molecules containing 3° alcohols.

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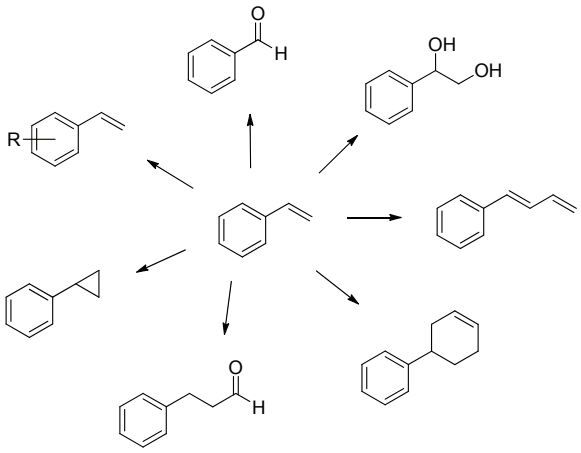
2. CHAPTER TWO

THE TITANIUM-MEDIATED OXIDATIVE ARYLATION OF HOMOALLYLIC ALCOHOLS

2.1. Introduction

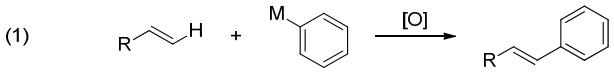
Aromatic rings are highly prevalent in natural products. They are also common structures in small molecules used as biological probes and active pharmaceutical ingredients. Often the synthetic routes to these small molecules involve styrene intermediates because the carbon-carbon double bond offers a convenient handle to introduce new stereocenters and build complexity into the molecule. Figure 2.1 shows a small sample of these transformations.

Figure 2.1. Synthetic utility of styrenes



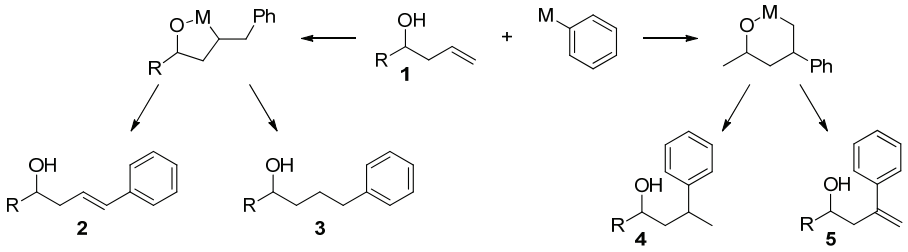
In theory, an oxidative coupling of an alkene with an organometallic reagent would provide styrenes (eq. 1). While many methods exist for the arylation of activated alkenes, the coupling of *unactivated* alkenes is lacking due to two main reasons.

Unactivated alkenes exhibit poor reactivity toward organometallic reagents. This problem is compounded by the lack of strong polarizing groups, which could otherwise control the regioselectivity of addition. Thus effective arylation reactions must overcome the poor reactivity while exhibiting chemoselectivity for one of the regioisomeric arylmetalation (Scheme 2.1, **3** or **4**) or oxidative arylation products (**2** or **5**).

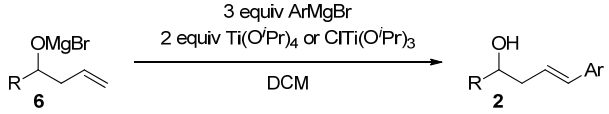


The issues of reactivity and regioselectivity may be addressed by employing a directing group. By coordinating with the organometallic species, the directing group would potentially favorably influence the rate of addition by increasing the local concentration of the reagents. Furthermore, the directing group may control the orientation of the alkene and the organometallic reagent and thus the regioselectivity of addition. For this study alcohols were chosen as the directing group because 1) they are excellent handles for further functionalization, and 2) alcohols and alkoxides coordinate with a variety of organometallic species. In particular, alcohols are known to coordinate with Group IV transition metals, which are capable of effecting transformations of alkenes. For example, allylic and homoallylic alcohols participate in zirconocene-catalyzed ethylmagnesiation reactions[1] and titanium-catalyzed asymmetric epoxidations.[2]

Scheme 2.1. Potential arylation and oxidative arylation products



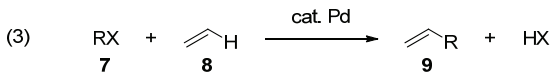
Prior to this study, the use of aryltitanium reagents was mainly limited to additions to carbonyls. Under the proper conditions, aryltitanium reagents are directed by homoallylic alcohols to react with alkenes (eq. 2). This chapter describes previous methods of generating styrene derivatives via arylation of alkenes and aryltitanium reagents more in depth. The optimization and mechanistic studies of the titanium-mediated oxidative arylation of homoallylic alcohols is then discussed.

(2) 

2.2. Background

2.2.1. Heck and Oxidative Heck Reactions

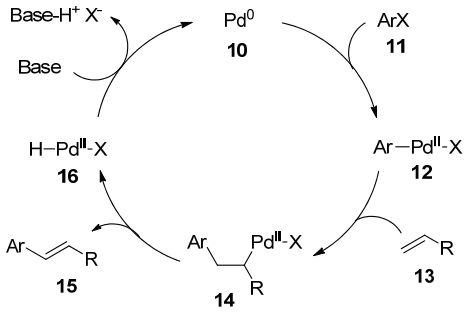
Since its simultaneous discovery by Mizoruki[3] and Heck in the 1970s,[4] the Mizoruki-Heck reaction (eq. 3) has become a staple of synthetic organic chemistry. Several reviews summarize the finer details of the reaction mechanism, the regioselectivity of addition, and variations which increase the substrate scope and yields or allow intramolecular or asymmetric reactions.[5-9] More recently, several research groups have reported oxidative Heck reactions which show promise for unactivated terminal olefins. A brief overview of the two reactions is provided herein with special attention to the regioselectivity of arylation of unactivated olefins.

(3) 

2.2.1.1. Heck Reaction

The Heck reaction adds aryl and vinyl halides or pseudohalides (eq. 3, X=I, Br, Cl, OTf) to alkenes in the presence of catalytic quantities of palladium. In general, these reactions follow the mechanism as shown in Figure 2.2. Palladium(0) first undergoes an oxidative addition to the aryl halide coupling partner. Coordination of the alkene occurs prior to migratory insertion, which is the regiodetermining step of the reaction. β-Hydride elimination from the alkylpalladium(II) species generates a new C–C bond. In the final step of the catalytic cycle, base assists the reductive elimination of HX from the palladium(II) hydride to regenerate Pd^0.

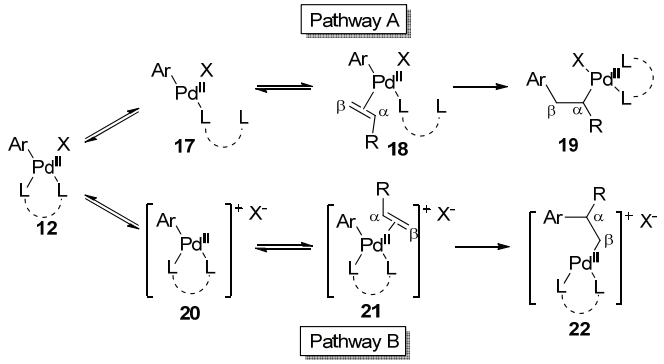
Figure 2.2. General Heck reaction mechanism



The Heck reaction follows one of two pathways for the coordination and migratory insertion of the C–C double bond (Figure 2.3), leading to different regioisomers.[5, 10] Pathway A proceeds through a neutral palladium complex and requires dissociation of a neutral ligand to allow coordination of the olefin. Arylation occurs preferentially at the less hindered (or β) position because steric influences dominate the regioselectivity of carbopalladation. Alternatively, in Pathway B, an anionic ligand dissociates to produce a cationic palladium complex and allow coordination of the

alkene. The cationic complex polarizes the C–C double bond so that arylation regioselectively occurs at the carbon with lower charge density (or α position).

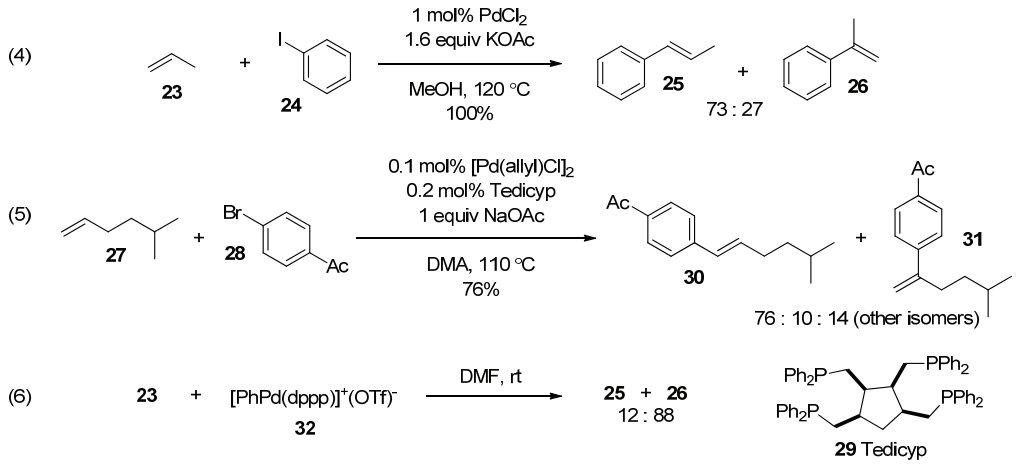
Figure 2.3. Neutral and cationic palladium intermediates



In general, unfunctionalized alkenes have received less attention than either electron-rich olefins (i.e. vinyl ethers) or electron-poor olefins (i.e. styrenes, enones). Thus the excellent levels of regiocontrol observed in the reactions of electron-rich and -poor alkenes is lacking for simple terminal alkenes. The few examples that exist are scattered throughout the literature and often appear as a single entry in an entire paper. Nonetheless, terminal unactivated alkenes have been used in both the neutral and cationic pathways; some of these are shown in Scheme 2.2. For example, Mizoroki's initial report with propene and iodobenzene resulted in a 3:1 selectivity for arylation at the terminal position (eq. 4).[3] Santelli and coworkers' tetradentate phosphine ligand **29** was able to give up to 10:1 selectivity for the terminal arylation products with alkenes containing branched alkyl groups; linear alkenes were much less selective (eq. 5).[11] The use of stoichiometric cationic palladium resulted in 1:7 selectivity for the arylation of propene (eq. 6).[12] Other examples with catalytic amounts of palladium utilized bidentate

phosphine ligands (1:9 terminal:internal),[13] ionic liquids (1:4),[14] or ethylene glycol (1:4)[15] to promote regioselective arylation at the internal carbon.

Scheme 2.2. Heck reactions of terminal olefins

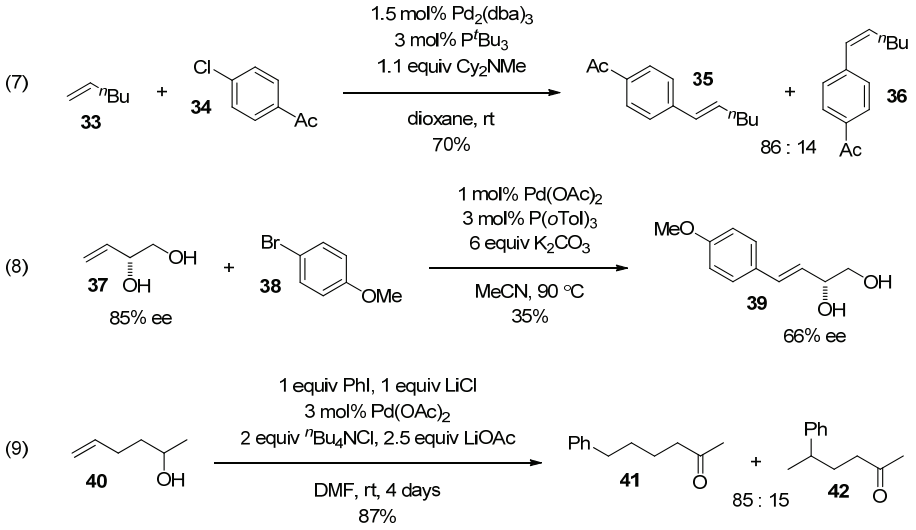


In addition to regioselectivity in the arylpalladation step, product ratios also depend on the β-hydride elimination step. This process can translate into olefin geometry (eq. 7)[16] or isomerization of the olefin along the starting alkyl chain.[6] After β-hydride elimination, the new C–C bond remains briefly coordinated with the palladium(II) hydride. If conditions favor olefin coordination, hydropalladation may form regioisomeric alkylpalladium species. Sequential hydride addition and eliminations carry the olefin along the length of the alkyl chain and provide extensive mixtures of products. This proves especially problematic in substrates containing enantioenriched stereocenters at the allylic position (eq. 8).[17] Reactions with alkenes containing alcohols allow the formation of ketones or aldehydes under the right conditions (eq. 9).[18-20]

Thus, the Heck reaction of unactivated alkenes proceeds with moderate to decent selectivity for both internal and terminal arylation. However, isomeric products are often

recovered due to reversible β-hydride elimination and hydropalladation of olefins formed during the reaction.

Scheme 2.3. Isomerization due to β-hydride elimination

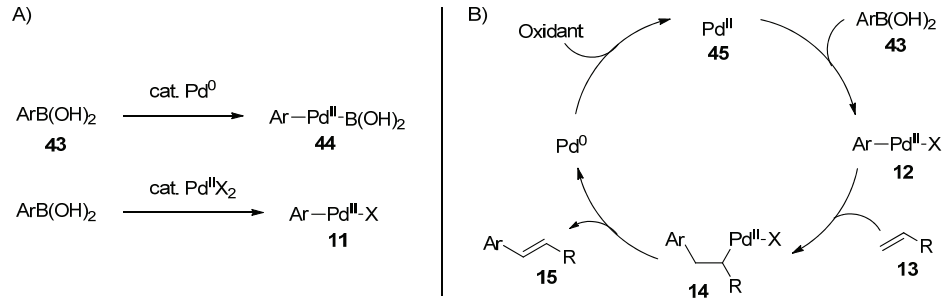


2.2.1.2. Oxidative Heck Reaction

A variant of the Heck reaction, the Oxidative Heck, exchanges the organohalide coupling partner for an organometallic reagent. Originally, the addition of vinyl boronic acids to methyl acrylate required stoichiometric amounts of palladium(II) acetate.[21] Two decades later, the reaction was extended to couple organosilanols or organostannanes and was made catalytic in palladium by the addition of stoichiometric oxidants.[22-24] However, these reactions generate toxic byproducts from the organostannanes or the copper oxidants. Alternatively, organoboronic acids may be coupled using either Pd^0 or Pd^{2+} catalysts. With Pd^0, the initial step of the catalytic cycle is an oxidative addition of the C–B bond;[25] catalytic Pd^{2+} enters the catalytic cycle *via* transmetalation of the organoboronic acid (Figure 2.4A).[26] Boronic acids are advantageous due to their low toxicity and commercial availability. In addition, the stoichiometric transition metal salts

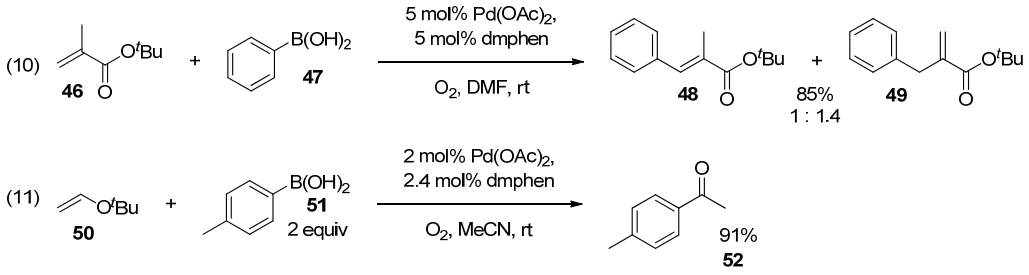
may be replaced by benzoquinone[27, 28] as the oxidant to regenerate Pd^{2+} and complete the catalytic cycle. The stability of boronic acids to air has even allowed the transition metal oxidants to be replaced by molecular oxygen, making the reactions milder and more environmentally friendly.[29]

Figure 2.4. General mechanism of Oxidative Heck reaction



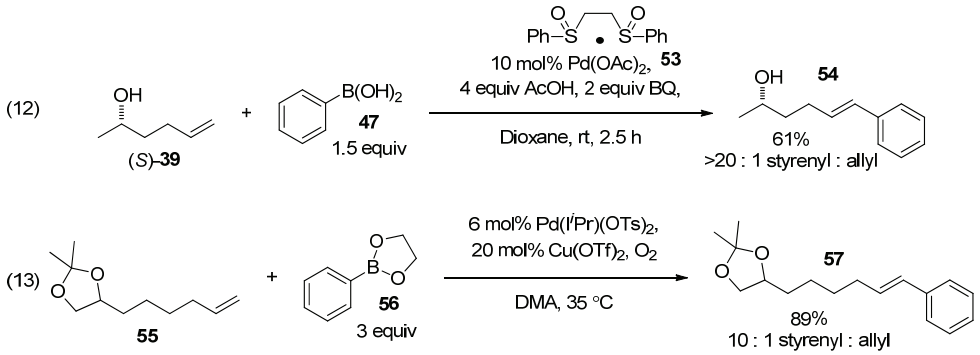
One of the drawbacks to the oxidative version compared with the traditional Heck reaction is that it often requires higher catalyst loadings (up to 10 mol%) under ligand-free conditions and results in homocoupled side products.[30] In part, the higher loadings are necessary to overcome the tendency of Pd^0 to form aggregates in the absence of ligands.[31] Lower catalyst loadings are possible with the addition of bidentate nitrogen ligands. In addition, nitrogenous ligand conditions facilitate the transmetalation of arylboronic acids to palladium and allow the reaction to occur in the absence of base, a critical component in traditional Heck couplings.[30]

Scheme 2.4. Oxidative Heck of electronically-modified alkenes



In general, the Oxidative Heck couplings follow the same regioselectivities for monosubstituted electron-poor (eq. 10)[30] and electron-rich alkenes (eq. 11)[28] as the traditional Heck reaction following the cationic pathway, forming terminal and internal arylation products, respectively.[26, 28, 30-33] Despite the high regioselectivities of arylpalladation, mixtures of vinyl and allyl arenes may result from either poor selectivity in the β-hydride elimination[34] or isomerization via reinsertion of the palladium hydride.[32] This is especially problematic when both products are conjugated with carbonyls as in equation 10.[28, 30]

Scheme 2.5. Oxidative Heck of unactivated olefins

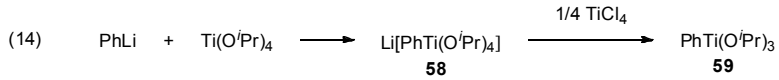


The primary advantage for the Oxidative Heck over traditional Heck couplings in terms of substrate scope is the ability to selectively form *E*-styrene derivatives from unactivated terminal olefins. Recent work by White and coworkers consistently achieved >20:1 selectivities for the linear arylation products using a Pd^{2+}/bis-sulfoxide catalyst (eq. 12).[34] They propose that chelation of the palladium with directing groups biases the system to add the aryl group at the terminal position, preferentially forming 5- and 6-membered rings with the internal alkyl palladium intermediate. Sigman also reported high regioselectivities for the linear styrene derivatives (eq. 13).[35] They attributed the

observed selectivity to the highly electrophilic palladium catalyst which is stabilized by an *N*-heterocyclic carbene ligand.

2.2.2. Organotitanium Compounds

The first organotitanium compound was formed by Herman and Nelson in 1952.[36] Their initial protocol combined PhLi and $Ti(O^iPr)_4$ to form a lithiated



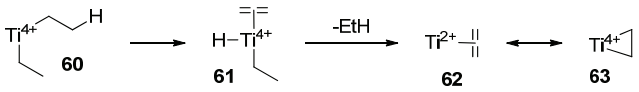
phenyltitanium "ate" complex. Treatment of the complex with $TiCl_4$ allowed the isolation of $PhTi(O^iPr)_3$ as a crystalline solid which melts at 88-90 °C. Subsequently, $ClTi(O^iPr)_3$ was found to be a better titanating agent and could be used with a variety of alkyl and aryl metal species.[37, 38] The stability of the organotitanium compounds depends on the number of alkyl substituents and their electronegativity. In general, stability decreases as more alkyl substituents are added and increases with increasing electronegativity (butyl < methyl < acetylenyl < *p*-anisyl < phenyl < 1-naphthyl).[39] The organotitanium compounds are water and oxygen sensitive. Whereas Grignard and organolithium compounds show little chemoselectivity for aldehydes or ketones and often result in mixtures of products (i.e. Aldol adducts), the corresponding organotitanium species are less reactive[40] and thus exhibit higher chemoselectivities for aldehydes in the presence of ketones and better functional group compatibility (i.e. NO_2, CN, I).[41, 42]

2.2.2.1. β-Hydride Elimination

In general, alkyltitanium compounds are less stable than their aromatic counterparts. Agostic interactions between the titanium and the H–C_β bond[43, 44] lead to

decomposition by β-hydride elimination of the alkyl group and formation of titanium hydride.[45, 46] Branched alkyltitanium compounds are even more prone to β-hydride elimination than straight-chain isomers, so much so that they are unstable even in solution.[33] Stability increases for those compounds for which elimination would result in highly strained olefins.

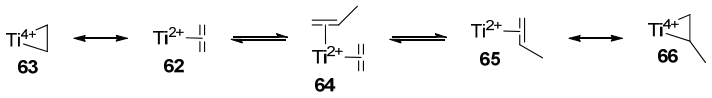
Scheme 2.6. Dialkyltitanium decomposition to titanacylcopropane



Dialkyltitanium complexes decompose *via* transfer of a β-hydrogen from one alkyl group to the other, thus forming one equivalent of alkane and the corresponding coordinated alkene (Scheme 2.6).[47] The titanium-alkene complex can be represented either as the titanacyclopropane (Ti^{4+}) or as Ti^{2+} coordinated with an alkene, with the titanacyclopropane the dominating structure.[48, 49] In addition, olefin exchange occurs;[45] initial association of the new alkene is followed by dissociation of the original alkene to give the new titanacyclopropane (Scheme 2.7).[50] The olefin equilibrium may be influenced by three factors. 1) Evaporation of smaller, uncomplexed olefins such as propene[51-53] or butene[54] drives the equilibrium toward complexation of less volatile olefins.[45] 2) The less-substituted olefin is preferentially incorporated into the titanium complex.[55] 1-Alkenes have replaced cyclohexene[55] and cyclopentene.[56, 57] 3) The equilibrium favors olefin complexes tethered to functional groups capable of coordinating with titanium. For example, 1-butene has been replaced by 1-alkenes bearing proximal esters.[54] Alkenes may also be exchanged for alkynes, generating the corresponding

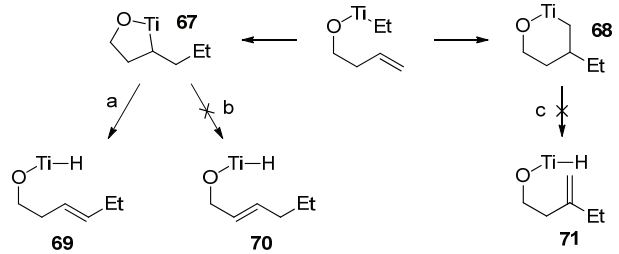
titanacyclopropene.[58] Titanacyclopropanes and -propenes behave as 1,2-dicarbanion equivalents, and their reactivity has been reviewed in detail by Kulinkovich[48] and Sato.[59]

Scheme 2.7. Interconversion of titanacyclopropanes



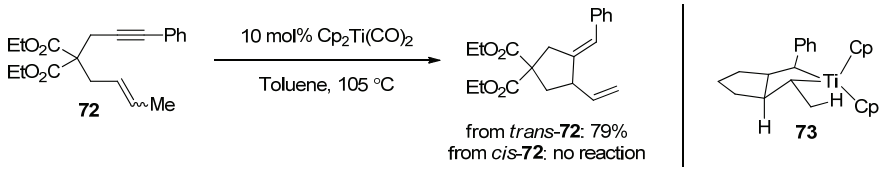
β-Hydride elimination greatly depends on the rotational freedom of the M–C–C–H dihedral angle.[47, 60, 61] Coleman and Thompson reported the formation of two different oxatitanacycles: oxatitanacyclopentane **67** and oxatitanacyclohexane **68**.[62-64] (Formation of these titanacycles is discussed in greater detail in Section 2.2.2.3.) The secondary alkyltitanium **67** possesses four β-hydrogens between the two adjacent carbons. Elimination of the exocyclic hydrogen (pathway a) generates the observed 3-hexen-1-ol; the corresponding elimination of the endocyclic hydrogen is not observed (pathway b). Although oxatitanacycle **68** only contains one hydrogen at the β position, it is an endocyclic hydrogen incapable of undergoing elimination (pathway c). The metallocycle restricts the rotational freedom relative to the acyclic analog, preventing the 0 ° dihedral angle which is optimal for elimination. Thus neither 2-hexen-1-ol nor the 1,1-disubstituted alkene is formed.

Scheme 2.8. β-Hydride elimination favors exocyclic hydrogen



Buchwald reported a titanocene-catalyzed ene reaction of 1,5-enynes (Scheme 2.9).[65] They observed a highly stereospecific β-hydride elimination, which required the starting *trans*-substituted alkene for optimal overlap of the H–C_β with the titanium orbital (**73**). *cis*-Olefin starting materials do not undergo cyclization because the β-hydrogen is not correctly geometrically positioned.

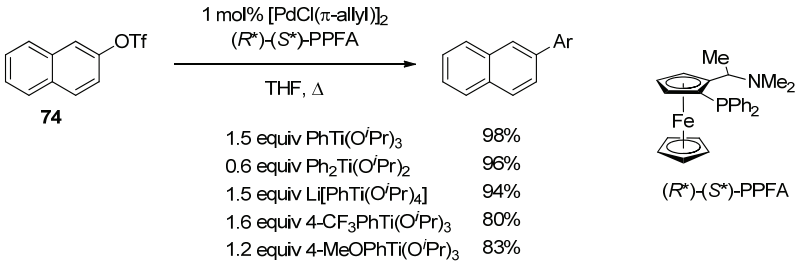
Scheme 2.9. Buchwald titanocene-catalyzed cycloisomerization



2.2.2.2. Aryltitanium Compounds

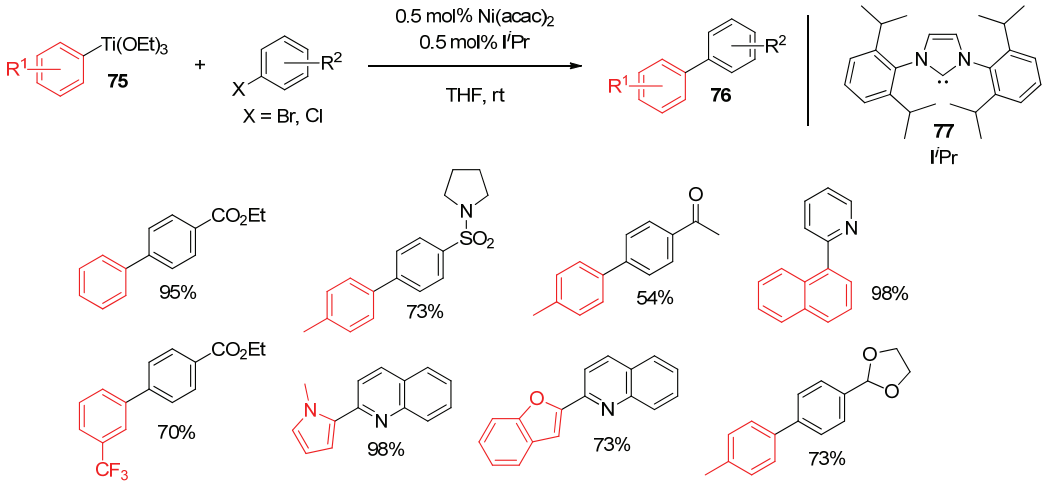
Aryltitanium compounds vary from their alkyl relatives with β hydrogens in that they are also capable of participating in transition metal catalyzed reactions. Hayashi reported the first use of methyl- and aryltitanium reagents as coupling partners for aryl triflate with catalytic amounts of palladium (Figure 2.5).[66] Yields were nearly quantitative

Figure 2.5. Palladium-catalyzed cross-coupling of ArTi(O^iPr)$_3$



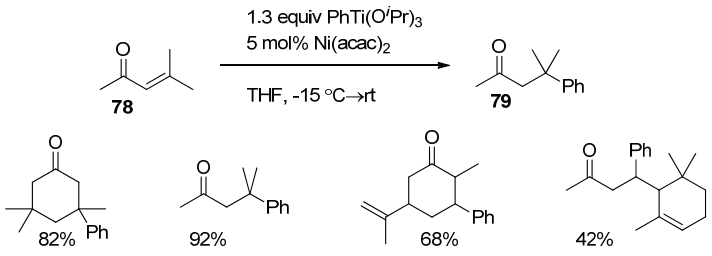
whether the PhTi(O^iPr)$_3$ was used as the isolated crystalline solid or prepared *in situ* from PhLi and ClTi(O^iPr)$_3$. Similarly, Ph_2Ti(O^iPr)$_2$ and ate complex Li[PhTi(O^iPr)$_4$] provided the cross-coupled product in excellent yields. The reaction required refluxing temperatures and varied little in the substitution on the coupling partners. Knochel

Figure 2.6. Nickel-catalyzed cross-coupling of ArTi(O^{i}Pr)$_3$



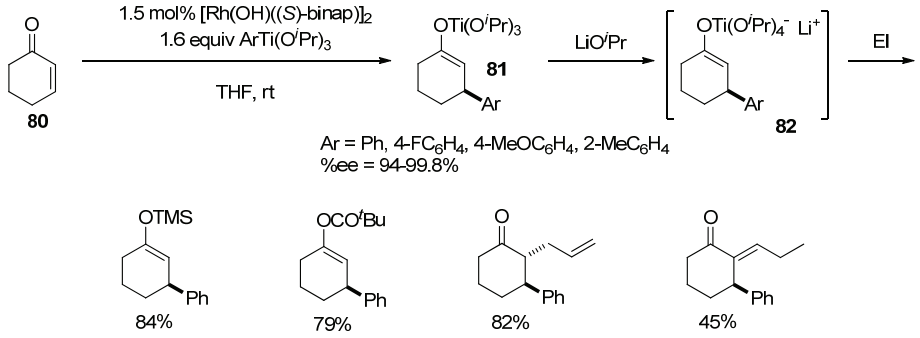
extended the reaction to include substituted aryltitanium species **75** and more functionalized aryl halides by using Ni(acac)$_2$ with N-heterocyclic carbene ligand **77**.[67] The highly efficient catalyst system used electron-rich, electron-poor, and heterocyclic aryltitanium compounds with aryl halides containing esters, ketones, heterocycles, and sulfonamides at room temperature. Similar functional group compatibility was later demonstrated under palladium catalysis, which also utilized aryl halides as coupling partners.[68] This method occurs in the absence of the solid inorganic bases, which are often necessary in biaryl cross-coupling reactions, and effectively couples sterically hindered aryl groups.

Figure 2.7. Nickel-catalyzed 1,4-conjugate addition to hindered enones



Furthermore, transition metal catalysts are capable of altering aryltitanium compounds' chemoselectivity for nucleophilic additions to carbonyls to favor 1,4-conjugate additions. $Ni(acac)_2$ is effective for the addition of $PhTi(O^iPr)_3$ or $MeTi(O^iPr)_3$ to sterically hindered enones (Figure 2.7), a challenging transformation for reactions involving catalytic amounts of copper.[69] An asymmetric variant is possible in the presence of a rhodium-binap complex (Figure 2.8).[70] 1,4-addition of $ArTi(O^iPr)_3$ proceeds with excellent enantioselectivity to form the titanium enolates **81**, which are reluctant to undergo trapping as the neutral complex. However, the addition of LiO^iPr results in the formation of titanium ate complex **82** that is much more reactive toward electrophilic trapping. Thus the enolate may be trapped on oxygen with trimethylsilyl chloride or pivaloyl chloride or on carbon with allyl bromide or propionaldehyde.

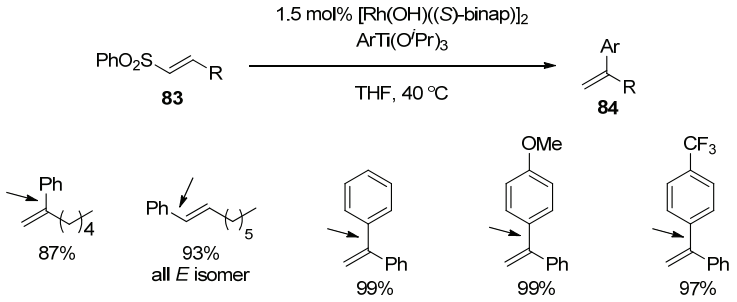
Figure 2.8. Rhodium-catalyzed asymmetric conjugate addition



The same rhodium-binap complex also catalyzes the *cine*-substitution of alkenyl sulfones **83** with $ArTi(O^iPr)_3$ (Figure 2.9).[71] As in the conjugate addition, the aryl group is transferred to the rhodium complex, which adds with complete regioselectivity to the electron-poor alkene. Isomerization *via* sequential β-hydride elimination and

hydrorhodation place the rhodium β to the sulfonyl group, which is eliminated to form the *cine*-substituted alkene.

Figure 2.9. Rhodium-catalyzed *cine*-substitution of alkenyl sulfones



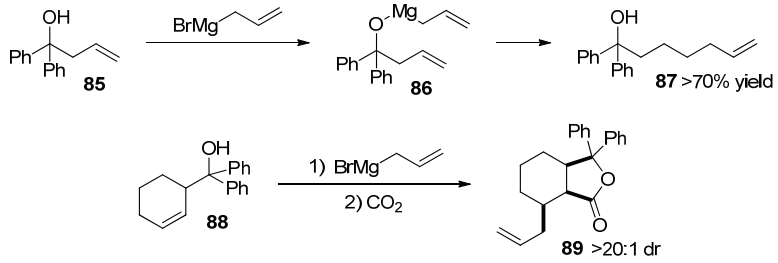
In general, aryltitanium compounds have had limited synthetic use outside of their ability to add to carbonyl compounds. Indeed, even their use as cross-coupling partners merely adds titanium to the list of organometallic species capable of participating in transition metal catalyzed biaryl cross-coupling. However, their ability to participate in transition metal catalyzed reactions indicates significant potential for use in novel transformations.

2.2.2.3. Carbometalation of Homoallylic Alcohols

Organometallic species are slow to add uncatalyzed to unactivated C–C double bonds. This phenomenon makes them compatible with a plethora of synthetic transformations. However, as unfunctionalized C–C double bonds are highly abundant in petroleum resources, conditions to add organometallic reagents across alkenes would be highly useful. In part, the presence of a homoallylic alcohol overcomes the poor reactivity of alkenes; coordination of organometallic reagents to the alcohol allows the alcohol to position the reactive component near the alkene to allow the reaction to take

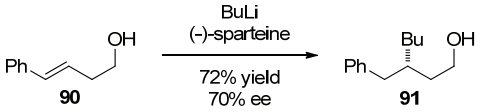
place.[72] This section focuses on directed carbometalations of homoallylic alcohols; a broader review on carbometalation of alkenes is presented in Chapter 3.

Scheme 2.10. Carbomagnesiation of homoallylic alcohols



One of the earliest of such transformations of homoallylic alcohols is the addition of allylmagnesium bromide (Scheme 2.10).[73] Mechanistic studies showed that *syn*-carbomagnesiation occurs intramolecularly from the allylmagnesium alkoxide.[74] A similar carbolithiation of homoallylic alcohol **90** produced **91** enantioselectively in the presence of (-)-sparteine (Scheme 2.11).[75] In contrast to the carbomagnesiation, which preferentially forms the five-membered oxametallacycle, carbolithiation here forms the six-membered ring to add the butyl group to the β carbon. Electronic bias of the styrene derivative may be responsible for this reverse in 5-*exo* versus 6-*endo* regioselectivity.

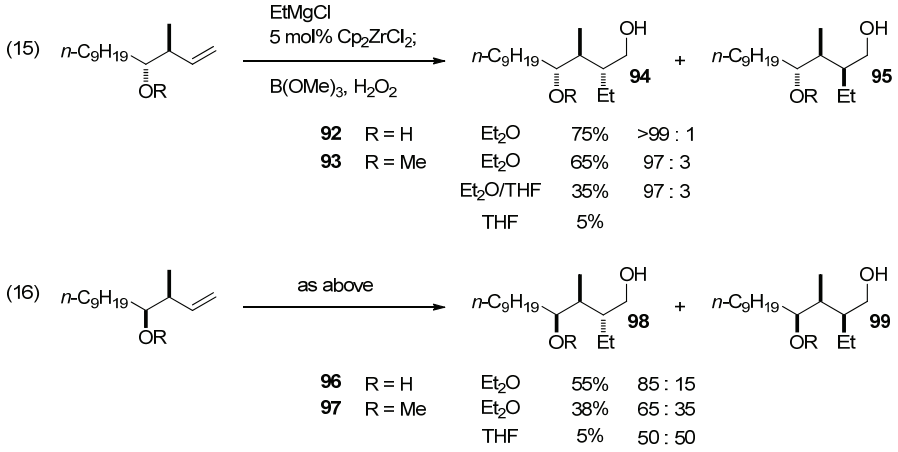
Scheme 2.11. Enantioselective carbolithiation of homoallylic alcohol



More recently Group IV metals have been shown to mediate olefin carbometalation. For example, Hoveyda employed zirconocene to catalyze the addition of ethyl Grignard to homoallylic alcohols and ethers (Figure 2.10).[76] The reaction benefits in terms of stereoselectivity and reactivity from coordination of the alcohol to the zirconocene catalyst. Yields are higher with the more Lewis basic alcohol **92** than with

the ether **93**. Competitive ligation of solvent (THF) further decreases the yield of the ethylated product. The diastereoselectivity and yield of the reaction are highly dependent on the stereochemistry of the starting material. When the alcohol and allylic substituent are *anti*, yields are good and diastereoselectivity is high (eq. 15). However, when the alcohol and allylic substituent are *syn*, diastereoselectivity and yield suffer (eq. 16). In each case, the allylic substituent is "the principal stereodifferentiating element," preferentially providing the *anti* diastereomer at the newly formed C–C bond. Unfortunately, this carbometalation procedure is limited as only ethyl groups may be incorporated.

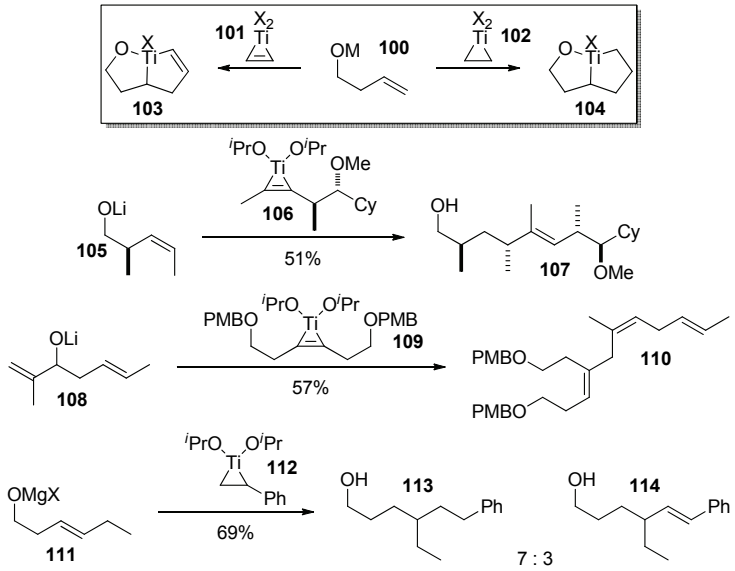
Figure 2.10. Hoveyda's ethylmagnesiation of homoallylic alcohols



Cha and Micalizio have shown organotitanium complexes, acting as 1,2-dicarbanion equivalents,[48] add uncatalyzed to homoallylic alcohols. The 1,2-dianion equivalent adds regioselectively to the distal carbon of the alkene to form [3.3.0] oxatitanabicycle intermediates (Scheme 2.12, **103** and **104**). Micalizio reported that unsymmetrical alkynes (i.e. titanacyclopropenes **106**) couple with alkenes containing homoallylic alcohols regioselectively at the less hindered position.[77, 78] For substrates in

which the alcohol is both allylic and homoallylic (i.e. **108**), reductive coupling is chemoselective for the less-substituted olefin first and then for the allylic position.[79] Cha added the styrene-derived titanacyclopropane **112** to homoallylic alcohols to provide both saturated (**113**) and unsaturated (**114**) alcohols.[80] Interestingly, they ascribe the regeneration of the styrene double bond to an endocyclic β-hydride elimination.

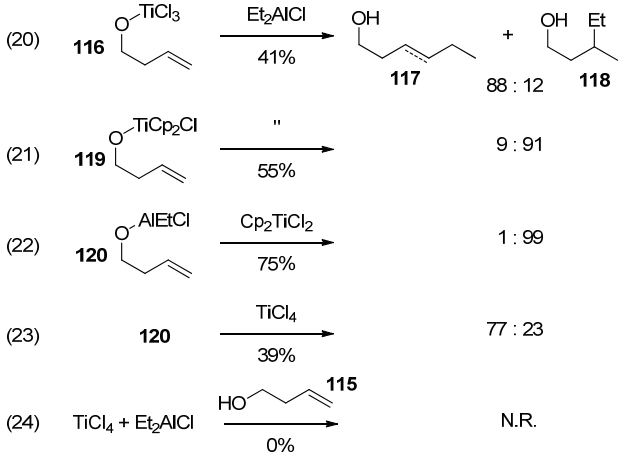
Scheme 2.12. Addition of 1,2-dianion equivalents



The related titanium-catalyzed Ziegler-Natta polymerization has enjoyed extensive application in industrial settings.[81, 82] The polymerization mechanism involves the addition of organotitanium species across the double bond of a monomer to form a new organotitanium species and continue the polymerization. In the early 1970s, a group led by Coleman and Thompson initiated a study using 3-buten-1-ol (**115**) to explore the polymerization growth step and determine the feasibility of harnessing the carbometalation for non-macromolecular synthesis.[63] Various titanium-**115** complexes (i.e. **116** and **119**) were formed and treated with diethylaluminium chloride (Et_2AlCl) to

form both the terminal (**117**) and internal (**118**) ethylation products in moderate yields. Ethylation was favored at the terminal position when titanium chlorides were used (eq. 20), but this selectivity reversed in the presence of cyclopentadienyl (Cp) ligands (eq. 21).[62, 64] The same trends were observed when the alcohol was first complexed with aluminum prior to addition of the titanium reagent (**120**), indicating the same active complex is generated by facile ligand exchange. However, two sets of conditions did not result in ethylation: premixing $TiCl_4$ with Et_2AlCl prior to addition of **115** at 0 °C and using triethylaluminum (Et_3Al) with the titanium alkoxide. In both cases, Ti^{4+} is reduced before ethylation can occur. Et_3Al is strong enough to reduce the titanium in the presence of the alkoxide; Et_2AlCl, although a milder reductant than Et_3Al, consumes the Ti^{4+} at higher temperatures in the absence of the homoallylic alcohol.

Scheme 2.13. Titanium-mediated ethylation of homoallylic alcohols

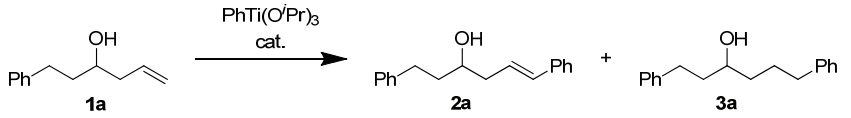


2.3. Oxidative Arylation

2.3.1. Optimization

Initially a nickel-catalyzed Oxidative Heck reaction directed by homoallylic alcohols was sought. After struggling to optimize the reaction with PhMgBr, I turned my attention to other organometallic nucleophiles. While PhLi, PhCu, Ph_2CuLi, Ph_2InCl, and Ph_2Zn failed to effect the desired transformation, $PhTi(O^iPr)_3$ showed potential by forming a mixture of oxidative arylation (**2**) and carbometalation (**3**) products (Table 2.1, entry 1). Screening solvents greatly increased the yield and reversed the selectivity to favor **2**. When it was attempted in the absence of nickel (entry 5), the reaction again proceeded to completion and with high selectivity. Thus the nickel catalyst was not involved in the transformation of **1** to **2**.

Table 2.1. Optimization of catalytic oxidative arylation

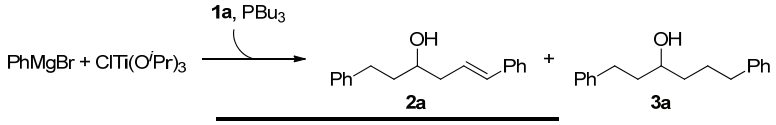


Entry	Catalyst	Solvent	Conv	% **2a**	% **3a**
1	10 mol% $Ni(acac)_2$	THF	68	9	14
2	"	Et_2O	56	40	3
3	"	DCM	100	49	6
4	10 mol% $Ni(acac)_2$ + 20 mol% PBu_3	DCM	100	71	4
5	20 mol% PBu_3	DCM	100	62	10

Attempts to increase the reaction scale and further optimize the reaction were met with difficulties reproducing the product yield and selectivity. A few examples of the widely varying results for reactions performed under the same conditions are shown in Table 2.2. Several factors which could influence the reaction outcome were examined. 1) Up to this point all reactions had been performed in 1 dram vials; larger scale reactions

require larger vessels. The difference in reactivity may be due to the differences in heat transfer between the thinner-walled vials and thicker-walled round bottom flasks. However, the results varied between vials of different sizes as well as between flasks of different sizes. 2) The septa on the vials may allow varying amounts of moisture or oxygen to enter the reaction atmosphere. Thus special care was taken to ensure the exclusion of moisture and oxygen from the reaction. Catalytic amounts of water or oxygen were then added back to the reaction but did little to improve or stabilize the yields and selectivities. 3) Decomposition of the Grignard or $ClTi(O^iPr)_3$ solutions may have occurred. Unfortunately, the use of new, freshly titrated PhMgBr did not result in the desired reproducibility. 4) The formation of $PhTi(O^iPr)_3$ may be sensitive to the order of addition of the PhMgBr and $ClTi(O^iPr)_3$. I varied which reagent was added first, examined how long the reagents were allowed to stir prior to addition of the substrate, and combined the reagents at different temperatures. Unfortunately, none of these were able to improve the reproducibility of the reaction.

Table 2.2. Poor reproducibility of oxidative arylation



Trial	% **2a**[a]	% **3a**
1	73	3
2	42	22
3	61	8
4	30	13

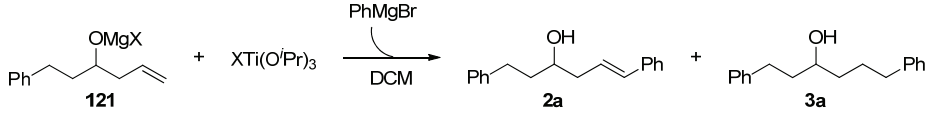
[a]GC yields using dodecane as an internal standard. 3 equiv PhMgBr, 3 equiv $ClTi(O^iPr)_3$, 20 mol% PBu_3 in DCM.

Finally, the order of addition of the $ClTi(O^iPr)_3$ and substrate was changed. Instead of adding the substrate and phosphine to pre-formed $PhTi(O^iPr)_3$, the substrate

was first deprotonated with one equivalent of PhMgBr at 0 °C prior to addition of the $ClTi(O^iPr)_3$. The reaction was allowed to stir for another hour before the addition of the remaining PhMgBr at -78 °C. This revised procedure greatly enhanced the reaction's reproducibility and implies the titanium alkoxide must be present in the reaction prior to the formation of the active arylating species. In contrast to the facile ligand exchange observed in Coleman and Thompson's ethylmetalation reaction (Scheme 2.13), the importance of the order of addition suggests a slow ligand exchange between the titanium alkoxide and phenyl Grignard. Furthermore, exclusion of the phosphine did not affect the reproducibility of the reaction. Its presence was merely an artifact from earlier high yielding results which happened to provide good selectivity.

With the reproducible procedure in hand, the stoichiometry of the Grignard and titanium species could be confidently optimized. Interestingly, changing the titanium source had little effect on product yields and ratios; titanium tetraisopropoxide and chlorotitanium triisopropoxide could be used interchangeably (Table 2.3). The reagent stoichiometry greatly impacted the yield of the oxidative arylation and carbometalation products. Using only 1 equiv of each reagent resulted in greatly decreased yields and much lower ratios of **2**:**3** (entry 1); with $ClTi(O^iPr)_3$, the selectivity was even reversed to favor **3** (entry 7). As the Grignard to titanium ratio increased from 1:1, the selectivity also greatly increased to favor the oxidative arylation product. Also, as more equivalents of Grignard and titanium were added to the reaction, the yield of **2** increased. Ultimately the optimized conditions employed 1 equiv PhMgBr as base, 2 equiv $Ti(O^iPr)_4$, and 3 equiv PhMgBr to provide **2a** in 91% yield with greater than 99:1 selectivity over **3a** (entry 6).

Table 2.3. Optimization of reagent stoichiometry



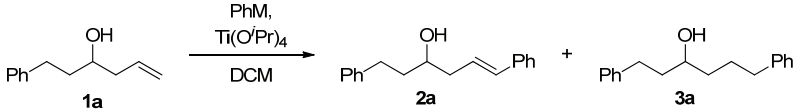
$Ti(O^iPr)_4$					$ClTi(O^iPr)_3$				
Entry	Equiv PhMgBr	Equiv Ti	% **2a**[a]	% **3a**	Entry	Equiv PhMgBr	Equiv Ti	% **2a**	% **3a**
1	1	1	32[b]	27	7	1	1	22[c]	57
2	1.5	1	67	1	8	1.5	1	70	8
3	2	1	62	0.4	9	2	1	77	0.4
4	3	1	69	0	10	3	1	71	0
5	2	2	82	5	11	2	2	83	17
6	3	2	93	0	12	3	2	91	0.5

[a]GC yields based on dodecane as an internal standard. [b]88% conversion. [c]93% conversion.

The synthetic utility of the oxidative arylation reaction could be further improved by expanding the aryl Grignard coupling partner. Thus, access to functionalized aryl metal species was needed. The most direct route would involve purchasing the arylmagnesium halides as several are commercially available as solutions in tetrahydrofuran (THF). Unfortunately, the use of THF as either the reaction medium or as the Grignard solvent greatly reduced conversion of the homoallylic alcohol due to increased formation of biphenyl thus precluding the use of commercially available Grignard reagents (Table 2.4, entry 2).[83] Alternatively, lithium-halogen exchange offers a common, rapid route to aryl metal species. The use of commerically available phenyllithium resulted in poor conversion, and none of the desired products were detected. Because the phenyllithium was available as a Bu_2O solution, lithium-halogen exchange procedures which exclude Bu_2O may still be effective. However, PhLi prepared *in situ* also failed to add to **1** (entry 4). The presence of lithium salts does not hinder the reaction as the addition of LiCl to reactions involving PhMgBr resulted in complete conversion to the desired product (entry 5). Most likely, the aryltitanium ate complexes

formed from the addition of aryllithium to $Ti(O^iPr)_4$ are incapable of undergoing the addition to the C–C double bonds.[46] This restricts the use of aryl metal reagents to arylmagnesium halides prepared in Et_2O prior to use in the reaction. When I_2 was used as the initiator for the magnesium insertion, the yield of **2** decreased relative to commerically available PhMgBr. Switching the aryl halide starting material to PhI further decreased the conversion and selectivity, indicating a halide effect on the oxidative arylation efficiency. Optimized conditions for the preparation of functionalized Grignard reagents require the use of 1,2-dibromoethane as the initiator for the magnesium insertion.

Table 2.4. Screening phenyl metal species



Entry[a]	PhM	PhM Solvent	Results
1	PhMgBr	3.0 M, Et_2O	93% yield of **2a**
2	PhMgBr	1.0 M, THF	Poor conversion, 12% of **2a**
3	PhLi	2.0 M, Bu_2O	Recovered **1a**
4	PhBr + ^{t}BuLi	0.5 M, Hex/Et_2O	Recovered **1a**
5	PhMgBr + LiCl	3.0 M, Et_2O	Full conversion to **2a**
6	PhBr + Mg^0 + I_2	1.9 M, Et_2O	62% yield of **2a**
7	PhI + Mg^0 + I_2	2.0 M, Et_2O	67% yield of **2a** (11:1 **2a**:**3a**)
8	PhBr + Mg^0 + $BrCH_2CH_2Br$	Et_2O	Full conversion to **2a**

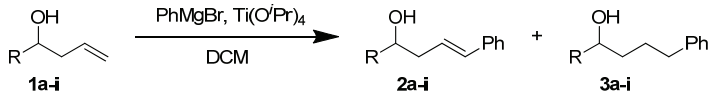
[a]2 equiv $Ti(O^iPr)_4$, 3 equiv PhM in DCM. [b]Reactions analyzed by GC.

2.3.2. Substrate Scope

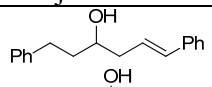
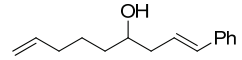
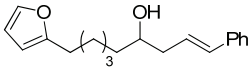
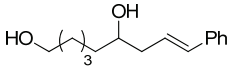
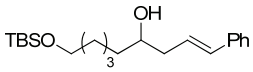
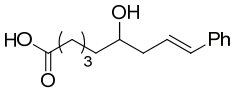
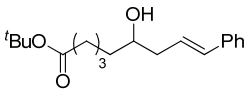
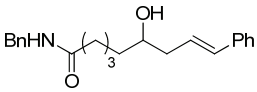
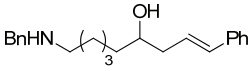
With the optimized conditions in hand, I proceeded to explore the substrate scope of both the homoallylic alcohol and aryl Grignard. First, the compatibility of various functional groups with the reaction conditions was examined(Table 2.5). Heterocycles, alcohols and their silyl ethers, carboxylic acids, amines, and amides were stable under the

optimized conditions. Aldehydes and Weinreb amides were not compatible, resulting in benzylic alcohols and hydroxamic acids, respectively. Notably, only olefins with a proximal alcohol reacted. Diene **2b** was isolated in good yield, and arylation of the remote olefin was not observed (entry 2). Substrates with an acidic proton required an additional equivalent of base to ensure complete conversion and selectivity for the oxidative arylation products (entries 4, 6, 8-9). *tert*-Butyl esters were partially hydrolyzed during the reaction (entry 7), but overall oxidative arylation efficiency was high.

Table 2.5. Oxidative arylation of homoallylic alcohols

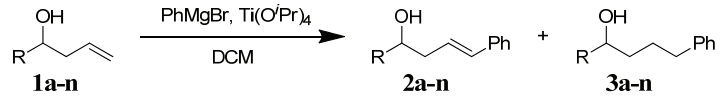


1a-i **2a-i** **3a-i**

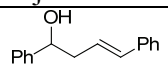
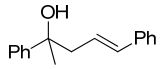
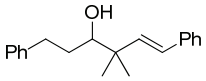
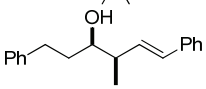
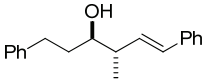
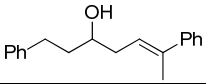
Entry	Substrate	Major Product[a]	**2**:**3**	Yield (%)[b]
1	**1a**		>99:1	91
2	**1b**		>99:1	74
3	**1c**		>99:1	69
4	**1d**		>99:1	80[c]
5	**1e**		>99:1	83
6	**1f**		4:1	74[c]
7	**1g**		>99:1	**2g**: 38 **2f**: 36
8	**1h**		>99:1	78[c]
9	**1i**		>99:1	94[c]

[a]1 equiv PhMgBr as base, 2 equiv $Ti(O^iPr)_4$, 3 equiv PhMgBr, 0.17 M in DCM, rt, overnight. [b]Combined yields of **2** and **3**. [c]Used 2 equiv PhMgBr as base.

Table 2.6. Sterically hindered homoallylic alcohols



1a-n **2a-n** **3a-n**

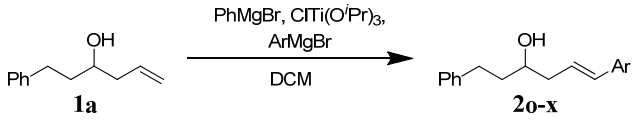
Entry	Substrate	Major Product[a]	**2**:**3**	Yield (%)[b]
1	**1j**		>99:1	91
2	**1k**		4.8:1	75[c]
3	**1l**		1.7:1	85
4	*syn*-**1m**		17:1[d]	68[c]
5	*trans*-**1m**		>99:1	81
6	*trans*-**1n**		>99:1	75[c]

[a]1 equiv PhMgBr as base, 2 equiv Ti(O^{i}Pr)$_4$, 3 equiv PhMgBr, 0.17 M in DCM, rt, overnight. [b]Combined yields of **2** and **3**. [c]Overnight at 40 °C. [d]Ratio of crude product 6:1 **2**:**3**.

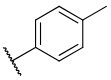
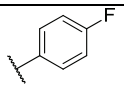
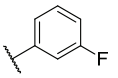
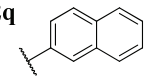
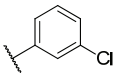
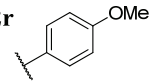
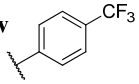
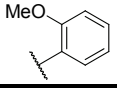
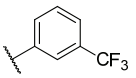
Sterically hindered substrates were also subjected to the standard conditions. While benzylic alcohols reacted with high selectivity (Table 2.6, entry 1), tertiary benzylic alcohols showed greatly decreased product selectivity. Fortunately, the selectivity could be favorably increased by heating the reaction at 40 °C (entry 2). Substitution at the allylic position also decreased product selectivity. For example, geminal dimethyl substituted **1l** resulted in a 1.7:1 **2l**:**3l** mixture. While *syn*-**1m** required heating to produce *syn*-**2m**:*syn*-**3m** in a 6:1 ratio, the products were isolated as a 17:1 mixture in good yield. Alternatively, *trans*-**1m** reacted with complete selectivity at room temperature to provide *trans*-**2m** in 81% yield. Substitution on the olefin was also examined. Unfortunately, 1,1-disubstituted olefins failed to react under the standard conditions. *cis*-Disubstituted olefins similarly failed to react at room temperatures and

provided complex mixtures of products at higher temperatures. In contrast, *trans*-disubstituted olefin **1n** was a suitable substrate at higher temperatures and formed the trisubstituted C–C double bond as a single regio- and stereoisomer (entry 6).

Table 2.7. Scope of substituted aryl Grignard reagents



1a **2o-x**

Entry	Ar[a]	Yield (%)[b] **2**:**3**	Entry	Ar	Yield (%) **2**:**3**
1	**2o** 	89 >99:1	6	**2t** 	73 5.3:1
2	**2p** 	89 1:2	7	**2u** 	60 (74) >99:1
3	**2q** 	69 >99:1	8	**2v** 	66 (75) >99:1
4	**2r** 	83[c] 1:1	9	**2w** 	50 (78) >99:1
5	**2s** 	75[c] >99:1	10	**2x** 	55 (74) >99:1

[a]1 equiv PhMgBr as base, 2 equiv Ti(O^{i}Pr)$_4$, 3 equiv ArMgBr, 0.17 M in DCM, rt, overnight. [b]Yields of isolated mixtures of **2** and **3**. Yields based on recovered starting materials in parenthesis. [c]Reaction time was 3 h.

The synthetic utility was further demonstrated by subjecting a series of aryl Grignards, prepared as concentrated ethereal solutions, to the reaction. Methyl-substitution had little electronic effect, but the steric hindrance of the *ortho*-methyl group disfavored β-hydride elimination (Table 2.7, entry 2). Reactions with electron-rich aryl Grignards were generally complete within 3 hours (entries 4 and 5). In contrast to the *o*-tolyl Grignard, *ortho*-methoxy substituted phenyl Grignard showed excellent selectivity for **2**; coordination of the methoxy group to the titanium may influence this selectivity. Longer reaction times resulted in arylation of **2**. In contrast, reactions with electron-poor

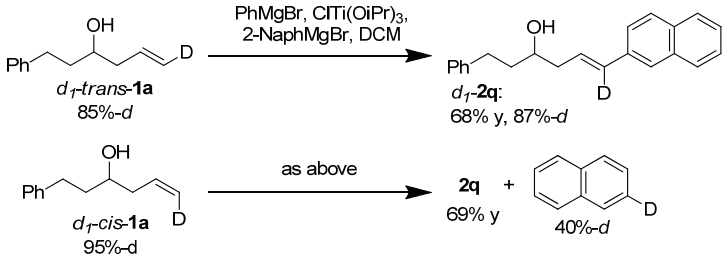
Grignards did not proceed to completion; longer reaction times and excess reagents did little to increase conversion (entries 6-10).

2.3.3. Mechanism

The isolation of both oxidative arylation (**2**) and carbometalation (**3**) products prompted us to examine how the two products were related to the reaction mechanism. Should **3** be an intermediate en route to **2**, a study of the mechanism could potentially reveal possibilities for reversing the product selectivity or expanding the substrate scope to include other coupling partners for the homoallylic alcohols. To be plausible, the mechanism must account for the sensitivity toward the order of addition, the high regioselectivity of the aryl addition, the high stereoselectivity of the new C–C double bond, and the lack of an obvious oxidant.

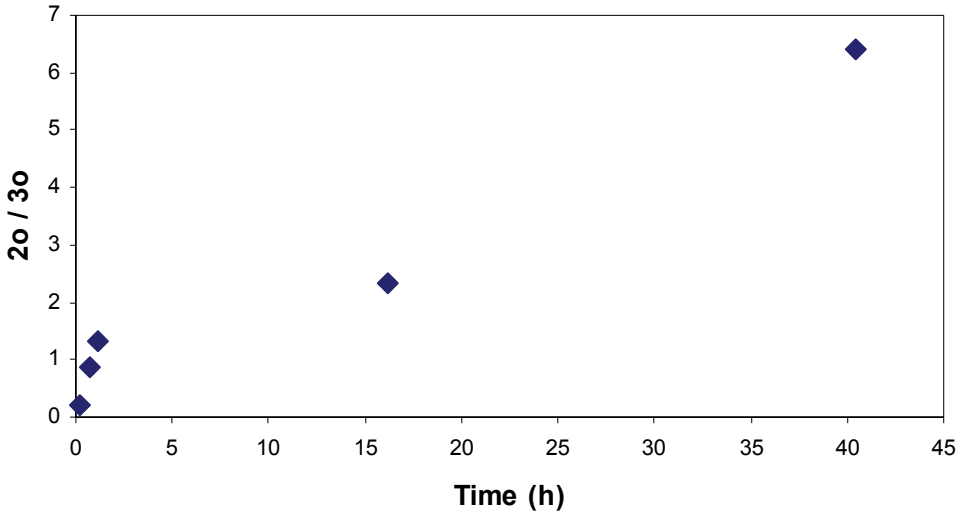
One early insight into the stereospecificity of the reaction was gained from the reactivity of *cis*- and *trans*-**1n**. As described earlier (Section 2.3.2), *trans*-**1n** provided the trisubstituted olefin as a single stereoisomer with isomerization of the methyl substituent whereas *cis*-**1n** failed to react under standard conditions. To confirm that this observation was indeed due to a stereospecific β-hydride elimination, deuterated substrates d_1-*trans*-**1a** and d_1-*cis*-**1a** were prepared and subjected to the reaction. As shown in Scheme 2.14,

Scheme 2.14. Stereospecificity of oxidative arylation



d_1-trans-**1a** reacts with 2-naphthyl Grignard with complete retention of deuterium incorporation to form the disubstituted *d_1*-**2q** as a single stereoisomer. Similarly, *d_1-cis*-**1a** and 2-naphthyl Grignard react to provide unlabeled **2q** and deuterated napthalene. A mixture of labeled and unlabeled naphthalene is recovered due to the use of 3 equiv of naphthyl Grignard. In addition to confirming the stereospecificity of the β-hydride elimination, the labeling study also reveals the final location of the eliminated hydrogen. The labeled naphthalene indicates the possibility of an aryltitanium hydride species which undergoes reductive elimination.

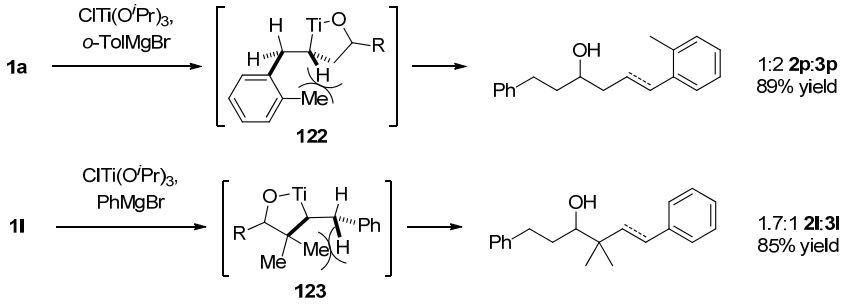
Figure 2.11. Changes in product ratio over time



Time course experiments using *p*-tolylmagnesium bromide revealed another characteristic of the reaction mechanism. Under conditions that provided mixtures of oxidative arylation (**2**) and carbometalation (**3**) products, the ratio of the two products increased over time to favor **2o** (Figure 2.11). For example, at 1 h and 100% conversion, the ratio of **2o**:**3o** was 1.3:1 whereas after 40 hours the ratio had increased to 6.4:1. This

implies the carbometalation product is an intermediate in the formation of **2**. Thus, those substrates which resulted in mixtures of oxidative arylation and carbometalation products may be examined in terms of steric interactions which disfavor the necessary β-hydride elimination to form **2** from **3**. In the reaction with *o*-tolylmagnesium bromide, aryltitanation generates alkyltitanium intermediate **122** (Scheme 2.15). The *syn*-pentane interaction between the *ortho*-methyl and α-H increases as **122** approaches the *syn*-coplanar conformation necessary for β-hydride elimination. Although overall arylation is efficient, the carbometalation product **3p** is favored 2:1 over **2p**. Similarly, geminal dimethyl substrate **1l** displays poor selectivity for the oxidative arylation product. In this case, the steric clash occurs between the H_{trans} and the methyl groups, disfavoring C–C bond rotation to achieve optimal alignment of the Ti and H_β (**123**).

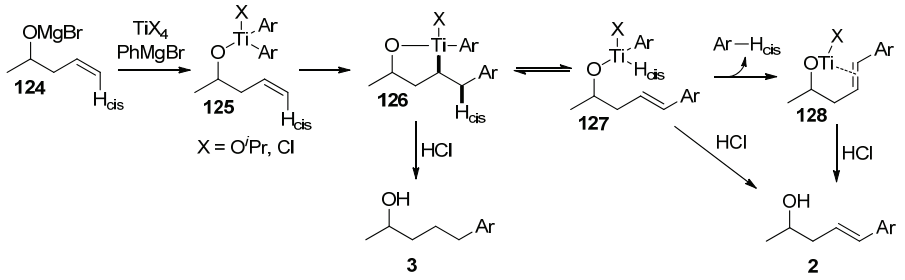
Scheme 2.15. Steric hindrance influences β-hydride elimination



Taken together, these experiments led us to propose the following mechanism (Scheme 2.16). First, the magnesium alkoxide undergoes a transmetalation to titanium. Addition of aryl Grignard may form diaryltitanium alkoxide **125**, which positions the aryltitanium bond near the proximal double bond. Aryltitanation then occurs regioselectively to form the five-membered oxatitanacycle **126**. A reversible, stereospecific β-hydride elimination of the exocyclic hydrogen provides aryltitanium

hydride **127**. Quenching at this stage yields mixtures of carbometalation and oxidative arylation products. However, over longer reaction times or in the presence of excess aryl Grignard (relative to titanium), the equilibrium is driven toward the formation of **2** by the reductive elimination of arene from **127** or transmetalation back to magnesium (not shown).

Scheme 2.16. Proposed oxidative arylation mechanism



2.4. Summary

This chapter described the novel use of aryltitanium species as reagents for the directed oxidative arylation of homoallylic alcohols. The reaction tolerates a wide range of functional groups on the homoallylic alcohol coupling partner as well as electronically- and sterically-modified aryl Grignard reagents. A study of the mechanism indicates the complete regioselectivity is due to the formation of a five-membered oxatitanacycle which undergoes a stereospecific β-hydride elimination. Accordingly, appropriate modifications to the reaction conditions could inhibit the elimination step and effectively reverse the selectivity in favor of the carbometalation products. A second year student in the Ready Laboratory, Bo Peng, has already made significant progress toward

optimizing the carbometalation product. Future developments from this study could include expanding the scope of directing groups and creating catalytic protocols.

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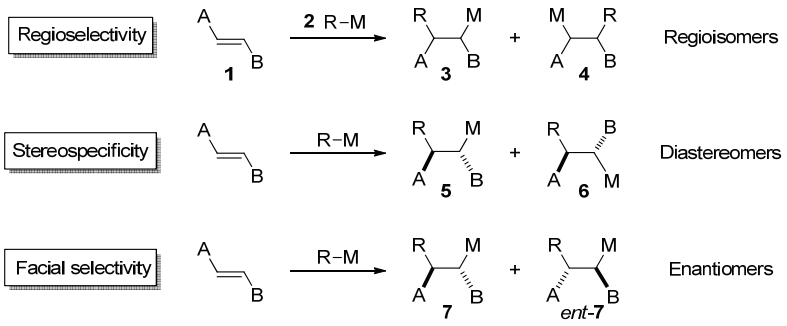
3. CHAPTER THREE

THE ARYLTITANATION OF ALLYLIC ALCOHOLS

3.1. Introduction

The carbometalation of alkenes is the addition of organometallic species across a carbon-carbon double bond to create a new carbon-carbon bond and a new carbon-metal bond. It represents a convenient construction of contiguous sp^3 stereocenters. However, alkene carbometalation has found limited application due to a few challenges. Perhaps the most restrictive of these challenges is the poor reactivity of organometallic reagents toward alkenes. While this property makes them stable during transformations of other functional groups, it hinders their participation in carbometalation reactions.

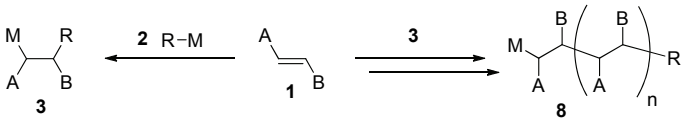
Figure 3.1. Selectivity in alkene carbometalation reactions



Furthermore, efficient carbometalation reactions must address several types of selectivity as nonselective reactions may lead to mixtures of regioisomers and stereoisomers (Figure 3.1). 1) Organometallic reagents that are capable of adding to alkenes require some method of distinguishing between the termini of the unsaturated C–C bond so that the addition occurs regioselectively. In the absence of regiodetermining

factors, carbometalation leads to mixtures of regioisomers (**3** and **4**). 2) Organometallic reagents may undergo either a *syn*- or *anti*-addition to the alkene. A lack of stereospecificity in the addition to internal alkenes affords a diastereomeric mixture of products (**5** and **6**). 3) Carbometalation of unsymmetrical alkenes also requires good control over facial selectivity. Nonselective addition provides mixtures of enantiomers **7** (or, if other stereocenters are present in the molecule, diastereomers). 4) Finally, the carbometalation must be chemoselective for the starting organometallic species in the presence of the organometallic product of the initial carbometalation (Scheme 3.1). When **3** has similar reactivity to that of **2**, polymerization occurs, and, although it is desirable for the formation of polymers, it is problematic for the synthesis of small molecules.

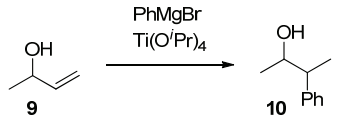
Scheme 3.1. Polymerization from non-chemoselective carbometalation



Different approaches have been taken to address these challenges. Directed carbometalations and intramolecular carbometalations take advantage of the proximity of organometallic species to overcome the typically poor reactivity of alkenes and to influence regioselectivity. Others activate alkenes to facilitate carbometalation by building them into strained ring systems or by incorporating another metal atom at a vinylic position. Alternatively, some methods utilize steric biases of unactivated terminal alkenes to control regioselectivity. In addition, several metals have been shown to add carbon anions to alkenes, either in the presence or absence of transition metal catalysts. The addition of aryl metal species to alkenes has received less attention than the

*alkyl*metalation of alkenes. Attempts to facilitate such a transformation have led to the development of a directed titanium-mediated arylation of allylic alcohols (Scheme 3.2).

Scheme 3.2. Aryltitanation of allylic alcohols



Although carbometalation reactions of alkenes have been reviewed previously,[1-4] selected carbometalations are reviewed here either because of their historical importance to the field of alkene carbometalation or because of their relevance to our aryltitanation of allylic alcohols. The background review is organized according to the type of alkene undergoing carbometalation. Finally, the chapter describes ongoing efforts toward exploring the aryltitanation.

3.2. Background

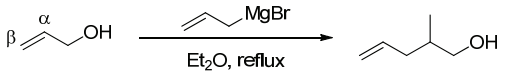
3.2.1. Directed Carbometalation of Alkenes

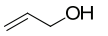
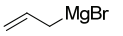
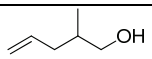
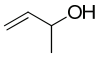
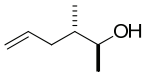
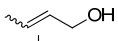
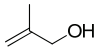
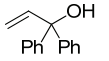
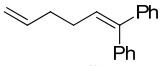
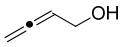
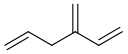
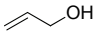
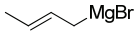
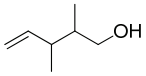
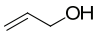
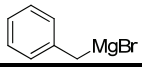
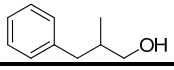
Some of the earliest reports of carbometalations of alkenes involve directing groups such as allylic and homoallylic alcohols. Allyl Grignard reagents were first shown to add uncatalyzed to homoallylic alcohols;[5] these were described in Chapter 2. The reaction scope was then extended to include other Grignards as well as organolithium reagents and other directing groups such as ethers, amines, and pyridine.

3.2.1.1. Addition of Grignard Reagents

Additions of Grignard reagents to allylic alcohols are highly regioselective for alkylation at the α position (Table 3.1) and are sensitive to the steric environment of the

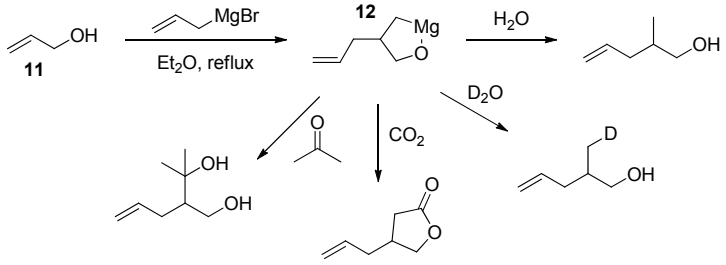
Table 3.1. Allylmagnesiation of allylic alcohols



Entry	Alcohol	Grignard	Product	Yield (%)
1				50
2				16, 8:1 dr
3			-	<5
4			-	<5
5				13
6				80
7				30
8				10

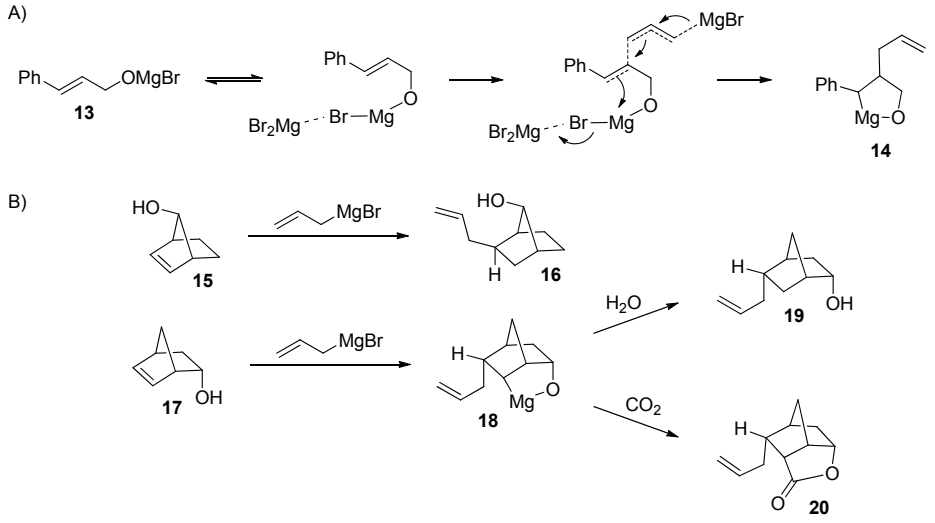
alcohol.[6] Methyl substitution on the carbinol greatly decreases yield (entry 2); allylation of the secondary alcohol provides an 8:1 mixture of diastereomers in 16% yield, favoring the *erythro* product. Methyl-substituted alkenes only provide trace amounts of products (entries 3 and 4). In contrast, cinnamyl alcohol reacts quantitatively and much faster than allyl alcohol.[7] Only 1,1-diphenyl-2-propen-1-ol (entry 5)[8] and allenyl alcohol (entry 6)[9] are selective for the regioisomeric addition product. The Grignard intermediate **12** may be trapped with a variety of electrophiles (Scheme 3.3).[6]

Scheme 3.3. Electrophilic trapping of allylmagnesiation product



Kinetic studies of the allylation of cinnamyl alcohol revealed that the transition state involves at least one alkoxide, an equivalent of allyl Grignard, and at least one magnesium bromide.[7] Thus researchers have proposed a mechanism whereby the magnesium alkoxide acts as an intramolecular electrophile (Figure 3.2A). This mechanism accounts for the observed diastereoselectivity for the allylation of 3-buten-2-ol; the allyl nucleophile would approach the alkene from the face opposite the methyl substituent. Furthermore, investigation of conformationally fixed alcoholic alkenes revealed the allyl addition occurs on the same face of the alkene as the alkoxide (Figure 3.2B).[10] Alcohol **15** was selectively allylated on the *exo* face, which is also the face favored sterically. However, alcohol **17** reverses the inherent facial selectivity to provide the *endo* allylation product (**19**). Trapping alkylmagnesium intermediate **18** with carbon dioxide affords lactone **20**.

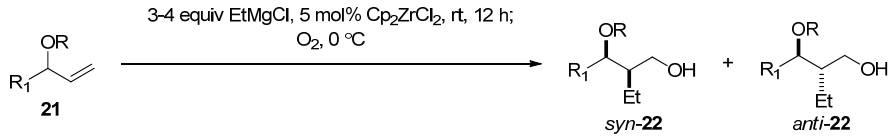
Figure 3.2. Mechanism of allylation

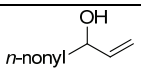
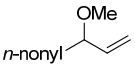
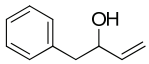
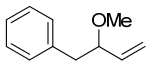
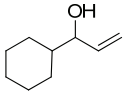
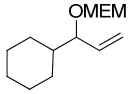


Hoveyda reported a zirconocene-catalyzed ethylmagnesiation of allylic and homoallylic alcohols and ethers (Table 3.2).[11] (See Chapter Two for a discussion on

homoallylic substrates.) In general, allylic alcohols generate the *syn* ethylation products.[12] The diastereomeric ratios are sensitive to changes in solvent and to substitution at the homoallylic position. Higher *syn*:*anti* ratios are observed in Et_2O than in THF and for less bulky substrates (entry 1 vs. 9).[11] In contrast, allylic ethers favor the *anti* diastereomer.[12] While diastereomeric ratios are insensitive to the identity of the solvent, selectivity for the *anti* diastereomer increases for substrates which are substituted at the homoallylic position (entry 12).[11] Although longer alkyl groups are incorporated in the homoallylic alcohols,[13] only ethylmagnesium chloride has been used with allylic substrates.

Table 3.2. Hoveyda's zirconium-catalyzed ethylmagnesiation

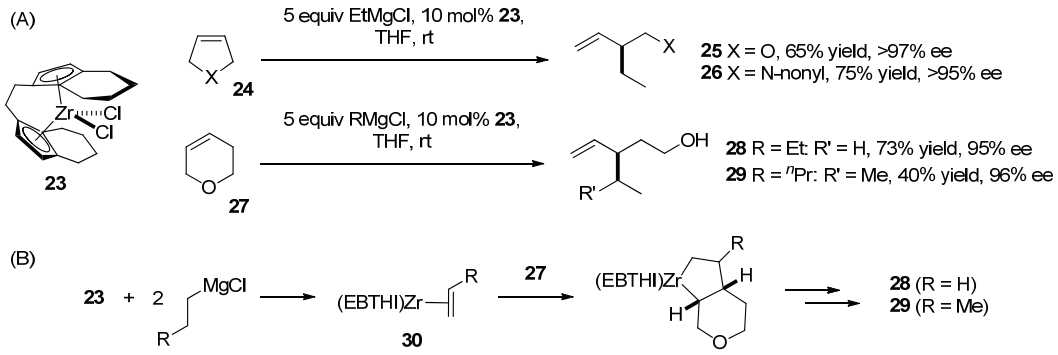


Entry	Substrate	Solvent	Yield	dr
1		Et_2O	70	95:5
2		THF	85	67:33
3		Et_2O	80	11:89
4		THF	70	11:89
5		Et_2O	54	85:15
6		THF	80	50:50
7		Et_2O	90	12:88
8		THF	80	14:86
9		Et_2O	47	75:25
10		THF	70	67:33
11		Et_2O	40	1:>99
12		THF	55	1:>99

While internal allylic alcohols are poor substrates for the zirconium-catalyzed ethylmagnesiation, cyclic alkenyl ethers and amines participate in an asymmetric carbomagnesiation reaction with the chiral catalyst ethylene-1,2-bis(η^5-4,5,6,7-tetrahydro-1-indenyl)zirconium dichloride ((EBTHI)$ZrCl_2$, **23**).[14] The intermediate alkyl

metal undergoes elimination of the heteroatom to open the ring and provide the linear products (Scheme 3.4). The diastereoselective and enantioselective reactions involve the formation of zirconocene-alkene complexes (**30**), which are the active alkylating reagents. Thus *n*-propyl Grignard is incorporated as an *iso*-propyl group (**29**).

Scheme 3.4. Enantioselective carbomagnesiation of alkenes



Other directing groups are also capable of promoting carbomagnesiation of alkenes. Additions to primary and tertiary allylic amines occur with the same regioselectivity as the corresponding alcohols in moderate yields (eq. 1).[15] More recently, pyridine substituted vinyl silanes **32** were found to direct addition of alkylmagnesium chlorides to the proximal alkene (Table 3.3).[16] These reactions improve upon the synthetic utility of directed carbomagnesiation as they achieve near-quantitative yields and incorporate a wider variety of alkyl groups. In addition, alkyl Grignard intermediate **33** is capable of trapping various electrophiles and participates in palladium-catalyzed Kumada couplings.

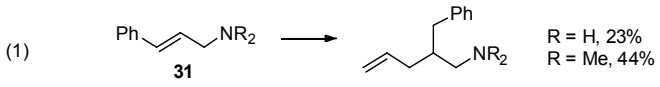
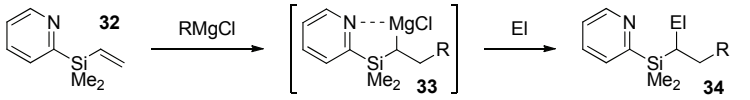


Table 3.3. Pyridyl-directed carbomagnesiation

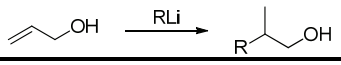


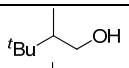
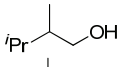
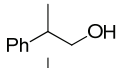
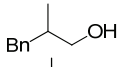
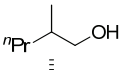
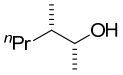
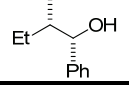
Entry	R	Electrophile (El)	Yield (%)
1	^{i}Pr	H_2O (H)	91
2	^{n}Bu	H_2O (H)	93
3	Ph	H_2O (H)	73
4	Allyl	H_2O (H)	94
5	Allyl	AllylBr (Allyl)	91
6	^{n}Bu	$CH_2NMe_2^+I^-$ (CH_2NMe_2)	93
7	Allyl	PhI, 5 mol% $Pd(PPh_3)_4$ (Ph)	77
8	Allyl	*p*ClPhBr, 2.5 mol% $Pd(PPh_3)_4$ (*p*ClPh)	93

3.2.1.2. Addition of organolithium reagents

The uncatalyzed addition of organolithium to allylic alcohols fares better than the corresponding Grignard additions in that a wider variety of alkyl groups may be incorporated (Table 3.4).[17] The presence of *N*,*N*,*N*',*N*'-tetramethylethylenediamine

Table 3.4. Organolithiation of allylic alcohols

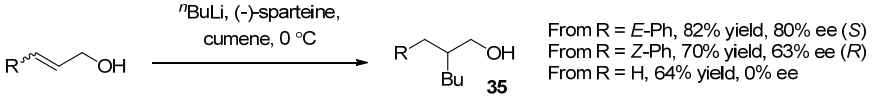


Entry	Alcohol	R	Product	Yield (%)
1		^{t}Bu		22
2		^{i}Pr		48
3		Ph		40
4		Bn		60
5		^{n}Pr		73
6		^{n}Pr		65, >50:1 dr
7		Et		30, 6:1 dr

(TMEDA) facilitates addition by breaking up oligomeric alkyllithium structures and polarizing the carbon-lithium bond,[17, 18] allowing incorporation of primary alkyl lithium species. Furthermore, carbolithiation occurs on the alkene face opposite that of uncatalyzed carbomagnesiation, providing the diastereomeric addition product.[19] In some cases, S_N2' products are observed; *cyclic* allylic alcohols undergo addition-elimination with 1°, 2°, and 3° alkyl lithium species.[17] Tertiary allylic amines also direct carbolithiation with the same regioselectivity.[20, 21]

Marek and Normant achieved an asymmetric variant by performing the carbolithiation of cinnamyl derivatives in the presence of (-)-sparteine (Scheme 3.5).[22] Lower enantioselectivities were observed in coordinating solvents such as Et_2O or THF, but ee's up to 85% were observed in cumene. Trapping of the benzylic lithium intermediates produces two contiguous chiral centers. Although the reported substrate scope is limited to the addition of simple alkyl groups (i.e. *n*Bu, *sec*-Bu, Bn) to cinnamyl derivatives, the reaction may be directed by allylic and homoallylic alcohols, *t*-butyl ethers, and 1°, 2°, and 3° amines. The starting olefin geometry is crucial for good enantioselectivities. While *E*-cinnamyl alcohol generates (*S*)-**35**, the *Z*-olefin provides (*R*)-**35** with (-)-sparteine. No stereoselectivity is observed for allyl alcohol.

Scheme 3.5. Enantioselective carbolithiation of cinnamyl derivatives

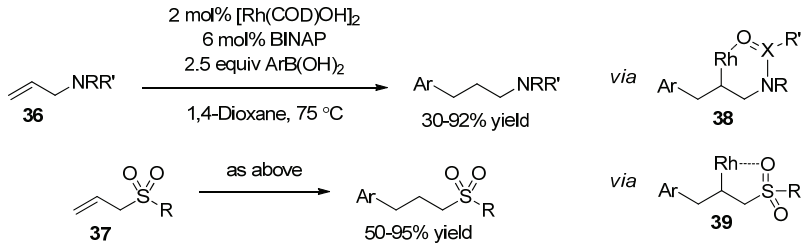


3.2.1.3. Addition of Arylboronic Acids

Protected allylic amines and allylic sulfones are capable of directing a rhodium-catalyzed arylmetalation of alkenes in the presence of arylboronic acids (Scheme 3.6).[23,

[24] When allylic amines are employed, the regioselectivity and yield of the arylation product depend on the identity of the protecting group.[24] Phthalyl and tosyl groups give the highest regioselectivities (>20:1 linear:branched and 7:1, respectively), while lower selectivities are observed for carbamates and amides. Substrates lacking an X==O (i.e. NHBn, NHPh) do not undergo arylation. In general, electron-poor aryl groups are incorporated in higher yields than electron-rich arylboronic acids.

Scheme 3.6. Rhodium-catalyzed arylation of allylic amines and sulfones



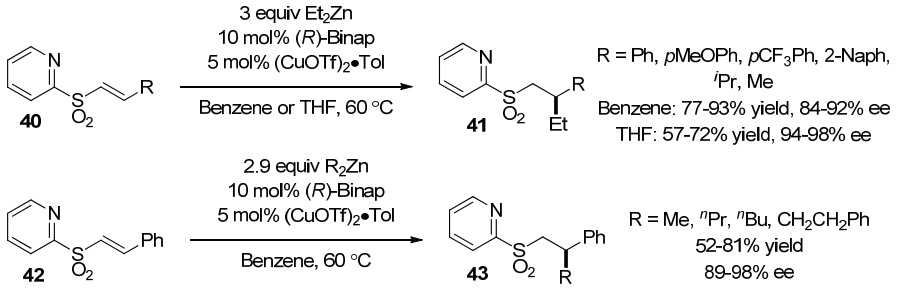
Allyl sulfones are more selective than their protected amine counterparts as only the linear products are observed under the reaction conditions.[23] High yields are obtained whether electron-rich or electron-poor arylboronic acids are employed. However, the method is limited to monosubstituted allylic sulfones or internal propargylic sulfones. Presumably coordination of the rhodium catalyst with the X==O group in both sulfone and amine substrates facilitates regioselectivity and reactivity.

3.2.1.4. Addition of Organozinc and Organotitanium Reagents

Pyridyl sulfones participate in copper-catalyzed asymmetric directed ethylzincations (Scheme 3.7).[25] Although the sulfone activates the alkene toward carbometalation, addition occurs only when the sulfone is substituted with a pyridine (**40**, **42**); phenyl vinyl sulfones do not undergo addition. The reaction affords either high yields or high enantioselectivities based on the solvent employed. Benzene provides

yields between 77-93% and enantioselectivities between 84-92%. Changing the solvent to THF results in decreased yields (57-72%) but improved ee's (94-98%). Furthermore, formation of salt-free diorganozinc reagents from Grignard reagents allows the incorporation of other alkyl groups.

Scheme 3.7. Enantioselective organozincation of vinyl sulfones



Ethyltitanium reagents undergo directed carbometalation with homoallylic alcohols.[26-28] These are described in detail in Chapter Two.

3.2.2.Carbometalation of Activated Alkenes

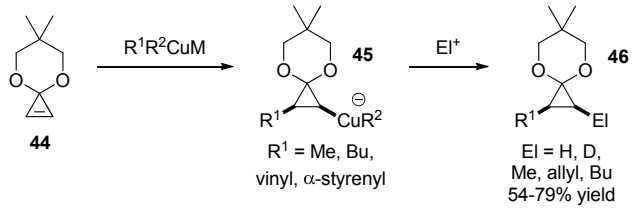
Alkenes may be activated either electronically by their substituents or sterically by their incorporation into strained ring systems. This section describes conditions which facilitate their carbometalation.

3.2.2.1. Carbocupration

Several organocuprates (R_2CuM) add to cyclopropene acetals **44** in good yield within minutes, allowing for the incorporation of methyl, butyl, and vinyl substituents on the cyclopropane (Scheme 3.8).[29] Other organometallic species (RLi, RMgX, RCu) resulted in either recovery of the starting acetal at low temperatures or decomposition at

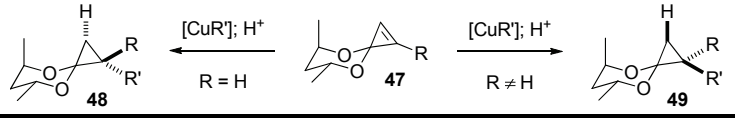
higher temperatures. The stereospecific *syn*-carbocupration provides cupriocyclopropanes **45**, which may be trapped with various electrophiles.

Scheme 3.8. Carbocupration of achiral cyclopropene acetals



When C_2-symmetric substrates **47** are subjected to the carbocupration, the addition occurred with varying levels of diastereocontrol (Table 3.5).[30] Disubstituted alkenes provided moderate levels of diastereoselectivity, favoring **48**. Trisubstituted alkenes are alkylated with the same regioselectivity (R incorporation distal to the axial acetal methyl), but products favor addition to the opposite face of the alkene **49**. The chirality of the acetal effectively transfers to the diastereoselectivity of the newly formed quaternary center. Transformation of the cyclopropane acetal *via* ring opening reactions or by removal of the acetal gives access to enantioenriched quaternary carbons, which are traditionally difficult to prepare.

Table 3.5. Carbocupration of chiral cyclopropene acetals

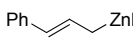
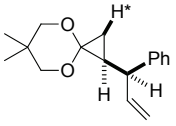
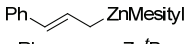
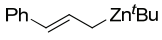
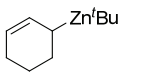
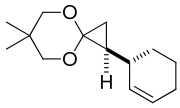
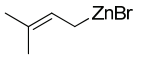
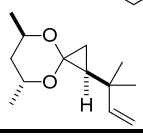
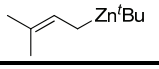


Entry	R	R'$_2$CuM	**48**:**49**	Yield (%)
1	H	Me_2CuLi	72:28	77
2	H	$Bu_2CuMgBr$	65:36	90
3	Et	Me_2CuLi	4:96	89
4	Ph	Me_2CuLi	1:99	65

3.2.2.2. Carbozincation

Nakamura and coworkers explored the uncatalyzed allylzincation of cyclopropene acetals (Table 3.6).[31] Several factors contribute to the high regio- and diastereoselectivities they observed. First, *syn* addition of allyl zinc reagents to C–C double bonds occurs in a highly S_E2' selective fashion, transforming the carbon γ to zinc into a new sp^3 center. The configuration of the newly formed center depends on the geometry of the starting olefin (entry 1 vs. 5). Second, the diastereoselectivity of addition is greatly influenced by the counterion on zinc. Lower selectivities are observed for allylzinc bromides, but exchanging the halide for a bulkier electron-rich ligand increases the diastereoselectivity (entry 1 vs. 3). Third, the diastereoselectivity is reversed when the reaction is performed in DCM as compared with THF (entry 2 vs. 1), indicating the acetal may have some directing effect in the absence of the strongly coordinating solvent. Finally, for C_2-symmetric substrates, olefin facial selectivity also benefits from bulkier ligands on zinc, most likely because of increased steric interactions with the acetal methyl groups (entry 6 vs. 7).

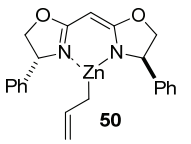
Table 3.6. Diastereoselective allylzincation of cyclopropene acetals

Entry	AllylZnX	Product	dr	Yield (%)
1			82:18	81 (H* = H)
2			38:62[a]	64 (H* = H)
3			94:6	97 (H* = H)
4			96:4	93 (H* = D)
5			99:1	85
6			91:9	94
7			98:2	98

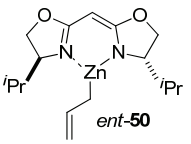
[a]Reaction performed in CH_2Cl_2 instead of THF.

The effect of the zinc ligand on the diastereoselectivity allowed the development of the first enantioselective allylmetalation of olefins.[32] When chiral bis(oxazoline) (BOX) ligands are coordinated with zinc, enantioselectivities up to >98% are observed (Table 3.7). In general, the diastereoselectivities are lower than with the achiral ligands. C_2-symmetric cyclopropene acetals are sensitive to the BOX ligands' preference to generate *R*- or *S*-enantiomers. The matched ligand affords the desired product in >98% ee (entry 4), while the mismatched ligand provides the racemic allylation product (entry 5). In addition, the chiral allyl zinc reagents are capable of adding to substituted cyclopropene acetals to generate quaternary carbon centers enantioselectively (entries 6 and 7).[33] Unfortunately, the synthetic utility of the method is limited by the use of stoichiometric amounts of the chiral ligand and exotic substrates and products.

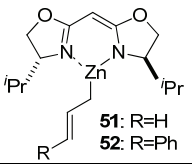
Table 3.7. Enantioselective allylzincation of cyclopropene acetals



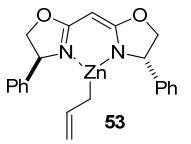
50



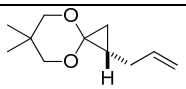
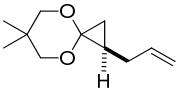
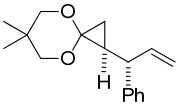
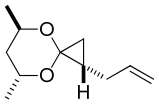
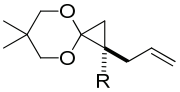
ent-**50**



51: R=H
52: R=Ph



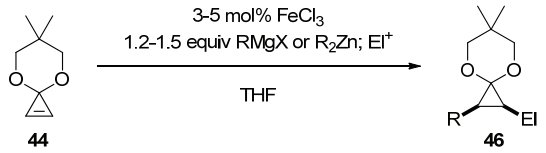
53

Entry	AllylZn(BOX)	Product	% ee (dr)	Yield (%)
1	**50**		96	85
2	*ent*-**50**		98	89
3	**52**		56 (73:27)	86
4	**51**		98	73
5	*ent*-**50**		0	76
6	**53**		>98	95 (R=Et)
7	**53**		98	83 (R=TMS)

3.2.2.3. Iron-catalyzed Carbometalation

Iron catalysts broaden the scope of carbanions available for use in the carbometalation of activated alkenes (Table 3.8). Both Grignard and dialkyl zinc reagents undergo *syn*-addition to cyclopropene acetal **44** in the presence of iron catalysts, and the organometal intermediate may be trapped with various electrophiles.[34] Primary alkyl, vinyl, and aryl Grignards are productive nucleophiles in the carbometalation. The advantage of the dialkyl zinc species is that they are milder nucleophiles; as such, esters may even be a part of the organometallic reacting partner (entry 4). Furthermore, addition of stoichiometric TMEDA and (*R*)-*p*-Tol-BINAP to the iron-catalyzed carbozincation provides enantioenriched substituted cyclopropane acetals **46** (entries 7 and 8).

Table 3.8. Iron-catalyzed carbometalation of cyclopropene acetals



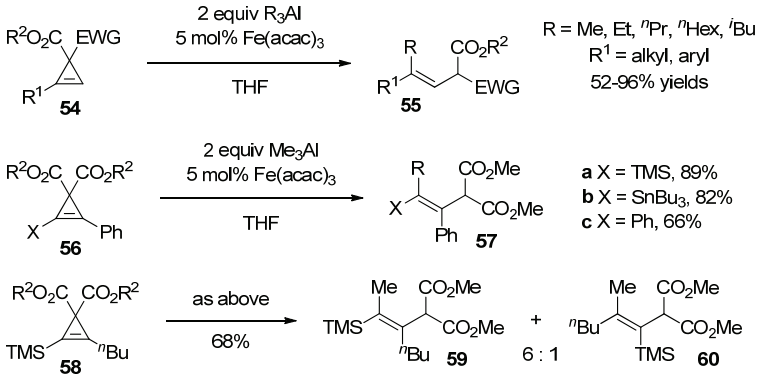
44 **46**

Entry	R_2M	El	Yield (%)
1	PhMgBr	H	96
2	VinylMgBr	H	75
3	Et_2Zn	H	73
4	$(^iPrO_2CCH_2CH_2)_2Zn$	H	76
5	PhMgBr	$CH_2CH{=}CH_2$	85
6	PhMgBr	Me	90
with 3 mol% (*R*)-*p*Tol-BINAP and 5 equiv TMEDA			
7	Pr_2Zn	H	62 (92% ee, *R*)
8	Et_2Zn	H	64 (90% ee, *R*)

When the acetal moiety is replaced by two electron-withdrawing groups, iron catalyzes a tandem carbo*alumination*-ring opening reaction to generate trisubstituted alkenes **55** (Scheme 3.9).[35] Although the optimized conditions require two equivalents of the trialkyl aluminum, yields above 60% are observed with as little as 0.5 equiv Et_3Al.

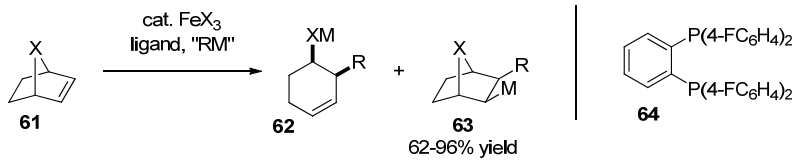
The alkyl substituents are regioselectively incorporated at the more substituted position. Furthermore, the reaction of 1,2-disubstituted cyclopropenes affords tetrasubstituted alkenes in good yields. Alkylation is regioselective for addition to the silyl- or stannyl-bearing carbon when the other substituent is aromatic (**56a-c**); lower selectivities are observed for alkyl substituted substrates (**58**).

Scheme 3.9. Iron-catalyzed tandem carbometalation-ring opening



Oxa- and azabicyclic alkenes **61** also participate in the iron-catalyzed carbometalation reactions (Scheme 3.10).[36] Carbometalation is selective for the *exo*-face of the bicycle. The choice of ligand on iron dictates whether the alkyliron intermediate undergoes β-heteroatom elimination (to give **62**) or transmetalation and electrophilic trapping. Conditions favoring ring-opening involve catalytic amounts of $FeCl_3$, excess TMEDA, and Grignard reagents. Alternatively, ligands that suppress β-hydride elimination such as **64** also suppress β-heteroatom elimination.[37] Optimized conditions to selectively form **63** (20:1 **63**:**62**) require 1.5 equivalents of dialkyl zinc (either R_2Zn or $RZnCH_2TMS$), 2 mol% **64**, and 1 mol% $FeCl_3$. The carbometalation intermediate may be trapped to provide *cis*-dialkylated products.

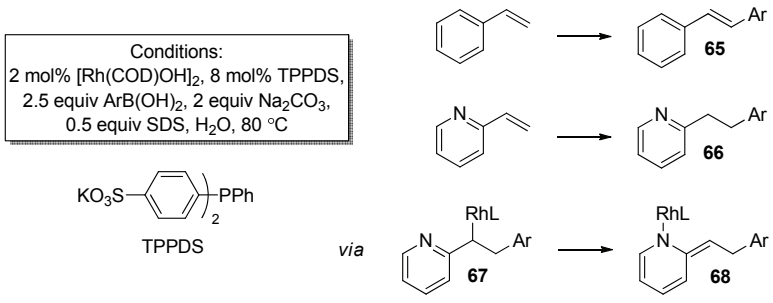
Scheme 3.10. Ring-opening vs. transmetalation of bicyclic alkenes



3.2.2.4. Rhodium-catalyzed Arylation

Vinyl arenes and vinyl hetereoaromatic compounds follow two different pathways in the rhodium-catalyzed arylation with arylboronic acids in aqueous media.[38] When vinyl arenes are used, rhodium catalyzes an addition/β-hydride elimination sequence to provide Heck-type products **65**. Alternatively, when vinyl heteroaromatic compounds are subjected to identical conditions, the initially formed alkyl rhodium intermediate **67** may tautomerize to the N-bound rhodium(I) **68**, which undergoes hydrolysis to provide the hydroarylation product **66**. Both electron-rich and electron-poor arylboronic acids participate in the reactions with both substrates.

Scheme 3.11. Rhodium-catalyzed addition of arylboronic acids



3.2.3.Carbometalation of Unactivated Alkenes

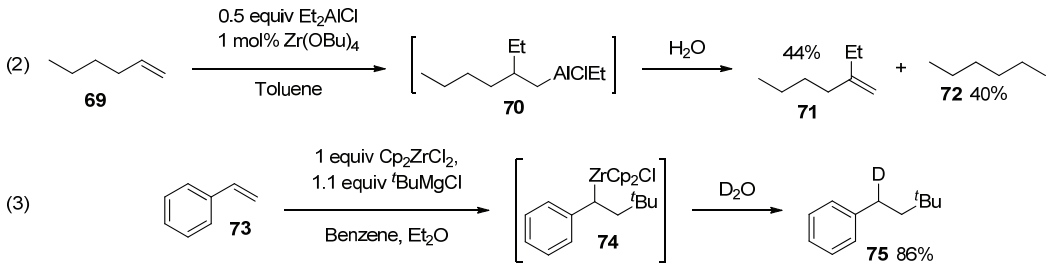
Of the different types of alkenes, unactivated alkenes such as terminal olefins are the most resistant toward reacting with organometallic species. However, even these are known to react either in the presence of a transition metal catalyst or in intramolecular

cases. Group IV metals are particularly adept at facilitating the carbometalation of unactivated alkenes.

3.2.3.1. Group IV Metals in Alkene Carbometalation

Beginning in the 1980s, several groups examined the possibility of using Group IV metals to effect the carbometalation of alkenes. The earliest results provided mixtures of carbometalation and hydrometalation products (Scheme 3.12). Dzhemilev found that zirconium tetrabutoxide catalyzes the ethylalumination of terminal olefins with diethylaluminum chloride (eq. 2), but the instability of the primary alkylaluminum **70** results in regeneration of the C–C double bond (**71**).[39] Cp_2ZrCl_2 shows no catalytic activity in this system. Shortly thereafter, Negishi successfully formed the carbometalation product of styrene and *tert*-butylmagnesium chloride in 86% yield in the presence of stoichiometric amounts of Cp_2ZrCl_2 (eq. 3).[40] Premixing the Grignard and zirconocene results in hydrometalation.

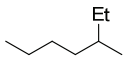
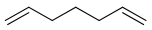
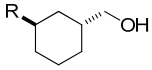
Scheme 3.12. Early examples of carbometalation with zirconium



Changing the nature of the organometallic species allowed the development of catalytic protocols (Table 3.9). Although it is ineffective as a catalyst with dialkylaluminum chlorides, Cp_2ZrCl_2 successfully catalyzes the addition of diethylmagnesium, ethyl Grignard, and *tri*ethylaluminum to the internal carbon of terminal alkenes with minimal amounts of the oxidative addition product (entries 1-3).[41-

[43] Catalytic amounts of titanium(IV) are also sensitive to the nature of the organometallic species. $TiCl_4$, $Ti(OBu)_4$, and $Ti(O^iPr)_4$ are all capable of catalyzing the addition of dialkylaluminum species to terminal olefins (entries 4-7). [41, 44] Use of alkylaluminum dichlorides and trialkylaluminum provide only starting material.[41, 44]

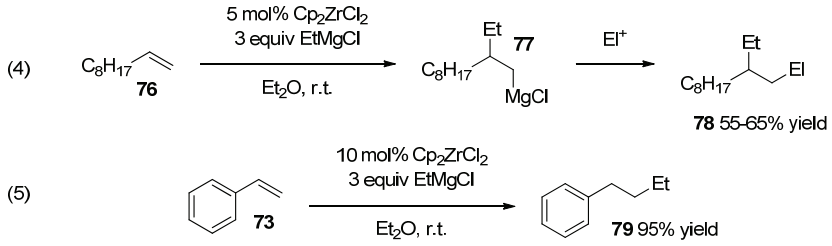
Table 3.9. Productive combinations of Group IV catalysts and nucleophiles

Entry	Alkene	Catalyst (mol %)	RM (equiv)	Product	Yield (%)
1	1-hexene	Cp_2ZrCl_2 (1)	Et_2Mg (1.5)		93
2		"	EtMgBr (1.5)		53
3		Cp_2ZrCl_2(0.7)[a]	Et_3Al (0.33)		90-98[b]
4		$TiCl_4$ (1)	Et_2AlCl (0.5)		>90[b]
5		$Ti(O^iPr)_4$ (2)	R_2AlCl (0.6)		R = Et, 88[c]
6					R = ^{i}Bu, 57[c]
7					R = ^{n}Pr, 76[c]

[a]4 mol% $^i Bu_3Al$ to activate Cp_2ZrCl_2. [b]No specific yield given. [c]After trapping with O_2.

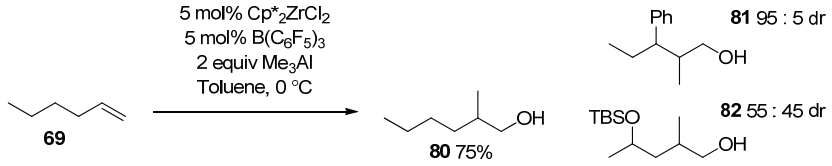
The zirconium-catalyzed carbometalation was further explored by various research groups, leading to three main systems. Hoveyda's conditions (eq. 4), described in part in Section 3.2.1.1, improve the yield of zirconocene-catalyzed carbometalations involving ethyl Grignard reagents.[12] Increasing the catalyst loading to 5 mol% and doubling the amount of EtMgBr provides the terminal alkyl metal species **77**, which may be trapped with various electrophiles in up to 65% yield. No diastereoinduction is observed for substrates containing only alkyl substituents at the allylic position.[14, 45] Negishi's protocol affords further improved yields (95% from styrene) when 10 mol% Cp_2ZrCl_2 and 3 equivalents of EtMgBr are used (eq. 5).[43, 45]

Scheme 3.13. Hoveyda's and Negishi's ethylmagnesiation



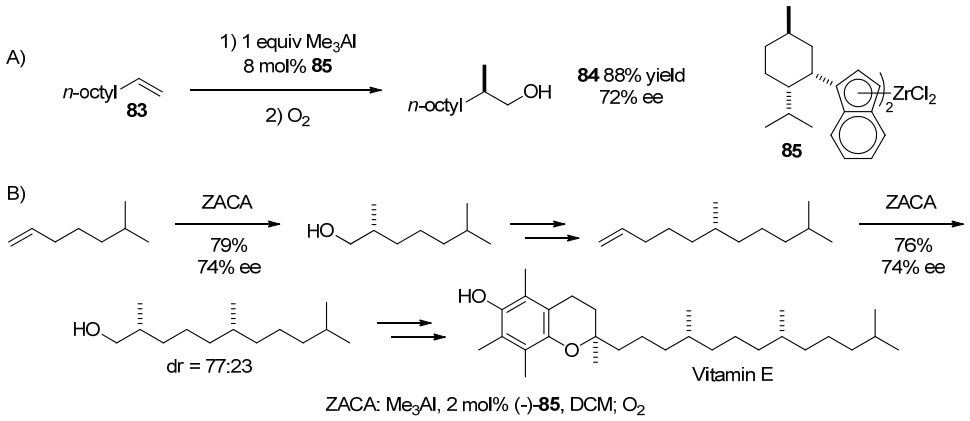
Waymouth's conditions employ catalytic amounts of $Cp^*_2ZrMe_2$ and $B(C_6F_5)_3$ to perform methylaluminations of terminal olefins in toluene (Scheme 3.14).[46] Good diastereocontrol is observed with branching at the allylic position (**81**), but homoallylic substituents (**82**) provide almost no diastereoinduction.[47]

Scheme 3.14. Waymouth's methylalumination



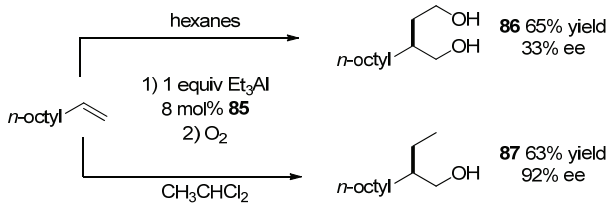
Two significant contributions from the Negishi Laboratory further expand the synthetic utility of the zirconium-catalyzed carboalumination reaction. First, changing the catalyst to dichlorobis(1-neomenthylindenyl)zirconium ($(NMI)_2ZrCl_2$, **85**) provides an enantioselective methylmetalation protocol for terminal alkenes, producing the alcohol in up to 85% ee (Scheme 3.15).[48] Methylation occurs exclusively on the *re* face of the alkene. This procedure, known as the ZACA reaction (Zr-catalyzed asymmetric carboalumination of alkenes), has been utilized in the total sysnthesis of vitamin E to install two of the molecule's three chiral centers (Scheme 3.15B).[49]

Scheme 3.15. Negishi's asymmetric carboalumination



Second, changing the solvent from hexanes to 1,1-dichloroethane alters the product selectivity (**86** vs. **87**) and dramatically increases the enantioselectivity (Scheme 3.16).[50] When longer 1° alkyl groups are used, they are also regioselectively incorporated as linear chains at the internal position; no isomerization to the *iso*- or *sec*-alkyl groups is observed, indicating different operating mechanisms in chlorinated versus nonpolar solvents.

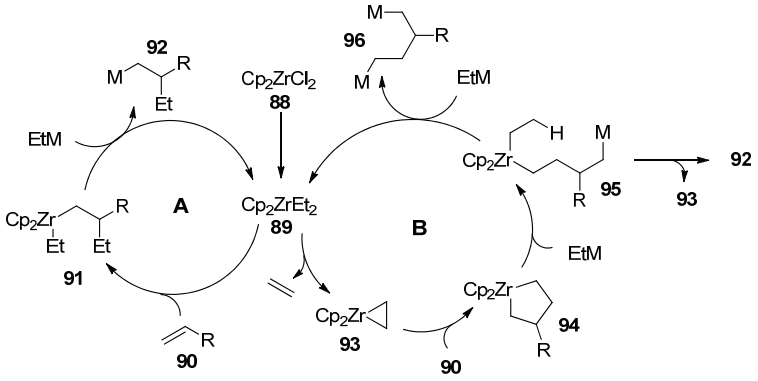
Scheme 3.16. Product selectivity based on solvent



The reactions with ethyl and higher alkyl metals are believed to proceed as follows. Zirconocene dichloride enters the catalytic cycle by transmetalation of two alkyl groups, shown here as ethyl (Figure 3.3). Depending on the reaction conditions, diethylzirconocene **89** may follow two different pathways. In chlorinated solvents (Negishi's conditions, M=$AlEt_2$), the reaction follows a noncyclic mechanism (catalytic

cycle A) as evidenced by the lack of isomerization when *n*-alkyl groups longer than ethyl are used. Carbometalation of the alkene is followed by transmetalation to form alkyl metal **92**.[50]

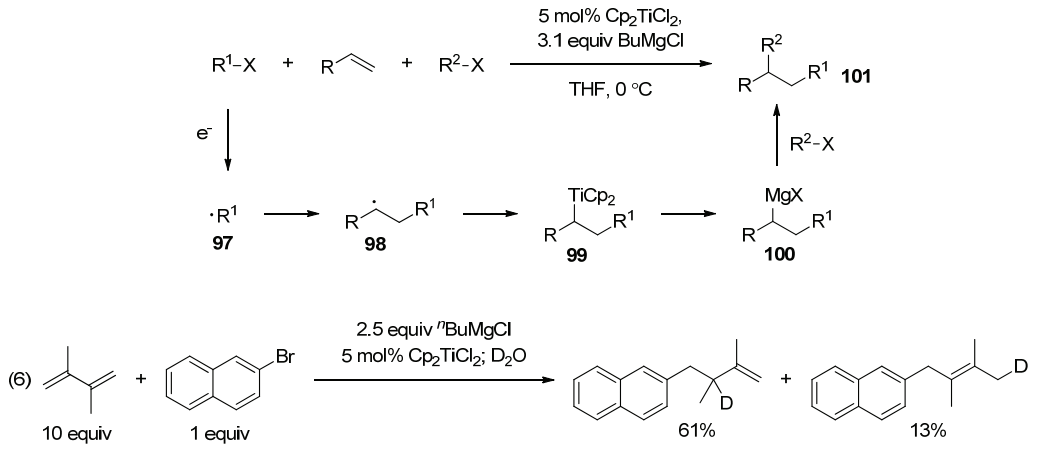
Figure 3.3. Mechanism of zirconium-catalyzed carbometalation



In non-chlorinated solvents, the zirconacyclopropane is formed and undergoes a regioselective addition to the alkene, generating zirconacyclopentane **93** (catalytic cycle B).[43, 51, 52] Site-selective transmetalation with an equivalent of EtM opens the cyclopentane. At this point, the reaction can follow one of two courses. Hoveyda performed extensive mechanistic studies with the allylic and homoallylic oxygenated alkenes to show that the dialkylzirconocene transfers a hydrogen from the ethyl ligand on **95** to generate zirconacyclopropane and **92**. That linear alkylmetal species (i.e. ^{n}Pr and ^{n}Bu) are incorporated as branched (i.e. ^{i}Pr and ^{s}Bu) groups further supports an alternative mechanism from that observed by Negishi (pathway A, chlorinated solvents).[43, 51, 52] Alternatively, transmetalation of **95** with EtM provides dimetal species **96**. The formation of **96** is favored over **92** for conditions involving either alkylaluminum species or a large excess of EtMgX in nonpolar solvents.[52]

In contrast to the zirconocene-catalyzed alkylations, titanocene catalyzes sequential alkylations at both termini of styrenes and dienes in the presence of *n*-butylmagnesium chloride and alkyl halides (Figure 3.4).[53, 54] When an excess of alkyl halide is used, the same alkyl group is incorporated at both positions (**101**, $R^1=R^2$). When two different alkyl halides are present, the more substituted alkyl halide (3°>2°>1°) is incorporated at the terminal position while the internal position is alkylated by less-hindered alkyl halides (1°>2°). The reaction is believed to occur via a radical mechanism. In the first alkylation step, a reduced titanocene transfers an electron to an alkyl halide. The alkyl radical **97** then adds to the alkene before combination of the new alkyl radical **98** with titanocene. Transmetalation to magnesium allows the second alkylation to take place *via* S_N2 displacement of the second alkyl halide. Because hindered alkyl halides are reluctant to undergo S_N2 displacement, Grignard intermediate **100** may be trapped with alternative electrophiles such as benzoyl chloride and D_2O.[53] Although only demonstrated with one example, titanocene catalyzes the radical *aryl*ation of a diene and an aryl bromide (eq. 6).

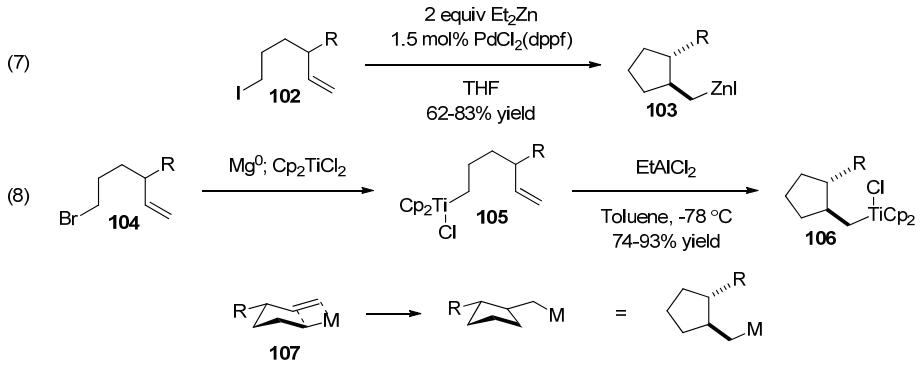
Figure 3.4. Titanocene-catalyzed double alkylation of alkenes



3.2.3.2. Intramolecular Carbometalation

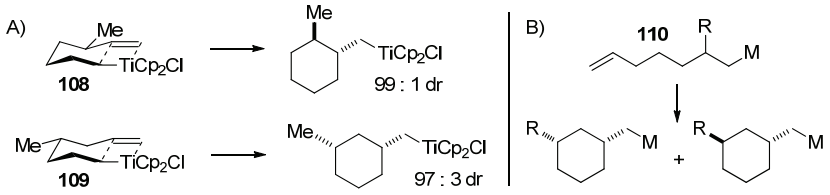
Tethering the carbanion with an alkene facilitates carbometalation by increasing the proximity of the reaction partners. Thus *n*-halo-1-alkenes are capable of cyclization upon metal-halogen exchange (Scheme 3.17). For example, 6-iodo-1-hexenes **102** undergo a palladium-catalyzed carbozincation to provide the 5-*exo*-cyclization products **103** (eq. 7).[55] Similarly, 6-bromo-1-hexenes **104**, upon formation of the alkyl titanocene, cyclize in the presence of Lewis acidic $EtAlCl_2$ with the same exclusive selectivity for 5-*exo* over 6-*endo* products (eq. 8).[56] Neither the Grignard intermediate nor the alkyl titanocene **105** *sans* $EtAlCl_2$ undergo cyclization. When allylic substituents are present, the cyclization is highly selective for the 1,2-*trans* substituted cyclopentane. This diastereoselectivity may be explained in terms of a chair-like transition state **107** with preferential placement of the allylic group in an equatorial position (Scheme 3.17).

Scheme 3.17. Diastereoselective 5-*exo* cyclization



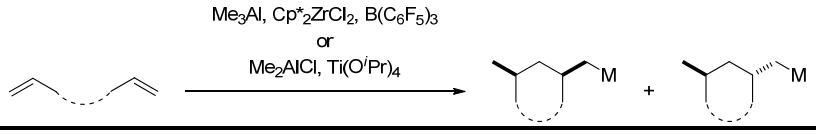
Diastereoselectivity in the cyclization of branched 7-bromo-1-heptenes is also controlled by a chair-like transition state (Scheme 3.18A).[57] Methyl substitution at either the C3 (**108**) or C4 (**109**) positions gives greater than 97:3 diastereoselectivities; distal methyl substitution at C5 provides no diastereoinduction (50:50 dr). The diastereomeric

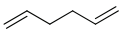
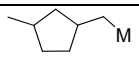
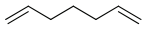
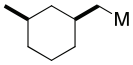
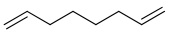
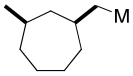
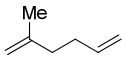
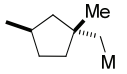
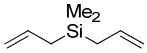
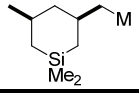
Scheme 3.18. Diastereoselectivity of 6-*exo* cyclizations



ratio when C6 is substituted greatly depends on the nature of the metal center (Scheme 3.18B). For titanocene (**110**, M = $TiCp_2Cl$), the *trans* product is favored (81:19 dr);[57] when titanium ligands are alkoxides (**110**, M = $Ti(O^iPr)_3$, the products greatly favor the *cis* adduct (5:>95 dr).[44]

Table 3.10. Diastereoselectivity of tandem carbometalation-cyclization



Entry	Substrate	Product	dr (*cis*:*trans*) M = Zr	dr (*cis*:*trans*) M = Ti
1			70 : 30	5 : >95
2			60 : 40	>95 : 5
3			65 : 35	[a]
4			0 : 100	2 : >98
5			100 : 0	>89 : 11

[a]No cyclization observed.

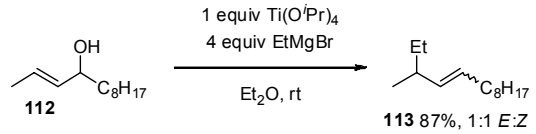
1,*n*-dienes **111** may undergo tandem carbometalation-cyclization reactions under Group IV catalysis. The catalyst involved determines the relative stereochemistry of the newly-formed stereocenters and the resulting ring size (Table 3.10). Waymouth's zirconocene-catalyzed methylalumination system generally provides 1,3-*cis*-substituted cyclopentanes,[46, 47] while product diastereoselectivity in Negishi's titanium-catalyzed

carboalumination changes based on ring size.[44] Both systems provide the same diastereomer from 1,6-dienes (entries 2 and 5) and from 1-methyl-1,5-hexadiene (entry 4).

3.2.4. Reductive Cross-coupling of Allylic Alcohols with Titanium Reagents

While zirconium catalyzes the carbometalation of unactivated terminal alkenes regioselectively at the internal carbon, the addition of organotitanium species to allylic alcohols and ethers typically occurs with the opposite regioselectivity to give the S_N2' displacement products. Kulinkovich first reported the titanium-mediated ethylation of

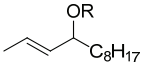
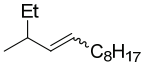
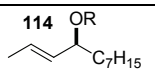
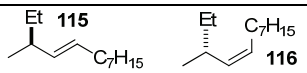
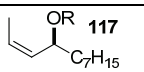
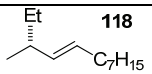
(9)



112 **113** 87%, 1:1 *E*:*Z*

112 with exclusive alkylation at alkene carbon distal to the alcohol.[58, 59] Although the reaction proceeds to 35% yield with 0.1 equiv Ti(O^{i}Pr)$_4$, up to 87% yields are obtained with stoichiometric quantities of titanium. The optimized conditions utilize 3-4 equiv EtMgBr and 1 equiv Ti(O^{i}Pr)$_4$ in Et_2O at room temperature (eq. 9). The geometry of the newly formed olefin is related to the nature of the allylic oxygen substituent; alcohols react with no stereoselectivity (Table 3.11, entry 1), while ethers are more selective for

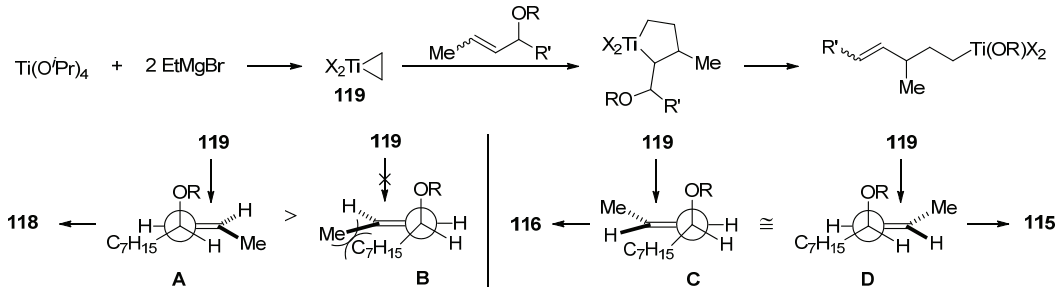
Table 3.11. Titanium-mediated reductive ethylation

Entry	Substrate	Product	R	*E*:*Z*	Yield (%)
1			H	1:1	87
2			Me	7:3	72
3			THP	95:5	71
4	 **114**	 **115** **116**	H	1.5:1	77
5			Me	2.2:1	70
6	 **117**	 **118**	H	>20:1	82
7			Me	7.5:1	74

the *trans* isomer (entries 2 and 3). In addition to the ethylation products, reductive elimination products were also observed in up to 50% for tertiary alcohols.

Cha later further explored the titanium-mediated alkylation and provided a stereochemical model for the observed selectivities.[60] The starting olefin geometry is more important than the substitution on the allylic oxygen to product *E*:*Z* selectivity (Table 3.11, entries 4-5 vs. 6-7). *E* alkenes typically provide lower *E*:*Z* ratios in the S_N2' products while *Z* alkenes give up to >20:1 selectivity. Cha demonstrated that a directed *syn*-addition of **119** is followed by *syn*-elimination of the β-oxygen (Figure 3.5). Thus $A^{1,2}$ strain restricts *Z* olefins to conformer **A**, facilitating a highly stereoselective reaction. In contrast, *E* olefins **114** are less bound by the same allylic strain, and *syn*-carbometalation occurs from both conformers **C** and **D**.

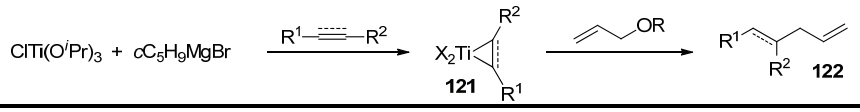
Figure 3.5. Allylic strain determines olefin geometry

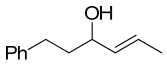
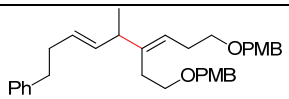
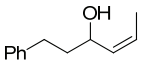
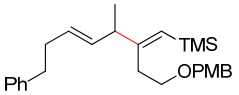
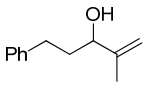
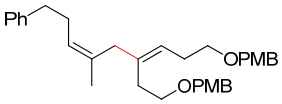
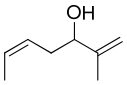
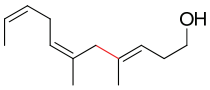
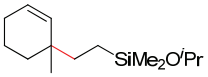
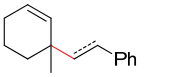
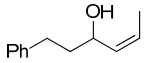
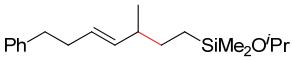
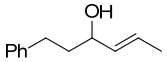
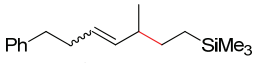
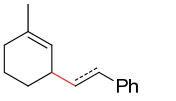
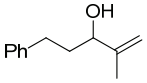
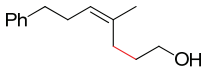
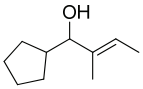
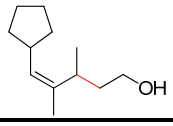


Although the reactions with alkyl Grignard reagents are effectively limited to ethylation,[60] allylic alcohols are capable of undergoing reductive couplings with alkenes[60, 61] and internal alkynes.[60, 62] These reactions require an excess of cyclopentylmagnesium chloride to generate the low-valent titanium-alkene or -alkyne complexes **121** (Table 3.12). Similar to the ethylation reactions, the *E*:*Z* selectivity depends on the starting alkene geometry with *Z*-alkene starting materials leading to

higher *E* selectivities (entry 1 vs. 2). 1,1-disubstituted allylic alcohols selectively provide *Z* products (entry 3). While coupling at either terminus of symmetrical alkynes leads to

Table 3.12. Reductive coupling of allylic alcohols



Entry	Alkene	Product	*E*:*Z*	Yield (%)[a]
1			1:1	67
2			8:1	59
3			1:>20	72
4[b]			1:>20	54[c]
5			-	74
6			-	75 (11:1)
7			10:1	53
8			1:1	58
9			-	35 (10:1)
10			1:>20	58[d]
11			1:>20	69[d]

[a]Saturated:Unsaturated products in parenthesis. [b]Alkyne substrate, R^1=CH$_2$CH$_2$OTBS R^2=Me. [c]Yield after desilylation. [d]Yield after oxidation.

the same product, unsymmetrical alkynes may give rise to regioisomeric alkenes. However, two types of unsymmetrical alkynes have shown excellent levels of regioselectivity – methyl-substituted alkynes couple at the methyl-substituted carbon

(entry 4),[63] and silyl-substituted alkynes are regioselective for coupling at the carbon distal to the silyl group (entry 2).[62] Thus the reductive coupling with alkynes provides an entry to highly substituted 1,4-dienes.

Reductive coupling with alkenes also leads to highly substituted olefins (Table 3.12, entries 5-10).[60, 61] However, the scope of alkenes available to participate in the coupling is limited; only styrene and vinyl silanes react efficiently. Both types of alkenes are incorporated regioselectively at the unsubstituted carbon and are capable of adding to trisubstituted alcoholic olefins, generating quaternary carbon centers (entries 5 and 6). Reactions with styrene provide mixtures of alkylated and alkenylated products (entries 6 and 9). In contrast, vinyl silanes give only the alkylation products and may be oxidized to the alcohol. The stereochemistry observed in the tandem coupling-oxidation reactions of olefins with substitution proximal to the alcohol (entries 10-11) complements the olefin stereochemistry obtained from Claisen rearrangements.

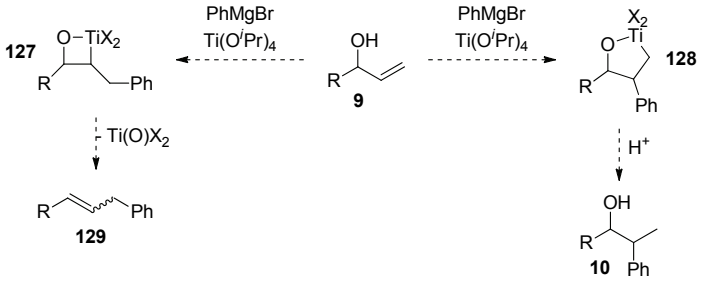
3.3. Aryltitanation of Allylic Alcohols

3.3.1. Optimization of Aryltitanation

During the course of exploring the substrate scope for the oxidative arylation of homoallylic alcohols (see Chapter Two), I wondered how the structurally-related allylic alcohol would perform. Literature precedent indicated the organotitanium species would add in an S_N2' fashion, eliminating the alcohol (**129**).[60, 61] Alternatively, regioisomeric addition of the aryltitanium would preserve the alcohol by providing a 5-membered oxatitanacycle **128**, reminiscent of an intermediate in the oxidative arylation. I was

pleased to find that subjection of **9** to the optimized oxidative arylation conditions provided a mixture of carbometalation **10** and substitution products **129**, favoring **10**. Because of the paucity of reactions for the arylmetalation of alkenes in the chemical literature and the potential synthetic utility of the products, the aryltitanation of allylic alcohols was further investigated.

Figure 3.6. Regioisomeric products from the aryltitanation of allylic alcohols

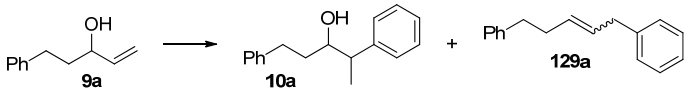


Among the first parameters tested was the identity of the aryl metal nucleophile. In the oxidative arylation reaction, aryl Grignards are essential for reactivity. However, the ability to employ phenyl lithium would expand the synthetic utility of the carbometalation reaction as lithium-halogen exchange represents a facile entry to functionalized aryl lithium species. Employment of PhLi as the nucleophile resulted in approximately 25% conversion of **9a** without providing any carbometalation product, precluding the further use of aryl lithium reagents in the aryltitanation. As in the oxidative arylation, the aryltitanation is specific for aryl Grignard reagents.

I next examined the effect of different solvents (Table 3.13). Both ether and THF inhibited the carbometalation reactivity, providing only starting material. Hexanes, dimethoxyethane, and 1,2-dichloroethane allowed 25-50% conversion of **9a**. The product ratios favored carbometalation (**10a**) over substitution (**129a**) 2:1 to 3:1. In toluene, the

product selectivity was reversed to favor **129a**, but conversion remained at approximately 50%. DCM was found to be the best solvent for the arylation reaction as it provided the highest conversion and selectivity for **10a**. Reactions in which the Grignard was added as a 1.0 M solution in THF were unsuccessful even though the reactions were performed in DCM.

Table 3.13. Product ratios in various solvents



Solvent	**9a**	**10a**	**129a**
Et_2O	94	1	5
THF	100	0	0
Toluene	47	22	31
Hexanes	57	27	16
DME	68	21	10
DCE	78	18	4
DCM	35	49	16

0.1 mmol scale, 2 equiv PhMgBr, 1 equiv $Ti(O^iPr)_4$, 0.16 M in solvent, 20 h. GC yields.

Subsequently, the reaction was performed in DCM at various concentrations. Initially dramatic increases in yield and mass balance were observed as the concentration decreased from 1.0 M to 0.05 M. However, at 1.0 M, a significant portion of the solvent comes from the 3.0 M solution of PhMgBr in ether. Because of the sensitivity of the reaction to the solvent, the Et_2O could potentially contribute to the decreased yields at higher concentrations; elimination of Et_2O from the reaction would allow for differentiation of the effects of solvent idenity and concentration in DCM. Thus the ethereal solvent was removed from the PhMgBr in vacuo and replaced with DCM prior to addition of the allylic alcohol.[64] In the absence of Et_2O, the concentration had the biggest influence on product selectivity. Higher concentrations were less selective for

carbometalation over substitution whereas lower concentrations achieved up to 6:1 selectivities. Unfortunately, the seemingly improved selectivity does not follow any well-defined trend, which suggests reproducing the results would be problematic.

Table 3.14. Effect of concentration and solvent system on product distribution

	PhMgBr with Et_2O				PhMgBr without Et_2O			
Conc.	Entry	% conv.	**10a**	**129a**	Entry	% conv.	**10a**	**129a**
1.0 M	1	60	4	10	6	77	31	20
0.5 M	2	74	25	10	7	57	37	10
0.25 M	3	77	30	9	8	60	39	9
0.1 M	4	86	41	10	9	29	13	3
0.05 M	5	90	39	11	10	81	62	10

0.1 mmol scale, 2 equiv PhMgBr, 1 equiv $Ti(O^iPr)_4$, in DCM, 20 h. GC yields based on internal standard.

Several different titanium(IV) sources were subjected to the reaction conditions. Unlike the oxidative arylation of homoallylic alcohols, $ClTi(O^iPr)_3$ and $Ti(O^iPr)_4$ favored different products in the carbometalation reaction – $ClTi(O^iPr)_3$ favored substitution whereas $Ti(O^iPr)_4$ was selective for carbometalation. When the $Ti(OR)_4$ contained primary or tertiary alkoxides (R = Me, Et, ^{n}Bu, ^{t}Bu), conversion ranged from 30-50% with no more than 6% of the carbometalation product formed. $Ti(O^cHex)_4$ showed similar conversion (61%) and selectivity (7:1 carbometalation:substitution) to the isopropoxide variant; as $Ti(O^iPr)_4$ is much more commonplace in organic laboratories, no further experiments were performed with $Ti(O^cHex)_4$. Chelating secondary alkoxides resulted in up to 30% conversion but provided no desired product. Because zirconium is in the same group as titanium and is a viable catalyst for carbometalation in other systems, zirconium(IV) sources were also tested in the carbometalation reaction (Table 3.15). A full equivalent of $Zr(O^iPr)_4{\cdot}^i$PrOH was able to provide the desired product with the same

selectivity as $Ti(O^iPr)_4$. Cp_2ZrCl_2 was unable to catalyze the arylation, but addition of $Ti(O^iPr)_4$ rescued the reactivity.

Table 3.15. Zirconium in the arylmetalation of allylic alcohols

Zirconium[a]	% conversion	**10a**	**129a**
1 equiv $Zr(O^iPr)_4$.^{i}PrOH	52	23	4
0.1 equiv Cp_2ZrCl_2	30	-	-
0.1 equiv Cp_2ZrCl_2, 1 equiv $Ti(O^iPr)_4$	81	44	10

[a]with 3 equiv PhMgBr in DCM. ^{1}H NMR yields based on external standard.

In hopes of further increasing the yield and selectivity, I examined the effect of various additives. Various alkoxides were screened in the event that a titanium "ate" complex facilitated arylation (Table 3.16, entries 2-5), but conversion decreased in every case. Phosphine ligands have been shown to stabilize organotitanium species[65] and were tested in the aryltitanation system (entries 6-14). Although initially they appeared to increase the mass balance, further optimization was fruitless, giving no improvement

Table 3.16. Additives screened in aryltitanation

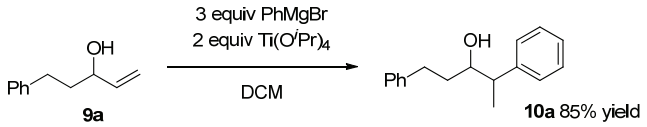
Entry[a]	Addititve	% conv.	**10a**	**129a**	Entry	Additive	% conv.	**10a**	**129a**
1	none	83	43	10	15	TMEDA	36	8	1
2[b]	H_2O	60	24	17	16	Et_3N	75	39	9
3[b]	KO^tBu	33	8	5	17	Pyridine	56	28	5
4[b]	^{i}PrOH	67	42	16	18	$ZnCl_2$	60	3	35
5[b]	MeOH	70	39	17	19	$InCl_3$	22	-	-
6	PBu_3	83	40	7	20	KCl	85	48	10
7	$P(OMe)_3$	39	11	2	21	TMSCl	94	27	13
8	PPh_3	83	49	9	22	LiCl	74	41	7
9	dppm	90	57	11	23	LiBr	80	39	8
10	dppe	83	59	14	24	LiOAc	63	26	6
11	dppp	81	62	12	25	K_2CO_3	71	35	8
12	dpppentane	80	60	11	26	MAO	80	30	17
13	dpph	77	58	11	27	$MgBr_2$•(OEt_2)	89	27	19
14	rac-Binap	80	61	13	28	4Å M.S.	79	30	10

[a]Unless otherwise noted, 1.0 equiv additive, 3 equiv PhMgBr, 2 equiv $Ti(O^iPr)_4$ in DCM. GC yields. [b]0.1 equiv additive, 2.1 equiv PhMgBr, 1 equiv $Ti(O^iPr)_4$ in DCM.

over the additive-free conditions (entry 1). Similarly, nitrogen-based ligands were unable to improve selectivity or yield (entries 15-17). In the reaction of the homoallylic alcohols with phenyl titanium reagents, indium chloride and zinc chloride each reverse the selectivity to favor carbometalation over oxidative arylation.[66] However, with allylic alcohols, $ZnCl_2$ greatly favored substitution products **129a**, and $InCl_3$ gave neither carbometalation nor substitution (entries 18-19). Other salts were also tested to no avail (entries 20-27).

Throughout the screening process incomplete conversions were consistently observed even after allowing the reactions to stir overnight. Dropwise addition of the Grignard, portionwise addition of the Grignard and titanium, and increasing the number of equivalents of "$PhTi(O^iPr)_3$" from 1 to 2 were all similarly unsuccessful at increasing conversion over a course of 20 hours. However, full conversion of the starting material is achieved after 64 hours when 3 equiv PhMgBr and 2 equiv $Ti(O^iPr)_4$ are employed. With these optimized conditions, **10a** is isolated in 85% yield (eq. 12).

(12)



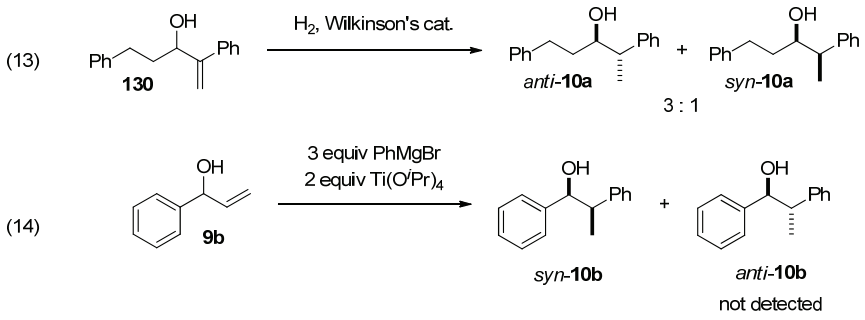
9a **10a** 85% yield

3.3.2. Diastereoselectivity in the Aryltitanation

The aryltitanation of allylic alcohols is highly diastereoselective as only a single diastereoisomer has been observed for every reaction providing **10a**. In order to determine which diastereoisomer is formed, allylic alcohol **130** underwent a directed hydrogenation (Scheme 3.19, eq. 13). *Anti*- and *syn*-**10a** were formed in a 3:1 ratio using

Wilkinson's catalyst.[67] The carbometalation product **10a** and the minor product from the directed hydrogenation eluted at the same retention time under identical gas chromatography conditions. Further evidence for the assigned relative stereochemistry was obtained by subjecting benzyl vinyl carbinol **9b** to the aryltitanation reaction (eq. 14). Alcohol **10b** was also formed as a single diastereoisomer. Comparison of **10b** with the reported ^{1}H NMR chemical shifts of both *syn*- and *anti*-**10b** confirmed that the carbometalation products are formed as the *syn* diastereomer.

Scheme 3.19. Determination of relative stereochemistry in aryltitanation

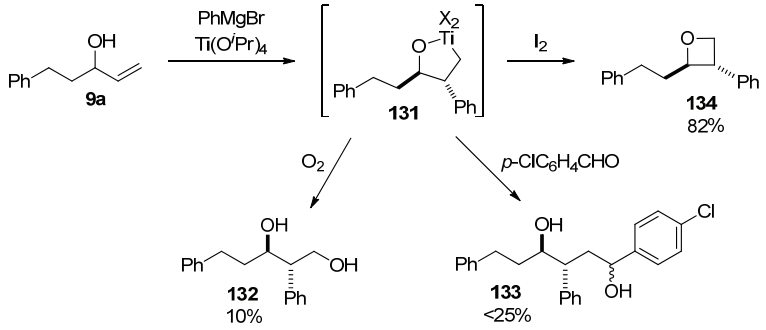


3.3.3. Electrophilic Trapping of Alkyltitanium Intermediates

Upon optimization for **10a**, the ability of titanium intermediate **131** to react with various electrophiles was briefly explored (Scheme 3.20). Thus several different electrophiles typically employed in such trapping experiments were added to the reaction mixtures after complete conversion of **9a**. Of these, pivaloyl chloride and carbon dioxide were not trapped. Sparging the reaction mixture with O_2 provided diol **132** in 10% yield. **10a** and substitution products accounted for the remainder of the starting material. Electrophilic trapping of I_2 afforded oxetane **134** in 82% yield. Presumably the primary

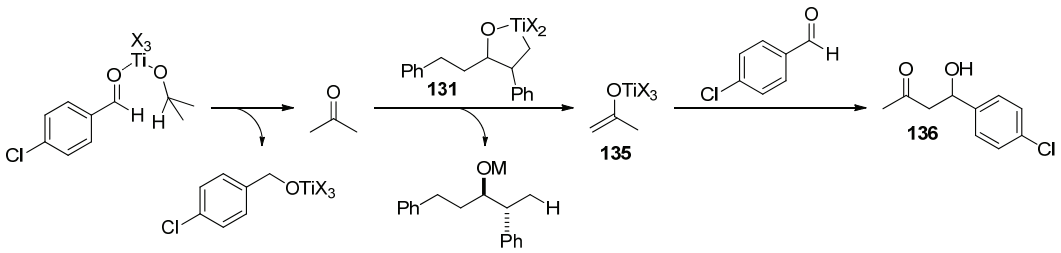
iodide is initially formed but undergoes intramolecular substitution by the proximal alkoxide.

Scheme 3.20. Electrophilic trapping of oxatitanacycle 131



Addition of *p*-chlorobenzaldehyde provided a mixture of several products, including the desired diol **133** as a mixture of epimers, **10a**, *p*-chlorobenzyl alcohol, and β-hydroxy ketone **136**. The mechanism in Figure 3.7 accounts for the formation of each of these products *en route* to **136**. First, a Meerwein-Ponndorf-Verley reaction of benzaldehyde with isopropoxide generates the *p*-chlorobenzyl alcohol and an equivalent of acetone. **131** is quenched by deprotonation of acetone. Finally, aldol addition of enolate **135** to a second equivalent of benzaldehyde affords **136**.

Figure 3.7. Formation of β-hydroxy ketone 136



3.4. Summary

Allylic alcohol **9a** undergoes a regioselective arylmetalation in the presence of stoichiometric amounts of phenyl Grignard and titanium tetraisopropoxide. No arylation occurs in the absence of titanium. Under the optimized conditions, the addition product is formed in 85% isolated yield as a single diastereoisomer, assigned as the *anti*-isomer. Furthermore, the alkyltitanium intermediate **131** may be trapped with I_2, O_2, and *p*-chlorobenzaldehyde in varying yields.

Although optimized conditions have been found, more work is needed to better describe the capabilities and the synthetic utility of the reaction. Neither the scope of the allylic alcohol nor of the aryl Grignard has been investigated at this point. Future work will establish which alkene substitution patterns undergo carbometalation, functional group compatibility, and the electronic and steric effects of substituents on the aryl Grignard. Although several typical electrophiles have been tested with varying success, the list of electrophiles to investigate has not been exhausted. Future work should expand the scope of electrophilic partners and provide conditions that deliver the trapped products in synthetically useful yields.

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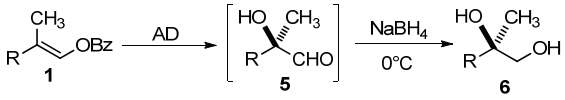
APPENDIX A
Experimental Details and ^{1}H and ^{13}C NMR Spectra for Chapter One Compounds

General:

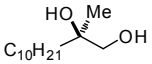
Unless otherwise stated, commercially available reagents were used as received and reactions were performed under a nitrogen atmosphere using freshly purified solvents. Solvents were purified using solvent purification columns purchased from Glass Contour, Laguna Beach, CA. All reactions were monitored by thin-layer chromatography (TLC) and/or gas chromatography (GC). TLC analysis was performed with E. Merck silica gel 60 F254 pre-coated plates (0.25 mm). GC was performed on an HP 6890N autosampling GC with an HP-5 capillary column and equipped with a FID detector. Flash chromatography was performed with indicated solvents using silica gel (particle size 0.032-0.063 μm) purchased from Sorbent Technologies. ^{1}H and ^{13}C NMR spectra were recorded on Varian Inova-500 or Inova-400 spectrometer. Chemical shifts are reported relative to internal chloroform ($CDCl_3$: 1H, δ = 7.26, 13C, δ = 77.26). Coupling constants are in Hz and are reported as d (doublet), t (triplet), q (quartet), p (pentet), sep (septet), and app for apparent. For signals having multiple coupling patterns, the coupling constant are listed in the same order as the pattern (e.g. dt, J = 2.0, 4.0; 2.0 is the coupling constant for the doublet and 4.0 is for the coupling constant for the triplet). Low-resolution mass spectra were acquired on a Shimadzu QP5000 GC/MS equipped with an electron impact ionization source (EI) or on an Agilent 1100 Series LC/MS equipped with a ZORBAX Eclipse XDB-C18 analytical column from Agilent (4.6 x 150mm, 5μm, Part #: 993967-902) and attached to an MSD VL series mass detector equipped with an electrospray ionization source (ES).

General procedure for the preparation of 1,2-diols from enol benzoates:



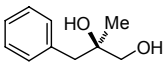
All AD reactions performed followed Sharpless' general procedure.[1] Thus, a 1:1 mixture of ^{t}BuOH/H_2O (0.1M based on olefin) was added to flask containing AD-mix β (1.4 g per 1 mmol of olefin) and the mixture was stirred to produce two clear phases. The resulting solution was then stirred at 0˚C until the dissolved salts precipitated. The olefin (1.0 equiv) in ^{t}BuOH was added and the slurry was stirred vigorously at 0˚C until the reaction was complete (12-24 hours). Once complete, $NaBH_4$ (6 equiv to olefin) was added to the mixture at 0˚C and the reaction was kept at this temperature until reduction was complete (about 2 hours). Saturated NH_4Cl was added and the reaction was extracted 3 times with EtOAc. The combined organic extracts were dried with $MgSO_4$ and concentrated to give crude diol product. The diols were further purified by flash chromatography. The ee's of the diols were determined from their monobenzoylated analogues (BzCl, Et_3N, cat. DMAP, CH_2Cl_2). Specific HPLC conditions and chromatograms are located in the section of the supporting information containing NMR spectra. Absolute stereochemistry was assigned by comparison of the optical rotation to reported values the reported value for **3c**.[2] For **3a**, **3c** and **3e**, we further confirmed that the major enantiomer was the same as obtained from dihydroxylation of the 1,1-disubstituted olefin. Other diols are assigned by analogy.

Characterization data for 1,2-diol compounds:



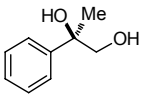
6a: 2-methyldodecane-1,2-diol

Chromatography (35% EtOAc in hexanes) provided 66 mg (78% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 0.88 (t, *J* = 6.7, 3H), 1.16 (s, 3H), 1.19-1.41 (m, 16H), 1.45-1.51 (m, 2H), 1.9 (br s, 2H), 3.41 (d, *J* = 10.9, 1H), 3.47 (d, *J* = 10.9, 1H). ^{13}C NMR ($CDCl_3$) δ = 14.3, 14.4, 21.3, 23.5, 24.0, 29.6, 29.8, 30.5, 32.1, 39.0, 70.0, 73.2. EI-MS (*m/z*): 216 $[M\text{-}CH_3]^+$. HPLC analysis of the monobenzoate (Chiralcel AS-H, 1 mL/min, 3% iPrOH/Hexanes; $t_{r(minor)}$ = 7.1 min, $t_{r(major)}$ = 8.2 min) indicated 96% ee. $[\alpha]^{20}_D$ = -2.4 (c = 0.51, $CHCl_3$).



6b: 2-methyl-3-phenylpropane-1,2-diol

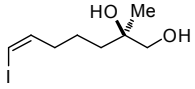
Chromatography (50% EtOAc in hexanes) provided 56 mg (84% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.15 (s, 3H), 1.81 (br s, 1H), 1.84 (br t, *J* = 5, 1H), 2.79 (d, 13.3, 1H), 2.86 (d, *J* = 13.3, 1H), 3.45 (dd, *J* = 10.9, 5.6, 2H), 3.51 (dd, J = 10.9, 5.6), 7.25 (m, 3H), 7.32 (t, *J* = 6.9, 2H). ^{13}C NMR ($CDCl_3$) δ = 23.9, 44.9, 69.5, 73.2, 126.9, 128.6, 130.7, 137.2. EI-MS (*m/z*): 166 $[M]^+$. HPLC analysis of the monobenzoate (Chiralcel AS-H, 1 mL/min, 3% iPrOH/Hexanes; $t_{r(minor)}$ = 18.5 min, $t_{r(major)}$ = 19.5 min) indicated 95% ee. $[\alpha]^{20}_D$ = -2.2 (c = 0.63, $CHCl_3$).



6c: 1-methyl-1-phenylethane-1,2-diol

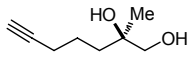
Chromatography (50% EtOAc in hexanes) provided 11 mg (75% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.54 (s, 3H), 2.55 (br s, 2H), 3.64 (d, *J* = 11.2, 1H), 3.81 (d, *J* = 11.2, 1H), 7.29 (t, *J* = 8.5, 1H), 7.38 (t, *J* = 7.9, 2H), 7.46 (d, *J* = 7.9, 2H). ^{13}C

NMR ($CDCl_3$) δ = 26.3, 71.3, 75.1, 125.3, 127.4, 128.7, 145.2. EI-MS (*m/z*): 152 $[M]^+$. HPLC analysis of the monobenzoate (Chiralcel AD-H, 1 mL/min, 3% EtOH/Hexanes; $t_{r(minor)}$ = 36.3 min, $t_{r(major)}$ = 39.9 min) indicated 95% ee. $[\alpha]^{20}_D$ = -5.8 (c = 0.55, EtOH); lit. $[\alpha]^{23}_D$ = -5.8 (c = 0.17, EtOH).[2]



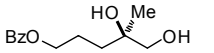
6d: (Z)-7-iodo-2-methylhept-6-ene-1,2-diol

Chromatography (50% EtOAc in hexanes) provided 48 mg (59% yield) of a pale yellow oil. ^{1}H NMR ($CDCl_3$) δ = 1.18 (s, 3H), 1.52-1.53 (m, 4H), 2.15-2.19 (m, 2H), 2.27 (br s, 2H), 3.42 (d, *J* = 10.9, 1H), 3.48 (d, *J* = 10.9, 1H), 6.16-6.23 (m, 2H). ^{13}C NMR ($CDCl_3$) δ = 22.4, 23.5, 35.3, 38.2, 70.0, 73.1, 83.1, 141.1. EI-MS (*m/z*): 255 $[M\text{-}CH_3]^+$. HPLC analysis of the monobenzoate (Chiralcel AS-H, 1 mL/min, 4% iPrOH/Hexanes; $t_{r(minor)}$ = 15.0 min, $t_{r(major)}$ = 18.1 min) indicated 96% ee. $[\alpha]^{20}_D$ = -3.1 (c = 0.61, $CHCl_3$).



6e: 2-methylhept-6-yne-1,2-diol

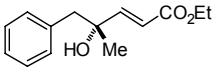
Chromatography (40% EtOAc in hexanes) provided 14.5mg (75% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.17 (s, 3H), 1.57-1.62 (m, 4H), 1.73-2.26 (br s, 2H), 1.96 (t, *J* = 2.6, 1H), 2.19-2.23 (m, 2H), 3.42 (d, *J* = 10.9, 1H), 3.48 (d, *J* = 10.9, 1H). ^{13}C NMR ($CDCl_3$) δ = 19.1, 23.0, 23.4, 37.8, 68.9, 70.0, 73.0, 84.5. EI-MS (*m/z*): 142 $[M]^+$. HPLC analysis of the monobenzoate (Chiralcel OJ-H, 1 mL/min, 6% iPrOH/Hexanes; $t_{r(minor)}$ = 17.7 min, $t_{r(major)}$ = 15.7 min) indicated 95% ee. $[\alpha]^{20}_D$ = -3.0 (c = 0.67, $CHCl_3$).



6f: 4,5-dihydroxy-4-methylpentyl benzoate

Chromatography (75% EtOAc in hexanes) provided 18 mg (87% yield) of a colorless oil. ^{1}H NMR ($CDCl_3$) δ = 1.23 (s, 1H), 1.57-1.72 (m, 2H), 1.82-1.93 (m, 3H), 3.50 (dd, *J* = 22.6, *J* = 10.8, 2H), 4.37 (t, *J* = 6.6, 2H), 7.45 (t, *J* = 7.8, 2H), 7.57 (t, *J* = 7.4, 1H), 8.04 (t, *J* = 8.4, 2H). ^{13}C NMR ($CDCl_3$) δ = 23.5, 23.5, 35.1, 65.5, 70.1, 72.8, 128.6, 129.8, 130.5, 133.7, 166.9. EI-MS (*m/z*): 131 $[M\text{-}PhCHO]^+$. HPLC analysis of the monobenzoate (Chiralcel AS-H, 1 mL/min, 6% iPrOH/Hexanes; $t_{r(minor)}$ = 25.5 min, $t_{r(major)}$ = 21.9 min) indicated 96% ee. $[\alpha]^{20}_D$ = -12.0 (c = 0.15, $CHCl_3$).

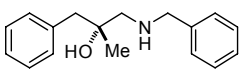
Transformations of α-hydroxy aldehyde 5b:



103: (*R*,*E*)-ethyl 4-hydroxy-4-methyl-5-phenylpent-2-enoate

α-Hydroxy aldehyde **5b** (0.52 mmol) was prepared as described in the general procedure from enol benzoate **1b** (0.52 mmol). After the asymmetric dihydroxylation reaction was complete the reaction mixture was extracted three times with Et_2O and diluted with 4mL toluene. Ether was removed under reduced pressure. Separately, 0.3 mmol (1.5 equiv) phosphonium bromide was dissolved in 2 mL CH_2Cl_2 and washed twice with 1M NaOH. Methylene chloride was removed under reduced pressure after diluting with 4 mL toluene. To the aldehyde in toluene was added the prepared ylide, and the solution was heated to 90°C for 3 hours at which point a second 0.3 mmol of prepared ylide in 4 mL toluene was added. After 90 minutes, the reaction was cooled to room temperature, dried over anhydrous Na_2SO_4, filtered, and concentrated. The product was purified by flash silica gel chromatography (2:3

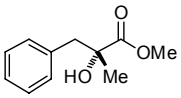
Et_2O:hexanes) to give 32.0 mg (68.3% isolated yield) of the desired compound. ^{1}H NMR ($CDCl_3$) δ = 1.28 (t, *J* = 7.1, 3H), 1.33 (s, 3H), 2.03 (s, 1H), 2.82 (d, *J* = 13.4, 1H), 2.92 (d, *J* = 13.4, 1H), 4.19 (dq, *J* = 7.1, *J* = 0.9, 2H), 5.92 (d, *J* = 15.6, 1H), 7.04 (d, *J* = 15.6, 1H), 7.16 (dd, *J* = 8.2, *J* = 1.7, 2H), 7.23-7.32 (m, 3H). ^{13}C NMR ($CDCl_3$) δ = 14.0, 27.0, 48.0, 60.2, 72.7, 118.9, 126.8, 128.2, 130.3, 135.6, 153.5, 166.4. FTIR (thin film) 3474, 2978, 1716, 1306 cm^{-1}. EI-MS (*m/z*): 189 [M-OCH_2CH_3]$^+$. $[\alpha]^{20}_D$ = +53.3 (c = 1.11, $CHCl_3$).



104: (*R*)-1-(benzylamino)-2-methyl-3-phenylpropan-2-ol

α-Hydroxy aldehyde **5b** (0.52 mmol) was prepared as described in the general procedure from enol benzoate **1b** (0.52 mmol). After the asymmetric dihydroxylation reaction was complete the reaction was extracted three times with Et_2O and dried over Na_2SO_4. Without evaporating to dryness, the solvent was exchanged to approximately 10 mL toluene under reduced pressure. Benzylamine (0.3 mmol, 1.5 equiv) and 4Å molecular sieves were added before bringing the temperature to 105°C. Imine formation was monitored by GC/MS. Upon completion, the molecular sieves were removed and the toluene evaporated under reduced pressure. The residue was diluted in 10 mL methanol and cooled to 0°C. After 1 hour, the reaction was quenched with saturated $NaHCO_3$ and extracted with Et_2O three times. After concentrating the combined organic layers, the residue was dissolved in hexanes was extracted with 1M HCl. The aqueous layer was washed with hexanes and then brought to pH 13 with 1M NaOH. After extracting the basic aqueous layer three times with EtOAc, the combined organic layers were dried over anhydrous Na_2SO_4, filtered, and concentrated to provide

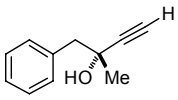
42.5 mg (84% yield) of the desired compound. No additional purification was necessary. ^{1}H NMR ($CDCl_3$) δ = 1.14 (s, 3H), 2.10 (br s, 1H), 2.55 (d, *J* = 11.98, 1H), 2.66 (d, *J* = 11.98, 1H), 2.75 (d, *J* = 13.3, 1H), 2.82 (d, *J* = 13.3, 1H), 3.81 (d, *J* = 7.4, 2H), 3.83 (s, 1H), 7.21-7.37 (m, 10H). ^{13}C NMR ($CDCl_3$) δ = 25.9, 46.8, 54.7, 58.2, 71.8, 126.6, 127.3, 128.3, 128.4, 128.7, 130.6, 138.0, 140.5. $[\alpha]^{20}_D$ = -3.1 (c = 0.975, $CHCl_3$).



105: (*R*)-methyl 2-hydroxy-2-methyl-3-phenylpropanoate

α-Hydroxy aldehyde **5b** (0.52 mmol) was prepared as described in the general procedure from enol benzoate **1b** (0.52 mmol) except $NaHCO_3$ (3 equiv) was included during the dihydroxylation. After the asymmetric dihydroxylation reaction was quenched with Na_2SO_3, the reaction mixture was diluted with CH_2Cl_2, washed with brine, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4 and concentrated to no less than 4 mL. The solvent was exchanged by adding 10 mL of dry MeOH and concentrating the volume to 4 mL. Dry MeOH was again added to bring the final reaction concentration to 0.05M in MeOH (about 10 mL). This solution was brought to 0˚C and KOH (dissolved in 1.0 mL MeOH, 0.76 g, 1.3 5mmol, 2.6 equiv) and I_2 (dissolved in 1.0 mL MeOH, 0.86 g, 0.68 mmol, 1.3 equiv) were added sequentially. After 1.5 hours at 0˚C, starting material was still present, so KOH (0.76 g in MeOH) and I_2 (0.86 g in MeOH) were added again. After stirring an additional 1.5 hours at 0˚C, the reaction was quenched with saturated aqueous $Na_2S_2O_3$. The reaction was filtered, washed with aqueous $NaHCO_3$, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$ and concentrated to give (*R*)-**105** (92% yield). ^{1}H NMR ($CDCl_3$) δ = 1.50 (s, 3H), 2.90 (d, *J* = 13.5, 1H), 3.01 (s, 1H), 3.07

(d, 13.5, 1H), 3.73 (s, 3H), 7.16 (m, 2H), 7.25 (m, 3H). ^{13}C NMR ($CDCl_3$) δ = 26.0, 46.7, 52.8, 75.5, 127.2, 128.4, 130.2, 136.2, 176.8. EI-MS (*m/z*): 194 $[M-1]^+$. $[\alpha]^{20}$ = +5.3 (c = 2.05, $CHCl_3$); lit. for (*S*)-**11** $[\alpha]^{20}$ = -113 (c = 1.0, $CHCl_3$).[3, 4, 5]



106: (*R*)-2-methyl-1-phenylbut-3-yn-2-ol

α-Hydroxy aldehyde **5b** (0.52 mmol) was prepared as described in the general procedure from enol benzoate **1b** (0.52 mmol) except $NaHCO_3$ (3 equiv) was included during the dihydroxylation. After the asymmetric dihydroxylation reaction was quenched with Na_2SO_3, the reaction mixture was diluted with CH_2Cl_2, washed with brine, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with Na_2SO_4 and concentrated to no less than 4 mL. The solvent was exchanged by adding 10 mL of dry MeOH and concentrating the volume to 4 mL. This was repeated 2 times and dry MeOH was again added to bring the final reaction concentration to ca 0.05 M (about 10 mL MeOH). This solution was cooled to 0˚C and K_2CO_3 (0.18 g, 1.3 mmol, 2.5 equiv) and $(MeO)_2POCN_2COMe$[6] (0.15 g, 0.78 mmol, 1.5 equiv, in 1.0 mL MeOH) were added sequentially. The reaction was stirred for 1 hour at 0˚C and 4 hours at room temperature, after which time it was diluted with CH_2Cl_2, washed with aqueous $NaHCO_3$, and extracted 3 times with CH_2Cl_2. The combined organic extracts were dried with $MgSO_4$, concentrated, and purified by flash chromatography (10% EtOAc/Hexanes) to give pure alkyne (64 mg, 77% yield). ^{1}H NMR ($CDCl_3$) δ = 1.56 (s, 3H), 2.02 (s, 1H), 2.47 (s, 1H), 2.93 (d, *J* = 13.3, 1H), 3.01 (d, *J* = 13.2, 1H), 7.31-7.34 (m, 5H). ^{13}C NMR ($CDCl_3$) δ = 29.7, 49.5, 68.1, 72.9, 87.4, 127.3, 128.4, 131.0, 136.2. EI-MS (*m/z*): 160 $[M-1]^+$. $[\alpha]^{20}_D$ = +5.4 (c = 0.71, $CHCl_3$).

1. Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992,** *57*, 2768.

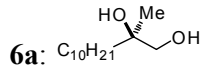
2. Fujisawa, T.; Watai, T.; Sugiyama, T.; Ukaji, Y. *Chem. Lett.* **1989,** *18*, 2045.

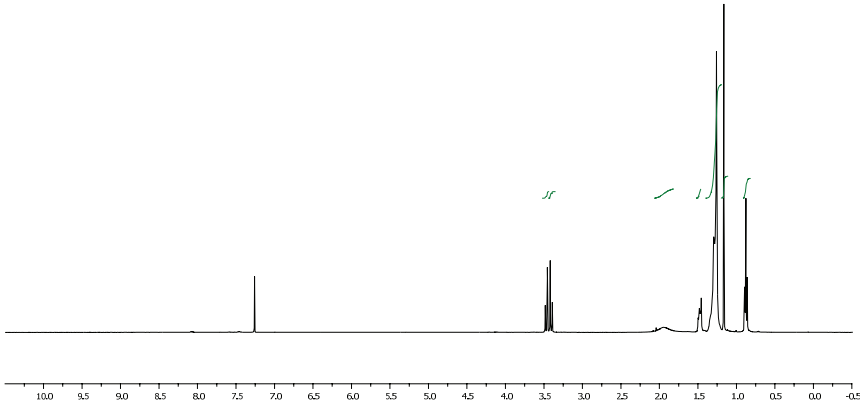
3. Boons, G.-J.; Downham, R.; Kim, K. S.; Ley, S. V.; Woods, M. *Tetrahedron* **1994,** *50*, 7157.

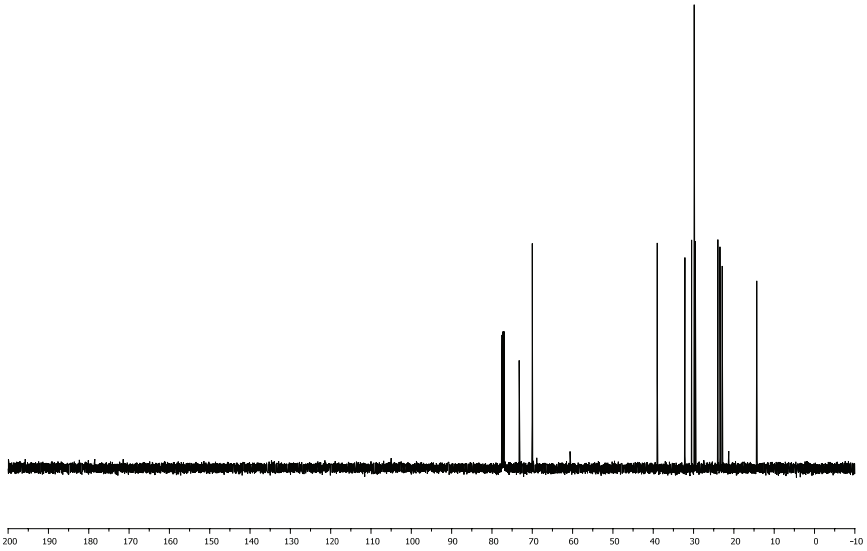
4. We have no explanation for the discrepancy in optical rotation. HPLC analysis of our sample indicates 89% ee. In this context, we note that the corresponding (S)-free acid ([α]20D = -32.1, reported by Lee et al, see ref. 13) has an optical rotation much closer to our value for the (R)-free acid ([α]20D = +28.7).

5. Lee, M.; Kim, D. H. *Bioorg. Med. Chem.* **2000,** *8*, 815.

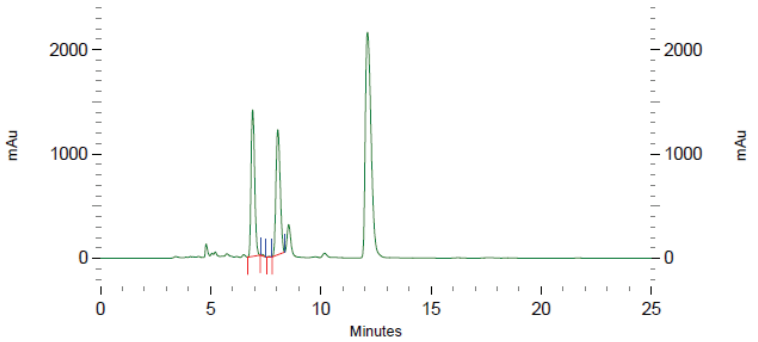
6. Ghosh, Arun K.; Bischoff, A.; Cappiello, J. *Eur. J. Org. Chem.* **2003,** *2003*, 821.

6a: 
HO
Me
OH
C10H21


10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

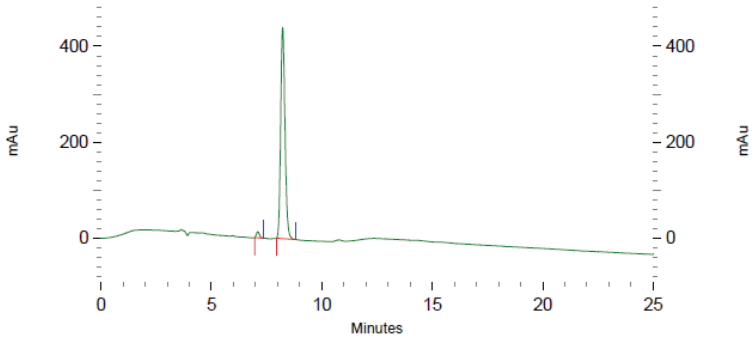
6a Racemate



Results

Retention Time	Height	Height %	Area	Area %
6.907	1403088	53.55	15824975	49.46
7.344	13128	0.50	106787	0.33
7.659	6079	0.23	45305	0.14
8.048	1197950	45.72	16016178	50.06
Totals	2620245	100.00	31993245	100.00

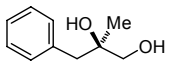
Chiral Compound

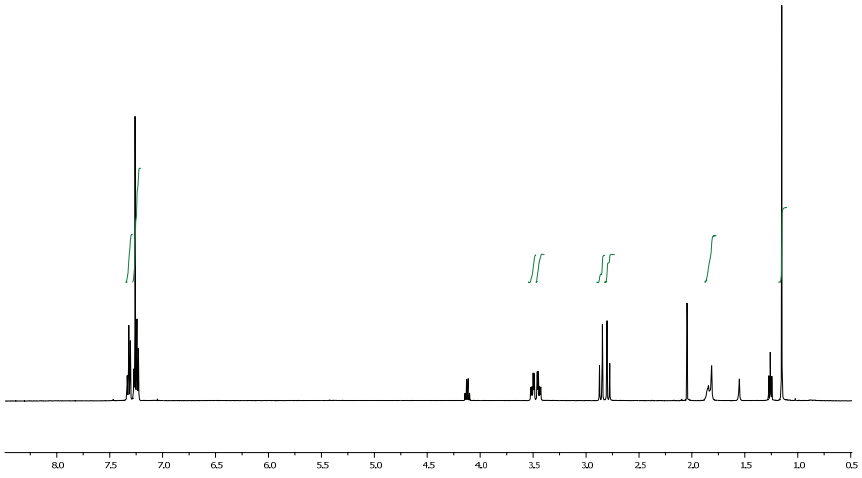


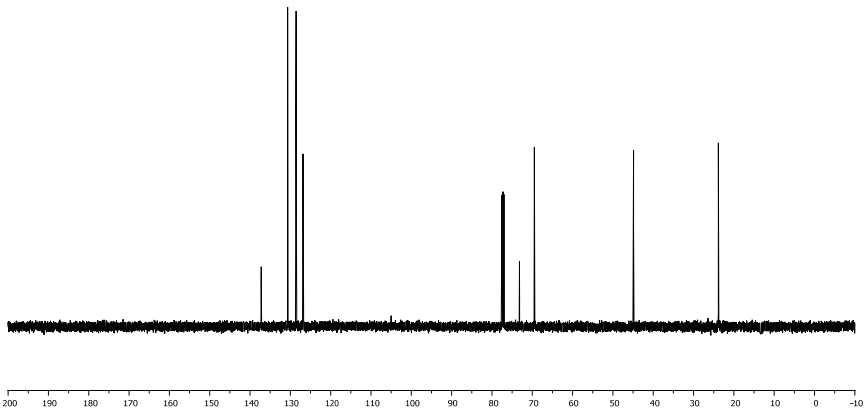
Results

Retention Time	Height	Height %	Area	Area %
7.093	12384	2.74	119496	1.95
8.219	439742	97.26	6008775	98.05
Totals	452126	100.00	6128271	100.00

HPLC conditions: Chiracel AS-H column, 1 mL/min flow rate, 3% ^{i}PrOH in hexanes

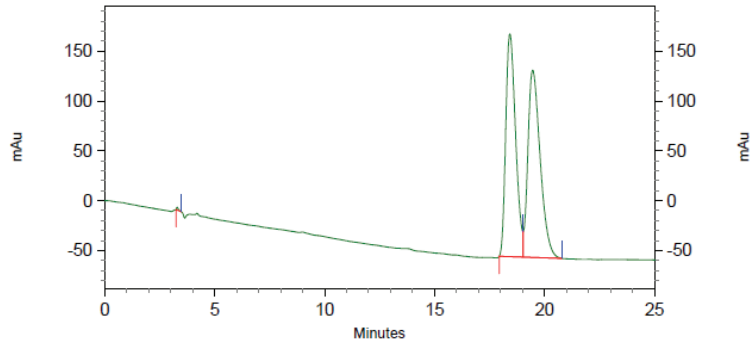
6b: 
HO
Me
OH


8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5


200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10

AD mix β

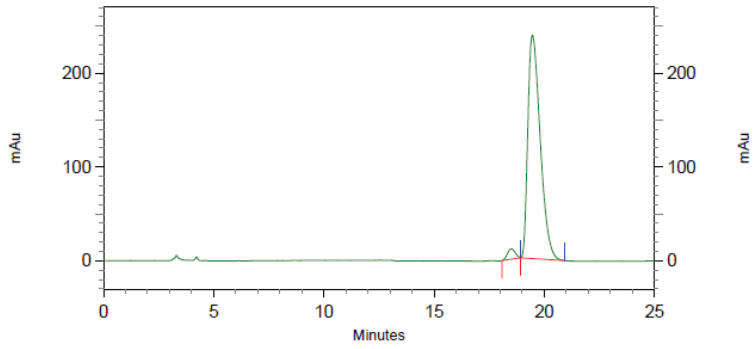
6b Racemate



Results

Retention Time	Height	Height %	Area	Area %
3.291	2899	0.70	16732	0.12
18.421	223626	53.95	6960638	48.70
19.461	187991	45.35	7315358	51.18
Totals	414516	100.00	14292728	100.00

Chiral Compound



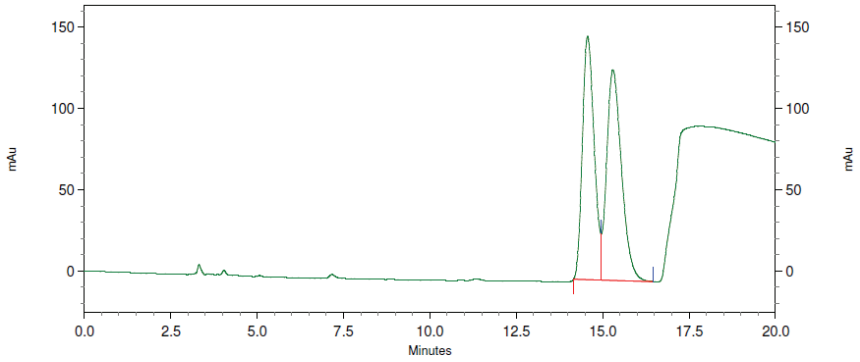
Results

Retention Time	Height	Height %	Area	Area %
18.496	11066	4.44	272034	2.85
19.456	238312	95.56	9286202	97.15
Totals	249378	100.00	9558236	100.00

HPLC conditions: Chiracel AS-H column, 1 mL/min flow rate, 3% ^{i}PrOH in hexanes

AD mix α

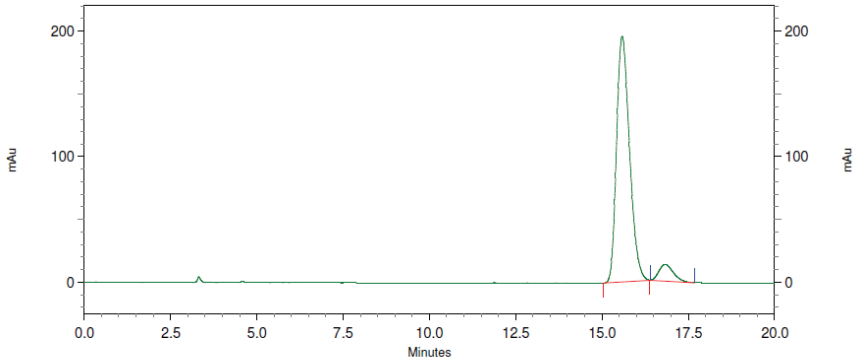
6b Racemate



1: 229 nm, 8 nm
Results

Retention Time	Area	Area %	Height	Height %
14.565	3558447	47.82	149624	53.63
15.296	3883622	52.18	129394	46.37
Totals	7442069	100.00	279018	100.00

Chiral Compound

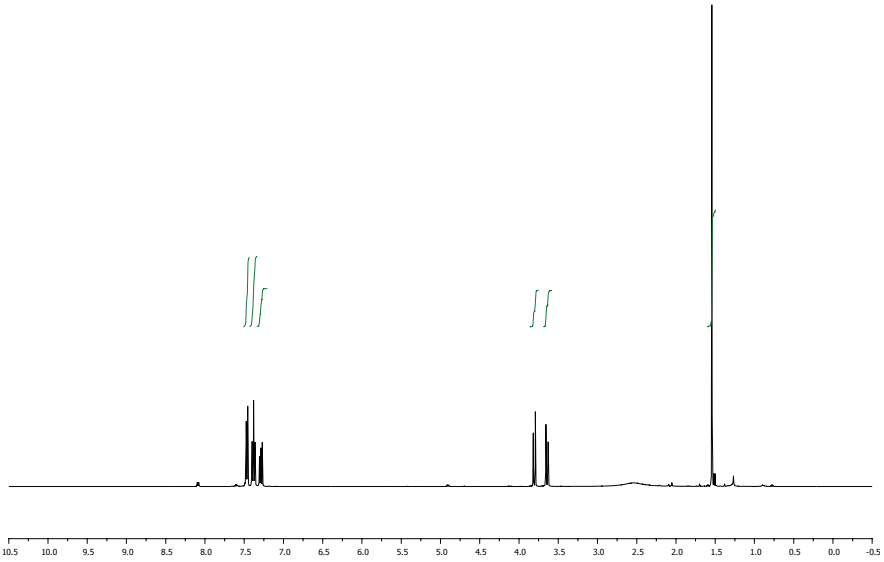


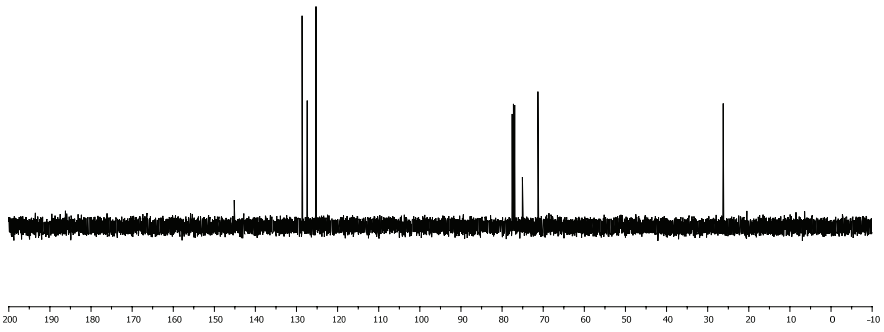
1: 229 nm, 8 nm
Results

Retention Time	Area	Area %	Height	Height %
15.579	5127974	93.04	195816	93.66
16.827	383594	6.96	13263	6.34
Totals	5511568	100.00	209079	100.00

HPLC conditions: Chiracel AS-H column, 1 mL/min flow rate, 4% ^{i}PrOH in hexanes

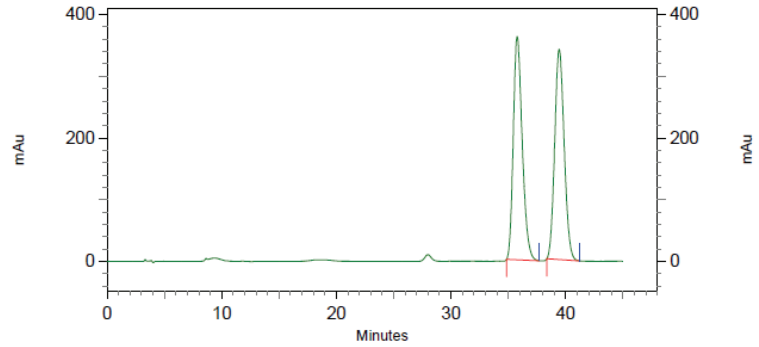
6c:


10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

AD mix β

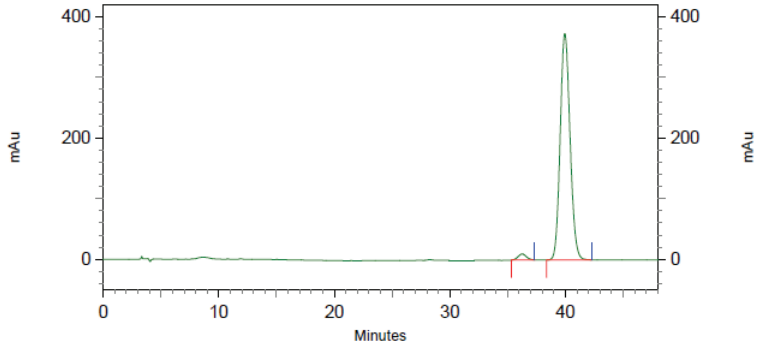
6c Racemate



Results

Retention Time	Height	Height %	Area	Area %
35.760	361800	51.50	19631544	50.02
39.429	340789	48.50	19615073	49.98
Totals	702589	100.00	39246617	100.00

Chiral Compound



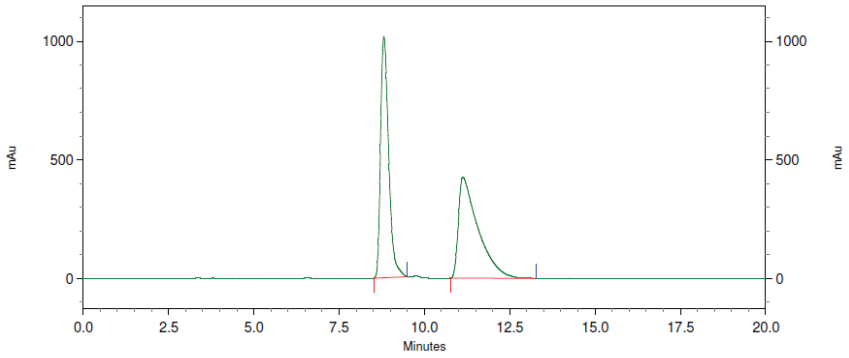
Results

Retention Time	Area	Area %	Height	Height %
36.256	498017	2.20	9864	2.57
39.941	22162535	97.80	373278	97.43
Totals	22660552	100.00	383142	100.00

HPLC conditions: Chiracel AD-H column, 1 mL/min flow rate, 3% EtOH in hexanes

AD mix α

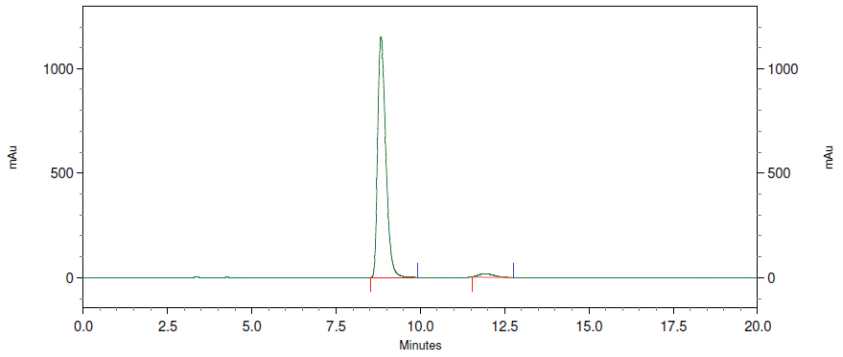
6c Racemate



1: 229 nm, 8 nm
Results

Retention Time	Area	Area %	Height	Height %
8.811	16812538	49.68	1017052	70.45
11.125	17030041	50.32	426510	29.55
Totals	33842579	100.00	1443562	100.00

Chiral Compound

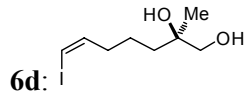


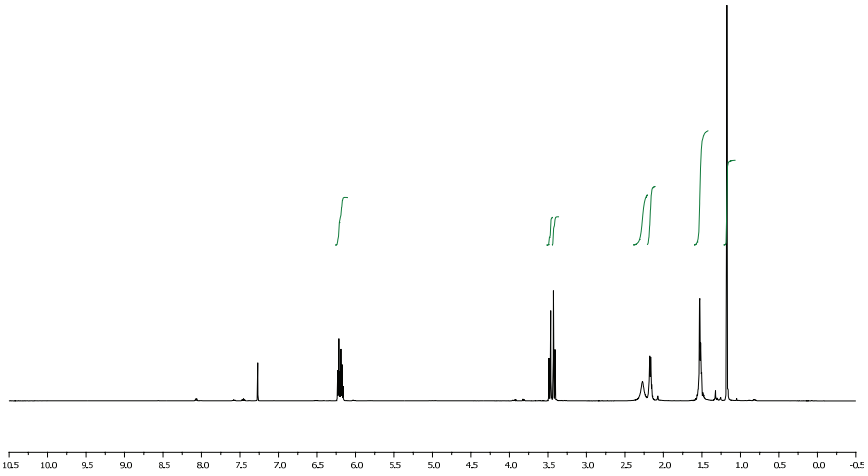
1: 229 nm, 8 nm
Results

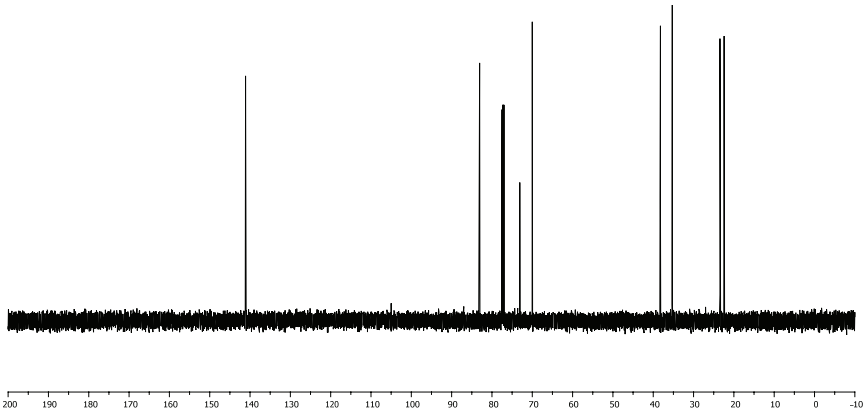
Retention Time	Area	Area %	Height	Height %
8.827	19385431	97.48	1152386	98.58
11.909	501407	2.52	16604	1.42
Totals	19886838	100.00	1168990	100.00

HPLC conditions: Chiracel AS-H column, 1 mL/min flow rate, 10% ^{i}PrOH in hexanes

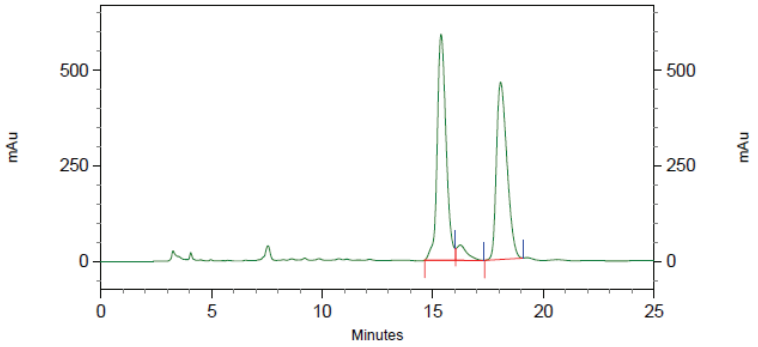
6d:







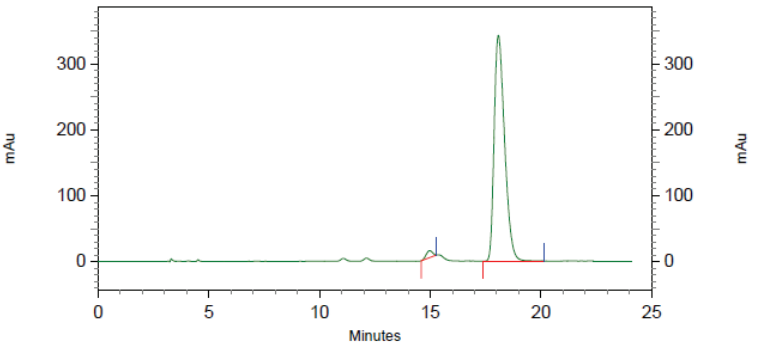
6d Racemate



Results

Retention Time	Height	Height %	Area	Area %
15.376	592106	54.00	16540451	49.71
16.245	40154	3.66	1332272	4.00
18.064	464143	42.33	15398122	46.28
Totals	1096403	100.00	33270845	100.00

Chiral Compound

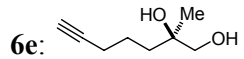


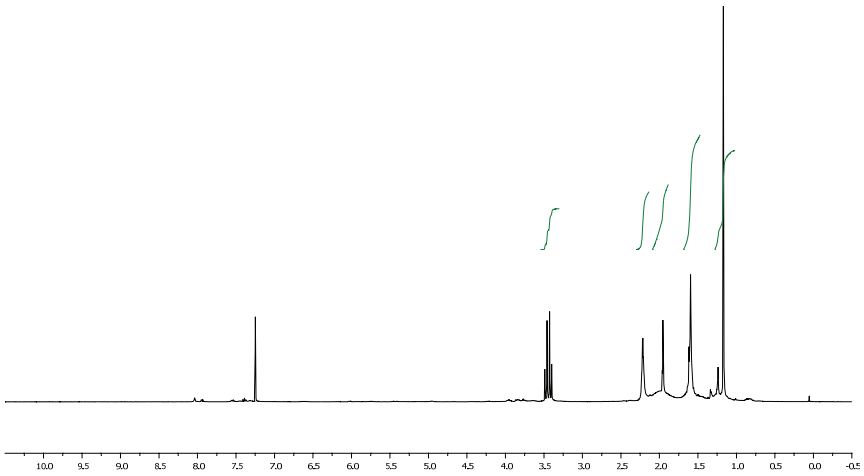
Results

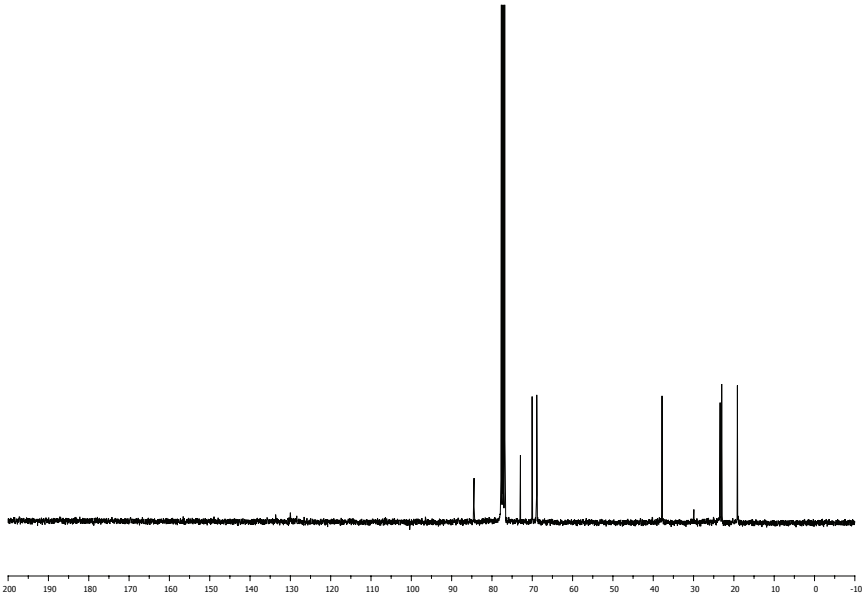
Retention Time	Height	Height %	Area	Area %
14.971	10548	2.98	210540	1.84
18.075	343293	97.02	11259673	98.16
Totals	353841	100.00	11470213	100.00

HPLC conditions: Chiracel AS-H column, 1 mL/min flow rate, 4% ^{i}PrOH in hexanes

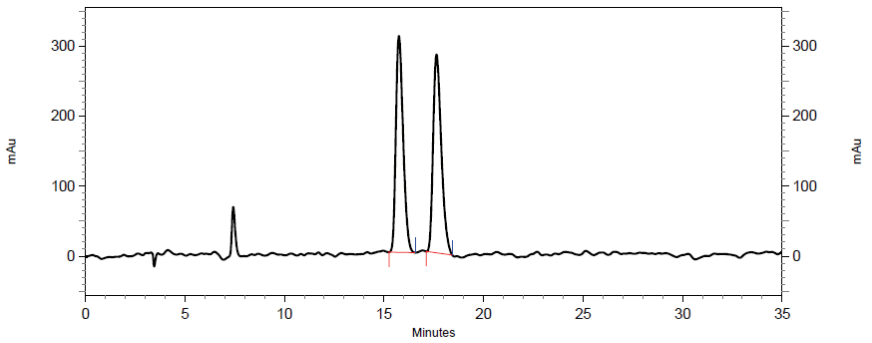
6e:







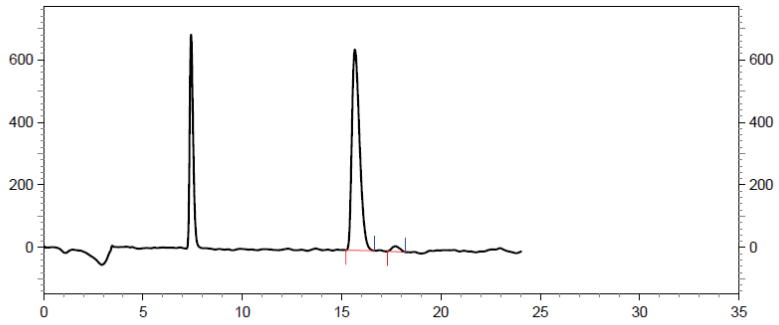
6e Racemate



1: 229 nm, 8 nm
Results

Retention Time	Area	Area %	Height	Height %
15.749	7840999	49.10	309371	52.17
17.637	8128339	50.90	283589	47.83
Totals	15969338	100.00	592960	100.00

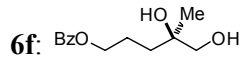
Chiral Compound

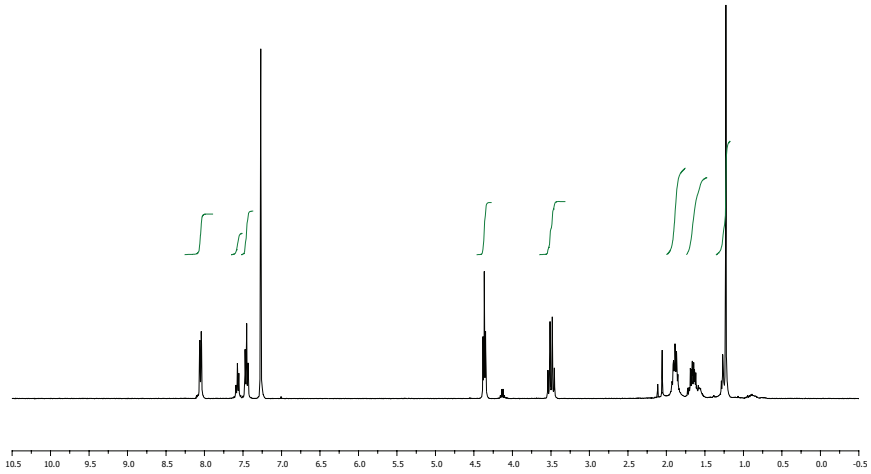


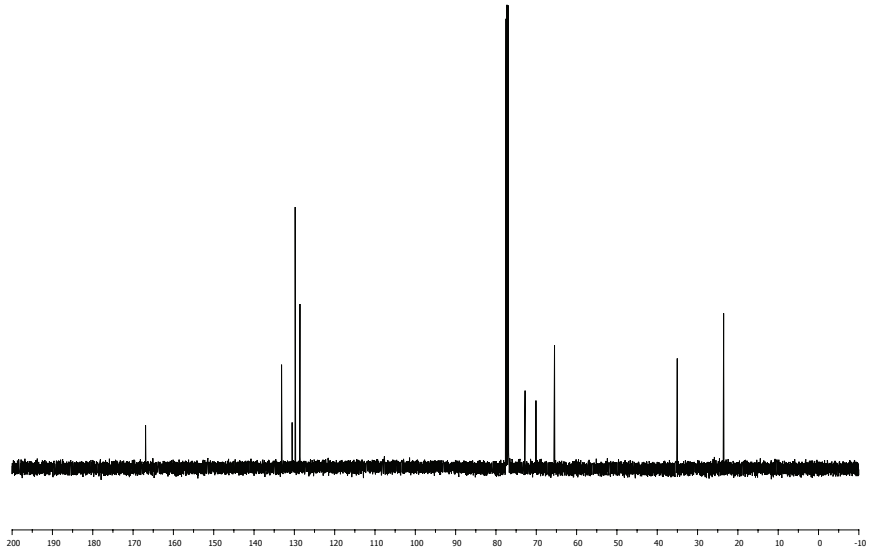
Retention Time	Area	Area %	Height	Height %
15.669	17436146	97.34	641591	97.40
17.707	476148	2.66	17094	2.60
Totals	17912294	100.00	658685	100.00

HPLC conditions: Chiracel OJ-H column, 1 mL/min flow rate, 6% ^{i}PrOH in hexanes

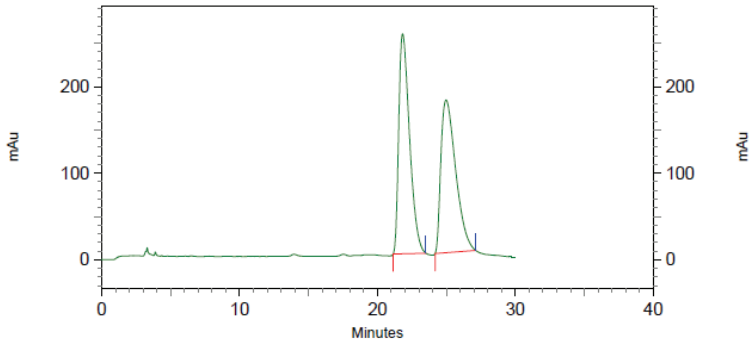
6f:


HO
Me
BzO
OH


10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5


200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

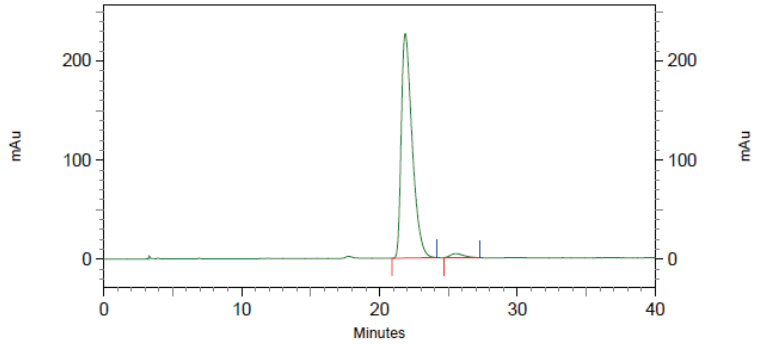
6f Racemate



Results

Retention Time	Height	Height %	Area	Area %
21.819	254170	59.03	13810232	51.22
24.976	176399	40.97	13152666	48.78
Totals	430569	100.00	26962898	100.00

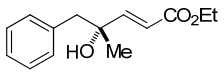
Chiral Compound

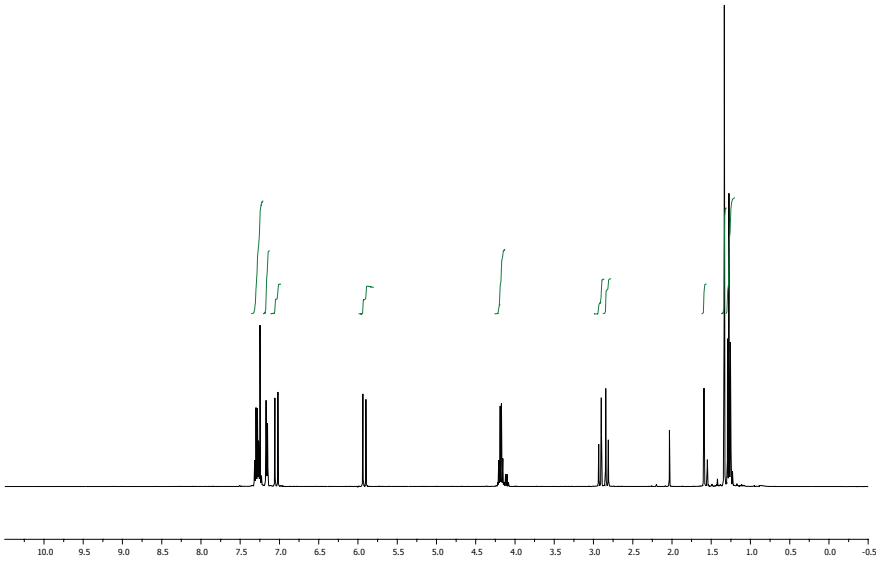


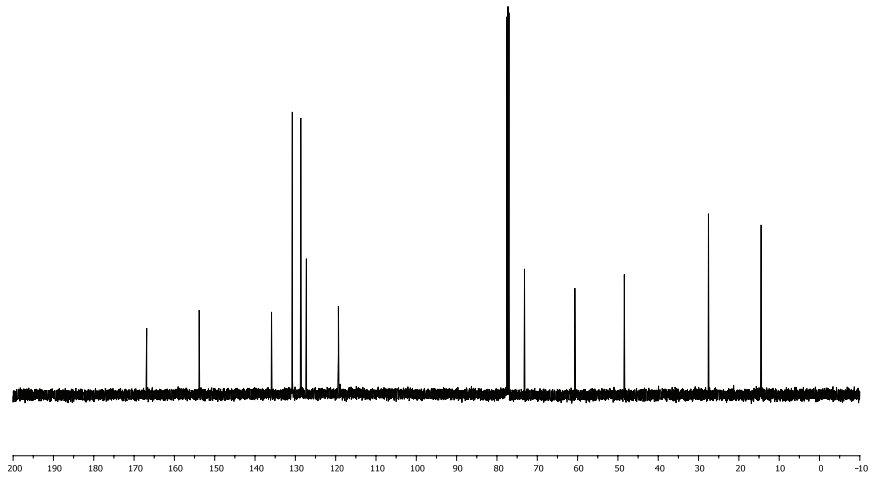
Results

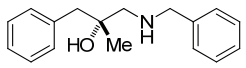
Retention Time	Height	Height %	Area	Area %
21.861	226660	98.22	12406375	97.79
25.509	4112	1.78	280068	2.21
Totals	230772	100.00	12686443	100.00

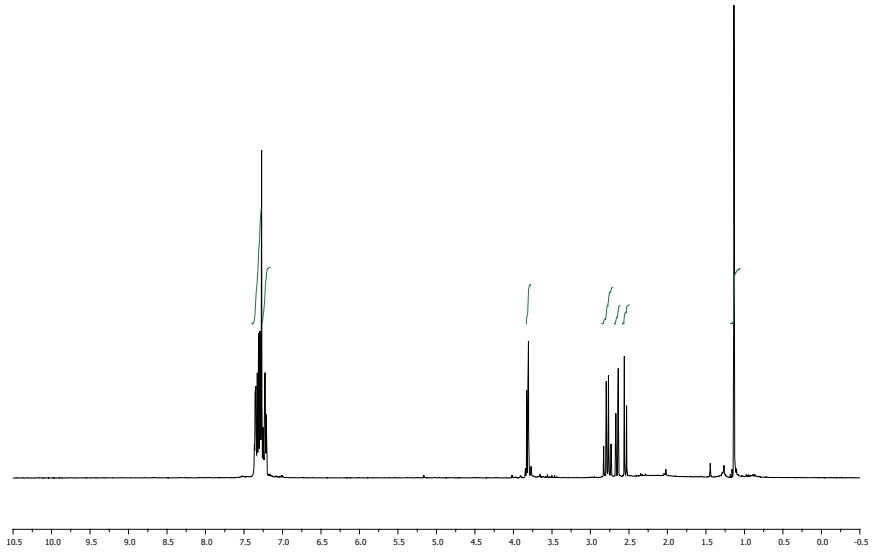
HPLC conditions: Chiracel AS-H column, 1 mL/min flow rate, 6% ^{i}PrOH in hexanes

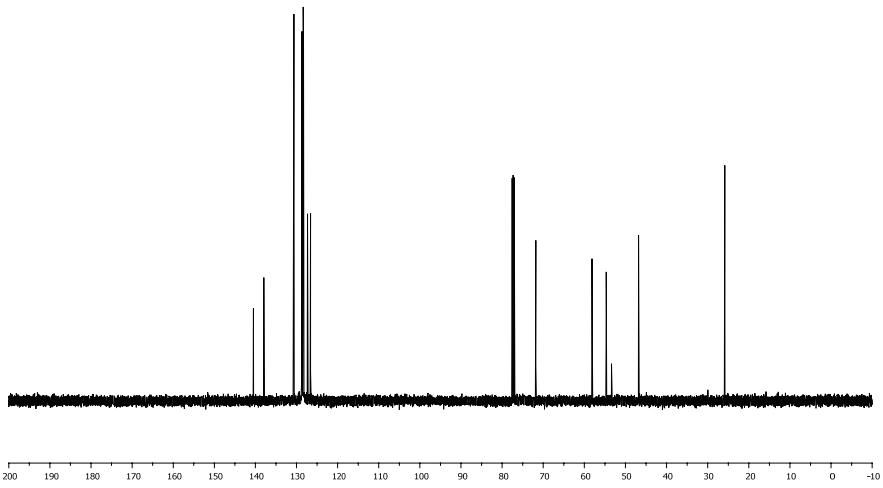
103: 
CO2Et
HO
Me

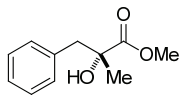

10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

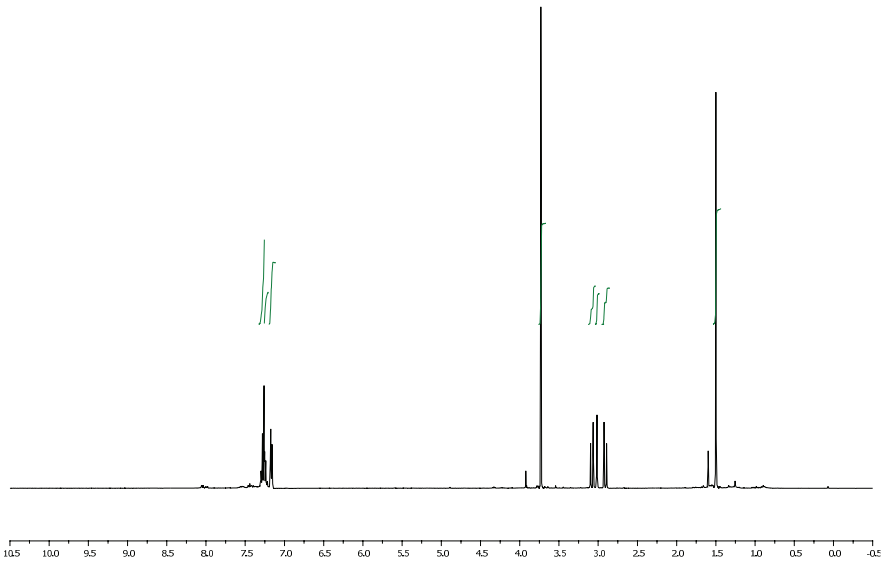

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

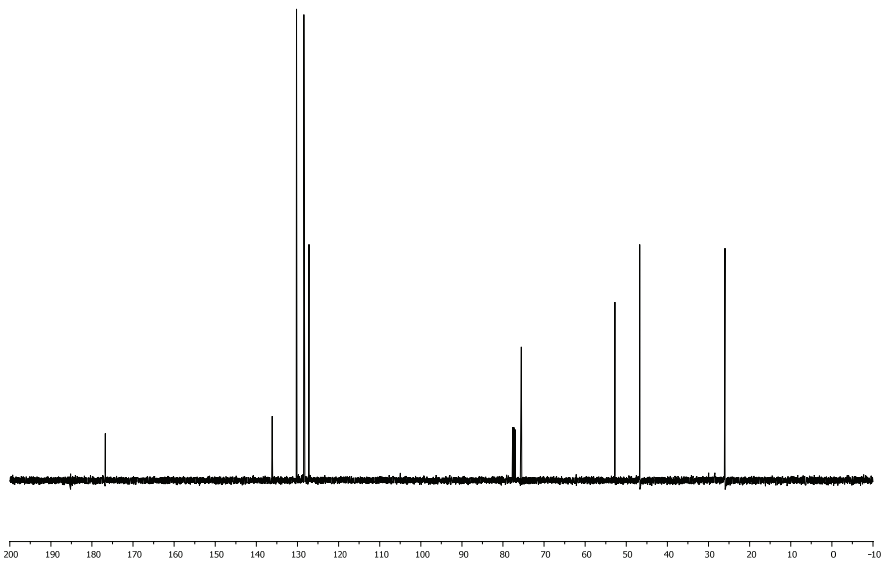
104: 
HO
Me
N
H


10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

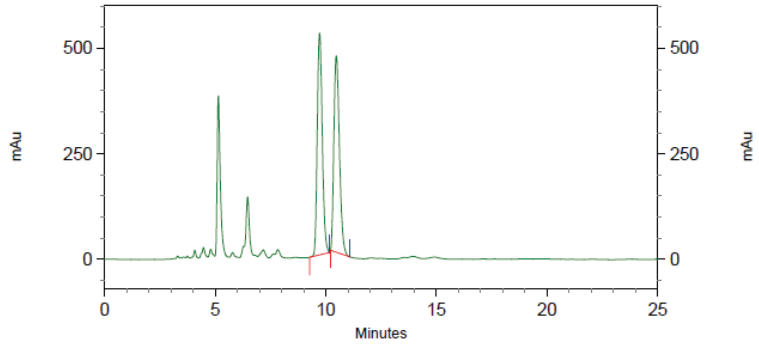

200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

105: 





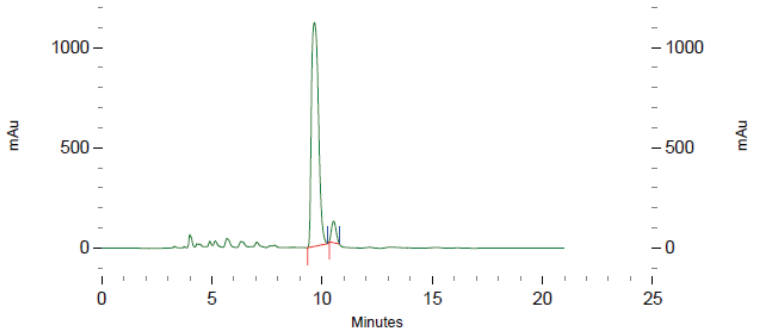
105 Racemate



Results

Retention Time	Height	Height %	Area	Area %
9.717	526466	53.04	8312159	50.51
10.469	466037	46.96	8145650	49.49
Totals	992503	100.00	16457809	100.00

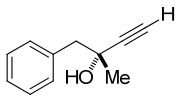
Chiral Compound

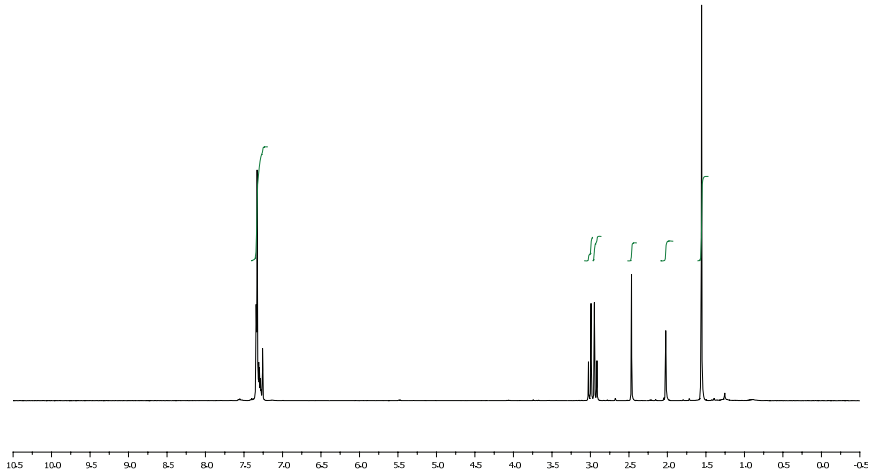


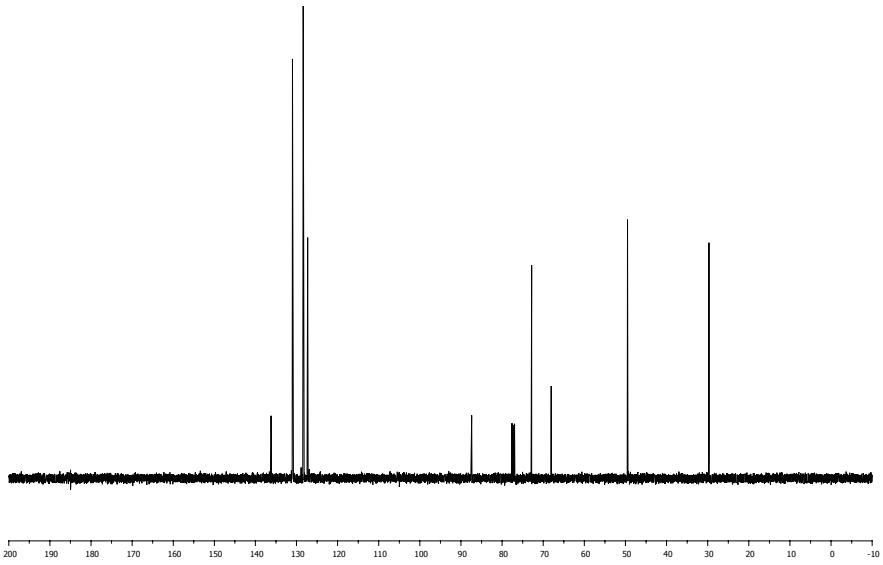
Results

Retention Time	Height	Height %	Area	Area %
9.648	1116109	91.22	24851518	94.08
10.517	107403	8.78	1563610	5.92
Totals	1223512	100.00	26415128	100.00

HPLC conditions: Chiracel OD-H column, 1 mL/min flow rate, 1% ^{i}PrOH in hexanes

106: 





APPENDIX B
Experimental Details and ^{1}H and ^{13}C NMR Spectra for Chapter Two Compounds

General Procedures:

Preparation of Homoallylic Alcohols:

Allylmagnesium bromide (1.0 M in Et_2O, 1.05 equiv.) was added dropwise to the aldehyde (0.1 M in Et_2O) at 0 °C. Upon completion (as determined by TLC), the reaction was quenched with 1 M HCl and extracted 3 times with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to yield the crude homoallylic alcohol product.

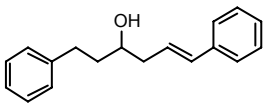
Titanium-mediated Oxidative Arylation:

PhMgBr (3.0 M in Et_2O, 0.33 mL, 1.0 equiv.) was added to a stirred solution of homoallylic alcohol (1.0 mmol) in 6 mL CH_2Cl_2 at 0 °C. After 5 minutes $Ti(O^iPr)_4$ (293 μL, 2.0 equiv.) was added and the yellow solution was removed from the ice bath and stirred at room temperature for one hour. The reaction was then brought to -78 °C, and PhMgBr (3.0 M in Et_2O, 1.0 mL, 3.0 equiv.) was added slowly dropwise. When the addition was complete, the reaction was removed from the ice bath and allowed to stir overnight at room temperature. The reaction was quenched with 1 M HCl (15 mL) and stirred until both phases became clear. The aqueous layer was extracted 3 times with Et_2O (20 mL). The combined organic extracts were washed with brine (30 mL), dried over Na_2SO_4, and concentrated under reduced pressure to yield the crude oxidative arylation product.

Preparation of Aryl Grignard Reagents:

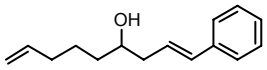
75 μL 1,2-dibromoethane was added to magnesium turnings (9.9 mmol, 240 mg) in 2 mL Et_2O. A solution of aryl bromide (9.0 mmol) in 1 mL Et_2O was then added slowly dropwise to the activated magnesium to maintain a gentle reflux. The solution continued stirring in a 30 °C heating mantle for 1 hour. The Grignard was allowed to cool to room temperature and titrated by No-D ^{1}H NMR[1, 2] using 1,5-cyclooctadiene as a standard before use in the oxidative arylation reaction.

Characterization Data:



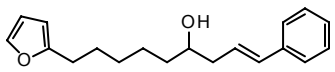
2a: (*E*)-1,6-diphenyl-5-hexene-3-ol

Chromatography (5-15% EtOAc in hexanes) provided 228 mg (90.5%) of a colorless oil. ^{1}H and ^{13}C NMR match reported spectra.[3]



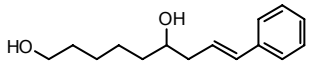
2b: (*E*)-1-phenyl-1,8-nonadien-4-ol

Isolated 159 mg (73.6%) of a colorless oil. ^{1}H NMR (500 MHz, cdcl$_3$) δ 7.37 (d, *J* = 7.7, 2H), 7.31 (t, *J* = 7.6, 2H), 7.22 (t, *J* = 7.3, 1H), 6.49 (d, *J* = 15.9, 1H), 6.24 (dt, *J* = 15.5, 7.2, 1H), 5.82 (ddt, *J* = 16.9, 10.2, 6.7, 1H), 5.03 (dd, *J* = 17.1, 1.0, 1H), 4.97 (dd, *J* = 9.5, 1.0, 1H), 3.78 – 3.71 (m, 1H), 2.49 – 2.42 (m, 1H), 2.31 (ddd, *J* = 14.8, 7.8, 1H), 2.13 – 2.05 (m, *J* = 6.5, 2H), 1.67 – 1.43 (m, 6H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 138.78, 137.35, 133.22, 128.66, 127.38, 126.42, 126.21, 114.78, 71.15, 41.28, 36.42, 33.81, 25.10. EI-MS (*m/z*): 216.05 $[M]^+$



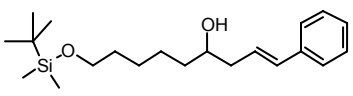
2c: (*E*)-9-(2'-furanyl)-1-phenyl-1-nonen-4-ol

Reaction performed on 0.5 mmol scale. Isolated 98 mg (69.1%). ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.39 – 7.34 (m, 2H), 7.34 – 7.27 (m, 3H), 7.25 – 7.19 (m, 1H), 6.48 (d, *J* = 15.8, 1H), 6.28 (dd, *J* = 3.2, 2.0, 1H), 6.23 (dd, *J* = 15.8, 7.8, 1H), 5.97 (dd, *J* = 3.1, 0.8, 1H), 3.78 – 3.67 (m, 1H), 2.63 (t, *J* = 7.5, 2H), 2.50 – 2.40 (m, 1H), 2.31 (ddd, *J* = 15.2, 7.6, 1H), 1.67 (p, *J* = 7.2, 3H), 1.57 – 1.45 (m, 4H), 1.45 – 1.32 (m, 3H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 156.57, 140.85, 137.41, 133.31, 128.72, 127.45, 126.50, 126.28, 110.22, 104.81, 71.27, 41.36, 36.96, 29.33, 28.18, 28.08, 25.62. EI-MS (*m/z*): 284.35 $[M]^+$



2d: (*E*)-9-phenyl-8-nonen-1,6-diol

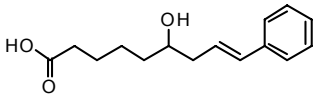
Used 2 equiv. PhMgBr to deprotonate prior to Ti(O^{i}Pr)$_4$ addition. Isolated 188 mg (80.2%) of a colorless oil. ^{1}H NMR (500 MHz, cdcl$_3$) δ 7.36 (d, *J* = 7.3, 2H), 7.31 (t, *J* = 7.6, 2H), 7.22 (t, *J* = 7.2, 1H), 6.48 (d, *J* = 15.8, 1H), 6.28 – 6.19 (m, 1H), 3.78 – 3.70 (m, 1H), 3.66 (t, *J* = 6.5, 2H), 2.51 – 2.41 (m, 1H), 2.37 – 2.27 (m, 1H), 1.65 – 1.57 (m, 3H), 1.57 – 1.47 (m, 4H), 1.47 – 1.34 (m, 4H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 137.37, 132.58, 128.51, 127.14, 126.68, 126.05, 71.06, 62.33, 41.15, 36.75, 32.53, 25.74, 25.41. ES-MS (*m/z*): 235.0 $[M+1]^+$



2e: (*E*)-9-(*tert*-butyldimethylsiloxy)-1-phenyl-1-nonen-4-ol

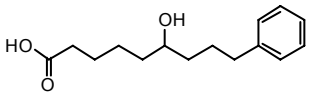
Reaction performed on 0.96 mmol scale and quenched with 10% citric acid. Isolated 265 mg (83.1%) of a colorless oil. ^{1}H NMR (500 MHz, cdcl$_3$) δ 7.37 (d, *J* = 7.4, 2H), 7.31 (t,

J = 7.6, 2H), 7.22 (t, J = 7.2, 1H), 6.48 (d, J = 15.9, 1H), 6.24 (dt, J = 15.2, 7.6, 1H), 3.73 (s, 1H), 3.61 (t, J = 6.5, 2H), 2.49 – 2.40 (m, 1H), 2.31 (dt, J = 14.0, 7.0, 1H), 1.62 – 1.57 (m, 1H), 1.57 – 1.44 (m, 6H), 1.44 – 1.30 (m, 4H), 0.89 (s, 9H), 0.05 (s, 6H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 137.43, 133.26, 128.71, 127.42, 126.55, 126.27, 71.29, 63.36, 41.34, 37.10, 33.00, 26.18, 26.05, 25.71, 18.56, -5.06. ES-MS (*m/z*): 384.8 $[M+Cl]^+$



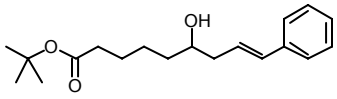
2f: (*E*)-6-hydroxy-9-phenyl-8-nonenoic acid

Used 2 equiv. PhMgBr to deprotonate prior to Ti(O^{i}Pr)$_4$ addition. Isolated 170 mg (68.4%) as a 4:1 mixture of **2f**:**3f**. ^{1}H NMR (500 MHz, cdcl$_3$) δ 7.39 (d, J = 7.7, 2H), 7.33 (t, J = 7.6, 2H), 7.29 – 7.19 (m, 1H), 6.49 (d, J = 15.8, 1H), 6.25 (dt, J = 15.2, 7.2, 1H), 3.81 – 3.73 (m, 1H), 2.50 – 2.41 (m, 1H), 2.41 – 2.31 (m, 4H), 1.74 – 1.60 (m, 2H), 1.60 – 1.38 (m, 5H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 179.02, 137.36, 133.15, 128.66, 127.37, 126.31, 126.22, 71.22, 41.13, 36.38, 25.21, 24.74. ES-MS (*m/z*): 247.0 $[M-1]^+$



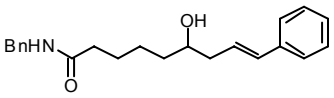
3f: 6-hydroxy-9-phenylnonanoic acid

The 4:1 mixture of **2f**:**3f** was hydrogenated with Pd/C in EtOH under an H_2 atmosphere to provide **3f** as a single product. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.28 (d, J = 7.4, 3H), 7.23 – 7.14 (m, 3H), 3.67 – 3.58 (m, 1H), 2.63 (td, J = 8.6, 2.0, 2H), 2.35 (t, J = 7.3, 2H), 1.85 – 1.71 (m, 1H), 1.71 – 1.56 (m, 3H), 1.56 – 1.30 (m, 7H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 179.45, 142.51, 128.59, 128.50, 125.94, 71.81, 37.16, 37.09, 36.04, 34.11, 27.64, 25.25, 24.79. ES-MS (*m/z*): 249.0 $[M-1]^+$



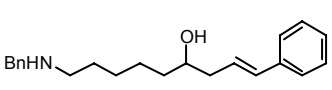
2g: (*E*)-*tert*-butyl 6-hydroxy-9-phenyl-8-nonenoate

Performed on a 0.5 mmol scale. Isolated 58.2 mg (38%) as the *tert*-butyl ester and 44.6 mg (36%) as a 4:1 mixture of **2f**:**3f**. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.36 (d, *J* = 7.1, 2H), 7.30 (t, *J* = 7.6, 2H), 7.22 (t, *J* = 7.2, 1H), 6.48 (d, *J* = 15.8, 1H), 6.23 (dt, *J* = 15.6, 7.2, 1H), 3.78 – 3.69 (m, 1H), 2.49 – 2.40 (m, 1H), 2.31 (ddd, *J* = 14.8, 7.4, 1H), 2.24 (t, *J* = 7.4, 2H), 1.68 (s, 1H), 1.66 – 1.57 (m, 2H), 1.57 – 1.47 (m, 4H), 1.47 (s, 9H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 173.35, 137.39, 133.25, 128.69, 127.42, 126.47, 126.26, 80.24, 71.02, 41.34, 36.67, 35.64, 28.29, 25.34, 25.14. ES-MS (*m/z*): 327.2 [M+Na]$^+$



2h: (*E*)-*N*-benzyl-6-hydroxy-9-phenyl-8-nonenamide

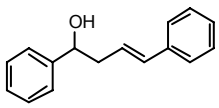
2 equiv. PhMgBr were used to deprotonate prior to Ti(O^{i}Pr)$_4$ addition. Isolated 263 mg (77.9%) of a colorless solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.31 (d, *J* = 7.2, 2H), 7.27 (d, *J* = 6.9, 3H), 7.25 – 7.13 (m, 5H), 6.41 (d, *J* = 15.9, 1H), 6.19 (dt, *J* = 15.6, 7.2, 1H), 6.07 (br s, 1H), 4.36 (d, *J* = 5.7, 2H), 3.71 – 3.62 (m, 1H), 2.42 – 2.32 (m, 1H), 2.26 (ddd, *J* = 15.2, 7.6, 1H), 2.17 (t, *J* = 7.5, 2H), 1.73 – 1.53 (m, 2H), 1.53 – 1.28 (m, 5H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 173.12, 138.52, 137.38, 133.03, 128.78, 128.66, 128.52, 127.90, 127.56, 127.36, 126.57, 126.20, 70.93, 43.64, 41.34, 36.61, 36.53, 25.65, 25.44. ES-MS (*m/z*): 338.2 [M+1]$^+$.



2i: (*E*)-9-(benzylamino)-1-phenyl-1-nonen-4-ol

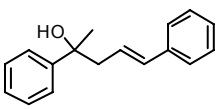
2 equiv. PhMgBr were used in the initial deprotonation, and the reaction was quenched with 10% citric acid. The aqueous phase was then brought

to pH 10 with 3N NaOH, extracted with Et_2O three times, washed with brine, dried over Na_2SO_4, and concentrated. Isolated 250 mg (94.4%) of an orange oil. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.41 – 7.28 (m, 9H), 7.25 – 7.19 (m, 1H), 6.48 (d, *J* = 15.8, 1H), 6.23 (dt, *J* = 15.2, 7.6, 1H), 3.80 (s, 2H), 3.76 – 3.68 (m, 1H), 2.64 (t, *J* = 7.2, 2H), 2.48 – 2.38 (m, 1H), 2.30 (dt, *J* = 15.2, 7.5, 1H), 1.91 (s, 1H), 1.61 – 1.44 (m, 5H), 1.44 – 1.29 (m, 4H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 140.17, 137.41, 132.99, 128.66, 128.54, 128.33, 127.34, 127.11, 126.69, 126.20, 71.06, 54.05, 49.31, 41.37, 36.95, 29.97, 27.41, 25.70. ES-MS (*m/z*): 324.2 $[M+1]^+$



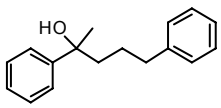
2j: (*E*)-1,4-diphenyl-3-buten-1-ol

Isolated 204 mg (90.7%) of a colorless solid. ^{1}H NMR and ^{13}C NMR match previously reported spectra.[4]



2k: (*E*)-2,5-diphenyl-4-penten-2-ol

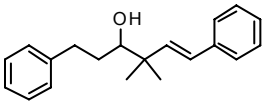
After the final PhMgBr addition, the reaction was stirred at 38 °C overnight. Isolated 197 mg as a 4.8:1 mixture of **2k** and **3k**. The major product matched previously reported ^{1}H and ^{13}C NMR spectra.[5]



3k: 2,5-diphenylpentan-2-ol

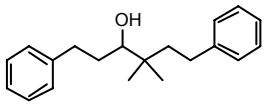
The 4.8:1 mixture of 2k:**3k** was hydrogenated with Pd/C in EtOH under an H_2 atmosphere to provide **3k** as a single product. ^{1}H NMR (500 MHz, cdcl$_3$) δ 7.43 (d, *J* = 7.0, 2H), 7.35 (t, *J* = 7.5, 2H), 7.24 (q, *J* = 7.5, 3H), 7.19 (t, *J* = 7.2, 1H), 7.14 (d, *J* = 7.2, 2H), 2.59 (dt, *J* = 8.5, 1.8, 2H), 1.93 – 1.81 (m, 2H), 1.74 (s, 1H), 1.71 – 1.60

(m, 1H), 1.57 (s, 3H), 1.55 – 1.44 (m, 1H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 147.98, 142.41, 128.57, 128.43, 128.32, 126.72, 125.89, 124.93, 74.81, 43.84, 36.22, 30.42, 25.95. EI-MS (*m/z*): 240.35 $[M]^+$



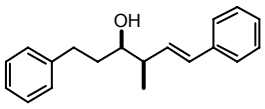
2l: (*E*)-4,4-dimethyl-1,6-diphenyl-5-hexen-3-ol

Isolated 240 mg as a 1.7:1 mixture of **2l**:**3l**; spectral peaks for **2l** were assigned after hydrogenation of the mixture. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.37 (d, *J* = 7.2, 1H), 7.34 – 7.25 (m, 4H), 7.25 – 7.19 (m, 4H), 7.19 (d, *J* = 8.5, 1H), 6.39 (d, *J* = 16.3, 1H), 6.20 (d, *J* = 16.3, 1H), 3.42 – 3.33 (m, 1H), 2.99 – 2.88 (m, 1H), 2.70 – 2.43 (m, 1H), 1.95 – 1.81 (m, 1H), 1.70 – 1.57 (m, 1H), 1.57 – 1.44 (m, 1H), 1.12 (s, 6H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 142.43, 137.53, 137.10, 128.69, 128.65, 128.63, 128.50, 127.36, 126.31, 125.94, 78.14, 41.51, 33.72, 33.37, 23.59, 23.07. EI-MS (*m/z*): 281.30 $[M+1]^+$



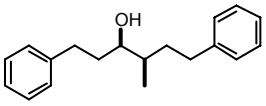
3l: 4,4-dimethyl-1,6-diphenylhexan-3-ol

The 1.7:1 mixture of **2l**:**3l** was hydrogenated with Pd/C in EtOH under an H_2 atmosphere to provide **3l** as a single product. ^{1}H NMR (500 MHz, cdcl$_3$) δ 7.39 – 7.31 (m, 4H), 7.29 (d, *J* = 7.4, 2H), 7.27 (t, *J* = 9.6, 4H), 3.42 (d, *J* = 10.5, 1H), 3.00 (ddd, *J* = 14.5, 10.5, 5.0, 1H), 2.75 – 2.60 (m, 2H), 2.56 (td, *J* = 12.8, 4.9, 1H), 1.98 – 1.88 (m, 1H), 1.70 (td, *J* = 12.8, 4.7, 2H), 1.57 (td, *J* = 13.8, 4.8, 2H), 1.02 (s, 3H), 1.01 (s, 3H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 143.36, 142.50, 128.66, 128.58, 128.52, 128.47, 126.00, 125.81, 78.17, 41.35, 37.80, 33.54, 33.43, 30.56, 23.18, 22.98. EI-MS (*m/z*): 282.40 $[M]^+$



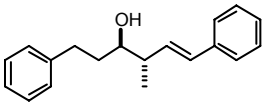
syn-**2m:** *syn*-4-methyl-1,6-diphenyl-5-hexen-3-ol

Performed on a 0.5 mmol scale. After the final PhMgBr addition, the reaction was stirred at 38 °C overnight. Isolated 90.8 mg (68.2%) as a pale yellow oil. ^{1}H NMR (400 MHz, cdcl$_3$) δ = 7.37 (d, *J*=7.1, 2H), 7.31 (dd, *J*=14.4, 7.1, 5H), 7.25 – 7.15 (m, 5H), 6.45 (d, *J*=16.0, 1H), 6.17 (dd, *J*=16.0, 8.0, 1H), 3.60 (ddd, *J*=9.3, 5.3, 3.0, 1H), 2.90 (ddd, *J*=14.5, 10.1, 5.2, 1H), 2.68 (ddd, *J*=13.8, 9.7, 6.8, 1H), 2.53 – 2.42 (m, 1H), 1.90 (dddd, *J*=13.5, 9.9, 6.8, 3.0, 1H), 1.79 – 1.67 (m, 1H), 1.54 (s, 1H), 1.15 (d, *J*=6.8, 3H), . ^{13}C NMR (126 MHz, cdcl$_3$) δ = 142.29, 137.44, 132.51, 130.75, 128.69, 128.63, 128.55, 127.37, 126.26, 125.97, 74.73, 43.55, 36.19, 32.62, 15.37. ES-MS (*m/z*): 249.0 $[M\text{-}OH]^+$



syn-**3m:** *syn*-4-methyl-1-phenylhexan-3-ol

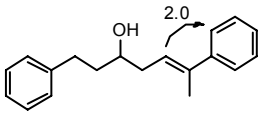
^{1}H NMR (400 MHz, cdcl$_3$) δ = 7.33 – 7.26 (m, 5H), 7.19 (dd, *J*=11.5, 7.4, 5H), 3.63 – 3.55 (m, 1H), 2.88 – 2.77 (m, 1H), 2.76 – 2.52 (m, 3H), 1.85 – 1.71 (m, 3H), 1.63 – 1.45 (m, 2H), 1.30 (s, 1H), 0.96 (d, *J*=6.6, 3H). ^{13}C NMR (126 MHz, cdcl$_3$) δ = 142.75, 142.37, 128.63, 128.60, 128.55, 128.53, 126.02, 125.91, 77.48, 77.23, 76.98, 74.66, 38.18, 36.36, 35.27, 33.80, 32.85, 13.84. ES-MS (*m/z*): 251.0 $[M\text{-}OH]^+$



anti-**2m:** *anti*-4-methyl-1,6-diphenyl-5-hexen-3-ol

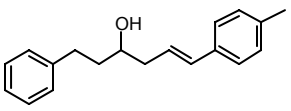
Isolated 217 mg (81.2%) as a viscous, colorless oil. ^{1}H NMR (400 MHz, cdcl$_3$) δ = 7.37 (d, *J*=7.6, 2H), 7.30 (dd, *J*=15.0, 7.3, 5H), 7.25 – 7.15 (m, 5H),

6.47 (d, *J*=15.9, 1H), 6.15 (dd, *J*=15.9, 8.6, 1H), 3.52 (ddd, *J*=9.0, 5.8, 3.2, 1H), 2.92 – 2.82 (m, 1H), 2.70 (ddd, *J*=13.7, 9.7, 6.7, 1H), 2.40 (dq, *J*=13.5, 6.6, 1H), 1.89 (dddd, *J*=13.6, 10.0, 6.6, 3.2, 1H), 1.81 – 1.69 (m, 1H), 1.62 (s, 1H), 1.13 (d, *J*=6.8, 3H). ^{13}C NMR (126 MHz, cdcl$_3$) δ = 142.37, 137.30, 131.81, 131.68, 128.70, 128.64, 128.54, 127.45, 126.31, 125.95, 74.59, 43.91, 36.46, 32.35, 16.95. ES-MS (*m/z*): 267.0 $[M+1]^+$



2n: (*E*)-1,6-diphenyl-5-hepten-3-ol

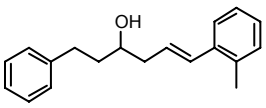
After final Grignard addition, the reaction was brought to 40 °C and kept at that temperature overnight. Isolated 200 mg (75.2%). NOE correlation (shown in the structure) confirmed the olefin stereochemistry. ^{1}H NMR (500 MHz, cdcl$_3$) δ 7.42 – 7.38 (m, 2H), 7.35 – 7.28 (m, 4H), 7.23 (dd, *J* = 14.9, 7.8, 4H), 5.82 (td, *J* = 7.4, 1.2, 1H), 3.78 (p, *J* = 6.2, 1H), 2.89 – 2.82 (m, 1H), 2.72 (ddd, *J* = 14.0, 9.0, 7.2, 1H), 2.43 (t, *J* = 6.8, 2H), 2.08 (s, 3H), 1.90 – 1.83 (m, 2H), 1.63 (s, 1H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 143.61, 142.17, 137.75, 128.56, 128.52, 128.33, 126.96, 125.93, 125.77, 123.82, 71.12, 38.67, 37.17, 32.24, 16.28. EI-MS (*m/z*): 266.25 $[M]^+$



2o: (*E*)-1-phenyl-6-*p*-tolyl-5-hexen-3-ol

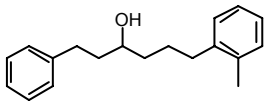
p-Tolylmagnesium bromide was prepared as a 1.85 M solution in Et_2O. Performed on a 0.5 mmol scale using $ClTi(O^iPr)_3$. Isolated 118 mg (88.6%) as a very pale yellow solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.33 – 7.16 (m, 10H), 7.12 (d, *J* = 8.0, 2H), 6.46 (d, *J* = 15.8, 1H), 6.16 (dt, *J* = 15.2, 7.6, 1H), 3.80 – 3.69 (m, 1H), 2.89 – 2.79 (m, 1H), 2.77 – 2.66 (m, 1H), 2.51 – 2.42 (m, 1H), 2.35 – 2.29 (m, 4H), 1.88 – 1.79 (m, 2H), 1.55 (s, 1H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 142.20, 137.22, 134.54, 133.30,

129.39, 128.61, 128.55, 126.16, 125.98, 125.10, 70.56, 41.45, 38.66, 32.23, 21.33. EI-MS (*m/z*): 266.20 $[M]^+$



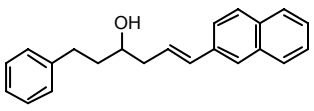
2p: (*E*)-1-phenyl-6-*o*-tolyl-5-hexen-3-ol

o-Tolylmagnesium bromide was prepared as a 2.96 M solution in Et_2O. Performed on a 0.5 mmol scale using $ClTi(O^iPr)_3$. Isolated 119 mg as a 1:2 mixture of **2p**:**3p**; spectral peaks for **2p** were assigned after hydrogenation of the mixture. ^1H NMR (400 MHz, $cdcl_3$) δ 7.43 (t, *J* = 3.9, 1H), 7.33 – 7.27 (m, 2H), 7.25 – 7.17 (m, 3H), 7.17 – 7.07 (m, 3H), 6.70 (d, *J* = 15.7, 1H), 6.10 (ddd, *J* = 15.2, 7.8, 6.8, 1H), 3.81 – 3.73 (m, 1H), 2.90 – 2.57 (m, 2H), 2.54 – 2.46 (m, 1H), 2.43 – 2.36 (m, 1H), 2.34 (s, 3H), 2.30 (s, 6H), 1.90 – 1.69 (m, 1H), 1.69 – 1.52 (m, 1H). ^{13}C NMR (126 MHz, $cdcl_3$) δ 142.19, 136.45, 135.23, 130.45, 130.33, 128.64, 127.55, 127.45, 126.25, 126.03, 125.64, 70.52, 41.76, 38.70, 32.27, 20.05. EI-MS (*m/z*): 266.25 $[M]^+$



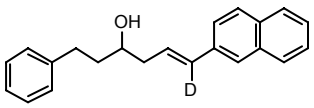
3p: 1-phenyl-6-*o*-tolylhexan-3-ol

^1H NMR (400 MHz, $cdcl_3$) δ 7.29 (d, *J* = 7.1, 2H), 7.21 (d, *J* = 7.0, 3H), 7.14 (s, 4H), 3.67 (s, 1H), 2.88 – 2.75 (m, 1H), 2.75 – 2.55 (m, 3H), 2.32 (s, 3H), 1.89 – 1.69 (m, 3H), 1.69 – 1.52 (m, 3H), 1.48 (s, 1H). ^{13}C NMR (126 MHz, $cdcl_3$) δ 142.26, 140.64, 135.96, 130.31, 128.94, 128.57, 126.05, 125.98, 71.35, 39.26, 37.57, 33.33, 32.21, 26.38, 19.49. EI-MS (*m/z*): 268.35 $[M]^+$



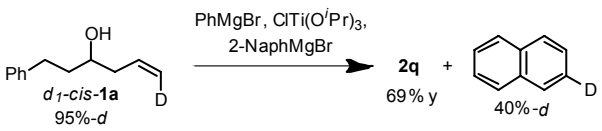
2q: (*E*)-6-(2'-naphthyl)-1-phenyl-5-hexen-3-ol

2-Naphthylmagnesium bromide was prepared as a 1.23 M solution in Et_2O. Performed on a 0.5 mmol scale using $ClTi(O^iPr)_3$. Isolated 105 mg (69.2%) of a yellow solid. ^1H NMR (500 MHz, cdcl$_3$) δ 7.78 (t, *J* = 8.4, 3H), 7.70 (s, 1H), 7.58 (dd, *J* = 8.5, 1.3, 1H), 7.50 – 7.40 (m, 2H), 7.35 – 7.15 (m, 5H), 6.65 (d, *J* = 15.9, 1H), 6.35 (dt, *J* = 15.5, 7.8, 1H), 3.85 – 3.75 (m, 1H), 2.86 (ddd, *J* = 14.5, 9.0, 6.2, 1H), 2.79 – 2.69 (m, 1H), 2.58 – 2.49 (m, 1H), 2.41 (dt, *J* = 14.7, 7.4, 1H), 1.94 – 1.80 (m, 2H), 1.55 (s, 1H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 142.16, 134.79, 133.77, 133.50, 132.99, 128.64, 128.60, 128.33, 128.07, 127.81, 126.69, 126.41, 126.03, 125.99, 125.88, 123.61, 70.62, 41.58, 38.73, 32.25. EI-MS (*m/z*): 302.25 $[M]^+$

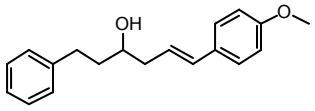


d$_1$-**2q:** (*E*)-6-(2'-naphthyl)-1-phenyl-(6-$^2H_1$)hexen-3-ol

Performed on a 0.5 mmol scale using *d*$_1$-*trans*-**1a** and $ClTi(O^iPr)_3$. 2-Naphthylmagnesium bromide was prepared as a 1.66 M solution in Et_2O. The reaction was quenched by the addition of 5 mmol *p*-nitrobenzaldehyde (0.5 M in 1:1 Et_2O:CH_2Cl_2) at 0 °C. After 2.5 hours, the reaction was worked up as usual. Deuterium incorporation was determined by ^1H NMR to be 87%. ^1H NMR (500 MHz, cdcl$_3$) δ 7.79 (t, *J* = 8.8, 3H), 7.70 (s, 1H), 7.59 (d, *J* = 8.5, 1H), 7.50 – 7.41 (m, 2H), 7.32 (t, *J* = 7.4, 2H), 7.29 – 7.17 (m, 3H), 6.64 (d, *J* = 15.5, 0H), 6.35 (s, 1H), 3.85 – 3.74 (m, 1H), 2.85 (dt, *J* = 14.5, 7.2, 1H), 2.75 (dt, *J* = 15.0, 7.5, 1H), 2.58 – 2.47 (m, 1H), 2.41 (dt, *J* = 14.8, 7.4, 1H), 1.98 – 1.75 (m, 3H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 142.16, 134.71, 133.76, 132.98, 128.64, 128.59, 128.07 (t, $^2J_{C\text{-}D}$ = 32.6), 126.57, 126.41, 126.03, 125.96, 125.88, 123.58, 70.61, 41.53, 38.74, 32.26. EI-MS (*m/z*): 303.35 $[M]^+$

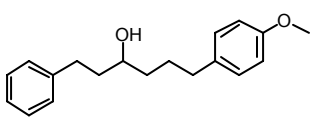


Performed on a 0.5 mmol scale. 2-Naphthylmagnesium bromide was prepared as a 1.66 M solution in Et_2O. The reaction was quenched by the addition of 5 mmol *p*-nitrobenzaldehyde (0.5 M in 1:1 Et_2O:CH_2Cl_2) at 0 °C. After 2.5 hours, the reaction was worked up as usual. Naphthalene deuterium incorporation was calculated from the crude GCMS using the algorithm described by Gruber *et al.* and found to be 40.2%.[6]



2r: (*E*)-6-(4'-methoxyphenyl)-1-phenyl-5-hexen-3-ol

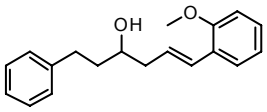
4-methoxyphenylmagnesium bromide was prepared as a 2.5 M solution in Et_2O. Performed on a 0.5 mmol scale using ClTi(O^{i}Pr)$_3$. Isolated 117 mg as a 1:1 mixture of **2r**:**3r**. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.33 – 7.26 (m, 4H), 7.20 (dd, *J* = 14.3, 7.1, 3H), 6.85 (d, *J* = 8.7, 2H), 6.43 (d, *J* = 15.8, 1H), 6.07 (dt, *J* = 14.8, 7.6, 1H), 3.81 (s, 3H), 3.77 – 3.70 (m, 1H), 2.89 – 2.79 (m, 1H), 2.76 – 2.66 (m, 1H), 2.50 – 2.41 (m, 1H), 2.32 (dt, *J* = 14.8, 7.4, 1H), 1.88 – 1.79 (m, 2H), 1.55 (s, 1H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 159.17, 142.24, 132.96, 130.16, 128.65, 128.59, 127.43, 126.01, 123.88, 114.14, 70.61, 55.48, 41.48, 38.70, 32.29. EI-MS (*m/z*): 282 [M]$^+$



3r: 6-(4'-methoxyphenyl)-1-phenylhexan-3-ol

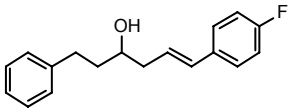
The 1:1 mixture of **2r**:**3r** was hydrogenated with Pd/C in EtOH under an H_2 atmosphere to provide **3r** as a single product. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.29 (t, *J* = 7.6, 2H), 7.19 (d, *J* = 6.0, 3H), 7.09 (d, *J* = 8.5, 2H), 6.83 (d, *J* = 8.8, 2H), 3.79 (s, 3H), 3.64 (ddd, *J* = 12.2, 7.8, 4.7, 1H), 2.78 (ddd, *J* = 14.6, 9.6, 5.8, 1H),

2.66 (ddd, *J* = 13.8, 9.4, 7.0, 1H), 2.57 (t, *J* = 7.4, 2H), 1.81 – 1.68 (m, 3H), 1.68 – 1.55 (m, 1H), 1.55 – 1.44 (m, 3H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 157.88, 142.30, 134.57, 129.46, 128.60, 126.01, 113.90, 71.42, 55.46, 39.27, 37.25, 35.11, 32.25, 27.85. ES-MS (*m/z*): 307.0 $[M+Na]^+$



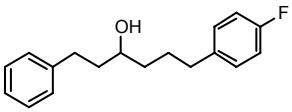
2s: (*E*)-6-(2'-methoxyphenyl)-1-phenyl-5-hexen-3-ol

o-Methoxyphenylmagnesium bromide was prepared as a 2.25 M solution in Et_2O. Performed on a 0.5 mmol scale using $ClTi(O^iPr)_3$. Isolated 106 mg (75%). ^{1}H and ^{13}C NMR spectra match previously reported spectra.[7] EI-MS (*m/z*): 282.25 $[M]^+$



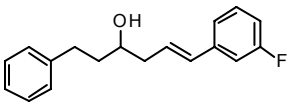
2t: (*E*)-6-(4'-fluorophenyl)-1-phenyl-5-hexen-3-ol

p-Fluorophenylmagnesium bromide was prepared as a 3.99 M solution in Et_2O. Performed on a 0.5 mmol scale using $ClTi(O^iPr)_3$. Isolated 99 mg of a 5.3:1 mixture of **2t**:**3t**; spectral peaks for the major product were assigned after hydrogenation of the mixture. ^{1}H NMR (400 MHz, cdcl3) δ 7.35 – 7.27 (m, 5H), 7.25 – 7.17 (m, 4H), 6.99 (t, J = 8.6, 2H), 6.44 (d, J = 16.0, 1H), 6.14 (dt, J = 15.4, 7.4, 1H), 3.80 – 3.72 (m, 1H), 2.89 – 2.80 (m, 1H), 2.77 – 2.67 (m, 1H), 2.50 – 2.42 (m, 1H), 2.34 (dt, J = 15.2, 7.6, 1H), 1.88 – 1.80 (m, 2H), 1.67 (br s, 1H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 162.26 (d, $^1J_{C\text{-}F}$ = 246.3), 142.11, 133.51 (d, $^4J_{C\text{-}F}$ = 3.3), 132.17, 128.62, 128.60, 127.72 (d, $^3J_{C\text{-}F}$ = 7.9), 126.05, 126.00, 115.57 (d, $^2J_{C\text{-}F}$ = 21.5), 70.58, 41.38, 38.72, 32.24.EI-MS (*m/z*): 270.20 $[M]^+$



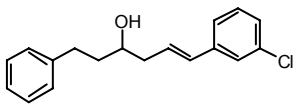
3t: 6-(4'-fluorophenyl)-1-phenylhexan-3-ol

The 5.3:1 mixture of **2t**:**3t** was hydrogenated with Pd/C in EtOH under an H_2 atmosphere to provide **3t**. ^{1}H NMR (500 MHz, cdcl$_3$) δ 7.35 (t, *J* = 7.5, 2H), 7.25 (d, *J* = 7.6, 3H), 7.23 – 7.14 (m, 2H), 7.02 (t, *J* = 8.6, 2H), 3.77 – 3.65 (m, 1H), 2.93 – 2.79 (m, 1H), 2.76 – 2.68 (m, 1H), 2.65 (t, *J* = 6.8, 2H), 1.91 – 1.75 (m, 3H), 1.75 – 1.63 (m, 1H), 1.63 – 1.43 (m, 3H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 161.39 (d, $^1J_{C\text{-}F}$ = 243.9), 142.21, 138.07, 129.86 (d, $^3J_{C\text{-}F}$ = 7.8), 128.61, 128.59, 126.04, 115.19 (d, $^2J_{C\text{-}F}$ = 21.5), 71.33, 39.28, 37.15, 35.20, 32.22, 27.73. EI-MS (*m/z*): 272.15 $[M]^+$



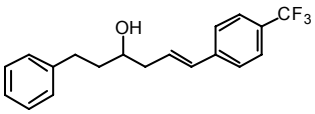
2u: (*E*)-6-(3'-fluorophenyl)-1-phenyl-5-hexen-3-ol

m-Fluorophenylmagnesium bromide was prepared as a 3.42 M solution in Et_2O. Performed on a 0.5 mmol scale using ClTi(O^{i}Pr)$_3$. Isolated 81 mg (60.2%) as a colorless solid and recovered 16.5 mg (0.09 mmol) of starting material. ^{1}H NMR (500 MHz, cdcl$_3$) δ 7.32 – 7.24 (m, 3H), 7.24 – 7.17 (m, *J* = 13.5, 7.1, 3H), 7.10 (d, *J* = 7.7, 1H), 7.05 (d, *J* = 10.2, 1H), 6.91 (td, *J* = 8.3, 1.8, 1H), 6.44 (d, *J* = 15.8, 1H), 6.24 (dt, *J* = 15.2, 7.6, 1H), 3.81 – 3.72 (m, 1H), 2.88 – 2.80 (m, 1H), 2.72 (ddd, *J* = 13.5, 8.8, 6.8, 1H), 2.51 – 2.43 (m, 1H), 2.36 (dt, *J* = 15.0, 7.5, 1H), 1.88 – 1.80 (m, 2H), 1.55 (s, 1H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 163.24 (d, $^1J_{C\text{-}F}$ = 245.1), 142.06, 139.72 (d, $^3J_{C\text{-}F}$ = 7.7), 132.17, 130.11 (d, $^3J_{C\text{-}F}$ = 8.5), 128.60, 127.86, 126.05, 122.16 (d, $^4J_{C\text{-}F}$ = 2.7), 114.19 (d, $^2J_{C\text{-}F}$ = 21.4), 112.66 (d, $^2J_{C\text{-}F}$ = 21.7), 70.53, 41.32, 38.72, 32.20. ES-MS (*m/z*): 270.9 $[M+1]^+$



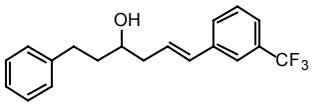
2v: (*E*)-6-(3'-chlorophenyl)-1-phenyl-5-hexen-3-ol

m-Chlorophenylmagnesium bromide was prepared as a 2.28 M solution in Et_2O. Performed on a 0.5 mmol scale using $ClTi(O^iPr)_3$. Isolated 95 mg (66.4%) as a colorless oil and recovered 11.9 mg (0.07 mmol) of starting material. ^1H NMR (500 MHz, cdcl$_3$) δ 7.38 (s, 1H), 7.33 (t, *J* = 7.5, 2H), 7.28 – 7.20 (m, 6H), 6.44 (d, *J* = 15.9, 1H), 6.27 (dt, *J* = 15.0, 7.5, 1H), 3.82 – 3.75 (m, 1H), 2.87 (ddd, *J* = 15.0, 9.0, 6.5, 1H), 2.75 (dt, *J* = 15.0, 7.5, 1H), 2.52 – 2.45 (m, 1H), 2.38 (dt, *J* = 14.5, 7.2, 1H), 1.92 – 1.77 (m, 3H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 142.04, 139.23, 134.63, 131.97, 129.92, 128.61, 128.00, 127.36, 126.16, 126.07, 124.53, 70.55, 41.37, 38.74, 32.22. EI-MS (*m/z*): 286.20 $[M]^+$



2w: (*E*)-1-phenyl-6-(4'-(trifluoromethyl)phenyl)-5-hexen-3-ol

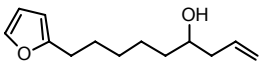
4-(Trifluoromethyl)phenylmagnesium bromide was prepared as a 2.03 M solution in Et_2O. Performed on a 0.5 mmol scale using $ClTi(O^iPr)_3$. Isolated 80.5 mg (50.3%) as a very pale yellow solid and recovered 31.1 mg of starting material (16.7%). ^1H NMR (400 MHz, cdcl$_3$) δ 7.55 (d, *J* = 8.2, 2H), 7.44 (d, *J* = 8.4, 2H), 7.33 – 7.26 (m, 2H), 7.25 – 7.17 (m, 3H), 6.51 (d, *J* = 15.9, 1H), 6.34 (dt, *J* = 15.2, 7.6, 1H), 3.84 – 3.74 (m, 1H), 2.89 – 2.79 (m, 1H), 2.77 – 2.67 (m, 1H), 2.54 – 2.45 (m, 1H), 2.39 (dt, *J* = 14.6, 7.3, 1H), 1.90 – 1.80 (m, 2H), 1.58 (s, 1H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 142.00, 140.83 (q, $^4J_{C\text{-}F}$ = 1.4), 131.98, 129.29, 129.21 (q, $^2J_{C\text{-}F}$ = 32.4), 128.64, 128.62, 126.41, 126.12, 125.66 (q, $^3J_{C\text{-}F}$ = 3.8), 124.41 (q, $^1J_{C\text{-}F}$ = 272.5), 70.60, 41.42, 38.79, 32.22. EI-MS (*m/z*): 320.15 $[M]^+$



2x: (*E*)-1-phenyl-6-(3'-(trifluoromethyl)phenyl)-5-hexen-3-ol

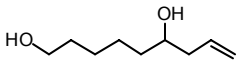
3-(trifluoromethyl)phenylmagnesium bromide was prepared as a 2.39 M solution in Et_2O. Performed on a 0.5 mmol scale using $ClTi(O^iPr)_3$. Isolated 88.3 mg (55.1%) as a pale yellow oil and recovered 22.7 mg (0.13 mmol) of starting material. ^{1}H NMR (500 MHz, cdcl$_3$) δ 7.60 (s, 1H), 7.51 (d, *J* = 7.6, 1H), 7.47 (d, *J* = 7.7, 1H), 7.41 (t, *J* = 7.7, 1H), 7.30 (t, *J* = 7.5, 2H), 7.25 – 7.17 (m, 3H), 6.50 (d, *J* = 15.9, 1H), 6.32 (dt, *J* = 15.0, 7.5, 1H), 3.82 – 3.75 (m, 1H), 2.85 (ddd, *J* = 14.5, 8.8, 6.5, 1H), 2.77 – 2.69 (m, 1H), 2.53 – 2.46 (m, 1H), 2.38 (dt, *J* = 14.8, 7.4, 1H), 1.89 – 1.82 (m, 2H), 1.62 (s, 1H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 142.02, 138.14, 131.87, 131.06 (q, *J* = 32.2), 129.44 (q, $^4J_{C\text{-}F}$ = 1.2), 129.14, 128.62, 128.53, 126.09, 124.33 (q, $^1J_{C\text{-}F}$ = 273.6), 123.93 (q, $^3J_{C\text{-}F}$ = 3.8), 122.86 (q, $^3J_{C\text{-}F}$ = 3.7), 70.56, 41.38, 38.77, 32.22. EI-MS (*m/z*): 320.45 $[M]^+$

Preparation and Characterization of Starting Materials:



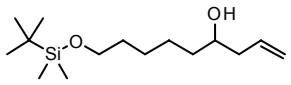
1c: 9-(2'-furanyl)-1-nonen-4-ol

The title compound was prepared from 6-bromohexan-1-ol as described by Cesati *et. al.*[8] The intermediate aldehyde was then allylated using the general procedure described above. ^{1}H NMR (500 MHz, cdcl$_3$) δ 7.29 (d, *J* = 1.0, 1H), 6.27 (dd, *J* = 3.0, 1.9, 1H), 5.97 (dd, *J* = 3.0, 1.0, 1H), 5.88 – 5.77 (m, 1H), 5.14 (d, *J* = 12.1, 2H), 3.67 – 3.60 (m, 1H), 2.62 (t, *J* = 7.6, 2H), 2.34 – 2.26 (m, 1H), 2.17 – 2.09 (m, 1H), 1.65 (p, *J* = 7.5, 2H), 1.58 (s, 1H), 1.51 – 1.43 (m, 3H), 1.41 – 1.31 (m, 3H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 156.58, 140.84, 135.03, 118.31, 110.21, 104.78, 70.77, 42.15, 36.85, 29.32, 28.16, 28.07, 25.58. EI-MS (*m/z*): 284.35 $[M]^+$



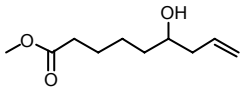
1d: 8-nonen-1,6-diol

$LiAlH_4$ (15.0 mmol, 569 mg, 1.5 equiv) was added portionwise to methyl 6-hydroxy-8-nonenoate (10.0 mmol, 1.86g) in 100 mL THF at 0 °C. The reaction was stirred for 3 hours before adding 0.5 mL H_2O, 0.5 mL 15% NaOH, and 1.5 mL H_2O sequentially. The suspension was filtered through Celite, rinsed with EtOAc, and concentrated to provide 1.08 g (68.4%) of a colorless oil, which needed no further purification. ^{1}H NMR (500 MHz, cdcl$_3$) δ 5.82 (dddd, *J* = 20.0, 9.5, 8.0, 6.5, 1H), 5.14 (d, *J* = 12.3, 2H), 3.70 – 3.61 (m, 3H), 2.38 – 2.25 (m, 1H), 2.14 (ddd, *J* = 15.0, 8.0, 1H), 1.65 – 1.54 (m, 3H), 1.54 – 1.33 (m, 6H), 1.28 (t, *J* = 5.3, 1H).^{13}C NMR (101 MHz, cdcl$_3$) δ 135.01, 118.45, 70.73, 63.14, 42.22, 36.91, 32.89, 25.96, 25.67. ES-MS (*m/z*): 141.1 $[M\text{-}OH]^+$



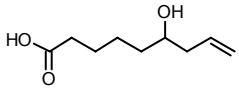
1e: 9-(*tert*-butyldimethylsiloxy)-1-nonen-4-ol

TBDMSCl (2.8 mmol, 419 mg, 1.2 equiv) in 2.7 mL DCM was added to a stirred solution of imidazole (3.5 mmol, 238 mg, 1.5 equiv) 8-nonen-1,6-diol (2.3 mmol, 367 mg) in 7.3 mL DCM at 0 °C. After 20 minutes, the reaction was brought to room temperature and stirred for 1 hour. The reaction was then quenched with saturated NH_4Cl. The aqueous phase was extracted 3 times with DCM, and the combined organic layers were dried over Na_2SO_4 and concentrated to provide 593 mg (94.6% yield) of the title compound without need for purification. ^{1}H NMR (400 MHz, cdcl$_3$) δ 5.94 – 5.73 (m, 1H), 5.20 – 5.06 (m, 2H), 3.68 – 3.62 (m, 1H), 3.60 (t, *J* = 6.4, 2H), 2.34 – 2.26 (m, 1H), 2.18 – 2.09 (m, 1H), 1.58 (s, 1H), 1.57 – 1.42 (m, 5H), 1.40 – 1.30 (m, 3H), 0.89 (s, 9H), 0.04 (s, 6H). ^{13}C NMR (126 MHz, cdcl$_3$) δ 135.33, 118.42, 71.01, 63.59, 42.37, 37.20, 33.22, 26.40, 26.27, 25.90, 18.78, -4.85. ES-MS (*m/z*): 307.0 $[M+Cl]^+$



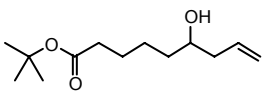
Methyl 6-hydroxy-8-nonenoate

Indium powder (55 mmol, 6.31 g, 1.0 equiv) was added to a vigorously stirred suspension of allyl iodide (55 mmol, 5.05 mL, 1.0 equiv) and methyl 6-oxohexanoate (55 mmol, 7.93 g) in 1 L H_2O at room temperature. After 5 days the reaction was incomplete by TLC, so another 0.2 equiv allyl iodide (11 mmol, 1.01 mL) was added to the reaction. Stirring was continued for another 2 hours at which time the reaction was judged complete by TLC. Half of the reaction was worked up at a time by filtering the suspension through a pad of SiO_2 and rinsing with EtOAc. The aqueous phase was extracted 3 times with EtOAc. The combined organic phases were washed 2 times with H_2O, washed once with brine, dried over Na_2SO_4, and concentrated to provide 9.75 g (93.4%) of a yellow oil, which needed no further purification. ^{1}NMR and ^{13}C NMR matched previously reported spectra.[9]



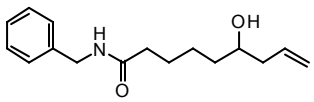
1f: 6-hydroxy-8-nonenoic acid

13 mL of a 3 M aqueous solution of NaOH was added to methyl 6-hydroxy-8-nonenoate (10 mmol, 1.86g) in 50 mL MeOH. The reaction was stirred for 4 hours before the pH was brought to ~2 with 1 M HCl. The reaction was extracted with Et_2O, washed with H_2O and brine, and then dried over Na_2SO_4 and concentrated to provide 1.32 g (76.6%) of a colorless oil, which needed no further purification. ^{1}H NMR (500 MHz, cdcl$_3$) δ 5.90 – 5.74 (m, 1H), 5.15 (s, 1H), 5.12 (d, J = 3.1, 1H), 3.72 – 3.61 (m, 1H), 2.37 (t, J = 7.4, 2H), 2.34 – 2.25 (m, 1H), 2.14 (ddd, J = 14.8, 7.8, 7.8, 1H), 1.74 – 1.58 (m, 2H), 1.57 – 1.34 (m, 4H). ^{13}C NMR (126 MHz, cdcl3) δ 178.77, 134.75, 118.04, 70.81, 41.80, 36.15, 34.07, 25.10, 24.71. ES-MS (*m/z*): 172.1 $[M]^+$



1g: *tert*-butyl 6-hydroxy-8-nonenoate

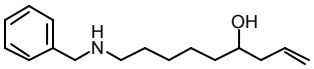
Prepared from *tert*-butyl 6-oxohexanoate as described in general procedures. ^{1}H NMR (400 MHz, cdcl$_3$) δ 5.82 (dddd, *J* = 20.0, 9.6, 8.0, 6.4, 1H), 5.17 – 5.07 (m, 2H), 3.70 – 3.59 (m, 1H), 2.34 – 2.25 (m, 1H), 2.22 (t, *J* = 7.4, 2H), 2.13 (ddd, *J* = 15.6, 7.8, 1H), 1.66 (s, 1H), 1.64 – 1.55 (m, 2H), 1.51 – 1.45 (m, 3H), 1.45 (s, 9H), 1.40 – 1.32 (m, 1H). ^{13}C NMR (101 MHz, cd$_2$cl$_2$) δ 173.31, 134.99, 118.02, 80.15, 70.47, 42.06, 36.47, 35.57, 28.20, 25.22, 25.07. ES-MS (*m/z*): 251.1 $[M+Na]^+$



1h: *N*-benzyl-6-hydroxy-8-nonenamide

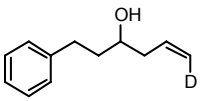
Me_3Al (2.0 M in toluene, 3.0 mL, 2.0 equiv) was added slowly dropwise to a -10 °C solution of benzylamine (6.0 mmol, 655 µL, 2.0 equiv) in 0.6 mL toluene. The reaction was allowed to warm to 4 °C and stirred for 90 minutes before stirring at room temperature for 1 hour. The reaction was then brought to -10 °C, and a solution of methyl 6-hydroxy-8-nonenoate (3.0 mmol, 559 mg) in 0.6 mL toluene was added slowly, rinsing with 0.4 mL toluene. After stirring overnight at room temperature, the viscous pale yellow solution was brought to 0 °C. 3 mL toluene was added before slowly quenching with 4.2 mL H_2O. 10% HCl was added to bring to pH 5, and the mixture was further diluted with H_2O. The aqueous phase was extracted 4 times with EtOAc, and the combined organic layers were washed with 1 M HCl and brine, dried over Na_2SO_4, and concentrated. SiO_2 column chromatography (80-90% EtOAc in hexanes) provided 680 mg (86.7%) of a colorless solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.33 – 7.27 (m, 2H), 7.26 – 7.21 (m, 3H), 6.12 (br s, 1H), 5.88 – 5.71 (m, 1H), 5.13 – 5.06 (m, 2H), 4.38 (d, *J* = 5.7, 2H), 3.69 – 3.54 (m, 1H), 2.29 – 2.22 (m, 1H), 2.19 (t, *J* = 7.6, 2H),

2.16 – 2.06 (m, 2H), 1.74 – 1.55 (m, 2H), 1.52 – 1.30 (m, 4H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 173.09, 138.56, 135.00, 128.78, 127.90, 127.56, 118.10, 70.49, 43.64, 42.12, 36.64, 36.43, 25.68, 25.41. ES-MS (*m/z*): 262.0 $[M+1]^+$



1i: 9-(benzylamino)-1-nonen-4-ol

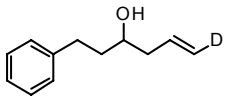
$LiAlH_4$ (1.0 M, 4.53 mL, 2.0 equiv) was added slowly dropwise to a solution of *N*-benzyl-6-hydroxy-8-nonenamide (2.26 mmol, 592 mg) in 3.5 mL THF at room temperature. The reaction was brought to reflux and stirred overnight. The reaction was then cooled to 0 °C before quenching by the sequential addition of 0.17 mL H_2O, 0.17 mL 15% NaOH, and 0.52 mL H_2O. The reaction was filtered through Celite and rinsed with DCM. Concentration provided 507 mg (90.6%) of a yellow oil, which needed no further purification. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.32 (d, *J* = 4.4, 4H), 7.29 – 7.21 (m, 1H), 5.82 (dddd, *J* = 20.4, 9.6, 8.0, 6.8, 1H), 5.13 (dd, *J* = 13.8, 1.5, 2H), 3.79 (s, 2H), 3.68 – 3.59 (m, 1H), 2.63 (t, *J* = 7.2, 2H), 2.35 – 2.24 (m, 1H), 2.13 (ddd, *J* = 14.8, 7.4, 1H), 1.81 (s, 1H), 1.54 (p, *J* = 7.2, 2H), 1.49 – 1.41 (m, 3H), 1.41 – 1.31 (m, 3H), 1.31 – 1.23 (m, 1H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 139.83, 135.17, 128.47, 128.30, 127.08, 117.73, 70.48, 53.86, 49.13, 42.08, 36.73, 29.76, 27.32, 25.57. ES-MS (*m/z*): 248.2 $[M+1]^+$



d$_1$-*cis*-**1a:** (*Z*)-1-phenyl-(6-^{2}H$_1$)hex-5-ene-3-ol

1-Phenyl-5-hexyn-3-ol (4.4 mmol, 767 mg) was dissolved in 5 mL hexanes and 2.5 mL THF and brought to -78 °C. *n*-Butyllithium (1.6M in hexanes, 6.9 mL, 2.5 equiv) was added slowly, and stirring continued for 1 hour. The reaction was

then quenched at -35 °C with 3 mL D_2O and allowed to warm to room temperature. The product was extracted three times with EtOAc, washed with brine, dried over Na_2SO_4, and concentrated. The crude deuterium-labeled alkyne (3.9 mmol), 40 mg Lindlar's catalyst and quinoline (92 µL, 0.2 equiv) were stirred in 40 mL toluene under an atmosphere of H_2, and the reaction was monitored by TLC. When the reaction was complete, the crude mixture was filtered through Celite, rinsed thoroughly with DCM, and concentrated. Isolated 480 mg (69.4%) as a pale yellow oil. Deuterium incorporation was determined by ^{1}H NMR to be 95%. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.29 (t, *J* = 7.4, 2H), 7.25 – 7.15 (m, 3H), 5.88 – 5.76 (m, 1H), 5.14 (d, *J* = 10.2, 1H), 3.74 – 3.63 (m, 1H), 2.82 (dt, *J* = 18.0, 9.0, 1H), 2.70 (dt, *J* = 18.0, 9.0, 1H), 2.39 – 2.28 (m, 1H), 2.19 (dt, *J* = 18.5, 9.2, 1H), 1.84 – 1.75 (m, 2H), 1.65 (br s, 1H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 142.17, 134.68, 128.54, 128.50, 125.92, 118.01 (t, $^2J_{C\text{-}D}$ = 23.6), 70.07, 42.14, 42.09, 38.53, 32.13. EI-MS (*m/z*): 177.15 $[M]^+$



d_1-trans-**1a:** (*E*)-1-phenyl-(6-$^2H_1$)hex-5-ene-3-ol

TBSOTf (1.52 mL, 1.5 equiv) was added to a 0 °C solution of 1-phenyl-5-hexyn-3-ol (4.4 mmol) and 2,6-lutidine (1.53 mL, 3.0 equiv) in 10 mL CH_2Cl_2. After 3 hours, the reaction was diluted with EtOAc, washed with water and with brine, dried over Na_2SO_4, and concentrated. The TBS-protected alkyne was dissolved in 4 mL THF and added dropwise to $Cp_2Zr(H)Cl$ (1.08 g, 1.05 equiv) in 4 mL THF. The alkyne was rinsed twice with 1 mL THF. After 2 hours, the reaction was quenched with 1 mL 20% DCl and 5 mL D_2O and stirred at room temperature for 1.5 hours. The product was extracted three times with Et_2O, washed with brine, dried over Na_2SO_4, and concentrated.

The crude TBS-protected deuterated alkene (2.95 mmol) was dissolved in 30 mL THF and brought to 0 °C. TBAF (1.0 M in THF, 3.24 mL, 1.1 equiv) was added, and the reaction allowed to warm to room temperature before the addition of another 0.5 mL TBAF. The reaction was stirred at 4 °C overnight and was then quenched with sat. NH_4Cl. The aqueous phase was extracted three times with Et_2O. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated. Isolated 441 mg (84.4%) as a pale yellow oil. Deuterium incorporation was determined by ^1H NMR to be 85%. ^1H NMR (400 MHz, $cdcl_3$) δ 7.28 (t, J = 7.4, 2H), 7.19 (dd, J = 14.2, 7.2, 4H), 5.82 (dt, J = 16.8, 7.2, 7.2, 1H), 5.11 (d, J = 17.2, 1H), 3.71 – 3.61 (m, 1H), 2.88 – 2.75 (m, 1H), 2.75 – 2.61 (m, 1H), 2.41 (br s, 1H), 2.35 – 2.25 (m, 1H), 2.20 (dt, J = 14.8, 7.5, 1H), 1.85 – 1.71 (m, 2H). ^{13}C NMR (126 MHz, $cdcl_3$) δ 142.10, 134.63, 128.43, 128.37, 125.78, 117.68 (t, $^2J_{C\text{-}D}$ = 24.1), 70.00, 41.98, 38.41, 32.02. EI-MS (*m/z*): 177.15 $[M]^+$

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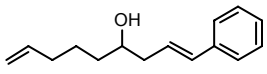
2b: 
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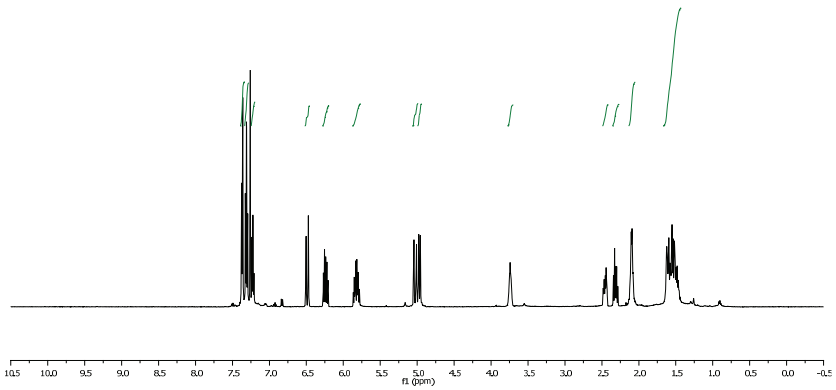
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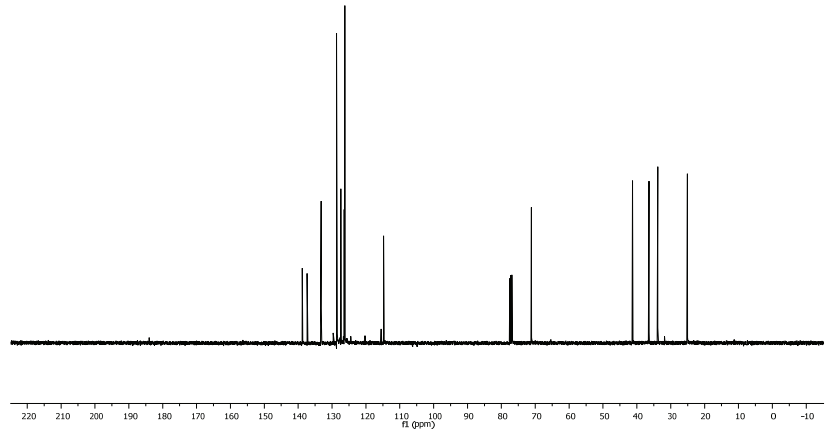
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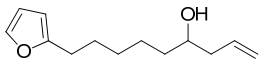
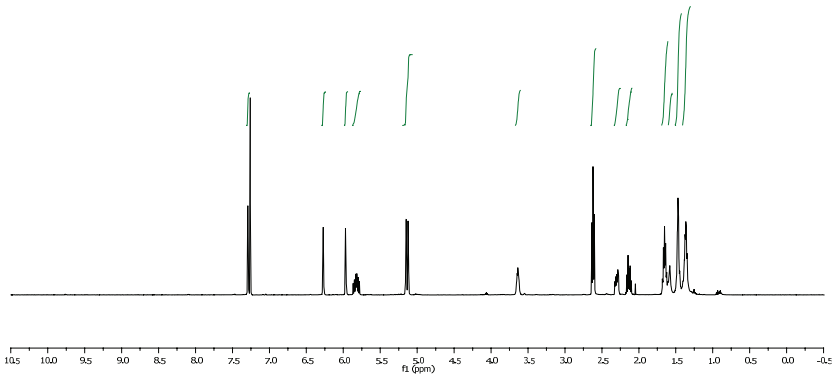
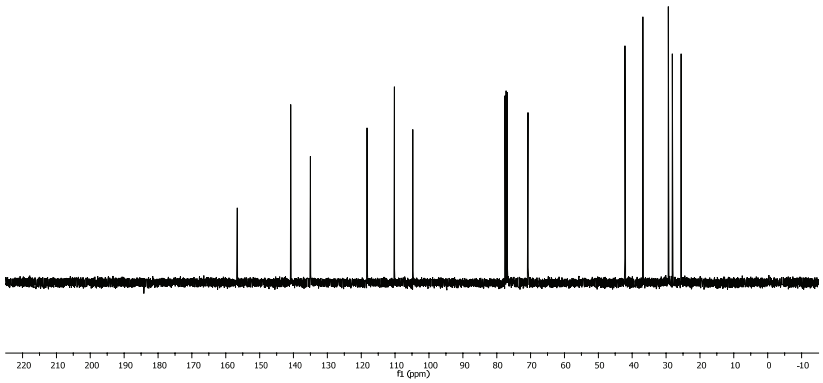
1c: 
OH
O


10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)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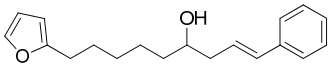
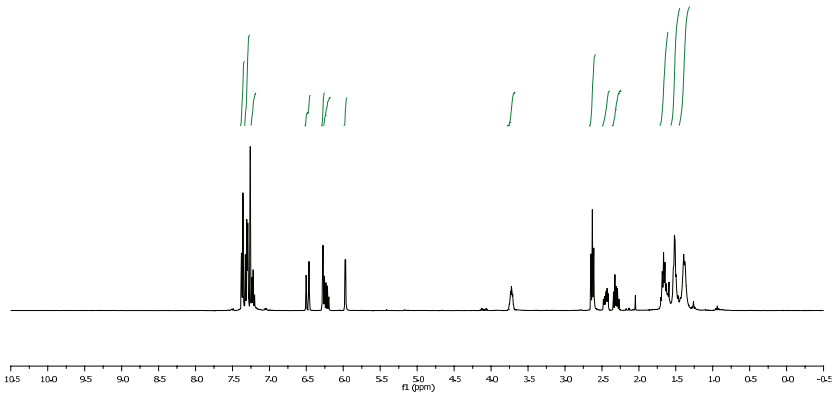
f1 (ppm)

2c:


OH
O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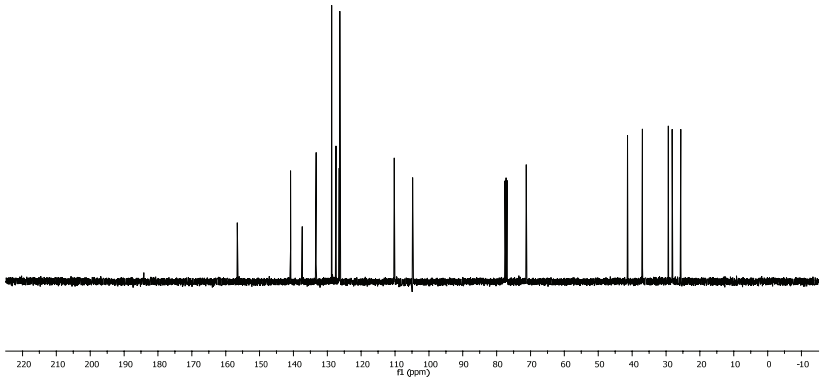
f1 (ppm)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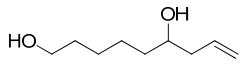
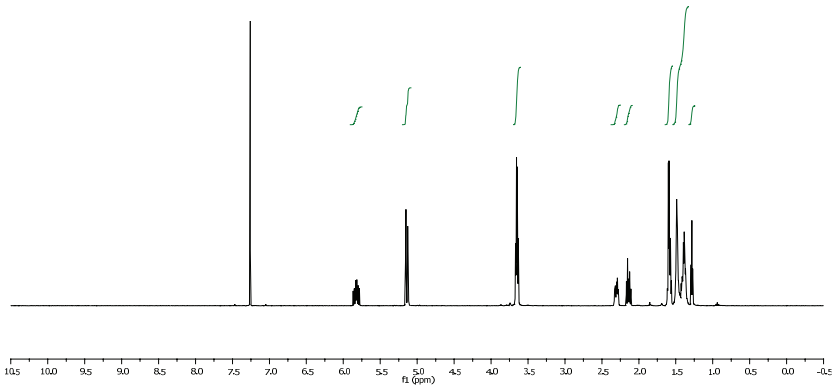
f1 (ppm)

1d: 
OH
HO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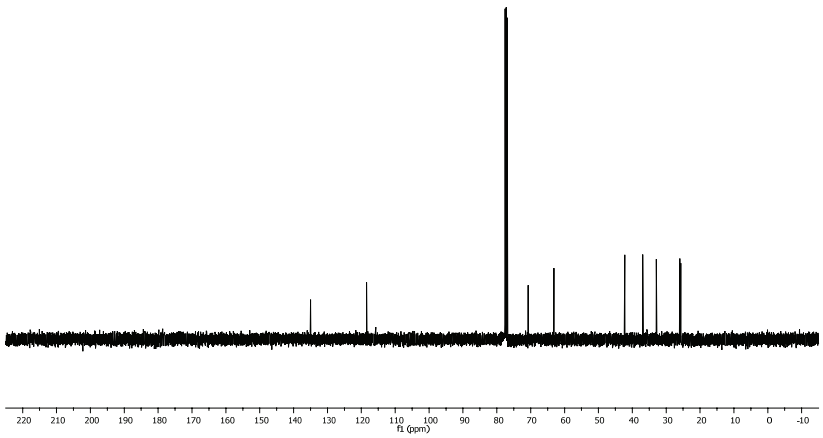
f1 (ppm)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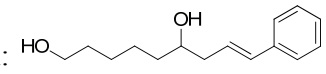
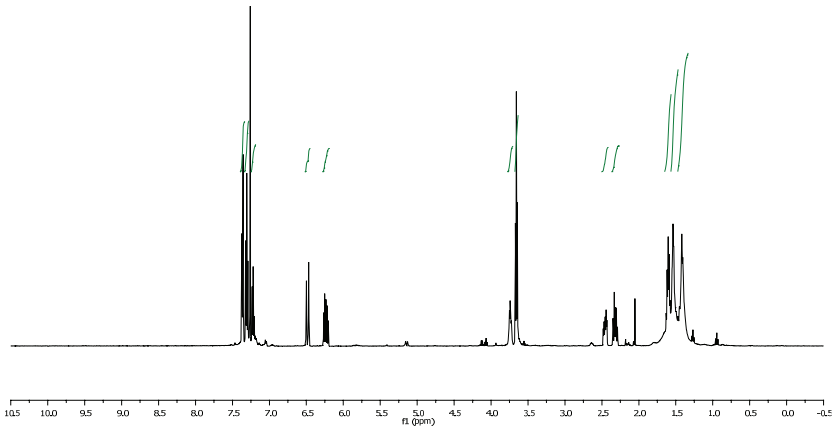
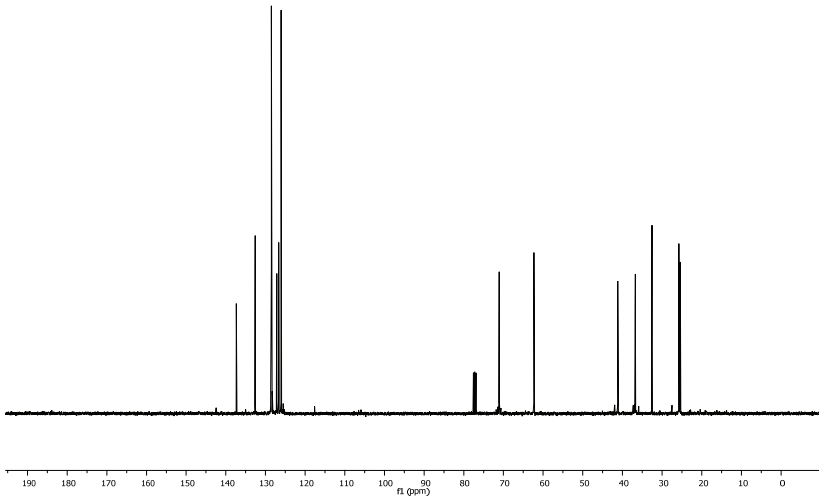
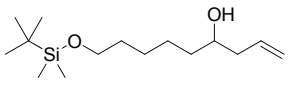
f1 (ppm)

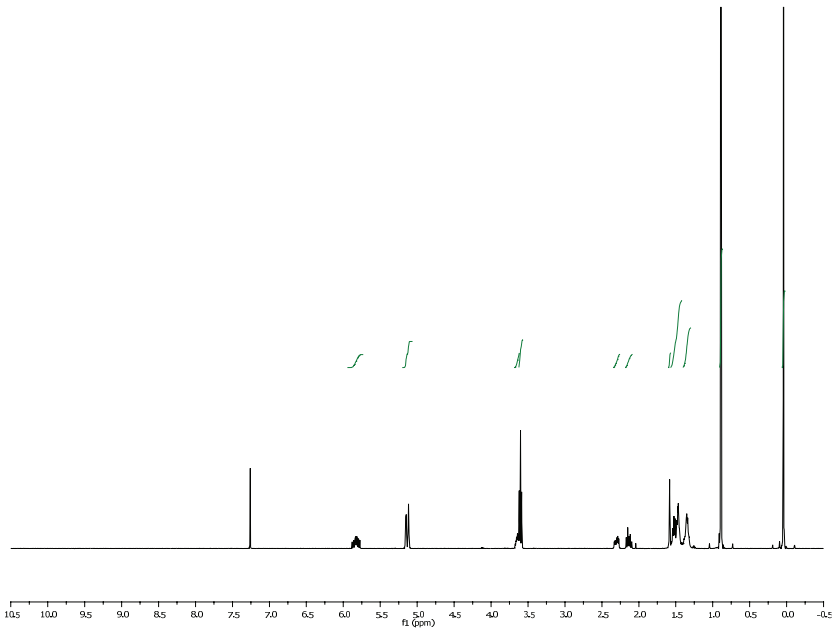
2d: 

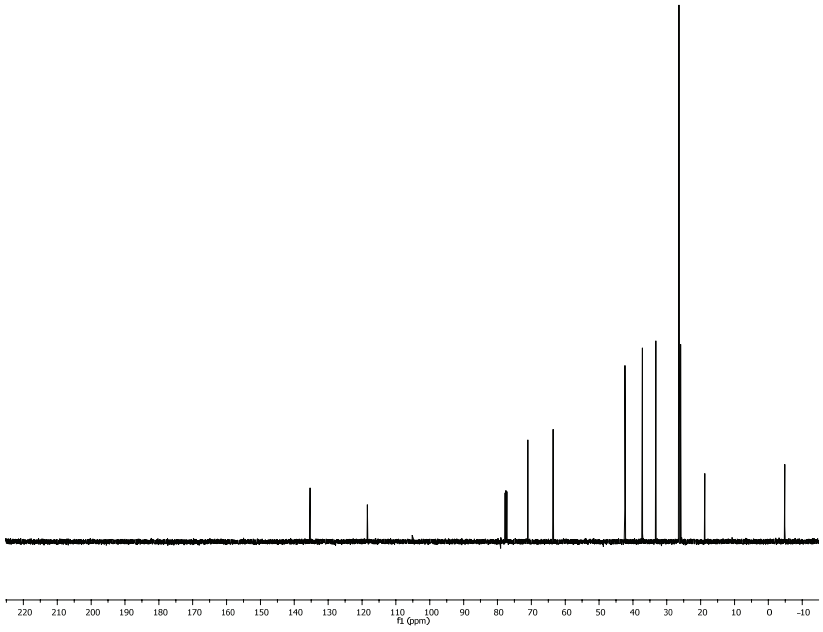




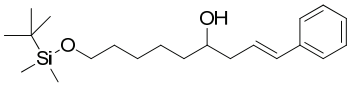
1e:

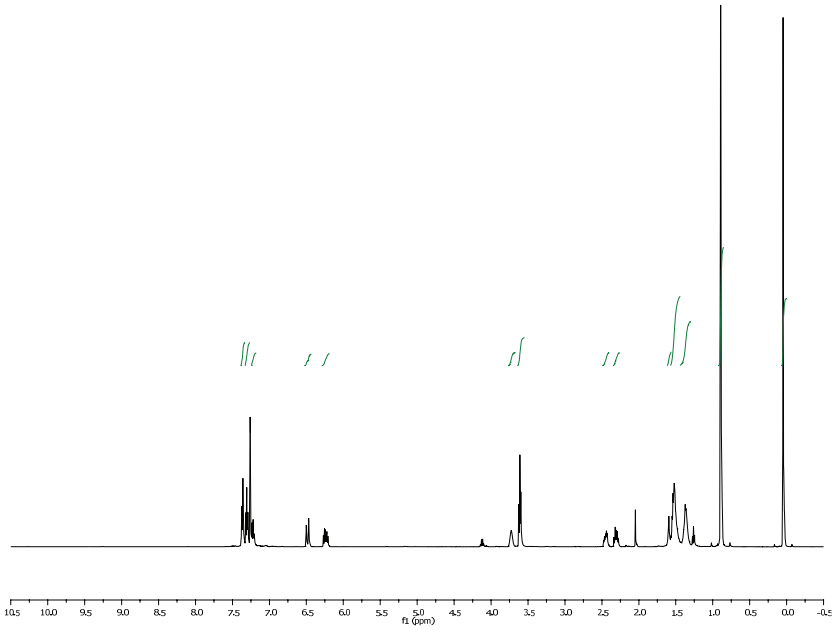






2e:


OH
Si
O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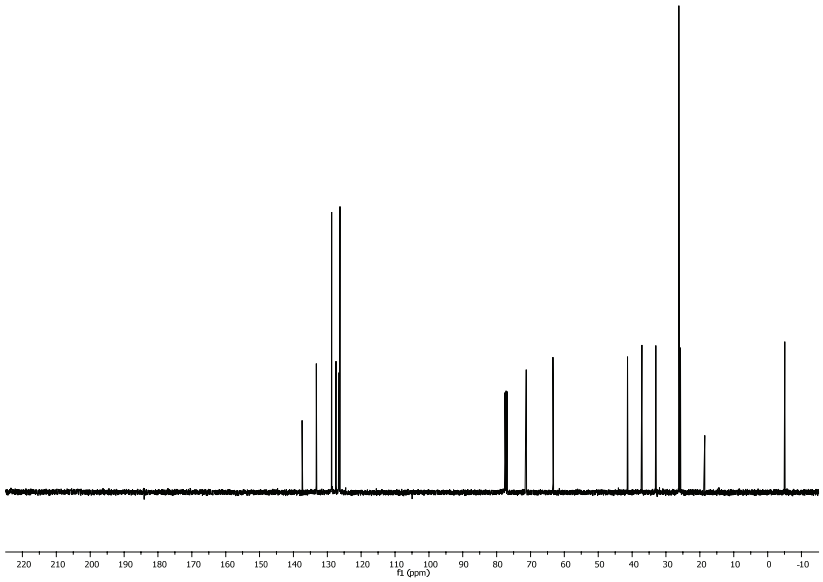
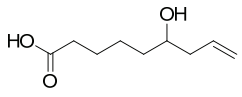
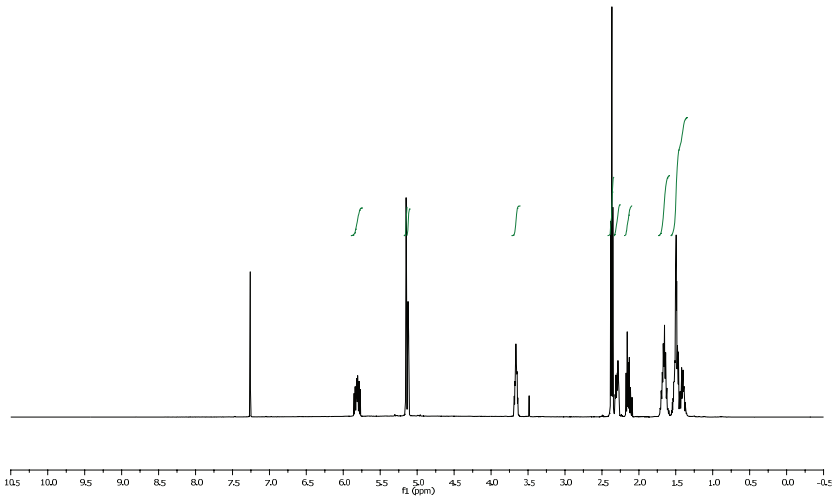
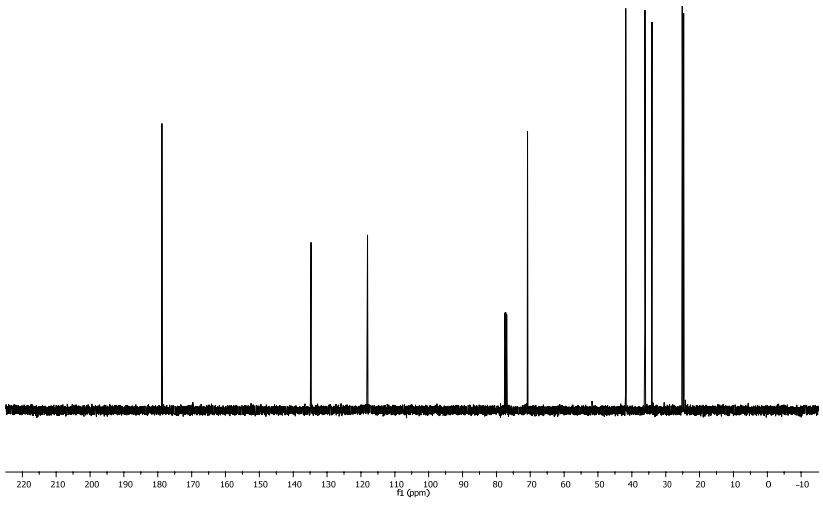
f1 (ppm)

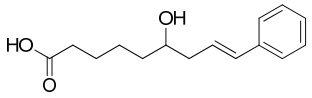

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

1f:

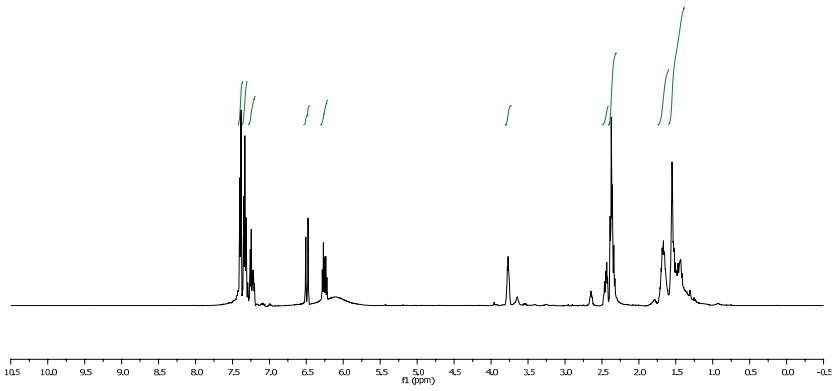


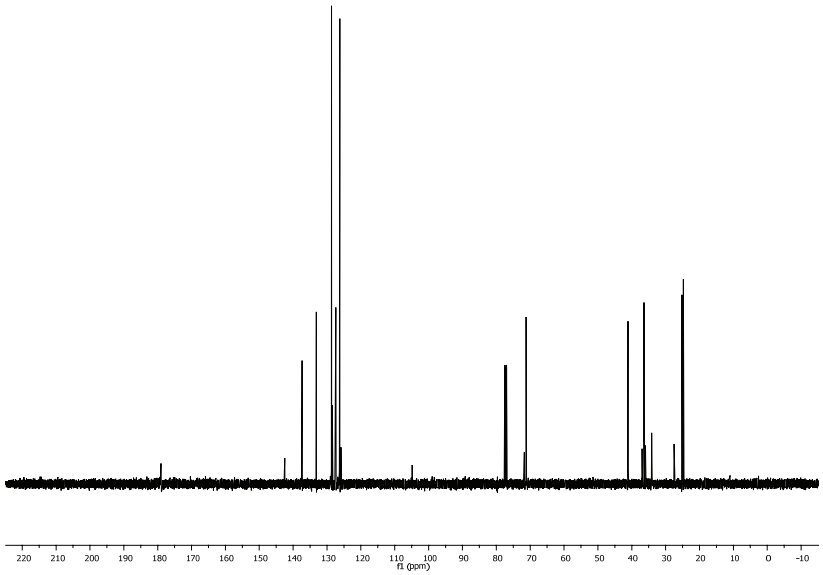




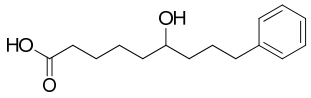
2f: 

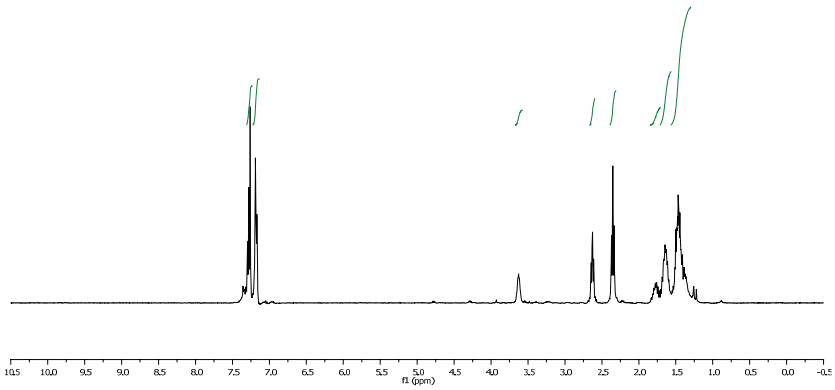
mixture of **2f** and **3f**

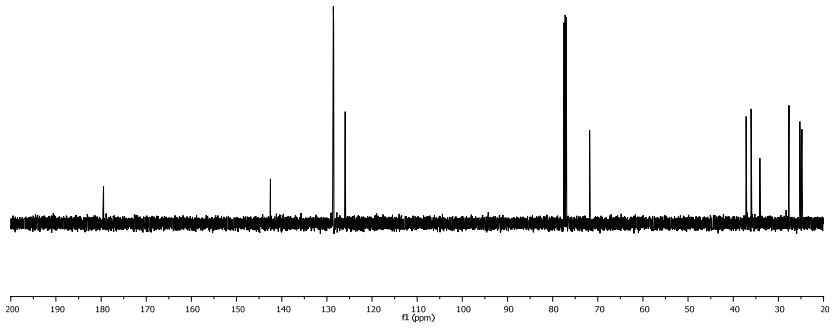




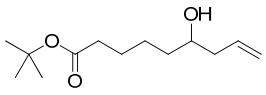
3f:

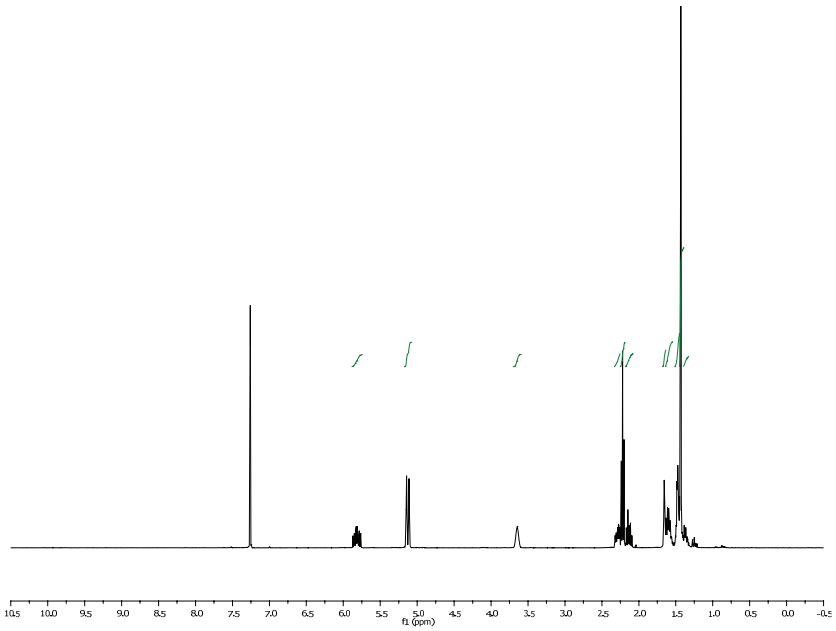






1g:


OH
O
O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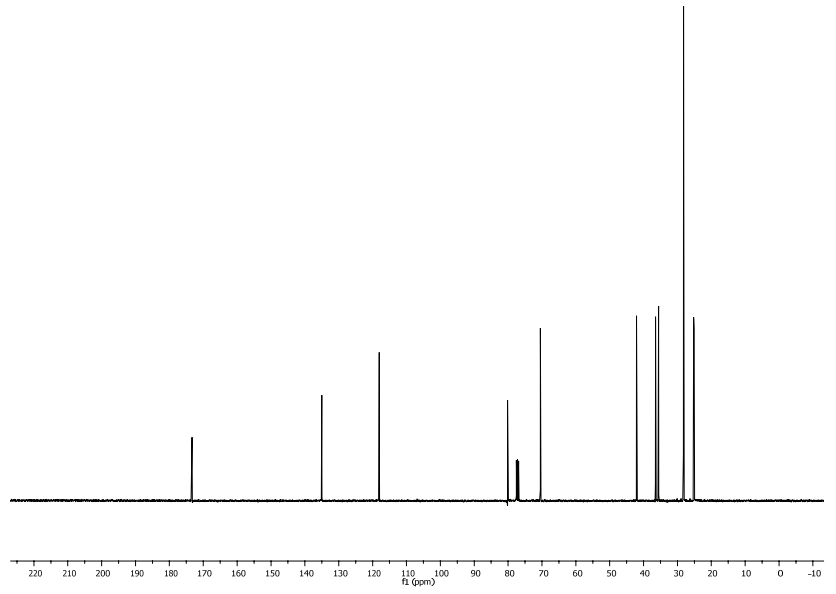
f1 (ppm)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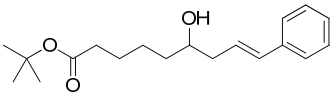
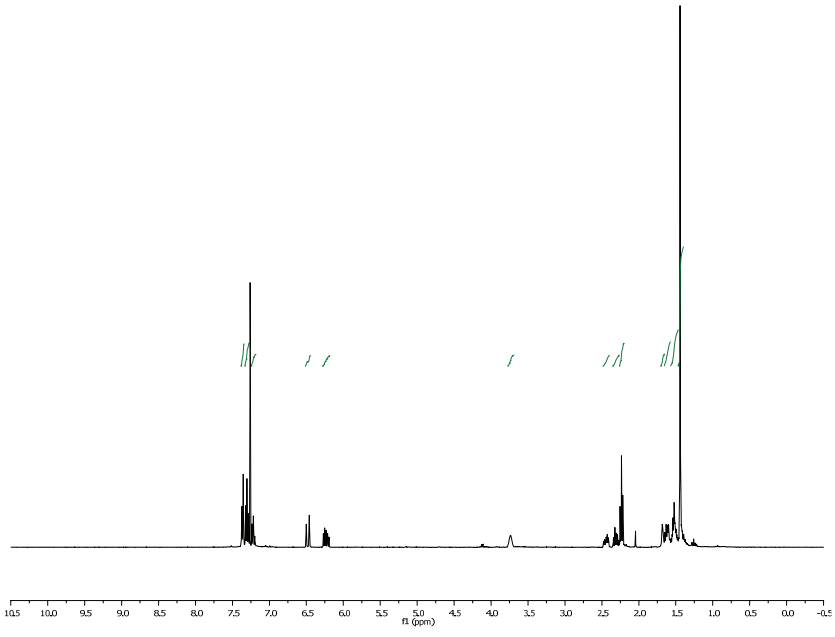
f1 (ppm)

2g:


OH
O
O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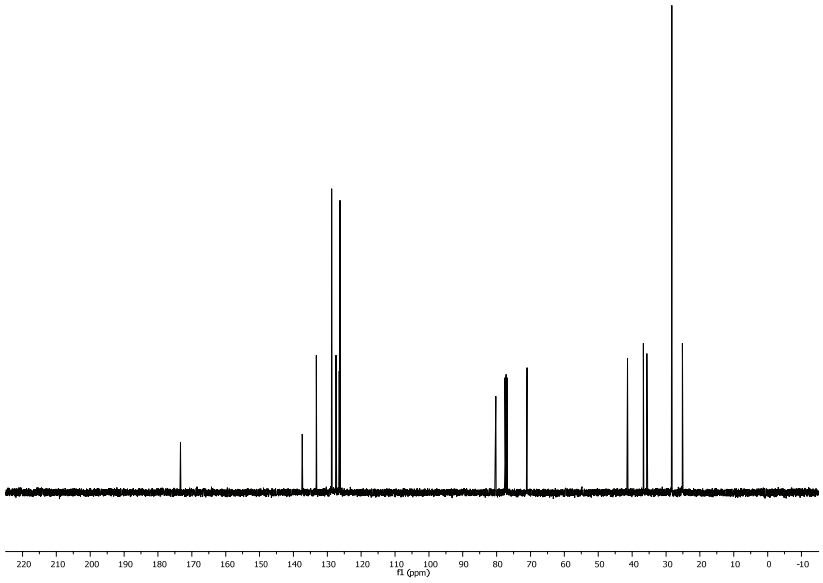
f1 (ppm)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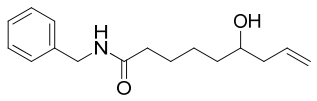
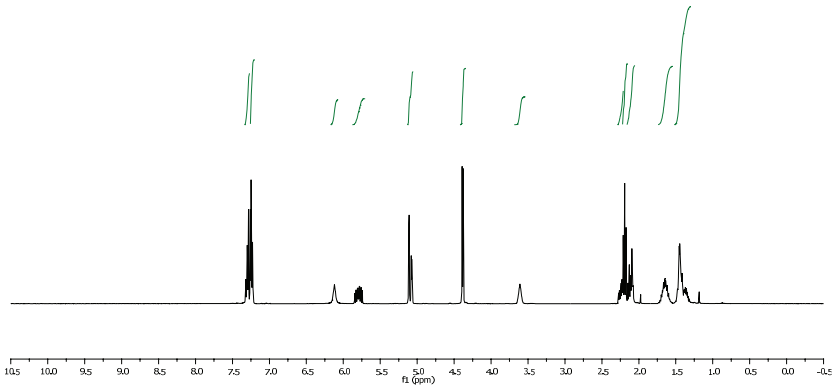
f1 (ppm)

1h:


OH
H
N
O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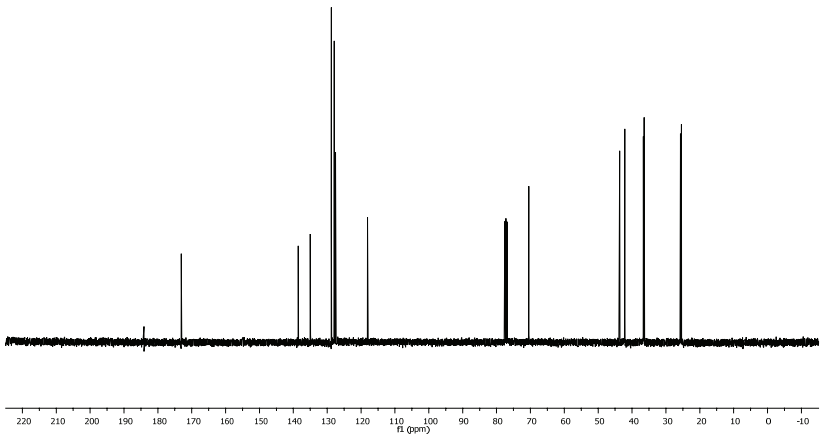
f1 (ppm)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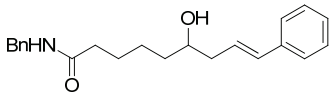
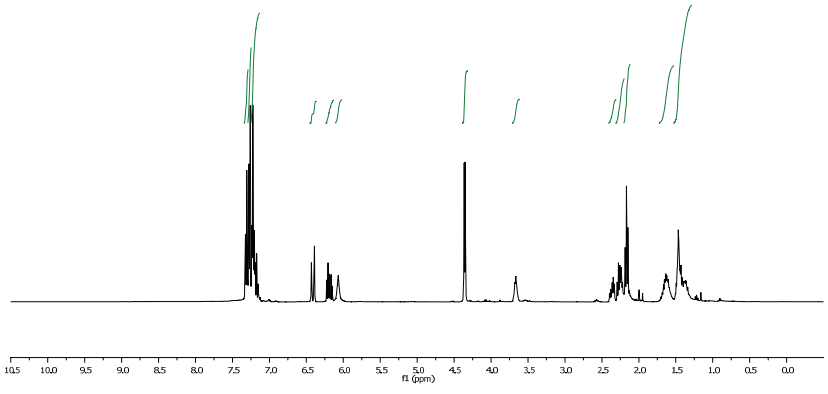
f1 (ppm)

2h:


OH
BnHN
O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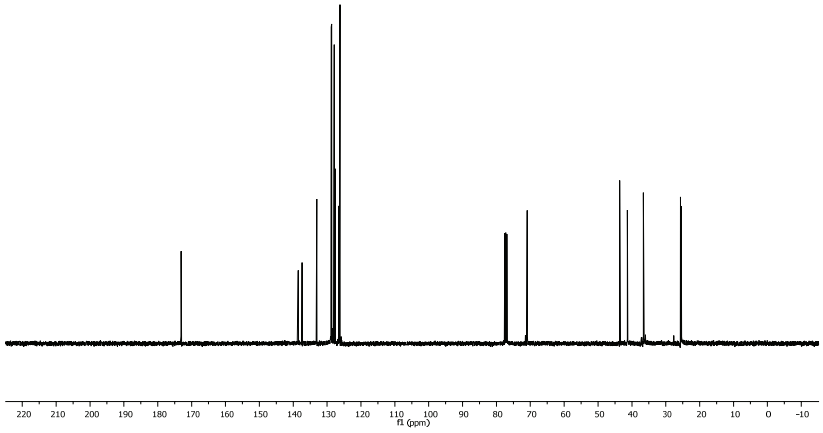
f1 (ppm)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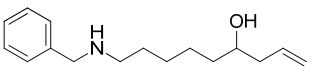
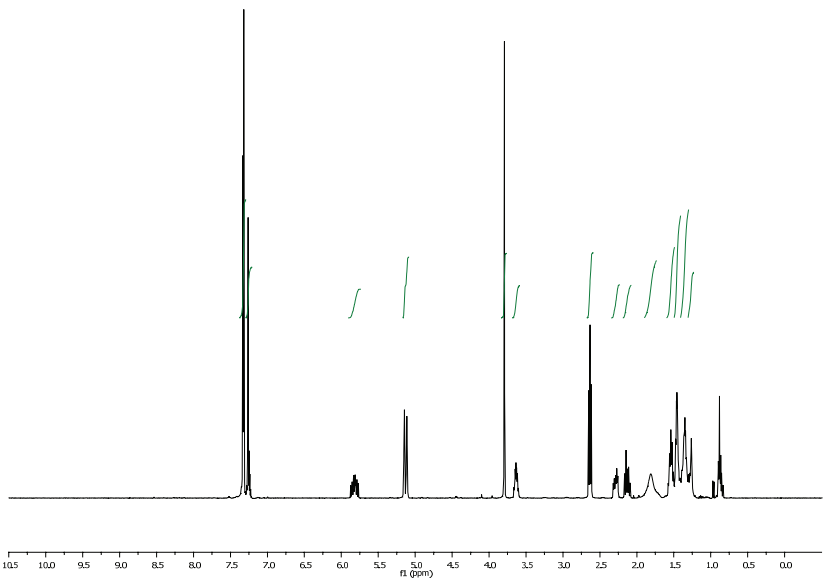
f1 (ppm)

1i:


H
N
OH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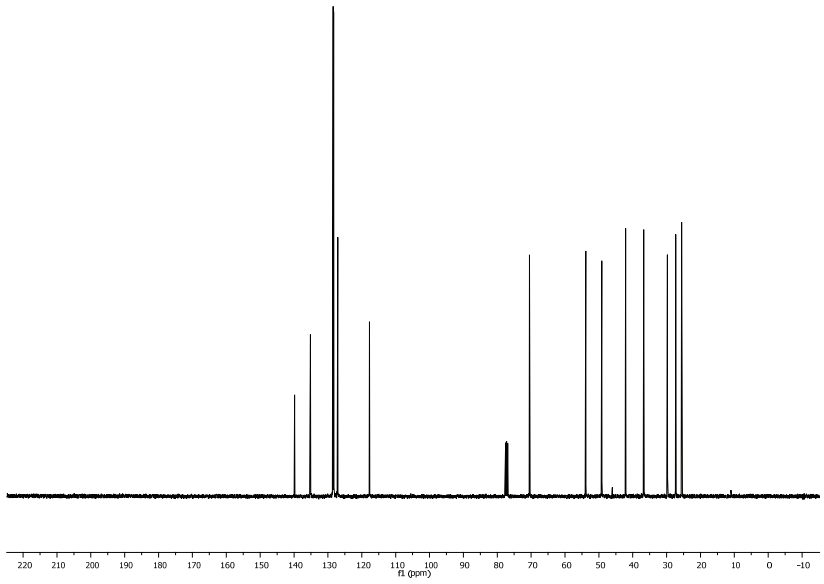
f1 (ppm)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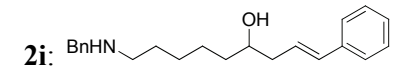
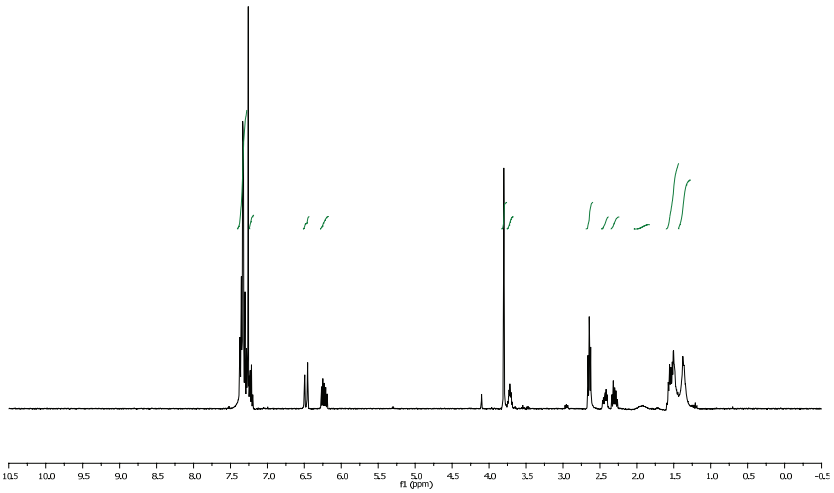
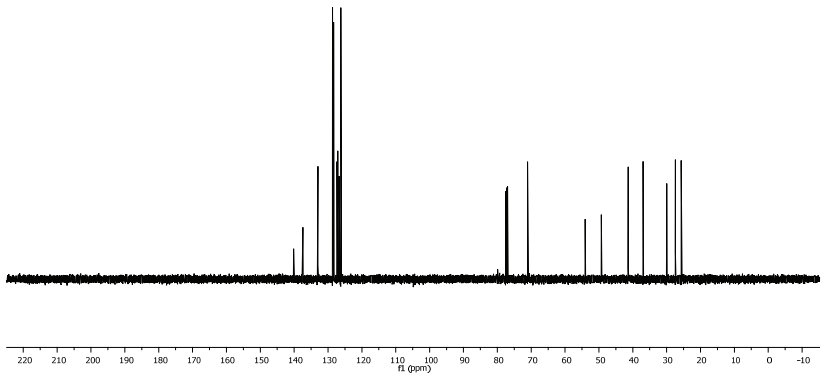
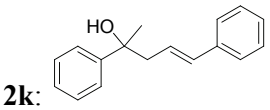
f1 (ppm)

2i: 

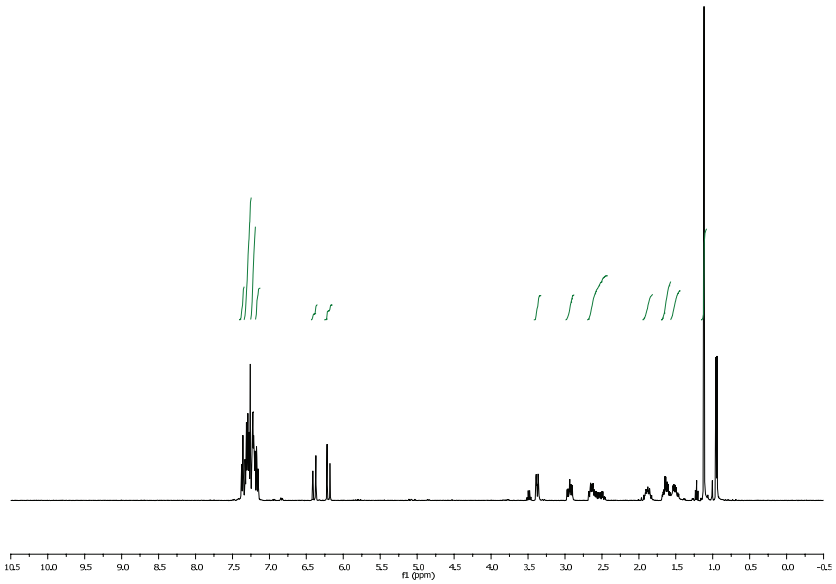


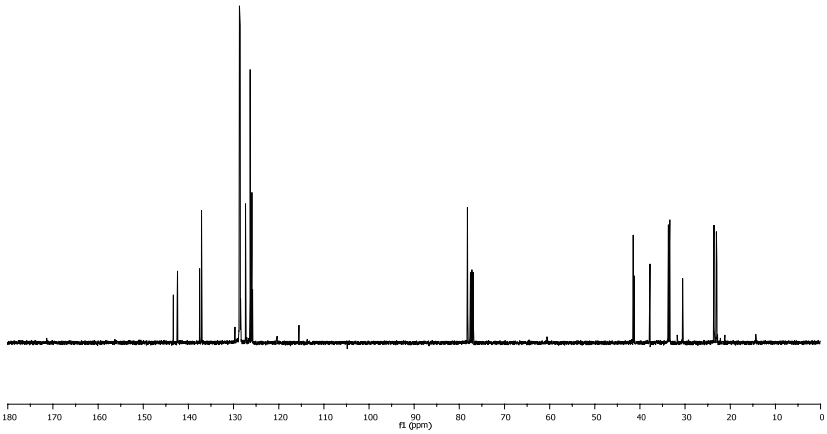




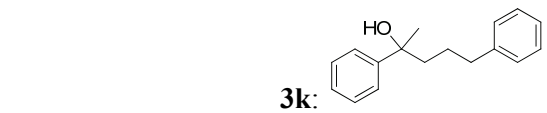
2k:

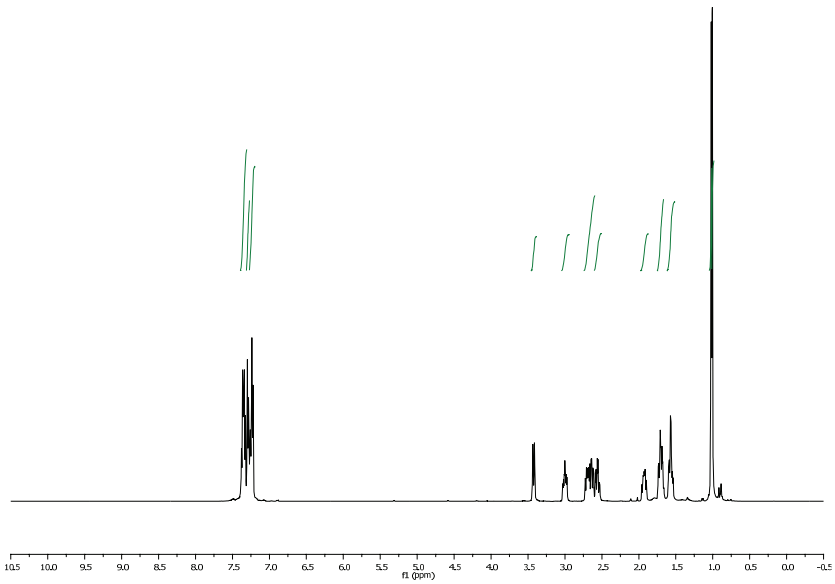
Mixture of **2k** and **3k**





3k:


HO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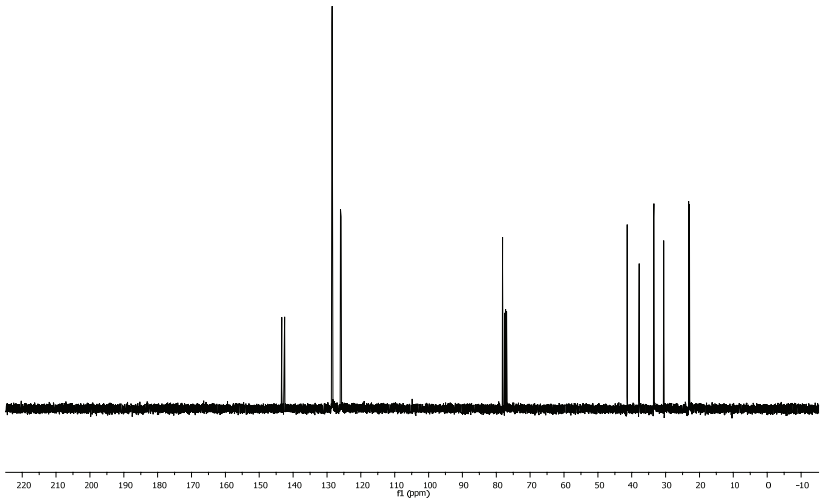
f1 (ppm)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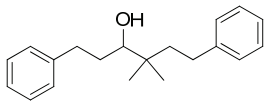
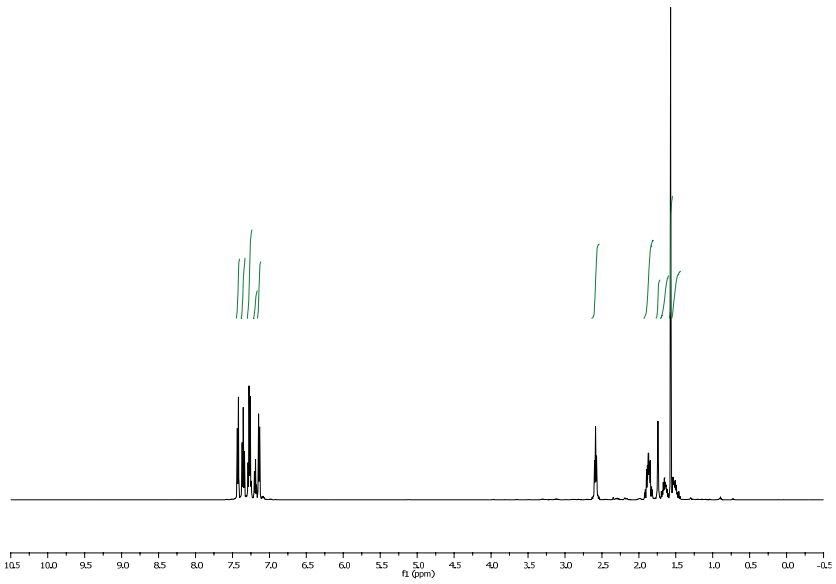
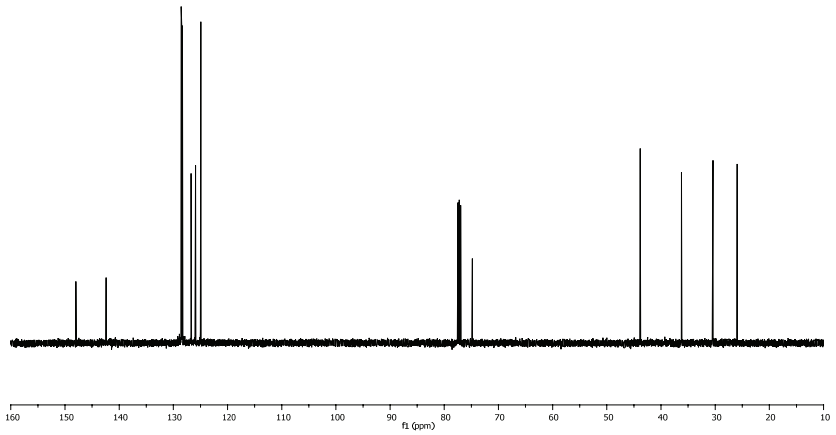
f1 (ppm)

3l:


OH


10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)


160
150
140
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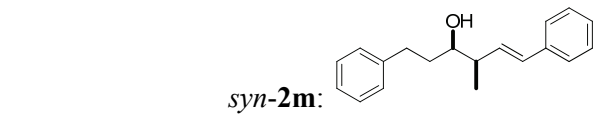
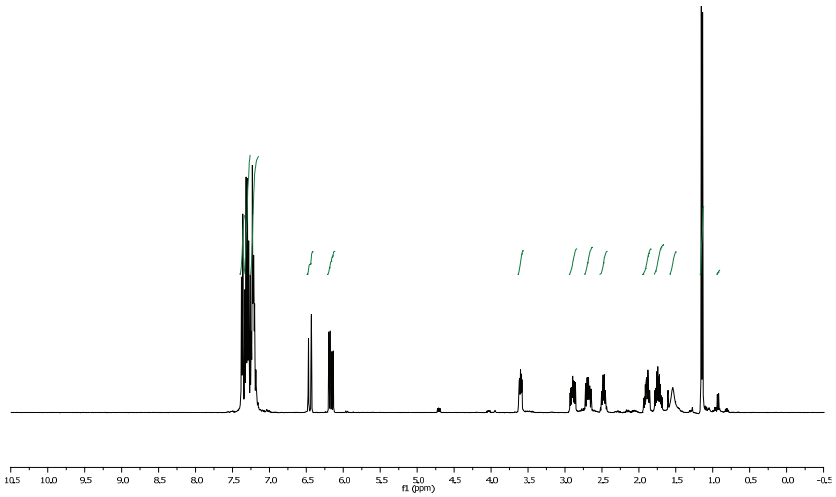
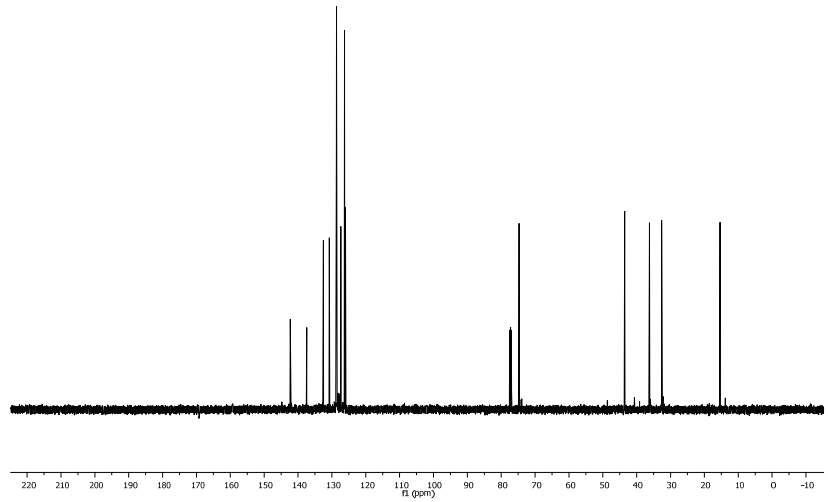
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

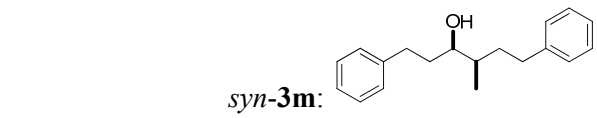
syn-**2m**:

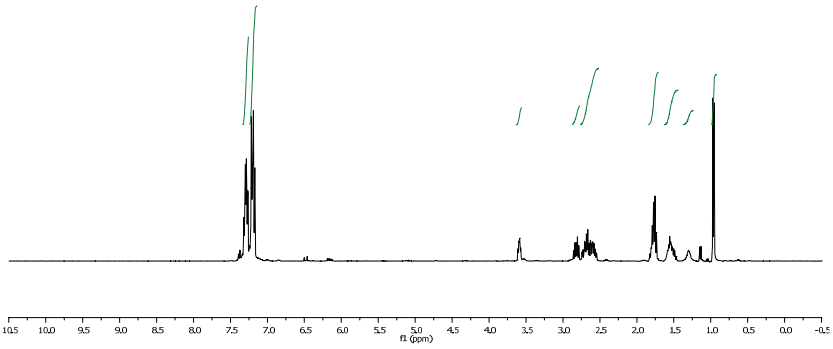


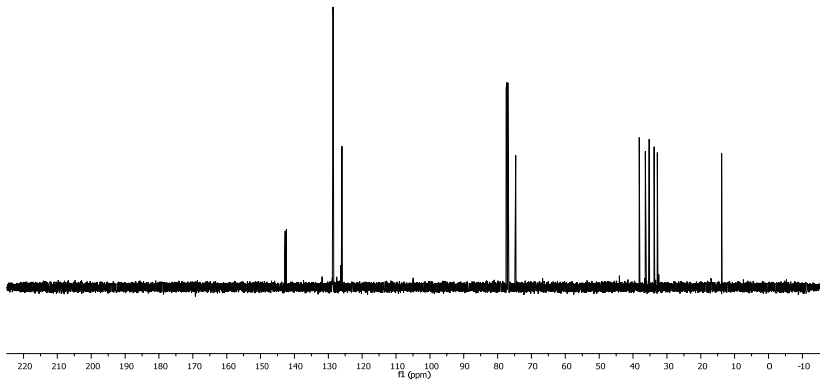




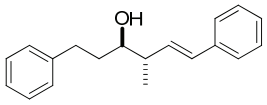
syn-**3m**:

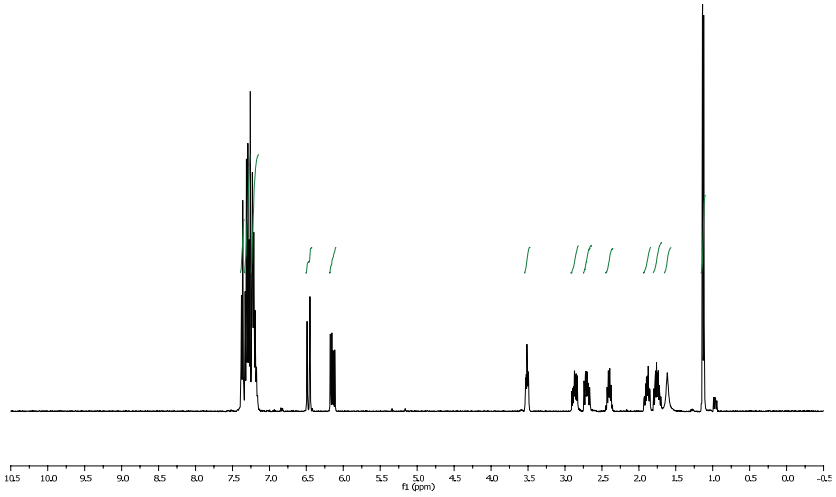

OH

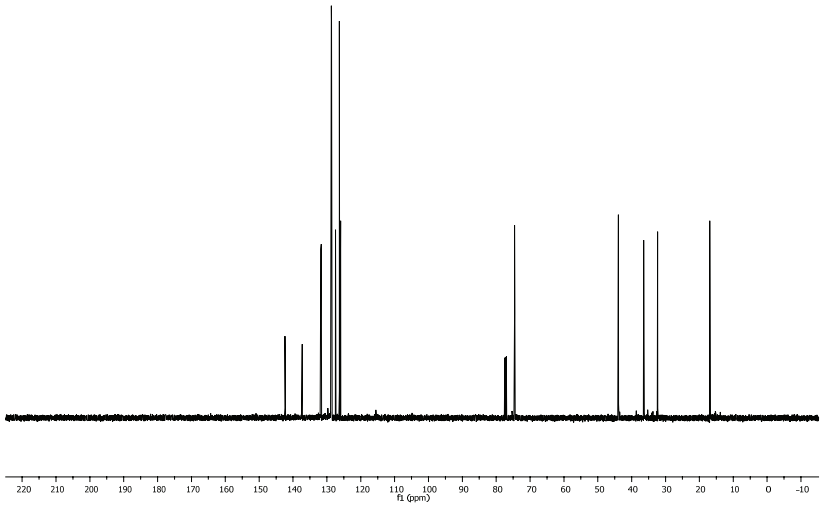

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

anti-**2m**:


OH


10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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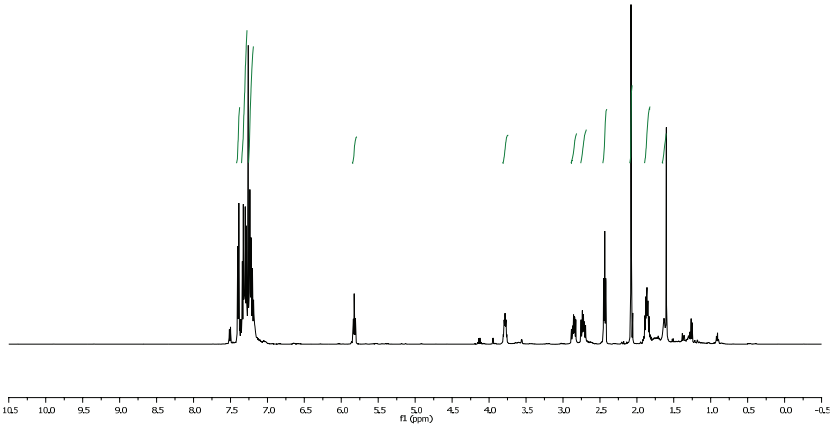
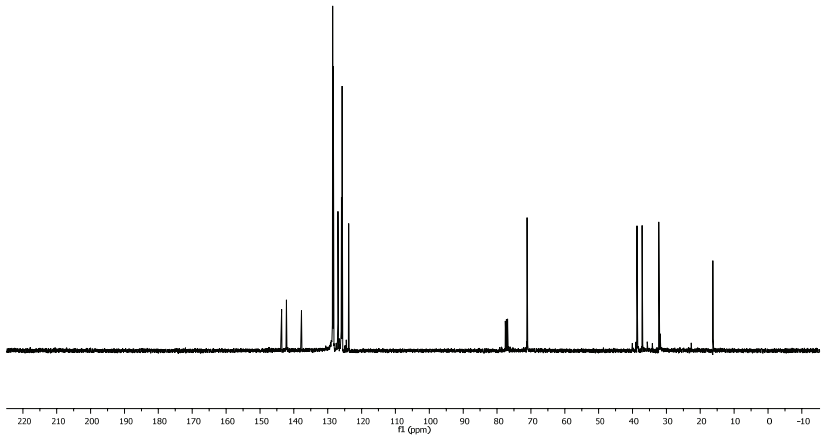
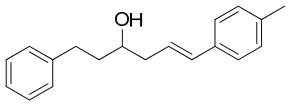
f1 (ppm)

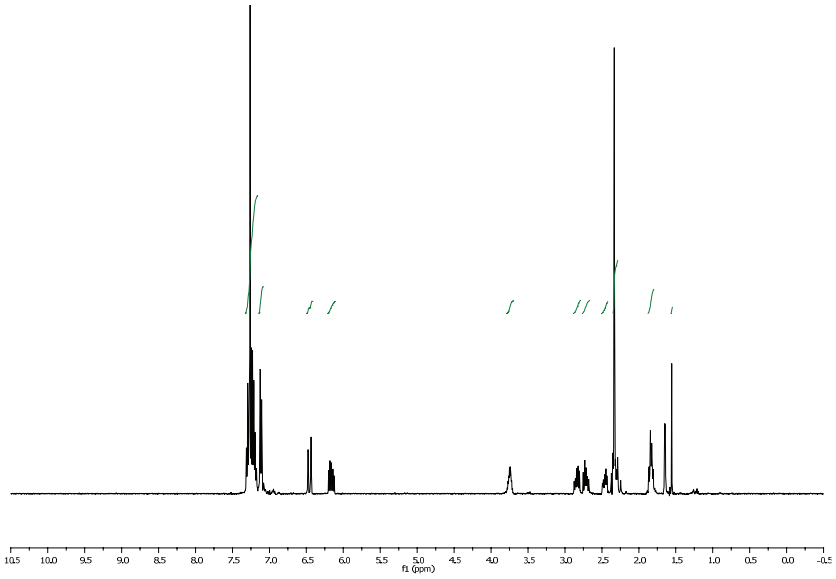
2n:

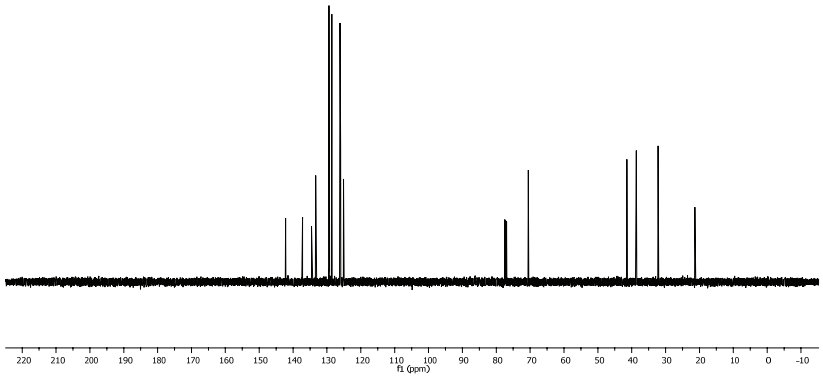

OH
10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

2o:


OH


10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)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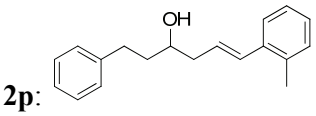
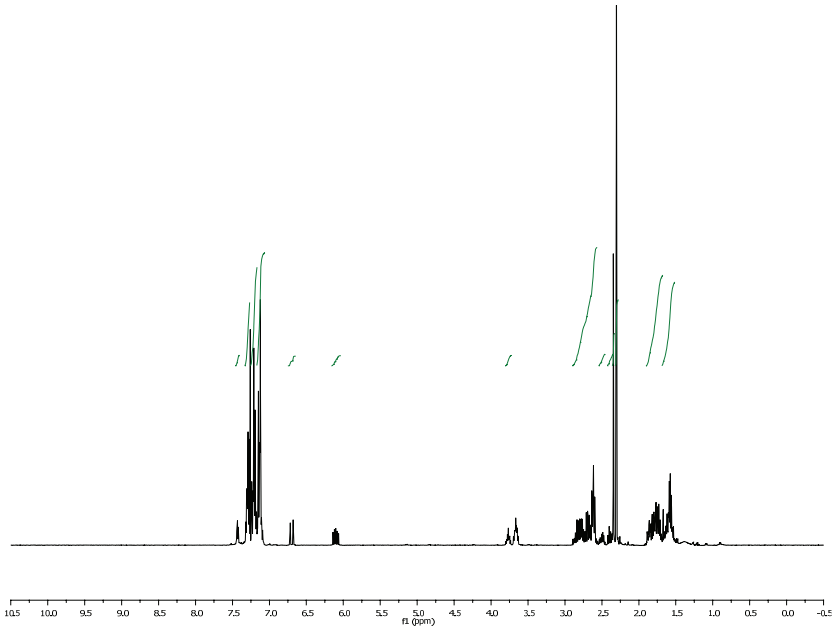
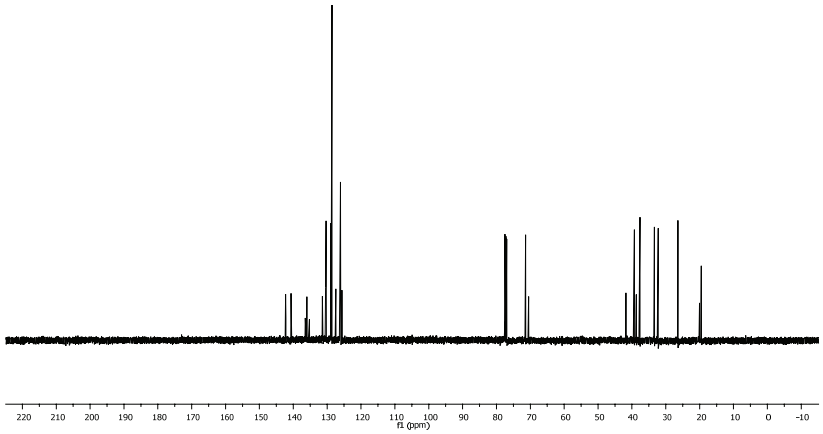
f1 (ppm)



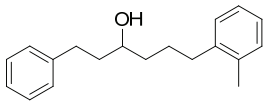
2p:

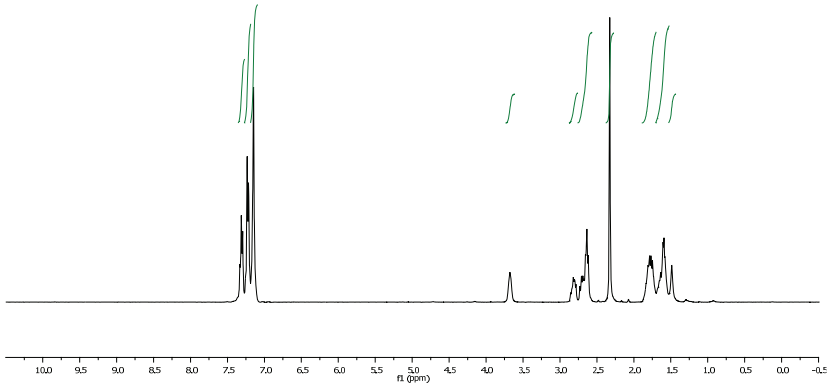
Mixture of **2p** and **3p**

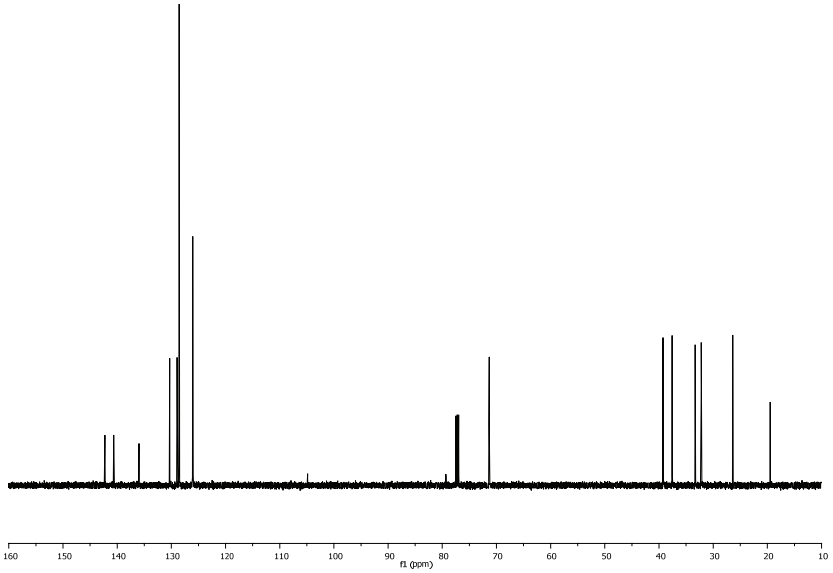


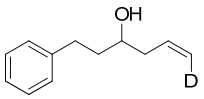


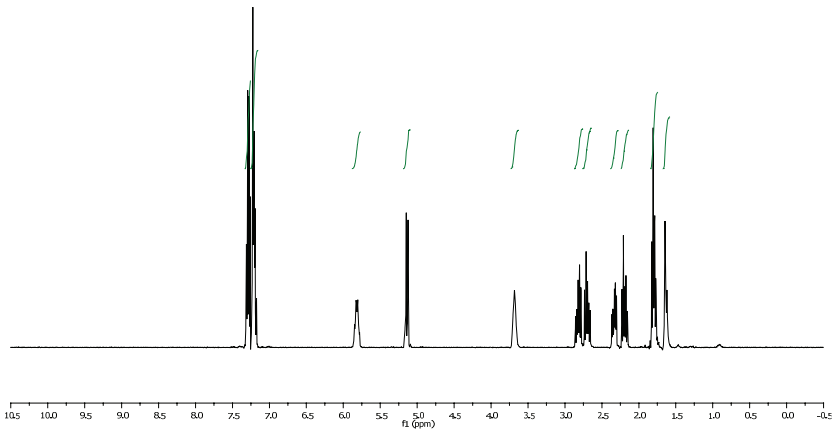
3p:

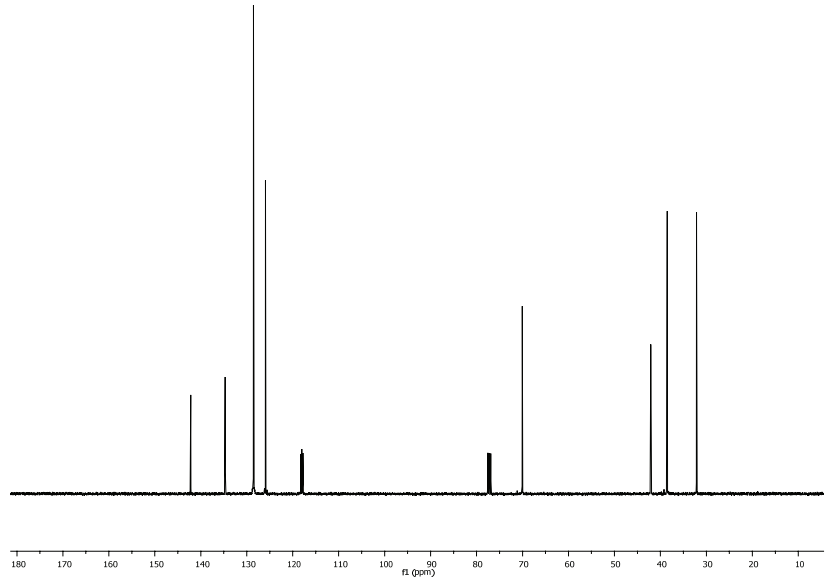

OH

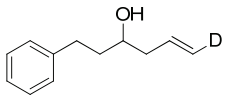

10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

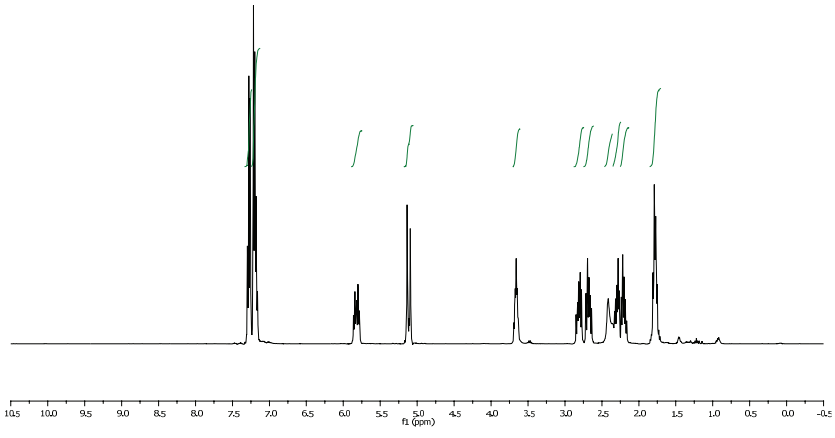

160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)

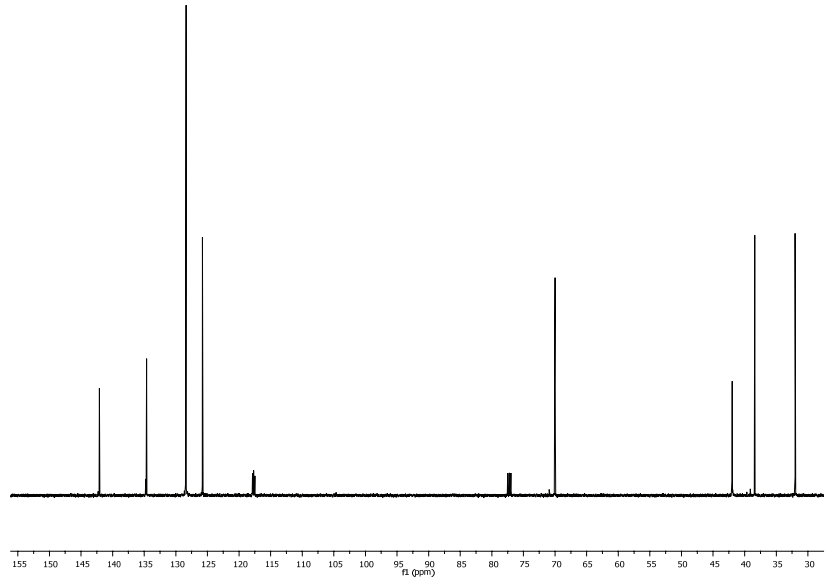
d$_1$-*cis*-**1a**: 

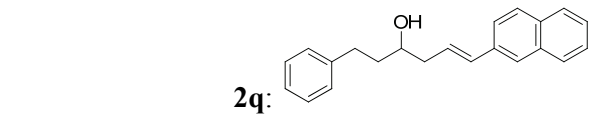




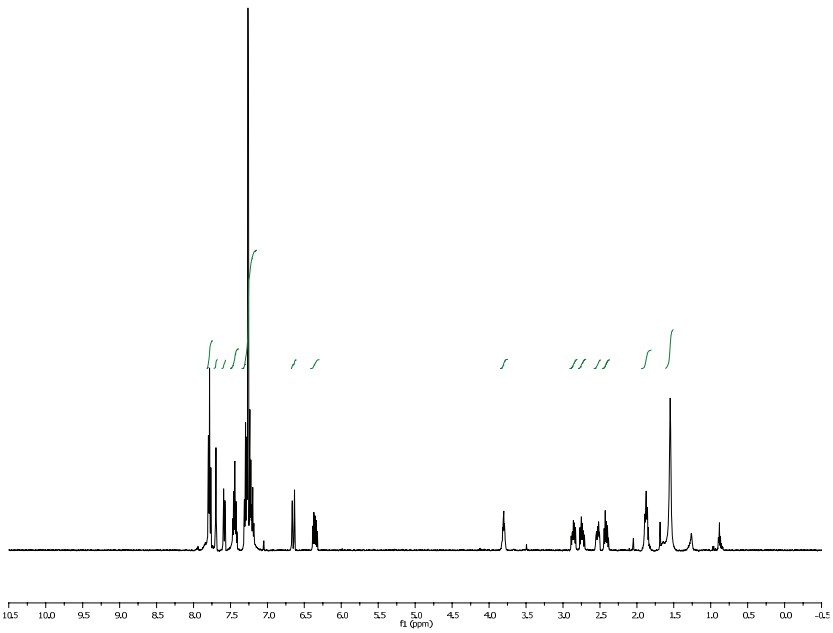
d$_1$-*trans*-**1a**: 

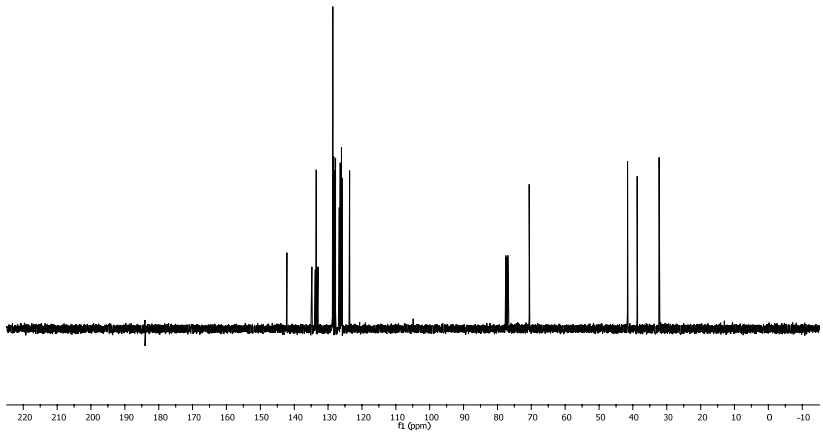




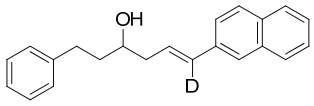


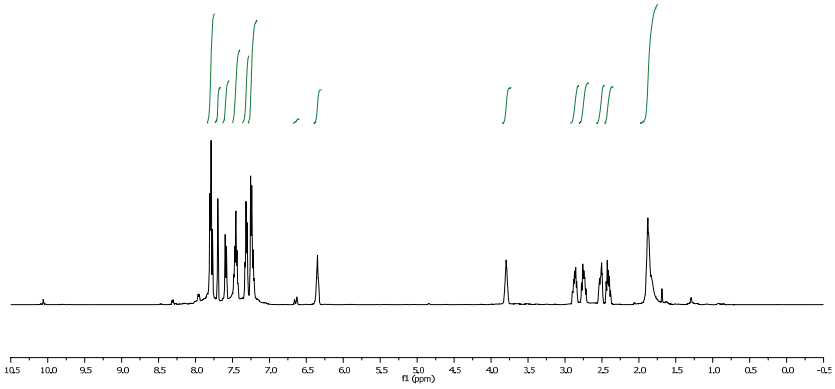
2q:

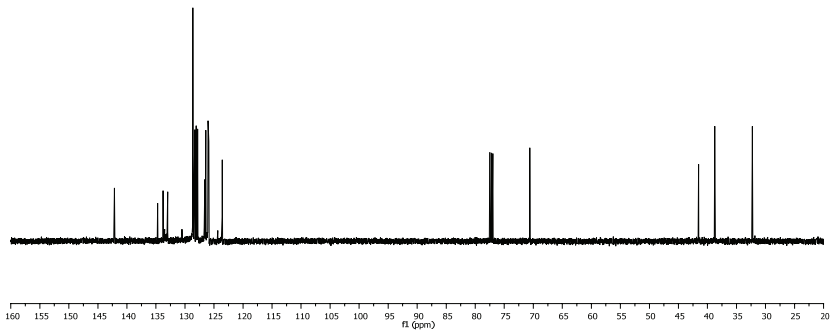




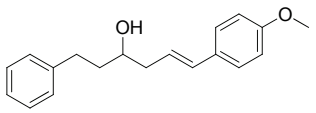
d_1-**2q**:

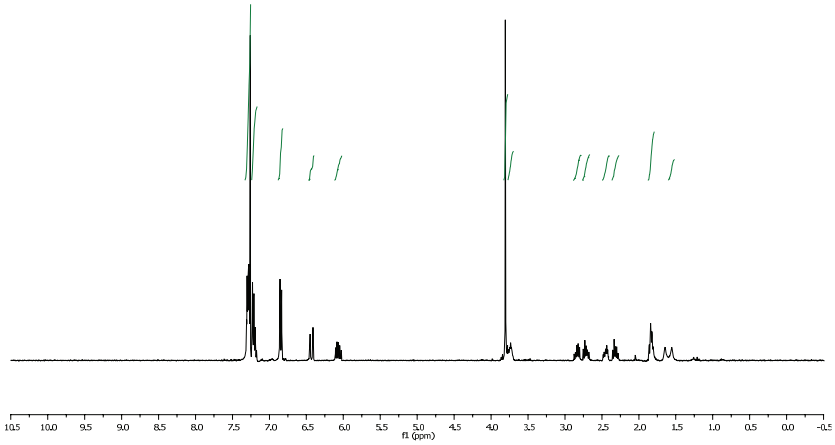


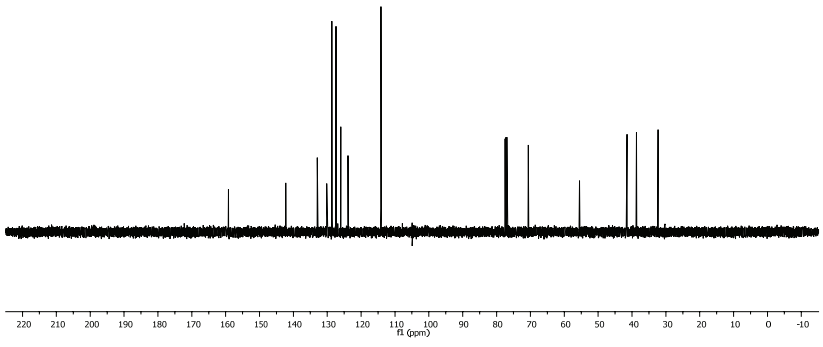




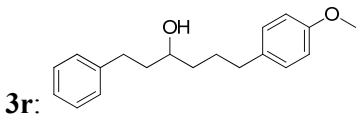
2r:

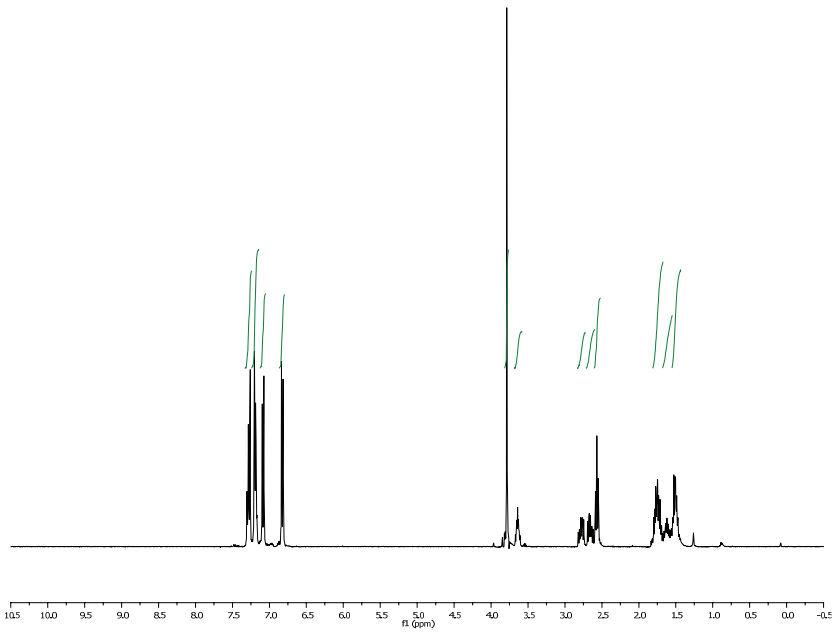

OH
O

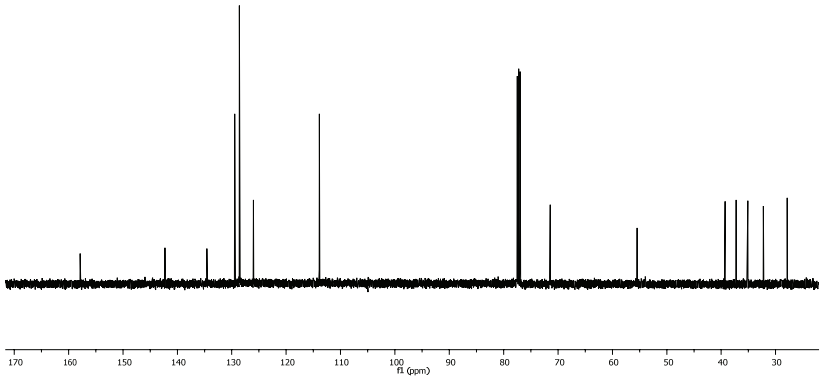

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

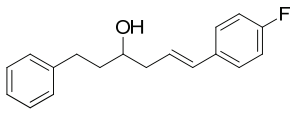

220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

3r:

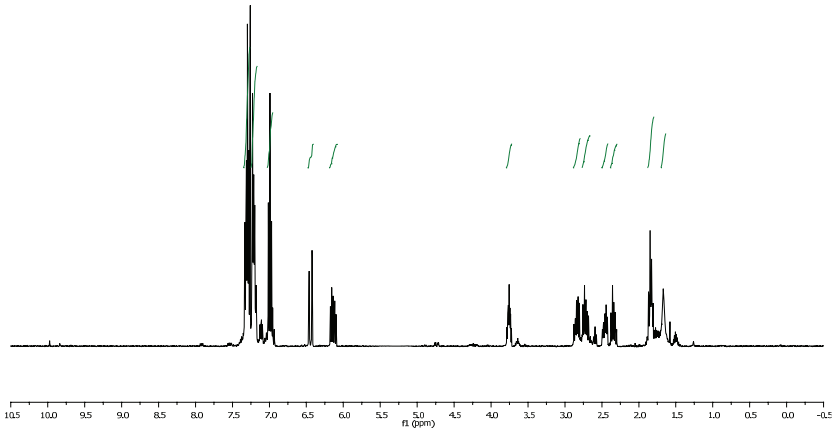

OH
O

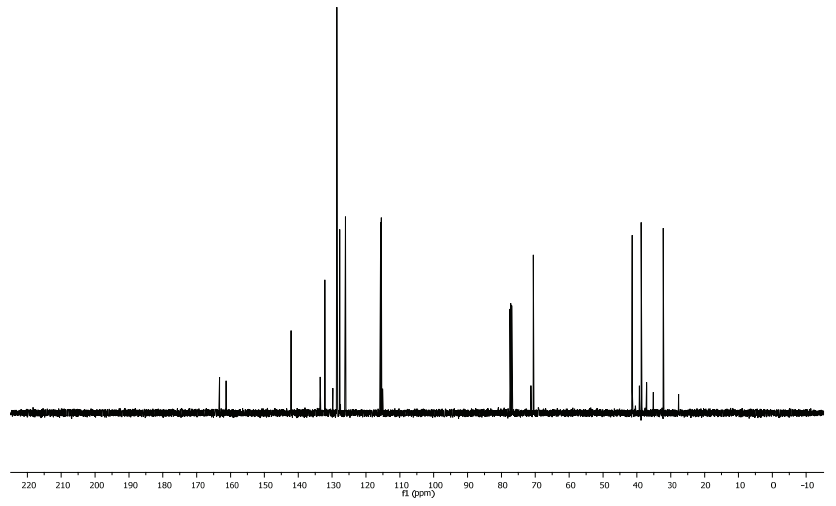

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


170 160 150 140 130 120 110 100 90 80 70 60 50 40 30
f1 (ppm)

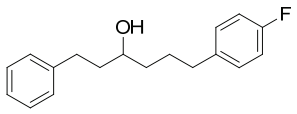
2t: 

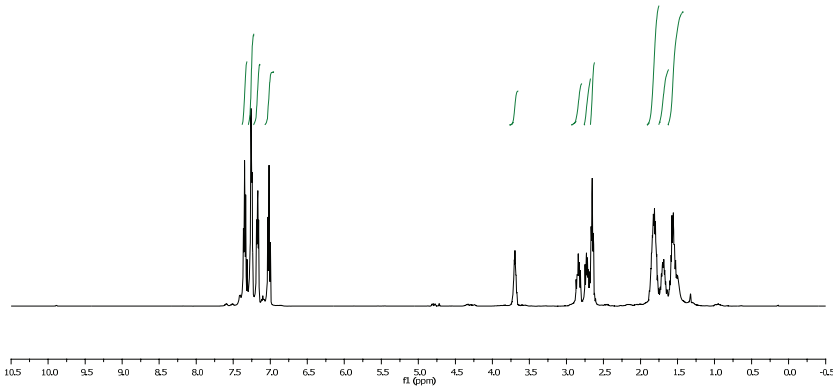
Mixture of **2t** and **3t**

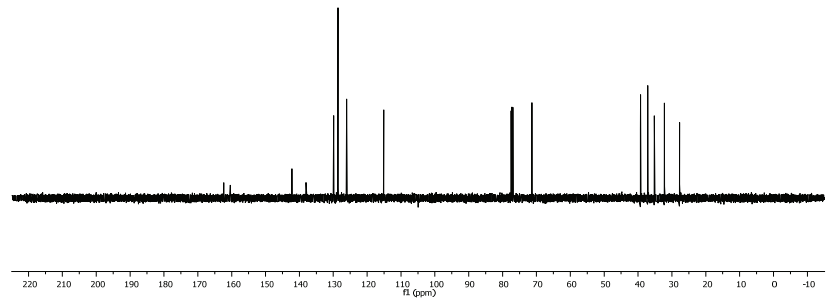




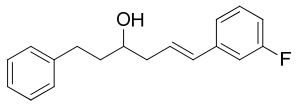
3t:

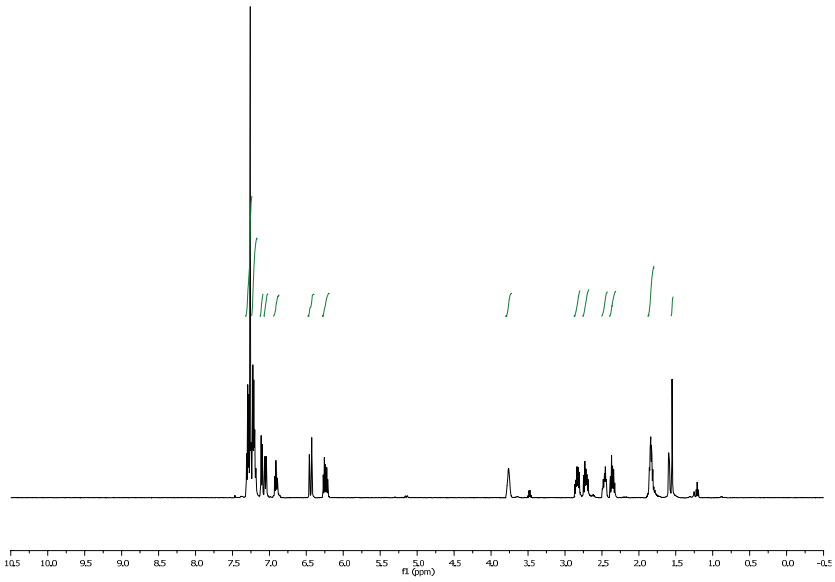

OH
F

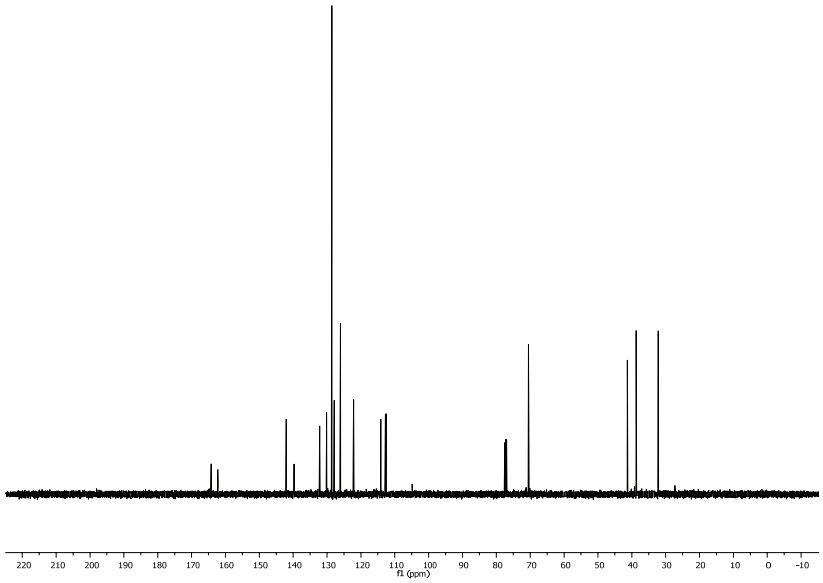

10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10
f1 (ppm)

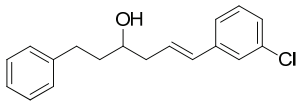
2u:

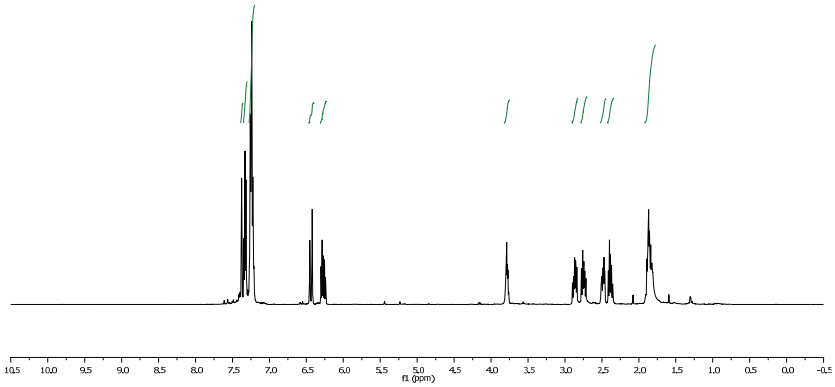


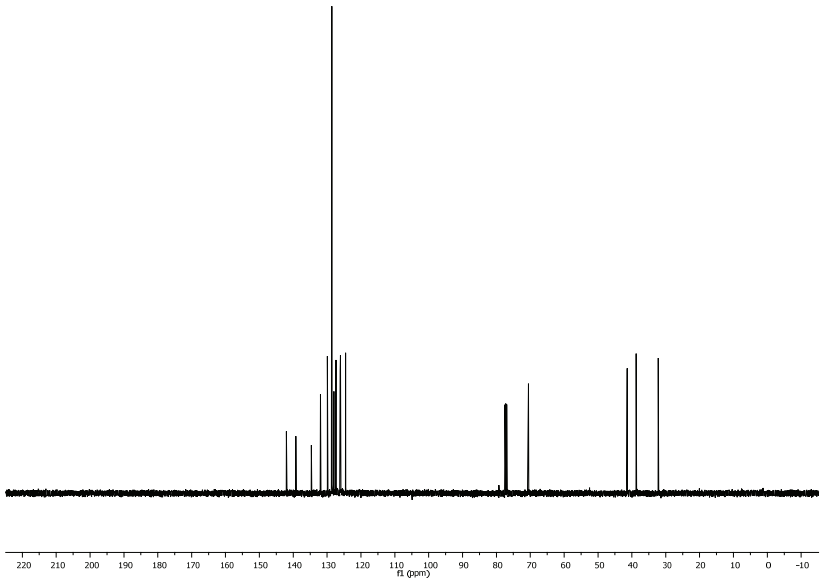




2v:







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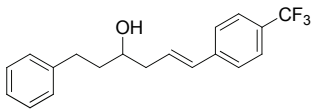
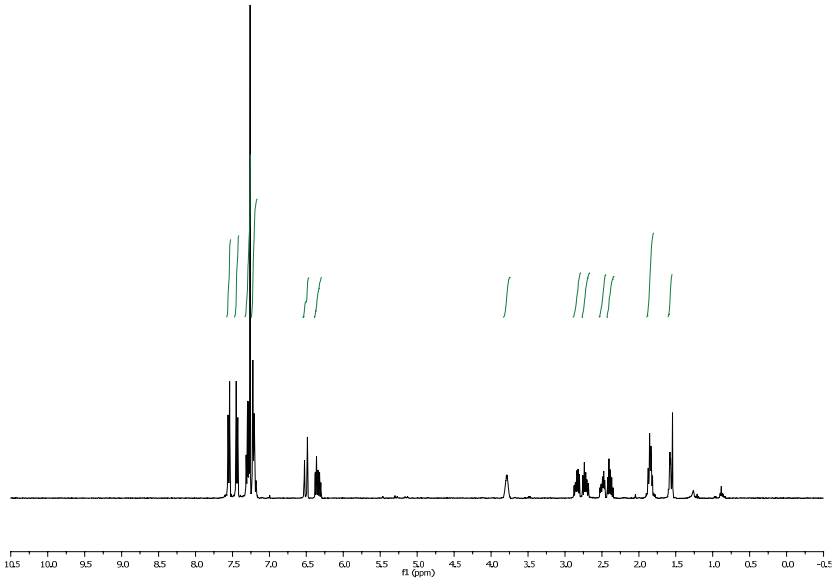

OH
CF3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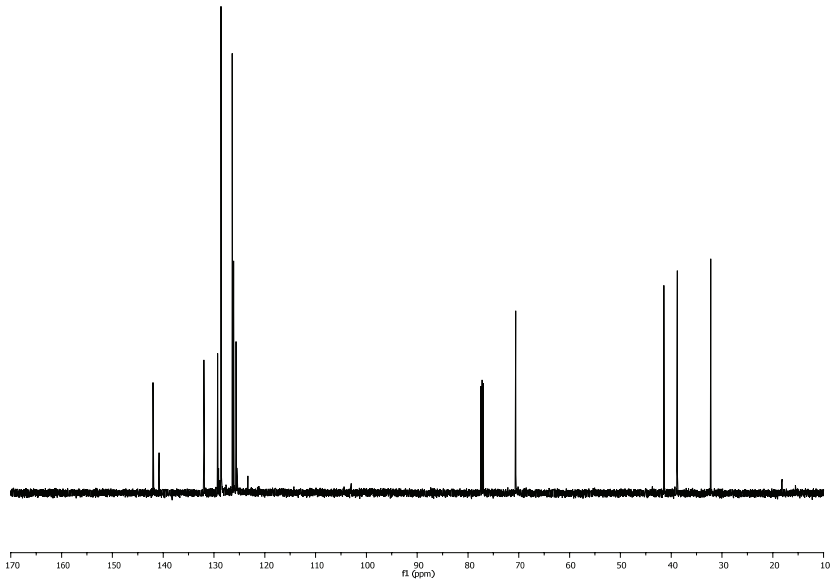
f1 (ppm)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f1 (ppm)

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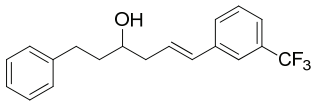
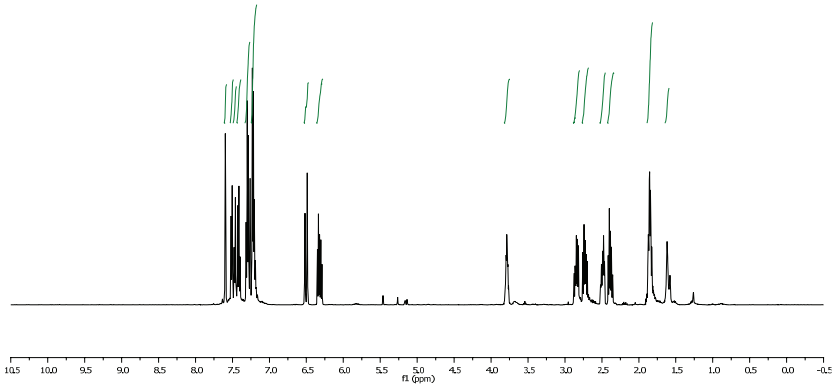
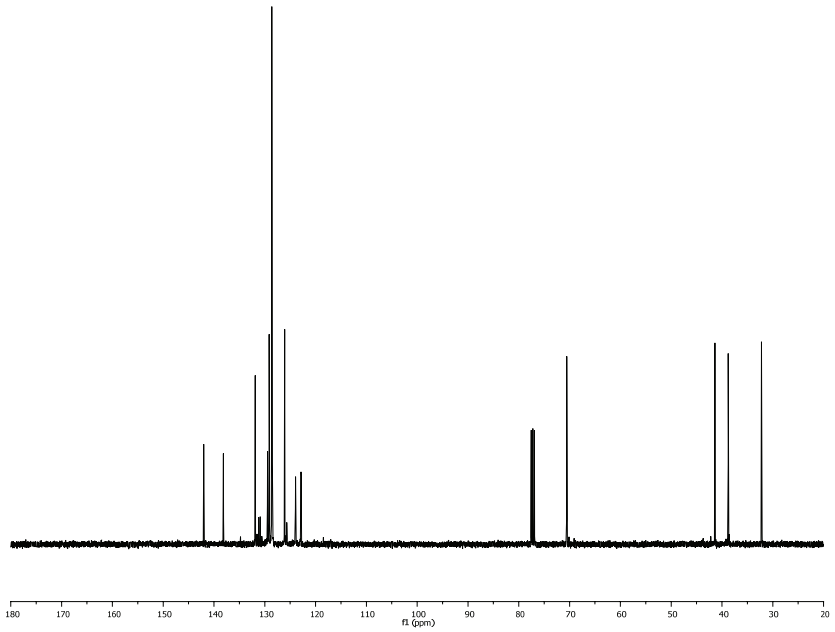


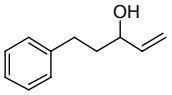




APPENDIX C
Experimental Details and ^{1}H and ^{13}C NMR Spectra for Chapter Three Compounds

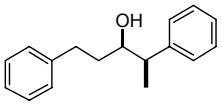
General Procedure:

PhMgBr (3.0 M in Et_2O, 3.0 equiv.) and $Ti(O^{i}Pr)_4$ (neat, 2.0 equiv.) were added sequentially to a stirred solution of allylic alcohol (1.0 equiv) in CH_2Cl_2 (0.5 M in alcohol) at 0 °C. After 5 minutes the yellow solution was removed from the ice bath and stirred at room temperature. When the reaction was complete as determined by TLC, the reaction was quenched with 1 M HCl and stirred until both phases became clear. The aqueous layer was extracted 3 times with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to yield the crude carbometalation product.



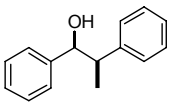
9a: 5-phenyl-1-penten-3-ol

To a 0 °C solution of 3-phenylpropionaldehyde in Et_2O (0.1 M) was slowly added vinylmagnesium bromide (1.05 equiv, 1M in THF). The reaction was allowed to stir at room temperature until complete as determined by TLC. The reaction was quenched with 1M HCl, and extracted 3times with Et_2O. The combined organic extracts were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure to yield the crude starting allylic alcohol. ^{1}H NMR (400 MHz, $cdcl_3$) δ 7.37 – 7.13 (m, 6H), 5.91 (ddd, *J* = 16.9, 10.4, 6.2, 1H), 5.25 (d, *J* = 17.2, 1H), 5.14 (d, *J* = 10.4, 1H), 4.14 (q, *J* = 6.2, 1H), 2.84 – 2.61 (m, 2H), 1.94 – 1.78 (m, 2H), 1.53 (s, 1H). ^{13}C NMR (101 MHz, $cdcl_3$) δ 141.96, 141.06, 128.49, 128.41, 125.84, 114.87, 72.35, 38.54, 31.67. ES-MS (*m/z*): 145.0 $[M\text{-}OH]^{+}$



10a: 1,4-diphenylpentan-3-ol

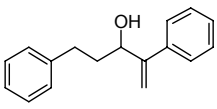
The carbometalation was allowed to stir for 72 hours prior to quenching. Isolated 204 mg (84.7%) as a colorless oil. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.34 – 7.11 (m, 10H), 3.71 (ddd, *J* = 8.9, 5.9, 3.4, 1H), 2.83 (dt, *J* = 11.1, 4.9, 2H), 2.62 (ddd, *J* = 14.0, 9.4, 6.9, 1H), 1.82 – 1.61 (m, 2H), 1.32 (d, *J* = 7.0, 3H), 1.25 (s, 1H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 144.49, 142.23, 128.67, 128.59, 128.52, 127.96, 126.63, 125.95, 75.78, 45.93, 36.50, 32.56, 15.84. ES-MS (*m/z*): 263.0 [M+Na]$^{+}$



10b: 1,2-diphenylpropan-1-ol

The carbometalation was allowed to stir for 44 hours prior to quenching but reached only 11% conversion. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.31 – 7.10 (m, 10H), 4.82 (dd, *J* = 5.5, 2.7, 1H), 3.12 (app quintet, *J* = 6.9, 1H), 1.86 (d, *J* = 3.1, 1H), 1.31 (d, *J* = 7.1, 3H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 143.73, 143.04, 128.46, 128.29, 128.19, 127.44, 126.68, 126.49, 78.92, 47.41, 15.06.

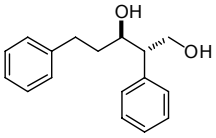
Chemical shifts for *anti*-**10b** as reported by Chung, *et al.*[1]: ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.41-7.28 (m, 10H), 4.68 (d, *J* = 8.6, 1H), 3.05 (dq, *J* = 8.6, 7.0, 1H), 1.91 (bs, 1H), 1.11 (d, *J* = 7.0, 3H). ^{13}C NMR (100 MHz, cdcl$_3$) δ 143.6, 142.8, 128.9, 128.5, 128.4, 128.3, 128.0, 127.2, 127.1, 79.9, 48.3, 18.5.



130: 2,5-diphenylpent-1-en-3-ol

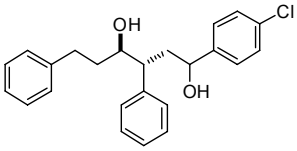
Prepared according to procedure by Mühlthau and Bach.[2] ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.44 – 7.34 (m, 6H), 7.34 – 7.28 (m, 2H), 7.21 (dd, *J* = 17.0, 7.5, 2H), 5.42 (d, *J* = 21.6, 2H), 4.71 (dd, *J* = 7.7, 4.2, 1H), 2.84 (ddd, *J* = 14.5, 10.0, 5.4, 1H), 2.80

(ddd, J = 14.0, 9.6, 6.8, 1H), 2.05 – 1.93 (m, 1H), 1.93 – 1.82 (m, 1H).^{13}C NMR (101 MHz, cdcl$_3$) δ 151.99, 141.99, 139.95, 128.64, 128.55, 128.51, 127.86, 127.05, 125.99, 112.92, 73.24, 37.67, 32.02. ES-MS (*m/z*): 221.0 [M-OH]$^+$



132: 2,5-diphenylpentane-1,3-diol

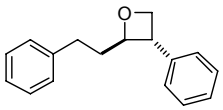
Upon complete conversion of **9a**, O_2 was bubbled through the reaction mixture for 5 minutes. The reaction was kept under an O_2 atmosphere for 22 hours before quenching with water and 1M HCl. The organic phase was extracted with DCM three times, dried over Na_2SO_4, and concentrated under reduced pressure. Isolated 12 mg (9.4%). ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.31 (t, J = 7.2, 2H), 7.27 – 7.20 (m, 3H), 7.19 – 7.11 (m, 3H), 7.08 (d, J = 7.0, 2H), 4.11 – 4.02 (m, 2H), 3.91 (dd, J = 10.9, 4.6, 1H), 2.88 (td, J = 8.1, 4.6, 1H), 2.79 (ddd, J = 14.4, 9.3, 5.8, 2H), 2.61 (ddd, J = 13.8, 9.2, 7.2, 1H), 1.79 – 1.49 (m, 3H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 141.94, 139.95, 129.03, 128.59, 128.58, 128.40, 127.32, 126.06, 75.91, 67.39, 53.81, 37.46, 31.73. ES-MS (*m/z*): 279.0 [M+Na]$^+$



133: 1-(4-chlorophenyl)-3,6-diphenylhexane-1,4-diol

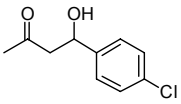
The carbometalation was performed as described in the General Procedure on 0.5 mmol of the starting allylic alcohol. The carbometalation reaction was complete after 72 hours, and *p*-chlorobenzaldehyde (3.0 equiv) was added as a 0.3 M solution in DCM. After 21 hours, the reaction was quenched with 1 M HCl; the aqueous layer was extracted with DCM 3 times, and the combined organic extracts were dried over Na_2SO_4 and concentrated under reduced

pressure. The desired product was solated by SiO_2 column chromatography as a 1:1.4 mixture with α-hydroxy ketone **136**. Chemical shifts for aromatic carbons were not assigned. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.40 – 7.12 (m, 12H), 7.07 (d, *J* = 7.0, 2H), 4.43 (dd, *J* = 10.6, 2.2, 1H), 3.74 (td, *J* = 8.7, 2.9, 1H), 3.05 – 2.98 (m, 1H), 2.80 – 2.74 (m, 1H), 2.59 (ddd, *J* = 13.8, 9.5, 6.9, 1H), 2.30 (ddd, *J* = 14.8, 10.7, 4.4, 1H), 1.95 (ddd, *J* = 14.4, 9.4, 2.4, 1H), 1.73 – 1.53 (m, 4H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 75.46, 72.02, 50.02, 42.66, 37.05, 32.19. ES-MS (*m/z*): 402.9 $[M+Na]^+$



134: 2(-2-phenylethyl)-3-phenyloxetane

The carbometalation was performed as described in the General Procedure on 0.5 mmol of the starting allylic alcohol. The carbometalation reaction was complete after 72 hours, and 2 equiv I_2 (0.07 M in CH_2Cl_2) was added and allowed to stir overnight. The reaction was quenched with 20% $Na_2S_2O_3$ and 1 M HCl. The aqueous layer was extracted with DCM 3 times, and the combined organic extracts were dried over Na_2SO_4 and concentrated to provide the crude oxetane. Isolation via SiO_2 column chromatography yielded 98 mg (82.3%) as a slightly yellow solid. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.38 – 7.21 (m, 5H), 7.21 – 7.05 (m, 5H), 3.83 (td, *J* = 8.9, 2.8, 1H), 3.76 (dd, *J* = 9.9, 3.9, 1H), 3.47 (t, *J* = 9.8, 1H), 2.93 (ddd, *J* = 9.8, 7.7, 3.9, 1H), 2.79 (ddd, *J* = 14.3, 9.7, 5.3, 1H), 2.61 (ddd, *J* = 13.8, 9.4, 7.0, 1H), 1.75 (dddd, *J* = 14.1, 9.8, 7.0, 2.8, 1H), 1.69 – 1.58 (m, 1H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 141.57, 140.82, 128.76, 128.58, 128.49, 128.24, 127.54, 126.10, 74.60, 54.82, 36.79, 32.14, 10.14. ES-MS (*m/z*): 221.0 $[M-H_2O]^+$



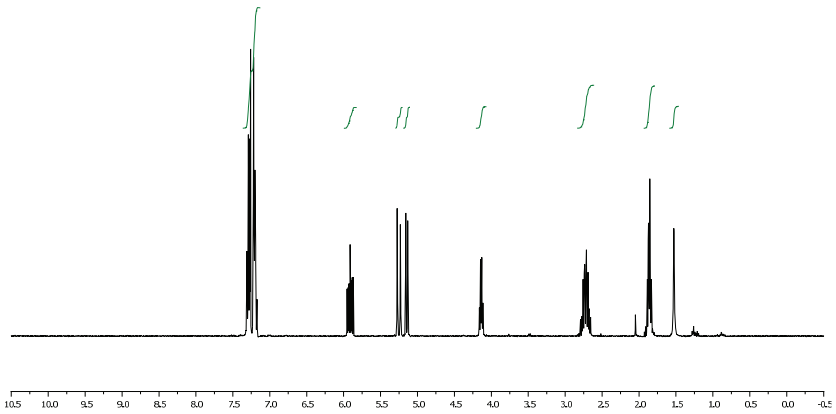
136: 4-(4-chlorophenyl)-4-hydroxybutan-2-one

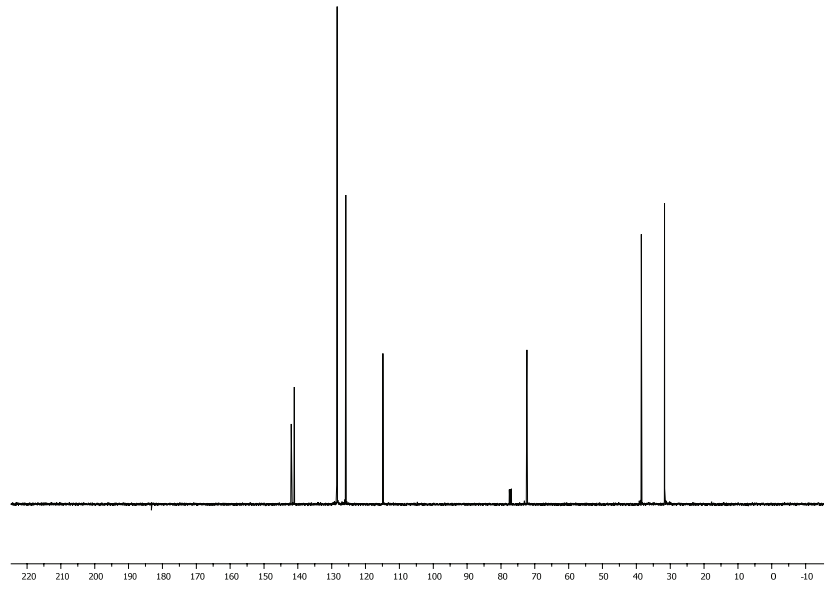
The title compound was coisolated as a 1.4:1 mixture with **133**. Characterization of the individual compounds was based on TOCSY, gCOSY, and HMBC correslations. Chemical shifts of aromatic carbons were not assigned. ^{1}H NMR (400 MHz, cdcl$_3$) δ 7.40 – 7.12 (m, 4H), 5.13 (dd, *J* = 4.4, 2.7, 1H), 3.40 (d, *J* = 2.5, 1H), 2.85 – 2.80 (m, 2H), 2.20 (s, 3H). ^{13}C NMR (101 MHz, cdcl$_3$) δ 209.16, 69.35, 51.99, 30.97. ES-MS (*m/z*): 181.0 $[M\text{-}OH]^+$

1. Chung, J. Y. L.; Mancheno, D.; Dormer, P. G.; Variankaval, N.; Ball, R. G.; Tsou, N. N. *Org. Lett.* **2008,** *10*, 3037.

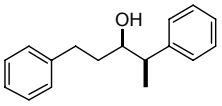
2. Mühlthau, F.; Bach, T. *Synthesis* **2005,** *2005*, 3428.

9a:





10a: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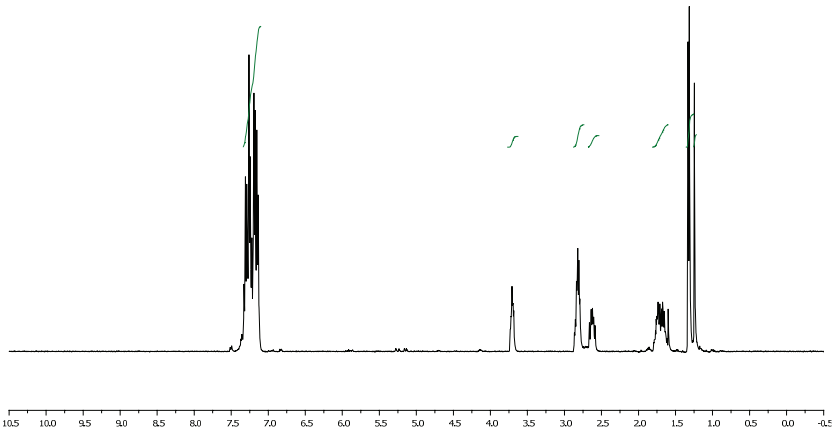
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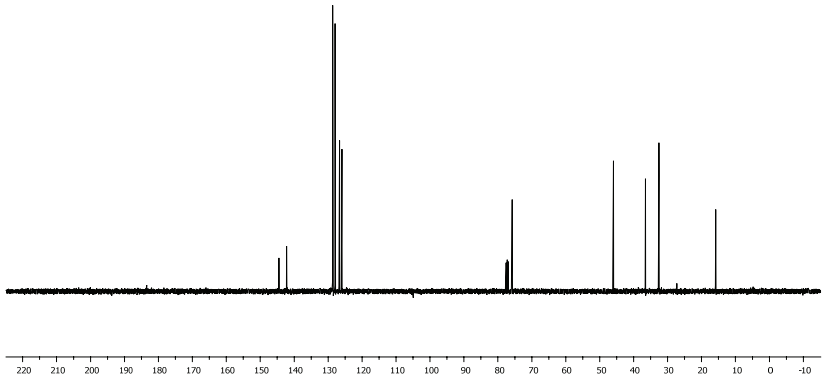
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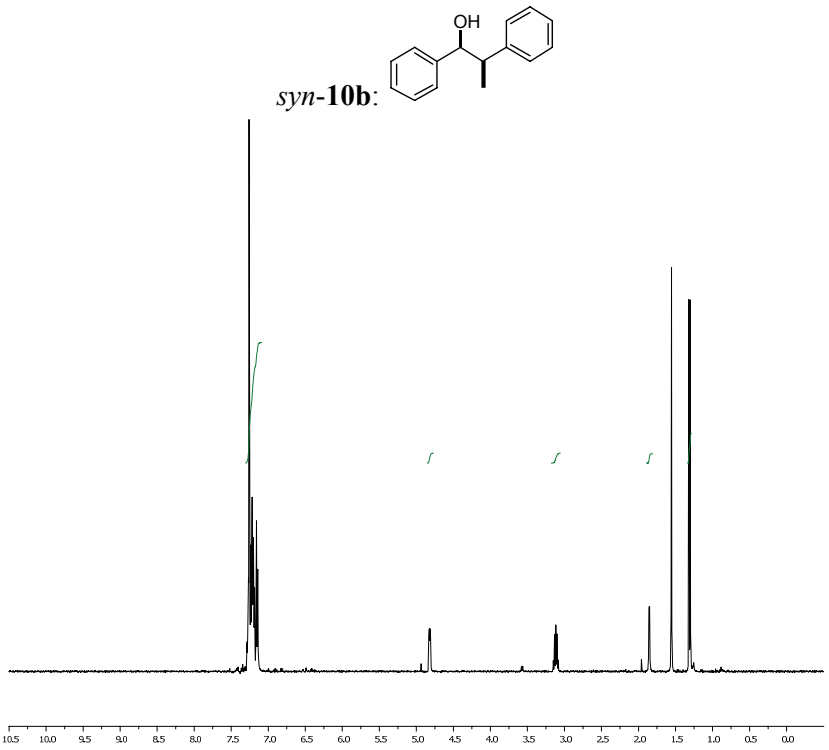
OH
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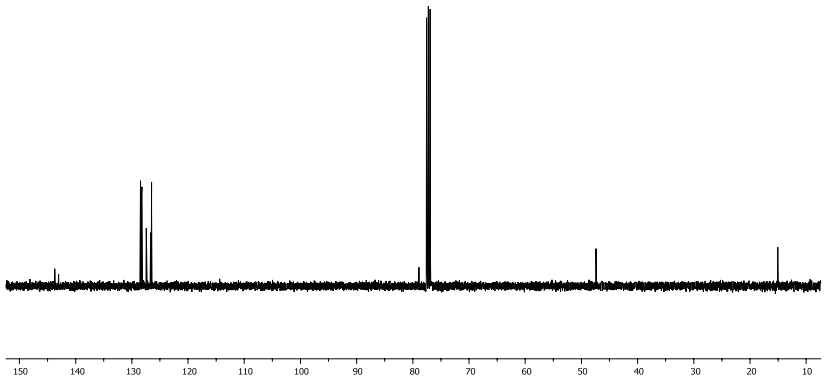
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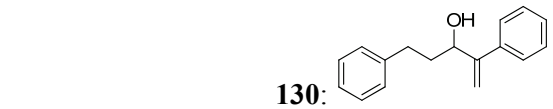
130: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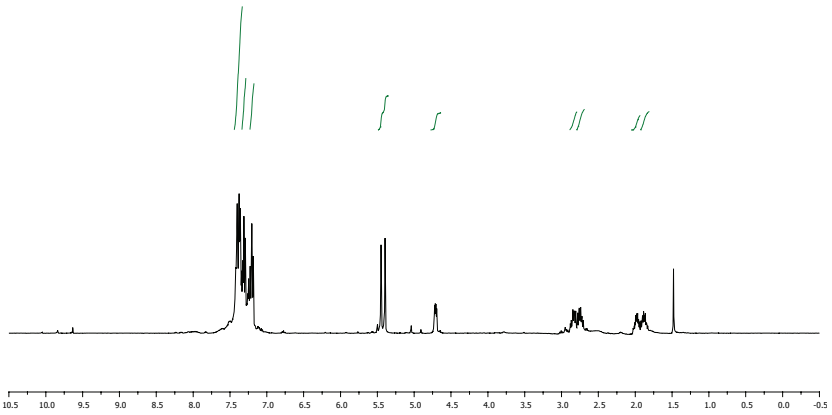
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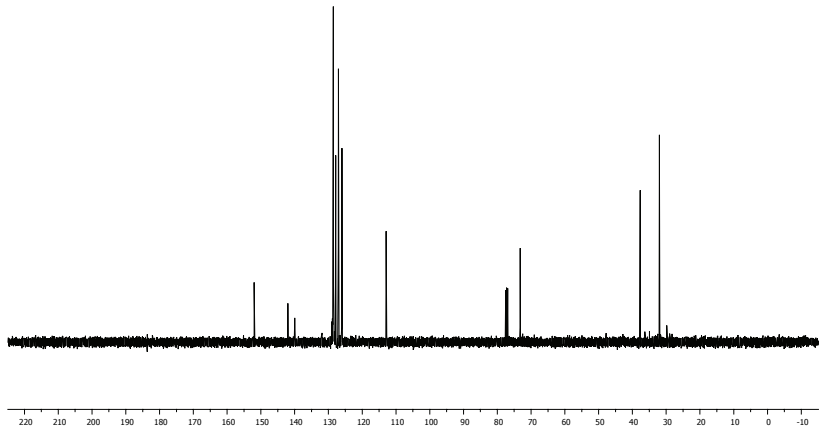
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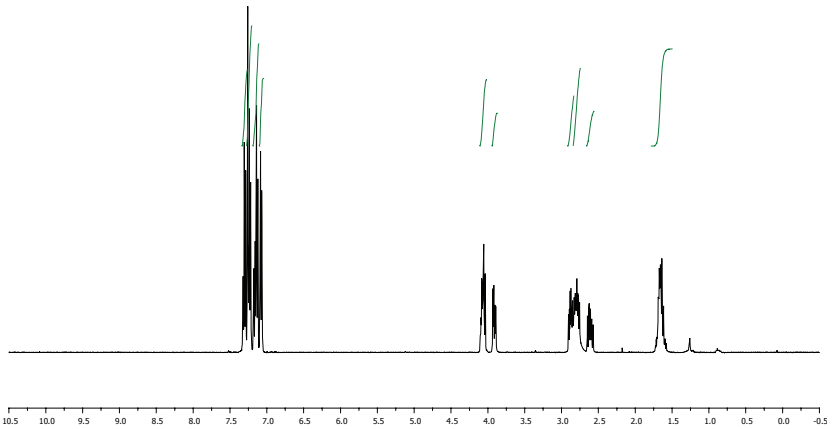
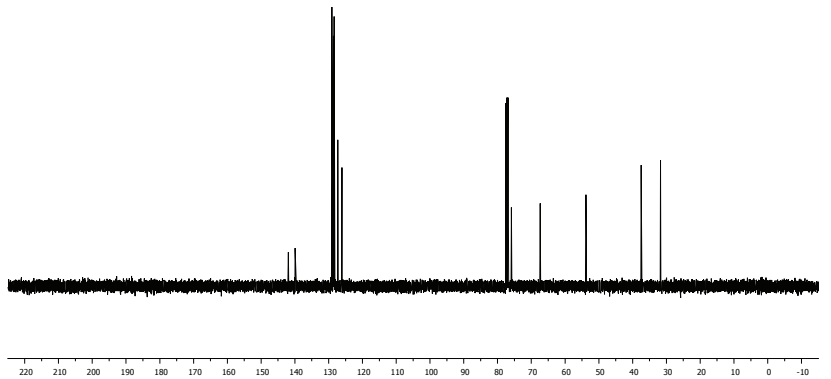
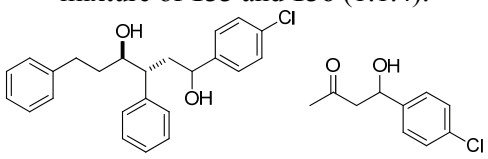
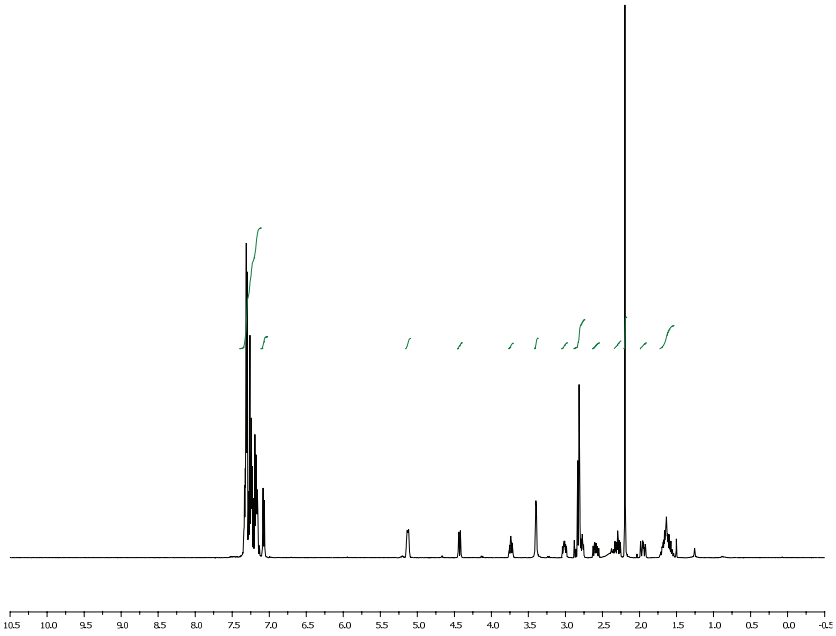
132:

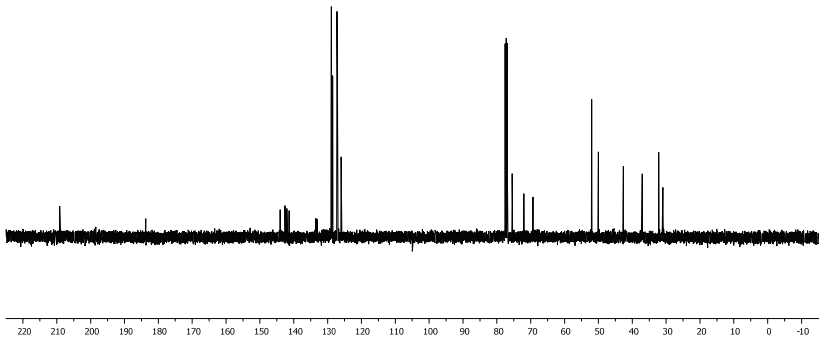




mixture of **133** and **136** (1:1.4):







134: