STEREOSELECTIVE REACTIONS OF ORGANOCOPPER REAGENTS WITH ACYCLIC ALLYLIC SUBSTRATES

by

Jennifer Lynne Belelie

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Abstract

Four different approaches to copper-mediated, stereoselective S_N2' reactions with acyclic substrates will be discussed. Each route was met with different degrees of success.

The first strategy developed employed 1,3-chirality transfer from the site bearing the leaving group to the site of attack. Chirality was introduced to allylic alcohols via Sharpless kinetic resolution chemistry (typically ≥90 %ee). These compounds were transformed to phosphate esters. With these substrates, regio- and stereoselectivities of up to 98% were possible during the copper coupling reactions. The efficiency of these reactions was highly dependent upon the substrate and the cuprate structure. The best regio- and stereoselectivities were obtained with substrates bearing bulky groups at the α-position. Unfortunately, highly stereoselective cuprate additions were limited to primary alkyl and benzylic groups. The coupling reactions occurred with *anti*-facial selectivity and retention of (*E*)-double bond geometry.

The next two routes employed Rossiter's cuprate to introduce chirality to the system. In the first approach, chiral cuprates were reacted with racemic allylic substrates, in hopes of alkylating one of the enantiomers and leaving the other one mostly unreacted (kinetic resolution). Unfortunately, all of the products recovered from these reactions were racemic. The second strategy used Rossiter's ligand in cuprate additions to prochiral substrates. The products recovered from these reactions were also racemic.

The final strategy involved 1,2-chirality transfer. Primary, secondary, tertiary alkyl and phenyl groups were introduced to δ-alkoxy- and δ-silyloxy-substituted substrates with *anti*-facial selectivities of ≥96%. The outcomes of these reactions were highly dependent upon the structure of the substrates and the nature of the organocopper reagents. The best results were achieved with bulky groups, such as *i*-Pr and Ph, on the site bearing the leaving group. The highest facial selectivities were achieved with CuCN-catalyzed Grignard reagents. It is hypothesized that the compounds react through a modified Felkin-Ahn conformation, in which the δ-oxy-substituent takes the role of the medium-sized group. This methodology was applied to non-racemic substrates to synthesize enantiomerically-enriched benzyloxy-substituted alkenes and alcohols.

When the alkoxy- and silyloxy-substituents were replaced with hydroxyl groups, the facial selectivities of the reactions changed from *anti* to *syn*. We believe that the reversal of selectivity is facilitated by formation of a mixed-cuprate species from the oxygen anion on the substrate and the incoming nucleophile. With the hydroxyl-substituted substrates, the selectivities of the reactions were directly proportional to the size of the group transferred from the cuprate. The highest facial selectivities were observed during *t*-Bu addition. In contrast to the alkoxy- or silyloxy-substituted systems, the best results were achieved with an *n*-Bu group on the leaving group site. Under certain conditions, diastereoselectivities of ≥98% were possible.

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To Mum and Dad,

for providing me with every opportunity

that you went without.

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List of Abbreviations

Ac	acetyl
aq	aqueous
ax	axial
Bn	benzyl
bp	boiling point
br	broad
n-Bu	*n*-butyl
n-BuLi	*n*-butyllithium
t-Bu	*tert*-butyl
c	concentration (g/100 mL)
Calcd	calculated
cat.	catalytic
Cbz	carbobenzoxy
d	doublet
DCHT	dicyclohexyl tartrate
de	diastereomeric excess
DIBAL	diisobutylaluminum hydride
DIC	1,3-diisopropylcarbodiimide
DMAP	4-dimethylaminopyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
3,5-DNB	3,5-dinitrobenzoyl
E^+	electrophile
ee	enantiomeric excess
ent-	enantiomer of
eq	equatorial
equiv	equivalent(s)
ES	electrospray
Et	ethyl

EtOAc	ethyl acetate
Et_2O	diethyl ether
EtOH	ethanol
EWG	electron-withdrawing group
FAB	fast atom bombardment
GC	gas chromatography
GC/MS	gas chromatography/mass spectrometry
h	hour(s)
HMPA	hexamethylphosphoric triamide
HOBT	1-hydroxybenzotriazole hydrate
HPLC	high performance liquid chromatography
Hz	hertz
i-Pr	isopropyl
IR	infrared
J	spin coupling constant
L*	chiral ligand
LDA	lithium diisopropylamide
lit.	literature
m/e	mass/charge
MAPP	*N*-methyl-1-phenyl-2-(1-piperidinyl)ethanamine
Me	methyl
MeLi	methyllithium
min	minutes
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
MTPA	α-methoxy-α-(trifluoromethyl)phenylacetyl
NaHMDS	sodium bis(trimethylsilyl)amide
NaOEt	sodium ethoxide
NBS	*N*-bromosuccinimide
NMR	nuclear magnetic resonance

Nu	nucleophile
PG	protecting group
Ph	phenyl
piv	pivalate
PMB	*para*-methoxybenzyl
PPTS	pyridinium *para*-toluenesulfonate
q	quartet
quint	quintet
RT	room temperature
s	singlet
SAMP	(*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine
SMe_2	dimethyl sulfide
S_N2	bimolecular nucleophilic substitution
S_N2'	bimolecular nucleophilic substitution with allylic rearrangement
t	triplet
T_0	initial temperature
t_0	initial time
TBAF	tetrabutylammonium fluoride
TBAI	tetrabutylammonium iodide
TBDMS	*tert*-butyldimethylsilyl
TBHP	*tert*-butylhydroperoxide
TEA	triethylamine
T_f	final temperature
t_f	final time
THF	tetrahydrofuran
TLC	thin-layer chromatography
TMS	tetramethylsilane
TMSCl	chlorotrimethylsilane
xs	excess

CHAPTER 1
INTRODUCTION

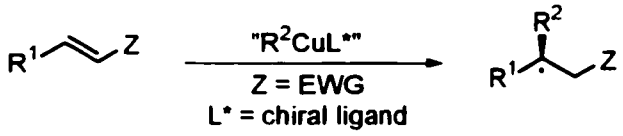
Enantiomers often behave differently than each other in chiral and biological systems and, for this reason, synthesizing compounds exhibiting high enantiomeric purity has become a very important goal in organic chemistry.[1] Designing asymmetric synthetic routes reduces the waste incurred through enantiomeric resolutions and diastereomeric separations.

Organometallic reagents are commonly used in these routes. For example, palladium, aluminum, tin, boron and copper are used extensively in asymmetric routes to complex molecules.[2] Organocopper reagents are especially valuable tools for highly regio- and stereoselective carbon-carbon bond forming reactions.[3,4,5,6]

The most common and well-studied transformations utilizing organocopper reagents are conjugate additions (Scheme 1), S_N2 alkylations (Scheme 2) and carbocuprations (Scheme 3).[6]

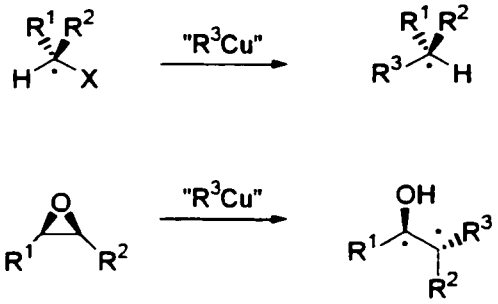
Conjugate or 1,4-additions involve the reaction of a nucleophile with an alkene directly attached to an electron-withdrawing group (EWG). Chirality at the position β to the EWG can be introduced via chiral ligands that are bound or associated with the acceptor molecule, or by adding chiral Lewis acids.[7] Another common method utilizes cuprates equipped with chiral ligands (Scheme 1).[7,8]

Scheme 1



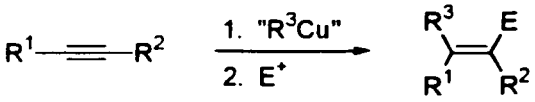
S_N2 alkylation is another typical copper-mediated reaction (Scheme 2). The transformation generally occurs with inversion of stereochemistry at the electrophilic carbon center.[9]

Scheme 2



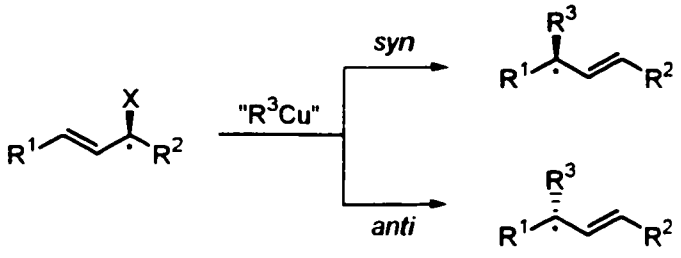
Carbocupration is a well-studied copper-mediated transformation (Scheme 3). Di-, tri- and tetrasubstituted alkenes can be formed with a high degree of regioselectivity when using organocopper reagents.[10]

Scheme 3

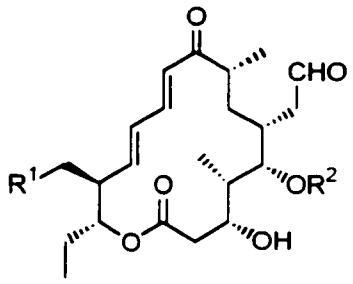


A lesser known, but extremely powerful, organocopper transformation is the S_N2' reaction (Scheme 4). The cuprate reagent attacks one side of the π system, with the double bond shifting to displace the leaving group (X). The reaction can occur with *syn*-[11] or *anti*-[12] facial selectivity.

Scheme 4



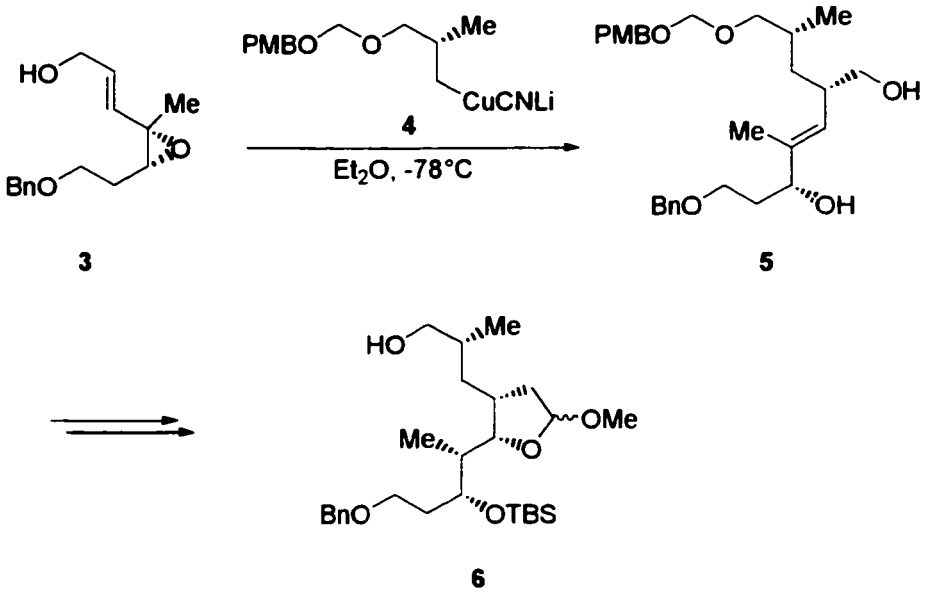
In recent years, more emphasis has been placed on copper-mediated S_N2' reactions and their utility in the design of regio- and stereoselective routes to complex molecules. For example, Marshall and coworkers used a highly complex S_N2' reaction to form a tylonolide subunit.[13,14] Tylonolide (**1**) is the aglycon of tylosin (**2**), a commercially important antibiotic. In particular, vinyloxirane **3** was reacted with cyanocuprate reagent **4** to yield the S_N2' product, diol **5**, in 55-60% yield, with complete *anti*-facial selectivity (Scheme 5). This diol was further transformed into compound **6**, a highly functionalized tylonolide subunit.[14]



1: R^1 = OH, R^2 = H
2: R^1 = Osugar, R^2 = sugar

Figure 1. Tylonolide (**1**) and tylosin (**2**).

Scheme 5



The potential of S_N2' reactions with organocopper reagents has yet to be realized. This thesis will focus on the applications of S_N2' copper-mediated reactions to the synthesis of α-chiral aldehydes.

1.1 α-Chiral Aldehydes and Related Compounds

α-Chiral aldehydes are versatile synthetic intermediates that can be transformed into a number of other functionalities without racemization. Many new synthetic routes may stem from easier access to the compounds shown in Figure 2,[15] which could provide precursors for natural products or compounds suitable for pharmaceutical use.[5]

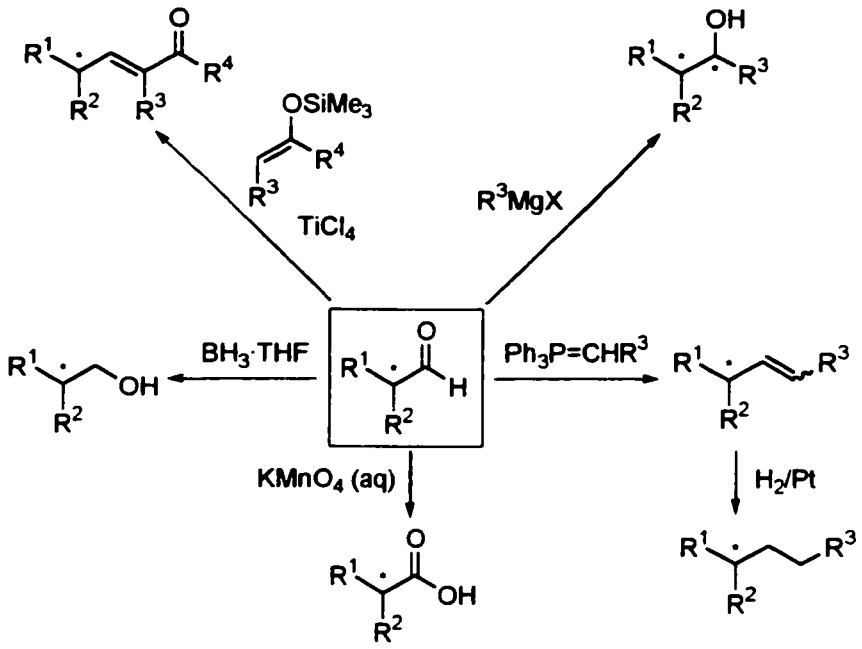
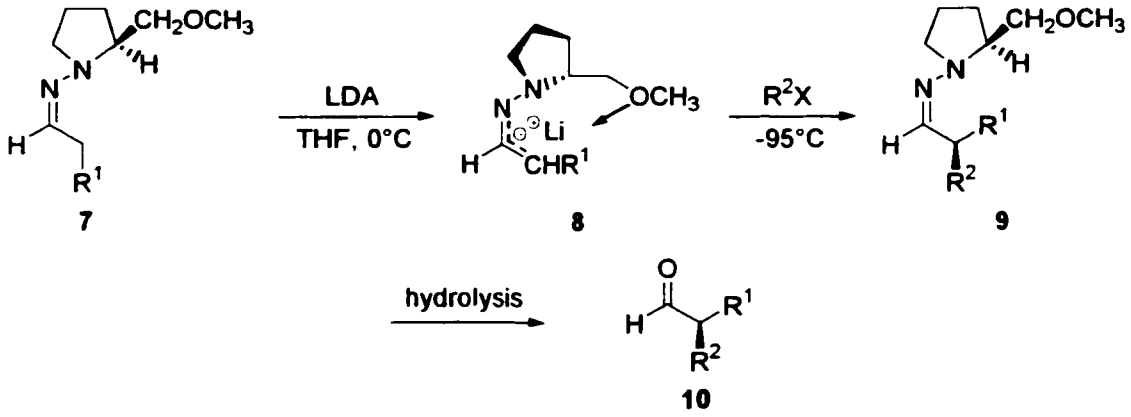


Figure 2. Some transformations of optically active, α-substituted aldehydes.

1.1.1 Traditional Strategies and Their Limitations

Most of the traditional routes to α-chiral aldehydes have used chiral auxiliaries. For example, Enders and Eichenauer investigated routes to these compounds via metalated chiral hydrazones (Scheme 6).[16] The aldehyde was converted to a chiral hydrazone (such as 7) via reaction with (*S*)-(-)-1-amino-2-(methoxymethyl)pyrrolidine (SAMP). The resulting compound was metalated using lithium diisopropylamide (LDA) to give reactive intermediate **8** that reacted with an alkyl halide. Product hydrazone **9** was hydrolyzed to give the desired aldehyde. High enantiomeric excesses were achieved with many aliphatic examples; however, low enantiomeric excesses resulted with phenyl-substituted aldehydes. The acidity of the proton α to the phenyl group was blamed for the observed racemization.[15]

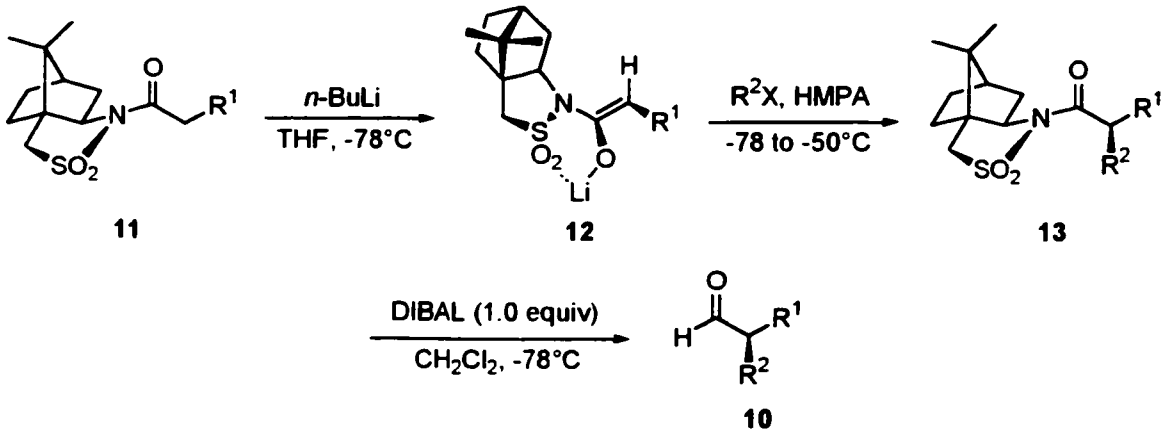
Scheme 6



R^1	R^2	ee of 10 (%)	Yield (%)
Me	Bn	>95	61
Me	$(CH_3)_2CH(CH_2)_2$	>90	60
n-Hex	Me	>95	61
Ph	Me	31	80

Oppolzer and coworkers have also done work in this field.[17] In the first steps of their method, *N*-acylbornane-10,2-sultam **11** was metalated with *n*-BuLi and the resulting intermediate **12** was trapped with an alkyl halide (Scheme 7). High diastereomeric excesses were achieved for a number of aliphatic additions. The chiral auxiliary was easily cleaved with DIBAL to afford the desired aldehyde **10** in high yield, usually with negligible loss of enantiomeric purity.[18]

Scheme 7

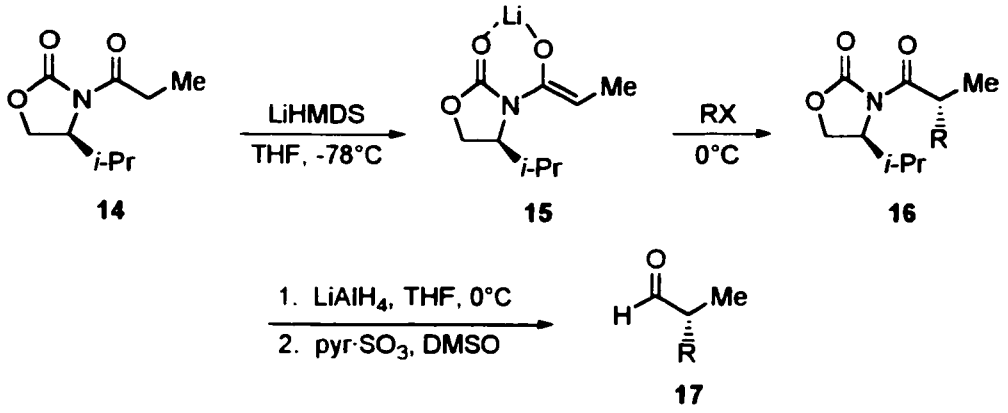


11 **12** **13** **10**

R^1	R^2	de of 13 (%)	ee of 10 (%)	Yield (%)
Bn	Me	94	94	81
Me	*n*-Oct	97	97	82
Ph	Et	98	90	77

Evans' method utilized oxazolidinones as chiral auxiliaries (Scheme 8).[19] The stereochemistry of the alkylation is controlled by the substituent on the oxazolidinone ring, as well as by enolate geometry (see **15**, Scheme 8). The diastereomeric excesses of the alkylated oxazolidinones were quite good when the introduced groups were alkyl or benzylic.[19,20] The chiral auxiliary was cleaved with $LiAlH_4$, leaving an alcohol that was oxidized to aldehyde **17** using Doering's conditions.[21] Less than 0.2% racemization was observed during the oxidation step.[20]

Scheme 8

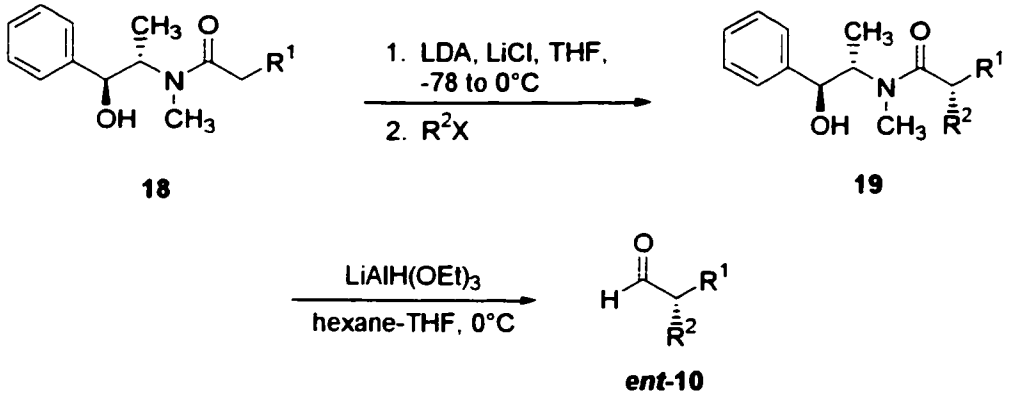


14 **15** **16** **17**

R	de of 16 (%)	Yield (%)
Bn	98	92
Et	92	53
H_2C=$CHCH_2$	96	71

More recently, Myers and coworkers investigated routes to α-substituted aldehydes using pseudoephedrine as a chiral auxiliary.[22] This amino alcohol is inexpensive and readily available in both enantiomeric forms. The synthetic route used closely resembles the one previously developed by Evans and coworkers (see Scheme 8).[20] Pseudoephedrine amide **18** was synthesized by reacting an activated carboxylic acid derivative with the amino alcohol. The amide enolate formed by reaction with LDA was alkylated using an alkyl halide. Newly substituted pseudoephedrine amide **19** was then reduced to the enantiomerically-enriched aldehyde ***ent*-10** using lithium triethoxyaluminum hydride [$LiAlH(OEt)_3$]. When benzylic or straight chain alkyl groups were introduced, the yields and enantiomeric excesses were typically high.[23]

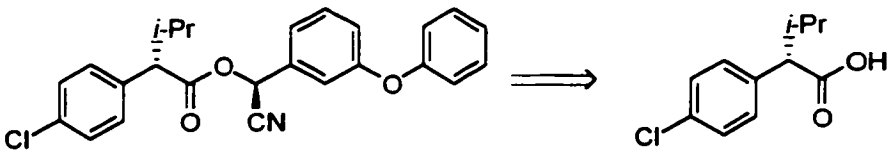
Scheme 9



18 **19** ***ent*-10**

R^1	R^2	ee of *ent*-10 (%)	Yield (%)
Me	Bn	95	76
Me	*n*-Bu	98	75
n-Bu	Bn	97	82
Ph	Et	90	80

All of the previously mentioned routes employed the same approach: form a chiral enolate and trap it with an alkyl or benzylic halide. The main limitation of this strategy is that it relies on S_N2 (bimolecular nucleophilic substitution) chemistry to introduce the substituent α to the carbonyl group. S_N2 reactions are favoured at primary carbon centres. As the number of alkyl groups surrounding the reaction centre increases, the reaction rate drops dramatically since the rate-controlling step involves bond formation with the nucleophile. For this reason, the electrophile cannot be a branched alkyl group. Moreover, vinyl and aryl compounds do not undergo S_N2 reactions. Consequently, compounds such as (*S*)-2-(4-chlorophenyl)-3-methylbutyric acid (**21**), an important chiral fragment of the insecticide, fenvalerate (**20**),[24] are inaccessible by these literature methods.[25]



20 **21**

Figure 3. Fenvalerate (**20**) and precursor (**21**).

1.1.2 Proposed Strategies

In order to circumvent the problems discussed above, it was desired to develop a new route to α-chiral aldehydes that eliminated the need for an S_N2 reaction sequence. Here, our focus turned to S_N2' (bimolecular nucleophilic substitution with allylic rearrangement) chemistry (Figure 4). This type of substitution reaction is prevalent with allylic substrates, especially if the carbon bearing the leaving group is sterically hindered. In an S_N2' mechanism, attack occurs at one end of the π system, with the double bond shifting to displace the leaving group. There is often a high degree of stereochemical control possible with S_N2' reactions.[5]

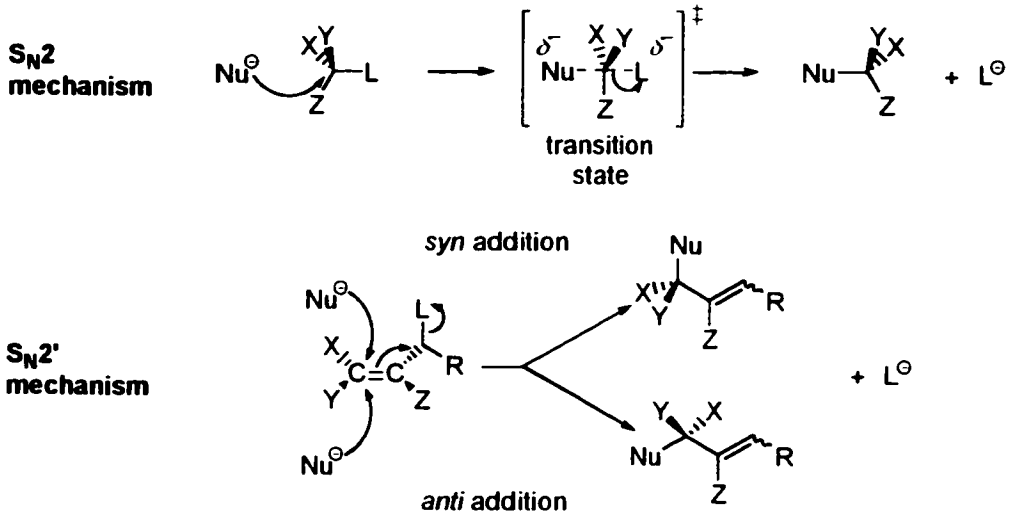
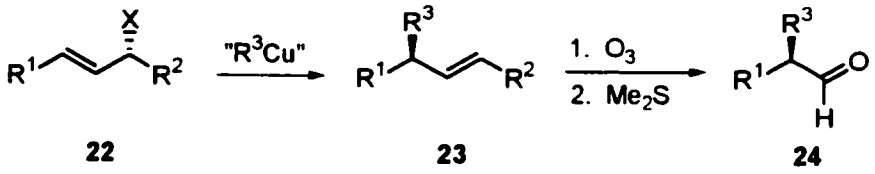


Figure 4. S_N2 versus S_N2' mechanism.

By invoking S_N2' chemistry, the role of the introduced group would change from that of an electrophile to that of a nucleophile. Hence, primary, secondary, tertiary, aryl and vinyl groups could be added to allylic systems, such as **22** (Scheme 10). The desired aldehyde **24** could then be generated through ozonolysis of the resulting alkene **23**.

Scheme 10



22 **23** **24**

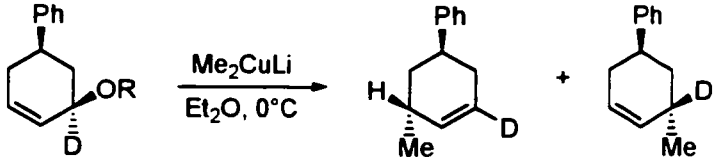
In recent years, Spino *et al.* developed a similar strategy to α-chiral carbonyl compounds.[26] In this case, a chiral auxiliary was used to invoke the desired chirality (see Section 1.2.2).

1.2 S_N2' Reactions Utilizing Organocuprates

Organocuprate reagents are readily used to form carbon-carbon bonds. These reagents are extremely important in asymmetric synthesis because they exhibit a high degree of regio- and stereoselectivity in many different types of coupling reactions.[5] Initially, the most successful and insightful studies on copper-mediated S_N2' reactions were conducted with cyclic substrates. Consequently, many of the proposed mechanisms for the substitution reactions are based upon the results of these studies.

Goering and Singleton[27] and Gallina and Ciattini[28] performed reactions with substituted cyclohexene compounds and homocuprate reagents. Gallina and Ciattini nicely summarized the results of the latter study in the late 1970's (Scheme 11).[28]

Scheme 11



25 **γ-26** **α-26**

R	Product 26 Distribution (%)	
	γ	α
HCO	58	42
Ac	51	49
PhCO	50	50
EtOCO	53	47
Me(Ph)NCO	54	46

There are two important points to note from these results. There was little to no bias for the γ- or α-regioisomer, suggesting that a symmetrical intermediate was formed in which the γ- and α-allylic positions became equivalent.[28] Secondly, the cuprate attack occurred with *anti*-facial selectivity.[28] In order to explain these results, Goering and Kantner developed the following mechanism (Figure 5),[29] which is still referenced today.[6]

1.2.1 Mechanism with Cyclic Allylic Substrates

In the first step of the sequence, the cuprate complexes with olefin **27** to form intermediate **28** (Figure 5). An S_N2' reaction occurs between the alkene and the cuprate to form σ-allyl copper (III) complex γ-**29**. At this point, there is a fork in the mechanistic pathway. The complex can undergo reductive elimination with retention of configuration to give product γ-**30**. Alternatively, complex γ-**29** can isomerize to σ-allyl copper (III) complex α-**29** through π-allyl complex **31**. Species α-**29** can reductively eliminate to form product α-**30**.[29] The propensity of the system to form the α- or γ-product depends upon both stereoelectronic and steric effects.[3]

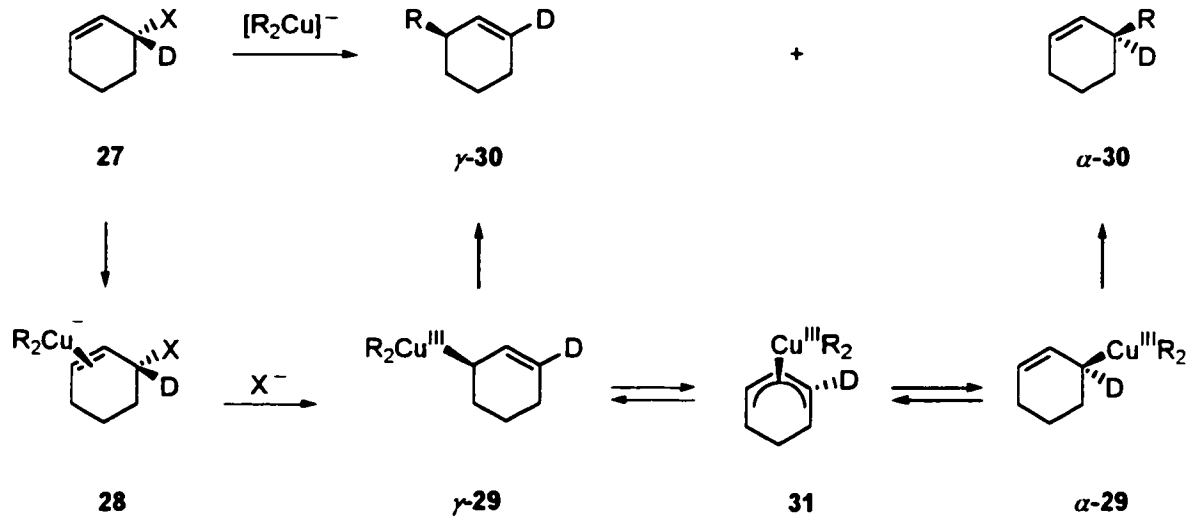
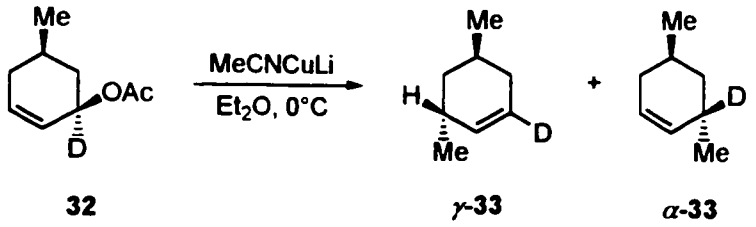


Figure 5. Proposed mechanism for formation of *anti* γ- or α-substituted products with an organocuprate reagent.

Following leads from Rudler's group[30] and Trost and Klun,[31] Goering and Kantner began experimenting with modified cuprate LiCuCNMe.[29] With this new reagent, compound γ-**33** was formed with 96% regioselectivity and an *anti*-facial preference of >95% (Scheme 12), a vast improvement over the reactions previously performed with Me_2CuLi (Scheme 11). Replacing one of the R groups on the cuprate with CN presumably causes reductive elimination to the γ-substituted product to be faster than isomerization to the π-allyl complex.

Without isomerization, this possible route to the α-substituted product is blocked. When both groups on the cuprate are R, π-allyl complex formation must be fast relative to reductive elimination, hence destroying the regioselectivity of the reaction.[29]

Scheme 12



32 **γ-33** **α-33**

The *anti*-facial selectivity observed is attributed to a favourable "bidentate" interaction between a filled d-orbital on Cu and the LUMO (π^*) on the γ-carbon and the antibonding orbital (σ^*) at the backside of the α-carbon. The electron density in the d orbital on the copper atom is expected to be quite diffuse, making the bidentate interaction possible. If this proposed transition state is correct, the required geometry would lead to an *anti*-addition of R (Figure 6).[32]

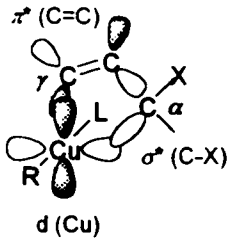
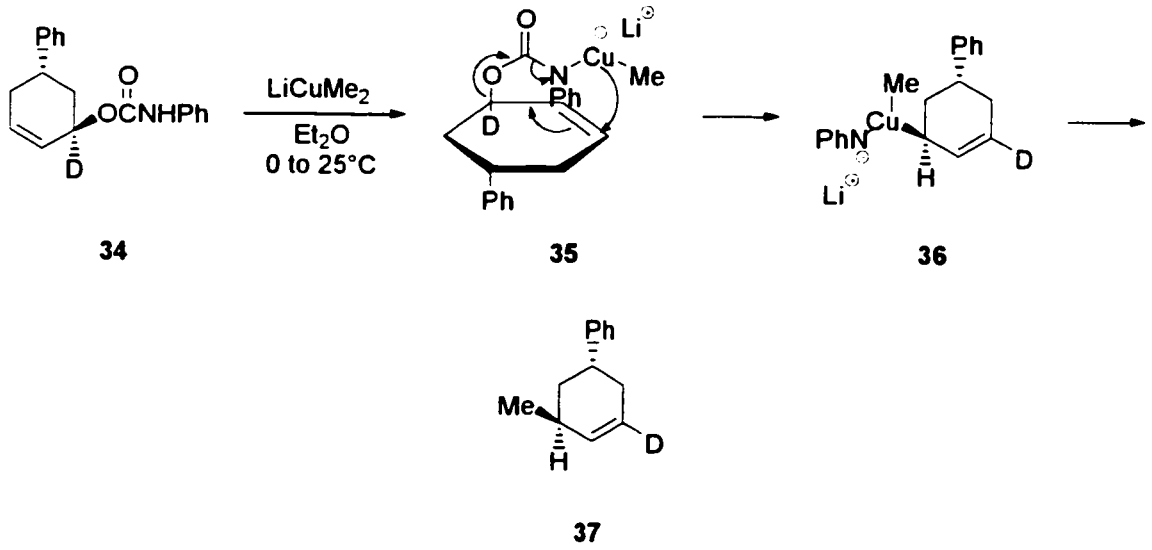


Figure 6. Proposed bidentate d-orbital interaction leading to observed *anti*-facial selectivity.

Since the initial studies, allylic substrates with other leaving groups, such as phosphate esters,[12] halides,[6] sulfonates[33] and vinyl-oxiranes,[13] have also been shown to exhibit *anti*-facial selectivity in copper-mediated S_N2' reactions.

During Gallina and Ciattini's study on cyclic allylic substrates, they made interesting observations involving leaving groups containing an ionizable proton. When they reacted *cis*-1-deuterio-5-phenyl-2-cyclohexylcarbamate (**34**) with $LiCuMe_2$, the reaction occurred with *syn*-facial selectivity (Scheme 13). The regioselectivity for the γ-product was >98%.[28] After doing probe studies, Goering and coworkers proposed that the reaction occurred through mixed-cuprate complex **35** to form σ-allyl copper (III) complex **36**. Complex **36** reductively eliminated to form *syn* γ-substituted compound **37**.[34]

Scheme 13



34 **35** **36**

37

Syn-facial selectivity has since been observed with oxybenzotriazole and thiolbenzotriazole leaving groups.[35]

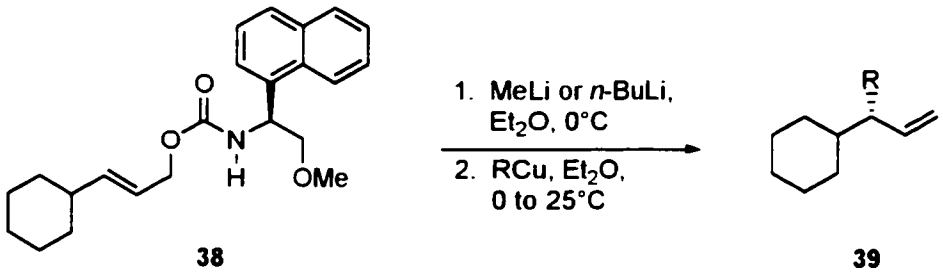
1.2.2 Reactions with Acyclic Allylic Substrates

In recent years, much more emphasis has been placed on acyclic substrates. When dealing with acyclic substrates, a new stereochemical concern arises: the geometry of the double bond. The lack of rigidity of these substrates also adds to the complexity of the reactions. As a result, it was unknown whether the same results could be expected for this new

class of reaction. Research was needed in this area. Previous studies with different types of cuprates on acyclic allylic substrates will be discussed in this section.

The simplest copper reagent known to exhibit S_N2' coupling is "RCu". These types of compounds are referred to as monoorganocopper reagents and are readily formed by reacting a copper (I) salt with an equivalent of an alkyllithium or Grignard reagent.[4] For example, Denmark and Marble studied monoorganocopper reagents and their reactions with chiral carbamates **38** (Scheme 14). In each case, the reaction occurred with an S_N2'/S_N2 ratio of greater than 100:1 and with high enantioselectivity.[11]

Scheme 14



38 **39**

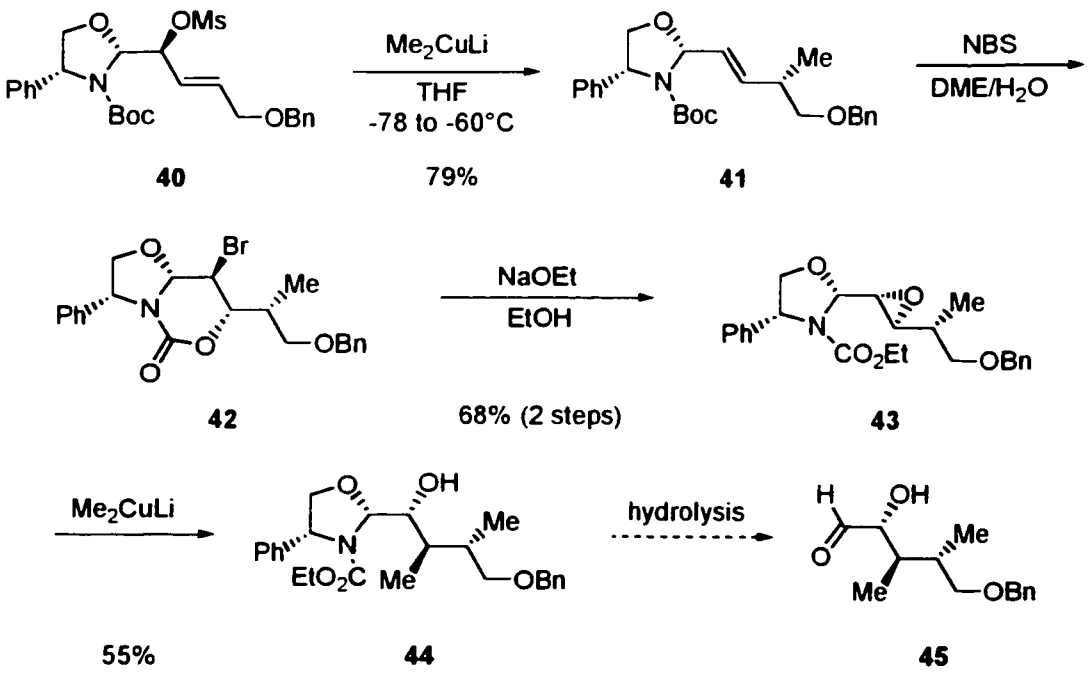
R	ee of 39 (%)	Yield (%)
Me	95	56
n-Bu	88	64
Ph	91	70

Lithium-based cuprates are quite popular in the literature. They come in many different forms, such as Gilman or homocuprates (R_2CuLi), cyanocuprates (RCuCNLi) and modified homocuprates ($R_2CuLi{\cdot}LiX$, where X is a halide or CN).[4]

Homocuprates are generally more stable and possess greater nucleophilicity than their monoorganocopper analogues. The reagents are typically formed by reacting two equivalents of an alkyllithium with CuI or $CuBr{\cdot}SMe_2$. It is imperative that the copper sources be purified prior to use.[4] A disadvantage of using Gilman cuprates is that only one of the alkyl ligands is transferred in the reaction. This problem can be overcome by introducing an inexpensive, non-transferable "dummy ligand" to replace one the alkyl ligands.[4] Non-transferable ligands are typically alkynyl, phenylsulfanyl, dialkylamino or phosphanyl-based.[6]

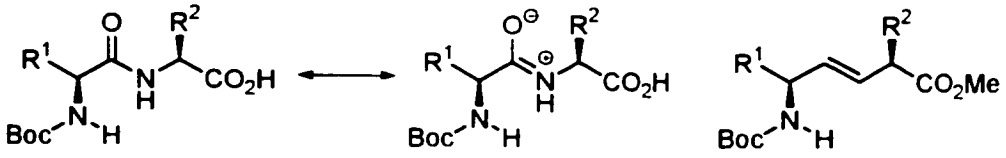
In developing a new route to enantiopure aldehydes, Agami and coworkers used Gilman cuprate, Me_2CuLi, to alkylate allylic mesylate **40** (Scheme 15).[33] The transformation occurred with complete S_N2' regioselectivity and *anti*-facial selectivity. The resulting *N*-Boc alkenyl oxazolidine **41** was epoxidized in two steps. Bicyclic carbamate intermediate **42**, formed by reaction with *N*-bromosuccinimide (NBS) in 1,2-dimethoxyethane (DME) and water, was opened with NaOEt/EtOH to form epoxide **43**. The epoxide was opened with Me_2CuLi to afford compound **44**, a protected aldehyde with three contiguous chiral centers. The protecting group could presumably be removed via hydrolysis. Unfortunately, the "lower order cuprate" route was only successful for introducing methyl groups.[33]

Scheme 15



Cyanocuprates are easily prepared by reacting an equivalent of alkyllithium with CuCN. The copper source is non-hygroscopic and light insensitive, making it easy to handle and store.[4] Ibuka *et al.* used cyanocuprates when developing a general route to alkene **47** (Figure 7). They hoped that these alkenes would provide access to new protease inhibitors.[36] Peptide **46** is an example of an enzyme substrate. Since (*E*)-alkene double bonds are isosteric to amide bonds (-CO-NH-), replacing the amide bond with a double bond was expected to

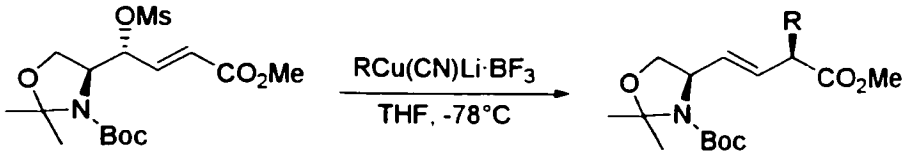
create inhibitors with high lipophilicity and high resistance to biodegradation.[37] In order to introduce groups α to the methyl ester with high regio- and stereoselectivity, the authors relied on cyanocuprates modified with boron trifluoride etherate ($BF_3 \cdot Et_2O$).[36] Addition of electron-deficient compounds, such as $BF_3 \cdot Et_2O$, often increases rates and yields of copper-coupling reactions, since they activate the substrate through complexation.[38] It is also possible that the Lewis acid additives modify the structure of the cuprates.[39] Ibuka and coworkers reported that $BF_3 \cdot Et_2O$ was essential to achieve high facial selectivity. In the examples shown (Scheme 16), all of the substitutions occurred with >99:1 *anti* facial selectivity.[36]



46 **47**

Figure 7. Dipeptide **46** and desired mimic **47**.

Scheme 16



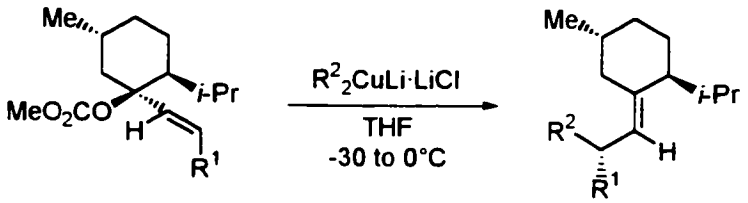
48 **49**

Yield: 97-98%
R = Me, *i*-Bu, Bn

Modified Gilman cuprates are widely used in the literature. For example, Spino and coworkers have used LiCl-modified cuprates in order to invoke highly stereoselective *anti* S_N2' reactions with allylic carbonates.[40] LiCl is typically added to increase the solubility of the copper source, CuI. By making CuI more soluble, the Cu^{1+} is less likely to be reduced to Cu(0), which is an unreactive species.[41] Using a chiral auxiliary based on (-)-menthone, Spino *et al.* introduced alkyl (primary, secondary, tertiary) and phenyl substituents to the system (see

Scheme 17 for representative examples). When R^1 was methyl, all additions occurred with de's greater than 99% and in moderate yield. The only disappointing yield came with vinyl addition (entry 4), as the S_N2, reduction and elimination products were also isolated. When R^2 was *i*-Pr or *t*-Bu, phenyl and substituted phenyl, additions occurred with high yields and diastereoselectivities (entries 8-10). However, when R^1 was phenyl or a related compound, the diastereoselectivities dropped dramatically (entries 6, 8-12), especially when the cuprate used was *i*-Pr or *t*-Bu. The authors hypothesized that larger cuprate reagents required longer times and higher temperatures to react, which may have led to the formation of radicals or ionic intermediates.[40]

Scheme 17



50 **51**

Entry	R^1	R^2	de of 51 (%)[a]	Yield (%)[a]
1	Me	Et	>99	75
2		*n*-Bu	>99	70
3[b]		*t*-Bu	>99	78
4		H_2C=CH	>99	20
5		Ph	>99	75
6		*p*-MeOPh	>99 (90)	44 (58)
7		2-furanyl	>99	65
8	*i*-Pr	Ph	>99 (82)	87 (67)
9		*p*-ClPh	>99 (82)	91 (63)
10	*t*-Bu	Ph	>99 (33[b])	72 (40)
11	*p*-MeOPh	*i*-Pr	33	59
12		*t*-Bu	14	49

[a] Yield and de in parentheses represent those obtained when the roles of R^1 and R^2 were reversed.
[b] *t*-BuCuCNLi was used.

The high level of diastereoselectivity achieved by Spino and coworkers was attributed to the energy difference between the two reactive rotamers of compound **50**. The authors believe that the S_N2' reaction preferentially occurred through rotamer **A** (Figure 8).[26]

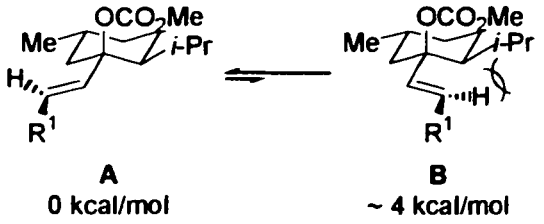
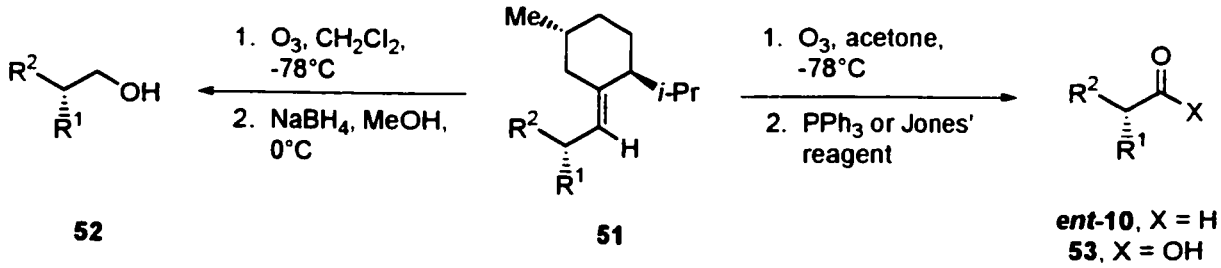


Figure 8. The two reactive rotamers of carbonate **50**.

In most cases, alkenes **51** could be cleaved with ozone to form alcohols, aldehydes or carboxylic acids (see **52**, ***ent*-10** and **53**, respectively, Scheme 18). Unfortunately, compounds containing a furan ring led to a number of products upon ozonolysis.[40]

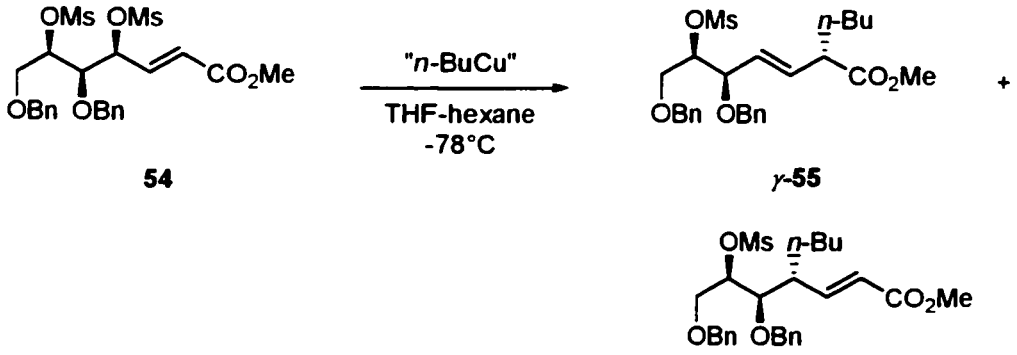
Scheme 18



When two equivalents of alkyllithium are mixed with one equivalent of CuCN, the result is $R_2CuLi{\cdot}LiCN$. These types of reagents were once called "higher-order cyanocuprates", but are now commonly referred to as cyano-Gilman reagents.[6] These "2:1 cuprates" are often more reactive than their lower order counterparts, although they tend to exhibit the same stereo- and regioselectivity.[5] The structures of these compounds will be discussed in detail in Section 1.2.3.

Cyano-Gilman cuprates have been used extensively. When working on the total synthesis of a biologically active natural product, Ibuka *et al.* needed to perform a transformation similar to the one shown in Scheme 19.[42] Initially, they tried the reaction with the lower order cuprate, *n*-Bu_2CuLi, and obtained a mixture of the α- and γ-substituted products, although the diastereoselectivity of the γ-alkylation was very high. They next tried a BF_3-modified Gilman cuprate, which gave a similar result. Fortunately, when *n*-$Bu_2Cu(CN)Li_2 \cdot BF_3$ was tried, the γ-alkylated product, obtained with extremely high diastereoselectivity, was the only product detected. The coupling occurred with *anti*-facial selectivity.[42]

Scheme 19

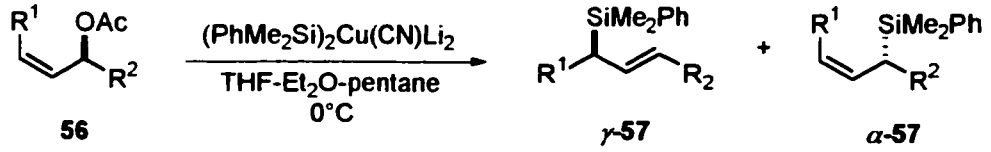


54 **γ-55** **α-55**

Reagent	Isolated Yield 55 (%)		de γ-55 (%)
	γ	α	
n-Bu_2CuLi	70	23	98:2
n-$Bu_2CuLi \cdot BF_3$	71	19	98:2
n-$Bu_2Cu(CN)Li_2 \cdot BF_3$	94	-	>99:1

Metals are also used in conjunction with copper sources to perform S_N2' reactions. Fleming and coworkers used silicon-modified cuprate reagents when developing a general and stereoselective route to allylsilanes. They found that silylcuprates added in an *anti*-S_N2' manner to *cis*-allylic acetate **56** with moderate regioselectivity and high facial selectivity (Scheme 20). Conversely, they could add silylcuprates to *cis*-allylic carbamate **58** with complete S_N2' regioselectivity and high *syn*-facial selectivity (Scheme 21).[43]

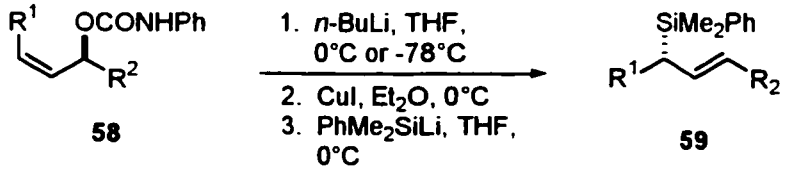
Scheme 20



56 *γ*-**57** *α*-**57**

R^1	R^2	Product 57 Distribution (%)		Yield (%)
		γ	*α*	
Ph	Me	88	12	60
Me	Ph	82	18	51
Me	*i*-Pr	100	-	83

Scheme 21

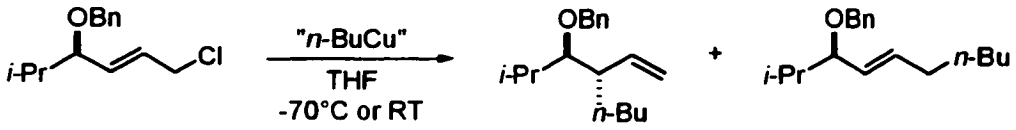


58 **59**

R^1	R^2	Yield (%)
Ph	Me	75
i-Pr	Me	64
Me	Ph	68
Me	*i*-Pr	87

Arai *et al.* used zinc- and titanium-modified cuprates to improve S_N2' reactions on primary allylic chlorides (Scheme 22).[44] When they tried the addition of a standard Gilman reagent to their systems, they were disappointed to find poor S_N2' regioselectivity. In an attempt to increase the observed regioselectivity, they developed new reagents containing copper coupled with zinc or titanium. With these modified cuprates, the S_N2' regioselectivity jumped to ≥98%. The modified Gilman reagent was formed by reacting one equivalent each of *n*-Bu_2CuLi and $ZnCl_2$. The catalytic copper reagents were generated from either *n*-Bu_2Zn or *n*-$BuTi(O\text{-}iPr)_3$ and $CuBr{\cdot}SMe_2$ (6 mol%). In all cases, only the *anti*-S_N2' diastereomer was formed.[44]

Scheme 22

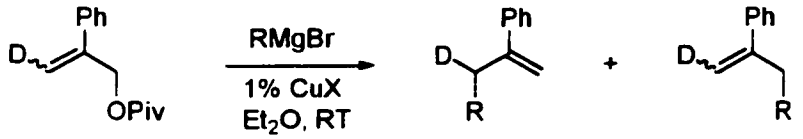


60 **γ-61** **α-61**

Reagent	Product 61 Distribution (%)		Yield (%)
	γ	α	
R_2CuLi	12	88	61
$R_2CuLi/ZnCl_2$	98	2	100
R_2Zn/cat. Cu	98	2	80
$RTi(O\text{-}iPr)_3$/cat. Cu	99	1	92

Perhaps the most popular metal used in conjunction with copper is magnesium, in copper-mediated S_N2' Grignard reactions.[4] Early work by Goering and coworkers showed that CuCN was a far superior catalyst, as opposed to copper halides, in achieving high regioselectivity in acyclic allylic systems.[45] In unbiased systems, CuCN catalysis allowed complete γ-substitution with a number of different Grignard reagents (Scheme 23). Unfortunately, the trend broke down for PhMgBr. Even in systems that were biased for α-substitution due to conjugation, CuCN catalysis allowed for the S_N2' product to be formed with high regioselectivity (Scheme 24).

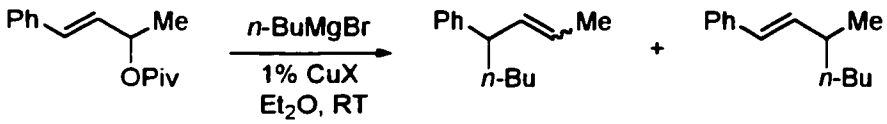
Scheme 23



62 *γ*-**63** *α*-**63**

R	X	Product 63 Distribution (%)		Yield (%)
		γ	*α*	
n-Bu	Cl	61	39	97
	CN	100	-	79
t-Bu	CN	100	-	76
i-Pr	CN	100	-	86
Ph	CN	53	47	80

Scheme 24

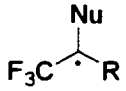


64 *γ*-**65** *α*-**65**

X	Product 65 Distribution (%)		Yield (%)
	γ	*α*	
CN	98	2	100
Cl	11	89	96
Br	15	85	92
I	14	86	86

Many groups have subsequently used this information to their advantage. For example, Yamazaki and coworkers[46] used this chemistry when developing novel methods to prepare compounds of general structure **66** (Figure 9). These types of targets are valuable since adding fluorines to methyl and methylene groups often increases the biological activity of organic compounds.[47] Using CuCN-catalyzed Grignard reagents modified with chlorotrimethylsilane (TMSCl), Yamazaki *et al.* were able to introduce many different alkyl groups α to the CF_3 group with complete γ-regioselectivity, coupled with high yields and bond

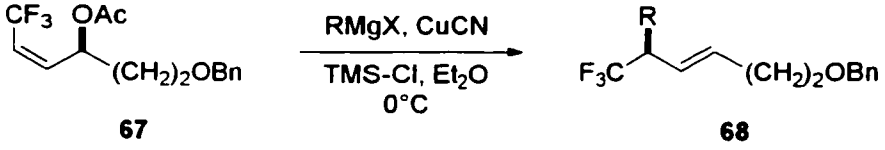
stereoselectivities (*E*:*Z* >99:1) (Scheme 25). When the *n*-BuMgBr/CuCN reaction was conducted on an enantiomerically-enriched substrate, they found that the reaction gave complete *anti*-facial selectivity.



66

Figure 9. Substituted trifluoromethyl compound.

Scheme 25

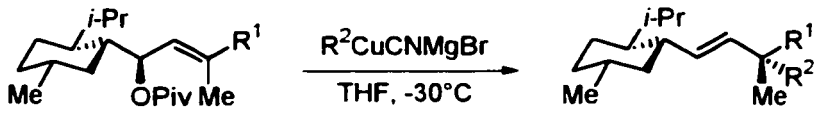


67 **68**

yield: 86-95%
R: *n*-Bu, *n*-C_7H_{15}, *i*-Pr
c-C_6H_{11}, *t*-Bu

Spino and coworkers have used Grignard reagents in conjunction with stoichiometric CuCN *en route* to α,α-disubstituted chiral carbonyl compounds.[48] In order to create a quaternary center, their originally designed substrate (see **50**, Scheme 17) was modified into substrate **69** (Scheme 26). With R_2CuLi, a mixture of regioisomers was formed and with CuCN catalyzed Grignard reactions, only starting material was recovered. However, by using a stoichiometric amount of CuCN, the desired regioisomers, coupled with excellent diastereoselectivities and yields, were obtained for a number of different systems. Unfortunately, *t*-Bu, Ph and Bn cuprates were too unreactive to be used with this substrate. Again, enantiomerically-enriched alkenes **70** were cleaved with ozone to form a number of different carbonyl or related compounds (see Scheme 18).[48]

Scheme 26



69 **70**

R^1	R^2	de of 70 (%)	Yield (%)
c-C_6H_{11}	*i*-Pr	>98	95
Bn	*i*-Pr	>98	92
Ph	*i*-Pr	91	90
$TBSO(CH_2)_3$	*i*-Pr	>98	95
$TBSO(CH_2)_3$	Et	>98	89
n-Bu	*n*-hept	>95	90

1.2.3 The "Higher-Order Cyanocuprate" Controversy

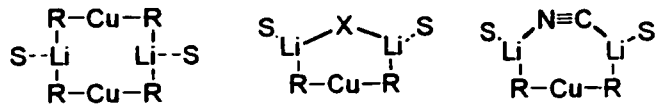
Lipshutz first developed "higher-order cyanocuprate" reagents in 1981. To explain their increased stability and reactivity, he and his coworkers postulated that the CN ligand was bound directly to Cu.[49] In this type of structure, the Cu would be tricoordinate (see **71**, Scheme 27). The existence of the higher-order cyanocuprate has been a matter of controversy since 1990, leading to many papers both supporting[50] and refuting[51] the possibility of Cu bound CN. Nakamura and Mori have recently published a review on the subject entitled, fittingly, "Wherefore Art Thou Copper? Structures and Reaction Mechanisms of Organocuprate Clusters in Organic Chemistry."[6]

Scheme 27

71

After the controversy began, Lipshutz supported his initial hypothesis with spectroscopic data.[50] He and his group prepared a number of related cuprates and compared their ^{1}H and ^{13}C NMR and IR data. For example, when comparing the ^{13}C NMR spectra of $Me_2CuCNLi_2$, $Me_2CuLi{\cdot}LiI$ and $Me_2CuLi{\cdot}LiBr$ in Me_2S, they found the signal due to the Me group of the cyanocuprate appeared at δ -8.53, but that the latter two compounds both gave signals at δ -9.65. From this and the other data, the group concluded that the higher-order cuprate was distinguishable from other modified-Gilman cuprates and, accordingly, that the CN must be bound directly to the copper.[50]

Bertz's first attack on Liphshutz's theory was published in 1990.[51] He had performed a series of NMR experiments on $R_2CuLi{\cdot}LiCN$ and RCuCNLi compounds. For the 2:1 reagents ($R_2CuLi{\cdot}LiCN$), the CN ^{13}C NMR shifts were approximately the same, regardless of the identity of R. Conversely, in the corresponding cyanocuprate analogues, all of the CN shifts were different from each other. These results suggested that the cyano group was bound to Cu in the cyanocuprate, but not in the 2:1 compounds.[51] In a further ^{13}C NMR study, he found that cyanocuprates exhibited ^{2}J couplings between the cyano and R carbons in $RCu(^{13}CN)Li$ compounds. However, the doublets collapsed to singlets if another equivalent of RLi was added in an attempt to form $R_2Cu(^{13}CN)Li_2$, suggesting that the ^{13}CN was no longer bound to the Cu.[52] Further ^{15}N and ^{6}Li NMR studies by Bertz's group seem to suggest that the CN resides on lithium.[53] Recently, solid-state X-ray structure data for cyano-Gilman reagents has been reported by van Koten's group. According to their results, the most thermodynamically stable form of these reagents places the CN group on Li.[54] From the data collected, it appears as though Bertz's structure for the cyano-Gilman reagent is most fitting. Consequently, the increased reactivity of CuCN-modified cuprates is now commonly attributed to the higher Lewis acidity of the LiCNLi "bridge," as compared to RCuR in R_2CuLi or LiXLi in $R_2CuLi{\cdot}LiX$ (Figure 10).[55]



72 **73** **74**

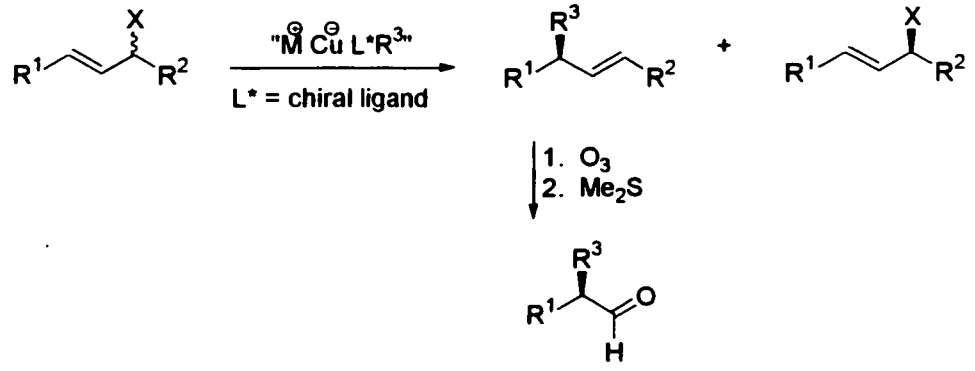
S = solvent
X = halogen

Figure 10. Probable solution structures of Gilman cuprate **72** and modified-Gilman cuprates **73** and **74**, respectively.

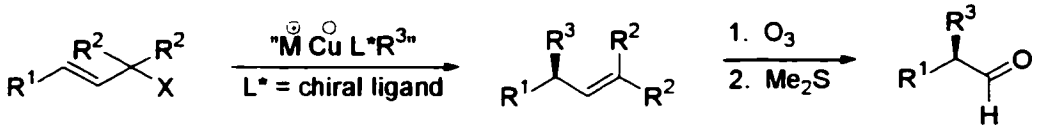
1.3 Outline of Thesis

The goal of this project was to develop a new route to α-chiral aldehydes utilizing S_N2' cuprate reactions. Chapter 2 will outline our preliminary results, which were based upon the 1,3-chirality transfer strategy outlined in Scheme 10. Chapter 3 will show the evolution of the project, including the use of chiral cuprates for attempted kinetic resolution (Scheme 28) and asymmetric addition (Scheme 29). Finally, Chapter 4 will focus on the application of 1,2-induction to the synthetic goal (Scheme 30).

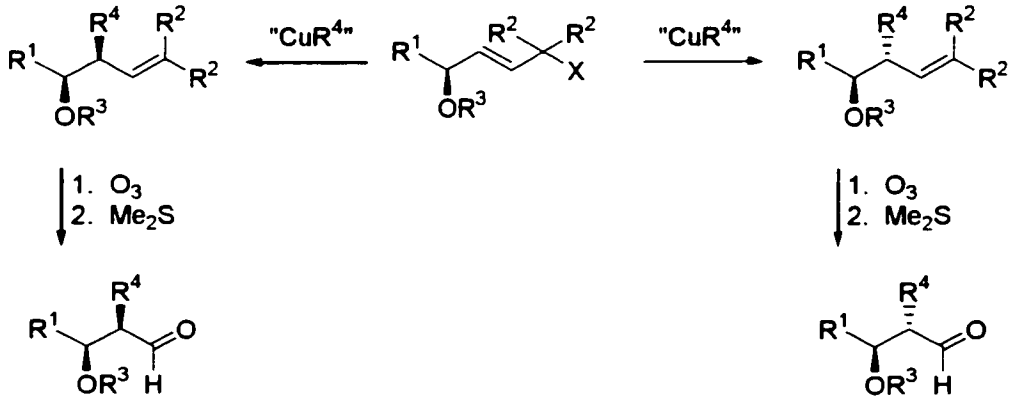
Scheme 28



Scheme 29



Scheme 30



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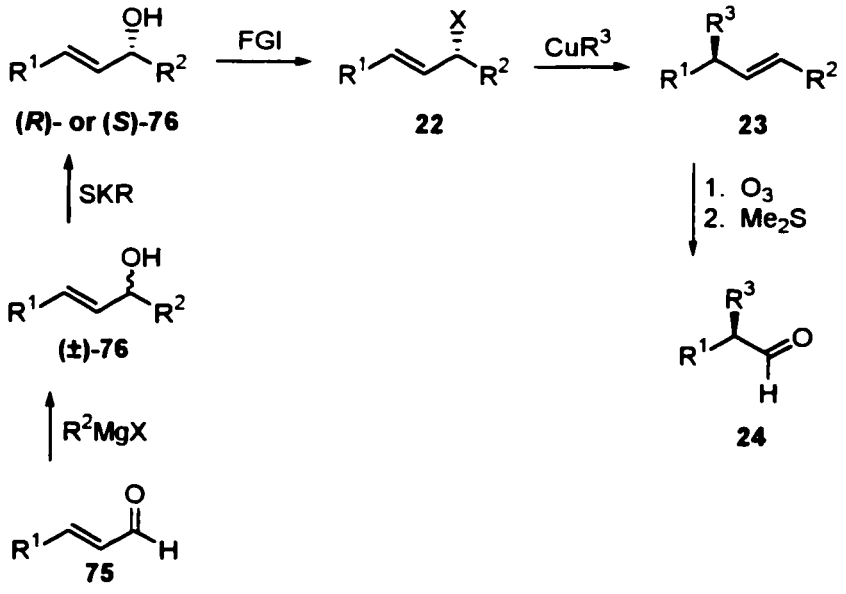
CHAPTER 2

1,3-CHIRALITY TRANSFER IN ALLYLIC SYSTEMS

2.1 Introduction

The first proposed route to α-chiral aldehydes is outlined in Scheme 31. In the first step of the reaction sequence, a racemic allylic alcohol is formed from an α,β-unsaturated aldehyde and a Grignard reagent. Chirality is introduced to the system using Sharpless kinetic resolution (SKR) methodology,[1] the first of two key steps in the synthetic scheme. At this point, the hydroxyl group is transformed into a good leaving group (X). The next key step is the displacement of this leaving group in an S_N2' reaction with an organocopper reagent. The resulting alkene **23** is cleaved with ozone to form the desired α-chiral aldehyde **24**. In this sequence there are several variables, each of which will be discussed in turn.

Scheme 31



The results of this study have recently been published in *The Journal of Organic Chemistry*.[2]

2.1.1 Sharpless Kinetic Resolution Methodology

In Scheme 31, the enantiomers of racemic allylic alcohol **(±)-76** are separated using the Sharpless kinetic resolution. Using a chiral Ti catalyst, this method can be used to resolve a wide variety of allylic alcohols by preferentially epoxidizing one of the enantiomers. The allylic alcohol binds to the chiral complex via the hydroxyl group.[3]

There are four essential components to this resolution: the allylic alcohol substrate, a titanium (IV) alkoxide, a chiral tartrate ester and an alkyl hydroperoxide. These components form an asymmetric complex in which the peroxy oxygen is preferentially delivered to one face of the allylic alcohol. The most successful combination is with Ti(O-*i*-Pr)$_4$ as the titanium source and *tert*-butyl hydroperoxide (TBHP) as the oxidant. Although a number of chiral tartrates can be used in the kinetic resolution, the best results are achieved with larger alkyl ester groups, such as isopropyl and cyclohexyl.[3]

The face of attack is determined by the absolute configuration of the tartrate used. From the "rules" illustrated in Figure 11, *D*-(-)-dialkyl tartrates deliver oxygen from the "top" face of the allylic alcohol, whereas *L*-(+)-dialkyl tartrates deliver oxygen from the "bottom" face. Hence, either enantiomer of the allylic alcohol can be obtained in high enantiomeric excess, further adding to the versatility of the methodology.[3]

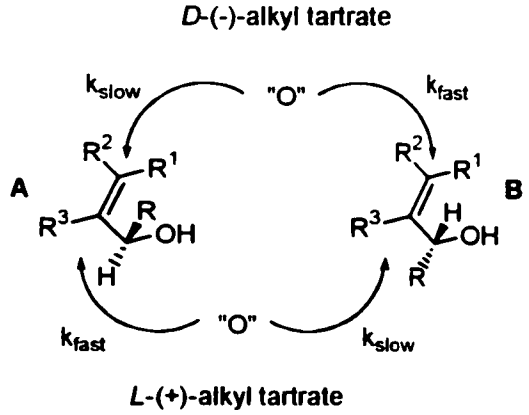


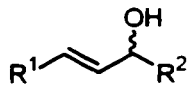
Figure 11. Enantiofacial selectivity of chiral tartrates during epoxidation of allylic alcohols.

The kinetic resolution uses steric interaction to achieve its facial selectivity. For example, in enantiomer **A** alkyl group "R" is oriented towards the direction of oxygen delivery

from the *D*-(-)-tartrate, whereas in enantiomer **B**, the same group faces the other direction. Consequently, in the former case, oxygen will be delivered at a slower rate (k_{slow}). The difference in the rates of epoxidation is often sufficiently large, such that one of the enantiomers of the allylic alcohol will remain mostly unoxidized, while the other undergoes complete epoxidation. The net result is a kinetic resolution of the enantiomers. When the *L*-(+)-tartrate is used, the opposite result is observed. Either the epoxy alcohol or the unreacted allylic alcohol can be obtained in high enantiomeric excess by modifying the reaction time.[3]

SKR has been used to resolve a wide variety of allylic alcohols with good yields and high enantiomeric excesses (see Table 1 for representative examples). The resolution typically works well, regardless of the identity of R^1 (entries 1-3); however, the efficiency of the reaction is greatly diminished with bulky substitutents at R^2 (entry 4).[3]

Table 1. Kinetic resolution of representative 1-substituted allylic alcohols.



(±)-76

Entry	R^1	R^2	ee (%)	Yield (%)[a]
1[4]	Me	*n*-$C_{12}H_{25}$	97	88
2[5]	H	*c*-C_6H_{11}	>98	64
3[3]	Ph	Et	99	nr[b]
4[6]	Me	*t*-Bu	≤5	25[c]

[a] Yields are based upon a possible 50% recovery of the enantiomerically-enriched alcohol.
[b] nr = not reported.
[c] Yield is based upon starting material consumed.

The proposed mechanism for the asymmetric epoxidation involves a number of titanium ligand exchanges (Figure 12).[3] The first equilibrium established is between the titanium alkoxide and the tartrate. The equilibrium lies far to the right, since the diol of the tartrate has a much higher binding constant than ROH, due to the chelate effect.[7] The OH groups on the diol are also more acidic because of the inductive effects of the carbonyl groups. When the allylic alcohol and TBHP are added to the solution, the ligand exchange continues. After the loaded catalyst is formed, the oxygen is transferred from the TBHP to the double bond of the allylic alcohol to form the product complex. The "loaded catalyst" is regenerated

when the epoxy alkoxide and O-*t*-Bu groups are replaced with TBHP and allylic alcohol molecules.[3]

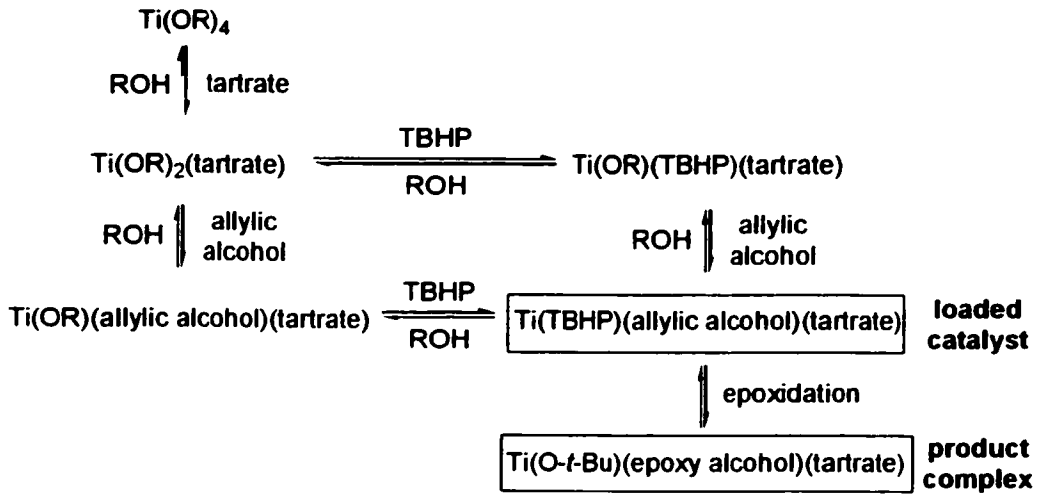
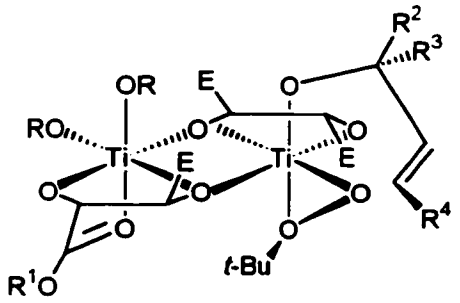


Figure 12. Proposed mechanism for ligand exchange during titanium-tartrate catalyzed epoxidation.[3]

The structure of the proposed loaded catalyst is shown in Figure 13. In this conformation, it is assumed that the distal peroxide oxygen is transferred to the olefin. The allylic alcohol binds to the remaining axial coordination site in a conformation determined by the stereoelectronic and stereochemical effects provided by the catalyst.[3]



E = CO_2R^1

Figure 13. Proposed structure of the allylic alcohol coordinated to the titanium catalyst complex.[3]

2.2 Results and Discussion

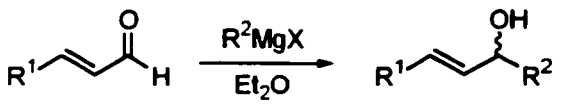
In this study, we wanted to control all variables within the synthetic route outlined in Scheme 31. Variation of R^1 and R^3 would allow this route to be used for a variety of α-substituted aldehydes. Although the R^2 group is "lost" during the ozonolysis step, it was hypothesized that its identity would be extremely important in determining the efficiency of the copper coupling reaction.

2.2.1 Allylic Alcohol Synthesis

The desired allylic alcohols contained two of the key variables, R^1 and R^2 (Table 2). It was presumed that the compounds could be formed by reaction of α,β-unsaturated aldehydes with Grignard reagents. Many of the prerequisite aldehydes are commercially available or can be formed using Horner-Wadsworth-Emmons chemistry, providing the freedom to vary R^1. It was also important to have control of the geometry of the double bond. The Grignard reaction is quite versatile, as R^2 can be primary, secondary and tertiary alkyl, allylic or aryl.

A number of different allylic alcohols were synthesized. According to Sharpless and coworkers, the identity of R^1 had little effect on the outcome of the kinetic resolution;[3] however, we knew from literature searching that cuprates could react with allylic substrates to form either the α- or γ-substituted products.[8] Consequently, the assumption was made that R^1 should be kept less sterically demanding than R^2, in order to promote reaction at the γ-site. In a similar manner, R^2 should be kept large to prevent α-attack. But, in order for the SKR to proceed as planned, R^2 could not be too bulky. Substrates with varying steric requirements were also synthesized in order to probe the factors influencing the reaction.

Table 2. Racemic allylic alcohol synthesis.

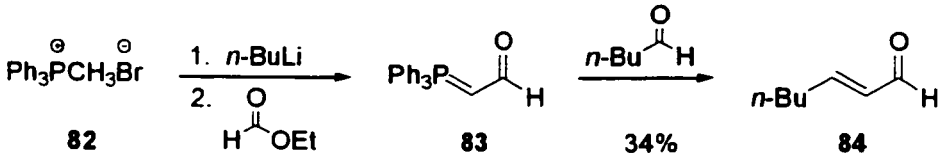


(±)-77-81

Entry	(±)-Allylic Alcohol	R^1	R^2	Yield (%)
1	**77**	Me	*n*-Bu	67
2	**78**	Me	*i*-Pr	66
3	**79**	Me	*c*-C_6H_{11}	79
4	**80**	Me	3-pentyl	76
5	**81**	*n*-Bu	*c*-C_6H_{11}	69

The allylic alcohols were formed in moderate to good yield. In most cases, (*E*)-crotonaldehyde (R^1 = Me), which is commercially available, was used. However, (*E*)-2-heptenal (**84**), used in the synthesis of alcohol **(±)-81**, was formed by reaction of formylmethylenetriphenylphosphorane (**83**) with valeraldehyde (Scheme 32).[9]

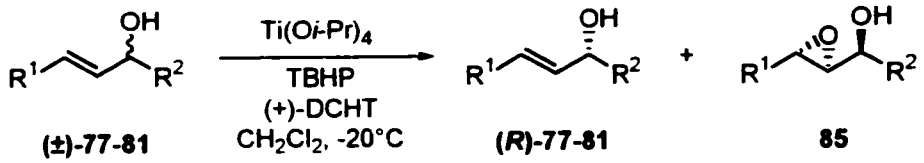
Scheme 32



2.2.2 Sharpless Kinetic Resolution Results

All of the allylic alcohols were resolved using Ti(O-*i*-Pr)$_4$ (0.10 equiv), TBHP (0.70 equiv) and (+)-dicyclohexyl tartrate (DCHT, 0.15 equiv). The reaction progress was monitored by GC (decane as internal standard) and was stopped when >50% of the starting material had been consumed.[1]

Table 3. Sharpless kinetic resolution of allylic alcohols.



(±)-77-81 (*R*)-77-81 85

Entry	(*R*)-Allylic Alcohol	ee (%)[a]	Yield (%)[b]
1	77	94	47
2	**78**	90	70
3	**79**	94[c]	60
4	**80**	84	83
5	**81**	94	53

[a] Determined by conversion to the corresponding (*R*)- or (*S*)-Mosher ester and analysis by ^{1}H and/or ^{19}F NMR spectroscopy.[1.10]
[b] Yields are based upon a possible 50% recovery of the enantiomerically-enriched alcohol.
[c] In another run, the ee was 90%, with a yield of 68%.

In general, the enantiomeric excesses were better when R^2 was less bulky. In all cases, the yield was inversely proportional to the enantiomeric excess achieved.

2.2.3 Leaving Groups for Allylic Substrates

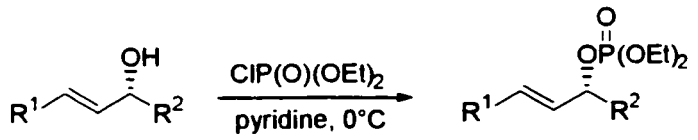
At this point in the project an important question arose: which leaving group(s) would be most effective in the copper coupling reaction? As was discussed in the introduction, there are numerous leaving groups that participate in S_N2' reactions with cuprates, with both *anti*- and *syn*-facial selectivity.[11]

We wanted to use an easy transformation that would not destroy the chiral allylic alcohol centre. The leaving group also needed to be reactive to cuprates. After searching the literature, it was decided that phosphate esters would be a good starting point, since they were known to exhibit high regio- and stereoselectivity during reactions with cuprate reagents.[12,13]

Forming the phosphate ester from the allylic alcohols was actually quite a challenge. Both deprotonation of the allylic alcohol with NaH, followed by trapping with diethyl chlorophosphate, and reaction of the allylic alcohol with the phosphorylating agent in the

presence of triethylamine (TEA) and a catalytic amount of dimethylaminopyridine (DMAP), yielded crude products exhibiting many impurity peaks on the ^{1}H NMR spectra. By ^{1}H NMR spectroscopy, the cleanest product was synthesized by reacting the alcohol with the phosphorylating agent in pyridine.[14] There were, however, a few impurity peaks. Several different methods of purification were tried, including silica and basic alumina column chromatography and Kugelrohr distillation. In all cases, only a small amount of material was recovered and the "purified" products looked much worse than the crude materials. The phosphate esters appeared to hydrolyze during chromatography, since some fractions contained the starting alcohol. The ^{1}H NMR spectra of the distilled products revealed many unknown peaks in the alkene region, indicating that the product must have decomposed or dimerized. Similar distillation problems have previously been reported.[15] Consequently, the crude phosphate esters were used in all of the subsequent copper coupling reactions. Since the functional group interconversion did not involve the hydroxyl carbon, it was assumed that there was no change in stereochemical integrity of this site during the transformation.

Table 4. Phosphorylation of allylic alcohols.



(*R*)-77-81 86-90

Entry	Phosphate Ester	R^1	R^2	Yield (%)
1	**86**	Me	*n*-Bu	60
2	**87**	Me	*i*-Pr	40
3	**88**	Me	*c*-C_6H_{11}	71
4	**89**	Me	3-pentyl	53
5	**90**	*n*-Bu	*c*-C_6H_{11}	71

In most cases, the phosphate esters were formed in reasonable yield. Due to their instability, the substrates were used promptly after synthesis.

2.2.4 S_N2' Reaction

Having developed an arsenal of allylic substrates, the coupling reactions were investigated. This part of the synthetic route was considered most important, since little work had been published on cuprate couplings with acyclic allylic substrates.[16]

A number of different cuprate reagents were investigated using phosphate ester **88** as a probe substrate. The following reagents were tried: *n*-BuMgBr/CuI (cat.), *n*-Bu_2CuLi and *n*-$Bu_2CuLi{\cdot}LiCN$. As expected, the CuI-catalyzed Grignard reaction gave a chromatographically inseparable mixture of three isomeric alkenes in a ratio of 67:25:8 by GC/MS analysis.[17] The reaction with the Gilman cuprate, *n*-Bu_2CuLi, gave a much better result, as only two regioisomers were obtained in a ratio of 88:12. The best result, however, was obtained with *n*-$Bu_2CuLi{\cdot}LiCN$, with a regioisomeric ratio of 92:8. We assumed that the isolated compounds were regioisomers, since they produced the same M$^+$ peak (194), but different MS fragmentation patterns. For example, the base peaks were 81 and 155 for the major and minor products, respectively.

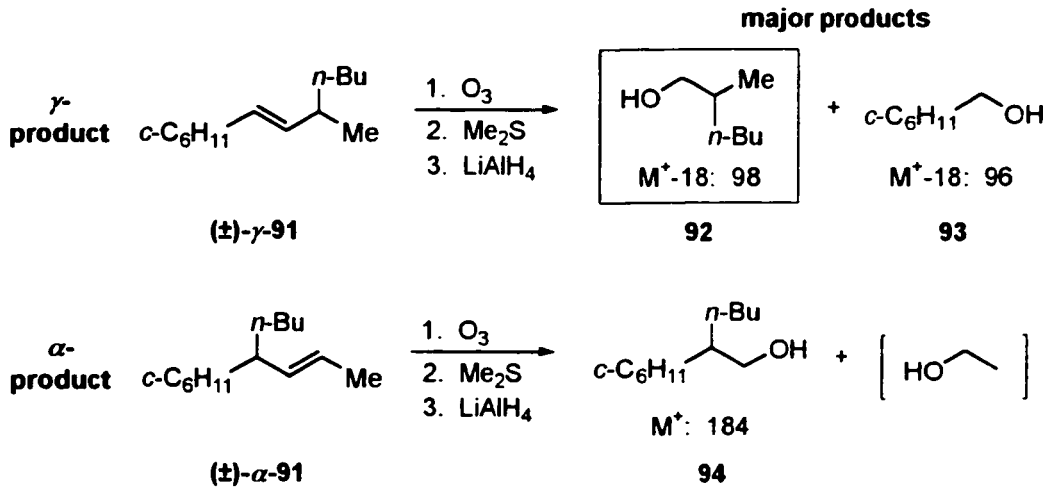
The ^{1}H NMR spectrum showed that the alkene protons of the major product were coupling with a coupling constant of approximately 16 Hz, indicating that they were *trans* to each other.[18] Protons of *cis*-double bonds typically exhibit coupling constants in the range of 6-12 Hz.[18] Based on literature records of cuprate couplings with phosphate esters, retention of the (*E*)-double bond geometry was expected.[12,19] There was also a methyl doublet appearing at δ 0.95, suggesting that the methyl group was once removed from a double bond, as opposed to being directly bound to it.[18] A methyl shift of $\sim\delta$ 1.7 is expected for vinylic methyl groups.[18] From the shift observed, it was assumed that the γ-regioisomer was preferentially formed. To confirm the suspicion, more analysis was required. Luckily, the answer was revealed when attempting to determine the facial selectivity of the reaction.

2.2.4.1 Enantiomeric Excess Determination

We required a method to determine the enantiomeric excesses of the alkenes. It is difficult to determine the enantiomeric excess of alkenes directly; so the compounds were

modified. In the first attempt, alkene (±)-**91** was cleaved with ozone and treated under reducing conditions to form the alcohols (Scheme 33). The mass spectra of the alcohols revealed that the major products had peaks at 98 and 96. These masses could be assigned to alcohols **92** and **93**, respectively, as M$^+$-18 fragments. Alcohols often do not exhibit molecular ion peaks and losing water (18) is a common fragmentation with these compounds.[18] The mass spectra confirmed that the major coupling compound was γ-substituted, as the α-product would have given one major peak with M$^+$ at 184 or an M$^+$-18 peak at 166 (Scheme 33).

Scheme 33

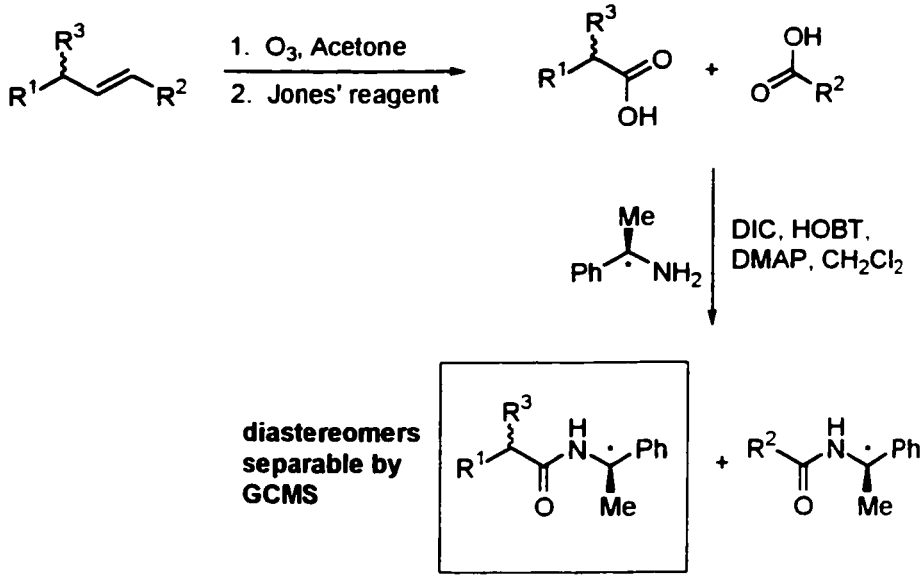


After separating the desired alcohol **92**, it was derivatized to form diastereomeric Mosher esters by reaction with (*R*)-(-)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride ((*R*)-MTPA-Cl) in the presence of TEA and DMAP in CH_2Cl_2.[1,10] The diastereomeric esters were analyzed by HPLC and ^{1}H and ^{19}F NMR spectroscopy. Unfortunately, in the ^{19}F NMR spectrum, the two signals corresponding to the CF_3 groups did not have baseline separation and in the ^{1}H NMR spectrum there were no signals to clearly measure the diastereomeric ratio. In the HPLC trace, again, the diastereomeric esters exhibited no baseline separation. The racemic alcohols were also derivatized with benzoyl chloride, in hopes of performing chiral HPLC analysis on the resulting esters. Unfortunately, baseline separation was not observed.

In a different approach, the alkene was cleaved with ozone and the resulting ozonide treated with Jones' reagent[20] to form the corresponding carboxylic acids. A mixture of the crude carboxylic acids was derivatized with (*R*)-1-phenylethylamine to form diastereomeric

amides (Scheme 34). After work-up, the amides were analyzed by GC/MS and, fortunately, the peaks corresponding to the diasteromeric amides were completely separable.

Scheme 34

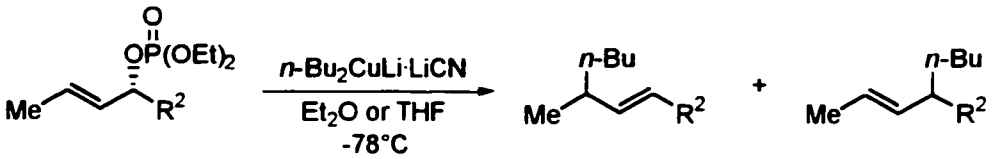


With a successful method to determine enantiomeric excess in hand, attention was turned to trying the methodology with enantiomerically-enriched substrates.

2.2.4.2 Structural Effects

Coupling reactions were performed using cyano-Gilman cuprates and the enantiomerically-enriched phosphates synthesized in Section 2.2.3 (Table 5).

Table 5. Structural effects.



86-90 *γ*-**91, 95-97** *α*-**91, 95-97**

Entry	Phosphate Ester Number	R^2	ee (%)	Alkene ee (%)	*γ*-Regio[a] (%)	Yield (%)	Number
1	**86**	*n*-Bu	94	40	67	74	**95**
2	**87**	*i*-Pr	90	76	91	72	**96**
3	**88**	*c*-C_6H_{11}	90	84	95	67	**91**
4[b]	**88**	*c*-C_6H_{11}	94	76	94	46	**91**
5	**89**	3-pent	84	82	96	53	**97**

[a] *γ*-Regio = regioselectivity for the *γ*-substituted product; determined by GC/MS ratios.
[b] The reaction was run with *n*-Bu_2CuLi.

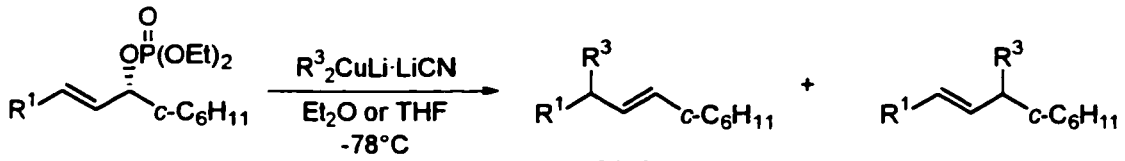
The substrates are listed in order of increasing steric bulk of R^2. As expected, the regioselectivity for the *γ*-substituted product was directly proportional to the steric bulk of R^2. Hence, the regioselectivity with *n*-Bu, a group with little steric demand, was only 67%, but jumped to 96% with a bulky 3-pentyl group in place. Logically, as the steric crowding at the *α*-site increased, attack was favoured at the less hindered *γ*-center.

Similarly, the loss of enantiomeric purity during the copper coupling was also directly proportional to the size of R^2. For example, there was almost no change in the enantiomeric excess when R^2 was 3-pentyl (see entry 5, Table 5). The implications of this result will be discussed in Section 2.2.4.5. Another interesting comparison occurs between entries 3 and 4. Using the same substrate, the reaction was run with *n*-Bu_2CuLi·LiCN (entry 3) and *n*-Bu_2CuLi (entry 4). Although the regioselectivity was essentially the same, the loss in enantiomeric purity was larger when the Gilman reagent (entry 4) was used. The yield with the cyano-Gilman was also comparatively higher. The different results seem to substantiate previous arguments that Gilman and cyano-Gilman reagents are indeed different.[16]

2.2.4.3 Nucleophile Influences

Attention was now focused on applying this method to different cuprates. Phosphate esters **88** and **90** were used for the investigations (Table 6).

Table 6. Effect of nucleophile.



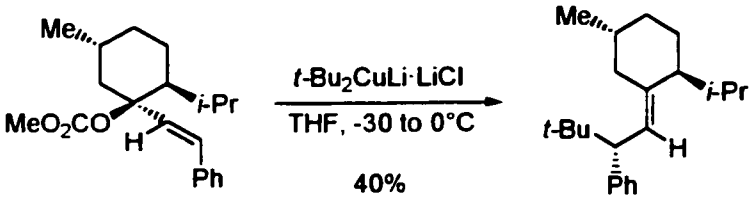
88, 90 **γ-91, 98, 99** **α-92, 98, 99**

Entry	Phosphate Ester			Alkene				
	Number	R^1	ee (%)	ee (%)	R^3	γ-Regio[a] (%)	Yield (%)	Number
1	**88**	Me	90	84	*n*-Bu	95	67	**91**
2	**88**	Me	90	32	*t*-Bu	95	67	**98**
3[b]	**88**	Me	90	48	*t*-Bu	88	46	**98**
4	**88**	Me	94	80	Bn	97	42	**99**
5	**90**	*n*-Bu	94	80	Me	85	40	***ent*-91**

[a] γ-Regio = regioselectivity for the γ-substituted product; determined by GC/MS ratios.
[b] The reaction was run in THF with HMPA (10% v/v) as a co-solvent.

After the reasonable success achieved utilizing *n*-Bu_2CuLi·LiCN, it was hoped that other cuprates would give similar results. It was disappointing to observe the drastic loss of enantiomeric purity when coupling the *t*-Bu cuprate with one of the probe substrates (Table 6, entry 2). Initially, it was hypothesized that a single electron transfer (SET) mechanism was at work in the *t*-Bu addition case, which was effectively destroying the chiral center. Spino and coworkers gave a similar explanation when observing facial scrambling during *t*-Bu group addition to carbonate **100** (Scheme 35).[21] They hypothesized that large cuprates, such as those containing *t*-Bu, would require longer times and temperatures to react, which could possibly lead to the formation of a radical or charged intermediate.[21]

Scheme 35



100 **101**

de = 33%

SET had also previously been observed when performing copper coupling reactions with leaving groups that are good electron acceptors, such as I^-. The net result of radical formation was a racemic product formed from an enantiomerically-enriched substrate.[22]

If there was a single electron transfer mechanism at work, two possible options for shutting it down were considered. The first would be to use another leaving group that was less likely to accept electrons. The other option involved using a polar co-solvent, such as hexamethylphosphoramide (HMPA). Typically, increasing solvent polarity increases cuprate reactivity; therefore, the reagent is more apt to give direct substitution, as opposed to acting through a radical species.[23] HMPA had also previously been shown to alter the solution structures of $R_2CuLi{\cdot}LiCN$.[24]

The first route explored was that of a new leaving group. Pivalate **102** and trifluoroacetate **103** were easily formed in 86% and 74% yields, respectively (Scheme 36).

Scheme 36

(±)-79

102: X = $COCMe_3$; 86%
103: X = $COCF_3$, 74%

The results of cuprate coupling reactions with these new substrates were surprising. By reaction with *n*-Bu_2CuLi, pivalate **102** yielded alcohol **(±)-79**, which was clearly generated from nucleophilic attack on the pivalate carbonyl. With *n*-$Bu_2CuLi{\cdot}LiCN$, small amounts of

the desired γ-substituted alkene and starting material were recovered, along with alcohol (±)-**79**. Similar results were obtained with trifluoroacetate **103**. Attacks on the carbonyl carbon of leaving groups during cuprate reactions have previously been reported.[25,26]

Next, the option of HMPA addition was explored. By adding HMPA (10% v/v) as a co-solvent to the *t*-Bu addition reaction in THF, the enantiomeric excess increased slightly to 48%, but the yield and regioselectivity dropped to 46% and 88%, respectively (entry 3, Table 6). Increasing the amount of HMPA used further decreased the yield of the desired product.

To further investigate the possibility of an SET reaction, addition of a benzyl cuprate was also tried, since this group should also be able to support radical formation. The result, however, showed that there was a much smaller decrease in the enantiomeric purity of the system (entry 4 vs. entry 2, Table 6). The anomalous behaviour of the *t*-Bu group remains unexplained.

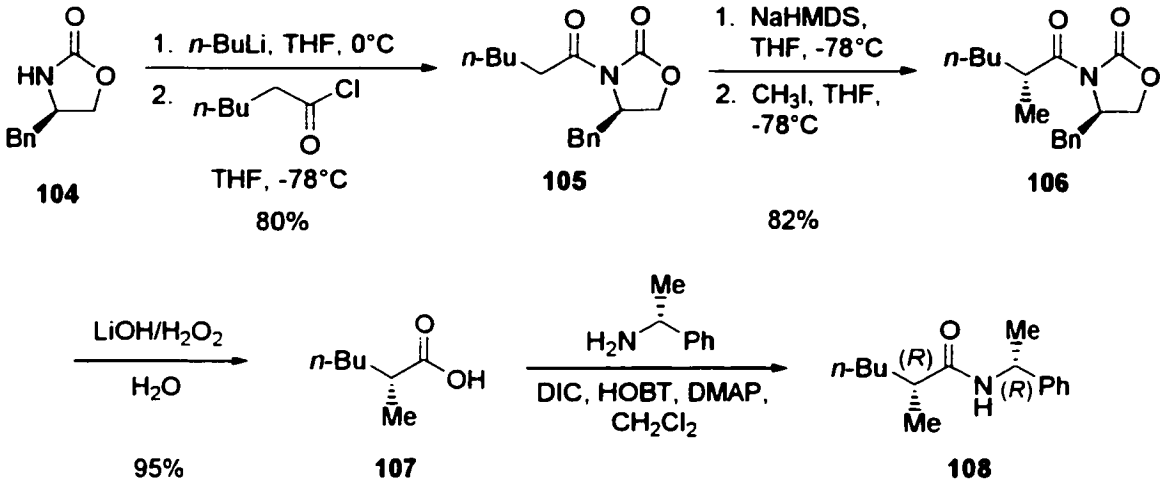
Finally, $Me_2CuLi{\cdot}LiCN$ was reacted with phosphate ester **90** to form ***ent*-91** (entry 5, Table 6). The loss of enantiomeric purity was greater than observed when its enantiomer was formed by addition of the *n*-Bu cuprate to phosphate ester **88** (entry 1, Table 6).

2.2.4.4 Facial Selectivity Determination

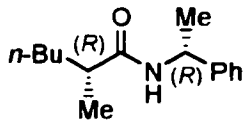
Up to this point it was assumed that the cuprate addition to the phosphate ester was occurring with *anti*-facial selectivity.[12,13] This hypothesis needed to be validated in order to complete the study of this system. In order to accomplish this goal, a standard of known configuration was constructed using Evans' oxazolidinone chemistry (Scheme 37).

(*R*)-4-(Phenylmethyl)-2-oxazolidinone (**104**) was converted to (*R*)-3-hexanoyl-4-benzyl-2-oxazolidinone (**105**) via reaction with *n*-BuLi and hexanoyl chloride. The resulting chiral auxiliary was transformed to the (*Z*)-enolate via deprotonation with sodium bis(trimethylsilyl)amide (NaHMDS). The enolate was subsequently trapped with MeI to form the alkylated oxazolidinone, after which the chiral auxiliary was cleaved with $LiOH/H_2O_2$ (aq) to form carboxylic acid **107**. The α-methylbenzylamide prepared from (*R*)-2-methylhexanoic acid and (*R*)-α-methylbenzylamine had a de of 94%.

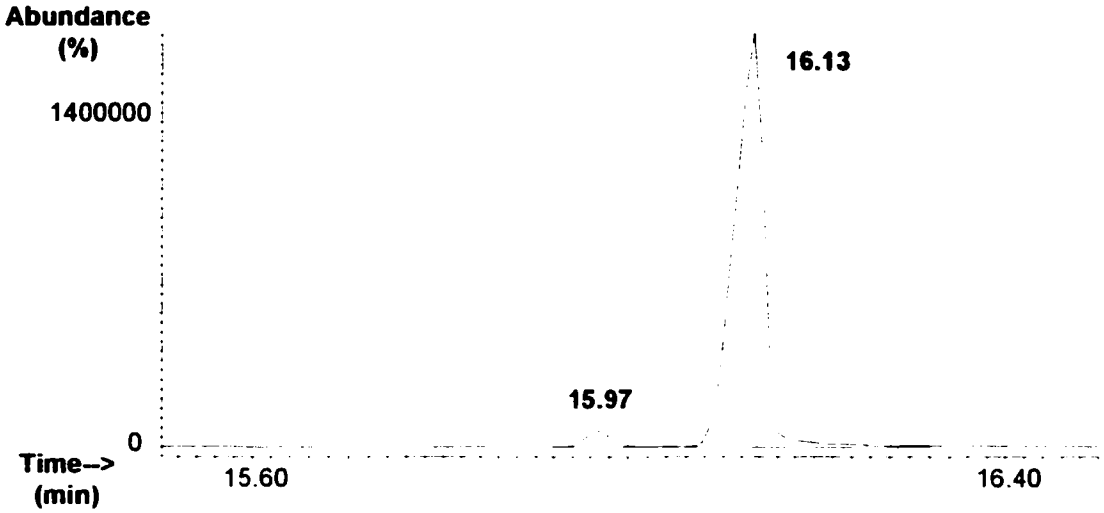
Scheme 37


1. n-BuLi, THF, 0°C
2. n-Bu Cl O
THF, -78°C
80%
1. NaHMDS, THF, -78°C
2. CH3I, THF, -78°C
82%
LiOH/H2O2
H2O
95%
H2N Ph
DIC, HOBT, DMAP, CH2Cl2
104
105
106
107
108

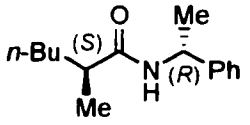
(a)



108



(b)



109

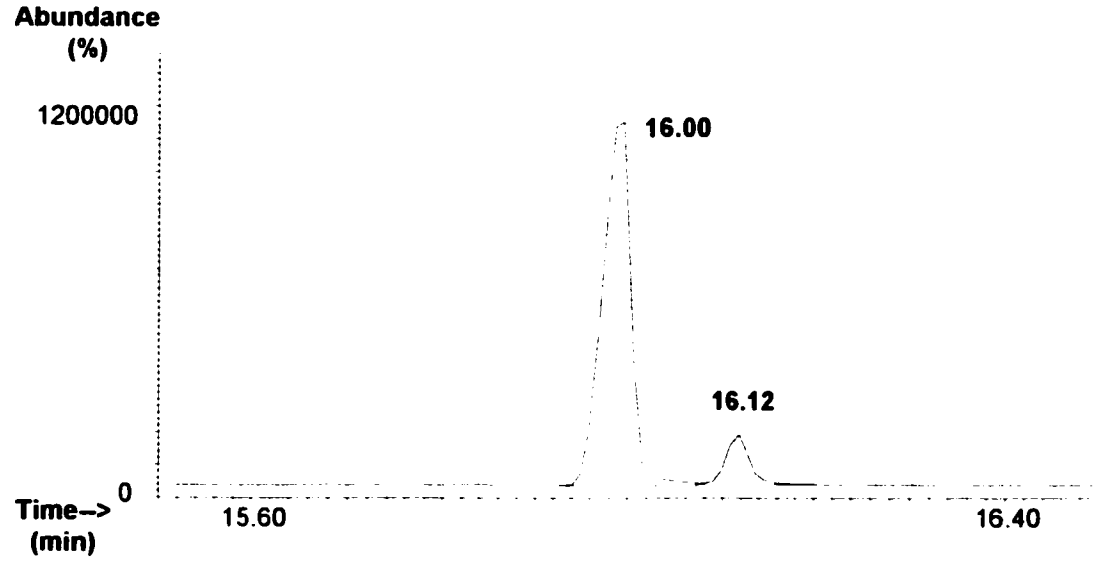
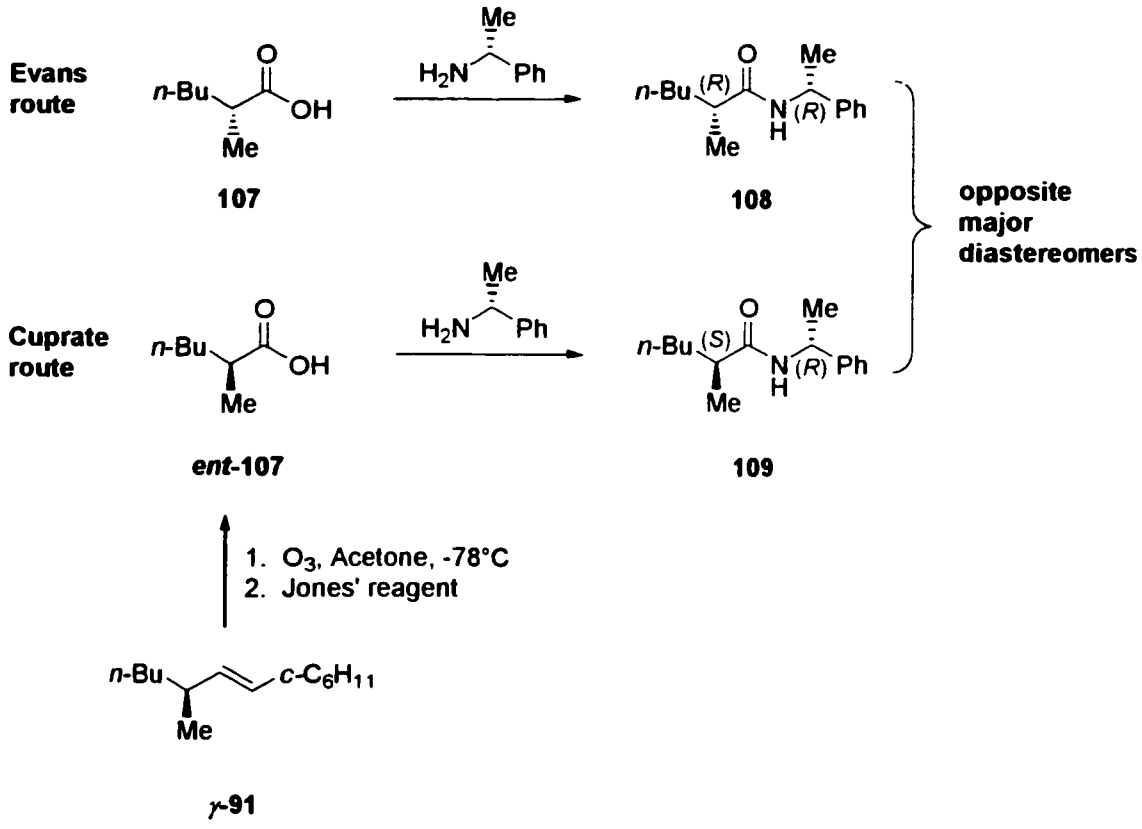


Figure 14. GC/MS traces of amides **108** (a) and **109** (b).

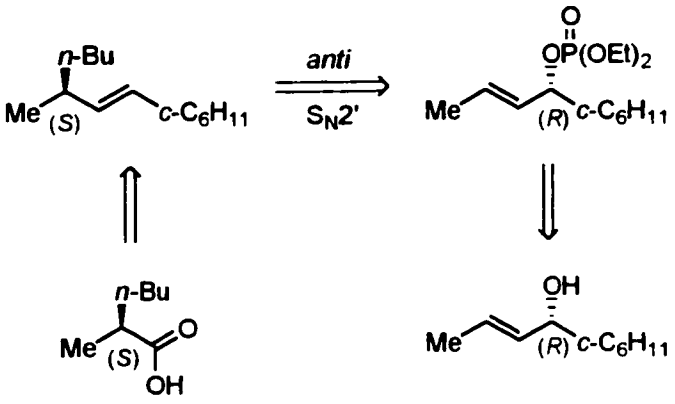
Amide **108** formed via Evans' chemistry showed a retention time of 16.13 min by GC/MS, whereas the major amide derived from cuprate alkene *γ*-**91** (see amide **109**) showed a retention time of 15.99 min (Figure 14). Spiking experiments confirmed that opposite major diastereomers had been formed (Scheme 38).

Scheme 38



We determined the facial preference of the reaction via the reasoning outlined in Scheme 39. From the Sharpless kinetic resolution rules it was known that the alcohol had the (*R*)-configuration.[3] The enantiomeric purity of the allylic substrate was assumed to be retained during the phosphorylation reaction. Since the amide and carboxylic acid showed (*S*)-configuration at the site α to the carbonyl, the alkene must have had the configuration shown (Scheme 39). Consequently, it was concluded that the copper coupling reaction occurred predominantly with *anti*-facial selectivity.

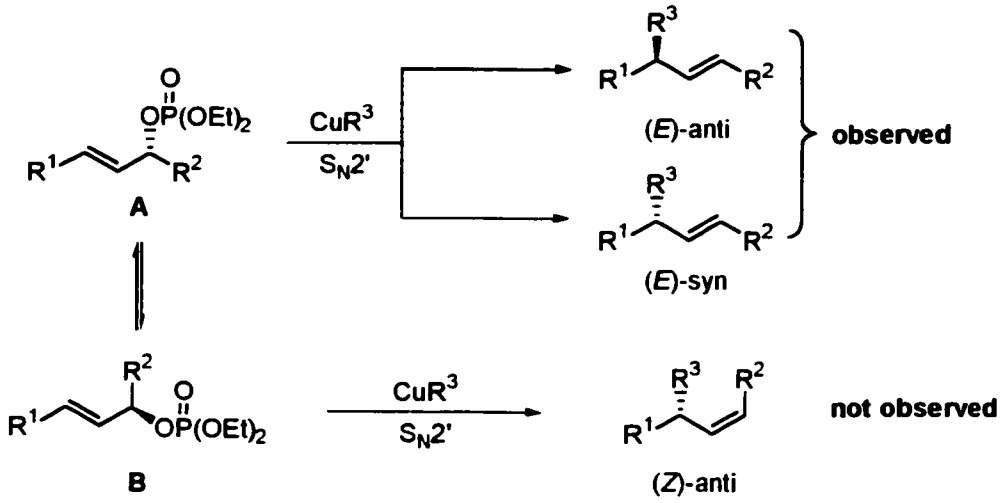
Scheme 39



2.2.4.5 Mechanistic Interpretation

The highest *anti*-S_N2' selectivity was achieved when the R^2 group was large. Initially, the steric dependence of the facial selectivity was explained as follows: large R^2 groups force the substrate to sit in a certain conformation, such that attack is favoured on only one face of the double bond. There are two possible conformations of the phosphate ester (see Scheme 40, **A** and **B**). Conformation **A** would lead to the (*E*)-*anti*-product, but conformation **B** would lead to the (*Z*)-*anti*-product. Since all of the products formed had (*E*)-double bond geometry, it is unlikely that this stereoselectivity argument is correct. A more reasonable explanation is that large R^2 groups hinder coordination between the incoming nucleophile and the phosphate group, which would lead to formation of the (*E*)-*syn*-alkene. As previously noted, reactions between cuprates and substrates with coordinating leaving groups occur with *syn*-facial selectivity.[27]

Scheme 40



2.2.5 Summary

The Sharpless kinetic resolution was used to synthesize a series of allylic alcohols with reasonable yields and enantiomeric purity. The allylic alcohols were derivatized to phosphate esters that could undergo copper-mediated S_N2' reactions with regioselectivities and facial selectivities of up to 98%. The regioselectivity and the facial selectivity were highly dependent upon the size of the group attached to the site bearing the leaving group (R^2). As its steric bulk increased, so did the regio- and stereoselectivity. The cuprate additions worked reasonably well for introducing primary and tertiary groups, with respect to regioselectivity; however, considerable facial scrambling was observed when introducing a tertiary group. The facial selectivity was determined to be *anti* by comparison to GC/MS retention times of a standard of known configuration.

2.3 Experimental

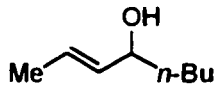
2.3.1 General Experimental

All reactions were performed using flame-dried glassware under an argon atmosphere. Diethyl ether (Et_2O) and tetrahydrofuan (THF) were freshly distilled from sodium benzophenone ketyl. Dichloromethane was freshly distilled from CaH_2. Pyridine was distilled from CaH_2 and stored over 3Å molecular sieves. $CuBr{\cdot}SMe_2$ was prepared as described by Wuts[28] and purified by recrystallization from Me_2S-hexanes. Benzyltributylstannane was prepared by a method similar to one developed by Seitz and coworkers.[29]

Melting points were taken on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained as either neat liquids or as a chloroform solution between sodium chloride plates on a Perkin-Elmer Spectrum RXI FT-IR system. IR absorption positions are given in cm^{-1}. NMR spectra were recorded using either a Bruker AC-200, AM-250 or Avance 300 spectrometer in $CDCl_3$, using tetramethylsilane (TMS, δ = 0.00 for ^1H) or deuterated chloroform ($CDCl_3$, t, δ = 77.0 for ^{13}C) as internal standards. ^1H NMR data are reported as follows: signal (integration, multiplicity, coupling constant, identity). ^{13}C NMR data are reported similarly. GC/MS analysis was conducted on a Hewlett Packard G1800A GCD system with a 30 m × 0.25 mm DB-5 column. The following temperature program was used: T_0 = 70°C, t_0 = 2.0 min, rate = 10°C/min, T_f = 250°C, t_f = 10.0 min. The mass spectral data is reported as: mass (% base peak). Optical rotations were recorded on a Perkin-Elmer 241 polarimeter using the sodium D line (589 nm), unless otherwise noted. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

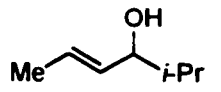
2.3.2 Representative Procedure for the Preparation of Allylic Alcohols via Grignard Reactions

(E)-2-Octen-4-ol [(±)-77][30]



n-Butylmagnesium bromide was prepared from Mg turnings (13 g, 0.52 mol) and *n*-butyl bromide (50 mL, 0.47 mol) in Et_2O (225 mL). The Grignard solution was cooled in an ice bath and crotonaldehyde (32 mL, 0.39 mol) in Et_2O (60 mL) was added dropwise. The reaction mixture was allowed to stand at RT for 1 h. The reaction was quenched by dropwise addition of saturated NH_4Cl (95 mL) with vigorous stirring and ice-cooling. The reaction mixture was allowed to stand for 1 h, after which time the Et_2O layer was decanted from the white precipitate. The precipitate was washed with Et_2O (2 × 70 mL). The combined ethereal layers were concentrated *in vacuo* to give a slightly yellow, viscous oil. The residue was distilled under aspirator pressure through a Vigreux column to afford a clear, colourless oil (33 g, 67% yield) with a boiling point of 72-74°C (24 torr). IR (neat) 3368 (br), 2958, 2932, 2860, 1674, 1454 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.61 (1H, dq, J = 15.3, 5.9 Hz, =C<u>H</u>CH_3), 5.48 (1H, dd, J = 15.3, 6.6 Hz, =C<u>H</u>CH), 4.03 (1H, dt, J = 6.6, 6.6 Hz, C<u>H</u>OH), 1.70 (3H, d, J = 5.9 Hz, CH_3HC=), 1.45 (1H br s, O<u>H</u>), 1.56-1.26 (6H, m, $(CH_2)_3CH_3$), 0.90 (3H, t, J = 6.6 Hz, CH_3CH_2); ^{13}C NMR (63 MHz, $CDCl_3$) δ 134.4, 126.3 (H<u>C</u>=<u>C</u>H), 72.9 (<u>C</u>HOH), 36.9, 27.5, 22.5 ($(CH_2)_3CH_3$), 17.5 (CH_3HC=), 13.9 (CH_3CH_2).

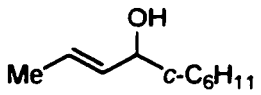
(E)-2-Methyl-4-hexen-3-ol [(±)-78][31]



The title compound was synthesized (66% yield) by replacing *n*-butylmagnesium bromide and magnesium with isopropylmagnesium chloride (Aldrich) in Representative Procedure 2.3.2. The compound was used without further purification. IR (neat) 3410 (br), 2961, 2874, 1672, 1248, 735 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.65 (1H, dq, J = 15.3, 6.0 Hz, =C<u>H</u>CH_3), 5.50 (1H, dd, J = 15.3, 7.3 Hz, =C<u>H</u>CH), 3.77 (1H, dd, J = 7.3, 6.7 Hz, C<u>H</u>OH), 1.73 (3H, d, J = 5.7 Hz, CH_3HC=), 1.73-1.67 (1H, m, C<u>H</u>$(CH_3)_2$), 1.56 (1H, br s, O<u>H</u>), 0.94 (3H, d, J = 6.7 Hz,

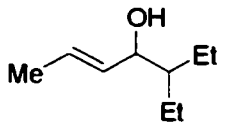
C<u>H</u>$_3$CHCH$_3$), 0.89 (3H, d, J = 6.8 Hz, C<u>H</u>$_3$CHCH$_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 132.1, 126.6 (H<u>C</u>=<u>C</u>H), 77.5 (<u>C</u>HOH), 33.3 (<u>C</u>H(CH$_3$)$_2$), 17.6 (2C), 17.0 (<u>C</u>H$_3$HC=, (CH$_3$)$_2$<u>C</u>H).

(E)-1-Cyclohexyl-2-buten-1-ol [(±)-79][1]



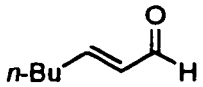
The title compound was synthesized by replacing *n*-butyl bromide with cyclohexyl chloride in Representative Procedure 2.3.2. The residue was distilled under high vacuum through a Vigreux column to afford a clear, colourless oil (79% yield) with a boiling point of 59-61°C (0.1 torr). IR (neat) 3401 (br), 2925, 2854, 1710, 1450, 968 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.62 (1H, dq, J = 15.8, 6.5 Hz, =C<u>H</u>CH$_3$), 5.47 (1H, dd, J = 15.8, 6.9 Hz, =C<u>H</u>CH), 3.76 (1H, dd, J = 6.9, 6.9 Hz, C<u>H</u>OH), 1.71 (3H, d, J = 6.5 Hz, C<u>H</u>$_3$HC=), 1.88-0.86 (11H, m, *c*-C$_6$<u>H</u>$_{11}$), 1.50 (1H, br s, O<u>H</u>); ^{13}C NMR (63 Hz, $CDCl_3$) δ 132.8, 127.3 (H<u>C</u>=<u>C</u>H), 77.5 (<u>C</u>HOH), 43.6, 28.7, 28.6, 26.5, 26.1, 26.0 (*c*-<u>C</u>$_6$H$_{11}$), 17.6 (<u>C</u>H$_3$HC=).

(E)-5-Ethyl-2-hepten-4-ol [(±)-80]



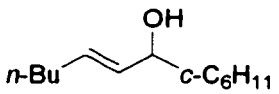
The title compound was synthesized by replacing *n*-butyl bromide with 3-bromopentane in Representative Procedure 2.3.2. The crude product was purified by column chromatography (30% hexanes in ethyl acetate) to give a clear, yellow oil (63% yield). IR (neat) 3381 (br), 2962, 2935, 2875, 1672, 1461, 1379 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.68 (1H, dq, J = 15.3, 6.2 Hz, =C<u>H</u>CH$_3$), 5.50 (1H, dd, J = 15.3, 7.2 Hz, =C<u>H</u>CH), 4.09-3.99 (1H, m, C<u>H</u>OH), 1.70 (3H, d, J = 6.2 Hz, C<u>H</u>$_3$HC=), 1.49-1.15 (6H, m, C<u>H</u>(C<u>H</u>$_2$CH$_3$)$_2$, O<u>H</u>), 0.97-0.81 (6H, m, 2 × C<u>H</u>$_3$CH$_2$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 132.9, 126.8 (H<u>C</u>=<u>C</u>H), 74.4 (<u>C</u>HOH), 46.8 (<u>C</u>H(CH$_2$CH$_3$)$_2$), 21.6, 21.3 (2 × <u>C</u>H$_2$CH$_3$), 17.5 (<u>C</u>H$_3$HC=), 11.5, 11.2 (2 × <u>C</u>H$_3$CH$_2$); MS (EI) *m/z* 142 (M$^+$, 0.1), 71 (100). Anal. Calcd for C$_9$H$_{18}$O: C, 76.00; H, 12.75. Found: C, 75.88; H, 12.66.

(E)-2-Heptenal (84)[32]



Formylmethylenetriphenylphosphorane (**83**) was prepared as described by Trippett and Walker and used without further purification.[9] A solution of this Wittig reagent (8.5 g, 28 mmol) and freshly distilled valeraldehyde (2.5 mL, 23 mmol) in benzene (150 mL) was heated at reflux for 20 h. The solvent was removed under reduced pressure and the residue was purified by flash silica column chromatography (10% Et_2O in hexanes) to give 0.90 g (34%) of a clear, yellow oil; IR (neat) 2961, 2933, 2874, 1690, 1639, 733, 649 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 9.52 (1H, d, J = 8.0 Hz, O=C<u>H</u>), 6.86 (1H, dt, J = 15.4, 6.9 Hz, =C<u>H</u>CH_2), 6.14 (1H, dd, J = 15.4, 8.0 Hz, =C<u>H</u>C=O), 2.36 (2H, dt, J = 6.9, 6.9 Hz, C<u>H</u>$_2$HC=), 1.54-1.26 (4H, m, (C<u>H</u>$_2$)$_2$CH$_3$), 0.92 (3H, m, C<u>H</u>$_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 194.0 (O=<u>C</u>H), 158.8 (=<u>C</u>HCH$_2$), 133.0 (=<u>C</u>HC=O), 32.4 (<u>C</u>H$_2$HC=), 29.9, 22.2 ((<u>C</u>H$_2$)$_2$CH$_3$), 13.7 (<u>C</u>H$_3$).

(E)-1-Cyclohexyl-2-hepten-1-ol [(±)-81][33]



The title compound was synthesized by replacing *n*-butyl bromide with cyclohexyl chloride and crotonaldehyde with (*E*)-heptenal (**84**) in Representative Procedure 2.3.2. The residue was purified by flash silica gel column chromatography (1:4 Et_2O:hexanes as solvent) to give a clear, colourless oil (69% yield). IR (neat) 3369 (br), 2925, 2853, 1670, 1450, 970 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.61 (1H, dt, J = 15.4, 6.6 Hz, =C<u>H</u>CH_2), 5.46 (1H, ddt, J = 15.4, 7.3, 1.2 Hz, =C<u>H</u>CH), 3.79-3.73 (1H, m, C<u>H</u>OH), 2.08-2.00 (2H, m, C<u>H</u>$_2$HC=), 1.89-0.86 (19H, m, *c*-C$_6$<u>H</u>$_{11}$, (C<u>H</u>$_2$)$_2$C<u>H</u>$_3$, O<u>H</u>); ^{13}C NMR (63 MHz, $CDCl_3$) δ 132.7, 131.5 (H<u>C</u>=<u>C</u>H), 77.5 (<u>C</u>HOH), 43.7 (*c*-<u>C</u>H(CH$_2$)$_5$), 31.9 (<u>C</u>H$_2$HC=), 31.4, 28.8, 28.7, 26.5, 26.1, 26.0, 22.1 (*c*-CH(<u>C</u>H$_2$)$_5$, (<u>C</u>H$_2$)$_2$CH$_3$), 13.7 (<u>C</u>H$_3$).

2.3.3 *General Procedure A: Kinetic Resolution of Allylic Alcohols*

Each of the allylic alcohols was kinetically resolved via the Sharpless protocol[1] using Ti(O-*i*-Pr)$_4$ (0.10 equiv), TBHP (0.70 equiv) and *L*-(+)-dicyclohexyltartrate (DCHT, 0.15 equiv) in CH_2Cl_2 at -20°C. The reaction progress was monitored by GC (decane as internal standard) and was stopped when >50% complete. The formed allylic epoxide and the desired allylic alcohol were separated by flash chromatography. Enantiomeric purities were determined by conversion to the corresponding (*R*)- or (*S*)-MTPA ester and analysis by ^{1}H and/or ^{19}F NMR spectroscopy.[1,10] Yields are based upon a possible 50% recovery of the enantiomerically-enriched alcohol.

(2E, 4R)-2-Octen-4-ol [(R)-77]

The reaction was performed using General Procedure A with substrate **(±)-77** (10 g, 80 mmol) for 5 h. The crude reaction mixture was purified by column chromatography (30% Et_2O in hexanes) to give 2.4 g (47%) of a clear, colourless oil. $[\alpha]_D$ = -6.1 (c = 3.3, EtOH). By ^{19}F NMR (282 MHz, C_6D_6) δ -71.50 (97), -71.56 (3) and ^{1}H NMR δ 5.33 (0.97H, ddq, J = 15.2, 7.7, 1.5 Hz), 5.23 (0.03H, ddq, J = 15.2, 7.7, 1.5 Hz), de of (*S*)-Mosher ester = 94%.

(4E, 3R)-2-Methyl-4-hexen-3-ol [(R)-78]

The reaction was performed using General Procedure A with substrate **(±)-78** (10 g, 88 mmol) for 13 h. The crude reaction mixture was purified by column chromatography (20% EtOAc in hexanes) to give 3.5 g (70%) of a clear, slightly yellow oil. $[\alpha]_D$ = -13.9 (c = 1.2, EtOH). By ^{19}F NMR (188 MHz, $CDCl_3$) δ -71.92 (95), -72.08 (5), de of (*R*)-Mosher ester = 90%.

(2E, 1R)-1-Cyclohexyl-2-buten-1-ol [(R)-79]

The reaction was performed using General Procedure A with substrate **(±)-79** (10 g, 65 mmol) for 15 h. The crude reaction mixture was purified by column chromatography (30% Et_2O in hexanes) to give 3.0 g (60%) of a clear, slightly yellow oil. $[\alpha]_D$ = -13.4 (c = 3.1, EtOH) [lit.:[1]

$[\alpha]_D$= -13.24 (c = 2.62, EtOH), ee = 95%]. By ^{19}F NMR (282 MHz, C_6D_6) δ -71.37 (97), -71.52 (3), de of (*S*)-Mosher ester = 94%. In another run, material of 90% ee (68% yield) was obtained.

(2E, 4R)-5-Ethyl-2-hepten-4-ol ***[(R)-80]***

The reaction was performed using General Procedure A with substrate **(±)-80** (6.0 g, 43 mmol) for 13 h. The crude reaction mixture was purified by column chromatography (20% EtOAc in hexanes) to give 2.5 g (83%) of a clear, colourless oil. $[\alpha]_D$ = -11.3 (c = 1.3, EtOH). By ^{19}F NMR (282 MHz, C_6D_6) δ -71.44 (92), -71.50 (8), de of (*R*)-Mosher ester = 84%.

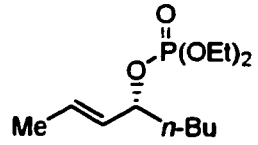
(2E, 1R)-1-Cyclohexyl-2-hepten-1-ol ***[(R)-81]***

The reaction was performed using General Procedure A with substrate **(±)-81** (2.5 g, 13 mmol) for 8 h. The crude reaction mixture was purified by column chromatography (20% Et_2O in hexanes) to give 0.66 g (53%) of a clear, colourless oil. $[\alpha]_D$ = -7.9 (c = 1.1, EtOH). By ^{19}F NMR (188 MHz, $CDCl_3$) δ -71.82 (97), -72.02 (3), de of (*R*)-Mosher ester = 94%.

2.3.4 General Procedure B: Conversion of Allylic Alcohols to Phosphate Esters

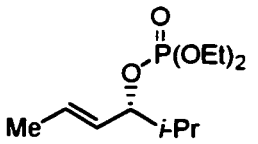
Diethyl chlorophosphate (1.1 equiv) was added dropwise to a solution of the allylic alcohol (1.0 equiv) in pyridine (2.5 mL/g substrate) at 0°C. After 1 h, the reaction mixture was quenched with water (2 mL/mL pyridine) and extracted with the same volume of Et_2O (2×). The combined extracts were washed with 1 M H_2SO_4, 1 M $NaHCO_3$ and water. After drying the organic layer over $MgSO_4$, the solvent was removed *in vacuo*. The crude phosphate esters were unstable to silica gel chromatography and distillation and were used without further purification.

Diethyl (2E, 4R)-2-octen-4-yl phosphate (86)



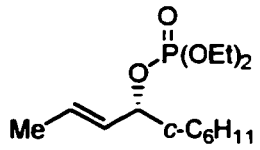
The reaction was performed using General Procedure B with substrate **(*R*)-77** (2.0 g, 16 mmol) to afford 2.5 g (60%) of a clear, slightly yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.75 (1H, dq, J = 15.3, 6.5 Hz, =C<u>H</u>CH$_3$), 5.49 (1H, ddq, J = 15.3, 8.0, 1.5 Hz, =C<u>H</u>CH), 4.69 (1H, dtd, J = 8.0, 7.0, 1.5 Hz, C<u>H</u>O), 4.14-4.00 (4H, m, 2 × OC<u>H</u>$_2$CH$_3$), 1.72 (3H, dd, J = 6.5, 1.5 Hz, C<u>H</u>$_3$HC=), 1.62-1.57 (2H, m, C<u>H</u>$_2$CHO), 1.41-1.28 (10H, m, (C<u>H</u>$_2$)$_2$CH$_3$, 2 × OCH$_2$C<u>H</u>$_3$), 0.90 (3H, t, J = 6.6 Hz, C<u>H</u>$_3$(CH$_2$)$_2$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 130.2, 129.1 (H<u>C</u>=<u>C</u>H), 79.9 (<u>C</u>HO), 63.2 (2C, d, $J_{C\text{-}P}$ = 5.3 Hz, 2 × O<u>C</u>H$_2$CH$_3$), 35.6 (<u>C</u>H$_2$CHO), 26.8, 22.1 ((<u>C</u>H$_2$)$_2$CH$_3$), 17.3 (<u>C</u>H$_3$HC=), 15.9 (2C, d, $J_{C\text{-}P}$ = 6.5 Hz, 2 × OCH$_2$<u>C</u>H$_3$), 13.7 (<u>C</u>H$_3$(CH$_2$)$_2$).

Diethyl (2E, 4S)-5-methyl-2-hexen-4-yl phosphate (87)



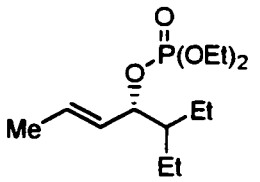
The reaction was performed using General Procedure B with substrate **(*R*)-78** (1.0 g, 8.8 mmol) to give 0.88 g (40%) of a clear, slightly yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.75 (1H, dq, J = 15.4, 6.6 Hz, =C<u>H</u>CH$_3$), 5.48 (1H, dd, J = 15.4, 8.0 Hz, =C<u>H</u>CH), 4.49 (1H, ddd, J = 8.0, 7.1, 7.1 Hz, C<u>H</u>O), 4.17-3.99 (4H, m, 2 × OC<u>H</u>$_2$CH$_3$), 1.96-1.82 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.74 (3H, d, J = 6.6 Hz, C<u>H</u>$_3$HC=), 1.45-1.20 (6H, m, 2 × OCH$_2$C<u>H</u>$_3$), 1.17-0.86 (6H, m, CH(C<u>H</u>$_3$)$_2$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 130.3, 128.0 (H<u>C</u>=<u>C</u>H), 84.7 (d, $J_{C\text{-}P}$ = 5.8 Hz, <u>C</u>HO), 63.2 (2C, d, $J_{C\text{-}P}$ = 5.8 Hz, 2 × O<u>C</u>H$_2$CH$_3$), 33.1 (d, $J_{C\text{-}P}$ = 6.7 Hz, <u>C</u>H(CH$_3$)$_2$), 17.8, 17.4 (2C) ((<u>C</u>H$_3$)$_2$CH, <u>C</u>H$_3$HC=), 15.9 (2C, d, $J_{C\text{-}P}$ = 7.1 Hz, 2 × OCH$_2$<u>C</u>H$_3$).

(1S, 2E)-1-Cyclohexyl-2-buten-1-yl diethyl phosphate (88)



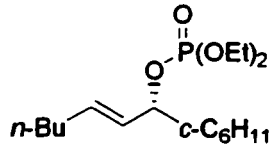
The reaction was performed using General Procedure B with substrate **(*R*)-79** (1.5 g, 9.7 mmol) to give 2.0 g (71%) of a clear, slightly yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.75 (1H, dq, J = 15.3, 6.4 Hz, =C<u>H</u>CH$_3$), 5.48 (1H, dd, J = 15.3, 8.3 Hz, =C<u>H</u>CH), 4.47 (1H, ddd, J = 8.3, 7.4, 7.4 Hz, C<u>H</u>O), 4.15-3.99 (4H, m, 2 × OC<u>H</u>$_2$CH$_3$), 1.85-1.48 (5H, m, *c*-C$_6$<u>H</u>$_{11}$), 1.72 (3H, d, J = 6.4 Hz, C<u>H</u>$_3$HC=), 1.34-0.89 (12H, m, 2 × OCH$_2$C<u>H</u>$_3$, *c*-C$_6$<u>H</u>$_{11}$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 130.1, 128.6 (H<u>C</u>=<u>C</u>H), 84.2 (d, $J_{C\text{-}P}$ = 6.0 Hz, <u>C</u>HO), 63.2 (2C, d, $J_{C\text{-}P}$ = 5.7 Hz, 2 × O<u>C</u>H$_2$CH$_3$), 42.8 (d, $J_{C\text{-}P}$ = 6.0 Hz, *c*-<u>C</u>H(CH$_2$)$_5$), 28.4, 28.1, 26.2, 25.8, 25.7 (*c*-CH(<u>C</u>H$_2$)$_5$), 17.4 (<u>C</u>H$_3$HC=), 15.8 (2C, 2 × OCH$_2$<u>C</u>H$_3$).

Diethyl (2E, 4S)-5-Ethyl-2-hepten-4-yl phosphate (89)



The reaction was performed using General Procedure B with substrate **(*R*)-80** (0.51 g, 3.6 mmol) to give 0.53 g (53%) of a clear, slightly yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.76 (1H, dq, J = 15.3, 6.4 Hz, =C<u>H</u>CH$_3$), 5.49 (1H, dd, J = 15.3, 6.3 Hz, =C<u>H</u>CH), 4.74-4.67 (1H, m, C<u>H</u>O), 4.11-3.99 (4H, m, 2 × OC<u>H</u>$_2$CH$_3$), 1.74 (3H, d, J = 6.4 Hz, C<u>H</u>$_3$HC=), 1.61-1.18 (11H, m, C<u>H</u>(C<u>H</u>$_2$CH$_3$)$_2$, 2 × OCH$_2$C<u>H</u>$_3$), 1.15-0.79 (6H, m, CH(CH$_2$C<u>H</u>$_3$)$_2$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 130.0, 128.4 (H<u>C</u>=<u>C</u>H), 82.0 (d, $J_{C\text{-}P}$ = 7.6 Hz, <u>C</u>HO), 63.3 (2C, d, $J_{C\text{-}P}$ = 5.7 Hz, 2 × O<u>C</u>H$_2$CH$_3$), 46.5 (d, $J_{C\text{-}P}$ = 5.7 Hz, C<u>H</u>(CH$_2$CH$_3$)$_2$), 21.7, 21.4 (CH(<u>C</u>H$_2$CH$_3$)$_2$), 17.7 (<u>C</u>H$_3$HC=), 16.1 (2C, d, $J_{C\text{-}P}$ = 7.6 Hz, 2 × OCH$_2$<u>C</u>H$_3$), 11.5, 11.3 (CH(CH$_2$<u>C</u>H$_3$)$_2$).

(1S, 2E)-1-Cyclohexyl-2-hepten-1-yl diethyl phosphate (**90**)



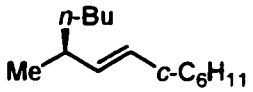
The reaction was performed using General Procedure B with substrate (***R*)-81** (0.43 g, 2.2 mmol) to give 0.45 g (71%) of a clear, slightly yellow oil; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.75 (1H, dt, J = 15.4, 6.6 Hz, =C<u>H</u>CH$_2$), 5.48 (1H, dd, J = 15.4, 7.7 Hz, =C<u>H</u>CH), 4.48 (1H, ddd, J = 7.7, 7.5, 7.5 Hz, C<u>H</u>O)), 4.12-3.99 (4H, m, 2 × OC<u>H</u>$_2$CH$_3$), 2.07-2.02 (2H, m, C<u>H</u>$_2$HC=), 1.85-1.54 (5H, m, *c*-C$_6$<u>H</u>$_{11}$, (C<u>H</u>$_2$)$_2$CH$_3$), 1.41-0.90 (16H, m, *c*-C$_6$<u>H</u>$_{11}$, (OCH$_2$C<u>H</u>$_3$)$_2$), 0.89 (3H, t, J = 7.1 Hz, (CH$_2$)$_2$C<u>H</u>$_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 135.3, 126.9 (H<u>C</u>=<u>C</u>H), 84.1 (<u>C</u>HO), 63.0 (2C, 2 × O<u>C</u>H$_2$CH$_3$), 42.6 (d, $J_{C\text{-}P}$ = 7.6 Hz, *c*-<u>C</u>H(CH$_2$)$_5$), 31.5 (<u>C</u>H$_2$HC=), 30.8, 28.2, 27.9, 26.0, 25.5 (2C), 21.8 (*c*-CH(<u>C</u>H$_2$)$_5$, (<u>C</u>H$_2$)$_2$CH$_3$), 15.6 (2C, 2 × OCH$_2$<u>C</u>H$_3$), 13.4 (<u>C</u>H$_3$(CH$_2$)$_2$).

2.3.5 *General Procedure C: Reaction of Cuprates with Phosphate Esters to Form Alkenes*

CuCN (2.0 equiv) was added to a three-necked flask equipped with a stir bar, low temperature thermometer, argon inlet and stopcock. The flask was flushed and evacuated with argon (3×). Either Et_2O or THF (25 mL/g substrate) was added via syringe and the system was cooled to -78 °C. The alkyllithium (4.0 equiv) of choice was added dropwise and the reaction mixture was allowed to stir until a mostly clear solution was formed. At this time, the phosphate ester (1.0 equiv) was added in solvent (2.5 mL/g substrate). The reaction mixture was allowed to stir for 1 h at -78°C. Completion of the reaction was monitored by TLC (100% hexanes). When complete, the reaction was quenched with 10% NH_4OH in saturated NH_4Cl solution (5 mL/mmol cuprate). The precipitate was removed by filtration and the filter cake was washed thoroughly with Et_2O. The organic layer was separated and dried with $MgSO_4$. The solvent was removed *in vacuo* and the residue was purified using column chromatography (100% hexanes). All enantiomeric excesses were determined by ozonolysis followed by derivatization (see Sections 2.2.4.1 and 2.3.6). The alkene regioisomers were not separable by

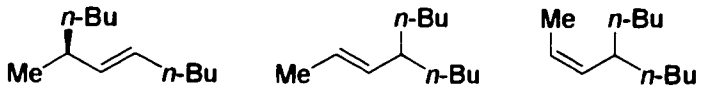
column chromatography. In most cases, only the spectral data for the major regioisomer is reported.

(1E, 3S)-1-Cyclohexyl-3-methyl-1-heptene (91)



The reaction was performed using General Procedure C with substrate **88** (0.31 g, 1.1 mmol) in THF and yielded 0.14 g (67%) of a clear, colourless oil; $[\alpha]_D$ = +13.2 (c = 1.3, EtOH), 84 %ee; IR (neat) 2919, 2853, 1666, 1449, 1378, 967 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.31 (1H, dd, J = 15.7, 5.9 Hz, HC=CH), 5.20 (1H, dd, J = 15.7, 7.0 Hz, HC=CH), 2.02-1.81 (2H, m, *c*-CH$(CH_2)_5$, $CHCH_3$), 1.71-1.00 (16H, m, *c*-$CH(CH_2)_5$, $(CH_2)_3CH_3$), 0.95 (3H, d, J = 6.6 Hz, CH_3CH), 0.87 (3H, t, J = 6.7 Hz, CH_3CH_2); ^{13}C NMR (63 MHz, $CDCl_3$) δ 135.0, 134.4 (HC=CH), 41.3 (*c*-$CH(CH_2)_5$), 37.6, 37.3 ($CH_2(CH_2)_2CH_3$, $CHCH_3$), 34.0, 32.2, 30.2, 26.9, 26.7, 23.4, 23.2, 21.5 (*c*-$CH(CH_2)_5$, $(CH_2)_2CH_3$, CH_3CH), 14.6 (CH_3CH_2); MS (EI) *m/z* (%) 194 (M^+, 17), 109 (55), 96 (71), 81 (100), 69 (50). Anal. Calcd for $C_{14}H_{26}$: C, 86.52; H, 13.48. Found: C, 86.60; H, 13.26.

(6E, 5S)-5-Methyl-6-undecene (γ-95), (2E)-4-butyl-2-octene (α-95) and (2Z)-4-butyl-2-octene

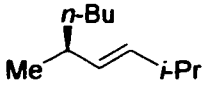


A **B** **C**

The reaction was performed using General Procedure C with substrate **86** (0.92 g, 3.4 mmol) in Et_2O and yielded 0.40 g (74%) of a clear, colourless oil. GC/MS analysis showed a mixture of 3 isomers, **A**, **B** and **C**, in a ratio of 67:25:8, respectively. The components were not separable by flash chromatography. The major diastereomer of this complex mixture was desired S_N2' product **A**, as shown by the large doublet in the ^1H NMR spectrum at δ 0.95, representing the methyl group β to the double bond. Evidence for the other two isomers (**B** and **C**) was seen by the appearance of doublets at δ 1.67 and δ 1.60, which presumably represent vinyl methyl groups. IR (neat) 2959, 2926, 2873, 2859, 1466, 1458, 1378 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.39-5.09 (2H, m, alkene protons), 2.03-1.94 (2.01H, m), 1.83

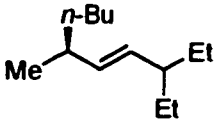
(0.33H, m), 1.67 (0.75H, d, J = 6.3 Hz), 1.60 (0.24H, d, J = 7.0 Hz), 1.34-1.24 (10.66H, m), 0.95 (2.01H, d, J = 6.8 Hz), 0.93-0.86 (6H, m); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.5, 136.4, 128.4, 128.3, 124.1, 42.9, 37.0, 36.8, 35.3, 32.3, 32.2, 32.0, 31.7, 29.8, 29.7, 29.6, 29.4, 27.2, 22.9, 22.7, 22.2, 21.0, 17.9, 14.1, 14.0; GC/MS: retention times, (EI) *m*/z (%) 7.31 min (25%), 168 (M^+, 0.6), 69 (100); 7.40 min (8%), 168 (M^+, 7), 69 (100); 7.54 min (67%), 168 (M^+, 5), 69 (100). Anal. Calcd for $C_{12}H_{24}$: C, 85.63; H, 14.37. Found: C, 85.76, 14.21.

(3E, 5S)-2,5-Dimethyl-2-nonene (96)



The reaction was performed using General Procedure C with substrate **87** (0.41 g, 1.6 mmol) in THF and yielded 0.18 g (72%) of a clear, colourless oil; $[\alpha]_D$ = +14.9 (c = 1.9, CH_2Cl_2), 76 %ee; IR (neat) 2959, 2929, 2873, 1718, 1466, 1379, 969 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.30 (1H, dd, J = 15.4, 6.3 Hz, =C<u>H</u>*i*-Pr), 5.20 (1H, dd, J = 15.4, 7.1 Hz, =C<u>H</u>CH*n*-Bu), 2.18 (1H, dqq, J = 6.3, 6.3, 6.3 Hz, C<u>H</u>$(CH_3)_2$), 2.01-1.98 (1H, m, C<u>H</u>*n*-Bu), 1.43-1.04 (9H, m, $(C\underline{H}_3)_2CH$, $C\underline{H}_3CH$*n*-Bu), 1.03-0.79 (9H, m, $(C\underline{H}_2)_3C\underline{H}_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 135.7, 133.4 (H<u>C</u>=<u>C</u>H), 37.0, 36.6, 31.0, 29.6, 22.8 (3C), 20.9 ($\underline{C}H_3\underline{C}H(\underline{C}H_2)_3$, $\underline{C}H(\underline{C}H_3)_2$), 14.1 ($\underline{C}H_3CH_2$); MS (EI) *m*/z (%) 154 (M^+, 8), 69 (89), 55 (100), 56 (44), 70 (39). Anal. Calcd for $C_{13}H_{26}$: C, 85.63; H, 14.37. Found: C, 85.56; H, 14.40.

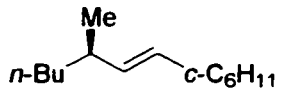
(4E, 6S)-3-Ethyl-6-methyl-4-decene (97)



The reaction was performed using General Procedure C with substrate **89** (0.21 g, 0.74 mmol) in Et_2O and yielded 71 mg (53%) of a clear, colourless oil; $[\alpha]_D$ = +16.0 (c = 0.67, EtOH), 82 %ee; IR (neat) 2960, 2927, 2860, 1664, 1459, 1378, 969 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 5.17 (1H, dd, J = 15.3, 7.8 Hz, <u>H</u>C=), 5.02 (1H, dd, J = 15.3, 8.4 Hz, <u>H</u>C=), 2.08-2.02 (1H, m, C<u>H</u>$(CH_2CH_3)_2$), 1.71-1.53 (1H, m, C<u>H</u>*n*-Bu), 1.43-1.01 (10H, m, $CH(C\underline{H}_2CH_3)_2$, $(C\underline{H}_2)_3CH_3$), 0.97-0.79 (12H, m, $CH(CH_2C\underline{H}_3)_2$, $C\underline{H}_3(CH_2)_3$, $C\underline{H}_3CH$); ^{13}C NMR (63 MHz,

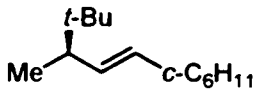
$CDCl_3$) δ 136.8, 132.5 (H<u>C</u>=<u>C</u>H), 46.4 (<u>C</u>H(CH_2CH_3)$_2$), 37.0, 36.9 (<u>C</u>H_2(CH_2)$_2$$CH_3$, <u>C</u>H$CH_3$), 29.7, 27.9 (2C), 22.8, 21.3 ((<u>C</u>H_2)$_2$$CH_3$, CH(<u>C</u>$H_2CH_3$)$_2$, <u>C</u>$H_3$CH), 14.1, 11.7 (2C) (CH(CH_2<u>C</u>H_3)$_2$, <u>C</u>H_3(CH_2)$_3$); MS (EI) *m/z* (%) 182 (M^+, 5), 97 (35), 83 (44), 69 (100), 55 (99). Anal. Calcd for $C_{13}H_{26}$: C, 85.63; H, 14.37. Found: C, 85.56; H, 14.46.

*(1E, 3R)-1-Cyclohexyl-3-methyl-1-heptene [**ent-91**]*



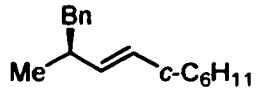
The reaction was performed using General Procedure C with substrate **90** (0.15 g, 0.53 mmol) with $Me_2CuCNLi_2$ (pre-formed at 0°C for 30 min) in Et_2O and yielded 41 mg (40%) of a clear, colourless oil; $[\alpha]_D$ = -13.4 (c = 1.1, EtOH), 80 %ee. Spectral data were identical to that reported for **γ-91** with the exception of optical rotation.

*1-[(1E, 3R)-3,4,4-Trimethyl-1-pentenyl]cyclohexanes (**98**)*



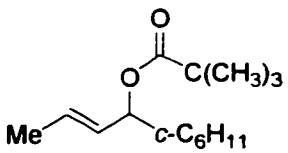
The reaction was performed using a modified version of General Procedure C. After addition of *t*-BuLi, the reaction mixture was allowed to warm to 0°C for 5 min, after which it was recooled to -78°C before addition of phosphate **88**. The reaction was performed using 0.10 g (0.35 mmol) of **88** in Et_2O and yielded 46 mg (67%) of a clear, colourless oil; $[\alpha]_D$ = +10.5 (c = 7.6, CH_2Cl_2), 32 %ee; IR (neat) 2964, 2926, 2853, 1664, 1477, 1393, 1364, 969 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.38-5.13 (2H, m, H<u>C</u>=C<u>H</u>), 1.71-1.56 (2H, m, *c*-C<u>H</u>(CH_2)$_5$, C<u>H</u>CH_3), 1.25-0.96 (10H, m, *c*-CH(C<u>H</u>$_2$)$_5$), 0.91 (3H, d, J = 6.9 Hz, C<u>H</u>$_3$CH), 0.82 (9H, s, (C<u>H</u>$_3$)$_3$C); ^{13}C NMR (63 MHz, $CDCl_3$) δ 136.0, 131.0 (H<u>C</u>=<u>C</u>H), 47.1, 40.8 (<u>C</u>HCH_3, *c*-<u>C</u>H(CH_2)$_5$), 33.4 (2C), 29.8, 27.5 (3C), 26.3, 26.2 (2C) (*c*-CH(<u>C</u>H_2)$_5$, <u>C</u>(<u>C</u>H_3)$_3$), 15.7 (<u>C</u>H_3CH); MS (EI) *m/z* (%) 194 (M^+, 3), 95 (48), 81 (100), 57 (79), 55 (50), 41 (42). Anal. Calcd for $C_{14}H_{26}$: C, 86.52; H, 13.48. Found: C, 86.56; H, 13.27.

*1-[(1E, 3S)-3-Methyl-4-phenyl-1-butenyl]cyclohexanes (**99**)*



To a mixture of CuCN (0.13 g, 1.4 mmol) and THF (5 mL) at 0°C was added dropwise MeLi (1.34 M, 2.10 mL, 2.8 mmol). After 0.5 h, benzyltributyltin (0.83 g, 2.2 mmol) in THF (1 mL) was added and the reaction mixture was allowed to stir for 0°C for 0.5 h. After cooling to -78°C, phosphate **88** (0.21 g, 0.72 mmol) in THF (0.5 mL) was added dropwise and the mixture was stirred for 1 h. Usual workup and purification as stated in General Procedure C to yield 70 mg (42%) of a clear, colourless oil; $[\alpha]_D$ = +26.4 (c = 1.1, EtOH), 80 %ee; IR (neat) 2954, 2925, 2855, 1699, 1499, 1456, 701 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.32-7.14 (5H, m, $C_6\underline{H}_5$), 5.38 (1H, dd, J = 15.4, 5.9 Hz, $\underline{H}C$=), 5.27 (1H, dd, J = 15.4, 5.4 Hz, $\underline{H}C$=), 2.64 (1H, A of ABX, dd, J_{obs} = 13.1, 7.0 Hz, $C\underline{H}_2Ph$), 2.52 (1H, B of ABX, dd, J_{obs} = 13.1, 7.3 Hz, $C\underline{H}_2Ph$), 2.42-2.26 (1H, X of ABX, m, $C\underline{H}Bn$), 1.91-1.80 (1H, m, *c*-$C\underline{H}(CH_2)_5$), 1.73-0.80 (10H, m, *c*-$CH(C\underline{H}_2)_5$), 0.99 (3H, d, J = 6.6 Hz, $C\underline{H}_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 141.1, 134.9, 132.9, 129.3 (2C), 128.0 (2C), 125.6 ($H\underline{C}$=$\underline{C}H$, ArC's), 44.0, 40.6, 38.4 ($\underline{C}HBn$, $\underline{C}H_2Ph$, *c*-$\underline{C}H(CH_2)_5$), 33.3 (2C), 26.3, 26.1 (2C) (*c*-$CH(\underline{C}H_2)_5$), 20.1 ($\underline{C}H_3$); MS (EI) *m/z* (%) 228 (M^+, 2), 137 (37), 95 (51), 81 (100), 55 (48). Anal. Calcd for $C_{17}H_{24}$: C, 89.41; H, 10.59. Found: C, 89.19; H, 10.30.

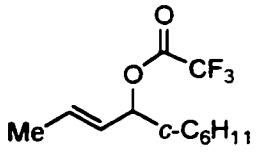
*(E)-1-Cyclohexyl-2-buten-1-yl trimethylacetate (**102**)*



Pivaloyl chloride (5.0 mL, 41 mmol) was added dropwise to a solution of alcohol **(±)-79** (5.0 g, 32 mmol) in pyridine (10 mL). The reaction mixture was allowed to stir for 2 h and was determined to be complete by TLC. Water (5 mL) was added and the reaction mixture was left to stir for 15 min. The reaction mixture was diluted with water (40 mL) and the product was extracted with hexanes (4 × 80 mL). The organic extracts were washed with cold 0.1 M $CuSO_4$ (3 × 300 mL), saturated $NaHCO_3$ solution (2 × 300 mL) and brine (2 × 300 mL). The organic layer was dried over $MgSO_4$ after which the solvent was removed *in vacuo*. The crude

oil was purified by column chromatography (10:1 hexanes:Et_2O) to afford 6.6 g (86% yield) of a clear, colourless oil. IR (neat) 2930, 2855, 1729, 1281, 1674 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 5.63 (1H, dq, 15.3, 6.5 Hz, =C<u>H</u>CH_3), 5.38 (1H, ddq, J = 15.3, 7.2, 1.6 Hz, =C<u>H</u>CH), 4.95 (1H, dd, J = 7.2, 7.2 Hz, C<u>H</u>O), 1.75-1.64 (8H, m, C<u>H</u>$_3$HC=, c-C_6<u>H</u>$_{11}$), 1.34-1.03 (6H, m c-C_6<u>H</u>$_{11}$), 1.20 (9H, s, (C<u>H</u>$_3$)$_3$C); ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.5 (<u>C</u>=O), 128.9, 128.3 (H<u>C</u>=<u>C</u>H), 72.3 (<u>C</u>HO), 41.9 (c-<u>C</u>H$(CH_2)_5$), 38.8 (<u>C</u>$(CH_3)_3$), 28.8, 28.3, 27.1 (3C), 26.4, 26.0, 25.9 (c-CH(<u>C</u>H$_2$)$_5$, C(<u>C</u>H$_3$)$_3$), 17.6 (<u>C</u>H$_3$HC=); MS (EI) m/z (%) 238 (M^+, 0.2), 85 (50), 81 (44), 57 (100), 41 (34). Anal. Calcd for $C_{15}H_{26}O_2$: C, 75.58; H, 10.99. Found: C, 75.70; H, 10.91.

*(E)-1-Cyclohexyl-2-buten-1-yl trifluoroacetate (**103**)*



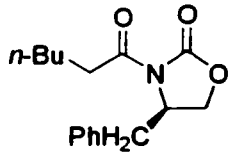
Trifluoroacetic anhydride (0.50 mL, 3.5 mmol) was added dropwise to a solution of alcohol **(±)-79** (0.50 g, 3.3 mmol) in pyridine (1 mL) at 0°C. The completion of the reaction was monitored by TLC. After 1 h, the reaction mixture was diluted with water (5 mL) and Et_2O (5 mL). The layers were separated and the organic layer was washed with 1 M HCl (2 × 5 mL), saturated $NaHCO_3$ solution (3 × 5 mL) and brine (5 mL) and dried over Na_2SO_4. The ethereal layer was concentrated *in vacuo* to afford 0.61 g (74%) of a clear orange oil that was used without further purification. IR (neat) 2933, 2858, 1781, 1674, 1381, 1220, 1164 cm^{-1}; ^{19}F NMR (282 MHz, $CDCl_3$) δ -75.53; ^1H NMR (250 MHz, $CDCl_3$) δ 5.86 (1H, dq, 15.4, 6.5 Hz, =C<u>H</u>CH_3), 5.47 (1H, dd, J = 15.4, 8.0 Hz, =C<u>H</u>CH), 5.13 (1H, dd, J = 8.0, 8.0 Hz, C<u>H</u>O), 1.87-1.50 (5H, m, c-C_6<u>H</u>$_{11}$), 1.74 (3H, d, J = 6.5 Hz, C<u>H</u>$_3$), 1.35-0.84 (6H, m, c-C_6<u>H</u>$_{11}$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 157.1 (<u>C</u>=O, q, $J_{C\text{-}F}$ = 40 Hz), 133.0, 126.0 (H<u>C</u>=<u>C</u>H), 116.6 (<u>C</u>F$_3$, q, $J_{C\text{-}F}$ = 283 Hz), 84.3 (<u>C</u>HO), 41.2 (c-<u>C</u>H$(CH_2)_5$), 28.3, 26.1, 25.9, 25.7, 25.6 (c-CH(<u>C</u>H$_2$)$_5$), 17.7 (<u>C</u>H$_3$); MS (EI) m/z (%) 137 (M^+ - OC(O)CF_3, 7), 107 (55), 81 (67), 79 (100), 77 (34), 69 (66), 68 (33), 67 (68), 55 (50), 51 (44).

2.3.6 *General Procedure D: Determining Facial Selectivity of Copper Coupling Reactions*

Derivatizations were typically run with ~10 mg of the alkene. The alkene (1.0 equiv) was dissolved in acetone (1 mL/mg substrate), cooled to -78 °C and treated with an excess of ozone. The reaction mixture was purged with argon, treated with Jones' reagent[20,34] (2.7 equiv) and allowed to warm to room temperature. The excess Jones' reagent was quenched with isopropanol (excess) and the solvent was removed *in vacuo*. The resulting residue was partitioned between Et_2O and water (~ 4:1 ratio) and the layers were separated. The organic layer was washed with 1 M HCl (3×). The carboxylic acids were extracted with 1 M NaOH. The aqueous layer was cooled to 0°C and reacidified with 6 M HCl, after which the carboxylic acids were extracted into Et_2O. The organic layer was dried with $MgSO_4$ and the solvent was removed *in vacuo*. The resulting mixture of carboxylic acids (1.0 equiv each) in CH_2Cl_2 (0.4 mL/mg substrates) was treated with diisopropyl carbodiimide (2.2 equiv), (*R*)-α-methylbenzylamine (2.2 equiv), HOBT (0.2 equiv), and DMAP (0.2 equiv). The progress of the reaction was monitored by TLC. Et_2O was added and the reaction mixture was washed with cold 1 M HCl, saturated $NaHCO_3$ and brine. The organic layer was dried with $MgSO_4$ and the solvent was removed *in vacuo*. The crude reaction mixture was analyzed by GC/MS to determine the diastereomeric ratio of the formed amides.

2.3.7 *Preparation of Standard of Known Absolute Configuration*

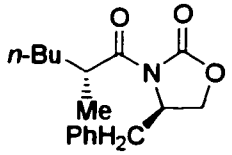
*(R)-3-Hexanoyl-4-benzyl-2-oxazolidinone (**105**)*



(*R*)-4-(Phenylmethyl)-2-oxazolidinone (**104**, prepared from (*D*)-phenylalanine and diethyl carbonate)[35] (1.0 g, 5.7 mmol) was dissolved in dry THF (20 mL) and cooled to 0°C at which time *n*-BuLi (1.02 M, 5.6 mL, 5.7 mmol) was added dropwise. The resulting solution was stirred at 0°C for 40 min and then cooled to -78°C. Hexanoyl chloride (1.0 mL, 7.2 mmol) was added dropwise via syringe and the reaction was allowed to stir for 1 h at -78°C. The

completion of the reaction was determined by TLC. The reaction was quenched by dropwise addition of saturated NH_4Cl (5 mL) at -78°C and was allowed to warm to RT. The reaction mixture was diluted with Et_2O (10 mL), washed with water (20 mL), saturated $NaHCO_3$ (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, after which the solvent was removed *in vacuo*. The resulting oil was purified by column chromatography (4:1 hexanes:Et_2O as solvent) to provide 1.3 g (80%) of a clear, slightly yellow oil; $[\alpha]_D$ = -93.2 (c = 1.0, EtOH) [lit. value for (*S*)-isomer: $[\alpha]_D$ = +97.5 (c = 1.03, EtOH)][36]; IR (neat) 3063, 1783, 1700, 746, 703 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.37-7.19 (5H, m, $C_6\underline{H}_5$), 4.68 (1H, X of ABX, m, NC$\underline{H}$), 4.24-4.13 (2H, m, CHC$\underline{H}_2$O), 3.34 (1H, A of ABX, dd, J_{obs} = 13.3, 3.3 Hz, C$\underline{H}_2$Ph), 3.01-2.82 (2H, m, C$\underline{H}_2$CO), 2.81-2.72 (1H, B of ABX, dd, J_{obs} = 13.3, 9.6 Hz, C$\underline{H}_2$Ph), 1.76-1.27 (6H, m, (C$\underline{H}_2$)$_3$CH$_3$), 0.91 (3H, t, J = 7.0 Hz, C$\underline{H}_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 173.3 ($CH_2\underline{C}$=O), 153.3 (N$\underline{C}$=OO), 135.3, 129.3 (2C), 128.8 (2C), 127.2 (ArC's), 66.1 (CH$\underline{C}H_2$O), 55.0 (N$\underline{C}$H), 37.9 ($\underline{C}H_2$Ph), 35.4, 31.2, 23.9, 22.3 (($\underline{C}H_2$)$_4$CH$_3$), 13.8 ($\underline{C}H_3$).

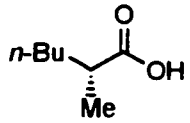
*(2'R,4R)-3-(2'-Methylhexanoyl)-4-benzyl-2-oxazolidinone (**106**)*



A procedure similar to the one outlined by Evans *et al.* was followed.[37] A solution of **105** in THF (5 mL) was added to sodium bis(trimethylsilyl)amide (1.0 M, 3.6 mL, 3.6 mmol) in THF (15 mL) at -78°C. After 1 h, methyl iodide (1.0 mL, 16 mmol) was added and the reaction mixture was stirred at -78°C until the reaction appeared complete by TLC (1 h). The reaction was quenched with saturated NH_4Cl solution (5 mL) and allowed to warm to RT. The reaction mixture was diluted with Et_2O (10 mL), washed with water (2 × 5 mL), saturated $NaHCO_3$ (2 × 5 mL) and brine (2 × 5 mL) and then dried over $MgSO_4$. The organic layer was concentrated *in vacuo* to give a residue that was purified by silica column chromatography (4:1 hexanes:Et_2O as solvent) to afford 0.78 g (82%) of a clear, pale yellow oil; $[\alpha]_D$ = -118.9 (c = 0.53, MeOH) [lit. value for opposite enantiomer: $[\alpha]_D$ = +104.4 (c = 0.47, MeOH), >95% de][38]; IR (neat) 3064, 1781, 1698, 1208 cm^{-1}; ^1H NMR (250 MHz, $CDCl_3$) δ 7.31-7.14 (5H, m, $C_6\underline{H}_5$), 4.62 (1H, X of ABX, m, NC$\underline{H}$), 4.18-4.07 (2H, m, CHC$\underline{H}_2$O), 3.66 (1H, tq, J = 6.8,

6.8Hz, C<u>H</u>CH$_3$), 3.23 (1H, A of ABX, dd, J_{obs} = 13.3, 3.3 Hz, C<u>H</u>$_2$Ph), 2.71 (1H, B of ABX, dd, J_{obs} = 13.3, 9.6 Hz, C<u>H</u>$_2$Ph), 1.73-1.10 (6H, m, (C<u>H</u>$_2$)$_3$CH$_3$), 1.17 (3H, d, J = 6.9 Hz, CH$_3$CH), 0.83 (3H, t, J = 6.9 Hz, CH$_3$CH$_2$); ^{13}C NMR (63 MHz, CDCl$_3$) δ 177.0 (CH<u>C</u>=O), 152.8 (N<u>C</u>=OO), 135.2, 129.2 (2C), 128.5 (2C), 126.9 (ArC's), 65.7 (CH<u>C</u>H$_2$O), 55.0 (N<u>C</u>H), 37.5 (Ar<u>C</u>H$_2$), 37.3 (<u>C</u>HCH$_3$), 32.8, 29.1, 22.4 ((<u>C</u>H$_2$)$_3$CH$_3$), 17.0 (<u>C</u>H$_3$CH), 13.6 (<u>C</u>H$_3$CH$_2$).

(R)-2-Methylhexanoic acid (107)



H_2O_2 (30%, 630 μL) and LiOH (0.11 g, 4.5 mmol) dissolved in water (2 mL) was added to **106** (0.44 g, 1.5 mmol) dissolved in a 4:1 mixture of THF and water (8 mL and 2 mL, respectively) at 0°C. After 0.5 h, Na_2SO_3 (0.86 g, 6.8 mmol) in water (5 mL) was added to quench excess peroxide. The acid was isolated by extracting the reaction mixture with CH_2Cl_2 (2 × 20 mL). The organic layer was dried over $MgSO_4$, after which the solvent was removed *in vacuo* to afford 0.19 g (95%) of a clear, colourless oil; $[\alpha]_D$ = -17.5 (c = 4.7, $CHCl_3$) [lit. value: $[\alpha]_D$ = -8 (c = 7.0, $CHCl_3$), 56% ee[39] or $[\alpha]_D$ = +19.00 (neat), 96% ee[40] for (*S*)-enantiomer; IR (neat) 2960 (br), 2950, 2863, 1708, 1467 cm^{-1}; ^{1}H NMR (250 MHz, $CDCl_3$) δ 2.47 (1H, X of ABM_2X, tq, J_{obs} = 6.9, 6.9 Hz, C<u>H</u>CH$_3$), 1.76-1.62 (1H, A of ABM_2X, m, C<u>H</u>$_2$CH), 1.41-1.38 (1H, B of ABM_2X, m, C<u>H</u>$_2$CH), 1.36-1.26 (2H, M_2 of ABM_2X, m, CH$_3$(CH$_2$)$_2$C<u>H</u>$_2$; 2H, m, C<u>H</u>$_2$CH$_3$), 1.20 (3H, d, J = 6.9 Hz, C<u>H</u>$_3$CH), 0.90 (3H, t, J = 6.9 Hz, C<u>H</u>$_3$CH$_2$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 183.5 (<u>C</u>=O), 39.4, 33.2 (<u>C</u>HCH$_3$, <u>C</u>H$_2$CH), 29.3, 22.5 ((<u>C</u>H$_2$)$_2$CH$_3$), 16.7 (<u>C</u>H$_3$CH), 13.8 (<u>C</u>H$_3$CH$_2$).

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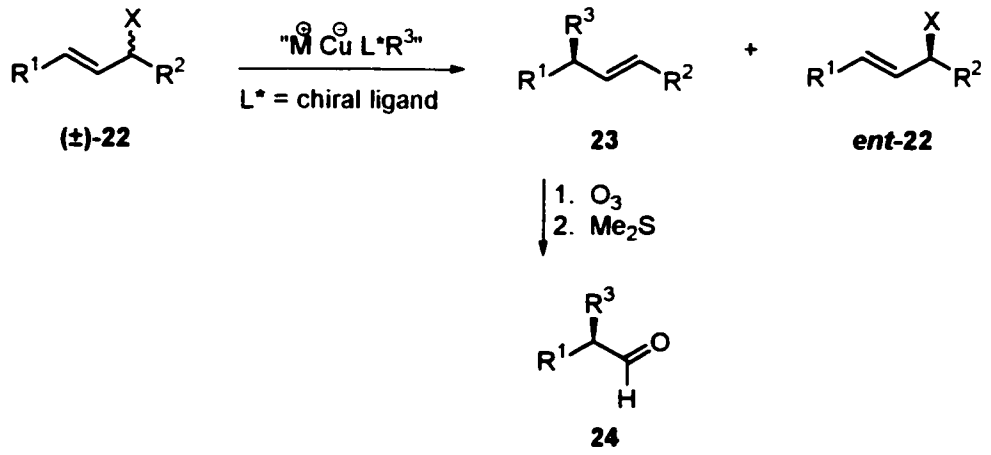
CHAPTER 3

REACTIONS OF ALLYLIC SUBSTRATES WITH CHIRAL CUPRATES

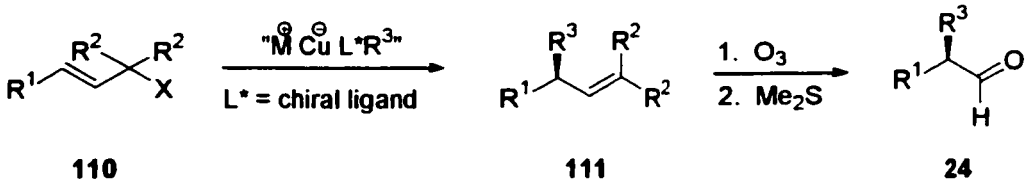
3.1 Introduction

The next two proposed routes to α-chiral aldehydes relied on chiral cuprate reagents. The first strategy involved a kinetic resolution of a racemic allylic substrate (Scheme 41). We envisioned chiral cuprate "$M^{+}Cu^{-}L^{*}R^{3}$" preferentially alkylating one enantiomer of the racemic mixture (see **(±)-22**), leaving the other enantiomer mostly unreacted. In the second route (Scheme 42), we proposed to introduce chirality to prochiral substrate **110** by reaction with a chiral cuprate. This route would reverse the chirality roles of the substrate and nucleophile from our previously developed route (Chapter 2). In each case, the resulting enantiomerically-enriched alkene could be cleaved with ozone to form the desired aldehyde **24**.

Scheme 41



Scheme 42

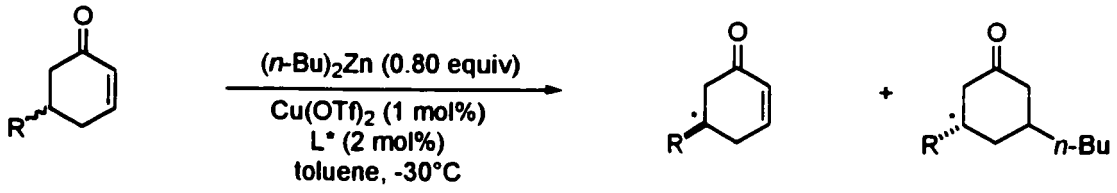


110 **111** **24**

3.1.1 Reactions of Chiral Organocopper Reagents with α,β-Unsaturated Ketones

A copper-catalyzed kinetic resolution is the key step in our first modified route to α-chiral aldehydes (Scheme 41). Kinetic resolutions are possible when one enantiomer of a racemic mixture is more easily transformed into a product than the other enantiomer.[1] The Sharpless kinetic resolution[2] (discussed in Chapter 2) is an excellent example of this type of methodology. Feringa and coworkers have recently developed an efficient kinetic resolution method for cyclic α,β-unsaturated ketones using copper chemistry (Scheme 43). During the copper-catalyzed dialkylzinc addition in the presence of a chiral phosphoramidite ligand, one of the enantiomers of the racemic cyclohexene-derivative was preferentially alkylated.[3] With ligand **118**, recovered enones **(ee)-112-114** had enantiomeric excesses of ≥99%. The authors did not determine the absolute configurations of the isolated compounds.[3]

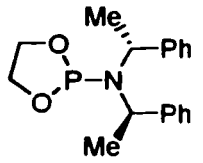
Scheme 43



(±)-112: R = Me
(±)-113: R = *i*-Pr
(±)-114: R = $SiMe_3$

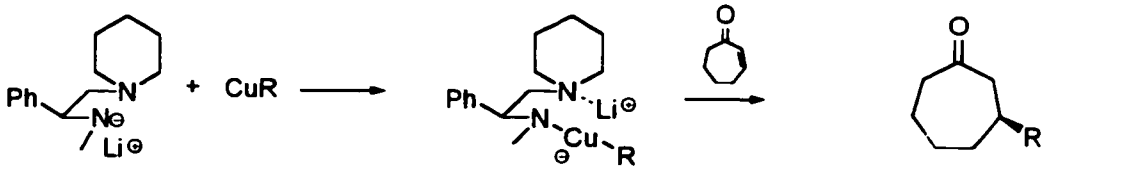
(ee)-112: R = Me
(ee)-113: R = *i*-Pr
(ee)-114: R = $SiMe_3$

115: R = Me
116: R = *i*-Pr
117: R = $SiMe_3$

L* =  **118**

The key step in the next proposed approach (Scheme 42) is an asymmetric alkyl addition using a chiral cuprate reagent. Historically, considerable effort has been applied to the study of chirally modified organocuprates for asymmetric 1,4-additions to α,β-unsaturated ketones. High enantiomeric excesses have been achieved in many cases.[4] Rossiter and coworkers developed one of the best ligands for enantiomeric conjugate additions to α,β-unsaturated ketones (Scheme 44). In their method, either (*R*)- or (*S*)-*N*-methyl-1-phenyl-2-(1-piperidinyl)ethanamine (MAPP) was reacted with an alkyllithium and a monoorganocopper reagent to form a dimeric species that preferentially alkylated one face of the enone (Figure 15). Enantiomeric excesses as high as 97% were achieved.[4,5]

Scheme 44



(*S*)-119

(*S*)-120: R = Me
(*S*)-121: R = *n*-Bu

122: R = Me, ee = 97%
123: R = *n*-Bu, ee = 96%

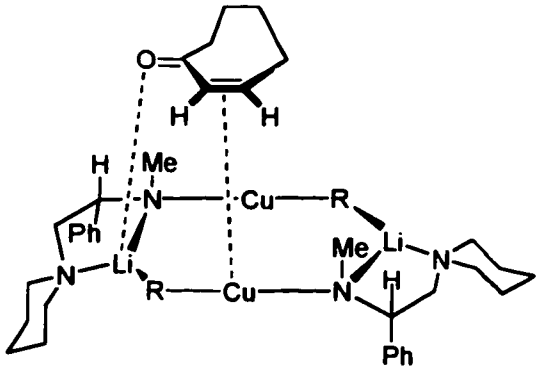


Figure 15. Proposed reactive conformation for asymmetric addition with Rossiter's chiral cuprate.[4]

3.1.2 1,4-Addition versus S_N2' Reaction

Mechanistically, the S_N2' reaction is quite similar to a 1,4-addition (Figure 16).[6] Both reactions involve attack on one side of the π system, with rearrangement of the double bond. In the carbonyl substrate, the electron density is pushed onto the oxygen;[4] in the allylic case, the leaving group departs with a negative charge.[7] Seeing these similarities, we hypothesized that high facial selectivities were possible during chiral cuprate additions to prochiral allylic substrates.

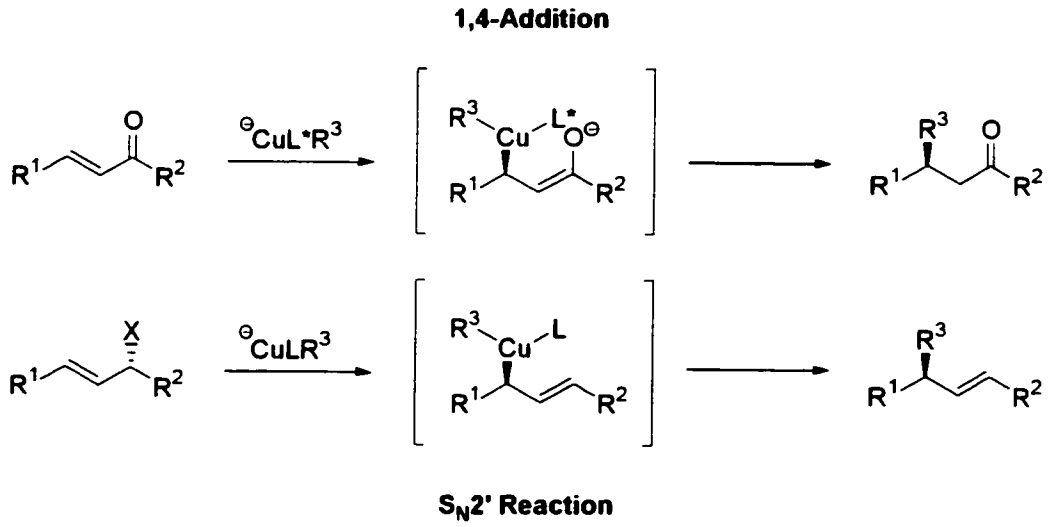


Figure 16. 1,4-Addition versus S_N2' reaction.

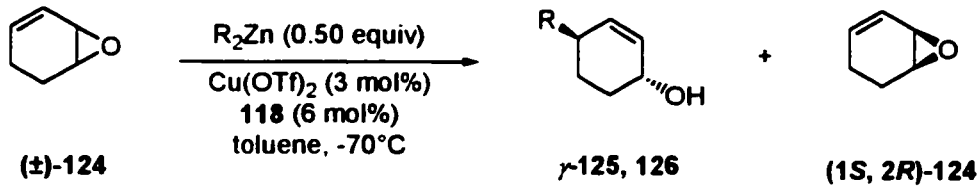
3.1.3 Reactions of Chiral Cuprates with Allylic Substrates

3.1.3.1 Kinetic Resolution

Some examples of copper-mediated kinetic resolutions of allylic substrates do exist in the literature. For example, Feringa and coworkers used copper catalysts equipped with chiral phosphoramidite ligands when resolving allylic epoxides.[8] The first substrate investigated is illustrated in Scheme 45.[9] Feringa's group formed **γ-125** and **γ-126** with high enantiomeric

excesses using the same ligand they had previously developed for 1,4-additions to cyclohexenone derivatives (see **118**, Scheme 43).[8,9]

Scheme 45



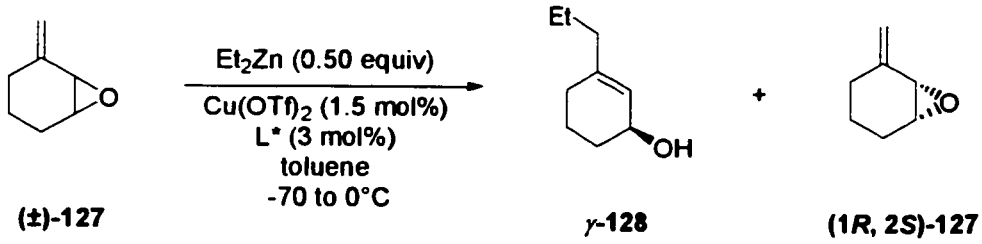
(±)-124 — γ-125, 126 — (1*S*, 2*R*)-124

γ-#	R	γ ee (%)	γ Yield (%)[a]
125	Me	92	66
126	Et	91	64

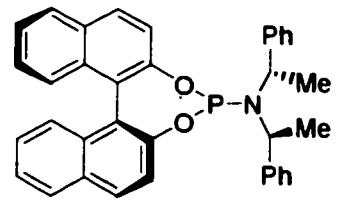
[a] Yields are based upon a possible 50% recovery of the γ-substituted enantiomerically-enriched product.

With binaphthol-based ligand **129**, Feringa *et al.* resolved epoxide (±)-**127** by preferentially transforming one of its enantiomers to allylic alcohol γ-**128** (Scheme 46). The γ-substituted product was recovered in 88 %ee and 89% yield.[10]

Scheme 46



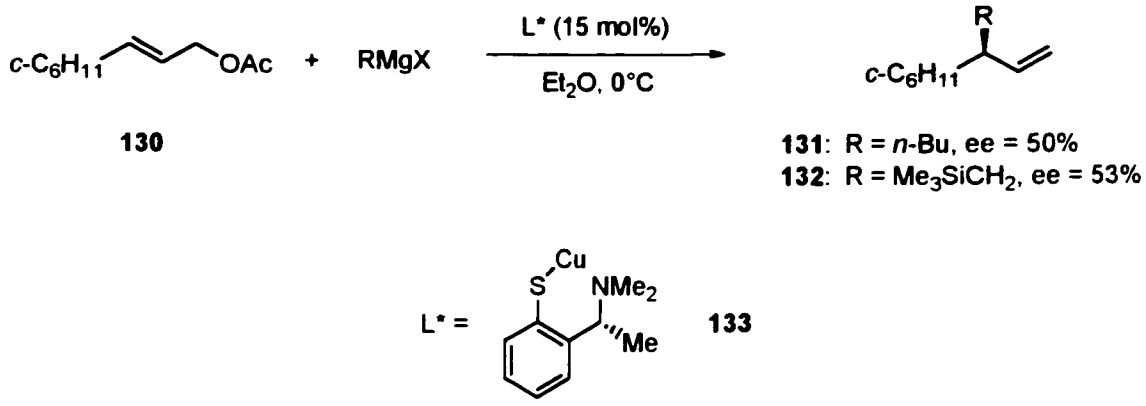
(±)-127 — γ-128 — (1*R*, 2*S*)-127

L* =  **129**

3.1.3.2 Reactions with Prochiral Substrates

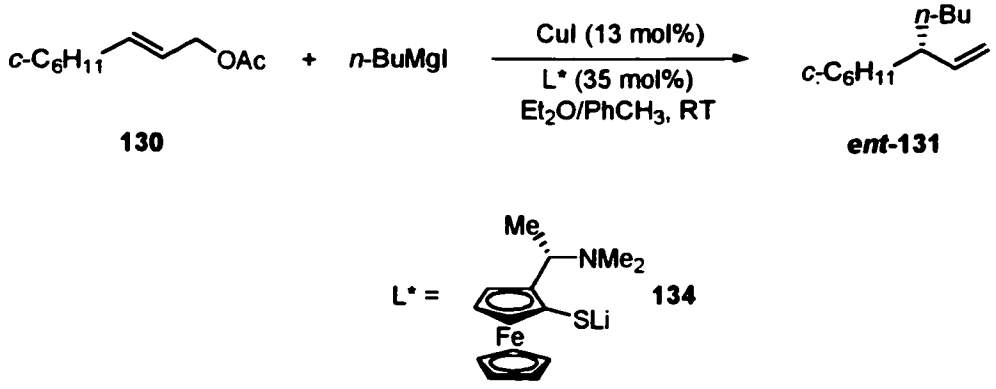
van Koten and Bäckvall were pioneers in developing enantioselective S_N2' reactions utilizing chiral cuprate reagents.[11,12] Using chiral ligand **133**, the reactions shown occurred with complete γ-regioselectivity (Scheme 47). Both *n*-Bu and Me_3SiCH_2 groups were added to the system with moderate facial selectivity.[13]

Scheme 47



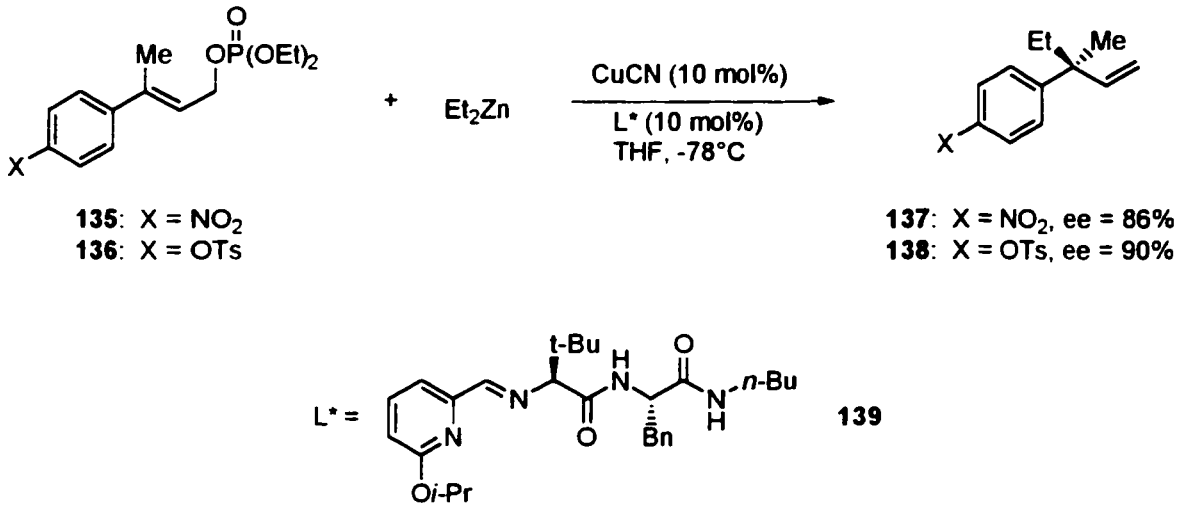
Bäckvall and coworkers recently developed new ferrocenyl thiolates for copper-catalyzed asymmetric substitution reactions with allylic acetates (Scheme 48). Under their best conditions, *n*-BuMgI was added to acetate **130** to form ***ent*-131**. The reaction occurred with 96% γ-regioselectivity and an enantiomeric excess of 64%.[14]

Scheme 48

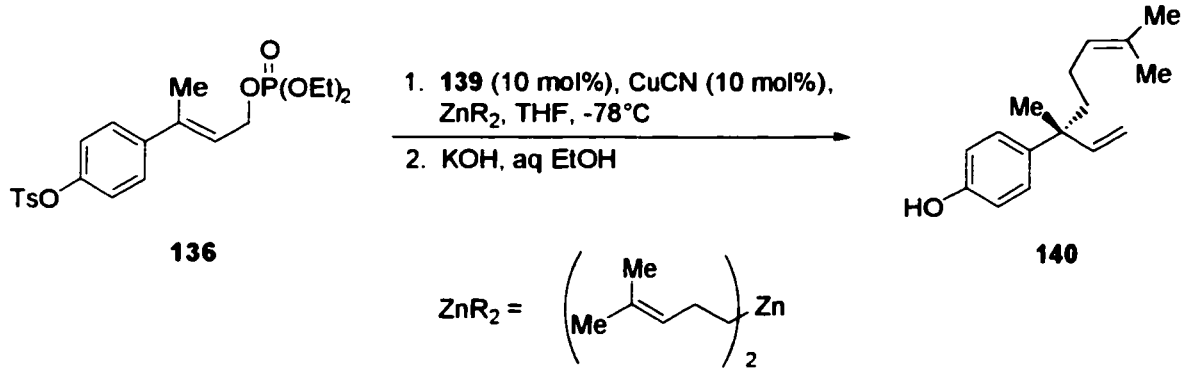


After surveying a number of peptide-based ligands, Hoveyda's group developed chiral ligand **139**, which participated in copper catalyzed allylic substitution reactions with high stereo- and regioselectivities (Scheme 49).[15] They used this methodology to synthesize the fish deterrent, (*R*)-(-)-sporochnol (**140**), in 82 %ee and 82% overall yield (Scheme 50).[15]

Scheme 49



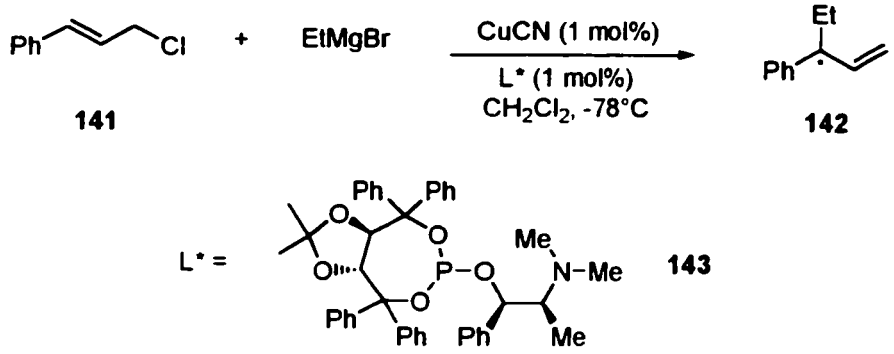
Scheme 50



Alexakis and coworkers developed chiral phosphorus ligand **143** for regio- and enantioselective S_N2' allylic substitutions with Grignard reagents (Scheme 51).[16] The best

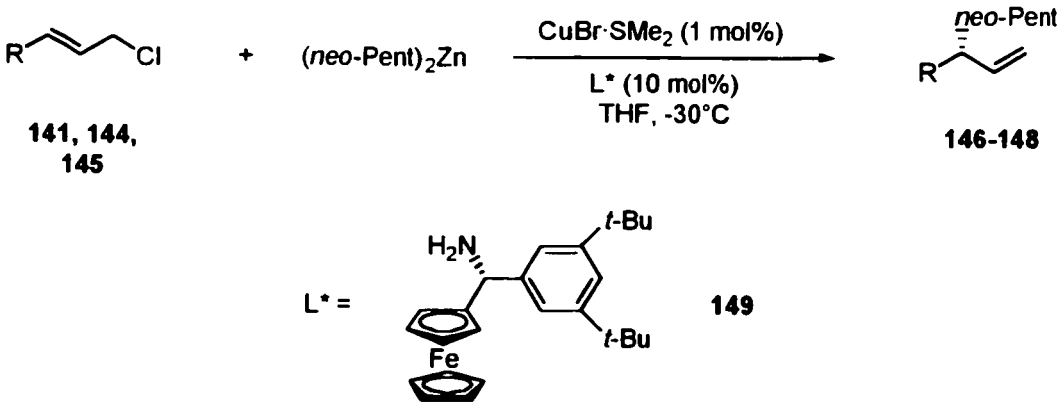
result occurred when adding EtMgBr to cinnamyl chloride (**141**), achieving a γ-regioselectivity of 88% and an enantiomeric excess of 73%. The absolute configuration of alkene **142** was not determined.[16]

Scheme 51



Dübner and Knochel[17] have also made contributions to this field of study.[14] They introduced *neo*-pentyl groups via diorganozinc reagents in the presence of ligand **147** to a number of different allylic chlorides (Scheme 52). All of the reactions illustrated occurred with γ-regioselectivities of ≥96%.[17]

Scheme 52



Product	R	ee (%)	Yield (%)
146	Ph	96	82
147	4-CF_3-C_6H_4	98	85
148	*c*-C_6H_{11}	90	84

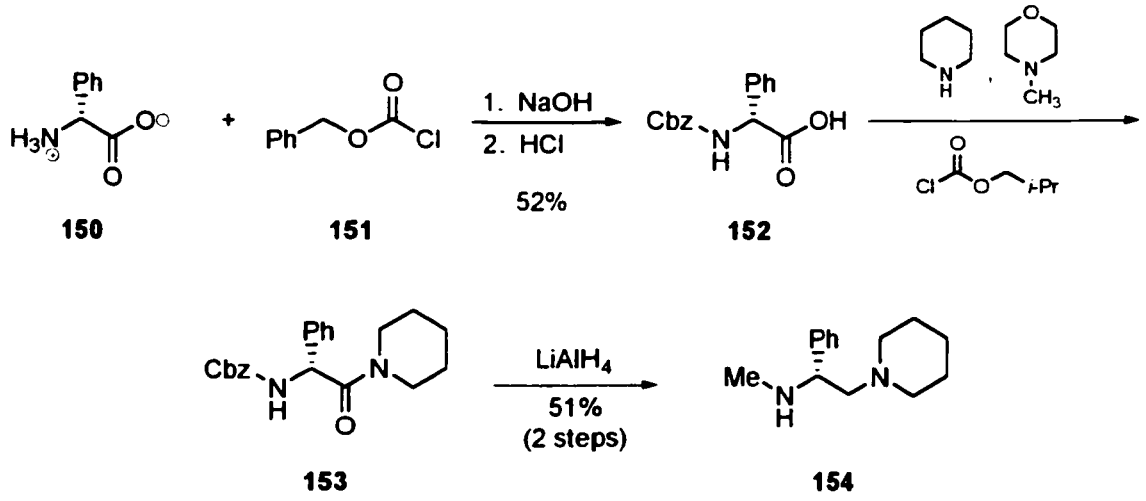
3.2 Results and Discussion

3.2.1 Kinetic Resolution Route

In designing our kinetic resolution route, we hoped that one face of the allylic substrate would be preferentially alkylated, leaving one enantiomer mostly unreacted. The first chiral cuprate chosen for investigation was the Rossiter ligand, which had been used for many successful conjugate additions.[4] This ligand was also used by another member of the Chong group, Dr. Kelvin H. Yong, to perform 1,2-additions to carbonyl compounds with good levels of enantioselectivity.[18]

The ligand synthesis began by the reaction of (*R*)-(-)-2-phenylglycine (**150**) and benzyl chloroformate (**151**) under basic conditions (Scheme 53). After work-up and purification, (*R*)-*N*-carbobenzyloxyphenylglycine (**152**) was isolated in 52% yield.[19] The protected phenylglycine was coupled with piperidine to form carbobenzyloxyamide **153**, which was reduced, without purification, to form (*R*)-*N*-methyl-1-phenyl-2-(1-piperidinyl)ethanamine [(*R*)-MAPP, **154**].[20]

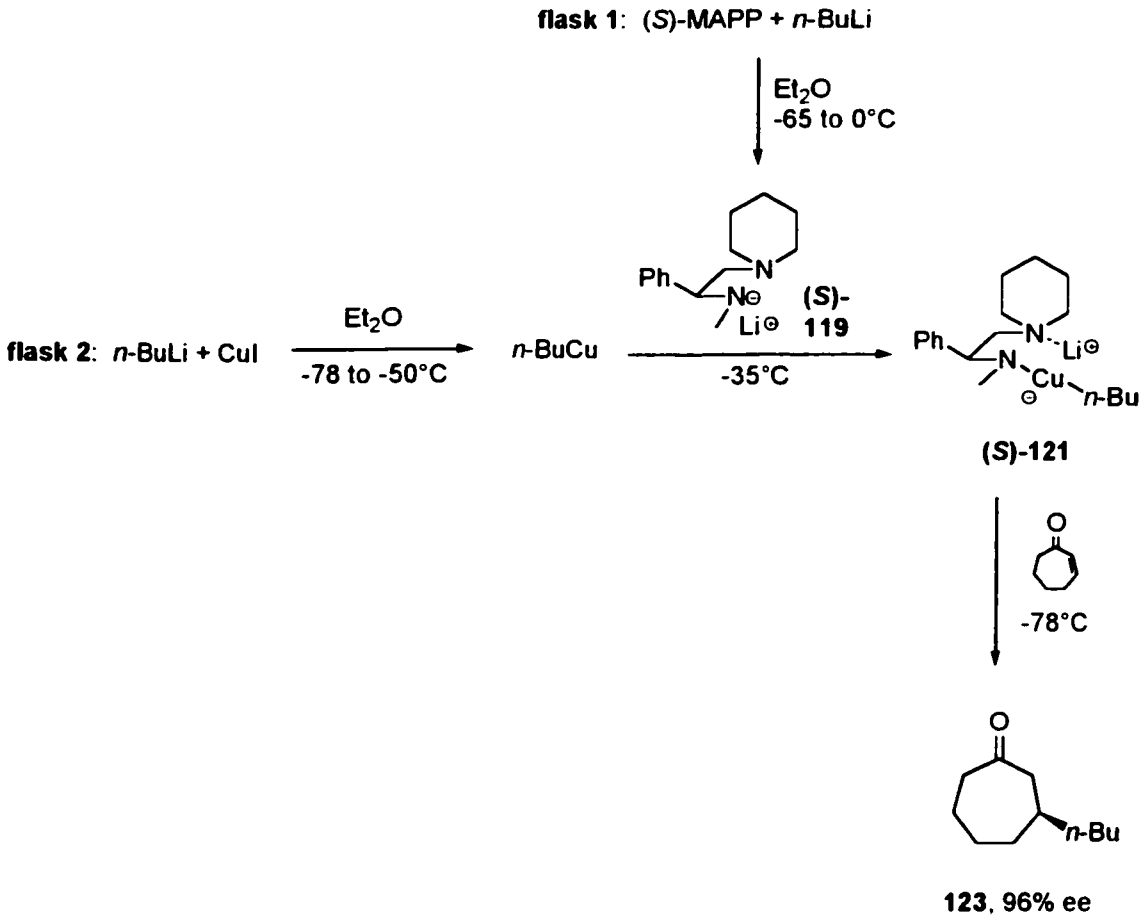
Scheme 53



With the chiral ligand in hand we were ready to try the asymmetric coupling reactions with allylic substrates. We used Rossiter's procedure for the 1,4-addition of cuprate **(*S*)-121** to 2-cycloheptenone as a guide (Scheme 54).[20] In the first step, (*S*)-MAPP was reacted with *n*-BuLi at -65°C to form lithium amide **119** (flask 1). The temperature was allowed to rise to

0°C to complete the reaction. In flask 2, *n*-Bu copper was formed by reacting CuI with *n*-BuLi at -78°C. The reaction mixture was warmed to -50°C and was kept here for 30 min. After this time, flasks 1 and 2 were warmed to -35°C and the amide was added to the monoorganocopper reagent via cannula. After 10 to 15 min, the reaction was cooled to -78°C. After waiting 30 min, the desired substrate was added and the reaction mixture was stirred for 1 h at -78°C before quenching.[20]

Scheme 54

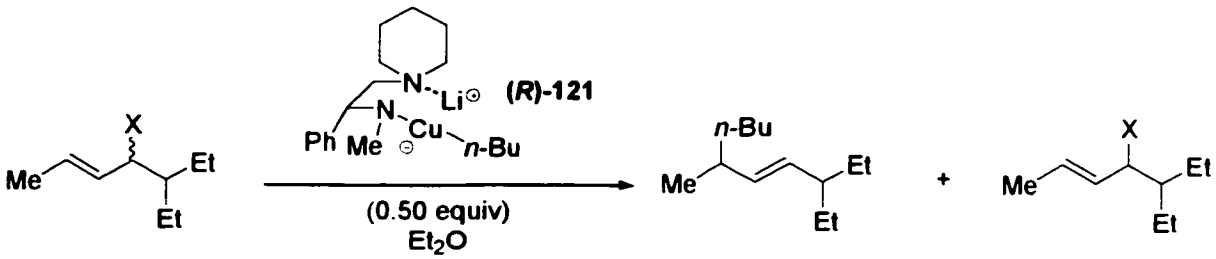


During our reactions with cyano-modified cuprate reagents, the highest regio- and stereoselectivities were achieved with allylic phosphate **89**;[21] therefore, it was the first substrate used with the new methodology. Under the standard conditions (Scheme 54), the attempted kinetic resolution of phosphate **(±)-89** occurred with unexpectedly low

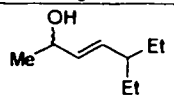
regioselectivity and no facial selectivity (entry 1, Table 7). The other product isolated from the chromatographic separation was not starting material, but an isomerized version of the precursor allylic alcohol. This observation seemed to suggest that the phosphate ester was too reactive and that the leaving group was departing before reaction with the cuprate could occur. The resulting radical or cationic species generated allylic alcohol **157** upon aqueous work-up.

We looked for other possible leaving groups that were less reactive. The methyl carbonate and pivalate esters were synthesized under standard conditions in quantitative and 52% yields, respectively. Using methyl carbonate **155** as the substrate, the coupling yield dropped dramatically, but the γ-regioselectivity was very high. Again, the recovered alkene was racemic. The standard reaction was run with pivalate **156**. When no product had formed after 1 h at -78°C (determined by TLC), the reaction was allowed to slowly warm to RT before quenching. Unfortunately, no product formed, even at an elevated temperature.

Table 7. Kinetic resolution results with Rossiter cuprate **(*R*)-121**.



89, 155, 156 **γ-97**

Entry	Allylic Substrate Number	Allylic Substrate Leaving Group (X)	ee (%)[a]	γ-Regio (%)[b]	Yield (%)	Other Isolated Compound
1	**89**	$P(O)(OEt)_2$	0	87	76	 **157**
2	**155**	C(O)OMe	0	96	19	SM
3[c]	**156**	Piv	N/A	N/A	0	SM

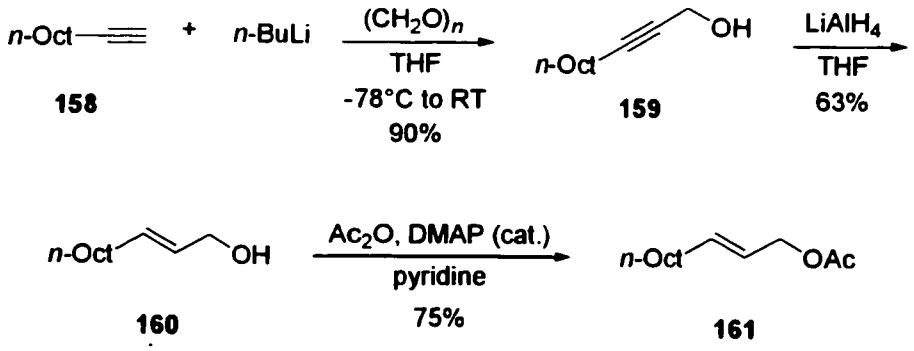
[a] The ee was determined as described in Chapter 2, Section 2.3.6.
[b] γ-Regio = regioselectivity for the γ-substituted alkene.
[c] The reaction mixture was allowed to warm from -78°C to RT before quenching.

From these results, we hypothesized that the phosphate and methyl carbonate esters were too reactive, which was leading to poor facial selectivity. It was also possible that the site bearing the leaving group was too hindered for complexation to occur between the chiral cuprate and these allylic substrates. It is believed that complexation between the substrate and Rossiter's chiral cuprate facilitates the high enantioselectivities observed during 1,4-additions to α,β-unsaturated ketones (see Figure 15).[4]

3.2.1.1 Reaction Probes

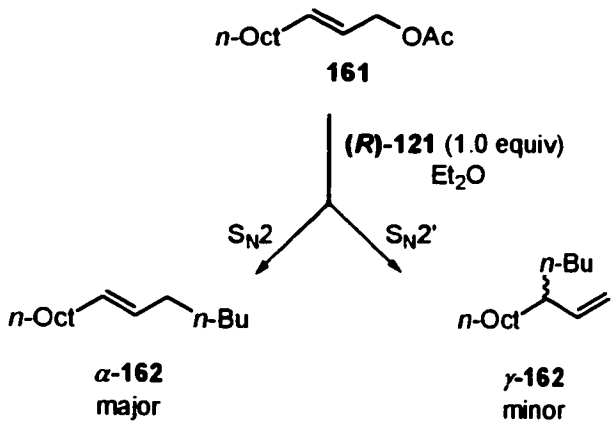
To probe the hypotheses formulated, we ran the Rossiter reaction using an acetate with less steric hindrance at the site bearing the leaving group. The acetate was chosen as the leaving group, since its reactivity lies between that of the phosphate ester and pivalate leaving groups. In the first step of the synthesis, 1-decyne (**158**) was deprotonated with *n*-BuLi and trapped with paraformaldehyde to form alkynol **159** (Scheme 55). The alkyne was preferentially reduced to the (*E*)-double bond via reaction with $LiAlH_4$. The resulting primary allylic alcohol was acetylated under standard conditions to form desired acetate **161**.

Scheme 55



The α-substituted alkene was the major product when acetate **161** was reacted with the Rossiter cuprate. The trace of γ-substituted product recovered was determined to be racemic (Scheme 56).

Scheme 56



3.2.1.2 Summary Kinetic Resolution Route

The Rossiter cuprate was partial to S_N2' reactions with phosphate and methyl carbonate esters when there was steric crowding at the α-substitution site. The analogous pivalate ester was unreactive to the chiral cuprate, even at elevated temperatures. The main product of the Rossiter cuprate reaction with primary acetates was the α-substituted product. In all cases, the recovered γ-substituted products were determined to be racemic after derivatization and GC/MS analysis.

3.2.2 Reactions with Achiral Substrates

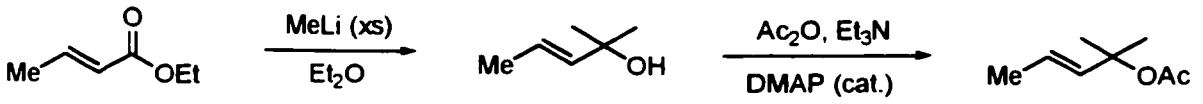
3.2.2.1 Substrate Design and Synthesis

At this point, our focus changed to reactions of chiral cuprates with prochiral substrates. From the results of our 1,3-chirality transfer route, we knew that γ-substitution in allylic substrates was favoured over α-substitution, provided that the site bearing the leaving group was hindered.[21] For this reason, we synthesized a number of substrates in which there

were two methyl groups attached to the α-substitution site. In addition to *trans*-substrates, we synthesized substrates with (*Z*)-double bond geometry to probe for differences in reactivity.

(*E*)-2-Methyl-3-penten-2-ol (**(*E*)-164**) was easily synthesized by reacting ethyl crotonate (**163**) with excess MeLi (Scheme 57). The product was very volatile, leading to a low isolated yield. The resulting alcohol was acetylated using acetic anhydride to generate the first desired acetate.

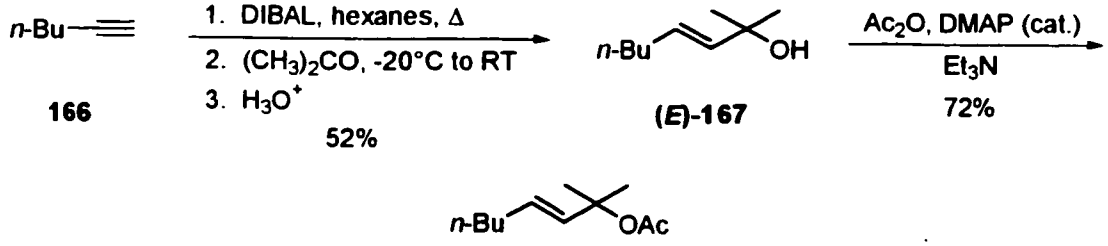
Scheme 57



163 48% **(*E*)-164** 69% **(*E*)-165**

The *n*-Bu analogue of compound **(*E*)-165** was also synthesized (Scheme 58). The first step involved *syn* hydroalumination of hexyne (**166**) using DIBAL. The resulting vinylalane was trapped with acetone to form tertiary allylic alcohol **(*E*)-167** in 52% yield. The desired acetate **(*E*)-168** was formed under standard conditions in 72% yield.

Scheme 58

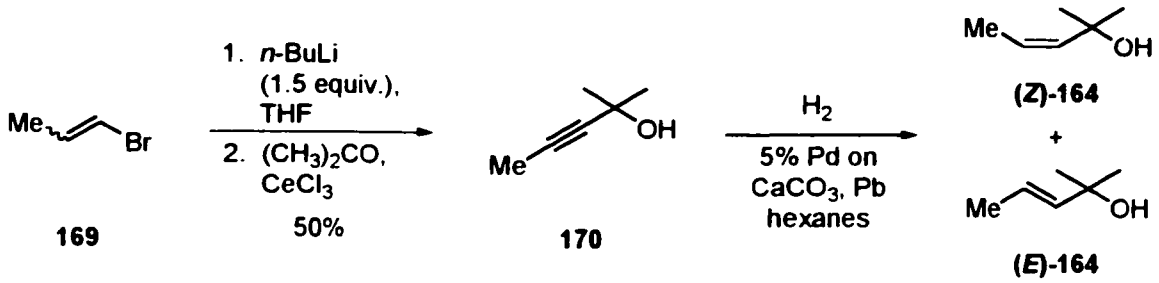


166 52% **(*E*)-167** 72% **(*E*)-168**

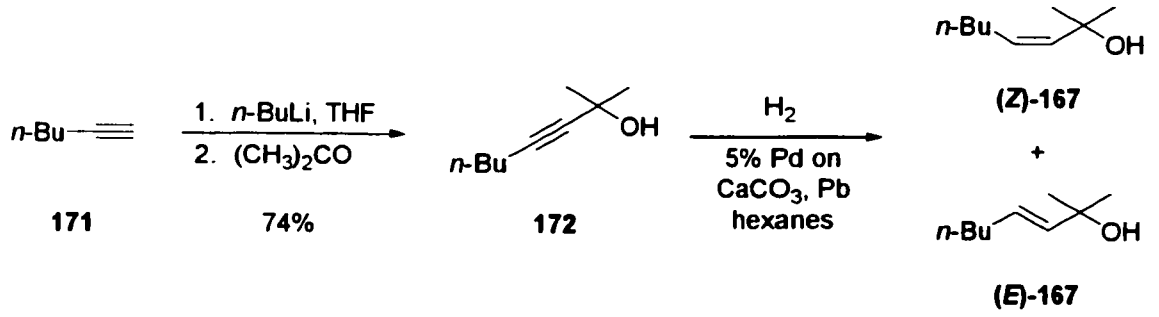
The (*Z*)-double bond analogues proved to be more difficult to synthesize. The prerequisite alkynols were formed via anion generation and trapping with acetone. With the

alkynols in hand, the triple bonds were exposed to H_2 in the presence of a poisoned catalyst.[22,23] Unfortunately, with compound **170**, **(*Z*)-164** and **(*E*)-164** were recovered in a 2:3 ratio (determined by GC/MS) (Scheme 59). When a similar hydrogenation was run with alkynol **172**, **(*Z*)-167** and **(*E*)-167** were recovered in a 4:1 ratio (determined by GC/MS) (Scheme 60).

Scheme 59

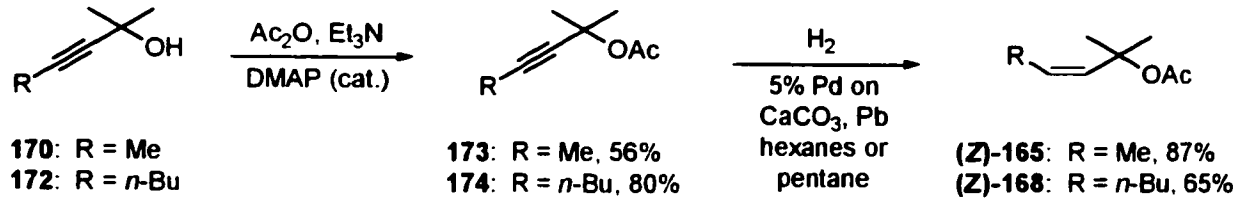


Scheme 60



At this point, a different strategy was employed. The alkynols were acetylated prior to reduction of the triple bond (Scheme 61). Using this procedure, both desired substrates were synthesized in reasonable yield.

Scheme 61



170: R = Me
172: R = *n*-Bu

173: R = Me, 56%
174: R = *n*-Bu, 80%

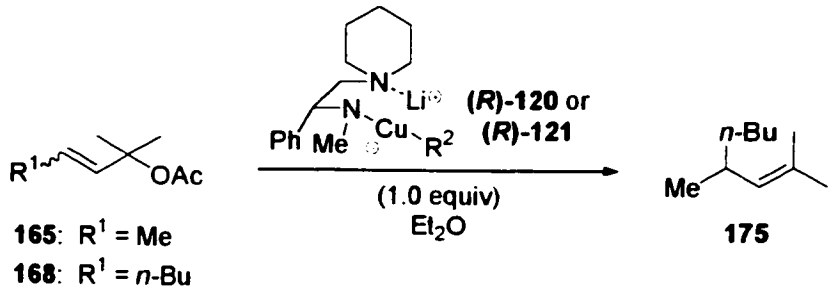
(*Z*)-165: R = Me, 87%
(*Z*)-168: R = *n*-Bu, 65%

3.3.2.2 Substitution Results

As discussed in Section 3.2.1, the standard conditions for a Rossiter asymmetric cuprate reaction requires deprotonation of the ligand with an alkyllithium, followed by reaction with a monoorganocopper reagent (see Scheme 54). The copper source for formation of the monoorganocopper reagents is CuI.[20]

A complex alkene mixture was recovered when the standard Rossiter reaction was run with acetate **(*E*)-165** and **(*R*)-120** (entry 1, Table 8). From the GC/MS analysis of the mixture, there appeared to be one compound (23% of sample) with an M^+ peak of 140, which we believed to be the desired alkene **175**. Four other compounds (remaining 77% of sample) with M^+ peaks of 164 appeared on the GC/MS trace. There were also many peaks in the alkene region of the crude ^{1}H NMR spectrum. We speculated that these compounds corresponded to isomers of a dimerized species that may have arisen from elimination of the acetate, followed by an S_N2' reaction (Scheme 62). It was possible that the cuprate was not forming, leaving excess *n*-BuLi that could cause these dimerizations to occur. We tested the hypothesis by reacting the substrate with *n*-BuLi at -78°C. Only deacetylation occurred under these conditions; therefore, a cuprate species was probably facilitating these side reactions.

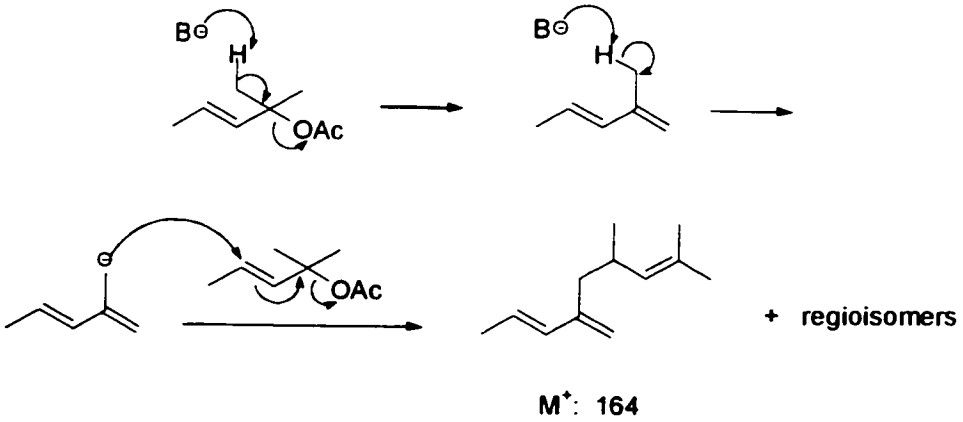
Table 8. Asymmetric cuprate additions.



Entry	SM	R^2	Cu Source	ee (%)	Yield (%)[a]
1	(*E*)-165	*n*-Bu	CuI	N/A	-
2[b]	(*E*)-165	*n*-Bu	CuCN	0	27
3[b]	(*E*)-165	*n*-Bu	$CuBr{\cdot}SMe_2$	0	5
4[b]	(*Z*)-165	*n*-Bu	$CuBr{\cdot}SMe_2$	N/A	nr
5[b]	(*E*)-168	Me	CuI	N/A	nr
6[b,c]	(*E*)-168	Me	CuI	N/A	-

[a] No reaction is denoted by nr.
[b] The reaction mixture was allowed to warm from -78°C to RT after adding the substrate.
[c] The chiral cuprate was formed at 0°C instead of -35°C.

Scheme 62



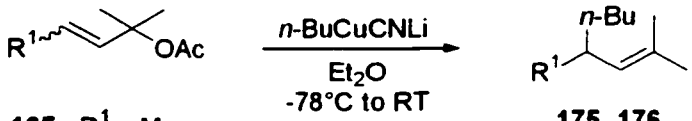
In an attempt to alter the properties of the cuprate reagent, we tried generating the chiral species with other copper sources. No product formed when the reaction was run with CuCN or $CuBr{\cdot}SMe_2$. The reactions were repeated, allowing the temperature to rise to RT

before quenching. In these cases (entries 2 and 3, Table 8), the yields were extremely low and the recovered alkenes were racemic. No improvement resulted by changing the geometry of the substrate double bond from (*E*) to (*Z*) (entry 3 vs. entry 4).

Substrate **(*E*)-168** was reacted with **(*R*)-121** using Rossiter's protocol and no product formed, even after warming the reaction mixture to RT. Methyl homocuprates are typically stable up to 0°C;[24] so, we warmed the cuprate to this temperature (instead of -35°C) to ensure formation of the desired cuprate species. The reaction mixture was recooled to -78°C before acetate addition. Under these conditions, another complex alkene mixture was formed.

Were our tertiary substrates too unreactive or was the cuprate causing the problem? In order to probe these questions, we reacted each of the tertiary acetates with a cyanocuprate (Table 9).

Table 9. Reactions with cyanocuprates.



165: R^1 = Me
168: R^1 = *n*-Bu

175, 176

Entry	SM	R^1	Product	Yield (%)
1	**(*E*)-165**	Me	175	26
2	**(*Z*)-165**	Me	175	29
3	**(*E*)-168**	*n*-Bu	176	31
4	**(*Z*)-168**	*n*-Bu	176	36

Although the yields are very low, the desired products were formed in each case, regardless of bond geometry; therefore, it appears as though the reactivity of the Rossiter cuprate is insufficient for these particular systems.

3.3.2.3 Summary of Reactions with Achiral Substrates

A series of tertiary acetates were synthesized for attempted asymmetric addition with Rossiter's chiral cuprate. Unfortunately, the chosen cuprate was, in most cases, too unreactive

for these systems. When alkylation did occur, the recovered alkenes were racemic. The tertiary acetates were reactive with achiral cyanocuprates, regardless of double bond geometry.

3.3 Experimental

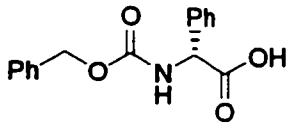
3.3.1 General Experimental

All reactions were performed using flame-dried glassware under an argon atmosphere. Diethyl ether (Et_2O) and THF (tetrahydrofuran) were freshly distilled from sodium benzophenone ketyl. Dichloromethane and hexanes were freshly distilled from CaH_2. Triethylamine and pyridine were distilled from CaH_2 and stored over 3Å molecular sieves. $CuBr{\cdot}SMe_2$ was prepared as described by Wuts[25] and purified by recrystallization from Me_2S-hexanes. CuI was purified by a Soxhlet extraction using THF as solvent.

Melting points were taken on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained as either neat liquids or as a chloroform solution between sodium chloride plates on a Perkin-Elmer Spectrum RXI FT-IR system. IR absorption positions are given in cm^{-1}. NMR spectra were recorded using either a Bruker AC-200, AM-250 or Avance-300 spectrometer in $CDCl_3$, using tetramethylsilane (TMS, δ = 0.00 for ^1H) or deuterated chloroform ($CDCl_3$, t, δ = 77.0 for ^{13}C) as internal standards. For spectra run in DMSO-d_6, DMSO-d_5 (quint, δ = 2.50 for ^1H) and DMSO-d_6 (septet, δ = 39.5 for ^{13}C) were used as internal standards. ^1H NMR data are reported as follows: signal (integration, multiplicity, coupling constant (if applicable), identity). ^{13}C NMR data are reported similarly. GC/MS spectra were run on a Hewlett Packard G1800A GCD system with a 30 m × 0.25 mm DB-5 column. The following temperature program was used: T_0 = 70°C, t_0 = 2.0 min, rate = 10°C/min, T_f = 250°C, t_f = 10.0 min. The mass spectral data is reported as: mass (% base peak). Optical rotations were recorded on a Perkin-Elmer 241 polarimeter using the sodium D line (589 nm), unless otherwise noted. Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

3.3.2 (R)-MAPP Synthesis

(R)-N-Carbobenzyloxyphenylglycine **(152)**[19]



(*R*)-(-)-2-Phenylglycine (**150**, 32 g, 0.21 mol) was added to NaOH (4 M, 55 mL, 0.22 mol). The reaction mixture was cooled to 0°C and benzyl chloroformate (**151**, 33 mL, 0.23 mol) was added dropwise over a period of 30 min. Additional NaOH (~10 mL) was added to keep the reaction mixture basic. Extra water (~100 mL) was also added to make stirring easier. After 10 min, water (65 mL) was added and the reaction mixture was filtered. The filtrate was washed with Et_2O (2 × 250 mL). The pH of the aqueous layer was adjusted to 3 by addition of 6 M HCl. The resulting precipitate was filtered, washed with water and dried under vacuum. The crude product was dissolved in ethyl acetate and the resulting mixture was filtered. The filtrate was reduced *in vacuo* and the remaining solid was recrystallized from EtOAc-hexanes to yield 32 g (52%) of a white crystalline solid (mp = 124-126°C, lit. mp = 125-128°C).[19] $[\alpha]_D$ = -105.5 (c = 1.1, MeOH), lit.: $[\alpha]_D$ = -108.5 (c = 1.0, MeOH).[19] ^{1}H NMR (200 MHz, DMSO-d_6) δ 8.13 (1H, d, J = 8.2 Hz, NH), 7.44-7.31 (10H, m, 2 × C_6H_5), 5.18 (1H, d, J = 8.2 Hz, CHNH), 5.04 (2H, s, CH_2Ph); ^{13}C NMR (75 MHz, DMSO-d_6) δ 172.0 (COOH), 155.8 (CONH), 137.3, 136.9, 128.4 (2C), 128.3 (2C), 127.9 (2C), 127.8, 127.7 (3C) (ArC's), 65.6 (CH_2Ph), 58.1 (CHNH).

(R)-N-Methyl-1-phenyl-2-1-(1-piperidinyl)ethanamine, (R)-MAPP ***(154)***[20]

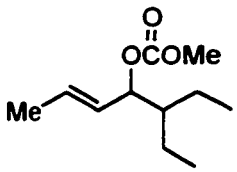
153 **154**

To a solution of (*R*)-*N*-carbobenzoxyphenylglycine (**152**, 9.9 g, 35 mmol) at -15°C in THF (100 mL) was added *N*-methylmorpholine (3.8 mL, 35 mmol) and isobutyl chloroformate (4.6 mL, 35 mmol). The reaction mixture was allowed to stir for 5 min before adding piperidine (3.4 mL, 34 mmol) in THF (10 mL). The reaction mixture was stirred for 1 h at -15°C and 4 h at RT to complete precipitation of the white solid. The reaction mixture was concentrated *in*

vacuo and dissolved in EtOAc (160 mL) and water (30 mL). The two-phase mixture was separated and the organic layer was washed with 1 M HCl (2 × 60 mL), water (30 mL), 5% $NaHCO_3$ solution (2 × 60 mL), water (60 mL) and brine (50 mL). The organic layer was dried with Na_2SO_4 and concentrated to form an oil. After trituration with hexanes, a white solid formed which was used without further purification. ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.41-7.26 (10H, m, 2 × $C_6\underline{H}_5$), 6.49 (1H, d, J = 7.4 Hz, N$\underline{H}$), 5.59 (1H, d, J = 7.4 Hz, C$\underline{H}$NH), 5.14 (1H, A of AB, d, J_{obs} = 12.3 Hz, C$\underline{H}_2$Ph), 5.01 (1H, B of AB, d, J_{obs} = 12.3 Hz, C$\underline{H}_2$Ph), 3.86-3.25 (4H, m, 2 × NC$\underline{H}_2$), 1.53-1.38 (6H, m, NCH$_2$(C$\underline{H}_2$)$_3$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 167.4 (CH$\underline{C}$ON), 155.3 (O$\underline{C}$ONH), 138.0, 136.3, 128.8 (2C), 128.2 (2C), 127.8 (3C), 127.6 (3C) (ArC's), 66.5 ($\underline{C}H_2$Ph), 55.4 ($\underline{C}$HNH), 46.2, 43.3 (2 × N$\underline{C}H_2$), 25.3, 25.1, 24.1 (($\underline{C}H_2$)$_3$CH$_2$N). Crude carbobenzoxyamide **152** (5.0 g, 14 mmol) was dissolved in THF (30 mL) and added dropwise to a suspension of $LiAlH_4$ (4.4 g, 116 mmol) in THF (40 mL) at 0°C. The suspension was refluxed for 12 h. The reaction mixture was cooled to 0°C, treated with THF (40 mL) and water (10 mL), followed by 15% NaOH solution (10 mL) and water (5 mL). The resulting suspension was filtered and the residue was washed with THF (25 mL). The filtrate and washings were combined and concentrated *in vacuo*. The resulting oil was dissolved in 1 M HCl (40 mL) and washed with Et_2O (2 × 50 mL). The aqueous layer was treated with 5 M KOH (until basic by pH paper) and extracted with Et_2O (2 × 50 mL). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*. The crude oil was distilled under vacuum pressure (118-119°C, 0.5 mmHg) to give 1.5 g (51%) of a clear, colourless oil. $[\alpha]_D$ = -105.8 (c = 2.1, $CHCl_3$), lit.: $[\alpha]_D$ = +109.1 (c = 1.88, $CHCl_3$, opposite enantiomer).[20] ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.34-7.23 (5H, m, $C_6\underline{H}_5$), 3.63 (1H, dd, J = 10.8, 3.6 Hz, C$\underline{H}$Ph), 2.55-2.22 (7H, m, N$\underline{H}$, 3 × NC$\underline{H}_2$), 2.29 (3H, s, NC$\underline{H}_3$), 1.62-1.40 (6H, m, NCH$_2$(C$\underline{H}_2$)$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.7, 128.2 (2C), 127.3 (2C), 126.9 (ArC's), 66.6 ($\underline{C}H_2$CH), 62.2 ($\underline{C}$HPh), 54.7 (2C, 2 × N$\underline{C}H_2$), 34.6 (N$\underline{C}H_3$), 26.1 (2C), 24.4 (($\underline{C}H_2$)$_3$CH$_2$N).

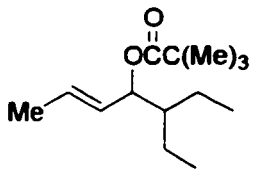
3.3.3 Kinetic Resolution Route: Substrate Syntheses

Methyl (E)-5-ethyl-2-hepten-4-yl carbonate (155)



n-Butyllithium (1.56 M, 9.0 mL, 14 mmol) was added slowly dropwise to a solution of (*E*)-5-ethyl-2-hepten-4-ol [**(±)-80**] (1.0 g, 7 mmol) in THF (70 mL) at -78°C. The reaction mixture was allowed to stir at -78°C for 30 min, after which time the temperature was raised to 0°C for 30 min. Dimethyl carbonate (1.2 mL, 43 mmol) was added and the reaction mixture was stirred for 0.5 h longer at 0°C, followed by 1.5 h at RT. The reaction was quenched with saturated NH_4Cl solution (50 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with brine (3 × 50 mL) and dried over $MgSO_4$. The solvent was removed *in vacuo* to afford 1.4 g (quantitative yield) of a crude product. The slightly yellow oil was used promptly (without purification) due to its instability. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.86 (1H, dq, J = 15.3, 6.5 Hz, =C<u>H</u>CH$_3$), 5.48 (1H, dd, J = 15.3, 8.0 Hz, =C<u>H</u>CH), 5.06 (1H, dd, J = 8.0, 5.4 Hz, C<u>H</u>OCO), 3.70 (3H, s, OC<u>H</u>$_3$), 1.73 (3H, d, J = 6.5 Hz, C<u>H</u>$_3$HC=), 1.56-1.15 (5H, m, C<u>H</u>(C<u>H</u>$_2$CH$_3$)$_2$), 0.85 (6H, m, 2 × C<u>H</u>$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.3 (<u>C</u>=O), 130.6, 127.3 (H<u>C</u>=<u>C</u>H), 81.2 (<u>C</u>HO), 54.4 (<u>C</u>H$_3$O), 37.7 (<u>C</u>HCH$_2$), 21.4 (2C, 2 × <u>C</u>H$_2$CH$_3$), 17.8 (<u>C</u>H$_3$HC=), 11.2, 11.1 (2 × <u>C</u>H$_3$CH$_2$).

(E)-5-Ethyl-2-hepten-4-yl pivalate (156)



Pivaloyl chloride (1.3 mL, 11 mmol) was added dropwise to a solution of alcohol **(±)-80** (1.5 g, 10 mmol) in pyridine (3 mL). After stirring at RT for 2 h, the reaction was deemed complete by TLC. Water (2 mL) was added and the reaction mixture was left to stir for 15 min. The reaction mixture was diluted with water (10 mL) and the product was extracted with

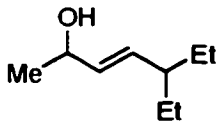
hexanes (4 × 20 mL). The organic extracts were washed with cold, dilute $CuSO_4$ (3 × 75 mL), saturated $NaHCO_3$ solution (2 × 75 mL) and brine (2 × 75 mL). The organic layer was dried over $MgSO_4$, after which the solvent was removed *in vacuo*. The crude oil was purified by column chromatography (15:1 hexanes:Et_2O) to afford 1.2 g (52% yield) of a clear, colourless oil. IR (neat) 2964, 2877, 1729 (C=O), 1674 (C=C), 1282, 1162, 966 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.65 (1H, dq, J = 15.2, 6.4 Hz, =C<u>H</u>CH$_3$), 5.38 (1H, dd, J = 15.2, 7.0 Hz, =C<u>H</u>CH), 4.95 (1H, dd, J = 7.0, 3.8 Hz, C<u>H</u>O), 1.71 (3H, d, J = 6.4 Hz, C<u>H</u>$_3$HC=), 1.39-1.27 (5H, m, C<u>H</u>(C<u>H</u>$_2$CH$_3$)$_2$), 1.20 (9H, s, (C<u>H</u>$_3$)$_3$C), 0.92 (6H, t, J = 7.0 Hz, 2 × C<u>H</u>$_3$CH$_2$); ^{13}C NMR (63 MHz, $CDCl_3$) δ 177.6 (<u>C</u>=O), 128.7, 128.1 (H<u>C</u>=<u>C</u>H), 75.8 (<u>C</u>HO), 45.1 (<u>C</u>H(CH$_2$CH$_3$)$_2$), 38.8 (<u>C</u>(CH$_3$)$_3$), 27.1 (3C, (<u>C</u>H$_3$)$_3$C), 21.9, 21.7 (2 × <u>C</u>H$_2$CH$_3$), 17.8 (<u>C</u>H$_3$HC=), 11.6, 11.2 (2 × <u>C</u>H$_3$CH$_2$); MS (EI) *m/z* (%) 226 (M^+, 0.1), 85 (42), 71 (30), 69 (30), 57 (100), 55 (26). Anal. Calcd for $C_{14}H_{26}O_2$: C, 74.29; H, 11.58. Found: C, 74.05; H, 11.70.

3.3.4 General Procedure A: Attempted Kinetic Resolution[20]

n-BuLi (1.2 equiv) was added dropwise to a solution of (*R*)-MAPP (**154**, 1.2 equiv) in Et_2O (7.5 mL/mmol chiral auxiliary) at -65°C. The resulting solution was stirred for 5 min at this temperature and then allowed to gradually warm to 0°C (flask 1). In a separate flask (flask 2), *n*-BuLi (1.0 equiv) was added dropwise to a slurry of the copper source (usually CuI, 1.0 equiv) and Et_2O (7.5 mL/mmol Cu source) at -78°C. The reaction mixture was allowed to warm to -50°C for 0.5 h. Flasks 1 and 2 were cooled to -35°C. The contents in flask 1 were added dropwise to flask 2 via cannula. After 10 to 15 min, the resulting solution was cooled to -78°C for 0.5 h. The desired substrate (2.0 equiv) in Et_2O (~1.0 mL/mmol substrate) was added dropwise to the reaction mixture. After 1 h at -78°C or warming to 0°C or RT (see section 3.2.1), the reaction mixture was hydrolyzed by adding 10% NH_4OH in NH_4Cl solution (10 mL/mmol chiral auxiliary) and warming to RT. The layers were separated and the aqueous phase was extracted with Et_2O (3 × V_{quench}). The combined organic phases were washed with 1 M HCl (2 × V_{quench}) to liberate the chiral auxiliary. (The acidic layer was retained, basified and extracted with Et_2O. The organic layer was concentrated *in vacuo* and

the crude (*R*)-MAPP was distilled for reuse.) The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The residue was purified via column chromatography. The enantiomeric excess of the product was determined by cleaving the double bond with ozone (oxidative work-up) and derivatizing the resulting carboxylic acid to a chiral amide (see Section 2.3.6 in Chapter 2).

(E)-5-Ethyl-3-hepten-2-ol (157)



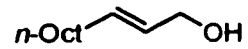
This compound was isolated from the attempted kinetic resolution (General Procedure A) of phosphate **(±)-89**. IR (neat) 3352 (br, OH), 2964, 2931, 2875, 1672 (C=C), 1458, 1379 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.53 (1H, dd, J = 15.5, 6.4 Hz, =C<u>H</u>CHOH), 5.38 (1H, dd, J = 15.5, 8.5 Hz, =C<u>H</u>CHEt$_2$), 4.31 (1H, dq, J = 6.4, 6.3 Hz, C<u>H</u>OH), 1.83-1.65 (1H, m, C<u>H</u>Et$_2$), 1.58-1.34 (4H, m, 2 × C<u>H</u>$_2$CH$_3$), 1.28 (3H, d, J = 6.3 Hz, C<u>H</u>$_3$CH), 1.24 (1H, br s, O<u>H</u>), 0.87-0.80 (6H, m, 2 × C<u>H</u>$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 134.4 (H<u>C</u>=<u>C</u>H), 69.0 (<u>C</u>HOH), 45.7 (<u>C</u>HEt$_2$), 27.4 (2C), 23.6 (<u>C</u>H$_3$CH, 2 × <u>C</u>H$_2$CH$_3$), 11.7 (2C, 2 × <u>C</u>H$_3$CH$_2$); MS (EI) *m*/z (%) 124 (M^+ - 18, 38), 109 (13), 95 (100), 82 (11), 81 (16), 79 (19), 77 (17), 71 (15), 69 (10), 68 (11), 67 (74), 55 (45), 53 (18).

Undec-2-yn-1-ol (159)[26]

n-BuLi (1.54 M, 24 mL, 36 mmol) was added dropwise (over 15 min) to a solution of 1-decyne (**158**, 6.5 mL, 36 mmol) in THF (150 mL) at -78°C. The resulting solution was stirred for 0.5 h. Paraformaldehyde (dried under vacuum overnight) (1.4 g, 47 mmol) was added in one portion and the reaction mixture was allowed to reach RT overnight. The reaction mixture was quenched with saturated NH_4Cl solution (50 mL) and extracted with Et_2O (2 × 75 mL). The combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the resulting oil was purified via Kugelrohr distillation under vacuum pressure (80-82°C, 0.5 mmHg) to afford 5.4 g (90%) of a clear, colourless oil. ^1H NMR (300 MHz, $CDCl_3$) δ 4.27-

4.24 (2H, dt, J = 6.1, 2.0 Hz, C$\underline{H}_2$OH), 2.21 (2H, tt, J = 7.0, 2.0 Hz, CH$_2$C$\underline{H}_2$C≡C), 1.53-1.47 (3H, m, O$\underline{H}$, C$\underline{H}_2$CH$_2$C≡C), 1.38-1.27 (10H, m, (C$\underline{H}_2$)$_5$CH$_3$), 0.88 (3H, t, J = 6.8 Hz, C$\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 82.3, 78.3 ($\underline{C}$≡$\underline{C}$), 51.1 ($\underline{C}$H$_2$OH), 31.8, 29.1, 29.0, 28.8, 28.5, 22.6 (($\underline{C}$H$_2$)$_6$CH$_3$), 18.6, 14.0 ($\underline{C}$H$_3$, CH$_2$$\underline{C}H_2$C≡).

(E)-2-Undecen-1-ol (160)[27]

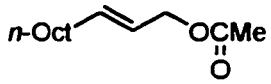


A solution of alkynol **159** (1.0 g, 6 mmol) in THF (7.5 mL) was added dropwise to a slurry of $LiAlH_4$ in THF (1.0 M, 6 mL, 6 mmol). The mixture was refluxed until the reaction was complete by TLC (~ 4 h). The mixture was cooled to -10°C and 2 M HCl was added dropwise until a granular salt precipitated. The reaction mixture was filtered and the precipitate was washed with hexanes (2 × 25 mL). The collective organic phases were washed with saturated $NaHCO_3$ solution (2 × 100 mL), brine (2 × 100 mL) and dried over Na_2SO_4. The starting material was removed from the desired compound by Kugelrohr distillation under aspirator pressure. There was 0.64 g (63%) of a clear, colourless oil remaining in the distillation flask. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.78-5.55 (2H, m, $\underline{H}$C=C$\underline{H}$), 4.09 (2H, dd, J = 4.9, 4.9 Hz, C$\underline{H}_2$OH), 2.06 (2H, dt, J = 6.2, 6.2 Hz, CH$_2$C$\underline{H}_2$HC=), 1.53-1.20 (13H, m, O$\underline{H}$, (C$\underline{H}_2$)$_6$CH$_3$), 0.88 (3H, t, J = 6.4 Hz, C$\underline{H}_3$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 133.2, 128.8 (H$\underline{C}$=$\underline{C}$H), 63.5 ($\underline{C}$H$_2$OH), 32.1, 31.8, 29.4, 29.2 (2C), 29.1, 22.6 (($\underline{C}$H$_2$)$_7$CH$_3$), 14.0 ($\underline{C}$H$_3$).

3.3.5 General Procedure B: Acetylation of Allylic Alcohols

Acetic anhydride (1.5 equiv) was added dropwise to the allylic alcohol (1.0 equiv), DMAP (0.10 equiv) and Et_3N (1.5 equiv) at RT. The reaction mixture was allowed to stir overnight. The resulting solution was diluted with Et_2O. The organic layer was washed with 1 M HCl (2×), saturated $NaHCO_3$ solution (3×) and brine (2×) and then dried over Na_2SO_4. The solvent was removed *in vacuo*.

(E)-2-Undecen-1-yl acetate (161)

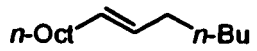


The reaction was performed using General Procedure B with alcohol **160**. The clear, pale yellow acetate was sufficiently pure and used without further purification (75% yield). IR (neat) 2927, 2856, 1744 (C=O), 1673 (C=C), 1462, 1231, 1025, 970, 735 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.77 (1H, dtt, J = 15.4, 6.7, 1.0 Hz, =C<u>H</u>$(CH_2)_2$), 5.56 (1H, dtt, J = 15.4, 6.4, 1.3, =C<u>H</u>CH_2O), 4.52 (2H, dd, J = 6.4, 1.0 Hz, C<u>H</u>$_2O$), 2.10-2.01 (2H, m, CH_2C<u>H</u>$_2HC$=), 2.06 (3H, s, C<u>H</u>$_3C$=O), 1.43-1.27 (12H, m, $CH_3(C$<u>H</u>$_2)_6$), 0.88 (3H, t, J = 6.7 Hz, C<u>H</u>$_3CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7 (<u>C</u>=O), 136.6, 123.6 (H<u>C</u>=<u>C</u>H), 65.2 (<u>C</u>H_2O), 32.2, 31.8, 29.4, 29.2, 29.1, 28.8, 22.6 ((<u>C</u>$H_2)_7CH_3$), 20.9 (<u>C</u>H_3C=O), 14.0 (<u>C</u>H_3CH_2); MS (EI) m/z 212 (M^+, 0.1), 96 (73), 82 (98), 81 (86), 67 (91), 55 (92), 54 (100). Anal. Calcd for $C_{13}H_{24}O_2$: C, 73.54; H, 11.39. Found: C, 73.70; H, 11.50.

3.3.6 General Procedure C: Asymmetric Cuprate Reaction

General Procedure 3.3.4 was followed, using 1.0 equiv of a prochiral substrate instead of 2.0 equiv of a racemic substrate. The enantiomeric excess of the product was determined by cleaving the double bond by ozonolysis with oxidative work-up and derivatizing the resulting carboxylic acids to diastereomeric amides (see Section 2.3.6 in Chapter 2).

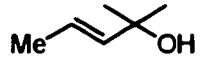
(E)-6-Pentadecene (α-162)[28]



The reaction was performed using General Procedure C with acetate **161**. The crude alkene was purified by column chromatography (100% hexanes) to afford a clear, colourless oil (50% yield). ^1H NMR (200 MHz, $CDCl_3$) δ 5.41-5.36 (2H, m, <u>H</u>C=C<u>H</u>), 2.05-1.95 (4H, m, 2 × =CHC<u>H</u>$_2$), 1.48-1.15 (18H, m, $CH_3(C$<u>H</u>$_2)_6CH_2HC$=$CHCH_2(C$<u>H</u>$_2)_3CH_3$), 0.88 (6H, m, 2 × <u>C</u>H_3); ^{13}C NMR (50 MHz, $CDCl_3$) δ 130.4 (2C, H<u>C</u>=<u>C</u>H), 32.6, 31.9, 31.4, 29.7, 29.5 (2C), 29.3, 29.2, 22.7 (2C), 22.6 ($CH_3(\underline{C}H_2)_7HC$=$CH(\underline{C}H_2)_4CH_3$), 14.1 (2C, 2 × <u>C</u>H_3).

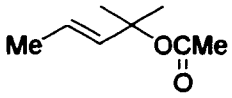
3.3.7 Achiral Substrate Syntheses

(E)-2-Methyl-3-penten-2-ol [(E)-164][29]



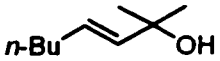
MeLi (1.4 M, 85 mL, 119 mmol) was added dropwise to a solution of ethyl crotonate (**163**, 5 mL, 40 mmol) in Et_2O (50 mL) at -10°C and the reaction mixture was allowed to stir until complete by TLC (~ 0.5 h). The reaction was quenched by adding 10% NH_4OH in NH_4Cl (75 mL) dropwise to the reaction mixture 0°C. The Et_2O and aqueous layers were separated and the aqueous layer was extracted with Et_2O (2 × 75 mL). The Et_2O was distilled away, leaving an oil that was purified by distillation under aspirator pressure (82-84°C, 24 torr) to give 1.9 g (48%) of a clear, colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71-5.59 (2H, m, H<u>C</u>=C<u>H</u>), 1.69 (3H, d, J = 4.8 Hz, C<u>H</u>$_3$HC=), 1.37 (1H, br s, O<u>H</u>), 1.30 (6H, s, (C<u>H</u>$_3$)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.1, 121.6 (H<u>C</u>=<u>C</u>H), 70.4 (<u>C</u>OH), 29.5 (2C, (<u>C</u>H$_3$)$_2$C), 17.4 (<u>C</u>H$_3$HC=).

(E)-2-Methyl-3-penten-2-yl acetate [(E)-165]



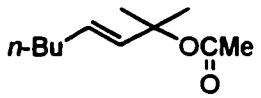
The reaction was performed using General Procedure B with alcohol (***E***)-**164**. The crude acetate was purified by distillation under aspirator pressure to afford a clear, colourless oil (69% yield). IR (neat) 2928, 2961, 2872, 1739 (C=O), 1676 (C=C), 1369, 1243 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.74 (1H, dq, J = 15.7, 1.3 Hz, =C<u>H</u>C), 5.65 (1H, dq, J = 15.7, 6.1 Hz, =C<u>H</u>CH$_3$), 1.97 (3H, s, C<u>H</u>$_3$C=O), 1.69 (3H, dd, J = 6.1, 1.3 Hz, <u>C</u>H$_3$HC=), 1.50 (6H, s, (C<u>H</u>$_3$)$_2$C); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.8 (<u>C</u>=O), 135.2, 127.3 (H<u>C</u>=<u>C</u>H), 80.3 (<u>C</u>(CH$_3$)$_2$), 26.6 (2C, (<u>C</u>H$_3$)$_2$C), 22.1 (<u>C</u>H$_3$C=O), 17.5 (<u>C</u>H$_3$HC=); MS (EI) *m/z* 142 (M$^+$, 0.5), 85 (55), 83 (30), 82 (57), 67 (100), 59 (11), 55 (32), 53 (12). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.40; H, 9.71.

(E)-2-Methyl-3-octen-2-ol [(E)-167][30]



A solution of 1-hexyne (**166**, 16 mL, 0.14 mol) in hexanes (30 mL) was treated with DIBAL (1.0 M, 145 mL, 0.15 mmol) dropwise, while maintaining the reaction temperature between 25 and 30°C (water bath). The solution was stirred for 0.5 h, after which time it was heated to 50°C for 4 h. The reaction mixture was cooled to -20°C and acetone (11 mL, 0.15 mmol) in hexanes (50 mL) was added dropwise. The reaction mixture was allowed to warm to RT and stir at this temperature for 1 h. The reaction mixture was poured into ice water (~200 mL), acidified with 6 M HCl and extracted with Et_2O (3 × 200 mL). The combined Et_2O extracts were washed with 5% sodium bicarbonate solution (2 × 200 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo*. The crude oil was distilled under aspirator pressure (160-164°C, 24 torr) to afford 10 g (52%) of a clear, colourless oil. IR (neat) 3368 (br, OH), 2962, 2861, 1669 (C=C), 1466, 1377, 1149 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.63-5.59 (2H, m, HC=CH), 2.03-1.97, (2H, m, CH_2HC=), 1.57-1.31 (5H, m, OH, $(CH_2)_2CH_3$), 1.31 (6H, s, $(CH_3)_2C$), 0.99-0.86 (3H, m, CH_3CH_2); ^{13}C NMR (50 MHz, $CDCl_3$) δ 137.8, 127.0 (HC=CH), 70.5 (COH), 31.7 (CH_2HC=), 31.4, 29.7 (2C), 22.1 ($(CH_2)_2CH_3$, $(CH_3)_2C$), 13.8 (CH_3CH_2).

(E)-2-Methyl-3-octen-2-yl acetate [(E)-168]



The reaction was performed using General Procedure B with alcohol **(*E*)-167**. The crude acetate was purified by distillation under aspirator pressure to afford a clear, colourless oil (71% yield). IR (neat) 2959, 2930, 2874, 1737 (C=O), 1665 (C=C), 1367, 1251, 1136, 1017 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.76 (1H, d, J = 15.7 Hz, =CHC), 5.61 (1H, dt, J = 15.7, 6.5 Hz, $=CHCH_2$), 2.25-2.00 (2H, m, CH_2HC=), 1.98 (3H, s, CH_3CO), 1.51 (6H, s, $(CH_3)_2C$), 1.48-1.27 (4H, m, $(CH_2)_2CH_3$), 0.90 (3H, t, J = 6.9 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 (C=O), 134.1, 129.2 (HC=CH), 80.4 ($C(CH_3)_2$), 31.8 (CH_2HC=), 31.2, 26.8 (2C), 22.2 ($(CH_2)_2CH_3$, $(CH_3)_2C$), 22.0 (CH_3C=O), 13.8 (CH_3CH_2); MS (EI) *m/z* 184 (M^+, 0.5), 127 (38),

95 (37), 85 (100), 71 (25), 69 (49), 67 (36). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.81; H, 10.84.

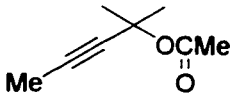
2-Methyl-3-pentyn-2-ol (170)[31]

Cerium (III) chloride heptahydrate ($CeCl_3 \cdot 7H_2O$, 12 g, 31 mmol) was weighed into a 3-neck flask (flask 1) equipped with a syringe inlet, argon inlet and dropping funnel. The reagent was dried by heating the flask in an oil bath under high vacuum pressure. The temperature was slowly increased from RT to 70°C (1 h), 70 to 120°C (4 h) and 120 to 140°C (2 h). The drying was continued at 140°C for 2 h. The flask was cooled to RT under argon, after which time THF (20 mL) was added. A second 3-neck flask (flask 2) equipped with an argon inlet, syringe inlet and dropping funnel was flame dried under vacuum and flushed with argon. (*Z*)/(*E*)-1-Bromopropene (2.6 mL, 30 mmol) and THF (20 mL) were added to the flask and the solution was cooled to -78°C. *n*-BuLi (1.56 M, 45 mmol) was added dropwise via the dropping funnel to this solution over a period of 10 min. The resulting milky mixture was stirred at -78°C for an additional 2 h. In flask 1, the $CeCl_3$-THF suspension was cooled to -78°C and the cold propynyllithium solution from flask 2 was added quickly to the stirred suspension via cannula. The resulting mixture was stirred for 1 h at -78°C, after which time acetone (1.5 mL, 20 mmol) in THF (100 mL) was added via the dropping funnel. The reaction mixture was stirred for 1 h at -78°C before allowing it to warm to RT. Saturated NH_4Cl solution (20 mL) was added to the reaction mixture and the product was extracted with Et_2O (3 × 60 mL). The organic layer was washed with brine (2 × 100 mL) and dried over Na_2SO_4. The ethereal layer was concentrated *in vacuo* to afford an oil that was purified via distillation under aspirator pressure to afford 1.0 g (50% yield) of a clear, yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.86 (1H, br s, O<u>H</u>), 1.82 (3H, s, <u>C</u>H$_3$C≡), 1.49 (6H, s, (<u>C</u>H$_3$)$_2$C); ^{13}C NMR (50 MHz, $CDCl_3$) δ 84.2, 78.0 (<u>C</u>≡<u>C</u>), 65.3 (<u>C</u>OH), 31.7 (2C, (<u>C</u>H$_3$)$_2$C), 3.4 (<u>C</u>H$_3$C≡).

2-Methyl-3-octyn-2-ol (172)[32]

A similar preparation was followed as previously described for undec-2-yn-1-ol (**159**), replacing 1-decyne with 1-hexyne and paraformaldehyde with acetone. The crude compound was purified by vacuum distillation (40-42°C, 0.5 mmHg) to provide a clear, colourless oil (74% yield). ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.18 (2H, t, J = 6.9 Hz, C$\underline{H}_2$C≡C), 1.81 (1H, br s, O$\underline{H}$), 1.49 (6H, s, (C$\underline{H}_3$)$_2$C), 1.48-1.37 (4H, m, (C$\underline{H}_2$)$_2$CH$_3$), 0.91 (3H, t, J = 7.1 Hz, C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 85.1, 81.8 ($\underline{C}$≡$\underline{C}$), 64.8 ($\underline{C}$OH), 31.4 (2C), 30.5, 21.6 (($\underline{C}$H$_2$)$_2$CH$_3$, ($\underline{C}$H$_3$)$_2$C), 18.0 ($\underline{C}$H$_2$C≡C), 13.3 ($\underline{C}$H$_3$CH$_2$).

2-Methyl-3-pentyn-2-yl acetate (173)



The reaction was performed using General Procedure B with alkynol **170**. The crude acetate was purified by distillation under aspirator pressure to afford a clear, colourless oil (56% yield). IR (neat) 2988, 2939, 2924, 2250 (C≡C), 1745 (C=O), 1368, 1269, 1245, 1137 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.01 (3H, s, C$\underline{H}_3$C=O), 1.84 (3H, s, C$\underline{H}_3$C≡), 1.63 (6H, s, (C$\underline{H}_3$)$_2$C); ^{13}C NMR (50 MHz, $CDCl_3$) δ 169.5 ($\underline{C}$=O), 80.4, 80.1 ($\underline{C}$≡$\underline{C}$), 72.5 ($\underline{C}$(CH$_3$)$_2$), 29.2 (2C), 22.1 ($\underline{C}$H$_3$C=O, ($\underline{C}$H$_3$)$_2$C), 3.6 ($\underline{C}$H$_3$C≡); MS (EI) *m/z* 140 (M$^+$, 8), 98 (70), 83 (100), 81 (53), 79 (52). Anal. Calcd for $C_8H_{12}O_2$: C, 68.55; H, 8.63. Found: C, 68.37; H, 8.48.

2-Methyl-3-octyn-2-yl acetate (174)

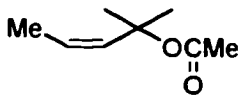
The reaction was performed using General Procedure B with alkynol **172**. The crude acetate was purified by column chromatography (20:1 hexanes:Et$_2$O) to afford a clear, colourless oil (80% yield). IR (neat) 2987, 2960, 2933, 2874, 2250 (C≡C), 1745 (C=O), 1467, 1367, 1265, 1244, 1135, 734 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 2.20 (2H, t, J = 6.9 Hz, C$\underline{H}_2$C≡), 2.01 (3H, s, C$\underline{H}_3$C=O), 1.63 (6H, s, (C$\underline{H}_3$)$_2$C), 1.50-1.27 (4H, m, (C$\underline{H}_2$)$_2$CH$_3$), 0.90 (3H, t, J = 7.2

Hz, C<u>H</u>$_3$CH$_2$);^{13}C NMR (75 MHz, $CDCl_3$) δ 169.2 (<u>C</u>=O), 84.4, 81.2 (<u>C</u>≡<u>C</u>), 72.4 (<u>C</u>(CH$_3$)$_2$), 30.5, 29.2 (2C), 21.9 ((<u>C</u>H$_2$)$_2$CH$_3$, (<u>C</u>H$_3$)$_2$C), 21.7, 18.2 (<u>C</u>H$_2$C≡C, CH$_3$<u>C</u>=O), 13.4 (<u>C</u>H$_3$CH$_2$); MS (EI) *m*/z 182 (M$^+$, 0.4), 140 (38), 125 (48), 98 (66), 83 (100), 79 (52). Anal. Calcd for $C_{11}H_{18}O_2$: C, 72.49; H, 9.95. Found: C, 72.33; H, 9.71.

3.3.8 General Procedure D: Hydrogenation of Alkynes to (Z)-Alkenes

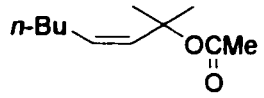
The alcohol (1.0 equiv), Lindlar catalyst[22,23] (0.1 equiv, 5% Pd on $CaCO_3$, Pb poisoning) and hexanes or pentane (~25 mL/g alcohol) were placed in a two-neck flask equipped with a three-way stopcock and two-way stopcock. The flask was evacuated (aspirator pressure) and flushed with argon several times using the three-way stopcock. The argon line was replaced with a hydrogen balloon and the system was evacuated and flushed with hydrogen, as previously described with argon. The reaction mixture was allowed to stir at ambient temperature until the reaction was complete (confirmed by TLC). The system was evacuated and the balloon was replaced with an argon line. The system was flushed with argon (3×). The catalyst was filtered from the reaction mixture through Celite and filter paper.

(Z)-2-Methyl-3-penten-2-yl acetate [(Z)-165]



The reaction was performed using General Procedure D with alkyne **173** and pentane. The clear, colourless alkene was sufficiently pure and used without further purification (87% yield). IR (neat) 2981, 2938, 1732 (C=O), 1446, 1368, 1256, 1145, 915, 734 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.61 (1H, dq, J = 11.7, 1.2 Hz, =C<u>H</u>C), 5.35 (1H, dq, J = 11.7, 6.8 Hz, =C<u>H</u>CH$_3$), 2.01 (3H, s, C<u>H</u>$_3$C=O), 1.74 (3H, dd, J = 6.8, 1.2 Hz, C<u>H</u>$_3$HC=), 1.55 (6H, s, (C<u>H</u>$_3$)$_2$C);^{13}C NMR (75 MHz, $CDCl_3$) δ 169.5 (<u>C</u>=O), 134.4, 124.6 (H<u>C</u>=<u>C</u>H), 80.0 (<u>C</u>(CH$_3$)$_2$), 27.9 (2C), 21.7 (<u>C</u>H$_3$C=O, (<u>C</u>H$_3$)$_2$C), 13.7 (<u>C</u>H$_3$HC=); MS (EI) *m*/z 142 (M$^+$, 0.2), 85 (100), 82 (53), 67 (82), 55 (54). Anal. Calcd for $C_8H_{14}O_2$: C, 67.57; H, 9.92. Found: C, 67.29; H, 9.86.

(Z)-2-Methyl-3-octen-2-yl acetate [(Z)-168]

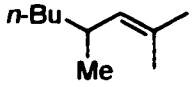


The reaction was performed using General Procedure D with alkyne **173** and hexanes. The clear, colourless alkene was sufficiently pure and used without further purification (65% yield). IR (neat) 3960, 2929, 2873, 2861, 1739 (C=O), 1655 (C=C), 1468, 1366, 1256, 1145, 915, 735 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 5.58 (1H, dt, J = 11.8, 1.5 Hz, =C<u>H</u>C), 5.35 (1H, dt, J = 11.8, 7.5 Hz, =C<u>H</u>CH_2), 2.20-2.01 (2H, m, C<u>H</u>$_2$HC=), 1.99 (3H, s, C<u>H</u>$_3$C=O), 1.54 (6H, s, (C<u>H</u>$_3$)$_2$C), 1.40-1.24 (4H, m, (C<u>H</u>$_2$)$_2$$CH_3$), 0.95 (3H, t, J = 6.8 Hz, C<u>H</u>$_3$$CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.4 (<u>C</u>=O), 133.2, 130.9 (H<u>C</u>=<u>C</u>H), 79.9 (<u>C</u>(CH$_3$)$_2$), 31.8, 28.1 (2C), 27.8, 22.5, 21.8 (<u>C</u>H$_3$C=O, (<u>C</u>H$_3$)$_2$C, (<u>C</u>H$_2$)$_3$CH$_3$), 13.9 (<u>C</u>H$_3$CH$_2$); MS (EI) *m/z* 184 (M^+, 0.8), 95 (56), 85 (100), 68 (40), 67 (51). Anal. Calcd for $C_{11}H_{20}O_2$: C, 71.70; H, 10.94. Found: C, 71.51; H, 10.70.

3.3.9 General Procedure E: Reactions with RCuCNLi

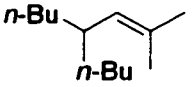
CuCN (1.2 equiv) was added to a flask and the system was evacuated and flushed with argon. Et_2O (20 mL/g CuCN) was added and the slurry was cooled to -78°C. *n*-BuLi (1.0 equiv) was added dropwise down the side of the flask. The reaction mixture was stirred at this temperature for ~5 min and then warmed slowly until most of the CuCN had dissolved. The system was recooled to -78°C before the dropwise addition of the acetate (1.0 equiv) in Et_2O (5 mL/g substrate). The reaction stirred at -78°C for 2 h, after which time it was allowed to warm to RT overnight. The reaction was quenched with 10% NH_4OH in saturated NH_4Cl (100 mL/g CuCN). The aqueous layer was extracted with Et_2O (3×). The combined organic layers were dried over Na_2SO_4 and concentrated *in vacuo*.

2,4-Dimethyl-2-octene (175)



The reaction was performed using General Procedure E with acetate **(*E*)-** or **(*Z*)-165**. The crude alkenes were purified via column chromatography (100% hexanes) to afford clear, colourless oils (26 or 29%, respectively). IR (neat) 2960, 2963, 2860, 1672 (C=C), 1452, 1378, 1114, 909, 737 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.86 (1H, dqq, J = 9.4, 1.3, 1.3 Hz, =C<u>H</u>), 2.31-2.26 (1H, m, C<u>H</u>HC=), 1.68 (3H, d, J = 1.3 Hz, C<u>H</u>$_3$C=), 1.60 (3H, d, J = 1.3 Hz, C<u>H</u>$_3$C=), 1.30-1.14 (6H, m, (C<u>H</u>$_2$)$_3$CH$_3$), 0.98-0.85 (6H, m, C<u>H</u>$_3$CH$_2$, C<u>H</u>$_3$CH); ^{13}C NMR (50 MHz, $CDCl_3$) δ 131.7 (=<u>C</u>), 129.5 (=<u>C</u>H), 37.6, 32.4, 29.8, 25.7, 22.9, 21.3 (<u>C</u>H$_3$<u>C</u>H, (<u>C</u>H$_2$)$_3$CH$_3$, <u>C</u>H$_3$C=), 15.3, 14.1 (<u>C</u>H$_3$CH$_2$, <u>C</u>H$_3$C=); MS (EI) *m/z* 140 (M^+, 15), 83 (100), 69 (19), 67 (7), 55 (44). Anal. Calcd for $C_{10}H_{20}$: C, 85.63; H, 14.37. Found: C, 85.89; H, 14.49.

4-Butyl-2-methyl-2-octene (176)



The reaction was performed using General Procedure E with acetate **(*E*)-** or **(*Z*)-168**. The crude alkenes were purified via column chromatography (100% hexanes) to afford clear, colourless oils (31 or 36%, respectively). IR (neat) 2925, 2857, 1674 (C=C), 1466, 1377, 850 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 4.83 (1H, dqq, J = 9.8, 1.0, 0.8 Hz, =C<u>H</u>), 2.15-2.10 (1H, m, C<u>H</u>*n*-Bu), 1.70 (3H, d, J = 0.8 Hz, C<u>H</u>$_3$C=), 1.59 (3H, d, J = 1.0 Hz, C<u>H</u>$_3$C=), 1.38-1.08 (12H, m, 2 × (C<u>H</u>$_2$)$_3$CH$_3$), 0.99-0.84 (6H, m, 2 × <u>C</u>H$_3$CH$_2$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 130.6 (=<u>C</u>), 130.3 (=<u>C</u>H), 37.9 (<u>C</u>HHC=), 36.0 (2C), 29.7 (2C), 23.0 (2C), 25.9 (2 × (<u>C</u>H$_2$)$_3$CH$_3$, <u>C</u>H$_3$C=), 18.2 (<u>C</u>H$_3$C=), 14.2 (2C, 2 × <u>C</u>H$_3$CH$_2$); MS (EI) *m/z* 182 (M^+, 9), 125 (32), 83 (18), 69 (100), 55 (17). Anal. Calcd for $C_{13}H_{26}$: C, 85.63; H, 14.37. Found: C, 85.64; H, 14.51.

3.4 References

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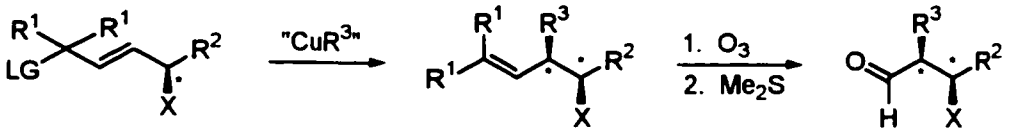
CHAPTER 4

1,2-INDUCTION IN δ-OXY-SUBSTITUTED ALLYLIC SYSTEMS

4.1 Introduction

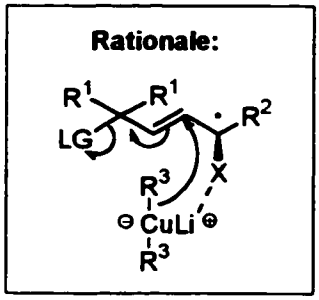
The last and most successful route to α-chiral aldehydes involved the use of δ-oxy-substituents to introduce chirality to the system (Scheme 63). Initially, we proposed to design substrates such as **177**, where X was a group that could coordinate to the incoming nucleophile. We hoped that this coordination would influence both the regio- and facial selectivity of the reaction. If an enantiomerically-enriched substrate were used, an alkene with two contiguous chiral centers would be generated. The resulting alkene **178** could be cleaved to form α,β-chiral aldehyde **179**. If X were bound to the allylic substrate via an oxygen atom, aldehyde **179** would be an aldol product, which is a highly desirable synthon in organic chemistry.[1]

Scheme 63



177 **178** **179**

LG = leaving group



Some of the results of this study have recently been published in *The Journal of Organic Chemistry*.[2]

4.1.1 Substituent-Directed Chemical Reactions

Substituents within a molecule often control the regio- and stereochemical outcomes of reactions. These substituents can impose steric hindrance, leading the incoming reagent to attack the more accessible side of the substrate. Alternatively, the added reagent can preassociate with the substituent, leading to *syn*-facial selectivity. The latter situation often occurs when metallic reagents react with substrates equipped with polar, oxygen-containing substituents.[3]

4.1.1.1 Reactions of α-Chiral Carbonyl Compounds with Organometallic Reagents

1,2-Induction commonly occurs when organometallic reagents react with α-chiral carbonyl compounds. Many models were developed to explain the typically high diastereoselectivities achieved during these transformations, the most important being the Cram chelation[4] and Felkin-Anh[5,6] models (Figure 17).[7]

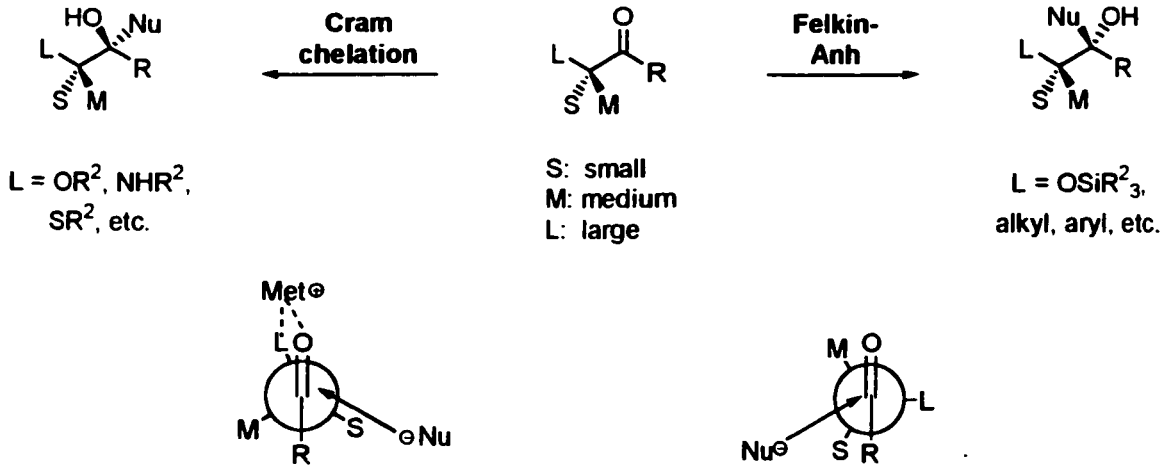


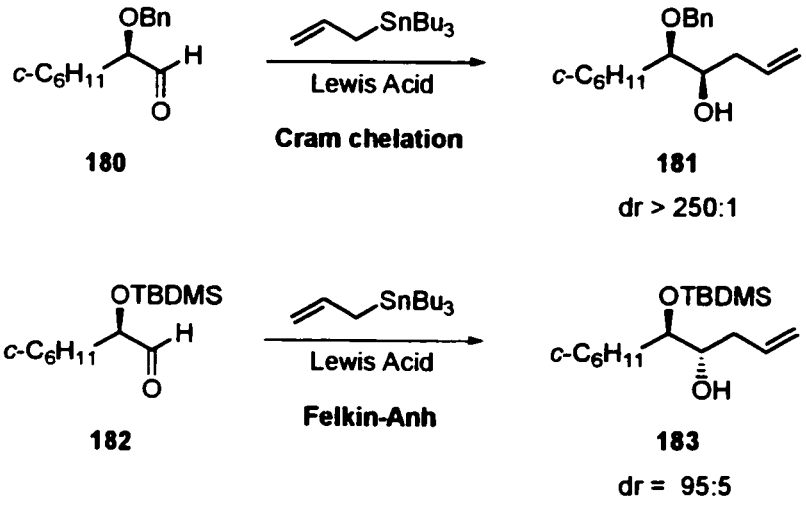
Figure 17. Comparing Cram chelation[4] and Felkin-Anh[5,6] models.

When L is an alkoxy, amino or a thiol group, coordination can occur between it, a metal cation (Met^+) and the carbonyl oxygen (Cram chelation). However, when L is a non-

coordinating group, such as silyloxy, alkyl or aryl, no coordination occurs and the Felkin-Anh product is formed preferentially.[7] High diastereoselectivities are possible under both reaction conditions.[7]

For example, benzyloxy groups often exhibit coordination with metal groups. When α-substituted aldehyde **180** was reacted with allyltributyltin in the presence of a Lewis acid, *syn* product **181** was formed preferentially (Scheme 64). The substrate reacted primarily through a Cram chelation conformation. However, when benzyl was replaced with *tert*-butyldimethylsilyl (TBDMS), a sterically bulky, typically non-coordinating group, the facial selectivity of the reaction was reversed.[8]

Scheme 64



180 **181** dr > 250:1

182 **183** dr = 95:5

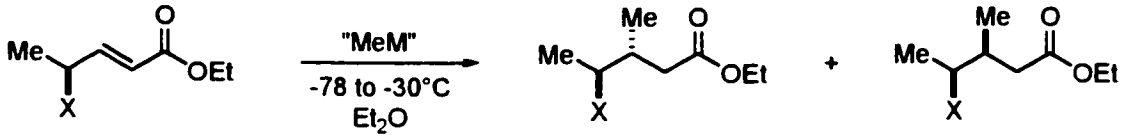
4.1.1.2 Michael Additions to γ-Alkoxy-α,β-Unsaturated Carbonyl Compounds

As discussed in Section 3.1.2, S_N2' reactions with allylic substrates are, in theory, quite similar to Michael additions to α,β-unsaturated carbonyl compounds.[9] In S_N2' reactions, however, issues such as geometrical isomerization and choice of leaving group must also be addressed.[10]

Many groups have studied Michael additions with γ-oxy-α,β-unsaturated carbonyl compounds and found that the stereochemical outcomes were not governed by coordination between the cuprate and the γ-substituent.[11,12,13,14] For example, when Yamamoto *et al.* reacted

α,β-unsaturated esters **184** and **185** with cuprate reagents, both substrates reacted with *anti*-facial selectivity (Scheme 65).[14] These results implied that coordination was not important in determining the facial selectivity of the reaction.[14]

Scheme 65



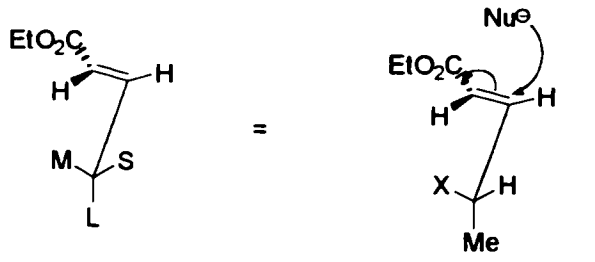
184: X = OBn
185: X = OTBDMS

***anti*-186-187**

***syn*-186-187**

Product	X	"RM"	*anti*:*syn*	Yield (%)
186	OBn	$RCuCNLi{\cdot}BF_3$	95:5	62
187	OTBDMS	$R_2CuLi{\cdot}LiCN{\cdot}BF_3$	92:8	55

The stereochemical outcomes of these reactions are often rationalized by a modified Felkin-Anh model, in which the γ-oxy-group takes the role of M (Figure 18).[7]



X = OBn, OTBDMS

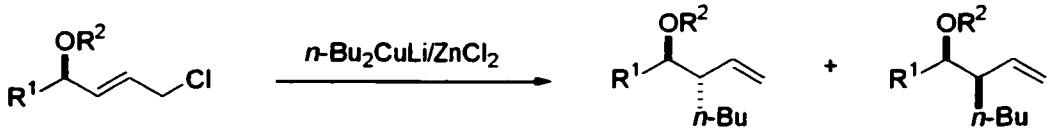
Figure 18. Possible Felkin-Anh conformation explaining *anti*-facial selectivity.[7]

4.1.1.3 Reactions with Allylic Substrates

After searching the literature, we found that one group had performed similar experiments between δ-oxy-substituted allylic substrates and zinc-modified cuprates.[10,15] Nakamura and coworkers concentrated on the addition of *n*-Bu reagents to allylic substrate

188 (Table 10). A few other experiments were run involving (*Z*)-substrates and different leaving groups.[10]

Table 10. S_N2' reactions with δ-oxy-allylic chlorides.



188 ***anti*-189** ***syn*-189**

Entry	R^1	R^2	γ-Regio (%)[a]	*anti*-de (%)	Yield (%)
1	Me	MOM	98	30	79
2	*n*-Pent	MOM	99	50	73
3	*i*-Pr	Bn	98	100	100
4[b]	*i*-Pr	Bn	98	80	100
5[c]	*i*-Pr	Bn	53	100	nr[d]
6	*i*-Pr	MOM	99	100	67
7	*i*-Pr	TIPS	98	100	93
8	*c*-Hex	MOM	99	100	86
9	*t*-Bu	MOM	99	100	79
10[b]	*t*-Bu	MOM	99	20	37

[a] γ-Regio = regioselectivity for the γ-isomer.
[b] The (*Z*)-substrate was used.
[c] Cl was replaced by Br.
[d] nr = not reported.

There were many interesting observations made during this study. The γ-regioselectivities were typically ≥98%, except when the leaving group was changed from Cl to Br (entry 5). The highest diastereoselectivities occurred when R^1 was sterically bulky (entries 3, 5-9) and the diastereoselectivity was independent of the coordinating ability of the R^2 substituent (entry 7). The (*Z*)-substrates gave similar γ-regioselectivities, but depressed diastereoselectivities (entries 4, 10), as compared to the results with the (*E*)-analogues.

Nakamura's group had laid the groundwork for an exciting new field of study. It was our task to further investigate the scope of these reactions.

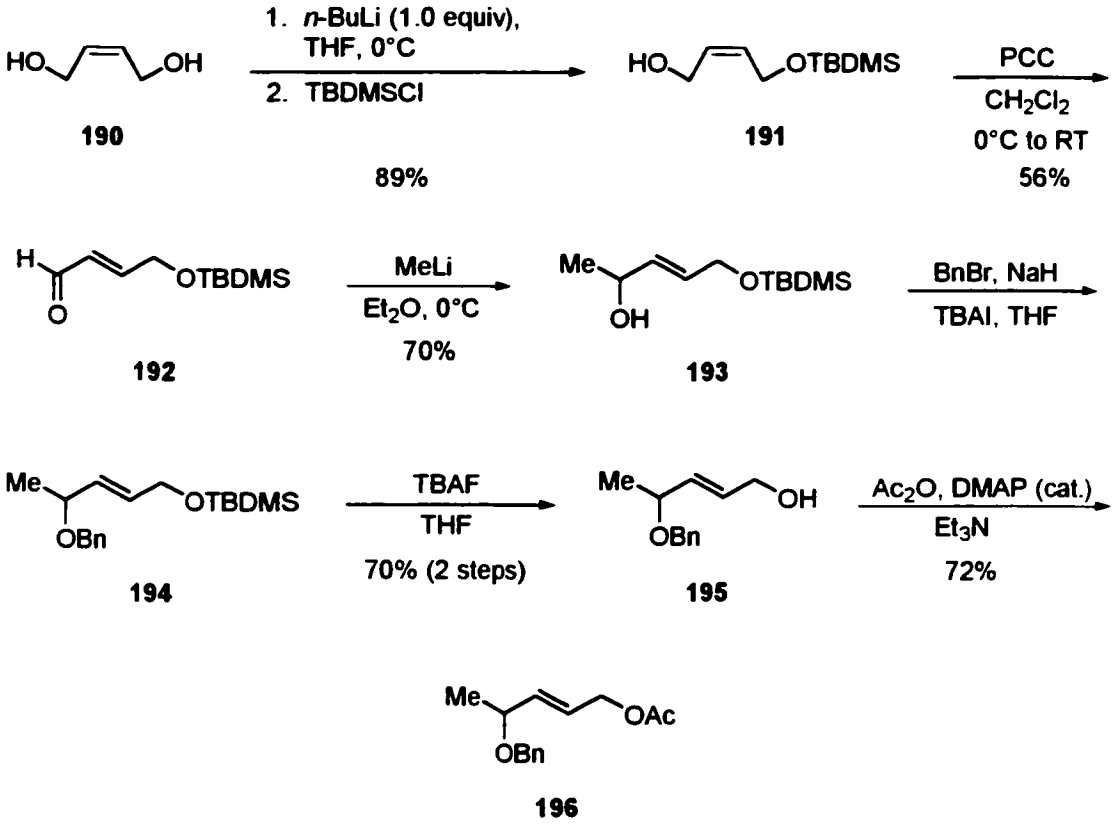
4.2 Results and Discussion

4.2.1 Substrate Design and Synthesis

For our first investigations, we chose to look at substrates such as **196** (Scheme 66), since benzyl groups had proven to be effective 1,2-inducting groups by Nakamura *et al.*[10] We also knew from our previous experience that acetates were easy to synthesize and purify, as well as reactive to a variety of cuprate reagents.

In the first step of the reaction sequence, *cis*-2-butene-1,4-diol was singly deprotonated with *n*-BuLi and trapped with *tert*-butyldimethylsilyl chloride to form monosilyl ether **191**. Pyridinium chlorochromate (PCC) was used in the next step to oxidize the primary alcohol and isomerize the *cis*-double bond to the *trans*-configuration. α,β-Unsaturated aldehyde **192** was reacted with MeLi to form an alcohol that was benzylated under standard conditions. The silyl protecting group was removed with tetrabutylammonium fluoride (TBAF), leaving the primary alcohol which was acetylated with acetic anhydride.

Scheme 66



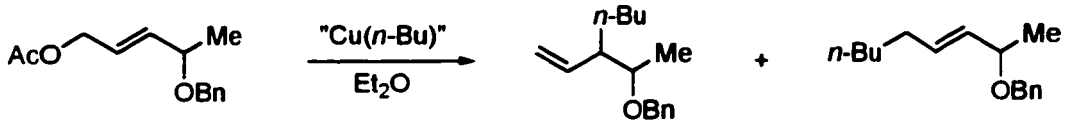
4.2.2 Preliminary Results and Subsequent Substrate Modification

The initial coupling results with acetate **196** are shown in Table 11. After analyzing the product from the first reaction, we were disappointed to find that the (*E*)-double bond was still intact, indicating that only the α-alkene was formed (entry 1).

At this point, we moved away from lithium cuprate chemistry and changed our focus to copper-catalyzed Grignard reactions. When the reaction was run with CuI, three peaks appeared on the GC/MS spectrum that exhibited the same molecular ion peak. From our first reaction, we knew that one of the peaks was the α-product, which left the other two as the diastereomers of the desired product. The regioselectivity of the reaction, therefore, was determined to be 40%. The GC/MS analysis also revealed that the diastereomers of the γ-product were separable and that the diastereoselectivity of the reaction was 37%.

When the copper source was changed to CuCN, the γ-regioselectivity jumped to 96% and the recovered alkene had a de of 50%. ^{1}H NMR analysis clearly showed that the γ-product had been formed, since there were two groups of protons in the alkene region in a ratio of 1:2 (RC<u>H</u>=C<u>H</u>$_2$, respectively).

Table 11. Preliminary copper coupling results.



196 **γ-197** **α-197**

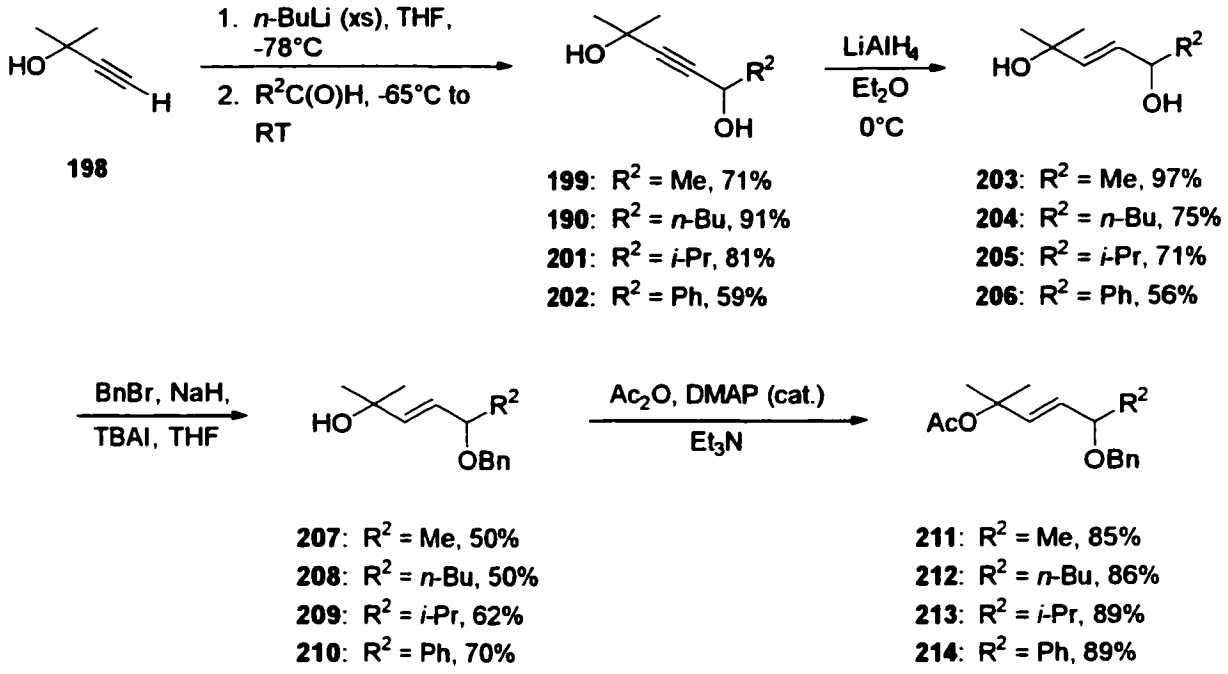
Entry[a]	Copper Species		γ-Regio[b] (%)	γ de (%)[c]	Yield (%)[d]
1	R_2CuLi		0	-	21
2	RMgBr	CuI	40	37	49
3		CuCN	96	50	54

[a] Entry 1 was performed with 2.0 equiv of reagent; entries 2-3 employed 2.0 equiv of *n*-BuMgBr with 10 mol% CuX.
[b] γ-Regio = regioselectivity for the γ-regioisomer.
[c] Determined by GC/MS of crude products.
[d] Percentage isolated yields of chromatographed products. The regioisomers were inseparable by column chromatography.

From the preliminary results we hypothesized that obtaining the γ-regioisomer preferentially during reactions with primary acetates would always be problematic. Accordingly, we modified the substrate to promote γ-attack. We believed that installing two methyl groups at the site bearing the leaving group would deter α-attack. Under this assumption, a number of different alkynols were synthesized with varying degrees of branching at R^2 (Scheme 67). Each synthesis began by a double deprotonation of 2-methyl-3-butyn-2-ol (**198**) with an excess of *n*-BuLi. The sp anion was trapped with a number of different aldehydes to form the alkynediols shown. The triple bonds were preferentially reduced to the (*E*)-double bonds via directed $LiAlH_4$ reactions and the resulting secondary alcohols were preferentially benzylated under standard conditions. This reaction posed problems for substrates with bulky R^2 groups. In these cases, the tertiary alcohols were also benzylated, leading to mixtures of benzyl ethers that were extremely difficult to separate via column chromatography. By using only a slight excess of benzyl bromide, the secondary

benzyl ethers were favoured; however, the yields suffered as a result. The final step of the reaction sequence involved acetylation of the tertiary allylic alcohol with acetic anhydride.

Scheme 67



198

199: R^2 = Me, 71%
190: R^2 = *n*-Bu, 91%
201: R^2 = *i*-Pr, 81%
202: R^2 = Ph, 59%

203: R^2 = Me, 97%
204: R^2 = *n*-Bu, 75%
205: R^2 = *i*-Pr, 71%
206: R^2 = Ph, 56%

207: R^2 = Me, 50%
208: R^2 = *n*-Bu, 50%
209: R^2 = *i*-Pr, 62%
210: R^2 = Ph, 70%

211: R^2 = Me, 85%
212: R^2 = *n*-Bu, 86%
213: R^2 = *i*-Pr, 89%
214: R^2 = Ph, 89%

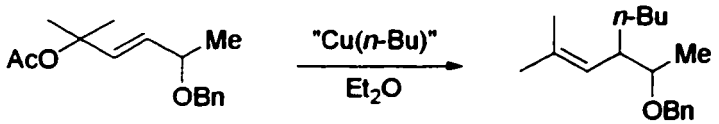
4.2.3 Regiochemical Control

Allylic acetate **211** was used as an initial probe substrate in a number of copper-mediated reactions (Table 12). Our initial goal to control regioselectivity was achieved with this substrate, as only the γ-regioisomer was isolated in each case.

With the cyanocuprate, the de of alkene **215** was only 15%, which was determined by GC/MS. Analysis of the ^{1}H NMR spectrum revealed two doublets in the alkene region in a ratio of approximately 60:40, confirming that diastereomeric γ-products had been formed.

The substrate was initially unreactive to the lower order cuprate, but by adding LiI, the desired alkene was formed with moderate selectivity (52%). The best result, however, came by reacting the substrate with a Grignard reagent in the presence of a catalytic amount of CuCN. We felt that this result was extremely promising; hence, we looked for other ways to improve the stereoselectivity of the reaction.

Table 12. Copper-mediated reactions with acetate **211**.



211 **215**

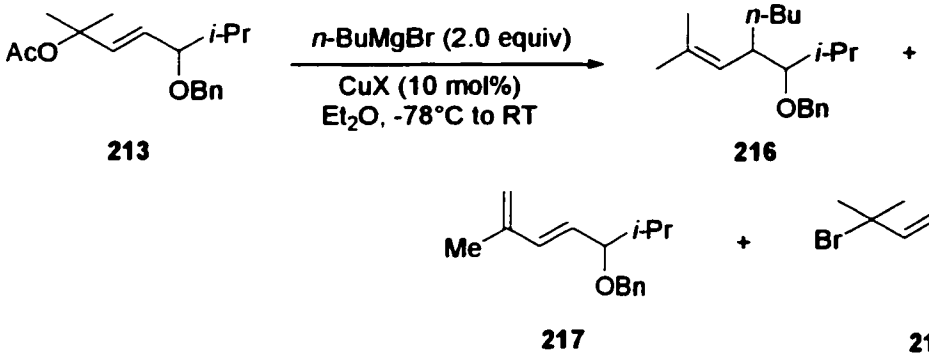
Entry[a]	Copper Species	de (%)[b]	Yield (%)[c]
1	RCuCNLi	15	42
2[d]	R_2CuLi	-	0
3	R_2CuLi + LiI	52	40
4	RMgBr + CuCN (cat.)	72	72

[a] Entries 1-3 were performed with 2.0 equiv of cuprate reagent; entry 4 employed 2.0 equiv of *n*-BuMgBr with 10 mol% CuCN
[b] Determined by GC/MS of crude products.
[c] Percentage isolated yields of chromatographed products.
[d] Only starting material and alcohols from acetate cleavage were recovered.

Taking note of Nakamura's results,[10] we decided to react our *i*-Pr-substituted substrate with *n*-BuMgBr in the presence of different copper catalysts (Table 13). His group had previously shown that higher de's were achieved when there was steric bulk at the site bearing the oxy-substituent.[10] With CuI and $CuBr{\cdot}SMe_2$ catalysis, the de's achieved were moderate; however, the yields were quite low.

We were confident that the first compounds isolated from the chromatographic separation were the desired γ-substituted alkenes. The ^1H NMR spectrum showed two proton doublets at δ 5.16 (major signal) and δ 4.89 (minor signal), which we assigned to the alkene protons on the diastereomeric γ-substituted compounds (see **216**). Since we were curious as to the reasons for the poor yield, we decided to identify the other products in the reaction mixture.

Table 13. Copper-catalyzed Grignard reactions with acetate **213**.



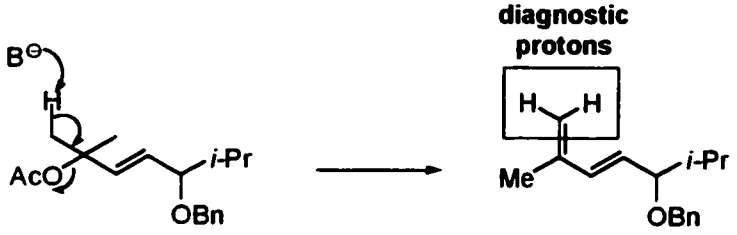
213 **216** **217** **218**

Entry	CuX	γ de (%)[a]	γ Yield (%)[b]
1	CuI	57	37
2	CuBr·SMe_2	69	12
3	CuCN	97	80

[a] Determined by GC/MS of crude products.
[b] Percentage isolated yields of chromatographed products.

The first side product analyzed was very difficult to purify, which made its identification particularly challenging. The ^{1}H NMR spectrum revealed a broad singlet integrating for two protons at approximately δ 5, a signal characteristic of a vinylidene group ($\underline{H}_2C{=}CR^1R^2$, Scheme 68). With this tip, we were able to discern the rest of the signals corresponding to elimination product **217**. We proposed that a basic cuprate species (B^-) was generated, which abstracted a proton from one of the geminal methyl groups. We were doubtful that excess Grignard reagent was responsible for this product, since these reagents typically give 1,2-addition products when reacting with carbonyl compounds.

Scheme 68

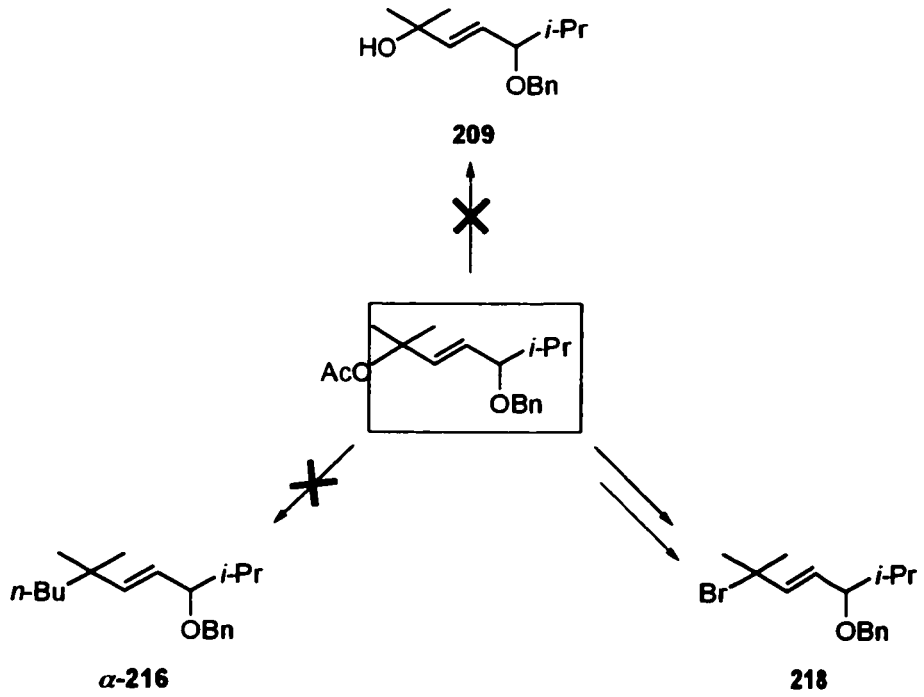


213 **217**

At a first glance, the other isolated product appeared to be alcohol **209**, the precursor to acetate **213**, since the ^{1}H NMR spectrum showed the same distinctive *trans*-double bond

coupling pattern (Scheme 69). After closer inspection, however, we realized that the alkene proton shifts were quite different. According to the ^{1}H NMR spectrum of the unknown compound, the backbone of the starting material was still intact (see box, Scheme 69). Consequently, the change in functionality must have occurred at the quaternary center. There was no evidence for any added protons, which ruled out formation of **α-216** (Scheme 69). The only aprotic nucleophiles present in the reaction mixture were halogens from the copper source and Grignard reagent. Since the same product was formed with CuI and CuBr·SMe_2 catalysis, the bromide from the Grignard reagent must be the nucleophile. From this information, we proposed that this side product was bromide **218**. The structure appeared to be confirmed by the ^{13}C NMR spectral data, in which the quaternary carbon appeared at δ 41.0.[16] It is not obvious how **218** was formed under these reaction conditions.

Scheme 69



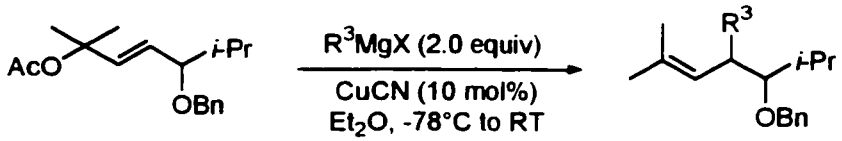
When the copper source was changed to CuCN, the yield of the desired product increased dramatically (entry 3, Table 13), with very little evidence of other side products. We were also pleased to find that the diastereoselectivity of this reaction was extremely high at 97%. These results differ markedly from those observed with copper halide catalysts. The CN

group must modify the cuprate species formed, either as a bound ligand or as a counter ion, to effect these positive changes.

4.2.3.1 Alkyl and Phenyl Group Addition

We tested the utility of the reaction with other Grignard reagents (Table 14). When adding primary methyl, ethyl and *n*-butyl groups, the products were formed with consistently high diastereoselectivities in good to excellent yields. In addition, both secondary and tertiary groups were added with similar results. These observations were a vast improvement over our previous attempts of *t*-Bu addition to our phosphate ester systems, when substantial facial scrambling occurred.[17]

Table 14. Effect of Grignard structure.



213 **216, 219-222**

Entry	Alkene	R^3	de (%)[a]	Yield (%)[b]
1	**219**	Me	96	77
2	**220**	Et	98	84
3	**216**	*n*-Bu	97	80
4	**221**	*i*-Pr	98	76
5	**222**	*t*-Bu	>98[c]	94

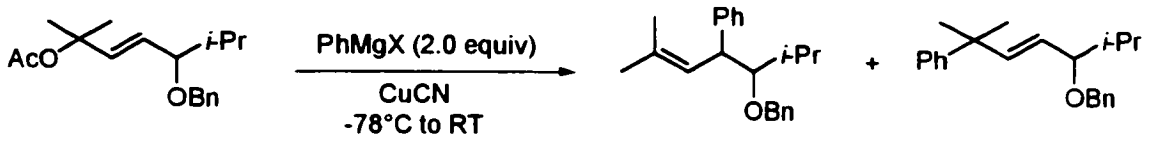
[a] Determined by GC/MS of crude products.
[b] Percentage isolated yields of chromatographed products.
[c] The second diastereomer was not visible by GC/MS and ^{1}H NMR spectroscopy.

Having tried a number of alkyl additions, we turned our attention to aryl group addition. Unfortunately, good results were much more difficult to achieve with this Grignard reagent (Table 15). Starting with our optimal reaction conditions and PhMgCl as the Grignard reagent, alkene **α-223** was recovered as the major product. By changing the solvent to THF, the yield of the desired product remained dismally low, but the yield of the α-product jumped

to 86%. It appears that α-product formation is enhanced in coordinating solvents, such as THF.

By replacing PhMgCl in THF with PhMgBr in Et_2O, we found improved results, although the yield of the γ-product was still quite low. Again, under these conditions (entry 3) we detected elimination product **217**. We also recovered quite a lot of biphenyl. From these results we hypothesized that the desired cuprate was not forming, possibly due to the lower reactivity of the Ph Grignard reagent. To ensure complete cuprate formation, we increased the amount of copper cyanide catalyst from 10 to 50 mol%. With this modification, the yield of the γ-product became synthetically useful at 75%. The diastereoselectivity of the recovered alkene was also extremely high (entry 4).

Table 15. Ph group addition to acetate **213**.



213 **γ-223** **α-223**

Entry	X	Solvent	mol % CuCN	γ de (%)[a]	γ Yield (%)[b]	α Yield (%)[b]
1	Cl	Et_2O	10	>98	6	54
2		THF	10	>98	8	86
3	Br	Et_2O	10	97	32	14
4			50	>98	75	trace

[a] Determined by GC/MS of crude products.
[b] Percentage isolated yields of chromatographed products.

4.2.3.2 Leaving Group Effects

A number of different substrates were synthesized from allylic alcohol **209** (Scheme 70) to determine the role of the leaving group in the copper-catalyzed reactions.

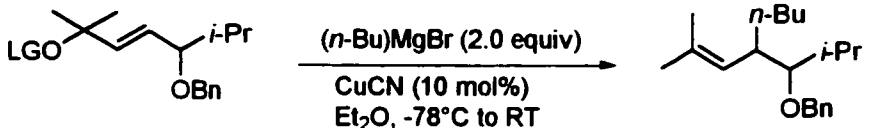
Scheme 70

209

224: LG = Piv, 42%
225: LG = CF_3CO, 84%
226: LG = PhNHCO, 60%

With these new substrates, the diastereoselectivities of the copper-coupling reactions were consistently high, regardless of the identity of the leaving group (Table 16). The yields of all of the transformations were reasonable. Fortuitously, the best overall results were achieved with acetate as the leaving group (entry 4).

Table 16. The role of the leaving group.



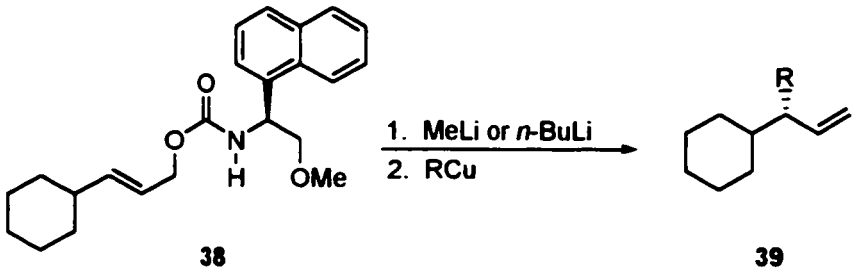
213, 224-226 **216**

Entry	LG	de (%)[a]	Yield (%)[b]
1	Piv	97	72
2	PhNHCO	92	60
3	CF_3CO	98	64
4	Ac	97	80

[a] Determined by GC/MS of crude products.
[b] Percentage isolated yields of chromatographed products.

It was interesting to note that the same major diastereomer was recovered in every case. It is well documented that leaving groups with ionizable protons, such as a carbamate (entry 2, Table 16), coordinate to incoming nucleophiles as the deprotonated species, effectively dictating the face of attack.[18,19] Most recently, Denmark and coworkers demonstrated this phenomenon with acyclic, allylic substrates (Scheme 71).[20]

Scheme 71



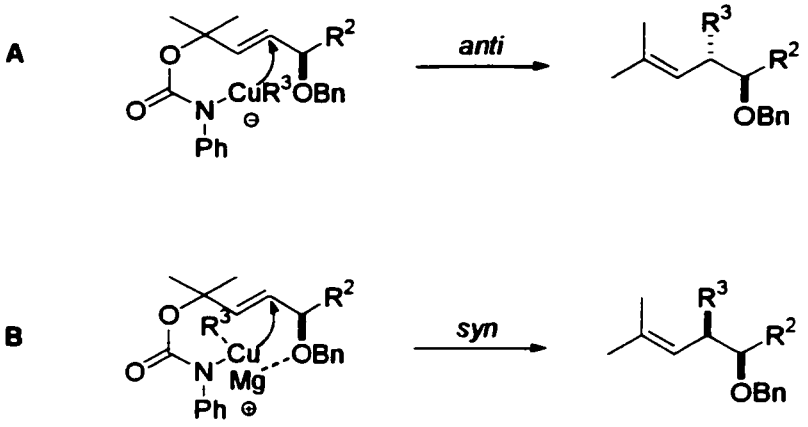
38 **39**

R = Me, 95%ee
R = *n*-Bu, 88%ee
R = Ph, 91%ee

The high level of stereoselectivity achieved in these reactions was attributed to the involvement of a mixed cuprate species formed from the carbamate and the organocopper reagent.[19]

From these results, we expected some coordination to occur between the phenyl carbamate and incoming nucleophile. This coordination could either enhance or diminish the observed facial selectivity, depending upon the role of the benzyloxy group (Scheme 72). For example, if the benzyloxy group behaved as a simple steric block, coordination between the leaving group and the cuprate could enhance the *anti*-facial selectivity. The carbamate would "guide" the reagent to add to the face opposite the δ-oxy substituent (**A**). If the benzyloxy group was a coordinating group, two possible outcomes could arise. The two coordinating groups could work in conjunction with each other to promote *syn*-facial selectivity (**B**). Alternatively, the amide and benzyloxy sites could compete for coordination to the nucleophile, leading to decreased *syn*-facial selectivity.

Scheme 72



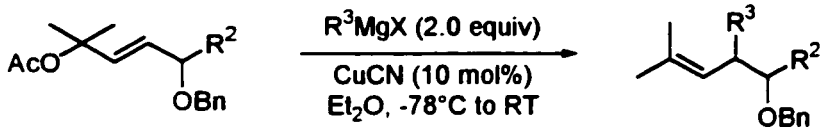
There was a small drop in diastereoselectivity with this leaving group suggesting that a competing mechanism may be at work. Perhaps the steric hindrance from the geminal methyl groups prevented effective coordination between the leaving group and the incoming nucleophile.

4.2.3.3 R^2 Effects

To probe the mechanism of these transformations, we ran a series of Grignard reactions with a number of different allylic acetates. The diastereomeric excesses for the product alkenes are shown in Table 17. The R^2 groups are listed in order of increasing steric bulk.

Diastereoselectivities of ≥96% were achieved for all additions to the *i*-Pr substrate. Similar results were obtained with a phenyl group as R^2. These results are similar to those previously obtained by Nakamura's group in which the highest diastereoselectivities resulted with a bulky group on the site bearing the oxy-substituent (see Table 10).[10] With our systems, the diastereoselectivities appeared to be directly proportional to the size of R^2. Within the results for each substrate, the diastereoselectivities did not vary greatly with the structure of the Grignard reagent. It was interesting to note, however, that the products of *i*-Pr additions (Group 3) consistently exhibited lower diastereomeric excesses than their congeners.

Table 17. Substrate structural effects.



211-214 **215, 216, 219, 221-223, 227-240**

Group	R^3	R^2, de (%)[a]			
		Me	*n*-Bu	*i*-Pr	Ph
1	Me	56	76	96	86[b]
2	*n*-Bu	72	80	97	>98[c]
3	*i*-Pr	48	58	97	94
4	*t*-Bu	66	74	>98[c]	>98[c]
5[d]	Ph	58[b]	76[b]	>98[c]	>98[c]

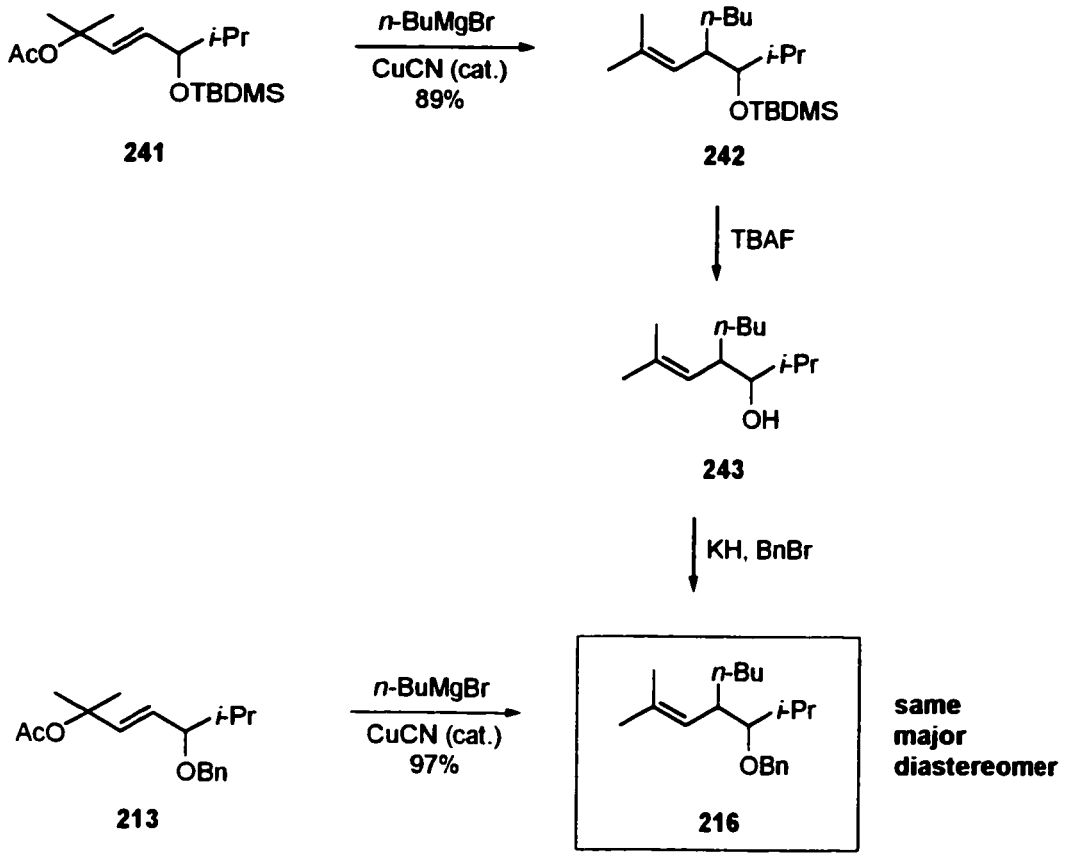
[a] Determined by GC/MS of crude products unless otherwise noted; see experimental section for yields.
[b] Determined by ^{1}H NMR spectroscopy.
[c] The second diastereomer was not visible by GC/MS and ^{1}H NMR spectroscopy.
[d] Reactions employed 50 mol% CuCN.

4.2.4 Facial Selectivity Determination

Perhaps the most important factor to determine was the role of the protecting group in the reaction. Initially, we envisioned the group coordinating to the incoming nucleophile to facilitate control of both the regio- and stereoselectivity of the reaction. Was coordination actually occurring between the substrate and the cuprate or would our results mirror those previously obtained by Nakamura and coworkers?[10]

As mentioned in the introduction, benzyl ethers typically coordinate to metal cations, whereas silyl ethers do not.[8] We planned to use this information to our advantage. We synthesized the OTBDMS analogue of benzyloxy-substituted acetate **213** and repeated the copper-catalyzed *n*-BuMgBr reaction (Scheme 73). The facial selectivity of the copper-coupling reaction was still relatively high at 89%. The TBDMS group was removed from alkene **242** using TBAF. The substrate was further transformed to the benzyl ether by reaction with potassium hydride (KH) and benzyl bromide (BnBr). When we looked at the ^{1}H NMR spectrum and GC/MS data of this compound, we discovered that the same major diastereomer had been formed in both cases. This observation suggested that no coordination was occurring between the incoming nucleophile and the protecting group.

Scheme 73



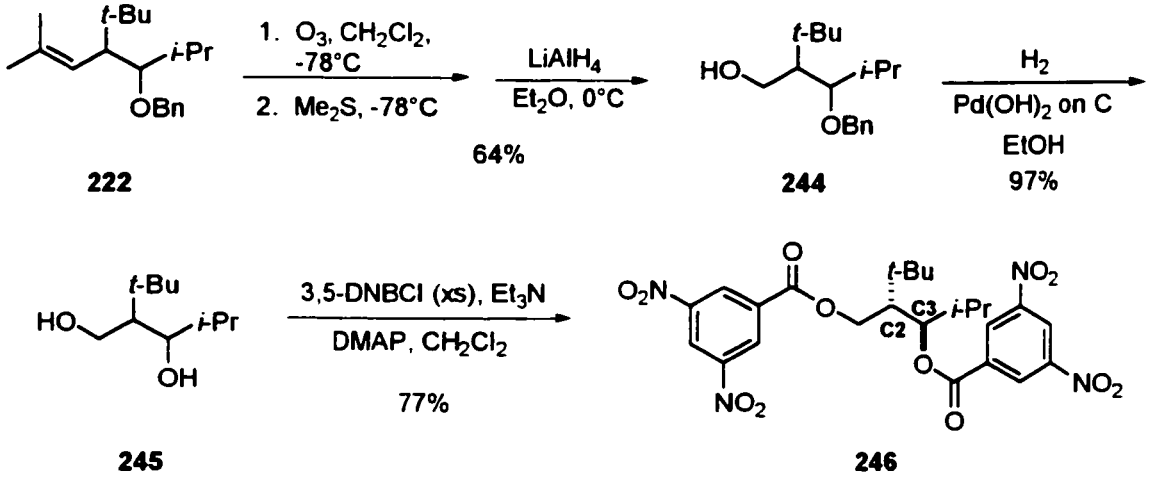
4.2.4.1 X-Ray Crystallographic Analysis

To confirm the suspicion that the protecting group and introduced group were *anti* to each other, we needed more data. We decided to use x-ray crystallography, a technique that is commonly used to determine the relative or absolute configurations of compounds.

Since the majority of our alkenes were oils, we needed to modify them to form crystalline solids. The best de was obtained when forming alkene **222**; so, this compound was chosen for transformation and stereochemical analysis (Scheme 74). The double bond was cleaved with ozone and the resulting ozonide was reacted with Me_2S to form the aldehyde. The isolated carbonyl compound was immediately reduced with $LiAlH_4$ to form alcohol **244**.

The benzyl group was removed via reaction with hydrogen in the presence of Pearlman's catalyst and the product diol was treated with excess 3,5-dinitrobenzoyl chloride (3,5-DNBCl) in the presence of TEA, DMAP and CH_2Cl_2 to form derivative **246**. After recrystallization from Et_2O/hexanes, a crystal structure of diester **246** was obtained. The x-ray crystallography data (see Appendix) confirmed an *anti*-relationship between the groups at C2 and C3.

Scheme 74

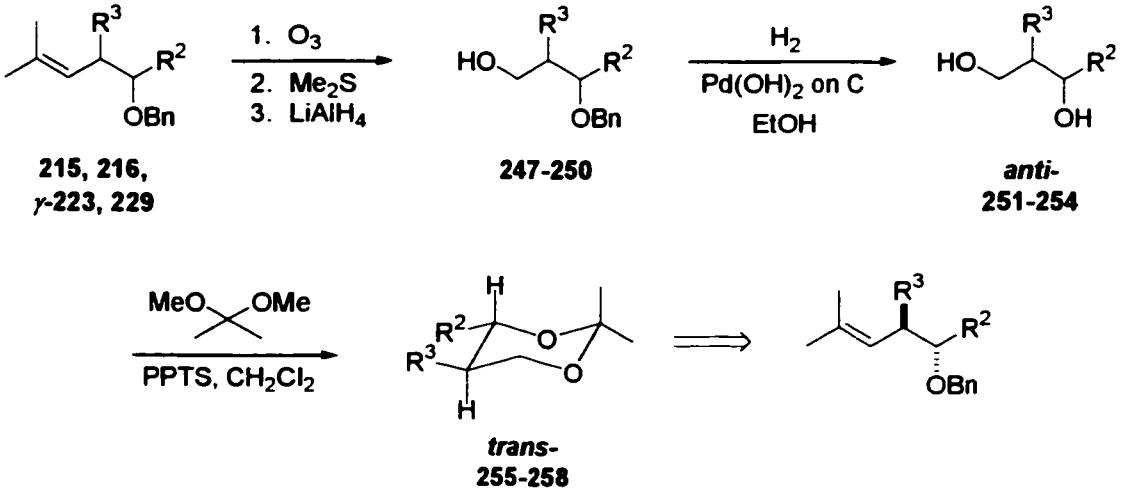


4.2.4.2 ^{1}H NMR Analysis of Cyclic Acetals

Since it was not feasible to obtain x-ray crystallography data for a derivative of each of the alkenes formed, we looked for an easier and more accessible method to determine the relationship between the two groups (Scheme 75). The alkenes were transformed to the diols as described previously. From these diols, 1,3-dioxanes ***trans*-255-258** were formed by reaction with 2,2-dimethoxypropane in the presence of catalytic pyridinium *p*-toluenesulfonate (PPTS) and the resulting species were analyzed via ^{1}H NMR spectroscopy.[21,22,23] The diagnostic portion of a sample spectrum is shown in Figure 19. H_a is showing a large geminal coupling with H_b and a smaller ax-eq coupling with H_d. H_b exhibits large couplings with H_a (geminal) and H_d (ax-ax). H_c exhibits a large ax-ax coupling with H_d and a smaller coupling with the methine proton from the *i*-Pr group. These results unequivocally show the *anti*

relationship between *n*-Bu and OBn groups in the original compound.[21,22,23] All of the other 1,3-dioxanes produced similar spectra (see Section 4.3.7).

Scheme 75



215, 216, *γ*-223, 229

247-250

***anti*-251-254**

***trans*-255-258**

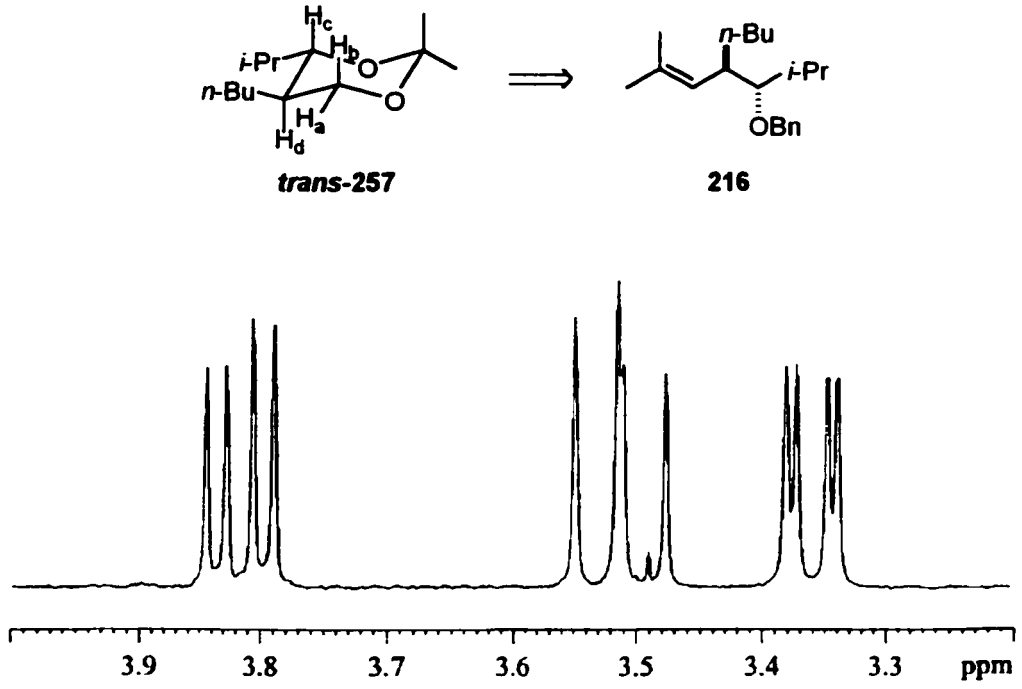


Figure 19. Diagnostic protons (H_a, H_b and H_c, respectively) from ^1H NMR spectrum of 1,3-dioxane ***trans*-257**.

Not every alkene was converted to the cyclic acetal for stereochemical analysis. We have analyzed a selection of products with different R^2 and R^3 groups and found that an *anti*-relative configuration prevailed in every case. For the compounds that were not derivatized for relative configuration analysis, we are confident in our *anti* assignment because of trends observed in the ^1H NMR spectra and GC/MS elution profiles. For all of the alkenes formed, the major vinyl proton doublet appeared 0.10-0.35 ppm downfield of the corresponding minor signal. On the GC traces, the major diastereomers always eluted before the minor components on a DB-5 column.

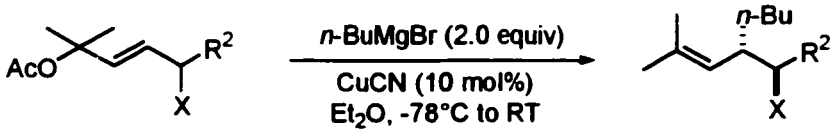
4.2.4.3 Protecting Group Probe

We tested the methoxymethoxy- and *tert*-butyldimethylsilyloxy-substituted allylic acetates with our reaction conditions. The methoxymethoxy group, another known metal coordinator,[24] was the main δ-oxy-substituent used in Nakamura's studies.[10]

With the *n*-Bu substrate, the diastereoselectivities were moderate for the TBDMS and MOM protecting groups and good for the Bn case. With the *i*-Pr group in place, the diastereoselectivities with the OMOM and OBn groups were more consistent with each other, with the OTBDMS substrate exhibiting a lower result. In each case, the *anti*-diastereomers were recovered as the major products, again indicating that coordination was not occurring between the δ-oxy-substituent and the incoming nucleophile.

The reasons for the differences in selectivities observed for the *n*-Bu analogues are unclear. Perhaps the OMOM group, with two sites of coordination, reacts partially through complexation in the less rigid *n*-Bu substrate. Unfortunately, this rationale does not apply to the OTBDMS analogue. Our theory on the depressed selectivities observed with this substrate will be discussed in Section 4.2.5.

Table 18. δ-Oxy-substituent probe.



212, 213, 241, 259-261 → **216, 232, 242, 262-264**

Group	R^2	X, de (%)[a] OBn	OTBDMS	OMOM
1	*n*-Bu	80	61	65
2	*i*-Pr	97	89	95

[a] Determined by GC/MS of crude products; see experimental section for yields.

4.2.5 Mechanistic Interpretation

In developing a mechanistic model for this reaction, it was useful to summarize our results from the previous sections.

1. The best results were achieved using a Grignard reagent in the presence of CuCN (cat.).
2. The highest de's and yields were consistently obtained, regardless of Grignard structure, with R^2 equal to *i*-Pr or Ph. The selectivity and yield increased consistently with increasing size of R^2 for all of the Gringard-cuprates used.
3. The identities of the leaving and protecting groups did not play a major role in determining the selectivity of the reaction.

These observations correlate nicely with a proposed mechanism recently discussed by Mengel and Reiser (Figure 20).[7] According to this mechanism, the reactive conformation would be similar to a Felkin-Anh conformation assumed by α-substituted aldehydes in which the α-groups are non-coordinating. In the adapted model, X would take the role of the medium-sized group (M) and R^2 would assume the role of the large group (L). The nucleophile (Nu^-) would attack from the side opposite to the anchor group (R^2) on the substrate. According to the model, the difference in size between X and R^2 would be extremely important in determining the facial selectivity of the reaction. Our results agree well with the prediction, as the highest de's were achieved with R^2 equal to *i*-Pr and Ph.

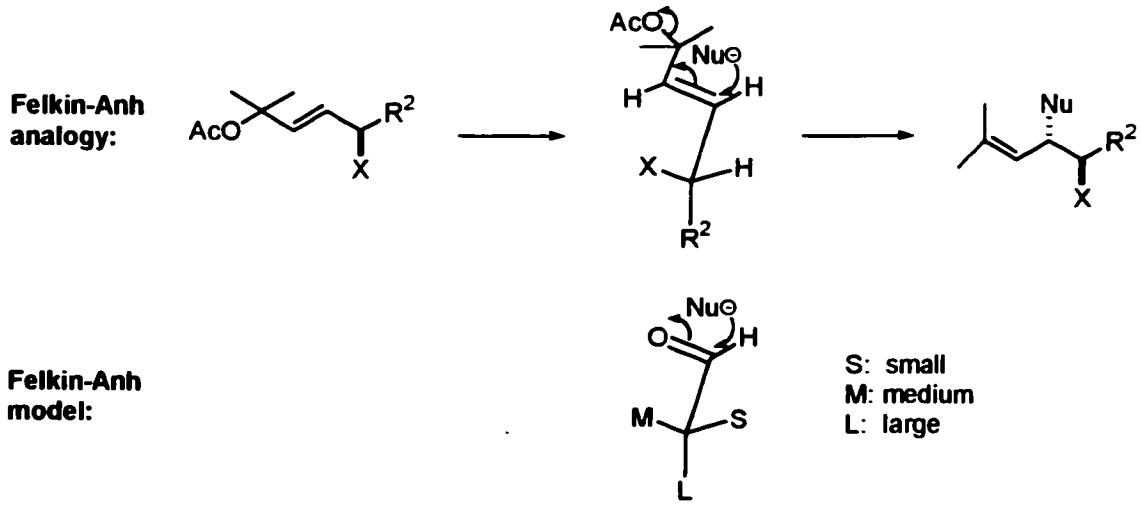


Figure 20. Possible Felkin-Anh-type conformation responsible for observed *anti*-facial selectivity.[7]

Since the groups are placed according to size in this model, the decreased facial selectivities observed with the OTBDMS-substituted allylic substrates become understandable. This group is quite bulky, which could increase the chance of it being recognized as the L group, especially with a small *n*-Bu group as R^2. This alternative reactive conformation would lead to increased formation of the *syn*-diastereomer.

4.2.6 Reactions with Enantiomerically-Enriched Substrates

To further explore the utility of our method, we ran a number of reactions with enantiomerically-enriched substrates. Carreira and coworkers have recently developed a method for forming non-racemic alkynols.[25] Chirality is introduced to the system via a complex formed between (1*S*, 2*R*)-*N*-methylephedrine (**265**), zinc triflate ($Zn(OTf)_2$) and triethylamine (Scheme 76).[25] For our desired substrate, the authors performed the reaction on a very small scale (~50 mg substrate).[25,26] We required a larger amount of compound; so, we increased the scale of the reaction considerably. We found that the ee of the formed alkynediol was inversely proportional to the scale of the reaction run. After much experimenting with addition and mixing times, the best enantiomeric excess achieved was 87%. Nonetheless, we had an enantiomerically-enriched substrate with which to measure the stereochemical efficiency of our cuprate coupling reaction.

After alkynediol **(*R*)-201** was formed, it was transformed to acetate **(*R*)-213** as described previously (see Scheme 67). Having this substrate in hand, we performed coupling reactions with different copper-modified Grignard reagents. The product alkenes were transformed to the alcohols to facilitate enantiomeric excess determination via chiral HPLC (Scheme 76). It is apparent from the results that the enantiomeric purity of the acetates was retained during the copper-catalyzed Grignard reactions (Table 19). These results were expected, as no reaction actually occurs at the site bearing the OBn group.

Scheme 76

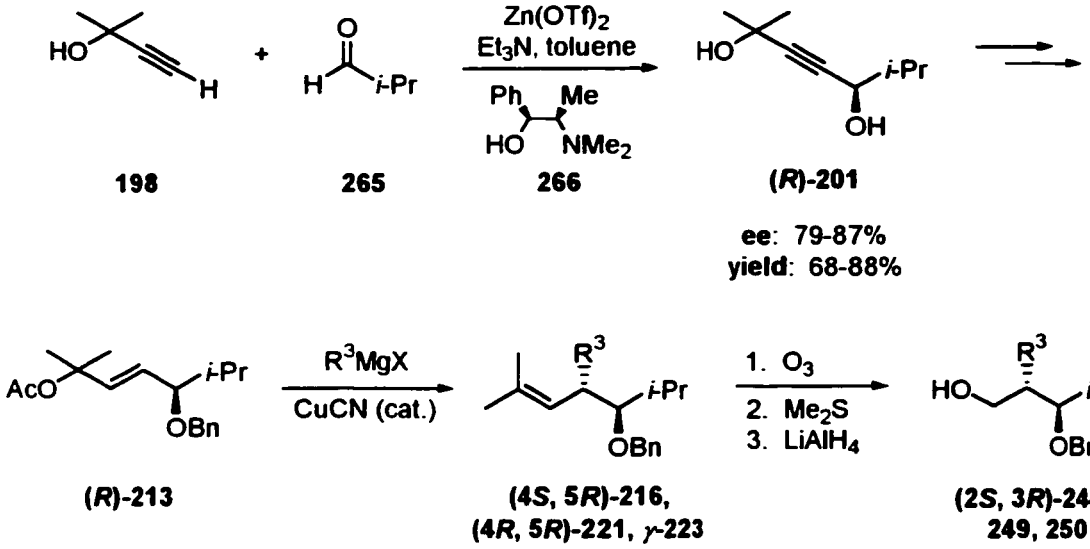
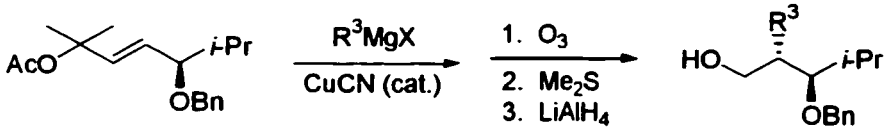


Table 19. Retention of enantiomeric excess during cuprate reaction.



(*R*)-213 **(2*S*, 3*R*)-244, 249, 250**

Entry	R^3	ee Acetate (%)[a]	ee Alcohol (%)[a]
1	*n*-Bu	82	83
2	*t*-Bu	82	84
3	Ph	79	80

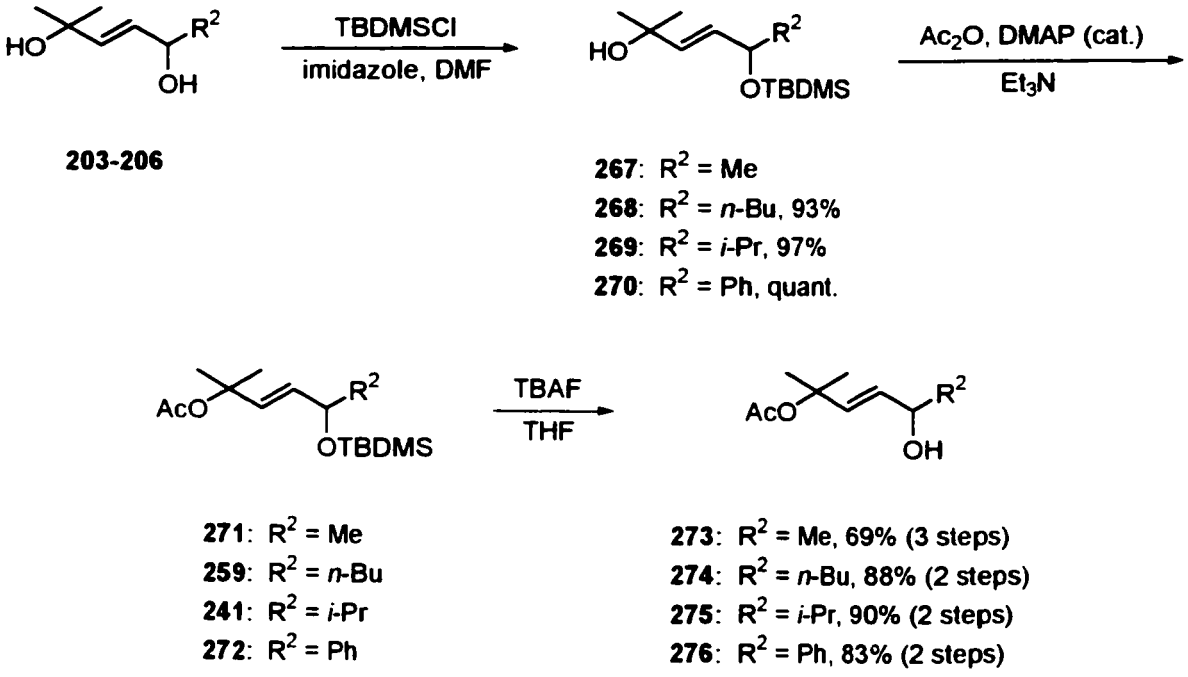
[a] Determined by HPLC on a Waters 600 instrument using a Chiracel OD column (4.6 × 150 mm). See Section 4.3.8 for solvent systems used.

4.2.7 Reversal of Facial Selectivity

Having developed an efficient method to preferentially synthesize *anti*-isomers, we strived to develop a selective route to *syn*-isomers. Our attention turned to δ-oxy-substituents equipped with ionizable protons. Previous research had shown *syn* additions to allylic alcohols were possible through complexation between the OH/O^- group and organocopper reagents.[27] We were curious to see if the same trend would apply with hydroxyl groups that

were not destined to become part of the leaving group. We synthesized the desired substrates by protecting the secondary hydroxyl groups as the TBDMS ethers, acetylating the tertiary alcohols and then removing the protecting groups via reaction with TBAF (Scheme 77).

Scheme 77



203-206

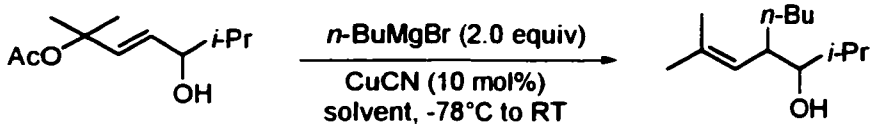
267: R^2 = Me
268: R^2 = *n*-Bu, 93%
269: R^2 = *i*-Pr, 97%
270: R^2 = Ph, quant.

271: R^2 = Me
259: R^2 = *n*-Bu
241: R^2 = *i*-Pr
272: R^2 = Ph

273: R^2 = Me, 69% (3 steps)
274: R^2 = *n*-Bu, 88% (2 steps)
275: R^2 = *i*-Pr, 90% (2 steps)
276: R^2 = Ph, 83% (2 steps)

Our best diastereoselectivities had been achieved with R^2 equal to *i*-Pr; accordingly, we used hydroxyl-substituted acetate **275** as a probe substrate in our new approach. We ran a number of CuCN-catalyzed Grignard reactions in different solvents (Table 20). THF, a solvent typically used during copper-mediated reactions,[28] gave very low diastereoselectivity and yield. Toluene, Et_2O and *tert*-butyl methyl ether (TBME) all gave moderate facial selectivities. The best results were achieved using methylene chloride, a solvent rarely used for these types of reactions.[29] Since methylene chloride is a non-coordinating solvent, we hypothesized that coordination between the incoming nucleophile and the substrate was important in determining the diastereoselectivity of the reactions. The THF may coordinate to the formed Mg-cuprate, effectively preventing formation of the coordinated reactive complex.[30]

Table 20. Copper-catalyzed Grignard reactions with δ-hydroxyl-substituted allylic acetate **275** in different solvents.



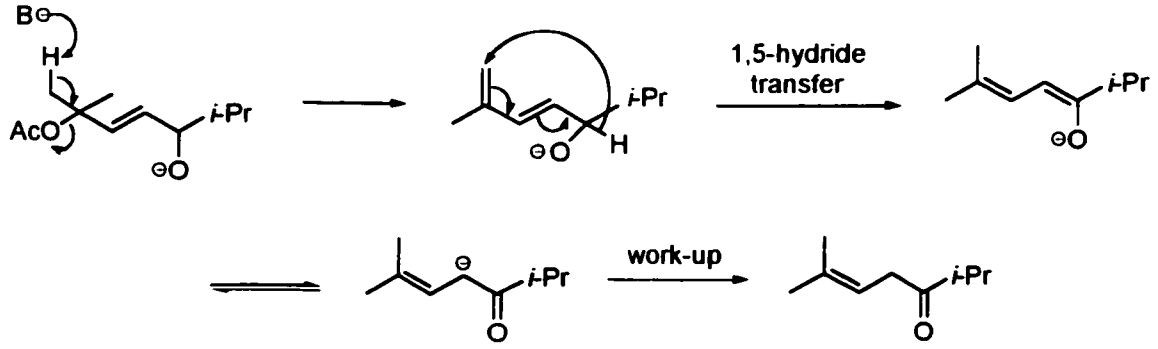
275 **243**

Entry	Solvent	de (%)[a]	Yield (%)[b]
1	THF	18	45
2	Toluene	41	48
3	TBME	45	44
4	Et_2O	49	57
5	CH_2Cl_2	69	57

[a] Determined by GC/MS of crude products.
[b] Percentage isolated yields of chromatographed products.

The yields achieved were much lower than had been previously obtained with alkyloxy- or silyloxy-substituted acetates. The major side product recovered in all cases was β,γ-unsaturated ketone **277** (Scheme 78). We proposed that this compound was formed via elimination of the acetate leaving group, followed by a 1,5-hydride shift to generate a carbonyl group.

Scheme 78



277

To minimize formation of side product **277** we increased the amount of copper cyanide catalyst from 10 to 50 mol%. We hoped that this adjustment would ensure complete formation of the cuprate reagent. We also quenched the reaction at a lower temperature (-25°C) to

prevent side reactions that were occurring at higher temperatures. Both of these modifications led to increased yields and diastereoselectivities.

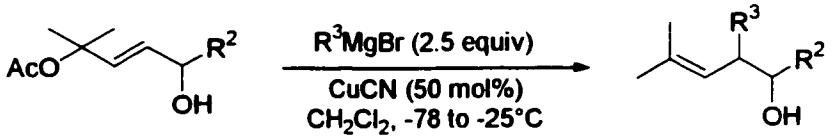
With these reaction conditions we tried changing the copper source to CuI and $CuBr{\cdot}SMe_2$. In both of these cases, mostly starting material and ketone **277** were recovered from the reaction mixture. These results again suggested that the CN ligand was important in determining the efficiency of these reactions.

Having developed the optimum reaction conditions, a series of copper-catalyzed Grignard reactions were performed (Table 21). There were no clear-cut trends observed, which is strikingly different to the results previously observed with the benzyloxy-substituted substrates.

With the hydroxyl group in place, the best diastereoselectivities were achieved when R^2 was *n*-Bu. These results were different from those observed with the benzyloxy-substituted analogues, where the best results arose with bulky *i*-Pr or Ph in the R^2 position. With these new reactions, the lowest and highest de's came when introducing *i*-Pr and *t*-Bu groups, respectively. Lower selectivities had previously been observed during *i*-Pr addition to the benzyloxy substrates, but the *t*-Bu additions usually yielded results similar to those achieved with the same substrate. Discounting the *i*-Pr additions, the diastereoselectivities observed with hydroxyl-substituted substrates were directly proportional to the size of R^3.

The trends observed between the benzyloxy- and hydroxyl-substrates were completely different. The benzyloxy selectivities were highly dependent upon the size of the anchor group on the substrate. On the other hand, the hydroxyl-substituted acetate reactions seemed to rely heavily on the size of the R^3 group. Whereas the best results were achieved in Et_2O with the benzyloxy-substituted acetates, better results were always observed using dichloromethane for the reactions with the hydroxyl-acetates (compare Groups 2 and 3 in Table 21). From these results we hypothesized that the two types of substrates were reacting via different mechanisms.

Table 21. Alkyl addition with δ-hydroxyl-substituted acetates.



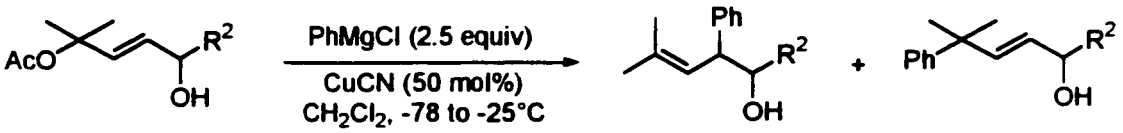
273-276 **243, 278-292**

Group	R^3	R^2, de (%)[a]			
		Me	***n*-Bu**	***i*-Pr**	**Ph**
1	Me	60	84	60	48
2	*n*-Bu	77	85	74	54[b]
3[c]	*n*-Bu	60	72	49	-
4	*i*-Pr	58	72	12	25
5	*t*-Bu	93	>98[d]	87[b]	70

[a] Determined by GC/MS of crude products unless otherwise noted; see experimental section for yields.
[b] Determined by ^{1}H NMR spectroscopy.
[c] The reactions were run in Et_2O.
[d] The second diastereomer was not visible by GC/MS and ^{1}H NMR spectroscopy.

With these substrates, phenyl group addition proved to be even more difficult than with the benzyl protecting group in place. Under standard conditions (see Table 21), the yields of the desired products were incredibly low (Table 22). A complex mixture was recovered when the reactions were run in Et_2O and THF. The best results were achieved by changing the Grignard reagent from PhMgBr in Et_2O to PhMgCl in THF. All of the synthesized substrates were subjected to these conditions (Table 22). Unfortunately, the reactions were plagued by low yields and, in most cases, low diastereoselectivities. This method does not appear to be a viable route to these compounds.

Table 22. Ph group addition to δ-hydroxyl-substituted acetates.



273-276 **γ-293-296** **α-293-296**

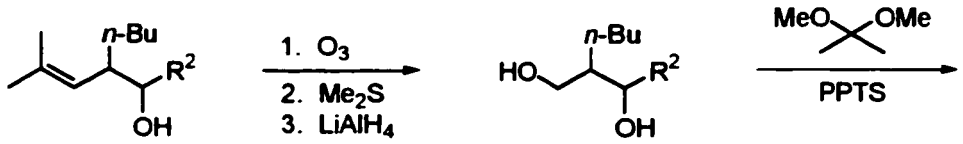
Entry	Alkene	R^2	γ de (%)[a]	γ Yield (%)[b]	α Yield (%)[b]
1	**293**	Me	45	29	26
2	**294**	*n*-Bu	70	28	34
3	**295**	*i*-Pr	55	19	17
4	**296**	Ph	81[c]	34	22

[a] Determined by ^{1}H NMR spectroscopy.
[b] Percentage isolated yields of chromatographed products.
[c] Determined by GC/MS.

4.2.7.1 Relative Configuration Determination

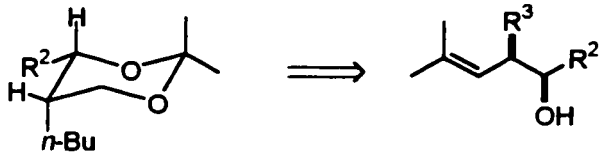
To confirm the suspicion that the *syn* product was forming preferentially, we synthesized a series of cyclic acetals (Scheme 79) and analyzed the ^{1}H NMR spectra.[22,23] A representative example is shown in Figure 21. Protons H_a and H_b were distinguished using NOE difference experiments. H_a exhibits a large geminal coupling with H_b and small ax-eq coupling with H_d. H_b has a large geminal coupling with H_a and a small eq-eq coupling with H_d. H_c shows a medium-sized coupling with the methine proton on the *i*-Pr group and a small eq-eq coupling with H_d. These results prove that the relationship between the hydroxyl and *n*-Bu groups on the precursor alkene is *syn*.[22,23]

Scheme 79



279: R^2 = Me
283: R^2 = *n*-Bu
***syn*-243**: R^2 = *i*-Pr
291: R^2 = Ph

***syn*-251**: R^2 = Me
***syn*-252**: R^2 = *n*-Bu
***syn*-253**: R^2 = *i*-Pr
297: R^2 = Ph



***cis*-255**: R^2 = Me
***cis*-256**: R^2 = *n*-Bu
***cis*-257**: R^2 = *i*-Pr
298: R^2 = Ph

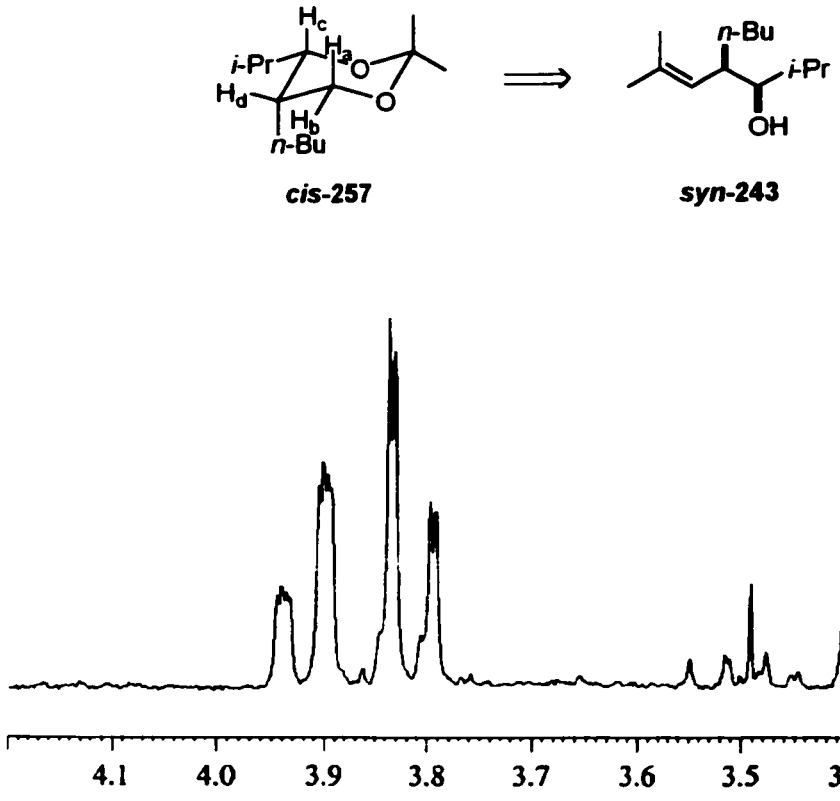
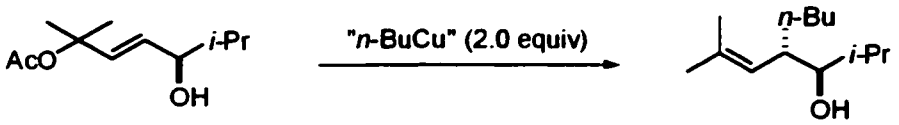


Figure 21. Diagnostic protons (H_a, H_b and H_c, respectively) from the ^1H NMR spectrum of 1,3-dioxane ***cis*-257**.

4.2.7.2 The Role of Magnesium

In order to probe the role of magnesium these new reactions, we briefly revisited lithium-based cuprate chemistry (Table 23).

Table 23. Lithium-based cuprate reactions with hydroxyl-substituted acetate **275**.



275 ***anti*-243**

Entry	Cuprate	Solvent	de (%)	Yield (%)
1	R_2CuLi	THF	93	37
2	RCuCNLi	Et_2O	72	44

With both of these cuprate reagents the *anti*-diastereomers were formed preferentially. Since the *anti*-product was still formed with the cyanocuprate, the results imply that the magnesium was necessary to invoke the *syn*-facial selectivity observed with the CuCN-catalyzed Grignard reactions.

4.2.7.3 Proposed Mechanism

With a hydroxyl group in place, the results of the copper-catalyzed Grignard reactions were markedly different. These new reactions were most successful in non-coordinating solvents (*i.e.*, CH_2Cl_2) and the relationships between the δ-oxy-substituents and the added groups were *syn*. It is also important to mention that the selectivity of these reactions was highly dependent upon the size of the R^3 group on the precursor Grignard reagent, rather than the size of the R^2 group on the substrate.

Based upon previously developed mechanisms,[19] we suggest that the oxygen anion coordinates to the incoming reagent to form a mixed-cuprate (Figure 22). The structure of the proposed cuprate is greatly simplified in the diagram, because, as previously mentioned, both Mg and CN are required for the observed facial selectivities. This species can react via two possible reactive conformations, **A** and **B**. In the **B** conformation, which would lead to the disfavoured, *anti*-product, there is 1,3-allylic strain between R^2 and an alkene proton. In the **A** conformation, the strain is much less; therefore, the *syn*-product is formed preferentially.

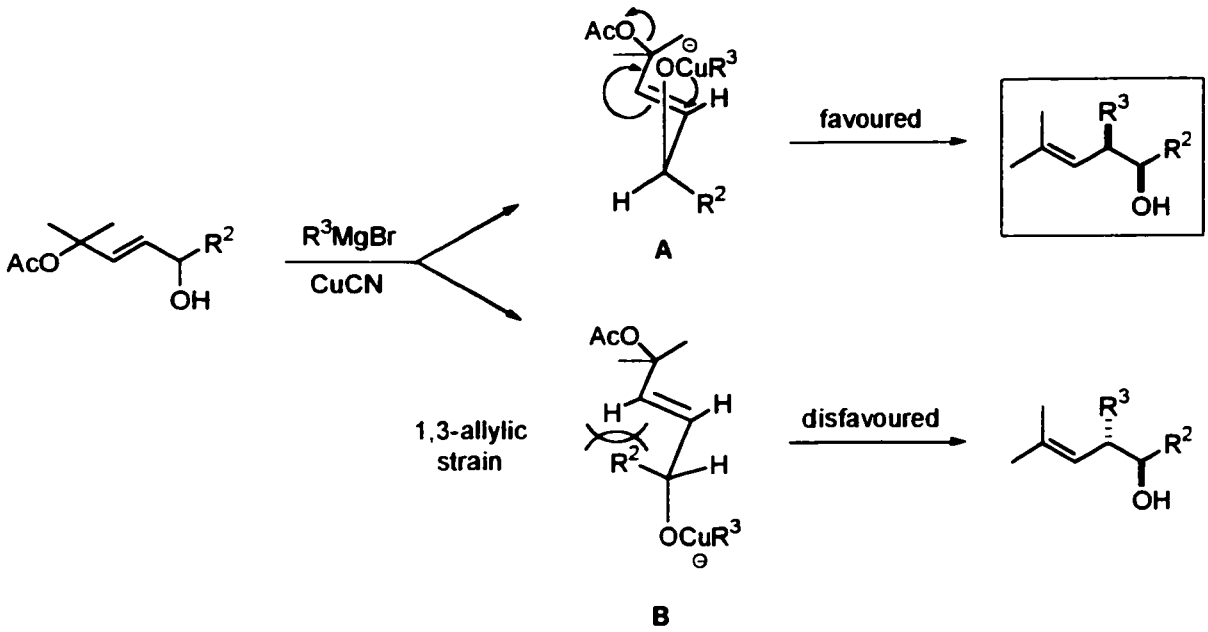
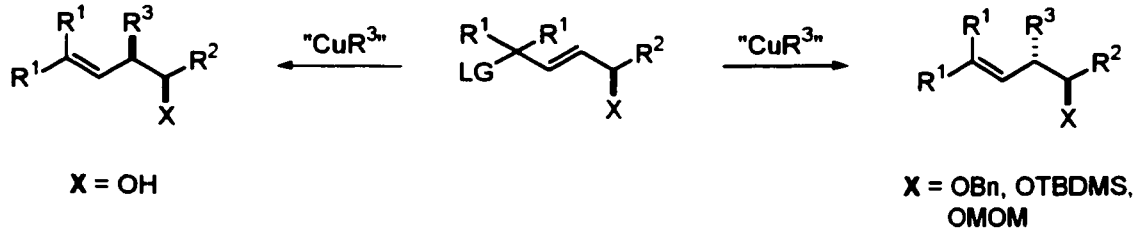


Figure 22. Possible substrate coordination leading to observed *syn*-facial selectivity.

According to the proposed mechanism, the observed *syn*-facial selectivity is achieved through "rigid" reactive conformation **A**. It may be difficult for large R^2 groups, such as *i*-Pr and Ph, to maintain such a conformation, leading to partial product formation via a non-coordinated type of species, as discussed previously for the benzyl-substituted substrates (see Section 4.2.5). This alternative mechanism would lead to formation of the *anti*-diastereomer.

4.2.8 Summary

Scheme 80



X = OH

X = OBn, OTBDMS, OMOM

A series of copper-mediated S_N2' reactions were run with a number of different allylic substrates. Higher regioselectivities occurred when R^1 was a methyl group, as opposed to a hydrogen. The highest diastereoselectivities occurred using copper cyanide-catalyzed Grignard reactions.

The couplings occurred with *anti*-facial selectivity when X was a benzyloxy, *tert*-butyldimethylsilyloxy or methoxymethoxy group. We propose that the reaction occurs through a Felkin-Anh-type reactive conformation. Diastereoselectivities of ≥98% were possible when introducing primary, secondary and tertiary alkyl and phenyl groups. These reactions occurred with good to excellent yields.

When X was OH, the facial selectivity was reversed to favour the *syn*-products. We propose that the coupling occurs through a "mixed-cuprate" system in which cuprate is coordinated to the substrate. In some cases, diastereoselectivities of ≥98% were possible.

4.3 Experimental

4.3.1 General Experimental

All reactions were performed using flame-dried glassware under an argon atmosphere. Diethyl ether and THF were freshly distilled from sodium benzophenone ketyl. Toluene was freshly distilled from sodium. Dichloromethane was freshly distilled from CaH_2. Pyridine was distilled from CaH_2 and stored over 3Å molecular sieves. $CuBr{\cdot}SMe_2$ was prepared as described by Wuts[31] and purified by recrystallization from Me_2S-hexanes. Grignard reagents (EtMgBr, *n*-BuMgBr, *i*-PrMgCl, *t*-BuMgCl) were prepared in ether under standard conditions and stored in sealed bottles under argon. The titre of the reagents was determined by titration with salicylaldehyde phenylhydrazone.[32] MeMgBr and PhMgBr were used as purchased from Aldrich Chemical Co. after titration.

Melting points were taken on a Mel-Temp apparatus and are uncorrected. Infrared spectra were obtained as either neat liquids or as a chloroform solution between sodium chloride plates on a Perkin-Elmer Spectrum RXI FT-IR system. IR absorption positions are given in cm^{-1}. NMR spectra were recorded using either a Bruker AC-200, AM-250, Avance-300 or Avance-500 spectrometer in $CDCl_3$, using tetramethylsilane (TMS, $\delta = 0.00$ for ^1H) or

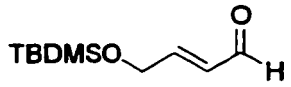
deuterated chloroform ($CDCl_3$, t, δ = 77.0 for ^{13}C) as internal standards. ^1H NMR data are reported as follows: signal (integration, multiplicity, coupling constant (if applicable), identity). ^{13}C NMR data are reported similarly. The mass spectral data is reported as: mass (% base peak). Optical rotations were recorded on a Perkin-Elmer 241 Polarimeter using the sodium D line (589 nm), unless otherwise noted. High pressure liquid chromatographs were recorded on a Waters 600 instrument using a Chiracel OD column (4.6 × 150 mm). Elemental analyses were performed by M-H-W Laboratories, Phoenix, AZ.

In the ^{13}C NMR peak listings, peaks due to the major diastereomer are denoted with an asterisk (*) if signals due to both diastereomers are distinguishable. All GC/MS analyses were conducted using an HP G1800A GCD system equipped with a 30 m × 0.25 mm DB-5 column. In general, the temperature program used for the separation of the diastereomeric benzyl and TBDMS ether alkenes (compounds listed in Tables 17 and 18) was T_0 = 180°C, t_0 = 20.0 min, rate = 20°C/min, T_f = 250°C, t_f = 5.0 min. (Program 1). In all cases, the temperature program used for separating the diastereomeric hydroxy alkenes (compounds listed in Tables 21 and 22) was T_0 = 70°C, t_0 = 10.0 min, rate = 20°C/min, T_f = 270°C, t_f = 10.0 min. (Program 2). The temperature programs used for separating the diastereomeric TBDMS and MOM ethers were the same as Program 2, replacing T_0 with 150°C (Program 3) and 125°C (Program 4), respectively.

*(Z)-4-tert-Butyldimethylsilyloxy-2-buten-1-ol (**191**)*

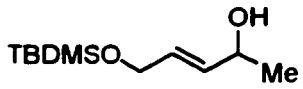
The compound was formed according to the method developed by Marshall and Garofalo[33] in 89% yield. ^1H NMR (200 MHz, $CDCl_3$) δ 5.79 (2H, m, HC=CH), 4.26 (2H, d, J = 3.6 Hz, CH_2OSi), 4.20 (2H, dd, J = 5.5 Hz, CH_2OH), 2.00 (1H, t, J = 5.5 Hz, OH), 0.90 (9H, s, $(CH_3)_3C$), 0.09 (6H, s, $(CH_3)_2Si$); ^{13}C NMR (50 MHz, $CDCl_3$) δ 131.0, 130.0 (HC=CH), 59.4, 58.4 (CH_2OH, CH_2OSi), 25.8 (3C, $(CH_3)_3C$), 18.2 ($C(CH_3)_3$), -5.4 ($(CH_3)_2Si$).

(E)-4-tert-Butyldimethylsilyloxy-2-butenal (192)



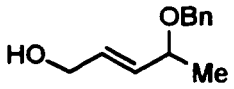
The compound was formed according to the method developed by Marshall and Garofalo[33] in 56% yield. ^{1}H NMR (200 MHz, $CDCl_3$) δ 9.63 (1H, d, J = 8.0 Hz, HC=O), 6.93 (1H, dt, J = 15.5, 3.3 Hz, =CHCH$_2$), 6.42 (1H, ddt, J = 15.5, 8.0, 2.1 Hz, =CHCHO), 4.46 (2H, dd, J = 3.3, 2.1 Hz, CH$_2$), 0.93 (9H, s, (CH$_3$)$_3$C), 0.10 (6H, s, (CH$_3$)$_2$Si); ^{13}C NMR (50 MHz, $CDCl_3$) δ 193.4 (C=O), 156.5 (=CHCH$_2$O), 130.5 (=CHCHO), 62.2 (CH$_2$O), 25.8 (3C, (CH$_3$)$_3$C), 18.3 (C(CH$_3$)$_3$), -5.5 ((CH$_3$)$_2$Si).

(E)-5-tert-Butyldimethylsilyloxy-3-penten-2-ol (193)



MeLi (1.4 M, 20 mL, 28 mmol) was added dropwise to a solution of aldehyde **192** (2.0 g, 9.7 mmol) in Et_2O (20 mL) at -10°C. The reaction was monitored via TLC and, at its completion 2 h), was quenched by dropwise addition of 10% NH_4OH in NH_4Cl (~10 mL). The organic and aqueous layers were separated and the aqueous layer was further extracted with Et_2O (3 × 10 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo* and the crude product was purified via silica gel chromatography (20% Et_2O in hexanes followed by 40% Et_2O in hexanes) to afford 1.6 g (78%) of the desired product as a clear, pale yellow oil. IR (neat) 3369 (br, OH), 2957, 2930, 2858, 1678 (C=C), 1472, 1124, 1084, 836 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.76-5.74 (2H, m, HC=CH), 4.35-4.32 (1H, m, CHOH), 4.18-4.17 (2H, m, CH$_2$OSi), 1.45 (1H, d, J = 4.2Hz, OH), 1.29 (3H, d, J = 6.4Hz, CH$_3$CH) 0.91 (9H, s, (CH$_3$)$_3$C) 0.08 (6H, s, (CH$_3$)$_2$Si); ^{13}C NMR (50 MHz, $CDCl_3$) δ 134.0, 129.2 (HC=CH), 68.2, 63.1 (CH$_2$OSi, CH$_2$OH), 25.9 (3C, (CH$_3$)$_3$C), 23.2 (CH$_3$CH), 18.4 (C(CH$_3$)$_3$), -5.2 (2C, (CH$_3$)$_2$Si); MS (EI) *m/z* (%) 198 (M$^+$- H_2O, 1), 141 (17), 75 (100), 73 (12). Anal. Calcd for $C_{11}H_{24}O_2Si$: C, 61.06; H, 11.18. Found: C, 60.89; H, 11.15.

(E)-4-Benzyloxy-2-pentenol (195)[34]

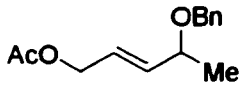


Monosilylated ether **193** (0.51 g, 2.3 mmol) in THF (5 mL) was added dropwise to a mixture of NaH (60%, 0.14 g, 3.6 mmol) and TBAI (34 mg, 0.093 mmol) in THF (10 mL). After H_2 evolution had ceased, benzyl bromide (0.90 mL, 7.6 mmol) was added dropwise via syringe and the reaction mixture was allowed to stir (in the dark) overnight. The reaction mixture was poured into water (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water (50 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The crude oil was dissolved in THF (10 mL) and TBAF (1.0 M, 4.7 mL, 4.7 mmol) was added dropwise. The reaction was monitored via TLC. At its completion, the reaction mixture was poured into water (50 mL) and extracted with Et_2O (3 × 50 mL). The combined organic layers were washed with water (50 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified via column chromatography (1:1 Et_2O:hexanes) to afford 0.33 g (73%, 2 steps) of a clear, colourless oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.36 (5H, m, $C_6\underline{H}_5$), 5.85 (1H, dt, J = 15.6, 5.2 Hz, =$\underline{C}$HCH$_2$), 5.70 (1H, dd, J = 15.6, 6.7 Hz, =C$\underline{H}$CH), 4.60 (1H, A of AB, d, J_{obs} = 11.9 Hz, C$\underline{H}_2$Ph) 4.44 (1H, B of AB, d, J_{obs} = 11.9 Hz, C$\underline{H}_2$Ph), 4.18 (2H, d, J = 5.2 Hz, C$\underline{H}_2$OH), 3.98 (1H, dq, J = 6.7, 6.7 Hz, C$\underline{H}$CH$_3$), 1.57 (1H, br s, O$\underline{H}$), 1.32 (3H, d, J = 6.7 Hz, C$\underline{H}_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 133.2, 130.9, 128.3 (2C), 127.6 (2C), 127.4 (ArC's, H$\underline{C}$=$\underline{C}$H), 75.1 ($\underline{C}$HCH$_3$), 70.0 ($\underline{C}$H$_2$Ph), 62.8 ($\underline{C}$H$_2$OH), 21.4 ($\underline{C}$H$_3$).

4.3.2 General Procedure A: Acetylation of Alcohols

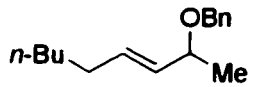
Acetic anhydride (1.5 equiv) was added dropwise to a solution of the alcohol (1.0 equiv), DMAP (0.10 equiv) and Et_3N (1.5 equiv). The reaction was monitored for completion by TLC. The reaction mixture was diluted with Et_2O and washed with 1 M HCl (2×), saturated $NaHCO_3$ (3×) and brine (2×). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*.

(E)-4-Benzyloxy-2-penten-1-yl acetate (196)



The reaction was performed using General Procedure A with alcohol **195** (0.30 g, 1.6 mmol) and afforded 0.31 g (84%) of a clear, yellow oil that was used without further purification. IR (neat) 3088, 3064, 2974, 2932, 2865, 1742 (C=O), 1676 (C=C), 1242, 736, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35-7.22 (5H, m, $C_6\underline{H}_5$), 5.85-5.65 (2H, m, $\underline{H}C{=}C\underline{H}$), 4.60 (2H, d, J = 4.3 Hz, $C\underline{H}_2HC{=}$), 4.59 (1H, A of AB, d, J_{obs} = 11.9 Hz, $C\underline{H}_2Ph$), 4.42 (1H, B of AB, d, J_{obs} = 11.9 Hz, $C\underline{H}_2Ph$), 3.97 (1H, dq, J = 6.3, 6.3 Hz, $C\underline{H}CH_3$), 2.09 (3H, s, $C\underline{H}_3CO$), 1.31 (3H, d, J = 6.3 Hz, $\underline{C}H_3CH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.7 ($\underline{C}{=}O$), 138.5, 136.2, 128.3 (2C), 127.6 (2C), 127.4, 125.6 ($H\underline{C}{=}\underline{C}H$, ArC's), 74.8 ($\underline{C}HOBn$), 70.1 ($\underline{C}H_2Ph$), 64.2 ($\underline{C}H_2OCO$), 21.2, 20.9 ($\underline{C}H_3C{=}O$, $\underline{C}H_3CH$); MS (EI) *m/z* (%) 219 (M^+-CH_3, 1), 107 (10), 92 (14), 91 (100), 68 (25). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.82; H, 7.60.

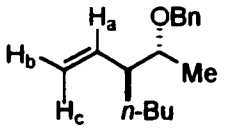
(E)-2-Benzyloxy-3-nonene (α-197)



Prior to the reaction, acetate **196** (193 mg, 0.82 mmol) was placed in Et_2O (2 mL) over 3Å sieves. *n*-BuLi (1.56 M, 2.0 mL, 3.1 mmol) was added dropwise to a suspension of $CuBr{\cdot}SMe_2$ (343 mg, 1.7 mmol) in Et_2O (4 mL) at -78°C. The reaction mixture was slowly warmed until most of the copper salt had dissolved and was then recooled to -78°C. The acetate was added dropwise to the suspension and the reaction was allowed to stir at this temperature for 2 h. The reaction was quenched with 10% NH_4OH in NH_4Cl (10 mL) and allowed to warm to RT. The organic and aqueous layers were separated and the aqueous layer was extracted with Et_2O (3 × 10 mL). The organic layer was dried over Na_2SO_4 and solvent removed *in vacuo* to afford 41 mg (21%) of a clear, colourless oil. IR (neat) 3089, 3065, 3031, 2958, 2928, 2858, 1946, 1872, 1805, 1704, 1668 (C=C), 1455, 1071, 734, 697cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.35-7.28 (5H, m, $C_6\underline{H}_5$), 5.61 (1H, dt, J = 15.4, 6.6 Hz, $=C\underline{H}CH_2$), 5.40 (1H, dd, J = 15.4, 6.9 Hz, $=C\underline{H}CH$), 4.59 (1H, A of AB, d, J_{obs} = 12.0 Hz, $C\underline{H}_2Ph$), 4.39 (1H, B of AB, d, J_{obs} = 12.0 Hz, $C\underline{H}_2Ph$), 3.87 (1H, dq, J = 6.9, 6.9 Hz, $C\underline{H}CH_3$), 2.04 (2H, dt,

J = 6.6, 6.6 Hz, C$\underline{H}_2$HC=), 1.44-0.92 (6H, m, (C$\underline{H}_2$)$_3$CH$_3$), 1.29 (3H, d, J = 6.9 Hz, C$\underline{H}_3$CH), 0.90 (3H, t, J = 6.6 Hz, C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.0, 133.4, 131.8, 128.3 (2C), 127.7 (2C), 127.3 (H$\underline{C}$=$\underline{C}$H, ArC's), 75.9 ($\underline{C}$HCH$_3$), 69.6 ($\underline{C}$H$_2$Ph), 32.1, 31.4, 29.0, 22.5, 21.9 (($\underline{C}$H$_2$)$_4$CH$_3$, $\underline{C}$H$_3$CH), 14.2 ($\underline{C}$H$_3$CH$_2$); MS (EI) *m/z* (%) 232 (M^+, 0.3), 107 (9), 92 (19), 91 (100), 55 (13). Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.63; H, 10.57.

(3R, 4S*)-4-Benzyloxy-3-butyl-1-pentene (γ-197)*



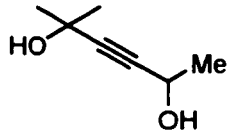
n-BuMgBr (2.78 M, 0.30 mL, 0.83 mmol) was added slowly dropwise to a solution of acetate **196** (92 mg, 0.39 mmol) and CuCN (6 mg, 0.07 mmol) dissolved in Et_2O (10 mL) at RT. After 1 h, the reaction was quenched and worked-up as described previously (see compound **α-197**) to afford 50 mg (54%) of as a clear, colourless oil. GC analysis indicated that **γ-197** was a mixture of isomers in a ratio of 75:25 (*anti:syn*), retention times 12.70 and 12.78 min, respectively. IR (neat) 3068, 3031, 2969, 2930, 2859, 1946, 1868, 1827, 1640 (C=C), 1455, 1376, 1098, 912, 734, 697 cm^{-1}; ^{1}H NMR (200 MHz, $CDCl_3$) δ 7.35-7.28 (5H, m, C$_6$H$_5$), 5.77-5.55 (1H, m, C$\underline{H}_a$), 5.10 (1H, dd, J = 10.4, 2.1 Hz, C$\underline{H}_b$), 5.05 (1H, dd, J = 16.4, 2.1 Hz, C$\underline{H}_c$), 4.73 (1H, A of AB, d, J_{obs} = 12.0 Hz, C$\underline{H}_2$Ph), 4.53 (1H, B of AB, d, J_{obs} = 12.0 Hz, C$\underline{H}_2$Ph), 3.52-3.38 (1H, m, C$\underline{H}$CH$_3$), 2.17-2.05 (1H, m, C$\underline{H}$*n*-Bu), 1.53-1.24 (6H, m, (C$\underline{H}_2$)$_3$CH$_3$), 1.15 (3H, d, J = 6.3 Hz, C$\underline{H}_3$CH), 0.88 (3H, t, J = 6.8 Hz, C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7; 139.4; 128.3, 128.2*; 127.6, 127.5; 127.3; 116.1 (H$_2\underline{C}$=$\underline{C}$, ArC's); 77.6 ($\underline{C}$HCH$_3$); 70.6 ($\underline{C}$H$_2$Ph); 49.7*, 49.5 ($\underline{C}$H*n*-Bu); 30.1, 29.7*; 29.7*, 29.5; 22.8 (($\underline{C}$H$_2$)$_3$CH$_3$); 16.8 ($\underline{C}$H$_3$CH); 14.1 ($\underline{C}$H$_3$CH$_2$); MS (EI) *m/z* (%) 232 (M^+, 0.02), 135 (9), 91 (100), 55 (14). Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.81; H, 10.29.

4.3.3 General Procedure B: Formation of Alkynediols

n-BuLi (~2.2 equiv) was added dropwise to a solution of 2-methyl-3-butyn-2-ol (**198**, 1.0 equiv) in THF (~100 mL/g substrate) at -78°C and the reaction mixture was allowed to stir at this temperature for 2 h. The temperature of reaction was raised to -65°C and the desired

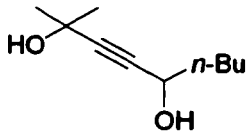
aldehyde (1.5 to 2.0 equiv) in THF (2 mL/mL aldehyde) was added dropwise. The reaction was allowed to run for approximately 6 h at -65°C before allowing it to warm to RT. The solution was poured into saturated NH_4Cl (~0.5 of initial volume of THF), the THF was stripped *in vacuo* and the remaining aqueous layer was extracted with ether (3 × V_{quench}). The organic extracts were dried over Na_2SO_4 and the solvent was removed *in vacuo*. The resulting oils were purified by column chromatography. The reductions to the alkenes, however, could be performed using crude material.

*2-Methyl-3-hexyne-2,5-diol (**199**)*[35]



The reaction was performed using General Procedure B with 2-methyl-3-butyn-2-ol (23 mL, 0.24 mol) and acetaldehyde (26 mL, 0.46 mol). The crude oil was fractionally distilled under vacuum pressure (Kugelrohr) to afford 21 g (71%) of a clear, pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.55 (1H, dq, J = 5.8, 5.8 Hz, C<u>H</u>OH), 2.18 (1H, br d, J = 5.8 Hz, CHO<u>H</u>), 2.08 (1H, br s, $(CH_3)_2$CO<u>H</u>), 1.52 (6H, s, $(C\underline{H}_3)_2$C), 1.46 (3H, d, J = 5.8 Hz, $C\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 88.4, 83.8 (<u>C</u>≡<u>C</u>), 64.7 (<u>C</u>$(CH_3)_2$), 57.7 (<u>C</u>HOH), 31.2, 31.1 ($(CH_3)_2$C), 24.1 ($\underline{C}H_3$CH).

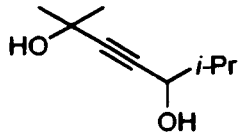
*2-Methyl-3-nonyne-2,5-diol (**200**)*



The reaction was performed using General Procedure B with 2-methyl-3-butyn-2-ol (7.0 mL, 72 mmol) and valeraldehyde (12 mL, 113 mmol). The crude oil was purified via column chromatography (1:1 EtOAc:hexanes) to afford 11 g (91%) of a clear, slightly yellow oil. IR (neat) 3339 (br, OH), 2982, 2959, 2935, 2863, 2236 (C≡C), 1460, 1377, 1237, 1166, 1033, 953 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.38 (1H, t, J = 6.6 Hz, C<u>H</u>OH), 1.98 (2H, br s, 2 × O<u>H</u>), 1.74-1.63 (2H, m, $C\underline{H}_2$CH), 1.52 (6H, s, $(C\underline{H}_3)_2$C), 1.48-1.32 (4H, m, $(C\underline{H}_2)_2CH_3$), 0.92 (3H, t,

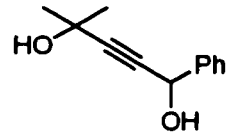
J = 7.0 Hz, C<u>H</u>$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 89.4, 83.2 (<u>C</u>≡<u>C</u>), 65.0 (<u>C</u>(CH$_3$)$_2$), 62.1 (<u>C</u>HCH$_3$), 37.3 (<u>C</u>H$_2$CH), 31.3 (2C, (<u>C</u>H$_3$)$_2$C), 27.3, 22.3 ((<u>C</u>H$_2$)$_2$CH$_3$), 14.0 (<u>C</u>H$_3$CH$_2$); MS (EI) *m*/z (%) 155 (M$^+$-CH$_3$, 2), 134 (39), 105 (22), 95 (94), 92 (72), 91 (100), 77 (65), 67 (32), 65 (38), 63 (24), 58 (24), 57 (22), 55 (41), 53 (37), 51 (43). Anal. Calcd for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.71; H, 10.48.

2,6-Dimethyl-3-heptyne-2,5-diol [(±)-201][25]



The reaction was performed using General Procedure B with 2-methyl-3-butyn-2-ol (19 mL, 0.20 mol) and isobutyraldehyde (35 mL, 0.39 mol). The crude oil was purified by column chromatography (5:1 hexanes:EtOAc to 1:1 hexanes:EtOAc) to afford 25 g (81%) of a clear, pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.20 (1H, d, J = 6.2 Hz, C<u>H</u>OH), 2.02 (1H, br s, O<u>H</u>), 1.99 (1H, br s, O<u>H</u>), 1.88 (1H, dqq, J = 6.2, 6.2, 6.2 Hz, C<u>H</u>(CH$_3$)$_2$), 1.53 (6H, s, (C<u>H</u>$_3$)$_2$C), 1.01 (3H, d, J = 6.2 Hz, C<u>H</u>$_3$CH), 0.97 (3H, d, J = 6.2 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 90.3, 81.8 (<u>C</u>≡<u>C</u>), 67.6 (<u>C</u>HOH), 65.0 (<u>C</u>OH), 34.4 (<u>C</u>H(CH$_3$)$_2$), 31.4, 31.3 ((<u>C</u>H$_3$)$_2$C), 18.1, 17.5 ((<u>C</u>H$_3$)$_2$CH).

4-Methyl-1-phenyl-2-pentyne-1,4-diol (202)[35]

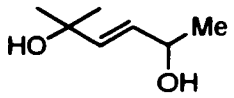


The reaction was performed using General Procedure B with 2-methyl-3-butyn-2-ol (10 mL, 103 mol) and benzaldehyde (7.0 mL, 69 mmol). The crude oil was purified by column chromatography (1:1 EtOAc:hexanes) to afford 7.7 g (59%) of a white, crystalline solid (mp = 73-75°C). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.51 (2H, m, C$_6$<u>H</u>$_5$), 7.37-7.25 (3H, m, C$_6$<u>H</u>$_5$), 5.43 (1H, s, C<u>H</u>), 3.34 (1H, br s, O<u>H</u>), 1.50 (6H, s, (C<u>H</u>$_3$)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.5, 128.4 (2C), 128.1, 126.7 (2C) (ArC's), 91.2, 81.8 (<u>C</u>≡<u>C</u>), 65.1, 64.0 (<u>C</u>HOH, <u>C</u>(CH$_3$)$_2$), 31.1 (2C, (<u>C</u>H$_3$)$_2$C).

4.3.4 General Procedure C: Formation of Alkenediols

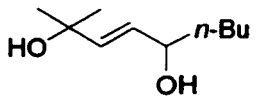
The desired alkynediol (1.0 equiv) in Et_2O was added dropwise to a slurry of $LiAlH_4$ (8.0 equiv wrt to H^-) in Et_2O (65 mL/g substrate) at 0°C. When the reaction was deemed to be complete (2-5 h) by TLC, crushed $Na_2SO_4 \cdot 10H_2O$ (~10 g/g LAH used) was slowly added to the slurry at 0°C. When the slurry had changed from gray to white, the organic layer was decanted and the remaining solid was extracted with warm EtOAc (3×). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*.

*(E)-2-Methyl-3-hexene-2,5-diol (**203**)*[36]



The reaction was performed using General Procedure C with alkynediol **197** (21 g, 0.16 mol). The resulting clear, pale yellow oil (20 g, 97%) was used without further purification. ^{1}H NMR (200 MHz, $CDCl_3$) δ 5.77 (1H, d, J = 15.7 Hz, =C<u>H</u>C), 5.72 (1H, dd, J = 15.7, 5.6 Hz, =C<u>H</u>CH), 4.31 (1H, dq, J = 5.6, 5.6 Hz, C<u>H</u>OH), 2.29 (1H, br s, O<u>H</u>), 2.12 (1H, br s, O<u>H</u>), 1.32 (6H, s, (C<u>H</u>$_3$)$_2$C), 1.29 (3H, d, J = 5.6 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.7, 130.7 (H<u>C</u>=<u>C</u>H), 70.4 (<u>C</u>(CH$_3$)$_2$), 68.2 (<u>C</u>HOH), 29.7, 29.5 ((<u>C</u>H$_3$)$_2$C), 23.3 (<u>C</u>H$_3$CH).

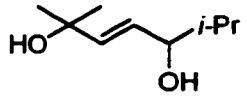
*(E)-2-Methyl-3-nonene-2,5-diol (**204**)*



The reaction was performed using General Procedure C with alkynediol **200** (2.5 g, 15 mmol). The crude oil was purified via column chromatography (3:2 EtOAc:hexanes) to afford 1.9 g (75%) of a clear, colourless oil. IR (neat) 3350 (br, OH), 2961, 2931, 2861, 1669 (C=C), 1466, 1377, 1362, 1236, 1153, 972 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.84 (1H, d, J = 15.7 Hz, =C<u>H</u>C), 5.68 (1H, dd, J = 15.7, 6.4 Hz, =C<u>H</u>CH), 4.14 (1H, dt, J = 6.4, 6.4 Hz, C<u>H</u>OH), 1.61-1.49 (4H, m, 2 × O<u>H</u>, C<u>H</u>$_2$CH), 1.39-1.24 (4H, m, (C<u>H</u>$_2$)$_2$CH$_3$), 1.33 (6H, s, (C<u>H</u>$_3$)$_2$C), 0.91 (3H, t, J = 6.8 Hz, C<u>H</u>$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 129.7 (H<u>C</u>=<u>C</u>H), 72.4 (<u>C</u>HOH), 70.4 (<u>C</u>OH), 36.9 (<u>C</u>H$_2$CH), 29.7, 29.5, 27.6, 22.5 ((<u>C</u>H$_2$)$_2$CH$_3$, (<u>C</u>H$_3$)$_2$C), 14.0

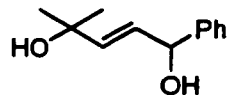
($\underline{C}H_3CH_2$); MS (EI) *m/z* (%) 154 (M^+-H_2O, 3), 136 (15), 107 (15), 105 (11), 97 (12), 95 (21), 94 (16), 93 (79), 92 (10), 85 (61), 80 (12), 79 (59), 77 (39), 69 (29), 65 (19), 57 (100), 53 (28), 51 (19). Anal. Calcd for $C_{10}H_{20}O_2$: C, 69.77; H, 11.63. Found: C, 69.82; H, 11.72.

(E)-2,6-Dimethyl-3-heptene-2,5-diol [(±)-205]



The reaction was performed using General Procedure C with alkynediol **(±)-201** (2.1 g, 13 mmol). The crude oil was purified via column chromatography (1:1 EtOAc:hexanes to 2:1 EtOAc:hexanes) to give 1.5 g (71%) of a clear, colourless oil. IR (neat) 3400 (br, OH), 2973, 2931, 2874, 1664 (C=C), 1467, 1381, 1216, 1151, 1015 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.85 (1H, d, J = 15.7 Hz, =C$\underline{H}$C), 5.69 (1H, dd, J = 15.7, 6.7 Hz, =C$\underline{H}$CH), 3.86 (1H, dd, J = 6.7, 6.3 Hz, C$\underline{H}$OH), 1.75 (1H, qqd, J = 6.8, 6.7, 6.3 Hz, C$\underline{H}(CH_3)_2$), 1.54 (2H, br s, 2 × O$\underline{H}$), 1.34 (6H, s, ($C\underline{H_3}$)$_2$C), 0.92 (3H, d, J = 6.7 Hz, C$\underline{H_3}$CH), 0.91 (3H, d, J = 6.8 Hz, C$\underline{H_3}$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.7, 127.8 (H$\underline{C}$=$\underline{C}$H), 77.4 ($\underline{C}$HOH), 70.5 ($\underline{C}$OH), 33.7 ($\underline{C}H(CH_3)_2$), 29.8, 29.5 (($\underline{C}H_3$)$_2$C), 18.1 (2C, ($\underline{C}H_3$)$_2$CH); MS (EI) *m/z* (%) 140 (M^+-H_2O, 8), 107 (90), 105 (57), 95 (47), 91 (100), 79 (68), 77 (50), 71 (71), 69 (74), 67 (59), 85 (61). Anal. Calcd for $C_9H_{18}O_2$: C, 68.31; H, 11.46. Found: C, 68.52; H, 11.44.

(E)-4-Methyl-1-phenyl-2-pentene-1,4-diol (206)



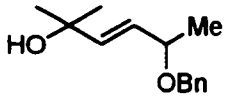
The reaction was performed using General Procedure C with alkynediol **202** (2.3 g, 12 mmol). The crude oil was purified column chromatography (3:2 EtOAc:hexanes) to give 1.3 g (56%) of a clear, colourless oil. IR (neat) 3351 (br, OH), 2974, 1951, 1884, 1812, 1664 (C=C), 1454, 1377, 1152, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (5H, m, $C_6\underline{H_5}$), 5.96 (1H, d, J = 15.6 Hz, =C$\underline{H}$C), 5.88 (1H, dd, J = 15.6, 5.5 Hz, =C$\underline{H}$CH), 5.21 (1H, d, J = 5.5 Hz, C$\underline{H}$OH), 1.92 (1H, br s, O$\underline{H}$), 1.42 (1H, br s, O$\underline{H}$), 1.32 (6H, s, ($C\underline{H_3}$)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.3, 138.9, 129.0, 128.4 (2C), 127.5, 126.2 (2C) (H$\underline{C}$=$\underline{C}$H, ArC's), 74.3 ($\underline{C}$OH), 70.5 ($\underline{C}$HOH), 29.6, 29.4 (($\underline{C}H_3$)$_2$C); MS (EI) *m/z* (%) 174 (M^+-H_2O, 14), 131 (100), 129 (24), 128

(22), 115 (35), 105 (63), 91 (54), 51 (23). Anal. Calcd for $C_{12}H_{16}O_2$: C, 74.97; H, 8.39. Found: C, 74.75; H, 8.19.

4.3.5 General Procedure D: Preparation of Monobenzyl Ethers

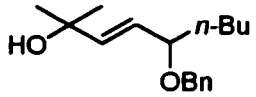
The desired diol (1.0 equiv) in THF was added dropwise to a suspension of NaH (1.1 equiv), TBAI (0.10 equiv) in THF (2.5 mL/100 mg substrate). When gas evolution had ceased, benzyl bromide (~1.1 equiv) was added dropwise. The reaction was allowed to stir in the dark overnight. The reaction was quenched by pouring the reaction mixture into water. The layers were then separated and the aqueous layer extracted with Et_2O (3×). The combined organic layers were washed with water and dried over Na_2SO_4. The solvent was removed *in vacuo*.

(E)-5-Benzyloxy-2-methyl-3-hexen-2-ol (207)



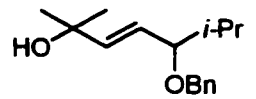
The reaction was performed using General Procedure D with diol **203** (1.0 g, 7.8 mmol). The crude oil was purified by column chromatography (2:1 hexanes:EtOAc) to give 0.85 g (50%) of a clear, colourless oil. IR (neat) 3401 (br, OH), 3030, 2974, 2929, 2866, 1950, 1809, 1740, 1665 (C=C), 1454, 1371, 1072, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 7.39-7.26 (5H, m, $C_6\underline{H}_5$), 5.83 (1H, d, J = 15.6 Hz, =C$\underline{H}$C), 5.60 (1H, dd, J = 15.6, 6.7 Hz, =C$\underline{H}$CH), 4.58 (1H, A of AB, d, J_{obs} = 12.0 Hz, C$\underline{H}_2$Ph), 4.43 (1H, B of AB, d, J_{obs} = 12.0 Hz, C$\underline{H}_2$Ph), 3.94 (1H, dq, J = 6.7, 6.7 Hz, C$\underline{H}$OBn), 1.43 (1H, br s, O$\underline{H}$), 1.34 (6H, s, (C$\underline{H}_3$)$_2$C), 1.30 (3H, d, J = 6.7 Hz, C$\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 138.8, 128.5, 128.3 (2C), 127.6 (2C), 127.4 (H$\underline{C}$=$\underline{C}$H, ArC's), 75.3 ($\underline{C}$HOBn), 70.4 ($\underline{C}$OH), 69.9 ($\underline{C}H_2$Ph), 29.7 (2C, ($\underline{C}H_3$)$_2$C), 21.6 ($\underline{C}H_3$CH); MS (EI) *m/z* (%) 202 (M^+-H_2O, 20), 92 (14), 91 (100), 69 (11). Anal. Calcd for $C_{14}H_{20}O_2$: C, 76.33; H, 9.15. Found: C, 76.12; H, 8.96.

(E)-5-Benzyloxy-2-methyl-3-nonen-2-ol (208)



The reaction was performed using General Procedure D with crude diol **204** (1.4 g, 7.9 mmol). The resulting oil was purified via column chromatography (3:2 hexanes:Et_2O) to give 1.0 g (50%, 2 steps) of a clear, colourless oil. IR (neat) 3401 (br, OH), 3031, 2960, 2932, 2861, 1948, 1870, 1808, 1664 (C=C), 1455, 1377, 1090, 734, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.26 (5H, m, $C_6\underline{H}_5$), 5.80 (1H, d, J = 15.7 Hz, =C$\underline{H}$C), 5.54 (1H, dd, J = 15.7, 7.9 Hz, =C$\underline{H}$CH), 4.58 (1H, A of AB, d, J_{obs} = 12.1 Hz, C$\underline{H}_2$Ph), 4.39 (1H, B of AB, d, J_{obs} = 12.1 Hz, C$\underline{H}_2$Ph), 3.74 (1H, dt, J = 7.9, 7.0 Hz, C$\underline{H}$OBn), 1.65-1.21 (7H, m, O$\underline{H}$, $(C\underline{H}_2)_3CH_3$), 1.33 (6H, s, $(C\underline{H}_3)_2C$), 0.88 (3H, t, J = 6.4 Hz, $C\underline{H}_3CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 138.8, 128.2, 128.2 (2C), 127.6, 127.3 (2C) (H$\underline{C}$=$\underline{C}$H, ArC's), 79.6 ($\underline{C}$HOBn), 70.4 ($\underline{C}$OH), 69.9 ($\underline{C}H_2$Ph), 35.4 ($\underline{C}H_2$CH), 29.7, 29.6, 27.5, 22.5 (($\underline{C}H_3)_2C$, $(\underline{C}H_2)_2CH_3$), 13.9 ($\underline{C}H_3CH_2$); MS (EI) *m*/z (%) 205 (M^+-*n*-Bu, 0.5), 108 (35), 107 (37), 93 (75), 79 (100), 77 (77), 51 (40). Anal. Calcd for $C_{17}H_{26}O_2$: C, 77.82; H, 9.99. Found: C, 77.62; H, 10.05.

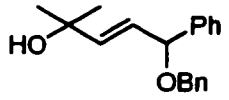
(E)-5-Benzyloxy-2,6-dimethyl-3-hepten-2-ol [(±)-209]



The reaction was performed using General Procedure D with crude diol **(±)-205** (1.8 g, 11 mmol). The resulting oil was purified via column chromatography (1:1 hexanes:Et_2O) to give 1.7 g (62%) of a clear, colourless oil. IR (neat) 3401 (br, OH), 3031, 2972, 1949, 1870, 1805, 1664 (C=C), 1455, 1366, 1147, 1068, 736, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.24 (5H, m, $C_6\underline{H}_5$), 5.79 (1H, d, J = 15.8 Hz, =C$\underline{H}$C), 5.54 (1H, dd, J = 15.8, 8.1 Hz, =C$\underline{H}$CH), 4.58 (1H, A of AB, d, J_{obs} = 12.1 Hz, C$\underline{H}_2$Ph), 4.37 (1H, B of AB, d, J_{obs} = 12.1 Hz, C$\underline{H}_2$Ph), 3.42 (1H, dd, J = 8.1, 6.8 Hz, C$\underline{H}$OBn), 1.82 (1H, dqq, J = 6.8, 6.8, 6.7 Hz, C$\underline{H}(CH_3)_2$), 1.49 (1H, br s, O$\underline{H}$), 1.35 (3H, s, C$\underline{H}_3$C), 1.34 (3H, s, C$\underline{H}_3$C), 0.97 (3H, d, J = 6.7 Hz, C$\underline{H}_3$CH), 0.87 (3H, d, J = 6.8 Hz, C$\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.0, 139.0, 128.2 (2C), 127.6 (2C), 127.2, 125.6 (H$\underline{C}$=$\underline{C}$H, ArC's), 85.0 ($\underline{C}$HOBn), 70.6 ($\underline{C}$OH), 70.1 ($\underline{C}H_2$Ph), 32.8 ($\underline{C}H(CH_3)_2$), 29.9, 29.7 (($\underline{C}H_3)_2C$), 18.8, 18.4 (($\underline{C}H_3)_2CH$); MS (EI) *m*/z (%) 205 (M^+-*i*-Pr,

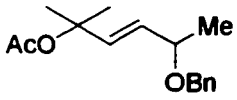
0.7), 108 (26), 107 (66), 106 (24), 105 (51), 91 (100), 79 (61), 77 (65), 51 (35). Anal. Calcd for $C_{16}H_{24}O_2$: C, 77.38; H, 9.74. Found: C, 77.16; H, 9.55.

(E)-1-Benzyloxy-4-methyl-1-phenyl-2-penten-4-ol (210)



The reaction was performed using General Procedure D with diol **206** (1.8 g, 9.4 mmol). The crude oil was purified via column chromatography (25% EtOAc in hexanes) to give 1.9 g (70 %) of a clear, colourless oil. IR (neat) 3400 (br, OH), 3030, 2973, 1951, 1880, 1811, 1662 (C=C), 1495, 1454, 1096, 1065, 974, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.26 (10H, m, 2 × $C_6\underline{H}_5$), 5.90 (1H, d, J = 15.7 Hz, =C$\underline{H}$C), 5.83 (1H, dd, J = 15.7, 5.8 Hz, =C$\underline{H}$CH), 4.85 (1H, d, J = 5.8 Hz, C$\underline{H}$OBn), 4.56-4.45 (2H, m, C$\underline{H}_2$Ph), 1.39 (1H, br s, O$\underline{H}$), 1.31 (6H, s, (C$\underline{H}_3$)$_2$C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.2, 140.1, 138.4, 128.5 (2C), 128.3 (2C), 127.7 (2C), 127.6, 127.6, 127.5, 126.9 (2C) (H$\underline{C}$=$\underline{C}$H, ArC's), 81.1 ($\underline{C}$HOBn), 70.6 ($\underline{C}$OH), 70.0 ($\underline{C}$H$_2$Ph), 29.6 (2C, ($\underline{C}$H$_3$)$_2$C); MS (EI) *m/z* (%) 191 (M^+- Bn, 0.4), 156 (51), 141 (34), 131 (56), 128 (43), 115 (53), 107 (44), 105 (60), 91 (83), 79 (79), 77 (100), 51 (62). Anal. Calcd for $C_{19}H_{22}O_2$: C, 80.82; H, 7.85. Found: C, 80.95; H, 7.72.

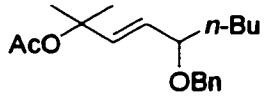
(E)-5-Benzyloxy-2-methyl-3-hexen-2-yl acetate (211)



The reaction was performed using General Procedure A with alcohol **207** (0.70 g, 3.2 mmol) and afforded 0.70 g (85%) of a clear, pale yellow oil that was used without further purification. IR (neat) 3031, 2978, 2932, 2866, 1952, 1873, 1736 (C=O), 1669 (C=C), 1367, 1249, 1018, cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.27 (5H, m, $C_6\underline{H}_5$), 5.93 (1H, d, J = 15.9 Hz, =C$\underline{H}$C), 5.55 (1H, dd, J = 15.9, 6.9 Hz, =C$\underline{H}$CH), 4.57 (1H, A of AB, d, J_{obs} = 12.0 Hz, C$\underline{H}_2$Ph), 4.40 (1H, B of AB, d, J_{obs} = 12.0 Hz, C$\underline{H}_2$Ph), 3.92 (1H, dq, J = 6.9, 6.9 Hz, C$\underline{H}$CH$_3$), 1.99 (3H, s, C$\underline{H}_3$C=O), 1.54 (3H, s, C$\underline{H}_3$C), 1.52 (3H, s, C$\underline{H}_3$C), 1.29 (3H, d, J = 6.9 Hz, C$\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 ($\underline{C}$=O), 138.8, 136.8, 130.2, 128.3 (2C), 127.7 (2C), 127.3 (H$\underline{C}$=$\underline{C}$H, ArC's), 79.9 ($\underline{C}$(CH$_3$)$_2$), 75.2 ($\underline{C}$HCH$_3$), 69.8 ($\underline{C}$H$_2$Ph), 26.9, 26.8, 22.3,

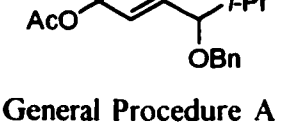
21.6 ((<u>C</u>H$_3$)$_2$C, <u>C</u>H$_3$CH, <u>C</u>H$_3$C=O); MS (EI) *m*/z (%) 203 (M$^+$-AcO, 0.1), 96 (20), 92 (10), 91 (100), 85 (22), 65 (12). Anal. Calcd for $C_{16}H_{22}O_3$: C, 73.25; H, 8.45. Found: C, 72.96; H, 8.20.

*(E)-5-Benzyloxy-2-methyl-3-nonen-2-yl acetate (**212**)*



The reaction was performed using General Procedure A with alcohol **208** (2.0 g, 7.5 mmol) and afforded 2.0 g (86%) of a clear, pale yellow oil that was used without further purification. IR (neat) 3031, 2933, 2861, 1948, 1738 (C=O), 1670 (C=C), 1637, 1249, 1120, 734, 698 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (5H, m, C$_6$<u>H</u>$_5$), 5.92 (1H, d, J = 15.9 Hz, =C<u>H</u>C), 5.49 (1H, dd, J = 15.9, 8.1 Hz, =C<u>H</u>CH), 4.59 (1H, A of AB, d, J_{obs} = 12.0 Hz, C<u>H</u>$_2$Ph), 4.37 (1H, B of AB, d, J_{obs} = 12.0 Hz, C<u>H</u>$_2$Ph), 3.74 (1H, dt, J = 8.1, 8.1 Hz, C<u>H</u>OBn), 1.99 (3H, s, C<u>H</u>$_3$C=O), 1.65-1.28 (6H, m, (C<u>H</u>$_2$)$_3$CH$_3$), 1.54 (3H, s, C<u>H</u>$_3$C), 1.52 (3H, s, C<u>H</u>$_3$C), 0.88 (3H, t, J = 6.6 Hz, C<u>H</u>$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 (<u>C</u>=O), 138.8, 137.6, 129.2, 128.2 (2C), 127.7 (2C), 127.3 (H<u>C</u>=<u>C</u>H, ArC's), 79.9 (<u>C</u>(CH$_3$)$_2$), 79.5 (<u>C</u>HOBn), 69.8 (<u>C</u>H$_2$Ph), 35.3 (<u>C</u>H$_2$CH), 27.5, 27.0, 26.8, 22.5 ((<u>C</u>H$_3$)$_2$C, (<u>C</u>H$_2$)$_2$CH$_3$), 22.2 (<u>C</u>H$_3$C=O), 14.0 (<u>C</u>H$_3$CH$_2$); MS (EI) *m*/z (%) 108 (36), 107 (35), 93 (78), 91 (92), 79 (100), 77 (74), 51 (37). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.82; H, 9.05.

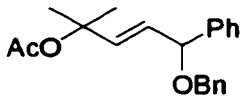
*(E)-5-Benzyloxy-2,6-dimethyl-3-hepten-2-yl acetate [(±)-**213**]*



The reaction was performed using General Procedure A with alcohol **209** (3.5 g, 14 mmol). The crude oil was purified using column chromatography (9:1 hexanes:Et$_2$O) to afford 3.6 g (89%) of a clear, colourless oil. IR (neat) 3031, 2959, 2933, 2872, 1737 (C=O), 1671 (C=C), 1455, 1382, 1252, 1141, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.24 (5H, m, C$_6$<u>H</u>$_5$), 5.89 (1H, d, J = 15.9, =C<u>H</u>C), 5.49 (1H, dd, J = 15.9, 8.3 Hz, =C<u>H</u>CH), 4.59 (1H, A of AB, d, J_{obs} = 12.1 Hz, C<u>H</u>$_2$Ph), 4.36 (1H, B of AB, d, J_{obs} = 12.1 Hz, C<u>H</u>$_2$Ph), 3.40 (1H, dd, J = 8.3, 7.0 Hz, C<u>H</u>OH), 1.83 (3H, s, C<u>H</u>$_3$C=O), 1.76 (1H, dqq, J = 7.0, 6.8, 6.7 Hz, C<u>H</u>(CH$_3$)$_2$), 1.54

(3H, s, C$\underline{H}_3$C), 1.53 (3H, s, C$\underline{H}_3$C), 0.96 (3H, d, J = 6.7 Hz, C$\underline{H}_3$CH), 0.86 (3H, d, J = 6.8 Hz, C$\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 ($\underline{C}$=O), 139.1, 138.8, 128.3, 127.8 (2C), 127.6, 127.4 (2C) (H$\underline{C}$=$\underline{C}$H, ArC's), 84.9 ($\underline{C}$HOBn), 80.0 ($\underline{C}$OAc), 70.1 ($\underline{C}H_2$Ph), 33.0 ($\underline{C}$H(CH_3)$_2$), 27.2, 27.1, 22.4 (($\underline{C}H_3$)$_2$C, $\underline{C}H_3$C=O), 19.0, 18.5 (($\underline{C}H_3$)$_2$CH); MS (EI) *m*/z (%) 247 (M^+-*i*-Pr, 0.3), 108 (35), 107 (74), 105 (30), 91 (100), 79 (66), 77 (52). Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.02. Found: C, 74.31; H, 9.09.

(E)-1-Benzyloxy-4-methyl-2-penten-4-yl acetate (214)



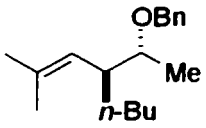
The reaction was performed using General Procedure A with alcohol **210** (1.8 g, 6.3 mmol). The crude oil was purified via column chromatography (10% Et_2O in hexanes) to afford 1.8 g (89%) of a clear, colourless oil. IR (neat) 3031, 2980, 2935, 2864, 1954, 1879, 1812, 1732 (C=O), 1454, 1367, 1251, 1129, 736, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.25 (10H, m, 2 × C$_6\underline{H}_5$), 6.04 (1H, d, J = 15.9 Hz, =C$\underline{H}$C), 5.76 (1H, dd, J = 15.9, 7.0 Hz, =C$\underline{H}$CH), 4.85 (1H, d, J = 7.0 Hz, C$\underline{H}$OBn), 4.58 (1H, A of AB, d, J_{obs} = 12.1 Hz, C$\underline{H}_2$Ph), 4.52 (1H, B of AB, d, J_{obs} = 12.1 Hz, C$\underline{H}_2$Ph), 1.98 (3H, s, C$\underline{H}_3$C=O), 1.54 (3H, s, C$\underline{H}_3$C), 1.50 (3H, s, C$\underline{H}_3$C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.9 ($\underline{C}$=O), 141.1, 138.4, 137.2 (2C), 128.8, 128.4 (2C), 128.3, 127.7, 127.6, 127.5 (2C), 126.9 (2C) (H$\underline{C}$=$\underline{C}$H, ArC's), 80.8 ($\underline{C}$HOBn), 80.0 ($\underline{C}$(CH_3)$_2$), 69.9 ($\underline{C}H_2$Ph), 26.8, 26.6, 22.3 (($\underline{C}H_3$)$_2$C, $\underline{C}H_3$C=O); MS (EI) *m*/z (%) 264 [M^+-AcOH (McLafferty rearrangement[16]), 1], 156 (100), 155 (49), 154 (31), 153 (30), 141 (57), 129 (34), 128 (47), 115 (62), 108 (59), 107 (43), 91 (84), 79 (71), 78 (38), 77 (93), 51 (55). Anal. Calcd for $C_{21}H_{24}O_3$: C, 77.75; H, 7.46. Found: C, 77.97; H, 7.31.

4.3.6 General Procedure E: Copper Cyanide Catalyzed Grignard Reactions of Acetates

The desired Grignard reagent (2.0 equiv) was added slowly dropwise to a slurry of the acetate (1.0 equiv) and CuCN (0.10 equiv, unless otherwise noted) in Et_2O (1 mL/10 mg substrate) at -78°C. The reaction was allowed to warm slowly to RT, after which it was quenched with 10% NH_4OH in NH_4Cl (~ 0.5 V_{Et2O}). The aqueous layers were extracted with Et_2O (3×) and the

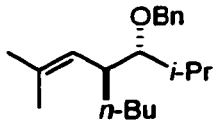
combined organic layers were dried over Na_2SO_4. An aliquot was removed for analysis by GC/MS. After the solvent was removed *in vacuo*, the crude alkene was typically purified via column chromatography.

(4R, 5S*)-5-Benzyloxy-4-butyl-2-methyl-2-hexene (215)*



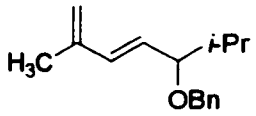
The reaction was performed using General Procedure E with acetate **211** (125 mg, 0.48 mmol), *n*-BuMgBr (0.35 mL, 2.71 M, 0.95 mmol) and CuCN (22 mg, 0.25 mmol). The crude oil (*anti*:*syn* = 86:14 by GC/MS analysis) was purified via column chromatography (4:1 hexanes:CH_2Cl_2) to give 90 mg (72%) of a clear, colourless oil. IR (neat) 3030, 2929, 2859, 1672 (C=C), 1454, 1376, 1097, 733, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.24 (5H, m, $C_6\underline{H}_5$), 4.99 (0.86H, d, J = 9.9 Hz, =C$\underline{H}$), 4.88 (0.14H, d, J = 8.3 Hz, =C$\underline{H}$), 4.60 (1H, A of AB, d, J_{obs} = 12.1 Hz, C$\underline{H}_2$Ph), 4.48 (0.86H, B of AB, d, J_{obs} = 12.1 Hz, C$\underline{H}_2$Ph), 4.47 (0.14H, B of AB, d, J_{obs} = 11.7 Hz, C$\underline{H}_2$Ph), 3.45 (0.86H, qd, J = 6.9, 3.9 Hz, C$\underline{H}$CH$_3$), 3.30 (0.14H, dq, J = 6.7, 6.7 Hz, C$\underline{H}$CH$_3$), 2.43-2.34 (1H, m, C$\underline{H}$CH$_2$), 1.72 (3H, s, C$\underline{H}_3$C=), 1.63 (0.40H, s, C$\underline{H}_3$C=), 1.59 (2.60H, s, C$\underline{H}_3$C=), 1.32-1.21 (6H, m, (C$\underline{H}_2$)$_3$CH$_3$), 1.15 (0.40H, d, J = 6.7 Hz, C$\underline{H}_3$CH), 1.11 (2.60H, d, J = 6.9 Hz, C$\underline{H}_3$CH), 0.87 (3H, t, J = 6.9 Hz, C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3; 132.5; 128.2 (2C); 127.6, 127.5* (2C); 127.3, 127.2*; 126.2 (H$\underline{C}$=$\underline{C}$H, ArC's); 78.7, 77.8* ($\underline{C}$HOBn); 70.8, 70.6* ($\underline{C}$H$_2$Ph); 44.0, 43.0* ($\underline{C}$HCH$_2$); 31.6, 30.4* ($\underline{C}$H$_2$CH); 29.9*, 29.5; 26.0; 23.0; 18.2; 17.1, 16.6* (($\underline{C}$H$_2$)$_2$CH$_3$, 2 × $\underline{C}$H$_3$C=, $\underline{C}$H$_3$CH); 14.2 ($\underline{C}$H$_3$CH$_2$); MS (EI) *m*/z (%) 260 (M^+, 0.3), 135 (18), 125 (27), 91 (100), 69 (64). GC/MS retention times (Program 2): 15.41 (*anti*), 15.49 (*syn*) min. Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 82.89; H, 10.60.

(4R, 5S*)-5-Benzyloxy-4-butyl-2,6-dimethyl-2-heptene (216)*



The reaction was performed using General Procedure E with acetate **213** (198 mg, 0.68 mmol), *n*-BuMgBr (0.51 mL, 2.71 M, 1.4 mmol) and CuCN (7 mg, 0.08 mmol). The crude oil (*anti*:*syn* = 98.5:1.5 by GC/MS analysis) was purified via column chromatography (10:1 hexanes: CH_2Cl_2) to give 158 mg (80%) of a clear, colourless oil. IR (neat) 3031, 2958, 2929, 2859, 1944, 1870, 1803, 1672 (C=C), 1454, 1382, 1096, 1070, 732, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.24 (5H, m, $C_6\underline{H}_5$), 5.17 (1H, d, J = 10.2 Hz, =C$\underline{H}$), 4.61-4.53 (2H, m, C$\underline{H}_2$Ph), 3.00 (1H, dd, J = 7.3, 3.6 Hz, C$\underline{H}$OBn), 2.53-2.43 (1H, m, C$\underline{H}$CH$_2$), 1.79 (1H, dqq, J = 7.3, 6.7, 6.7 Hz, C$\underline{H}$(CH$_3$)$_2$), 1.71 (3H, s, C$\underline{H}_3$C=), 1.60 (3H, s, C$\underline{H}_3$C=), 1.50-1.08 (6H, m, (C$\underline{H}_2$)$_3$CH$_3$), 0.99 (3H, d, J = 6.7 Hz, C$\underline{H}_3$CH), 0.89 (3H, d, J = 6.7 Hz, C$\underline{H}_3$CH), 0.87 (3H, t, J = 6.8 Hz, C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4, 131.6, 128.2 (2C), 127.6 (2C), 127.2, 126.0 (C=C, ArC's), 88.8 (CHOBn), 75.0 (CH$_2$OBn), 41.2 (CH(CH$_3$)$_2$), 33.1 (CHCH$_2$), 31.5 (CH$_2$CH), 29.8, 26.0, 23.0, 20.0 ((CH$_2$)$_2$CH$_3$, 2 × CH$_3$C=), 18.9, 18.4 ((CH$_3$)$_2$CH), 14.2 (CH$_3$CH$_2$); MS (EI) *m/z* (%) 245 (M^+-*i*-Pr, 0.6), 123 (11), 95 (18), 91 (100), 81 (22), 79 (17), 77 (14), 69 (38). GC/MS retention times (Program 1): 7.89 (*anti*), 8.08 (*syn*) min. Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.51; H, 10.91.

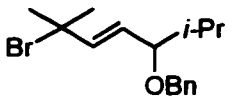
(E)-5-Benzyloxy-2,6-dimethyl-1,3-heptadiene (217)



This compound was isolated as a side product from the coupling reaction (General Procedure E) with acetate **213**, *n*-BuMgBr and CuCN, as a clear, colourless oil. IR (neat) 3082, 3065, 3030, 2959, 2871, 1667 (C=C), 1656 (C=C), 1454, 1138, 1089, 1068, 970, 734, 697; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (5H, m, $C_6\underline{H}_5$), 6.28 (1H, d, J = 15.8 Hz, =C$\underline{H}$C), 5.59 (1H, dd, J = 15.8, 8.3 Hz, =C$\underline{H}$CH), 4.99 (2H, s, =C$\underline{H}_2$), 4.60 (1H, A of AB, d, J_{obs} = 12.0 Hz, C$\underline{H}_2$Ph), 4.35 (1H, d, J_{obs} = 12.0 Hz, C$\underline{H}_2$Ph), 3.51 (1H, dd, J = 8.3, 6.7 Hz, C$\underline{H}$OBn), 1.88 (1H, ddq, J = 6.8, 6.8, 6.7 Hz, C$\underline{H}$(CH$_3$)$_2$), 1.85 (3H, s, C$\underline{H}_3$C=), 0.98 (3H, d, J = 6.8 Hz, C$\underline{H}_3$CH), 0.89

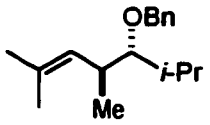
(3H, d, J = 6.8 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.5, 139.0, 136.1, 129.0, 128.2 (2C), 127.6 (2C), 127.2, 116.4 (ArC's, H_2<u>C</u>=<u>C</u>, H<u>C</u>=<u>C</u>H), 85.4 (<u>C</u>HOBn), 70.1 (<u>C</u>H_2Ph), 33.1 (<u>C</u>HCH$_3$), 18.9, 18.7, 18.5 (3 × <u>C</u>H$_3$); MS (EI) *m/z* (%) 187 (M^+-*i*-Pr, 6), 122 (27), 108 (40), 107 (95), 106 (16), 105 (42), 92 (13), 91 (100), 79 (72), 78 (14), 77 (60), 65 (15), 51 (23).

(E)-5-Benzyloxy-2-bromo-2,6-dimethyl-3-heptene (218)



The reaction was performed using General Procedure E with *n*-BuMgBr and either CuBr·SMe_2 or CuI and afforded the title compound as the major product by ^{1}H NMR analysis (14 and 19% yield, respectively, after column chromatography; low yield is attributed to instability). IR (neat) 3030, 2960, 2872, 1946, 1864, 1805, 1659 (C=C), 1468, 1454, 1377, 1367, 1088, 734, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.23 (5H, m, C_6<u>H</u>$_5$), 5.74 (1H, d, J = 15.8 Hz, =C<u>H</u>C), 5.28 (1H, dd, J = 15.8, 8.5 Hz, =C<u>H</u>CH), 4.59 (1H, A of AB, d, J_{obs} = 12.1 Hz, C<u>H</u>$_2$Ph), 4.33 (1H, B of AB, d, J_{obs} = 12.1 Hz, C<u>H</u>$_2$Ph), 3.37 (1H, dd, J = 8.5, 7.4 Hz, C<u>H</u>OBn), 1.83 (1H, dqq, J = 7.4, 6.8, 6.7 Hz, C<u>H</u>(CH$_3$)$_2$), 1.04 (3H, s, C<u>H</u>$_3$C), 1.01 (3H, s, C<u>H</u>$_3$C), 0.97 (3H, d, J = 6.7 Hz, C<u>H</u>$_3$CH), 0.87 (3H, d, J = 6.8 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.6, 142.5, 139.1, 128.2 (2C), 127.6 (2C), 127.2, 126.6 (H<u>C</u>=<u>C</u>H, ArC's), 86.1 (<u>C</u>HOBn), 69.8 (<u>C</u>H_2Ph), 41.0 (<u>C</u>Br), 33.0 (<u>C</u>H(CH$_3$)$_2$), 23.5, 23.2, 19.1, 18.6 ((<u>C</u>H$_3$)$_2$C, (<u>C</u>H$_3$)$_2$CH); MS (FAB) 231.2 $(M\text{-}Br)^+$.

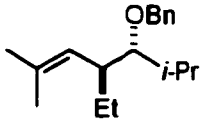
(4R, 5S*)-5-Benzyloxy-2,4,6-trimethyl-2-heptene (219)*



The reaction was performed using General Procedure E with acetate **213** (152 mg, 0.52 mmol), MeMgBr (0.35 mL, 2.94 M, 1.0 mmol) and CuCN (26 mg, 0.29 mmol). The crude oil (*anti*:*syn* = 98:2 by GC/MS analysis) was purified via column chromatography (6:1 hexanes: CH_2Cl_2) to give 99 mg (77%) of a clear, colourless oil. IR (neat) 3031, 2960, 2870, 1945, 1865, 1804, 1743, 1672 (C=C), 1455, 1096, 1067, 733, 697 cm^{-1}; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.36-7.24 (5H, m, C_6<u>H</u>$_5$), 5.21 (1H, d, J = 9.6 Hz, =C<u>H</u>), 4.61 (1H, A of AB q, d, J_{obs} = 11.2

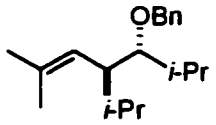
Hz, C$\underline{H}_2$Ph), 4.56 (1H, B of AB q, d, J_{obs} = 11.2 Hz, C$\underline{H}_2$Ph), 2.93 (1H, dd, J = 6.5, 4.6 Hz, C$\underline{H}$OBn), 2.69-2.63 (1H, m, C$\underline{H}$HC=), 1.80 (1H, qqd, J = 6.9, 6.7, 6.5 Hz, C$\underline{H}$(CH$_3$)$_2$), 1.69 (3H, s, C$\underline{H}_3$C=), 1.61 (3H, s, C$\underline{H}_3$C=), 0.99 (3H, d, J = 6.9 Hz, C$\underline{H}_3$CHCH$_3$), 0.98 (3H, d, J = 6.7 Hz, C$\underline{H}_3$CHCH$_3$), 0.90 (3H, d, J = 6.8 Hz, C$\underline{H}_3$CHHC=); ^{13}C NMR (75 MHz, CDCl$_3$) δ 139.4, 130.5, 128.2 (2C), 127.5 (2C), 127.3, 127.2 (ArC's, $\underline{C}$=$\underline{C}$H), 89.6 ($\underline{C}$HOBn), 75.1 ($\underline{C}$H$_2$Ph), 35.6 ($\underline{C}$HHC=), 31.3 ($\underline{C}$H(CH$_3$)$_2$), 25.9, 20.0, 19.0, 18.3, 17.9 (2 × $\underline{C}$H$_3$C=, ($\underline{C}$H$_3$)$_2$CH, $\underline{C}$H$_3$CHHC=); MS (EI) *m*/z (%) 246 (M$^+$, 0.1), 91 (100), 83 (40), 79 (10), 77 (13), 67 (18), 65 (13), 55 (23). GC/MS retention times (Program 1): 14.09 (*anti*), 14.32 (*syn*) min. Anal. Calcd for $C_{17}H_{26}O$: C, 82.89; H, 10.64. Found: C, 82.55; H, 10.60.

(4R, 5S*)-5-Benzyloxy-4-ethyl-2,6-dimethyl-2-heptene (220)*



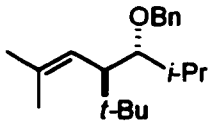
The reaction was performed using General Procedure E with acetate **213** (151 mg, 0.52 mmol), EtMgBr (0.55 mL, 1.89 M, 1.0 mmol) and CuCN (24 mg, 0.26 mmol). The crude oil (*anti*:*syn* = 99:1 by GC/MS analysis) was purified via column chromatography (6:1 hexanes: CH_2Cl_2) to give 114 mg (84%) of a clear, colourless oil. IR (neat) 3032, 2960, 2872, 1944, 1870, 1803, 1672 (C=C), 1454, 1097, 1068, 733, 697 cm^{-1}; ^{1}H NMR (500 MHz, CDCl$_3$) δ 7.37-7.24 (5H, m, C$_6\underline{H}_5$), 5.16 (1H, d, J = 10.3 Hz, =C$\underline{H}$), 4.60-4.55 (2H, m, C$\underline{H}_2$Ph), 3.02 (1H, dd, J = 7.4, 3.6 Hz, C$\underline{H}$OBn), 2.42-2.37 (1H, m, C$\underline{H}$CH$_2$), 1.79 (1H, dqq, J = 7.4, 6.8, 6.7 Hz, C$\underline{H}$(CH$_3$)$_2$), 1.72 (3H, s, C$\underline{H}_3$), 1.61 (3H, s, C$\underline{H}_3$), 1.55-1.48 (1H, m, C$\underline{H}_2$CH$_3$), 1.41-1.35 (1H, m, C$\underline{H}_2$CH$_3$), 0.98 (3H, d, J = 6.7 Hz, C$\underline{H}_3$CH), 0.88 (3H, d, J = 6.8 Hz, C$\underline{H}_3$CH), 0.84 (3H, t, J = 7.4 Hz, C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 139.4, 131.9, 128.2 (2C), 127.5 (2C), 127.2, 125.5 ($\underline{C}$=$\underline{C}$H, ArC's), 88.8 ($\underline{C}$HOBn), 75.0 ($\underline{C}$H$_2$Ph), 43.1 ($\underline{C}$HEt), 31.6 ($\underline{C}$H(CH$_3$)$_2$), 26.3, 26.0, 19.9, 19.0, 18.4 ($\underline{C}$H$_2$CH$_3$, 2 × $\underline{C}$H$_3$C=, ($\underline{C}$H$_3$)$_2$CH), 12.2 ($\underline{C}$H$_3$CH$_2$); MS (EI) *m*/z (%) 217 (M$^+$-*i*-Pr, 1), 97 (33), 91 (100), 81 (21), 55 (31). GC/MS retention times (Program 2): 14.86 (*anti*), 15.03 (*syn*) min. Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.21; H, 10.76.

(4R, 5S*)-5-Benzyloxy-4-isopropyl-2,6-dimethyl-2-heptene (221)*



The reaction was performed using General Procedure E with acetate **213** (206 mg, 0.71 mmol), *i*-PrMgCl (0.83 mL, 1.65 M, 1.4 mmol) and CuCN (8 mg, 0.09 mmol). The crude oil (*anti*:*syn* = 98.5:1.5 by GC/MS analysis) was purified via column chromatography (6:1 hexanes: CH_2Cl_2) to give 148 mg (76%) of a clear, colourless oil. IR (neat) 3031, 2959, 2927, 2871, 1944, 1870, 1803, 1673 (C=C), 1454, 1384, 1096, 1070, 733, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.36-7.24 (5H, m, $C_6\underline{H}_5$), 5.24 (1H, d, J = 10.8 Hz, =C$\underline{H}$), 4.58 (2H, s, C$\underline{H}_2$Ph), 3.22 (1H, dd, J = 6.8, 3.8 Hz, C$\underline{H}$OBn), 2.17 (1H, ddd, J = 10.8, 7.2, 3.8 Hz, C$\underline{H}$HC=), 1.88-1.76 (2H, m, 2 × C$\underline{H}$(CH_3)$_2$), 1.73 (3H, s, C$\underline{H}_3$C=), 1.59 (3H, s, C$\underline{H}_3$C=), 0.98 (3H, d, J = 6.7 Hz, C$\underline{H}_3$CH), 0.95 (3H, d, J = 6.6 Hz, C$\underline{H}_3$CH), 0.90 (3H, d, J = 6.7 Hz, C$\underline{H}_3$CH), 0.83 (3H, d, J = 6.8 Hz, C$\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 132.2, 128.1 (2C), 127.4 (2C), 127.1, 124.2 (C=C, ArC's), 86.2 (CHOBn), 74.7 (C$\underline{H}_2$Ph), 47.5 (CHHC=), 31.4, 29.3 (2 × C$\underline{H}$(CH_3)$_2$), 26.1, 21.7, 19.9 (2C), 18.6 (2C) (2 × ($\underline{C}H_3$)$_2$CH, 2 × $\underline{C}H_3$C=); MS (EI) *m*/z (%) 231 (M^+-*i*-Pr, 0.6), 123 (38), 111 (29), 91 (100), 81 (26), 79 (22), 77 (36), 69 (37), 55 (22). GC/MS retention times (Program 2): 15.32 (*anti*), 15.54 (*syn*) min. Anal. Calcd for $C_{19}H_{30}O$: C, 83.15; H, 11.02. Found: C, 83.40; H, 10.81.

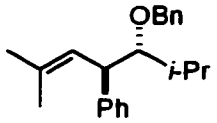
(4R, 5R*)-5-Benzyloxy-4-tert-butyl-2,6-dimethyl-2-heptene (222)*



The reaction was performed using General Procedure E with acetate **213** (499 mg, 1.7 mmol), *t*-BuMgCl (3.3 mL, 1.03 M, 3.4 mmol) and CuCN (17 mg, 0.19 mmol) to give 464 mg (94%) of a clear, colourless oil. The resulting product was sufficiently clean and did not require purification. The second diastereomer was not visible by GC/MS and ^1H NMR spectroscopy. IR (neat) 3031, 2959, 2930, 2930, 1944, 1864, 1804, 1671 (C=C), 1454, 1361, 1096, 1071, 732, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.22 (5H, m, $C_6\underline{H}_5$), 5.49 (1H, d, J = 10.8 Hz, =C$\underline{H}$), 4.61 (1H, A of AB, d, J_{obs} = 11.5 Hz, C$\underline{H}_2$Ph), 4.57 (1H, B of AB, d, J_{obs} = 11.5 Hz,

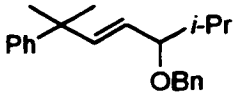
C<u>H</u>$_2$Ph), 3.39 (1H, d, J = 6.9 Hz, C<u>H</u>OBn), 2.17 (1H, d, J = 10.8 Hz, C<u>H</u>*t*-Bu), 1.87 (1H, dqq, J = 6.9, 6.9, 6.8 Hz, C<u>H</u>(CH$_3$)$_2$), 1.74 (3H, s, C<u>H</u>$_3$C=), 1.59 (3H, s, C<u>H</u>$_3$C=), 0.98 (3H, d, J = 6.9 Hz, C<u>H</u>$_3$CH), 0.91 (9H, s, (C<u>H</u>$_3$)$_3$C), 0.87 (3H, d, J = 6.8 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5, 131.7, 128.1 (2C), 127.0 (3C), 123.6 (<u>C</u>=<u>C</u>H, ArC's), 84.3 (<u>C</u>HOBn), 72.3 (<u>C</u>H$_2$Ph), 48.7 (<u>C</u>H*t*-Bu), 34.4 (<u>C</u>(CH$_3$)$_3$), 32.2 (<u>C</u>H(CH$_3$)$_2$), 28.7 (3C, (<u>C</u>H$_3$)$_3$C), 26.3, 19.4, 19.0, 18.8 (2 × <u>C</u>H$_3$C=, (<u>C</u>H$_3$)$_2$CH); MS (EI) *m*/z (%) 245 (M$^+$-*i*-Pr, 0.3), 125 (31), 109 (13), 91 (100), 69 (19), 57 (18). GC/MS retention time (Program 2): 16.04 min. Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.09; H, 11.15.

(4R, 5R*)-5-Benzyloxy-2,6-dimethyl-4-phenyl-2-heptene (γ-223)*



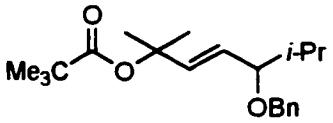
The reaction was performed using General Procedure E with acetate **213** (201 mg, 0.69 mmol), PhMgBr (0.49 mL, 2.82 M, 1.4 mmol) and CuCN (32 mg, 0.36 mmol). The crude oil (homogenous by GC/MS and ^{1}H NMR analysis) was purified via column chromatography (6:1 hexanes: CH_2Cl_2) to give 160 mg (75%) of a clear, colourless oil. IR (neat) 3028, 2962, 2955, 2870, 1945, 1870, 1803, 1671 (C=C), 1452, 1094, 1070, 752, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.16 (10H, m, 2 × C$_6$<u>H</u>$_5$), 5.67 (1H, d, J = 9.6 Hz, =C<u>H</u>), 4.32 (1H, A of AB, d, J_{obs} = 10.7 Hz, C<u>H</u>$_2$Ph), 4.13 (1H, B of AB, d, J_{obs} = 10.7 Hz, C<u>H</u>$_2$Ph), 3.78 (1H, dd, J = 9.6, 5.6 Hz, C<u>H</u>OBn), 3.31 (1H, dd, J = 5.6, 5.6 Hz, C<u>H</u>Ph), 1.73 (3H, s, C<u>H</u>$_3$C=), 1.72-1.66 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.59 (3H, s, C<u>H</u>$_3$C=), 0.97 (3H, d, J = 7.5 Hz, C<u>H</u>$_3$CH), 0.92 (3H, d, J = 7.3 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.0, 139.0, 132.9, 128.4 (2C), 128.3 (2C), 128.1 (2C), 127.9 (2C), 127.3, 125.9, 124.2 (<u>C</u>=<u>C</u>H, ArC's), 89.6 (<u>C</u>HOBn), 75.2 (<u>C</u>H$_2$Ph), 47.1 (<u>C</u>HPh), 31.4 (<u>C</u>H(CH$_3$)$_2$), 26.0, 20.1, 18.2, 18.0 (2 × <u>C</u>H$_3$C=, (<u>C</u>H$_3$)$_2$CH); MS (EI) *m*/z (%) 265 (M$^+$-*i*-Pr, 0.3), 157 (40), 145 (65), 129 (56), 128 (29), 91 (100), 77 (32). GC/MS retention time (Program 1): 18.59 min (*anti*). Anal. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15. Found: C, 85.80; H, 9.12.

(E)-5-Benzyloxy-2,6-dimethyl-2-phenyl-3-heptene (α-223)



This compound was isolated (13%) as a side product from the coupling reaction (General Procedure E) with acetate **213**, PhMgBr and CuCN, as a clear, colourless oil. This compound was the major product (86%) if using General Procedure E with acetate **213**, PhMgCl and CuCN in THF. IR (neat) 3087, 3062, 3030, 2964, 2929, 2870, 1945, 1870, 1803, 1752, 1663 (C=C), 1454, 1380, 1087, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.17 (10H, m, 2 × $C_6\underline{H}_5$), 5.82 (1H, d, J = 15.8 Hz, =C$\underline{H}$C), 5.40 (1H, dd, J = 15.8, 8.5 Hz, =C$\underline{H}$CH), 4.62 (1H, A of AB, d, J_{obs} = 12.1 Hz, C$\underline{H}_2$Ph), 4.37 (1H, B of AB, d, J_{obs} = 12.1 Hz, C$\underline{H}_2$Ph), 3.44 (1H, dd, J = 8.5, 7.4 Hz, C$\underline{H}$OBn), 1.84 (1H, dqq, J = 7.4, 6.8, 6.7 Hz, C$\underline{H}$(CH$_3$)$_2$), 1.45 (3H, s, C$\underline{H}_3$C), 1.43 (3H, s, C$\underline{H}_3$C), 0.98 (3H, d, J = 6.7, C$\underline{H}_3$CH), 0.90 (3H, d, J = 6.8 Hz, C$\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.7, 144.6, 139.1, 128.2 (2C), 128.1 (2C), 127.6 (2C), 127.2, 126.1 (2C), 125.8, 125.4 (H$\underline{C}$=$\underline{C}$H, ArC's), 85.6 ($\underline{C}$HOBn), 69.9 ($\underline{C}$H$_2$Ph), 40.6 ($\underline{C}$Ph), 33.0 ($\underline{C}$H(CH$_3$)$_2$), 28.8 (2C), 19.0, 18.6 (($\underline{C}$H$_3$)$_2$C, ($\underline{C}$H$_3$)$_2$CH); MS (EI) *m*/z (%) 265 (M^+-*i*-Pr, 3), 200 (32), 157 (79), 143 (54), 129 (61), 115 (42), 105 (59), 91 (100), 79 (60), 77 (90). Anal. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15. Found: C, 85.80; H, 8.96.

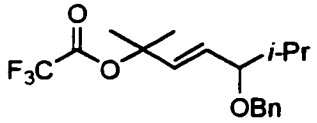
(E)-5-Benzyloxy-2,6-dimethyl-3-hepten-2-yl pivalate (224)



n-BuLi (0.29 mL, 1.55 M, 0.45 mmol) was added dropwise to a solution of alcohol **209** (102 mg, 0.41 mmol) in THF (2 mL) and the resulting solution was stirred for 30 min. The pivavoyl chloride (55μL, 0.45 mmol) in THF (1 mL) was added to the solution dropwise. The solution was heated at reflux until complete by TLC (1 h). The solution was cooled to 0°C and hydrolyzed with water (1 mL). The aqueous layer was extracted with Et_2O (3 × 5 mL) and the combined organic layers were dried over Na_2SO_4. The solvent was removed *in vacuo*. The crude oil was purified by column chromatography (5% Et_2O in hexanes) to afford 58 mg (42%) of a clear, colourless oil. IR (neat) 3032, 2973, 2934, 2874, 1728 (C=O), 1480, 1283, 1176, 1119, 1068, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.24 (5H, m, $C_6\underline{H}_5$), 5.87

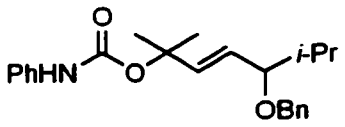
(1H, d, J = 15.9 Hz, =C<u>H</u>C), 5.52 (1H, dd, J = 15.9, 8.4 Hz, =C<u>H</u>CH), 4.59 (1H, A of AB, d, J_{obs} = 12.2 Hz, C<u>H</u>$_2$Ph), 4.36 (1H, B of AB, d, J_{obs} = 12.2 Hz, C<u>H</u>$_2$Ph), 3.39 (1H, dd, J = 8.4, 7.1 Hz, C<u>H</u>OBn), 1.77 (1H, dqq, 7.1, 6.8, 6.7 Hz, C<u>H</u>(CH$_3$)$_2$), 1.54 (3H, s, C<u>H</u>$_3$CO), 1.51 (3H, s, C<u>H</u>$_3$CO), 1.17 (9H, s, (C<u>H</u>$_3$)$_3$C), 0.96 (3H, d, J = 6.7 Hz, C<u>H</u>$_3$CH), 0.86 (3H, d, J = 6.8 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 177.2 (<u>C</u>=O), 144.3, 139.0, 128.2, 127.8 (2C), 127.4, 127.2 (2C) (H<u>C</u>=<u>C</u>H, ArC's), 84.6 (<u>C</u>HOBn), 79.2 (O<u>C</u>(CH$_3$)$_2$), 69.8 (<u>C</u>H$_2$Ph), 39.1 (<u>C</u>(CH$_3$)$_3$), 32.8 (<u>C</u>H(CH$_3$)$_2$), 27.1 (3C, (<u>C</u>H$_3$)$_3$C), 26.9, 26.5, 18.8, 18.4 ((<u>C</u>H$_3$)$_2$C, (<u>C</u>H$_3$)$_2$CH); MS (EI) m/z (%) 289 (M^+- i-Pr, 0.3), 107 (20), 91 (100), 79 (16), 77 (12), 57 (29). Anal. Calcd for $C_{21}H_{32}O_3$: C, 75.86; H, 9.70. Found: C, 76.02; H, 9.57.

(E)-5-Benzyloxy-2,6-dimethyl-3-hepten-2-yl trifluoroacetate (225)



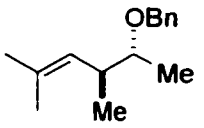
Trifluoroacetic anhydride (0.24 mL, 1.7 mmol) was added dropwise to a solution of alcohol **209** (0.33 g, 1.3 mmol) in pyridine (3.5 mL) at 0°C. After the reaction was complete by TLC (3 h) it was quenched by pouring it into cold water (4 mL). The resulting mixture was diluted with Et_2O (4 mL) and washed with 1 M HCl (4 mL), saturated $NaHCO_3$ solution (3 × 4 mL), water (2 × 4 mL) and brine (4 mL). The organic layer was dried over Na_2SO_4 and concentrated *in vacuo* to afford 0.38 g (84%) of a clear, pale yellow oil. The crude trifluoroacetate was used without purification due to its instability. IR (neat) 3033, 2963, 2874, 1950, 1781 (C=O), 1672 (C=C), 1456, 1368, 1220, 1170, 1109, 736, 698 cm^{-1}; ^{19}F (282 MHz, $CDCl_3$) δ -76.02 (s); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.24 (5H, m, C$_6$<u>H</u>$_5$), 5.89 (1H, d, J = 16.0 Hz, =C<u>H</u>C), 5.68 (1H, dd, J = 16.0, 7.9 Hz, =C<u>H</u>CH), 4.57 (1H, A of AB, d, J_{obs} = 12.0 Hz, C<u>H</u>$_2$Ph), 4.35 (1H, B of AB, d, J_{obs} = 12.0 Hz, C<u>H</u>$_2$Ph), 3.45 (1H, dd, J = 7.9, 7.2 Hz, C<u>H</u>OBn), 1.82 (1H, dqq, J = 7.2, 6.9, 6.7 Hz, C<u>H</u>(CH$_3$)$_2$), 1.67 (3H, s, C<u>H</u>$_3$C), 1.64 (3H, s, C<u>H</u>$_3$C), 1.01 (3H, d, J = 6.7 Hz, C<u>H</u>$_3$CH), 0.86 (3H, d, J = 6.9 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.2 (q, $J_{C\text{-}F}$ = 45 Hz, <u>C</u>=O), 138.6, 135.3, 130.6, 128.3 (2C), 127.7 (2C), 127.4 (H<u>C</u>=<u>C</u>H, ArC's), 116.3 (q, $J_{C\text{-}F}$ = 285 Hz, <u>C</u>F$_3$), 86.0 (<u>C</u>(CH$_3$)$_2$), 84.4 (<u>C</u>HOBn), 70.3 (<u>C</u>H$_2$Ph), 32.8 (<u>C</u>H(CH$_3$)$_2$), 26.5, 26.4 ((<u>C</u>H$_3$)$_2$CO), 18.0, 18.3 ((<u>C</u>H$_3$)$_2$CH).

(E)-5-Benzyloxy-2,6-dimethyl-3-hepten-2-yl-N-phenylcarbamate (226)



A procedure to similar to the one above was followed, replacing trifluoroacetic anhydride with phenyl isocyanate. The crude solid was purified via column chromatography (1:7 EtOAc:hexanes) to afford a white solid (60% yield, mp = 84-86°C). IR ($CHCl_3$) 3437 (NH), 3018, 2962, 2935, 2872, 1950, 1726 (C=O), 1521, 1440, 1383, 1216, 1122, 755, 698 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37-7.24 (9H, m, $C_6\underline{H}_5CH_2$, $NHC_6\underline{H}_4$), 7.06 (1H, dd, J = 7.3, 7.3 Hz, *p*-H from NHPh), 6.50 (1H, br s, N$\underline{H}$), 5.99 (1H, d, J = 16.0 Hz, =C$\underline{H}$C), 5.58 (1H, dd, J = 16.0, 8.3 Hz, =C$\underline{H}$CH), 4.62 (1H, A of AB, d, J_{obs} = 12.1 Hz, C$\underline{H}_2$Ph), 4.39 (1H, B of AB, d, J_{obs} = 12.1 Hz, C$\underline{H}_2$Ph), 3.43 (1H, dd, J = 8.3, 7.5 Hz, C$\underline{H}$OBn), 1.32 (1H, dqq, J = 7.5, 6.8, 6.7 Hz, C$\underline{H}(CH_3)_2$), 1.62 (3H, s, C$\underline{H}_3$C), 1.60 (3H, s, C$\underline{H}_3$C), 0.97 (3H, d, J = 6.7 Hz, C$\underline{H}_3$CH), 0.91 (3H, d, J = 6.8 Hz, C$\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.2 (C=O), 138.9, 138.7, 138.2, 128.9 (2C), 128.2 (2C), 127.8, 127.7 (2C), 127.2, 123.1, 118.5 (2C) (H$\underline{C}$=$\underline{C}$H, ArC's), 84.7 ($\underline{C}$HOBn), 80.2 ($\underline{C}(CH_3)_2$), 70.0 ($\underline{C}H_2$Ph), 32.8 ($\underline{C}H(CH_3)_2$), 27.4, 27.2, 18.8, 18.4 ($(CH_3)_2C$, ($\underline{C}H_3)_2CH$); MS (ES+) *m/z* $(M+NH_4)^+$: 385.48. Anal. Calcd for $C_{23}H_{29}NO_3$: C, 75.17; H, 7.95; N, 3.81. Found: C, 75.21; H, 7.90; N, 3.93.

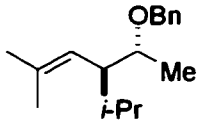
(4R, 5S*)-5-Benzyloxy-2,4-dimethyl-2-hexene (227)*



The reaction was performed using General Procedure E with acetate **211** (78 mg, 0.30 mmol), MeMgBr (0.20 mL, 2.94 M, 0.59 mmol) and CuCN (14 mg, 0.16 mmol). The crude oil (*anti*:*syn* = 78:22 by GC/MS analysis) was purified via column chromatography (4:1 hexanes:CH_2Cl_2) to give 50 mg (77%) of a clear, colourless oil. IR (neat) 3031, 2971, 2927, 2870, 1946, 1871, 1804, 1672 (C=C), 1453, 1375, 1096, 1065, 734, 697 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.26 (5H, m, $C_6\underline{H}_5$), 5.04 (0.78H, d, J = 9.3 Hz, =C$\underline{H}$), 4.98 (0.22H, d, J = 8.9 Hz, =C$\underline{H}$), 4.62 (0.22H, A of AB, d, J_{obs} = 11.5 Hz, C$\underline{H}_2$Ph), 4.60 (0.78H, A of AB, d, J_{obs} = 12.0 Hz, C$\underline{H}_2$Ph), 4.50 (0.78H, B of AB, d, J_{obs} = 12.0 Hz, C$\underline{H}_2$Ph), 4.46 (0.22H, B of

AB, d, J_{obs} = 11.5 Hz, C$\underline{H}_2$Ph), 3.43 (0.78H, dq, J = 6.8, 6.8 Hz, C$\underline{H}$OBn), 3.32 (0.22H, dq, J = 6.7, 6.7 Hz, C$\underline{H}$OBn), 2.66-2.54 (0.78H, m, C$\underline{H}$HC=), 2.52-2.46 (0.22H, m, C$\underline{H}$HC=), 1.70 (3H, s, C$\underline{H}_3$C=), 1.63 (0.66H, s, C$\underline{H}_3$C=), 1.60 (2.34H, s, C$\underline{H}_3$C=), 1.15 (0.66H, d, J = 6.7 Hz, $\underline{C}$H$_3$CHOBn), 1.11 (2.34H, d, J = 6.8 Hz, $\underline{C}$H$_3$CHOBn), 1.01 (0.66H, d, J = 6.7 Hz, $\underline{C}$H$_3$CHHC=), 0.97 (2.34H, d, J = 6.8 Hz, $\underline{C}$H$_3$CHHC=); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3; 131.5; 128.2 (2C); 127.6, 127.5* (2C); 127.4, 127.3*; 127.2 ($\underline{C}$=$\underline{C}$H, ArC's); 79.5, 78.4* ($\underline{C}$HOBn); 70.8, 70.6* ($\underline{C}$H$_2$Ph); 38.7, 37.2* ($\underline{C}$HHC=); 25.9; 18.0, 17.5*; 17.1, 16.1*; 16.0 (2 × $\underline{C}$H$_3$C=, 2 × $\underline{C}$H$_3$CH); MS (EI) *m/z* (%) 203 (M$^+$-CH$_3$, 1), 135 (17), 95 (18), 91 (100), 83 (63), 79 (12), 77 (11), 67 (15), 65 (12), 55 (33). GC/MS retention times (Program 2): 12.79 (*anti*), 12.91 (*syn*) min. Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.68; H, 9.92.

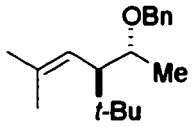
(4R, 5S*)-5-Benzyloxy-4-isopropyl-2-methyl-2-hexene (228)*



The reaction was performed using General Procedure E with acetate **211** (202 mg, 0.77 mmol), *i*-PrMgCl (0.66 mL, 2.30 M, 1.5 mmol) and CuCN (7 mg, 0.08 mmol). The crude oil (*anti*:*syn* = 74:26 by GC/MS analysis) was purified via column chromatography (3:1 hexanes: CH_2Cl_2) to give 132 mg (70%) of a clear, colourless oil. IR (neat) 3031, 2966, 2927, 2870, 1945, 1870, 1805, 1674 (C=C), 1454, 1372, 1114, 1093, 1071, 734, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.60-7.24 (5H, m, C$_6\underline{H}_5$), 5.13 (0.74H, d, J = 10.3 Hz, =C$\underline{H}$), 4.90 (0.26H, d, J = 10.7 Hz, =C$\underline{H}$), 4.62 (1H, A of AB, d, J_{obs} = 11.9 Hz, C$\underline{H}_2$Ph), 4.44 (0.26H, B of AB, d, J_{obs} = 11.6 Hz, C$\underline{H}_2$Ph), 4.40 (0.74H, B of AB, J_{obs} = 11.9 Hz, C$\underline{H}_2$Ph), 3.68 (0.74H, qd, J = 6.2, 3.8 Hz, C$\underline{H}$OBn), 3.45 (0.26H, dq, J = 8.6, 6.1 Hz, C$\underline{H}$OBn), 2.31 (0.26H, ddd, J = 10.7, 8.6, 4.4, C$\underline{H}$HC=), 2.22-2.05 (0.26H, m, C$\underline{H}$(CH$_3$)$_2$), 1.98-1.90 (0.74H, m, C$\underline{H}$HC=), 1.84-1.75 (0.74H, m, C$\underline{H}$(CH$_3$)$_2$), 1.75 (2.22H, s, C$\underline{H}_3$C=), 1.74 (0.78H, s, C$\underline{H}_3$C=), 1.63 (0.78H, s, C$\underline{H}_3$C=), 1.59 (2.22H, s, C$\underline{H}_3$C=), 1.12 (3H, d, J = 6.2 Hz, C$\underline{H}_3$CHOBn), 0.88 (2.22H, d, J = 6.6 Hz, C$\underline{H}_3$CHCH$_3$), 0.82 (3H, d, J = 6.7 Hz, C$\underline{H}_3$CHCH$_3$), 0.77 (0.78H, d, J = 6.8 Hz, C$\underline{H}_3$CHCH$_3$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.5*, 139.2; 133.9, 132.8*; 128.4, 128.3* (2C); 127.9, 127.6*; 127.5*, 127.3 (2C); 124.4 ($\underline{C}$=$\underline{C}$H, ArC's); 76.1, 75.9* ($\underline{C}$HOBn); 70.8, 70.7*

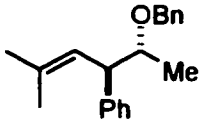
($\underline{C}H_2Ph$); 51.1*, 49.8 ($\underline{C}H$*i*-Pr); 29.3*, 27.8 ($\underline{C}HCH_3$); 26.3*, 26.2; 21.5, 21.4*; 20.5*, 18.7; 18.5*, 17.5; 17.8*, 17.2 (2 × $\underline{C}H_3C$=, $\underline{C}H_3CH$, ($\underline{C}H_3)_2CH$); MS (EI) *m*/z (%) 231 (M^+-Me, 0.2), 91 (100), 82 (18), 81 (20), 77 (27), 69 (38), 67 (35), 55 (25). GC/MS retention times (Program 1): 4.33 (*anti*), 4.51 (*syn*) min. Anal. Calcd for $C_{17}H_{26}O$: C, 82.87; H, 10.64. Found: C, 82.68; H, 10.50.

(4R, 5R*)-5-Benzyloxy-4-tert-butyl-2-methyl-2-hexene (229)*



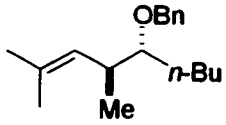
The reaction was performed using General Procedure E with acetate **211** (200 mg, 0.76 mmol), *t*-BuMgCl (1.5 mL, 1.03 M, 1.6 mmol) and CuCN (7 mg, 0.08 mmol). The crude oil (*anti*:*syn* = 83:17 by GC/MS analysis) was purified via column chromatography (6:1 hexanes: CH_2Cl_2) to give 144 mg of ***anti*-229** and 32 mg of ***syn*-229** (total 176 mg, 89%) of a clear, colourless oil. IR (neat) 3031, 2965, 2929, 2868, 1945, 1871, 1804, 1672 (C=C), 1454, 1375, 1094, 1076, 733, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) ***anti*-229**: δ 7.34-7.26 (5H, m, $C_6\underline{H}_5$), 5.41 (1H, d, J = 11.0 Hz, =C$\underline{H}$), 4.60 (1H, A of AB, d, J_{obs} = 11.7 Hz, C$\underline{H}_2$Ph), 4.38 (1H, B of AB, J_{obs} = 11.7 Hz, C$\underline{H}_2$Ph), 3.90 (1H, qd, J = 6.2, 1.6 Hz, C$\underline{H}$OBn), 1.92 (1H, dd, J = 11.0, 1.6 Hz, C$\underline{H}$*t*-Bu), 1.78 (3H, s, C$\underline{H}_3$C=), 1.59 (3H, s, C$\underline{H}_3$C=), 1.08 (3H, d, J = 6.2 Hz, C$\underline{H}_3$CH), 0.91 (9H, s, ($C\underline{H}_3)_3C$); ***syn*-229**: δ 7.36-7.24 (5H, m, $C_6\underline{H}_5$), 5.06 (1H, d, J = 11.0 Hz, =C$\underline{H}$), 4.54 (1H, A of AB, d, J_{obs} = 11.7 Hz, C$\underline{H}_2$Ph), 4.49 (1H, B of AB, d, J_{obs} = 11.7 Hz, C$\underline{H}_2$Ph), 3.62 (1H, qd, J = 6.1, 5.0 Hz, C$\underline{H}$OBn), 2.40 (1H, dd, J = 11.0, 5.0 Hz, C$\underline{H}$*t*-Bu), 1.75 (3H, s, C$\underline{H}_3$C=), 1.65 (3H, s, C$\underline{H}_3$C=), 1.13 (3H, d, J = 6.1 Hz, C$\underline{H}_3$CH), 0.90 (9H, s, ($C\underline{H}_3)_3C$); ^{13}C NMR (75 MHz, $CDCl_3$) ***anti*-229**: δ 139.3, 133.0, 128.1 (2C), 127.4, 127.1 (2C), 122.3 ($\underline{C}$=$\underline{C}$H, ArC's), 75.0 ($\underline{C}$HOBn), 70.2 ($\underline{C}H_2$Ph), 53.5 ($\underline{C}$H*t*-Bu), 34.2 ($\underline{C}(CH_3)_3$), 28.8 (3C, ($\underline{C}H_3)_3C$), 26.3, 18.6, 18.3 (2 × $\underline{C}H_3C$=, $\underline{C}H_3CH$); ***syn*-229**: δ 139.1, 132.8, 128.2 (2C), 127.7 (2C), 127.3, 123.2 ($\underline{C}$=$\underline{C}$H, ArC's), 76.0 ($\underline{C}$HOBn), 70.1 ($\underline{C}H_2$Ph), 51.7 ($\underline{C}$H*t*-Bu), 33.4 ($\underline{C}(CH_3)_3$), 28.7 (3C, ($\underline{C}H_3)_3C$), 26.2, 18.5, 18.1 (2 × $\underline{C}H_3C$=, $\underline{C}H_3CH$); MS (EI) *m*/z (%) both diastereomers: 231 (M^+-*t*-Bu, 0.2), 125 (20, 91 (100), 69 (29), 67 (21), 57 (26), 55 (20). GC/MS retention times (Program 2): 14.82 (*anti*), 15.02 (*syn*) min. Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 83.29; H, 10.61.

(4R, 5R*)-5-Benzyloxy-2-methyl-4-phenyl-2-hexene (230)*



The reaction was performed using General Procedure E with acetate **211** (202 mg, 0.77 mmol), PhMgBr (0.54 mL, 2.82 M, 1.5 mmol) and CuCN (37 mg, 0.41 mmol). The crude oil (*anti*:*syn* = 79:21 by ^{1}H NMR analysis) was purified via column chromatography (3:2 hexanes: CH_2Cl_2) to give 139 mg (64%) of a clear, colourless oil. IR (neat) 3086, 3028, 2971, 2927, 2863, 1947, 1871, 1806, 1672 (C=C), 1452, 1374, 1092, 735, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.18 (10H, m, 2 × $C_6\underline{H}_5$), 5.58 (0.79H, d, J = 9.4 Hz, =C$\underline{H}$), 5.42 (0.21H, d, J = 9.3 Hz, =C$\underline{H}$), 4.57 (0.79H, A of AB, d, J_{obs} = 12.0 Hz, C$\underline{H}_2$Ph), 4.48 (0.21H, A of AB, d, J_{obs} = 11.6 Hz, C$\underline{H}_2$Ph), 4.43 (0.79H, B of AB, d, J_{obs} = 12.0 Hz, C$\underline{H}_2$Ph), 4.27 (0.21H, B of AB, d, J_{obs} = 11.6 Hz, C$\underline{H}_2$Ph), 3.75-3.65 (1H, m, C$\underline{H}$OBn), 3.62-3.55 (1H, m, C$\underline{H}$Ph), 1.75 (2.37H, s, C$\underline{H}_3$C=), 1.72 (0.63H, s, C$\underline{H}_3$C=), 1.65 (0.63H, s, C$\underline{H}_3$C=), 1.61 (2.37H, s, C$\underline{H}_3$C=), 1.20 (0.63H, d, J = 5.9 Hz, C$\underline{H}_3$CH), 1.09 (2.37H, d, J = 6.2 Hz, C$\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.4; 138.9*, 138.6; 133.1*, 132.9; 128.8*, 128.7 (2C); 128.2 (2C); 128.1*, 128.0 (2C); 127.5 (2C); 127.2; 125.9*, 125.8; 124.8 (C=$\underline{C}$H, ArC's); 80.0, 79.9* ($\underline{C}$HOBn); 71.0 ($\underline{C}H_2$Ph); 50.9, 50.5* ($\underline{C}$HPh); 26.0; 18.2; 17.9*, 17.5 (2 × $\underline{C}H_3$C=, $\underline{C}H_3$CH); MS (EI) *m*/*z* (%) 173 (M^+-OBn, 4), 157 (12), 146 (13), 145 (80), 129 (17), 128 (13), 117 (12), 115 (12), 105 (10), 91 (100), 79 (4), 77 (21), 65 (14), 51 (13). GC/MS retention time (Program 2): 18.55 (*anti*) min. Anal. Calcd for $C_{20}H_{24}O$: C, 85.67; H, 8.63. Found: C, 85.50; H, 8.48.

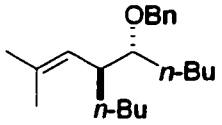
(4R, 5S*)-5-Benzyloxy-2,4-dimethyl-2-nonene (231)*



The reaction was performed using General Procedure E with acetate **212** (126 mg, 0.41 mmol), MeMgBr (0.28 mL, 2.94 M, 0.82 mmol) and CuCN (19 mg, 0.21 mmol). The crude oil (*anti*:*syn* = 88:12 by GC/MS analysis) was purified via column chromatography (9:1 hexanes:CH_2Cl_2) to give 80 mg (75%) of a clear, colourless oil. IR (neat) 2930, 2860, 1944, 1804, 1671 (C=C), 1454, 1067, 733, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 (5H, m,

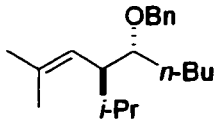
$C_6\underline{H}_5$), 5.07 (0.88H, d, J = 9.4Hz, =C$\underline{H}$), 5.02 (0.12H, d, J = 9.4 Hz, =C$\underline{H}$), 4.59 (1H, A of AB, d, J_{obs} = 11.5 Hz, C$\underline{H}_2$Ph), 4.53 (1H, B of AB, d, J_{obs} = 11.5 Hz, C$\underline{H}_2$Ph), 3.22-3.18 (1H, m, C$\underline{H}$OBn), 2.72-2.63 (1H, m, C$\underline{H}$CH$_3$), 1.70 (3H, s, C$\underline{H}_3$C=), 1.61 (3H, s, C$\underline{H}_3$C=), 1.55-1.19 (6H, m, (C$\underline{H}_2$)$_3$CH$_3$), 0.98 (3H, d, J = 6.9 Hz, C$\underline{H}_3$CH), 0.91 (3H, t, J 6.9 Hz, C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.2; 131.3*, 130.8; 128.2 (2C); 127.9; 128.8, 127.7* (2C); 127.3 (C=$\underline{C}$H, ArC's); 83.8, 83.3* ($\underline{C}$HOBn); 72.0, 71.9* ($\underline{C}$H$_2$Ph); 36.3, 35.3* ($\underline{C}$HCH$_3$); 31.2, 30.7*; 28.4*, 27.7; 25.9; 22.9*, 22.6 (($\underline{C}$H$_2$)$_3$, $\underline{C}$H$_3$C=); 18.0*, 17.9; 17.2, 16.3* ($\underline{C}$H$_3$CH, $\underline{C}$H$_3$C=); 14.1 ($\underline{C}$H$_3$CH$_2$); MS (EI) *m/z* (%) 203 (M$^+$-*n*-Bu, 0.1), 95 (34), 83 (38), 81 (22), 79 (26), 77 (20), 67 (32), 55 (32). GC/MS retention times (Program 2): 15.31 (*anti*), 15.41 (*syn*) min. Anal. Calcd for $C_{18}H_{28}O$: C, 83.02; H, 10.84. Found: C, 82.91; H, 10.69.

(4R, 5S*)-5-Benzyloxy-4-butyl-2-methyl-2-nonene (232)*



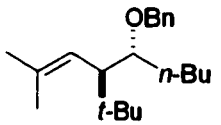
The reaction was performed using General Procedure E with acetate **212** (203 mg, 0.67 mmol), *n*-BuMgBr (0.48 mL, 2.71 M, 1.3 mmol) and CuCN (8 mg, 0.09 mmol). The crude oil (*anti*:*syn* = 90:10 by GC/MS analysis) was purified via column chromatography (6:1 hexanes: CH_2Cl_2) to give 178 mg (89%) of a clear, colourless oil. IR (neat) 3031, 2957, 2930, 2859, 1672 (C=C), 1455, 1377, 1095, 1067, 732, 697 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.26 (5H, m, $C_6\underline{H}_5$), 5.02 (0.90H, d, J = 9.5 Hz, =C$\underline{H}$), 4.92 (0.10H, d, J = 9.6 Hz, =C$\underline{H}$), 4.57-4.51 (2H, AB of AB, m, C$\underline{H}_2$Ph), 3.29-3.16 (1H, m, C$\underline{H}$OBn), 2.55-2.39 (1H, m, C$\underline{H}$HC=), 1.72 (3H, s, C$\underline{H}_3$C=), 1.60 (3H, s, C$\underline{H}_3$C=), 1.62-1.12 (12H, m, 2 × (C$\underline{H}_2$)$_3$CH$_3$), 0.96-0.79 (6H, m, 2 × C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3*, 139.0; 132.3*, 132.2; 128.2*, 127.9 (2C); 127.7 (2C); 127.3; 126.5, 126.2* (C=$\underline{C}$H, ArC's); 83.0, 82.7* ($\underline{C}$HOBn); 71.9*, 71.8 ($\underline{C}$H$_2$Ph); 41.7, 41.1* ($\underline{C}$HHC=); 31.5, 31.0*; 30.7; 30.0*, 29.7; 28.6*, 27.7; 26.0; 22.9 (2C); 18.4, 18.2* (2 × ($\underline{C}$H$_2$)$_3$CH$_3$, 2 × $\underline{C}$H$_3$C=); 14.1 (2C, 2 × $\underline{C}$H$_3$CH$_2$); MS (EI) *m/z* (%) 245 (M$^+$-*n*-Bu, 0.1), 137 (40), 109 (26), 108 (25), 107 (23), 95 (100), 91 (93), 81 (97), 79 (64), 77 (56), 69 (37), 55 (36). GC/MS retention times (Program 1): 11.39 (*anti*), 11.63 (*syn*) min. Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.12; H, 11.15.

(4R, 5S*)-5-Benzyloxy-4-isopropyl-2-methyl-2-nonene (233)*



The reaction was performed using General Procedure E with acetate **212** (205 mg, 0.67 mmol), *i*-PrMgCl (0.80 mL, 1.65 M, 1.3 mmol) and CuCN (7 mg, 0.08 mmol). The crude oil (*anti*:*syn* = 79:21 by GC/MS analysis) was purified via column chromatography (6:1 hexanes: CH_2Cl_2) to give 166 mg (85%) of a clear, colourless oil. IR (neat) 3031, 2957, 2930, 2870, 1674 (C=C), 1454, 1096, 1068, 733, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (5H, m, $C_6\underline{H}_5$), 5.16 (0.79H, d, J = 10.8 Hz, =C$\underline{H}$), 4.90 (0.21H, d, J = 10.9 Hz, =C$\underline{H}$), 4.57 (0.79H, A of AB, d, J_{obs} = 11.6 Hz, C$\underline{H}_2$Ph), 4.55 (0.21H, A of AB, d, J_{obs} = 11.2 Hz, C$\underline{H}_2$Ph), 4.49 (0.21H, B of AB, d, J_{obs} = 11.2 Hz, C$\underline{H}_2$Ph), 4.47 (0.79H, B of AB, d, J_{obs} = 11.6 Hz, C$\underline{H}_2$Ph), 3.51-3.45 (0.79H, m, C$\underline{H}$OBn), 2.45-2.35 (0.21H, m, C$\underline{H}$OBn), 2.10-2.00 (1H, m, C$\underline{H}$*i*-Pr), 1.80 (1H, dqq, J = 6.8, 6.8, 6.8 Hz, C$\underline{H}(CH_3)_2$), 1.74 (3H, s, C$\underline{H}_3$C=), 1.62 (0.63H, s, C$\underline{H}_3$C=), 1.59 (2.37H, s, C$\underline{H}_3$C=), 1.43-1.20 (6H, m, $(C\underline{H}_2)_3CH_3$), 0.91-0.77 (9H, m, $(C\underline{H}_3)_2CH$, $C\underline{H}_3CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.4*, 139.0; 133.3, 132.5*; 128.1*, 128.0 (2C); 127.5*, 127.4 (2C); 127.2; 124.2*, 122.7 (C=CH, ArC's); 80.6*, 79.8 (CHOBn); 71.7*, 71.3 ($C\underline{H}_2$Ph); 48.4*, 47.0 (C$\underline{H}$*i*-Pr); 31.7*, 30.7 (C$\underline{H}(CH_3)_2$); 29.2; 28.2*, 27.0; 26.2, 26.0*; 23.0; 21.5*, 21.4; 20.5; 18.5 ($(C\underline{H}_2)_3CH_3$, 2 × C$\underline{H}_3$C=, $(C\underline{H}_3)_2$CH); 14.1 ($C\underline{H}_3CH_2$); MS (EI) *m*/z (%) 197 (M^+-Bn, 0.2), 123 (31), 95 (60), 91 (100), 81 (71), 79 (48), 77 (44), 69 (34). GC/MS retention times (Program 1): 8.05 (*anti*), 8.36 (*syn*) min. Anal. Calcd for $C_{20}H_{32}O$: C, 83.27; H, 11.18. Found: C, 83.51; H, 10.99.

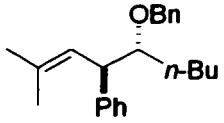
(4R, 5R*)-5-Benzyloxy-4-tert-butyl-2-methyl-2-nonene (234)*



The reaction was performed using General Procedure E with acetate **212** (202 mg, 0.66 mmol), *t*-BuMgCl (1.3 mL, 1.03 M, 1.3 mmol) and CuCN (6 mg, 0.07 mmol). The crude oil (*anti*:*syn* = 87:13 by GC/MS analysis) was purified via column chromatography (10:1 hexanes: CH_2Cl_2) to give 180 mg (89%) of a clear, colourless oil. IR (neat) 3031, 2957, 2863, 1944, 1865, 1804,

1671 (C=C), 1455, 1363, 1096, 1069, 732, 696 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.26 (5H, m, $C_6\underline{H}_5$), 5.41 (0.87H, d, J = 11.0 Hz, =C$\underline{H}$), 5.10 (0.13H, d, J = 9.2 Hz, =C$\underline{H}$), 4.58 (0.87H, A of AB, d, J_{obs} = 11.6 Hz, C$\underline{H}_2$Ph), 4.55 (0.13H, A of AB, d, J_{obs} = 10.2 Hz, C$\underline{H}_2$Ph), 4.43 (0.87H, B of AB, d, J_{obs} = 11.6 Hz, C$\underline{H}_2$Ph), 4.39 (0.13H, B of AB, d, J_{obs} = 10.2 Hz, C$\underline{H}_2$Ph), 3.62-3.58 (0.87H, m, C$\underline{H}$OBn), 3.51-3.45 (0.13H, m, C$\underline{H}$OBn), 2.48-2.44 (0.13H, d, 10.9 Hz, C$\underline{H}$*t*-Bu), 2.06 (0.87H, d, J =11.0 Hz, C$\underline{H}$*t*-Bu), 1.77 (2.61H, s, C$\underline{H}_3$C=), 1.74 (0.39H, s, C$\underline{H}_3$C=), 1.64 (0.39H, s, C$\underline{H}_3$C=), 1.59 (2.61H, s, C$\underline{H}_3$C=), 1.42-1.15 (6H, m, (C$\underline{H}_2$)$_3$CH$_3$) 0.91 (9H, s, (C$\underline{H}_3$)$_3$C), 0.91 (3H, m, C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 139.3*, 138.9; 132.9*, 132.7; 128.2, 128.1* (2C); 127.4*, 127.3 (2C); 127.1; 123.0, 122.5* (C=C$\underline{H}$, ArC's); 80.1, 79.9* (C$\underline{H}$OBn); 70.6 (C$\underline{H}_2$Ph); 50.3*, 49.5 (C$\underline{H}$*t*-Bu); 34.1*, 33.2 (C(CH$_3$)$_3$); 32.1*, 32.0 (C$\underline{H}_2$CHOBn); 28.9*, 28.8 (3C, (C$\underline{H}_3$)$_3$C); 28.7*, 28.1; 26.3; 23.0*, 22.8; 18.5*, 18.4 (2 × C$\underline{H}_3$C=, (C$\underline{H}_2$)$_2$CH$_3$); 14.2, 14.1* (C$\underline{H}_3$CH$_2$); MS (EI) *m*/z (%) 245 (M^+-*t*-Bu, 0.1), 95 (42), 91 (100), 81 (27), 77 (27), 57 (30). GC/MS retention times (Program 1): 9.56 (*anti*), 9.71 (*syn*) min. Anal. Calcd for $C_{21}H_{34}O$: C, 83.38; H, 11.33. Found: C, 83.52; H, 11.42.

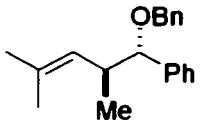
(4R, 5R*)-5-Benzyloxy-2-methyl-4-phenyl-2-nonene (235)*



The reaction was performed using General Procedure E with acetate **212** (201 mg, 0.66 mmol), PhMgBr (0.47 mL, 2.82 M, 1.3 mmol) and CuCN (31 mg, 0.34 mmol). The crude oil (*anti*:*syn* = 88:12 by ^1H NMR analysis) was purified via column chromatography (4:1 hexanes: CH_2Cl_2) to give 145 mg (68%) of a clear, colourless oil. IR (neat) 3028, 2957, 2930, 2860, 1945, 1871, 1804, 1671 (C=C), 1453, 1093, 1071, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.33-7.18 (10H, m, 2 × $C_6\underline{H}_5$), 5.63 (0.88H, d, J = 9.4 Hz, =C$\underline{H}$), 5.47 (0.12H, J = 9.5 Hz, =C$\underline{H}$), 4.44 (1H, A of AB, d, J_{obs} = 11.3 Hz, C$\underline{H}_2$Ph), 4.38 (1H, B of AB, d, J_{obs} = 11.3 Hz, C$\underline{H}_2$Ph), 3.71 (1H, dd, J = 9.5, 5.1 Hz, C$\underline{H}$OBn), 3.60-3.54 (1H, m, C$\underline{H}$Ph), 1.76 (2.64H, s, C$\underline{H}_3$C=), 1.72 (0.36H, s, C$\underline{H}_3$C=), 1.64 (0.36H, s, C$\underline{H}_3$C=), 1.61 (2.64H, s, C$\underline{H}_3$C=), 1.47-1.35 (2H, m, C$\underline{H}_2$CH), 1.35-1.20 (4H, m, (C$\underline{H}_2$)$_2$CH$_3$), 0.88-0.82 (3H, m, C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7*, 143.5; 138.9*, 138.6; 133.2*, 132.7; 128.5, 128.3* (2C); 128.2 (2C); 128.1 (2C); 128.0, 127.9* (2C); 127.7, 127.3*; 125.9; 124.8, 124.4* (C=C$\underline{H}$, ArC's); 83.6 (C$\underline{H}$OBn);

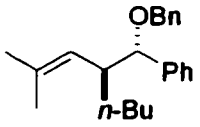
72.5, 72.4* ($\underline{C}H_2Ph$); 49.0, 48.3* ($\underline{C}HPh$); 32.3*, 31.8 ($\underline{C}H_2CH$); 28.0*, 27.7; 26.1, 26.0*; 22.8; 18.2 (2 × $\underline{C}H_3CH$=, ($\underline{C}H_2$)$_2CH_3$); 14.1 ($\underline{C}H_3CH_2$); MS (EI) *m/z* (%) 265 (M^+-*n*-Bu, 0.1), 157 (49), 145 (54), 143 (22), 129 (47), 128 (24), 91 (100), 79 (25), 77 (27). GC/MS retention time (Program 1): 22.81 (*anti, syn*) min. Anal. Calcd for $C_{23}H_{30}O$: C, 85.66; H, 9.38. Found: C, 85.72; H, 9.48.

(1R, 2R*)-1-Benzyloxy-2,4-dimethyl-1-phenyl-3-pentene (236)*



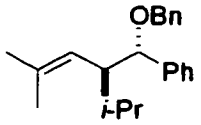
The reaction was performed using General Procedure E with acetate **214** (151 mg, 0.47 mmol), MeMgBr (0.31 mL, 2.94 M, 0.91 mmol) and CuCN (22 mg, 0.25 mmol). The crude oil (*anti*:*syn* = 93:7 by ^{1}H NMR analysis) was purified via column chromatography (2:1 hexanes: CH_2Cl_2) to give 121 mg (92%) of a clear, colourless oil. IR (neat) 3030, 2965, 2869, 1949, 1881, 1909, 1672 (C=C), 1495, 1453, 1094, 1066, 734, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37-7.26 (10H, m, 2 × $C_6\underline{H}_5$), 5.02 (0.93H, d, J = 9.3 Hz, =C$\underline{H}$), 4.93 (0.07H, d, J = 10.1Hz, =C$\underline{H}$), 4.51 (0.93H, A of AB, d, J_{obs} = 12.3 Hz, C$\underline{H}_2$Ph), 4.59 (0.07H, A of AB, d, J_{obs} = 11.9 Hz, C$\underline{H}_2$Ph), 4.26 (0.07H, B of AB, d, J_{obs} = 11.9 Hz, C$\underline{H}_2$Ph), 4.23 (0.93H, B of AB, d, J_{obs} = 12.3 Hz, C$\underline{H}_2$Ph), 4.12 (0.93H, d, J = 6.4 Hz, C$\underline{H}$OBn), 4.06 (0.07H, d, J = 7.3 Hz, C$\underline{H}$OBn), 2.79 (1H, dqd, J = 9.3, 6.8, 6.4 Hz, C$\underline{H}CH_3$), 1.69 (3H, s, C$\underline{H}_3$C=), 1.46 (3H, s, C$\underline{H}_3$C=), 0.83 (3H, d, J = 6.8 Hz, C$\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.9, 138.9, 131.8, 128.2 (2C), 127.6 (2C), 127.5 (2C), 127.4, 127.3, 127.2 (C=$\underline{C}$H, ArC's), 85.5 ($\underline{C}$HOBn), 70.3 ($\underline{C}H_2$Ph), 39.3 ($\underline{C}HCH_3$), 25.8, 17.9, 17.4 (2 × $\underline{C}H_3$C=, $\underline{C}H_3$CH); MS (EI) *m/z* (%) 173 (M^+-OBn, 2), 142 (19), 129 (27), 128 (18), 115 (16), 91 (100), 79 (27), 77 (32), 51 (18). GC/MS retention time (Program 1): 11.32 (*anti, syn*) min. Anal. Calcd for $C_{20}H_{24}O$: C, 85.67; H, 8.63. Found: C, 85.47; H, 8.65.

(1R, 2R*)-1-Benzyloxy-2-butyl-4-methyl-1-phenyl-3-pentene (237)*



The reaction was performed using General Procedure E with acetate **214** (301 mg, 0.93 mmol), *n*-BuMgBr (0.70 mL, 2.77 M, 1.9 mmol) and CuCN (10 mg, 0.11 mmol). The crude oil (homogenous by GC/MS and ^{1}H NMR analysis) was purified via column chromatography (10:1 hexanes: CH_2Cl_2) to give 281 mg (94%) of a clear, colourless oil. IR (neat) 3030, 2957, 2928, 2858, 1672 (C=C), 1454, 1091, 1068, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.25 (10H, m, 2 × $C_6\underline{H}_5$), 4.96 (1H, d, J = 9.9 Hz, =C$\underline{H}$), 4.52 (1H, A of AB, d, J_{obs} = 12.3 Hz, C$\underline{H}_2$Ph), 4.24 (1H, B of AB, d, J_{obs} = 12.3 Hz, C$\underline{H}_2$Ph), 4.24 (1H, d, J = 5.0 Hz, C$\underline{H}$OBn), 2.56 (1H, ddt, J = 9.9, 5.0, 5.0 Hz, C$\underline{H}$CH$_2$), 1.68 (3H, C$\underline{H}_3$C=), 1.49-0.99 (6H, m, (C$\underline{H}_2$)$_3$CH$_3$), 1.31 (3H, s, C$\underline{H}_3$C=), 0.83 (3H, t, J = 6.8 Hz, C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.3, 139.1, 132.9, 128.1 (2C), 127.8 (2C), 127.5 (2C), 127.4 (2C), 127.2, 127.0, 125.6 (C=C, ArC's), 84.5 (C$\underline{H}$OBn), 70.3 (C$\underline{H}_2$Ph), 45.1 (C$\underline{H}$CH$_2$), 31.6, 29.6, 25.9, 22.8, 18.0 (2 × C$\underline{H}_3$C=, (C$\underline{H}_2$)$_3$CH$_3$), 14.1 (C$\underline{H}_3$CH$_2$); MS (EI) *m/z* (%) 215 (M$^+$-OBn, 0.2), 197 (14), 91 (100), 69 (18). GC/MS retention time (Program 2): 19.30 (*anti*) min. Anal. Calcd for $C_{22}H_{30}O$: C, 85.66; H, 9.38. Found: C, 85.78; H, 9.52.

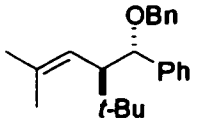
(1R, 2R*)-1-Benzyloxy-2-isopropyl-4-methyl-1-phenyl-3-pentene (238)*



The reaction was performed using General Procedure E with acetate **214** (150 mg, 0.46 mmol), *i*-PrMgCl (0.56 mL, 1.64 M, 0.92 mmol) and CuCN (5 mg, 0.05 mmol). The crude oil (*anti*:*syn* = 97:3 by GC/MS analysis) was purified via column chromatography (7:2 hexanes: CH_2Cl_2) to give 119 mg (83%) of a clear, colourless oil. IR (neat) 3030, 2961, 2868, 1946, 1871, 1806, 1676 (C=C), 1454, 1096, 1068, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.22 (10H, m, 2 × $C_6\underline{H}_5$), 5.15 (1H, d, J = 10.3 Hz, =C$\underline{H}$), 4.49 (1H, A of AB, d, J_{obs} = 12.0 Hz, C$\underline{H}_2$Ph), 4.48 (1H, d, J = 5.0 Hz, C$\underline{H}$OBn), 4.22 (1H, B of AB, d, J_{obs} = 12.0 Hz, C$\underline{H}_2$Ph), 2.22 (1H, ddd, J = 10.3, 6.7, 5.0 Hz, C$\underline{H}$*i*-Pr), 1.74 (1H, qqd, J = 6.8, 6.7, 6.7 Hz, C$\underline{H}$(CH$_3$)$_2$),

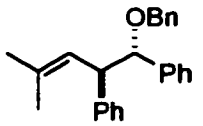
1.67 (3H, s, C<u>H</u>$_3$C=), 1.12 (3H, s, C<u>H</u>$_3$C=), 0.88 (3H, d, J = 6.7 Hz, C<u>H</u>$_3$CH), 0.80 (3H, d, J = 6.8 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.9, 139.0, 133.4, 128.1 (2C), 127.8 (2C), 127.5 (2C), 127.4 (2C), 127.2, 126.9, 123.0 (<u>C</u>=<u>C</u>H, ArC's), 82.6 (<u>C</u>HOBn), 70.4 (CH_2Ph), 52.0 (<u>C</u>H*i*-Pr), 29.3 (<u>C</u>H(CH_3)$_2$), 25.9, 21.4, 19.8, 17.8 (2 × <u>C</u>H$_3$C=, (<u>C</u>H$_3$)$_2$C); MS (EI) *m*/z (%) 201 (M^+-OBn, 2), 157 (84), 143 (33), 129 (52), 108 (35), 107 (27), 105 (34), 91 (100), 79 (51), 77 (58), 51 (28). GC/MS retention times (Program 1): 15.40 (*anti*), 15.84 (*syn*) min. Anal. Calcd for $C_{22}H_{28}O$: C, 85.66; H, 9.15. Found: C, 85.42; H, 9.37.

(1R, 2S*)-1-Benzyloxy-2-tert-butyl-4-methyl-1-phenyl-3-pentene (239)*



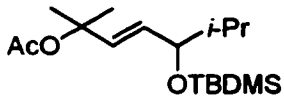
The reaction was performed using General Procedure E with acetate **214** (150 mg, 0.46 mmol), *t*-BuMgCl (0.99 mL, 0.99 M, 0.98 mmol) and CuCN (5 mg, 0.06 mmol) to give 129 mg (86%) of a clear, colourless oil (homogenous by GC/MS and ^{1}H NMR analysis). IR (neat) 3030, 2953, 2908, 2866, 1946, 1871, 1671 (C=C), 1453, 1362, 1094, 1068, 745, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.19 (10H, m, 2 × C$_6$<u>H</u>$_5$), 5.42 (1H, d, J = 11.0 Hz, =C<u>H</u>), 4.78 (1H, d, J = 1.4 Hz, C<u>H</u>OBn), 4.44 (1H, A of AB, d, J_{obs} = 11.6 Hz, C<u>H</u>$_2$Ph), 4.28 (1H, B of AB, d, J_{obs} = 11.6 Hz, C<u>H</u>$_2$Ph), 2.05 (1H, dd, J = 11.0, 1.4 Hz, C<u>H</u>*t*-Bu), 1.64 (3H, s, C<u>H</u>$_3$C=), 0.98 (9H, s, (C<u>H</u>$_3$)$_3$C), 0.85 (3H, s, C<u>H</u>$_3$C=); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.8, 138.8, 133.6, 128.1 (2C), 127.7 (2C), 127.6, 127.2, 126.8 (2C), 126.5, 120.4 (<u>C</u>=<u>C</u>H, ArC's), 81.4 (<u>C</u>HOBn), 70.4 (<u>C</u>H$_2$Ph), 55.4 (<u>C</u>H*t*-Bu), 34.1 (<u>C</u>(CH$_3$)$_3$), 28.9 (3C, (<u>C</u>H$_3$)$_3$C), 26.0, 17.3 (<u>C</u>H$_3$C=); MS (EI) *m*/z (%) 215 (M^+-OBn, 1), 158 (21), 157 (50), 143 (30), 128 (23), 115 (20), 108 (23), 91 (100), 79 (35), 77 (39), 57 (64), 51 (21). GC/MS retention time (Program 1): 17.48 (*anti*) min. Anal. Calcd for $C_{23}H_{30}O$: C, 85.66; H, 9.38. Found: C, 85.76; H, 9.50.

(1R, 2S*)-1-Benzyloxy-4-methyl-1,2-diphenyl-3-pentene (240)*



The reaction was performed using General Procedure E with acetate **214** (151 mg, 0.46 mmol), PhMgBr (0.33 mL, 2.81 M, 0.93 mmol) and CuCN (22 mg, 0.25 mmol). The crude oil (homogenous by GC/MS and ^{1}H NMR analysis) was purified via column chromatography (3:1 hexanes: CH_2Cl_2) to give 118 mg (74%) of a clear, colourless oil. IR (neat) 3062, 3028, 2968, 2913, 2861, 1948, 1872, 1806, 1671 (C=C), 1453, 1092, 1069, 767, 699 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31-7.10 (15H, m, 3 × $C_6\underline{H}_5$), 5.66 (1H, d, J = 9.3 Hz, =C$\underline{H}$), 4.52 (1H, d, J = 6.1 Hz, C$\underline{H}$OBn), 4.52 (1H, A of AB, d, J_{obs} = 12.2 Hz, C$\underline{H}_2$Ph), 4.24 (1H, B of AB, d, J_{obs} = 12.2, C$\underline{H}_2$Ph), 3.79 (1H, dd, J = 9.3, 6.1 Hz, C$\underline{H}$HC=), 1.72 (3H, s, $\underline{C}H_3$C=), 1.37 (3H, s, $\underline{C}H_3$C=); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9, 140.7, 138.7, 133.5, 128.6 (2C), 128.2 (2C), 127.0 (2C), 127.8 (2C), 127.5, 127.4 (2C), 127.3 (2C), 127.2, 125.9, 124.0 ($\underline{C}$=$\underline{C}$H, ArC's), 85.5 ($\underline{C}$HOBn), 70.5 ($\underline{C}H_2$Ph), 51.9 ($\underline{C}$HHC=), 26.0, 18.0 (2 × $\underline{C}H_3$C=); MS (EI) *m*/z (%) 235 (M^+-OBn, 3), 219 (21), 143 (24), 108 (29), 91 (100), 79 (30), 77 (35). GC/MS retention time (Program 2): 21.91 (*anti*) min. Anal. Calcd for $C_{25}H_{26}O$: C, 87.68; H, 7.65. Found: C, 87.54; H, 7.77.

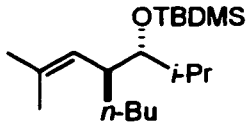
(E)-5-tert-Butyldimethylsilyloxy-2,6-dimethyl-3-hepten-2-yl acetate (241)



The reaction was performed using General Procedure A with silyl ether **270** (0.92 g, 3.4 mmol). The crude oil was purified via column chromatography (1:1 hexanes:CH_2Cl_2) to afford 0.77 g (70%, 2 steps) of a clear, colourless oil. IR (neat) 2958, 2931, 2889, 2859, 1740 (C=O), 1671 (C=C), 1472, 1383, 1251, 1128, 1068, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.82 (1H, d, J = 15.9 Hz, =C$\underline{H}$C), 5.52 (1H, dd, J = 15.9, 6.9 Hz, =C$\underline{H}$CH), 3.77 (1H, dd, J = 6.9, 6.4 Hz, C$\underline{H}$OSi), 1.95 (3H, s, C$\underline{H}_3$C=O), 1.69 (1H, qqd, J = 6.8, 6.8, 6.4 Hz, C$\underline{H}$(CH_3)$_2$), 1.49 (3H, s, C$\underline{H}_3$CO), 1.48 (3H, s, C$\underline{H}_3$CO), 0.87 (9H, s, ($\underline{CH}_3$)$_3$C), 1.03 (3H, d, J = 6.8 Hz, C$\underline{H}_3$CH), 0.82 (3H, d, J = 6.8 Hz, C$\underline{H}_3$CH), 0.01 (3H, s, C$\underline{H}_3$Si), -0.02 (3H, s, C$\underline{H}_3$Si); ^{13}C

NMR (75 MHz, $CDCl_3$) δ 169.8 (C=O), 134.9, 130.6 (HC=CH), 80.1 (COAc), 78.2 (CHOSi), 34.7 ($CH(CH_3)_2$), 27.0 (2C, $(CH_3)_2C$), 25.9 (3C, $(CH_3)_3C$), 22.2 (CH_3C=O), 18.3 (CH_3CH), 18.2 ($C(CH_3)_3$), 18.0 (CH_3CH), -4.2, -5.0 ($(CH_3)_2Si$); MS (EI) *m/z* (%) 271 (M^+-*i*-Pr, 1), 211 (53), 117 (12), 107 (17), 95 (13), 91 (15), 77 (11), 75 (100), 73 (14), 57 (16), 56 (18). Anal. Calcd for $C_{17}H_{34}O_3Si$: C, 64.92; H, 10.89. Found: C, 65.16; H, 10.67.

(4R, 5S*)-4-Butyl-5-tert-butyldimethylsilyloxy-2,6-dimethyl-2-heptene (242)*



The reaction was performed using General Procedure E with acetate **241** (200 mg, 0.63 mmol), *n*-BuMgBr (0.47 mL, 2.71 M, 1.3 mmol) and CuCN (8 mg, 0.09 mmol). The crude oil (*anti*:*syn* = 95:5 by GC/MS analysis) was purified via column chromatography (hexanes) to give 160 mg (81%) of a clear, colourless oil. IR (neat) 2958, 2929, 2858, 1672 (C=C), 1472, 1384, 1252, 1055, 835 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.06 (1H, d, J = 10.0 Hz, =CH), 3.29 (1H, dd, J = 5.1, 3.8 Hz, CHOSi), 2.35-2.26 (1H, m, CH*n*-Bu), 1.74-1.64 (1H, m $CH(CH_3)_2$), 1.68 (3H, s, CH_3C=), 1.56 (3H, s, CH_3C=), 1.39-1.05 (6H, m, $(CH_2)_3CH_3$), 0.88 (9H, s, $(CH_3)_3C$), 0.87-0.79 (9H, m, $(CH_3)_2CH$, CH_3CH_2), 0.00 (6H, s, $(CH_3)_2Si$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 130.6 (=C), 127.2 (=CH), 80.4 (CHOSi), 42.2 (CH*n*-Bu), 33.1 ($CH(CH_3)_2$), 32.3, 30.0, 26.2 (3C), 26.1, 23.1, 20.2, 18.6 (2 × CH_3C=, $(CH_2)_3CH_3$, CH_3CH, $(CH_3)_3C$), 18.5 ($C(CH_3)_3$), 18.4 (CH_3CH), -3.7 (2C, $(CH_3)_2Si$); MS (EI) *m/z* (%) 312 (M^+, 0.1), 188 (17), 187 (100), 131 (19), 75 (53), 73 (83), 69 (24). GC/MS retention times (Program 3): 8.99 (*anti*), 9.23 (*syn*) min. Anal. Calcd for $C_{19}H_{40}OSi$: C, 73.00; H, 12.90. Found: C, 72.84; H, 12.83.

4.3.7 General Procedure F: Determination of Relative Configuration

The alkene (1.0 equiv) was dissolved in CH_2Cl_2, cooled to -78°C and treated with excess ozone. The reaction mixture was purged with argon, treated with Me_2S (2.1 equiv) and allowed to warm to room temperature. The reaction mixture was diluted with Et_2O, washed

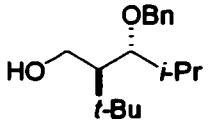
with H_2O (3×) and the organic layer was dried over Na_2SO_4. The solvent was removed *in vacuo*.

The crude reaction mixture was dissolved in Et_2O and added dropwise to a suspension of $LiAlH_4$ (8.0 equiv wrt H^-) in Et_2O at 0°C. The reaction mixture was allowed to warm to room temperature and was stirred until no starting material remained (by TLC). The reaction mixture was then recooled to 0°C and quenched slowly with finely-ground $Na_2SO_4 \cdot 10H_2O$ (~10 g/g $LiAlH_4$). The reaction mixture was allowed to stir until the solid turned from grey to white. The organic layer was decanted and the remaining salt was extracted with warm EtOAc (3×). The combined organic layers were dried over Na_2SO_4 and the solvent was removed *in vacuo*.

If the substrate contained a benzyl ether, it was reacted with H_2 (balloon) over 20% $Pd(OH)_2/C$ (10% w/w) in EtOH. The reaction mixture was filtered through Celite (to separate catalyst) and the filtrate was dried over Na_2SO_4. The solvent was removed *in vacuo*.

The resulting crude diol was cyclized to the acetal according to the procedure developed by Mori and Maemoto.[37] The diol (1.0 equiv) and 2,2-dimethoxypropane (4.0 equiv) were dissolved in dry CH_2Cl_2 and treated with PPTS (0.05-0.10 equiv). At the completion of the reaction (monitored by TLC), the reaction mixture diluted with ether, and washed with saturated $NaHCO_3$ (3×) and brine (2×). The organic layer was dried with Na_2SO_4 and concentrated *in vacuo*. ^1H NMR analysis was conducted on the crude cyclic acetals.[21,22,23] (NB: Only the analysis of the major diastereomer is given.)

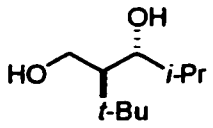
(2R, 3S*)-3-Benzyloxy-2-tert-butyl-4-methyl-1-pentanol (244)*



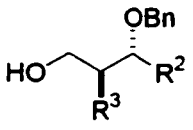
IR (neat) 3546 (br, OH), 3090, 3066, 2902, 1469, 1068 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.37 (5H, m, $C_6\underline{H}_5$), 4.66 (1H, A of AB, d, J_{obs} = 10.7 Hz, $C\underline{H}_2Ph$), 4.59 (1H, B of AB, d, J_{obs} = 10.7 Hz, $C\underline{H}_2Ph$), 3.88-3.79 (2H, m, $C\underline{H}_2OH$), 3.54 (1H, dd, J = 4.1, 3.2 Hz, $C\underline{H}OBn$), 2.03-1.92 (1H, m, $C\underline{H}t$-Bu), 1.50-1.46 (1H, m, $C\underline{H}(CH_3)_2$), 1.13 (1H, br s, $O\underline{H}$), 1.01 (6H, d, J = 6.7 Hz, $(C\underline{H}_3)_2CH$), 0.77 (9H, s, $(C\underline{H}_3)_3C$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.2, 128.5 (2C), 127.7, 127.5 (2C) (ArC's), 85.5, 74.0, 62.1 ($\underline{C}H_2OH$, $\underline{C}HOBn$, $\underline{C}H_2OBn$), 51.2 ($\underline{C}Ht$-Bu), 33.6

(C̲H(CH$_3$)$_2$), 32.6 (C̲(CH$_3$)$_3$), 28.7 (3C, (C̲H$_3$)$_3$C), 19.4, 17.7 ((C̲H$_3$)$_2$CH); MS (EI) *m/z* (%) 221 (M$^+$-*i*-Pr, 10), 141 (30), 91 (100), 83 (39), 77 (44), 70 (62), 69 (38), 57 (89), 55 (55), 51 (33). Anal. Calcd for $C_{17}H_{28}O_2$: C, 77.22; H, 10.67. Found: C, 77.02; H, 10.39.

(2R, 3S*)-2-tert-Butyl-4-methyl-1,3-pentanediol (245)*



^{1}H NMR (300 MHz, CDCl$_3$) δ 3.99-3.90 (2H, m, C̲H$_2$OH), 3.59 (1H, d, J = 7.9 Hz, C̲HOH), 2.66 (2H, br s, 2 × O̲H), 1.85 (1H, dqq, J = 7.9, 6.9, 6.7 Hz, C̲H(CH$_3$)$_2$), 1.39 (1H, dd, J = 4.1, 3.6 Hz, C̲H*t*-Bu), 1.01 (9H, s, (C̲H$_3$)$_3$C), 1.01 (3H, d, J = 6.9 Hz, C̲H$_3$CH), 0.90 (3H, d, J = 6.7 Hz, C̲H$_3$CH); ^{13}C NMR (75 MHz, CDCl$_3$) δ 78.2 (C̲HOH), 61.7 (C̲H$_2$OH), 49.7 (C̲H*t*-Bu), 34.0 (C̲H(CH$_3$)$_2$), 33.0 (C̲(CH$_3$)$_3$), 29.0 (3C, (C̲H$_3$)$_3$C), 20.0, 18.7 ((CH$_3$)$_2$CH).



247: R^2 = Me, R^3 = *n*-Bu
248: R^2 = *n*-Bu, R^3 = *n*-Bu
249: R^2 = *i*-Pr, R^3 = *n*-Bu
250: R^2 = *i*-Pr, R^3 = Ph

(2R, 3S*)-3-Benzyloxy-2-butyl-1-butanol (247)*

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.37-7.26 (5H, m, C$_6$H̲$_5$), 4.68 (1H, A of AB, d, J_{obs} = 11.6 Hz, C̲H$_2$Ph), 4.41 (1H, A of AB, d, J_{obs} = 11.6 Hz, C̲H$_2$Ph), 3.87 (1H, A′ of A′B′X′, dd, J_{obs} = 11.2, 2.5 Hz, C̲H$_2$OH), 3.66-3.54 (1H, m, B′ of A′B′X′, C̲H$_2$OH; 1H, m, C̲HCH$_3$), 2.16 (1H, br s, O̲H), 1.54-1.43 (1H, X′ of A′B′X′, m, C̲H*n*-Bu), 1.43-1.19 (6H, m, (C̲H$_2$)$_3$CH$_3$), 1.29 (3H, d, J = 6.2 Hz, C̲H$_3$CH), 0.90 (3H, t, J = 6.8 Hz, C̲H$_3$CH$_2$); ^{13}C NMR (75 MHz, CDCl$_3$) δ 138.4, 128.5 (2C), 127.8 (2C), 127.7 (ArC's), 78.5, 71.1 (C̲HOBn, C̲H$_2$Ph), 63.8 (C̲H$_2$OH), 46.1 (C̲H*n*-Bu), 30.0, 28.4, 23.1 (C̲H$_2$)$_3$CH$_3$), 17.7, 14.1 (C̲H$_3$CH$_2$, C̲H$_3$CH).

(2R, 3S*)-3-Benzyloxy-2-butyl-1-heptanol (248)*

^{1}H NMR (300 MHz, CDCl$_3$) δ 7.37-7.26 (5H, m, C$_6$H̲$_5$), 4.65 (1H, A of AB, d, J_{obs} = 11.3 Hz, C̲H$_2$Ph), 4.46 (1H, B of AB, d, J_{obs} = 11.3 Hz, C̲H$_2$Ph), 3.89 (1H, A′ of A′B′X′, dd, J_{obs} = 11.2, 2.6 Hz, C̲H$_2$OH), 3.60 (1H, B′ of A′B′X′, dd, J_{obs} = 11.2, 5.5 Hz, C̲H$_2$OH), 3.50 (1H, dt, J =

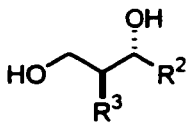
5.5, 5.5 Hz, CHOBn), 2.02 (1H, br s, OH), 1.80-1.53 (1H, X′ of A′B′X′, m, CH*n*-Bu; 2H, m, CH_2CH), 1.53-1.10 (10H, $(CH_2)_3CH_3$, $(CH_2)_2CH_3$), 1.00-0.81 (6H, m, 2 × CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.8, 128.4 (2C), 127.8, 127.7 (2C) (ArC's), 83.3, 72.2 (CHOBn, CH_2Ph), 63.3 (CH_2OH), 42.5 (CH*n*-Bu), 30.9, 29.6, 28.4, 27.4, 22.9, 22.9 (2 × $(CH_2)_3CH_3$), 14.1, 14.0 (2 × CH_3CH_2).

(2R, 3S*)-3-Benzyloxy-2-butyl-4-methyl-1-pentanol (249)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61-7.26 (5H, m, C_6H_5), 4.67 (1H, A of AB, d, J_{obs} = 10.8 Hz, CH_2Ph), 4.60 (1H, B of AB, d, J_{obs} = 10.8 Hz, CH_2Ph), 3.88 (1H, A′ of A′B′X′, dd, J_{obs} = 11.3, 2.5 Hz, CH_2OH), 3.67 (1H, B′ of A′B′X′, dd, J_{obs} = 11.3, 5.0 Hz, CH_2OH), 3.24 (1H, dd, J = 6.6, 4.1 Hz, CHOBn), 2.02 (1H qqd, J = 6.8, 6.6, 6.6 Hz, $CH(CH_3)_2$), 1.67-1.27 (1H, m, X′ of A′B′X′, CH*n*-Bu; 7H, m, OH, $(CH_2)_3CH_3$), 1.05 (3H, d, J = 6.6 Hz, CH_3CH), 0.97 (3H, d, J = 6.8 Hz, CH_3CH), 0.91 (3H, t, J = 7.0 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.4, 128.6, 127.9 (2C), 127.8 (2C) (ArC's), 89.8, 75.7 (CHOBn, CH_2Ph), 63.1 (CH_2OH), 41.8 (CH*n*-Bu), 31.5, 29.7 (2C), 23.1, 20.0, 18.7 ($CH(CH_3)_2$, $(CH_2)_3CH_3$, $(CH_3)_2CH$), 14.2 (CH_3CH_2).

(2R, 3S*)-3-Benzyloxy-4-methyl-2-phenyl-1-pentanol (250)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.39-7.21 (10H, m, 2 × C_6H_5), 4.72 (1H, A of AB, d, J_{obs} = 10.9 Hz, CH_2Ph), 4.68 (1H, B of AB, d, J_{obs} = 10.9 Hz, CH_2Ph), 4.04 (1H, A′ of A′B′X′, dd, J_{obs} = 11.0, 6.5 Hz, CH_2OH), 3.98 (1H, B′ of A′B′X′, dd, J_{obs} = 11.0, 5.1 Hz, CH_2OH), 3.75 (1H, dd, J = 9.0, 3.1 Hz, CHOBn), 3.07 (1H, X′ of A′B′X′, ddd, J_{obs} = 9.0, 6.5, 5.1 Hz, CHPh), 1.73 (1H, qqd, J = 7.0, 6.8, 3.1 Hz, $CH(CH_3)_2$), 1.73 (1H, br s, OH), 1.03 (3H, d, J = 7.0 Hz, CH_3CH), 0.89 (3H, d, J = 6.8 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 138.2, 128.6 (2C), 128.4 (2C), 128.2, 127.7 (2C), 127.6 (2C), 126.7 (ArC's), 87.8 (CHOBn), 75.1 (CH_2Ph), 65.7 (CH_2OH), 50.8 (CHPh), 30.7 ($CH(CH_3)_2$), 20.3, 16.2 ($(CH_3)_2CH$).



anti-251: R^2 = Me, R^3 = *n*-Bu
anti-252: R^2 = *n*-Bu, R^3 = *n*-Bu
anti-253: R^2 = *i*-Pr, R^3 = *n*-Bu
anti-254: R^2 = *i*-Pr, R^3 = Ph

(2R, 3S*)-2-Butyl-1,3-butanediol* ***(anti-251)***

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (1H, A of ABX, dd, J_{obs} = 11.0, 2.7 Hz, C$\underline{H}_2$OH), 3.93 (1H, dq, J = 6.2, 6.2 Hz, C$\underline{H}$OH), 3.70 (1H, B of ABX, dd, J_{obs} = 11.0, 6.3 Hz, C$\underline{H}_2$OH), 2.10 (2H, br s, 2 × O$\underline{H}$), 1.52-1.27 (1H, X of ABX, m, C$\underline{H}$*n*-Bu; 6H, CH(C$\underline{H}_2$)$_3$CH$_3$), 1.29 (3H, d, J = 6.2 Hz, C$\underline{H}_3$CH), 0.90 (3H, t, J = 6.6 Hz, C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.8, 64.4 (C$\underline{C}$HOH, $\underline{C}$H$_2$OH), 46.1 (C$\underline{C}$H*n*-Bu), 29.4, 28.0, 23.0, 21.8 (($\underline{C}$H$_2$)$_3$CH$_3$), 14.0 ($\underline{C}$H$_3$CH$_2$).

(2R, 3S*)-2-Butyl-1,3-heptanediol* ***(anti-252)***

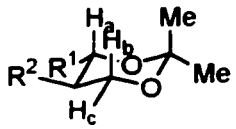
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (1H, A of ABX, dd, J_{obs} = 11.0, 2.3 Hz, C$\underline{H}_2$OH), 3.73-3.62 (1H, B of ABX, m, C$\underline{H}_2$OH; 1H, m, C$\underline{H}$OH), 2.15 (2H, br s, 2 × O$\underline{H}$), 1.60-1.22 (1H, m, X of ABX, C$\underline{H}$CH$_2$OH; 12H, m, 2 × (C$\underline{H}_2$)$_3$CH$_3$), 1.01-0.83 (6H, m, 2 × C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.7, 64.0 (C$\underline{C}$HOH, $\underline{C}$H$_2$OH), 44.1 (C$\underline{C}$HCH$_2$OH), 35.2, 29.5, 28.3, 27.9, 22.9, 22.7 (2 × ($\underline{C}$H$_2$)$_3$CH$_3$), 14.0 (2C, 2 × $\underline{C}$H$_3$CH$_2$).

(2R, 3S*)-2-Butyl-4-methyl-1,3-pentanediol* ***(anti-253)***

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.93 (1H, A of ABX, dd, J_{obs} = 11.0, 2.8 Hz, C$\underline{H}_2$OH), 3.70 (1H, B of ABX, dd, J_{obs} = 11.0, 5.6 Hz, C$\underline{H}_2$OH), 3.38 (1H, dd, J = 5.9, 5.9 Hz, C$\underline{H}$OH), 2.83 (2H, br s, 2 × O$\underline{H}$), 1.87 (1H, qqd, J = 6.8, 6.7, 5.9 Hz, C$\underline{H}$(CH$_3$)$_2$), 1.69-1.58 (1H, X of ABX, m, C$\underline{H}$*n*-Bu), 1.49-1.20 (6H, m, (C$\underline{H}_2$)$_3$CH$_3$), 0.97 (3H, d, J = 6.7 Hz, C$\underline{H}_3$CH), 0.93 (3H, d, J = 6.8 Hz, C$\underline{H}_3$CH), 0.91 (3H, t, J = 6.5 Hz, C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.0 (C$\underline{C}$HOH), 64.3 ($\underline{C}$H$_2$OH), 41.2 (C$\underline{C}$H*n*-Bu), 30.8, 29.3, 28.4, 23.0 (C$\underline{C}$H(CH$_3$)$_2$, ($\underline{C}$H$_2$)$_3$CH$_3$), 19.6, 17.0 (($\underline{C}$H$_3$)$_2$CH), 14.0 ($\underline{C}$H$_3$CH$_2$).

(2R, 3S*)-4-Methyl-2-phenyl-1,3-pentanediol (anti-254)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35 (5H, m, $C_6\underline{H}_5$), 4.10 (1H, A of ABX, dd, J_{obs} = 10.9, 7.9 Hz, $C\underline{H}_2OH$), 3.97 (1H, dd, J = 9.5, 2.5 Hz, $C\underline{H}OH$), 3.88 (1H, B of ABX, dd, J_{obs} = 10.9, 4.5 Hz, $C\underline{H}_2OH$), 2.97 (1H, ddd, J = 9.5, 7.9, 4.5 Hz, $C\underline{H}Ph$), 2.39 (2H, br s, 2 × $O\underline{H}$), 1.50 (1H, qqd, J = 7.0, 6.8, 2.5 Hz, $C\underline{H}(CH_3)_2$), 0.93 (3H, d, J = 7.0 Hz, $C\underline{H}_3CH$), 0.86 (3H, d, J = 6.8 Hz, $C\underline{H}_3CH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 140.0, 128.7 (2C), 128.1 (2C), 126.9 (ArC's), 80.5 ($\underline{C}HOH$), 67.5 ($\underline{C}H_2OH$), 50.7 ($\underline{C}HPh$), 30.0 ($\underline{C}H(CH_3)_2$), 20.0, 14.1 (($\underline{C}H_3)_2CH$).



***trans*-255**: R^1 = Me, R^2 = *n*-Bu
***trans*-256**: R^1 = *n*-Bu, R^2 = *n*-Bu
***trans*-257**: R^1 = *i*-Pr, R^2 = *n*-Bu
***trans*-258**: R^1 = *i*-Pr, R^2 = Ph

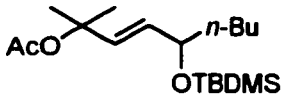
***trans*-255**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (1H, A of ABX, dd, J_{obs} = 11.6, 5.1 Hz, H_c), 3.71 (1H, dq, J = 10.0, 6.1 Hz, H_a), 3.58 (1H, B of ABX, dd, J_{obs} = 11.6, 11.3 Hz, H_b), 1.44 (3H, s, Me_{ax}), 1.39 (3H, s, Me_{eq}), 1.34-1.17 (1H, X of ABX, m, $C\underline{H}n$-Bu; 6H, m, $(C\underline{H}_2)_3CH_3$), 1.19 (3H, d, J = 6.1 Hz, $C\underline{H}_3CH_a$), 0.91 (3H, t, J = 6.8 Hz, $C\underline{H}_3CH_2$).

***trans*-256**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (1H, A of ABX, dd, J_{obs} = 11.5, 5.2 Hz, H_c), 3.56 (1H, B of ABX, dd, J_{obs} = 11.5, 11.0 Hz, H_b), 3.51 (1H, ddd, J = 10.5, 7.7, 2.5 Hz, H_a), 1.59-1.25 (1H, m, X of ABX, $C\underline{H}n$-Bu; 12H, m, $(C\underline{H}_2)_3CH_3$, $(C\underline{H}_2)_3CH_3$), 1.41 (3H, s, Me_{ax}), 1.38 (3H, s, Me_{eq}), 0.92 (3H, t, J = 6.9 Hz, $C\underline{H}_3CH_2$), 0.90 (3H, t, J = 6.9 Hz, $C\underline{H}_3CH_2$).

***trans*-257**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.84 (1H, A of ABX, J_{obs} = 11.4, 5.0 Hz, H_c), 3.55 (1H, B of ABX, dd, J_{obs} = 11.4, 10.1 Hz, H_b), 3.38 (1H, dd, J = 10.1, 2.5 Hz, H_a), 1.84 (1H, qqd, J = 6.9, 6.8, 2.5 Hz, $C\underline{H}(CH_3)_2$), 1.76-1.62 (1H, X of ABX, m, $C\underline{H}n$-Bu), 1.38 (3H, s, Me_{ax}), 1.35 (3H, s, Me_{eq}), 1.33-1.14 (6H, m, $(C\underline{H}_2)_3CH_3$), 0.95 (3H, d, J = 6.9 Hz, $C\underline{H}_3CH$), 0.91 (3H, t, J = 6.9 Hz, $C\underline{H}_3CH_2$), 0.88 (3H, d, J = 6.8 Hz, $C\underline{H}_3CH$).

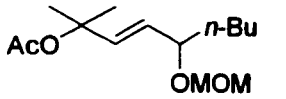
***trans*-258**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.19 (5H, m, $C_6\underline{H}_5$), 3.99 (1H, A of ABX, dd, J_{obs} = 11.4, 10.9 Hz, H_b), 3.96 (1H, dd, J = 10.8, 2.3 Hz, H_a), 3.85 (1H, B of ABX, dd, J_{obs} = 11.4, 5.3 Hz, H_c), 2.98 (1H, X of ABX, ddd, J_{obs} = 10.9, 10.8, 5.3 Hz, $C\underline{H}Ph$), 1.56 (3H, s, Me_{ax}), 1.51 (1H, qqd, J = 5.3, 5.2, 2.3 Hz, $C\underline{H}(CH_3)_2$), 1.45 (3H, s, Me_{eq}), 0.87 (3H, d, J = 5.3 Hz, $C\underline{H}_3CH$), 0.84 (3H, d, J = 5.2 Hz, $C\underline{H}_3CH$).

(E)-5-tert-Butyldimethylsilyloxy-2-methyl-3-nonen-2-yl acetate (259)



The reaction was performed using General Procedure A with silyl ether **268** (1.1 g, 3.8 mmol). The crude oil was purified via column chromatography (2:1 hexanes: CH_2Cl_2) to afford 0.88 g (68%, 2 steps) of a clear, colourless oil. IR (neat) 2957, 2931, 2859, 1740 (C=O), 1472, 1366, 1250, 1128, 1089, 836 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.83 (1H, d, J = 15.8 Hz, =C<u>H</u>C), 5.53 (1H, dd, J = 15.8, 6.6 Hz, =C<u>H</u>CH), 4.04 (1H, dt, J = 6.6, 6.3 Hz, C<u>H</u>OSi), 1.93 (3H, s, C<u>H</u>$_3$C=O), 1.48 (3H, s, C<u>H</u>$_3$CO), 1.47 (3H, s, C<u>H</u>$_3$CO), 1.43-1.19 (6H, m, (C<u>H</u>$_2$)$_3$CH$_3$), 0.87-0.83 (3H, m, C<u>H</u>$_3$CH$_2$), 0.86 (9H, s, (C<u>H</u>$_3$)$_3$C), 0.01 (3H, s, C<u>H</u>$_3$Si), -0.01 (3H, s, C<u>H</u>$_3$Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 (<u>C</u>=O), 133.8, 132.2 (H<u>C</u>=<u>C</u>H), 80.1 (<u>C</u>OAc), 73.3 (<u>C</u>HOSi), 37.9 (<u>C</u>H$_2$CH), 27.5, 26.9, 26.6, 25.9 (3C), 22.6, 22.3 ((<u>C</u>H$_3$)$_2$C, (<u>C</u>H$_2$)$_2$CH$_3$, <u>C</u>H$_3$C=O, (<u>C</u>H$_3$)$_3$C), 18.2 (<u>C</u>(CH$_3$)$_3$), 14.1 (<u>C</u>H$_3$CH$_2$), -4.3, -4.9 ((<u>C</u>H$_3$)$_2$Si); MS (EI) *m*/z (%) 271 (M^+-*t*-Bu, 0.3), 211 (16), 117 (16), 93 (14), 79 (12), 77 (10), 75 (100), 73 (24), 57 (11). Anal. Calcd for $C_{18}H_{36}O_3Si$: C, 65.80; H, 11.04. Found: C, 66.00; H, 11.26.

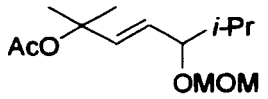
(E)-5-Methoxymethyl-2-methyl-3-nonen-2-yl acetate (260)



TBAI (90 mg, 0.24 mmol) was added to a flask and the system was evacuated and flushed with argon (3×). Hydroxy-acetate **274** (502 mg, 2.34 mmol) in CH_2Cl_2 (12.5 mL) was added to the flask and the reaction mixture was cooled to 0°C. *N,N*-Diisopropylethylamine (0.60 mL, 3.44 mmol) and chloromethyl methyl ether (MOMCl, 0.21 mL, 2.76 mmol) were added and the reaction was allowed to stir for 1 h at 0°C and overnight at ambient temperature. At the completion of the reaction (confirmed by TLC), the mixture was diluted with Et_2O (20 mL) and the layers were separated. The aqueous layer was extracted with Et_2O (20 mL) and the combined organic layers were washed with 1 M HCl (2 × 20 mL), saturated $NaHCO_3$ (3 × 20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4, after which the solvent was removed *in vacuo*. The crude oil was purified by column chromatography (1:4 Et_2O:hexanes) to afford 462 mg (76% yield) of a clear, colourless oil. IR (neat) 2934, 1739

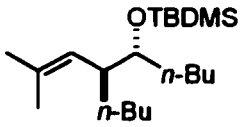
(C=O), 1468, 1368, 1249, 1155, 1098, 1039 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.91 (1H, d, J = 15.9 Hz, =CHC), 5.45 (1H, dd, J = 15.9, 8.1 Hz, =CHCH), 4.72 (1H, A of AB, d, J_{obs} = 6.7 Hz, CH_2O), 4.51 (1H, B of AB, d, J_{obs} = 6.7 Hz, CH_2O), 4.01 (1H, dt, J = 8.1, 7.4 Hz, CHHC=), 3.37 (3H, s, CH_3O), 1.98 (3H, s, $CH_3C=O$), 1.81-1.55 (2H, m, CH_2CH), 1.52 (3H, s, CH_3C), 1.50 (3H, s, CH_3C), 1.45-1.22 (4H, m, $(CH_2)_2CH_3$), 0.92 (3H, t, J = 6.8 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 (C=O), 137.9, 128.3 (HC=CH), 93.4 (CH_2O), 79.8 ($C(CH_3)_2$), 76.2 (CHO), 55.3 (CH_3O), 35.2 (CH_2CH), 27.5, 27.0, 26.7, 22.5, 22.2 (($CH_3)_2C$, $(CH_2)_2CH_3$, $CH_3C=O$), 14.0 (CH_3CH_2); MS (EI) *m*/z (%) 201 (M^+-*n*-Bu, 0.4), 136 (32), 94 (23), 93 (100), 91 (55), 85 (40), 79 (77), 77 (41), 60 (28), 57 (33). Anal. Calcd for $C_{14}H_{26}O_4$: C, 65.09; H, 10.14. Found: C, 64.86; H, 10.16.

(E)-5-Methoxymethyl-2,6-dimethyl-3-hepten-2-yl acetate (261)



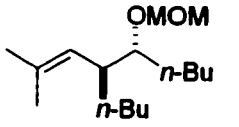
The reaction (similar to the one outlined above) was run using hydroxy-acetate **275** (501 mg, 2.50 mmol). The crude oil was purified via column chromatography (1:4 Et_2O:hexanes) to afford 440 mg (72% yield) of a clear, colourless oil. IR (neat) 2958, 2889, 1739 (C=O), 1471, 1368, 1251, 1132, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.88 (1H, d, J = 16.0 Hz, =CHC), 5.44 (1H, dd, J = 16.0, 8.3 Hz, =CHCH), 4.72 (1H, A of AB, d, J_{obs} = 6.7 Hz, CH_2O), 4.51 (1H, B of AB, d, J_{obs} = 6.7 Hz, CH_2O), 3.71 (1H, dd, J = 8.3, 6.7 Hz, CHHC=), 3.37 (3H, s, CH_3O), 1.98 (3H, s, $CH_3C=O$), 1.80 (1H, qqd, J = 6.8, 6.7, 6.7 Hz, $CH(CH_3)_2$), 1.52 (3H, s, CH_3C), 1.51 (3H, s, CH_3C), 0.97 (3H, d, J = 6.7 Hz, CH_3CH), 0.89 (3H, d, J = 6.8 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.8 (C=O), 139.0, 126.6 (HC=CH), 93.5 (CH_2O), 81.4 (CHO), 79.8 ($C(CH_3)_2$), 55.4 (CH_3O), 32.7 ($CH(CH_3)_2$), 27.1, 26.8 (($CH_3)_2C$), 22.2 ($CH_3C=O$), 18.7, 18.4 (($CH_3)_2CH$); MS (EI) *m*/z (%) 201 (M^+-*i*-Pr, 0.1), 122 (41), 107 (100), 105 (28), 91 (78), 79 (50), 77 (28), 60 (29). Anal. Calcd for $C_{13}H_{24}O_4$: C, 63.91; H, 9.90. Found: C, 63.78; H, 9.76.

(4R, 5S*)-4-Butyl-5-tert-butyldimethylsilyloxy-2-methyl-2-nonene (262)*



The reaction was performed using General Procedure E with acetate **259** (149 mg, 0.45 mmol), *n*-BuMgBr (0.51 mL, 2.77 M, 1.4 mmol) and CuCN (6 mg, 0.07 mmol). The crude oil (*anti*:*syn* = 81:19 by ^{1}H NMR analysis) was purified via column chromatography (hexanes) to give 130 mg (89%) of a clear, colorless oil. IR (neat) 2930, 2859, 1672, 1463, 1378, 1255, 1084, 1055, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.94 (0.81H, d, J = 10.0 Hz, =C<u>H</u>), 4.90 (0.19H, d, J = 10.0 Hz, =C<u>H</u>), 3.51-3.45 (0.81H, m, C<u>H</u>O), 3.46 (0.19H, dt, J = 5.5, 5.5 Hz, C<u>H</u>O), 2.28-2.21 (1H, m, C<u>H</u>*n*-Bu), 1.69 (0.57H, s, C<u>H$_3$</u>C=), 1.68 (2.43H, s, C<u>H$_3$</u>C=), 1.58 (3H, s, C<u>H$_3$</u>C=), 1.46-0.96 (12H, m, 2 × (C<u>H$_2$</u>)$_3$CH$_3$), 0.88-0.83 (6H, m, 2 × C<u>H$_3$</u>CH$_2$), 0.87 (9H, s, (C<u>H$_3$</u>)$_3$C), 0.02 (2.43, s, C<u>H$_3$</u>Si), 0.01 (3.57, s, C<u>H$_3$</u>Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.9*, 131.2 (=<u>C</u>); 127.6, 126.5* (=<u>C</u>H); 76.0, 75.4* (<u>C</u>HO); 43.6, 43.2* (<u>C</u>H*n*-Bu); 34.4, 33.6*; 30.7, 30.6*; 30.1*, 29.7; 28.3*, 27.0; 26.1; 26.0 (3C); 23.0 (2C); 18.4*, 18.3; 18.2, 18.1* (2 × (<u>C</u>H$_2$)$_3$CH$_3$, <u>C</u>(CH$_3$)$_3$, 2 × <u>C</u>H$_3$C=, (<u>C</u>H$_3$)$_3$C); 14.2 (2C, 2 × <u>C</u>H$_3$CH$_2$); -4.2, -4.3*; -4.4*, -4.5 (2 × <u>C</u>H$_3$Si); MS (EI) m/z (%) 312 (M$^+$-15, 1), 73 (100). GC/MS retention time (Program 2): 14.56 (*anti*, *syn*) min. Anal. Calcd for $C_{20}H_{42}OSi$: C, 73.54; H, 12.96. Found: C, 73.35; H, 12.78. The major isomer was identified as the *anti* isomer by desilylation and comparison of GC retention times with **283**.

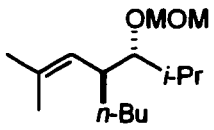
(4R, 5S*)-4-Butyl-5-methoxymethyl-2-methyl-2-nonene (263)*



The reaction was performed using General Procedure E with acetate **260** (150 mg, 0.58 mmol), *n*-BuMgBr (0.43 mL, 2.71 M, 1.17 mmol) and CuCN (7 mg, 0.08 mmol). The crude oil (*anti*:*syn* = 83:17 by GC/MS analysis) was purified via column chromatography (1:1 hexanes:CH_2Cl_2) to afford 126 mg (85%) of a clear, colourless oil. IR (neat) 2930, 2821, 1675 (C=C), 1467, 1378, 1148, 1098, 1043 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (0.83H, d, *J* = 8.9 Hz, =C<u>H</u>), 4.95 (0.17H, d, *J* = 8.9 Hz, =C<u>H</u>), 4.70-4.62 (2H, m, C<u>H$_2$</u>O), 3.47-3.32 (1H, m,

C<u>H</u>O), 3.39 (3H, s, C<u>H</u>$_3$O), 2.50-2.33 (1H, m, C<u>H</u>*n*-Bu), 1.72 (3H, s, C<u>H</u>$_3$C=), 1.62 (3H, s, C<u>H</u>$_3$C=), 1.58-1.03 (12H, m, 2 × (C<u>H</u>$_2$)$_3$CH$_3$), 0.90-0.86 (6H, m, 2 × C<u>H</u>$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.8*, 132.5 (=<u>C</u>); 126.1, 125.9* (=<u>C</u>H); 96.2*, 95.9 (<u>C</u>H$_2$O); 81.5 (<u>C</u>HO); 55.8, 55.6* (<u>C</u>H$_3$O); 41.7*, 41.6 (<u>C</u>H*n*-Bu); 31.5*, 31.4; 31.2, 31.0*; 30.1*, 29.8; 28.4*, 27.7; 26.1; 23.1; 23.0; 18.4*, 18.3 (2 × (<u>C</u>H$_2$)$_3$CH$_3$, 2 × <u>C</u>H$_3$C=); 14.2 (2C, 2 × <u>C</u>H$_3$CH$_2$); MS (EI) *m*/z (%) 167 (69), 138 (22), 137 (34), 109 (28), 95 (64), 85 (52), 83 (26), 82 (35), 81 (100), 79 (24), 69 (53), 68 (59), 67 (50), 57 (37), 55 (62). GC/MS retention times (Program 4): 17.54 (*anti*), 18.33 (*syn*) min. Anal. Calcd for $C_{16}H_{32}O_2$: C, 74.94; H, 12.58. Found: C, 75.12; H, 12.70.

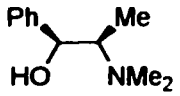
(4R, 5S*)-4-Butyl-5-methoxymethyl-2,6-dimethyl-2-heptene (264)*



The reaction was performed using General Procedure E with acetate **263** (150 mg, 0.61 mmol), *n*-BuMgBr (0.45 mL, 2.71 M, 1.22 mmol) and CuCN (6 mg, 0.07 mmol). The crude oil (*anti*:*syn* = 97.5:2.5 by GC/MS analysis) was purified via column chromatography (1:1 hexanes:CH_2Cl_2) to afford 130 mg (88%) of a clear, colourless oil. IR (neat) 2959, 2821, 1663 (C=C), 1467, 1383, 1149, 1096, 1042 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.08 (1H, d, J = 9.4 Hz, =C<u>H</u>), 4.69 (1H, A of AB, d, J_{obs} = 6.8 Hz, C<u>H</u>$_2$O), 4.64 (1H, B of AB, d, J_{obs} = 6.8 Hz, C<u>H</u>$_2$O), 3.40 (3H, s, C<u>H</u>$_3$O), 3.13 (1H, dd, J = 6.7, 3.8 Hz, C<u>H</u>O), 2.51-2.36 (1H, m, C<u>H</u>*n*-Bu), 1.83 (1H, qqd, J = 6.8, 6.7, 6.7 Hz, C<u>H</u>(CH$_3$)$_2$), 1.72 (3H, s, C<u>H</u>$_3$C=), 1.61 (3H, s, C<u>H</u>$_3$C=), 1.48-1.10 (6H, m, (C<u>H</u>$_2$)$_3$CH$_3$), 0.94 (3H, d, J = 6.8 Hz, C<u>H</u>$_3$CH), 0.91 (3H, t, J = 6.8 Hz, C<u>H</u>$_3$CH$_2$), 0.90 (3H, d, J = 6.7 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 131.8 (=<u>C</u>), 126.0 (=<u>C</u>H), 98.2 (<u>C</u>H$_2$O), 88.0 (<u>C</u>HO), 56.0 (<u>C</u>H$_3$O), 40.8 (<u>C</u>H*n*-Bu), 32.9 (<u>C</u>H(CH$_3$)$_2$) 31.1 (<u>C</u>H$_2$CH), 29.7, 26.0, 23.0, 19.9, 18.7, 18.4 (2 × <u>C</u>H$_3$C=, (<u>C</u>H$_2$)$_2$CH$_3$, (<u>C</u>H$_3$)$_2$CH), 14.2 (<u>C</u>H$_3$CH$_2$); MS (EI) *m*/z (%) 167 (72), 137 (36), 109 (20), 95 (55), 93 (29), 85 (86), 83 (40), 82 (26), 81 (94), 27 (79), 69 (100), 68 (61), 67 (67), 57 (54), 55 (95), 53 (29). GC/MS retention times (Program 4): 10.53 (*anti*), 10.88 (*syn*) min. Anal. Calcd for $C_{15}H_{30}O_2$: C, 74.33; H, 12.47. Found: C, 74.50; H, 12.58.

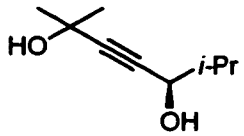
4.3.8 Synthesis of Enantiomerically-Enriched Compounds

(1S, 2R)-(+)-N-Methylephedrine (266)[38,39]



(1*S*, 2*R*)-Ephedrine hemihydrate (10 g, 58 mmol ephedrine), formaldehyde (15 mL, 37% in water, 201 mmol) and formic acid (8 mL, 96% in water, 204 mmol) were refluxed for 3 h. When the reaction mixture had cooled to RT, concentrated HCl (5 mL) was added. The reaction was concentrated *in vacuo* to remove excess formaldehyde and formic acid. The residue was dissolved in the minimum amount of water. The solution was saturated with solid KOH while cooling on ice until basic by pH paper. The resulting mixture was extracted with Et_2O (3×) and the combined organic layers were dried with Na_2SO_4 and concentrated *in vacuo*. The resulting solid was recrystallized from petroleum ether to afford 4.6 g (45%) of a colourless, crystalline solid (mp: 87-88°C, lit. mp = 87-87.5°C). $[\alpha]_D$ = +29.6 (c = 4.85, MeOH), lit.: $[\alpha]_D$ = +29.2 (c = 4, MeOH). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.22 (5H, m, $C_6\underline{H}_5$), 4.96 (1H, d, J = 3.8 Hz, C<u>H</u>OH), 3.38 (1H, br s, O<u>H</u>), 2.57 (1H, qd, J = 6.7, 3.8 Hz, C<u>H</u>CH$_3$), 2.35 (6H, s, (C<u>H</u>$_3$)$_2$N), 0.82 (3H, d, J = 6.8 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz) δ 142.2, 128.0 (2C), 126.7, 125.9 (2C) (ArC's), 72.2 (<u>C</u>HOH), 65.3 (<u>C</u>HCH$_3$), 43.0 (2C, (<u>C</u>H$_3$)$_2$N), 10.1 (<u>C</u>H$_3$CH).

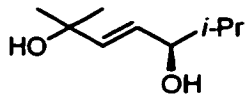
(5R)-2,6-Dimethyl-3-heptyne-2,5-diol [(R)-201][25,26]



A flask was charged with $Zn(OTf)_2$ (2.6 g, 7.1 mmol) and (+)-*N*-methylephedrine (**266**, 1.4 g, 7.7) and was evacuated and flushed with argon (3×). Toluene (20 mL) and triethylamine (1.1 mL, 7.9 mmol) were added, and the resulting mixture was stirred vigorously for 2 h at RT. After this time, 2-methyl-3-butyn-2-ol (**198**, 0.74 mL, 7.6 mmol) was added dropwise. The reaction mixture was allowed to stir for 1 h before adding isobutyraldehyde (**265**, 0.58 mL, 6.4 mmol) dropwise over 1 h (syringe pump). The reaction was allowed to stir for 4 h. After this time, saturated NH_4Cl solution (50 mL) was added. The reaction mixture was poured into a separatory funnel containing Et_2O (150 mL). The layers were separated and the aqueous layer

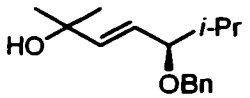
was extracted with Et_2O (3 × 150 mL). The combined organic layers were washed with brine (150 mL), dried over Na_2SO_4 and concentrated *in vacuo*. The product was purified via column chromatography (40% EtOAc in hexanes) to give 1.5 g (88%) of the desired product. By ^{19}F NMR (282 MHz, $CDCl_3$) δ -71.68 (92), -72.01 (8) or ^1H NMR (300 Hz, $CDCl_3$) δ 5.40 (0.92H, d, J = 5.7 Hz), 5.36 (0.08H, d, J = 5.6 Hz), de of mono-(*S*)-Mosher ester[40,41] = 84% (secondary alcohol is derivatized preferentially). $[\alpha]_D$ = -1.4 (c = 1.0, $CHCl_3$), lit.: $[\alpha]_D$ = -1.5 (c = 1.0, $CHCl_3$). The compound showed the same spectral characteristics as was outlined previously for compound **(±)-201**.

(3E, 5R)-2,6-Dimethyl-3-heptene-2,5-diol [(R)-205]



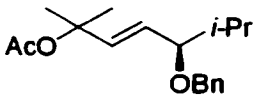
$[\alpha]_D$ = -18.9 (c = 1.0, $CHCl_3$). The compound showed the same spectral characteristics as **(±)-205**.

(3E, 5R)-5-Benzyloxy-2,6-dimethyl-3-hepten-2-ol [(R)-209]



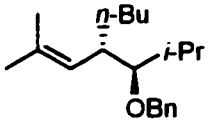
$[\alpha]_D$ = +35.1 (c = 1.0, $CHCl_3$). The compound showed the same spectral characteristics as **(±)-209**.

(3E, 5R)-5-Benzyloxy-2,6-dimethyl-3-hepten-2-yl acetate [(R)-213]



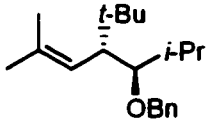
$[\alpha]_D$ = +38.2 (c = 1.0, $CHCl_3$, 82 %ee by HPLC). The compound showed the same spectral characteristics as **(±)-213**. HPLC conditions: 0.2% *i*-PrOH in hexanes. Retention times: 9.05 (91%), 11.89 (9%) min.

(2E, 4S, 5R)-5-Benzyloxy-4-butyl-2,6-dimethyl-2-heptene [(4S, 5R)-216]



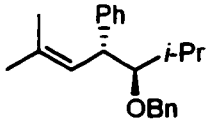
$[\alpha]_D$ = +28.5 (c = 1.0, $CHCl_3$). The compound showed the same spectral characteristics as **(±)-216**.

(2E, 4R, 5R)-5-Benzyloxy-4-tert-butyl-2,6-dimethyl-2-heptene [(4R, 5R)-222]



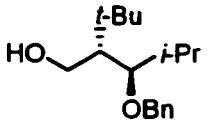
$[\alpha]_D$ = +80.4 (c = 1.0, $CHCl_3$). The compound showed the same spectral characteristics as **(±)-222**.

(2E, 4R, 5R)-5-Benzyloxy-2,6-dimethyl-2-heptene [(4R, 5R)-γ-223]



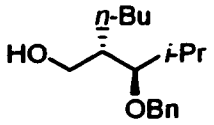
$[\alpha]_D$ = -62.7 (c = 1.0, $CHCl_3$). The compound showed the same spectral characteristics as **(±)-γ-223**.

(2S, 3R)-3-Benzyloxy-2-tert-butyl-4-methyl-1-pentanol [(2S, 3R)-244]



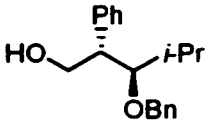
$[\alpha]_D$ = +2.0 (c = 1.6 $CHCl_3$, 83 %ee by HPLC). The compound showed the same spectral characteristics as **(±)-244**. HPLC conditions: 0.2% *i*-PrOH in hexanes. Retention times: 17.57 (91.5%), 20.73 (8.5%) min.

(2S, 3R)-3-Benzyloxy-2-butyl-4-methyl-1-pentanol [(2S, 3R)-249]



$[\alpha]_D$ = -9.9 (c = 2.1 $CHCl_3$, 84 %ee by HPLC). The compound showed the same spectral characteristics as **(±)-249**. HPLC conditions: 0.5% *i*-PrOH in hexanes. Retention times: 21.29 (92%), 24.52 (8%) min.

(2S, 3R)-3-Benzyloxy-4-methyl-2-phenyl-1-pentanol [(2S, 3R)-250]

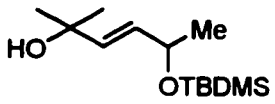


$[\alpha]_D$ = -58.1 (c = 2.0 $CHCl_3$, 80 %ee by HPLC). The compound showed the same spectral characteristics as **(±)-250**. HPLC conditions: 5% *i*-PrOH in hexanes. Retention times: 14.82 (90%), 19.24 (10%) min.

*4.3.9 General Procedure G: Monosilylation of Alkenediols **201-204** to Prepare Ethers **267-270***[42]

To a solution of the desired diol (1.0 equiv) and imidazole (2.5 equiv) in DMF (2 mL/g substrate) was added *tert*-butyldimethylsilyl chloride (1.0 equiv). The reaction was stirred at ambient temperature and monitored by TLC. When complete (usually 12-18 h), it was diluted with Et_2O, washed with water (3×) and dried over Na_2SO_4. The solvent was removed *in vacuo*. Due to their instability, the compounds were often used without purification.

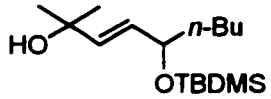
(E)-5-tert-Butyldimethylsilyloxy-2-methyl-3-hexen-2-ol (267)



The reaction was performed using General Procedure G with diol **203** (1.5 g, 12 mmol) to afford 2.5 g (91%, crude) of a clear, slightly yellow oil. IR (neat) 3369 (br, OH), 2858, 2930, 2887, 1676 (C=C), 1473, 1464, 1256, 1143, 1097, 834 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.74 (1H, d, J = 15.6 Hz, =C<u>H</u>C), 5.65 (1H, dd, J = 15.6, 5.0 Hz, =C<u>H</u>CH), 4.28 (1H, qd, J =

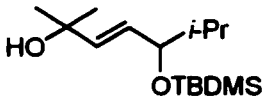
6.3, 5.0 Hz, C<u>H</u>O), 1.54 (1H, br s, O<u>H</u>), 1.29 (6H, s, (C<u>H</u>$_3$)$_2$COH), 1.20 (3H, d, J = 6.3 Hz, C<u>H</u>$_3$CH), 0.87 (9H, s, (C<u>H</u>$_3$)$_3$C), 0.04 (3H, s, C<u>H</u>$_3$Si), 0.03 (3H, s, C<u>H</u>$_3$Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 131.3 (H<u>C</u>=<u>C</u>H), 70.5 (<u>C</u>OH), 68.8 (<u>C</u>HO), 29.7 (<u>C</u>H$_3$COH), 25.9 (3C, (<u>C</u>H$_3$)$_3$C), 25.7 (<u>C</u>H$_3$COH), 24.5 (<u>C</u>H$_3$CH), 18.3 (<u>C</u>(CH$_3$)$_3$), -4.6, -4.8 ((<u>C</u>H$_3$)$_2$Si); MS (EI) *m*/z (%) 226 (M$^+$- H_2O, 0.1), 94 (10), 79 (24), 75 (100).

(E)-5-tert-Butyldimethylsilyloxy-2-methyl-3-nonen-2-ol (268)



The reaction was performed using General Procedure G with diol **204** (3.6 g, 21 mmol) to give 5.6 g (93%, crude) of a clear, slightly yellow oil. IR (neat) 3369 (br, OH), 2958, 2859, 1677 (C=C), 1255, 1074, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.72 (1H, d, J = 15.7 Hz, =C<u>H</u>C), 5.60 (1H, dd, J = 15.7, 6.0 Hz, =CHC<u>H</u>), 4.06 (1H, td, J = 6.2, 6.0 Hz, C<u>H</u>O), 1.50-1.27 (7H, m, O<u>H</u>, (C<u>H</u>$_2$)$_3$CH$_3$), 1.29 (6H, s, (C<u>H</u>$_3$)$_2$COH), 0.89-0.84 (3H, m, C<u>H</u>$_3$CH$_2$), 0.87 (9H, s, (C<u>H</u>$_3$)$_3$C), 0.02 (3H, s, C<u>H</u>$_3$Si), 0.00 (3H, s, C<u>H</u>$_3$Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 137.3 (=<u>C</u>HC), 130.3 (=<u>C</u>HCH), 73.1 (<u>C</u>HO), 70.5 (<u>C</u>OH), 38.1 (<u>C</u>H$_2$CHOSi), 29.7, 27.5, 25.9 (3C), 25.7, 22.6 ((<u>C</u>H$_3$)$_2$CO, (<u>C</u>H$_2$)$_2$CH$_3$, (<u>C</u>H$_3$)$_3$C), 18.2 (<u>C</u>(CH$_3$)$_3$), 14.0 (<u>C</u>H$_3$CH$_2$), -4.2, -4.8 ((<u>C</u>H$_3$)$_2$Si); MS (EI) *m*/z (%) 268 (M$^+$-H_2O, 1), 211 (20), 93 (10), 81 (12), 75 (100), 73 (27).

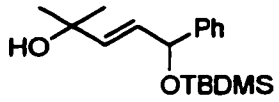
(E)-5-tert-Butyldimethylsilyloxy-2,6-dimethyl-3-hepten-2-ol (269)



The reaction was performed using General Procedure G with diol **205** (1.0 g, 6.3 mmol) to give 1.6 g (97%, crude) of a clear, slightly yellow oil. IR (neat) 3369 (br, OH), 2858, 2930, 2858, 1667 (C=C), 1472, 1252, 1065, 836 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.71 (1H, d, J = 15.7 Hz, =C<u>H</u>C), 5.53 (1H, dd, J = 15.7, 6.4 Hz, =C<u>H</u>CH), 3.79 (1H, dd, J = 6.5, 6.4 Hz, C<u>H</u>O), 1.63 (1H, qqd, 7.0, 6.8, 6.5 Hz, C<u>H</u>(CH$_3$)$_2$), 1.43 (1H, br s, O<u>H</u>), 1.30 (6H, s, (C<u>H</u>$_3$)$_2$COH), 0.87 (9H, s, (C<u>H</u>$_3$)$_3$C), 0.86 (3H, d, J = 7.0 Hz, C<u>H</u>$_3$CH), 0.82 (3H, d, J = 6.8 Hz, C<u>H</u>$_3$CH), 0.01 (3H, s, C<u>H</u>$_3$Si), -0.02 (3H, s, C<u>H</u>$_3$Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 138.6, 128.4 (H<u>C</u>=<u>C</u>H), 78.0 (<u>C</u>HO), 70.5 (<u>C</u>OH), 34.6 (<u>C</u>H(CH$_3$)$_2$), 29.7 (2C, (<u>C</u>H$_3$)$_2$COH), 25.8

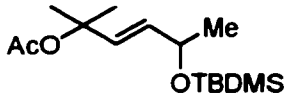
(3C, ($\underline{C}H_3)_3C$), 25.7 ($\underline{C}(CH_3)_3$), 18.4, 17.9 (($\underline{C}H_3)_2CH$), -4.1, -4.9 (($\underline{C}H_3)_2Si$); MS (EI) *m/z* (%) 229 (M^+-*i*-Pr, 0.8), 107 (14), 105 (14), 91 (10), 75 (100), 73 (24). Anal. Calcd for $C_{15}H_{32}O_2Si$: C, 66.12; H, 11.84. Found: C, 66.39; H, 11.60.

(E)-1-tert-Butyldimethylsilyloxy-4-methyl-1-phenyl-2-penten-4-ol (270)



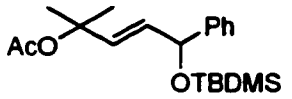
The reaction was performed using General Procedure G with diol **206** (1.7 g, 8.9 mmol) to give 2.7 g (quantitative, crude) of a clear, slightly yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.30-7.21 (5H, m, $C_6\underline{H}_5$), 5.87 (1H, d, J = 15.4 Hz, =C$\underline{H}$C), 5.73 (1H, dd, J = 15.4, 6.0 Hz, =C$\underline{H}$CH), 5.17 (1H, d, J = 6.0 Hz, C$\underline{H}$O), 1.54 (1H, br s, O$\underline{H}$), 1.30 (6H, s, ($C\underline{H}_3)_2CO$), 0.89 (9H, s, ($C\underline{H}_3)_3C$), 0.05 (3H, s, $C\underline{H}_3Si$), -0.02 (3H, s, $C\underline{H}_3Si$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.9, 137.3, 130.3, 128.1 (2C), 126.9, 125.9 (2C) (H$\underline{C}$=$\underline{C}$H, ArC's), 75.0 ($\underline{C}$HO), 70.5 ($\underline{C}$OH), 29.6, 29.5 (($\underline{C}H_3)_2CO$), 25.8 (3C, ($\underline{C}H_3)_3C$), 25.6 ($\underline{C}(CH_3)_3$), -4.5, -4.8 (($\underline{C}H_3)_2Si$).

(E)-5-tert-Butyldimethylsilyloxy-2-methyl-3-hexen-2-yl acetate (271)



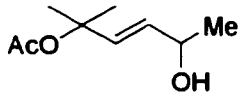
The reaction was performed using General Procedure A with silyl ether **267** (2.5 g, 10 mmol) to give 2.6 g (85%, crude) of a clear, colourless oil. IR (neat) 2957, 2930, 2858, 1740 (C=O), 1473, 1368, 1251, 835 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.85 (1H, d, J = 15.8 Hz, =C$\underline{H}$C), 5.61 (1H, dd, J = 15.8, 5.7 Hz, =C$\underline{H}$CH), 4.29 (1H, qd, J = 6.3, 5.7 Hz, C$\underline{H}$O), 1.95 (3H, s, $C\underline{H}_3$C=O), 1.49 (3H, s, $C\underline{H}_3$COAc), 1.48 (3H, s, $C\underline{H}_3$CO), 1.20 (3H, d, J = 6.3 Hz, $C\underline{H}_3$CH), 0.87 (9H, s, ($C\underline{H}_3)_3C$), 0.03 (6H, s, ($C\underline{H}_3)_2Si$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 ($\underline{C}$=O), 133.1, 133.0 (H$\underline{C}$=$\underline{C}$H), 80.2 ($\underline{C}$OAc), 69.1 ($\underline{C}$HO), 27.0, 26.6, 25.9 (3C), 24.5, 22.4 (($\underline{C}H_3)_2CO$, ($\underline{C}H_3)_3C$, $\underline{C}H_3CH$, $\underline{C}H_3C$=O), 18.4 ($\underline{C}(CH_3)_3$), -4.5, -4.8 (($\underline{C}H_3)_2Si$); MS (EI) *m/z* (%) 229 (M^+-*t*-Bu, 0.3), 169 (26), 117 (27), 75 (100), 73 (19). Anal. Calcd for $C_{15}H_{30}O_3Si$: C, 62.89; H, 10.55. Found: C, 62.65; H, 10.46.

(E)-1-tert-Butyldimethylsilyloxy-4-methyl-1-phenyl-2-penten-4-yl acetate (272)



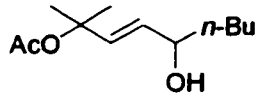
The reaction was performed using General Procedure A with silyl ether **270** (2.7 g, 8.7 mmol) to yield 2.2 g (74%) of a clear, slightly yellow oil that was used without further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32-7.24 (5H, m, $C_6\underline{H}_5$), 6.04 (1H, d, J = 15.7 Hz, =C$\underline{H}$C), 5.67 (1H, dd, J = 15.7, 6.6 Hz, =C$\underline{H}$CH), 5.17 (1H, d, J = 6.6 Hz, C$\underline{H}$O), 1.95 (3H, s, $C\underline{H}_3$C=O), 1.49 (6H, s, $(C\underline{H}_3)_2$CO), 0.90 (9H, s, $(C\underline{H}_3)_3$C), 0.06 (3H, s, $C\underline{H}_3$Si), 0.01 (3H, s, $C\underline{H}_3$Si); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.0 (C=O), 143.8, 134.5, 131.8, 128.2 (2C), 127.0, 126.0 (2C) (HC=CH, ArC's), 80.2 (COAc), 75.2 (CHO), 27.0, 26.7, 26.0 (3C), 22.3 ($(C\underline{H}_3)_2$CO, $(C\underline{H}_3)_3$C, $C\underline{H}_3$C=O), 18.4 ($\underline{C}(CH_3)_3$), -4.3, -4.8 ($(C\underline{H}_3)_2$Si).

(E)-5-Hydroxy-2-methyl-3-hexen-2-yl acetate (273)



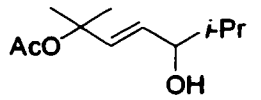
Silyl ether **271** (2.1 g, 7.2 mmol) in THF (20 mL) was treated with TBAF (1.0 M in THF, 14 mL, 14 mmol) at ambient temperature for 2 h. The reaction mixture was poured into water (20 mL) and extracted with Et_2O (3 × 20 mL). The combined organic layers were washed with water (50 mL), dried with Na_2SO_4 and concentrated *in vacuo*. The resulting oil was purified via column chromatography (3:2 Et_2O:hexanes) to afford 0.83 g (69%, 3 steps) of a clear, colourless oil. IR (neat) 3420 (br, OH), 2978, 2932, 1732 (C=C), 1368, 1258, 1123 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.95 (1H, d, J = 15.8 Hz, =C$\underline{H}$C), 5.70 (1H, dd, J = 15.8, 6.2 Hz, =C$\underline{H}$CH), 4.37 (1H, qd, J = 6.4, 6.2 Hz, C$\underline{H}$OH), 1.99 (3H, s, $C\underline{H}_3$C=O), 1.61 (1H, br s, O$\underline{H}$), 1.52 (6H, s, $(C\underline{H}_3)_2$C), 1.29 (3H, d, J = 6.4 Hz, $C\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (C=O), 133.9, 132.5 (HC=CH), 80.2 (COAc), 68.0 (CHOH), 26.9, 26.5, 23.0, 22.2 ($(C\underline{H}_3)_2$CO, $C\underline{H}_3$CH, $C\underline{H}_3$C=O); MS (EI) *m/z* (%) 154 (M^+-H_2O, 0.1), 97 (20), 94 (43), 91 (27), 79 (100), 78 (11), 77 (76), 69 (49), 60 (43), 53 (22), 51 (20). Anal. Calcd for $C_9H_{16}O_3$: C, 62.77; H, 9.36. Found: C, 62.54; H, 9.46.

(E)-5-Hydroxy-2-methyl-3-nonen-2-yl acetate (274)



This compound was from prepared crude silyl ether **259** (5.1 g, 16 mmol) and TBAF (1.0 M in THF, 31 mL, 31 mmol) as described for **273**. The resulting oil was purified via column chromatography (1:1 Et_2O:hexanes) to afford 2.9 g (88%, 2 steps) of a clear, colourless oil. IR (neat) 3474 (br, OH), 2957, 2933, 2888, 2861, 1738 (C=O), 1367, 1252, 1125 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.94 (1H, d, J = 15.8 Hz, =C<u>H</u>C), 5.65 (1H, dd, J = 15.8, 6.7 Hz, =C<u>H</u>CH), 4.09 (1H, dt, J = 6.7, 6.5 Hz, C<u>H</u>OH), 1.98 (3H, s, C<u>H</u>$_3$C=O), 1.66 (1H, br s, O<u>H</u>), 1.61-1.17 (6H, m, (C<u>H</u>$_2$)$_3$CH$_3$), 1.52 (3H, s, C<u>H</u>$_3$C), 1.51 (3H, s, C<u>H</u>$_3$C), 0.90 (3H, t, J = 6.6 Hz, C<u>H</u>$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (<u>C</u>=O), 134.8, 131.6 (H<u>C</u>=<u>C</u>H), 80.1 (<u>C</u>OAc), 72.2 (<u>C</u>HOH), 36.6 (<u>C</u>H$_2$CH), 27.4, 26.9, 26.6, 22.5, 22.2 ((<u>C</u>H$_3$)$_2$CO, (<u>C</u>H$_2$)$_2$CH$_3$, <u>C</u>H$_3$C=O), 13.9 (<u>C</u>H$_3$CH$_2$); MS (EI) *m/z* (%) 157 (M$^+$-*n*-Bu, 0.3), 122 (40), 107 (100), 105 (38), 97 (21), 91 (86), 79 (48), 77 (31), 71 (41), 69 (34), 67 (27). Anal. Calcd for $C_{12}H_{22}O_3$: C, 67.26; H, 10.35. Found: C, 67.39; H, 10.47.

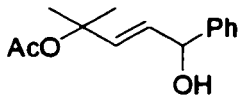
(E)-5-Hydroxy-2,6-dimethyl-3-hepten-2-yl acetate (275)



This compound was prepared from crude silyl ether **241** (6.5 g, 21 mmol) and TBAF (1.0 M in THF, 42 mL, 42 mmol) as described for **273**. The resulting oil was purified via column chromatography (1:1 Et_2O:hexanes) to afford 3.7 g (90%, 2 steps) of a clear, colourless oil. IR (neat) 3484 (br, OH), 2960, 2874, 1736 (C=O), 1469, 1368, 1253, 1126 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.90 (1H, d, J = 16.0 Hz, =C<u>H</u>C), 5.60 (1H, dd, J = 16.0, 6.9 Hz, =C<u>H</u>CH), 3.82 (1H, dd, J = 6.9, 6.4 Hz, C<u>H</u>OH), 1.96 (3H, s, C<u>H</u>$_3$C=O), 1.69 (1H, qqd, J = 6.8, 6.8, 6.4 Hz, C<u>H</u>(CH$_3$)$_2$), 1.65 (1H, br s, O<u>H</u>), 1.51 (6H, s, (C<u>H</u>$_3$)$_2$C), 0.91 (3H, d, J = 6.8 Hz, C<u>H</u>$_3$CH), 0.87 (3H, d, J = 6.8 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 (<u>C</u>=O), 136.0, 129.7 (H<u>C</u>=<u>C</u>H), 80.1 (<u>C</u>OAc), 77.4 (<u>C</u>HOH), 33.7 (<u>C</u>H(CH$_3$)$_2$), 27.0, 26.8, 22.2, 18.1, 18.0 ((<u>C</u>H$_3$)$_2$CO, <u>C</u>H$_3$C=O, (<u>C</u>H$_3$)$_2$CH); MS (EI) *m/z* (%) 182 (M$^+$-H$_2$O, 0.1), 107 (19), 97 (100), 91

(16), 79 (16), 71 (44), 69 (33), 68 (16), 67 (12), 60 (18), 55 (18), 53 (11). Anal. Calcd for $C_{11}H_{20}O_3$: C, 65.97; H, 10.07. Found: C, 65.88; H, 9.88.

(E)-1-Hydroxy-4-methyl-1-phenyl-2-penten-4-yl acetate (276)

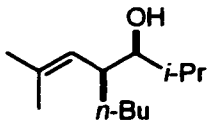


This compound was prepared from crude silyl ether **272** (2.1 g, 6.2 mmol) and TBAF (1.0 M in THF, 12 mL, 12 mmol) as described for **273**. The resulting oil was purified via column chromatography (1:1 Et_2O:hexanes) to afford 1.2 g (83%, 2 steps) of a clear, colourless oil. IR (neat) 3452 (br, OH), 3030, 2981, 1952, 1883, 1812, 1732 (C=O), 1368, 1256, 1128, 733, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.38-7.26 (5H, m, $C_6\underline{H}_5$), 6.11 (1H, d, J = 15.8 Hz, =C$\underline{H}$C), 5.84 (1H, dd, J = 15.8, 6.2 Hz, =C$\underline{H}$CH), 5.24 (1H, d, J = 6.2 Hz, C$\underline{H}$OH), 1.99 (3H, s, C$\underline{H}_3$C=O), 1.58 (1H, br s, O$\underline{H}$), 1.54 (3H, s, C$\underline{H}_3$C), 1.52 (3H, s, C$\underline{H}_3$C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.1 ($\underline{C}$=O), 142.6, 135.6, 130.4, 128.5 (2C), 127.6, 126.3 (2C) (H$\underline{C}$=$\underline{C}$H, ArC's), 80.1 ($\underline{C}$OAc), 74.3 ($\underline{C}$HOH), 26.9, 26.6 (($\underline{C}H_3)_2C$), 22.3 ($\underline{C}H_3$C=O); MS (EI) *m/z* (%) 216 (M^+-H_2O, 1), 156 (80), 155 (37), 154 (40), 153 (31), 152 (22), 145 (57), 141 (48), 129 (34), 128 (43), 115 (54), 105 (100), 78 (27), 77 (64), 76 (24), 60 (41), 51 (36). Anal. Calcd for $C_{14}H_{18}O_3$: C, 71.77; H, 7.74. Found: C, 71.60; H, 7.85.

4.3.10 General Procedure H: Grignard Additions to Hydroxy Acetates 273-276

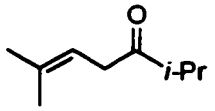
The desired Grignard reagent (2.5 equiv) was added to a slurry of the acetate (1.0 equiv) and CuCN (0.5 equiv) in CH_2Cl_2 (1 mL/10 mg substrate) at -78°C. The reaction was allowed to warm to -25°C where it was kept until completion (monitored by TLC, 2-12 h). Quench and work-up of the reaction mixture was performed as outlined previously (see Section 4.3.6).

(4R, 5R*)-4-Butyl-2,6-dimethyl-2-hepten-5-ol (243)*



The reaction was performed using General Procedure H with hydroxy acetate **275** (101 mg, 0.50 mmol), *n*-BuMgBr (0.45 mL, 2.77 M, 1.3 mmol) and CuCN (24 mg, 0.27 mmol). The crude oil (*anti*:*syn* = 13:87 by GC/MS analysis) was purified via column chromatography (7.5% Et_2O in hexanes) to afford 73 mg (73%) of a clear, colourless oil. IR (neat) 3401 (br, OH), 2959, 2930, 2886, 1676 (C=C), 1467, 1378, 1107, 736 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.98 (0.12H, d, J = 10.2 Hz, =C$\underline{H}$), 4.86 (0.88H, d, J = 10.1 Hz, =C$\underline{H}$), 3.18 (1H, dd, J = 7.5, 4.0 Hz, C$\underline{H}$OH), 2.36-2.26 (1H, m, C$\underline{H}$*n*-Bu), 1.80-1.69 (1H, m, C$\underline{H}(CH_3)_2$), 1.76 (0.36H, s, C$\underline{H_3}$C=), 1.72 (2.64H, s, C$\underline{H_3}$C=), 1.65 (0.36H, s, C$\underline{H_3}$C=), 1.62 (2.64H, s, C$\underline{H_3}$C=), 1.44 (1H, br s, O$\underline{H}$), 1.34-1.04 (6H, m, $(C\underline{H_2})_3CH_3$), 0.95 (3H, d, J = 6.9 Hz, C$\underline{H_3}$CH), 0.90 (3H, t, J = 7.1 Hz, C$\underline{H_3}CH_2$), 0.85 (3H, d, J = 6.7 Hz, C$\underline{H_3}$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.8, 132.1* (=$\underline{C}$); 126.6*, 125.4 (=$\underline{C}$H); 80.0*, 79.0 ($\underline{C}$HOH); 42.0*, 41.6 ($\underline{C}$H*n*-Bu); 31.8, 30.8* ($\underline{C}H(CH_3)_2$); 30.4*, 30.2 ($\underline{C}H_2$CH); 29.4; 25.9; 23.0; 20.3*, 20.1; 18.4; 16.4, 15.6* (2 × $\underline{C}H_3$C=, $(\underline{C}H_2)_2CH_3$, $(\underline{C}H_3)_2$CH); 14.2 ($\underline{C}H_3CH_2$); MS (EI) *m/z* (%) 198 (M^+, 0.1), 126 (28), 111 (12), 84 (13), 84 (13), 73 (22), 70 (20), 69 (100), 67 (10), 57 (33), 56 (50), 55 (33). GC/MS retention times (Program 2): 10.12 (*anti*), 10.32 (*syn*) min. Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.58; H, 13.24.

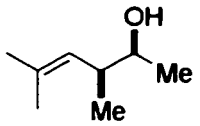
2,6-Dimethyl-5-hepten-3-one (277)[43]



This compound was isolated as the main side product from coupling reactions (General Procedure H) using acetate **275**. IR (neat) 2971, 2932, 2876, 1714 (C=O), 1677 (C=C), 1467, 1382 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.30 (1H, t, J = 7.0 Hz, =C$\underline{H}$), 3.17 (2H, d, J = 7.0 Hz, C$\underline{H_2}$), 2.66 (1H, qq, J = 6.9, 6.9 Hz, C$\underline{H}(CH_3)_2$), 1.75 (3H, s, C$\underline{H_3}$C=), 1.63 (3H, s, C$\underline{H_3}$C=), 1.11 (6H, d, J = 6.9 Hz, $(C\underline{H_3})_2$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 213.2 ($\underline{C}$=O),

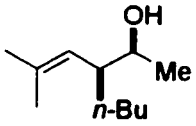
135.2 (=C), 116.1 (=CH), 40.2 (2C, CH(CH_3)$_2$, CH_2), 25.7, 18.2 (2C), 18.0 (2 × CH_3C=, (CH_3)$_2$CH).

(4R, 5R*)-2,4-Dimethyl-2-hexen-5-ol (278)*[44]



The reaction was performed using General Procedure H with hydroxy acetate **273** (98 mg, 0.57 mmol), MeMgBr (0.49 mL, 2.94 M, 1.4 mmol) and CuCN (26 mg, 0.29 mmol). The crude oil (*anti*:*syn* = 20:80 by GC/MS analysis) was purified via column chromatography (30% Et_2O in hexanes) to afford 27 mg (37%) of a clear, colourless oil. IR (neat) 3392 (br, OH), 2970, 2929, 2873, 1676 (C=C), 1450, 1376, 1090 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.98 (1H, d, J = 9.8 Hz, =CH), 3.64 (0.80H, dq, J = 6.3, 6.3 Hz, CHOH), 3.47 (0.20H, dq, J = 6.3, 6.3 Hz, CHOH), 2.50 (0.80H, dqd, J = 9.8, 6.7, 6.3 Hz, CHHC=), 2.36-2.25 (0.20H, m, CHHC=), 1.76 (0.60H, s, CH_3C=), 1.75 (0.60H, s, CH_3C=), 1.72 (2.40H, s, CH_3C=), 1.65 (2.40H, s, CH_3C=), 1.47 (1H, br s, OH), 1.19 (0.60H, d, J = 6.3 Hz, CH_3CHOH), 1.14 (2.40H, d, J = 6.3 Hz, CH_3CHOH), 0.98 (2.40H, d, J = 6.7 Hz, CH_3CHHC=), 0.94 (0.60H, d, J = 6.7 Hz, CH_3CHHC=); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.8 (=C); 127.0, 126.5* (=CH); 72.1*, 71.8 (CHOH); 42.0, 39.7* (CHHC=); 26.1, 26.0*; 20.2, 20.0*; 18.2*, 17.9; 17.0, 16.8* (2 × CH_3C=, 2 × CH_3CH); MS (EI) *m/z* (%) 128 (M^+, 2), 95 (22), 84 (86), 83 (69), 69 (91), 67 (30), 56 (11), 55 (100), 53 (13). GC/MS retention times (Program 2): 4.32 (*anti*), 4.50 (*syn*) min.

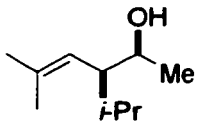
(4R, 5R*)-4-Butyl-2-methyl-2-hexen-5-ol (279)*



The reaction was performed using General Procedure H with hydroxy acetate **273** (76 mg, 0.44 mmol), *n*-BuMgBr (0.39 mL, 2.77 M, 1.1 mmol) and CuCN (20 mg, 0.23 mmol). The crude oil (*anti*:*syn* = 11:89 by GC/MS analysis) was purified via column chromatography (30% Et_2O in hexanes) to afford 52 mg (69%) of a clear, colourless oil. IR (neat) 3369 (br, OH), 2963, 2928, 2859, 1675 (C=C), 1451, 1376, 1096 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.90 (1H, d, J

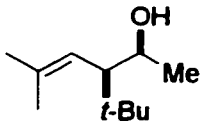
= 10.2 Hz, =C<u>H</u>), 3.66 (0.89H, dq, *J* = 6.3, 6.3 Hz, C<u>H</u>OH), 3.53 (0.11H, dq, *J* = 6.3, 6.3 Hz, C<u>H</u>OH), 2.40-2.30 (0.89H, m, C<u>H</u>*n*-Bu), 2.22-2.09 (0.11H, m, C<u>H</u>*n*-Bu), 1.77 (0.33H, s, C<u>H</u>$_3$C=), 1.75 (2.67H, s, C<u>H</u>$_3$C=), 1.65 (3H, s, C<u>H</u>$_3$C=), 1.60-1.21 (7H, m, O<u>H</u>, (C<u>H</u>$_2$)$_3$CH$_3$), 1.18 (0.33H, d, *J* = 6.3 Hz, C<u>H</u>$_3$CH), 1.11 (2.67H, d, *J* = 6.3 Hz, C<u>H</u>$_3$CH), 0.90 (3H, t, *J* = 7.0 Hz, C<u>H</u>$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.5 (=<u>C</u>); 125.9, 124.9* (=<u>C</u>H); 71.2*, 70.7 (<u>C</u>HOH); 46.4, 45.4* (<u>C</u>H*n*-Bu); 31.5*, 31.2 (<u>C</u>H$_2$CH); 29.6; 26.1*, 26.0; 22.9*, 22.8; 20.3, 19.9*; 18.5 (2 × <u>C</u>H$_3$C=, (<u>C</u>H$_2$)$_2$CH$_3$, <u>C</u>H$_3$CH); 14.1 (<u>C</u>H$_3$CH$_2$); MS (EI) *m*/z (%) 170 (M$^+$, 0.1), 109 (35), 95 (65), 81 (42), 69 (100), 67 (57), 56 (28), 55 (58). GC/MS retention times (Program 2): 8.27 (*anti*), 8.41 (*syn*) min. Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.46; H, 12.98.

(4R, 5R*)-4-Isopropyl-2-methyl-2-hexen-5-ol (280)*



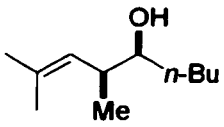
The reaction was performed using General Procedure H with hydroxy acetate **273** (101 mg, 0.58 mmol), *i*-PrMgCl (0.89 mL, 1.64 M, 1.5 mmol) and CuCN (26 mg, 0.29 mmol). The crude oil (*anti*:*syn* = 21:79 by GC/MS analysis) was purified via column chromatography (25% Et_2O in hexanes) to afford 64 mg (71%) of a clear, colourless oil. IR (neat) 3368 (br, OH), 2964, 2928, 1674 (C=C), 1453, 1384, 1074 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.05 (0.21H, d, *J* = 10.7 Hz, =C<u>H</u>), 4.93 (0.79H, *J* = 10.7 Hz, =C<u>H</u>), 3.86 (0.79H, qd, *J* = 6.9, 6.3 Hz, C<u>H</u>OH), 3.77 (0.21H, dq, *J* = 6.4, 6.2 Hz, C<u>H</u>OH), 2.22 (0.79H, ddd, *J* = 10.7, 6.8, 6.3 Hz, C<u>H</u>*i*-Pr), 2.05-1.95 (0.21H, m, C<u>H</u>*i*-Pr), 1.87-1.70 (1H, m, C<u>H</u>(CH$_3$)$_2$), 1.80 (0.63H, s, C<u>H</u>$_3$C=), 1.77 (2.37H, s, C<u>H</u>$_3$C=), 1.65 (3H, s, C<u>H</u>$_3$C=), 1.51 (1H, br s, O<u>H</u>), 1.18 (0.63H, d, *J* = 6.2 Hz, C<u>H</u>$_3$CH), 1.10 (2.37H, d, *J* = 6.9 Hz, C<u>H</u>$_3$CH), 0.89 (3H, d, *J* = 6.9 Hz, C<u>H</u>$_3$CH), 0.84 (2.37H, d, *J* = 6.9 Hz, C<u>H</u>$_3$CH), 0.82 (0.63H, d, *J* = 7.5 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.8, 135.6* (=<u>C</u>); 122.1*, 122.0 (=<u>C</u>H); 68.5 (<u>C</u>HOH); 51.9*, 51.5 (<u>C</u>H*i*-Pr); 28.8, 28.7* (<u>C</u>H(CH$_3$)$_2$); 26.2; 21.7, 20.9*; 20.8, 19.9*; 19.0; 18.5*, 17.8 (2 × <u>C</u>H$_3$C=, <u>C</u>H$_3$CH, (<u>C</u>H$_3$)$_2$CH); MS (EI) *m*/z (%) 156 (M$^+$, 0.2), 95 (32), 82 (22), 81 (22), 69 (100), 67 (45), 57 (30), 56 (26), 55 (58). GC/MS retention times (Program 2): 6.57 (*anti*), 6.70 (*syn*) min. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.75; H, 12.78.

(4R, 5S*)-4-tert-Butyl-2-methyl-2-hexen-5-ol (281)*



The reaction was performed using General Procedure H with hydroxy acetate **273** (101 mg, 0.59 mmol), *t*-BuMgCl (1.5 mL, 0.99 M, 1.5 mmol) and CuCN (27 mg, 0.30 mmol). The crude oil (*anti*:*syn* = 3:97 by GC/MS analysis) was purified via column chromatography (25% Et_2O in hexanes) to afford 79 mg (79%) of a clear, colourless oil. IR (neat) 3392 (br, OH), 2966, 2869, 1672 (C=C), 1478, 1450, 1394, 1070 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.12 (1H, d, J = 11.2 Hz, =C<u>H</u>), 4.03-3.87 (1H, m, C<u>H</u>OH), 2.34 (1H, dd, J = 11.2, 4.8 Hz, C<u>H</u>*t*-Bu), 1.79 (3H, s, C<u>H</u>$_3$C=), 1.66 (3H, s, C<u>H</u>$_3$C=), 1.34 (1H, d, J = 8.4 Hz, O<u>H</u>), 1.14 (3H, d, J = 6.4 Hz, C<u>H</u>$_3$CH), 0.92 (9H, s, (C<u>H</u>$_3$)$_3$C); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.5 (=<u>C</u>), 121.6 (=<u>C</u>H), 68.4 (<u>C</u>HOH), 54.3 (<u>C</u>H*t*-Bu), 33.3 (<u>C</u>(CH$_3$)$_3$), 28.6 (3C, (<u>C</u>H$_3$)$_3$C), 26.3, 21.2, 18.4 (2 × <u>C</u>H$_3$C=, <u>C</u>H$_3$CH); MS (EI) *m*/z (%) 170 (M^+, 0.1), 96 (75), 95 (27), 83 (40), 82 (38), 81 (40), 70 (69), 69 (74), 67 (47), 57 (100), 55 (54). GC/MS retention times (Program 2): 7.33 (*anti*), 7.50 (*syn*) min. Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.60; H, 13.25.

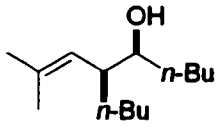
(4R, 5R*)-2,4-Dimethyl-2-nonen-5-ol (282)*



The reaction was performed using General Procedure H with hydroxy acetate **274** (200 mg, 0.93 mmol), MeMgBr (0.79 mL, 2.94 M, 2.3 mmol) and CuCN (42 mg, 0.47 mmol). The crude oil (*anti*:*syn* = 8:92 by GC/MS analysis) was purified via column chromatography (1:1 Et_2O:hexanes) to afford 140 mg (88%) of a clear, colourless oil. IR (neat) 3351 (br, OH), 2959, 2873, 1676 (C=C), 1455, 1377 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.99 (1H, d, J = 9.6 Hz, =C<u>H</u>), 3.44-3.32 (0.92, m, C<u>H</u>OH), 3.32-3.24 (0.08H, m, C<u>H</u>OH), 2.50 (1H, ddq, J = 9.6, 6.9, 6.9 Hz, C<u>H</u>CH$_3$), 1.74 (0.24H, s, C<u>H</u>$_3$C=), 1.71 (2.76H, s, C<u>H</u>$_3$C=), 1.67 (0.24H, s, C<u>H</u>$_3$C=), 1.64 (2.76H, s, C<u>H</u>$_3$C=), 1.60-1.19 (6H, m, (C<u>H</u>$_2$)$_3$CH$_3$), 0.97 (3H, d, J = 6.9 Hz, C<u>H</u>$_3$CH), 0.92 (3H, t, J = 6.1 Hz, C<u>H</u>$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 132.1 (=<u>C</u>); 127.1*, 126.8 (=<u>C</u>H); 76.1*, 75.6 (<u>C</u>OH); 38.9, 38.6* (<u>C</u>HCH$_3$); 33.8*, 33.7 (<u>C</u>H$_2$CH); 31.5*, 29.5;

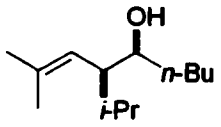
28.3*, 27.9; 25.9*, 25.2; 22.8*, 22.7; 18.1, 16.3* (2 × $\underline{C}H_3C$=, $(\underline{C}H_2)_2CH_3$, $\underline{C}H_3CH$); 14.0 ($\underline{C}H_3CH_2$); MS (EI) *m/z* (%) 170 (M^+, 0.2), 109 (25), 95 (38), 84 (79), 83 (21), 81 (27), 69 (100), 67 (43), 55 (50). GC/MS retention times (Program 2): 8.54 (*anti*), 8.63 (*syn*) min. Anal. Calcd for $C_{11}H_{22}O$: C, 77.58; H, 13.02. Found: C, 77.39; H, 13.19.

(4R, 5R*)-4-Butyl-2-methyl-2-nonen-5-ol (283)*



The reaction was performed using General Procedure H with hydroxy acetate **274** (100 mg, 0.47 mmol), *n*-BuMgBr (0.42 mL, 2.77 M, 1.2 mmol) and CuCN (22 mg, 0.25 mmol). The crude oil (*anti*:*syn* = 7:93 by GC/MS analysis) was purified via column chromatography (15% Et_2O in hexanes) to afford 83 mg (84%) of a clear, colourless oil. IR (neat) 3368 (br, OH), 2957, 2930, 2872, 1675 (C=C), 1466, 1377, 1041 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 4.94 (0.07H, d, J = 11.2 Hz, =C$\underline{H}$), 4.90 (0.93H, d, J = 10.2 Hz, =C$\underline{H}$), 3.48-3.34 (1H, m, C$\underline{H}$OH), 2.42-2.30 (1H, m, C$\underline{H}$HC=), 1.77 (0.21H, s, $C\underline{H}_3C$=), 1.74 (2.79H, s, $C\underline{H}_3C$=), 1.64 (3H, s, $C\underline{H}_3C$=), 1.56 (1H, br s, O$\underline{H}$), 1.51-1.08 (12H, m, 2 × $(C\underline{H}_2)_3CH_3$), 0.90 (3H, t, J = 6.8 Hz, $C\underline{H}_3CH_2$), 0.88 (3H, t, J = 7.0 Hz, $C\underline{H}_3CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.1, 133.8* (=$\underline{C}$); 125.6*, 125.4 (=$\underline{C}$H); 75.3*, 74.6 ($\underline{C}$HOH); 44.5*, 44.4 ($\underline{C}$HHC=); 34.2, 33.6*; 31.5, 31.1*; 29.6; 28.3*; 28.0; 26.0; 22.9; 22.7; 18.5, 18.4* (2 × $\underline{C}H_3C$=, 2 × $(\underline{C}H_2)_3CH_3$); 14.1 (2C, 2 × $\underline{C}H_3CH_2$); MS (EI) *m/z* (%) 194 (M^+-H_2O, 7), 137 (56), 96 (23), 95 (100), 81 (67), 79 (20), 69 (72), 67 (36), 57 (30), 56 (27), 55 (51). GC/MS retention times (Program 2): 11.82 (*anti*), 11.92 (*syn*) min. Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found: C, 78.94; H, 13.10.

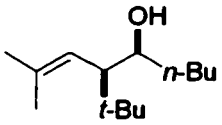
(4R, 5R*)-4-Isopropyl-2-methyl-2-nonen-5-ol (284)*



The reaction was performed using General Procedure H with hydroxy acetate **274** (101 mg, 0.47 mmol), *i*-PrMgCl (0.71 mL, 1.64 M, 1.2 mmol) and CuCN (22 mg, 0.24 mmol). The crude oil (*anti*:*syn* = 14:86 by GC/MS analysis) was purified via column chromatography

(20% Et_2O in hexanes) to afford 63 mg (68%) of a clear, colorless oil. IR (neat) 3368 (br, OH), 2959, 2931, 2872, 1673 (C=C), 1464, 1382, 1035 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.07 (0.14H, d, J = 10.7 Hz, HC=), 4.91 (0.86H, d, J = 10.7 Hz, HC=), 3.58 (1H, ddd, J = 6.8, 6.8, 2.1 Hz, CHO), 2.19 (0.86H, ddd, J = 10.7, 6.8, 6.8 Hz, CHHC=), 2.06 (0.14H, ddd, J = 10.7, 6.8, 6.0 Hz, CHHC=), 1.87 (1H, dqq, J = 6.8, 6.7, 6.7 Hz, $CH(CH_3)_2$), 1.79 (0.42H, s, CH_3C=), 1.76 (2.58H, s, CH_3C=), 1.64 (3H, s, CH_3C=), 1.58-1.05 (7H, m, OH, $(CH_2)_3CH_3$), 0.92 (3H, t, J = 7.0 Hz, CH_3CH_2), 0.91 (0.42H, d, J = 6.7 Hz, CH_3CH), 0.88 (2.58H, d, J = 6.7 Hz, CH_3CH), 0.83 (2.58H, J = 6.7 Hz, CH_3CH), 0.82 (0.42H, d, J = 6.7 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.8, 135.1* (=C); 122.5*, 122.3 (=CH); 72.5*, 72.1 (CHO); 50.7*, 50.0 (CHHC=); 34.7, 33.4*; 28.8, 28.5*; 28.3*, 27.9; 26.2; 22.8, 22.7*; 21.5, 21.0* ($(CH_2)_3CH_3$, $CHCH_3$, 2 × CH_3C=); 18.6; 18.5; 14.1 ($(CH_3)_2CH$, CH_3CH_2); MS (EI) *m/z* (%) 180 (M^+-H_2O, 4), 137 (31), 138 (28), 112 (22), 95 (80), 81 (63), 69 (100), 67 (30), 57 (50), 56 (27), 55 (45). Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 78.36; H, 13.01.

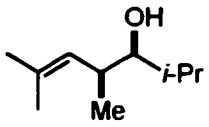
(4R, 5S*)-4-tert-Butyl-2-methyl-2-nonen-5-ol (285)*



The reaction was performed using General Procedure H with hydroxy acetate **274** (99 mg, 0.46 mmol), *t*-BuMgCl (1.2 mL, 0.99 M, 1.2 mmol) and CuCN (21 mg, 0.24 mmol). The crude oil (homogenous by GC/MS and ^1H NMR analysis) was purified via column chromatography (12.5% Et_2O in hexanes) to afford 83 mg (83%) of a clear, colourless oil. IR (neat) 3436 (br, OH), 2957, 2872, 1671 (C=C), 1478, 1467, 1394, 1376, 1363, 1010 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.08 (1H, d, J = 11.2 Hz, =CH), 3.79-3.63 (1H, m, CHOH), 2.31 (1H, dd, J = 11.2, 5.0 Hz, CH*t*-Bu), 1.77 (3H, s, CH_3C=), 1.65 (3H, s, CH_3C=), 1.55-1.13 (6H, m, $(CH_2)_3CH_3$), 1.20 (1H, d, J = 8.2 Hz, OH), 0.92 (9H, s, $(CH_3)_3C$), 0.90 (3H, t, J = 6.8 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.7 (=C), 122.5 (=CH), 72.8 (CHOH), 54.2 (CH*t*-Bu), 34.7 (CH_2CH), 33.5 ($C(CH_3)_3$), 28.9 (3C, $(CH_3)_3C$), 28.5, 26.4, 22.8, 18.4 (2 × CH_3C=, $(CH_2)_2CH_3$), 14.2 (CH_3CH_2); MS (EI) *m/z* (%) 194 (M^+-H_2O, 5), 137 (54), 109 (45), 95 (98), 83 (21), 70 (37), 69 (53), 67 (43), 57 (100), 55 (53), 53 (22). GC/MS retention time (Program

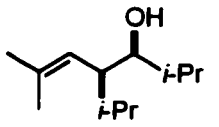
2): 10.96 (*syn*) min. Anal. Calcd for $C_{14}H_{28}O$: C, 79.18; H, 13.29. Found: C, 79.32; H, 13.31.

(4R, 5R*)-2,4,6-Trimethyl-2-hepten-5-ol (286)*



The reaction was performed using General Procedure H with hydroxy acetate **275** (150 mg, 0.75 mmol), MeMgBr (0.64 mL, 2.94 M, 1.9 mmol) and CuCN (35 mg, 0.39 mmol). The crude oil (*anti*:*syn* = 20:80 by GC/MS analysis) was purified via column chromatography (15% Et_2O in hexanes) to afford 59 mg (50%) of a clear, colourless oil. IR (neat) 3401 (br, OH), 2963, 2872, 1673 (C=C), 1451, 1384 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 5.03 (0.20H, d, J = 9.5 Hz, =C<u>H</u>), 4.98 (0.80H, d, J = 9.5 Hz, =C<u>H</u>), 3.14 (0.80H, dd, J = 6.9, 4.7 Hz, C<u>H</u>OH), 3.09 (0.20H, dd, J = 7.2, 4.5 Hz, C<u>H</u>OH), 2.54-2.42 (1H, m, C<u>H</u>HC=), 1.81-1.69 (1H, m, C<u>H</u>$(CH_3)_2$), 1.69 (3H, s, C<u>H</u>$_3$C=), 1.63 (3H, s, C<u>H</u>$_3$C=), 1.32 (1H, br s, O<u>H</u>) 0.99 (3H, d, J = 6.6 Hz, <u>C</u>H_3CH), 0.95 (3H, d, J = 6.9 Hz, C<u>H</u>$_3$CH), 0.87 (3H, d, J = 6.7 Hz, C<u>H</u>$_3$CH) ; ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.9, 130.9* (=<u>C</u>); 127.0*, 126.9 (=<u>C</u>H); 80.7*, 80.0 (<u>C</u>HOH); 36.2, 36.0* (<u>C</u>HHC=); 30.4*, 29.8; 26.0, 25.8*; 20.2, 20.1*; 18.2, 17.9*; 17.5, 16.2*; 16.0*, 15.6 (<u>C</u>H_3CH, $(\underline{C}H_3)_2\underline{C}$H, 2 × <u>C</u>$H_3$C=); MS (EI) *m*/z (%) 156 (M^+, 1), 84 (100), 83 (38), 73 (34), 69 (100), 55 (70). GC/MS retention times (Program 2): 6.53 (*anti*), 6.74 (*syn*) min. Anal. Calcd for $C_{10}H_{20}O$: C, 76.86; H, 12.90. Found: C, 76.65; H, 12.85.

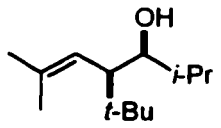
(4R, 5R*)-4-Isopropyl-2,6-dimethyl-2-hepten-5-ol (287)*



The reaction was performed using General Procedure H with hydroxy acetate **275** (100 mg, 0.50 mmol), *i*-PrMgCl (0.76 mL, 1.64 M, 1.3 mmol) and CuCN (23 mg, 0.25 mmol). The crude oil (*anti*:*syn* ≈ 50:50 by GC/MS analysis) was purified via column chromatography (15% Et_2O in hexanes) to afford 63 mg (68%) of a clear, colourless oil. IR (neat) 3401 (br, OH), 2959, 2929, 2872, 1673 (C=C), 1467, 1385, 1367, 990 cm^{-1}; ^1H NMR (300 MHz,

$CDCl_3$) δ 5.09 (0.50H, d, J = 9.3 Hz, =C<u>H</u>), 4.84 (0.50H, d, J = 10.7 Hz, =C<u>H</u>), 3.41 (0.50H, dd, J = 9.8, 2.8 Hz, C<u>H</u>OH), 3.35 (0.50H, dd, J = 5.9, 5.9 Hz, C<u>H</u>OH), 2.30 (0.50H, ddd, J = 10.7, 9.8, 2.8 Hz, C<u>H</u>HC=), 2.21-2.09 (1H, m, C<u>H</u>HC=, C<u>H</u>$(CH_3)_2$), 1.82-1.68 (1.50H, m, 2 × C<u>H</u>$(CH_3)_2$), 1.77 (1.50H, s, C<u>H</u>$_3$C=), 1.72 (1.50 H, s, C<u>H</u>$_3$C=), 1.64 (1.50H, s, C<u>H</u>$_3$C=), 1.63 (1.50H, s, C<u>H</u>$_3$C=), 1.44 (0.50H, br s, O<u>H</u>), 1.43 (0.50H, br s, O<u>H</u>), 1.00-0.74 (12H, m, 2 × $(C\underline{H}_3)_2CH$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.3, 133.4 (=<u>C</u>); 122.3, 121.8 (=<u>C</u>H); 76.8, 76.4 (<u>C</u>HOH); 47.2, 47.1 (<u>C</u>HHC=); 30.4, 30.2 (<u>C</u>H$(CH_3)_2$); 28.7, 27.9 (<u>C</u>H$(CH_3)_2$); 26.2, 26.1; 21.6, 21.4; 20.8, 19.9; 18.7, 18.6; 18.5, 16.8; 16.0, 13.9 (2 × <u>C</u>H$_3$C=, 2 × $(\underline{C}H_3)_2CH$); MS (EI) *m/z* (%) 184 (M^+, 0.1), 123 (24), 112 (35), 95 (30), 81 (26), 69 (100), 57 (51), 56 (37). GC/MS retention times (Program 2): 8.55, 8.78 min. Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.28; H, 12.93.

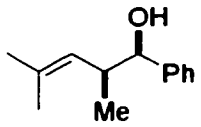
(4R, 5S*)-4-tert-Butyl-2,6-dimethyl-2-hepten-5-ol (288)*



The reaction was performed using General Procedure H with hydroxy acetate **275** (100 mg, 0.50 mmol), *t*-BuMgCl (1.3 mL, 0.99 M, 1.3 mmol) and CuCN (22 mg, 0.25 mmol). The crude white solid (*anti*:*syn* = 6:94 by ^{1}H NMR analysis) was purified via column chromatography (10% Et_2O in hexanes) to afford 82 mg (83%) of a white, crystalline solid (mp = 45-47°C). IR (KBr) 3415 (br s), 2967, 1478, 1385, 1095 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 5.26 (0.06H, d, J = 10.9 Hz, =C<u>H</u>), 4.88 (0.94H, d, J = 11.0 Hz, =C<u>H</u>), 3.49 (0.94H, dd, J = 9.0, 7.0 Hz, C<u>H</u>OH), 3.41 (0.06H, dd, J = 8.6, 7.6 Hz, C<u>H</u>OH), 2.17 (0.06H, dd, J = 10.9, 8.6 Hz, C<u>H</u>*t*-Bu), 2.08 (0.94H, dd, J = 11.0, 9.0 Hz, C<u>H</u>*t*-Bu), 1.79-1.72 (1H, m, C<u>H</u>$(CH_3)_2$), 1.60 (3H, s, C<u>H</u>$_3$C=), 1.55 (3H, s, C<u>H</u>$_3$C=), 1.09 (1H, d, J = 7.0 Hz, O<u>H</u>), 0.93 (9H, s, $(C\underline{H}_3)_3C$), 0.93-0.89 (3H, m, C<u>H</u>$_3$CH), 0.72 (3H, d, J = 6.8 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 134.4, 131.5* (=<u>C</u>); 124.5*, 121.0 (=<u>C</u>H); 77.3, 76.9* (<u>C</u>HOH); 51.6*, 48.9 (<u>C</u>H*t*-Bu); 34.2*, 34.0 (<u>C</u>$(CH_3)_3$); 33.3, 30.8* (<u>C</u>H$(CH_3)_2$); 29.0*, 28.5 (3C, $(\underline{C}H_3)_3C$); 26.4, 26.0*; 20.9*, 19.8; 19.0, 18.6*; 13.6 (2 × <u>C</u>H$_3$C=, $(\underline{C}H_3)_2CH$); MS (EI) *m/z* (%) 198 (M^+, 0.03), 126 (21), 124 (27), 123 (20), 109 (45), 95 (10), 83 (24), 70 (97), 69 (48), 57 (100), 55

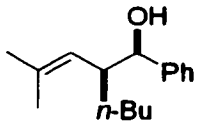
(32). GC/MS retention time (Program 2): 9.27 (*anti*, *syn*) min. Anal. Calcd for $C_{13}H_{26}O$: C, 78.72; H, 13.21. Found: C, 79.02; H, 13.07.

(1R, 2S*)-2,4-Dimethyl-1-phenyl-3-penten-1-ol (289)*



The reaction was performed using General Procedure H with using hydroxy acetate **276** (125 mg, 0.54 mmol), MeMgBr (0.45 mL, 2.94 M, 1.3 mmol) and CuCN (25 mg, 0.28 mmol). The crude oil (*anti*:*syn* = 26:74 by GC/MS analysis) was purified via column chromatography (20% Et_2O in hexanes) to afford 74 mg (72%) of a clear, colourless oil. IR (neat) 3401 (br, OH), 3030, 2966, 2871, 1947, 1880, 1806, 1672 (C=C), 1453, 1377, 1021, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35 (5H, m, $C_6\underline{H}_5$), 5.08 (0.26H, d, J = 9.8 Hz, =C$\underline{H}$), 4.96 (0.74H, d, J = 9.8 Hz, =C$\underline{H}$), 4.54 (0.74H, d, J = 6.2 Hz, C$\underline{H}$OH), 4.24 (0.26H, d, J = 8.6 Hz, C$\underline{H}$OH), 2.81-2.71 (0.74H, m, C$\underline{H}$CH$_3$), 2.69-2.61 (0.26H, m, C$\underline{H}$CH$_3$), 1.91 (1H, br s, O$\underline{H}$), 1.79 (0.78H, s, C$\underline{H}_3$C=), 1.69 (0.78H, s, C$\underline{H}_3$C=), 1.64 (2.22H, s, C$\underline{H}_3$C=), 1.47 (2.22H, s, C$\underline{H}_3$C=), 0.98 (2.22H, d, J = 6.7Hz, C$\underline{H}_3$CH), 0.77 (0.78, d, J = 6.7 Hz, C$\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1*, 142.6; 135.4, 132.9*; 128.1, 127.8* (2C); 127.5, 127.1*; 126.5 (2C); 126.3 (C=CH, ArC's); 79.0, 78.2* (CHOH); 41.4, 39.8* (CHCH$_3$); 26.0, 25.8*; 18.3, 17.9*; 17.2, 16.3* (2 × CH$_3$C=, CH$_3$CH); MS (EI) *m*/z (%) 190 (M^+, 1), 172 (29), 157 (96), 143 (24), 142 (47), 115 (30), 107 (100), 105 (22), 91 (27), 84 (63), 79 (55), 77 (48), 69 (26), 55 (30), 51 (20). GC/MS retention times (Program 2): 11.86 (*syn*), 12.04 (*anti*) min. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.86; H, 9.30.

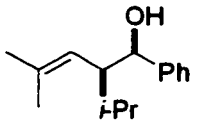
(1R, 2S*)-2-Butyl-4-methyl-1-phenyl-3-penten-1-ol (290)*



The reaction was performed using General Procedure H with hydroxy acetate **276** (100 mg, 0.43 mmol), *n*-BuMgBr (0.39 mL, 2.77 M, 1.1 mmol) and CuCN (22 mg, 0.24 mmol). The crude oil (*anti*:*syn* = 23:77 by ^1H NMR analysis) was purified via column chromatography

(15% Et_2O in hexanes) to afford 78 mg (79%) of a clear, colourless oil. IR (neat) 3401 (br, OH), 3030, 2957, 2928, 2859, 1945, 1875, 1804, 1676 (C=C), 1453, 1377, 1038, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.34-7.21 (5H, m, $C_6\underline{H}_5$), 4.99 (0.23H, d, J = 10.3 Hz, =C$\underline{H}$), 4.83 (0.77H, d, J = 10.2 Hz, =C$\underline{H}$), 4.56 (0.77H, d, J = 6.3 Hz, C$\underline{H}$OH), 4.28 (0.23H, d, J = 8.3 Hz, C$\underline{H}$OH), 2.73-2.56 (0.77H, m, C$\underline{H}$*n*-Bu), 2.56-2.44 (0.23H, m, C$\underline{H}$*n*-Bu), 1.95 (1H, s, O$\underline{H}$), 1.65 (3H, s, $C\underline{H}_3C$=), 1.47 (3H, s, $C\underline{H}_3C$=), 1.37-0.96 (6H, m, $(C\underline{H}_2)_3CH_3$), 0.87 (2.31H, t, J = 6.9 Hz, $C\underline{H}_3CH_2$), 0.80 (0.69H, t, J = 6.8 Hz, $C\underline{H}_3CH_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.1; 134.4; 123.1; 127.8*, 127.5 (2C); 127.0, 126.6* (2C); 125.6, 124.9* (C=C$\underline{H}$, ArC's); 77.8, 77.7* (C$\underline{H}$OH); 47.1, 45.4* (C$\underline{H}$*n*-Bu); 31.2, 30.8* ($C\underline{H}_2$CH); 29.5; 26.1, 25.9*; 22.9*, 22.7; 18.6, 18.2* (2 × $C\underline{H}_3C$=, $(C\underline{H}_2)_2CH_3$); 14.1*, 14.0 ($C\underline{H}_3CH_2$); MS (EI) *m/z* (%) 232 (M^+, 0.2), 157 (100), 143 (65), 142 (22), 141 (20), 129 (69), 128 (33), 115 (34), 91 (70), 79 (21), 77 (33), 69 (28). GC/MS retention time (Program 2): 14.74 (*anti*, *syn*) min. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.80; H, 10.52.

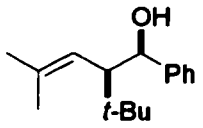
(1R, 2S*)-2-Isopropyl-4-methyl-1-phenyl-3-penten-1-ol (291)*



The reaction was performed using General Procedure H with hydroxy acetate **276** (101 mg, 0.43 mmol), *i*-PrMgCl (0.65 mL, 1.64 M, 1.1 mmol) and CuCN (20 mg, 0.22 mmol). The crude oil (*anti*:*syn* = 38:62 by GC/MS analysis) was purified via column chromatography (15% Et_2O in hexanes) to afford 69 mg (74%) of a clear, colourless oil. IR (neat) 3401 (br, OH), 2961, 2927, 2871, 1945, 1872, 1803, 1674 (C=C), 1453, 1384, 1367, 1036, 757, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.19 (5H, m, $C_6\underline{H}_5$), 5.18 (0.38H, d, J = 10.6 Hz, =C$\underline{H}$), 4.82 (0.62H, d, J = 10.8 Hz, =C$\underline{H}$), 4.63 (0.62H, d, J = 8.2 Hz, C$\underline{H}$OH), 4.55 (0.38H, d, J = 8.4 Hz, C$\underline{H}$OH), 2.58 (0.62H, ddd, J = 10.8, 8.2, 5.0 Hz, C$\underline{H}$*i*-Pr), 5.06 (0.38H, ddd, J = 10.6, 8.4, 4.2 Hz, C$\underline{H}$*i*-Pr), 2.10-1.85 (1.62, m, $C\underline{H}(CH_3)_2$, O$\underline{H}$), 1.82 (1.14H, s, $C\underline{H}_3C$=), 1.59 (3H, s, $C\underline{H}_3C$=), 1.53-1.41 (0.38H, m, $C\underline{H}(CH_3)_2$), 1.33 (1.86H, s, $C\underline{H}_3C$=), 0.95 (1.86H, d, J = 6.8 Hz, $\underline{C}H_3CH$), 0.89 (1.86H, d, J = 6.8 Hz, $\underline{C}H_3CH$), 0.85 (1.14H, d, J = 6.8Hz, $\underline{C}H_3CH$), 0.80 (1.14H, d, J = 6.8 Hz, CH_3CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.7*, 143.1; 138.3, 135.0*; 128.2, 127.8* (2C); 127.4, 126.9*; 127.1, 126.8 (2C); 121.2, 121.0* (C=C$\underline{H}$, ArC's); 75.6,

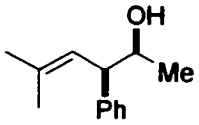
75.5* (CHOH); 52.5, 51.5* (CH*i*-Pr); 28.5, 27.9* (CH$(CH_3)_2$); 26.4, 26.0*; 21.9, 21.6*; 18.4, 18.0*; 17.4*, 17.2 (2 × CH_3C=, $(CH_3)_2CH$); MS (EI) *m*/z (%) 200 (M^+-H_2O, 15), 157 (100), 143 (59), 142 (30), 141 (22), 129 (67), 128 (33), 115 (32), 105 (22), 91 (52), 79 (20), 69 (21). GC/MS retention times (Program 2): 13.31 (*syn*), 13.47 (*anti*) min. Anal. Calcd for $C_{15}H_{22}O$: C, 82.52; H, 10.16. Found: C, 82.36; H, 10.22.

(1R, 2R*)-2-tert-Butyl-4-methyl-1-phenyl-3-penten-1-ol (292)*



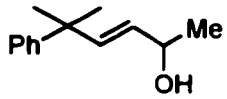
The reaction was performed using General Procedure H with hydroxy acetate **276** (100 mg, 0.43 mmol), *t*-BuMgCl (1.1 mL, 0.99 M, 1.1 mmol) and CuCN (21 mg, 0.23 mmol). The crude white solid (*anti*:*syn* = 15:85 by GC/MS analysis) was purified via column chromatography (10% Et_2O in hexanes) to afford 71 mg (72%) of a clear, colourless oil. IR (neat) 3436 (br, OH), 3030, 2963, 2909, 2869, 1945, 1882, 1804, 1675 (C=C), 1454, 1366, 1014, 701 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.30-7.18 (5H, m, C_6H_5), 5.30 (0.15H, d, J = 10.7 Hz, =CH), 5.02 (0.15H, d, J = 2.8 Hz, CHOH), 4.92 (0.85H, d, J = 11.2 Hz, =CH), 4.75 (0.85H, d, J = 7.0 Hz, CHOH), 2.58 (0.85H, dd, J = 11.2, 7.0 Hz, CH*t*-Bu), 2.26 (0.15H, dd, J = 10.7, 2.8 Hz, CH*t*-Bu), 1.81 (1H, br s, OH), 1.58 (3H, s, CH_3C=), 1.42 (3H, s, CH_3C=), 0.98 (1.35H, s, $(CH_3)_3C$), 0.93 (7.65H, s, $(CH_3)_3C$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.6; 134.0; 127.9, 127.8* (2C); 127.5, 127.2* (2C); 126.8*, 126.0; 122.9*, 119.6 (C=CH, ArC's); 76.1*, 73.9 (CHOH); 55.5, 54.5* (CH*t*-Bu); 33.9 ($C(CH_3)_3$); 28.7 (3C, $(CH_3)_3C$); 26.3, 26.1*; 18.2 (2 × CH_3C=); MS (EI) *m*/z (%) 214 (M^+-H_2O, 6), 158 (24), 157 (61), 143 (39), 129 (51), 128 (30), 115 (26), 91 (31), 77 (27), 57 (100). GC/MS retention times (Program 2): 13.70 (*syn*), 13.86 (*anti*) min. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.59; H, 10.61.

(4R, 5S*)-2-Methyl-4-phenyl-2-hexen-5-ol (γ-293)*



The reaction was performed using General Procedure H with hydroxy acetate **273** (85 mg, 0.49 mmol), PhMgCl (0.64 mL, 1.92 M, 1.2 mmol) and CuCN (24 mg, 0.27 mmol). The crude oil (*anti*:*syn* = 27:73 by ^{1}H NMR analysis) was purified via column chromatography (20% Et_2O in hexanes) to afford 27 mg (29%) of a clear, colourless oil. IR (neat) 3391 (br, OH), 3028, 2971, 2927, 1945, 1872, 1804, 1670 (C=C), 1451, 1376, 1078, 754, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.19 (5H, m, $C_6\underline{H}_5$), 3.41 (0.27H, dd, J = 9.9, 8.5 Hz, =C$\underline{H}$), 5.39 (0.73H, d, J = 9.8 Hz, =C$\underline{H}$), 4.01 (0.73H, dq, J = 8.5, 6.2 Hz, C$\underline{H}$OH), 3.94-3.87 (0.27H, m, C$\underline{H}$OH), 3.47 (0.73H, dd, J = 9.8, 8.5 Hz, C$\underline{H}$Ph), 3.41 (0.27H, dd, J = 9.9, 8.5 Hz, C$\underline{H}$Ph), 1.78 (0.81H, s, $C\underline{H}_3$C=), 1.72 (2.19H, s, $C\underline{H}_3$C=), 1.71 (0.81H, s, $C\underline{H}_3$C=), 1.67 (2.19H, s, $C\underline{H}_3$C=), 1.57 (1H, br s, O$\underline{H}$), 1.22 (2.19H, d, J = 6.2 Hz, $C\underline{H}_3$CH), 1.08 (0.81H, d, J = 6.2 Hz, $C\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.4; 133.7; 128.8*, 128.6 (2C); 128.2*, 127.9 (2C); 126.6*, 126.4; 124.6*, 124.4 (C=C, ArC's); 71.7*, 71.5 (CHOH); 53.2 (CHPh); 26.2, 26.2*; 20.5*, 20.3; 18.3 (2 × $C\underline{H}_3$C=, $C\underline{H}_3$CH); MS (EI) *m*/z (%) 172 (M^+-H_2O, 13), 157 (39), 146 (69), 131 (100), 129 (51), 117 (22), 115 (28), 91 (44). GC/MS retention time (Program 2): 11.84 (*anti*, *syn*) min. Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.81; H, 9.41.

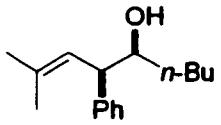
(E)-2-Methyl-2-phenyl-3-hexen-5-ol (α-293)



This compound was isolated (26%) from the coupling reaction (General Procedure H) using hydroxy acetate **273**, PhMgCl and CuCN, as a clear, colourless oil. IR (neat) 3342 (br, OH), 3023, 2968, 1945, 1872, 1802, 1669 (C=C), 1494, 1446, 1363, 1060, 978, 764, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.17 (5H, m, $C_6\underline{H}_5$), 5.87 (1H, d, J = 15.7 Hz, =C$\underline{H}$C), 5.58 (1H, dd, J = 15.7, 6.6 Hz, =C$\underline{H}$CH), 4.35 (1H, dq, J = 6.6, 6.3 Hz, C$\underline{H}$OH), 1.56 (1H, br s, O$\underline{H}$), 1.41 (3H, s, $C\underline{H}_3$C), 1.40 (3H, s, $C\underline{H}_3$C), 1.31 (3H, d, J = 6.3 Hz, $C\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.5, 140.3, 130.4, 128.1 (2C), 126.0 (2C), 125.8 (H$\underline{C}$=$\underline{C}$H, ArC's), 69.1

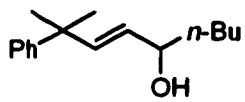
(CHOH), 40.0 (CPh), 28.6 (2C, $(CH_3)_2C$), 23.5 (CH_3CH); MS (EI) *m/z* (%) 172 (M^+-H_2O, 24), 157 (46), 143 (26), 142 (30), 129 (100), 128 (34), 115 (30), 91 (32), 77 (32). Anal. Calcd for $C_{13}H_{18}O$: C, 82.06; H, 9.53. Found: C, 81.81; H, 9.78.

(4R, 5S*)-2-Methyl-4-phenyl-2-nonen-5-ol (γ-294)*



The reaction was performed using General Procedure H with hydroxy acetate **274** (149 mg, 0.70 mmol), PhMgCl (0.91 mL, 1.92 M, 1.8 mmol) and CuCN (32 mg, 0.36 mmol). The crude oil (*anti*:*syn* = 15:85 by ^{1}H NMR analysis) was purified via column chromatography (15% Et_2O in hexanes) to afford 45 mg (28%) of a clear, colourless oil. IR (neat) 3454 (br, OH), 3027, 2957, 2859, 1944, 1871, 1803, 1671 (C=C), 1452, 1377, 1074, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.19 (5H, m, C_6H_5), 5.50 (0.15H, d, J = 10.2 Hz, =CH), 5.40 (0.85H, d, J = 9.6 Hz, =CH), 3.78 (1H, td, J = 8.1, 2.6 Hz, CHOH), 3.51 (1H, dd, J = 9.6, 8.1 Hz, CHPh), 1.77 (0.45H, s, CH_3C=), 1.72 (2.55H, s, CH_3C=), 1.68 (0.45H, s, CH_3C=), 1.65 (2.55H, s, CH_3C=), 1.62-128 (7H, m, OH, $(CH_2)_3CH_3$), 0.92 (2.55H, t, J = 6.8 Hz, CH_3CH_2), 0.82 (0.45H, t, J = 6.8 Hz, CH_3CH_2); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.5; 133.4; 128.7*, 128.6 (2C); 128.3*, 128.0 (2C); 126.5*, 126.3; 124.8*, 124.5 (C=CH, ArC's); 75.4*, 75.2 (CHOH); 51.8*, 51.6 (CHPh); 34.1*, 34.0 (CH_2CH); 28.1*, 28.0; 26.0*, 25.9; 22.7*, 22.6; 18.3 (2 × CH_3C=, $(CH_2)_2CH_3$); 14.1*, 14.0 (CH_3CH_2); MS (EI) *m/z* (%) 232 (M^+, 0.1), 157 (80), 145 (22), 143 (55), 131 (100), 129 (97), 128 (51), 91 (75), 77 (23), 65 (13). GC/MS retention time (Program 2): 14.99 (*anti*, *syn*) min. Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.53; H, 10.27.

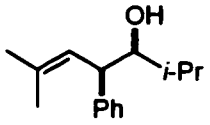
(E)-2-Methyl-2-phenyl-3-nonen-5-ol (α-294)



This compound was isolated (34%) from the coupling reaction (General Procedure H) using hydroxy acetate **274**, PhMgCl and CuCN, as a clear, colourless oil. IR (neat) 3339 (br, OH), 2962, 2872, 1802, 1494, 1468, 1030, 976, 700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.17

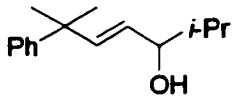
(5H, m, $C_6\underline{H}_5$), 5.87 (1H, d, J = 15.7 Hz, =C$\underline{H}$), 5.53 (1H, dd, J = 15.7, 7.1 Hz, =C$\underline{H}$CH), 4.14 (1H, dt, J = 7.1, 6.7 Hz, C$\underline{H}$OH), 1.68-1.46 (2H, m C$\underline{H}_2$CH), 1.42 (3H, s, C$\underline{H}_3$C), 1.41 (3H, s, C$\underline{H}_3$C), 1.41-1.16 (4H, m, (C$\underline{H}_2$)$_2$CH$_3$), 0.93 (3H, t, J = 6.9 Hz, C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.4, 129.5, 129.2, 128.1 (2C), 126.0 (2C), 125.8 (H$\underline{C}$=$\underline{C}$H, ArC's), 73.4 ($\underline{C}$HOH), 40.1 (CPh), 37.1 ($\underline{C}$H$_2$CH), 28.7, 28.6, 27.7, 22.6 (2 × $\underline{C}$H$_3$C=, ($\underline{C}$H$_2$)$_2$CH$_3$), 14.0 ($\underline{C}$H$_3$CH$_2$); MS (EI) *m*/z (%) 217 (M$^+$-CH$_3$, 0.1), 214 (24), 171 (47), 157 (67), 143 (56), 129 (100), 128 (34), 115 (30), 105 (36), 91 (80), 77 (26). Anal. Calcd for $C_{16}H_{24}O$: C, 82.70; H, 10.41. Found: C, 82.58; H, 10.27.

(4R, 5S*)-2,6-Dimethyl-4-phenyl-2-hepten-5-ol (γ-295)*



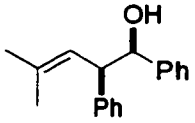
The reaction was performed using General Procedure H with hydroxy acetate **275** (100 mg, 0.50 mmol), PhMgBr (0.65 mL, 1.92 M, 1.3 mmol) and CuCN (22 mg, 0.25 mmol). The crude oil (*anti*:*syn* = 22:78 by ^{1}H NMR analysis) was purified via column chromatography (15% Et_2O in hexanes) to afford 44 mg (41%) of a clear, colourless oil. IR (neat) 3474 (br, OH), 3027, 2965, 2930, 2930, 2872, 1945, 1870, 1670 (C=C), 1451, 1377, 993, 755, 701 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-7.19 (5H, m, $C_6\underline{H}_5$), 5.51 (0.22H, d, J = 9.5Hz, =C$\underline{H}$), 5.39 (0.78H, d, J = 9.5 Hz, =C$\underline{H}$), 3.65 (1H, dd, J = 8.8, 3.1 Hz, C$\underline{H}$OH), 3.59 (1H, dd, J = 9.5, 8.8 Hz, C$\underline{H}$Ph), 1.90 (0.78H, qqd, J = 6.9, 6.8, 3.1 Hz, C$\underline{H}$(CH$_3$)$_2$), 1.77 (0.66H, s, C$\underline{H}_3$C=), 1.70 (2.34H, s, C$\underline{H}_3$C=), 1.67 (3H, s, C$\underline{H}_3$C=), 1.60-1.47 (0.22H, m, C$\underline{H}$(CH$_3$)$_2$), 1.41 (1H, br s, O$\underline{H}$), 1.04 (3H, d, J = 6.9 Hz, C$\underline{H}_3$CH), 0.93 (0.66H, d, J = 6.8 Hz, C$\underline{H}_3$CH), 0.92 (2.34H, d, J = 6.8 Hz, C$\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.9; 132.5; 128.7, 128.6* (2C); 138.3*, 127.9 (2C); 126.5*, 126.2; 125.2*, 124.3 ($\underline{C}$=$\underline{C}$H, ArC's); 79.7, 79.4* ($\underline{C}$HOH); 49.1*, 48.5 ($\underline{C}$HPh); 29.9*, 29.6 ($\underline{C}$H(CH$_3$)$_2$); 26.1, 26.0*; 20.6*, 20.2; 18.3, 18.2*; 15.9, 14.9* (2 × $\underline{C}$H$_3$C=, ($\underline{C}$H$_3$)$_2$CH); MS (EI) *m*/z (%) 218 (M$^+$, 1), 146 (67), 145 (26), 131 (100), 129 (27), 91 (32). GC/MS retention time (Program 2): 13.38 (*anti*, *syn*) min. Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.66; H, 10.17.

(E)-2,6-Dimethyl-2-phenyl-3-hepten-5-ol (α-295)



This compound was isolated (21%) from the coupling reaction (General Procedure H) using hydroxy acetate **275**, PhMgCl and CuCN, as a clear, colourless oil. IR (neat) 3349 (br, OH), 3087, 3047, 2965, 2931, 1662 (C=C), 1474, 1234, 754, 692 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.35-7.18 (5H, m, $C_6\underline{H}_5$), 5.87 (1H, d, J = 15.7 Hz, =C$\underline{H}$C), 5.53 (1H, dd, J = 15.7, 7.3 Hz, =C$\underline{H}$CH), 3.88 (1H, dd, J = 7.3, 6.9 Hz, C$\underline{H}$OH), 1.81 (1H, dqq, J = 6.9, 6.8, 6.8 Hz, C$\underline{H}(CH_3)_2$), 1.42 (3H, s, C$\underline{H}_3$C), 1.41 (3H, s, C$\underline{H}_3$C), 0.96 (3H, d, J = 6.8 Hz, C$\underline{H}_3$CH), 0.92 (3H, d, J = 6.8 Hz, C$\underline{H}_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 149.0, 142.4, 129.6, 128.1 (2C), 126.1 (2C), 125.8 (H$\underline{C}$=$\underline{C}$H, ArC's), 78.4 ($\underline{C}$HOH), 40.3 ($\underline{C}(CH_3)_2$), 34.0 ($\underline{C}H(CH_3)_2$), 28.8, 28.7, 18.3, 18.2 (($\underline{C}H_3)_2C$, ($\underline{C}H_3)_2CH$); MS (EI) *m/z* (%) 200 (M^+-H_2O, 42), 185 (38), 157 (100), 143 (67), 142 (26), 129 (59), 128 (37), 115 (29), 105 (40), 91 (73), 77 (30). Anal. Calcd for $C_{15}H_{22}O$: C, 82.51; H, 10.16. Found: C, 82.70; H, 9.91.

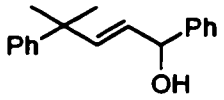
(1R, 2R*)-4-Methyl-1,2-diphenyl-3-penten-1-ol (γ-296)*



The reaction was performed using General Procedure H with hydroxy acetate **276** (125 mg, 0.54 mmol), PhMgBr (0.47 mL, 2.81 M, 1.3 mmol) and CuCN (25 mg, 0.28 mmol). The crude oil (*anti*:*syn* = 10:90 by GC/MS) was purified via column chromatography (20% Et_2O in hexanes) to afford 46 mg (34%) of a white, crystalline solid (mp = 65-67°C). IR ($CHCl_3$) 3437 (br, OH), 3029, 2970, 1948, 1879, 1805, 1752, 1684 (C=C), 1494, 1451, 1049, 759, 700 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.50-7.04 (10H, m, 2 × $C_6\underline{H}_5$), 5.65 (0.10H, d, J = 9.9 Hz, =C$\underline{H}$), 5.36 (0.90H, d, J = 9.8 Hz, =C$\underline{H}$), 4.82 (0.90H, d, J = 8.4 Hz, C$\underline{H}$OH), 4.78 (0.10H, d, J = 7.8 Hz, C$\underline{H}$OH), 3.79 (0.90H, dd, J = 9.8, 8.4 Hz, C$\underline{H}$Ph), 1.86 (1H, br s, O$\underline{H}$), 1.79 (0.30H, s, C$\underline{H}_3$C=), 1.64 (0.30H, s, C$\underline{H}_3$C=), 1.57 (2.70H, s, C$\underline{H}_3$C=), 1.28 (2.70H, s, C$\underline{H}_3$C=); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.2*, 142.0; 141.9*, 141.6; 136.5, 134.0*; 133.1; 128.7*, 128.3 (2C); 128.4*, 128.2 (2C); 127.8*, 27.7 (2C); 127.4, 126.9* (2C); 126.7*, 126.6; 123.8*, 123.6

(C=CH, ArC's); 78.3, 78.2* (CHOH); 53.6, 53.3* (CHPh); 26.2, 25.8* (CH_3C=); 18.3, 17.8* (CH_3C=); MS (EI) *m*/z (%) 252 (M^+, 1), 234 (65), 219 (86), 217 (30), 204 (40), 165 (30), 146 (34), 145 (34), 144 (34), 143 (82), 141 (31), 129 (100), 128 (97), 106 (45), 105 (56), 91 (97), 77 (84), 51 (52). GC/MS retention times (Program 2): 17.46 (*syn*), 17.80 (*anti*) min. Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.78; H, 8.14.

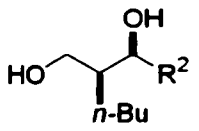
(E)-4-Methyl-1,4-diphenyl-2-penten-1-ol (α-296)



This compound was isolated (22%) from the coupling reaction (General Procedure H) using hydroxy acetate **276**, PhMgCl and CuCN, as a clear, colourless oil. IR (neat) 3339 (br, OH), 3029, 2967, 1950, 1880, 1810, 1663 (C=C), 1494, 1363, 1232, 763, 699 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.44-7.17 (10H, m, 2 × C_6H_5), 6.02 (1H, d, J = 15.6 Hz, =CHC), 5.74 (1H, dd, J = 15.6, 6.8 Hz, =CHCH), 5.26 (1H, dd, J = 6.8, 3.3 Hz, CHOH), 1.88 (1H, d, J = 3.3 Hz, OH), 1.43 (3H, s, CH_3), 1.41 (3H, s, CH_3); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.4, 143.2, 141.7, 129.5, 128.5 (2C), 128.1 (2C), 127.5, 126.2 (2C), 126.0 (2C), 125.8 (HC=CH, ArC's), 75.2 (CHOH), 40.2 ($C(CH_3)_2$), 28.6, 28.5 (($CH_3)_2C$); MS (EI) *m*/z (%) 252 (M^+, 1), 234 (78), 191 (34), 143 (70), 128 (47), 115 (96), 91 (100). Anal. Calcd for $C_{18}H_{20}O$: C, 85.67; H, 7.99. Found: C, 85.56; H, 7.95.

4.3.11 Cis-1,3-Dioxanes

Compounds ***syn*-251-253** and **297**, and ***cis*-255-257** and **298** were synthesized as described in General Procedure F (Section 4.3.7).



syn-251: R^2 = Me
syn-252: R^2 = *n*-Bu
syn-253: R^2 = *i*-Pr
297: R^2 = Ph

(2R, 3R*)-2-Butyl-1,3-butanediol (**syn-251**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 4.13 (1H, qd, J = 6.5, 3.1 Hz, C<u>H</u>OH), 3.84 (1H, A of ABX, dd, J_{obs} = 10.8, 7.7 Hz, C<u>H</u>$_2$OH), 3.75 (1H, B of ABX, dd, J_{obs} = 10.8, 3.8 Hz, C<u>H</u>$_2$OH), 2.64 (1H, br s, O<u>H</u>), 2.60 (1H, br s, O<u>H</u>), 1.80-1.68 (1H, X of ABX, m, C<u>H</u>*n*-Bu), 1.40-1.20 (6H, m, (C<u>H</u>$_2$)$_3$CH$_3$), 1.22 (3H, d, J = 6.5 Hz, C<u>H</u>$_3$CH), 0.93 (3H, t, J = 6.9 Hz, C<u>H</u>$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 71.0 (<u>C</u>HOH), 64.1 (<u>C</u>H$_2$OH), 44.8 (<u>C</u>H*n*-Bu), 30.0, 25.8, 22.9, 18.5 ((<u>C</u>H$_2$)$_3$CH$_3$, <u>C</u>H$_3$CH), 13.9 (<u>C</u>H$_3$CH$_2$).

(2R, 3R*)-2-Butyl-1,3-heptanediol (**syn-252**)*

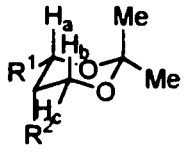
^{1}H NMR (300 MHz, $CDCl_3$) δ 3.88 (1H, td, J = 6.3, 3.4 Hz, C<u>H</u>OH), 3.85 (1H, A of ABX, dd, J_{obs} = 10.8, 6.6 Hz, C<u>H</u>$_2$OH), 3.77 (1H, B of ABX, dd, J_{obs} = 10.8, 3.6 Hz, C<u>H</u>$_2$OH), 2.14 (2H, br s, 2 × O<u>H</u>), 1.75-1.62 (1H, X of ABX, m, C<u>H</u>CH$_2$OH), 1.61-1.18 (12H, m, 2 × (C<u>H</u>$_2$)$_3$CH$_3$), 0.95-0.88 (6H, m, 2 × C<u>H</u>$_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 75.4 (<u>C</u>HOH), 64.7 (<u>C</u>H$_2$OH), 44.1 (<u>C</u>HCH$_2$OH), 32.8, 29.9, 28.5, 24.8, 22.9, 22.7 (2 × (<u>C</u>H$_2$)$_3$CH$_3$), 14.0 (2C, 2 × <u>C</u>H$_3$CH$_2$).

(2R, 3R*)-2-Butyl-4-methyl-1,3-pentanediol (**syn-253**)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (1H, A of ABX, dd, J_{obs} = 10.8, 4.6 Hz, C<u>H</u>$_2$OH), 3.80 (1H, B of ABX, dd, J_{obs} = 10.8, 2.6 Hz, C<u>H</u>$_2$OH), 3.49 (1H, dd, J = 8.9, 2.2 Hz, C<u>H</u>OH), 2.16 (2H, br s, 2 × O<u>H</u>), 1.84 (1H, dqq, J = 8.9, 6.8, 6.6 Hz, C<u>H</u>(CH$_3$)$_2$), 1.69-1.14 (1H, X of ABX, m, C<u>H</u>*n*-Bu; 6H, m, (C<u>H</u>$_2$)$_3$CH$_3$), 1.02 (3H, d, J = 6.6 Hz, C<u>H</u>$_3$CH), 0.94 (3H, t, J = 7.0 Hz, C<u>H</u>$_3$CH$_2$), 0.87 (3H, d, J = 6.7 Hz, C<u>H</u>$_3$CH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 81.2 (<u>C</u>HOH), 64.9 (<u>C</u>H$_2$OH), 40.9 (<u>C</u>H*n*-Bu), 31.0, 29.8, 23.0, 22.4 ((<u>C</u>H$_2$)$_3$CH$_3$), 19.5, 19.1 ((<u>C</u>H$_3$)$_2$CH), 14.0 (<u>C</u>H$_3$CH$_2$).

(1R, 2S*)-2-Butyl-1-phenyl-1,3-propanediol (297)*

^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.26 (5H, m, $C_6\underline{H}_5$), 5.03 (1H, d, J = 3.7 Hz, C$\underline{H}$OH), 3.75 (2H, d, J = 4.9 Hz, C$\underline{H}_2$OH), 2.30 (2H, br s, 2 × O$\underline{H}$), 2.01-1.88 (1H, m, C$\underline{H}$*n*-Bu), 1.43-1.09 (6H, m, (C$\underline{H}_2$)$_3$CH$_3$), 0.86 (3H, t, J = 6.9 Hz, C$\underline{H}_3$CH$_2$); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 128.0 (2C), 127.1, 126.2 (2C) (ArC's), 79.1 (C$\underline{H}$OH), 64.5 (C$\underline{H}_2$OH), 45.9 (C$\underline{H}$*n*-Bu), 29.6, 24.6, 22.8 ((C$\underline{H}_2$)$_3$CH$_3$), 13.9 (C$\underline{H}_3$CH$_2$).



***cis*-255**: R^1 = Me, R^2 = *n*-Bu
***cis*-256**: R^1 = *n*-Bu, R^2 = *n*-Bu
***cis*-257**: R^1 = *i*-Pr, R^2 = *n*-Bu
298: R^1 = Ph, R^2 = *n*-Bu

NB: The identities of H_b and H_c were distinguished, where possible, by NOE difference experiments.

***cis*-255**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.21 (1H, qd, J = 6.5, 2.6 Hz, H_a), 4.00 (1H, A of ABX, dd, J_{obs} = 11.8, 2.7 Hz, H_b or H_c), 3.80 (1H, B of ABX, dd, J_{obs} = 11.8, 1.8 Hz, H_b or H_c), 1.77-1.58 (1H, X of ABX, m, C$\underline{H}$*n*-Bu), 1.45 (3H, s, Me_{ax}), 1.38 (3H, s, Me_{eq}), 1.36-1.16 (6H, m, (C$\underline{H}_2$)$_3$CH$_3$), 1.15 (3H, d, J = 6.5 Hz, C$\underline{H}_3$CH), 0.94 (3H, t, J = 7.1 Hz, C$\underline{H}_3$CH$_2$).

***cis*-256**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.98 (1H, A of ABX, dd, J_{obs} = 11.9, 2.5 Hz, H_b), 3.92 (1H, dd, J = 5.5, 2.4 Hz, H_a), 3.81 (1H, B of ABX, dd, J_{obs} = 11.9, 1.5 Hz, H_c), 1.57-1.09 (1H, X of ABX, m, C$\underline{H}$*n*-Bu; 12H, m, 2 × (C$\underline{H}_2$)$_3$CH$_3$), 1.44 (3H, s, Me_{ax}), 1.38 (3H, s, Me_{eq}), 0.93 (3H, t, J = 7.1 Hz, C$\underline{H}_3$CH$_2$), 0.93 (3H, t, J = 6.6 Hz, C$\underline{H}_3$CH$_2$).

***cis*-257**. ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.95 (1H, A of ABX, dd, J_{obs} = 11.7, 1.0 Hz, H_b), 3.84 (1H, B of ABX, dd, J_{obs} = 11.7, 1.6 Hz, H_c), 3.40 (1H, dd, J = 9.8, 2.0 Hz, H_a), 1.86-1.56 (1H, X of ABX, m, C$\underline{H}$*n*-Bu; 1H, m, C$\underline{H}$(CH$_3$)$_2$), 1.55-1.06 (6H, m, (C$\underline{H}_2$)$_3$CH$_3$), 1.42 (3H, s, Me_{ax}), 1.38 (3H, s, Me_{eq}), 0.94 (3H, d, J = 6.5 Hz, C$\underline{H}_3$CH), 0.93 (3H, t, J = 7.1 Hz, C$\underline{H}_3$CH$_2$), 0.81 (3H, d, J = 6.7 Hz, C$\underline{H}_3$CH).

298. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.36-7.21 (5H, m, $C_6\underline{H}_5$), 5.19 (1H, d, J = 2.2 Hz, H_a), 4.21 (1H, A of ABX, dd, J_{obs} = 11.7, 1.5 Hz, H_b), 3.91 (1H, B of ABX, dd, J_{obs} = 11.7, 1.5 Hz, H_c), 1.65-1.54 (1H, m, X of ABX, C$\underline{H}$*n*-Bu, 1.52 (3H, s, Me_{ax}), 1.26 (3H, s, Me_{eq}), 1.26-0.92 (6H, m, (C$\underline{H}_2$)$_3$CH$_3$), 0.78 (3H, t, J = 7.2 Hz, C$\underline{H}_3$CH$_2$).

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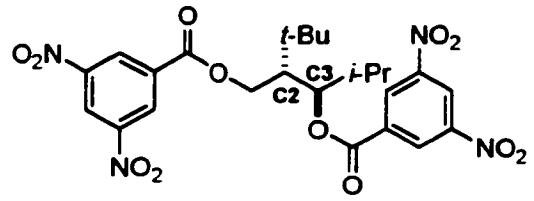
APPENDIX



246

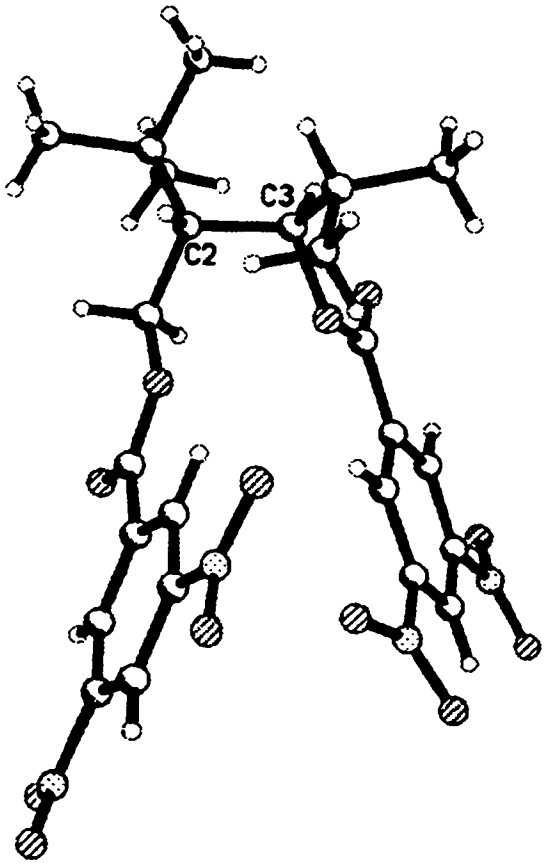


Figure A1. Crystal stucture for bis(DNB) ester **246**.

Table A1. Crystal data and structure refinement for **246**.

Empirical formula	$C_{24}H_{26}N_4O_{12}$	
Formula weight	562.49	
Temperature	150 (1) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P1	
Unit cell dimensions	a = 8.3027(4) Å	α = 109.0750(10)°
	b = 11.8058(6) Å	β = 92.4700(10)°
	c = 14.5166(7) Å	γ = 103.1900(10)°
Volume, Z	1298.56(11) Å^3, 2	
Density (calculated)	1.439 Mg/m^3	
Absorption coefficient	0.117 mm^{-1}	
F(000)	588	
Crystal size	0.45 × 0.33 × 0.20 mm	
θ range for data collection	1.89 to 27.88°	
Limiting indices	$-10 \le h \le 10$, $-15 \le k \le 15$, $-19 \le l \le 19$	
Reflections collected	14045	
Independent reflections	6202 (R_{int} = 0.0368)	
Completeness to θ = 27.88°	100.0%	
Absorption correction	Integration	
Max. and min. transmission	0.9785 and 0.9511	
Refinement method	Full-matrix least-squares on F^2	
Data/restraints/parameters	6202/0/367	
Goodness-of-fit on F^2	1.805	
Final R indices [I>2σ(I)]	R1 = 0.0424, wR2 = 0.0862	
R indices (all data)	R1 = 0.0500, wR2 = 0.0876	
Extinction coefficient	0.0089(10)	
Largest diff. peak and hole	0.254 and –0.218 eÅ^{-3}	

Table A2. Atomic coordinates [$\times 10^4$] and equivalent isotropic displacement parameters [$Å^2 \times 10^3$] for **246**. U(eq) is defined as one third of the trace of the orthogonalized U_{ij} tensor.

	x	y	z	U(eq)
C(1)	-32(2)	2012(1)	1499(1)	35(1)
C(2)	766(2)	2982(1)	1064(1)	29(1)
C(3)	2687(2)	3217(1)	1127(1)	28(1)
O(4)	360(1)	2542(1)	2563(1)	35(1)
C(5)	-188(2)	1750(1)	3028(1)	32(1)
O(6)	-900(1)	676(1)	2624(1)	42(1)
C(7)	142(2)	2358(1)	4118(1)	32(1)
C(8)	1012(2)	3584(1)	4578(1)	34(1)
C(9)	1192(2)	4084(1)	5590(1)	36(1)
C(10)	529(2)	3415(1)	6169(1)	40(1)
C(11)	-313(2)	2194(1)	5687(1)	38(1)
C(12)	-503(2)	1643(1)	4679(1)	34(1)
N(13)	2121(2)	5394(1)	6068(1)	46(1)
O(14)	2144(1)	5867(1)	6953(1)	62(1)
O(15)	2785(2)	5940(1)	5543(1)	65(1)
N(16)	-1092(2)	1440(1)	6264(1)	49(1)
O(17)	-1592(1)	316(1)	5843(1)	56(1)
O(18)	-1224(2)	1986(1)	7120(1)	71(1)
C(19)	-79(2)	2647(1)	-6(1)	32(1)
C(20)	850(2)	3545(1)	-485(1)	38(1)
C(21)	-99(2)	1321(1)	-639(1)	38(1)
C(22)	-1877(2)	2777(1)	18(1)	45(1)
C(23)	3633(2)	4589(1)	1566(1)	33(1)
C(24)	3508(2)	5164(1)	2657(1)	45(1)
C(25)	5441(2)	4766(1)	1368(1)	45(1)
O(26)	3306(1)	2611(1)	1751(1)	31(1)
C(27)	3810(2)	1585(1)	1334(1)	29(1)
O(28)	3804(1)	1082(1)	468(1)	42(1)
C(29)	4375(1)	1118(1)	2103(1)	28(1)
C(30)	4959(2)	51(1)	1808(1)	31(1)
C(31)	5488(2)	-361(1)	2526(1)	31(1)
C(32)	5479(1)	234(1)	3514(1)	32(1)
C(33)	4886(2)	1280(1)	3775(1)	29(1)
C(34)	4326(1)	1733(1)	3092(1)	29(1)
N(35)	6129(1)	-1481(1)	2233(1)	38(1)
O(36)	6881(1)	-1694(1)	2877(1)	49(1)
O(37)	5853(1)	-2134(1)	1365(1)	52(1)
N(38)	4873(1)	1948(1)	4822(1)	35(1)
O(39)	5706(1)	1707(1)	5420(1)	43(1)
O(40)	4038(1)	2702(1)	5046(1)	47(1)

Table A3. Bond Lengths [Å] and angles [°] for **246**.

C(1)-O(4)	1.4553(15)	C(1)-C(2)	1.5192(17)
C(2)-C(3)	1.5487(16)	C(2)-C(19)	1.5629(17)
C(3)-O(26)	1.4657(13)	C(3)-C(23)	1.5320(17)
O(4)-C(5)	1.3353(14)	C(5)-O(6)	1.2013(15)
C(5)-C(7)	1.4919(18)	C(7)-C(8)	1.3834(18)
C(7)-C(12)	1.3936(17)	C(8)-C(9)	1.3798(18)
C(9)-C(10)	1.3815(19)	C(9)-N(13)	1.4753(18)
C(10)-C(11)	1.3772(2)	C(11)-C(12)	1.3776(18)
C(11)-N(16)	1.4781(17)	N(13)-O(14)	1.2191(15)
N(13)-O(15)	1.2233(15)	N(16)-O(18)	1.2223(16)
N(16)-O(17)	1.2251(17)	C(19)-C(21)	1.5302(17)
C(19)-C(20)	1.5349(17)	C(19)-C(22)	1.5361(17)
C(23)-C(25)	1.5214(18)	C(23)-C(24)	1.5245(18)
O(26)-C(27)	1.3349(13)	C(27)-O(28)	1.2014(14)
C(27)-C(29)	1.4983(16)	C(29)-C(34)	1.3888(16)
C(29)-C(30)	1.3953(16)	C(30)-C(31)	1.3796(17)
C(31)-C(32)	1.3765(17)	C(31)-N(35)	1.4787(15)
C(32)-C(33)	1.3787(17)	C(33)-C(34)	1.3802(16)
C(33)-N(38)	1.4684(16)	N(35)-O(37)	1.2218(14)
N(35)-O(36)	1.2260(14)	N(38)-O(40)	1.2210(13)
N(38)-O(39)	1.2292(13)		
O(4)-C(1)-C(2)	108.65(10)	C(1)-C(2)-C(3)	113.12(10)
C(1)-C(2)-C(19)	110.51(10)	C(3)-C(2)-C(19)	112.31(9)
O(26)-C(3)-C(23)	105.89(10)	O(26)-C(3)-C(2)	110.75(9)
C(23)-C(3)-C(2)	114.09(9)	C(5)-O(4)-C-(1)	114.27(10)
O(6)-C(5)-O(4)	124.49(12)	O(6)-C(5)-C(7)	123.27(12)
O(4)-C(5)-C(7)	112.22(11)	C(8)-C(7)-C(12)	119.90(12)
C(8)-C(7)-C(5)	122.91(11)	C(12)-C(7)-C(5)	117.17(12)
C(9)-C(8)-C(7)	118.88(12)	C(8)-C(9)-C(10)	122.87(13)
C(8)-C(9)-N(13)	118.19(12)	C(10)-C(9)-N(13)	118.94(12)
C(11)-C(10)-C(9)	116.58(12)	C(10)-C(11)-C(12)	122.91(12)
C(10)-C(11)-N(16)	119.15(13)	C(12)-C(11)-N(16)	117.93(13)
C(11)-C(12)-C(7)	118.81(13)	O(14)-N(13)-O(15)	124.44(13)
O(14)-N(13)-C(9)	118.05(13)	O(15)-N(13)-C(9)	117.50(12)
O(18)-N(16)-O(17)	124.79(13)	O(18)-N(16)-C(11)	117.49(14)
O(17)-N(16)-C(11)	117.70(12)	C(21)-C(19)-C(20)	108.94(10)
C(21)-C(19)-C(22)	109.26(11)	C(20)-C(19)-C(22)	107.35(10)
C(21)-C(19)-C(2)	111.13(10)	C(20)-C(19)-C(2)	110.49(11)
C(22)-C(19)-C(2)	109.59(10)	C(25)-C(23)-C(24)	111.40(11)
C(25)-C(23)-C(3)	110.58(10)	C(24)-C(23)-C(3)	113.07(10)
C(27)-O(26)-C(3)	119.35(9)	O(28)-O(27)-O(26)	125.83(11)
O(28)-C(27)-C(29)	123.75(11)	O(26)-C(27)-C(29)	110.41(10)
C(34)-C(29)-C(30)	120.37(11)	C(34)-C(29)-C(27)	120.80(10)
C(30)-C(29)-C(27)	118.83(11)	C(31)-C(30)-C(29)	118.12(12)
C(32)-C(31)-C(30)	123.19(11)	C(32)-C(31)-N(35)	117.66(11)

C(30)-C(31)-N(35)	119.13(11)	C(31)-C(32)-C(33)	116.95(11)
C(32)-C(33)-C(34)	122.64(12)	C(32)-C(33)-N(38)	118.58(11)
C(34)-C(33)-N(38)	118.78(11)	C(33)-C(34)-C(29)	118.73(11)
O(37)-N(35)-O(36)	124.81(11)	O(37)-N(35)-C(31)	117.38(11)
O(36)-N(35)-C(31)	117.81(12)	O(40)-N(38)-O(39)	124.15(11)
O(40)-N(38)-C(33)	118.28(10)	O(39)-N(38)-C(33)	117.57(10)

Table A4. Hydrogen coordinates ($\times 10^4$) and isotropic displacement parameters ($Å^2 \times 10^3$) for **246**.

	x	y	z	U(eq)
H(1X)	-1231	1764	1316	42
H(1Y)	394	1284	1248	42
H(2)	535	3762	1459	35
H(3)	2981	2872	464	34
H(8)	1469	4064	4211	40
H(10)	645	3772	6850	48
H(12)	-1052	809	4379	41
H(20X)	228	3406	-1102	56
H(20Y)	1933	3407	-594	56
H(20Z)	971	4383	-59	56
H(21X)	-800	747	-393	58
H(21Y)	1014	1218	-614	58
H(21Z)	-525	1166	-1306	58
H(22X)	-2355	2656	-632	68
H(22Y)	-1874	3591	451	68
H(22Z)	-2525	2166	251	68
H(23)	3116	5033	1224	39
H(24X)	2355	5034	2760	68
H(24Y)	4028	6038	2878	68
H(24Z)	4062	4783	3021	68
H(25X)	5979	4318	1674	67
H(25Y)	6007	5632	1631	67
H(25Z)	5480	4461	672	67
H(30)	4991	-369	1147	37
H(32)	5856	-57	3983	38
H(34)	3922	2437	3291	34

Table A5. Anisotropic displacement parameters [$Å^2 \times 10^3$] for 24. The anisotropic displacement factor exponent takes the form: $-2\pi^2[(ha^*)^2U_{11} + \ldots + 2hka^*b^*U_{12}]$.

	U11	U22	U33	U23	U13	U12
C(1)	39(1)	30(1)	34(1)	10(1)	7(1)	5(1)
C(2)	33(1)	22(1)	33(1)	9(1)	9(1)	10(1)
C(3)	35(1)	26(1)	30(1)	13(1)	9(1)	14(1)
O(4)	43(1)	29(1)	32(1)	11(1)	11(1)	5(1)
C(5)	27(1)	32(1)	39(1)	14(1)	10(1)	8(1)
O(6)	50(1)	32(1)	40(1)	12(1)	9(1)	-1(1)
C(7)	26(1)	34(1)	38(1)	15(1)	9(1)	10(1)
C(8)	30(1)	36(1)	39(1)	16(1)	9(1)	10(1)
C(9)	29(1)	37(1)	42(1)	10(1)	2(1)	11(1)
C(10)	35(1)	54(1)	33(1)	13(1)	4(1)	18(1)
C(11)	31(1)	50(1)	41(1)	25(1)	9(1)	13(1)
C(12)	28(1)	35(1)	42(1)	16(1)	6(1)	9(1)
N(13)	40(1)	43(1)	48(1)	5(1)	-3(1)	12(1)
O(14)	69(1)	55(1)	46(1)	-2(1)	-6(1)	20(1)
O(15)	69(1)	43(1)	66(1)	11(1)	6(1)	-7(1)
N(16)	40(1)	72(1)	46(1)	36(1)	8(1)	16(1)
O(17)	54(1)	60(1)	72(1)	43(1)	19(1)	16(1)
O(18)	77(1)	100(1)	39(1)	35(1)	10(1)	9(1)
C(19)	34(1)	28(1)	36(1)	13(1)	5(1)	11(1)
C(20)	44(1)	35(1)	41(1)	19(1)	6(1)	16(1)
C(21)	48(1)	31(1)	35(1)	10(1)	0(1)	10(1)
C(22)	37(1)	45(1)	60(1)	22(1)	5(1)	13(1)
C(23)	34(1)	26(1)	41(1)	15(1)	6(1)	9(1)
C(24)	54(1)	28(1)	46(1)	5(1)	5(1)	5(1)
C(25)	36(1)	42(1)	59(1)	23(1)	8(1)	6(1)
O(26)	41(1)	27(1)	31(1)	12(1)	7(1)	16(1)
C(27)	30(1)	25(1)	34(1)	11(1)	8(1)	10(1)
O(28)	63(1)	39(1)	32(1)	12(1)	11(1)	29(1)
C(29)	26(1)	25(1)	35(1)	13(1)	6(1)	7(1)
C(30)	31(1)	26(1)	36(1)	11(1)	8(1)	8(1)
C(31)	28(1)	25(1)	45(1)	17(1)	10(1)	10(1)
C(32)	28(1)	32(1)	43(1)	22(1)	7(1)	9(1)
C(33)	27(1)	29(1)	32(1)	13(1)	6(1)	6(1)
C(34)	26(1)	24(1)	37(1)	12(1)	5(1)	8(1)
N(35)	41(1)	32(1)	54(1)	22(1)	16(1)	16(1)
O(36)	56(1)	46(1)	64(1)	34(1)	15(1)	28(1)
O(37)	70(1)	39(1)	53(1)	13(1)	15(1)	30(1)
N(38)	35(1)	37(1)	36(1)	17(1)	6(1)	11(1)
O(39)	49(1)	50(1)	37(1)	23(1)	3(1)	17(1)
O(40)	53(1)	58(1)	38(1)	14(1)	9(1)	32(1)