New Strategies for Hydroxyl-Directed Organic Reactions

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NEW STRATEGIES FOR HYDROXYL-DIRECTED ORGANIC REACTIONS

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ABSTRACT: Described herein are four different research projects spanning over two different research groups. The first two projects describe the development and application of scaffolding catalysts for the (1) site-selective siliyation of ribonucleosides and (2) the distal and diastereoselective hydroformylation of homoallylic alcohols. These projects emphasize the effectiveness of scaffolding catalysts to bind a hydroxyl-containing substrate and control the site- or regioselectivity of a reaction using said substrate. The third project describes a hydroxyl-directed diboration of homoallylic and bis-homoallylic alcohols. The hydroxyl-containing 1,2-bis(boronates) are valuable intermediates for further synthetic manipulations. One such manipulation, a hydroxyl-directed Suzuki cross-coupling reaction, is the focus of the final project. This directed cross-coupling reaction forges carbon-carbon bonds in a stereoselective manner, highlighted in the total synthesis of the naturally occurring compound, debromohamigeran E.

Dedicated to:

My parents, Katherine A. Powers and Doug Blaisdell, my brother, Hugh Blaisdell, and long-time friend, Bob Groves.

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List of Abbreviations

Å: angstrom

Ac: acetyl

acac: acetylacetonate

AIBN: azobisisobutyronitrile

BISBI: 2,2'-bis[(diphenyl-phosphino)methyl]-l,l'-biphenyl

Boc: *tert*-butoxycarbonyl

Bz: benzoyl

CAM: Cerium Ammonium Molybdate

CAN: cerium(IV) ammonium nitrate

cat: catechol

COD: 1,5-cyclooctadiene

conv: conversion

c-Pentyl: cyclopentyl

CPME: cyclopentyl methyl ether

Cy: cyclohexyl

DABCO: 1,4-diazabicyclo[2.2.2]octane

dan: diaminonaphthalenyl

DART: direct analysis in real time

dba: dibenzylideneacetone

DBU: 1,8-diazabicyclo[5.4.0]undec-7-ene

DCC: diboration/cross-coupling

DCE: 1,2-dichloroethane

DCM: dichloromethane

DG: directing group

DIPEA: *N,N*-Diisopropylethylamine

DMAP: *N,N*-4-dimethylaminopyridine

DME: 1,2-dimethoxyethane

DMF: *N,N*-dimethylformamide

DMSO: dimethylsulfoxide

DMTr: 4,4’-dimethoxytrityl

dppp: 1,3-bis(diphenylphosphino)-propane

DTM: *tert*-butyldithiomethyl

dr: diastereomeric ration

ee: enantiomeric excess

equiv: equivalent

er: enantiomeric ratio

EtOAc: ethyl acetate

ETT: 5-ethylthio-1*H*-tetrazole

gCOSY: gradient correlation spectroscopy

h: hours

HRMS: high resolution mass spectrometry

Ib: isobutyl

Ipc: isopinocampheyl

LAH: lithium aluminium hydride

m-CPBA: *meta*-chloroperoxybenzoic acid

m-DPPB: *meta*-(diphenylphosphanyl)benzoyl

MHz: megahertz

MS: molecular sieves

NBS: *N*-bromosuccinimide

NHC: *N*-heterocyclic carbene

nbd: norbornadiene

NMI: *N*-methylimidazole

NMO: *N*-Methylmorpholine-*N*-Oxide

NMR: nuclear magnetic resonance

NOESY: nuclear Overhauser effect spectroscopy

Pac: phenoxyacetyl

PCC: pyridinium chlorochromate

Ph: phenyl

pin: pinacol

Piv: pivaloyl

PMA: phosphomolybdic acid

PMP: 1,2,2,6,6-pentamethylpiperidine

ppm: parts per million

PPTS: pyridinium *p*-toluenesulfonate

psi: pounds per square inch

Py: pyridine

Quinap: 1-(2-diphenylphosphino-1-naphthyl)isoquinoline

rac: racemic

rr: regiomeric ratio

RT: room temperature

SFC: supercritical fluid chromatography

TBAF: tetrabutylammonium fluoride

TBDPS: *tert*-butyldiphenylsilyl

TBS: *tert*-butyldimethylsilyl

TEMPO: 2,2,6,6-tetramethyl-1-piperidinyloxy free radical

TES: triethylsilyl

Tf: trifluoromethanesulfonyl

THF: tetrahydrofuran

THP: tetrahydropyranyl

$TIPDSiCl_2$: 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane

TLC: thin layer chromatography

Ts: *para*-toluenesulfonyl

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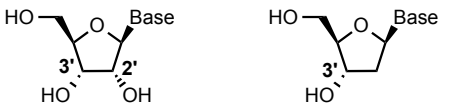
Chapter 1: Site-Selective Silylation of Ribonucleosides

1.1 Introduction

Ribonucleosides are composed of a ribose sugar and a nucleobase segment. When linked together by a phosphodiester bond, ribonucleosides make up the general structure of RNA. Unlike DNA, the ribose moiety found in RNA contains hydroxyl groups at both the 2` and 3` carbons of the pentose ring (Scheme 1.1). The presence of a hydroxyl group at the 2` carbon allows RNA to adopt an A-form double helix rather than the B-form geometry typically associated with DNA.[1] Furthermore, the additional hydroxyl group makes RNA more susceptible to hydrolysis than DNA. Of course, this susceptibility is what allows RNA to fulfill the role of a *temporary* transmitter of genetic information.

Scheme 1.1 General Structures of RNA and DNA Nucleosides



1.1.1 Automated RNA Synthesis

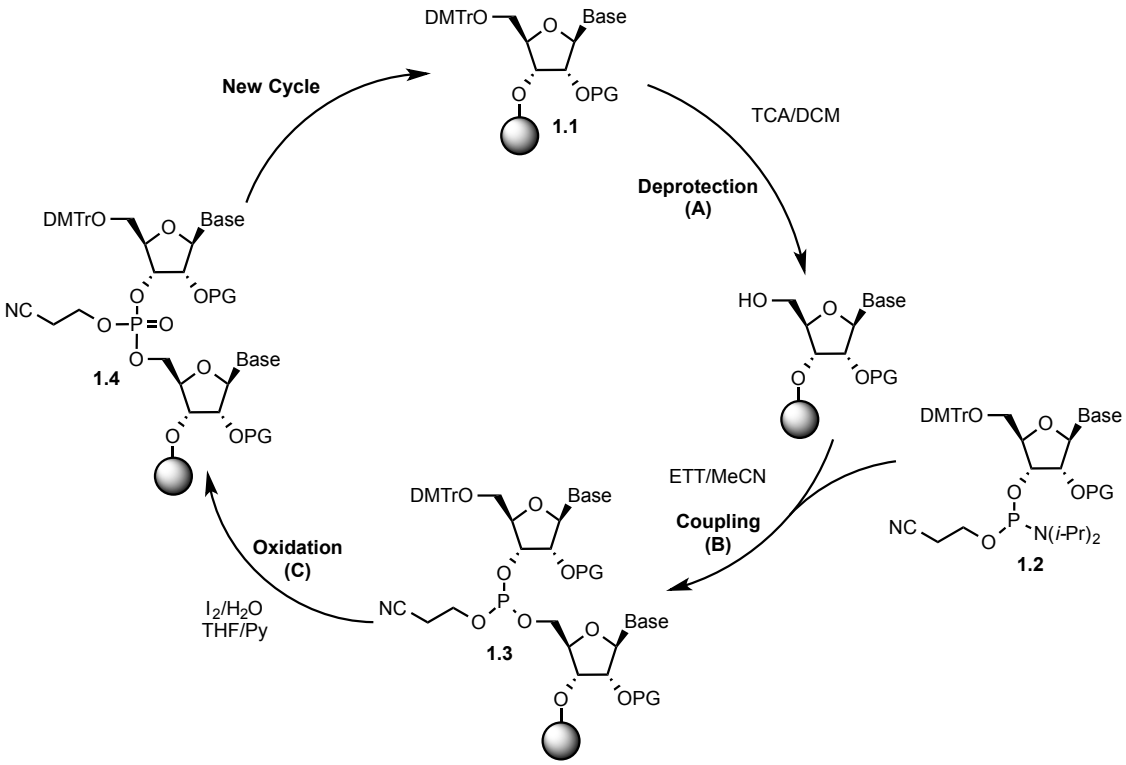
In addition to the biological differences brought on by the 2`-hydroxyl group, its presence also introduces added complexity to the chemical synthesis of RNA. The production of synthetic DNA benefited greatly from the development of solid-phase

[1] Salazar, M.; Fedoroff, O.; Miller, J.; Ribeiro, N.; Reid, B. *Biochemistry* **1993**, *32*, 4207 – 4215.

automated synthesizers. Solid-support methods for the synthesis of RNA have also been developed, though to a lesser degree of efficiency (Scheme 1.2).[2] Typically, a 4,4'-dimethoxytrityl (DMTr)-protected ribonucleoside **1.1** is subjected to deprotection conditions (Scheme 1.2, A), followed by coupling to a nucleotide phosphoramidite **1.2** using a tetrazole activator, such as 5-ethylthio-1*H*-tetrazole (ETT) (Scheme 1.2, B). Unreacted solid-supported ribonucleosides are "capped" by reaction with acetic anhydride, which prevents additional ribonucleosides adding to this group. The phosphite **1.3** is oxidized to form the phosphate-linked ribonucleotides **1.4** (Scheme 1.2, C) and the whole process can then be repeated in order to lengthen the RNA strand. Once the appropriate length is reached, the 2-cyanoethyl group and the solid-support can be cleaved with mild base.

[2] Somoza, A. *Chem. Soc. Rev.,* **2008**, *37*, 2668 – 2675

Scheme 1.2 The Synthetic Strategy of an Automated RNA Synthesizer



1.1.2 Importance of Ribonucleoside Functionalization

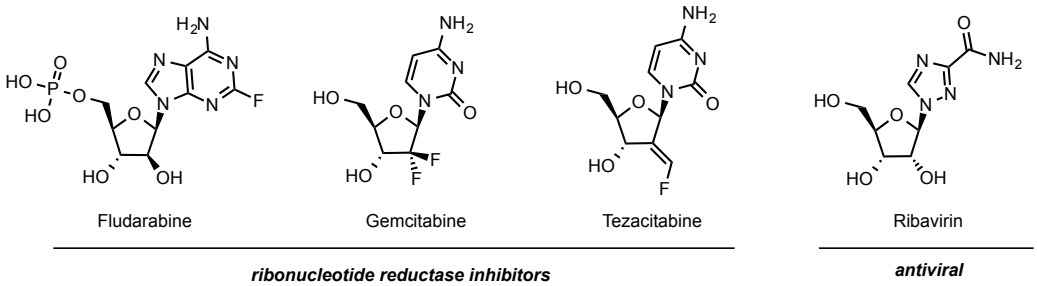
The efficiency of this method of RNA synthesis depends heavily on the accessibility of the required nucleoside monomer units. Generally, in the synthesis of deoxyribonucleoside monomers, the 3`- and the 5`-hydroxyl groups are readily differentiated. However, in the case of ribonucleosides, the presence of two adjacent secondary hydroxyl groups greatly complicates matters due to their similar reactivities, especially during the installation of the phosphoramidite group.

In addition to artificial RNA synthesis, the ribonucleoside scaffold has become an increasingly popular template for pharmaceuticals (Scheme 1.3).[3] These nucleoside

[3] Jordheim, L. P.; Durantel, D.; Zoulim, F.; Dumontet, C. *Nat. Rev. Drug Discov.* **2013**, *12*, 447 – 464.

analogs target a wide variety of diseases including cancer (ribonucleotide reductase inhibitors)[4] and viral infections.[5] Notably, the 2`-hydroxyl group in many of these therapeutics has been manipulated in some manner, while the 3`-hydroxyl group remains unfunctionalized.

Scheme 1.3 Examples of Therapeutics Containing a Modified Ribonucleoside Motif



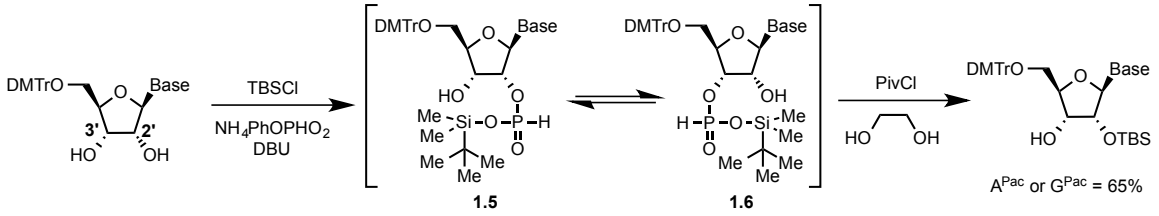
1.2 Examples of Selective Silylation of Ribonucleosides

The *tert*-butyldimethylsilyl (TBS) protecting group, is one of the most popular means of protecting the secondary hydroxyl groups found in ribonucleosides. Its value lies in its tolerance for DMTr deprotection conditions, while still being readily removable by a fluoride anion source, such as TBAF. The classical means of accessing monosilylated (either 2`- or 3`-) ribonucleosides is to subject the free nucleoside to an unselective silylation reaction and resolve the mixture of the two products by chromatographic separation.[6] This method is extremely time inefficient, and unwanted byproduct formation is unavoidable. For this reason, some have worked to develop methods for the selective silylation of ribonucleosides.

[4] Shao, J.; Zhou, B.; Chu, B.; Yen, Y. *Curr. Cancer Drug Targets* **2006**, *6*, 409 – 431.
[5] Dapp, M. J.; Bonnac, C.; Patterson, S. E.; Mansky, L. M. *J. Virol.* **2014**, *88*, 354 – 363.
[6] MatulicAdamic, J.; Beigelman, L.; Portmann, S.; Egli, R.; Usman, N. *J. Org. Chem.* **1996**, *61*, 3909 – 3911.

Jones and coworkers[7] found that selective silylation of the 2`-hydroxyl could be achieved by using *tert*-butyldimethylsilyl chloride (TBSCl) and ammonium phenyl-H-phosphonate (Scheme 1.4). It is believed that the phosphonate first forms a diester with the silyl chloride. This species undergoes transesterification with the ribonucleoside to form a mixture of phosphitylated products **1.5** and **1.6**. Transfer of the silyl group occurs mostly at the more acidic 2`-hydroxyl group[8]; the authors report observing 10-15% 3`-protected product. Unfortunately, this methodology has been demonstrated only with phenoxyacetyl-protected adenosine ($\mathbf{A}^{\mathbf{Pac}}$) and guanidine ($\mathbf{G}^{\mathbf{Pac}}$).

Scheme 1.4 Phosphonate-Mediated 2`-Hydroxyl Silylation of A^{Pac} and G^{Pac}

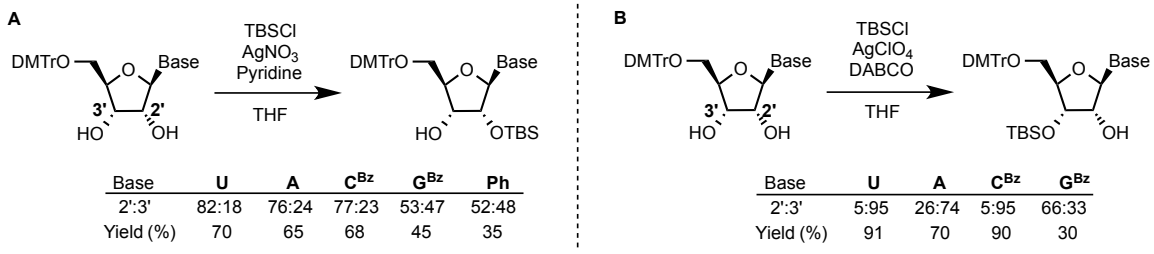


Ogilvie and coworkers[9] have developed two procedures for the selective silylation of either the 2`- or 3`-hydroxyl groups (Scheme 1.5). When using TBSCl as the silyl chloride and $AgNO_3$ as a stoichiometric additive, selective silylation of the 2`-hydroxyl was observed (Scheme 1.5, A). While uridine (**U**), adenosine (**A**) and benzoyl-protected cytosine ($\mathbf{C}^{\mathbf{Bz}}$) gave useful yields of the 2`-protected product, benzoyl-protected guanidine ($\mathbf{G}^{\mathbf{Bz}}$) and an unnatural phenyl-substituted ribonucleoside (**Ph**) gave poor

[7] Song, Q.; Wang, W.; Fischer, A.; Zhang, X.; Gaffney, B.; Jones, R. *Tetrahedron Lett.* **1999**, *40*, 4153 – 4156.
[8] For studies focused on the determination of the pKas of the 2` and 3` hydroxyls of adenosine, see: Åström, H.; Limén, E.; Strömberg, R. *J. Am. Chem. Soc.* **2004**, *126*, 14710 – 14711.
[9] Hakimelahi, G.; Proba, Z.; Ogilvie, K. *Can. J. Chem.,* **1982**, *60*, 1106 – 1113.

selectivity. It should be noted that, in general, the separation of the two isomers by column chromatography is not trivial. While the specific role of $AgNO_3$ is unknown, when $TBSNO_3$ was used in place of $TBSCl/AgNO_3$, similar selectivities were observed. Interestingly, when silver perchlorate ($AgClO_4$) was used instead of $AgNO_3$, silylation became selective for the 3`-protection with good yields observed for most of the ribonucleosides (Scheme 1.5, B). Although no explanation was given for the switch in selectivity, the authors asserted that 3`-silylation resulted from a direct reaction with the 3`-hydroxyl group, and was not a consequence of silyl transfer from the 2`-silylated product.

Scheme 1.5 $AgNO_3$ and $AgClO_4$-Mediated 2`- and 3`-Hydroxyl Silylation



Base	U	A	C^{Bz}	G^{Bz}	Ph
2':3'	82:18	76:24	77:23	53:47	52:48
Yield (%)	70	65	68	45	35

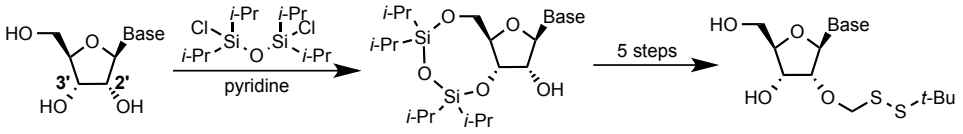
Base	U	A	C^{Bz}	G^{Bz}
2':3'	5:95	26:74	5:95	66:33
Yield (%)	91	70	90	30

Another method to selectively functionalize the 2`-hydroxyl group involves the use of a disiloxane protecting group to simultaneously mask both the 3`- and 5`-hydroxyl groups. Kwiatkowski and coworkers[10] utilized this strategy for selective installation of a *tert*-butyldithiomethyl (DTM) group at the 2`-hydroxyl (Scheme 1.6). Using 1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane ($TIPDSiCl_2$), the 3`- and 5`-hydroxyl groups were smoothly protected, thereby allowing further functionalization of the 2`-hydroxyl

[10] Semenyuk, A.; Földesi, A.; Johansson, T.; Estmer-Nilsson, C.; Blomgren, P.; Brännvall, M.; Kirsebom, L.; Kwiatkowski, M. *J. Am. Chem. Soc.,* **2006**, *128*, 12356 – 12357.

group. The disiloxane protecting group could later be removed using a fluoride anion source, affording the 2`-protected product.

Scheme 1.6 3`- and 5`-Hydroxyl Silyl Protection



Base	U	A^{Bz}	C^{Bz}	G^{Ib}
Yield (%)	44	45	57	44

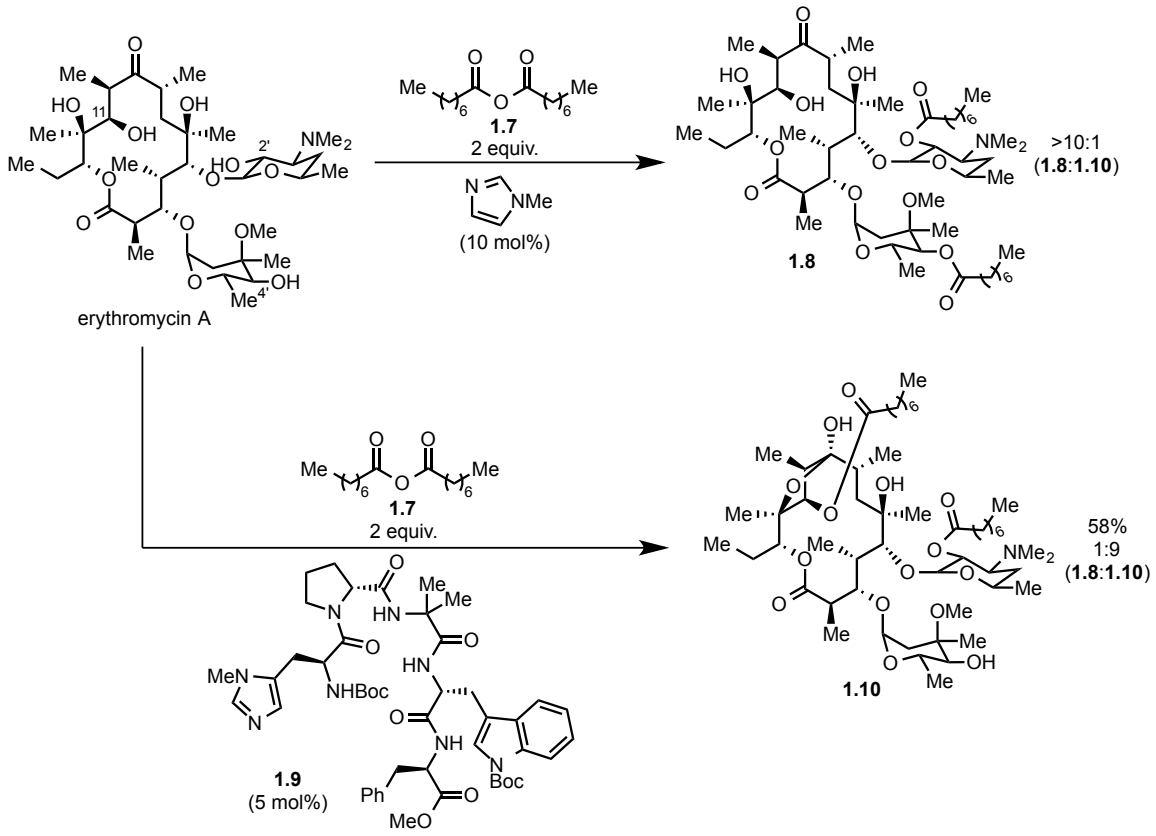
1.3 Selected Examples of Site-Selective Functionalization of Complex Molecules

The development of techniques to perform a wide variety of site-selective functionalizations on complex molecules has been an ongoing goal for synthetic chemists. Site-selective control can be accomplished by using inherent chemical selectivity within the molecule or through the use of a catalyst. The ability to perform such late stage functionalizations on complex molecules provides an efficient and rapid means of synthesizing related analogs.

Miller and coworkers have developed a class of small peptides that catalyze the selective functionalization of various complex molecules. The site-selective functionalization of erythromycin A was achieved using different imidazole-based catalysts (Scheme 1.7).[11] The two most reactive hydroxyl groups (C2' and C4') could be selectively protected using **1.7** and *N*-methylimidazole, yielding **1.8** in a greater than 10:1 ratio relative to **1.10**. Alternatively, the hydroxyl groups at C2' and C11 could be functionalized with **1.7** using chiral catalyst **1.9**, furnishing **1.10** in 58% yield.

[11] Lewis, C. A.; Miller, S. J. *Angew. Chem., Int. Ed.* **2006**, *45*, 5616 – 5619.

Scheme 1.7 Site-Selective Functionalization of Erythromycin A

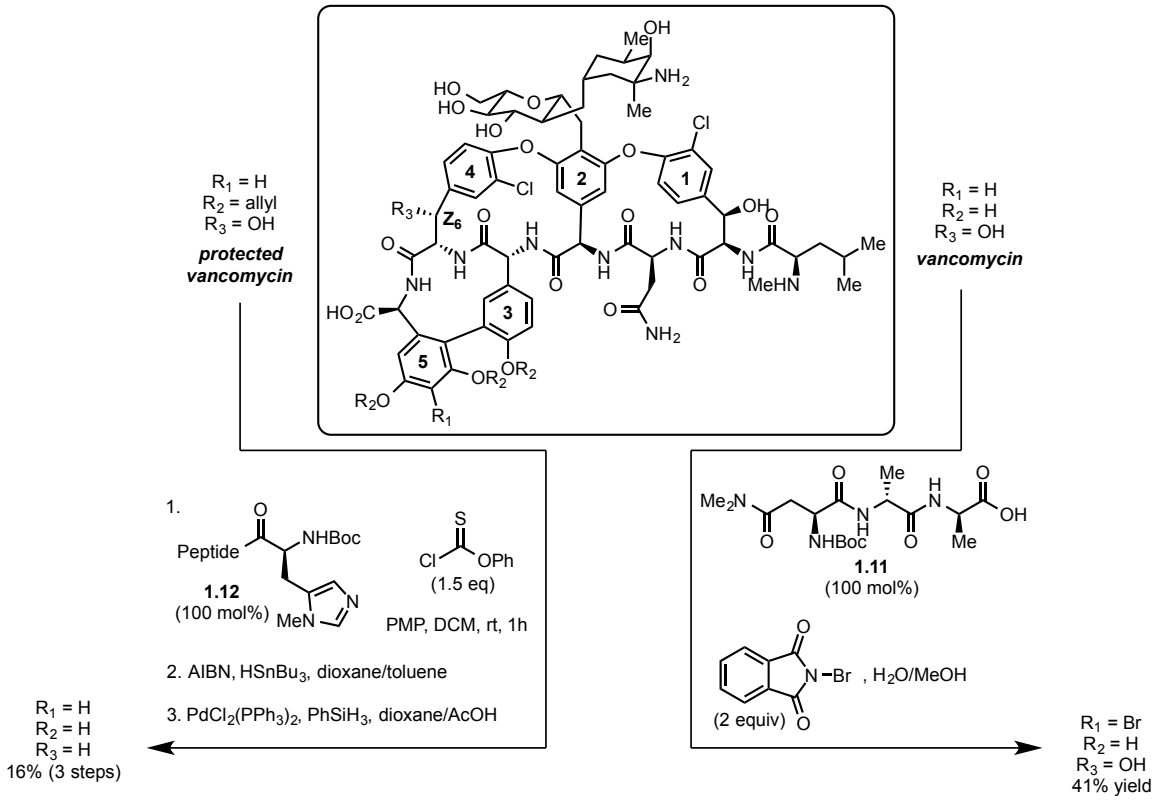


In addition to selective protection of polyols, Miller and coworkers have investigated the site-selective bromination of vancomycin.[12] Using peptide **1.11** and *N*-bromopthalimide as a brominating agent, arene 5 of vancomycin was selectively brominated (Scheme 1.8). Without a catalyst, the reaction proceeds in a completely unselective manner, furnishing a complex mixture of aryl bromination products. Furthermore, Miller and coworkers [13] have also developed a site-selective dehydroxylation reaction of a protected analog of vancomycin. Peptide **1.12** proved to efficiently transfer phenyl thionoformate to the Z_6 hydroxyl group. The resulting

[12] Pathak, T.; Miller, S. *J. Am. Chem. Soc.* **2012**, *134*, 6120 – 6123.
[13] Fowler, B.; Laemmerhold, K.; Miller, S. *J. Am. Chem. Soc.* **2012**, *134*, 9755 – 9761.

thiocarbonyl ester can then be subjected to deoxygenation conditions, yielding Z_6-dehydroxylated vancomycin after a deprotection step (Scheme 1.8).

Scheme 1.8 Site-Selective Functionalization of Vancomycin

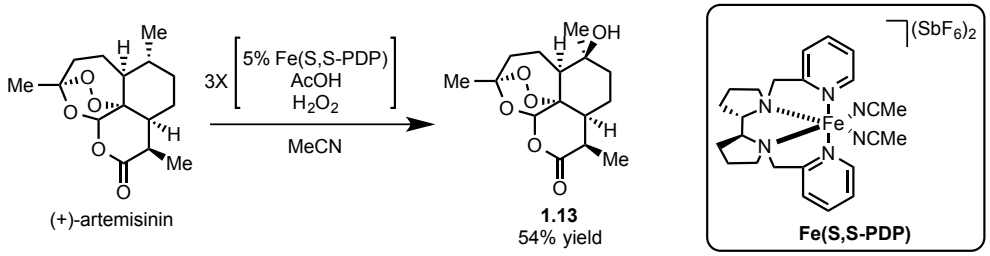


In 2007, White and coworkers[14] disclosed a site-selective C−H oxidation reaction using an iron catalyst and hydrogen perioxide. The methodology proved to be effective for the late stage oxidation of a variety of complex molecules. More specifically, (+)-artemisinin, a natural product effective in the treatment of malaria, was subjected to the mild oxidation conditions. Fascinatingly, only one of the five tertiary C−H bonds present was oxidized to the alcohol, furnishing **1.13** in 54% isolated yield (Scheme 1.9).

[14] Chen, M. S.; White, M. C. *Science* **2007**, *318*, 783 – 787.

The high selectivity observed was attributed solely to the electronic and steric properties of the activated C–H bond.

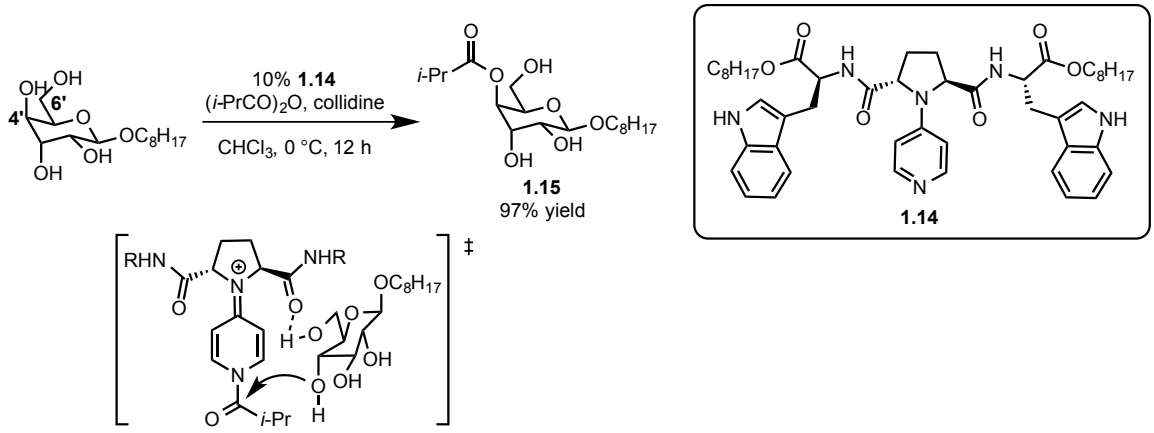
Scheme 1.9 Site-Selective C–H Oxidation of (+)-Artemisinin



Kawabata and coworkers[15] developed a C_2-symmetric chiral 4-pyrrolidino-pyridine catalyst system that successfully catalyzed the site-selective acylation of monosaccardies (Scheme 1.10). When subjecting octyl β-D-glucopyranoside to isobutyric anhydride and the 4-pyrrolidinopyridine catalyst **1.14**, the secondary hydroxyl group at C4 was preferentially acylated, yielding **1.15** in excellent yield. It should be noted that acylation at C4 is favored over acylation at the less hindered primary alcohol at C6, which is presumed to participate in hydrogen bonding with the amide carbonyl of the DMAP catalyst.

[15] Kawabata, T; Muramatsu, W; Nishio, T.; Shibata, N.; Schedel, H. *J. Am. Chem. Soc.,* **2007**, *129*, 12890 – 12895

Scheme 1.10 Catalytic, Site-Selective Acylation of Monosaccarides



1.4 Notable Catalysts for the Recognition of 1,2-Diols

As already noted, 1,2-diols are a common motif in many naturally occurring molecules. Additionally, symmetric *syn*-1,2-diols are a common substrate for desymmetrization methodologies. Further extension of these methods, by the development of catalysts that can recognize and selectively functionalize such diols, would be a powerful tool for site selective catalysis. Moreover, a catalyst that selectively binds to a 1,2-diol motif can be particularly useful for the site-selective functionalization of polyhydroxylated molecules (monosaccarides, ribonucleosides, etc.).

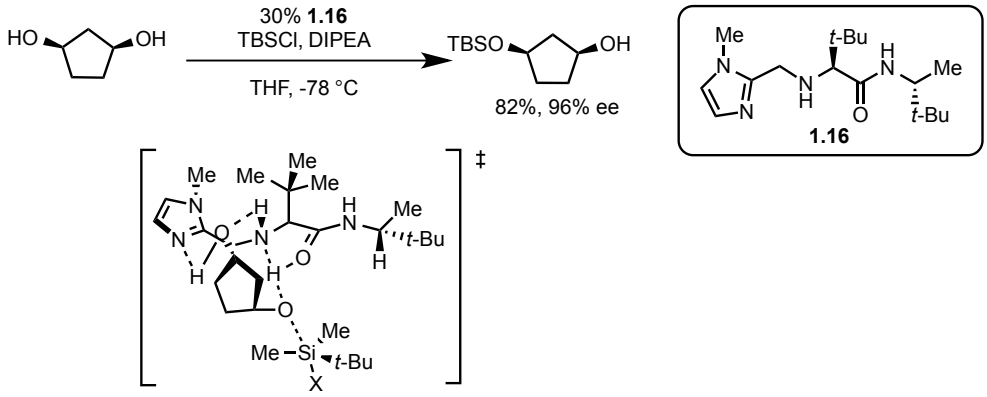
1.4.1 Peptide-Based Catalyst

In 2006, Hoveyda and Snapper [16] disclosed peptide catalyst **1.16** for the desymmetrization of 1,2- and 1,3-diols via silyl transfer (Scheme 1.11). The reaction proceeds with excellent yields and enantioselectivities for the majority of the substrates investigated. It is proposed that **1.16** binds the diol (through hydrogen-bonding with the

[16] Zhao, Y.; Rodrigo, J.; Hoveyda, A. H.; Snapper, M. L. *Nature* **2006**, *443*, 67 – 70

amide and imidazole functionalities) and activates one of the hydroxyl groups for silylation. The efficiency of the reaction was later greatly improved by the use of 5-ethylthiotetrazole as a co-catalyst, which is proposed to further activate the silyl chloride.[17] In addition to the desymmetrization of 1,2- and 1,3-diols, these peptide catalysts have shown to be effective for the resolution of racemic 1,2-diols[18] and the desymmetrization of *meso*-1,2,3-triols.[19]

Scheme 1.11 Peptide-Catalyzed Desymmetrization of 1,2- and 1,3-Diols



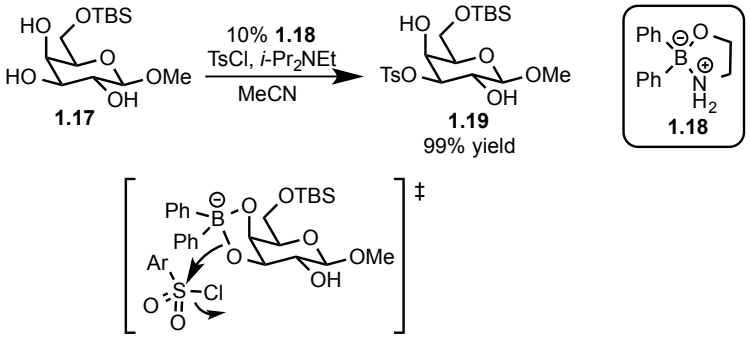
1.4.2 Borinic Acid Catalyst

Taylor and coworkers[20] have developed a borinic acid catalyst system for the selective functionalization of 1,2-diols. The diaryl borinic catalyst **1.18** binds to the diol, forming a tetracoordinate borinate complex, which will react with an electrophile. In

[17] Manville, N.; Alite, H.; Haeffner, F.; Hoveyda, A. H.; Snapper, M. L. *Nat. Chem.* **2013**, *5*, 768 – 774
[18] (a) Zhao, Y.; Mitra, A. W.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem., Int. Ed.* **2007**, *46*, 8471 – 8474. (b) Rodrigo, J. M.; Zhao, Y.; Hoveyda, A. H.; Snapper, M. L. *Org. Lett.* **2011**, *13*, 3778 – 3781.
[19] You, Z.; Hoveyda, A. H.; Snapper, M. L. *Angew. Chem. Int. Ed.* **2009**, *48*, 547 – 550.
[20] (a) Lee, D.; Taylor, M. S. *J. Am. Chem. Soc.* **2011**, *133*, 3724 – 3727. (b) Lee, D.; Williamson, C. L.; Chan, L.; Taylor, M. S. *J. Am. Chem. Soc.* **2012**, *134*, 8260 – 8267.

addition to simple 1,2-diols, the method can be used for the site selective functionalization of carbohydrates as well. The tosylation of **1.17** yields **1.19** in 99% yield (Scheme 1.12). In addition to sulfonyl chlorides, the scope of electrophiles used includes acyl chlorides and benzyl bromide.

Scheme 1.12 Site-Selective Functionalization of Monosaccharides with a Borinic Catalyst



1.4.3 Copper Ion Catalyst

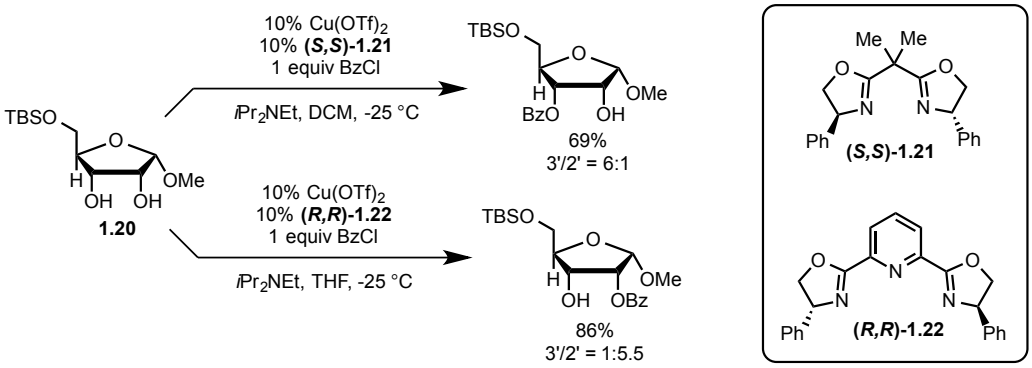
Another effective mode of activating 1,2-diols is through the use of copper ion catalysis. This approach is inspired by lectin proteins, which are known to bind sugars through a coordination of their metal centers to the sugars' 1,2-diol units. In 2003, Matsumura and coworkers[21] disclosed the asymmetric benzoylation of 1,2-diols using copper ion-induced activation. Dong and coworkers[22] have expanded on this methodology through the site-selective acylation and tosylation of a variety of different carbohydrates. The efficiency of this method was displayed through the selective

[21] Matsumura, Y.; Maki, T.; Murakami, S.; Onomura, O. *J. Am. Chem. Soc.* **2003**, *125*, 2052 – 2053

[22] Chen, I.; Kou, K. G.; Le, D. N.; Rathbun, C. M.; Dong, V. M. *Chem. Eur. J.* **2014**, *20*, 5013 – 5018

acylation of ribofuranoside **1.20** (Scheme 1.13). Both structural isomers were accessed through variation of the catalyst's ligand structure. (*S,S*)-**1.21** proved to favor the 3`-benzoylated product while the 2`-benzoylated product was the major isomer observed when (*R,R*)-**1.22** was used as the ligand.

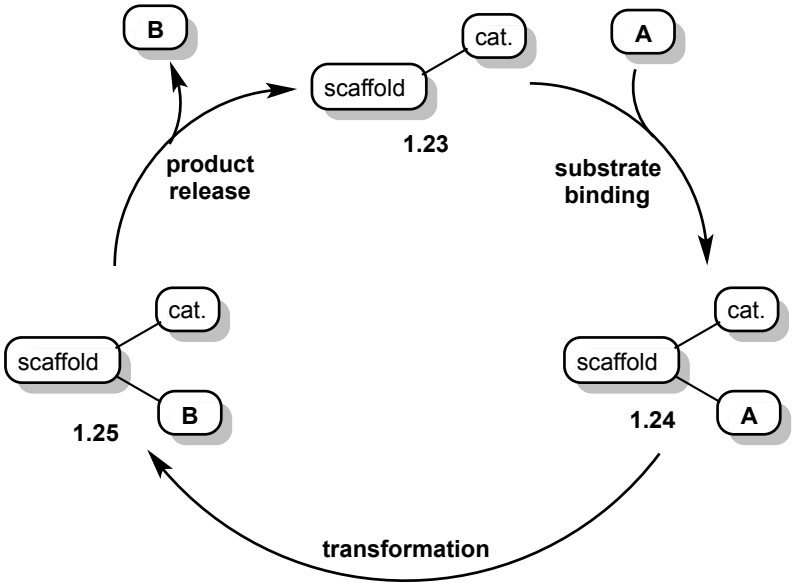
Scheme 1.13 Copper-Catalyzed Acylation of Ribofuranosides



1.4.4 Scaffolding Catalyst

Scaffolding catalysis has been successfully used for the recognition and functionalization of 1,2-diols. In its simplest form, scaffolding catalysis is the use of a catalyst (**1.23)** that will reversibly bind a molecule of substrate (**1.24**) and undergo an induced intramolecular reaction (**1.25**). The release of product will turn over the catalyst. The key to an effective scaffolding catalyst is the rapid and reversible binding interaction between substrate and catalyst (Scheme 1.14).

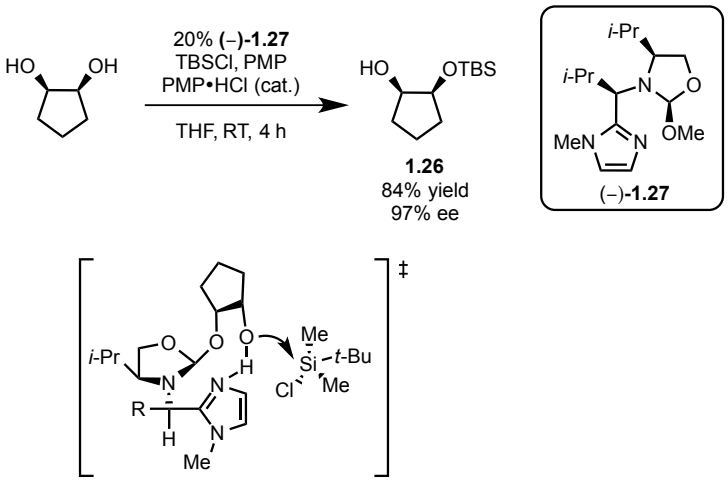
Scheme 1.14 Catalytic Cycle of a Scaffolding Catalyst



In 2011, Tan and coworkers[23] reported scaffolding catalyst **1.27** for the desymmetrization of 1,2-diols via silyl transfer (Scheme 1.15). The catalyst contains both a *N,O*-acetal substrate binding site and a catalytic imidazole portion. As mentioned previously, this class of catalysts benefits from an ability to form a reversible covalent bond with the diol substrate, forming a reactive diol-catalyst intermediate. This intermediate rapidly undergoes silylation and the monosilylated product is liberated from the catalyst. For the desymmetrization of *syn*-1,2-cyclopentane diol, the monoprotected product **1.26** was isolated in 84% yield and 97% enantioselectivity using catalyst (−)-**1.27**.

[23] (a) Sun, X.; Worthy, A. D.; Tan, K. L *Angew. Chem., Int. Ed.* **2011**, *50*, 8167 – 8171. (b) Giustra, Z. X.; Tan, K. L. *Chem. Commun.,* **2013**, *49*, 4370 – 4372.

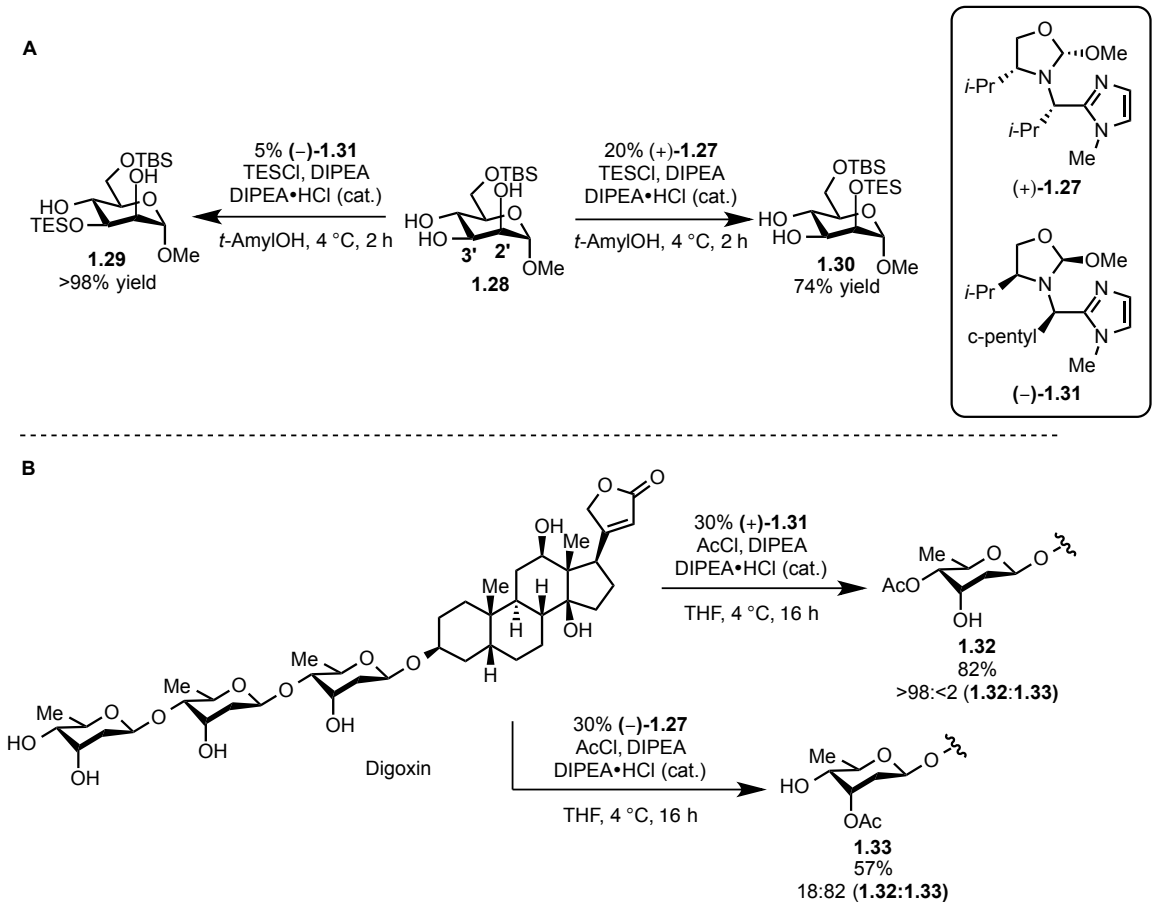
Scheme 1.15 Desymmetrization of 1,2-Diols Using a Scaffolding Catalyst



In addition to the desymmetrization of 1,2-diols, these scaffolding catalysts have been shown to be efficient for the regiodivergent resolution of racemic 1,2-diols[24] and the site-selective functionalization of different polyhydroxylated complex molecules.[25] For the latter case, both the 2`- and the 3`-silylated isomers (**1.29** and **1.30**) of mannose derivative **1.28** were isolated as the major product depending on which pseudoenantiomer of catalyst ((−)**-1.31** and **(**+**)-1.27**) was used (Scheme 1.16, A). In addition to monosaccharides, the site-selective acylation of the natural product digoxin was examined. Both hydroxyl groups of the 1,2-diol motif were selectively acylated, yielding **1.32** and **1.33** in 82% and 57% yield, respectively (Scheme 1.16, B).

[24] (a) Worthy, A.; Sun, X.; Tan, K. *J. Am. Chem. Soc.* **2012**, *134*, 7321 – 7324. (b) Sun, X.; Worthy, A.; Tan, K. *J. Org. Chem.* **2013**, *78*, 10494 – 10499.
[25] Sun, X.; Lee, H.; Lee, S.; Tan, K. L. *Nat. Chem.* **2013**, *5*, 790 – 795.

Scheme 1.16 Site-Selective Functionalization of Polyhydroxylated Complex Molecules with a Scaffolding Catalyst



1.5 Site-Selective Silylation of Ribonucleosides Using Scaffolding Catalysis[26]

Given the success of scaffolding catalysts in the selective functionalization of carbohydrates, we sought to expand their use for the site-selective silylation of ribonucleosides. A selective, one-step procedure to isolate a single structural isomer would be a substantial improvement over the current technology (Section 1.2). Being able to obtain either one of the valuable monomers in a good ratio (>10:1) would

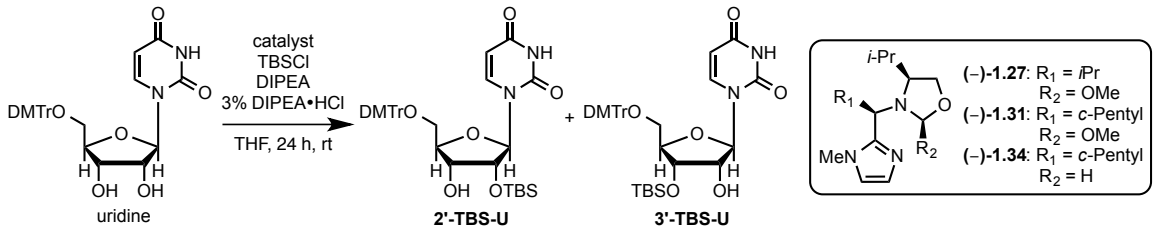
[26] (a) Blaisdell, T. P.; Lee, S.; Kasaplar, P.; Sun, X.; Tan, K. L. *Org. Lett.* **2013**, *15*, 4710 – 4713. (b) Lee, S., Blaisdell, T. P., Kasaplar, P., Sun, X. and Tan, K. L. *Curr. Protoc. Nucleic Acid Chem.* **2014,** *57*, 2.17.1 – 2.17.11.

eliminate the need for a lengthy purification step. The overall usefulness of such a procedure would also depend, however, on the availability of the catalyst required. Fortunately, all the organocatalysts used in this work could be derived from inexpensive and commercially available starting materials in two or three steps.[16a, 17a, 18]

1.5.1 Reaction Optimization

Initial studies were focused on 2`-protection of uridine using TBSCl. A common catalyst for the silylation of alcohols is *N*-methylimidazole (NMI), which was used as a control catalyst. As shown (entry 1, Table 1.1), reaction with NMI was only moderately selective. However, when employing either scaffolding catalyst (−)-**1.27** or (−)-**1.31**, there was a significant increase in the selectivity for **2`-TBS-U** and moderate conversion (entries 2-3, Table 1.1). When using catalyst (−)-**1.34**, which lacks a diol substrate-binding site, the reaction became sluggish and essentially unselective (entry 4, Table 1.1). As the concentration of the reaction and the amount of TBSCl used were increased, full conversion was achieved with no loss of selectivity using catalyst (−)-**1.31** (entry 5, Table 1.1). Reducing the catalyst loading to 10 mol% had no effect on conversion or selectivity and **2`-TBS-U** was isolated in 93% yield (entry 6, Table 1.1). Selectivity was maintained with 5 mol% of (−)-**1.31**, although the conversion decreased to 88% (entry 7, Table 1.1).

Table 1.1 TBS-Protection of D-Uridine: Reaction Optimization



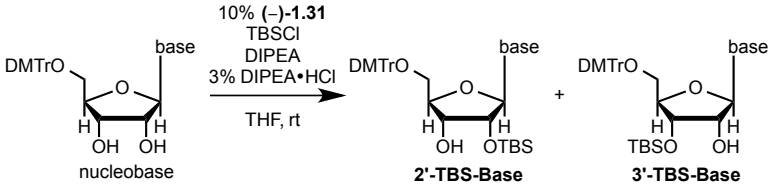
entry	mol% of catalyst	equiv TBSCl/DIPEA	conc of uridine	conversion (%)[a]	2'-TBS:3'-TBS[b]
1	20% NMI	1.5/2.0	0.2 M	100	71:29
2	20% **(–)-1.27**	1.5/2.0	0.2 M	70	98:2
3	20% **(–)-1.31**	1.5/2.0	0.2 M	72	98:2
4	20% **(–)-1.34**	1.5/2.0	0.2 M	45	45:55
5	20% **(–)-1.31**	2.0/1.5	1.0 M	100	98:2
6	10% **(–)-1.31**	2.0/1.5	1.0 M	100 (93)[c]	98:2
7	5% **(–)-1.31**	2.0/1.5	1.0 M	88 (84)[c]	98:2

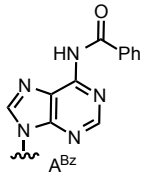
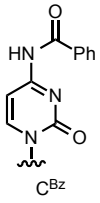
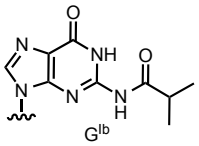
[a] Conversion determined by ^{1}H NMR using trimethoxybenzene as an internal standard. [b] Ratio was determined by ^{1}H NMR. [c] Isolated yield.

1.5.2 Selective Silylation of Natural Ribonucleosides with tert-Butyldimethylsilyl Chloride

With optimization studies complete, the remaining ribonucleoside substrates were studied. The TBS-protection of $\mathbf{A^{Bz}}$ using catalyst (–)-**1.31** gave excellent selectivity for **2`-TBS-A$^{Bz}$** and good yield (entry 1, Table 1.2). Likewise, the silylation of $\mathbf{C^{Bz}}$ gave both excellent selectivity and yield (entry 2, Table 1.2). The silylation of $\mathbf{G^{Ib}}$ required 20 mol% (–)-**1.31** and an extended reaction time to furnish **2`-TBS-G^{Ib}** in 97:3 selectivity and a 75% yield (entry 3, Table 1.2).

Table 1.2 TBS-Protection of the Other Natural Ribonucleosides



entry[a]	nucleobase	conc of nucleobase	time	2'-TBS:3'-TBS[c]	yield (%)[d]
1		0.5 M	24 h	95:5	82%
2		1.0 M	24 h	98:2	91%
3[b]		0.5 M	48 h	97:3	75%

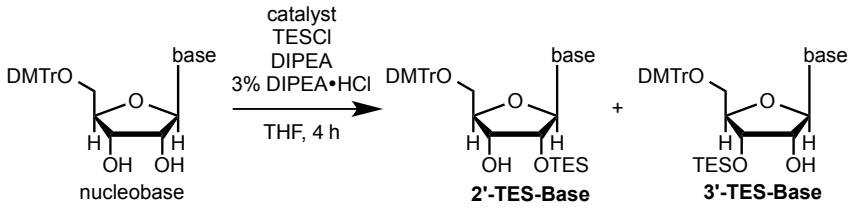
[a] Reactions performed with 2 equiv. of TBSCl, 1.5 equiv. of DIPEA and 3 mol % DIPEA-HCl [b] 20 mol % **(–)-1.31**. [c] Ratio was determined by ^{1}H NMR. [d] Isolated yield.

1.5.3 Selective Silylation of Natural Ribonucleosides with Triethylsilyl Chloride

With conditions developed for the selective silylation of the 2`-hydroxyl group, we turned our attention to accessing the 3`-protected ribonucleosides. A common way of overturning the site-selectivity in similar reactions is to use the opposite enantiomer of catalyst.[24] Unfortunately, when using TBSCl as the electrophile, both low conversions and selectivies were observed with catalyst (+)-**1.27**. As demonstrated in the NMI control reaction, the 3`-hydroxyl group is less reactive then its 2`-counterpart. Therefore, its functionalization requires a correspondingly more reactive electrophile. Reaction with triethylsilyl chloride (TESCl) was thus attempted in place of TBSCl. For 3`-TES

protection, (+)-**1.27** and (+)-**1.31** were used as catalysts, providing great selectivities (>10:1) and good isolated yields for **U**, $\mathbf{A^{Bz}}$ and $\mathbf{C^{Bz}}$ (entries 1, 3 and 5, Table 1.3). Moreover, only 5 mol% loading of catalyst was necessary for reaction completion within four hours. The guanosine substrate required 20 mol% (+)-**1.27** to obtain moderate selectivity and yield (entry 7, Table 1.3). The 2`-hydroxyl can also be selectively TES-protected using similar reaction conditions with (−)-**1.31** as the catalyst. Excellent selectivies and good yields were observed for all ribonucleosides substrates, with $\mathbf{G^{Ib}}$ requiring 10 mol% (−)-**1.31** (entries 2, 4, 6 and 8, Table 1.3).

Table 1.3 TES-Protection of the Natural Ribonucleosides



entry[a]	nucleobase	mol% of catalyst	2'-TES:3'-TES[b]	yield (%)[c]
1	U	5% (+)-**1.27**	7:93	80
2	U	5% (−)-**1.31**	>98:<2	86
3	A^{Bz}	5% (+)-**1.27**	4:96	85
4	A^{Bz}	5% (−)-**1.31**	98:2	88
5	C^{Bz}	5% (+)-**1.31**	2:98	86
6	C^{Bz}	5% (−)-**1.31**	98:2	86
7	G^{Ib}	20% (+)-**1.27**	14:86	78
8	G^{Ib}	10% (−)-**1.31**	92:8	71

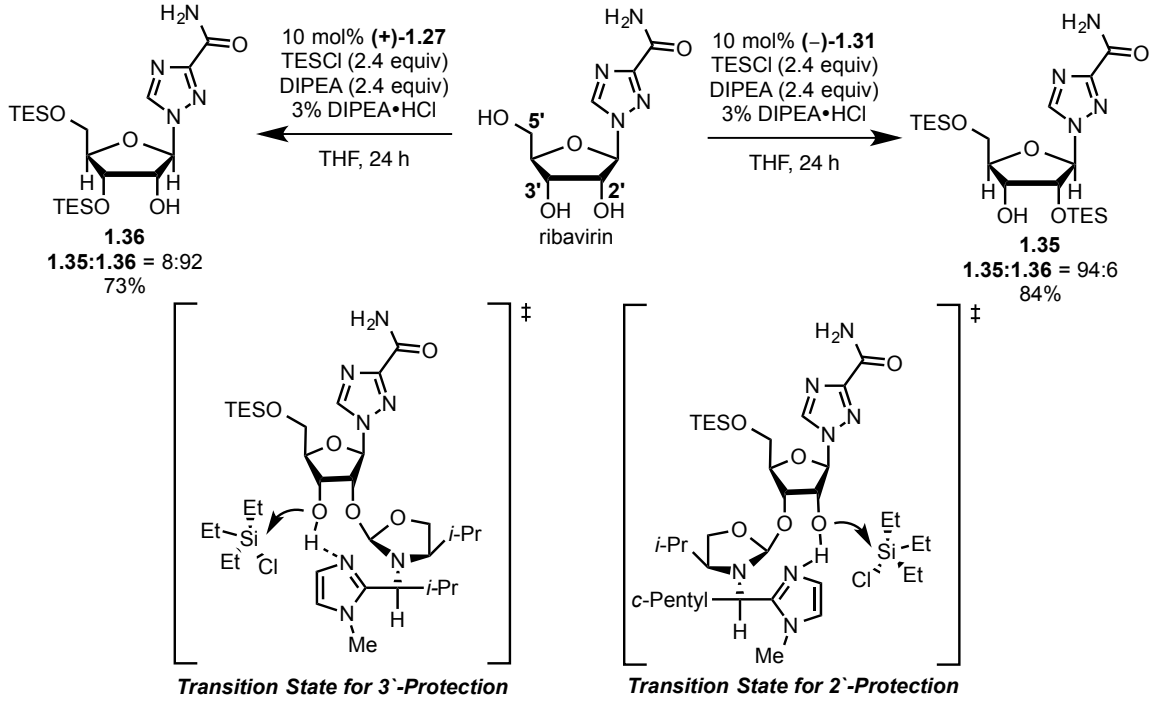
[a] Reactions performed with 1.2 equiv. of TBSCl, 1.2 equiv. of DIPEA and 3 mol % DIPEA-HCl [b] Ratio was determined by ^{1}H NMR. [c] Isolated yield.

1.5.4 Selective Silylation of Ribavirin

With the development of a procedure to selectively protect both the 2`- and 3`-hydroxyl groups of the natural ribonucleosides, we extended this methodology to the antiviral agent, ribavirin. Ribavirin is one of the most renowned antiviral drugs and is

currently on the World Health Organization's list of "essential medicines." Since its discovery in 1972, a multitude of derivatives have been synthesized.[27] When using (–)-**1.31**, unprotected ribavirin undergoes silylation at both the 5`- and 2`-hydroxyl groups with high selectivity (Scheme 1.17). Similar selectivity for silylation at the 5`- and 3`-positions was observed when using (+)-**1.27** as the catalyst. Both **1.35** and **1.36** can be considered important intermediates for the synthesis of analogs of ribavirin.

Scheme 1.17 Selective Silylation of Ribavirin.



[27] (a) Smee, D. F.; Alaghamandan, H. A.; Kini, G. D.; Robins, R. K. *Antiviral Res.* **1988**, *10*, 253 – 262. (b) Tam, R.C.; Ramasamy, K.; Bard, J.; Pai, B. *Antimicrobial Agents* **2000**, 1276 – 1283. (c) Liu, W. Y.; Li, H. Y.; Zhao, B. X.; Shin, D. S.; Lian, S.; Miao, J. Y. *Carbohydrate Res.* **2009**, *344*, 1270 – 1275.

1.6 Conclusion

Through the use of scaffolding catalysis, the site-selective silylation of ribonucleosides was accomplished. Both the 2`- and the 3`-protected products of all four ribonucleosides were obtained in useful yields and selectivities. This methodology was extended to functionalization of unnatural ribonucleosides, highlighted through the selective silylation of ribavirin. The work outlined is an excellent illustration of the power of scaffolding catalysis for the site-selective functionalization of complex molecules.

1.7 Experimental Section

1.7.1 General Considerations

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. *N,N*-Diisopropylethylamine and chlorotriethylsilane were purchased from Sigma Aldrich and distilled over CaH_2 before use. Flash column chromatography was performed using EMD Silica Gel 60 (230-400 mesh) and ACS grade solvents as received from Fisher Scientific. All experiments were performed in oven or flame dried glassware under an atmosphere of nitrogen or argon using standard syringe techniques, except where otherwise noted. All reactions were run with dry, degassed solvents dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC). ^{1}H, ^{13}C, and gCOSY NMR were performed on a Varian Gemini 400 MHz, Varian Gemini 500 MHz or a Varian Unity Inova 500 MHz spectrometer. Deuterated solvents were purchased from Cambridge Isotope Labs and stored over 3Å molecular sieves. All NMR chemical shifts are reported in ppm relative to residual

solvent for ^{1}H and ^{13}C NMR. Signals are quoted as singlet (s), doublet (d), triplet (t), quartet (q), multiplet (m), and broad singlet (br s). Coupling constants are reported in Hz. All IR spectra were gathered on a Bruker Alpha FT-IR equipped with a single crystal diamond ATR module and values are reported in cm^{-1}. HRMS data were generated in Boston College facilities.

All protected ribonucleosides[28] and catalysts[16a,17a,18] were prepared following the previously reported procedures.

The catalysts are commercially available through Strem: **1.27**: 07-1222 and 07-1223 **1.31**: 07-1226 and 07-1227.

1.7.2 Silyl-Protection of Ribonucleosides, Representative Procedures

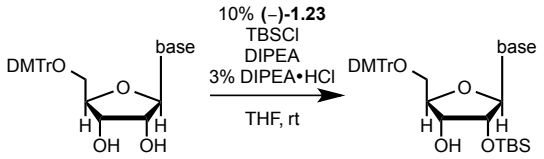
General procedure for optimization of uridine silylation (Table 1.1)

In a dry box, a suspension of the protected ribonucleoside (0.20 mmol), catalyst (0.04 mmol, 20 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.1 mg, 0.006 mmol, 3 mol %) in anhydrous THF (0.5 mL) was prepared in an oven-dried round-bottom flask. The suspension was brought out of the dry box, and *N,N*-diisopropylethylamine (52 μL, 0.3 mmol, 1.5 eq) was added to the stirring reaction mixture at room temperature, followed by dropwise addition of *tert*-butyldimethylsilyl chloride (60 mg, 0.40 mmol, 2.0 eq) in THF (0.5 mL). The reaction was stirred at room temperature for 24 hours. DIPEA (30 μL) and methanol (50 μL) was added to quench the

[28] Preparation of protected ribonucleoside: (a) DMTr-AdBz : Urata, H.; Hara, H.; Hirata, Y.; Ohmoto, N.; Akagi, M. *Tetrahedron: Asymmetry* **2005**, *16*, 2908 – 2917. (b) DMTr-CyBz : Cui, Z.; Zhang, B. *Helv. Chim. Acta* **2007**, *90*, 297 – 310. Hakimelahi, G. H.; Proba, Z. A.; Ogilvie, K. K. *Can. J. Chem.* **1982**, *60*, 1106 – 1113. (c) DMTr-GuIb: Mourani, R.; Damha, M. *Nucleosides, Nucleotides Nucleic Acids* **2006**, *25*, 203 – 229.

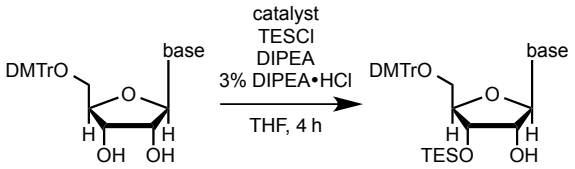
reaction. The reaction mixture was put through a plug of silica gel (2 cm) and washed with EtOAc (15 mL). The solvent was removed under reduced pressure. Proton NMR was taken to determine conversion and product ratio using 1,3,5-trimethoxybenzene as internal standard.

General procedure A for Site-Selective Silylation of Ribonucleosides (Table 1.2)



In a dry box, a suspension of the protected ribonucleoside (0.30 mmol), catalyst (0.03 mmol, 10 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.5 mg, 0.009 mmol, 3 mol %) in anhydrous THF (0.2 mL) was prepared in an oven-dried round-bottom flask. The suspension was brought out of the dry box, and *N,N*-diisopropylethylamine (78 μL, 0.45 mmol, 1.5 eq) was added to the stirring reaction mixture at room temperature, followed by dropwise addition of *tert*-butyldimethylsilyl chloride (90 mg, 0.60 mmol, 2.0 eq) in THF (0.1 mL). The reaction was stirred at room temperature for 24 hours. DIPEA (30 μL) and methanol (50 μL) was added to quench the reaction. The reaction mixture was put through a plug of silica gel (2 cm) and washed with EtOAc (15 mL). The solvent was removed under reduced pressure. Column chromatography on silica gel afforded the pure TBS-protected product.

General procedure B for Site-Selective Silylation of Ribonucleosides (Table 1.3)



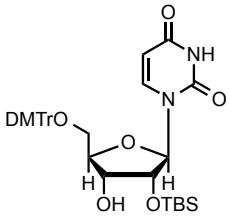
In a dry box, a mixture of the protected ribonucleoside (0.20 mmol), catalyst (0.01 mmol, 5 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.5 mg, 0.006 mmol, 3 mol %) in anhydrous THF (1 mL) was prepared in an oven-dried round-bottom flask. The mixture was brought out of the dry box, and *N,N*-diisopropylethylamine (42 μL, 0.24 mmol, 1.2 eq) was added to the stirring reaction at room temperature, followed by dropwise addition of triethylsilyl chloride (40 μL, 0.24 mmol, 1.2 eq). The reaction was stirred at room temperature for 4 hours. MeOH (50 μL) was added to quench the reaction. The reaction mixture was put through a plug of silica gel (2 cm) and washed with EtOAc (15 mL). The solvent was removed under reduced pressure. Column chromatography on silica gel afforded the pure TES-protected product.

General procedure C for Site-Selective Silylation of Ribavirin (Scheme 1.16)

In a dry box, a suspension of the ribavirin (0.20 mmol), catalyst (0.02 mmol, 10 mol %), and *N,N*-diisopropylethylamine hydrochloride (1.5 mg, 0.006 mmol, 3 mol %) in anhydrous THF (1 mL) was prepared in an oven-dried round-bottom flask. The suspension was brought out of the dry box, and *N,N*-diisopropylethylamine (84 μL, 0.48 mmol, 2.4 eq) was added to the stirring reaction at room temperature, followed by dropwise addition of triethylsilyl chloride (80 μL, 0.48 mmol, 2.4 eq). The reaction was stirred at room temperature for 24 hrs. MeOH (100 μL) was added to quench the reaction. The reaction mixture was put through a plug of silica gel (2 cm) and washed with EtOAc

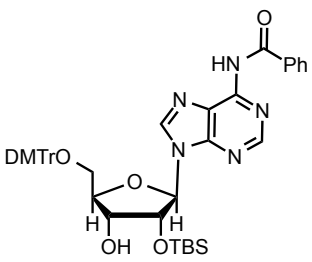
(15 mL). The solvent was removed under reduced pressure. Column chromatography on silica gel afforded the pure TES-protected product.

1.7.3 Full Characterization



2'-*O*-TBS-5'-*O*-DMTr-uridine (2`-TBS-U). The general procedure A was followed for the TBS-protection of 5'-*O*-DMTr-Uridine (168 mg, 0.30 mmol) using catalyst **(-)-1.23** (8.4 mg, 0.03 mmol, 10 mol %). Column chromatography (Ethyl acetate/Hexanes = 1:2 to 1:1) afforded the pure product 2'-*O*-TBS-5'-*O*-DMTr-uridine as a white solid (184 mg, 93%, 2':3' = >98:<2).

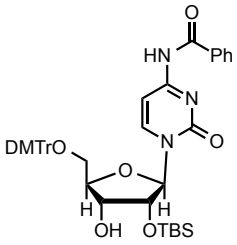
^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.28 (br s, 1H), 7.94 (d, 1H, *J* = 8.5 Hz), 7.38 (d, 1H, *J* = 7.0 Hz), 7.32-7.23 (m, 7H), 6.85 (d, 1H, *J* = 9.0 Hz), 5.96 (d, 1H, *J* = 3.0 Hz), 5.30 (d, 1H, *J* = 8.5 Hz), 4.37-4.34 (m, 2H), 4.11-4.10 (m, 1H), 3.80 (s, 6H), 3.54-3.48 (m, 2H), 2.59 (d, 1H, *J* = 6.0 Hz), 0.93 (s, 9H), 0.19 (s, 3H), 0.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 125 MHz) δ 163.5, 159.0, 158.9, 150.5, 144.5, 140.4, 135.4, 135.2, 130.4, 130.3, 128.3 128.2, 127.4, 113.5, 113.5, 102.5, 88.9, 87.4, 83.7, 76.5, 70.6, 62.5, 55.4, 25.9, 18.2, -4.4, -5.0 IR: 3534, 2951, 2929, 1680, 1508, 1460, 1250, 1175, 1115, 1034, 908, 829, 728 cm^{-1}. HRMS (DART-ESI+) calcd. for $C_{36}H_{44}N_2O_8Si$: $[M+H]^+$: 661.2945, found: 661.2926.



***N*^{6}-benzoyl-2'-*O*-TBS-5'-*O*-DMTr-adenosine (2`-TBS-A^{Bz}).** The general procedure A was followed for the TBS-protection of *N*^{6}-benzoyl-5'-*O*-DMTr-adenosine (164 mg, 0.20 mmol) using catalyst **(-)-1.23** (5.6 mg, 0.02 mmol, 10 mol %) in 0.5 M

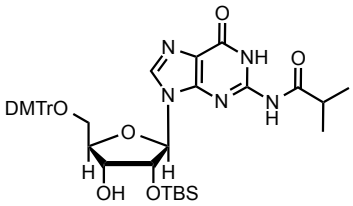
concentration in THF for 48 h. Column chromatography (Dichloromethane/methanol = 100:0 to 95:5) afforded the pure product N^6-benzoyl-2'-*O*-TBS-5'-*O*-DMTr-adenosine as a white solid (130 mg, 82%, 2':3' = 95:5).

^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ 9.10 (s, 1H), 8.73 (s, 1H), 8.23 (s, 1H), 8.03 (d, 2H, *J* = 7.8 Hz), 7.60 (m, 1H), 7.52 (m, 2H), 7.45 (d, 2H, *J* = 7.8 Hz), 7.33 (d, 4H, *J* = 8.8 Hz), 7.24 - 7.31 (m, 2H), 7.22 (m, 1H), 6.81 (d, 4H, *J* = 8.8 Hz), 6.11 (d, 1H, 5.4 Hz), 5.02 (t, 1H, *J* = 5.4 Hz), 4.36 (m, 1H), 4.29 (m, 1H), 3.78 (s, 6H), 3.54 (dd, 1H, *J* = 10.8, 2.9 Hz), 3.40 (dd, 1H, *J* = 10.8, 3.9 Hz), 2.72 (d, 1H, *J* = 3.9 Hz), 0.84 (s, 9H), -0.01 (s, 3H), -0.14 (s, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz) 164.7, 158.8, 153.1, 151.9, 149.8, 144.7, 141.9, 135.8, 133.9, 133.0, 130.3, 129.1, 128.3, 128.1, 128.0, 127.2, 123.4, 113.4, 88.6, 86.9, 84.5, 75.9, 71.7, 63.5, 55.4, 25.8, 18.1, -4.7, -5.0. IR: 2929, 1703, 1608, 1580, 1508, 1489, 1454, 1258, 1135, 1002, 908, 728 cm^{-1}. HRMS (DART-ESI+) calcd. for $C_{44}H_{50}N_5O_7Si$: $[M+H]^+$: 788.3474, found: 788.3478.



***N*^{4}-benzoyl-2'-*O*-TBS-5'-*O*-DMTr-cytidine (2`-TBS-C^{Bz}).** The general procedure A was followed for the TBS-protection of N^4-benzoyl-5'-*O*-DMTr-cytidine (195 mg, 0.30 mmol) using catalyst **(-)-1.23** (8.4 mg, 0.03 mmol, 10 mol %). Column chromatography (Ethyl acetate/hexanes = 1:2 to 1:1) afforded the pure product N^4-benzoyl-2'-*O*-TBS-5'-*O*-DMTr-cytidine as a white solid (208 mg, 91%, 2':3' = 98:2).

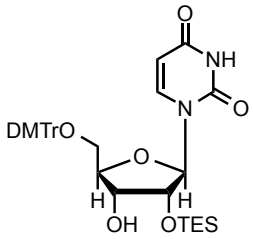
^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ 8.52 (d, 1H, *J* = 6.8), 7.89 (d, 2H, *J* = 7.3), 7.60 (t, 1H, *J* = 7.8 Hz), 7.46 - 7.54 (m, 2H), 7.43 (d, 2H, *J* = 7.3 Hz), 7.24 - 7.37 (m, 7H), 6.88 (d, 4H, *J* = 8.8 Hz), 5.93 (s, 1H), 4.33 - 4.44 (m, 1H), 4.31 (d, 1H, *J* = 3.9 Hz), 4.11 (d, 1H, *J* = 7.8 Hz), 3.82 (s, 6H), 3.59 (dd, 1H, *J* = 12.1, 2.0 Hz), 3.52 (dd, 1H, *J* = 11.6, 2.7 Hz), 2.42 (d, 1H, *J* = 9.3 Hz), 0.93 (s, 9H), 0.31 (s, 3H), 0.20 (s, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 158.9, 144.3, 135.8, 135.5, 133.3, 130.3, 130.3, 129.2, 128.5, 128.3, 127.7, 127.4, 113.5, 90.9, 87.4, 83.4, 69.3, 61.6, 55.4, 26.0, 18.3, -4.2, -5.2 IR: 2929, 2855, 1699, 1656, 1484, 1445, 1252, 1176, 1116, 831, 788,726 cm^{-1}. HRMS (DART-ESI+) calcd. for $C_{43}H_{50}N_3O_8Si$: $[M+H]^+$: 764.3362, found: 764.3364.



N^2-isobutyl-2'-*O*-TBS-5'-*O*-DMTr-guanosine (2`-TBS-G^{Ib}). The general procedure A was followed for the TBS-protection of N^2-isobutyl-5'-*O*-DMTr-guanosine (131 mg, 0.20 mmol) using catalyst **(-)-1.23** (11.2 mg, 0.04 mmol, 20 mol %) in 0.5 M concentration in THF for 48 h. Column chromatography (Dichloromethane/methanol = 100:0 to 95:5) afforded the pure product N^2-isobutyl-2'-*O*-TBS-5'-*O*-DMTr-guanosine as a white solid (114 mg, 74%, 2':3' = 97:3).

^{1}H NMR (500 MHz, $CDCl_3$-*d*) δ 11.92 (s, 1H), 7.78 (s, 1H), 7.45 (d, 2H, *J* = 9.3 Hz), 7.43 (d, 2H, *J* = 8.8), 7.10 - 7.30 (m, 5H), 6.81 (d, 2H, *J* = 9.3 Hz), 6.78 (d, 2H, *J* = 8.8 Hz), 5.71 (d, 1H, *J* = 7.3 Hz), 5.32 (dd, 1H, *J* = 13.5, 8.1 Hz), 4.34 (d, 1H, *J* = 4.9 Hz), 4.23 (s, 1H), 3.77 (s, 3H), 3.75 (s, 3H), 3.60 (dd, 1H, *J* = 10.8, 1.5 Hz), 3.02 (dd, 1H, *J* = 11.0, 2.7 Hz), 2.78 (s, 1 H), 1.14 - 1.21 (m, 2H), 0.85 (s, 9H), 0.78 (d, 3H, *J* = 6.8 Hz),

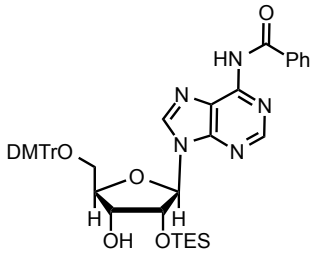
0.49 (d, 3H, *J* = 6.8 Hz), 0.04 (s, 3H), -0.18 (s, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz) δ 178.3, 159.1, 159.1, 148.3, 147.2, 145.5, 139.6, 136.5, 135.9, 135.9, 130.2, 130.2, 128.3, 128.2, 127.5, 123.1, 113.6, 113.6, 88.6, 86.3, 84.7, 74.0, 71.3, 63.9, 55.5, 36.2, 25.8, 18.5, 18.1, -4.8, -4.9 IR: 2928, 2856, 1678, 1608, 1560, 1508, 1464, 1251, 1207, 1177, 1153, 1096, 1036, 835, 783 cm^{-1}. HRMS (DART-ESI+) calcd. for $C_{41}H_{52}N_5O_8Si$: $[M+H]^+$: 770.3580, found: 770.3574.



2'-*O*-TES-5'-*O*-DMTr-uridine (2`-TES-U). The general procedure B was followed for the TES-protection of 5'-*O*-DMTr-Uridine (112 mg, 0.20 mmol) using catalyst **(-)-1.23** (3.1 mg, 0.01 mmol, 5 mol%). Column chromatography (Dichloromethane/Methanol = 99.5:0.5 to 99:1) afforded the pure product 2'-*O*-TES-5'-*O*-DMTr-uridine as a white solid (114 mg, 86%, 2':3' = >98:<2).

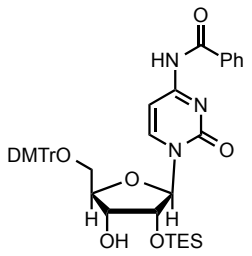
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.67 (br s, 1H), 7.94 (d, 1H, *J* = 8.0 Hz), 7.37 (m, 2H), 7.27 (m, 7H), 6.84 (d, 4H, *J* = 9.0 Hz), 5.94 (d, 1H, *J* = 3.0 Hz), 5.29 (dd, 1H, *J* = 8.3, 2.3 Hz), 4.37 – 4.33 (m, 2H), 4.13 – 4.10 (m, 1H), 3.80 (s, 6H), 3.53 – 3.46 (m, 2H), 2.66 – 2.64 (m, 1H), 0.98 (t, 9H, *J* = 8.0 Hz), 0.70 (q, 6H, *J* = 8.0 Hz). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 163.5, 158.9, 158.9, 150.5, 144.5, 140.5, 135.4, 135.2, 130.4, 130.3, 128.3, 128.2, 127.4, 113.5,113.5, 102.5, 88.9, 87.4, 83.7, 76.2, 70.6, 62.5, 55.4, 6.7, 4.7 IR: 3197, 3058, 2955, 2912, 2876, 2836, 1680, 1607, 1582, 1508, 1458, 1413, 1381, 1332, 1299, 1249, 1175, 1114, 1087, 1062, 1033, 1005, 912, 876, 827, 791, 729, 701, 583, 557,

419 cm^{-1}. HRMS (DART-ESI+) calcd. for $C_{36}H_{44}N_2O_8NaSi$: $[M+Na]^+$: 683.2770, found: 683.2759.



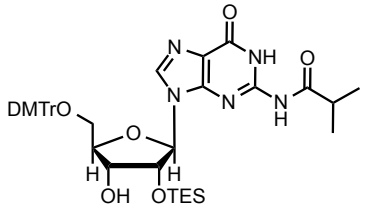
N^6-benzoyl-2'-*O*-TES-5'-*O*-DMTr-adenosine (2`-TES-A^{Bz}). The general procedure B was followed for the TES-protection of N^6-benzoyl-5'-*O*-DMTr-adenosine (135 mg, 0.20 mmol) using catalyst **(-)-1.23** (3.1 mg, 0.01 mmol, 5 mol %). Column chromatography (Dichloromethane/Methanol = 99.5:0.5 to 99:1) afforded the pure product N^6-benzoyl-2'-*O*-TES-5'-*O*-DMTr-adenosine as a white solid (138 mg, 88%, 2':3' = 98:2).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.04 (s, 1H), 8.72 (s, 1H), 8.22 (s, 1H), 8.03 (d, 2H, *J* = 7.5), 7.62 – 7.59 (m, 1H), 7.54 – 7.51 (m, 2H), 7.44 (d, 2H, *J* = 7.5 Hz), 7.35 – 7.32 (m, 4H), 7.28 – 7.25 (m, 2H), 7.23 – 7.20 (m, 1H), 6.82 – 6.79 (m, 4H), 6.09 (d, 1H, *J* = 6.0 Hz), 5.08 (t, 1H, *J* = 5.5 Hz), 4.38 – 4.35 (m, 1 H), 4.29 – 4.27 (m, 1H), 3.78 (d, 6H, *J* = 1.0 Hz), 3.53 (dd, 1H, *J* = 10.5, 3.5 Hz), 3.38 (dd, 1H, *J* = 10.5, 3.5 Hz), 2.79 (d, 1H, *J* = 4), 0.82 (t, 9H, *J* = 8.0 Hz), 0.57 – 0.43 (m, 6H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 164.5, 158.6, 152.8, 151.7, 149.6, 144.5, 141.9, 135.6, 133.7, 132.8, 130.1, 128.9, 128.1, 127.9, 127.8, 127.0, 123.3, 113.2, 88.5, 86.7, 84.2, 75.1, 71.6, 63.3, 55.2, 6.4, 4.4 IR: 3296, 3060, 2954, 2912, 2876, 2836, 1703, 1608, 1581, 1508, 1454, 1413, 1327, 1297, 1246, 1175, 1134, 1088, 1070, 1031, 1003, 909, 857, 828, 793, 728, 704, 645, 584, 488, 404 cm^{-1}. HRMS (DART-ESI+) calcd. for $C_{44}H_{50}N_5O_7Si$: $[M+H]^+$: 788.3520, found: 788.3475.



N^4-benzoyl-2'-*O*-TES-5'-*O*-DMTr-cytidine (2`-TES-C^{Bz}). The general procedure B was followed for the TES-protection of N^4-benzoyl-5'-*O*-DMTr-cytidine (130 mg, 0.20 mmol) using catalyst **(-)-1.23** (3.1 mg, 0.01 mmol, 5 mol %). Column chromatography (Dichloromethane/Methanol = 99.5:0.5 to 99:1) afforded the pure product N^4-benzoyl-2'-*O*-TES-5'-*O*-DMTr-cytidine as a white solid (131 mg, 86%, 2':3' = 98:2).

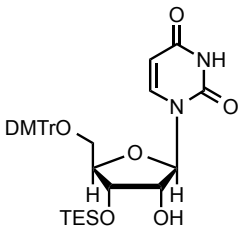
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.50 (d, 1H, *J* = 9.5 Hz), 7.87 (d, 1H, *J* = 9.5 Hz), 7.57 (m, 1H), 7.48 (m, 2H), 7.42 (m, 2H), 7.32 (m, 9H), 7.25 (m, 2H), 6.86 (m, 4H), 5.89 (d, 1H, *J* = 1.5 Hz), 4.37 (m, 1H), 4.29 (dd, 1H, *J* = 6.0, 1.5 Hz), 4.10 (m, 1H), 3.79 (d, 6H, *J* = 1.0 Hz), 3.55 (m, 2H), 2.49 (d, 1H, *J* = 12.0 Hz), 0.97 (t, 9H, *J* = 10.0 Hz), 0.78 (m, 6H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 158.9, 144.3, 135.8, 135.5, 133.2, 130.3, 130.2, 129.1, 128.4, 128.2, 127.7, 127.3, 113.5, 91.0, 87.3, 83.3, 77.6, 77.2, 76.9, 76.7, 69.1, 61.6, 55.4, 6.8, 4.7 IR: 3062, 2953, 2911, 2875, 2836, 1698, 1663, 1609, 1554, 1508, 1481, 1446, 1380, 1361, 1298, 1247, 1175, 1113, 1060, 1032, 1003, 966, 903, 828, 788, 730, 701, 679, 584, 534, 494 cm^{-1}. HRMS (DART-ESI+) calcd. for $C_{43}H_{50}N_3O_8Si$: $[M+H]^+$: 764.3374, found: 764.3362.



N^2-isobutyl-2'-*O*-TES-5'-*O*-DMTr-guanosine (2`-TES-G^{Ib}). A modified general procedure B was followed for the TES-protection of N^2-isobutyl-5'-*O*-DMTr-guanosine (131 mg, 0.20 mmol) using 10 mol % of catalyst **(-)-1.23** (6.2 mg, 0.02 mmol). Column

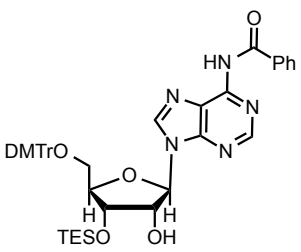
chromatography (Ethyl acetate/Hexanes = 1:2 to 1:1) afforded the pure product N^2-isobutyl-2'-*O*-TES-5'-*O*-DMTr-guanosine as a white solid (109 mg, 71%, 2':3' = 92:8). *Note: This substrate undergoes silyl transfer within 8 hrs of isolation.*

^{1}H NMR ($CDCl_3$, 500 MHz) δ 11.89 (br s, 1H), 7.76 (s, 1H), 7.60 – 7.57 (m, 2H), 7.44 – 7.40 (m, 4H), 7.27 – 7.21 (m, 2H), 7.15 (s, 1H), 6.80 – 6.75 (m, 4H), 6.70 (d, 1H, *J* = 7.2 Hz), 5.34 – 5.31 (m, 1H), 4.32 (d, 1H, *J* = 4.8), 4.20 (s, 1H), 3.76 (s, 3H), 3.74 (s, 3H), 3.57 (dd, 1H, *J* = 10.8, 1.6 Hz), 3.00 (dd, 1H, J = 10.8, 2.8 Hz), 2.83 (s, 1H), 1.22 – 1.15 (m, 1H), 0.83 (t, 9H, *J* = 8.0 Hz), 0.78 (d, 3H, *J* = 6.4 Hz), 0.58 – 0.43 (m, 6H), 0.48 (d, 3H, *J* = 6.8 Hz). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 178.2, 158.8, 158.8, 155.4, 148.1, 146.9, 145.3, 139.5, 136.3, 135.7, 130.0, 130.0, 128.1, 128.0, 127.2, 113.3, 113.3, 88.3, 86.1, 84.4, 73.5, 71.1, 63.7, 55.3, 35.9, 18.3, 18.3, 6.4, 4.4 IR: 3151, 2954, 2935, 2876, 1674, 1606, 1558, 1508, 1463, 1445, 1405, 1377, 1301, 1249, 1176, 1143, 1093, 1034, 1018, 948, 913, 868, 829, 790, 729, 702, 644, 617 596, 583, 549, 506, 417 cm^{-1}. HRMS (DART-ESI+) calcd. for $C_{41}H_{52}N_5O_8Si$: $[M+H]^+$: 770.3581, found: 770.3580.



3'-*O*-TES-5'-*O*-DMTr-uridine (3`-TES-U). The general procedure B was followed for the TES-protection of 5'-*O*-DMTr-Uridine (112 mg, 0.20 mmol) using catalyst **(+)-1.21** (2.8 mg, 0.01 mmol, 5 mol %). Column chromatography (Dichloromethane/Methanol = 99.5:0.5 to 99:1) afforded the pure product 3'-*O*-TES-5'-*O*-DMTr-uridine as a white solid (106 mg, 80%, 2':3' = 7:93).

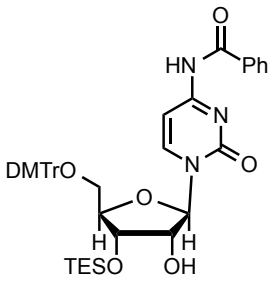
^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.36 (br s, 1H), 7.82 (d, 1H, *J* = 10.0 Hz), 7.35 – 7.22 (m, 9H), 6.82 (dd, 4H, *J* = 2.0, 11.0 Hz), 5.96 (d, 1H, *J* = 5.5 Hz), 5.36 (dd, 1H, *J* = 10.0, 3.0 Hz), 4.36 – 4.34 (m, 1H), 4.16 – 4.12 (m, 1H), 4.05 – 4.03 (m, 1H), 3.78 (s, 6H), 3.58 (dd, 1H, *J* = 13.5, 3.0 Hz), 3.30 (dd, 1H, *J* = 13.5, 3.0), 2.89 (d, 1H, *J* = 8.0 Hz), 0.87 (t, 9H, *J* = 10.0 Hz), 0.57 – 0.46 (m, 6H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 163.3, 159.0, 150.6, 144.2, 140.4, 135.3, 135.2, 130.3, 128.4, 128.2, 127.4, 113.5, 113.4, 102.7, 89.5, 87.3, 84.2, 75.4, 71.2, 62.4, 55.4, 6.8, 4.8 IR: 3441, 3170, 3058, 2954, 2911, 2875, 2836, 1692, 1608 1581, 1508, 1459, 1415, 1389, 1300, 1250, 1176, 1150, 1112, 1066, 1035, 1002, 910, 829, 729, 704, 676, 648, 633, 585, 427 cm^{-1}. HRMS (DART-ESI+) calcd. for $C_{36}H_{44}N_2O_8NaSi$: $[M+Na]^+$: 683.2771, found: 683.2759.



N^6-benzoyl-3'-*O*-TES-5'-*O*-DMTr-adenosine (3`-TES-A^{Bz}). The general procedure B was followed for the TES-protection of N^6-benzoyl-5'-*O*-DMTr-adenosine (135 mg, 0.20 mmol) using catalyst **(+)-1.21** (2.8 mg, 0.01 mmol, 5 mol %). Column chromatography (Dichloromethane/Methanol = 99.5:0.5 to 99:1) afforded the pure product N^6-benzoyl-3'-*O*-TES-5'-*O*-DMTr-adenosine as a white solid (134 mg, 85%, 2':3' = 4:96).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.10 (br s, 1H), 8.75 (s, 1H), 8.24 (s, 1H), 8.01 (d, 2H, *J* = 5.6 Hz), 7.60 – 7.57 (m, 1H), 7.51 – 7.48 (m, 2H), 7.40 – 7.38 (m, 2H), 7.30 – 7.23 (m, 6H), 7.21 – 7.19 (m, 1H), 6.79 (d, 4H, *J* = 8.5 Hz), 6.07 (d, 1H, *J* = 4.5 Hz), 4.79 – 4.76 (m, 1H), 4.60 – 4.58 (m, 1H), 4.19 (q, 1H, *J* = 4.0 Hz), 3.77 (s, 3H), 3.76 (s, 3H), 3.53

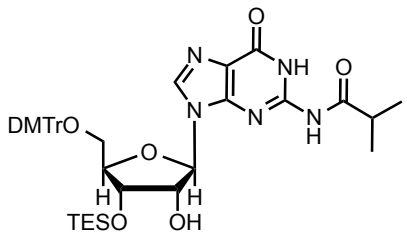
(dd, 1H, J = 10.5, 3.5 Hz), 3.30 (d, 1H, J = 6.5 Hz), 3.27 (dd, J = 11.0, 4.0 Hz, 1H), 0.92 (t, 9H, J = 8.0), 0.64 – 0.54 (m, 6H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 164.5, 158.6, 152.7, 151.7, 149.6, 144.4, 141.9, 135.6, 135.5, 133.7, 132.7, 130.0, 128.8, 128.1, 127.9, 127.8, 126.9, 123.5, 113.2, 113.2, 89.2, 86.6, 84.7, 74.6, 71.9, 62.8, 55.2, 6.6, 4,7 IR: 3280, 3058, 2953, 2912, 2875, 2836, 1702, 1608, 1580, 1508, 1454, 1412, 1327, 1298, 1245, 1175, 1141, 1068, 1032, 1002, 909, 827, 791, 727, 703, 645, 583, 404 cm^{-1}. HRMS (DART-ESI+) calcd. for $C_{44}H_{50}N_5O_7Si$: $[M+H]^+$: 788.3520, found: 788.3480.



N^4-benzoyl-3'-*O*-TES-5'-*O*-DMTr-cytidine (3`-TES-C^{Bz}). The general procedure B was followed for the TES-protection of N^4-benzoyl-5'-*O*-DMTr-cytidine (130 mg, 0.20 mmol) using catalyst **(+)-1.21** (2.8 mg, 0.01 mmol, 5 mol %). Column chromatography (Dichloromethane/Methanol = 99.5:0.5 to 99:1) afforded the pure product N^4-benzoyl-3'-*O*-TES-5'-*O*-DMTr-cytidine as a white solid (131 mg, 86%, 2':3' = 2:98).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.41 (d, 1H, J = 10.0 Hz), 7.86 (d, 2H, J = 9.0 Hz), 7.59 (m, 1H), 7.49 (m, 2H), 7.38 – 7.24 (m, 9H), 6.84 (m, 4H), 6.06 (d, 1H, J = 3.5 Hz), 4.34 (m, 1H), 4.15 (m, 2H), 3.80 (d, 6H, J = 2 Hz), 3.68 (dd, 1H, J = 13.5, 3.5 Hz), 3.32 (dd, 1H, J = 13.5, 3 Hz), 3.11 (bs, 1H), 0.84 (t, 9H, J =10 Hz), 0.55 – 0.43 (m, 6H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 162.5, 158.9, 144.9, 144.0, 135.3, 133.2, 130.3, 130.3, 129.1, 128.5, 128.1, 127.8, 127.4, 113.4, 91.3, 87.2, 83.9, 70.7, 61.7, 55.4, 6.7, 4.7 IR: 3066, 2999, 2953, 2912, 2876, 2837, 1698, 1660, 1609, 1557, 1509, 1484, 1447, 1416, 1372, 1301,

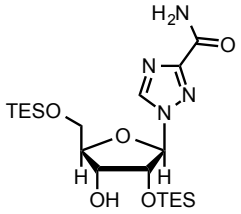
1252, 1176, 1152, 1112, 1066, 1034, 1002, 895, 830, 789, 728, 704, 585, 549, 512, 493, 421 cm^{-1}. HRMS (DART-ESI+) calcd. for $C_{43}H_{50}N_3O_8Si$: $[M+H]^+$: 764.3379, found: 764.3362.



N^2-isobutyl-3'-*O*-TES-5'-*O*-DMTr-guanosine (3`-TBS-G^{Ib}). A modified general procedure B was followed for the TES-protection of N^2-isobutyl-5'-*O*-DMTr-guanosine (131 mg, 0.20 mmol) using 20 mol % of catalyst **(+)-1.21** (5.6 mg, 0.04 mmol). Column chromatography (Ethyl acetate/Hexanes = 1:2 to 1:1) afforded the pure product N^2-isobutyl-3'-*O*-TES-5'-*O*-DMTr-guanosine as a white solid (120 mg, 78%, 2':3' = 14:86). *Note: This substrate undergoes silyl transfer within 8 hrs of isolation.*

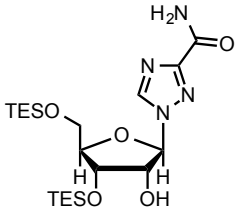
^{1}H NMR ($CDCl_3$, 400 MHz) δ 11.91 (br s, 1H), 7.81 (s, 1H), 7.73 (s, 1H), 7.51 (d, *J* = 8.8, 2H), 7.38 (d, *J* = 8.8, 4H), 7.28 – 7.14 (m, 3H), 6.82 – 6.77 (m, 4H), 5.68 (d, *J* = 6.8, 1H), 4.88 – 4.83 (m, 1H), 4.46 – 4.43 (m, 1H), 4.06 (s, 1H), 3.75 (dd, *J* = 4, 1.6, 6H), 3.53 (d, *J* = 11.2, 1H), 3.24 (d, *J* = 8.4, 1H), 3.07 – 3.03 (m, 1H), 1.65 (m, 1H), 0.92 (d, *J* = 7.2, 3H), 0.85 (t, *J* = 8, 9H), 0.70 (d, *J* = 6.8, 3H), 0.55 – 0.45 (m, 6H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 178.2, 158.8, 155.4, 148.0, 147.0, 144.7, 138.6, 136.0, 135.6, 129.9, 129.9, 128.1, 128.0, 127.1, 122.5, 113.3, 89.3, 86.2, 85.0, 73.3, 71.1, 62.8, 55.3, 36.1, 18.5, 18.5, 6.6, 4.6. IR: 3140, 3061, 2954, 2911, 2876, 2837, 1677, 1607, 1560, 1509, 1464, 1446, 1403, 1376, 1301, 1250, 1207, 1176, 1151, 1099, 1068, 1034, 1016, 948,

875, 828, 790, 728, 703, 642, 595, 583, 541, 416 cm^{-1}. HRMS (DART-ESI+) calcd. for $C_{41}H_{51}N_5O_8NaSi$: $[M+Na]^+$: 792.34010, found: 792.339911.



2',5'-*O*-TES-ribavirin (1.25). The general procedure C was followed for the TES-protection of ribavirin (49 mg, 0.20 mmol) using catalyst **(-)-1.23** (6.2 mg, 0.02 mmol, 10 mol %). Column chromatography (Dichloromethane/Methanol = 99.5:0.5 to 99:1) afforded the pure product 2',5'-*O*-TES-ribavirin as a white solid (80 mg, 84%, 2',5':3',5' = 94:6).

^1H NMR (500 MHz, $CDCl_3$-*d*) δ 8.58 (s, 1H), 6.95 (br s, 1H), 5.96 (br s, 1H), 5.83 (d, 1H, *J* = 3.5 Hz), 4.57 (m, 1H), 4.26 (m, 1H), 4.16 (m, 1H), 3.96 (dd, 1H, *J* = 11.75, 2.75 Hz), 3.80 (dd, 1H, *J* = 11.25, 2.75 Hz), 2.60 (d, 1H, *J* = 6.5 Hz), 0.94 (m, 18H), 0.63 (m, 12H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 160.7, 156.7, 143.8, 93.3, 85.7, 76.8, 70.3, 61.9, 6.6, 6.4, 4.5, 4.1 IR: 3328, 2954, 2877, 1696, 1597, 1465, 1414, 1379, 1344, 1283, 1240, 1186, 1128, 1074, 1002, 975, 910, 868, 841, 793, 729, 527 cm^{-1}. HRMS (DART-ESI+) calcd. for $C_{20}H_{41}N_4O_5Si_2$: $[M+H]^+$: 473.26155, found: 473.26180.



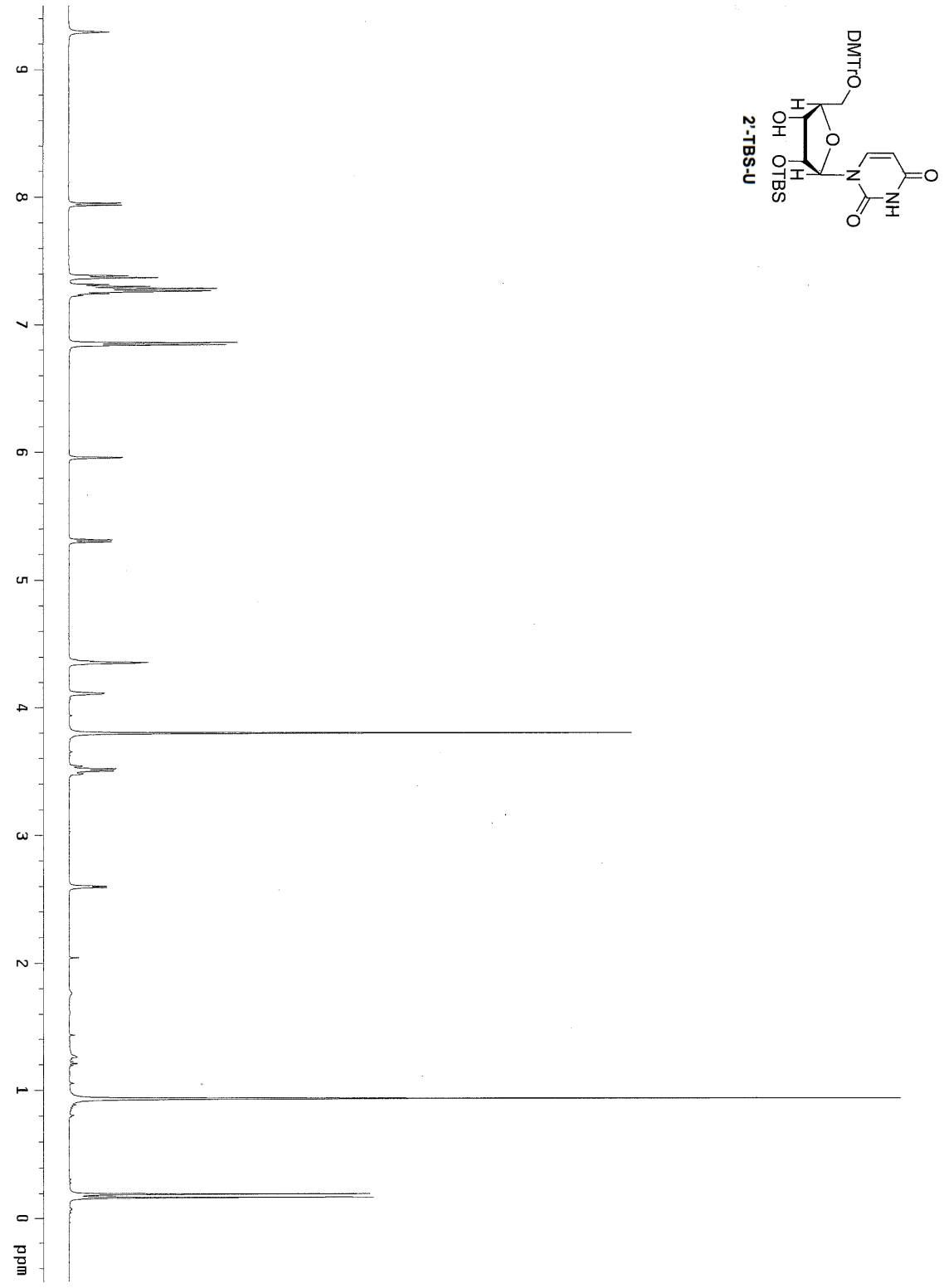
3',5'-*O*-TES-ribavirin (1.26). The general procedure C was followed for the TES-protection of ribavirin (49 mg, 0.20 mmol) using catalyst **(+)-1.21** (6.2 mg, 0.02 mmol, 10 mol %). Column chromatography (Dichloromethane/Methanol = 99.5:0.5 to 99:1) afforded the pure product 3',5'-*O*-TES-ribavirin as a white solid (69 mg, 73%, 2',5':3',5' = 8:92).

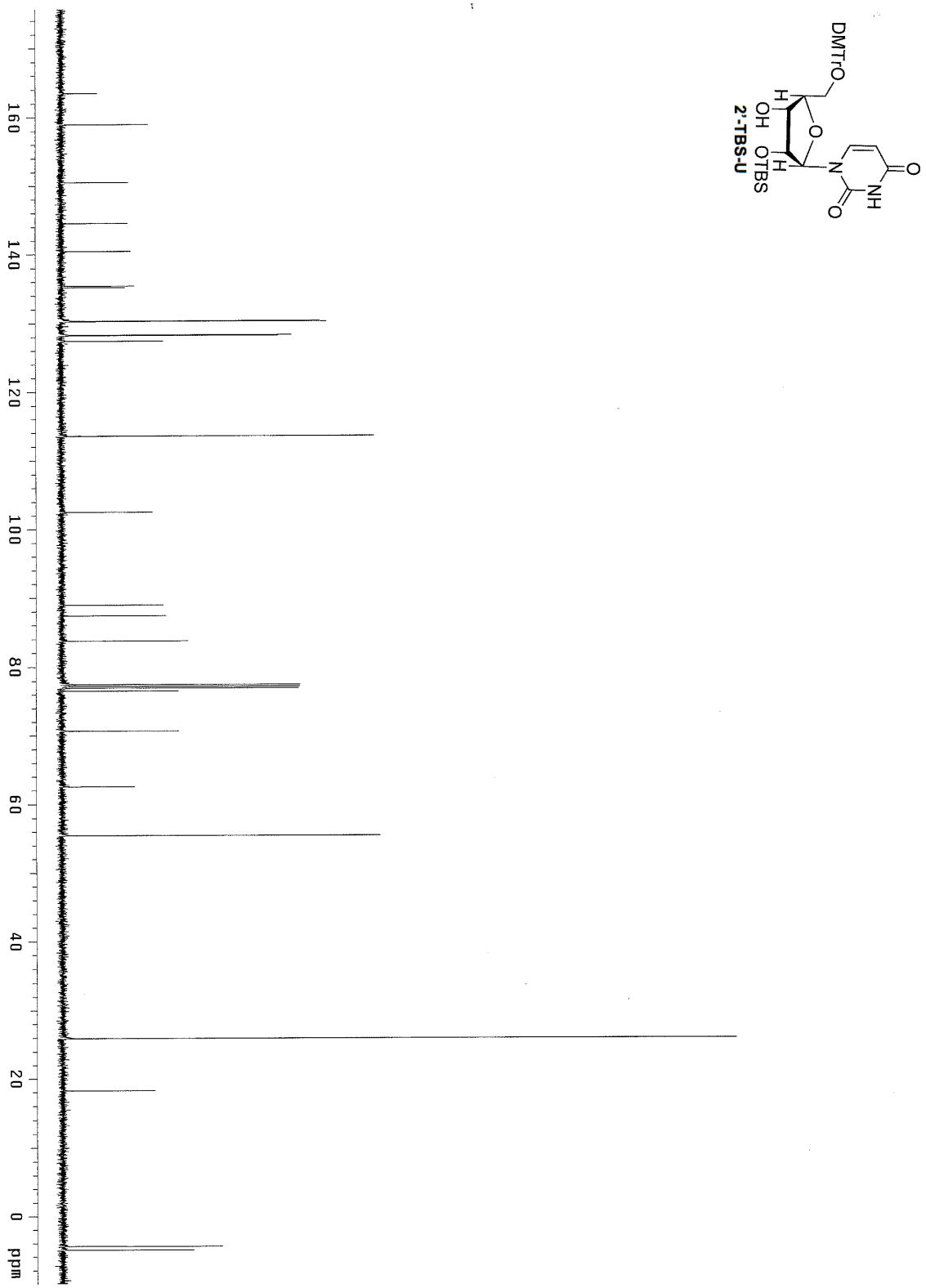
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.53 (s, 1H), 6.98 (br s, 1H), 5.95 (br s, 1H), 5.91 (d, 1H, *J* = 2.5 Hz), 4.46 (t, 1H, *J* = 5.5 Hz), 4.40 (dd, 1H, J = 5, 2.5 Hz), 4.11 (m, 1H), 3.94 (dd, 1H, *J* = 11, 3.5 Hz), 3.74 (dd, 1H, *J* = 11.5, 3 Hz), 2.95 (br s, 1H), 0.96 (m, 18H), 0.64 (m, 12H). ^{13}C NMR ($CDCl_3$, 500 MHz) δ 160.8, 156.9, 143.7, 93.0, 85.2, 75.7, 70.1, 61.1, 6.6, 6.6, 4.6, 4.1 IR: 3326, 2954, 2911, 2876, 1686, 1599, 1466, 1414, 1378, 1286, 1239, 1185, 1116, 1074, 1005, 973, 901, 839, 787, 725, 677, 547 cm^{-1}. HRMS (DART-ESI+) calcd. for $C_{20}H_{41}N_4O_5Si_2$: $[M+H]^+$: 473.26155, found: 473.26016.

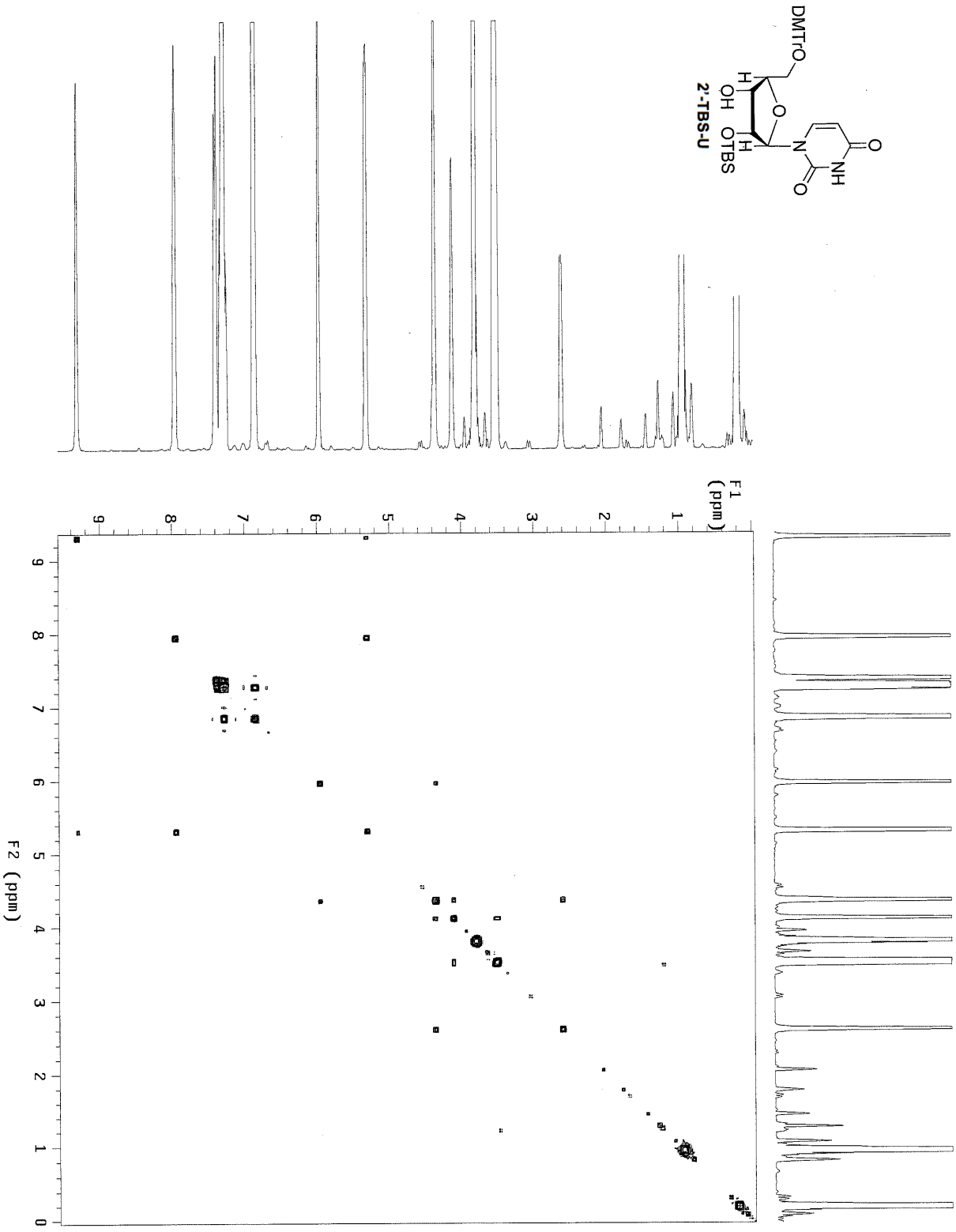
1.7.4 Spectral Data

For all published spectral data see the following link: http://pubs.acs.org/doi/suppl/10.1021/ol402023c

See below for examples of ^{1}H, ^{13}C and NOESY spectra:


DMTrO
H
OH
O
N
H
OTBS
O
NH
O
2'-TBS-U
9
8
7
6
5
4
3
2
1
0
ppm


DMTrO
H
OH
2'-TBS-U
O
H
OTBS
N
O
NH
O
160
140
120
100
80
60
40
20
0
ppm


DMTrO
H
OH
2'-TBS-U
O
N
H
OTBS
O
NH
O
F1 (ppm)
F2 (ppm)

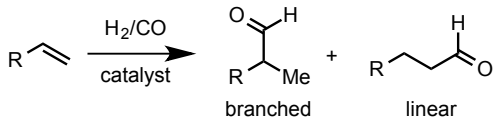
Chapter 2: Distal Selective Hydroformylation of Internal Olefins Using Scaffolding Ligands

2.1 Introduction

The functionalization of olefins has been a centerpiece for the development of novel organic reactions for many years. One reason for this is the availability of olefin starting materials, in large part due to the use of simple alkenes as feedstocks for the petrochemical industry. Additionally, the ability to control the olefin-geometry of multi-substituted alkenes has become quite practical. Hydroformylation is an olefin functionalization reaction that has been extensively studied, due to its practicality and usefulness on an industrial scale. Also known as the "oxo process," hydroformylation is the addition of hydrogen and carbon monoxide (CO) across an olefin to yield aldehyde-containing products (Scheme 2.1). It has become one of the largest homogenously catalyzed reactions in industry, producing over 10 million tons of aldehyde products annually.[1] Like most olefin functionalization reactions, the control of regioselectivity is a major challenge in hydroformylation. The two possible structural isomers formed from the hydroformylation of a terminal olefin are the linear and the branched products. When considering the hydroformylation of internal olefins, two constitutional isomers are formed; for simplicity of this thesis we refer to the aldehyde forming near a functional group as the proximal isomer and far as the distal isomer.

[1] Franke, R.; Selent, D.; Börner, A. *Chem. Rev.* **2012**, *112*, 5675 – 5732.

Scheme 2.1 Hydroformylation of Terminal Olefins

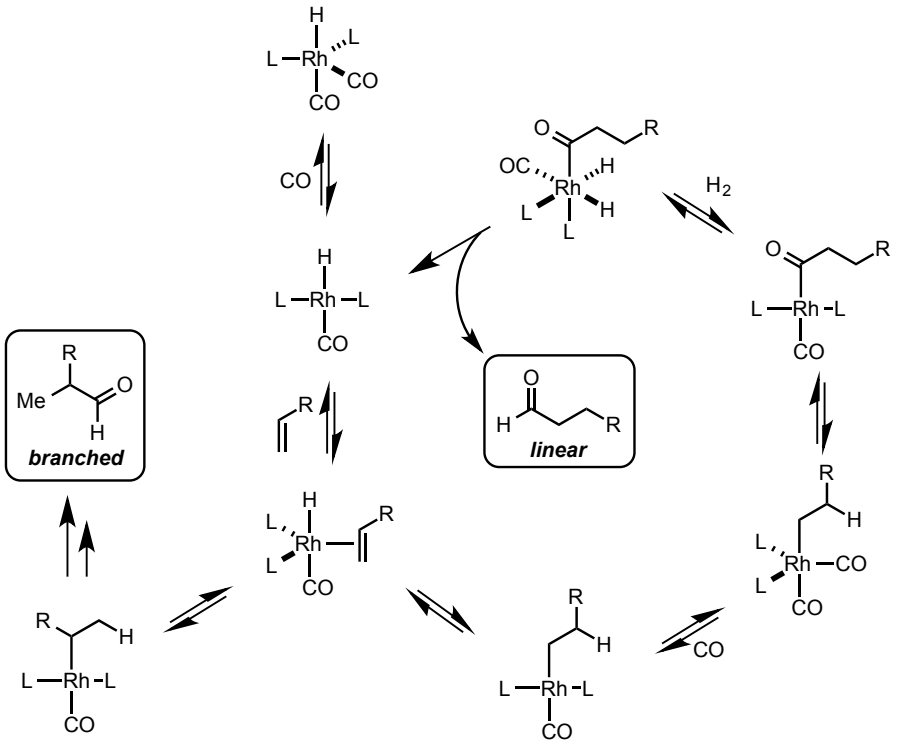


2.1.1 Mechanism of Hydroformylation

The mechanism of hydroformylation (Scheme 2.2) initiates by the dissociation of CO, followed by coordination of the olefin substrate. Hydrometallation affords both the branched and linear rhodium alkyl intermediates. Upon coordination of CO, migratory insertion yields isomeric metal acyl intermediates, which, upon oxidative addition of hydrogen gas, reductively eliminate to afford two aldehyde isomers. For most systems, the regiochemical outcome is determined during the hydrometallation step. Due to steric considerations, the linear product is favored for simple terminal alkene substrates. It should be noted that there are a number of electronically-biased substrates that do favor the branched hydroformylation products (styrenes, vinyl acetates, allyl cyanides)[2].

[2] (a) Whiteker, G. T., Babin, J. E. WO9393839, 1993. (b) Mazuela, J.; Coll, M.; Pámies, O.; Diéguez, M. *J. Org. Chem*. **2009**, *74*, 5440 – 5445. (c) Clark, T. P.; Landis, C. R.; Freed, S. L.; Klosin, J.; Abboud, K. A. *J. Am. Chem. Soc*. **2005**, *127*, 5040 – 5042. (d) Breeden, S.; Cole-Hamilton, D. J.; Foster, D. F.; Schwarz, G. J.; Wills, M. *Angew. Chem. Int. Ed*. **2000**, *39*, 4106 – 4108.

Scheme 2.2 Mechanism for the Hydroformylation of a Terminal Olefin



2.2 Linear-Selective Hydroformylation

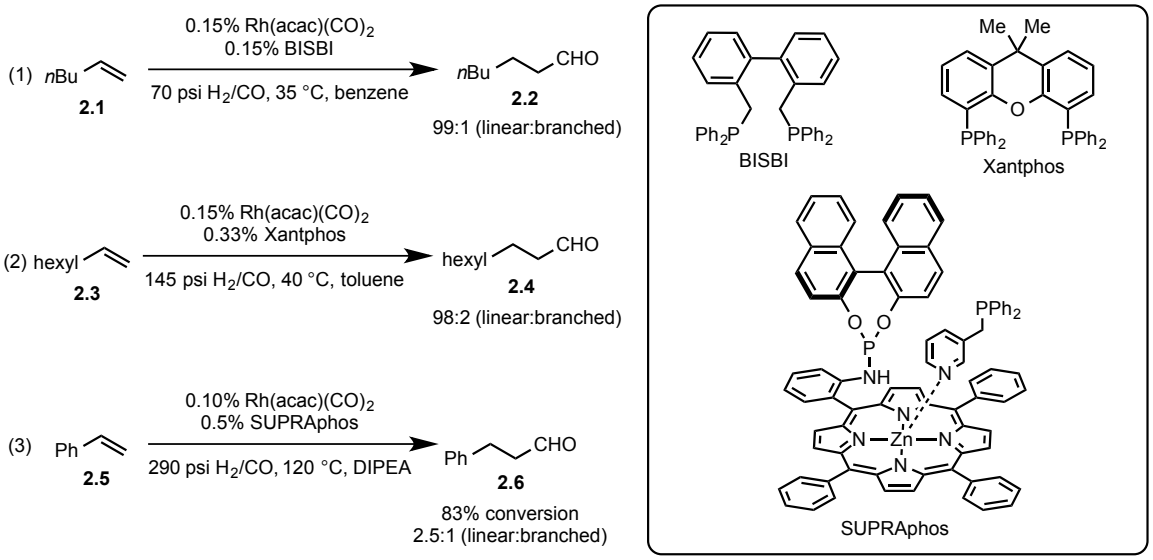
Due to its industrial applications, many groups have developed active catalysts for the linear-selective hydroformylation of terminal alkenes.[1,3] For instance, Casey and coworkers[4] have reported high selectivity for the linear aldehyde using bidentate phosphine ligands with large bite angles (Scheme 2.3, Eq. 1). It has been demonstrated that 2,2'-bis[(diphenyl-phosphino)methyl]-l,l'-biphenyl (BISBI) produces the linear aldehyde of **2.1** in a 99:1 ratio to the branched aldehyde. Similarly, van Leeuwen and

[3] (a) *Rhodium Catalyzed Hydroformylation*; van Leeuwen, P. W. N. M., Claver, C., Eds.; Kluwer Academic Publishers: Dordrecht, Netherlands, 2000. (b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev.* **2000**, *100*, 2741 – 2769. (c) van Leeuwen, P. W. N. M.; Sandee, A. J.; Reek, J. N. H.; Kamer, P. C. J. *J. Mol. Catal. A: Chem.* **2002**, *182-183*, 107 – 123.

[4] Casey, C. P.; Whiteker, G. T.; Melville, M. G.; Petrovich, L. M.; Gavney, J. A.; Powell, D. R. *J. Am. Chem. Soc.* **1992**, *114*, 5535 – 5543.

coworkers[5] disclosed the use of Xantphos and related derivatives for linear-selective hydroformylation. Using Xantphos, the hydroformylation of **2.3** proceeded in a 98:2 mixture of products favoring the linear isomer **2.4** (Scheme 2.3, Eq. 2). Reek and coworkers [6] disclosed the linear-selective hydroformylation of **2.5** using the supramolecular bidentate ligand, SUPRAphos (Scheme 2.3, Eq. 3). The two ligands used, a phosphoramidite and phosphine, are joined through a zinc(II)porphyrin–pyridine interaction. This catalyst system favors the less favored linear aldehyde of **2.5** by a ratio of 2.5:1.

Scheme 2.3 Linear-Selective Hydroformylation



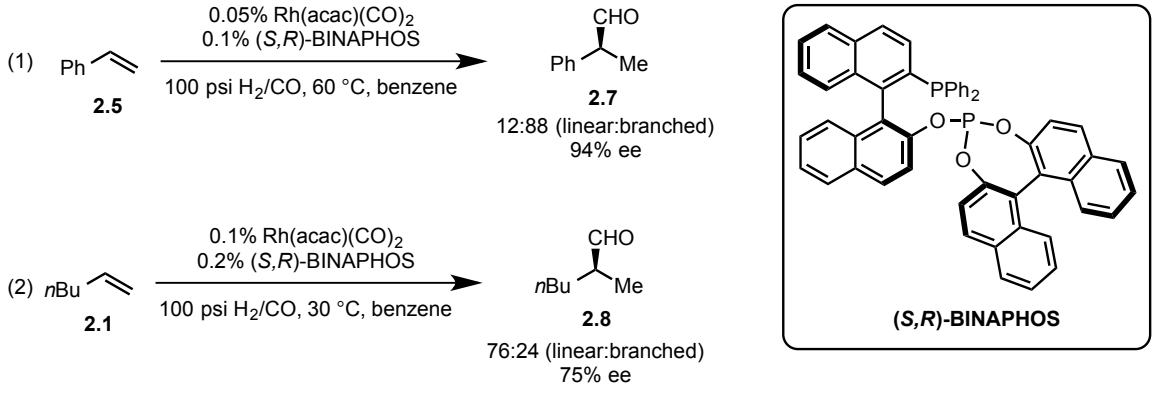
[5] Kranenburg, M.; van der Burgt, Y. E. M.; Kamer, P. C. J.; van Leeuwen, P. W. N. M.; Goubitz, K.; Fraanje, J. *Organometallics* **1995**, *14*, 3081 – 3089.
[6] Goudriaan, P. E.; Kuil, M.; Jiang, X.-B.; van Leeuwen, P. W. N. M.; Reek, J. N. H. *Dalton Trans.* **2009**, 1801 – 1805.

2.3 Branch-Selective Hydroformylation

In addition to its industrial importance, hydroformylation is an atom economical transformation of high synthetic value. Much of this utility hinges on the development of branch-selective hydroformylation, both from a regio- and stereochemical standpoint. In the absence of a directing group, obtaining even modest regiocontrol (>5:1) for the branched product of an unactivated alkene is an extraordinary achievement. The control of regiochemistry becomes especially crucial when a more elaborate olefin substrate is used.

Takaya and coworkers[7] reported a highly enantioselective hydroformylation of terminal olefins using the novel BINAPHOS ligand, a phosphine-phosphite bidentate ligand. Using (*S*,*R*)-BINAPHOS, the branched product **2.7** from the hydroformylation of **2.5** was achieved in a 88:12 ratio and 94% ee (Scheme 2.4, Eq. 1). However, the hydroformylation of **2.1** provided the branched product **2.8** as the minor structural isomer and in diminished enantioselectivity (75% ee) (Scheme 2.4, Eq. 2).

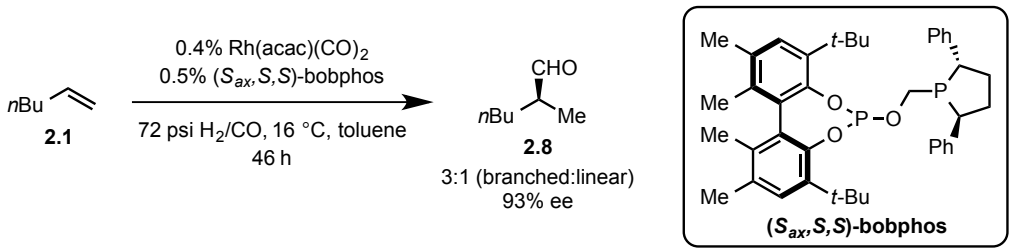
Scheme 2.4 Branch-Selective Hydroformylation with (*S,R*)-BINAPHOS



[7] Sakai, N.; Mano, S.; Nozaki, K.; Takaya, H. *J. Am. Chem. Soc.* **1993**, *115*, 7033 – 7034.

Clarke and coworkers[8] have started to address some of the problems associated with the asymmetric hydroformylation of unactivated terminal olefins (Scheme 2.5). With the development of bobphos, a phosphine-phosphite bidentate ligand, the hydroformylation of **2.1** proceeds in a 3:1 regioselectivity favoring the branched product **2.8** with a 93% enantioselectivity. Although a tremendous step forward for the field of hydroformylation, this methodology has some drawbacks including sub-ambient reaction temperatures and long reaction times.

Scheme 2.5 Branch-Selective Hydroformylation with (S_{ax},*S*,*S*)-Bobphos



2.4 Stoichiometric Directing Groups in Hydroformylation

The predictable control of regiochemistry is the paramount challenge in the context of hydroformylation. In addition to developing traditional catalyst systems to control regioselectivity, many research groups have also found success in the use of directing groups.[9] By appending a Lewis basic functionality to the substrate, the reaction could potentially proceed in an extremely selective fashion, through a reduction in activation entropy. As shown below, this association of substrate and ligand can yield

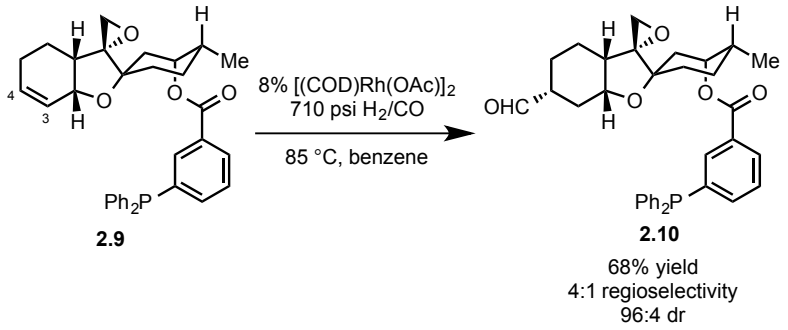
[8] Noonan, G. M.; Fuentes, J. A.; Cobley, C. J.; Clarke, M. L. *Angew. Chem., Int. Ed.* **2012**, *51*, 2477 – 2480.

[9] For reviews related to directed reactions (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307 – 1370. (b) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450 – 2494.

hydroformylation products with almost complete control of both regio- and stereochemistry.

In the context of the total synthesis of (+)-phyllanthocin, Burke and coworkers[10] utilized a cleavable phosphine-containing directing group for the selective installation of an aldehyde (Scheme 2.6). In the absence of a phosphine directing group, the authors observed a unselective mixture of hydroformylation products. The use of the *meta*-(diphenylphosphanyl)benzoyl (*m*-DPPB) group proved vital for both a regio- and diastereoselective hydroformylation of **2.9**, yielding **2.10** in 68% yield.

Scheme 2.6 Directed Hydroformylation Towards the Total Synthesis of (+)-Phyllanthocin

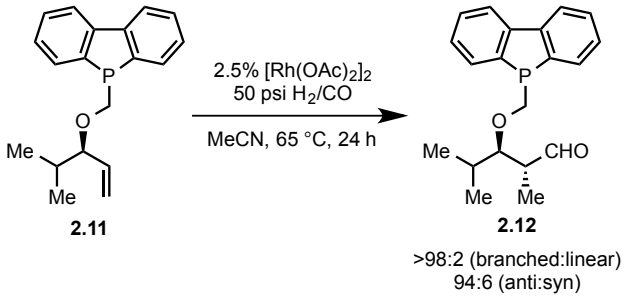


Leighton and coworkers[11] have described dibenzophosphole groups as an adequate directing moiety for the hydroformylation of allylic alcohols (Scheme 2.7). Synthesized from the subsequent methoxymethyl ether and dibenzophosphole lithium, **2.11** undergoes branched-selective hydroformylation favoring the *anti* product **2.12**. This

[10] Burke, S. D.; Cobb, J. E. *Tetrahedron Lett.* **1986**, *27*, 4237 – 4240.
[11] Krauss, I. J.; Wang, C. C.-Y.; Leighton, J. L. *J. Am. Chem. Soc.* **2001**, *123*, 11514 – 11515.

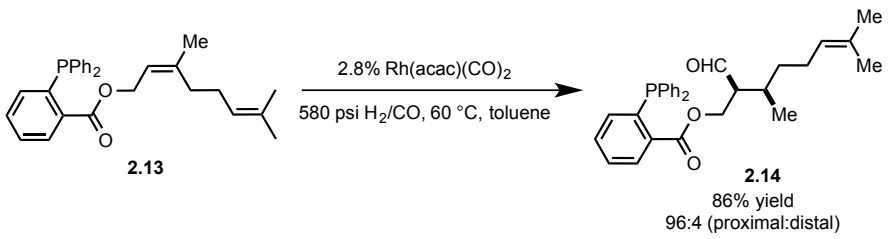
methodology offers an alternative approach to the synthesis of aldol-like products, after the directing group is cleaved with reductive deprotection conditions.

Scheme 2.7 Dibenzophosphole Directed Hydroformylation



Breit and coworkers[12] have found that when appending *o*-DPPB to primary allylic alcohols, the hydroformylation proceeds in an extremely selective manner (Scheme 2.8). When subjecting the nerol derived *o*-DPPB ester **2.13** to hydroformylation conditions, the proximal product **2.14** is observed in a 96:4 ratio and isolated in 86% yield. This observation is in line with Keuleman's rule,[13] which states that hydroformylation will occur in an effort to not form a quaternary carbon atom. However, it should be noted that the reaction proceeds with complete site-selectivity for the proximal trisubstitued olefin.

Scheme 2.8 *o*-DPPB Directed Hydroformylation



[12] Breit, B.; Grünanger, C. U.; Abillard, O. *Eur. J. Org. Chem.* **2007**, 2497 – 2503.
[13] Keulemans, A. I. M.; Kwantes, A.; van Bavel, T. *Recl. Trav. Chim. Pays-Bas* **1948**, *67*, 298 – 308.

2.5 Catalytic Directing Groups in Hydroformylation

Although an effective way to control selectivity, the use of phosphine-containing stoichiometric directing groups is hampered by clear drawbacks. Those drawbacks include being wasteful in an atom economical sense as well as requiring a multistep sequence for the addition and removal of the group from the substrate and product, respectively. An alternative approach is the development of catalytic directing groups.[14] Relying on the ability to reversibly covalently bond to the substrate, these catalysts induce the sought-after intramolecularity of a directed reaction while existing in catalytic quantities.

Breit and coworkers have developed a catalytic directing group strategy for the branch-selective hydroformylation of homoallylic[15] (Scheme 2.9) and bis-homoallylic[16] alcohols. When using methyl phosphinite **2.16** as a ligand, **2.15** undergoes proximal hydroformylation, which produces the γ-lactone **2.17** upon PCC oxidation in an 85% yield. Phosphinite **2.16** is presumed to undergo transesterification, forming a phosphine-bound substrate adduct, which undergoes directed hydroformylation, favoring a six-membered cyclic hydrometallation transition state **2.18**. The transesterification is assumed to be rapid enough to outcompete the linear-selective background reaction.

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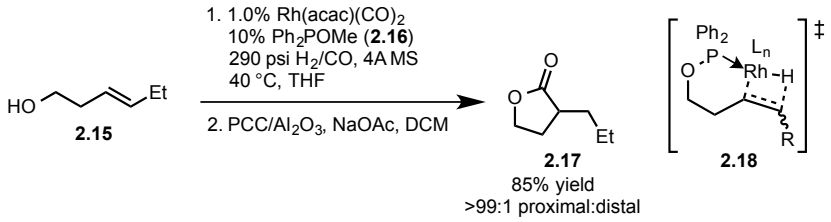
[14] (a) Park, Y. J.; Park, J. W.; Jun, C. H. *Acc. Chem. Res.* **2008**, *41*, 222 – 234. (b) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450 – 2494. (c) Tan, K. L. *ACS Catal.* **2011**, *1*, 877 – 886.

[15] Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *120*, 7456 – 7459.

[16] Grünanger, C. U.; Breit, B. *Angew. Chem., Int. Ed.* **2010**, *49*, 967 – 970.

Scheme 2.9 Breit's Catalytic Directed Hydroformylation of Alkenyl Alcohols



Tan and coworkers[17] have developed a scaffolding catalyst for the proximal-selective hydroformylation of homoallylic alcohols (Scheme 2.10). The azaphosphole ligand **2.21** undergoes an exchange reaction with a molecule of substrate. The covalently bound ligand-substrate complex undergoes directed hydroformylation upon Rh coordination to the phosphine (through transition state **2.22)**. The hydroformylation of **2.19** proceeds with good regio- and diastereocontrol. The observed *anti* diastereomer **2.20** is attributed to the minimization of $A^{1,3}$-strain during the hydrometallation step. In addition to homoallylic alcohols, **2.21** and an enantiopure variant have been successful in the proximal-selective hydroformylation of both allylic alcohols[18] and amines.[19]

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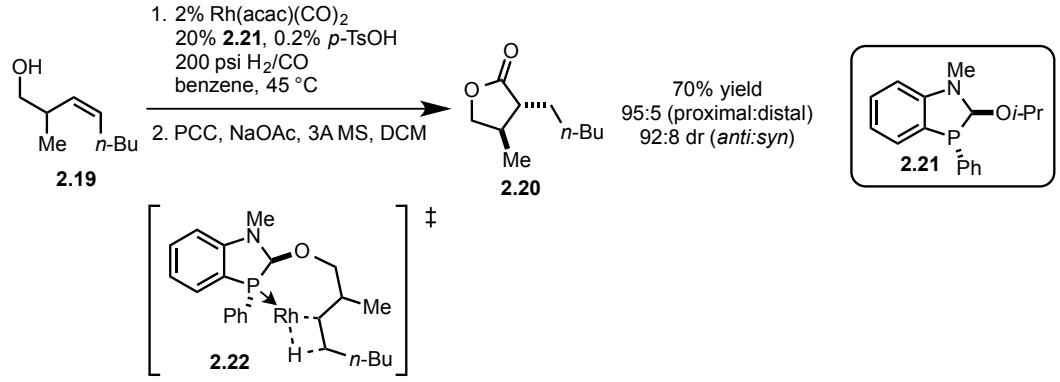
[17] Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210 – 9211.

[18] (a) Sun, X.; Frimpong, K.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 11841 – 11843. (b) Lightburn, T. E.; De Paolis, O. A.; Cheng, K. A.; Tan, K. L. *Org. Lett.* **2011**, *13*, 2686 – 2689.

[19] (a) Worthy, A. D.; Gagnon, M. M.; Dombrowski, M. T.; Tan, K. L. *Org. Lett.* **2009**, *11*, 2764 – 2767. (b) Worthy, A. D.; Joe, C. L.; Lightburn, T. E.; Tan, K. L. *J. Am. Chem. Soc.* **2010**, *132*, 14757 – 14759. (c) Joe, C. L.; Tan, K. L. *J. Org. Chem.* **2011**, *76*, 7590 – 7596.

Scheme 2.10 Scaffolding Catalysis for the Proximal Hydroformylation of Homoallylic Alcohols



2.6 Distal Hydroformylation Using Supramolecular Catalysis

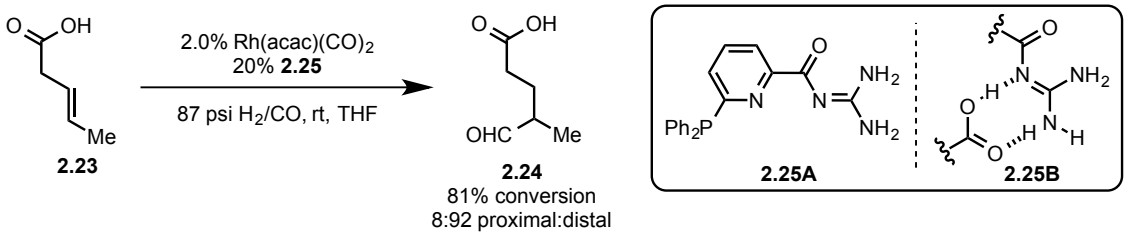
The hydroformylation of unactivated 1,2-disubstitited olefins typically occurs slower then that of a terminal olefin and, in most cases, with no bias for one structural isomer over the other. This observation is unsurprising when considering the similar electronic and steric environments of the olefinic carbons. As seen in Sections 2.4 and 2.5, when using stoichiometric or catalytic directing groups, the regiochemical outcome typically favors the proximal over distal product (with the Burke example being the lone exception). The use of supramolecular catalysts has been a successful means of accessing the distal hydroformylation product in excellent selectivity.

In 2008, Breit and coworkers[20] disclosed a supramolecular catalyst for the distal hydroformylation of unsaturated carboxylic acids (Scheme 2.11). Catalyst **2.25A** contains an acylguanidinium-based unit bound to a phosphine donor through a pyridine linker. The hydroformylation of **2.23** undergoes formylation at the distal-most olefinic carbon with a high level of regiocontrol yielding **2.24**. It is presumed that the

[20] Šmejkal, T.; Breit, B. *Angew. Chem., Int. Ed.* **2008**, *47*, 311 – 315.

acylguanidinium functionality establishes a two-point hydrogen-bonding interaction with the carboxylic acid (**2.25B**), thus preorganizing the substrate for distal hydroformylation.

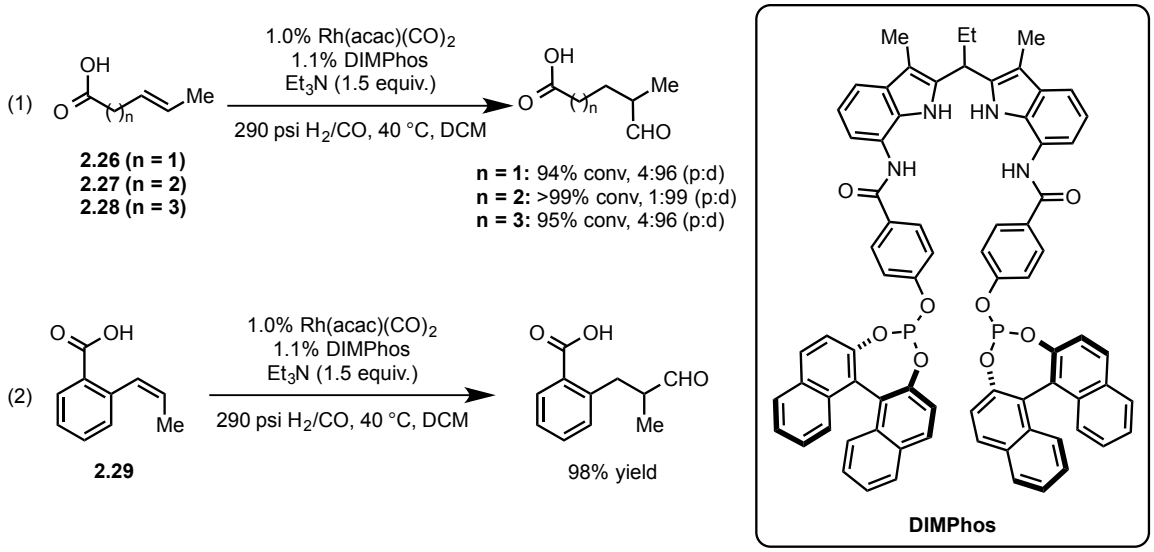
Scheme 2.11 Supramolecular Distal-Selective Hydroformylation of Unsaturated Carboxylic Acids



Reek and coworkers [21] have reported an effective supramolecular hydroformylation catalyst using the bidentate DIMphos ligand. Carboxylic acid substrates **2.26-2.28** undergo hydroformylation in a facile and selective manner to form the distal aldehydes (Scheme 2.12, Eq. 1). Additionally, carboxylic acid-containing vinyl arenes, such as **2.29**, are viable substrates under these reaction conditions, furnishing the distal hydroformylation products (Scheme 2.12, Eq. 2). Due to π-benzyl stabilization, the proximal product (α-aldehyde) is typically the favored isomer. The regiochemical control is attributed to the ability of the diamidodiindolylmethane pocket to bind strongly to the carboxylic acid functionality.

[21] (a) Dydio, P.; Detz, R. J.; Reek, J. N. H. *J. Am. Chem Soc.* **2013**, *135*, 10817 – 10828. (b) Dydio, P.; Reek, J. N. H. A*ngew. Chem. Int. Ed.* **2013**, *52*, 3878 – 3882.

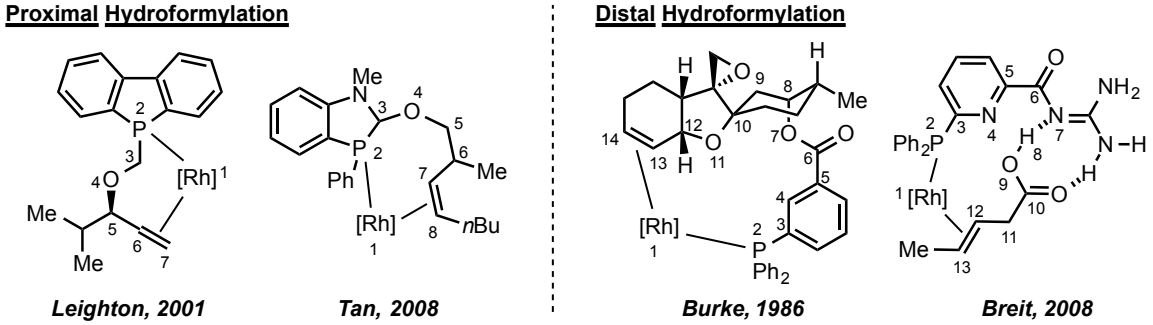
Scheme 2.12 Supramolecular Distal-Selective Hydroformylation of Unsaturated Carboxylic Acids and Vinyl Arenes Using DIMphos



2.7 Distal Hydroformylation Using Scaffolding Catalysis

With the success of scaffolding catalysis in the proximal-selective hydroformylation of alkenyl alcohols and amines in our laboratory, we pursued a scaffold design that would favor the distal product. In doing this, we sought to better understand what makes a directing group selective for one structural isomer over the other (Scheme 2.13). When considering some proximal-selective examples, the intermediates leading to the proximal aldehyde products are six- and seven-membered metallocycles. Conversely, the distal-selective intermediates typically have macrocyclic rhodacycles, falling usually between 13 and 14 atoms. Unlike the proximal-selective examples, these distal metallocycles always contain an extremely rigid array of sp^2 hybridized carbon atoms. This rigid portion seems to be important in maintaining an energy difference between the proximal and distal rhodacycles.

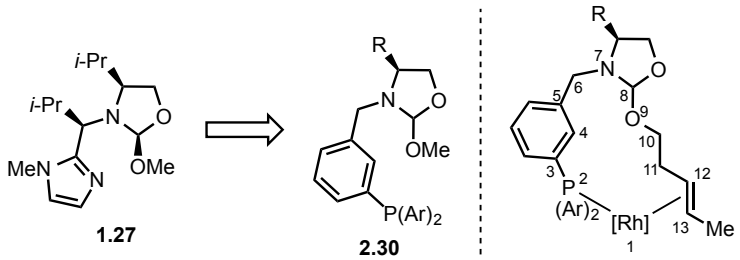
Scheme 2.13 Metallocycle Size for Directed Hydroformylation Examples



2.7.1 Scaffold Inspiration and Synthesis

Due to the need for a large metallocycle, removing the phosphine from the exchange ring of proximal-selective ligand **2.21** seemed necessary. As discussed in Chapter 1, the N,O-acetal portion of **1.27** is extremely efficient for the exchange of both primary and secondary alcohols. With this in mind, we developed ligand scaffold **2.30** as a possible distal-selective ligand (Scheme 2.14).[22] Closely resembling the Breit supramolecular catalyst **2.25**, **2.30** would also form a 13-membered metallocycle when producing the distal product.

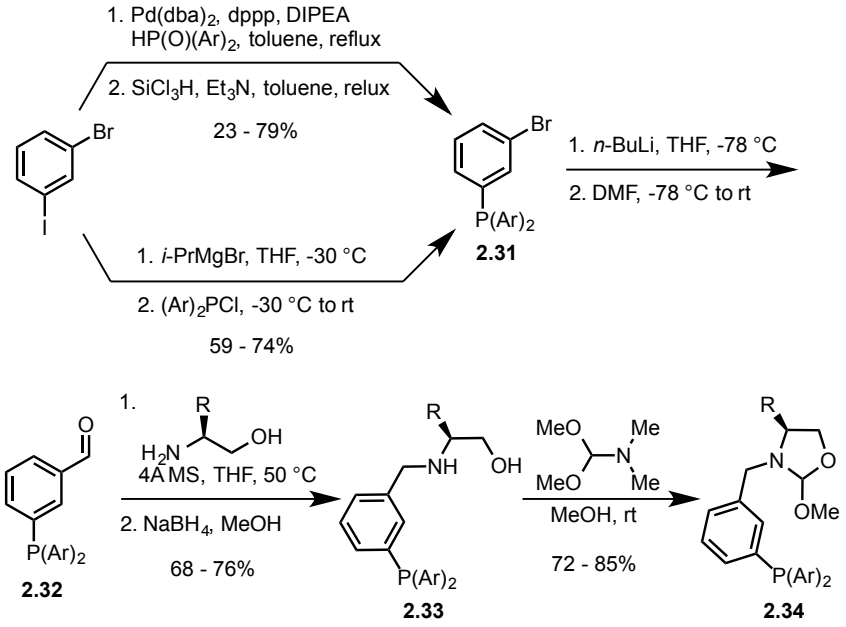
Scheme 2.14 Development of a Distal-Selective Scaffolding Ligand



[22] **2.30** proved to be the most promising scaffolding for the hydroformylation of homoallylic alcohols. The distal-selectivities observed with *ortho*-substituted or heteroaromatic-containing linkers were considerably lower then those observed with **2.30**. See page 87 for this data.

Similar to **1.27**, we envisioned that the synthesis of a library of **2.30**-based ligands would be practical due to the modularity of the scaffold (Scheme 2.15). The brominated triarylated phosphine **2.31** was attained from 2-bromoiodobenzene by either a cross-coupling of the secondary phosphine oxide followed by a silane reduction or a Grignard exchange followed by addition of the chlorophosphine. Next, **2.31** was subjected to lithium-halogen exchange conditions followed by the addition of *N*,*N*-dimethylformamide to furnish the benzaldehyde derivative **2.32**. Condensation of **2.32** with an amino alcohol, followed by $NaBH_4$ reduction of the imine yielded **2.33**. A simple cyclization of **2.33** using *N*,*N*-dimethylformamide dimethylacetal in methanol produced **2.34**, which typically exist as a 1:1 mixture of diastereomers.

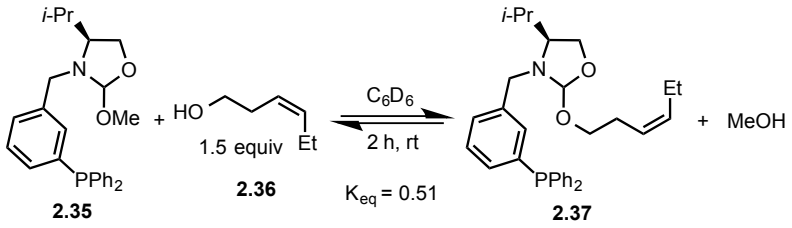
Scheme 2.15 Synthetic Route for Distal-Selective Scaffolding Ligand



2.7.2 Probing the Equilibration Constant

In order to probe whether this new ligand would be a suitable scaffolding catalyst, **2.35** was synthesized and subjected to exchange conditions with homoallylic alcohol **2.36**. The ligand-substrate complex **2.37** was observed and, after two hours at room temperature, the K_{eq} of the exchange reaction was determined to be 0.51 (Scheme 2.16). This exchange reaction was deemed favorable, which is necessary in order to suppress the unselective background reaction.

Scheme 2.16 NMR Exchange Experiments with Ligand **2.35** and Alcohol **2.36**

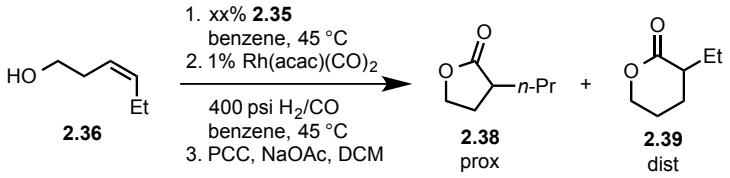


2.7.3 Initial Experiments on Simple Homoallylic Alcohols

To gauge the performance of **2.35** as a distal-selective scaffold ligand, it was used for the hydroformylation of **2.36**, a simple *cis*-homoallylic alcohol. At lower loadings of **2.35**, the hydroformylation of **2.36** produced an unselective mixture of regioisomers (Entries 1-2, Table 2.1). It is of note that these regiochemical outcomes were similar to the control reaction when PPh_3 was used as the ligand (54:46, proximal:distal). However, with 5% loading of **2.35**, the δ-lactone **2.39** was observed in a 79:21 ratio with the proximal regioisomer **2.38** (Entry 3, Table 2.1). Interestingly, as the amount of **2.35** added was increased, there is little effect on the regioselectivity of the reaction (Entries 4-

5, Table 2.1). However, with this increase, there appeared to be phosphine inhibition of the catalyst, as the conversion started to diminish.

Table 2.1 Effect of **2.35** on the Distal Hydroformylation of **2.36**

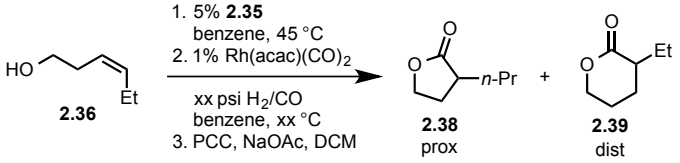


entry	mol % of **2.35**	conversion (%)[a]	regioselectivity[b] (prox:dist)
1	1%	>95	49:51
2	2.5%	>95	42:58
3	5%	90	21:79
4	10%	73	22:78
5	25%	78	22:78

[a] Conversion determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] Ratio was determined by gas chromatography after the oxidation.

The reaction temperature and pressure of syn gas are two important variables when developing an efficient hydroformylation method. Employing ligand **2.35** in the hydroformylation of **2.36**, a direct correlation between the pressure of syn gas and conversion was observed (Entries 1-5, Table 2.2). This trend was accompanied with a minor decrease in regioselectivity. From this data, a CO/H_2 pressure of 400 psi proved to be the most efficient. As expected, as the reaction temperature was increased, full conversion was obtained while the regioselectivity suffered, possibly due to an unselective background reaction (Entries 1 and 6-9, Table 2.2).

Table 2.2 Effect of Pressure and Temperature on the Distal Hydroformylation of **2.36**



entry	H_2/CO (psi)	temperature (°C)	conversion (%)[a]	regioselectivity[b] (prox:dist)
1	400	45	90	21:79
2	300	45	74	23:77
3	200	45	87	23:77
4	100	45	84	24:76
5	50	45	84	25:75
6	400	35	73	20:80
7	400	55	93	24:76
8	400	65	>95	28:72
9	400	75	>95	33:67

[a] Conversion determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] Ratio was determined by gas chromatography after the oxidation.

2.8 Distal and Diastereoselective Hydroformylation Using Scaffolding Catalysis[23]

With promising regioselectivities observed for straight-chain homoallylic alcohols, we turned our attention to homoallylic alcohols with allylic stereocenters. As shown previously for the proximal-selective hydroformylation,[17] the diastereoselectivity of these substrates can be effectively controlled when using scaffolding catalysts.

2.8.1 Ligand Optimization for the Distal-Selective Hydroformylation

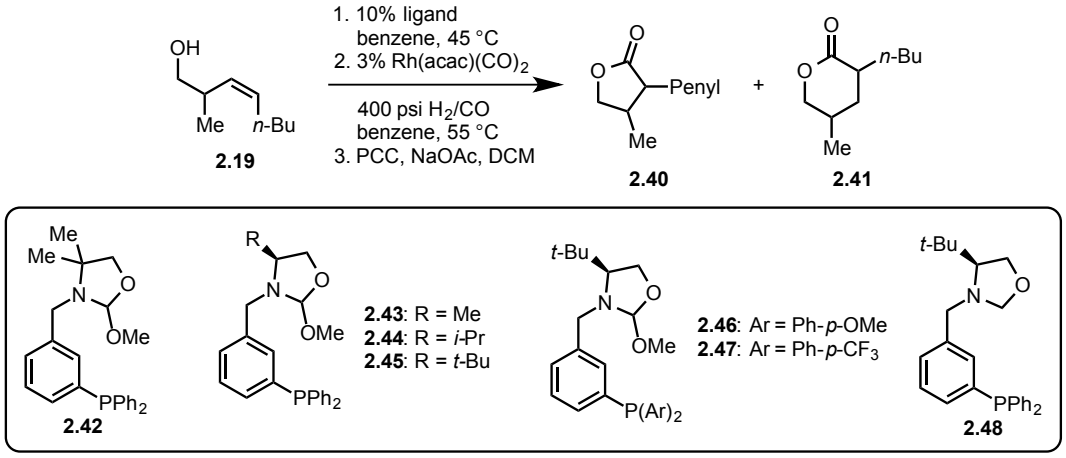
Using **2.19** as an optimization substrate, a small library of scaffolding ligands were screened. The hydroformylation of **2.19** with PPh_3 produced an unselective mixture of isomers in low conversion (Entry 1, Table 2.3). Transitioning to **2.42** as the ligand afforded moderate regio- and diastereocontrol, favoring the *anti* diastereomer of the δ-lactone **2.41** (Entry 2, Table 2.3). Importantly, when compared to PPh_3, **2.42** gave

[23] Joe, C. L.; Blaisdell, T. P.; Geoghan, A. F.; Tan, K. L. *J. Am. Chem. Soc.* **2014**, *136*, 8556 – 8559.

significantly higher conversion, highlighting the rate accelerating affect when employing scaffolding ligands. As ligands with stereogenic centers on the oxazolidine ring were screened, it was expected that a matched-mismatched effect would be observed between substrate and catalyst. Therefore, both enantiomers of **2.19** were synthesized and subjected to hydroformylation using ligand **2.44**. The hydroformylation of (*S*)-**2.19** selectively yielded the distal product, albeit in diminished regio- and diastereoselectivities (Entry 3, Table 2.3). In contrast, (*R*)-**2.19** afforded the distal product **2.41** with an 88:12 dr and 91:9 regioselectivity (Entry 4, Table 2.3). Due to the presence of a matched-mismatched effect, we chose to use enantioenriched substrate for further ligand optimization and substrate scope analysis. Manipulation of the group appended to the amino alcohol backbone proved to have a noticeable effect on activity of the ligand, with the alanine-derived ligand **2.43** affording poorer conversion, regio- and diastereoselectivity (Entry 5, Table 2.3). On the contrary, the more sterically bulky **2.45** ligand bolstered the conversion of (*S*)-**2.19** to 92%, while maintaining regio- and diastereoselectivities similar to those of **2.44** (Entry 6, Table 2.3). Modulating the electronics of the phosphine had a moderate effect on the ligand's efficiency. The more electron-rich **2.46** ligand displayed a severe decline in conversion and a minor regression in regio- and diastereoselectivity (Entry 7, Table 2.3). Although similar, the electron-deficient **2.47** ligand failed to outperform its electronically neutral counterpart, **2.45** (Entry 8, Table 2.3). Consequently, **2.45** was found to be the most effective distal-selective scaffolding ligand. In order to test whether **2.45** is truly preforming as a scaffolding catalyst, ligand **2.48**, which lacks a substrate-binding site, was synthesized and used in the hydroformylation conditions (Entry 9, Table 2.3). **2.48** was shown to be

an ineffective ligand for hydroformylation, producing an unselective product mixture with a conversion of 44%. Notably, the results using control catalyst **2.48** are similar to those obtained with PPh_3 as the ligand, highlighting the importance of the substrate-binding site to obtain high levels of activity and selectivity. Finally, in an effort to catalyze substrate exchange with **2.45**, a catalytic amount of *para*-toluenesulfonic acid was added to the reaction (Entry 10, Table 2.3). This additive increased the conversion to 95% without affecting the selectivity of the reaction. Upon purification, **2.41** was isolated as a mixture of diastereomers in a 78% yield (Entry 1, Table 2.4).

Table 2.3 Screening of Distal-Selective Scaffolding Ligands



entry	substrate	ligand	conversion (%)[a]	regioselectivity[b] (prox:dist)	diastereoselectivity[c] (anti:syn)
1	rac-**2.19**	PPh_3	30	46:54	53:47
2	rac **2.19**	**2.42**	60	19:81	76:24
3	(*S*)-**2.19**	**2.44**	65	28:72	67:33
4	(*R*)-**2.19**	**2.44**	87	9:91	88:12
5	(*R*)-**2.19**	**2.43**	55	24:76	74:26
6	(*R*)-**2.19**	**2.45**	92	9:91	87:13
7	(*R*)-**2.19**	**2.46**	63	14:86	84:16
8	(*R*)-**2.19**	**2.47**	88	10:90	85:15
9	(*R*)-**2.19**	**2.48**	44	44:56	58:42
10[d]	(*R*)-**2.19**	**2.45**	95	9:91	87:13

[a] Conversion determined by ^1H NMR using 1,3,5-trimethoxybenzene as an internal standard. [b] Ratio was determined by gas chromatography after the oxidation. [c] Ratio was determined by ^1H NMR (CD_3OD) after oxidation. [d] Reaction run using 0.1% *p*-TsOH.

2.8.2 Investigation of the Substrate Scope

An assortment of enantioenriched substrates were synthesized and subjected to hydroformylation conditions with **2.45** as the ligand. The *trans* substrate **2.50** was modestly selective for distal product **2.51** (Entry 2, Table 2.4). In agreement with the $A^{1,3}$-strain model[9,24], the major diastereomer observed was the *syn* product, albeit in only a 68:32 dr. Due to their selective nature, a variety of *cis*-alkenyl alcohols were prepared. Most of the substrate modifications involve alterations to the group at the allylic position. **2.52** underwent hydroformylation in an extremely regioselective manner (95:5 rr), furnishing lactone **2.53** in a 91:9 dr (Entry 3, Table 2.4). In addition to alkyl groups, heteroatom-containing **2.54** produced the distal isomer **2.55** in 85:15 rr and 89:11 dr (Entry 4, Table 2.4). Substrates containing aromatic substituents at the allylic position were also examined. The hydroformylation of **2.56** furnished the distal product **2.57** with good regio- and diastereoselectivities (Entry 5, Table 2.4). More electron rich substrates, **2.58** and **2.66**, generated the distal products in very good regioselectivies (Entries 6 and 10, Table 2.4). The mildly deactivated halogen-containing aryl substrates, **2.60** and **2.62**, underwent hydroformylation providing synthetically useful regio- and diastereoselectivities for the distal products (Entry 7-8, Table 2.4). The terminal olefin substrate **2.68** was only moderately selective for the distal product (Entry 11, Table 2.4). This result was surprising due to the likelihood that the distal (linear) product is the more favored isomer. The low level of regioselection may be an indication that the pathways leading to both the proximal and distal products are both directed by the scaffolding catalyst.

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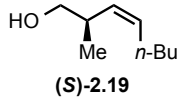
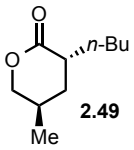
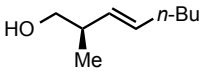
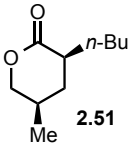
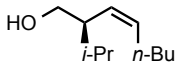
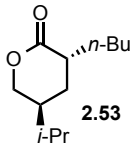
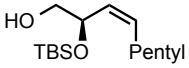
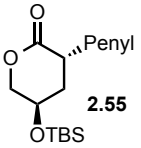
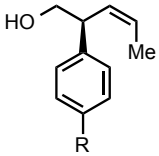
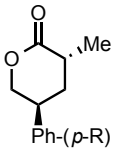
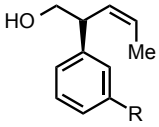
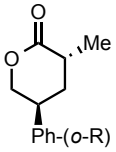
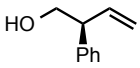
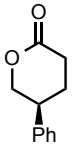
[24] Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841 – 1860.

Table 2.4 Distal-Selective Hydroformylation of Various Homoallylic Alcohols

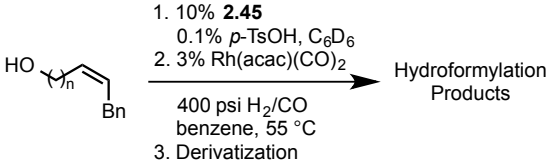
entry	substrate	major product	regioselectivity[a] (prox:dist)	diastereoselectivity[a] (anti:syn)	yield (%)[b]
1[c]	 **(*S*)-2.19**	 **2.49**	9:91	87:13	78%
2[c]	 **2.50**	 **2.51**	20:80	32:68	52%
3[d]	 **2.52**	 **2.53**	5:95	91:9	53%
4[e]	 **2.54**	 **2.55**	15:85	89:11	50%
5[e]	 **2.56**: R = H	 **2.57**: R = H	12:88	83:17	66%
6[e]	**2.58**: R = OMe	**2.59**: R = OMe	7:93	88:12	72%
7[e]	**2.60**: R = Br	**2.61**: R = Br	13:87	89:11	62%
8[e]	**2.62**: R = Cl	**2.63**: R = Cl	12:88	87:13	68%
9[e]	 **2.64**: R = CF_3	 **2.65**: R = CF_3	9:91	91:9	73%
10[e]	**2.66**: R = OMe	**2.67**: R = OMe	9:91	86:14	77%
11[f]	 **2.68**	 **2.69**	16:84	----	80%

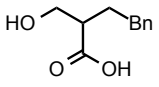
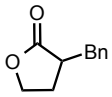
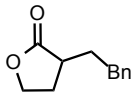
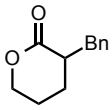
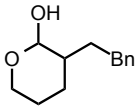
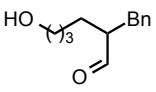
[a]Regio- and diastereoselectivities were determined by GC or ^{1}H NMR after oxidation. [b]Isolated yields of combined distal lactone products. [c](i) 10 mol % **2.45**, 0.10 mol % p-TsOH, 45 °C, benzene; (ii) 3 mol % $Rh(acac)(CO)_2$, 55 °C, 400 psi H_2/CO, benzene; (iii) PCC, NaOAc, 3 Å sieves, DCM. [d]Standard conditions except 20 mol % **2.45** and 6 mol % $Rh(acac)(CO)_2$ were used. [e]Standard conditions except 12 mol % **2.45** and 4 mol % $Rh(acac)(CO)_2$ were used. [f]Standard conditions except the hydroformylation was run at 35 °C using 5 mol % **2.45** and 2 mol % $Rh(acac)(CO)_2$.

To further investigate the origin of regioselectivity observed with **2.45**, we began to probe other alkenyl alcohol substrates. Allylic alcohol **2.70** is fully consumed during hydroformylation, generating an unselective mixture of regioisomers (Entry 1, Table 2.5). It should be noted that when using PPh_3 as the ligand, the reaction proceeded in a

marginally proximal-selective fashion. As demonstrated above, the hydroformylation of homoallylic alcohols was noticeably distal-selective relative to the PPh_3 control reaction (Entry 2, Table 2.5). Furthermore, when considering conversion, the directed example proceeds at roughly double the rate compared to the PPh_3 reaction. Both the **2.45** and the PPh_3-mediated reactions for the bis-homoallylic alcohol **2.72** proceeded in a generally unselective manner (Entry 3, Table 2.5). Nevertheless, the conversion when using **2.45** was more then double that of the control reaction. This observation could possibly suggest that both regioisomers were accessed through directed pathways, both of which have similar energy barriers.

Table 2.5 Hydroformylation of Different Alkenyl Alcohols Using **2.45**



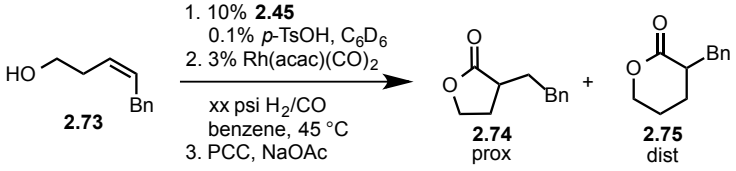
entry	n	proximal product	distal product	conversion (%)[a]	regioselectivity[b] (prox:dist)
1[c]	n = 1 **2.70**			>99% (>99%)[f]	58:42 (67:33)
2[d]	n = 2 **2.71**			84% (40%)[f]	21:79 (57:43)
3[e]	n = 3 **2.72**			89% (36%)[f]	46:54 (59:41)

[a]Conversion based on remaining starting material after the hydroformylation reaction using mesitylene as an internal standard. [b]Regioselectivities (proximal:distal) were determined by ^1H NMR. [c]Crude hydroformylation reaction was subjected to Pinnick oxidation. [d]Crude hydroformylation reaction was subjected to PCC oxidation. [e]No derivatization of the crude hydroformylation reaction was carried out. [f]Results in parentheses run under identical conditions, except PPh_3 was used rather than ligand **2.45**.

2.9 Enantio- and Distal-Selective Hydroformylation

Due to the effectiveness of **2.45** as a distal-selective ligand, the use of **2.45** or an analog as a ligand for enantioselective hydroformylation was considered. In addition to respectable conversion and regioselectivity, the hydroformylation of **2.73** yielded **2.75** in 19% ee (Entry 1, Table 2.6). Similar to a trend observed by Landis and coworkers[25], as the pressure of syn gas was decreased, the enantioselectivity improved, reaching 37% ee at 100 psi. (Entries 2-3, Table 2.6). Although quite low, this result suggests the possibility that a more effective scaffolding ligand can be synthesized to obtain synthetically useful enantioselectivites. Unfortunately, such a ligand has yet to be discovered.

Table 2.6 Enantioselective Hydroformylation Using **2.45**



entry	H_2/CO (psi)	conversion (%)[a]	regioselectivity[a] (prox:dist)	ee[b]
1	400	84	21:79	19
2	250	94	29:71	20
3	100	>95	23:77	37

[a] Conversion determined by ^{1}H NMR using 1,3,5-trimethoxybenzene as an internal standard.
[b] Determined by HPLC after the oxidation.

2.10 Conclusion

Through the development of a novel class of scaffolding ligands, one of the few examples of distal-selective hydroformylation of 1,2-disubstituted olefins was achieved.

[25] Watkins, A. L.; Landis, C. R. *J. Am. Chem. Soc.* **2010**, *132*, 14027 – 14029.

This methodology separates itself from other distal examples by affording high levels of diastereoselectivity for the hydroformylation products. Together with proximal-selective methods, scaffolding catalysts have become a viable approach towards solving some of the major issues plaguing hydroformylation, as well as a promising solution for other olefin functionalization reactions.

2.11 Experimental Section

2.11.1 General Considerations

Unless otherwise noted, all reagents were obtained from commercial suppliers and used without further purification. Lithium reagents were titrated against 2-pentanol using 1,10-phenanthroline as the indicator. Flash column chromatography was performed using Silicycle silica gel, SiliaFlash P60 (230-400 mesh) and ACS grade solvents as received from Fisher Scientific. All experiments were performed in oven or flame dried glassware under an atmosphere of nitrogen or argon using standard syringe and cannula techniques, except where otherwise noted. All reactions were run with dry, degassed solvents dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC). ^{1}H, ^{13}C, ^{31}P, and ^{19}F NMR were performed on either Varian Gemini 400 MHz, Varian Unity Inova 500 MHz, Varian Gemini 500 MHz, or Varian 600 MHz spectrometers. Deuterated solvents were purchased from Cambridge Isotope Labs and stored over 3Å molecular sieves. C_6D_6 was degassed by three successive freeze-pump-thaw cycles and stored over 3Å molecular sieves in a dry box under a nitrogen atmosphere. All NMR chemical shifts are reported in ppm relative to residual solvent for ^{1}H and ^{13}C and external standard (neat H_3PO_4) for ^{31}P NMR. Coupling constants are

reported in Hz. All IR spectra were gathered on a Bru5ker Alpha FT-IR equipped with a single crystal diamond ATR module and values are reported in cm^{-1}. HRMS and X-ray crystal structure data were generated in Boston College facilities. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. An Agilent Technologies 7890A gas chromatography system equipped with a 7683B Series Injector was used to introduce samples into a J&W Scientific column (HP-5, 30 m x 0.320 mm ID x 0.25 μm film thickness) or Supelco Gamma Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness). Detection was by FID and data was worked up with Agilent Technologies GC ChemStation software. Retention times are reported in minutes. Hydroformylation was performed in an Argonaut Technologies Endeavor® Catalyst Screening System using 1:1 H_2/CO supplied by Airgas, Inc.

2.11.2 Ligand Characterization

The following compounds were synthesized according to literature procedures and matched all reported spectroscopic data: (3-bromophenyl)diphenylphosphane (10212-03-0), [26] 3-(diphenylphosphanyl)benzaldehyde (50777-69-0), [27] bis(4-methoxyphenyl)phosphine oxide (15754-51-5), [28] bis(4-

[26] Boezio, A. A.; Charette, A. B.; Poupon, J-C. *Angew. Chem. Int. Ed.* **2006**, *45*, 1415 – 1420.
[27] Benet-Buchholz, J.; Escudero-Adan, E. C.; Freixa, Z.; Gulyas, H.; Rivillo, D.; Van Leeuwen, P. W. N. M. *Angew. Chem. Int. Ed.* **2007**, *46*, 7247 – 7250.
[28] Bayardon, J.; Maillard, D.; Sinou, D.; Cavazzini, M.; Pozzi, G.; Quici, S. *Tetrahedron: Asymm.* **2003**, *14*, 2215 – 2224.

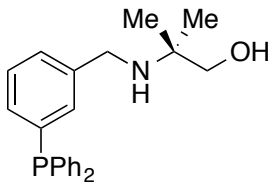
(trifluoromethyl)phenyl)phosphine oxide (15929-43-8),[29] bis(3,5-bis(trifluoromethyl)phenyl)phosphine oxide (15979-14-3).[30]

General Procedure A (Reductive Amination): To a round-bottom flask containing 4 Å molecular sieves was added the 3-phosphinobenzaldehyde (1 equivalent) and amino alcohol (1.5 – 1.7 equivalents) in THF (0.3 M relative to benzaldehyde). The solution was heated to 50 °C with vigorous stirring. After 6 hours, the molecular sieves were filtered off and the resulting mixture was concentrated to a viscous residue, which was dissolved in anhydrous methanol (0.3 M). The solution was cooled to 0 °C, sodium borohydride was added (3 equivalents), and the reaction was allowed to warm to room temperature over 2 hours. The methanol was removed under reduced pressure, the residue was diluted with dichloromethane (20 mL), and the reaction was quenched by the addition of water (10 mL) at 0 °C. The aqueous layer was extracted dichloromethane (2 x 20 mL) and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by column chromatography afforded the title compound.

General Procedure B (Ligand Closure): *N,N*-dimethylformamide dimethylacetal (5 equivalents) was added to a solution of amino alcohol from the reductive amination (1 equivalent) in freshly distilled methanol (0.1 M relative to amino alcohol) and the

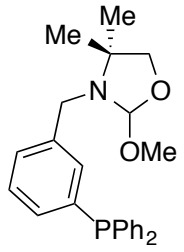
[29] McDougal, N. T; Streuff, J.; Mukherjee, H.; Virgil, S. C.; Stoltz, B. M. *Tetrahedron Lett.* **2010**, *51*, 5550 – 5554.
[30] Busaca, C. A.; Lorenz, J. C.; Grinberg, N.; Haddad, N.; Hrapchak, M.; Latli, B.; Lee, H.; Sabila, P.; Saha, A.; Sarvestani, M.; Shen, S.; Varsolona, R.; Wei, X.; Senanayake, C. H. *Org. Lett.* **2005**, *7*, 4277 – 4280.

reaction was stirred at room temperature for 3 hours. The volatiles were removed on high vacuum and the residue was re-dissolved in dry methanol (0.1 M). After stirring for 2 hours at room temperature, the volatiles were removed under vacuum. The crude residue was brought into the glovebox and extracted with dry, degassed pentane (2 x 15 mL). Removal of the pentane under vacuum afforded the title compound.



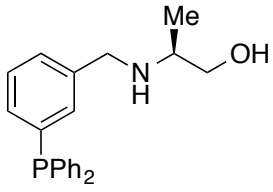
2-((3-(diphenylphosphanyl)benzyl)amino)-2-methylpropan-1-ol. Synthesized according to the General Procedure A for reductive amination. Imine formation was carried out with 3-(diphenylphosphanyl)benzaldehyde (500 mg, 1.72 mmol) and 2-amino-2-methylpropan-1-ol (250 mg, 2.97 mmol) in THF (9 mL). Reduction of the imine occurred in methanol (9 mL) with sodium borohydride (195 mg, 5.15 mmol). Purification by column chromatography (50% EtOAc/Hex containing 1% Et_3N) afforded the title compound as a colorless solid (469 mg, 76%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 – 7.35 (m, 12H), 7.26 – 7.27 (m, 1H), 7.13 – 7.16 (m, 1H), 3.63 (s, 2H), 3.30 (s, 2H), 1.10 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 141.2 (d, J_{C-P} = 7.6 Hz), 137.6 (d, J_{C-P} = 11.4 Hz), 137.4 (d, J_{C-P} = 10.5 Hz), 133.9 (d J_{C-P} = 20.0 Hz), 133.7 (d, J_{C-P} = 23.8 Hz), 132.5 (d, J_{C-P} = 16.2 Hz), 128.9, 128.8 (d, J_{C-P} = 5.7 Hz), 128.7, 128.6 (d, J_{C-P} = 6.7 Hz), 68.6, 54.2, 46.4, 24.4; ^{31}P NMR ($CDCl_3$, 202 MHz) δ – 5.4; IR: 2967, 1476, 1433, 1051, 742, 694, 467 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{23}H_{27}N_1O_1P_1$ $[M+H]^+$: 364.1830, found: 364.1837.



3-(3-(diphenylphosphanyl)benzyl)-2-methoxy-4,4-dimethyl-oxazolidine (2.42). Synthesized according to the General Procedure B using *N,N*-dimethylformamide dimethylacetal (814 μL, 6.13 mmol) and 2-((3-(diphenylphosphanyl)benzyl)amino)-2-methylpropan-1-ol (446 mg, 1.23 mmol) in freshly distilled methanol (12 mL). The closure was cycled with 12 mL anhydrous methanol. Extraction with pentane (2 x 10 mL) and removal of pentane under vacuum afforded the title compound as a colorless solid (457 mg, 92%).

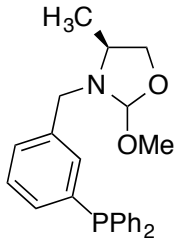
^{1}H NMR (C_6D_6, 500 MHz) δ 7.57 (d, 1H, J = 7.8 Hz), 7.43 (dt, 4H, J = 7.8, 1.5 Hz), 7.31 – 7.34 (m, 1H), 7.28 (d, 1H, J = 7.3 Hz), 7.03 – 7.12 (m, 7H), 5.16 (s, 1H), 3.65 (d, 1H, J = 4.9 Hz), 3.63 (d, 1H, J = 11.7 Hz), 3.51 (d, 1H, J = 7.3 Hz), 3.43 (d, 1H, J = 14.1 Hz), 3.01 (s, 3H), 0.90 (s, 3H), 0.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 140.2 (d, $J_{C\text{-}P}$ = 6.9 Hz), 137.5 (d, $J_{C\text{-}P}$ = 9.2 Hz), 137.0 (d, $J_{C\text{-}P}$ = 10.7 Hz), 134.2 (d, $J_{C\text{-}P}$ = 19.8 Hz), 133.9 (d, $J_{C\text{-}P}$ = 19.1 Hz), 133.3 (d, $J_{C\text{-}P}$ = 19.8 Hz), 129.4, 128.9, 128.7 (d, $J_{C\text{-}P}$ = 6.7 Hz), 128.6 (d, $J_{C\text{-}P}$ = 6.7 Hz), 128.6 (d, $J_{C\text{-}P}$ = 6.9 Hz), 112.2, 78.5, 59.5, 51.0, 47.1, 24.4, 22.9; ^{31}P NMR (C_6D_6 , 202 MHz) δ – 5.4; IR: 2965, 2877, 1726, 1476, 1433, 1387, 1323, 1245, 1092, 1076, 1039, 940, 743, 695, 495 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{25}H_{29}N_1O_2P_1$ $[M+H]^+$: 406.1936, found: 406.1918.



(*S*)-2-((3-(diphenylphosphanyl)benzyl)amino)propan-1-ol. Carried out according to General Procedure A. The imine was synthesized from 3-(diphenylphosphanyl)benzaldehyde (600 mg, 2.07 mmol) and (*S*)-2-aminopropan-1-ol (202 mg, 2.69 mmol) in tetrahydrofuran (7 mL).

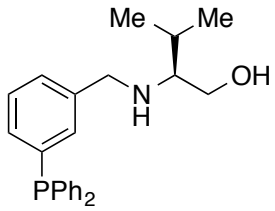
Reduction occurred in anhydrous methanol (7 mL) with sodium borohydride (235 mg, 6.21 mmol). Purification using silica gel chromatography (1% Et_3N/EtOAc) afforded the title compound as a colorless oil (456 mg, 64%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 – 7.35 (m, 12H), 7.27 – 7.26 (m, 1H), 7.15 – 7.18 (m, 1H), 3.82 (d, 1H, J = 13.2 Hz), 3.70 (d, 1H, J = 13.2 Hz), 3.54 – 3.57 (m, 1H), 3.22 (dd, 1H, J = 10.8, 6.9 Hz), 2.76 – 2.80 (m, 1H), 1.04 (s, 3H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 140.8 (d, $J_{C\text{-}P}$ = 7.6 Hz), 137.6 (d, $J_{C\text{-}P}$ = 11.5 Hz), 137.4 (d, $J_{C\text{-}P}$ = 10.7 Hz), 133.9 (d, $J_{C\text{-}P}$ = 19.8 Hz), 133.6 (d, $J_{C\text{-}P}$ = 22.9 Hz), 132.6 (d, $J_{C\text{-}P}$ = 16.8 Hz), 128.9, 128.8 (d, $J_{C\text{-}P}$ = 6.1 Hz), 128.7, 128.6 (d, $J_{C\text{-}P}$ = 6.7 Hz), 65.7, 53.9, 51.1, 17.4; ^{31}P NMR ($CDCl_3$, 202 MHz) δ – 5.4; IR: 3299, 2967, 2870, 1477, 1435, 1214, 1172, 1118m 1091, 1027, 998, 745, 726, 696, 541 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{22}H_{25}N_1O_1P_1$ $[M+H]^+$: 350.1674, found: 350.1685; $[\alpha]_D^{20}$ = + 6.72 (c = 0.600, $CHCl_3$, l = 50 mm).



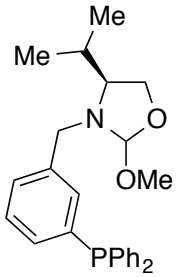
(4*S*)-3-(3-(diphenylphosphanyl)benzyl)-2-methoxy-4-methyloxazolidine (2.43). Synthesized using General Procedure B with (*S*)-2-((3-(diphenylphosphanyl)benzyl)amino)propan-1-ol (355 mg, 1.03 mmol), freshly distilled methanol (15 mL) and *N,N*-dimethylformamide dimethylacetal (684 μL, 5.15 mmol). Extraction with pentane (2 x 10 mL) and removal of the volatiles under reduced pressure to afforded the title compound as a viscous oil as a 1:1 mixture of diastereomers (325 mg, 81 %).

^{1}H NMR (C_6D_6, 500 MHz) δ 7.64 (d, 0.5H, J = 8.3 Hz), 7.50 (d, 0.5H, J = 7.8 Hz), 7.41-7.44 (m, 4H), 7.30 – 7.34 (m, 1.5H), 7.20 (d, 0.5H, J = 7.8 Hz), 7.03 – 7.16 (m, 7H), 5.22 (s, 0.5H), 5.10 (s, 0.5H), 3.97 (t, 0.5H, J = 7.3 Hz), 3.75 (d, 0.5H, J = 13.2 Hz), 3.70 (dd, 0.5H, J = 7.6, 6.6 Hz), 3.59 (t, 1H, J = 13.7 Hz), 3.36 – 3.43 (s, 1.5H), 3.12 (s, 1.5H), 3.05 – 3.09 (m, 0.5H), 3.01 (s, 1.5H), 2.67 – 2.73 (m, 0.5H), 0.74 (d, 1.5H, J = 6.0 Hz), 0.70 (d, 1.5H, J = 6.0 Hz); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 139.3 (d, J_{C-P} = 7.6 Hz), 138.7 (d, J_{C-P} = 6.9 Hz), 137.1 – 137.6 (11 signals), 133.8 – 134.5 (8 signals), 132.7 (d, J_{C-P} = 19.0 Hz), 132.5 (d, J_{C-P} = 17.5 Hz), 128.9, 128.8 (d, J_{C-P} = 1.5 Hz), 128.7 (d, J_{C-P} = 6 .1 Hz), 128.6 (d, J_{C-P} = 6.9 Hz), 113.5, 110.3, 72.8, 72.1, 56.8, 54.0, 53.3, 52.6, 50.8, 49.4, 17.3, 17.0; ^{31}P NMR (C_6D_6, 202 MHz) δ – 5.4, – 5.5; IR: 2966, 2886, 1477, 1434, 1345, 1289, 1156, 1064, 744, 697, 495 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{24}H_{27}N_1O_2P_1$ $[M+H]^+$: 392.1779, found: 392.1782; $[\alpha]_D^{20}$ = + 32.9 (c = 0.465, $CHCl_3$, l = 50 mm).



(*S*)-2-((3-(diphenylphosphanyl)benzyl)amino)-3-methylbutan-1-ol. A solution of (*S*)-2-amino-3-methylbutan-1-ol (1.97 g, 19.1 mmol) and 3-(diphenylphosphanyl)benzaldehyde (3.69 g, 12.7 mmol) in DCM (100 mL) was stirred at room temperature for 3 hours. Triethylamine (2.7 mL, 19 mmol) and $NaBH(OAc)_3$ (5.38 g, 25.4 mmol) were added to the flask and the reaction as allowed to stir at room temperature overnight. The reaction was partitioned between water (70 mL) and DCM (150 mL). The organic layer was washed with an additional portion of water (70 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (1% Et_3N/EtOAc) to afford the title compound as a colorless oil (4.18 g, 88%).

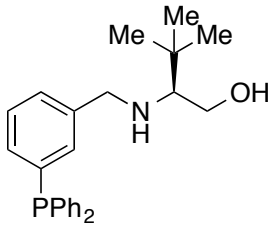
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 – 7.35 (m, 13 H), 7.15 – 7.19 (m, 1H), 3.78 (d, 1H, *J* = 13.0 Hz), 3.71 (d, 1H, *J* = 13.5 Hz), 3.59 (dd, 1H, *J* = 10.5, 4.0 Hz), 3.33 (dd, 1H, *J* = 11.0, 4.0 Hz), 2.38 – 2.42 (m, 1H), 1.80 – 1.85 (m, 1H), 0.92 (d, 3H, *J* = 7.0 Hz), 0.87 (d, 3H, *J* = 7.0 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 140.9 (d, $J_{C\text{-}P}$ = 7.9 Hz), 137.7 (d, $J_{C\text{-}P}$ = 11.2 Hz), 137.4 (d, $J_{C\text{-}P}$ = 2.2 Hz), 137.3, 133.9 (d, $J_{C\text{-}P}$ = 19.1 Hz), 133.7 (d, $J_{C\text{-}P}$ = 21.3), 132.6 (d, $J_{C\text{-}P}$ = 16.8 Hz), 128.9 (d, $J_{C\text{-}P}$ = 11.2 Hz), 128.9 (d, $J_{C\text{-}P}$ = 5.6 Hz), 128.7 (d, $J_{C\text{-}P}$ = 6.7 Hz), 63.9, 60.6, 51.4, 29.0, 19.8, 18.6; ^{31}P NMR ($CDCl_3$, 202 MHz) δ – 5.4; IR: 3367, 2957, 2872, 1586, 1476, 1434, 1180, 1092, 1042, 998, 788, 744, 696, 497 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{24}H_{29}N_1O_1P_1$ $[M+H]^+$: 378.1987, found: 378.1975; $[\alpha]_D^{20}$ = + 3.86 (*c* = 0.680, $CHCl_3$, *l* = 50 mm).



(4*S*)-3-(3-(diphenylphosphanyl)benzyl)-4-isopropyl-2-methoxyoxazolidine (2.44). Followed General Procedure B with (*S*)-2-((3-(diphenylphosphanyl)benzyl)amino)-3-methylbutan-1-ol (1.23 g, 3.28 mmol), freshly distilled methanol (32 mL) and *N,N*-dimethylformamide dimethylacetal (2.2 mL 16 mmol). Extraction with pentane (2 x 20 mL) and removal of the volatiles were removed under vacuum yielded the pure product as a colorless oil that exists as a 1:1 mixture of diastereomers (1.09 g, 80%).

^{1}H NMR (C_6D_6, 500 MHz) δ 7.58 (d, 0.5H, *J* = 7.8 Hz), 7.47 (d, 0.5H, *J* = 7.8 Hz), 7.40-7.37 (m, 4H), 7.33-7.27 (m, 1.5H), 7.20 (d, 0.5H, *J* = 7.8 Hz), 7.09-6.99 (m, 7H), 5.15 (s, 0.5H), 5.04 (s, 0.5H), 3.86 (dd, 0.5H, *J* = 8.3, 7.8 Hz), 3.83 (d, 0.5H, *J* = 13.2 Hz), 3.69

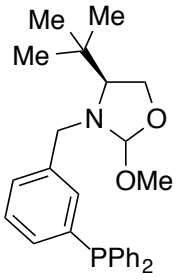
(dd, 0.5H, J = 7.3, 7.8 Hz), 3.64 (dd, 0.5H, J = 7.8, 5.9 Hz), 3.63 (d, 0.5H, J = 10.0 Hz), 3.54 (dd, 1H, J = 14.7, 13.2 Hz), 3.40 (d, 0.5H, J = 14.2 Hz), 3.01 (s, 1.5H), 2.95 (s, 1.5H), 2.94 – 2.90 (m, 0.5H), 2.44 (app q, 0.5H, J = 7.3 Hz), 1.56-1.49 (m, 1H), 0.74 (d, 1.5H, J = 6.9 Hz), 0.65 (d, 1.5H, J = 3.4 Hz), 0.63 (d, 1.5H, J = 3.4 Hz), 0.57 (d, 1.5H, J = 6.9 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 139.6 (d, J_{C-P} = 6.7 Hz), 139.2 (d, J_{C-P} = 6.7 Hz), 137.2 – 137.5 (6 signals), 134.5 (d, J_{C-P} = 9.5 Hz), 134.3 (d, J_{C-P} =10.5 Hz), 133.9 (d, J_{C-P} = 20.0 Hz), 132.9 (d, J_{C-P} = 20.0 Hz), 132.6 (d, J_{C-P} = 19.1 Hz), 129.6 (d, J_{C-P} = 19.1 Hz), 128.9, 128.7 (d, J_{C-P} = 6.7 Hz), 128.6 (d, J_{C-P} = 13.4 Hz), 114.6, 110.6, 68.4, 67.5, 66.0, 63.6, 57.0, 52.9, 51.4, 50.1, 31.1, 28.6, 20.4, 19.6, 17.7, 15,5; ^{31}P NMR (C_6D_6, 202 MHz) δ – 5.4, – 5.5; IR: 3069, 2929, 2279, 1884, 1817, 1585, 1364, 1155, 1057, 744, 697, 494 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{26}H_{31}N_1O_2P_1$ $[M+H]^+$: 420.2092, found: 420.2099; $[\alpha]_D^{20}$ = + 34.7 (c = 0.480, $CHCl_3$, l = 50 mm).



(*S*)-2-((3-(diphenylphosphanyl)benzyl)amino)-3,3-dimethylbutan-1-ol. Followed General Procedure A using (*S*)-2-amino-3,3-dimethylbutan-1-ol (884 mg, 7.54 mmol), 3-(diphenylphosphanyl)benzaldehyde (1.46 g, 5.03 mmol) and THF (18 mL). The imine was reduced with $NaBH_4$ (382 mg, 10.1 mmol) in anhydrous methanol (18 mL). Silica gel column chromatography (100 % EtOAc) to afford the title compound as a colorless oil (1.27 g, 64%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.28 – 7.34 (m, 13H), 7.17 – 7.18 (m, 1H), 3.83 (d, 1H, J = 13.2 Hz), 3.79 (d, 1H, J = 12.7 Hz), 3.60 (dd, 1H, J = 10.7, 4.9 Hz), 3.37 (dd, 1H, J =

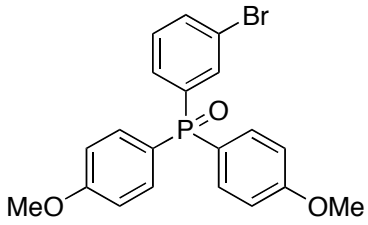
10.7, 6.4 Hz), 2.30 – 2.32 (m, 1H), 0.90 (s, 9H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 140.9 (d, $J_{C\text{-}P}$ = 6.7 Hz), 137.8 (d, $J_{C\text{-}P}$ = 11.5 Hz), 137.3 (d, $J_{C\text{-}P}$ = 10.5 Hz), 133.9 (d, $J_{C\text{-}P}$ = 20.0 Hz), 133.7 (d, $J_{C\text{-}P}$ = 21.9 Hz), 132.7 (d, 18.1 Hz), 129.0, 128.9 (d, $J_{C\text{-}P}$ = 6.7 Hz), 128.8, 128.7 (d, $J_{C\text{-}P}$ = 7.6 Hz), 67.1, 60.2, 54.1, 34.6, 27.0; ^{31}P NMR ($CDCl_3$, 202 MHz) δ – 5.4; IR: 3338, 2952, 2867, 1476, 1434, 1413, 1091, 1043, 1026, 997, 788, 743, 695, 495 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{25}H_{31}N_1O_1P_1$ $[M+H]^+$: 392.2143, found: 394.2148; $[\alpha]_D^{20}$ = − 0.873 (*c* = 0.655, $CHCl_3$, *l* = 50 mm).



(4*S*)-4-(*tert*-butyl)-3-(3-(diphenylphosphanyl)benzyl)-2-methoxyoxazolidine (2.45). Synthesized according to General Procedure B with *N,N*-dimethylformamide dimethylacetal (2.00 mL, 14.9 mmol), (*S*)-2-((3-(diphenylphosphanyl)benzyl)amino)-3,3-dimethylbutan-1-ol (1.17 g, 2.99 mmol) and methanol (30 mL). Extraction and removal of the volatiles under vacuum yielded a pale yellow oil that exists as a 1:1 mixture of diastereomers (1.10 g, 84%).

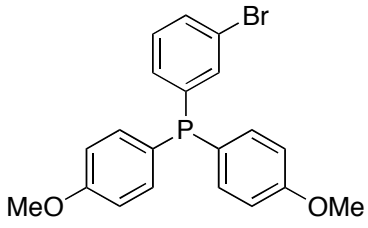
^{1}H NMR (C_6D_6, 500 MHz) δ 7.66 (d, 0.5H, *J* = 7.3 Hz), 7.59 (d, 0.5H, *J* = 7.3 Hz), 7.41 – 7.45 (m, 4H), 7.31 – 7.37 (m, 1H), 7.03 – 7.14 (m, 8H), 5.05 (s, 0.5H), 5.03 (s, 0.5H), 4.16 (d, 0.5H, *J* = 13.6 Hz), 3.90 – 3.93 (m, 0.5H), 3.82 (d, 0.5H, *J* = 13.7 Hz), 3.73 – 3.78 (m, 1H), 3.69 (dd, 0.5H, *J* = 8.3, 2.4 Hz), 3.61 (d, 1H, *J* = 6.9 Hz), 2.92 (s, 1.5H), 2.91 (s, 1.5H), 2.51 – 2.54 (m, 0.5H), 2.48 – 2.51 (m, 0.5H), 0.78 (s, 4.5H), 0.77 (s, 4.5H); ^{13}C NMR ($CDCl_3$, 101 MHz) δ 140.2 (d, $J_{C\text{-}P}$ = 6.1 Hz), 140.0 (d, $J_{C\text{-}P}$ = 6.1 Hz), 137.6 (d, $J_{C\text{-}P}$ =10.7 Hz), 137.4 (d, $J_{C\text{-}P}$ = 4.6 Hz), 137.3 (d, $J_{C\text{-}P}$ = 3.8 Hz), 137.1 (d, $J_{C\text{-}P}$

= 17.7 Hz), 133.6 – 134.3 (7 signals), 132.9 (d, J_{C-P} = 21.4 Hz), 132.5 (d, J_{C-P} = 22.1 Hz), 129.3, 128.9 (d, J_{C-P} = 6.9 Hz), 128.8, 128.7 (d, J_{C-P} = 6.9 Hz), 128.4 (d, J_{C-P} = 7.0 Hz), 115.6, 110.5, 73.1, 68.5, 66.5, 65.4, 60.1, 53.0, 52.4, 52.3, 35.3, 33.8, 26.9, 26.4; ^{31}P NMR (C_6D_6, 202 MHz) δ – 5.6; IR: 2953, 2898, 1477, 1437, 1393, 1360, 1198, 1141, 1085, 1065, 998, 946, 744, 696, 496 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{27}H_{33}N_1O_2P_1$ $[M+H]^+$: 434.2249, found: 434.2232; $[\alpha]_D^{20}$ = + 25.2 (*c* = 0.495, $CHCl_3$, *l* = 50 mm).



(3-bromophenyl)bis(4-methoxyphenyl)phosphine oxide. To a 100 mL, flame-dried, round-bottom flask in the glovebox was added bis(dibenzylideneacetone)palladium (317 mg, 0.552 mmol) and 1,3-bis(diphenylphosphino)propane (228 mg, 0.552 mmol). The flask was fitted with a dry reflux condenser, and the apparatus was brought out of the glovebox and placed under argon. Toluene (22 mL), bis(4-methoxyphenyl)phosphine oxide (4.00 g, 15.3 mmol), 1-bromo-3-iodobenzene (2.35 mL, 18.4 mmol), and Hunig's base (3.37 mL, 19.3 mmol) were added to the flask successively. The reaction was heated to reflux overnight. After being cooled to room temperature, the crude mixture was partitioned between water (20 mL) and ethyl acetate (70 mL). The layers were separated and the aqueous layer was extracted with an additional portion of ethyl acetate (50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel chromatography (2% Et_3N/EtOAc) to afford an off white solid (3.31 g, 52%).

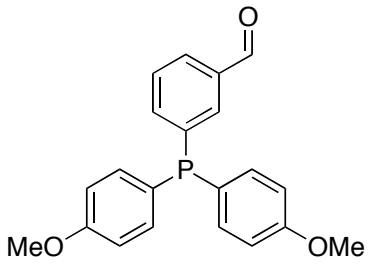
^{1}H NMR ((CD$_3$)$_2$CO, 500 MHz) δ 7.81 (d, 1H, J = 11.7 Hz), 7.76 (d, 1H, J = 7.8 Hz), 7.65 (s, 1H), 7.61 (app dd, 4H, J = 11.3 Hz, 8.8 Hz), 7.46 – 7.50 (app dt, 1H, J = 7.8 Hz, 2.9 Hz), 7.09 (app dd, 4H, J = 8.8 Hz, 2.0 Hz), 3.87 (s, 6H); ^{13}C NMR (CDCl$_3$, 126 MHz) δ 162.8 (d, J_{C-P} = 2.7 Hz), 136.5 (d, J_{C-P} = 101 Hz), 134.8 (d, J_{C-P} = 2.9 Hz), 134.4 (d, J_{C-P} = 10.5 Hz), 133.7 (d, J_{C-P} = 11.4 Hz), 130.6 (d, J_{C-P} = 8.6 Hz), 130.2 (d, J_{C-P} = 13.4 Hz), 123.4 (d, J_{C-P} = 112 Hz), 123.2 (d, J_{C-P} = 14.3 Hz), 114.3 (d, J_{C-P} = 13.4 Hz), 55.5; ^{31}P NMR (CDCl$_3$, 202 MHz) δ + 27.5; IR: 1595, 1502, 1254, 1177, 1118, 802, 547 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{20}H_{19}Br_1O_3P_1$ $[M+H]^+$: 417.0255, found: 417.0249.



(3-bromophenyl)bis(4-methoxyphenyl)phosphine. To a solution of (3-bromophenyl)bis(4-methoxyphenyl)-phosphine oxide (3.22 g, 7.72 mmol) in toluene (77 mL) was added triethylamine (5.90 mL, 42.5 mmol). The solution was cooled to 0 °C and trichlorosilane (3.90 mL, 38.6 mmol) was added slowly to the stirring solution. The flask was fitted with a reflux condenser and the solution was heated to reflux overnight. The reaction was cooled to 0 °C and quenched by the addition of 30% NaOH (40 mL). The aqueous layer was extracted with dichloromethane (2 x 50 mL) and the combined organic layers were washed with an additional portion of water (30 mL). The organic layer was dried over $MgSO_4$, filtered, and concentrated to yield an opaque oil that was used in the next step without purification (3.00 g, 97%).

^{1}H NMR (CDCl$_3$, 500 MHz) δ 7.41 – 7.43 (m, 1H), 7.34 (d, 1H, J = 6.5 Hz), 7.24 – 7.27 (m, 5H), 7.16 – 7.18 (m, 1H), 6.90 (d, 4H, J = 8.5 Hz), 3.81 (s, 6H); ^{13}C NMR (CDCl$_3$,

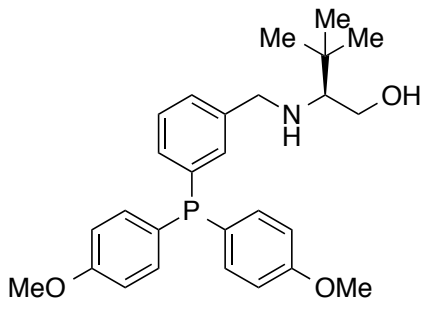
126 MHz) δ 160.6, 142.3 (d, J_{C-P} = 15.3 Hz), 135.6 (d, J_{C-P} = 21.9 Hz), 135.5 (d, J_{C-P} = 19.1 Hz), 131.7 (d, J_{C-P} = 19.1 Hz), 131.4, 130.1 (d, J_{C-P} = 5.7 Hz), 127.6 (d, J_{C-P} = 7.6 Hz), 123.2 (d, J_{C-P} = 6.7 Hz), 114.6 (d, J_{C-P} = 8.6 Hz), 55.4; ^{31}P NMR ($CDCl_3$, 202 MHz) δ – 7.8; IR: 1596, 1500, 1255, 1179, 1120, 829, 548 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{20}H_{19}Br_1O_2P_1$ $[M+H]^+$: 401.0306, found: 401.0291.



3-(bis(4-methoxyphenyl)phosphino)benzaldehyde. To a -78 °C solution of (3-bromophenyl)bis(4-methoxyphenyl)phosphine (3.23 g, 8.05 mmol) in THF (81 mL) was added *n*-BuLi (3.63 mL, 8.86 mmol, 2.44 M solution in hexanes). After stirring at this temperature for 50 minutes, DMF (1.20 mL, 16.1 mmol) was added and the resulting solution was warmed to room temperature over 4 hours. The reaction was quenched by the addition of saturated ammonium chloride (60 mL) and extracted with ethyl acetate (150 mL). The organic layer was extracted with an additional portion of water (40 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification of the crude reaction mixture on silica gel (15% EtOAc/Hex) afforded the title compound as a colorless oil (1.53 g, 57%).

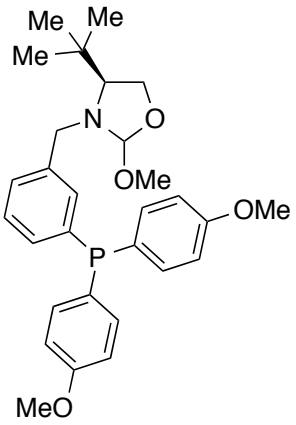
^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.93 (s, 1H), 7.81 (d, 1H, J = 6.8 Hz), 7.74 (d, 1H, J = 6.8 Hz), 7.45 – 7.51 (m, 2H), 7.25 – 7.29 (m, 4H), 6.91 (d, 4H, J = 8.3 Hz), 3.82 (s, 6H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 192.4, 160.8, 141.1 (d, J_{C-P} = 13.4 Hz), 138.9 (d, J_{C-P} = 18.1 Hz), 136.5 (d, J_{C-P} = 4.8 Hz), 135.6 (d, J_{C-P} = 21.0 Hz), 134.8 (d, J_{C-P} = 19.1 Hz), 129.2 (d, J_{C-P} = 5.7 Hz), 129.0, 127.4 (d, J_{C-P} = 7.6 Hz), 114.6 (d, J_{C-P} = 8.6 Hz), 55.4; ^{31}P

NMR ($CDCl_3$, 202 MHz) δ – 8.8; IR: 1698, 1594, 1498, 1287, 1250, 1178, 828 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{21}H_{20}O_3P_1$ $[M+H]^+$: 351.1150, found: 351.1146.



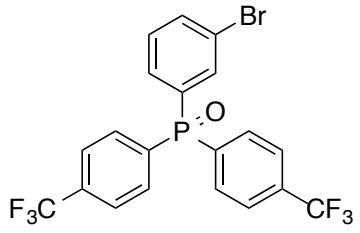
(*S*)-2-((3-(bis(4-methoxyphenyl)phosphanyl)-benzyl)amino)-3,3-dimethylbutan-1-ol. Followed General Procedure A. Imine formation was carried out with (*S*)-2-amino-3,3-dimethylbutan-1-ol (216 mg, 1.84 mmol) and 3-(bis(4-methoxyphenyl)-phosphino)benzaldehyde (322 mg, 0.920 mmol). The imine was reduced with $NaBH_4$ (104 mg, 2.76 mmol) in anhydrous methanol. Work-up and silica gel chromatography of the resulting crude reside (1% Et_3N/EtOAc) to gave the title compound as a colorless oil (172 mg, 41%).

^1H NMR ($CDCl_3$, 500 MHz) δ 7.20 – 7.28 (m, 7H), 7.11 – 7.14 (m, 1H), 6.88 (d, 4H, J = 8.8 Hz), 3.83 (d, 1H, J = 13.1 Hz), 3.80 (s, 6H), 3.78 (d, 1H, J = 12.8 Hz), 3.60 (dd, 1H, J = 10.7, 4.9 Hz), 3.38 (dd, 1H, J = 10.7, 5.9 Hz), 2.30 – 2.32 (m, 1H), 0.91 (s, 9H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 160.5, 140.8 (d, J_{C-P} = 6.9 Hz), 139.2 (3, J_{C-P} = 11.6 Hz), 135.5 (d, J_{C-P} = 20.8 Hz), 133.0 (d, J_{C-P} = 20.8 Hz), 132.1 (d, J_{C-P} = 17.3 Hz), 128.7 (d, J_{C-P} = 5.8 Hz), 128.4, 128.3, 114.4 (d, J_{C-P} = 6.9 Hz), 67.1, 60.2, 55.4, 54.1, 34.6, 27.5; ^{31}P NMR ($CDCl_3$, 202 MHz) δ – 8.6; IR: 3376, 2954, 2869, 1594, 1497, 1402, 1364, 1285, 1177, 1095, 1030, 827, 796, 531 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{27}H_{35}N_1O_3P_1$ $[M+H]^+$: 452.2355, found: 452.2373; $[\alpha]_D^{20}$ = − 2.89 (c = 0.485, $CHCl_3$, l = 50 mm).



(4*S*)-3-(3-(bis(4-methoxyphenyl)phosphanyl)benzyl)-4-(*tert*-butyl)-2-methoxyoxazolidine (2.46). Synthesized according to General Procedure B using *N,N*-dimethylformamide dimethylacetal (254 μL, 1.91 mmol), and (*S*)-2-((3-(bis(4-methoxyphenyl)phosphanyl)benzyl)amino)-3,3-dimethylbutan-1-ol (172 mg, 0.381 mmol) in methanol (5.5 mL). Extraction in the glovebox with degassed pentane (2 x 10 mL) and removal of the volatiles under reduced pressure gave the title compound as a viscous oil (167 mg, 89 %).

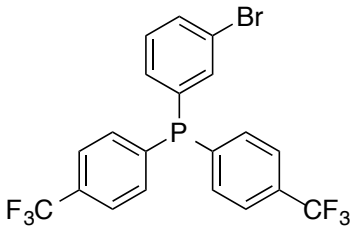
^{1}H NMR (C_6D_6, 600 MHz) δ 7.70 (d, 0.6H, J = 7.3 Hz), 7.62 (d, 0.6H, J = 7.8 Hz), 7.37 – 7.47 (m, 5H), 7.12 – 7.20 (m, 1.8H), 6.73 – 6.76 (m, 4H), 5.10 (s, 0.6H), 5.08 (s, 0.4H), 4.22 (d, 0.4H, J = 13.7 Hz), 3.93 (t, 0.4H, J = 8.1 Hz), 3.87 (d, 0.4H, J = 13.7 Hz), 3.75 – 3.81 (m, 1.2H), 3.70 (dd, 0.4H, J = 8.3, 2.4 Hz), 3.65 (d, 1.2H, J = 5.4 Hz), 3.24 (s, 3.6H), 3.23 (s, 2.4H), 2.95 (s, 3H), 2.56 (dd, 0.4H, J = 7.8, 2.4 Hz), 2.52 (t, 0.6H, J = 8.3 Hz), 0.81 (s, 5.4H), 0.79 (s, 3.6H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 160.5, 139.9 (d, $J_{C\text{-}P}$ = 5.8 Hz), 139.8 (d, $J_{C\text{-}P}$ = 5.8 Hz), 138.8 (d, $J_{C\text{-}P}$ = 10.4 Hz), 138.5 (d, $J_{C\text{-}P}$ = 9.2 Hz), 135.5 (d, $J_{C\text{-}P}$ = 20.8 Hz), 135.4 (d, $J_{C\text{-}P}$ = 20.8 Hz), 135.1 (d, $J_{C\text{-}P}$ = 8.4 Hz), 133.6 (d, $J_{C\text{-}P}$ = 17.3 Hz), 133.1 (d, $J_{C\text{-}P}$ = 17.3 Hz), 132.2 (d, $J_{C\text{-}P}$ = 20.8 Hz), 131.8 (d, $J_{C\text{-}P}$ = 20.8 Hz), 128.5 – 128.8 (7 signals), 128.3 (d, $J_{C\text{-}P}$ = 8.1 Hz), 115.6, 114.4 (d, $J_{C\text{-}P}$ = 8.1 Hz), 110.5, 73.1, 68.5, 66.6, 65.4, 60.2, 55.4, 53.1, 52.4, 52.3, 35.3, 33.8, 26.8, 26.4; ^{31}P NMR (C_6D_6, 202 MHz) δ – 8.7; IR: 2952, 2900, 1593, 1496, 1461, 1304, 1283, 1244, 1094, 1063, 1030, 826, 796, 530 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{29}H_{37}N_1O_4P_1$ $[M+H]^+$: 494.2460, found: 494.2445; $[\alpha]_D^{20}$ = + 20.8 (c = 0.570, $CHCl_3$, l = 50 mm).



(3-bromophenyl)bis(4-(trifluoromethyl)phenyl)-phosphine oxide. To a flame-dried, 25-mL, round-bottom flask in a dry box was added bis(4-(trifluoromethyl)phenyl)phosphine oxide (1.50 g, 4.44 mmol), bis(dibenzylideneacetone)palladium (926 mg, 0.160 mmol), and 1,3-bis(diphenylphosphino)propane (660 mg, 0.160 mmol). The flask was brought out of the dry box and was placed under nitrogen. The flask was charged, successively, with toluene (5 mL), 3-bromo-1-iodobenzene (0.682 mL, 5.35 mmol), and *N,N*-diisopropylethylamine (1.01 mL, 5.62 mmol) and the reaction was heated to reflux overnight. The reaction was cooled to room temperature and was partitioned between water (20 mL) and DCM (40 mL). The aqueous layer was washed with an additional portion of DCM (40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by silica gel chromatography (20% EtOAc/Hex containing 1% Et_3N) to yield the title compound as colorless solid (1.91 g, 88%).

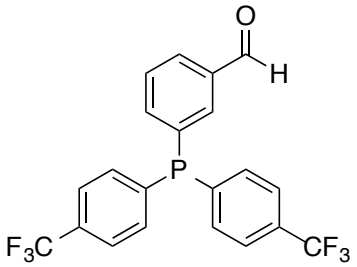
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 – 7.83 (m, 10H), 7.56 (dd, 1H, J = 12.0, 8.0 Hz), 7.39 (dt, 1H, J = 8.0, 3.5 Hz); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 136.1 (d, $J_{C\text{-}P}$ = 3.1 Hz), 135.7 (d, $J_{C\text{-}P}$ = 103.0 Hz), 134.7 (d, $J_{C\text{-}P}$ = 10.7 Hz), 134.6 (dq, $J_{C\text{-}P,F}$ = 32.8, 3.1 Hz), 133.7 (d, $J_{C\text{-}P}$ = 103.0 Hz), 132.7 (d, $J_{C\text{-}P}$ = 10.7 Hz), 130.8 (d, $J_{C\text{-}P}$ = 13.0 Hz), 130.6 (d, $J_{C\text{-}P}$ = 9.9 Hz), 126.0 – 126.1 (m), 123.9 (d, $J_{C\text{-}P}$ = 15.3 Hz), 123.6 (d, $J_{C\text{-}F}$ = 273 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ – 63.8; ^{31}P NMR ($CDCl_3$, 202 MHz) δ + 25.3; IR: 3057, 1611,

1504, 1321, 1128, 1062, 836, 766, 685, 572 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{20}H_{13}Br_1F_6O_1P_1$ $[M+H]^+$: 492.9713, found: 492.9792.



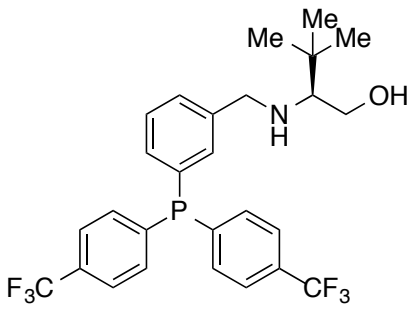
(3-bromophenyl)bis(4-(trifluoromethyl)phenyl)-phosphane. To a flame-dried flask was added (3-bromophenyl)bis(4-(trifluoromethyl)phenyl)phosphine oxide (1.00 g, 2.03 mmol), Et_3N (1.57, 11.2 mmol), and toluene (20 mL). The solution was cooled to 0 °C and trichlorosilane was added dropwise. The flask was fitted with a reflux condenser and the reaction was heated to reflux overnight. The solution was cooled to room temperature, quenched by the addition of 30% NaOH (30 mL), and further diluted with water (10 mL). The aqueous layer was extracted with DCM (3 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Silica gel chromatography (20% EtOAc/Hex) afforded the title compound as a colorless oil (932 mg, 95%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.63 (d, 4H, J = 8.0 Hz), 7.55 (d, 1H, J = 8.0 Hz), 7.45 (d, 1H, J = 7.5 Hz), 7.40 (t, 4H, J = 8.0 Hz), 7.21 – 7.22 (m, 2H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 140.6 (d, J_{C-P} = 13.7 Hz), 137.9 (d, J_{C-P} =14.4 Hz), 136.3 (d, J_{C-P} = 22.0 Hz), 133.8 (d, J_{C-P} = 19.8 Hz), 133.0, 132.5 (d, J_{C-P} = 19.5 Hz), 131.4 (q, J_{C-P} = 33.0 Hz), 130.5 (d, J_{C-P} = 6.8 Hz), 128.8 (d, J_{C-P} = 24.8 Hz), 125.6 – 125.6 (m), 125.2 (q, J_{C-F} = 272 Hz), 123.5 (d, J_{C-P} = 8.4 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ – 62.9; ^{31}P NMR ($CDCl_3$, 202 MHz) δ – 5.3; IR: 1606, 1396, 1166, 1106, 831, 781, 686 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{20}H_{13}Br_1F_6P_1$ $[M+H]^+$: 476.9842, found: 476.9842.



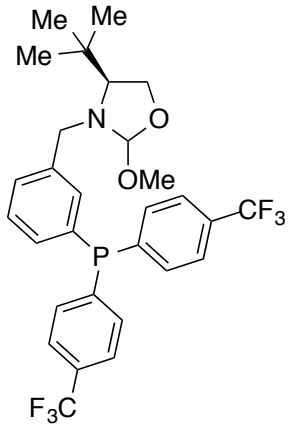
3-(bis(4-(trifluoromethyl)phenyl)phosphanyl)benz-aldehyde. To a flame-dried, round-bottom flask was added (3-bromophenyl)-bis((4-trifluoromethyl)phenyl)phosphine (789 mg, 1.84 mmol) and THF (10 mL). The solution was cooled to – 78 °C, *n*-BuLi (0.884 mL, 2.21 mmol, 2.50 M solution in hexanes) was added dropwise, and the reaction was stirred for 30 minutes at this temperature. *N,N*-dimethylformamide (0.226 mL, 23.0 mL) was added to the solution and the cold bath was removed. The reaction continued to stir at room temperature for 2 hours and was quenched by the addition of water (10 mL). The aqueous layer was extracted with DCM (3 x 15 mL). The combined organic layers were dried over $MgSO_4$, filtered, a concentrated *in vacuo*. The crude reaction was purified by silica gel chromatography (10% EtOAc/Hex) to afford the title compound as a colorless oil (371 mg, 47%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 9.98 (s, 1H), 7.92 (d, 1H, J = 7.3 Hz), 7.86 (d, 1H, J = 7.8 Hz), 7.64 (d, 4H, J = 7.8 Hz), 7.53 – 7.58 (m, 2H), 7.41 (t, 4H, J = 7.6 Hz); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 191.8, 140.7 (d, $J_{C\text{-}P}$ = 14.3 Hz), 139.6 (d, $J_{C\text{-}P}$ = 19.1 Hz), 137.2 (d, $J_{C\text{-}P}$ = 14.3 Hz), 137.0 (d, $J_{C\text{-}P}$ = 6.7 Hz), 135.3 (d, $J_{C\text{-}P}$ = 22.9 Hz), 134.1 (d, $J_{C\text{-}P}$ = 20.2 Hz), 131.7 (q, $J_{C\text{-}F}$ = 32.4 Hz), 130.8, 129.9 (d, $J_{C\text{-}P}$ = 5.7 Hz), 125.7 – 125.9 (m), 124.0 (q, $J_{C\text{-}F}$ = 273 Hz); ^{19}F NMR ($CDCl_3$, 470 MHz) δ – 62.9; ^{31}P NMR ($CDCl_3$, 202 MHz) δ – 6.1; IR: 3062, 2852, 2302, 1926, 1701, 1397, 1124, 1060, 1016, 794, 600 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{21}H_{14}F_6O_1P_1$ $[M+H]^+$: 427.0687, found: 427.0683.



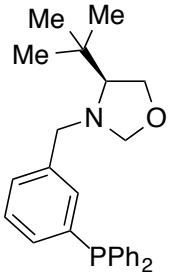
(*S*)-2-((3-(bis(4-(trifluoromethyl)phenyl)-phosphanyl)benzyl)amino)-3,3-dimethylbutan-1-ol. Synthesized according to General Procedure A using (*S*)-2-amino-3,3-dimethylbutan-1-ol (125 mg, 1.07 mmol), THF (8 mL), and 3-(bis(4-(trifluoromethyl)phenyl)phosphanyl). Reduction of the imine was carried out with $NaBH_4$ (94 mg, 2.5 mmol) in anhydrous methanol (6 mL). After workup, the crude residue as purified by column chromatography (1% Et_3N/EtOAc) to afford the title compound as a colorless oil (218 mg, 50%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.72 (s, 1H), 7.60 (d, 4H, J = 7.8 Hz), 7.35 – 7.41 (m, 5H), 7.31 (d 1H, J = 7.3 Hz), 7.19 (app t, 1H, J = 7.3 Hz), 3.88 (d, 1H, J = 13.2 Hz), 3.82 (d, 1H, J = 13.2 Hz), 3.61 – 3.64 (m, 1H), 3.37 – 3.40 (m, 1H), 2.32 (dd, 1H, J = 5.9, 4.9 Hz), 0.90 (s, 9H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 141.7 (d, J_{C-P} = 9.3 Hz), 135.3 (d, J_{C-P} = 10.4 Hz), 133.8 – 134.6 (6 signals), 133.0 (d, J_{C-P} = 18.5 Hz), 131.3 (q, J_{C-F} = 32.4 Hz), 129.8, 129.4 (d, J_{C-P} = 2.3 Hz), 124.2 (q, J_{C-F} = 273 Hz), 67.4, 60.4, 54.1, 34.6, 27.5; ^{31}P NMR ($CDCl_3$, 202 MHz) δ – 5.6; ^{19}F NMR ($CDCl_3$, 470 MHz) δ – 62.9; IR: 3415, 2958, 2870, 1477, 1396, 1323, 1127, 1107, 1060, 1016, 997, 832, 599 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{27}H_{29}F_6N_1O_1P_1$ $[M+H]^+$: 528.1891, found: 528.1874; $[\alpha]_D^{20}$ = + 4.44 (*c* = 0.540, $CHCl_3$, *l* = 50 mm).



(4*S*)-3-(3-(bis(4-(trifluoromethyl)phenyl)phosphanyl)-benzyl)-4-(*tert*-butyl)-2-methoxyoxazolidine (2.47). Followed General Procedure B using *N,N*-dimethylformamide dimethylacetal (256 μL, 1.90 mmol), (*S*)-2-((3-(bis(4-(trifluoromethyl)phenyl)phosphanyl)benzyl)amino)-3,3-dimethylbutan-1-ol (200 mg, 0.380 mmol), and methanol (6 mL). Extraction pentane (2 x 10 mL) and concentration under reduced pressure afforded the title compound as a viscous oil (198 mg, 92%).

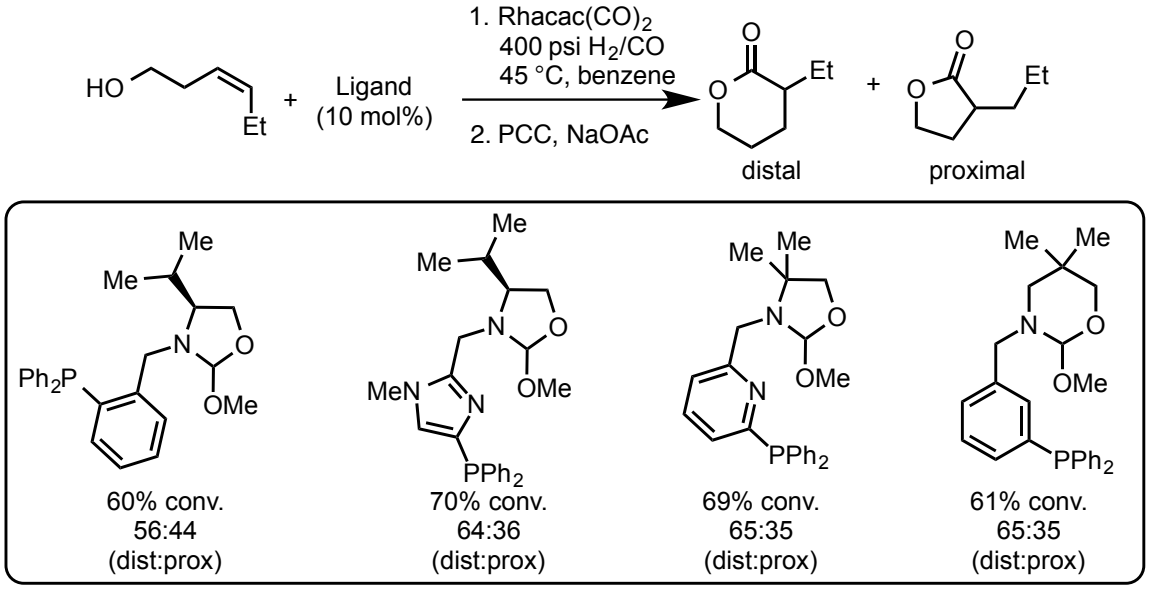
^{1}H NMR (C_6D_6, 500 MHz) δ 7.57 (d, 0.6H, J = 7.8 Hz), 7.53 (d, 0.4H, J = 7.8 Hz), 7.41 (d, 0.4H, J = 7.8 Hz), 7.07 – 7.28 (m, 10.6H), 4.98 (s, 0.4H), 4.96 (s, 0.6H), 4.19 (d, 0.4H, J = 13.7 Hz), 3.88 (t, 0.4H, J = 8.1 Hz), 3.85 (d, 0.4H, J = 13.7 Hz), 3.76 (t, 0.6H, J = 8.1 Hz), 3.64 – 3.70 (m, 1.6H), 3.58 (d, 0.6H, J = 15.2 Hz), 2.90 (s, 1.2H), 2.87 (s, 1.8H), 2.52 (dd, 0.4H, J = 7.8, 2.4 Hz), 2.46 (dd, 0.6H, J = 8.8, 7.8 Hz), 0.74 (s, 3.6H), 0.73 (s, 5.4H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 141.7 – 142.0 (5 signals), 141.9 (d, $J_{C\text{-}P}$ = 5.8 Hz), 140.9 (d, $J_{C\text{-}P}$ = 5.8 Hz), 135.1 (d, $J_{C\text{-}P}$ = 10.4 Hz), 134.8 (d, $J_{C\text{-}P}$ = 9.4 Hz), 133.7 – 134.2 (8 signals), 133.2 (d, $J_{C\text{-}P}$ = 24.3 Hz), 132.8 (d, $J_{C\text{-}P}$ = 24.3 Hz), 131.2 (q, $J_{C\text{-}F}$ = 32.4 Hz), 129.9, 129.8, 129.1 (d, $J_{C\text{-}P}$ = 9.3 Hz), 128.9 (d, $J_{C\text{-}P}$ = 8.1 Hz), 125.6, 124.2 (q, $J_{C\text{-}F}$ = 273 Hz), 115.9, 110.3, 73.3, 68.5, 66.4, 65.4, 60.0, 53.0, 52.4, 52.2, 35.3, 33.8, 26.8, 26.3; ^{31}P NMR (C_6D_6, 202 MHz) δ – 5.8; ^{19}F NMR ($CDCl_3$, 564 MHz) δ – 62.9 IR: 2956, 1606, 1477, 1396, 1320, 1164, 1124, 1106, 1059, 1016, 998, 831, 700, 599, 514 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{29}H_{31}F_6N_1O_2P_1$ $[M+H]^+$: 570.1997, found: 570.1985; $[\alpha]_D^{20}$ = + 16.4 (c = 0.475, $CHCl_3$, l = 50 mm).



(*S*)-4-(*tert*-butyl)-3-(3-(diphenylphosphanyl)benzyl)oxazolidine (2.48). To a stirring suspension of (*S*)-2-((3-(diphenylphosphanyl)-benzyl)amino)-3,3-dimethylbutan-1-ol (383 mg, 0.979 mmol) and paraformaldehyde (44 mg, 1.5 mmol) in anhydrous toluene (25 mL) was added *p*-toluenesulfonic acid monohydrate (39 mg, 0.20 mmol). The solution was heated to reflux overnight with azeotropic removal of water. The reaction was cooled to room temperature and the volatiles were removed under reduced pressure. The remaining residue was diluted with chloroform (30 mL) and washed with saturated $NaHCO_3$ (15 mL). The aqueous layer was extracted with an additional portion of chloroform (30 mL), the combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Flash column chromatography (10% EtOAc/Hex) afforded the product as a colorless oil (203 mg, 51%).

^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.27 – 7.36 (m, 13H), 7.19 (t, 1H, J = 7.5 Hz), 4.18 (d, 1H, J = 5.9 Hz), 4.00 (d, 1H, J = 6.4 Hz), 3.95 (t, 1H, J = 8.3 Hz), 3.79 (d, 1H, J = 13.7 Hz), 3.72 (d, 1H, J = 13.2 Hz), 3.50 (dd, 1H, J = 8.8, 7.3 Hz), 2.71 (t, 1H, J = 7.3 Hz), 0.82 (s, 9H); ^{13}C NMR ($CDCl_3$, 151 MHz) δ 140.8, 137.5 (d, $J_{C\text{-}P}$ = 10.4 Hz), 137.4 (d, $J_{C\text{-}P}$ = 9.3 Hz), 134.1 (d, $J_{C\text{-}P}$ = 25.4 Hz), 133.9 (d, $J_{C\text{-}P}$ = 18.5 Hz), 132.6 (d, $J_{C\text{-}P}$ = 19.7 Hz), 129.2 128.9, 128.7 (d, $J_{C\text{-}P}$ = 6.9 Hz), 128.6 (d, $J_{C\text{-}P}$ = 6.9 Hz), 87.2, 73.6, 66.7, 62.2, 34.6, 26.4; ^{31}P NMR ($CDCl_3$, 202 MHz) δ – 5.5; IR: 2953, 2867, 1477, 1434, 1392, 1157, 1068, 1013, 913, 743, 696, 495 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{26}H_{31}N_1O_1P_1$ $[M+H]^+$: 404.2143, found: 404.2131; $[\alpha]_D^{20}$ = − 6.43 (c = 0.435, $CHCl_3$, l = 50 mm).

Probing of Scaffolding Ligands with Other Linkers:

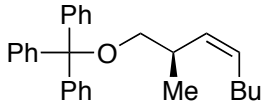


2.11.3 Substrate Syntheses and Characterization

The following compounds were synthesized according to literature procedures and matched all reported spectroscopic data: (*S*)-2-methyl-3-(trityloxy)propanal (111865-84-0),[31] 2-(((*R*)-4,4-dibromo-2-methylbut-3-en-1-yl)oxy)tetrahydro-2*H*-pyran (1156545-93-5), [32] methyl (*S*)-2-(hydroxymethyl)-3-methylbutanoate (189938-05-4), [33] (*R*)-2-phenyloxirane (20780-53-4),[34] (*R*)-2-(4-chlorophenyl)oxirane (21019-51-2),[34] (*R*)-2-(4-

[31] Gaunt, M. J.; Jessiman, A. S.; Orsini, P.; Tanner, H. R.; Hook, D. F.; Ley, S. V. *Org. Lett.* **2003**, *5*, 4819 – 4922.
[32] Ley, S. V.; Tackett, M. N.; Maddess, M. L.; Anderson, J. C.; Brennan, P. E.; Cappi, M. W.; Heer, J. P.; Helgen, C.; Masakuni, K.; Kouklovsky, C.; Marsden, S. P.; Norman, J.; Osborn, D. P.; Palomero, M. A.; Pavey, J. B. J.; Pinel, C.; Robinson, L. A.; Schnaubelt, J.; Scott, J. S.; Spilling, C. D; Watanabe, H.; Wesson, K. E.; Willis, M. C. *Chem. Eur. J.* **2009**, *15*, 2874 – 2009.
[33] Imogai, H.; Larcheveque, M. *Tetrahedron: Asymm.* **1997**, *8*, 965 – 972.
[34] Shaus, S. E.; Brandes, B. D.; Larrow, J. F.; Tokunaga, M.; Hansen, K. B.; Gould, A. E.; Furrow, M. E.; Jacobsen, E. N. *J. Am. Chem. Soc.* **2002**, *124*, 1307 – 1315.

bromophenyl)oxirane (62566-68-1),[35] (*R*)-2-(4-methoxyphenyl)oxirane (62600-73-1),[36] (*R*)-1-(3-(trifluoromethyl)phenyl)ethane-1,2-diol, [37] (*R*)-2-(3-(methoxy)phenyl)oxirane (62600-72-0),[34] (*R*,*Z*)-non-3-ene-1,2-diol.[38]

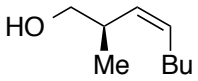


(*R*,*Z*)-(((2-methyloct-3-en-1-yl)oxy)methanetriyl)tribenzene. To a stirring suspension of (1-pentyl)triphenylphosphonium bromide (3.00 g, 7.26 mmol) in THF (30 mL) at – 78 °C was added *n*-butyllithium (2.2 mL, 2.4 M solution in hexanes). The reaction was stirred at – 78 °C for 10 minutes and was then allowed to warm to 0 °C over 25 minutes. The bright orange solution was re-cooled to – 78 °C and (*S*)-2-methyl-3-(trityloxy)propanal (1.60 g, 4.84 mmol) was added as a solution in THF (5 mL). The reaction was quenched by the addition of water (20 mL), extracted with Et_2O (3 x 40 mL), and the combined organic phases were dried over $MgSO_4$. Filtration and removal of the solvent under reduced pressure afforded a yellow residue, which was subjected to silica gel chromatography (15% DCM/Hex) to afford the title compound as a colorless oil (1.58 g, 85%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 7.44 – 7.46 (m, 6H), 7.27 – 7.30 (m, 6H), 7.21 – 7.24 (m, 3H), 5.34 – 5.38 (m, 1H), 5.14 – 5.18 (m, 1H), 2.94 – 2.97 (m, 1H), 2.86 – 2.89 (m, 1H), 2.74 – 2.80 (m, 1H), 2.03 – 2.07 (m, 2H), 1.29 – 1.34 (m, 4H), 1.00 (d, 3H, *J* = 6.4 Hz), 0.90 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7, 133.1, 130.3, 129.0,

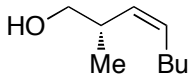
[35] Barlow, T.; Dipple, A. *Chem. Res. Toxicol.* **1998**, *11*, 44 – 53.
[36] Kawasaki, K.; Katsuki, T. *Tetrahedron* **1997**, *53*, 6337 – 6350.
[37] Sasmal, P. K.; Vamseekrishna, C.; Potluri, V.; Tehim, A.; Gai, Y.; Zhang, H. Substituted Heterocyclic Acetamides as Kappa Opioid Receptor (KOR) Agonists. International Application No: PCT/CN2013/000230, May 5, 2013.
[38] Dussault, P. H.; Schultz, J. A. *J. Am. Chem. Soc.* **1999**, *64*, 8419 – 8422.

127.9, 127.0, 86.4, 68.5, 33.0, 32.3, 27.5, 22.6, 18.4, 14.2; IR 2957, 2927, 2870, 1491, 1449, 1065, 1034, 774, 763, 705 cm^{-1}; HRMS (ESI^+) calcd. for $C_{28}H_{32}O_1Na_1$ $[M+Na]^+$: 407.2351, found: 407.2349; $[\alpha]_D^{20} = -39.4$ (*c* = 0.420, $CHCl_3$, *l* = 50 mm).

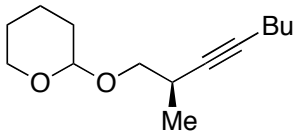


(*R*,*Z*)-2-methyloct-3-en-1-ol ((*R*)-2.19). In a round-bottom flask *p*-toluenesulfonic acid monohydrate (635 mg, 3.34 mmol) and (*R*,*Z*)-(((2-methyloct-3-en-1-yl)oxy)methanetriyl)tribenzene (3.21 g, 8.35 mmol) were stirred in dichloromethane (14 mL) and anhydrous methanol (10 mL) overnight. The volatiles were removed *in vacuo* and the residue was partitioned between saturated sodium bicarbonate (20 mL) and dichloromethane (40 mL). The aqueous layer was washed with an additional portion of dichloromethane (40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (15% EtOAc/Hex), affording a colorless oil (743 mg, 62%).

^1H NMR (600 MHz, $CDCl_3$) δ 5.50 – 5.54 (m, 1H), 5.11 (dt, 1H, *J* = 11.2, 1.2 Hz), 3.48 (dd, 1H, *J* = 10.6, 5.9 Hz), 3.33 (dd, 1H, *J* = 10.6, 8.2 Hz), 2.68 – 2.73 (m, 1H), 2.02 – 2.12 (m, 2H), 1.42 (br s, 1H), 1.30 – 1.36 (m, 4H), 0.94 (d, 3H, *J* = 7.0 Hz), 0.89 (t, 3H, *J* = 7.0 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 132.7, 132.1, 67.9, 35.0, 32.3, 27.6, 22.6, 17.2, 14.2; IR 3330, 2956, 2927, 2972, 1456, 1378, 1068, 1002, 990, 713, 607 cm^{-1}; HRMS (DART-TOF) calcd. for $C_9H_{19}O_1$ $[M+H]^+$: 143.1436, found: 143.1430; $[\alpha]_D^{20} = +11.8$ (*c* = 0.805, $CHCl_3$, *l* = 50 mm).



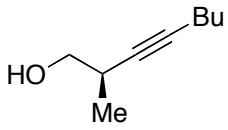
(*S*,*Z*)-2-methyloct-3-en-1-ol ((*S*)-2.19). Same experimental procedure followed as (*R*,*Z*)-2-methyloct-3-en-1-ol and all spectral and analytical data are identical except for the optical rotation $[\alpha]_D^{20} = -9.51$ (*c* = 0.745, $CHCl_3$, *l* = 50 mm).



2-(((*R*)-2-methyloct-3-yn-1-yl)oxy)tetrahydro-2*H*-pyran. To a solution of 2-(((*R*)-4,4-dibromo-2-methylbut-3-en-1-yl)oxy)tetrahydro-2*H*-pyran (2.18 g, 6.64 mmol) in THF (50 mL) at – 78 °C was added *n*-BuLi (6.10 mL, 14.6 mmol, 2.40 M solution in hexanes). The reaction was stirred at this temperature for 45 minutes and 1-iodobutane (3.80 mL, 33.3 mmol) was added. After warming the room temperature over 40 minutes, the reaction was heated to 55 °C for 3 hours. The reaction was cooled to room temperature, quenched by the addition of saturated aqueous NH_4Cl (30 mL), diluted further with water (5 mL), and extracted with dichloromethane (2 x 40 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Silica gel chromatography (3% EtOAc/Hex) afforded the title compound as a colorless oil that exists as a 1:1 mixture of diastereomers (1.04 g, 70%).

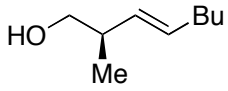
^{1}H NMR (500 MHz, $CDCl_3$) δ 4.65 (t, 0.5H, *J* = 3.4 Hz), 4.63 (t, 0.5H, *J* = 3.4 Hz), 3.84 – 3.91 (m, 1H), 3.73 (dd, 0.5H, *J* = 9.5, 6.1 Hz), 3.55 (dd, 0.5H, *J* = 9.5, 8.1 Hz), 3.50 – 3.51 (m, 1H), 3.45 (dd, 0.5H, *J* = 9.3, 6.4 Hz), 3.25 (dd, 0.5H, *J* = 9.5, 7.6 Hz), 2.66 – 2.70 (m, 1H), 2.14 (t, 2H, *J* = 6.9 Hz), 1.82 – 1.85 (m, 1H), 1.68 – 1.73 (m, 1H), 1.36 – 1.63 (m, 8H), 1.17 (d, 3H, *J* = 6.9 Hz), 0.89 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 99.1, 98.8, 82.3, 82.2, 81.3, 81.2, 72.1, 72.0, 62.4, 622, 31.4, 31.3, 30.8, 30.7,

27.0, 26.9, 25.7, 22.1, 19.6, 19.5, 18.6, 18.5, 18.4, 13.8; IR 2933, 2812, 1123, 1061, 1034, 973 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{14}H_{25}O_2$ $[M+H]^+$: 225.1855, found: 225.1855.



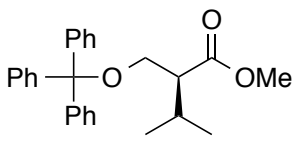
(*R*)-2-methyloct-3-yn-1-ol. To a round-bottom flask containing *p*-TsOH monohydrate (130 mg, 0.674 mmol) was added 2-(((*R*)-2-methyloct-3-yn-1-yl)oxy)tetrahydro-2*H*-pyran (1.51 g, 6.74 mmol) in anhydrous methanol (20 mL). The reaction was allowed to stir at room temperature until all starting material was consumed (approx. 3 hours). The solution was transferred to a separatory funnel, diluted with dichloromethane (40 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL). The layers were separated and the aqueous layer was extracted with an additional portion of dichloromethane (30 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Silica gel chromatography (15% EtOAc/Hex) afforded the title compound as a colorless oil (788 mg, 83%).

^{1}H NMR (600 MHz, $CDCl_3$) δ 3.53 (dd, 1H, *J* = 10.3, 5.6 Hz), 3.44 (dd, 1H, *J* = 10.3, 7.1 Hz), 2.62 – 2.65 (m, 1H), 2.16 (dt, 2H, *J* = 7.3, 2.2 Hz), 1.81 (br s, 1H), 1.45 – 1.49 (m, 2H), 1.35 – 1.44 (m, 2H), 1.13 (d, 3H, *J* = 7.1 Hz), 0.90 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 82.9, 81.5, 67.3, 31.3, 29.8 22.1, 18.6, 17.5, 13.8; IR 3340, 2958, 2932, 2874, 1457, 1379, 1329, 1039, 1015 cm^{-1}; HRMS (DART-TOF) calcd. for $C_9H_{17}O_1$ $[M+H]^+$: 141.1279, found: 141.1281; $[\alpha]_D^{20}$ = + 15.2 (*c* = 1.13, $CHCl_3$, *l* = 50 mm).



(*R*,*E*)-2-methyloct-3-en-1-ol (2.50). A flame-dried, three-neck, round-bottom flask fitted with a dry ice condenser was charged with ammonia (7.2 mL) at – 78 ° C. Sodium metal (328 mg, 14.3 mmol) was added piece-wise at this temperature, upon which time the solution turned deep blue. The solution was allowed to stir while warming to – 35 °C over 20 minutes and (*R*)-2-methyloct-3-yn-1-ol (0.500 g, 3.57 mmol) was added drop-wise as a solution in THF (4 mL). The reaction was allowed to stir for 3 hours at – 30 °C and was quenched by the careful addition of solid NH_4Cl (approx. 10 eq). The ammonia was allowed to evaporate and the reaction mixture was diluted with water (15 mL). Extraction with dichloromethane (2 x 30 mL), followed by drying over $MgSO_4$ and concentration *in vacuo* showed that trace amounts of starting material remained. The crude residue was re-subjected to the same reaction conditions and work-up procedure. Purification on a short plug of silica afforded the title compound as a colorless oil (419 mg, 83%).

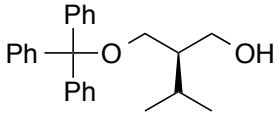
^{1}H NMR (600 MHz, $CDCl_3$) δ 5.50 – 5.55 (m, 1H), 5.22 – 5.26 (m, 1H), 3.44 – 3.48 (m, 1H), 3.32 – 3.36 (m, 1H), 2.27 – 2.32 (m, 1H), 2.00 – 2.02 (m, 2H), 1.44 (br s, 1H), 1.26 – 1.37 (m, 4H), 0.97 (d, 3H, J = 7.0 Hz), 0.88 (d, 3H, J = 7.0 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 132.7, 132.4, 67.5, 40.0, 32.5, 31.9, 22.4, 16.8, 14.1; IR 3340, 2957, 2924, 2972, 1457, 1378, 1034, 968 cm^{-1}; HRMS (DART-TOF) calcd. for $C_9H_{19}O_1$ $[M+H]^+$: 143.1436, found: 143.1433; $[\alpha]_D^{20}$ = + 17.8 (c = 0.920, $CHCl_3$, l = 50 mm).



methyl-(*S*)-3-methyl-2-((trityloxy)methyl)butanoate. Trityl chloride (3.00 g, 10.6 mmol), DMAP (74 mg, 0.59 mmol),

methyl-(*S*)-2-(hydroxymethyl)-3-methylbutanoate (865 mg, 5.92 mmol), and dichloromethane (20 mL) were added to a round-bottom flask under nitrogen. Triethylamine (1.64 mL, 11.8 mmol) was added to the vigorously stirred solution slowly and the reaction was stirred at room temperature overnight. The reaction was quenched by the addition of saturated NH_4Cl (30 mL) and extracted with dichloromethane (2 x 60 mL). The combined organics were washed with water (20 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude reside was purified by silica gel chromatography (10% EtOAc/Hex) to afford the title compound as a viscous oil (2.25 g, 98%).

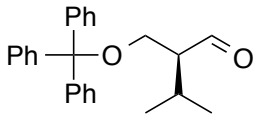
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.42 (m, 6H), 7.27 – 7.31 (m, 6H), 7.21 – 7.24 (m, 3H), 3.73 (s, 3H), 3.33 (t, 1H, J = 8.8 Hz), 3.25 (dd, 1H, J = 8.8, 5.4 Hz), 2.39 – 2.44 (m, 1H), 1.86 – 1.90 (m, 1H), 0.89 (t, 3H, J = 7.1 Hz), 0.83 (d, 3H, J = 6.5 Hz), 0.76 (d, 3H, J = 6.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 144.2, 128.9, 127.9, 127.2, 86.8, 63.4, 53.5, 51.5, 28.1, 20.8, 20.7; IR 1961, 1736, 1491, 1448, 1221, 1195, 1079, 1033, 773, 763, 747, 633 cm^{-1}; HRMS (ESI$^+$) calcd. for $C_{26}H_{28}O_3Na_1$ $[M+Na]^+$: 411.1936, found: 411.1938; $[\alpha]_D^{20}$ = + 14.3 (c = 0.355, $CHCl_3$, l = 50 mm).



(*R*)-3-methyl-2-((trityloxy)methyl)butan-1-ol. To a suspension of lithium aluminum hydride (210 mg, 5.52 mmol) in THF (12 mL) at 0 °C was added a solution of methyl-(*S*)-3-methyl-2-((trityloxy)methyl)butanoate (1.43 g, 3.58 mmol) in THF (6 mL). The reaction was allowed to warm to room temperature overnight. After cooling to 0 °C, the reaction was quenched by the slow,

drop-wise addition of water (2.5 mL). Anhydrous $MgSO_4$ was added to the flask, and the slurry was filtered and concentrated under reduced pressure to afford the title compound as a viscous colorless oil (1.30 g, 98%).

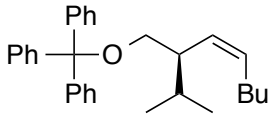
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 – 7.45 (m, 6H), 7.29 – 7.33 (m, 6H), 7.23 – 7.26 (m, 3H), 3.72 – 3.76 (m, 1H), 3.65 – 3.70 (m, 1H), 3.38 (dd, 1H, *J* = 9.3, 3.9 Hz), 3.19 (dd, 1H, *J* = 9.3, 7.3 Hz), 2.42 (dd, 1H, *J*= 6.9, 4.9 Hz), 1.72 – 1.77 (m, 1H), 1.59 – 1.62 (m, 1H), 0.83 (d, 3H, *J* = 6.9 Hz), 0.76 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.0, 128.8, 128.1, 127.3, 87.5, 65.3, 64.7, 47.2, 26.9, 20.5; IR 3428, 2957, 2974, 1490, 1338, 1219, 1153, 1065, 1031 1002, 762, 745, 704, 648 cm^{-1}; HRMS (ESI^+) calcd. for $C_{25}H_{28}O_2Na_1$ $[M+Na]^+$: 383,1987, found: 383.1990; $[\alpha]_D^{20}$ = + 23.1 (*c* = 0.170, $CHCl_3$, *l* = 50 mm).



(*S*)-3-methyl-2-((trityloxy)methyl)butanal. To a solution of oxalyl chloride (1.10 mL, 12.5 mmol) in DCM (31 mL) at – 78 °C was added DMSO (2.20 mL, 31.3 mmol). After stirring at this temperature for 30 minutes a solution of (*R*)-3-methyl-2-((trityloxy)methyl)butan-1-ol (2.26 g, 6.27 mmol) in DCM (6 mL) was added drop-wise. The reaction mixture was stirred at – 78 °C for a further 45 minutes before Et_3N (3.50 mL, 25.0 mmol) was added drop-wise to the solution. After 15 minutes, the mixture was warmed to 0 °C and quenched by the addition of water (30 mL) then extracted with DCM (2 x 50 mL). The combined organic layers were washed with saturated $NaHCO_3$ (30 mL), brine (20 mL), dried over $MgSO_4$,

filtered, and concentrated under reduced pressure to afford a yellow oil that was used in the next reaction immediately without further purification.

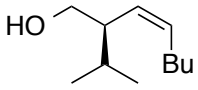
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.66 (d, 1H, *J* = 3.5 Hz), 7.36 – 7.39 (m, 6H), 7.24 – 7.26 (m, 6H), 7.20 – 7.22 (m, 3H), 3.35 (d, 2H, *J* = 6.0 Hz), 2.26 – 2.30 (m, 1H), 2.05 – 2.08 (m, 1H), 0.85 (d, 3H, *J* = 7.0 Hz), 0.77 (d, 3H, *J* = 6.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 205.0, 143.9, 128.8, 128.0, 127.3, 87.1, 61.2, 59.0, 26.2, 20.7, 20.2.



(*R*,*Z*)-(((2-isopropyloct-3-en-1-yl)oxy)methanetriyl)tribenzene. To a suspension of (1-pentyl)triphenylphosphonium bromide (3.12 g, 7.56 mmol) in THF (40 mL) at –78 °C was added *n*-butyllithium (3.00 mL, 6.93 mmol, 2.30 M in pentane). The bright solution was stirred at -78 °C for 15 minutes, warmed to 0 °C over 30 minutes, and re-cooled to –78 °C. (*S*)-3-methyl-2-((trityloxy)methyl)butanal (2.26 g, 6.30 mmol) was added as a solution in THF (6 mL) and the reaction was allowed to warm to room temperature overnight. The reaction was quenched by the addition of water (30 mL) and extracted with diethyl ether (2 x 60 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated. Silica gel chromatography (10% DCM/Hex) afforded the title compound as a colorless oil (1.98 g, 76%).

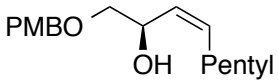
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.46 (m, 6H), 7.27 – 7.30 (m, 6H), 7.20 – 7.23 (m, 3H), 5.47 – 5.52 (m, 1H), 5.21 – 5.26 (m, 1H), 2.97 – 3.04 (m, 2H), 2.46 – 2.49 (m, 1H), 2.05 – 2.08 (m, 2H), 1.84 – 1.89 (m, 1H), 1.31 – 1.35 (m, 4H), 0.90 (t, 3H, *J* = 6.9 Hz),

0.77 (d, 3H, J = 6.9 Hz), 0.74 (d, 3H, J = 6.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 144.7, 131.9, 129.6, 129.0, 127.8, 127.0, 65.6, 44.1, 32.3, 29.0, 27.7, 22.7, 21.1, 18.8, 14.3; IR 2955, 2925, 2870, 1490, 1448, 1068, 1032, 898, 762, 744, 632 cm^{-1}; HRMS (ESI^+) calcd. for $C_{30}H_{36}O_1Na_1$ $[M+Na]^+$: 435.2664, found: 435.2659; $[\alpha]_D^{20}$ = − 44.8 (c = 0.525, $CHCl_3$, l = 50 mm).



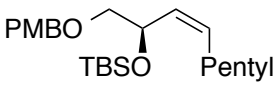
(*R*,*Z*)-2-isopropyloct-3-en-1-ol (2.52). A solution of glacial acetic acid (32 mL), water (3.5 mL), and (*R*,*Z*)-(((2-isopropyloct-3-en-1-yl)oxy)methanetriyl)tribenzene (1.98 g, 4.80 mmol) was heated to 50 °C for 5 hours. The reaction was cooled to room temperature and the volatiles removed under reduced pressure. Trityl alcohol was precipitated out by the addition of hexanes and filtered off. The organic layer was concentrated *in vacuo* and the crude reside was subjected to column chromatography (7% EtOAc/Hex) to afford the title compound as a colorless oil (531 mg, 65%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.65 – 5.70 (m, 1H), 5.12 – 5.16 (m, 1H), 3.66 – 3.68 (m, 1H), 3.34 – 3.37 (m, 1H), 2.05 – 2.10 (m, 2H), 1.57 – 1.64 (m, 1H), 1.32 – 1.35 (m, 5H), 0.91 (d, 3H, J = 6.8 Hz), 0.89 – 0.91 (m, 3H), 0.86 (d, 3H, J = 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 134.9, 129.1, 64.9, 46.8, 32.2, 29.4, 27.8, 22.6, 21.0, 19.9, 14.2; IR 3331, 2956, 2927, 1465, 1214, 1060, 1034, 1013, 750, 668 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{11}H_{23}O_1$ $[M+H]^+$: 171.1749, found: 171.1747; $[\alpha]_D^{20}$ = − 3.26 (c = 0.470, $CHCl_3$, l = 50 mm).



(*R*,*Z*)-1-((4-methoxybenzyl)oxy)non-3-en-2-ol. A round-bottom flask was charged with (*R*,*Z*)-non-3-ene-1,2-diol (200 mg, 1.26 mmol), dibutyltin oxide (430 mg, 1.71 mmol), and toluene (10 mL). The reaction was heated to reflux with azeotropic removal of water overnight. The reaction was cooled to room temperature and the Dean-Stark apparatus was removed. To the flask was added tetrabutylammonium iodide (650 mg, 1.76 mmol) and 4-methoxybenzyl chloride (276 mg, 1.76 mmol) and the reaction was heated to reflux for 4 hours. After cooling to room temperature, the reaction was quenched with water (10 mL) and extracted with DCM (2 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. Purification by silica gel chromatography (12% EtOAc/Hex) afforded the title compound as a colorless oil (318 mg, 91%, contains 30% of an inseparable impurity).

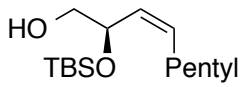
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 (d, 2H, J = 9.3 Hz), 6.88 (d, 2H, J = 8.3 Hz), 5.54 – 5.56 (m, 1H), 5.34 – 5.35 (m, 1H), 4.63 – 4.65 (m, 1H), 4.50 (m, 2H), 3.81 (s, 3H), 3.42 (dd, 1H, J = 9.5, 3.8 Hz), 3.33 (dd, 1H, J = 9.8, 8.3 Hz), 2.37 (br s, 1H), 2.02 – 2.12 (m, 2H), 1.24 – 1.38 (m, 6H), 0.88 (t, 3H, J = 7.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.7, 134.6, 129.7, 129.6, 127.9, 114.1, 74.0, 73.2, 67.1, 55.5, 31.6, 29.5, 28.1, 22.7, 14.2; IR 3448, 3007, 2955, 2927, 2856, 1612, 1586, 1513, 1464, 1247, 1174, 1100, 1074, 1036, 821, 756 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{17}H_{30}N_1O_3$ $[M+NH_4]^+$: 296.2226, found: 296.2235; $[\alpha]_D^{20}$ = − 36.8 (c = 0.445, $CHCl_3$, l = 50 mm).



(*R*,*Z*)-*tert*-butyl((1-((4-methoxybenzyl)oxy)non-3-en-2-yl)oxy)dimethylsilane. To a 50-mL round-bottom flask was

added (*R*,*Z*)-1-((4-methoxybenzyl)oxy)non-3-en-2-ol (318 mg, 1.14 mmol), 2,6-lutidine (0.33 mL, 2.9 mmol), and DCM (11 mL). The solution was cooled to 0 °C and TBSOTf (0.52 mL, 2.3 mmol) was added slowly over 3 minutes. The reaction was allowed to warm to room temperature over 90 minutes, quenched by the addition of saturated NH_4Cl (15 mL), and extracted with DCM (2 x 30 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by silica gel chromatography (1% EtOAc/Hex) to afford the product as a colorless oil (301 mg, 67%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (app dd, 2H, *J* = 6.4, 2.0 Hz), 6.86 (app dd, 2H, *J* = 6.4, 2.0 Hz), 5.40 – 5.45 (m, 1H), 5.30 – 5.34 (m, 1H), 4.62 – 4.65 (m, 1H), 4.57 (d, 1H, *J* = 11.7 Hz), 4.50 (d, 1H, *J* = 11.7 Hz), 3.81 (s, 3H), 3.41 (dd, 1H, *J* = 10.0, 7.1 Hz), 3.33 (dd, 1H, *J* = 10.3, 4.9 Hz), 2.01 – 2.06 (m, 2H), 1.25 – 1.36 (m, 6H), 0.89 (s, 9H), 0.88 (t, 3H, *J* = 8.3 Hz), 0.070 (s, 3H), 0.056 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 159.2, 131.6, 131.0, 130.8, 129.3, 113.9, 75.0, 73.2, 68.9, 55.5, 31.8, 29.5, 28.2, 26.1, 22.7, 18.5, 14.2, -4.3, -4.4; IR 2955, 2928, 2855, 1513, 1463, 1248, 1172, 1120, 1091, 1039, 1006, 834, 776 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{23}H_{39}O_2Si_1$ $[M+H-H_2O]^+$: 375.2719, found: 375.2718; $[\alpha]_D^{20} = -7.55$ (*c* = 0.620, $CHCl_3$, *l* = 50 mm).



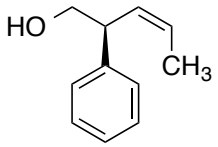
(*R*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)non-3-en-1-ol (2.54). To a vigorously stirred solution of (*R*,*Z*)-*tert*-butyl((1-((4-methoxybenzyl)oxy)non-3-en-2-yl)oxy)dimethylsilane (150 mg, 0.38 mmol), DCM (6 mL), and water (1.5 mL) at 0 °C was added DDQ (106 mg). The reaction was allowed to

warm to room temperature over 2 hours and was quenched by the addition of a 1:1:1 mixture of saturated aqueous sodium thiosulfate:saturated aqueous sodium bicarbonate:water (10 mL). The aqueous layer was extracted with DCM (2 x 30 mL) and the combined organic layers were dried over $MgSO_4$. Filtration, and removal of the solvent *in vacuo* afforded a crude residue, which was purified by silica gel chromatography (10% EtOAc/Hex) to afford the title compound as a colorless oil (87 mg, 84%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.44 – 5.49 (m, 1H), 5.26 – 5.30 (m, 1H), 4.51 – 4.55 (m, 1H), 3.40 (dd, 2H, J = 7.1, 5.6 Hz), 1.98 – 2.08 (m, 3H), 1.25 – 1.38 (m, 6H), 089 (s, 9H), 0.88 (t, 3H, J = 8.3 Hz), 0.081 (s, 3H), 0.058 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 132.7, 129.9, 70.2, 66.9, 31.7, 29.5, 28.1, 26.0, 22.7, 18.3, 14.2, -4.0, -4.6; IR 3439, 2956, 2928, 2857, 1463, 1235, 1095, 1062, 1036, 1005, 835, 812 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{15}H_{31}O_1Si_1$ $[M+H-H_2O]^+$: 255.2144, found: 255.2140; $[\alpha]_D^{20}$ = + 3.99 (c = 0.315, $CHCl_3$, l = 50 mm).

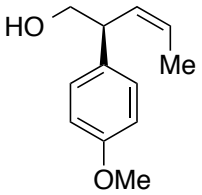
General Procedure C (Preparation of Aryl Substrates): To a suspension enantiopure aryloxirane (1 equiv) and CuCl(COD) (0.10 equiv) in THF (0.40 M) at – 78 °C was added (*Z*)-prop-1-en-1-ylmagnesium bromide (1.5 equiv, 1.0 M solution in THF). The reaction was allowed to warm to room temperature over 8 hours, quenched by the addition of water (15 mL), and extracted with EtOAc (2 x 40 mL). The combined organic phases were dried over $MgSO_4$, filtered, and concentrated under reduced

pressure. The crude reside was subjected to silica gel chromatography (20% EtOAc/Hex) to afford the title compound.



(*S*,*Z*)-2-phenylpent-3-en-1-ol (2.56). Synthesized according to General Procedure C using (*R*)-2-phenyloxirane (1.64 mL, 19.3 mmol) to afford the title compound as a colorless oil (1.43 g, 46%).

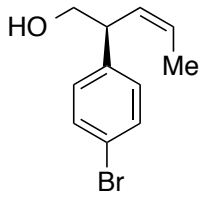
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 – 7.34 (m, 2H), 7.22 – 7.27 (m, 3H), 5.71 – 5.74 (m, 1H), 5.59 – 5.64 (m, 1H), 3.85 – 3.90 (m, 1H), 3.79 – 3.81 (m, 1H), 3.70 – 3.73 (m, 1H), 1.70 (dd, 3H, *J* = 6.5, 1.5 Hz), 1.47 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 141.8, 130.2, 129.0, 128.0, 127.6, 126.9, 67.2, 46.3, 13.5; IR 3560, 3026, 1493, 1452, 1050, 757, 714, 699, 668 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{11}H_{13}$ $[M+H-H_2O]^+$: 145.1018, found: 145.1020; $[\alpha]_D^{20}$ = + 164 (*c* = 0.440, $CHCl_3$, *l* = 50 mm).



(*S*,*Z*)-2-(4-methoxyphenyl)pent-3-en-1-ol (2.58). Synthesized according to General Procedure C using (*R*)-2-(4-methoxyphenyl)oxirane (795 mg, 5.29 mmol) to afford the title compound as a yellow oil (674 mg, 85%).

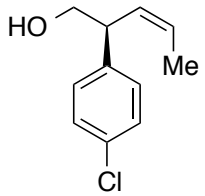
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, 2H, *J* = 8.3 Hz), 6.87 (d, 2H, *J* = 8.8 Hz), 5.68 – 5.72 (m, 1H), 5.56 – 5.60 (m, 1H), 3.80 – 3.85 (m, 1H), 3.79 (s, 3H), 3.74 – 3.78 (m, 1H), 3.66 – 3.70 (m, 1H), 1.69 (dd, 3H, *J* = 6.8, 2.0 Hz), 1.45 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 158.6, 133.7, 130.5, 128.9, 127.3, 114.4, 67.3, 55.5, 45.4, 13.5; IR 3394, 3011,

2934, 2836, 1610, 1511, 1464, 1248, 1178, 1036, 828, 703 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{12}H_{15}O_1$ $[M+H-H_2O]^+$: 175.1123, found: 175.1127; $[\alpha]_D^{20}$ = + 157 (*c* = 0.450, $CHCl_3$, *l* = 50 mm).



(*S*,*Z*)-2-(4-bromophenyl)pent-3-en-1-ol (2.60). Synthesized according to General Procedure C using (*R*)-2-(4-bromophenyl)oxirane (1.00 g, 5.02 mmol) to afford the title compound as a yellow oil (662 mg, 55%).

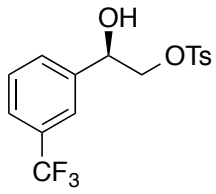
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 (d, 2H, *J* = 8.3 Hz), 7.13 (d, 2H, *J* = 8.3 Hz), 5.70 – 5.75 (m, 1H), 5.54 – 5.58 (m, 1H), 3.81 – 3.84 (m, 1H), 3.76 – 3.79 (m, 1H), 3.70 (dd, 1H, *J* = 10.8, 7.3 Hz), 1.68 (d, 3H, *J* = 6.9 Hz), 1.47 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.9, 132.0, 129.7, 129.6, 128.1, 120.7, 67.0, 45.7, 13.5; IR 3362, 3016, 2930, 2874, 1487, 1377, 1214, 1072, 1052, 1010, 819, 785, 729, 668 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{11}H_{12}Br_1$ $[M+H-H_2O]^+$: 223.0122, found: 223.0115; $[\alpha]_D^{20}$ = + 133 (*c* = 0.710, $CHCl_3$, *l* = 50 mm).



(*S*,*Z*)-2-(4-chlorophenyl)pent-3-en-1-ol (2.62). Synthesized according to General Procedure C using (*R*)-2-(4-chlorophenyl)oxirane (1.88 g, 12.2 mmol) to afford the title compound as a yellow oil (700 mg, 30%).

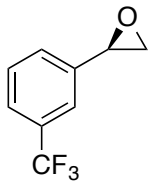
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (d, 2H, *J* = 8.3 Hz), 7.18 (d, 2H, *J* = 8.3 Hz), 5.71 – 5.75 (m, 1H), 5.54 – 5.58 (m, 1H), 3.82 – 3.87 (m, 1H), 3.76 – 3.79 (m, 1H), 3.68 – 3.72 (m, 1H), 1.68 (d, 3H, *J* = 6.8 Hz), 1.48 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.4,

132.6, 129.7, 129.3, 129.0, 128.0, 67.1, 45.6, 13.5; IR 3362, 2932, 2875, 1491, 1092, 1048, 1014, 823, 735, 582 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{11}H_{23}Cl_1$ $[M+H-H_2O]^+$: 179.0628, found: 179.0634; $[\alpha]_D^{20}$ = + 166 (*c* = 0.870, $CHCl_3$, *l* = 50 mm).



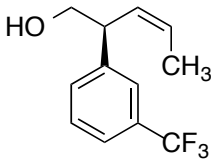
(*R*)-2-hydroxy-2-(3-(trifluoromethyl)phenyl)ethyl 4-methylbenzenesulfonate. To a solution of (*R*)-1-(3-(trifluoromethyl)phenyl)ethane-1,2-diol (3.00 g, 13.8 mmol) in anhydrous pyridine (59 mL) at 0 °C was added *p*-toluenesulfonyl chloride (2.90 g, 15.2 mmol). The reaction was stirred under nitrogen overnight while warming to room temperature. The reaction was quenched by the addition of water (20 mL) and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude reside was purified by silica gel chromatography (20% EtOAc/Hex) to afford the title compound as a yellow oil (2.32 g, 44%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, 2H, *J* = 8.3 Hz), 7.47 – 7.57 (m, 3H), 7.45 (d, 1H, *J* = 7.6 Hz), 7.32 (d, 2H, *J* = 8.3 Hz), 5.03 – 5.06 (m, 1H), 4.16 (dd, 1H, *J* = 10.8, 3.4 Hz), 4.04 (dd, 1H, *J* = 10.5, 8.1 Hz), 2.87 (br s, 1H), 2.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 145.2, 139.6, 132.6, 131.5 (q, J_{C-F} = 32.4 Hz), 130.2, 129.9, 129.4, 128.1, 125.5, 124.1 (q, J_{C-F} = 273 Hz), 123.3, 74.1, 71.6, 29.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ – 62.7; IR 3394, 3513, 1357, 1329, 1190, 1173, 1124, 1097, 1073, 974, 828, 811, 750, 703, 670, 662, 554 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{16}H_{19}F_3N_1O_4S_1$ $[M+NH_4]^+$: 378.0987, found: 378.0979; $[\alpha]_D^{20}$ = − 33.6 (*c* = 0.780, $CHCl_3$, *l* = 50 mm).



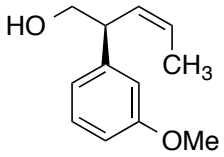
(*R*)-2-(3-(trifluoromethyl)phenyl)oxirane. A solution of (*R*)-2-hydroxy-2-(3-(trifluoromethyl)phenyl)ethyl 4-methylbenzenesulfonate (2.00 g, 5.39 mmol) in THF (9 mL) and 6 M aqueous NaOH (9 mL) was stirred vigorously at room temperature for 4 hours. The reaction was diluted with water (15 mL) and extracted with EtOAc (3 x 50 mL). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated *in vacuo* to afford the pure epoxide as a colorless oil (1.00 g, 93%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 – 7.57 (m, 1H), 7.54 (s, 1H), 7.46 – 8.47 (m, 2H), 3.92 (dd, 1H, J = 3.9, 2.5 Hz), 3.18 (dd, 1H, J = 5.4, 4.4 Hz), 2.89 (dd, 1H, J = 5.6, 2.7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 139.0, 131.3 (q, $J_{C\text{-}F}$ = 32.4 Hz), 129.2, 129.0, 125.2, 124.1 (q, $J_{C\text{-}F}$ = 273 Hz), 122.5, 52.0, 51.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ – 62.8; IR 2956, 2924, 2365, 2359, 1329, 1165, 1126, 1099, 1073, 1031, 803 cm^{-1}; HRMS (DART-TOF) calcd. for $C_9H_8F_3O_1$ $[M+H]^+$: 189.0527, found: 189.0531; $[\alpha]_D^{20}$ = − 3.39 (c = 0.860, $CHCl_3$, l = 50 mm).



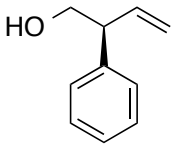
(*S*,*Z*)-2-(3-(trifluoromethyl)phenyl)pent-3-en-1-ol (2.64). Synthesized according to General Procedure C using (*R*)-2-(3-(trifluoromethyl)phenyl)oxirane (700 mg g, 3.72 mmol) to afford the title compound as a yellow oil (376 mg, 44%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.50 (m, 4H), 5.75 – 5.79 (m, 1H), 5.58 – 5.63 (m, 1H), 3.91 – 3.96 (m, 1H), 3.81 (dd, 1H, J = 10.9, 6.4 Hz), 3.75 (dd, 1H, J = 7.3, 3.4 Hz), 1.70 (d, 3H, J = 6.9 Hz), 1.51 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.9, 131.4, 131.2 (q, $J_{C\text{-}F}$ = 31 Hz), 129.3, 129.2, 128.5, 124.7, 124.3 (q, $J_{C\text{-}F}$ = 273 Hz), 123.8, 67.0, 46.0, 13.5; ^{19}F NMR (470 MHz, $CDCl_3$) δ – 62.6; IR 3362, 1447, 1328, 1163, 1123, 1095, 802, 718, 702 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{12}H_{12}F_3$ $[M+H\text{-}H_2O]^+$: 213.0891, found: 213.0892; $[\alpha]_D^{20}$ = + 108 (c = 0.515, $CHCl_3$, l = 50 mm).



(*S*,*Z*)-2-(3-methoxyphenyl)pent-3-en-1-ol (2.66). Synthesized according to General Procedure C using (*R*)-2-(3-(methoxy)phenyl)oxirane (630 mg, 4.20 mmol) to afford the title compound as a yellow oil (270 mg, 34%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 (t, 1H, J = 7.8 Hz), 6.86 (d, 1H, J = 7.8 Hz), 6.77 – 6.80 (m, 2H), 5.70 – 5.74 (m, 1H), 5.57 – 5.62 (m, 1H), 3.85 – 3.87 (m, 1H), 3.80 (s, 3H), 3.78 – 3.82 (m, 1H), 3.71 – 3.73 (m, 1H), 1.70 (d, 3H, J = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 160.1, 143.4, 130.1, 129.9, 127.7, 120.3, 114.0, 112.0, 67.1, 55.4, 46.3, 13.5; IR 3389, 2933, 2875, 1600, 1584, 1488, 1465, 1453, 1433, 1288, 1152, 1047, 778, 697 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{12}H_{15}O_1$ $[M+H\text{-}H_2O]^+$: 175.1123, found: 173.1130; $[\alpha]_D^{20}$ = + 208 (c = 0.375, $CHCl_3$, l = 50 mm).



(*S*)-2-phenylbut-3-en-1-ol (2.68). To a suspension of (*R*)-phenyloxirane (1.00 g, 8.32 mmol) and CuCl(COD) (172 mg, 0.84 mmol) in THF (12

mL) at – 78 °C was added vinylmagnesium bromide (10.0 mL, 10.0 mmol, 1.0 M solution in THF). The reaction as allowed to warm to room temperature over 8 hours. The reaction was quenched by the addition of saturated NH_4Cl (30 mL) and extracted with ethyl acetate (3 x 40 mL). The combined organics were dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by silica gel chromatography (10% EtOAc/Hex) to afford the title compound as a colorless oil (872 mg, 71%).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.37 (m, 2H), 7.24 – 7.27 (m, 3H), 5.99 – 6.06 (m, 1H), 5.18 – 5.24 (m, 2H), 3.83 – 3.85 (m, 2H), 3.54 (q, 1H, J = 7.3 Hz), 1.53 (br s); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.8, 138.4, 129.0, 128.2, 127.2, 117.3, 66.3, 52.7; IR 3355, 3028, 2876, 1493, 1453, 1054, 1029, 994, 918, 756, 700, 680 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{10}H_{11}$ $[M+H-H_2O]^+$: 131.0861, found: 131.0867; $[\alpha]_D^{20}$ = + 67.5 (c = 0.545, $CHCl_3$, l = 50 mm).

2.11.4 Characterization of Hydroformylation

General Hydroformylation Procedure. The Endeavor was charged with 500 μL of benzene per reaction well to fill the void volume between reactor wall and reaction tube, and oven dried glass reaction vials were placed into the wells. The Endeavor was sealed and purged with nitrogen (4×100 psi). The necessary injection(s) were made (see below). The Endeavor was purged with nitrogen (1×100 psi), stirring was started at 250 rpm, and the Endeavor was heated to and held at 55 ˚C for 10 minutes. Stirring was stopped, the Endeavor was charged with 400 psi H_2/CO, stirring was re-initiated at 700 rpm, and the Endeavor was maintained at constant reaction temperature of 55 °C and pressure of 400

psi H_2/CO for 15 h. The Endeavor was vented to ambient pressure and cooled to ambient temperature. The reaction vials were removed from the Endeavor, and the benzene was removed *in vacuo*. A solution of mesitylene in chloroform-*d* (100 μL, 0.5408 M) was added. The conversion of the reaction was determined by ^{1}H NMR in chloroform-*d* with respect to remaining starting material. The solvent was removed under reduced pressure. The crude hydroformylation mixture was added, as a solution in dichloromethane (3 mL), to a scintillation vial containing pyridinium chlorochromate (128.7 mg, 0.597 mmol), sodium acetate (16.0 mg, .195 mmol), and 4 Å molecular sieves. The reaction was stirred for 12 hours at room temperature and eluted through a short plug of silica gel (100% Et_2O). The regio- and diastereoselectivities were determined by either GC or ^{1}H NMR.

General Procedure D: In a dry box, (*R*,*Z*)-2-methyloct-3-en-1-ol (28.4 mg, 0.200 mmol), (4*S*)-4-(*tert*-butyl)-3-(3-(diphenylphosphanyl)benzyl)-2-methoxyoxazolidine (8.7 mg, 0.020 mmol), a *p*-toluenesulfonic acid in benzene (351 μL, 2.0 x 10^{-4} mmol, 5.7 x 10^{-4} M solution) were mixed in C_6D_6 (0.8 mL) and allowed to equilibrate in a sealed NMR tube for 3 hours at 45 °C. (Note: the appearance of free MeOH can be monitored by ^{1}H NMR.) The solution was concentrated in the dry box to remove the generated MeOH, the residue was re-dissolved in C_6D_6, and was allowed to equilibrate for an additional 3 hours at 45 °C before being concentrated again in the dry box. The resulting mixture was dissolved in benzene (3.5 mL), mixed with 3% Rh(acac)$(CO)_2$ (1.5 mg, 0.006 mmol), and injected into the Endeavor, followed by 0.5 mL benzene to wash the injection port.

General Procedure E: Same as General Procedure D, except 20% (4*S*)-4-(*tert*-butyl)-3-(3-(diphenylphosphanyl)benzyl)-2-methoxyoxazolidine (17.3 mg, 0.040 mmol) and 6% $Rh(acac)(CO)_2$ (3.1 mg, 0.012 mmol) were used.

General Procedure F: Same as General Procedure D, except 12% (4*S*)-4-(*tert*-butyl)-3-(3-(diphenylphosphanyl)benzyl)-2-methoxyoxazolidine (10.4 mg, 0.024 mmol) and 4% $Rh(acac)(CO)_2$ (2.1 mg, 0.008 mmol) were used.

General Procedure G: Same as General Procedure D, except 5% (4*S*)-4-(*tert*-butyl)-3-(3-(diphenylphosphanyl)benzyl)-2-methoxyoxazolidine (4.4 mg, 0.010 mmol) and 2% $Rh(acac)(CO)_2$ (1.1 mg, 0.004 mmol) were used.

Gas Chromatography Analysis Methods

GC Method A: J&W Scientific column (HP-5, 30 m x 0.320 mm ID x 0.25 μm film thickness): 120 °C for 8 min, ramp 8 °C/min to 136 °C, 136 °C for 2 min, ramp 10 °C/min to a final temperature of 220 °C, 220 °C for 3 min.

GC Method B: J&W Scientific column (HP-5, 30 m x 0.320 mm ID x 0.25 μm film thickness): 120 °C for 8 min, ramp 8 °C/min to 136 °C, 136 °C for 1 min, ramp 10 °C/min to a final temperature of 220 °C, 220 °C for 6 min.

GC Method C: Supelco Gamma Dex 120 (30 m × 0.25 mm × 0.25 μm film thickness) 60 °C for 5 min, ramp 1 °C/min to 150 °C, 150 °C for 10 min, ramp 8 °C/min to a final temperature of 220 °C.

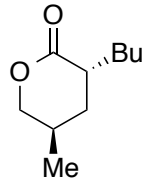
GC Method D: J&W Scientific column (HP-5, 30 m x 0.320 mm ID x 0.25 μm film thickness): 140 °C for 6 min, ramp 40 °C/min to 220 °C, 220 °C for 5 min.

GC Method E: J&W Scientific column (HP-5, 30 m x 0.320 mm ID x 0.25 μm film thickness): 140 °C for 3 min, ramp 8 °C/min to 220 °C, 220 °C for 10 min.

GC Method F: J&W Scientific column (HP-5, 30 m x 0.320 mm ID x 0.25 μm film thickness): 120 °C for 8 min, ramp 8 °C/min to 136 °C, 136 °C for 1 min, ramp 10 °C/min to a final temperature of 220 °C, 220 °C for 10 min

Table 2.4, Entry 1

(*R*,*Z*)-2-methyloct-3-en-1-ol was subjected to hydroformylation using General Procedure D. Achiral GC analysis using GC Method A afforded three peaks corresponding to each γ-lactone product (6.80 min and 7.93 min) and the combined δ-lactone products (8.47 min). The diastereoselectivity of the reaction was determined by ^{1}H NMR in CD_3OD. Silica gel chromatography (10% EtOAc/Hex) afforded the following compounds:

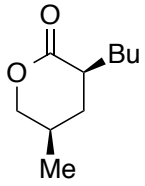


(3*R*,5*R*)-3-butyl-5-methyltetrahydro-2*H*-pyran-2-one (2.49). Isolated as a colorless oil (27 mg, 78%). **GC Method A**: 8.47 min.; ^{1}H NMR (500

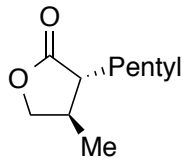
MHz, $CDCl_3$) δ 4.20 (dd, 1H, *J* = 10.8, 4.9 Hz), 3.89 (t, 1H, *J* = 10.8 Hz), 2.46 – 2.51 (m, 1H), 2.12 – 2.17 (m, 1H), 1.84 – 1.88 (m, 1H), 1.69 – 1.72 (m, 2H), 1.42 – 1.45 (m, 1H), 1.33 – 1.37 (m, 4H), 1.00 (d, 3H, *J* = 6.9 Hz), 0.91 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 73.2, 37.5, 32.7, 31.2, 29.3, 27.0, 22.8, 17.2, 14.2; IR 2957, 2931, 2872, 1740, 1459, 1380, 1341, 1103, 1047, 1007, 725 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{10}H_{19}O_2$ $[M+H]^+$: 171.1380, found: 171.1384; $[\alpha]_D^{20}$ = − 34.0 (*c* = 0.405, $CHCl_3$, *l* = 50 mm).

Proof of Absolute Stereochemistry:

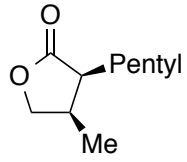
The absolute stereochemistry was confirmed by 1D nOe experiements between the C(3) and C(5) hydrogen atoms. No nOe via a 1,3-diaxial interaction is observed between these groups. An nOe correlation is observed between the C(5)-H and the C(3)-butyl substituent; an nOe correlation is also observed between the C(3)-H and the C(5)-methyl substituent. See spectroscopic data for further details.



(3*S*,5*R*)-3-butyl-5-methyltetrahydro-2*H*-pyran-2-one. **GC Method A**: 8.47 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (dd, 1H, *J* = 11.3, 3.9 Hz), 3.83 – 3.90 (m, 1H), 2.39 – 2.43 (m, 1H), 2.03 – 2.12 (m, 1H), 1.86 – 1.92 (m, 1H), 1.67 – 1.71 (m, 1H), 1.44 – 1.51 (m, 2H), 1.23 – 1.33 (m, 4H), 0.97 (d, 3H, *J* = 6.4 Hz), 0.95 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 74.8, 40.4, 34.4, 31.5, 29.0, 28.8, 22.8, 17.6, 14.2; IR 2978, 2931, 2973, 1734, 1459, 1213, 1155, 1109, 1045, 749, 750 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{10}H_{19}O_2$ $[M+H]^+$: 171.1380, found: 171.1384; $[\alpha]_D^{20}$ = + 3.4 (*c* = 0.260, $CHCl_3$, *l* = 50 mm).



***anti*-4-methyl-3-pentyldihydrofuran-2(3*H*)-one.** This compound has been synthesized previously in our laboratories and all spectroscopic data are in accord. **GC Method A**: 6.80 min.



***syn*-4-methyl-3-pentyldihydrofuran-2(3*H*)-one**. This compound has been synthesized previously in our laboratories and all spectroscopic data are in accord. **GC Method A**: 7.93 min.

GC Trace for the Determination of Regioselectivity

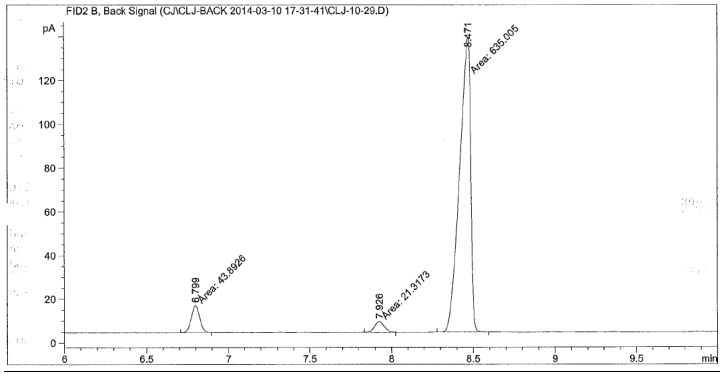
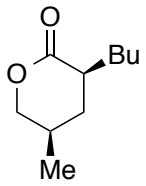


Table 2.4, Entry 2

(*R*,*E*)-2-methyloct-3-en-1-ol was subjected to hydroformylation using General Procedure D. Achiral GC analysis using GC Method A afforded three peaks corresponding to each γ-lactone product (6.80 min and 7.93 min) and the combined δ-lactone products (8.47 min). The diastereoselectivity of the reaction was determined by ^{1}H NMR in CD_3OD. Silica gel chromatography (10% EtOAc/Hex) afforded the following compounds:



(3*S*,5*R*)-3-butyl-5-methyltetrahydro-2*H*-pyran-2-one (2.51). Isolated as a colorless oil (18 mg, 52%). **GC Method A**: 8.47 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.28 (dd, 1H, *J* = 11.3, 3.9 Hz), 3.83 – 3.90 (m, 1H), 2.39 – 2.43 (m, 1H), 2.03 – 2.12 (m, 1H), 1.86 – 1.92 (m, 1H), 1.67 – 1.71 (m, 1H), 1.44 – 1.51 (m, 2H), 1.23 – 1.33 (m, 4H), 0.97 (d, 3H, *J* = 6.4 Hz), 0.95 (t, 3H, *J* = 7.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 74.8, 40.4, 34.4, 31.5, 29.0, 28.8, 22.8, 17.6, 14.2; IR 2978, 2931, 2973, 1734, 1459, 1213, 1155, 1109, 1045, 749, 750 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{10}H_{19}O_2$ $[M+H]^+$: 171.1380, found: 171.1384; $[\alpha]_D^{20}$ = + 3.4 (*c* = 0.260, $CHCl_3$, *l* = 50 mm).

GC Trace for the Determination of Regioselectivity

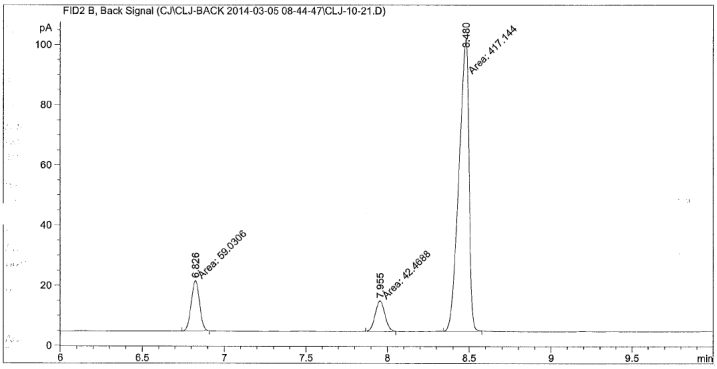
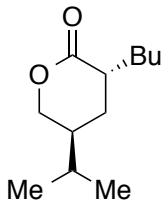


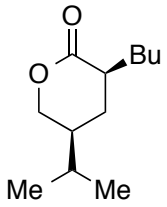
Table 2.4, Entry 3

(*R*,*Z*)-2-isopropyloct-3-en-1-ol was subjected to hydroformylation using General Procedure E. Achiral GC analysis using GC Method B afforded three peaks corresponding to the γ-lactone product (12.19 min) and the combined δ-lactone products (13.68 min). The diastereoselectivity of the reaction was determined by chiral GC

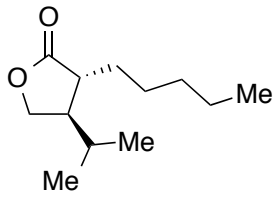
analysis using GC Method C to afford two signals, t_{minor} = 107.6 min, t_{major} = 107.9 min. Silica gel chromatography (10% EtOAc/Hex) afforded the following compounds:



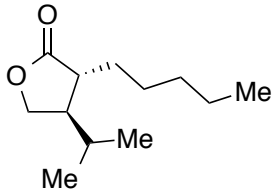
(3*R*,5*S*)-3-butyl-5-isopropyltetrahydro-2*H*-pyran-2-one (2.53). Isolated as a colorless oil (22 mg, 57%). **GC Method B**: 13.68 min, **GC Method C**: 107.9 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.25 (dd, 1H, *J* = 11.7, 4.9 Hz), 3.98 – 4.02 (m, 1H), 2.39 – 2.41 (m, 1H), 1.81 – 1.85 (m, 2H), 1.74 – 1.79 (m, 1H), 1.56 – 1.61 (m, 2H), 1.30 – 1.40 (m, 4H), 0.94 (d, 3H, *J* = 6.9 Hz), 0.92 (d, 3H, *J* = 7.3 Hz), 0.90 (t, 3H, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.8, 70.2, 38.7, 37.6, 30.9, 29.9, 29.3, 28.5, 22.8, 20.2, 19.9, 14.1; IR 2957, 2932, 2873, 1746, 1467, 1390, 1370, 1245, 1165, 1151, 1114, 1071, 1031 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{12}H_{23}O_2$ $[M+H]^+$: 199.1698, found: 199.1703; $[\alpha]_D^{20}$ = − 58.6 (*c* = 0.480, $CHCl_3$, *l* = 50 mm).



(3*S*,5*S*)-3-butyl-5-isopropyltetrahydro-2*H*-pyran-2-one. Isolated with (3*R*,5*S*)-3-butyl-5-isopropyltetrahydro-2*H*-pyran-2-one in an 88:12 ratio. **GC Method B**: 13.7 min, **GC Method C**: 107.6 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 (ddd, 1H, *J* = 10.3, 5.1, 1.7 Hz), 4.04 (dd, 1H, *J* = 11.3, 9.0 Hz), 2.39 – 2.41 (m, 1H), 2.04 – 2.10 (m, 1H), 1.74 – 1.85 (m, 2H), 1.56 – 1.61 (m, 1H), 1.30 – 1.40 (m, 6H), 0.94 (d, 3H, *J* = 6.9 Hz), 0.92 (d, 3H, *J* = 7.3 Hz), 0.90 (t, 3H, *J* = 6.9 Hz).

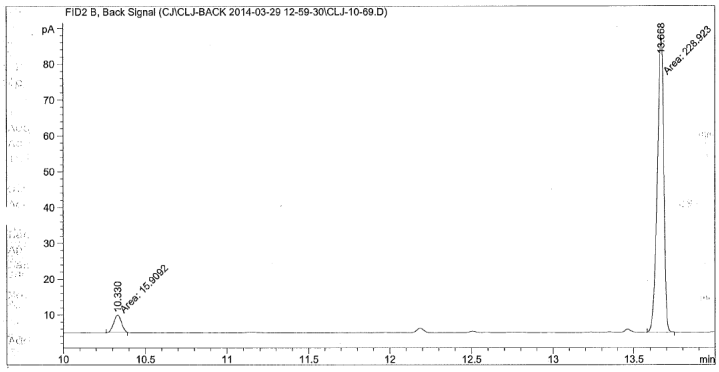


(3*R*,4*R*)-4-isopropyl-3-pentyldihydrofuran-2(3*H*)-one. **GC Method B**: 12.15 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.29 – 4.32 (m, 1H), 3.95 – 3.98 (m, 1H), 2.32 (q, 1H, *J* = 6.5 Hz), 2.09 – 2.12 (m, 1H), 1.64 – 1.77 (m, 3H), 1.41 – 1.49 (m, 1H), 1.29 – 1.32 (m, 5H), 0.96 (d, 3H, *J* = 7.0 Hz), 0.91 (d, 3H, *J* = 7.1 Hz), 0.89 (t, 3H, *J* = 6.8 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 180.1, 69.5, 46.4, 43.2, 32.0, 30.8, 30.6, 26.5, 22.6, 20.3, 19.2, 14.2.



(3*R*,4*R*)-4-isopropyl-3-pentyldihydrofuran-2(3*H*)-one. Not observed or isolated in any hydroformylation reaction (reactions carried out with ligand **3c** and control reactions with PPh_3).

GC Trace for Determination of Regioselectivity



GC Trace for Determination of Diastereoselectivity

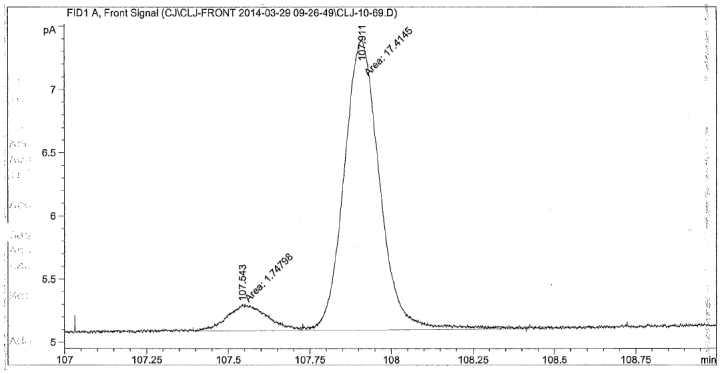
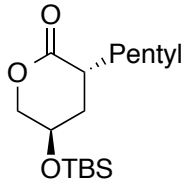
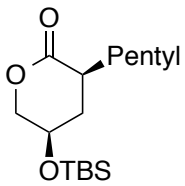


Table 2.4, Entry 4

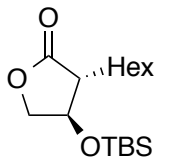
(*R*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)non-3-en-1-ol was subjected to hydroformylation using General Procedure F. Achiral GC analysis using GC Method F afforded four peaks corresponding to each γ-lactone product (18.26 min and 18.61 min) and each δ-lactone product (18.97 min and 19.13 min). Silica gel chromatography (10% EtOAc/Hex) afforded the following compounds:



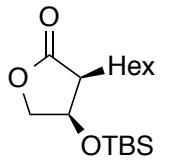
(*R*,*Z*)-2-((*tert*-butyldimethylsilyl)oxy)non-3-en-1-ol (2.55). Isolated as a colorless oil (30.9 mg, 51%). **GC Method F**: 18.97 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.27 (dd, 1H, *J* = 13.0, 5.1 Hz), 4.10 – 4.15 (m, 1H), 2.72 – 2.78 (m, 1H), 1.96 – 2.01 (m, 1H), 1.85 – 1.89 (m, 1H), 1.72 – 1.75 (m, 1H), 1.45 – 1.50 (m, 1H), 1.27 – 1.34 (m, 7H), 0.88 (s, 9H), 0.87 (t, 3H, *J* = 8.3 Hz), 0.076 (s, 3H), 0.072 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.2, 73.3, 64.1, 36.0, 33.9, 31.8, 30.9, 26.4, 25.9, 23.0, 18.2, 14.2, -4.7; IR 2954, 2929, 2858, 1737, 1464, 1255, 1213, 1102, 1059, 1026, 1007, 837, 807, 778 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{16}H_{33}O_3Si_1$ $[M+H]^+$: 301.2199, found: 301.2199; $[\alpha]_D^{20} = -9.7$ (*c* = 775, $CHCl_3$, *l* = 50 mm).



(3*S*,5*R*)-5-((*tert*-butyldimethylsilyl)oxy)-3-pentyltetrahydro-2*H*-pyran-2-one. **GC Method F**: 19.13 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.21 (dd, 1H, *J* = 11.0, 2.7 Hz), 4.05 (dd, 1H, *J* = 11.0, 5.6 Hz), 2.34 – 2.39 (m, 1H), 2.24 – 2.29 (m, 1H), 1.85 – 1.90 (m, 1H), 1.54 – 1.60 (m, 2H), 1.29 – 1.33 (m, 7H), 0.88 (s, 9H), 0.87 (t, 3H, *J* = 8.3 Hz), 0.077 (s, 3H), 0.072 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 72.9, 65.1, 38.2, 35.3, 31.9, 30.9, 26.6, 25.9, 22.7, 18.2, 14.2, -4.6.



(3*R*,4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-3-hexyldihydrofuran-2(3*H*)-one. **GC Method F**: 18.26 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.32 – 3.45 (m, 1H), 4.24 – 4.27 (m, 1H), 3.95 – 3.98 (m, 1H), 2.43 – 2.46 (m, 1H), 1.69 – 1.73 (m, 1H), 1.47 – 1.56 (m, 1H), 1.42 – 1.48 (m, 2H), 1.25 – 1.32 (m, 6H), 0.88 (s, 9H), 0.87 (t, 3H, *J* = 8.3 Hz), 0.082 (s, 3H), 0.066 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 73.4, 73.3, 48.8, 31.8, 29.3, 28.4, 27.0, 25.8, 22.8, 18.0, 14.2, -4.4, -4.6.



(3*S*,4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-3-hexyldihydrofuran-2(3*H*)-one. **GC Method F**: 18.61 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.51 – 4.53 (m, 1H), 3.83 (dd, 1H, *J* = 11.3, 3.4 Hz), 3.67 (dd, 1H, *J* = 11.3, 2.9 Hz), 2.69 – 2.71 (m, 1H), 2.31 – 2.36 (m, 1H), 1.94 – 1.98 (m, 1H), 1.85 – 1.87 (m, 1H), 1.29 – 1.41 (m, 7H), 0.89 (s, 9H), 0.87 (t, 3H, *J* = 7.3 Hz), 0.077 (s, 3H), 0.062 (s, 3H).

GC Trace for the Determination of Regio- and Diastereoselectivity

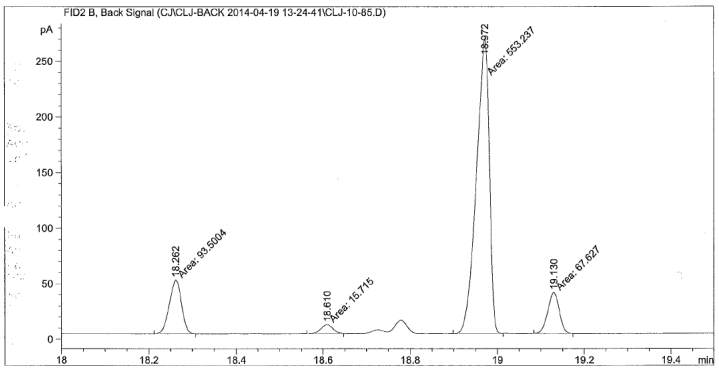
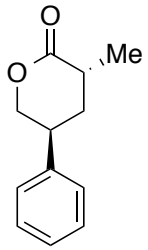


Table 2.4, Entry 5

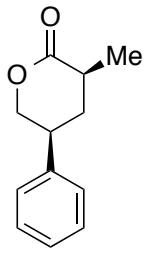
(*S*,*Z*)-2-phenylpent-3-en-1-ol was subjected to hydroformylation using General Procedure F. Achiral GC analysis using GC Method D afforded three peaks corresponding to each γ-lactone product (7.67 min and 7.73 min) and the combined δ-lactone products (8.46 min). The diastereoselectivity of the reaction was determined by ^{1}H NMR in $CDCl_3$. Silica gel chromatography (10% EtOAc/Hex) afforded the following compounds:



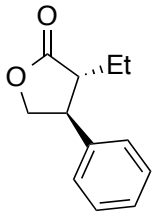
(3*R*,5*S*)-3-methyl-5-phenyltetrahydro-2*H*-pyran-2-one (2.57). Isolated as a colorless semi-solid (25 mg, 66%). **GC Method D**: 8.46 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.35 – 7.38 (m, 2H), 7.25 – 7.30 (m, 3H), 4.33 – 4.41 (m, 2H), 3.28 – 3.32 (m, 1H), 2.82 – 2.86 (m, 1H), 2.28 – 2.34 (m, 1H), 1.95 – 2.02 (m, 1H), 1.31 (d, 3H, J = 6.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 140.6, 129.2, 127.6, 127.4, 72.3, 38.5, 34.6, 33.1, 16.8; IR 2973, 2935, 1742, 1380, 1214, 1161, 1117, 1080, 1054, 1033, 755, 701, 668 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{12}H_{15}O_2$ $[M+H]^+$: 191.1072, found: 191.1067; $[\alpha]_D^{20}$ = − 25.1(*c* = 0.255, $CHCl_3$, *l* = 50 mm).

Proof of Absolute Stereochemistry:

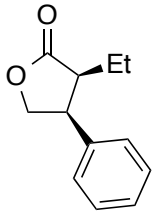
The absolute stereochemistry was confirmed by 1D nOe experiements between the C(3) and C(5) hydrogen atoms. No nOe via a 1,3-diaxial interaction is observed between these groups. An nOe correlation is observed between the C(5)-H and the C(3)-methyl substituent; an nOe correlation is also observed between the C(3)-H and the C(5)-aryl substituent. See spectroscopic data for further details.



(3*S*,5*S*)-3-methyl-5-phenyltetrahydro-2*H*-pyran-2-one. **GC Method D**: 8.46 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.36 (m, 2H), 7.27 – 7.30 (m, 1H), 7.23 – 7.25 (m, 2H), 4.48 – 4.50 (m, 1H), 4.26 (dd, 1H, *J* = 11.3, 10.3 Hz), 3.25 – 3.31 (m, 1H), 2.69 – 2.74 (m, 1H), 2.27 – 2.33 (m, 1H), 1.99 (q, 1H, *J* = 12.7 Hz), 1.36 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 140.3, 129.1, 127.6, 127.3, 74.5, 40.4, 36.2, 35.8, 16.9.



***anti*-3-ethyl-4-phenyldihydrofuran-2(3*H*)-one**. This compound has been synthesized previously in our laboratories and all spectroscopic data are in accord. **GC Method D**: 7.67 min.



***syn*-3-ethyl-4-phenyldihydrofuran-2(3*H*)-one**. This compound has been synthesized previously in our laboratories and all spectroscopic data are in accord. **GC Method D**: 7.73 min.

GC Trace for the Determination of Regioselectivity

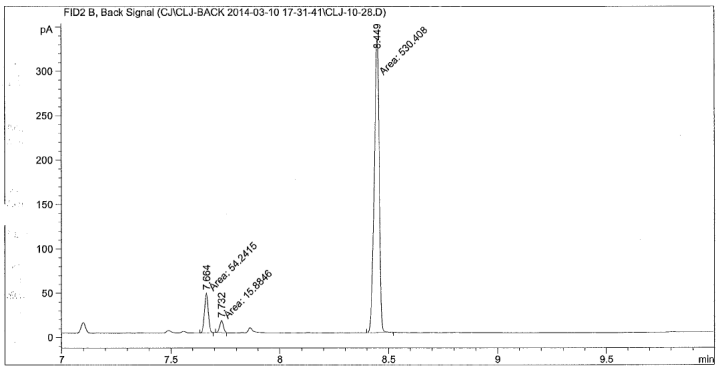
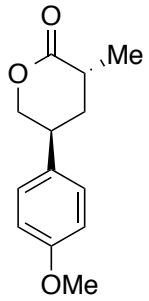


Table 2.4, Entry 6

(*S*,*Z*)-2-(4-methoxyphenyl)pent-3-en-1-ol was subjected to hydroformylation using General Procedure F. Achiral GC analysis using GC Method B afforded two peaks corresponding to the combined γ-lactone products (18.16 min and 17.73 min) and the combined δ-lactone products (19.48 min). The diastereoselectivity of the reaction was determined by ^{1}H NMR in $CDCl_3$. Silica gel chromatography (15% EtOAc/Hex) afforded the following compounds:

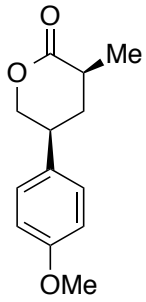


(3*R*,5*S*)-5-(4-methoxyphenyl)-3-methyltetrahydro-2*H*-pyran-2-one (2.59). Isolated as a colorless solid (32 mg, 72%). **GC Method B**: 19.48 min; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.17 (d, 2H, J = 8.8 Hz), 6.88 (d, 2H, J = 8.8 Hz), 4.30 – 4.36 (m, 2H), 3.80 (s, 3H), 3.21 – 3.28 (m, 1H), 2.78 – 2.86 (m, 1H), 2.23 – 2.29 (m, 1H), 1.92 – 1.98 (m, 1H), 1.30 (d, 3H, J = 6.7 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 159.0, 132.5, 128.4, 114.5, 72.5, 55.5, 37.6, 34.7, 33.0, 16.9; IR 2936, 1740, 1612, 130, 1278, 1248, 1214, 1161, 1084, 1055, 1033,

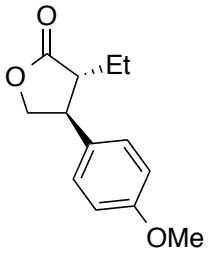
831, 750 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{13}H_{17}O_3$ $[M+H]^+$: 221.1178, found: 221.1184; $[\alpha]_D^{20} = -16.2$ ($c = 0.420$, $CHCl_3$, $l = 50$ mm).

Proof of Absolute Stereochemistry:

The absolute stereochemistry was confirmed by 1D nOe experiements between the C(3) and C(5) hydrogen atoms. No nOe via a 1,3-diaxial interaction is observed between these groups. An nOe correlation is observed between the C(5)-H and the C(3)-methyl substituent; an nOe correlation is also observed between the C(3)-H and the C(5)-aryl substituent. See spectroscopic data for further details.

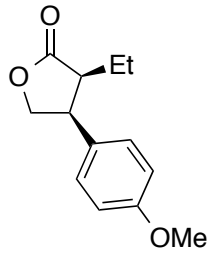


(3*S*,5*S*)-5-(4-methoxyphenyl)-3-methyltetrahydro-2*H*-pyran-2-one. **GC Method B**: 19.48 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, 2H, J = 8.8 Hz), 6.82 (d, 2H, J = 8.8 Hz), 4.45 (ddd, 1H, J = 13.2, 5.1, 2.2 Hz), 4.19 (t, 1H, J = 10.8 Hz), 3.80 (s, 3H), 3.20 – 3.26 (m, 1H), 2.66 – 2.71 (m, 1H), 2.23 – 2.29 (m, 1H), 1.84 (q, 1H, J = 12.7 Hz), 1.34 (d, 3H, J = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.1, 159.1, 132.2, 128.3, 114.4, 74.7, 55.5, 39.6, 36.2, 35.9, 17.3.



(3*R*,4*S*)-3-ethyl-4-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one. **GC Method B**: 17.73 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.18 (d, 2H, J = 8.8 Hz), 6.90 (d, 2H, J = 8.8 Hz), 4.49 – 4.52 (m, 1H), 4.06 – 4.09 (m, 1H), 3.81 (s, 3H), 3.34 – 3.42 (m, 1H), 2.61 – 2.66 (m, 1H), 1.77 –

1.83 (m, 1H), 1.67 – 1.73 (m, 1H), 0.94 (t, 3H, J = 7.6 Hz); ^{13}C NMR (101 MHz, $CDCl_3$) δ 178.4, 159.3, 130.4, 128.5, 114.7, 72.4, 55.5, 47.9, 46.6, 22.1, 11.2.



(3*S*,4*S*)-3-ethyl-4-(4-methoxyphenyl)dihydrofuran-2(3*H*)-one. **GC Method B**: 18.16 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, 2H, J = 8.8 Hz), 6.85 (d, 2H, J = 8.3 Hz), 4.55 (dd, 1H, J = 9.3, 5.9 Hz), 4.43 (dd, 1H, J = 9.3, 2.5 Hz), 3.80 (s, 3H), 3.65 – 3.69 (m, 1H), 2.67 – 2.72 (m, 1H), 1.61 – 1.66 (m, 1H), 1.07 – 1.12 (m, 1H), 0.90 (t, 3H, J = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.9, 130.8, 128.9, 128.1, 114.5, 73.0, 55.5, 46.5, 44.2, 19.4, 12.3.

GC Trace for the Determination of Regioselectivity

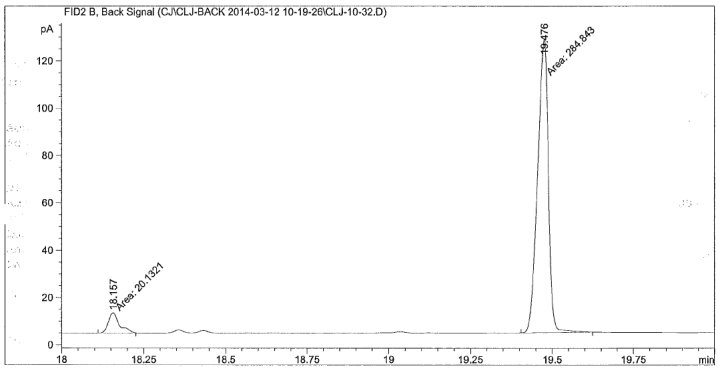
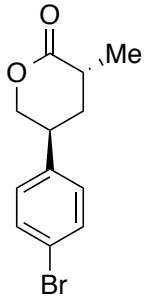
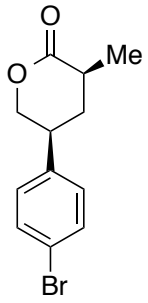


Table 2.4, Entry 7

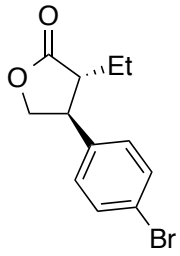
(*S*,*Z*)-2-(4-bromophenyl)pent-3-en-1-ol was subjected to hydroformylation using General Procedure F. The regioselectivity and diastereoselectivity of the hydroformylation reaction was determined by ^{1}H NMR in $CDCl_3$. Silica gel chromatography (15% EtOAc/Hex) afforded the following compounds:



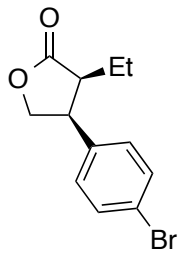
(3*R*,5*S*)-5-(4-bromophenyl)-3-methyltetrahydro-2*H*-pyran-2-one (2.61). Isolated as a colorless solid (33 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.47 (d, 2H, *J* = 8.3 Hz), 7.12 (d, 2H, *J* = 8.3 Hz), 4.29 – 4.37 (m, 2H), 3.23 – 3.29 (m, 1H), 2.78 – 2.83 (m, 1H), 2.21 – 2.27 (m, 1H), 1.94 – 2.00 (m, 1H), 1.29 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 139.5, 132.3, 129.1, 121.5, 71.9, 38.0, 34.6, 33.0, 16.9; IR 2973, 2936, 1743, 1490, 1361, 1160, 1117, 1074, 1056, 1034, 1009, 821, 752 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{12}H_{14}Br_1O_2$ $[M+H]^+$: 269.0177, found: 269.0187; $[\alpha]_D^{20} = -22.9$ (*c* = 0.640, $CHCl_3$, *l* = 50 mm).



(3*S*,5*S*)-5-(4-bromophenyl)-3-methyltetrahydro-2*H*-pyran-2-one. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, 2H, *J* = 8.8 Hz), 7.11 (d, 2H, *J* = 8.8 Hz), 4.46 – 4.49 (m, 1H), 4.22 (dd, 1H, *J* = 11.5, 9.5 Hz), 3.23 – 3.27 (m, 1H), 2.68 – 2.73 (m, 1H), 2.27 – 2.33 (m, 1H), 1.83 (q, 1H, *J* = 12.4 Hz), 1.35 (d, 3H, *J* = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.9, 139.5, 132.3, 129.0, 121.5, 73.9, 39.9, 36.0, 35.7, 17.1.



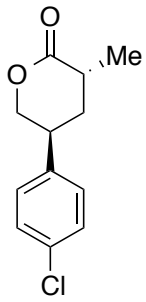
(3*R*,4*S*)-4-(4-bromophenyl)-3-ethyldihydrofuran-2(3*H*)-one. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.50 (d, 2H, *J* = 8.3 Hz), 7.14 (d, 2H, *J* = 8.3 Hz), 4.52 (t, 1H, *J* = 8.8 Hz), 4.07 (t, 1H, *J* = 9.5 Hz), 3.37 – 3.43 (m, 1H), 2.62 – 2.66 (m, 1H), 1.78 – 1.84 (m, 1H), 1.67 – 1.72 (m, 1H), 0.93 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.8, 137.8, 132.5, 129.1, 121.9, 71.9, 47.9, 46.8, 22.2, 11.3.



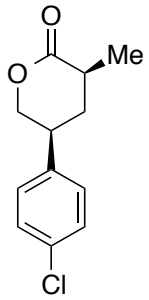
(3*S*,4*S*)-4-(4-bromophenyl)-3-ethyldihydrofuran-2(3*H*)-one. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.45 (d, 2H, *J* = 8.8 Hz), 7.03 (d, 2H, *J* = 8.8 Hz), 4.55 (dd, 1H, *J* = 9.3, 6.4 Hz), 4.40 (dd, 1H, *J* = 9.3, 2.0 Hz), 3.65 – 3.69 (m, 1H), 2.73 (dt, 1H, *J* = 8.3, 5.4 Hz), 1.61 – 1.66 (m, 1H), 1.01 – 1.08 (m, 1H), 0.90 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.3, 137.9, 132.3, 129.5, 121.8, 72.5, 46.3, 44.5, 19.4, 12.3.

Table 2.4, Entry 8

(*S*,*Z*)-2-(4-chlorophenyl)pent-3-en-1-ol was subjected to hydroformylation using General Procedure F. The regioselectivity and diastereoselectivity of the hydroformylation reaction was determined by ^{1}H NMR in $CDCl_3$. Silica gel chromatography (15% EtOAc/Hex) afforded the following compounds:



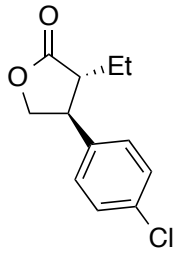
(3*R*,5*S*)-5-(4-chlorophenyl)-3-methyltetrahydro-2*H*-pyran-2-one (2.63). Isolated as a colorless oil (30 mg, 68%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (d, 2H, *J* = 8.3 Hz), 7.19 (d, 2H, *J* = 8.3 Hz), 4.29 – 4.37 (m, 2H), 3.25 – 3.31 (m, 1H), 2.79 – 2.84 (m, 1H), 2.22 – 2.28 (m, 1H), 1.95 – 2.01 (m, 1H), 1.31 (d, 3H, *J* = 6.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.0, 139.0, 133.4, 129.3, 128.7, 71.9, 37.9, 34.5, 32.9, 16.8; IR 2973, 2936, 1743, 1493, 1413, 1236, 1161, 1117, 1090, 1057, 1034, 827 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{12}H_{14}Cl_1O_2$ $[M+H]^+$: 225.0682, found: 221.0689; $[\alpha]_D^{20} = -22.4$ (*c* = 0.500, $CHCl_3$, *l* = 50 mm).



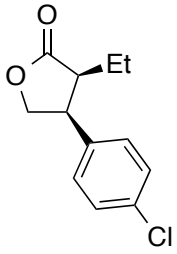
(3*S*,5*S*)-5-(4-chlorophenyl)-3-methyltetrahydro-2*H*-pyran-2-one. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dd, 2H, *J* = 6.4, 2.0 Hz), 7.16 (dd, 2H, *J* = 6.4, 2.0 Hz), 4.46 – 4.49 (m, 1H), 4.22 (dd, 1H, *J* = 11.3, 9.8 Hz), 3.23 – 3.29 (m, 1H), 2.67 – 2.73 (m, 1H), 2.27 – 2.32 (m, 1H), 1.82 (dd, 1H, *J* = 24.9, 12.7 Hz), 1.35 (d, 3H, *J* = 7.3 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 173.9, 138.9, 133.5, 129.3, 128.6, 74.0, 39.8, 36.0, 35.8, 17.2.

Proof of Absolute Stereochemistry:

The absolute stereochemistry was confirmed by 1D nOe experiements between the C(3) and C(5) hydrogen atoms. An nOe correlation is observed between these two hydrogen substituents. See spectroscopic data for further details.



(3*R*,4*S*)-4-(4-chlorophenyl)-3-ethyldihydrofuran-2(3*H*)-one. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (d, 2H, *J* = 8.3 Hz), 7.20 (d, 2H, *J* = 8.3 Hz), 4.52 (t, 1H, *J* = 8.6 Hz), 4.08 (t, 1H, *J* = 9.3 Hz), 3.39 – 3.45 (m, 1H), 2.62 – 2.66 (m, 1H), 1.78 – 1.84 (m, 1H), 1.67 – 1.73 (m, 1H), 0.94 (t, 3H, *J* = 7.6 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.9, 137.24 133.9, 129.6, 128.8, 72.0, 47.9, 46.8, 22.2, 11.3.

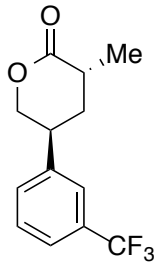


(3*S*,4*S*)-4-(4-chlorophenyl)-3-ethyldihydrofuran-2(3*H*)-one. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (dd, 2H, *J* = 6.4, 2.0 Hz), 7.10 – 7.11 (m, 2H), 4.56 (dd, 1H, *J* = 9.3, 5.9 Hz), 4.42 (dd, 1H, *J* = 9.3, 2.0 Hz), 3.68 – 3.72 (m, 1H), 2.71 – 2.78 (m, 1H), 1.62 – 1.68 (m, 1H), 1.03 = 1.09 (m, 1H),

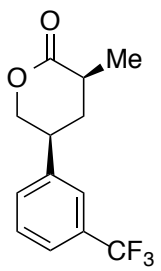
0.91 (t, 3H, J = 7.3 Hz); ^{13}C NMR (151 MHz, $CDCl_3$) δ 178.3, 137.4, 133.7, 129.3, 129.2, 72.6, 46.3, 44.4, 19.4, 12.3.

Table 2.4, Entry 9

(*S*,*Z*)-2-(3-trifluoromethylphenyl)pent-3-en-1-ol was subjected to hydroformylation using General Procedure F. The regioselectivity and diastereoselectivity of the hydroformylation reaction was determined by ^{1}H NMR in $CDCl_3$. Silica gel chromatography (15% EtOAc/Hex) afforded the following compounds:

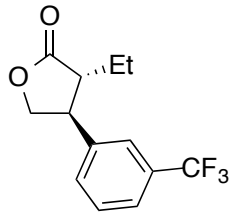


(3*R*,5*S*)-3-methyl-5-(3-(trifluoromethyl)phenyl)tetrahydro-2*H*-pyran-2-one (2.65). Isolated as a colorless oil (38 mg, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, 1H, J = 7.8 Hz), 7.45 – 7.49 (m, 3H), 4.34 – 4.41 (m, 2H), 3.33 – 3.40 (m, 1H), 2.82 – 2.87 (m, 1H), 2.27 – 2.33 (m, 1H), 1.99 – 2.05 (m, 1H) 1.30 (d, 3H, J = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.9, 141.6, 131.5 (q, $J_{C\text{-}F}$ = 32 Hz), 130.9, 129.7, 124.5, 124.1, 124.0 (q, $J_{C\text{-}F}$ = 272 Hz), 71.7, 38.4, 34.5, 32.9, 16.8; ^{19}F NMR (470 MHz, $CDCl_3$) δ − 62.7; IR 2977, 2939, 1745, 1382, 1162, 1121, 1059, 917, 805, 704, 664 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{13}H_{14}F_3O_2$ $[M+H]^+$: 259.0946, found: 259.0946; $[\alpha]_D^{20}$ = − 16.4 (c = 0.600, $CHCl_3$, l = 50 mm).

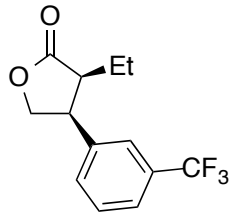


(3*S*,5*S*)-3-methyl-5-(3-(trifluoromethyl)phenyl)tetrahydro-2*H*-pyran-2-one. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.55 (d, 1H, J = 7.3 Hz), 7.46 – 7.50 (m, 3H), 4.51 (ddd, 1H, J = 13.7, 5.4, 2.2 Hz), 4.27 (dd, 1H, J = 11.3, 9.8 Hz), 3.33 – 3.38 (m, 1H), 2.70 – 2.75 (m, 1H), 2.32 – 2.36 (m, 1H), 1.85

(m, 1H), 1.36 (d, 3H, J = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 173.7, 141.5, 131.4, (q, $J_{C\text{-}F}$ = 32 Hz), 130.0, 129.7, 124.6, 124.2 (q $J_{C\text{-}F}$ = 273 Hz), 124.1, 73.3, 40.2, 36.0, 35.7, 17.1; ^{19}F NMR (470 MHz, $CDCl_3$) δ − 62.7.



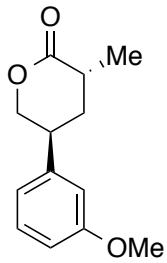
(3*R*,4*S*)-3-ethyl-4-(3-(trifluoromethyl)phenyl)dihydrofuran-2(3*H*)-one. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (d, 1H, J = 7.8 Hz), 7.46 – 7.57 (m, 3H), 4.58 (t, 1H, J = 8.6 Hz), 4.13 (t, 1H, J = 9.5 Hz), 3.51 (app q, 1H, J = 9.6 Hz), 2.66 – 2.73 (m, 1H), 1.81 – 1.86 (m, 1H), 1.70 – 1.76 (m, 1H), 0.95 (t, 3H, J = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 177.6, 129.9, 131.8 (q, $J_{C\text{-}F}$ = 32 Hz), 130.8, 130.0, 125.0, 124.4, 124.1 (q, $J_{C\text{-}F}$ = 272 Hz), 71.9, 47.9, 47.1, 22.3, 11.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ − 62.7.



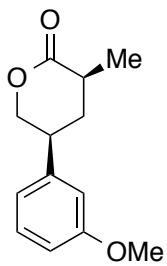
(3*S*,4*S*)-3-ethyl-4-(3-(trifluoromethyl)phenyl)dihydrofuran-2(3*H*)-one. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.57 (d, 1H, J = 7.8 Hz), 7.48 (t, 1H, J = 7.8 Hz), 7.40 (s, 1H), 7.38 (d, 1H, J = 7.8 Hz), 4.60 (dd, 1H, J = 9.3, 6.4 Hz), 4.46 (dd, 1H, J = 9.5, 2.2 Hz), 3.78 – 3.81 (m, 1H), 2.76 – 2.81 (m, 1H), 1.62 – 1.66 (m, 1H), 1.00 – 1.06 (m, 1H), 0.93 (t, 3H, J = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.1, 139.9, 131.4 (q, $J_{C\text{-}F}$ = 32 Hz), 130.8, 129.8, 124.9, 124.8, 124.0 (q, $J_{C\text{-}F}$ = 273 Hz), 72.3, 46.3, 44.9, 19.5, 12.2; ^{19}F NMR (470 MHz, $CDCl_3$) δ − 62.7.

Table 2.4, Entry 10

(*S*,*Z*)-2-(3-methoxyphenyl)pent-3-en-1-ol was subjected to hydroformylation using General Procedure F. Achiral GC analysis using GC Method E afforded three peaks corresponding to each γ-lactone product (10.36 min and 10.51 min) and the combined δ-lactone products (12.02 min). The diastereoselectivity of the reaction was determined by ^{1}H NMR in $CDCl_3$. Silica gel chromatography (15% EtOAc/Hex) afforded the following compounds:

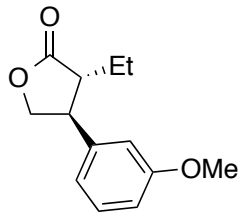


(3*R*,5*S*)-5-(3-methoxyphenyl)-3-methyltetrahydro-2*H*-pyran-2-one (2.67). Isolated as a colorless solid (34 mg, 77%). **GC Method E**: 12.02 min.; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.28 (m, 1H), 6.77 – 6.83 (m, 3H), 4.33 – 4.38 (m, 2H), 3.81 (s, 3H), 3.25 – 3.28 (m, 1H), 2.80 – 2.85 (m, 1H), 2.26 – 2.32 (m, 1H), 1.96 – 2.00 (m, 1H), 1.30 (d, 3H, J = 6.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 175.4, 160.2, 142.2, 132.2, 119.6, 113.7, 112.4, 72.2, 55.5, 38.5, 34.6, 33.0, 16.8; IR 2936, 1742, 1601, 1585, 1488, 1456, 1263, 1159, 1117, 1085, 1035, 781, 670 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{13}H_{17}O_3$ $[M+H]^+$: 221.1178, found: 221.1172; $[\alpha]_D^{20} = -13.1$ (c = 1.01, $CHCl_3$, l = 50 mm).

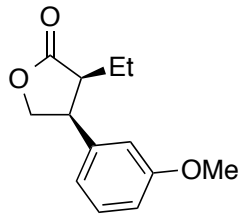


(3*S*,5*S*)-5-(3-methoxyphenyl)-3-methyltetrahydro-2*H*-pyran-2-one. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.30 (m, 1H), 6.77 – 6.83 (m, 3H), 4.49 (ddd, 1H, J = 11.3, 5.4, 2.5 Hz), 4.25 (dd, 1H, J = 11.3, 10.3 Hz), 3.80 (s, 3H), 3.22 – 3.27 (m, 1H), 2.67 – 2.73 (m, 1H), 2.27 – 2.32 (m, 1H), 1.83 –

1.91 (m, 1H), 1.35 (d, 3H, *J* = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 174.0, 160.2, 141.9, 130.2, 119.5, 113.5, 112.6, 74.4, 55.4, 40.4, 36.2, 35.8, 17.3.



(3*R*,4*S*)-3-ethyl-4-(3-methoxyphenyl)dihydrofuran-2(3*H*)-one. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 (t, 1H, *J* = 7.3 Hz), 6.83 – 6.87 (m, 2H), 6.79 (s, 1H), 4.53 (t, 1H, *J* = 8.6 Hz), 4.12 (t, 1H, *J* = 9.3 Hz), 3.82 (s, 3H), 3.38 – 3.44 (m, 1H), 2.67 – 2.71 (m, 1H), 1.77 – 1.85 (m, 1H), 1.69 – 1.76 (m, 1H), 0.96 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.3, 160.3, 140.4, 130.4, 119.7, 113.7, 112.8, 72.2, 55.5, 47.8, 47.3, 22.2, 11.2.



(3*S*,4*S*)-3-ethyl-4-(3-methoxyphenyl)dihydrofuran-2(3*H*)-one. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (d, 1H, *J* = 7.8 Hz), 6.82 (dd, 1H, *J* = 8.3, 2.4 Hz), 6.75 (d, 1H, *J* = 7.8 Hz), 6.69 (app t, 1H, *J* = 2.0 Hz), 4.55 (dd, 1H, *J* = 9.3, 5.9 Hz), 4.46 (dd, 1H, *J* = 9.3 2.5 Hz), 3.79 (s, 3H), 3.66 – 3.69 (m, 1H), 2.69 – 2.74 (m, 1H), 1.61 – 1.66 (m, 1H), 1.08 – 1.14 (m, 1H), 0.92 (t, 3H, *J* = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$) δ 178.7, 160.1, 140.4, 130.2, 120.0, 113.9, 112.8, 72.7, 55.4, 46.4, 45.0, 22.8, 14.3.

GC Trace for the Determination of Regioselectivity

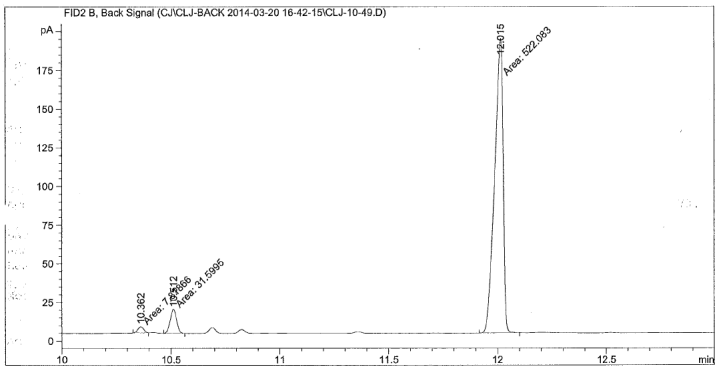
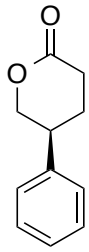


Table 2.4, Entry 11

(*S*)-2-phenylbut-3-en-1-ol was subjected to hydroformylation using General Procedure G. The regioselectivity of the hydroformylation reaction was determined by ^{1}H NMR in $CDCl_3$. Silica gel chromatography (15% EtOAc/Hex) afforded the following compounds:



(*S*)-5-phenyltetrahydro-2*H*-pyran-2-one (2.69). Isolated as a colorless solid (28 mg, 80%). This compound has been synthesized previously in our laboratories (in racemic form) and all spectroscopic data are in accord. $[\alpha]_D^{20}$ = + 25.1 (*c* = 0.520, $CHCl_3$, *l* = 50 mm).

Table 2.5

The following compounds have been synthesized previously and are in accord with reported NMR spectra: (*Z*)-4-phenylbut-2-en-1-ol (**2.70**),[39] 5-phenylpent-3-yn-1-ol,[40] (*Z*)-

[39] Nicolaou, K. C.; Yue, E. W.; la Greca, S.; Nadin, A.; Yang, Z. Leresche, J. E.; Tsuri, T.; Naniwa, Y.; de Riccardis, F. *Chem. Eur. J.* **1995**, *1*, 467 – 494.

6-phenylhex-4-en-1-ol (**2.72**),[41] 3-hydroxy-2-(2-phenylethyl)propionic acid,[42] 3-benzyldihydrofuran-2(3*H*)-one,[43] 3-benzyltetrahydro-2*H*-pyran-2-ol,[44] 3-benzyltetrahydro-2*H*-pyran-2-one.[45]

General Procedure H: In a dry box, the appropriate alcohol substrate (0.200 mmol), (4*S*)-4-(*tert*-butyl)-3-(3-(diphenylphosphanyl)benzyl)-2-methoxyoxazolidine (8.7 mg, 0.020 mmol), a *p*-toluenesulfonic acid in benzene (351 μL, 2.0 x 10^{-4} mmol, 5.72 x 10^{-4} M solution) were mixed in C_6D_6 (0.8 mL) and allowed to equilibrate in a sealed NMR tube at 45 °C for 3 hours. (Note: the appearance of methanol can be monitored by ^{1}H NMR). The solution was concentrated in the dry box to remove the generated MeOH, the residue was redissolved in C_6D_6, and was allowed to equilibrate for an additional 4 hours at 45 °C before being concentrated again in the dry box. The appearance of free MeOH can be monitored by ^{1}H NMR. The resulting mixture was dissolved in benzene (3.5 mL), mixed with 3% Rh(acac)$(CO)_2$ (1.5 mg, 0.006 mmol), and injected into the Endeavor, followed by 0.5 mL benzene to wash the injection port.

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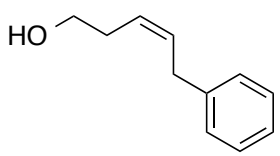
[40] Qian, M.; Negishi, E. *Tetrahedron* **2005**, *46*, 2927 – 2930.
[41] Kwon, H.; Park, C.; Lee, S.; Youn, J.-H.; Kang, S. *Chem. Eur. J.* **2008**, *14*, 1023 – 1028.
[42] Gersh, M.; Gut, F.; Korotkov, V. S.; Lehmann, J.; Bottcher, T.; Rusch, M.; Hedberg, C.; Waldmann, H.; Klebe, G.; Sieber, S. A. *Angew Chem. Int. Ed.* **2013**, *52*, 3009 – 3014.
[43] Miao, L.; Haque, I.; Manzoni, M. R.; Tham, W. S.; Chemler, S. R. *Org. Lett.* **2010**, *12*, 4739 – 4741.
[44] Newsome, P. W.; Kuehn, C.; Takusagawa, F.; Takacs, J. M. *Tetrahedron* **1990**, *46*, 5507 – 5522.
[45] Evans, D. A.; Kwan, E. E.; Scheerer, O. R. *J. Org. Chem.* **2013**, *78*, 175 – 203.

General Procedure I (Control reaction using PPh_3 as ligand): In a dry box, the appropriate alcohol substrate (0.200 mmol), triphenylphosphine (5.2 mg, 0.020 mmol), and $Rh(acac)(CO)_2$ (1.5 mg, 0.006 mmol) were mixed in benzene (3.5 mL). The resulting yellow solution was injected into the Endeavor, followed by 0.5 mL benzene to wash the injection port.

Table 2.5, Entry 1

The reaction was carried out according to General Procedure H and I. Upon completion of the hydroformylation reaction, the benzene was removed *in vacuo* and internal standard (mesitylene in $CDCl_3$) was added to determine conversion, based on remaining starting material, by ^1H NMR. The mixture was concentrated on a rotary evaporator in a glass scintillation vial. To the vial was added a magnetic stir bar, acetonitrile (0.75 mL), water (0.75 mL), sodium phosphate (144 mg, 1.20 mmol), and 35% aqueous H_2O_2 (0.120 mL, 1.23 mmol). The reaction was cooled to 0 °C and a solution of sodium chlorite (tech. grade, 80%, 138 mg, 1.2 mmol) in water (0.75 mL), was added dropwise. The reaction was stirred and warmed to room temperature over 3 hours. The reaction as quenched by the addition of sodium sulfite (spatula tip) and 1M aqueous HCl (3 mL). The reaction was extracted with DCM (3 x 10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude reaction was analyzed by ^1H NMR in $CDCl_3$ to determine the regioselectivity of the reaction.

Table 2.5, Entry 2

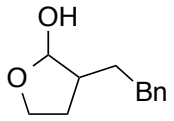


(*Z*)-5-phenylpent-3-en-1-ol (2.71). A round-bottom flask was charged with Lindlar's catalyst (330 mg) and purged with nitrogen. 5-phenylpent-3-yn-1-ol (660 mg, 4.11 mmol) in MeOH (12.5 mL) was added followed by quinoline (35 μL, 0.27 mmol). The flask was evacuated and refilled with H_2 four times, fitted with a H_2 balloon, and stirred at room temperature under H_2 for 2.5 h. The reaction was filtered through a plug of silica and concentrated. Column chromatography (20% EtOAc/Hex) yielded a light yellow oil (495 mg, 76%).

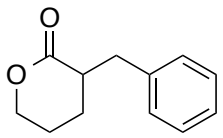
^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 – 8.31 (m, 2H), 7.18 – 7.21 (m, 3H), 5.74 – 5.79 (m, 1H), 5.51 – 5.56 (m, 1H), 3.71 (t, 2H, *J* = 6.6 Hz), 3.45 (d, 2H, *J* = 7.3 Hz), 2.44 – 2.48 (m, 2H), 1.44 (br s, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 140.9, 131.6, 128.7, 128.5, 126.4, 126.2, 62.5, 33.8, 31.0; IR 3337, 3025, 2939, 2883, 1602, 1495, 1453, 1400, 1047, 738, 679, 621, 562 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{11}H_{15}O_1$ $[M+H-H_2O]^+$: 163.1123, found: 163.1128.

The reaction was carried out according to General Procedure H and I. Upon completion of the hydroformylation reaction, the benzene was removed *in vacuo* and internal standard (mesitylene in $CDCl_3$) was added to determine conversion, based on remaining starting material, by ^{1}H NMR. The regioselectivity of the reaction was determined at this point by comparison of the lactol peaks in the crude ^{1}H NMR. The solvent was removed under reduced pressure. The crude hydroformylation mixture was added, as a solution in

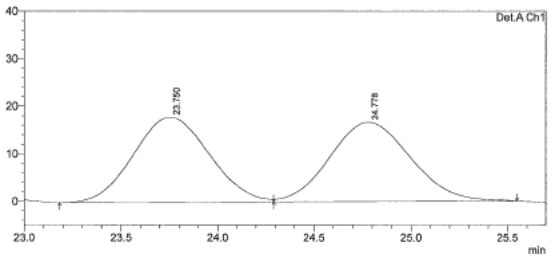
dichloromethane (3 mL), to a scintillation vial containing pyridinium chlorochromate (129 mg, 0.597 mmol), sodium acetate (16.0 mg, 0.195 mmol), and 4 Å molecular sieves. The reaction was stirred for 12 hours at room temperature, eluted through a short plug of silica gel (100% Et_2O), concentrated under reduced pressure, and subjected to silica gel chromatography (20% EtOAc/Hex). HPLC analysis of the δ-lactone was used to determine the enantioselectivity of the hydroformylation reaction.



3-phenethyltetrahydrofuran-2-ol. Exists as a 1:1 mixture of diastereomers. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.30 (m, 4H), 7.18 – 7.21 (m, 6H), 5.34 (t, 1H, *J* = 3.7 Hz), 5.22 (t, 1H, *J* = 2.4 Hz), 4.09 – 4.13 (m, 1H), 4.03 (dd, 1H, *J* = 15.7, 7.3 Hz), 3.93 – 3.97 (m, 1H), 3.82 (dd, 1H, *J* = 15.7, 7.3 Hz), 3.04 (d, 1H, *J* = 2.9 Hz), 2.83 (d, 1H, *J* = 2.9 Hz), 2.66 – 2.70 (m, 4H), 2.17 – 2.22 (m, 1H), 2.11 – 2.14 (m, 1H), 2.01 – 2.04 (m, 1H), 1.91 – 1.98 (m, 1H), 1.76 – 1.84 (m, 2H), 1.57 – 1.65 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.4, 142.0, 128.6, 128.5, 126.1, 126.0, 103.4, 98.4, 67.3, 67.1, 46.2, 44.0, 34.8, 34.4, 34.3, 30.7, 20.5, 29.1; IR 3394, 2930, 2858, 1496, 1454, 1118, 1029, 1012, 986, 908, 749, 699, 497 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{12}H_{15}O_1$ $[M+H-H_2O]^+$: 175.1123, found: 175.1118.



3-benzyltetrahydro-2*H*-pyran-2-one. PCC oxidation and chromatography (15% EtOAc/Hex) afforded the title compound as a colorless oil). All spectroscopic data for this compound are in accord with previously published reports.[45] **HPLC** (OD-H, 0.50 mL/min, 5% *i*-PrOH, 95% hexanes, 220 nm) $t_{r(minor)}$ = 23.2 min and $t_{r(major)}$ = 24.2 min, 19% ee.



Peak#	Ret. Time	Area	Height	Area %	Height %
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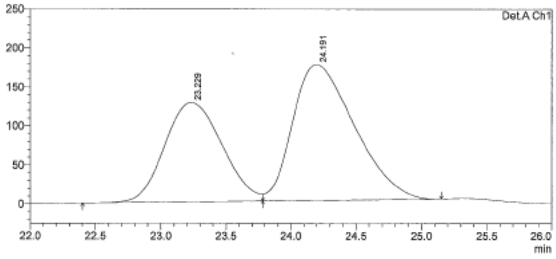
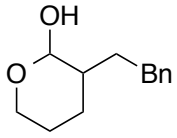
2	24.778	479468	16606	49.729	48.224
Total		964166	34434	100.000	100.000



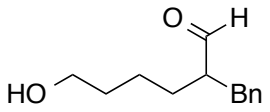
Peak#	Ret. Time	Area	Height	Area %	Height %
1	23.229	3879459	127157	40.391	42.204
2	24.191	5725203	174137	59.609	57.796
Total		9604663	301294	100.000	100.000

Table 2.5, Entry 3

The reaction was carried out according to General Procedure H and I. Upon completion of the hydroformylation reaction, the benzene was removed *in vacuo* and internal standard (mesitylene in $CDCl_3$) was added to determine conversion, based on remaining starting material, by ^1H NMR. The regioselectivity of the reaction was determined at this point by comparison of the lactol and aldehyde peaks in the crude ^1H NMR.



3-phenethyltetrahydro-2*H*-pyran-2-ol. Exists as a 1:1 mixture of diastereomers. ^1H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.29 (m, 4H), 7.18 – 7.21 (m, 6H), 5.11 (d, 1H, J = 2.5 Hz), 4.48 (d, 1H, J = 6.4 Hz), 3.97 – 4.02 (m, 2H), 3.55 – 3.58 (m, 1H), 3.47 – 3.50 (m, 1H), 2.60 – 2.73 (m, 4H), 1.99 – 2.03 (m, 2H), 1.67 – 1.76 (m, 2H), 1.45 – 1.61 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 142.6, 128.5, 125.9, 99.7, 94.0, 65.4, 60.0, 41.5, 39.4, 33.5, 33.2, 27.4, 25.5, 24.9, 23.8; IR 3387, 2933, 2855, 1496, 1454, 1273, 1130, 1072, 1027, 986, 903, 867, 577, 544 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{13}H_{17}O_1$ $[M+H-H_2O]^+$: 189.1279, found: 189.1284.

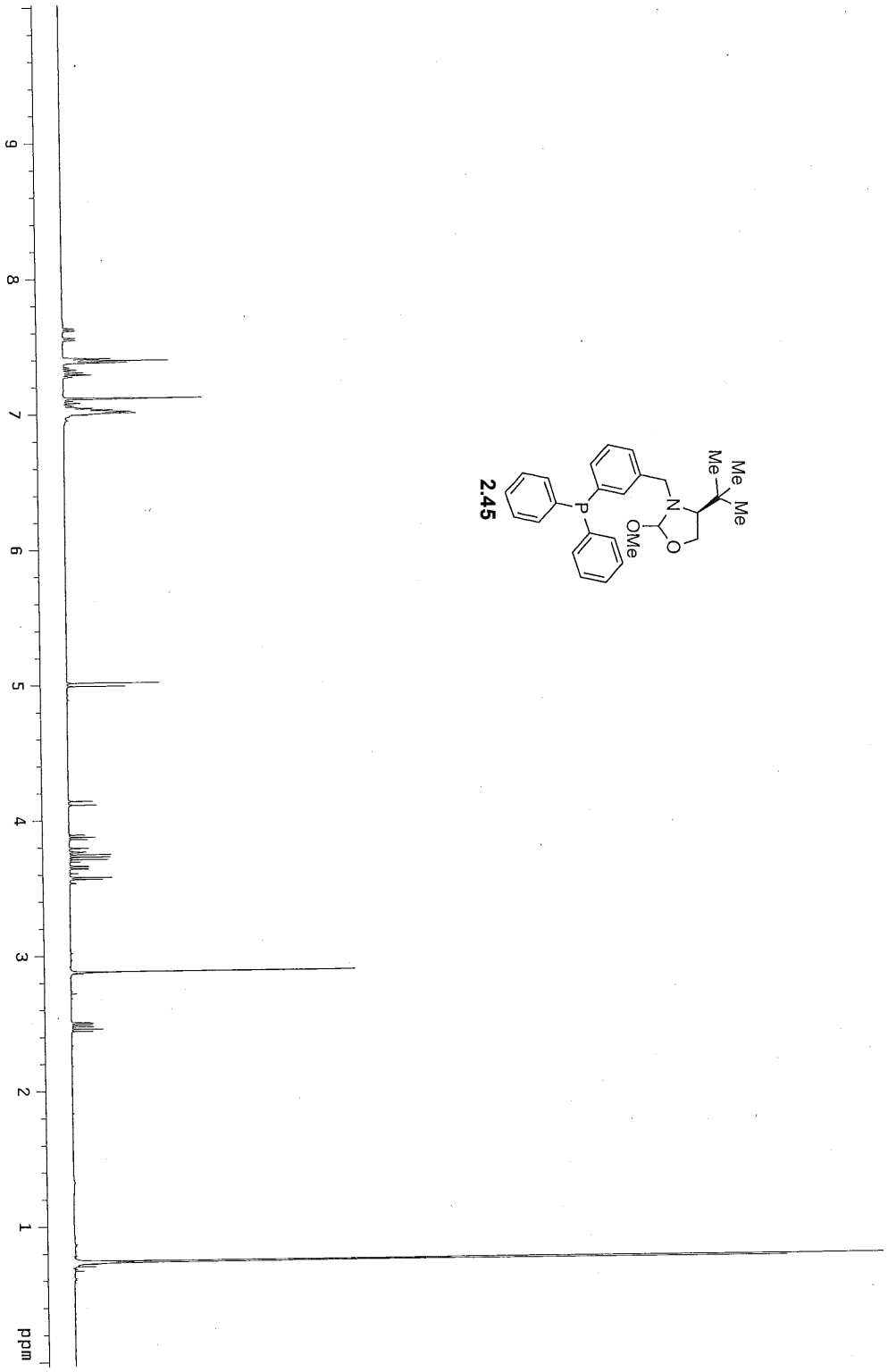


2-benzyl-6-hydroxyhexanal. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.65 (d, 1H, J = 5.0 Hz), 7.25 – 7.30 (m, 2H), 7.15 – 7.22 (m, 3H), 3.61 (t, 2H, J = 6.4 Hz), 3.00 (dd, 1H, J = 14.1, 7.3 Hz), 2.74 (dd, 1H, J = 14.2, 6.8 Hz), 2.62 – 2.64 (m, 1H), 1.35 – 1.67 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 204.7, 138.9, 129.1, 128.7, 126.6, 62.7, 53.6, 35.2, 32.8, 28.4, 23.4; IR 3027, 2935, 2861, 1703, 1454, 1406, 1210, 1170, 1072, 1053, 1030, 744, 699, 543 cm^{-1}; HRMS (DART-TOF) calcd. for $C_{13}H_{17}O_2$ $[M-H]^+$: 205.1229, found: 205.1227.

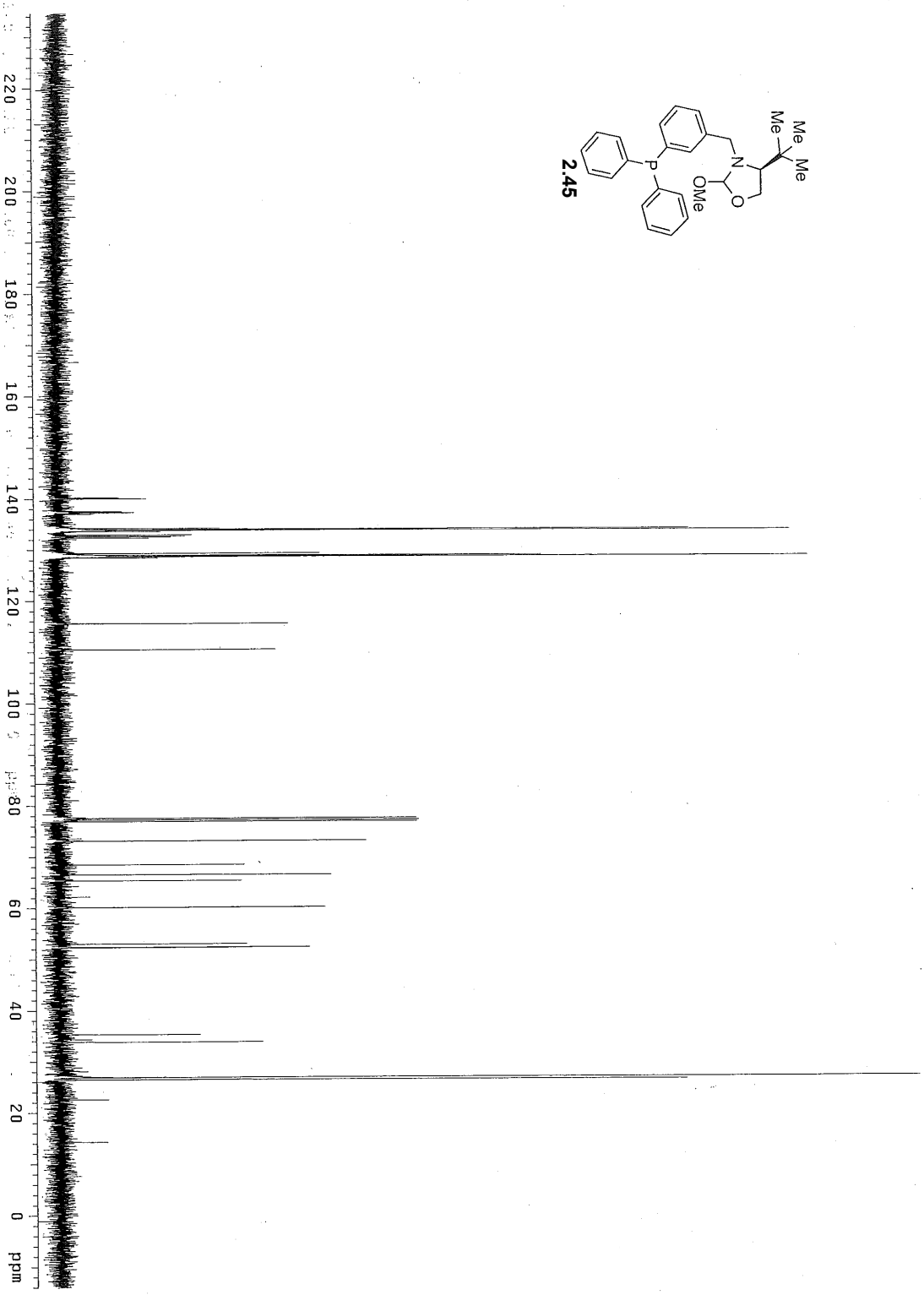
2.11.5 Spectral Data

For all published spectral data see the following link: http://pubs.acs.org/doi/suppl/10.1021/ja504247g

See below for examples of ^{1}H, ^{13}C and ^{31}P spectra:



2.45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Me
Me
N
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O
P
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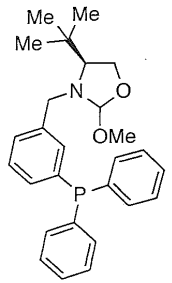
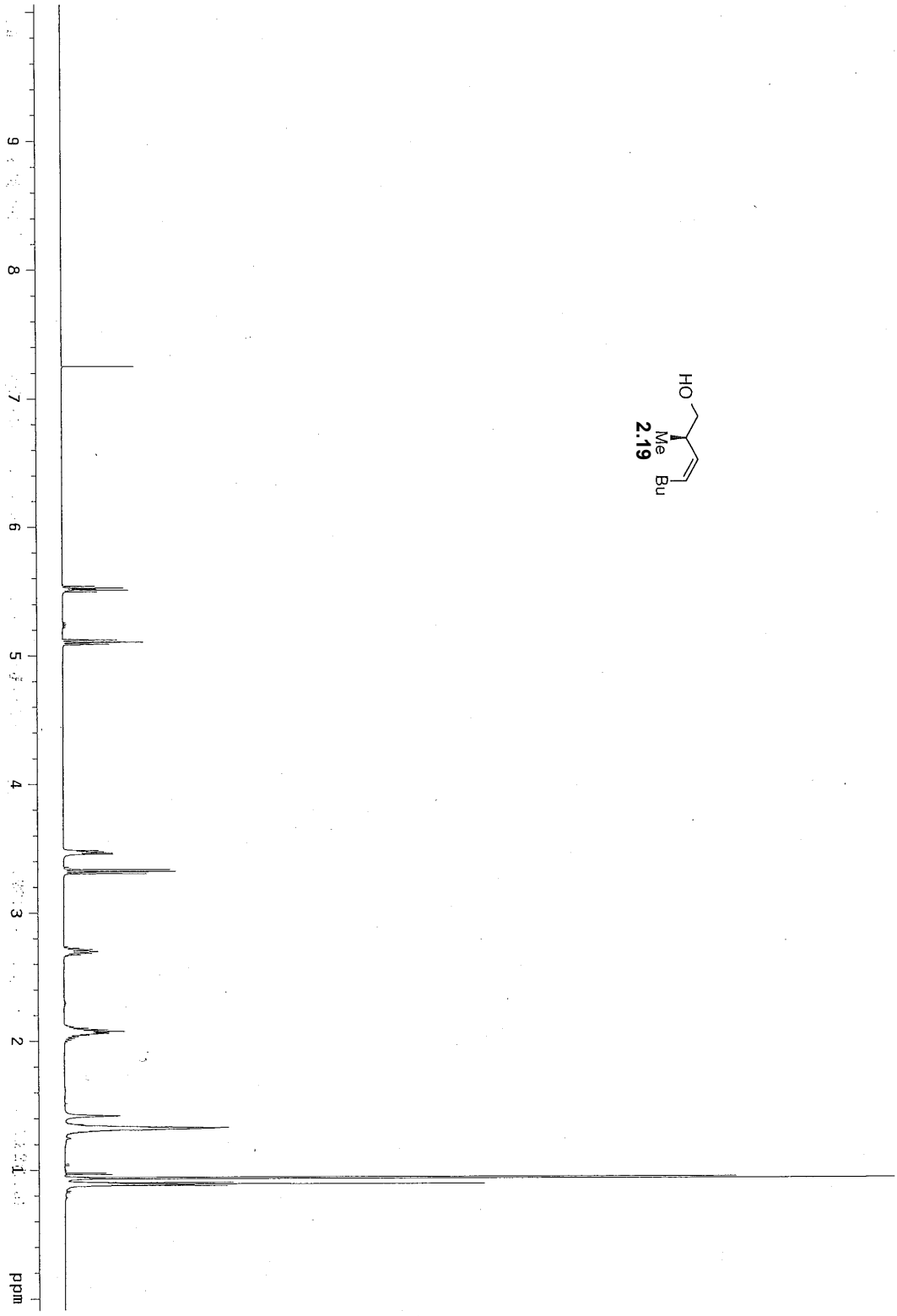
0
ppm



2.45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Bu
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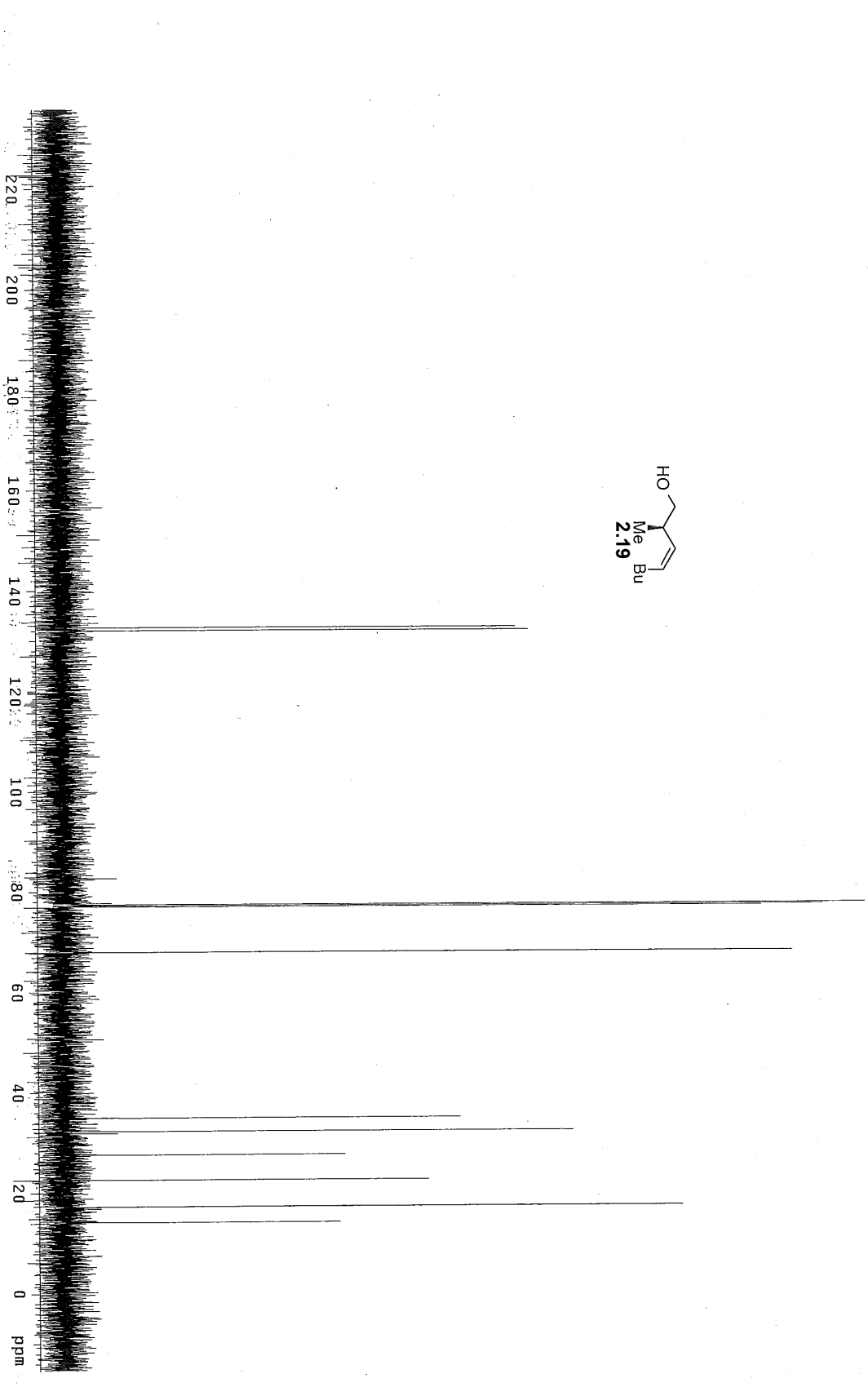
ppm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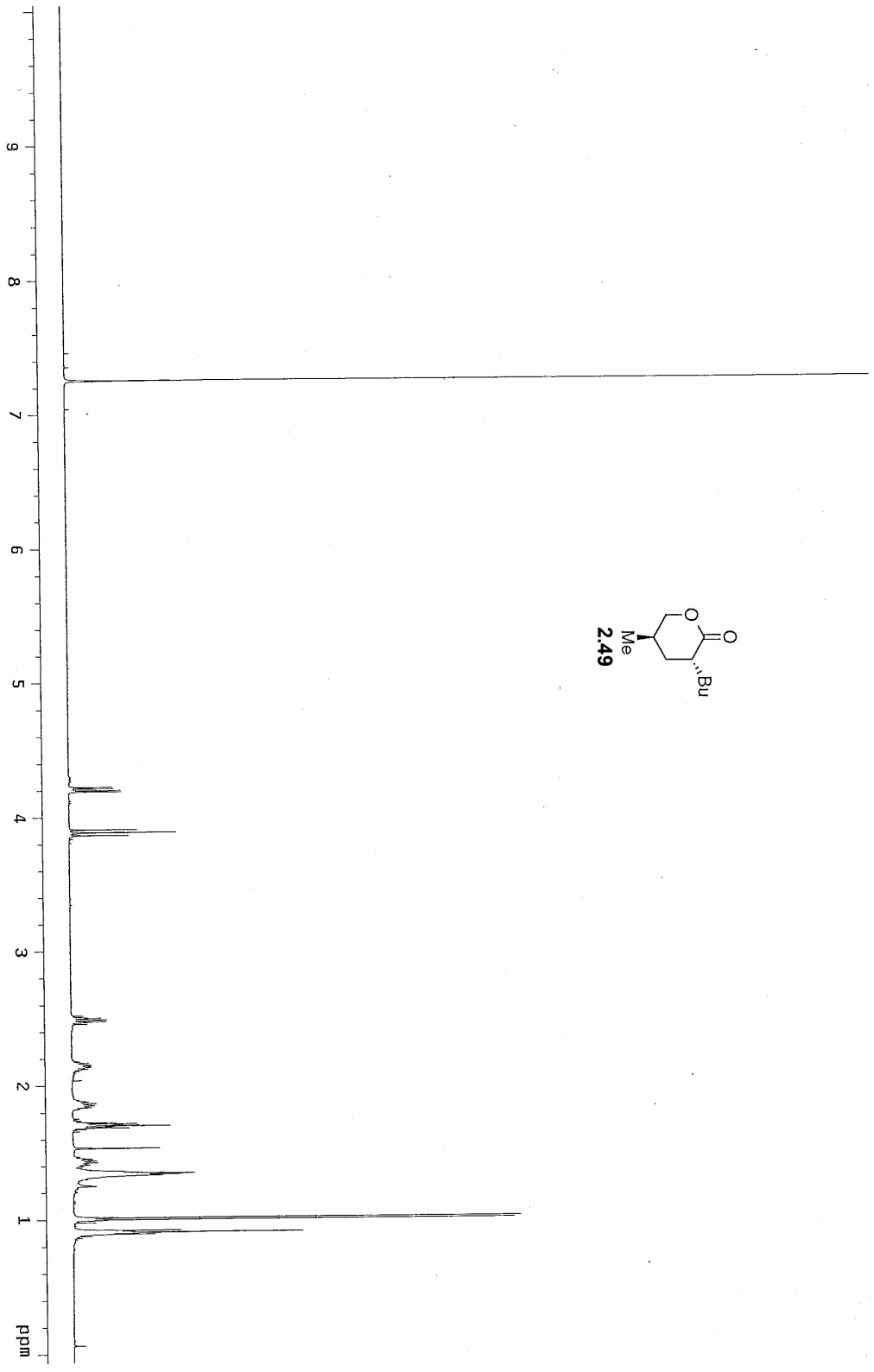
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ppm
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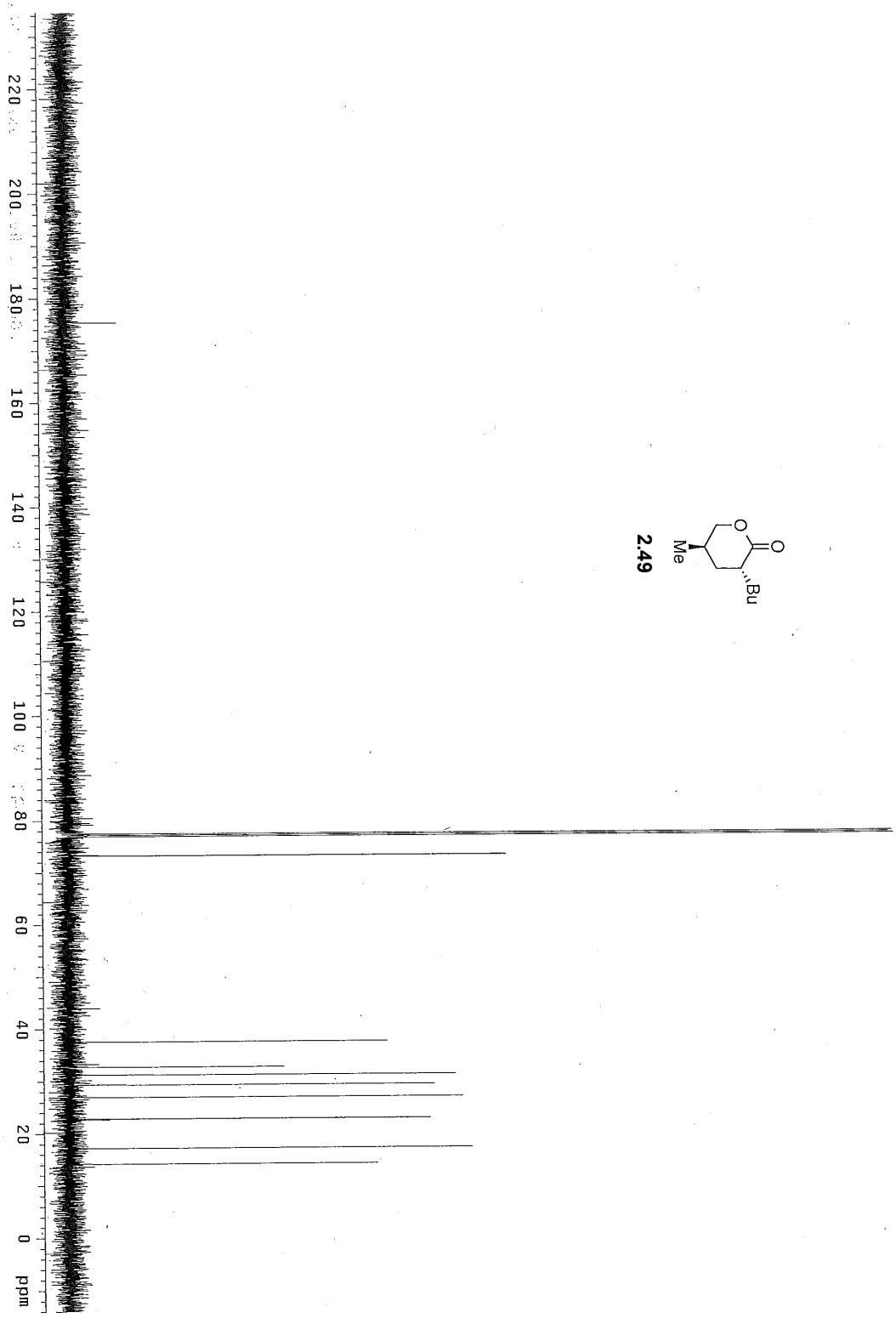
Me
Bu
2.49



2.49

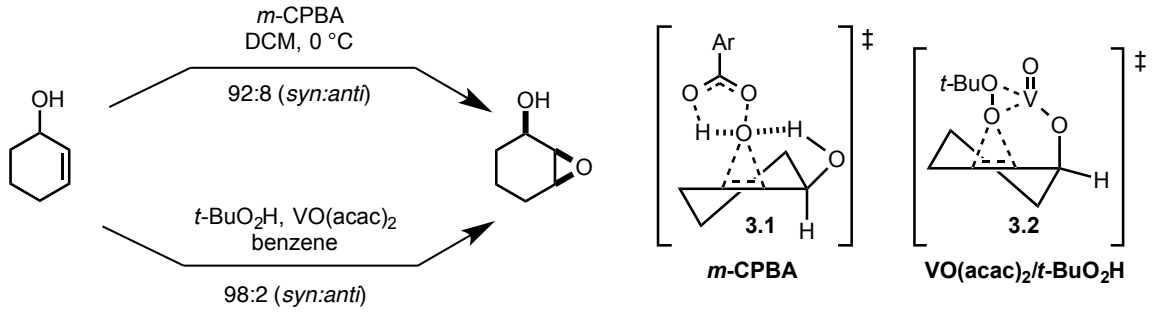
Chapter 3: The Stereoselective, Hydroxyl-Directed Diboration of Alkenyl Alcohols

3.1 Introduction

The use of directing groups has been a long-standing approach for the stereoselective functionalization of olefins.[1] Through a reversible preassociation between the substrate and either reagent or catalyst, an otherwise unselective reaction can attain high levels of regio- and stereoselectivity. In many cases, the directing group involved does not need to be a highly specialized group (Section 2.4), but rather a common functional group. For example, one of the most well-known classes of directed reactions is the hydroxyl-assisted epoxidation of alkenes (Scheme 3.1). These directed epoxidations can occur in two distinct ways: (1) hydrogen bonding to a peracid reagent (**3.1**)[2] or (2) alkoxide coordination to a metal catalyst (such as Ti or V) (**3.2**).[3] In either case, this mode of activation, by the hydroxyl group, can both control the selectivity of the reaction as well as improve the rate as compared to the undirected reaction.

[1] For reviews related to directed reactions (a) Hoveyda, A. H.; Evans, D. A.; Fu, G. C. *Chem. Rev.* **1993**, *93*, 1307 – 1370. (b) Rousseau, G.; Breit, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 2450 – 2494.
[2] Sabol, J. S.; Cregge, R. J. *Tetrahedron Lett.* **1989**, *30*, 3377 – 3380.
[3] Sato, T.; Gotoh, Y.; Watanabe, M.; Fujisawa, T. *Chem. Lett.* **1993**, 1533 – 1536.

Scheme 3.1 Directed Epoxidation Methodologies



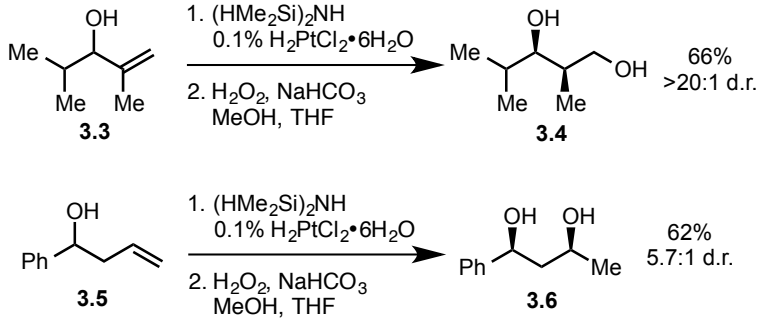
3.2 Selected Examples of Directed and Intramolecular Hydrometallative and Bismetallative Reactions

The use of hydrometallation and bismetallation reagents has been a popular method for the stereoselective functionalization of olefins. In addition to catalyst-controlled alkene functionalization, intramolecular and directed reactions have been two popular techniques for the control of regio-, chemo-, and stereoselectivity of these reactions. With regard to intramolecular reactions, by covalently tethering the hydrometallic or bismetallic reagent to the alkene substrate, the functionalization occurs in a relatively active and predictable fashion. Conversely, directed reactions rely on the inherent electrophilicity of the metallic reagents to permit a transient association with a Lewis basic directing group, which facilitates the directed reaction pathway. This section will highlight notable example of both directed and intramolecular functionalizations of alkenes using hydrometallic or bismetallic reagents.

3.2.1 Hydrosilylation

Tamao and Ito[4] have developed the directed hydrosilylation of allylic and homoallylic alcohols. Using extremely low quantities of a Pt catalyst, the hydrosilylation of **3.3** and **3.5** furnishes the 1,3-diols **3.4** and **3.6**, respectively, in moderate yields and good to excellent stereocontrol (Scheme 3.2). It is suggested that the selectivity arises from a covalent association between the alkoxide of the substrate and the hydrosilyl reagent. Interestingly, the hydroxyl group directs the silicon atom to the β-olefinic carbon, whether that carbon is proximal or distal carbon, relative to the directing group. Similar to intermolecular examples, the hydrosilyl-substrate intermediate undergoes Pt-catalyzed hydrosilylation, starting with the oxidative addition into the Si-H bond.

Scheme 3.2 Directed Hydrosilylation of Alkenyl Alcohols

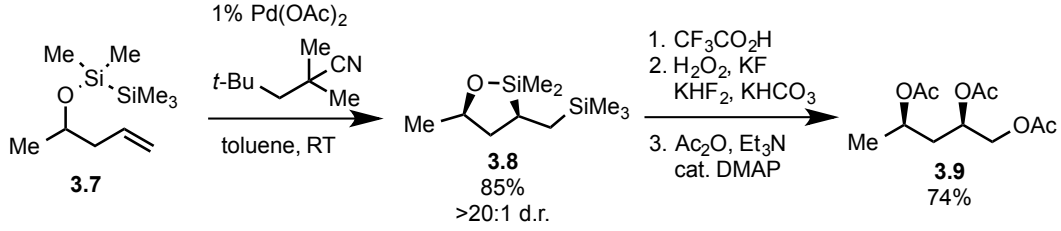


[4] (a) Tamao, K.; Nakajima, T.; Sumiya, R.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1986,** *108*, 6090 – 6093. (b) Tamao, K.; Nakajima, T.; Arai, H.; Higuchi, N.; Ito, Y. *J. Am. Chem. Soc.* **1988,** *110*, 3712 – 3714.

3.2.2 Bis(silylation)

Ito and coworkers[5] have disclosed the intramolecular bis(silylation) of disilanyl alkenes, which are easily synthesized from the corresponding homoallylic alcohols. With the olefin and disilane covalently bound, the intramolecular bis(silylation) of the alkene proceeds rapidly. Using $Pd(OAc)_2$ and a isocyanide ligand, **3.7** is transformed to the *syn* diastereomer **3.8** in 85% yield and >20:1 dr (Scheme 3.3). It should be noted that when similar conditions were used for a similar intermolecular bis(silylation) of an alkene, no reaction was observed. Oxasilolane **3.8** can be oxidized and acylated to the protected 1,3,4-triol **3.9** in good yield.

Scheme 3.3 Intramolecular Bis(silylation)



3.2.3 Silylformylation

Leighton and coworkers[6] disclosed an intramolecular silylformylation of siloxy alkenes using a Rh catalyst and CO at elevated pressure. Siloxy olefin **3.10** undergoes silylformylation, furnishing oxasilolane **3.11** in moderate yield and diastereoselectivity, after reduction of the aldehyde and protection of the subsequent alcohol (Scheme 3.4).

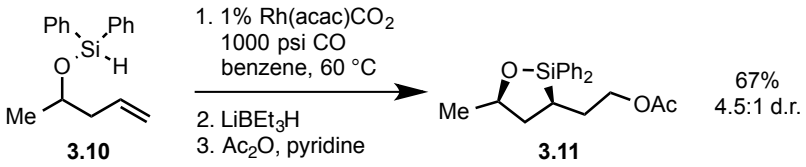
---

[5] (a) Murakami, M.; Andersson, P. G.; Suginome, M.; Ito, Y. *J. Am. Chem. Soc.* **1991,** *113*, 3987 – 3988. (b) Murakami, M.; Suginome, M.; Fujimoto, K.; Nakamura, H.; Andersson, P. G.; Ito, Y. *J. Am. Chem. Soc.* **1993,** *115*, 6487 – 6498.

[6] Leighton, J. L.; Chapman, E. *J. Am. Chem. Soc.* **1997,** *119*, 12416 – 12417.

The high pressure of CO gas is necessary to out compete the competitive, undesirable hydrosilylation reaction.

Scheme 3.4 Intramolecular Silylformylation

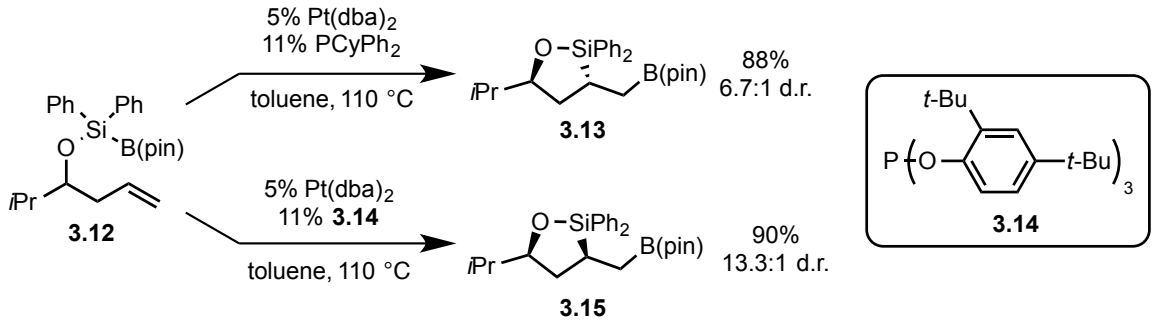


3.2.4 Silaboration

In 2006, Suginome and coworkers[7] reported the Pt-catalyzed intramolecular silylboration of alkenes. Interestingly, a powerful ligand effect allowed for the selective synthesis of both diastereomers of the boronate-containing oxasilolane products. When using diphenylcyclohexyl phosphine ($PCyPh_2$) as the ligand, the silylboration of **3.12** yields the *anti* product **3.13** in good yield and selectivity. This observed selectivity is overturned when phosphite **3.14** is used as the ligand, producing the *syn* product **3.15** in great yield and diastereoselectivity (Scheme 3.5). The researchers concluded that bulkier ligands, especially phosphites, favored the formation of the *syn* diastereomer.

[7] Ohmura, T.; Furukawa, H.; Suginome, M. *J. Am. Chem. Soc.* **2006,** *128*, 13366 – 13367.

Scheme 3.5 Intramolecular Silaboration

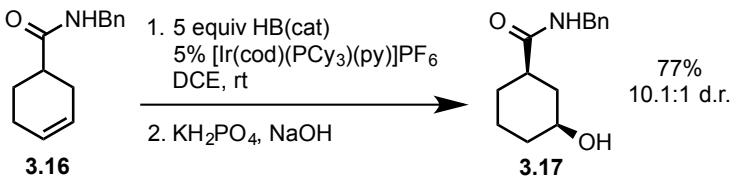


3.2.5 Hydroboration

The hydroboration of olefins is an excellent example of a reaction that has benefitted greatly from the use of directing groups. Evans and coworkers[8] reported one of the first examples of a directed hydroboration in 1991. The presence of an amide functionality provided both a rate enhancement and a means of controlling selectivity of the hydroboration of both cyclic and acyclic alkenes using catecholborane. For example, olefin **3.16** undergoes the Ir-catalyzed hydroboration and subsequent oxidation to yield **3.17** in good yield and diastereoselectivity (Scheme 3.6). It should be noted that none of the other regioisomer is observed. Takacs and coworkers[9] have expanded this concept to the amide-directed enantioselective hydroboration using pinacolborane and a chiral phosphoramidite-iridium catalyst.

[8] Evans, D. A.; Fu, G. C. *J. Am. Chem. Soc.* **1991,** *113*, 4043 – 4044.
[9] Smith, S. M.; Thacker, N. C.; Takacs, J. M. *J. Am. Chem. Soc.* **2008,** *130*, 3734 – 3735.

Scheme 3.6 Amide-Directed Hydroboration

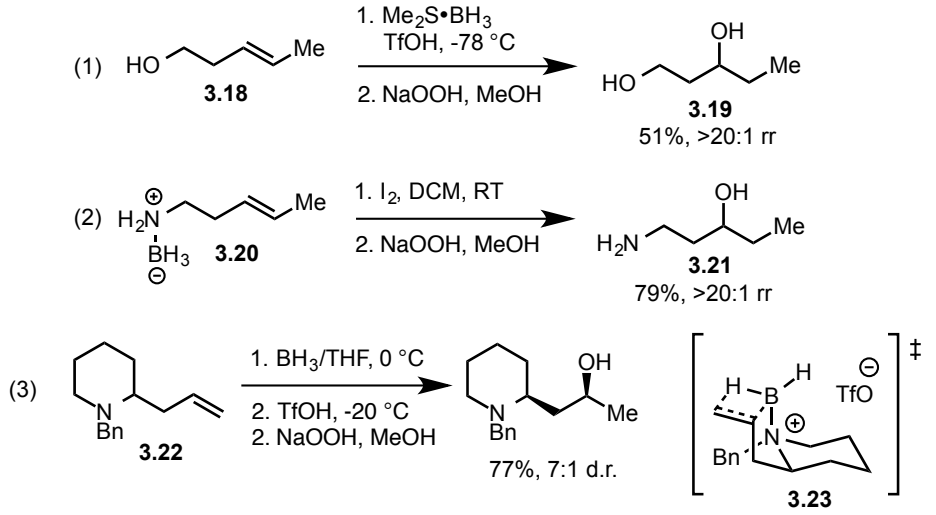


3.16 **3.17**

Vedejs and coworkers[10] have examined the use of other functional groups as directing groups for hydroboration. Homoallylic alcohol **3.18** associates with an activated borane (derived form $Me_2S{\bullet}BH_3$ and TfOH), initiating a directed hydroboration and generating **3.19** as the favored regioisomer in moderate yield after an oxidative work-up (Scheme 3.7, Eq. 1). A similar outcome occurs when starting from the amine-borane complex **3.20**, yielding **3.21** in good yield and excellent regioselectivity after oxidation (Scheme 3.7, Eq. 2). The concept was extended to piperidine-containing olefin substrates such as **3.22**, yielding the amino alcohol products with good diastereoselectivity (Scheme 3.7, Eq. 3). The proposed transition state **3.23** is used to account for the diastereomer observed.

[10] (a) Scheideman, M.; Wang, G.; Vedejs, E. *J. Am. Chem. Soc.* **2008,** *130*, 8669 – 8676. (b) Wang, G.; Vedejs, E. *Org. Lett.* **2009**, *11*, 1059 – 1061.

Scheme 3.7 Vedejs' Directed Hydroboration



3.3 Stereoselective Methods for Installing 1,2-Bis(boronates)

The early development of the diboration of alkynes[11] fueled the discovery of catalyst systems for the diboration of alkenes. The discovery of Rh-[12] and Pt-catalyst systems[13] triggered an early example of a Pt-catalyzed, enantioselective diboration using a chiral diboron reagent.[14] These initial catalyst systems have functioned as inspiration for the development of efficient asymmetric diboration reactions. Over the past decade, the diboration reaction has become a proficient means of functionalizing olefins. The development of asymmetric transition-metal catalyzed systems has allowed for the use of cheap, achiral diboron reagents, such as $B_2(pin)_2$ and $B_2(cat)_2$. Like all hydrometallation

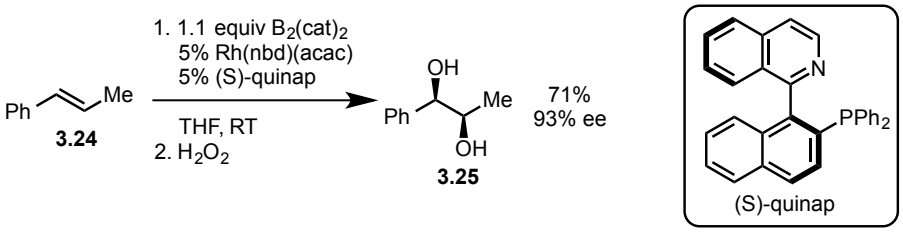
[11] (a) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc.,* **1993**, *115*, 11018 – 11019. (b) Iverson, C. N.; Smith, III, M. R. *J. Am. Chem. Soc.,* **1995**, *117*, 4403 – 4404. (c) Ishiyama, T.; Matsuda, N.; Murata, M.; Ozawa, F.; Suzuki, A.; Miyaura, N. *Organometallics*, **1996**, *15*, 713 – 720.
[12] Baker, R. T; Nguyen, P.; Marder, T. B.; Westcott, S. A. *Angew. Chem., Int. Ed.,* **1995**, *34*, 1336 – 1338.
[13] Iverson, C. N.; Smith, III, M. R. *Organometallics*, **1997**, *16*, 2757 – 2759.
[14] Marder, T. B.; Norman, N. C.; Rice, C. R. *Tetrahedron Lett.* **1998**, *39*, 155 – 158.

and bismetallation reactions, the usefulness of diboration hinges on the utility of its products. In addition to oxidation to the 1,2-diol or a homologation/oxidation sequence to the 1,4-diol, these 1,2-bis(boronates) can undergo a regioselective cross-coupling to furnish a readily functionalizable mono-organoboronate (Chapter 4).

3.3.1 Generating Chiral 1,2-Bis(boronates) from Olefins

In 2003, Morken and coworkers[15] disclosed the first example of a catalytic, asymmetric diboration of alkenes. Using a Rh/(*S*)-quinap catalyst, the diboration proceeds with excellent enantioselectivites for most of the di- and trisubstituted olefins screened. The diboration of styrene **3.24** using the catalyst and $B_2(cat)_2$ yields the internal 1,2-diol **3.25** in 71% yield and 93% enantioselectivity, after oxidation (Scheme 3.8). Further studies demonstrated that some bulkier terminal olefins also undergo diboration in a selective fashion.

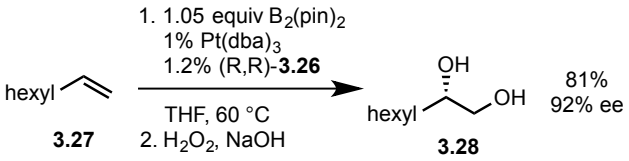
Scheme 3.8 Rh-Catalyzed Asymmetric Diboration of Internal Olefins

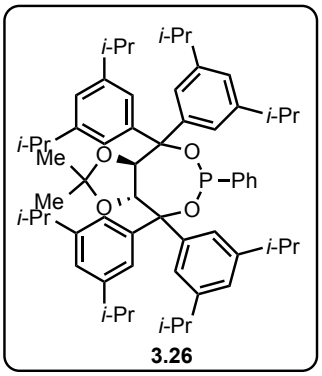


[15] (a) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc.* **2003**, *125*, 8702 – 8703. (b) Trudeau, S., Morgan, J. B.; Shrestha, M.; Morken, J. P. *J. Org. Chem.,* **2005**, *70*, 9538 – 9544.

In 2009, and further improved in 2013, Morken and coworkers[16] reported the first catalytic, asymmetric diboration of terminal alkenes. Using a Pt/**3.26** catalyst, the diboration of simple terminal olefins generally proceeds in high selectivities. Using $B_2(pin)_2$ as the diboron reagent, **3.27** undergoes diboration to yield the diol **3.28** in 81% yield and 92% *ee* after oxidation (Scheme 3.9). It is of note that the diboration of most di- and trisubstituted olefins does not occur under these conditions. Additionally, the presence of hydroxyl groups, sterically unhindered ethers, and alkynes are believed to poison the Pt catalyst, leading to no reaction or diminished selectivity. However, these conditions have been successfully adapted to the 1,2-diboration of 1,3-dienes[17] and vinyl boronate esters.[18]

Scheme 3.9 Pt-Catalyzed Asymmetric Diboration of Terminal Olefins

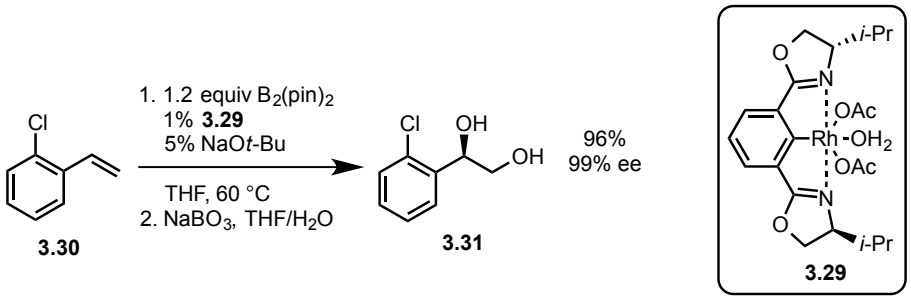




[16] (a) Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210 – 13211. (b) Coombs, J. R.; Haeffner, F.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 11222 – 11231.
[17] Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. *Angew. Chem., Int. Ed.* **2012**, *51*, 521 – 524.
[18] Coombs, J. R; Zhang, L.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 16140 – 16143.

Nishiyama and coworkers[19] have also developed an efficient diboration of terminal olefins. Using 1% **3.29** and 5% NaO*t*-Bu, the diboration of alkyl and aryl α-olefins using $B_2(pin)_2$ occurs with excellent selectivities. The diboration and $NaBO_3$ oxidation of **3.30** yields diol **3.31** in 96% yield and 99% ee (Scheme 3.10). Similar to Pt-catalyzed systems, the diboration of more substituted olefins proceeds in lower yields and enantioselectivities.

Scheme 3.10 Rh-Catalyzed Asymmetric Diboration of Terminal Olefins



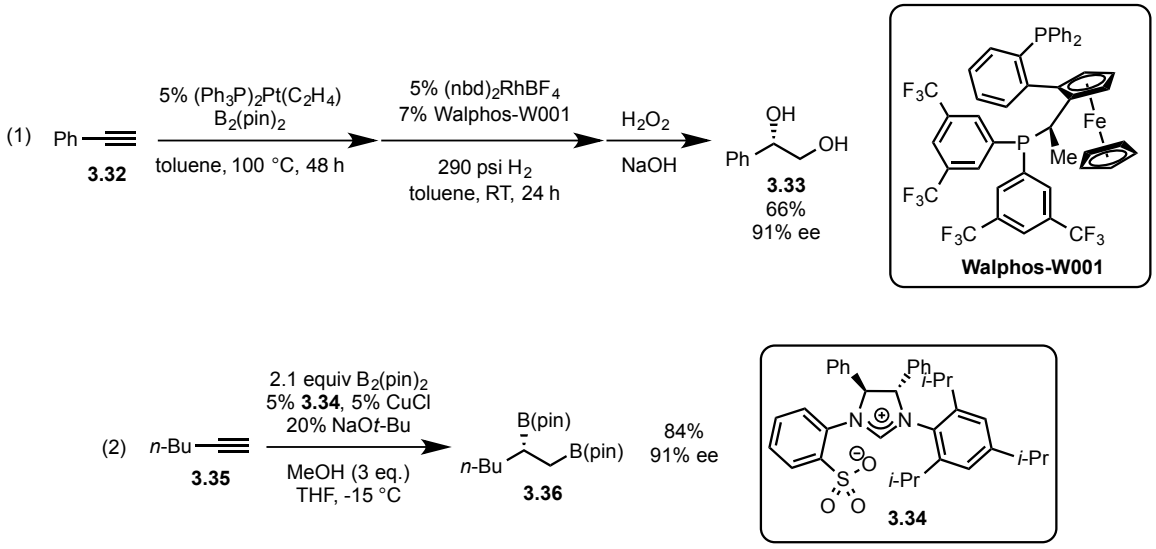
3.3.2 Generating Chiral 1,2-Bis(boronates) from Terminal Alkynes

Morken and coworkers[20] described an alternative approach to the synthesis of chiral 1,2-bis(boronates) through the Rh-catalyzed asymmetric hydrogenation of vinyl 1,2-bis(boronates). Interestingly, this reaction can be included in a one-pot sequence starting from the terminal alkyne. Alkyne **3.32** is subjected to *syn*-selective diboration, followed by the enantioselective hydrogenation of the vinyl diboronate using a Rh/Walphos catalyst. Oxidation of the vicinal diboronate yields the diol **3.33** in 66%

[19] Toribatake, K.; Nishiyama, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 11011 – 11015.
[20] Morgan, J. B.; Morken, J. P. *J. Am. Chem. Soc.* **2004**, *126*, 15338 – 15339.

yield and 91% ee (Scheme 3.11). Hoveyda and coworkers[21] reported another method for the synthesis of chiral 1,2-bis(boronates) through sequential copper-catalyzed hydroborations of alkynes. Using a Cu-**3.34** catalyst, **3.35** undergoes an initial hydroboration to form the vinylboronate, which upon a second hydroboration furnishes **3.36** in 84% yield and 91% ee (Scheme 3.11). One reason for the success of the reaction is attributed to the ability of the catalyst to selectively form the terminal vinyl boronate during the first hydroboration.

Scheme 3.11 Chiral 1,2-Bis(boronates) from Terminal Alkynes



3.4 Hydroxyl-Directed Diboration[22]

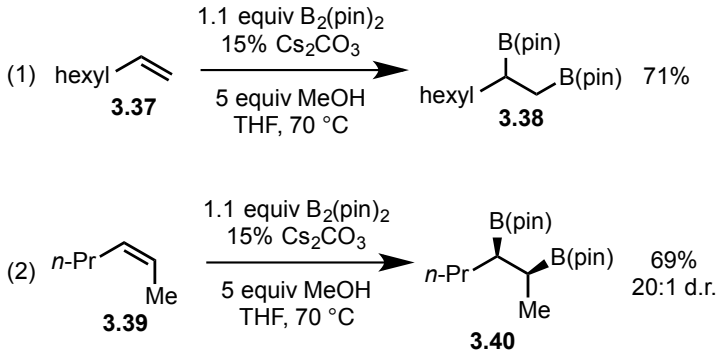
3.4.1 Inspiration

Our research initially set out to investigate whether a hydroxyl group could serve as a suitable directing group for a diboration of olefins. In part, this research was inspired

[21] Lee, Y.; Jang, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 18234 – 18235.
[22] Blaisdell, T. P.; Caya, T. C.; Zhang, L.; Sanz-Marco, A.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 9264 – 9267.

by the work of Fernández and coworkers,[23] who disclosed a transition metal-free diboration of terminal and internal olefins. In that report, they propose that *in situ* formation of a methoxide anion, from a carbonate base and methanol, is an adequate activator of the diboron reagent for diboration. For terminal olefin **3.37**, the reaction furnishes **3.38** in good yield (Scheme 3.12, Eq. 1). It should be noted that, in all cases, only very small amounts (<5%) of the hydroborated product is observed. The diboration is shown to be *syn*-selective, yielding **3.40** in good yield and excellent diastereoselectivity from the diboration of **3.39** (Scheme 3.12, Eq. 2).

Scheme 3.12 Transition Metal-Free Diboration of Alkenes

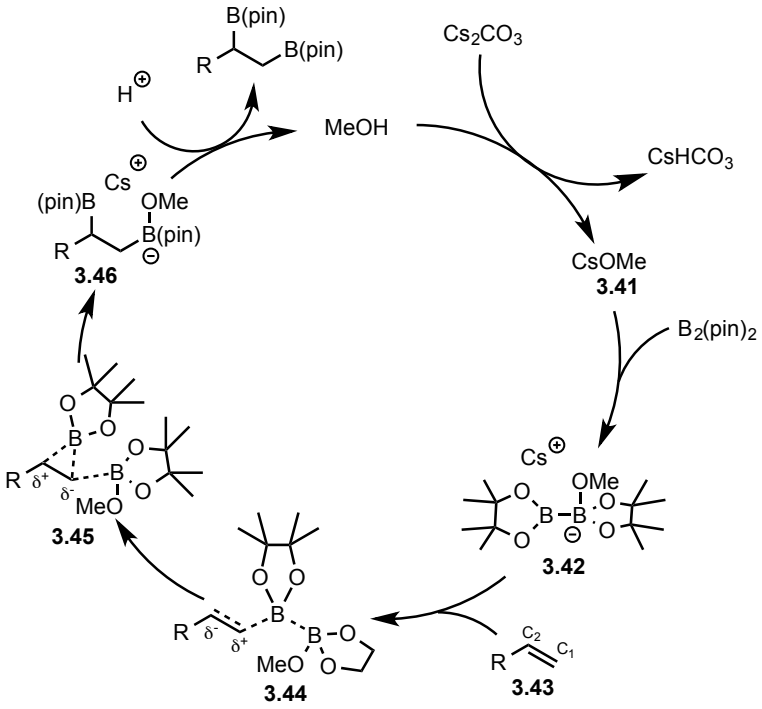


As mentioned above, the proposed mechanism suggests the formation and function of CsOMe is imperative to the success of the reaction (Scheme 3.13). Although appearing to require catalytic amounts, the authors mentioned that excess methanol is required for an optimal reaction outcome. Next, CsOMe reacts with $B_2(pin)_2$ creating the sp^2-sp^3 diboron species **3.42**. This activated diboron species reacts with the C_1 carbon of olefin **3.43** to form **3.44**, which rapidly forms borocycle **3.45** as a transition state.

[23] Bonet, A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyás, H.; Fernández, E. *Angew. Chem., Int. Ed.* **2011**, *50*, 7158 – 7161.

Opening of **3.45**, yields **3.46**, which upon protonation, generates the 1,2-bis(boronate) product.

Scheme 3.13 Mechanism for the Transition Metal-Free Diboration of Alkenes



3.4.2 Directed Diboration of Alkynes

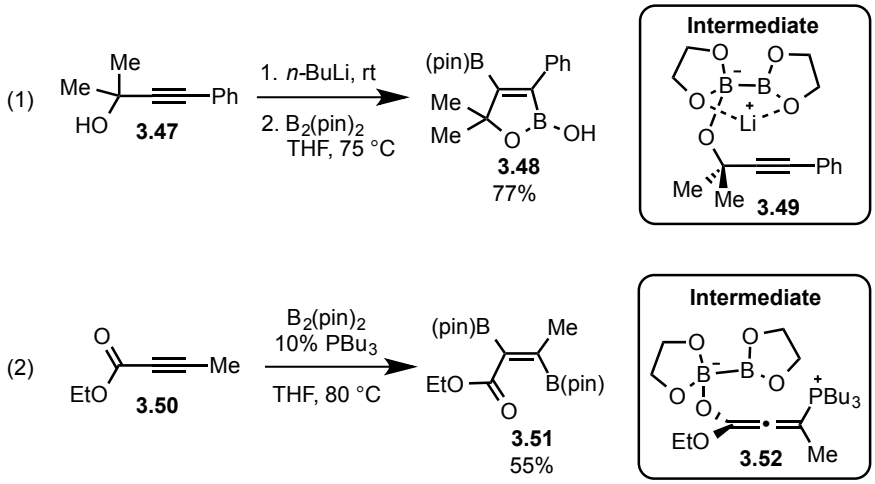
As shown earlier, many hydrometallation and bismetallation reactions have been aided by the use of directing groups (Section 3.2). Surprisingly, at the time of our research, there were no examples of a directed diboration. However, since then, there have been two reports of the directed diboration of alkynes.

In 2014, Hirano and Uchiyama[24] disclosed the hydroxyl-directed diboration of propargylic alcohols. Internal alkynes, such as **3.47**, are subjected to deprotonation conditions followed by the addition of $B_2(pin)_2$ to furnish the *trans* cyclic vinyldiboronate **3.48** in good yield (Scheme 3.14, Eq. 1). Through a series of computational studies, the hydroxyl group was shown to play a major role in lowering the activation energy barrier of the boryl addition to the alkyne. Interestingly, the lithium counterion is proposed to coordinate to the oxygen atoms of both boronates (as shown in **3.49**) as well as stabilize the negative charge build up on the distal alkynyl carbon after the first borylation.

In 2015, Ohmiya and Sawamura[25] published the synthesis of similar products through the organocatalyzed diboration of 2-alkynoates. Using $B_2(pin)_2$ and a catalytic amount of $P(Bu)_3$, **3.50** was transformed to the *trans* vinyldiboronate **3.51** in moderate yield (Scheme 3.14, Eq. 2). The observed reactivity and selectivity is justified through a proposed zwitterionic allenolate intermediate **3.52**, which directs the first borylation. In addition to diboration, the methodology was extended to a *trans*-selective silylboration.

[24] Nagashima, Y.; Hirano, K.; Takita, R.; Uchiyama, M. *J. Am. Chem. Soc.* **2014,** *136*, 8532 – 8535.
[25] Nagao, K.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2015**, *17*, 1304 – 1307.

Scheme 3.14 Directed Diboration of Alkynes



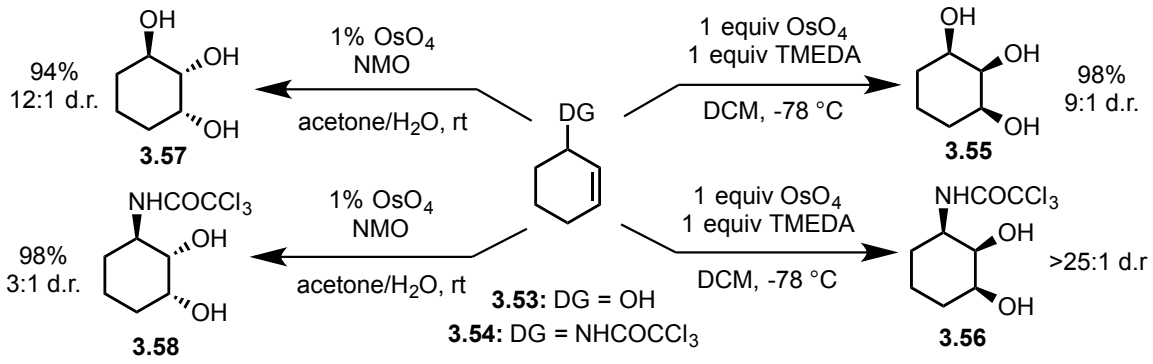
3.4.3 Directed Dihydroxylation

As previously shown, a 1,2-bis(boronate) can be smoothly transformed to the 1,2-diol using stereoretentive oxidation conditions. Therefore, a directed diboration/oxidation sequence would serve as an alternative to a directed dihydroxylation reaction of alkenes. In a related process, Donohoe and coworkers[26] have developed hydroxyl- and amine-directed dihydroxylations. Subjecting **3.53** or **3.54** to one equivalent of both OsO_4 and TMEDA, yields *syn* products **3.55** and **3.56**, respectively, in good to excellent diastereoselectivity (Scheme 3.15). It is presumed that OsO_4, once ligated by TMEDA, participates in hydrogen bonding with the proton of the directing group. It is believed that the active osmium species is generated when TMEDA binds OsO_4 in a bidentate fashion. Due to steric considerations, reaction of **3.53** or **3.54** with traditional,

[26] (a) Donohoe, T. J.; Blades, K.; Moore, D. R.; Waring, M. J.; Winter, J. J. G.; Helliwell, M.; Newcombe, N.; Stemp, G. *J. Org. Chem.* **2002,** *67*, 7946 – 7956. (b) Donohoe, T. J.; Mitchell, L.; Waring, M. J.; Helliwell, M.; Bell, A.; Newcombe, N. *J. Org. Biomol. Chem.* **2003**, *1*, 2173. (c) Donohoe, T. J. *Synlett* **2002**, 1223. (d) Donohoe, T. J.; Bataille, C. J. R.; Innocenti, P. *Organic Reactions* **2012**, *76*, 1 – 48.

catalytic dihydroxylation conditions, favors the formation of the *anti* products **3.57** and **3.58**, respectively.

Scheme 3.15 Amine and Hydroxyl-Directed Dihydroxylation



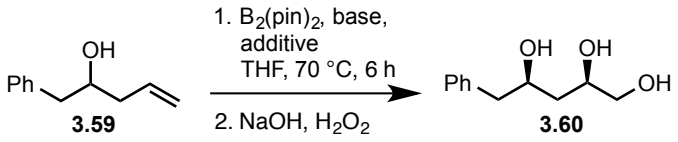
3.5 Optimization of Reaction Conditions

As we began our initial experiments, we subjected homoallylic alcohol **3.59** to similar reaction conditions used by Fernandez. There was no observed reaction between **3.59** and $B_2(pin)_2$ (Table 3.1, Entry 1). Surprisingly, this was also the case when using a deprotonated form of **3.59** (Table 3.1, Entry 2). Unexpectedly, when five equivalents of methanol were added to the mixture of $B_2(pin)_2$ and deprotonated **3.59**, the olefin was mostly consumed and, after oxidation, the 1,3,4-*syn*-triol **3.60** was observed in good selectivity (Table 3.1, Entry 3). Now, with methanol as an additive, only a catalytic amount of base is needed for the reaction. As the base was varied, there was a clear effect on both the conversion and selectivity of the reaction (Table 3.1, Entries 4-8). Most notably, when screening carbonate bases, a counterion effect was observed; the reaction proceeded in a more selective fashion when using bases with larger cations. The diboration of **3.59** using Na_2CO_3, K_2CO_3, and Cs_2CO_3 furnished **3.60** with

diastereoselectivies of 7.9:1, 10.4:1, and 12.5:1, respectively (Table 3.1, Entries 6-8). For this reason and due to its air stability, Cs_2CO_3 was decided to be the most suitable base for this transformation.

Due to its apparent importance to the reaction, the alcohol additive was further studied. Sterically encumbered alcohols, such as isopropanol and *tert*-butanol, furnished **3.60** in diminished conversion and selectivity (Table 3.1, Entries 9-10). The use of water as an additive yielded poor conversion and selectivity (Table 3.1, Entry 11). The use of electron deficient alcohols, such as phenol and 2,2,2-trifluoroethanol, afforded lower conversion (Table 3.1, Entries 12-13). In an effort to bolster the conversion of the reaction, the amount of Cs_2CO_3 and $B_2(pin)_2$ were increased and full conversion was observed (Table 3.1, Entry 14). With these new conditions, the amount of methanol added was investigated. Interestingly, with more methanol (17 equivalents) added, there was an enhancement in selectivity (Table 3.1, Entry 15). Under these optimized conditions, **3.60** was isolated in 74% yield and a 12.9:1 d.r. It should be noted that, with even higher amounts of methanol, the selectivity starts to diminish (Table 3.1, Entries 16-18). Fascinatingly, the reaction is still modestly selective when methanol is used as a solvent (Table 3.1, Entry 18).

Table 3.1 Reaction Optimization



3.59 **3.60**

entry	base (equiv)	$B_2(pin)_2$ (equiv)	additive (equiv)	conversion (%)[a]	d.r.[b]
1	none	1.05	-	<5	na
2	NaH (1.0)	1.05	-	<5	na
3	NaH (1.0)	1.05	MeOH (5)	87	12.5:1
4	NaO*t*Bu (0.15)	1.05	MeOH (5)	83	7.7:1
5	KO*t*Bu (0.15)	1.05	MeOH (5)	90	12.3:1
6	Na_2CO_3 (0.15)	1.05	MeOH (5)	68	7.9:1
7	K_2CO_3 (0.15)	1.05	MeOH (5)	90	10.4:1
8	Cs_2CO_3 (0.15)	1.05	MeOH (5)	87	12.5:1
9	Cs_2CO_3 (0.15)	1.05	*i*-PrOH (5)	64	7.4:1
10	Cs_2CO_3 (0.15)	1.05	*t*-BuOH (5)	42	9.5:1
11	Cs_2CO_3 (0.15)	1.05	H_2O (5)	9	3.8:1
12	Cs_2CO_3 (0.15)	1.05	PhOH (5)	51	13.2:1
13	Cs_2CO_3 (0.15)	1.05	CF_3CH_2OH (5)	45	5.6:1
14	Cs_2CO_3 (0.30)	2.0	MeOH (5)	>95	9.9:1
15	Cs_2CO_3 (0.30)	2.0	MeOH (17)	>95 (74%)[c]	12.9:1
16	Cs_2CO_3 (0.30)	2.0	MeOH (25)	>95	12.1:1
17	Cs_2CO_3 (0.30)	2.0	MeOH (50)	>95	9.5:1
18	Cs_2CO_3 (0.30)	2.0	MeOH (solvent)	>95	5.7:1

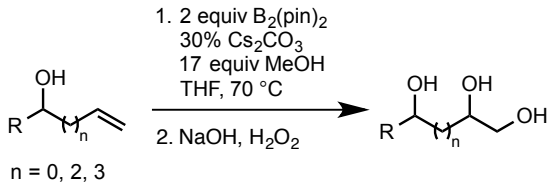
[a] Conversion determined by ^{1}H NMR using trimethoxybenzene as an internal standard. [b] Diasteroselectivity was determined by SFC. [c] Number in parenthesis is the isolated yield.

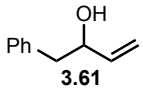
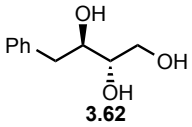
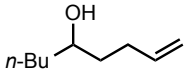
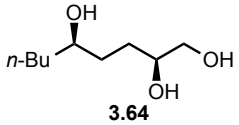
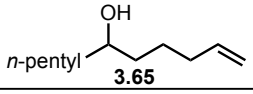
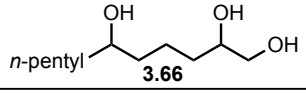
3.6 Exploration of the Substrate Scope

With **3.59** undergoing diboration in a selective manner, other alkenyl alcohols were synthesized and subjected to the optimized conditions. Allylic alcohol **3.61** was only slightly selective for the *anti* 1,2,3-triol **3.62** (Table 3.2, Entry 1). This modest selectivity could be attributed to the background reaction and not a directed pathway. Diboration of bis-homoallylic alcohol **3.63** yields the *syn*-1,4,5-triol **3.64** in good yield and selectivity (Table 3.2, Entry 2). Although not the level of stereocontrol observed with **3.59**, **3.63** is believed to proceed through a directed pathway. The diboration of tris-

homoallyic alcohol **3.65** yielded the triol **3.66** as an unselective mixture of diastereomers (Table 3.2, Entry 3).

Table 3.2 Diboration of Other Alkenyl Alcohols



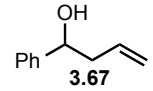
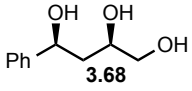
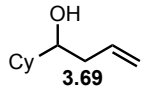
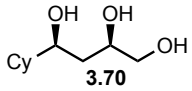
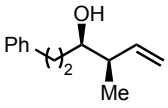
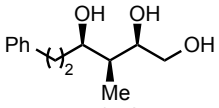
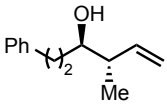
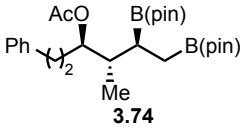
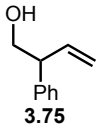
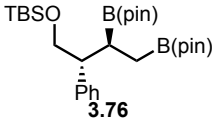
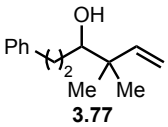
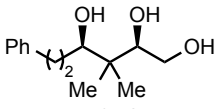
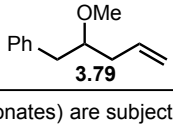
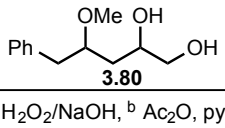
entry	substrate	major product	yield (%)	d.r.[a]
1	 **3.61**	 **3.62**	47	1.8:1
2	 **3.63**	 **3.64**	70	6:1
3	 **3.65**	 **3.66**	77	1:1

[a] Diastereoselectivity was determined by ^{1}H NMR

Due to the high selectivity observed for **3.59**, the diboration of various homoallylic alcohols was investigated. Phenyl-substituted **3.67** proceeded in good yield and selectivity furnishing the *syn* product **3.68** (Table 3.3, Entry 1). Surprisingly, increasing the steric bulk at the position α with respect to the hydroxyl group (**3.69**) led to only moderate diastereocontrol (Table 3.3, Entry 2). This reaction extends to homoallylic alcohols with allylic substitution, as well. The reaction of **3.71**, **3.73, 3.75** and **3.77** delivered the respective diboration products **3.72**, **3.74, 3.76** and **3.78** in good to excellent selectivities (Table 3.3, Entries 3-6). Due to low isolated yields of the triols, **3.74** and **3.76** were isolated as the protected acetate and the silyl ether, respectively. It is of note

that most of the 1,2-bis(boronates) containing an unprotected alcohol are unstable to silica purification. On silica gel, it is likely that the boronate esters are being slowly hydrolyzed to the boronic acid. The methyl ether **3.79** reacted under the diboration conditions affords **3.80** as an unselective mixture of diastereomers (Table 3.3, Entry 7). This observation suggests, while not necessary for the reactivity of the olefin, a free hydroxyl group is an essential feature to control the diastereoselective outcome of the reaction.

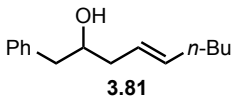
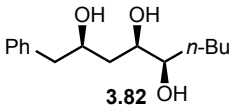
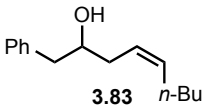
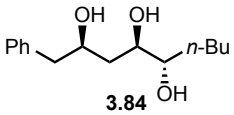
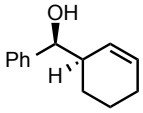
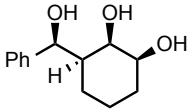
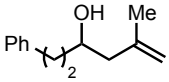
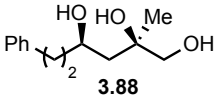
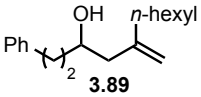
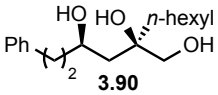
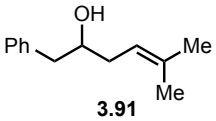
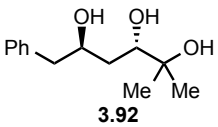
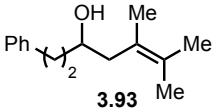
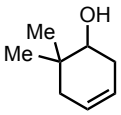
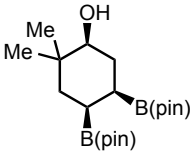
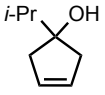
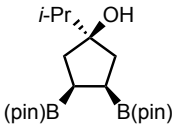
Table 3.3 Diboration of Various Terminal Homoallylic Alcohols

entry	substrate	major product	yield	d.r.
1[a]	 **3.67**	 **3.68**	84%	14:1
2[a]	 **3.69**	 **3.70**	51%	5:1
3[a]	 **3.71**	 **3.72**	80%	7:1
4[b]	 **3.73**	 **3.74**	66%	>20:1
5[c]	 **3.75**	 **3.76**	56%	11:1
6[a]	 **3.77**	 **3.78**	69%	>20:1
7[a]	 **3.79**	 **3.80**	78%	1:1

Bis(boronates) are subjected to [a] H_2O_2/NaOH, [b] Ac_2O, pyridine,[c] TBSCl, imidazole

Internal olefin substrates **3.81**, **3.83** and **3.85** participate in the reaction, yielding the 1,3,4-triol products **3.82**, **3.84** and **3.86** in moderate to excellent diastereoselectivies (Table 3.4, Entries 1-3). For these products, it can be elaborated that the reaction occurs with *syn* addition of the diboron reagent to the olefin. Alcohols containing 1,1-disubstituted olefins, **3.87** and **3.89**, undergo the reaction, yielding **3.88** and **3.90**, respectively with excellent diastereocontrol (Table 3.4, Entries 4-5). The substrate scope was extended to trisubstituted olefin **3.91**, which underwent diboration to yield the *anti* product **3.92** (Table 3.4, Entry 6). It is believed that **3.91** underwent diboration in a directed fashion due to the inactivity of trisubstituted olefins to undirected Fernandez diboration conditions. The more substituted **3.93** was unreactive toward the directed diboration reaction (Table 3.4, Entry 7). Cyclic olefins **3.94** and **3.96** partook in the reaction yielding the corresponding cyclic boronates **3.95** and **3.97** in tremendous diastereocontrol (Table 3.4, Entries 8-9).

Table 3.4 Diboration of Various Internal Homoallylic Alcohols

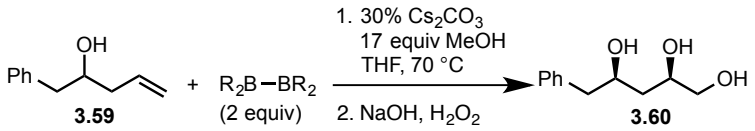
entry	substrate	major product	yield	d.r.
1[a]	 **3.81**	 **3.82**	64%	5:1
2[a]	 **3.83**	 **3.84**	79%	9:1
3[a]	 **3.85**	 **3.86**	94%	>20:1
4[a]	 **3.87**	 **3.88**	64%	17:1
5[a]	 **3.89**	 **3.90**	64%	>20:1
6[a]	 **3.91**	 **3.92**	55%	2:1
7	 **3.93**	No product	N/A	N/A
8[d]	 **3.94**	 **3.95**	75%	>20:1
9[d]	 **3.96**	 **3.97**	60%	>20:1

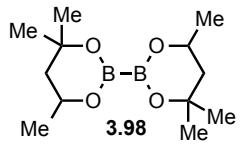
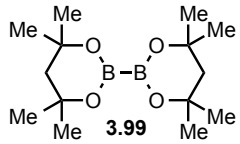
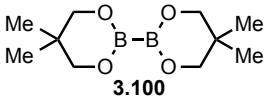
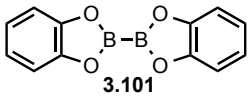
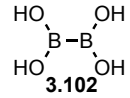
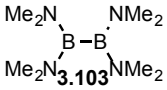
Bis(boronates) are subjected to [a] H_2O_2/NaOH, [b] Ac_2O, pyridine,[c] TBSCl, imidazole or (d) isolated as is.

In addition to studying different substrates, the diboron reagent used was varied for the diboration of **3.59**. The diboronate esters derived from 1,3-diols **3.98**, **3.99** and **3.100** furnished **3.60** in very similar selectivies (Table 3.5, Entries 1-3). Notably, lower

conversions are observed in cases where a more sterically hindered diboron is used. Catechol-derived diboron **3.101** underwent diboration in an unselective manner (Table 3.5, Entry 4). The slight preference for the *anti* diastereomer could arise from the undirected background reaction. Tetrahydroxyl diboron **3.102** participated in the diboration of **3.59**, albeit with low selectivity (Table 3.5, Entry 5). Unlike **3.102**, tetradimethylamine diboron **3.103** undergoes diboration in an extremely selective manner (Table 3.5, Entry 6). It is presumed that in excess methanol and elevated temperatures, the amine ligands bound to boron are exchanged for methoxy groups. It is noteworthy that the use of these diboron reagents offers a more atom-economical diboration reaction, due to their low molecular weights. Additionally, purification of the product after oxidation becomes trivial with no diol originating from the diboron reagent present. In the case of **3.103**, the amine generated, dimethylamine, is volatile and removed upon work up. To our knowledge, this is the first example of a diboration using either **3.102** or **3.103** as a diboron reagent.

Table 3.5 Diboration of **3.59** Using Various Diboron Reagents



entry	R_2B-BR_2	conversion (%)[a]	d.r. (syn:anti)[b]
1	 **3.98**	75%	7.8:1
2	 **3.99**	51%	8.0:1
3	 **3.100**	>95%	7.7:1
4	 **3.101**	67%	1:1.5
5	 **3.102**	87%	2.6:1
6	 **3.103**	>95%	>20:1

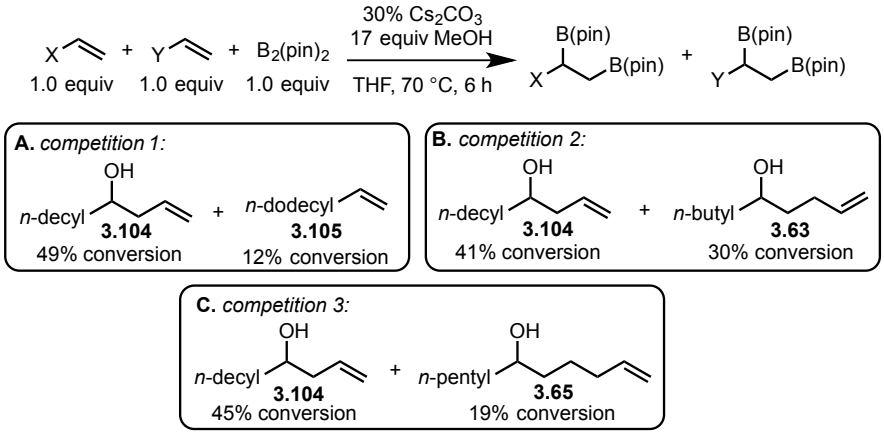
[a] Conversion determined by ^{1}H NMR using trimethoxybenzene as an internal standard.
[b] Diastereoselectivity was determined by SFC.

3.7 Probing Reactions

As demonstrated with the diboration of **3.79** (Table 3.3, Entry 7), the role that the hydroxyl group plays is vital to the selectivity of the reaction. In an effort to investigate the effect of the hydroxyl group and its relative distance from the alkene, a series of competition experiments were pursued. Equal amounts of **3.104**, **3.105** and $B_2(pin)_2$ were subjected to the diboration conditions. The conversion observed for homoallylic alcohol **3.104** was greater then 4x the conversion of **3.105** (Scheme 3.16, A). This observation suggests a lower limit of reaction rate ratio of ~4. Unsurprisingly, the diboration of **3.104**

and **3.63**, which both underwent a selective diboration, proceeded with similar rates (Scheme 3.16, B). The competition between **3.104** and **3.65** resembled that of the competition between **3.104** and **3.105** (Scheme 3.16, C). This is likely due to the inability of **3.65** to undergo a directed diboration.

Scheme 3.16 Competition Experiments



In addition to exploring the effect of the hydroxyl group within this reaction, we also wanted to study the interesting counterion effect observed in Table 3.1, Entries 4-8. The reactivity and selectivity seem to rely heavily on the base used. We hypothesized that the counterion of the base is mechanistically relevant to the efficiency of the reaction. It was envisioned that, through the use of crown ethers, the importance of cations to the reaction could be explored. The diboration of **3.59** with K_2CO_3 proceeds with full conversion and good selectivity (Table 3.6, Entry 1). However, upon addition of 18-crown-6 to the reaction, the conversion and, to a lesser degree, selectivity begin to

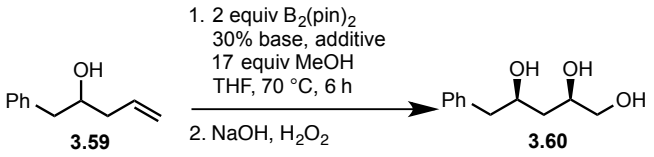
diminish (Table 3.6, Entries 2-5).[27] Low conversion suggests that the sequestering of the cation inhibits both the directed and undirected pathways. However, due to the slight decrease in selectivity, it is possible that the directed pathway is affected to a larger extent. Although similar inhibition is observed for 15-crown-5 (Table 3.6, Entry 6), reactivity and selectivity are restored with 12-crown-4 as an additive (Table 3.6, Entry 7). Furthermore, this phenomenon is witnessed with Cs_2CO_3 as the base and 18-crown-6 as an additive (Table 3.6, Entry 8).

Another observation of interest is the inability of amines to serve as bases during the diboration reaction. Using DBU as a base, the diboration of **3.59** does not proceed, recovering only starting olefin after oxidation (Table 3.6, Entry 9). Interestingly, when DBU and $B_2(pin)_2$ are heated in deuterated methanol (CD_3OD), the formation of a tetracoordinate boron species can be determined by ^{11}B NMR. When using Cs_2CO_3 as the base, the same ate complex is observed in a comparable reaction time. These experiments suggest that the ability of DBU to serve as a proper base for diboration is unrelated to its ability to form a tetracoordinate boron species. One possible explanation is that amine bases lack a suitable counterion. In order to test this hypothesis, a catalytic amount of sodium chloride (NaCl) was added to the diboration of **3.59** using DBU as a base. The addition of NaCl introduces a sodium cation, which has been shown to produce a selective reaction (Table 3.1, Entries 3-4, 6). In the presence of NaCl, the reaction proceeds, albeit with low conversion, yielding **3.60** with good selectivity (Table 3.6, Entry 10). Concerned with poor solubility of NaCl in tetrahydrofuran, the reaction

[27] For binding affinity constants for different cations and crown ethers, see: Steed, J. W.; Atwood, J. L. Cation Binding by Crown Ethers. *Supramolecular Chemistry*, 2nd Ed. John Wiley & Sons, Ltd. United Kingdom **2009**.

was run in methanol, furnishing **3.60** in full conversion and moderate selectivity (Table 3.6, Entry 11). In the absence of DBU, NaCl is unsuccessful in catalyzing the reaction (Table 3.6, Entry 12).

Table 3.6 Effect of the Counterion During the Diboration of **3.59**



3.59 **3.60**

entry	base	additive (equiv)	conversion (%)[a]	d.r.[b]
1	K_2CO_3	-	>95	8.4:1
2	K_2CO_3	18-crown-6 (0.6)	61	7.3:1
3	K_2CO_3	18-crown-6 (1.2)	44	5.1:1
4	K_2CO_3	18-crown-6 (2.4)	15	4.5:1
5	K_2CO_3	18-crown-6 (4.8)	15	5.3:1
6	K_2CO_3	15-crown-5 (1.2)	32	6.4:1
7	K_2CO_3	12-crown-4 (1.2)	>95	10.9:1
8	Cs_2CO_3	18-crown-6 (1.2)	31	5.3:1
9	DBU	-	<5	-
10	DBU	NaCl (0.3)	25	12.4:1
11[c]	DBU	NaCl (0.3)	>95	5.2:1
12	-	NaCl (0.3)	<5	-

[a] Conversion determined by ^{1}H NMR using trimethoxybenzene as an internal standard. [b] Diastereoselectivity was determined by SFC. [c] Methanol used as solvent

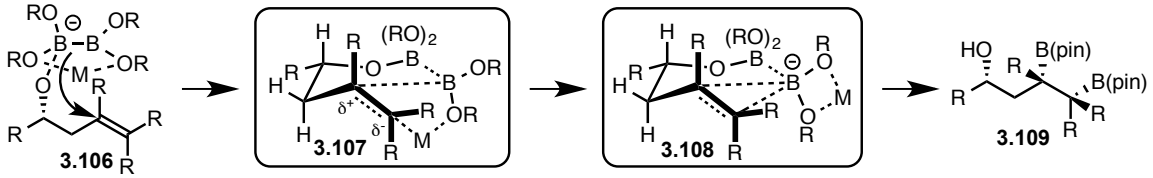
3.8 Stereochemical Model

The unselective diboration of **3.79** demonstrates that the presence of a hydroxyl group is essential for stereoinduction (Table 3.3, Entry 7). Furthermore, the distance between the hydroxyl group and alkene is essential for stereoselective diboration (Table 3.2). Therefore, it is estimated that the hydroxyl group and the diboron reagent associate with one another. We propose that this association can occur in one of two ways: (1) alkoxide coordination to the diboron reagent or (2) hydrogen-bonding of the hydroxyl

group to one of the oxygen atoms of the diboron reagent. However, the possibility of a hydrogen-bonding interaction between substrate and diboron reagent is unlikely due to the selective nature of the diboration of **3.59**, where the solvent used is methanol (Table 3.1, Entry 18). For this reason, it is believed that the directed pathway requires an substrate alkoxide/$(B(OR)_2)_2$ association (Scheme 3.17, **3.106**).

Another variable that appears to be vital for the success of the reaction is the base used, and more specifically, the counterion of the base. As described, large cations generate a more selective reaction (Table 3.1, Entries 6-8) and, upon the addition of crown ethers (potentially sequestering the cation), the reaction conversion starts to diminish (Table 3.6, Entries 1-8). It is possible that during the first boryl addition to the proximal olefinic carbon, the cation stabilizes the negative charge build up at the distal carbon (Scheme 3.17, **3.107)**. It is conceivable that the cation is crucial in the facilitation of this addition. In line with the mechanism proposed by Fernandez, after the boryl addition, the boron shifts to the distal carbon, forming a 3-membered boracycle transition state **3.108**. At this point, the proximal carbon binds to the sp^3 boron atom, breaking the already weakened B-B bond and generating the 1,2-bis(boronate) **3.109**.

Scheme 3.17 Stereochemical Model for Hydroxyl-Directed Diboration



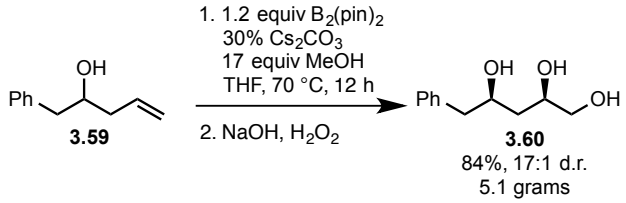
Another curious feature of this reaction is the role of methanol. As presented, a reaction without the addition of methanol fails to undergo diboration (Table 3.1, Entries 1-2). The most likely function of methanol is to solubilize the base during the course of

the reaction. The amount of base, and therefore counterion, solubilized is crucial for the conversion and selectivity of the reaction (Table 3.6, 10-11). This is plausible rationale for the need of excess methanol during Fernandez's diboration, even though the reaction should only need a catalytic amount of alcohol additive (Scheme 3.13).

3.9 Directed Diboration As a Synthetic Tool

To study whether this methodology is an efficient means for the synthesis of 1,3,4-triols, the scalability of the diboration of **3.59** was examined. Using only 1.2 equivalents of $B_2(pin)_2$, the reaction with **3.59** (31 mmol) furnished 5.1 grams of **3.60** in excellent yield and diastereoselectivity. Notably, the reaction was carried out in an open flask without precautions taken to avoid moisture contamination.

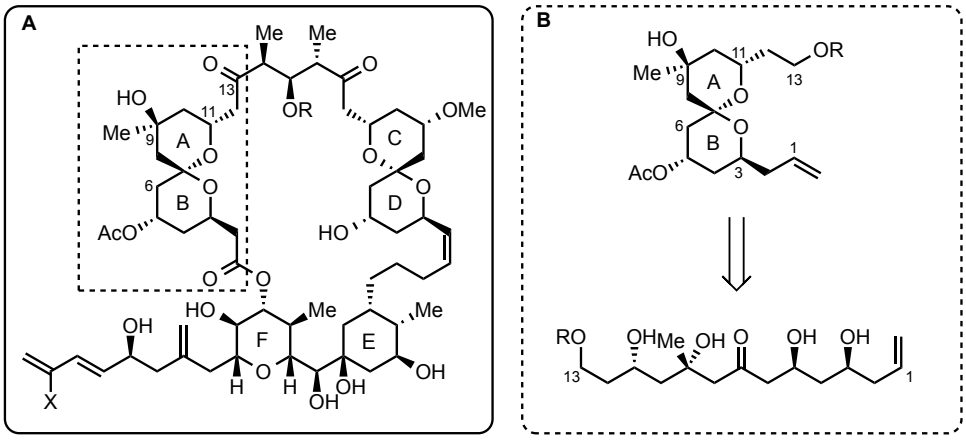
Scheme 3.18 Large-Scale Diboration of **3.59**



In an effort to highlight the synthetic applicability of this method, the synthesis of the C6-C13 fragment of spongistatin was examined. With six separate 1,3-diol motifs, spongistatin serves as an ideal synthetic target for directed diboration methodology (Scheme 3.19, A). Isolated in 1993, the spongistatin family of natural products exhibit subnanomolar efficacy for the inhibition of a variety of different human cancer cell

lines.[28] A multitude of syntheses of spongistatin 1 and 2 have been reported,[29] including studies associated with the synthesis of the AB and CD spiroketals.[30] In most cases, these spiroketals have been synthesized though an assortment of allylmetallations (Scheme 3.19, B). With the utilization of diboration and cross coupling (Chapter 4) methodologies, we envisioned accessing similar structural patterns.

Scheme 3.19 Spongistatin and a Common Approach to the AB Fragment



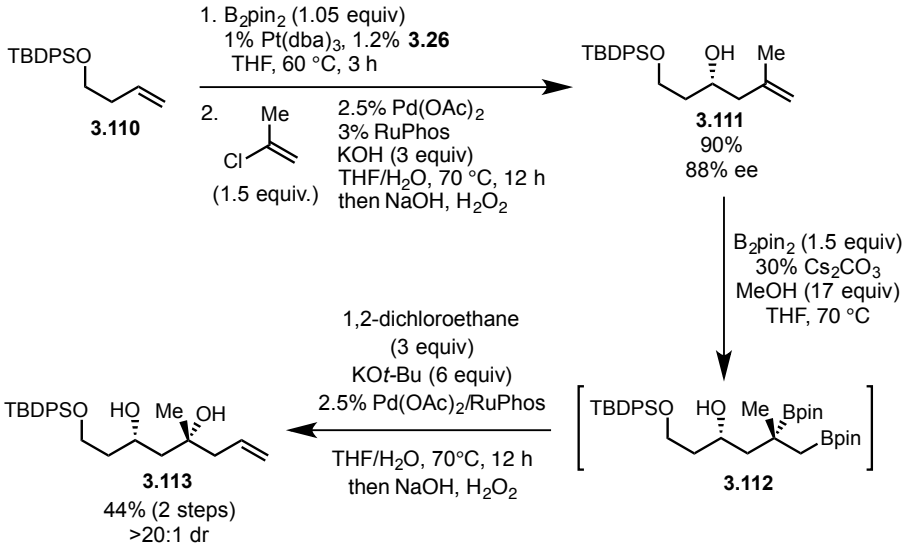
spongistatin 1 X = Cl, R = Ac
spongistatin 2 X = H, R = Ac
spongistatin 4 X = Cl, R = H

Starting from silyl ether **3.110**, an asymmetric diboration/cross coupling/oxidation strategy was performed to yield homoallylic alcohol **3.111** in 90% yield and 88% ee (Scheme 3.20). Directed diboration of **3.111** yielded the bis(boronate) **3.112**, which after

[28] Pettit, G. R.; Cichacz, Z. A.; Gao, F.; Herald, C. L.; Boyd, M. R.; Schmidt, J. M.; Hooper, J. N. A. *J. Org. Chem.* **1993**, *58*, 1302 – 1304.
[29] Reviews: (a) Yeung, K.-S.; Paterson, I. *Chem. Rev.* **2005**, *105*, 4237 – 4313. (b) Paterson, I.; Coster, M. J. Strategies and Tactics in Organic Synthesis; Elsevier: London, UK, **2004**; Vol. 4, p 211.
[30] (a) Paterson, I.; Oballa, R. M.; Norcross; R. D. *Tetrahedron Lett.* **1996**, *37*, 8581 – 8584. (b) Crimmins, M. T.; Washburn, D. G. *Tetrahedron Lett.* **1998**, *39*, 7487 – 7490. (c) Smith, A. B. III; Corbett, R. M.; Pettit, G. R.; Chapuis, J.-C.; Schmidt, J. M.; Hamel, E.; Jung, M. K. *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2039 – 2042. (d) Crimmins, M. T.; Smith, A. C. *Org. Lett.* **2006**, *8*, 1003 – 1006. (e) Allais, F.; Cossy, J. *Org. Lett.* **2006**, *8*, 3655 – 3657.

solvent removal, was subjected a palladium-catalyzed cross-coupling with chloroethene, formed *in situ* from 1,2-dichloroethane. After oxidation, the 1,3-diol **3.113** was yielded in a 44% yield and excellent stereocontrol.

Scheme 3.20 Synthesis of C6-C13 Fragment of Spongistatin 1



3.10 Conclusion

The hydroxyl group has been proven to be a viable directing group for the transition-metal free diboration of olefins. A variety of different homo- and bis-homoallylic alcohols participate in the stereoselective diboration reaction. The substrate is proposed to bind to the diboron reagent resulting in tetracoordinate boron alkoxide species. The reaction has been shown to be an efficient synthetic tool for the synthesis of 1,3,4-triols and, when combined with cross-coupling methodology, a surrogate for allylmetallation chemistry.

3.11 Experimental Section

3.11.1 General Considerations

^{1}H NMR spectra were measured using a Varian Unity Inova 500 MHz and Varian Gemini 400 MHz spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.24 ppm, CD_3OD: 3.31 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and assignment. Proton-decoupled ^{13}C NMR spectra were recorded on Varian Unity Inova 500 MHz (125 MHz) or Varian Gemini 400 MHz (100 MHz) spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.0 ppm, CD_3OD: 49.2 ppm). Infrared (IR) spectra were recorded on a Bruker α-P Spectrometer. Frequencies are reported in wavenumbers (cm^{-1}) as follows: strong (s), broad (br), medium (m), and weak (w). High resolution mass spectrometry (HRMS) and X-ray diffraction were performed at Merkert Chemistry Center, Boston College, Chestnut Hill, MA.

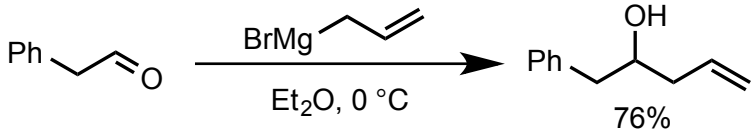
Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230 x 400 mesh) purchased from Silicycle. Thin layer chromatography (TLC) was conducted on 250 μm glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm), potassium permanganate ($KMnO_4$), and Seebach's "magic" stain (phosphomolybic acid/cerium(IV) sulfate/sulfuric acid/water). Analytical supercritical fluid chromatography (SFC) was performed using a Thar Supercritical Chromatograph equipped with an auto sampler and a Waters photoiodide array detector with methanol as the modifier. Melting points

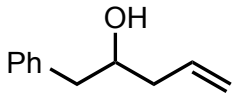
were obtained using a Laboratory Devices, Inc. Mel-Temp II apparatus.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon unless specifically mentioned otherwise. Tetrahydrofuran, dichloromethane, and diethyl ether were purified using Pure Solv MD-4 solvent purification system (Innovative Technology, Inc.) by passing the solvent through two activated alumina columns after being purged with argon. Ethyl acetate, triethylamine, and diisopropylamine were distilled from calcium hydride. Bis(pinacolato)diboron was obtained from Allychem Co., Ltd. and recrystallized from pentane prior to use. All other chemicals were purchased from Aldrich, Fisher Scientific, or Alfa Aesar and used without further purification.

3.11.2 Preparation of Homoallylic Alcohols

*Preparation of 1-phenylpent-4-en-2-ol (**3.59**):*



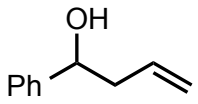


The title compound was prepared as shown above using standard procedure. A flame dried round bottom flask was charged with 2-phenylacetaldehyde (1.95 mL, 16.65 mmol) and diethyl ether (17 mL) and cooled to 0 °C. Allylmagnesium bromide (20.8 mL, 20.8 mmol, 1.00 M solution in diethyl ether) was added dropwise over 30 minutes. The cooling bath was removed and the reaction mixture was allowed to warm to room temperature and stir for one hour. A saturated aqueous solution of NH_4Cl was added to the flask until the white precipitate disappears. The layers were separated and the aqueous layer was washed with ethyl acetate (3 x 50 mL).

The organic layers were combined and washed with a brine solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude reaction mixture was purified by column chromatography on silica gel (2.5-10% ethyl acetate/hexanes, R_f = 0.50 in 20% ethyl acetate/hexanes, stain in $KMnO_4$) to afford a clear, colorless oil (2.1 g, 76%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.71 (1H, br s), 2.17 – 2.52 (1H, m), 2.29 – 2.36 (1H, m), 2.71(1H, dd, J = 13.4 Hz, 8.2 Hz), 2.81 (1H, dd, J = 13.4 Hz, 5.0 Hz), 3.84 – 3.90 (1H, m), 5.12 – 5.18 (2H, m), 5.80 – 5.91 (1H, m), 7.20 – 7.24 (3H, m), 7.29 – 7.32 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 41.2, 43.3, 71.7, 118.1, 126.5, 128.5, 129.4, 134.7, 138.4; IR (neat): 3403.4 (w), 3064.4 (m), 3027.7 (m), 2978.1 (m), 2918.5 (w), 1640.5 (m), 1603.7 (w), 1495.4 (m), 1454.1 (m), 1113.6 (m), 1078.4 (m), 915.3 (m), 744.5 (m), 700.1 (s) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{13}$ [M+H-H_2O]: calculated: 145.1017, found: 145.1022.

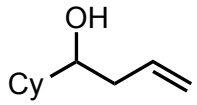
*Preparation of 1-phenylbut-3-en-1-ol (**3.67**):*



The title compound was prepared according to the same procedure as 1-phenylpent-4-en-2-ol with minor modifications. The crude product was purified on silica gel (3% ethyl acetate in hexanes) to afford the title compound as a clear oil (1.9 g, 95% yield). Spectral data are in agreement with the literature.[31]

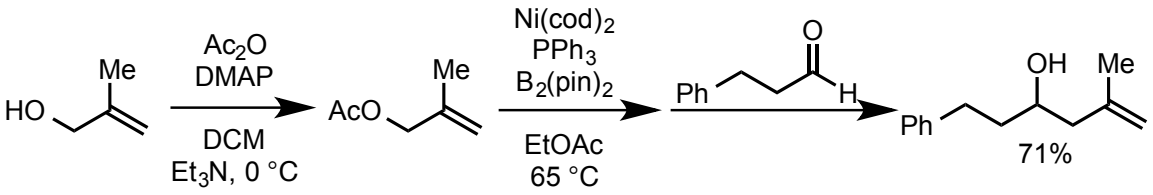
[31] Ishiyama, T.; Ahiko, T.; Miyaura, N. *J. Am. Chem. Soc.* **2002**, *124*, 12414 – 12415.

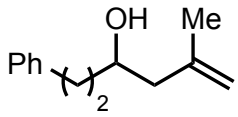
*Preparation of 1-cyclohexylbut-3-en-1-ol (**3.69**):*



The title compound was prepared according to the same procedure as 1-phenylpent-4-en-2-ol with minor modifications. The crude product was purified on silica gel (5-10% ethyl acetate in hexanes) to afford the title compound as a pale yellow oil (0.44 g, 18%). Spectral data are in agreement with literature.[32]

*Preparation of 5-methyl-1-phenylhex-5-en-1-ol (**3.87**):*



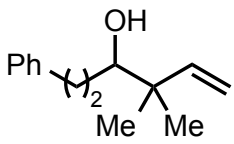


The title compound was prepared according to the following procedure as reported in the literature.[33] To a flame-dried round bottom flask equipped with a magnetic stirbar was added β-methallyl alcohol (7.4 mL, 88 mmol) and acetic anhydride (8.3 mL, 88 mmol) under a nitrogen atmosphere. The flask was cooled to 0 °C and DMAP (0.11 g, 0.88 mmol) was quickly added and the flask was sealed. A mixture of triethylamine (7 mL) and DCM (7 mL) was prepared in a separate flame-dried flask, then added dropwise to the first flask. The reaction mixture was allowed to stir while warming to room temperature for 2 h. The reaction mixture was poured into a flask containing 2 M HCl and ice, and the aqueous and organic layers were separated. The aqueous layer was washed with DCM (2 x 10 mL) and the combined organic layers were washed with saturated aqueous sodium bicarbonate solution. The

[32] Thadani, A. N.; Batey, R. A. *Org. Lett.* **2002**, *4*, 3827 – 3830.
[33] Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett.* **2012**, *14*, 1416 – 1419.

organic layer was separated, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude product was purified by silica gel (5-10% ethyl acetate in hexanes) to afford 2-methylallyl acetate as a clear liquid (7.4 g, 74% yield). The purified acetate was then used in the following procedure. An oven-dried 20 mL scintillation vial equipped with a magnetic stirbar was brought into the glovebox. To the vial was sequentially added $Ni(cod)_2$ (60 mg, 0.22 mmol), PPh_3 (58 mg, 0.22 mmol), ethyl acetate (8 mL), 2-methylallyl acetate (0.50 g, 4.4 mmol), and $B_2(pin)_2$ (1.11 g, 4.40 mmol). The vial was tightly sealed and stirred at 65 °C for 12 h. The reaction mixture was then cooled to room temperature and 3-phenylpropionaldehyde (0.61 mL, 4.6 mmol) was added. The reaction was stirred at room temperature for 24 h before being quenched with 10 mL of a 1:1 mixture of water and diethyl ether. The organic and aqueous layers were separated, and the aqueous layer was extracted with diethyl ether (3 x 5 mL). The combined organic layers were dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude product was purified on silica gel (5-10% ethyl acetate in hexanes) to afford the title compound as a pale yellow oil (0.59 g, 71% yield). Spectral data are in agreement with the literature.

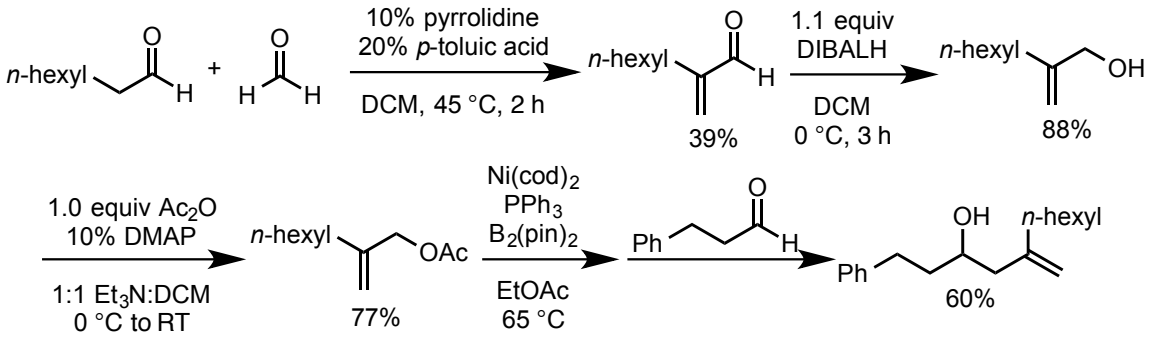
*Preparation of 4,4-dimethyl-1-phenylhex-5-en-3-ol (**3.77**):*

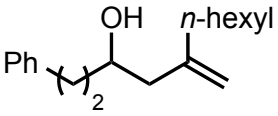


The desired compound was prepared according to the same procedure as 5-methyl-1-phenylhex-5-en-1-ol with minor modifications. 3-methylbut-2-en-1-ol was used to prepare the necessary acetate substrate. The crude product was purified on silica gel (5-10% ethyl acetate in hexanes) to afford

the title compound as a pale yellow oil (0.70 g, 88% yield). Spectral data are in agreement with the literature.[34]

*Preparation of 5-methylene-1-phenylundecan-3-ol (**3.89**):*





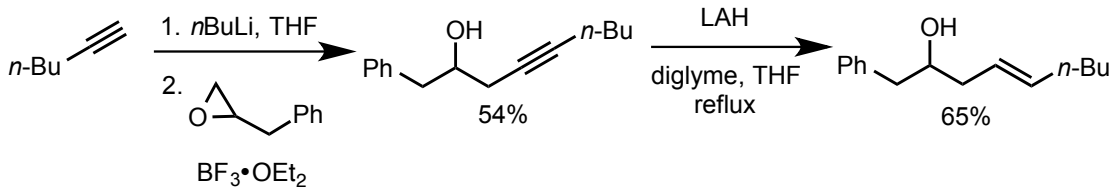
The desired compound was prepared according to the sequence shown above. The α-methylenation step was followed from a literature procedure.[35] Preparation of the necessary acetate and borylation/allylation follow the same procedure for the preparation of 5-methyl-1-phenylhex-5-en-1-ol with minor modifications. The final product of the sequence was purified on silica gel (5% ethyl acetate in hexanes) and isolated as a colorless oil (0.85 g, 60%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 7.0 Hz), 1.32-1.21 (6H, m), 1.47-1.33 (2H, m), 1.81-1.72 (3H, m), 1.98 (2H, t, J = 7.5 Hz), 2.12-2.05 (1H, m), 2.27-2.22 (1H, m), 2.85-2.65 (2H, m), 3.71 (1H, m), 4.81 (1H, s), 4.87 (1H, s), 7.21-7.14 (3H, m), 7.29-7.25 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 27.7, 29.0, 31.7, 32.1, 35.8,

[34] Kobayashi, S.; Nishio, K. *J. Org. Chem*. **1994**, *59*, 6620 – 6628.
[35] Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 8770 – 8773.

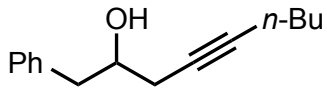
38.8, 44.6, 68.1, 112.3, 125.8, 128.4, 128.4, 142.2, 146.8,; IR (neat): 2925.6 (m), 2856.0 (m), 1642.7 (w), 1495.5 (w), 1454.2 (m), 1051.2 (m), 892.4 (m), 744.9 (m), 697.9 (m); HRMS-(ESI+) for $C_{18}H_{28}O$ [M+H-H_2O]: calculated: 243.2113, found: 243.2115.

*Preparation of (E)-1-phenylnon-4-en-2-ol (**3.81**):*

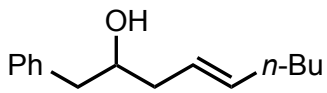


The title compound was prepared as shown above from 1-hexyne. To a flame-dried, round-bottomed flask equipped with a stir bar was added 1-hexyne (2.66 mL, 23.1 mmol) and THF (43 mL) under N_2. The reaction mixed was cooled to -78°C. To the flask, *n*BuLi (9.30 mL, 23.1 mmol, 2.50 M) was added dropwise and stirred for 30 mins at -78°C. 2-(phenylmethyl)oxirane (2.07 g, 15.4 mmol) and $BF_3 \cdot OEt_2$ (2.02 mL, 12.7 mmol) were added dropwise to the flask at - 78°C. Allow the reaction to warm to rt and stir at rt for 1.5 hours. Quench with saturated aqueous NH_4Cl (40 mL), diluted with diethyl ether and allow the layers were separated. The aqueous layer was washed with diethyl ether (3 x 50 mL) and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated in vacuo. The crude product was purified by column chromatography on SiO_2 (0-10% ethyl acetate/ hexanes, R_f = 0.35 in 9:1 hexanes:ethyl acetate, stain in $KMnO_4$) to afford a clear, colorless oil (2.7 g, 54%). To a flame-dried, round- bottomed flask equipped with a reflux condenser and stir bar in the glove box was added $LiAlH_4$ (0.394 g, 10.4 mmol). Outside the glove box, THF (1.5 mL) was added and the flask was cooled to 0°C in an

ice/water bath. Add diglyme (5.3 mL) and 1-phenylnon-4-yn-2-ol (0.75 g, 3.5 mmol) dropwise to the reaction flask. Heat the reaction to reflux for 6 days. Sequentially quench the reaction with water (0.40 mL), 2.5 M NaOH (aq) (0.40 mL) and water (1.3 mL). Pour solution into 2.5 M HCl (5.0 mL) and dilute with pentane. The aqueous layer was washed with pentane (3 x 25 mL). The combined organic layer was washed with water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (0-10% ethyl acetate/ hexanes, R_f = 0.35 in 9:1 hexanes:ethyl acetate, stain in $KMnO_4$) to afford a clear, colorless oil (0.49 g, 65%).



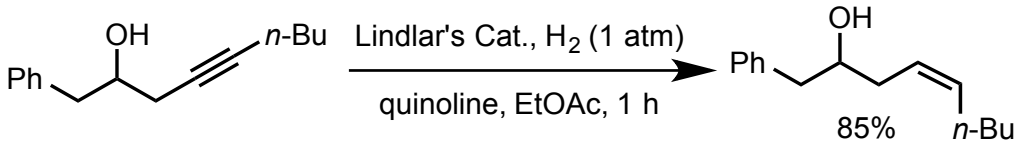
1-phenylnon-4-yn-2-ol. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (3H, t, J = 7.5 Hz), 1.39-1.53 (4H, m), 1.98 (1H, br s), 2.18-2.22 (2H, m), 2.36 (2H, qdt, J = 16.3 Hz, 5.8 Hz, 2.3 Hz), 2.82 (1H, dd, J = 13.8 Hz, 7.3 Hz), 2.90 (1H, dd, J = 13.3 Hz, 5.8 Hz), 3.94 (1H, pentet, J = 6.0 Hz), 7.22-7.26 (3H, m), 7.30-7.33 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.6, 18.4, 22.0, 26.8, 31.1, 42.5, 71.2, 75.8, 83.6, 126.5, 128.5, 129.4, 138.0; IR (neat): 3400.7 (w), 3027.6 (w), 2956.2 (m), 2929.3 (s), 2871.4 (m), 1496.1 (m), 1454.2 (m), 1069.0 (s), 1045.3 (s), 741.7 (s), 699.1 (s) cm^{-1}; HRMS- (ESI+) for $C_{15}H_{21}O$ [M+H]: calculated: 217.1592, found: 217.1599.



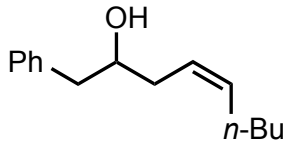
(E)-1-phenylnon-4-en-2-ol (3.81). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (3H, t, J = 6.8 Hz), 1.29-1.39 (4H, m), 1.72 – 1.73 (1H, m), 2.05 (1H, q, J = 7.0 Hz), 2.13-2.18 (1H, m), 2.25-2.30 (1H, m), 2.72 (1H,

dd, J = 13.5, 8.0), 2.81 (1H, dd, J = 13.3, 5.3 Hz), 3.80 – 3.86 (1H, m), 5.42 – 5.48 (1H, m), 5.54 – 5.60 (1H, m), 7.22 – 7.25 (3H, m), 7.30 – 7.33 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 13.9, 22.2, 31.6, 32.4, 40.0, 43.2, 72.0, 125.6, 126.4, 128.5, 129.4, 134.8, 138.6; IR (neat): 3556.6 (w), 3418.3 (w), 3062.5 (w), 3027.0 (m), 2955.5 (m), 2923.8 (s), 2871.0 (m), 2856.0 (m), 1602.0 (w), 1495.7 (m), 1454.1 (m), 969.5 (s), 740.9 (s), 698.7 (s) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{26}NO$ [M+NH_4]: calculated: 236.2014, found: 236.2002.

*Preparation of (Z)-1-phenylnon-4-en-2-ol (**3.83**):*

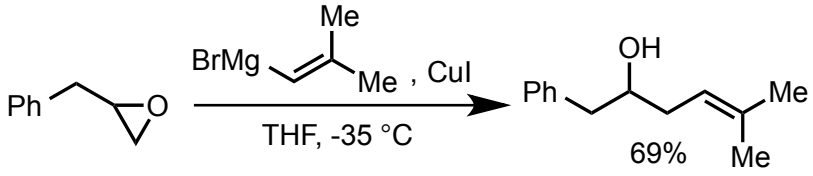


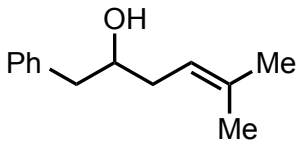
The title compound was prepared as shown above from 1-phenylnon-4-yn-2-ol. To a flame-dried, round-bottomed flask equipped with a stir bar was added Lindlar's catalyst (15 mg). To the flask, ethyl acetate (3.6 mL) and quinoline (35 μL, 0.30 mmol) were added. 1-phenylnon-4-yn-2-ol (306 mg, 1.42 mmol) was then added to the flask. The flask was evacuated and refilled (3x) with H_2 from a balloon. The reaction was allowed to stir at rt for 1 hr. After one hour, the reaction mixture was put through a plug of silica and washed with EtOAc (25 mL) and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (0-10% ethyl acetate/hexanes, R_f = 0.35 in 9:1 hexanes:ethyl acetate, stain in $KMnO_4$) to afford a clear, colorless oil (0.26 g, 85%).



(Z)-1-phenylnon-4-en-2-ol (3.83). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 7.0 Hz), 1.25-1.37 (4H, m), 1.63 (1H, br s), 2.02 – 2.07 (2H, m), 2.23-2.32 (2H, m), 2.70 (1H, dd, J = 13.8 Hz, 8.2 Hz), 2.82 (1H, dd, J = 13.8 Hz, 4.6 Hz), 3.84 (1H, pentet, J = 6.2 Hz), 5.40 – 5.46 (1H, m), 5.53 – 5.60 (1H, m), 7.20 – 7.24 (3H, m), 7.28 – 7.32 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 22.3, 27.1, 31.8, 34.6, 43.3, 72.4, 124.8, 126.4, 128.5, 129.4, 133.5, 138.6; IR (neat): 3395.7 (w), 3062.3 (w), 3025.9 (w), 2954.9 (m), 2857.4 (m), 1602.5 (w), 1495.4 (m), 1453.9 (m), 1078.4 (m), 742.8 (m), 698.1 (s) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{26}NO$ [M+NH_4]: calculated: 236.2014, found: 236.2013.

*Preparation of 5-methyl-1-phenylhex-4-en-2-ol (**3.91**):*



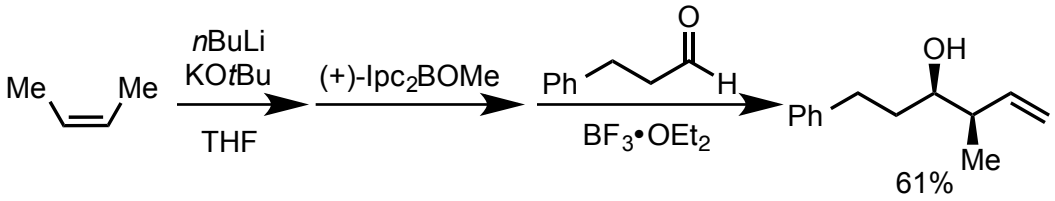


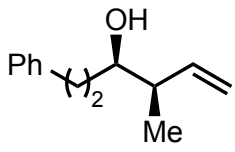
5-methyl-1-phenylhex-4-en-2-ol (**3.91**). The title compound was prepared as shown above using standard procedure. A flamed dried round bottom flask was charged with 2-methyl-1-propenylmagnesium bromide (16.4 mL, 8.20 mmol, 0.50 M solution in THF) and cooled to -35 °C. Copper(I) iodide (81 mg, 0.37 mmol) was added and stirred for 15 minutes at -35 °C. 2-(phenylmethyl)oxirane (1.00 g, 7.45 mmol) was added dropwise to the flask over 20 minutes. Allow the reaction to warm to room temperature and stir for 1.5 hours. The reaction mixture was poured into a separatory funnel containing 12 M HCl (4.0 mL)

and brine (60 mL). The layers were separated and the aqueous layer was washed with ethyl acetate (3 x 25 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude reaction mixture was purified by column chromatography on silica gel (5-10% ethyl acetate/hexanes, R_f = 0.25 in 10% ethyl acetate/hexanes, stain in $KMnO_4$) to afford a clear, yellow oil (0.98 g, 69%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 1.63 (3H, s), 1.64 (1H, s), 1.74 (3H, s), 2.21 (2H, t, J = 6.6 Hz), 2.70 (1H, dd, J = 13.6 Hz, 7.6 Hz), 2.81 (1H, dd, J = 13.4 Hz, 5.0 Hz), 3.82 (1H, pentet, J = 6.4 Hz), 5.20 (1H, t, J = 7.4 Hz), 7.19-7.24 (3H, m), 7.28-7.31 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ18.0, 25.9, 35.5, 43.3, 72.6, 119.9, 126.3, 128.5, 129.4, 135.1, 138.7; IR (neat): 3404.0 (w), 3062.0 (w), 3027.2 (w), 2967.1 (w), 2913.8 (s), 1601.8 (w), 1495.2 (m), 1452.4 (m), 1048.1 (m), 740.5 (s), 698.1 (s) cm^{-1}; HRMS-(ESI+) for $C_{13}H_{19}O$ [M+H]: calculated: 191.1436, found: 191.1435.

*Preparation of (3R,4R)-4-methyl-1-phenylhex-5-en-3-ol (**3.71**):*



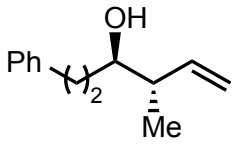


The title compound was synthesized by following a literature procedure.[36] To a stirred mixture of potassium *tert*-butoxide (2.8 g, 25 mmol), THF (7 mL), and cis-2-butene (9.0 mL, 0.10 mol), *n*-

[36] Herbert C. Brown , Krishna S. Bhat, *J. Am. Chem. Soc.* **1986**, *108*, 5919 – 5923.

butyllithium in hexanes (2.3 M, 25 mmol) was added at -78 °C. After complete addition of n-butyllithium, the mixture was stirred at -45 °C for 10 min. The resulting solution was cooled to -78 °C, and to it was added dropwise methoxydiisopinocampheylborane in THF (1.0 M, 25 mmol). After the reaction mixture was stirred at -78 °C for 30 min, boron trifluoride etherate (4.00 mL, 33.5 mmol) was added dropwise. Then aldehyde (5.3 mL, 40 mmol) was added dropwise at -78 °C. The mixture was now stirred at -78 °C for 3 h and then treated with 18.3 mL (55.0 mmol) of 3.00 M NaOH and 7.5 mL of 30% H_2O_2, and the contents were refluxed for 1 h. The organic layer was separated, washed with water (30 mL) and brine (30 mL), and dried over anhydrous Na_2SO_4. The residue, after removal of the solvent, was purified on silica gel chromatography (1-3% ethyl acetate/hexanes) to furnish the desired product (2.9 g, 61% yield) with spectral properties reported in literature.[37]

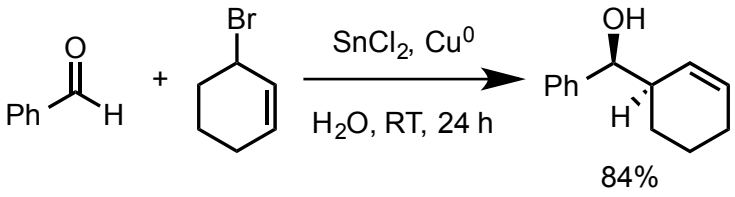
*Preparation of (3R,4S)-4-methyl-1-phenylhex-5-en-3-ol (**3.73**):*

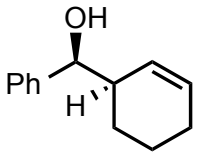


The title compound was prepared according to the same procedure as (3R,4R)-4-methyl-1-phenylhex-5-en-3-ol with minor modifications. The crude product was carefully purified by silica gel chromatography (1-3% ethyl acetate/hexanes) to furnish the desired product (1.7 g, 58%) with spectral properties reported in literature.[38]

[37] Kobayashi, S.; Nishio, K. *J. Org. Chem.* **1994**, *59*, 6620 – 6628.
[38] Roush, W.R.; Ando, K.; Powers, D.B.; Palkowitz, A.D.; Halterman, R.L. *J. Am. Chem, Soc.* **1990**, *112*, 6339 – 6348.

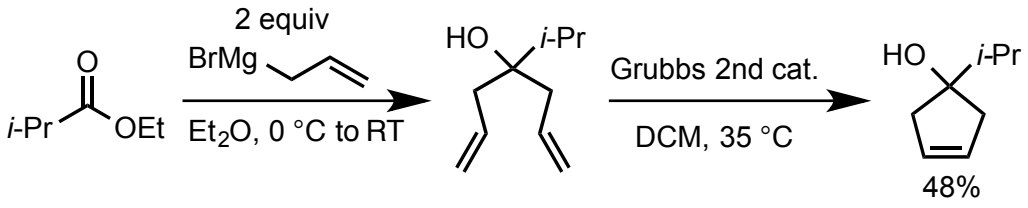
*Preparation of cyclohex-2-enyl(phenyl)methanol (**3.85**):*



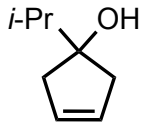


The title compound was synthesized by following literature procedure. To a mixture of benzaldehyde (1.0 mL, 10 mmol) and 3-bromocyclohexene (1.73 mL, 15.0 mmol) in water (10 mL), $SnCl_2 \bullet H_2O$ (4.5 g, 20 mmol) and copper powder (0.64 g, 10 mmol) were added. This mixture was vigorously stirred at room temperature for 24 h. Then the mixture was extracted with ether (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered and concentrated by rotary evaporation. The crude material was purified on silica gel (3% ethyl acetate in hexanes) to afford the title compound as a clear, colorless oil (1.58 g, 84%). Spectral properties are in agreement with the literature.[39]

*Preparation of 1-isopropylcyclopent-3-en-1-ol (**3.96**):*



[39] Tan, X.-H.; Tao, C.-Z.; Hou, Y.-Q.; Luo, L.; Liu, L.; Guo Q.-X. *Chinese Journal of Chemistry*, **2005**, *23*, 237 – 241.



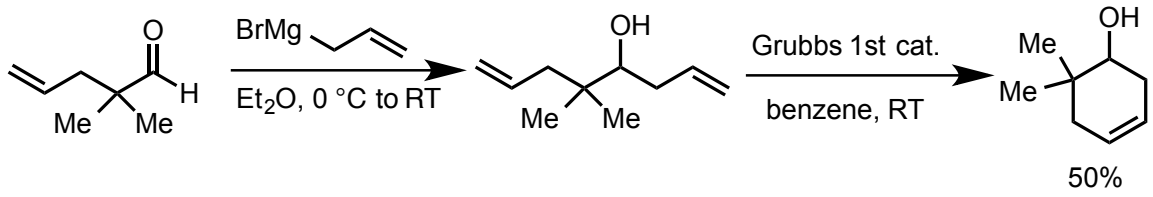
The title compound was prepared according to the following two-step sequence. To a flame-dried round bottom flask equipped with a magnetic stirbar, added allylmagnesium bromide solution (1.0 M in diethyl ether, 41 mmol) under a nitrogen atmosphere. The flask was cooled to 0 °C, at which time a solution of ethyl isobutyrate (2.60 mL, 19.4 mmol) and diethyl ether (13 mL) was added dropwise to the Grignard reagent. The solution was allowed to stir while slowly warming to room temperature. After 6 h, the flask was cooled to 0 °C and quenched with saturated aqueous ammonium chloride. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 20 mL). The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated by rotary evaporation. The crude product was purified on silica gel (2.5-5% ethyl acetate in hexanes) to afford 4-isopropylhepta-1,6-dien-4-ol as a pale yellow oil (1.88 g, 63%).

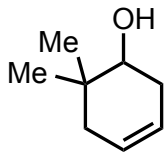
A flame-dried round bottom flask equipped with a magnetic stirbar was brought into a glovebox and charged with 4-isopropylhepta-1,6-dien-4-ol (1.30 g, 8.43 mmol), Grubbs 2nd generation olefin metathesis catalyst (72 mg, 0.084 mmol), and dichloromethane (30 mL). The flask was sealed, removed from the glovebox, and stirred at 35 °C until TLC indicated the consumption of starting material. The reaction mixture was concentrated by rotary evaporation and the crude product purified on silica gel (10% ethyl acetate in hexanes) to afford the product as a colorless oil (0.48 g, 48%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 5.70 (2H, s), 2.49 (2H, dd, J = 16.0 Hz, 1.0 Hz), 2.27 (2H, dd, J = 15.5 Hz, 1.0 Hz), 1.78 (1H, pentet, J = 7.0 Hz), 0.96 (3H, s), 0.95 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 128.7, 84.0, 45.6, 36.8, 17.6; IR (neat): 3415.1 (w), 2961.8

(m), 2932.9 (m), 2879.9 (m), 900.3 (m), 860.1 (m), 671.5 (m) cm^{-1}; HRMS-(ESI+) for $C_8H_{14}O$ [M+H−H_2O]: calculated: 109.1017, found: 109.1020.

*Preparation of 6,6-dimethylcyclohex-3-en-1-ol (**3.94**):*





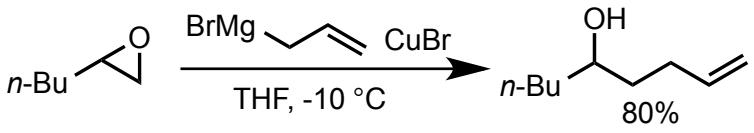
The title compound was prepared according to the following two-step sequence. To a flame-dried round bottom flask equipped with a magnetic stirbar was added allylmagnesium bromide solution (1 M in diethyl ether, 14.3 mL). The flask was cooled to 0 °C, and a solution of 2,2-dimethylpent-4-enal (1.8 mL, 13 mmol) in diethyl ether (20 mL) was slowly added to the Grignard reagent. The reaction mixture was stirred and allowed to slowly warm to room temperature. The reaction was quenched with 1 M HCl, and the aqueous and organic layers were separated. The aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was purified on silica gel (5% ethyl acetate in hexanes) to afford 5,5-dimethylocta-1,7-dien-4-ol (1.60 g, 80%).

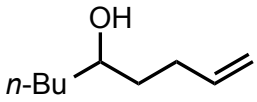
For the ring-closing metathesis, a flame-dried round bottom flask equipped with a magnetic stirbar was brought into a glovebox and charged with 5,5-dimethylocta-1,7-dien-4-ol (1.30 g, 8.43 mmol), Grubbs 1st generation catalyst (69 mg, 0.040 mmol), and dichloromethane (30 mL). The flask was sealed, removed from the box, and stirred at

room temperature until TLC indicated consumption of the starting material. The reaction mixture was concentrated by rotary evaporation and purified on silica gel (10% ethyl acetate in hexanes) to afford the title compound as a colorless oil (0.52 g, 50%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (3H, s), 0.92 (3H, s), 1.41 (1H, br s), 1.84-1.80 (1H, m), 2.02-1.91 (2H, m), 2.35-2.30 (1H, m), 3.50 (1H, t, J = 11 Hz), 5.59-5.50 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.0, 26.3, 31.7, 33.6, 37.4, 73.9, 123.2, 126.0; IR (neat): 3383.2 (br, m), 3025.0 (m), 2954.6 (m), 2925.9 (m), 2897.1 (m), 1055.7 (s), 982.8 (m), 897.5 (w), 771.1 (w), 658.8 (s) cm^{-1}; HRMS-(ESI+) for $C_8H_{14}O$ [M+H-H_2O]: calculated: 109.1017, found: 109.1020.

*Preparation of non-1-en-5-ol (**3.63**):*



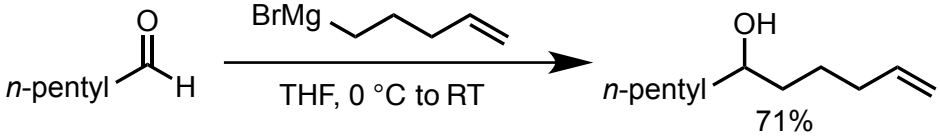


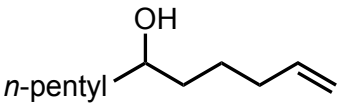
The title compound was prepared as shown above using standard procedure. A flamed dried round bottom flask was charged with copper(I) bromide (73 mg, 0.51 mmol) and allylmagnesium bromide (4.5 mL, 4.5 mmol, 1.0 M solution in diethyl ether). The flask was cooled to -10 °C and 2-butyloxirane (0.36 mL, 3.0 mmol) in tetrahydrofuran (19 mL) was added slowly. The reaction was allowed to warm to room temperature overnight. A saturated aqueous solution of ammonium chloride (10 mL) was added to the flask. The layers were separated and the aqueous layer was washed with diethyl ether (3 x 25 mL). The organic layers were combined and

washed with a brine solution. The organic layer was dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by column chromatography on silica gel (0-10% ethyl acetate in hexanes) to afford a clear, colorless oil (0.35 g, 80%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 0.89 (3H, t, J = 7.0 Hz), 1.26 – 1.60 (9H, m), 2.07 – 2.24 (2H, m), 3.60 (1H, pentet, J = 2.8 Hz), 4.93 – 5.06 (2H, m), 5.78 – 5.88 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.7, 27.8, 30.1, 36.4, 37.2, 71.5, 114.7, 138.6; IR (neat): 3345.9 (m), 3077.9 (w), 2956.7 (m), 2928.9 (s), 2859.3 (m), 1640.9 (m), 1452.7 (m), 1125.6 (m), 1038.0 (m), 994.4 (m), 908.0 (s), 640.8 (w) cm^{-1}; HRMS-(ESI+) for $C_9H_{19}O$ [M+H]: calculated: 143.1436, found: 143.1429.

*Preparation of undec-1-en-6-ol (**3.65**):*



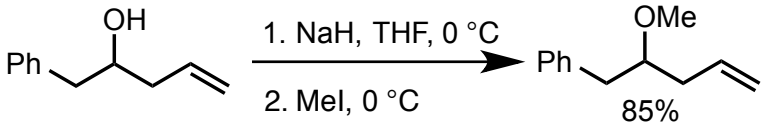


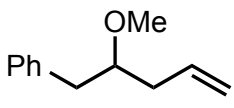
The title compound was prepared according to the following procedure. To a flame-dried round bottom flask equipped with a magnetic stirbar, added ground magnesium turnings (0.53 g, 22 mmol). The flask was flame dried and then backfilled with nitrogen. The flask was then charged with THF (39 mL), cooled to 0 °C, and then 5-bromo-1-pentene (2.30 mL, 19.4 mmol) was added and allowed to slowly warm to room temperature. To a flame-dried narrow bottom flask, added hexanal (2.20 mL, 17.6 mmol) and THF (24 mL). The round bottom

flask containing the prepared Grignard reagent was cooled to 0 °C, and the hexanal solution was transferred to this flask by syringe. The solution was allowed to slowly warm to room temperature. After 12 h, the reaction was cooled to 0 °C and quenched with 15 mL of saturated aqueous ammonium chloride. The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude product was purified on silica gel (5-10% ethyl acetate in hexanes) to afford the title compound as a colorless oil (2.14 g, 71%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (3H, t, J = 7 Hz), 1.55-1.26 (12H, m), 2.08-2.04 (2H, m), 3.58 (1H, m), 5.01-4.92 (2H, m), 5.83-5.75 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.6, 24.9, 25.3, 31.9, 33.7, 36.9, 37.5, 71.8, 114.5, 138.8; IR (neat): 3336.6 (br, m), 2927.6 (s), 2858.2 (m), 1641.1 (m), 1458.4 (m), 1126.0 (m), 993.1 (m), 908.1 (s), 635.6 (m) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{22}O$ [M+H]: calculated: 171.1749, found: 171.1743.

*Preparation of (2-methoxypent-4-en-1-yl)benzene (**3.79**):*



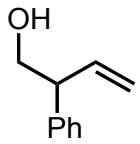


The title compound was prepared as shown above using standard procedure. A flamed dried round bottom flask was charged with 1-phenylpent-4-en-2-ol (200 mg, 1.23 mmol) and tetrahydrofuran (2 mL) and cooled to 0 °C. Sodium hydride (59 mg, 2.5 mmol) was added in one shot and stirred at 0°C for 10

minutes. Iodomethane (0.22 mL, 3.6 mmol) was added dropwise to the flask and the reaction was allowed to warm to room temperature overnight. A saturated aqueous solution of NH_4Cl (2 mL) was added to the flask. The layers were separated and the aqueous layer was washed with ethyl acetate (3 x 10 mL). The organic layers were combined and washed with a brine solution. The organic layer was dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by column chromatography on silica gel (0-5% ethyl acetate in hexanes) to afford a clear, colorless oil (0.18 g, 85%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 2.18 – 2.30 (2H, m), 2.73 (1H, dd, J = 13.8 Hz, 6.2 Hz), 2.82 (1H, dd, J = 13.8 Hz, 6.6 Hz), 3.19 (3H, t, J = 0.8 Hz), 3.44 (1H, pentet, J = 6 Hz), 5.05 – 5.06 (1H, m), 5.08 – 5.09 (1H, m), 5.79 – 5.90 (1H, m), 7.17 – 7.21 (3H, m), 7.24 – 7.29 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 37.5, 39.8, 57.0, 81.7, 117.1, 126.1, 128.2, 129.4, 134.7, 138.9; IR (neat): 3063.8 (w), 3027.7 (w), 2977.6 (w), 2927.9 (m), 2822.6 (w), 1640.2 (w), 1604.3 (w), 1495.0 (m), 1454.0 (m), 1359.0 (m), 1094.2 (s), 911.9 (s), 743.3 (s), 698.0 (s) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{13}$ [M+H-CH_3OH]: calculated: 145.1017, found: 145.1020.

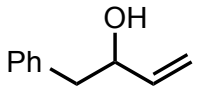
*Preparation of 2-phenylbut-3-en-1-ol (**3.75**):*



The title compound was synthesized by following literature procedure.[40]

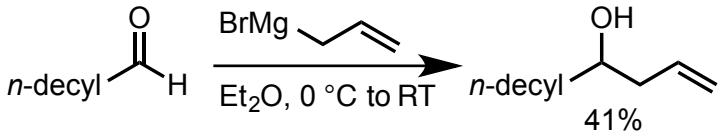
[40] Lightburn, T. E.; Dombrowski, M. T.; Tan, K. L. *J. Am. Chem. Soc.* **2008**, *130*, 9210 – 9211.

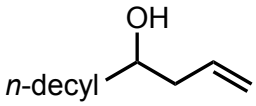
*Preparation of 1-phenylbut-3-en-2-ol (**3.61**):*



The title compound was synthesized by following literature procedure.[41]

*Preparation of tetradec-1-en-4-ol (**3.104**):*



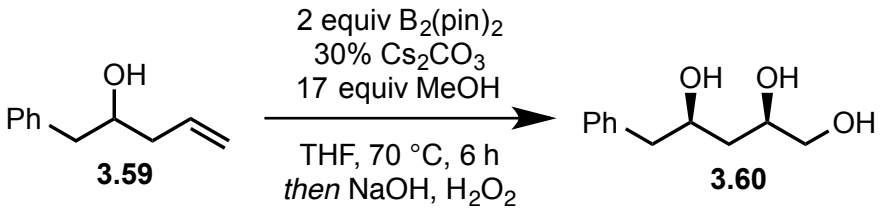


The title compound was prepared as shown above using standard procedure. See the synthesis of **3.59** for an identical procedure. The crude reaction mixture was purified by column chromatography on silica gel (2.5-5% ethyl acetate/hexanes, R_f = 0.60 in 20% ethyl acetate/hexanes, stain in $KMnO_4$) to afford a clear, colorless oil (0.87 g, 41%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 7.1 Hz), 1.22 – 1.34 (14H, m), 1.43 – 1.49 (3H, m), 1.53 – 1.55 (1H, m), 2.14 (1H, dt, J = 14.2 Hz, 7.8 Hz), 2.28 – 2.33 (1H, m), 3.61 – 3.67 (1H, m), 5.12 (1H, s), 5.14 – 5.16 (1H, m), 5.79 – 5.87 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.7, 25.7, 29.3, 29.6, 29.6, 31.9, 36.8, 41.9, 70.7, 118.0, 134.9; IR (neat): 3341.6 (w), 3076.9 (w), 2922.2 (s), 2853.0 (s), 1641.2 (w), 1465.2 (m), 1021.2 (m), 993.7 (m), 911.6 (s), 721.2 (w) cm^{-1}; HRMS- (ESI+) for C14H27 [M+H-H_2O]: calculated: 195.21128, found: 195.21197.

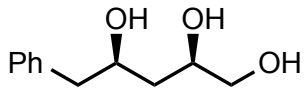
[41] Lin, H.; Liu, Y.; Wu, Z-L. *Chem. Comm.* **2011**, *47*, 2610 – 2612

3.11.3 Diboration of Homoallylic Alcohols, Representative Procedure



In a glovebox under an argon atmosphere, an oven-dried 2 dram vial equipped with a magnetic stirbar was charged with 1-phenylpent-4-en-2-ol (40 mg, 0.50 mmol), bis(pinacolato)diboron (254 mg, 1.00 mmol), THF (1.0 mL, 0.50 M), and cesium carbonate (49 mg, 0.15 mmol). The vial was sealed with a cap with a septum, and removed from the glovebox. Under a line of nitrogen, methanol (0.34 mL, 8.5 mmol) was added to the reaction mixture. The nitrogen line was removed and the septum was covered with electrical tape. The reaction vial was placed in an oil bath at 70 °C for 6 h. After 6 h, the vial was allowed to cool to room temperature and then transferred to a 20 mL vial with about 1 mL of THF. The vial was cooled to 0 °C, followed by the dropwise addition of 3 M sodium hydroxide (1 mL) and 30% aqueous hydrogen peroxide (1 mL). The reaction was allowed to slowly warm to room temperature while stirring for at least 4 h. After the necessary time period, the vial was again cooled to 0 °C and cautiously quenched with saturated aqueous sodium thiosulfate (2 mL), then diluted with water. The aqueous later was extracted with ethyl acetate (5 x 5 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified on silica gel (25-100% ethyl acetate in hexanes) to afford a clear oil (72 mg, 64%).

3.11.4 Full Characterization and Stereochemical Proofs



syn-5-phenylpentane-1,2,4-triol (**3.60**). The diboration was performed according to the representative procedure with 1-phenylpent-4-en-2-ol (40 mg, 0.50 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), methanol (0.34 mL, 8.5 mmol) and tetrahydrofuran (1 mL). The crude reaction mixture was purified on silica gel (50-100% ethyl acetate in hexanes) to afford a clear, colorless oil (73 mg, 74%).

^{1}H NMR (500 MHz, CD_3OD): δ 1.54 (1H, dt, J = 14 Hz, 8.3 Hz), 1.69 (1H, dt, J = 14.0 Hz, 4.5 Hz), 2.72 – 2.80 (2H, m), 3.30 (1H, pentet, J = 1.5 Hz), 3.42 (1H, dd, J = 11.5 Hz, 6.5 Hz), 3.47 (1H, dd, J = 11.5 Hz, 4.8 Hz), 3.79 – 3.83 (1H, m), 3.99 – 4.04 (1H, m), 7.15 – 7.19 (1H, m), 7.21 – 7.27 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 38.4, 44.6, 66.6, 72.3, 73.0, 126.7, 128.7, 129.4 137.7; IR (neat): 3332.4 (m), 3027.5 (w), 2920.1 (m), 1495.3 (m), 1453.4 (m), 1266.1 (m), 1079.7 (m), 1031.1 (m), 734.8 (s), 698.7 (s) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{17}O_3$ [M+H]: calculated: 197.1178, found: 197.1177.

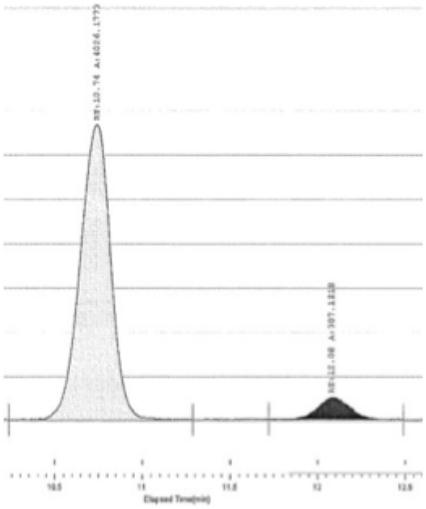
Proof of Stereochemistry:

The diastereoselectivity was determined from SFC analysis, where the products of the reaction were compared to products from an OsO_4/NMO dihydroxylation of the substrate. Diastereomer ratio was determined to be 13:1. To prove relative stereochemistry, the triol was silyl protected and cyclized to form the acetonide. The ^{13}C NMR displayed characteristic carbon signals for a syn-1,3-diol.[42]

[42] Rychnovsky, S. D.; Rodgers, B.; Yang, G. *J. Org. Chem.,* **1993**, *58*, 3511 – 3515.

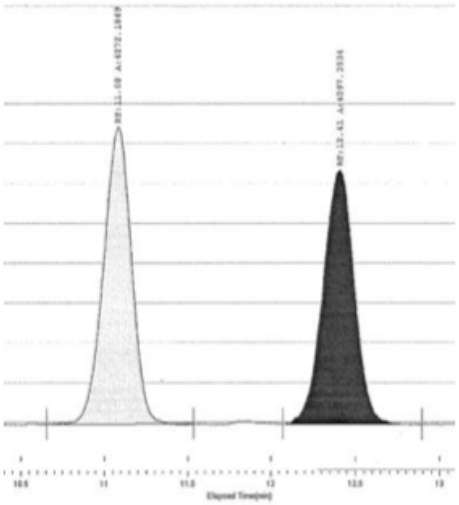
SFC (2EP 4.6x250, 35 °C, 3mL/min, 5% MeOH, 100 bar)

Reaction Products



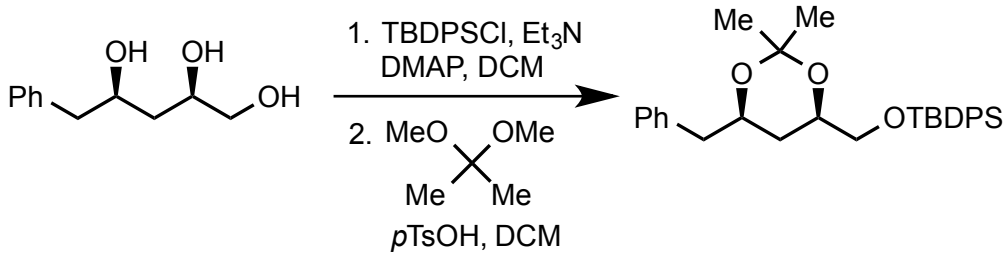
Peak No	% Area	Area	RT (min)
1	92.9125	4026.1773	10.74
2	7.0875	307.1218	12.08
Total:	100	4333.2991	

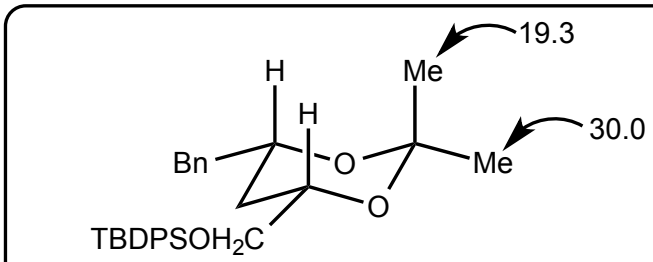
OsO_4/NMO



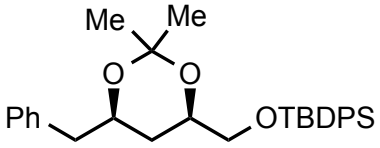
Peak No	% Area	Area	RT (min)
1	51.0445	4272.1869	11.08
2	48.9555	4097.3534	12.41
Total:	100	8369.5403	

Preparation of ((6-benzyl-2,2-dimethyl-1,3-dioxan-4-yl)methoxy)(tert-butyl)diphenyl-silane.





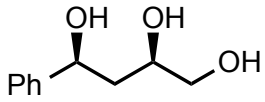
Characteristic ^{13}C Resonances for the Acetonide



((6-benzyl-2,2-dimethyl-1,3-dioxan-4-yl)methoxy)(tert-butyl)diphenylsilane. The title compound was prepared as shown above using standard procedure.

^1H NMR (400 MHz, $CDCl_3$): δ 1.05 (9H, s), 1.20 (1H, q, J = 11.5 Hz), 1.42 (3H, s), 1.43 (3H, s), 1.55 (1H, dt, J = 12.5 Hz, 2.3 Hz), 2.64 (1H, dd, J = 13.5 Hz, 7.0 Hz), 2.95 (1H, dd, J = 13.5 Hz, 5.8 Hz), 3.54 (1H, dd, J = 10.3 Hz, 5.8 Hz), 3.72 (1H, dd, J = 10.3 Hz, 5.3), 3.91 – 3.96 (1H, m), 4.03 – 4.08 (1H, m), 7.22 – 7.25 (3H, m), 7.29 – 7.32 (2H, m), 7.35 – 7.39 (4H, m), 7.41 – 7.45 (2H, m), 7.66 – 7.68 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.3, 19.8, 26.8, 30.0, 33.2, 43.1, 67.5, 69.8, 69.9, 98.5, 126.3, 127.6, 127.6, 128.2, 129.5, 129.6, 129.6, 133.7, 133.8, 135.7, 135.7, 138.0; IR (neat): 2991.3 (m), 2930.2 (m), 3857.6 (m), 1427.4 (m), 1378.3 (m), 1198.7 (m), 1106.5 (s), 937.8 (m), 697.9

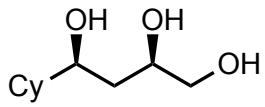
(s), 612.2 (m), 502.1 (s) cm^{-1}; HRMS-(ESI+) for $C_{30}H_{38}O_3SiNa$ [M+Na]: calculated: 497.2491, found: 497.2491.



*4-phenylbutane-1,2,4-triol (**3.68**)*. The diboration was performed according to the representative procedure with 1-phenylbut-3-en-1-ol (74 mg, 0.50 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), methanol (0.34 mL, 8.5 mmol), and tetrahydrofuran (1 mL). The crude material was purified on silica gel (30%-100% EtOAc/Hexane) to afford the title compound was obtained as a white solid (74 mg, 85%). Spectral data is in agreement with the literature.[43]

Analysis/Proof of Stereochemistry:

The relative stereochemistry was determined to be syn by comparison to the ^1H NMR data within the literature. Diastereomer ratio was determined to be 14.3:1.



*4-cyclohexylbutane-1,2,4-triol (**3.70**)*. Prepared according to the general diboration/oxidation procedure using 1-cyclohexylbut-3-en-1-ol (77 mg, 0.50 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), methanol (0.34 mL, 8.5 mmol), and THF (1 mL). The crude product was purified on silica gel (25-100% ethyl acetate in hexanes) to afford the title compound as a clear, colorless oil (48 mg, 51%).

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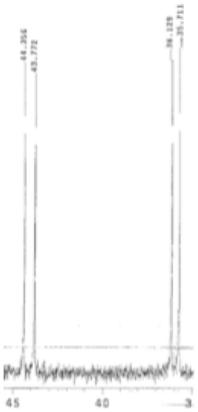
[43] a) Asano, K.; Matsubara, S. *Org. Lett.* **2012**, *14*, 1620 – 1623; (b) Kang, J. Y.; Connell, B. T. *J. Am. Chem. Soc.* **2011**, *132*, 7826 – 7827.

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.05-0.92 (2H, m), 1.25-1.07 (3H, m), 1.35-1.27 (1H, m), 1.59-1.47 (2H, m), 1.68-1.60 (2H, m), 1.80-1.69 (3H, m), 3.50-3.41 (2H, m), 3.64-3.56 (2H, m), 3.86-3.79 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 26.1, 26.2, 27.9, 28.7, 35.7, 44.3, 66.8, 72.9; IR (neat): 3329.9 (br, m), 2921.3 (m), 2850.8 (m), 1448.2 (m), 1318.3 (m), 1042.4 (m), 976.1 (m), 891.5 (m), 845.9 (m), 732.3 (m); HRMS-(ESI+) for $C_{10}H_{20}O_3$ [M+H-H_2O]: calculated: 189.1491, found: 189.1490.

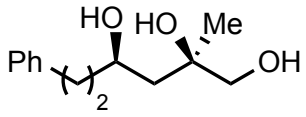
Analysis of Stereochemistry:

The starting material was subjected to dihydroxylation with osmium tetroxide and 4-methylmorpholine N-oxide to give a mixture of diastereomers as determined by ^{13}C NMR. Diastereomer ratio from the diboration/oxidation sequence was then determined by comparison of the ^{13}C NMR and was found to be 5.3:1. Relative stereochemistry was assigned by analogy.

OsO_4/NMO



Diboration/Oxidation

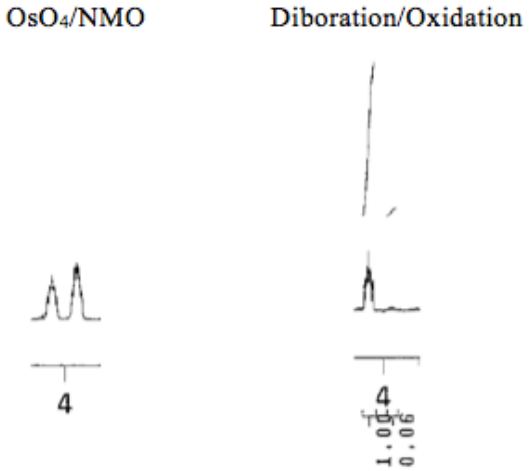


2-methyl-6-phenylhexane-1,2,4-triol ***(3.88)***. The title compound was prepared according to the general diboration procedure using 5-methyl-1-phenylhex-5-en-1-ol (95 mg, 0.50 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), MeOH (0.34 mL, 8.5 mmol), and THF (1 mL).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.21 (3H, s), 1.49-1.46 (1H, d, J = 15.0 Hz), 1.86-1.70 (3H, m), 2.79-2.64 (2H, m), 3.41 (2H, s), 4.11-4.04 (1H, m), 7.20-7.15 (3H, m), 7.30-7.25 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.8, 31.8, 40.0, 40.7, 68.3, 70.8, 73.1, 125.9, 128.4, 128.5, 141.7; IR (neat): 3331.2 (br, m), 2925.9 (m), 2862.4 (w), 1453.5 (m), 1046.4 (s), 897.2 (m), 849.2 (m), 746.2 (s), 697.8 (s); HRMS-(ESI+) for $C_{13}H_{20}O_3$ [M+H]: calculated: 225.1491, found: 225.1485.

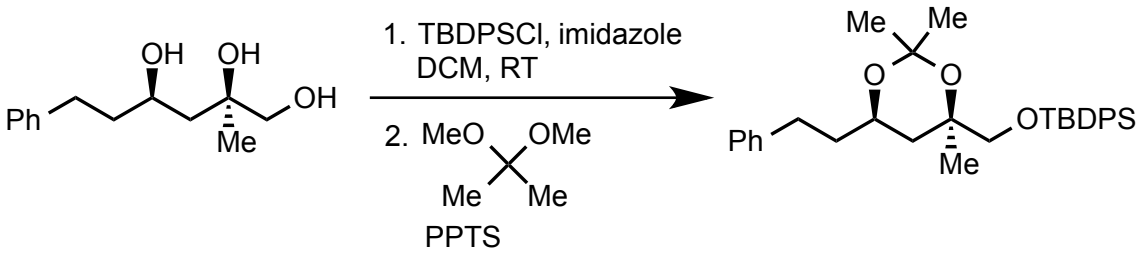
Analysis of Diastereoselectivity:

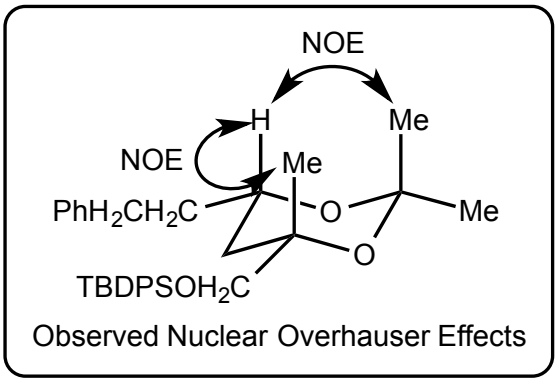
The starting material was subjected to dihydroxylation with osmium tetroxide and 4-methylmorpholine N-oxide to give a mixture of diastereomers as determined by ^{1}H NMR. Diastereomer ratio from the diboration/oxidation sequence was then determined by comparison of the ^{1}H NMR spectra and was found to be 17:1.

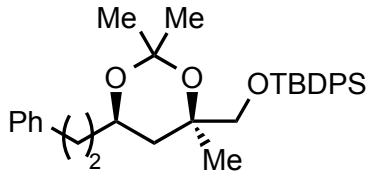


Proof of Stereochemistry:

The purified triol was protected as an acetonide by the sequence shown below, and stereochemistry was proven using 2D NMR (NOE).





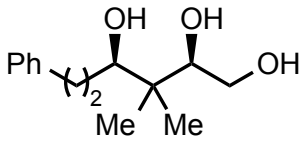


tert-butyldiphenyl(((4R,6R)-2,2,4-trimethyl-6-phenethyl-1,3- dioxan-4-yl)methoxy)silane. An oven-dried 20 mL vial equipped with a magnetic stirbar was charged with 2-methyl-6-phenylhexane-1,2,4-triol (85 mg, 0.38 mmol) and dichloromethane (3.8 mL). The vial was cooled to 0 °C, and imidazole (31 mg, 0.46 mmol) was quickly added. The vial was then charged with *tert*-butyldiphenylsilyl chloride (0.11 mL, 0.42 mmol) and allowed to stir to room temperature. The reaction was quenched with saturated aqueous sodium bicarbonate. The layers were separated and the organic layer was sequentially washed with water and then brine. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude product was purified on silica gel (5-10% ethyl acetate in hexanes) to afford a white solid (0.11 g, 63%).

To an oven-dried 20 mL vial equipped with a magnetic stirbar, added the silyl-protected triol (0.11 g, 0.24 mmol), dichloromethane (3 mL), and 2,2-dimethoxypropane (0.44 mL, 3.60 mmol). The vial was cooled to 0 °C, then pyridinium *p*-toluenesulfonate (5 mg, 0.02 mmol) was quickly added. The reaction was stirred while warming to room temperature, then quenched with triethylamine and concentrated by rotary evaporation. The crude material was purified on silica gel (10% ethyl acetate in hexanes) to afford a clear, colorless film (0.10 mg, 84%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (9H, s), 1.36-1.34 (6H, d, J = 10.5 Hz), 1.45 (3H, s), 1.48-1.47 (2H, d, J = 5.0 Hz), 1.88-1.71 (2H, m), 2.82-2.65 (2H, m), 3.45-3.41 (2H, m), 3.92-3.90 (1H, m), 7.21-7.17 (3H, m), 7.30-7.27 (2H, m), 7.43-7.35 (6H, m), 7.68-7.67 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.4, 23.8, 25.1, 26.9, 31.3, 31.7, 37.3, 38.1,

64.4, 73.1, 73.5, 98.4, 125.7, 127.6, 127.6, 128.3, 128.5, 129.5, 129.6, 133.7, 133.7, 135.7, 135.7, 142.1; IR (neat): 2929.8 (w), 2857.2 (w), 1427.5 (w), 1376.4 (w), 1157.4 (m), 821.4 (m), 739.4 (m), 698.2 (m), 503.2 (m), 488.1 (m) cm^{-1}; HRMS-(ESI+) for $C_{33}H_{44}O_3Si$ [M+Na]: calculated: 525.7598, found: 525.2794.



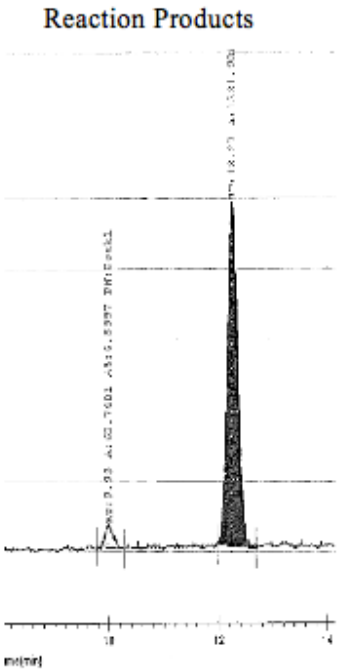
3,3-dimethyl-6-phenylhexane-1,2,4-triol ***(3.78)***. Prepared according the general diboration/oxidation procedure using 4,4-dimethyl-1-phenylhex-5-en-3-ol (102 mg, 0.500 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), methanol (0.34 mL, 8.5 mmol), and tetrahydrofuran (1 mL). The crude product was purified on silica gel (25-100% ethyl acetate in hexanes) to afford the title compound as a white solid (83 mg, 69%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.80 (3H, s), 0.90 (3H, s), 1.89-1.61 (2H, m), 2.33-2.17 (1H, s), 2.82-2.71 (1H, s), 2.92-2.58 (2H, m), 3.25-3.11 (1H, s), 3.64-3.55 (3H, m), 3.74-3.67 (1H, m), 7.31-7.26 (2H, m), 7.22-7.16 (3H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.7, 21.8, 33.0, 33.3, 40.3, 62.6, 78.2, 79.3, 126.0, 128.5, 128.5, 142.1; IR (neat): 3315.5 (br, w), 2969.7 (w), 2928.5 (w), 2878.7 (w), 1071.2 (w), 1054.2 (w), 926.7 (w), 893.8 (w), 745.7 (w), 701.8 (w); HRMS-(ESI+) for $C_{14}H_{22}O_3$ [M+H]: calculated: 239.1647, found: 239.1652; Melting point: 90-95 °C.

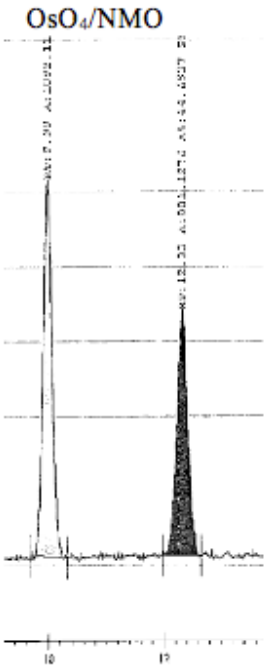
Analysis of Stereochemistry:

The starting material was subjected to dihydroxylation with OsO_4/NMO to give a mixture of diastereomers as determined by SFC analysis. Diastereomer ratio from the diboration/oxidation sequence was then determined by comparison of the SFC data and was found to be >20:1.

SFC (2EP 4.6x250, 35 °C, 3mL/min, 3% MeOH, 100 bar)



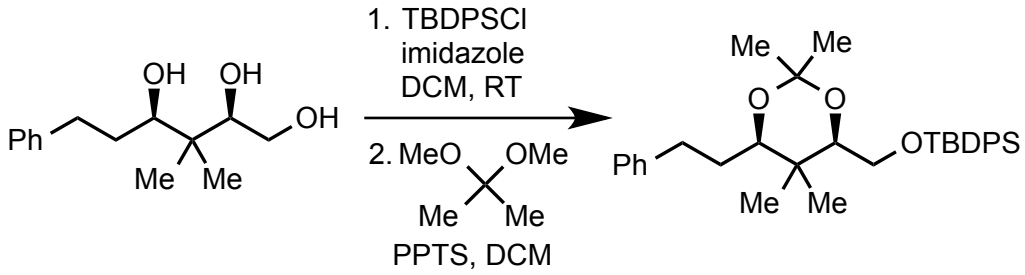
Peak No	% Area	Area	RT (min)
1	4.5397	63.7401	9.99
2	95.4603	1321.9886	12.27
Total:	100	1385.7287	

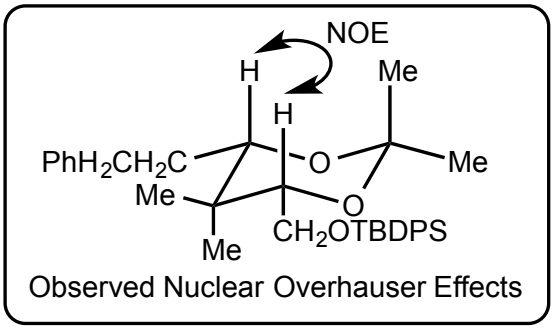


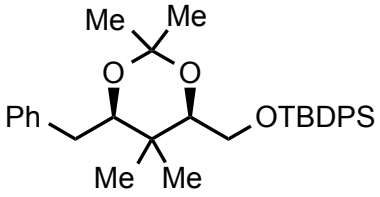
Peak No	% Area	Area	RT (min)
1	55.3383	1092.1198	9.98
2	44.6537	881.1276	12.33
Total:	100	1973.2474	

Proof of Stereochemistry:

The purified triol was silyl protected and cyclized as an acetonide by the sequence shown below. Absolute stereochemistry was proven using 2D NMR (NOE)



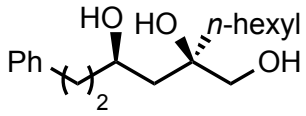




tert-butyldiphenyl(((4R,6R)-2,2,5,5-tetramethyl-6-phenethyl-1,3-dioxan-4-yl)methoxy)silane. An oven-dried 20 mL vial equipped with a magnetic stirbar was charged with 3,3-dimethyl-6-phenylhexane-1,2,4-triol (35 mg, 0.15 mmol) and dichloromethane (1.5 mL). The vial was cooled to 0 °C, and imidazole (12 mg, 0.18 mmol) was quickly added. The vial was then charged with *tert*-butyldiphenylsilyl chloride (40 μL, 0.16 mmol) and allowed to stir to room temperature. The reaction was quenched with saturated aqueous sodium bicarbonate. The layers were separated and the organic layer was sequentially washed with water and then brine. The organic layer was separated, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude product was purified on silica gel (5-10% ethyl acetate in hexanes) to afford a white solid (50 mg, 69%).

To an oven-dried 20 mL vial equipped with a magnetic stirbar, added the silyl-protected triol (50 mg, 0.10 mmol), dichloromethane (0.6 mL), and 2,2-dimethoxypropane (0.18 mL, 1.5 mmol). The vial was cooled to 0 °C, then pyridinium *p*-toluenesulfonate (3 mg, 0.01 mmol) was quickly added. The reaction was stirred while warming to room temperature, then quenched with triethylamine and concentrated by rotary evaporation. The crude material was purified on silica gel (2.5-10% ethyl acetate in hexanes) to afford a clear, colorless film (16 mg, 30%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.58 (3H, s), 0.72 (3H, s), 1.03 (9H, s), 1.38 (3H, s), 1.43 (3H, s), 1.70-1.56 (2H, m), 2.51-2.44 (1H, m), 2.85-2.78 (1H, m), 3.34-3.31 (1H, m), 3.56-3.53 (1H, m), 3.62-3.58 (1H, m), 3.79-3.76 (1H, dd, J = 11.0 Hz, 3.0 Hz), 7.19-7.15 (3H, m), 7.28-7.24 (2H, m), 7.42-7.32 (6H, m), 7.70-7.65 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.2, 19.2, 19.4, 20.5, 26.8, 29.7, 30.1, 30.2, 32.4, 34.6, 63.9, 76.7, 79.2, 98.5, 125.7, 127.5, 127.6, 128.2, 128.6, 129.5, 129.6, 133.7, 134.1, 135.7, 135.8, 142.4; IR (neat): 2930.7 (w), 2856.3 (w), 1463.3 (w), 1427.6 (w), 1377.8 (w), 1105.5 (m), 1043.4 (m), 737.7 (m), 698.3 (s), 608.7 (m), 503.4 (s); HRMS-(ESI+) for $C_{33}H_{44}O_3Si$ [M+Na]: calculated: 539.2957, found: 539.2941.

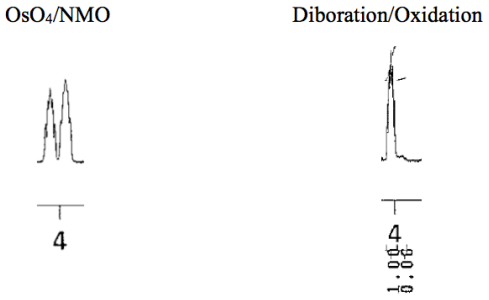


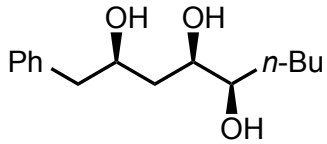
*2-hexyl-6-phenylhexane-1,2,4-triol (**3.90**)*. Prepared according to the general diboration procedure using 5-methylene-1-phenylundecan-3-ol (0.13 g, 0.50 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), methanol, (0.34 mL, 8.5 mmol) and tetrahydrofuran (1 mL) (50 mg, 64%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (3H, t, J = 7.0 Hz), 1.31-1.10 (10H, m), 1.59-1.50 (2H, m), 1.88-1.67 (2H, m), 2.51 (1H, s), 2.78-2.64 (2H, m), 2.86 (1H, s), 3.13 (1H, s), 3.48-3.41 (2H, q, J = 10.0 Hz), 4.06-3.99 (1H, m), 7.20-7.15 (3H, m), 7.29-7.25 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 23.9, 29.9, 31.7, 31.9, 37.5, 40.1, 42.0, 68.2, 68.7, 74.6, 126.0, 128.4, 128.5, 141.7; IR (neat): 3355.6 (br, m), 2927.7 (m), 2856.8 (m), 1495.5 (w), 1454.4 (w), 1313.5 (w), 1057.0 (w), 1031.2 (m), 746.5 (w), 698.5 (m); HRMS-(ESI+) for $C_{18}H_{30}O_3$ [M+H]: calculated: 295.2273, found: 295.2287.

Analysis of Stereochemistry:

The starting material was subjected to dihydroxylation with OsO_4/NMO to give a mixture of diastereomers as determined by ^{1}H NMR. Diastereomer ratio from the diboration/oxidation sequence was then determined by comparison of the ^{1}H NMR and was found to be 16.7:1. Absolute stereochemistry was assigned by analogy.





1-phenylnonane-2,4,5-triol ***(3.82)***. The diboration was performed according to the representative procedure with (E)-1-phenylnon-4-en-2-ol (109 mg, 0.5 mmol), $B_2(pin)_2$ (254

mg, 1.0 mmol), Cs_2CO_3 (53 mg, 0.15 mmol), methanol, (.34 mL, 8.5 mmol) and tetrahydrofuran (1 mL). The crude reaction mixture was purified by column chromatography on silica gel (25-100% ethyl acetate in hexanes) to afford a white solid (82 mg, 65%).

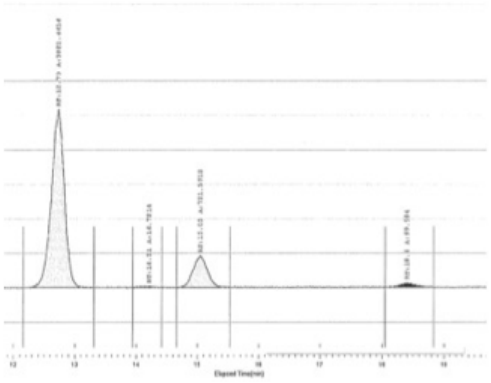
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (3H, t, J = 7.3 Hz), 1.24 – 1.52 (6H, m), 1.64 – 1.74 (2H, m), 2.39 (1H, d, J = 6.0 Hz), 2.76 (1H, dd, J = 13.8 Hz, 7.8 Hz), 2.81 (1H, dd, J = 13.5 Hz, 5.5 Hz), 2.85 (1H, br s), 3.37 – 3.41 (1H, m), 3.60 (1H, d, J = 3.0 Hz), 3.67 – 3.71 (1H, m), 4.09 – 4.14 (1H, m), 7.21 – 7.26 (3H, m), 7.30 – 7.34 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.7, 27.9, 33.3, 39.2, 44.7, 73.1, 74.5, 74.6, 126.7, 128.7, 129.4, 137.7; IR (neat): 3315.3 (s), 3232.1 (s), 3077.4 (w), 3061.3 (w), 3036.1 (s), 2955.2 (m), 2914.0 (m), 2871.3 (m), 1497.3 (m), 1449.8 (m), 1093.9 (s), 1041.4 (s), 861.7 (m), 780.2 (m), 700.2 (s) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{25}O_3$ [M+H]: calculated: 253.1804, found: 253.1801.

Analysis of Stereochemistry:

The diastereoselectivity was attained from SFC analysis, where the products of the reaction were compared to those products from an OsO_4/NMO dihydroxylation of the substrate.

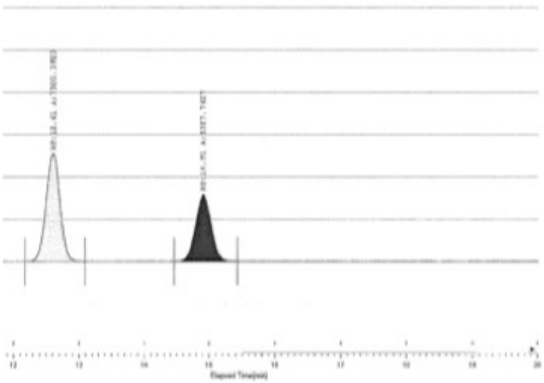
SFC (2EP 4.6x250, 35 °C, 3mL/min, 3% MeOH, 100 bar)

Reaction Products



Peak No	% Area	Area	RT (min)
1	82.0215	3822.6616	12.73
2	0.3588	16.7214	14.21
3	15.4829	721.5918	15.05
4	2.1367	99.584	18.4
Total:	99.9999	4660.5588	

OsO_4/NMO

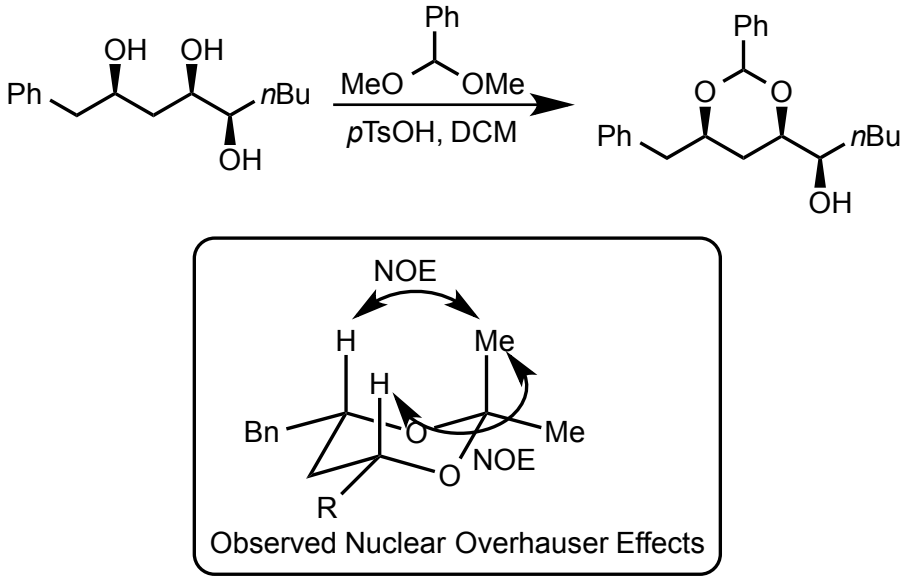


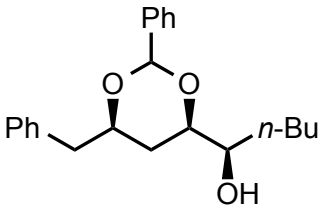
Peak No	% Area	Area	RT (min)
1	57.8104	7300.3923	12.61
2	42.1896	5327.7627	14.91
Total:	100	12628.155	

Proof of Stereochemistry:

The relative stereochemistry was determined as syn by NOESY NMR of the 1-(6-benzyl-2- phenyl-1,3-dioxan-4-yl)pentan-1-ol synthesized from the resulting triol in the sequence shown below. Similar triols have been cyclized using a similar approach.[44]

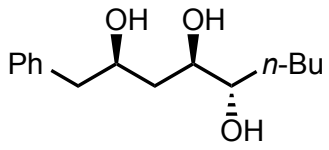
[44] Esteve, J.; Matas, S.; Pellicena, M.; Romea, P.; Urpi, F.; Velasco, J.; Font-Bardia, M. *Eur. J. Org. Chem*. **2010**, *16*, 3146 – 3151.





1-(6-benzyl-2-phenyl-1,3-dioxan-4-yl)pentan-1-ol. The title compound was prepared as shown above using standard procedure.

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (3H, t, J = 7.0 Hz), 1.26 – 1.42 (3H, m), 1.44 – 1.63 (5H, m), 2.36 (1H, d, J = 5.0 Hz), 2.80 (1H, dd, J = 13.5 Hz, 6.5 Hz), 3.10 (1H, dd, J = 14 Hz, 7 Hz), 3.50 – 3.54 (1H, m), 3.66 – 3.70 (1H, m), 4.01 – 4.06 (1H, m), 5.54 (1H, s), 7.23 – 7.28 (3H, m), 7.30 – 7.40 (5H, m), 7.48 – 7.51 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.0, 22.7, 27.6, 32.0, 32.3, 42.5, 73.8, 77.4, 79.7, 100.5, 126.1, 126.5, 128.2, 128.4, 128.8, 129.5, 137.6, 138.4; IR (neat): 3576.7 (w), 3461.4 (w), 2953.7 (m), 2928.6 (m), 2858.6 (m), 1602.3 (w), 1495.0 (m), 1453.7 (m), 1400.0 (m), 1376.4 (m), 1106.2 (s), 1011.7 (s), 750.7 (s), 698.2 (s) cm^{-1}; HRMS-(ESI+) for $C_{22}H_{29}O_3$ [M+H]: calculated: 341.2117, found: 341.2119.



1-phenylnonane-2,4,5-triol ***(3.84)***. The diboration was performed according to the representative procedure with (Z)-1-phenylnon-4-en-2-ol (109 mg, 0.500 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), methanol (0.34 mL, 8.5 mmol) in tetrahydrofuran (1 mL). The crude reaction mixture was purified by column chromatography on silica gel (25-100% ethyl acetate in hexanes) to afford a white solid (0.10 g, 79%).

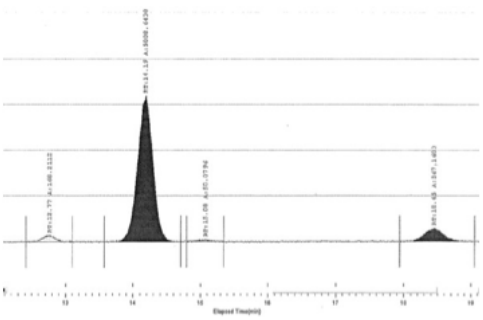
^{1}H NMR (500 MHz, $CDCl_3$ with one drop of D_2O): δ 0.90 (3H, t, J = 7.0 Hz), 1.26 – 1.52 (6H, m), 1.62 – 1.74 (2H, m), 2.74 (1H, dd, J = 13.3 Hz, 8.3 Hz), 2.84 (1H, dd, J = 13.8 Hz, 4.3 Hz), 3.59 (1H, pentet, J = 4.3 Hz), 3.78 (1H, dt, J = 9.0 Hz, 3.3 Hz), 4.06 – 4.11 (1H, m), 4.71 (1H, br s), 7.20 – 7.24 (3H, m), 7.31 – 7.34 (2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.7, 28.2, 31.6, 36.1, 44.8, 73.3, 74.2, 75.0, 126.8, 128.7, 129.4, 137.6; IR (neat): 3319.1 (s), 3246.4 (s), 3088.1 (w), 3060.9 (w), 3031.6 (s), 2950.0 (m), 2913.4 (m), 2870.8 (m), 1495.9 (m), 1451.8 (m), 1091.1 (s), 1046.9 (s), 853.7 (m), 748.4 (m), 695.6 (s) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{25}O_3$ [M+H]: calculated: 253.1804, found: 253.1794.

Analysis/Proof of Stereochemistry:

The diastereoselectivity was attained from SFC analysis, where the products of the reaction were compared to those products from an OsO_4/NMO dihydroxylation of the substrate. To prove relative stereochemistry, the triol was crystallized out of hexanes and methanol (long needle-like crystal).

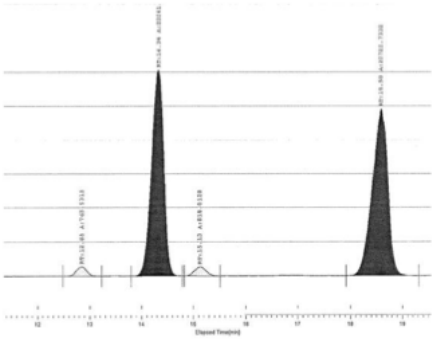
SFC (2EP 4.6x250, 35 °C, 3mL/min, 3% MeOH, 100 bar)

Reaction Products

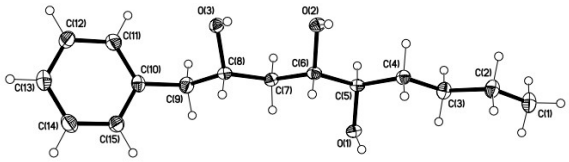


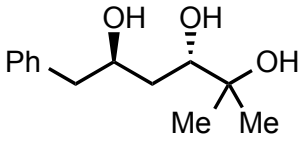
Peak No	% Area	Area	RT (min)
1	2.9031	168.2112	12.77
2	86.4439	5008.6438	14.19
3	0.8643	50.0796	15.08
4	9.7886	567.1603	18.45
Total:	99.9999	5794.0949	

OsO_4/NMO



Peak No	% Area	Area	RT (min)
1	1.7992	765.5315	12.85
2	47.5741	20241.9485	14.34
3	1.9226	818.0128	15.13
4	48.7041	20722.7332	18.58
Total:	100	42548.226	





anti-2-methyl-6-phenylhexane-2,3,5-triol ***(3.92)***. The diboration was performed according to the representative procedure with 5-methyl-1-phenylhex-4-en-2-ol (95 mg, 0.50 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), methanol (0.34 mL, 8.5 mmol) in tetrahydrofuran (1 mL). The crude reaction mixture was purified by column chromatography on silica gel (50-100% ethyl acetate in hexanes) to afford a white solid (62 mg, 55%).

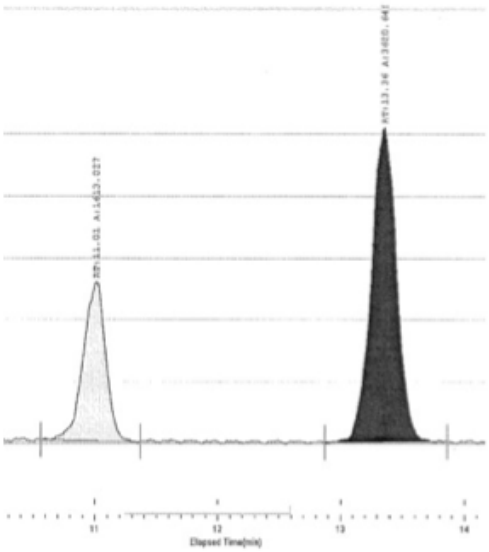
^{1}H NMR (400 MHz, $CDCl_3$): δ 1.11 (3H, s), 1.16 (3H, s), 1.51 - 1.65 (2H, m), 2.70 – 2.82 (2H, m), 3.73 (1H, dd, J = 10.0 Hz, 2.8 Hz), 4.09 – 4.15 (1H, m), 7.18 – 7.30 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 23.4, 26.4, 37.1, 43.9, 70.1, 72.9, 74.6, 76.7, 126.5, 128.6, 129.4, 138.4; IR (neat): 3385.0 (m), 2971.4 (m), 2921.5 (m), 1496.0 (m), 1377.6 (m), 1225.4 (m), 1056.9 (s), 743.9 (m), 699.2 (s) cm^{-1}; HRMS-(ESI+) for $C_{13}H_{21}O_3$ [M+H]: calculated: 225.1491, found: 225.1490.

Analysis/Proof of Stereochemistry:

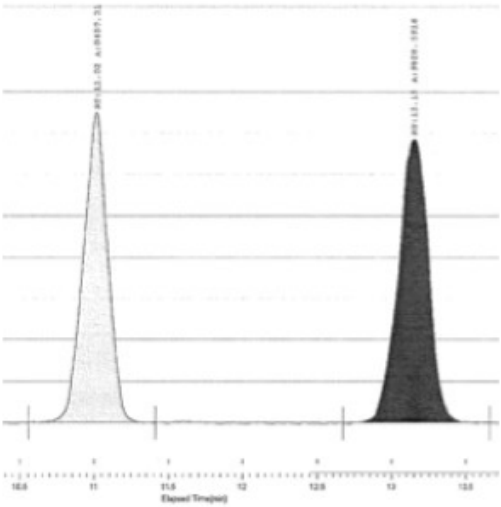
The diastereoselectivity was determined from SFC analysis, where the products of the reaction were compared to those products from an OsO_4/NMO dihydroxylation of the substrate. To prove relative stereochemistry, the triol was crystallized out of hexanes/ethyl acetate.

SFC (2EP 4.6x250, 35 °C, 3mL/min, 3% MeOH, 100 bar)

Reaction Products

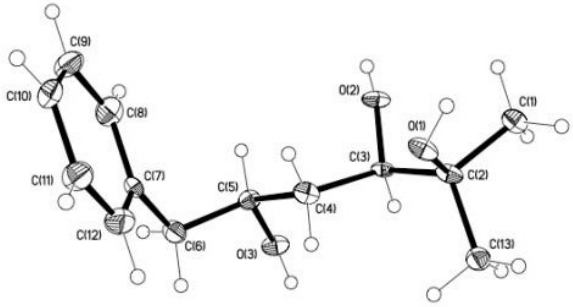


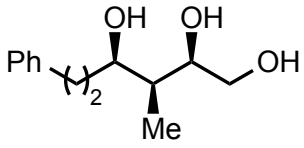
OsO_4/NMO



Peak No	% Area	Area	RT (min)
1	30.8202	1613.027	11.01
2	69.1798	3620.6493	13.36
Total:	100	5233.6763	

Peak No	% Area	Area	RT (min)
1	46.3444	8489.3146	11.02
2	53.6556	9828.5916	13.15
Total:	100	18317.9062	





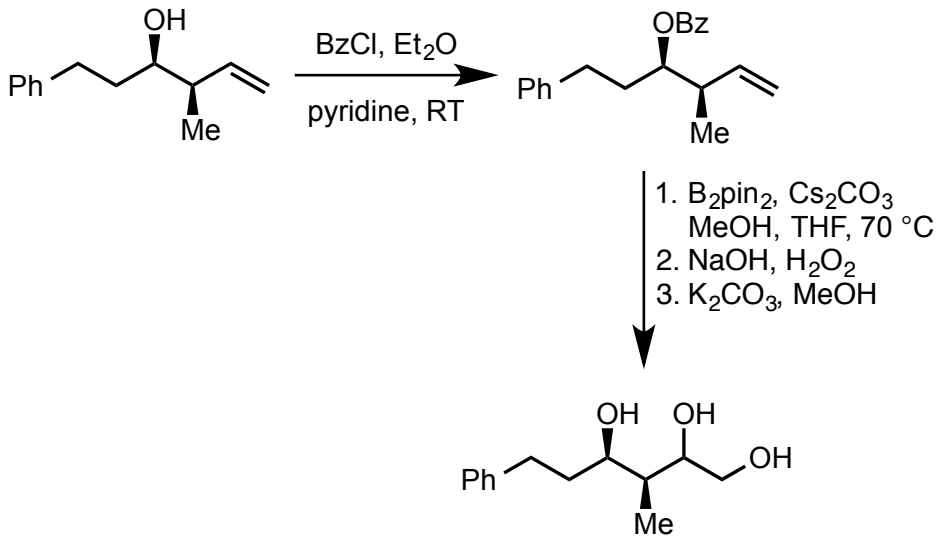
(2R,3S,4R)-3-methyl-6-phenylhexane-1,2,4-triol ***(3.72)***. The diboration was performed according to the representative procedure with (3R,4R)-4-methyl-1-phenylhex-5-en-3-ol (95 mg, 0.50 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), methanol (0.34 mL, 8.5 mmol), and tetrahydrofuran (1 mL). The crude material was

purified on silica gel (30-100% ethyl acetate in hexanes) to afford the title compound as a clear, colorless oil (89 mg, 79%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (3H, d, J = 12.5 Hz), 1.65 (1H, m), 1.72 (1H, m), 1.86 (1H, m), 2.64 (1H, m), 2.75 (1H, m), 3.57 (1H, dd, J = 3.5 Hz, 10.5 Hz), 3.65 (1H, dd, J = 7.0 Hz, 11.0 Hz), 3.85 (1H, p, J = 3.5 Hz), 3.90 (1H, m), 7.18 (3H, m), 7.26 (2H, m); ^{13}C NMR: δ 6.6, 32.7, 37.1, 39.6, 64.7, 74.6, 76.3, 126.2, 1286, 128.7, 141.9; IR (neat): 3346.3 (s), 2940.3 (s), 2886.1 (m), 1495.7 (w), 1454.4 (m), 1099.3 (m), 1062.6 (m), 1028.6 (m), 748.3 (m), 699.3 (s); HRMS-(ESI+) for $C_{13}H_{21}O_3$ [M+H]: calculated: 225.1491, found: 225.1489.

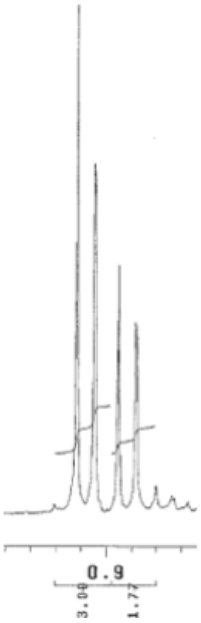
Analysis of Stereochemistry:

Diastereomer ratio was determined to be 6.8:1 based on comparison of the ^{1}H NMR of the product with triol that was obtained from a non-selective diboration shown in the sequence below:



To an oven-dried 6-dram vial equipped with a magnetic stirbar, added (*3R,4R*)-4-methyl-1-phenylhex-5-en-3-ol (190 mg, 1.00 mmol) and Et_2O (2 mL), and the reaction mixture was cooled to 0°C. Pyridine (0.12 mL, 1.5 mmol) and benzoyl chloride (0.17 mL, 1.5 mmol) were added. The reaction mixture was allowed to warm to room temperature and stir overnight. Then the reaction was quenched with *N,N'*-dimethylethylenediamine at 0 °C and extracted with Et_2O. The organic layer was washed with brine, dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The crude material was purified on silica gel (3% ethyl acetate in hexanes) to afford the Bz-protected alkene as a colorless oil (0.19 g, 64%). Then the diboration was performed according to the representative procedure with Bz-protected alkene (0.19 g, 0.64 mmol) followed by treatment of the crude material with K_2CO_3 (0.88 g, 6.4 mmol) in MeOH (6.4 mL) and stirring for 12h. Then the reaction mixture was diluted with water, the organic layer was separated, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was purified on silica gel (3% ethyl acetate in hexanes) to give the title compound as a clear, colorless oil (80 mg, 56%) and a mixture of diastereomers as determined by ^1H NMR.

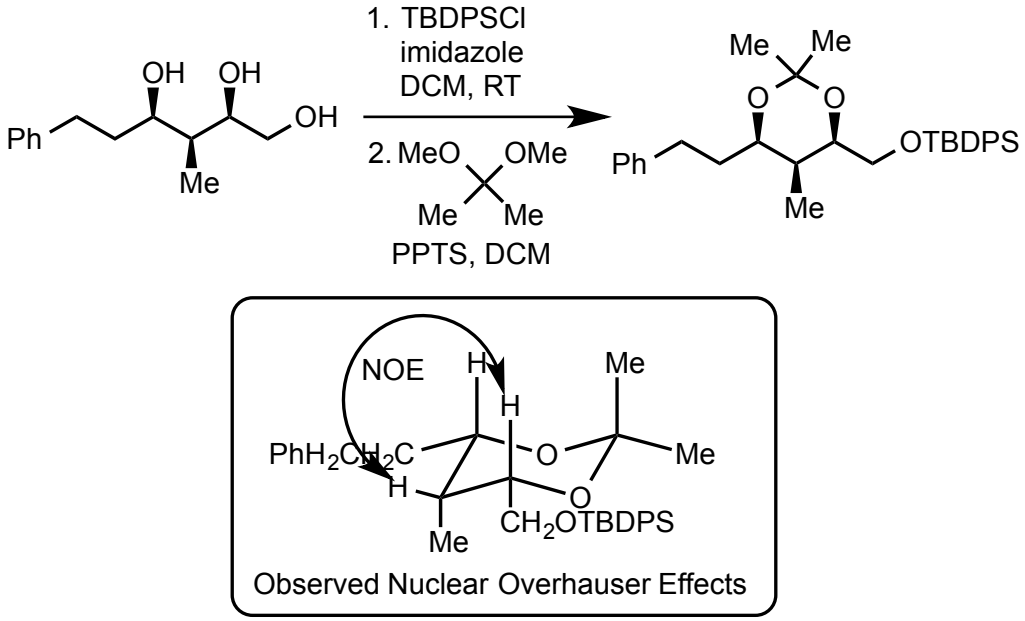
Non-directed Diboration/Oxidation/Deprotection

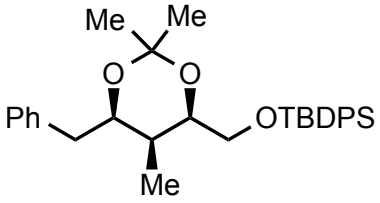


Directed Diboration/Protection

Proof of Stereochemistry:

The relative stereochemistry was determined to be *syn* by measuring the coupling constants of the carbonyl hydrogen atoms from the ^{1}H NMR of the tert-butyldiphenyl(((*4R,5S,6R*)-2,2,5-trimethyl-6-phenethyl-1,3-dioxan-4-yl)methoxy)silane synthesized from the sequence shown below.

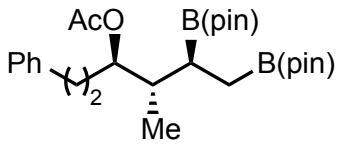




tert-butyldiphenyl(((4R,5S,6R)-2,2,5-trimethyl-6-phenethyl-1,3-dioxan-4-yl)methoxy)silane. To an oven-dried 6-dram vial equipped with a magnetic stirbar, added (*2R,3S,4R*)-3-methyl-6-phenylhexane-1,2,4-triol (111 mg, 0.500 mmol), imidazole (41 mg, 0.6 mmol), and dichloromethane (5ml) under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C, and *tert*-butyldiphenylsilyl chloride (0.14 ml, 0.55 mmol) was added. Then the reaction mixture was allowed to warm to room temperature and stir for 2 h, at which time the reaction was quenched with saturated aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was purified on silica gel (10% ethyl acetate in hexanes) to afford the TBDPS-protected triol (0.17 g, 72%). To a mixture of TBDPS-protected triol (0.17 g, 0.36 mmol) and 2,2-dimethoxypropane (0.67 mL, 5.4 mmol) in dichloromethane (3.6 mL) at 0 °C, added

pyridinium *p*-toluenesulfonate (9.0 mg, 0.036 mmol). The reaction mixture was allowed to warm to room temperature and stir overnight under a nitrogen atmosphere. Then triethylamine was added and the reaction mixture was concentrated by rotary evaporation. The crude material was purified on silica gel (3% ethyl acetate in hexanes) to afford the title compound as a white solid (0.16 g, 89%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.79 (3H, d, J = 6.5 Hz), 1.04 (9H, s), 1.36 (6H, s), 1.54 (1H, m), 1.61 (1H, m), 1.88 (1H, m), 2.59 (1H, m), 2.73 (1H, m), 3.57 (1H, dd, J = 10.5 Hz, 7.5 Hz), 3.66 (1H, dd, J = 10.5 Hz, 6.5 Hz), 3.82 (1H, m), 3.96 (1H, ddd, J = 1.0 Hz, 6.5 Hz, 7.5 Hz), 7.17-7.20 (3H, m), 7.26-7.29 (2H, m), 7.33-7.42 (6H, m), 7.64-7.66 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 5.0, 19.6, 20.0, 27.2, 30.2, 32.0, 32.8, 34.8, 64.6, 72.6, 74.1, 99.6, 126.6, 128.4, 128.5, 129.2, 129.4, 130.4, 130.5, 134.6, 134.6, 136.5, 136.5, 143.0; IR(neat): 2932.2 (m), 2857.1 (m), 1427.5 (m), 1378.6 (m), 1197.5 (m), 1135.6 (m), 1109.7 (s), 938.1 (m), 833.4 (m), 777.7 (m), 739.0 (m), 698.1(s); HRMS-(ESI+) for $C_{32}H_{42}O_3SiNa$ [M+Na]: calculated: 525.7523, found: 525.2803.



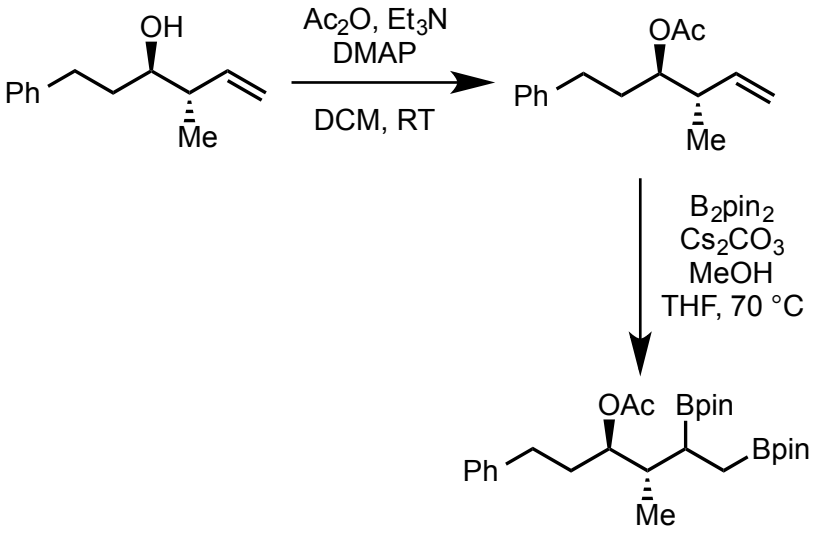
*(3R,4S,5S)-4-methyl-1-phenyl-5,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl acetate (**3.74**).* The diboration was performed according to the representative procedure using (*3R,4S*)-4-methyl-1-phenylhex-5-en-3-ol (95 mg, 0.50 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), methanol (0.34 mL, 8.5 mmol), and tetrahydrofuran (1 mL) . After the diboration was complete, the reaction mixture was concentrated, and dichloromethane (2.5 mL), triethylamine (2.5 mL), and a single crystal

of 4-(dimethylamino)pyridine were added under a nitrogen atmosphere. Then the reaction mixture was cooled to 0 °C, and acetic anhydride (0.1 mL, 1.1 mmol) was added. The reaction mixture was allowed to warm to room temperature and stir for 12 h. Then the reaction mixture was diluted with 1 M HCl. The organic layer was separated and washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was purified on silica gel (3% ethyl acetate in hexanes) to isolate the title compound as a clear, colorless oil (0.17 g, 68%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.74 (1H, s), 0.75 (2H, d, J = 3 Hz), 0.84 (3H, d, J = 6.5 Hz), 1.19 (12H, s), 1.22 (12H, d, J = 4.5 Hz), 1.79 (1H, m), 1.91 (2H, m), 2.00 (3H, s), 2.59 (2H, m), 4.94 (1H, m), 7.14 (3H, m), 7.25 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.9, 21.4, 24.8, 25.1, 25.2, 32.3, 33.0, 38.6, 76.3, 83.0, 83.3, 125.9, 128.5, 128.6, 142.4, 171.0; 11B NMR ($CDCl_3$, 160 MHz): 34.3 (2B); IR(neat): 2977.0 (m), 2931.9 (m), 1733.0 (m), 1403.3 (s), 1371.0 (s), 1311.9 (s), 1238.5 (s), 1142.7 (s) cm^{-1}; HRMS-(ESI+) for $C_{27}H_{48}B_2NO_6$ [M+NH_4]: calculated: 504.3668, found: 504.3690.

Analysis of Stereochemistry:

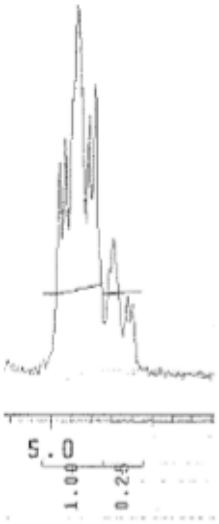
Diastereomer ratio was determined to be >20:1 based on comparison of the ^{1}H NMR of the product with bis(boronate) that was obtained from a non-selective diboration shown in the sequence below:



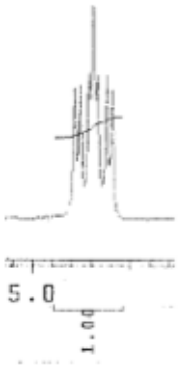
To an oven-dried 6-dram vial equipped with a magnetic stirbar was added (*3R,4S*)-4-methyl-1-phenylhex-5-en-3-ol (0.10 g, 0.53 mmol), dichloromethane (2.5 mL), triethylamine (2.5 mL), and a single crystal of 4-(dimethylamino)pyridine under a nitrogen atmosphere. Then the reaction mixture was cooled to 0 °C, and acetic anhydride (0.10 mL, 1.1 mmol) was added. The reaction mixture was allowed to warm to room temperature and stir for 12 h. Then the reaction mixture was diluted with 1 M HCl. The organic layer was separated and washed with saturated aqueous sodium bicarbonate, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was purified on silica gel (3% ethyl acetate in hexanes) to afford the (*3R,4S*)-4-methyl-1-phenylhex-5-en-3-yl acetate as colorless oil (80 mg, 65% yield). The diboration was performed according to the representative procedure using (*3R,4S*)-4-methyl-1-phenylhex-5-en-3-yl acetate (80 mg, 0.35 mmol), Cs_2CO_3 (36 mg, 0.11 mmol), $B_2(pin)_2$ (0.18 g, 0.70 mmol), methanol (0.24 mL, 6.0 mmol), and tetrahydrofuran (1.4 mL). The crude material was purified on silica gel (3% ethyl acetate in hexanes) to give a mixture of diastereomers as a clear, colorless oil (0.12 g, 68%) determined by ^{1}H NMR..

Diastereomer ratio from the diboration/oxidation sequence was then determined by comparison of the ^{1}H NMR spectra and was found to be greater than 20:1 in the directed diboration reaction.

Non-Directed Diboration

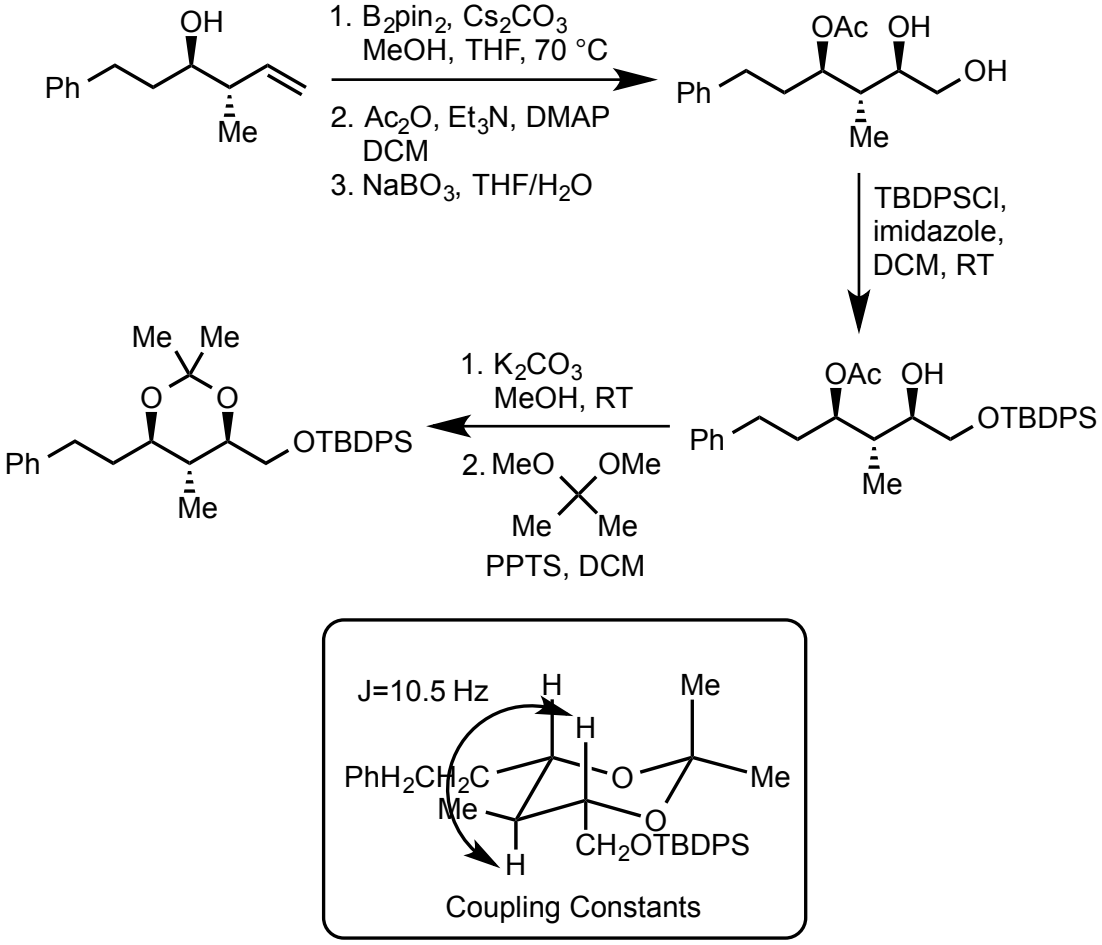


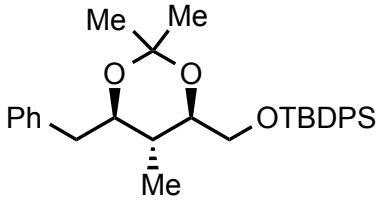
Directed Diboration/Protection



Proof of Stereochemistry:

The relative stereochemistry was determined to be syn by measuring the coupling constants of the carbonyl hydrogens from the ^{1}H NMR of the tert-butyldiphenyl(((4R,5R,6R)- 2,2,5-trimethyl-6- phenethyl-1,3-dioxan-4-yl)methoxy)silane synthesized from the resulting triol.

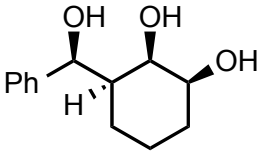




tert-butyldiphenyl(((4R,5R,6R)-2,2,5-trimethyl-6-phenethyl-1,3-dioxan-4-yl)methoxy)silane. To an oven-dried 6-dram vial equipped with a magnetic stirbar was added (*3R,4S,5S*)-4-methyl-1-phenyl-5,6-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl acetate, sodium perborate hydrate (0.5 g, 5 mmol), tetrahydrofuran (3 mL), and water (3 mL) were added at room temperature and stirred for 1 h. Then the reaction was diluted with ethyl acetate, and the organic layer was separated. The aqueous layer was extracted with ethyl acetate (3 x 15 mL), the organic layers were combined and dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material

was purified on silica gel (20% ethyl acetate in hexanes) to afford the acylated triol (62 mg, 46% yield). Then to a 6-dram vial was added the acylated triol (62 mg, 0.23 mmol), imidazole (19 mg, 0.28 mmol), and dichloromethane (2.5 mL) under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C, and *tert*-butyldiphenylsilyl chloride (0.07 mL, 0.25 mmol) in dichloromethane was added. Then the reaction mixture was allowed to warm to room temperature and stir for 2 h, at which time it was quenched with saturated aqueous sodium bicarbonate. The organic layer was separated, washed with water and brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was purified on silica gel (3% ethyl acetate in hexanes) to afford the TBDPS-protected acylated triol (93 mg, 84%). Then, the TBDPS-protected acylated triol was placed in a 6-dram vial (93 mg, 0.19 mmol) and was dissolved in methanol (2 mL). Potassium carbonate (55 mg, 0.40 mmol) was added at room temperature and stirred for 2.5 h. Then the methanol was evaporated and the residue was taken up in dichloromethane, washed with water and brine, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was immediately redissolved in dichloromethane (2 mL). 2,2-dimethoxypropane (0.24 mL, 2.0 mmol), and pyridinium *p*-toluenesulfonate (3.0 mg, 0.013 mmol) were added at 0 °C. The reaction mixture was allowed to warm to room temperature and stir overnight under nitrogen. Then triethylamine was added and the reaction mixture was concentrated by rotary evaporation. The crude material was purified on silica gel (3% ethyl acetate in hexanes) to afford the title compound as a white solid (61 mg, 93%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.69 (3H, d, J = 7 Hz), 1.03 (9H, s), 1.36 (3H, s), 1.43 (3H, s), 1.54 (1H, m), 1.65 (1H, m), 1.91 (1H, m), 2.60 (1H, m), 2.80 (1H, m), 3.38 (1H, m), 3.47 (1H, ddd, J = 10.5 Hz, 4.5 Hz, 3.5 Hz), 3.71 (1H, dd, J = 11.5 Hz, 4.5 Hz), 3.74 (1H, dd, J = 11.0 Hz, 3.5 Hz), 7.16 (3H, m), 7.25 (2H, m), 7.33-7.40 (6H, m), 7.67-7.72 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 12.3, 19.6, 19.8, 27.0, 30.3, 31.4, 34.9, 35.1, 65.9, 73.1, 75.7, 98.1, 125.8, 127.7, 127.7, 128.4, 128.8, 129.7, 134.1, 134.1, 135.9, 136.0, 142.7; IR(neat): 2930.4 (m), 2856.5 (m), 1427.7 (m), 1378.5 (m), 1201.1 (m), 1186.3 (m), 1166.4 (m), 1110.8 (s), 739.8 (m), 699.8 (s) cm^{-1}; HRMS-(ESI+) for $C_{32}H_{42}O_3SiNa$ [M+Na]: calculated: 525.7523, found: 525.2803.



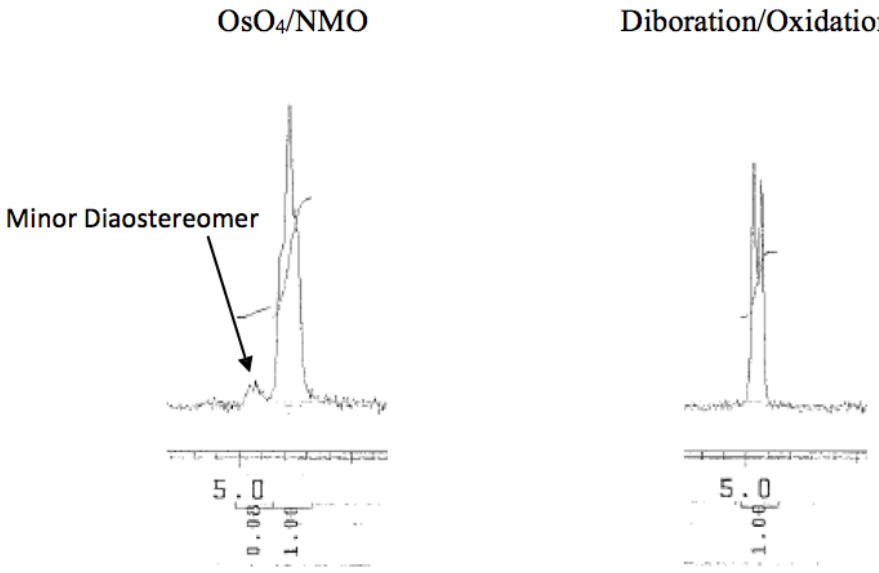
3-(hydroxy(phenyl)methyl)cyclohexane-1,2-diol ***(3.86)***. The diboration was performed according to the representative procedure with cyclohex-2-enyl(phenyl)methanol (94 mg, 0.50 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), methanol (0.34 mL, 8.5 mmol), and tetrahydrofuran (1 mL). The crude material was purified on silica gel (30-100% ethyl acetate in hexanes) to afford the title compound as a white solid (0.10 mg, 94%).

^{1}H NMR (500 MHz, CD_3OD): δ 1.27 (1H, ddd, J = 13.0 Hz, 4.0 Hz, 4.0 Hz), 1.51 (1H, ddd, J = 12.5 Hz, 8.0 Hz, 4.0 Hz), 1.62 (3H, m), 1.78 (2H, m), 3.37 (1H, ddd, J = 12.0 Hz, 5.0 Hz, 3.0 Hz), 3.52 (1H, s), 4.73 (1H, d, J = 8.0 Hz), 7.25-7.28 (1H, m), 7.33-7.36 (2H, m), 7.40-7.41 (2H, m); ^{13}C NMR (100 MHz, CD_3OD): δ 20.3, 23.1, 27.6, 48.2, 71.5, 72.6, 76.4, 127.0, 127.4, 128.3, 144.3; IR (neat): 3360.7, 2936.4, 2861.1, 1449.9, 1093.7,

1070.0, 979.2, 762.4, 702.4, 652.4; HRMS-(ESI-) for $C_{13}H_{17}O_3$ [M-H]: calculated: 221.1178, found: 221.1182.

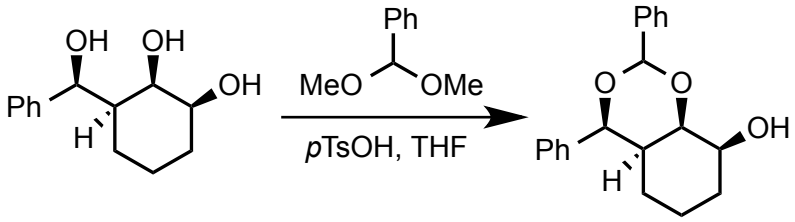
Analysis of Stereochemistry:

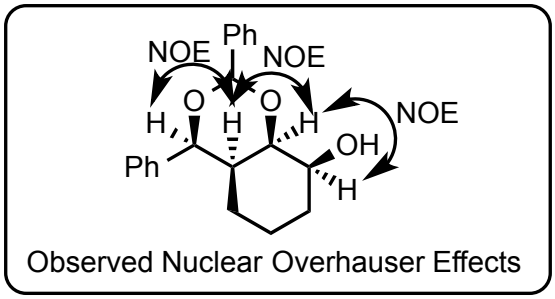
The starting material was subjected to dihydroxylation with osmium tetroxide and 4-methylmorpholine N-oxide to give a mixture of diastereomers as determined by ^{1}H NMR. Diastereomer ratio from the diboration/oxidation sequence was then determined by comparison of the ^{1}H NMR spectra and was found to be greater than 20:1.

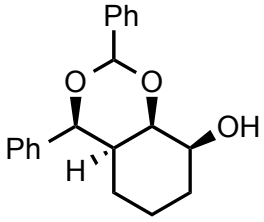


Proof of Stereochemistry:

The relative stereochemistry was determined as syn by NOESY NMR of the 2,4-diphenylhexahydro-4H-benzo[d][1,3]dioxin-8-ol synthesized from the resulting triol in the sequence shown below.



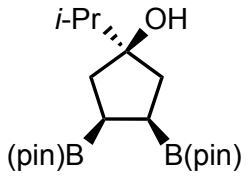




2,4-diphenylhexahydro-4H-benzo[d][1,3]dioxin-8-ol. To a mixture of 3-(hydroxy(phenyl)methyl)cyclohexane-1,2-diol (45 mg, 0.20 mmol) and (dimethoxymethyl)benzene (0.1 mL, 0.5 mmol) in THF (2 mL), added *p*-toluenesulfonic acid monohydrate (2 mg, 0.01 mmol). The reaction mixture was allowed to stir overnight at room temperature. Then the reaction mixture was concentrated by rotary evaporation and purified on silica gel (10% ethyl acetate in hexanes) to afford the title compound as a white solid (36 mg, 58%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (1H, m), 1.12 (1H, qt, J = 13.5 Hz, 3.5 Hz), 1.60 (2H, m), 1.70 (1H, m), 1.77 (2H, m), 2.33 (1H, b), 3.62 (1H, b), 4.32 (1H, s), 5.06 (1H, d, J = 2.5 Hz), 5.77 (1H, s), 7.24 (1H, m), 7.32 (4H, m), 7.38-7.43 (3H, m), 7.58-7.61 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 23.0, 30.0, 40.7, 71.9, 79.3, 81.2, 101.9, 125.5, 126.7, 127.3, 128.3, 128.4, 129.2, 138.8, 139.9; IR(neat): 2938.5 (m), 1449.8 (m), 1404.6

(m), 1157.9 (m), 1062.0 (s), 1009.9 (s), 763.2 (m), 719.6 (m), 698.0 (s) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{23}O_3$ [M+H]: calculated: 311.1647, found: 311.1641.



*1-isopropyl-3,4-bis(4,4,5,5-tetramethyl-1,2,3-dioxaborolan-2-yl)-cyclopentanol (**3.97**).* The diboration was performed according to the general procedure with slight modifications using 1-isopropylcyclopent-3-en-1-ol (63 mg, 0.50 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), methanol (0.34 mL, 8.5 mmol), and THF (1 mL). No oxidation was performed. The crude reaction mixture was purified on silica gel (5-10% ethyl acetate in hexanes) to afford the product as a white solid (116 mg, 61%).

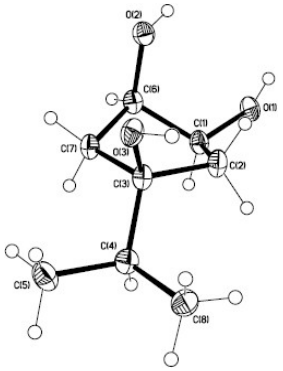
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.94-1.90 (2H, m), 1.66 (2H, dd, J = 14.0 Hz, 6.0 Hz), 1.46-1.43 (1H, m), 1.25-1.23 (25H, m), 1.20 (1H, d, J = 4.5 Hz), 0.93 (3H, s), 0.92 (3H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 85.1, 83.3, 42.5, 37.4, 25.0, 24.9, 24.8, 17.7; 11B NMR (160 MHz, $CDCl_3$): δ 30.5; IR (neat): 3524.3 (w), 2975.6 (m), 2932.2 (m), 2874.4 (m), 1378.4 (m), 1307.4 (m), 1143.2 (m), 1007.0 (m), 858.2 (m); HRMS-(ESI+) for $C_{20}H_{38}B_2O_5$ [M+H−H_2O]: calculated: 363.2878, found: 363.2893.

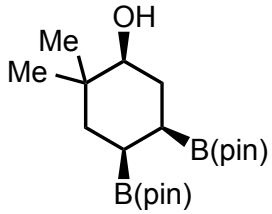
Analysis of Stereochemistry:

Diastereomer ratio was determined to be greater than 20:1 based on analysis of ^{1}H and ^{13}C NMR data.

Proof of Stereochemistry:

To prove relative stereochemistry, the compound was subjected to standard oxidation conditions and the triol was crystallized out of hexanes, ethyl acetate, and methanol (long white crystals).





*2,2-dimethyl-4,5-bis(4,4,5,5-tetramethyl-1,2,3-dioxaborolan-2-yl)cyclohexanol (**3.95**)*. The diboration was performed according to the general procedure with using 6,6-dimethylcyclohex-3-en-1-ol (63 mg, 0.50 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), methanol (0.34 mL, 8.5 mmol), and THF (1 mL). No oxidation was performed. The crude reaction mixture was purified on silica gel (5-10% ethyl acetate in hexanes) to afford the product as a white solid (0.14 g, 75%).

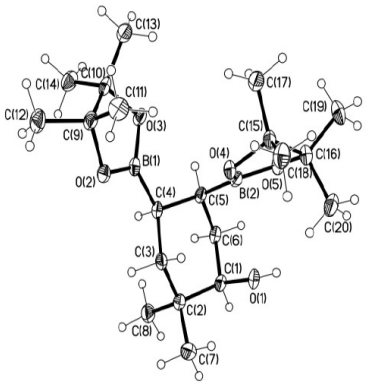
^{1}H NMR (500 MHz, $CDCl_3$): δ 3.36 (1H, br s), 1.95 (1H, br s), 1.80-1.69 (3H, m), 1.25-1.20 (26H, m), 0.90 (6H, br s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 83.2, 82.8, 75.0, 31.8, 25.0, 24.8, 24.6; 11B NMR (160 MHz, $CDCl_3$): δ 34.3; IR (neat): 3490.4 (w), 2976.2 (m), 2929.6 (m), 2865.4 (m), 1378.4 (m), 1305.1 (m), 1214.1 (m), 967.0 (m), 855.2 (m) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{38}B_2O_5$ [M+H]: calculated: 381.2984, found: 381.2978.

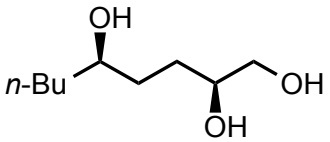
Analysis of Stereochemistry:

Diastereomer ratio was determined to be greater than 20:1 based on analysis of ^{1}H and ^{13}C NMR data.

Proof of Stereochemistry:

Recrystallized from ethyl acetate and hexanes.





*nonane-1,2,5-triol (**3.64**)*. The diboration was performed according to the representative procedure with non-1-en-5-ol (36 mg, 0.25 mmol), $B_2(pin)_2$ (0.13 g, 0.50 mmol), Cs_2CO_3 (26 mg, 0.075 mmol), methanol (0.17 mL, 4.3 mmol) in tetrahydrofuran (1 mL). The crude reaction mixture was purified on silica gel (50-100% ethyl acetate in hexanes) to afford a white solid (31 mg, 70%).

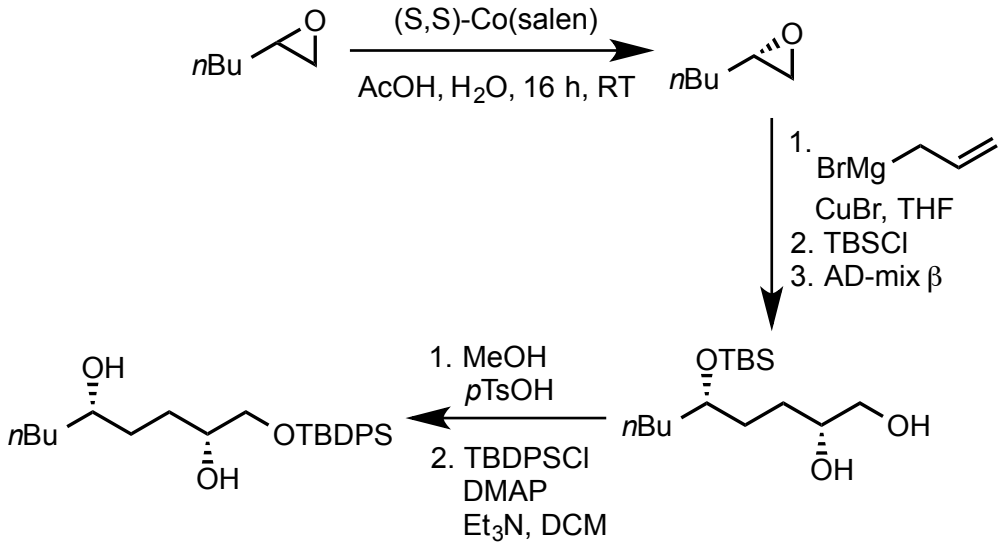
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.91 (3H, t, J = 7.0 Hz), 1.24 – 1.72 (10H, m), 2.24 (2H, br s), 3.03 (1H, br s), 3.48 (1H, dd, J = 11.0 Hz, 7.5 Hz), 3.65 (1H, dd, J = 11.3 Hz, 3.3 Hz), 3.65 – 3.69 (m, 1H), 3.73 – 3.77 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 22.7, 27.9, 29.1, 33.0, 37.1, 66.8, 71.8, 72.1; IR (neat): 3310.7 (m), 2952.7 (m), 2934.5

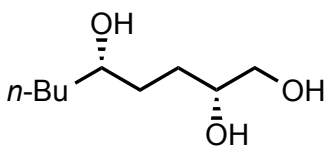
(m), 2871.7 (m), 858.7 (m), 1466.4 (m), 1442.1 (m), 1342.9 (m), 1046.2 (m), 1013.3 (s), 965.4 (m), 870.6 (m), 504.8 (m) cm^{-1}; HRMS-(ESI+) for $C_9H_{21}O_3$ [M+H]: calculated: 177.1491, found: 177.1488.

Analysis/Proof of Stereochemistry:

The diastereoselectivity was attained from SFC analysis, where the TBDPS-protected products of the reaction were compared to the TBDPS-protected products from an OsO_4/NMO dihydroxylation of the substrate. To prove relative stereochemistry, the TBDPS-protected product was synthesized using asymmetric reactions to make to enantioenriched TBDPS- protected product.

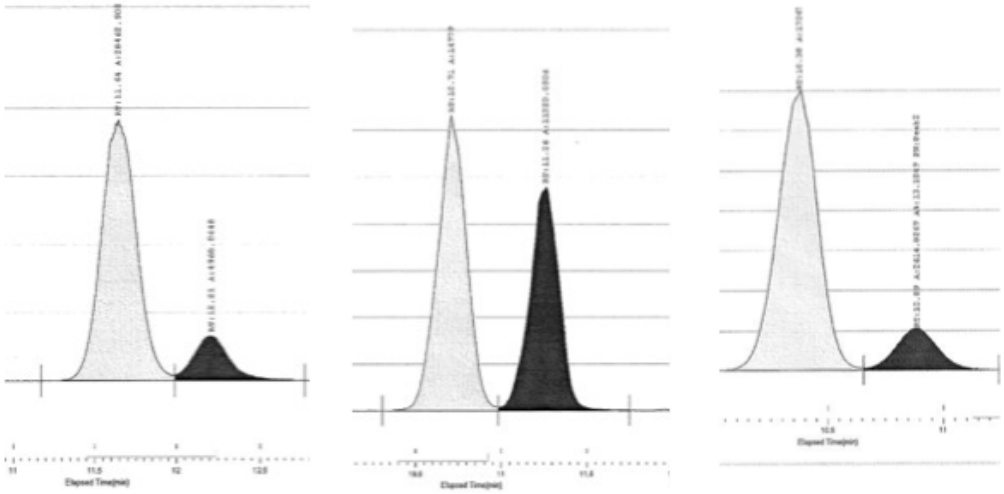
Preparation of 1-((tert-butyldiphenylsilyl)oxy)nonane-2,5-diol:





The title compound was prepared as shown above using standard procedure. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (3H,

t, J = 7.0 Hz), 1.07 (9H, s), 1.20 – 1.67 (10H, m), 3.51 (1H, dd, J = 10.3 Hz, 7.8 Hz), 3.56 – 3.62 (1H, m), 3.65 (1H, dd, J = 10.5 Hz, 3.5 Hz), 3.76 (1H, sept, J = 4.0 Hz), 7.38 – 7.46 (6H, m), 7.65 – 7.67 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 19.2, 22.7, 26.8, 27.9, 29.4, 33.9, 37.3, 68.0, 71.9, 72.1, 127.8, 129.8, 133.1, 135.5; IR (neat): 3347.2 (w), 2954.0 (m), 2929.2 (m), 2857.5 (m), 1463.1 (m), 1427.4 (m), 1111.4 (s), 701.0 (s), 613.5 (m), 504.5 (s) cm^{-1}; $C_{25}H_{35}O_2Si$ [M-H_2O]: calculated: 395.2406, found: 395.2418.



Reaction Products

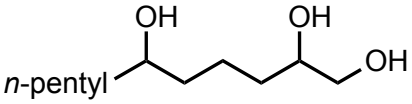
Peak No	% Area	Area	RT (min)
1	85.1394	28462.9084	11.64
2	14.8606	4968.0448	12.21
Total:	100	33430.9532	

OsO_4/NMO

Peak No	% Area	Area	RT (min)
1	56.1966	14779.3812	10.71
2	43.8034	11520.0506	11.26
Total:	100	26299.4318	

Synthesized Authentic Product

Peak No	% Area	Area	RT (min)
1	86.7151	17067.9162	10.38
2	13.2849	2614.8269	10.89
Total:	100	19682.7431	

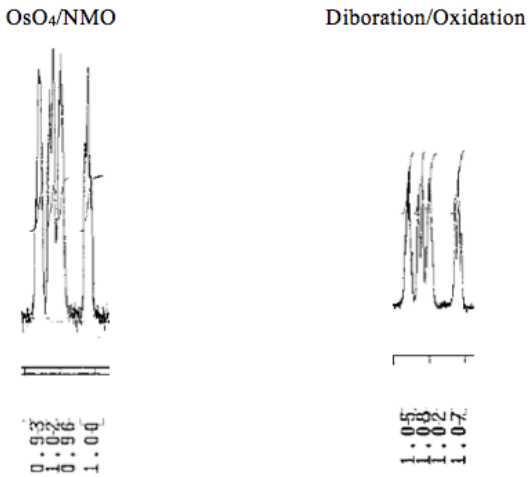


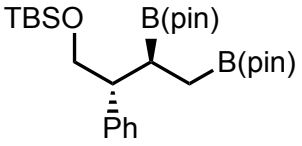
undecane-1,2,6-triol ***(3.66)***. Prepared according to the general diboration/oxidation procedure using undec-1-en-6-ol (85 mg, 0.50 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), methanol (0.34 mL, 8.5 mmol), and THF (1 mL). The crude product was purified on silica gel (25-50% ethyl acetate in hexanes) to afford the title compound as a white solid (79 mg, 77%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (3H, t, J = 7.0 Hz), 1.26-1.35 (5H, m), 1.37-1.54 (9H, m), 1.54-1.62 (1H, m), 1.79 (1H, s), 2.05 (1H, s), 3.42-3.46 (1H, m), 3.59-3.61 (1H, m), 3.64-3.66 (1H, m), 3.70-3.73 (1H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.0, 21.5, 21.6, 22.6, 25.3, 25.3, 31.8, 32.9, 33.0, 36.9, 37.1, 37.5, 37.6, 66.7, 66.8, 71.8, 72.0, 72.1; IR (neat): 3331.2 (br, m), 2925.9 (m), 2862.4 (w), 1453.5 (m), 1046.4 (s), 897.2 (m), 849.2 (m), 746.2 (s), 697.8 (s); HRMS-(ESI+) for $C_{11}H_{24}O_3$ [M+H]: calculated: 205.1804, found: 205.1806; melting point: 77-80 °C.

Analysis of Stereochemistry:

The starting material was subjected to dihydroxylation with osmium tetroxide and 4-methylmorpholine N-oxide to give a mixture of diastereomers as determined by ^{1}H NMR. Diastereomer ratio from the diboration/oxidation sequence was then determined by comparison of the ^{1}H NMR and was found to be 1:1.





*tert-butyldimethyl(2-phenyl-3,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)silane (**3.76**).* The diboration was performed according to the representative procedure using 2-phenylbut-3-en-1-ol (74 mg, 0.50 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), methanol (0.34 mL, 8.5 mmol), and tetrahydrofuran (1 mL) . After the diboration was complete, the reaction mixture was concentrated, and dichloromethane (2.3 mL) and imidazole (0.30 g, 4.4 mmol), were added to the flask. Then the reaction mixture was cooled to 0 °C, and TBSCl (0.22 g, 1.5 mmol) in toluene (0.5 mL) was added. The reaction mixture was allowed to warm to room temperature and stir for 12 h. Then the reaction mixture was diluted with sat. ammonium chloride (aq) and the aqueous layer was extracted with DCM (3x10 mL). The organic layers were combined, dried over sodium sulfate, filtered, and concentrated by rotary evaporation. The crude material was purified on silica gel (2.5% ethyl acetate in hexanes) to isolate the title compound as a white solid (0.15 g, 57%).

^{1}H NMR (400 MHz, $CDCl_3$): δ -0.18 (3H, app t, J = 3.0 Hz), -0.13 (3H, app t, J = 2.8 Hz), 0.66 (2H, m), 0.74 (9H, app t, J = 2.6 Hz), 1.16 (6H, s), 1.17 (6H, s), 1.21 (6H, s), 1.23 (6H, s), 0.59 - 0.73 (1H, m), 2.87 (1H, dt, J = 11.3 Hz, 7.5 Hz), 3.69 (1H, dd, J = 9.8 Hz, 8.6 Hz), 3.85 (1H, dd, J = 9.8 Hz, 5.0 Hz), 7.08 – 7.22 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ -5.5, 18.2, 24.7, 24.9, 24.9, 24.9, 25.8, 51.1, 66.8, 82.7, 83.0, 125.7, 127.7, 128.9, 143.4; 11B NMR (160 MHz, $CDCl_3$): δ 33.8; IR (neat): 3027.5 (w), 2977.5 (m), 2928.2 (m), 2856.3 (m), 1602.7 (w), 1493.6 (m), 1369.1 (m), 1369.1 (s), 1312.9 (s),

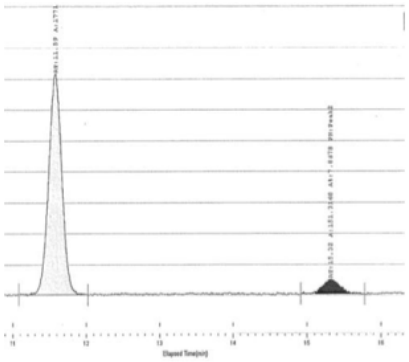
1252.6 (s), 1140.8 (s), 1103.6 (s), 833.8 (s), 773.3 (s), 698.9 (s) cm^{-1}; HRMS- (ESI+) for $C_{28}H_{51}B_2O_5Si$ [M+H]: calculated: 517.3692, found: 517.3712.

Analysis of Stereochemistry:

The diastereoselectivity was attained from SFC analysis, where the oxidized products of the directed diboration reaction were compared to those of an OsO_4/NMO dihydroxylation of the substrate.

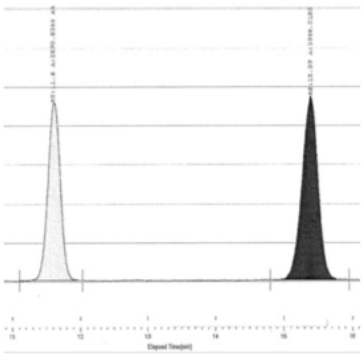
SFC (2EP 4.6x250, 35 °C, 3mL/min, 5% MeOH, 100 bar)

Reaction Products



Peak No	% Area	Area	RT (min)
1	92.1322	1771.9171	11.59
2	7.8678	151.3168	15.32
Total:	100	1923.2339	

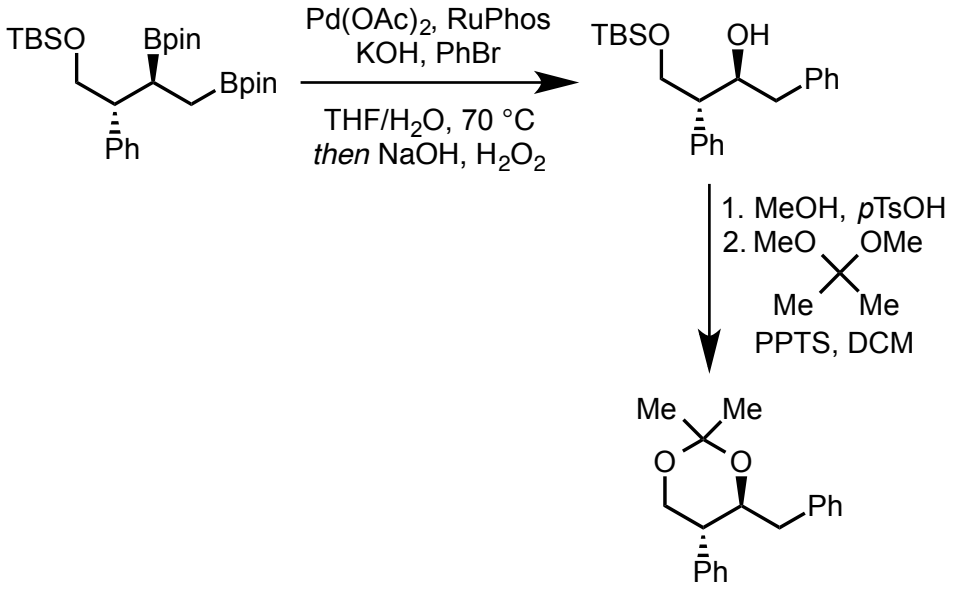
OsO_4/NMO

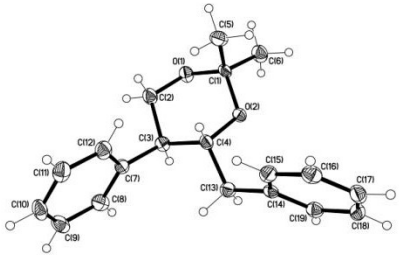


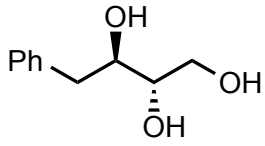
Peak No	% Area	Area	RT (min)
1	42.2707	2890.8344	11.6
2	57.7293	3948.0185	15.39
Total:	100	6838.8529	

Proof of Stereochemistry:

The reaction sequence shown below was used to form the acetonide, which was recrystallized from ethyl acetate and hexanes.







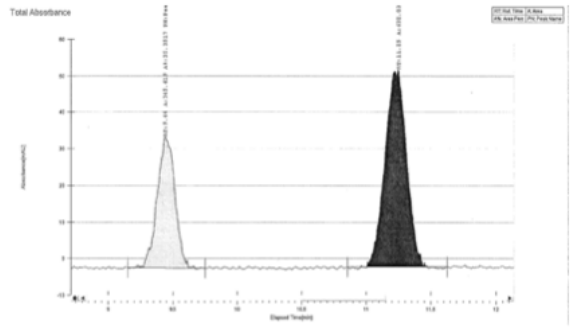
*4-phenylbutane-1,2,3-triol (**3.62**)*. The diboration was performed according to the representative procedure with tetradec-1-en-4-ol (37 mg, 0.25 mmol), Cs_2CO_3 (26 mg, 0.075 mmol), $B_2(pin)_2$ (0.13 g, 0.50 mmol), methanol (0.17 mL, 4.3 mmol), and tetrahydrofuran (0.5 mL). The crude material was purified on silica gel (50%-100% EtOAc/Hexanes) to afford the title compound was obtained as a mixture of diastereomers (1.8:1) as a clear oil (21 mg, 47%). ^{1}H NMR (500 MHz, CD3OD): δ 2.62 (1H, dd, J = 14.0 Hz, 9.0 Hz), 3.04 (1H, dd, J = 13.5 Hz, 3.5 Hz), 3.49 – 3.45 (1H, m), 3.63 – 3.58 (1H, m), 3.72 – 3.71 (1H, m), 3.77 (1H, dd, J = 11.0 Hz, 3.5 Hz), 7.14 – 7.19 (1H, m), 7.25 – 7.26 (4H, m); ^{13}C NMR (125 MHz, CD3OD): δ 39.2, 63.3, 72.8, 73.4, 125.6, 127.7, 129.2, 139.1; IR (neat): 3343.1 (s),

3061.4 (w), 3027.5 (w), 2924.1 (m), 1603.3 (w), 1495.2 (m), 1453.7 (m), 1063.1 (s), 1029.9 (s), 745.7 (m), 699.4 (s) cm^{-1}; HRMS- (ESI+) for $C_{10}H_{15}O_3$ [M+H]: calculated: 183.10212, found: 183.10270.

Determination of diastereoselectivity:

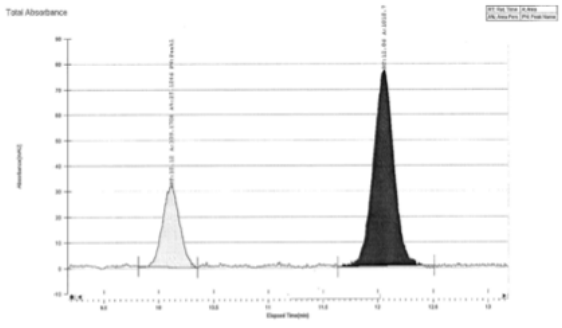
The diastereoselectivity was determined from SFC analysis, where the products of the reaction were compared to products from an OsO_4/NMO dihydroxylation of the substrate. Diastereomer ratio was determined to be 1.8:1.

SFC (2EP 4.6x250, 35 °C, 3mL/min, 5% MeOH, 100 bar)



Peak Info

Peak No	% Area	Area	RT (min)
1	35.3517	345.619	9.44
2	64.6483	632.0391	11.25
Total:	100	977.6581	



Peak Info

Peak No	% Area	Area	RT (min)
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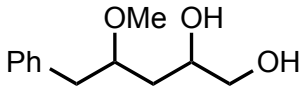
2	74.8754	1010.7851	12.06
Total:	100	1349.9559	



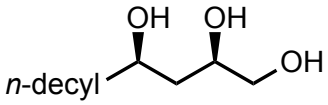
4-methoxy-5-phenylpentane-1,2-diol (***3.80***). The diboration was performed according to the representative procedure with (2-methoxypent-4-en-1-yl)benzene (88 mg, 0.50 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), Cs_2CO_3 (53 mg, 0.15 mmol), methanol (.34 mL, 8.5 mmol) in tetrahydrofuran (1

mL). The crude reaction mixture was purified by on silica gel (50-100% ethyl acetate in hexanes) to afford a clear, colorless oil (80 mg, 76%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.45 (0.5H, ddd, J = 16.0 Hz, 8.3 Hz, 3.3 Hz), 1.51-1.69 (1.5H, m), 2.71 (1H, ddd, J = 13.5 Hz, 8.3 Hz, 7.3 Hz), 2.98 (1H, dt, J = 13.5 Hz, 5.0 Hz), 3.36 – 3.42 (0.5H, m), 3.37 (1.5H, s), 3.42 (1.5H, s), 3.51 (0.5H, dd, J = 11.5, 4.0 Hz), 3.55 (0.5H, dd, J = 11.5 Hz, 3.5 Hz), 3.64 - 3.73 (1H, m), 3.80 - 3.85 (0.5H, m), 3.94 - 3.98 (0.5H, m), 7.17 - 7.23 (3H, m), 7.26 - 7.31 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 24.8, 36.1, 36.7, 39.7, 39.8, 56.7, 57.3, 66.6, 66.9, 69.3, 71.7, 80.0, 82.8, 126.3, 126.4, 128.4, 128.5, 129.4, 129.5, 137.7, 138.2; IR (neat): 3380.4 (m), 2931.0 (m), 2828.0 (w), 1602.9 (w), 1495.1 (m), 1453.8 (m), 1082.7 (s), 746.3 (m), 700.1 (s) cm^{-1}; HRMS-(ESI+) for $C_{12}H_{19}O_3$ [M+H]: calculated: 211.1334, found: 211.1336.

Analysis of Stereochemistry:

Diastereomer ratio was determined to be 1:1 based on analysis of the ^{1}H NMR spectrum.



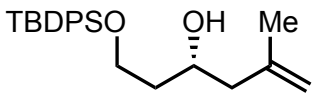
syn-tetradecane-1,2,4-triol. The diboration was performed according to the representative procedure with tetradec-1-en-4-ol (0.11 g, 0.50 mmol), Cs_2CO_3 (49 mg, 0.15 mmol), $B_2(pin)_2$ (254 mg, 1.00 mmol), methanol (0.34 mL, 8.5 mmol), and tetrahydrofuran (1 mL). The crude material was purified on silica gel (50%-100% EtOAc/Hexanes) to afford the title compound was obtained as a white solid (56 mg, 53%). ^{1}H NMR (500 MHz, $CDCl_3$/drop of D_2O): δ - 0.88 (3H, t, J = 6.9 Hz), 1.22 – 1.34 (14H, m), 1.35 – 1.42 (1H, m), 1.43 – 1.52 (2H, m), 1.53 – 1.59 (2H, m), 1.60 – 1.70 (1H, m), 3.47 (1H, dd, J = 11.3 Hz, 6.4 Hz), 3.63 (1H,

dd, J = 11.0 Hz, 3.2 Hz), 3.86 – 3.93 (1H, m), 3.93 – 3.99 (1H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.7, 25.3, 29.3, 29.6, 29.6, 31.9, 38.3, 39.0, 66.8, 72.5, 72.6; IR (neat): 3356.4 (m), 2955.6 (m), 2921.3 (s), 2852.0 (s), 1655.3 (w), 1465.4 (m), 1065.0 (s), 587.3 (s), 504.3 (s) cm^{-1}; HRMS- (ESI+) for $C_{14}H_{29}O_2$ [M+H-H_2O]: calculated: 229.21675, found: 229.21716.

Analysis of Diastereoselectivity:

Diastereomer ratio from the diboration/oxidation sequence was determined by ^{1}H NMR spectra and was found to be 8.5:1.

3.11.5 Fragment Synthesis



(R)-1-((tert-butyldiphenylsilyl)oxy)-5-methylhex-5-en-3-ol ***(3.111)***. To an oven-dried 16-mL vial with magnetic stir bar in the dry box was added $Pt(dba)_3$ (4.5 mg, 5.0 μmol), (*R,R*)-3,5-di-iso-propylphenyl-TADDOLPPh (5.5 mg, 6.0 μmol), $B_2(pin)_2$ (133 mg, 525 μmol) and tetrahydrofuran (0.5 mL). The vial was sealed with a teflon septum cap, removed from the dry box, and heated to 80 °C in an oil bath for 20 minutes. The vial was cooled to room temperature, returned to the dry box and charged with (but-3-en-1-yloxy)(*tert*-butyl)diphenylsilane (155 mg, 500 μmol). The vial was sealed, removed from the dry box and stirred at 60 °C for 3 h. The vial was cooled to room temperature, returned to the dry box and charged with solid potassium hydroxide (84.2 mg, 1.50 mmol), $Pd(OAc)_2$ (3.1 mg, 12.5 μmol)/RuPhos (7 mg, 15 μmol) (added as a 1:1.2 solution in THF (1 mL)), tetrahydrofuran (3.05 mL) and 2-chloroprop-1-ene (65 μL, 750 μmol). The vial was sealed, removed from the dry box,

and H_2O (sparged with N_2 for 30 min, 0.45 mL) was added through the teflon septum cap. The vial was heated to 70 °C and stirred for 12 h. The reaction mixture was transferred to a 50-mL round bottom flask and cooled to 0 °C (ice/water) and charged with 3 M sodium hydroxide (2 mL), and 30% hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h at which time the vial was cooled to 0 °C and saturated aqueous sodium thiosulfate was added dropwise over 5 min. The reaction mixture was diluted with ethyl acetate and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by column chromatography on silica gel (2.5-5% ethyl acetate/hexanes, R_f = 0.4 in 10% ethyl acetate/hexanes, stain in $KMnO_4$) to afford a clear, colorless oil (165 mg, 90%).

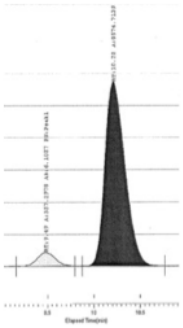
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (9H, s), 1.68 – 1.74 (2H, m), 1.77 (3H, s), 2.18 (1H, dd, J = 13.8 Hz, 5.3 Hz), 2.25 (1H, dd, J = 13.8 Hz, 7.8 Hz), 2.99 (1H, d, J = 2.0 Hz), 3.83 – 3.92 (2H, m), 4.04 – 4.10 (1H, m), 4.78 (1H, s), 4.85 (1H, s), 7.38 – 7.46 (6H, m), 7.68 – 7.70 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.1, 22.5, 26.8, 38.3, 46.1, 63.0, 68.7, 113.0, 127.7, 129.8, 133.1, 135.5, 142.8; IR (neat): 3449.9 (w), 3071.2 (w), 2930.3 (m), 2856.9 (m), 1647.2 (w), 1589.5 (w), 1471.6 (m), 1427.3 (m), 1107.8 (s), 1076.3 (s), 736.0 (s), 699.5 (s), 613.0 (s), 502.2 (s), 487.3 (s) cm^{-1}; HRMS-(ESI+) for $C_{23}H_{33}O_2Si$ [M+H]: calculated: 369.22498, found: 369.22487. $[\alpha]_D$ = -2.459 (c = 0.4875, CH2Cl2, l = 50 nm).

Analysis of Stereochemistry:

The title compound was compared to the racemic analogue derived from the racemic diboration of (but-3-en-1-yloxy)(*tert*-butyl)diphenylsilane. The resulting racemic diboron was transformed into 1-((*tert*-butyldiphenylsilyl)oxy)-5-methylhex-5-en-3-ol as described above for the enantioenriched variant.

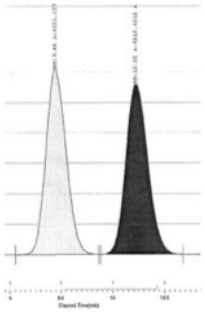
Chiral SFC (Chiracel, OD-H, 35 °C, 3 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of 1-((tert-butyldiphenylsilyl)oxy)-5-methylhex-5-en-3-ol.

Reaction Products

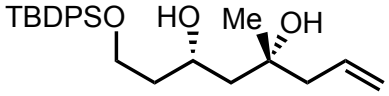


Peak No	% Area	Area	RT (min)
1	6.1027	557.2978	9.49
2	93.8973	8574.7139	10.22
Total:	100	9132.0117	

Racemic



Peak No	% Area	Area	RT (min)
1	49.9153	4201.1373	9.44
2	50.0847	4215.4012	10.22
Total:	100	8416.5385	



*(3S,5R)-1-((tert-butyldiphenylsilyl)oxy)-5-methyloct-7-ene-3,5- diol (**3.113**).* To an oven-dried 16-mL vial with magnetic stir bar in the dry box was added 1-((*tert*-butyldiphenylsilyl)oxy)-5-methylhex-5-en-3-ol (90 mg, 240 μmol), Cs_2CO_3 (25 mg, 7.0 μmol), $B_2(pin)_2$ (94 mg, 370 μmol) and tetrahydrofuran (1 mL). The vial was sealed with a teflon septum cap and removed from the dry box. To the vial was added methanol (0.17 mL, 4.2 mmol). The reaction mixture was heated to 70 °C in an oil bath overnight. The vial was cooled to

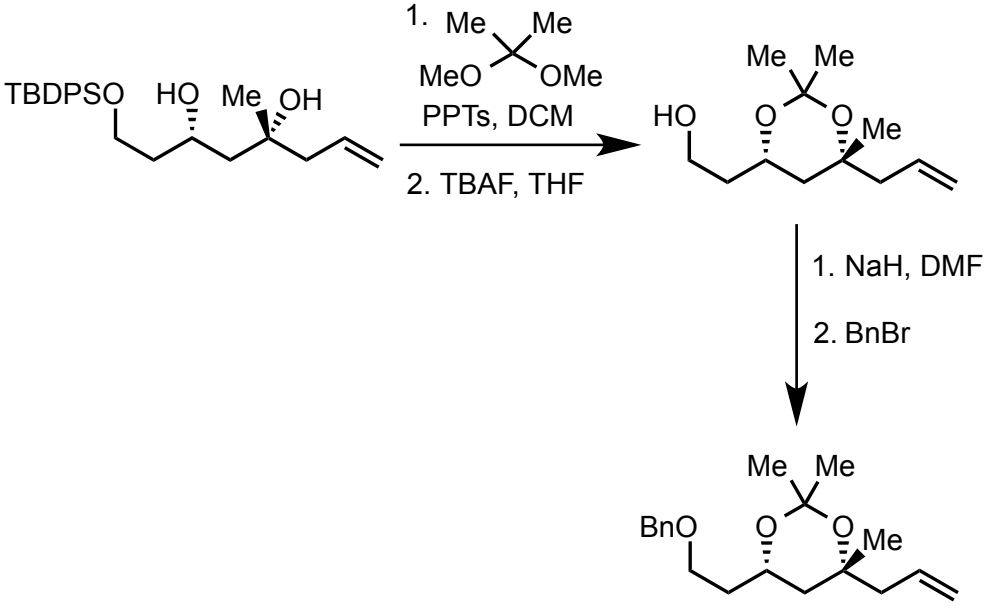
room temperature and concentrated by rotary evaporation within the vial. The residue was then put on hi-vac for 1 hour to ensure the evaporation of methanol. The vial was then brought into the dry box and charged with potassium *tert*-butoxide (162 mg, 1.44 mmol), $Pd(OAc)_2$ (1.5 mg, 6.0 μmol)/RuPhos (2.8 mg, 6.0 μmol) (added as a 1:1 solution in THF (1 mL)), tetrahydrofuran (1.3 mL) and 1,2-dichloroethane (57 μL, 0.72 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N2 for 30 min, 0.23 mL) was added through the teflon septum cap. The vial was heated to 70 °C and stirred for 12 h. The reaction mixture was transferred to a 50-mL round bottom flask and cooled to 0 °C (ice/water) and charged with 3 M sodium hydroxide (1 mL), and 30% hydrogen peroxide (0.5 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h at which time the vial was cooled to 0 °C and saturated aqueous sodium thiosulfate was added dropwise over 5 min. The reaction mixture was diluted with ethyl acetate and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by column chromatography on silica gel (5-20% ethyl acetate/hexanes, R_f = 0.3 in 30% ethyl acetate/hexanes, stain in $KMnO_4$) to afford a clear, colorless oil (44 mg, 44%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (9H, s), 1.30 (3H, s), 1.44 (1H, dd, J = 14.3 Hz, 2.25 Hz), 1.58 – 1.63 (1H, m), 1.72 (1H, dd, J = 14.5 Hz, 11.0 Hz), 1.75 – 1.82 (1H, m), 2.20 – 2.28 (2H, m), 3.72 (1H, s), 3.84 – 3.91 (2H, m), 3.93 (1H, s), 4.32 (1H, t, J = 9.8 Hz), 5.07 – 5.13 (2H, m), 5.87 – 5.94 (1H, m), 7.39 – 7.47 (6H, m) 7.67 – 7.69 (4H, m); ^{13}C

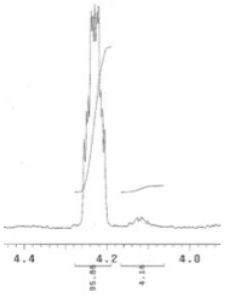
NMR (125 MHz, $CDCl_3$): δ 19.0, 25.9, 26.8, 39.2, 45.9, 48.7, 63.0, 69.4, 72.4, 118.1, 127.8, 129.9, 133.0, 134.3, 135.5; IR (neat): 3351.1 (w), 3071.3 (w), 2930.6 (m), 2857.0 (m), 1640.2 (w), 1589.3 (w), 1427.1 (m), 1106.7 (s), 1085.4 (s), 735.8 (s), 699.6 (s), 687.6 (s), 613.0 (s), 502.7 (s), 487.4 (s) cm^{-1}; HRMS-(ESI+) for $C_{25}H_{37}O_3Si$ [M+H]: calculated: 413.2512, found: 413.2496. $[\alpha]_D$ CH2Cl2, l = 50 nm).

Analysis of Stereochemistry:

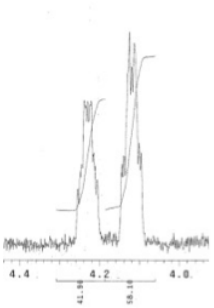
The title compound was subjected to the reactions below, which gave a previously characterized compound, which served as proof of stereochemistry. [45] The diastereoselectivity of the diboration was determined by a directed diboration and oxidation of 1-((*tert*-butyldiphenylsilyl)oxy)-5-methylhex-5-en-3-ol. The product of this reaction was compared to those products from an OsO_4/NMO dihydroxylation of 1-((*tert*-butyldiphenylsilyl)oxy)-5-methylhex-5-en-3-ol.



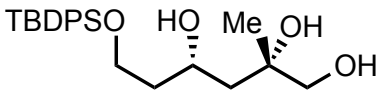
[45] Allais, F.; Cossy, J. *Org. Lett.* **2006**, *8*, 3655 – 3657.



Reaction Products



OsO_4/NMO



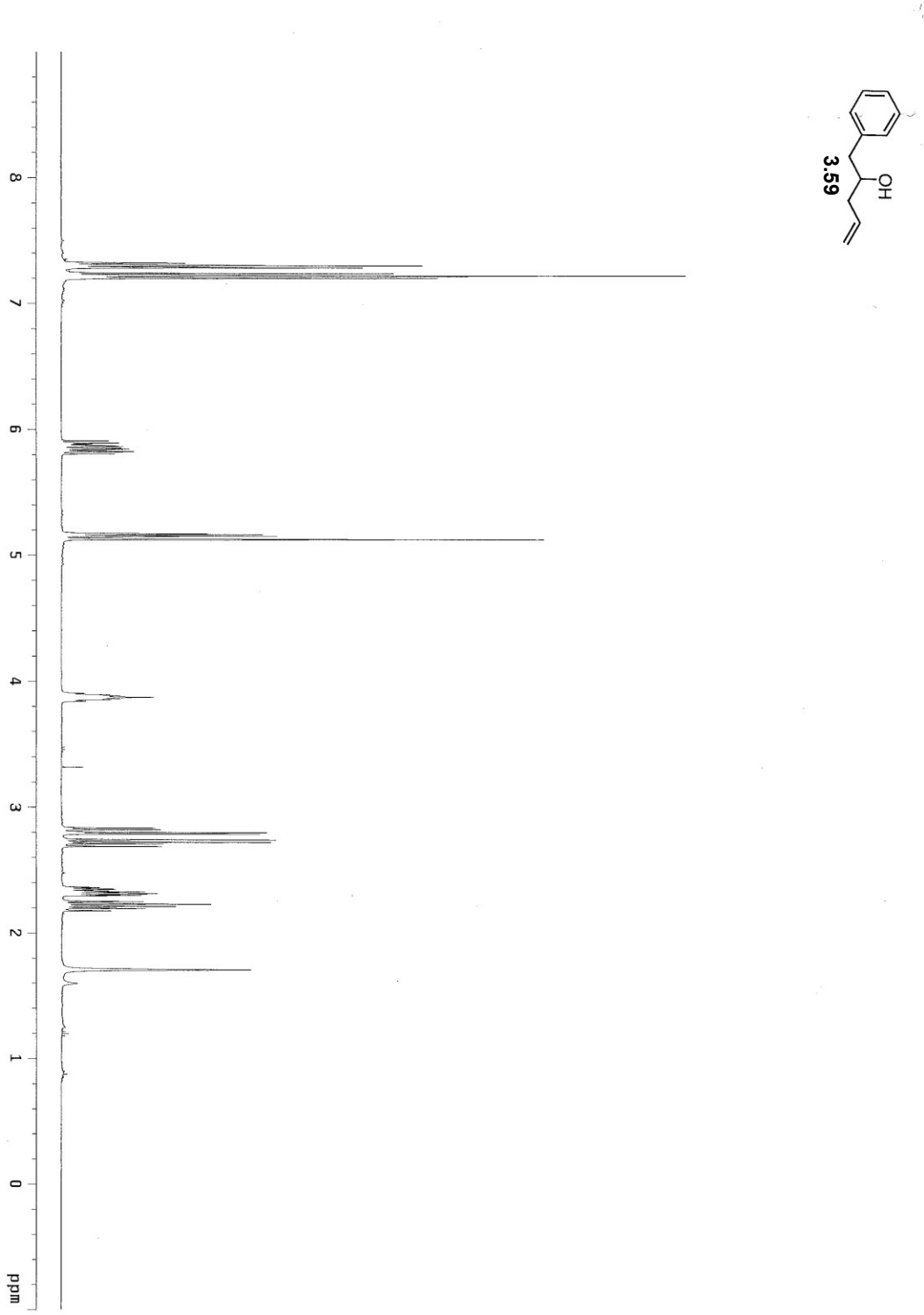
(2S,4S)-6-((tert-butyldiphenylsilyl)oxy)-2-methylhexane-1,2,4-triol. The diboration was performed according to the representative procedure with 1-((*tert*-butyldiphenylsilyl)oxy)-5-methylhex-5-en-3-ol (69 mg, 0.19 mmol), $B_2(pin)_2$ (71 mg, 1.5 mmol), Cs_2CO_3 (20 mg, 0.057 mmol), methanol (0.13 mL, 3.23 mmol) in tetrahydrofuran (0.76 mL, 0.25 M). The crude reaction mixture was purified by column chromatography on silica gel (25-100% ethyl acetate/hexanes, R_f = 0.25 in 75% ethyl acetate/hexanes, stain in $KMnO_4$) to afford a clear, colorless oil (48 mg, 65%).

^{1}H NMR (500 MHz, CD_3OD): δ 1.04 (9H, s), 1.21 (3H, s), 1.56 – 1.65 (2H, m), 1.67 – 1.78 (2H, m), 3.36 (2H, q, J = 17.3 Hz, 11.3 Hz), 3.75 – 3.85 (2H, m), 4.21 – 4.26 (1H, m), 7.38 – 7.44 (6H, m) 7.66 – 7.69 (4H, m); ^{13}C NMR (125 MHz, CD_3OD): δ 18.6, 23.0, 25.9, 40.7, 43.8, 60.6, 65.6, 69.8, 72.7, 127.4, 129.4, 133.5, 135.3; IR (neat): 3382.5 (m), 3070.6 (w), 3048.6 (w), 2930.4 (m), 2856.9 (m), 1589.2 (w), 1471.5 (m), 1187.5 (m), 1106.9 (s), 1087.5 (s), 822.20 (m), 736.3 (s), 700.6 (s), 613.0 (s), 503.6 (s), 488.6 (s) cm^{-1}; HRMS-(ESI+) for $C_{23}H_{35}O_4Si$ [M+H]: calculated: 403.2305, found: 403.2319.

3.11.6 Spectral Data

For all published spectral data see the following link: http://pubs.acs.org/doi/suppl/10.1021/ja504228p

See below for examples of ^{1}H and ^{13}C spectra: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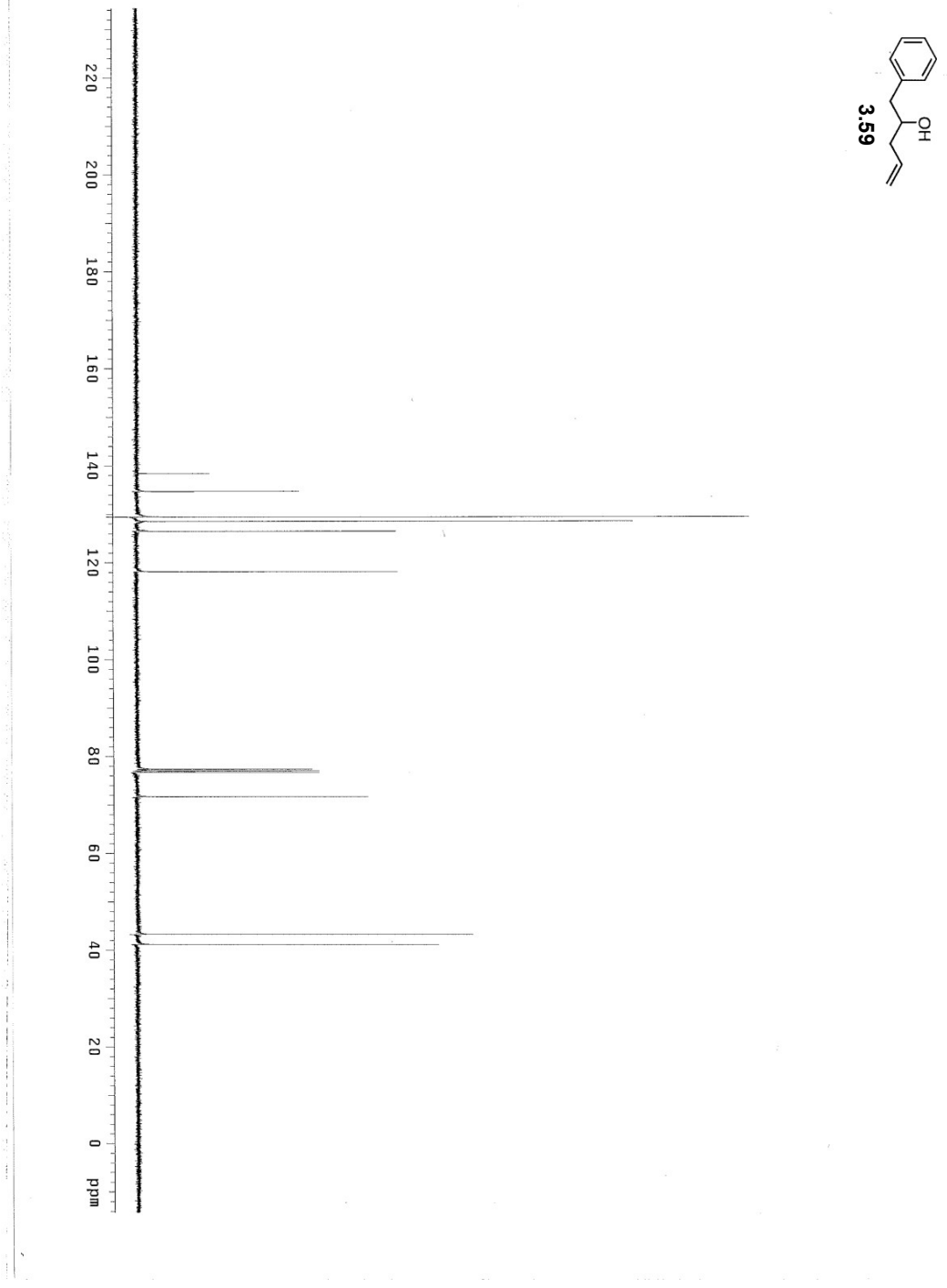
0
ppm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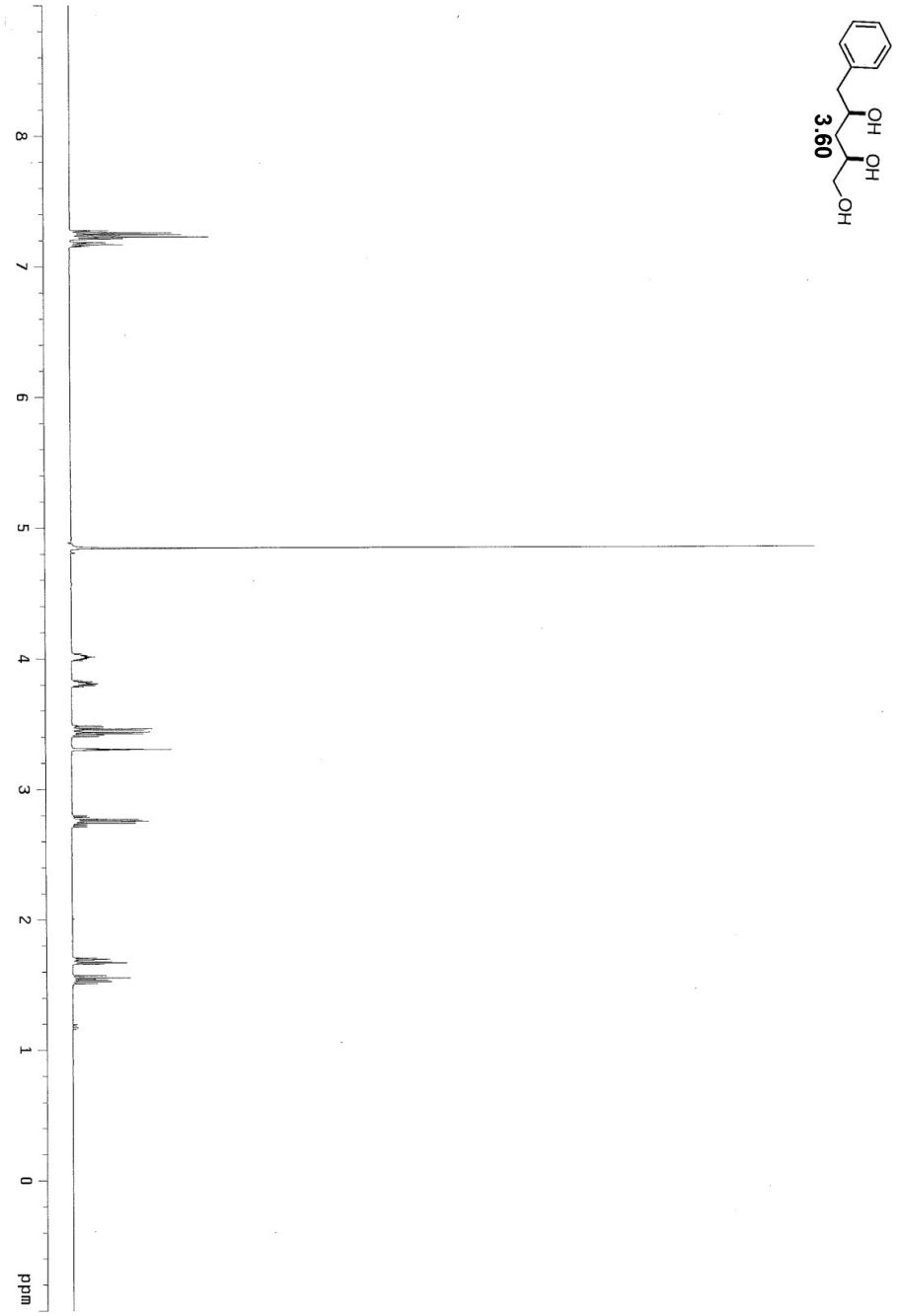
ppm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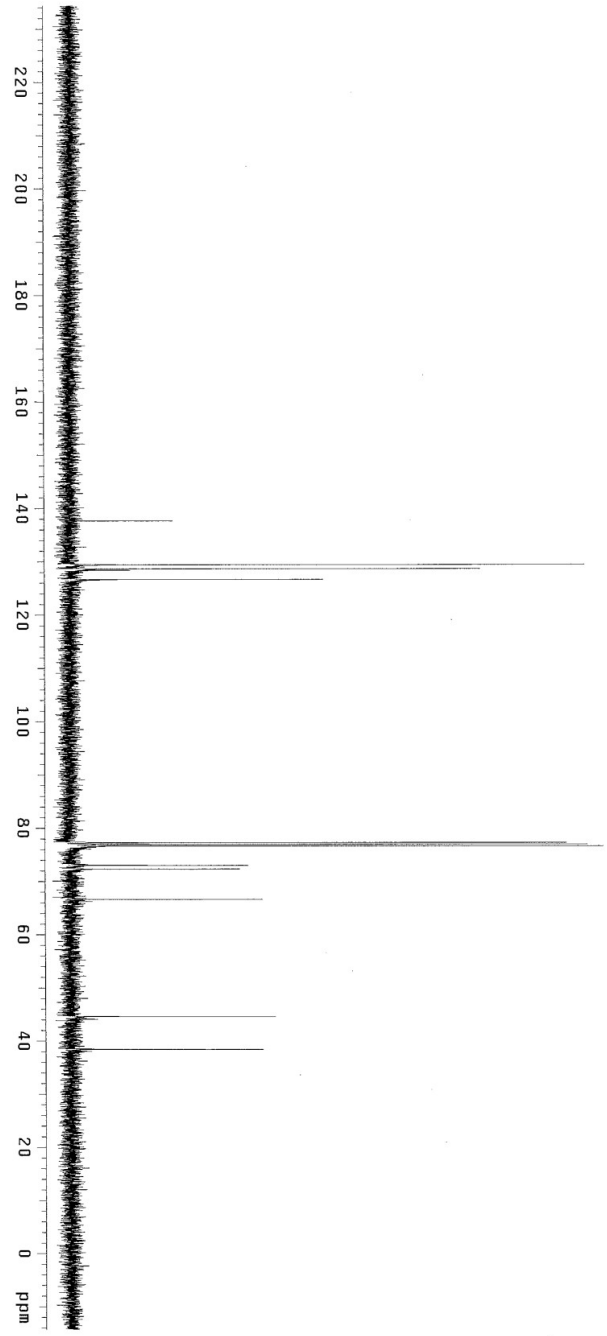
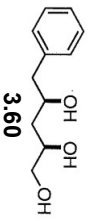
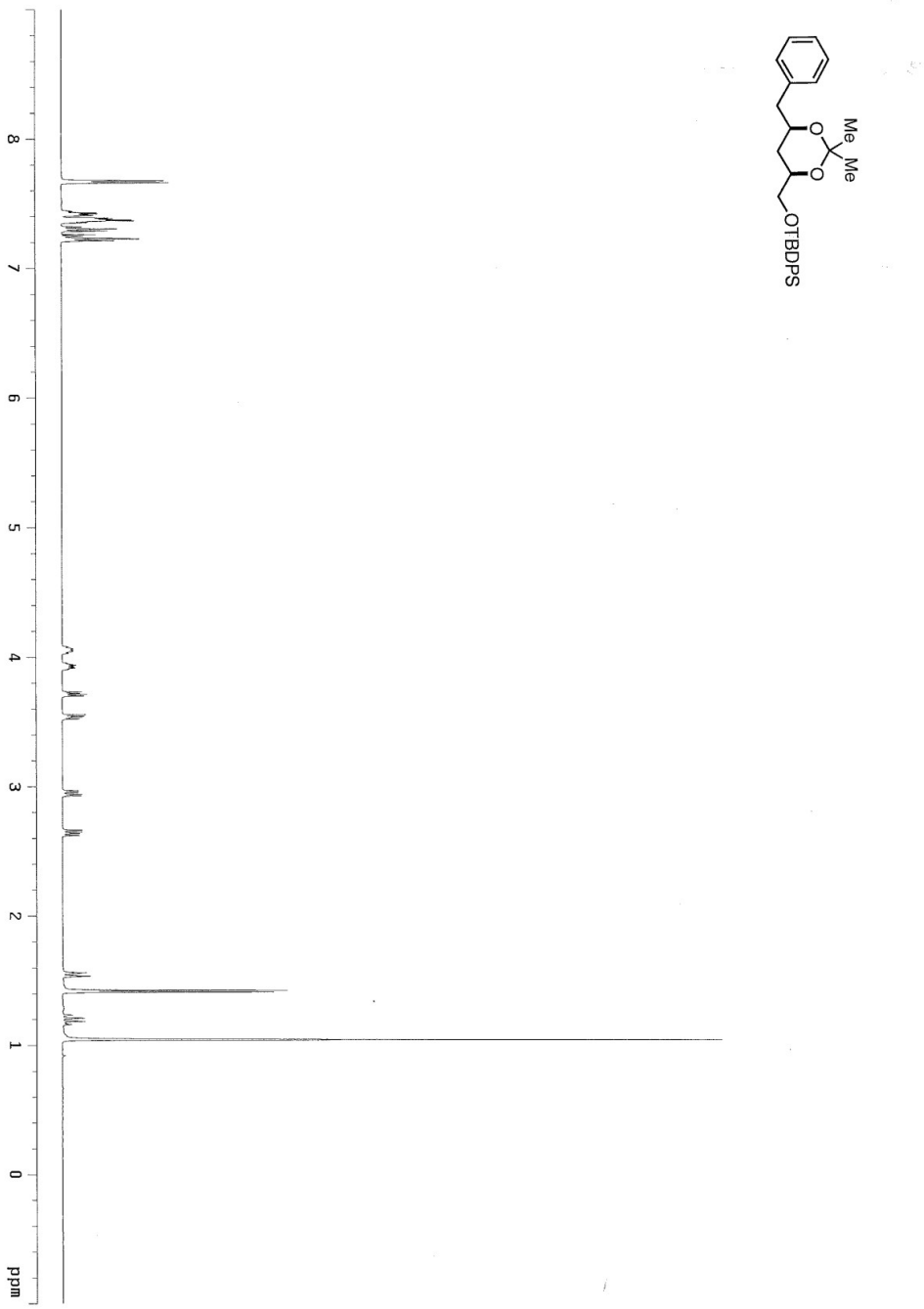




3.60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5
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2
1
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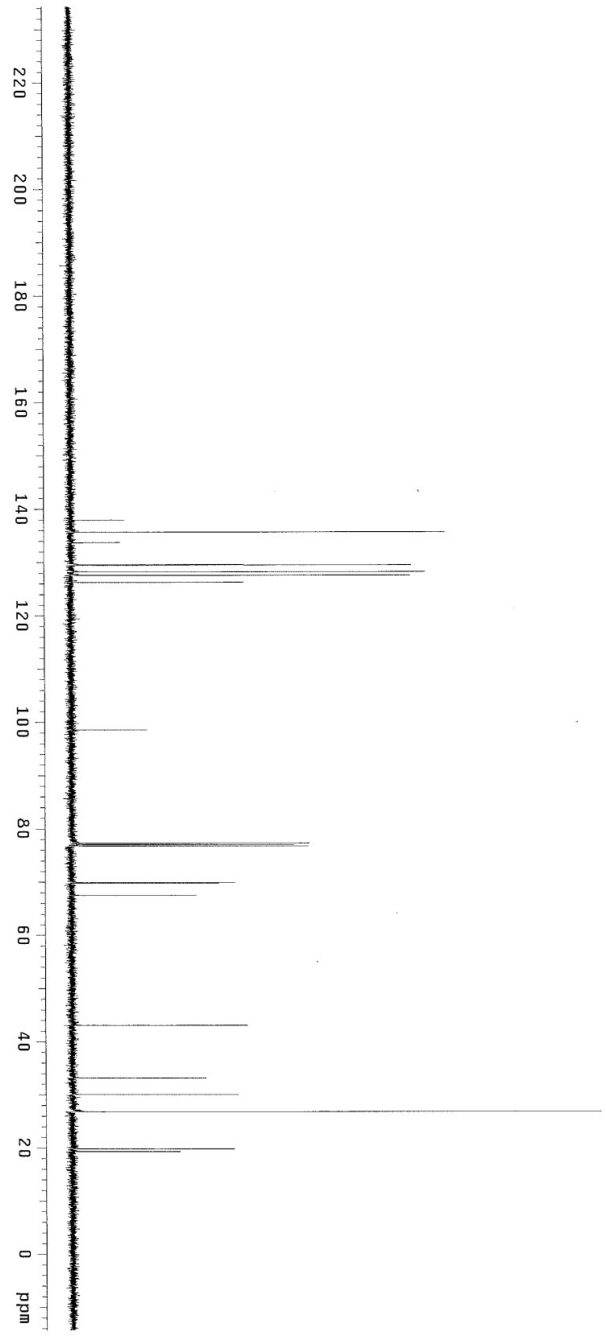
ppm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80
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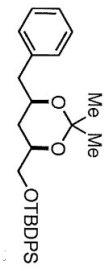
0
ppm


Me
Me
O
O
OTBDPS

Chapter 4: The Stereo- and Regiospecific, Hydroxyl-Directed Cross-Coupling of Secondary Boronates

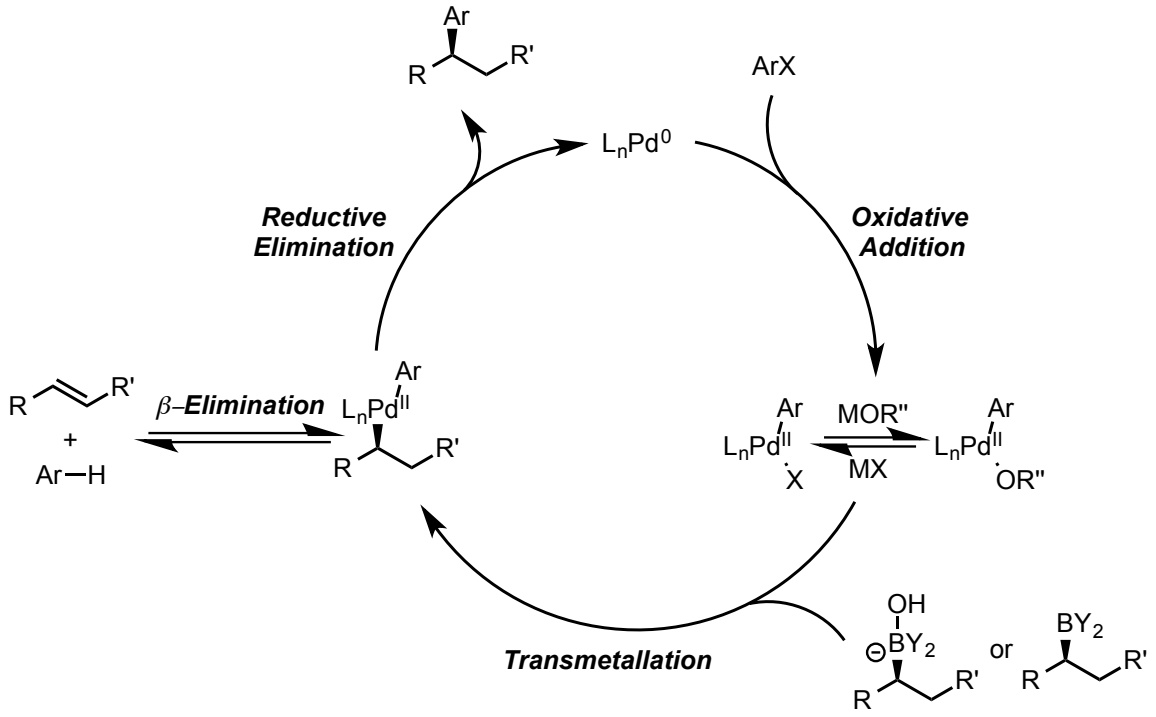
4.1 Introduction

With the ongoing development of novel borylation transformations (Chapter 3), efficient methods for the formation of C-C bonds from these organoboronates, especially in a stereospecific manner, are necessary. Over the past three decades, the Suzuki-Miyaura cross-coupling reaction has been developed as one such method. While the Suzuki reaction has been developed broadly, the cross-coupling of congested alkyl organoboronates, such as secondary and tertiary boronates, has been, until recently, an underdeveloped area of research. These substrates pose a handful of mechanistic challenges (Scheme 4.1). For one, the rate of transmetallation for secondary and, to a larger degree, tertiary organoboronates is much slower then that of a primary organoboronate. For this precise reason, many research groups have utilized organotrifluoroboronates, compounds that undergo a rapid transmetallation without substantial protodeborylation. Secondly, the transmetallation can occur with either retention or inversion of stereochemistry;[1] if both pathways are competitive, the enantiopurity of the product is likely to be diminished. Finally, the intermediate after transmetallation can either undergo a productive reductive elimination, furnishing the coupled product, or β-hydride elimination, creating olefin-containing byproducts. For bulkier organoboronates containing β-hydrides, a slow reductive elimination may instead

[1] For early mechanistic studies relating to stereochemical consideration for the Suzuki-Miyaura cross-coupling reaction, see: (a) Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem.* **1998**, *63*, 458 – 460. (b) Matos, K.; Soderquist, J. *J. Org. Chem.* **1998**, *63*, 461 – 470.

result in a more favorable β-hydride elimination. Recently, in an effort to overcome these difficulties, many research groups have developed reactions, both transition-metal catalyzed and not, for the stereospecific coupling of secondary and tertiary organoboronates.[2]

Scheme 4.1 Catalytic Cycle of the Suzuki-Miyaura Cross-Coupling Reaction



4.2 Early Examples of the Pd-Catalyzed Cross-Couplings of Secondary Organoboronates

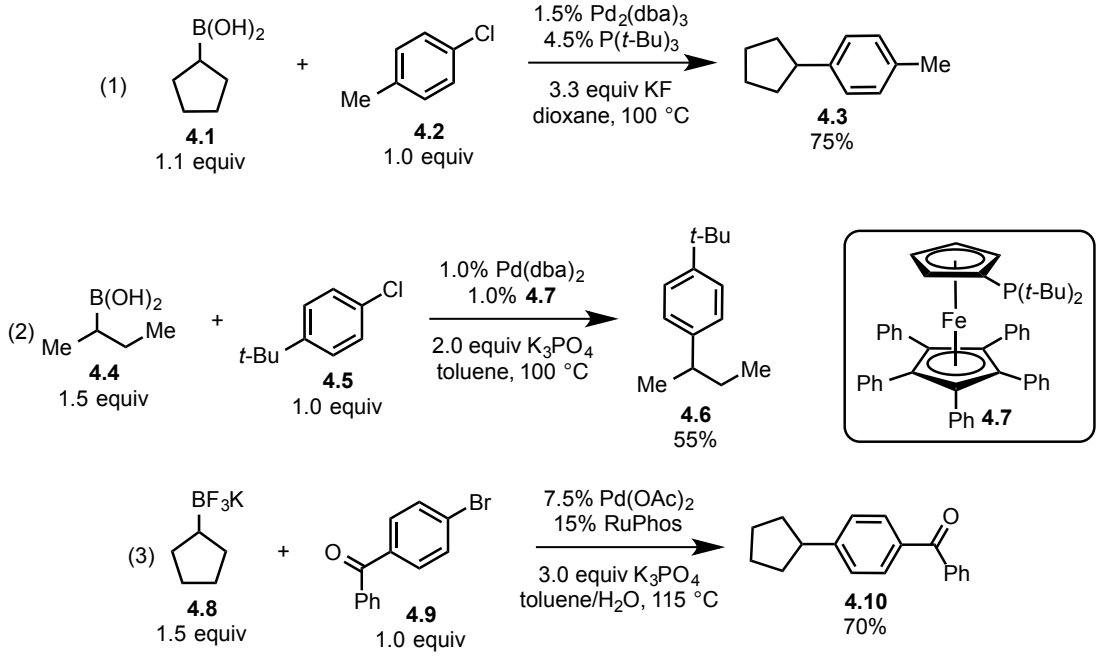
With the development of catalytic Csp^2-Csp^2 Suzuki-Miyaura cross-coupling procedures, some research groups began to investigate whether these methods could be adapted to Csp^2-Csp^3 couplings with secondary alkyl organoboronates. In 2000, Fu and

[2] For an excellent recent review see: Leonori, D.; Aggarwal, V. K. *Angew. Chem., Int. Ed.*, **2015**, *54*, 1082 – 1096.

coworkers[3] reported an isolated example of boronic acid **4.1** undergoing Pd-catalyzed coupling with **4.2** to furnish the coupled product **4.3** in good yield (Scheme 4.2, Eq. 1). Similarly, Hartwig and coworkers[4] disclosed an isolated example of the acyclic boronic acid **4.4** participating in Pd-catalyzed cross-coupling with **4.5** to furnish the coupled product **4.6** in 55% yield (Scheme 4.2, Eq. 2). Interestingly, the ferrocene-derived ligand **4.7** also proved effective for Csp^2-Csp^2, Csp^2-N, and Csp^2-O bond forming cross-coupling reactions. In 2008, Van der Hoogenband and coworkers[5] reported a RuPhos-mediated coupling reaction of secondary organotrifluoroboronates. The coupling of **4.8** and **4.9** generates the coupled product **4.10** in 70% yield (Scheme 4.2, Eq. 3). The cross-coupling of an acyclic organotrifluoroboronate proceeds slower and is hampered by a competitive β-hydride elimination. Later that year, Molander and coworkers[6] published similar conditions for the coupling of secondary organotrifluoroboronates, improving the coupling of acyclic substrates.

[3] Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc.* **2000**, *122*, 4020 – 4028.
[4] Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem.* **2002**, *67*, 5553 – 5566.
[5] van der Hoogenband, A.; Lange, J.; Terpstra, J.; Koch, M.; Visser, G.; Visser, M.; Korstanje, T.; Jastrzebski, J. *Tetrahedron Lett.* **2008**, *49*, 4122 – 4124.
[6] Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc.* **2008**, *130*, 9257 – 9259.

Scheme 4.2 Early Examples of Suzuki-Miyaura Cross-Coupling of Secondary Boronates



4.3 Stereospecific, Pd-Catalyzed Cross-Coupling of Secondary Organoboronates

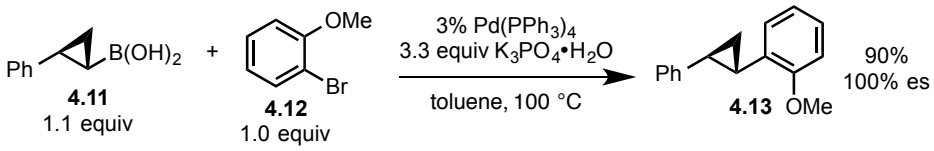
4.3.1 Cyclopropyl Boronates

Early studies of the stereospecific cross-coupling of secondary boronates involved the use of cyclopropyl boronic acids and esters. This privileged set of substrates undergoes a relativity efficient transmetallation due to the carbons of the cyclopropyl group having sp^2-like hybridization. Additionally, these substrates are less likely to undergo β-hydride elimination. In 1998, Deng and coworkers[7] reported the coupling of enantioenriched cyclopropylboronic acids with aryl and acryloyl halides. Using 3% $Pd(PPh_3)_4$, the reaction of **4.11** with **4.12** produced the coupled product **4.13** in 90% yield with complete retention of stereochemistry (Scheme 4.3). The enriched

[7] Zhou, S.-M.; Deng, M.-Z.; Xia, L.-J.; Tang, M.-H. *Angew. Chem., Int. Ed.* **1998**, *37*, 2845 – 2847.

cyclopropylboronic acids were synthesized from a cyclopropanation of the vinyl boronate esters of *N,N,N′,N′*-tetramethyltartaric acid diamide followed by hydrolysis. Notably, the reaction with the auxiliary-containing cyclopropyl boronate ester was sluggish under the reaction conditions. Therefore, a hydrolysis of the auxiliary was necessary.

Scheme 4.3 Stereospecific Cross-Coupling of Cyclopropyl Borinic Acids

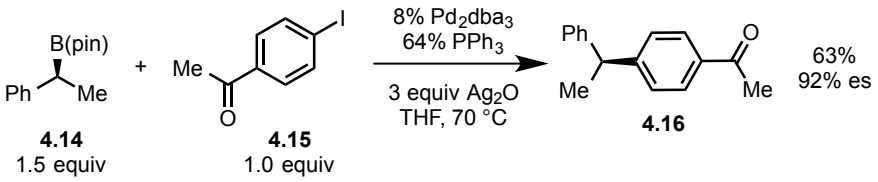


4.3.2 Benzylic Boronates

In addition to cyclopropylborons, secondary benzylic boronates are an active substrate for Suzuki cross-coupling. Crudden and coworkers[8] developed a stereoretentive coupling of benzylic boronate esters and aryl iodides. In the presence of Pd_2dba_3 and PPh_3, arene **4.15** reacts with excess **4.14** to yield the coupled product **4.16** in 63% yield and 92% enantiospecificity (es) (Scheme 4.4). The starting boronates are easily accessed from enantioselective hydroboration of the subsequent styrene.[9] Using similar conditions, the authors have extended the reaction to dibenzylic boronic ester substrates, developing an effective way to synthesize enantioenriched triarylmethanes.[10]

[8] Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024 – 5025.
[9] Crudden, C. M.; Hleba, Y. B; Chen, A. C. *J. Am. Chem. Soc.* **2004**, *126*, 9200 – 9201.
[10] Matthew, S. C.; Glasspoole, B. W.; Eisenberger, P.; Crudden, C. M. *J. Am. Chem. Soc.* **2014**, *136*, 5828 – 5831.

Scheme 4.4 Stereospecific Cross-Coupling of Secondary Benzylic Boronates



4.3.3 Amide-Assisted Cross-Coupling

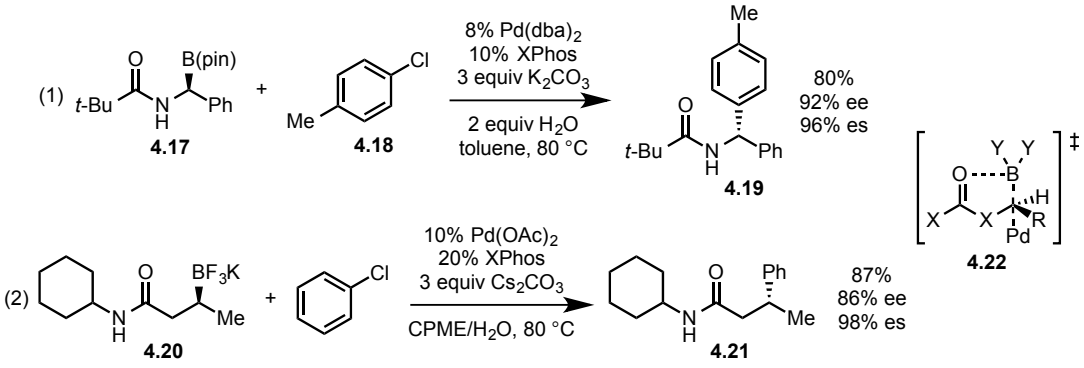
Suginome and coworkers[11] disclosed the first ever Suzuki coupling to occur with stereoinversion. The benzyl boronate **4.17** and **4.18** undergo coupling, furnishing **4.19** in 80% yield and 96% es (Scheme 4.5, 1). The inversion of stereochemistry is rationalized by chelation of the amide carbonyl to the boronate, as shown in transition state **4.22**, allowing for an outer-sphere transmetallation (S_E2 pathway). Fascinatingly, with the addition of Lewis acids (such as Zr(O*i*-Pr)$_4$), the selectivity is overturned and the coupling occurs with retention.[12] It is proposed that the Lewis acid additive disrupts the intramolecular chelation between the carbonyl and boronate, allowing for a retentive coupling, similar to the reaction reported by Crudden (Scheme 4.4).

Using a similar β-carbonyl activating strategy, Molander and coworkers[13] reported the first stereospecific cross-coupling of secondary, nonbenzylic organotrifluoroboronates. The coupling of **4.20** and chlorobenzene in cyclopentyl methyl ether (CPME) and water proceeds with excellent enantiospecificity, yielding the inverted product **4.21** in 87% yield (Scheme 4.5, 2). Unlike the substrates studied by Suginome, **4.20** is vulnerable to β-hydride elimination. However, it is proposed that the carbonyl

[11] Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191 – 13193.
[12] Awano, T.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2011**, *133*, 20738 – 20741.
[13] Sandrock, D. L.; Jean-Gérard, L.; Chen, C.; Dreher, S. D.; Molander, G. A. *J. Am. Chem. Soc*. **2010**, *132*, 17108 – 17110.

stabilizes the alkyl Pd complex after transmetallation, preventing it from adopting conformations necessary for β-hydride elimination (*syn*-periplanar to the β-hydrogen atoms).

Scheme 4.5 Amide-Assisted Stereospecific Cross-Coupling of Secondary Boronates

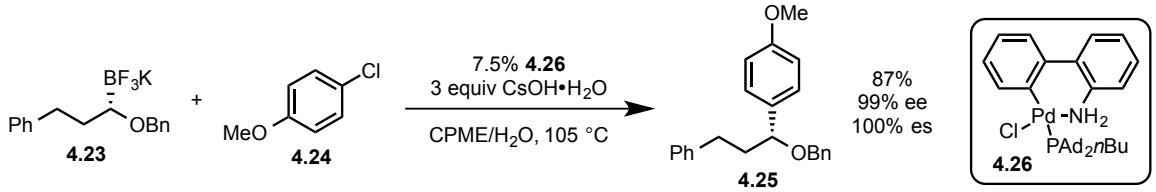


4.3.4 α-Alkoxy Boronates

In 2012, Molander and coworkers[14] published the cross-coupling of α-alkoxy organotrifluoroboronates with a variety of aryl chlorides. The starting organotrifluoroboronates were prepared in high enantioselectivity through a Matteson homologation of the primary (*S*,*S*)-dicyclohexylethanediol (DICHED) boronate. Using precatalyst **4.26**, the coupling of **4.23** and **4.24** occurs with complete stereospecificity, affording **4.25** with retention of configuration (Scheme 4.6). It is proposed that β-hydride elimination is circumvented due to a benzyl stabilization of the alkyl Pd complex after transmetallation.

[14] Molander, G. A.; Wisniewski, S. R. *J. Am. Chem. Soc.* **2012**, *134*, 16856 – 16868.

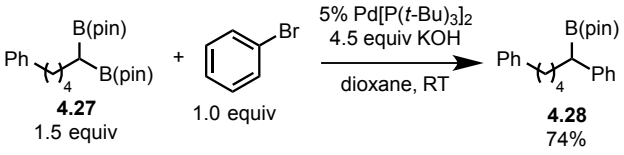
Scheme 4.6 Stereospecific Cross-Coupling of Secondary α-Alkoxy Organotrifluoroborates.



4.3.5 1,1-Bis(boronates)

Shibata and coworkers[15] disclosed the ability of 1,1-bis(boronates) to partake in cross-coupling with aryl bromides at ambient temperature. The coupling of **4.27** and bromobenzene furnishes the secondary boronate **4.28** in 74% yield (Scheme 4.7). It is suggested that with a second boronate present, the amount of anionic borate species is increased, speeding up transmetallation. Additionally, the empty p orbital stabilizes the alkyl-Pd σ-bond, mitigating the likelihood of β-hydride elimination.

Scheme 4.7 Cross-Coupling of 1,1-Bis(boronates).

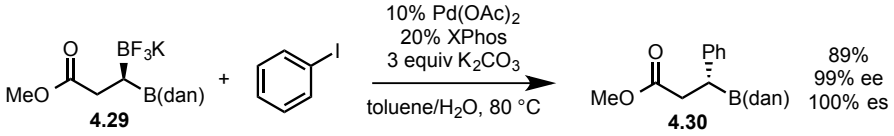


In an effort to expand on the use of 1,1-diborons as nucleophiles, Hall and coworkers[16] reported the cross-coupling of chiral 3,3-diboronyl carboxyesters with aryl and vinyl bromides. These differentiated diboryl species are synthesized from the asymmetric conjugate borylation of 1,8-diaminonaphthalenyl boronylacrylates using

[15] Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033 – 11035.
[16] Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nature Chem.* **2011**, *3*, 894 – 899.

$B_2(pin)_2$. The coupling of **4.29** and iodobenzene yields the product **4.30** with complete stereoinversion (Scheme 4.8). Similar to the observations of Suginome and Molander, the inversion of stereochemistry is due to intramolecular chelation between the ester carbonyl oxygen and the boron atom, allowing for an outer-sphere transmetallation.

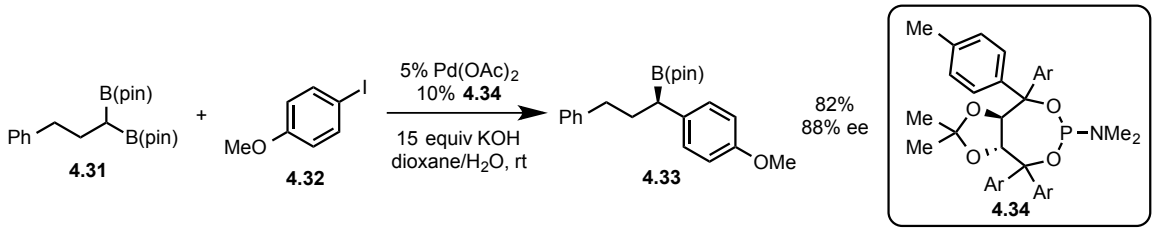
Scheme 4.8 Ester-Assisted Cross-Coupling of 1,1-Bis(boronates).



Chiral organoboronates can be attained through the enantioselective cross-coupling of achiral 1,1-bis(boronates). Morken and coworkers[17] reported the coupling of 1,1-bis(pinacolboronate) esters with aryl halides using phosphoramidite ligand **4.34**. The cross-coupling of **4.31** and **4.32** affords **4.33** in 82% yield and 88% ee (Scheme 4.9). The scope of electrophiles was extended to vinyl halides using a Josiphos-type ligand.[18] Interestingly, through isotope-labeling experiments, the transmetallation was shown to occur with inversion of stereochemistry. It is possible that the transmetallation could occur through a desymmetrization of the 1,1-bis(boronates) or a dynamic kinetic resolution of the product of a mono-hydrolysis.

[17] Sun, C.; Potter, B.; Morken, J. P. *J Am. Chem. Soc.* **2014**, *136*, 17918 – 17921.
[18] Potter, B.; Szymaniak, A. A.; Edelstein, E. K.; Morken, J. P. *J. Am. Chem. Soc.* **2014**, *136*, 17918 – 17921.

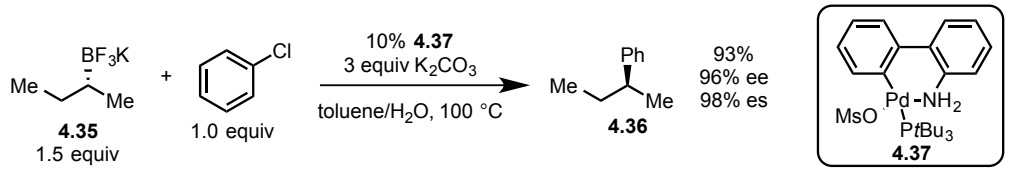
Scheme 4.9 Enantioselective Cross-Coupling of Achiral 1,1-Bis(boronates).



4.3.6 Unactivated Secondary Alkyl Boronates

In 2014, Biscoe and coworkers[19] published the first stereospecific cross-coupling of unactivated secondary alkyl boronates. Using precatalyst **4.37**, the reaction of chlorobenzene with excess chiral organotrifluoroboronate **4.35** yielded the coupled product **4.36** in excellent yield and stereospecificity (Scheme 4.10). **4.35** was synthesized using Brown's chiral auxiliary approach[20] in a 25% yield from (+)-α-pinene. The authors report that the reaction proceeds with inversion of stereochemistry. To rationalize this observation, the authors draw parallels between the transmetallation of unactivated secondary alkyl boronates and the invertive electrophilic substitution reaction using secondary boranes.[21]

Scheme 4.10 Stereospecific Cross-Coupling of Unactivated Secondary Boronates



[19] Li, L.; Zhao, S.; Joshi-Pangu, A.; Diane, M.; Biscoe, M. R. *J. Am. Chem. Soc.* **2014**, *136*, 14027 – 14030.
[20] Joshi N. N.; Pyun, C.; Mahindroo, V.; Singaram, B.; Brown, H. C. *J. Org. Chem.* **1992**, *57*, 504 – 511.
[21] (a) Kabalka, G. W.; Gooch, E. E. *J. Org. Chem.* **1980**, *45*, 3578 – 3580. (b) Larouche-Gauthier, R.; Elford, T. G.; Aggarwal, V. K. *J. Am. Soc. Chem.* **2011**, *133*, 16794 – 16797.

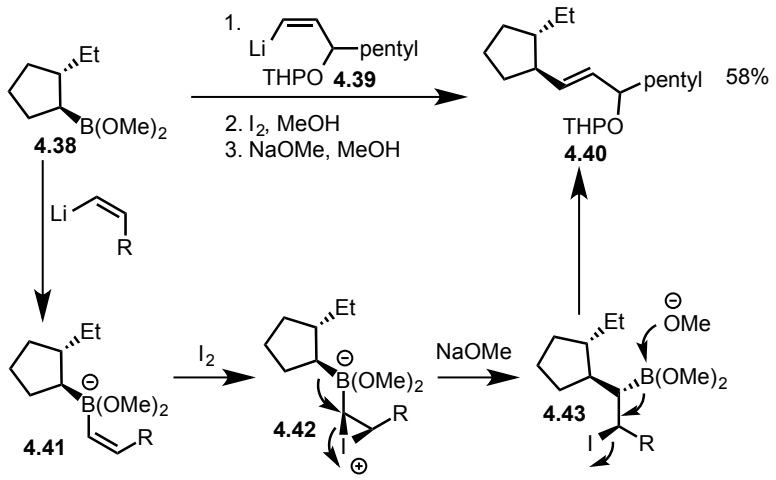
4.4 Transition-Metal Free Couplings of Secondary and Tertiary Boronates

Although the Suzuki-Miyaura cross-coupling of secondary boronates has advanced greatly in the last decade, the reaction is not general and, in many cases, requires excess chiral boronate. For these reasons, some research groups have developed transition-metal free couplings. These methods capitalize on the ability of organoboronates to form characterizable tetracoordinate complexes and to undergo stereoretentive 1,2-migrations.

Expanding on work first reported by Zweifel[22], Evans and coworkers[23] developed the stereospecific coupling of boronic esters and vinyl lithiums, also known as the Zweifel olefination. Subjection of **4.38** to vinyl lithium **4.39**, followed by iodine and methoxide base, furnishes **4.40** in 58% yield (Scheme 4.11). **4.38** and **4.39** are presumed to form *ate* complex **4.41**, which, in the presence of I_2, forms iodonium ion **4.42**. This intermediate undergoes a 1,2-migration followed by base-catalyzed elimination to afford olefin product **4.40**. The isolation of the *trans* product is evidence of an *anti* elimination of the alkyl iodide intermediate **4.43**.

[22] Zweifel, G.; Arzoumanian, H.; Whitney, C. C. *J. Am. Chem. Soc.* **1967**, *89*, 3652 – 3653.
[23] Evans, D. A.; Crawford, T. C.; Thomas, R. C.; Walker, J. A. *J. Org. Chem.* **1976**, *41*, 3947 – 3953.

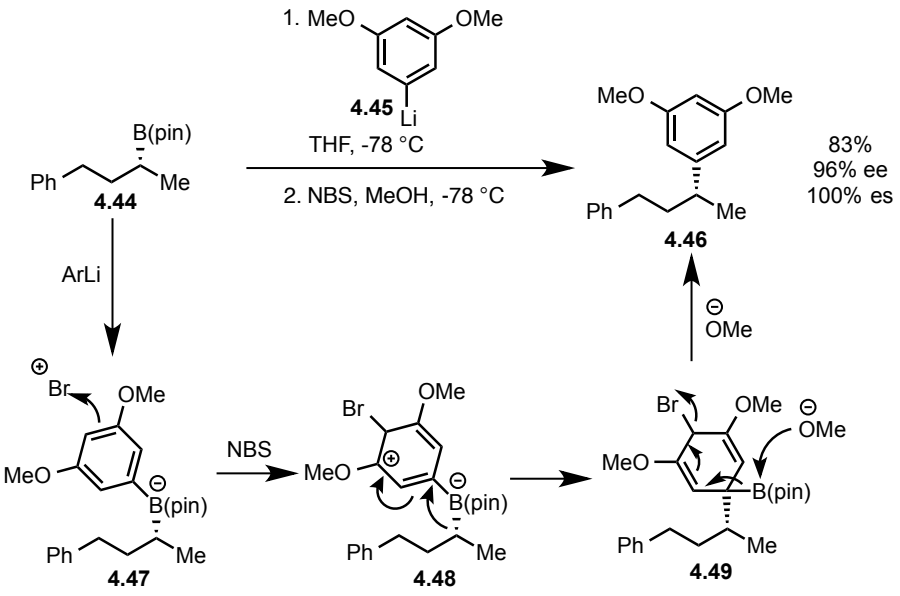
Scheme 4.11 Zweifel Olefination



This idea of electrophile-mediated 1,2-migration has been expanded upon by Aggarwal and coworkers[24] through the coupling of secondary and tertiary chiral boronates with lithiated arenes. Reaction of **4.44** and **4.45**, followed by addition of *N*-bromosuccinimide, affords **4.46** in 83% yield and 96% ee with complete retention of stereochemistry (Scheme 4.12). The reaction mechanism features a temporary bromination of the *ate* complex **4.47**, to furnish the zwitterionic intermediate **4.48**. A 1,2-migration followed by an elimination results in the stereodefined product **4.46**. Although a great complement to Suzuki coupling methodologies, the reaction scope for arenes is limited. Of course, like any aromatic electrophilic substitution reaction, the arenes used must be electron-rich. Furthermore, arenes containing electron-donating groups at the *ortho* and *para* positions are not tolerated.

[24] Bonet, A.; Odachowski, M.; Leonori, D.; Essafi, S.; Aggarwal, V. K. *Nature Chem.* **2014**, *6*, 584 – 589.

Scheme 4.12 Transition-Metal Free Couplings of Secondary and Tertiary Boronates



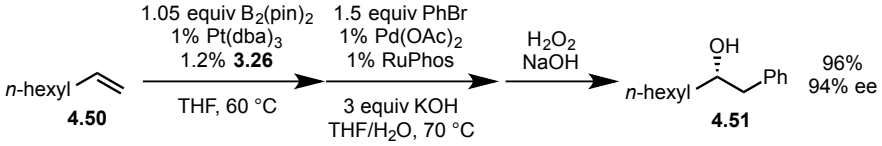
4.5 Borylation/Cross-Coupling Cascades

The combination of borylation and cross-coupling methods has been an effective way of generating molecular complexity from simple starting materials.[25] Morken and coworkers[26] developed a diboration/cross-coupling (DCC) strategy for the synthesis of a variety of chiral molecules from simple terminal olefins. **4.50** is subjected to Pt-catalyzed diboration (Section 3.3), followed by a regioselective cross-coupling of the primary boronate and oxidation of the secondary boronate to afford **4.51** in excellent yield and enantioselectivity (Scheme 4.13). In addition to aryl halides, vinyl chlorides participate in the coupling reaction, yielding valuable chiral homoallylic boronates. Intriguingly, these cross-coupling conditions are specific for 1,2-bis(boronates), with

[25] Examples of one-pot hydroboration/cross-coupling strategies: (a) Collier, P.; Campbell, A.; Patel, I.; Raynham, T.; Taylor, R. *J. Org. Chem.* **2002**, *67*, 1802 – 1815. (b) Konno, T; Chae, J; Tanaka, T; Ishihara, T. *Chem. Commun.* **2004**, 690 – 691.
[26] Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. *Nature* **2014**, *505*, 386 – 390.

simple primary boronates not undergoing coupling. This enhanced reactivity is attributed to the neighboring boronate possibly coordinating to one of the pinacol oxygen atoms, enhancing the Lewis acidity of the primary boronate. To demonstrate the applicability of the DCC strategy, the secondary boronate products were subjected to oxidation, amination and homologation conditions to synthesize a variety of useful enantioenriched compounds.

Scheme 4.13 Diboration/Cross-Coupling (DCC) Strategy



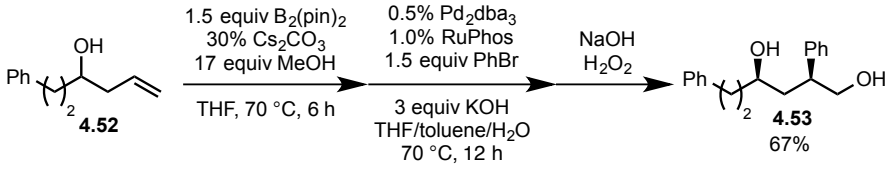
4.6 Directed Diboration/Cross-Coupling Cascade[27]

Inspired by the efficiency of the DCC strategy, we began to investigate whether directed diboration methodology (Chapter 3) could be combined with a cross-coupling transformation in a similar fashion. The directed diboration of homoallylic alcohol **4.52** afforded the expected 1,2-bis(boronate) after solvent removal. The crude vicinal boronate was subjected to a sequential cross-coupling with bromobenzene and subsequent oxidation. Surprisingly, this sequence afforded the 1,4-diol product **4.53** in 67% yield (Scheme 4.14). Most notably, the regiochemical outcome of the cross-coupling was opposite to that of the DCC strategy. This was unforeseen due to the secondary boronate having inherently less reactivity than its primary counterpart.

[27] Blaisdell, T. P.; Morken, J. P. *J. Am. Chem. Soc.* **2015**, *accepted.* (DOI: 10.1021/jacs.5b05477)

Furthermore, the transmetallation appeared to have occurred with retention of configuration. The most noticeable difference between this coupling and the DCC coupling is the presence of a hydroxyl group. As discussed in Section 4.3.3, the presence of a Lewis basic group β to an organoboronate can facilitate cross-coupling. However, these cross-couplings almost always occur with inversion of stereochemistry. Therefore, it is believed that this unusual reactivity is independent of the internal chelation between hydroxyl and boronate. Instead, it is possible that, under basic conditions, the alkoxide of the substrate covalently directs the Pd-catalyst during transmetallation. A strong association between substrate and catalyst could possibly explain the regiochemical outcome, with the catalyst being delivered in close proximity to the secondary boronate.

Scheme 4.14 Directed Diboration/Cross-Coupling of **4.52**



4.7 Examples of Directed Cross-Coupling

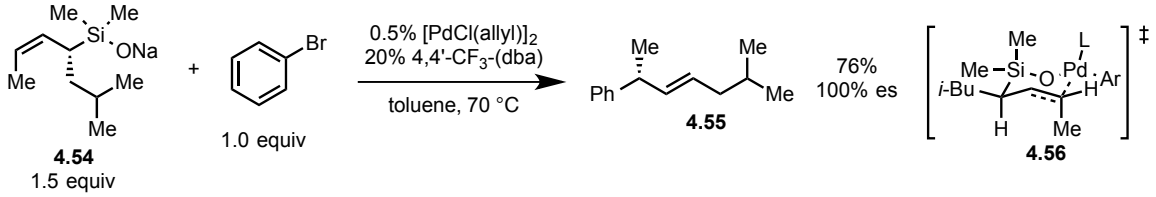
Although common for C-H activation methodologies, the use of substrate directing groups to control the reactivity and selectivity of cross-coupling reactions is not as common.[28] In one tangentially related process, Denmark and coworkers[29] reported the

[28] Olefin directed Negishi cross-coupling: Nielsen, D. K.; Huang, C.-Y.; Doyle, A. G. *J. Am. Chem. Soc.* **2013**, *135*, 13605 – 13609.

[29] (a) Denmark, S. E.; Werner, N. S. *J. Am. Chem. Soc.* **2008**, *130*, 16382 – 16393. (b) Denmark, S. E.; Werner, N. S. *J. Am. Chem. Soc.* **2010**, *132*, 3612 – 3620. Related work: (c) Tymonko, S. A.; Smith, R. C.; Ambrosi, A.; Ober, M. H.; Wang, H.; Denmark, S. E.

coupling of allylic silanolates and aryl bromides. Using a Pd catalyst, **4.54** and bromobenzene react to afford **4.55** in 76% yield with complete enantiospecificity (Scheme 4.15). The oxygen atom of the silanolate is presumed to bind to Pd through halide displacement. This substrate/catalyst species undergoes a chair-like *syn* S_E' transmetallation **4.56**, yielding an alkyl aryl Pd^{II} species which, upon reductive elimination, yields **4.55**.

Scheme 4.15 Cross-Coupling of Allylic Silanolates and Aryl Bromides

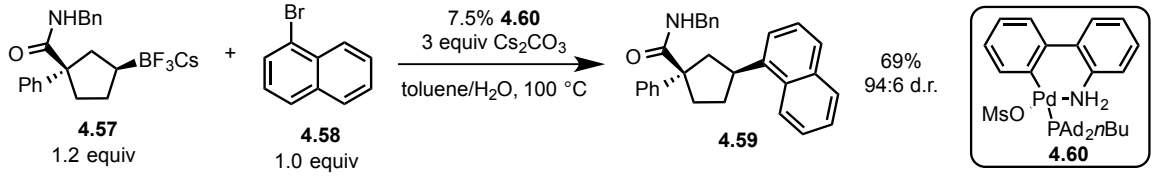


Recently, Takacs and coworkers[30] have disclosed the amide-directed cross-coupling of organotrifluoroboronates. The coupling of **4.57** and **4.58** furnishes **4.59** in 69% yield and 94:6 diastereoselectivity (Scheme 4.16). However, what separates this methodology from the work of Suginome and Molander (Scheme 4.5) is that the cross-coupling occurs with retention of stereochemistry. As previously mentioned, if the oxygen atom of the carbonyl chelates to the boronate, an outer-sphere transmetallation would be expected, affording the product with stereoinversion. Although the mechanism is unclear, it is possible that the transmetallation is directed by the covalent association of the Pd catalyst with the nitrogen atom of amide.

J. Am. Chem Soc. **2015**, *137*, 6200 – 6218. (d) Tymonko, S. A.; Smith, R. C.; Ambrosi, A.; Denmark, S. E. *J. Am. Chem. Soc.* **2015**, *137*, 6192 – 6199.

[30] Hoang, G. L.; Yang, Z.-D.; Smith, S. M.; Pal, R.; Miska, J. L.; Pérez, D., E.; Pelter, L. S. W.; Zeng, X. C.; Takacs, J. M. *Org. Lett.* **2015**, *17*, 940 – 943.

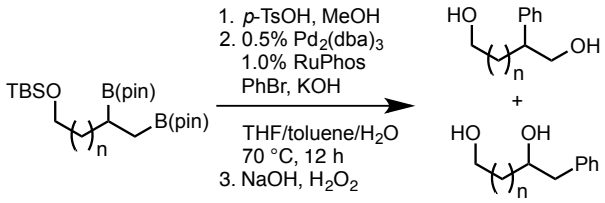
Scheme 4.16 Amide-Directed Cross-Coupling of Organotrifluoroboronates

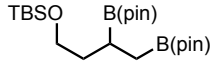
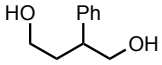
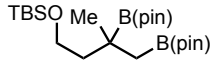
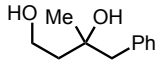
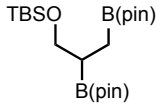
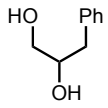
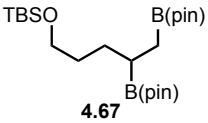
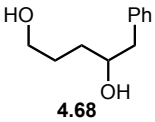


4.8 Further Exploration of Directing Effect

In an effort to further investigate the effect of a free alcohol group on the cross-coupling of organoboronates, a series of hydroxyl-containing boronates were synthesized. Due to the instability of the alcohol-containing boronates to silica chromatography, borylated alkyl silyl ethers were synthesized and subjected to a sequential TBS deprotection, Suzuki coupling and oxidation strategy (Table 4.1). Through this reaction sequence, **4.61** afforded the 1,4-diol **4.62** in 72% yield (Table 4.1, Entry 1). For more sterically congested boronate **4.63**, the coupling occurred at the primary boronate, yielding **4.64** in poor yield (Table 4.1, Entry 2). This observation was in agreement with the regioselectivity observed during the synthesis of **3.113** (Scheme 3.20). With the directing group at the α-position (**4.65**) or the γ-position (**4.67**) with respect to the 1,2-bis(boronate), the secondary boronate remained unreacted (Table 4.1, Entries 3-4). Interestingly, when compared to **4.67**, the amplified ability of **4.65** to undergo a primary-selective coupling was justified by the presence of an alcohol group at the β-position.

Table 4.1 Hydroxyl-Directed Cross-Coupling of 1,2-Bis(boronates)

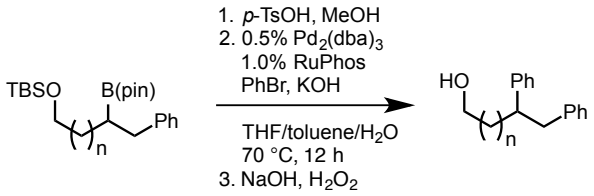


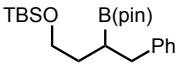
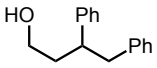
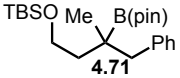
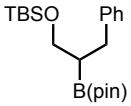
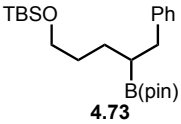
entry	substrate	major product	yield[a]
1	 **4.61**	 **4.62**	72%
2	 **4.63**	 **4.64**	32%
3	 **4.65**	 **4.66**	77%
4	 **4.67**	 **4.68**	29%

[a]Yield determined by ^{1}H NMR versus 1,3,5-trimethoxybenzene as an internal standard.

Due to the neighboring effect observed in the DCC methodology, we began to investigate the generality of the directing effect by examining the reactivity of boronate substrates outside of the 1,2-diboryl motif (Table 4.2). Gratifyingly, **4.69** underwent the deprotection/coupling sequence to yield **4.70** in 70% yield (Table 4.2, Entry 1). Again, the tertiary boronate **4.71** remained unreactive to cross-coupling conditions (Table 4.2, Entry 2). Similar to the related 1,2-bis(boronates), **4.72** and **4.73** did not undergo cross-coupling as well, emphasizing the necessity of the hydroxyl group to be at the β-position with respect to the organoboronate (Table 4.2, Entries 3-4).

Table 4.2 Hydroxyl-Directed Cross-Coupling of Secondary Boronates



entry	substrate	major product	yield[a]
1	 **4.69**	 **4.70**	70%
2	 **4.71**	no reaction	-
3	 **4.72**	no reaction	-
4	 **4.73**	no reaction	-

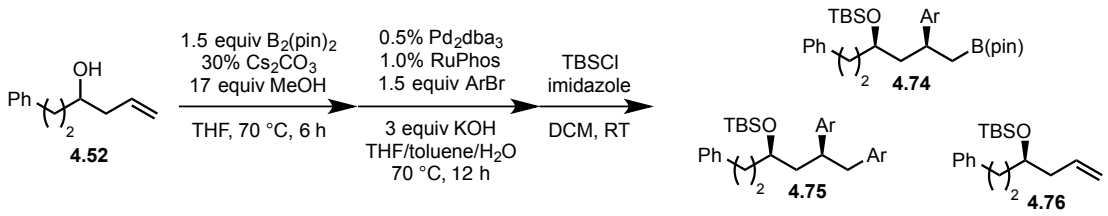
[a]Yield determined by ^{1}H NMR versus 1,3,5-trimethoxybenzene as an internal standard.

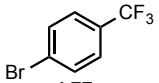
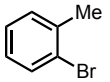
4.9 Reaction Optimization

As demonstrated above, a combination of toluene, tetrahydrofuran (1:1) and water as the solvent, was found effective for the cross-coupling reaction. Further investigation of this observation revealed that the solvent used was a critical feature to the success of the reaction. This observation was most noticeable when cross-coupling with sterically bulky and electron-deficient arenes (Table 4.3). For example, when homoallylic alcohol **4.52** was subjected to a diboration/coupling/silyl protection sequence with aryl bromides **4.77** and **4.78** in THF as the organic solvent, the coupling proceeded with full consumption of the 1,2-bis(boronate), but afforded substantial amounts of **4.75** and **4.76** (Table 4.3, Entries 1 and 5). **4.75** is assumed to originated from a second cross-coupling of product **4.74**. **4.76** is believed to arrive from a β-deborylation event after

transmetallation occurs. It is likely that **4.76** does not arrive from the silylation of unreacted **4.52** due to the diboration proceeding with full conversion of olefin. Noticeably, when using toluene as the reaction solvent, the amount of **4.75** surged while the β-deborylation product **4.76** was nonexistent (Table 4.3, Entries 2 and 6). In both cases above, when a 1:1 mixture of THF and toluene was used, **4.74** became the major product (Table 4.3, Entries 3 and 7). In the case of **4.77**, the amount of bis-coupling observed was diminished by lowering the amount of **4.77** added (1.5 equivalents to 1.1 equivalents) (Table 4.3, Entry 4). In the case of **4.78**, a considerable amount of **4.76** was observed, whereas **4.75** was undetected (Table 4.3, Entry 7).

Table 4.3 Effect of Solvent on Reaction Outcome



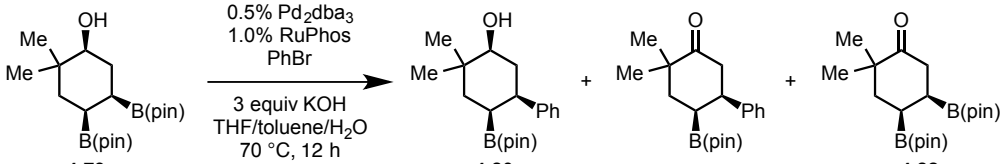
entry	ArX	solvent	conversion[a]	ratio of products[a] **(4.74 : 4.75 : 4.76)**
1	 **4.77**	THF	>95%	56:20:24
2		Toluene	79%	42:58:–
3		THF/Toluene (1:1)	77%	78:22:–
4[b]		THF/Toluene (1:1)	84%	94:6:–
5	 **4.78**	THF	>95%	73:8:19
6		Toluene	95%	24:76:–
7		THF/Toluene (1:1)	>95%	81:–:19

[a] Determined by ^{1}H NMR. [b] Used 1.1 equivalents of ArBr

In addition to bis-coupling and β-deborylation byproducts, some substrates participated in Pd-catalyzed oxidation of the hydroxyl group. As previously

demonstrated[31], aryl halides can act as terminal oxidants for the Pd-catalyzed oxidations of alcohols. One such substrate that was prone to oxidation was the diboronate **4.79**. As mentioned in Chapter 3, **4.79** can be isolated with no need for oxidation or protection of the alcohol, making it an ideal substrate to study the cross-coupling reaction. Using 1.05 equivalents of bromobenzene, the coupling of **4.79** afforded a mixture of **4.80**, **4.81**, and **4.82** (Scheme 4.17). With two equivalents of bromobenzene added, full conversion of **4.79** was attained, displaying a 60:40 ratio of **4.80** to **4.81**. From the product mixtures of both experiments, it was apparent that the cross-coupling reaction outcompetes the oxidation reaction. However, under these conditions, **4.80** was prone to undergo oxidation in the presence of excess aryl bromide. Although seemingly unavoidable during the cross-coupling of **4.79**, this oxidation reaction was undetected for the majority of substrates screened.

Scheme 4.17 Pd-Catalyzed Oxidation



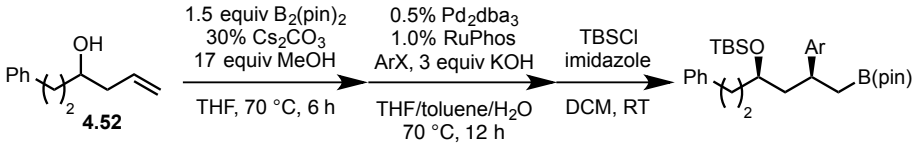
	4.80	4.81	4.82
1.05 equiv PhBr (47% conversion):	13%	25%	9%
2.0 equiv PhBr (>98% conversion):	40%	60%	-

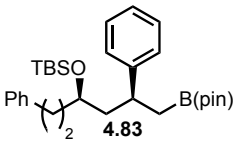
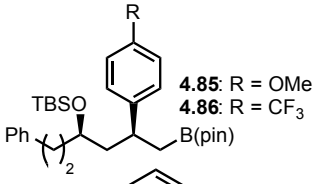
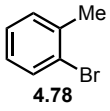
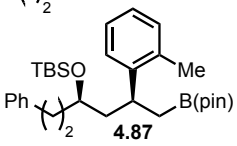
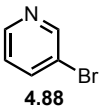
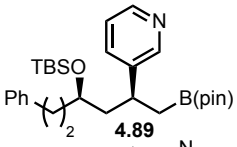
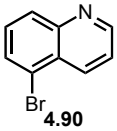
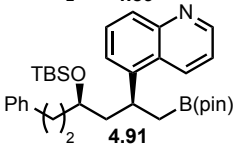
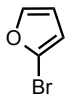
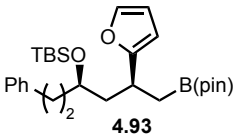
[31] (a) Tamaru, Y.; Yamamoto, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* **1979**, *20*, 1401 – 1404. (b) Tamaru, Y.; Yamada, Y.; Inoue, K.; Yamamoto, Y.; Yoshida, Z. *J. Org. Chem.* **1983**, *48*, 1286 – 1292. (c) Bei, X.; Hagemeyer, A.; Volpe, A.; Saxton, R.; Turner, H.; Guram, A. *J. Org. Chem.* **2004**, *69*, 8626 – 8633. For a review, see: Muzart, J. *Tetrahedron* **2003**, *59*, 5789 – 5816.

4.10 Substrate Scope

Due to the ability of the directed diboration and directed cross-coupling methodologies to be merged together, the two transformations were investigated as a reaction cascade starting from homoallylic alcohols. The products of this sequence were subjected to silylation or acylation conditions prior to isolation. This diboration/cross-coupling/protection sequence was performed on **4.52**, in an effort to investigate what electrophiles participated in the coupling reaction (Table 4.4). Aryl bromides, iodides and triflates all underwent cross-coupling to furnish **4.83** after TBS protection (Table 4.4, Entries 1-3). Aryl chlorides and tosylates did not participate in the reaction. Both electron-rich and electron-poor arenes furnished the corresponding products in good isolated yields over the three-step sequence (Table 4.4, Entries 4-5). The sterically encumbered arene **4.78** underwent the coupling efficiently, forming **4.87** in 72% yield (Table 4.4, Entry 6). The coupling of heteroaromatic coupling partners **4.88**, **4.90**, and **4.92** furnished products **4.89**, **4.91**, and **4.93** in moderate yield (Table 4.4, Entries 7-9).

Table 4.4 Scope of Hydroxyl-Directed Cross-Coupling: Aryl Halides



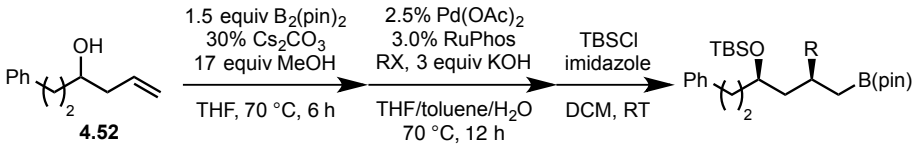
entry	ArX	product[a]	yield[b]
1	X = Br		85%
2	X = I		70%
3	X = OTf		73%
		4.83	
4	**4.84**: R = OMe		77%
5[c]	**4.77**: R = CF_3		78%
		4.85: R = OMe **4.86**: R = CF_3	
6	 **4.78**	 **4.87**	72%
7	 **4.88**	 **4.89**	52%
8	 **4.90**	 **4.91**	57%
9	 **4.92**	 **4.93**	51%

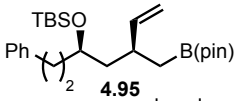
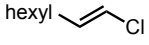
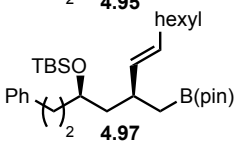
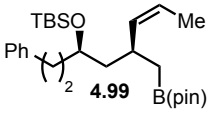
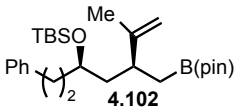
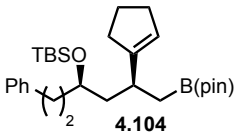
[a] Product observed in >20:1 diastereoselectivity. [b] Isolated yields after purification
[c] 1.1 equivalents of aryl bromide used

In an effort to expand the scope of tolerated coupling partners, the use of vinyl halides as coupling partners was studied. **4.94**, prepared *in situ* from 1,2-dichloroethane, successfully underwent coupling with the diboronate of **4.52** to furnish **4.95** in 75% yield (Table 4.5, Entry 1). Vinyl chlorides **4.96** and **4.98** both participated in the coupling reaction, yielding products **4.97** and **4.99**, respectively, in good yields over the three

reactions (Table 4.5, Entries 2-3). Couplings with **4.100**, **4.101**, and **4.103** were also achieved, albeit requiring higher catalyst loadings (Table 4.5, Entries 4-6).

Table 4.5 Scope of Hydroxyl-Directed Cross-Coupling: Vinyl Halides



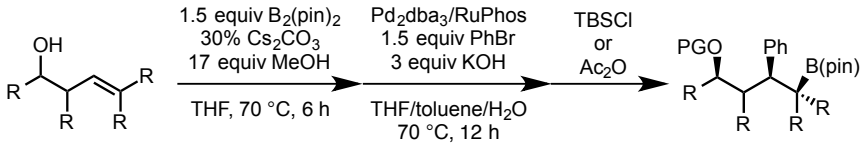
entry	RX	product [a]	yield [b]
1[c]	 **4.94**	 **4.95**	75%
2	 **4.96**	 **4.97**	54%
3	 **4.98**	 **4.99**	63%
4[d] 5[d]	 **4.100**: X = Cl **4.101**: X = Br	 **4.102**	70% 64%
6[d]	 **4.103**	 **4.104**	51%

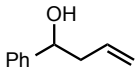
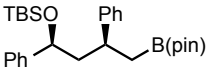
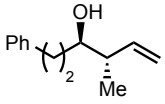
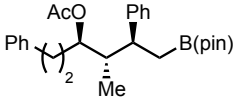
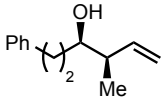
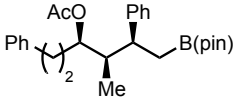
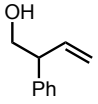
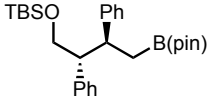
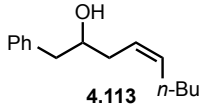
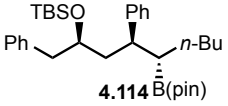
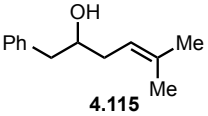
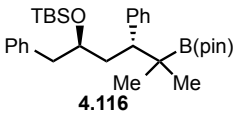
[a] Product observed in >20:1 diastereoselectivity. [b] Isolated yields after purification
[c] XX formed *in situ* from 1,2-dichloroethane (3 equiv) and KO*t*-Bu (6 equiv)
[d] Run with 10% $Pd(OAc)_2$ and 12% RuPhos

Next, the cross-coupling of bromobenzene and a variety of different 1,2-bis(boronates) were examined (Table 4.6). Phenyl-substituted olefin **4.105** underwent diboration/cross-coupling/silylation to yield **4.106** in 68% yield (Table 4.6, Entry 1). Substituted homoallylic alcohols **4.107**, **4.109**, and **4.111** all participated in the reaction sequence, producing **4.108**, **4.110**, and **4.112**, respectively, in good yields (Table 4.6, Entries 2-4). Internal diboronates, derived from olefins **4.113** and **4.115**, underwent

cross-coupling, affording **4.114** and **4.116**, respectively, in moderate yields (Table 4.6, Entries 5-6). The diastereoselectivities resembled the selectivities observed in Tables 3.3 and 3.4.

Table 4.6 Scope of Hydroxyl-Directed Cross-Coupling: 1,2-Bis(boronates)



entry	substrate	product	yield [a]	dr [b]
1	 **4.105**	 **4.106**	68%	>20:1
2	 **4.107**	 **4.108**	73%	>20:1
3	 **4.109**	 **4.110**	76%	4.2:1
4	 **4.111**	 **4.112**	53%	13:1
5	 **4.113**	 **4.114**	63%	7.3:1
6	 **4.115**	 **4.116**	46%	1.6:1

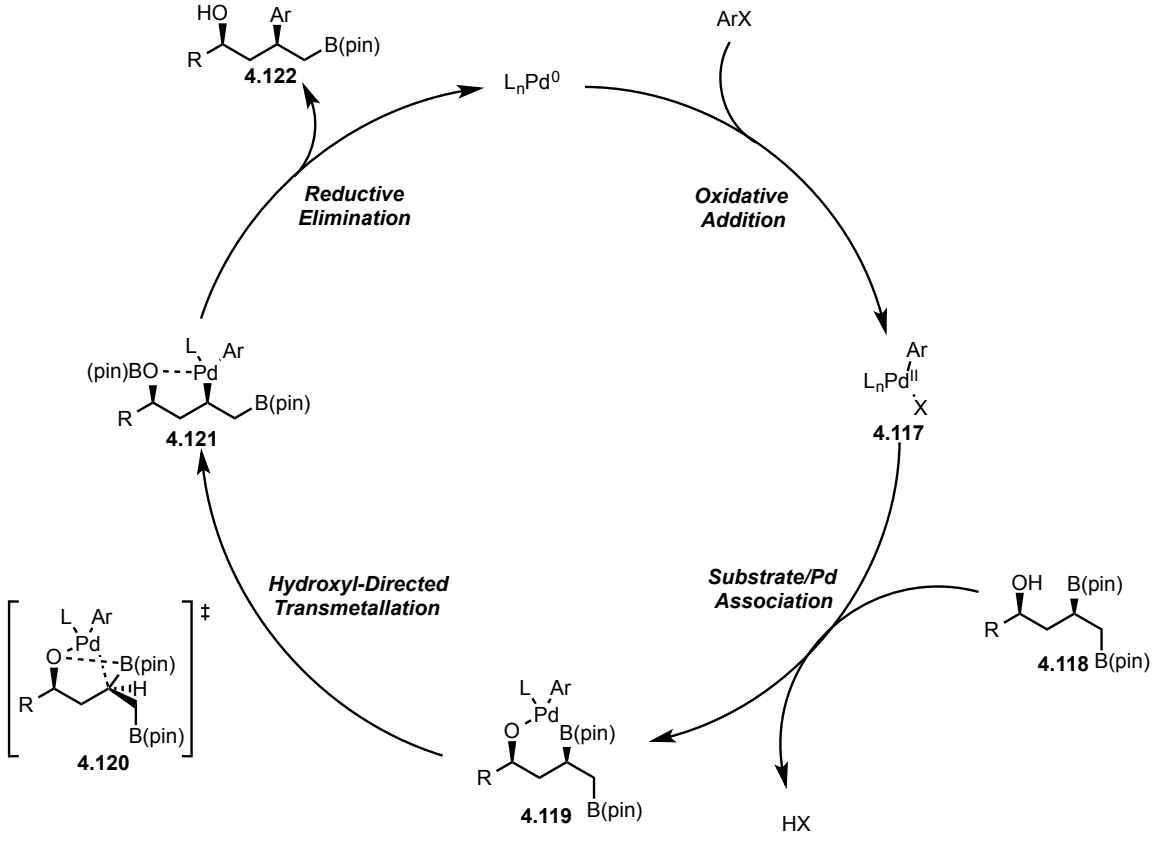
[a] Isolated yields after purification. [b] Determined by ^{1}H NMR

4.11 Proposed Catalytic Cycle

The totality of the experiments described above suggests that the regio- and stereoselectivity of a Suzuki cross-coupling reaction can be controlled by the presence of

a hydroxyl group (Scheme 4.18). This control suggests an association between substrate and catalyst, similar to that shown in **4.119**. This species can be attained through a halide displacement from complex **4.117** by **4.118**. It is proposed that **4.119** undergoes a hydroxyl-directed transmetallation perhaps via **4.120** affording borate **4.121**. Reductive elimination and dissociation of the borate (presumably with KOH), furnishes the coupled product **4.122**.

Scheme 4.18 Hydroxyl-Directed Cross-Coupling Catalytic Cycle



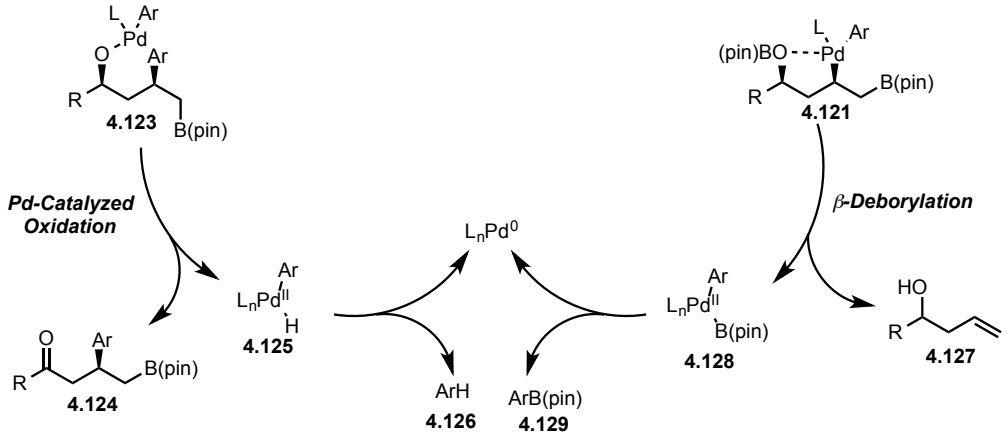
As described in Section 4.9, the cross-coupling of hydroxyl-containing substrates can be hampered by an oxidation reaction of the free alcohol to the ketone. This oxidation reaction is suspected to occur through the formation of Pd-product complex **4.123** (Scheme 4.19). As previously observed, the oxidation of the product is much more

likely to occur than the oxidation of the uncoupled starting diboronate. Unable to participate in a directed cross-coupling reaction, **4.123** is vulnerable to β-hydride elimination yielding ketone **4.124** and **4.125**, which can undergo reductive elimination to yield Pd^0 and **4.126**.

Unlike this infrequent oxidation reaction, the presence of β-deborylation was detected in most substrates classes, especially for electron-poor electrophiles as well as sterically hindered electrophiles and boronates. β-deborylation is believed to occur from Pd^{II} complex **4.121**, yielding homoallylic alcohol **4.127** and **4.128** (Scheme 4.19). **4.128** can undergo reductive elimination to afford Pd^0 and aryl boronate **4.129**.[32] The intramolecular chelation of Pd by the borate is believed to help mitigate β-deborylation by preventing the ability of **4.121** to adapt a conformation associated with elimination (*syn*-periplanar to the primary boronate). This could explain why switching solvents from THF to toluene helps to alleviate β-deborylation. THF diminishes this intramolecular chelation by competing for coordination sites on the palladium atom. Conversely, non-polar solvents, such as toluene, do not coordinate to the palladium atom, amplifying the chelation of the borate. Additionally, coupling partners associated with a slower reductive elimination (hindered and electron-deficient aryl halides) are more susceptible to β-deborylation. It is posited that a slower reductive elimination allows for β-deborylation to become more competitive.

[32] **4.129** can be detected by the crude ^{1}H NMR.

Scheme 4.19 Side Reactions in Cross-Coupling Catalytic Cycle



4.12 Synthetic Applications

The combination of directed diboration and cross-coupling methods allows for rapid and efficient functionalization of homoallylic alcohols. We envisioned that this complexity-generating sequence of reactions could aid in the synthesis of pharmaceuticals and natural products. In particular, we imagined the ability to access molecules with β-oxygenation relative to a stereocenter.

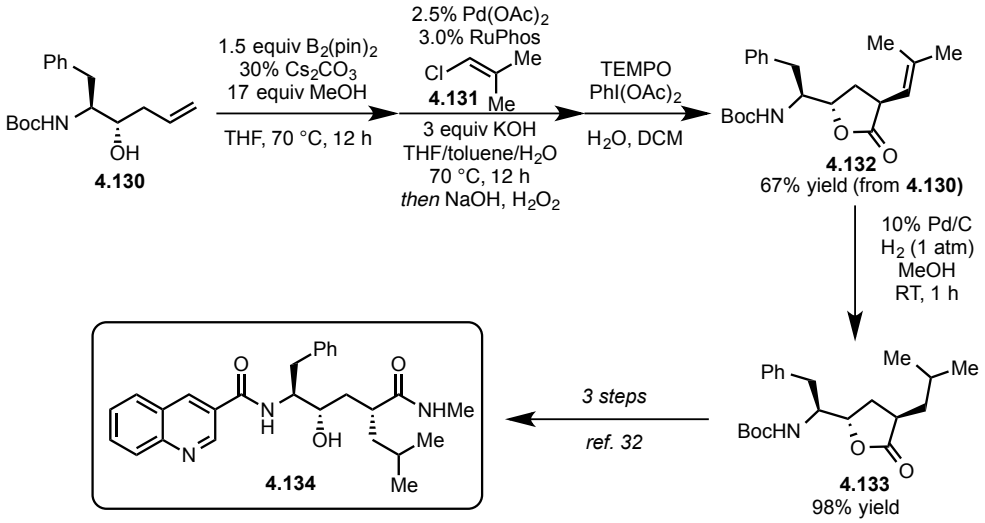
4.12.1 CCR-1 Antagonist

CC-chemokine receptor-1 antagonist **4.134** was discovered by Pfizer for the treatment of autoimmune diseases and organ transplant rejection.[33] We proposed an efficient synthesis of γ-lactone **4.133**, a known intermediate to **4.134** (Scheme 4.20). Homoallylic alcohol **4.130** was assembled by the reduction and allylation of Boc-L-

[33] Kath, J. C.; Brissette, W. H.; Brown, M. F.; Conklyn, M.; DiRico, A. P.; Dorff, P.; Gladue, R. P.; Lillie, B. M.; Lira, P. D.; Mairs, E. N.; Martin, W. H.; McElroy, E. B.; McGlynn, M. A.; Paradis, T. J.; Poss, C. S.; Stock, I. A.; Tylaska, L. A.; Zheng, D. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2169 – 2173.

Phenylalanine.[34] Directed diboration, cross-coupling with **4.131** and oxidation yielded the expected 1,4-diol, which upon oxidation yielded the unsaturated lactone **4.132**, in 67% yield over the four steps. A near quantitative hydrogenation of the trisubstituted olefin furnished **4.133**. **4.133** can be further transformed into CCR1 antagonist **4.134** in three steps following literature procedure.[32]

Scheme 4.20 Synthesis of CCR-1 Antagonist



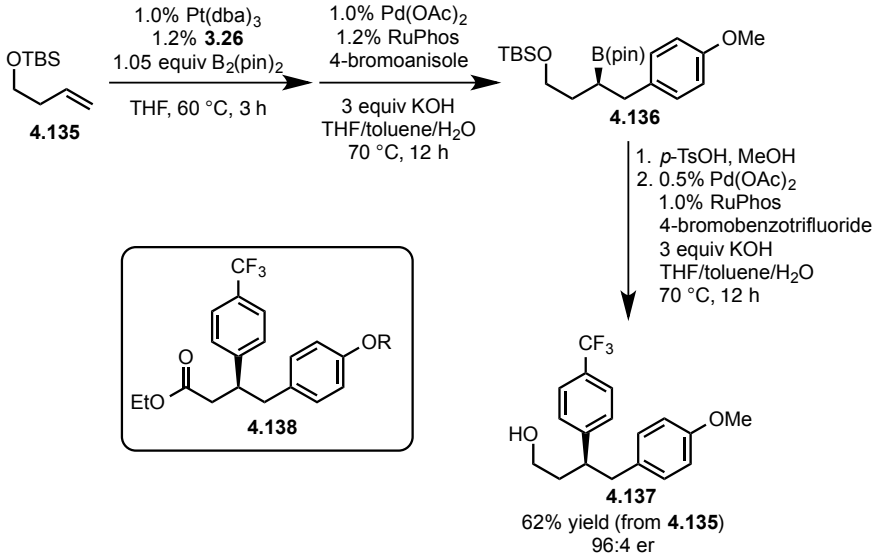
4.12.2 Vitronectin Receptor Antagonist

In addition to being combined with directed diboration methodologies, the directed coupling reaction can be used in tandem with the DCC sequence. This combination allows for the formation of contiguous C-C bonds in a stereo- and regioselective manner. Such a strategy would allow access to 1,2-bisarylated compounds such as **4.137**, a potential precursor to vitronectin receptor antagonists **4.138** (Scheme

[34] Diaz, L. C.; Diaz, G.; Ferreira, A. A.; Meira, P. R. R.; Ferreira, E. *Synthesis* **2003**, *4*, 603 – 622.

4.21).[35] Silyl ether **4.135** undergoes asymmetric diboration and cross-coupling with 4-bromoanisole to furnish organoboronate **4.136**. Without purification, **4.136** is subjected to a TBS deprotection and cross-coupling with 4-bromobenzotrifluoride to afforded **4.137** in 64% yield over four steps and 91% ee.

Scheme 4.21 Synthesis of Vitronectin Receptor Antagonist



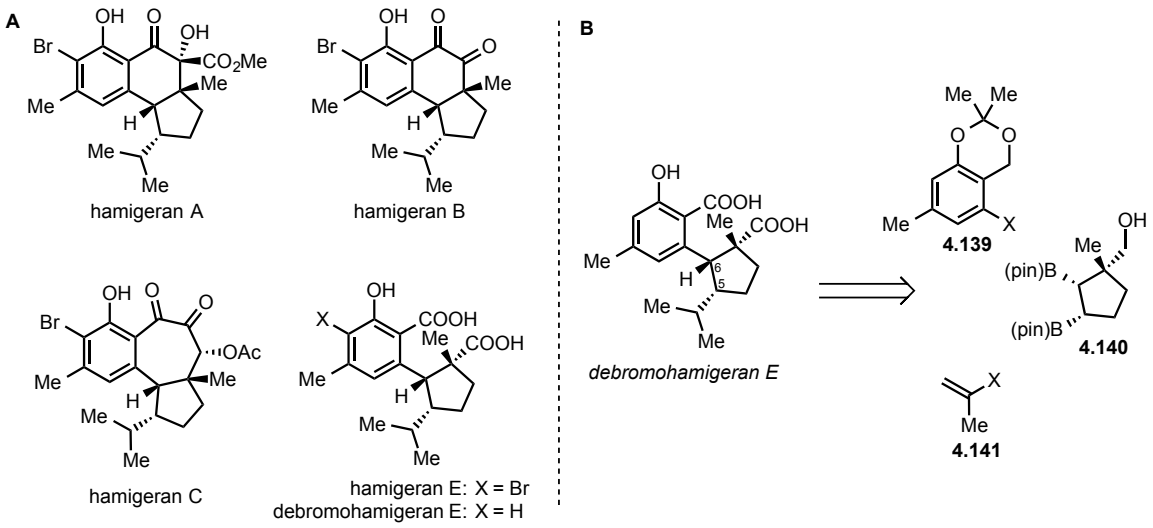
4.12.3 Debromohamigeran E

Finally, to demonstrate the synthetic usefulness of the directed cross-coupling methodology, the total synthesis of debromohamigeran E was performed. The hamigerans are a family of natural products containing a highly substituted cyclopentane ring with three or four contiguous stereocenters (Scheme 4.22, A). Isolated from the poecliosclerid sponge *Hamigera tarangaensis* in 1995, the hamigerans have shown to be

[35] Manley, P. J.; Miller, W. H.; Uzinskas, I. N. (SmithKline Beecham Corporation) Patent EP1218005 A2, July 3, 2002

moderately cytotoxic toward cancer cells and exert antiviral activity.[36] Because it hasn't been addressed by total synthesis [37] and because of its interesting structure, debromohamigeran E became the focus of our synthetic efforts. The construction of the *cis* substituents at C5 and C6 were anticipated through consecutive functionalizations of bis(boronate) **4.140** with **4.139** and **4.141** (Scheme 4.22, B). A site-selective directed cross-coupling reaction was planned as a means of differentiating the two secondary organoboronates.

Scheme 4.22 The Hamigerans and Retrosynthetic Analysis of Debromohamigeran E



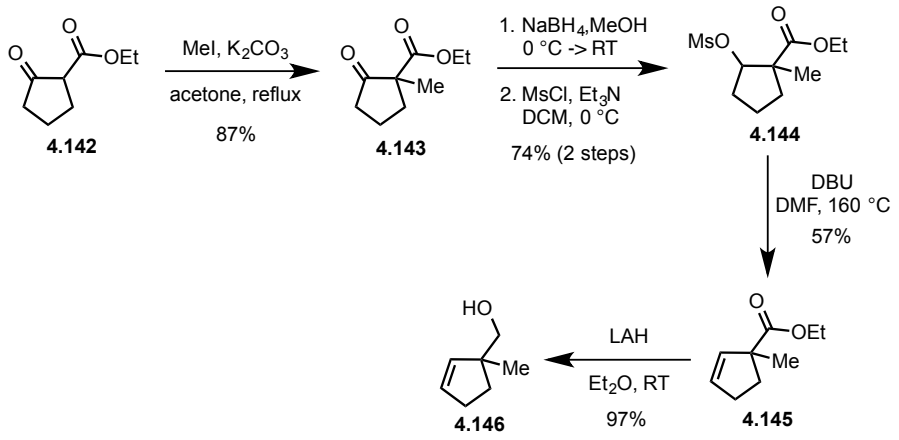
Naturally, diboronate **4.140** was expected to be derived from a directed diboration of **4.146**. The racemic, five-step synthesis of **4.146** is shown in Scheme 4.23. The methylation of β-keto ester **4.142** afforded **4.143** in good yield. A ketone reduction and

[36] (a) Cambie, R. C.; Lal, A. R.; Kernan, M. R.; Bergquist, P. R. *J. Nat. Prod.* **1995**, *58*, 940 – 942. (b) Wellington, K. D.; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. *J. Nat. Prod.* **2000**, *63*, 79 – 85.

[37] Debromohamigeran E has never been synthesized, while hamigeran E has been synthesized once: Nicolaou, K. C.; Gray, D. L. F.; Tae, J. *J. Am. Chem. Soc.* **2004**, *126*, 613 – 627.

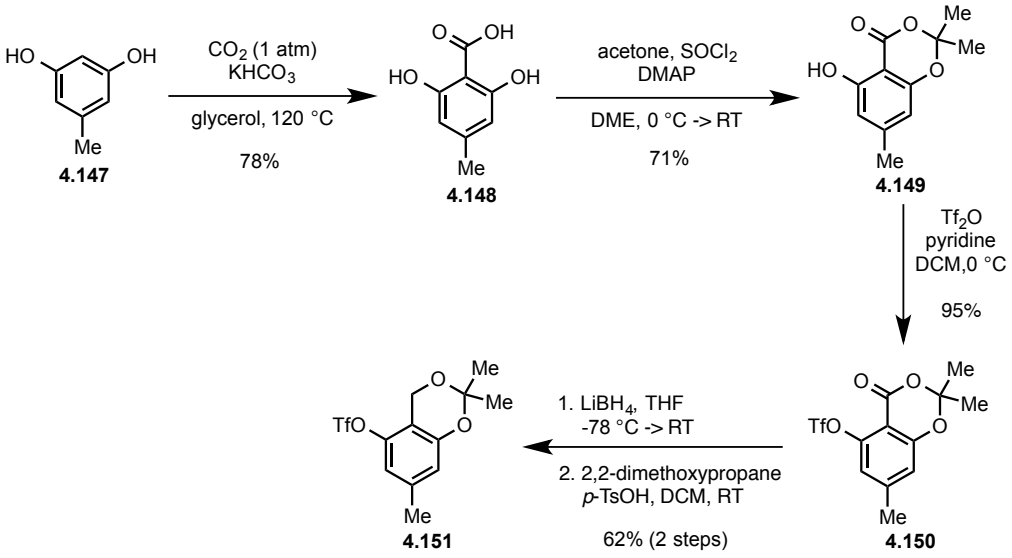
mesylation of the subsequent alcohol yielded mesylate **4.144** in 74% yield. DBU-promoted elimination furnished **4.145** in 50% yield. Finally, **4.146** was isolated from an LAH reduction of **4.145**.

Scheme 4.23 Synthesis of Homoallylic Alcohol **4.146**



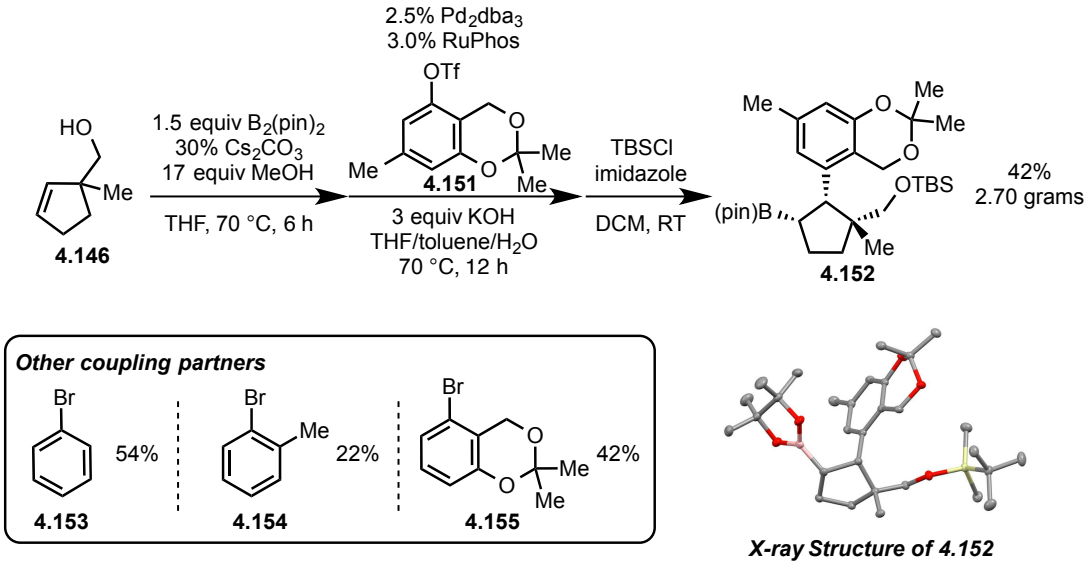
The most suitable aryl coupling partner was found to be triflate **4.151** (*vide infra*), which was synthesized from diphenol **4.147** in five steps (Scheme 4.24). Carboxylation of **4.147** afforded carboxylic acid **4.148** in 78% yield. Cyclization of **4.148** with acetone yielded **4.149** in 71% yield. Triflate **4.150** was smoothly formed using Tf_2O. Lastly, **4.150** was reduced with $LiBH_4$ and cyclized to form acetonide **4.151** in moderate yield over two steps.

Scheme 4.24 Synthesis of **4.151**



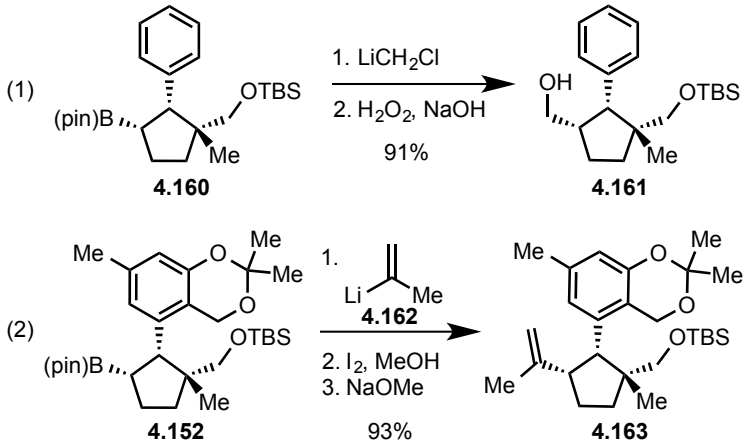
With **4.146** and **4.151** in hand, the diboration/coupling/protection sequence was investigated (Scheme 4.25). Gratifyingly, the 1,2-bis(boronate) of **4.146** and **4.151** underwent coupling and furnished **4.152** in 42% yield after TBS protection. Moreover, the yield of the reaction sequence was identical when run on larger scale, affording 2.70 grams of **4.152**. Although only a moderate yield was observed for the coupling with **4.151** (and related aryl bromides **4.153, 4.154,** and **4.155**), other possible coupling partners (**4.156**, **4.157, 4.158** and **4.159**) did not participate in the cross-coupling reaction. It is presumed that the unhindered nature of **4.151** was crucial for the success of the coupling.

Scheme 4.25 Diboration/Cross-Coupling/Protection of **4.146**



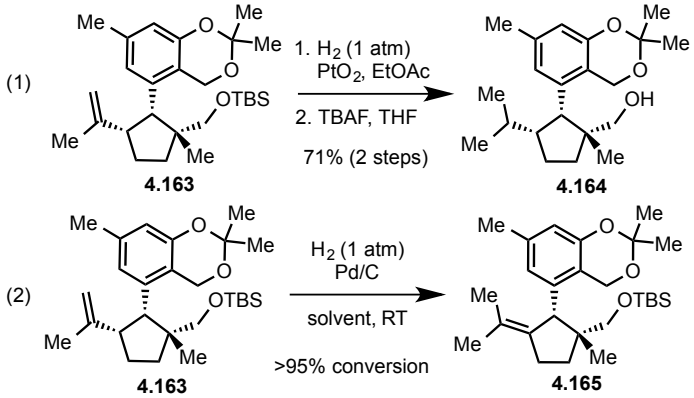
With a reliable means of accessing **4.152**, a stereoretentive method for the installation of a propenyl group (as a precursor to an isopropyl group) was desired. In initial experiments, **4.160** was shown to react during a homologation/oxidation sequence, providing primary alcohol **4.161** (Scheme 4.26, Eq. 1). With this in mind, a Zweifel olefination with lithium species **4.162** was attempted, affording **4.163** in excellent yield (Scheme 4.26, Eq. 2). Similar to diboration/coupling sequence, the olefination reaction was effective on a larger scale, yielding 2.10 grams of **4.163**.

Scheme 4.26 Zweifel Olefination of **4.152**



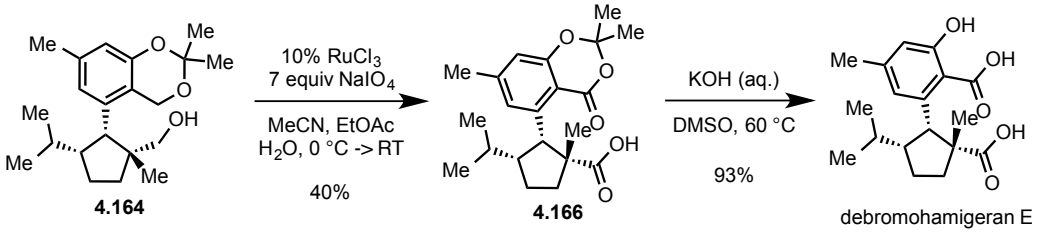
A sequential Pt-catalyzed hydrogenation and desilylation of **4.163** yielded **4.164** in 71% yield (Scheme 4.27, Eq. 1). A variety of Pd-catalyzed hydrogenation conditions lead to olefin isomerization to the unreactive tetrasubstituted olefin byproduct **4.165** (Scheme 4.27, Eq. 2). Hydrogenation of **4.163** using PtO_2 resulted in only 10-15% isomerization to the tetrasubstituted olefin, which could be separated after TBAF deprotection. Efforts to hydrogenate the isomerized byproduct **4.165** failed to yield **4.164**.

Scheme 4.27 Hydrogenation of **4.163**



Next, **4.164** was subjected to Ru-catalyzed bis-oxidation resulting in **4.166** in a moderate yield (Scheme 4.28). A simple hydrolysis of **4.166** afforded debromohamigeran E in 93% yield. This 11-step (longest linear) sequence is the first synthesis of debromohamigeran E. Esterification of debromohamigeran E with ethyl iodide furnished the diester, which was in accord with spectral data, previously reported during isolation.

Scheme 4.28 Endgame Synthesis of Debromohamigeran E



4.13 Conclusion

Alcohol-containing organoboronate esters have been shown to undergo an unprecedented Suzuki-Miyaura cross-coupling reaction. Alkoxide association with the Pd catalyst allows for a directed transmetallation that occurs with retention of stereochemistry. A transmetallation with retention of stereochemistry separates this methodology from other cross-coupling reactions that highlight internal Lewis basic activation of the organoboronate. The directed coupling methodology can be combined with the directed diboration transformation described in Chapter 3, producing a valuable, complexity-generating sequence of reactions. This series of reactions was employed during the synthesis of debromohamigeran E and other synthetic targets of interest.

4.14 Experimental Section

4.14.1 General Considerations

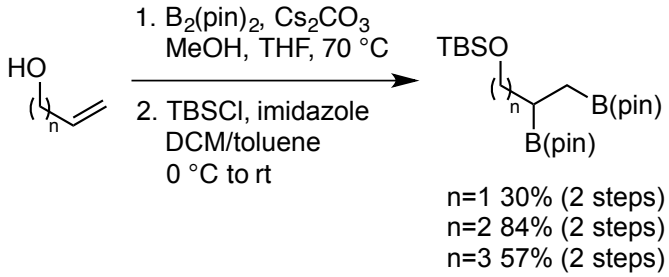
^{1}H NMR spectra were recorded on either a Varian Gemini-500 (500 MHz), or a Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet, app = apparent), and coupling constants (Hz). ^{13}C NMR spectra were recorded on either a Varian Gemini-500 (125 MHz), or a Varian Inova-500 (125 MHz) spectrometer with complete proton decoupling. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.0 ppm). Infrared (IR) spectra were recorded on a Bruker alpha spectrophotometer. Bands are characterized as broad (br), strong (s), medium (m), and weak (w) (ν max cm^{-1}). High resolution mass spectrometry (DART) was performed at the Mass Spectrometry Facility, Boston College.

Liquid Chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230×450 Mesh) purchased from Silicycle. Thin Layer Chromatography was performed on 25 μm silica gel plates purchased from Silicycle. Visualization was performed using ultraviolet light (254 nm), potassium permanganate ($KMnO_4$) in water, ninhydrin with acetic acid in ethanol, phosphomolybdic acid (PMA) in ethanol, or phosphomolybdic acid and cerium(IV) sulfate in ethanol with sulfuric acid (Seebach). Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar Supercritical Chromatograph equipped with an auto sampler and a Waters photodiode array detector with isopropanol as the modifier.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran, toluene, diethyl ether and dichloromethane were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after being purged with argon.

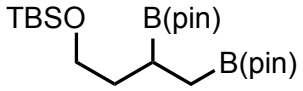
4.14.2 Preparation of Substrates

Preparation of Bis(boronates) ***4.61, 4.63, 4.65,*** *and* ***4.67****:*



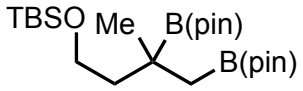
To an oven-dried 50 mL round bottom flask with magnetic stir bar was added $B_2(pin)_2$ (2.54 g, 10 mmol), Cs_2CO_3 (0.53 g, 1.50 mmol) and THF (10 mL). The alkenol (5.00 mmol) and methanol (3.44 mL, 85.0 mmol) were added sequentially to the reaction flask. The flask was sealed with a rubber septum and sealed with electrical tape. The flask was heated at 70 °C and allowed to stir for 6 hours. The reaction was cooled to room temperature and concentrated *in vacuo* (ensuring that all methanol has been removed from the residue). To the residue was added dichloromethane (23 mL) and imidazole (3.02 g, 44.4 mmol). The reaction mixture was cooled to 0 °C and a solution of TBSCl (2.24 g, 14.9 mmol) in toluene (5 mL). The reaction was sealed and allowed to warm to room temperature overnight. The reaction mixture was quenched with NH_4Cl (15 mL). The layers were allowed to separate and the aqueous layer was extracted with

dichloromethane (3 x 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified on SiO_2.



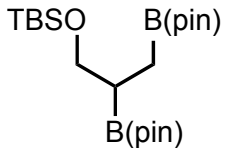
(3,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)(*tert*-butyl)dimethylsilane. (4.61) Prepared according to the general procedure using 3-buten-1-ol (0.43 mL, 5.00 mmol). The crude material was purified on SiO_2 (2.5% to 10% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (1.86 g, 84% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03 (6H, s), 0.88 (9H, s), 0.80-0.90 (2H, m), 1.13-1.19 (1H, m), 1.22 (24H, s), 1.51-1.58 (1H, m), 1.68-1.75 (1H, m), 3.57-3.66 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.2, 18.4, 24.7, 24.8, 24.8, 24.9, 26.0, 36.6, 62.9, 82.8, 82.8; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.2; IR (neat): 2977.5 (w), 2928.8 (w), 2857.2 (w), 1470.9 (w), 1369.7 (s), 1311.1 (s), 1253.5 (m), 1140.6 (s), 1092.8 (s), 967.6 (m), 833.2 (s), 773.7 (s), 667.8 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{22}H_{47}B_2O_5Si$ [M+H]: calculated: 441.3379, found: 441.3387.



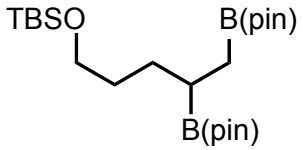
***tert*-butyldimethyl(3-methyl-3,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)silane. (4.63)** Prepared according to the general procedure using 3-methylbut-3-en-1-ol (0.50 mL, 5.00 mmol). The crude material was purified on SiO_2 (2.5% to 10% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (1.40 g, 62% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.04 (6H, s), 0.72 (1H, d, J = 15.7 Hz), 0.88 (9H, s), 0.95 (1H, d, J = 15.7 Hz), 0.98 (3H, s), 1.21 (6H, s), 1.22 (6H, s), 1.23 (12H, s), 1.53-1.59 (1H, m), 1.62-1.68 (1H, m), 3.64 (2H, t, J = 8.8 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.2, -5.1 18.4, 24.5, 24.7, 24.8, 24.8, 25.0, 26.0, 44.5, 61.4, 82.8, 82.9; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.0; IR (neat): 2977.3 (w), 2955.7 (w), 2929.0 (w), 2857.2 (w), 1463.6 (w), 1360.2 (s), 1307.7 (s), 1253.1 (m), 1214.0 (w), 1139.7 (s), 1086.0 (s), 939.5 (s), 833.7 (m), 773.5 (m), 664.2 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{23}H_{49}B_2O_5Si$ [M+H]: calculated: 455.3535, found: 455.3517.



(2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)(*tert*-butyl)dimethylsilane. (4.65) Prepared according to the general procedure using allyl alcohol (0.14 mL, 2.00 mmol). The crude material was purified on SiO_2 (2.5% to 10% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (0.23 g, 30% yield).

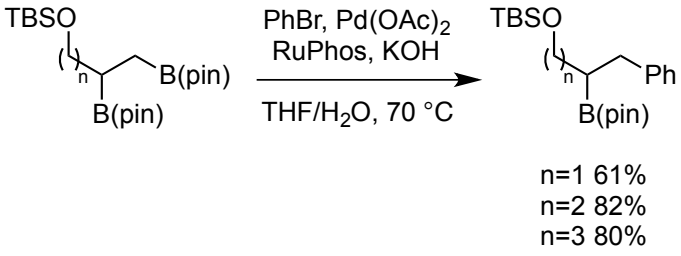
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.01 (6H, s), 0.86 (9H, s), 0.79-0.93 (2H, m), 1.22 (24H, s), 1.34-1.37 (1H, m), 3.64 (2H, d, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.4, 18.3, 24.7, 24.7, 24.8, 24.8, 24.8, 24.9, 26.0, 66.5, 82.8, 82.8; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.1; IR (neat): 2977.8 (w), 2929.0 (w), 2856.4 (w), 1470.6 (w), 1369.6 (s), 1313.3 (s), 1255.3 (m), 1214.0 (w), 1142.0 (s), 1087.2 (s), 1004.8 (s), 938.1 (m), 835.4 (s), 774.6 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{21}H_{45}B_2O_5Si$ [M+H]: calculated: 427.3222, found: 427.3244.



((4,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)(tert-butyl)dimethylsilane. (4.67) Prepared according to the general procedure using 4-penten-1-ol (0.52 mL, 5.00 mmol). The crude material was purified on SiO_2 (2.5% to 10% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (1.30 g, 57% yield).

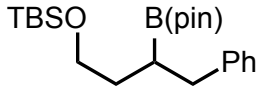
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03 (6H, s), 0.88 (9H, s), 0.77-0.90 (2H, m), 1.08-1.14 (1H, m), 1.22 (24H, s), 1.29-1.36 (1H, m), 1.41-1.48 (1H, m), 1.50-1.56 (1H, m), 3.57 (2H, t, J = 6.9 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.2, 18.4, 24.7, 24.8, 24.8, 24.9, 26.0, 29.9, 32.3, 63.7, 82.8, 82.8; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.0; IR (neat): 2977.5 (w), 2929.1 (w), 2857.0 (w), 1470.7 (w), 1369.6 (s), 1311.1 (s), 1251.0 (m), 1141.1 (s), 1097.1 (s), 968.2 (m), 834.0 (s), 774.1 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{23}H_{49}B_2O_5Si$ [M+H]: calculated: 455.3535, found: 455.3544.

*Procedure for Preparation of Substrates **4.69, 4.71, 4.72**, and **4.73**:*



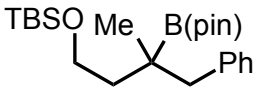
To an oven-dried 25 mL round bottom flask with magnetic stir bar in the dry box was added the 1,2-bis(boronate) (1.00 mmol), tetrahydrofuran (9.1 mL), potassium hydroxide (168 mg, 3.00 mmol), $Pd(OAc)_2$ (2.4 mg, 10 μmol), RuPhos (5.6 mg, 12 μmol) and bromobenzene (158 μL, 1.50 mmol). The flask was sealed with a rubber septum,

removed from the dry box, and heated to 70 ºC in an oil bath for 12 hours. The reaction mixture was cooled to room temperature and H_2O (10 mL) was added. The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2.



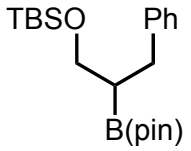
tert-butyldimethyl(4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)silane. (4.69) Prepared according to the general procedure using (3,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)(tert-butyl)dimethylsilane (0.44 g, 1.00 mmol). The crude material was purified on SiO_2 (2.5% to 5% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (0.32 g, 82% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02 (3H, s), 0.03 (3H, s), 0.88 (9H, s), 1.13 (6H, s), 1.16 (6H, s), 1.38-1.46 (1H, m), 1.58-1.71 (2H, m), 2.67 (1H, dd, J = 13.7 Hz, 7.8 Hz), 2.73 (1H, dd, J = 13.7 Hz, 8.3 Hz), 3.54-3.59 (1H, m), 3.62-3.67 (1H, m), 7.11-7.15 (1H, m), 7.19-7.24 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.3, -5.2, 18.4, 24.7, 24.8, 26.0, 34.1, 37.1, 62.9, 83.0, 125.6, 128.0, 128.9, 142.1; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.2; IR (neat): 2954.6 (w), 2928.1 (w), 2856.5 (w), 1471.2 (w), 1378.7 (m), 1318.5 (m), 1251.8 (m), 1143.3 (s), 1096.2 (s), 833.9 (s), 774.6 (s), 743.5 (w), 698.2 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{22}H_{40}BO_3Si$ [M+H]: calculated: 391.2840, found: 391.2849.



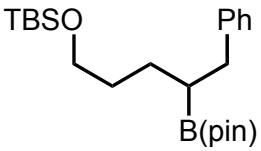
***tert*-butyldimethyl(3-methyl-4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)silane. (4.71)** Prepared according to the general procedure using *tert*-butyldimethyl(3-methyl-3,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)silane (454 mg, 1.00 mmol). The crude material was purified on SiO_2 (2.5% to 5% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (263 mg, 65% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05 (6H, s), 0.89 (9H, s), 0.91 (3H, s), 1.19 (6H, s), 1.22 (6H, s), 1.48-1.54 (1H, m), 1.72-1.78 (1H, m), 2.53 (1H, d, J = 13.2 Hz), 2.78 (1H, d, J = 13.2 Hz), 3.69 (2H, t, J = 7.8 Hz), 7.14-7.17 (1H, m), 7.19-7.24 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.3, 18.3, 21.7, 24.8, 25.0, 26.0, 42.0, 45.3, 61.2, 83.1, 125.6, 127.6, 130.4, 139.8; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.1; IR (neat): 2954.7 (w), 2928.4 (w), 2856.1 (w), 1463.0 (w), 1370.4 (m), 1310.1 (m), 1141.1 (s), 1086.5 (s), 832.9 (s), 773.4 (s), 738.1 (w), 701.3 (m), 664.0 cm^{-1}; HRMS-(DART-TOF) for $C_{23}H_{42}BO_3Si$ [M+H]: calculated: 405.2996, found: 405.3007.



tert-butyldimethyl(3-phenyl-2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)silane. (4.72) Prepared according to the general procedure using (3,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)(tert-butyl)dimethylsilane (87 mg, 0.20 mmol). The crude material was purified on SiO_2 (2.5% to 5% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (46 mg, 61% yield).

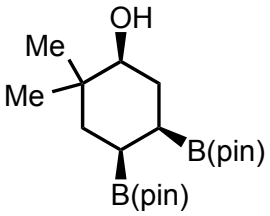
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.02 (6H, s), 0.89 (9H, s), 1.16 (6H, s), 1.17 (6H, s), 1.57 (1H, quintet, J = 7.33 Hz), 2.72 (1H, dd, J = 13.7 Hz, 7.8 Hz), 2.79 (1H, dd, J = 13.7 Hz, 7.8 Hz), 3.62 (1H, dd, J = 9.8 Hz, 6.4 Hz), 3.67 (1H, dd, J = 9.8 Hz, 6.9 Hz), 7.12-7.15 (1H, m), 7.20-7.25 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.4, 18.3, 24.8, 24.8, 25.9, 33.2, 63.6, 83.1, 125.5, 128.0, 129.0, 142.0; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.8; IR (neat): 3027.3 (w), 2978.0 (w), 2953.9 (w), 2856.1 (w), 1471.1 (w), 1388.6 (m), 1369.4 (m), 1319.9 (m), 1143.4 (s), 1092.9 (s), 1004.8 (m), 832.7 (s), 773.5 (s), 743.7 (m), 697.5 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{21}H_{38}BO_3Si$ [M+H]: calculated: 377.2683, found: 377.2683.



tert-butyldimethyl((5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)silane. (4.73) Prepared according to the general procedure using ((4,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)(tert-butyl)dimethylsilane (0.45 g, 1.00 mmol). The crude material was purified on SiO_2 (2.5% to 5% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (0.32 g, 80% yield).

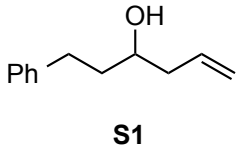
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03 (6H, s), 0.88 (9H, s), 1.13 (6H, s), 1.16 (6H, s), 1.36 (1H, q, J = 7.3 Hz), 1.43 (2H, q, J = 7.7 Hz), 1.48-1.61 (2H, m), 2.66 (1H, dd, J = 13.7 Hz, 7.3 Hz), 2.72 (1H, dd, J = 13.7 Hz, 8.3 Hz), 3.57 (2H, t, J = 6.6 Hz), 7.11-7.15 (1H, m), 7.18-7.24 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.3, 18.3, 24.7, 24.8, 26.0, 27.2, 32.4, 37.3, 63.4, 83.0, 125.5, 128.0, 128.8, 142.2; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.8; IR (neat): 2977.4 (w), 2928.5 (w), 2856.1 (w), 1495.0 (w), 1385.0 (m), 1318.8 (m),

1251.5 (m), 1143.0 (s), 1098.2 (s), 1005.6 (w), 832.9 (s), 773.6 (s), 743.3 (w), 697.7 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{23}H_{42}BO_3Si$ [M+H]: calculated: 405.2996, found: 405.2991.

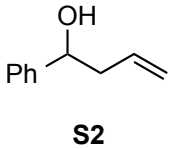


2,2-dimethyl-4,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexan-1-ol. (4.79) Prepared according to the literature procedure.[38] All spectral data are in accord with the literature.

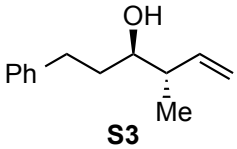
Preparation of Substrates used for Scheme 3:



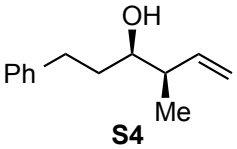
S1
*(used for **19-25** and **32-36**)*



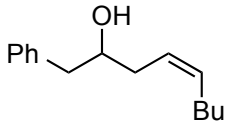
S2
*(used for **26**)*



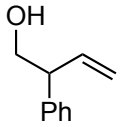
S3
*(used for **27**)*



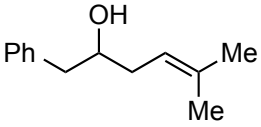
S4
*(used for **28**)*



S5
*(used for **29**)*



S6
*(used for **30**)*



S7
*(used for **31**)*

The substrates in Scheme 3 were prepared according to literature procedures.[38]

[38] T. P. Blaisdell, T. C. Caya, L. Zhang, A. Sanz-Marco, and J. P. Morken *J. Am. Chem. Soc.* **2014**, *136*, 9264 – 9267.

4.14.3 Procedures

*Experimental Procedure for Diboration/Cross-Coupling/Oxidation (Synthesis of **4.53**)*

To an oven-dried 2-dram vial with magnetic stir bar was added homoallylic alcohol (0.25 mmol), Cs_2CO_3 (26 mg, 75 μmol), $B_2(pin)_2$ (95 mg, 0.38 mmol), tetrahydrofuran (1 mL, [substrate] = 0.25 M) and methanol (0.17 mL, 4.25 mmol). The vial was sealed with a teflon septum cap and heated to 70 ºC for 6 h. The reaction was cooled to room temperature and concentrated *in vacuo* (ensuring that all methanol has been removed from the residue). The flask was brought to a dry box and charged with solid potassium hydroxide (42 mg, 0.75 mmol), $Pd_2(dba)_3$/RuPhos (added as a 1:2 solution in THF (0.005 M); 0.25 mL for 0.5 mol% $Pd_2(dba)_3$), tetrahydrofuran (0.95 mL), toluene (1.2 mL) and electrophile (0.38 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.23 mL) was added through the teflon septum cap. The vial was heated to 70 ºC and stirred for 12 h. The reaction mixture was transferred to a 25-mL round bottom flask and cooled to 0 ºC (ice/water) and charged with 3 M sodium hydroxide (0.5 mL), and 30% hydrogen peroxide (0.5 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h at which time the vial was diluted with ethyl acetate and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2.

Experimental Procedure for Deprotection/Cross-Coupling/Oxidation (Tables 4.1-4.2)

To an oven-dried 4-dram vial with magnetic stir bar was added the silyl ether (0.25 mmol), methanol (2 mL) and *p*TsOH (cat.). The reaction mixture was stirred at room temperature for 2 hours. The reaction was concentrated *in vacuo* (ensuring that all methanol has been removed from the residue). The flask was brought to a dry box and charged with solid potassium hydroxide (42 mg, 0.75 mmol), $Pd_2(dba)_3$/RuPhos (added as a 1:2 solution in THF (0.005 M); 0.25 mL for 0.5 mol% $Pd_2(dba)_3$), tetrahydrofuran (0.95 mL), toluene (1.2 mL) and bromobenzene (28 μL, 0.253 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.23 mL) was added through the teflon septum cap. The vial was heated to 70 ºC and stirred for 12 h. The reaction mixture was transferred to a 25-mL round bottom flask and cooled to 0 ºC (ice/water) and charged with 3 M sodium hydroxide (0.5 mL), and 30% hydrogen peroxide (0.5 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h at which time the vial was diluted with ethyl acetate and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation.

Experimental Procedure for Cross-Coupling of Cyclic Bis(boronate) ***4.79***.

A oven-dried flask was brought to a dry box and charged with 2,2-dimethyl-4,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexan-1-ol (95 mg, 0.25 mmol), solid potassium hydroxide (42 mg, 0.75 mmol), $Pd_2(dba)_3$/RuPhos (added as a 1:2 solution in THF (0.005 M); 0.25 mL for 0.5 mol% $Pd_2(dba)_3$), tetrahydrofuran (0.95 mL),

toluene (1.2 mL) and bromobenzene (0.26 or 0.50 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.23 mL) was added through the teflon septum cap. The vial was heated to 70 ºC and stirred for 12 h. The reaction mixture was cooled to room temperature and H_2O (5 mL) was added. The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude product was purified on silica gel (5% ethyl acetate in hexanes).

Experimental Procedure for Diboration/Cross-Coupling/Protection (Tables 4.4-4.6)

To an oven-dried 2-dram vial with magnetic stir bar was added homoallylic alcohol (0.25 mmol), Cs_2CO_3 (26 mg, 75 μmol), $B_2(pin)_2$ (95.0 mg, 0.38 mmol), tetrahydrofuran (1 mL, [substrate] = 0.25 M) and methanol (0.17 mL, 4.25 mmol). The vial was sealed with a teflon septum cap and heated to 70 ºC for 6 h. The reaction was cooled to room temperature and concentrated *in vacuo* (ensuring that all methanol has been removed). The flask was brought to a dry box and charged with solid potassium hydroxide (42 mg, 0.75 mmol), $Pd_2(dba)_3$/RuPhos (added as a 1:2 solution in THF (0.005 M); 0.25 mL for 0.5 mol% $Pd_2(dba)_3$), tetrahydrofuran (0.95 mL), toluene (1.2 mL) and electrophile (39 μL, 0.38 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.23 mL) was added through the teflon septum cap. The vial was heated to 70 ºC and stirred for 12 h. The reaction mixture was cooled to room temperature and H_2O (5 mL) was added. The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in a 4-dram vial.

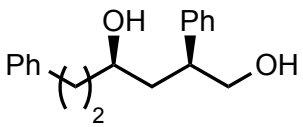
TBSCl Protection

To the crude residue was added dichloromethane (1.2 mL) and imidazole (151 mg, 2.22 mmol). The reaction mixture was cooled to 0 °C and a solution of TBSCl (112 mg, 0.74 mmol) in toluene (0.25 mL). The reaction was sealed and allowed to warm to room temperature and stirred for 4 hours. The reaction mixture was quenched with aq. NH_4Cl (5 mL). The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2.

Ac_2O Protection

To the residue was added dichloromethane (1.2 mL), triethylamine (1.2 mL), and a single crystal of 4-(dimethylamino)pyridine under a nitrogen atmosphere. The reaction mixture was cooled to 0 °C and acetic anhydride (52 μL, 0.55 mmol) was added. The reaction mixture was allowed to warm to room temperature and stirred for 12 h. The reaction mixture was diluted with 1 M HCl. The organic layer was separated and washed with saturated aqueous $NaHCO_3$, dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2.

4.14.4 Full Characterization

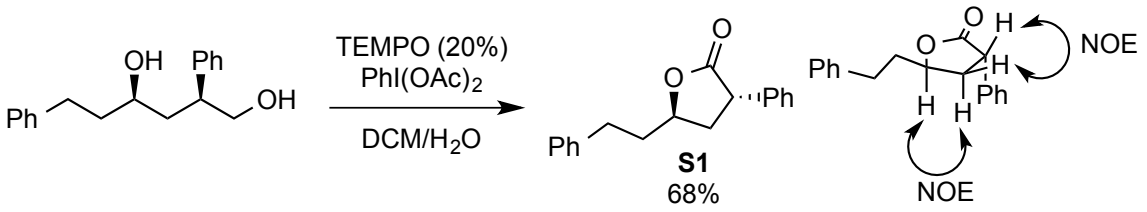


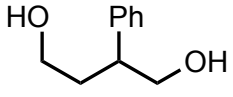
2,6-diphenylhexane-1,4-diol. (4.53) Prepared according the general diboration/cross-coupling/oxidation procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and bromobenzene

(39 μL, 0.38 mmol). The crude product was purified on silica gel (40% ethyl acetate in hexanes) to afford the title compound as a colorless oil (45 mg, 67%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.75-1.88 (3H, m), 1.92-1.98 (1H, m), 2.60-2.66 (1H, m), 2.74-2.79 (1H, m), 3.01 (1H, quintet, J = 6.4 Hz), 3.71-3.80 (3H, m), 7.15-7.18 (3H, m), 7.20-7.22 (3H, m), 7.24-7.28 (2H, m), 7.30-7.33 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.8, 32.0, 38.8, 40.6, 44.9, 67.2, 69.5, 125.8, 126.9, 127.8, 128.4, 128.4, 128.8, 142.0, 142.6; IR (neat): 3330.5 (br), 3026.4 (w), 2928.8 (w), 1602.0 (w), 1493.9 (w), 1452.9 (w), 1265.3 (w), 1029.4 (m), 734.9 (s), 697.7 (s), 604.2 (m), 549.6 (m), 528.7 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{18}H_{22}O_2$ [M+H]: calculated: 271.1698, found: 271.1699.

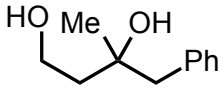
Proof of Stereochemistry: The relative stereochemistry was determined by NOESY NMR of the corresponding lactone derived from the 1,4-diol (as shown below).



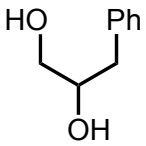


2-phenylbutane-1,4-diol. (4.62) Prepared according the general deprotection/cross-coupling/oxidation procedure using (3,4-

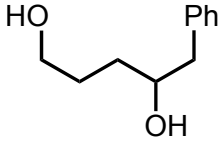
bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)(tert-butyl)dimethyl-silane (110 mg, 0.25 mmol). The NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. All spectral data are in accord with the literature.[39]



3-methyl-4-phenylbutane-1,3-diol. (4.64) Prepared according the general deprotection/cross-coupling/oxidation procedure using *tert*-butyldimethyl(3-methyl-3,4-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)-silane (114 mg, 0.25 mmol). The NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. All spectral data are in accord with the literature.[40]



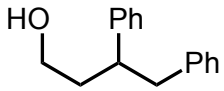
3-phenylpropane-1,2-diol. (4.66) Prepared according the general deprotection/cross-coupling/oxidation procedure using (2,3-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)propoxy)(tert-butyl)dimethylsilane (87 mg, 0.20 mmol). The NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. All spectral data are in accord with the literature.[41]



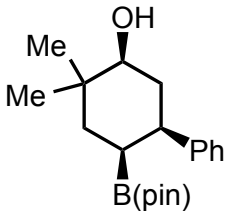
5-phenylpentane-1,4-diol. (4.68) Prepared according the general deprotection/cross-coupling/oxidation procedure using ((4,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)(tert-butyl)dimethylsilane

[39] Gotoh, H.; Masui, R.; Ogino, H.; Shoji, M.; Hayashi, Y. *Angew. Chem. Int. Ed.,* **2006**, *45*, 6853 – 6856.
[40] Frye, S. V.; Eliel, E. L. *J. Org. Chem.* **1985**, *50*, 3402 – 3404.
[41] Kwon, M. S.; Park, I. S.; Jang, J. S.; Lee, J. S.; Park, J. *Org. Lett.* **2007**, *9*, 3417 – 3419.

(114 mg, 0.25 mmol). The NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. All spectral data are in accord with the literature.[42]



3,4-diphenylbutan-1-ol. (4.70) Prepared according the general deprotection/cross-coupling/oxidation procedure using tert-butyldimethyl(4-phenyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)silane (49 mg, 0.13 mmol). The NMR yield was determined using 1,3,5-trimethoxybenzene as an internal standard. All spectral data are in accord with the literature.[43]



2,2-dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexan-1-ol. (4.80) Prepared according the procedure for cross-coupling of cyclic bis(boronate).

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.90 (6H, s), 1.00 (3H, s), 1.02 (6H, s), 1.04 (3H, s), 1.65-1.71 (2H, m), 1.81 (1H, dd, J = 12.9 Hz, 1.8 Hz), 2.00 (1H, d, J = 12.3 Hz), 2.22 (1H, q, J = 11.7 Hz), 2.84 (1H, dt, J = 12.3 Hz, 3.5 Hz), 3.47 (1H, dd, J = 11.2 Hz, 4.1 Hz), 7.10-7.13 (1H, m), 7.21-7.24 (2H, m), 7.27-7.29 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 19.5, 24.1, 24.8, 29.3, 33.3, 35.7, 41.6, 42.8, 78.7, 82.6, 82.7, 125.4, 127.4, 127.5, 127.7, 145.3; IR (neat): 3398.0 (w), 2975.9 (m), 2946.0 (m), 2866.6 (m), 1388.6 (m), 1370.5 (m), 1316.3 (s), 1142.0 (s), 965.5 (m), 858.8 (m), 751.2 (m), 696.5 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{20}H_{32}BO_3$ [M+H]: calculated: 331.2445, found: 331.2458.

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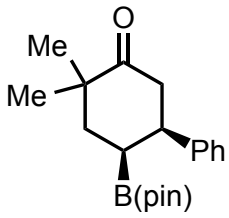
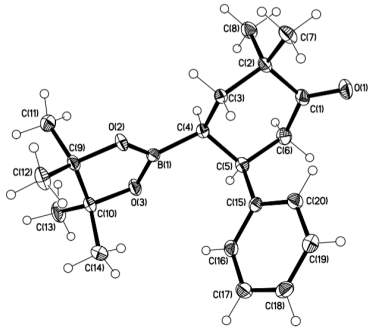
[42] Kelly, B. D.; Lambert, T. H. *Org. Lett.* **2011**, *13*, 740 – 743.
[43] Ito, H.; Nagahara, T.; Ishihara, K.; Saito, S.; Yamamoto, H. *Angew. Chem. Int. Ed.* **2004**, *43*, 994 – 997.

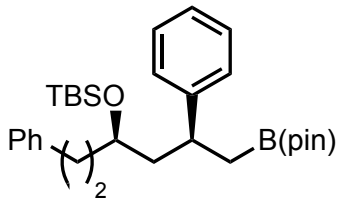


2,2-dimethyl-5-phenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)cyclohexan-1-one. (4.81) Prepared according the procedure for cross-coupling of cyclic bis(boronate).

^{1}H NMR (600 MHz, $CDCl_3$): δ 1.04 (6H, s), 1.14 (6H, s), 1.19 (3H, s), 1.22 (3H, s), 1.73 (1H, dd, J = 13.5 Hz, 2.9 Hz), 1.93-2.01 (2H, m), 2.71 (1H, dd, J = 14.7 Hz, 4.7 Hz), 2.83 (1H, dd, J = 14.7 Hz, 6.5 Hz), 3.61 (1H, q, J = 4.7 Hz), 7.13-7.17 (3H, m), 7.21-7.24 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 24.6, 25.0, 25.6, 26.0, 37.9, 43.5, 44.0, 45.1, 83.3, 126.4, 128.0, 128.3, 143.7, 217.2; IR (neat): 2975.3 (m), 2925.0 (w), 2866.2 (w), 1701.4 (s), 1371.6 (s), 1323.3 (s), 1111.5 (s), 967.1 (s), 851.9 (m), 694.4 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{20}H_{30}BO_3$ [M+H]: calculated: 329.2288, found: 329.2304.

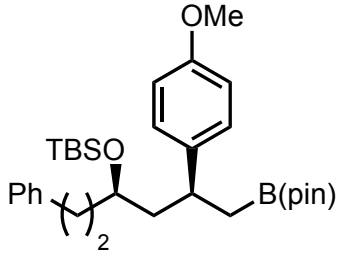
Proof of Stereochemistry: The relative stereochemistry was determined by crystal structure determination (as shown below).





tert-butyl((-1,5-diphenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl)oxy)dimethylsilane. (4.83) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and bromobenzene (39 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (57 mg, 85%).

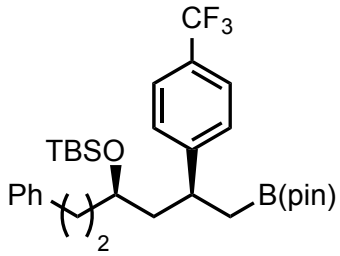
^{1}H NMR (500 MHz, $CDCl_3$): δ -0.11 (3H, s), -0.06 (3H, s), 0.87 (9H, s), 1.09 (6H, s), 1.10 (6H, s), 1.07-1.12 (1H, m), 1.18 (1H, dd, J = 15.2 Hz, 6.9 Hz), 1.67-1.74 (1H, m), 1.78-1.88 (3H, m), 2.53 (1H, dd, J = 11.3 Hz, 5.4 Hz), 2.73 (1H, dd, J = 13.7 Hz, 5.4 Hz), 2.86 (1H, quintet, J = 8.3 Hz), 3.43 (1H, quintet, J = 6.4 Hz), 7.13-7.18 (6H, m), 7.22-7.29 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.6, -4.4, 18.1, 24.7, 24.7, 25.9, 31.2, 38.1, 38.2, 46.6, 69.8, 82.9, 125.5, 125.9, 127.3, 128.2, 128.3, 128.4, 143.0, 146.9; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.4; IR (neat): 2977.1 (w), 2928.3 (w), 2856.2 (w), 1453.7 (w), 1369.4 (s), 1318.4 (s), 1253.5 (m), 1143.9 (s), 1066.4 (s), 967.1 (m), 881.5 (m), 832.9 (s), 772.4 (s), 697.8 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{30}H_{48}BO_3Si$ [M+H]: calculated: 495.3466, found: 495.3477.



tert-butyl((-5-(4-methoxyphenyl)-1-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl)oxy)-dimethylsilane. (4.85) Prepared according the general diboration/cross-coupling/protection procedure using 1-

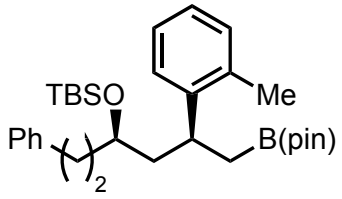
phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 4-bromoanisole (47 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (101 mg, 77%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.09 (3H, s), -0.05 (3H, s), 0.88 (9H, s), 1.06 (1H, dd, J = 15.7 Hz, 8.8 Hz), 1.10 (6H, s), 1.11 (6H, s), 1.15 (1H, dd, J = 15.2 Hz, 6.8 Hz), 1.66-1.73 (1H, m), 1.79 (2H, t, J = 7.9 Hz), 1.78-1.87 (1H, m), 2.53 (1H, dd, J = 13.7 Hz, 4.9 Hz), 2.73 (1H, dd, J = 13.7 Hz, 5.4 Hz), 2.82 (1H, quintet, J = 7.3 Hz), 3.43 (1H, sextet, J = 3.9 Hz), 3.78 (3H, s), 6.79-6.80 (2H, m), 7.07-7.09 (2H, m), 7.16-7.19 (3H, m), 7.26-7.29 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.6, -4.4, 18.1, 24.7, 24.7, 25.9, 31.2, 37.2, 38.2, 46.7, 55.3, 69.8, 82.9, 113.6, 125.5, 128.1, 128.3, 128.4, 139.0, 143.1, 157.7; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.6; IR (neat): 2977.0 (w), 2928.6 (w), 2855.9 (w), 1510.7 (m), 1462.2 (w), 1369.0 (s), 1318.6 (m), 1245.6 (s), 1143.6 (s), 967.2 (m), 830.5 (s), 807.6 (s), 772.8 (m), 698.4 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{31}H_{50}BO_4Si$ [M+H]: calculated: 525.3571, found: 525.3589.



tert-butyldimethyl((1-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(4-(trifluoromethyl)-phenyl)hexan-3-yl)oxy)silane. (4.86) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 4-bromobenzotrifluoride (39 μL, 0.275 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (110 mg, 78%).

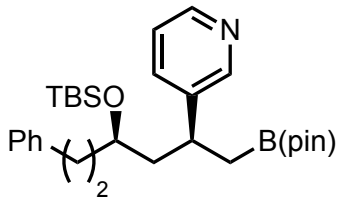
^{1}H NMR (500 MHz, $CDCl_3$): δ -0.08 (3H, s), -0.05 (3H, s), 0.88 (9H, s), 1.05-1.11 (1H, m), 1.09 (12H, s), 1.19 (1H, dd, J = 15.2 Hz, 6.4 Hz), 1.67-1.74 (1H, m), 1.78-1.84 (1H, m), 1.83 (2H, t, J = 6.4 Hz), 2.54 (1H, dd, J = 11.2 Hz, 5.9 Hz), 2.70 (1H, dd, J = 13.7 Hz, 5.4 Hz), 2.95 (1H, quintet, J = 7.8 Hz), 3.44 (1H, sextet, J = 4.4 Hz), 7.14-7.19 (3H, m), 7.25-7.28 (4H, m), 7.49-7.51 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.5, -4.5, 18.1, 24.6, 24.7, 25.9, 31.1, 37.9, 38.4, 46.2, 69.5, 83.1, 125.1 (q, J = 3.9 Hz), 125.6, 127.7, 128.3, 128.3, 142.7, 151.3; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.5; IR (neat): 2977.9 (w), 2929.8 (w), 2857.1 (w), 1471.4 (m), 1370.2 (m), 1322.9 (s), 1254.3 (m), 1163.1 (m), 1123.2 (s), 1067.2 (s), 833.2 (s), 773.1 (s), 745.6 (m), 698.5 (m), 606.5 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{31}H_{46}BF_3O_3Si$ [M+H]: calculated: 563.3340, found: 563.3345.



tert-butyldimethyl((1-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-5-(o-tolyl)hexan-3-yl)oxy)silane. (4.87) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 2-bromotoluene (45 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (92 mg, 72%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.05 (3H, s), 0.00 (3H, s), 0.90 (9H, s), 1.04 (12H, s), 1.05 (1H, dd, J = 15.2 Hz,, 9.3 Hz), 1.16 (1H, dd, J = 15.7 Hz, 6.4 Hz), 1.67-1.86 (4H, m), 2.35 (3H, s), 2.56 (1H, dd, J = 11.3 Hz, 4.9 Hz), 2.68 (1H, dd, J = 13.7 Hz, 5.9 Hz), 3.24 (1H, quintet, J = 6.8 Hz), 3.58 (1H, quintet, J = 5.9 Hz), 7.02-7.09 (2H, m), 7.14-

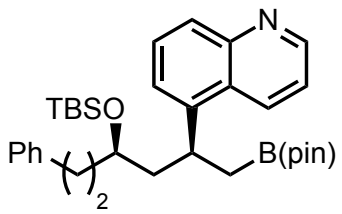
7.18 (4H, m), 7.22-7.28 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.5, -4.5, 18.1, 19.9, 24.5, 24.7, 25.9, 31.3, 32.1, 39.3, 46.3, 69.8, 82.8, 125.4, 125.5, 126.0, 126.0, 128.3, 128.3, 130.0, 135.5, 142.9, 145.5; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.4; IR (neat): 2976.4 (w), 2952.2 (w), 2928.1 (w), 2856.3 (w), 1461.9 (w), 1367.0 (s), 1317.8 (s), 1254.0 (m), 1144.1 (s), 1066.3 (m), 967.6 (m), 833.2 (s), 772.6 (s), 698.1 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{31}H_{50}BO_3Si$ [M+H]: calculated: 509.3622, found: 509.3641.



3-(4-((tert-butyldimethylsilyl)oxy)-6-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-2-yl)pyridine. (4.89) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 3-bromopyridine (36 μL, 0.38 mmol). The crude product was purified on silica gel (2% MeOH in DCM) to afford the title compound as a colorless oil (64 mg, 52%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.08 (3H, s), -0.06 (3H, s), 0.87 (9H, s), 1.09 (12H, s), 1.04-1.12 (1H, m), 1.21 (1H, dd, J = 15.6 Hz, 6.4 Hz), 1.68-1.75 (1H, m), 1.79-1.87 (3H, m), 2.51-2.57 (1H, m), 2.67-2.73 (1H, m), 2.92 (1H, quintet, J = 7.7 Hz), 3.46 (1H, quintet, J = 5.9 Hz), 7.15-7.20 (4H, m), 7.25-7.28 (2H, m), 7.49-7.50 (1H, m), 8.41-8.44 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.5, -4.5, 18.0, 24.7, 24.7, 25.9, 31.1, 35.4, 38.5, 46.2, 69.6, 83.1, 123.2, 125.6, 128.3, 134.4, 142.2, 142.7, 147.5, 149.6; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.2; IR (neat): 3026.6 (w), 2977.1 (w), 2928.8 (m), 2856.2 (w), 1369.7 (s), 1317.3 (m), 1252.3 (m), 1143.2 (s), 1068.2 (m), 833.2 (s), 772.9 (s), 715.1

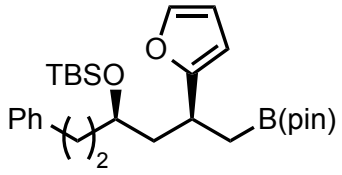
(m), 698.6 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{29}H_{47}BNO_3Si$ [M+H]: calculated: 496.3418, found: 496.3435.



5-(4-((tert-butyldimethylsilyl)oxy)-6-phenyl-1-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-2-yl)quinolone. (4.91) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 5-bromoquinoline (78 μL, 0.38 mmol). The crude product was purified on silica gel (2% MeOH in DCM) to afford the title compound as a colorless oil (90 mg, 66%).

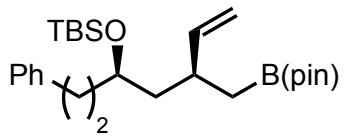
^{1}H NMR (500 MHz, $CDCl_3$): δ -0.03 (3H, s), 0.04 (3H, s), 0.88 (6H, s), 0.93 (9H, s), 0.96 (6H, s), 1.24-1.29 (1H, m), 1.35 (1H, dd, J = 15.7 Hz, 5.4 Hz), 1.69-1.79 (2H, m), 1.86 (1H, quintet, J = 6.4 Hz), 2.00 (1H, quintet, J = 6.85 Hz), 2.46-2.52 (1H, m), 2.56-2.63 (1H, m), 3.64 (1H, quintet, J = 5.9 Hz), 3.85 (1H, s), 7.07 (2H, d, J = 7.5 Hz), 7.15 (1H, t, J = 7.0 Hz), 7.23 (2H, t, J = 7.0 Hz), 7.39 (1H, dd, J = 9.0 Hz, 4.0 Hz), 7.50 (1H, d, J = 7.0), 7.66 (1H, t, J = 7.5 Hz), 7.95 (1H, d, J = 8.5 Hz), 8.63 (1H, d, J = 8.5 Hz), 8.90 (1H, dd, J = 4.0 Hz, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.4, -4.4, 18.1, 24.4, 24.5, 24.7, 26.0, 31.1, 39.2, 46.6, 69.8, 82.9, 120.4, 123.7, 125.6, 126.8, 127.6, 128.2, 128.3, 129.0, 132.5, 142.5, 144.3, 148.6, 149.7; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.5; IR (neat): 3063.6 (w), 3027.1 (w), 2976.0 (w), 2951.8 (m), 2928.3 (m), 2856.1 (w), 1594.9 (m), 1572.5 (m), 1499.3 (m), 1470.8 (m), 1361.3 (s), 1323.6 (m), 1252.5 (m), 1142.9 (s), 1060.6 (m),

832.9 (s), 800.0 (s), 773.0 (s), 739.2 (m), 698.4 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{33}H_{49}BNO_3Si$ [M+H]: calculated: 546.3575, found: 546.3598.



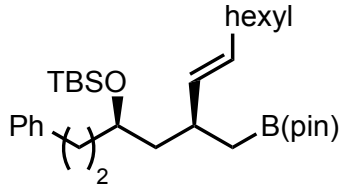
tert-butyl((5-(furan-2-yl)-1-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl)oxy)dimethylsilane. (4.93) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 2-bromofuran (33 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (62 mg, 51%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.02 (3H, s), 0.00 (3H, s), 0.89 (9H, s), 1.12 (2H, t, J = 6.36 Hz), 1.17 (6H, s), 1.17 (6H, s), 1.67-1.76 (2H, m), 1.81-1.94 (2H, m), 2.57 (1H, dd, J = 11.2 Hz, 4.9 Hz), 2.73 (1H, dd, J = 13.7 Hz, 5.4 Hz), 3.02 (1H, quintet, J = 7.8 Hz), 3.59 (1H, quintet, J = 5.4 Hz), 5.93 (1H, d, J = 2.9 Hz), 6.23 (1H, t, J = 2.5 Hz), 7.15-7.19 (3H, m), 7.25-7.28 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.6, -4.5, 18.1, 24.7, 24.8, 25.9, 31.3, 31.4, 38.5, 44.0, 69.8, 83.0, 104.0, 109.7, 125.5, 128.3, 128.4, 140.4, 142.9, 160.0; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.6; IR (neat): 2977.3 (w), 2950.9 (w), 2928.7 (w), 2856.3 (w), 1461.5 (w), 1368.3 (s), 1318.5 (m), 1253.7 (m), 1143.9 (s), 1068.0 (m), 1006.3 (m), 967.5 (m), 833.3 (s), 773.1 (s), 728.0 (m), 698.2 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{28}H_{46}BO_4Si$ [M+H]: calculated: 485.3258, found: 485.3274.



tert-butyldimethyl((1-phenyl-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)hept-6-en-3-yl)oxy)-silane. (4.95) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 1,2-dichloroethane (59 μL, 0.75 mmol). KO*t*-Bu (168 mg, 1.5 mmol) was used instead of KOH. The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (83 mg, 75%).

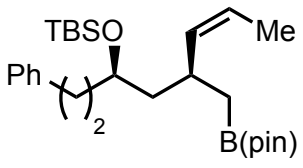
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05 (6H, s), 0.79-0.91 (2H, m), 0.91 (9H, s), 1.22 (12H, s), 1.49-1.58 (2H, m), 1.64-1.71 (1H, m), 1.80-1.87 (1H, m), 2.33 (1H, q, J = 6.9 Hz), 2.59 (1H, td, J = 13.7 Hz, 5.4 Hz), 2.75 (1H, td, J = 13.2 Hz, 5.4 Hz), 3.72 (1H, quintet, J = 6.4 Hz), 4.89 (1H, dd, J = 10.3 Hz, 1.5 Hz), 4.93 (1H, d, J = 17.1 Hz), 5.67 (1H, quintet, J = 9.2 Hz), 7.15-7.20 (3H, m), 7.26-7.29 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.4, -4.3, 18.1, 24.9, 26.0, 31.3, 36.6, 38.3, 44.5, 70.0, 83.0, 113.1, 125.5, 128.2, 128.4, 143.1, 144.1; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.4; IR (neat): 2977.4 (w), 2952.9 (w), 2928.1 (m), 2856.4 (w), 1471.2 (w), 1368.3 (s), 1318.6 (m), 1254.4 (m), 1144.2 (s), 1061.3 (s), 967.6 (m), 833.8 (s), 772.9 (s), 698.1 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{26}H_{46}BO_3Si$ [M+H]: calculated: 445.3309, found: 445.3320.



tert-butyldimethyl(((E)-1-phenyl-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) methyl)tridec-6-en-3-yl)oxy)-silane. (4.97) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25

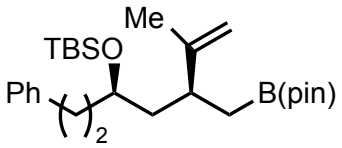
mmol) and (E)-1-chlorooct-1-ene (63 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (71 mg, 54%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05 (6H, s), 0.77-0.90 (2H, m), 0.89 (3H, t, J = 6.8 Hz), 0.91 (9H, s), 1.22 (12H, s), 1.24-1.34 (8H, m), 1.43-1.56 (2H, m), 1.67 (1H, sextet, J = 5.9 Hz), 1.81-1.87 (1H, m), 1.93-1.95 (2H, m), 2.21-2.27 (1H, m), 2.57 (1H, td, J = 13.7 Hz, 4.9 Hz), 2.76 (1H, td, J = 13.7 Hz, 5.4 Hz), 3.71 (1H, septet, J = 3.9 Hz), 5.22 (1H, dd, J = 15.2 Hz, 8.3 Hz), 5.33 (1H, dt, J = 15.2 Hz, 6.9 Hz), 7.15-7.20 (3H, m), 7.26-7.29 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): -4.4, -4.2, 14.1, 18.1, 22.6, 24.8, 24.9, 24.9, 25.0, 26.0, 28.9, 29.6, 31.4, 31.8, 32.5, 35.5, 38.2, 45.2, 70.2, 82.9, 125.5, 128.2, 128.4, 129.3, 135.5, 143.1; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.5; IR (neat): 2954.5 (w), 2926.0 (m), 2855.3 (w), 1461.7 (w), 1369.6 (m), 1317.2 (m), 1253.6 (m), 1144.3 (m), 1079.2 (m), 1059.8 (m), 967.7 (m), 833.3 (s), 772.6 (s), 697.9 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{32}H_{58}BO_3Si$ [M+H]: calculated: 529.4248, found: 529.4262.



tert-butyldimethyl(((Z)-1-phenyl-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)oct-6-en-3-yl)oxy)silane. (4.99) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and (Z)-1-chloroprop-1-ene (31 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (78 mg, 68%).

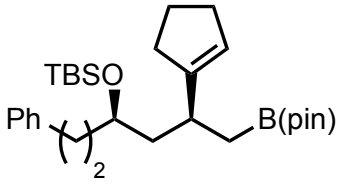
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.05 (3H, s), 0.06 (3H, s), 0.75 (1H, dd, J = 15.7 Hz, 8.3 Hz), 0.86 (1H, dd, J = 15.2 Hz, 5.7 Hz), 0.91 (9H, s), 1.21 (12H, s), 1.43-1.49 (1H, m), 1.56 (1H, t, J = 3.9 Hz), 1.59 (3H, dd, J = 6.9 Hz, 1.5 Hz), 1.67 (1H, sextet, J = 5.4 Hz), 1.79-1.86 (1H, m), 2.56 (1H, td, J = 11.7 Hz, 4.9 Hz), 2.62 -2.69 (1H, m), 2.76 (1H, td, J = 13.7 Hz, 5.4 Hz), 3.65 (1H, septet, J = 4.4 Hz), 5.17 (1H, td, J = 10.3 Hz, 1.5 Hz), 5.34-5.40 (1H, m), 7.15-7.19 (3H, m), 7.26-7.29 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): -4.4, -4.2, 13.2, 18.1, 24.8, 24.9, 26.0, 29.6, 31.6, 38.7, 45.5, 70.3, 82.9, 122.3, 125.5, 128.3, 128.4, 136.6, 143.1; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.6; IR (neat): 2977.5 (w), 2952.4 (w), 2928.5 (m), 2856.6 (w), 1461.9 (w), 1405.7 (s), 1362.2 (m), 1320.3 (m), 1253.9 (m), 1144.2 (s), 1062.9 (s), 967.8 (m), 833.5 (s), 772.4 (s), 730.7 (m), 697.7 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{27}H_{48}BO_3Si$ [M+H]: calculated: 459.3466, found: 459.3489.



tert-butyldimethyl((6-methyl-1-phenyl-5-((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)hept-6-en-3-yl)oxy)silane. (4.102) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 2-chloroprop-1-ene (32 μL, 0.38 mmol). Cross-coupling run with 10 mol % $Pd(OAc)_2$ and 12 mol % RuPhos. The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (80 mg, 70%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.04 (3H, s), 0.05 (3H, s), 0.91 (9H, s), 0.82-0.93 (2H, m), 1.21 (12H, s), 1.47-1.52 (1H, m), 1.57-1.64 (1H, m), 1.66 (3H, s), 1.69 (1H, quintet, J

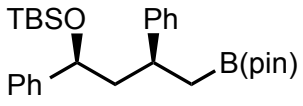
= 5.9 Hz), 1.80-1.87 (1H, m), 2.36-2.43 (1H, m), 2.58 (1H, td, J = 11.7 Hz, 4.9 Hz), 2.75 (1H, td, J = 12.7 Hz, 5.2 Hz), 3.61-3.65 (1H, m), 4.66 (1H, s), 4.68 (1H, s), 7.15-7.19 (3H, m), 7.26-7.28 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): -4.4, -4.3, 18.1, 18.2, 24.8, 24.9, 25.9, 31.1, 38.2, 39.5, 42.8, 70.1, 83.0, 110.4, 125.5, 128.2, 128.4, 143.2, 149.1; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.5; IR (neat): 2977.3 (w), 2928.8 (w), 2856.5 (w), 1461.5 (w), 1361.9 (m), 1317.1 (m), 1253.5 (m), 1144.1 (s), 1061.5 (m), 967.7 (m), 833.0 (s), 772.3 (s), 697.9 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{27}H_{48}BO_3Si$ [M+H]: calculated: 459.34658, found: 459.34576.



tert-butyl((5-(cyclopent-1-en-1-yl)-1-phenyl-6-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl)oxy)dimethylsilane. (4.104) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylhex-5-en-3-ol (44 mg, 0.25 mmol) and 1-chlorocyclopent-1-ene (37 μL, 0.38 mmol). Cross-coupling run with 10 mol % $Pd(OAc)_2$ and 12 mol % RuPhos. The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (62 mg, 51%).

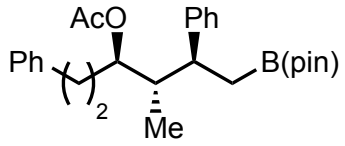
^{1}H NMR (500 MHz, $CDCl_3$): δ 0.03 (3H, s), 0.04 (3H, s), 0.90 (9H, s), 0.83-0.94 (2H, m), 1.20 (12H, s), 1.48-1.53 (1H, m), 1.59-1.70 (2H, m), 1.77-1.87 (3H, m), 2.23 (2H, t, J = 7.8 Hz), 2.14-2.27 (2H, m), 2.52-2.60 (1H, m), 2.59 (1H, td, J = 11.7 Hz, 4.9 Hz), 2.74 (1H, td, J = 13.2 Hz, 4.9 Hz), 3.61 (1H, septet, J = 4.9 Hz), 5.30 (1H, s), 7.15-7.19 (3H, m), 7.25-7.28 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): -4.5, -4.3, 18.1, 23.4, 24.8, 24.8,

26.0, 31.1, 31.2, 32.0, 33.6, 38.2, 43.4, 70.2, 82.9, 123.6, 125.5, 128.2, 128.4, 143.1, 148.6; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.6; IR (neat): 2976.9 (w), 2928.1 (w), 2855.3 (w), 1461.7 (w), 1368.6 (s), 1313.4 (m), 1252.9 (m), 1144.2 (m), 1031.1 (w), 967.7 (w), 938.5 (w), 808.4 (s), 772.5 (s), 746.7 (w), 698.1 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{29}H_{50}BO_3Si$ [M+H]: calculated: 485.3622, found: 485.3627.



tert-butyl(1,3-diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)dimethylsilane. (4.106) Prepared according the general diboration/cross-coupling/protection procedure using 1-phenylbut-3-en-1-ol (44 mg, 0.25 mmol) and bromobenzene (39 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (80 mg, 68%).

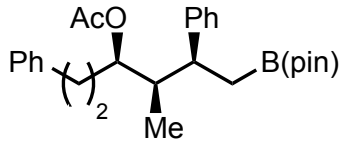
^{1}H NMR (500 MHz, $CDCl_3$): δ -0.27 (3H, s), -0.08 (3H, s), 0.81 (9H, s), 1.03 (6H, s), 1.05 (6H, s), 1.02-1.07 (1H, m), 1.17 (1H, dd, J = 15.2 Hz, 6.36 Hz), 1.96 (1H, quintet, J = 6.85 Hz), 2.12 (1H, quintet, J = 6.16 Hz), 2.73 (1H, quintet, J = 7.33 Hz), 4.39 (1H, t, J = 6.36 Hz), 7.13-7.16 (1H, m), 7.18-7.19 (2H, m), 7.21-7.24 (4H, m), 7.25-7.29 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.0, -4.7, 18.1, 24.6, 24.7, 25.8, 37.5, 49.9, 73.3, 82.8, 125.8, 126.9, 127.9, 128.1, 145.3, 147.0; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.2; IR (neat): 2977.1 (w), 2954.5 (w), 2928.5 (w), 2856.2 (w), 1453.8 (w), 1369.0 (s), 1318.9 (m), 1252.7 (m), 1144.2 (s), 1068.9 (m), 967.8 (m), 834.1 (s), 774.0 (s), 697.6 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{28}H_{42}BO_3Si$ [M+H]: calculated: 465.2996, found: 466.3014.



(3R,4S,5S)-4-methyl-1,5-diphenyl-6-(4,4,5,5-tetra-methyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl acetate.

(4.108) Prepared according the general diboration/cross-coupling/protection procedure using (*3R,4S*)-4-methyl-1-phenylhex-5-en-3-ol (48 mg, 0.25 mmol) and bromobenzene (39 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a white solid (80 mg, 73%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (3H, d, J = 6.85 Hz), 0.98 (6H, s), 0.99 (6H, s), 1.04 (1H, dd, J = 15.2 Hz, 11.2 Hz), 1.24 (1H, dd, J = 15.2 Hz, 4.4 Hz), 1.76-1.81 (2H, m), 1.99 (3H, s), 2.02-2.08 (1H, m), 2.29-2.35 (1H, m), 2.48-2.54 (1H, m), 2.68-2.73 (1H, m), 4.59 (1H, quintet, J = 4.4 Hz), 7.07-7.08 (2H, m), 7.13-7.17 (4H, m), 7.23-7.26 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.7, 21.2, 24.5, 24.6, 24.6, 30.6, 32.3, 43.2, 43.7, 75.9, 82.9, 125.8, 126.1, 127.9, 128.1, 128.3, 128.3, 141.9, 144.9, 170.6; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.5; IR (neat): 3027.0 (w), 2975.9 (m), 2931.7 (w), 1732.0 (s), 1495.1 (w), 1453.4 (m), 1365.8 (s), 1319.4 (m), 1234.8 (s), 1143.6 (s), 988.4 (m), 966.6 (m), 846.6 (m), 747.8 (m), 698.0 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{27}H_{38}BO_4$ [M+H]: calculated: 437.2863, found: 437.2853.

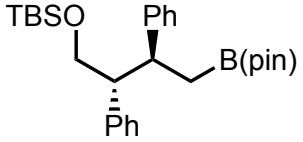


(3R,4R,5S)-4-methyl-1,5-diphenyl-6-(4,4,5,5-tetra-methyl-1,3,2-dioxaborolan-2-yl)hexan-3-yl acetate.

(4.110) Prepared according the general diboration/cross-coupling/protection procedure using (3R,4R)-4-methyl-1-phenylhex-5-en-3-ol (48 mg, 0.25 mmol) and bromobenzene

(39 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a white solid (83 mg, 76%).

^{1}H NMR (500 MHz, $CDCl_3$): δ 0.75 (3H, d, J = 6.85 Hz), 0.97 (6H, s), 0.99 (6H, s), 1.11 (1H, dd, J = 15.2 Hz, 10.8 Hz), 1.33 (1H, dd, J = 15.2 Hz, 4.9 Hz), 1.80-1.90 (2H, m), 1.99 (3H, s), 1.96-2.04 (1H, m), 2.58-2.65 (2H, m), 2.72-2.77 (1H, m), 5.19 (1H, septet, J = 2.93 Hz), 7.09-7.15 (3H, m), 7.17-7.24 (5H, m), 7.26-7.30 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.8, 21.2, 24.5, 24.6, 32.2, 34.3, 42.8, 44.0, 74.7, 82.8, 125.9, 125.9, 128.0, 128.1, 128.2, 128.3, 128.3, 128.4, 141.7, 145.4, 170.9; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.4; IR (neat): 3060.4 (w), 3027.6 (w), 2976.9 (w), 2931.1 (w), 1731.1 (s), 1368.2 (s), 1320.8 (m), 1237.0 (s), 1143.4 (s), 966.3 (m), 908.8 (m), 846.8 (m), 735.2 (s), 698.7 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{27}H_{38}BO_4$ [M+H]: calculated: 437.2863, found: 437.2868.

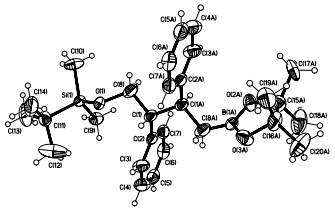


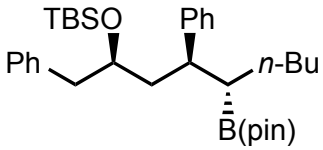
tert-butyl(2,3-diphenyl-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)dimethylsilane. (4.112) Prepared according the general diboration/cross-coupling/protection procedure using 2-phenylbut-3-en-1-ol (37 mg, 0.25 mmol) and bromobenzene (39 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a white solid (62 mg, 53%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.28 (3H, s), -0.24 (3H, s), 0.73 (9H, s), 0.89 (6H, s), 0.92 (6H, s), 0.89-0.97 (2H, m), 2.81 (1H, quintet, J = 4.9 Hz), 3.24 (1H, sextet, J = 5.4

Hz), 3.48-3.51 (2H, m), 7.14-7.21 (2H, m), 7.23-7.28 (8H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.8, -5.7, 18.2, 24.3, 24.6, 25.8, 42.8, 56.5, 65.5, 82.7, 126.0, 126.1, 127.8, 127.9, 128.3, 129.2, 142.9, 145.4; ^{11}B NMR (160 MHz, $CDCl_3$): δ 33.5; IR (neat): 3028.1 (w), 2977.0 (w), 2954.0 (w), 2928.0 (m), 2895.9 (w), 2856.1 (w), 1601.8 (w), 1494.2 (w), 1470.3 (w), 1452.8 (w), 1361.3 (m), 1322.4 (m), 1252.1(m), 1144.5 (m), 1105.5 (s), 834.1 (s), 773.4 (m), 756.2 (m), 698.1 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{28}H_{44}BO_3Si$ [M+H]: calculated: 467.3153, found: 467.3156.

Proof of Stereochemistry: The relative stereochemistry was determined by crystal structure determination (as shown below).

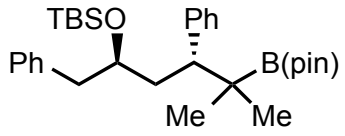




tert-butyl((1,4-diphenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)nonan-2-yl)oxy)dimethylsilane. (4.114) Prepared according the general diboration/cross-coupling/protection procedure using (Z)-1-phenylnon-4-en-2-ol (55 mg, 0.25 mmol) and bromobenzene (39 μL, 0.38 mmol). The crude product was purified on silica gel (100%

hexanes to 50% DCM in hexanes) to afford the title compound as a colorless oil (85 mg, 63%).

^{1}H NMR (500 MHz, $CDCl_3$): δ -0.71 (3H, s), -0.40 (3H, s), 0.68 (9H, s), 0.75 (3H, t, J = 6.35 Hz), 1.01-1.14 (3H, m), 1.14-1.22 (3H, m), 1.26-1.29 (1H, m), 1.29 (12H, s), 1.76 (1H, ddd, J = 13.7 Hz, 10.3 Hz, 3.4 Hz), 1.90 (1H, td, J = 12.7 Hz, 2.9 Hz), 2.35 (1H, dd, J = 13.7 Hz, 9.29 Hz), 2.67 (1H, td, J = 13.7 Hz, 3.4 Hz), 2.99 (13.7 Hz, 1.96 Hz), 3.27 (1H, t, J = 9.78), 7.00-7.01 (2H, m), 7.09-7.12 (1H, m), 7.16-7.21 (5H, m), 7.29-7.32 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -5.7, -5.1, 13.9, 17.8, 22.7, 25.0, 25.1, 25.8, 29.3, 31.3, 42.5, 44.7, 45.4, 72.2, 83.2, 125.7, 126.1, 127.8, 128.0, 128.3, 129.9, 140.1, 144.7; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.6; IR (neat): 2954.6 (w), 2927.2 (m), 2856.0 (w), 1454.1 (w), 1405.0 (m), 1317.5 (m), 1254.1 (m), 1142.6 (s), 1079.8 (m), 1066.5 (m), 830.4 (s), 809.2 (m), 773.9 (s), 698.9 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{33}H_{54}BO_3Si$ [M+H]: calculated: 537.3935, found: 537.3924.

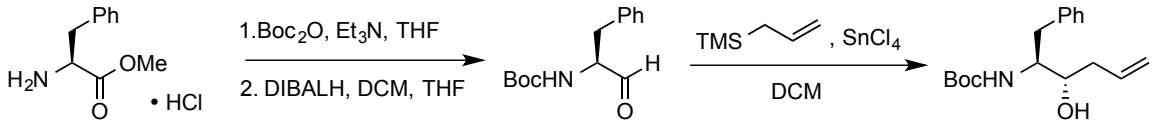


tert-butyldimethyl((5-methyl-1,4-diphenyl-5-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)hexan-2-yl)oxy)-silane. (4.116) Prepared according the general diboration/cross-coupling/protection procedure using 5-methyl-1-phenylhex-4-en-2-ol (48 mg, 0.25 mmol) and bromobenzene (39 μL, 0.38 mmol). The crude product was purified on silica gel (100% hexanes to 50% DCM in hexanes) to afford the title compound as a white solid (58 mg, 46%).

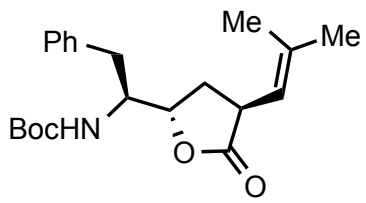
^{1}H NMR (500 MHz, $CDCl_3$): δ -0.13 (3H, s), -0.10 (3H, s), 0.72 (3H, s), 0.76 (3H, s), 0.91 (9H, s), 1.14 (6H, s), 1.17 (6H, s), 1.50-1.54 (1H, m), 1.97 (1H, td, J = 13.2 Hz, 2.0 Hz), 2.54 (1H, dd, J = 13.2 Hz, 7.8 Hz), 2.70 (1H, dd, J = 13.2 Hz, 4.4 Hz), 2.86 (1H, dd, J = 12.2 Hz, 2.0 Hz), 3.49 (1H, m), 6.88-6.89 (2H, m), 7.02-7.03 (2H, m), 7.12-7.15 (3H, m), 7.15-7.18 (1H, m), 7.20-7.23 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ -4.6, -4.1, 18.1, 20.7, 24.2, 24.6, 24.8, 26.0, 38.3, 45.3, 48.6, 71.9, 82.9, 125.7, 125.8, 127.2, 128.0, 129.7, 130.1, 138.9, 141.6; ^{11}B NMR (160 MHz, $CDCl_3$): δ 34.2; IR (neat): 3027.3 (w), 2953.2 (m), 2928.5 (m), 2889.4 (w), 2856.3 (w), 1471.2 (m), 1370.7 (m), 1343.8 (m), 1306.1 (m), 1252.8 (m), 1135.3 (s), 1083.2 (s), 1063.6 (s), 964.5 (m), 832.8 (s), 772.9 (s), 743.2 (s), 698.7 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{31}H_{50}BO_3Si$ [M+H]: calculated: 509.3622, found: 509.3610.

4.14.5 Synthesis of CCR-1 Antagonist

tert-Butyl (S)-(1-oxo-3-phenylpropan-2-yl)carbamate and tert-butyl ((2S,3S)-3-hydroxy-1-phenylhex-5-en-2-yl)carbamate (**4.130)** were prepared following literature procedures (shown below). All spectral data are in accord with the literature.[44]



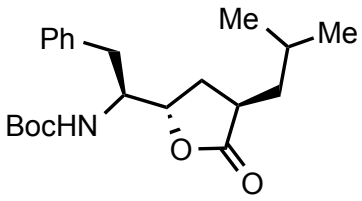
[44] Diaz, L. C.; Diaz, G.; Ferreira, A. A.; Meira, P. R. R.; Ferreira, E. *Synthesis* **2003**, *4*, 603 – 622.



***tert*-butyl ((S)-1-((2S,4S)-4-(2-methylprop-1-en-1-yl)-5-oxotetrahydrofuran-2-yl)-2-phenylethyl)carbamate. (4.132)** To an oven-dried 2-dram vial with magnetic stir bar was added tert-butyl ((2S,3S)-3-hydroxy-1-phenylhex-5-en-2-yl)carbamate (73 mg, 0.25 mmol), Cs_2CO_3 (26 mg, 75 μmol), $B_2(pin)_2$ (95 mg, 0.38 mmol), tetrahydrofuran (1 mL, [substrate] = 0.25 M) and methanol (0.17 mL, 4.25 mmol). The vial was sealed with a teflon septum cap and heated to 70 ºC for 12 h. The reaction was cooled to room temperature and concentrated *in vacuo* (ensuring that all methanol has been removed from the residue). The flask was brought to a dry box and charged with solid potassium hydroxide (42 mg, 0.75 mmol), $Pd(OAc)_2$/RuPhos (added as a 1:1.2 solution in THF (0.025 M); 0.25 mL for 2.5 mol% $Pd(OAc)_2$), tetrahydrofuran (0.95 mL), toluene (1.2 mL) and 1-chloro-2-methylpropene (37 μL, 0.38 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.23 mL) was added through the teflon septum cap. The vial was heated to 70 ºC and stirred for 12 h. The reaction mixture was transferred to a 25-mL round bottom flask and cooled to 0 ºC (ice/water) and charged with 3 M sodium hydroxide (0.5 mL), and 30% hydrogen peroxide (0.5 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h at which time the vial was diluted with ethyl acetate and the aqueous and organic layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation into 20 mL vial. To the residue was added DCM (2.8 mL), H_2O (0.83 mL), $PhI(OAc)_2$ (0.36 g, 1.10 mmol), and TEMPO (8 mg, 0.05 mmol). The reaction was allowed to stir for 4 h at room temperature. The reaction mixture was quenched with sat.

$NaHCO_3$ (4 mL). The layers were allowed to separate and the aqueous layer was extracted with DCM (3 x 10 mL). The combined organic layers were washed with brine, dried with Na_2SO_4, filtered and concentrated with rotatory evaporation. The crude material was purified on SiO_2 (5% to 15% EtOAc/hexanes, stain with $KMnO_4$) to afford the title compound as a colorless oil (60 mg, 67% yield).

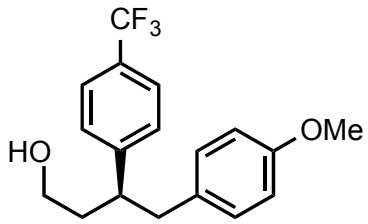
^{1}H NMR (500 MHz, $CDCl_3$): δ 1.39 (9H, s), 1.69 (3H, s), 1.73 (3H, s), 1.92-1.98 (1H, m), 2.40-2.46 (1H, m), 2.86-2.94 (2H, m), 3.52 (1H, q, J = 8.8 Hz), 4.03 (1H, q, J = 7.8 Hz), 4.50 (1H, t, J = 6.9 Hz), 4.56 (1H, d, J = 9.3 Hz), 5.04 (1H, d, J = 8.8 Hz), 7.23-7.26 (3H, m), 7.29-7.32 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): 18.3, 25.6, 28.0, 28.2, 32.0, 39.2, 39.6, 54.6, 78.1, 80.0, 119.7, 126.7, 128.6, 129.3, 137.1, 137.8, 155.8, 178.7; IR (neat): 3330.1 (br), 2975.5 (w), 2931.3 (w), 1767.7 (s), 1691.6 (s), 1517.3 (m), 1365.1 (m), 1246.4 (m), 1159.8 (s), 1060.9 (m), 960.9 (w), 736.5 (w), 699.4 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{21}H_{33}N_2O_4$ [M+NH_4]: calculated: 377.2440, found: 377.2438.



***tert*-butyl ((S)-1-((2S,4R)-4-isobutyl-5-oxotetrahydro-furan-2-yl)-2-phenylethyl)-carbamate. (4.133)** To an oven-dried 10 mL round bottom flask was added Pd/C (4.2 mg). A solution of tert-butyl ((S)-1-((2S,4S)-4-(2-methylprop-1-en-1-yl)-5-oxotetrahydro-furan-2-yl)-2-phenylethyl)carbamate (14 mg, 39 μmol) and methanol (1.5 mL) were added to the flask and it was sealed with a rubber septum. The flask was evacuated and refilled with H_2 gas three times and allowed to stir for 1 h at room temperature under 1 atm of H_2. The reaction mixture was filtered through a plug of celite

and washed with EtOAc. The solution was concentrated with rotatory evaporation to afford the title compound cleanly as a colorless oil (13.8 mg, 98% yield). All spectral data are in accord with the literature.[45]

4.14.6 Synthesis of Vitronectin Receptor Antagonist



(S)-4-(4-methoxyphenyl)-3-(4-(trifluoromethyl)-phenyl)-butan-1-ol. (4.137) To an oven-dried 16-mL vial with magnetic stir bar in the dry box was added $Pt(dba)_3$ (4.5 mg, 5.0 μmol), (S,S)-3,5-di-iso-propylphenylTADDOLPPh (5.5 mg, 6.0 μmol), $B_2(pin)_2$ (133 mg, 525 μmol) and tetrahydrofuran (0.5 mL). The vial was sealed with a teflon septum cap, removed from the dry box, and heated to 80 °C in an oil bath for 20 minutes. The vial was cooled to room temperature, returned to the dry box and charged with (but-3-en-1-yloxy)(tert-butyl)dimethylsilane (115 μL, 500 μmol). The vial was sealed, removed from the dry box and stirred at 60 °C for 3 h. The vial was cooled to room temperature, returned to the dry box and charged with solid potassium hydroxide (84 mg, 1.50 mmol), $Pd(OAc)_2$ (1.1 mg, 5.0 μmol)/RuPhos (2.3 mg, 6.0 μmol) (added as a 1:1.2 solution in THF (1 mL)), tetrahydrofuran (3.05 mL) and 4-bromoanisole (66 μl, 525 μmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.45 mL) was added through the teflon septum cap. The vial was heated to 70 °C and stirred for 12 h. The reaction mixture was cooled to room temperature and water (4 mL) was added. The layers were allowed to separate and the aqueous layer was extracted with

[45] Kempf, D. J. *J. Org. Chem.* **1986**, *51*, 3921-3926.

dichloromethane (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in a 4-dram vial. The crude boronate was dissolved in MeOH (4 mL) and *p*-TsOHxH_2O (5 mg). The vial was capped and stirred at room temperature for 1 hour and concentrated, ensuring all the methanol was removed. The crude deprotected intermediate was returned to the dry box and charged with solid potassium hydroxide (84.0 mg, 1.50 mmol), $Pd_2(dba)_3$/RuPhos (added as a 1:2 solution in THF (0.01 M); 0.25 mL for 0.5 mol% $Pd_2(dba)_3$, tetrahydrofuran (2.0 mL), toluene (2.3 mL) and 4-bromobenzotrifluoride (77 μL, 0.55 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.45 mL) was added through the teflon septum cap. The vial was heated to 70 ºC and stirred for 16 h. The reaction mixture was cooled to room temperature and sat. NH_4Cl (aq.) (3 mL) was added. The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2 (10% to 25% EtOAc/hexanes, stain with CAM) to afford the title compound as a colorless oil (101 mg, 62% yield).

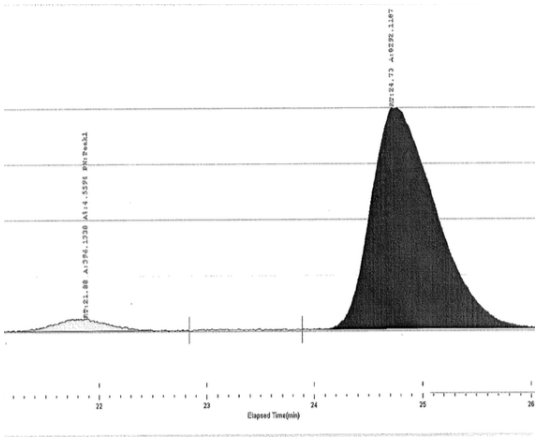
^{1}H NMR (600 MHz, $CDCl_3$): δ 1.82 – 1.88 (1H, m), 1.98 – 2.04 (1H, m), 2.83 (1H, dd, J = 13.5 Hz, 8.2 Hz), 2.88 (1H, dd, J = 14.1 Hz, 7.0 Hz), 3.04 – 3.09 (1H, m), 3.38 – 3.42 (1H, m), 3.51 – 3.55 (1H, m), 3.76 (3H, s), 6.75 (2H, d, J = 8.2 Hz), 6.92 (2H, d, J = 8.8 Hz), 7.23 (2H, d, J = 8.2), 7.51 (2H, d, J = 8.2 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): 38.0, 42.6, 44.3, 55.2, 60.7, 113.6, 125.3, 125.3, 125.3, 125.3, 128.1, 130.0, 131.6, 148.6, 157.9; ^{19}F NMR (564 MHz, $CDCl_3$): -62.3; IR (neat): 3365.8 (w), 2935.4 (m), 2837.7

(w), 1613.8 (m), 1511.3 (s), 1323.3 (s), 1244.9 (s), 1161.4 (s), 1113.9 (s), 1068.1 (s), 1035.2 (s), 1017.1 (s), 837.6 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{18}H_{23}F_3NO_2$ $[M+NH_4]$: calculated: 342.1681, found: 342.1667. $[\alpha]_D^{20}$ = -33.4 (c = 1.02, $CHCl_3$, l= 50 nm).

Analysis of Stereochemistry: The title compound was compared to the racemic analogue derived from the racemic diboration of (but-3-en-1-yloxy)(tert-butyl)dimethylsilane. The resulting racemic diboron was transformed into 4-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)butan-1-ol. as described for the enantioenriched variant.

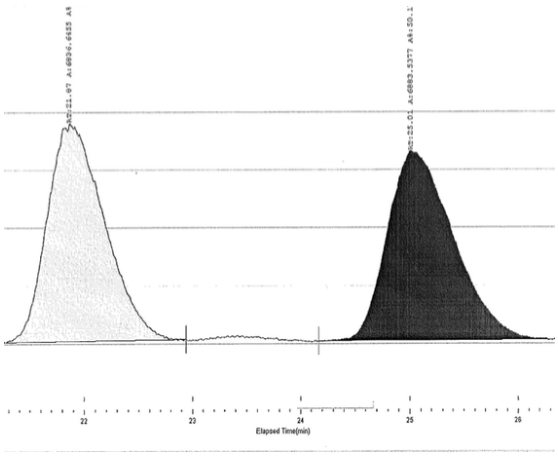
Chiral SFC (Chiracel, OD-H, 35 °C, 3 mL/min, 5% Isopropanol, 100 bar, 210-270nm) – analysis of (S)-4-(4-methoxyphenyl)-3-(4-(trifluoromethyl)phenyl)butan-1-ol.

Reaction Products



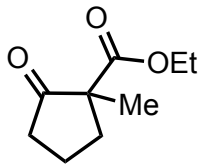
Peak No	% Area	Area	RT (min)
1	4.5594	396.1338	21.88
2	95.4406	8292.1187	24.73
Total:	100	8688.2525	

Racemic

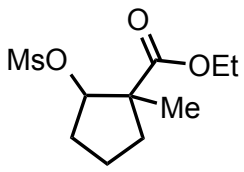


Peak No	% Area	Area	RT (min)
1	49.8291	6836.6455	21.87
2	50.1709	6883.5377	25.01
Total:	100	13720.1832	

4.14.7 Synthesis of Debromohamigeran E



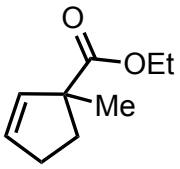
ethyl 1-methyl-2-oxocyclopentane-1-carboxylate. (4.143) To an oven-dried round-bottomed flask with magnetic stir bar and septum was added ethyl 2-oxocyclopentanecarboxylate (4.45 mL, 30 mmol) and acetone (99 mL). Add potassium carbonate (8.29 g, 60.0 mmol) and MeI (3.74 mL, 60.0 mmol) to the flask. Heat the reaction to reflux for 4 hours. Add MeI (3.74 mL, 60.0 mmol). Stir the reaction overnight at reflux. Cool the flask to room temperature and filter the reaction mixture through a plug of SiO_2 and wash with acetone. The collected organic fraction was concentrated with rotatory evaporation. The crude material was purified on SiO_2 (2.5% to 10% EtOAc in hexanes, stained with CAM) to afford the title compound as a colorless oil (4.44 g, 87% yield). All spectral data are in accord with the literature.[46]



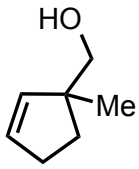
ethyl 1-methyl-2-((methylsulfonyl)oxy)cyclopentane-1-carboxylate. (4.144) To an oven-dried round-bottomed flask with magnetic stir bar and septum was added MeOH (31 mL) and $NaBH_4$ (1.18 g, 31.3 mmol). Cool the flask to -78 ºC and add ethyl 1-methyl-2-oxocyclopentane-1-carboxylate (4.44 g, 26.1 mmol) in MeOH (51 mL). Slowly warm the reaction to room temperature and stir for two hours. Quench the reaction with brine. The layers were allowed to separate and the aqueous layer was extracted with DCM (3 x 60 mL). The combined organic layers was dried with Na_2SO_4, filtered and concentrated with rotatory evaporation. The crude alcohol was taken up in DCM (57 mL) and cooled to 0 ºC. Add

[46] Pichlmair, S.; de Lera Ruiz, M.; Basu, K.; Paquette, L. A. *Tetrhedron* **2006**, *62*, 5178 – 5194.

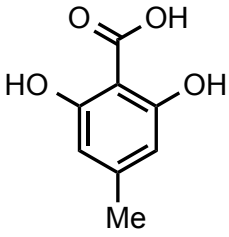
Et_3N (10.9 mL, 78.3 mmol) and MsCl (2.63 mL, 33.9 mmol) to the flask dropwise. Allow the reaction to stir at 0 ºC for two hours. Quench the reaction with water. The layers were allowed to separate and the aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layers was dried with Na_2SO_4, filtered and concentrated with rotatory evaporation. The crude material was purified on SiO_2 (15% to 30% EtOAc in hexanes, stained with CAM) to afford the title compound as a colorless oil (4.54 g, 74% yield). All spectral data are in accord with the literature.[48]



ethyl 1-methylcyclopent-2-ene-1-carboxylate. (4.145) Prepared following literature procedures from ethyl 1-methyl-2-((methylsulfonyl)oxy)cyclopentane-1-carboxylate.[48] All spectral data are in accord with the literature. [48]

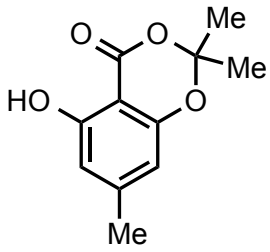


(1-methylcyclopent-2-en-1-yl)methanol. (4.146) Prepared following literature procedures from ethyl 1-methylcyclopent-2-ene-1-carboxylate.[12] All spectral data are in accord with the literature. [48]

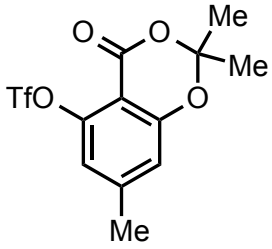


2,6-dihydroxy-4-methylbenzoic acid. (4.148) Prepared following literature procedures. [47] All spectral data are in accord with the literature.

[47] Crombie, L.; Games, D. E.; James, A. W. G. *J. Chem. Soc., Perkin Trans. 1,* **1996**, *22*, 2715 – 2724.



5-hydroxy-2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-4-one. (4.149) To an oven-dried vial with magnetic stir bar and a teflon septum cap was added 2,6-dihydroxy-4-methylbenzoic acid (5.80 g, 34.5 mmol), DMAP (0.21 g, 1.72 mmol) and 1,2-dimethoxyethane (26 mL, [substrate] = 1.33 M) under N_2. The vial was cooled to 0 ºC and added acetone (3.29 mL, 44.8 mmol) and $SOCl_2$ (3.26 mL, 44.8 mmol). Stir at 0 ºC for 1 hour and allowed to warm to room temperature. Stir at room temperature for 23 hours. Quench the reaction with sat. $NaHCO_3$. The layers were allowed to separate and the aqueous layer was extracted with Et_2O (3 x 40 mL). The combined organic layers was dried with $MgSO_4$, filtered and concentrated with rotatory evaporation. The crude material was purified on SiO_2 (2.5% to 10% EtOAc in hexanes, stained with CAM) to afford the title compound as a white solid (5.06 g, 71% yield). All spectral data are in accord with the literature.[48]

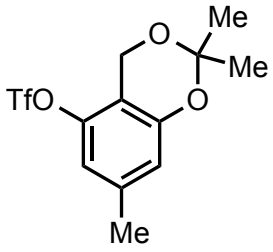


2,2,7-trimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl trifluoromethanesulfonate. (4.150) To an oven-dried vial with magnetic stir bar and a teflon septum cap was added 5-hydroxy-2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-4-one (5.71 g, 27.4 mmol) and dichloromethane (27.4 mL, [substrate] = 1.0 M) under N_2. The vial was cooled to 0 ºC and added pyridine (7.95 mL, 98.7 mmol) and Tf_2O (7.50 mL, 32.91 mmol). Stir at 0 ºC for 1.5 hours. Quench the reaction with H_2O. The layers were allowed to separate and the aqueous layer was extracted with Et_2O (3 x 30 mL). The combined organic layers was dried with $MgSO_4$, filtered and concentrated with rotatory evaporation. The crude

[48] Blencowe, P. S.; Barrett, A. G. M. *Eur. J. Org. Chem.,* **2014**, *22*, 4844 – 4853.

material was purified on SiO_2 (5% to 10% EtOAc in hexanes, stained with CAM) to afford the title compound as a white solid (8.86 g, 95% yield).

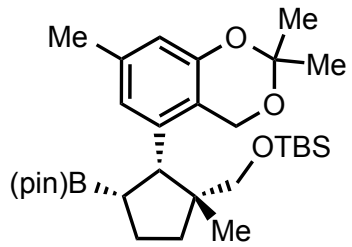
^{1}H NMR (600 MHz, $CDCl_3$): δ 1.71 (6H, s), 2.41 (3H, s), 6.78 (1H, s), 6.84 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$): 22.0, 25.4, 105.5, 106.7, 117.4, 118.0, 118.7 (q, J = 321 Hz), 148.4, 148.7, 157.2; IR (neat): 1744.4 (s), 1630.0 (s), 1425.0 (s), 1282.9 (s), 1197.4 (s), 1159.5 (s), 1135.9 (s), 1048.8 (s), 987.0 (s), 854.8 (s), 600.2 (s) cm^{-1}; ^{19}F NMR (564 MHz, $CDCl_3$): -73.2; HRMS-(DART-TOF) for $C_{12}H_{12}F_3O_6S$ [M+H]: calculated: 341.03067, found: 341.03106.



2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-5-yl trifluoromethane-sulfonate. (4.151) To an oven-dried vial with magnetic stir bar and a teflon septum cap was added 2,2,7-trimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl trifluoromethanesulfonate (8.65 mg, 25.4 mmol) and THF (150 mL) under N_2. The vial was cooled to -78 ºC and added 2M $LiBH_4$ in THF (50.8 mL, 102 mmol). Slowly warm the reaction to room temperature and stir overnight. Quench the reaction 1M HCl (aq.). The layers were allowed to separate and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organic layers was dried with Na_2SO_4, filtered and concentrated with rotatory evaporation. The crude material was put through a plug of SiO_2 and wash with EtOAc. To an oven-dried vial with magnetic stir bar and a teflon septum cap was added the crude alcohol and DCM (254 mL, [substrate] = 0.1 M) under N_2. Add 2,2-dimethoxypropane (15.57 mL, 127.1 mmol) and *p*-TsOH (cat.). Stir the reaction at room temperature for 1 hour.

Quench the reaction with sat. $NaHCO_3$. The layers were allowed to separate and the aqueous layer was extracted with DCM (3 x 30 mL). The combined organic layers was dried with Na_2SO_4, filtered and concentrated with rotatory evaporation. The crude material was purified on SiO_2 (2.5% to 10% EtOAc in hexanes, stained with CAM) to afford the title compound as a colorless oil (3.90 g, 47% yield).

^{1}H NMR (500 MHz, $CDCl_3$): δ 1.54 (3H, s). 1.55 (3H, s), 2.32 (3H, s), 4.86 (2H, s), 6.68 (2H, s); ^{13}C NMR (150 MHz, $CDCl_3$): 21.3, 24.5, 57.1, 100.1, 110.1, 113.4, 117.5, 118.6 (q, J = 320 Hz), 139.4, 145.0, 152.5; ^{19}F NMR (470 MHz, $CDCl_3$): -73.7; IR (neat): 1635.2 (w), 1578.1 (w), 1455.3 (m), 1207.3 (s), 1138.0 (s), 975.0 (m), 842.3 (m), 824.6 (m), 610.9 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{12}H_{13}F_3O_5S$ [M]: calculated: 326.04358, found: 326.04474.



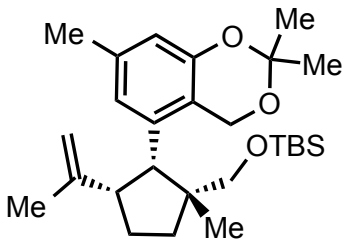
tert-butyldimethyl((1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,7-trimethyl-4H-benzo-[d][1,3]-dioxin-5-yl)cyclopentyl)methoxy)silane. (4.152)

To an oven-dried 2-dram vial with magnetic stir bar was added (1-methylcyclopent-2-en-1-yl)methanol (1.34 g, 12.0 mmol), Cs_2CO_3 (1.17 g, 3.58 mmol), $B_2(pin)_2$ (4.55 g, 17.9 mmol), tetrahydrofuran (23.9 mL, [substrate] = 0.5 M) and methanol (8.23 mL, 203 mmol). The vial was sealed with a teflon septum cap and heated to 70 ºC for 12 h. The reaction was cooled to room temperature and concentrated *in vacuo* (ensuring that all methanol has been removed from the residue). The flask was brought to a dry box and charged with solid potassium hydroxide (2.01 g, 35.9 mmol),

$Pd_2(dba)_3$ (274 mg, 0.30 mmol), RuPhos (279 mg, 0.60 mmol), tetrahydrofuran (54 mL), toluene (54 mL) and 2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-5-yl trifluoromethane-sulfonate (3.90 g, 12.0 mmol). The vial was sealed, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 10.8 mL) was added through the teflon septum cap. The vial was heated to 70 ºC and stirred for 12 h. The reaction mixture was cooled to room temperature and sat. NH_4Cl (aq.) (15 mL) was added. The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 40 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation in a 4-dram vial. To the residue was added dichloromethane (54 mL) and imidazole (7.22 g, 106 mmol). The reaction mixture was cooled to 0 °C and a solution of TBSCl (5.35 g, 35.5 mmol) in toluene (12 mL). The reaction was sealed and allowed to warm to room temperature overnight. The reaction mixture was quenched with sat. NH_4Cl (20 mL). The layers were allowed to separate and the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2 (1% to 2% EtOAc in hexanes, stained with CAM) to afford the title compound as a white solid (2.70 g, 43% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ -0.14 (3H, s), -0.14 (3H, s), 0.79 (9H, s), 0.84 (6H, s), 0.96 (6H, s), 1.13 (3H, s), 1.46 (3H, s), 1.50 (3H, s), 1.70 – 1.76 (1H, m), 1.99 – 2.05 (1H, m), 2.09 – 2.17 (2H, m), 2.21 (3H, s), 2.82 (1H, d, J = 7.63 Hz), 3.08 (2H, s), 4.84 (1H, d, J = 14.7 Hz), 5.00 (1H, d, J = 14.1 Hz), 6.39 (1H, s), 6.40 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$): -5.8, -5.8, 18.4, 21.5, 23.0, 24.5, 24.6, 24.8, 25.8, 26.0, 26.2, 35.3, 49.4,

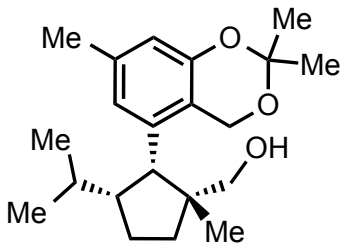
50.8, 60.3, 68.7, 82.6, 98.0, 114.8, 115.7, 120.4, 136.6, 141.2, 150.7; IR (neat): 3344.9 (m), 2953.2 (w), 2855.8 (w), 1618.9 (m), 1582.1 (m), 1375.9 (m), 1315.4 (m), 1250.8 (w), 1135.3 (m), 1079.1 (m), 1061.3 (m), 833.7 (s), 775.0 (s), 668.1 (m) cm^{-1}; HRMS-(DART-TOF) for $C_{30}H_{52}BO_5Si$ [M+H]: calculated: 531.36771, found: 531.36760.



tert-butyldimethyl((1-methyl-3-(prop-1-en-2-yl)-2-(2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-5-yl)cyclopentyl)-methoxy)silane. (4.163) To an oven-dried 2-dram vial with magnetic stir bar was added Et_2O (21 mL) and 2-bromopropene (675 μL, 7.63 mmol). Cool to -78 ºC and add *t*BuLi (11.8 mL, 1.30 M) dropwise. Allow the reaction to stir at -78 ºC for two hours. Allow the reaction to warm to room temperature and stir for 15 minutes. Once again, cool the flask to -78 ºC and add a solution of tert-butyldimethyl((1-methyl-3-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)-2-(2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-5-yl)cyclopentyl)methoxy)silane (2.70 g, 5.09 mmol) in Et_2O (24 mL) dropwise. Allow the reaction to stir at -78 ºC for 45 minutes and 15 minutes at 0 ºC. At 0 ºC, add a solution of I_2 (1.94 g, 7.63 mmol) and MeOH (41 mL) and stir for 15 minutes. Add NaOMe (824 mg, 15.26 mmol) in MeOH (17 mL) dropwise and allow the reaction mixture to warm to room temperature and continue to stir for three hours. Concentrate the reaction mixture by rotary evaporation. Take up the crude mixture in Et_2O and wash organic layer with 5% $Na_2S_2O_3$, 5% NaOH, 5% NaOH (with 10% H_2O_2), 5% $Na_2S_2O_3$, and brine, sequentially. The combined organics were dried over $MgSO_4$, filtered, and concentrated by rotary evaporation. The crude material

was purified on SiO_2 (1% to 2% EtOAc in hexanes, stained with CAM) to afford the title compound as a yellow oil (2.10 g, 93% yield).

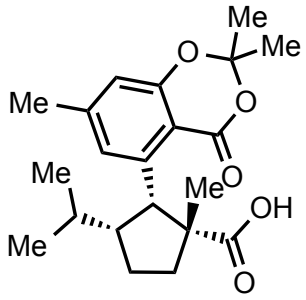
^{1}H NMR (600 MHz, $CDCl_3$): δ -0.15 (3H, s), -0.14 (3H, s), 0.80 (9H, s), 1.25 (3H, s), 1.39 (3H, s), 1.43 (3H, s), 1.51 (3H, s), 1.48 – 1.55 (1H, m), 1.71 – 1.77 (1H, m), 1.98 – 2.04 (1H, m), 2.13 – 2.19 (1H, m), 2.20 (3H, s), 2.79 (1H, d, J = 7.6 Hz), 3.03 (1H, d, J = 10.0 Hz), 3.08 (1H, d, J = 9.4 Hz), 3.20 (1H, q, J = 9.4 Hz), 4.64 (1H, s), 4.69 (1H, s), 4.75 (1H, d, J = 14.7 Hz), 5.01 (1H, d, J = 14.7 Hz), 6.29 (1H, s), 6.44 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$): -5.8, -5.8, 18.4, 21.6, 22.8, 23.0, 26.0, 26.1, 26.7, 27.1, 34.2, 49.5, 49.8, 50.1, 60.4, 69.1, 98.0, 110.1, 115.1, 115.5, 122.0, 136.1, 137.0, 145.7, 150.7; IR (neat): 2952.9 (m), 2928.6 (m), 2855.6 (m), 1581.8 (m), 1462.4 (m), 1370.3 (m), 1318.5 (m), 1203.8 (m), 1133.6 (m), 1085.0 (m), 833.9 (s), 775.2 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{27}H_{45}O_3Si$ [M+H]: calculated: 445.31380, found: 445.31174.



(3-isopropyl-1-methyl-2-(2,2,7-trimethyl-4H-benzo[d]-[1,3]-dioxin-5-yl)cyclopentyl)methanol. (4.164) To an oven-dried round-bottomed flask with magnetic stir bar was added tert-butyldimethyl((1-methyl-3-(prop-1-en-2-yl)-2-(2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-5-yl)cyclopentyl)methoxy)silane (1.12 g, 2.52 mmol), PtO_2 (30 mg) and EtOAc (133 mL). Evacuate and refill the flask with H_2 (10x). The reaction was stirred at room temperature for 3 hours under a H_2 atmosphere. The reaction mixture was put through a plug of celite and washed with EtOAc. The combined organics were concentrated by rotary evaporation. The crude silyl ether and THF (32)

was added to an oven-dried round-bottomed flask with magnetic stir bar. Add TBAF (7.6 mL, 1M) was added dropwise to the reaction mixture at room temperature and stirred overnight. The reaction mixture was quenched with water. The layers were allowed to separate and the aqueous layer was extracted with EtOAc (3 x 50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2 (1% to 5% EtOAc in hexanes, stained with CAM) to afford the title compound as a colorless oil (593 mg, 71% yield).

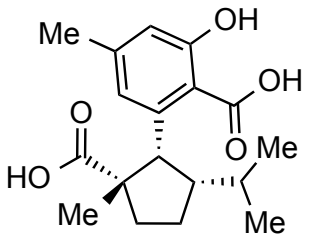
^{1}H NMR (600 MHz, $CDCl_3$): δ 0.59 (3H, d, J = 6.5 Hz), 0.88 (3H, d, J = 7.1 Hz), 1.01 (1H, t, J = 5.28 Hz), 1.23 (3H, s), 1.39 – 1.47 (2H, m), 1.48 (3H, s), 1.51 (3H, s), 1.67 – 1.79 (2H, m), 2.11 – 2.22 (2H, m), 2.27 (3H, s), 2.62 (1H, d, J = 6.5 Hz), 3.08 (1H, dd, J = 10.6 Hz, 5.9 Hz), 3.12 (1H, dd, J = 10.6 Hz, 3.53 Hz), 4.80 (1H, d, J = 14.7 Hz), 5.03 (1H, d, J = 14.7 Hz), 6.41 (1H, s), 6.51 (1H, s); ^{13}C NMR (150 MHz, $CDCl_3$): 21.7, 22.2, 24.3, 24.9, 26.5, 29.5, 29.9, 33.7, 49.6, 49.8, 51.3, 60.7, 69.3, 98.3, 115.3, 115.8, 122.0, 136.6, 137.6, 151.2; IR (neat): 3467.8 (w), 2952.7 (m), 2868.0 (m), 1617.3 (w), 1579.7 (m), 1453.2 (m), 1382.6 (m), 1313.9 (m), 1281.6 (m), 1159.8 (s), 1026.5 (s), 864.3 (s), 737.7 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{21}H_{31}O_2$ [M+H-H_2O]: calculated: 315.23240, found: 315.23312.



3-isopropyl-1-methyl-2-(2,2,7-trimethyl-4-oxo-4H-benzo[d]-[1,3]dioxin-5-yl)cyclopentane-1-carboxylic acid. (4.166) To a round-bottomed flask with magnetic stir bar was added (3-isopropyl-1-methyl-2-(2,2,7-trimethyl-4H-benzo[d][1,3]dioxin-

5-yl)cyclopentyl)methanol (61.6 mg, 185 μmol), MeCN (1.54 mL) and EtOAc (1.54 mL). The reaction mixture was cooled to 0 ºC. A solution of $NaIO_4$ (0.28 g, 1.30 mmol) and $RuCl_3$ (4.2 mg, 18.5 μmol) in H_2O (2.5 mL) was added dropwise to the reaction at 0 ºC over 1 hour. The reaction was allowed to stir at 0 ºC for 2 hours and at room temperature for 12 hours. The reaction was quench with 6M HCl (0.4 mL) and diluted with water (4 mL). The aqueous layer was extracted with EtOAc (5 x 5 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified on SiO_2 (10% to 30% EtOAc in hexanes, stained with CAM) to afford the title compound as a clear oil (27 mg, 41% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.62 (3H, d, J = 6.5 Hz), 0.84 (3H, d, J = 6.5 Hz), 1.15 – 1.20 (1H, m), 1.54 (3H, s), 1.62 (3H, s), 1.69 (3H, s), 1.70 – 1.78 (2H, m), 2.09 – 2.14 (1H, m), 2.21 – 2.27 (1H, m), 2.32 (3H, s), 2.65 – 2.71 (1H, m), 4.66 (1H, d, J = 7.0 Hz), 6.63 (1H, s), 6.68 (1H, s), 9.56 (1H, br s); ^{13}C NMR (150 MHz, $CDCl_3$): 21.7, 21.9, 22.3, 24.9, 25.8, 28.3, 29.0, 29.9, 33.5, 49.3, 51.3, 57.1, 105.0, 111.7, 116.2, 125.6, 145.3, 146.1, 156.8, 162.3, 179.3; IR (neat): 2956.3 (w), 2871.2 (w), 1730.1 (s), 1696.6 (s), 1616.2 (m), 1571.3 (m), 1265.3 (s), 1210.5 (m), 1157.0 (m), 1045.1 (m), 735.8 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{21}H_{29}O_5$ [M+H]: calculated: 361.2015, found: 361.2014.



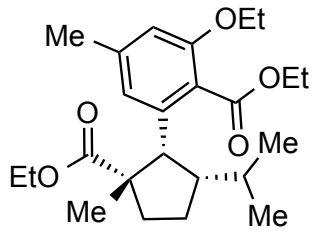
debromohamigeran E. To a round-bottomed flask with magnetic stir bar was added 3-isopropyl-1-methyl-2-(2,2,7-trimethyl-4-oxo-4H-benzo[d][1,3]dioxin-5-yl)cyclopentane-1-carboxylic acid (23.0 mg, 63.8 μmol), DMSO (4 mL) and 48%

aqueous KOH (0.95 mL). The reaction flask was heated to 60 ºC and stirred for 1 hour. The reaction is cool to room temperature and 2M HCl (aq.) is added dropwise until a pH of 2 is reached. The aqueous layer was extracted with EtOAc (8 x 2 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The residue is heated at 35 ºC under hi-vac until the DMSO is distilled away from the product. ^{1}H NMR showed product contaminated with DMSO. The determined yield of the reaction accounts for the DMSO present. (18.9 mg, 93% yield).

^{1}H NMR (600 MHz, $CDCl_3$): δ 0.59 (3H, d, J = 6.46 Hz), 0.81 (3H, d, 6.46 Hz), 1.03-1.08 (1H, m), 1.55 (3H, s), 1.72-1.78 (1H, m), 1.82-1.87 (1H, m), 2.11-2.24 (2H, m), 2.29 (3H, s), 2.63-2.71 (1H, m), 3.66 (1H, d, J = 6.45 Hz), 6.47 (1H, s), 6.67 (1H, s); IR (neat): 3414.7 (w), 2956.5 (w), 2925.5 (w), 2870.4 (w), 1612.6 (m), 1263.1 (m), 1218.3 (m), 1192.4 (m), 1010.4 (m), 949.7 (m), 876.3 (m), 735.9 (s) cm^{-1}; HRMS-(DART-TOF) for $C_{18}H_{25}O_5$ [M+H]: calculated: 321.1702, found: 321.1716.

The purification of debromohamigeran E proved to be difficult and full characterization could not be performed. Instead, similar to isolation studies [49], the crude debromohamigeran E was subjected to alkylation conditions to form triethyldebromohamigeran E.

[49] Wellington, K. D; Cambie, R. C.; Rutledge, P. S.; Bergquist, P. R. *J. Nat. Prod.* **2000**, *63*, 79 – 85.



triethyldebromohamigeran E. To an oven-dried vial with magnetic stir bar was added debromohamigeran E (10 mg, 31.2 μmol) and acetone (5 mL). To the vial was added potassium carbonate (1.00 g) and MeI (1.00 mL). The vial was sealed and heated to 55 ºC overnight. Cool the flask to room temperature and filter the reaction mixture through a plug of SiO_2 and wash with EtOAc. The collected organic fraction was concentrated with rotatory evaporation. The crude material was purified on SiO_2 (5% to 10% EtOAc in hexanes, stained with CAM) to afford the title compound as a clear oil (8.1 mg, 64% yield). All spectral data are in accord with the literature.[49]

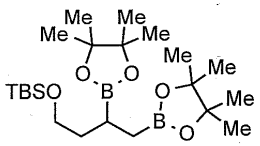
Triethyldebromohamigeran E: Comparison of ^{1}H and ^{13}C NMR Shifts

^{1}H NMR (ppm)	***Reported ^{1}H NMR (ppm)***	***^{13}C NMR (ppm)***	***Reported ^{13}C NMR (ppm)***
0.77	0.77	13.5	13.5
0.81	0.81	14.3	14.3
0.85	0.85	14.7	14.7
1.32	1.32	22.1	22.1
1.34	1.33	22.1	22.1
1.37	1.36	22.2	22.2
1.40	1.40	28.3	28.3
1.56	1.58	29.2	29.2
1.81	1.81	29.8	29.8
2.04	2.05	34.1	34.1
2.10	2.10	51.8	51.8
2.29	2.29	54.7	54.7
2.73	2.73	56.3	56.3
3.15	3.14	60.0	60.0
3.62	3.62	60.6	60.6
3.75	3.75	64.2	64.2
3.97	3.97	110.9	110.9
3.98	3.98	121.9	121.9
4.33	4.34	123.6	123.6
4.38	4.37	138.9	138.9
6.49	6.49	139.1	139.1
6.53	6.53	155.7	155.6
		168.5	168.6
		175.8	175.8

4.14.8 Spectral Data

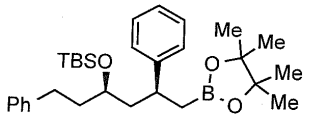
For all published spectral data see the following link: http://pubs.acs.org/doi/suppl/10.1021/jacs.5b05477

See below for examples of ^{1}H and ^{13}C spectra:

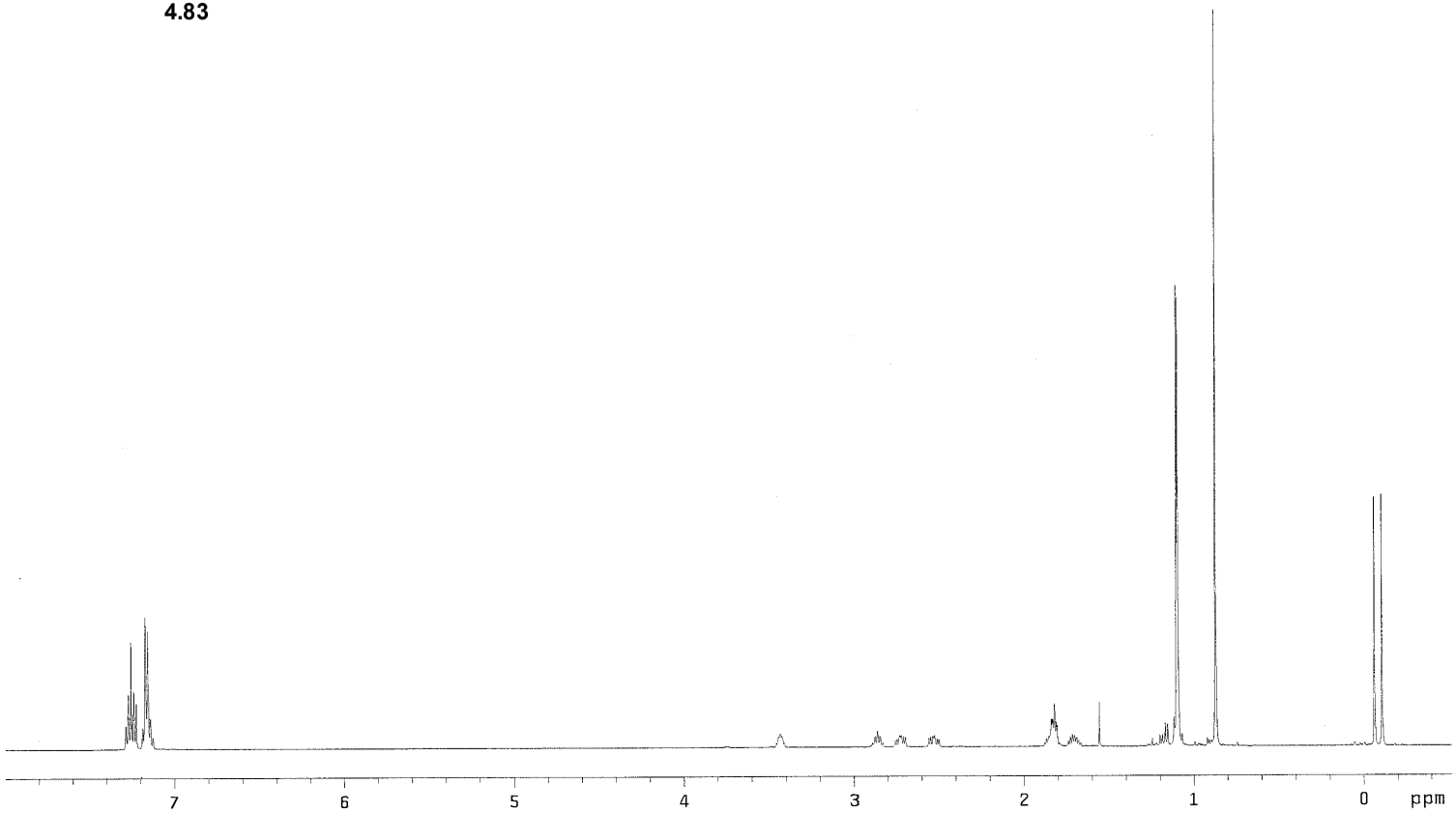


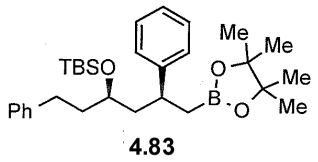
4.61

TBSO
Me
Me
Me
Me
Me
Me
Me
Me
O
B
O
O
B
O
4.61
220
200
180
160
140
120
100
80
60
40
20
0
ppm



4.83

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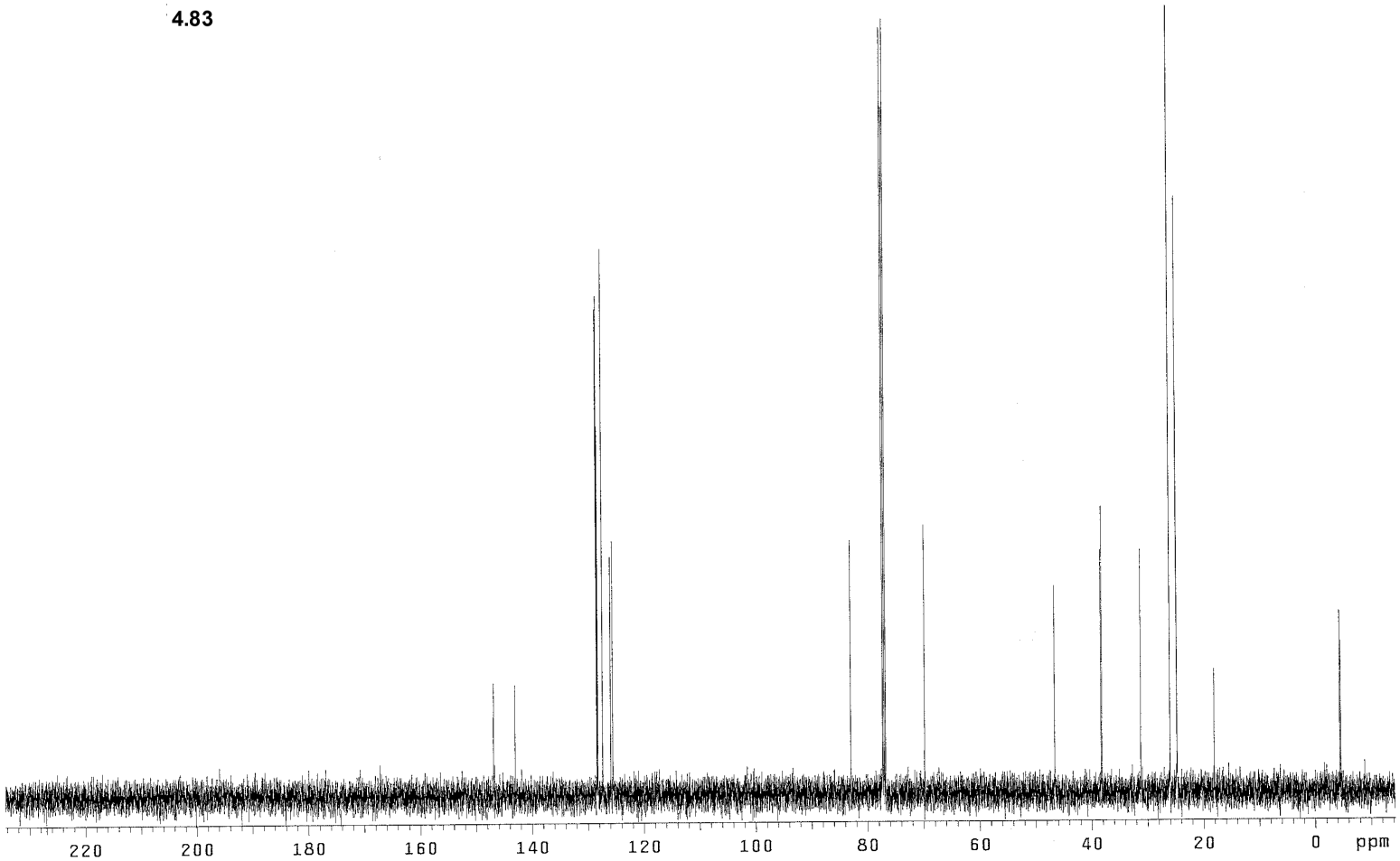
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