Synthesis and Utility of Organoboron Reagents for Enantioselective Synthesis

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Boston College

The Graduate School of Arts and Sciences

Department of Chemistry

SYNTHESIS AND UTILITY OF ORGANOBORON REAGENTS FOR ENANTIOSELECTIVE SYNTHESIS

A dissertation

by

CHRISTOPHER HENRY SCHUSTER

submitted in partial fulfillment of the requirements

for the degree of

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SYNTHESIS AND UTILITY OF ORGANOBORON REAGENTS FOR ENANTIOSELECTIVE SYNTHESIS

by

CHRISTOPHER HENRY SCHUSTER

Dissertation Advisor:

Professor James P. Morken

ABSTRACT: Described herein are three distinct projects centered on the formation and use of carbon-boron bonds. In the first, the enantioselective platinum-catalyzed 1,4-diboration of *trans*-1,3-dienes is advanced in both selectivity and scope through the development of a novel class of electron rich chiral monodentate phosphines. Under the action of the new ligands, highly selective diboration is maintained at reduced loadings of catalyst. Secondly, enantioenriched 1,2-bis(pinacol boronates) are engaged in regioselective Suzuki-Miyaura cross-coupling with aryl and vinyl electrophiles. A tandem diboration cross-coupling sequence is successfully implemented to afford homobenzylic and homoallylic pinacol boronates directly from terminal olefins, which subsequently undergo oxidation, amination or homologation of the remaining carbon-boron bond to arrive at a range of enantioenriched products. Lastly, aryl electrophiles containing tethered allylboronate units undergo efficient intramolecular coupling in the presence of a chiral palladium catalyst to give enantioenriched carbocyclic products.

Dedicated to:

My parents, James H. Schuster and Susan R. Schuster, for their love and unconditional support as well as my father's countless lessons in seeing the world as a collection of simple machines and my mother's many brave attempts to teach spelling.

ACKNOWLEDGEMENTS

First, I would like to give thanks to my advisor, Professor James P. Morken. Jim has not only served as an excellent advisor but also as an ideal scientific role model. Much of my growth as a chemist has been a result of attempts to emulate his mixture of enthusiasm and patience that is brought to every meeting and chalkboard conversation. Graduate school can be a series of moments were you realize how little you know and Jim has taught me to view these as exciting learning opportunities rather than discouraging set-backs. With this much improved outlook, I look forward to having many more of these little moments.

During my stay in the Morken group, I have had the pleasure of working alongside nearly 50 chemists at various stages of their careers and without them graduate school would not have been the incredible experience that it was. In particular, I would like to thank Dr. Dan Custar, Ph.D. for his advice and guidance, both chemical and non-chemical. I enjoyed collaborating with Scott Mlynarski and Ryan Coombs and learned a great deal through the many ups, downs, and moments of head-scratching that accompanied our projects. I shared many great white board discussions with Mike Ardolino and always walked away with a little more knowledge about chemistry, beer, or food depending on which way the conversation drifted. I would also like to thank Tom Caya, Meredith Eno, Bo Potter, Dr. Bob Kyne, Dr. Rob Ely, and Dr. Laura Kliman.

I am grateful to Bo Potter, Tom Blaisdell, and Ryan Coombs for taking the time to proof read this thesis and providing many helpful suggestions.

Lastly, I would like to thank my family. Without their love and support, I could have never completed graduate school. It turns out hunting for frogs with my nephew Cody was a great way to clear the head and re-focus. Finally, I owe everything to Candice Joe. I thought I knew what working hard meant before I meet her, and then she lapped me 4x in notebooks and I changed my thinking. She has made my life better in so many ways, and I can’t wait for what comes next.

List of Abbreviations

Å: angstrom

Ac: acetyl

acac: acetylacetonyl

Ad: adamantyl

Aliquat 336: trioctylmethylammonium chloride

approx: approximately

AQN: anthraquinone

$B_2(cat)_2$: bis(catecholato)diboron

$B_2(pin)_2$: bis(pinacolato)diboron

BARF: tetrakis[3,5-bis(trifluoromethyl)phenyl] borate

9-BBN: 9-borabicyclo[3.3.1]nonane

BHT: 2,6-di-*t*butyl-4-methylphenol

BINOL: 1,1'-bi-2,2'-naphthol

Bn: benzyl

Boc: *t*butoxycarbonyl

BSA: *N*,*O*-bis(trimethylsilyl)acetamide

Bz: benzoyl

CAN: cerium(IV) ammonium nitrate

cat: catechol

Cbz: benzyloxycarbonyl

cod: 1,5-cyclooctadiene

conv: conversion

Cy: cyclohexyl

dan: 1,8-diaminonaphthalene

DART: direct analysis in real time

dba: dibenzylideneacetone

DCE: 1,2-dichloroethane

DCM: dichloromethane

dcpe: 1,2-bis(dicyclohexylphosphino) ethane

DHQD: dihydroquinidine

DI: deionized

DIBAL: diisobutylaluminum hydride

dippf: 1,1'-bis(diisopropylphosphino) ferrocene

DMAP: *N*,*N*-4-dimethylaminopyridine

DME: 1,2-dimethoxyethane

DMF: *N*,*N*-dimethylformamide

DMSO: dimethylsulfoxide

dppb: 1,4-bis(diphenylphosphino)butane

dppe: 1,2-bis(diphenylphosphino)ethane

dppf: 1,1'-bis(diphenylphosphino) ferrocene

dppm: 1,1-bis(diphenylphosphino) methane

dppp: 1,3-bis(diphenylphosphino) propane

dr: diastereomeric ratio

elim: elimination

ent: enantiomer

eq: equation

equiv: equivalent(s)

er: enantiomeric ratio

ESI: electrospray ionization

EtOAc: ethyl acetate

GLC: gas liquid chromatography

h: hours

HKR: hydrolytic kinetic resolution

HPLC: high performance liquid chromatography

HRMS: high resolution mass spectrometry

Hz: Hertz

imid: imidazole

IPA: isopropanol

IR: infrared spectroscopy

LAH: lithium aluminum hydride

M: molar

mCPBA: *meta* chloroperbenzoic acid

MDPP: menthyldiphenylphosphine

Men: menthyl

NBS: *N*-bromosuccinimide

nbd: norbornadiene

NCS: *N*-chlorosuccinimide

NHC: *N*-heterocyclic carbene

NMDPP: neomenthyldiphenylphosphine

NMO: *N*-methylmorpholine oxide

NMR: nuclear magnetic resonance

NR: no reaction

Ph-BPE: 1,2-bis(2,5-diphenylphospholano) ethane

PhH: benzene

pin: pinacol

PMA: phosphomolybdic acid

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

ppm: parts per million

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

rac: racemic

red: reductive

RT: room temperature

salen: bis(salicylidine)ethylenediamine

SFC: supercritical fluid chromatography

solv: solvent

TADDOL: 2,2-dimethyl-α,α,α',α'-tetraaryl-1,3-dioxolane-4,5-dimethanol

TBAF: tetrabutylammonium fluoride

TBDPS: *t*butyldiphenylsilyl

TBS: *t*butyldimethylsilyl

Temp: temperature

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

TES: triethylsilyl

Tf: trifluoromethanesulfonyl

THF: tetrahydrofuran

TIPS: triisopropylsilyl

TLC: thin layer chromatography

TMEDA: *N*,*N*,*N*',*N*'-tetramethylethylenediamine

TMS: trimethylsilyl

TOF: turnover frequency

tol: toluene

TON: turnover number

Ts: *p*-toluenesulfonyl

UV: ultraviolet

xylyl: dimethylphenyl

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CHAPTER 3: ENANTIOSELECTIVE CARBOCYCLE FORMATION THROUGH INTRAMOLECULAR PALLADIUM CATALYZED ALLYL-ARYL COUPLING

Chapter 1

Development of a New Class of Tunable Monodentate Chiral Ligands for Enantioselective Catalysis; Utility in Highly Efficient 1,4-Diboration of *trans*-1,3-Dienes

1.1 Introduction

The use of organoboron compounds towards the synthesis of complex molecules has continued to evolve from the pioneering work of H. C. Brown, D. S. Matteson and others.[1] Progress in this area has resulted in the development of many useful strategies to transform boron-carbon bonds into a variety of carbon-heteroatom or carbon-carbon bonds, often in a stereospecific fashion.[2] While these developments hold great potential for utility in synthesis, the stereoselective preparation of organoboron compounds continues to be a challenging problem. As part of the greater effort to achieve this objective, metal-catalyzed addition of diboron reagents to unsaturated molecules has been gaining attention as a reliable and efficient method for the preparation of these valuable intermediates.[3]

---

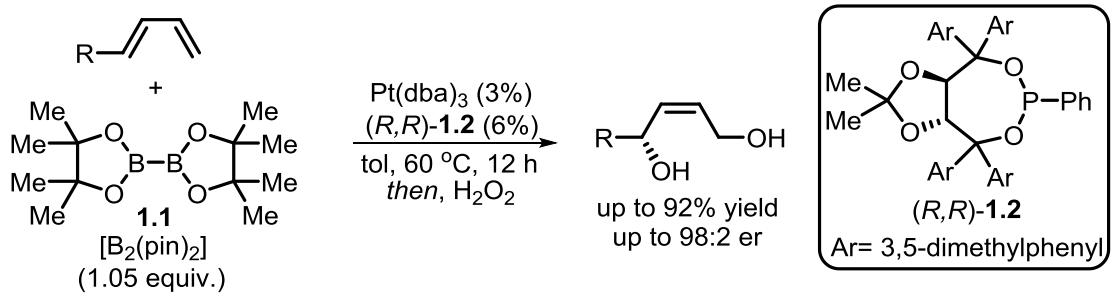
[1] (a) Hall, D. G. Ed. *Boronic Acids: Preparation and Applications in Organic Synthesis and Medicine*; Wiley-VHC Verlag: Weinheim, **2005**. (b) Matteson, D. S. *J. Org. Chem*. **2013**, *78*, 10009. (c) Brown, H. C. *From Little Acorns to Tall Oaks – From Boranes Through Organoboranes*; Nobel Lecture, 8 December, **1979**.

[2] (a) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859. (b) Mattesson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer: Berlin, **1995**. (c) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457. (d) Thomas, S. P.; French, R. M.; Jheengut, V.; Aggarwal, V. K. *Chem. Rec.* **2009**, *9*, 24. (e) Scott, H. K.; Aggarwal, V. K. *Chem. Eur. J*. **2011**, *17*, 13124.

[3] (a) Ishiyama, T.; Miyaura, N. *Chem.Rec.* **2004**, *3*, 271. (b) Beletskaya, I.; Moberg, C. *Chem. Rev*. **2006**, *106*, 2320. (c) Burks, H. E.; Morken, J. P. *Chem. Commun*. **2007**, 4717. (d) Takaya, J.; Iwasawa, N. *ACS Catal*. **2012**, *2*, 1993.

Built upon the foundation of studies by Suzuki,[4] Miyaura,[5] Marder,[6] and Smith,[7] the Morken group has developed several examples of transition metal-catalyzed enantioselective additions of diboron reagents to unsaturated starting materials, including alkenes,[8] allenes,[9] and conjugated dienes.[10] In particular, the enantioselective Pt-catalyzed 1,4-diboration of *trans*-1,3-dienes offers rapid entry to unique products from simple starting materials (Scheme 1.1).[11] Morken and coworkers found with the use of a slight excess of $B_2(pin)_2$ (**1.1**) and employing TADDOL based phosphonite ligand **1.2**, a variety of terminal *trans*-1,3-dienes smoothly underwent diboration in a regioselective fashion, forming products containing exclusively (*Z*) olefin isomers. Utilizing an

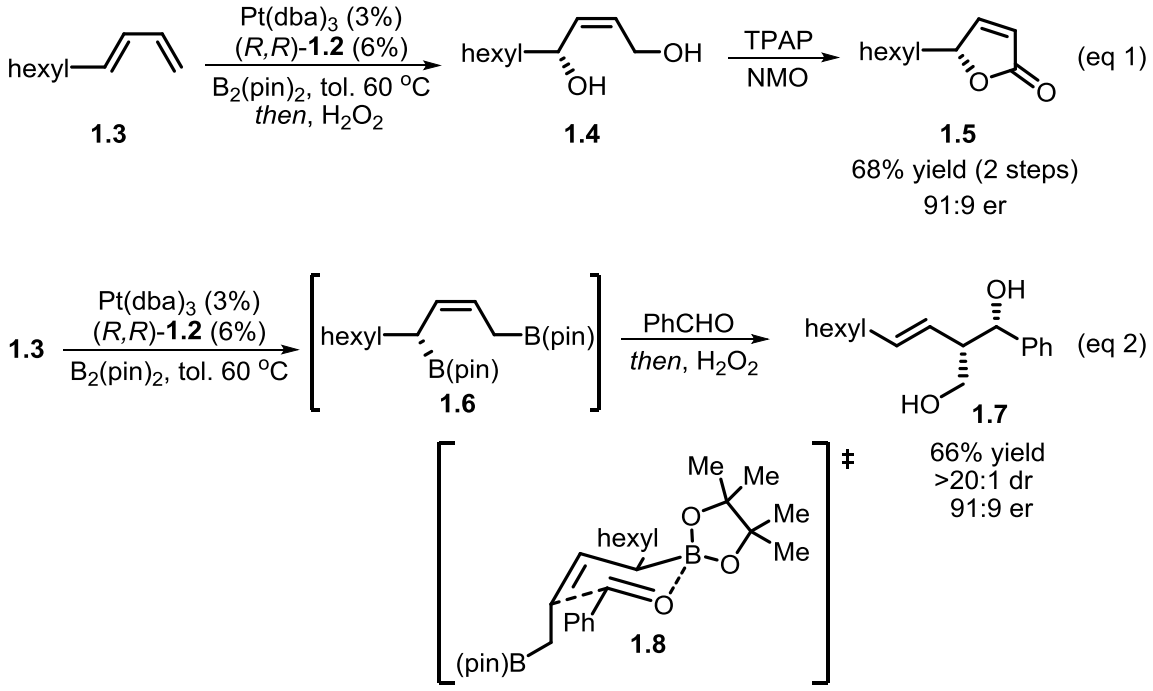
Scheme 1.1: Platinum Catalyzed 1,4-Diboration of *trans*-1,3-Dienes by Morken



[4] Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. *J. Am. Chem. Soc*. **1993**, *115*, 11018.
[5] (a) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun*. **1996**, 2073. (b) Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun*. **1997**, 689. (c) Ishiyama, T.; Kitano, T.; Miyaura, N. *Tetrahedron Lett*. **1998**, *39*, 2357.
[6] (a) Lesley, G.; Nguyen, P.; Taylor, N. J.; Marder, T. B. *Organometallics* **1996**, *15*, 5137. (b) Clegg, W.; Johann, T. R. F.; Marder, T. B.; Norman, N. C.; Orpen, A. G.; Peakman, T. M.; Quayle, M. J.; Rice, C. R.; Scott, A. J. *J. Chem. Soc. Dalton Trans*. **1998**, 1431. (c) Thomas, R. L.; Souza, F. E. S.; Marder, T. B. *J. Chem. Soc. Dalton Trans*. **2001**, 1650.
[7] (a) Iverson, C. N.; Smith, M. R., III, *Organometallics* **1996**, *15*, 5155. (b) Iverson, C. N.; Smith, M. R., III, *Organometallics* **1997**, *16*, 2757.
[8] (a) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc*. **2003**, *125*, 8702. (b) Trudeau, S.; Morgan, J. B.; Shrestha, M.; Morken, J. P. *J. Org. Chem*. **2005**, *70*, 9538. (c) Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc*. **2009**, *131*, 13210. (d) Coombs, J. R.; Haeffner, F.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc*. **2013**, *135*, 11222.
[9] (a) Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc*. **2004**, *126*, 16328. (b) Burks, H. E.; Liu, S.; Morken, J. P. *J. Am. Chem. Soc.* **2007**, *129*, 8766.
[10] (a) Ely, R. J.; Morken, J. P. *Org. Lett*. **2010**, *12*, 4248. (b) Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. *Angew. Chem. Int. Ed*. **2012**, *51*, 521. (c) Ferris, G. E.; Hong, K.; Roundtree, I. A.; Morken, J. P. *J. Am. Chem. Soc*. **2013**, *135*, 2501.
[11] Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc*. **2009**, *131*, 9134.

oxidative work-up, the corresponding 1,4-diols can easily be accessed in good yield and with good to excellent enantioselectivities. Further oxidation of the 1,4-diol products affords valuable enantioenriched butenolides in good yield and without racemization (Scheme 1.2, equation 1). Notably, the 1,4-diboron adducts participate in selective carbonyl allylborations to afford, after subsequent oxidation, the 1,3-diol products in good yield and with excellent stereocontrol (equation 2). Interestingly, the allylation proceeds through the closed 6-membered transition state **1.8**, in which bond formation takes place at the least hindered carbon site, forming the product as a single diastereo- and regioisomer.

Scheme 1.2: Access to Butenolide Motifs and Allylation Adducts through Diboration

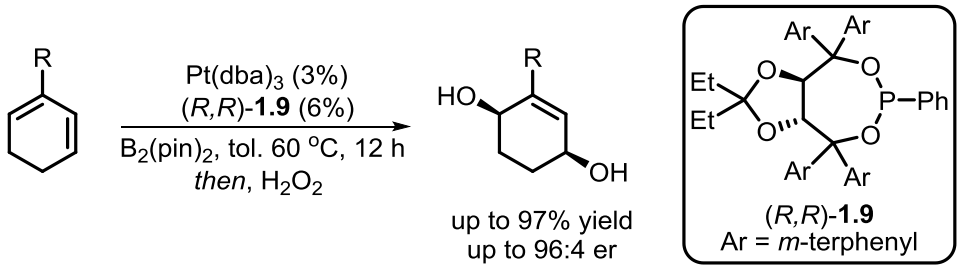


Subsequent to this initial study, the Morken group has expanded upon the utility of 1,4-diboration by further examining cyclic substrates (Scheme 1.3).[12] Extensive

[12] Hong, K.; Morken, J. P. *J. Org. Chem*. **2011**, *76*, 9102.

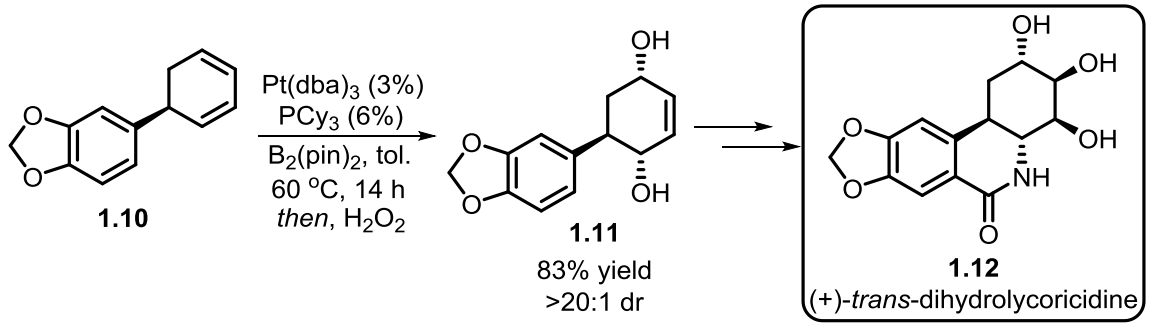
optimization lead to the use of **1.9** as the chiral ligand, achieving high enantioselectivities for a range of cyclic diene substrates. The synthetic value of the resulting cyclic 1,4-diols was highlighted by the total synthesis of (+)-*trans*-dihydrolycoricidine (Scheme 1.4).[13]

Scheme 1.3: Improved Conditions for Cyclic Diene Diboration



Enantioenriched cyclic diene **1.10** smoothly underwent 1,4-diboration utilizing PCy_3 as the achiral ligand to give the desired cyclic 1,4-diol **1.11** (after subsequent oxidation) in a highly diastereoselective manner. Further elaboration rapidly afforded the natural product **1.12**. While both of these reports highlight the potential of 1,4-diboration technology to positively impact synthesis, limitations still remained.

Scheme 1.4: Utility of Highly Diastereoselective Diboration in Synthesis

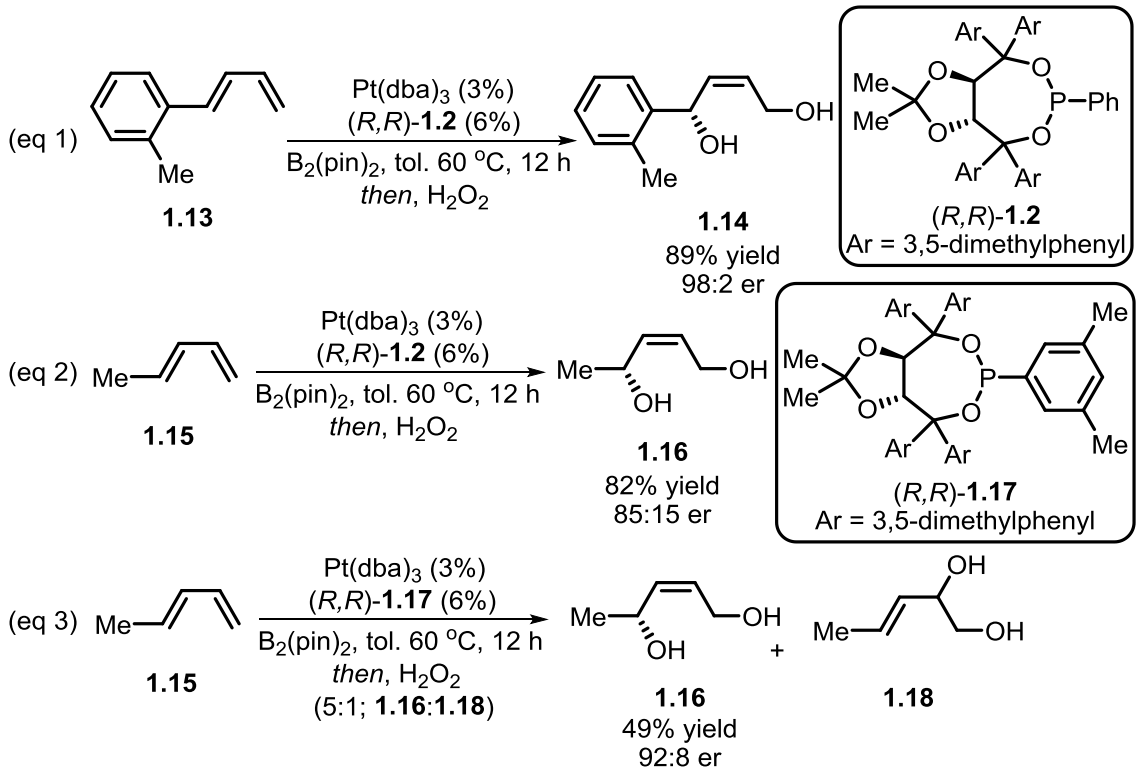


A closer inspection of the scope of 1,4-diboration of *trans*-1,3-dienes reveals a strong dependence on the steric bulk of the substrate (Scheme 1.5).[11] For example, the

[13] Poe, S. L.; Morken, J. P. *Angew. Chem. Int. Ed*. **2011**, *50*, 4189.

initial results with highly optimized TADDOL based phosphonites gave up to 98:2 er for *o*-tolyl substitution (equation 1); however, only 85:15 er was obtained with simple methyl substitution (equation 2).[14] Additionally, 3,4-disubstitution generally resulted in reduced levels of selectivity, further limiting the substrate scope of this useful transformation. Further extensive ligand optimization based on a TADDOL scaffold identified **1.17**, which slightly improved enantioselectivity, but at the expense of less efficient 1,4-diboration (equation 3). While still useful for cyclic 1,3-diene systems, the optimized

Scheme 1.5: 1,4-Diboration of Sterically Unencumbered Substrates

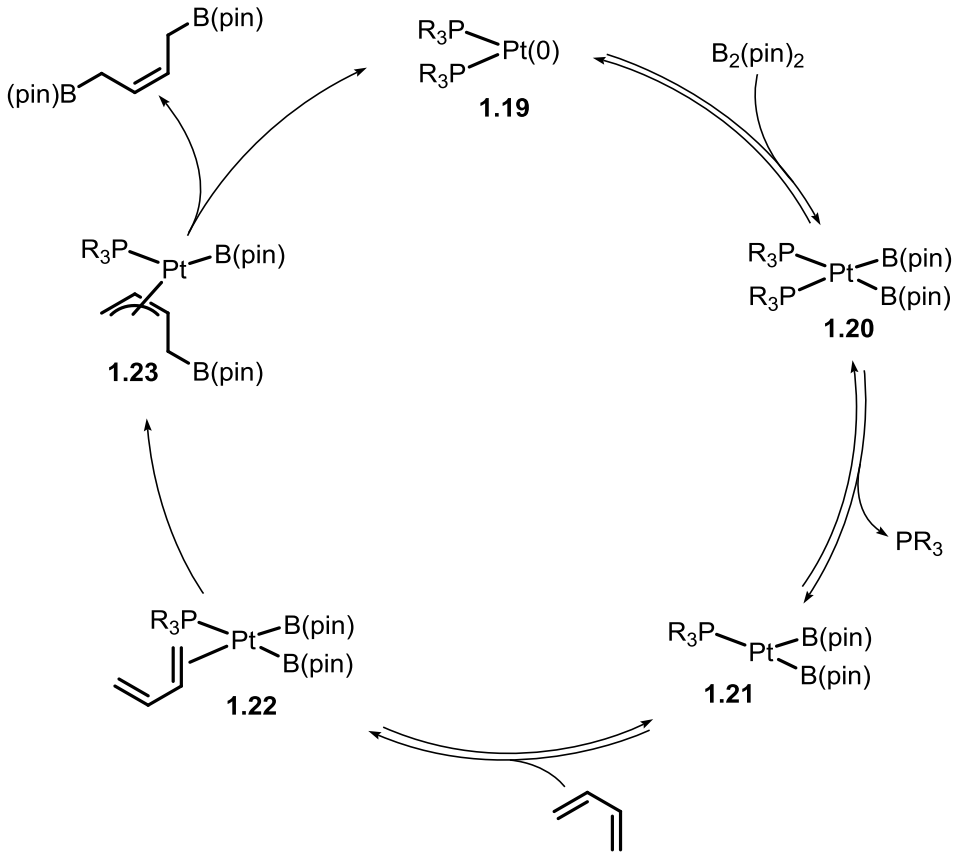


catalyst is ineffective for targeting important acyclic methyl substituted motifs, which are ubiquitous in polypropionate natural products. This class of natural products represents an important opportunity, as many polyketides possess highly promising and potent

[14] Kliman, L. T. Ph.D. Dissertation, Boston College, **2011** pg 26.

biological activity and their efficient stereoselective construction is often quite challenging.[15] Successfully extending the scope of 1,4-diboration of 1,3-dienes to afford methyl substituted stereogenic centers would add another highly efficient tool to the synthetic chemist's arsenal which could be employed to help tackle challenging problems in synthesis.

Scheme 1.6: Proposed Catalytic Cycle of 1,4-Diboration of 1,3-dienes



A closer look at the catalytic cycle for diene diboration, first proposed by Miyaura[5a] and supported by detailed concurrent studies by Smith[7a] and Marder[6a] on similar systems, reveals important features which need to be considered to improve the

[15] (a) Paterson, I. *Pure & Appl. Chem*. **1992**, *64*, 1821. (b) Cragg, G. M.; Grothaus, P. G.; Newman, D. J. *Chem. Rev*. **2009**, *109*, 3012. (c) Sharma, P.; Powell, K. J.; Burnley, J.; Awaad, A. S.; Moses, J. E. *Synthesis* **2011**, 2865.

desired diboration reaction. The cycle begins with oxidative addition of $B_2(pin)_2$ to *bis*-ligated Pt(0) **1.19** to give a *bis*-boryl Pt(II) intermediate **1.20** (Scheme 1.6). Reversible ligand dissociation, followed by coordination of substrate gives olefin complex **1.22**, followed by rate limiting migratory insertion to give π-allyl species **1.23**. Reductive elimination of the remaining boryl group releases product and gives Pt(0), which may rebind the ligand to close the cycle.

To design an effective catalyst for diboration of 1,3-dienes, several features must be considered. The first fundamental step, oxidative addition, was found by Smith[7a] to be reversible when employing $B_2(pin)_2$ as the diboron reagent, leading to an equilibrium concentration of **1.19** and **1.20**. From **1.20**, ligand dissociation was found to be necessary for substrate binding and the use of chelating bidentate phosphine ligands or increased amounts of monodentate ligands disfavors formation of **1.21** resulting in greatly decreased reactivity. Following migratory insertion, reductive elimination, possibly from a highly reactive 3-coordinate Pt(II) species, gives the desired product, closing the cycle. Additionally, related diboration reactions have been shown to benefit from Lewis basic ligands, [5c, 6c, 9] possibly stabilizing Pt(II) intermediate **1.20** and leading to a higher concentration of active catalyst. Taken together, these observations point to the need for an electron rich, monodentate phosphorus ligand that possesses sufficient steric bulk so as to encourage formation of mono-ligated platinum species **1.21** in solution. While the previously examined TADDOL phosphonites fulfilled some of these attributes, they were unable to be tuned sufficiently to give high selectivities in all cases. Seeking to improve upon the initial results obtained in the 1,4-diboration of *trans*-1,3-dienes, it was reasoned a new class of electron rich, bulky, and highly tunable monodentate phosphorus ligands

could overcome several of the challenges encountered, allowing for a more generally useful reaction. This chapter describes the development of OxaPhos and its use in highly efficient and enantioselective 1,4-diboration reactions.

1.2 Background

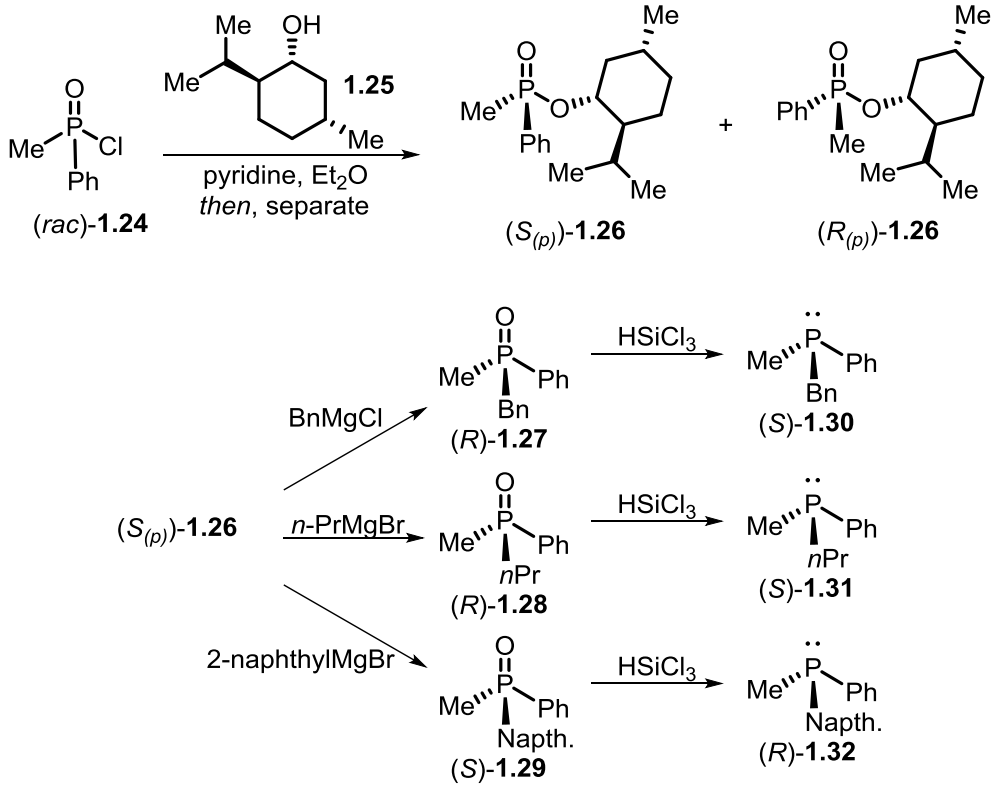
1.2.1 Early Ligand Development and the Beginnings of Asymmetric Catalysis

The development of chiral monodentate ligands for asymmetric catalysis has evolved from a fundamental curiosity to an indispensable tool over the last 50 years. An important class of phosphorus compounds in which the phosphorus itself exhibits central chirality (so-called P-chiral[16]) served as a suitable starting off point for early ligand development. While the existence of configurationally stable P-chiral phosphorus compounds was confirmed experimentally by Meisenheimer and Lichtenstadt as early as 1911,[17] applications for these interesting compounds did not become evident until the mid-1960's. It was during this time that two landmark developments set the stage for asymmetric catalyst development.

In 1966, Sir Wilkinson introduced $Rh(PPh_3)_3Cl$ as a highly efficient homogeneous catalyst for the hydrogenation of isolated olefins.[18] While transition metal catalyzed hydrogenations were well known at the time, this was the first example of a well-defined homogenous catalyst with rates comparable to those of analogous heterogeneous

[16] For reviews, see: (a) Pietrusiewicz, K. M.; Zablocka, M. *Chem. Rev*. **1994**, *94*, 1375. (b) Crepy, K. V. L.; Imamoto, T. *Top. Curr. Chem*. **2003**, *229*, 1. (c) Grabulosa, A.; Granell, J.; Muller, G. *Coord. Chem. Rev*. **2007**, *251*, 25.
[17] Meisenheimer, J.; Lichtenstadt, L. *Chem. Ber*. **1911**, *44*, 356.
[18] Osborn, J. A.; Jardine, F. H.; Young, J. F.; Wilkinson, G. *J. Chem. Soc. A* **1966**, 1711.

Scheme 1.7: Mislow's P-Chiral Phosphine Synthesis

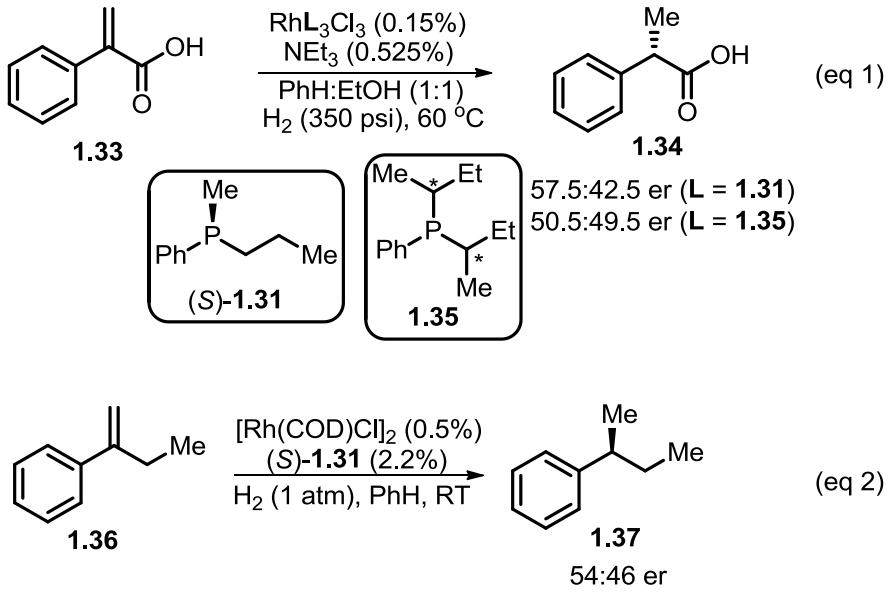


systems. Around the same period, methods by Mislow[19] and Horner[20] emerged which improved the synthesis of P-chiral compounds (Scheme 1.7). Previously, a resolution of the corresponding phosphine oxide or phosphonium salt in which all substituents are pre-installed, was required to gain access to the enriched target. By utilizing menthol (**1.25**) as a chiral auxiliary, a resolution was accomplished to give diastereomerically pure phosphinates (**1.26**). Stereospecific substitution with a variety of Grignard reagents afforded the enantiomerically enriched phosphine oxides **1.27**-**1.29**, followed by stereoretentive reduction to give the corresponding phosphines **1.30**-**1.32**. Importantly, this method allowed for the preparation of many enriched P-chiral compounds from a

[19] Korpiun, O.; Mislow, K. *J. Am. Chem. Soc*. **1967**, *89*, 4784.
[20] Horner, L.; Balzer, W. D. *Tetrahedron Lett*. **1965**, *6*, 1157.

pre-resolved common intermediate, eliminating the tedious resolution of each individual target.

Scheme 1.8: Seminal Asymmetric Hydrogenation by Knowles and Horner

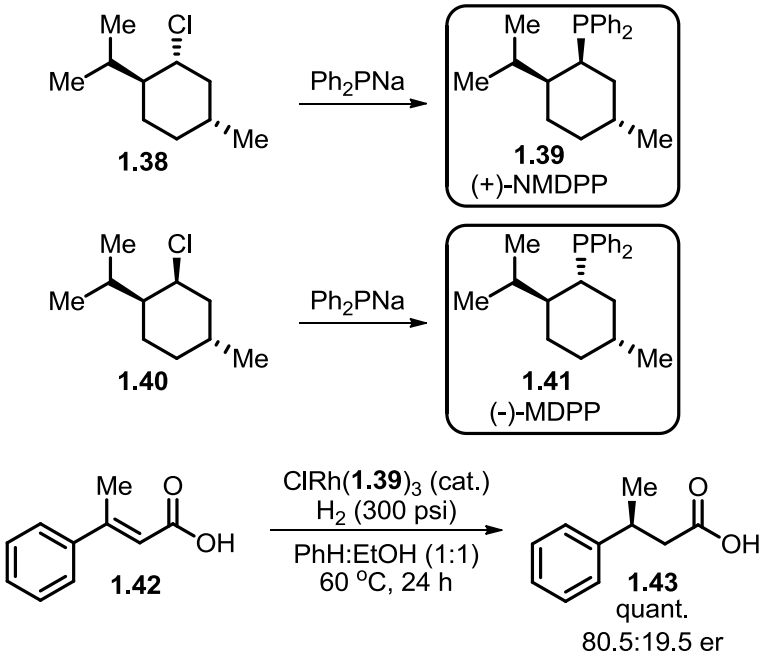


With more efficient means to access the rare P-chiral phosphines in hand, Knowles and Horner independently replaced the triphenylphosphine in Wilkinson's catalyst with an enantioenriched phosphine, and employed the resulting catalyst to hydrogenate a prochiral olefin. As shown in Scheme 1.8, small but measurable enantioselectivities were obtained by both Knowles[21] (equation 1) and Horner[22] (equation 2) when utilizing the enantioenriched P-chiral methylphenyl-*n*-propylphosphine (**1.31**). Notably, Knowles also examined chiral phosphine **1.35**, in which chirality is centered on the carbon groups instead of phosphorus itself. These results lead to Knowles' conclusion[23] "We felt strongly that, if one wanted to get high *ee* values, the asymmetry would have to be directly on the phosphorus. That is where the action is." Recognizing

[21] Knowles, W. S.; Sabacky, M. J. *Chem. Commun*. **1968**, 1445.
[22] Horner, L.; Siegel, H.; Buthe, H. *Angew. Chem. Int. Ed*. **1968**, *7*, 942.
[23] Knowles, W. S. *Angew. Chem. Int. Ed*. **2002**, *41*, 1998.

the potential of their work, Knowles and Sabacky conclude their initial 1968 report; [21] "The inherent generality of this method offers almost unlimited opportunities for matching substrates with catalysts in a rational manner and we are hopeful that our current effort will result in real progress towards complete stereospecificity."

Scheme 1.9: Preparation and Utility of Morrison's Menthol-Derived Ligands



Carrying on in the spirit of Knowles' quest for stereospecificity, research into ligand development for asymmetric catalysis, and in particular for asymmetric hydrogenation, began to expand rapidly in the early 1970's. In 1971, Morrison reported the novel ligand neomenthyldiphenylphosphine (NMDPP, **1.39**) and its use in the reduction of (*E*)-β-methylcinnamic acid **1.42** (Scheme 1.9).[24] Importantly, this was the first example of enantioselectivity exceeding the 50% *ee* mark, giving chemists the hope of achieving highly selective reactions. Morrison's NMDPP is also the first example of a

[24] Morrison, J. D.; Burnett, R. E.; Aguiar, A. M.; Morrow, C. J.; Phillips, C. *J. Am. Chem. Soc*. **1971**, *93*, 1301.

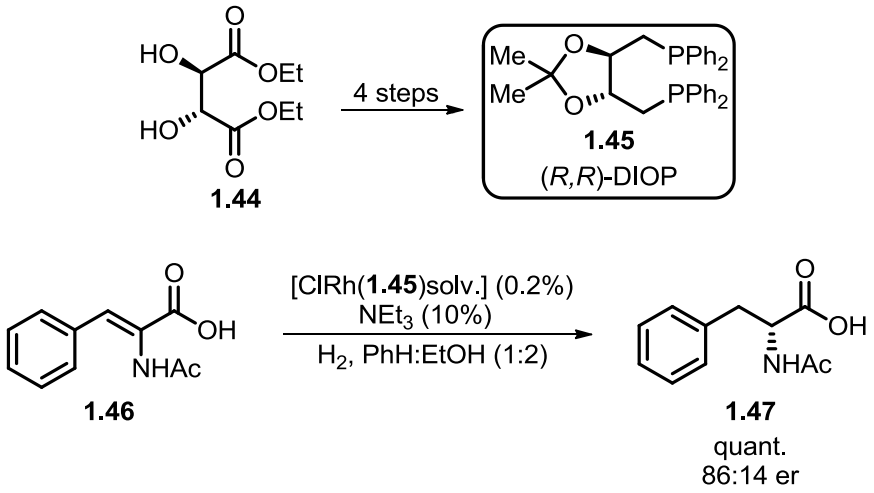
non-P-chiral phosphorus ligand to achieve meaningful levels of selectivity in asymmetric catalysis, changing the notion that chiral information needed to be as close to the metal as possible to effectively induce selectivity. Notably, the use of carbon based stereogenic centers opened the opportunity for utilization of the chiral pool, eliminating the need for an asymmetric synthesis of stereogenic phosphorus centers. Utilizing this approach, Morrison and co-workers easily prepared both NMDPP **1.39** and the diastereomeric compound MDPP **1.41** on preparative scale (46 g and 28 g respectively).[25]

1.2.2 The Rise of Bidentate Chiral Phosphorus Ligands for Asymmetric Catalysis

Carbon based chirality was again utilized in a 1971 report by Kagan which would usher in a new era in asymmetric catalysis.[26] Based on Wilkinson's observation that ligand dissociation was required for the initiation of catalytic hydrogenation, it was believed the chelating nature of diphosphines would in general retard catalyst activity.[18] Utilizing (+)-diethyl tartrate (**1.44**) from the chiral pool, a bidentate phosphine ligand, DIOP (**1.45**), was prepared by Dang and Kagan and examined in rhodium catalyzed hydrogenation (Scheme 1.10). The selectivities obtained for the reduction of acetamide **1.46** (86:14 er) were the highest yet obtained for catalytic asymmetric hydrogenation, effectively shattering the previously held beliefs regarding bidentate ligands in catalysis. Notably, a direct comparison to Wilkinson's catalyst in the hydrogenation of **1.46** revealed a significantly higher rate was obtained when DIOP was used as ligand (relative rate = 8.8 vs 1 for $RhCl(PPh_3)_3$).[27]

[25] Morrison, J. D.; Masler, W. F. *J. Org. Chem*. **1974**, *39*, 270.
[26] Dang, T. P.; Kagan, H. B. *Chem. Commun*. **1971**, 481.
[27] Kagan, H. B.; Dang, T. P. *J. Am. Chem. Soc*. **1972**, *94*, 6429.

Scheme 1.10: Kagan's Use of the Chelating Diphosphine DIOP

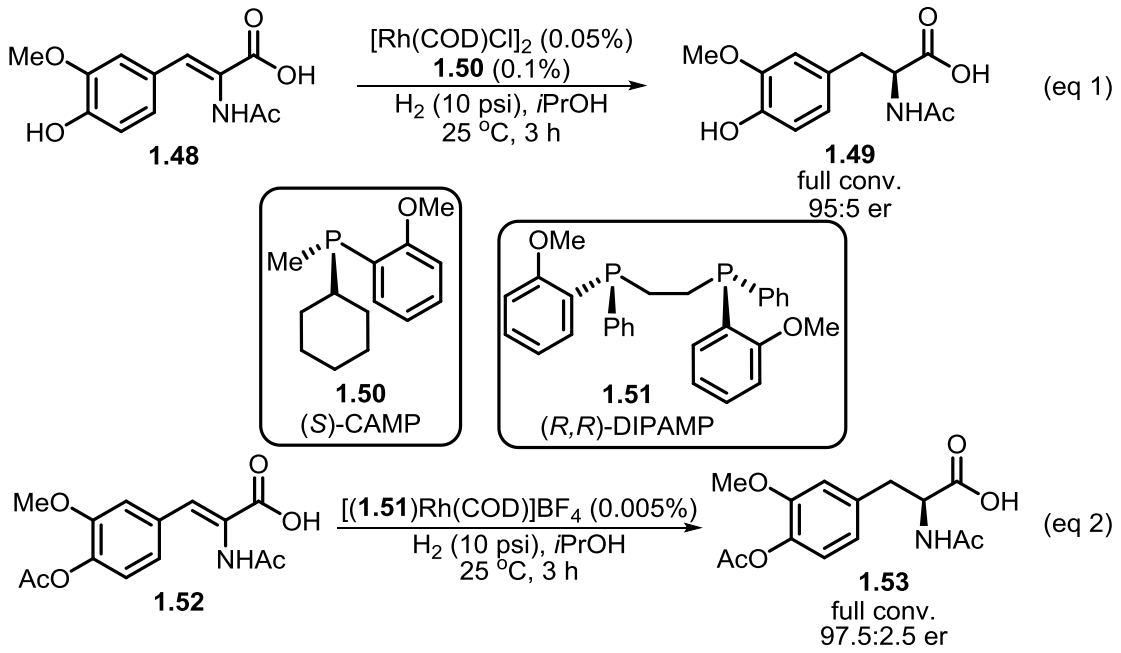


Kagan's report of DIOP had profound implications for asymmetric ligand design and attention rapidly moved away from monodentate phosphines. The shift occurred so quickly that a report by Knowles just one year later went nearly unnoticed by the field.[28] After several iterations, Knowles obtained high selectivity for the reduction of the L-DOPA precursor **1.48**, achieving up to 95:5 er with the use of the P-chiral phosphine CAMP (**1.50**) (Scheme 1.11, equation 1).[29] Despite this early impressive result, the excitement surrounding bidentate ligands had already taken hold, and it became a widely held notion that the more rigid, cyclic, chelating catalyst structures afforded by the use of diphosphines generally resulted in more selective catalysts. As such, chiral bidentate ligand development grew rapidly after Kagan's seminal report, and research into new chiral monodentate phosphine ligands dwindled. Even Knowles began developing bidentate ligands for asymmetric hydrogenation, leading to the report of DIPAMP (**1.51**)

[28] Nugent, W. A. *Angew. Chem. Int. Ed*. **2012**, *51*, 8936.
[29] Knowles, W. S.; Sabacky, M. J.; Vineyard, B. D. *J. Chem. Soc. Chem. Commun*. **1972**, 10.

in 1977.[30] Interestingly, the production of L-DOPA by Monsanto based on asymmetric hydrogenation first utilized CAMP **1.50** as the chiral ligand, but was later switched to DIPAMP **1.51** (Scheme 1.11, equation 2).[23]

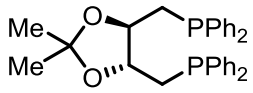
Scheme 1.11: Asymmetric Hydrogenation for Production of L-Dopa Precursors by Knowles



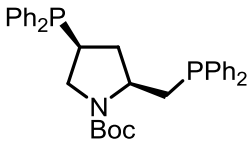
The development of chiral bidentate phosphine ligands continued to dominate asymmetric catalysis for the next few decades, resulting in many creative uses of molecular structures (Figure 1.1).[31] Notable examples include the development of BINAP **1.58** by Noyori,[32] DuPhos **1.60** by Burk,[33] and Josiphos **1.61** by Togni.[34] The

[30] Vineyard, B. D.; Knowles, W. S.; Sabacky, M. J.; Bachman, G. L.; Weinkauff, D. J. *J. Am. Chem. Soc.* **1977**, *99*, 5946.
[31] For a review featuring many bidentate phosphorus ligands, see: Tang, W.; Zhang, X. *Chem. Rev*. **2003**, *103*, 3029.
[32] (a) Miyashita, A.; Yasuda, A.; Takaya, H.; Torium, K.; Ito, T.; Souchi, T.; Noyori, R. *J. Am. Chem. Soc*. **1980**, *102*, 7932. (b) Noyori, R.; Takaya, H. *Acc. Chem. Res*. **1990**, *23*, 345. (c) Noyori, R. *Angew. Chem. Int. Ed*. **2002**, *41*, 2008.
[33] (a) Burk, M. J. *J. Am. Chem. Soc*. **1991**, *113*, 8518. (b) Burk, M. J.; Feaster, J. E.; Nugent, W. A.; Harlow, R. L. *J. Am. Chem. Soc*. **1993**, *115*, 10125.

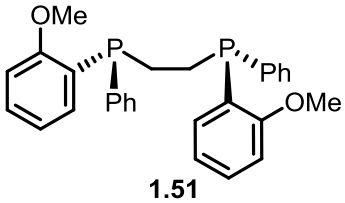
Figure 1.1: Selected Examples of Chiral Bidentate Phosphine Ligands



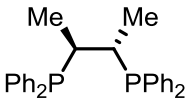
1.45
(*R,R*)-DIOP
Kagan (1971)



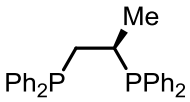
1.54
(*R,S*)-BPPM
Achiwa (1976)



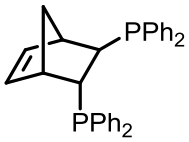
1.51
(*R,R*)-DIPAMP
Knowles (1977)



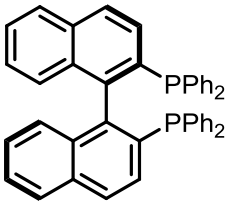
1.55
(*S,S*)-chiraphos
Bosnich (1977)



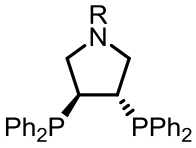
1.56
(*R*)-prophos
Bosnich (1978)



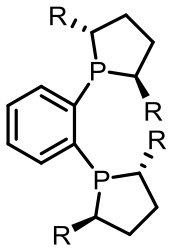
1.57
(*R,R*)-norphos
Brunner (1979)



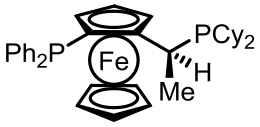
1.58
(*R*)-BINAP
Noyori (1980)



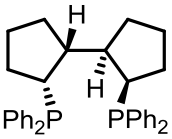
1.59
(*R,R*)-pyrphos
Nagal (1986)



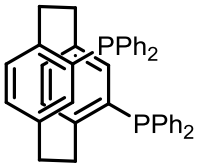
1.60
(*R,R*)-DuPhos
Burk(1991)



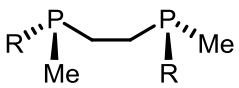
1.61
(*R,S*$_{(pl)}$)-Josiphos
Togni (1994)



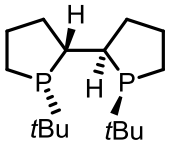
1.62
(*R,R*)-BICP
Zhang (1997)



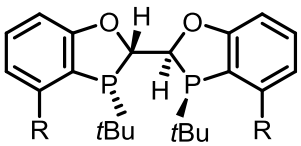
1.63
(*R*)-phanephos
Pye & Rossen (1997)



1.64
(*R,R*)-BisP*
Imamoto (1998)



1.65
(*S,S,R,R*)-TangPhos
Zhang (2002)



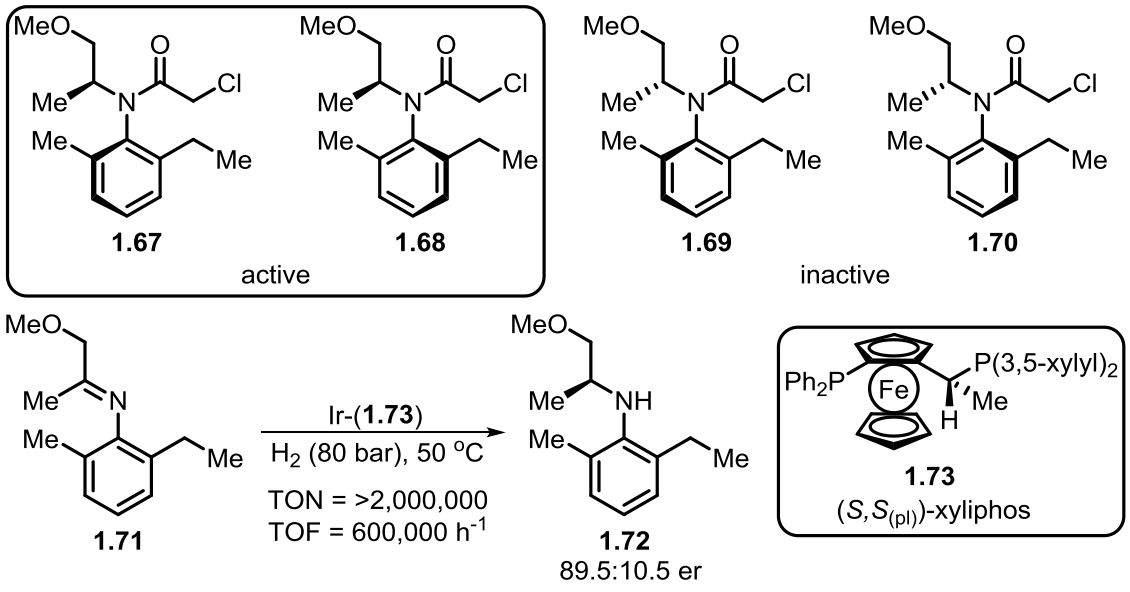
1.66
(*S,S,S,S*)-BIBOP
Tang & Senanayake (2010)

---

[34] (a) Togni, A.; Breutel, C.; Schnyder, A.; Spindler, F.; Landert, H.; Tijani, A. *J. Am. Chem. Soc*. **1994**, *116*, 4062. (b) Togni, A. *Angew. Chem. Int. Ed*. **1996**, *35*, 1475. (c) Blaser, H-U.; Pugin, B.; Spindler, F.; Thommen, M. *Acc. Chem. Res*. **2007**, *40*, 1240.

huge success of bidentate chiral ligands is highlighted by their frequent use in the large scale asymmetric synthesis of many biologically active compounds.[35] For example, the largest industrial scale catalytic asymmetric hydrogenation is utilized to produce >10,000 tons of the pesticide metolachlor (isomers **1.67**-**1.70**) per year (Scheme 1.12).[36] Utilizing an iridium complex of the Josiphos derivative xyliphos (**1.73**), turnover numbers of over 2,000,000 are obtained with incredibly high reaction rates. With such successful results obtained with bidentate ligands for many reactions, particularly asymmetric hydrogenation, monodentate ligands remained severely underdeveloped.

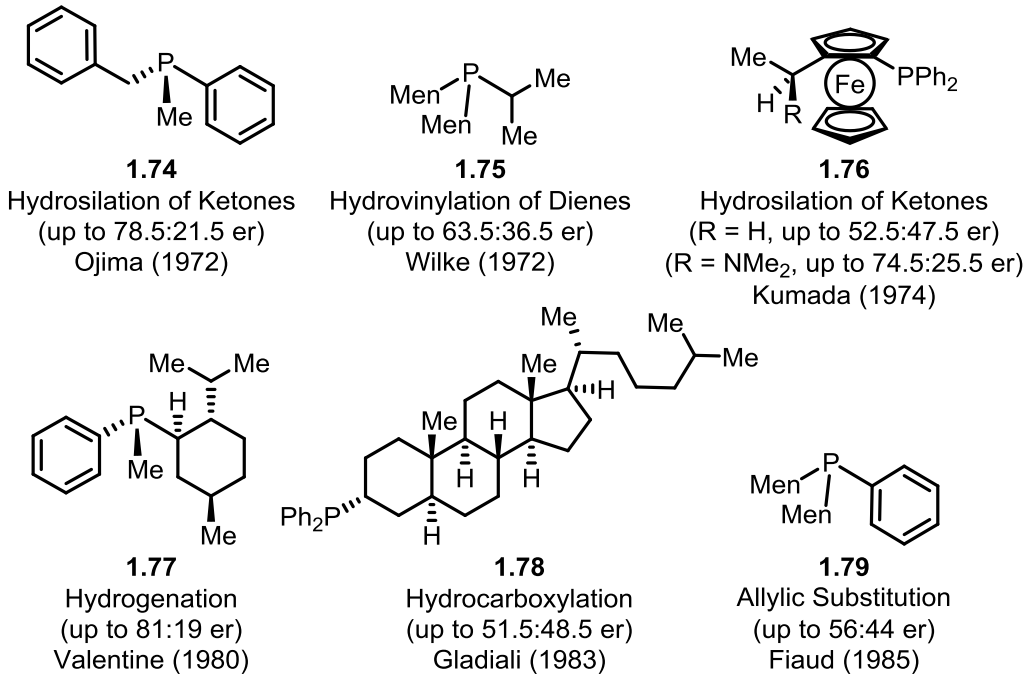
Scheme 1.12: Highly Efficient Asymmetric Hydrogenation to give Active Metolachlor Isomers



[35] (a) Busacca, C. A.; Fandrick, D. R.; Song, J. J.; Senanayake, C. H. *Adv. Synth. Catal*. **2011**, *353*, 1825. (b) Farina, V.; Reeves, J. T.; Senanayake, C. H.; Song, J. J. *Chem. Rev*. **2006**, *106*, 2734.
[36] Blaser, H-U. *Adv. Synth. Catal*. **2002**, *344*, 17.

1.2.3 Renaissance of Monodentate Phosphorus Ligands

Figure 1.2: Selected Chiral Monodentate Phosphines (1972-1985)



1.74
Hydrosilation of Ketones
(up to 78.5:21.5 er)
Ojima (1972)

1.75
Hydrovinylation of Dienes
(up to 63.5:36.5 er)
Wilke (1972)

1.76
Hydrosilation of Ketones
(R = H, up to 52.5:47.5 er)
(R = NMe_2, up to 74.5:25.5 er)
Kumada (1974)

1.77
Hydrogenation
(up to 81:19 er)
Valentine (1980)

1.78
Hydrocarboxylation
(up to 51.5:48.5 er)
Gladiali (1983)

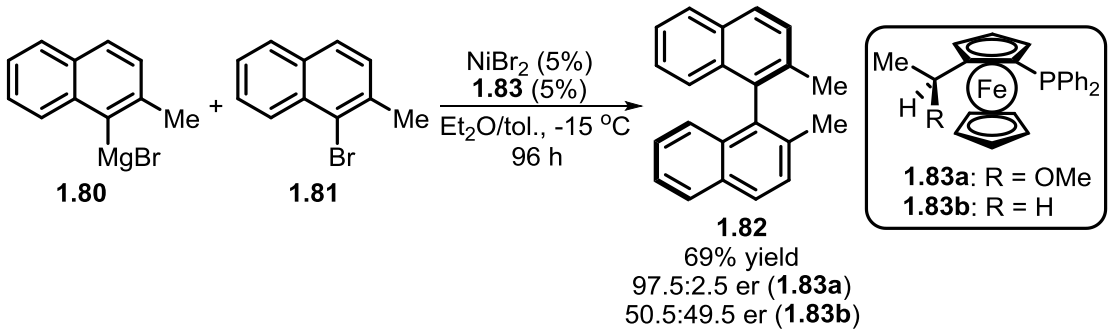
1.79
Allylic Substitution
(up to 56:44 er)
Fiaud (1985)

Early chiral monodentate ligand development entered a quiet hibernation period after 1972, despite the success of Knowles' CAMP ligand in hydrogenation.[29] The field remained relatively stagnant over the next 20 years, undoubtedly due, in part, to the firm establishment of bidentate doctrine, which held that chelating ligands generally led to highly organized, rigid catalyst structures, enforcing reliable interactions with prochiral substrates. Thankfully, monodentate ligands were not completely forgotten and sporadic reports continued to appear in the literature, though through the mid 1980's, the prospects for achieving highly selective catalysis with monodentate ligands continued to look quite grim (Figure 1.2).[37] Novel ligand structure development came to a near standstill, with Mislow's P-chiral approach and Morrison's use of menthyl-based substituents

[37] Lagasse, F.; Kagan, H. B. *Chem. Pharm. Bull*. **2000**, *48*, 315.

dominating new reports (with the notable exceptions of **1.76**[39] and **1.78**[38]). The relatively difficult synthesis of P-chiral molecules and the inherit lack of structural flexibility of the menthyl approach likely contributed to this slow progress. It wasn't until a 1988 report by Hayashi and Ito that the picture began to brighten.

Scheme 1.13: Enantioselective Biaryl Formation by Hayashi and Ito

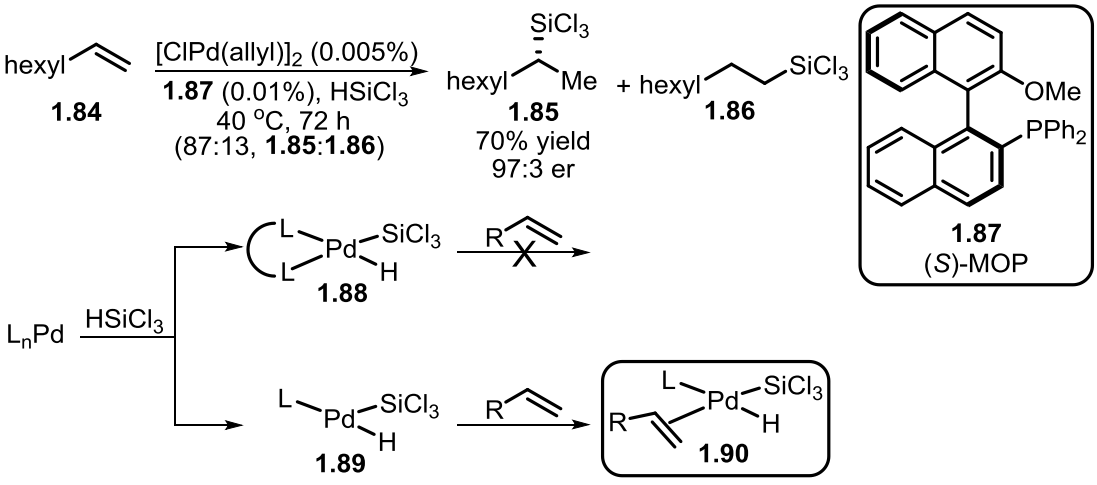


Utilizing Kumada's ferrocene-based ligand **1.83**[39] together with a nickel pre-catalyst, Hayashi and Ito were able to couple two hindered naphthalene fragments to obtain chiral 2,2'-substituted-1,1'-binaphthyl compounds, achieving up to 97.5:2.5 er (Scheme 1.13).[40] The authors note that the use of bidentate ligands such as BINAP (**1.58**) or chiraphos (**1.55**) resulted in almost no reactivity at room temperature, possibly due to the highly hindered nature of the reactants. Interestingly, the corresponding ligand without the methoxy group (**1.83b**) gives nearly racemic product, providing strong support for the predicted interaction of the methoxy substituent with the incoming Grignard reagent.[39] Importantly, the ferrocene-based class of ligands was one of the first examples of a rationally designed framework that not only provided an effective chiral environment, but also allowed facile derivatization in the search for the optimal structure.

[38] Gladiali, S.; Faedda, G.; Marchetti, M.; Botteghi, C. *J. Organomet. Chem*. **1983**, *244*, 289.
[39] (a) Hayashi, T.; Yamamoto, K.; Kumada, M. *Tetrahedron Lett*. **1974**, *15*, 4405. (b) Hayashi, T.; Kumada, M. *Acc. Chem. Res*. **1982**, *15*, 395.
[40] Hayashi, T.; Hayashizaki, K.; Kiyoi, T.; Ito, Y. *J. Am. Chem. Soc*. **1988**, *110*, 8153.

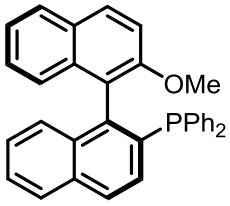
Notably, Hayashi and Ito's 1988 report was the first time a catalytic asymmetric reaction employing monodenate phosphorus ligands had broken the 90% *ee* mark since 1972. In 1991, Hayashi was once again able to achieve high enantioselectivities utilizing a monodentate phosphine ligand.[41] While examining chiral catalysts for use in palladium catalyzed hydrosilation of terminal olefins, bidentate ligands such as chiraphos (**1.55**) and BINAP (**1.58**) were found to strongly inhibit catalyst activity (no reaction at 80 ^{o}C). To achieve a selective and efficient reaction, the authors designed a new class of monodentate phosphine ligands based on a binaphthyl backbone (**1.87**). Under action of the new MOP ligands, exceedingly efficient catalysis was achieved, affording the desired branched alkyl silanes in good yield and with high enantioselectivities. The vast difference in reactivity between the monodentate and bidentate systems was attributed to the ability to access Pd(II) intermediate **1.89** with use of a monophosphorus ligand, where olefin binding can occur at an empty coordination site (**1.90**), whereas the corresponding Pd(II) species **1.88** containing a bidentate ligand is unable to effectively bind substrate.

Scheme 1.14: Highly Efficient Hydrosilation by Hayashi

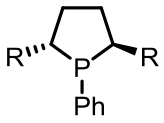


[41] Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc*. **1991**, *113*, 9887.

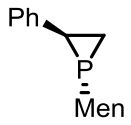
Figure 1.3: Selected Chiral Monodentate Phosphorus Ligands from the 1990's



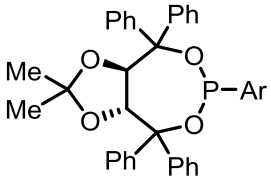
1.87
Hydrosilation of Olefins
(up to 97.5:2.5 er)
Hayashi (1991)



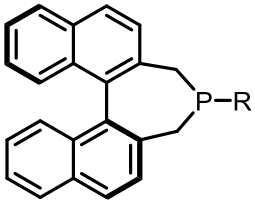
1.91
Allylic Substitution
(up to 55:45 er)
Hydrogenation
(up to 91:8 er)
Fiaud (1991&1999)



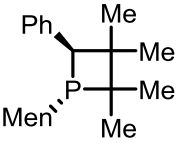
1.92
Hydrogenation
(up to 88:12 er)
Marinetti (1993)



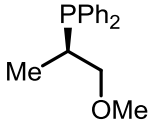
1.93
Hydrosilation of Ketones
(up to 93.5:6.5 er)
Seebach (1993)



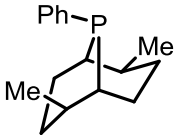
1.94
Hydroformylation
(up to 60:40 er)
Gladiali (1994)



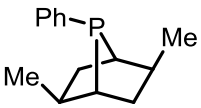
1.95
Hydrosilation of Ketones
(up to 77:23 er)
Marinetti (1994)



1.96
Biaryl Coupling
(up to 84.5:15.5 er)
Brunner (1996)



1.97
Allylic Substitution
(up to 98.5:1.5 er)
Hamada (1996)



1.98
Allylic Substitution
(up to 99.5:0.5 er)
Zhang (1997)

Following these two pivotal reports, interest in developing new chiral monodentate phosphorus ligands was revived, and a greater variety of structures began to appear throughout the 1990's (Figure 1.3). This slow, but steady groundswell of interest prompted Kagan to write an influencial review in 2000 summarizing the application of chiral monodentate phosphines in metal catalyzed reactions.[37] In the conclusion of the review, Kagan notes "We can expect that they [monodentate phosphines] will play a role

of increasing importance in many aspects of organometallic catalysis."[42] It has previously been pointed out with some irony that it was Kagan's success with DIOP which caused the catalysis world to shift focus away from monodentate ligands in the first place.[43,28] In any event, coming from a highly respected source in the field, Kagan's review added fuel to the fire for chiral monodentate ligand development, and the disclosure of novel phosphorus compounds rapidly accelerated shortly thereafter and has continued unabated to this day.[44]

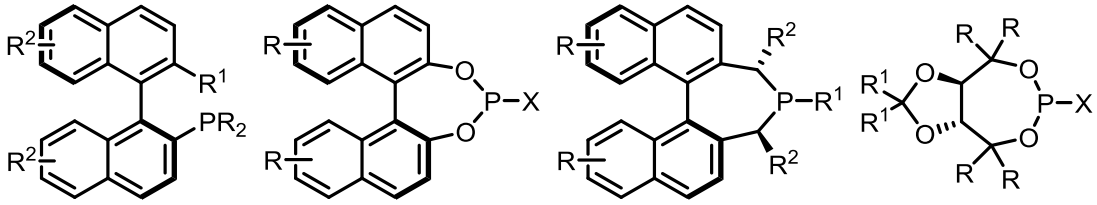
1.2.4 Key Design Features of Highly Successful Ligand Scaffolds

With over 1000 chiral monodentate phosphorus ligands described,[45] select families of ligand scaffolds have proven highly successful in a diverse array of reactions (Figure 1.4). Among this select group of compounds are the MOP-based ligands (**1.99**) first reported by Hayashi,[41] the TADDOL-based ligands (**1.102**) developed by Seebach,[46] the BINOL-based phosphonites,[47] phosphoramidites,[48] and phosphites[49] (**1.100**) first disclosed for hydrogenation by Pringle, Feringa, and Reetz respectively, and the Binepine-based ligands[50] (**1.101**) developed by Gladiali and subsequently Beller. In his

[42] Lagasse, F.; Kagan, H. B. *Chem. Pharm. Bull*. **2000**, *48*, 323.
[43] Komarov, I. V.; Borner, A. *Angew. Chem. Int. Ed*. **2001**, *40*, 1197.
[44] For recent examples of chiral monodentate phosphorus ligand development, see: (a) Huang, Y.; Li, Y.; Leung, P. H.; Hayashi, T. *J. Am. Chem. Soc*. **2014**, *136*, 4865. (b) Han, Z. S.; Goyal, N.; Herbage, M. A.; Sieber, J. D.; Qu, B.; Xu, Y.; Li, Z.; Reeves, J. T.; Desrosiers, J-N.; Ma, S.; Grinberg, N.; Lee, H.; Mangunuru, H. P. R.; Zhang, Y.; Krishnamurthy, D.; Lu, B. Z.; Song, J. J.; Wang, G.; Senanayake, C. H. *J. Am. Chem. Soc*. **2013**, *135*, 2474. (c) Xu, G.; Fu, W.; Liu, G.; Senanayake, C. H.; Tang, W. *J. Am. Chem. Soc*. **2014**, *136*, 570.
[45] (a) Armin Borner (Ed.) "*Phosphorus Ligands in Asymmetric Catalysis*", Wiley-VCH, **2008**. (b) Paul C. J. Kramer, Piet, W. N. M. van Leeuwen (Eds.) "*Phosphorus (III) Ligands in Homogeneous Catalysis*", John Wiley and Sons, **2012**.
[46] Seebach, D.; Hayakawa, M.; Sakaki, J.; Schweizer, W. B. *Tetrahedron* **1993**, *49*, 1711.
[47] Claver, C.; Fernandez, E.; Gillon, A.; Heslop, K.; Hyett, D. J.; Martorell, A.; Orpen, A. G.; Pringle, P. G. *Chem. Commun*. **2000**, 961.
[48] Hulst, R.; de Vries, N. K.; Feringa, B. L. *Tetrahedron Asymm*. **1994**, *5*, 699.
[49] Reetz, M. T.; Mehler, G. *Angew. Chem. Int. Ed*. **2000**, *39*, 3889.
[50] Gladiali, S.; Dore, A.; Fabbri, D.; De Lucchi, O.; Manassero, M. *Tetrahedron Asymm*. **1994**, *5*, 511.

initial report of phosphorus compounds incorporating a TADDOL unit, Seebach notes, "It is probably a dream of all researchers working in the field of enantioselective reactions that, once upon a time, they will find a ligand system which – by slight variations of a parent compound – is capable of functioning for most of the principal reactions of organic synthesis."[51]

Figure 1.4: Highly Versatile Monodentate Ligand Scaffolds



1.99
MOP Scaffold
R = alkyl, aryl

1.100
BINOL Scaffold
X = R, OR, NR_2

1.101
BINEPINE Scaffold
R^1 = alkyl, aryl
R^2 = H, alkyl

1.102
TADDOL Scaffold
X = R, OR, NR_2
R = alkyl, aryl
R^1 = H, alkyl

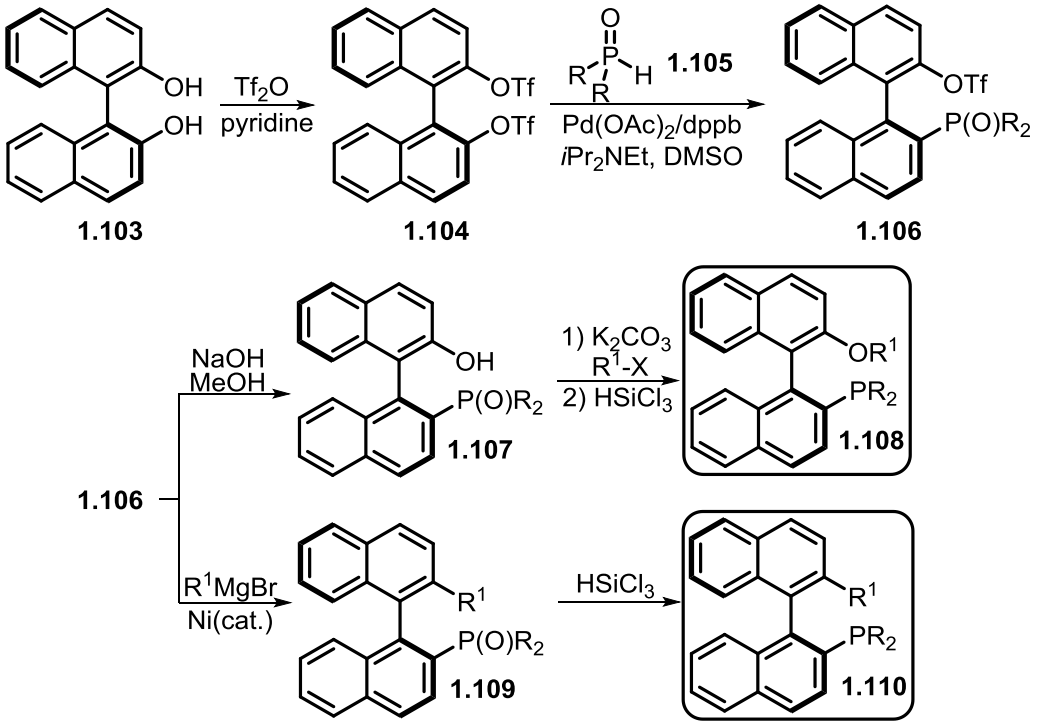
While this "Holy Grail" of structures remains to be discovered, some of the scaffolds in Figure 1.4 arguably come close. Developing a new class of ferrocene-based mono- and bidentate phosphine ligands,[39] Kumada set forth a list of three key design features which were considered: "(1) a highly efficient chiral structure to bring about high stereoselectivity; (2) a functional group that can be substituted by other appropriate groups as occasion demands; (3) easy preparation in large quantities."[52] Perhaps an important fourth feature to add is; (4) the ability to easily access both enantiomers of the ligand in question. For instance, many creative structures based on naturally occurring carbohydrate scaffolds[53] easily pass the first three objectives; however, the production of

[51] Seebach, D.; Hayakawa, M.; Sakaki, S.; Schweizer, W. B. *Tetrahedron* **1993**, *49*, p. 1712.
[52] Hayashi, T.; Kumada, M. *Acc. Chem. Res*. **1982**, *15*, p. 396.
[53] Dieguez, M.; Pamies, O.; Ruiz, A.; Diaz, Y.; Castillon, S.; Claver, C. *Coord. Chem. Rev*. **2004**, *248*, 2165.

only one enantiomer of carbohydrate by Nature ultimately limits their synthetic utility.[54] Taken together, these guidelines stipulate a successful ligand structure should be selective, tuneable, scalable, and available in both mirror image forms.

1.2.4.1 MOP-Based Ligands for Enantioselective Catalysis

Scheme 1.15: General Synthesis of MOP Ligands

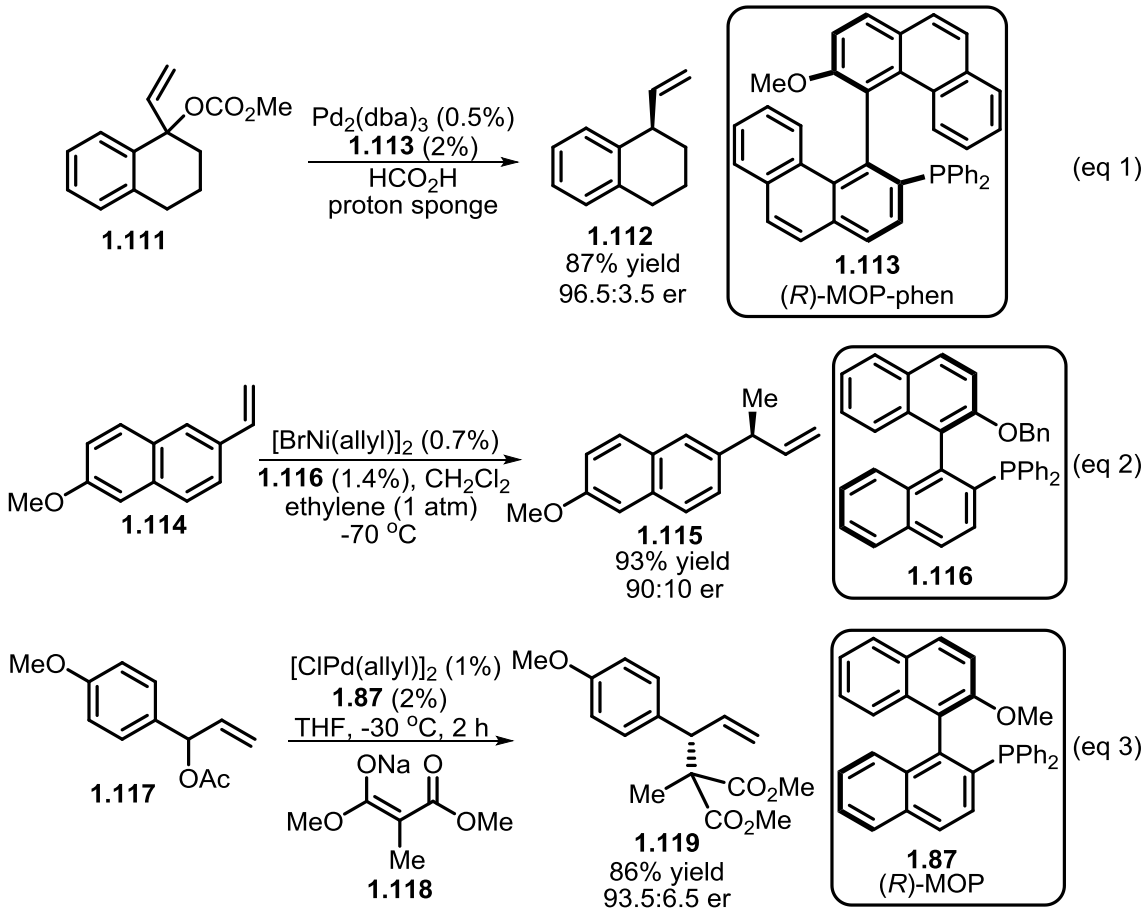


Ligands of the general structure **1.99**, or so-called MOP ligands have grown in popularity ever since their introduction by Hayashi in 1991.[55] The synthesis of this class of ligands begins with 2,2'-dihydroxy-1,1'-binaphthylene (BINOL, **1.103**), a compound that has become widely available in both enantiomers due to the high demand of binaphthyl-based ligands in asymmetric catalysis. Formation of the bis-triflate **1.104** followed by Pd-catalyzed coupling of secondary phosphine oxide **1.105** to one of the two

[54] For example, as of April 2014: the price of (*D*)-Mannitol = $48.60/kg (Aldrich); (*L*)-Mannitol = $172.70/100 mg (TCI).
[55] (a) Hayashi, T.; *J. Organomet. Chem*. **1999**, *576*, 195. (b) Hayashi, T. *Acc. Chem. Res*. **2000**, *33*, 354.

equivalent sites gives phosphine oxide **1.106**. At this stage the monotriflate can either be utilized in a Kumada coupling to install an R group to give **1.109**, or be suponified to reveal a hydroxyl group (**1.107**) followed by alkylation to forge an ether. Facile reduction of the phosphine oxide then gives the free phosphines **1.108** and **1.110**. This general synthetic approach allows for incorporation of a variety of groups on phosphorus to facilitate the tuning of both steric and electronic parameters, and allows access to additional chiral space *via* incorporation of a variety of groups at the 2' position.[56]

Scheme 1.16: Select Examples of MOP Ligands in Asymmetric Catalysis



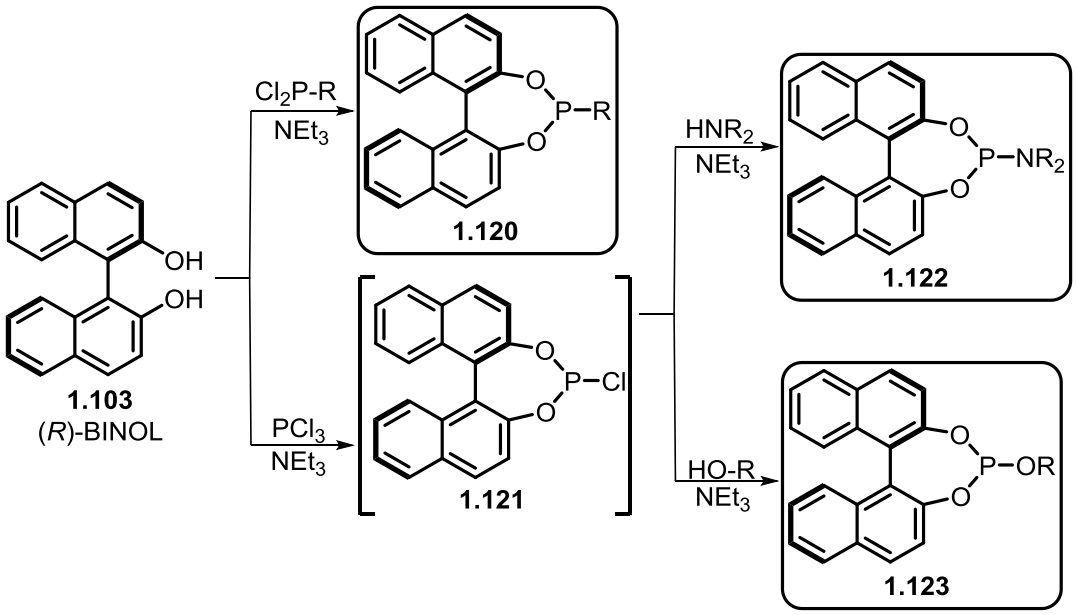
A variety of successful applications for MOP ligands in asymmetric catalysis have appeared, a small sample of which are highlighted in Scheme 1.16. Notably,

[56] Pereira, M. M.; Calvete, M. J. F.; Carrilho, R. M. B.; Abreu, A. R. *Chem. Soc. Rev*. **2013**, *42*, 6990.

Hayashi demonstrated that other non-racemic aryl diol backbones may be used to extend the range of MOP ligand structures available.[55] Utilizing ligand **1.113**, a stereoconvergent reduction of racemic allyl electophiles **1.111** was accomplished to afford terminal olefins such as **1.112** in a highly enantioselective fashion (equation 1).[57] By changing the character of the ligand ether functionality, RajanBabu and coworkers were able to implement ligand **1.116** in a highly regio- and enantioselective nickel catalyzed hydrovinylation (equation 2).[58] Importantly, by utilizing the properly functionalized starting material **1.114**, the reaction could be used to forge naproxen precursor **1.115**. Finally, Hayashi was able to utilize MOP **1.87** in the regio- and enantioselective palladium catalyzed allylic alkylation (equation 3).[59]

1.2.4.2 Binol-Derived Phosphonite, Phosphites, and Phosphoramidites for Enantioselective Catalysis

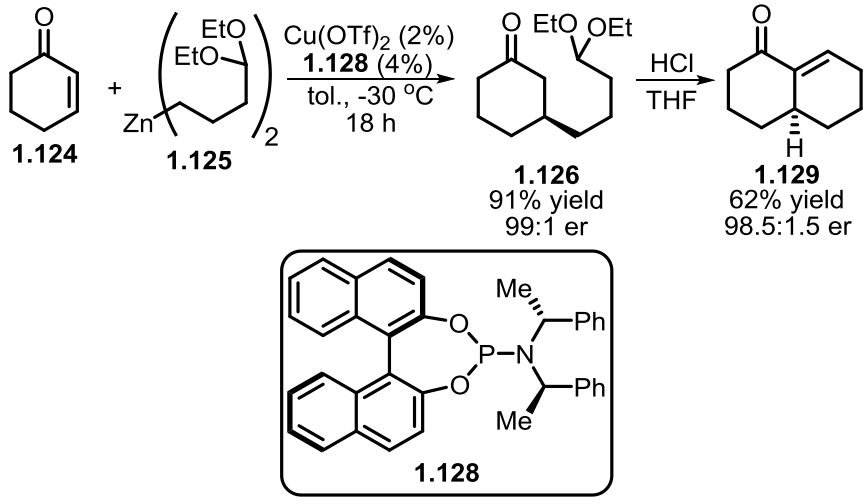
Scheme 1.17: Preparation of Binol-Derived Monophosphorus Ligands



[57] Hayashi, T.; Kawatsura, M.; Iwamura, H.; Yamaura, Y.; Uozumi, Y. *Chem. Commun*. **1996**, 1767.
[58] Nandi, M.; Jin, J.; RajanBabu, T. V. *J. Am. Chem. Soc.* **1999**, *121*, 9899.
[59] Hayashi, T.; Kawatsura, M.; Uozumi, Y. *Chem. Commun*. **1997**, 561.

BINOL **1.103** has also been utilized in a more direct fashion to give some of the most widely reported groups of monodentate phosphorus compounds in enantioselective catalysis. The corresponding groups of phosphonites (**1.120**), phosphites (**1.123**), and phosphoramidites (**1.122**) are easily prepared as shown in Scheme 1.17.[56] While these compounds are generally more π-acidic than phosphines, resulting in less electron-rich metal complexes, they have the practical advantages of being much more oxygen stable and are generally easier to prepare. Notably, the synthesis of phosphites and phosphoramidites allows for the facile incorporation of a huge array of readily available alcohols and amines. This efficient diversity-oriented synthesis readily lends itself to combinatorial approaches to catalyst optimization and allows for rapid identification of the best catalyst.[60]

Scheme 1.18: Copper Catalyzed Conjugate Addition-Annulation Sequence by Feringa

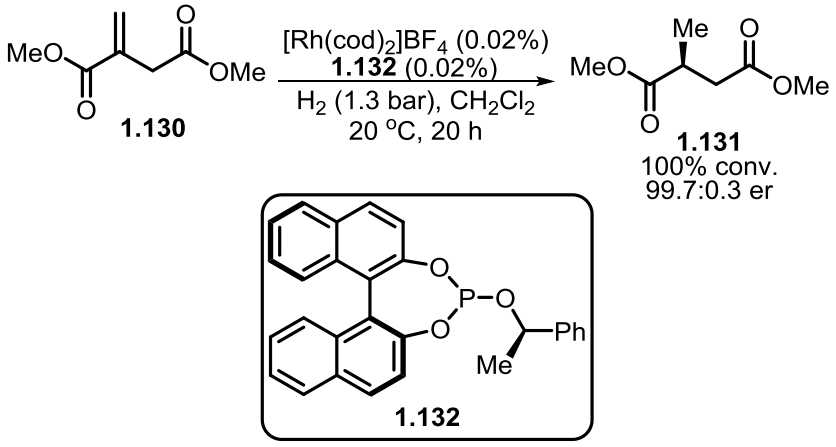


In particular, Feringa and coworkers have been instrumental in the development and implementation of what has become one of the largest classes of phosphorus based

[60] Lefort, L.; Boogers, J. A. F.; de Vries, A. H. M.; de Vries, J. G. *Org. Lett*. **2004**, *6*, 1733.

ligands: the phosphoramidites.[61] In one example of asymmetric catalysis with these ligands, Feringa disclosed a highly efficient two step procedure to produce enantioenriched decalin systems, which are complementary to the method of Hajos and Parrish (Scheme 1.18).[62] Utilizing phosphoramidite **1.128** under copper catalysis, a highly enantioselective conjugate addition of alkyl zinc **1.125** to cyclohexenone, followed by acid promoted ring formation gives **1.129** in good yield and with excellent selectivity. The use of monophosphites in enantioselective hydrogenation has been pioneered by the Reetz group, which was the first to show that, under the action of rhodium complexes derived from simple monophosphites, exceedingly high levels of enantioselectivity could be obtained.[49] For example, under very mild conditions ligand **1.132** was employed in rhodium catalyzed hydrogenation of **1.130**, achieving up to 5000 TON and affording the product in 99.4 % *ee*. Following the initial report by Pringle,[47] Reetz also showed the utility of monodentate phosphonites in asymmetric hydrogenation (Scheme 1.20).[63]

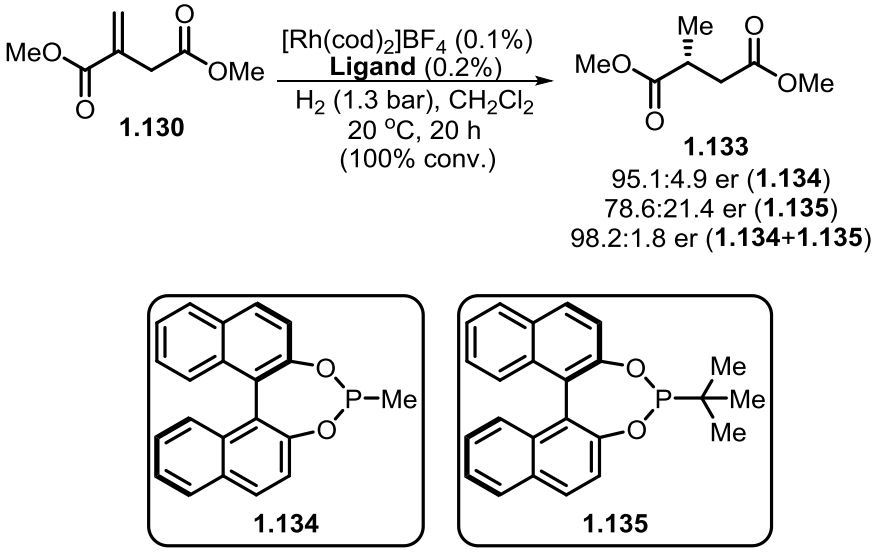
Scheme 1.19: Highly Enantioselective Hydrogenation by Reetz



[61] Teichert, J. F.; Feringa, B. L. *Angew. Chem. Int. Ed*. **2010**, *49*, 2486.
[62] Naasz, R.; Arnold, L. A.; Pineschi, M.; Keller, E.; Feringa, B. L. *J. Am. Chem. Soc*. **1999**, *121*, 1104.
[63] Reetz, M. T.; Sell, T.; Meiswinkel, A.; Mehler, G. *Angew. Chem. Int. Ed*. **2003**, *42*, 790.

The Reetz group has also examined the use of combinatorial asymmetric catalysis to identify the optimal catalyst from a collection of mixed monodentate ligands on a ML_2 complex.[64] For instance, when a library of 50 ligands is screened in a particular reaction, there are 50 homocombinations and 1225 heterocombinations possible, all of which give unique catalysts. Often catalysts derived from a heteromixture of ligands can be more selective than those derived from homomixtures of either ligand component (Scheme 1.20).[63] It is worth pointing out that while monodenate ligands can easily be utilized in this powerful approach, bidentate ligands are unable to take part. To gain access to the corresponding 1225 unique complexes utilizing bidentate ligands with mixed phosphorus donors, 1225 individual ligands would need to be prepared, versus just 50 monodentate ligands.

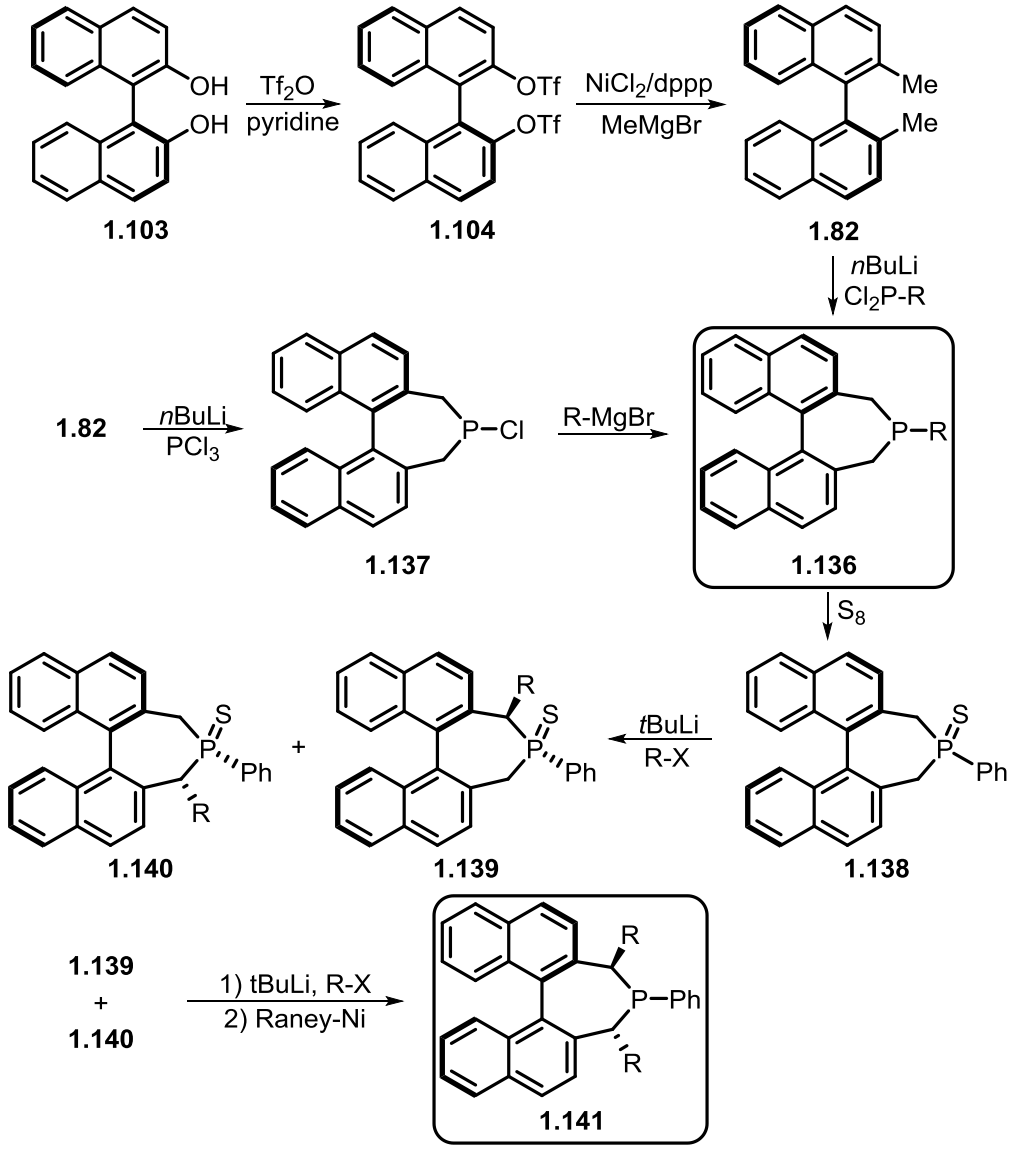
Scheme 1.20: Mixture of Simple Monodentate Phosphonites to Improve Selectivity by Reetz



1.2.4.3 Binepines as Monodentate Phosphines for Asymmetric Catalysis

[64] Reetz, M. T. *Angew. Chem. Int. Ed*. **2008**, *47*, 2556.

Scheme 1.21: Synthesis of the BINEPINE Monodentate Ligand Scaffold

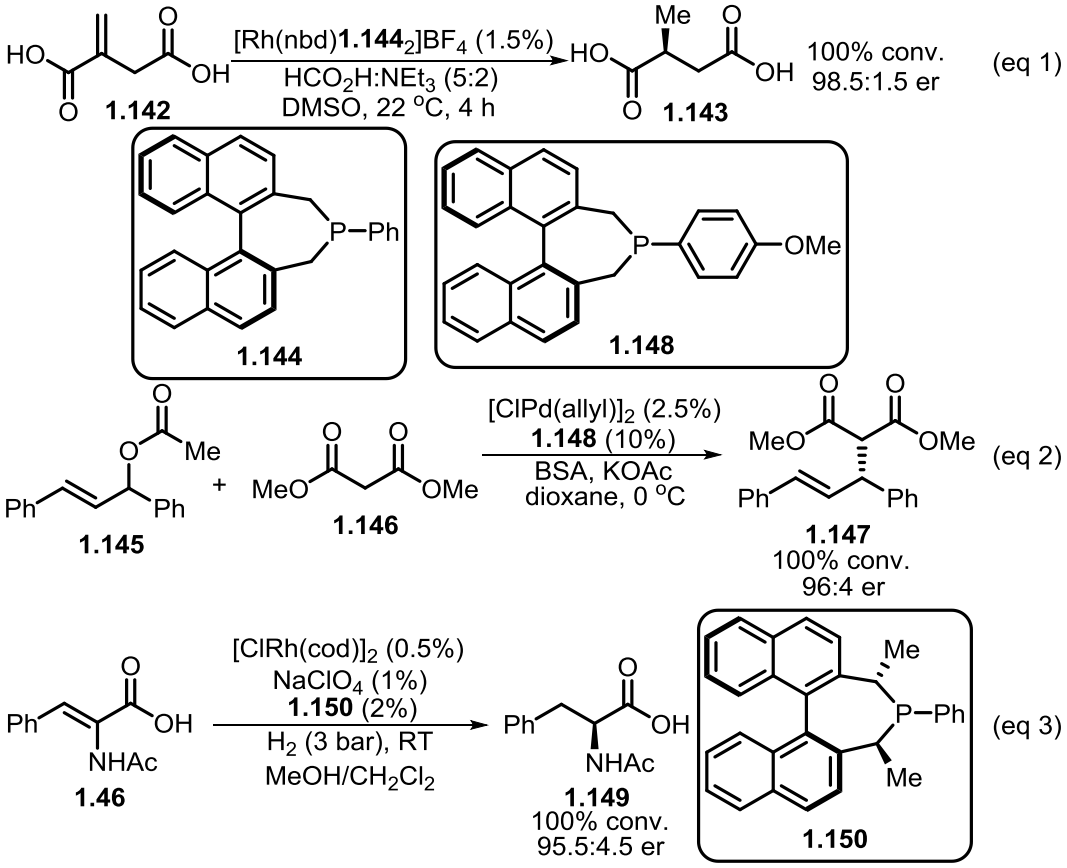


First reported by Gladiali in 1994,[50] the BINEPINES are another class of highly useful monodentate ligands which employ a binaphthyl backbone containing axial chirality (Scheme 1.21).[65] Utilizing BINOL **1.103** as a starting material, formation of the bistriflate, followed by double Kumada coupling with MeMgBr gives **1.82**. Double lithiation, followed by trapping with a dichlorophosphine affords the product **1.136**. Alternatively, the dilithio species may be trapped with PCl_3 to afford the chlorophosphine

[65] Gladiali, S.; Alberico, E.; Junge, K.; Beller, M. *Chem. Soc. Rev*. **2011**, *40*, 3744.

1.137, which can be further reacted with Grignard or alkyllithium reagents to give the target structures. Sulfination of the phosphine **1.136** acidifies the benzylic protons sufficiently to allow for incorporation of additional groups following deprotonation. Interestingly, monoalkylation destroys the C_2 symmetry of the scaffold, generating two new stereogenic centers, at the benzylic site and centered at phosphorus. A second addition occurs in a stereoselective fashion to give **1.141** following reduction, restoring the C_2 symmetry of the ligand. The flexible synthesis allows for generation of extensive structural diversity and the BINEPINES are one of the only flexible monodentate ligand scaffolds to afford di- or even trialkyl phosphines, which are highly valuable in cases where the formation of an electon rich metal complex is beneficial for catalysis.

Scheme 1.22: Examples of BINEPINE ligands in Asymmetric Catalysis



Utilizing BINEPINE **1.144**, Gladiali was able to show the highly enantioselective transfer hydrogenation of **1.142** under mild conditions (Scheme 1.22, equation 1).[66] Importantly, this is one of the only known examples of a monodenate phosphine complex promoting a selective transfer hydrogenation. Beller demonstrated the utility of binepine **1.148** in palladium catalyzed allylic alkylation reactions, forging **1.147** in good yield and with excellent enantioselectivity (equation 2).[67] Finally, dialkylated binepine **1.150** was shown by Widhalm to promote the selective hydrogenation of **1.46**, affording amino acid adduct **1.149** with good enantioselectivity under mild conditions (equation 3).[68]

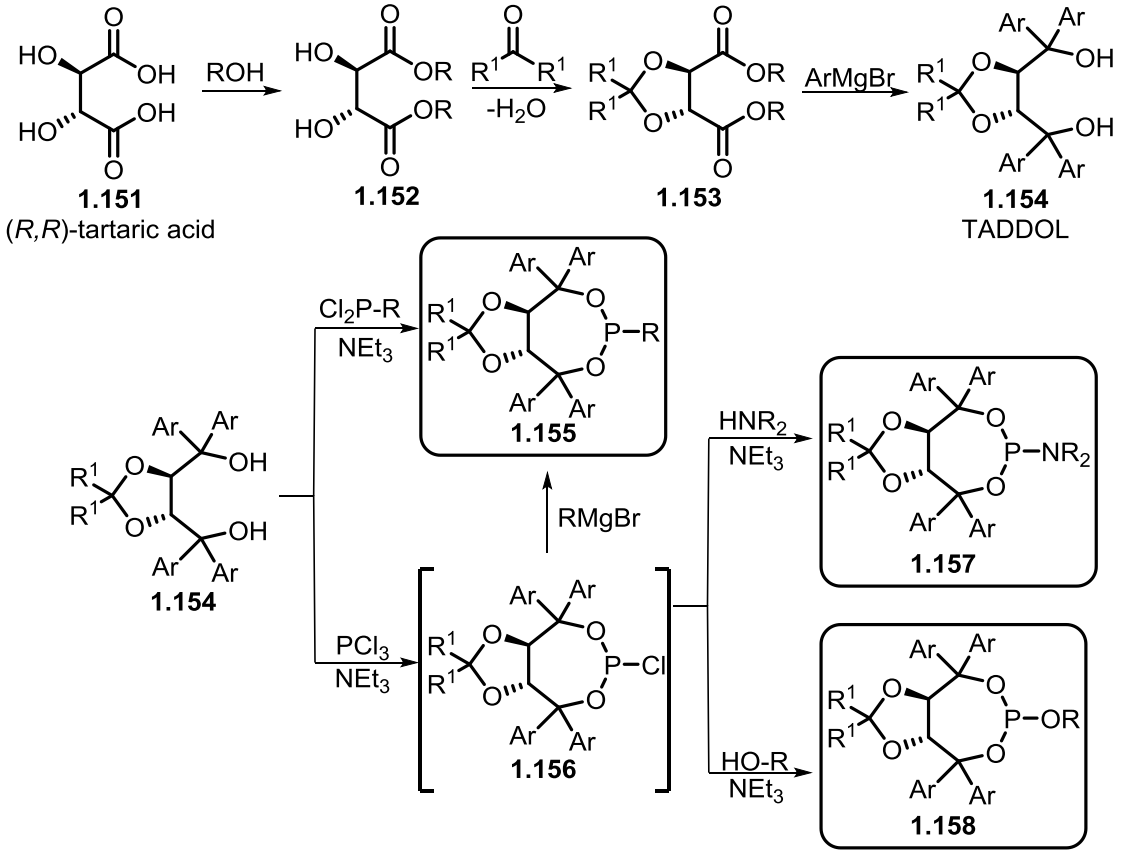
1.2.4.4 TADDOL-based Phosphorus Compounds for Asymmetric Catalysis

First disclosed by Seebach in 1993,[69,46] phosphorus compounds based on TADDOL are one of the only highly successful families of chiral monodentate ligands which are not based on a biaryl framework.[70] Beginning from tartaric acid, which is readily available in both enantiomeric forms,[71] the corresponding diester **1.152** undergoes ketal formation to give **1.153** (Scheme 1.23). Exhaustive reaction with the appropriate Grignard reagent gives the parent TADDOL **1.154**.[72] Utilizing similar approaches used in BINOL-based ligand syntheses, diol **1.154** can be treated with dichlorophosphine to give the corresponding phosphonite **1.155**. Likewise, treatment with PCl_3, initially gives chlorophosphite **1.156**, which may be treated with Grignard reagents to again give

[66] Alberico, E.; Niedda, I.; Taras, R.; Gladiali, S. *Helv. Chim. Acta*. **2006**, *89*, 1716.
[67] Alberico, E.; Gladiali, S.; Taras, R.; Junge, K.; Beller, M. *Tetrahedron Asymm*. **2010**, *21*, 1406.
[68] Kasak, P.; Mereiter, K.; Widhalm, M. *Tetrahedron Asymm*. **2005**, *16*, 3416.
[69] Sakaki, J.; Schweizer, W. B.; Seebach, D. *Helv. Chim. Acta*. **1993**, *76*, 2654.
[70] (a) Seebach, D.; Beck, A. K.; Heckel, A. *Angew. Chem. Int. Ed*. **2001**, *42*, 92. (b) Lam, H. W. *Synthesis* **2011**, 2011.
[71] As of April 2014, the price of (*R,R*)-tartaric acid = $37.60/100 g (Aldrich); (*S,S*)-tartaric acid = $99.20/100 g (Aldrich).
[72] For the first report of tetra-Grignard addition of PhMgBr to tartrate, see: Frankland, P. F.; Twiss, D. F. *J. Chem. Soc*. **1904**, 1666.

phosphonites **1.155**, or with either amines or alcohols in the presence of base to give the corresponding phosphoramidites **1.157** or phosphites **1.158** respectively. Notably, the use of acyclic diolate backbones,[73] and secondary aryl alcoholates[70] have been disclosed.

Scheme 1.23: General Synthesis of TADDOL-based Monophosphorus Ligands

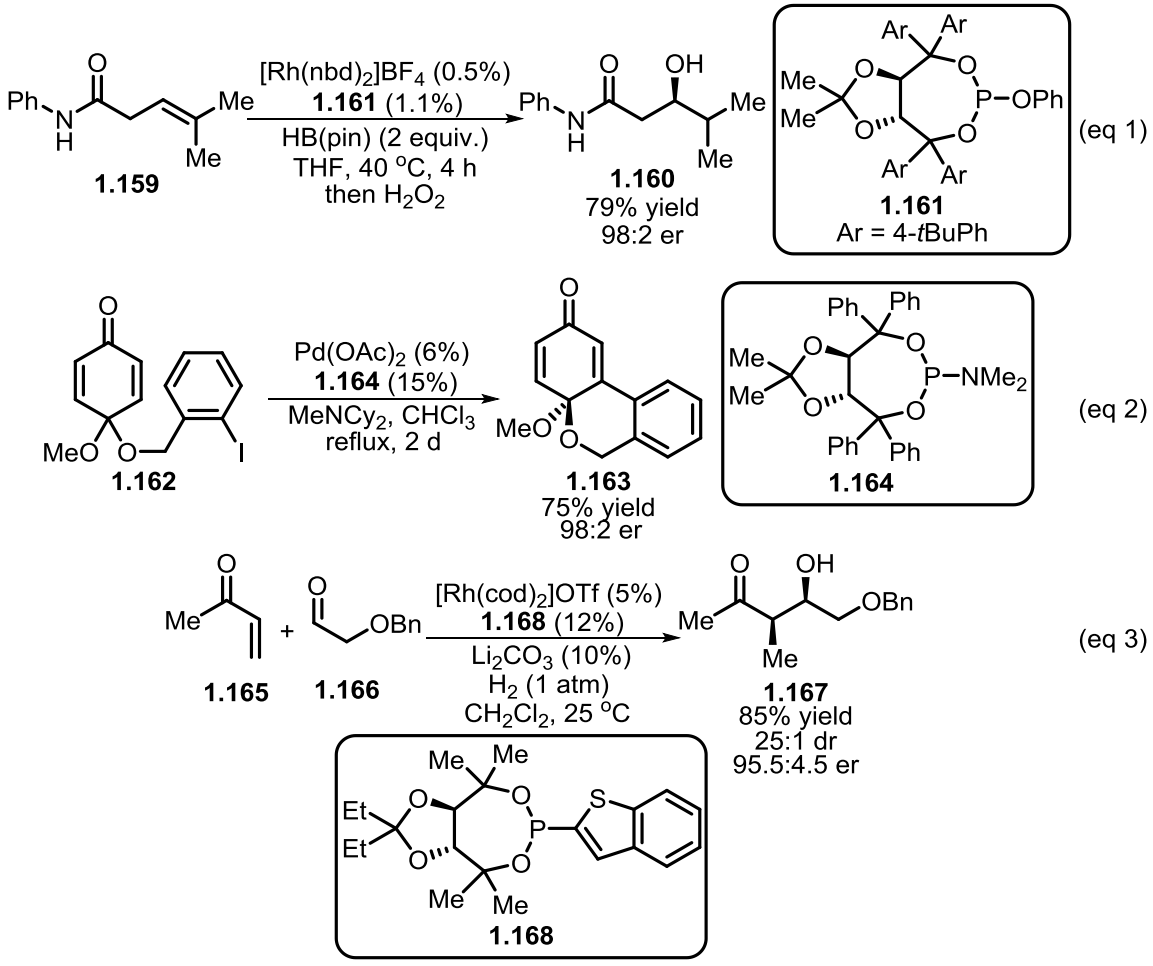


With a highly tunable structure, and a steric environment that is complementary to the biaryl-based monodentate ligands, TADDOL-derived phosphorus ligands have seen widespread use in asymmetric catalysis (Scheme 1.24). For example, Takacs was able to utilize TADDOL-derived phosphite **1.161** in the highly regio- and enantioselective hydroboration of β, γ unsaturated amides (equation 1).[74] After oxidation the

[73] Teller, H.; Fluegge, S.; Goddard, R.; Fuerstner, A. *Angew. Chem. Int. Ed*. **2010**, *49*, 1949.
[74] Smith, S. M.; Thacker, N. C.; Takacs, J. M. *J. Am. Chem. Soc*. **2008**, *130*, 3734.

corresponding alcohol **1.160** was obtained in good yield and with excellent levels of enantioselectivity. Utilizing the dimethylamino TADDOL-derived phosphoramidite **1.164**, Feringa and coworkers achieved a highly selective intramolecular Heck cyclization to transform the symmetric starting material **1.162** into the desired product **1.163** (equation 2).[75] Finally, Krische employed a modified tetra-alkyl based scaffold to forge phosphonite **1.168**, which was utilized in a highly diastereo- and enatioselective hydrogenative coupling (equation 3).[76]

Scheme 1.24: Use of TADDOL-derived Monophosphorus Ligands in Asymmetric Catalysis



[75] Imbos, R.; Minnaard, A. J.; Feringa. B. L. *J. Am. Chem. Soc*. **2002**, *124*, 184.
[76] Bee, C.; Han, S. B.; Hassan, A.; Iida, H.; Krische, M. J. *J. Am. Chem. Soc*. **2008**, *130*, 2746.

Despite the enormous progress made in chiral monodentate ligand development, it is still not possible to predict which ligand structures will be selective for a given reaction. While computational methods may act as a guiding tool, ultimately the proof is in testing the actual compounds to evaluate their selectivity. As such, the continued development of unique ligands which follow the guidelines set out by Kumada[52] remains of great importance to the continued success of enantioselective catalysis. Having exhausted established chiral monodentate phosphorus ligand scaffolds in the quest to improve the scope and selectivity of platiunum catalyzed 1,4-diboration of *trans*-1,3-dienes,[77] the development of a new class of tunable ligands was initiated. By accessing unique chiral space, the new ligands would hold the potential to not only solve outstanding issues in diboration, but to also become a general tool for enantioselective catalysis, complementary to the highly successful monodenate phosphorus compounds mentioned above.

1.3 Development of a New Class of Oxaphospholane Ligands and Utility in the Efficient 1,4-Diboration of *trans*-1,3-Dienes.[78]

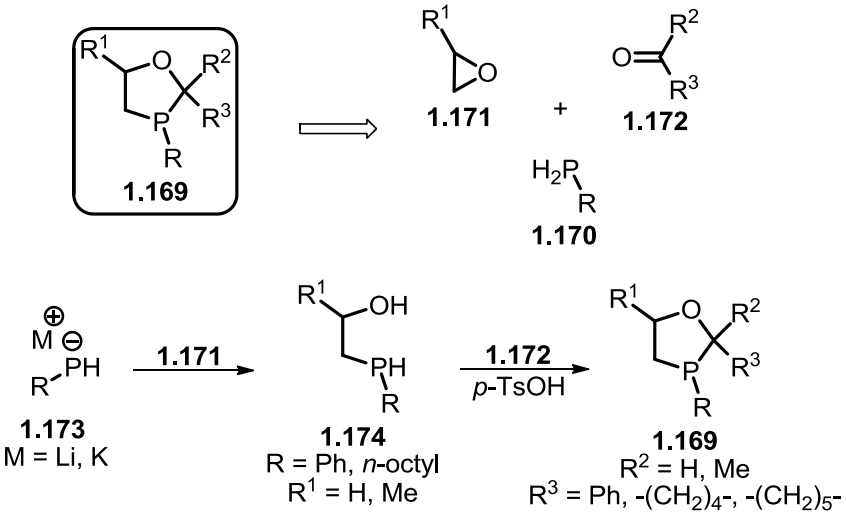
1.3.1 Design Aspects of the Oxaphospholane Scaffold

The search for a suitable scaffold upon which to build a new monodentate ligand class was guided by the principals outlined by Kumada, as well as the requirements established for platinum catalyzed diboration of dienes. Perhaps the most important feature of any scaffold is the ability to tune the steric environment about the phosphorus atom. The majority of the successful scaffolds mentioned earlier exhibit C_2-symmetry, which generally simplifies their synthesis, but ultimately limits the type of steric

[77] Kliman, L. T., Ph. D. Dissertation, Boston College, **2011**, pgs13-23.
[78] Schuster, C. H.; Li, B.; Morken, J. P. *Angew. Chem. Int. Ed*. **2011**, *50*, 7906.

environment which can be assembled around phosphorus. Phosphine structures which are not C_2-symmetric, yet are still easily assembled would enable one to quickly probe unique chiral space during structure optimization. While there are many examples of non C_2-symmetric monophosphorus ligands reported in the literature (see Figure 1.4), arguably none of these structures would be considered highly tunable, and as a result, logical reaction development around such structures becomes difficult.

Scheme 1.25: Novel 1,3-Oxaphospholane Structure by Issleib

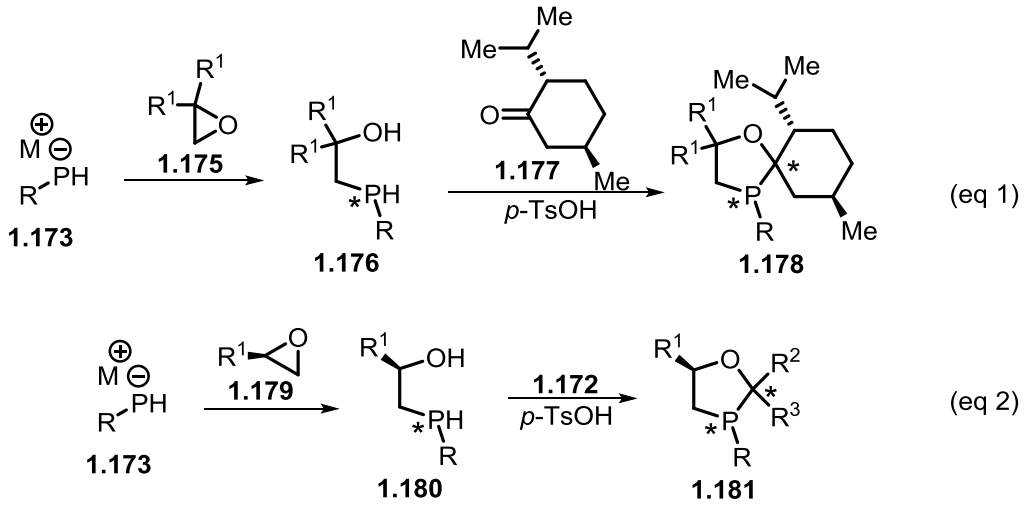


Importantly, over many decades of fascinating main group research outside the world of asymmetric catalysis, the study of phosphorus compounds has resulted in a rich variety of structures. One such example by the group of Isslieb is shown in Scheme 1.25. As part of a series of reports on phosphorus heterocycles,[79] Isslieb described the synthesis of 1,3-oxaphospholane structures **1.169** and examined their general chemical reactivity. Notably, the synthesis of the oxaphospholanes is quite convergent: starting from a primary phosphine, deprotonation followed by treatment with an epoxide gives secondary

[79] (a) Issleib, K.; Roloff, H. R. *Chem. Ber*. **1965**, *98*, 2091. (b) Oehme, H.; Isslieb, K.; Leissring, E. *Tetrahedron* **1972**, *28*, 2587.

phosphine **1.174**. Treatment of **1.174** with a ketone or aldehyde under acidic conditions results in phospha-ketal formation to give the desired cyclic compound **1.169**.

Scheme 1.26: Approaches to Selectively Introduce Chirality to Scaffold



While the 1,3-oxaphospholane structures reported by Issleib were never prepared in an enantiomerically or diastereomerically pure fashion, several features of these compounds are attractive from a ligand design standpoint. The convergent synthesis brings together three roughly equal parts: an epoxide, a primary phosphine, and a ketone or aldehyde, all of which are readily available. The two step sequence naturally lends itself to library formation for optimization purposes. In order to form an enantiopure structure, there are two possible handles with which to work; the carbonyl component and the epoxide (Scheme 1.26). While there are certain enantiopure ketones available from the chiral pool, such as menthone **1.177**, often times both enantiomers are not readily accessible, and the reliance upon a specific chiral group for this component severely hampers the flexibility of the scaffold and risks a return to the dark ages of monodentate ligand design (see: Figure 1.2). The choice of the epoxide as the source of chirality has

several advantages. Through use of the Jacobsen HKR,[80] both enantiomers of many epoxides are readily accessed in enantiopure form. Importantly, this allows for a high degree of tunablitiy at the 5-position and facilitates the incorporation of achiral ketones and aldehydes into the parent structure (equation 1). The highly modular nature of the oxaphospholane synthesis and the wide variation in structure available to the epoxide and carbonyl components qualify the scaffold as a highly tunable structure, passing Kumada's list of desired characteristics.

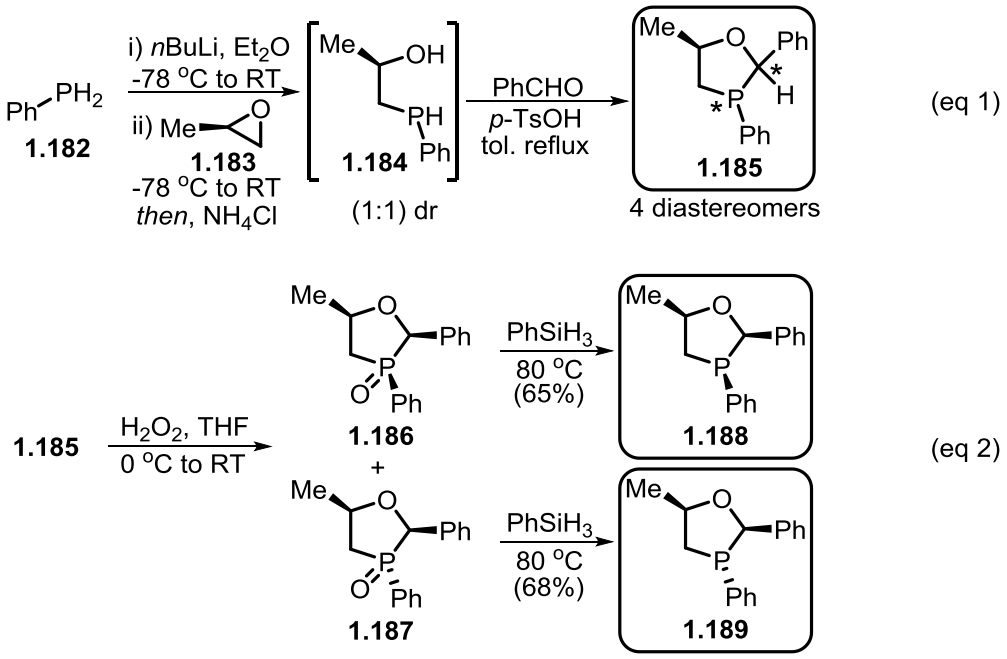
Several features of the new ligand scaffold also make it an attractive candidate for use in platinum catalyzed diboration reactions. Depending on the choice of primary phosphine employed during the synthesis, either a dialkyl-aryl phosphine, or a trialkylphosphine is formed in the cyclized structure. Along with BINEPINE (**1.136**, Scheme 1.21), this constitutes one of the most electron rich monodentate ligand scaffolds available and as a result, could provide for highly efficient diboration.[5c,6c,9] If large groups are employed in the phospha-ketal position, phosphines with especially large cone angles[81] could be accessible, possibly resulting in favorable formation of monoligated metal complexes (**1.21**, Scheme 1.6), further accelerating diboration.

[80] (a) Jacobsen, E. N. *Acc. Chem. Res*. **2000**, *33*, 421. (b) Schaus, 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.

[81] For a detailed discussion of cone angle effects in catalysis, see: Tolman, C. A. *Chem. Rev*. **1977**, *77*, 313.

1.3.2 Synthetic Approches to the Oxaphospholane Scaffold

Scheme 1.27: Initial Synthesis of Oxaphospholane Ligands

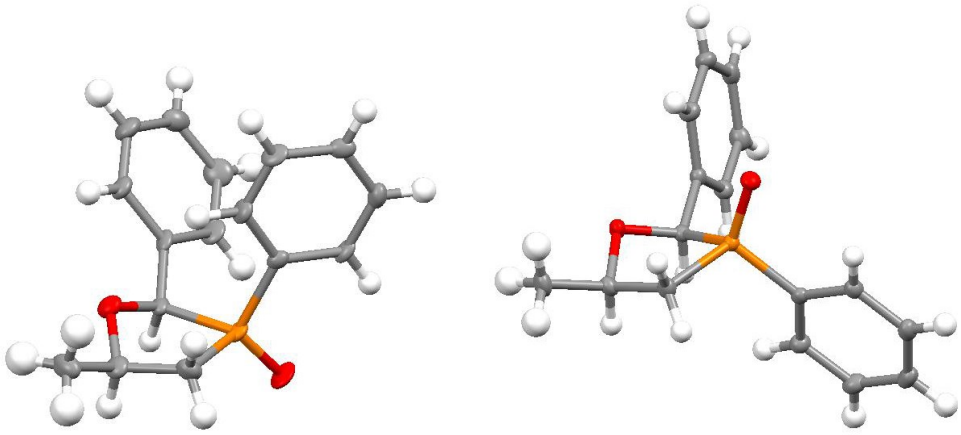


Due to its commercial availability, phenyl phosphine was chosen as a suitable primary phosphine and initial attempts to forge the secondary phosphine **1.184** centered on the use of propylene oxide together with CsOH as base[82] (Scheme 1.27). Unfortunately, this proved to be rather inefficient, affording large amounts of oxidized starting material and very small amounts of product formation. Fortunately, the deprotonation of $PhPH_2$ with n-butyllithium[83] in ether proved to be successful, affording secondary phosphine **1.184** as a roughly 1:1 mixture of diastereomers. Due to the highly air sensitive nature of **1.184**, the crude mixture was used directly in the phosphaketal formation. For example, direct treatment of **1.184** with catalytic *p*-toluenesulfonic acid and benzaldehyde gave the cyclized structure **1.185**, but as a mixture of diastereomers.

[82] Fox, D. L.; Robinson, A. A.; Frank, J. B.; Salvatore, R. N. *Tetrahedron Lett*. **2003**, *44*, 7579.
[83] Koch, T.; Blaurock, S.; Somoza, F. Jr.; Hey-Hawkins, E. *Eur. J. Inorg. Chem*. **2000**, 2167.

After all attempts to directly separate the diasteromers at the phosphine stage failed, an alternative approach was taken. Oxidation with hydrogen peroxide gave the corresponding air-stable phosphine oxide diastereomers **1.186** and **1.187**, which were easily separated via silica gel chromatography. Notably, the phosphine oxides are often crystalline compounds and the absolute stereochemistry of **1.186** and **1.187** was assigned by single crystal X-ray analysis (Figure 1.5).[84] With diastereomerically pure phosphine oxides **1.186** and **1.187** in hand, stereoretentive silane reduction was performed to give the corresponding phosphines **1.188** and **1.189**.[85]

Figure 1.5: X-Ray Structure of Phosphine Oxides 1.186 (left) and 1.187 (right)

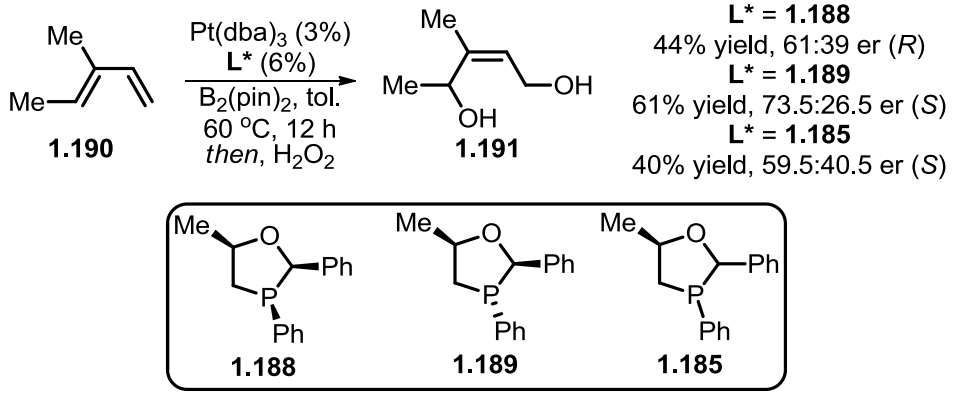


Seeking to improve the platinum catalyzed diboration of 3,4-disubstituted trans-dienes, **1.190** was chosen as a model substrate to evaluate the new oxaphospholane ligands. As shown in Scheme 1.28, the all syn diastereomer (*R,R,R*)-**1.188** gave the 1,4-diol product **1.191** in 61:39 er in favor of the (*R*) enantiomer of product. Interestingly, the (*R,S,R*) diastereomer **1.189** favored formation of the (*S*) enantiomer of 1,4-diol product in 73.5:26.5 er with the unresolved crude mixture **1.185** affording the desired

[84] All crystal structures discussed were solved at Boston College by Dr. Bo Li.
[85] Marsi, K. L. *J. Org. Chem*. **1974**, *39*, 265.

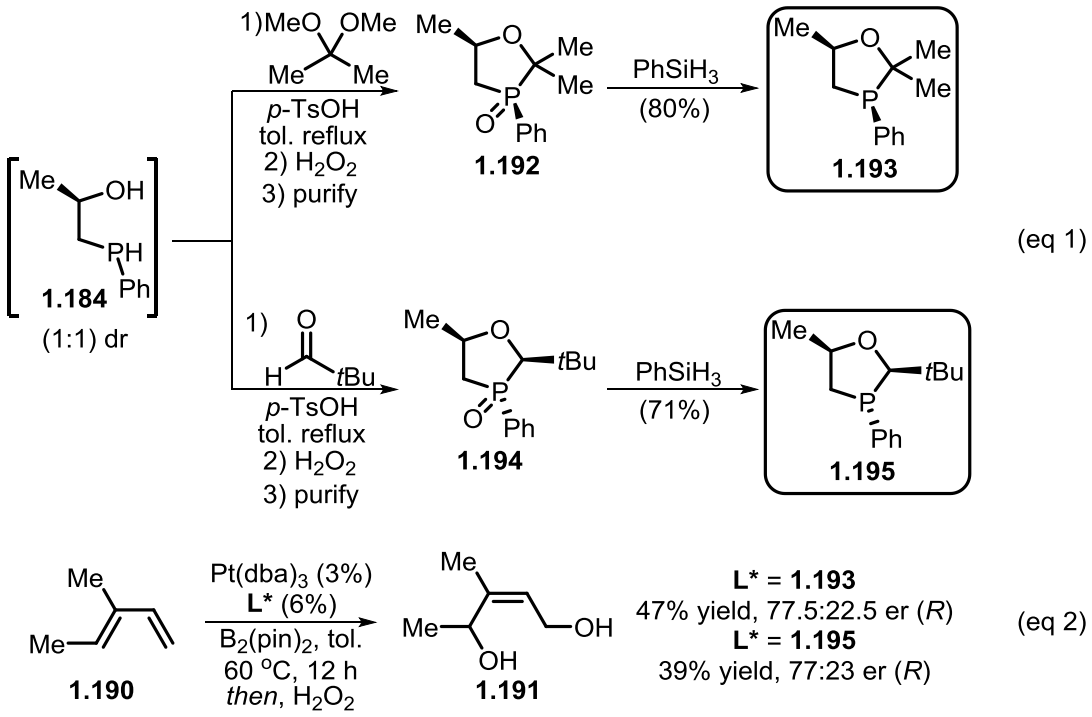
product in 59.5:40.5 er. Though only modest levels of enantioselectivity were obtained, these initial results highlighted features that were important in moving forward. Notably, separation of the phosphine diastereomers is vital to achieve higher selectivites and the stereochemistry of the phosphorus atom itself appears to dominate the stereochemical outcome in platinum catalyzed diboration.

Scheme 1.28: Initial Results in Platinum Catalyzed Diboration of 1.190



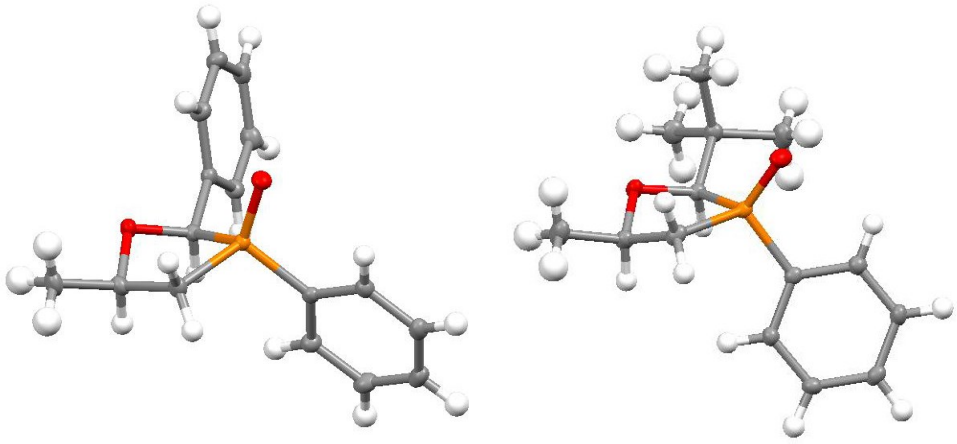
Seeking to understand which additional features of the oxaphospholane scaffold influence selectivity in diboration, the substitution at the phosphaketal position was varied by condensing both 2,2-dimethoxypropane and pivaldehyde onto the secondary phosphine **1.184** (Scheme 1.29). After oxidation, phosphine oxides **1.192** and **1.194** were isolated and reduced to give the corresponding phosphines **1.193** and **1.195**. Upon testing in platinum catalyzed diboration, these oxaphospholane ligands afforded the desired 1,4-diol **1.191** in 77.5:22.5 er and 77:23 er for **1.193** and **1.195** respectively. Importantly, establishing an achiral center at the phosphaketal site is not detrimental in the case of **1.193**. Again, the stereochemistry at phosphorus seems to dominate the stereochemical course of diboration, with **1.193** and **1.188** both having a preference for the *R* enantiomer of diol **1.191**.

Scheme 1.29: Synthesis and Evaluation of Ligands 1.193 and 1.195



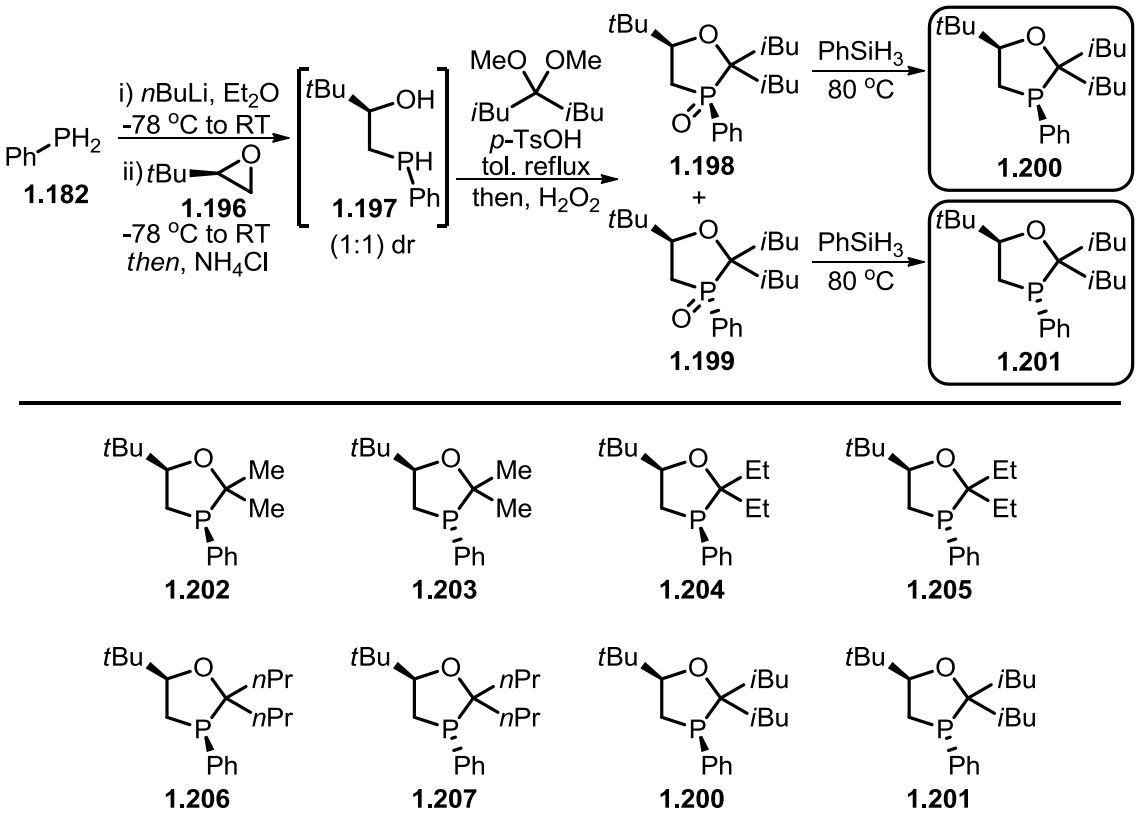
Surprisingly, substitution of the phenyl group in **1.189** for the *tert*-butyl group in **1.195** results in a complete turnover in enantioselection for diboration. Analysis of the X-ray structures of the corresponding phosphine oxides **1.187** and **1.194** reveals both ligands contain very similar conformations about the oxaphospholane structure, with both the ketal substituent and the epoxide-derived methyl group occupying pseudo equatorial positions (Figure 1.6). While the phenyl ring attached to phosphorus and the pucker of the 5-membered ring are somewhat different between the two structures, it is possible that the larger *tert*-butyl group changes the steric priority as seen by the metal, switching the enantiopreference during diboration. In any case, the somewhat simplified ligand structure created by the use of symmetric ketones was deemed a better scaffold to target, not only for the inherent ease of synthesis, but also because the enantioselectivity obtained from **1.193** was the highest obtained in early screening.

Figure 1.6: X-Ray Structures of Phosphine Oxides 1.187 (left) and 1.194 (right)



In addition to changing the phosphaketal substituents, various epoxides were utilized to incorporate different groups at the 5-position of the 1,3-oxaphospholane, quickly revealing *tert*-butyl oxirane **1.196** as optimal (Scheme 1.30). Utilizing these findings, a small ligand library was prepared and examined in platinum catalyzed diboration. As shown in Scheme 1.30, use of the dimethylketals of the corresponding ketones was found to greatly improve the rate of phosphaketal formation, possibly due to the in situ formation of a highly reactive oxocarbenium ion. Unfortunately, the dimethylketals derived from ketones with groups larger than isobutyl could not be prepared and this limited the size of group that was incorporated into the ligand scaffold. Importantly, the ligand synthesis could be carried out in a one-pot sequence to directly deliver the desired phosphine oxides as a 1:1 mixture of phosphorus epimers. Notably, this method was amenable to scale-up and was utilized to prepare 5 g of a 1:1 mixture of **1.198** and **1.199**.

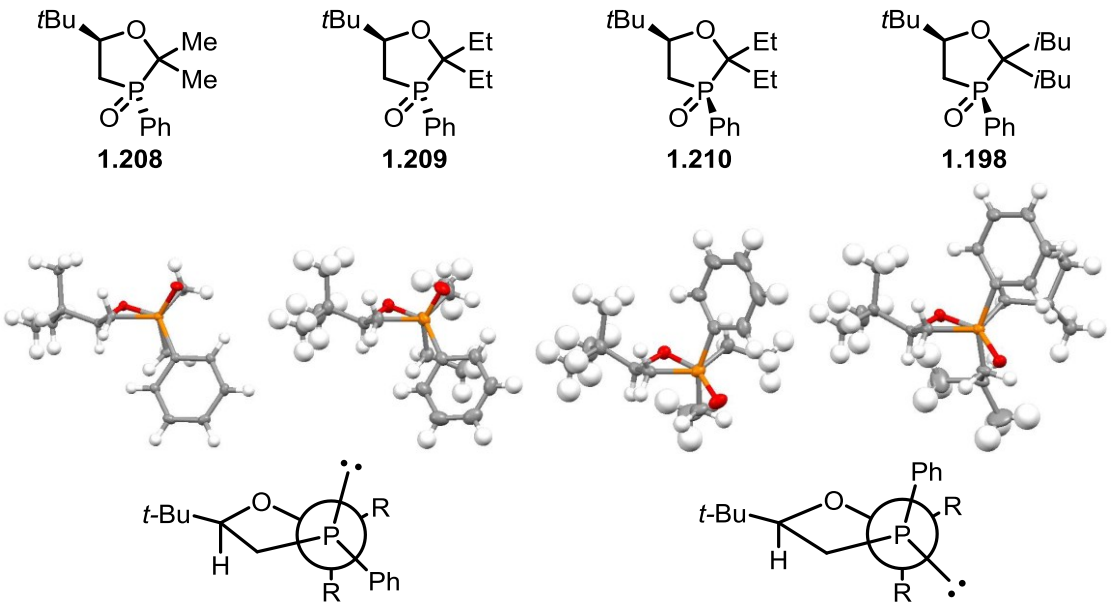
Scheme 1.30: Example One-Pot Synthesis and Preparation of Small Library



Structurally, the oxaphospholanes display a large amount of rigidity with the large *tert*-butyl group acting as an effective conformational anchor. A comparison of the X-ray structures of phosphine oxides shows a highly conserved 5-membered ring conformation, for all diastereoisomers and ketal substituents (Figure 1.7). Notably, the phosphorus oxygen in the *trans* diastereomers (**1.208** and **1.209**) is orthogonal to the carbon oxygen bond of the phosphaketal, whereas in the *cis* diastereomers (**1.210** and **1.198**), the phosphorus oxygen aligns in a near perfect antiperiplanar orientation. One can imagine in the corresponding reduced phosphines that the lone pair on phosphorus may be very well positioned for possible donation into the σ* orbital of the carbon oxygen bond in the *cis* diastereomer, but not in the *trans* diastereomer. Importantly, the new oxaphospholane ligands were predicted to be relatively electron rich, and the potential phosphorus lone

pair to σ* donation just mentioned could possibly attenuate the Lewis basicity of the *cis* diastereomer and lead to differences in reactivity between the two epimeric compounds.

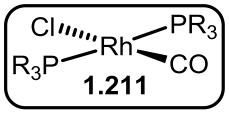
Figure 1.7: Stereochemical Characteristics of *Cis* and *Trans* Phosphine Oxides



To measure possible differences between the electronic properties of the two diastereomers, a *trans*-[ClRh(CO)L_2] complex was prepared utilizing **1.204** and **1.205** (Table 1.1).[86] Importantly, the $CO_{(Rh)}$ stretching frequency in the complexes is nearly identical, indicating that phosphorus lone pair donation to the σ* orbital of the carbon oxygen bond is likely not significant, possibly due to poor orbital overlap between the second row carbon-centered orbital and the third row phosphorus. Notably, the stretching frequencies obtained indicate that both **1.204** (entry 2) and **1.205** (entry 3) are relatively electron rich, similar to $PPhCy_2$ (entry 4) and significantly more so than TADDOL-derived phosphoramidites **1.164** and **1.212** (entries 6 and 7 respectively).[9b]

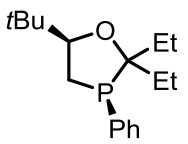
[86] Otto,S.; Roodt, A. *Inorg. Chim. Acta*. **2004**, *357*, 1.

Table 1.1: Measurement of Carbonyl Stretch in *Trans*-Rh(I) Complex 1.211

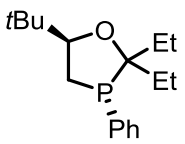


1.211

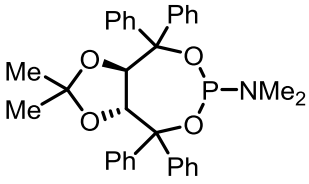
entry	PR_3	$\nu(CO_{Rh})$ (cm^{-1})
1	PCy_3	1943
2	**1.204**	1961
3	**1.205**	1962
4	$PPhCy_2$	1964
5	PPh_3	1979
6	**1.164**	1984
7	**1.212**	1984
8	$P(OEt)_3$	1996



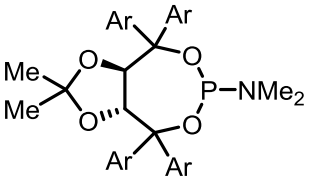
1.204



1.205



1.164



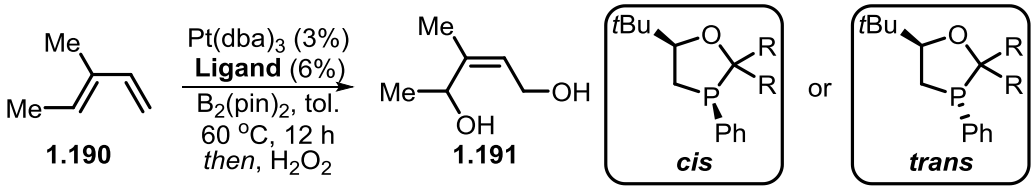
1.212

Ar = 3,5-dimethylphenyl

1.3.3 Evaluation of Oxaphospholane Ligands in Platinum Catalyzed Diboration

Having successfully prepared a highly tunable and electron rich class of monodentate phosphines, attention was then focused on applying the new ligands to platinum catalyzed 1,4-diboration of *trans*-1,3-dienes. Utilizing **1.190** as the benchmark substrate, a small library of oxaphospholane ligands was screened (Table 1.2). Following the trend observed previously, the stereochemistry of phosphorus appears to dominate the stereochemical outcome of the reaction, with the *cis* epimer providing the *R* enantiomer of **1.191** and the *trans* epimer providing the *S* enantiomer. Interestingly, while the two diastereomers exhibit nearly equal levels of selectivity with geminal methyl groups at the phosphaketal postion (entries 1 and 2), as the size of these groups increase, the selectivity provided by the *cis* diastereomer increases and the *trans* selectivity decreases. Importantly, **1.200** gave the highest selectivity, providing **1.191** in good yield and with excellent levels of enantioselectivity.

Table 1.2: Evaluation of Oxaphospholanes in Platinum Catalyzed Diboration

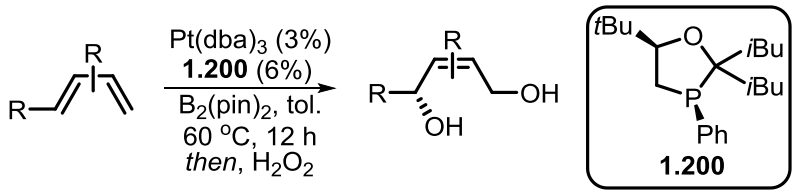


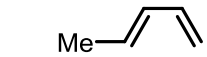
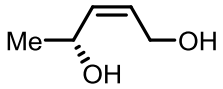
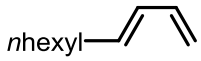
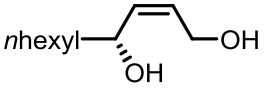
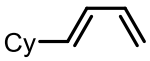
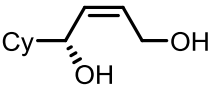
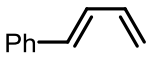
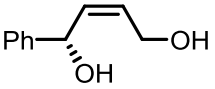
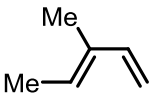
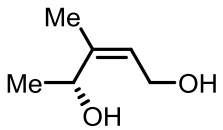
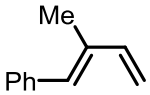
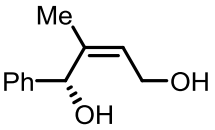
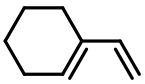
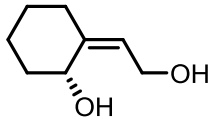
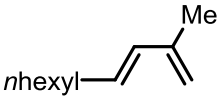
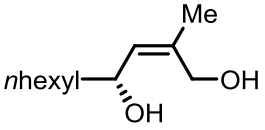
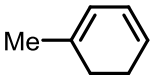
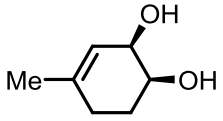
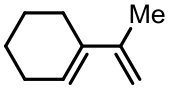
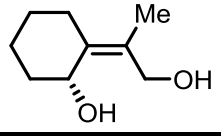
Entry	**Ligand**	*cis/trans*	R	% yield (**1.191**)	er (**1.191**)
1	**1.202**	*cis*	Me	52	84.5:15.5 (*R*)
2	**1.203**	*trans*	Me	66	83:17 (*S*)
3	**1.204**	*cis*	Et	71	98:2 (*R*)
4	**1.205**	*trans*	Et	67	83:17 (*S*)
5	**1.206**	*cis*	*n*Pr	49	98.5:1.5 (*R*)
6	**1.207**	*trans*	*n*Pr	78	54.5:45.5 (*S*)
7	**1.200**	*cis*	*i*Bu	82	99:1 (*R*)
8	**1.201**	*trans*	*i*Bu	75	57.5:42.5 (*S*)

With the optimized ligand in hand, a variety of 1,3-dienes were examined in platinum catalyzed diboration with the use of **1.200**. As shown in Table 1.3, the new oxaphospholane ligand proved to promote efficient diboration for both hindered (entries 3 and 4) and non-hindered (entries 1 and 2) monosubstituted 1,3-dienes, affording the desired 1,4-diol products in good to excellent yield and with excellent levels of enantioselectivity. Importantly, the new catalyst system achieved especially high enantioselectivities with the use of 3,4-disubstituted dienes (entries 5-7). Although 2,4-disubstitution proved to be challenging (entry 8), the use of a trisubstituted diene afforded the corresponding tetrasubstituted olefin product with moderate levels of enantioselectivity and as a single olefin isomer (entry 10). Notably, the results obtained with the use of the oxaphospholane ligand are a substantial improvement over those

obtained with the optimized TADDOL-derived phosphonites, especially in the cases of simple methyl substitution (entry 1), and 3,4-disubstitution (entries 5-7).

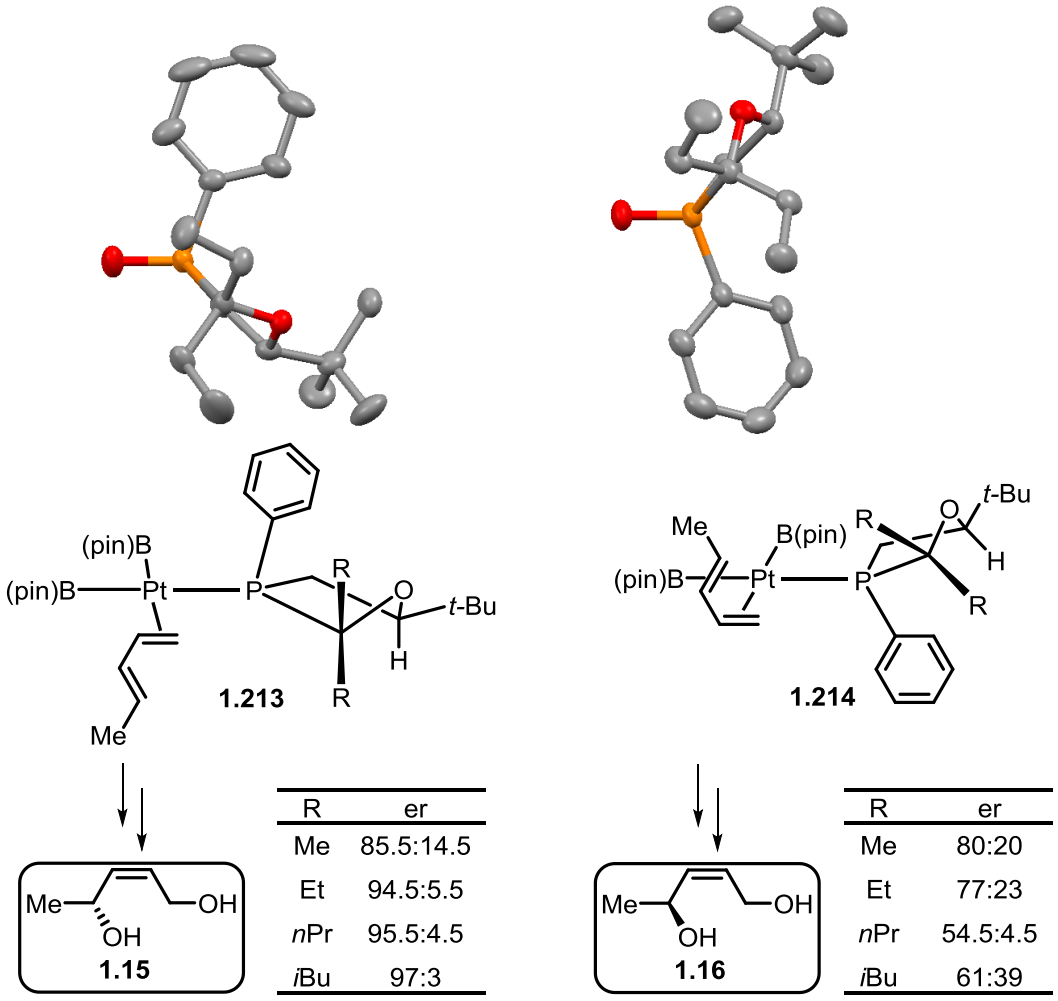
Table 1.3: Scope of Platinum Catalyzed Diboration with 1.200



Entry	Substrate	Product	Yield (%)	er[a]
1			86	97:3 (85:15)
2			>98	97.5:2.5 (92:8)
3			>98	98:2 (95.5:4.5)
4			65	96:4 (92:8)
5			82	99:1 (90.5:9.5)
6			61	98:2 (85:15)
7			96	99:1
8			92	65.5:34.5 (93:7)
9			95	94.5:5.5 (93:7)
10			82	82.5:17.5

a) values in parentheses are selectivities obtained with optimal TADDOL-based phosphonites

Figure 1.8: Tentative Stereochemical Model for Selectivity Employing *Cis* (Left) and *Trans* (Right) Oxaphospholane Diastereomers



R	er
Me	85.5:14.5
Et	94.5:5.5
*n*Pr	95.5:4.5
*i*Bu	97:3

R	er
Me	80:20
Et	77:23
*n*Pr	54.5:4.5
*i*Bu	61:39

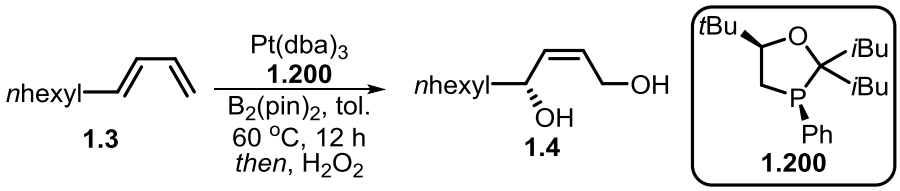
Seeking to rationalize the results obtained in Tables 2 and 3, a stereochemical model for the 1,4-diboration of *trans*-1,3-dienes was developed. According to the proposed mechanism for platinum catalyzed diboration of dienes (Scheme 1.6), after oxidative addition of $B_2(pin)_2$, substrate binding occurs to give bisboryl Pt(II) complexs **1.213** and **1.214** (Figure 1.8). Importantly, selective binding of one pro-chiral face of the diene is likely the enantiodetermining step of the reaction. Utilizing the crystal structures of **1.209** and **1.210** as a guide, it seems plausible that prior to substrate binding, the

bisboryl platinum complexes **1.213** and **1.214** would orient one boryl group *trans* to the bulky ligand, and one in the next least hindered site, adjacent to the methylene group on the oxaphospholane ring. As such, this leaves an open coordination site in the square plane of platinum adjacent to the conjested phosphaketal center. Driven by steric interactions with the complex, it is likely that the terminal olefin of the diene coordinates selectively to the platinum, with the backbone of the diene facing away from the ligand bulk. This leaves two possible binding modes; one in which the diene approaches from the top of the complex, and one in which approach occurs from the bottom.

In the case of the *cis* diastereomer **1.213**, approach is effectively blocked from the top face by the phenyl ring attached to phosphorus and the bottom approach is more open, with the phosphaketal substituents projecting primarily towards the reader. Subsequent migratory insertion followed by reductive elimination predicts formation of the *R* enantiomer of product, which matches the results obtained. As the bulk of the phosphaketal substituents increases, an increase in selectivity is observed, most likely due to an enhanced preference to place the diene backbone away from the ligand. In the case of the *trans* diastereomer **1.214**, a similar, but opposite orientation of the phenyl ring attached to phosphorus blocks approach from the bottom face, however, the phosphaketal substituents are oriented much differently than in the *cis* case. Instead of projecting primarily towards the reader, the substituent *cis* to the *tert*-butyl group points towards the top face of the complex. When this is a methyl group, the top face is still somewhat unhindered, and a similar level of enantioselectivity compared to the *cis* diastereomer is observed in diboration (Table 1.2, entries 1 and 2). If the size of the group is increased, the top face becomes more effectively blocked, and substrate binding becomes less

selective with *trans* **1.201** (R = *i*Bu) giving an inferior level of selectivity as compared to the *cis* **1.200** (R = *i*Bu).

Table 1.4: Variation in Metal:Ligand Ratio and Lowered Catalyst Loading



Entry	Pt (mol %)	**1.200** (mol %)	% yield (**1.4**)	TON	er (**1.4**)
1	1	2	<5	-	-
2	1	2	90	90	96.5:3.5
3	1	1.95	97	97	97.5:2.5
4	1	1.1	98	98	97.5:2.5
5	1	0.5	71	71	95.5:4.5
6	0.1	0.2	98	980	97.5:2.5
7	0.05	0.1	95	1900	97:3
8	0.02	0.04	95	4750	97:3

Noting the exceptionally high yields obtained in the diboration of certain substrates, it was reasoned the catalyst loading could likely be lowered and an efficient diboration still achieved. Utilizing *trans*-1,3-decadiene **1.3**, a series of experiments were performed to test the effect of both ligand and platinum loading on the reaction outcome (Table 1.4). Suspecting that small amounts of oxygen may be detrimental to the catalyst at lower loadings, the substrate was rigorously deoxygenated in addition to the solvent. Under these conditions, a 2:1, ligand:metal ratio resulted in no reaction (entry 1). It is plausible that the formation of ML_2 complexes inhibits diboration reaction (see: Scheme 1.6), and a small amount of oxygen derived from non-degassed substrate under the normal conditions acts to consume a portion of the ligand, providing access to

catalytically active ML_1 species. To test this hypothesis, the experiment was repeated, again with deoxygenated substrate (entry 2). After 4 hours, TLC analysis indicated no reaction and the reaction was briefly exposed to air, sealed, and the reaction resumed for an additional 2 hours, giving the desired product with good yield and nearly undiminished levels of enantioselectivity. Notably, utilizing a slightly less than 2:1 ratio of ligand:metal (entry 3) and a nearly 1:1 ratio (entry 4) both result in efficient diboration, further supporting a ML_1 species as the active catalyst. Interestingly, employing a 1:2 ratio of ligand to metal in diboration (entry 5), results in formation of the desired product in good yield and also with high levels of enantioselectivity, indicating a high level of ligand acceleration. Upon further lowering of the catalyst loading with a 2:1 ratio of ligand:metal it was found that efficient diboration still occurs (entries 6-8). Importantly, full conversion can still be attained with catalyst loading as low as 0.02 mol %, delivering **1.4** in excellent yield and with excellent levels of enantioselectivity (entry 8). Utilizing a TADDOL-derived phosphonite ligand under the same conditions resulted in 23% conversion at 0.1% loading and <5% conversion at 0.02% loading, indicating greatly enhanced catalyst efficiency with the use of **1.200**.

1.3.4 Efforts to Remedy the Limitations of the Oxaphospholane Scaffold

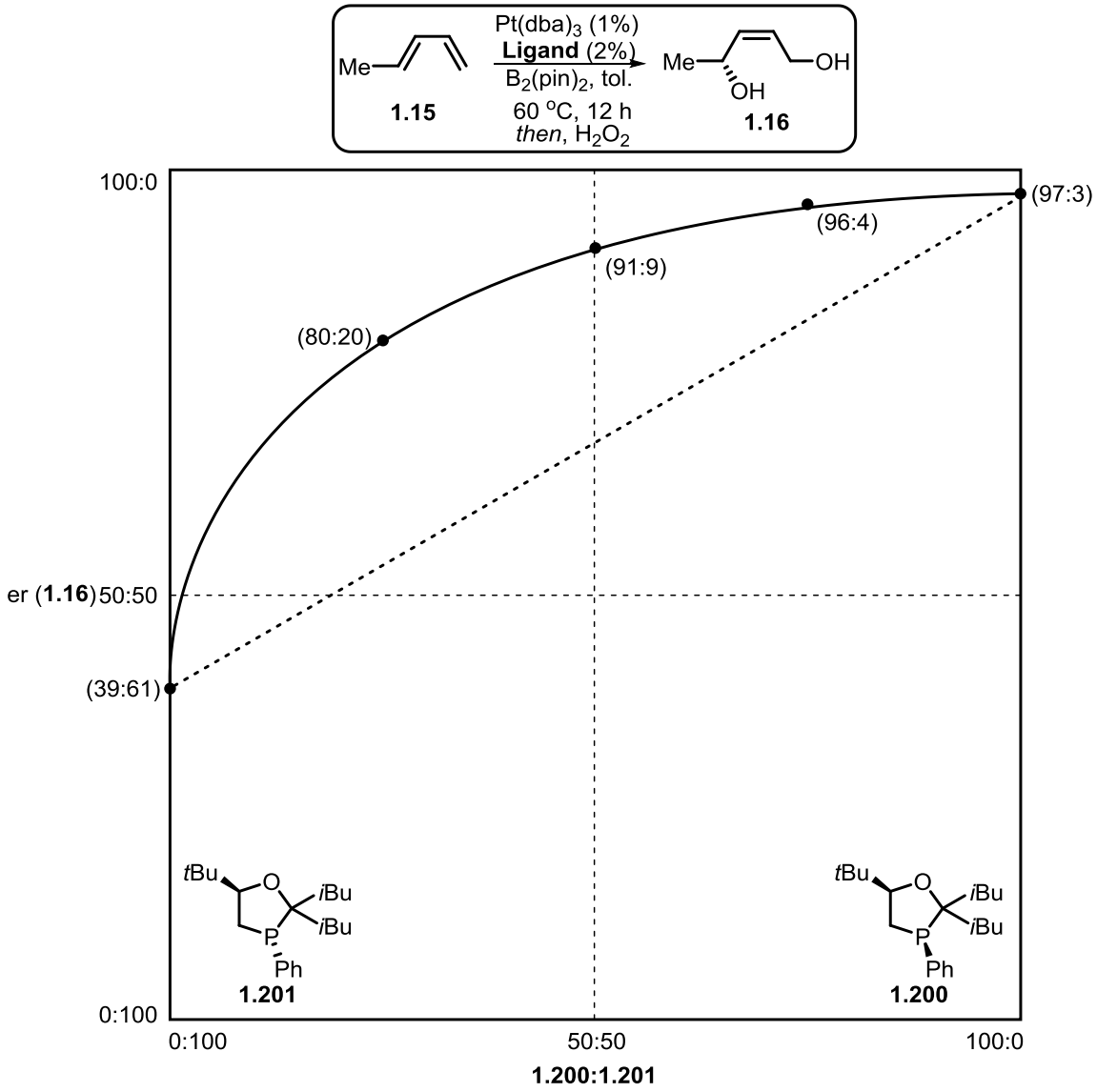
With the potential of the oxaphospholanes to serve as effective ligands in asymmetric catalysis firmly established, efforts were made to overcome certain challenges encountered while developing the new scaffold. One of the most difficult aspects associated with preparing the oxaphospholanes is the separation of phosphorus epimers. Ideally, a diastereoselective synthesis would eliminate the need to separate the non-selective *trans* diastereomer, and provide a higher overall yield of the desired *cis*

diastereomer. Unfortunately, even under cryogenic conditions, attack of the lithium phenylphosphide occurs to give secondary phosphine **1.197** as a 1:1 ratio of diastereomers (Scheme 1.30). Even if this was prepared as a single diastereomer, it is unclear if the stereochemical information would be retained upon cyclization, with the possibility of protonation of **1.197** to give an achiral phosphorus under the acidic reaction conditions, ultimately leading to phosphorus epimerization. In the absence of a diastereoselective synthesis, perhaps the best way to obtain a high yield of the desired *cis* diastereomer is to reduce the *trans* phosphine oxide utilizing conditions which proceed with inversion of phosphorus configuration;[16] however, this approach still requires the separation of phosphorus epimers.

Due to the significantly different steric environments surrounding phosphorus in the *cis* and *trans* diastereomers, it seemed plausible that one diastereomer is more effective in catalysis than the other. Importantly, if the reactivity differences were significant enough, it may not be necessary to obtain diastereomerically pure oxaphospholane and still achieve a highly selective reaction. To test this scenario, the diboration of **1.15** was examined utilizing a mixture of *trans* **1.201** and *cis* **1.200** (Figure 1.9). Incredibly, a significant non-linear effect is observed which favors the product obtained by action of the *cis* diastereomer, with even a 3:1 diastereomeric ratio of ligand affording nearly the same level of enantioselectivity as was obtained with diastereomerically pure *cis* **1.200**. While it is unclear why the non-linear effect is observed, it is possible that either the *cis* diasteromer of the oxaphospholane binds platinum more effectively than the *trans* diastereomer and leads to selective formation of *cis*-ligand containing ML_1 complexes, or that the ML_1 complexes derived from the *cis*

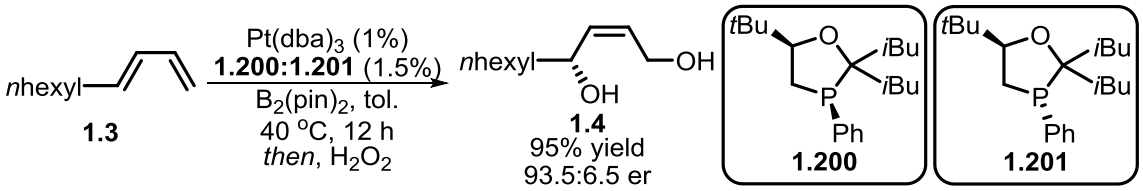
and *trans* ligands are formed equally and the *cis*-derived complex is significantly more reactive than the *trans*-derived complex. Further adjustment of the reaction conditions utilizing a 1:1 mixture of ligand diastereomers results in a slight enhancement in selectivity (91:9 er versus 93.5:6.5 er), but still significantly short of results obtained with diastereomerically pure *cis* ligand (Scheme 1.31).

Figure 1.9: Non-linear Relationship Between Ligand dr and Diboration Product er



Importantly, any method that avoids tedious chromatography and enriches the *cis* diastereomer, even to a small degree could be useful due to the strong non-linear effect. For example, treatment of a 1:1 mixture of **1.200** and **1.201** with one equivalent of benzyl bromide results in the slightly more rapid alkylation of the *trans* oxaphospholane, giving rise to a 1.92:1.00; *cis*:*trans* mixture of remaining free phosphines (Scheme 1.32). After simple filtration to remove the phosphonium bromide byproducts, the 1.92:1.00 mixture was utilized in the diboration of **1.3**, affording the desired product **1.4** in excellent yield and with high enantioselectivity. While this method shows promise for the simple resolution of oxaphospholane diastereomers, the alkylation is not perfectly selective and a significant amount of valuable *cis* diastereomer is destroyed.

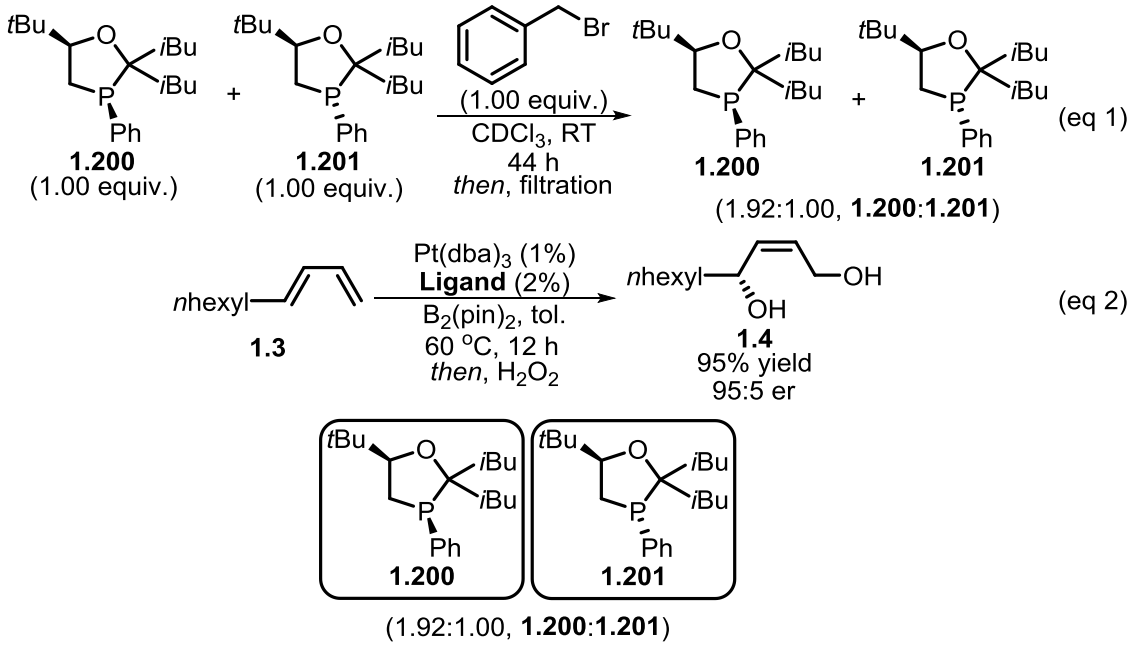
Scheme 1.31: Optimized Diboration Utilizing 1:1 dr Oxaphospholane Ligand



The last remaining position of the oxaphospholane scaffold to be explored is the substituent attached to phosphorus. Future efforts to tune this position could result in valuable new ligands which are even more electron rich than those described above. This is the most difficult position to tune primarily because of the lack of commercially available primary phosphines. While they may be accessed via reduction of the corresponding dichlorophosphines and phosphonates, the difficulty in handling and isolating these reactive starting materials is not appealing. Perhaps a more convenient approach would be to change the order of assembly completely (Scheme 1.33). In 1995, Noyori and coworkers described the highly enantioselective hydrogenation of

β-ketophosphonates **1.216** to give secondary alcohols **1.217**.[87] While the original motivation for this research was to create a practical route to the antibiotic fosfomycin **1.218**, the enantioenriched adducts of this hydrogenation could be of use for oxaphospholane synthesis.

Scheme 1.32: Selective Benzylation of Unresolved Mixture of Diastereomers and Use in Diboration

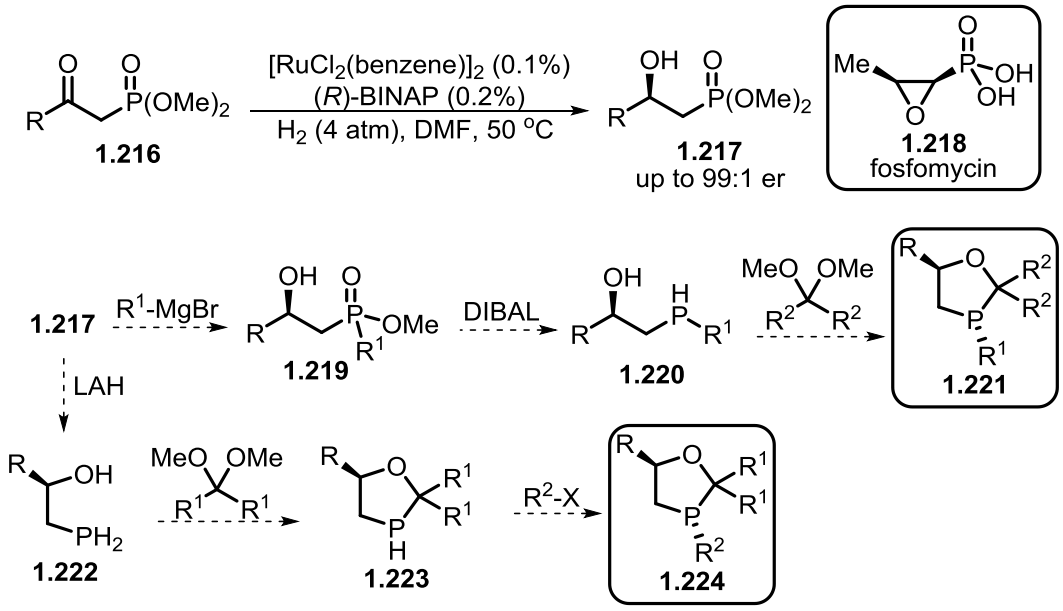


Notably, the β-ketophosphonate starting materials are readily prepared on large scale through the Arbuzov reaction. After subsequent enantioselective hydrogenation, intermediate **1.217** could be utilized as an electrophile in a Grignard addition to arrive at phosphinate **1.219**. A subsequent reduction of phosphorus would deliver secondary phosphine **1.220**, intercepting the previously established synthesis, but with a custom group on phosphorus. Alternatively, phosphonate intermediate **1.217** could be reduced directly to give primary phosphine **1.222**. Subsequent phosphaketal formation would

[87] Kitamura, M.; Tokunaga, M.; Noyori, N. *J. Am. Chem. Soc*. **1995**, *117*, 2931.

then give rise to secondary phosphine **1.223**, which could then be alkylated to give the final phosphaketal structure **1.224**. Additionally, secondary phosphine **1.223** could be useful for studying the stereochemistry of phosphorus in the 5-membered oxaphospholane scaffold. Protonation of phosphorus would render phosphorus achiral and give an opportunity for possible diastereoselective deprotonation to establish the desired stereochemistry.

Scheme 1.33: Possible Complimentary Routes to Oxaphospholane Ligands Utilizing Enantioselective Hydrogenation by Noyori



1.4 Conclusion

The synthesis of a new class of chiral monodentate phosphine ligands has been accomplished. The highly modular nature of the ligand scaffold allows for rapid library preparation for screening purposes. The new ligands are electron rich and access unique chiral space compared to other monodentate scaffolds, potentially offering advantages in certain metal catalyzed enantioselective reactions. The oxaphospholanes proved to be

highly useful for the platinum catalyzed diboration of *trans*-1,3-dienes, extending the substrate range and affording the desired 1,4-addition products in excellent yields and with superior levels of enantioselectivity. Reaction efficiency under action of the new ligands far surpasses previous results obtained with the use of TADDOL-derived phosphonite ligands, achieving yields of up to 98%, enantioselectivities up to 99:1 er, and turn over numbers approaching 5000. Having made a positive impact in enantioselective diboration, it is our hope that the oxaphospholanes will become a useful tool in the greater field of asymmetric catalysis.

1.5 Experimental Section

1.5.1 General Information

^{1}H NMR spectra were measured using a Varian Gemini-500 (500 MHz) spectrometer 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, or C_6D_6: 7.16 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). $^{13}C\{^{1}H\}$NMR spectra were measured using a Varian Inova 500 (126 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.0 ppm, or C_6D_6: 128.4 ppm). $^{31}P\{^{1}H\}$NMR spectra were measured using a Varian Inova 500 (202 MHz) spectrometer. Chemical shifts are reported in ppm using phosphoric acid as the external standard (H_3PO_4: 0.0 ppm). Infrared (IR) spectra were measured using 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) was

performed at Boston College, Chestnut Hill, MA. Single crystal x-ray analysis of phosphine oxides was performed at Boston College. Elemental analysis was measured by Robertson Microlit Laboratories, Madison, NJ.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography was performed on 25 μm silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm) and phosphomolybdic acid (PMA). Analytical chiral gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a split mode capillary injection system, a flame ionization detector, and a Supleco β-Dex 120 column with helium as the carrier gas. Analytical chiral high-performance liquid chromatography (HPLC) was performed on an Agilent 1120 compact chromatograph equipped with gradient pump and variable wavelength detector. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar Supercritical Chromatograph equipped with auto sampler and a Waters photodiode array detector with methanol as the modifier.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Toluene and diethyl ether 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. Benzene and $CDCl_3$ were distilled from calcium hydride under an atmosphere of N_2. Potassium tetrachloroplatinate(II) was purchased from Acros Organics. Dibenzylideneacetone was

purchased from Oakwood Chemicals. Tetrabutylammonium chloride was purchased from Fluka. Sodium acetate was purchased from Fisher Scientific. Bis(pinacolato)diboron ($B_2(pin)_2$) was obtained from Allychem Co., Ltd. and recrystallized from pentane prior to use. Phenylphosphine, tricyclohexylphosphine, and (1*R*,2*R*)-(-)-1,2-cyclohexanediamino-N,N'-bis(3,5-di-*tert*-butylsalicylidene)cobalt(II) were purchased from Strem Chemicals, Inc. and used without further purification. Racemic 2-(*tert*-butyl)oxirane was purchased from Alfa Aesar and resolved using Jacobsen HKR to give (*R*)-2-(*tert*-butyl)oxirane in greater than 99% *ee*, in accordance with the literature.[88] 3,3-dimethoxypentane and 4,4-dimethoxy-2,6-dimethylheptane were prepared from the parent ketones using the literature procedure.[89] (*trans*)-1,3-pentadiene, (*trans*)-3-methyl-1,3-pentadiene, and 1-methyl-1,3-cyclohexadiene were purchased from Chem Samp Co, and were used without further purification. The following dienes were prepared by Wittig olefination of the commercially available α,β-unsaturated aldehydes with methyltriphenylphosphonium bromide and potassium *tert*-butoxide in tetrahydrofuran: (*trans*)-1-Phenyl-1,3-butadiene,[90] (*trans*)-1-cyclohexyl-1,3-butadiene,[91] (*trans*)-1,3-decadiene,[92] 1-vinylcyclohexene,[93] 1-(prop-1-ene-2-yl)-cyclohex-1-ene,[94] and (*trans*)-(2-methylbuta-1,3-dien-1-yl)benzene.[95] All spectra are in accordance with the literature references.

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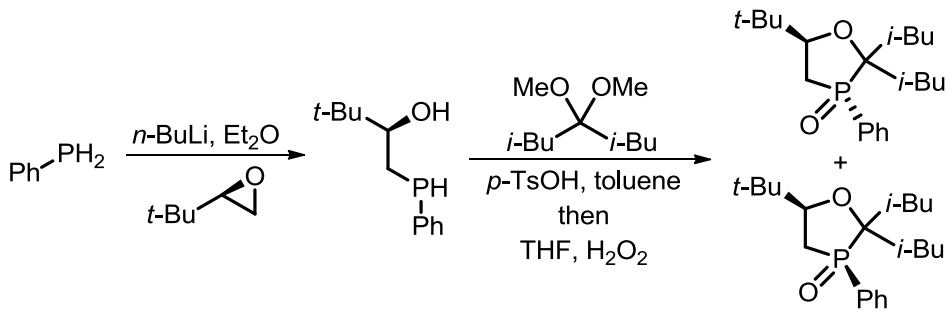
1.5.2 Experimental Procedures

1.5.2.1 Preparation of $Pt(dba)_3$.

Tris(dibenzylideneacetone)platinum was prepared using a modification of the literature procedure.[96] To a three-neck 500 mL round-bottom flask equipped with a magnetic stir bar and reflux condenser was added dibenzylideneacetone (3.95 g, 16.8 mmol), tetrabutylammonium chloride (2.00 g, 7.20 mmol), and sodium acetate (3.55 g, 43.3 mmol). Methanol (210 mL) was added and the solution was warmed to 70 °C in an oil bath until the solids dissolved (5 minutes). In a separate 50 mL pear-shaped flask was added potassium tetrachloroplatinate (1.00 g, 2.41 mmol) and water (8 mL), and the mixture gently warmed until solids dissolved. The contents of the pear shaped flask were transferred to the three-neck flask and the reaction was allowed to stir at 70 °C for 3 hours. After 3 hours, the reaction was cooled to ambient temperature, transferred to a one-neck 500 mL round-bottom flask and concentrated by rotary evaporation to half the volume. The reaction mixture was then filtered on a Büchner funnel and the remaining solids were washed with copious amounts of water and methanol until all visible yellow dibenzylideneacetone crystals were removed. The resulting solid residue was placed under high vacuum for 24 hours to remove residual methanol and water. This procedure furnished a dark solid (1.03 g, 48%) consistent with $Pt(dba)_3$. Anal Calc'd for $C_{51}H_{42}O_3Pt$: C, 68.22; H, 4.71. Found: C, 67.09; H, 4.49 (average of two experiments). Platinum analysis was performed by ICP Optical Emission Spectroscopy; calculated for $Pt(dba)_3$: 21.73% Pt; found 21.92% (average of two experiments).

[96] Lewis, L. N.; Krafft, T. A.; Huffman, J. C. *Inorg. Chem.* **1992**, *31*, 3555. Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134.

1.5.2.2 Representative Procedure for Preparation of Phosphine Oxides

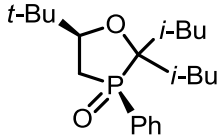


(5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane 3-oxide.[97] To a flame-dried 200 mL round-bottom flask was added diethyl ether (26 mL) followed by phenylphosphine (1.43 mL, 13.0 mmol). The resulting clear, colorless solution was cooled to -78 °C (dry ice/acetone) and treated dropwise with *n*-BuLi (2.42 M in hexanes, 5.6 mL, 14 mmol). After stirring at -78 °C for 5 minutes, the flask was removed from the cold bath and allowed to stir at room temperature for 1 hour. The resulting bright yellow, opaque mixture was then recooled to -78 °C and treated dropwise with (*R*)-2-(*tert*-butyl)oxirane (**1**) (sparged with argon, 1.29 g, 13.0 mmol). The reaction was again allowed to warm to room temperature and stirred for 1.5 hours, after which aqueous ammonium chloride (sparged with argon, 4 M, 20 mL) was slowly added. After 15 minutes, the organic layer was removed *via* syringe, and an additional amount of diethyl ether (25 mL) was added to the aqueous layer, stirred, and again the organic layer was removed *via* syringe. The organic layers were combined in a flame-dried round-bottom flask under argon charged with sodium sulfate, stirred, then transferred to a flame-dried 500 mL three-neck flask under argon containing activated 4 Å mol sieves and equipped

[97] Oehme, H.; Issleib, K.; Leissring, E. *Tetrahedron* **1972**, *28*, 2587. Koch, T.; Blaurock, S.; Somoza, F.; Hey-Hawkins, E. *Eur. J. Inorg. Chem*. **2000**, 2167.

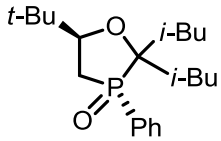
with reflux condenser. All volatiles were removed under reduced pressure, and the resulting crude residue was treated with a solution of toluene (53 mL) containing *p*-toluenesulfonic acid (1.55 g, 8.15 mmol) and 4,4-dimethoxy-2,6-dimethylheptanone (16.55 g, 87.9 mmol). The resulting solution was heated to reflux for 14 hours, after which the reaction was allowed to cool to room temperature before being transferred to an argon-purged 300 mL flask. The crude reaction mixture was diluted with THF (40 mL), cooled to 0 ^{o}C (ice/water), and slowly treated with H_2O_2 (30 wt% in H_2O, 3.2 mL, 31 mmol). After stirring at room temperature for 2 hours, the reaction mixture was again cooled to 0 ^{o}C and treated with saturated aqueous sodium thiosulfate (10 mL), followed by saturated aqueous sodium bicarbonate (45 mL). The mixture was diluted with ethyl acetate (50 mL), and the organic and aqueous layers were separated. The aqueous layer was further extracted with ethyl acetate (4 x 75 mL). The combined organic layers were dried over sodium sulfate and the solvent removed under reduced pressure. The crude material was purified (SiO_2, 30% ethyl acetate in hexane) to give 4.4 g (48%) of a 1:1 mixture of phosphorus epimers. In order to obtain isomerically pure compound, the mixture of epimers (500 mg) was further purified (SiO_2, 100% Et_2O) to give both *trans* (267 mg) and *cis* (179 mg), along with mixed material (50 mg).

1.5.2.3 Characterization of Phosphine Oxides



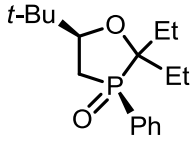
(3*S*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane 3-oxide. R_f = 0.50 (100% Et_2O, UV) ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.24 (3H, d, *J* = 7.0 Hz), 0.73 (3H, d, *J* = 6.5 Hz), 0.97 (9H, s), 0.98 (3H, d, *J* = 8.0 Hz), 1.06 (3H, d, *J* = 6.5 Hz), 1.32-1.45 (2H, m), 1.72-1.82 (2H, m), 1.90-1.98 (1H, m), 2.00-

2.07 (1H, m), 2.13 (2H, dd, J = 12.0 Hz, 8.0 Hz), 4.05 (1H, app dt, J = 8.5 Hz, 1.0 Hz), 7.43-7.52 (3H, m), 7.77-7.81 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 23.2, 23.6, 23.9, 24.0, 24.5 (d, J_{C-P} = 1.9 Hz), 24.9, 25.9, 31.1 (d, J_{C-P} = 70.8 Hz), 34.6 (d, J_{C-P} = 6.0 Hz), 35.6 (d, J_{C-P} = 6.0 Hz), 41.1 (d, J_{C-P} = 3.1 Hz), 79.9, 83.3 (d, J_{C-P} = 68.8 Hz), 128.1 (d, J_{C-P} = 11.2 Hz), 131.6 (d, J_{C-P} = 2.8 Hz), 131.9 (d, J_{C-P} = 8.4 Hz), 132.3; ^{31}P NMR (202 MHz, $CDCl_3$): δ 59.0; IR (neat): 2954.5 (s), 2868.9 (m), 1467.6 (w), 1207.4 (m), 1168.7 (w), 741.8 (w), 698.5 (w), 518.4 (w) cm^{-1}; HRMS-(ESI+) for $C_{21}H_{36}O_2P$ [M+H]: calculated: 351.2453, found: 351.2465. $[\alpha]_D^{20}$ = +2.50 (c = 0.440, $CHCl_3$, l = 50 mm).



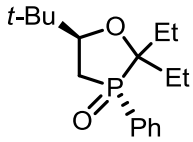
(3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane 3-oxide. R_f = 0.57 (100% Et_2O, UV) ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.63 (3H, d, J = 6.6 Hz), 0.91 (3H, d, J = 6.6 Hz), 0.94-0.97 (1H, m), 0.98 (3H, d, J =6.4 Hz), 0.99 (3H, d, J = 6.1 Hz), 1.00 (9H, s), 1.37 (1H, ddd, J = 14.9 Hz, 12.0 Hz, 8.7 Hz), 1.66-1.74 (1H, m), 1.82-1.98 (3H, m), 2.16 (1H, ddd, J = 20.2 Hz, 15.0 Hz, 10.8 Hz), 2.35 (1H, ddd, J = 15.2 Hz, 5.7 Hz, 4.6 Hz), 3.82 (1H, ddd, J = 10.8 Hz, 5.8 Hz, 2.3 Hz), 7.46-7.56 (3H, m), 7.75-7.79 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 23.5, 24.3, 24.3 (d, J_{C-P} = 9.3 Hz), 24.7 (d, J_{C-P} = 4.2 Hz), 24.7, 24.8, 25.8, 30.7 (d, J_{C-P} = 68.4 Hz), 34.6 (d, J_{C-P} = 6.5 Hz), 40.1 (d, J_{C-P} = 9.3 Hz), 41.7, 81.6 (d, J_{C-P} = 1.9 Hz), 83.9 (d, J_{C-P} = 67.9 Hz), 128.4 (d, J_{C-P} = 11.2 Hz), 131.2 (d, J_{C-P} =83.3 Hz), 131.5 (d, J_{C-P} = 8.4 Hz), 131.8 (d, J_{C-P} = 2.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 59.0; IR (neat): 2951.2 (m), 2868.1 (w), 1466.6 (w), 1437.1 (w), 1364.8 (w), 1193.1 (m), 1012.5 (w), 745.3 (s), 698.6 (m), 534.7 (s), 506.8 (m) cm^{-1}; HRMS-(ESI+) for $C_{21}H_{36}O_2P$ [M+H]: calculated: 351.2453, found: 351.2463. $[\alpha]_D^{20}$ = -7.85 (c = 0.438, $CHCl_3$, l = 50 mm).

(5*R*)-5-(*tert*-butyl)-2,2-diethyl-3-phenyl-1,3-oxaphospholane 3-oxide. The reaction was performed according to the general procedure using diethyl ether (9.0 mL), phenylphosphine (0.48 mL, 4.3 mmol), *n*-BuLi (2.42 M in hexanes, 1.88 mL, 4.54 mmol), and (*R*)-2-(*tert*-butyl)oxirane (**1**) (0.43 g, 4.3 mmol) to arrive at the secondary phosphine (**2**), followed by the use of toluene (9.0 mL), 3,3-dimethoxypentane (2.10 g, 15.9 mmol), and *p*-toluenesulfonic acid (0.205 g, 1.08 mmol) to give cyclized product. Oxidation of the crude material was carried out using THF (10 mL), and H_2O_2 (30 wt %, 0.75 mL, 13 mmol). The crude oxidation product was purified (SiO_2, 35-80 % ethyl acetate in hexane) to give 0.58 g (46%) of a 1:1 mixture of phosphorus epimers. In order to obtain isomerically pure compound, the mixture of epimers (250 mg) was further purified (SiO_2, 30% ethyl acetate in hexane) to give both *trans* (102 mg) and *cis* (95 mg), along with mixed material (50 mg).



(3*S*,5*R*)-5-(*tert*-butyl)-2,2-diethyl-3-phenyl-1,3-oxaphospholane 3-oxide. R_f = 0.29 (100% EtOAc, UV) ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.56 (3H, t, J = 7.0 Hz), 0.92 (3H, t, J = 7.0 Hz), 1.01 (9H, s), 1.24 (1H, app septet, J = 7.5 Hz), 1.70 (1H, app ddq, J = 29.5 Hz, 15.5 Hz, 8.0 Hz), 1.88 (1H, app dsextets, J = 7.5 Hz, 1.5 Hz), 2.08-2.24 (3H, m), 3.93 (1H, ddd, J = 10.0 Hz, 6.5 Hz, 2.0 Hz), 7.47-7.56 (3H, m), 7.81-7.85 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 5.4 (d, $J_{C\text{-}P}$ = 7.9 Hz), 7.9 (d, $J_{C\text{-}P}$ = 2.3 Hz), 19.7, (d, $J_{C\text{-}P}$ = 6.4 Hz), 24.6 (d, $J_{C\text{-}P}$ = 4.7 Hz), 25.6, 30.7 (d, $J_{C\text{-}P}$ = 71.3 Hz), 34.3 (d, $J_{C\text{-}P}$ = 6.0 Hz), 80.2, 82.0 (d, $J_{C\text{-}P}$ = 70.6 Hz), 128.2 (d, $J_{C\text{-}P}$ = 11.7 Hz), 131.4 (d, $J_{C\text{-}P}$ = 86.1 Hz), 131.6 (d, $J_{C\text{-}P}$ = 8.8 Hz), 131.7 (d, $J_{C\text{-}P}$ = 2.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 59.4; IR (neat): 2966.6 (m), 2876.5 (w), 1438.0 (w), 1209.8 (s),

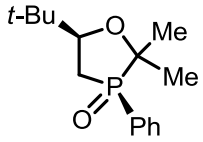
998.4 (m), 739.5 (w), 697.9 (w), 523.1 (w), 512.7 (w) cm^{-1}; HRMS-(ESI+) for $C_{17}H_{28}O_2P$ [M+H]: calculated: 295.1827, found: 295.1833. $[\alpha]_D^{20}$ = +16.3 (*c* = 0.360, $CHCl_3$, *l* = 50 mm).



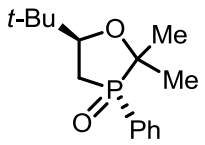
(3*R*,5*R*)-5-(*tert*-butyl)-2,2-diethyl-3-phenyl-1,3-oxaphospholane 3-oxide. R_f = 0.40 (100% EtOAc, UV) ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.70 (3H, t, *J* = 7.5 Hz), 0.95 (3H, t, *J* = 7.5 Hz), 1.00 (9H, s), 1.02-1.08 (1H, m), 1.47 (1H, app dpent, *J* = 19.5 Hz, 7.5 Hz), 1.84 (1H, app ddt, *J* = 19.5 Hz, 15.0 Hz, 7.5 Hz), 2.09 (1H, app ddt, *J* = 15.0 Hz, 9.5 Hz, 7.5 Hz), 2.20 (1H, ddd, *J* = 20.0 Hz, 15.0 Hz, 11.0 Hz), 2.38 (1H, app dt, *J* = 14.0 Hz, 5.0 Hz), 3.71 (1H, ddd, *J* = 11.5 Hz, 5.5 Hz, 2.5 Hz), 7.47-7.52 (3H, m), 7.74-7.80 (2H, m) ; ^{13}C NMR (126 MHz, $CDCl_3$): δ 6.3 (d, J_{C-P} = 8.9 Hz), 8.4 (d, J_{C-P} = 2.2 Hz), 22.9 (d, J_{C-P} = 11.2 Hz), 24.9, 25.6, 30.4 (d, J_{C-P} = 68.1 Hz), 34.3 (d, J_{C-P} = 6.7 Hz), 81.5 (d, J_{C-P} = 1.5 Hz), 82.4 (d, J_{C-P} = 69.6 Hz), 128.5 (d, J_{C-P} = 11.2 Hz), 130.9 (d, J_{C-P} = 84.5 Hz), 131.1 (d, J_{C-P} = 8.9 Hz), 131.9 (d, J_{C-P} = 3.0 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 59.2; IR (neat): 2961.9 (m), 2872.9 (w), 1437.3 (w), 1198.8 (s), 1173.7 (m), 1109.1 (m), 1002.1 (m), 745.7 (s), 696.9 (m), 532.5 (m) cm^{-1}; HRMS-(ESI+) for $C_{17}H_{28}O_2P$ [M+H]: calculated: 295.1827, found: 295.1830. $[\alpha]_D^{20}$ = +17.79 (*c* = 1.052, $CHCl_3$, *l* = 50 mm).

(5*R*)-5-(*tert*-butyl)-2,2-dimethyl-3-phenyl-1,3-oxaphospholane3-oxide. The reaction was performed according to the general procedure using diethyl ether (12 mL), phenylphosphine (0.65 mL, 5.9 mmol), *n*-BuLi (2.50 M in hexanes, 2.50 mL, 6.25 mmol), and (*R*)-2-(*tert*-butyl)oxirane (**1**) (0.59 g, 5.9 mmol) to arrive at the secondary

phosphine (**2**), followed by the use of toluene (12 mL), 2,2-dimethoxypropane (2.19 mL, 17.8 mmol), and *p*-toluenesulfonic acid (0.170 g, 0.899 mmol) to give cyclized product. Oxidation of the crude material was carried out using THF (15 mL), and H_2O_2 (30 wt %, 1.80 mL, 17.6 mmol). The crude oxidation product was purified (SiO_2, 50-100 % ethyl acetate in hexane) to give 0.78 g (49%) of a 1:1 mixture of phosphorus epimers. In order to obtain isomerically pure compound, the mixture of epimers (300 mg) was further purified (SiO_2, 40% ethyl acetate in hexane) to give both *trans* (98 mg) and *cis* (107 mg), along with mixed material (90 mg).



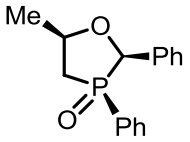
(3*S*,5*R*)-5-(*tert*-butyl)-2,2-dimethyl-3-phenyl-1,3-oxaphospholane 3-oxide. R_f = 0.22 (100% EtOAc, UV) ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.00 (9H, s), 1.05 (3H, d, J = 13.7 Hz), 1.54 (3H, d, J = 10.8 Hz), 2.09-2.22 (2H, m), 4.01 (1H, ddd, J = 10.3 Hz, 5.9 Hz, 2.2 Hz), 7.46-7.56 (3H, m), 7.75-7.79 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.1 (d, $J_{C\text{-}P}$ = 6.5 Hz), 24.4 (d, $J_{C\text{-}P}$ = 5.6 Hz), 25.7, 29.9 (d, $J_{C\text{-}P}$ = 70.7 Hz), 34.2 (d, $J_{C\text{-}P}$ = 6.5 Hz), 76.6 (d, $J_{C\text{-}P}$ = 72.6 Hz), 81.0, 128.4 (d, $J_{C\text{-}P}$ = 11.2 Hz), 130.9 (d, $J_{C\text{-}P}$ = 88.8 Hz), 131.3 (d, $J_{C\text{-}P}$ = 8.8 Hz), 131.9 (d, $J_{C\text{-}P}$ = 3.3 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 59.0; IR (neat): 2958.0 (m), 2931.1 (w), 2870.1 (w), 1437.8 (w), 1213.7 (s), 1201.7 (m), 1147.8 (m), 1006.5 (m), 741.7 (m), 697.6 (m), 505.4 (m) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{24}O_2P$ [M+H]: calculated: 267.1514, found: 267.1520. $[\alpha]_D^{20}$ = +39.5 (c = 0.362, $CHCl_3$, l = 50 mm).



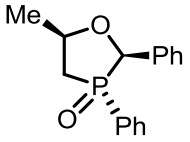
(3*R*,5*R*)-5-(*tert*-butyl)-2,2-dimethyl-3-phenyl-1,3-oxaphospholane 3-oxide. R_f = 0.26 (100% EtOAc, UV) ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (3H, d, *J* = 14.2 Hz), 0.99 (9H, s) 1.51 (3H, d, *J* = 11.3 Hz), 2.22 (1H, ddd, *J* = 19.8 Hz, 14.9 Hz, 11.3 Hz), 2.40 (1H, app dt, *J* = 14.9 Hz, 5.6 Hz), 3.79 (1H, ddd, *J* = 11.3 Hz, 5.4 Hz, 2.4 Hz), 7.49-7.58 (3H, m), 7.74-7.78 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 23.2 (d, $J_{C\text{-}P}$ = 11.2 Hz), 24.1 (d, $J_{C\text{-}P}$ = 1.9 Hz), 25.6, 29.7 (d, $J_{C\text{-}P}$ = 68.4 Hz), 34.2 (d, $J_{C\text{-}P}$ = 7.0 Hz), 76.8 (d, $J_{C\text{-}P}$ = 71.6 Hz), 82.1 (d, $J_{C\text{-}P}$ = 2.3 Hz), 128.6 (d, $J_{C\text{-}P}$ = 11.2 Hz), 130.5 (d, $J_{C\text{-}P}$ = 86.5 Hz), 130.8 (d, $J_{C\text{-}P}$ = 8.8 Hz), 132.1 (d, $J_{C\text{-}P}$ = 2.8 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 58.2; IR (neat): 3053.6 (w), 2956.5 (s), 2925.7 (m), 2869.1 (w), 1436.7 (w), 1213.7 (s), 1193.9 (s), 1165.6 (s), 1143.8 (s), 1004.6 (m), 747.7 (m), 697.3 (m) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{24}O_2P$ [M+H]: calculated: 267.1514, found: 267.1517. $[\alpha]_D^{20}$ = -9.17 (*c* = 0.620, $CHCl_3$, *l* = 50 mm).

(5*R*)-5-methyl-2,3-diphenyl-1,3-oxaphospholane 3-oxide. The reaction was performed according to the general procedure using diethyl ether (47 mL), phenylphosphine (2.59 mL, 23.5 mmol), *n*-BuLi (2.48 M in hexanes, 10.0 mL, 24.7 mmol), and (*R*)-2-methyloxirane (1.98 mL, 28.2 mmol) to arrive at the secondary phosphine. The crude secondary phosphine was taken up in toluene (36 mL) and divided into thirds (12 mL). To the 12 mL of toluene solution was added benzaldehyde (1.51 mL, 14.9 mmol), and *p*-toluenesulfonic acid (0.170 g, 0.899 mmol) to give cyclized product as a mixture of diastereomers which was examined in platinum catalyzed diboration. Oxidation of a portion of the crude material (104.6 mg, 0.408 mmol) was carried out using THF (2 mL) and H_2O_2 (30 wt %, 0.50 mL, 4.9 mmol). The crude oxidation product was purified (SiO_2, 100% ethyl acetate) to give both (2*R*, 3*S*, 5*R*)-5-methyl-2,3-diphenyl-1,3-

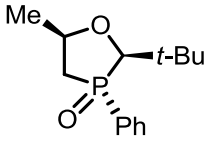
oxaphospholane 3-oxide (25.9 mg, 23%) along with (2*R*, 3*R*, 5*R*)-5-methyl-2,3-diphenyl-1,3-oxaphospholane 3-oxide (24.2 mg, 22%).



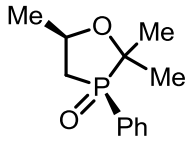
(2*R*, 3*S*, 5*R*)-5-methyl-2,3-diphenyl-1,3-oxaphospholane 3-oxide. R_f = 0.29 (100% EtOAc, UV) ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 50.7.



(2*R*, 3*R*, 5*R*)-5-methyl-2,3-diphenyl-1,3-oxaphospholane 3-oxide. R_f = 0.16 (100% EtOAc, UV) ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 56.6.

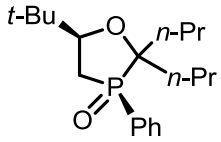


(2*R*, 3*R*, 5*R*)-2-(*tert*-butyl)-5-methyl-3-phenyl-1,3-oxaphospholane 3-oxide. The reaction was performed according to the general procedure using diethyl ether (47 mL), phenylphosphine (2.59 mL, 23.5 mmol), *n*-BuLi (2.48 M in hexanes, 10.0 mL, 24.7 mmol), and (*R*)-2-methyloxirane (1.98 mL, 28.2 mmol) to arrive at the secondary phosphine. The crude secondary phosphine was taken up in toluene (36 mL) and divided into thirds (12 mL). To the 12 mL of toluene solution was added pivaldehyde (1.62 mL, 14.9 mmol), and *p*-toluenesulfonic acid (0.170 g, 0.899 mmol) to give cyclized product as a mixture of diastereomers. Oxidation of a portion of the crude material (615.3 mg, 2.44 mmol) was carried out using THF (5 mL) and H_2O_2 (30 wt %, 1.0 mL, 9.8 mmol). The crude oxidation product was purified (SiO_2, 100% ethyl acetate) to give the title compound as a white solid (70.0 mg, 11%). R_f = 0.20 (100% EtOAc, UV) ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 52.2.

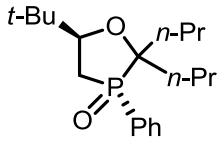


(3*S*, 5*R*)-2,2,5-trimethyl-3-phenyl-1,3-oxaphospholane 3-oxide. The reaction was performed according to the general procedure using diethyl ether (6.0 mL), phenylphosphine (0.35 mL, 3.1 mmol), *n*-BuLi (2.48 M in hexanes, 1.33 mL, 3.30 mmol), and (*R*)-2-methyloxirane (0.26 mL, 3.3 mmol) to arrive at the secondary phosphine, followed by the use of toluene (6.0 mL), 3,3-dimethoxypropane (1.10 mL, 8.92 mmol), and *p*-toluenesulfonic acid (85.6 mg, 0.45 mmol) to give cyclized product. Oxidation of the crude material was carried out using THF (5 mL) and H_2O_2 (30 wt %, 1.0 mL, 9.8 mmol). The crude oxidation product was purified (SiO_2, 100% ethyl acetate) to give the title compound as a white solid (239.6 mg, 34%). R_f = 0.17 (100% EtOAc, UV) ^{31}P NMR (121.4 MHz, $CDCl_3$): δ 59.4.

(5*R*)-5-(tert-butyl)-3-phenyl-2,2-dipropyl-1,3-oxaphospholane 3-oxide. The reaction was performed according to the general procedure using diethyl ether (9.0 mL), phenylphosphine (0.48 mL, 4.3 mmol), *n*-BuLi (2.42 M in hexanes, 1.88 mL, 4.54 mmol), and (*R*)-2-(*tert*-butyl)oxirane (0.43 g, 4.3 mmol) to arrive at the secondary phosphine, followed by the use of toluene (9.0 mL), 3,3-dimethoxyheptane (4.91 g, 30.7 mmol), and *p*-toluenesulfonic acid (0.205 g, 1.08 mmol) to give cyclized product. Oxidation of the crude material was carried out using THF (10 mL), and H_2O_2 (30 wt %, 0.75 mL, 13 mmol). The crude oxidation product was purified (SiO_2, 35-80 % ethyl acetate in hexane) to give 238.6 mg (17%) of a 1:1 mixture of phosphorus epimers. In order to obtain isomerically pure compound, the mixture of epimers (200 mg) was further purified (SiO_2, 35% ethyl acetate in hexane) to give both *trans* (49.7 mg) and *cis* (68.4 mg), along with mixed material (40 mg).

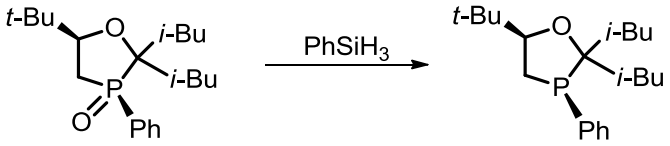


(3*S*, 5*R*)-5-(tert-butyl)-3-phenyl-2,2-dipropyl-1,3-oxaphospholane 3-oxide. R_f = 0.28 (100% EtOAc, UV) ^{31}P NMR (202 MHz, $CDCl_3$): δ 59.8.



(3*R*, 5*R*)-5-(tert-butyl)-3-phenyl-2,2-dipropyl-1,3-oxaphospholane 3-oxide. R_f = 0.38 (100% EtOAc, UV) ^{31}P NMR (202 MHz, $CDCl_3$): δ 59.0.

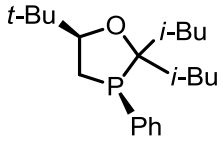
1.5.2.4 Representative Procedure for Phenylsilane Reduction



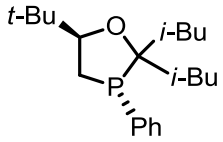
(3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane.[98] (3*S*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane 3-oxide (100 mg, 0.285 mmol) was placed in the bottom of a 10 mL pear-shaped flask. The flask was then sealed and purged with argon, followed by treatment with phenylsilane (0.11 mL, 0.86 mmol) at room temperature. After 10 minutes, the clear, colorless solution was carefully heated to 80 ^{o}C under argon for 12 hours. The flask was removed from heat, cooled to room temperature, and placed under vacuum for 1 hour. The flask was taken into the dry box and the crude reaction mixture taken up in benzene and eluted through a pipet-plug of basic alumina. The solvent was removed under reduced pressure to give the product as a colorless, viscous oil (76.7 mg, 80%).

[98] Marzi, K. L. *J. Org. Chem*. **1974**, *39*, 265.

1.5.2.5 Characterization of Phosphines

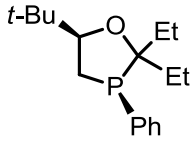


(3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.45 (3H, d, J = 6.5 Hz), 0.80 (3H, d, J = 6.5 Hz), 1.00 (3H, d, J = 6.5 Hz), 1.03 (3H, d, J = 6.5 Hz), 1.05 (9H, s), 1.44 (1H, app dt, J = 14.5 Hz, 4.5 Hz), 1.54 (1H, app septet, J = 6.3 Hz), 1.58-1.75 (3H, m), 1.87-1.98 (2H, m), 2.29 (1H, ddd, J = 27.5 Hz, 13.5 Hz, 6.0 Hz), 3.67 (1H, ddd, J = 11.0 Hz, 6.5 Hz, 1.5 Hz), 7.31-7.37 (3H, m), 7.61-7.65 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 23.9 (d, $J_{C\text{-}P}$ = 20.5 Hz), 24.1 (d, $J_{C\text{-}P}$ = 3.8 Hz), 24.7, 24.8, 24.9 (d, $J_{C\text{-}P}$ = 2.8 Hz), 25.3 (d, $J_{C\text{-}P}$ = 3.8 Hz), 26.9, 30.7 (d, $J_{C\text{-}P}$ = 14.0 Hz), 34.5 (d, $J_{C\text{-}P}$ = 1.4 Hz), 42.5, 43.7, (d, $J_{C\text{-}P}$ = 39.1 Hz), 84.4 (d, $J_{C\text{-}P}$ = 2.8 Hz), 90.1 (d, $J_{C\text{-}P}$ = 19.6 Hz), 127.9 (d, $J_{C\text{-}P}$ = 7.9 Hz), 129.1 (d, $J_{C\text{-}P}$ = 1.4 Hz), 135.2 (d, $J_{C\text{-}P}$ = 21.9 Hz), 139.3 (d, $J_{C\text{-}P}$ = 25.0 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 6.7.

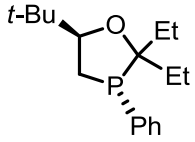


(3*S*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane. The reaction was performed according to the general procedure using (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane 3-oxide (22.1 mg, 63.1 μmol) and phenylsilane (23 μL, 0.19 mmol), to give the product as a colorless, viscous oil (15.6 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.64 (3H, d, J = 6.6 Hz), 0.84 (3H, d, J = 6.6 Hz), 0.99 (9H, s), 1.02 (3H, d, J = 6.9 Hz), 1.01-1.07 (2H, m), 1.08 (3H, dd, J = 6.5 Hz, 0.7 Hz), 1.71-1.80 (3H, m), 1.86-1.98 (1H, m), 1.90 (1H, ddd, J = 21.0 Hz, 14.3 Hz, 11.0 Hz), 2.19 (1H, app dt, J = 14.2 Hz, 4.2 Hz), 3.80 (1H, ddd, J = 11.0 Hz, 4.4 Hz, 1.5 Hz), 7.31-7.36 (3H, m), 7.42-7.45 (2H, m); ^{13}C NMR (126 MHz,

$CDCl_3$): δ 21.2, 24.5 (d, $J_{C\text{-}P}$ = 2.3 Hz), 25.0, 25.1 (d, $J_{C\text{-}P}$ = 3.3 Hz), 25.2 (d, $J_{C\text{-}P}$ = 1.4 Hz), 25.4 (d, $J_{C\text{-}P}$ = 13.5 Hz), 26.0 (d, $J_{C\text{-}P}$ = 10.7 Hz), 26.5, 34.2 (d, $J_{C\text{-}P}$ = 1.4 Hz), 44.6, 47.8 (d, $J_{C\text{-}P}$ = 27.0 Hz), 87.3 (d, $J_{C\text{-}P}$ = 3.3 Hz), 89.4 (d, $J_{C\text{-}P}$ = 23.3 Hz), 128.1 (d, $J_{C\text{-}P}$ = 6.5 Hz), 128.3, 132.9 (d, $J_{C\text{-}P}$ = 19.1 Hz), 136.8 (d, $J_{C\text{-}P}$ = 27.9 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 0.6.

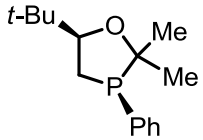


(3*R*,5*R*)-5-(*tert*-butyl)-2,2-diethyl-3-phenyl-1,3-oxaphospholane. The reaction was performed according to the general procedure using (3*S*,5*R*)-5-(*tert*-butyl)-2,2-diethyl-3-phenyl-1,3-oxaphospholane 3-oxide (70.0 mg, 0.238 mmol) and phenylsilane (90 μL, 0.71 mmol), to give the product as a colorless, viscous oil (64.4 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.60 (3H, t, J = 7.6 Hz), 0.86 (3H, dt, J = 7.1 Hz, 0.7 Hz), 1.06 (9H, s), 1.23-1.32 (1H, m), 1.61 (1H, app ddq, J = 14.9 Hz, 10.5 Hz, 7.6 Hz), 1.72-1.78 (2H, m), 1.97 (1H, ddd, J = 13.7 Hz, 11.0 Hz, 7.3 Hz), 2.27 (1H, ddd, J = 27.1 Hz, 13.7 Hz, 6.1 Hz), 3.53 (1H, ddd, J = 11.0 Hz, 6.1 Hz, 1.5 Hz), 7.30-7.36 (3H, m), 7.62-7.66 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 6.9 (d, $J_{C\text{-}P}$ = 16.8 Hz), 9.4 (d, $J_{C\text{-}P}$ = 5.1 Hz), 25.7 (d, $J_{C\text{-}P}$ = 1.4 Hz), 26.4 (d, $J_{C\text{-}P}$ = 41.4 Hz), 26.7, 30.0 (d, $J_{C\text{-}P}$ = 14.0 Hz), 34.3 (d, $J_{C\text{-}P}$ = 1.4 Hz), 84.6 (d, $J_{C\text{-}P}$ = 2.3 Hz), 89.4 (d, $J_{C\text{-}P}$ = 17.2 Hz), 127.9 (d, $J_{C\text{-}P}$ = 7.9 Hz), 129.1 (d, $J_{C\text{-}P}$ = 1.4 Hz), 134.8 (d, $J_{C\text{-}P}$ = 21.4 Hz), 138.5 (d, $J_{C\text{-}P}$ = 24.2 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 0.5.

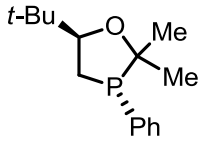


(3*S*,5*R*)-5-(*tert*-butyl)-2,2-diethyl-3-phenyl-1,3-oxaphospholane. The reaction was performed according to the general procedure using (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diethyl-3-phenyl-1,3-oxaphospholane 3-oxide (71.6 mg, 0.243

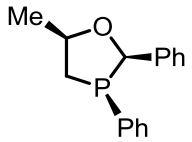
mmol) and phenylsilane (0.11 mL, 0.89 mmol), to give the product as a colorless, viscous oil (51.9 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.72 (3H, t, J = 7.2 Hz), 1.00 (9H, s), 1.00-1.04 (1H, m), 1.06 (3H, dt, J = 7.3 Hz, 1.2 Hz), 1.18-1.27 (1H, m), 1.67-1.87 (2H, m), 1.90 (1H, ddd, J = 19.9 Hz, 14.3 Hz, 11.5 Hz), 2.19 (1H, ddd, J = 14.4 Hz, 4.1 Hz, 3.4 Hz), 3.78 (1H, ddd, J = 11.2 Hz, 4.2 Hz, 1.5 Hz), 7.32-7.37 (3H, m), 7.42-7.45 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 7.7 (d, J_{C-P} = 2.3 Hz), 9.8 (d, J_{C-P} = 14.4 Hz), 25.6 (d, J_{C-P} = 10.2 Hz), 26.2, 27.5, 30.9 (d, J_{C-P} = 31.6 Hz), 34.1 (d, J_{C-P} = 1.4 Hz), 87.5 (d, J_{C-P} = 3.7 Hz), 89.0 (d, J_{C-P} = 21.4 Hz), 128.2 (d, J_{C-P} = 6.5 Hz), 132.7 (d, J_{C-P} = 18.6 Hz), 133.7 (d, J_{C-P} = 19.1 Hz), 136.2 (d, J_{C-P} = 26.1 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ -0.4.



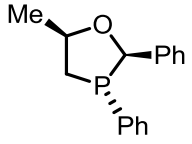
(3*R*,5*R*)-5-(*tert*-butyl)-2,2-dimethyl-3-phenyl-1,3-oxaphospholane. The reaction was performed according to the general procedure using (3*S*,5*R*)-5-(*tert*-butyl)-2,2-dimethyl-3-phenyl-1,3-oxaphospholane 3-oxide (59.0 mg, 0.222 mmol) and phenylsilane (82 μL, 0.67 mmol), to give the product as a colorless, viscous oil (45.8 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (3H, d, J = 7.6 Hz), 1.06 (9H, s), 1.41 (3H, d, J = 18.1 Hz), 2.07 (1H, ddd, J = 13.8 Hz, 11.1 Hz, 7.3 Hz), 2.29 (1H, ddd, J = 26.2 Hz, 13.7 Hz, 5.9 Hz), 3.63 (1H, ddd, J = 11.0 Hz, 6.1 Hz, 1.7 Hz), 7.31-7.36 (3H, m), 7.58-7.61 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.9 (d, J_{C-P} = 3.3 Hz), 26.7, 27.8 (d, J_{C-P} = 41.4 Hz), 30.5 (d, J_{C-P} = 14.0 Hz), 34.1 (d, J_{C-P} = 1.9 Hz), 82.2 (d, J_{C-P} = 14.9 Hz), 85.3 (d, J_{C-P} = 2.8 Hz), 128.0 (d, J_{C-P} = 7.9 Hz), 129.2 (d, J_{C-P} = 0.9 Hz), 134.4 (d, J_{C-P} = 21.4 Hz), 139.0 (d, J_{C-P} = 23.7 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 3.0.



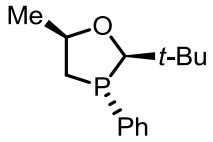
(3*S*,5*R*)-5-(*tert*-butyl)-2,2-dimethyl-3-phenyl-1,3-oxaphospholane. The reaction was performed according to the general procedure using (3*R*,5*R*)-5-(*tert*-butyl)-2,2-dimethyl-3-phenyl-1,3-oxaphospholane 3-oxide (63.0 mg, 0.237 mmol) and phenylsilane (88 μL, 0.71 mmol), to give the product as a colorless, viscous oil (46.6 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.97 (9H, s), 1.04 (3H, d, J = 6.1 Hz), 1.51 (3H, d, J = 19.1 Hz), 2.04 (1H, ddd, J = 18.9 Hz, 14.5 Hz, 11.0 Hz), 2.24 (1H, ddd, J = 14.5 Hz, 4.8 Hz, 3.2 Hz), 3.95 (1H, ddd, J = 11.1 Hz, 4.8 Hz, 1.0 Hz), 7.31-7.38 (3H, m), 7.44-7.48 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 25.2, 25.5 (d, $J_{C\text{-}P}$ = 11.2 Hz), 28.7, 30.6 (d, $J_{C\text{-}P}$ = 37.2 Hz), 33.0 (d, $J_{C\text{-}P}$ = 1.4 Hz), 82.1 (d, $J_{C\text{-}P}$ = 19.1 Hz), 87.7 (d, $J_{C\text{-}P}$ = 3.3 Hz), 127.2 (d, $J_{C\text{-}P}$ = 6.1 Hz), 127.6, 131.6 (d, $J_{C\text{-}P}$ = 18.1 Hz), 135.6 (d, $J_{C\text{-}P}$ = 25.6 Hz); ^{31}P NMR (202 MHz, $CDCl_3$): δ 4.6.



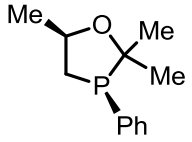
(2*R*, 3*R*, 5*R*)-5-methyl-2,3-diphenyl-1,3-oxaphospholane. The reaction was performed according to the general procedure using (2*R*, 3*S*, 5*R*)-5-methyl-2,3-diphenyl-1,3-oxaphospholane 3-oxide (33.0 mg, 0.120 mmol) and phenylsilane (0.10 mL, 0.81 mmol), to give the product as a colorless, viscous oil (20.0 mg, 65%). ^{31}P NMR (202 MHz, $CDCl_3$): δ 0.3.



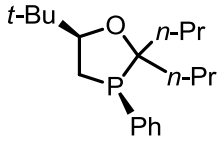
(2*R*, 3*S*, 5*R*)-5-methyl-2,3-diphenyl-1,3-oxaphospholane. The reaction was performed according to the general procedure using (2*R*, 3*R*, 5*R*)-5-methyl-2,3-diphenyl-1,3-oxaphospholane 3-oxide (38.0 mg, 0.140 mmol) and phenylsilane (0.17 mL, 1.4 mmol), to give the product as a colorless, viscous oil (24.3 mg, 68%). ^{31}P NMR (202 MHz, $CDCl_3$): δ 2.2.



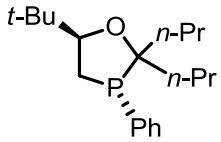
(2*R*, 3*S*, 5*R*)-2-(*tert*-butyl)-5-methyl-3-phenyl-1,3-oxaphospholane. The reaction was performed according to the general procedure using (2*R*, 3*R*, 5*R*)-2-(*tert*-butyl)-5-methyl-3-phenyl-1,3-oxaphospholane 3-oxide (70.0 mg, 0.277 mmol) and phenylsilane (0.34 mL, 2.8 mmol), to give the product as a colorless, viscous oil (46.2 mg, 71%). ^{31}P NMR (202 MHz, $CDCl_3$): δ -16.1.



(3*R*, 5*R*)-2,2,5-trimethyl-3-phenyl-1,3-oxaphospholane. The reaction was performed according to the general procedure using (3*S*, 5*R*)-2,2,5-trimethyl-3-phenyl-1,3-oxaphospholane 3-oxide (239.6 mg, 1.07 mmol) and phenylsilane (0.40 mL, 3.2 mmol), to give the product as a colorless, viscous oil (178.1 mg, 80%). ^{31}P NMR (202 MHz, $CDCl_3$): δ 6.8.



(3*R*, 5*R*)-5-(tert-butyl)-3-phenyl-2,2-dipropyl-1,3-oxaphospholane. The reaction was performed according to the general procedure using (3*S*, 5*R*)-5-(tert-butyl)-3-phenyl-2,2-dipropyl-1,3-oxaphospholane 3-oxide (49.7 mg, 0.154 mmol) and phenylsilane (0.10 mL, 0.81 mmol), to give the product as a colorless, viscous oil (38.7 mg, 82%). ^{31}P NMR (202 MHz, $CDCl_3$): δ 2.0.



(3*S*, 5*R*)-5-(tert-butyl)-3-phenyl-2,2-dipropyl-1,3-oxaphospholane. The reaction was performed according to the general procedure using (3*R*, 5*R*)-5-(tert-butyl)-3-phenyl-2,2-dipropyl-1,3-oxaphospholane 3-oxide (68.4 mg,

0.212 mmol) and phenylsilane (0.12 mL, 0.97 mmol), to give the product as a colorless, viscous oil (57.1 mg, 88%). ^{31}P NMR (202 MHz, $CDCl_3$): δ 1.2.

1.5.2.6 Preparation of Rhodium Complexes

(*trans*)-Chlorocarbonylbis(*cis*-Et-OxaPhos)rhodium. To a 20 mL scintillation vial in the dry box was added chlorodicarbonylrhodium(I) dimer (3.4 mg, 8.7 μmol) followed by C_6D_6 (0.2 mL). The resulting yellow solution was transferred to a second vial containing ***cis*-Et-OxaPhos** (10.0 mg, 36 μmol) and immediate evolution of gas was observed. The resulting clear, dark yellow solution was transferred to an NMR tube with rinsing (0.6 mL). The tube was sealed and brought out of the dry box for analysis.

(*trans*)-Chlorocarbonylbis(*cis*-Et-OxaPhos)rhodium. ^{1}H NMR (500 MHz, C_6D_6): δ 0.73-0.82 (2H, m), 0.88 (6H, t, J = 7.6 Hz), 0.95 (18H, s), 0.98 (6H, t, J = 7.3 Hz), 1.83-1.90 (2H, m), 1.96-2.08 (2H, m), 2.27-2.35 (2H, m), 2.51-2.59 (4H, m), 3.61-3.67 (2H, m), 7.08-7.20 (6H, m), 8.44-8.48 (4H, m); ^{13}C NMR (126 MHz, C_6D_6): δ 7.4 (t, J = 6.5 Hz), 10.2 (t, J = 1.4 Hz), 26.7, 27.7, 28.9 (t, J = 12.6 Hz), 32.3 (t, J = 15.4 Hz), 34.7 (t, J = 2.3 Hz), 83.9, 89.5 (dt, J = 10.7 Hz, 1.9 Hz), 128.7, 131.1, 135.6 (dt, J = 16.3 Hz, 1.4 Hz), 136.5 (t, J = 6.5 Hz), 189.9 (dt, J = 72.1 Hz, 16.7 Hz); ^{31}P NMR (202 MHz, C_6D_6): δ 49.7 (d, $J_{P\text{-}Rh}$ = 124.0 Hz); IR (neat): 2962.2 (m), 2873.2 (w), 1960.7 (s), 1435.0 (w), 1395.0 (w), 1096.4 (w), 696.9 (w) cm^{-1}; HRMS-(TOF MS ES+) for $C_{35}H_{54}O_3NaP_2ClRh$ [M+Na]: calculated: 745.2189, found: 745.2166.

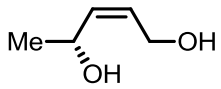
(*trans*)-Chlorocarbonylbis(*trans*-Et-OxaPhos)rhodium. To a 20 mL scintillation vial in the dry box was added chlorodicarbonylrhodium(I) dimer (3.4 mg, 8.7 μmol) followed by ***trans*-Et-OxaPhos** as a solution in toluene (0.75 mL, 36 μmol). Immediate evolution of gas was observed and the resulting dark yellow solution was gently stirred for 5 minutes, after which the solvent was removed under reduced pressure. The resulting yellow residue was taken up in C_6D_6 (0.6 mL) and transferred to an NMR tube which was sealed and brought out of the dry box for analysis.

(*trans*)-Chlorocarbonylbis(*trans*-Et-OxaPhos)rhodium. ^{1}H NMR (500 MHz, C_6D_6): δ 0.79 (6H, t, *J* = 7.3 Hz), 0.93 (18H, s), 0.92-0.97 (2H, m), 1.52 (6H, t, *J* = 7.3 Hz), 1.58-1.67 (2H, m), 2.37-2.49 (2H, m), 2.61-2.68 (4H, m), 2.78 (2H, ddd, *J* = 14.7 Hz, 12.0 Hz, 1.0 Hz), 3.79 (2H, app ddt, *J* = 12.0 Hz, 3.6 Hz, 1.7 Hz), 7.02-7.12 (6H, m), 8.07-8.11 (4H, m); ^{13}C NMR (126 MHz, C_6D_6): δ 8.7 (t, *J* = 2.8 Hz), 10.7 (t, *J* = 4.2 Hz), 26.5, 29.1 (dt, *J* = 14.9 Hz, 1.4 Hz), 30.3 (t, *J* = 7.4 Hz), 30.7 (t, *J* = 2.3 Hz), 35.0 (t, *J* = 2.3 Hz), 86.7, 90.3 (dt, *J* = 8.8 Hz, 1.4 Hz), 128.9 (t, *J* = 4.7 Hz), 130.4, 132.7 (t, *J* = 14.4 Hz), 134.2 (t, *J* = 5.6 Hz), 188.8 (dt, *J* = 73.0 Hz, 16.8 Hz); ^{31}P NMR (202 MHz, C_6D_6): δ 37.8 (d, $J_{P\text{-}Rh}$ = 125.0 Hz); IR (neat): 2955.0 (m), 2868.4 (w), 1961.7 (s), 1433.9 (w), 1132.6 (m), 1066.5 (m), 741.9 (w), 696.3 (m) cm^{-1}; HRMS-(TOF MS ES+) for $C_{35}H_{54}O_3NaP_2ClRh$ [M+Na]: calculated: 745.2189, found: 745.2201.

1.5.2.7 Representative Procedure for Diene Diboration/Oxidation

A 20 mL flame-dried scintillation vial equipped with magnetic stir bar in the dry box was charged with $Pt(dba)_3$ (23.5 mg, 26.4 μmol), followed by the addition of toluene (8.2 mL). (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane was then added as a solution in toluene (0.0916 M, 0.57 mL), followed by $B_2(pin)_2$ (233.0 mg, 0.925 mmol). The vial was then sealed, removed from the dry box and heated to 80 ^oC for 20 minutes, during which the reaction mixture changes from a dark purple solution to a light yellow solution. After cooling to room temperature, the vial was returned to the dry box and (*E*)-penta-1,3-diene (**3**) (60.0 mg, 0.881 mmol) was added. The vial was sealed, removed from the dry box, and heated to 60 ^oC for 12 hours. The reaction was then cooled to 0 ^oC, diluted with THF (2 mL), and treated with 3 M aqueous NaOH (2 mL) and H_2O_2 (30 wt % in H_2O, 1 mL). The vial was warmed slowly to room temperature and stirred for 4 hours, after which the reaction was again cooled to 0 ^oC and carefully treated with saturated aqueous sodium thiosulfate (2 mL). The reaction mixture was diluted with ethyl acetate (15 mL) and water (10 mL) and the layers were separated. The aqueous layer was further extracted with ethyl acetate (4 x 15 mL) and the combined organic layers were dried over sodium sulfate and the solvent removed under reduced pressure. The crude material was purified (SiO_2, 50-100 % ethyl acetate in hexane) to give the product as a colorless oil (76.9 mg, 85%).

1.5.2.8 Characterization of 1,4-Diols and Proof of Stereochemistry

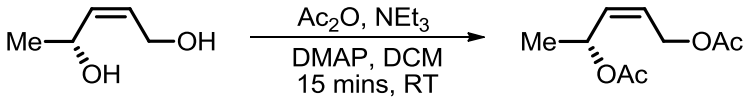


(*R*,*Z*)-pent-2-ene-1,4-diol (Table 3, entry 1). R_f = 0.10 (50% EtOAc in hexane, PMA) Prepared according to the general procedure using (*E*)-penta-1,3-diene (60.0 mg, 0.881 mmol), $Pt(dba)_3$ (23.5 mg, 26.4 μmol), (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane (0.57 mL, 0.0916 M, 53 μmol), $B_2(pin)_2$ (233.0 mg, 0.925 mmol), and toluene (8.8 mL). Crude material was purified (SiO_2, 50-100% ethyl acetate in hexane) to give the product as a colorless oil (76.9 mg, 85%). Spectral data are in accordance with the literature.[99] HRMS-(ESI+) for $C_5H_{14}NO_2$ [M+NH_4]: calculated: 120.1025, found: 102.1023. $[\alpha]_D^{20}$ = +4.833 (*c* = 1.062, $CHCl_3$, *l* = 50 mm).

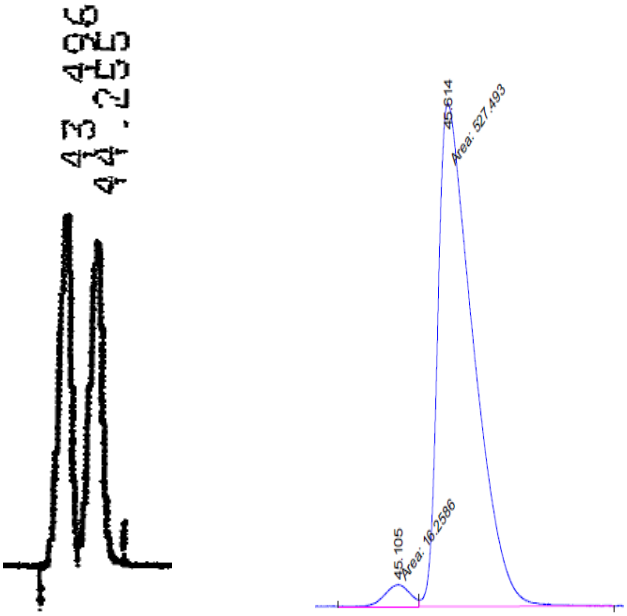
[99] Cho, H. Y.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 16140.

Analysis of Stereochemistry:

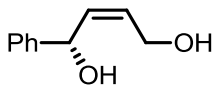
The resulting 1,4-diol was converted to the corresponding diacetate as shown below. The racemic compound was prepared through a diboration/oxidation sequence utilizing PCy_3 as ligand. The absolute stereochemistry was assigned by analogy.



Chiral GLC (β-dex, Supelco, 90 °C, 20 psi) – analysis of the diacetate of (Z)-pent-2-ene-1,4-diol.



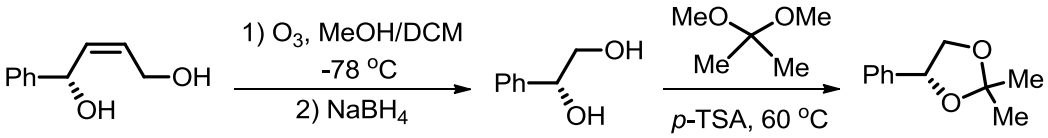
racemic reaction product



(*S,Z*)-1-phenylbut-2-ene-1,4-diol (Table 3, entry 2). R_f = 0.22 (50% EtOAc in hexane, PMA/UV) Prepared according to the general procedure using (*E*)-buta-1,3-dien-1-ylbenzene (40.0 mg, 0.307 mmol), $Pt(dba)_3$ (8.3 mg, 9.2 μmol), (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane (0.26 mL, 0.0718 M, 18 μmol), $B_2(pin)_2$ (81.9 mg, 0.322 mmol), and toluene (3.1 mL). Crude material was purified (SiO_2, 40-60% ethyl acetate in hexanes) to give the product as a colorless residue (38.9 mg, 77%). Spectral data are in accordance with the literature.[100] HRMS-(ESI+) for $C_{10}H_{11}O$ [M+H-H_2O]: calculated: 147.0810, found: 147.0803. $[\alpha]_D^{20}$ = +85.8 (*c* = 0.340, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry:

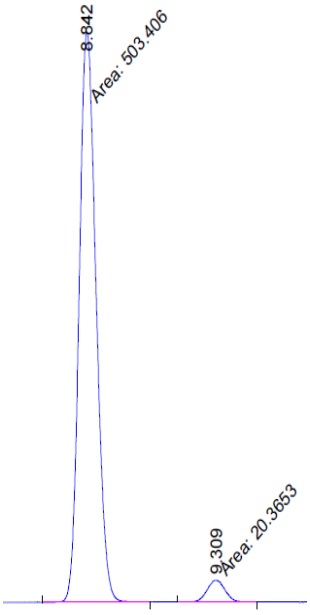
The resulting 1,4-diol was subjected to ozonolysis and reduction as shown below. The 1,2-diol was then treated with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid to afford the corresponding ketal. The racemic ketal was prepared through dihydroxylation of styrene with osmium tetraoxide and 4-methylmorpholine N-oxide. The authentic sample was prepared from the Sharpless asymmetric dihydroxylation of styrene utilizing AD-mix α.[101]



[100] Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134.
[101] Jacobsen, E. N.; Markd, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1988**, *110*, 1968.

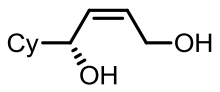
Chiral GLC (β-dex, Supelco, 140 ℃, 20 psi) – analysis of the acetonide of 1-phenylethane-1,2-diol.

racemic



reaction product

authentic



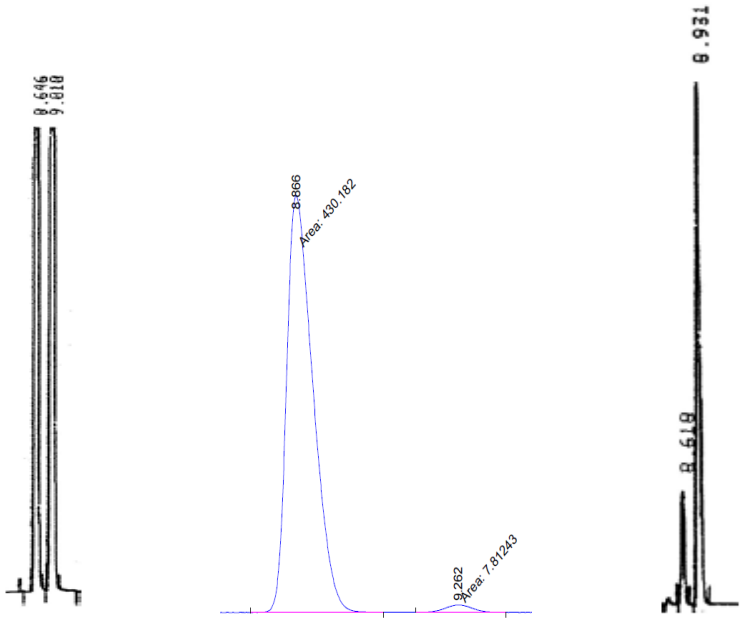
(*R*,*Z*)-1-cyclohexylbut-2-ene-1,4-diol (Table 3, entry 3). R_f = 0.21 (50% EtOAc in hexane, PMA) Prepared according to the general procedure using (*E*)-buta-1,3-dien-1-ylcyclohexane (35.0 mg, 0.257 mmol), $Pt(dba)_3$ (6.9 mg, 7.7 μmol), (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane (0.22 mL, 0.0718 M, 15 μmol), $B_2(pin)_2$ (68.5 mg, 0.270 mmol), and toluene (2.6 mL). Crude material was purified (SiO_2, 40-60% ethyl acetate in hexanes) to give the product as a colorless residue (43.3 mg, 98%). Spectral data are in accordance with the literature.[102] HRMS-(ESI+) for $C_{10}H_{22}NO_2$ [M+NH_4]: calculated: 188.1651, found: 188.1650. $[\alpha]_D^{20}$ = +37.3 (*c* = 0.705, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry:

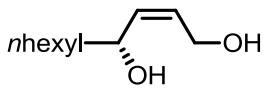
The resulting 1,4-diol was subjected to ozonolysis and reduction as described above. The 1,2-diol was then treated with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid to afford the corresponding ketal. The racemic ketal was prepared through dihydroxylation of vinyl cyclohexane with osmium tetraoxide and 4-methylmorpholine N-oxide. The authentic sample was prepared from the Sharpless asymmetric dihydroxylation of vinyl cyclohexane utilizing AD-mix α.[103]

[102] Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134.
[103] Jacobsen, E. N.; Markd, I; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1988**, *110*, 1968.

Chiral GLC (β-dex, Supelco, 130 ℃, 20 psi) – analysis of the acetonide of 1-cyclohexylethane-1,2-diol.



racemic reaction product authentic



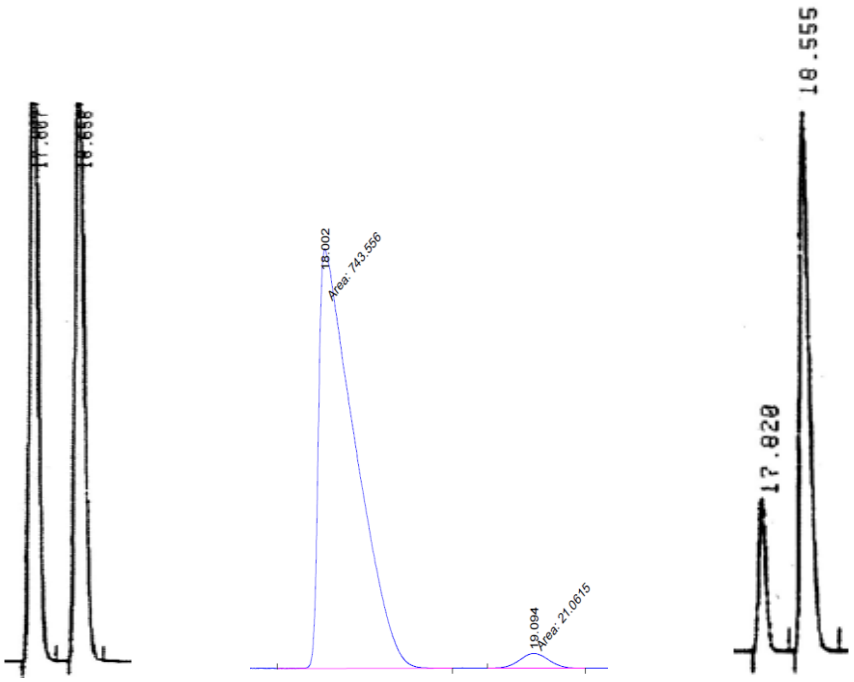
(*R*,*Z*)-dec-2-ene-1,4-diol (Table 3, entry 4). R_f = 0.24 (50% EtOAc in hexane, PMA) Prepared according to the general procedure using (*E*)-deca-1,3-diene (40.0 mg, 0.289 mmol), $Pt(dba)_3$ (7.8 mg, 8.7 μmol), (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane (0.24 mL, 0.0718 M, 17 μmol), $B_2(pin)_2$ (77.1 mg, 0.303 mmol), and toluene (2.9 mL). Crude material was purified (SiO_2, 40-70% ethyl acetate in hexanes) to give the product as a colorless residue (49.1 mg, 98%). Spectral data are in accordance with the literature.[104] HRMS-(ESI+) for $C_{10}H_{24}NO_2$ [M+NH_4]: calculated: 190.1807, found: 190.1806. $[\alpha]_D^{20}$ = +18.4 (*c* = 0.756, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry:

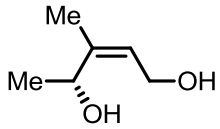
The resulting 1,4-diol was subjected to ozonolysis and reduction as described above. The 1,2-diol was then treated with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid to afford the corresponding ketal. The racemic ketal was prepared through dihydroxylation of 1-octene with osmium tetraoxide and 4-methylmorpholine N-oxide. The authentic sample was prepared from the Sharpless asymmetric dihydroxylation of 1-octene utilizing AD-mix α.[105]

[104] Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134.
[105] Jacobsen, E. N.; Markd, I; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1988**, *110*, 1968.

Chiral GLC (β-dex, Supelco, 100 ℃, 20 psi) – analysis of the acetonide of octane-1,2-diol.



racemic reaction product authentic

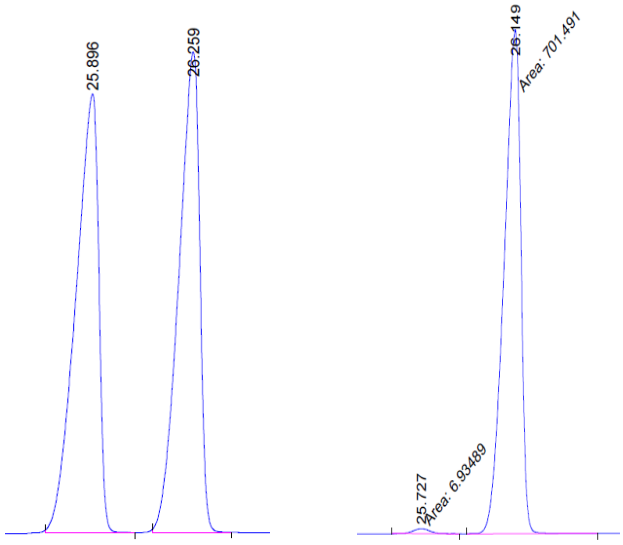


(*R*,*Z*)-3-methylpent-2-ene-1,4-diol (Table 3, entry 5). R_f = 0.16 (2:1 EtOAc:hexane, PMA) Prepared according to the general procedure using (*E*)-3-methylpenta-1,3-diene (60.0 mg, 0.697 mmol), $Pt(dba)_3$ (19.7 mg, 20.9 μmol), (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane (0.48 mL, 0.0916 M, 42 μmol), $B_2(pin)_2$ (195.0 mg, 0.732 mmol), and toluene (7.0 mL). Crude material was purified (SiO_2, 50-100% ethyl acetate in hexanes) to give the product as a colorless residue (65.4 mg, 81%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.24 (3H, d, *J* = 6.6 Hz), 1.74 (3H, s), 3.06 (2H, br s), 4.01 (1H, dd, *J* = 12.3 Hz, 6.1 Hz), 4.23 (1H, dd, *J* = 12.5 Hz, 8.3 Hz), 4.70 (1H, q, *J* = 6.6 Hz), 5.45 (1H, t, *J* = 7.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.9, 21.1, 57.6, 65.5, 124.8, 142.7; IR (neat): 3320.3 (br), 2972.2 (m), 2922.4 (w), 1437.8 (w), 1371.0 (w), 1101.1 (m), 1067.8 (s), 1025.2 (s), 986.0 (s) cm^{-1}; HRMS-(ESI+) for $C_6H_{16}NO_2$ [M+NH_4]: calculated: 134.1181, found: 134.1177. $[\alpha]_D^{20}$ = -6.406 (*c* = 0.714, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The resulting 1,4-diol was converted to the corresponding bis acetate as shown above. The racemic compound was prepared through a diboration/oxidation sequence utilizing PCy_3 as ligand, followed by conversion to the corresponding racemic diacetate.

Chiral GLC (β-dex, Supelco, 90 °C for 5 min, ramp 2 °C/min to 180 °C, 20 psi) – analysis of the diacetate of (Z)-3-methylpent-2-ene-1,4-diol.

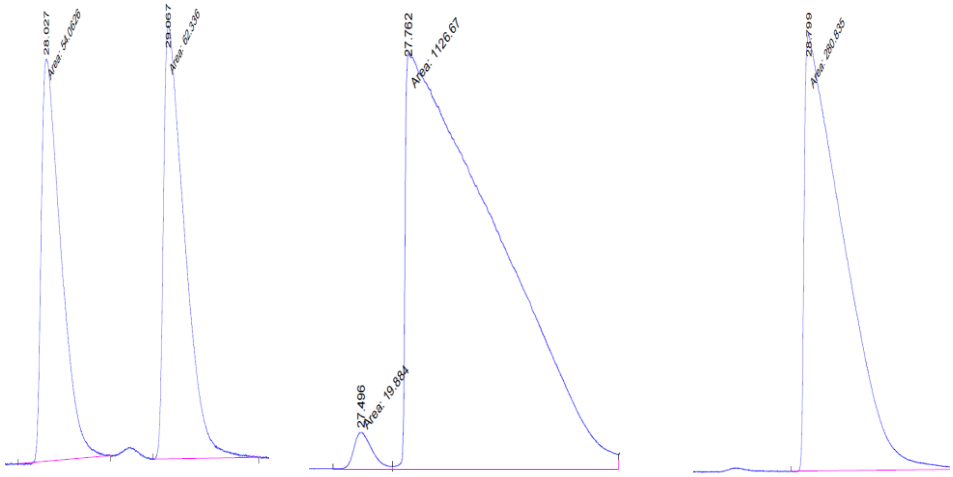


racemic reaction product

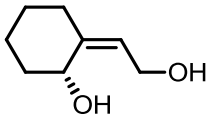
Proof of absolute stereochemistry:

The 1,4-diol was converted to 2,3-butanediol through ozonolysis/reduction as described above. The 2,3-diol was then directly analyzed by GLC. Racemic 2,3-butanediol and (2*R*,3*R*)-2,3-butanediol were purchased from Aldrich and were compared to the reaction product

Chiral GLC (β-dex, Supelco, 50 °C, ramp 1 °C/min to 160 °C, 20 psi) – analysis of 2,3-butanediol.



racemic reaction product authentic

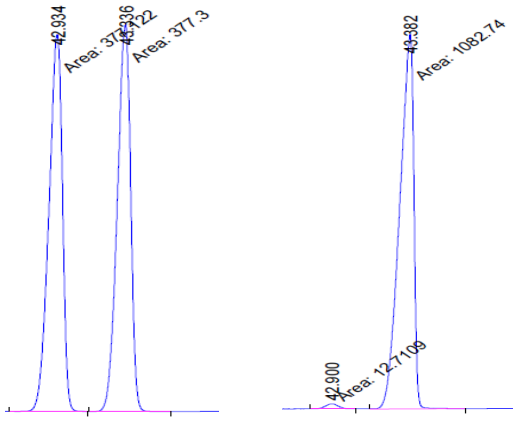


(*R*,*Z*)-2-(2-hydroxyethylidene)cyclohexanol (Table 3, entry 6). R_f = 0.12 (50% EtOAc in hexane, PMA) Prepared according to the general procedure using 1-vinylcyclohex-1-ene (60.0 mg, 0.555 mmol), $Pt(dba)_3$ (14.9 mg, 16.6 μmol), (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane (0.46 mL, 0.0718 M, 33 μmol), $B_2(pin)_2$ (147.9 mg, 0.582 mmol), and toluene (5.6 mL). Crude material was purified (SiO_2, 50-100% ethyl acetate in hexanes) to give the product as a colorless residue (76.0 mg, 96%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.33-1.42 (1H, m), 1.47-1.60 (2H, m), 1.67-1.87 (3H, m), 2.01 (1H, app dt, *J* = 13.5 Hz, 4.3 Hz), 2.43 (1H, app dt, *J* = 12.5 Hz, 3.9 Hz), 2.90 (2H, br s), 4.05 (1H, dd, *J* = 12.1 Hz, 6.2 Hz), 4.27 (1H, dd, *J* = 12.1 Hz, 8.1 Hz), 4.64 (1H, t, *J* = 3.4 Hz), 5.46 (1H, t, *J* = 7.1 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 21.8, 27.7, 32.9, 34.5, 57.5, 66.4, 122.4, 145.0; IR (neat): 3294.6 (br), 2929.1 (s), 2858.7 (m), 1435.9 (w), 1095.6 (w), 1061.6 (w), 991.2 (s), 975.4 (s) cm^{-1}; HRMS-(ESI+) for $C_8H_{18}NO_2$ [M+NH_4]: calculated: 160.1338, found: 160.1337. $[\alpha]_D^{20}$ = -127 (*c* = 0.318, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The resulting 1,4-diol was converted to the corresponding diacetate as shown above. The racemic compound was prepared through a diboration/oxidation sequence utilizing PCy_3 as ligand.

Chiral GLC (β-dex, Supelco, 90 °C for 5 min, ramp 2 °C/min to 180 °C, 20 psi) – analysis of the diacetate of (Z)-2-(2-hydroxyethylidene)cyclohexanol.

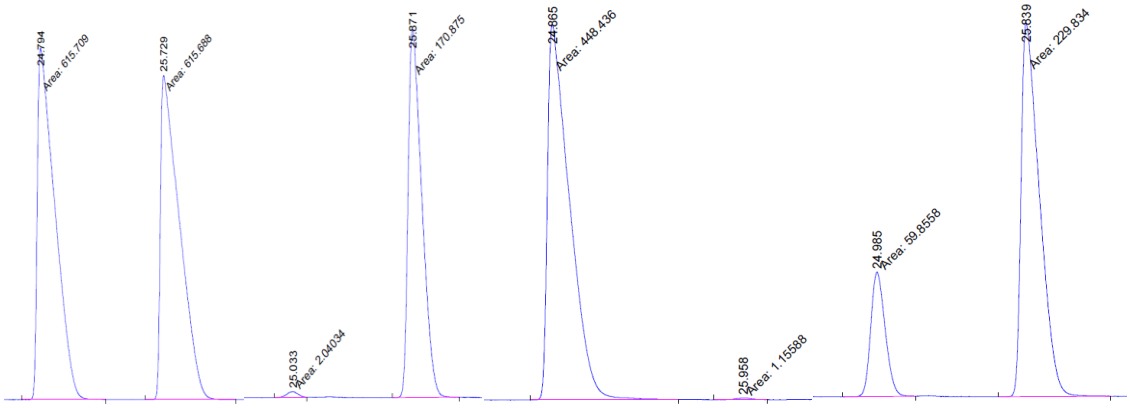


racemic reaction product

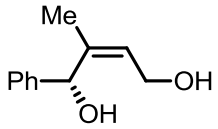
Proof of absolute stereochemistry:

The 1,4-diol was converted to 1,2-cyclohexanediol through ozonolysis/reduction as described above. The 1,2-diol was then treated with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid to afford the corresponding acetonide. The racemic sample was prepared through treatment of racemic (*trans*)-1,2-cyclohexanediol with 2,2-dimethoxypropane and *p*-toluenesulfonic acid. The authentic sample was prepared from (1*S*,2*S*)-*trans*-cyclohexanediol purchased from Fluka.

Chiral GLC (β-dex, Supelco, 60 °C for 5 min, ramp 2 °C/min to 160 °C, 20 psi) – analysis of the acetonide of trans-1,2-cyclohexanediol.



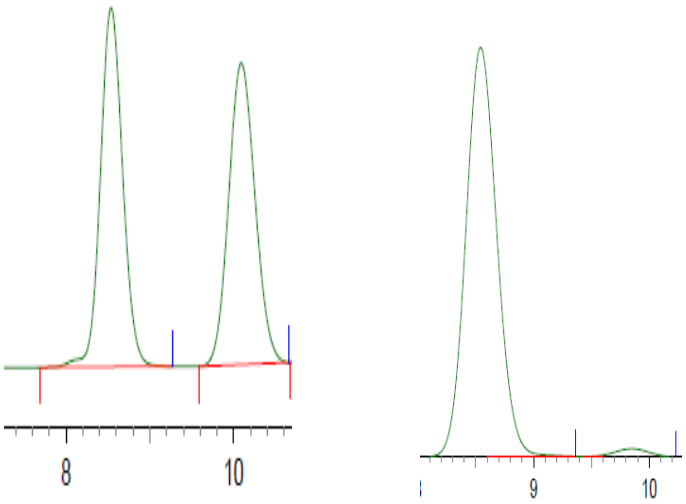
racemic reaction product authentic coinjection of reaction product + racemic



(*S,Z*)-2-methyl-1-phenylbut-2-ene-1,4-diol (Table 3, entry 7). R_f = 0.28 (50% EtOAc in hexane, PMA) Prepared according to the general procedure using (*E*)-(2-methylbuta-1,3-dien-1-yl)benzene (35.0 mg, 0.243 mmol), $Pt(dba)_3$ (6.5 mg, 7.3 μmol), (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane (0.18 mL, 0.0801 M, 15 μmol), $B_2(pin)_2$ (64.8 mg, 0.255 mmol), and toluene (2.4 mL) to afford an inseparable 1:2.4 mixture of the 1,2- and 1,4-dihydroxylation prodcuts. To facilitate purification, the crude reaction mixture was dissolved in THF:Et_2O:H_2O (1:1:1) and $NaIO_4$ (4 equiv) was added at room temperature (oxidative cleavage of both the 1,2-diboration product and pinacol). The reaction mixture was stirred for 2 h, after which time it was diluted with ethyl acetate, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and the solvent was removed under reduced pressure. The crude material was purified (SiO_2, 40-60% ethyl acetate in hexanes) to give the product as a colorless oil (26.3 mg, 61%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.63 (3H, s), 2.16-3.20 (2H, br s), 4.23 (1H, ddd, *J* = 12.5 Hz, 6.4 Hz, 1.0 Hz), 4.42 (1H, dd, *J* = 12.5 Hz, 8.1 Hz), 5.64 (1H, t, *J* = 6.9 Hz), 5.68 (1H, s), 7.24-7.28 (1H, m), 7.32-7.37 (4H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 18.5, 58.3, 71.6, 125.7, 126.3, 127.3, 128.3, 141.3, 141.8; IR (neat): 3324.1 (br), 3028.2 (w), 2921.8 (m), 1493.4 (w), 1449.8 (m), 1007.0 (s), 735.1 (m), 699.6 (s) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{18}NO_2$ [M+NH_4]: calculated: 196.1338, found: 196.1342. $[\alpha]_D^{20}$ = +119 (*c* = 0.400, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

Chiral HPLC (Chiracel OD-R, 10% isopropanol, 1.0 mL/min, 220 nm) – analysis of (Z)-2-methyl-1-phenylbut-2-ene-1,4-diol

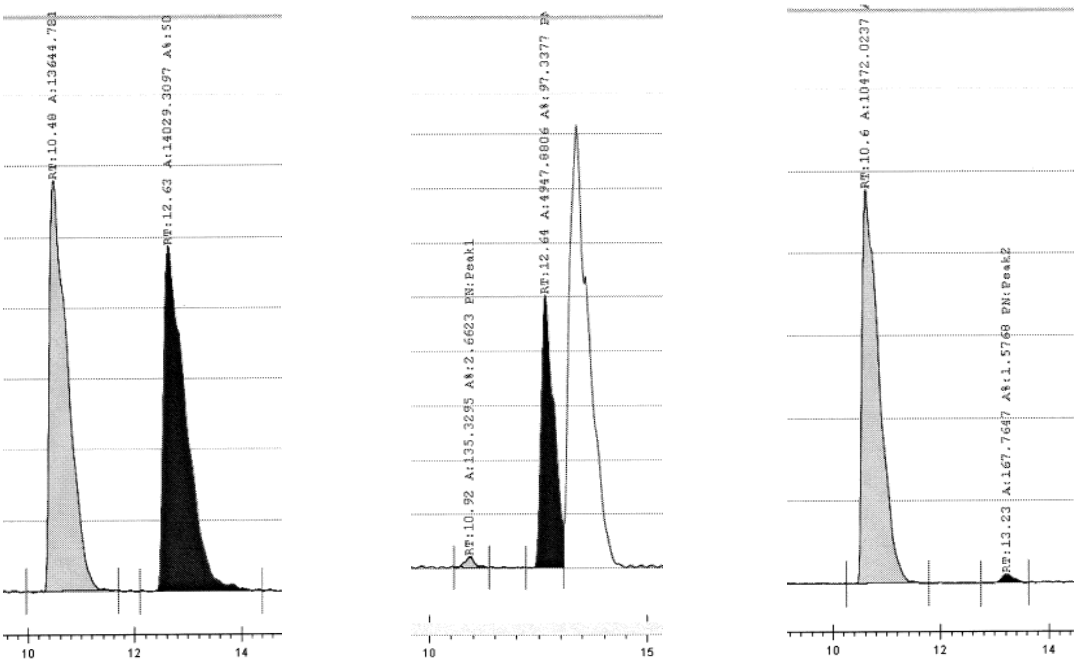


racemic reaction product

Proof of Stereochemistry:

The 1,4-diol was converted to 1-phenylpropane-1,2-diol through ozonolysis/reduction as described above. The racemic diol was prepared through dihydroxylation of (*trans*)-*β*-methylstyrene with osmium tetraoxide and 4-methylmorpholine N-oxide. The authentic sample was prepared from the Sharpless asymmetric dihydroxylation of (*trans*)-*β*-methylstyrene utilizing AD-mix α.[106]

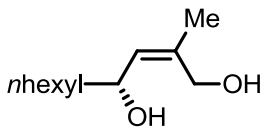
Chiral SFC (Diacel,OD-H, 35 °C, 5 mL/min, 5% MeOH, 100 bar, 210-270nm) – analysis of 1-phenylpropane-1,2-diol.



racemic (syn diol) reaction product authentic (syn diol)

(mixture of syn and anti diols)

[106] Norrby, P-O.; Becker, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1996**, *118*, 35.

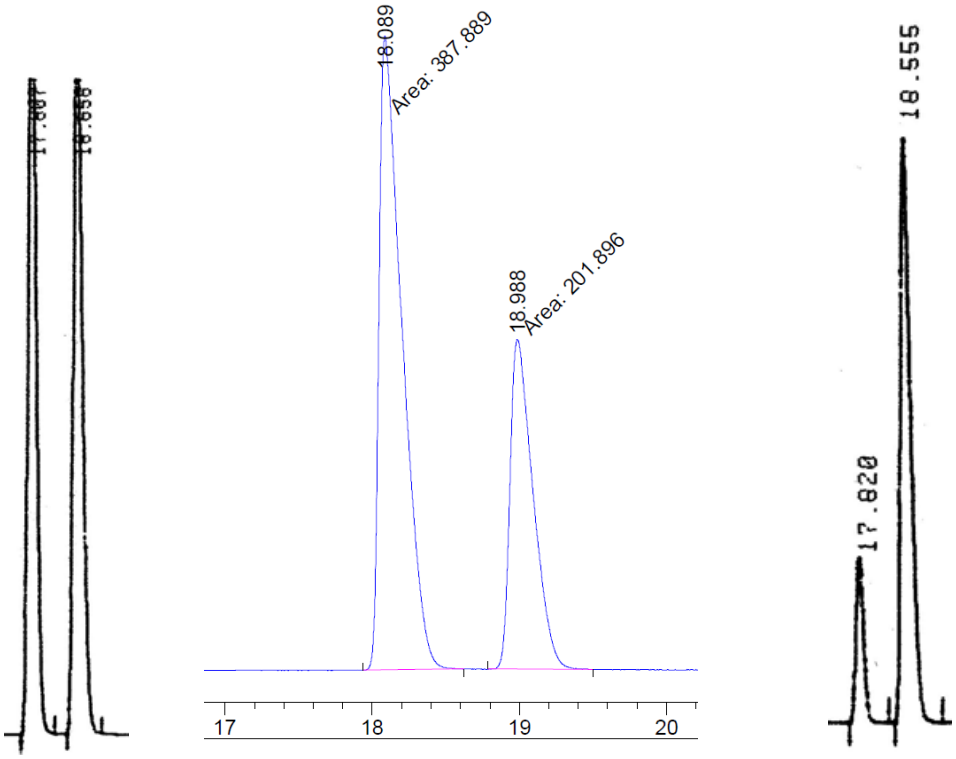


(*R*,*Z*)-2-methyldec-2-ene-1,4-diol. R_f = 0.29 (50% EtOAc in hexane, PMA) Prepared according to the general procedure using (*E*)-2-methyldeca-1,3-diene (35.0 mg, 0.230 mmol), $Pt(dba)_3$ (6.2 mg, 6.9 μmol), (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane (0.19 mL, 0.0718 M, 14 μmol), $B_2(pin)_2$ (77.1 mg, 0.303 mmol), and toluene (2.3 mL). Crude material was purified (SiO_2, 40-70% ethyl acetate in hexanes) to give the product as a colorless residue (39.2 mg, 92%). Spectral data are in accordance with the literature.[107]

[107] Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134.

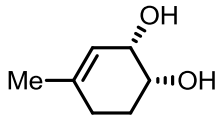
Proof of Stereochemistry:

The resulting 1,4-diol was subjected to ozonolysis and reduction as described above. The 1,2-diol was then treated with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid to afford the corresponding ketal. The racemic ketal was prepared through dihydroxylation of 1-octene with osmium tetraoxide and 4-methylmorpholine N-oxide. The authentic sample was prepared from the Sharpless asymmetric dihydroxylation of 1-octene utilizing AD-mix α.[108]



racemic reaction product authentic

[108] Jacobsen, E. N.; Markd, I; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. *J. Am. Chem. Soc.*, **1988**, *110*, 1968.



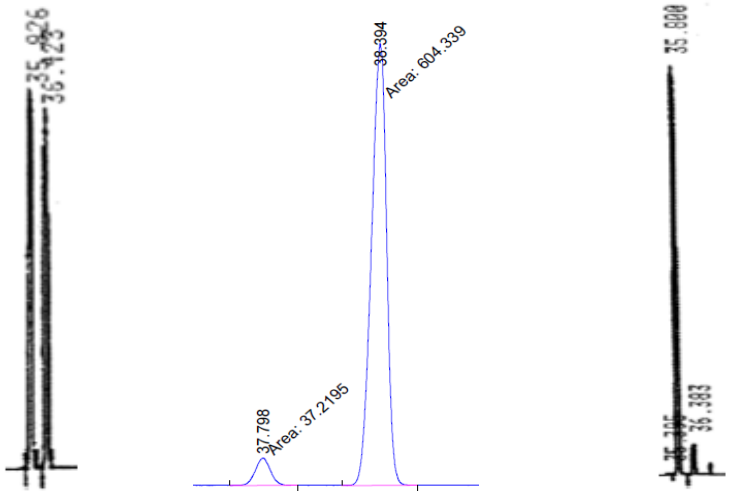
(1*R*,2*S*)-4-methylcyclohex-3-ene-1,2-diol. R_f = 0.10 (50% EtOAc in hexane, PMA) Prepared according to the general procedure using 1-methylcyclohexa-1,3-diene (35.0 mg, 0.372 mmol), $Pt(dba)_3$ (10.1 mg, 11.2 μmol), (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane (0.24 mL, 0.0916M, 22 μmol), $B_2(pin)_2$ (99.2 mg, 0.391 mmol), and toluene (3.7 mL). Crude material was purified (SiO_2, 50-100 % ethyl acetate in hexanes) to give the product as a white solid (45.2 mg, 95% yield of inseparable mixture of 1,2- and 1,4-product). Spectral data are in accordance with the literature.[109] HRMS-(ESI+) for $C_7H_{16}NO_2$ [M+NH_4]: calculated: 146.1181, found: 146.1179. $[\alpha]_D^{20}$ = -27.2 (*c* = 0.282, $CHCl_3$, *l* = 50 mm).

[109] Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134.

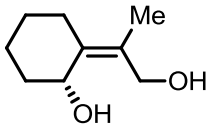
Proof of Stereochemistry:

The resulting 1,2-diol was converted to the corresponding diacetate as shown above. The racemic compound was prepared through a diboration/oxidation sequence utilizing PCy_3 as ligand. The authentic sample was prepared through diboration/oxidation of 1-methyl-1,3-cyclohexadiene, using (*S*,*S*) TADDOL ligand.[20]

Chiral GLC (β-dex, Supelco, 90 °C for 5 min, ramp 2 °C/min to 160 °C, 20 psi) – analysis of the diacetate of 4-methylcyclohex-3-ene-1,2-diol.



racemic reaction product authentic

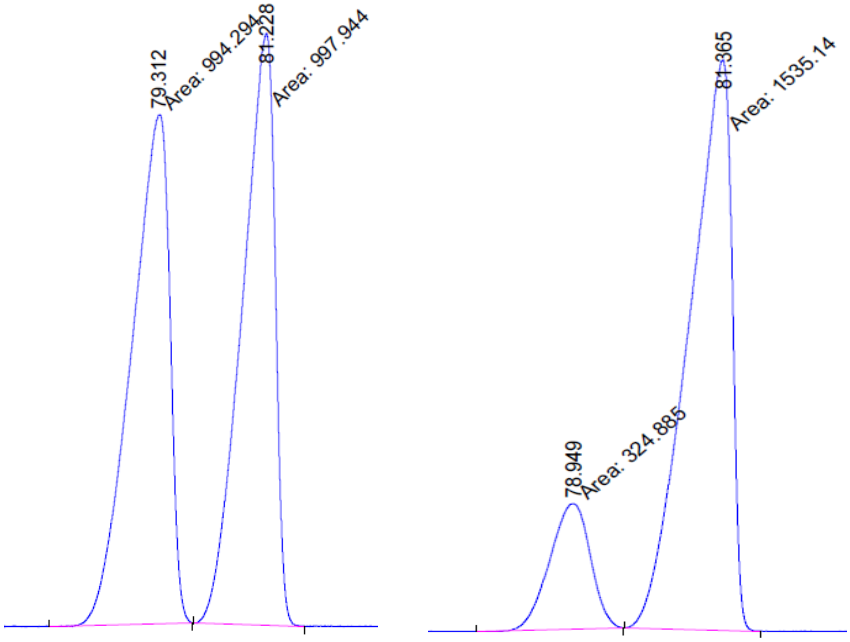


(*R*,*Z*)-2-(1-hydroxypropan-2-ylidene)cyclohexanol. R_f = 0.16 (50% EtOAc in hexane, PMA) Prepared according to the general procedure using 1-(prop-1-en-2-yl)cyclohex-1-ene (35.0 mg, 0.286 mmol), $Pt(dba)_3$ (7.7 mg, 8.6 μmol), (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane (0.19 mL, 0.0916 M, 17 μmol), $B_2(pin)_2$ (76.3 mg, 0.300 mmol), and toluene (2.9 mL). Crude material was purified (SiO_2, 45-90% ethyl acetate in hexanes) to give the product as a colorless residue (36.7 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20-1.28 (1H, m), 1.43-1.52 (2H, m), 1.77 (3H, d, *J* = 1.5 Hz), 1.71-1.82 (2H, m), 1.89-1.95 (1H, m), 2.19 (1H, app dt, *J* = 13.6 Hz, 3.2 Hz), 2.42 (1H, app dt, *J* = 14.2 Hz, 3.4 Hz), 2.79 (2H, br s), 3.90 (1H, d, *J* = 11.5 Hz), 4.37 (1H, d, *J* = 11.5 Hz), 4.83 (1H, t, *J* = 2.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 17.1, 20.1, 25.4, 26.7, 34.0, 62.5, 65.9, 128.4, 138.0; IR (neat): 3321.3 (br), 2930.7 (s), 2856.6 (m), 1445.2 (w), 1072.4 (w), 985.5 (s), 959.1 (m) cm^{-1}; HRMS-(ESI+) for $C_9H_{15}O$ [M+H-H_2O]: calculated: 139.1123, found: 139.1126. $[\alpha]_D^{20}$ = -50.1 (*c* = 0.646, $CHCl_3$, *l* = 50 mm)

Analysis of Stereochemistry:

The resulting 1,4-diol was converted to the corresponding diacetate as shown above. The racemic compound was prepared through a diboration/oxidation sequence utilizing PCy_3 as ligand.

Chiral GLC (β-dex, Supelco, 125 °C, 20 psi) – analysis of the diacetate of (Z)-2-(1-hydroxypropan-2-ylidene)cyclohexanol.

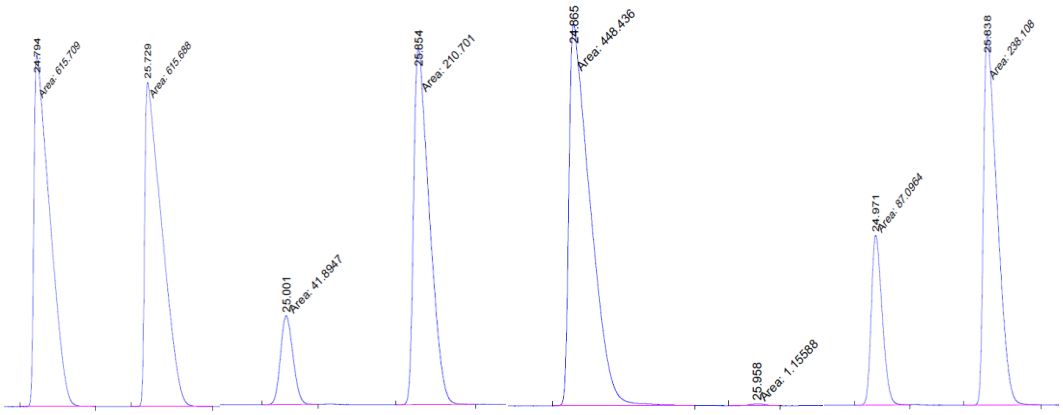


racemic reaction product

Proof of absolute stereochemistry:

The 1,4 diol was converted to 1,2-hexanediol through ozonolysis/reduction as described above. The 1,2-diol was then treated with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid to afford the corresponding acetonide. The racemic sample was prepared through treatment of racemic (*trans*)-1,2-cyclohexanediol with 2,2-dimethoxypropane and *p*-toluenesulfonic acid. The authentic sample was prepared from (1*S*,2*S*)-*trans*-cyclohexanediol purchased from Fluka.

Chiral GLC (β-dex, Supelco, 60 °C for 5 min, ramp 2 °C/min to 160 °C, 20 psi) – analysis of the acetonide of trans-1,2-cyclohexanediol.



racemic reaction product authentic product coinjection of reaction product + racemic

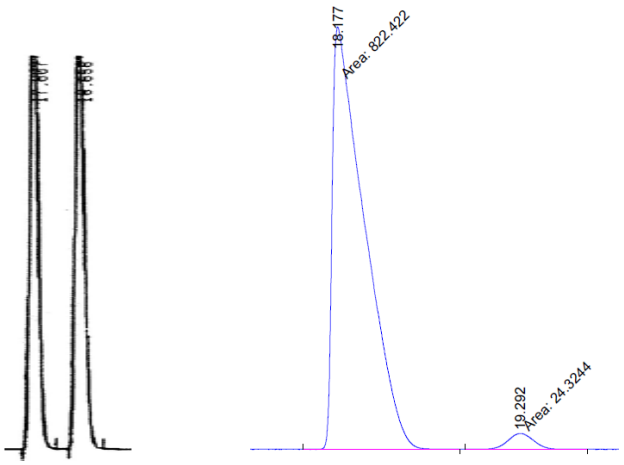
1.5.2.9 Procedure for Low Catalyst Loading

A 20 mL flame-dried scintillation vial with magnetic stir bar in the dry box was charged with $Pt(dba)_3$ as a solution in tetrahydrofuran (11.1 mM, 65 μL), followed by the addition of toluene (sparged with nitrogen, 3.5 mL). (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane was then added as a solution in toluene (19.7 mM, 73 μL), followed by $B_2(pin)_2$ (964.5 mg, 3.78 mmol). The vial was sealed, removed from the dry box and heated to 80 ^oC for 25 minutes, during which the reaction mixture changed from a light purple solution to a very light yellow solution. After cooling to room temperature, the vial was returned to the dry box and *trans*-1,3-decadiene (sparged with nitrogen, 0.500 g, 3.62 mmol) was added. The vial was sealed, removed from the dry box, and heated to 60 ^oC for 18 hours. The reaction was transferred to a 100 mL round-bottom flask, cooled to 0 ^oC, diluted with tetrahydrofuran (30 mL), and water (10 mL), then treated with 3M aqueous NaOH (4.5 mL) and H_2O_2 (30 wt % in H_2O, 3.5 mL). The flask was warmed slowly to room temperature and stirred for 7 hours, after which the reaction was again cooled to 0 ^oC and carefully treated with saturated aqueous sodium thiosulfate (7 mL). The reaction mixture was diluted with ethyl acetate (50 mL) and water (20 mL) and the layers separated. The aqueous layer was extracted with additional ethyl acetate (4 x 40 mL) and the combined organic layers were dried over sodium sulfate followed by removal of the solvent under reduced pressure. The crude material was purified (SiO_2, 40-70% ethyl acetate in hexanes) to give the product as a colorless oil (594 mg, 95%).

Proof of Stereochemistry:

The resulting 1,4-diol was subjected to ozonolysis and reduction as described above. The 1,2-diol was then treated with 2,2-dimethoxypropane and a catalytic amount of *p*-toluenesulfonic acid to afford the corresponding ketal. The racemic ketal was prepared through dihydroxylation of 1-octene with osmium tetraoxide and 4-methylmorpholine N-oxide.

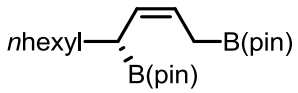
Chiral GLC (β-dex, Supelco, 100 ℃, 20 psi) – analysis of the acetonide of octane-1,2-diol.



racemic reaction product

1.5.2.10 Preparation and Isolation of Diboron Adduct of trans-1,3-decadiene

A 20 mL flame-dried scintillation vial equipped with magnetic stir bar in the dry box was charged with $Pt(dba)_3$ (3.2 mg, 3.6 μmol), followed by the addition of toluene (1.5 mL). (3*R*,5*R*)-5-(*tert*-butyl)-2,2-diisobutyl-3-phenyl-1,3-oxaphospholane was then added as a solution in toluene (0.0197 M, 0.20 mL), followed by $B_2(pin)_2$ (92.0 mg, 0.362 mmol). The vial was then sealed, removed from the dry box and heated to 80 ^oC for 20 minutes, during which the reaction mixture changes from a dark purple solution to a light yellow solution. After cooling to room temperature, the vial was returned to the dry box and (*E*)-deca-1,3-diene (50.0 mg, 0.362 mmol) was added. The vial was sealed, removed from the dry box, and heated to 60 ^oC for 5 hours. After cooling to room temperature, the reaction mixture was then passed through a plug of SiO_2 (10% ethyl acetate in hexane). The resulting clear, slightly yellow solution was concentrated under reduced pressure to give the product as a clear, slightly yellow oil (138.6 mg, 98%).



(*R*,*Z*)-2,2'-(dec-2-ene-1,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). R_f = 0.51 (10% EtOAc in hexane, PMA) ^1H NMR (500 MHz, $CDCl_3$): δ 0.86 (1H, t, *J* = 7.1 Hz), 1.21 (6H, s), 1.22 (6H, s), 1.23 (12H, s), 1.23-1.30 (7H, m), 1.30-1.38 (2H, m), 1.49-1.56 (1H, m), 1.61 (1H, ddd, *J* = 16.1, 7.3, 1.5 Hz), 1.71 (1H, ddd, *J* = 16.1, 8.3, 1.5 Hz), 2.03 (1H, q, *J* = 7.3 Hz), 5.30 (1H, app tt, *J* = 10.3, 1.7 Hz), 5.44-5.49 (1H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.1, 22.6, 24.6, 24.7, 24.8, 24.8, 29.2, 29.4, 31.3, 31.8, 82.8, 83.0, 123.2, 130.8; IR (neat): 2977.4 (m), 2924.8 (m), 2854.7 (w), 1466.8 (w), 1348.9 (s), 1317.5 (s), 1142.0 (s), 968.1

(m), 848.9 (m) cm^{-1}; HRMS-(ESI+) for $C_{22}H_{43}B_2O_4$ [M+H]: calculated: 393.3347, found: 393.3345. $[\alpha]_D^{20}$ = -37.4 (*c* = 0.596, $CHCl_3$, *l* = 50 mm).

1.5.2.11 X-ray Crystal Structure Data

Figure 1.10: Structure of Phosphine Oxide 1.186 (hydrogens omitted for clarity)

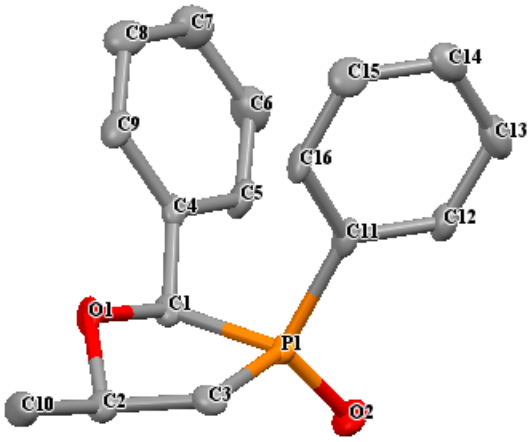


Table 1. Crystal data and structure refinement for sad.

Identification code	C16H17O2P	
Empirical formula	C16 H17 O2 P	
Formula weight	272.27	
Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Triclinic	
Space group	P 1	
Unit cell dimensions	a = 6.131(3) Å	α= 87.618(6)°.
	b = 8.576(4) Å	β= 86.207(6)°.
	c = 14.381(7) Å	γ = 75.072(6)°.
Volume	728.8(6) $Å^3$	
Z	2	
Density (calculated)	1.241 Mg/m^3	
Absorption coefficient	0.184 mm^{-1}	
F(000)	288	
Crystal size	0.09 x 0.02 x 0.02 mm^3	
Theta range for data collection	2.46 to 25.99°.	

Index ranges	-7<=h<=7, -10<=k<=10, -17<=l<=17
Reflections collected	7877
Independent reflections	5482 [R(int) = 0.0495]
Completeness to theta = 25.99°	98.8 %
Absorption correction	Semi-empirical from equivalents
Max. and min. transmission	0.9963 and 0.9837
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	5482 / 321 / 345
Goodness-of-fit on F^2	1.062
Final R indices [I>2sigma(I)]	R1 = 0.0780, wR2 = 0.1674
R indices (all data)	R1 = 0.1043, wR2 = 0.1806
Absolute structure parameter	-0.02(15)
Extinction coefficient	na
Largest diff. peak and hole	0.749 and -0.429 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for sad. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P(1)	-524(2)	8186(2)	7142(1)	17(1)
O(1)	2611(6)	5560(4)	7601(3)	20(1)
O(2)	-2824(6)	8484(5)	6768(3)	28(1)
C(1)	292(9)	6299(6)	7895(4)	19(1)
C(2)	2841(9)	5706(6)	6589(4)	20(1)
C(3)	1945(9)	7524(6)	6337(4)	19(1)
C(4)	-43(9)	6512(6)	8917(4)	18(1)
C(5)	-2309(9)	7044(6)	9320(4)	23(1)
C(6)	-2690(10)	7304(7)	10251(4)	32(1)
C(7)	-916(11)	7016(8)	10854(4)	32(1)
C(8)	1306(10)	6497(7)	10468(4)	28(1)
C(9)	1723(9)	6256(6)	9515(4)	20(1)
C(10)	5326(9)	5014(7)	6285(4)	26(1)
C(11)	-240(9)	9836(6)	7813(4)	19(1)
C(12)	-2128(9)	11136(6)	7978(4)	21(1)
C(13)	-2055(10)	12416(7)	8517(4)	28(1)

C(14)	-24(11)	12428(7)	8917(4)	28(1)
C(15)	1920(10)	11123(7)	8750(4)	27(1)
C(16)	1808(9)	9881(6)	8201(4)	19(1)
P(2)	281(2)	11790(2)	2863(1)	21(1)
O(3)	3440(6)	9975(5)	1757(3)	24(1)
O(4)	-2251(6)	12430(5)	2894(3)	31(1)
C(17)	1380(8)	9830(6)	2237(4)	19(1)
C(18)	2994(9)	11576(7)	1319(4)	25(1)
C(19)	1992(10)	12811(7)	2082(4)	27(1)
C(20)	1725(8)	8331(6)	2851(4)	20(1)
C(21)	-162(9)	8006(7)	3387(4)	27(1)
C(22)	103(10)	6657(8)	3956(4)	32(1)
C(23)	2216(11)	5549(7)	4012(4)	28(1)
C(24)	4067(10)	5840(7)	3486(4)	29(1)
C(25)	3826(9)	7189(7)	2913(4)	23(1)
C(26)	5230(10)	11805(8)	855(4)	34(2)
C(27)	1388(9)	11589(6)	4005(4)	18(1)
C(28)	-48(9)	12082(6)	4784(4)	20(1)
C(29)	778(10)	11938(7)	5666(4)	24(1)
C(30)	3076(9)	11299(6)	5779(4)	22(1)
C(31)	4547(9)	10774(7)	5012(4)	24(1)
C(32)	3751(9)	10957(7)	4129(4)	23(1)

Table 3. Bond lengths [Å] and angles [°] for sad.

P(1)-O(2)	1.498(4)
P(1)-C(11)	1.796(6)
P(1)-C(3)	1.826(5)
P(1)-C(1)	1.885(6)
O(1)-C(1)	1.443(6)
O(1)-C(2)	1.457(6)
C(1)-C(4)	1.483(7)
C(1)-H(1A)	1.0000
C(2)-C(10)	1.527(7)
C(2)-C(3)	1.550(7)
C(2)-H(2B)	1.0000

C(3)-H(3A)	0.9900
C(3)-H(3B)	0.9900
C(4)-C(9)	1.394(7)
C(4)-C(5)	1.436(7)
C(5)-C(6)	1.362(8)
C(5)-H(5A)	0.9500
C(6)-C(7)	1.401(9)
C(6)-H(6A)	0.9500
C(7)-C(8)	1.403(8)
C(7)-H(7A)	0.9500
C(8)-C(9)	1.392(8)
C(8)-H(8A)	0.9500
C(9)-H(9A)	0.9500
C(10)-H(10A)	0.9800
C(10)-H(10B)	0.9800
C(10)-H(10C)	0.9800
C(11)-C(12)	1.400(7)
C(11)-C(16)	1.417(7)
C(12)-C(13)	1.382(8)
C(12)-H(12A)	0.9500
C(13)-C(14)	1.407(9)
C(13)-H(13A)	0.9500
C(14)-C(15)	1.424(9)
C(14)-H(14A)	0.9500
C(15)-C(16)	1.371(8)
C(15)-H(15A)	0.9500
C(16)-H(16A)	0.9500
P(2)-O(4)	1.506(4)
P(2)-C(27)	1.804(5)
P(2)-C(19)	1.834(6)
P(2)-C(17)	1.884(5)
O(3)-C(17)	1.430(6)
O(3)-C(18)	1.454(7)
C(17)-C(20)	1.506(7)
C(17)-H(17A)	1.0000
C(18)-C(26)	1.539(8)

C(18)-C(19)	1.542(8)
C(18)-H(18A)	1.0000
C(19)-H(19A)	0.9900
C(19)-H(19B)	0.9900
C(20)-C(25)	1.408(7)
C(20)-C(21)	1.428(7)
C(21)-C(22)	1.370(9)
C(21)-H(21A)	0.9500
C(22)-C(23)	1.400(9)
C(22)-H(22A)	0.9500
C(23)-C(24)	1.393(8)
C(23)-H(23A)	0.9500
C(24)-C(25)	1.374(8)
C(24)-H(24A)	0.9500
C(25)-H(25A)	0.9500
C(26)-H(26A)	0.9800
C(26)-H(26B)	0.9800
C(26)-H(26C)	0.9800
C(27)-C(28)	1.388(7)
C(27)-C(32)	1.430(7)
C(28)-C(29)	1.386(8)
C(28)-H(28A)	0.9500
C(29)-C(30)	1.392(8)
C(29)-H(29A)	0.9500
C(30)-C(31)	1.391(8)
C(30)-H(30A)	0.9500
C(31)-C(32)	1.378(8)
C(31)-H(31A)	0.9500
C(32)-H(32A)	0.9500

O(2)-P(1)-C(11)	112.3(2)
O(2)-P(1)-C(3)	118.3(2)
C(11)-P(1)-C(3)	110.3(2)
O(2)-P(1)-C(1)	114.0(2)
C(11)-P(1)-C(1)	107.3(2)
C(3)-P(1)-C(1)	92.7(2)

C(1)-O(1)-C(2)	108.2(4)
O(1)-C(1)-C(4)	112.7(4)
O(1)-C(1)-P(1)	104.7(3)
C(4)-C(1)-P(1)	116.5(4)
O(1)-C(1)-H(1A)	107.5
C(4)-C(1)-H(1A)	107.5
P(1)-C(1)-H(1A)	107.5
O(1)-C(2)-C(10)	108.0(4)
O(1)-C(2)-C(3)	106.4(4)
C(10)-C(2)-C(3)	113.6(4)
O(1)-C(2)-H(2B)	109.6
C(10)-C(2)-H(2B)	109.6
C(3)-C(2)-H(2B)	109.6
C(2)-C(3)-P(1)	103.7(3)
C(2)-C(3)-H(3A)	111.0
P(1)-C(3)-H(3A)	111.0
C(2)-C(3)-H(3B)	111.0
P(1)-C(3)-H(3B)	111.0
H(3A)-C(3)-H(3B)	109.0
C(9)-C(4)-C(5)	117.6(5)
C(9)-C(4)-C(1)	123.8(5)
C(5)-C(4)-C(1)	118.6(5)
C(6)-C(5)-C(4)	120.5(5)
C(6)-C(5)-H(5A)	119.7
C(4)-C(5)-H(5A)	119.7
C(5)-C(6)-C(7)	121.8(6)
C(5)-C(6)-H(6A)	119.1
C(7)-C(6)-H(6A)	119.1
C(6)-C(7)-C(8)	118.1(6)
C(6)-C(7)-H(7A)	121.0
C(8)-C(7)-H(7A)	121.0
C(9)-C(8)-C(7)	120.7(6)
C(9)-C(8)-H(8A)	119.7
C(7)-C(8)-H(8A)	119.7
C(8)-C(9)-C(4)	121.3(5)
C(8)-C(9)-H(9A)	119.4

C(4)-C(9)-H(9A)	119.4
C(2)-C(10)-H(10A)	109.5
C(2)-C(10)-H(10B)	109.5
H(10A)-C(10)-H(10B)	109.5
C(2)-C(10)-H(10C)	109.5
H(10A)-C(10)-H(10C)	109.5
H(10B)-C(10)-H(10C)	109.5
C(12)-C(11)-C(16)	117.8(5)
C(12)-C(11)-P(1)	119.0(4)
C(16)-C(11)-P(1)	123.1(4)
C(13)-C(12)-C(11)	122.2(5)
C(13)-C(12)-H(12A)	118.9
C(11)-C(12)-H(12A)	118.9
C(12)-C(13)-C(14)	119.4(5)
C(12)-C(13)-H(13A)	120.3
C(14)-C(13)-H(13A)	120.3
C(13)-C(14)-C(15)	119.2(5)
C(13)-C(14)-H(14A)	120.4
C(15)-C(14)-H(14A)	120.4
C(16)-C(15)-C(14)	120.1(6)
C(16)-C(15)-H(15A)	120.0
C(14)-C(15)-H(15A)	120.0
C(15)-C(16)-C(11)	121.2(5)
C(15)-C(16)-H(16A)	119.4
C(11)-C(16)-H(16A)	119.4
O(4)-P(2)-C(27)	112.5(2)
O(4)-P(2)-C(19)	118.2(3)
C(27)-P(2)-C(19)	108.4(3)
O(4)-P(2)-C(17)	114.4(2)
C(27)-P(2)-C(17)	109.4(2)
C(19)-P(2)-C(17)	92.1(3)
C(17)-O(3)-C(18)	107.2(4)
O(3)-C(17)-C(20)	112.0(4)
O(3)-C(17)-P(2)	104.5(3)
C(20)-C(17)-P(2)	115.2(3)
O(3)-C(17)-H(17A)	108.3

C(20)-C(17)-H(17A)	108.3
P(2)-C(17)-H(17A)	108.3
O(3)-C(18)-C(26)	108.2(4)
O(3)-C(18)-C(19)	107.6(4)
C(26)-C(18)-C(19)	112.7(5)
O(3)-C(18)-H(18A)	109.4
C(26)-C(18)-H(18A)	109.4
C(19)-C(18)-H(18A)	109.4
C(18)-C(19)-P(2)	104.1(4)
C(18)-C(19)-H(19A)	110.9
P(2)-C(19)-H(19A)	110.9
C(18)-C(19)-H(19B)	110.9
P(2)-C(19)-H(19B)	110.9
H(19A)-C(19)-H(19B)	109.0
C(25)-C(20)-C(21)	117.3(5)
C(25)-C(20)-C(17)	123.4(5)
C(21)-C(20)-C(17)	119.3(5)
C(22)-C(21)-C(20)	120.6(5)
C(22)-C(21)-H(21A)	119.7
C(20)-C(21)-H(21A)	119.7
C(21)-C(22)-C(23)	120.9(6)
C(21)-C(22)-H(22A)	119.5
C(23)-C(22)-H(22A)	119.5
C(24)-C(23)-C(22)	119.1(6)
C(24)-C(23)-H(23A)	120.4
C(22)-C(23)-H(23A)	120.4
C(25)-C(24)-C(23)	120.6(5)
C(25)-C(24)-H(24A)	119.7
C(23)-C(24)-H(24A)	119.7
C(24)-C(25)-C(20)	121.4(5)
C(24)-C(25)-H(25A)	119.3
C(20)-C(25)-H(25A)	119.3
C(18)-C(26)-H(26A)	109.5
C(18)-C(26)-H(26B)	109.5
H(26A)-C(26)-H(26B)	109.5
C(18)-C(26)-H(26C)	109.5

H(26A)-C(26)-H(26C)	109.5
H(26B)-C(26)-H(26C)	109.5
C(28)-C(27)-C(32)	118.6(5)
C(28)-C(27)-P(2)	120.2(4)
C(32)-C(27)-P(2)	121.2(4)
C(29)-C(28)-C(27)	120.8(5)
C(29)-C(28)-H(28A)	119.6
C(27)-C(28)-H(28A)	119.6
C(28)-C(29)-C(30)	120.0(5)
C(28)-C(29)-H(29A)	120.0
C(30)-C(29)-H(29A)	120.0
C(31)-C(30)-C(29)	120.3(5)
C(31)-C(30)-H(30A)	119.8
C(29)-C(30)-H(30A)	119.8
C(32)-C(31)-C(30)	120.0(5)
C(32)-C(31)-H(31A)	120.0
C(30)-C(31)-H(31A)	120.0
C(31)-C(32)-C(27)	120.1(5)
C(31)-C(32)-H(32A)	119.9
C(27)-C(32)-H(32A)	119.9

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for sad. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P(1)	10(1)	20(1)	22(1)	0(1)	-3(1)	-3(1)
O(1)	4(2)	20(2)	31(2)	-1(2)	1(1)	3(1)
O(2)	14(2)	33(2)	36(2)	-2(2)	-10(2)	-5(2)
C(1)	10(3)	20(3)	29(3)	-2(2)	-3(2)	-5(2)
C(2)	14(3)	22(3)	26(3)	-1(2)	-3(2)	-6(2)
C(3)	13(3)	25(3)	22(3)	-5(2)	2(2)	-10(2)
C(4)	14(3)	11(2)	29(3)	0(2)	-4(2)	-3(2)
C(5)	12(3)	25(3)	28(3)	7(2)	-3(2)	0(2)

C(6)	22(3)	35(4)	36(3)	-2(3)	10(2)	-5(3)
C(7)	29(3)	37(4)	31(3)	2(3)	6(3)	-12(3)
C(8)	24(3)	36(4)	29(3)	0(3)	-3(2)	-16(3)
C(9)	9(3)	25(3)	28(3)	4(2)	-1(2)	-7(2)
C(10)	17(3)	33(3)	27(3)	-7(3)	-1(2)	1(2)
C(11)	8(3)	23(3)	24(3)	7(2)	3(2)	-1(2)
C(12)	13(3)	22(3)	25(3)	5(2)	0(2)	-1(2)
C(13)	27(3)	20(3)	36(4)	-3(2)	8(3)	-4(2)
C(14)	37(4)	20(3)	28(3)	1(2)	3(3)	-12(3)
C(15)	22(3)	30(3)	33(3)	3(3)	-1(2)	-16(2)
C(16)	8(2)	18(3)	31(3)	6(2)	-1(2)	-1(2)
P(2)	8(1)	23(1)	29(1)	0(1)	-1(1)	0(1)
O(3)	13(2)	26(2)	32(2)	1(2)	-2(2)	-3(2)
O(4)	8(2)	39(3)	42(3)	-7(2)	-3(2)	4(2)
C(17)	11(3)	26(3)	17(3)	-2(2)	-3(2)	1(2)
C(18)	12(3)	34(3)	28(3)	0(2)	-2(2)	-3(2)
C(19)	31(3)	28(3)	22(3)	6(2)	-3(2)	-9(3)
C(20)	7(2)	28(3)	23(3)	-8(2)	0(2)	0(2)
C(21)	7(3)	37(3)	36(3)	-2(3)	-2(2)	-4(2)
C(22)	23(3)	38(4)	40(4)	0(3)	-4(3)	-19(3)
C(23)	38(3)	22(3)	26(3)	1(2)	-9(2)	-11(2)
C(24)	17(3)	27(3)	38(4)	-1(3)	-5(2)	3(2)
C(25)	11(3)	25(3)	29(3)	-3(2)	0(2)	0(2)
C(26)	21(3)	54(4)	28(3)	10(3)	-1(2)	-13(3)
C(27)	15(3)	14(3)	25(3)	3(2)	-2(2)	-4(2)
C(28)	8(3)	18(3)	33(3)	-1(2)	4(2)	-3(2)
C(29)	22(3)	21(3)	27(3)	-2(2)	8(2)	-4(2)
C(30)	22(3)	19(3)	29(3)	5(2)	-8(2)	-11(2)
C(31)	8(3)	27(3)	38(3)	4(2)	-5(2)	-7(2)
C(32)	11(3)	28(3)	30(3)	-1(2)	6(2)	-4(2)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for sad.

	x	y	z	U(eq)

H(1A)	-637	5562	7725	23
H(2B)	1897	5078	6306	24
H(3A)	1516	7682	5682	23
H(3B)	3095	8119	6431	23
H(5A)	-3552	7217	8934	27
H(6A)	-4200	7690	10499	38
H(7A)	-1208	7168	11506	38
H(8A)	2538	6309	10861	34
H(9A)	3239	5910	9267	24
H(10A)	6234	5683	6521	40
H(10B)	5500	5004	5603	40
H(10C)	5838	3909	6537	40
H(12A)	-3506	11137	7712	25
H(13A)	-3364	13282	8618	34
H(14A)	48	13296	9293	33
H(15A)	3296	11114	9020	32
H(16A)	3128	9034	8078	23
H(17A)	286	9769	1762	22
H(18A)	1871	11664	833	30
H(19A)	1044	13819	1811	32
H(19B)	3205	13074	2418	32
H(21A)	-1615	8732	3348	32
H(22A)	-1163	6471	4318	38
H(23A)	2383	4610	4403	33
H(24A)	5510	5099	3524	35
H(25A)	5103	7354	2550	27
H(26A)	6274	11840	1336	51
H(26B)	4933	12820	488	51
H(26C)	5906	10903	444	51
H(28A)	-1618	12524	4712	24
H(29A)	-225	12275	6194	29
H(30A)	3642	11222	6383	27
H(31A)	6102	10289	5096	29
H(32A)	4774	10663	3602	28

Table 6. Torsion angles [°] for sad.

C(2)-O(1)-C(1)-C(4)	-168.6(4)
C(2)-O(1)-C(1)-P(1)	-41.0(4)
O(2)-P(1)-C(1)-O(1)	136.9(3)
C(11)-P(1)-C(1)-O(1)	-98.1(3)
C(3)-P(1)-C(1)-O(1)	14.1(3)
O(2)-P(1)-C(1)-C(4)	-97.8(4)
C(11)-P(1)-C(1)-C(4)	27.2(4)
C(3)-P(1)-C(1)-C(4)	139.4(4)
C(1)-O(1)-C(2)-C(10)	176.7(4)
C(1)-O(1)-C(2)-C(3)	54.3(5)
O(1)-C(2)-C(3)-P(1)	-39.8(4)
C(10)-C(2)-C(3)-P(1)	-158.5(4)
O(2)-P(1)-C(3)-C(2)	-105.1(4)
C(11)-P(1)-C(3)-C(2)	123.6(4)
C(1)-P(1)-C(3)-C(2)	14.1(4)
O(1)-C(1)-C(4)-C(9)	9.1(7)
P(1)-C(1)-C(4)-C(9)	-112.1(5)
O(1)-C(1)-C(4)-C(5)	-172.3(4)
P(1)-C(1)-C(4)-C(5)	66.6(6)
C(9)-C(4)-C(5)-C(6)	0.8(8)
C(1)-C(4)-C(5)-C(6)	-178.0(5)
C(4)-C(5)-C(6)-C(7)	-2.1(9)
C(5)-C(6)-C(7)-C(8)	2.1(9)
C(6)-C(7)-C(8)-C(9)	-0.9(9)
C(7)-C(8)-C(9)-C(4)	-0.4(8)
C(5)-C(4)-C(9)-C(8)	0.4(8)
C(1)-C(4)-C(9)-C(8)	179.1(5)
O(2)-P(1)-C(11)-C(12)	4.3(5)
C(3)-P(1)-C(11)-C(12)	138.7(4)
C(1)-P(1)-C(11)-C(12)	-121.7(4)
O(2)-P(1)-C(11)-C(16)	-176.8(4)
C(3)-P(1)-C(11)-C(16)	-42.4(5)
C(1)-P(1)-C(11)-C(16)	57.2(5)
C(16)-C(11)-C(12)-C(13)	-1.4(8)

P(1)-C(11)-C(12)-C(13)	177.5(4)
C(11)-C(12)-C(13)-C(14)	0.0(8)
C(12)-C(13)-C(14)-C(15)	0.5(8)
C(13)-C(14)-C(15)-C(16)	0.5(8)
C(14)-C(15)-C(16)-C(11)	-2.0(8)
C(12)-C(11)-C(16)-C(15)	2.4(8)
P(1)-C(11)-C(16)-C(15)	-176.5(4)
C(18)-O(3)-C(17)-C(20)	-170.4(4)
C(18)-O(3)-C(17)-P(2)	-45.1(4)
O(4)-P(2)-C(17)-O(3)	142.8(3)
C(27)-P(2)-C(17)-O(3)	-89.9(4)
C(19)-P(2)-C(17)-O(3)	20.4(4)
O(4)-P(2)-C(17)-C(20)	-93.8(4)
C(27)-P(2)-C(17)-C(20)	33.4(4)
C(19)-P(2)-C(17)-C(20)	143.8(4)
C(17)-O(3)-C(18)-C(26)	176.1(4)
C(17)-O(3)-C(18)-C(19)	54.0(5)
O(3)-C(18)-C(19)-P(2)	-35.0(5)
C(26)-C(18)-C(19)-P(2)	-154.2(4)
O(4)-P(2)-C(19)-C(18)	-111.2(4)
C(27)-P(2)-C(19)-C(18)	119.2(4)
C(17)-P(2)-C(19)-C(18)	8.0(4)
O(3)-C(17)-C(20)-C(25)	-2.1(7)
P(2)-C(17)-C(20)-C(25)	-121.3(5)
O(3)-C(17)-C(20)-C(21)	179.5(4)
P(2)-C(17)-C(20)-C(21)	60.3(6)
C(25)-C(20)-C(21)-C(22)	1.9(8)
C(17)-C(20)-C(21)-C(22)	-179.6(5)
C(20)-C(21)-C(22)-C(23)	-1.4(9)
C(21)-C(22)-C(23)-C(24)	0.7(9)
C(22)-C(23)-C(24)-C(25)	-0.6(9)
C(23)-C(24)-C(25)-C(20)	1.3(9)
C(21)-C(20)-C(25)-C(24)	-1.9(8)
C(17)-C(20)-C(25)-C(24)	179.7(5)
O(4)-P(2)-C(27)-C(28)	-3.2(5)
C(19)-P(2)-C(27)-C(28)	129.5(4)

C(17)-P(2)-C(27)-C(28)	-131.5(4)
O(4)-P(2)-C(27)-C(32)	178.2(4)
C(19)-P(2)-C(27)-C(32)	-49.1(5)
C(17)-P(2)-C(27)-C(32)	49.9(5)
C(32)-C(27)-C(28)-C(29)	-1.3(8)
P(2)-C(27)-C(28)-C(29)	-179.9(4)
C(27)-C(28)-C(29)-C(30)	0.3(8)
C(28)-C(29)-C(30)-C(31)	-1.3(8)
C(29)-C(30)-C(31)-C(32)	3.2(8)
C(30)-C(31)-C(32)-C(27)	-4.1(8)
C(28)-C(27)-C(32)-C(31)	3.2(8)
P(2)-C(27)-C(32)-C(31)	-178.2(4)

Symmetry transformations used to generate equivalent atoms:

Figure 1.11: Structure of Phosphine Oxide 1.187 (hydrogens omitted for clarity)

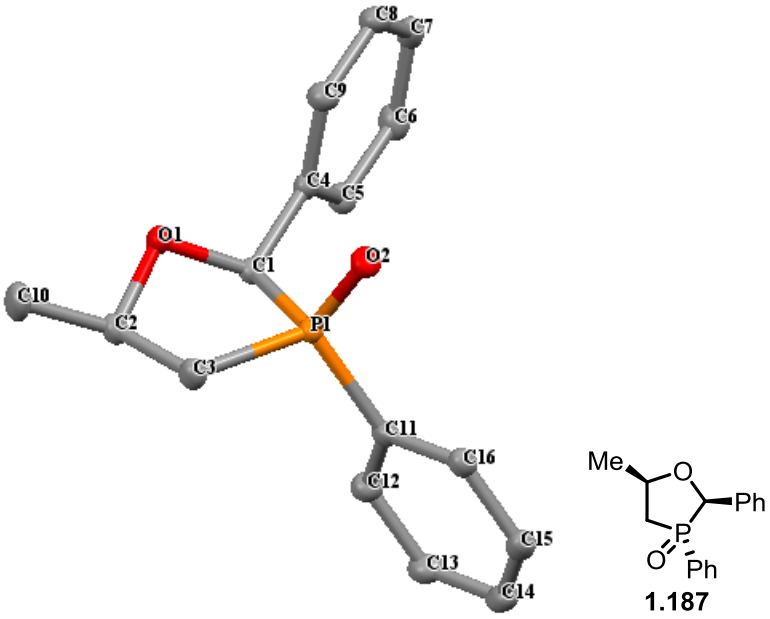


Table 1. Crystal data and structure refinement for sd.

Identification code	C16H17O2P
Empirical formula	C16 H17 O2 P
Formula weight	272.27

Temperature	100(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P 21 21 21	
Unit cell dimensions	a = 9.1557(17) Å	α= 90°.
	b = 10.0562(19) Å	β= 90°.
	c = 14.930(3) Å	γ = 90°.
Volume	1374.7(4) $Å^3$	
Z	4	
Density (calculated)	1.316 Mg/m^3	
Absorption coefficient	0.195 mm^{-1}	
F(000)	576	
Crystal size	0.23 x 0.13 x 0.08 mm^3	
Theta range for data collection	2.61 to 28.27°.	
Index ranges	-12<=h<=11, -13<=k<=13, -19<=l<=19	
Reflections collected	16686	
Independent reflections	3373 [R(int) = 0.0199]	
Completeness to theta = 28.27°	99.5 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9846 and 0.9566	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3373 / 17 / 223	
Goodness-of-fit on F^2	1.081	
Final R indices [I>2sigma(I)]	R1 = 0.0285, wR2 = 0.0732	
R indices (all data)	R1 = 0.0287, wR2 = 0.0734	
Absolute structure parameter	0.01(6)	
Extinction coefficient	na	
Largest diff. peak and hole	0.500 and -0.188 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for sd. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P(1)	4721(1)	7913(1)	8218(1)	13(1)
O(1)	2738(1)	6357(1)	7663(1)	17(1)
O(2)	4079(1)	9262(1)	8349(1)	19(1)
C(1)	4009(1)	6955(1)	7262(1)	14(1)
C(2)	3249(1)	5665(1)	8450(1)	18(1)
C(3)	4093(2)	6684(1)	9021(1)	18(1)
C(4)	3649(1)	7719(1)	6431(1)	15(1)
C(5)	4478(1)	7480(1)	5664(1)	18(1)
C(6)	4197(2)	8175(1)	4876(1)	22(1)
C(7)	3087(1)	9109(1)	4845(1)	20(1)
C(8)	2260(1)	9354(1)	5608(1)	21(1)
C(9)	2538(1)	8668(1)	6399(1)	19(1)
C(10)	1961(2)	5039(2)	8913(1)	25(1)
C(11)	6685(1)	7936(1)	8183(1)	15(1)
C(12)	7524(1)	6948(1)	7764(1)	20(1)
C(13)	9040(1)	7018(1)	7798(1)	23(1)
C(14)	9725(1)	8052(1)	8249(1)	23(1)
C(15)	8898(1)	9036(1)	8658(1)	22(1)
C(16)	7379(1)	8982(1)	8624(1)	18(1)

Table 3. Bond lengths [Å] and angles [°] for sd.

P(1)-O(2)	1.4912(9)
P(1)-C(11)	1.7987(12)
P(1)-C(3)	1.8158(13)
P(1)-C(1)	1.8416(12)
O(1)-C(1)	1.4404(14)
O(1)-C(2)	1.4438(15)
C(1)-C(4)	1.4964(16)
C(1)-H(1)	0.975(13)
C(2)-C(10)	1.5052(18)

C(2)-C(3)	1.5406(17)
C(2)-H(2)	0.966(14)
C(3)-H(3A)	0.981(14)
C(3)-H(3B)	0.976(13)
C(4)-C(5)	1.3953(17)
C(4)-C(9)	1.3953(17)
C(5)-C(6)	1.3917(17)
C(5)-H(5)	0.940(13)
C(6)-C(7)	1.3848(19)
C(6)-H(6)	0.957(14)
C(7)-C(8)	1.3896(19)
C(7)-H(7)	0.957(13)
C(8)-C(9)	1.3920(17)
C(8)-H(8)	0.940(14)
C(9)-H(9)	0.938(13)
C(10)-H(10A)	0.976(15)
C(10)-H(10B)	0.966(15)
C(10)-H(10C)	0.954(15)
C(11)-C(16)	1.3949(17)
C(11)-C(12)	1.4028(17)
C(12)-C(13)	1.3901(17)
C(12)-H(12)	0.961(13)
C(13)-C(14)	1.389(2)
C(13)-H(13)	0.948(14)
C(14)-C(15)	1.387(2)
C(14)-H(14)	0.959(14)
C(15)-C(16)	1.3929(18)
C(15)-H(15)	0.960(14)
C(16)-H(16)	0.930(13)

O(2)-P(1)-C(11)	112.72(5)
O(2)-P(1)-C(3)	114.13(6)
C(11)-P(1)-C(3)	110.14(6)
O(2)-P(1)-C(1)	115.97(5)
C(11)-P(1)-C(1)	109.72(5)
C(3)-P(1)-C(1)	92.49(6)

C(1)-O(1)-C(2)	106.09(9)
O(1)-C(1)-C(4)	112.35(9)
O(1)-C(1)-P(1)	100.51(7)
C(4)-C(1)-P(1)	116.90(8)
O(1)-C(1)-H(1)	108.0(10)
C(4)-C(1)-H(1)	109.5(9)
P(1)-C(1)-H(1)	109.0(9)
O(1)-C(2)-C(10)	108.76(11)
O(1)-C(2)-C(3)	107.03(9)
C(10)-C(2)-C(3)	114.63(11)
O(1)-C(2)-H(2)	108.3(10)
C(10)-C(2)-H(2)	108.7(10)
C(3)-C(2)-H(2)	109.2(10)
C(2)-C(3)-P(1)	104.24(8)
C(2)-C(3)-H(3A)	115.4(10)
P(1)-C(3)-H(3A)	111.9(10)
C(2)-C(3)-H(3B)	112.0(10)
P(1)-C(3)-H(3B)	105.8(10)
H(3A)-C(3)-H(3B)	107.2(14)
C(5)-C(4)-C(9)	119.10(11)
C(5)-C(4)-C(1)	118.21(10)
C(9)-C(4)-C(1)	122.68(10)
C(6)-C(5)-C(4)	120.46(11)
C(6)-C(5)-H(5)	120.5(11)
C(4)-C(5)-H(5)	119.1(11)
C(7)-C(6)-C(5)	120.29(12)
C(7)-C(6)-H(6)	121.1(11)
C(5)-C(6)-H(6)	118.7(11)
C(6)-C(7)-C(8)	119.53(12)
C(6)-C(7)-H(7)	121.6(11)
C(8)-C(7)-H(7)	118.7(11)
C(7)-C(8)-C(9)	120.54(12)
C(7)-C(8)-H(8)	119.3(11)
C(9)-C(8)-H(8)	120.1(11)
C(8)-C(9)-C(4)	120.08(12)
C(8)-C(9)-H(9)	120.5(11)

C(4)-C(9)-H(9)	119.4(11)
C(2)-C(10)-H(10A)	114.0(12)
C(2)-C(10)-H(10B)	109.8(13)
H(10A)-C(10)-H(10B)	105.5(17)
C(2)-C(10)-H(10C)	111.0(12)
H(10A)-C(10)-H(10C)	107.0(17)
H(10B)-C(10)-H(10C)	109.3(16)
C(16)-C(11)-C(12)	119.65(11)
C(16)-C(11)-P(1)	116.83(9)
C(12)-C(11)-P(1)	123.49(9)
C(13)-C(12)-C(11)	119.66(12)
C(13)-C(12)-H(12)	118.1(10)
C(11)-C(12)-H(12)	122.3(11)
C(14)-C(13)-C(12)	120.42(12)
C(14)-C(13)-H(13)	121.0(11)
C(12)-C(13)-H(13)	118.6(11)
C(15)-C(14)-C(13)	120.08(12)
C(15)-C(14)-H(14)	117.0(11)
C(13)-C(14)-H(14)	122.9(11)
C(14)-C(15)-C(16)	120.08(12)
C(14)-C(15)-H(15)	120.5(11)
C(16)-C(15)-H(15)	119.4(11)
C(15)-C(16)-C(11)	120.10(12)
C(15)-C(16)-H(16)	121.5(11)
C(11)-C(16)-H(16)	118.4(11)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for sd. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P(1)	13(1)	13(1)	14(1)	0(1)	0(1)	0(1)
O(1)	15(1)	16(1)	19(1)	2(1)	-1(1)	-3(1)
O(2)	18(1)	15(1)	22(1)	-2(1)	1(1)	2(1)

C(1)	14(1)	13(1)	15(1)	0(1)	0(1)	0(1)
C(2)	21(1)	14(1)	19(1)	2(1)	0(1)	-1(1)
C(3)	20(1)	20(1)	15(1)	3(1)	0(1)	-3(1)
C(4)	15(1)	15(1)	15(1)	0(1)	-1(1)	-2(1)
C(5)	19(1)	16(1)	20(1)	0(1)	2(1)	0(1)
C(6)	26(1)	23(1)	16(1)	0(1)	4(1)	-3(1)
C(7)	22(1)	21(1)	18(1)	3(1)	-4(1)	-7(1)
C(8)	17(1)	23(1)	24(1)	4(1)	-4(1)	1(1)
C(9)	17(1)	23(1)	18(1)	0(1)	1(1)	2(1)
C(10)	28(1)	24(1)	25(1)	5(1)	1(1)	-10(1)
C(11)	14(1)	16(1)	15(1)	4(1)	0(1)	1(1)
C(12)	19(1)	19(1)	21(1)	-2(1)	0(1)	2(1)
C(13)	18(1)	28(1)	22(1)	1(1)	2(1)	5(1)
C(14)	15(1)	30(1)	23(1)	8(1)	-1(1)	-2(1)
C(15)	20(1)	23(1)	21(1)	4(1)	-5(1)	-4(1)
C(16)	20(1)	17(1)	16(1)	1(1)	-2(1)	-1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for sd.

	x	y	z	U(eq)
H(1)	4698(17)	6247(14)	7117(10)	17
H(2)	3909(18)	4970(15)	8261(11)	22
H(3A)	4900(17)	6319(17)	9377(11)	22
H(3B)	3452(17)	7160(16)	9433(10)	22
H(5)	5223(16)	6837(15)	5684(12)	22
H(6)	4784(18)	7992(17)	4360(10)	26
H(7)	2830(20)	9551(16)	4300(10)	25
H(8)	1480(17)	9961(17)	5577(12)	26
H(9)	2008(18)	8860(17)	6921(10)	23
H(10A)	1240(20)	5679(18)	9135(14)	38
H(10B)	2290(20)	4554(18)	9434(11)	38
H(10C)	1460(20)	4448(18)	8520(12)	38
H(12)	7089(18)	6216(15)	7448(11)	24

H(13)	9590(18)	6340(16)	7515(12)	27
H(14)	10766(15)	8126(17)	8297(12)	27
H(15)	9365(19)	9763(15)	8961(11)	26
H(16)	6804(18)	9632(15)	8892(11)	21

Table 6. Torsion angles [°] for sd.

C(2)-O(1)-C(1)-C(4)	-179.85(9)
C(2)-O(1)-C(1)-P(1)	-54.84(9)
O(2)-P(1)-C(1)-O(1)	-85.27(8)
C(11)-P(1)-C(1)-O(1)	145.61(7)
C(3)-P(1)-C(1)-O(1)	33.17(8)
O(2)-P(1)-C(1)-C(4)	36.58(10)
C(11)-P(1)-C(1)-C(4)	-92.54(9)
C(3)-P(1)-C(1)-C(4)	155.02(9)
C(1)-O(1)-C(2)-C(10)	178.82(10)
C(1)-O(1)-C(2)-C(3)	54.46(11)
O(1)-C(2)-C(3)-P(1)	-25.70(11)
C(10)-C(2)-C(3)-P(1)	-146.39(10)
O(2)-P(1)-C(3)-C(2)	115.36(8)
C(11)-P(1)-C(3)-C(2)	-116.69(9)
C(1)-P(1)-C(3)-C(2)	-4.62(9)
O(1)-C(1)-C(4)-C(5)	-130.52(11)
P(1)-C(1)-C(4)-C(5)	114.04(11)
O(1)-C(1)-C(4)-C(9)	50.54(15)
P(1)-C(1)-C(4)-C(9)	-64.91(13)
C(9)-C(4)-C(5)-C(6)	-0.36(18)
C(1)-C(4)-C(5)-C(6)	-179.34(11)
C(4)-C(5)-C(6)-C(7)	-0.11(19)
C(5)-C(6)-C(7)-C(8)	0.34(19)
C(6)-C(7)-C(8)-C(9)	-0.1(2)
C(7)-C(8)-C(9)-C(4)	-0.4(2)
C(5)-C(4)-C(9)-C(8)	0.60(18)
C(1)-C(4)-C(9)-C(8)	179.54(12)
O(2)-P(1)-C(11)-C(16)	25.50(11)
C(3)-P(1)-C(11)-C(16)	-103.22(10)

C(1)-P(1)-C(11)-C(16)	156.37(9)
O(2)-P(1)-C(11)-C(12)	-156.42(10)
C(3)-P(1)-C(11)-C(12)	74.86(11)
C(1)-P(1)-C(11)-C(12)	-25.55(12)
C(16)-C(11)-C(12)-C(13)	0.41(18)
P(1)-C(11)-C(12)-C(13)	-177.62(10)
C(11)-C(12)-C(13)-C(14)	0.6(2)
C(12)-C(13)-C(14)-C(15)	-1.1(2)
C(13)-C(14)-C(15)-C(16)	0.6(2)
C(14)-C(15)-C(16)-C(11)	0.4(2)
C(12)-C(11)-C(16)-C(15)	-0.88(19)
P(1)-C(11)-C(16)-C(15)	177.28(9)

Symmetry transformations used to generate equivalent atoms:

Figure 1.12: Structure of Phosphine Oxide 1.194 (hydrogens omitted for clarity)

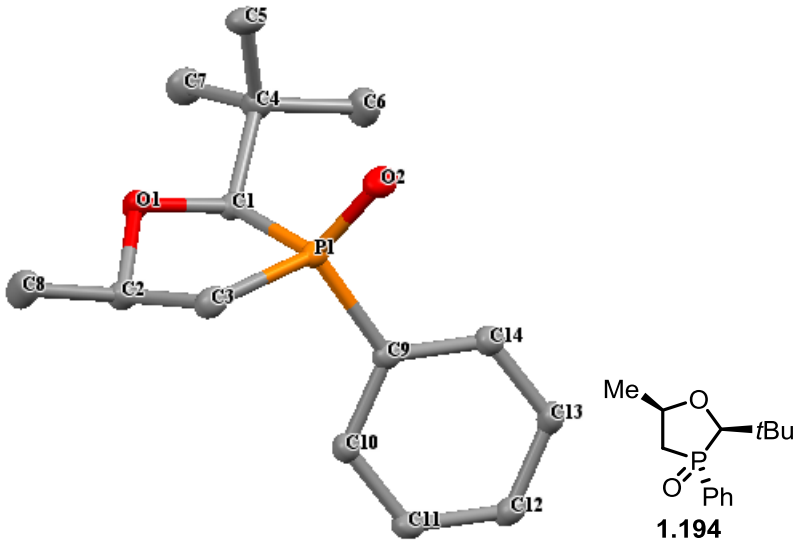


Table 1. Crystal data and structure refinement for C14H21O2P.

Identification code	C14H21O2P
Empirical formula	C14 H21 O2 P
Formula weight	252.28
Temperature	100(2) K
Wavelength	0.71073 Å
Crystal system	Orthorhombic

Space group	P 21 21 21	
Unit cell dimensions	a = 6.0808(10) Å	α= 90°.
	b = 11.639(2) Å	β= 90°.
	c = 19.719(3) Å	γ = 90°.
Volume	1395.7(4) $Å^3$	
Z	4	
Density (calculated)	1.201 Mg/m^3	
Absorption coefficient	0.186 mm^{-1}	
F(000)	544	
Crystal size	0.25 x 0.10 x 0.05 mm^3	
Theta range for data collection	2.71 to 28.27°.	
Index ranges	-8<=h<=8, -15<=k<=15, -25<=l<=25	
Reflections collected	16794	
Independent reflections	3413 [R(int) = 0.0211]	
Completeness to theta = 28.27°	99.2 %	
Absorption correction	Semi-empirical from equivalents	
Max. and min. transmission	0.9908 and 0.9550	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	3413 / 21 / 217	
Goodness-of-fit on F^2	1.106	
Final R indices [I>2sigma(I)]	R1 = 0.0298, wR2 = 0.0769	
R indices (all data)	R1 = 0.0306, wR2 = 0.0774	
Absolute structure parameter	0.03(6)	
Extinction coefficient	na	
Largest diff. peak and hole	0.607 and -0.212 $e.Å^{-3}$	

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for C14H21O2P. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
P(1)	5265(1)	5579(1)	9685(1)	15(1)
O(1)	3091(2)	5330(1)	8555(1)	17(1)
O(2)	7712(1)	5644(1)	9693(1)	24(1)
C(1)	3920(2)	4591(1)	9072(1)	15(1)
C(2)	2120(2)	6330(1)	8872(1)	19(1)

C(3)	3863(2)	6821(1)	9346(1)	19(1)
C(4)	5317(2)	3628(1)	8758(1)	19(1)
C(5)	7149(2)	4109(1)	8312(1)	25(1)
C(6)	6297(3)	2910(1)	9335(1)	28(1)
C(7)	3796(3)	2869(1)	8330(1)	25(1)
C(8)	1404(3)	7142(1)	8318(1)	30(1)
C(9)	4230(2)	5262(1)	10521(1)	16(1)
C(10)	2088(2)	5521(1)	10723(1)	18(1)
C(11)	1463(2)	5349(1)	11395(1)	20(1)
C(12)	2940(2)	4897(1)	11861(1)	20(1)
C(13)	5047(2)	4608(1)	11655(1)	20(1)
C(14)	5695(2)	4792(1)	10988(1)	19(1)

Table 3. Bond lengths [Å] and angles [°] for C14H21O2P.

P(1)-O(2)	1.4897(9)
P(1)-C(9)	1.8027(12)
P(1)-C(3)	1.8073(13)
P(1)-C(1)	1.8591(12)
O(1)-C(1)	1.4254(13)
O(1)-C(2)	1.4477(14)
C(1)-C(4)	1.5363(16)
C(1)-H(1)	0.962(13)
C(2)-C(8)	1.5104(17)
C(2)-C(3)	1.5242(18)
C(2)-H(2)	0.979(13)
C(3)-H(3A)	0.949(13)
C(3)-H(3B)	0.994(13)
C(4)-C(5)	1.5256(18)
C(4)-C(6)	1.5325(17)
C(4)-C(7)	1.5328(18)
C(5)-H(5A)	0.971(15)
C(5)-H(5B)	0.985(14)
C(5)-H(5C)	0.952(15)
C(6)-H(6A)	0.989(15)
C(6)-H(6B)	0.963(15)

C(6)-H(6C)	0.991(14)
C(7)-H(7A)	0.992(14)
C(7)-H(7B)	0.977(14)
C(7)-H(7C)	0.974(14)
C(8)-H(8A)	0.954(15)
C(8)-H(8B)	0.980(15)
C(8)-H(8C)	0.993(15)
C(9)-C(14)	1.3927(17)
C(9)-C(10)	1.3947(16)
C(10)-C(11)	1.3925(16)
C(10)-H(10)	0.934(13)
C(11)-C(12)	1.3885(18)
C(11)-H(11)	0.949(13)
C(12)-C(13)	1.3851(18)
C(12)-H(12)	0.939(13)
C(13)-C(14)	1.3904(17)
C(13)-H(13)	0.950(13)
C(14)-H(14)	0.952(14)

O(2)-P(1)-C(9)	110.44(5)
O(2)-P(1)-C(3)	115.75(6)
C(9)-P(1)-C(3)	109.69(6)
O(2)-P(1)-C(1)	118.56(5)
C(9)-P(1)-C(1)	108.37(5)
C(3)-P(1)-C(1)	92.68(6)
C(1)-O(1)-C(2)	108.69(8)
O(1)-C(1)-C(4)	110.40(9)
O(1)-C(1)-P(1)	104.32(7)
C(4)-C(1)-P(1)	118.01(8)
O(1)-C(1)-H(1)	110.2(9)
C(4)-C(1)-H(1)	109.1(10)
P(1)-C(1)-H(1)	104.6(9)
O(1)-C(2)-C(8)	107.93(10)
O(1)-C(2)-C(3)	106.45(10)
C(8)-C(2)-C(3)	114.16(11)
O(1)-C(2)-H(2)	112.0(10)

C(8)-C(2)-H(2)	106.6(10)
C(3)-C(2)-H(2)	109.8(9)
C(2)-C(3)-P(1)	104.73(8)
C(2)-C(3)-H(3A)	106.4(10)
P(1)-C(3)-H(3A)	107.9(11)
C(2)-C(3)-H(3B)	115.6(10)
P(1)-C(3)-H(3B)	113.1(9)
H(3A)-C(3)-H(3B)	108.8(13)
C(5)-C(4)-C(6)	110.14(12)
C(5)-C(4)-C(7)	109.56(11)
C(6)-C(4)-C(7)	109.25(11)
C(5)-C(4)-C(1)	111.57(10)
C(6)-C(4)-C(1)	108.32(10)
C(7)-C(4)-C(1)	107.94(10)
C(4)-C(5)-H(5A)	104.6(12)
C(4)-C(5)-H(5B)	114.2(12)
H(5A)-C(5)-H(5B)	105.8(15)
C(4)-C(5)-H(5C)	112.4(12)
H(5A)-C(5)-H(5C)	113.9(17)
H(5B)-C(5)-H(5C)	105.9(16)
C(4)-C(6)-H(6A)	111.0(11)
C(4)-C(6)-H(6B)	109.5(12)
H(6A)-C(6)-H(6B)	110.3(17)
C(4)-C(6)-H(6C)	107.5(11)
H(6A)-C(6)-H(6C)	108.1(16)
H(6B)-C(6)-H(6C)	110.5(16)
C(4)-C(7)-H(7A)	107.2(12)
C(4)-C(7)-H(7B)	109.4(11)
H(7A)-C(7)-H(7B)	106.3(15)
C(4)-C(7)-H(7C)	110.2(12)
H(7A)-C(7)-H(7C)	110.1(15)
H(7B)-C(7)-H(7C)	113.4(16)
C(2)-C(8)-H(8A)	112.0(12)
C(2)-C(8)-H(8B)	107.7(11)
H(8A)-C(8)-H(8B)	109.9(16)
C(2)-C(8)-H(8C)	111.9(12)

H(8A)-C(8)-H(8C)	106.1(16)
H(8B)-C(8)-H(8C)	109.2(16)
C(14)-C(9)-C(10)	119.57(11)
C(14)-C(9)-P(1)	117.44(9)
C(10)-C(9)-P(1)	122.90(9)
C(11)-C(10)-C(9)	119.70(11)
C(11)-C(10)-H(10)	120.9(10)
C(9)-C(10)-H(10)	119.3(10)
C(12)-C(11)-C(10)	120.47(11)
C(12)-C(11)-H(11)	123.2(10)
C(10)-C(11)-H(11)	116.4(10)
C(13)-C(12)-C(11)	119.80(11)
C(13)-C(12)-H(12)	122.8(11)
C(11)-C(12)-H(12)	117.3(11)
C(12)-C(13)-C(14)	120.10(11)
C(12)-C(13)-H(13)	119.6(10)
C(14)-C(13)-H(13)	120.2(10)
C(13)-C(14)-C(9)	120.31(12)
C(13)-C(14)-H(14)	120.4(10)
C(9)-C(14)-H(14)	119.1(10)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C14H21O2P. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ...\ + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
P(1)	16(1)	16(1)	14(1)	-2(1)	1(1)	-3(1)
O(1)	23(1)	15(1)	14(1)	-2(1)	-2(1)	3(1)
O(2)	18(1)	33(1)	20(1)	-4(1)	1(1)	-5(1)
C(1)	17(1)	14(1)	14(1)	0(1)	0(1)	-1(1)
C(2)	22(1)	16(1)	18(1)	-2(1)	0(1)	4(1)
C(3)	27(1)	13(1)	17(1)	-1(1)	2(1)	-2(1)
C(4)	23(1)	15(1)	19(1)	-2(1)	0(1)	3(1)
C(5)	24(1)	29(1)	23(1)	-7(1)	6(1)	1(1)

C(6)	37(1)	22(1)	27(1)	0(1)	-5(1)	9(1)
C(7)	32(1)	18(1)	26(1)	-6(1)	-3(1)	0(1)
C(8)	45(1)	22(1)	22(1)	0(1)	-4(1)	11(1)
C(9)	18(1)	13(1)	15(1)	-2(1)	0(1)	-2(1)
C(10)	19(1)	18(1)	17(1)	0(1)	-1(1)	2(1)
C(11)	18(1)	22(1)	19(1)	-1(1)	3(1)	2(1)
C(12)	27(1)	17(1)	14(1)	0(1)	2(1)	0(1)
C(13)	25(1)	19(1)	16(1)	0(1)	-3(1)	4(1)
C(14)	19(1)	19(1)	18(1)	-2(1)	0(1)	1(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for C14H21O2P.

	x	y	z	U(eq)
H(1)	2720(20)	4254(13)	9321(7)	18
H(2)	800(20)	6135(14)	9132(8)	22
H(3A)	4870(30)	7227(14)	9068(8)	23
H(3B)	3310(30)	7350(13)	9704(7)	23
H(5A)	7860(30)	3435(15)	8123(9)	38
H(5B)	6620(30)	4558(15)	7921(8)	38
H(5C)	8110(30)	4603(15)	8556(9)	38
H(6A)	7020(30)	2211(15)	9158(10)	42
H(6B)	7330(30)	3368(16)	9586(9)	42
H(6C)	5070(30)	2666(16)	9632(9)	42
H(7A)	4680(30)	2209(15)	8167(9)	38
H(7B)	2650(30)	2545(15)	8619(9)	38
H(7C)	3220(30)	3303(16)	7947(8)	38
H(8A)	320(30)	6806(17)	8028(9)	44
H(8B)	800(30)	7832(15)	8534(9)	44
H(8C)	2650(30)	7364(16)	8019(9)	44
H(10)	1070(30)	5773(13)	10400(7)	22
H(11)	-10(20)	5549(13)	11507(8)	24
H(12)	2460(30)	4821(14)	12311(7)	24
H(13)	6070(30)	4325(14)	11979(7)	24

H(14)	7170(20)	4653(14)	10852(8)	22

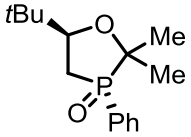
Table 6. Torsion angles [°] for C14H21O2P.

C(2)-O(1)-C(1)-C(4)	-170.06(10)
C(2)-O(1)-C(1)-P(1)	-42.32(10)
O(2)-P(1)-C(1)-O(1)	-104.42(8)
C(9)-P(1)-C(1)-O(1)	128.73(8)
C(3)-P(1)-C(1)-O(1)	16.96(8)
O(2)-P(1)-C(1)-C(4)	18.50(11)
C(9)-P(1)-C(1)-C(4)	-108.35(9)
C(3)-P(1)-C(1)-C(4)	139.87(9)
C(1)-O(1)-C(2)-C(8)	175.88(11)
C(1)-O(1)-C(2)-C(3)	52.91(12)
O(1)-C(2)-C(3)-P(1)	-36.25(11)
C(8)-C(2)-C(3)-P(1)	-155.22(10)
O(2)-P(1)-C(3)-C(2)	134.43(8)
C(9)-P(1)-C(3)-C(2)	-99.81(9)
C(1)-P(1)-C(3)-C(2)	10.80(9)
O(1)-C(1)-C(4)-C(5)	54.71(13)
P(1)-C(1)-C(4)-C(5)	-65.08(13)
O(1)-C(1)-C(4)-C(6)	176.11(11)
P(1)-C(1)-C(4)-C(6)	56.32(13)
O(1)-C(1)-C(4)-C(7)	-65.71(12)
P(1)-C(1)-C(4)-C(7)	174.51(8)
O(2)-P(1)-C(9)-C(14)	-18.83(11)
C(3)-P(1)-C(9)-C(14)	-147.57(9)
C(1)-P(1)-C(9)-C(14)	112.57(10)
O(2)-P(1)-C(9)-C(10)	157.83(10)
C(3)-P(1)-C(9)-C(10)	29.09(12)
C(1)-P(1)-C(9)-C(10)	-70.77(11)
C(14)-C(9)-C(10)-C(11)	2.49(18)
P(1)-C(9)-C(10)-C(11)	-174.10(9)
C(9)-C(10)-C(11)-C(12)	-1.54(19)
C(10)-C(11)-C(12)-C(13)	-0.38(19)
C(11)-C(12)-C(13)-C(14)	1.34(19)

C(12)-C(13)-C(14)-C(9)	-0.38(18)
C(10)-C(9)-C(14)-C(13)	-1.54(18)
P(1)-C(9)-C(14)-C(13)	175.23(9)

Symmetry transformations used to generate equivalent atoms:

Figure 1.13: X-ray Structures Available from the Cambridge Crystallographic Data Centre



1.208

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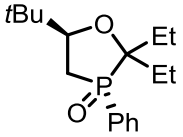

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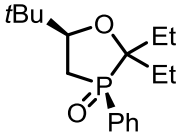

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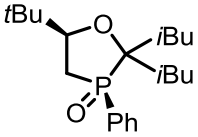
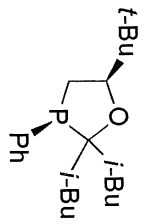


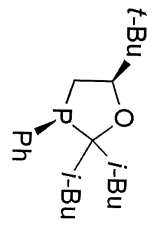
1.198

820560

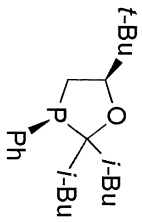
^{1}H NMR



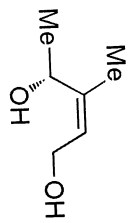
^{13}C NMR



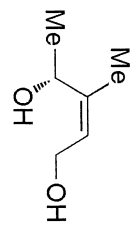
^{31}P NMR



^{1}H NMR



^{13}C NMR



Chapter 2

Development of Tandem Diboration Cross-Coupling: Unlocking Terminal Alkenes for Enantioselective Synthesis

2.1 Introduction

Alkenes represent one of the most common functional groups in organic chemistry and are readily available both directly from industry on enormous scale and through facile synthesis from a plethora of starting materials.[1] Accordingly, an overwhelming amount of reaction chemistry has been developed to utilize alkenes for the preparation of a vast array of products.[2] In particular, monosubstituted, or so called α-olefins, are an important feed-stock for industrial chemistry, participating in a range of large scale reactions including polymerization,[3] hydroformylation,[4] and oxidative processes.[5]

Importantly, terminal alkenes contain two prochiral faces and are capable of participating in enantioselective transformations. Despite this great potential, most catalytic, asymmetric reactions are forced to employ electronically biased terminal olefins, such as styrene, in order to selectively choose one of the difficult-to-distinguish prochiral faces. For instance, in a recent report from Shibata,[6] intermolecular hydroamination proceeds with good levels of selectivity when utilizing *p*-methoxystyrene

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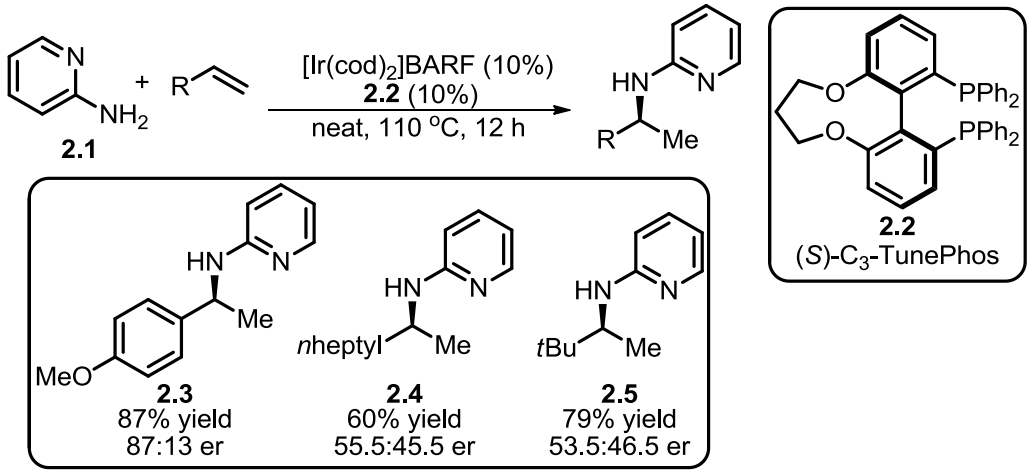
[1] (a) Wissermel, K.; Arpe, H. J. *Industrial Organic Chemistry*, 4th Ed.; Wiley-VCH: Germany, **2003**. (b) Takeda, T. *Modern Carbonyl Olefination*; Wiley-VCH, Weinheim, **2004**.
[2] (a) Patai, S. *The Chemistry of Alkenes*; John Wiley & Sons Ltd.: London, **1964**. (b) Zabicky, J. *The Chemistry of Alkenes*, Vol. 2; John Wiley & Sons Ltd.: London, **1970**.
[3] Resconi, L.; Cavallo, L.; Fait, A.; Piemontesi, F. *Chem. Rev*. **2000**, *100*, 1253.
[4] Franke, R.; Selent, D.; Borner, A. *Chem. Rev*. **2012**, *112*, 5675.
[5] (a) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*, Wiley-Interscience, New York, **2002**. (b) Keith, J. A.; Henry, P. M. *Angew. Chem. Int. Ed*. **2009**, *48*, 9038.
[6] Pan, S.; Endo, K.; Shibata, T. *Org. Lett*. **2012**, *14*, 780.

in the presence of a chiral iridium catalyst to give benzylic aniline **2.3** in 87:13 er; however, when a non-biased olefin such as 1-nonene is employed, nearly racemic product is obtained (Scheme 2.1). Notably, the authors eliminated the possibility of simple steric effects on selectivity by examining a bulky aliphatic olefin, which also gave nearly racemic product (**2.5**).

Scheme 2.1: Intermolecular Hydroamination by Shibata

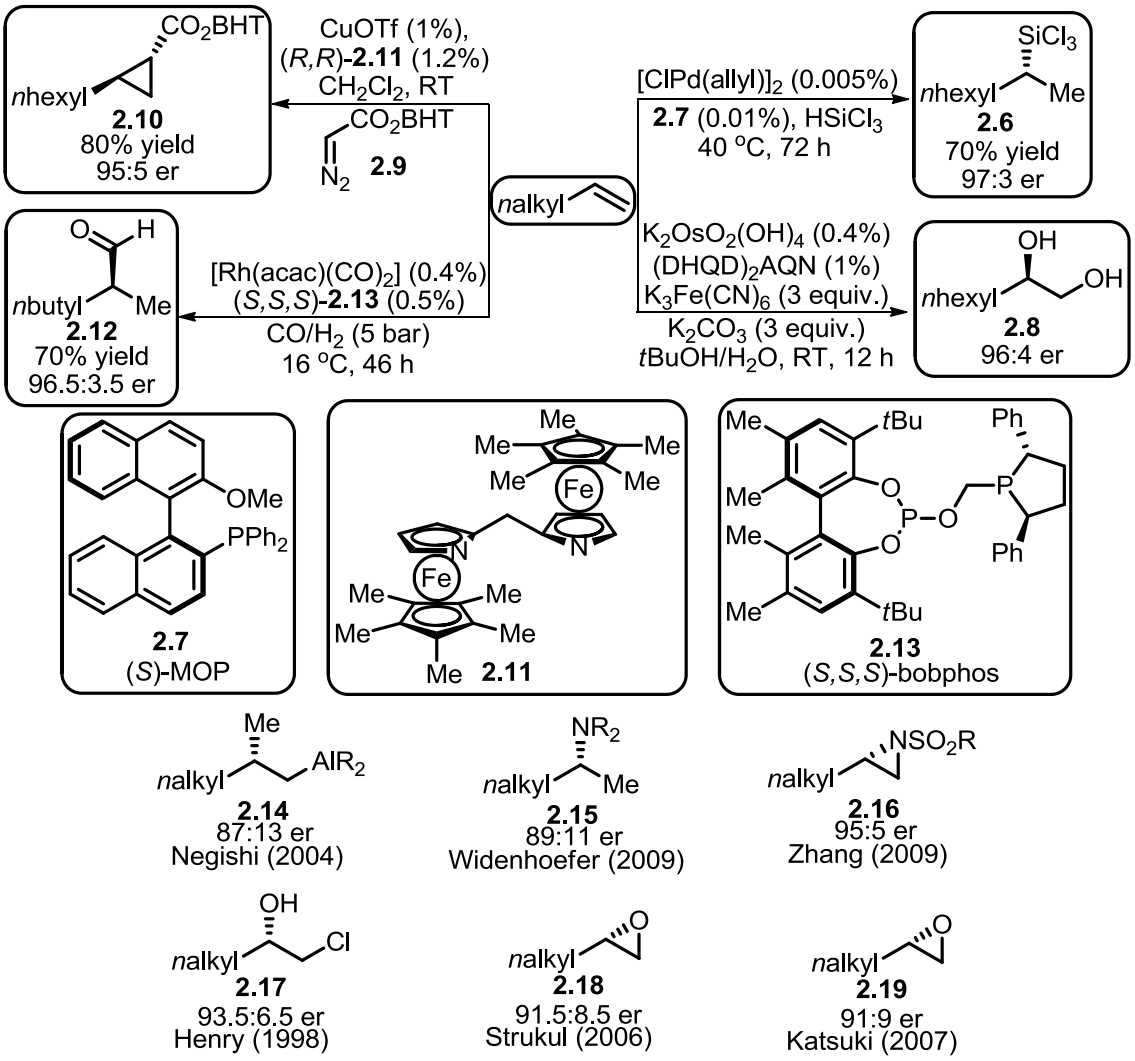


Seeking to overcome this difficult challenge in asymmetric catalysis, a number of research groups have made important advances towards engaging unbiased terminal alkenes in highly selective reactions (Scheme 2.2). Highlights include Hayashi's highly regio- and enantioselective palladium-catalyzed hydrosilation[7] (to give **2.6**), Sharpless' improved ligand design for osmium-catalyzed dihydroxylation[8] (to give **2.8**), Fu's highly efficient azaferrocene-copper catalyzed cyclopropanation[9] (to give **2.10**), and Clarke's recently disclosed branch-selective hydroformylation[10] (to give **2.12**). Additional

[7] Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc*. **1991**, *113*, 9887.
[8] Becker, H.; Sharpless, K. B. *Angew. Chem. Int. Ed*. **1996**, *35*, 448.
[9] Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc*. **1998**, *120*, 10270.
[10] Noonan, G. M.; Fuentes, J. A.; Cobley, C. J.; Clark, M. L. *Angew. Chem. Int. Ed*. **2012**, *51*, 2477.

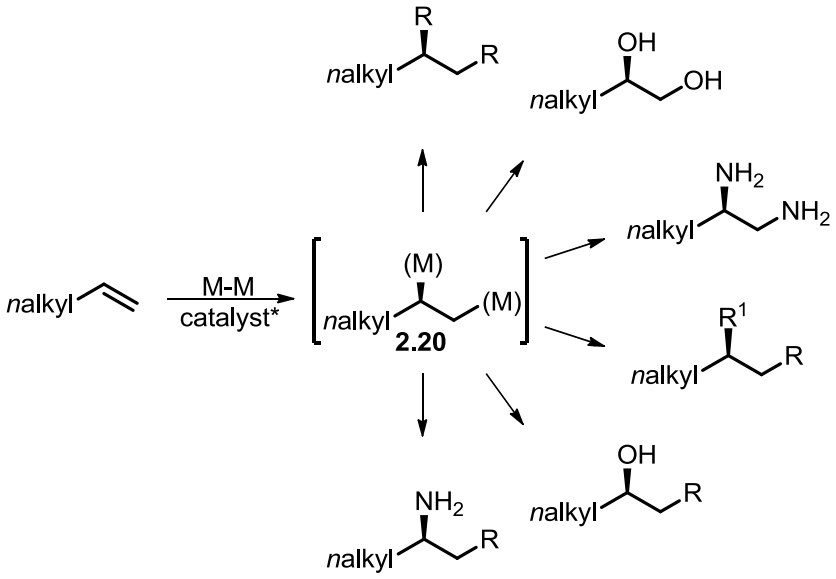
examples showcase the potential for catalytic carbon-carbon[11a] (**2.14**), carbon-nitrogen[11b,c] (**2.15** and **2.16**) and carbon-oxygen[11d-f] (**2.17**-**2.19**) bond formation. While these pioneering developments have progressed the field greatly, the full synthetic potential of α-olefins as an attractive reservoir of starting materials has yet to be realized.

Scheme 2.2: Selected Examples of Catalytic Enantioselective Functionalizations



[11] (a) Negishi, E.; Tan, Z.; Liang, B.; Nouak, T. *Proc. Nat. Acad. Sci*. **2004**, *101*, 5782. (b) Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc*. **2009**, *131*, 5372. (c) Subbarayan, V.; Ruppel, J. V.; Zhu, S.; Perman, J. A.; Zhang, X. P. *Chem. Commun*. **2009**, 4266. (d) El-Qisairi, A.; Hamed, O.; Henry, P. M. *J. Org. Chem*. **1998**, *63*, 2790. (e) Colladon, M.; Scarso, A.; Sgarbossa, P.; Michelin, R. A.; Strukul, G. *J. Am. Chem. Soc*. **2006**, *128*, 14006. (f) Sawada, Y.; Matsumoto, K.; Katsuki, T. *Angew. Chem. Int. Ed*. **2007**, *46*, 4559.

Scheme 2.3: Enantioselective Dimetallation Strategy for Terminal Olefin Functionalization

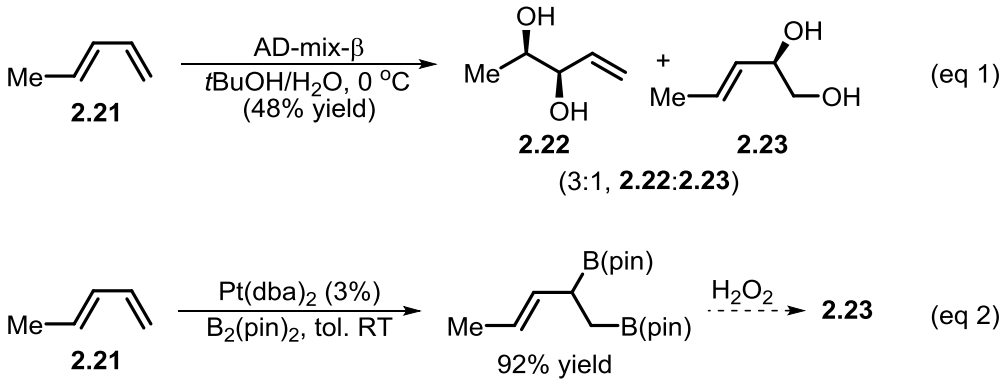


An additional approach involves the use of enantioselective catalysis to prepare a common reactive intermediate that can subsequently participate in a variety of well established, stoichiometric reactions. These so-called dimetallation[12] reactions conveniently allow for the use of a single chiral catalyst to transform the alkene starting material into enantioenriched **2.20**. Depending on the identity of (**M**), **2.20** may be transformed into a wide range of functionalities, effectively connecting the readily available terminal alkene starting materials with the desired products. Importantly, this approach may also offer complementary chemoselectivity to the methods described in Scheme 2.2. For example, treatment of *trans*-1,3-pentadiene **2.21** with AD-mix-β under the standard Sharpless conditions results in a 3:1 mixture of products favoring dihydroxylation of the internal olefin (Scheme 2.4, equation 1).[13] Alternatively, Miyaura

[12] (a) Suginome, M.; Ito, Y. *Chem. Rev*. **2000**, *100*, 3221. (b) Beletskaya, I.; Moberg, C. *Chem. Rev*. **2006**, *106*, 2320.
[13] Xu, D.; Crispino, G. A.; Sharpless, K. B. *J. Am. Chem. Soc*. **1992**, *114*, 7570.

reported the selective platinum catalyzed 1,2-diboration of **2.21**, which after oxidation results in a net dihydroxylation reaction to yield exclusively **2.23** (equation 2).[14]

Scheme 2.4: Complementary Regioselectivity *via* Dimetallation

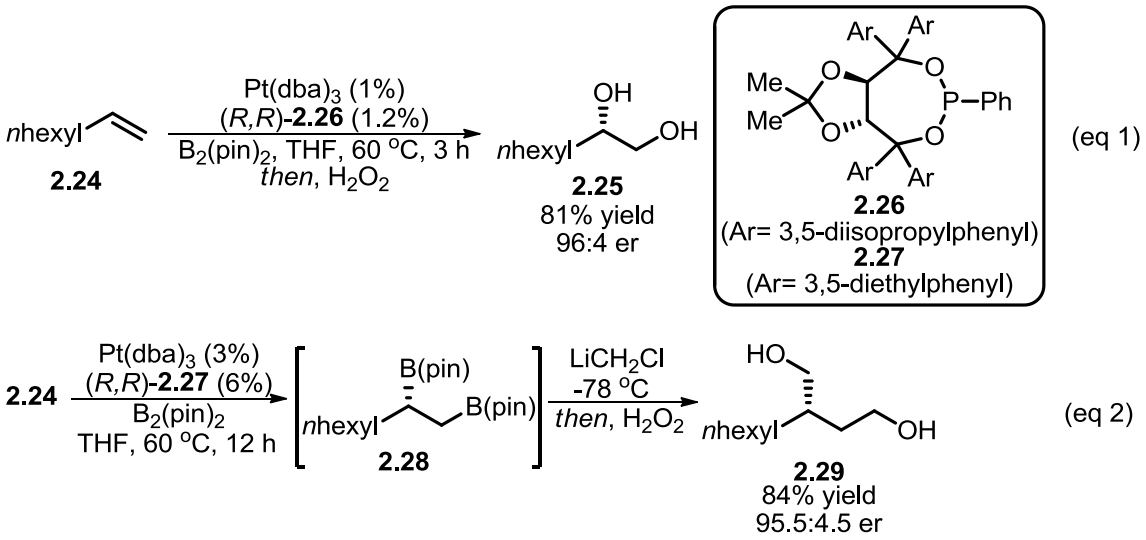


In this light, the Morken group has recently reported the highly enantioselective platinum catalyzed diboration of terminal alkenes.[15] Complementary to the previously reported rhodium catalyzed diboration of internal alkenes,[16] the more recent work utilized simple, unhindered terminal alkenes to give bench stable 1,2-bis(pinacol boronate) alkanes (Scheme 2.5). Upon oxidative work-up, the corresponding 1,2-diols were obtained in high yields and with excellent levels of enantioselectivity. Notably, this result compares favorably to osmium-catalyzed asymmetric dihydroxylation of terminal olefins (Scheme 2.2, **2.8**). In addition to oxidation, the 1,2-bis(pinacol boronates) may participate in a rich variety of reactions developed to transform carbon-boron bonds into a range of valuable products.[17] For example, treatment of 1,2-bis(pinacol boronate) **2.28**

[14] Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun*. **1997**, 689.
[15] (a) Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210. (b) Coombs, J. R.; Haeffner, F.; Kliman, L. T.; Morken. J. P. *J. Am. Chem. Soc*. **2013**, *135*, 11222.
[16] (a) Morgan, J. B.; Miller, S. P.; Morken, J. P. *J. Am. Chem. Soc*. **2003**, *125*, 8702. (b) Trudeau, S.; Morgan, J. B.; Shrestha, M.; Morken, J. P. *J. Org. Chem*. **2005**, *70*, 9538.
[17] (a) Matteson, D. S. *Tetrahedron* **1989**, *45*, 1859. (b) Mattesson, D. S. *Stereodirected Synthesis with Organoboranes*; Springer: Berlin, **1995**. (c) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457. (d)

with two equivalents of chloromethyllithium results in a double homologation reaction, revealing the corresponding 1,4-diol **2.29** after subsequent oxidation.[15a]

Scheme 2.5: Enantioselective Diboration of Terminal Olefins by Morken



In order to unlock the full potential of the 1,2-bis(pinacol boronates) and achieve many of the reactions outlined in Scheme 2.3, a regioselective functionalization is required. Many of the commonly used carbon-boron bond transformations take advantage of boron's ability to undergo so-called 1,2-metallate rearrangements, which possess the ability to effectively insert a nucleophilic atom into the carbon-boron bond. One could imagine taking advantage of this mode of reactivity to selectively functionalize a single carbon-boron bond either through selective "ate" formation or through taking advantage of differences in migratory aptitude between the primary and secondary alkyl groups.[18] In 2005, the Morken group was able to selectively react with the primary carbon-boron bond of a 1,2-bis(catechol boronate) by utilizing **2.31** in a

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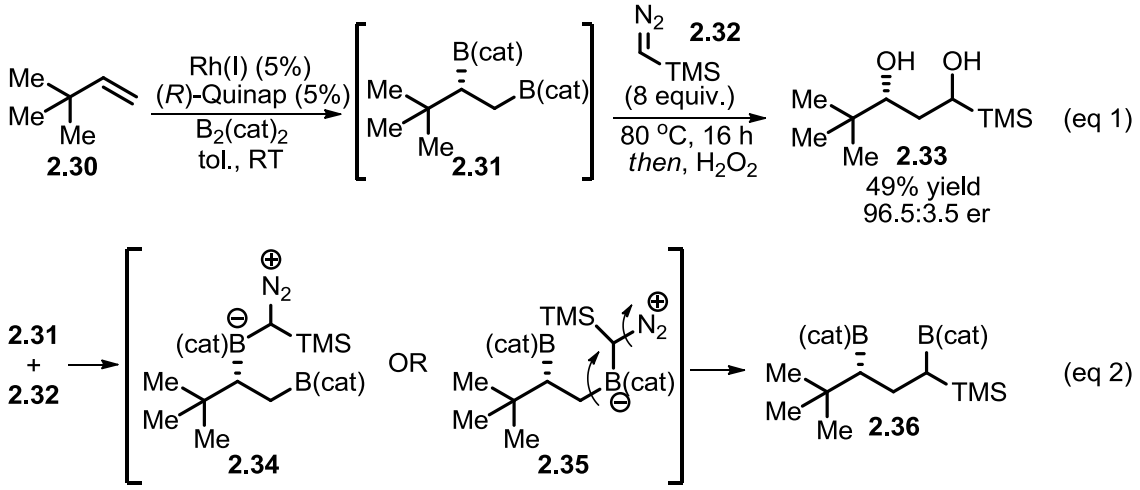
Thomas, S. P.; French, R. M.; Jheengut, V.; Aggarwal, V. K. *The Chemical Record* **2009**, *9*, 24. (e) Scott, H. K.; Aggarwal, V. K. *Chem. Eur. J.* **2011**, *17*, 13124.

[18] Bottoni, A.; Lombardo, M.; Neri, A.; Trombini, C. *J. Org. Chem*. **2003**, *68*, 3397.

homologation reaction (Scheme 2.6).[19] After enantioselective rhodium catalyzed diboration of terminal alkene **2.30**, treatment with four equivalents of **2.32** in two portions, followed by subsequent oxidation gave the corresponding 1,3-diol **2.33** in moderate yield and with no loss of enantiopurity. It was noted that in light of the generally favorable migration of secondary groups over primary,[20] the regioselectivity obtained may be due to favorable formation of a primary "ate" complex **2.35**, which then undergoes the desired 1,2-metallate rearrangement.

Scheme 2.6: Selective Mono-Homologation by Morken

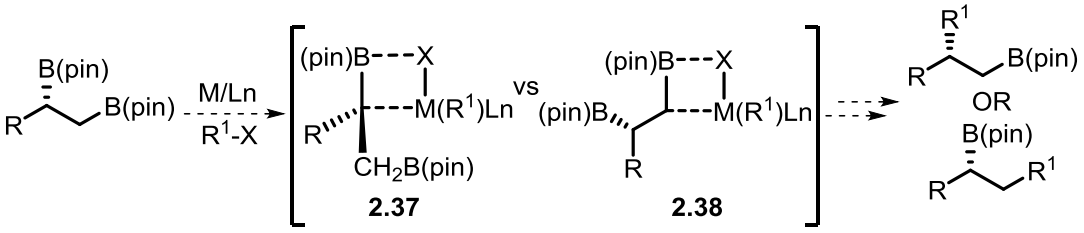


While the challenging mono-homologation of 1,2-bis(catechol boronates) esters was shown to be possible, the prospects of achieving a similar reaction with the corresponding 1,2-bis(pinacol boronates) may be impractical. More difficult "ate" formation due to the greater donicity of the pinacolato oxygens versus the catecholato oxygens, as well as greater steric hindrance about the boron atom, generally renders pincol boronates less conducive to this mode of reactivity, usually requiring somewhat

[19] Kalendra, D. M.; Duenes, R. A.; Morken, J. P. *Synlett* **2005**, 1749.
[20] Soderquist, J. A.; Najafi, M. R. *J. Org. Chem*. **1986**, *51*, 1330.

harsher conditions. In addition to 1,2-metallate rearrangements, perhaps the most useful transformation available to organoboron compounds is a transmetallation reaction, giving rise to carbon-transition metal bond formation and enabling cross-coupling reactions.[21] In principal, steric differences surrounding the carbons undergoing transmetallation (**2.37** versus **2.38**) could result in a significant rate disparity between primary and secondary, thereby enabling selective functionalization.[22] Notably, this approach would leave the remaining secondary pinacol boronate available for further functionalization, effectively connecting abundant terminal alkene starting materials with a diverse array of enantioenriched products in a rapid fashion. This chapter describes the development of an efficient protocol for engaging 1,2-bis(pinacol boronates) as nucleophilic partners in cross-coupling and its use in tandem with asymmetric diboration to afford a variety of enantiomerically enriched adducts directly from unbiased terminal alkenes.

Scheme 2.7: Use of Cross-Coupling to Selectively Functionalize 1,2-bis(pinacol boronates)



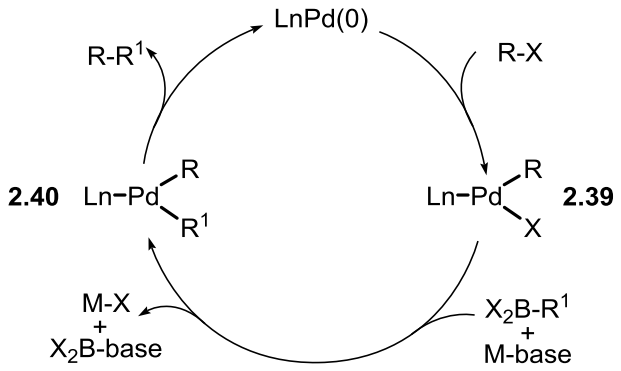
[21] For selected reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457. (b) Negishi, E. *Handbook of Organopalladium Chemistry for Organic Synthesis*, Vol. 1; Wiley: New York, **2002**. (c) de Meijere, A.; Diederich, F., Eds. *Metal-Catalyzed Cross-Coupling Reactions*, 2nd Ed.; Wiley-VHC: Weinheim, Germany, **2004**.

[22] The majority of alkyl Suzuki reactions occur at a primary carbon; however, secondary alkyl Suzuki reactions are known, see: Jana, R.; Pathak, T. P.; Sigman, M. S. *Chem. Rev*. **2011**, *111*, 1417.

2.2 Background

Importantly, the successful development of a selective coupling reaction necessitates engaging alkyl pinacol boronates as the nucleophilic partners in Suzuki-Miyaura cross-coupling. Historically, this has been one of the most difficult classes of boron compounds to utilize in cross-coupling and the development of successful couplings involving alkyl boronic esters has closely mirrored advances in the mechanistic understanding of the Suzuki-Miyaura reaction.[21,22] Similar to other cross-coupling reactions, the fundamental catalytic cycle consists of a sequence of three elementary steps; (1) oxidative addition of an appropriate electrophile to Pd(0) to give Pd(II) intermediate **2.39**, (2) transmetallation of the nucleophilic component to install a second carbon group on Pd (**2.40**), followed by (3) reductive elimination to release the product and regenerate Pd(0) (Scheme 2.8).

Scheme 2.8: Basic Catalytic Cycle for Suzuki-Miyaura Cross-Coupling

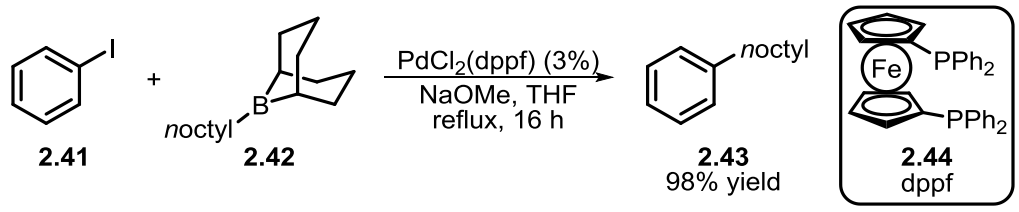


Notably, when R^1 is an alkyl group containing β hydrogens, problematic β-hydride elimination may compete with reductive elimination, resulting in non-productive consumption of the nucleophilic partner. Additionally, unlike the corresponding

Kumada[23] or Negishi[24] couplings, Suzuki-Miyaura reactions require the addition of base to promote transmetallation, the success of which is intimately related to both the character of the base and the nature of the boron compound employed.[25] Accordingly, the first successful employment of B-alkyl compounds in cross-coupling required the careful combination of boron component, base, and catalyst to both avoid β-hydride elimination and promote transmetallation.

2.2.1 Early Developments in B-alkyl Suzuki-Miyaura Cross-Couping

Scheme 2.9: Seminal B-alkyl Cross-Coupling by Suzuki

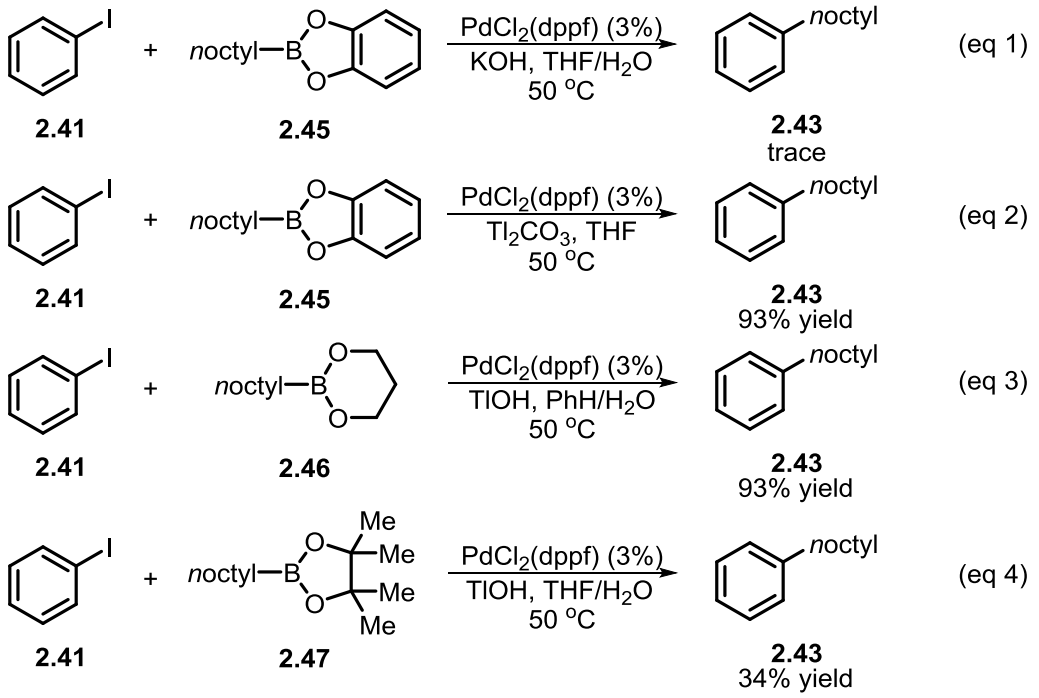


In 1986, the Suzuki group disclosed the first example of a B-alkyl cross-coupling reaction (Scheme 2.9).[26] Previously, Hayashi developed the highly effective $PdCl_2$(dppf) pre-catalyst for efficient cross-coupling of both alkyl Grignard reagents and alkyl zinc reagents.[27] The high selectivity for product formation and general lack of β hydride elimination was attributed to the large bite angle of the dppf ligand **2.44**, which compresses the other groups in the Pd(II) square plane, accelerating reductive elimination. Realizing that alkyl palladium species derived from boron nucleophiles are prone to the same deleterious side reactions, Suzuki also examined the use of

[23] For a recent review, see: Knappke, C. E. I.; von Wangelin, A. J. *Chem. Soc. Rev*. **2011**, *40*, 4948.
[24] For a recent review, see: Negishi, E.; Hu, Q.; Huang, Z.; Qian, M.; Wang, G. *Aldrichimica Acta* **2005**, *38*, 71.
[25] Miyaura, N. *J. Organomet. Chem*. **2002**, *653*, 54.
[26] Miyaura, N.; Ishiyama, T.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett*. **1986**, *27*, 6369.
[27] Hayashi, T.; Konishi, M.; Kobori, Y.; Kumada, M.; Higuchi, T.; Hirotsu, K. *J. Am. Chem. Soc*. **1984**, *106*, 158.

$PdCl_2$(dppf). Importantly, both aryl and vinyl electrophiles were successfully coupled to trialkyl boranes in the presence of hydroxide or methoxide base. The alkyl 9-BBN derivatives could be prepared conveniently by an *in situ* hydroboration of the corresponding terminal alkene followed by direct use in cross-coupling.

Scheme 2.10: Suzuki's Use of Boronic Esters for B-alkyl Coupling



Seeking to extend this reactivity to alkyl boronic esters, which are more easily isolated and purified than their corresponding trialkyl borane counterparts, Suzuki and Miyaura examined their use under the previously optimized conditions (Scheme 2.10).[28] Utilizing standard bases, such as sodium carbonate, hydroxide, or methoxide resulted in only trace amounts of desired coupling products (equation 1). Following Kishi's observation[29] that thallium bases greatly accelerate cross-coupling of vinyl boronic acids,

[28] (a) Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett*. **1989**, 1405. (b) Miyaura, N.; Ishiyama, T.; Sasaki, H.; Ishikawa, M.; Satoh, M.; Suzuki, A. *J. Am. Chem. Soc*. **1989**, *111*, 314.
[29] Uenishi, J.; Beau, J-M.; Armstrong, R. W.; Kishi, Y. *J. Am. Chem. Soc*. **1987**, *109*, 4756.

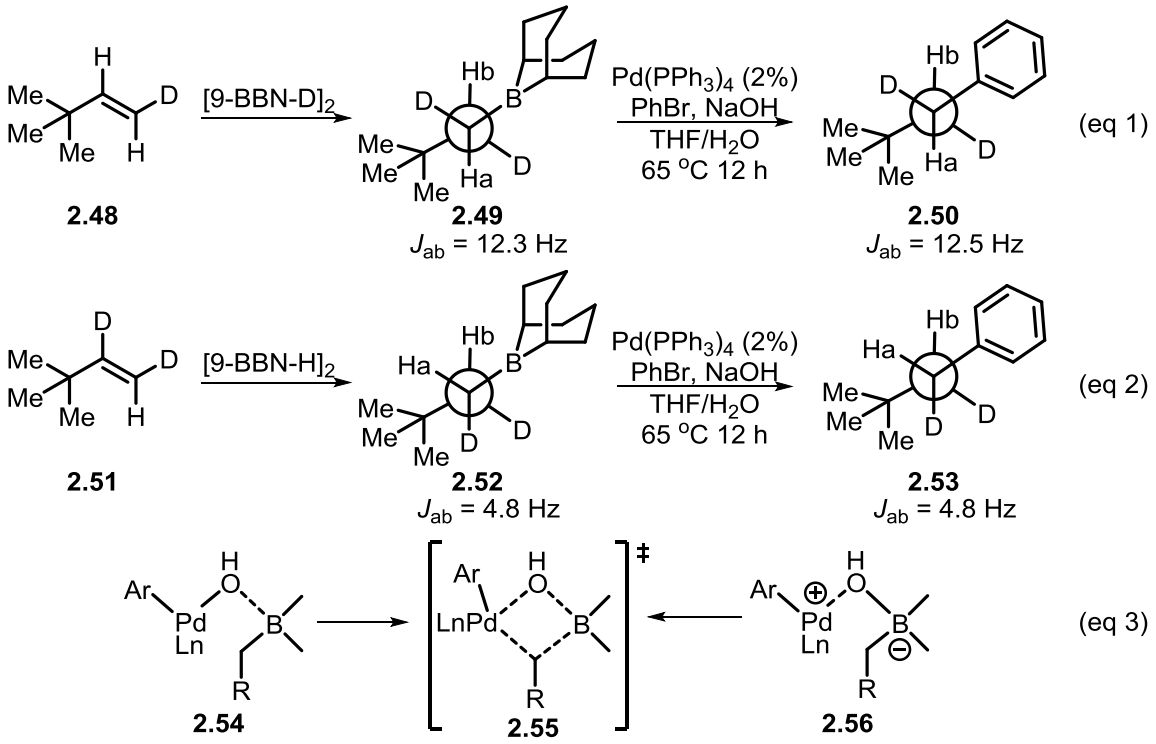
Suzuki examined their use with alkyl boronic esters. Again utilizing Hayashi's $PdCl_2$(dppf) pre-catalyst, efficient cross-coupling was achieved with the use of thallium carbonate and thallium hydroxide with both alkyl catechol boronates and alkyl propylene glycol boronates, respectively (equations 2 & 3); however, the use of alkyl pinacol boronates resulted in much lower reactivity (equation 4). The reactivity trend observed is likely explained by attenuated Lewis acidity of boronic esters compared to boranes, which discourages formation of nucleophilic "ate" complexes and as a result slows transmetallation. While the use of thallium bases can overcome these difficulties, in the case of the alkyl catechol boronates and the alkyl propylene glycol boronates, the alkyl pinacol boronates remained significantly less reactive.

2.2.2 Mechanistic Features of the B-Alkyl Suzuki-Miyaura Reaction

Following this seminal work by Suzuki, the B-alkyl cross-coupling reaction became a highly useful method for the construction of carbon-carbon bonds involving sp^3 hybridized centers.[30] The alkyl boranes became particularly popular and dominated the first 10 years of B-alkyl couplings because of their convenient preparation from olefins and their superior levels of reactivity compared to alkyl boronate esters, the latter of which generally required the use of highly toxic thallium bases. As interest continued to grow surrounding the B-alkyl Suzuki-Miyaura reaction, detailed mechanistic studies began to appear.

[30] (a) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed*. **2001**, *40*, 4544. (b) Nicolaou, K. C.; Bulger, P. G.; Sarlah, D. *Angew. Chem. Int. Ed*. **2005**, *44*, 4442.

Scheme 2.11: Stereochemical Course of Cross-Coupling by Soderquist

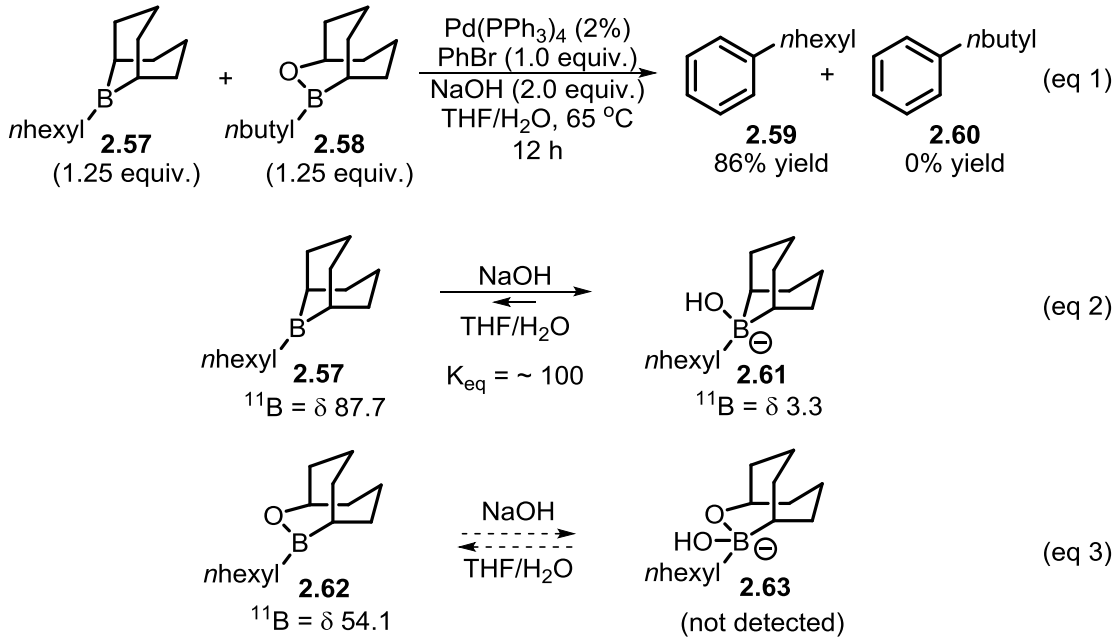


In 1998, the groups of both Woerpel[31] and Soderquist[32] reported the stereochemical course of transmetallation in the B-alkyl Suzuki-Miyaura cross-coupling. Due to the generally inefficient coupling of secondary alkyls,[28b] both studies utilized deuterium incorporation to access stereodefined primary alkyl boranes (Scheme 2.11). By measuring the coupling constants[33] of H_a and H_b in both **2.50** and **2.53**, both Woerpel and Soderquist showed that the coupling reactions proceeded with retention of configuration at carbon. Soderquist noted that this result was consistent with the 4-membered transition state model **2.55**, which had been suggested previously[21a] as the mode of transmetallation in Suzuki-Miyaura cross-coupling. Recognizing that transition

[31] Ridgway, B. H.; Woerpel, K. A. *J. Org. Chem*. **1998**, *63*, 458.
[32] Matos, K.; Soderquist, J. A. *J. Org. Chem*. **1998**, *63*, 461.
[33] Whitesides, G. M.; Bock, P. L.; Boschetto, D. J.; Rasmussen, J. R.; Demers, J. M. *J. Am. Chem. Soc*. **1974**, *96*, 2814.

state **2.55** could possibly arise from either palladium hydroxo-intermediate **2.54** or hydroxyborate **2.56**, Soderquist and co-workers probed the system by changing the nature of the alkyl boron species, noting that differences in the Lewis acidity of boron may have a significant influence on the pathway to transition state **2.55**.

Scheme 2.12: Competition Between Borane and Borinate by Soderquist



Utilizing borane **2.57** and borinate **2.58**, a competition experiment revealed product formation derived solely from the borane (Scheme 2.12).[32] Seeking a suitable explanation for this level of selectivity, Soderquist examined the interaction of sodium hydroxide with both **2.57** and **2.62**. Importantly, treatment of borane **2.57** with sodium hydroxide resulted in formation of hydroxyborate complex **2.61** with an estimated K_{eq} of about 10^2; however, subjecting borinate **2.62** to the same conditions resulted in no detectable formation of the corresponding hydroxy complex **2.63**, reflecting the greatly diminished Lewis acidity of the borinate versus the borane. Notably under the standard

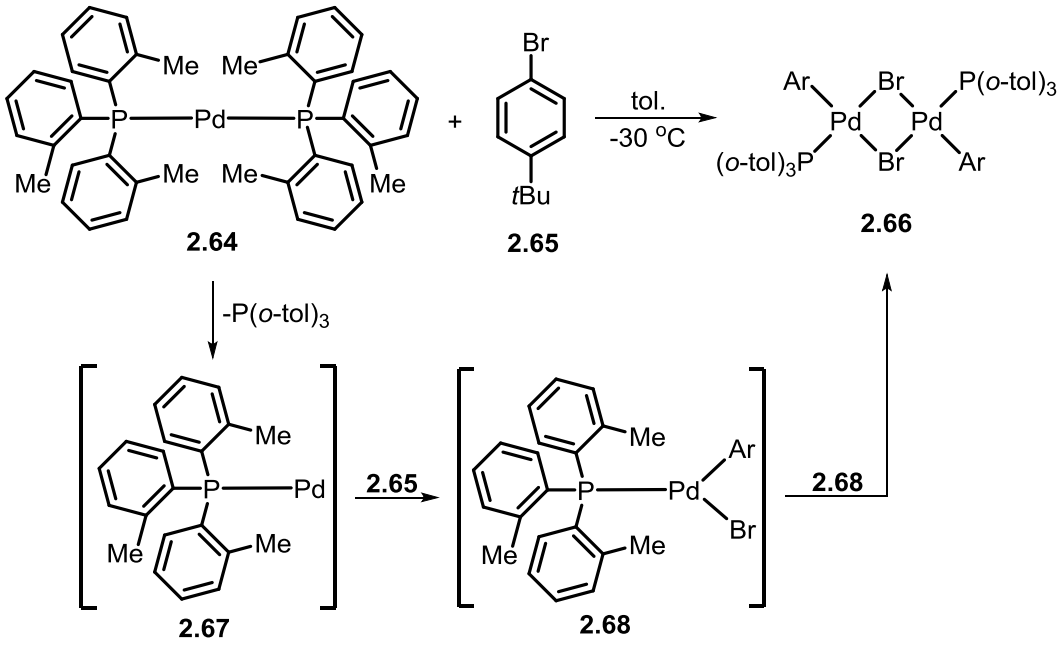
coupling conditions in equation 1, it is likely that a significant amount of complex **2.61** is present, whereas borinate **2.58** likely remains neutral.

Soderquist then employed kinetics to compare cross-coupling reactions of borane **2.57** and borinate **2.62** in the hopes of gleaning information which may point to formation of transition state **2.55** through either palladium hydroxo **2.54** or hydroxyborate **2.56** (Scheme 2.11). In the end, it was found that cross-coupling reactions employing borane **2.57** were zero-order in **2.57**, but were first-order in PhBr, pointing to oxidative addition as the rate limiting step of the cycle. Interestingly, reactions involving borinate **2.62** were found to be zero-order in **2.62**, zero-order in PhBr and first-order in hydroxide, possibly indicating that hydrolysis of a Pd(II) halide complex to a palladium hydroxo complex is rate limiting. Taken together, the authors conclude that due to the facile formation of hydroxyborate **2.61**, the alkyl borane likely reacts through formation of intermediate **2.56**, whereas alkyl borinate **2.62** likely reacts through association with a palladium hydroxo species as depicted in **2.54**.[32]

Following this important study by Soderquist, the continued development of B-alkyl cross-couplings has benefitted tremendously from studies in other areas of Suzuki-Miyaura cross-coupling. Due in large part to the pioneering efforts from the groups of Buchwald, Hartwig, and Fu, more and more efficient catalysts have appeared for both carbon-carbon as well as carbon-heteroatom bond formation. These improvements have been dominated by rigorous studies of each step involved in the catalytic cycle, resulting in a very detailed understanding of palladium catalyzed cross-coupling mechanisms.

2.2.2.1 Oxidative Addition in Suzuki-Miyaura Cross-Couplings

Scheme 2.13: Oxidative Addition through Monoligated Pd(0) by Hartwig

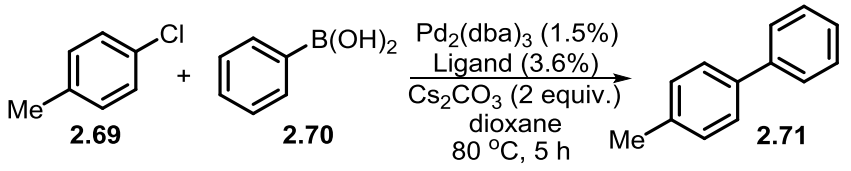


Due to common overlap with other coupling reactions, oxidative addition has become a well understood and highly studied process. Depending on the nature of electrophile and nucleophile employed, oxidative addition can often be the rate-limiting step in Suzuki-Miyaura cross-coupling, especially with the use of chloride electrophiles.[34] In 1995, Hartwig studied the use of Pd(0) complexes containing two bulky triaryl phosphine ligands in stoichiometric oxidative addition reactions (Scheme 2.13).[35] Through use of kinetic data, the oxidative addition of aryl bromide **2.65** to palladium was found to proceed first through ligand dissociation to give the highly reactive monoligated **2.67**, which subsequently undergoes oxidative addition, ultimately giving dimer **2.66**. The discovery of monoligated palladium species for efficient oxidative addition dramatically altered the status quo. Previously, it was generally believed that the

[34] Saito, S.; Oh-tani, S.; Miyaura, N. *J. Org. Chem*. **1997**, *62*, 8024.
[35] Hartwig, J. F.; Paul, F. *J. Am. Chem. Soc*. **1995**, *117*, 5373.

presence of multiple electron rich phosphine donors would lead to complexes containing a correspondingly electron rich metal center and thus facilitate oxidative addition reactions. The Hartwig study showed the importance of coordination number in such processes and led researchers to develop catalyst systems which gain access to monoligated Pd(0) species.[36]

Scheme 2.14: Suzuki-Miyaura Cross-Coupling with Aryl Chlorides by Fu



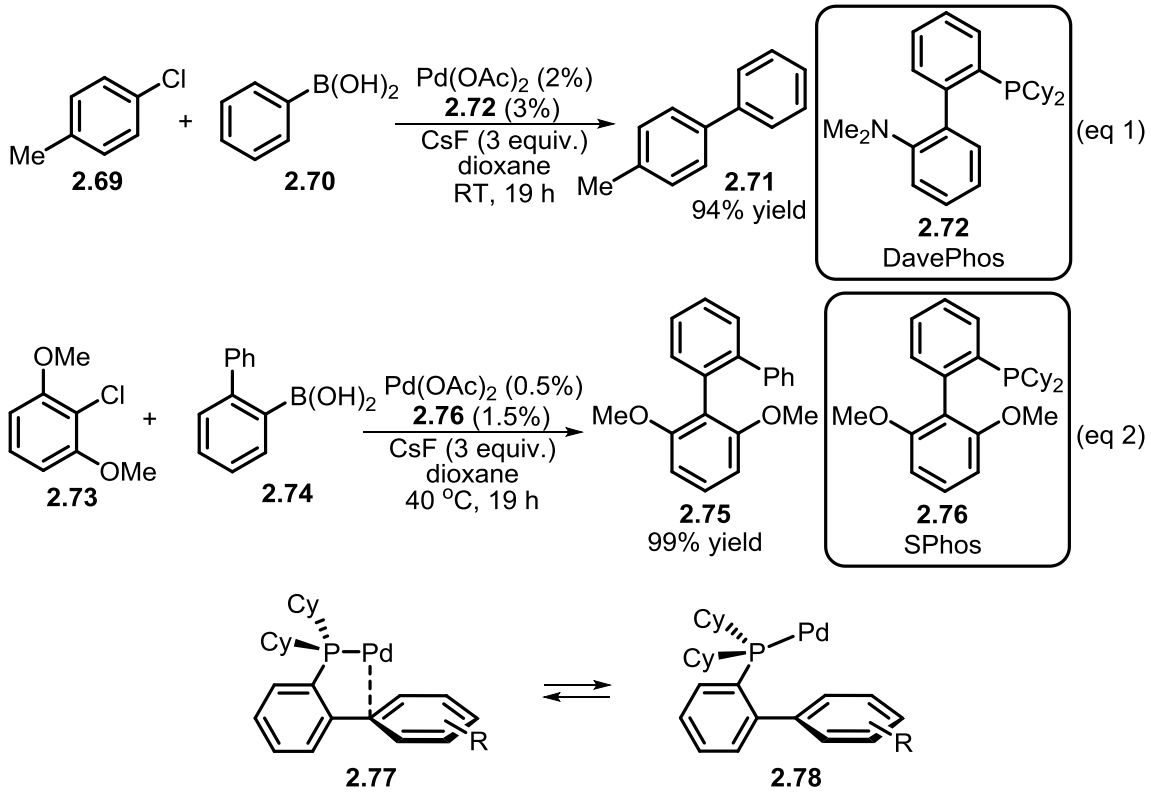
Ligand	Yield (**2.71**)
P*t*Bu$_3$	86%
P(*o*-tol)$_3$	10%
$Cy_2P(CH_2)_2PCy_2$	0%

In 1998, Fu showed that difficult aryl chlorides could efficiently participate in Suzuki-Miyaura cross-coupling reactions with the use of a Pd/P*t*Bu$_3$ catalyst mixture (Scheme 2.14).[37] Importantly, the use of either Hartwig's triorthotolyl phosphine or an electron rich bidentate phosphine, such as dicyclohexylphosphinoethane failed to promote the desired coupling reaction, highlighting the need for both access to monoligated palladium species and strong electron donors.[38] As shown by Buchwald in 1998, dialkyl-biaryl phosphines have the ability to promote exceedingly efficient coupling reactions.[39] The unique structure of this ligand class allows for interaction of the distal aryl ring with palladium as shown in **2.77** (Scheme 2.15). This labile interaction is thought to lead to greater catalyst stability by preventing precipitation of Pd(0), as well as facilitate formation of highly reactive monoligated palladium

[36] Christmann, U.; Vilar, R. *Angew. Chem. Int. Ed*. **2005**, *44*, 366.
[37] Littke, A. F.; Fu, G. C. *Angew. Chem. Int. Ed*. **1998**, *37*, 3387.
[38] Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc*. **2000**, *122*, 4020.
[39] Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc*. **1998**, *120*, 9722.

complexes.[40] Importantly, both unreactive electrophiles (equation 1) and sterically hindered coupling partners (equation 2) participated smoothly in coupling reactions under mild conditions.[40c]

Scheme 2.15: Highly Effective Biaryl Ligands by Buchwald



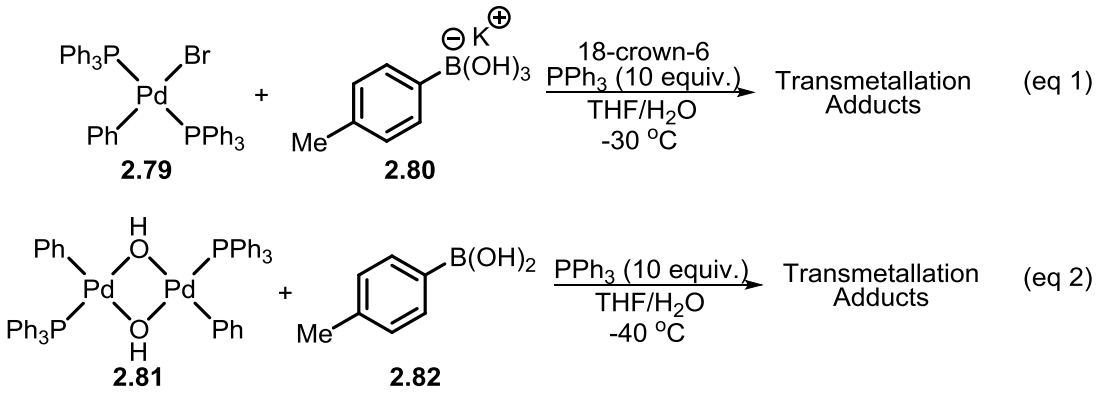
2.2.2.2 Transmetallation in Suzuki-Miyaura Cross-Coupling

While oxidative addition is usually rate-limiting when aryl and vinyl boronates are employed as coupling partners, transmetallation is often found to be rate-limiting for alkyl boronates. Following the studies by Soderquist,[32] Carrow and Hartwig recently provided some of the first quantitative data to strongly support a palladium hydroxo

[40] (a) For crystal structure of arene-Pd interaction, see: Reid, S. M.; Boyle, R. C.; Mague, J. T.; Fink, M. J. *J. Am. Chem. Soc*. **2003**, *125*, 7816. For more extensive discussion, see: (b) Wolfe, J. P.; Singer, R. A.; Yang, B. H.; Buchwald, S. L. *J. Am. Chem. Soc*. **1999**, *121*, 9550. (c) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc*. **2005**, *127*, 4685.

species in combination with a neutral boronate as the active pair in transmetallation reactions (Scheme 2.16).[41] Reaction rates were determined for transmetallation between an isolated palladium halide complex **2.79** and a preformed hydroxyborate **2.80** (equation 1), as well as between an isolated palladium hydroxo complex **2.81** and a neutral boronic acid **2.82** (equation 2). Importantly, transmetallation to palladium hydroxo complex **2.81** was found to be roughly 14,000 times faster than the transmetallation to halide complex **2.79**.

Scheme 2.16: Measuring Rates of Transmetallation by Hartwig



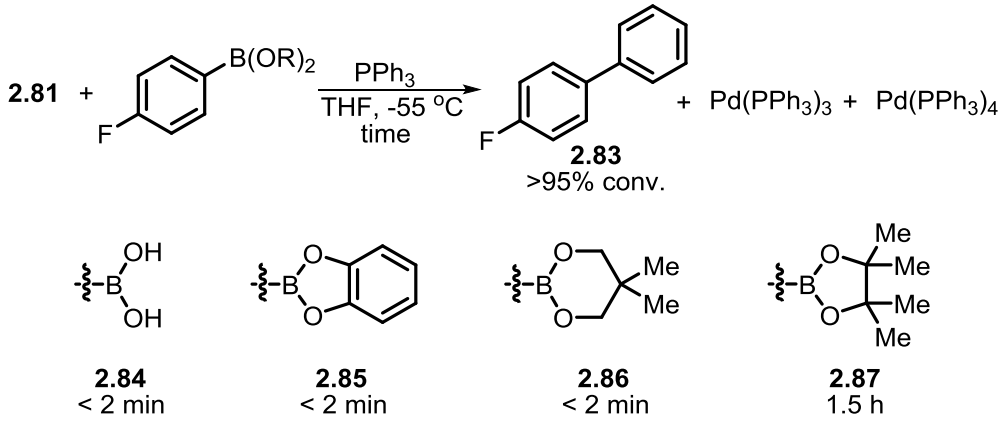
K_{rel}	Coupling Partners
1	(eq 1)
1.4×10^4	(eq 2)

The authors also measured the equilibrium concentrations of both halide and hydroxo complexes of palladium as well as the equilibrium concentrations of both hydroxy borate and neutral boronic acid. Considering all four species are present in reasonable amounts under standard reaction conditions, Carrow and Hartwig conclude that due to the significantly more rapid transmetallation through the palladium hydroxo complex with neutral boronic acid, the vast majority of coupling reaction likely proceeds

[41] Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc*. **2011**, *133*, 2116.

through this pathway and not through transmetallation to palladium halide complex **2.79**. Stoichiometric transmetallations with isolated palladium hydroxo complex **2.81** also proved to be rapid for both catechol boronate **2.85** and neopentyl glycol boronate **2.86**, but was significantly slower with the use of pinacol boronate **2.87**, highlighting the difficulty associated with the use of this sterically encoumbered ester (Scheme 2.17).

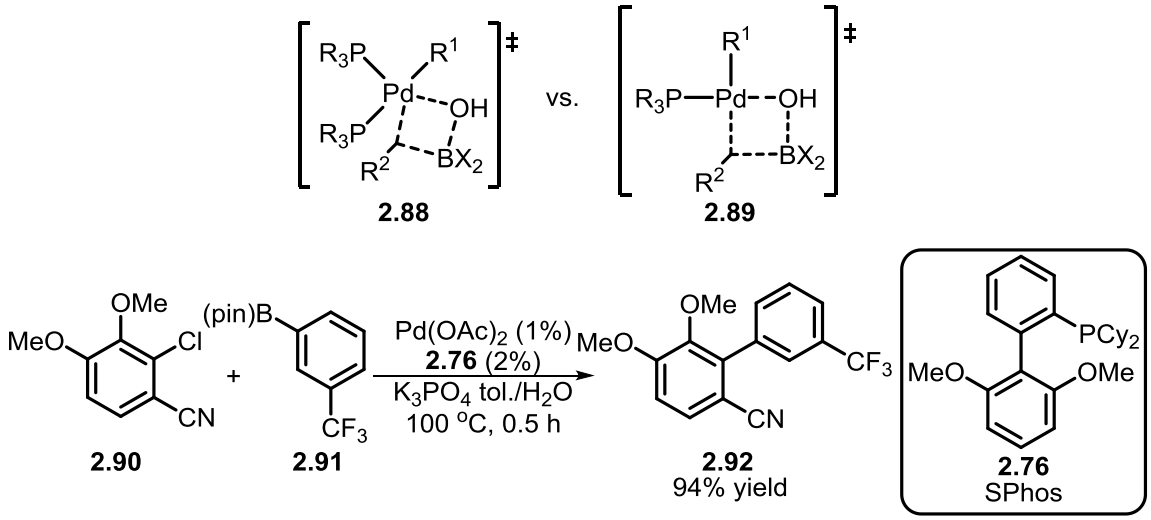
Scheme 2.17: Facile Transmetallation of Boron Nucleophiles by Hartwig



In addition to proper activation of the boron nucleophiles, having a ligand set on palladium which can facilitate transmetallation is also vital for efficient cross coupling. In general, the need to access the postulated 4-membered transition state during transmetallation requires that a certain amount of free space about palladium be available for the incoming nucleophile (Scheme 2.18). Bidentate ligands, which result in formation of coordinatively saturated Pd(II) species following oxidative addition, tend to crowd the metal and slow transmetallation (**2.88**). Conversely, employing bulky monodentate ligands encourages formation of monoligated species that are not only beneficial to oxidative addition as described above, but also allow for three coordinate Pd(II) complexes (**2.89**), which are postulated to be more reactive for transmetallation.[40b] For instance, the Buchwald group demonstrated the ability of biaryl ligands to form

active catalysts which are capable of achieving efficient cross-coupling with the use of weak nucleophiles such as electron poor aryl pinacol boronates (Scheme 2.18).[40c]

Scheme 2.18: Difficult Transmetallation Accomplished by Buchwald



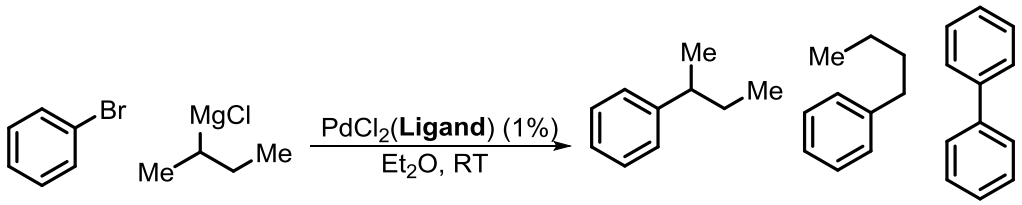
2.2.2.3 Reductive Elimination in Suzuki-Miyaura Cross-Coupling

The final step in the catalytic cycle of many reactions is reductive elimination, which releases the desired product and regenerates the reduced catalyst which is capable of undergoing further reaction. While this step is rarely rate-limiting in Suzuki-Miyaura cross-coupling, efficient reductive elimination is vital in cases where β-hydrogens are present in the coupling partners in order to avoid side reactions. To solve problems associated with these β-hydride eliminations, efforts were made to expediate reductive elimination by utilizing large bite angle diphosphine ligands.[42] Expanding upon Hayashi's work, van Leeuwen further examined the effect of bite angle on the efficiency of Kumada coupling between *sec*-BuMgCl **2.94** and PhBr (Table 2.1).[43] Upon increasing the bite angle, more efficient coupling was obtained, with DPEphos **2.98** (P-Pd-P,

[42] van Leeuwen, P. W. N. M.; Kramer, P. C. J.; Reek, J. N. H.; Dierkes, P. *Chem. Rev*. **2000**, *100*, 2741.
[43] Kranenburg, M.; Kramer, P. C. J.; van Leeuwen, P. W. N. M. *Eur. J. Inorg. Chem*. **1998**, 155.

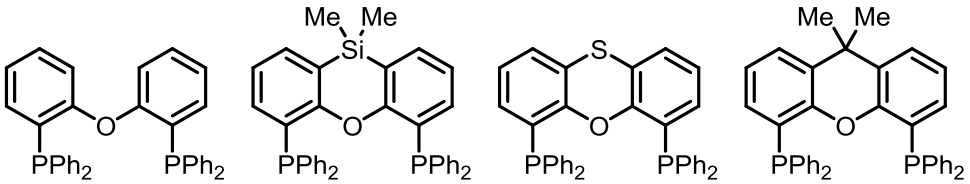
102°) being the most efficient, delivering the desired product with both the highest selectivity and the highest reaction rate (entry 5).

Table 2.1: Kumada Coupling Efficiency as a Function of Ligand Bite Angle by van Leeuwen



2.93 **2.94** **2.95** **2.96** **2.97**

Entry	**Ligand**	∠ P-Pd-P	TOF (h^{-1})	time (h)	Conv. (%)	**2.95**(%)	**2.96**(%)	**2.97**(%)
1	**dppe**	85°	-	48	4	0	0	-
2	**dppp**	91°	-	24	67	69	31	-
3	**dppb**	98°	-	8	98	51	25	-
4	**dppf**	96°	79	2	100	95	2	3
5	**DPEphos**	103°	181	2	100	98	1	1
6	**sixantphos**	109°	36	16	59	67	17	16
7	**thixantphos**	110°	24	16	37	51	17	32
8	**xantphos**	111°	24	16	24	41	19	40

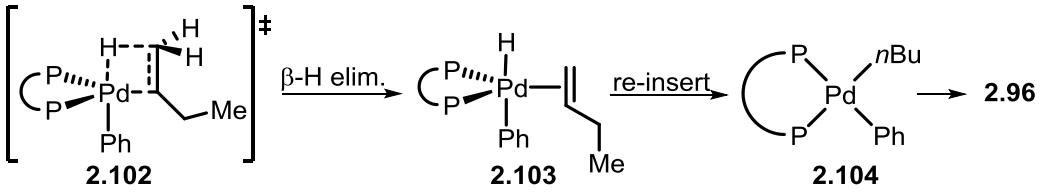


2.98 DPEphos **2.99** sixantphos **2.100** thixantphos **2.101** xantphos

Interestingly, further increasing the phosphine bite angle results in large amounts of side product formation (Table 2.1, entries 6-8). This trend was rationalized by the stabilization of trigonal bipyramidal geometries with ligands containing sufficiently large bite angles (Scheme 2.19). Not only does this geometry slow reductive elimination, it may also accelerate β-hydride elimination through transition state **2.102**. Subsequent re-

insertion and reductive elimination affords *n*BuPh **2.96**. The formation of biphenyl **2.97** was thought to occur through a second oxidative addition to arrive at a diaryl Pd(IV) complex, followed by reductive elimination to give **2.97**, although Grignard exchange between PhBr and *sec*BuMgCl was not ruled out.[43]

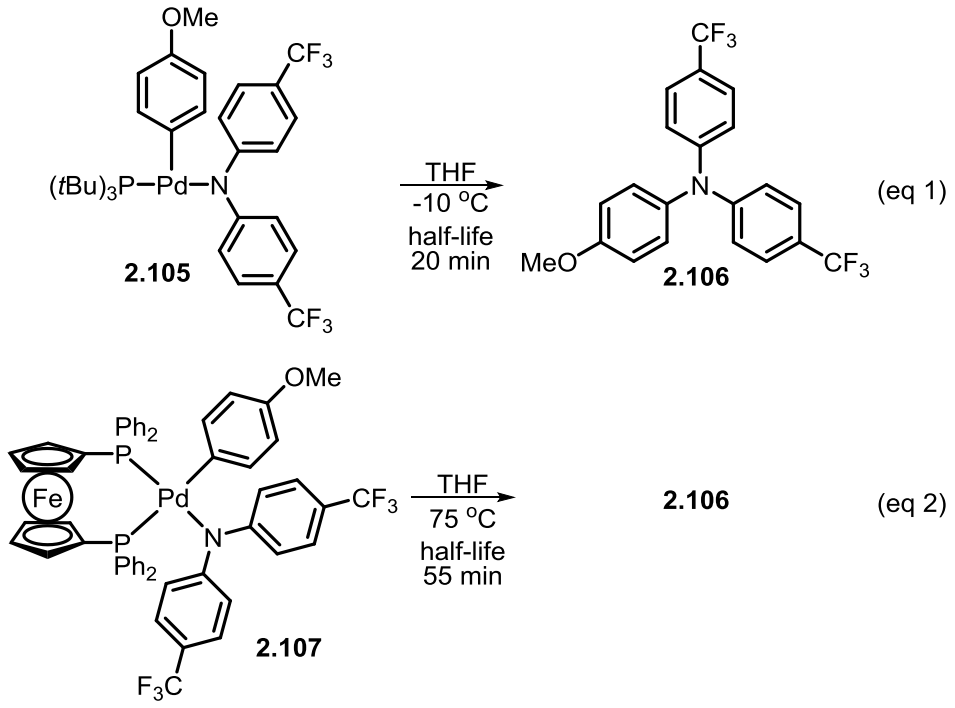
Scheme 2.19: Stabilization of Trigonal Bipyramidal Intermediates with Large Bite Angle Ligands



In addition to studies utilizing large bidentate ligands, several reports have examined the role of large monophosphine ligands in reductive elimination.[36] In 2004, Hartwig and coworkers were able to isolate a long-predicted 3-coordinate T-shaped monoligated Pd(II) complex **2.105**, which lacked any detectable agostic interactions (Scheme 2.20).[44] While previous reports had proposed reductive elimination proceeding through 3-coordinate intermediates,[45] Hartwig was the first to be able to monitor reductive elimination directly from these intermediates. Utilizing ^{19}F NMR, the rate of reductive elimination from **2.105** was determined. Importantly, the addition of P*t*Bu$_3$ to the system did not affect the rate of elimination, indicating that the reaction proceeds directly from the 3-coordinate intermediate and not through initial coordination of an additional phosphine. Finally, a direct comparison of elimination rates for complex **2.105** and the corresponding 4-coordinate Pd(II) complex **2.107** reveals a significantly faster elimination for **2.105**.

[44] Yamashita, M.; Hartwig, J. F. *J. Am. Chem. Soc*. **2004**, *126*, 5344.
[45] Tatsumi, K.; Hoffman, R.; Yamamoto, A.; Stille, J. K. *Bull. Chem. Soc. Jpn*. **1981**, *54*, 1857.

Scheme 2.20: Reductive Elimination from 3-Coordinate Intermediates by Hartwig



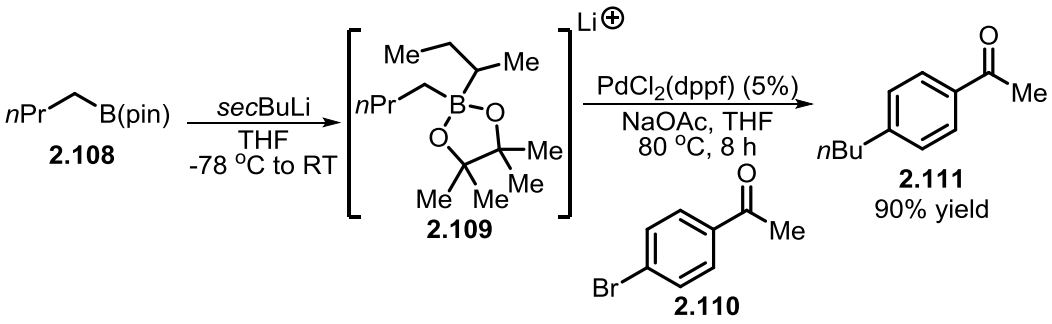
While the classical approaches to accelerating oxidative addition and reductive elimination resulted in many improved cross-coupling reactions, it was often the case that modifications to increase the efficiency of one step resulted in inhibition of another and resulted in only minor rate enhancements for the system as a whole. Recent developments concerning the high activity of ML_1 complexes have resulted in catalysts which are capable of accelerating all the elementary steps involved in the basic Suzuki-Miyaura cycle.[36] In particular, the groups of Hartwig and Buchwald have made pivotal contributions to the field, allowing for incredibly efficient carbon-carbon and carbon-heteroatom bond formation.

2.2.3 Alkyl Pinacol Boronates in Suzuki-Miyaura Cross-Coupling

As the mechanistic understanding of Suzuki-Miyaura cross-coupling improved over time, various efforts have been made to extend the range of couplings to include

alkyl pinacol boronates.[46] The greatly reduced Lewis acidity of alkyl pinacol boronates combined with the more sterically congested environment about boron results in a diminished interaction between Lewis base activators and alkyl boronates in Suzuki-Miyaura reactions, whether the activator be a palladium bound base, or external reagent. As a result, early efforts to engage alkyl pinacol boronates focused on proper base selection, as shown by Suzuki with the first example employing thallium bases (Scheme 2.10).[28a] An alternative approach was developed by Falck, whereby one equivalent of *sec*-BuLi was added to an alkyl pinacol boronate to generate the corresponding lithium borate complex **2.109** (Scheme 2.21).[47] Upon reacting with aryl bromide **2.110** for 8 h in the presence of $PdCl_2$(dppf), the desired coupled product was isolated in excellent yield. While this approach is undoubtedly useful for certain substrate pairings, the use of very strong base limits the scope to unfuctionalized boronate partners.

Scheme 2.21: Suzuki-Miyaura Cross-Coupling with Pre-formed Borates by Falck

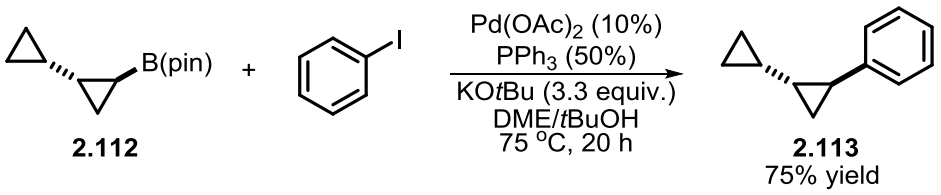


In 2001, de Meijere reported the use of cyclopropyl pinacol boronates in Suzuki-Miyaura cross-coupling (Scheme 2.22).[48] Utilizing potassium *tert*-butoxide in a DME/*tert*-butanol solvent system, iodobenzene was successfully coupled to **2.112** to give

[46] Doucet, H. *Eur. J. Org. Chem*. **2008**, 2013.
[47] Zou, G.; Falck, J. R. *Tetrahedron Lett*. **2001**, *42*, 5817.
[48] Löhr, S.; de Meijere, A. *Synlett* **2001**, 489.

the desired product **2.113** in good yield. The relatively efficient coupling of the secondary alkyl pinacol boronate **2.112** is notable, although the high degree of s-character present in the boron-carbon bond of the starting material may contribute to its enhanced reactivity compared to other secondary alkyl pinacol boronates.

Scheme 2.22: Use of Cyclopropyl Boronates by de Meijere



2.112

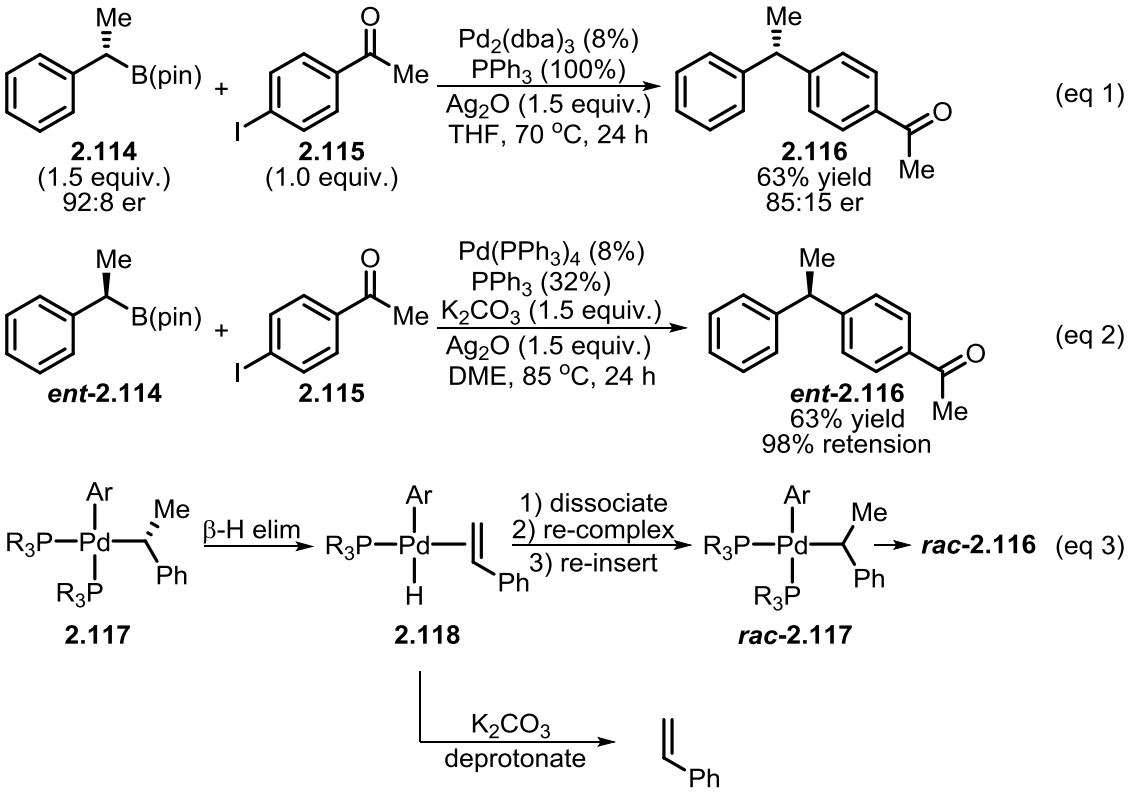
2.113
75% yield

More recently, Crudden and co-workers developed the stereoretentive Suzuki-Miyaura cross-coupling of secondary benzylic pinacol boronates (Scheme 2.23).[49] Taking advantage of their previously developed asymmetric hydroboration of styrene derivatives,[50] a variety of aryl electrophiles were successfully coupled in moderate yields and with good levels of stereoretention. Notably, under the standard reaction conditions, primary non-benzylic alkyl pinacol boronates failed to undergo any reaction, indicating the important role the benzylic position plays in imparting reactivity to this class of compounds. In a follow-up study to their initial communication, the Crudden group found the addition of potassium carbonate greatly improved the stereospecificity of the coupling reaction (equation 2).[51] Racemization was postulated to be occurring through a β-hydride elimination, dissociation, and reinsertion sequence as illustrated in equation 3. Rather than preventing this process from occurring, the addition of potassium carbonate was thought to intercept palladium hydride **2.118**, disrupting the racemization pathway

[49] Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc*. **2009**, *131*, 5024.
[50] Crudden, C. M.; Hleba, Y. B.; Chen, A. C. *J. Am. Chem. Soc*. **2004**, *126*, 9200.
[51] Glasspoole, B. W.; Oderinde, M. S.; Moore, B. D.; Antoft-Finch, A.; Crudden, C. M. *Synthesis* **2013**, *45*, 1759.

through deprotonation, ultimately leading to formation of styrene instead of racemic product.

Scheme 2.23: Stereoretentive Coupling of Benzylic Boronates by Crudden

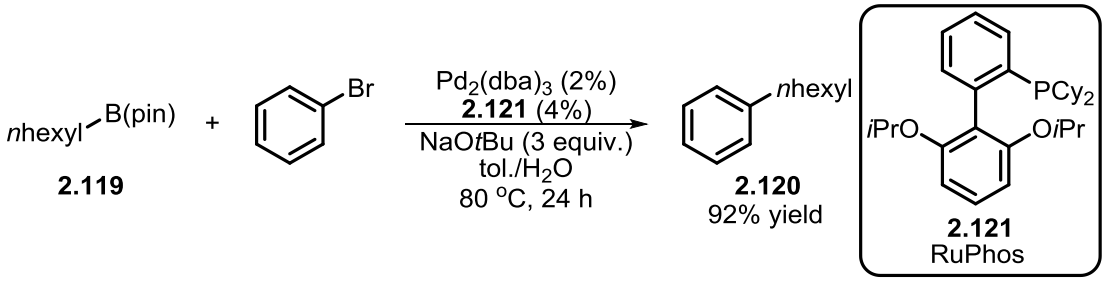


As a footnote in their recent communication regarding the copper-catalyzed borylation of alkyl halides, Marder and Liu disclosed the successful Suzuki-Miyaura cross-coupling of primary alkyl boronates with aryl bromides and chlorides (Scheme 2.24).[52] In the presence of Buchwald's RuPhos **2.121**[53] and Pd(0), good to excellent yields of the desired coupling products were obtained. While this represents a significant advance in the scope of useful alkyl pinacol boronates for Suzuki-Miyaura cross-

[52] Yang, C-T.; Zhang, Z-Q.; Tajuddin, H.; Wu, C-C.; Liang, J.; Liu, J-H.; Fu, Y.; Czyzewska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem. Int. Ed*. **2012**, *51*, 528.
[53] Charles, M. D.; Schultz, P.; Buchwald, S. L. *Org. Lett*. **2005**, *7*, 3965.

coupling, no explanation was given to account for the high levels of reactivity reached under these reaction conditions.

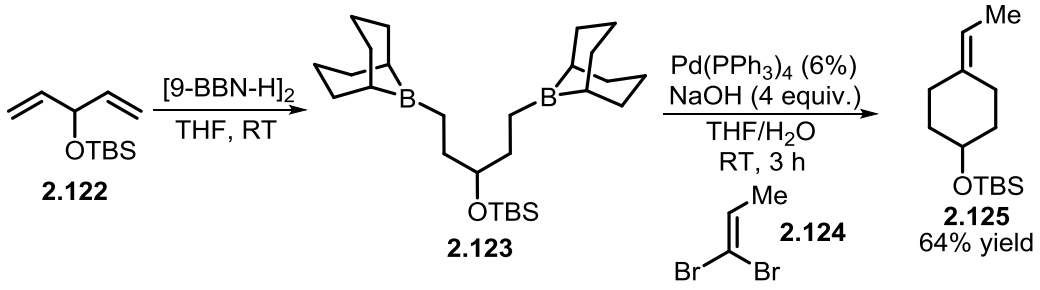
Scheme 2.24: Efficient Coupling of Unactivated Alkyl Pinacol Boronates by Marder and Liu



2.2.4 Alkyl Diboron Nucleophiles in Suzuki-Miyaura Cross-Coupling

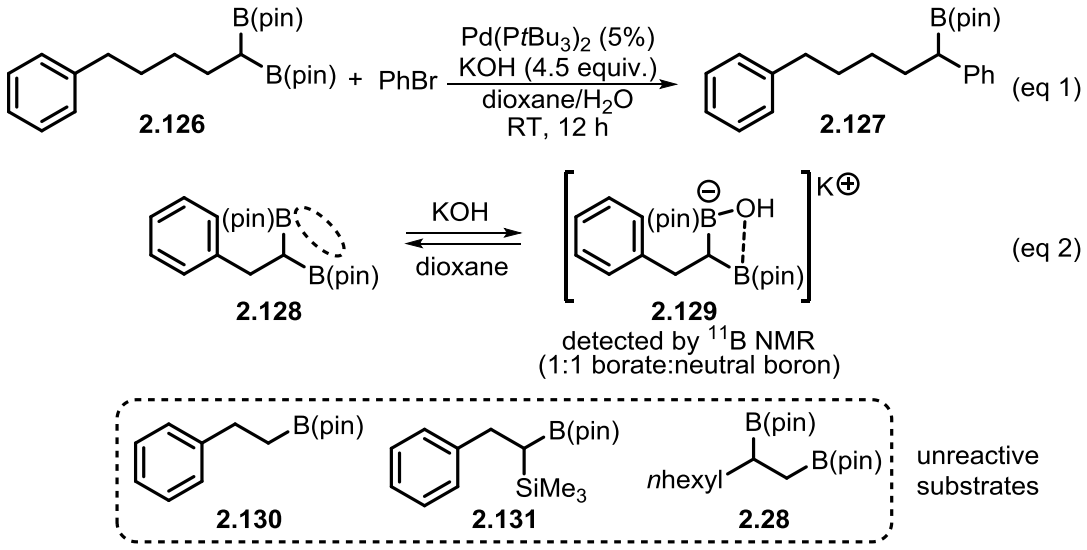
The vast majority of Suzuki-Miyaura cross-coupling reactions have utilized nucleophilic partners that contain a single boron group. The introduction of additional boron groups affords compounds which are capable of undergoing further reactions, thereby increasing their synthetic value. For instance, Soderquist forged the diborane **2.123** *via* a double hydroboration of diene **2.122** (Scheme 2.25).[54] A subsequent double cross-coupling with one equivalent of 1,1-vinyl dibromide **2.124** under mild conditions afforded the desired carbocyclic product **2.125** in good yield.

Scheme 2.25: Double B-alkyl Suzuki-Miyaura Coupling by Soderquist



[54] Soderquist, J. A.; León, G.; Colberg, J. C. Martinez, I. *Tetrahedron Lett*. **1995**, 36, 3119.

Scheme 2.26: Facile Coupling of 1,1-Bis(pincol boronates) by Shibata

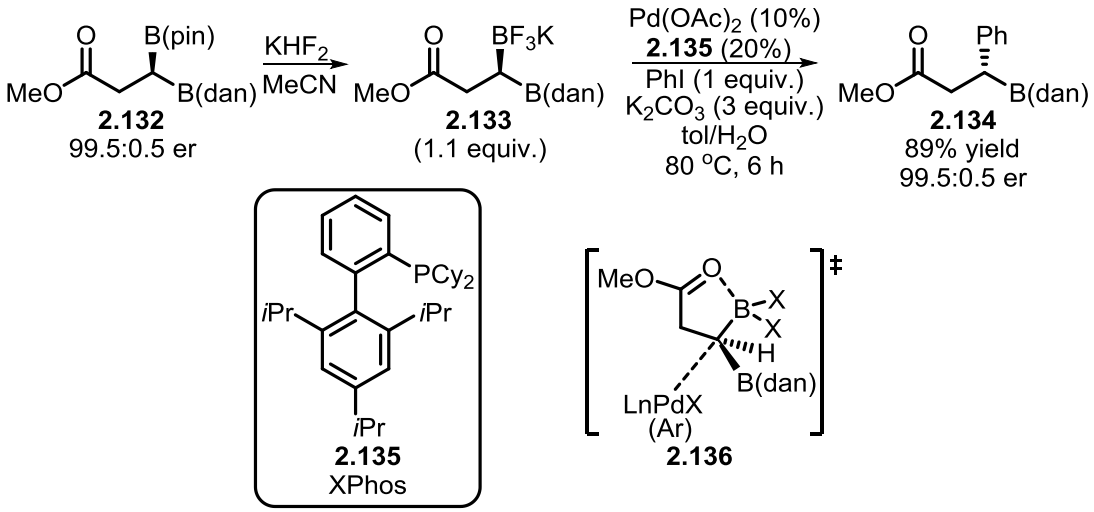


More recently, Shibata and coworkers reported the use of 1,1-bis(pinacol boronates) as nucleophilic partners in Suzuki-Miyaura cross-coupling (Scheme 2.26).[55] Surprisingly, efficient coupling with a variety of aryl bromides was accomplished at room temperature utilizing [Pd(P*t*Bu$_3$)$_2$] in the presence of potassium hydroxide. Using ^{11}B NMR, Shibata confirmed the unique ability of the 1,1-bis(pinacol boronates) to form borate complexes with potassium hydroxide at room temperature (equation 2). Notably, this is in stark contrast to Soderquist's investigation of primary alkyl borinates, which did not form detectable borate complexes at room temperature (Scheme 2.12).[32] Computational evidence shows a large LUMO distribution surrounding the 1,1-bis(pinacol boronate) moiety **2.128**, indicating possible neighboring group participation, which stabilizes the formation of monoborate **2.129**. Supporting this hypothesis is the absence of reactivity when employing geminal silyl boronate **2.131**, 1,2-bis(pinacol boronate) **2.28**, and primary mono boronate **2.130**. Subsequent to this initial

[55] (a) Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc*. **2010**, *132*, 11033. (b) Endo, K.; Ohkubo, T.; Shibata, T. *Org. Lett*. **2011**, *13*, 3368. (c) Endo, K.; Ohkubo, T.; Ishioka, T.; Shibata, T. *J. Org. Chem*. **2012**, *77*, 4826.

communication, the Shibata group has investigated both the use of simple 1,1-bis(pinacol boronate) methane[55b] as well as couplings with benzylic and allylic electrophiles.[55c]

Scheme 2.27: Stereospecific Coupling with Inversion by Hall

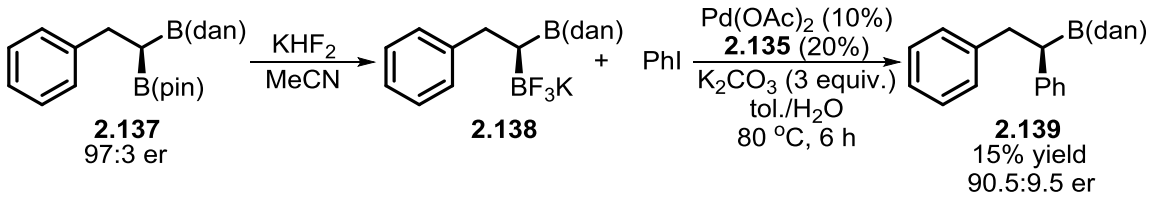


Following this seminal work by Shibata, Hall and coworkers reported the use of enantioenriched dissimilar 1,1-diboron compounds for use in cross-coupling reactions (Scheme 2.27).[56] The 1,1-B(pin)-B(dan) **2.132** was prepared with high enantioselectivity *via* a slight modification to the procedure by Yun,[57] and subsequently transformed into the corresponding trifluoroborate **2.133**. Using nearly identical conditions first developed by Molander,[58] Hall was able to couple a variety of aryl and vinyl bromides with no loss of enantiopurity. Interestingly, the coupling reaction proceeds with inversion of configuration, following similar observations by Molander[58] and Suginome.[59] The stereochemical outcome of the coupling was rationalized by internal activation of boron by the ester carbonyl group as shown in **2.136**. Transmetallation then occurs by attack of

[56] Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nature Chem*. **2011**, *3*, 894.
[57] Lee, J. E.; Yun, J. *Angew. Chem. Int. Ed*. **2008**, *47*, 145.
[58] Sandrock, D. L.; Jean-Gérard, L.; Chen, C.; Dreher, S. D.; Molander, G. A. *J. Am. Chem. Soc*. **2010**, *132*, 17108.
[59] Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc*. **2010**, *132*, 13191.

palladium through the backside of the carbon-boron bond, resulting in inversion of the stereocenter.

Scheme 2.28: Recent Stereoretentive Coupling by Yun



2.137
97:3 er

2.138

2.139
15% yield
90.5:9.5 er

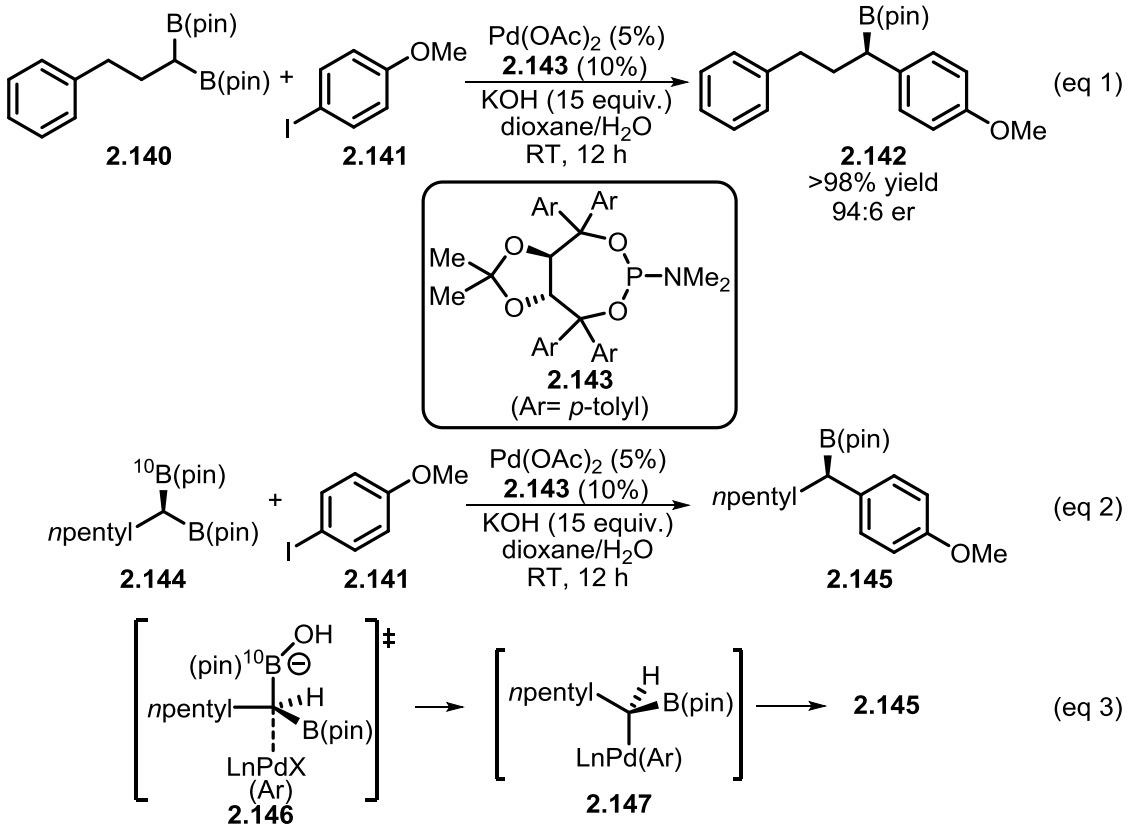
In 2013, Yun and coworkers reported the synthesis of enantioenriched 1,1-diborons by the highly regio- and enantioselective hydroboration of vinyl-B(dan) starting materials (Scheme 2.28).[60] Utilizing the same conditions reported by Hall,[56] Yun was able to engage 1,1-diboron **2.138** in Suzuki-Miyaura cross-coupling to give the desired product **2.139**, albeit in low yield and with significant loss of enantiopurity. Notably, in the absence of a Lewis basic carbonyl group that is capable of internal activation, stereoretentive coupling occurs.

Very recently, the Morken group disclosed the enantioselective synthesis of benzylic pinacol boronates via the desymmetrization of geminal 1,1-bis(pinacol boronates) through Suzuki-Miyaura cross-coupling (Scheme 2.29).[61] Building on earlier work by Shibata,[55] a variety of 1,1-bis(pinacol boronates) and aryl iodides were shown to participate in the enantioselective coupling, affording the desired benzylic pinacol boronates in excellent yield and with high levels of enantioselectivity. Seeking to learn more about the mode of stereoselection in the coupling process, Morken and coworkers submitted enantioenriched and isotopically labeled germinal diboron **2.144** to the

[60] Feng, X.; Jeon, H.; Yun, J. *Angew. Chem. Int. Ed*. **2013**, *52*, 3989.
[61] Sun, C.; Potter, B.; Morken, J. P. *J. Am. Chem. Soc*. **2014**, *136*, 6534.

standard coupling conditions (equation 2). Upon workup, **2.145** was obtained in good yield and selectivity and with loss of the isotope label, signaling that coupling takes place with inversion of configuration, possibly through transition state **2.146** (equation 3). Interestingly, the stereochemical pathway is different than that obtained by Yun (Scheme 2.28), highlighting the unique effect of geminal pinacol boronates on the coupling process.

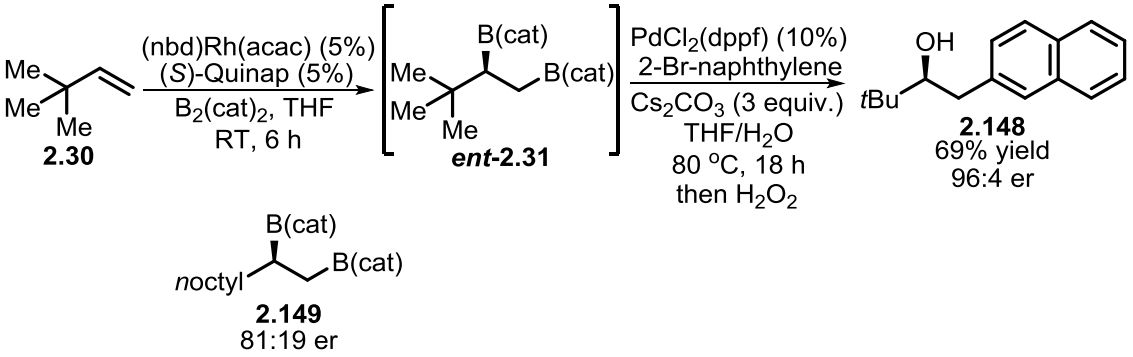
Scheme 2.29: Enantioselective Suzuki-Miyaura Cross-Coupling of 1,1-Bis(pinacol boronates by Morken



In addition to geminal diboron compounds, vicinal diboron compounds have also been utilized in Suzuki-Miyaura cross-coupling. In 2004, Morken and coworkers extended the rhodium catalyzed diboration of alkenes to include sterically hindered

terminal olefins.[62] Without isolation of the intermediate 1,2-bis(catechol borontate) **2.31**, treatment with 2-bromonaphthalene in the presence of $PdCl_2$(dppf) and cesium carbonate resulted in successful coupling and the desired secondary alcohol **2.148** was isolated in good yield and with excellent enantioselectivity after subsequent oxidation (Scheme 2.30). This method successfully accomplished a one-pot carbo-hydroxylation of terminal olefins; however, an unfortunate limitation is the requirement of very large substituents to achieve high levels of enantioselectivity in the diboration reaction, with smaller substituents resulting in low levels of selectivity (i.e. **2.149**).

Scheme 2.30: Tandem Diboration and Suzuki-Miyaura Cross-Coupling by Morken

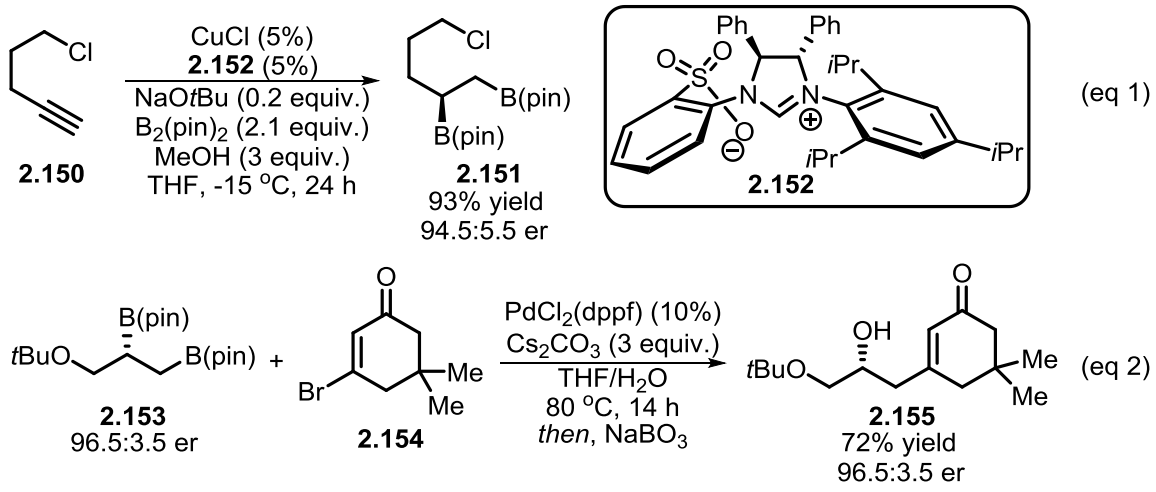


Finally, in 2009 the Hoveyda group reported the highly enantioselective preparation of 1,2-bis(pinacol boronates) by the regioselective copper catalyzed double hydroboration of terminal alkynes (Scheme 2.31).[63] Highlighting the functional group tolerance of the copper catalyst, 1,2-bis(pinacol boronates) could easily be forged in the presence of tethered alkyl halides (**2.151**, equation 1). Importantly, 1,2-bis(pinacol boronate) **2.153** was shown to undergo Suzuki-Miyaura cross-coupling with activated electrophile **2.154**, and after subsequent oxidation, gave the desired secondary alcohol

[62] Miller, S. P.; Morgan, J. B.; Nepveux, F. J.; Morken, J. P. *Org. Lett*. **2004**, *6*, 131.
[63] Lee, Y.; Jang, H.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2009**, *131*, 18234.

2.155 in good yield and with no loss of enantiopurity. While this result certainly highlights the feasibility of achieving successful coupling with the use of vicinal pinacol boronates, the need of a highly activated electrophile emphasizes the high degree of difficulty associated with this class of nucleophiles as opposed to their catechol boronate counterparts, which proceed smoothly under the same exact reaction conditions (Scheme 2.30). Seeking to greatly expand the range of enantioenriched products that can easily be accessed from terminal alkenes, a search for conditions to successfully engage 1,2-bis(pinacol boronate) intermediates in efficient and general Suzuki-Miyaura cross-coupling was initiated.

Scheme 2.31: Suzuki-Miyaura Cross-Coupling of 1,2-Bis(pinacol boronates) by Hoveyda



2.3 Development of a General Suzuki-Miyaura Cross-Coupling Protocol for 1,2-Bis(pinacol boronates)[64]

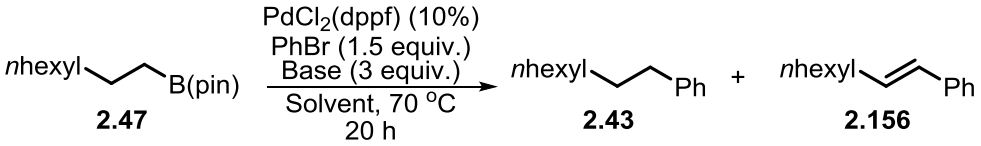
2.3.1 Initial Examination of Reaction Conditions

Notably, the desired coupling of 1,2-bis(pinacol boronates) in Suzuki-Miyaura reactions requires the use of what is formally an alkyl pinacol boronate. It was reasoned

[64] Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. *Nature* **2014**, *505*, 386.

if suitable conditions for the coupling of simple alkyl pinacol boronates were discovered, that these conditions would also apply to the desired coupling of the 1,2-bis(pinacol boronates). While the work of Marder and Liu[52] showed the ability of these notoriously stubborn nucleophiles to participate in coupling reactions, at the time this project was initiated, the most promising catalyst systems for this type of nucleophile involved the use of Hayashi's $PdCl_2$(dppf).[27] Initial experiments examined the use of this pre-catalyst together with bromobenzene and **2.47** as a model alkyl pinacol boronate (Table 2.2).

Table 2.2: Examination of Various Bases For Suzuki-Miyaura Cross-Coupling of OctylB(pin)



2.47 **2.43** **2.156**

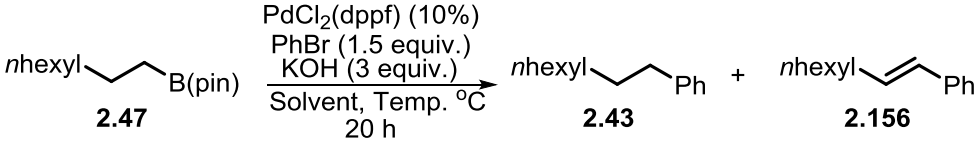
Entry	Base	Solvent	**2.43** (%)[a]	**2.156** (%)[a]
1	Cs_2CO_3	THF:H_2O (10:1)	21	0
2	Cs_2CO_3	THF:H_2O (32:1)	47	trace
3	K_2CO_3	THF:H_2O (32:1)	7	0
4	Na_2CO_3	THF:H_2O (32:1)	0	0
5	K_3PO_4	THF:H_2O (32:1)	9	0
6	KOAc	THF:H_2O (32:1)	0	0
7	CsF	THF:H_2O (32:1)	5	0
8	LiOH	THF:H_2O (14:1)	42	1
9	NaOH	THF:H_2O (14:1)	51	trace
10	KOH	THF:H_2O (14:1)	57	1
11	KOH	THF:H_2O (32:1)	60	7
12	$Ca(OH)_2$	THF:H_2O (32:1)	trace	trace
13	$Ba(OH)_2$	THF:H_2O (32:1)	46	trace

a) conversion based on crude ^{1}H NMR

Utilizing the conditions found to be useful for both Morken[62] and Hoveyda[63] resulted in clean formation of the desired octyl benzene **2.43** albeit with very low conversion of starting material (Table 2.2, entry 1). Realizing the difficult

transmetallation likely proceeds through palladium hydroxo intermediates as shown by Hartwig, the amount of water in the reaction mixture was decreased (entry 2). Lower ratios of water were found by Hartwig to encourage a higher concentration of palladium hydroxo complexes versus palladium halide complexes, presumably due to less efficient solvation of the free base.[41] Indeed upon lowering the amount of water from 1:10 to 1:32 relative to THF, a significant increase in conversion to product was observed (entry 2). While other bases resulted in almost no product formation (entries 3-7) the use of hydroxide bases greatly improved conversion. Potassium hydroxide provided the best conversion (entry 11), although small amounts of styrene by-product **2.156** were formed, presumably from a transmetallation/β-hydride elimination sequence which can form 1-octene *in situ*, setting the stage for a subsequent Heck coupling with bromobenzene.

Table 2.3: Examination of Various Solvents for Suzuki-Miyaura Cross-Coupling of OctylB(pin)



2.47 **2.43** **2.156**

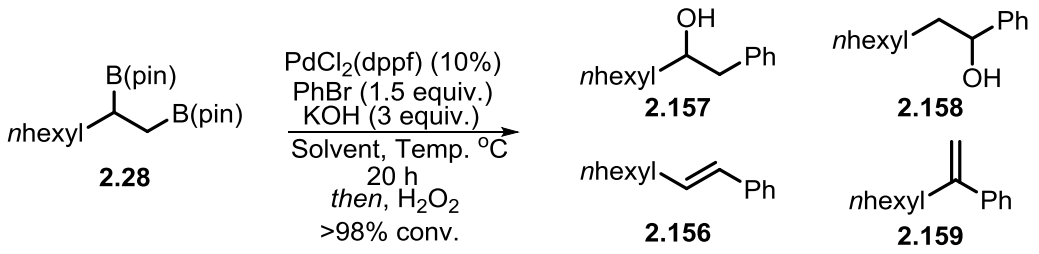
Entry	Solvent	Temp. (°C)	**2.43** (%)[a]	**2.156** (%)[a]
1	THF:H_2O (32:1)	70	60	7
2	THF	70	41	37
3	DMF:H_2O (32:1)	70	6	2
4	DMF	70	40	23
5	PhH:H_2O (32:1)	70	39	0
6	PhH	70	21	30
7	dioxane:H_2O (32:1)	70	60	0
8	dioxane:H_2O (32:1)	100	85	0

a) conversion based on crude ^{1}H NMR

In an effort to further improve conversion and prevent formation of **2.156**, additional solvents were examined (Table 2.3). Notably, the use of anhydrous solvents

generally leads to large amounts of **2.156** (entries 2, 4, and 6), with both dimethylformamide (entries 3 and 4) and benzene (entries 5 and 6) based systems affording lower conversion than those based on THF (entries 1 and 2). Importantly, the use of 1,4-dioxane led to improved reaction efficiency, achieving up to 85% conversion to octyl benzene and no detectable formation of **2.156** at 100 ^{o}C (entry 8).

Table 2.4: Initial Use of 1,2-Bis(pinacol boronate) in Suzuki-Miyaura Cross-Coupling



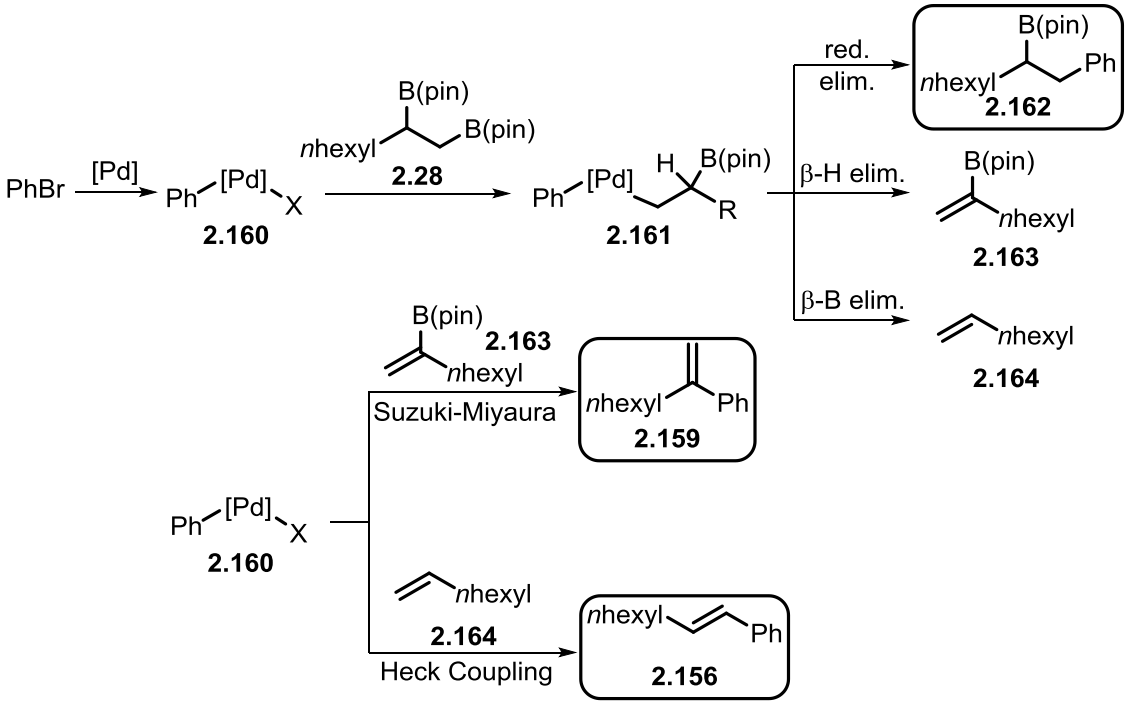
Entry	Solvent	Temp. (^{o}C)	**2.157** (%)[a,b]	**2.158** (%)[a]	**2.156** (%)[a]	**2.159** (%)[a]
1	dioxane:H_2O (32:1)	100	70 (40)	13	11	6
2	dioxane:H_2O (10:1)	100	85 (42)	0	8	7
3	THF:H_2O (32:1)	70	50 (45)	0	28	22
4	THF:H_2O (10:1)	70	74 (62)	19	7	0
5	THF:H_2O (8:1)	70	65 (38)	15	16	4
6	THF:H_2O (6:1)	70	53 (40)	20	23	4
7	THF:H_2O (4:1)	70	75 (36)	25	0	0
8	THF:H_2O (10:1)	50	42 (32)	30	20	8
9	THF:H_2O (10:1)	RT	33 (24)	48	11	8

a) percentage of known products identified by crude ^{1}H NMR. b) isolated yield in parentheses

Having achieved good reaction efficiency in the model reaction system with octylB(pin), the Suzuki-Miyaura cross-coupling of 1,2-bis(pinacol boronates) was then examined (Table 2.4). Unfortunately, utilizing the optimized conditions found from coupling with octylB(pin) afforded the desired product **2.157** in very low yield and with formation of several by-products when the nucleophile was switched to 1,2-bis(pinacol

boronate) **2.28** (entry 1), serving as a humbling reminder that sometimes there simply isn't an appropriate model system. Further examination of the reaction conditions identified a correlation between the amount of water in the reaction and the yield of the desired product, with a 10:1 ratio of THF:water affording the highest yield of **2.157** (entry 4). Incredibly, full conversion was observed in all cases, even when the reaction was maintained at ambient temperature (entry 9).

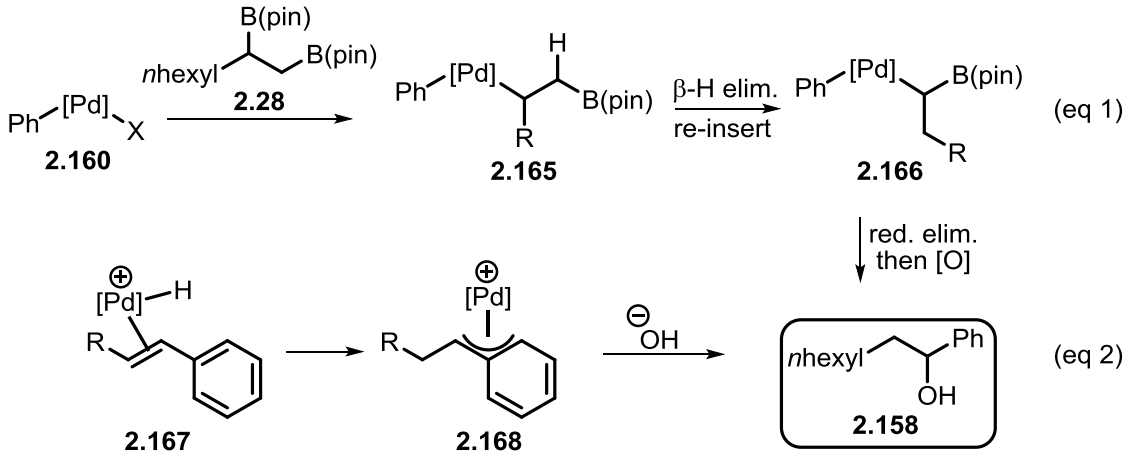
Scheme 2.32: Possible Side Reactions Operating During Coupling Reaction



While the 1,2-bis(pinacol boronate) **2.28** appeared to be quite reactive under the conditions examined in Table 2.4, the large amounts of by-product formation ultimately resulted in low yields of the desired product. To minimize the detrimental formation of these by-products, an effort was made to rationalize how they were created (Scheme 2.32). It is plausible that after oxidative addition of bromobenzene to Pd(0), **2.160** could undergo the desired transmetallation to arrive at palladium alkyl complex **2.161**, which

could subsequently undergo reductive elimination to afford the desired secondary pinacol boronate **2.162**. However, if reductive elimination is not efficient, competitive β-hydride and β-boryl eliminations could result in formation of vinyl boronate **2.163** and 1-octene **2.164** respectively. Upon formation of these species, it is reasonable to expect that under the reaction conditions, the vinyl boronate **2.163** could participate in a Suzuki-Miyaura cross-coupling with Pd(II) intermediate **2.160** and 1-octene **2.164** in a Heck coupling with **2.160**, delivering by-products **2.159** and **2.156** respectively (equation 2).

Scheme 2.33: Possible Pathways to Benzylic Alcohol 2.158 During Cross-Coupling

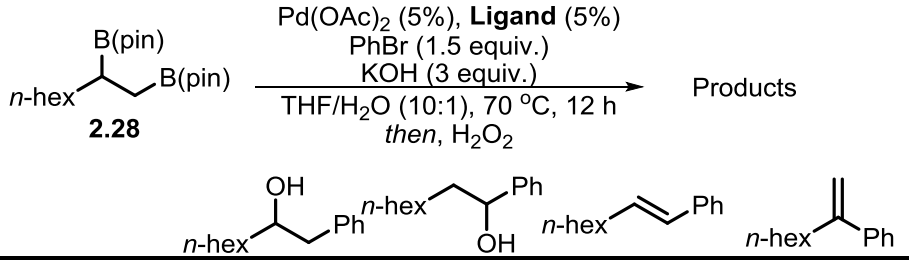


The benzylic alcohol by-product **2.158** could arise from two possible reaction pathways (Scheme 2.33). Although there are relatively few reports of Suzuki-Miyaura cross-couplings involving secondary alkyl boron compounds,[28,65] it is possible that a successful transmetallation to the secondary pinacol boronate of **2.28** could occur (equation 1). As evidenced by Molander,[66] secondary alkyl palladium intermediates such

[65] For examples of secondary B-alkyl Suzuki-Miyaura couplings, see: (a) Littke, A. F.; Dai, C.; Fu, G. C. *J. Am. Chem. Soc*. **2000**, *122*, 4020. (b) Kataoka, N.; Shelby, Q.; Stambuli, J. P.; Hartwig, J. F. *J. Org. Chem*. **2002**, *67*, 5553. (c) van den Hoogenband, A.; Lange, J. H.M.; Terpstra, J. W.; Koch, M.; Visser, G. M.; Visser, M.; Korstanje, T. J.; Jastrzebski, J. T. B. H. *Tetrahedron Lett*. **2008**, *49*, 4122.
[66] Dreher, S. D.; Dormer, P. G.; Sandrock, D. L.; Molander, G. A. *J. Am. Chem. Soc*. **2008**, *130*, 9257.

as **2.165** are especially prone to elimination and re-insertion events, often resulting in isomerization to a lower energy species. Such a sequence could result in formation of α-boryl palladium alkyl **2.166**, which after reductive elimination and subsequent oxidation would afford benzylic alcohol **2.158**. Alternatively, a palladium hydride species such as **2.167**, derived from a Heck coupling, could reinsert to give an electrophilic π-benzyl complex **2.168** (equation 2). External attack by hydroxide could result in direct formation of benzylic alcohol **2.158**.

Table 2.5: Improving Reaction Efficiency Through Proper Ligand Choice



Entry	Ligand	2.157[a]	2.158[a]	2.156[a]	2.159[a]
1	dppf	74%	19%	7%	-
2	dippf	77%	22%	1%	-
3	dcpe	66%	30%	1%	3%
4	DPEphos	85%	14%	1%	-
5	xantphos	85%	13%	2%	-
6	XPhos	82%	14%	4%	-
7	SPhos	96%	2%	-	2%
8	RuPhos	99%	1%	-	-

a) product distribution determined by crude ^{1}H NMR analysis (full conversion)

Importantly, the formation of all the identified by-products in Schemes 32 and 33 appears to ultimately derive from alkyl palladium complex **2.161** due to non-efficient reductive elimination. Efforts were then extended to expediate reductive elimination in the hopes of encouraging desired product formation and suppressing non-productive β-

elimination pathways (Table 2.5). Increasing the steric bulk of the diphosphine ligand employed did not result in a significant improvement to reaction efficiency (entries 2 and 3). Utilizing larger bite angle diphosphines such as DPEphos (entry 4) and xantphos (entry 5) resulted in significant improvement to the coupling reaction with 85% of the product mixture containing the desired **2.157** in both cases. Alternatively, the use of the biaryl Buchwald ligands, in particular SPhos (entry 7) and RuPhos (entry 8), resulted in highly selective formation of **2.157**. This may be rationalized by efficient reductive elimination occurring through highly reactive 3-coordinate intermediates, which were shown by Hartwig to undergo rapid reductive elimination.[44] The incredible ability of Buchwald's ligands, and in particular RuPhos, to stabilize these 3-coordinate intermediates throughout the catalytic cycle likely leads to their high efficiency in the Suzuki-Miyaura cross-coupling of 1,2-bis(pinacol boronates).[40c,67]

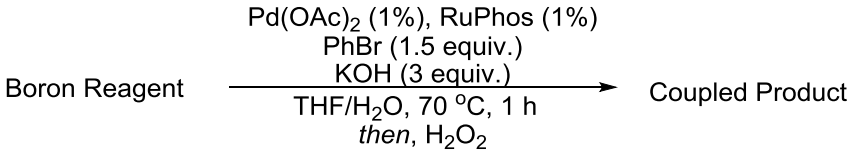
2.3.2 Investigations Concerning the Unique Reactivity of 1,2-Bis(pinacol boronates)

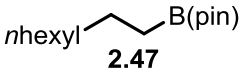
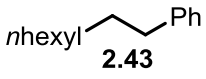
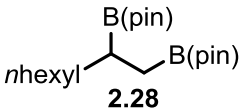
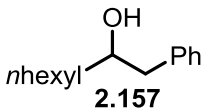
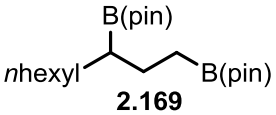
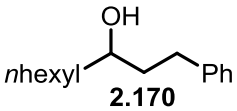
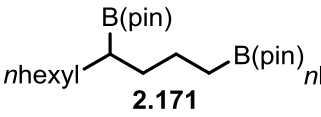
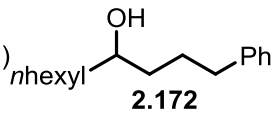
Interestingly, transmetallation, the step which was predicted to be the most challenging, was easily achieved under the optimized conditions (Table 2.5, entry 8). This level of reactivity is somewhat mystifying, given the normally lethargic nature of alkyl pinacol boronates in Suzuki-Miyaura cross-couplings.[21] To further investigate, a series of alkyl pinacol boronates were prepared and subjected to the optimized coupling conditions with 1 mol % catalyst loading for one hour (Table 2.6). Remarkably, high reactivity was observed only in the case of the 1,2-bis(pinacol boronate) **2.28** (entry 2), and only minimal conversion was obtained for 1,3-bis(pinacol boronate) **2.169** (entry 3) and 1,4-bis(pinacol boronate) **2.171** (entry 5), as well as mono pinacol boronate **2.47**

[67] For a review featuring the extensive use of biaryl phosphines, see: Surry, D. S.; Buchwald, S. L. *Angew. Chem. Int. Ed*. **2008**, *47*, 6338.

(entry 1). Despite both increased catalyst loading and prolonged reaction times, the 1,3-bis(pincol boronate) **2.169** achieved only moderate conversion to the desired product (entry 4). This leap in efficiency is quite surprising considering the subtle change in substrate, and taken together, the data displayed in Table 2.6 points to the presence of a pinacol boronate in the vicinal position as being vital for enhanced reactivity of the primary boronate.

Table 2.6: Evaluation of Alkyl Pinacol Boronate Reactivity



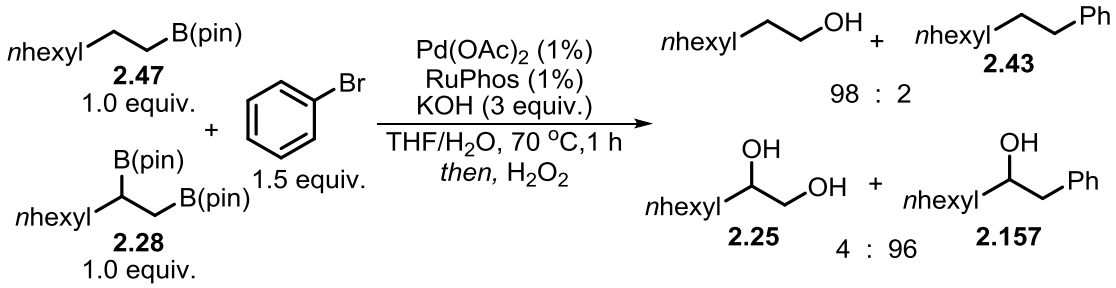
Entry	Boron Reagent	Product	Conversion	Yield
1	 **2.47**	 **2.43**	<5%	n.d.
2	 **2.28**	 **2.157**	91%	86%
3	 **2.169**	 **2.170**	<5%	n.d.
4[a]			31%	n.d.
5	 **2.171**	 **2.172**	9%	n.d.

a) 5% catalyst employed for 20 hours

To gain additional insight into this puzzling system, a competition experiment was performed whereby the catalyst had the opportunity to engage either simple alkyl pinacol boronate **2.47** or 1,2-bis(pinacol boronate) **2.28** in a one-pot coupling reaction with bromobenzene (Scheme 2.34). After oxidative work-up, analysis of the crude reaction mixture revealed nearly full conversion of the 1,2-bis(pinacol boronate) to

coupling product **2.157** and only trace amount of product **2.43** from alkyl pinacol boronate **2.47**, indicating a greater than 50-fold rate enhancement. While at first this result may not be surprising given the reactivity differences observed in the isolated coupling reactions of **2.47** and **2.28** (Table 2.6), important insight can be obtained from this experiment.

Scheme 2.34: One-Pot Competition Between 1,2-Bis(pinacol boronate) and OctylB(pin)

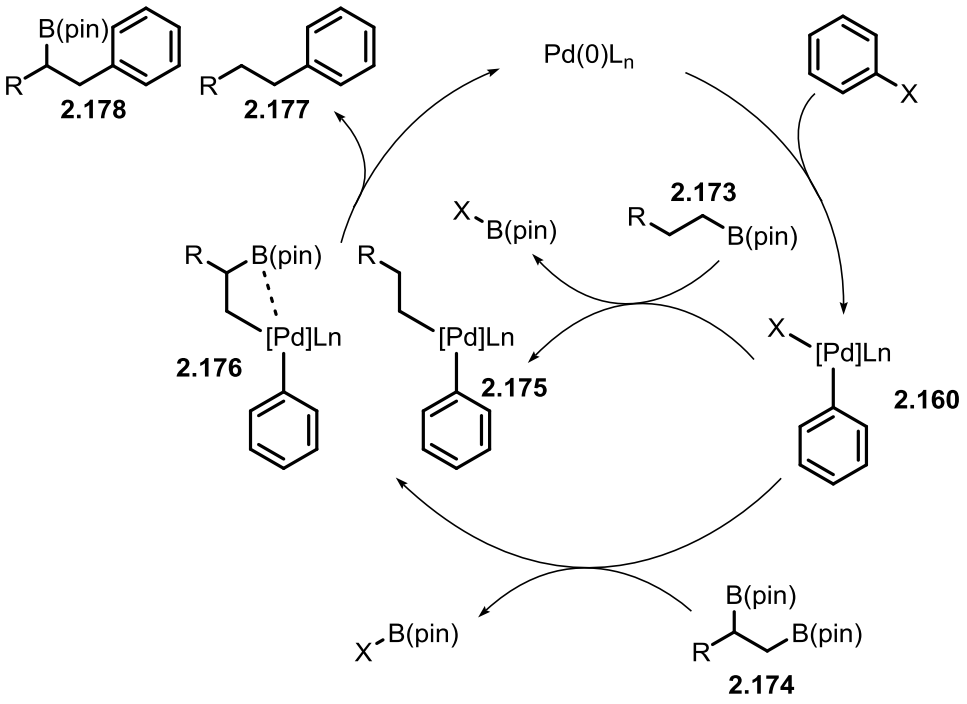


It is reasonable to assume that oxidative addition is not dependent on the presence of either nucleophile, and that the rate enhancement observed for 1,2-bis(pinacol boronate) **2.28** is a consequence of either accelerated transmetallation, or reductive elimination relative to octyl pinacol boronate **2.47** (Scheme 2.35). If transmetallation occurred at a similar rate for both **2.173** and **2.174**, then a rapid reductive elimination from palladium alkyl **2.176**, possibly accelerated by Lewis acid assistance from the remaining secondary pinacol boronate,[68] could account for the rapid formation of **2.178**. However, if this were the case, the relatively slow rate of reductive elimination from **2.175** would result in the sequestration of palladium over time and lead to a rate depression for both the formation of both **2.178** and **2.177** (assuming irreversible transmetallation). The similar rates of 1,2-bis(pinacol boronate) coupling observed in

[68] For a study featuring the use of several types of electron acceptors to induce reductive elimination, see: Yamamoto, T.; Abla, M.; Murakami, Y. *Bull. Chem. Soc. Jpn*. **2002**, *75*, 1997.

both Table 2.6 and Scheme 2.34 point instead to a rapid transmetallation of these nucleophiles relative to octyl pinacol boronate **2.47**. Importantly, this is in accordance with the observation that reductive elimination is rarely rate-limiting in Suzuki-Miyaura cross-coupling.[42]

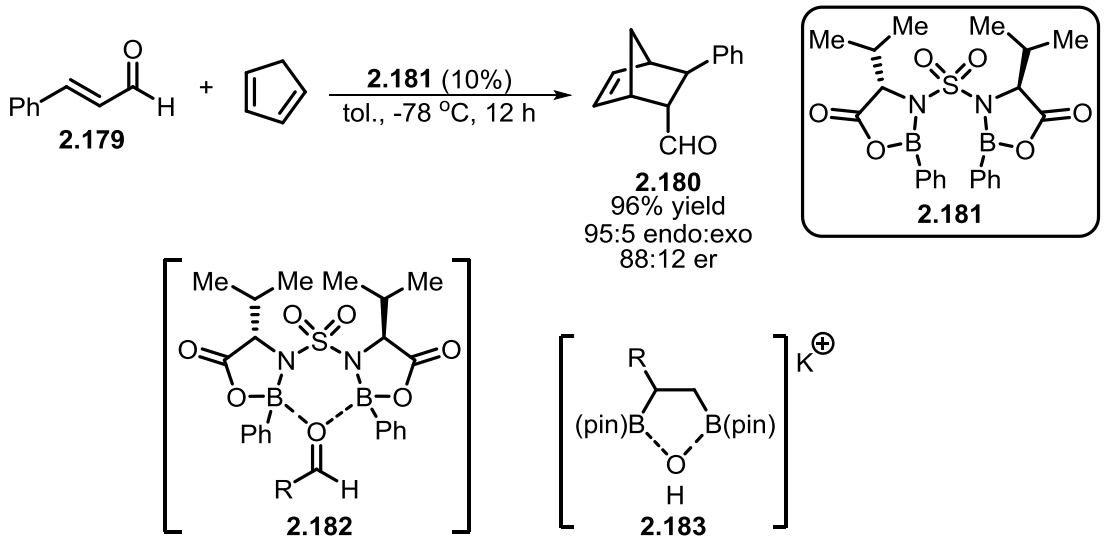
Scheme 2.35: Proposed Catalytic Cycle for One-Pot Competition



To account for the unique ability of 1,2-bis(pinacol boronates) to undergo transmetallation, several features were considered. Following the work of Soderquist,[32] which highlighted the important relationship between boron reagent Lewis acidity and reactivity in cross-coupling, it was reasoned that the presence of the vicinal boronate might serve to enhance the Lewis acidity of the reagent as a whole. Interestingly, Shea and coworkers showed the ability of (L)-valine derived diboron Lewis acids such as **2.181** to serve as effective catalysts for the asymmetric Diels-Alder reaction between

cinnamyl aldehyde **2.179** and cyclopentadiene (Scheme 2.36).[69] This report lends credence to the notion of the 1,2-bis(pinacol boronates) functioning as effective Lewis acids, possibly forming stable "ate" complexes with an equivalent of hydroxide to give **2.183**.

Scheme 2.36: Use of Bidentate Lewis Acid Catalyst for Asymmetric Diels-Alder Reaction by Shea

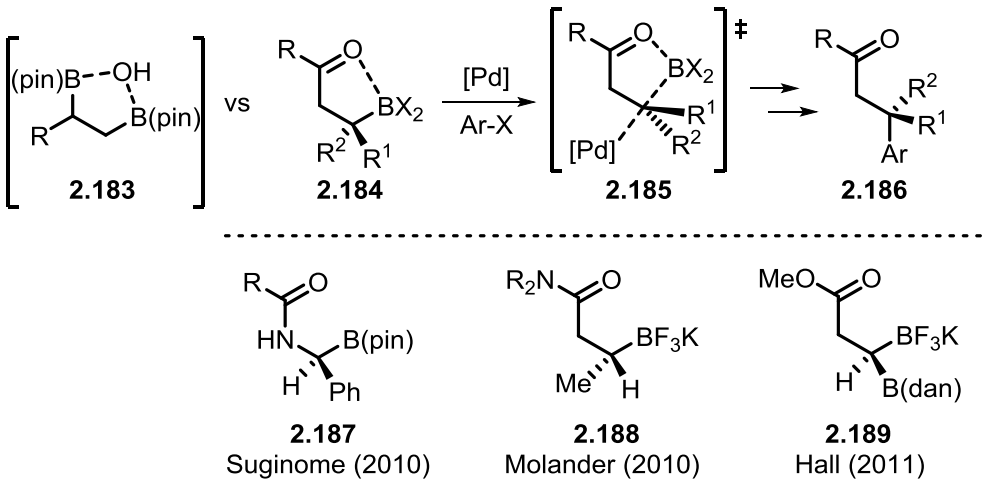


Notably, structure **2.183** maps on well to several reports that invoke coordination of an internal Lewis base to an alkyl boron species as being important for reactivity in Suzuki-Miyaura cross-coupling reactions (Scheme 2.37). Importantly, Suginome,[59] Molander,[58] as well as Hall[56] reported the cross-coupling of these nucleophiles to proceed with inversion of configuration at the transmetallating carbon, presumably through a back-side attack of palladium as shown in **2.185**. In order to test this hypothesis, deuterium labeled 1,2-bis(pinacol boronate) **2.190** was prepared and subjected to the standard cross-coupling conditions together with vinyl chloride **2.191** (Scheme 2.38).

[69] Rodriguez, A. A.; Zhao, C.; Shea, K. J. *Org. Lett*. **2009**, *11*, 713.

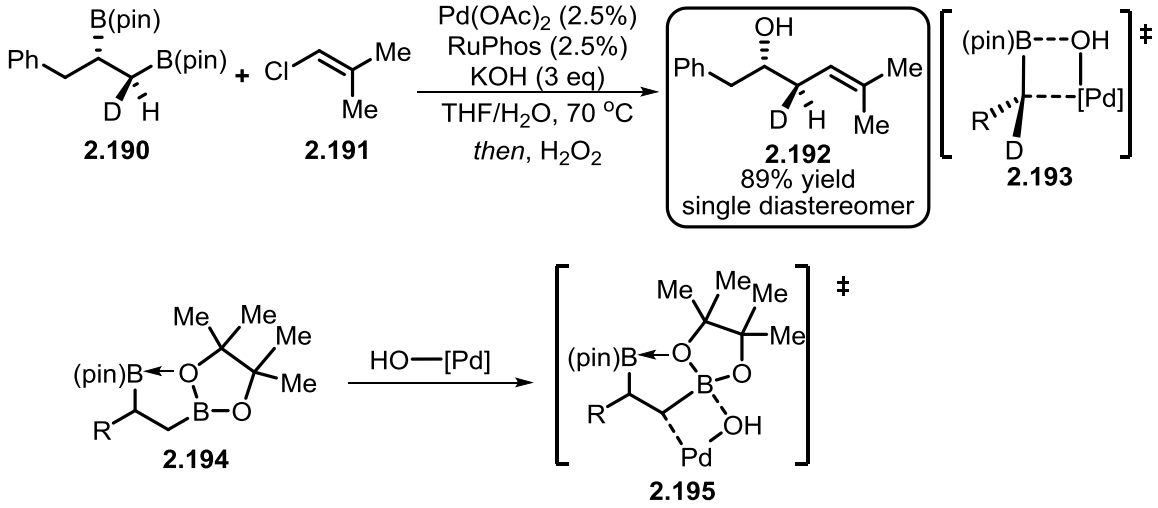
Interestingly, complete retention of configuration was obtained, affording **2.192** as a single diastereomer in 89% yield.

Scheme 2.37: Comparison to Cross-Couplings Known to Proceed with Inversion of Stereochemistry



This result suggests that transmetallation proceeds through a closed 4-membered transition state such as **2.193**, and not through the back-side attack to palladium depicted in Scheme 2.37. The unique stabilization of 4-membered transition state **2.193** exhibited by the 1,2-bis(pinacol boronates) could be rationalized by possible donation of one of the primary boronate oxygen lone pairs to the empty p-orbital of the secondary pinacol boronate **2.194**. This interaction would effectively enhance the Lewis acidity of the primary pinacol boronate, encouraging base complexation, likely with a palladium hydroxo species, and lead to accelerated transmetallation through transition state **2.195**. This example of neighboring group participation is unique to the 1,2-bis(pinacol boronates) and is not observed for either the 1,3-bis(pinacol boronate) or the 1,4-bis(pinacol boronate), possibly due to a lack of effective donation depicted in **2.195**.

Scheme 2.38: Stereochemical Outcome of Transmetallation and Proposed Mode of Acceleration by Neighboring Group Participation

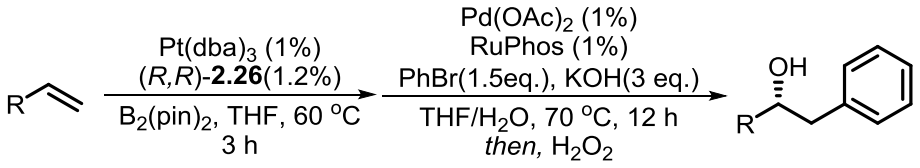


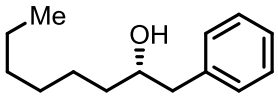
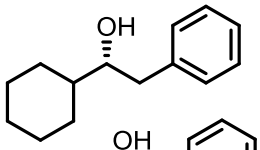
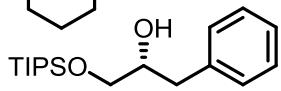
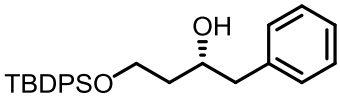
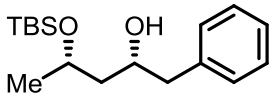
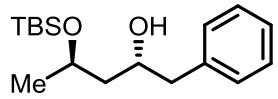
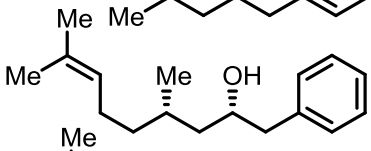
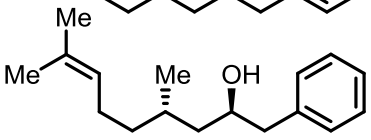
2.3.3 Scope of One-Pot Asymmetric Diboration/Cross-Coupling Sequence

With highly efficient conditions for Suzuki-Miyaura cross-coupling of 1,2-bis(pinacol boronates) in hand, a one-pot diboration-cross-coupling protocol was developed. Importantly, the presence of both the platinum catalyst and a slight excess of $B_2(pin)_2$ from the diboration reaction did not adversely affect the cross-coupling step, with the tandem reaction of 1-ocetene with bromobenzene affording the desired secondary alcohol in excellent yield and with high levels of enantioselectivity after oxidative work-up (Table 2.7, entry 1). The use of *in situ* generated 1,2-bis(pinacol boronates) allowed for the direct use of a variety of terminal olefins under the optimized conditions, utilizing bromobenzene as a model electrophile. Although use of styrene derivatives resulted in rapid protodeboration of the intermediate 1,2-bis(pinacol boronates) under the reaction conditions, the use of sterically hindered aliphatic olefins proceeded smoothly (entry 2). Oxygenation in the allylic (entry 3) and homoallylic (entries 4-6) positions was well tolerated, affording the desired secondary alcohols in

good to excellent yields and with high levels of stereoselectivity. Importantly, when either β-carbon substituted (entries 7 and 8) or β-oxygen substituted (entries 5 and 6) stereocenters are present, effective catalyst control produces the desired products with excellent diastereoselectivity.

Table 2.7: Alkenes Examined In One-Pot Diboration Cross-Coupling

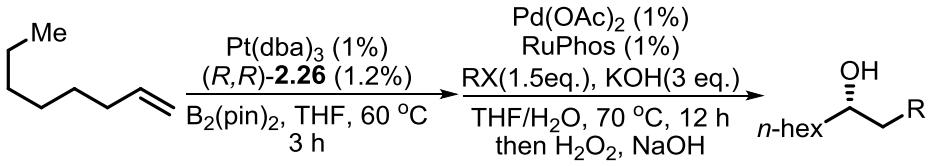


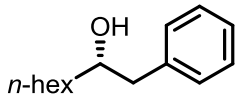
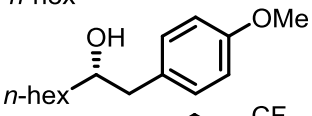
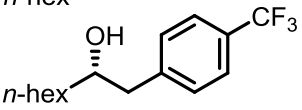
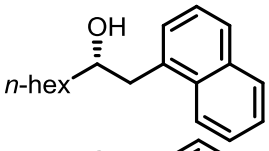
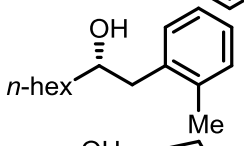
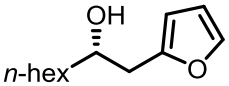
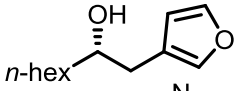
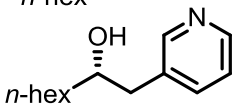
Entry	Product	Yield (%)	er [dr]
1		96	96.5:3.5
2		93	99:1
3		88	95:5
4[a]		62	94.5:5.5
5		88	[>20:1]
6		94	[17:1]
7		97	[>20:1]
8[b]		96	[>20:1]

a) (*R,R*)-**2.27** employed in diboration; b) (*S,S*)-**2.26** employed in diboration

In addition to terminal olefin coupling partners, a variety of aryl electophiles were examined with the use of 1-octene as a model alkene (Table 2.8). While both chloro- and

Table 2.8: Examination of Aryl Electrophiles with 1-Octene



Entry	Product	X	Yield (%)	er
1		Cl	88	96.5:3.5
2		Br	96	96.5:3.5
3		I	30	96.5:3.5
4		OTf	48	96.5:3.5
5		Br	96	96.5:3.5
6		Br	93	96.6:3.5
7		Br	90	95:5
8		Br	80	94:6
9[a]		Br	79	95.5:4.5
10[a]		Br	63	96:4
11		Br	84	97:3

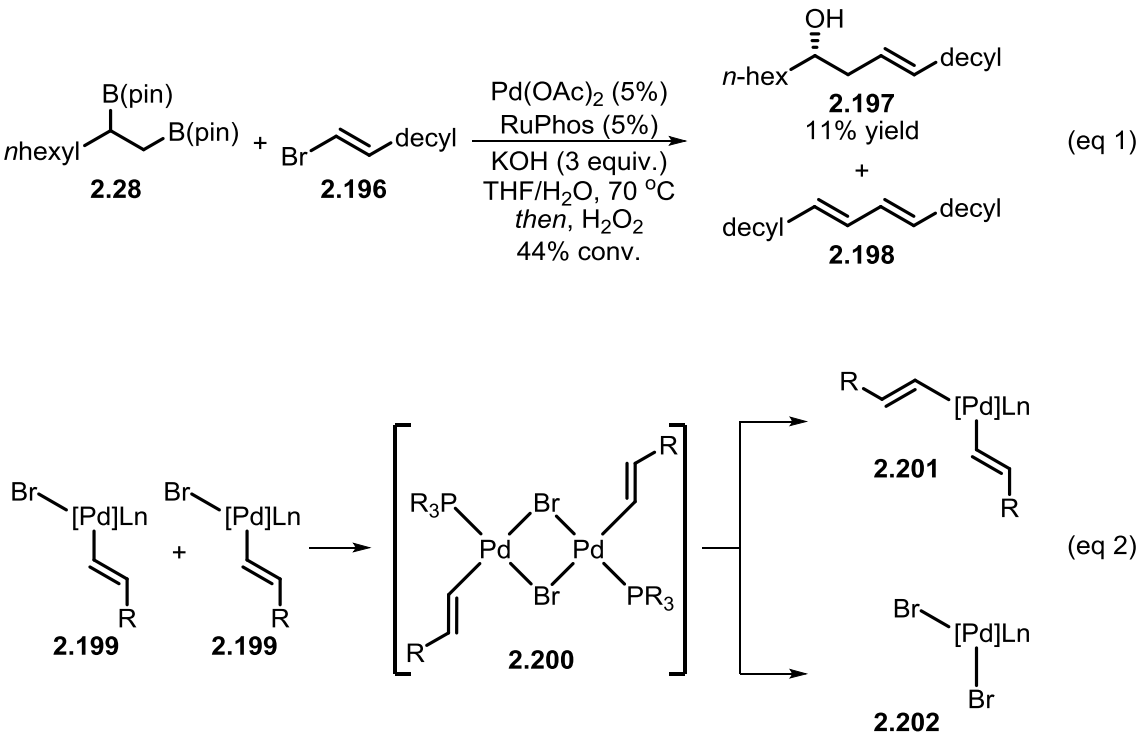
a) LiCl (1.0 eq.) added

bromobenzene (entries 1 and 2) participated effectively in cross-coupling, the use of iodobenzene or phenyltriflate led to poor yields of the desired product (entries 3 and 4).[70] The use of both electron rich (entry 5) and electron deficient (entry 6) aryl groups, as well as those which are sterically encumbered (entries 7 and 8) resulted in the formation of the desired products in good to excellent yields and with high enantioselectivities.

[70] For a report exhibiting this same general trend, see: Molander, G. A.; Wisniewski, S. R. *J. Am. Chem. Soc*. **2012**, *134*, 16856.

Importantly, heteroaromatic electrophiles were also successfully engaged in the tandem sequence, affording the desired secondary alcohols in good yields and with excellent enantioselectivities (entries 9-11).

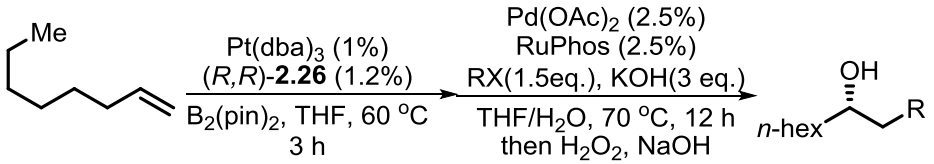
Scheme 2.39: Initial Attempts to Utilize Vinyl Bromides Resulting in Electrophile Dimerization

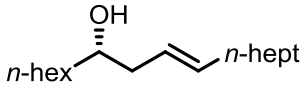
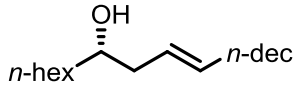
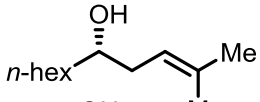
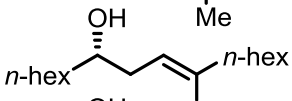
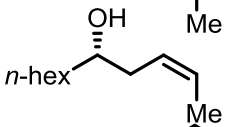
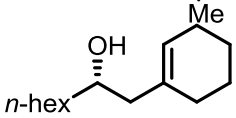
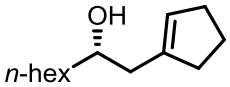
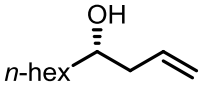


Notably, the use of vinyl electophiles in the tandem diboration cross-coupling sequence would give rise to highly valued homoallylic alcohols from vastly different starting materials than traditional carbonyl allylation methods.[71] While bromoarenes participated smoothly in cross-coupling reactions with the 1,2-bis(pinacol boronates), vinyl bromides were much more problematic, leading to only a 12% yield of the desired product **2.197** and large amounts of homo-dimer **2.198** with the use of **2.196** (Scheme 2.39). The inefficiency of this reaction could arise from the ability of bromine to bridge

[71] Yus, M.; González-Gómez, J. C.; Foubelo, F. *Chem. Rev*. **2011**, *111*, 7774.

Table 2.9: Synthesis of Homoallylic Alcohols Through Use of Vinyl Electrophiles



Entry	Product	X	Yield (%)	er
1		I	<5	-
2		Br	12	96.5:3.5
3		Cl	92	96.5:3.5
4		Cl	92	96.5:3.5
5		Cl	90	96.5:3.5
6		Cl	86	96.5:3.5
7		Br	83	96:4
8		Cl	90	96:4
9[a]		Cl	90	96:4

a) 3 equiv. 1,2-dichloroethane and 6 equiv. KO*t*Bu added

two palladium complexes, resulting in rapid disproportionation of palladium bromide complex **2.199** and leading to formation of diene **2.198** by way of divinyl complex **2.201**.[72] In an effort to avoid dimerization of Pd(II) intermediates, vinyl chlorides were examined due to less efficient bridge formation by chloride ions. Gratifyingly, this approach proved fruitful, with the use of *trans*-disubstituted (Table 2.9, entry 3), *cis*-disubstituted (entry 6), trisubstituted (entries 4, and 5), and cyclic vinyl chlorides (entries

[72] For a case where bridging bromide dimers are found to be the inactive resting state in a coupling reaction, see: Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc*. **1994**, *116*, 5969.

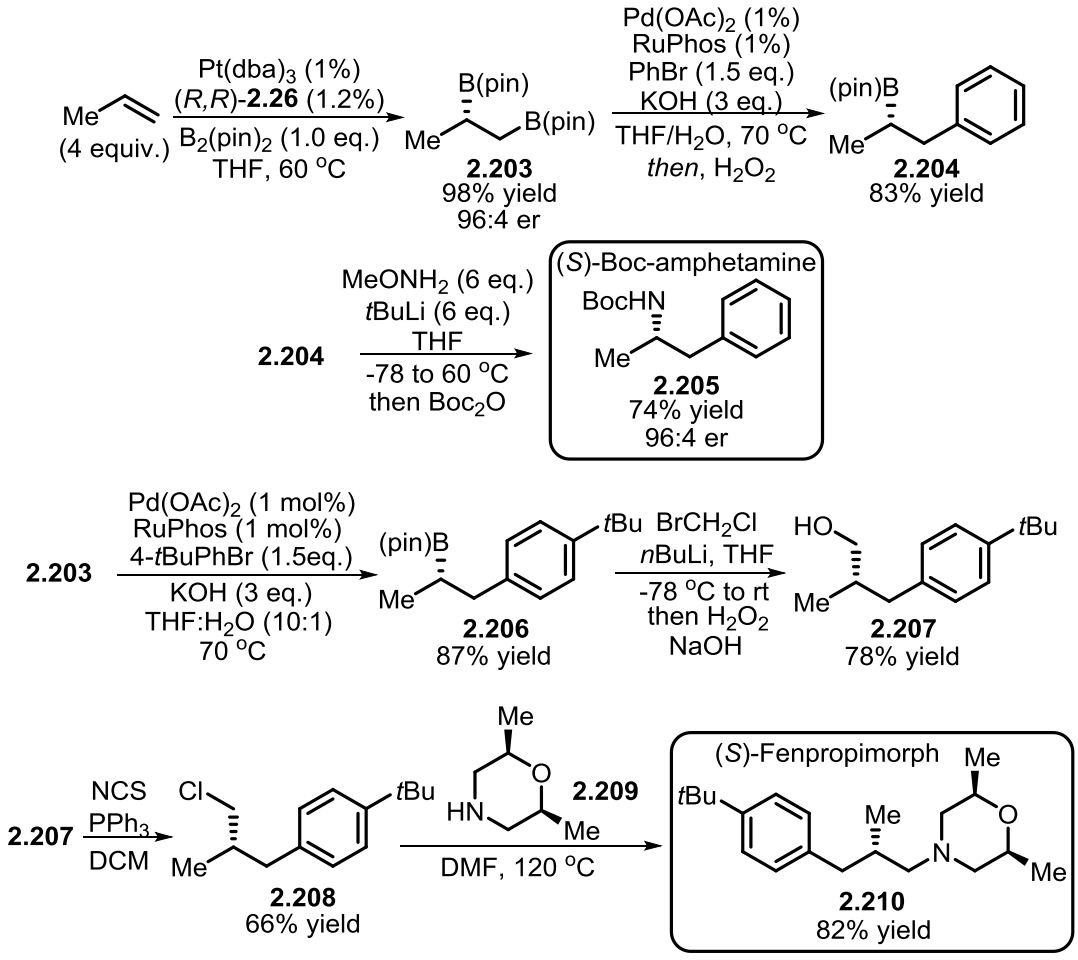
7 and 8) leading to the desired homoallylic alcohols in high yields and with excellent enantioselectivities. Importantly, the stereochemical information pre-programed into the vinyl chloride component is maintained in the product homoallylic alcohols, affording structures which are very difficult to obtain from allylation reactions. Notably, the use of gaseous vinyl chloride can be avoided by the use of 1,2-dichloroethane with additional equivalents of potassium *tert*butoxide as base, which likely leads to formation of vinyl chloride *in situ* and ultimately gives the desired terminal olefin product (entry 9).

2.3.4 Utility of Tandem Diboration Cross-Coupling in Target Oriented Synthesis

Importantly, the direct products obtained from Suzuki-Miyaura cross-coupling of 1,2-bis(pinacol boronates) contain an enantioenriched secondary homobenzylic or homoallylic pinacol boronate, which is capable of participating in additional functionalizations.[17] For instance, standard organoboron transformations, such as amination[73] and homologation,[74] can be implemented, often in a single flask operation. These overall sequences can result in formal enantioselective and regiospecific addition of oxygen and carbon, nitrogen and carbon, or two different carbon groups across a simple, unactivated terminal alkene. Individually, each operation represents a valuable synthetic tool, and would be worthy of a devoted catalyst to accomplish each transformation. To showcase the ability of tandem diboration cross-coupling to access a wide variety of chiral motifs from simple olefins, a number of medicinally important structures were prepared (Scheme 2.40 and Scheme 2.41).

[73] Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc*. **2012**, *134*, 16449.
[74] Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687.

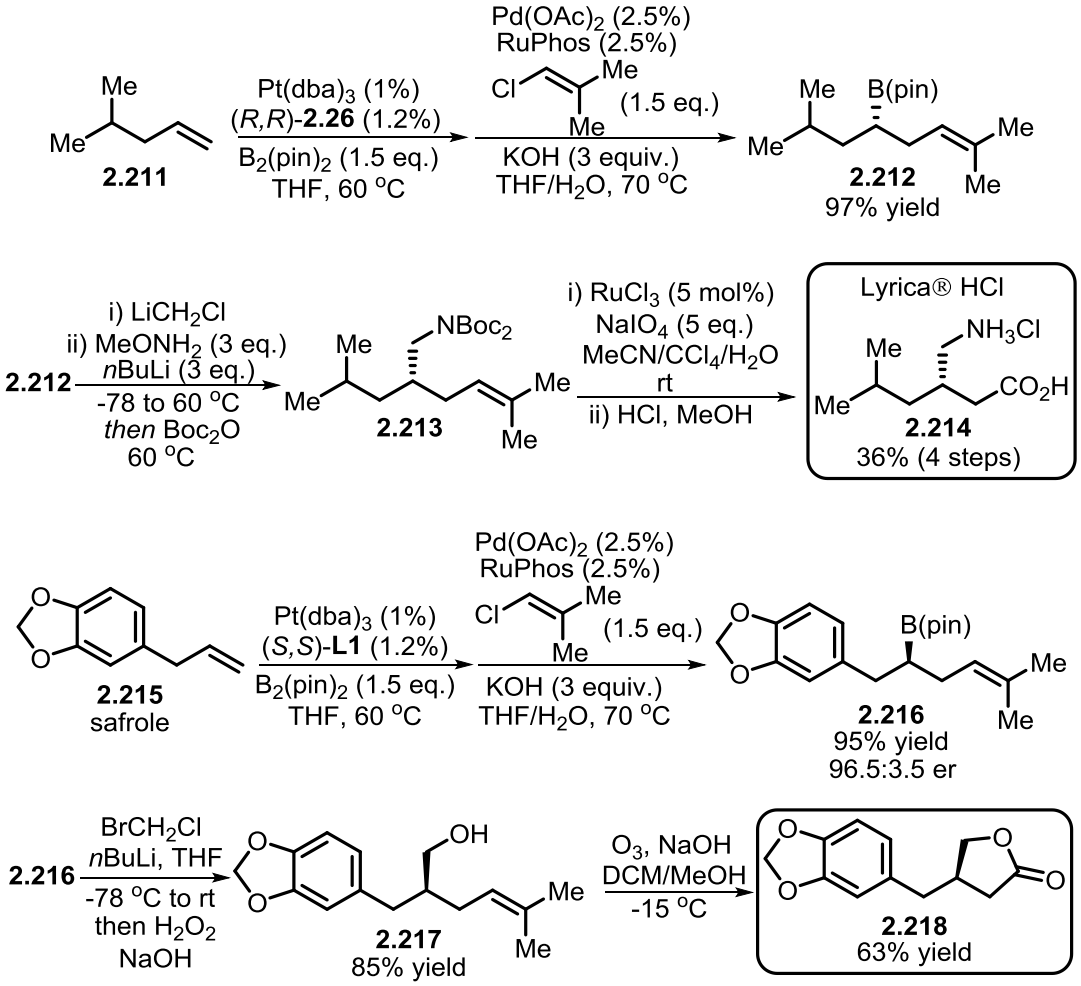
Scheme 2.40: Synthesis of Amphetamine and Fenpropimorph from Propene via Diboration Cross-Coupling



Utilizing abundant propene gas as the starting material, efficient asymmetric diboration gives 1,2-bis(pinacol boronate) **2.203** in nearly quantitative yield and with excellent levels of enantioselectivity (Scheme 2.40). Suzuki-Miyaura cross-coupling with bromobenzene, followed by stereospecific amination with deprotonated methoxy amine[73] and *in situ* Boc protection rapidly delivers (*S*)-Boc-amphetamine **2.205**. The use of simple building blocks to forge this biologically active compound highlights the potential of this sequence to be implemented towards diversity oriented approaches for analog preparation. Similarly, utilizing **2.203**, a cross-coupling, homologation, oxidation

sequence gives primary alcohol **2.207**. Chlorination followed by simple displacement with secondary amine **2.209** affords the more active enantiomer of the potent fungicide fenpropimorph[75] **2.210** in good yield.

Scheme 2.41: Preparation of Lyrica and Key Lignan Intermediate Through Diboration Cross-Coupling



In addition to utilizing aryl electrophiles in synthesis, the use of vinyl electrophiles opens alternative synthetic strategies (Scheme 2.41). For example, the tandem diboration cross-coupling of simple alkene **2.211** and chloroisobutylene affords

[75] Himmele, W.; Pommer, E-H. *Angew. Chem. Int. Ed*. **1980**, *19*, 184.

secondary enantioenriched pinacol boronate **2.212** in excellent yield. Homologation, followed by amination and oxidative olefin cleavage with acidic work-up provide the pharmaceutical Lyrica (pregabalin) **2.214**.[76] Lignan lactones are a structurally related group of natural products which exhibit a wide range of biological activity.[77] Starting from commercially available safrole **2.215**, key intermediate **2.218** is rapidly prepared via diboration cross-coupling, homologation, and oxidative olefin cleavage. Importantly, enantioenriched lactone **2.218** can be elaborated by simple alkylation to give rise to a variety of lignan natural products.[78] The versatility of this method allows one to consider simple terminal alkenes as powerful retrons for motifs which contain a methylene adjacent to a chiral center containing carbon, nitrogen, or oxygen substituents.

2.4 Conclusion

The use of 1,2-bis(pinacol boronates) in efficient Suzuki-Miyaura cross-coupling has been accomplished. The unique reactivity of these nucleophilic partners has been found to proceed through facile transmetallation compared to both other bis(pinacol boronates) as well as simple primary mono(pinacol boronates). When used in a one-pot tandem sequence with enantioselective platinum catalyzed diboration, readily available terminal alkenes are quickly transformed into a wide range of chiral products for use in complex molecule synthesis. This sequence affords useful structural motifs from non-traditional starting materials which are widely available and easily prepared. The huge range of alkenes and coupling partners available, together with the additional

[76] Hoekstra, M. S.; Sobieray, D. M.; Schwindt, M. A.; Mulhern, T. A.; Grote, T. M.; Huckabee, B. K.; Hendrickson, V. S.; Franklin, L. C.; Granger, E. J.; Karrick, G. L.; *Org. Process Res. Dev*. **1997**, *1*, 26.
[77] Pan, J-Y.; Chen, S-L.; Yang, M-H.; Wu, J.; Sinkkonen, J.; Zou, K. *Nat. Prod. Rep*. **2009**, *26*, 1251.
[78] Itoh, T.; Chika, J.; Takagi, Y.; Nishiyama, S. *J. Org. Chem*. **1993**, *58*, 5717.

functionalizations possible with homobenzylic and homoallylic pinacol boronates make this a potentially powerful method for diversity oriented synthesis.

2.5 Experimental Section

2.5.1 General Information

^{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 ($CDCl_3$: 7.24 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 (ESI) 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. Analytical chiral gas-liquid chromatography (GLC) was performed on a Hewlett-Packard 6890 Series chromatograph equipped with a split mode capillary injection system, a flame ionization detector, and a Supleco β-Dex 120 column with helium as the carrier gas. Analytical chiral high-performance liquid chromatography (HPLC) was performed on a Agilent 1120 liquid chromatograph equipped with a UV detector and a Daciel Chiracel-OD-R column.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran 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. RuPhos, 1-bromo-4-(trifluoromethyl)benzene, 4-bromoanisole, potassium *tert*-butoxide and 4-methyl-1-pentene were purchased from Acros. 2-Bromofuran was purchased from Accela Chembio. (*R*)-2-Methyloxirane, (*rac*)-2-methyloxirane, vinylmagnesium bromide, *N*-chlorosuccinamide, imidazole, copper bromide, cyclohexanone, allyl alcohol, but-3-en-1-ol, 1-octene, 1-octyne, vinyl cyclohexane, (*S*)-(-)-citronellal, bromobenzene, chlorobenzene, iodobenzene, 2-bromotoluene, 1-bromonaphthalene, 3-bromofuran, 3-bromopyridine, 1-chloro-1-cyclopentene, 1,2-dichloroethane, bromochloromethane, and 1-bromo-4-*tert*-butylbenzene were purchased from Aldrich. *N*-Bromosuccinamide, 1-dodecyne, and lithium chloride were purchased from Alfa Aesar. Propene and 1-chloro-2-methylpropene were purchased from ChemSampCo. Safrole was purchased from Chem Service, Inc. Potassium hydroxide

was purchased from Fisher Scientific. Triisopropylchlorosilane and *tert*-butyldiphenylchlorosilane were purchased from Gelest. *tert*-Butyldimethylchlorosilane was purchased from Oakwood Chemical. *cis*-1-Chloropropene was purchased from Pure Chemistry Scientific. Palladium Acetate was purchased from Strem Chemicals. All chemicals were used as received.

2.5.2 Experimental Procedures

2.5.2.1 Preparation of $Pt(dba)_3$.

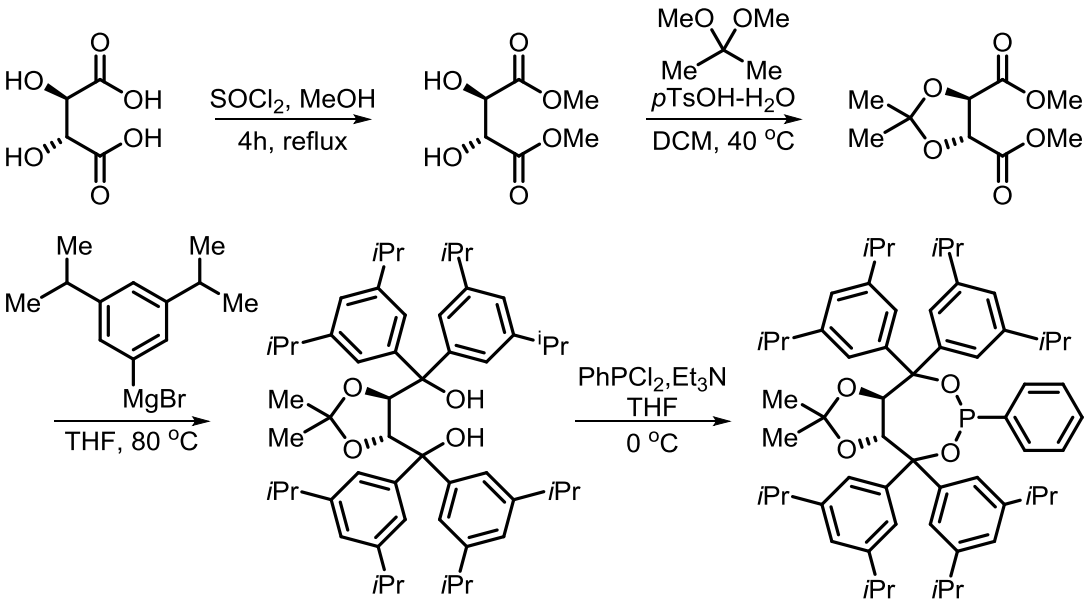
Tris(dibenzylideneacetone)platinum was prepared using the literature procedure[79] with slight modification but can also be purchased through Strem chemicals (order #: 78-1360). To a 3-neck 500-mL round-bottomed flask equipped with magnetic stir bar and reflux condenser was added dibenzylideneacetone (3.95 g, 16.8 mmol), tetrabutylammonium chloride (2.0 g, 7.2 mmol), and sodium acetate (3.55 g, 43.3 mmol). The solids were dissolved in methanol (210 mL) and the solution was warmed to 70 ºC and allowed to stir for 5 min. To a 50-mL pear-shaped flask was added potassium tetrachloroplatinate (1.00 g, 2.41 mmol). The potassium salt was dissolved in water (8 mL) with mild heating. The 3-neck round-bottom flask was charged with the potassium tetrachloroplatinate solution and the reaction was allowed to stir at 70 ºC for 5 h. After 5 h, the reaction was cooled to ambient temperature, transferred to a 500-mL round-bottom flask and concentrated by rotary evaporation until only a slurry of salts remained. The reaction mixture was filtered on a Büchner funnel; solids were washed with copious amounts of methanol until no yellow dibenzylideneacetone crystals were visible. The platinum catalyst was placed under the high vacuum for 24 h to remove residual

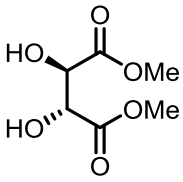
[79] Lewis, L. N.; Krafft, T. A.; Huffman, J. C. *Inorg. Chem.* **1992**, *31*, 3555.

methanol and water, and tris(dibenzylideneacetone)platinum was obtained as a dark solid (1.305 g, 60% yield). Spectroscopic characterization of the platinum catalyst is in accordance with spectra reported in the literature.[80]

2.5.2.2 Preparation of TADDOL-based Phosphonite Ligands

(*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh was synthesized according to literature procedure[81], but can also be purchased through Strem chemicals (order #: 15-1513).

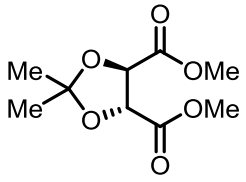




(2*R*,3*R*)-dimethyl 2,3-dihydroxysuccinate. A flame dried 2-neck round-bottomed flask with magnetic stir bar and condenser was charged with (*R,R*)-tartaric acid (30.0 g, 0.199 mol). The apparatus was purged with N_2, and methanol (95 mL) was added. The reaction flask was fitted with an outlet at the top of a condenser, which was connected to a bubbler containing a saturated aqueous

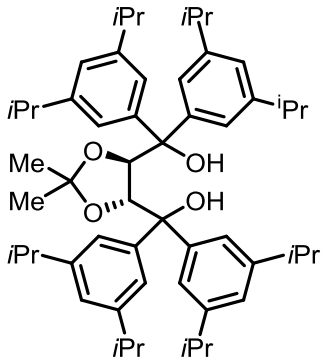
[80] Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978.
[81] Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. *Angew. Chem. Int. Ed.* **2012**, *51*, 521.

solution of $NaHCO_3$. The reaction flask and the bubbler were both cooled to 0 °C and $SOCl_2$ (74.3 mL, 1.02 mol) was added drop wise to the reaction. Once the evolution of HCl (g) slowed, the reaction was removed from the ice bath and heated to reflux for 4 hours. The reaction was then cooled to room temperature and condensed *in vacuo* until only a viscous oil remained. The crude material was then diluted with distilled H_2O (50 mL) and EtOAc (50 mL). The layers were separated and the aqueous layer was then further extracted with EtOAc (10 x 50 mL). The combined organics were dried over Na_2SO_4, filtered and condensed *in vacuo*. The resulting crude diester was taken directly to the next step without purification.



(4*R*,5*R*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate. A 2-neck round-bottomed flask with magnetic stir bar and condenser was charged with (*R,R*)-dimethyl tartrate and *p*-toluenesulfonic acid monohydrate (18.9 g, 0.099 mol). The apparatus was purged with N_2, and the reaction was diluted with DCM (275 mL). 2,2-dimethoxypropane (156 mL, 1.30 mol) was added, and the reaction was brought to reflux and stirred for 4 hours. The reaction was then cooled to room temperature and condensed *in vacuo*. The crude residue was then diluted with distilled H_2O (50 mL) and EtOAc (50 mL). The layers were separated and the aqueous layer was then extracted with EtOAc (3 x 50 mL). The combined organics were dried over Na_2SO_4, filtered and condensed *in vacuo*. The crude material was then

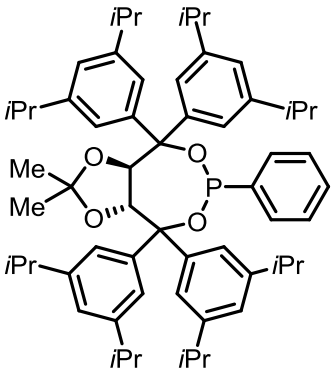
distilled (~120 °C at 1 torr) to afford the pure title compound (36.22 g, 83% yield). Spectral data are in accordance with the literature[82].



(*R*,*R*)-3,5-di-*iso*-propylphenylTADDOL. To a flame-dried 1 L 2-neck round-bottomed flask equipped with magnetic stir bar and reflux condenser was added crushed magnesium turnings (4.097 g, 168.5 mmol) under N_2. The apparatus was flame-dried again, a single cystal of I_2 was added followed by addition of tetrahydrofuran (230 mL). To another flame dried 250-mL round-bottom flask was added 1-bromo-3,5-di-*iso*-propylbenzene [(33.7 g, 140 mmol), prepared according to literature procedure[83] from 2,6-di-*iso*-propylaniline] and tetrahydrofuran (90 mL). The solution of 1-bromo-3,5-di-*iso*-propylbenzene in tetrahydrofuran was slowly added to the magnesium mixture at ambient temperature *via* cannula. The reaction was heated to reflux at 80 ºC in an oil bath for 3 hours, at which time the reaction was cooled to 0 ºC, and a solution of (4*R*,5*R*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (6.13 g, 28.1 mmol) in tetrahydrofuran (30 mL) was added slowly *via* syringe. The reaction was allowed to reflux for 12 h, after which it was cooled to 0 ºC and quenched with saturated aqueous NH_4Cl (40 mL). The organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 60 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude material was purified by crystallization from methanol to afford the title compound

[82] Kobayashi, Y.; Kokubo, Y.; Aisaka, T.; Saigo, K. *Tetrahedron: Asymmetry*, **2008**, *19*, 2536.
[83] Diemer, V.; Chaumeil. H.; Defoin, A.; Fort, A.; Boeglin, A.; Carré, C. *Eur. J. Org. Chem.* **2006**, *12*, 2727.

as a white crystalline solid (20.1 g, 89% yield). Spectral data are in accordance with the literature.[81]

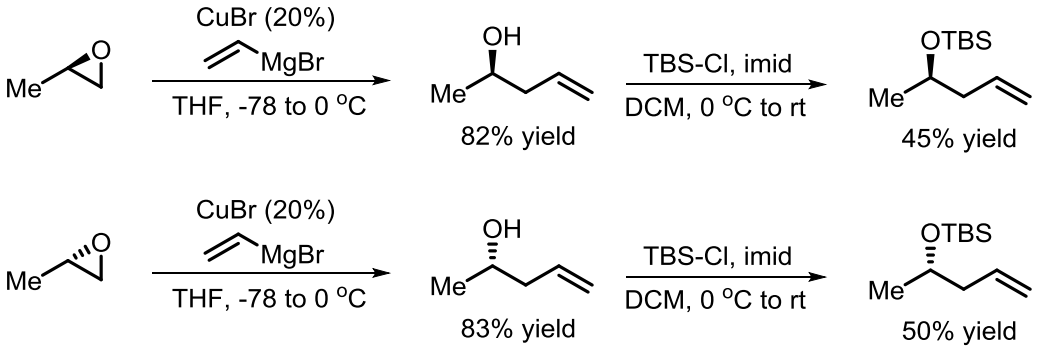


(*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh. To a flame dried 100 mL round-bottomed flask equipped with magnetic stir bar was added (*R,R*)-3,5-di-*iso*-propylphenylTADDOL (3.50 g, 4.36 mmol) and tetrahydrofuran (44 mL, 0.1 M) under N_2. Triethylamine (2.06 mL, 14.8 mmol) was added and the reaction mixture was cooled to 0 ºC in an ice bath. Dichlorophenylphosphine (0.65 mL, 4.8 mmol) was added dropwise at 0 ºC. The reaction was brought to ambient temperature and was allowed to stir for 2 h. The reaction was diluted with Et_2O (40 mL), filtered through celite, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (2% ethyl acetate in hexanes, with 1% Et_3N to prevent hydrolysis) to afford the title compound as a white solid (3.65 g, 92% yield). Spectral data are in accordance with the literature.[81]

2.5.2.3 Preparation of Substrates

Preparation of Alkenes

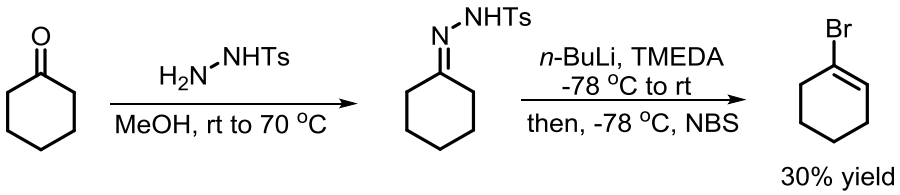
(Allyloxy)triisopropylsilane[84] and (but-3-en-1-yloxy)(tert-butyl)diphenylsilane[85] were prepared through silyl protection of prop-2-en-1-ol and but-3-en-1-ol following literature procedures. (*S*)-4,8-dimethylnona-1,7-diene was prepared according to the literature procedure.[86] (*R*)-*tert*-butyldimethyl(pent-4-en-2-yloxy)silane and (*S*)-*tert*-butyldimethyl(pent-4-en-2-yloxy)silane were prepared according to the literature procedure[87] as shown below. (*S*)-2-Methyloxirane was prepared from (*rac*)-2-methyloxirane utilizing Jacobsen HKR according to the literature procedure.[88] All spectral data are in accordance with the literature.



[84] Ziegler, D. T.; Steffens, A. M.; Funk, T. W. *Tet. Lett*. **2010**, *51*, 6726.
[85] Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210.
[86] Coombs, J. R.; Haeffner, F.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135,* 11222.
[87] Figueroa, R.; Hsung, R. P.; Guevarra, C. C. *Org. Lett*. **2007**, *9*, 4857.
[88] Schaus, 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.

Preparation of Electrophiles

1-Bromocyclohex-1-ene. Prepared according to the literature procedure[89] as shown below. All spectral data are in accordance with the literature.



(*E*)-1-chlorododec-1-ene. The title compound was prepared according to the literature procedure[90] with slight modification. A flame-dried round-bottomed flask with magnetic stir bar was purged with N_2 and charged with 1-dodecyne (2.00 mL, 9.36 mmol) and hexane (9.8 mL, 0.96 M). The reaction flask was cooled to 0 ºC and DIBAL-H (1.75 mL, 9.82 mmol) was added dropwise. The reaction mixture was stirred at room temperature for 30 min and at 50 ºC for 5 h. The reaction mixture was then cooled to -30 ºC and diluted with dry diethyl ether. *N*-chlorosuccinamide (1.50 g, 11.2 mmol) was added, and the reaction flask was purged with N_2. The reaction was warmed to room temperature and stirred for 24 h. The reaction mixture was poured into a separatory funnel containing 6 M HCl (20 mL) and ice chips. The layers were separated and the aqueous layer was extracted with pentane (3 x 35 mL). The combined organics were then washed with 1 M NaOH (50 mL) and 10% sodium sulfite (50 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified on SiO_2 to afford the title compound as a colorless oil (1.05 g, 56% yield).

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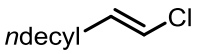
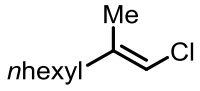
[89] Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 277.
[90] Ney, J. E.; Hay, M. B.; Yang, Q.; Wolfe, J. P. *Adv. Synth. Catal.* **2005**, *347*, 1614.



(*E*)-1-chlorododec-1-ene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91 (1H, d, *J* = 13.0 Hz), 5.87 (1H, dt, *J* = 13.0 Hz, 7.0 Hz), 2.02 (2H, app q, *J* = 7.0 Hz), 1.38-1.32 (2H, m), 1.30-1,24 (16H, m), 0.86 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.1, 116.6, 31.9, 30.9, 29.6, 29.5, 29.4, 29.3, 29.0, 28.9, 22.7, 14.1; IR (neat): 2922 (s), 2853 (m), 1634 (w), 1464 (m), 1377 (w), 933 (s), 804 (m), 721 (m) cm^{-1}; HRMS-(ESI+) for $C_{12}H_{27}ClN$ [M+NH_4^+]: calculated: 220.1832, found: 220.1832.

(*E*)-1-chloro-2-methyloct-1-ene. The title compound was prepared according to literature procedure[91] with slight modification. A flame-dried round bottom flask with magnetic stir bar was charged with $ZrCp_2Cl_2$ (1.98 g, 6.77 mmol). The flask was fitted with a septum, purged with N_2, and diluted with dichloromethane (9.7 mL, [substrate] = 0.7 M). $AlMe_3$ (1.62 mL, 16.9 mmol) was then added to the reaction dropwise at room temperature. After stirring at room temperature for 10 min, the reaction was cooled to 0 ºC and 1-octyne (1.00 mL, 6.77 mmol) was added dropwise. The reaction was warmed to room temperature and stirred for 14 h. A solution of *N*-chlorosuccinamide (2.71 g, 20.3 mmol) in tetrahydrofuran (40 mL) was then added to the reaction at 0 ºC. After stirring at room temperature for 24 h, the reaction mixture was poured into a separatory funnel containing 6 M HCl (20 mL) and ice chips. The layers were separated and the aqueous layer was extracted with pentane (3 x 30 mL). The combined organics were then washed with 1 M NaOH (40 mL) and 10% sodium sulfite (40 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified on SiO_2 to afford the title compound as a colorless oil (632 mg, 58% yield).

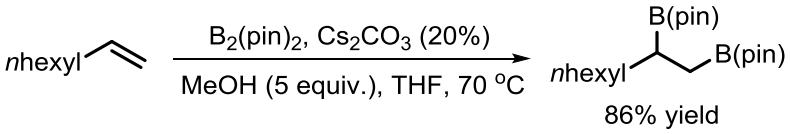
[91] Van Horn, D. E.; Negishi, E. *J. Am. Chem. Soc.* **1978**, *100*, 2252.



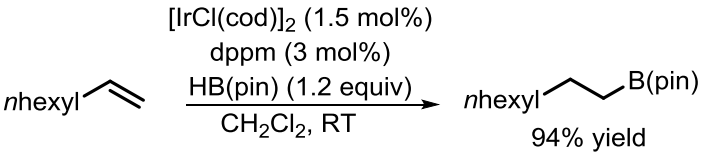
(*E*)-1-chloro-2-methyloct-1-ene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.76 (1H, d, *J* = 1.0 Hz), 2.03 (2H, t, *J* = 7.0 Hz), 1.74 (3H, d, *J* = 1.5 Hz), 1.39 (2H, app pent, *J* = 7.5 Hz), 1.30-1.22 (8H, m), 0.87 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.9, 111.6, 37.1, 31.6, 28.8, 27.5, 22.6, 16.3, 14.0; IR (neat): 2927 (s), 2856 (m), 1639 (w), 1458 (m), 1378 (m), 1309 (m), 1111 (w), 787 (m), 771 (s) cm^{-1}.

Preparation of Alkyl Boron Compounds

2,2'-(octane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Prepared according to the literature procedure[92] as shown below. All spectral data are in accordance with the literature.

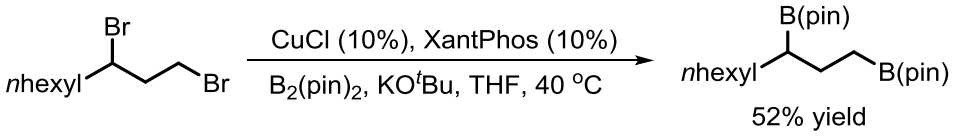


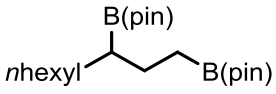
4,4,5,5-tetramethyl-2-octyl-1,3,2-dioxaborolane. Prepared according to the literature procedure[93] as shown below. All spectral data are in accordance with the literature.



[92] Bonet, A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyás, H.; Fernández, E. *Angew. Chem. Int. Ed.,* **2011**, *50*, 7158.
[93] Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron*, **2004**, *60*, 10695.

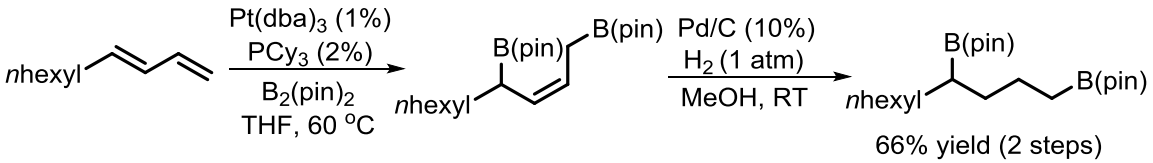
2,2'-(nonane-1,3-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Prepared according to the literature procedure as shown below.[94]



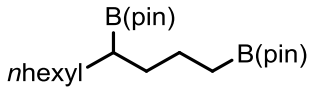


2,2'-(nonane-1,3-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42-1.54 (2H, m), 1.31-1.40 (2H, m), 1.24-1.30 (8H, m), 1.22 (24H, s), 0.90-0.96 (1H, m), 0.86 (3H, t, J = 6.9 Hz), 0.70-0.82 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 82.8, 82.7, 31.8, 31.2, 29.6, 29.1, 25.4, 24.84, 24.80, 22.6, 14.1; IR (neat): 2977.2 (w), 2923.7 (m), 2854.9 (w), 1460.3 (w), 1370.3 (s), 1312.7 (s), 1271.5 (w), 1214.6 (w), 1143.7 (s), 968.4 (w), 865.8 (w), 847.9 (w) cm^{-1}; HRMS-(ESI+) for $C_{21}H_{43}B_2O_4$ [M+H]: calculated: 381.3347, found: 381.3350.

2,2'-(decane-1,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). The title compound was prepared as shown below. *Trans*-1,3-decadiene was subjected to platinum catalyzed diboration according to the previously reported procedure.[95] The resulting unsaturated product was then hydrogenated to give the desired product.



[94] Kubota, K.; Ito, H. *Org. Lett.,* **2012**, *14*, 890.
[95] Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.,* **2009**, *131*, 9134.



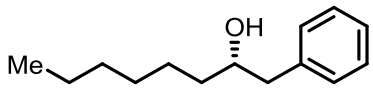
2,2'-(decane-1,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29-1.44 (6H, m), 1.16-1.29 (32H, m), 0.91-0.99 (1H, m), 0.84-0.87 (3H, m), 0.72-0.77 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 82.74, 82.68, 34.1, 31.8, 31.2, 29.6, 29.2, 24.79, 24.76, 23.7, 22.6, 14.1; IR (neat): 2977.3 (w), 2923.7 (m), 2855.0 (w), 1460.5 (w), 1370.9 (s), 1314.7 (s), 1254.1 (w), 1238.8 (w), 1214.7 (w), 1144.6 (s), 968.1 (w), 847.6 (w), 725.6 (w) cm^{-1}; HRMS-(ESI+) for $C_{22}H_{45}B_2O_4$ [M+H]: calculated: 395.3504, found: 395.3508.

2.5.2.4 General Procedure for Alkene Diboration/Cross-coupling/Oxidation

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), $B_2(pin)_2$ (133.3 mg, 525 μmol) and tetrahydrofuran (0.5 mL, [substrate] = 1.0 M). The vial was sealed with a teflon septum cap, removed from the dry box, and heated to 80 ºC in an oil bath for 20 minutes. The vial was cooled to room temperature, returned to the dry box and charged with alkene (500 μmol). The vial was sealed, removed from the dry box and stirred at 60 ºC 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), $Pd(OAc)_2$/RuPhos (added as a 1:1 solution in THF (0.018 M); 0.27 mL for 1 mol%, 0.70 mL for 2.5 mol%), tetrahydrofuran (3.78 mL or 3.35 mL, [substrate] = 0.1 M; 10:1 THF:H_2O) and electrophile (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 ºC and stirred for 12 h. The reaction mixture was transferred to a 50-mL round bottom flask and cooled to 0 ºC (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 ºC 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.

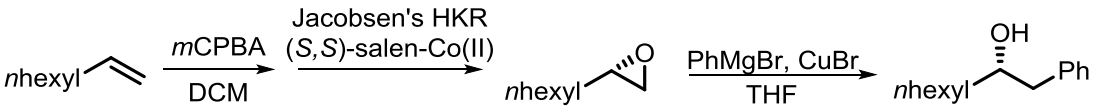
2.5.2.5 Full Characterization and Proof of Stereochemistry



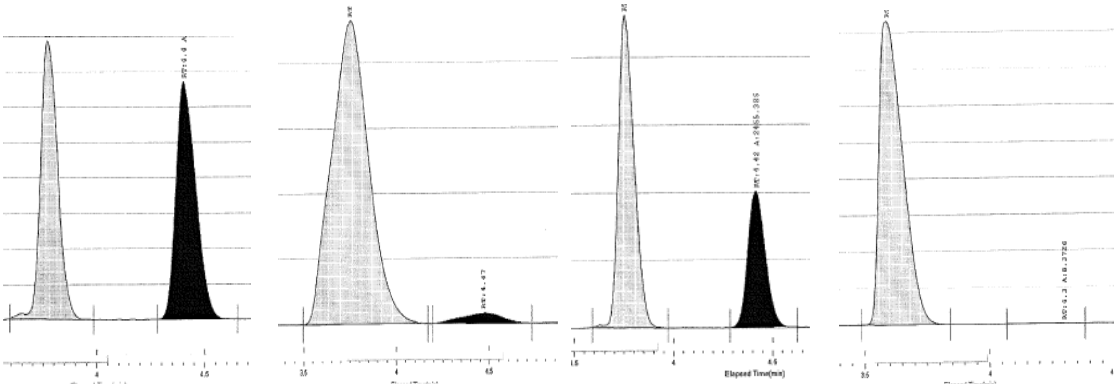
(*S*)-1-phenyloctan-2-ol. Prepared according to the general procedure using octene (56.1 mg. 0.500 mmol) and bromobenzene (117.8 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the product as a colorless oil (99.1 mg, 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.23 (2H, m), 7.24-7.20 (3H, m), 3.80 (1H, app tt, J = 9.0 Hz, 4.5 Hz), 2.82 (1H, dd, J = 13.5 Hz, 4.5 Hz), 2.63 (1H, dd, J = 13.5 Hz, 8.5 Hz), 1.54-1.46 (4H, m), 1.37-1.25 (6H, m), 0.88 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7, 129.4, 128.5, 126.4, 72.6, 44.0, 36.8, 31.8, 29.3, 25.7, 22.6, 14.0; IR(neat): 3385 (br, m), 2925 (s), 2855 (m), 1495 (w), 1454 (m), 1079 (m), 1031 (m), 742 (m), 698 (s) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{26}NO$ [M+NH_4]: calculated 224.2014, found: 224.2021; $[\alpha]_D^{20}$ = +8.222 (c = 2.043, $CHCl_3$, l = 50 nm).

Proof of Stereochemistry:

The title compound was compared to racemic alcohol prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. The authentic (*S*)-isomer was prepared as described below:

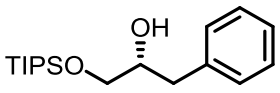


Chiral SFC (Chiracel, OD-H, 35 °C, 5 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of 1-phenyloctan-2-ol.



racemic | Diboration/ cross- coupling product | Coinjection of product + racemic | authentic

Peak No	% Area	Area	RT (min)
1	96.4188	12965.0521	3.75
2	3.5812	481.5449	4.47
Total:	100	13446.597	

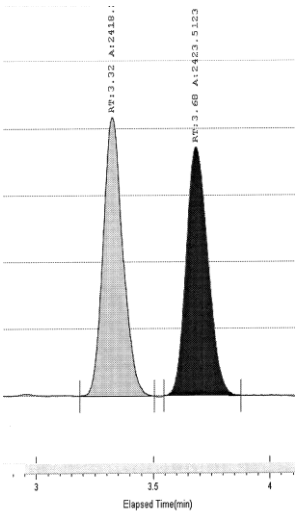


(*R*)-1-phenyl-3-((triisopropylsilyl)oxy)propan-2-ol. Prepared according to the general procedure using (allyloxy)triisopropylsilane (107.2 mg, 0.500 mmol) except (*R,R*)-diethylphenylTADDOPPh (8.0 mg, 10 μmol) was employed as the ligand. Diboration was carried out for 8 h at 60 ºC followed by cross-coupling, which was performed without modification using bromobenzene (117.8 mg, 0.750 mmol) as the electrophile with 1 mol% Pd/RuPhos. The crude organoboron product was not oxidized by $NaOH/H_2O_2$; instead the crude reaction mixture was diluted with THF (5 mL) and water (10 mL), followed by treatment with sodium perborate monohydrate (500 mg, 5.0 mmol). After the usual workup, the crude material was purified on silica gel (7% EtOAc/hexanes, stain with Seebach) to afford the product as a viscous oil (126.5 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.29-7.32 (2H, m), 7.21-7.25 (3H, m), 3.89-3.94 (1H, m), 3.71 (1H, dd, J = 9.8 Hz, 3.9 Hz), 3.58 (1H, dd, J = 9.8 Hz, 6.9 Hz), 2.76-2.83 (2H, m), 2.51 (1H, br s), 1.09-1.15 (3H, m), 1.06 (18H, d, J = 4.4 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.3, 129.3, 128.4, 126.3, 72.9, 66.6, 39.6, 17.9, 11.9; IR (neat): 3452.2 (br.), 2941.5 (s), 2865.2 (s), 1602.4 (w), 1496.1 (w), 1462.2 (m), 1117.7 (s), 882.0 (s), 786.6 (m), 742.9 (m), 698.8 (s), 682.0 (s) cm^{-1}; HRMS-(ESI+) for $C_{18}H_{33}O_2Si$ [M+H]: calculated: 309.2250, found: 309.2251. $[\alpha]_D^{20}$ = -2.660 (c = 2.192, $CHCl_3$, l = 50 mm).

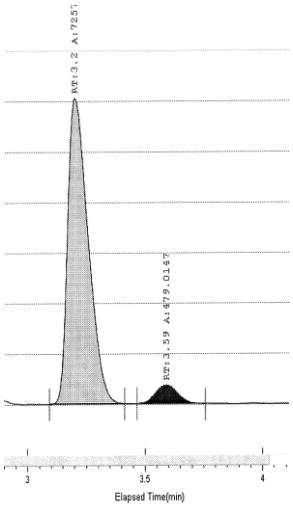
Analysis of Stereochemistry:

The title compound was compared to racemic alcohol prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

Chiral SFC (Chiracel, OD-H, 35 ^oC, 5 mL/min, 2% Isopropanol, 100 bar, 210-270nm) – analysis of 1-phenyl-3-((triisopropylsilyl)oxy)propan-2-ol.

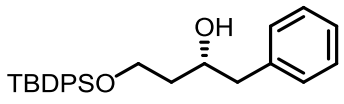


racemic



Diboration/
cross- coupling
product

Peak No	% Area	Area	RT (min)
1	93.8086	7257.8164	3.2
2	6.1914	479.0147	3.59
Total:	100	7736.8311	

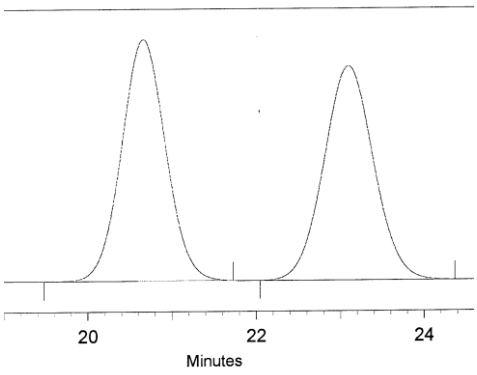


(*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-1-phenylbutan-2-ol. Prepared according to the general procedure using (but-3-en-1-yloxy)(*tert*-butyl)diphenylsilane (155.3 mg, 0.500 mmol) and bromobenzene (117.8 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (5% EtOAc/hexanes, stain with Seebach) to afford the product as a viscous oil (196.9 mg, 97%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70-7.73 (4H, m), 7.45-7.48 (2H, m), 7.40-7.44 (4H, m), 7.31-7.34 (2H, m), 7.23-7.26 (3H, m), 4.16-4.21 (1H, m), 3.91 (1H, ddd, *J* = 10.5 Hz, 5.2 Hz, 5.2 Hz), 3.85 (1H, ddd, *J* = 10.5 Hz, 7.8 Hz, 4.6 Hz), 3.19 (1H, br s), 2.89 (1H, dd, *J* = 13.7 Hz, 7.1 Hz), 2.79 (1H, dd, *J* = 13.7 Hz, 6.1 Hz), 1.71-1.81 (2H, m), 1.10 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6, 135.53, 135.51, 133.1, 133.0, 129.78, 129.76, 129.4, 128.4, 127.7(assumed 2), 126.2, 72.4, 63.1, 44.0, 37.7, 26.8, 19.0; IR (neat): 3457.7 (br.), 3069.7 (w), 3026.5 (w), 2930.2 (w), 2857.1 (w), 1427.4 (w), 1109.6 (m), 1081.1 (m), 822.6 (w), 700.2 (s), 614.1 (w), 505.2 (m) cm^{-1}; HRMS-(ESI+) for $C_{26}H_{33}O_2Si$ [M+H]: calculated: 405.2250, found: 405.2238. $[\alpha]_D^{20}$ = +0.934 (*c* = 1.606, $CHCl_3$, *l* = 50 mm).

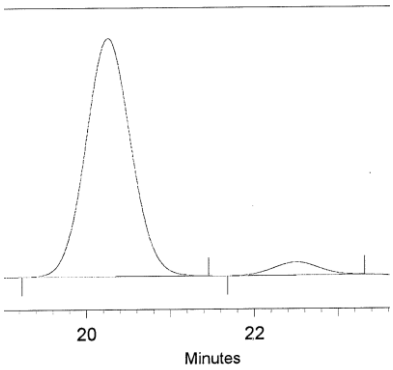
Analysis of Stereochemistry:

The title compound was compared to racemic alcohol prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

Chiral HPLC (Chiracel, OD-R, 0.5% Isopropanol, 0.5 mL/min, 220nm) – analysis of ***)*** *4-((tert-butyldiphenylsilyl)oxy)-1-phenylbutan-2-ol.*

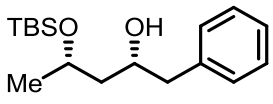


racemic



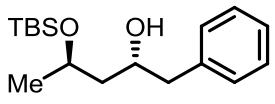
Diboration/
cross- coupling
product

Retention Time	Area	Area %
20.260	143392434	94.78
22.497	7897575	5.22
Totals	151290009	100.00



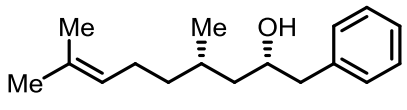
(2*R*,4*S*)-4-((*tert*-butyldimethylsilyl)oxy)-1-phenylpentan-2-ol. Prepared according to the general procedure using (*S*)-*tert*-butyldimethyl(pent-4-en-2-yloxy)silane (100.2 mg, 0.500 mmol) and bromobenzene (117.8 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude organoboron product was not oxidized by $NaOH/H_2O_2$; instead the crude reaction mixture was diluted with THF (5 mL) and water (10 mL), followed by treatment with sodium perborate monohydrate (500 mg, 5.0 mmol). After the usual workup, the crude material was purified on silica gel (10% EtOAc/hexanes, stain with Seebach) to afford the product as a viscous oil (129.1 mg, 88%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27-7.32 (2H, m), 7.20-7.23 (3H, m), 3.99-4.07 (2H, m), 3.50 (1H, br s), 2.85 (1H, dd, *J* = 13.7 Hz, 6.4 Hz), 2.69 (1H, dd, *J* = 13.7 Hz, 6.8 Hz), 1.52-1.62 (2H, m), 1.16 (3H, d, *J* = 5.9 Hz), 0.91 (9H, s), 0.12 (3H, s), 0.10 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6, 129.5, 128.3, 126.2, 72.4, 69.9, 44.7, 44.1, 25.8, 24.5, 17.9, -3.9, -4.8; IR (neat): 3468.4 (br.), 3028.0 (w), 2955.0 (w), 2929.3 (m), 2856.6 (w), 1375.2 (w), 1254.8 (m), 1135.8 (w), 1089.8 (m), 834.6 (s), 775.3 (s), 699.5 (m) cm^{-1}; HRMS-(ESI+) for $C_{17}H_{31}O_2Si$ [M+H]: calculated: 295.2093, found: 295.2106. $[\alpha]_D^{20}$ = +27.65 (*c* = 2.296, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry: *Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.*



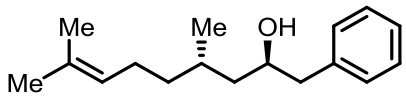
(2*R*,4*R*)-4-((*tert*-butyldimethylsilyl)oxy)-1-phenylpentan-2-ol. Prepared according to the general procedure using (*R*)-*tert*-butyldimethyl(pent-4-en-2-yloxy)silane (100.2 mg, 0.500 mmol) and bromobenzene (117.8 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude organoboron product was not oxidized by $NaOH/H_2O_2$; instead the crude reaction mixture was diluted with THF (5 mL) and water (10 mL), followed by treatment with sodium perborate monohydrate (500 mg, 5.0 mmol). After the usual workup, the crude material was purified on silica gel (10% EtOAc/hexanes, stain with Seebach) to afford the product as a viscous oil (138.0 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-7.31 (2H, m), 7.19-7.23 (3H, m), 4.17-4.23 (2H, m), 3.23 (1H, br s), 2.82 (1H, dd, *J* = 13.7 Hz, 7.3 Hz), 2.70 (1H, dd, *J* = 13.7 Hz, 5.9 Hz), 1.64 (1H, ddd, *J* = 14.2, Hz, 9.8 Hz, 3.4 Hz), 1.54 (1H, ddd, *J* = 14.2 Hz, 5.9 Hz, 2.4 Hz), 1.19 (3H, d, *J* = 5.9 Hz), 0.90 (9H, s), 0.09 (3H, s), 0.08 (3H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.8, 129.3, 128.4, 126.2, 69.3, 67.4, 44.4, 43.8, 25.8, 22.9, 17.9, -4.5, -5.0; IR (neat): 3459.5 (br.), 3028.1 (w), 2955.4 (m), 2929.2 (m), 2856.6 (m), 1462.5 (w), 1375.7 (w), 1255.1 (m), 1090.1 (m), 1015.4 (m), 835.0 (s), 775.3 (s), 699.6 (m) cm^{-1}; HRMS-(ESI+) for $C_{17}H_{31}O_2Si$ [M+H]: calculated: 295.2093, found: 295.2103. $[\alpha]_D^{20}$ = -13.09 (*c* = 1.255, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry: *Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.*



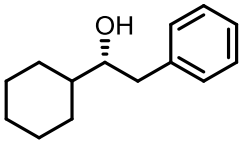
(2*S*,4*S*)-4,8-dimethyl-1-phenylnon-7-en-2-ol. Prepared according to the general procedure using (*S*)-4,8-dimethylnona-1,7-diene (76.1 mg. 0.500 mmol) and bromobenzene (117.8 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the product as a colorless oil (120.7 mg, 97% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37-7.34 (2H, m), 7.29-7.23 (3H, m), 5.13 (1H, app dt, *J* = 7.0 Hz, 1.0 Hz), 3.95 (1H, app tt, *J* = 8.5 Hz, 4.5 Hz), 2.86 (1H, dd, *J* = 13.5 Hz, 4.5 Hz), 2.64 (1H, dd, *J* = 13.5 Hz, 8.5 Hz), 2.09-1.93 (2H, m), 1.74-1.69 (1H, m), 1.72 (3H, s), 1.64 (3H, s), 1.53-1.42 (3H, m), 1.21-1.26 (1H, m), 0.99 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6, 131.2, 129.4, 128.5, 126.4, 124.7, 70.7, 44.5, 44.3, 36.6, 29.3, 25.7, 25.3, 20.2, 17.6; IR(neat): 3388 (br, m), 2959 (s), 2922 (s), 1495 (w), 1453 (m), 1376 (m), 1030 (m), 699 (s) cm^{-1}; HRMS-(ESI+) for $C_{17}H_{27}O$ [M+H]: calculated 247.2062, found: 247.2062; $[\alpha]_D^{20}$ = +3.698 (*c* = 2.920, $CHCl_3$, *l* = 50 nm).

Analysis of Stereochemistry: *Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.*



(2*R*,4*S*)-4,8-dimethyl-1-phenylnon-7-en-2-ol. Prepared according to the general procedure using (*S*)-4,8-dimethylnona-1,7-diene (76.1 mg. 0.500 mmol) and bromobenzene (117.8 mg, 0.750 mmol) with 1 mol% Pd/RuPhos, except (*S,S*)-3,5-di-*iso*-propylphenyl-TADDOLPPh ligand was employed in the diboration. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the product as a colorless oil (119.6 mg, 96% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.30 (2H, m), 7.24-7.20 (3H, m), 5.08 (1H, app dt, *J* = 7.0 Hz, 1.5 Hz), 3.91 (1H, app tt, *J* = 8.0 Hz, 3.5 Hz), 2.79 (1H, dd, *J* = 14.0 Hz, 4.0 Hz), 2.64 (1H, dd, *J* = 14.0 Hz, 8.5 Hz), 2.02-1.91 (2H, m), 1.72-1.60 (1H, m), 1.66 (3H, s), 1.58 (3H, s), 1.54 (1H, ddd, *J* = 13.5 Hz, 9.5 Hz, 4.5 Hz), 1.41 (1H, s), 1.34-1.16 (3H, m), 0.89 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.6, 131.2, 129.4, 128.5, 126.4, 124.8, 70.3, 44.8, 44.2, 37.9, 28.9, 25.7, 25.5, 19.1, 17.6; IR(neat): 3378 (br, m), 2962 (m), 2925 (s), 1495 (w), 1452 (m), 1376 (m), 1078 (m), 1029 (m), 744 (m), 698 (s) cm^{-1}; HRMS-(ESI+) for $C_{17}H_{25}$ [M+H-H_20]: calculated 229.1956, found: 229.1963; $[\alpha]_D^{20}$ = +1.657 (*c* = 2.855, $CHCl_3$, *l* = 50 nm).

Analysis of Stereochemistry: *Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.*

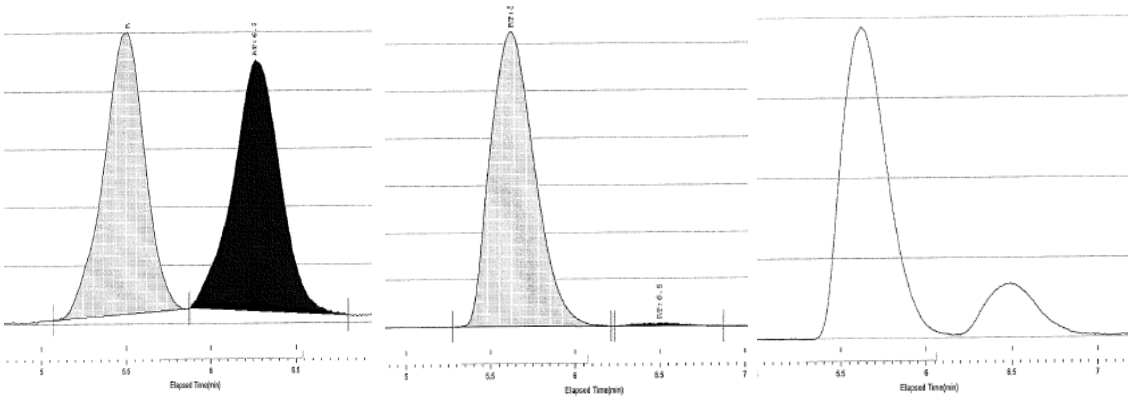


(*R*)-1-cyclohexyl-2-phenylethan-1-ol. Prepared according to the general procedure using vinyl cyclohexane (55.1 mg. 0.500 mmol) and bromobenzene (117.8 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the product as a white solid (95.2 mg, 93% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.29 (2H, m), 7.23-7.20 (3H, m), 3.56 (1H, ddd, J = 9.5 Hz, 5.5 Hz, 3.5 Hz), 2.87 (1H, dd, J = 14.0 Hz, 3.5 Hz), 2.58 (1H, dd, J = 14.0 Hz, 9.5 Hz), 1.87-1.94 (1H, m), 1.80-1.74 (3H, m), 1.69-1.66 (1H, m), 1.44 (1H, s), 1.43-1.38 (1H, m), 1.31-1.04 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.2, 129.4, 128.5, 126.3, 76.7, 43.2, 40.8, 29.3, 28.0, 26.5, 26.3, 26.2; IR(neat): 3329 (br, m), 2924 (s), 2853 (m), 1494 (m), 1444 (m), 1085 (m), 1033 (s), 749 (s), 698 (s) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{24}NO$ [M+NH_4]: calculated 222.1857, found: 222.1855; $[\alpha]_D^{20}$ = +20.08 (c = 2.360, $CHCl_3$, l = 50 nm).

Analysis of Stereochemistry:

The title compound was compared to racemic alcohol prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

Chiral SFC (Chiracel, OD-H, 35 ^{o}C, 3 mL/min, 5% Isopropanol, 100 bar, 210-270nm) – analysis of 1-cyclohexyl-2-phenylethan-1-ol.

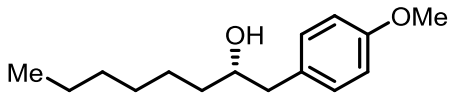


racemic

Diboration/ cross- coupling product

Coinjection of product + racemic

Peak No	% Area	Area	RT (min)
1	98.978	5617.8678	5.62
2	1.022	58.0081	6.5
Total:	100	5675.8759	

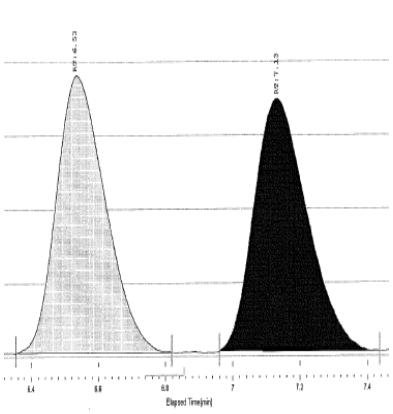


(*S*)-1-(4-methoxyphenyl)octan-2-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and 1-bromo-4-methoxybenzene (140.3 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (10-30% EtOAc/hexanes, stain with PMA) to afford the product as a colorless oil (107.6 mg, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.11 (2H, d, J = 8.5 Hz), 6.84 (2H, d, J = 8.5 Hz), 3.79-3.72 (1H, m), 3.78 (3H, s), 2.76 (1H, dd, J = 13.5 Hz, 4.0 Hz), 2.56 (1H, dd, J = 13.5 Hz, 8.5 Hz), 1.50-1.44 (4H, m), 1.35-1.24 (6H, m), 0.87 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.2, 130.6, 130.3, 113.9, 72.7, 55.2, 43.1, 36.7, 31.8, 29.3, 25.7, 22.6, 14.1; IR(neat): 3404 (br, m), 2926 (s), 2855 (m), 1611 (m), 1510 (s), 1464 (w), 1244 (s), 1177 (m), 1037 (s), 817 (m) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{28}NO_2$ [M+NH_4]: calculated 254.2120, found: 254.2117; $[\alpha]_D^{20}$ = +6.468 (c = 1.258, $CHCl_3$, l = 50 nm).

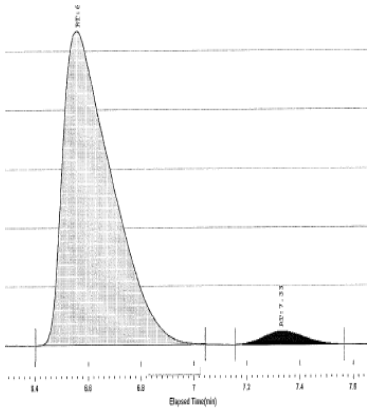
Analysis of Stereochemistry:

The title compound was compared to racemic alcohol prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

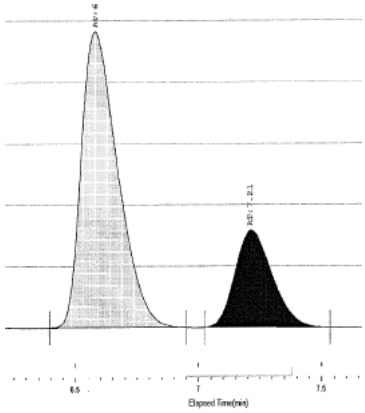
Chiral SFC (Chiracel, OD-H, 35 °C, 5 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(4-methoxyphenyl)octan-2-ol.



racemic

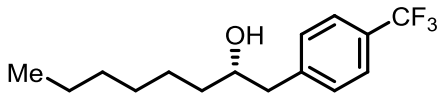


Diboration/ cross- coupling product



Coinjection of product + racemic

Peak No	% Area	Area	RT (min)
1	96.5959	13536.3379	6.56
2	3.4041	477.0303	7.33
Total:	100	14013.3682	

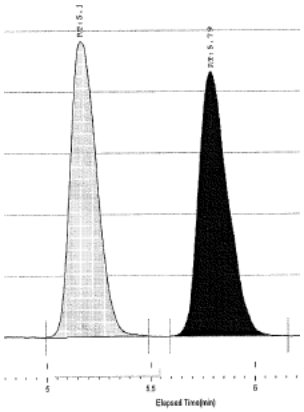


(*S*)-1-(4-(trifluoromethyl)phenyl)octan-2-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and 1-bromo-4-(trifluoromethyl)benzene (168.8 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (10-30% EtOAc/hexanes, stain with PMA) to afford the product as a yellow oil (116.6 mg, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.55 (2H, d, *J* = 8.0 Hz), 7.32 (2H, d, *J* = 8.0 Hz), 3.82 (1H, app tt, *J* = 8.0 Hz, 4.5 Hz), 2.85 (1H, dd, *J* = 13.5 Hz, 4.5 Hz), 2.71 (1H, dd, *J* = 13.5 Hz, 8.0 Hz), 1.52-1.43 (4H, m), 1.42 (1H, s), 1.35-1.24 (6H, m), 0.87 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.9, 129.7, 128.9, 128.6, 125.5, 125.4, 125.3, 125.2, 123.2, 72.5, 43.7, 37.0, 31.9, 29.2, 25.6, 22.6, 14.0; ^{19}F NMR (470 MHz, $CDCl_3$): -62.4; IR(neat): 3363 (br, m), 2928 (m), 2857 (m), 1618 (w), 1322 (s), 1161 (m), 1120 (s), 1066 (s), 1019 (m), 818 (w) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{25}F_3NO$ [M+NH_4]: calculated 292.1888, found: 292.1896; $[\alpha]_D^{20}$ = +6.082 (*c* = 2.955, $CHCl_3$, *l* = 50 nm).

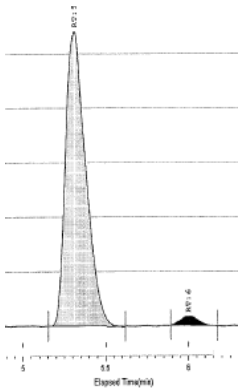
Analysis of Stereochemistry:

The title compound was compared to racemic alcohol prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

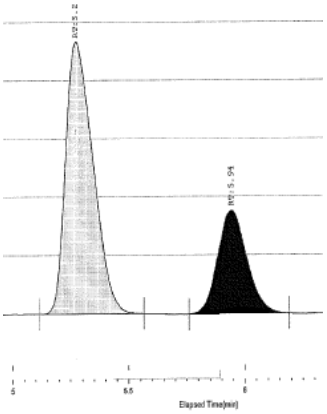
Chiral SFC (Chiracel, OD-H, 35 ^{o}C, 5 mL/min, 1% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(4-(trifluoromethyl)phenyl)octan-2-ol.



racemic

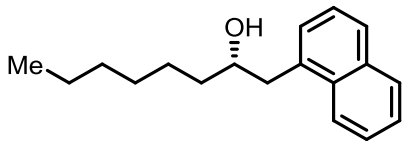


Diboration/ cross- coupling product



Coinjection of product + racemic

Peak No	% Area	Area	RT (min)
1	97.4335	4594.588	5.31
2	2.5665	121.0262	6
Total:	100	4715.6142	

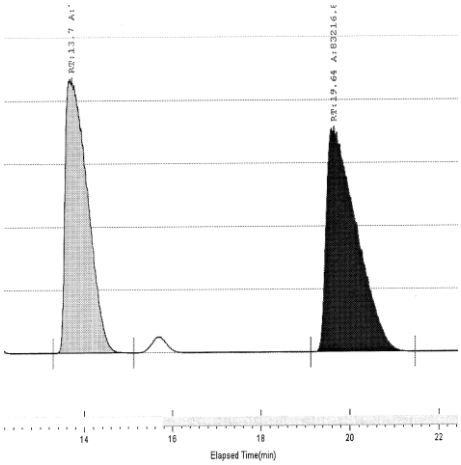


(*S*)-1-(naphthalen-1-yl)octan-2-ol. Prepared according to the general procedure using 1-octene (56.1 mg, 0.500 mmol) and 1-bromonaphthalene (155.3 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7% EtOAc/hexanes, stain with Seebach) to afford the product the product as a white solid (120.3 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (1H, d, *J* = 8.3 Hz), 7.87 (1H, d, *J* = 8.3 Hz), 7.77 (1H, d, *J* = 8.3 Hz), 7.47-7.54 (2H, m), 7.43 (1H, app t, *J* = 8.3 Hz), 7.38 (1H, d, *J* = 6.4 Hz), 3.96-4.01 (1H, m), 3.36 (1H, dd, *J* = 13.9 Hz, 4.2 Hz), 3.05 (1H, dd, *J* = 13.9 Hz, 8.6 Hz), 1.61-1.66 (2H, m), 1.53-1.60 (3H, m), 1.26-1.45 (6H, m), 0.89 (3H, t, *J* = 7.1 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.8, 134.0, 132.2, 128.8, 127.6, 127.3, 125.9, 125.6, 125.4, 123.8, 71.9, 41.2, 37.3, 31.8, 29.3, 25.7, 22.6, 14.0; IR (neat): 3368.6 (w), 3045.4 (w), 2952.7 (m), 2925.8 (s), 2855.0 (m), 1596.3 (w), 1509.7 (w), 1464.6 (w), 1396.46 (w), 1079.3 (w), 1021.0 (w), 790.5 (s), 775.8 (s) cm^{-1}; HRMS-(ESI+) for $C_{18}H_{28}NO$ [M+NH_4]: calculated: 274.2171, found: 274.2166. $[\alpha]_D^{20}$ = +18.46 (*c* = 2.412, $CHCl_3$, *l* = 50 mm).

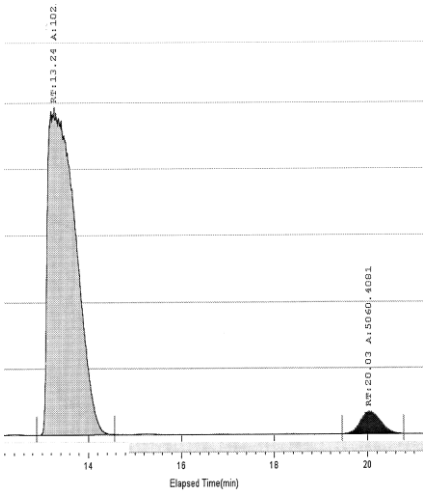
Analysis of Stereochemistry:

The title compound was compared to racemic alcohol prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

Chiral SFC (Chiracel, OD-H, 35 ^oC, 5 mL/min, 5% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(naphthalen-1 -yl)octan-2-ol.

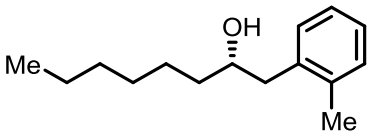


racemic



Diboration/ cross- coupling product

Peak No	% Area	Area	RT (min)
1	95.2779	102104.7771	13.24
2	4.7221	5060.4081	20.03
Total:	100	107165.1852	

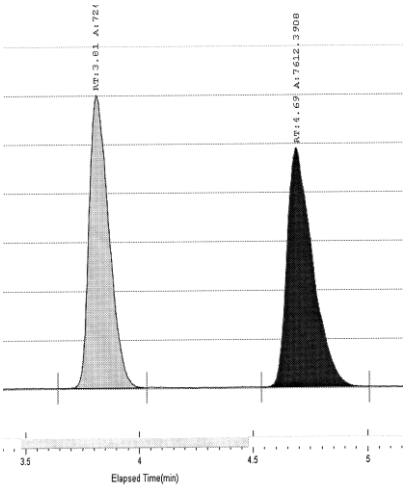


(*S*)-1-(*o*-tolyl)octan-2-ol. Prepared according to the general procedure using 1-octene (56.1 mg, 0.500 mmol) and 2-bromotoluene (128.3 mg, 0.750 mmol). The crude reaction mixture was purified on silica gel (7% EtOAc/hexanes, stain with PMA) to afford the product as a viscous oil (89.1 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13-7.19 (4H, m), 3.78-3.84 (1H, m), 2.85 (1H, dd, J = 13.7 Hz, 4.2 Hz), 2.68 (1H, dd, J = 13.7 Hz, 8.8 Hz), 2.34 (3H, s), 1.48-1.59 (4H, m), 1.28-1.44 (7H, m), 0.91 (3H, t, J = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.0, 136.6, 130.4, 130.1, 126.5, 126.0, 71.7, 41.3, 37.1, 31.8, 29.3, 25.7, 22.6, 19.6, 14.0; IR (neat): 3394.5 (br), 3018.1 (w), 2953.9 (m), 2925.7 (s), 2855.8 (m), 1493.0 (w), 1459.2 (m), 1378.3 (w), 1124.2 (w), 1054.3 (w), 1033.8 (w), 741.5 (s) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{28}NO$ [M+NH_4]: calculated: 238.2171, found: 238.2179. $[\alpha]_D^{20}$ = + 12.13 (c = 1.722, $CHCl_3$, l = 50 mm).

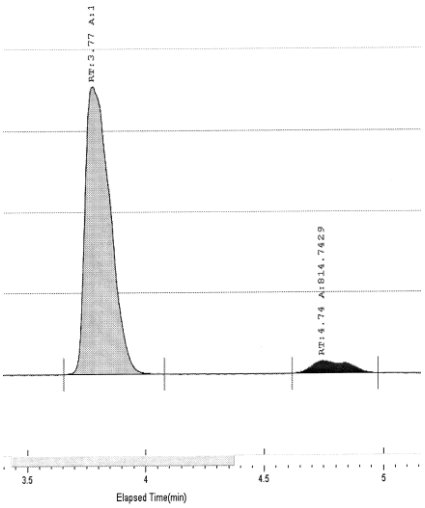
Analysis of Stereochemistry:

The title compound was compared to racemic alcohol prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

Chiral SFC (Chiracel, OD-H, 35 °C, 5 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(o-tolyl)octan-2-ol.

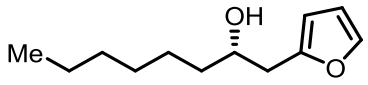


racemic



Diboration/
cross- coupling
product

Peak No	% Area	Area	RT (min)
1	94.066	12915.4287	3.77
2	5.934	814.7429	4.74
Total:	100	13730.1716	

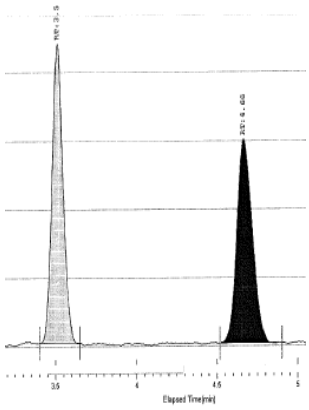


(*S*)-1-(furan-2-yl)octan-2-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and 2-bromofuran (110.2 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. Lithium chloride (21.2 mg, 0.500 mmol) was added for the cross-coupling. The crude reaction mixture was purified on silica gel (10-30% EtOAc/hexanes, stain with PMA) to afford the product as a yellow oil (76.6 mg, 79% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (1H, d, J = 1.0 Hz), 6.29 (1H, dd, J = 3.0 Hz, 2.0 Hz), 6.08 (1H, dd, J = 2.0 Hz, 1.0 Hz), 3.86 (1H, br s), 2.82 (1H, dd, J = 14.5 Hz, 3.5 Hz), 2.70 (1H, dd, J = 14.5 Hz, 8.0 Hz), 1.77 (1H, s), 1.47-1.41 (4H, m), 1.35-1.27 (6H, m), 0.86 (3H, t, J = 6.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.9, 141.6, 110.3, 106.9, 70.5, 36.7, 36.1, 31.8, 29.2, 25.6, 22.6, 14.0; IR(neat): 3373 (br, m), 2925 (s), 2856 (s), 1458 (w), 1146 (m), 1125 (m), 1007 (s), 724 (s), 599 (m) cm^{-1}; HRMS-(ESI+) for $C_{12}H_{21}O_2$ [M+H]: calculated 197.1542, found: 197.1538; $[\alpha]_D^{20}$ = +6.167 (c = 1.157, $CHCl_3$, l = 50 nm).

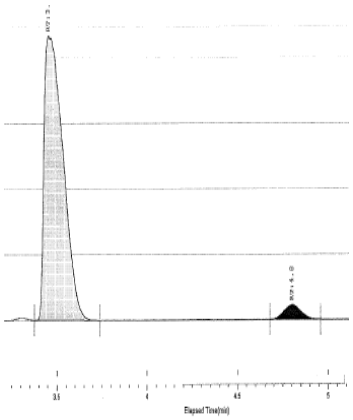
Analysis of Stereochemistry:

The title compound was compared to racemic alcohol prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

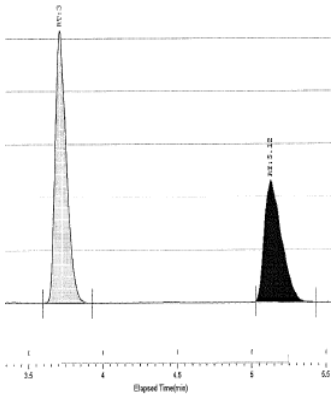
Chiral SFC (Chiracel, AD-H, 35 ^{o}C, 5 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(furan-2-yl)octan-2-ol.



racemic

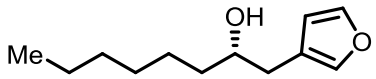


Diboration/ cross- coupling product



Coinjection of product + racemic

Peak No	% Area	Area	RT (min)
1	95.5478	15731.3028	3.45
2	4.4522	733.0325	4.8
Total:	100	16464.3353	

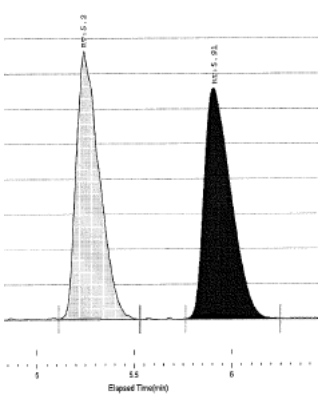


(*S*)-1-(furan-3-yl)octan-2-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and 3-bromofuran (110.2 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. Lithium chloride (21.2 mg, 0.500 mmol) was added for the cross-coupling. The crude reaction mixture was purified on silica gel (10-30% EtOAc/hexanes, stain with PMA) to afford the product as a yellow oil (62.1 mg, 63% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (1H, d, J = 1.5 Hz), 7.29 (1H, s), 6.29 (1H, s), 3.72 (1H, br s), 2.61 (1H, dd, J = 14.5 Hz, 3.5 Hz), 2.47 (1H, dd, J = 14.5 Hz, 8.5 Hz), 1.54 (1H, s), 1.50-1.42 (4H, m), 1.344-1.24 (6H, m), 0.87 (3H, dd, J = 6.0 Hz, 4.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 143.1, 140.2, 121.2, 111.4, 71.4, 36.8, 32.9, 31.8, 29.3, 25.7, 22.6, 14.1; IR(neat): 3399 (br, m), 2926 (s), 2856 (s), 1682 (w), 1465 (m), 1159 (w), 1065 (m), 1024 (s), 873 (s), 726 (m), 600 (s) cm^{-1}; HRMS-(ESI+) for $C_{12}H_{21}O_2$ [M+H]: calculated 197.1542, found: 197.1538; $[\alpha]_D^{20}$ = -2.898 (c = 1.173, $CHCl_3$, l = 50 nm).

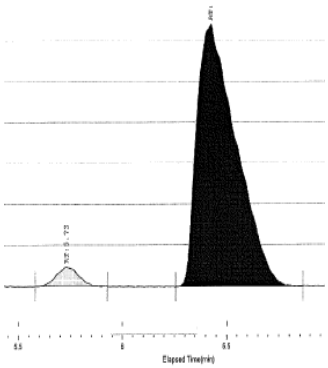
Analysis of Stereochemistry:

The title compound was compared to racemic alcohol prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

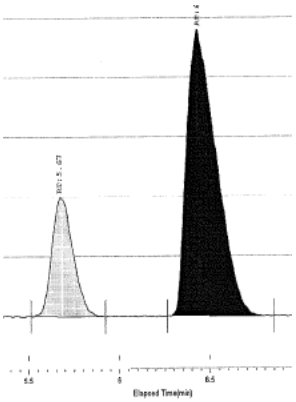
Chiral SFC (Chiracel, AD-H, 35 ^{o}C, 5 mL/min, 2% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(furan-3-yl)octan-2-ol.



racemic

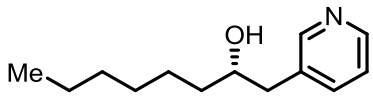


Diboration/ cross- coupling product



Coinjection of product + racemic

Peak No	% Area	Area	RT (min)
1	3.9849	350.6136	5.73
2	96.0151	8447.8573	6.42
Total:	100	8798.4709	

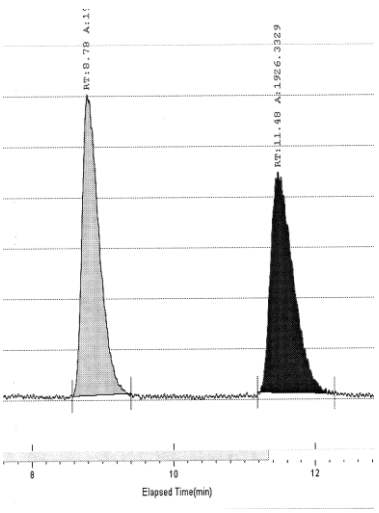


(*S*)-1-(pyridin-3-yl)octan-2-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and 3-bromopyridine (118.5 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (5% MeOH in ethyl acetate, stain with $KMnO_4$) to afford the product as a viscous oil (89.1 mg, 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.41 (1H, s), 8.39 (1H, d, *J* = 4.4 Hz), 7.55 (1H, d, *J* = 7.8 Hz), 7.20 (1H, dd, *J* = 7.8 Hz, 4.9 Hz), 3.78-3.82 (1H, m), 2.78 (1H, dd, *J* = 13.7 Hz, 4.4 Hz), 2.65 (1H, dd, *J* = 13.9 Hz, 8.1 Hz), 2.42 (1H, br s), 1.42-1.56 (3H, m), 1.22-1.41 (7H, m), 0.87 (3H, t, *J* = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.5, 147.5, 137.1, 134.5, 123.2, 72.2, 41.0, 37.1, 31.8, 29.2, 25.6, 22.5, 14.0; IR (neat): 3263.6 (br.), 2953.6 (m), 2925.6 (s), 2855.2 (m), 1577.6 (w), 1479.3 (w), 1465.4 (w), 1424.4 (m), 1126.7 (w), 1046.5 (w), 1030.6 (w), 713.6 (s) cm^{-1}; HRMS-(ESI+) for $C_{13}H_{22}NO$ [M+H]: calculated: 208.1701, found: 208.1706. $[\alpha]_D^{20}$ = + 9.816 (*c* = 1.738, $CHCl_3$, *l* = 50 mm).

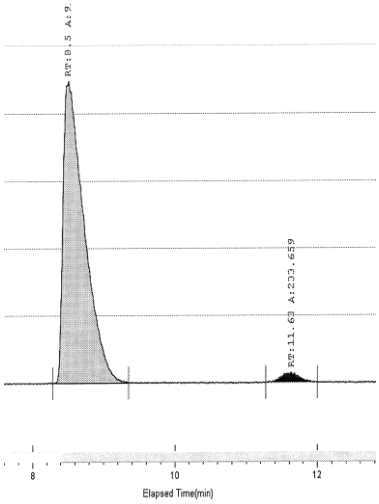
Analysis of Stereochemistry:

The title compound was compared to racemic alcohol prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

Chiral SFC (Chiracel, OD-H, 35 ^oC, 5 mL/min, 5% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(pyridin-3 -yl)octan-2-ol.

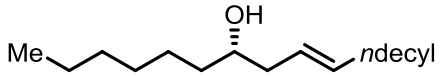


racemic



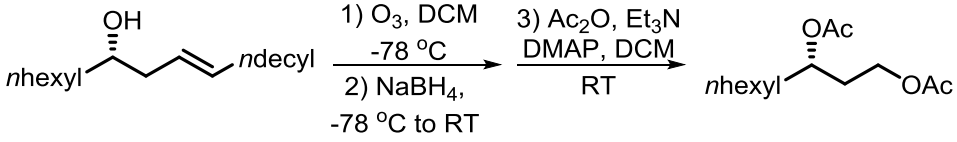
Diboration/
cross- coupling
product

Peak No	% Area	Area	RT (min)
1	97.5218	9194.9843	8.5
2	2.4782	233.659	11.63
Total:	100	9428.6433	



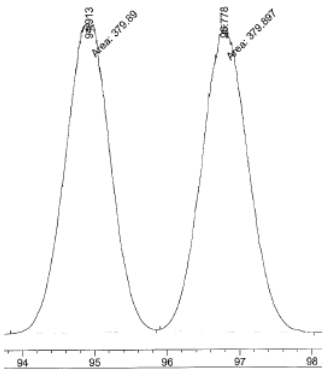
(*S,E*)-icos-9-en-7-ol. Prepared according to the general procedure using 1-octene (56.1 mg, 0.500 mmol) and (*E*)-1-chlorododec-1-ene (151.7 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the product as a colorless oil (136.5 mg, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.52 (1H, ddd, *J* = 15.0 Hz, 7.0 Hz, 6.5 Hz), 5.38 (1H, ddd, *J* = 15.0 Hz, 7.0 Hz, 6.5 Hz), 3.56 (1H, br s), 2.21 (1H, app dt, *J* = 14.0 Hz, 4.5 Hz), 2.06-1.98 (3H, m), 1.55 (1H, s), 1.44-1.41 (4H, m), 1.35-1.24 (22H, m), 0.87-0.85 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.8, 125.8, 70.9, 40.7, 36.7, 32.7, 31.9, 31.8, 29.7, 29.6, 29.5, 29.4, 29.3, 29.2, 29.1, 25.7, 22.7, 22.6, 14.1, 14.0; IR(neat): 3361 (br, m), 2922 (s), 2853 (s), 1465 (m), 1377 (w), 1041 (w), 969 (m), 722 (w) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{44}NO$ [M+NH_4]: calculated: 314.3423, found: 314.3438; $[\alpha]_D^{20}$ = -0.862 (*c* = 1.623, $CHCl_3$, *l* = 50 nm).

Analysis of Stereochemistry

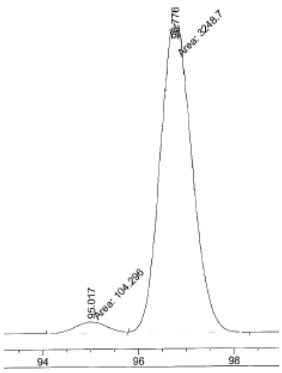


The title compound was converted to the corresponding bis-acetate as shown above. The resulting bis-acetate was compared to racemic material prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

Chiral GLC (β-dex, Supelco, 115 ºC, 20 psi) – analysis of the bis-acetate of nonane-1,3-diol derived from icos-9-en-7-ol.

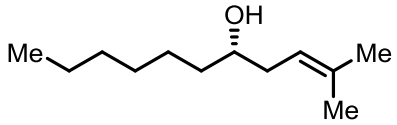


racemic



Diboration/
cross- coupling
product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	95.017	MM	0.7082	104.29550	2.45446	3.11052
2	96.776	MM	0.7742	3248.69800	69.93708	96.88948

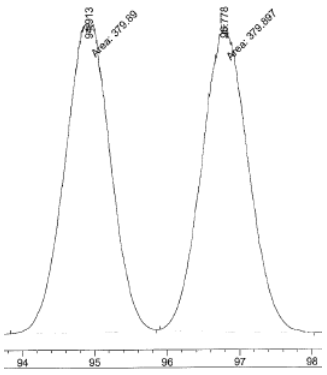


(*S*)-2-methylundec-2-en-5-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and 1-chloro-2-methylpropene (84.4 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the product as a colorless oil (84.9 mg, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.15 (1H, app ddt, J = 8.0 Hz, 2.5 Hz, 1.0 Hz), 3.52 (1H, app tt, J = 11.5 Hz, 7.0 Hz), 2.17-2.08 (2H, m), 7.20 (3H, d, J = 1.0 Hz), 1.62 (3H, s), 1.50 (1H, s), 1.46-1.38 (4H, m), 1.34-1.23 (6H, m), 0.86 (3H, t, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 135.1, 120.2, 71.7, 36.8, 36.3, 31.8, 29.4, 25.9, 25.7, 22.6, 17.9, 14.1; IR(neat): 3348 (br, m), 2925 (s), 2856 (s), 1453 (m), 1376 (m), 1124 (w), 1050 (m), 863 (w) cm^{-1}; HRMS-(ESI+) for $C_{12}H_{25}O$ [M+H]: calculated: 185.1905, found: 185.1901; $[\alpha]_D^{20}$ = +2.896 (c = 1.243, $CHCl_3$, l = 50 nm).

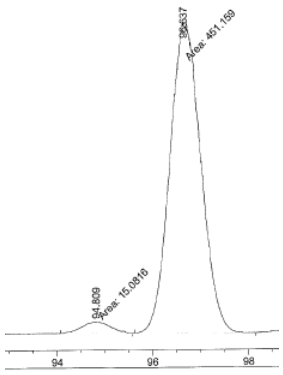
Analysis of Stereochemistry:

The title compound was converted to the corresponding bis-acetate as shown above. The resulting bis-acetate was compared to racemic material prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

Chiral GLC (β-dex, Supelco, 115 ºC, 20 psi) – analysis of the bis-acetate of nonane-1,3-diol derived from 2-methylundec-2-en-5-ol.

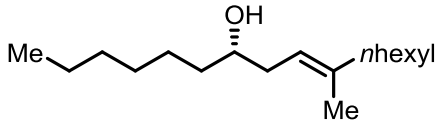


racemic



Diboration/
cross- coupling
product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	94.809	MM	0.6747	15.08162	3.72553e-1	3.23473
2	96.637	MM	0.7512	451.15884	10.01019	96.76527

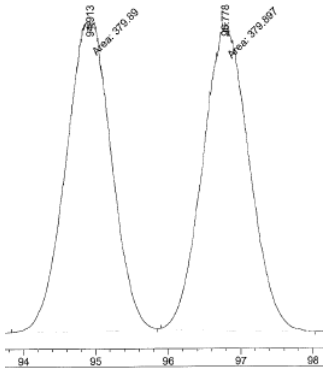


(*S*,*E*)-10-methylhexadec-9-en-7-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and (*E*)-1-chloro-2-methyloct-1-ene (120.5 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (5-10% EtOAc/hexanes, stain with PMA) to afford the product as a colorless oil (114.6 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.14 (1H, dd, J = 7.5 Hz, 7.0 Hz), 3.57 (1H, dddd, J = 12.0 Hz, 11.5 Hz, 6.5 Hz, 5.0 Hz), 2.19-2.10 (2H, m), 1.99 (2H, app t, J = 7.5), 1.60 (3H, s), 1.52 (1H, s), 1.45-1.34 (5H, m), 1.30-1.24 (13H, m), 0.87-0.85 (6H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 139.2, 119.7, 71.7, 39.9, 36.8, 36.1, 31.8, 31.7, 29.4, 29.0, 28.8, 27.9, 25.7, 22.6, 22.5, 16.2, 14.1; IR(neat): 3355 (br, m), 2924 (s), 2855 (m), 1457 (m), 1378 (w), 1123 (m), 1040 (m), 888 (m), 723 (m) cm^{-1}; HRMS-(ESI+) for $C_{17}H_{35}O$ [M+H]: calculated: 255.2688, found: 255.2690; $[\alpha]_D^{20}$ = +5.19 (c = 0.770, $CHCl_3$, l = 50 nm).

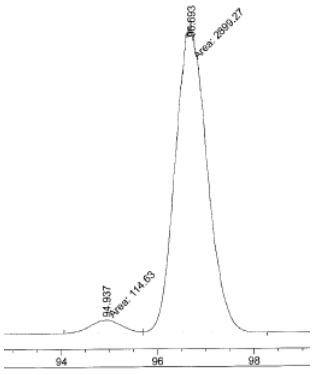
Analysis of Stereochemistry:

The title compound was converted to the corresponding bis-acetate as shown above. The resulting bis-acetate was compared to racemic material prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

Chiral GLC (β-dex, Supelco, 115 ºC, 20 psi) – analysis of the bis-acetate of nonane-1,3-diol derived from (E)-10-methylhexadec-9-en-7-ol.

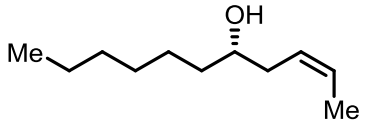


racemic



Diboration/
cross- coupling
product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	94.937	MM	0.7220	114.62968	2.64623	3.80337
2	96.693	MM	0.7502	2899.26758	64.40867	96.19663

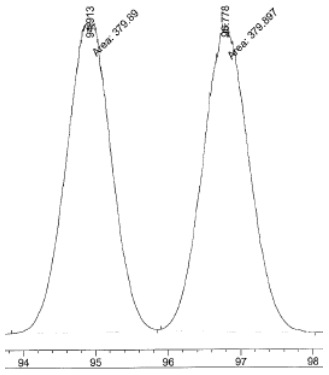


(*S*,*Z*)-undec-2-en-5-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and (*Z*)-1-chloro-1-propene (57.4 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the product as a viscous oil (75.8 mg, 89% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.63 (1H, dqd, *J* = 10.5 Hz, 6.5 Hz, 1.5 Hz), 5.42 (1H, dddd, *J* = 10.5 Hz, 7.5 Hz, 3.5 Hz, 1.5 Hz), 3.61 (1H, app tt, *J* = 12.0 Hz, 6.0 Hz), 2.20-2.19 (2H, m), 1.62 (3H, dd, *J* = 6.5 Hz, 1.5 Hz), 1.52 (1H, s), 1.47-1.41 (4H, m), 1.33-1.23 (6H, m), 0.86 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 127.2, 126.2, 71.5, 36.9, 34.9, 31.8, 29.3, 25.7, 22.6, 14.1, 13.0; IR(neat): 3349 (br, m), 2926 (s), 2856 (m), 1457 (m), 1375 (w), 1125 (w), 1040 (m), 853 (w), 701 (m) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{21}$ [M+H-H_2O]: calculated: 153.1643, found: 153.1640; $[\alpha]_D^{20}$ = -1.885 (*c* = 1.803, $CHCl_3$, *l* = 50 nm).

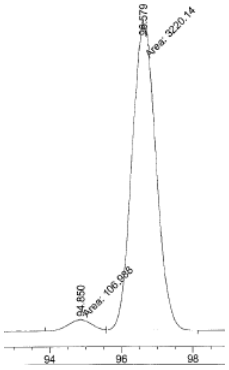
Analysis of Stereochemistry:

The title compound was converted to the corresponding bis-acetate as shown above. The resulting bis-acetate was compared to racemic material prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

Chiral GLC (β-dex, Supelco, 115 ºC, 20 psi) – analysis of the bis-acetate of nonane-1,3-diol derived from (Z)-undec-2-en-5-ol.

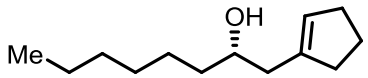


racemic



Diboration/ cross- coupling product

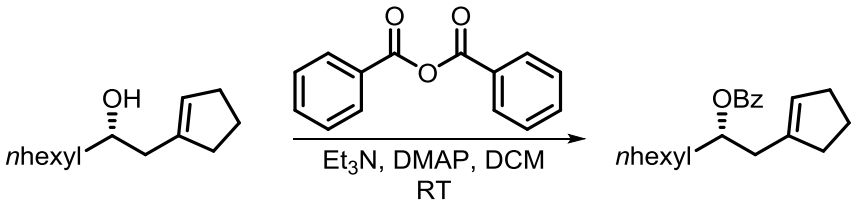
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	94.850	MM	0.7143	106.98758	2.49647	3.21562
2	96.579	MM	0.7685	3220.13867	69.83436	96.78438



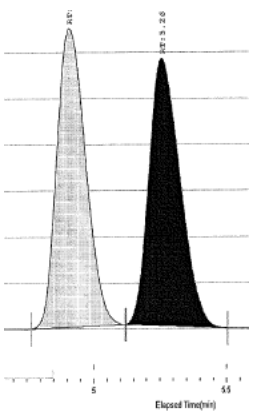
(*S*)-1-(cyclopent-1-en-1-yl)octan-2-ol. Prepared according to the general procedure with 1-octene (56.1 mg. 0.500 mmol) and 1-chlorocyclopent-1-ene (76.9 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the product as a colorless oil (88.2 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.47 (1H, s), 3.70 (1H, dddd, J = 9.0 Hz, 7.0 Hz, 5.0 Hz, 4.0 Hz), 2.33-2.28 (2H, m), 2.46-2.16 (2H, m), 1.89-1.82 (2H, m), 1.59 (1H, s), 1.46-1.41 (4H, m), 1.33-1.23 (8H, m), 0.86 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.4, 127.1, 69.4, 39.5, 37.2, 35.1, 32.5, 31.8, 29.4, 26.0, 23.4, 22.6, 14.1; IR(neat): 3368 (br, m), 2925 (s), 2852 (s), 1465 (m), 1377 (w), 1295 (w), 1030 (m), 967 (m) cm^{-1}; HRMS-(ESI+) for $C_{13}H_{23}$ [M+H-H_2O]: calculated: 179.1799, found: 179.1802; $[\alpha]_D^{20}$ = +7.18 (c = 0.863, $CHCl_3$, l = 50 nm).

Analysis of Stereochemistry:

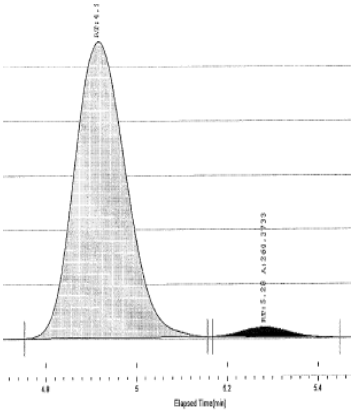
The title compound was converted to the corresponding benzoate as shown below. The resulting benzoate was compared to racemic benzoate prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.



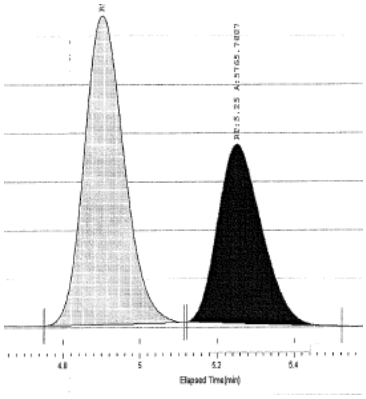
Chiral SFC (Chiracel, OD-H, 35 °C, 3 mL/min, 2% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(cyclopent-1-en-1-yl)octan-2-yl benzoate.



racemic

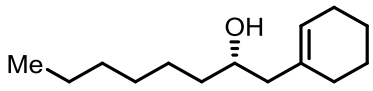


Diboration/ cross- coupling product



Coinjection of product + racemic

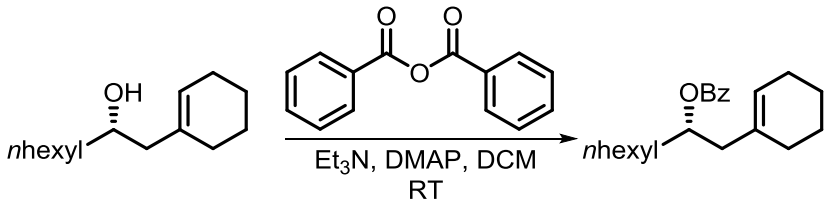
Peak No	% Area	Area	RT (min)
1	96.9859	8506.9002	4.91
2	3.0141	264.3733	5.28
Total:	100	8771.2735	



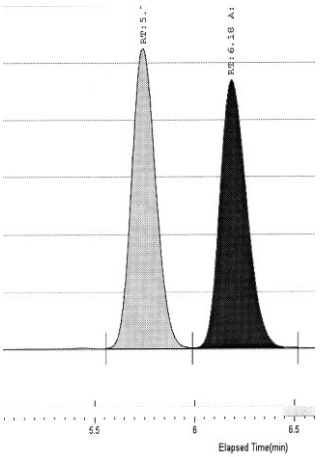
(*S*)-1-(cyclohex-1-en-1-yl)octan-2-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and 1-bromocyclohexene (120.8 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7% EtOAc/hexanes, stain with PMA) to afford the product as a viscous oil (87.2 mg, 83% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.53 (1H, s), 3.63-3.68 (1H, m), 1.86-2.14 (6H, m), 1.54-1.68 (5H, m), 1.40-1.49 (3H, m), 1.25-1.38 (7H, m), 0.88 (3H, t, J = 6.6 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.9, 124.9, 68.6, 46.6, 37.1, 31.8, 29.4, 28.4, 25.7, 25.3, 22.9, 22.6, 22.3, 14.1; IR (neat): 3358.2 (br.), 2923.6 (s), 2855.8 (m), 1458.1 (w), 1437.8 (w), 1081.6 (w), 1051.4 (w), 919.4 (w), 797.5 (w), 723.6 (w) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{25}$ [M+H-H_2O]: calculated: 193.1956, found: 193.1958. $[\alpha]_D^{20}$ = + 9.708 (c = 1.222, $CHCl_3$, l = 50 mm).

Analysis of Stereochemistry:

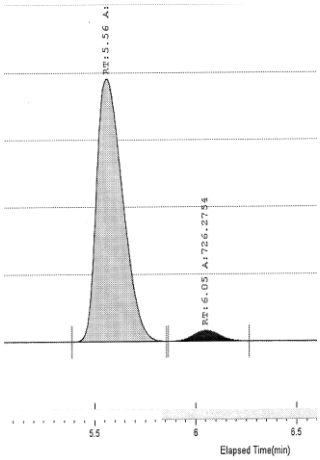
The title compound was converted to the corresponding benzoate as shown below. The resulting benzoate was compared to racemic benzoate prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.



Chiral SFC (Chiracel, OD-H, 35 °C, 3 mL/min, 2% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(cyclohex-1-en-1-yl)octan-2-yl benzoate.

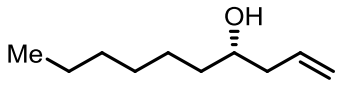


racemic



Diboration/
cross- coupling
product

Peak No	% Area	Area	RT (min)
1	95.9963	17413.957	5.56
2	4.0037	726.2754	6.05
Total:	100	18140.2324	

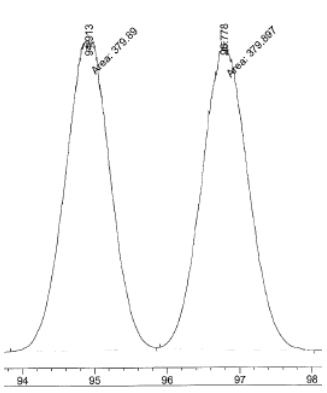


(S)-dec-1-en-4-ol. Prepared according to the general procedure with 1-octene (56.1 mg. 0.500 mmol) and 1,2-dichloroethane (0.12 mL, 1.5 mmol) with 2.5 mol% Pd/RuPhos, except potassium *tert*-butoxide (336.6 mg, 3.00 mmol) was used instead of potassium hydroxide. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the product as a colorless oil (70.4 mg, 90% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.80 (1H, dddd, J = 17.5 Hz, 10.0 Hz, 8.0 Hz, 7.0 Hz), 5.12 (1H, d, J = 8.0 Hz), 5.09 (1H, s), 3.64-3.59 (1H, m), 2.27 (1H, ddd, J = 10.0 Hz, 6.5 Hz, 5.5 Hz), 2.11 (1H, app dt, J = 15.0 Hz, 7.0 Hz), 1.62 (1H, s), 1.46-1.37 (4H, m), 1.31-1.22 (6H, m), 0.86 (3H, t, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.9, 117.9, 70.7, 41.9, 36.8, 31.8, 29.3, 25.6, 22.6, 14.0; IR(neat): 3360 (br, m), 2926 (s), 2856 (s), 1640 (w), 1458 (m), 1123 (m), 993 (m), 911 (s), 640 (m) cm^{-1}; HRMS-(ESI+) for $C_{10}H_{21}O$ [M+H]: calculated: 157.1592, found: 157.1597; $[\alpha]_D^{20}$ = -4.999 (c = 1.400, $CHCl_3$, l = 50 nm).

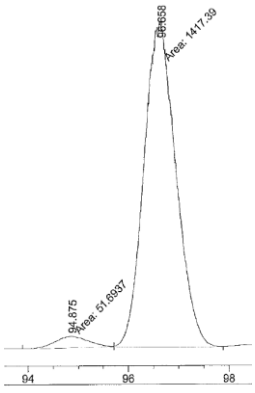
Analysis of Stereochemistry:

The title compound was converted to the corresponding bis-acetate as shown above. The resulting bis-acetate was compared to racemic bis-acetate prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

Chiral GLC (β-dex, Supelco, 115 ºC, 20 psi) – analysis of the bis-acetate of nonane-1,3-diol derived from dec-1-en-4-ol.

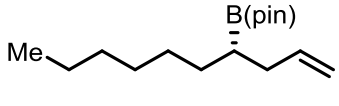


racemic

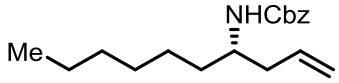


Diboration/
cross- coupling
product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	94.875	MM	0.7421	51.69366	1.16097	3.51877
2	96.658	MM	0.7305	1417.38940	32.33957	96.48123



(*S*)-2-(dec-1-en-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol), 1,2-dichloroethane (0.12 mL, 1.5 mmol) with 2.5 mol% Pd/RuPhos, except potassium *tert*-butoxide (336.6 mg, 3.00 mmol) was used instead of potassium hydroxide in cross-coupling and no oxidation was performed. The crude reaction mixture was diluted with water (10 mL) and hexanes (15 mL) and the layers were separated. The aqueous layer was extracted with hexanes (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered and concentrated *in vacuo*. The crude reaction mixture was purified on silica gel (2-5% EtOAc/hexanes, stain with PMA) to afford the product as a pale-yellow oil (129.6 mg, 97% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.78 (1H, app ddt, J = 17.0 Hz, 10.0 Hz, 6.5 Hz, 6.5 Hz), 4.98 (1H, ddd, J = 17.0 Hz, 3.0 Hz, 1.0 Hz), 4.90 (1H, dd, J = 10.0 Hz, 3.0 Hz), 2.18-2.06 (2H, m), 1.41-1.32 (4H, m), 1.30-1.22 (6H, m), 1.20 (12H, s), 1.04 (1H, app tt, J = 8.5 Hz, 8.5 Hz, 6.5 Hz, 6.5 Hz), 0.85 (3H, t, J = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.7, 114.6, 82.9, 35.6, 31.8, 30.9, 29.5, 29.1, 24.8, 24.7, 22.6, 14.1; IR(neat): 2977 (w), 2923 (m), 2854 (w), 1380 (s), 1315 (s), 1246 (w), 1143 (s), 907 (m), 863 (m) cm^{-1}; HRMS-(ESI+) for $C_{16}H_{32}BO_2$ [M+H]: calculated: 267.2495, found: 267.2486; $[\alpha]_D^{20}$ = -9.449 (c = 2.476, $CHCl_3$, l = 50 nm).



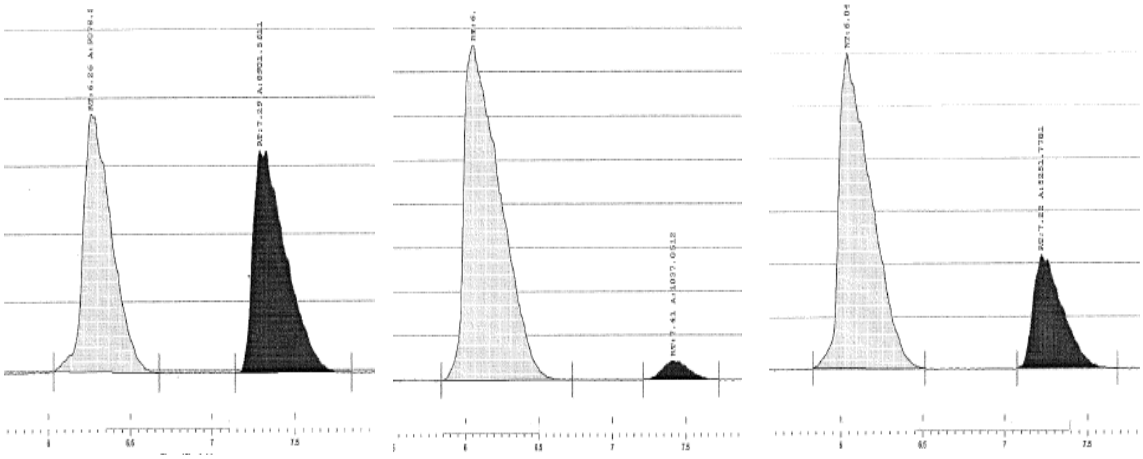
Benzyl (*S*)-dec-1-en-4-ylcarbamate. The title compound was prepared from (*S*)-2-(dec-1-en-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (115 mg, 0.432 mmol) according to literature procedure[96] without modification. After stirring at 60° C for 12 h, the reaction flask was cooled to room temperature and benzyl chloroformate (3.1 equiv.) was added. After stirring at room temperature for 1 h the reaction was quenched with water (8 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (5% EtOAc/hexanes, stain with Seebach stain) to afford the product as a white solid (88.9 mg, 71% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36-7.27 (5H, m), 5.75 (1H, app ddt, J = 16.5 Hz, 9.0 Hz, 7.0 Hz), 5.07-5.05 (3H, m), 5.03 (1H, s), 4.54 (1H, br s), 3.71-3.65 (1H, m), 2.25 (1H, app dt, J = 13.0 Hz, 6.5 Hz), 2.17 (1H, app dt, J = 13.5 Hz, 6.5 Hz), 1.50-1.44 (1H, m), 1.38-1.24 (9H, m), 0.86 (3H, t, J = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 136.7, 134.3, 128.5, 128.0, 117.8, 66.5, 50.7, 39.4, 34.6, 31.7, 29.1, 25.8, 22.6, 14.0; IR(neat): 3324 (br, w), 2926 (m), 2855 (w), 1692 (s), 1530 (m), 1454 (w), 1225 (m), 1027 (m), 911 (m), 695 (s), 457 (m) cm^{-1}; HRMS-(ESI+) for $C_{18}H_{28}NO_2$ [M+H]: calculated: 290.2120, found: 290.2109; $[\alpha]_D^{20}$ = -19.97 (c = 1.392, $CHCl_3$, l = 50 nm).

[96] Mlynarski, S. N.; Karns, A. S.; Morken, J. P. *J. Am. Chem. Soc.* **2012**, *134*, 16449.

Analysis of Stereochemistry:

The title compound was compared to racemic Cbz-protected amine prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.

Chiral SFC (Chiracel, OD-H, 35 ^{o}C, 4 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of Benzyl (S)-dec-1-en-4-ylcarbamate.



racemic

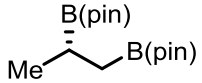
Diboration/ cross- coupling product

Coinjection of product + racemic

Peak No	% Area	Area	RT (min)
1	96.1659	26011.0919	6.05
2	3.8341	1037.0512	7.41
Total:	100	27048.1431	

2.5.2.6 Preparation Boc Protected (S)-amphetamine

(*S*)-2,2'-(propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). To an oven-dried 15-mL graduated pressure vessel with magnetic stir bar in the dry box was added $Pt(dba)_3$ (35.3 mg, 39.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenyl-TADDOLPPh (43.0 mg, 47.0 μmol), $B_2(pin)_2$ (1.00 g, 3.94 mmol) and toluene (3.9 mL, $[B_2(pin)_2]$ = 1.0 M). The pressure vessel was sealed, removed from the dry box, and heated to 80 ºC in an oil bath for 20 minutes. The pressure vessel was removed from the oil bath, cooled to room temperature, and then further cooled to -78 ºC. The pressure vessel cap was removed and quickly exchanged with a septum. The vial was purged with N_2. Propene gas was then bubbled through the diboration solution at -78 ºC until the reaction volume increased approx. 1.0 mL (*d*=0.614 g/mL at -47.8 ºC, approx. 15 mmol). The septum was then quickly exchanged for the pressure vessel cap, and the vessel was sealed. The reaction was warmed to room temperature and then heated to 60 ºC and stirred for 12 h. The vessel was cooled to room temperature and the reaction was condensed *in vacuo* to afford the crude product. The title compound was purified on silica gel (5% EtOAc/hexanes, stain with Seebach stain) to afford a viscous, pale-yellow oil (1.152 g, 98% yield).

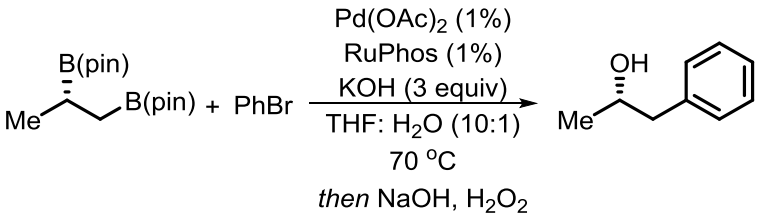


(*S*)-2,2'-(propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (24H, s), 1.25-1.13 (1H, m), 0.97 (3H, d, *J* = 7.0 Hz), 0.88 (1H, dd, *J* = 15.5 Hz, 8.5 Hz), 0.76 (1H, dd, *J* = 15.5 Hz, 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 82.8, 82.7, 24.82, 24.77, 24.72, 24.67, 24.6, 18.3; IR(neat): 2977 (m), 2871 (w), 1461 (w), 1370 (s), 1311 (s), 1217 (m), 1193 (s), 968

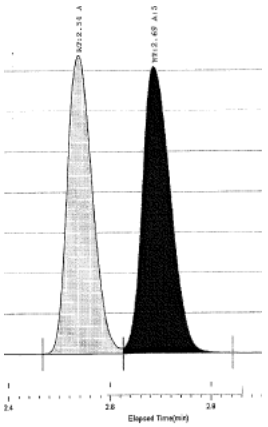
(m) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{30}B_2O_4$ [M+H]: calculated: 297.2408, found: 297.2415; $[\alpha]_D^{20}$ = +2.239 (*c* = 1.250, $CHCl_3$, *l* = 50 nm).

Analysis of Stereochemistry:

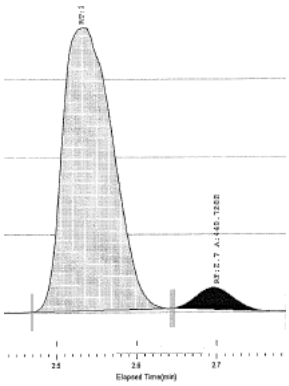
The title compound was subjected to standard cross-coupling conditions as shown below with bromobenzene and oxidized to (*S*)-1-phenylpropan-2-ol. The resulting alcohol was compared to commercially available racemic 1-phenylpropan-2-ol. Absolute stereochemistry was assigned through analogy.



Chiral SFC (Chiracel, OD-H, 35 °C, 5 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of 1-phenyl-2-propanol.



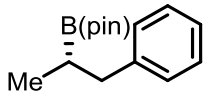
racemic



Diboration/ cross- coupling product

Peak No	% Area	Area	RT (min)
1	94.6436	7787.4224	2.53
2	5.3564	440.7288	2.7
Total:	100	8228.1512	

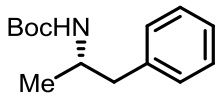
(*S*)-4,4,5,5-tetramethyl-2-(1-phenylpropan-2-yl)-1,3,2-dioxaborolane. To an oven-dried 16-mL vial with magnetic stir bar in the dry box was added (*S*)-2,2'-(propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (148 mg, 0.500 mmol), potassium hydroxide (84.2 mg, 1.50 mmol), tetrahydrofuran (4.3 mL), $Pd(OAc)_2$/RuPhos (0.27 mL, 1:1 ratio $Pd(OAc)_2$:RuPhos, [$Pd(OAc)_2$/RuPhos] = 0.018 M in THF), and bromobenzene (86.4 mg, 0.550 mmol). The vial was sealed with a teflon septum cap, removed from the dry box, H_2O (sparged with N_2 for 30 min, 0.45 mL) was added through the septum cap. The vial was heated to 70 ºC and stirred for 12 h. The reaction mixture was diluted with dichloromethane (25 mL) and water (10 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (2-5% EtOAc/hexanes, stain with PMA) to afford the product as a viscous oil (102.3 mg, 83% yield).



(*S*)-4,4,5,5-tetramethyl-2-(1-phenylpropan-2-yl)-1,3,2-dioxaborolane. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 (2H, dd, *J* = 7.5 Hz, 7.0 Hz), 7.20 (2H, d, *J* = 7.0 Hz), 7.15 (1H, app t, *J* = 7.5 Hz), 2.81 (1H, dd, *J* = 14.0 Hz, 8.0 Hz), 2.55 (1H, dd, *J* = 14.0 Hz, 8.0 Hz), 1.38 (1H, app tq, *J* = 14.0 Hz, 7.5 Hz), 1.20 (6H, s), 1.19 (6H, s), 0.97 (3H, d, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 142.3, 128.9, 127.9, 125.5, 82.9, 38.9, 24.7, 24.6, 24.5, 15.1; IR(neat): 2977 (m), 1460 (m), 1380 (s), 1270 (m), 1142 (s), 967 (m), 744 (m), 698 (s) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{24}BO_2$

[M+H]: calculated: 247.1869, found: 247.1878; $[\alpha]_D^{20}$ = +0.444 (*c* = 1.350, $CHCl_3$, *l* = 50 nm).

***tert*-butyl (*S*)-(1-phenylpropan-2-yl)carbamate.** The title compound was prepared according to literature procedure[96] with slight modification. A flame-dried, 25-mL round-bottomed flask equipped with a magnetic stir bar and septum was purged with N_2. After 5 min, *O*-methylhydroxylamine solution (0.81 mL, 2.6 mmol, 3.28 M in THF) was added and diluted with THF (4 mL). The reaction flask was cooled to -78° C in a dry ice/acetone bath. A solution of *t*-butyl lithium in pentane (1.05 mL, 2.6 mmol, 1.7 M) was added dropwise and the reaction was allowed to stir at -78° C for 30 min. A separate flame-dried conical flask was charged with (*S*)-4,4,5,5-tetramethyl-2-(1-phenylpropan-2-yl)-1,3,2-dioxaborolane (108 mg, 439 μmol) and diluted with THF (2 mL) under N_2. The solution of boronic acid pinacol ester was then added dropwise to the solution of deprotonated O-methylhydroxylamine dropwise. The reaction flask was warmed to room temperature and then heated to 60° C. After stirring at 60° C for 24 h, the reaction flask was cooled to room temperature and Boc anhydride (0.62 mL, 2.7 mmol) was added. After stirring at room temperature for 1 h the reaction was quenched with water (8 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (7% EtOAc/hexanes, stain with ninhydrin) to afford the product as a white solid (76.6 mg, 74% yield).

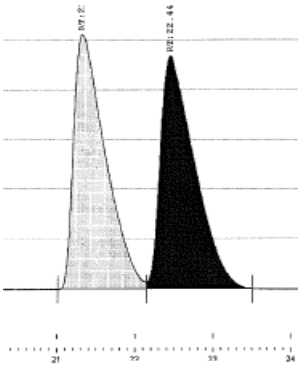


***tert*-butyl (*S*)-(1-phenylpropan-2-yl)carbamate.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-2.35 (2H, m), 7.21-7.15 (3H, m), 4.37 (1H, br s), 3.90 (1H, br s), 2.82 (1H, dd, *J* = 13.0 Hz, 5.0 Hz), 2.64 (1H, dd, *J* = 13.0 Hz, 7.0 Hz), 1.41 (9H, s), 1.06 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2, 138.2, 129.5, 128.3, 126.3, 79.1, 47.2, 43.0, 28.4, 20.1; IR(neat): 3342 (br, w), 2975 (w), 1687 (s), 1496 (s), 1453 (m), 1390 (m), 1246 (s), 1165 (s), 1029 (w), 699 (s) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{22}NO_2$ [M+H]: calculated: 236.1650, found: 236.1650; $[\alpha]_D^{20}$ = -9.422 (*c* = 1.460, $CHCl_3$, *l* = 50 nm).

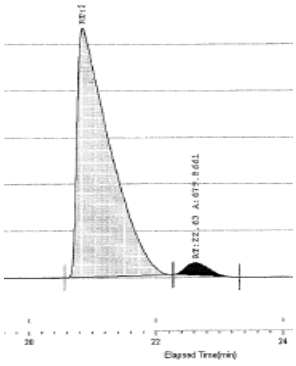
Analysis of Stereochemistry:

The title compound was compared to racemic carbamate derived from diboration/cross-coupling/amination of propene using PCy_3 as the ligand. Absolute stereochemistry was assigned through analogy.

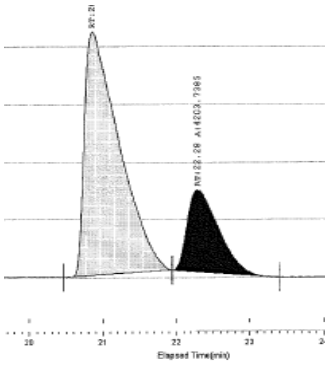
Chiral SFC (Chiracel, OD-H, 35 °C, 1.5 mL/min, 1% Isopropanol:Hexanes (1:1), 100 bar, 210-270nm) – analysis of tert-butyl (1-phenylpropan-2-yl)carbamate.



racemic



amination product

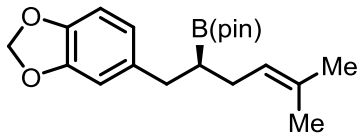


Coinjection of product + racemic

Peak No	% Area	Area	RT (mir
1	96.5611	19090.1498	20.84
2	3.4389	679.8661	22.63
Total:	100	19770.0159	

2.5.2.7 Preparation of Lignan Precursor 2.218

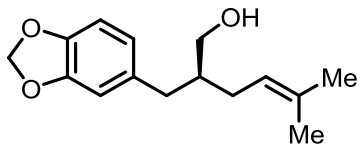
(*S*)-2-(1-(benzo[d][1,3]dioxol-5-yl)-5-methylhex-4-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To an oven-dried 16-mL vial with magnetic stir bar in the dry box was added $Pt(dba)_3$ (4.5 mg, 5.0 μmol), (*S,S*)-3,5-di-*iso*-propylphenyl-TADDOLPPh (5.5 mg, 6.0 μmol), $B_2(pin)_2$ (133.3 mg, 525 μmol) and tetrahydrofuran (0.5 mL, [substrate] = 1.0 M). The vial was sealed with a teflon cap, removed from the dry box, and heated to 80 ºC in an oil bath for 20 minutes. The vial was cooled to room temperature, returned to the dry box and charged with safrole (81.1 mg, 500 μmol). The vial was sealed, removed from the dry box and stirred at 60 ºC 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), $Pd(OAc)_2$/RuPhos (0.70 mL, 1:1 ratio $Pd(OAc)_2$:RuPhos, [$Pd(OAc)_2$/RuPhos] = 0.018 M in THF), tetrahydrofuran (3.35 mL, [substrate] = 0.1 M; 10:1 THF:H_2O) and 1-chloro-2-methylpropene (67.8 mg, 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 ºC and stirred for 12 h. The reaction mixture was cooled to room temperature and diluted with dichloromethane (25 mL) and water (10 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (2-5% EtOAc/hexanes, stain with PMA) to afford the product as a viscous oil (163.7 mg, 95% yield).



(*S*)-2-(1-(benzo[d][1,3]dioxol-5-yl)-5-methylhex-4-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.68 (1H, d, *J* = 1.5 Hz), 6.66 (1H, d, *J* = 7.5 Hz), 6.63 (1H, dd, *J* = 7.5 Hz, 1.0 Hz), 5.87 (2H, s), 5.10 (1H, app td, *J* = 7.5 Hz, 1.5 Hz), 2.61 (1H, dd, *J* = 14.0 Hz, 8.5 Hz), 2.56 (1H, dd, *J* = 14.0 Hz, 7.5 Hz), 2.11-2.01 (2H, m), 1.65 (3H, s), 1.56 (3H, s), 1.32 (1H, app tt, *J* = 15.0 Hz, 7.5 Hz), 1.14 (6H, s), 1.13 (6H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.3, 145.3, 136.2, 131.7, 124.1, 121.5, 109.4, 107.8, 100.6, 82.9, 36.7, 29.4, 25.7, 24.8, 24.6, 17.9; IR(neat): 2976 (w), 2925 (w), 1488 (s), 1440 (m), 1322 (m), 1241 (s), 1142 (s), 967 (m), 926 (m), 804 (m) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{30}BO_4$ [M+H]: calculated: 345.2237, found: 345.2253; $[\alpha]_D^{20}$ = +0.857 (*c* = 1.410, $CHCl_3$, *l* = 50 nm).

(*S*)-2-(benzo[d][1,3]dioxol-5-ylmethyl)-5-methylhex-4-en-1-ol. A flame-dried round bottom flask equipped with magnetic stir bar was charged with (*S*)-2-(1-(benzo[d][1,3]dioxol-5-yl)-5-methylhex-4-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (166 mg, 484 μmol). The flask was sealed with a septum and purged with N_2, and then diluted with tetrahydrofuran (4.8 mL, [substrate] = 0.1 M). Bromochloromethane (65 μL, 0.97 mmol) was added and the reaction was cooled to -78 ºC, followed by the dropwise addition of *n*-butyllithium (0.94 mmol) at -78 ºC. The reaction was stirred at -78 ºC for 10 minutes, then warmed to room temperature and stirred for 12 h. The reaction mixture was cooled to 0 ºC and charged with 3 M sodium hydroxide (2 mL) and 30% hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and stirred for 4 h, then cooled to 0 ºC and was quenched with saturated sodium thiosulfate. 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). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (15% EtOAc/hexanes, stain with PMA) to afford the product as a viscous oil (102.3 mg, 85% yield).

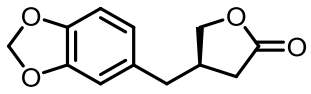


(*S*)-2-(benzo[d][1,3]dioxol-5-ylmethyl)-5-methylhex-4-en-1-ol. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.70 (1H, d, *J* = 8.0 Hz), 6.66 (1H, d, *J* = 1.5 Hz), 6.60 (1H, dd, *J* = 8.0 Hz, 2.0 Hz), 5.90 (2H, s), 5.15 (1H, app tdd, *J* = 7.5 Hz, 3.0 Hz, 1.5 Hz), 3.51 (1H, dd, *J* = 12.0 Hz, 5.0 Hz), 3.49 (H, dd, *J* = 10.5 Hz, 5.0 Hz), 2.55 (1H, dd, *J* = 14.0 Hz, 8.0 Hz), 2.51 (1H, dd, *J* = 14.0 Hz, 6.5 Hz), 2.06-1.96 (2H, m), 1.82-1.74 (1H, m), 1.69 (3H, d, *J* = 1.0 Hz), 1.58 (3H, s), 1.28 (1H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.5, 145.6, 134.9, 133.2, 122.3, 121.9, 109.5, 108.0, 100.7, 65.0, 43.4, 37.2, 29.5, 25.8, 17.8; IR(neat): 3362 (br, m), 2918 (m), 2880 (m), 1488 (s), 1440 (m), 1243 (s), 1188 (m), 1037 (s), 930 (m), 765 (m) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{21}O_3$ [M+H]: calculated: 249.1491, found: 249.1483; $[\alpha]_D^{20}$ = -23.25 (*c* = 1.246, $CHCl_3$, *l* = 50 nm).

(*R*)-4-(benzo[d][1,3]dioxol-5-ylmethyl)dihydrofuran-2(3H)-one. The title compound was prepared according to literature procedure[97] using (*S*)-2-(benzo[d][1,3]dioxol-5-ylmethyl)-5-methylhex-4-en-1-ol (76 mg, 31 μmol). The crude reaction mixture was

[97] Garofalo, A. W.; Marshall, J. A. *J. Org. Chem.* **1993**, *58*, 3675.

purified on silica gel (20% EtOAc/hexanes, stain with PMA) to afford the title compound as a viscous oil (42.6 mg, 63% yield).

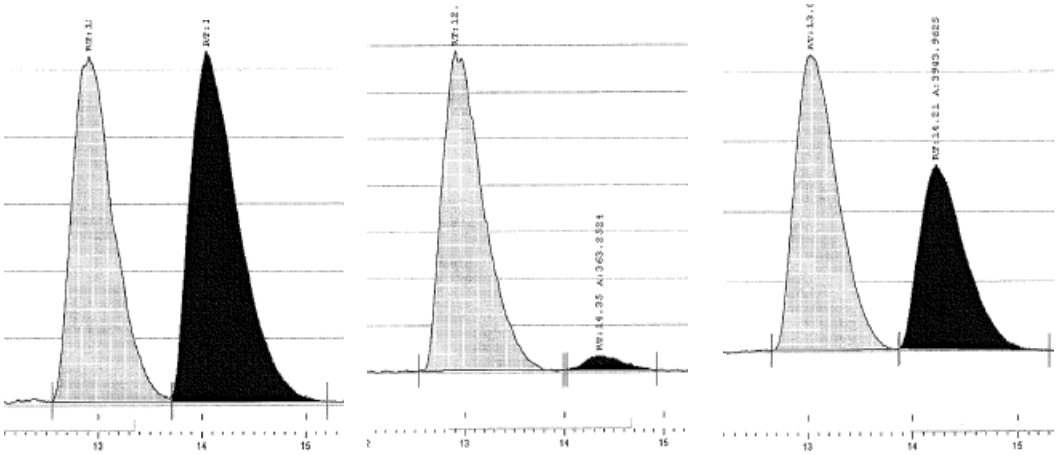


(*R*)-4-(benzo[d][1,3]dioxol-5-ylmethyl)dihydrofuran-2(3H)-one. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 (1H, d, *J* = 7.5 Hz), 6.61 (1H, d, *J* = 1.5 Hz), 6.58 (1H, dd, *J* = 7.5 Hz, 1.5 Hz), 5.92 (2H, s), 4.31 (1H, dd, *J* = 9.5 Hz, 7.5 Hz), 4.00 (1H, dd, *J* = 9.5 Hz, 6.5 Hz), 2.77 (1H, app tt, *J* = 15.5 Hz, 7.0 Hz), 2.72-2.63 (2H, m), 2.57 (1H, dd, *J* = 17.5 Hz, 8.0 Hz), 2.25 (1H, dd, *J* = 17.5 Hz, 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6, 147.9, 146.4, 131.9, 121.6, 108.8, 108.4, 101.0, 72.5, 38.7, 37.3, 34.1; IR(neat): 2910 (w), 1771 (s), 1489 (s), 1442 (m), 1240 (s), 1169 (s), 1035 (s), 1013 (s), 924 (m), 771 (m) cm^{-1}; HRMS-(ESI+) for $C_{12}H_{13}O_4$ [M+H]: calculated: 221.0814, found: 221.0825; $[\alpha]_D^{20}$ = +2.38 (*c* = 0.685, $CHCl_3$, *l* = 50 nm).

Analysis of Stereochemistry:

The title compound was compared to a racemic mixture of lactone formed by mixing equimolar amounts of (*R)*-lactone and (*S)*-lactone derived from diboration using (*S,S*)-3,5-di-isopropylphenyl-TADDOLPPh and (*R,R*)-3,5-di-isopropylphenyl-TADDOLPPh ligands. Absolute stereochemistry was assigned through analogy.

Chiral SFC (Chiracel, AD-H, 35 ^{o}C, 5 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of 4-(benzo[d][1,3]dioxol-5-ylmethyl)dihydrofuran-2(3H)-one.



racemic

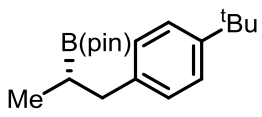
Diboration/ cross-coupling product

Coinjection of product + racemic

Peak No	% Area	Area	RT (min)
1	96.4392	9838.1707	12.89
2	3.5608	363.2524	14.35
Total:	100	10201.4231	

2.5.2.8 Preparation of (S)-Fenpropimorph

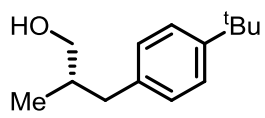
(*S*)-2-(1-(4-(tert-butyl)phenyl)propan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To an oven-dried 16-mL vial with magnetic stir bar in the dry box was added (*S*)-2,2'-(propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (148 mg, 0.500 mmol), potassium hydroxide (84.2 mg, 1.50 mmol), tetrahydrofuran (4.28 mL), $Pd(OAc)_2$/RuPhos (0.27 mL, 1:1 ratio $Pd(OAc)_2$:RuPhos, [$Pd(OAc)_2$/RuPhos] = 0.018 M in THF), and 1-bromo-4-tertbuylbenzene (117.2 mg, 0.550 mmol). The vial was sealed with a teflon septum cap, removed from the dry box, and H_2O (sparged with N_2 for 30 min, 0.45 mL) was added through the septum cap. The vial was heated to 70 ºC and stirred for 12 h. The reaction mixture was diluted with dichloromethane (25 mL) and water (10 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (2-5% EtOAc/hexanes, stain with PMA) to afford the product as a viscous oil (143.9 mg, 95% yield).



(*S*)-2-(1-(4-(tert-butyl)phenyl)propan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 (2H, d, *J* = 8.5 Hz), 7.13 (2H, d, *J* = 8.5 Hz), 2.77 (1H, dd, *J* = 14.0 Hz, 8.0 Hz), 2.53 (2H, dd, *J* = 13.5 Hz, 8.5 Hz), 1.44-1.31 (1H, m), 1.21 (9H, s), 1.19 (6H, s), 1.17 (6H, s), 0.97 (3H, d, *J* = 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.3, 139.2, 128.1, 124.8, 82.9, 38.4, 34.5, 31.4, 24.7, 24.6, 15.2; IR(neat): 2960 (m), 1460 (w), 1404 (m), 1379 (s), 1315 (s),

1214 (m), 1142 (s), 857 (m), 836 (m) cm^{-1}; HRMS-(ESI+) for $C_{19}H_{32}BO_2$ [M+H]: calculated: 303.2495, found: 303.2507; $[\alpha]_D^{20}$ = +3.126 (*c* = 1.535, $CHCl_3$, *l* = 50 nm).

(*S*)-3-(4-(tert-butyl)phenyl)-2-methylpropan-1-ol. A flame-dried round bottom flask equipped with magnetic stir bar was charged with (*S*)-2-(1-(4-(tert-butyl)phenyl)propan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (143 mg, 0.473 mmol). The flask was sealed with a septum and purged with N_2, and then diluted with tetrahydrofuran (4.7 mL, [substrate] = 0.1 M). Bromochloromethane (95 μL, 1.4 mmol) was added and the reaction was cooled to -78 ºC, followed by the dropwise addition of *n*-butyllithium (0.55 mL, 1.3 mmol) at -78 ºC. The reaction stirred at -78 ºC for 10 minutes, then warmed to room temperature and stirred for 12 h. The reaction mixture was cooled to 0 ºC and charged with 3 M sodium hydroxide (2 mL) and 30% hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and stirred for 4 h, then cooled to 0 ºC and quenched with saturated sodium thiosulfate. 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). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on SiO_2 column (10% EtOAc/hexanes, stain with PMA) to afford the product as a viscous oil (83.2 mg, 85% yield).

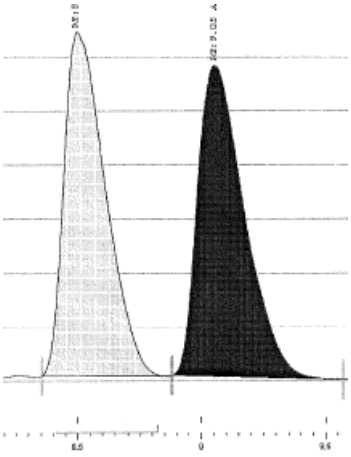


(*S*)-3-(4-(tert-butyl)phenyl)-2-methylpropan-1-ol. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (2H, d, *J* = 8.0 Hz), 7.10 (2H, d, *J* = 8.0 Hz), 3.53 (1H, dd, *J* = 11.0 Hz, 6.5 Hz), 3.46 (1H, dd, *J* = 10.5 Hz, 6.5 Hz), 2.70 (1H, dd, *J* = 13.5 Hz, 6.5 Hz), 2.40 (1H, dd, *J* = 13.5 Hz, 8.0 Hz), 1.93 (1H, app tt, *J* = 13.5 Hz, 6.5 Hz), 1.43 (1H, br s), 1.30 (9H, s), 0.92 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.6, 137.5, 128.8, 125.1, 67.7, 39.2, 37.7, 34.3, 31.4, 16.6; IR(neat): 3343 (br, m), 2958 (s), 2869 (s), 1510 (m), 1460 (m), 1363 (m), 1268 (w), 1034 (s), 825 (m), 570 (s) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{23}O$ [M+H]: calculated: 207.1750, found: 207.1754; $[\alpha]_D^{20}$ = -6.070 (*c* = 1.120, $CHCl_3$, *l* = 50 nm).

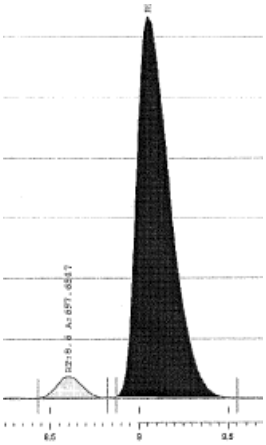
Analysis of Stereochemistry:

The title compound was compared to the racemic analogue derived from diboration of propene using PCy_3 as the ligand. The resulting racemic diboron was transformed into 3-(4-(tert-butyl)phenyl)-2-methylpropan-1-ol as described above for the enantioenriched variant. Absolute stereochemistry was assigned by analogy.

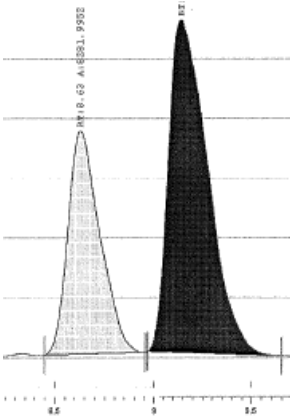
Chiral SFC (Chiracel, OD-H, 35 ^{o}C, 3 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of 3-(4-(tert-butyl)phenyl)-2-methylpropan-1-ol.



racemic



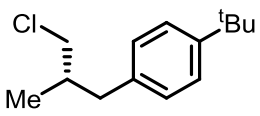
Diboration/ cross-coupling product



Coinjection of product + racemic

Peak No	% Area	Area	RT (min)
1	4.125	697.6547	8.6
2	95.875	16215.0605	9.05
Total:	100	16912.7152	

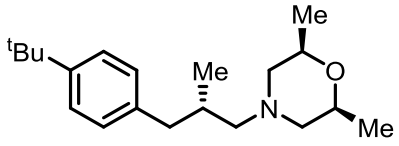
(*S*)-1-(tert-butyl)-4-(3-chloro-2-methylpropyl)benzene. To a solution of (*S*)-3-(4-(tert-butyl)phenyl)-2-methylpropan-1-ol (61.0 mg, 0.296 mmol) in dichloromethane (4.8 mL, [substrate] = 0.06 M) was added *N*-chlorosuccinimide (63.2 mg, 0.473 mmol) and triphenylphosphine (101 mg, 0.384 mmol). The reaction stirred at room temperature for 12 h under an atmosphere of N_2. The solvent was then removed *in vacuo*, and the resulting crude residue was triturated with hexane before being filtered through a plug of SiO_2 with hexane. The filtrate was concentrated to afford the title compound as a colorless oil, which was used without any additional purification (49.9 mg, 75% yield).



(*S*)-1-(tert-butyl)-4-(3-chloro-2-methylpropyl)benzene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (2H, d, *J* = 8.5 Hz), 7.09 (2H, d, *J* = 8.5 Hz), 3.46 (1H, dd, *J* = 11.0 Hz, 5.0 Hz), 3.39 (1H, dd, *J* = 11.0 Hz, 6.0 Hz), 2.71 (1H, dd, *J* = 14.0 Hz, 7.0 Hz), 2.50 (1H, dd, *J* = 13.5 Hz, 7.0 Hz), 2.10 (1H, app ddt, *J* = 14.0 Hz, 13.5 Hz, 7.0 Hz), 1.30 (9H, s), 1.02 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.9, 136.7, 128.8, 125.2, 50.5, 39.6, 37.4, 34.4, 31.4, 17.8; IR(neat): 2960 (s), 2869 (m), 1509 (m)1458 (m), 1363 (m), 1268 (m), 1109 (w), 842 (s), 728 (m), 569 (s) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{20}Cl$ [M-H]: calculated 223.1254, found: 223.1253; $[\alpha]_D^{20}$ = +13.1 (*c* = 0.904, $CHCl_3$, *l* = 50 nm).

(*S*)-1-[3-(4-*tert*-Butylmethyl)-2-methyl]propyl-*cis*-3,5-dimethylmorpholine. The title compound was prepared from (*S*)-1-(tert-butyl)-4-(3-chloro-2-methylpropyl)benzene

(46.0 mg, 0.205 mmol) according to literature procedure[98] without modification. The crude reaction mixture was purified on silica gel (25% EtOAc/hexanes, stain with PMA) to afford the product as a viscous oil (51.5 mg, 82% yield).

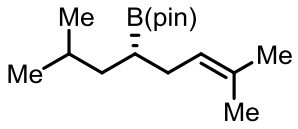


(*S*)-1-[3-(4-*tert*-Butylmethyl)-2-methyl]propyl-*cis*-3,5-dimethylmorpholine. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (2H, d, *J* = 8.0 Hz), 7.06 (2H, d, *J* = 8.0 Hz), 3.69-3.63 (2H, m), 2.75 (1H, dd, *J* = 13.5 Hz, 5.0 Hz), 2.70-2.64 (2H, m), 2.27 (1H, dd, *J* = 13.0 Hz, 8.0 Hz), 2.17 (1H, dd, *J* = 12.5 Hz, 7.5 Hz), 2.08 (1H, dd, *J* = 12.0 Hz, 7.5 Hz), 1.99-1.90 (1H, m), 1.67 (1H, dd, *J* = 11.0 Hz, 10.5 Hz), 1.64 (1H, dd, *J* = 11.0 Hz, 10.5 Hz), 1.29 (9H, s), 1.134 (3H, d, *J* = 6.5 Hz), 1.132 (3H, d, *J* = 6.0 Hz), 0.84 (3H, d, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.4, 137.9, 128.8, 124.9, 71.7, 71.6, 65.0, 60.1, 59.8, 40.7, 34.3, 31.9, 31.4, 19.2, 18.0; IR(neat): 2965 (m), 2867 (m), 2773 (w), 1458 (m), 1373 (m), 1322 (m), 1143 (s), 1083 (s), 835 (m) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{34}NO$ [M+H]: calculated: 304.2640, found: 304.2641; $[\alpha]_D^{20}$ = -1.21 (*c* = 0.824, $CHCl_3$, *l* = 50 nm).

[98] Avdagić, A.; Gelo-Pujić, M.; Sunjić, V. *Synthesis*, **1995**, 1427.

2.5.2.9 Preparation of (S)-(+)-Pregabalin Hydrochloride

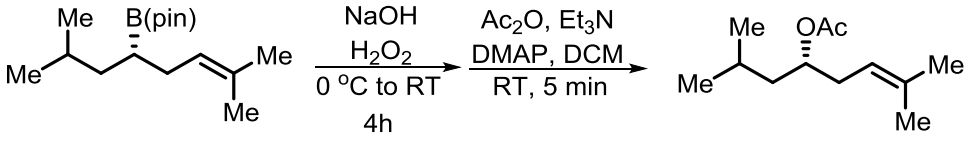
(*S*)-2-(2,7-dimethyloct-6-en-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To an oven-dried 16-mL vial with magnetic stir bar in the dry box was added $Pt(dba)_3$ (4.5 mg, 5.0 μmol), (*R,R*)-3,5-di-isopropylphenyl-TADDOLPPh (5.5 mg, 6.0 μmol), $B_2(pin)_2$ (133.3 mg, 525 μmol) and tetrahydrofuran (0.5 mL, [substrate] = 1.0 M). The vial was sealed with a teflon septum cap, removed from the dry box, and heated to 80 ºC in an oil bath for 20 minutes. The vial was cooled to room temperature, returned to the dry box and charged with 4-methyl-1-pentene (42.1 mg, 500 μmol). The vial was sealed, removed from the dry box and stirred at 60 ºC 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), $Pd(OAc)_2$/RuPhos (0.70 mL, 1:1 ratio $Pd(OAc)_2$:RuPhos, [$Pd(OAc)_2$/RuPhos] = 0.018 M in THF), tetrahydrofuran (3.35 mL, [substrate] = 0.1 M; 10:1 THF:H_2O) and 1-chloro-2-methylpropene (67.8 mg, 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 ºC and stirred for 12 h. The reaction mixture was diluted with dichloromethane (25 mL) and water (10 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (2-5% EtOAc/hexanes, stain with PMA) to afford the product as a yellow oil (129.2 mg, 97% yield).



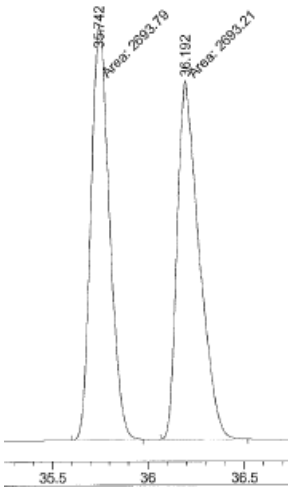
(*S*)-2-(2,7-dimethyloct-6-en-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.09 (1H, ddd, *J* = 7.5 Hz, 7.0 Hz, 1.0 Hz), 2.07-1.97 (2H, m), 1.64 (3H, d, *J* = 1.0 Hz), 1.58 (3H, s), 1.53 (1H, app tt, *J* = 13.5 Hz, 6.5 Hz), 1.33 (1H, ddd, *J* = 13.5 Hz, 9.5 Hz, 6.5 Hz), 1.23-1.14 (1H, m), 1.20 (6H, s), 1.19 (6H, s), 1.13-1.05 (1H, m), 0.84 (6H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 131.1, 124.6, 82.8, 40.6, 30.2, 27.4, 25.7, 24.8, 24.6, 23.1, 22.5, 17.9; IR(neat): 2955 (w), 2868 (w), 1466 (m), 1379 (s), 1317 (s), 1245 (m), 1143 (s), 966 (w), 861 (m) cm^{-1}; HRMS-(ESI+) for $C_{16}H_{32}BO_2$ [M+H]: calculated: 267.2495, found: 267.2490; $[\alpha]_D^{20}$ = -4.227 (*c* = 1.088, $CHCl_3$, *l* = 50 nm).

Analysis of Stereochemistry:

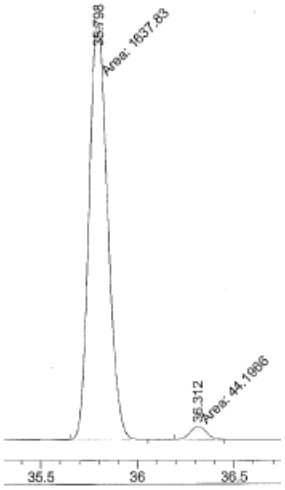
The title compound was oxidized to the corresponding alcohol and protected as described below. The resulting acyl ester was compared to racemic material derived from diboration employing PCy_3 as the ligand followed by cross-coupling as described above. Absolute stereochemistry was assigned through analogy.



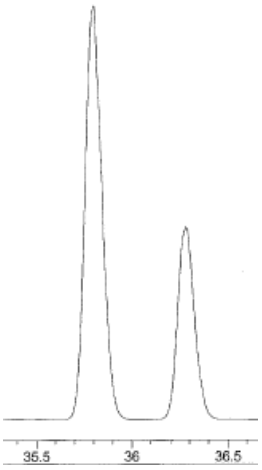
Chiral GLC (β-dex, Supelco, 50 ºC for 5 min, 2 ºC/min ramp to 180 ºC, 20 psi) – analysis of 2,7-dimethyloct-6-en-4-yl acetate.



racemic



Diboration/ cross-coupling product



Coinjection of product + racemic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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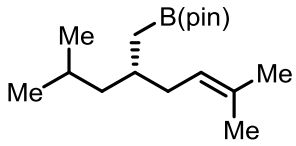
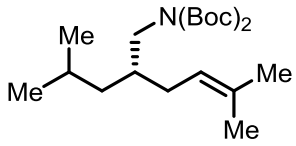
2	36.312	MM	0.0974	44.19661	7.56519	2.62758

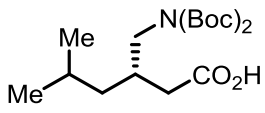


(*S*)-2-(2-isobutyl-5-methylhex-4-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. A flame-dried round bottom flask equipped with magnetic stir bar was charged with (*S*)-2-(2,7-dimethyloct-6-en-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (130 mg, 0.488 mmol). The flask was sealed with a septum and purged with N_2, and then diluted with tetrahydrofuran (4.8 mL, [substrate] = 0.1 M). Bromochloromethane (65 μL, 0.97 mmol) was added and the reaction was cooled to -78 ºC, followed by the dropwise addition of *n*-butyllithium (0.39 mL, 0.95 mmol) at -78 ºC. The reaction was stirred at -78 ºC for 10 minutes, then warmed to room temperature and stirred for 12 h. The reaction was quenched with H_2O (5 mL) and diluted with dichloromethane (15 mL). The aqueous and organic layers were separated, and the aqueous layer was extracted with dichloromethane (3 x 15 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was placed on the high-vac until all of the 1-bromobutane byproduct was removed. The crude material was subjected to amination without additional purification.

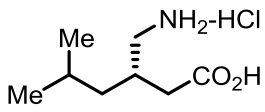


***Bis*-Boc-(*S*)-2-isobutyl-5-methylhex-4-en-1-amine**. The title compound was prepared according to literature procedure[96] without modification. After stirring at 60 ºC for 18 h, di-*tert*-butyl dicarbonate (0.68 mL, 3.0 mmol, 6.1 equiv) was added. The reaction stirred at 60 ºC for 24 h before being cooled to room temperature. The reaction mixture was diluted with water (10 mL) and ethyl acetate (20 mL). The layers were separated and the aqueous layer was extracted with EtOAc (3 x 20 mL). The combined organics were dried over Na_2SO_4, filtered, and

concentrated by rotary evaporation. The crude material was subjected to alkene oxidation without purification.



***N,N-bis*-Boc-(*S*)-3-(aminomethyl)-5-methylhexanoic acid.** The title compound was prepared according to literature procedure[99] without modification from *bis*-Boc-(*S*)-2-isobutyl-5-methylhex-4-en-1-amine (assumed 0.488 mmol). The crude reaction mixture was purified on silica gel (15% ethyl acetate in hexanes with 0.25% AcOH, stain with ninhydrin) to afford the title compound with >95% purity as a colorless oil (79.6 mg, 45% yield) . ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.54 (1H, dd, J = 14.0 Hz, 5.0 Hz), 3.48 (1H, dd, J = 14.0 Hz, 8.0 Hz), 2.32-2.19 (2H, m), 1.63-1.54 (1H, m), 1.46-1.38 (1H, m), 1.44 (18H, s), 1.15-1.05 (2H, m), 0.85 (3H, d, J = 6.0 Hz), 0.81 (3H, d, J = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 178.6, 152.8, 82.4, 50.0, 41.7, 37.2, 32.6, 28.0, 25.2, 22.8, 22.5; HRMS-(ESI+) for $C_{18}H_{34}NO_6$ [M+H]: calculated: 360.2386, found: 360.2392.



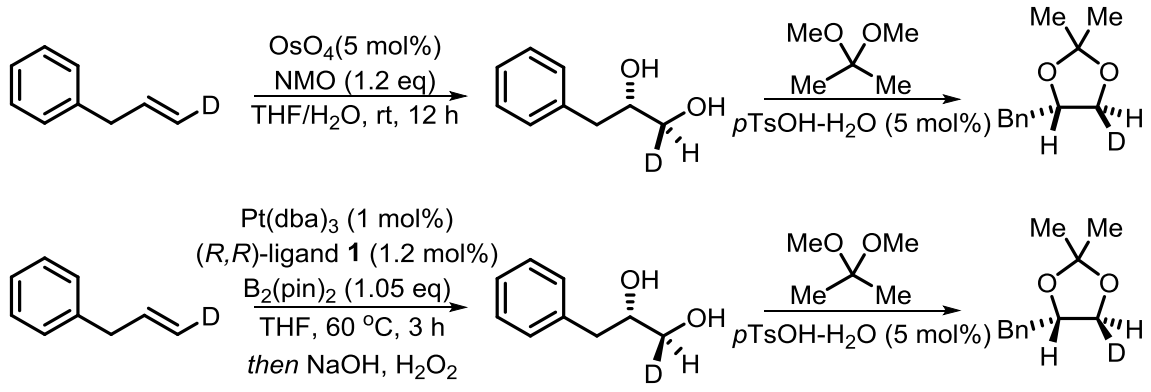
(*S*)-(+)-Pregabaline Hydrochloride. A flame-dried round bottom flask with magnetic stir bar was charged with *bis*-Boc-(*S*)-2-isobutyl-5-methylhex-4-en-1-amine (79.6 mg, 221 μmol) and hydrogen chloride in methanol (1.7 mL, 10 equiv., [HCl] in MeOH = 1.25 M). The reaction stirred at room temperature for 12 hours before being concentrated *in vacuo*. The crude residue was dissolved in diethyl ether (2 mL) and left undisturbed until a white precipitate formed.

[99] Chen, Y. K.; Lurain, A. E.; Walsh, P. J. *J. Am. Chem. Soc.* **2002**, *124*, 12225.

The solids were collected and washed with cold hexane to afford the title compound as a white solid (36.9 mg, 85% yield). All spectra data are in accordance with the literature[100]. $[\alpha]_D^{20}$ = +10.64 (*c* = 1.050, H_2O, *l* = 50 nm); lit.: +11.2 (*c* = 1.19, H_2O).

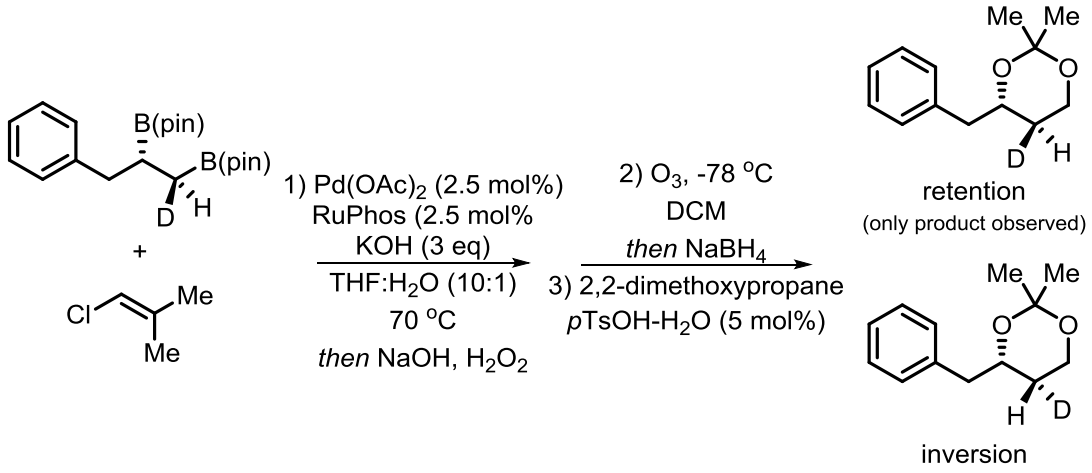
2.5.2.10 Deuterium Labeled Studies

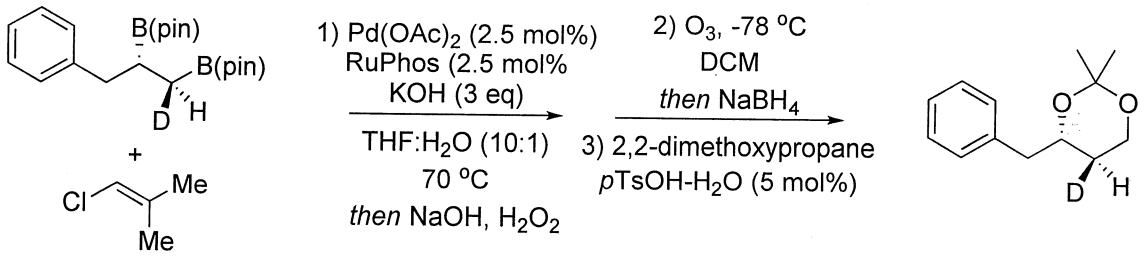
Hydroboration of 3-phenyl-1-propyne was performed according to the literature procedure[101] using AcOD as the deuterium source for boron/deuterium exchange. ^{1}H NMR showed 75% deuterium incorporation in the resulting alkene with geometry as shown. Syn-addition of bis(pinacolato)diboron in the platinum-catalyzed diboration of terminal alkenes was proven through comparison of acetonides derived from the 1,2-diol product of OsO_4 dihydroxylation. ^{1}H NMR of the resulting two acetonides were identical.



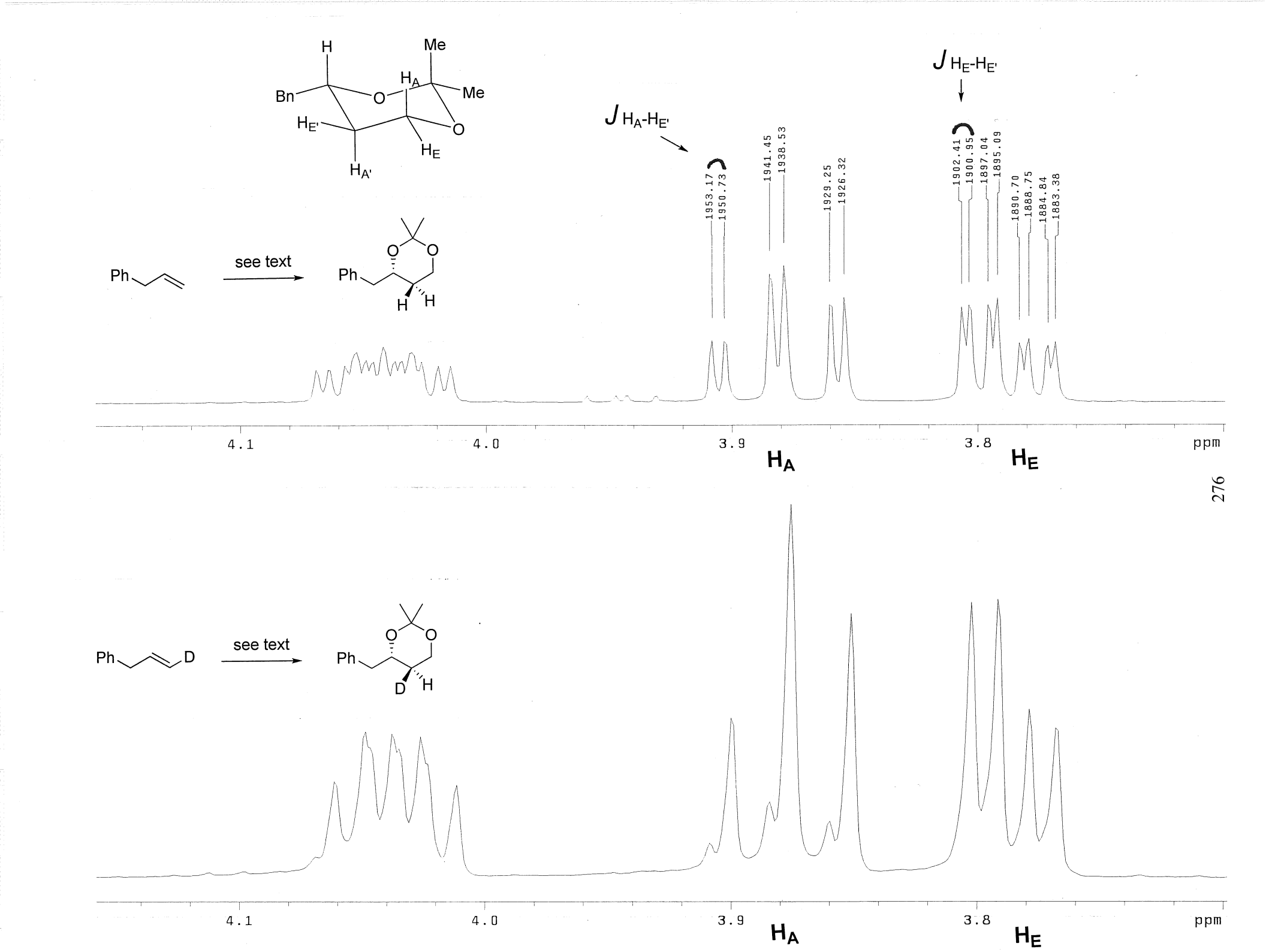
[100] Yu, H.J; Shao, C.; Cui, Z.; Feng, C. G.; Lin, G. Q. *Chem. Eur. J.* **2012**, *18*, 13274.
[101] Ellis, N. M.; Molander, G. A. *J. Org. Chem.* **2008**, *73*, 6841.

The stereochemical outcome of transmetallation in the palladium catalyzed cross-coupling was determined through ^{1}H NMR analysis of the 1,3-diol derived acetonide as described below. The resulting acetonide was compared to the analogous product employing allylbenzene as the substrate. ^{1}H NMR of deuterium labeled substrate showed disappearance of *J* H_A-$H_{E'}$ coupling (see NMR) consistent with an equatorial deuterium with an anti-relationship to the benzyl group.




B(pin)
B(pin)
D
H
+
Cl
Me
Me
1) Pd(OAc)2 (2.5 mol%)
RuPhos (2.5 mol%
KOH (3 eq)
THF:H2O (10:1)
70 °C
then NaOH, H2O2
2) O3, -78 °C
DCM
then NaBH4
3) 2,2-dimethoxypropane
pTsOH-H2O (5 mol%)
O
O
D
H

9
8
7
6
5
4
3
2
1
ppm


H
Me
Bn
H_A
Me
O
$H_{E'}$
O
H_E
$H_{A'}$
$J_{H_A-H_{E'}}$
$J_{H_E-H_{E'}}$
1953.17
1950.73
1941.45
1938.53
1929.25
1926.32
1902.41
1900.95
1897.04
1895.09
1890.70
1888.75
1884.84
1883.38
Ph
see text
Ph
O
O
H
H
4.1
4.0
3.9
3.8
ppm
H_A
H_E
Ph
D
see text
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H
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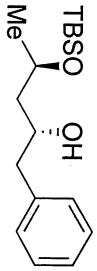
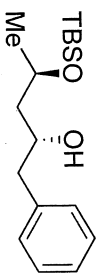
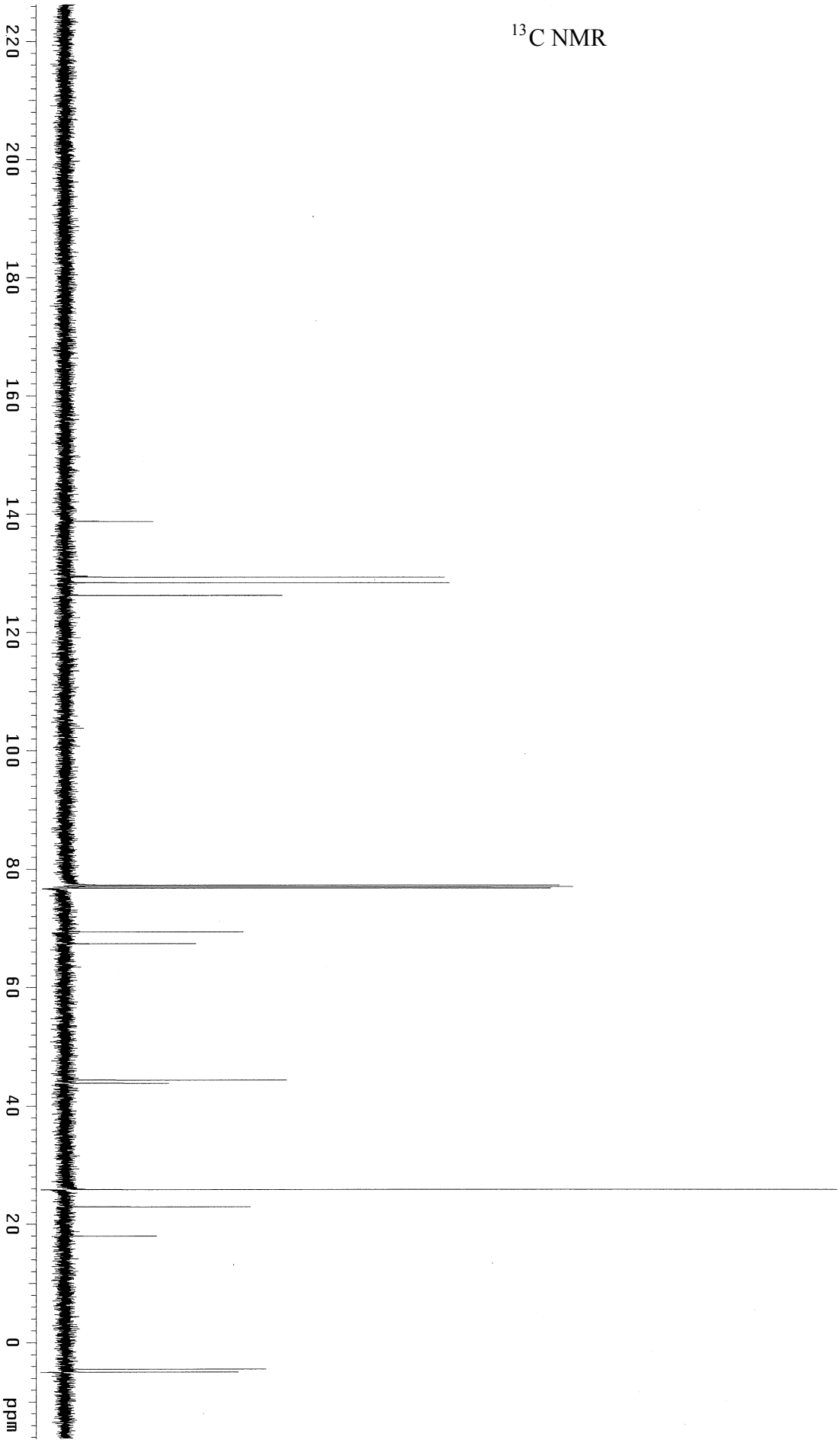
3.8
ppm
H_A
H_E

^{1}H NMR

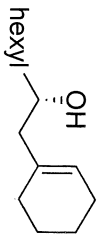


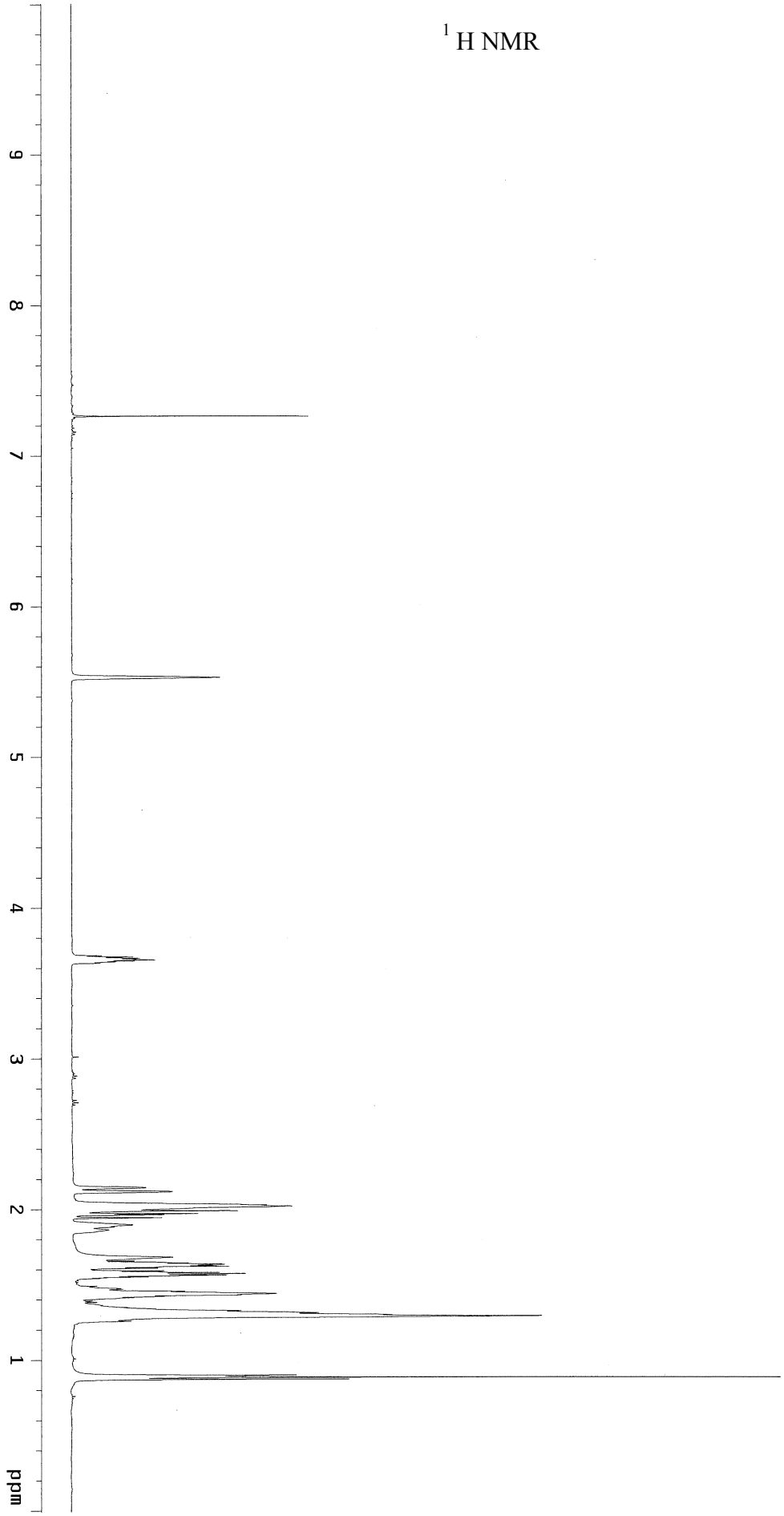
^{13}C NMR



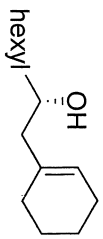


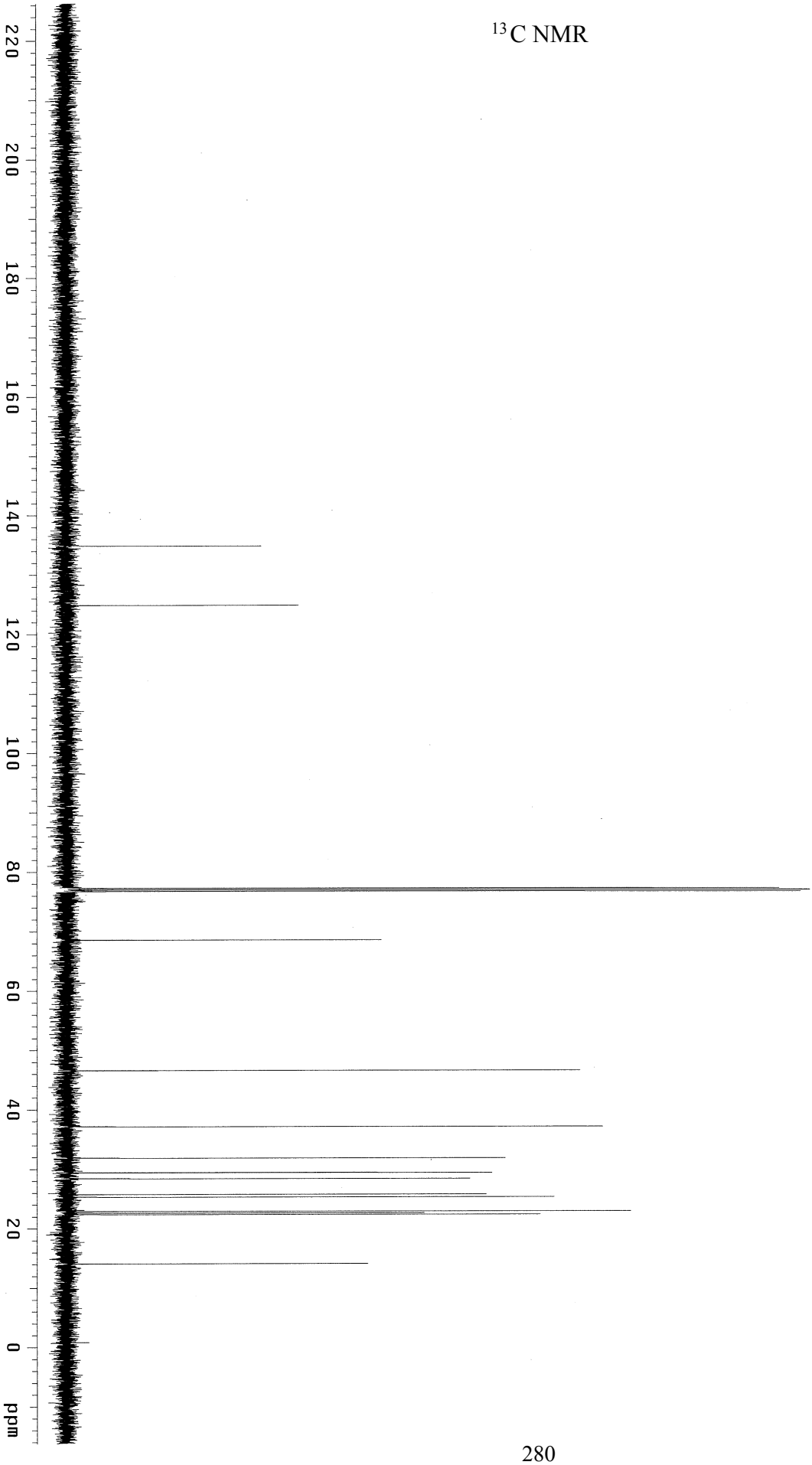
^{1}H NMR





^{13}C NMR





Chapter 3

Enantioselective Carbocycle Formation through Intramolecular Palladium Catalyzed Allyl-Aryl Coupling

3.1 Introduction

Carbocycles of various sizes form the backbone of an incredible array of compounds in organic chemistry. Nature often employs these structural features in the never-ending battle with entropy to gain access to molecules exhibiting well-defined geometries. Accordingly, the stereoselective synthesis of carbocycles has received an enormous amount of attention from around the globe for well over a century. Modern efforts have been extended to increase the range and efficiency with which carbocycles can be forged, resulting in many reliable strategies. Perhaps one of the most useful and general catalytic methods for ring forming reactions is the ring closing metathesis reaction (RCM) (Scheme 3.1).[1] Importantly, when utilizing an enantiopure catalyst, non-racemic, chiral cyclic structures may be forged through either a kinetic resolution of chiral dienes (equation 1),[2] or through the desymmetrization of trienes (equation 2).[3] While this versatile approach holds great promise for future synthetic applications, the

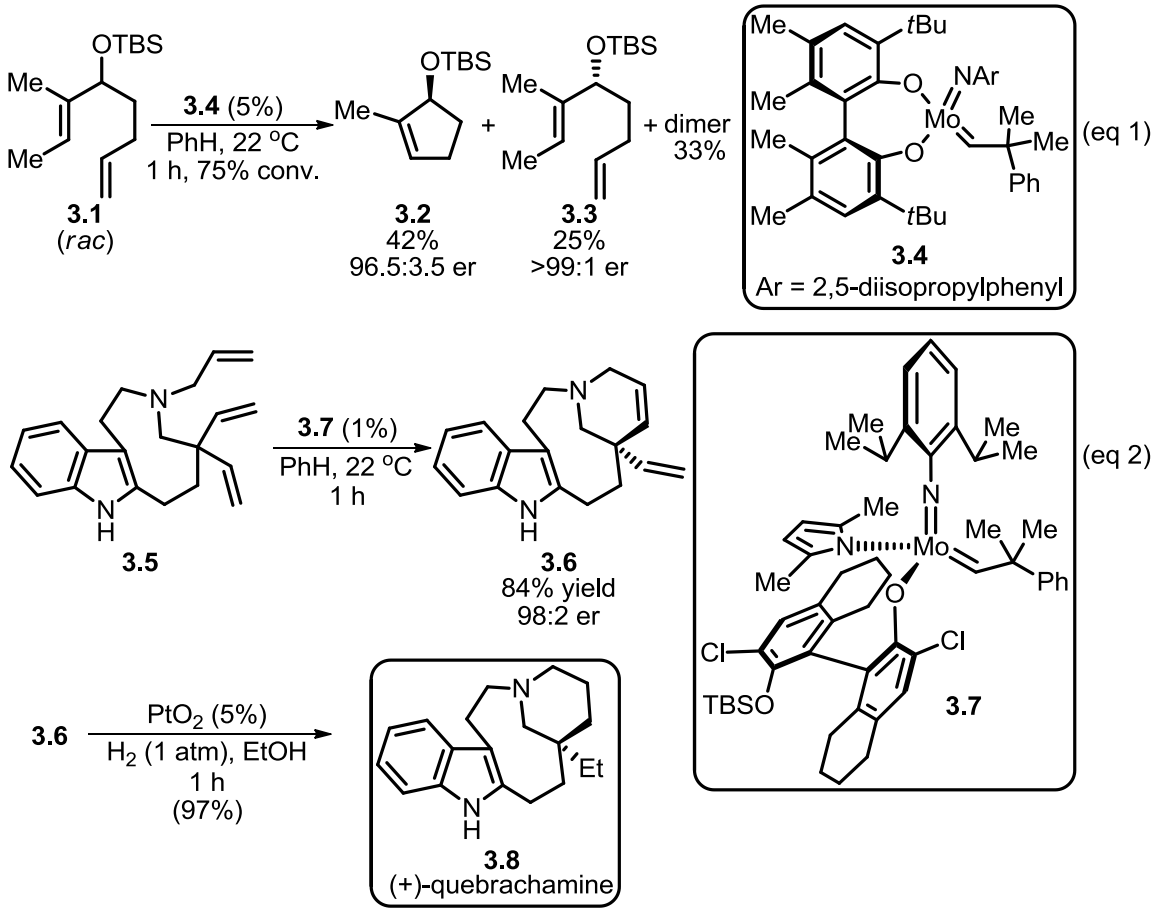
[1] (a) Grubbs, R. H. *Handbook of Metathesis* (Wiley-VCH, **2003**). For selected reviews, see: (b) Grubbs, R. H.; Miller, S. J.; Fu, G. C. *Acc. Chem. Res*. **1995**, *28*, 446. (c) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed*. **2003**, *42*, 4592. (d) Deiters, A.; Martin, S. F. *Chem. Rev*. **2004**, *104*, 2199. (e) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243. (f) Hoveyda, A. H. *J. Org. Chem*. **2014**, DOI: 10.1021/jo500467z.

[2] Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. *J. Am. Chem. Soc*. **1998**, *120*, 4041.

[3] (a) Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933. See also: (b) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett*. **2001**, *3*, 3225.

most widely utilized catalytic enantioselective method for the synthesis of carbocycles remains the intramolecular Heck reaction.[4]

Scheme 3.1: Representative Examples of Enantioselective Ring Formation through Metathesis



The power of the enantioselective intramolecular Heck reaction to forge complex cyclic frameworks has been utilized in a highly creative manner to accomplish the synthesis of numerous natural products. Beginning with the pioneering work of

[4] For selected reviews, see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev*. **2003**, *103*, 2945. (b) Shibasaki, M.; Vogl, E. M.; Oshima, T. *Adv. Synth. Catal*. **2004**, *346*, 1533. (c) McCartney, D.; Guiry, P. J. *Chem. Soc. Rev*. **2011**, *40*, 5122.

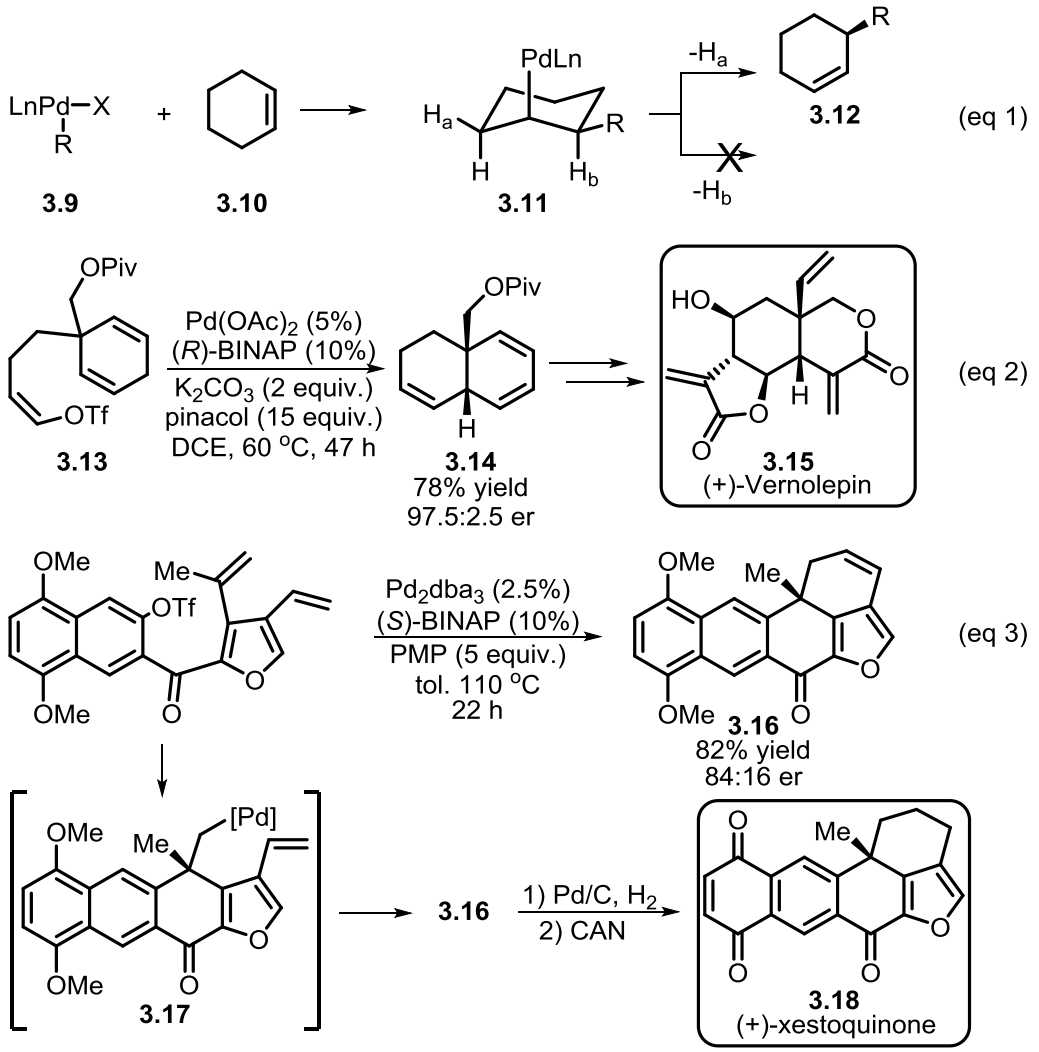
Overman[5] and Shibasaki,[6] the success of the enantioselective Heck reaction has been closely tied to an understanding of subtle features that dictate reactivity and selectivity in these reactions.[7] A common challenge encountered in the Heck reaction is achieving selective β-hydride elimination to generate the desired product and avoid re-insertion/elimination sequences, which can lead to racemization or to formation of achiral product. To avert this, most successful approaches toward enantioselective Heck reactions utilize substrates which afford alkyl palladium intermediates that are pre-disposed to eliminate in the desired fashion.

Carbo-palladation in Heck reactions proceeds through a *syn* addition of carbon and palladium across the reacting π-system. As such, when cyclic alkenes undergo Heck coupling, the stereochemical outcome of the *syn* addition forces β-hydride elimination to occur away from the newly formed carbon-carbon bond, thereby avoiding destruction of the stereogenic center (Scheme 3.2, equation 1). For example, Shibasaki and coworkers utilized symmetric vinyl triflate **3.13** to forge *cis*-decalin **3.14** in a highly enantioselective fashion *en route* to the natural product vernolepin **3.15** (equation 2).[8] Notably, when bond formation occurs to create an exocyclic alkyl palladium species, unrestricted bond rotation can lead to non-selective β-hydride elimination, often resulting in achiral product formation. Undesired elimination can be blocked by the use of olefin partners which result in formation of difficult-to-establish quaternary stereocenters. Keay and coworkers were able to take advantage of this powerful approach to rapidly assemble the polycyclic

[5] Carpenter, N. E.; Kucera, D. J.; Overman, L. E. *J. Org. Chem*. **1989**, *54*, 5846.
[6] Sato, Y.; Sodeoka, M.; Shibasaki, M. *J. Org. Chem*. **1989**, *54*, 4738.
[7] For a review of mechanistic features of the Heck reaction, see: Knowles, J. P.; Whiting, A. *Org. Biomol. Chem*. **2007**, *5*, 31.
[8] Ohrai, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M. *J. Am. Chem. Soc*. **1994**, *116*, 11737.

core of xestoquinone **3.18** (equation 3).[9] After oxidative addition, migratory insertion of the proximal 1,1-disubstituted olefin establishes the quaternary center and gives primary alkyl palladium **3.17**, which undergoes further cyclization to give the desired pentacyclic product **3.16**.

Scheme 3.2: Examples of Enantioselective Intramolecular Heck Reaction by Shibasaki and Keay

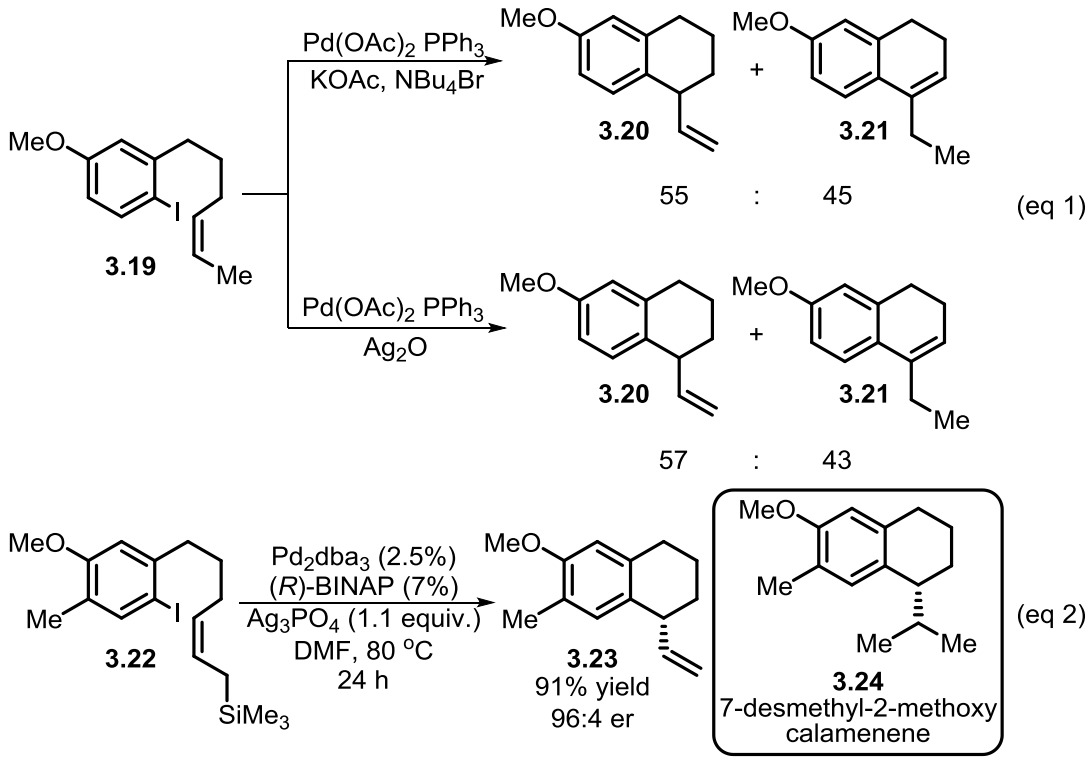


While β-hydride elimination can be effectively controlled when quaternary centers are established, the generation of exocyclic alkyl palladium intermediates

[9] Maddaford, S. P.; Anderson, N. G.; Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc*. **1996**, *118*, 10766.

adjacent to tertiary centers often results in formation of achiral products. For instance, Tietze showed that under both neutral and cationic conditions, **3.19** underwent Heck cyclization to afford a mixture of the desired exocyclic olefin **3.20** and the undesired **3.21** (Scheme 3.3, equation 1).[10] To overcome non-selective elimination, an allyl silane was found to function as a suitable alkene coupling partner to give the desired exocyclic product **3.23**. Tietze utilized this silyl terminated Heck strategy to efficiently access the sesquiterpene natural product **3.24** in four steps from **3.22** (equation 2).[10]

Scheme 3.3: Tietze's Use of Allyl Silanes to Direct Elimination in Heck Cyclizations

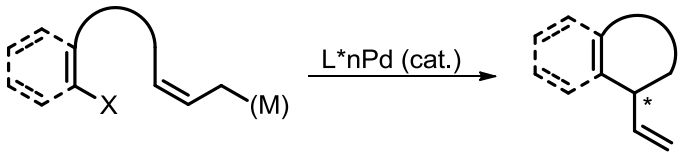


Although the enantioselective intramolecular Heck reaction has been shown to efficiently forge carbocycles in sufficiently biased systems, the formation of certain

[10] (a) Tietze, L. F.; Schimpf, R. *Angew. Chem. Int. Ed*. **1994**, *33*, 1089. (b) Tietze, L. F.; Thede, K.; Schimpf, R.; Sannicoló, F. *Chem. Commun*. **2000**, 583. (c) Tietze, L. F.; Modi, A. *Eur. J. Org. Chem*. **2000**, 1959.

tertiary carbon centers remains a significant challenge. Tietze's use of allyl silanes to direct elimination shows a potential way forward, but perhaps a more general solution would be to utilize enantioselective intramolecular cross-coupling to deliver carbocycles with concomitant formation of sterodefined tertiary centers. Such an approach could avoid the regioselective elimination issues that plague intramolecular Heck reactions. In particular, the use of an allyl-metal coupling partner would result in formation of useful exocyclic olefins that are not easily accessed by traditional Heck methods (Scheme 3.4). This chapter describes the development of an enantioselective intramolecular coupling reaction between aryl halides and tethered allyl pinacol boronates.

Scheme 3.4: Intramolecular Coupling to Establish Enantioenriched Tertiary Centers



3.2 Background

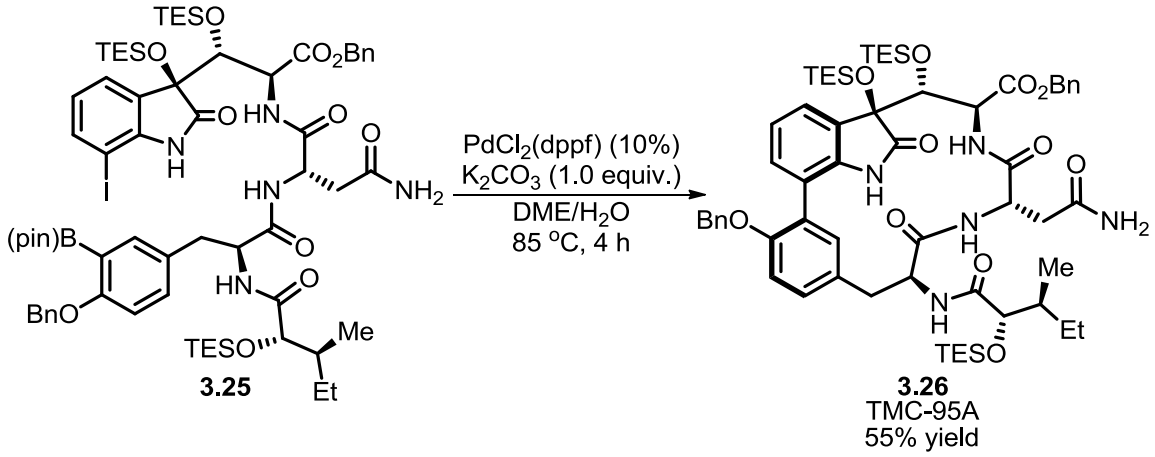
3.2.1 Intramolecular Suzuki-Miyaura Cross-Coupling

Though intramolecular allyl coupling reactions[11] are known which employ both tin[12] and indium[13] based allyl nucleophiles, intramolecular coupling reactions involving

[11] For a review of cyclizations featuring organosilanes and organostannanes, see: Méndez, M.; Echavarren, A. M. *Eur. J. Org. Chem*. **2002**, 15. For a review of allyl tin and allyl indium reagents, see: Roy, U. K.; Roy, S. *Chem. Rev*. **2010**, *110*, 2472.
[12] Selected examples involving allyl stannanes: (a) Trost, B. M.; Walchi, R. *J. Am. Chem. Soc*. **1987**, *109*, 3487. (b) Grigg, R.; Sansano, J. M. *Tetrahedron* **1996**, *52*, 13441.
[13] Selected examples involving ally indiums: (a) Seomoon, D.; Lee, K.; Kim, H.; Lee, P. H. *Chem. Eur. J.* **2007**, *13*, 5197. (b) Lee, K.; Kim, H.; Mo, J.; Lee, P. H. *Chem. Asian. J*. **2011**, *6*, 2147.

boron-based nucleophiles have thus far been limited to the use of sp^2-based boronates[14] and alkyl 9-BBN derivatives.[15] A very recent example of a difficult macrocyclization was accomplished by Evano and coworkers with the use of an intramolecular Suzuki-Miyaura coupling (Scheme 3.5).[16] Utilizing conditions developed by Zhu,[17] the authors were able to furnish the desired macrocycle **3.26** employing aryl pinacol boronate **3.25** in moderate yield and as a single atropisomer.

Scheme 3.5: Macrocyclization through Intramolecular Suzuki-Miyaura coupling by Evano



In addition to aryl-aryl intramolecular Suzuki-Miyaura coupling, intramolecular B-alkyl couplings have proven useful for synthesis. In 2000, Danishefsky and Chemler showed the ability of intramolecular coupling to forge challenging transannular

[14] For selected examples, see: (a) Carbonnelle, A-C.; Zhu, J. *Org. Lett*. **2000**, *2*, 3477. (b) Kaiser, M.; Siciliano, C.; Assfalg-Machleidt, I.; Groll, M.; Milbradt, A. G.; Moroder, L. *Org. Lett*. **2003**, *5*, 3435. (c) Lepine, R.; Zhu, J. *Org. Lett*. **2005**, *7*, 2981.

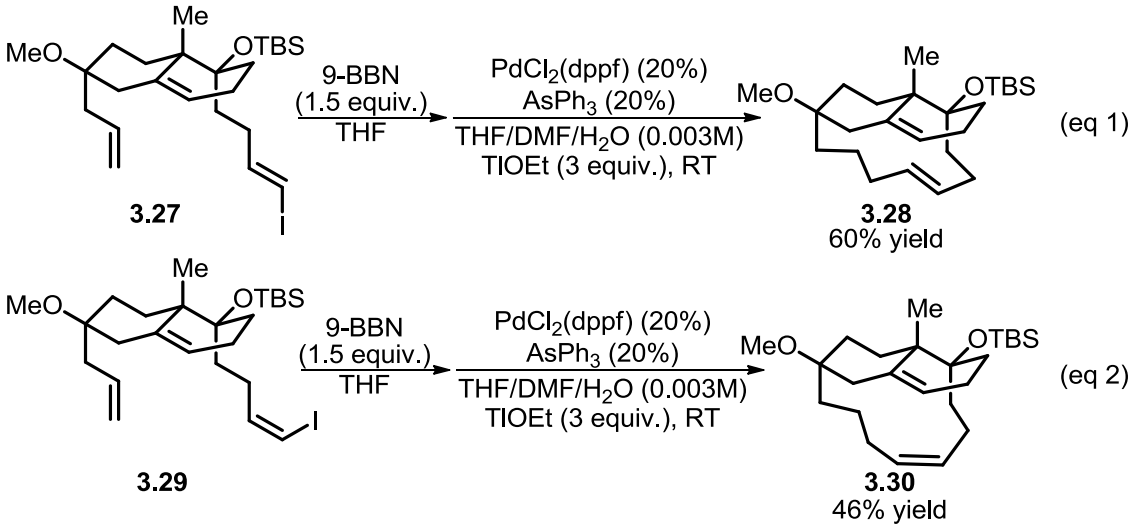
[15] For reviews, see: (a) Miyaura, N.; Suzuki, A. *Chem. Rev*. **1995**, *95*, 2457. (b) Chemler, S. R.; Trauner, D.; Danishefsky, S. J. *Angew. Chem. Int. Ed*. **2001**, *40*, 4544. (c) Jana, R.; Pathek, T. P.; Sigman, M. S. *Chem. Rev*. **2011**, *111*, 1417.

[16] Coste, A.; Bayle, A.; Marrot, J.; Evano, G. *Org. Lett*. **2014**, *16*, 1306.

[17] (a) Jia, Y.; Bois-Choussy, M.; Zhu, J. *Org. Lett*. **2007**, *9*, 2401. (b) Jia, Y.; Bois-Choussy, M.; Zhu, J. *Angew. Chem. Int. Ed*. **2008**, *47*, 4167. (c) Wang, Z.; Bois-Choussy, M.; Jia, Y.; Zhu, J. *Angew. Chem. Int. Ed*. **2010**, *49*, 2018.

macrocycles (Scheme 3.6).[18] Regioselective hydroboration with 9-BBN followed by *in situ* coupling utilizing $PdCl_2$(dppf) and thallium ethoxide at room temperature gave the desired product **3.28** in good yield (equation 1). Importantly, *cis* vinyl iodide **3.29** underwent intramolecular coupling with similar levels of efficiency to give the sterocomplementary macrocycle **3.30** (equation 2). The authors attempted the corresponding ring closing metathesis to produce either **3.28** or **3.30**, but obtained no desired reaction with the use of Grubbs 1st generation catalyst.

Scheme 3.6: Transannular Cyclization through B-alkyl Suzuki-Miyaura Coupling by Danishefsky

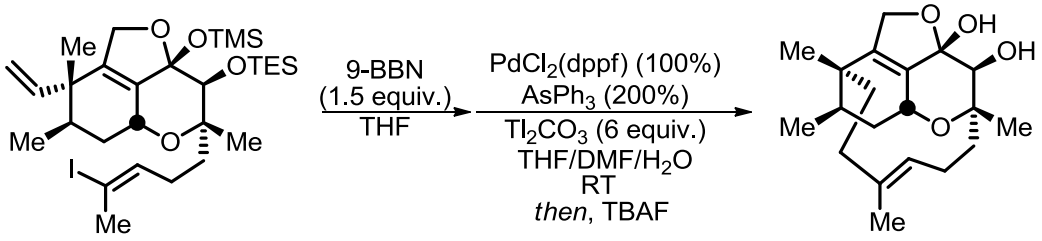


Following Danishefsky's report, Halcomb and Mohr disclosed the synthesis of the diterpene phomactin A **3.32** (Scheme 3.7).[19] The key penultimate step to establish the 12-membered transannular macrocycle was accomplished by a tandem hydroboration with 9-BBN followed by intramolecular Suzuki-Miyaura coupling utilizing similar

[18] Chemler, S. R.; Danishefsky, S. J. *Org. Lett*. **2000**, *2*, 2695.
[19] Mohr, P. T.; Halcomb, R. L. *J. Am. Chem. Soc*. **2003**, *125*, 1712.

conditions to those of Danishefsky. Finally, treatment with TBAF gave natural product **3.32** in good yield.

Scheme 3.7: Synthesis of Phomactin A *via* Transannular Cyclization by Halcomb



3.31 **3.32**
(+)-phomactin A
29% yield (2 steps)

3.2.2 Intermolecular Coupling with Allyl Boron Based Nucleophiles

While allyl boronates as of yet have not been utilized in intramolecular coupling reactions, they have been employed in an intermolecular manner with a wide variety of electrophiles.[20] Although there are notable examples of allyl boranes[21] and allyl trifluoroborates[22] in Suzuki-Miyaura cross-coupling reactions with aryl electrophiles, the majority of reports have utilized allyl boronate esters as nucleophilic partners. The first report utilizing allyl boronates in coupling reactions was reported by Hallberg in 1987 (Scheme 3.8).[23] Initially, Hallberg approached the reaction of allyl pinacol boronate **3.33**

[20] For recent examples with allyl electrophiles, see: (a) Le, H.; Batten, A.; Morken, J. P. *Org. Lett*. **2014**, *16*, 2096. (b) Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc*. **2014**, *136*, 7092. With unsaturated carbonyls, see: (c) Zhang, P.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 12550. (d) Brozek, L. A.; Sieber, J. D.; Morken, J. P. *Org. Lett*. **2011**, *13*, 995. With propargyl electrophiles, see: (e) Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc*. **2012**, *134*, 8770. (f) Ardolino, M. J.; Eno, M. S.; Morken, J. P. *Adv. Synth. Catal*. **2013**, *355*, 3413. With acid chlorides, see: (g) Al-Masum, M.; Liu, K-Y. *Tetrahedron Lett*. **2011**, *52*, 5090. With aldimines, see: (h) Viera, E. M.; Snapper, M. L.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2011**, *133*, 3332. With β-lactones, see: (i) Niyomchon, S.; Audisio, D.; Luparia, M.; Maulide, N. *Org. Lett*. **2013**, *15*, 2318.

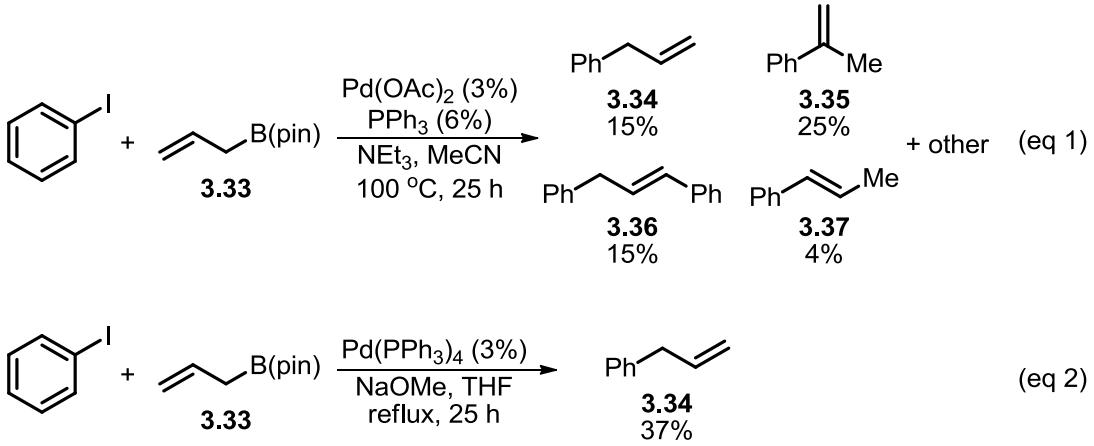
[21] (a) Kalinin, V. N.; Denisov, F. S.; Bubnov, Y. N. *Mendeleev Commun*. **1996**, *6*, 206. (b) Fürstner, A.; Seidel, G. *Synlett* **1998**, 161. (c) Fürstner, A.; Leitner, A. *Synlett* **2001**, 290. (d) Dai, Q.; Xie, X.; Xu, S.; Ma, D.; Tang, S.; She, X. *Org. Lett*. **2011**, *13*, 2302.

[22] (a) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett*. **2006**, *35*, 704. (b) Al-Masum, M.; Alam, S. *Tetrahedron Lett*. **2009**, *50*, 5201.

[23] Nilsson, K.; Hallberg, A. *Acta Chem. Scand*. **1987**, *41b*, 569.

with iodobenzene as a Heck reaction, assuming the terminal olefin would readily participate in migratory insertion and the boron moiety would behave as an unreactive alkyl boronate and not participate. Upon examining the reaction of **3.33** with iodobenzene under common Heck conditions, a wide distribution of products was obtained, most of which did not contain the boron moiety (equation 1). Interestingly, utilizing conditions found to be effective for vinyl boronate Suzuki-Miyaura cross-couplings gave allyl benzene **3.34** as the sole product, albeit in low yield (equation 2). Concluding his report, Hallberg notes,[24] "the synthetic value of allyl boronates, exemplified by (**3.33**), as substrates in the Heck arylation seem to be limited."

Scheme 3.8: Seminal Report of Allyl Boronate Coupling by Hallberg

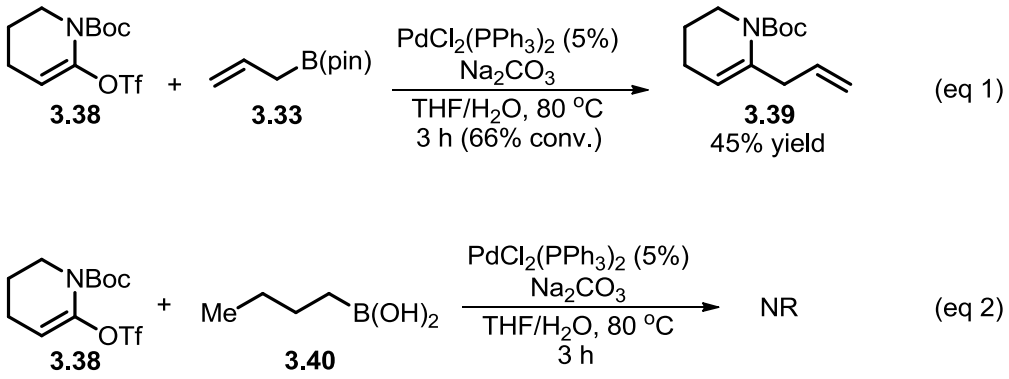


Following this report, the use of allyl boronates in cross-coupling reactions lay dormant for 14 years until a 2001 report from the group of Occhiato.[25] Utilizing allyl pinacol boronate **3.33**, vinyl triflate **3.38** was shown to successfully participate in Suzuki-Miyaura cross-coupling to afford the desired amide **3.39** in moderate yield (Scheme 3.9, equation 1). In addition to examining other boron nucleophiles, the authors subjected

[24] Nilsson, K.; Hallberg, A. *Acta Chem. Scand*. **1987**, *41b*, p.573.
[25] Occhiato, E. G.; Trabocchi, A.; Guarna, A. *J. Org. Chem*. **2001**, *66*, 2459.

alkyl boronic acid **3.40** to the standard reaction conditions (equation 2). Interestingly, in stark contrast to the allyl boronate cases, no desired product was obtained and only starting material remained.

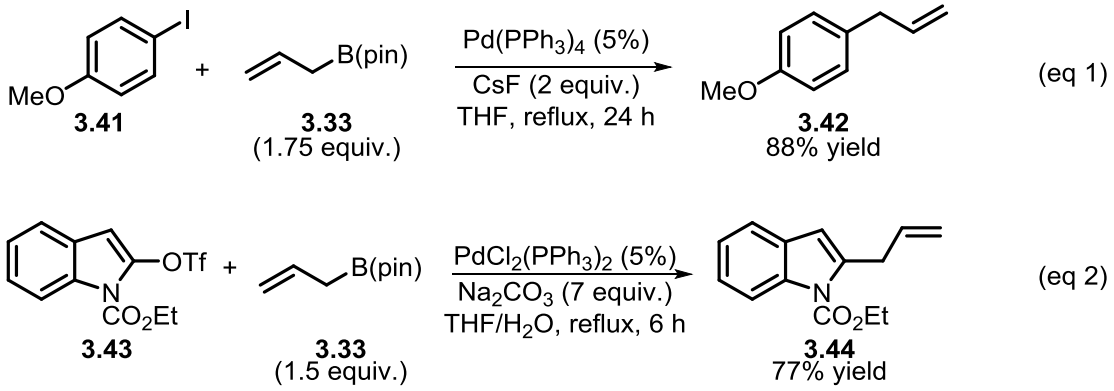
Scheme 3.9: Coupling of Vinyl Triflates and Allyl Boronates by Occhiato



The utility of allyl boronates in cross-coupling reactions gained traction in the mid 2000's with the first disclosures of synthetically appealing yields. In 2005, Kotha and coworkers described the use of a variety of aryl iodides as electrophilic partners in Suzuki-Miyaura cross-coupling reactions with allyl pinacol boronate **3.33** (Scheme 3.10, equation 1).[26] The authors noted that use of allyl tributyltin nucleophiles gave tin impurities that were difficult to separate from the allyl benzene products, whereas use of the allyl boronates gave clean reaction products along with easily removed boron byproducts. The Rossi group also found allyl pinacol boronate **3.33** participated in efficient cross-coupling with indole triflates **3.43** to give the desired allylated products in good to excellent yields (equation 2).[27]

[26] Kotha, S.; Behera, M.; Shah, V. R. *Synlett* **2005**, 1877.
[27] Rossi, E.; Abbiati, G.; Canevari, V.; Celentano, G.; Magri, E. *Synthesis* **2006**, 299.

Scheme 3.10: Independent Reports of Efficient Allyl Boronate Coupling by Kotha and Rossi

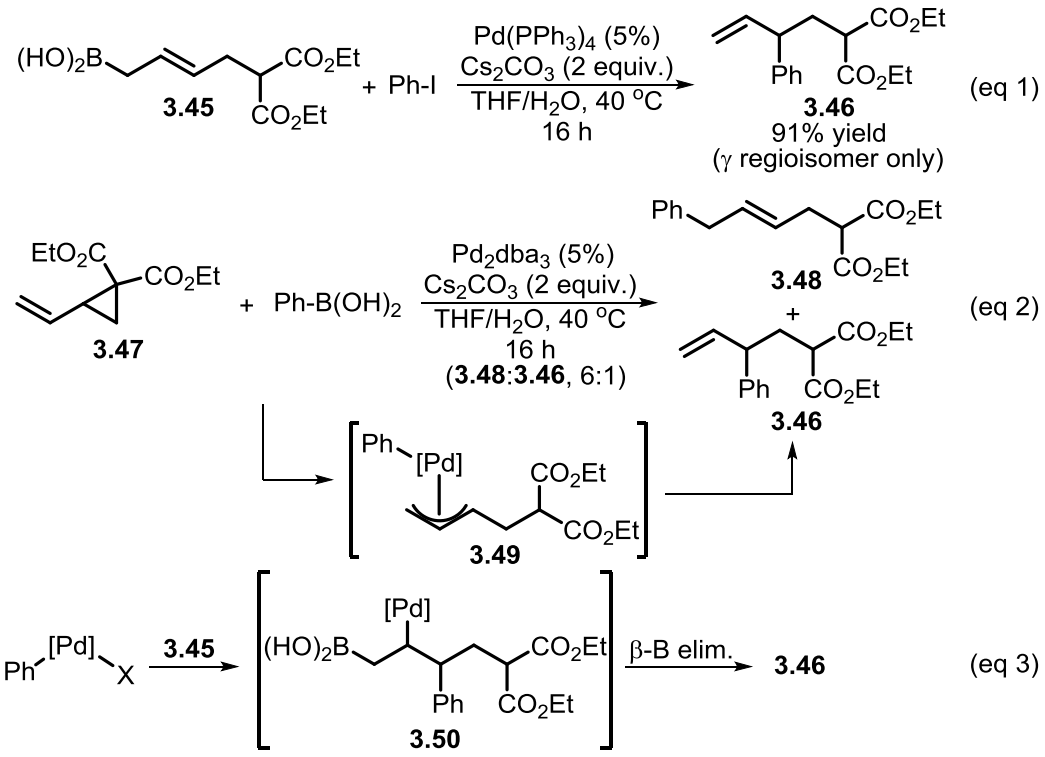


An important extension to the use of allyl boronates in cross-coupling is the ability to utilize substituted allyl partners to arrive at a greater range of products. This introduces the issue of regioselectivity when coupling with electrophiles, as bond formation can occur at either the α-position (carbon bound to boron in the substrate) or the γ-position (distill olefinic carbon in the substrate). In 2006, Szabó disclosed the first report of highly γ-selective coupling between terminal allyl boronic acids and aryl electrophiles (Scheme 3.11, equation 1).[28] Seeking to learn more about the origin of regioselectivity in these reactions, an experiment was performed in which the character of the coupling partners was reversed (equation 2). Oxidative addition to **3.47** and transmetallation of phenyl boronic acid should result in formation of Pd(II) π-allyl intermediate **3.49**, intercepting the same palladium species that could be formed in equation 1. Notably, the regioselectivity is reversed in equation 2 relative to equation 1, favoring terminal addition product **3.48** over **3.46**. In light of this result, the authors conclude that the exclusive formation of γ-product **3.46** in equation 1 likely does not arise through formation of palladium π-allyl intermediate **3.49**, although the different

[28] Sebelius, S.; Olsson, V. J.; Wallner, O. A.; Szabó, K. J. *J. Am. Chem. Soc*. **2006**, *128*, 8150.

supporting ligands involved with equations 1 and 2 was not discussed. Alternatively, Szabó and coworkers proposed that the reaction of **3.45** and iodobenzene proceeds through a highly regioselective Heck type addition, which is terminated with β-boryl elimination to give **3.46** (equation 3).

Scheme 3.11: Highly γ-Selective Coupling of Allyl Boronic Acids by Szabó

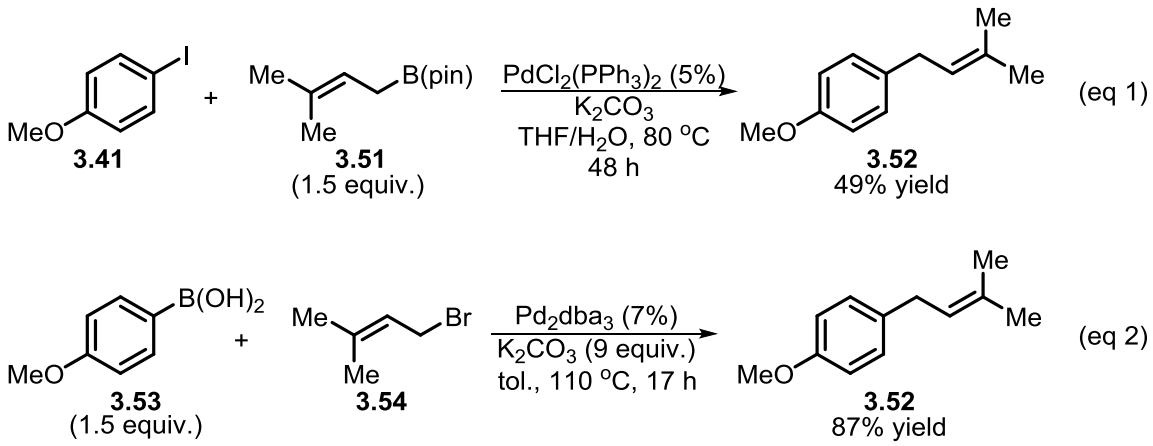


In 2009, Schmalz and Podestá reported the use of prenylboronate **3.51** in Suzuki-Miyaura cross-coupling reactions with iodoarenes as shown in Scheme 3.12.[29] Though the authors do not include any discussion regarding the regioselectivity of the reaction, isolated yields of the α coupling adducts were moderate in most cases (equation 1). The authors examined a variety of coupling conditions for both allyl boronates and aryl electrophiles as well as the reversed pairing of allyl bromides and aryl boronic acids

[29] Gerbino, D. C.; Mandolesi, S. D.; Schmalz, H-G.; Podestá, J. C. *Eur. J. Org. Chem*. **2009**, 3964.

(equation 2). Upon obtaining higher yields with the use of allyl electrophiles and aryl boronic acids, Schmalz and Podestá conclude this is the ideal substrate pairing, although it is instructive to point out that more efficient conditions reported by Kotha[26] were not examined and the overall yields of allylated arenes are on the order seen by Hallberg[23] more than 20 years earlier!

Scheme 3.12: Prenylation of Arenes by Suzuki-Miyaura Cross-Coupling by Schmalz and Podestá

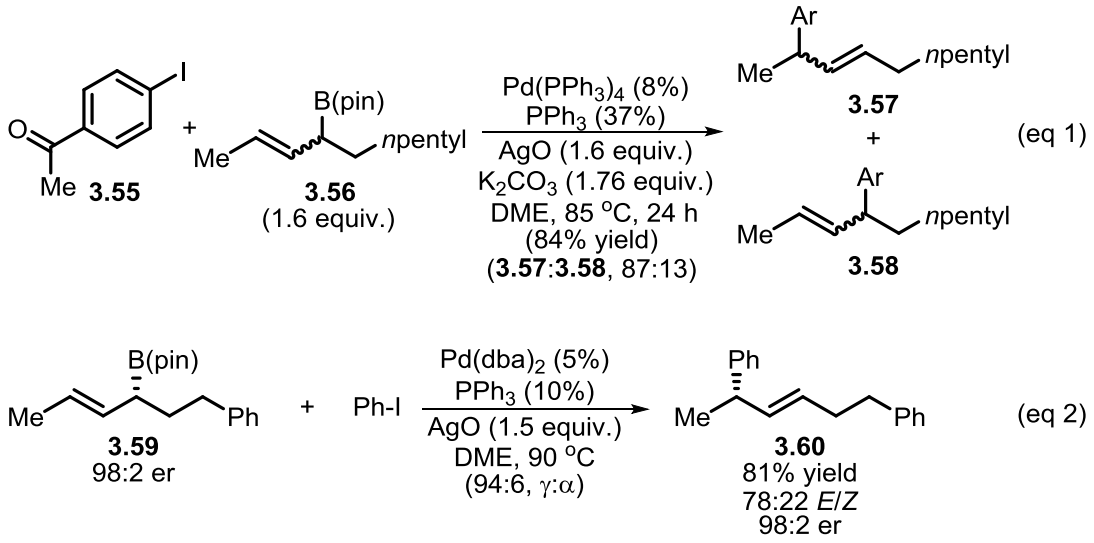


More recently, the Crudden group reported the successful cross-coupling of internal allyl pinacol boronates with aryl iodides (Scheme 3.13).[30] The authors found that the regioselectivity of the reaction was dictated primarily by the relative steric size of the groups attached to the allyl boronate. For example, aryl iodide **3.55** was coupled to allyl pinacol boronate **3.56** in good yield and with moderate regioselectivity, with the major isomer **3.57** derived from bond formation adjacent to the smaller methyl group (equation 1). Notably, the allyl boronate substrates as well as the arylated products are chiral and hold the potential to be applied towards asymmetric synthesis. Recognizing this

[30] Glasspoole, B. W.; Ghozati, K.; Moir, J. W.; Crudden, C. M. *Chem. Commun*. **2012**, *48*, 1230.

potential, the Crudden group later teamed up with Aggarwal and coworkers to utilize enantioenriched internal allyl boronates in Suzuki-Miyaura cross-coupling (equation 2).[31] Importantly, complete retention of configuration was obtained when enriched allyl boronate **3.59** was coupled with iodobenzene utilizing slightly modified conditions from the 2012 report.

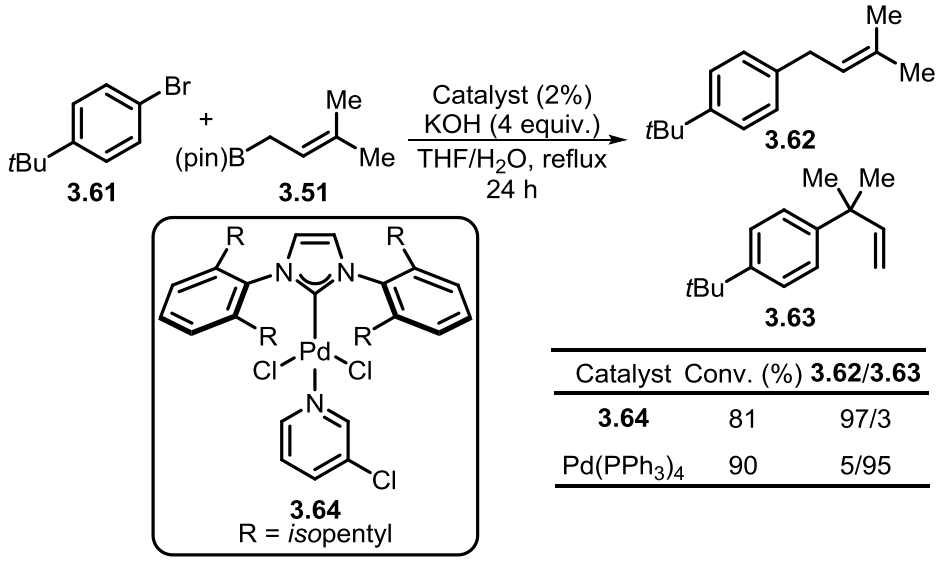
Scheme 3.13: Suzuki-Miyaura Cross-Coupling of Internal Allyl Boronates by Crudden



Building upon Smaltz and Podestá's 2009 report,[29] the Organ group reported the highly α-selective coupling of 3,3-disubstituted allyl pinacol boronates with a variety of aryl electrophiles (Scheme 3.14).[32] With the use of bulky Pd-PEPPSI pre-catalyst **3.64**, highly regioselective prenylation of aryl bromide **3.61** is accomplished (equation 1). Notably, the regioselectivity was highly dependent upon the choice of catalyst, with the use of $Pd(PPh_3)_4$ leading to γ-coupling adduct **3.63** as the major product under the same conditions. Seeking to better understand the unique reactivity obtained with

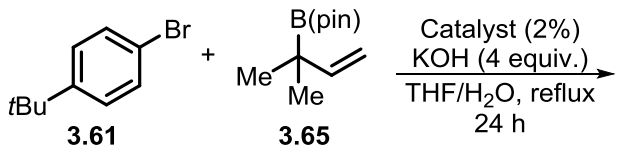
[31] Chausset-Boissarie, L.; Ghozati, K.; LaBine, E.; Chen, J. L-Y.; Aggarwal, V. K.; Crudden, C. M. *Chem. Eur. J.* **2013**, *19*, 17698.
[32] Farmer, J. L.; Hunter, H. N.; Organ, M. G. *J. Am. Chem. Soc*. **2012**, *134*, 17470.

Scheme 3.14: Highly α-Selective Prenylation of Aryl Halides by Organ



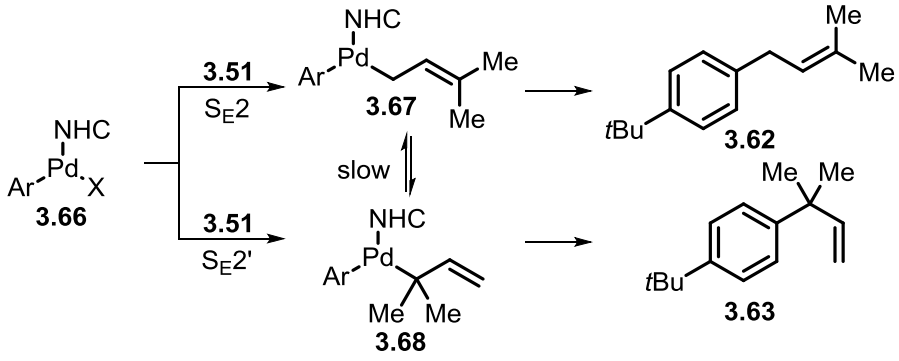
Catalyst	Conv. (%)	**3.62**/**3.63**
3.64	81	97/3
$Pd(PPh_3)_4$	90	5/95

(eq 1)



Catalyst	Conv. (%)	**3.62**/**3.63**
3.64	6	100/0
$Pd(PPh_3)_4$	30	30/70

(eq 2)

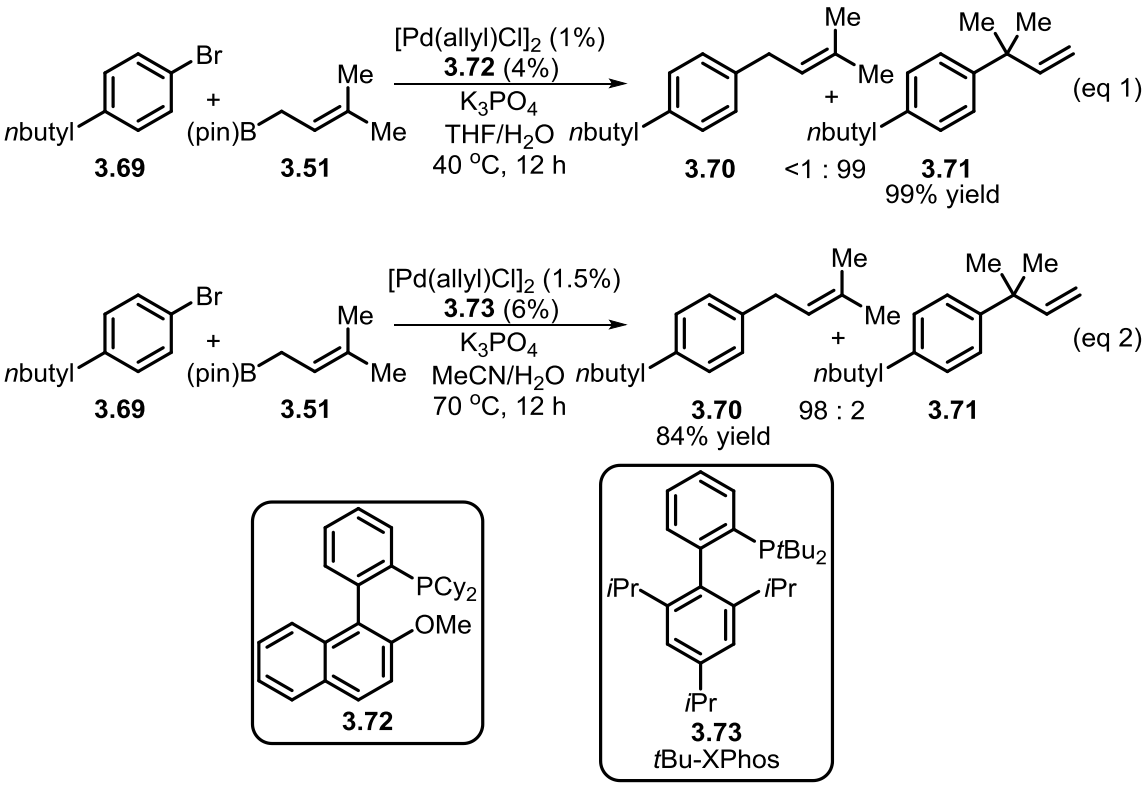


(eq 3)

pre-catalyst **3.64**, Organ and coworkers prepared tertiary allyl boronate **3.65** and examined its use under the standard conditions (equation 2). With the use of the Pd-PEPPSI pre-catalyst **3.64**, almost no conversion is observed, leading the authors to conclude that transmetallation in this system likely proceeds through an S_E2 rather than an S_E2' mechanism. The lack of efficient olefin scrambling in cases with stereodefined *E* or *Z* allyl boronates points to slow π-σ-π isomerization relative to reductive elimination

(equation 3). The increased product formation with the use of $Pd(PPh_3)_4$ in equation 2 could be derived from more efficient S_E2' transmetallation relative to **3.64**.

Scheme 3.15: Regiodivergent Suzuki-Miyaura Cross-Coupling with Prenyl Boronates by Buchwald



Recently, the Buchwald group examined the use of dialkylbiaryl phosphines for prenylation reactions of aryl and heteroaryl halides.[33] Noting the work of Organ, the authors recongnized the opportunity to develop a set of regiodivergent conditions for coupling prenyl pinacol boronates by properly tuning the ligand. Importantly, with the use of 2-methoxynaphthyl substituted **3.72**, nearly complete γ selectivity was obtained under relatively mild conditions (Scheme 3.15, equation 1). Alternatively, the use of tertbutyl XPhos **3.73** resulted in a complete reversal of regioselectivity, affording α

[33] Yang, Y.; Buchwald, S. L. *J. Am. Chem. Soc.* **2013**, *135*, 10642.

coupling product **3.70** under slightly modified conditions (equation 2). The authors speculate that while most systems typically afford the γ coupling product **3.71**, the selective formation of α product **3.70** can be explained by the reluctance of the bulky **3.73** derived catalyst to form branched σ-allyl species that are required for γ product formation.

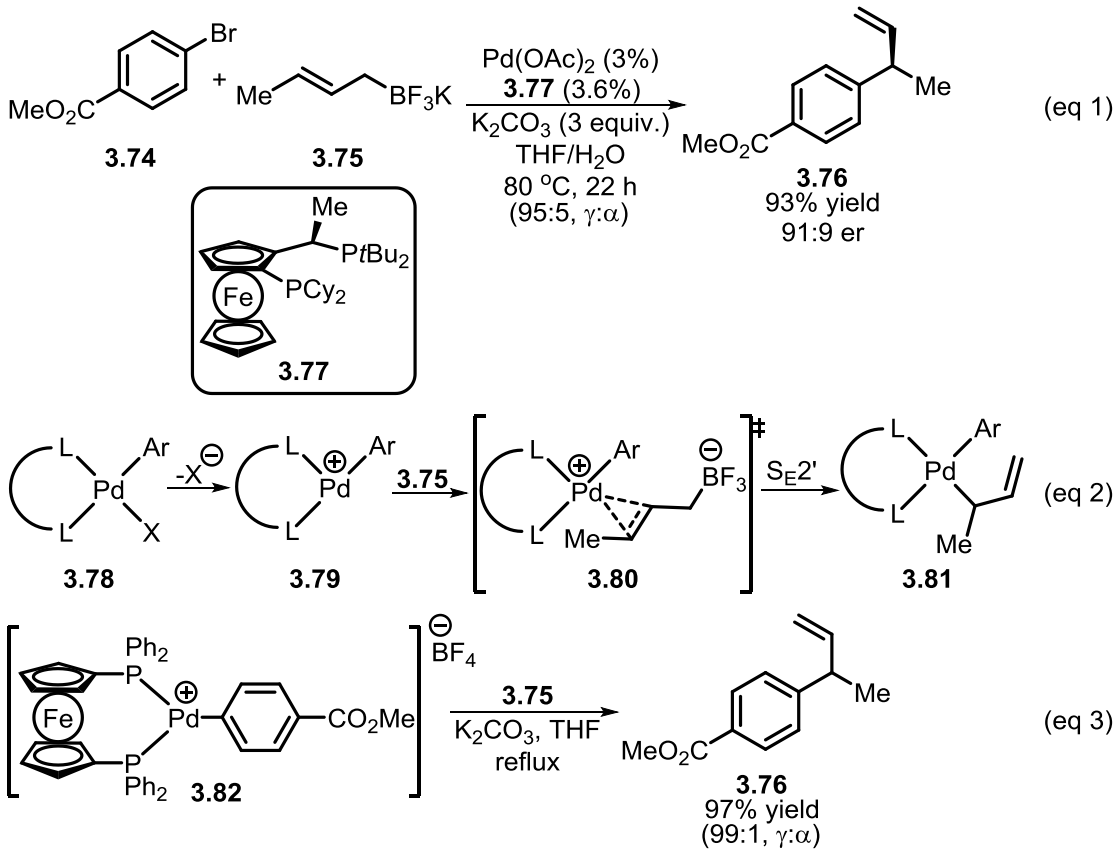
3.2.3 Enantioselective Coupling of Allyl Boronates and Aryl Electrophiles

Although there have been a number of successful cross-coupling reactions between aryl electrophiles and allyl boronate nucleophiles, the only enantioselective example of this reaction remains the work of Miyaura.[34] Utilizing electron rich and sterically hindered Josiphos derivative **3.77**, highly regioselective coupling of *trans*-crotyl trifluoroborate **3.75** and a variety of aryl bromides was achieved (Scheme 3.16). For example, aryl bromide **3.74** smoothly underwent cross-coupling to afford the desired crotylated product **3.76** with good regiocontrol and with good levels of enantioselectivity (equation 1).

In a follow-up report, Miyaura and coworkers investigated the mode of stereoselection during the coupling reaction.[35] Utilizing a variety of *p*-substituted aryl bromides, the corresponding Pd(II) adducts were prepared and treated with crotyl boronate **3.75 (**equation 2). From the relative reaction rates obtained for the conversion of Pd(II) intermediate **3.78** to the coupled products, a Hammett plot was generated which gave a ρ value of -0.7, indicating a buildup of positive charge in the rate-determining

[34] Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett*. **2006**, *35*, 1368.
[35] Yamamoto, Y.; Takada, S.; Miyaura, N. *Organometallics* **2009**, *28*, 152.

Scheme 3.16: Enantioselective Coupling of Crotyl Trifluoroborates and Aryl Bromides by Miyaura



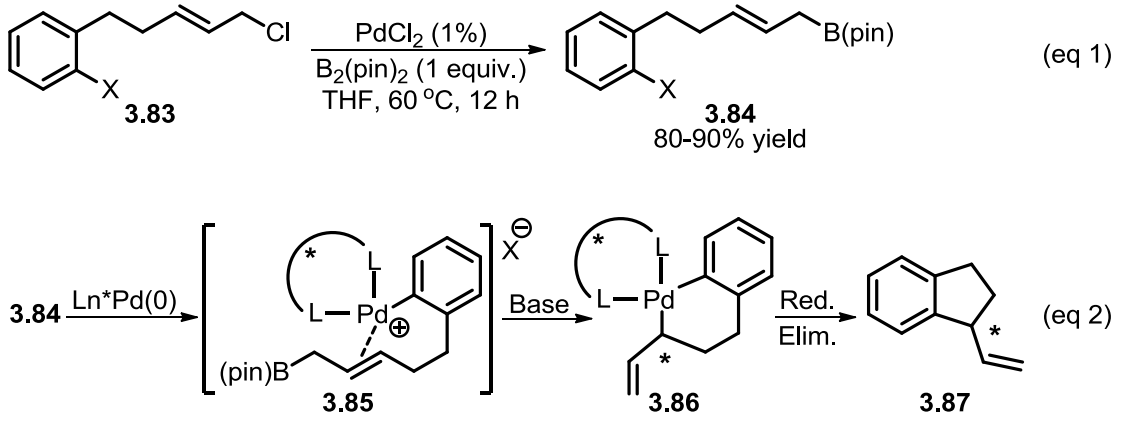
step. Together with information obtained from DFT calculations, Miyaura and coworkers propose that Pd(II) intermediates **3.78** first undergo rate-limiting loss of bromide to give cationic intermediate **3.79** (equation 2). Subsequent stereochemical determining transmetallation through open transition state **3.80**, followed by rapid reductive elimination affords the desired product. To further support this hypothesis, cationic aryl palladium **3.82** was prepared and subjected to the standard cross-coupling conditions (equation 3). Upon workup, the desired crotylated product **3.76** was obtained in excellent yield and as a single regioisomer, corroborating the formation of cationic palladium intermediates in the catalytic reaction.

3.3 Development of an Enantioselective Intramolecular Suzuki-Miyaura Coupling Utilizing Aryl Electrophiles with Tethered Allyl Boronates[36]

3.3.1 Initial Examination of Reaction Conditions

One of the most difficult aspects of performing an intramolecular coupling is gaining access to substrates which have both electrophilic and nucleophilic components in the same molecule.[37] While there are many routes to allyl boronates from various starting materials,[38] most of the reaction conditions involved do not tolerate the presence of an aryl halide. Importantly, this issue was overcome with the use of a mild borylation method developed by the Morken lab which utilizes allyl electrophiles such as **3.83** (Scheme 3.17, equation 1).[39]

Scheme 3.17: Substrate Preparation and Proposed Intramolecular Coupling Reaction

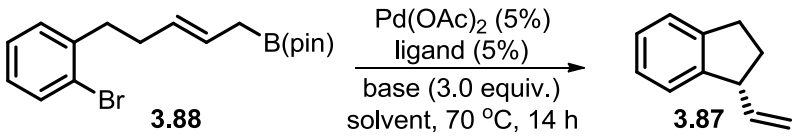


[36] Schuster, C. H.; Coombs, J. R.; Kasun, Z. A.; Morken, J. P. (*Manuscript in preparation*).
[37] For a highly useful strategy for *in situ* formation of nucleophile-electrophile pairs followed by direct intramolecular coupling, see: Kelly, T. R.; Li, Q.; Bhushan, V. *Tetrahedron Lett.* **1990**, *31*, 161.
[38] For a recent example from allyl magnesiums, see: (a) Clary, J. W.; Rettenmaier, T. J.; Snelling, R.; Bryks, W.; Banwell, J.; Wipke, N. T.; Singaram, B. *J. Org. Chem*. **2011**, *76*, 9602. From vinyl boronates: (b) Matteson, D. S.; Majumdar, D. *J. Am. Chem. Soc*. **1980**, *102*, 7588. (c) Brown, H. C.; Singh, S. M.; Rangaishenvi, M. V. *J. Org. Chem*. **1986**, *51*, 3150. (d) Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc*. **2010**, *132*, 4025. From allyl electrophiles: (e) Dutheuil, G.; Selander, N,; Szabó, K. J.; Aggarwal, V. K. *Synthesis* **2008**, 2293. (f) Guzman-Martinez, A.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2010**, *132*, 10634. (g) Larsson, J. M.; Szabó, K. J. *J. Am. Chem. Soc*. **2013**, *135*, 443. From 1,3-dienes: (h) Wu, J. Y.; Moreau, B.; Ritter, T. *J. Am. Chem. Soc*. **2009**, *131*, 12915. (i) Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc*. **2010**, *132*, 2534. From olefins: (j) Kiesewetter, E. T.; O'Brian, R. V.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. *J. Am. Chem. Soc*. **2013**, *135*, 6026.
[39] Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett*. **2012**, *14*, 1416.

With convenient access to allyl boronate substrates such as **3.84**, approaches to the intramolecular Suzuki-Miyaura coupling were considered. After oxidative addition, formation of cationic palladium intermediate **3.85** would be in line with observations by Miyaura in the related intermolecular systems (equation 2).[35] Accordingly, the use of suitable bidentate ligands should allow for selective binding of the tethered prochiral allyl boronate moiety, followed by S_E2' transmetallation to establish the new carbon-palladium bond in an enantioselective fashion. In a similar fashion to Miyaura's case, a rapid reductive elimination from σ-allyl intermediate **3.86** would afford the desired vinyl substituted carbocyle **3.87** without loss of the stereochemistry established during transmetallation. Importantly, unlike intermolecular counterparts, regioselectivity in the intramolecular coupling would likely be controlled by selective palladacycle formation.

Initial attempts to achieve the desired intramolecular coupling utilizing **3.88** as a model substrate are outlined in Table 3.1. The use of a variety of bidentate chiral phosphine ligands generally resulted in efficient conversion to the desired carbocyclic product **3.87** in a regioselective fashion, albeit with low levels of enantioselectivity (entries 1-6). Notably, these observations are in stark contrast to results obtained by Miyaura under similar reaction conditions for the intermolecular coupling of aryl halides and allyl boronates.[34] The use of cesium fluoride under anhydrous conditions resulted in a slight improvement in selectivity with the use of Me-DuPhos (entry 8); however, the overall levels of selectivity remained very low.

Table 3.1: Initial Examination of Bidentate Ligands for Intramolecular Coupling

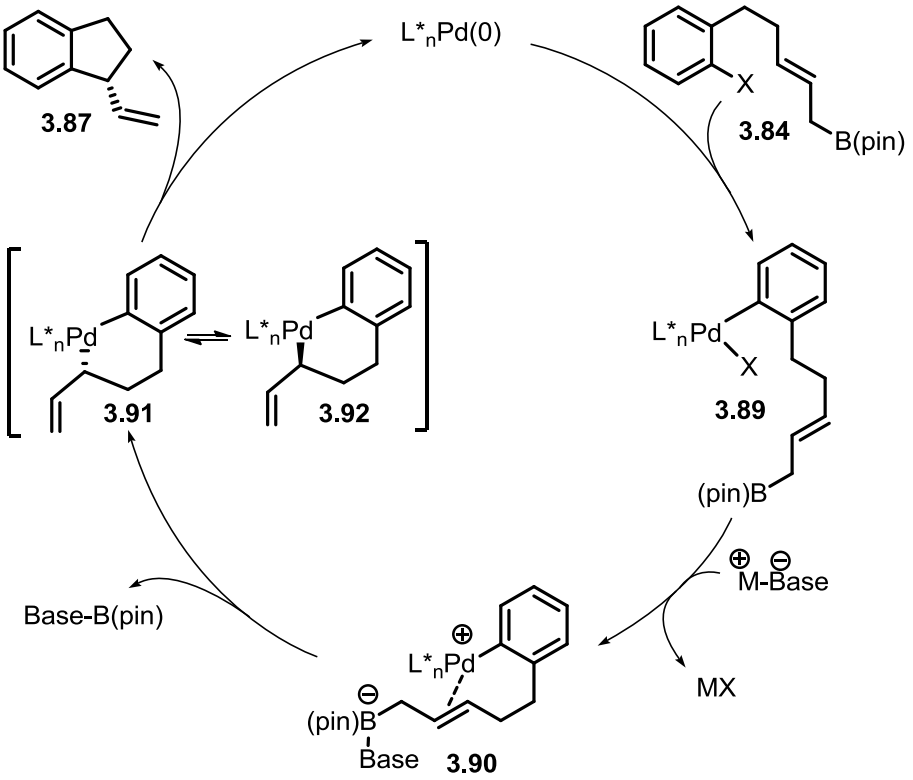


Entry	Base	Solvent	Ligand	Conv. (%)	er
1	KOH	THF/H_2O	(*R,S*)-JosiPhos	>98	51:49
2	KOH	THF/H_2O	(*S*)-Binap	>98	51:49
3	KOH	THF/H_2O	(*R,R*)-QuinoxP*	>98	56:44
4	KOH	THF/H_2O	(*R,R*)-Ph-BPE	>98	51:49
5	KOH	THF/H_2O	(*S,S*)-*i*Pr-DuPhos	>98	56:44
6	KOH	THF/H_2O	(*R,R*)-Me-DuPhos	>98	57:43
7	CsF	THF/H_2O	(*R,R*)-Me-DuPhos	63	56:44
8	CsF	THF	(*R,R*)-Me-DuPhos	>98	59:41

Seeking to uncover the origin of the poor selectivities obtained in Table 3.1, the proposed catalytic cycle for intramolecular coupling was considered (Scheme 3.18). It was reasoned that stereoselectivity could be imparted during either one of two steps during the catalytic cycle; transmetallation, or reductive elimination. As discussed above, Miyaura and coworkers found for intermolecular couplings that transmetallation was the stereochemistry determining step.[35] The Josiphos-based catalyst was able to effectively select one of the prochiral faces of the crotyl boronate, followed by S_E2' transmetallation to establish a palladium-carbon bond in an enantioselective fashion. To suppress competing allyl isomerization, a subsequent rapid reductive elimination of the product was found to be essential to achieve high regio- and enantioselectivity. In the intramolecular case, it is possible that a similar mode of selectivity is operative and the low selectivities could be attributed to either poor facial selectivity in the transmetallation

step, or to racemization of the σ-allyl palladium **3.91** through π-σ-π isomerization prior to reductive elimination.[40]

Scheme 3.18: Proposed Catalytic Cycle of Intramolecular Allyl-Aryl Coupling



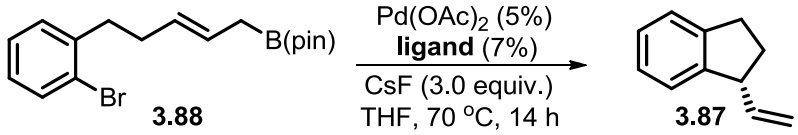
3.3.2 Attempts to Utilize Allyl Isomerization to Improve Enantioselectivity

While either one of these two pathways potentially accounts for the poor selectivities obtained with the use of the chiral bidentate phosphine ligands examined in Table 3.1, the allyl isomerization pathway provides a way forward in the event of non-selective transmetallation. Notably, the use of bidentate phosphine ligands results in the formation of 18 electron palladium π-allyl intermediates during isomerization from **3.91** to **3.92**. It was postulated that the employment of monodentate ligands might allow for

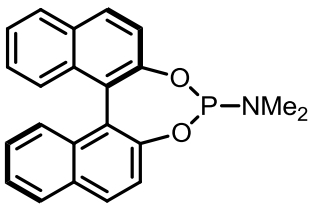
[40] For selected reviews featuring allyl-Pd intermediates, see: (a) Jolly, P. W. *Angew. Chem. Int. Ed*. **1985**, *24*, 283. (b) Trost, B. M.; Van Vranken, D. L. *Chem. Rev*. **1996**, *96*, 395. (c) Pregosin, P. S.; Salzmann, R. *Coord. Chem. Rev*. **1996**, *155*, 35.

more facile isomerization through lower energy 16 electron π-allyl species. Following this hypothesis, a series of monodentate chiral phosphorus ligands were then evaluated (Table 3.2). While the use of BINOL-derived phosphoramidites **3.93**-**3.96** resulted in low levels of enantioselectivity, the use of TADDOL-derived ligands proved fruitful, generally affording superior levels of selectivity compared to those obtained with bidentate phosphine ligands. Dimethylamino phosphoramidite **3.98** gave marginally higher selectivity than the corresponding phenyl phosphonite **3.97**, and augmentation of the TADDOL size resulted in a slight improvement as well (**3.99**). The use of larger amino groups provided significantly less selective coupling (**3.100**), and thus **3.99** was identified as the optimal ligand.

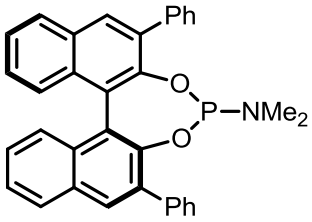
Table 3.2: Examination of Chiral Monodentate Phosphorus Ligands



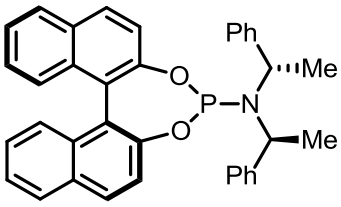
3.88 **3.87**



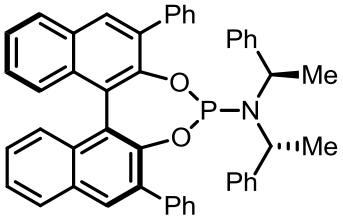
3.93
>98% conv.
50.4:49.6 er



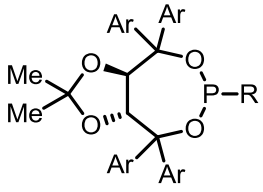
3.94
40% conv.
50.8:49.2 er



3.95
>98% conv.
55.5:44.5 er



3.96
>98% conv.
49.2:50.8 er

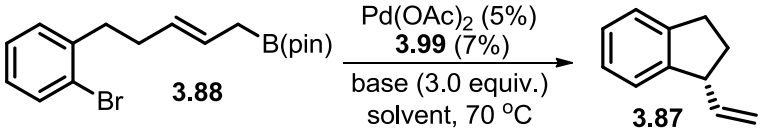


	conv. (%)	er
3.97	>98	82:18
3.98	>98	83:17
3.99	>98	84:16
3.100	>98	71:29

3.97: Ar = 3,5-dimethylphenyl, R = -Ph
3.98: Ar = 3,5-dimethylphenyl, R = -NMe_2
3.99: Ar = 3,5-di*t*butylphenyl, R = -NMe_2
3.100: Ar = 3,5-di*t*butylphenyl, R = -piperidine

In an effort to further improve reaction efficiency, additional conditions were examined (Table 3.3). While promoting efficient ring closure in most cases, the use of bases other than CsF gave inferior levels of enantioselectivity (entries 1-5). Similarly, both polar (entries 3, 6-8) and non-polar (entries 9 and 10) solvents proved to be suitable reaction media, with THF affording the best selectivity. The wide range of selectivities obtained with the use of various bases is puzzling, and perhaps suggests other roles, in addition to boron activation, are operative.

Table 3.3: Further Examination of Reaction Conditions

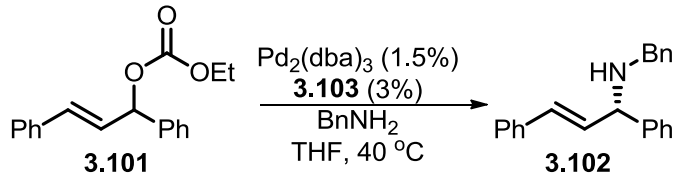


Entry	Base	Solvent	Conv. (%)	er
1	Cs_2CO_3	THF	>98	68:32
2	K_3PO_4	THF	>98	56:44
3	CsF	THF	>98	84:16
4	KF	THF	24	76:24
5	TBAF	THF	>98	46:54
6	CsF	MeCN	>98	61:39
7	CsF	EtOAc	74	83:17
8	CsF	dioxane	>98	82:18
9	CsF	toluene	>98	74:26
10	CsF	hexane	>98	74:26

Importantly, similar observations have been made suggesting a relationship between enantioselectivity and counter ion identity in certain allylic alkylation reactions.[41] For example, Togni and coworkers reported the highly enantioselective

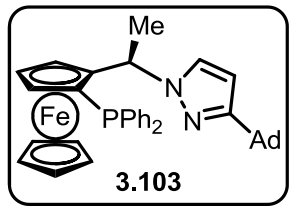
[41] Trost, B. M.; Toste, F. D. *J. Am. Chem. Soc*. **1999**, *121*, 4545.

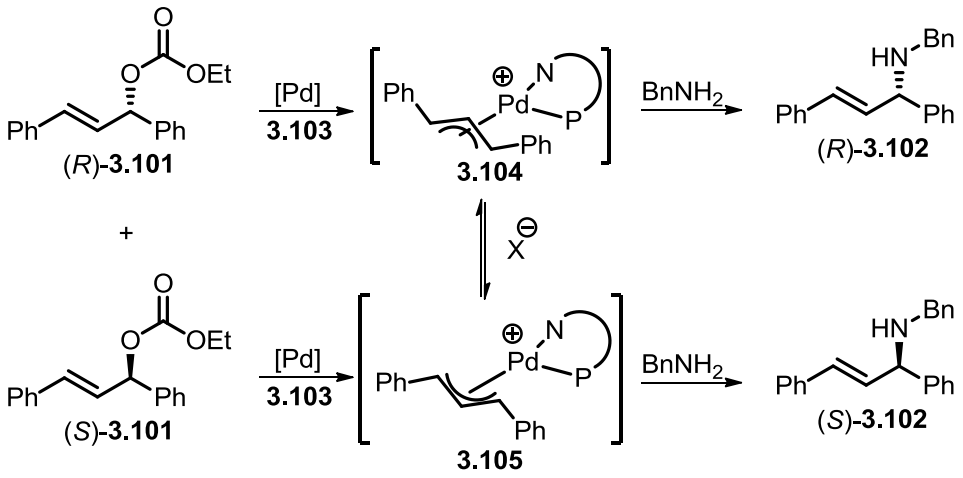
Scheme 3.19: Influence of Coordinating Anions on Allyl Isomerization by Togni



(eq 1)

Additive (2 equiv.)	er (**3.102**)
NBu_4Cl	99.5:0.5
NBu_4Br	98.5:1.5
NBu_4BF_4	95:5
NBu_4PF_6	84:16





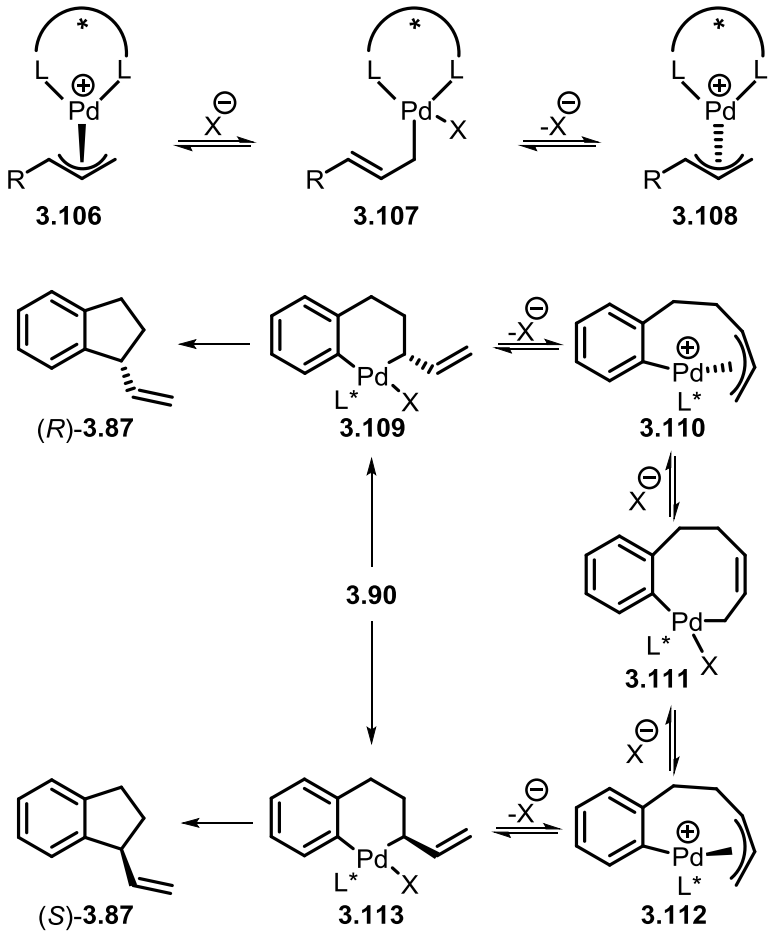
(eq 2)

palladium catalyzed allylic amination of allyl electrophile **3.101** (Scheme 3.19).[42] Utilizing ferrocene-based P-N ligand **3.103**, highly selective addition of benzyl amine was accomplished to forge the desired product **3.102** (equation 1). Interestingly, the authors found that added tetrabutylammonium salts had a strong influence on the level of selectivity obtained in the reaction, with more coordinating anions giving significantly higher selectivities than non-coordinating anions. This trend was attributed to the ability of coordinating anions to promote the interconversion between π-allyl **3.104** and π-allyl **3.105** (equation 2).[40b] With efficient interconversion, rapid collapse of both the *R*-

[42] Burckhardt, U.; Baumann, M.; Togni, A. *Tetrahedron Asymm*. **1997**, *8*, 155.

electrophile oxidative addition adduct and the *S*-electrophile oxidative addition adduct to the favored π-allyl species **3.104** occurs before external attack by benzyl amine to give the desired product **3.102**. When this interconversion is slow, attack of benzyl amine on both **3.104** and **3.105** occurs, resulting in reduced levels of enantioselecivity.

Scheme 3.20: Comparison of Lewis Base Effects on Allyl Isomerization



During allyl equilibration in palladium catalyzed allylic substitution reactions which proceed through outer sphere attack, only the electrophile component is bound to palladium.[40b,c] While this might seem obvious in the case of outer sphere nucleophile attack, it raises a key issue when seeking to equilibrate allyl systems which simultaneously have the other coupling partner attached to palladium, such as

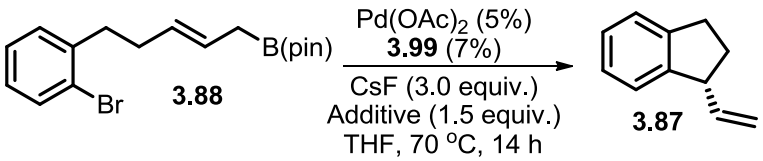
intramolecular allyl-aryl cross-coupling (Scheme 3.20). The addition of Lewis base promoters to π-allyl complex **3.106** can efficiently lead to the rapid interconversion of **3.106** and **3.108** through σ-allyl complex **3.107** without the risk of side reactions (equation 1). In the iso-electronic case of allyl-aryl coupling with monodenate ligands, the addition of sufficiently strong Lewis bases not only promotes allyl isomerization, but can also lead to accelerated reductive elimination as shown extensively in Suzuki-Miyaura cross-couplings by Amatore and Jutand.[43] In the event of a non-selective transmetallation, both σ-allyl **3.109** and σ-allyl **3.113** will be formed, with the opportunity to equilibrate to the more stable diastereomer as shown in equation 2. The relative rates of isomerization and reductive elimination are vital to achieving a selective reaction and the addition of Lewis bases which promote isomerization, but stop short of inducing reductive elimination is of paramount importance. These factors may help to explain the results obtained in the base screen shown in Table 3.3, with the F^- from cesium fluoride striking a beneficial balance between promoting isomerization versus reductive elimination (entry 3), while the F^- derived from tetrabutylammonium fluoride may detrimentally promote reductive elimination (entry 5).[43b]

Seeking to strike a balance between promoting isomerization and avoiding rapid reductive elimination, a variety of Lewis base additives were examined (Table 3.4). While the use of tetrabutylammonium chloride and bromide (entries 1 and 2), as well as lithium chloride (entry 6) resulted in slightly elevated levels of enantioselectivity, all other additives examined resulted in lower levels of enantioselectivity compared to

[43] For effects of hydroxide on reductive elimination, see: (a) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. Eur. J.* **2011**, *17*, 2492. For effects of fluoride on reductive elimination, see: (b) Amatore, C.; Jutand, A.; Le Duc, G. *Angew. Chem. Int. Ed.* **2012**, *51*, 1379.

reaction without additive. Notably, the use of lithium bromide may result in a salt methathesis with cesium fluoride, leading to formation of lithium fluoride, and thereby consuming the base and leading to no reaction (entry 7).

Table 3.4: Examination of Lewis Base Additives in Allyl-Aryl Coupling

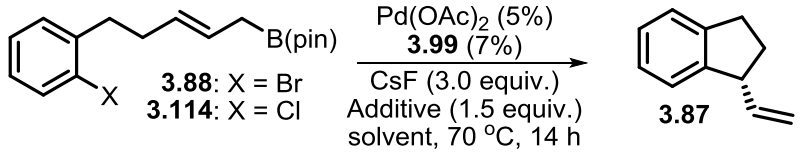


Entry	Additive	Conv. (%)	er
1	NBu_4Cl	70	90:10
2	NBu_4Br	78	87:13
3	NBu_4I	>98	57:43
4	NBu_4OAc	>98	78:22
5	Ph_3PMeBr	35	76:24
6	LiCl	>98	85:15
7	LiBr	0	-
8	CsCl	>98	82:18
9	$Ph_2MeP{=}O$	>98	83:17
10	cyclohexene	>98	81:19
11	NEt_3	>98	84:16

With tetrabutylammonium chloride yielding the best results in Table 3.4, additional ammonium chlorides were examined (Table 3.5). Unfortunately, both smaller (entry 2) and larger (entries 3 and 4) ammonium chlorides resulted in lower levels of enantioselectivity compared to tetrabutylammonium chloride (entry 1). Further examination of a variety of polar solvents resulted in no further improvement (entries 5-8). Notably, the use of aryl bromides as substrates results in the release of bromide salts into the reaction mixture as oxidative addition takes place. With chloride based additives generally providing higher levels of enantioselectivity compared to bromide additives, it

was reasoned the use of aryl chlorides could possibly result in a more selective coupling reaction. Indeed upon utilizing aryl chloride **3.114**, elevated levels of enantioselectivity were obtained (entry 9), which were further augmented with the use of tetrabutylammonium chloride (entry 10). Unfortunately, the use of additives often resulted in less efficient coupling, with incomplete conversions observed. Taken together, the use of aryl chlorides without additive was found to yield the best results, achieving full conversion with good levels of enantioselectivity.

Table 3.5: Further Examination of Ammonium Chloride Additives

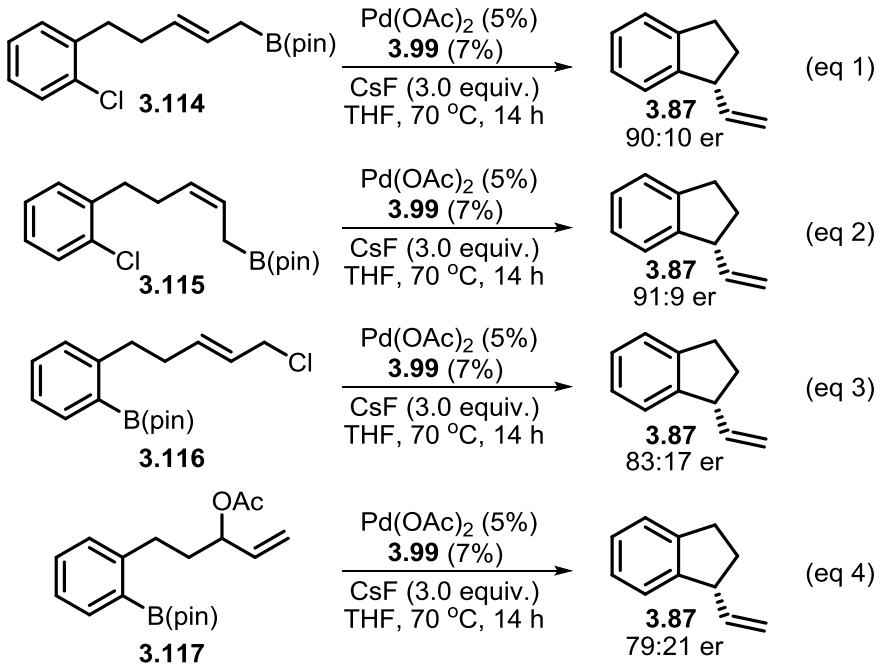


Entry	X	Additive	Solvent	Conv. (%)	er
1	Br	NBu_4Cl	THF	70	90:10
2	Br	NEt_4Cl	THF	>98	81:19
3	Br	*n*tetradecylNMe_3Cl	THF	>98	78:22
4	Br	Aliquat 336	THF	>98	68:32
5	Br	NBu_4Cl	dioxane	>98	84:16
6	Br	NBu_4Cl	MeCN	>98	72:28
7	Br	NBu_4Cl	Me-THF	>98	86:14
8	Br	NBu_4Cl	MTBE	>98	80:20
9	Cl	-	THF	>98	90:10
10	Cl	NBu_4Cl	THF	45	93:7

To test whether the proposed mode of enantioselection shown in Scheme 3.20 is operative, a series of substrates were prepared in which the nucleophile and electrophile pairings were adjusted (Scheme 3.21). If transmetallation was stereodetermining in the intamolecular coupling, following the intermolecular precedent established by Miyaura,[35] it was reasoned that changing the geometry of the allyl boronate moiety should have a

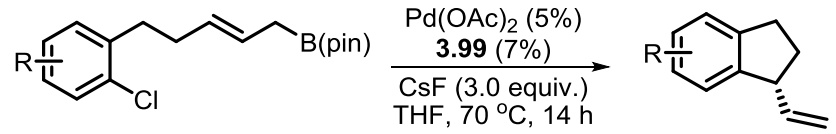
significant impact on the stereochemical outcome of the coupling reaction. Importantly, employing the *E*-allyl boronate **3.114** under the standard reaction conditions produces the same enantiomer of product that is observed when the *Z*-allyl boronate **3.115** is used, and with nearly identical levels of selectivity (equations 1 and 2). Additionally, the use of substrates with electronically inverse coupling partners also resulted in formation of the same enantiomer of product, albeit with lower levels of enantioselectivity, possibly due to the need to correct for the initial stereochemistry established during oxidative addition (equations 3 and 4). Since the likelihood of achieving similar levels of selectivity during transmetallation of vastly different species is remote, it seems probable that allyl equilibration of the transmetallation adducts results in stereochemical convergence to a common palladacycle intermediate **3.91**, followed by reductive elimination to give the desired carbocycle **3.87**.

Scheme 3.21: Examination Alternative Coupling Partners for Allyl-Aryl Coupling



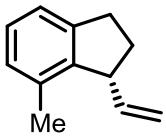
3.3.3 Scope of Enantioselective Intramolecular Allyl-Aryl Coupling

Table 3.6: Scope of Enantioselective Intramolecular Allyl-Aryl Coupling

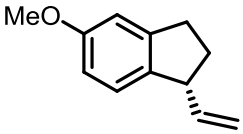


3.87
76% yield (90%)[a]
90:10 er

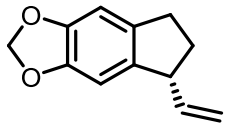
3.118
68% yield
93:7 er



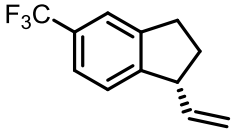
3.119
64% yield
69:31 er (83:17)[b]



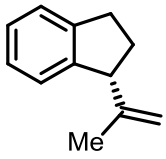
3.120
76% yield
90:10 er



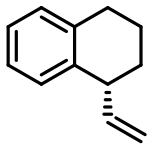
3.121
52% yield
92:8 er



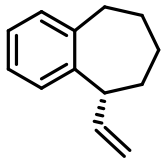
3.122
56% yield
75:25 er (88:12)[c]



3.123
80% yield
77:23 er



3.124
53% yield
86:14 er



3.125
49% yield
62:38 er

(a) Yield determined by ^{1}H NMR versus internal standard (b) selectivity obtained with use of aryl bromide with NB_4Cl (1.5 equiv.) (c) selectivity obtained with NBu_4Cl (1.5 equiv.)

With an improved understanding of the mode enantioselection, the scope of the intramolecular allyl-aryl coupling reaction was examined (Table 3.6). Substrates containing substitution *meta* relative to the site of carbocycle formation gave enhanced enantioselectivities (**3.118** and **3.121**), while substitution in the *ortho* position **3.119** led to lower levels of selectivity, possibly due to enhanced rates of reductive elimination. Importantly, the use of the corresponding aryl bromide with added tetrabutylammonium chloride can enhance selectivity to achieve moderate levels of enantioinduction for this

more challenging substitution pattern. Both electron rich (**3.120**) and electron poor (**3.122**) substrates engage smoothly in intramolecular coupling, with electron poor substrates benefiting from the use of tetrabutylammonium chloride, albeit with low conversion of the starting material. Notably, substitution on the allyl boronate moiety is well tolerated and **3.123** is produced in good yield and with moderate enantioselectivity. Changing the tether length between the aryl electrophile and the allyl boronate allows for efficient formation of both 6- (**3.124**) and 7-membered rings (**3.125**) in moderate yield and with moderate levels of enantioselectivity. Considering allyl isomerization presumably proceeds through 9 and 10 membered palladacycles for the formation of **3.124** and **3.125** respectively, the observation of enantioselectivity of any kind for formation of these products is quite remarkable.

3.4 Conclusion

The development of the first example of enantioselective intramolecular Suzuki-Miyaura coupling between aryl electrophiles and tethered allyl boronates has been accomplished. Moderate to good levels of enantioselectivity were obtained when employing monodentate TADDOL-derived phosphoramidite ligands to give the desired carbocyclic products as single regioisomers in moderate to good yields. Further investigation utilizing various coupling partners uncovered a novel mode of enantioinduction through rapid allyl-equilibration prior to reductive elimination. Notably, this unique feature is in stark contrast to the features governing selectivity in Miyaura's intermolecular case, and points to possible applications in future reaction development.

3.5 Experimental Section

3.5.1 General Information

^{1}H NMR spectra were measured using a Varian Gemini-500 (500 MHz) spectrometer 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). $^{13}C\{^{1}H\}$NMR spectra were measured using a Varian Inova 500 (126 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.0 ppm). $^{31}P\{^{1}H\}$NMR spectra were measured using a Varian Inova 500 (202 MHz) spectrometer. Chemical shifts are reported in ppm using phosphoric acid as the external standard (H_3PO_4: 0.0 ppm). Infrared (IR) spectra were measured using 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) was performed at Boston College, Chestnut Hill, MA.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO_2, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography was performed on 25 μm silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm), phosphomolybdic acid (PMA), potassium permanganate ($KMnO_4$), and Seebach's "magic" stain (phosphomolybdic acid, $Ce(SO_4)_2$, sulfuric acid). Analytical chiral gas-liquid chromatography (GLC) was also performed on an Agilent Technologies 6850 Series

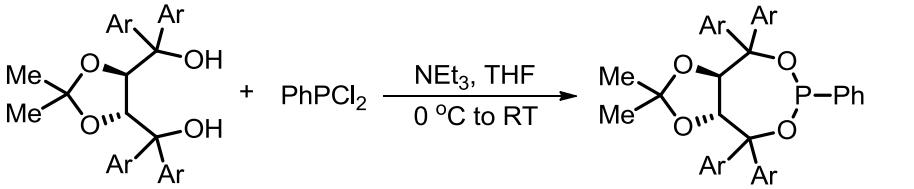
chromatograph with a flame ionization detector, and a Supelco β –Dex 120 column with helium as the carrier gas. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar Supercritical Chromatograph equipped with auto sampler and a Waters photodiode array detector with methanol as the modifier.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran, dichloromethane and diethyl ether 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. Dimethylformamide was dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC). Triethylamine was purchased from Aldrich and refluxed over calcium hydride prior to use. Palladium acetate ($Pd(OAc)_2$), rhodium cyclooctadiene chloride dimer ($[RhCl(COD)]_2$), phosphorus trichloride, and triisopropyl phosphine were purchased from Strem Chemicals and used as received. Catechol borane, (*R*,*R*)-tartaric acid, 2,2'-bipyridine, and 3,5-ditertbutylbromobenzene were purchased from Alfa Aesar and used as received. $B_2(pin)_2$ was obtained from AllyChem and recrystallized from pentane prior to use. 2-Iodobromobenzene and 2-Iodochlorobenzene were purchased from Matrix Scientific and used as received. All other reagents were obtained from Aldrich or Fisher and used as received.

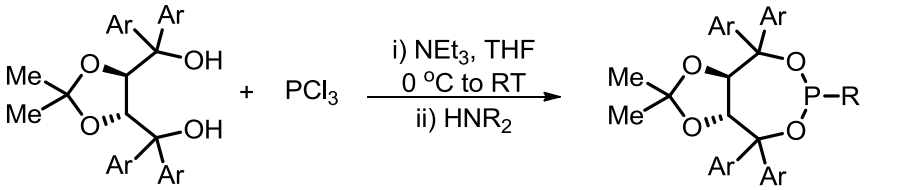
3.5.2 Experimental Procedures

3.5.2.1 Preparation of TADDOL-based ligands

Ligands **3.97, 3.98**[44], **3.99**[45], and **3.100**[46] were prepared according to the general reaction schemes shown below. All spectral data are in accordance with the literature.



3.97: Ar = 3,5-dimethylphenyl

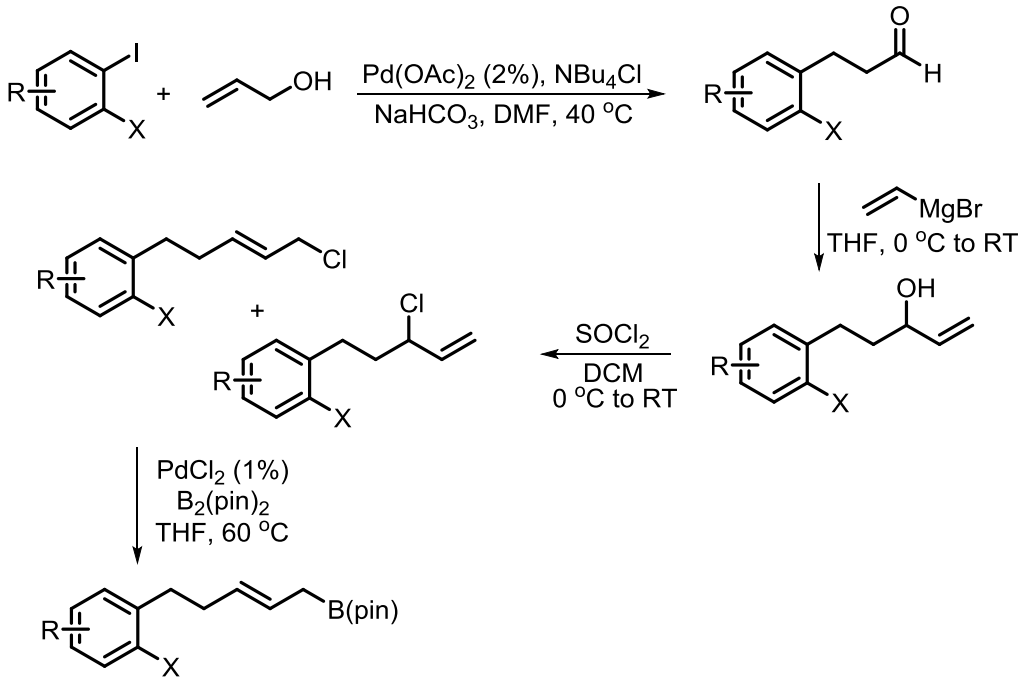


3.98: Ar = 3,5-dimethylphenyl, R = -NMe_2
3.99: Ar = 3,5-di*t*butylphenyl, R = -NMe_2
3.100: Ar = 3,5-di*t*butylphenyl, R = -piperidine

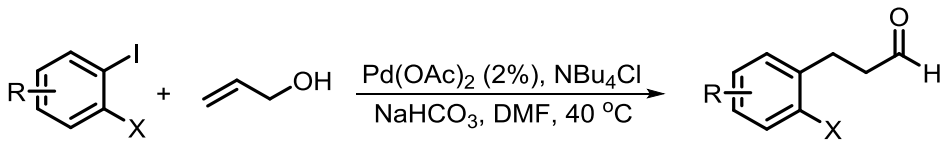
[44] Boele, M. D. K.; Kamer, P. C. J.; Lutz, M.; Spek, A. L.; de Vries, J. G.; van Leeuwen, P. W. N. M.; van Strijdonck, G. P. F. *Chem. Eur. J.* **2004**, *10*, 6232.
[45] Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. *Org. Lett.*, **2005**, *7*, 5505.
[46] Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978.

3.5.2.2 Representative procedures for preparation of starting materials

Unless otherwise noted, allyl boronate starting materials were prepared according to the general method shown below.



General procedure for aldehyde synthesis[47]

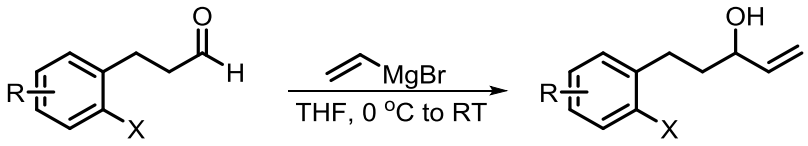


To a flame-dried round-bottomed flask equipped with magnetic stir bar in the glovebox was added $Pd(OAc)_2$ (0.02 equiv.). The flask was removed from the glovebox, charged with tetrabutylammonium chloride (1.00 equiv.) and sodium bicarbonate (2.50 equiv.) and sealed with a septum. The flask was evacuated and back-filled with nitrogen (3x) followed by addition of dimethylformamide (0.5 M). After stirring at room temperature for 10 minutes, aryl iodide (1.00 equiv.) followed by allyl alcohol (1.50 equiv.) were

[47] Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202.

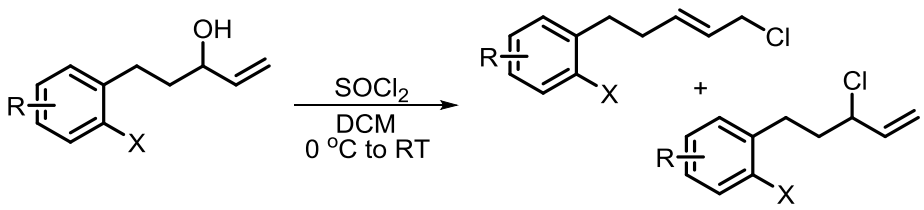
added and the resulting mixture was heated to 40 °C for 12 hours. The resulting dark reaction mixture was cooled to room temperature, diluted with diethyl ether (50 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic layers washed with a 50/50 water/brine solution (2 x 50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The pure aldehyde products were isolated after SiO_2 chromatography unless otherwise noted.

General procedure for allylic alcohol synthesis



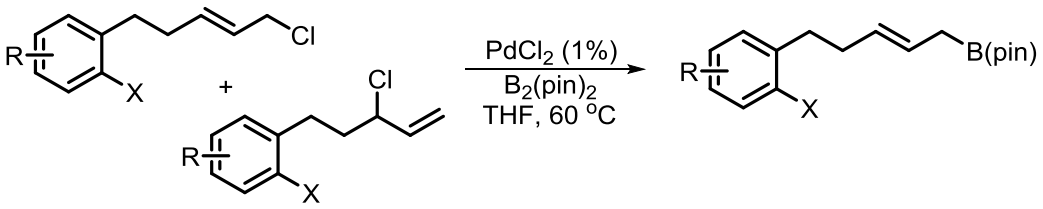
To a flame-dried round-bottomed flask equipped with magnetic stir bar under nitrogen was added vinyl magnesium bromide (1.0 M in THF, 2.00 equiv.). The solution was cooled to 0 °C (ice/water bath) and treated dropwise with aldehyde (0.5 M in THF, 1.00 equiv.). After stirring at room temperature for 1 hour, the resulting yellow solution was returned to 0 °C and excess vinyl magnesium bromide was carefully quenched with water (5 mL) followed by addition of saturated aqueous ammonium chloride (20 mL). The resulting mixture was diluted with ethyl acetate (50 mL) and water (20 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The pure allylic alcohol products were isolated after SiO_2 chromatography.

General procedure for allylic chloride synthesis



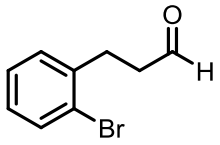
To a flame-dried round-bottomed flask equipped with magnetic stir bar under nitrogen was added thionyl chloride (10.00 equiv.). The flask was cooled to 0 ^{o}C (ice/water bath) and an outlet line was installed in order to allow continuous nitrogen flow from the inlet through the outlet line which was bubbled through a 90/10 saturated aqueous sodium bicarbonate/water solution. Allylic alcohol (0.25 M in DCM, 1.00 equiv.) was then added dropwise and stirred at 0 ^{o}C for 30 minutes. After stirring at room temperature for 2 hours, the reaction mixture was diluted with DCM and poured over solid ice (75 mL) in a separatory funnel. The layers were separated and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (75 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude material was purified *via* SiO_2 chromatography to give a mixture of internal and terminal chloride products.

General procedure for allyl-boronate synthesis[48]



To an oven-dried vial equipped with magnetic stir bar in the glovebox was added $PdCl_2$ (0.01 equiv.) followed by $B_2(pin)_2$ (1.00 equiv.) and THF (1.0 M). The resulting mixture was stirred for approximately 1 minute followed by addition of allyl chloride (mixture of regio isomers, 1.00 equiv.). The vial was sealed with a cap, removed from the glovebox and heated to 60 °C for 12 hours with vigorous stirring. After cooling to room temperature, the reaction mixture was passed through a plug of SiO_2, eluding with 10% ethyl acetate in hexane (200 mL). The resulting solution was concentrated under reduced pressure to give the crude material which was subsequently purified via SiO_2 chromatography. (NOTE: the allyl-boronate products suffer slow decomposition on SiO_2 and purification is best carried out in an expedient fashion.)

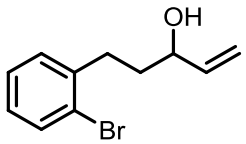
3.5.2.3 Preparation of starting materials



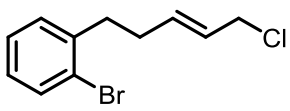
3-(2-bromophenyl)propanal. Prepared according to the general procedure utilizing $Pd(OAc)_2$ (47.6 mg, 0.212 mmol), tetrabutylammonium chloride (2.95 g, 10.6 mmol), sodium bicarbonate (2.23 g, 26.5 mmol), dimethylformamide (21 mL), 2-bromoiodobenzene (1.36 mL, 10.6 mmol), and allyl alcohol (1.10 mL, 15.9 mmol). The crude material was purified (SiO_2, 6% ethyl acetate in hexanes) to give the desired product as a clear, yellow oil (1.99 g, 88%). R_f =

[48] Zhang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett*. **2012**, *14*, 1416.

0.29 (5% ethyl acetate in hexane, UV/magic stain). All spectral data are in accordance with the literature.[49]



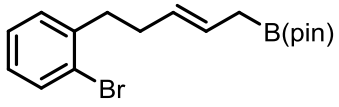
5-(2-bromophenyl)pent-1-en-3-ol. Prepared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 18.7 mL, 18.7 mmol), 3-(2-bromophenyl)propanal (1.99 g, 9.34 mmol), and THF (19 mL). The crude material was purified (SiO_2, 12% ethyl acetate in hexanes) to give the desired product as a clear, slightly yellow oil (1.94 g, 86%). R_f = 0.24 (10% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.53 (1H, dd, *J* = 7.8, 1.0 Hz), 7.26-7.21 (2H, m), 7.07-7.04 (1H, m), 5.93 (1H, ddd, *J* = 17.1, 10.3, 5.9 Hz), 5.28 (1H, ddd (app dt's), *J* = 17.1, 1.5 Hz), 5.16 (1H, ddd (app dt's), *J* = 10.3, 1.5 Hz), 4.17 (1H, ddd (app q), *J* = 6.4 Hz), 2.88 (1H, ddd, *J* = 13.7, 9.3, 5.9 Hz), 2.81 (1H, ddd, *J* = 13.7, 9.3, 6.9 Hz), 1.91-1.80 (2H, m), 1.73 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.2, 140.8, 132.8, 130.4, 127.6, 127.4, 124.4, 115.0, 72.4, 36.9, 32.0; IR (neat): 3359.9 (br), 3066.8 (w), 2931.3 (m), 2864.0 (m), 1643.6 (w), 1566.8 (w), 1470.6 (s), 1438.7 (m), 1045.4 (m), 1022.1 (s), 990.6 (m), 923.6 (s), 748.9 (s), 658.5 (m) cm^{-1}; HRMS-(DART) for: $C_{11}H_{12}Br$ $[M+H-H_2O]^+$: calculated: 223.0122, found: 223.0118.



(*E*)-1-bromo-2-(5-chloropent-3-en-1-yl)benzene. Prepared according to the general procedure utilizing thionyl chloride (2.27 mL, 31.3 mmol), 5-(2-bromophenyl)pent-1-en-3-ol (750 mg, 3.11 mmol), and

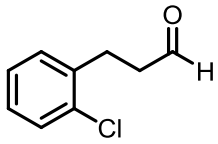
[49] Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202.

DCM (12.4 mL). The crude material was purified (SiO_2, 2% ethyl acetate in hexane) to give the desired product as a 10:1 mixture of the title compound: 1-bromo-2-(3-chloropent-4-en-1-yl)benzene (clear, colorless oil (650.4 mg, 81%). R_f = 0.78 (10% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 7.54 (1H, dd, *J* = 8.3, 1.0 Hz), 7.26-7.19 (2H, m), 7.07 (1H, ddd (app dt's), *J* = 7.3, 2.0 Hz), 5.84 (1H, dt's, *J* = 15.2, 6.9 Hz), 5.66 (1H, dtt's, *J* = 15.2, 6.9, 1.5 Hz), 4.04 (2H, d, *J* = 6.8 Hz), 2.84 (2H, t, *J* = 7.3 Hz), 2.40 (2H, dt's (app q), *J* = 7.8 Hz); (minor isomer) δ 7.54 (1H, d, *J* = 8.3 Hz), 7.26-7.19 (2H, m), 7.10-7.05 (1H, m), 5.96 (1H, ddd, *J* = 17.1, 10.3, 7.8 Hz), 5.32 (1H, d, *J* = 17.1 Hz), 5.19 (1H, d, *J* = 10.3 Hz), 4.38 (1H, ddd (app q), *J* = 7.8 Hz), 2.95 (1H, ddd, *J* = 13.7, 9.3, 5.9 Hz), 2.89-2.82 (1H, m), 2.18-2.08 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): (both isomers (one overlapping signal)) δ 140.6, 140.1, 138.2, 134.5, 132.9, 132.8, 130.5, 130.4, 127.9, 127.7, 127.5, 127.4, 126.8, 124.4, 116.9, 62.2, 45.2, 37.9, 35.5, 33.1, 32.1; IR (neat): 3054.3 (w), 3037.0 (w), 3011.4 (w), 2950.5 (m), 2931.3 (m), 2860.6 (w), 1665.2 (m), 1592.5 (w), 1566.8 (m), 1470.6 (s), 1438.7 (s), 1249.7 (m), 1023.5 (s), 965.1 (s), 747.9 (s), 676.1 (s), 657.4 (s), 444.3 (m) cm^{-1}; HRMS-(DART) for: $C_{11}H_{12}Br$ $[M+H-HCl]^+$: calculated: 223.0122, found: 223.0121.

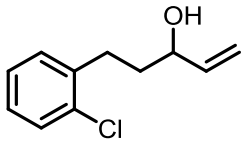


(*E*)-2-(5-(2-bromophenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizing $PdCl_2$ (4.2 mg, 0.024 mmol), $B_2(pin)_2$ (599.6 mg, 2.36 mmol), THF (2.4 mL), and (*E*)-1-bromo-2-(5-chloropent-3-en-1-yl)benzene (10:1 with regio-isomeric allyl chloride, 612.9 mg, 2.36 mmol). The crude material was purified (SiO_2, 4% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (538.0 mg, 65%).

R_f = 0.36 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (1H, d, *J* = 7.8 Hz), 7.23-7.19 (2H, m), 7.06-7.01 (1H, m), 5.55-5.43 (2H, m), 2.77 (2H, t, *J* = 7.8 Hz), 2.30 (2H, dt (app q), *J* = 5.9 Hz), 1.65 (2H, d, *J* = 6.8 Hz), 1.25 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.4, 132.7, 130.4, 129.5, 127.4, 127.2, 125.9, 124.5, 83.1, 36.4, 32.8, 24.8; IR (neat): 3057.0 (w), 2977.3 (m), 2930.1 (m), 2862.4 (w), 1664.3 (w), 1591.9 (w), 1469.8 (m), 1438.8 (m), 1359.7 (s), 1323.1 (s), 1271.9 (m), 1213.7 (m), 1164.4 (m), 1142.3 (s), 1022.7 (m), 966.1 (s), 846.6 (s), 747.4 (s), 657.5 (m), 444.9 (w) cm^{-1}; HRMS-(DART) for: $C_{17}H_{25}BBrO_2$ $[M+H]^+$: calculated: 351.1131, found: 351.1136.



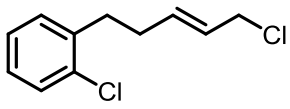
3-(2-chlorophenyl)propanal. Prepared according to the general procedure utilizing $Pd(OAc)_2$ (44.9 mg, 0.20 mmol), tetrabutylammonium chloride (2.78 g, 10.0 mmol), sodium bicarbonate (2.10 g, 25.0 mmol), dimethylformamide (20 mL), 2-chloroiodobenzene (1.22 mL, 10.0 mmol), and allyl alcohol (1.02 mL, 15.0 mmol). The crude material was purified (SiO_2, 6% ethyl acetate in hexane) to give the desired product as a clear, slightly yellow oil (1.5592 g, 92%). R_f = 0.40 (10% ethyl acetate in hexanes, UV/magic stain). All spectral data are in accordance with the literature.[50]



5-(2-chlorophenyl)pent-1-en-3-ol. Prepared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 8.00 mL, 8.00 mmol), 3-(2-chlorophenyl)propanal (674.5 mg, 4.00 mmol), and THF (8.0 mL). The crude material was purified (SiO_2, 12% ethyl acetate in hexanes) to

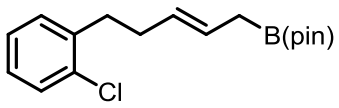
[50] Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202.

give the desired product as a clear, colorless oil (675 mg, 86%). R_f = 0.22 (10% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 (1H, dd, *J* = 7.8, 1.5 Hz), 7.25 (1H, dd, *J* = 7.3, 2.0 Hz), 7.18 (1H, ddd (app dt's), *J* = 7.8, 1.5 Hz), 7.14 (1H, ddd (app dt's), *J* = 7.8, 2.0 Hz), 5.93 (1H, ddd, *J* = 17.1, 10.3, 5.9 Hz), 5.28 (1H, ddd (app dt's), *J* = 17.1, 1.5 Hz), 5.15 (1H, ddd (app dt's), *J* = 10.3, 1.0 Hz), 4.16 (1H, ddd (app q), *J* = 5.9 Hz), 2.88 (1H, ddd, *J* = 13.7, 9.3, 6.5 Hz), 2.80 (1H, ddd, *J* = 13.7, 9.8, 6.9 Hz), 1.91-1.80 (2H, m), 1.75 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.8, 139.5, 133.9, 130.4, 129.5, 127.3, 126.8, 115.0, 72.5, 36.7, 29.5; IR (neat): 3374.8 (br), 3072.8 (w), 2929.1 (m), 2863.2 (w), 1643.6 (w), 1571.6 (w), 1474.3 (s), 1443.0 (m), 1133.3 (w), 1051.5 (s), 1031.5 (m), 990.9 (m), 923.9 (s), 750.2 (s), 679.7 (m) cm^{-1}; HRMS-(DART) for: $C_{11}H_{12}Cl$ $[M+H-H_2O]^+$: calculated: 179.0628, found: 179.0631.



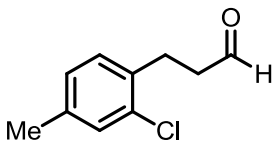
(*E*)-1-chloro-2-(5-chloropent-3-en-1-yl)benzene. Prepared according to the general procedure utilizing thionyl chloride (2.27 mL, 31.1 mmol), 5-(2-chlorophenyl)pent-1-en-3-ol (750 mg, 3.11 mmol), and DCM (12.4 mL). The crude material was purified (SiO_2, 2% ethyl acetate in hexanes) to give the desired product as a 9:1 mixture of the title compound: 1-chloro-2-(3-chloropent-4-en-1-yl)benzene (clear, colorless oil (650.4 mg, 81%)). R_f = 0.77 (10% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 7.35 (1H, d, *J* = 7.8 Hz), 7.22-7.20 (2H, m), 7.18-7.13 (1H, m), 5.84 (1H, dt's, *J* = 15.2, 6.9, 6.9 Hz), 5.66 (1H, dt's, *J* = 15.2, 7.3, 7.3 Hz), 4.04 (2H, d, *J* = 7.3 Hz), 2.84 (2H, t, *J* = 7.3 Hz), 2.40 (2H, dt's (app q), *J* = 7.3 Hz); (minor isomer) δ 7.35 (1H, d, *J* = 7.8 Hz), 7.27-7.25 (1H, m), 7.18-7.13 (2H, m), 5.96 (1H, ddd, *J* = 16.6, 10.3, 8.3 Hz), 5.32 (1H, d, *J* = 16.6

Hz), 5.19 (1H, d, J = 10.3 Hz), 4.37 (1H, ddd (app q), J = 6.9 Hz), 2.96 (1H, ddd, J = 14.2, 8.8, 6.4 Hz), 2.89-2.82 (1H, m), 2.17-2.11 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): (both isomers) δ 138.9, 138.4, 138.2, 134.6, 133.9, 133.9, 130.5, 130.4, 129.6, 129.5, 127.7, 127.4, 126.8, 126.7, 126.7, 116.8, 62.2, 45.1, 37.8, 32.9, 32.0, 30.5; IR (neat): 3063.8 (w), 3035.5 (w), 2933.5 (m), 2861.0 (w), 1665.3 (w), 1593.9 (w), 1571.8 (w), 1474.2 (s), 1441.7 (s), 1349.0 (w), 1250.1 (s), 1122.7 (w), 1069.0 (w), 1051.3 (s), 1036.2 (s), 965.6 (s), 749.3 (s), 675.2 (s), 445.4 (m) cm^{-1}; HRMS-(DART) for: $C_{11}H_{12}Cl$ [M+H-HCl]$^+$: calculated: 179.0628, found: 179.0620.

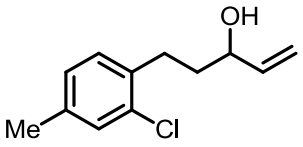


(*E*)-2-(5-(2-chlorophenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizing $PdCl_2$ (3.8 mg, 0.021 mmol), $B_2(pin)_2$ (544.7 mg, 2.15 mmol), THF (2.1 mL), and (*E*)-1-chloro-2-(5-chloropent-3-en-1-yl)benzene (9:1 with regio-isomeric allyl chloride, 500 mg, 2.15 mmol). The crude material was purified (SiO_2, 5% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (525.7 mg, 80%). R_f = 0.36 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (1H, dd, J = 7.8, 1.0 Hz), 7.20 (1H, dd, J = 7.8, 2.0 Hz), 7.16 (1H, ddd (app dt's), J = 7.8, 2.0 Hz), 7.11 (1H, ddd (app dt's), J = 7.8, 2.0 Hz), 5.58-5.42 (2H, m), 2.77 (2H, t, J = 7.8 Hz), 2.31 (2H, dt's (app q), J = 5.9 Hz), 1.65 (2H, d, J = 6.8 Hz), 1.25 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.7, 133.9, 130.4, 129.6, 129.3, 127.0, 126.5, 125.8, 83.1, 33.8, 32.6, 24.7; IR (neat): 3059.8 (w), 2978.3 (m), 2931.5 (m), 1641.2 (w), 1572.0 (w), 1473.9 (m), 1443.2 (m), 1361.1 (s), 1326.0 (s), 1272.7 (m), 1214.3 (w), 1143.6 (s),

1051.7 (w), 967.3 (s), 882.3 (w), 847.9 (s), 750.4 (s), 675.7 (m), 578.5 (w) cm^{-1}; HRMS-(DART) for: $C_{17}H_{25}BClO_2$ $[M+H]^+$: calculated: 307.1636, found: 307.1631.

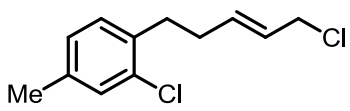


3-(2-chloro-4-methylphenyl)propanal. Prepared according to the general procedure utilizing $Pd(OAc)_2$ (112 mg, 0.500 mmol), tetrabutylammonium chloride (6.95 g, 25.0 mmol), sodium bicarbonate (5.25 g, 62.5 mmol), dimethylformamide (50 mL), 2-chloro-1-iodo-4-methylbenzene (6.31 mL, 25.0 mmol), and allyl alcohol (2.55 mL, 37.5 mmol). The crude material was purified (SiO_2, 5% ethyl acetate in hexanes) to give the desired product as a clear, slightly yellow oil (2.20 g, 48%). R_f = 0.40 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (1H, s), 7.18 (1H, d, *J*= 1.0 Hz), 7.12 (1H, d, *J*= 8.0 Hz), 6.99 (1H, dd, *J*= 8.0, 1.5 Hz), 3.02 (2H, t, *J* = 7.5 Hz), 2.77 (2H, td, *J* = 7.5, 1.0 Hz), 2.30 (3H, s) ; ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.2, 137.9, 134.7, 133.4, 130.2, 130.0, 127.7, 43.6, 25.7, 20.6; IR (neat): 2923.8 (w), 2821.7 (w), 2722.7 (w), 1722.8 (s), 1610.3 (w), 1494.3 (s), 1446.8 (m), 1406.4 (m), 1214.7 (w), 1052.6 (s), 878.3 (s), 818.9 (s), 687.3 (m), 563.8 (m), 409.9 (m) cm^{-1}; HRMS-(DART) for: $C_{10}H_{10}ClO$ $[M-H]^+$: calculated: 181.0420, found: 181.0426.



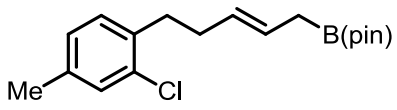
5-(2-chloro-4-methylphenyl)pent-1-en-3-ol. Prepared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 11.0 mL, 11.0 mmol), 3-(2-chloro-4-methylphenyl)propanal (1.00 g, 5.74 mmol), and THF (11.0 mL). The crude material was purified (SiO_2, 10% ethyl acetate in hexanes) to give the desired product as a clear, slightly yellow oil (1.05 g, 91%). R_f = 0.31 (10% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17 (1H, d, *J* = 1.0 Hz), 7.12 (1H, d, *J* = 7.5 Hz),

6.99 (1H, dd, *J* = 8.0, 1.0 Hz), 5.92 (1H, ddd, *J* = 16.5, 10.0, 6.0 Hz), 5.27 (1H, ddd (app dt's), *J* = 17.0, 1.5 Hz), 5.15 (1H, ddd (app dt's), *J* = 11.0, 1.0 Hz), 4.15 (1H, ddd (app q), *J* = 6.5 Hz), 2.83 (1H, ddd, *J* = 15.0, 9.0, 6.0 Hz), 2.76 (1H, ddd, *J* = 14.5, 9.5, 7.0 Hz), 2.30 (3H, s), 1.86-1.81 (2H, m), 1.77 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.8, 137.3, 136.2, 133.5, 130.1, 129.9, 127.6, 114.9, 72.5, 36.9, 29.0, 20.6; IR (neat): 3348.7 (br), 2979.6 (s), 2923.4 (m), 2864.6 (m), 1610.5 (s), 1494.6 (m), 1452.4 (m), 1425.5 (m), 1311.6 (s), 1180.4 (s), 1109.5 (s), 1109.5 (s), 1048.3 (s), 990.4 (s), 923.1 (m), 820.2 (s), 687.4 (m) cm^{-1}; HRMS-(DART) for: $C_{12}H_{14}Cl$ $[M+H-H_2O]^+$: calculated: 193.0784, found: 193.0774.

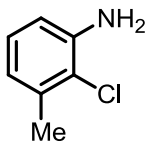


(*E*)-2-chloro-1-(5-chloropent-3-en-1-yl)-4-methylbenzene Prepared according to the general procedure utilizing thionyl chloride (3.44 mL, 47.5 mmol), 5-(2-chloro-4-methylphenyl)pent-1-en-3-ol (1.00 g, 4.75 mmol), and DCM (14.4 mL). The crude material was purified (SiO_2, 2% ethyl acetate in hexanes) to give the desired product as a 6.7:1 mixture of the title compound: 2-chloro-1-(3-chloropent-4-en-1-yl)-4-methylbenzene (997 mg, 90%)). R_f = 0.38 (4% DCM in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 7.16 (1H, s), 7.06 (1H, d, *J*= 7.5 Hz), 6.98 (1H, d, *J*= 7.0 Hz), 5.81 (1H, dt's, *J* = 15.5, 6.5 Hz), 5.64 (1H, dt's, *J* = 15.0, 7.0 Hz), 4.02 (2H, d, *J* = 7.0 Hz), 2.77 (2H, t, *J* = 7.5 Hz), 2.40 (2H, dt's (app q), *J* = 7.0 Hz), 2.29 (3H, s); (minor isomer) δ 7.16 (1H, s), 7.12 (1H, d, *J*= 7.5), 7.07-6.97 (1H, m), 5.93 (1H, ddd, *J* = 17.0, 10.0, 8.0 Hz), 5.29 (1H, d, *J* = 16.5 Hz), 5.17 (1H, d, *J* = 10.0 Hz), 4.34 (1H, ddd (app q), *J* = 7.5 Hz), 2.89 (1H, ddd, *J* = 14.5, 9.0, 6.5 Hz), 2.83-2.76 (1H, m), 2.29 (3H, s), 2.16-2.06 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): (both isomers, one overlapping signal) δ 138.3, 137.7, 137.4, 135.7, 135.2,

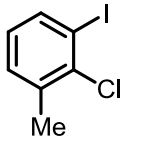
134.8, 133.6, 133.5, 130.3, 130.2, 130.1, 129.9, 127.6, 127.5, 126.7, 116.8, 62.3, 45.2, 37.9, 32.5, 32.1, 30.1, 20.7; IR (neat): 3033.1 (w), 2924.7 (m), 2831.3 (w), 1665.8 (w), 1610.1 (w), 1494.1 (s), 1441.2 (m), 1250.1 (m), 1214.6 (w), 1049.7 (s), 966.0 (s), 930.9 (w), 875.0 (s), 817.9 (s), 686.6 (s), 573.2 (m), 446.5 (w) cm^{-1}; HRMS-(DART) for: $C_{12}H_{14}Cl$ $[M+H-HCl]^+$: calculated: 193.0784, found: 193.0788.



(*E*)-2-(5-(2-chloro-4-methyl-phenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizing $PdCl_2$ (7.0 mg, 0.039 mmol), $B_2(pin)_2$ (997 mg, 3.93 mmol), THF (3.9 mL), and (*E*)-2-chloro-1-(5-chloropent-3-en-1-yl)-4-methylbenzene (6.67:1 with regio-isomeric allyl chloride, 900 mg, 3.93 mmol). The crude material was purified (SiO_2, 5% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (1.08 g, 85%). R_f = 0.42 (5% ethyl acetate in hexanes, UV/magic stain). ^1H NMR (500 MHz, $CDCl_3$): δ 7.14 (1H, s), 7.08 (1H, d, *J* = 7.5 Hz), 6.96 (1H, dd, *J*= 7.5, 1.0 Hz), 5.53-5.42 (2H, m), 2.72 (2H, t, *J* = 8.0 Hz), 2.30-2.26 (2H, m), 2.28 (3H, s), 1.65 (2H, d, *J* = 6.5 Hz), 1.25 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 136.9, 136.5, 133.5, 130.1, 129.8, 129.7, 127.3, 125.7, 83.1, 33.4, 32.8, 24.7, 20.6; IR (neat): 2977.8 (m), 2928.3 (w), 2862.9 (w), 1610.5 (w), 1451.3 (w), 1360.2 (s), 1325.1 (s), 1272.4 (w), 1214.2 (w), 1164.8 (s), 1050.1 (w), 1004.5 (s), 882.2 (m), 847.2 (m), 818.1 (m), 686.3 (w), 673.9 (w), 575.9 (w), 449.9 (w) cm^{-1}; HRMS-(DART) for: $C_{18}H_{27}BClO_2$ $[M+H]^+$: calculated: 321.1793, found: 321.1797.

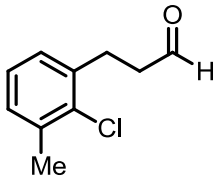


2-chloro-3-methylaniline. To a solution of 2-chloro-1-methyl-3-nitrobenzene (5.00 g, 29.1 mmol) in ethanol (48 mL) was added Fe(0) (4.88g, 87.4 mmol) and conc. HCl (2.43 mL) at room temperature. The reaction mixture was heated to reflux for 1.5 hours and then cooled to room temperature. The solvent was removed under reduced pressure and the residue was diluted with sat. aq. NH_4Cl and extracted with ethyl acetate (3 x 75 mL). The organic layers were combined and washed with DI H_2O (75 mL), brine (75 mL), dried over sodium sulfate, and concentrated under reduced pressure. The crude material was purified (SiO_2, 5% ethyl acetate in hexanes) to give the product as a clear, yellow oil (2.78g, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.96 (1H, dd (app t), *J*= 8.0 Hz), 6.65-6.63 (2H, m), 4.07 (2H, br s), 2.35 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.0, 136.8, 126.7, 120.3, 119.8, 113.3, 20.4; IR (neat): 3471.2 (br), 3381.2 (br), 3060.8 (w), 3026.1 (w), 2979.9 (w), 2950.3 (w), 1611.3 (s), 1469.5 (s), 1313.1 (m), 1167.7 (w), 1095.2 (w), 1048.0 (s), 943.9 (w), 764.9 (s), 708.5 (m), 598.2 (s) cm^{-1}; HRMS-(DART) for: C_7H_9ClN $[M]^+$: calculated: 142.0424, found: 142.0426.



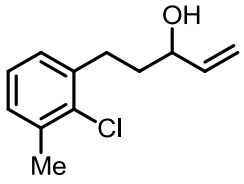
2-chloro-1-iodo-3-methylbenzene. To a 250 mL round-bottomed flask equipped with a magnetic stir bar was added 2-chloro-3-methylaniline (2.25 g, 15.9 mmol), followed by DI H_2O (41 mL) and conc. HCl (8.1 mL). The reaction mixture was cooled to 0 ^oC (ice/water bath) and treated dropwise with a solution of sodium nitrite (1.42 g, 20.6 mmol) in DI H_2O (10 mL), maintaining the reaction temperature to less than 10 ^oC. After completing addition, the reaction mixture was allowed to stir at 0 ^oC for 30 minutes. To the mixture was added dropwise a solution of potassium iodide (4.22 g, 25.4 mmol) in DI H_2O (10 mL). The mixture rapidly turned to

a deep black solution. After the addition was complete, the mixture was heated to 60 ^{o}C and allowed to stir for 1 h. The cooled solution was washed with 10% sodium bicarbonate (50 mL), 1M sodium thiosulfate (50 mL), 10% hydrochloric acid (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified (SiO2, 100% hexanes), to give the product as a clear, slightly yellow oil (2.51 g, 63%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.70 (1H, d, *J*= 8.0 Hz), 7.20 (1H, d, *J*= 8.0 Hz), 6.86 (2H, t, *J* = 7.5 Hz), 2.45 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 138.1, 137.9, 137.7, 130.6, 127.7, 98.9, 22.4; IR (neat): 3052.6 (w), 2977.9 (w), 2952.1 (w), 2921.9 (w), 1579.0 (w), 1441.0 (s), 1398.7 (s), 1375.9 (m), 1251.6 (w), 1179.5 (w), 1090.7 (m), 1048.1 (s), 893.9 (s), 828.3 (s), 716.7 (s), 697.8 (s), 556.3 (m) cm^{-1}; HRMS-(DART) for: C_7H_6ClI $[M]^+$: calculated: 251.9203, found: 251.9213.

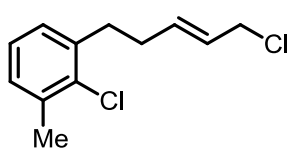


3-(2-chloro-3-methylphenyl)propanal. To a flame-dried round-bottomed flask equipped with magnetic stir bar in the glovebox was added $Pd(OAc)_2$ (71.3 mg, 0.32 mmol). The flask was removed from the glovebox, charged with tetrabutylammonium chloride (5.29 g, 19.0 mmol) and sodium bicarbonate (3.33 g, 39.7 mmol) and sealed with a septum. The flask was evacuated and back-filled with nitrogen (3x) followed by addition of dimethylformamide (32 mL). After stirring at room temperature for 10 minutes, 2-chloro-1-iodo-3-methylbenzene (2.50 g, 9.90 mmol) followed by allyl alcohol (2.16 mL, 31.7 mmol) were added and the resulting mixture was heated to 40 ^{o}C for 12 hours. The resulting dark reaction mixture was cooled to room temperature, diluted with diethyl ether (50 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted with diethyl

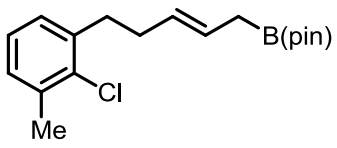
ether (3 x 50 mL) and the combined organic layers washed with a 50/50 water/brine solution (2 x 50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude reaction mixture was partially purified using flash chromatography (SiO_2, 10% ethyl acetate in hexanes) to give a clear, yellow oil (crude, 1.21 g) which was used in the next step without any further purification.



5-(2-chloro-3-methylphenyl)pent-1-en-3-ol. Prepared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 13.3 mL, 13.3 mmol), 3-(2-chloro-3-methylphenyl)propanal (1.21 g, 6.63 mmol), and THF (13.3 mL). The crude material was purified (SiO_2, 10% ethyl acetate in hexanes) to give the desired product as a clear, slightly yellow oil (1.12 g, 54% over 2 steps). R_f = 0.37 (10% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40-7.05 (3H, m), 5.93 (1H, ddd, *J* = 17.0, 11.0, 6.5 Hz), 5.28 (1H, ddd (app dt's), *J* = 17.0, 1.5 Hz), 5.15 (1H, ddd (app dt's), *J* = 10.5, 1.5, 1.5 Hz), 4.14 (1H, ddd (app q), *J* = 6.0 Hz), 2.89 (1H, ddd, *J* = 14.5, 9.5, 6.0 Hz), 2.81 (1H, ddd, *J*= 14.0, 9.5, 6.5 Hz), 2.39 (3H, s), 1.91-1.80 (2H, m), 1.66 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.9, 139.6, 136.6, 134.2, 128.7, 127.9, 126.1, 114.9, 72.5, 36.7, 30.0, 20.8; IR (neat): 3334.1 (br), 2979.4 (w), 2925.2 (w), 2862.9 (w), 1466.2 (m), 1453.7 (m), 1419.2 (m), 1380.5 (w), 1166.6 (w), 1043.2 (s), 989.5 (s), 922.4 (s), 770.2 (s), 725.1 (s) cm^{-1}; HRMS-(DART) for: $C_{12}H_{12}Cl$ $[M+H-H_2O]^+$: calculated: 191.0628, found: 191.0626.

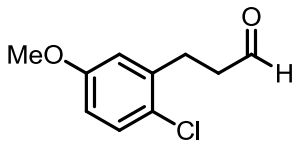


(*E*)-2-chloro-1-(5-chloropent-3-en-1-yl)-3-methylbenzene. Prepared according to the general procedure utilizing thionyl chloride (2.53 mL, 34.5 mmol), 5-(2-chloro-3-methylphenyl)pent-1-en-3-ol (734 mg, 3.48 mmol), and DCM (12.4 mL). The crude material was purified (SiO_2, 2% ethyl acetate in hexanes) to give the desired product as a 6.7:1 mixture of the title compound: 2-chloro-1-(3-chloropent-4-en-1-yl)-3-methylbenzene (655 mg, 82%). R_f = 0.38 (4% DCM in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 7.11-7.04 (3H, m), 5.85 (1H, dt's, *J* = 15.0, 7.0 Hz), 5.66 (1H, dt's, *J* = 15.5, 7.0 Hz), 4.04 (2H, d, *J* = 7.0 Hz), 2.84 (2H, t, *J* = 7.0 Hz), 2.42-2.37 (2H, m), 2.40 (3H, s); (minor isomer) δ 7.11-7.04 (3H, m), 5.95 (1H, ddd (app dt's), *J* = 16.5, 10.0 Hz), 5.31 (1H, d, *J* = 17.0 Hz), 5.19 (1H, d, *J* = 10.5 Hz), 4.37 (1H, ddd (app q), *J* = 7.5 Hz), 2.96 (1H, ddd (app dt's), *J* = 15.0, 9.0 Hz), 2.89-2.83 (1H, m), 2.40 (3H, s), 2.16-2.11 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): (both isomers) δ 139.1, 138.6, 138.3, 136.8, 136.6, 134.9, 134.23, 134.18, 129.0, 128.8, 128.0, 127.8, 126.6, 126.2, 126.1, 116.8, 62.4, 45.2, 37.8, 33.5, 32.0, 31.1, 20.8, 20.8; IR (neat): 3054.7, (w), 2951.7 (m), 2858.6 (w), 1665.6 (w), 1466.7 (s), 1453.9 (s), 1439.9 (m), 1249.7 (m), 1044.8 (s), 965.2 (s), 771.4 (s), 679.0 (m), 630.0 (s), 566.0 (w) cm^{-1}; HRMS-(DART) for: $C_{12}H_{14}Cl$ $[M+H-HCl]^+$: calculated: 193.0784, found: 193.0785.



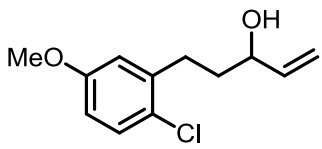
(*E*)-2-(5-(2-chloro-3-methylphenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizing $PdCl_2$ (5.1 mg, 0.029 mmol), $B_2(pin)_2$ (726 mg, 2.86 mmol), THF (2.9 mL), and (*E*)-2-chloro-1-(3-chloropent-4-en-1-yl)-3-methylbenzene (6.7:1 with

regio-isomeric allyl chloride, 655 mg, 2.86 mmol). The crude material was purified (SiO_2, 5% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (789 mg, 86%). R_f = 0.38 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.07-7.04 (3H, m), 5.54-5.43 (2H, m), 2.78 (2H, t, *J* = 8.0 Hz), 2.38 (3H, s), 2.30 (2H, dt's (app q), *J* = 6.5 Hz), 1.65 (2H, d, *J* = 6.0 Hz), 1.25 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.9, 136.3, 134.2, 129.8, 128.4, 127.8, 125.9, 125.6, 83.1, 34.4, 32.6, 24.7, 20.8; IR (neat): 2977.6 (m), 2930.3 (s), 1466.8 (w), 1359.3 (s), 1323.6 (s), 1213.8 (s), 1164.8 (s), 1107.7 (m), 882.7 (w), 846.6 (m), 770.6 (m), 724.2 (s), 673.7 (s) cm^{-1}; HRMS-(DART) for: $C_{18}H_{27}BClO_2$ $[M+H]^+$: calculated: 321.1793, found: 321.1785.

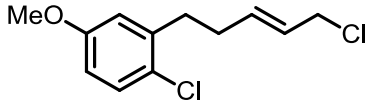


3-(2-chloro-5-methoxyphenyl)propanal. Prepared according to the general procedure utilizing $Pd(OAc)_2$ (33.4 mg, 0.149 mmol), tetrabutylammonium chloride (2.07 g, 7.45 mmol), sodium bicarbonate (1.56 g, 18.6 mmol), dimethylformamide (15 mL), 1-chloro-2-iodo-4-methoxybenzene (2.00 g, 7.45 mmol), and allyl alcohol (0.76 mL, 11 mmol). The crude material was purified (SiO_2, 20% ethyl acetate in hexanes) to give the desired product as a clear, slightly yellow oil (1.25 g, 84%). R_f = 0.49 (30% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (1H, s), 7.23 (1H, d, *J*= 9.0 Hz), 6.78 (1H, d, *J*= 2.0 Hz), 6.70 (1H, dd, *J*= 8.5, 3.0 Hz), 3.77 (3H, s), 3.01 (2H, t, *J* = 7.5 Hz), 2.78 (2H, t, *J* = 7.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 200.9, 158.3, 138.8, 130.0, 125.0, 116.0, 113.1, 55.3, 43.3, 26.3; IR (neat): 3003.4 (w), 2938.8 (w), 2836.1 (w), 2723.9 (w), 1721.6 (s), 1597.3 (m), 1575.8 (m), 1476.3 (s), 1408.5 (m), 1298.2 (s), 1278.3 (s), 1241.1 (s), 1191.1 (s), 1021.7 (s), 868.8 (w), 805.4 (m), 630.9 (s), 858.7 (w)

cm^{-1}; HRMS-(DART) for: $C_{10}H_{15}ClNO_2$ $[M+NH_4]^+$: calculated: 216.0791, found: 216.0788.

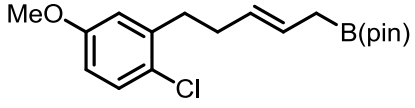


5-(2-chloro-5-methoxyphenyl)pent-1-en-3-ol. Prepared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 12.0 mL, 12.0 mmol), 3-(2-chloro-5-methoxyphenyl)propanal (1.20 g, 6.04 mmol), and THF (12.0 mL). The crude material was purified (SiO_2, 10% ethyl acetate in hexanes) to give the desired product as a clear, slightly yellow oil (1.22 g, 89%). R_f = 0.22 (10% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.23 (1H, d, *J*= 9.0 Hz), 6.79 (1H, d, *J* = 3.0 Hz), 6.69 (1H, dd, *J* = 3.0, 8.5 Hz), 5.92 (1H, ddd, *J* = 16.5, 10.0, 5.5 Hz), 5.27 (1H, ddd (app dt's), *J* = 17.0, 1.5 Hz), 5.16 (1H, ddd (app dt's), *J* = 10.5, 1.5 Hz), 4.16 (1H, ddd (app q), *J* = 6.5 Hz), 3.77 (3H, s), 2.83 (1H, ddd, *J* = 14.0, 9.5, 6.5 Hz), 2.75 (1H, ddd, *J* = 14.0, 9.5, 6.5 Hz), 1.90-1.79 (2H, m), 1.69 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.3, 140.8, 140.4, 130.0, 125.3, 115.9, 115.0, 112.8, 72.4, 55.4, 36.7, 29.8; IR (neat): 3360.6 (br), 3003.1 (w), 2936.2 (m), 2864.5 (s), 2836.7 (s), 1597.0 (m), 1575.3 (m), 1476.0 (s), 1419.8 (s), 1277.2 (s), 1161.7 (s), 1023.3 (s), 923.9 (m), 855.2 (s), 631.7 (s), 460.6 (s) cm^{-1}; HRMS-(DART) for: $C_{12}H_{14}ClO$ $[M+H-H_2O]^+$: calculated: 209.0733, found: 209.0731.



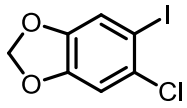
(*E*)-1-chloro-2-(5-chloropent-3-en-1-yl)-4-methoxybenzene. Prepared according to the general procedure utilizing thionyl chloride (3.52 mL, 48.5 mmol), 5-(2-chloro-5-methoxyphenyl)pent-1-

en-3-ol (1.10 g, 4.85 mmol), and DCM (16 mL). The crude material was purified (SiO_2, 2% ethyl acetate in hexanes) to give the desired product as a 5:1 mixture of the title compound: 1-chloro-2-(3-chloropent-4-en-1-yl)-4-methoxybenzene (clear, colorless oil (1.08 g, 91%)). R_f = 0.65 (10% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 7.23 (1H, d, *J* = 8.5 Hz), 6.84 (1H, d, *J* = 3.5 Hz), 6.70 (1H, dd, *J* = 8.5, 3.0 Hz), 5.83 (1H, dt's, *J* = 15.0, 7.0 Hz), 5.66 (1H, dtt's, *J* = 15.0, 7.5, 1.0 Hz), 4.03 (2H, d, *J* = 7.0 Hz), 3.78 (3H, s), 2.78 (2H, t, *J* = 8.0 Hz), 2.38 (2H, dt's (app q), *J* = 7.0 Hz); (minor isomer) δ 7.24 (1H, d, *J* = 8.5 Hz), 6.79 (1H, d, *J* = 3.5 Hz), 6.71 (1H, dd, *J* = 8.5, 3.5 Hz), 5.94 (1H, ddd, *J* = 17.0, 10.0, 7.5 Hz), 5.31 (1H, ddd (app dt's), *J* = 17.0, 1.0 Hz), 5.18 (1H, d, *J* = 10.5 Hz), 4.36 (1H, ddd (app q), *J* = 7.5 Hz), 3.79 (3H, s), 2.89 (1H, ddd, *J* = 13.5, 9.5, 6.0 Hz), 2.83-2.76 (1H, m), 2.17-2.07 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): (both isomers) δ 158.3, 158.2, 139.8, 139.4, 138.2, 134.6, 130.2, 130.0, 126.8, 125.3, 116.9, 116.1, 116.0, 115.9, 113.0, 112.8, 62.2, 55.4, 45.2, 37.7, 36.6, 33.2, 31.9, 30.8; IR (neat): 3003.5 (w), 2939.1 (w), 2836.7 (w), 2723.3 (w), 1723.4 (s), 1597.8 (m), 1576.2 (m), 1477.5 (s), 1420.4 (m), 1356.3 (m), 1299.0 (m), 1279.1 (s), 1063.9 (m), 1022.5 (m), 936.3 (w), 870.0 (m), 631.3 (m) cm^{-1}; HRMS-(DART) for: $C_{12}H_{14}Cl_2O$ $[M]^+$: calculated: 244.0422, found: 244.0422.



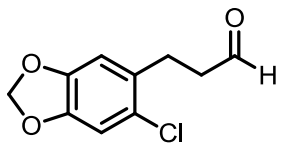
(*E*)-2-(5-(2-chloro-5-methoxyphenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizing $PdCl_2$ (5.3 mg, 0.030 mmol), $B_2(pin)_2$ (259 mg, 3.00 mmol), THF (3.0 mL), and (*E*)-1-chloro-2-(5-chloropent-3-en-1-yl)-4-methoxybenzene (5:1 with regio-isomeric allyl chloride, 733 mg, 3.00 mmol). The crude

material was purified (SiO_2, 5% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (917 mg, 91%). R_f = 0.47 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.21 (1H, d, *J* = 9.0 Hz), 7.75 (1H, d, *J* = 3.0 Hz), 6.66 (1H, dd, *J* = 9.0, 3.5 Hz), 5.54-5.42 (2H, m), 3.77 (3H, s), 2.72 (2H, t, *J* = 8.0 Hz), 2.29 (2H, dt's (app q), *J* = 7.5 Hz), 1.65 (2H, d, *J* = 7.0 Hz), 1.24 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 158.1, 140.7, 129.8, 129.6, 125.8, 125.3, 115.8, 112.5, 83.1, 55.4, 34.1, 32.6, 24.7; IR (neat): 2977.8 (m), 2935.2 (m), 2837.8 (w), 1397.3 (w), 1575.7 (w), 1476.4 (s), 1360.4 (s), 1325.3 (s), 1275.2 (m), 1240.5 (s), 1162.2 (m), 1143.6 (s), 1108.5 (m), 1026.6 (s), 881.9 (m), 846.9 (w), 631.3(w) cm^{-1}; HRMS-(DART) for: $C_{18}H_{26}BClO_3$ $[M]^+$: calculated: 336.1664, found: 336.1679.

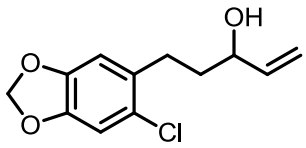


5-chloro-6-iodobenzo[d][1,3]dioxole. To an oven-dried 250 mL RBF equipped with a stir bar was added a solution of 5-chlorobenzo[d][1,3]dioxole (2.00 g, 12.8 mmol) in acetonitrile (60 mL). To the flask was added trifluoroacetic acid (2.90 g, 25.4 mmol) followed by *N*-iodosuccinimide (8.60 g, 38.2 mmol), and the mixture was allowed to stir in the dark at room temperature under nitrogen for 24 hours. The dark brown solution was concentrated under reduced pressure and the crude residue was purified (SiO_2, 0-4% ethyl acetate in hexanes) to give the desired product as a slightly yellow oil (1.80 g, 50%). R_f = 0.52 (5% ethyl acetate in hexanes, UV/magic stain). All spectral data are in accordance with the literature.[51]

[51] Xiong, C.; Changgeng, Q.; Haixiao, Z. PCT Int. Appl., 2008115719, 25 Sep 2008.

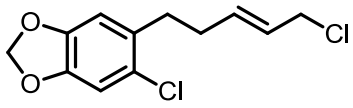


3-(6-chlorobenzo[d][1,3]dioxol-5-yl)propanal. Prepared according to the general procedure utilizing $Pd(OAc)_2$ (28.6 mg, 0.128 mmol), tetrabutylammonium chloride (1.77 g, 6.37 mmol), sodium bicarbonate (1.34 g, 15.9 mmol), dimethylformamide (20 mL), 5-chloro-6-iodobenzo[d][1,3]dioxole (1.80 g, 6.37 mmol), and allyl alcohol (0.65 mL, 9.6 mmol). The crude material was purified (SiO_2, 6% ethyl acetate in hexanes) to give the desired product as a clear, slightly yellow oil (771 mg, 57%). R_f = 0.42 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.81 (1H, t, *J* = 1.5 Hz), 6.82 (1H, s), 6.71 (1H, s), 5.94 (2H, s,), 2.96 (2H, t, *J* = 7.5 Hz), 2.74 (2H, td, *J* = 7.0, 1.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.1, 146.8, 146.7, 130.9, 125.2, 110.0, 109.9, 101.7, 43.8, 26.1; IR (neat): 2898.4 (w), 2826.2 (w), 2726.4 (w), 1721.7 (s), 1503.7 (s), 1477.2 (s), 1413.2 (m), 1237.7 (s), 1160.0 (w), 1119.7 (s), 1035.4 (s), 931.7 (s), 863.3 (m), 838.6 (m), 433.0 (w) cm^{-1}; HRMS-(DART) for: $C_{10}H_{10}ClO$ $[M]^+$: calculated: 212.0240, found: 212.0237.



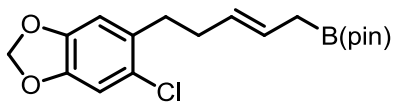
5-(6-chlorobenzo[d][1,3]dioxol-5-yl)pent-1-en-3-ol. Prepared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 7.2 mL, 7.2 mmol), 3-(6-chlorobenzo[d][1,3]dioxol-5-yl)propanal (765 mg, 3.60 mmol), and THF (36 mL). The crude material was purified (SiO_2, 10% ethyl acetate in hexanes) to give the desired product as a clear, slightly yellow oil (726 mg, 84%). R_f = 0.24 (10% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.81 (1H, s), 6.71 (1H, s), 5.96-5.87 (1H, m), 5.93 (2H, s), 5.26 (1H, ddd (app dt's), *J* = 17.5, 1.0 Hz), 5.14 (1H, ddd (app dt's), *J* = 11.0, 1.0 Hz), 4.13 (1H, ddd (app q), *J* = 6.0 Hz), 2.76 (1H, ddd, *J* =

14.5, 8.5, 6.5 Hz), 2.69 (1H, ddd, *J*= 14.5, 9.0, 6.5 Hz), 1.82-1.76 (2H, m), 1.73 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.6, 146.4, 140.8, 132.4, 125.1, 114.9, 109.8, 109.8, 101.5, 72.3, 36.9, 29.4; IR (neat): 3378.6 (br), 2894.8 (m), 1503.1 (s), 1477.2 (s), 1412.4 (m), 1232.9 (s), 1158.3 (w), 1117.8 (s), 1037.6 (s), 992.1 (m), 931.8 (s), 861.5 (m), 837.2 (m), 722.4 (w), 692.1 (w) cm^{-1}; HRMS-(DART) for: $C_{12}H_{13}ClO_3$ $[M]^+$: calculated: 240.0553, found: 240.0557.

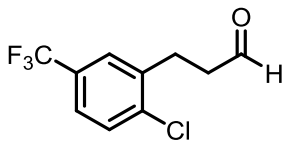


(E)-5-chloro-6-(5-chloropent-3-en-1-yl)benzo-[d][1,3]-dioxole. Prepared according to the general procedure utilizing thionyl chloride (2.19 mL, 30.1 mmol), 5-(6-chlorobenzo-[d][1,3]dioxol-5-yl)pent-1-en-3-ol (726 mg, 3.01 mmol), and DCM (8.5 mL). The crude material was purified (SiO_2, 2% ethyl acetate in hexanes) to give the desired product as a 11:1 mixture of the title compound: 5-chloro-6-(3-chloropent-4-en-1-yl)benzo[d][1,3]dioxole (701 mg, 90%). R_f = 0.28 (4% DCM in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 6.82 (1H, s), 6.66 (1H, s), 5.94 (2H, s), 5.81 (1H, dt's, *J* = 15.0, 7.0 Hz), 5.64 (1H, dtt's, *J* = 15.0, 7.5, 1.0 Hz), 4.03 (2H, d, *J* = 7.0 Hz), 2.72 (2H, t, *J* = 7.5 Hz), 2.33 (2H, dt's (app q), *J* = 7.0 Hz); (minor isomer) δ 6.82 (1H, s), 6.72 (1H, s), 5.96-5.89 (1H, m), 5.95 (2H, s), 5.30 (1H, d, *J* = 17.0 Hz), 5.18 (1H, d, *J* = 10.5 Hz), 4.34 (1H, ddd (app q), *J* = 8.0 Hz), 2.84 (1H, ddd, *J* = 14.0, 8.5, 5.5 Hz), 2.77-2.70 (1H, m), 2.12-2.02 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): (both isomers) δ 146.7, 146.7, 146.6, 146.5, 138.3, 134.5, 131.9, 131.3, 126.8, 125.3, 125.2, 116.9, 110.0, 109.9, 109.8, 109.8, 101.6, 101.5, 62.2, 45.2, 37.9, 32.9, 32.2, 30.5; IR (neat): 2897.5 (w), 1502.8 (m), 1475.8 (s), 1412.2 (m), 1232.3 (s), 1170.4 (w), 1117.5 (m), 1037.3 (s), 965.3 (m), 933.8 (s), 860.9

(m), 839.4 (m), 722.6 (w), 677.0 (m), 438.2 (w) cm^{-1}; HRMS-(DART) for: $C_{12}H_{12}ClO_2$ $[M]^+$: calculated: 258.0214, found: 258.0215.

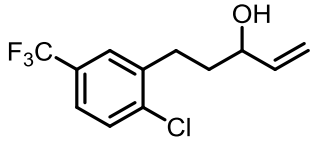


(*E*)-2-(5-(6-chlorobenzo[d][1,3]dioxol-5-yl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizing $PdCl_2$ (4.8 mg, 0.027 mmol), $B_2(pin)_2$ (686.6 mg, 2.70 mmol), THF (2.7 mL), and (*E*)-5-chloro-6-(5-chloropent-3-en-1-yl)benzo[d][1,3]dioxole (11:1 with regio-isomeric allyl chloride, 701 mg, 2.70 mmol). The crude material was purified (SiO_2, 5% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (797 mg, 84%). R_f = 0.30 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.79 (1H, s), 6.65 (1H, s), 5.90 (2H, s), 5.50-5.45 (1H, m) 5.43-5.37 (1H, m), 2.64 (2H, t, *J* = 7.5 Hz), (2H, dt's (app q), *J* = 8.0 Hz), 1.62 (2H, d, *J*= 7.0 Hz), 1.22 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.4, 146.2, 132.8, 129.5, 125.9, 125.1, 109.9, 109.7, 101.4, 83.2, 33.7, 32.8, 24.7; IR (neat): 2977.8 (w), 2929.2 (w), 1503.8 (m), 1476.7 (s), 1358.0 (s), 1324.0 (s), 1233.3 (s), 1165.0 (m), 1143.0 (s), 1116.5 (s), 1037.8 (s), 1004.5 (s), 966.8 (s), 935.0 (s), 845.7 (s), 722.6 (w), 693.2 (w), 674.3 (w), 438.1 (w) cm^{-1}; HRMS-(DART) for: $C_{18}H_{24}BClO_4$ $[M]^+$: calculated: 350.1456, found: 350.1458.



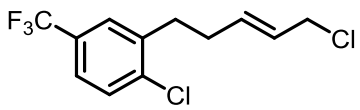
3-(2-chloro-5-(trifluoromethyl)phenyl)propanal. Prepared according to the general procedure utilizing $Pd(OAc)_2$ (22.5 mg, 0.100 mmol), tetrabutylammonium chloride (1.39 g, 5.00 mmol), sodium bicarbonate (1.05 g, 12.5 mmol), dimethylformamide (10 mL), 4-chloro-3-iodobenzotrifluoride (0.78

mL, 5.0 mmol), and allyl alcohol (0.51 mL, 7.5 mmol). The crude material was purified (SiO_2, 6% ethyl acetate in hexanes) to give the desired product as a clear, slightly yellow oil (922.5 mg, 78%). R_f = 0.42 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.82 (1H, d, J = 1.0 Hz), 7.51 (1H, d, J = 1.5 Hz), 7.46 (1H, d, J = 8.3 Hz), 7.41 (1H, d, J = 8.8 Hz), 3.10 (2H, t, J = 7.3 Hz), 2.83 (2H, t, J = 7.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 200.1, 139.1, 137.6, 130.1, 129.4 (q, J_{C-F} = 32.4 Hz), 127.3 (q, J_{C-F} = 3.8 Hz), 124.6 (q, J_{C-F} = 3.8 Hz), 123.6 (q, J_{C-F} = 271.8 Hz), 43.0, 26.0; IR (neat): 2942.7 (w), 2901.9 (w), 2826.4 (w), 2728.2 (w), 1724.5 (s), 1610.3 (m), 1583.2 (w), 1412.4 (m), 1325.2 (s), 1276.6 (m), 1165.4 (s), 1119.2 (s), 1080.9 (s), 1056.0 (s), 904.1 (s), 825.5 (s), 728.7 (m), 507.5 (m), 458.1 (m), 439.6 (m), 386.3 (w) cm^{-1}; HRMS-(DART) for: $C_{10}H_7ClF_3O$ $[M-H]^+$: calculated: 235.0138, found: 235.0140.



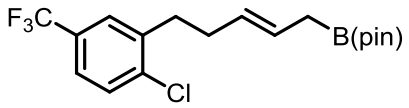
5-(2-chloro-5-(trifluoromethyl)phenyl)pent-1-en-3-ol. Prepared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 31.0 mL, 31.0 mmol), 3-(2-chloro-5-(trifluoromethyl)phenyl)propanal (3.6552 g, 15.5 mmol), and THF (30 mL). The crude material was purified (SiO_2, 12% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (3.6363 g, 90%). R_f = 0.26 (10% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.51 (1H, d, J = 2.0 Hz), 7.45 (1H, d, J = 8.3 Hz), 7.39 (1H, d, J = 8.3 Hz), 5.92 (1H, ddd, J = 17.1, 10.3, 6.4 Hz), 5.28 (1H, d, J = 17.1 Hz), 5.17 (1H, d, J = 10.3 Hz), 4.17 (1H, ddd (app q), J = 6.4 Hz), 2.96-2.90 (1H, m), 2.87-2.81 (1H, m), 1.96-1.77 (3H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.6, 137.7, 137.7, 129.9, 129.2 (q, J_{C-F} = 32.4 Hz), 127.2 (q, J_{C-F} = 3.8 Hz), 124.2 (q, J_{C-F} = 3.8 Hz),

123.8 (q, $J_{C\text{-}F}$ = 271.8 Hz), 115.3, 72.4, 36.3, 29.5; IR (neat): 3348.4 (br), 3082.8 (w), 2937.1 (w), 2870.9 (w), 1644.9 (m), 1482.4 (m), 1412.0 (m), 1362.2 (s), 1274.4 (m), 1166.2 (s), 1121.0 (s), 1080.3 (s), 1042.0 (s), 990.0 (m), 924.9 (s), 823.9 (s), 730.3 (m), 513.3 (m), 441.0 (m), 385.7 (m) cm^{-1}; HRMS-(DART) for: $C_{12}H_{11}ClF_3$ $[M+H\text{-}H_2O]^+$: calculated: 247.0501, found: 247.0504.



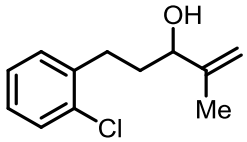
(*E*)-1-chloro-2-(5-chloropent-3-en-1-yl)-4-(trifluoromethyl)benzene. Prepared according to the general procedure utilizing thionyl chloride (8.36 mL, 115 mmol), 5-(2-chloro-5-(trifluoromethyl)phenyl)pent-1-en-3-ol (2.8113 g, 10.7 mmol), and DCM (45 mL). The crude material was purified (SiO_2, 2% ethyl acetate in hexanes) to give the desired product as a 10:1 mixture of the title compound: 1-chloro-2-(3-chloropent-4-en-1-yl)-4-trifluoromethyl)benzene (clear, colorless oil (2.1999 g, 72%). R_f = 0.51 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 7.51-7.38 (3H, m), 5.81 (1H, dt's, *J* = 15.1, 6.8, 6.8 Hz), 5.65 (1H, dtt's, *J* = 15.1, 6.8, 1.5 Hz), 4.02 (2H, dd, *J* = 6.8, 1.0 Hz), 2.88 (2H, t, *J* = 7.3 Hz), 2.41 (2H, dt's (app q), *J* = 7.3 Hz); (minor isomer) δ 7.51-7.38 (3H, m), 5.94 (1H, ddd, *J* = 17.1, 10.2, 7.8 Hz), 5.32 (1H, ddd (app dt's), *J* = 17.1, 1.0 Hz), 5.21 (1H, d, *J* = 9.8 Hz), 4.37 (1H, ddd (app q), *J* = 7.8 Hz), 3.03-2.97 (1H, m), 2.93-2.86 (1H, m), 2.16-2.11 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): (major isomer) δ 139.9, 133.7, 130.0, 129.2 (q, $J_{C\text{-}F}$ = 32.4 Hz), 127.4, 127.2 (q, $J_{C\text{-}F}$ = 3.8 Hz), 124.3 (q, $J_{C\text{-}F}$ = 3.8 Hz), 123.8 (q, $J_{C\text{-}F}$ = 271.8 Hz), 117.1, 44.9, 32.9, 31.6; IR (neat): 3039.3 (w), 2946.3 (m), 2866.1 (w), 1666.7 (w), 1609.5 (w), 1412.5 (m), 1325.3 (s), 1275.9 (m), 1166.7 (s), 1121.5 (s), 1080.0 (s), 1047.6 (m), 966.5 (m), 894.8 (m),

825.4 (s), 679.5 (m), 514.3 (w), 442.3 (w) cm^{-1}; HRMS-(DART) for: $C_{12}H_{11}ClF_3$ $[M-Cl]^+$: calculated: 247.0501, found: 247.0508.



(*E*)-2-(5-(2-chloro-5-(trifluoromethyl)phenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

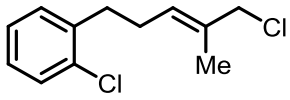
Prepared according to the general procedure utilizing $PdCl_2$ (10.6 mg, 0.060 mmol), $B_2(pin)_2$ (1.52 g, 6.00 mmol), THF (6.0 mL), and (*E*)-1-chloro-2-(5-chloropent-3-en-1-yl)-4-(trifluoromethyl)benzene (10:1 with regio-isomeric allyl chloride, 1.699 g, 6.00 mmol). The crude material was purified (SiO_2, 5% ethyl acetate in hexane) to give the desired product as a clear, colorless and viscous oil (1.96 g, 87%). R_f = 0.35 (5% ethyl acetate in hexane, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46-7.41 (2H, m), 7.37 (1H, dd, *J* = 8.3, 2.0 Hz), 5.54-5.48 (1H, m), 5.45-5.40 (1H, m), 2.81 (2H, t, *J* = 7.8 Hz), 2.32 (2H, dtd's (app dq), *J* = 7.8, 7.8, 7.8, 1.5 Hz), 1.64 (2H, d, *J* = 7.3 Hz), 1.24 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.7, 137.7, 129.8, 129.0 (q, *JC-F* = 33.4 Hz), 128.8, 127.2 (q, *JC-F* = 3.8 Hz), 126.6, 123.9 (q, *JC-F* = 3.8 Hz), 123.9 (q, *JC-F* = 271.9 Hz), 83.2, 33.8, 32.3, 24.6; IR (neat): 2979.7 (m), 2932.5 (w), 2868.1 (w), 1609.2 (w), 1480.9 (w), 1453.9 (w), 1326.6 (s), 1166.6 (m), 1127.1 (s), 1082.3 (s), 967.3 (m), 847.0 (m), 824.9 (m), 674.0 (w), 513.3 (w) cm^{-1}; HRMS-(DART) for: $C_{18}H_{24}BClF_3O_2$ $[M+H]^+$: calculated: 375.1510, found: 375.1519.



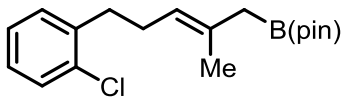
5-(2-chlorophenyl)-2-methylpent-1-en-3-ol. To a flame-dried, two-neck round-bottomed flask equipped with magnetic stir bar was added freshly ground magnesium turnings (326.2 mg, 13.4 mmol). The flask was

equipped with a reflux condenser and the apparatus placed under vacuum and flame-dried once more. After cooling to room temperature, the apparatus was back-filled with nitrogen and the magnesium turnings were vigorously stirred for 1 hour. THF (12 mL) was added followed by 2-bromopropene (1.08 mL, 12.2 mmol). After approximately 5 minutes, the reaction mixture became a slightly cloudy brown color and began to reflux. After refluxing under the heat of the reaction approximately 10 minutes, the reaction was returned to reflux for an additional 30 minutes, and the resulting light brown mixture was cooled to 0 ^{o}C (ice/water bath) and treated dropwise with a solution of 3-(2-chlorophenyl)propanal (1.03 g, 6.10 mmol) in THF (12 mL). After stirring at room temperature for 1 hour, the resulting brown, cloudy mixture was returned to 0 ^{o}C and excess Grignard reagent was carefully quenched with water (5 mL) followed by addition of saturated aqueous ammonium chloride (20 mL). The resulting mixture was diluted with ethyl acetate (50 mL) and water (20 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified (SiO_2, 12% ethyl acetate in hexanes) to give the desired product as a clear, slightly yellow oil (1.1141 g, 87%). R_f = 0.23 (10% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (1H, d, *J* = 7.8 Hz), 7.25 (1H, d, *J* = 7.3 Hz), 7.19 (1H, dd (app t), *J* = 7.3 Hz), 7.14 (1H, ddd (app dt's), *J* = 7.8, 1.5 Hz), 5.01 (1H, s), 4.90 (1H, s), 4.13 (1H, dd (app t), *J* = 6.9 Hz), 2.85 (1H, ddd, *J* = 13.7, 10.8, 5.9 Hz), 2.76 (1H, ddd, *J* = 13.7, 10.3, 6.4 Hz), 1.95-1.81 (2H, m), 1.77 (3H, s), 1.70 (1H, br s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.2, 139.6, 133.9, 130.4, 129.5, 127.3, 126.8, 111.2, 75.3, 34.7, 29.8, 17.6; IR (neat): 3352.6 (br), 3070.8 (w), 2940.4 (w), 2865.2 (w),

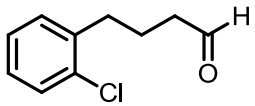
1650.7 (w), 1474.2 (m), 1443.0 (m), 1168.3 (w), 1051.6 (m), 1028.4 (m), 901.5 (m), 749.4 (s), 680.1 (m), 554.0 (w), 452.8 (w) cm^{-1}; HRMS-(DART) for: $C_{12}H_{14}Cl$ [M+H-H2O]$^+$: calculated: 193.0784, found: 193.0790.



(*E*)-1-chloro-2-(5-chloro-4-methylpent-3-en-1-yl)benzene. Prepared according to the general procedure utilizing thionyl chloride (2.84 mL, 39.4 mmol), 5-(2-chlorophenyl)-2-methylpent-1-en-3-ol (830.4 mg, 3.94 mmol), and DCM (20 mL). The crude material was purified (SiO_2, 2% ethyl acetate in hexanes) to give the desired product as a 5:1 mixture of the title compound: 1-chloro-2-(3-chloro-4-methylpent-4-en-1-yl)benzene (clear, colorless oil, 758.7 mg, 84%). R_f = 0.48 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 7.36-7.32 (1H, m), 7.20-7.12 (3H, m), 5.60 (1H, t, *J* = 7.3 Hz), 4.01 (2H, s), 2.79 (2H, t, *J* = 7.3 Hz), 2.37 (2H, dt's (app q), *J* = 7.3 Hz), 1.67 (3H, s); (minor isomer) δ 7.36-7.32 (1H, m), 7.26-7.22 (1H, m), 7.20-7.12 (2H, m), 5.05 (1H, s), 4.94 (1H, q, *J* = 1.0 Hz), 4.40 (1H, dd (app t), *J* = 7.7 Hz), 2.92-2.84 (1H, m), 2.81-2.74 (1H, m), 2.19-2.11 (2H, m), 1.85 (3H, d, *J* = 1.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): (both isomers, one overlapping signal) δ 144.1, 139.0, 138.4, 133.9, 132.8, 130.5, 130.5, 129.6, 129.4, 129.3, 127.7, 127.4, 1126.8, 126.7, 114.4, 66.0, 52.2, 36.2, 33.1, 31.1, 28.1, 17.1, 14.0; IR (neat): 3064.4 (w), 2944.9 (w), 2861.4 (w), 1474.2 (m), 1442.0 (m), 1263.1 (m), 1122.6 (w), 1051.5 (m), 1036.8 (m), 909.3 (w), 749.8 (s), 679.6 (s), 455.9 (w), 443.4 (w) cm^{-1}; HRMS-(DART) for: $C_{12}H_{14}Cl$ [M-Cl]$^+$: calculated: 193.0784, found: 193.0788.

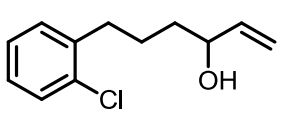


(*E*)-2-(5-(2-chlorophenyl)-2-methylpent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizing $PdCl_2$ (5.8 mg, 0.033 mmol), $B_2(pin)_2$ (840.8 mg, 3.31 mmol), THF (3.3 mL), and (*E*)-1-chloro-2-(5-chloro-4-methylpent-3-en-1-yl)benzene (5:1 with regio-isomeric allyl chloride, 758.7 mg, 3.31 mmol). The crude material was purified (SiO_2, 5% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (1.0045 g, 95%). R_f = 0.40 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (1H, dd, *J* = 7.8, 1.5 Hz), 7.21 (1H, dd, *J* = 7.8, 2.0 Hz), 7.16 (1H, ddd (app dt's), *J* = 7.3, 1.5 Hz), 7.11 (1H, ddd (app dt's), *J* = 7.3, 2.0 Hz), 5.18 (1H, t, *J* = 6.9 Hz), 2.74 (2H, t, *J* = 7.8 Hz), 2.31 (2H, dt's (app q), *J* = 7.8 Hz), 1.67 (2H, s), 1.61 (3H, s), 1.25 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.9, 133.9, 132.9, 130.5, 129.3, 127.1, 126.5, 123.0, 83.1, 33.9, 28.3, 24.7, 17.8; IR (neat): 3070.6 (w), 2977.3 (m), 2931.9 (w), 2864.3 (w), 1475.0 (s), 1440.3 (s), 1372.1 (m), 1324.3 (m), 1147.8 (m), 1052.2 (w), 966.6 (w), 850.9 (w), 751.0 (m), 673.6 (m) cm^{-1}; HRMS-(DART) for: $C_{18}H_{27}BClO_2$ $[M+H]^+$: calculated: 321.1793, found: 321.1794.

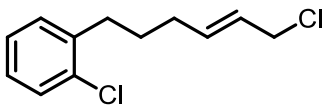


4-(2-chlorophenyl)butanal. Prepared according to the general procedure utilizing $Pd(OAc)_2$ (46.5 mg, 0.21 mmol), tetrabutylammonium chloride (22.88 g, 10.4 mmol), sodium bicarbonate (2.18 g, 25.9 mmol), dimethylformamide (21 mL), 2-chloroiodobenzene (2.47 g, 10.4 mmol), and but-3-en-1-ol (1.12 g, 15.5 mmol). The crude material was purified (SiO_2, 6% ethyl acetate in hexanes) to give the desired product as a 11:1 mixture of the title compound: 3-(2-chlorophenyl)butanal (clear, slightly yellow oil (1.64 g, 87%)). R_f = 0.40 (10% ethyl

acetate in hexanes, UV/magic stain). All spectral data are in accordance with the literature.[52]



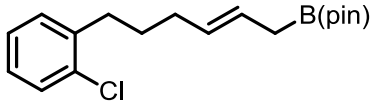
6-(2-chlorophenyl)hex-1-en-3-ol. Prepared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 18.0 mL, 18.0 mmol), 4-(2-chlorophenyl)butanal (1.64 g, 8.99 mmol), and THF (50 mL). The crude material was purified (SiO_2, 10% ethyl acetate in hexanes) to give the desired product as a 15:1 mixture of the title compound: 5-(2-chlorophenyl)hex-1-en-3-ol (clear, slightly yellow oil (1.80 g, 87%)). R_f = 0.39 (10% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (1H, dd, *J* = 7.5, 1.5 Hz), 7.22-7.11 (3H, m), 5.87 (1H, ddd, *J* = 17.0, 10.5, 6.5 Hz), 5.23 (1H, ddd (app dt's), *J* = 17.5, 1.5, 1.5 Hz), 5.11 (1H, ddd (app dt's), *J* = 10.0, 1.5 Hz), 4.14 (1H, ddd (app q), *J* = 6.5 Hz), 2.76 (2H, t, *J* = 7.5Hz), 1.80-1.56 (5H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.0, 139.8, 133.9, 130.3, 129.4, 127.2, 126.7, 114.8, 73.0, 36.5, 33.3, 25.5; IR (neat): 3356.1 (br), 3069.5 (w), 2932.2 (m), 2863.2 (m), 1474.2 (s), 1460.4 (m), 1317.0 (w), 1276.3 (w), 1109.3 (w), 1053.1 (s), 990.5 (s), 922.8 (s), 750.3 (s), 679.1 (m), 456.4 (w) cm^{-1}; HRMS-(DART) for: $C_{12}H_{14}Cl$ $[M+H-H_2O]^+$: calculated: 193.0784, found: 193.0781.



(*E*)-1-chloro-2-(6-chlorohex-4-en-1-yl)benzene. Prepared according to the general procedure utilizing thionyl chloride (3.44 mL, 47.5 mmol), 6-(2-chlorophenyl)hex-1-en-3-ol (1.00 g, 4.75 mmol), and DCM (13.4 mL). The crude material was purified (SiO_2, 2% DCM in hexanes) to give the desired product as a 5:1mixture of the title compound: 1-chloro-2-(4-chlorohex-5-en-1-yl)benzene: (*E*)-1-chloro-2-(6-chlorohex-4-en-2-yl)benzene (691 mg, 59%). R_f = 0.56

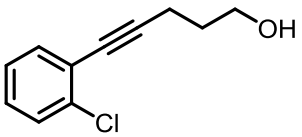
[52] Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. *J. Am. Chem. Soc.* **2001**, *123*, 12202.

(5% DCM in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 7.34 (1H, dd, *J*= 8.0, 1.0 Hz), 7.24-7.12 (3H, m), 5.81 (1H, dt's, *J* = 15.0, 6.5, 6.5 Hz), 5.66 (1H, dtt's, *J* = 15.5, 7.0, 1.0 Hz), 4.05 (2H, d, *J* = 7.5 Hz), 2.74 (2H, t, *J* = 8.0 Hz), 2.15 (2H, dt's (app q), *J* = 7.0 Hz), 1.77-1.72 (2H, m); (minor isomer) δ 7.35-7.26 (1H, m), 7.24-7.12 (3H, m), 5.89 (1H, ddd, *J* = 16.5, 9.5, 8.0 Hz), 5.27 (1H, dd, *J* = 17.0, 1.0 Hz), 5.14 (1H, d, *J* = 10.0 Hz), 4.38 (1H, ddd (app q), *J* = 7.5 Hz), 2.77 (2H, t, *J*= 7.5 Hz), 1.93-1.72 (4H, m); ^{13}C NMR (126 MHz, $CDCl_3$): (both major isomers) δ 139.7, 139.4, 138.5, 135.4, 133.9, 133.5, 130.4, 130.3, 129.5, 129.5, 127.4, 127.3, 126.8, 126.7, 126.5, 116.6, 62.8, 45.4, 37.8, 33.0, 32.9, 31.6, 28.8, 26.6; IR (neat): 3065.2 (w), 2015.7 (w), 2932.9 (m), 2862.8 (w), 1665.4 (w), 1571.6 (w), 1474.1 (s), 1442.4 (s), 1249.5 (m), 1122.9 (w),1076.9 (s), 965.8 (s), 928.0 (s), 750.2 (s), 679.0 (s), 458.7 (w), 441.6 (w) cm^{-1}; HRMS-(DART) for: $C_{12}H_{14}Cl$ $[M+H-HCl]^+$: calculated: 193.0784, found: 193.0778.

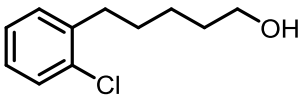


(*E*)-2-(6-(2-chlorophenyl)hex-2-en-1-yl)-4,4,5,5-tetra-methyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizing $PdCl_2$ (16.9 mg, 0.0955 mmol), $B_2(pin)_2$ (2.43 g, 9.55 mmol), THF (9.6 mL), and (*E*)-1-chloro-2-(6-chlorohex-4-en-1-yl)benzene (5:1 with regio-isomeric allyl chloride, 2.06 g, 9.55 mmol). The crude material was purified (SiO_2, 0-10% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (2.32 g, 79%). R_f = 0.35 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (1H, dd, *J* = 7.5, 1.5 Hz), 7.21 (1H, dd, *J* = 7.5, 2.0 Hz), 7.16 (1H, ddd (app td's), *J* = 7.5, 1.0 Hz), 7.11 (1H, ddd (app td's), *J* = 7.5, 2.0 Hz), 5.53-5.39 (2H, m), 2.71 (2H, t, *J* = 8.0 Hz), 2.06 (2H, dt's (app q), *J* = 7.0 Hz), 1.70-1.64 (4H, m),(2H, m),

1.25 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.2, 139.9, 130.4, 130.2, 129.4, 127.0, 126.6, 125.5, 83.1, 33.0, 32.3, 29.5, 24.8; IR (neat): 2977.7 (w), 2928.5 (w), 2860.1 (w), 1473.9 (m), 1442.5 (w), 1359.6 (s), 1323.4 (s), 1272.1 (m), 1213.7 (w), 1143.0 (s), 1052.5 (m), 965.8 (s), 883.1 (w), 846.2 (s), 780.9 (s), 675.2 (m), 578.0 (w), 457.9 (w) cm^{-1}; HRMS-(DART) for: $C_{18}H_{27}BClO_2$ $[M+H]^+$: calculated: 321.1793, found: 321.1786.



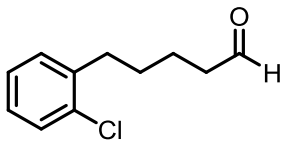
5-(2-chlorophenyl)pent-4-yn-1-ol. Prepared according to the literature procedure[53] utilizing CuI (28.6 mg, 0.150 mmol), $PdCl_2(PPh_3)_2$ (105.3 mg, 0.150 mmol), triethylamine (12.5 mL), 2-chloroiodobenzene (0.61 mL, 5.0 mmol), and pent-4-yn-1-ol (0.56 mL, 6.0 mmol). The crude material was purified (SiO_2, 20% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (924.1 mg, 95%). R_f = 0.29 (25% ethyl acetate in hexanes, UV/$KMnO_4$). All spectral data are in accordance with the literature.[10]



5-(2-chlorophenyl)pentan-1-ol. To a 50 mL round-bottomed flask equipped with magnetic stir bar was added PtO_2 (22.7 mg, 0.100 mmol) followed by methanol (20 mL) and 5-(2-chlorophenyl)pent-4-yn-1-ol (973.3 mg, 5.00 mmol). The flask was sealed with a septum and a three-way inlet equipped with vacuum line and hydrogen balloon was added. The flask was briefly evacuated until the reaction mixture began to boil, then backfilled with hydrogen. After repeating this sequence three additional times, the reaction mixture was vigorously stirred under positive hydrogen pressure (balloon) at room temperature for 24 hours. The resulting

[53] Gericke, K. M.; Chai, D. I.; Lautens, M. *Tetrahedron* **2008**, *64*, 6002.

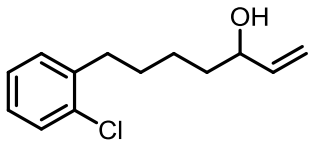
dark reaction mixture was diluted with 25% ethyl acetate in hexanes (20 mL) and eluted through a small plug of SiO_2 with additional 25% ethyl acetate in hexanes (150 mL). The resulting clear, colorless solution was concentrated under reduced pressure. The crude material was purified (SiO_2, 20% ethyl acetate in hexanes) to give the desired product (830.7 mg, 84%) and a small amount (>5%) of inseparable de-chlorinated by-product. R_f = 0.30 (25% ethyl acetate in hexanes). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (1H, dd, *J* = 7.8, 1.0 Hz), 7.21 (1H, dd, *J* = 7.8, 2.0 Hz), 7.17 (1H, ddd (app dt's), *J* = 7.3, 1.5 Hz), 7.12 (1H, ddd (app dt's), *J* = 7.3, 2.0 Hz), 3.65 (2H, t, *J* = 6.9 Hz), 2.74 (2H, t, *J* = 7.8 Hz), 1.69-1.59 (4H, m), 1.53 (1H, br s), 1.47-1.41 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.0, 133.8, 130.3, 129.4, 127.1, 126.6, 62.8, 33.5, 32.5, 29.5, 25.5; IR (neat): 3324.8 (br), 3063.4 (w), 3017.3 (w), 2931.5 (s), 2859.2 (m), 1594.0 (w), 1571.5 (w), 1473.3 (s), 1441.9 (m), 1069.9 (s), 1049.8 (s), 1031.4 (s), 746.9 (s), 678.8 (s), 456.9 (m), 444.0 (m) cm^{-1}; HRMS-(DART) for: $C_{11}H_{14}Cl$ $[M+H-H_2O]^+$: calculated: 181.0784, found: 181.0775.



5-(2-chlorophenyl)pentanal. Prepared according to the literature procedure.[54] To a 50 mL round-bottomed flask equipped with magnetic stir bar was added tetrakis(acetonitrile) copper(I) hexafluorophosphate (37.3 mg, 0.100 mmol) followed by acetonitrile (2 mL). To the resulting clear, colorless solution was added 2,2'-bipyridine (15.6 mg, 0.100 mmol) as a solution in acetonitrile (2 mL), resulting in immediate formation of a brown reaction mixture. TEMPO (15.6 mg, 0.100 mmol) as a solution in acetonitrile (2 mL) was added

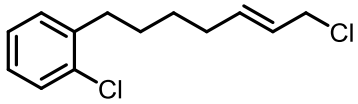
[54] Hoover, J. M.; Stahl, S. S. *J. Am. Chem. Soc*. **2011**, *133*, 16901.

followed by N-methylimidazole (16.4 mg, 0.200 mmol) as a solution in acetonitrile (2 mL). After stirring at room temperature open to air for approximately 5 minutes, 5-(2-chlorophenyl)pentan-1-ol (397.4 mg, 2.00 mmol) was added as a solution in acetonitrile (2 mL). The resulting brown reaction mixture was vigorously stirred at room temperature open to air until the reaction became blue/green in color and TLC analysis indicated consumption of starting material (5 hours). The reaction mixture was concentrated under reduced pressure, and the resulting residue was taken up in 10% ethyl acetate in hexanes (10 mL) and eluted through a short plug of SiO_2 with additional 10% ethyl acetate in hexanes solution (150 mL). The resulting clear, slightly yellow solution was concentrated under reduced pressure and the crude material was purified (SiO_2, 6% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (385.6 mg, 98%). R_f = 0.27 (5% ethyl acetate in hexanes, UV/$KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 9.83 (1H, s), 7.40 (1H, d, *J* = 7.3 Hz), 7.28-7.23 (2H, m), 7.20 (1H, ddd (app dt's), *J* = 7.8, 2.0 Hz), 2.82 (2H, t, *J* = 7.8 Hz), 2.54 (2H, t, *J* = 6.8 Hz), 1.81-1.71 (4H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 201.4, 138.5, 132.9, 129.4, 128.5, 126.4, 125.8, 42.7, 32.3, 28.2, 20.7; IR (neat): 3063.5 (w), 2935.7 (m), 2862.9 (w), 2822.0, (w), 2718.3 (w), 1722.4 (s), 1594.1 (w), 1571.5 (w), 1474.0 (m), 1442.8 (m), 1072.7 (m), 1050.7 (m), 1030.9 (m), 751.4 (s), 678.8 (m), 459.9 (w) cm^{-1}; HRMS-(DART) for: $C_{11}H_{14}ClO$ $[M+H]^+$: calculated: 197.0733, found: 197.0738.



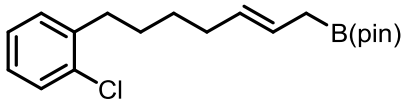
7-(2-chlorophenyl)hept-1-en-3-ol. Prepared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 7.80 mL, 7.80 mmol), 5-(2-chlorophenyl)pentanal (761.2 mg, 3.87 mmol), and

THF (8.0 mL). The crude material was purified (SiO_2, 12% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (692.8 mg, 80%). R_f = 0.28 (10% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (1H, dd, *J* = 6.4, 1.5 Hz), 7.21 (1H, dd, *J* = 7.8, 2.0 Hz), 7.17 (1H, ddd (app dt's), *J* = 6.8, 1.5 Hz), 7.12 (1H, ddd (app dt's), *J* = 7.3, 2.0 Hz), 5.87 (1H, ddd, *J* = 17.1, 10.3, 6.4 Hz), 5.22 (1H, ddd (app dt's), *J* = 17.1, 1.5 Hz), 5.11 (1H, ddd (app dt's), *J* = 10.3, 1.5 Hz), 4.12 (1H, ddd (app q), *J* = 6.4 Hz), 2.75-2.72 (2H, m), 1.70-1.38 (7H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.2, 140.0, 133.8, 130.2, 129.4, 127.1, 126.6, 114.6, 73.1, 36.7, 33.5, 29.6, 25.1; IR (neat): 3361.9 (br), 3068.9 (w), 2933.6 (m), 2859.9 (m), 1643.7 (w), 1571.6 (w), 1474.0 (m), 1442.4 (m), 1131.2 (w), 1051.3 (m), 1032.1 (m), 990.6 (m), 921.4 (m), 750.1 (s), 680.2 (w) cm^{-1}; HRMS-(DART) for: $C_{13}H_{21}ClNO$ $[M+NH_4]^+$: calculated: 242.1312, found: 242.1311.



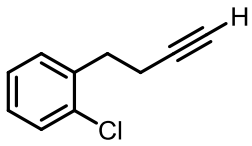
(*E*)-1-chloro-2-(7-chlorohept-5-en-1-yl)benzene. Prepared according to the general procedure utilizing thionyl chloride (2.13 mL, 29.2 mmol), 7-(2-chlorophenyl)hept-1-en-3-ol (655.7 mg, 2.92 mmol), and DCM (12 mL). The crude material was purified (SiO_2, 2% ethyl acetate in hexanes) to give the desired product as a 5:1 mixture of the title compound: 1-chloro-2-(5-chlorohept-6-en-1-yl)benzene (clear, colorless oil, 619.0 mg, 87%). R_f = 0.51 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): (major isomer) δ 7.34 (1H, dd, *J* = 7.8, 1.0 Hz), 7.22-7.16 (2H, m), 7.13 (1H, ddd (app dt's), *J* = 7.8, 2.0 Hz), 5.78 (1H, dt's, *J* = 15.2, 6.4 Hz), 5.63 (1H, dtt's, *J* = 15.2, 7.3, 1.5 Hz), 4.03 (2H, dd, *J* = 6.4, 1.0 Hz), 2.74 (2H, t, *J* = 7.8 Hz), 2.12 (2H, dt (app q), *J* = 7.3 Hz), 1.68-1.61 (2H,

m), 1.48 (2H, tt's (app q), J = 7.3 Hz); (minor isomer) δ 7.34 (1H, dd, J = 7.8, 1.0 Hz), 7.22-7.11 (3H, m), 5.89 (1H, ddd, J = 17.1, 10.3, 8.3 Hz), 5.26 (1H, d, J = 16.6 Hz), 5.14 (1H, d, J = 9.8 Hz), 4.35 (1H, ddd (app q), J = 7.3 Hz), 2.76-2.72 (2H, m), 1.93-1.80 (2H, m), 1.70-1.45 (4H, m); ^{13}C NMR (126 MHz, $CDCl_3$): (both isomers) δ 140.0, 139.8, 138.7, 135.8, 133.9, 133.9, 130.3, 130.3, 129.5, 129.4, 127.2, 127.2, 126.7, 126.7, 126.1, 116.4, 63.0, 45.4, 38.0, 33.4, 33.4, 31.8, 29.2, 29.1, 28.5, 26.2; IR (neat): 3064.8 (w), 3016.2 (w), 2932.6 (m), 2858.7 (m), 1737.4 (w), 1665.6 (w), 1595.0 (w), 1571.5 (w), 1474.0 (m), 1441.9 (m), 1348.6 (w), 1249.8 (m), 1052.1 (w), 966.3 (m), 750.8 (s), 678.9 (m) cm^{-1}; HRMS-(DART) for: $C_{13}H_{16}Cl_2$ $[M]^+$: calculated: 242.0629, found: 242.0628.



(*E*)-2-(7-(2-chlorophenyl)hept-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizing $PdCl_2$ (4.2 mg, 0.024 mmol), $B_2(pin)_2$ (606.9 mg, 2.39 mmol), THF (2.4 mL), and (*E*)-1-chloro-2-(7-chlorohept-5-en-1-yl)benzene (5:1 with regio-isomeric allyl chloride, 581.2 mg, 2.39 mmol). The crude material was purified (SiO_2, 6% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (604.4 mg, 76%). R_f = 0.40 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (1H, dd, J = 7.8, 1.5 Hz), 7.20 (1H, dd, J = 7.8, 2.0 Hz), 7.16 (1H, ddd (app dt's), J = 7.3, 1.5 Hz), 7.11 (1H, ddd (app dt's), J = 7.3, 2.0 Hz), 5.46 (1H, dt's, J = 15.2, 7.8 Hz), 5.39 (1H, dt's, J = 15.2, 6.9 Hz), 2.71 (2H, t, J = 7.8 Hz), 2.03 (2H, dt's (app q), J = 6.9 Hz), 1.64 (2H, d, J = 6.9 Hz), 1.62-1.58 (2H, m), 1.42 (2H, tt's (app p), J = 7.8 Hz), 1.24 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 140.3, 133.9, 130.6, 130.3, 129.3, 127.0, 126.6, 125.0, 83.1, 33.4, 32.5, 29.3, 29.2, 24.7; IR (neat): 3061.1

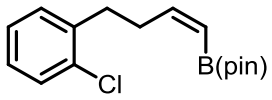
(w), 2978.1 (m), 2928.6 (m), 2857.6 (w), 1474.1 (m), 1442.6 (m), 1359.0 (s), 1325.4 (s), 1272.4 (w), 1144.3 (s), 966.7 (s), 846.9 (m), 750.4 (s), 676.4 (w) cm^{-1}; HRMS-(DART) for: $C_{19}H_{29}BClO_2$ $[M+H]^+$: calculated: 335.1949, found: 335.1945.



1-(but-3-yn-1-yl)-2-chlorobenzene. Prepared according to the literature procedure.[55] To a flame-dried 250 mL round-bottomed flask equipped with magnetic stir bar was added K_2CO_3 (1.382 g, 10.0 mmol). The flask was sealed with a septum and evacuated, then back-filled with nitrogen (3x). Dry methanol (25 mL) was added, followed by 3-(2-chlorophenyl)propanal (843.1 mg, 5.00 mmol) as a solution in dry methanol (12.5 mL), and diethyl (1-diazo-2-oxopropyl)phosphonate (Ohira-Bessman reagent 1.321 g, 6.00 mmol) as a solution in dry methanol (12.5 mL). The resulting cloudy, yellow reaction mixture was stirred at room temperature for 12 hours. The reaction was diluted with diethyl ether (75 mL) and 5% aqueous sodium bicarbonate and the layers separated. The aqueous layer was extracted with diethyl ether (2 x 50 mL) and the combined organic layers were washed with brine (75 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified (SiO_2, 100% hexanes) to give the desired product as a clear, colorless oil (548.6 mg, 67%). R_f = 0.55 (100% hexanes, UV/$KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 (1H, dd, *J* = 7.8, 1.5 Hz), 7.29 (1H, dd, *J* = 7.3, 2.0 Hz), 7.21 (1H, ddd (app dt's), *J* = 7.3, 1.5 Hz), 7.18 (1H, ddd (app dt's), *J* = 7.3, 2.0 Hz), 2.98 (2H, t, *J* = 7.3 Hz), 2.53 (2H, dt's, *J* = 7.3, 2.9 Hz), 1.99 (1H, t, *J* = 2.9 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 137.8, 133.9, 130.7, 129.5, 127.9, 126.7, 83.4, 69.0, 32.6, 18.6; IR (neat): 3300.0 (m), 2362.7 (w), 2322.4 (w), 1474.7 (w), 1444.3 (w), 1053.3 (w), 1038.7

[55] Gung, B. W.; Dickson, H. *Org. Lett*. **2002**, *4*, 2517.

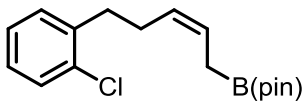
(w), 750.0 (s), 637.6 (m) cm^{-1}; HRMS-(DART) for: $C_{10}H_{10}Cl$ $[M+H]^+$: calculated: 165.0471, found: 165.0469.



(*Z*)-2-(4-(2-chlorophenyl)but-1-en-1-yl)-4,4,5,5-tetramethyl-1, 3,2-dioxaborolane. Prepared according to the literature procedure.[56] To an oven-dried scintillation vial in the glovebox equipped with magnetic stir bar was added chloro(1,5-cyclooctadiene)rhodium(I) dimer (19.3 mg, 0.039 mmol), triisopropylphosphine (25.1 mg, 0.157 mmol), cyclohexane (7.0 mL), triethylamine (0.37 mL, 2.6 mmol), and catecholborane (0.28 mL, 2.6 mmol). The reaction mixture was stirred for 30 minutes followed by addition of 1-(but-3-yn-1-yl)-2-chlorobenzene (516.7 mg, 3.14 mmol). After stirring at room temperature for 2 hours, pinacol (463.5 mg, 3.92 mmol) was added in one portion and the vial was removed from the glovebox and stirred at room temperature for 12 hours. The resulting dark reaction mixture was diluted with 10% ethyl acetate in hexanes (10 mL) and eluted through a short plug of SiO_2 with additional 10% ethyl acetate in hexanes (150 mL). The resulting clear, yellow solution was concentrated under reduced pressure and the crude material was purified (SiO_2, 5% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (>40:1 Z:E, 586.8 mg, 77%). R_f = 0.37 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33 (1H, dd, *J* = 7.8, 1.5 Hz), 7.23 (1H, dd, *J* = 7.3, 2.0 Hz), 7.17 (1H, ddd (app dt's), *J* = 7.3, 1.5 Hz), 7.12 (1H, ddd (app dt's), *J* = 7.8, 2.0 Hz), 6.48 (1H, dt's, *J* = 13.7, 6.9 Hz), 5.38 (1H, dt's, *J* = 13.7, 1.0 Hz), 2.84-2.81 (2H, m), 2.76-2.71 (2H, m), 1.25 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 153.3, 139.4, 134.0, 130.6, 129.3, 127.2, 126.5, 82.8, 33.5, 32.2, 24.8; IR (neat): 3066.8 (w), 2978.5 (m), 2929.9 (w),

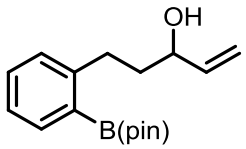
[56] Ohmura, T.; Yamamoto, Y.; Miyaura, N. *J. Am. Chem. Soc*. **2000**, *122*, 4990.

2862.2 (w), 1628.6 (m), 1474.4 (w), 1439.5 (m), 1422.5 (m), 1321.4 (m), 1261.7 (s), 1144.3 (s), 1053.4 (w), 968.8 (w), 749.2 (s), 677.8 (w) cm^{-1}; HRMS-(DART) for: $C_{16}H_{23}BClO_2$ $[M+H]^+$: calculated: 293.1480, found: 293.1478.



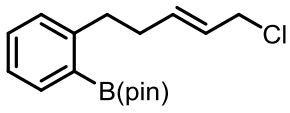
(*Z*)-2-(5-(2-chlorophenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To a flame-dried 50 mL round-bottomed flask equipped with magnetic stir bar under nitrogen was added (*Z*)-2-(4-(2-chlorophenyl)but-1-en-1-yl)-4,4,5,5-tetramethyl-1, 3,2-dioxaborolane (522.5 mg, 1.79 mmol), followed by THF (18 mL) and bromochloromethane (0.15 mL, 2.3 mmol). The resulting clear, colorless solution was cooled to -78 ^oC (dry ice/acetone bath) and treated dropwise with *n*-butyllithium (2.5 M in hexane, 0.93 mL, 2.3 mmol). After stirring at -78 ^oC for 20 minutes, the cooling bath was removed and the reaction mixture was allowed to slowly warm to room temperature and stirred an additional 3 hours. The resulting slightly cloudy reaction mixture was cooled to 0 ^oC (ice/water bath) and water (10 mL) was slowly added. The mixture was diluted with ethyl acetate (50 mL) and additional water (20 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified (SiO_2, 6% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (339.6 mg, 62%). R_f = 0.35 (5% ethyl acetate in hexanes, UV/magic stain). ^1H NMR (500 MHz, $CDCl_3$): δ 7.33 (1H, dd, *J* = 7.8, 1.5, Hz), 7.23 (1H, dd, *J* = 7.3, 1.5 Hz), 7.17 (1H, ddd (app dt's), *J* = 7.3, 1.5 Hz), 7.12 (1H, ddd (app dt's), *J* = 7.8, 2.0 Hz), 5.58-5.52 (1H, m), 5.48-5.42 (1H, m), 2.78 (2H, t, *J* = 7.8 Hz), 2.36 (2H, dt's (app q), *J* = 7.8 Hz), 1.67 (2H, d, *J* = 7.8 Hz), 1.24 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 139.7, 133.9, 130.4,

129.3, 128.3, 127.2, 126.6, 125.3, 83.2, 33.5, 27.1, 24.7; IR (neat): 3059.7 (w), 2978.2 (m), 2930.9 (w), 2864.6 (w), 1473.9 (w), 1443.5 (w), 1324.7 (s), 1272.5 (w), 1214.1 (w), 1143.8 (s), 1052.6 (w), 967.8 (w), 882.9 (w), 847.3 (w), 749.1 (m) cm^{-1}; HRMS-(DART) for: $C_{17}H_{25}BClO_2$ $[M+H]^+$: calculated: 307.1636, found: 307.1645.



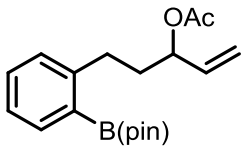
5-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pent-1-en-3-ol. To a flame-dried two-neck 250 mL round-bottomed flask equipped with magnetic stir bar in the glovebox was added sodium hydride (576.0 mg, 24.0 mmol). The flask was sealed with septa, removed from the glovebox and equipped with a reflux condenser. THF (50 mL) was added and the resulting mixture was cooled to 0 ^oC (ice/water bath). To the cooled, stirring mixture was added 5-(2-bromophenyl)pent-1-en-3-ol (2.900 g, 12.0 mmol) as a solution in THF (10 mL). The resulting slightly yellow reaction mixture was then removed from the bath, warmed to room temperature, then heated to 80 ^oC in an oil bath. After 2.5 hours the resulting yellow-orange reaction mixture was cooled to room temperature, then to -78 ^oC (dry ice/acetone bath) and treated dropwise with *n*-butyllithium (2.51 M in hexane, 5.3 mL, 13 mmol), resulting in a slight darkening of the reaction mixture. After stirring for approximately 5 minutes at -78 ^oC, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.93 mL, 19.2 mmol) was added dropwise. The reaction was stirred at -78 ^oC for an additional 10 minutes, then warmed to room temperature. After 2 hours, the reaction was cooled to 0 ^oC (ice/water bath) and slowly quenched with the dropwise addition of water (6 mL). The reaction was diluted with ethyl acetate (75 mL) and additional water (50 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered and

concentrated under reduced pressure. The crude material was purified (SiO_2, 20% ethyl acetate in hexanes) to give the desired product as an inseparable mixture of the title compound and proto-debrominated starting material (5:1 respectively), (clear, slightly yellow, viscous oil, 2.8722 g, 83%). R_f = 0.28 (25% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.81 (1H, d, *J* = 6.9 Hz), 7.37 (1H, ddd (app dt's), *J* = 7.8, 1.5 Hz), 7.24-7.18 (2H, m), 5.89 (1H, ddd, *J* = 17.1, 10.5, 5.4 Hz), 5.25 (1H, ddd (app dt's), *J* = 17.1, 1.5 Hz), 5.08 (1H, ddd (app dt's), *J* = 10.7, 1.5 Hz), 4.11-4.07 (1H, m), 3.04-2.93 (3H, m), 1.90-1.76 (2H, m), 1.37 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 148.8, 141.1, 136.4, 131.2, 129.3, 125.2, 113.9, 83.8, 71.5, 40.7, 31.2, 24.9, 24.6; IR (neat): 3445.3 (br), 3067.2 (w), 2978.2 (m), 2931.0 (w), 2868.6 (w), 1644.3 (w), 1599.5 (m), 1568.8 (w), 1442.0 (m), 1381.1 (s), 1346.8 (s), 1311.7 (s), 1144.5 (s), 1071.4 (m), 861.6 (m), 661.1 (m) cm^{-1}; HRMS-(DART) for: $C_{17}H_{24}BO_2$ $[M+H-H_2O]^+$: calculated: 271.1869, found: 271.1871.



(*E*)-2-(2-(5-chloropent-3-en-1-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizing thionyl chloride (1.10 mL, 15.0 mmol), 5-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pent-1-en-3-ol (as a 5:1 mixture with proto-debrominated material described above) (432.3 mg, 1.50 mmol), and DCM (6.0 mL). The crude material was purified (SiO_2, 6% ethyl acetate in hexanes) to give the desired product as a 9:1 mixture of the title compound: 2-(2-(3-chloropent-4-en-1-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (clear, colorless oil, 368.8 mg, 80%). R_f = 0.38 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): (major isomer)

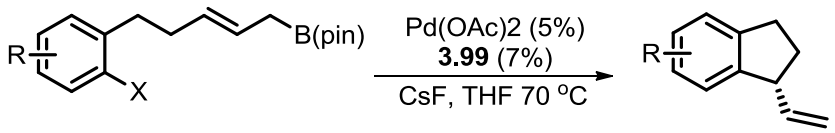
δ 7.81 (1H, d, *J* = 7.3 Hz), 7.36 (1H, dd (app t), *J* = 7.3 Hz), 7.21 (1H, dd (app t), *J* = 7.3 Hz), 7.17 (1H, d, *J* = 7.3 Hz), 5.86 (1H, ddd, *J* = 14.4, 7.1, 6.9 Hz), 5.65 (1H, ddd, *J* = 14.2, 7.1, 6.9 Hz), 4.05 (2H, d, *J* = 7.3 Hz), 2.98 (2H, t, *J* = 7.8 Hz), 2.34 (2H, dt's (app q), *J* = 7.8 Hz), 1.36 (12H, s); (minor isomer) δ 7.84-7.78 (1H, m), 7.39-7.32 (1H, m), 7.24-7.14 (2H, m), 5.97 (1H, ddd, *J* = 17.1, 10.3, 8.3 Hz), 5.30 (1H, d, *J* = 17.1 Hz), 5.17 (1H, d, *J* = 10.3 Hz), 4.41 (1H, ddd (app q), *J* = 7.3 Hz), 3.10-2.92 (2H, m), 2.14-2.06 (2H, m), 1.36 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): (both isomers) δ 148.5, 148.0, 138.8, 136.4, 136.2, 135.7, 131.0, 130.9, 129.4, 129.2, 126.0, 125.4, 125.2, 116.3, 83.5, 83.4, 63.0, 45.5, 41.4, 35.7, 35.3, 33.0, 24.9, 24.9; IR (neat): 3065.6 (w), 2977.4 (m), 2932.4 (m), 2867.3 (w), 1664.7 (w), 1599.3 (m), 1569.1 (w), 1488.3 (m), 1441.5 (s), 1380.5 (s), 1344.6 (s), 1311.5 (s), 1261.7 (s), 1213.8 (m), 1142.9 (s), 1115.2 (s), 1075.5 (s), 1039.7 (m), 962.0 (s), 862.0 (s), 759.9 (s), 673.5 (s) cm^{-1}; HRMS-(DART) for: $C_{17}H_{25}BClO_2$ $[M+H]^+$: calculated: 307.1636, found: 307.1636.



5-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pent-1-en-3-yl acetate. To a flame-dried 50 mL round-bottomed flask equipped with magnetic stir bar was added 4-dimethylaminopyridine (18.3 mg, 0.150 mmol). The flask was sealed with a septum, evacuated, and back-filled with nitrogen followed by addition of DCM (7.5 mL), triethylamine (0.63 mL, 4.5 mmol), and acetic anhydride (0.28 mL, 3.0 mmol). 5-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pent-1-en-3-ol (as a 5:1 mixture with proto-debrominated material described above) (432.3 mg, 1.50 mmol) as a solution in DCM (7.5 mL). After stirring at room temperature for 3 hours, TLC analysis indicated consumption of starting

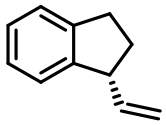
material and the reaction mixture was diluted with DCM (20 mL) and water (20 mL). The layers were separated and the aqueous layer was extracted with DCM (3 x 25 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified (SiO_2, 8% ethyl acetate in hexanes) to give the desired product as a clear, colorless oil (437.2 mg, 88%). R_f = 0.24 (5% ethyl acetate in hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.79 (1H, d, *J* = 7.3 Hz), 7.35 (1H, dd (app t), *J* = 7.3 Hz), 7.20-7.16 (2H, m), 5.86 (1H, ddd, *J* = 17.1, 10.3, 6.4 Hz), 5.34 (1H, ddd (app q), *J* = 5.9 Hz), 5.28 (1H, d, *J* = 17.1 Hz), 5.19 (1H, d, *J* = 10.8 Hz), 2.96-2.86 (2H, m), 2.08 (2H, s), 1.96-1.84 (2H, m), 1.35 (12H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 170.3, 148.6, 136.6, 136.3, 131.0, 129.2, 125.2, 116.4, 83.4, 74.9, 37.4, 31.7, 24.9, 24.8, 21.2; IR (neat): 3066.0 (w), 2977.8 (m), 2934.7 (w), 2871.7 (w), 1736.1 (s), 1646.9 (w), 1599.5 (m), 1569.5 (w), 1488.5 (m), 1442.1 (m), 1371.2 (s), 1345.2 (s), 1312.8 (s), 1233.3 (s), 1144.1 (s), 1110.7 (m), 1079.8 (m), 1021.5 (s), 962.5 (m), 861.5 (m), 755.8 (m), 661.2 (s) cm^{-1}; HRMS-(DART) for: $C_{19}H_{31}BNO_4$ $[M+NH_4]^+$: calculated: 348.2346, found: 348.2362.

3.5.2.4 Representative procedure for intramolecular coupling



To an oven-dried 2-dram vial equipped with magnetic stir bar in the glovebox was added **3.99** (0.07 equiv.), followed by cesium fluoride (3.00 equiv.), 1,3,5-trimethoxy benzene (internal standard, 10.0 mg), substrate (1.00 equiv.) and $Pd(OAc)_2$ (0.05 equiv.) as a solution in THF (0.2 M in substrate) resulting in a yellow-orange reaction mixture. The vial was sealed with a cap, removed from the glovebox and heated to 70 ^{o}C with vigorous stirring for 14 hours. The resulting grey, cloudy reaction mixture was cooled to room temperature, diluted with diethyl ether (2 mL) and passed through a short plug of SiO_2, eluding with additional diethyl ether (10 mL). The resulting clear, yellow solution was concentrated under reduced pressure and the crude reaction material analyzed for conversion and yield by ^{1}H NMR analysis. The pure cyclized products were isolated after SiO_2 chromatography.

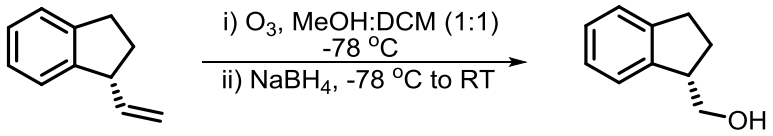
3.5.2.5 Full characterization and proof of stereochemistry



(*R*)-1-vinyl-2,3-dihydro-1*H*-indene. Prepared according to the general procedure utilizing **3.99** (17.3 mg, 0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (*E*)-2-(5-(2-chlorophenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (76.7 mg, 0.250 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), and THF (1.25 mL). The crude material was purified (SiO_2, 100% pentane) to give the desired product as a clear, colorless oil (27.5 mg, 76%). R_f = 0.34 (100% hexanes, UV/$KMnO_4$). ^1H NMR (500 MHz, $CDCl_3$): δ 7.27-7.25 (1H, m), 7.20-7.17 (3H, m), 5.89 (1H, ddd, *J* = 17.1, 9.3, 8.3 Hz), 5.18 (1H, dd, *J* = 17.1, 1.0 Hz), 5.12 (1H, dd, *J* = 9.8, 1.0 Hz), 3.78 (1H, ddd (app q), *J* = 8.3 Hz), 2.99-2.86 (2H, m), 2.36 (1H, dddd (app dtd's), *J* = 11.7, 7.8, 3.9 Hz), 1.88 (1H, dddd (app dq's), *J* = 12.7, 8.8 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.6, 143.9, 141.1, 126.5, 126.2, 124.4, 124.3, 114.8, 49.8, 33.1, 31.6; IR (neat): 3070.7 (w), 2954.6 (m), 2939.3 (m), 2926.2 (m), 2848.2 (m), 1638.4 (w), 1474.6 (m), 1457.7 (m), 1437.5 (w), 991.7 (m), 913.0 (s), 768.2 (m), 742.2 (s) cm^{-1}; HRMS-(DART) for: $C_{11}H_{13}$ $[M+H]^+$: calculated: 145.1017, found: 145.1024. $[\alpha]_D^{20}$ = -69.23 (*c* = 1.360, $CHCl_3$, *l* = 50 mm).

Proof of stereochemistry:

The title compound was subjected to tandem ozonolysis/reduction as shown below to give (*S*)-(2,3-dihydro-1*H*-inden-1-yl)methanol and the specific rotation was measured ($[\alpha]_D^{20}$ = -11.5 (*c* = 0.550, benzene, *l* = 50 mm). This value was compared to the known literature value[57] ($[\alpha]_D^{20}$ = -14.3 (benzene, 85% *ee* material) for (*S*)-(2,3-dihydro-1*H*-inden-1-yl)methanol.



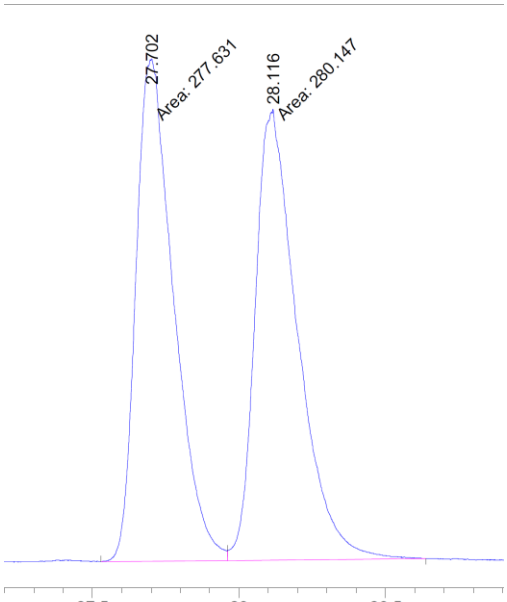
Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (*E*)-2-(5-(2-chlorophenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and Pd(dppf)Cl_2 as the pre-catalyst.

[57] Caro, Y.; Torrado, M.; Masaguer, C. F.; Raviña, E. *Tetrahedron Asymm*. **2003**, *14*, 3689.

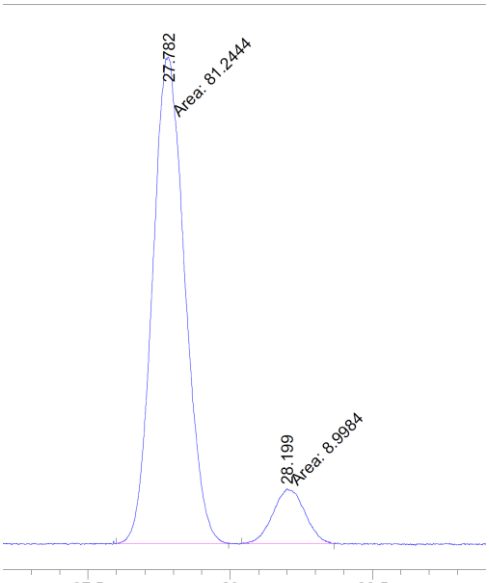
Chiral GLC (β-dex, Supelco, 80 °C for 5 min, ramp 1 °C/min to 150 °C, 20 psi) – analysis of 1-vinyl-2,3-dihydro-1H-indene.

Racemic Material



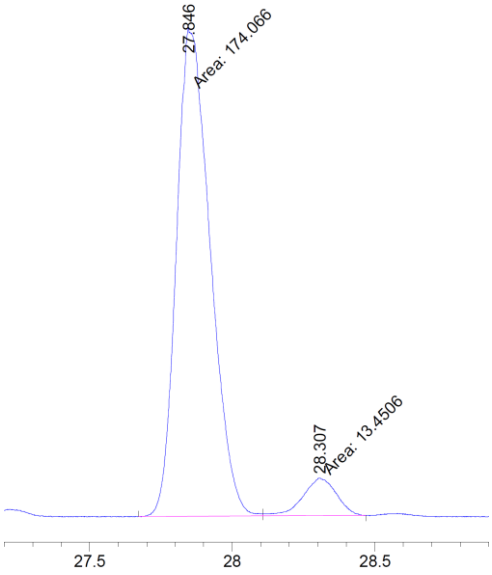
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	27.702	MF	0.1490	277.63089	31.05866	49.77444
2	28.116	FM	0.1676	280.14709	27.85743	50.22556
Totals :				557.77798	58.91609	

Standard Conditions

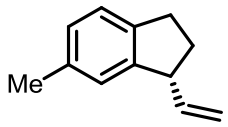


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	27.782	MM	0.1311	81.24442	10.32570	90.02868
2	28.199	MM	0.1293	8.99840	1.15978	9.97132
Totals :				90.24282	11.48548	

Standard Conditions + NBu_4Cl



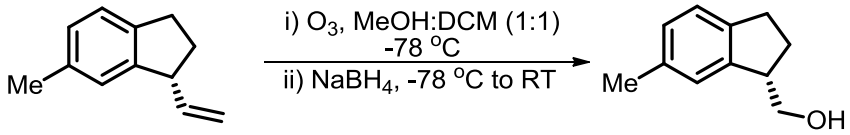
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	27.846	MF	0.1373	174.06595	21.13496	92.82700
2	28.307	FM	0.1373	13.45055	1.63301	7.17300
Totals :				187.51650	22.76797	



(*R*)-6-methyl-1-vinyl-2,3-dihydro-1H-indene. Prepared according to the general procedure utilizing **3.99** (17.3 mg, 0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (*E*)-2-(5-(2-chloro-4-methylphenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborol-ane (80.2 mg, 0.250 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), and THF (1.25 mL). The crude material was purified (SiO_2, 100% pentane) to give the desired product as a clear, colorless oil (27.0 mg, 68%). R_f = 0.38 (100% hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.13 (1H, d, *J*= 7.5 Hz), 6.98 (1H, d, *J* = 11.5 Hz), 6.97 (1H, s), 5.85 (1H, ddd (app dt's), *J* = 17.0, 8.5 Hz), 5.16 (1H, d, *J* = 17.0 Hz), 5.09 (1H, d, *J* = 10.0 Hz), 3.72 (1H, ddd (app q), *J* = 8.5 Hz), 2.99 (1H, ddd, *J* = 15.0, 9.0, 3.5 Hz), 2.83 (1H, ddd (app dt's), *J* = 15.5, 8.0 Hz), 2.36-2.30 (1H, m), 2.33 (3H, s), 1.85 (1H, dddd (app dq's), *J* = 12.5, 8.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 145.8, 141.3, 140.9, 135.8, 127.3, 125.0, 124.1, 114.7, 49.8, 33.3, 31.2, 21.2; IR (neat): 3004.3 (w), 2922.8 (s), 2855.7 (m), 1732.8 (w), 1612.5 (m), 1491.0 (s), 1452.4 (m), 1439.4 (m), 1230.3 (w), 1119.4 (w), 1037.3 (s), 911.4 (s), 885.6 (w), 808.4 (s), 687.3 (w), 447.8 (w), 422.7 (w) cm^{-1}; HRMS-(DART) for: $C_{12}H_{15}$ $[M+H]^+$: calculated: 159.1174, found: 159.1177. $[\alpha]_D^{20}$ = -73.6 (*c* = 0.535, $CHCl_3$, *l* = 50 mm).

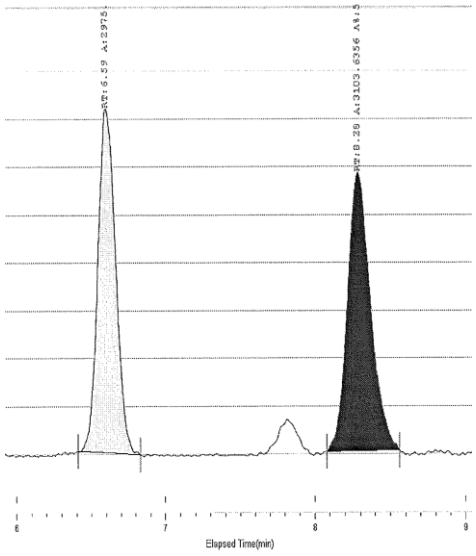
Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (*E*)-2-(5-(2-chloro-4-methylphenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxa-borolane and $Pd(OAc)_2$ / PCy_3 as the pre-catalyst. The title compound was subjected to tandem ozonolysis/reduction as shown below to give (*S*)-(6-methyl-2,3-dihydro-1H-inden-1-yl)methanol. Further analysis of stereochemistry was performed on (*S*)-(6-methyl-2,3-dihydro-1H-inden-1-yl)methanol. Absolute stereochemistry was assigned by analogy.



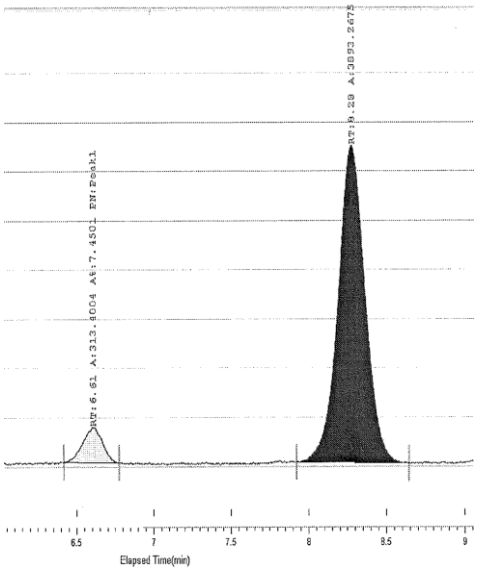
Chiral SFC (Chiracel OJ-H, 3% IPA/hexane, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-(6-methyl-2,3-dihydro-1H-inden-1-yl)methanol

Racemic Material

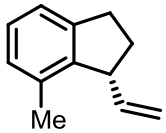


Peak No	% Area	Area	RT (min)
1	48.9441	2975.2647	6.59
2	51.0559	3103.6356	8.28
Total:	100	6078.9003	

Standard Conditions



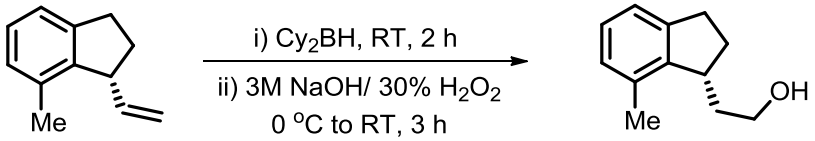
Peak No	% Area	Area	RT (min)
1	7.4501	313.4004	6.61
2	92.5499	3893.2675	8.28
Total:	100	4206.6679	



(*R*)-7-methyl-1-vinyl-2,3-dihydro-1H-indene. Prepared according to the general procedure utilizing **3.99** (17.3 mg, 0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (*E*)-2-(5-(2-chloro-3-methylphenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (80.2 mg, 0.250 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), and THF (1.25 mL). The crude material was purified (SiO_2, 100% pentane) to give the desired product as a clear, colorless oil (28.9 mg, 73%). R_f = 0.36 (100% hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.10-7.06 (2H, m), 6.96-6.95 (1H, m), 5.87 (1H, ddd, *J* = 17.0, 10.0, 8.0 Hz), 4.97-4.90 (2H, m), 3.82 (1H, ddd (app td's), *J* = 8.0, 2.0 Hz), 3.00 (1H, ddd (app dt's), *J*= 16.5, 9.0 Hz), 2.82 (1H, ddd, *J*= 16.0, 9.0, 3.0 Hz) 2.33-2.25 (1H, m), 2.26 (3H, s), 1.94 (1H, dddd (app ddt's), *J* = 13.0, 5.5, 3.0 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 143.9. 143.4, 140.0, 134.8, 127.5, 126.9, 121.9, 113.3, 48.3, 32.5, 31.2, 18.8; IR (neat): 3017.9 (w), 2939.6 (m), 2847.7 (m), 1633.9 (w), 1596.6 (w), 1474.6 (m), 1459.4 (m), 1377.6 (w) 991.9 (m), 908.6 (s), 811.1 (s), 686.1 (m) 603.5 (w) cm^{-1}; HRMS-(DART) for: $C_{12}H_{15}$ $[M+H]^+$: calculated: 159.1174, found: 159.1176. $[\alpha]_D^{20}$ = -7.31 (*c* = 0.950, $CHCl_3$, *l* = 50 mm).

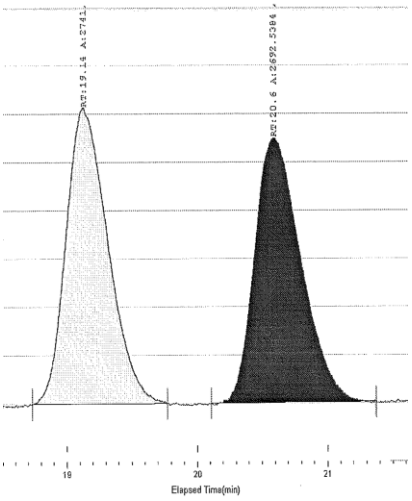
Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (*E*)-2-(5-(2-chloro-3-methylphenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and Pd(dppf)Cl_2 as the pre-catalyst. The title compound was subjected to tandem hydroboration/oxidation as shown below to give (*R*)-2-(7-methyl-2,3-dihydro-1H-inden-1-yl)ethanol. Further analysis of stereochemistry was performed on (*R*)-2-(7-methyl-2,3-dihydro-1H-inden-1-yl)ethanol. Absolute stereochemistry was assigned by analogy.



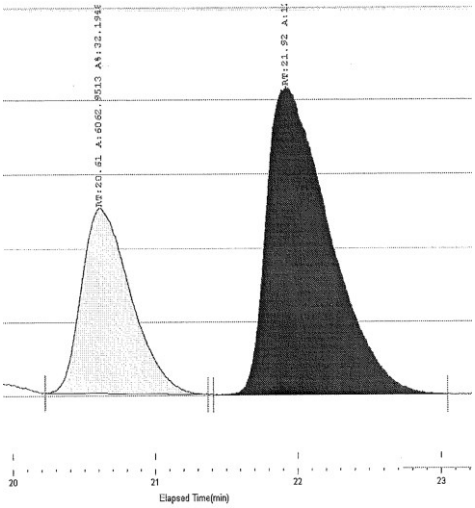
Chiral SFC (Chiracel OJ-H, 3% IPA/hexane, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2-(7-methyl-2,3-dihydro-1H-inden-1-yl)ethanol.

Racemic Material

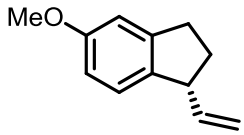


Peak No	% Area	Area	RT (min)
1	50.4504	2741.4917	19.14
2	49.5496	2692.5384	20.6
Total:	100	5434.0301	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	32.1948	6062.9513	20.61
2	67.8052	12769.151	21.92
Total:	100	18832.1023	



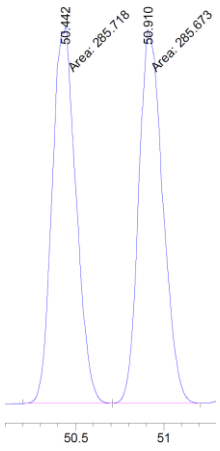
(*R*)-5-methoxy-1-vinyl-2,3-dihydro-1H-indene. Prepared according to the general procedure utilizing **3.99** (17.3 mg, 0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (*E*)-2-(5-(2-chloro-5-methoxy-phenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (84.2 mg, 0.250 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), and THF (1.25 mL). The crude material was purified (SiO_2, 100% pentane) to give the desired product as a clear, colorless oil (40.2 mg, 77%). R_f = 0.18 (100% hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.05 (1H, d, *J*= 8.0 Hz), 6.90 (1H, s), 6.74 (1H, dd, *J* = 8.5, 2.5 Hz), 5.84 (1H, ddd, *J* = 17.5, 10.0, 8.5 Hz), 5.12 (1H, ddd (app dq's), *J* = 17.0, 1.0 Hz), 5.07 (1H, ddd (app dq's), *J* = 10.0, 1.0 Hz), 3.80 (3H, s), 3.70 (1H, ddd (app q), *J* = 8.0 Hz), 2.91 (1H, ddd, *J* = 15.5, 8.5, 3.5 Hz), 2.84 (1H, ddd (app dt's), *J* = 16.0, 8.0 Hz), 2.34 (1H, ddd (app dtd's), *J*= 12.5, 8.0, 4.0 Hz), 1.86 (1H, dddd (app dq's), *J* = 12.5, 8.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.0, 145.5, 141.6, 137.8, 124.8, 114.4, 112.0, 109.9, 55.4, 49.0, 33.5, 31.8; IR (neat): 3077.1 (w), 2996.4 (w), 2940.1 (m), 2833.3 (w), 1605.4 (m), 1584.9 (w), 1487.5 (s), 1378.3 (m), 1253.6 (m), 1240.7 (s), 1118.1 (s), 1032.9 (s), 991.9 (m), 864.9 (s), 839.9 (m), 806.6 (m), 697.8 (w), 627.1 (w), 435.7 (m) cm^{-1}; HRMS-(DART) for: $C_{12}H_{15}O$ $[M+H]^+$: calculated: 175.1123, found: 175.1127. $[\alpha]_D^{20}$ = -84.00 (*c* = 1.040, $CHCl_3$, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (*E*)-2-(5-(2-chloro-5-methoxy-phenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxa-borolane and Pd(dppf)Cl_2 as the pre-catalyst. Absolute stereochemistry was assigned by analogy.

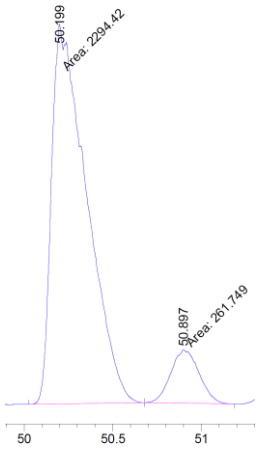
Chiral GLC (β-dex, Supelco, 90 °C for 5 min, ramp 1 °C/min to 140 °C, 20 psi) – analysis of (R)-5-methoxy-1-vinyl-2,3-dihydro-1H-indene.

Racemic Material

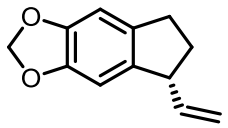


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	50.442	MM	0.1567	285.71756	30.39396	50.00391
2	50.910	MM	0.1585	285.67285	30.03251	49.99609
Totals :				571.39041	60.42647	

Standard Conditions



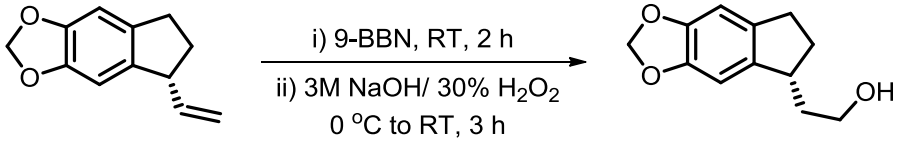
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	50.199	MM	0.2294	2294.41724	166.71036	89.76009
2	50.897	MM	0.1855	261.74902	23.51253	10.23991
Totals :				2556.16626	190.22289	



(*R*)-5-vinyl-6,7-dihydro-5H-indeno[5,6-d][1,3]dioxole. Prepared accord-ing to the general procedure utilizing **3.99** (17.3 mg, 0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (*E*)-2-(5-(6-chlorobenzo[d][1,3]dioxol-5-yl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (87.7 mg, 0.250 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), and THF (1.25 mL). The crude material was purified (SiO_2, 100% pentane) to give the desired product as a clear, colorless oil (25.4 mg, 54%). R_f = 0.08 (100% hexanes, UV/magic stain). ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.69 (1H, s), 6.61 (1H, s), 6.74 (1H, dd, *J* = 8.5, 2.5 Hz), 5.91 (2H, dd, *J*= 3.5, 1.0 Hz), 5.80 (1H, ddd, *J* = 17.0, 10.0, 8.0 Hz), 5.12 (1H, ddd (app dq's), *J* = 17.0, 1.0 Hz), 5.06 (1H, ddd (app dq's), *J* = 9.0, 1.0 Hz), 3.64 (1H, ddd (app q), *J* = 8.0 Hz), 2.83 (1H, ddd, *J* = 15.0, 8.0, 3.5 Hz), 2.76 (1H, ddd (app dt's), *J* = 15.5, 9.0 Hz), 2.33 (1H, ddd (app dtd's), *J*= 12.0, 7.0, 3.5 Hz), 1.86 (1H, dddd (app dq's), *J* = 13.0, 8.5 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 146.7, 146.4, 141.4, 138.5, 136.6, 114.7, 105.0, 105.0, 100.9, 49.7, 33.6, 31.4; IR (neat): 3076.4 (w), 2929.0, m), 2850.1 (m), 1768.3 (w), 1637.7 (w), 1470.6 (s), 1351.5 (m), 1294.2 (s), 1268.1 (s), 1170.5 (s), 1038.1 (s) 992.7 (m), 940.0 (s), 913.4 (s), 855.8 (s), 823.1 (m), 775.1 (w), 682.1 (w), 419.2 (m) cm^{-1}; HRMS-(DART) for: $C_{12}H_{12}O_2[M+H]^+$: calculated: 188.0837, found: 188.0834. $[\alpha]_D^{20}$ = -69.2 (*c* = 0.590, $CHCl_3$, *l* = 50 mm).

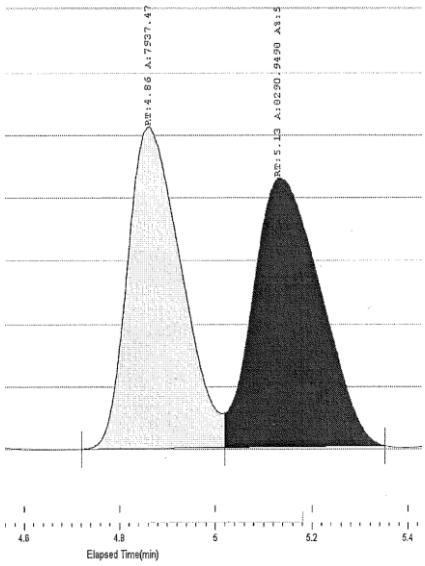
Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (*E*)-2-(5-(6-chlorobenzo[d][1,3]dioxol-5-yl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and Pd(dppf)Cl_2 as the pre-catalyst. The title compound was subjected to tandem hydroboration/oxidation as shown below to give (*R*)-2-(6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-5-yl)ethanol. Further analysis of stereochemistry was performed on (*R*)-2-(6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-5-yl)ethanol. Absolute stereochemistry was assigned by analogy.



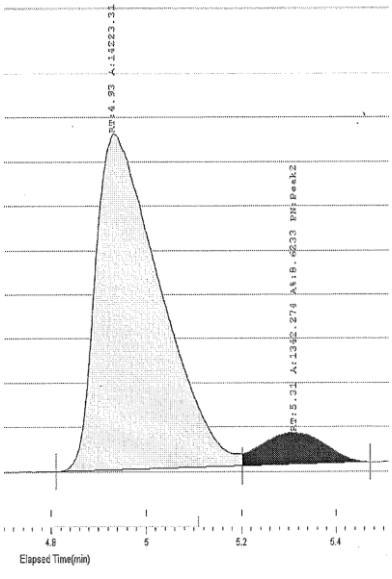
Chiral SFC (Chiracel ODR-H, 1% IPA/hexane, 2 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2-(6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-5-yl)ethanol.

Racemic Material

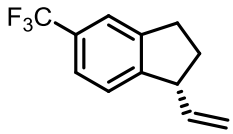


Peak No	% Area	Area	RT (min)
1	48.9109	7937.4771	4.86
2	51.0891	8290.9498	5.13
Total:	100	16228.4269	

Standard Conditions



Peak No	% Area	Area	RT (min)
1	91.3767	14223.3138	4.93
2	8.6233	1342.274	5.31
Total:	100	15565.5878	



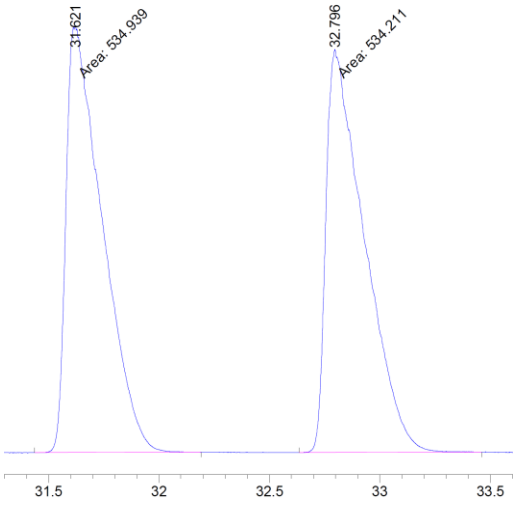
(*R*)-5-(trifluoromethyl)-1-vinyl-2,3-dihydro-1*H*-indene. Prepared according to the general procedure utilizing **3.99** (17.3 mg, 0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (*E*)-2-(5-(2-chloro-5-(trifluoromethyl)phenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (93.7 mg, 0.250 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), and THF (1.25 mL). The crude material was purified (SiO_2, 100% pentane) to give the desired product as a clear, colorless oil (30.7 mg, 58%). R_f = 0.64 (100% hexanes, UV/$KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (1H, s), 7.43 (1H, dd, *J* = 7.8, 1.0 Hz), 7.24 (1H, d, *J* = 7.8 Hz), 5.84 (1H, ddd, *J* = 17.1, 10.3, 7.8 Hz), 5.17 (1H, ddd (app dt's), *J* = 17.1, 1.0 Hz), 5.14 (1H, ddd (app dt's), *J* = 10.3, 1.0 Hz), 3.79 (1H, ddd (app q), *J* = 8.3 Hz), 2.99 (1H, ddd, *J* = 15.7, 8.8, 3.4 Hz), 2.91 (1H, ddd (app dt's), *J* = 16.1, 8.3 Hz), 2.40 (1H, dddd (app dtd's), *J* = 12.7, 7.8, 3.4 Hz), 1.91 (1H, dddd (app dq's), *J* = 12.7, 8.3 Hz); ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.7, 144.7, 140.1, 129.1 (q, J_{C-F} = 32.4 Hz), 124.5 (q, J_{C-F} = 272.8 Hz), 124.5, 123.4 (q, J_{C-F} = 3.8 Hz), 121.3 (q, J_{C-F} = 3.8 Hz), 115.7, 49.6, 33.1, 31.4; IR (neat): 3079.6 (w), 2939.1 (m), 2858.8 (w), 1433.4 (w), 1333.1 (s), 1290.3 (m), 1121.9 (s), 1061.1 (m), 992.2 (w), 918.6 (m), 889.8 (m), 851.1 (w), 830.1 (m) cm^{-1}; HRMS-(DART) for: $C_{12}H_{12}F_3$ $[M+H]^+$: calculated: 213.0891, found: 213.0890. $[\alpha]_D^{20}$ = -40.3 (*c* = 0.960, $CHCl_3$, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (*E*)-2-(5-(2-chloro-5-(trifluoromethyl)phenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and Pd(dppf)Cl_2 as the pre-catalyst. Absolute stereochemistry was assigned by analogy.

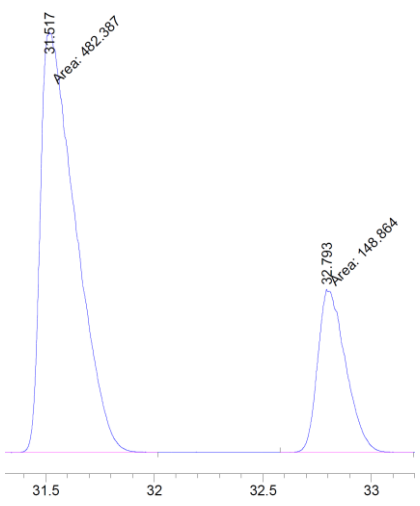
Chiral GLC (β-dex, Supelco, 80 °C for 5 min, ramp 1 °C/min to 150 °C, 20 psi) – analysis of 5-(trifluoromethyl)-1-vinyl-2,3-dihydro-1H-indene.

Racemic Material

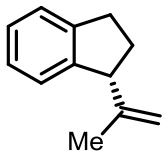


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	31.621	MM	0.1899	534.93860	46.93755	50.03403
2	32.796	MM	0.2010	534.21088	44.30485	49.96597
Totals :				1069.14948	91.24239	

Standard Conditions



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	31.517	MM	0.1879	482.38672	42.79670	76.41761
2	32.793	MM	0.1489	148.86403	16.66365	23.58239
Totals :				631.25075	59.46035	



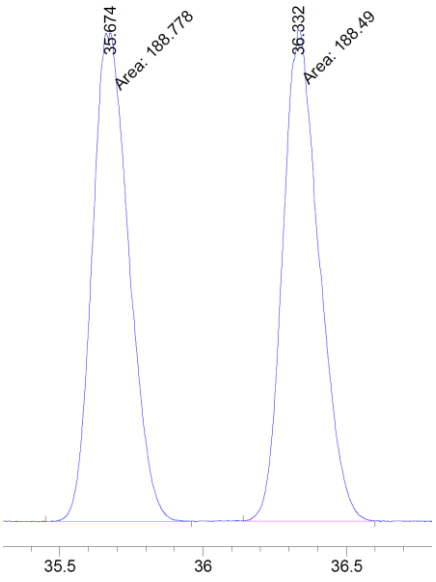
(*R*)-1-(prop-1-en-2-yl)-2,3-dihydro-1*H*-indene. Prepared according to the general procedure utilizing **3.99** (17.3 mg, 0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (*E*)-2-(5-(2-chlorophenyl)-2-methylpent-2-en-1-yl)-4,4,5, 5-tetramethyl-1,3,2-dioxaborolane (80.2 mg, 0.250 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), and THF (1.25 mL). The crude material was purified (SiO_2, 100% pentane) to give the desired product as a clear, colorless oil (31.5 mg, 80%). R_f = 0.43 (100% hexanes, UV/$KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26-7.22 (1H, m), 7.20-7.11 (3H, m), 4.86-4.85 (1H, m), 4.84-4.83 (1H, m), 3.87 (1H, dd (app t), *J* = 8.3 Hz), 2.98 (1H, ddd, *J* = 15.7, 8.8, 4.4 Hz), 2.89 (1H, ddd (app dt's), *J* = 15.7, 7.8 Hz), 2.32-2.25 (1H, m), 2.02-1.94 (1H, m), 1.66 (3H, s); ^{13}C NMR (126 MHz, $CDCl_3$): δ 147.3, 145.2, 144.3, 126.5, 126.1, 124.5, 124.3, 111.6, 53.3, 31.7, 31.2, 19.2; IR (neat): 3069.8 (w), 3021.2 (w), 2957.4 (m), 2944.1 (m), 2848.0 (w), 1644.2 (m), 1477.0 (m), 1457.1 (m), 1437.0 (w), 1373.5 (w), 891.1 (s), 742.2 (s) cm^{-1}; HRMS-(DART) for: $C_{12}H_{15}$ $[M+H]^+$: calculated: 159.1174, found: 159.1176. $[\alpha]_D^{20}$ = -25.43 (*c* = 1.050, $CHCl_3$, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (*E*)-2-(5-(2-chlorophenyl)-2-methylpent-2-en-1-yl)-4,4,5,5-tetramethyl -1,3,2-dioxaborolane and Pd(dppf)Cl_2 as the pre-catalyst. Absolute stereochemistry was assigned by analogy.

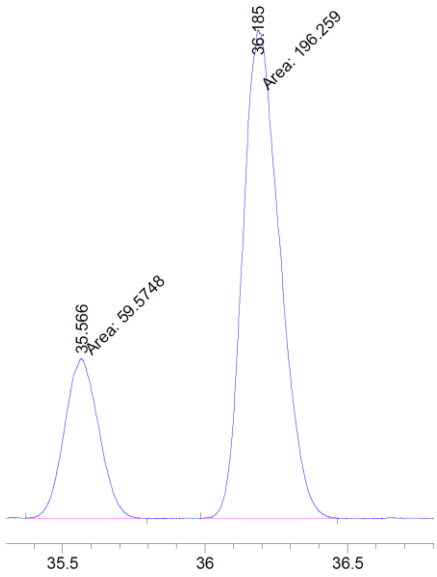
Chiral GLC (β-dex, Supelco, 80 °C for 5 min, ramp 1 °C/min to 150 °C, 20 psi) – analysis of 1-(prop-1-en-2-yl)-2,3-dihydro-1H-indene.

Racemic Material

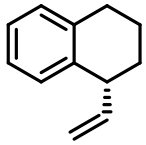


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	35.674	MM	0.1485	188.77815	21.18037	50.03820
2	36.332	MM	0.1475	188.48993	21.30090	49.96180
Totals :				377.26808	42.48127	

Standard Conditions



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	35.566	MM	0.1400	59.57478	7.09374	23.28648
2	36.185	MM	0.1511	196.25943	21.64572	76.71352
Totals :				255.83421	28.73946	



(*R*)-1-vinyl-1,2,3,4-tetrahydronaphthalene. Prepared according to the general procedure utilizing **(*R,R*)-L2** (17.3 mg, 0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (*E*)-2-(6-(2-chlorophenyl)hex-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (80.2 mg, 0.250 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), and THF (1.25 mL). The crude material was purified (SiO_2, 100% pentane) to give the desired product as a clear, colorless oil (21.8 mg, 55%). R_f = 0.38 (100% hexanes, UV/magic stain). All spectral data are in accordance with the literature.[58] HRMS-(DART) for: $C_{12}H_{15}[M+H]^+$: calculated: 159.1174, found: 159.1181. $[\alpha]_D^{20}$ = -21.636 (*c* = 0.610, $CHCl_3$, *l* = 50 mm).

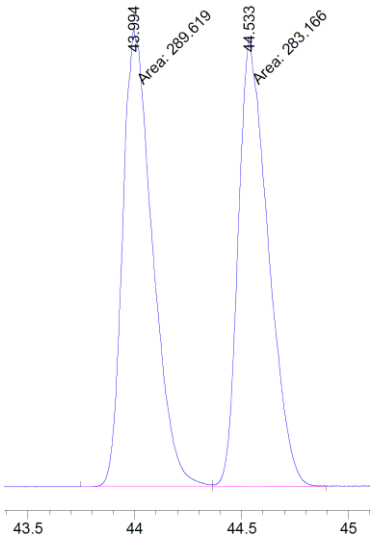
Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (*E*)-2-(6-(2-chlorophenyl)hex-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and $Pd(dppf)Cl_2$ as the pre-catalyst. Absolute stereochemistry was assigned by analogy.

[58] Namba, K.; Yamamoto, H.; Sasaki, I.; Mori, K.; Imagawa, H.; Nishizawa, M. *Org. Lett.* **2008**, *10*, 1767.

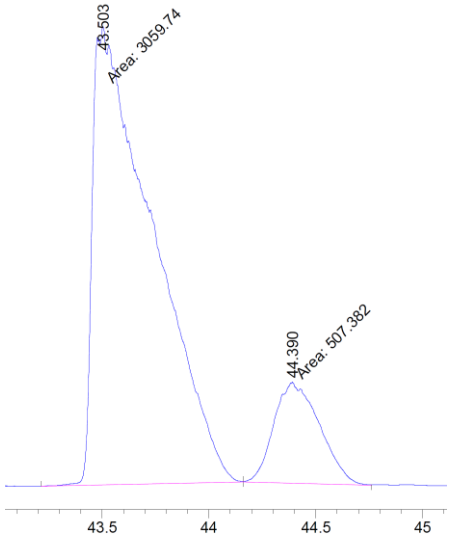
Chiral GLC (β-dex, Supelco, 80 °C for 5 min, ramp 1 °C/min to 150 °C, 20 psi) – analysis of (R)-1-vinyl-1,2,3,4-tetrahydronaphthalene.

Racemic Material

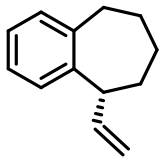


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	43.994	MF	0.1618	289.61905	29.82614	50.56328
2	44.533	FM	0.1613	283.16623	29.25908	49.43672
Totals :				572.78528	59.08522	

Standard Conditions



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	43.503	MM	0.3270	3059.74146	155.95407	85.77616
2	44.390	MM	0.2460	507.38211	34.37797	14.22384
Totals :				3567.12357	190.33204	



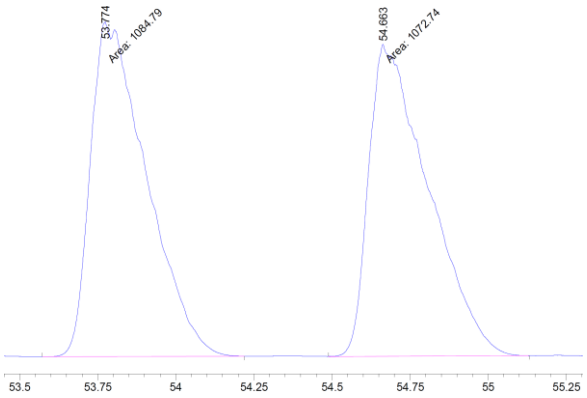
(*R*)-5-vinyl-6,7,8,9-tetrahydro-5*H*-benzo[7]annulene. Prepared according to the general procedure utilizing **3.99** (17.3 mg, 0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (*E*)-2-(7-(2-chlorophenyl)hept-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (83.7 mg, 0.250 mmol), $Pd(OAc)_2$ (2.8 mg, 0.013 mmol), and THF (1.25 mL). The crude material was purified (SiO_2, 100% pentane) to give the desired product as a clear, colorless oil (21.6 mg, 50%). R_f = 0.40 (100% hexanes, UV/$KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.14-7.12 (2H, m), 7.11-7.09 (2H, m), 6.16 (1H, ddd, *J* = 17.6, 10.3, 6.4 Hz), 5.12 (1H, ddd (app dt's), *J* = 10.3, 1.5 Hz), 4.92 (1H, d, *J* = 17.6 Hz), 3.64-3.61 (1H, m), 2.88-2.83 (1H, m), 2.81-2.76 (1H, m), 1.96-1.84 (2H, m), 1.81-1.69 (2H, m), 1.68-1.58 (2H, m); ^{13}C NMR (126 MHz, $CDCl_3$): δ 144.0, 142.8, 141.1, 129.7, 128.1, 126.1, 125.9, 114.4, 48.8, 36.2, 33.2, 28.9, 28.0; IR (neat): 3071.2 (w), 3014.7 (w), 2922.5 (s), 2852.5 (m), 1639.3 (w), 1489.4 (w), 1474.1 (w), 1444.7 (w), 1053.1 (w), 1001.2 (w), 913.6 (m), 746.8 (s) cm^{-1}; HRMS-(DART) for: $C_{13}H_{17}$ $[M+H]^+$: calculated: 173.1330, found: 173.1331. $[\alpha]_D^{20}$ = -6.75 (*c* = 0.385, $CHCl_3$, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (*E*)-2-(7-(2-chlorophenyl)hept-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and Pd(dppf)Cl_2 as the pre-catalyst. Absolute stereochemistry was assigned by analogy.

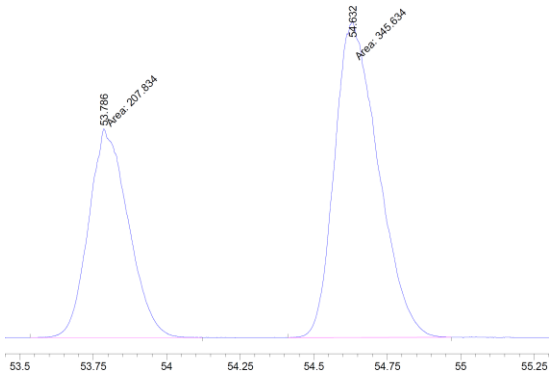
Chiral GLC (β-dex, Supelco, 80 °C for 5 min, ramp 1 °C/min to 150 °C, 20 psi) – analysis of 5-vinyl-6,7,8,9-tetrahydro-5H-benzo[7]annulene.

Racemic Material



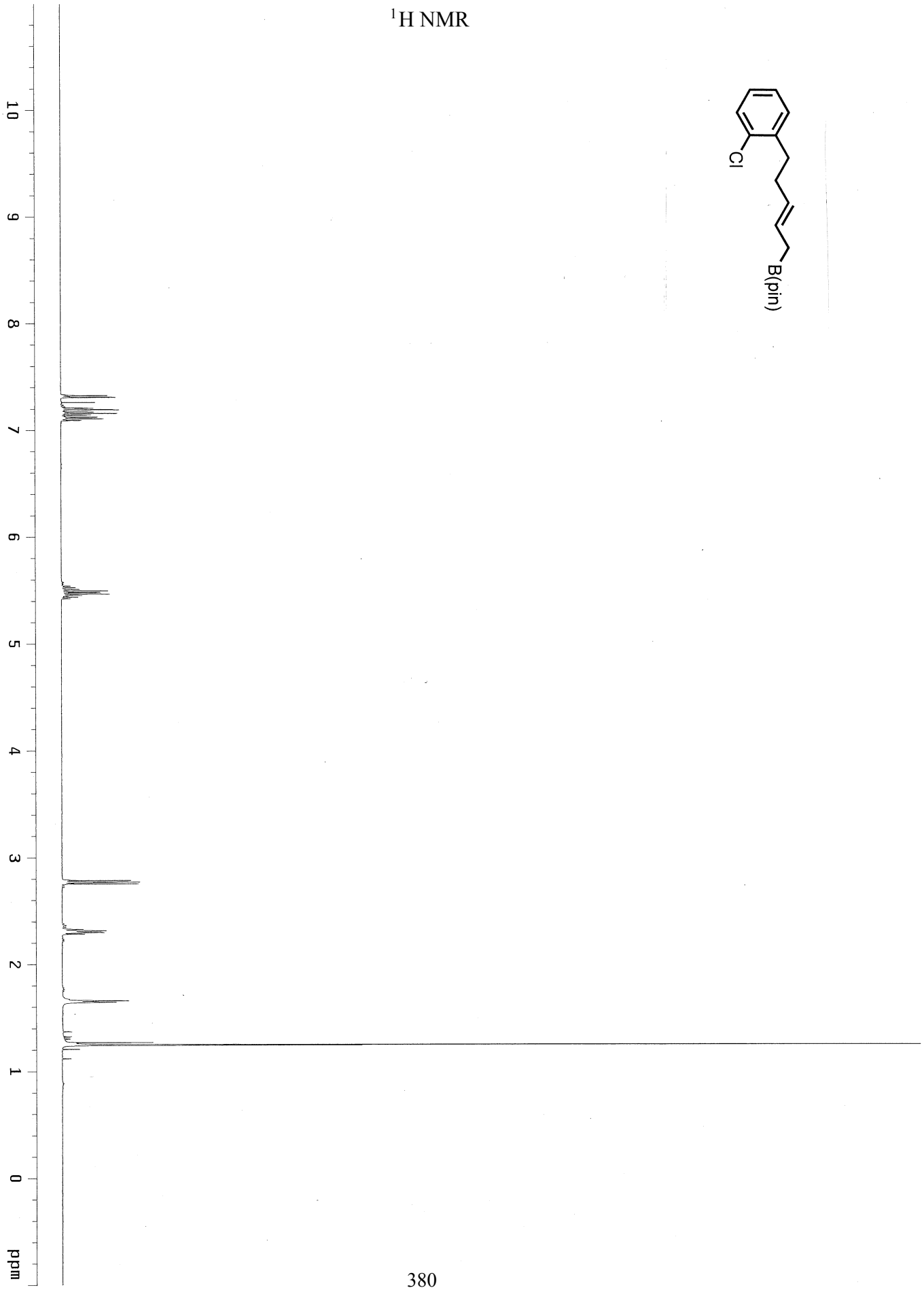
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	53.774	MM	0.2081	1084.78577	86.89310	50.27924
2	54.663	MM	0.2209	1072.73657	80.92230	49.72076
Totals :				2157.52234	167.81540	

Standard Conditions

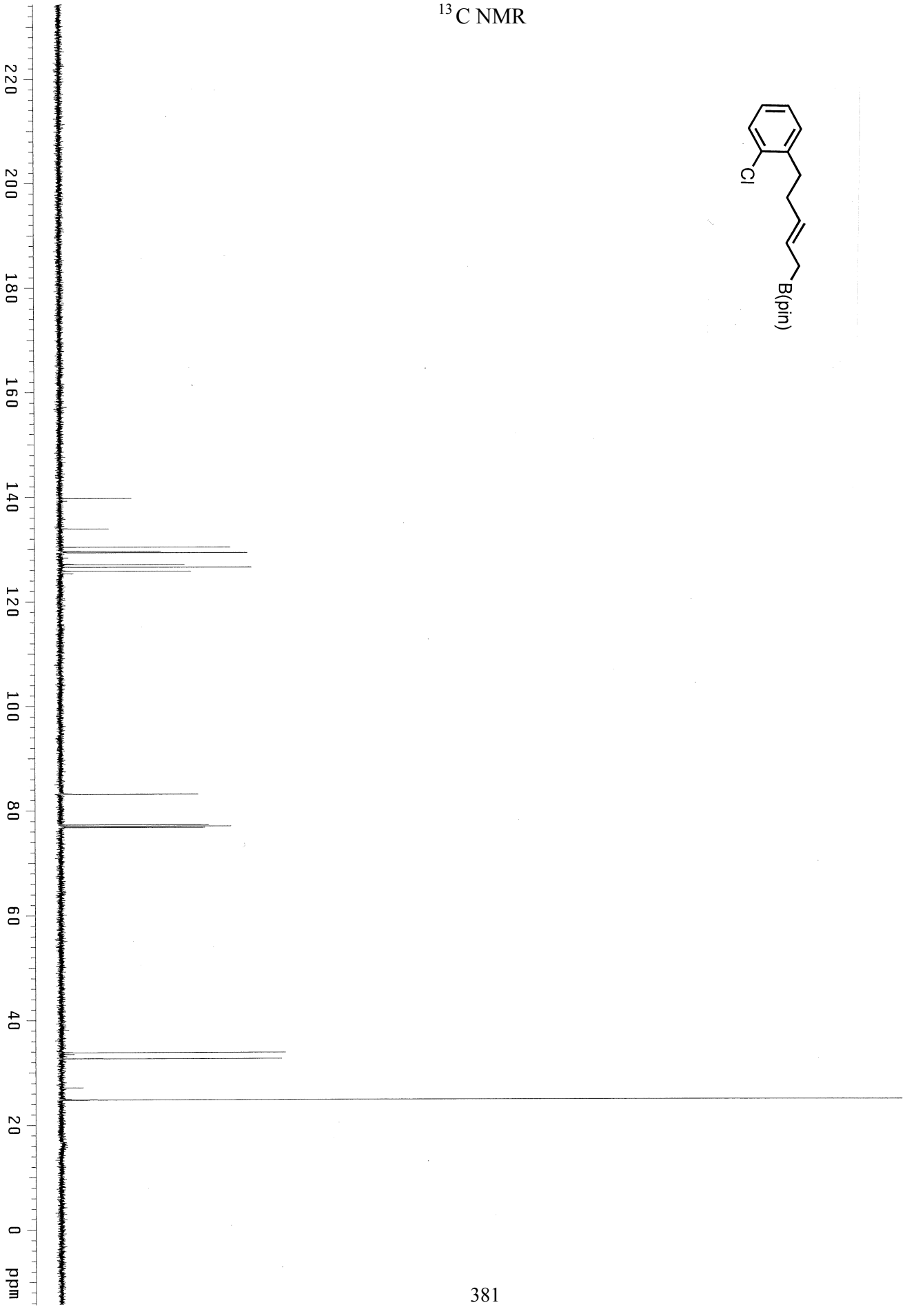


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	53.786	MM	0.1567	207.83444	22.09879	37.55128
2	54.632	MM	0.1719	345.63385	33.50714	62.44872
Totals :				553.46829	55.60593	

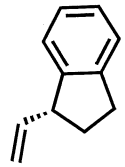
^{1}H NMR

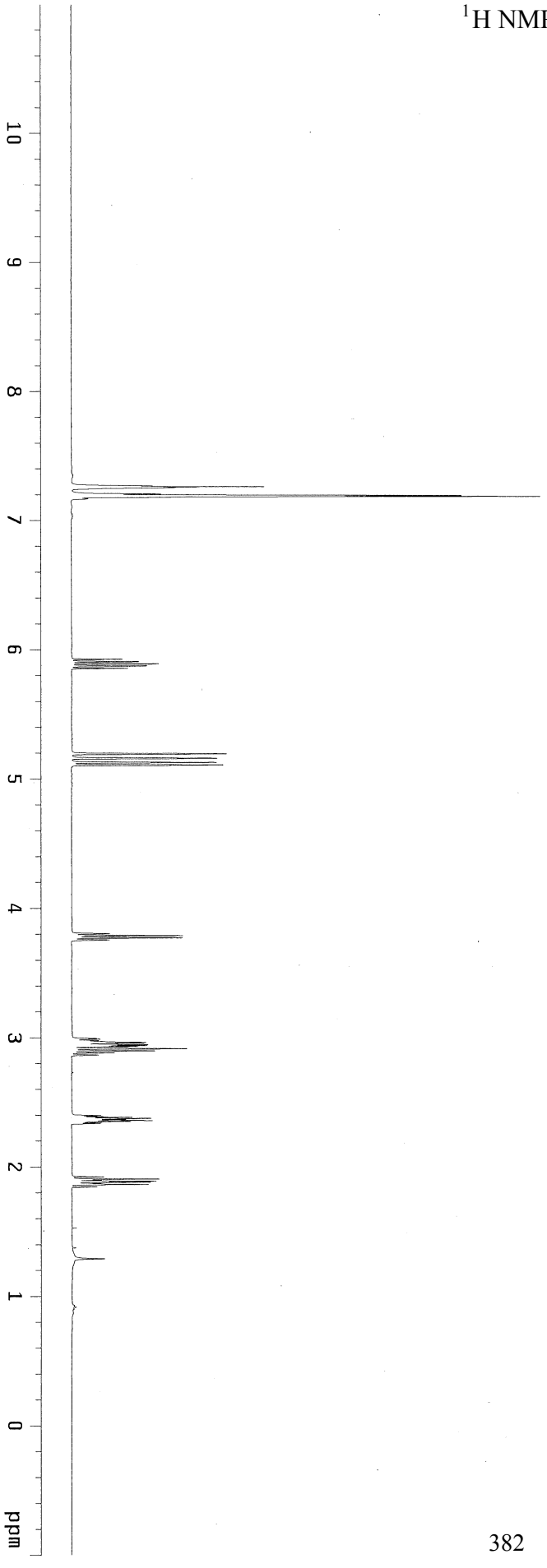


^{13}C NMR



^{1}H NMR





^{13}C NMR