Utilizing Terminal Alkenes in Asymmetric Synthesis: Development and Application of Efficient Diboration/Cross-Coupling Cascades

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UTILIZING TERMINAL ALKENES IN ASYMMETRIC SYNTHESIS: DEVELOPMENT AND APPLICATION OF EFFICIENT DIBORATION/CROSS-COUPLING CASCADES

a dissertation

by

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submitted in partial fulfillment of the requirements

for the degree of

Doctor of Philosophy

August 2014

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ABSTRACT: The first highly enantioselective diboration of unfunctionalized terminal alkenes has been developed using a platinum-phosphonite complex. This transformation produces versatile 1,2-bis(boronate)esters that can manipulated chemoselectively to generate a pletheroa of enantioenriched structural motifs. When combined with an appropriate palladium catalyst, the diboration product undergoes an efficient alkyl boron cross-coupling with aryl and vinyl electrophiles producing a wide range of enantioenriched homobenzylic and homoallylic boronates. Alternatively, when the 1,2-bis(boronate)ester diboration product contains an adjacent *Z*-olefin (derived from diboration of *cis*-1,3-dienes), allylation to aldehydes can be achieved delivering the *syn*-diastereomer of product exclusively with excellent chirality transfer. Notably, the products obtained from the two described reactions contain an additional boronate moiety, which can be further functionalized through known carbon-boron bond transformations.

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List of Abbreviations

Ac: acetyl

Aq: aqueous

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

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

BINAP: 2,2'-bis(diphenylphosphino)-1,1'-binapthyl

Bn: benzyl

Boc: *tert*-butoxycarbonyl

Boc_2O: di-*tert*-butyldicarbonate

cod: cyclooctadiene

Cy: cyclohexyl

DART: direct analysis in real time

dba: dibenzylidene acetone

DCM: dichloromethane

dcpe: 1,2-bis(dicyclohexyl)ethane

DFT: density functional theory

DIBALH: di-*iso*-butylaluminum hydride

dippf: 1,1'-bis(di-*iso*-propylphosphino)ferrocene

DMF: dimethylformamide

DMS: dimethylsulfide

DPEphos: bis-[2-(diphenylphosphino)

phenyl]ether

dppb: 1,4-bis(diphenylphosphino)butane

dppbenzene: 1,4-bis(diphenylphosphino) benzene

dppe: 1,2-bis(diphenylphosphino)ethane

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

dppp: 1,3-bis(diphenylphosphino)propane

dr: diastereomeric ration

eq: equation

equiv: equivalent

ee: enantiomeric excess

ESI: electrospray ionization

EtOAc: ethyl acetate

GLC: gas liquid chromatography

h: hour(s)

HPLC: high performance liquid chromatography

Ipc: *iso*-pinocampheyl

IR: infrared spectroscopy

kcal: kilocalorie

L: ligand

LAH:lithium aluminum hydride

LG: leaving group

M: molar

NaHMDS: sodium bis(trimethylsilyl)amide

nbd: norbornene

NMO: N-methylmorpholino N-Oxide

NMR: nuclear magnetic resonance

pin: pinacol

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

rt: room temperature

RuPhos: 2-dicyclohexylphosphino-2',6'-di-*iso*-propoxybiphenyl

SFC: supercritical fluid chromatography

SPhos: 2-dicyclohexylphosphino-2',6'-dimethyoxybiphenyl

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

TBDPS: *tert*-butyldiphenylsilyl

TBS: *tert*-butyldimethylsilyl

TFA: trifluoroacetyl

THF: tetrahydrofuran

TPAP: tetrapropylammonium perruthenate

Ts: p-toluenesulfonate

Xantphos: 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

XPhos: 2-dicyclohexylphosphino-2',4',6'-tri-*iso*-propylbiphenyl

xylyl: 3,5-dimethylphenyl

y: yield

Chapter 1

Enantioselective Platinum-Catalyzed Diboration of Terminal Alkenes: Development, Scope and Utility

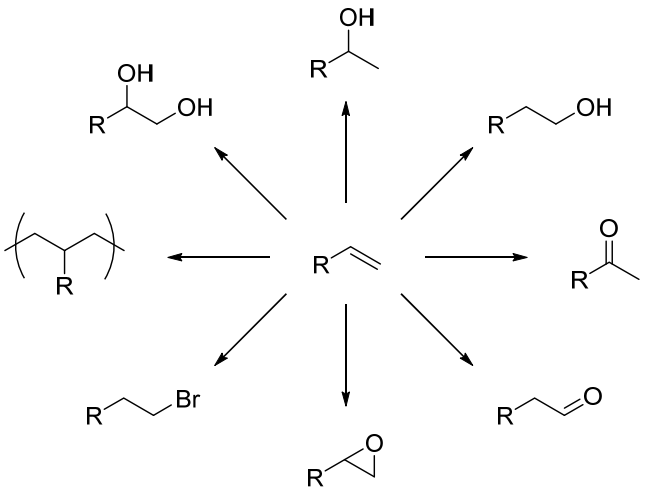
1.1 Introduction

The development of novel asymmetric transformations of simple prochiral hydrocarbons is of prominent importance in synthetic chemistry. Specifically, the use of terminal alkenes as substrates is particularly attractive due to the large abundance of commercially available linear α-olefins. Simple aliphatic α-olefins are generally produced through the thermal cracking of natural gas; a process performed on a multi-million ton scale annually, which leads to an inexpensive commodity chemical ideal for reaction methodology.[1] This low cost of production has initiated intense interest in transforming alkenes into more complex products through various oxidation, halogenation and polymerization reactions (Scheme 1.1). However, despite the abundance of unfunctionalized α-olefins, their use in chemical transformations employing a high level of asymmetric induction is limited.[2]

[1] Weissermel, K.; Arpe, H. J. *Industrial Organic Chemistry*, 4th ed.; Wiley-VCH: Germany, 2003; Chapter 3.

[2] This chapter does not include asymmetric transformations of electronically biased dienes or styrenes.

Scheme 1.1 Functionalization of Terminal Alkenes



The discrepancy in available asymmetric transformations for terminal alkenes compared to internal alkenes can be rationalized through the small steric bias of the prochiral faces of the olefin. Internal di-, tri- and tetra-substituted alkenes are more sterically biased, which generates a greater energy difference between coordination of the two faces of the olefin with the chiral catalyst. The relatively small energy difference exhibited by α-olefin coordination makes generating a highly asymmetric transformation difficult, although not impossible. Several successful asymmetric transformations of terminal alkenes have been reported over the past two decades, generating complex chiral products from simple commodity chemicals.

While the examples reported offer groundbreaking advances in the field of asymmetric catalysis, only a few of these exist. Dimetallation of alkenes offers an attractive solution to this limitation, allowing for the formation of numerous complex products through simple known carbon-metal bond functionalizations. A variety of racemic dimetallations have been reported using tin, silicon, germanium and boron

dimetallating reagents.[3] Manipulation of the dimetallated intermediates can be achieved, but reactions of organo-tin, silicon and germanium compounds are limited to oxidation, protonation and select cross-coupling reactions. Comparatively, organoboron reagents are far more versatile and have been used in oxidation,[4] amination,[5] phosphination,[6] and homologation reactions.[7] Additionally, cross-coupling of organoboranes has been extensively studied and remains one of the most utilized transformations for the construction of carbon-carbon bonds.[8] Diboron reagents are also non-toxic and less expensive than other dimetallation reagents making them the ideal reagent for developing an asymmetric dimetallation of α-olefins. In this chapter, I will discuss known asymmetric transformations of aliphatic α-olefins and present the first highly enantioselective diboration of α-olefins. This reaction converts simple, commercially available alkenes into functionalized bis(boronate) intermediates that can be further manipulated into complex structural motifs.

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[3] (a) Obora, Y.; Tsuji, Y.; Kakehi, T.; Kobayashi, M.; Shinkai, Y.; Ebihara, M.; Kawamura, T. *J. Chem Soc., Perkin Trans. 1* **1995**, 599. (b) Onozawa, S. Y.; Hatanaka, Y.; Choi, N.; Tanaka, M. *Organometallics* **1997**, *16*, 5389. (c) Suginome, M.; Ito, Y. *Chem Rev.* **2000**, *100*, 3221.

[4] (a) Zweifel, G.; Brown, H. C. *Org. React*. **1963**, *13*, 1. (b) Brown, H. C.; Snyder, C.; Subba Rao, B. C.; Zweifel, G. *Tetrahedron* **1986**, *42*, 5505. (c) Kabalka, G. W.; Wadgaonkar, P. P.; Shoup, T. M. *Organometallics* **1990**, *9*, 1316.

[5] (a) Brown, H. C.; Midland, M. M.; Levy, A. B. *J. Am. Chem. Soc.* **1973**, *95*, 2394. (b) Brown, H. C.; Kim, K. W.; Cole, T. E.; Singaram, B. *J. Am. Chem. Soc*. **1986**, *108*, 6761. (c) Knight, F. I.; Brown, J. M.; Lazzari, D.; Ricci, A.; Blacker, A. J. *Tetrahedron* **1997**, *53*, 11411. (d) Fernandez, E.; Maeda, K.; Hooper, M. W.; Brown, J. M. *Chem. Eur. J*. **2000**, *6*, 1840.

[6] Draper, P. M.; Chan, T. H.; Harpp, D. N. *Tetrahedron Lett.* **1970**, *11*, 1687.

[7] (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687. (b) Chen, A.; Ren, L.; Crudden, C. M. *J. Org. Chem*. **1999**, *64*, 9704. (c) Thomas, S. P.; French, R. M.; Jheengut, V.; Aggarwal, V. K. *Chemical Record*, **2009**, *9*, 24.

[8] (a) Suzuki, A.; Miyaura, N.; Abiko, S.; Itoh, M.; Brown, H. C.; Sincalir, J. A.; Midland, M. M. *J. Am. Chem. Soc*. **1973**, *95*, 3080. (b) Leung, T.; Zweifel, G. *J. Am. Chem. Soc*. **1974**, *96*, 5620. (c) Yamada, K.; Miyaura, N.; Itoh, M.; Suzuki, A. *Synthesis* **1977**, 679. (d) Hara, S.; Dojo, H.; Kato, T.; Suzuki, A. *Chem. Lett*. **1983**, 1125.

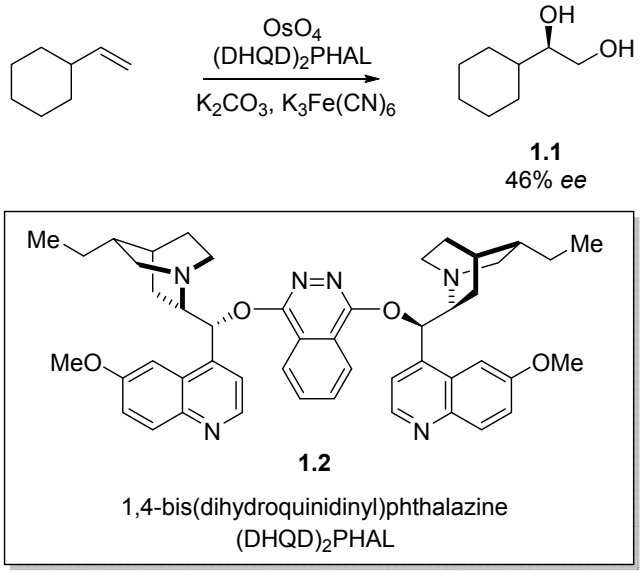
1.2 Background

1.2.1 Enantioselective Oxidation of Alkenes

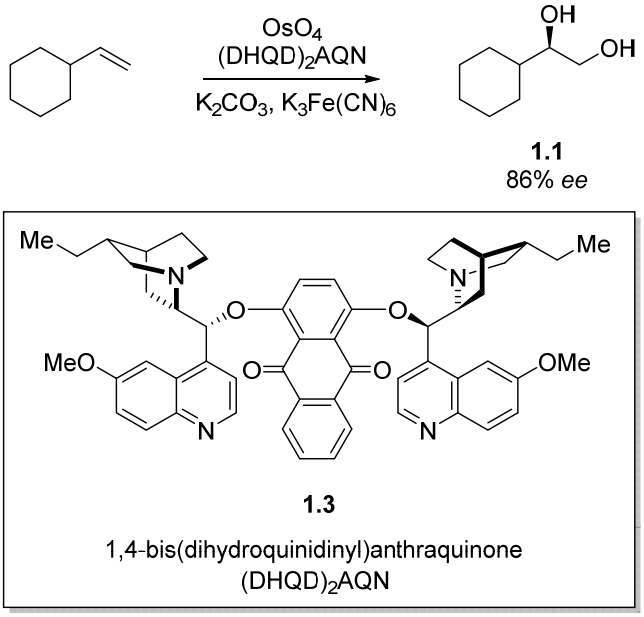
Catalytic oxidation of terminal alkenes remains the most studied asymmetric transformations to date with success in controlling both the oxidation state and regioselectivity of the product. One of the first examples was the osmium-catalyzed dihydroxylation reported by Sharpless and co-workers in 1980. This reaction utilized a dihydroquinine-phthalazine ligand to induce selectivity and produces *syn*-1,2-diols with modest enantioselectivities among substrates investigated; however, the stereoinduction with α-olefins is generally poor (Scheme 1.2).[9] Importantly, the authors reported an accelerated reaction rate when chiral amines were used compared to free osmium tetroxide, allowing for further optimization. In 1996, a new ligand class containing an anthraquinone scaffold was employed in asymmetric dihydroxylation, which generated 1,2-diols from terminal alkenes in excellent enantiomeric excess (Scheme 1.3).[10] While the original phthalazine ligand class is now commercially available in either enantiomer, the anthraquinone derivatives are not, requiring several synthetic steps to obtain the optimal ligand for α-olefin dihydroxylation.

[9] Hentges, S. G.; Sharpless K. B. *J. Am. Chem. Soc.* **1980**, *102*, 4263.
[10] Becker, H. Sharpless, K. B. *Angew. Chem. Int. Ed.* **1996**, *35*, 448.

Scheme 1.2 Sharpless Asymmetric Dihydroxylation with $(DHQD)_2PHAL$ Ligands



Scheme 1.3 Sharpless Asymmetric Dihydroxylation with $(DHQD)_2AQN$ Ligands

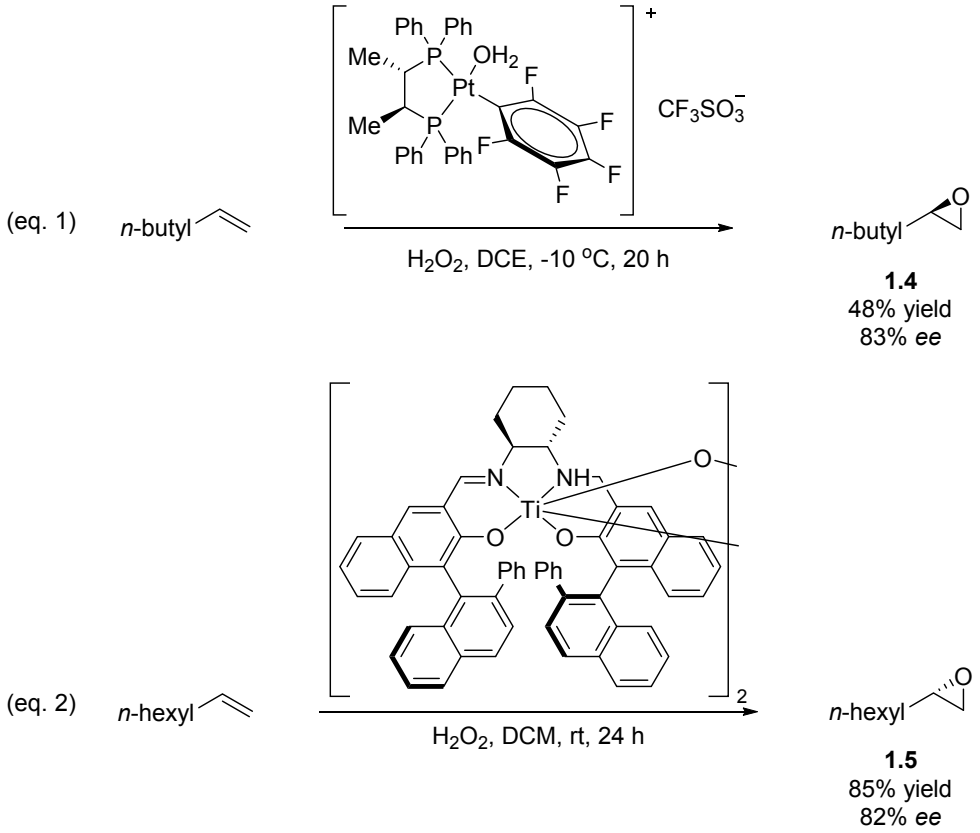


Another successful catalytic oxidative transformation of terminal alkenes is asymmetric epoxidation, which can be performed by using either a platinum (eq 1)[11] or

[11] Colladon, M.; Scarso, A.; Sgarbossa, P.; Michelin, R. A.; Strukul, G. *J. Am. Chem. Soc.* **2006**, *128*, 14006.

titanium (eq 2)[12] catalyst. While both catalyst systems generate epoxides from mono-substituted alkenes and offer similar levels of enantiomeric excess, the platinum(II) catalyst displays greater chemoselectivity when unconjugated diene substrates are used (Scheme 1.4).

Scheme 1.4 Asymmetric Epoxidation of Terminal Alkenes

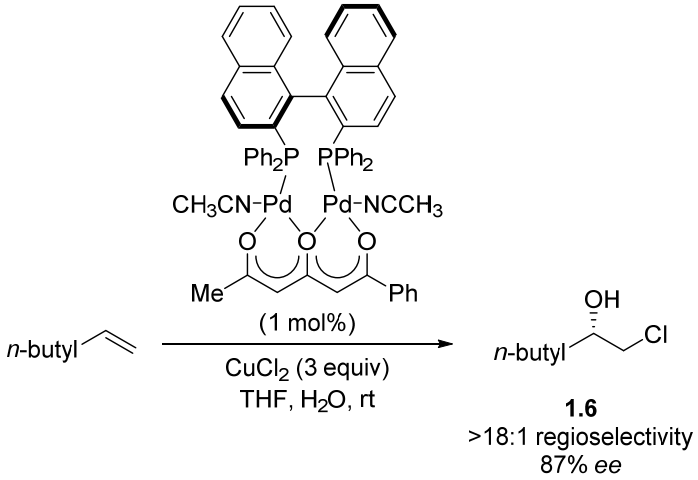


In addition to dihydroxylation and epoxidation, other catalytic asymmetric oxidations have been achieved including hydroxychlorination. Inspired by the Wacker oxidation, Henry and co-workers revealed that the combination of a bimetallic

[12] Sawada, Y.; Matsumoto, K. Katsuki, T. *Angew. Chem. Int. Ed.* **2007**, *46*, 4559.

palladium(II) catalyst and copper(II) chloride successfully transforms a terminal alkene into a chlorohydrin with high regio- and enantioselectivity (Scheme 1.5).[13]

Scheme 1.5 Pd-Catalyzed Asymmetric Hydroxychlorination



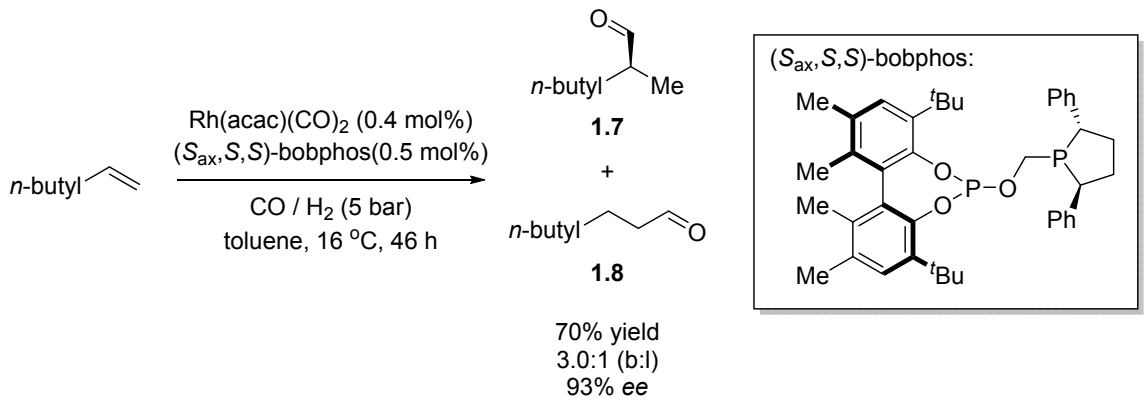
1.2.2 Asymmetric Hydrofunctionalization of Alkenes.

Hydroformylation is an extensively studied transformation where a transition metal catalyst creates a new carbon-carbon bond and furnishes a versatile aldehyde functional group. The reaction employs simple starting materials: an alkene, carbon monoxide and hydrogen. Since its discovery in 1938, hydroformylation has been continuously optimized through the discovery of more reactive catalysts allowing for decreased catalyst loadings and more convenient reaction pressures. Despite the tremendous effort in the field of hydroformylation, the linear regioisomer is still predominately formed for unfunctionalized alkenes.[14] In 2012, Clarke and co-workers disclosed a unique bidentate phosphine-phosphite ligand that was able to deliver the

[13] El-Qisairi, A.; Hamed, O.; Henry, P. M. *J. Org. Chem.* **1998**, *63*, 2790.
[14] (a) Roelen, O. *Ger. Offen.* **1938**, 949, 548. (b) Ojima, I.; Tsai, C.-Y.; Tzamarioudaki, M.; Bonafoux, D. *Org. React.* **2000**, *56*, 1.

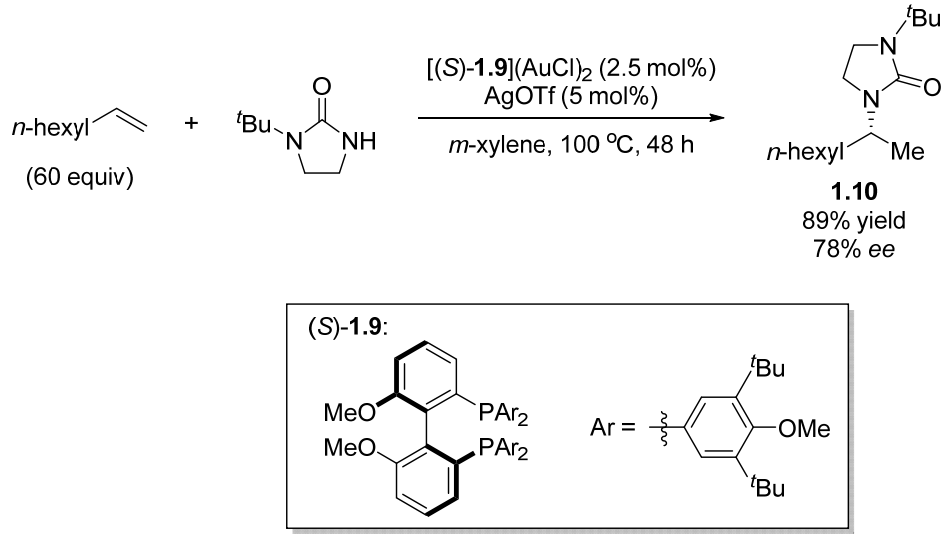
branched product **1.7** as the major regioisomer with excellent enantioselectivity (Scheme 1.6).[15]

Scheme 1.6 Asymmetric Rhodium-Catalyzed Hydroformylation of Terminal Alkenes



The intermolecular asymmetric hydroamination of unfunctionalized alkenes has similarly been reported.[16] This transformation requires large excess of alkene and is limited to cyclic ureas, but delivers the Markovnikov hydroamination product as a single regioisomer in synthetically useful enantioselectivities (Scheme 1.7).

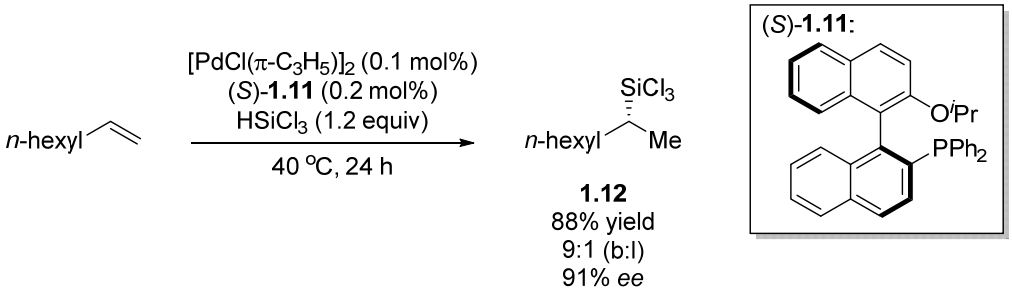
Scheme 1.7 Asymmetric Gold-Catalyzed Hydroamination of Terminal Alkenes



[15] Nooman, G. M.; Fuentes, J. A.; Cobley, C. J.; Clarke, M. L. *Angew. Chem. Int. Ed.* **2012**, *51*, 2477.
[16] Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2009**, *131*, 5372.

The enantioselective hydrosilylation of terminal alkenes has also been achieved, generating chiral secondary alcohols upon oxidation. Numerous transition metals including platinum, rhodium and nickel have been used to promote hydrosilylation of α-olefins; however, the linear silyl-alkane product is generated selectively.[17] Hayashi and co-workers disclosed a palladium-monophosphine complex that efficiently catalyzes the addition of trichlorosilane across a terminal alkene generating the branched alkyl silane **1.12** with excellent asymmetric induction (Scheme 1.8).[18]

Scheme 1.8 Asymmetric Palladium-Catalyzed Hydrosilylation of Terminal Alkenes

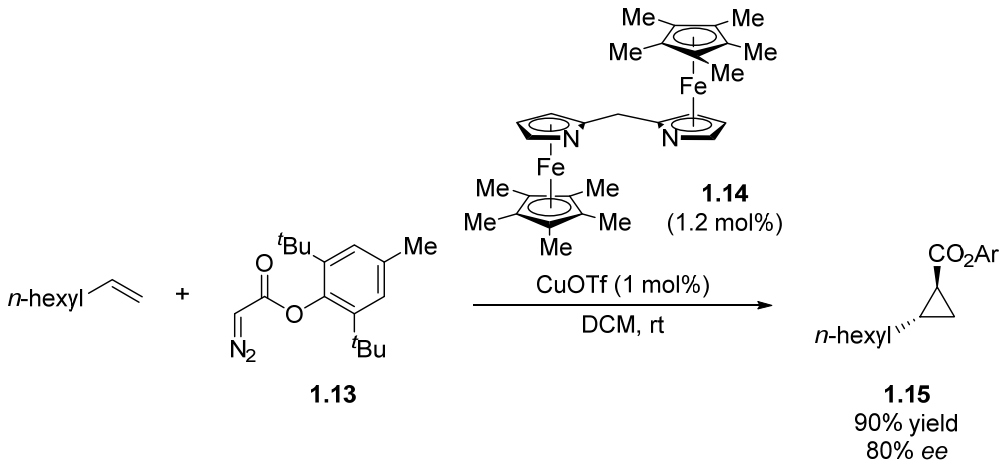


1.2.3 Cyclopropanation of Alkenes.

Asymmetric cyclopropanation of aryl and aliphatic substituted terminal alkenes was achieved using α-diazo esters and a copper(I) catalyst (Scheme 1.9).[19] This transformation utilizes a novel C_2-symmetric bisazaferrocene ligand (**1.14**) bound to copper and generates the *trans*-substituted cyclopropane ring (**1.15**) in high enantiomeric excess.

[17] Ojima, I. *The Chemistry of Organic Silicon Compounds*; Patai, S., Rapport, Z., Eds.; John Wiley: Chichester, 1989; p 1479.
[18] Uozumi, Y.; Hayashi, T. *J. Am. Chem. Soc.* **1991**, *113*, 9887.
[19] Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 10270.

Scheme 1.9 Asymmetric Copper-Catalyzed Cyclopropanation of Terminal Alkenes

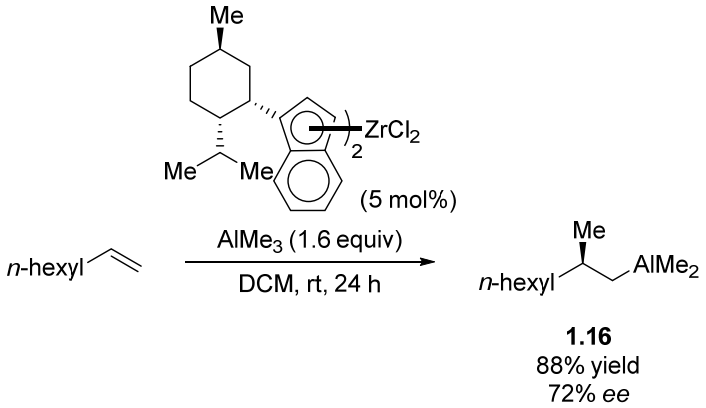


1.2.4 Carbometallation of Alkenes.

The addition of a carbon-metal bond across a carbon-carbon π-system is an efficient strategy for chain elongation of carbon frameworks. In 2004, Negishi rendered this transformation asymmetric by employing a catalytic amount of a chiral zirconium reagent in the presence of stoichiometric trialkyl aluminum (Scheme 1.10).[20] While only moderate levels of enantiopurity were obtained, this reaction was particularly attractive because it offered a solution to an inherent problem associated with all the reactions described above. The transformation produced a carbon-aluminum bond, allowing for the formation of multiple products through additional manipulation of a single intermediate.

[20] Tan, Z.; Liang, B.; Novak, T.; Negishi, E-I. *PNAS*, **2004**, *101*, 5782.

Scheme 1.10 Asymmetric Zirconium-Catalyzed Carbometallation of Terminal Alkenes



1.16
88% yield
72% *ee*

1.2.5 Dimetallation of Alkenes.

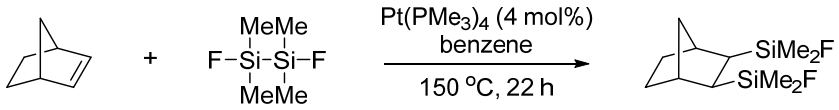
While all of the reactions described above offer impressive advances in the field of asymmetric catalysis, they have had variable impact in synthetic chemistry. The majority of these transformations create a single enantioenriched product, requiring multiple functional group manipulations to achieve the desired structural motif found in synthetic targets. Moreover, selectivity is often moderate. It is in this context that a more generalized transformation would be advantageous. As previously discussed, one possible solution is asymmetric dimetallation, a reaction that generates two carbon-metal bonds poised for additional manipulation. This strategy would allow access to multiple complex structural motifs, from a single intermediate, by applying known carbon-metal bond transformations.

1.2.5.1 Disilyation of Alkenes.

The first catalytic dimetallation of an alkene was reported by Tanaka and co-workers in 1990 and utilized a platinum-phosphine complex to perform the

intermolecular addition of a disilane to ethylene.[21] The efficacy of this transformation was dependent on the electronics of the silane reagent, delivering 1,2-bis(silyl)ethane in 95% yield when an electron-deficient disilane reagent **1.17** (1,2-difluoro-1,1,2,2-tetramethyldisilane) was used. While this reaction proceeded smoothly with $Pt(PPh_3)_4$, more electron-rich and less sterically-demanding phosphine ligands were required for more hindered alkenes and electron-rich disilane reagents. This transformation was applied to norborene with limited success, generating 2-exo,3-exo-bis(dimethylfluorosilyl)norbornane **1.18** as the sole product in 26% yield (Scheme 1.11), which is consistent with a *syn*-addition of the disilane reagent across the alkene.

Scheme 1.11 Platinum-Catalyzed Disilylation of Alkenes



1.17 **1.18** 26% yield

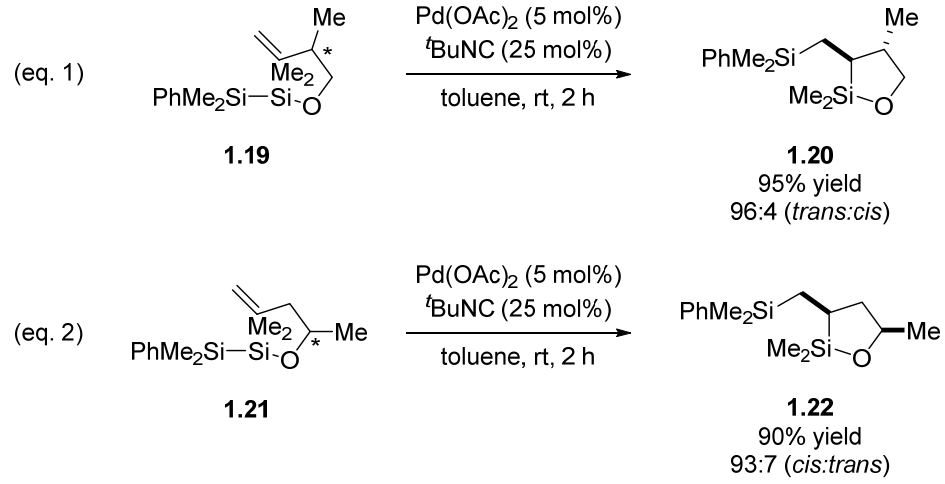
Catalytic intramolecular disilylations of alkenes was later achieved by Ito and Suginome utilizing a $Pd(acac)_2$/isocyanide catalyst.[22] This transformation requires tethering the disilanyl group to the alkene through heteroatom bonding and was first utilized in diastereoselective cyclization generating substituted 1,2-oxasilolanes with the major diastereomer dependent on substitution of the substrate [i.e. 3,4-*trans* (eq 1) vs 3.5-*cis* (eq 2)] (Scheme 1.12). This transformation was retarded in the absence of *tert*-alkyl isocyanide allowing the authors to eventually render the cyclization asymmetric by

[21] Hayashi, T.; Kobayashi, T.-A.; Kawamoto, A. M.; Yamashita, H.; Tanaka, M. *Organometallics* **1990**, *9*, 280.

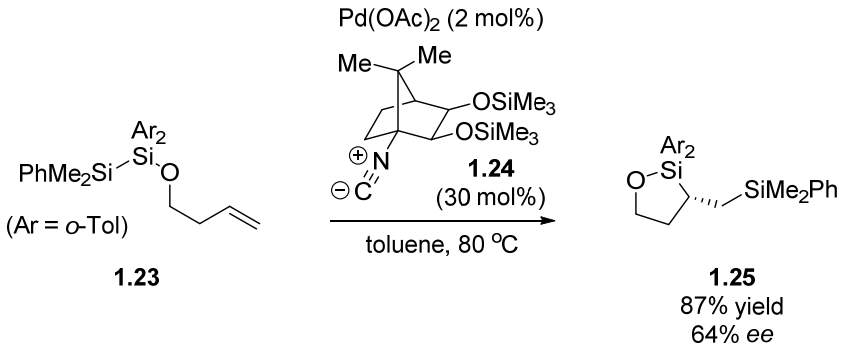
[22] (a) Murakami, M.; Suginome, M.; Fujimoto, K.; Nakamura, H.; Andersson, P. G. Ito, Y. *J. Am. Chem. Soc.* **1993**, *115*, 6487. (b) Suginome, M.; Iwanami, T.; Ohmori, Y.; Matsumoto, A.; Ito, Y. *Chem. Eur. J.* **2005**, *11*, 2954.

employing a chiral isocyanide ligand **1.24** derived from (+)-ketopinic acid (Scheme 1.13).[23] While the cyclic product **1.25** was obtained with only modest enantioselectivity, the authors were able to demonstrate utility of the transformation through oxidation of the carbon-silicon bonds, arriving at synthetically relevant non-racemic polyols.

Scheme 1.12 Platinum-Catalyzed Diastereoselective Intramolecular Disilylation



Scheme 1.13 Platinum-Catalyzed Enantioselective Intramolecular Disilylation



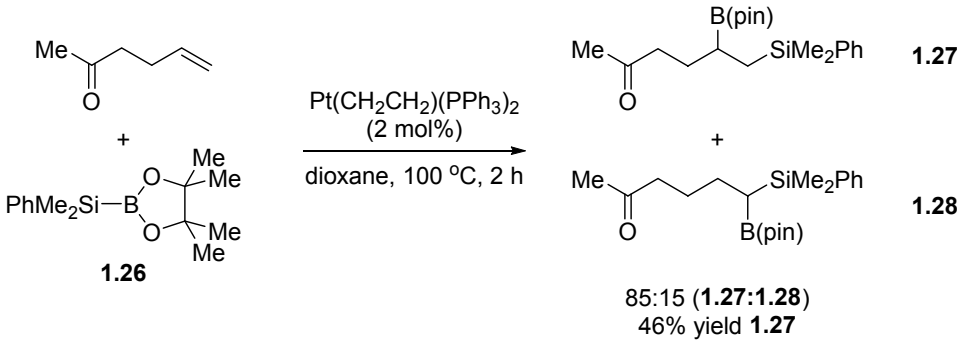
1.2.5.2 Silaboration of Alkenes.

In addition to disilylation, Ito and Suginome also demonstrated that silaboranes can be effectively added across terminal alkenes (Scheme 1.14).[24] This reaction proceeds

[23] Suginome, M.; Nakamura, H.; Ito, Y. *Tetrahedron Lett.* **1997**, *38*, 555.
[24] Suginome, M.; Nakamura, H.; Ito, Y. *Angew. Chem. Int. Ed.* **1997**, *36*, 2516.

with high control of regioselectivity generating compound **1.27** as the major product while the other regioisomer is not observed. Instead, the major byproduct is the 1,1-disubstituted alkane **1.28**. Importantly, this transformation generates a product containing different carbon-metal bonds allowing for orthogonal functionalization.

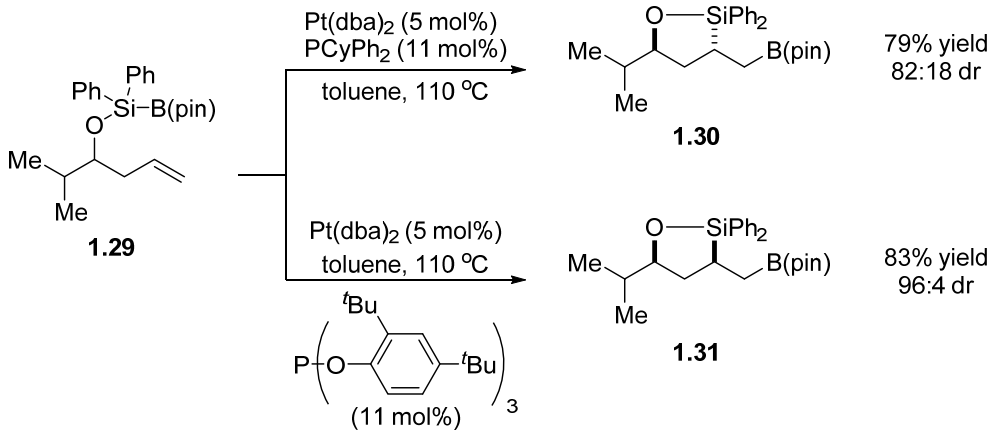
Scheme 1.14 Platinum-Catalyzed Silaboration of Terminal Alkenes



Regioselective intramolecular silaboration has also been achieved under platinum catalysis.[25] By tethering the silicon of the silaboration reagent to the alkene through an ether linkage, the opposite regioisomer is produced compared to the intermolecular variant (Scheme 1.15). Interestingly, diastereomeric control can be achieved through judicious choice of phosphine ligand used.

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

Scheme 1.15 Platinum-Catalyzed Diastereoselective Intramolecular Silaboration



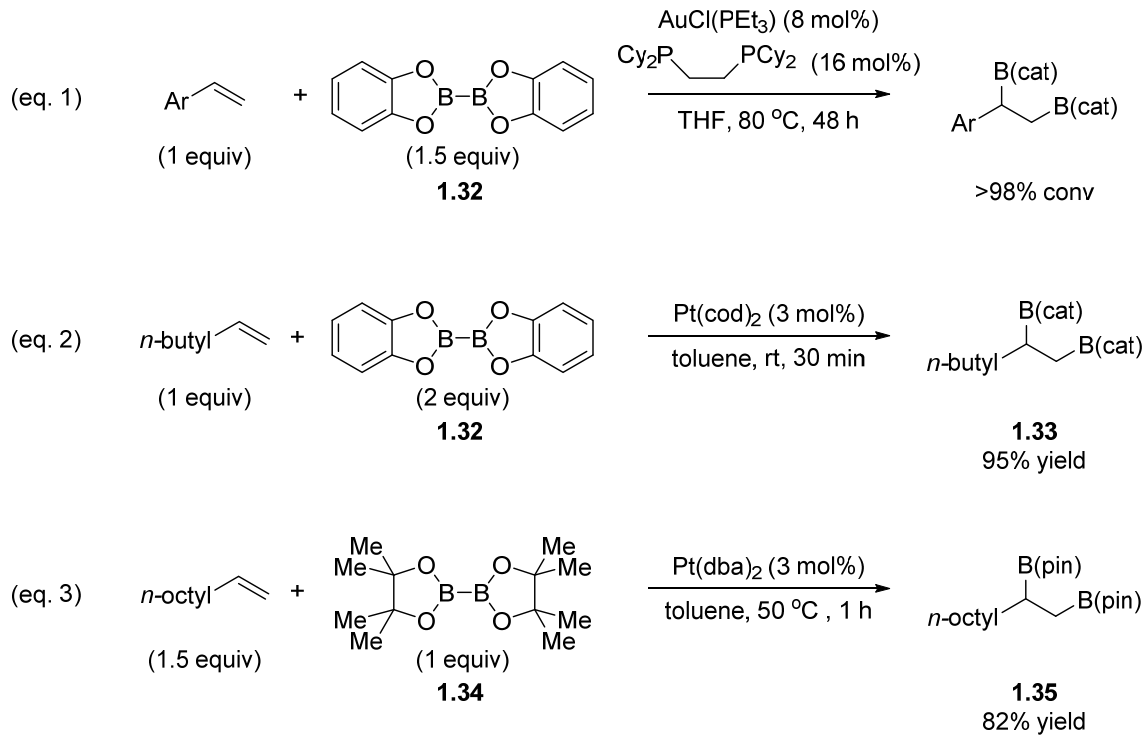
1.2.5.3 Diboration of Alkenes.

Catalytic diboration of alkenes was first reported by Marder and Baker in 1995 where they disclosed the successful addition of bis(catecholato)diboron (**1.32**) across vinylarenes catalyzed by a gold(I)-phosphine complex (Scheme 1.16, eq. 1).[26] The reaction required excess diboron (1.5 equiv) and heating with prolonged reaction times, but high conversion of vinylarenes was observed without competing β-hydride elimination. Since the seminal report, numerous research groups have focused on developing more efficient and cost effective catalyst systems as well as expanding the substrate scope to include non-activated alkenes. In 1997, the research groups of Smith[27] and Miyaura[28] independently discovered different phosphine-free platinum(0) catalysts that efficiently promote the diboration of alkenes. Similar to the methodology developed by Marder and Baker, Smith utilized bis(catecholato)diboron but reported an improved substrate scope that included terminal alkenes and strained cycloalkenes (Scheme 1.16, eq. 2). Miyaura was able to perform an analogous transformation under platinum

[26] Baker, R. T.; Nguyen, P.; Marder, T. B.; Westcott, S. A. *Angew. Chem. Int. Ed.* **1995**, *34*, 1336.
[27] Iverson, C. N.; Smith, M. R. *Organometallics*, **1997**, *16*, 2757.
[28] Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun*. **1997**, 689

catalysis using bis(pinacolato)diboron (**1.34**), a less expensive and more stable diboron source (Scheme 1.16, eq. 3).

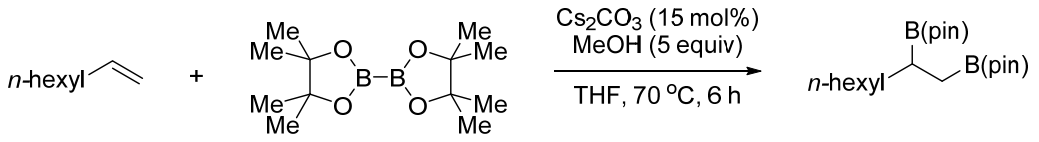
Scheme 1.16 Non-Asymmetric Metal Catalyzed Diboration of Terminal Alkenes



Remarkably, metal-free diboration of unfunctionalized alkenes has also been achieved. Fernández recently reported the addition of several diboron compounds, including bis(catecholato)diboron (**1.32**) and bis(pinacolato)diboron (**1.34**), across terminal and internal (cyclic and acyclic) alkenes through Lewis-base activation (Scheme 1.17).[29] This transformation possesses a unique reactivity between a nucleophilic alkene and base-activated nucleophilic reagent.

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

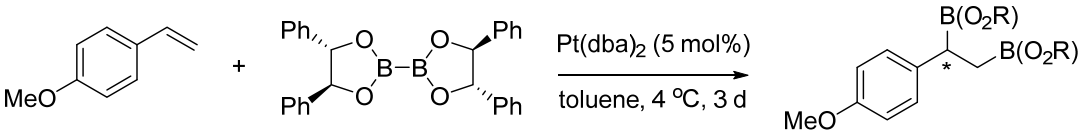
Scheme 1.17 Metal-Free Diboration of Alkenes



1.34 **1.36**
71% yield

Initial efforts to render the diboration of alkenes asymmetric focused on the addition of chiral diboron reagents to olefins using phosphine-free platinum catalysis (Scheme 1.18).[30] Several chiral diborons derived from dimethyl-*L*-tartrate and other commercially available diols were surveyed, with diboron **1.37** delivering highest diastereoselectivities. While synthetically useful yields were obtained with prolonged reaction times, the diastereoselectivity was moderate and never exceeded 80:20 dr.

Scheme 1.18 Diastereoselective Diboration of Terminal Alkenes



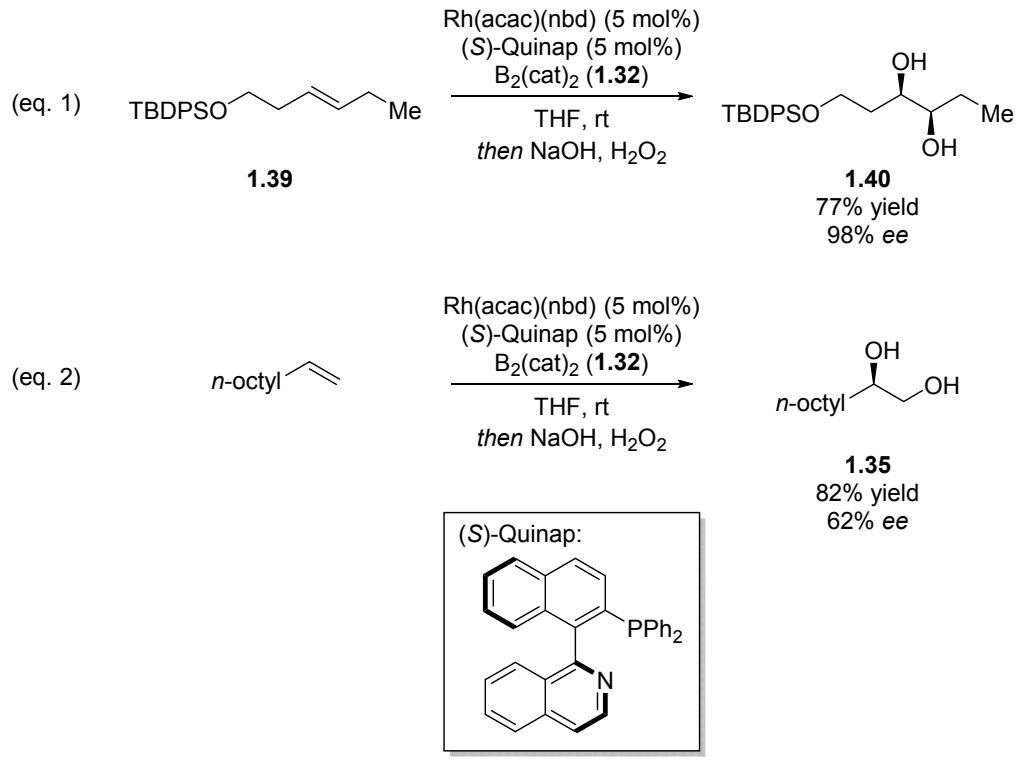
1.37 **1.38**
80% yield
80:20 dr

The first highly enantioselective diboration of alkenes was reported by the Morken group in 2003.[31] Inspired by asymmetric hydroboration catalysts, Morken et al. investigated chiral rhodium(I) salts and found that (*S*)-QUINAP was an effective ligand for diboration, delivering *syn*-1,2-diols with high enantioselectivity upon oxidation (Scheme 1.19). While products derived from tri- and *trans*-1,2-di-substituted alkenes (eq. 1) were obtained in excellent enantiomeric excess, terminal alkenes (eq. 2) and

[30] Marder, T. B.; Norman, N. C.; Rice, C. R. *Tetrahedron Lett.*, **1998**, *39*, 155.
[31] (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.

internal *cis*-alkenes void of α-substitution proceeded with only moderate asymmetric induction.

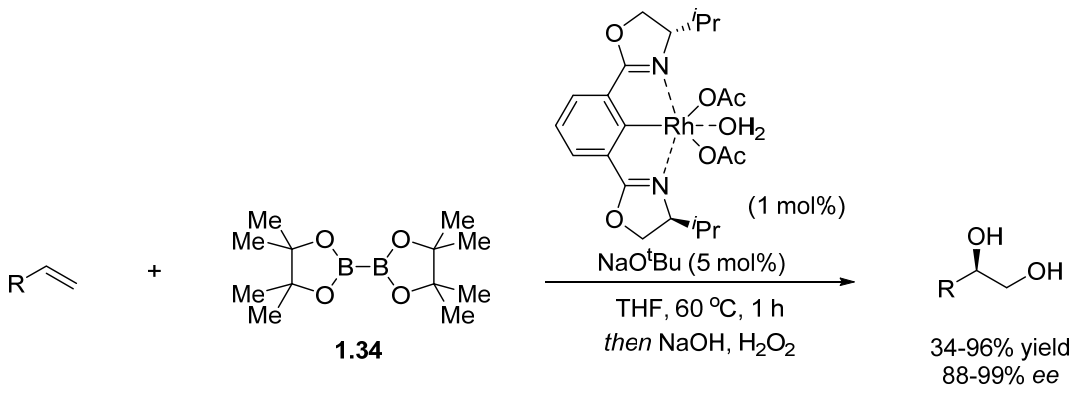
Scheme 1.19 Asymmetric Diboration of Alkenes with Rh-Quinap



The discrepancy in substrate scope with rhodium catalysis was recently solved by Nishiyama and co-workers, who performed rhodium-catalyzed diboration in the presence of a C_2-symmetric bis(oxazolinyl)phenyl ligand. Under the conditions described in Scheme 1.20, aryl and aliphatic α-olefins undergo efficient diboration delivering the corresponding 1,2-diols with excellent enantioselectivity across all substrates examined.[32]

[32] Toribatake, K.; Nishiyama, H. *Angew. Chem. Int. Ed.* **2013**, *52*, 11011.

Scheme 1.20 Asymmetric Diboration of Terminal Alkenes with Rh(Phebox)

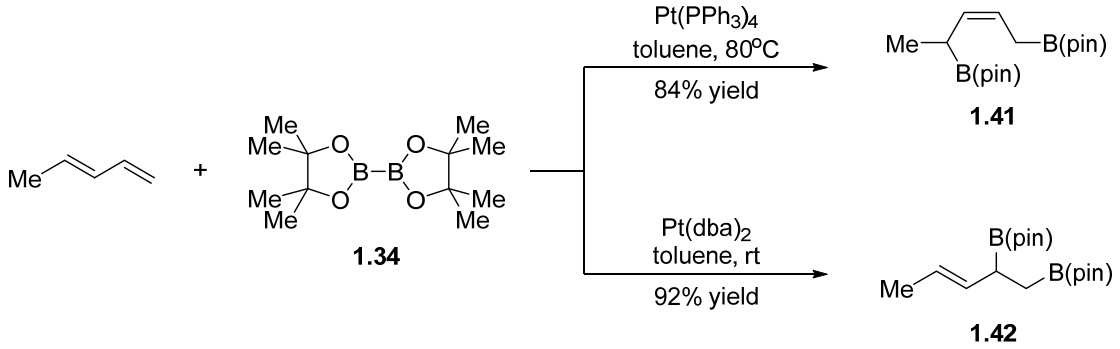


1.3 Development of Enantioselective Platinum-Catalyzed 1,2-Diboration of Terminal Alkenes[33]

Following the success of rhodium-catalyzed diboration of alkenes, the Morken group aimed to extend the asymmetric diboration methodology to include terminal *trans*-1,3-dienes and were inspired by work reported by Miyaura. As described above, Miyaura et al. investigated the platinum(0)-catalyzed diboration with bis(pinacolato)diboron. Their studies extended to include *trans*-1,3-dienes and uncovered a drastic influence of ligand on the regioselectivity of product (Scheme 1.21).[34] When *trans*-1,3-pentadiene was subjected to the reaction with $Pt(PPh_3)_4$ as the catalyst, the 1,4-addition product (**1.41**) is obtained as a single regioisomer in 84% yield; however, when the diboration is performed with $Pt(dba)_2$, the 1,2-product (**1.42**) is produced exclusively in 92% yield. This observation inspired the possibility of rendering 1,4-diboration of *trans*-1,3-dienes asymmetric through use of a suitable chiral phosphine ligand.

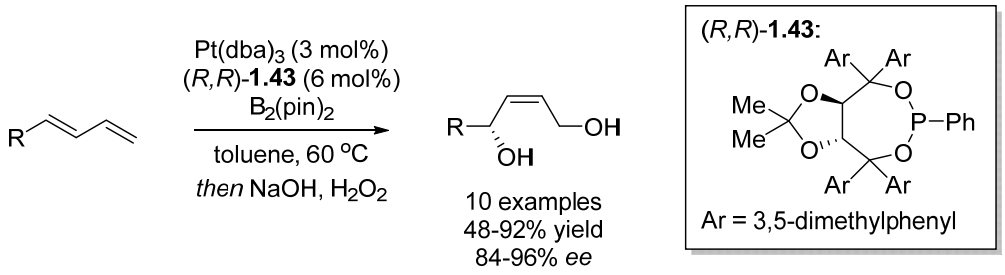
[33] Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210.
[34] Ishiyama, T.; Yamamoto, M.; Miyaura, N. *Chem. Commun*. **1996**, 2073.

Scheme 1.21 Ligand Effects of Platinum-Catalyzed Diboration of trans-1,3-dienes.



In 2009, the Morken group published the first asymmetric 1,4-diboration of *trans*-1,3-dienes (Scheme 1.22).[35] This transformation employed a chiral monodentate phosphonite ligands derived from tartaric acid and upon oxidation, delivered the 1,4-diols in excellent yield and enantioselectivity.

Scheme 1.22 Asymmetric Pt-Catalyzed 1,4-Diboration of *Trans*-1,3-Dienes

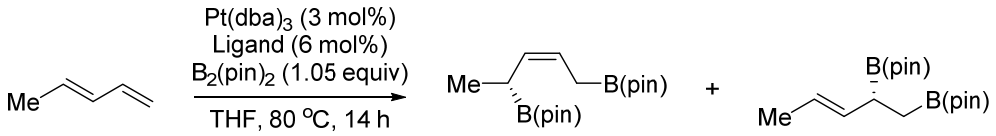


While the 1,4-product was generated preferentially for linear aliphatic *trans*-1,3-dienes, several phosphoramidite ligands examined led to measurable amounts of the 1,2-addition product. Initially, the 1,2-addition product was believed to be formed through a phosphine-free platinum catalyst, similar to results reported by Miyaura; however, upon isolation, the corresponding 1,2-diols obtained were optically enriched (Table 1.1). This

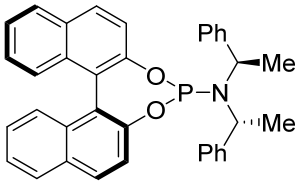
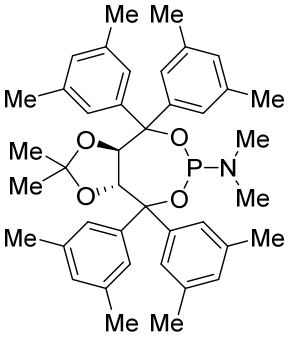
[35] Burks, H. E.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 9134.

observation unmasked the potential for a platinum-catalyzed asymmetric diboration of simple aliphatic α-olefins in the presence of an appropriate chiral phosphine ligand.

Table 1.1 1,2-Diboration Product of Pt-catalyzed Diboration of *trans*-1,3-Pentadiene



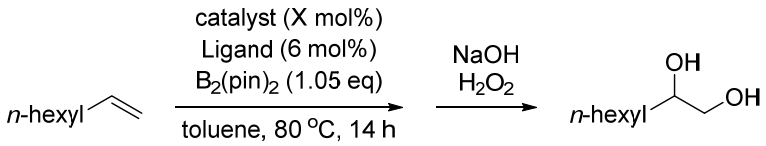
1.41 **1.42**

entry	ligand	yield 1.41 (%)[a]	*ee* 1.41 (%)[b]	yield 1.42 (%)[a]	*ee* 1.42 (%)[b]
1	none	0	-	91	0
2		17	24	13	4
3		77	40	21	26

a) Yield based on isolated material. b) Determined by GC employing a chiral stationary phase.

Initial investigation into the enantioselective 1,2-diboration of terminal alkenes began with a survey of potential transition metal catalysts employing 1-octene as the model substrate with bis(pinacolato)diboron (Table 1.2). As expected from Miyaura's observations, diboration of 1-octene with $Pt(dba)_3$ without the addition of a phosphine ligand generated the 1,2-diol **1.36** in 80% yield. Interestingly, when tricyclohexylphosphine was added, desired product **1.36** was obtained in 89% yield. Both Ni(0)- and Pd(0)-catalysts proved ineffective in the diboration of 1-octene (entries 3 and 4).

Table 1.2 Transition Metal Catalyst Screen for 1,2-Diboration of 1-Octene



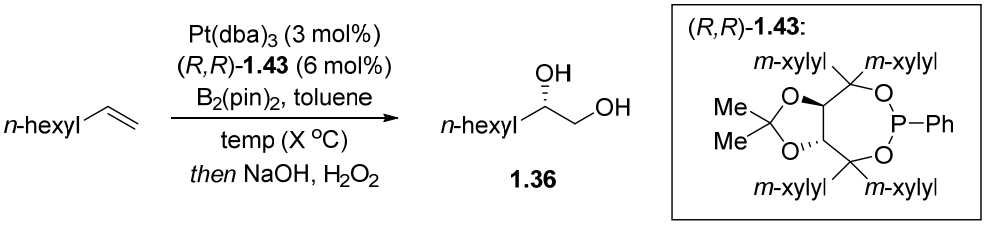
1.36

entry	catalyst (X mol%)	ligand	yield 1.36 (%)[a]
1	$Pt(dba)_3$ (3 mol%)	-	80
2	$Pt(dba)_3$ (3 mol%)	PCy_3	89
3	$Ni(cod)_2$ (5 mol%)	PCy_3	0
4	$Pd_2(dba)_3$ (2.5 mol%)	PCy_3	0

a) Percent yield on isolated 1,2-diol.

To learn more about this reaction, a survey of reaction temperature was performed. As shown in Table 1.3, performing the diboration at temperatures lower than 40 ºC resulted in a drastic drop of asymmetric induction as well as decreased yields even when excess diboron was used. While decreased conversions were not surprising, the drop in enantioselectivity was unanticipated. Often, lowering the temperature of a reaction improves selectivity in asymmetric catalysis; however, the opposite trend was observed for Pt-catalyzed 1,2-diboration of terminal alkenes. The observed drop in enantiopurity could potentially arise from a ligand-free background diboration with $Pt(dba)_3$, generating racemic product. This hypothesis inspired us to investigate a possible temperature dependence of phopsphonite-platinum coordination.

Table 1.3 Temperature Screen for Pt-Catalyzed 1,2-Diboration of 1-Octene



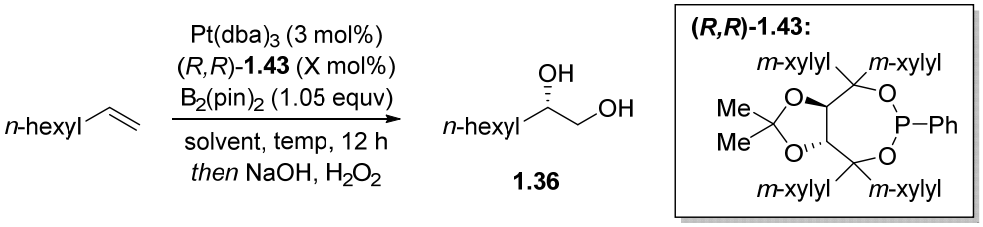
entry	temp (°C)	yield 1.36 (%)[b]	*ee* 1.36 (%)[c]
1[a]	4	<10	44
2[a]	23	37	62
3[a]	40	85	80
4	60	81	84
5	80	98	82

a) Reaction run with 2 equiv of $B_2(pin)_2$ b) Yield of isolated product c) determined by GC analysis of product derivative using a chiral stationary phase.

The previously discussed results were all performed with a 1 hour pre-complexation of ligand and metal in toluene at room temperature followed by addition of $B_2(pin)_2$ and 1-octene prior to heating at the specified reaction temperature. The results summarized in Table 1.3 either suggests that a room temperature pre-complexation may be insufficient to effectively promote phosphonite-platinum coordination or the coordination could be reversible with equilibrium favoring the uncoordinated metal-ligand at low temperatures. Alternatively, the observed decrease in enantioselectivity at lower temperatures may be independent of phosphonite-platinum coordination. If the reaction pathway leading to the minor enantiomer of product may exhibits a larger entropy of activation, decreasing the temperature of the reaction would result in greater formation of the minor enantiomer. In order to gain insight into platinum-ligand coordination, a systematic examination of complexation conditions was performed while maintaining a constant concentration of platinum and diboron. Entry 1 (Table 1.4) summarizes the previous results under the initial conditions generating the desired 1,2-

diol **1.36** in 81% yield and 84% *ee*. As anticipated, increasing the concentration of ligand relative to platinum (entry 2), while maintaining a room temperature complexation, resulted in an increase in enantiopurity of the product. This outcome is consistent with an altered equilibrium in favor of the ligand-platinum complex. Performing the complexation of platinum and ligand at elevated temperature for 30 minutes resulted in a similar selectivity of product (entry 3) without requiring an excess of 3 equivalents of ligand relative to platinum. To gain insight into whether the putative phosphonite-platinum binding was reversible, the complexation was executed at 60 ºC followed by a room temperature diboration (entry 4). Under these reaction conditions the desired product was obtained in 15% yield with 76% *ee* suggesting a reversible phosphonite-platinum binding at lower temperatures. Further investigation into the metal-ligand complex uncovered the importance of diboron in the complexation mixture, generating the desired product in near quantitative yield with 88% *ee* when the diboration was performed at 60 ºC as well as maintaining similar levels of enantiomeric excess when the reaction was performed at room temperature (entries 5 and 6). Utilizing tetrahydrofuran as the solvent revealed similar reactivity to reactions performed in toluene (entry 1 vs entry 7), but ultimately a shorter pre-complexation time was achieved (entry 8). Additional attempts to improve the enantioselectivity of the transformation through addition of excess ligand proved unsuccessful delivering the desired product in similar selectivity but in only 9% isolated yield (entry 9). Collectively, the results summarized in Table 1.4 highlight an important correlation between pre-complexation mixture, complexation temperature and reaction temperature with enantioselectivity of platinum-catalyzed 1,2-diboration of terminal alkenes.

Table 1.4 Survey of Complexation Conditions for Pt-Catalyzed Diboration of 1-Octene

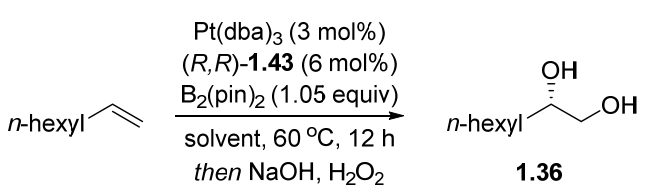


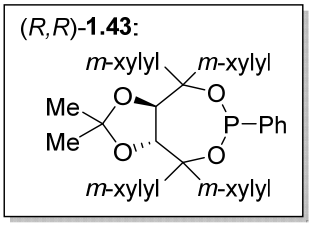
entry	pre-complex	X mol%	complex cond.	temp (°C)	solvent	yield (%)[a]	ee (%)[b]
1	Pt, ligand	6	rt, 1 h	60 °C	toluene	81	84
2	Pt, ligand	10	rt, 1 h	60 °C	toluene	98	88
3	Pt, ligand	6	60 °C, 30 min	60 °C	toluene	95	86
4	Pt, ligand	6	60 °C, 30 min	rt	toluene	15	76
5	Pt, ligand, $B_2(pin)_2$	6	60 °C, 30 min	60 °C	toluene	99	88
6	Pt, ligand, $B_2(pin)_2$	6	60 °C, 30 min	rt	toluene	39	86
7	Pt, ligand	6	rt, 1 h	60 °C	THF	83	86
8	Pt, ligand, $B_2(pin)_2$	6	80 °C, 20 min	60 °C	THF	87	88
9	Pt, ligand, $B_2(pin)_2$	10	80 °C, 20 min	60 °C	THF	9	88

a) Yield of isolated product. b) determined by GC analysis of product derivative using a chiral stationary phase.

Selectivity in asymmetric transformations is often highly influenced by the nature of reaction solvent where polarity and coordination of a solvent can either improve or degrade stereoinduction. Investigation into pre-complexation conditions uncovered an unanticipated result; toluene and tetrahydrofuran, solvents representing drastic polarity differences, performed with comparable efficacy in with respect to both reactivity and selectivity. To gain insight into the importance of solvent in platinum-catalyzed diboration of terminal alkenes, a short survey was performed (Table 1.5). Interestingly, while diboration still proceeded in the presence of other ethereal solvents (entry 3 and 4), asymmetric induction was diminished. Similar levels of enantiopurity were obtained with ethyl acetate, while acetone effectively inhibited the transformation. With no apparent trend, attempts to improve the selectivity of the transformation through solvent effects were abandoned.

Table 1.5 Effect of Solvent in Enantioselective Pt-Catalyzed Diboration of 1-Octene



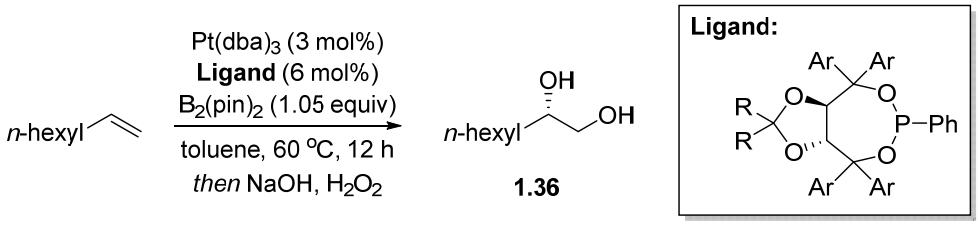


entry	solvent	dielectric constant	yield (%)[a]	ee (%)[b]
1	toluene	2.38	81	84
2	tetrahydrofuran	7.5	87	88
3	1,4-dioxane	2.25	74	81
4	diethyl ether	4.33	73	26
5	ethyl acetate	6.02	65	87
6	acetone	21	0	-

a) Yield of isolated product. b) determined by GC analysis of product derivative using a chiral stationary phase.

With the optimal reaction conditions established, a survey of TADDOL-derived phosphonite ligands was performed. Preceding studies in platinum-catalyzed diboration of *trans*-1,3-dienes[35] revealed a correlation between aryl substitution of the TADDOL backbone and ketal-protecting groups with observed enantioselectivity, allowing for a focused ligand survey (Table 1.6). Decreasing the substituent size at the 3- and 5-position of the aryl ring (entries 1 and 2) proved detrimental, delivering the desired product **1.36** in only 24% yield and 60% *ee* when the parent phenyl group was introduced into the ligand. Increasing the steric encumbrance of the substituent even slightly from methyl to ethyl [(*R,R*)-**1.46**] was beneficial providing diol **1.36** in 84% yield and 92% *ee* (entry 5). Further increase of the steric encumbrance to a *tert*-butyl-substituted aryl ring however resulted in diminished enantiopurity of the product (entry 6). Manipulation of the ketal-protecting group to the formaldehyde-derived TADDOL-phosphonite (*R,R*)-**1.48** proved detrimental, delivering only trace amount of desired product in a greatly reduced 64% *ee* (entry 7).

Table 1.6 TADDOL-Derived Phosphonite Ligand Screen in Pt-Catalyzed Diboration of 1-Octene

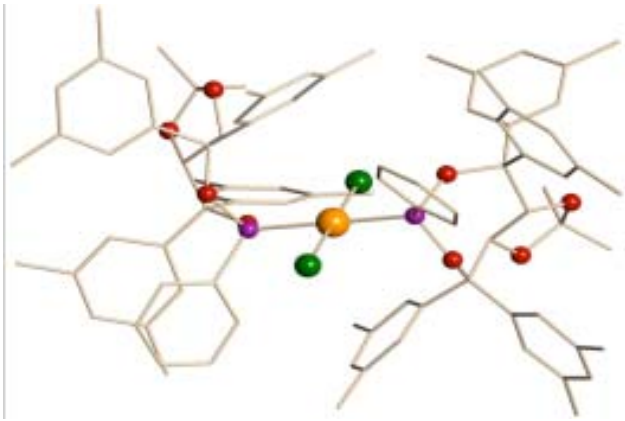


entry	ligand	Ar	R	yield (%)[a]	ee (%)[b]
1	(*R,R*)-**1.44**	Ph	Me	24	60
2	(*R,R*)-**1.45**	3,5-$(MeO)_2$Ph	Me	76	80
3	(*R,R*)-**1.43**	3,5-Me_2Ph	Me	81	84
4[c]	(*R,R*)-**1.43**	3,5-Me_2Ph	Me	87	88
5[c]	(*R,R*)-**1.46**	3,5-Et_2Ph	Me	84	92
6	(*R,R*)-**1.47**	3,5-$^t Bu_2$Ph	Me	74	80
7[c]	(*R,R*)-**1.48**	3,5-Me_2Ph	H	ND	64

[a] Percent yield of isolated product. [b] Determined by GC analysis of a derivative using a chiral stationary phase.
[c] Diboration carried out in THF.

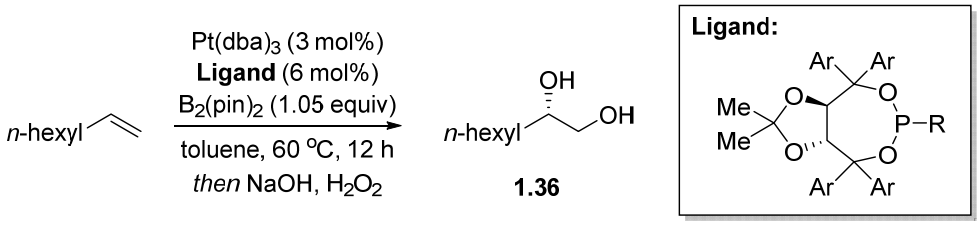
To better understand the origin of enantioselectivity and correlation with ligand substitution, a crystal structure of the phosphonite-platinum complex was prepared. While a crystal complex of the active catalytic species was not observed, a trans-bisligated phosphonite-platinum(II) complex containing two chlorides was obtained with ligand (*R,R*)-**1.43** (Figure 1.1). X-ray analysis of the complex revealed the presence of a pseudo-equatorial aryl ring of the phosphonite ligand on top of the platinum atom, which may serve to heavily influence facial selectivity upon coordination to the olefin substrate. Incorporation of larger substituents in the meta positions of the aryl ring may decrease potential bond rotation of the aryl ring while simultaneously increasing the energy difference associated with alternative modes of substrate binding, resulting in a more enantioselective transformation.

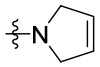
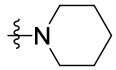
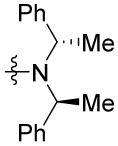
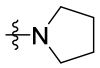
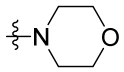
Figure 1.1 X-Ray structure of $PtCl_2[(R,R)$-**1.43**$]_2$



In addition to the phosphonite ligands examined, several TADDOL-derived phosphoramidite ligands were surveyed in the enantioselective diboration of 1-octene. Modifications of the amine moiety and aryl group incorporated in the TADDOL-backbone were performed providing a range of structurally diverse ligands (Table 1.7). While the desired product **1.36** was obtained in moderate to good yields, none of the ligands examined surpassed the reactivity and selectivity observed with (*R,R*)-3,5-diethylphenylTADDOL phenyl phosphonite.

Table 1.7 TADDOL-Derived Phosphoramidite Ligand Screen in Pt-Catalyzed Diboration of 1-Octene



entry	ligand	Ar	R	yield (%)[a]	*ee* (%)[b]
1	(*R*,*R*)-**1.49**	Ph	NMe_2	68	68
2	(*R*,*R*)-**1.50**	Ph	NEt_2	35	40
3	(*R*,*R*)-**1.51**	Ph		66	66
4	(*R*,*R*)-**1.52**	Ph		35	70
5	(*R*,*R*)-**1.53**	Ph		41	5
6	(*R*,*R*)-**1.54**	3,5-Me_2Ph	NMe_2	77	80
7[c]	(*R*,*R*)-**1.54**	3,5-Me_2Ph	NMe_2	78	84
8	(*R*,*R*)-**1.55**	3,5-Me_2Ph		76	82
9	(*R*,*R*)-**1.56**	3,5-Me_2Ph		40	76
10	(*R*,*R*)-**1.57**	3,5-^{t}Bu$_2$Ph	NMe_2	40	56

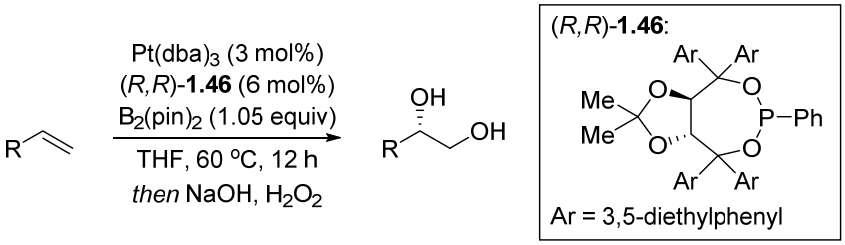
[a] Percent yield of isolated product. [b] Determined by GC analysis of a derivative using a chiral stationary phase. [c] Diboration carried out in THF.

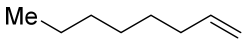
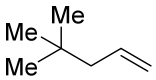
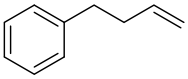
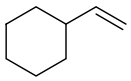
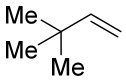
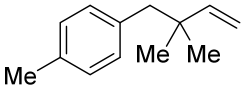
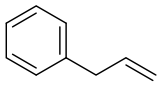
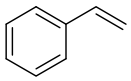
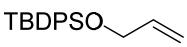
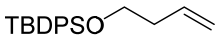
With the optimal reaction conditions and ligand structure established, the scope of platinum-catalyzed diboration of α-olefins was investigated (Table 1.8). Besides 1-octene, several other aliphatic α-olefins were shown to be suitable substrates for asymmetric diboration, generating the corresponding enantioenriched 1,2-diols in good yield and in high selectivity (entries 1-3). Sterically encumbered alkenes, including those

with adjacent quaternary centers, also reacted with high levels of asymmetric induction albeit with reduced reactivity (entries 5 and 6). Substrates bearing protected oxygen functionality were also tolerated (entries 9 and 10) delivering poly-hydroxylated products in excellent yield and enantioselectivity. Importantly, allylic oxygenation (entry 9) did not afford detectable byproducts arising through competing π-allyl chemistry, reactivity that has been previously reported with transition-metal complexes and diboron compounds.[36] Platinum-catalyzed diboration also tolerates α-aryl substitution delivering the 1,2-diol in 84% yield with 86% enantiomeric excess when styrene is subjected to the reaction conditions (entry 8). Extension of the substrate scope to include internal acyclic and cyclic alkenes was unsuccessful highlighting the chemoselective nature of platinum-catalyzed diboration (Figure 1.2).

[36] (a) Ishiyama, T.; Ahiko, T.; Miyaura, N. *Tetrahedron Lett.* **1996**, *37*, 6889. (b) Murata, M.; Watanabe, S.; Masuda, Y. *Tetrahedron Lett.* **2000**, *41*, 5877. (c) Trudeau, S.; Morgan, J. B.; Shrestha, M.; Morken, J. P. *J. Org. Chem.* **2005**, *70*, 9538. (d) Ito, H.; Kawakami, C.; Sawamura, M. *J. Am. Chem. Soc.* **2005**, *127*, 16034. (e) Olsson, V. J.; Sebelius, S.; Selander, N.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 4588. (f) Ito, H.; Ito, S.; Sasaki, Y.; Matsuura, K.; Sawamura, M. *J. Am. Chem. Soc.* **2007**, *129*, 14856.

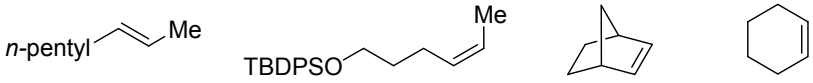
Table 1.8 Eantioselective Pt-Catalyzed Diboration of Alkenes Substrate Scope.



entry	substrate	yield (%)[a]	ee (%)[b]
1		83	92
2		77	94
3		80	94
4		87	94
5		46	90
6		52	87
7		86	93
8		84	86
9		93	90[c]
10		92	90

[a] Percent yield of purified material. Value is average of two experiments. [b] Determined by GC or SFC analysis employing a chiral stationary phase. [c] Oxidation carried out with H_2O_2 in a buffer at pH = 7.

Figure 1.2 Unreactive Alkenes for Pt-Catalyzed Diboration



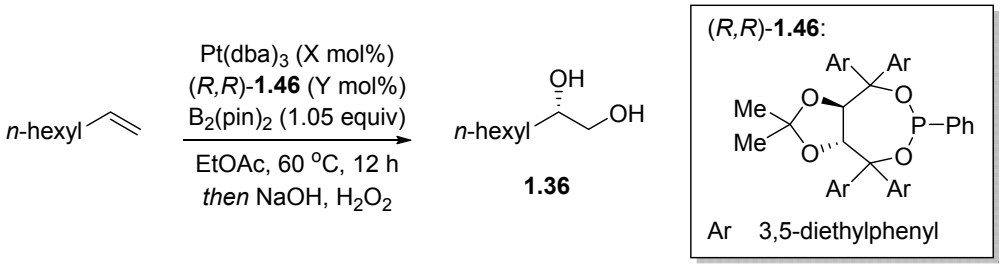
1.58 **1.59** **1.60** **1.61**

1.4 Utility of Platinum-Catalyzed 1,2-Diboration of Terminal Alkenes

1.4.1 Decreased Catalyst Loading.

To highlight potential application in organic synthesis and to render Pt-catalyzed diboration on larger scale more attractive, the diboration of 1-octene was investigated with lowered catalyst loadings (Table 1.9). As depicted in entry 2, diboration with 0.6 mol% $Pt(dba)_3$ in ethyl acetate delivered the corresponding 1,2-diol **1.36** after oxidation. This reaction occurred with comparable asymmetric induction to a 3 mol% loading of catalyst (Table 1.5, entry 5). Further reduction of platinum to 0.3 mol% (entry 3) was successful at retaining reaction efficiency and resulted in only a minimal decrease of enantiopurity.

Table 1.9 Pt-Catalyzed Diboration of 1-Octene with Decreased Catalyst Loading



entry	$Pt(dba)_3$ (X mol%)	(*R,R*)-1.46 (Y mol%)	yield (%)[a]	*ee* (%)[b]
1[c]	3.0	6.0	83	92
2	0.6	1.2	87	88
3	0.3	0.6	83	84

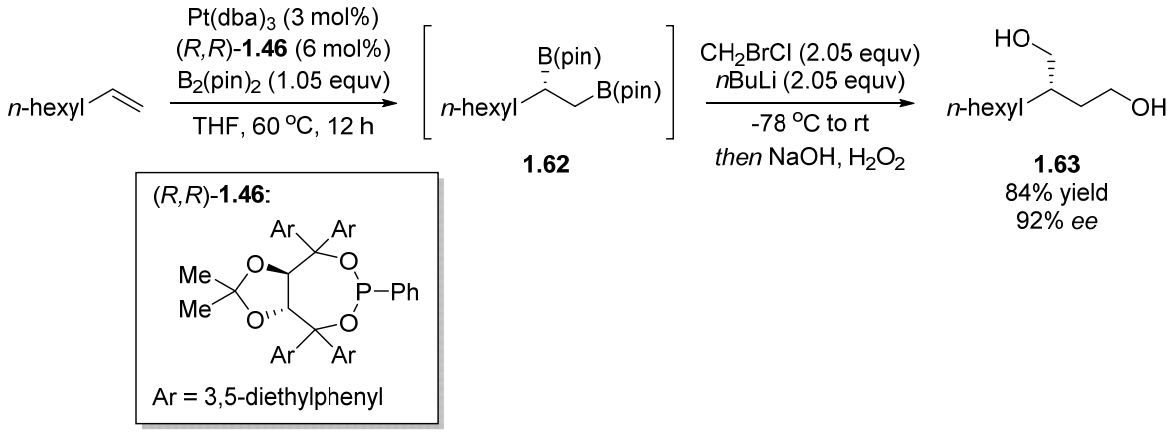
a) Yield of isolated product. b) determined by GC analysis of product derivative using a chiral stationary phase.
c) Reaction run in THF

1.4.2 Matteson Homologation of bis(boronate) Intermediate.

As discussed in section 1.2, the attractive feature of asymmetric diboration lies in the predictable reactivity of the boron atom. While direct oxidation of the bis(boronate) ester intermediate offers a synthetic solution to challenging dihydroxylation substrates,

the synthetic power of platinum-catalyzed diboration lies in additional manipulation of the newly formed carbon-boron bonds. To demonstrate reaction versatility, the bis(boronate) intermediate was subjected to homologation conditions reported by Matteson and co-workers.[37] Following diboration at 60 ºC, the reaction mixture was cooled to -78 ºC and treated with $LiCH_2Cl$ (2.05 equiv) forming a bis-borate intermediate. Warming the borate intermediate promotes a 1,2-rearrangement, effectively inserting a single methylene in both carbon-boron bonds of **1.62** with retention of configuration. Upon oxidation, 1,4-diol **1.63** is isolated as a single product in 84% yield with complete conservation of enantiopurity (Scheme 1.23).

Scheme 1.23 Single Flask Diboration/Homologation/Oxidation Sequence



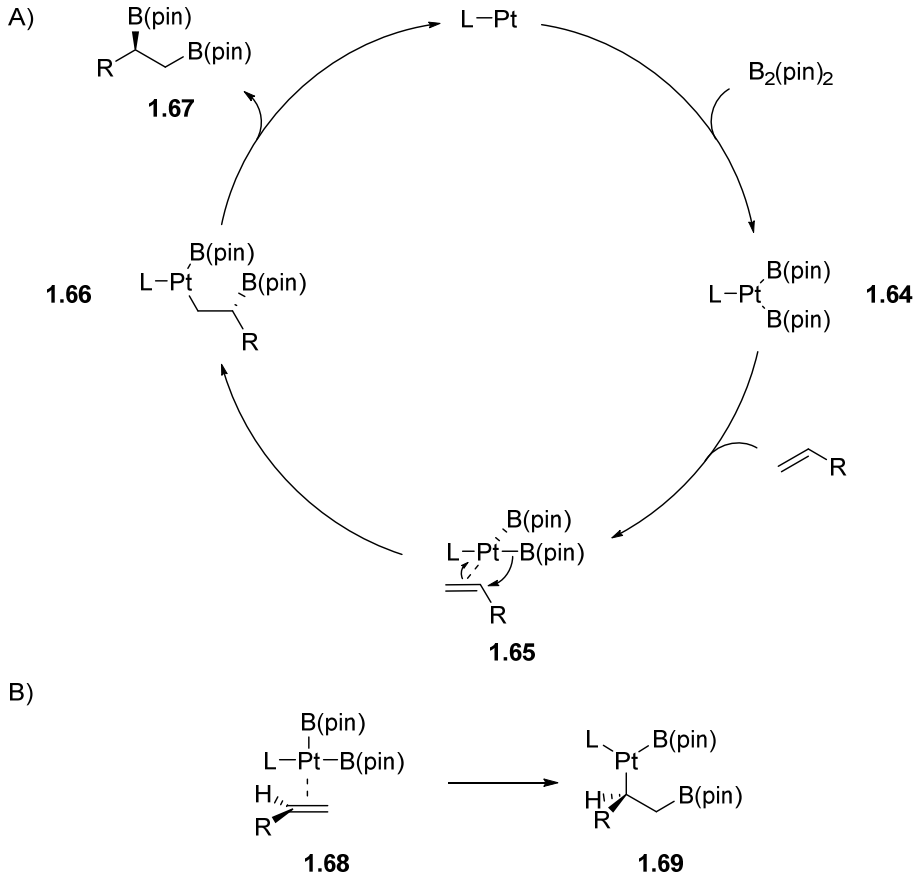
1.5 Mechanism for Platinum-Catalyzed Diboration of Terminal Alkenes

The mechanism for platinum-catalyzed diboration of alkenes is thought to proceed as depicted in Scheme 1.24.[27] Following oxidative addition with bis(pinacolato)diboron and coordination to the olefin, intermediate **1.65** undergoes a

[37] (a) Sadhu, K. M.; Matteson, D. S. *Organometallics* **1985**, *4*, 1687. (b) Chen, A.; Ren, L.; Crudden, C. M. *J. Org. Chem*. **1999**, *64*, 9704. (c) Aggarwal et al *Chemical Record*, **2009**, *9*, 24.

migratory insertion to generate the less sterically hindered platinum(II) complex **1.66**. Reductive elimination of intermediate **1.66** produces the desired bis(boronate) product and regenerates platinum(0). Since the publication disclosing the first enantioselective platinum-catalyzed diboration of terminal alkenes in 2009, Morken and co-workers have performed an in depth investigation to fully elucidate the precise mechanism of the transformation.[38] Through experimental and computational analysis, Morken et al. have determined that the migratory insertion actually proceeds as depicted in Scheme 1.24, B, to generate the more hindered internal platinum-alkyl complex 1.**69**.

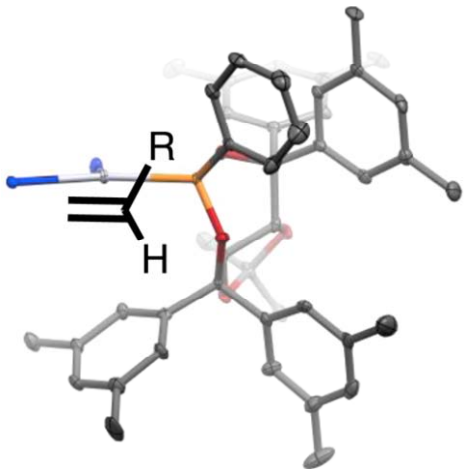
Scheme 1.24 Proposed Mechanism for Platinum-Catalyzed Diboration of Alkenes



[38] Coombs, J. R.; Haeffner, F.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 11222.

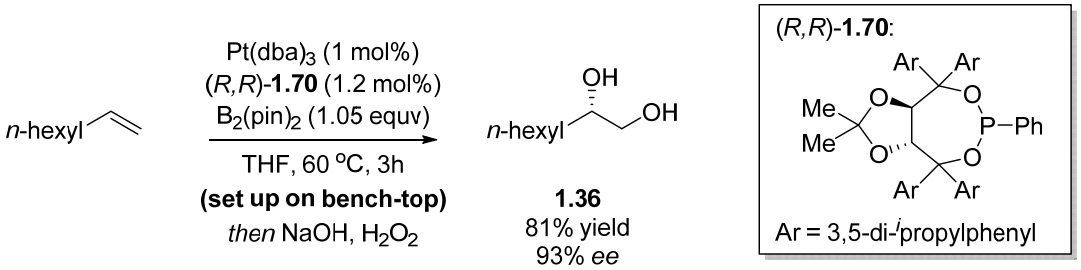
The migratory insertion of intermediate **1.64** to form the internal platinum-carbon bond has a direct effect on the stereochemical outcome of the diboration. In order for the observed pathway to proceed, the olefin must coordinate to platinum with the terminal carbon in proximity to the migrating boryl ligand, which places the substituted carbon of the olefin in closer proximity to the phosphonite ligand. To minimize the steric interaction with the pseudo-equatorial aryl ring on the ligand, the R-group of the olefin is directed up, which is consistent with the observed stereochemistry obtained in the platinum-catalyzed diboration (Figure 1.3).

Figure 1.3 Proposed Model for the Stereochemical Outcome in Enantioselective Diboration



In addition to illuminating the precise mechanism of platinum-catalyzed diboration, further optimization was performed with respect to reaction concentration, reaction time, and phosphonite to platinum ratio (Scheme 1.25). Most importantly the diboration can now be performed on the bench-top while retaining the reactivity and selectivity of the reaction.

Scheme 1.25 Improved Reaction Conditions for Pt-Catalyzed Diboration of 1-Octene



1.6 Conclusions

The first highly enantioselective diboration of terminal alkenes has been developed. This transformation utilizes a TADDOL-derived phosphonite ligand and successfully converts simple aliphatic and aryl α-olefins into enantio-enriched 1,2-bis(boronate)esters. Oxidation of the bis(boronate)ester intermediate produces 1,2-diols in excellent yields with higher enantiopurity than conventional asymmetric dihydroxylation catalysts. Additional manipulation of the bis(boronate)ester intermediate can also be achieved, arriving at synthetically challenging 1,4-diols by employing Matteson's carbon-boron bond homologation.

1.7 Experimental

1.7.1 General Information.

^{1}H NMR spectra were recorded on Varian Unity Inova 500 MHz and Varian Gemini 400 MHz spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 7.24 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, br = broad, m = multiplet), coupling constants (Hz) and assignment. $^{13}C\{^{1}H\}$NMR spectra were recorded on Varian Unity Inova 500 MHz (125 MHz) and Varian Gemini 400 MHz (100 MHz) spectrometers. Chemical shifts are reported in ppm with the solvent resonance as the internal standard ($CDCl_3$: 77.00 ppm). $^{31}P\{^{1}H\}$NMR (162 MHz) were recorded on a Varian Unity Inova 400 spectrometer. Chemical shifts are reported for ^{31}P NMR spectra using phosphoric acid as an external standard. Infrared (IR) spectra were recorded on a Bruker α-P Spectrometer. Frequencies are reported in wavenumbers (cm^{-1}) as follows: strong (s), broad (br), medium (m), and weak (w). High-resolution mass spectrometry (ESI) was performed at Boston College, Chestnut Hill, MA. 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), phosphomolybdic acid (PMA), and potassium permanganate ($KMnO_4$).

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 □-Dex 120 column with helium as the carrier gas. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Berger Instruments Supercritical Chromatograph equipped with an Alcott auto sampler and a Knauer UV detector with methanol as the modifier. Analytical chiral high-performance liquid chromatography (HPLC) was performed on a Shimadzu SCL-10A liquid chromatograph equipped with a UV detector and a Daicel Chiracel-OD column.

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. Ethyl acetate was distilled from calcium hydride and degassed. Triethylamine was distilled from calcium hydride. 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 was obtained from Allychem Co., Ltd. and recrystallized from pentane prior to use. Dichlorophenylphosphine was purchased from Strem Chemicals, Inc. and used without further purification. 1-octene, 4,4-dimethyl-1-pentene, 4-phenyl-1-butene, vinyl cyclohexane, 3,3-dimethyl-1-butene, allylbenzene, styrene, *tert*-butyldiphenylsilyl chloride, imidazole, and bromochloromethane were purchased from Aldrich and used without further purification.

1.7.2 Preparation of $Pt(dba)_3$.

Tris(dibenzylideneacetone)platinum was prepared using the literature procedure[39] with slight modification. 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 h, 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 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 brown solid (1.84 g, 85% yield) 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).

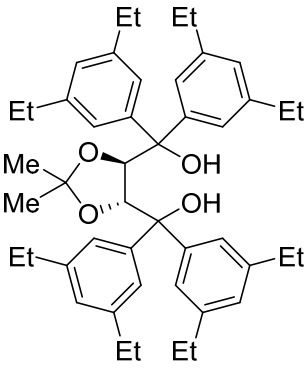
[39] Lewis, L. N.; Krafft, T. A.; Huffman, J. C. *Inorg. Chem.* **1992,** *31*, 3555.

1.7.3 Ligand Synthesis

1.7.3.1 Preparation of (R,R)-3,5-diethylphenylTADDOL.

3,5-DiethylphenylTADDOL was prepared according to the literature procedure[40] with slight modification. To a flame dried 100 mL 2-neck round bottom flask equipped with magnetic stir bar and reflux condenser was added crushed magnesium turnings (401.0 mg, 16.50 mmol) under N_2. The apparatus was flame-dried again, a single crystal of I_2 was added and the reaction mixture was diluted with tetrahydrofuran (29 mL). To another flame dried 25 mL pear-shaped flask was added 1-bromo-3,5-diethylbenzene (3.91 g, 18.3 mmol) and tetrahydrofuran (12 mL). The solution of 1-bromo-3,5-diethylbenzene in tetrahydrofuran was slowly added to the magnesium mixture at room temperature via syringe. The reaction was allowed to reflux at 80 ˚C in an oil bath for 2 h, at which time the reaction was cooled to 0 ˚C, and a solution of (4*R*,5*R*)-2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylic acid in tetrahydrofuran (4 mL) was added slowly via syringe. The reaction was allowed to reflux for 12 h, after which it was cooled to 0 ˚C and quenched with NH_4Cl (10 mL, sat. aq.). The organic and aqueous layers were separated and the aqueous layer was extracted with ethyl acetate (3 x 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (1-50% ethyl acetate/hexanes) to afford the title compound as a yellow solid (2.23 g, 88% yield).

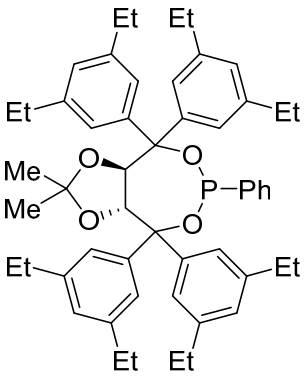
[40] Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978.



3,5-DiethylphenylTADDOL. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.94 (6H, s), 1.13 (12H, t, *J* = 7.6 Hz), 1.22 (12H, t, *J* = 7.6 Hz), 2.54 (8H, q, *J* = 7.6 Hz), 2.61 (8H, q, *J* = 7.2 Hz), 3.78 (2H, s), 4.67 (2H, s), 6.91 (2H, s), 6.96 (2H, s), 7.00 (4H, s), 7.20 (4H, s); ^{13}C NMR ($CDCl_3$): δ 15.51, 15.94, 27.04, 28.94, 29.08, 76.68, 77.00, 77.32, 78.29, 81.00, 109.2, 124.6, 125.8, 126.1, 126.5, 142.6, 142.7, 143.6, 145.9. IR (neat): 3299 (br w), 2962 (s), 2930 (m), 1599 (w), 1457 (m), 1238 (w), 1063 (m) 871 (s), 746 (m) cm^{-1}. $[\alpha]_D^{20}$ = +8.555 (*c* = 0.522, $CHCl_3$, *l* = 50 mm).

1.7.3.2 Preparation of (R,R)-3,5-diethylphenylTADDOLPPh.

To a flame dried 100 mL round bottom flask equipped with magnetic star bar was added 3,5-diethylphenylTADDOL (2.23 g, 3.23 mmol) and tetrahydrofuran (32.3 mL, 0.1 M) under N_2. Triethylamine (1.53 mL, 10.9 mmol) was added via syringe and the reaction mixture was brought to 0 ˚C in an ice bath. Dichlorophenylphosphine (0.48 mL, 3.55 mmol) was added dropwise via syringe at 0 °C, the reaction was brought to room temperature and was allowed to stir for 2 h. The reaction was diluted with Et_2O, filtered through celite and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (5% ethyl acetate/hexanes) to afford the title compound as a white solid (2.31 g, 90% yield).



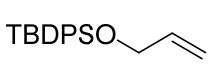
(*R,R*)-3,5-DiethylphenylTADDOLPPh (1.43). ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.18 (3H, s), 1.20 (24H, m), 1.55 (3H, s), 2.60 (16H, m), 4.89 (1H, d, *J* = 8.4 Hz), 5.65 (1H, dd, *J* = 8.4 Hz, 4.8 Hz), 6.87 (1H, s), 6.93 (2H, s), 6.96 (1H, s), 7.07 (2H, s), 7.16 (2H, s), 7.30 (2H, s), 7.47 (3H, s), 7.55 (2H, s), 7.86 (2H, s); ^{13}C NMR ($CDCl_3$): δ 15.42, 15.53, 15.73, 15.92, 24.64, 27.95, 28.94, 29.12, 82.53, 82.77, 83.01, 83.52, 83.59, 84,29, 110.9, 124.5, 124.6, 125.9, 126.3, 126.4, 126.5, 126.6, 128.1, 128.2, 129.7, 130.0, 130.3, 141.5, 141.6, 142.6, 142.9, 143.3, 143.5, 146.3, 146.9. ^{31}P NMR (162 MHz, $CDCl_3$): δ 156.7. IR (neat): 2962 (s), 2931 (m), 2872 (w), 1599 (w), 1458 (m), 1160 (m), 1069 (m), 875 (s), 806 (m) cm^{-1}. $[\alpha]_D^{20}$ = -59.63 (*c* = 0.660, $CHCl_3$, *l* = 50 mm).

1.7.4 Preparation of Alkenes

Preparation of Allyloxy(tert-butyl)diphenylsilane.

To a flame-dried, round bottom flask was added imidazole (3.52 g, 51.6 mmol). The flask was purged with nitrogen and charged with allyl alcohol (1.00 g, 17.2 mmol) and dichloromethane (34.4 mL). tert-Butyldiphenylsilyl chloride (13.4 mL, 51.6 mmol) and triethylamine (7.2 mL, 51.6 mmol) were added to the reaction mixture under nitrogen atmosphere and the reaction was allowed to stir at room temperature for 20 h. The reaction was then diluted with dichloromethane (30 mL) and washed with brine (15 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude product was purified by column chromatography on SiO_2

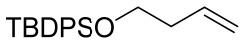
(100% hexanes) to give the title compound as a clear, colorless liquid (4.39 g, 86% yield).



Allyloxy(*tert*-butyl)diphenylsilane. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (9H, s, SiC(C**H$_3$**)$_3$), 4.26-4.28 (2H, m, SiOC**H$_2$**), 5.17 (1H, dd, *J* = 10.8 Hz, 2.0 Hz, HC=C**H$_{cis}$**H$_{trans}$), 5.44 (1H, dd, *J* = 16.8 Hz, 2.8 Hz, HC=CH$_{cis}$**H$_{trans}$**), 5.98 (1H, ddt, *J* = 18.8 Hz, 8.4 Hz, 4.0 Hz, SiOCH$_2$C**H**=CH$_2$), 7.40-7.49 (6H, m, Si**Ar**), 7.71-7.76 (4H, m, Si**Ar**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 26.9, 64.6, 113.9, 127.6, 129.6, 133.6, 135.5, 136.9; IR (neat): 2931.3 (w), 2857.5 (m), 1427.5 (m), 1134.0 (m), 1111.4 (s), 1079.1 (m), 823.8 (m), 739.8 (m), 701.1 (s) cm^{-1}; HRMS-(ESI+) for $C_{19}H_{25}OSi$ [M+H]: calculated: 297.1675, found: 297.1669.

Preparation of (but-3-enyloxy)(tert-butyl)diphenylsilane.

To a flame-dried, round bottom flask was added imidazole (2.83 g, 41.6 mmol). The flask was purged with nitrogen and charged with 3-buten-1-ol (1.0 g, 13.8 mmol) and dichloromethane (27.7 mL). tert-Butyldiphenylsilyl chloride (10.8 mL, 41.6 mmol) and triethylamine (5.8 mL, 41.6 mmol) were added to the reaction mixture under nitrogen atmosphere and the reaction was allowed to stir at room temperature for 20 h. The reaction was then diluted with dichloromethane (30 mL) and washed with brine (15 mL). The layers were separated and the aqueous layer was extracted with dichloromethane (3 x 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude product was purified by column chromatography on SiO_2 (100% hexanes) to give the title compound as a clear, colorless liquid (3.88 g, 90% yield).



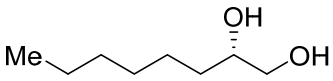
(But-3-enyloxy)(tert-butyl)diphenylsilane. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.19 (9H, s, OSiC(C**H**$_3$)$_3$), 2.44 (2H, dd, *J* = 13.2 Hz, 6.4 Hz, SiOCH$_2$C**H**$_2$), 3.84 (2H, t, *J* = 6.4 Hz), 5.11-5.20 (2H, m, CH$_2$CH=C**H**$_2$), 5.95 (1H, ddt, *J* = 16.8 Hz, 10.0 Hz, 6.8 Hz, CH$_2$C**H**=CH$_2$), 7.46-7.53 (6H, m, Si**Ar**), 7.80-7.82 (4H, m, Si**Ar**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.3, 26.9, 37.3, 63.5, 116.3, 127.6, 129.5, 133.9, 135.3, 135.5; IR (neat): 2930.5 (w), 2857.5 (w), 1427.4 (m), 1104.9 (s), 1087.7 (s), 910.6 (m), 822.4 (m), 736.3 (m), 698.8 (s) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{27}OSi$ [M+H]: calculated: 311.1831, found: 311.1834.

1.7.5 Representative Procedure for Alkene Diboration/Oxidation.

To an oven-dried 6-dram vial with magnetic stir bar in the dry box was added Pt(dba)$_3$ (18.3 mg, 20.4 μmol), (*R,R*)-3,5-diethylphenyl-TADDOLPPh (32.0 mg, 40.1 μmol), $B_2(pin)_2$ (178.2 mg, 701.7 μmol) and tetrahydrofuran (6.7 mL, [substrate] = 0.1 M). The vial was sealed with a polypropylene cap, removed from the dry box, and heated to 80 °C in an oil bath for 30 min. The vial was cooled to room temperature, returned to the dry box and charged with 1-octene (75.0 mg, 668.8 μmol). The vial was sealed, removed from the dry box, and stirred at 60 °C for 12 h. The reaction mixture was cooled to 0 °C (ice/water) and charged with 3 M sodium hydroxide (2 mL), and 30% hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h at which time the vial was cooled to 0 °C (ice/water) 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 washed with ethyl acetate (3 x 15 mL). The combined organic layers

were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (30-70% ethyl acetate/hexanes) to afford a clear, colorless oil (81.1 mg, 83% yield).

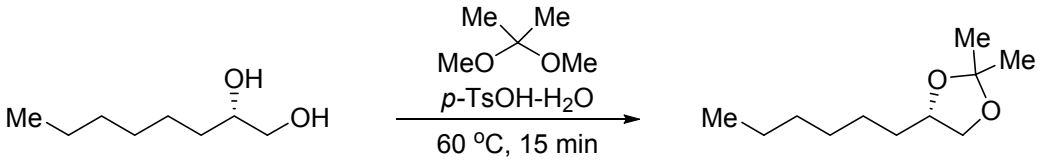
1.7.6 Characterization and Proof of Stereochemistry (Table 1.8)



(*S*)-Octane-1,2-diol. The diboration was performed according to the general procedure with 1-octene (75.0 mg, 668.8 μmol), $Pt(dba)_3$ (18.3 mg, 20.4 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (32.0 mg, 40.1 μmol), and $B_2(pin)_2$ (178.2 mg, 701.7 μmol) in tetrahydrofuran (6.7 mL, 0.1 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate/hexanes, stain in $KMnO_4$) to afford a white solid (81.1 mg, 83% yield). Spectral data are in accordance with the literature.[41] HRMS-(ESI+) for $C_8H_{19}O_2$ [M+H]: calculated: 147.1385, found: 147.1380. $[\alpha]_D^{20} = -1.538$ (*c* = 0.784, $CHCl_3$, *l* = 50 mm).

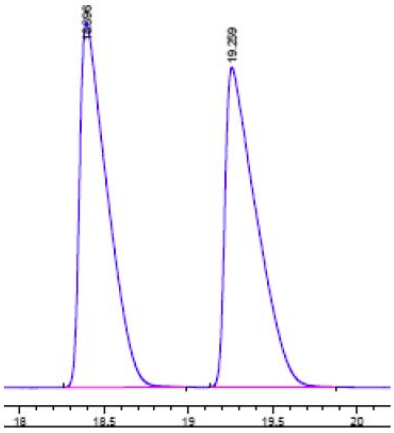
Proof of Stereochemistry:

The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid (below). The resulting ketal was compared to the racemic ketal of octane-1,2-diol prepared from dihydroxylation of 1-octene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The authentic (*S*)-isomer was prepared from the Sharpless asymmetric dihydroxylation of 1-octene utilizing AD-mix-α.[42]

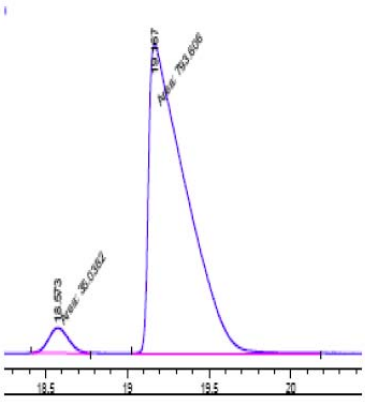


[41] Emmanuvel, L.; Shaikh, T. M. A.; Sudalai, A.; *Org. Lett.*, **2005**, *7*, 5071.
[42] Jacobsen, E.N.; Markd, I; Mungall, W.S.; Schrcider, G.; Sharpless, K.B.; *J. Am. Chem. Soc.*, **1988**, *110*, 1968.

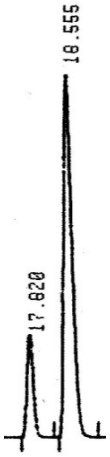
Chiral GLC (β-dex, Supelco, 100 °C, 20 psi) – analysis of the acetonide of octane-1,2-diol.



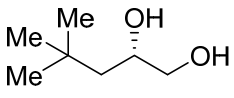
racemic



diboration



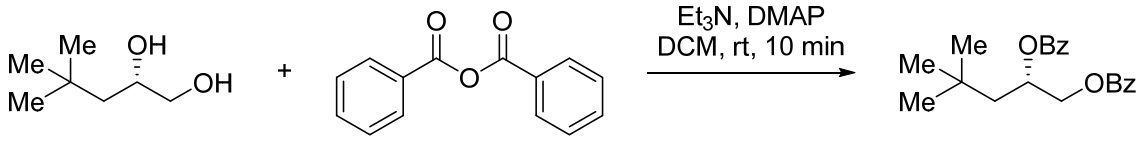
authentic



(*S*)-4,4-Dimethylpentane-1,2-diol. The diboration was performed according to the general procedure with 4,4-dimethyl-1-pentene (75.0 mg, 763.8 μmol), $Pt(dba)_3$ (20.8 mg, 23.2 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (36.5 mg, 45.8 μmol), and $B_2(pin)_2$ (203.7 mg, 802.2 μmol) in tetrahydrofuran (7.6 mL, 0.1 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate/hexanes, stain in $KMnO_4$) to afford a clear, colorless oil that could not be separated from pinacol (115.5 mg, 2:1 product:pinacol = 77% yield). Spectral data are in accordance with the literature.[43] HRMS-(ESI+) for $C_7H_{17}O_2$ [M+H]: calculated 133.1226, found: 133.1231.

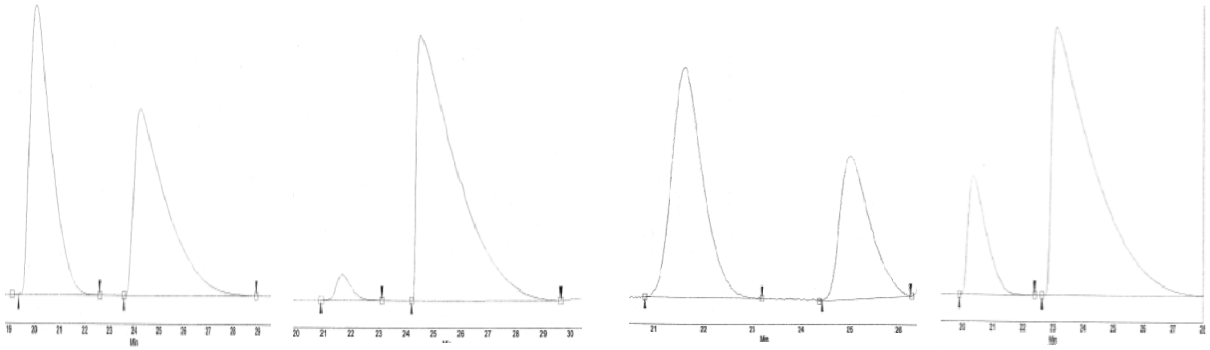
Proof of Stereochemistry:

The resulting 1,2-diol was treated with benzoic anhydride, triethylamine and catalytic 4-(dimethylamino)pyridine (below). The resulting bis(benzoate) was compared to the racemic bis(benzoate) of 4,4-dimethylpentane-1,2-diol prepared from dihydroxylation of 4,4-dimethyl-1-pentene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The authentic (*R*)-isomer was prepared from the Sharpless asymmetric dihydroxylation of 4,4-dimethyl-1-pentene utilizing AD-mix-β.

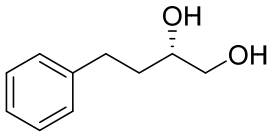


[43] Trudeau, S.; Morgan, J. M.; Shrestha, M.; Morken, J. P.; *J. Org. Chem.*, **2005**, *70*, 9538.

Chiral SFC (Chiracel OD-H, 0% MeOH, 3 mL/min, 150 bar, 50 ˚C, 220 nm) – anaylysis of the bis(benzoate) of 4,4-dimethylpentane-1,2-diol.



racemic diboration authentic coinjection of diboration product



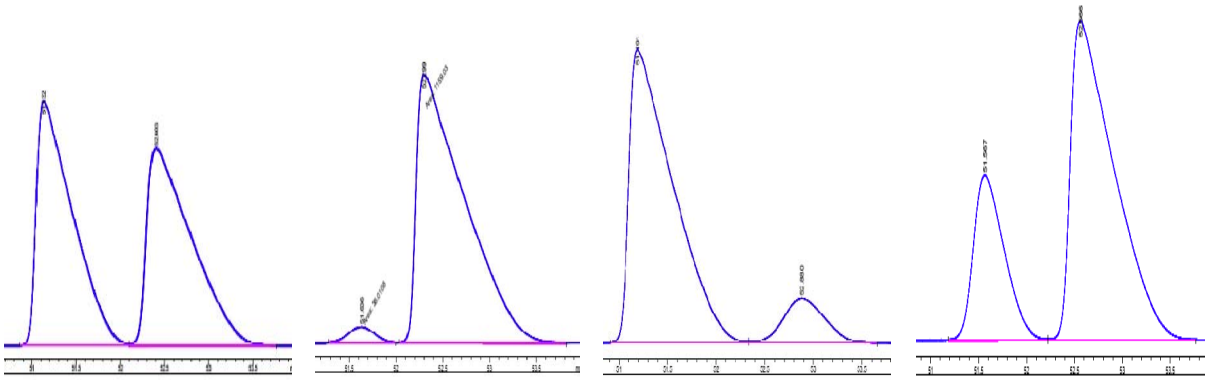
(*S*)-4-Phenylbutane-1,2-diol. The diboration was performed according to the general procedure with 4-phenyl-1-butene (75.0 mg, 571.6 μmol), $Pt(dba)_3$ (15.6 mg, 17.4 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (27.3 mg, 34.3 μmol), and $B_2(pin)_2$ (152.4 mg, 600.2 μmol) in tetrahydrofuran (5.72 mL, 0.1 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate/hexanes, stain in $KMnO_4$) to afford a clear, colorless oil (81.7 mg, 86% yield). Spectral data are in accordance with the literature.[44] HRMS-(ESI+) for $C_{10}H_{15}O_2$ [M+H]: calculated: 167.1072, found: 167.1077. $[\alpha]_D^{20} = -16.240$ (*c* = 1.143, $CHCl_3$, *l* = 50 mm).

Proof of stereochemistry:

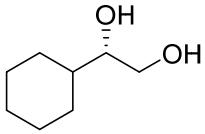
The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The resulting ketal was compared to the racemic ketal of 4-phenylbutane-1,2-diol prepared from treatment of 4-phenyl-1-butene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The authentic (*R*)-isomer was prepared from the Sharpless asymmetric dihydroxylation of 4-phenyl-1-butene utilizing AD-mix-β.

[44] Stead, D.; O'Brien, P.; Sanderson, A.; *Org. Lett.*, **2008**, *10*, 1409.

Chiral GLC (β-dex, Supelco, 100 °C, 20 psi) – analysis of the acetonide of 4-phenylbutane-1,2-diol.



racemic | diboration | authentic | coinjection of diboration product



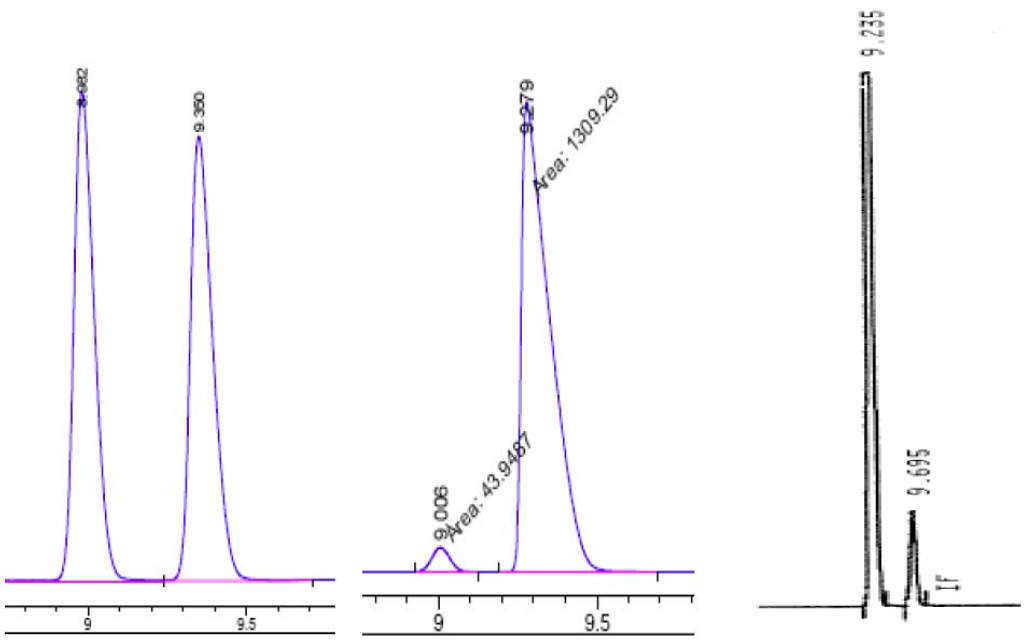
(*S*)-1-Cyclohexylethane-1,2-diol. The diboration was performed according to the general procedure with vinyl cyclohexane (75.0 mg, 680.6 μmol), $Pt(dba)_3$ (18.6 mg, 20.7 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (32.5 mg, 40.8 μmol), and $B_2(pin)_2$ (181.5 mg, 714.6 μmol) in tetrahydrofuran (6.8 mL, 0.1 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate/hexanes, stain in $KMnO_4$) to afford a clear, colorless oil (85.4 mg, 87% yield). Spectral data are in accordance with the literature.[45] HRMS-(ESI+) for $C_8H_{17}O_2$ [M+H]: calculated: 145.1229, found: 145.1222. $[\alpha]_D^{20} = +3.921$ (c = 0.510, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry:

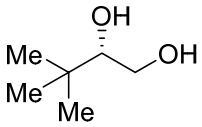
The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The resulting ketal was compared to the racemic ketal of 1-cyclohexylethane-1,2-diol prepared from treatment of vinyl cyclohexane with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The authentic (*R*)-isomer was prepared from the Sharpless asymmetric dihydroxylation of vinyl cyclohexane utilizing AD-mix-β.

[45] Miller, S. P.; Morgan, J. B.; Nepveux, F. J.; Morken, J. P. *Org. Lett.* **2004**, *6*, 131.

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



racemic diboration product authentic

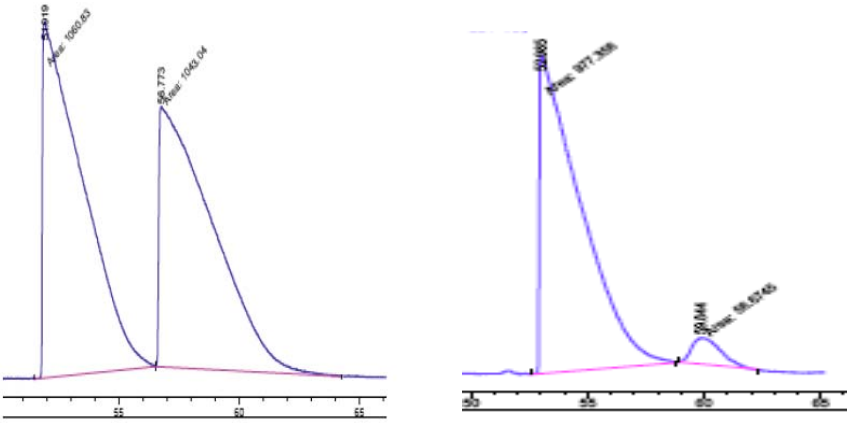


(*S*)-3,3-Dimethylbutane-1,2-diol. The diboration was performed according to the general procedure with 3,3-dimethyl-1-butene (75.0 mg, 891.2 µmol), $Pt(dba)_3$ (24.4 mg, 27.1 µmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (42.6mg, 53.5 µmol), and $B_2(pin)_2$ (237.6 mg, 935.8 µmol) in tetrahydrofuran (8.9 mL, 0.1 M). The crude reaction mixture was purified on silica gel (40-70% ether/pentane, stain in $KMnO_4$) to afford a clear, colorless oil that was inseparable from pinacol (193.7 mg, 1:3 product:pinacol = 46% yield). Spectral data are in accordance with the literature.[45] HRMS-(ESI+) for $C_6H_{15}O_2$ [M+H]: calculated: 119.1072, found: 119.1074.

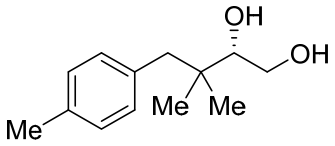
Proof of Stereochemistry:

The title compound was compared to racemic 3,3-dimethylbutane-1,2-diol prepared from treatment of 3,3-dimethyl-1-butene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The absolute stereochemistry was assigned by analogy.

Chiral GLC (β-dex, Supelco, 90 ℃, 20 psi) – analysis of 3,3-dimethylbutane-1,2-diol.



racemic diboration product

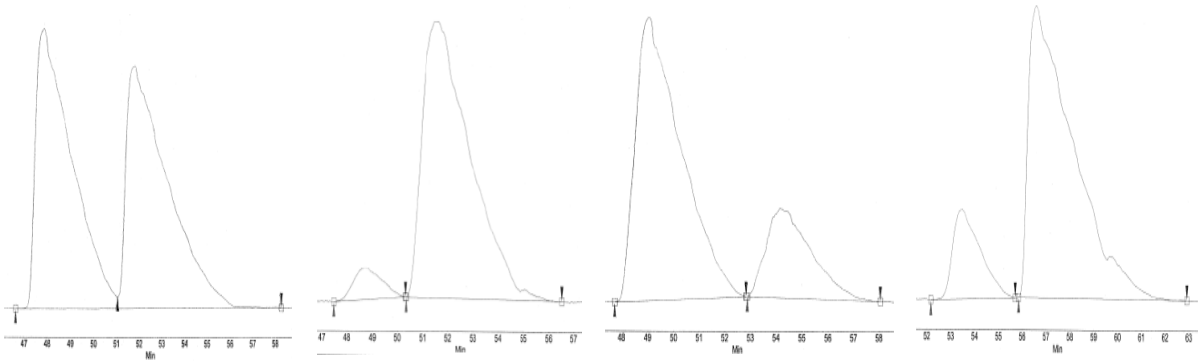


(*S*)-3,3-Dimethyl-4-*p*-tolylbutane-1,2-diol. The diboration was performed according to the general procedure with 3,3-dimethyl-4-(4-methylphenyl)-1-butene (75.0 mg, 430.3 μmol), $Pt(dba)_3$ (11.7 mg, 13.0 μmol), (*R*,*R*)-3,5-diethylphenylTADDOLPPh (20.6 mg, 25.8 μmol) and $B_2(pin)_2$ (114.6 mg, 451.8 μmol) in tetrahydrofuran (4.3 mL, 0.1 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate/hexanes) to afford a clear, colorless oil (46.6 mg, 52% yield). Spectral data are in accordance with the literature.[45] HRMS-(ESI+) for $C_{13}H_{21}O_2$ [M+H]: calculated: 209.1542, found: 209.1545. $[\alpha]_D^{20}$ = -4.202 (*c* = 0.691, $CHCl_3$, *l* = 50 mm).

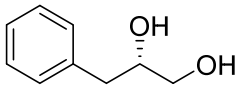
Proof of Stereochemistry:

The title compound was compared to the racemic 1,2-diol prepared from dihydroxylation of 3,3-dimethyl-4-(4-methylphenyl)-1-butene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The authentic (*R*)-isomer was prepared from the Sharpless asymmetric dihydroxylation of 3,3-dimethyl-4-(4-methylphenyl)-1-butene utilizing AD-mix-β.

Chiral SFC (Chiracel OD-H, 0.7% MeOH, 3 mL/min, 150 psi, 50 ˚C, 220 nm) – analysis of 3,3-dimethyl-4-p-tolylbutane-1,2- diol.



racemic | diboration | authentic | coinjection of diboration product

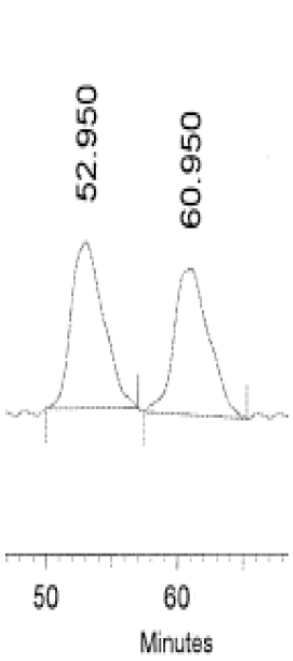


(*S*)-3-Phenylpropane-1,2-diol. The diboration was performed according to the general procedure with allylbenzene (75.0 mg, 634.6 μmol), $Pt(dba)_3$ (17.3 mg, 19.3 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (30.3 mg, 38.1 μmol), and $B_2(pin)_2$ (169.2 mg, 666.3 μmol) in tetrahydrofuran (6.3 mL, 0.1 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate/hexanes, stain in $KMnO_4$) to afford a white solid (83.8 mg, 87% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.66-2.76 (2H, m, PhC**H$_2$**), 2.83 (2H, br s, O**H** x 2), 3.44 (1H, dd, *J* = 11.2 Hz, 7.2 Hz, HOC**H$_A$**H$_B$), 3.61 (1H, dd, *J* = 11.2 Hz, 2.8 Hz, HOCH$_A$**H$_B$**), 3.85-3.90 (1H, m, CH_2C**H**OH), 7.17-7.23 (3H, m, CH_2**Ph**), 7.26-7.30 (2H, m, CH_2**Ph**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 39.8, 65.9, 73.0, 126.5, 128.5, 129.3, 137.7; IR (neat): 3363.1 (br s), 2939.5 (w), 1495.8 (m), 1454.2 (m), 1089.7 (s), 1069.0 (s), 1030.6 (s), 745.3 (m), 699.6 (s) cm^{-1}; HRMS-(ESI+) for $C_8H_9O_1$ [M-$H_2$0+H]: calculated: 121.0653, found: 121.0657. $[\alpha]_D^{20}$ = -17.877 (*c* = 0.576, $CHCl_3$, *l* = 50 mm).

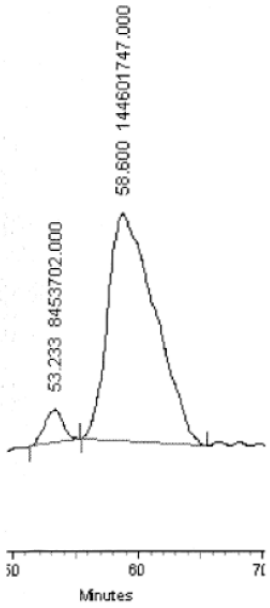
Proof of Stereochemistry:

The title compound was compared to racemic 3-phenylpropane-1,2-diol prepared from treatment of allylbenzene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The authentic (*R*)-isomer was prepared from the Sharpless asymmetric dihydroxylation of allylbenzene utilizing AD-mix-β.

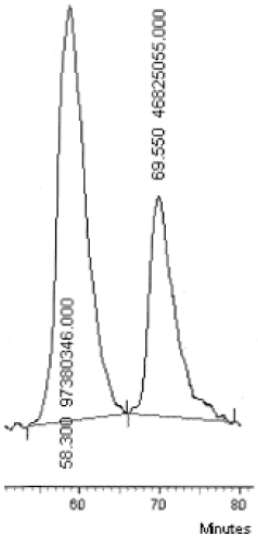
Chiral HPLC (Chiracel OD, 2.0% IPA, 1.5 mL/min, 220 nm)-analysis of 3-phenylpropane-1,2-diol.



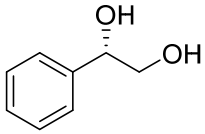
racemic



diboration product



authentic

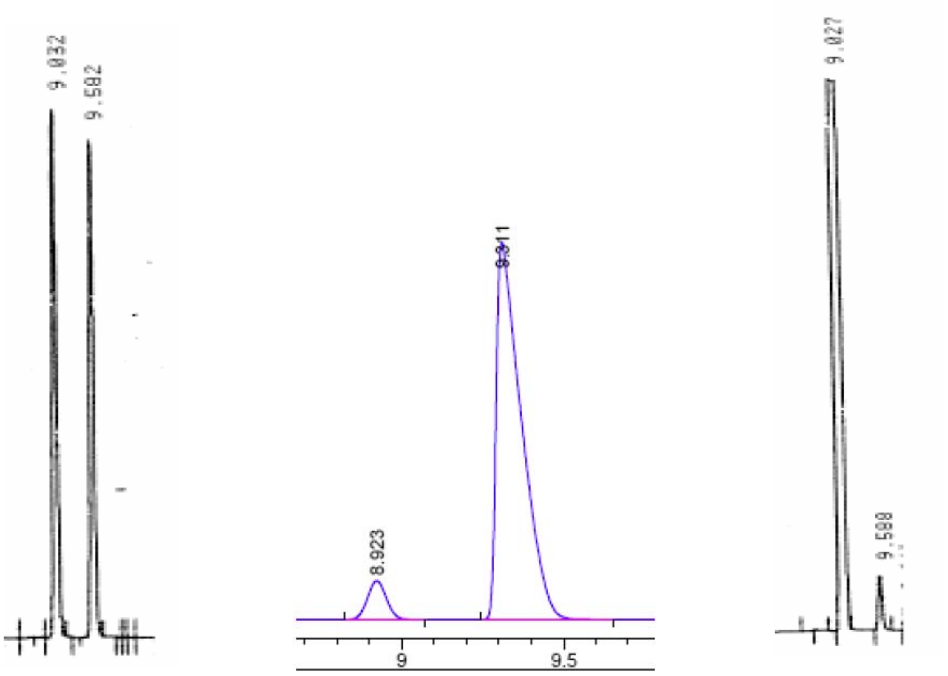


(*S*)-1-Phenylethane-1,2-diol. The diboration was performed according to the general procedure with styrene (75.0 mg, 720.1 μmol), $Pt(dba)_3$ (19.7 mg, 21.9 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (34.4 mg, 43.2 μmol), and $B_2(pin)_2$ (192.0 mg, 756.1 μmol) in tetrahydrofuran (7.2 mL, 0.1 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate/hexanes, stain in $KMnO_4$) to afford a white solid (83.6 mg, 84% yield). Spectral data are in accordance with the literature.[45] HRMS-(ESI+) for $C_8H_9O_1$ [M-H_2O+H]: calculated: 121.0653, found: 121.0656. $[\alpha]_D^{20}$ = +53.883 (*c* = 1.146, $CHCl_3$, *l* = 50 mm).

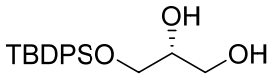
Proof of Stereochemistry:

The title compound was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The resulting ketal was compared to the racemic ketal of 1-phenylethane-1,2-diol prepared from treatment of styrene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The authentic (*R*)-isomer was prepared from the Sharpless asymmetric dihydroxylation of styrene utilizing AD-mix-β.

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



racemic diboration product authentic

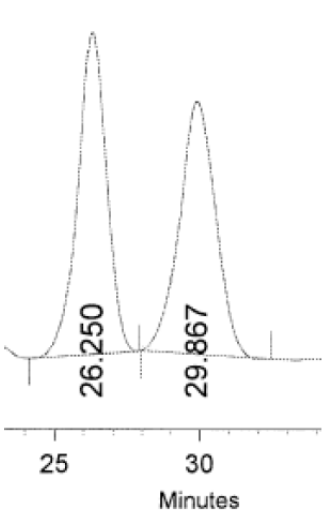


(*R*)-3-(*tert*-Butyldiphenylsilyloxy)propane-1,2-diol. The diboration was performed according to the general procedure with allyloxy(*tert*-butyl)diphenylsilane (75.0 mg, 250.3 μmol), $Pt(dba)_3$ (6.9 mg, 7.7 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (12.1 mg, 15.2 μmol), and $B_2(pin)_2$ (67.5 mg, 265.7 μmol) in tetrahydrofuran (2.5 mL, 0.1 M). The crude reaction mixture was purified on silica gel (20-30% ethyl acetate/hexanes) to afford a white solid (77.7 mg, 93% yield). R_f = 0.39 (50% ethyl acetate/hexane, stain in $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.05 (9H, s, SiCH(**C**$\mathbf{H_3}$)$_\mathbf{3}$), 1.94 (1H, br s, O**H**), 2.55 (1H, br s, O**H**), 3.61-3.74 (4H, m, SiOC$\mathbf{H_2}$CHOHC$\mathbf{H_2}$OH), 3.76-3.82 (1H, m, $SiOCH_2C$**H**OH), 7.36-7.45 (6H, m, Si**Ar**), 7.62-7.65 (4H, m, Si**Ar**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 26.9, 63.8, 65.2, 71.9, 127.8, 129.8, 132.8, 135.4; IR (neat): 3375.5 (br s), 2930.6 (m), 2857.8 (w), 1427.6 (m), 1111.7 (s), 823.7 (w), 740.3 (w), 701.6 (s) cm^{-1}; HRMS-(ESI+) for $C_{19}H_{30}NO_3Si$ [M+NH_4^+]: calculated: 348.1995, found: 348.2000. $[\alpha]_D^{20}$ = +1.836 (*c* = 1.534, $CHCl_3$, *l* = 50 mm).

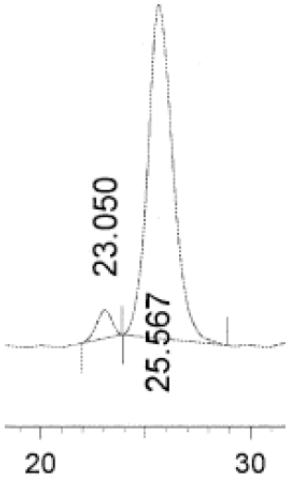
Proof of Stereochemistry:

The title compound was compared to racemic 3-(*tert*-Butyldiphenylsilyloxy)propane-1,2-diol prepared from treatment of allyloxy(*tert*-butyl)diphenylsilane with osmium tetroxide and 4-methylmorpholine *N*-oxide. Absolute stereochemistry was assigned by analogy.

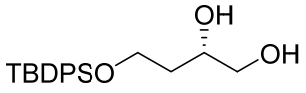
Chiral HPLC (Chiracel-OD, 2.0 % IPA, 1.5 mL/min, 220 nm) – analysis of the title compound.



racemic



diboration product

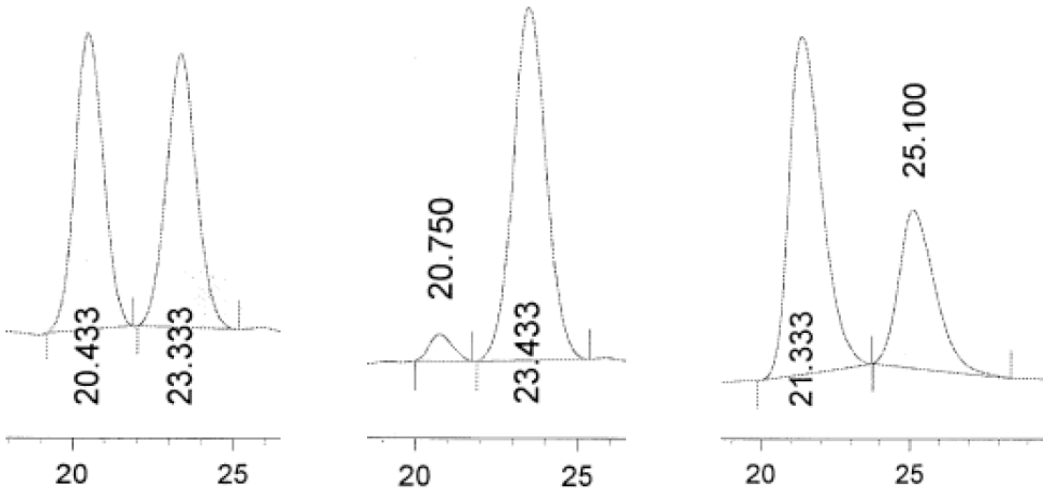


(*S*)-4-(*tert*-Butyldiphenylsilyloxy)butane-1,2-diol. The diboration was performed according to the general procedure with (but-3-enyloxy)(tert-butyl)diphenylsilane (100.0 mg, 322.1 μmol), $Pt(dba)_3$ (8.8 mg, 9.8 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (15.4 mg, 19.3 μmol), and $B_2(pin)_2$ (85.9 mg, 338.2 μmol) in tetrahydrofuran (3.2 mL, 0.1 M). The crude reaction mixture was purified on silica gel (30-60% ethyl acetate/hexanes) to afford a clear, colorless oil that could not be separated from pinacol (137.1 mg, 1:1 product:pinacol = 92% yield). R_f = 0.26 (50% ethyl acetate/hexane, stain in $KMnO_4$); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.03 (9H, s, $SiC(C\mathbf{H_3})_3$), 1.59-1.66 (1H, m, $SiOCH_2C\mathbf{H_A}H_B$), 1.72-1.81 (1H, m, $SiOCH_2CH_A\mathbf{H_B}$), 3.50 (1H, dd, *J* = 11.2 Hz, 6.4 Hz, $OHCHC\mathbf{H_A}H_BOH$), 3.62 (1H, dd, *J* = 11.2 Hz, 3.6 Hz, $OHCHCH_A\mathbf{H_B}OH$), 3.85 (2H, t, *J* = 5.2 Hz, $SiOC\mathbf{H_2}$), 3.97-4.01 (1H, m, $SiOCH_2CH_2C\mathbf{H}OH$), 7.35-7.45 (6H, m, Si**Ar**), 7.64-7.66 (4H, m, Si**Ar**); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.1, 24.9, 34.9, 62.5, 66.7, 71.6, 127.7, 129.8, 132.9, 135.5; IR (neat): 3380.8 (br s), 2930.1 (w), 2857.6 (w), 1427.6 (m), 1110.2 (s), 822.8 (w), 737.4 (m), 701.5 (s), 688.8 (m) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{29}O_3Si$ [M+H]: calculated: 345.1886, found: 345.1878. $[\alpha]_D^{20}$ = +2.224 (*c* = 1.065, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry:

The title compound was compared to racemic 4-(*tert*-butyldiphenylsilyloxy)butane-1,2-diol prepared from treatment of (but-3-enyloxy)(tert-butyl)diphenylsilane with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The authentic (*R*)-isomer was prepared from the Sharpless asymmetric dihydroxylation of (but-3-enyloxy)(tert-butyl)diphenylsilane utilizing AD-mix-β.

Chiral HPLC (Chiracel-OD, 2.0% IPA, 1.5 mL/min, 220 nm) – analysis of the title compound.

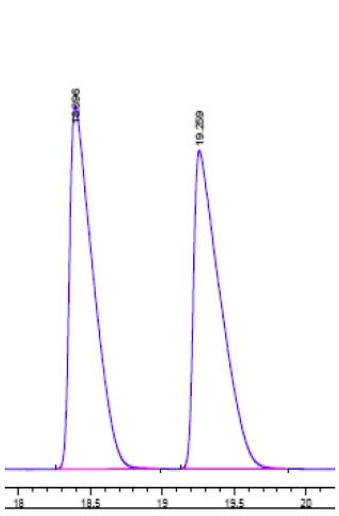


racemic diboration product authentic

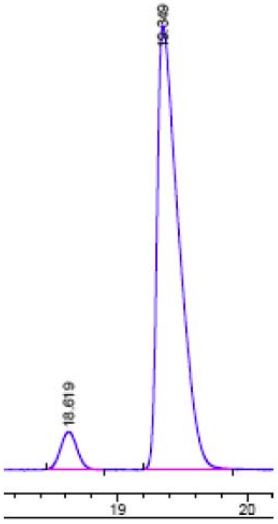
1.7.7 Procedure For Decreased Catalyst Loading Experiment

To an oven-dried 6-dram vial with magnetic stir bar in the dry box was added $Pt(dba)_3$ (14.6 mg, 16.3 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (25.6 mg, 32.1 μmol), $B_2(pin)_2$ (712.8 mg, 2.81 mmol) and ethyl acetate (5.3 mL, 0.5 M). The vial was sealed with a polypropylene cap, removed from the dry box, and heated to 80 °C in an oil bath for 30 min. The vial was cooled to room temperature, returned to the dry box and charged with 1-octene (300.0 mg, 2.67 mmol). The vial was sealed, removed from the dry box, and stirred at 60 °C for 12 h. The reaction mixture was cooled to 0 °C (ice/water) and charged with 3 M sodium hydroxide (4 mL), and 30% hydrogen peroxide (2 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h at which time the vial was cooled to 0 °C (ice/water) 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 washed with ethyl acetate (3 x 20 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (30-70% ethyl acetate/hexanes) to afford a white solid (340.1 mg, 87% yield).

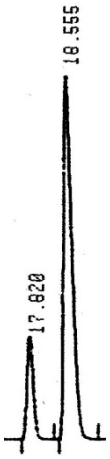
Chiral GLC (β-dex, Supelco, 100 °C, 20 psi) – analysis of the acetonide of octane-1,2-diol



racemic



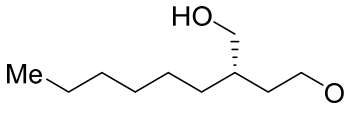
diboration product



authentic

1.7.8 Procedure for Alkene Diboration/Homologation/Oxidation

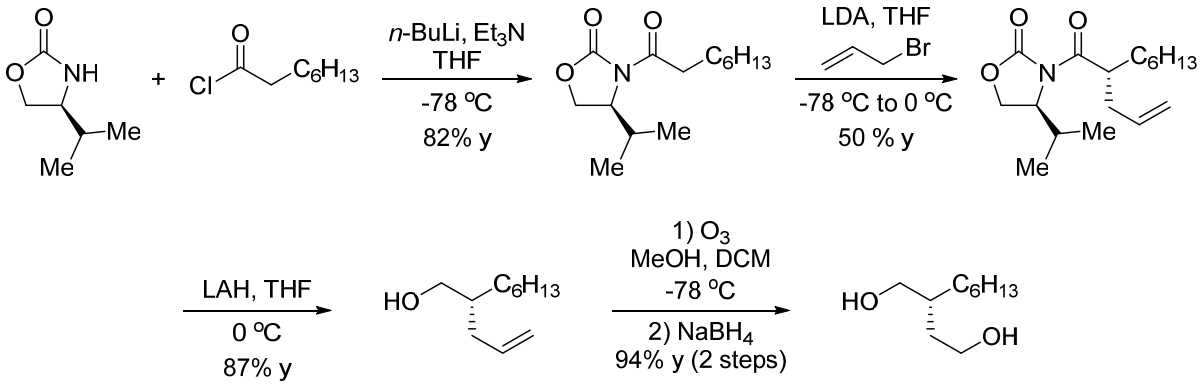
To an oven-dried 6-dram vial with magnetic stir bar in the dry box was added $Pt(dba)_3$ (12.2 mg, 13.6 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (21.3 mg, 26.7 μmol), $B_2(pin)_2$ (118.8 mg, 467.9 μmol) and tetrahydrofuran (4.5 mL, 0.1 M). The vial was sealed with a polypropylene cap, removed from the dry box, and heated to 80 °C in an oil bath for 30 min. The vial was cooled to room temperature, returned to the dry box and charged with 1-octene (50.0 mg, 445.6 μmol). The vial was sealed, removed from the dry box, and stirred at 60 °C for 12 h, after which the reaction was cooled to room temperature, fitted with a septum, and placed under nitrogen atmosphere. The crude reaction mixture was then charged with bromochloromethane (7.0 μL, 980 μmol) and cooled to -78 °C. *n*-BuLi (37.0 μL, 980 μmol) was added dropwise under nitrogen atmosphere and the reaction was allowed to stir at -78 °C for 10 min, at which time it was warmed to room temperature and stirred for 12 h. The reaction mixture was cooled to 0 °C (ice/water) and charged with 3 M sodium hydroxide (2 mL), and 30% hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h, at which time the vial was cooled to 0 °C (ice/water) 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 washed with ethyl acetate (3 x 20 mL) and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (30-70% ethyl acetate/hexanes) to afford the desired 1,4-diol as a clear, colorless oil (64.6 mg, 83% yield).



(*S*)-2-Hexylbutane-1,4-diol. ^{1}H (400 MHz, $CDCl_3$): δ 0.85 (3H, t, *J* = 6.8 Hz, $(CH_2)_5C\mathbf{H_3}$), 1.19-1.35 (10H, m, $(C\mathbf{H_2})_5$), 1.52-1.71 (3H, m, $HOCH_2C\mathbf{H}C\mathbf{H_2}CH_2OH$), 2.97 (2H, br s, O**H** x 2), 3.45 (1H, dd, *J* = 10.8 Hz, 6.8 Hz, $C\mathbf{H_A}H_BOH$), 3.61-3.65 (2H, m, $C\mathbf{H_2}OH$), 3.73-3.78 (1H, m, $CH_A\mathbf{H_B}OH$); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 22.6, 27.0, 29.6, 31.7, 31.8, 35.8, 39.3, 61.2, 66.4; IR (neat): 3318.0 (br s), 2955.6 (m), 2925.0 (s), 2856.5 (m), 1466.2 (w), 1043.9 (w) cm^{-1}; HRMS-(ESI+) for $C_{10}H_{23}O_2$ [M+H]: calculated 175.1698, observed: 175.1693. $[\alpha]_D^{20}$ = -10.115 (*c* = 0.680, $CHCl_3$, *l* = 50 mm).

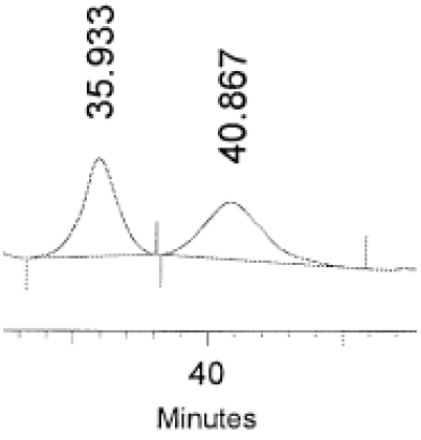
Proof of Stereochemistry

The Matteson homologation reaction is known to proceed with retention of stereochemistry.[37] The authentic (*R*)-isomer of the title compound was prepared using Evan's alkylation,[46] followed by ozonolysis and reduction as shown below.

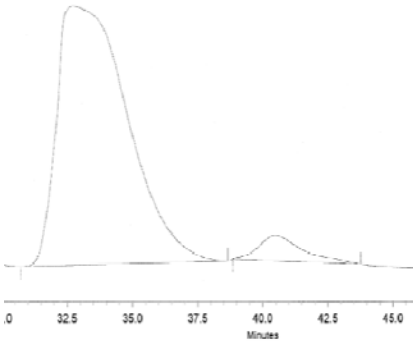


[46] Evans, D. A.; Ennis, M. D.; Mathre, D. J.; *J. Am. Chem. Soc*, **1982**, *104*, 1737.

Chiral HPLC (Chiracel-OD, 1.0 mL/min, 0.5% IPA, 220 nm) – analysis of the bis(benzoate) of 2-hexylbutane-1,4-diol.

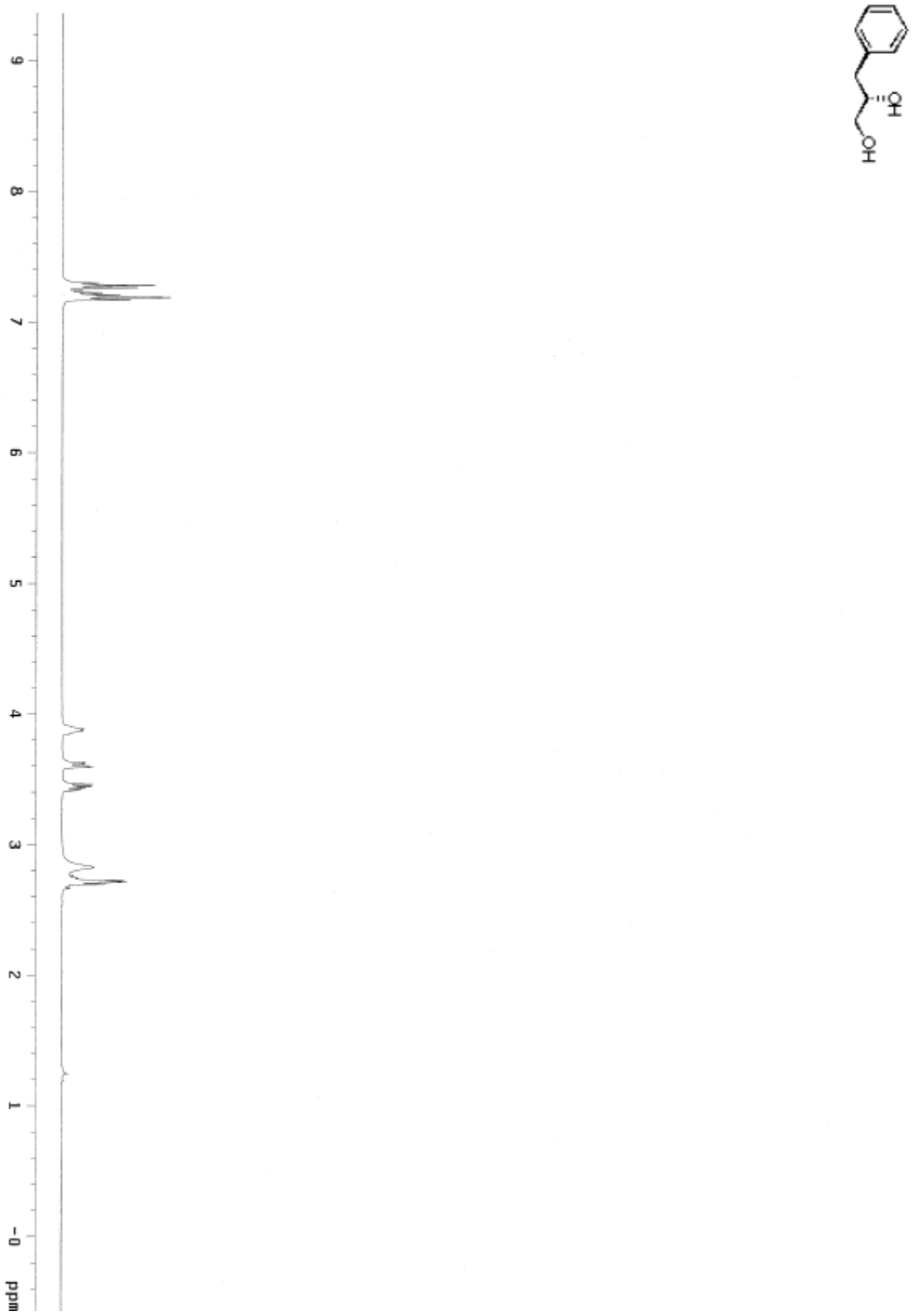


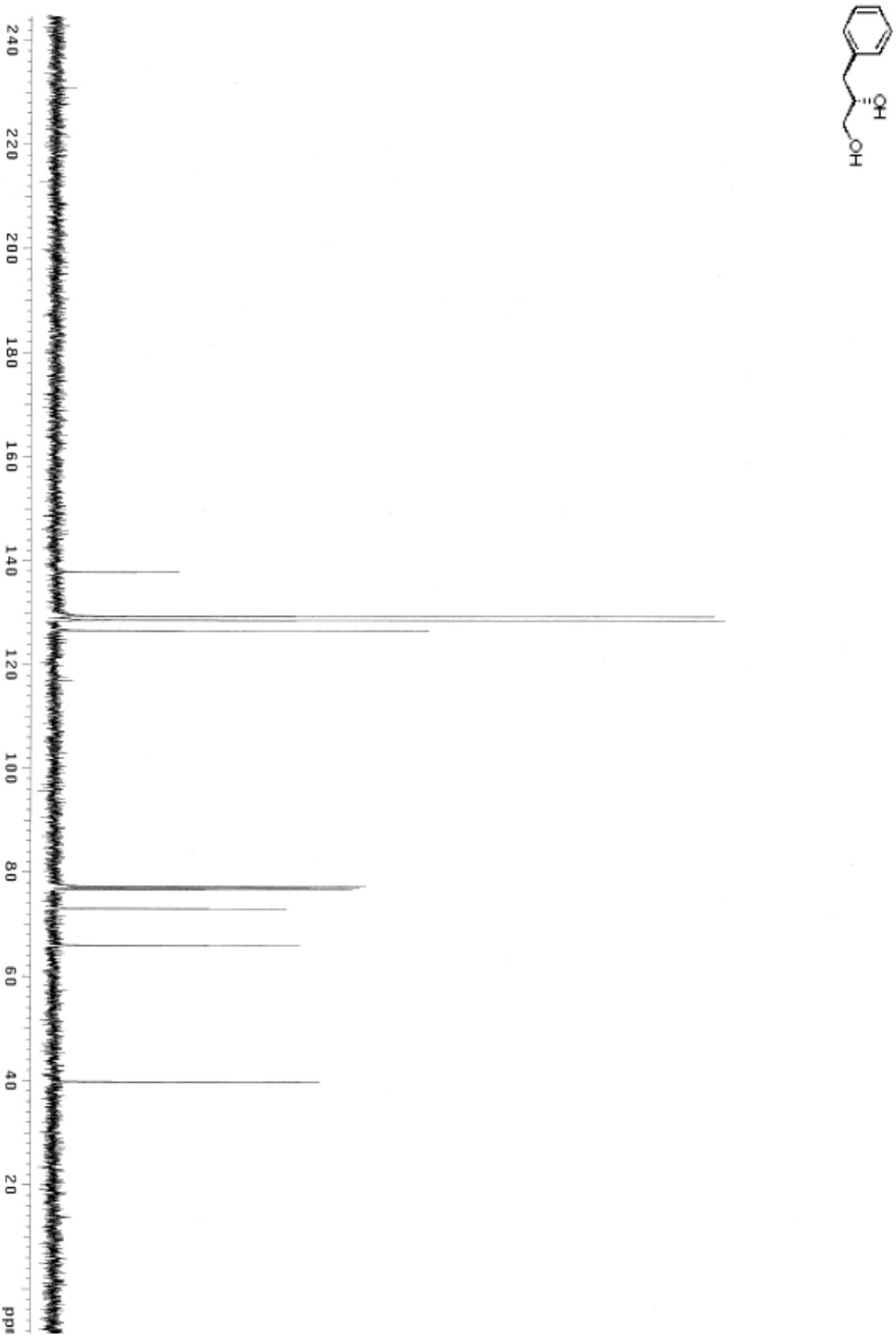
racemic



diboration/homologation

1.8 Representative NMR Spectra




240
220
200
180
160
140
120
100
80
60
40
20
ppm

Chapter 2

Development and Scope of Platinum-Catalyzed Diboration of *Cis*-1,3-Dienes and 4,4-Disubstituted Dienes: Application to Polypropionate Synthesis

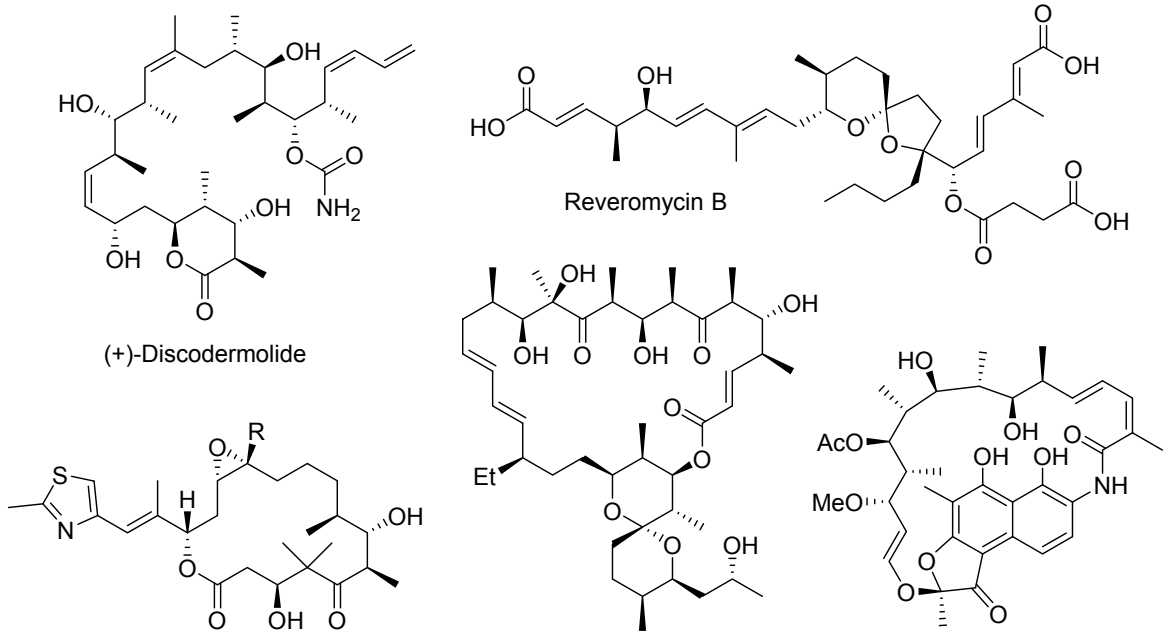
2.1 Introduction

Polyketides are a structurally diverse class of secondary metabolites present in nearly all living organisms. Nearly 10,000 polyketides have been identified and it is estimated that polyketides are five times more likely to possess useful biological activity compared to other families of natural products.[1] In fact, small molecule therapeutics inspired by this class of natural products account for nearly 20% of the top-selling small molecule medicines and have been applied as antibiotics, antifungals, cancer chemotherapeutics as well as cholesterol lowering agents. Because polyketides have complex structural motifs and promising biological activity, the chemistry community has expressed significant interest in their synthesis.

The enormous class and diversity of polyketides necessitates further classification into smaller subgroups: fatty acids, aromatic polyketides and polypropionates. Although the structural core of polyketides is varied, there are several functional motifs that remain universal. One of the most ubiquitous motifs is the *syn*-methyl-hydroxyl stereodiad, which is highly conserved in polypropionates (Scheme 2.1).

[1] (a) Newman, D. J.; Cragg, G. M. *J. Nat. Prod.* **2007**, *70*, 461. (b) Newman, D. J. Grothaus, P. G.; Cragg, G. M. *Chem. Rev.* **2009**, *109*, 3012. (c) Koskinen, A. M. P.; Karisalmi, K. *Chem. Soc. Rev.* **2005**, *34*, 677.

Scheme 2.1 Polyketide Natural Products



Due to the prevalence of the *syn* stereodyad, numerous reactions designated to controlling the stereochemistry of this motif have been developed. The relative and absolute configuration is generally controlled through use of stoichiometric chiral reagents, although a few catalytic methods have recently emerged. While excellent stereocontrol can be obtained with current methods, the majority generate a product containing a terminal alkene. This functional group often requires several synthetic manipulations to obtain the substitution present in the targeted natural product. In this context, a catalytic and enantioselective method to construct a *syn*-polypropionate motif containing a more versatile synthetic handle would be advantageous in the field of polyketide synthesis.

2.2 Background

2.2.1 Enantioselective Aldol Reactions

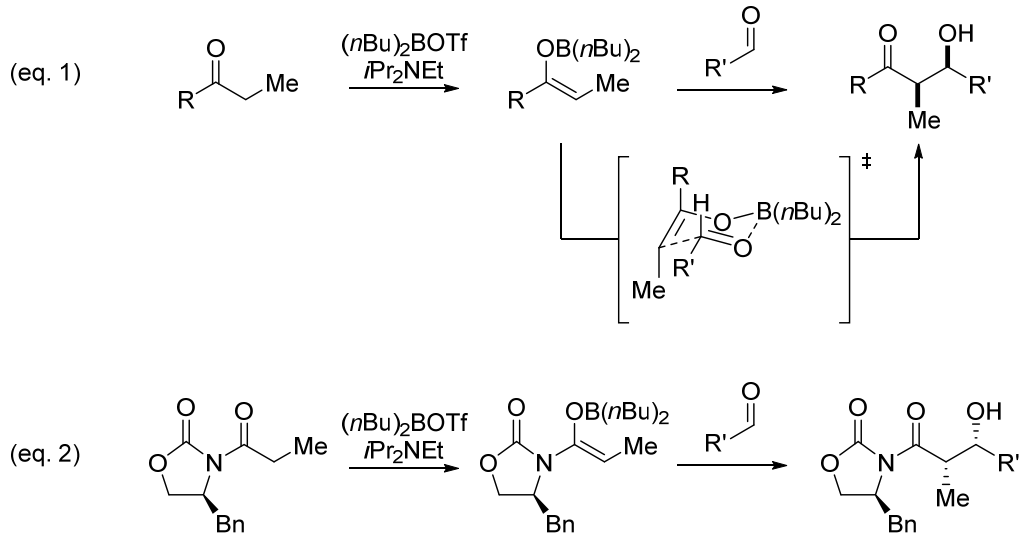
The stereoselective synthesis of *syn*-polypropionate motifs was first achieved through aldol reactions of isomerically pure enolates (Scheme 2.2, eq 1).[2] While only diastereoselective, the realization that this transformation occurs through a predictable closed six-membered chair transition state allowed for future improvement. Since the initial discovery, the aldol reaction has been rendered asymmetric by Evans through incorporation of a chiral oxazolidinone (Scheme 2.2, eq 2).[3] This auxiliary effectively controls both the enolate geometry as well as the facial selectivity of the reaction, thereby creating an enantioselective transformation. Since the pioneering work reported by Evans, several other chiral auxiliaries have been reported.[4] While high levels of asymmetric induction can be achieved, use of stoichiometric chiral auxiliaries is undesirable and cost-prohibitive for large scale synthesis. The high cost associated with chiral auxiliaries generated interest in developing catalytic alternatives.

[2] (a) Cuse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J.; Heathcock, C. H. *J. Org. Chem.* **1980**, *45*, 1066. (b) Dhar, R. K.; Bakshi, R. K.; Pandiarajan, P. K.; Singaram, B.; Brown, H. C. *J. Am. Chem. Soc.* **1989**, *111*, 3441.

[3] Bartroli, J.; Shih, T. L.; Evans, D. A. *J. Am. Chem. Soc.* **1981**, *103*, 2127.

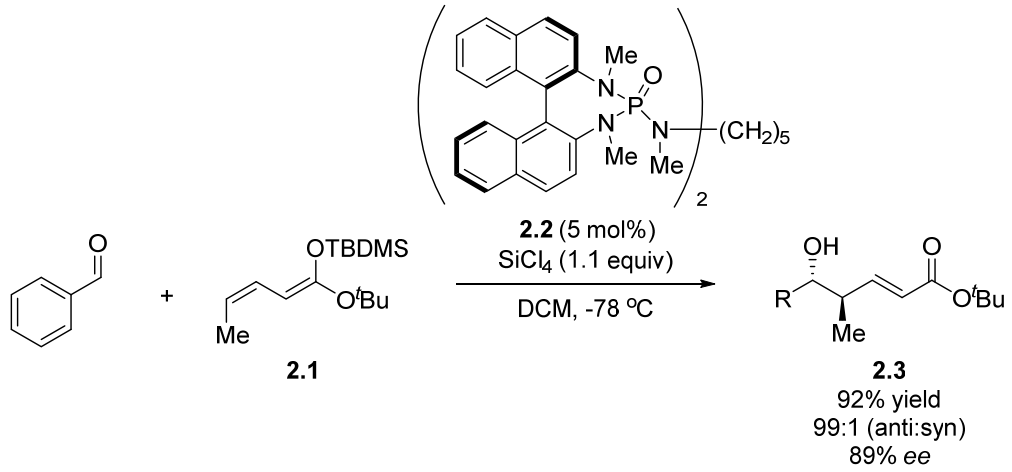
[4] (a) Qin, H. Arya, P. *Tetrahedron* **2000**, *56*, 917. (b) Geary, L. M.; Hultin, P. G. *Tetrahedron: Asymmetry* **2009**, *20*, 131. (c) Vicario, J. L.; Badia, D.; Carrillo, L.; Reyes, E.; Etxebarria, J. *Curr. Org. Chem.* **2005**, *9*, 219.

Scheme 2.2 Stereoselective Aldol Reaction



Enantioselective aldol reactions have also been used to generate products containing a functionalized olefin (Scheme 2.3).[5] These reactions proceed through an open-transition state and generally produce the *anti*-diastereomer preferentially, regardless of dienolate geometry. This stereoconvergent transformation delivers the desired product **2.3** in excellent yield and enantioselectivity.

Scheme 2.3 Enantioselective Vinylogous Aldol Reaction



[5] (a) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem. Int. Ed.* **2005**, *44*, 4682. (b) Denmark, S. E.; Beutner, G. L. *J. Am. Chem. Soc.* **2003**, *125*, 7800.

2.2.2 Carbonyl Crotylation

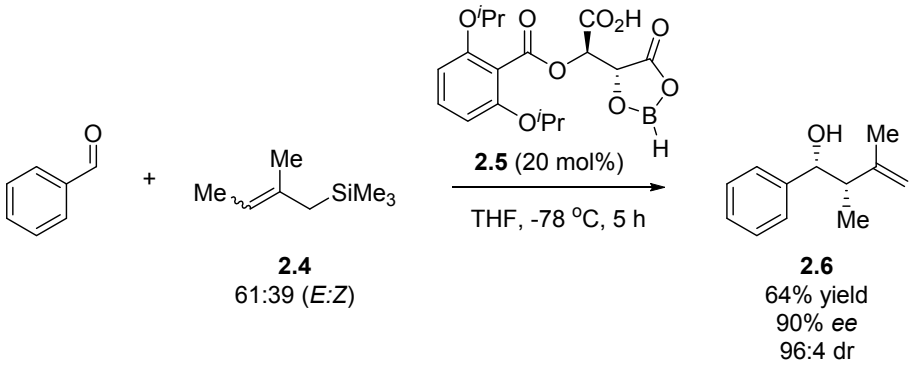
The *syn*-polypropionate motif can also be established through addition of allyl-metal reagents to prochiral aldehydes. In these reactions, the nature of the metal dictates the reactivity and thereby enables either a closed-transition state (Type I) or an open-transition state (Type II).[6] While different operative mechanisms for stereoinduction are observed, both classes of allylation reagents can react with high diastereo- and enantio-control.

2.2.2.1 Crotylsilation

Allylsilane reagents can participate in allylation of aldehydes and, depending on the substitution pattern on the silicon atom, either an open- or closed-transition state operates. In 1991, Yamamoto and co-workers disclosed the addition of substituted allyltrimethylsilane reagents to aldehydes in the presence of a chiral (acyloxy)borane complex **2.5** (Scheme 2.4).[7] This transformation requires substituted allylsilanes, with simple allyltrimethylsilane unreactive to aldehyde addition even at elevated temperatures. Importantly, the diastereomeric purity of the product (**2.6**, 96:4 *syn:anti*) was found to be independent of the starting olefin geometry (**2.4**, 61:39 *E:Z*), which is consistent with an extended transition state model.

[6] Fu, J.; Denmark, S. E. *Chem. Rev.* **2003**, *103*, 2763.
[7] Furuta, K.; Mouri, M.; Yamamoto, H. *Synlett*, **1991**, 561.

Scheme 2.4 Asymmetric Crotylsilation with Chiral (Acyloxy)Borane Catalyst



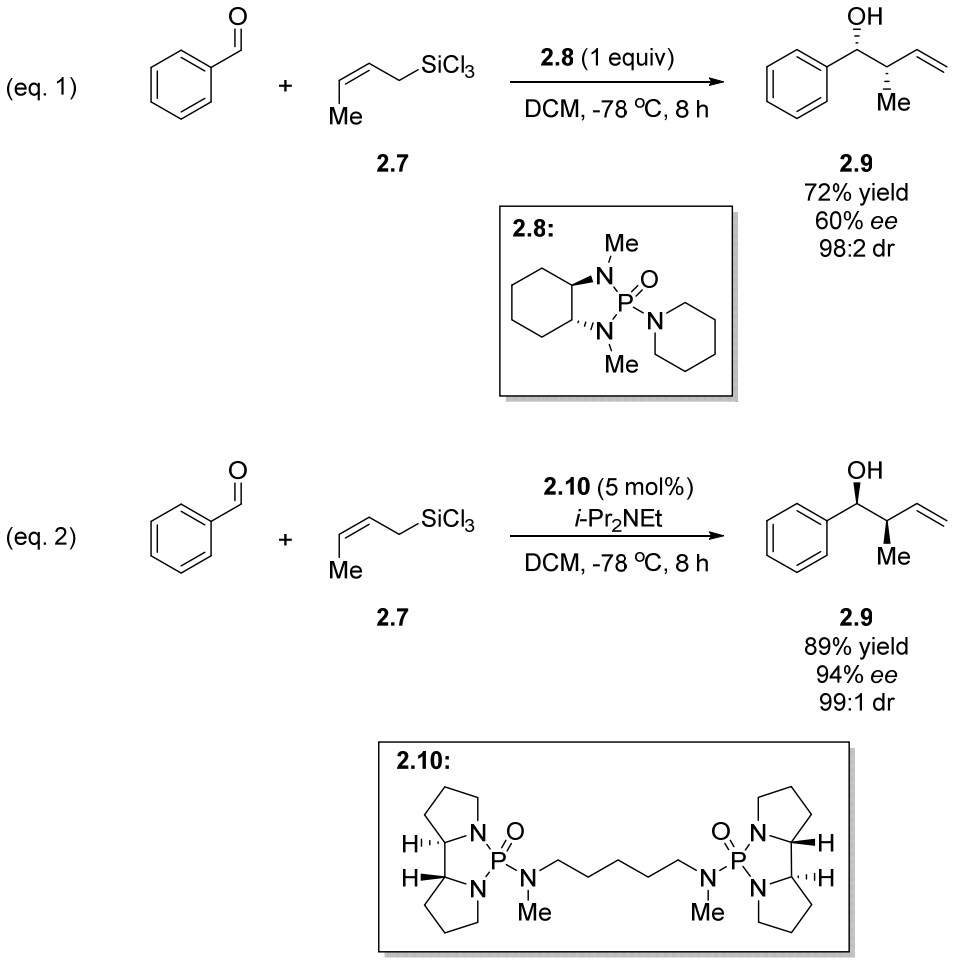
In addition to trimethylsilane reagents, trichlorosilanes have been used successfully in the asymmetric diastereoselective allylation of aldehydes. However, in contrast to trimethylsilane analogues, the olefin geometry in crotyltrichlorosilanes directly influences the diastereomeric ratio of the products, suggesting a closed transition state.[8] In the course of studying this reaction, Kobayashi reported an interesting rate acceleration that occurs when reactions are run in DMF. This observed acceleration was rationalized through activation of the electron deficient silicon with the Lewis basic DMF. Following this hypothesis, Denmark began studying chiral Lewis bases in hopes of controlling the stereochemistry of the addition.[9] In 1994, Denmark reported moderate asymmetric induction when 1 equivalent of phosphoramide **2.8** was added to the reaction (Scheme 2.5, eq 1). This transformation was greatly improved through use of a chiral bisphosphoramide (**2.10**). The new conditions require only 5 mol% of **2.10** and delivered product **2.9** in 94% *ee* with near perfect diastereoselectivity (Scheme 2.5, eq 2). Unfortunately, this methodology is only highly selective for aromatic aldehydes. While

[8] (a) Kobayashi, S.; Nishio, T. *Tetrahedron Lett.* **1993**, *34*, 3453. (b) Kobayashi, S.; Nishio, K. *Synthesis* **1994**, 457.

[9] Denmark, S. E.; Coe, D. M.; Pratt, N. E.; Griedel, B. D. *J. Org. Chem.* **1994**, *59*, 6161. (b) Denmark, S. E.; Fu, J. *J. Am. Chem. Soc.* **2001**, *123*, 9488.

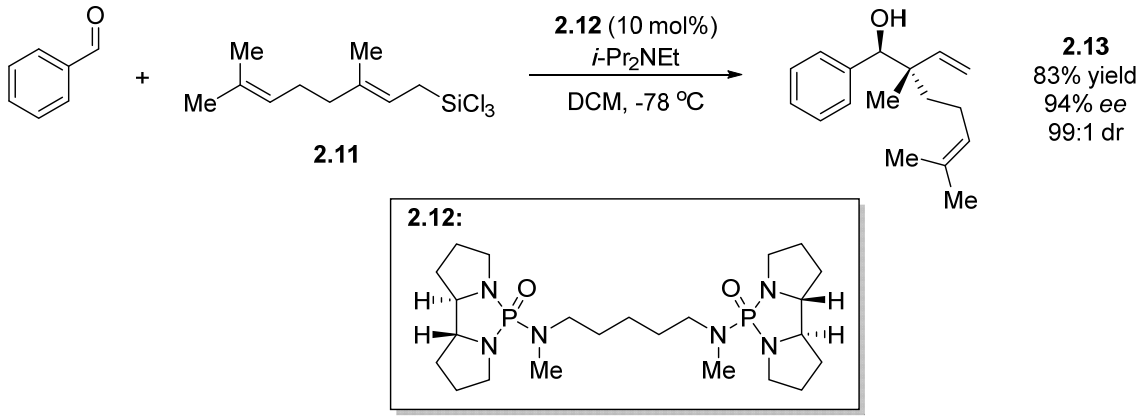
α,β-unsaturated enals react with diminished asymmetric induction, aliphatic aldehydes are generally not compatible.

Scheme 2.5 Asymmetric Crotylsilation with Chiral Lewis Base



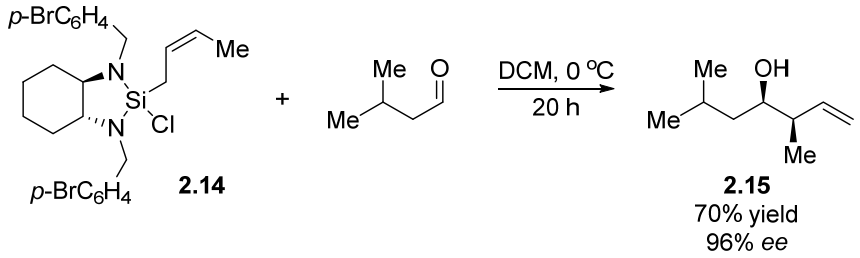
Although Denmark's asymmetric crotylsilation methodology is unsuccessful with aliphatic aldehydes, the bisphosphoramide has been applied to the synthesis of challenging stereo-defined quaternary centers. As shown in Scheme 2.6, trisubstituted allyl silane **2.11** undergoes efficient allylation in the presence of 10 mol% **2.12**, delivering the desired homoallylic alcohol **2.13** in 83% yield with excellent diastereo- and enantioselectivity.

Scheme 2.6 Synthesis of Stereo-Defined Quaternary Centers Through Asymmetric Allylsilation



The extension of asymmetric crotylsilation to include aliphatic aldehydes has been accomplished by Leighton and co-workers through use of a crotylsilane reagent containing a chiral diamine backbone (**2.14**).[10] This reagent reacts with aldehydes through a closed-transition state requiring complete control of olefin stereochemistry in order to obtain high levels of diastereoselectivity. While technically demanding, this process can effectively deliver the *syn* diastereomer (>20:1 dr) in high yields with excellent enantioselectivity (Scheme 2.7).

Scheme 2.7 Asymmetric Crotylsilation with Chiral Diamine Reagents

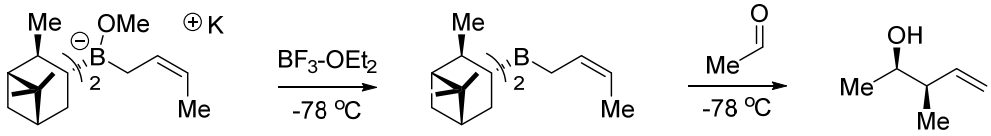


[10] Hackman, B. M.; Lombardi, P. J. Leighton, J. L. *Org. Lett.* **2004**, *6*, 4375.

2.2.2.2 Crotylboration

Allylboranes, in contrast to allylsilanes, contain an empty p-orbital which enables them to react almost exclusively as a Type I allylation reagent through coordination of a lone pair of electrons on the carbonyl oxygen with the boron atom. This coordination renders the allylboron more nucleophilic and the carbonyl more electrophilic and leads to an increase in reactivity. Unfortunately, the highly Lewis acidic nature of an allylborane reagent also enables coordination of the olefin of the reagent to the empty p-orbital on boron, promoting a borotropic rearrangement.[11] While inconsequential with allyl substitution, the *E/Z* geometry of crotyl reagents is eroded resulting in a less diastereoselective transformation. In 1986, Brown disclosed a solution to prevent the undesired rearrangement allowing for the first highly diastereo- and enantioselective allylation of crotylborane reagents.[12] This transformation uses chiral crotylborane reagent **2.16**, formed through hydroboration of commercially available (+)-α-pinene, and generates the desired product **2.18** in 75% yield with excellent stereocontrol (Scheme 2.8).

Scheme 2.8 Asymmetric Crotylboration with Isopinocampheylboranes

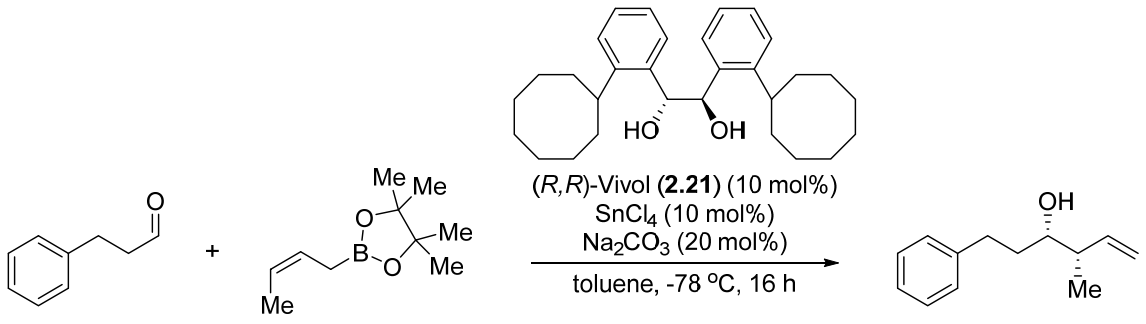


2.16 **2.17** **2.18**
75% yield
95% *ee*
>99:1 dr

[11] Brown, H. C.; Jadhav, P. K.; Bhat, K. S. *J. Am. Chem. Soc.* **1985**, *107*, 2564.
[12] (a) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 293. (b) Brown, H. C.; Bhat, K. S. *J. Am. Chem. Soc.* **1986**, *108*, 5919.

The asymmetric crotylboration of aldehydes is an effective strategy to construct *syn*-propionate motifs and this reaction has received tremendous attention since the seminal reports published by Brown and co-workers. Dennis Hall, one of the major contributors in this field, has developed a transformation that uses stable crotylboronic acid pinacol ester reagents and requires only a catalytic amount of the chirality source.[13] This reaction uses a Lewis acid-assisted Bronsted acid (LBA) bifunctional catalyst, developed by Yamamoto[14], to generate homoallylic alcohols in good yield with high diastereo- and enantioselectivity (Scheme 2.9). Notably, the reaction uses configurationally stable boronic esters as reagents. Thus, undesired borotropic rearrangements are not problematic under the reaction conditions.

Scheme 2.9 Vivol/Sn Catalyzed Asymmetric Crotylboration of Aldehydes



Another significant example of asymmetric crotylboration was reported by Aggarwal and co-workers in 2010.[15] Instead of inducing asymmetry through

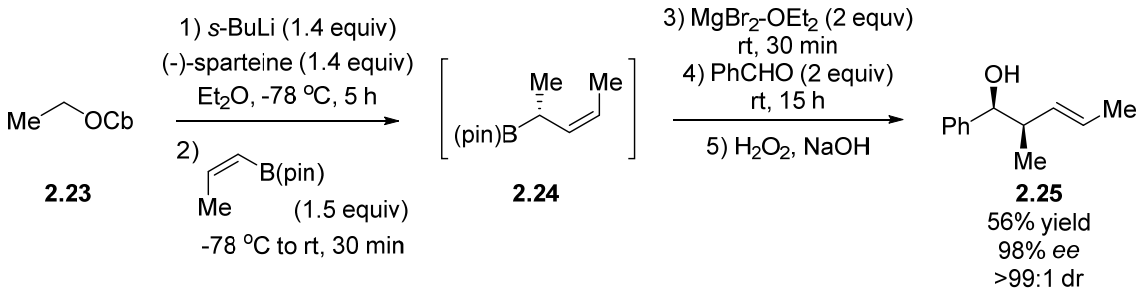
[13] (a) Rauniyar, V.; Zhai, H.; Hall, D. G. *J. Am. Chem. Soc.* **2008**, *130*, 8481. (b) Rauniyar, V.; Hall, D. G. *J. Org. Chem.* **2009**, *74*, 4236.

[14] (a) Ishihara, K.; Kaneeda, M.; Yamamoto, H. *J. Am. Chem. Soc.* **1994**, *116*, 11179. (b) Nakamura, S.; Kaneeda, M.; Ishihara, K.; Yamamoto, H. *J. Am. Chem. Soc.* **2000**, *122*, 8120. (c) Ishihara, K.; Nakashima, D.; Hiraiwa, Y.; Yamamoto, H. *J. Am. Chem. Soc.* **2003**, *125*, 24.

[15] Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 4025.

coordination of a Lewis base or Lewis acid, they utilize a strategy developed by Hoppe[16] to perform an enantiospecific lithiation of achiral carbamate **2.23**, which upon complexation with a vinyl boronate undergoes a 1,2-migration generating enantiopure α-chiral allyl boronate **2.24** (Scheme 2.10). Successive addition of an aldehyde results in an allylation reaction generating the desired product **2.25** in moderate yield with excellent diastereo- and enantioselectivity.

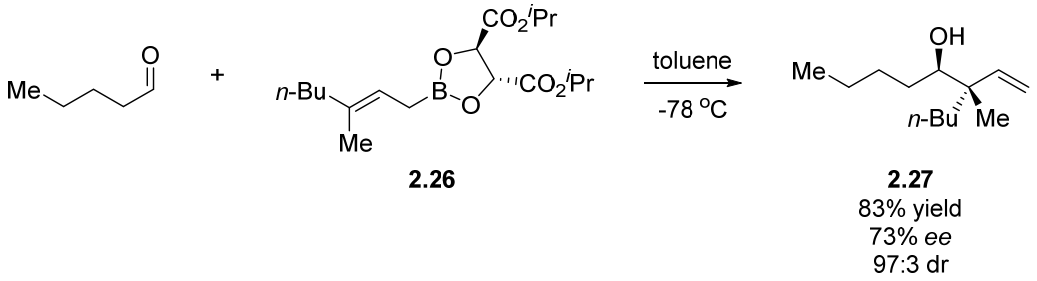
Scheme 2.10 Asymmetric Lithiation/Homologation/Crotylboration of Aldehydes



The formation of stereo-defined quaternary centers through asymmetric allylboration has also been investigated, but less extensively.[17] The first example was reported in 1996 and involved trisubstituted allylboronates containing a chiral tartrate-derived ester backbone (Scheme 2.11). These reagents underwent efficient addition to aliphatic and aryl aldehydes generating homoallylic alcohols bearing α-quaternary centers in good yields with high diastereoselectivity, but with only modest enantioinduction.

[16] (a) Hoppe, D. *Angew. Chem., Int. Ed.* **1984**, *23*, 932. (b) Hoppe, D.; Hense, T. *Angew. Chem., Int. Ed.* **1997**, *36*, 2282.
[17] Yamamoto, Y.; Hara, S.; Suzuki, A. *Synlett*, **1996**, 883.

Scheme 2.11 Synthesis of Stereo-Defined Quaternary Centers Through Asymmetric Allyboration



2.26

2.27
83% yield
73% *ee*
97:3 dr

2.2.3 Syn-Polypropionate Formation with Functionalized Olefins

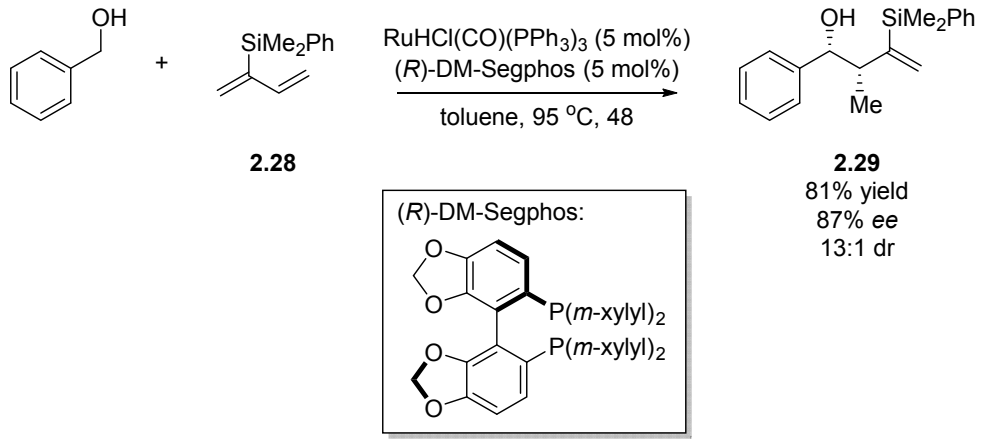
Although the methods discussed to this point effectively create a *syn*-polypropionate motif with high diastereo- and enantio-control, they all contain an unfunctionalized terminal alkene in the product. Further elaboration of this alkene in the context of natural product synthesis often requires multiple steps and functional group interconversions. In this regard, methods that install the desired *syn*-polypropionate motif concurrently with a functional group handle on the olefin are particularly attractive and have been the goal of several research projects.

Krische has addressed this problem through a ruthenium-catalyzed hydrohydroxyalkylation of functionalized butadienes and primary alcohols.[18] In this transformation, the ruthenium catalyst oxidizes the primary alcohol to the corresponding aldehyde, generating a ruthenium hydride, which then reacts with butadiene **2.28** generating an allyl-ruthenium complex. The large silyl group favors the formation of the *E*-olefin in this allyl-complex. Upon coordination of the aldehyde to ruthenium, allylation delivers the *syn*-diastereomer as the major product in good yield with high

[18] (a) Zbieg, J. R.; Fukuzumi, T.; Krische, M. J. *Adv. Synth. Catal.* **2010**, *352*, 2416. (b) Zbieg, J. R.; Moran, J.; Krische, M. J. *J. Am. Chem. Soc.* **2011**, *133*, 10582.

enantioselectivity (Scheme 2.12). This reaction generates a vinyl silane that can be further functionalized through cross-coupling, oxidation, or diastereoselective hydroboration.[19]

Scheme 2.12 *Syn*-Hydrohydroxyalkylation of 2-Silyl-Butadienes

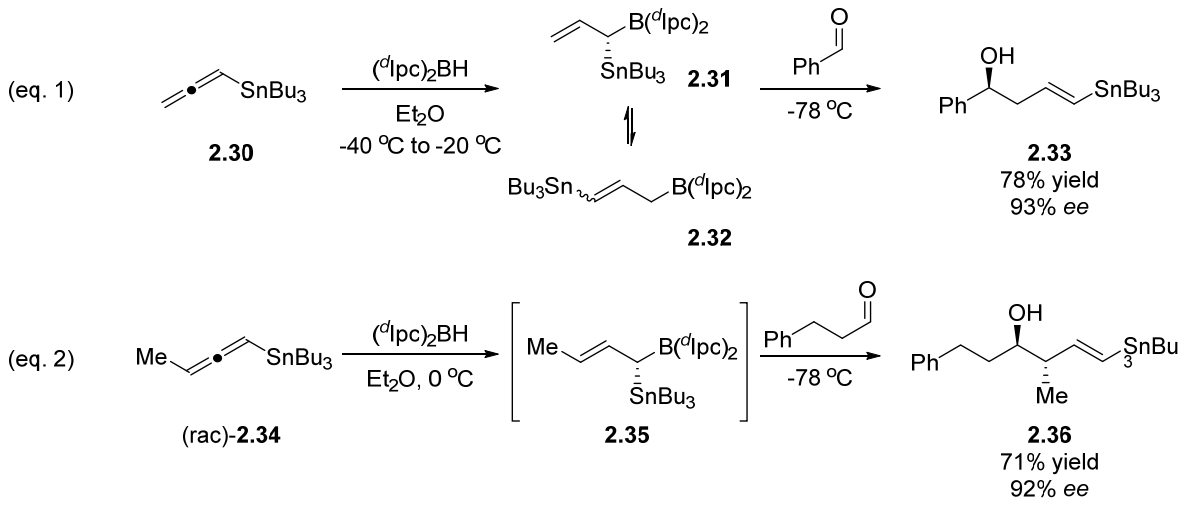


Roush has developed an alternative method to install a synthetic handle on the alkene. Asymmetric hydroboration of allenyl stannane **2.30** with diisopinocampheylborane generates an equilibrating mixture of **2.31** and **2.32** favoring **2.31** with the α-stereochemistry being controlled by the chiral borane reagent. Addition of an aldehyde generates the homoallylic alcohol **2.33** containing a vinyl stannane in good yield with excellent enantioselectivity (Scheme 2.13, eq 1).[20] Roush and co-workers also investigated the reaction of substituted allenylstannes to generate propionate motifs through this methodology (Scheme 2.13, eq 2).[21] Hydroboration of racemic stannane **2.34** was found to be enantioconvergent, generating a single allylborane **2.35**. Subsequent allylation generated the *anti*-diastereomer **2.36** as the major product in high

[19] (a) Anderson, J. C.; Munday, R. H. *J. Org. Chem.* **2004**, *69*, 8971. (b) Smitrovich, J. H.; Woerpel, K. A. *J. Org. Chem.* **1996**, *61*, 6044. (c) Coleman, R. S.; Gurrala, S. R. *Org. Lett.* **2005**, *7*, 1849.
[20] Chen, M.; Ess, D. H.; Roush, W. R. *J. Am. Chem. Soc.* **2010**, *132*, 7881.
[21] Chen, M.; Roush, W. R. *J. Am. Chem. Soc.* **2011**, *133*, 5744.

yield and enantioselectivity. While this transformation effectively establishes a useful synthetic handle, it requires stoichiometric amounts of a chirality source, uses toxic tin reagents, and is only effective at generating the *anti*-diastereomer.

Scheme 2.13 Enantioselective Synthesis of (*E*)-δ-Stannyl Homoallylic Alcohols



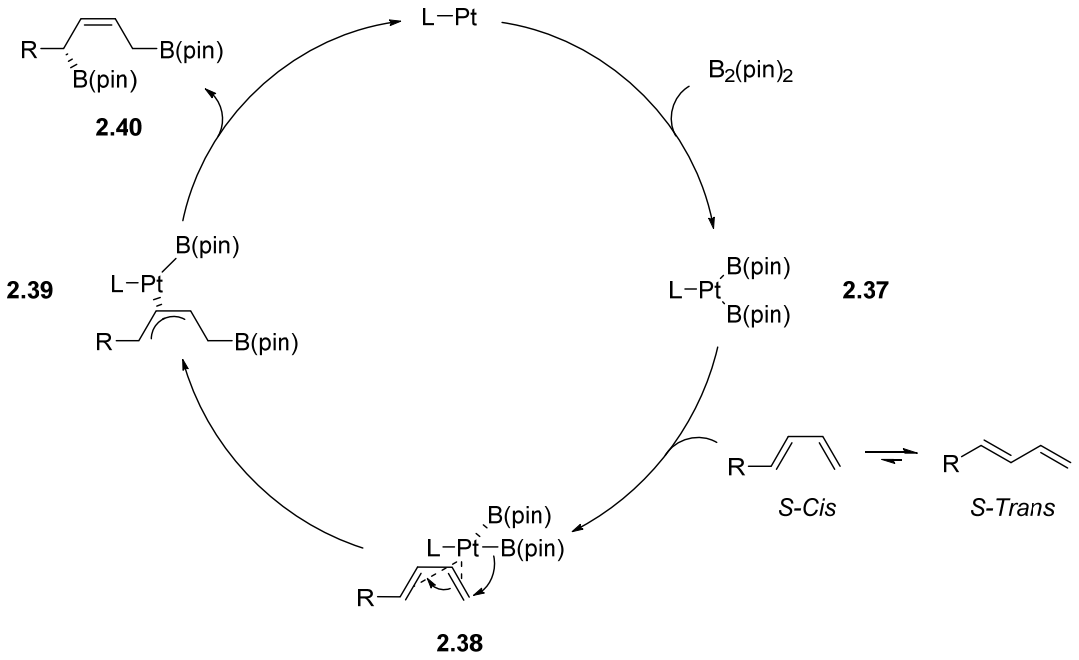
2.3 Development and Substrate Scope for Enantioselective Platinum-Catalyzed 1,2-Diboration of Cis-1,3-Dienes and 4,4-Disubstituted Dienes.

The synthesis of *syn*-polyprionate motifs with high control of diastereo- and enantioselectivity has received extensive attention in the chemistry community over the past several decades. Despite all of the advances in this field, novel catalytic methods that effectively control stereochemistry and install a handle for additional synthetic functionalization would have an enormous impact in polyketide synthesis. We envisioned a possible solution could be achieved through asymmetric platinum-catalyzed diboration.

As discussed in chapter 1, section 1.3, *trans*-1,3-dienes undergo platinum-catalyzed diboration generating a 1,4-bis(boronate)ester containing a *Z*-olefin. The olefin

stereochemistry in the product is consistent with coordination between platinum and the *S-cis* conformer of the diene. This delivers a π-allyl platinum complex **2.39** upon migratory insertion (Scheme 2.14). Reductive elimination from complex **2.39** generates the observed product containing a *Z*-olefin (**2.40**).

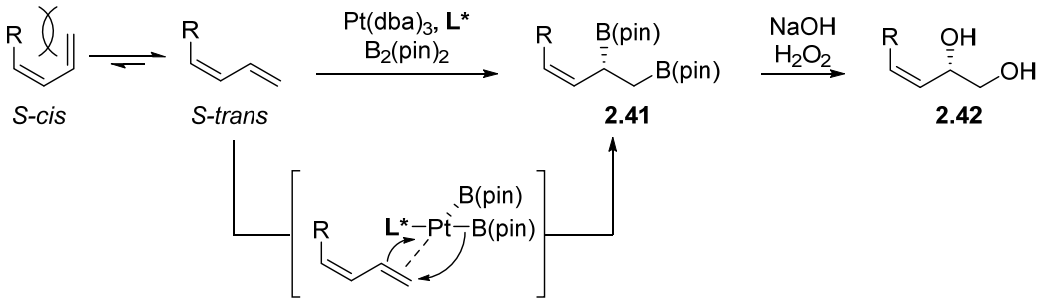
Scheme 2.14 Proposed Mechanism for Pt-Catalyzed 1,4-Diboration of *Trans*-1,3-Dienes



The *S-cis* conformation, while accessible for *trans*-1,3-dienes, is higher in energy relative to the *S-trans* conformation due to an increased $A^{(1,3)}$ interaction. This penalizing interaction is further amplified when *cis*-substituents are introduced. We hypothesized that the *S-cis* conformation of *cis*-dienes may be energetically forbidden under the diboration conditions, forcing the diene to interact with platinum through the *S-trans* conformation. If this occurred, *cis*-1,3-dienes might react similarly to terminal alkenes and undergo a 1,2-diboration of the α-olefin. If the 1,2-diboration mechanism is operative, the stereochemistry of the internal olefin should be conserved, resulting in formation of an α-chiral *Z*-allylboronate **2.41** (Scheme 2.15). Oxidation of this

intermediate would generate enantioenriched *Z*-allylic diols, effectively achieving a chemoselective oxidation of a single olefin in a conjugated diene.

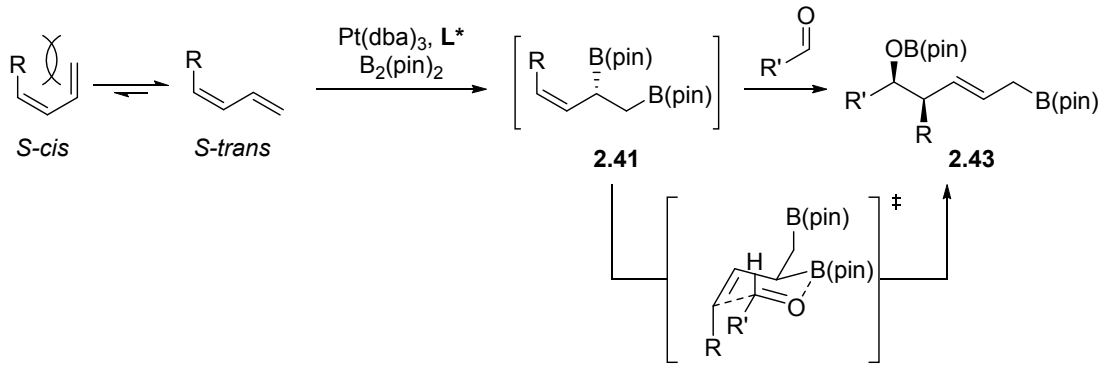
Scheme 2.15 Proposed Reactivity of *Cis*-1,3-Dienes in Pt-Catalyzed Diboration



Although enantioenriched *Z*-allylic diols are important compounds themselves, utilizing the intermediate α-chiral *Z*-allylboronate in allylation reactions with aldehydes would be more valuable. Following the studies reported by Hoffmann[22], the intermediate bis(boronate)ester **2.41** should react with aldehydes through a six-membered chair-transition state as shown in Scheme 2.16 where the R′ of the aldehyde and the terminal $CH_2B(pin)$ adopt the equatorial positions to avoid penalizing *syn*-pentane interactions with the vinylic R group. This transformation would generate the *syn*-diastereomer selectively. Overall, this process represents an asymmetric catalytic allylation that delivers a product containing a functionalized alkene, effectively solving two major problems associated with current methods used for polypropionate synthesis.

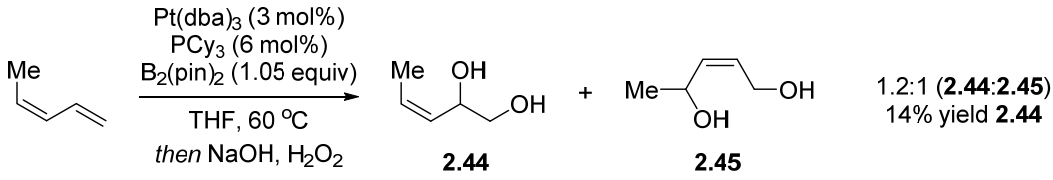
[22] (a) Hoffmann, R. F. *Pure Appl. Chem.* **1988**, *60*, 123. (b) Hoffmann, R. W.; Niel, G.; Schlapbach, A. *Pure Appl. Chem.* **1990**, *62*, 1993. (c) Hoffmann, R. W.; Zeiss, H.-J. *J. Org. Chem.* **1981**, *46*, 1309. (d) Hoffmann, R. W.; Zeiss, H.-J. *Angew. Chem., Int. Ed.* **1979**, *18*, 306.

Scheme 2.16 Application of α-chiral *Z*-allylboronate in Allylation of Aldehydes



Before investigating selectivity in allylation, we first had to determine the outcome of reactions of *cis*-1,3-dienes in platinum catalyzed diboration. To test the validity of our hypothesis, commercially available *cis*-1,3-pentadiene was subjected to standard diboration conditions. This diene was chosen as a test substrate for two reasons: 1) the allylation product formed following the proposed reaction pathway would contain a *syn*-methyl substituent, and would have the most impact in polyketide synthesis; 2) methyl substitution generates the least penalizing $A^{(1,3)}$ interaction in the *S-cis* conformation compared to bulkier substituted *cis*-dienes and therefore should be the least regio- and enantioselective substrate examined. Excitingly, when PCy_3 was used as the ligand in the diboration, the desired 1,2-diol **2.44** was formed as the major regioisomer in 14% yield (Scheme 2.17). Although the regioselectivity of the diboration was lower than anticipated, we were encouraged that introduction of the *cis*-substituent was successful in controlling the reaction pathway to favor 1,2-diboration (1,2:1,4 = 1.2:1). As discussed in chapter 1, the 1,2:1,4-product ratio in trans-1,3-diene diboration was ligand dependent, suggesting possible improvement in regioselectivity with chiral ligands.

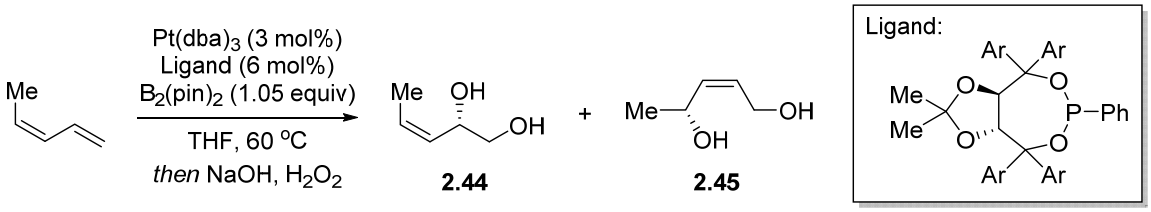
Scheme 2.17 Platinum-Catalyzed 1,2-Diboration of *Cis*-1,3-Pentadiene



Following the success in terminal alkene diboration, TADDOL-derived phosphonite ligands were examined in the 1,2-diboration of *cis*-1,3-pentadiene (Table 2.1). A direct correlation between the steric encumbrance of the aryl group and selectivity of the diboration was observed. In addition to affecting enantioselectivity, *meta*-substitution of the aryl ring proved crucial in generating an efficient transformation. While the phenyl- and xylyl-derived ligands generated 1,2-diols with comparable enantioselectivity, only trace amount of desired product **2.44** was formed with ligand (*R,R*)-**2.46** (entry 1 and 2). Increasing the steric encumbrance with the diethyl substituted ligand (*R,R*)-**2.49** successfully increased enantioselectivity to 87% (entry 4). Unfortunately, a further increase in substituent size to *iso*-propyl proved detrimental and led to a decrease in observed enantioselectivity (entry 7). It was rationalized that a ligand containing *iso*-butyl substitution (υ(R) = 0.68), which is sterically in between ethyl (υ(R) = 0.56) and *iso*-propyl (υ(R) = 0.76), might further increase the enantioselectivity of the diboration.[23] To test this hypothesis, (*R,R*)-**2.50** was synthesized and examined in the diboration of *cis*-1,3-pentadiene. Excitingly, the *iso*-butyl derived phosphonite delivered the desired 1,2-diol in 69% yield and 90% enantiomeric excess (entry 6).

[23] (a) υ(R) = steric-effect substituent constant determined from van der Waals radii: Charton, M. *J. Am. Chem. Soc.* **1975**, *97*, 1552. (b) Hansch, C.; Leo, A. *Substituent Constants for Correlation Analysis in Chemistry and Biology*, John Wiley & Songs, New York, **1979**

Table 2.1 Ligand Survey for Enantioselective Pt-Catalyzed 1,2-Diboration of *Cis*-1,3-Pentadiene



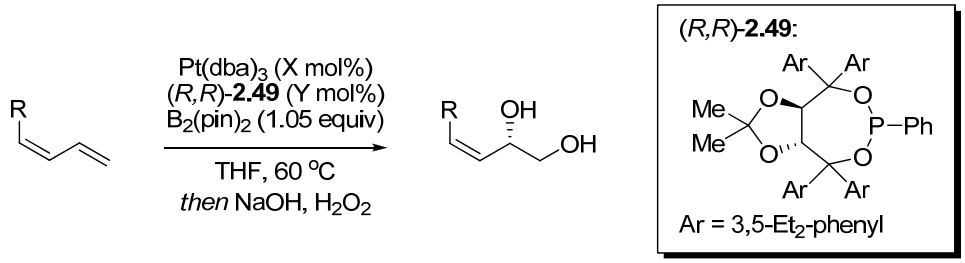
entry	ligand	Ar	1,2:1,4[a]	yield 1,2 (%)[b]	*ee* 1,2 (%)[c]
1	(*R,R*)-**2.46**	Ph	ND	<10	80
2	(*R,R*)-**2.47**	3,5-Me_2Ph	5.3:1	47	80
3	(*R,R*)-**2.48**	3,5-MeO_2Ph	4:1	19	80
4	(*R,R*)-**2.49**	3,5-Et_2Ph	4:1	52	87
5[d]	(*R,R*)-**2.49**	3,5-Et_2Ph	3:1	47	86
6	(*R,R*)-**2.50**	3,5-$^{i}Bu_2$Ph	5:1	69	90
7	(*R,R*)-**2.51**	3,5-$^{i}Pr_2$Ph	3.8:1	22	84
8	(*R,R*)-**2.52**	3,5-Ph_2Ph	2:1	28	80
9	(*R,R*)-**2.53**	3,5-$^{t}Bu_2$Ph	1:2.6	12	75

[a] Ratio determined by ^{1}H NMR of crude reaction mixture [b] Percent yield of purified material. Value is average of two experiments. [c] Determined by GC employing a chiral stationary phase. [d] Diboration run in toluene

Through optimization of ligand structure, the selectivity of the 1,2-diboration of *cis*-1,3-pentadiene was eventually improved and now it can be performed with excellent asymmetric induction. Unfortunately, the optimal ligand (*R,R*)-**2.50** is more challenging to prepare than other derivatives and requires several additional steps. In order to avoid superfluous use of ligand, optimization of platinum:ligand ratio and catalyst loading was performed (Table 2.2). Both the nonyl- and cyclohexyl-substituted *cis*-dienes were examined in diboration with (*R,R*)-**2.49**. When the ligand to metal ratio was decreased from 2:1 to 1.2:1, the diboration of the nonyl-substituted diene exhibited a decrease in both regioselectivity and isolated yield (entry 1 and 2). Under the same conditions, the cyclohexyl-substituted diene displayed a similar decrease in regioselectivity and isolated

yield, but also suffered a slight decrease in enantioselectivity (entry 3 and 4). The diboration of *cis*-1,3-pentadiene was then explored with a decreased catalyst loading while maintaining a ligand to metal ratio of 2:1 (entry 5). Diboration under these conditions proved ineffective, resulting in a dramatic decrease in isolated yield as well as a measurable decrease in enantioselectivity. Collectively, the data suggests a ligand to metal ratio of 2:1 with 3 mol% platinum is required to maintain reactivity and selectivity in the 1,2-diboration of *cis*-1,3-dienes.

Table 2.2 Optimization of Metal:Ligand Ratio in Pt-Catalyzed Diboration of *Cis*-1,3-Pentadiene



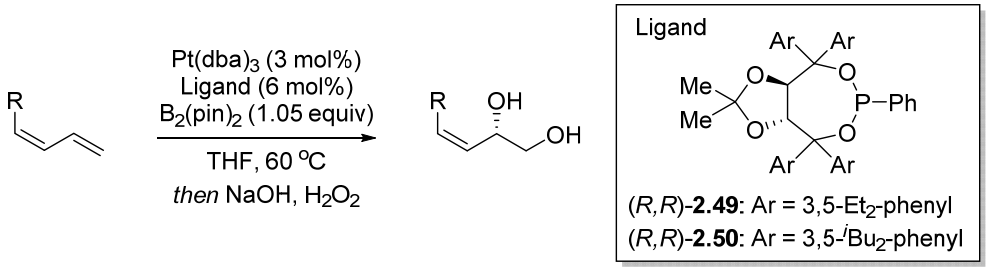
entry	R	$Pt(dba)_3$ (X mol%)	(*R,R*)-2.49 (Y mol%)	1,2:1,4[a]	yield 1,2 (%)[b]	*ee* 1,2 (%)[c]
1	nonyl	3 mol%	6 mol%	6:1	85	90
2	nonyl	3 mol%	3.6 mol%	4:1	74	90
3	Cy	3 mol%	6 mol%	4:1	77	94
4	Cy	3 mol%	3.6 mol%	2.3:1	63	92
5	Me	0.6 mol%	1.2 mol%	ND	15	85

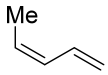
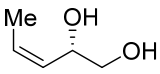
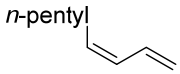
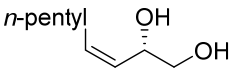
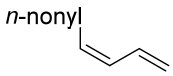
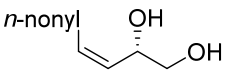
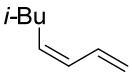
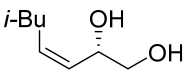
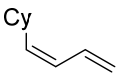
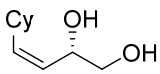
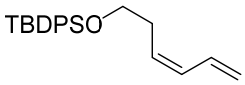
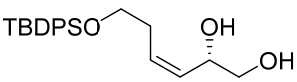
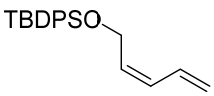
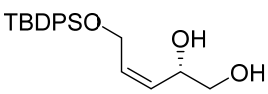
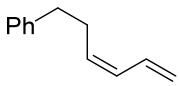
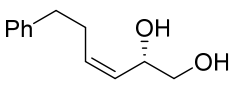
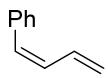
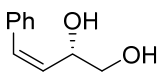
[a] Ratio determined by ^1H NMR of crude reaction mixture. [b] Percent yield of purified material. Value is average of two experiments. [c] Determined by GC employing a chiral stationary phase.

With the optimal catalyst ratio and ligand structure established, the substrate scope for platinum-catalyzed 1,2-diboration of *cis*-1,3-dienes was explored (Table 2.3). Importantly, while ligand (*R,R*)-**2.50** was required to obtain high enantioselectivity in the diboration of *cis*-1,3-pentadiene (entry 1 vs 2), ligand (*R,R*)-**2.49** proved sufficient for

other dienes examined. Enantioselectivity in the 1,2-diboration of *cis*-dienes increased with longer *n*-alkyl substitution of the substrate from methyl to nonyl while maintaining a highly regioselective transformation (entries 1, 3, and 4). The diboration also tolerated more sterically hindered *cis*-dienes containing α-substitution, delivering the desired 1,2-diol with excellent enantioselectivity and up to 14:1 regioselectivity (entries 5 and 6). Interestingly, while silyl-protected homoallylic alcohols were found to be suitable substrates in *cis*-diene diboration (entry 7), silyl-protected allylic alcohols failed to participate and resulted in substrate decomposition. *Cis*-diene substrates containing distant aromatic functionality were also tolerated and predominately underwent 1,2-diboration with high enantioselectivity (entry 9); however, when the aromatic ring was brought into conjugation the enantioselectivity was greatly reduced (entry 10).

Table 2.3 Enantioselective Pt-Catalyzed 1,2-Diboration of *Cis*-1,3-Diene Substrate Scope



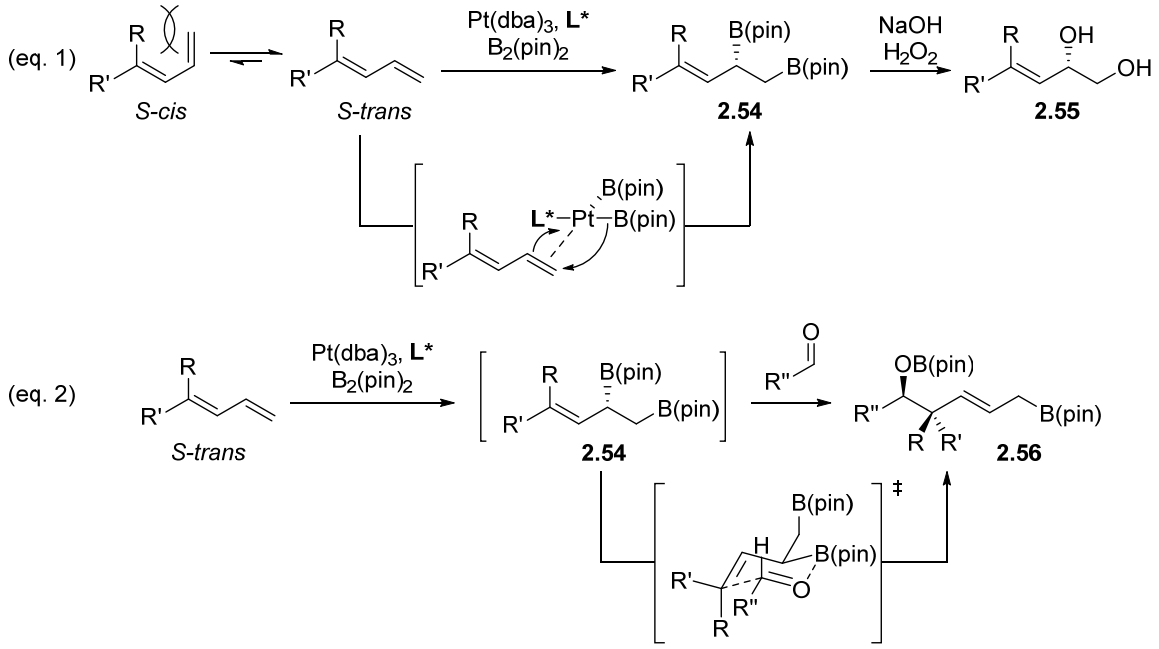
entry	substrate	product	1,2:1,4	yield 1,2 (%)[a]	*ee* 1,2 (%)[b]
1			4:1	52	87
2[c]			5:1	69	90
3			4:1	70	90
4			6:1	85	92
5			14:1	94	92
6			4:1	77	94
7			3:1	56	90
8			NA	0	NA
9			4:1	62	90
10			3:1	55	62

[a] Percent yield of purified material. Value is average of two experiments. [b] Determined by GC or SFC analysis employing a chiral stationary phase. [c] Diboration performed with (*R,R*)-**2.50**

Following the success of enantioselective 1,2-diboration of *cis*-1,3-dienes, the diboration of 4,4-disubstituted dienes was investigated. Similar to *cis*-1,3-dienes, 4,4-disubstituted dienes exhibit an increased $A^{(1,3)}$ interaction in the *S-cis* conformation which should promote a 1,2-diboration pathway from the more stable *S-trans* conformation

(Scheme 2.18, eq 1). 1,2-Diboration of a 4,4-disubstituted diene would generate an α-chiral allylboronate **2.54** containing a trisubstituted olefin which, upon addition to aldehydes, would produce an enantio-enriched homoallylic alcohols bearing an α-quaternary center (Scheme 2.18, eq 2).

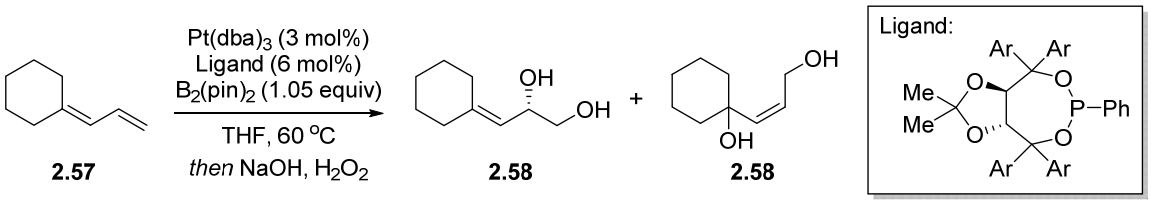
Scheme 2.18 Platinum-Catalyzed 1,2-Diboration of 4,4-Disubstituted Dienes



To determine if this transformation is possible, 4,4-disubstited diene **2.57** was subjected to standard diboration conditions with PCy_3 (Table 2.4, entry 1). Excitingly, the desired 1,2-diol **2.58** was obtained as a single regioisomer in 64% yield. A survey of TADDOL-derived phosphonite ligands was then performed. Similar to terminal alkenes and *cis*-1,3-dienes, substituents at the *meta* positions on the aryl ring had a direct influence on the enantioselectivity of the transformation with (*R,R*)-**2.51** and (*R,R*)-**2.53** effectively promoting similar levels of asymmetric induction (entry 4 and 6). Ultimately ligand (*R,R*)-**2.51** was chosen due to the increased reactivity and higher isolated yield of

reaction product. Decreasing the ligand to metal ratio from 2:1 to 1.2:1 did not affect the regio- or enantioselectivity in the diboration (entry 7).

Table 2.4 Ligand Optimization for Pt-Catalyzed 1,2-Diboration of 4,4-Disubstituted Dienes



2.57 **2.58** **2.58**

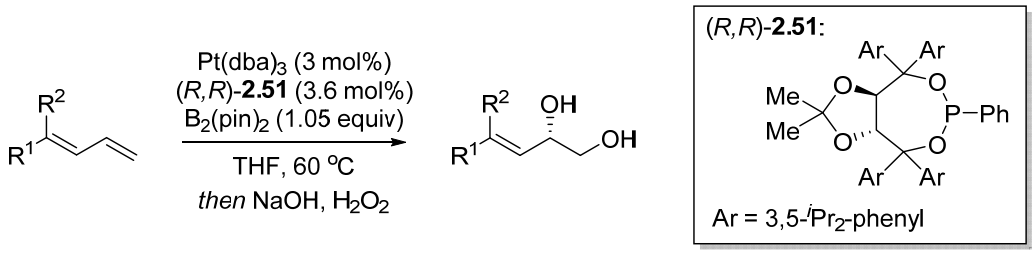
entry	ligand	Ar	conv (%)[a]	1,2:1,4[a]	yield 1,2 (%)[b]	*ee* 1,2 (%)[c]
1	PCy_3	-	81	>20:1	64	-
2	(*R,R*)-**2.47**	3,5-Me_2Ph	78	>20:1	75	80
3	(*R,R*)-**2.49**	3,5-Et_2Ph	93	>20:1	78	90
4	(*R,R*)-**2.51**	3,5-$^i Pr_2$Ph	96	>20:1	80	94
5	(*R,R*)-**2.52**	3,5-Ph_2Ph	90	>20:1	85	86
6	(*R,R*)-**2.53**	3,5-$^t Bu_2$Ph	75	>20:1	70	94
7[d]	(*R,R*)-**2.51**	3,5-$^i Pr_2$Ph	95	>20:1	78	94

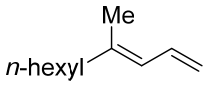
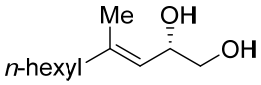
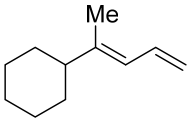
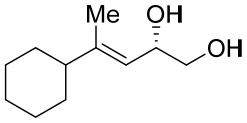
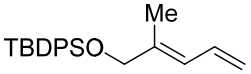
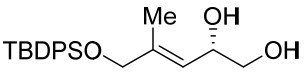
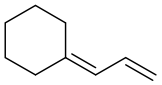
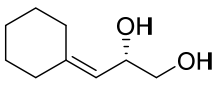
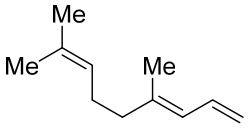
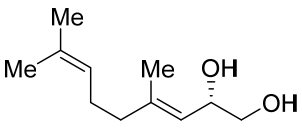
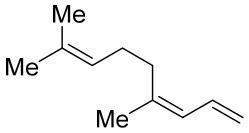
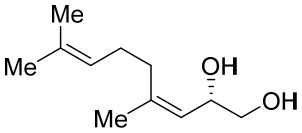
[a] Determined by ^{1}H NMR of crude reaction mixture [b] Percent yield of purified material. [c] Determined by GC employing a chiral stationary phase. [d] Diboration with 3 mol% $Pt(dba)_3$/3.6 mol% (*R,R*)-**2.51**.

With the optimized conditions in hand, the substrate scope of platinum-catalyzed 1,2-diboration of 4,4-disubstituted dienes was investigated (Table 2.5). In addition to exocyclic dienes, acyclic 4,4-disubstituted dienes with linear or branching alkyl substitution were well tolerated, and generated the desired 1,2-diols in good yield with excellent enantioselectivity (entry 1 and 2). Unlike *cis*-1,3-dienes, 4,4-disubstituted dienes containing allylic oxygenation underwent clean 1,2-diboration and did not produce byproducts arising from competing π-allyl chemistry detected (entry 3). Importantly, the 1,2-diboration was not affected by the stereochemistry of the internal olefin, with opposite stereoisomers generating the corresponding products with nearly identical yields and selectivities (entry 5 and 6). In general, 4,4-disubstituted dienes were superior

substrates in enantioselective 1,2-diboration compared to *cis*-1,3-dienes, reacting exclusively to generate the 1,2-product with greater asymmetric induction.

Table 2.5 Enantioselective Pt-Catalyzed 1,2-Diboration of 4,4-Disubstituted Diene Substrate Scope



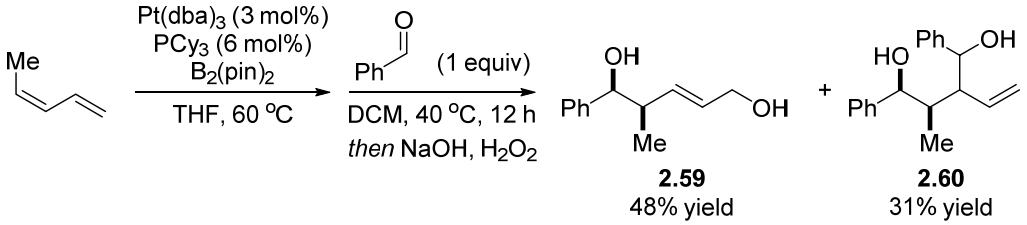
entry	substrate	product	yield (%)[a]	ee (%)[b]
1			67	94
2			84	96
3			87	96
4			78	94
5			82	96
6			86	96

[a] Percent yield of purified material. Value is average of two experiments. [b] Determined by GC or SFC analysis employing a chiral stationary phase.

2.4 Development and Scope of a Tandem 1,2-Diboration/Allylation Sequence for *Cis*-1,3-Dienes and 4,4-Disubstituted Dienes

With an efficient and highly enantioselective 1,2-diboration of *cis*-1,3-dienes and 4,4-disubstituted dienes established, we began to explore the application of the α-chiral bis(boronate)ester intermediates in allylation to determine if a stereoinductive addition could be achieved. Initial studies on development of a one-pot diboration/allylation sequence were performed with *cis*-1,3-pentadiene, which would generate a less sterically hindered transition state (Scheme 2.16) compared to bulkier *cis*-dienes or 4,4-disubstituted dienes. Following diboration of the substrate in THF, the solvent was removed and benzaldehyde (1 equiv) and CH_2Cl_2 were added. The reaction mixture was heated to 40 ºC for 12 hours and then subjected to oxidation. Excitingly, the desired allylation product **2.59** was isolated in 48% yield as a single diastereomer (Scheme 2.19). Further analysis of the crude reaction mixture uncovered the bis-allylation product **2.60** which was formed in 31% yield.

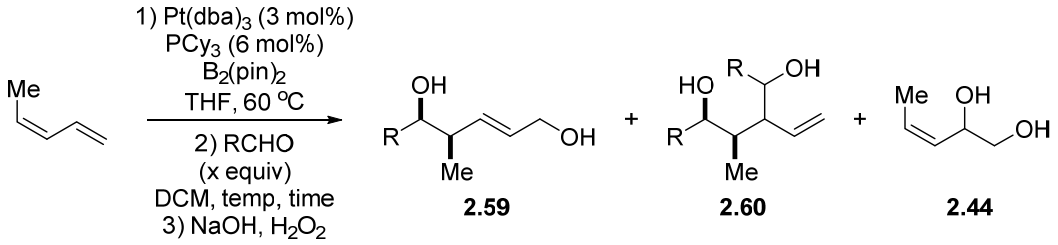
Scheme 2.19 Initial Result for Tandem Diboration/Allylation of *Cis*-1,3-Pentadiene



In order to improve the isolated yield of the desired product **2.59**, the reaction conditions were optimized to suppress formation of the bis-allylation byproduct (Table 2.6). Performing the allylation at room temperature with simultaneous dilution of the reaction proved ineffective and led to an increase in byproduct formation (entry 2). Further decrease in reaction temperature to 4 ºC successfully depressed byproduct

formation but, unsurprisingly, also suppressed the initial allylation, resulting in a lowered isolated yield (entry 3). Ultimately, formation of the bis-allylation byproduct with benzaldehyde could be avoided through addition of less than one equivalent of aldehyde (entry 4 and 5). Allylation of less reactive aldehydes, such as isobutyraldehdye, occurred with less bis-allylation product when run at room temperature, but furnished less of the initial allylation reaction (entry 6). Unfortunately, heating the reaction mixture to 40 ºC resulted in byproduct formation, even when less reactive aldehydes were used (entry 7).

Table 2.6 Optimization of Tandem Diboration/Allylation Conditions for *Cis*-1,3-Pentadiene



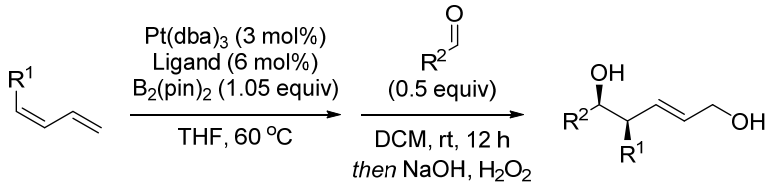
entry	R	(x equiv)	conc	temp (ºC)	time	2.59 y (%)[a]	2.60 y (%)[a]	2.44 y (%)
1	Ph	1.0	0.5 M	40	8 h	48	31	7
2	Ph	1.0	0.1 M	23	40 h	40	42	10
3	Ph	1.0	0.1 M	4	24 h	37 (46)	0	39
4	Ph	0.5	0.25 M	23	12 h	68	0	ND
5	Ph	0.3	0.1 M	23	12 h	63 (79)	0	43
6	*i*-Pr	1.0	0.1 M	23	12 h	10	0	54
7	*i*-Pr	1.0	0.1	40	24 h	48	12	6

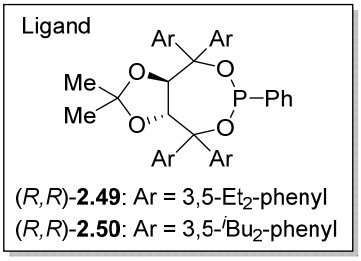
a) Isolated yield based on aldehyde. Value in paratheses is the % conversion in allylation based on aldehyde.

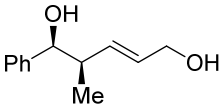
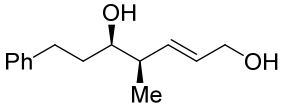
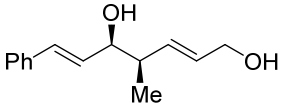
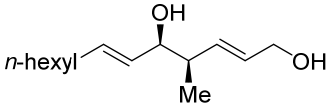
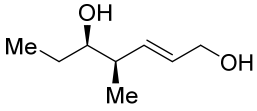
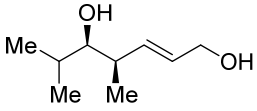
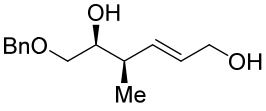
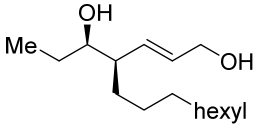
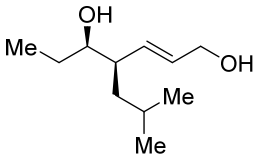
With the optimized conditions for allylation established, the scope of the tandem sequence employing *cis*-1,3-dienes was explored (Table 2.7). By controlling the stoichiometry of the reaction, the mono-allylation product was obtained in synthetically useful yields with near perfect chirality transfer for a variety of aldehydes. The allylation

tolerated α,β-unsaturation (entries 3 and 4), linear or α-branched alkyl substitution (entries 2, 5 and 6), and even α-oxygenation (entry 7) to generate the 1,5-diols containing the *syn*-polypropionate motif as a single diastereomer. In addition to *cis*-1,3-pentadiene, other *cis*-dienes exhibited similar reactivity in the tandem diboration/allylation sequence, effectively delivering a variety of complex structural motifs from simple hydrocarbons in a single-flask operation (entry 8 and 9).

Table 2.7 Enantioselective 1,2-Diboration of Cis-1,3-Dienes/Allylation Substrate Scope



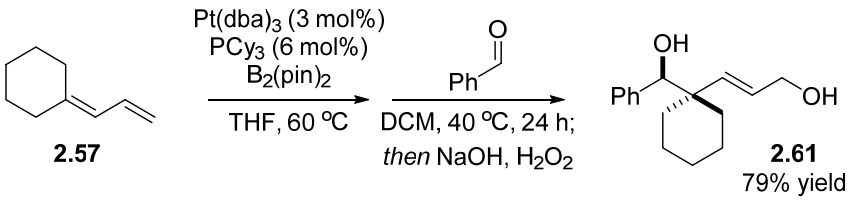


entry	product	yield (%)[a]	*ee* (%)[b]	es[c]
1		71	88	98
2		66	88	98
3		64	90	>99
4		66	92	>99
5		72	88	98
6		62	86	96
7		72	88	98
8[d]		90	94	>99
9[d]		68	92	>99

[a] Percent yield of purified material. Value is average of two experiments. [b] Determined by GC or SFC analysis employing a chiral stationary phase. [c] Enantiospecificity (es) calculated as follows: (%*ee* allylation product/ %ee diboration product)*100. [d] Diboration performed with (*R,R*)-**2.49**.

Extending the tandem diboration/allylation sequence to include 4,4-disubstituted dienes is particularly attractive due to the possibility of generating a stereo-defined all-carbon quaternary center. Although the intermediate trisubstituted allylboronate is more hindered, the efficiency in allylation of *cis*-dienes with hindered aldehydes was encouraging. Initial investigation into allylation was performed with exocyclic diene **2.57**, eliminating the concern of diastereoselectivity in the allylation. Following diboration in THF, the solvent was removed and benzaldehyde (1 equiv) and CH_2Cl_2 were added and the reaction was heated to 40 ºC for 24 hours. Upon oxidation, the desired 1,5-diol **2.61** was obtained in 79% yield and was the only allylation product detected (Scheme 2.20). Interestingly, the steric encumbrance of the newly formed quaternary center appeared to effectively halt the second allylation resulting in a selective transformation.

Scheme 2.20 Initial Result for Tandem Diboration/Allylation of 4,4-Disubstituted Dienes

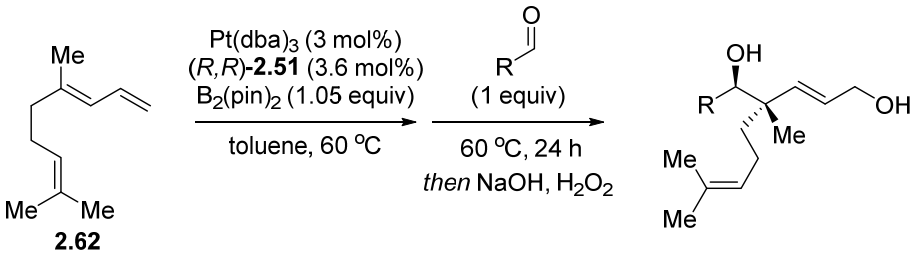


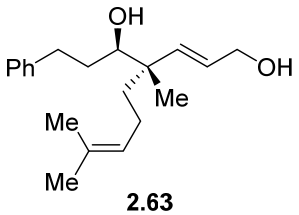
2.57

2.61
79% yield

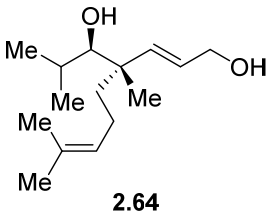
The tandem diboration/allylation sequence was also investigated with unsymmetrical 4,4-disubstiuted dienes to determine if the allylation was diastereoselective. As shown in Table 2.8, the geranial derived diene **2.62** displayed excellent reactivity in the tandem diboration/allylation reaction sequence with alkyl, aryl and α,β-unsaturated aldehydes. In all cases examined, the allylation proceeded with near perfect chirality transfer generating the desired 1,5-diols in high yield with excellent diastereoselectivity.

Table 2.8 Enantioselective 1,2-Diboration of 4,4-Disubstituted Dienes/Allylation Substrate Scope

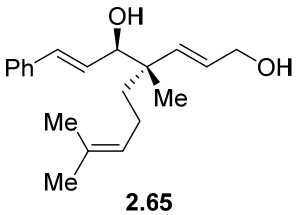




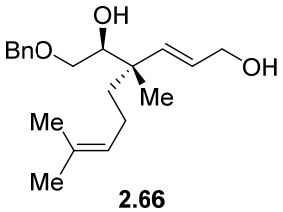
2.63
72% yield
>20:1 dr
94% *ee*



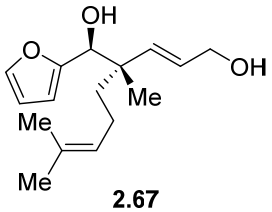
2.64
58% yield
>20:1 dr
94% *ee*



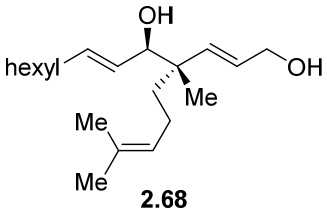
2.65
87% yield
>20:1 dr
96% *ee*



2.66
74% yield
>20:1 dr
94% *ee*



2.67
80% yield
>20:1 dr
92% *ee*

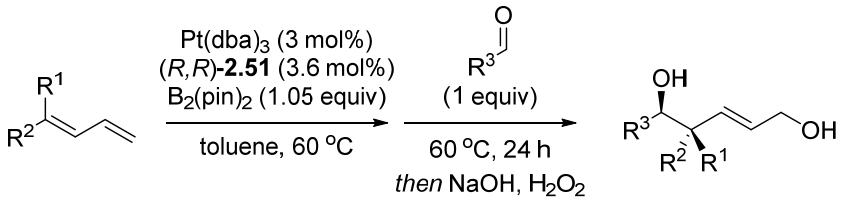


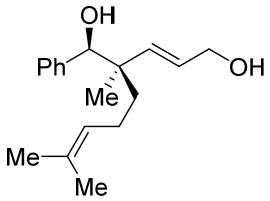
2.68
75% yield
>20:1 dr
94% *ee*

Yield is of isolated product and is the average of two experiments. Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture. Enantioselectivity was determined by HPLC or SFC analysis employing a chiral stationary phase.

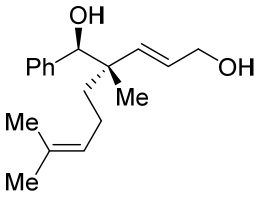
The high diastereoselectivity obtained in the allylation products suggests a closed transition state pathway is still operative even with the sterically hindered allylboronate reagents derived from 4,4-disubstituted dienes. This predictable transition state should also allow formation of either diastereomer through controlling the geometry of the internal olefin in the diene. As demonstrated in Table 2.9, through judicious choice of diene substrate either diastereomer can be obtained selectively while maintaining high control of chirality transfer.

Table 2.9 Diastereomeric Control Through Diene Geometry

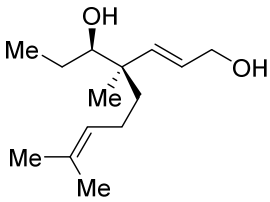




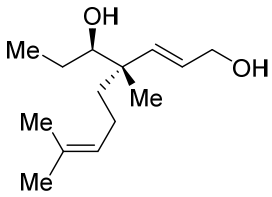
2.69
(R^1= prenyl, R^2= Me)
85% yield
9:1 dr
92% *ee*



2.70
(R^1= Me, R^2= prenyl)
87% yield
>20:1 dr
94% *ee*



2.71
(R^1= prenyl, R^2= Me)
67% yield
>20:1 dr
92% *ee*



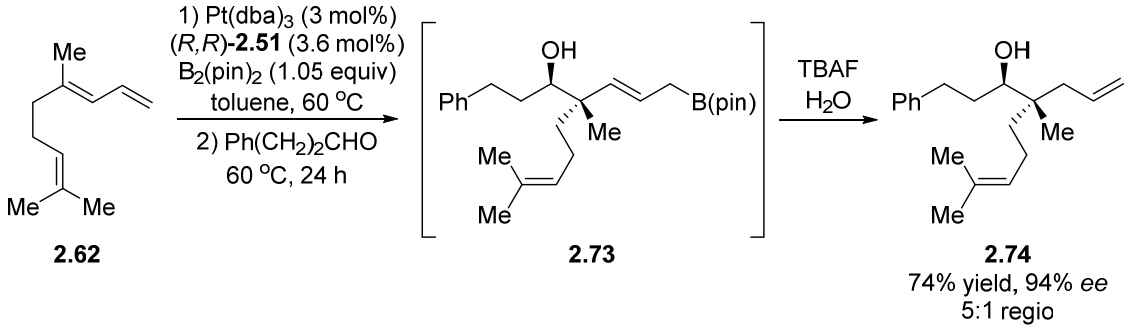
2.72
(R^1= Me, R^2= prenyl)
67% yield
>20:1 dr
90% *ee*

Yield is of isolated product and is the average of two experiments. Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture. Enantioselectivity was determined by HPLC or SFC analysis employing a chiral stationary phase.

2.5 Utility of Enantioselective Platinum Catalyzed 1,2-Diboration/Allylation Products

As discussed in section 2.3, an attractive feature of the enantioselective 1,2-diboration/allylation reaction is the formation of the versatile allylboronate. This functional group can undergo cross-coupling reactions with aryl[24] and allyl[25] electrophiles and it can participate in numerous other reactions including protodeboronation.[26] To demonstrate the synthetic utility of this functional group, the crude allylation product **2.73** was subjected to protodeboronation conditions developed by Aggarwal. Under these conditions, an S_E2' protodeboronation pathway is observed generating the terminal alkene **2.74** as the major regioisomer in 74% yield (Scheme 2.21).

Scheme 2.21 Tandem 1,2-Diboration/Allylation/Protodeboronation Reaction



The allylboronate formed in the product can also be utilized in reactions that manipulate the carbon-boron bond directly, such as Matteson homologation. Addition of $LiCH_2Cl$ to the crude allylation product **2.75**, followed by oxidation, generates the 1,6-diol **2.76** in 83% yield over four steps; the diastero- and enantioselectivity is unaffected.

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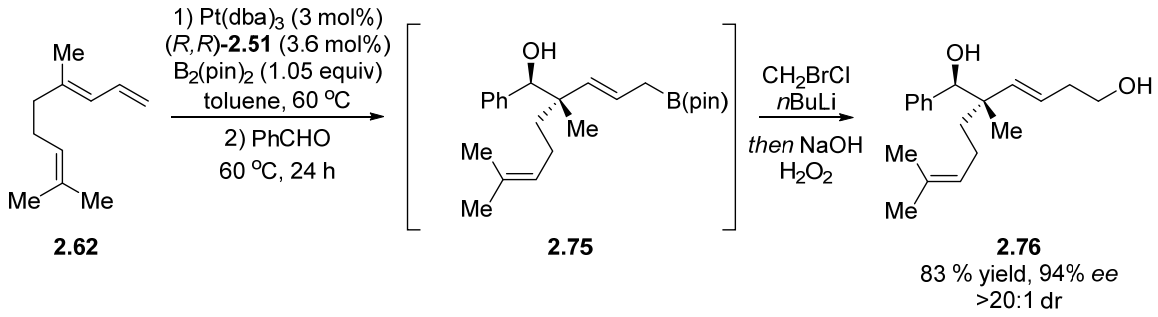
[24] (a) Yamamoto, Y.; Takada, S.; Miyaura, N. *Chem. Lett.* **2006**, *35*, 704. (b) Farmer, J. L.; Hunter, H. N. Organ M. G. *J. Am. Chem. Soc.* **2012**, *134*, 17470

[25] (a) Zhang, P.; Brozek, L. A.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 10686. (b) Zhang, P.; Le, H.; Kyne, R. E.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 9716. (c) Brozek, L. A.; Ardolino, M. J.; Morken, J. P. *J. Am. Chem. Soc.* **2011**, *133*, 16778.

[26] Nave, S.; Sonawane, R. P.; Elford, T. G.; Aggarwal, V. K. *J. Am. Chem. Soc.* **2010**, *132*, 17096.

Scheme 2.22 Tandem 1,2-Diboration/Allylation/Homologation/Oxidation Reaction



2.6 Conclusions

Employing a platinum-phosphonite catalyst, an efficient and highly enantioselective 1,2-diboration of *cis*-1,3-dienes and 4,4-disubtituted dienes was developed. Oxidation of the diboration intermediate enables direct access to enantioenriched allylic 1,2-diols. Importantly, the α-chiral allylboronate intermediates can also be used in allylation reactions generating homoallylic alcohols containing either a *syn*-polypropionate motif or an α-quaternary center with excellent diastereo- and enantiocontrol. This transformation constructs an additional allylboron functional group that can be further manipulated. This offers streamlined synthesis of polyketide natural products from simple prochiral hydrocarbons.

2.7 Experimental

2.7.1 General Information

^{1}H NMR spectra were recorded on either a Varian Gemini-400 (400 MHz), a Varian Gemini-500 (500 MHz), a Varian Inova-500 (500 MHz), or a Varian Gemini-600 (600 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-400 (100 MHz), a Varian Gemini-500 (125 MHz), or a Varian Gemini-600 (150 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, ν_{max} cm^{-1}. Bands are characterized as broad (br), strong (s), medium (m), and weak (w). 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, or phosphomolybdic acid (PMA) in ethanol. 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 Supelco β-Dex 120 column with helium as the carrier gas. Analytical

chiral supercritical fluid chromatography (SFC) was performed on a TharSFC Method Station II equipped with Waters 2998 Photodiode Array Detector.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran, dichloromethane, acetonitrile, 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. Triethylamine was distilled from calcium hydride. 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. Norbornene was purchased from Aldrich and was sublimed prior to use. Bis(pinacolato)diboron was generously donated by Allychem Co., Ltd. and was recrystallized from pentane prior to use. Dichlorophenylphosphine, tris(dibenzylidenacetone) dipalladium (0), and tri-*t*-butylphosphine, were purchased from Strem Chemicals, Inc. and used without further purification. (*Z*)-Penta-1,3-diene was purchased from ChemSampCo and was used without purification. 1,3,5-Tribromobenzene was purchased from Alfa Aesar. Benzaldehyde, hydrocinnamaldehyde, cinnamaldehyde, nonenal, propionaldehyde, *iso*-butyraldehyde, and benzyloxyacetaldehyde were purchased from Aldrich and distilled prior to use. All other reagents were purchased from Aldrich and used without further purification.

2.7.2 Preparation of Pt(dba)$_3$

Tris(dibenzylideneacetone)platinum was prepared using the literature procedure[27] with slight modification. 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 (210.0 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 (8.0 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 h. After 3 h, 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 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 brown solid (1.84 g, 85% yield) 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).

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

2.7.3 Preparation of $Pt_2(dba)_3$

Tris(dibenzylideneacetone)diplatinum was prepared using the literature procedure.[1] To a two-neck 25 mL round-bottom flask equipped with a magnetic stir bar and reflux condenser was added dibenzylideneacetone (1.98 g, 8.43 mmol), tetrabutylammonium chloride (1.00 g, 3.61 mmol), and sodium acetate (1.78 g, 21.8 mmol). Methanol (102.0 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 (500.0 mg, 1.20 mmol) and water (6.3 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 h, 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 yellow dibenzylideneacetone crystals were removed. The solid product was then dissolved in hot tetrahydrofuran (100 mL) and filtered. The filtrate volume was reduced to 10 mL using rotary evaporation and then methanol (12 mL) was slowly added. After cooling the solution to - 25 °C in the freezer for 1 h the crystallized product was isolated by filtration, washed with methanol (40 mL) and dried under vacuum to provide a black crystalline solid (348.9 mg, 53% yield). Anal Calc'd for $C_{51}H_{42}O_3Pt_2$: C, 56.04; H, 3.87. Found: C, 56.40; H, 3.73 (average of two experiments). Platinum analysis was performed by ICP Optical Emission Spectroscopy; calculated for $Pt_2(dba)_3$: 35.70% Pt; found 33.72% (average of two experiments).

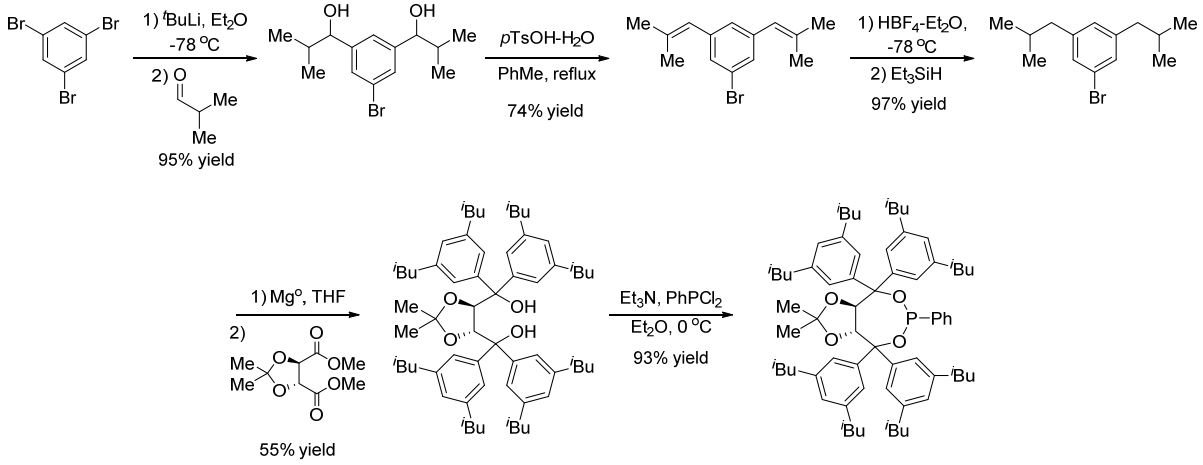
2.7.4 Preparation of Pt(nbe)$_3$[28]

A flame-dried 100 mL 3-neck round-bottomed flask equipped with magnetic stir bar and addition funnel was charged with finely powdered $PtCl_2(COD)$[29] (3.50 g, 9.35 mmol) and freshly sublimed norbornene (7.00 g, 74.3 mmol) under N_2. Diethyl ether (10.7 mL, 0.88 M) was added, and the reaction was cooled to -30 °C (dry ice/ethanol/ethylene glycol). The addition funnel was charged with a freshly prepared solution of cyclooctatetraene dilithium (46.3 mL, 0.20 M), which was then added dropwise to the reaction while maintaining an internal temperature of -30 °C. The light brown reaction mixture was allowed to warm to room temperature and the solvent was removed *in vacuo*. The remaining residue was dried for an additional hour before being brought into the glove box where the solid was scraped and washed with dry and degassed hexane (3 x 100 mL). The extract was filtered through a plug of alumina and the filtrate was evaporated *in vacuo* to produce an off-white solid which was used without further purification (1.67 g, 52% yield). Anal Calc'd for $C_{21}H_{30}Pt$: C, 52.82; H, 6.33. Found: C, 52.84; H, 6.29.

[28] Reagents for Transition Metal Complex and Organometallic Syntheses. *Inorganic Syntheses*; Angelici, R.J., Ed.; Wiley: New York, 1990; Vol. 28; p 127.
[29] Baker, M. V.; Brown, H. D.; Simpson, P. V.; Skelton, B. W.; White, A. H.; Williams, C. C. *J. Organometallic Chem.* **2006**, *691*, 5845.

2.7.5 Ligand Synthesis

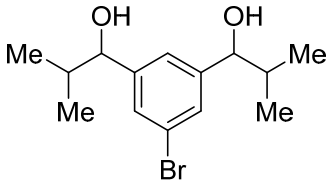
2.7.5.1 Preparation of (R,R)-3,5-di-iso-butylphenylTADDOLPPh.



Preparation of 1,1'-(5-bromo-1,3-phenylene)bis(2-methylpropan-1-ol).[30]

To a flame-dried 1 L round-bottomed flask equipped with magnetic stir bar was added 1,3,5-tribromobenzene (4.00 g, 12.7 mmol) and diethyl ether (500.0 mL) under N_2. The reaction was cooled to -78 °C and tert-butyllithium (33.2 mL, 1.7 M solution in pentane) was added dropwise *via* syringe. After stirring at -78 °C for 2 h, *iso*-butyraldehyde (4.60 mL, 50.8 mmol) was added and the reaction was allowed to warm to 0 °C before being quenched with saturated aqueous ammonium chloride (20 mL). The organic and aqueous layers were separated and the aqueous layer was washed with diethyl ether (3 x 50 mL). The combined organic layers were washed with brine (50 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by flash chromatography on silica gel (100% dichloromethane, then 100% ethyl acetate) to afford a brown solid (3.64 g, 95% yield).

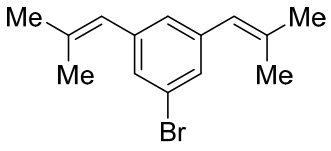
[30] Matsuda, K.; Nakamura, N.; Takahashi, K.; Inoue, K.; Koga, N.; Iwamura, H. *J. Am. Chem. Soc.* **1995**, *117*, 5550.



1,1'-(5-bromo-1,3-phenylene)bis(2-methylpropan-1-ol). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.80 (6H, d, J = 7.0 Hz), 0.94 (6H, d, J = 6.5 Hz), 1.86 (2H, d, J = 2.5 Hz), 1.91 (2H, m), 4.36 (2H, dd, J = 6.5 Hz, 2.5 Hz), 7.14 (1H, dd, J = 5.5 Hz 1.5 Hz), 7.35 (2H, dd, J = 2.5 Hz, 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.05, 19.15, 19.17, 35.55, 79.41, 122.49, 123.65, 123.71, 128.72, 128.74, 145.93, 145.96; IR (neat): 3364.1 (m), 2960.1 (s), 2872.8 (m), 1572.7 (w), 1467.5 (m), 1156.8 (w), 1033.1 (s), 710.8 (m) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{25}BrNO_2$ [M+NH_4]: calculated: 318.1068, found: 318.1057.

Preparation of 1-bromo-3,5-bis(2-methylprop-1-en-1-yl)benzene.

To a flame-dried 250 mL 3-neck round-bottomed flask equipped with magnetic stir bar and reflux condenser was added 1,1'-(5-bromo-1,3-phenylene)bis(2-methylpropan-1-ol) (3.64 g, 12.1 mmol) and *p*-TsOH•H_2O (1.62 g, 8.55 mmol). The reaction apparatus was purged with N_2 and toluene (120.0 mL) was added. The reaction mixture was brought to reflux and stirred for 36 h. After completion, the reaction was cooled to room temperature and diluted with ethyl acetate (60 mL). The organics were washed with saturated aqueous sodium bicarbonate (3 x 50 mL), dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by flash chromatography on silica gel (100% hexanes) to afford a colorless oil (2.36 g, 74% yield).

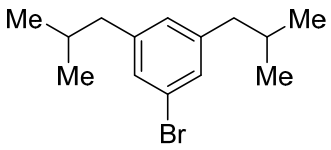


1-bromo-3,5-bis(2-methylprop-1-en-1-yl)benzene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.83 (6H, d, J = 1.0 Hz), 1.86

(6H, d, J = 1.5 Hz), 6.16 (2H, br s), 6.96 (1H, s), 7.15 (2H, d, J = 1.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.66, 27.03, 122.00, 124.19, 128.07, 129.14, 137.06, 140.49; IR (neat): 2969.6 (m), 2911.6 (m), 1655.8 (w), 1589.1 (m), 1555.2 (s), 1444.5 (m), 873.7 (s) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{18}Br$ [M+H]: calculated: 265.0592, found: 265.0603.

Preparation of 1-bromo-3,5-di-iso-butylbenzene.[31]

To a flame-dried 250 mL round-bottomed flask equipped with magnetic stir bar was added 1-bromo-3,5-bis(2-methylprop-1-en-1-yl)benzene (2.36 g, 8.89 mmol) and dichloromethane (88.0 mL) under N_2. The reaction was cooled to -78 °C and HBF_4•OEt_2 (4.70 mL, 34.7 mmol) was added. After stirring at -78 °C for 3 h, triethylsilane (11.1 mL, 69.4 mmol) was added and the reaction was allowed to stir overnight while slowly warming to room temperature. Saturated aqueous sodium bicarbonate (50 mL) was added and the organic and aqueous layers were separated. The aqueous layer was washed with ethyl acetate (3 x 25 mL). The combined organics were washed with brine (25 mL), dried over Na_2SO_4, filtered and concentrated by rotary evaporation. The crude material was purified by flash chromatography on silica gel (100% hexanes) to afford a colorless oil (2.32 g, 97% yield).



1-bromo-3,5-di-*iso*-butylbenzene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.87 (12H, d, J = 7.0 Hz), 1.82 (2H, m), 2.39 (4H, d, J = 7.5 Hz), 6.18 (1H, d, J = 1.5 Hz), 7.09 (2H, d, J = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.52, 30.39, 45.25, 122.09, 129.01, 129.54, 143.80; IR (neat): 2954.0 (s),

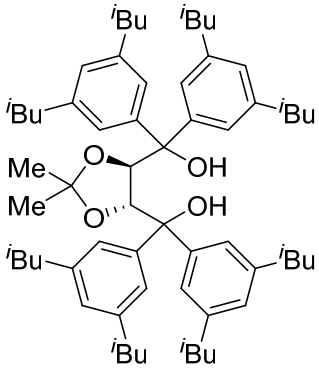
[31] Stadler, D.; Mühlthau, F.; Rubenbauer, P.; Herdtweck, E.; Bach, T. *Synlett*, **2006**, *16*, 2573.

2923.5 (m), 1601.7 (w), 1568.5 (s), 1440.9 (m), 1167.4 (w), 865.4 (m), 700.1 (m) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{22}Br$ [M+H]: calculated 269.0905, found: 269.0899.

Preparation of 3,5-di-iso-butylphenylTADDOL.

3,5-Di-*iso*-butylphenylTADDOL was prepared according to the literature procedure [32] with slight modification. To a flame-dried 100 mL 2-neck round-bottomed flask equipped with magnetic stir bar and reflux condenser was added crushed magnesium turnings (439.0 mg, 18.05 mmol) under N_2. The apparatus was flame-dried again, a single crystal of I_2 was added and the reaction mixture was diluted with tetrahydrofuran (29.0 mL). To another flame dried 25 mL pear-shaped flask was added 1-bromo-3,5-di-*iso*-butylbenzene (4.37 g, 16.3 mmol) and tetrahydrofuran (12.0 mL). The solution of 1-bromo-3,5-diethylbenzene in tetrahydrofuran was slowly added to the magnesium mixture at room temperature *via* syringe. The reaction was heated to reflux at 80 °C in an oil bath for 3 h, at which time the reaction was cooled to 0 °C, and a solution of (4*R*,5*R*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate (788.0 mg, 3.61 mmol) in tetrahydrofuran (4.0 mL) was added slowly *via* syringe. The reaction was allowed to reflux for 12 h, after which it was cooled to 0 °C and quenched with saturated aqueous NH_4Cl (10 mL). The organic and aqueous layers were separated and the aqueous layer was washed with ethyl acetate (3 x 30 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel (1-50% ethyl acetate/hexanes) to afford the title compound as a yellow solid (1.79 g, 55% yield).

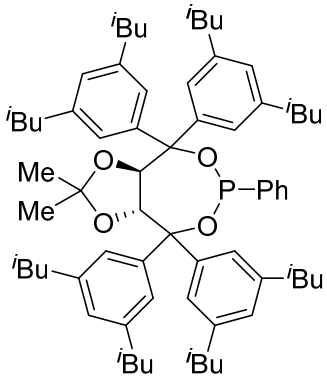
[32] Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978.



3,5-Di-iso**-butylphenylTADDOL.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.77 (24H, d, *J* = 6.5 Hz), 0.84 (24H, dd, *J* = 6.5 Hz, 3.5 Hz), 1.68 (4H, m), 1.81 (4H, m), 2.32 (8H, d, *J* = 7.0 Hz), 2.40 (8H, d, *J* = 7.0 Hz), 3.52 (2H, s), 4.68 (2H, s), 6.74 (2H, s), 6.81 (2H, s), 6.89 (4H, d, *J* = 1.5 Hz), 7.10 (4H, s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.24, 22.29, 22.34, 22.42, 27.00, 30.14, 30.33, 31.32, 45.41, 45.52, 77.32, 78.10, 81.28, 109.14, 125.81, 126.89, 128.70, 129.07, 139.97, 140.69, 142.60, 145.52, 148.20; IR (neat): 3320.1 (w), 2953.2 (s), 2923.4 (m), 2867.7 (m), 1601.1 (w), 1464.5 (m), 1166.8 (w), 881.7 (w) cm^{-1}; HRMS-(TOF MS ES+) for $C_{63}H_{94}O_4Na$ [M+Na]: calculated:937.7050, found: 937.7065.

Preparation of (R,R)-3,5-di-iso-butylphenylTADDOLPPh.

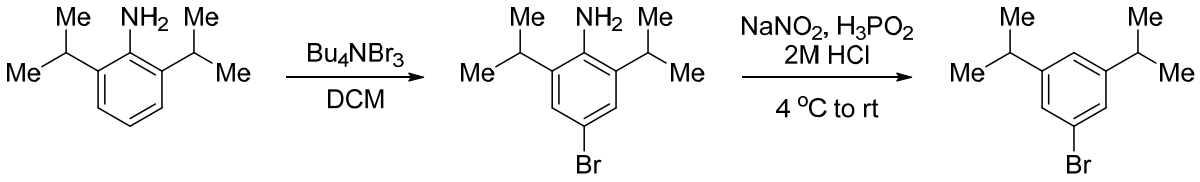
To a flame-dried 50 mL round-bottomed flask equipped with magnetic star bar was added 3,5-di-*iso*-butylphenylTADDOL (1.79 g, 1.95 mmol) and tetrahydrofuran (19.5 mL) under N_2. Triethylamine (0.90 mL, 6.60 mmol) was added *via* syringe and the reaction mixture was cooled to 0 °C in an ice bath. Dichlorophenylphosphine (0.30 mL, 2.14 mmol) was added dropwise *via* syringe at 0 °C, the reaction was brought to room temperature and was allowed to stir for 2 h. The reaction was diluted with Et_2O (20 mL) under N_2, quickly filtered through celite and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel (5% ethyl acetate/hexanes) to afford the title compound as a white solid (1.85 g, 93% yield).



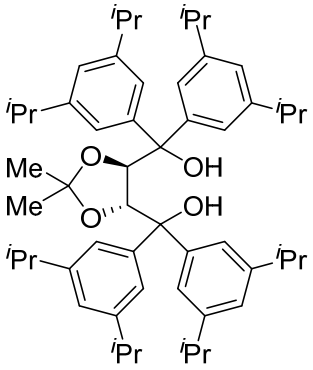
(*R,R*)-3,5-di-*iso*-butylphenylTADDOLPPh. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.06 (3H, s), 0.70 (24H, t, J = 6.8 Hz), 0.74 (24H, d, *J* = 6.0 Hz), 1.37 (3H, s), 1.58-1.71 (8H, m), 2.25 (8H, d, *J* = 6.8 Hz), 2.29 (8H, d, *J* = 7.2 Hz), 4.76 (1H, d, *J* = 8.8 Hz), 5.50 (1H, dd, *J* = 8.4 Hz, 4.4 Hz), 6.58 (1H, s), 6.63 (2H, s), 6.71 (1H, s), 6.83 (2H, s), 6.92 (1H, s), 7.01 (2H, s), 7.14 (1H, s), 7.34 (5H, br s), 7.69 (2H, br s); ^{13}C NMR (100 MHz, $CDCl_3$): δ 22.20, 22.24, 22.25, 22.36, 22.42, 24.79, 27.76, 30.16, 30.17, 30.23, 30.55, 45.38, 45.50, 45.64, 77.20, 82.41, 82.45, 82.49, 82.72, 83.36, 83.44, 84.18, 84.23, 110.79, 125.82, 125.89, 127.17, 127.20, 127.75, 128.08, 128.14, 128.80, 128.89, 128.91, 129.03, 129.95, 130.19, 130.32; ^{31}P NMR (202 MHz, $CDCl_3$): δ 156.11; IR (neat): 2952.7 (s), 2921.9 (m), 2867.5 (w), 1600.2 (w), 1464.4 (m), 1161.9 (m), 1038.2 (m), 802.7 (m) cm^{-1}; HRMS-(TOF MS ES+) for $C_{69}H_{98}O_4P$ [M+H]: calculated: 1021.7203, found: 1021.7190.

2.7.5.2 Preparation of 3,5-di-iso-propylphenylTADDOL

3,5-di-*iso*-propylphenylTADDOL was prepared according to the procedure described above for the synthesis of 3,5-di-*iso*-butylphenylTADDOL using 1-bromo-3,5-diisopropylbenzene (prepared according to the literature procedure[33] described below)



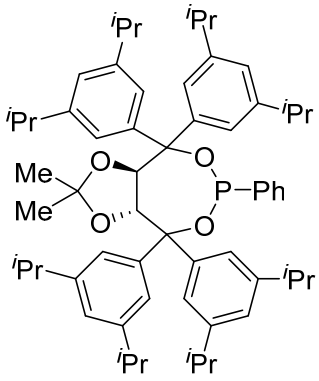
[33] Diemer, V.; Chaumeil, H.; Defoin, A.; Fort, A.; Boeglin, A.; Carré, C. *Eur. J. Org. Chem.* **2006**, *12*, 2727.



3,5-di-*iso*-propylphenylTADDOL. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (6H, s), 1.06 (24H, dd, *J* = 7.5 Hz, 7.0 Hz), 1.16 (24H, dd, *J* = 7.0 Hz, 1.5 Hz), 2.72 (4H, app q, *J* = 7.0 Hz), 2.81 (4H, app q, *J* = 7.0 Hz), 3.63 (2H, s), 4.61 (2H, s), 6.86 (2H, s), 6.92 (2H, s), 6.95 (4H, d, *J* = 1.5 Hz), 7.16 (4H, d, J = 1.7 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.87, 23.96, 24.00, 24.39, 26.95, 30.32, 34.16, 34.33, 78.50, 81.23, 108.9, 123.2, 123.4, 123.5, 124.5, 142.5, 145.8, 147.3, 148.0; IR (neat): 3235.4 (w), 2967.2 (s), 2868.4 (m), 1599.3 (m), 1463.7 (m), 1073.2 (m), 872.4 (s), 739.8 (s), 709.6 (m) cm^{-1}; HRMS-(+MALDI) for $C_{55}H_{78}O_4Na$ [M+Na]: calculated 825.5792, found: 825.5770. $[\alpha]_{D25}$ = +19.88 (c = 0.97, $CHCl_3$, *l* = 50 mm).

Preparation of (R,R)-3,5-di-iso-propylphenylTADDOLPPh.

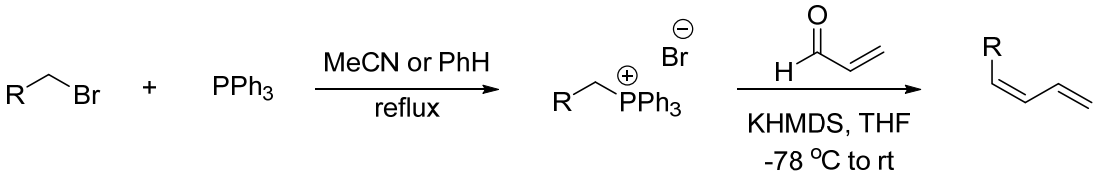
To a flame dried 50 mL round bottom flask equipped with magnetic star bar was added 3,5-di-iso-propylphenylTADDOL (1.09 g, 1.36 mmol) and tetrahydrofuran (13.6 mL, 0.1 M) under N_2. Triethylamine (0.65 mL, 4.64 mmol) was added via syringe and the reaction mixture was brought to 0 °C in an ice bath. Dichlorophenylphosphine (0.20 mL, 1.50 mmol) was added dropwise via syringe at 0 °C. The reaction was brought to room temperature and was allowed to stir for 2 h. The reaction was diluted with Et_2O (20 mL), filtered through celite and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (3% ethyl acetate/hexanes, with 1% Et_3N to prevent hydrolysis) to afford the title compound as a white solid (1.03 g, 83%).



(R,R)-3,5-di-iso-propylphenylTADDOLPPh. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.11 (3H, s), 1.10-1.25 (48H, m), 1.51 (3H, s), 2.78-2.84 (8H, m), 4.91 (1H, d, *J* = 8.5 Hz), 5.58 (1H, dd, *J* = 8.5 Hz, 4.0 Hz), 6.83 (1H, s), 6.91 (2H, s), 6.94 (1H, s), 6.98 (2H, d, *J* = 2.0 Hz), 7.18 (2H, br s), 7.34 (2H, s), 7.44-7.47 (3H, m), 7.51 (2H, s), 7.86-7.90 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 23.86, 23.90, 23.98, 24.12, 24.19, 27.99, 34.03, 34.12, 34.16, 34.43, 82.76, 82.83, 83.22, 83.39, 83.84, 83.89, 84.31, 84.34. 110.4, 123.1, 123.3, 123.4, 123.5, 123.6, 124.7, 124.8, 125.1, 128.1, 128.2, 129.9, 130.1, 130.4, 141.4, 141.7, 142.1, 142.2, 146.2, 146.3, 146.8, 147.1, 147.3, 147.8, 147.9; ^{31}P NMR (202 MHz, $CDCl_3$): δ 155.41; IR (neat): 2957.6 (s), 2868.3 (w), 1598.6 (w), 1464.9 (m), 1162.7 (w), 1027.6 (m), 877.8 (s), 799.7 (m), 735.3 (s), 693.3 (m) cm^{-1}. $[\alpha]_{D25}$ = -50.4 (*c* = 0.34, $CHCl_3$, *l* = 50 mm).

2.7.6 Preparation of Cis-1,3-Dienes

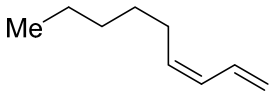
2.7.6.1 Representative Procedure for cis-Selective Wittig Olefination[34]



To a flame-dried 2-neck round-bottomed flask equipped with a reflux condenser was added triphenylphosphine (16.68 g, 63.61 mmol) under N_2, followed by acetonitrile (42.4 mL). 1-Bromohexane (7.00 g, 42.4 mmol) was then added *via* syringe and the reaction mixture was heated to 90 °C in an oil bath for 24 h. The reaction mixture was

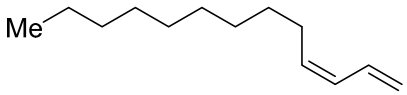
[34] Chhen, A.; Vaultier, M.; Carriê, R. *Tetrahedron Lett.* **1989**, *30*, 4953.

then cooled to room temperature and the solvent was removed by rotary evaporation to give the phosphonium salt as a white solid (17.83 g, 98%). To a flame-dried round bottomed flask was added potassium bis(trimethylsilyl)amide (3.27, 16.4 mmol) and the phosphonium salt (7.00 g, 16.4 mmol) in the glove box. The flask was sealed and brought to the bench. THF (227.0 mL) was added *via* syringe under N_2 and the solution was cooled to -78 °C (dry ice/acetone). The reaction mixture was allowed to stir at -78 °C for 1 h. To a second flame-dried round-bottomed flask was added acrolein (1.64 mL, 24.6 mmol) and THF (100.0 mL). The acrolein solution was cooled to -78 °C and was then slowly transferred *via* cannula to the ylide solution. The reaction mixture was stirred at -78 °C for 1 h, and then at room temperature for 1 h. The solvent was then removed by rotary evaporation to $^1/_4$ of the original volume. The crude mixture was diluted with pentane (150 mL) and washed with H_2O (3 x 100 mL). The layers were separated and the combined organics were dried with Na_2SO_4, filtered, and carefully concentrated (due to product volatility). The crude product was purified by flash chromatography on silica gel (100 % pentane, R_f = 0.83, stain in $KMnO_4$) to provide a clear, colorless liquid (1.69 g, 83%).

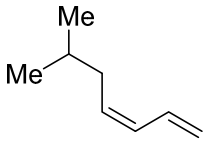


(*Z*)-nona-1,3-diene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (3H, t, *J* = 6.0 Hz), 1.26-1.34 (4H, m), 1.38 (2H, dddd, *J* = 7.5 Hz, 7.5 Hz, 7.5 Hz, 7.5 Hz), 2.17 (2H, dt, *J* = 8.0 Hz, 8.0 Hz, 8.0 Hz), 5.07 (1H, d, *J* = 10.0 Hz), 5.17 (1H, d, *J* = 16.5 Hz), 5.45 (1H, ddd, *J* = 7.5 Hz, 7.5 Hz, 7.5 Hz), 5.98 (1H, dd, *J* = 11.0 Hz, 11.0 Hz), 6.63 (1H, dt, *J* = 17.0 Hz, 11.0 Hz, 11.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 22.5, 27.7, 29.3, 31.4, 116.6, 129.1, 132.3, 133.0; IR (neat): 2954.3 (m), 2925.4

(s), 2858.6 (m), 1465.3 (m), 1363.3 (w), 1076.4 (w), 967.4 (s), 726.5 (w) cm^{-1}; HRMS-(ESI+) for C_9H_{17} [M+H]: calculated: 125.1330, found: 125.1331.

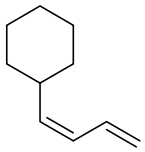


(*Z*)-trideca-1,3-diene. The title compound was prepared according to the representative procedure with the following modifications: The phosphonium salt was made using 1-bromodecane as the electrophile, and benzene as the solvent. The phosphonium salt was a viscous oil, and was used without purification. The olefination reaction was performed without modification to provide a clear, colorless liquid (1.15 g, 54%, R_f = 0.70 in 100% hexanes, stain in $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 7.0 Hz), 1.24-1.31 (10H, m), 1.36 (2H, dddd, *J* = 6.5 Hz, 6.5 Hz, 6.5 Hz, 6.5 Hz), 2.16 (2H, ddd, *J* = 7.5 Hz, 7.5 Hz, 7.5 Hz), 5.06 (1H, d, *J* = 10.0 Hz), 5.15 (1H, d, *J* = 17.0 Hz), 5.44 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 8.0 Hz), 5.98 (1H, dd, *J* = 11.0 Hz, 11.0 Hz), 6.62 (1H, dt, *J* = 17.0 Hz, 11.0 Hz, 11.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.7, 27.7, 29.25, 29.33, 29.5, 29.58, 29.62, 31.9, 116.6, 129.1, 132.3, 133.1; IR (neat): 2955.6 (w), 2922.4 (s), 2853.4 (m), 1464.8 (w), 1434.4 (w), 1377.3 (w), 995.4 (m), 900.3 (s), 783.9 (w), 721.5 (w), 653.6 (w) cm^{-1}; HRMS-(ESI+) for $C_{13}H_{25}$ [M+H]: calculated: 181.1956, found: 181.1948.

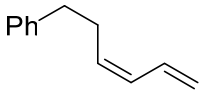


(*Z*)-6-methylhepta-1,3-diene. The title compound was prepared according to the representative procedure with the following modifications: The phosphonium salt was purchased from Aldrich. The olefination reaction was performed without modification to provide a clear, colorless liquid (1.45 g,

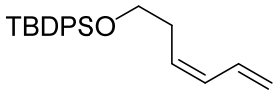
55%, R_f = 0.82 in 100% pentane, stain in $KMnO_4$). ^1H NMR (500 MHz, $CDCl_3$): δ 0.89 (6H, d, *J* = 7.0 Hz), 1.64 (1H, m), 2.06 (2H, dd, *J* = 7.5 Hz, 7.5 Hz), 5.06, (1H, d, *J* = 10.0 Hz), 5.16 (1H, d, *J* = 17.0 Hz), 5.46 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 8.0 Hz), 6.03 (1H, dd, *J* = 11.0 Hz, 11.0 Hz), 6.62 (1H, dt, *J* = 17.0 Hz, 11.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.3, 28.7, 36.8, 116.7, 129.9, 131.8, 132.5; IR (neat): 2955.5 (s), 2925.8 (s), 2869.9 (m), 1696.9 (w), 1466.7 (m), 1367.4 (m), 1150.3 (w), 1078.3 (w), 969.6 (s) cm^{-1}; HRMS-(ESI+) for C_8H_{15} [M+H]: calculated: 111.1174, found: 111.1174.



(*Z*)-buta-1,3-dien-1-ylcyclohexane. The title compound was prepared according to the representative procedure with the following modifications: The phosphonium salt made using (bromomethyl)cyclohexane as the electrophile and acetonitrile as the solvent. The phosphonium salt was isolated as a white solid (8.26 g, 71%). The olefination reaction was performed without modification to provide a clear, colorless liquid (1.06 g, 83%, R_f = 0.58 in 100% hexanes, stain in $KMnO_4$). ^1H NMR (500 MHz, $CDCl_3$): δ 1.03-1.12 (2H, m), 1.13-1.20 (1H, m), 1.23-1.33 (3H, m), 1.51-1.73 (4H, m), 2.40-2.46 (1H, m), 5.05 (1H, d, *J* = 10.5 Hz), 5.16 (1H, d, *J* = 16.5 Hz), 5.29 (1H, dd, *J* = 10.0 Hz, 10.0 Hz), 5.88 (1H, dd, *J* = 11.0 Hz, 11.0 Hz), 6.64 (1H, dt, *J* = 10.5 Hz, 17.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.8, 26.0, 33.2, 36.8, 116.6, 127.2, 132.6, 138.9; IR (neat): 2922.2 (s), 2851.0 (m), 1697.0 (w), 1448.8 (w), 1361.0 (w), 970.6 (w), 890.2 (w) cm^{-1}; HRMS-(ESI+) for $C_{10}H_{17}$ [M+H]: calculated: 137.1330, found: 137.1330.



(*Z*)-hexa-3,5-dien-1-ylbenzene. The title compound was prepared according to the representative procedure with the following modifications: The phosphonium salt was made using (3-bromopropyl)benzene as the electrophile, and acetonitrile as the solvent. The phosphonium salt was a white solid, and was used without purification. The olefination reaction was performed without modification to provide a clear, colorless liquid (930 mg, 53%, R_f = 0.50 in 100% hexanes, stain in $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.51 (2H, dt, *J* = 7.5 Hz, 7.5 Hz, 7.5 Hz), 2.70 (2H, t, *J* = 7.5 Hz), 5.08 (1H, d, *J* = 10.0 Hz), 5.18 (1H, d, *J* = 17.0 Hz), 5.49 (1H, dt, *J* = 7.5 Hz, 7.5 Hz), 6.01 (1H, dd, *J* = 11.0 Hz, 11.0 Hz), 6.60 (1H, dt, *J* = 16.5 Hz, 10.5 Hz), 7.17-1.20 (3H, m), 7.30 (2H, t, *J* = 8.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 29.6, 35.8, 117.2, 125.9, 128.3, 128.4, 129.7, 131.6, 132.1, 141.7; IR (neat): 2923.9 (w), 1495.5 (m), 1453.8 (m), 969.3 (s), 745.9 (m), 698.4 (s) cm^{-1}; HRMS-(ESI+) for $C_{12}H_{15}$ [M+H]: calculated: 159.1174, found: 159.1179.



(*Z*)-*tert*-butyl(hexa-3,5-dien-1-yloxy)diphenylsilane. The title compound was prepared according to the representative procedure with the following modifications: 3-bromopropan-1-ol was protected as the silyl ether and used as the electrophile to make the phosphonium salt with acetonitrile as the solvent. The phosphonium salt was an off-white solid, and was used without purification. The olefination reaction was performed without modification to provide a clear, colorless liquid (953 mg, 61%, R_f= 0.40 in 100% hexanes, stain in $KMnO_4$). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03 (9H, s), 2.43 (2H, dt, *J* = 8.0 Hz, 8.0 Hz), 3.68 (2H, t, *J* = 7.0 Hz), 5.06 (1H, d, *J* = 10.0 Hz), 5.16 (1H, d, *J* = 16.5 Hz), 5.46 (1H, dt, *J* = 8.0 Hz, 8.0 Hz), 6.04

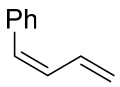
(1H, dd, J = 11.5 Hz, 11.5 Hz), 6.52 (1H, dt, J = 17.0 Hz, 10.0 Hz), 7.34-7.41 (6H, m), 7.65 (2H, d, J = 1.5 Hz), 7.66 (2H, d, J = 1.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 19.2, 26.8, 31.3, 63.4, 117.2, 127.60, 128.6, 129.6, 130.9, 132.3, 133.9, 135.6; IR (neat): 2857.4 (w), 1427.5 (w), 1107.6 (m), 822.9 (w), 700.7 (s), 505.3 (m) cm^{-1}; HRMS-(ESI+) for $C_{22}H_{29}OSi$ [M+H]: calculated 337.1987, found: 337.1975.

2.7.6.2 Preparation of (Z)-buta-1,3-dien-1-ylbenzene

The borylation of phenylacetylene was performed following the literature procedure without modification.[35] The resulting alkynyl pinacolboronate was subjected to hydroboration/protodeboronation according to the literature procedure.[36] The resulting (*Z)*-alkenyl pinacolboronate was then subjected to a Suzuki cross-coupling with vinyl bromide as follows: To a flame-dried, round-bottomed flask equipped with magnetic stir bar was added $Pd_2(dba)_3$ (99.0 mg, 0.11 mmol) and $P(^tBu)_3$ (87.9 mg, 0.44 mmol) in the glove box. The flask was sealed and brought to the bench. (*Z*)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane (1.00 g, 2.47 mmol) was added as a solution in THF (10.0 mL) *via* syringe under N_2. The reaction mixture was then charged with THF (62.0 mL), and aqueous potassium hydroxide (4.30 mL, 13.0 mmol). The flask was cooled to 0 °C and vinyl bromide (13.0 mL of 1.0 M solution in THF, 13.0 mmol) was added dropwise *via* syringe. The reaction was allowed to slowly warm to room temperature while stirring overnight. Saturated ammonium chloride (20 mL) was added to the reaction and the aqueous and organic layers were separated. The aqueous layer was washed with ethyl acetate (3 x 30 mL). The combined organics were dried over Na_2SO_4, filtered, and

[35] Miyasaka, M.; Okamoto, M.; Takahashi, H.; Inoue, E.; Tanemura, K.; Takagi, K.; Nishihara, Y. *J. Am. Chem. Soc.* **2007**, *129*, 12634.
[36] Ellis, N. M.; Molander, G. A. *J. Org. Chem.*, **2008**, *73*, 6841.

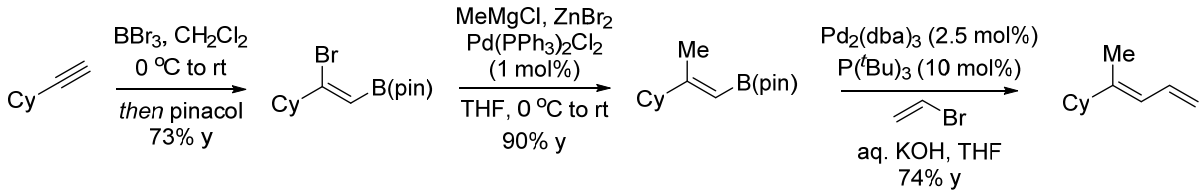
concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel (100% hexanes, R_f = 0.57, visualize by UV) to provide a clear, colorless liquid (270 mg, 48% yield).



(*Z*)-buta-1,3-dien-1-ylbenzene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.22 (1H, d, *J* = 10.5 Hz), 5.36 (1H, d, *J* = 17.0 Hz), 6.26 (1H, dd, *J* = 11.5 Hz, 11.5 Hz), 6.46 (1H, d, *J* = 11.5 Hz), 6.88 (1H, dt, *J* = 17.0 Hz, 11.0 Hz), 7.22-7.25 (1H, m), 7.31-7.36 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 119.6, 127.0, 128.4, 129.0, 130.4, 130.8, 133.2, 137.4; IR (neat): 29.18.6 (w), 1629.6 (m), 1450.1 (m), 968.1 (s), 694.3 (s), 638.9 (s) cm^{-1}; HRMS-(ESI+) for $C_{10}H_{11}$ [M+H]: calculated 131.0861, found: 131.0865.

2.7.7 Preparation of 4,4-Disubstituted Dienes

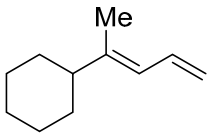
Preparation of (E)-penta-2,4-dien-2-ylcyclohexane



The title compound was prepared as shown above from cyclohexylacetylene according to the literature procedure.[37] The Suzuki-Miyaura cross coupling was carried out according to the literature procedure[38] with slight modification as follows: To a flame dried 250 mL round-bottomed flask equipped with a stir bar in the glove box was added $Pd_2(dba)_3$ (173.0 mg, 189.0 μmol) and P(*t*Bu)$_3$ (153.0 mg, 754.0 μmol). The reaction mixture was removed from the glove box and the vinylboronic acid pinacol ester (1.89 g,

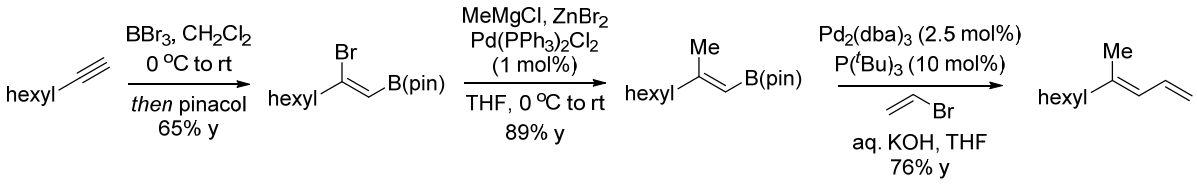
[37] Wang, C.; Tobrman, T.; Xu, Z.; Negishi, E. *Org. Lett.* **2009**, *11,* 4092.
[38] Posner, G. H.; Tang, P. *J. Org. Chem.* **1978**, *43***,** 4131.

7.54 mmol) was added under N_2 via syringe as a solution in THF (125 mL). Degassed aqueous KOH (3.0 M, 7.5 mL, 22.63 mmol) was then added to the reaction, followed by vinyl bromide (1.0 M in THF, 22.6 mL, 22.6 mmol). The reaction was allowed to stir at rt for 12 hours under N_2, at which time the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the layers were separated. The aqueous layer was washed with dichloromethane (3 x 100 mL) and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (100% hexane, R_f = 0.67, stain in CAM) to afford an inseparable heterogeneous mixture of a colorless oil and a white solid (913.5 mg, 30:1 product:homodimerized diene, 74%). The diene mixture can be further purified (to remove the homodimer) by Kugelrohr distillation under N_2 at 200 °C to afford the title compound as a clear, colorless oil (323.0 mg, 29%).

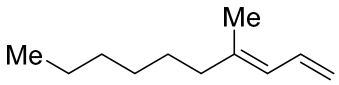


(E)-penta-2,4-dien-2-ylcyclohexane. ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.09-1.30 (5H, m), 1.64-1.70 (3H, m), 1.72 (3H, s), 1.72-1.77 (2H, m), 1.88 (1H, dddd, *J* = 11.5 Hz, 11.5 Hz, 3.0 Hz, 3.0 Hz), 4.96 (1H, dd, *J* = 10.0 Hz, 2.0 Hz), 5.08 (1H, dd, *J* = 16.5 Hz, 2.0 Hz), 5.84 (1H, d, *J* = 11.0 Hz), 6.59 (1H, ddd, *J* = 16.5 Hz, 10.0 Hz, 10.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.0, 26.3, 26.6, 31.6, 47.5, 114.5, 123.4, 133.6, 144.8; IR (neat): 3082.7 (w), 2924.1 (s), 2852.1 (s), 1646.7 (w), 1448.1 (m), 1019.4 (w), 985.1 (m), 890.3 (s), 657.8 (m) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{19}$ [M+H]: calculated: 151.1487, found: 151.1482.

Preparation of (E)-4-methyldeca-1,3-diene

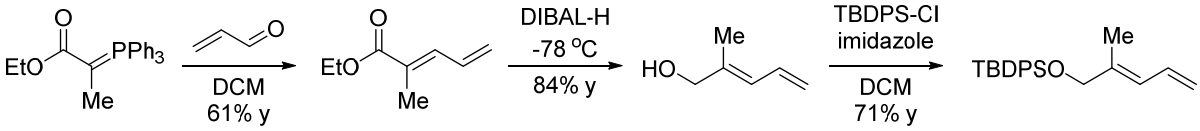


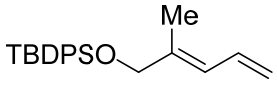
The title compound was prepared as shown above from 1-octyne according to the literature procedure.[37] The Suzuki-Miyaura cross coupling was carried out as described above for (*E*)-penta-2,4-dien-2-ylcyclohexane with slight modification as follows: To a flame-dried, round-bottomed flask equipped with a stir bar in the glove box was added $Pd_2(dba)_3$ (132.0 mg, 144.2 μmol) and P(*t*Bu)$_3$ (117.0 mg, 578.3 μmol). The reaction mixture was removed from the glove box and the vinylboronic acid pinacol ester (1.45 g, 5.77 mmol) was added under N_2 via syringe as a solution in THF (95 mL). Degassed aqueous KOH (3.0 M, 5.80 mL, 17.3 mmol) was then added to the reaction, followed by vinyl bromide (1.0 M in THF, 17.3 mL, 17.3 mmol). The reaction was allowed to stir at rt for 12 hours under N_2, at which time the reaction was quenched with saturated aqueous NH_4Cl (50 mL) and the layers were separated. The aqueous layer was washed with dichloromethane (3 x 100 mL) and the organic layers were combined, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (100% hexane, R_f = 0.69, stain in PMA) to afford a clear, colorless oil as an inseparable mixture of the desired diene and homodimer product (716.0 mg, 24:1 product:homodimer, 76%). The diene mixture can be further purified (to remove the homodimer) by Kugelrohr distillation under N_2 at 225 °C to afford the title compound as a clear, colorless oil (235.0 mg, 27%).



(E)-4-methyldeca-1,3-diene. ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 6.0 Hz); 1.23-1.30 (6H, m); 0.87 (3H, t, *J* = 6.5 Hz), 1.23-1.30 (6H, m), 1.37-1.43 (2H, m), 1.73 (3H, s), 2.02 (2H, t, *J* = 7.0 Hz), 4.95 (1H, dd, *J* = 10.0 Hz, 2.0 Hz), 5.06 (1H, dd, *J* = 17.0 Hz, 2.5 Hz), 5.83 (1H, dd, *J* = 11.0 Hz, 1.9 Hz), 6.56 (1H, ddd, *J* = 17.0 Hz, 11.0 Hz, 11.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 16.5, 22.6, 27.8, 29.0, 31.8, 39.8, 114.3, 125.3, 133.5, 140.0; IR (neat): 2956.8 (m), 2926.5 (s), 2885.9 (m), 1651.4 (w), 1457.5 (w), 1418.6 (w), 1379.2 (w), 986.0 (m), 896.0 (s), 657.1 (w) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{21}$ [M+H]: calculated: 153.1643, found: 153.1646.

Preparation of (E)-tert-butyl((2-methylpenta-2,4-dien-1-yl)oxy)diphenylsilane

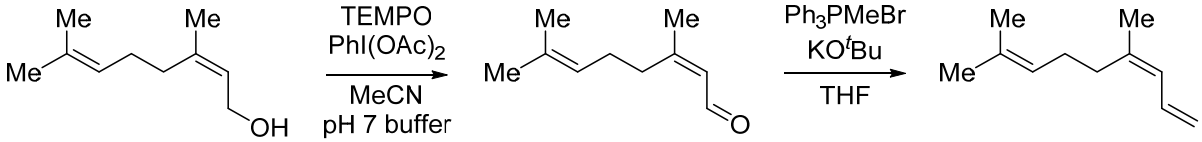




(E)-tert-butyl((2-methylpenta-2,4-dien-1-yl)oxy)diphenylsilane. The title compound was prepared as shown above using standard procedures. The crude product was purified by column chromatography on SiO_2 (2% ethyl acetate/hexanes, R_f = 0.37, stain in $KMnO_4$) to afford a viscous, clear, colorless oil (715.0 mg, 71%, 20:1 *E*:*Z*). ^{1}H NMR (500 MHz, $CDCl_3$): 1.06 (9H, s), 1.70 (3H, s), 4.09 (2H, d, *J* = 0.5 Hz), 5.06 (1H, dd, *J* = 10.5 Hz, 1.0 Hz), 5.17 (1H, dd, *J* = 17.0 Hz, 1.5 Hz), 6.17 (1H, dd, *J* = 11.0 Hz, 0.5 Hz), 6.61 (1H, ddd, *J* = 17.0 Hz, 10.5 Hz, 10.5 Hz), 7.35-7.43 (6H, m), 7.66-7.68 (4H, m); ^{13}C NMR (125 MHz,

$CDCl_3$): δ 13.9, 19.3, 26.8, 68.3, 116.2, 124.2, 127.6, 129.6, 132.8, 133.6, 135.5, 137.5; IR (neat): 2958.2 (w), 2930.5 (m), 2893.2 (w), 2856.3 (m), 1471.8 (w), 1462.0 (w), 1427.1 (m), 1380.4 (w), 1362.1 (w), 1207.9 (w), 1187.5 (w), 1148.4 (w), 1106.3 (s), 1066.6 (m), 1028.8 (m), 989.9 (m), 939.8 (w), 900.1 (m), 823.0 (m), 739.0 (m), 699.3 (s), 659.1 (w), 615.8 (m), 596.5 (m), 573.5 (w), 503.1 (s), 488.1 (s), 431.0 (w) cm^{-1}; HRMS-(ESI+) for $C_{22}H_{29}OSi$ [M+H]: calculated: 337.1988, found: 337.1997.

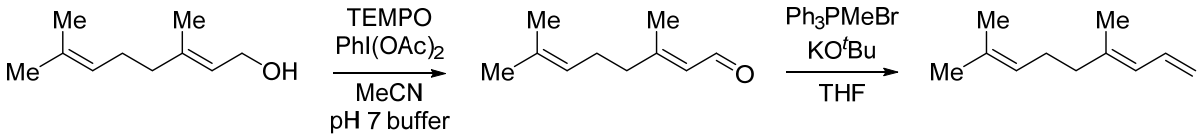
Preparation of (Z)-4,8-dimethylnona-1,3,7-triene



To a 50 mL round-bottomed flask equipped with a stir bar was added iodobenzene diacetate (2.30 g, 7.13 mmol) and TEMPO (101.3 mg, 0.65 mmol). Acetonitrile (6.5 mL) and pH 7 buffer (1.6 mL) were then added, and the reaction mixture was cooled to 0 °C in an ice bath. Nerol (1.00 g, 6.48 mmol) was added via syringe at 0 °C and the reaction was allowed to stir for 3 h (slowly warming to rt). The reaction was then quenched with saturated aqueous sodium thiosulfate (5 mL) and the layers were separated. The aqueous layer was washed with DCM (3 x 20 mL) and the combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (2-5% ethyl acetate/hexanes, R_f = 0.45 in 5:1 hexanes:ethyl acetate, stain in PMA) to afford the aldehyde as a clear, colorless oil (987.4 mg, 100%). To a flame-dried, round-bottomed flask in the glove box was added triphenylphosphonium bromide (2.76 g, 7.78 mmol) and potassium *t*-butoxide (873.4 mg, 7.78 mmol). The flask was sealed, brought to the bench,

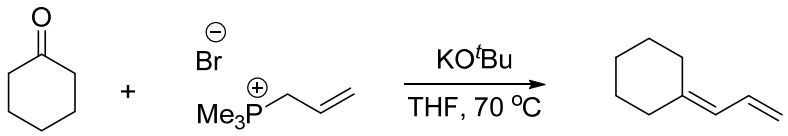
and charged with THF (20 mL) under N_2. The aldehyde (987.4 mg, 6.49 mmol) was then added as a solution in THF (6 mL). The reaction mixture was allowed to stir at rt for 30 min and was then diluted with Et_2O (30 mL). The solution was filtered over a pad of silica gel and the filtrate was concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (100% hexanes, R_f = 0.60 in 5:1 hexanes:ethyl acetate, stain in PMA) to afford the title compound as a clear, colorless oil (821.3 mg, 84%). All spectral data were in accordance with the literature.[39]

Preparation of (E)-4,8-dimethylnona-1,3,7-triene



The title compound was prepared from geraniol according to the procedure described above for (*Z*)-4,8-dimethylnona-1,3,7-triene. The crude product was purified by column chromatography on SiO_2 (100% hexanes, R_f = 0.56 in 5:1 hexanes:ethyl acetate, stain in PMA) to afford the title compound as a clear, colorless oil (918.8 mg, 95%). All spectral data were in accordance with the literature.[39]

Preparation of allylidenecyclohexane



The title compound was prepared according to the literature procedure with slight modification.[40] To a flame-dried, round-bottomed flask in the glove box was added the

[39] Davi, M.; Lebel, H. *Org. Lett.* **2009**, *11*, 41.
[40] Tamura, R.; Saegusa, K.; Kakihana, M.; Oda, D. *J. Org. Chem.* **1988**, *53*, 2723.

phosphonium salt (3.00 g, 15.22 mmol) and potassium *t*-butoxide (1.71 g, 15.22 mmol). The flask was sealed, brought to the bench, and THF (51 mL) was added via syringe under N_2. The reaction mixture was cooled to 0 °C in an ice bath and charged with cyclohexanone (1.3 mL, 12.69 mmol, freshly distilled from $MgSO_4$). The flask was then fitted with a flame-dried reflux condenser and was heated to 70 °C in an oil bath for 14 h. The reaction mixture was then cooled to rt and diluted with diethyl ether (50 mL) and the layers were separated. The organic layer was washed with DI H_2O (2 x 25 mL) then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude product was purified by column chromatography on SiO_2 (100% hexanes) to give the title compound as a clear, colorless oil (1.36 g, 88%). All spectral data were in accordance with the literature.[41]

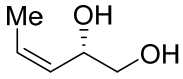
2.7.8 Representative Procedure for Diboration/Oxidation of Cis-1,3-Dienes.

To an oven-dried 6-dram vial with magnetic stir bar in the glove box was added $Pt(dba)_3$ (8.7 mg, 10.0 μmol), (*R,R*)-3,5-diethylphenyl-TADDOLPPh (15.4 mg, 19.3 μmol), $B_2(pin)_2$ (85.9 mg, 338.1 μmol) and tetrahydrofuran (3.2 mL, [substrate] = 0.1 M). The vial was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C in an oil bath for 20 min. The vial was cooled to room temperature, returned to the glove box and charged with (*Z*)-nona-1,3-diene (40.0 mg, 322.0 μmol). The vial was sealed, removed from the glove box, and stirred at 60 °C for 12 h. The reaction mixture was cooled to 0 °C (ice/water) and charged with 3 M sodium hydroxide (2 mL), and 30% hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (2 mL) was added dropwise over 5 min. The reaction mixture

[41] Meagher, T. P.; Yet, L.; Hsiao, C. N.; Shechter, H. *J. Org. Chem.* **1998**, *63*, 4181.

was diluted with ethyl acetate (5 mL) and the aqueous and organic layers were separated. The aqueous layer was washed with ethyl acetate (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by column chromatography on silica gel (30-60% ethyl acetate/hexanes) to afford a clear, colorless oil (35.7 mg, 70%).

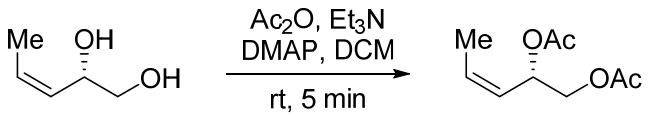
2.7.9 Characterization and Proof of Stereochemistry (Table 2.3)



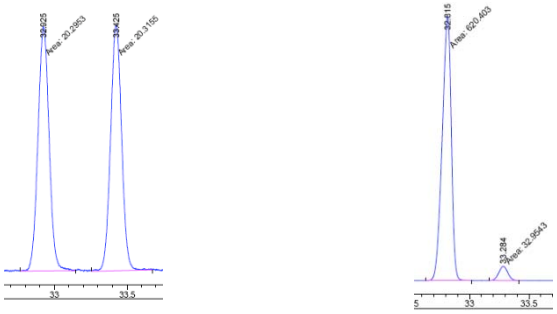
(*S,Z*)-pent-3-ene-1,2-diol. The diboration was performed according to the representative procedure with (Z)-penta-1,3-diene (40.0 mg, 587.2 μmol), $Pt(dba)_3$ (15.8 mg, 17.6 μmol), (*R,R*)-3,5-di-iso-butylphenylTADDOLPPh (35.9 mg, 35.2 μmol), and $B_2(pin)_2$ (156.5 mg, 616.4 μmol) in tetrahydrofuran (5.8 mL, 0.1 M). The crude reaction mixture was purified on silica gel (40-75% ethyl acetate/hexanes, R_f = 0.11 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (41.3 mg, 69% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.68 (3H, dd, *J* = 6.5 Hz, 1.5 Hz), 2.46 (2H, br s), 3.47 (1H, dd, *J* = 11.0 Hz, 8.0 Hz), 3.56 (1H, dd, *J* = 11.5 Hz, 3.5 Hz), 4.56 (1H, ddd, *J* = 8.5 Hz, 8.5 Hz, 8.5 Hz), 5.36 (1H, ddd, *J* = 10.5 Hz, 8.5 Hz, 1.5 Hz), 5.65 (1H, dddd, *J* = 10.5 Hz, 7.0 Hz, 7.0 Hz, 7.0 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ 13.5, 66.2, 68.3, 128.7, 128.8; IR (neat): 3333.5 (s), 2921.0 (m), 1441.3 (m), 1067.3 (s), 1024.6 (s), 718.1 (m) cm^{-1}; HRMS-(ESI+) for $C_5H_{14}NO_2$ [M+NH_4]: calculated: 120.1024, found: 120.1021. $[\alpha]^{25}_D$ = +24.91 (*c* = 0.58, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry:

The enantioselectivity was determined by treating the resulting 1,2-diol with acetic anhydride and triethylamine to afford the bis(acetate) for GLC analysis as shown below. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction.



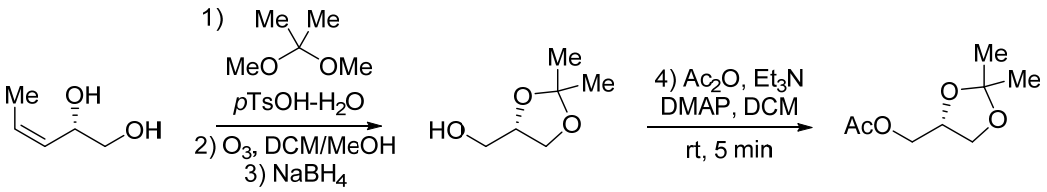
Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 2 °C/min to 130 °C, 20 psi, s/r = 35:1) - analysis of (Z)-pent-3-ene-1,2-diyl diacetate.



racemic diboration product

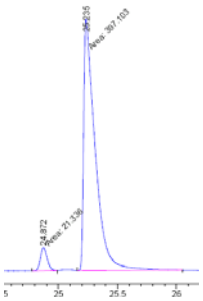
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	32.815	MM	0.0885	620.40283	116.85755	94.95616
2	33.284	MM	0.0868	32.95425	6.32439	5.04384

The absolute configuration was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol (below). The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.



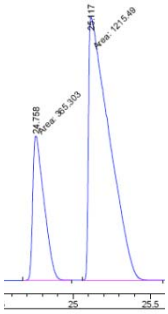
Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.

racemic



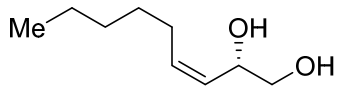
derived from reaction product

authentic



coinjection of authentic + racemic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.872	MM	0.0660	21.33599	5.39037	5.09895
2	25.235	MM	0.1126	397.10287	58.80334	94.90105

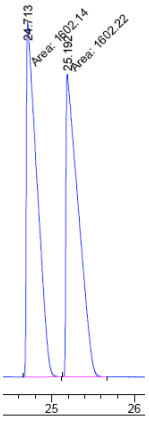


(*S,Z*)-non-3-ene-1,2-diol. The diboration was performed according to the representative procedure with (*Z*)-nona-1,3-diene (40.0 mg, 322.0 μmol), $Pt(dba)_3$ (8.7 mg, 10.0 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (15.4 mg, 19.3 μmol), and $B_2(pin)_2$ (85.9 mg, 338.1 μmol) in tetrahydrofuran (3.2 mL, 0.1 M). The crude reaction mixture was purified on silica gel (30-60% ethyl acetate/hexanes, R_f = 0.18 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (35.7 mg, 70% yield). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.87 (3H, t, *J* = 7.2 Hz), 1.24-1.31 (4H, m), 1.32-1.38 (2H, m), 1.52 (2H, br s), 2.03-2.13 (2H, m), 3.48 (1H, dd, *J* = 11.4 Hz, 7.8 Hz), 3.57 (1H, dd, *J* = 11.4 Hz, 4.2 Hz), 4.54 (1H, ddd, *J* = 9.0 Hz, 9.0 Hz, 3.6 Hz), 5.35 (1H, dd, *J* = 10.2 Hz, 10.2 Hz), 5.58 (1H, ddd, *J* = 10.8 Hz, 7.2 Hz, 7.2 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 22.5, 27.9, 29.3, 31.4, 66.4, 68.6, 127.8, 135.0; IR (neat): 3479.53 (br w), 2955.8 (s), 2928.7 (s), 2858.7 (m), 2361.9 (w), 1734.0 (s), 1458.3 (m), 1376.6 (m), 1230.2 (s), 1176.0 (s), 1121.3 (s), 1093.4 (s), 1041.3 (s) cm^{-1}; HRMS-(ESI+) for $C_9H_{22}N_1O_2$ [M+NH_4]: calculated: 176.1651, found: 176.1644. $[\alpha]^{25}_D$ = +12.37 (*c* = 0.91, $CHCl_3$, *l* = 50 mm).

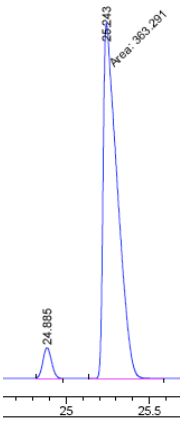
Proof of Stereochemistry:

The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

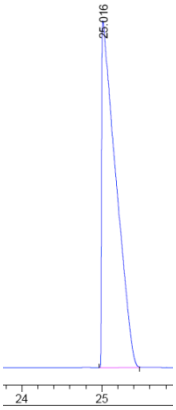
Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



racemic

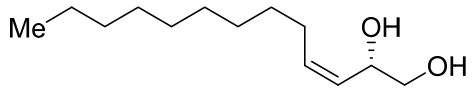


derived from reaction product



authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.885	BB	0.0564	19.32054	5.31722	5.04965
2	25.243	MM	0.0984	363.29132	61.50985	94.95035

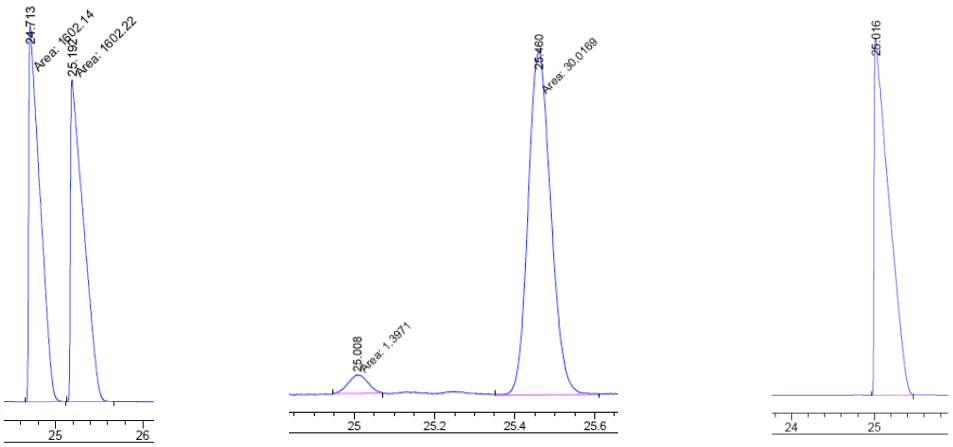


(*S,Z*)-tridec-3-ene-1,2-diol. The diboration was performed according to the representative procedure with (*Z*)-trideca-1,3-diene (40.0 mg, 221 μmol), $Pt(dba)_3$ (6.1 mg, 5.5 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (10.6 mg, 13.3 μmol), and $B_2(pin)_2$ (59.1 mg, 232 μmol) in tetrahydrofuran (2.2 mL, 0.1 M). The crude reaction mixture was purified on silica gel (30-50% ethyl acetate/hexanes, R_f = 0.25 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (40.4 mg, 85%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 6.5 Hz), 1.24-1.30 (12H, m), 1.31-1.38 (2H, m), 1.89 (2H, br s), 2.04-2.14 (2H, m), 3.48 (1H, dd, *J* = 11.0 Hz, 8.0 Hz), 3.56 (1H, dd, *J* = 11.0 Hz, 3.5 Hz), 4.54 (1H, ddd, *J* = 7.5 Hz, 7.5 Hz, 3.0 Hz), 5.34 (1H, dd, *J* = 8.5 Hz, 8.5 Hz), 5.58 (1H, ddd, *J* = 12.0 Hz, 7.5 Hz, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 22.7, 28.0, 29.26, 29.30, 29.47, 29.53, 29.6, 31.9, 66.4, 68.6, 127.8, 135.0; IR (neat): 3363.4 (br m), 2955.2 (m), 2922.9 (s), 2858.8 (m), 1464.6 (w), 1376.8 (m), 1180.4 (m), 1154.8 (m), 1112.1 (w), 1075.2 (m), 1025.8 (m), 950.7 (m), 884.2 (m) cm^{-1}; HRMS-(ESI+) for $C_{13}H_{30}N_1O_2$ [M+NH_4]: calculated: 232.2277, found: 232.2271. $[\alpha]^{25}_D$ = +4.70 (c = 0.51, $CHCl_3$, l = 50 mm).

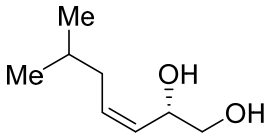
Proof of Stereochemistry.

The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	25.008	MM	0.0567	1.39710	4.10396e-1	4.44737
2	25.460	MM	0.0654	30.01688	7.64383	95.55263

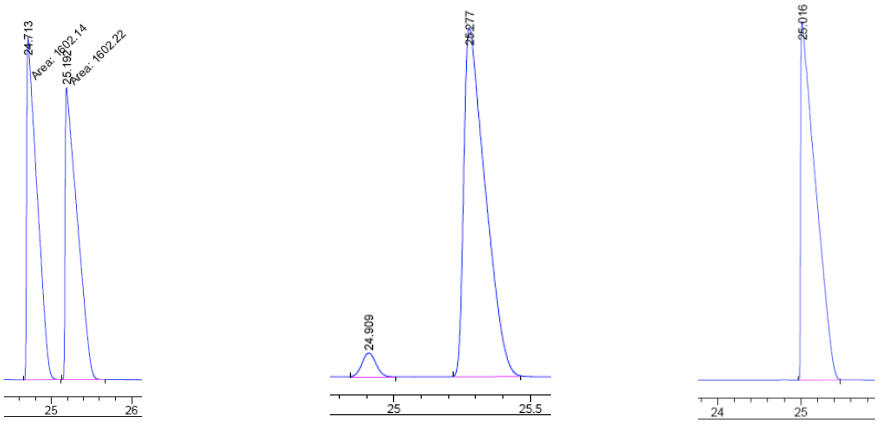


(*S*,*Z*)-6-methylhept-3-ene-1,2-diol. The diboration was performed according to the representative procedure with (*Z*)-6-methylhepta-1,3-diene (50.0 mg, 453 μmol), $Pt(dba)_3$ (12.2 mg, 13.6 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (17.4 mg, 21.8 μmol), and $B_2(pin)_2$ (120.9 mg, 476.4 μmol) in tetrahydrofuran (4.5 mL, 0.1 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate/hexanes, R_f = 0.22 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (61.5 mg, 94%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (3H, d, *J* = 5.0 Hz), 0.89 (3H, d, *J* = 4.5 Hz), 1.23 (2H, br s), 1.62 (1H, m), 1.93-2.04 (2H, m), 3.47 (1H, dd, *J* = 10.5 Hz, 7.5 Hz), 3.56 (1H, dd, *J* = 11.0 Hz, 3.5 Hz), 4.52 (1H, ddd, *J* = 8.5 Hz, 8.5 Hz, 3.5 Hz), 5.39 (1H, dd, *J* = 11.0 Hz, 9.0 Hz), 5.59 (1H, ddd, *J* = 10.5 Hz, 7.5 Hz, 7.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.2, 22.3, 28.5, 66.3, 68.6, 128.5, 133.5; IR (neat): 3346.2 (br m), 2954.7 (s), 2924.1 (s), 2869.4 (m), 1717.4 (w), 1464.3 (m), 1383.8 (m), 1367.0 (m), 1075.0 (s), 1026.9 (m) 869.8 (w) cm^{-1}; HRMS-(ESI+) for $C_8H_{20}N_1O_2$ [M+NH_4]: calculated: 162.1494, found: 162.1497. $[\alpha]^{25}_D$ = +9.42 (c = 0.53, $CHCl_3$, l = 50 mm).

Proof of Stereochemistry.

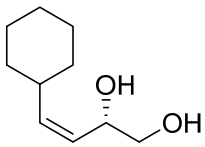
The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



racemic | derived from reaction product | authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.909	BB	0.0559	12.92987	3.59962	4.29653
2	25.277	BB	0.0778	288.00732	52.66652	95.70347

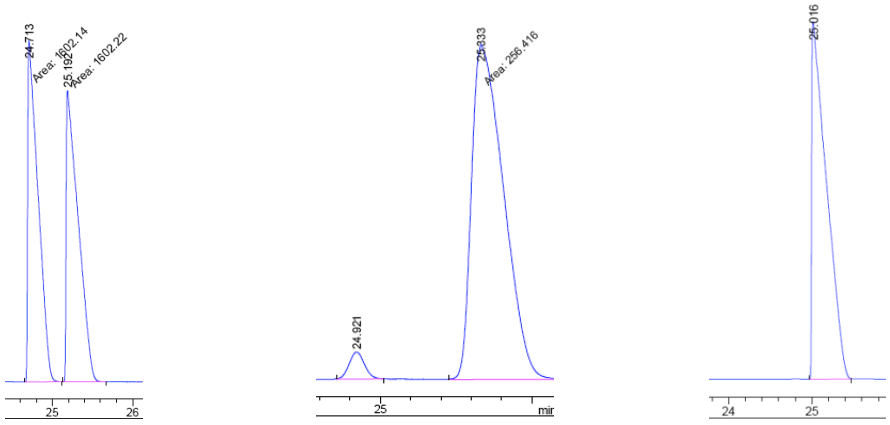


(*S*,*Z*)-4-cyclohexylbut-3-ene-1,2-diol. The diboration was performed according to the representative procedure with (*Z*)-buta-1,3-dien-1-ylcyclohexane (50.0 mg, 367 μmol), $Pt(dba)_3$ (10.0 mg, 9.2 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (17.6 mg, 22.0 μmol), and $B_2(pin)_2$ (97.9 mg, 385 μmol) in tetrahydrofuran (3.7 mL, 0.1 M). The crude reaction mixture was purified on silica gel (30-50% ethyl acetate/hexanes, R_f = 0.22 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (48.1 mg, 77%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.03-1.18 (3H, m), 1.22-1.31 (3H, m), 1.62-1.72 (4H, m), 1.9 (2H, br s), 2.25-2.33 (1H, m), 3.48 (1H, dd, *J* = 11.0 Hz, 8.0 Hz), 3.55 (1H, dd, *J* = 11.0 Hz. 4.0 Hz), 4.55 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 4.0 Hz), 5.24 (1H, dd, *J* = 11.0 Hz, 9.0 Hz), 5.43 (1H, dd, *J* = 10.5 Hz, 10.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 25.66, 25.74, 25.8, 33.3, 33.5, 37.1, 66.7, 68.8, 125.8, 140.8; IR (neat): 3361.9 (br m), 2921.2 (s), 2849.7 (m), 1447.5 (m), 1373.0 (w), 1324.5 (w), 1146.9 (w), 1069.1 (m), 1025.5 (m), 947.9 (w), 889.6 (w), 744.7 (w) cm^{-1}; HRMS-(ESI+) for $C_{10}H_{22}N_1O_2$ [M+NH_4]: calculated: 188.1651, found: 188.1643. $[\alpha]^{25}_D$ = +9.50 (*c* = 0.52, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry.

The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



racemic | derived from reaction product | authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
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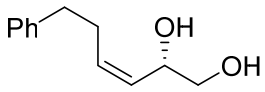
2	25.333	MM	0.1224	256.41574	34.92316	96.26683

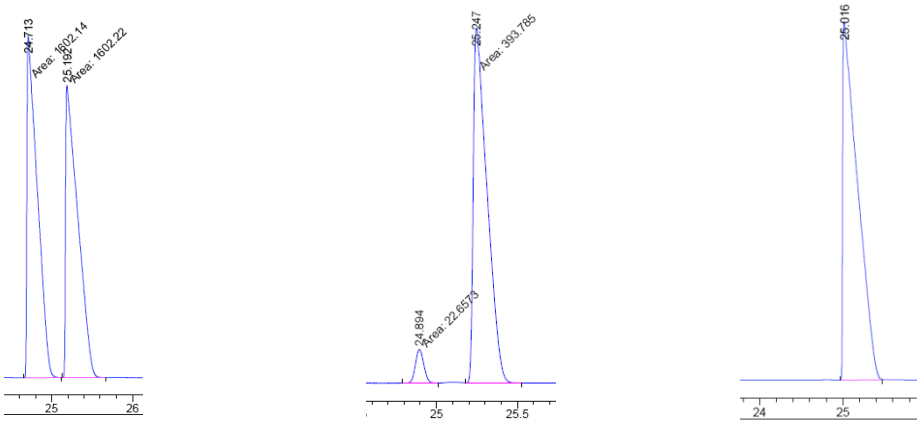


(*S*,*Z*)-6-phenylhex-3-ene-1,2-diol. The diboration was performed according to the representative procedure with (*Z*)-buta-1,3-dien-1-ylbenzene (30.0 mg, 230 μmol), $Pt(dba)_3$ (6.2 mg, 6.9 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (11.0 mg, 13.8 μmol), and $B_2(pin)_2$ (61.4 mg, 241 μmol) in tetrahydrofuran (2.3 mL, 0.1 M). The crude reaction mixture was purified on silica gel (40-60% ethyl acetate/hexanes, R_f = 0.24 in 50% ethyl acetate/hexanes, stain in PMA) to afford a white solid (20.8 mg, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.25 (2H, br s), 3.54 (1H, dd, *J* = 10.5 Hz, 7.5 Hz), 3.67 (1H, d, *J* = 9.5 Hz), 4.63 (1H, ddd, *J* = 8.5 Hz, 8.5 Hz, 3.0 Hz), 5.59 (1H, dd, *J* = 11.5 Hz, 9.5 Hz), 6.60 (1H, d, *J* = 11.5 Hz), 7.20-7.23 (3H, m), 7.27-7.30 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 29.9, 35.6, 66.2, 68.7, 127.6, 128.3, 128.7, 129.7, 133.4, 136.2; IR (neat): 3350.7 (s), 2925.7 (w), 1493.4 (w), 1071.1 (s), 1020.4 (m), 699.4 (s) cm^{-1}; HRMS-(ESI+) for $C_{10}H_{16}NO_2$ [M+NH_4]: calculated: 182.1181, found: 182.1173. $[\alpha]^{25}_D$ = +9.12 (*c* = 0.49, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry.

The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.

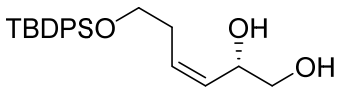


racemic

derived from reaction product

authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.894	MM	0.0596	22.65732	6.33500	5.44069
2	25.247	MM	0.0982	393.78497	66.81371	94.55931



(*S*,*Z*)-6-((*tert*-butyldiphenylsilyl)oxy)hex-3-ene-1,2-diol. The diboration was performed according to the representative procedure with ((*Z*)-tert-butyl(hexa-3,5-dien-1-yloxy)diphenylsilane (60.0 mg, 178 μmol), $Pt(dba)_3$ (4.8 mg, 5.3 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (8.5 mg, 10.7 μmol), and $B_2(pin)_2$ (47.5 mg, 187 μmol) in tetrahydrofuran (1.8 mL, 0.1 M). The crude reaction mixture was purified on silica gel (20-50% ethyl acetate/hexanes, R_f = 0.44 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear colorless oil that was inseparable from the 1,4-diol and pinacol (58.3 mg, 6.1:1.6:1 product:1,4-diol:pinacol = 62% yield). ^{1}H NMR (500 MHz, $CDCl_3$): **1,2-diol:** δ 1.03 (9H, s), 1.96 (1H, br s), 2.32 (1H, ddd, *J* = 13.0 Hz, 6.0 Hz, 6.0 Hz), 2.36 (1H, br s), 2.44 (1H, ddd, *J* = 14.5 Hz, 7.0 Hz, 7.0 Hz), 3.46 (1H, dd, *J* = 11.0 Hz, 7.5 Hz), 3.55 (1H, d, *J* = 9.5 Hz), 3.62-3.69 (2H, m), 4.45 (1H, d, *J* = 3.5 Hz), 5.53 (1H, dd, *J* = 10.5 Hz, 8.0 Hz), 5.62 (1H, ddd, *J* = 10.5 Hz, 8.0 Hz, 8.0 Hz), 7.36-7.43 (6H, m), 7.63-7.66 (4H, m); **1,4-diol:** δ 1.04 (9H, s), 1.56 (2H, br s), 1.65 (1H, dddd, *J* = 13.5 Hz, 4.0 Hz, 4.0 Hz, 4.0 Hz), 1.86 (1H, dddd, *J* = 19.0 Hz, 8.5 Hz, 8.5 Hz, 5.0 Hz), 3.83 (1H, ddd, *J* = 10.5 Hz, 4.0 Hz, 4.0 Hz), 3.86 (1H, ddd, *J* = 10.5 Hz, 5.0 Hz, 5.0 Hz), 4.17 (1H, dd, *J* = 13.0 Hz, 5.5 Hz), 4.27 (1H, dd, *J* = 13.0 Hz, 6.5 Hz), 4.76 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 4.0 Hz), 5.57 (1H, m), 5.73 (1H, ddd, *J* = 11.5 Hz, 6.0 Hz, 6.0 Hz), 7.36-7.43 (6H, m), 7.63-7.66 (4H, m); ^{13}C NMR (100 MHz, $CDCl_3$): **mixture of diols** δ 9.0, 19.2, 26.8, 29.7, 31.3, 38.7, 58.9, 62.7, 63.2, 66.2, 67.9, 68.3, 127.7, 127.8, 129.7, 129.90, 129.92, 130.4, 130.4, 131.0, 133.4, 134.4, 135.56, 135.59; IR (neat): 3354.6 (m), 2928.9 (m), 1471.6 (w), 1427.4 (m), 1108.6 (s), 700.9 (s), 504.6 (s) cm^{-1}; HRMS-(ESI+) for $C_{22}H_{30}O_3Si$ [M+H]: calculated: 371.2042, found: 371.2059. $[\alpha]^{25}_D$ = +10.2 (*c* = 0.45, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry.

The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

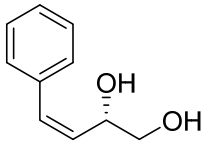
Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.

racemic

derived from reaction product

authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.940	MM	0.0596	19.99112	5.59123	5.32877
2	25.300	MM	0.0969	355.16321	61.06040	94.67123

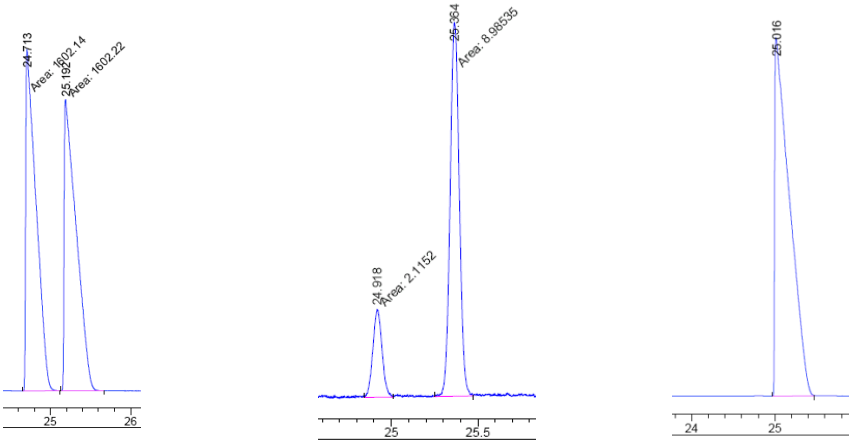


(*S*,*Z*)-4-phenylbut-3-ene-1,2-diol. The diboration was performed according to the representative procedure with (*Z*)-buta-1,3-dien-1-ylbenzene (30.0 mg, 230 μmol), $Pt(dba)_3$ (6.2 mg, 6.9 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (11.0 mg, 13.8 μmol), and $B_2(pin)_2$ (61.4 mg, 241 μmol) in tetrahydrofuran (2.3 mL, 0.1 M). The crude reaction mixture was purified on silica gel (40-60% ethyl acetate/hexanes, R_f = 0.24 in 50% ethyl acetate/hexanes, stain in PMA) to afford a white solid (20.8 mg, 55% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 2.25 (2H, br s), 3.54 (1H, dd, *J* = 10.5 Hz, 7.5 Hz), 3.67 (1H, d, *J* = 9.5 Hz), 4.63 (1H, ddd, *J* = 8.5 Hz, 8.5 Hz, 3.0 Hz), 5.59 (1H, dd, *J* = 11.5 Hz, 9.5 Hz), 6.60 (1H, d, *J* = 11.5 Hz), 7.20-7.23 (3H, m), 7.27-7.30 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 66.2, 68.7, 127.6, 128.3, 128.7, 129.7, 133.4, 136.2; IR (neat): 3350.7 (s), 2925.7 (w), 1493.4 (w), 1071.1 (s), 1020.4 (m), 699.4 (s) cm^{-1}; HRMS-(ESI+) for $C_{10}H_{16}NO_2$ [M+NH_4]: calculated: 182.1181, found: 182.1173. $[\alpha]^{25}_D$ = +9.12 (*c* = 0.49, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry.

The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.

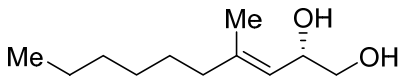


Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.918	MM	0.0611	2.11520	5.76821e-1	19.05490
2	25.364	MM	0.0613	8.98535	2.44295	80.94510

2.7.10 Representative Procedure for Enantioselective Diboration/Oxidation of 4,4-Disubstituted Dienes

To an oven-dried 6-dram vial with magnetic stir bar in the glove box was added $Pt(dba)_3$ (8.9 mg, 9.9 μmol), (*R,R*)-3,5-di-*iso*-propylTADDOLPPh (10.8 mg, 11.9 μmol), $B_2(pin)_2$ (88.0 mg, 346 μmol) and tetrahydrofuran (3.3 mL, [substrate] = 0.1 M). The vial was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C in an oil bath for 20 min. The vial was cooled to room temperature, returned to the glove box and charged with (*E*)-4-methyldeca-1,3-diene (50.0 mg, 328 μmol). The vial was sealed, removed from the glove box, and stirred at 60 °C for 12 h. The reaction mixture was cooled to 0 °C (ice/water) and charged with 3 M sodium hydroxide (2 mL), and 30% hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (2 mL) was added dropwise over 5 min. The reaction mixture was diluted with ethyl acetate (5 mL) and the aqueous and organic layers were separated. The aqueous layer was washed with ethyl acetate (3 x 15 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified by column chromatography on silica gel (35-75% ethyl acetate/hexanes, R_f = 0.18 in 50% ethyl acetate/hexane, stain in PMA) to afford a clear, colorless oil that was inseparable from pinacol (89.1 mg, 1:1.5 product:pinacol = 76%).

2.7.11 Characterization and Proof of Stereochemistry (Table 2.5)

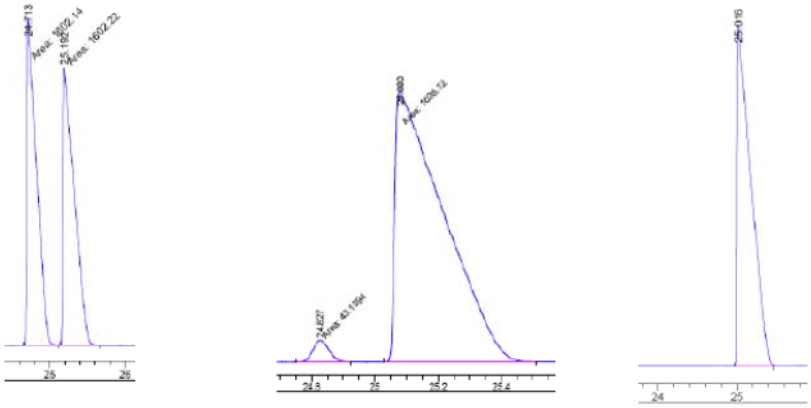


(*S*,*E*)-4-methyldec-3-ene-1,2-diol. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.85 (3H, t, *J* = 7.0 Hz), 1.22-1.29 (6H, m), 1.33-1.39 (2H, m), 1.67 (3H, d, *J* = 1.0 Hz), 1.97 (2H, t, *J* = 7.0 Hz), 1.92 (2H, br s), 3.44 (1H, dd, *J* = 11.0 Hz, 8.0 Hz), 3.53 (1H, dd, *J* = 11.0 Hz, 3.5 Hz), 4.45 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 4.5 Hz), 5.11 (1H, dd, *J* = 8.5 Hz, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 16.7, 22.6, 27.6, 28.9, 31.7, 39.6, 66.4, 69.4, 122.6, 141.7; IR (neat): 3362.7 (br m), 2995.7 (m), 2926.3 (s), 2856.8 (m), 1458.0 (m), 1379.0 (m), 1075.2 (m), 1027.1 (m), 873.6 (w) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{26}NO_2$ [M+NH_4]: calculated: 204.1964, found: 204.1962. $[\alpha]^{25}_D$ = +8.27 (*c* = 0.94, ethyl acetate, *l* = 50 mm).

Proof of Stereochemistry.

The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic p-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.

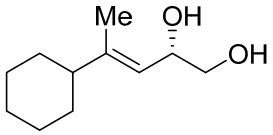


racemic

derived from reaction product

authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.827	MM	0.0570	43.13941	12.60305	2.58124
2	25.080	MM	0.1765	1628.12439	153.72232	97.41876



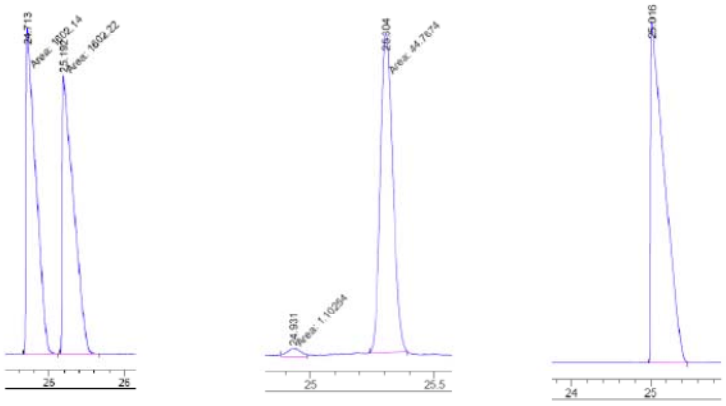
(*S,E*)-4-cyclohexylpent-3-ene-1,2-diol. The diboration was performed according to the representative procedure with (*E*)-penta-2,4-dien-2-ylcyclohexane (50.0 mg, 332 μmol), $Pt(dba)_3$ (8.9 mg, 9.9 μmol), (*R,R*)-3,5-di-*iso*-propylTADDOLPPh (10.8 mg, 12.0 μmol), and $B_2(pin)_2$ (88.7 mg, 349 μmol) in tetrahydrofuran (3.3 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (40-65% ethyl acetate/hexane, R_f = 0.18 in 50% ethyl acetate in hexane, stain in PMA) to afford a white solid (50.1 mg, 82%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06-1.28 (6H, m), 1.64-.167 (2H, m), 1.66 (3H, s), 1.73 (2H, d, *J* = 13.0 Hz), 1.82 (1H, dddd, *J* = 11.0 Hz, 11.0 Hz, 2.5 Hz, 2.5 Hz), 2.16 (1H, br s), 2.26 (1H, br s), 3.43 (1H, dd, *J* = 11.0 Hz, 8.0 Hz), 3.53 (1H, dd, *J* = 11.5 Hz, 3.5 Hz), 4.46 (1H, ddd, *J* = 8.5 Hz, 8.5 Hz, 4.0 Hz), 5.11 (1H, d, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 15.1, 26.2, 26.55, 26.56, 31.67, 31.69, 47.2, 66.4, 69.4, 121.0, 146.4; IR (neat): 3405.5 (m), 3287.9 (br m), 2920.5 (s), 2848.2 (m), 1461.8 (w), 1444.6 (m), 1384.4 (w), 1343.4 (w), 1264.0 (w), 1214.3 (w), 1103.3 (m), 1079.1 (m), 1057.6 (m), 1026.7 (s), 978.2 (w), 990.7 (m), 876.4 (m), 827.2 (m), 704.5 (br m), 641.0 (m), 550.8 (m) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{24}NO_2$ [M+NH_4]: calculated: 202.1807, found: 202.1813. $[\alpha]^{25}_D$ = +17.7 (c = 2.12, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry.

The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic

material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.

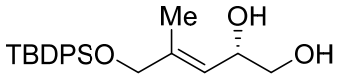


racemic

derived from reaction product

authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.931	MM	0.0619	1.10254	2.96929e-1	2.40363
2	25.304	MM	0.0580	44.76743	12.87476	97.59637



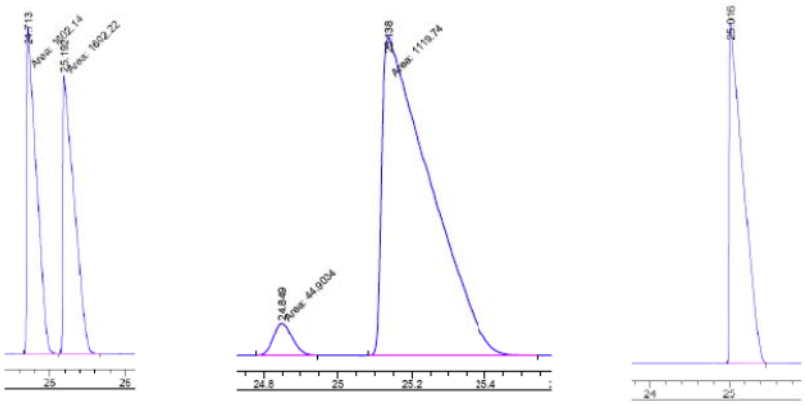
(*S,E*)-5-((tert-butyldiphenylsilyl)oxy)-4-methylpent-3-ene-1,2-diol. The diboration was performed according to the representative procedure with (*E*)-tert-butyl(2- methylpenta-2,4-dienyloxy)diphenylsilane (100.0 mg, 297.1 μmol), $Pt(dba)_3$ (8.0 mg, 8.9 μmol), (*R,R*)-3,5-di-iso-propylphenylTADDOLPPh (9.7 mg, 10 μmol), and $B_2(pin)_2$ (79.0 mg, 311 μmol) in tetrahydrofuran (3.0 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (35-65% ethyl acetate/ hexanes, R_f = 0.20 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil that was inseparable from pinacol (127.8 mg, 1:1 product:pinacol = 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.04 (9H, s), 1.63 (3H, s), 1.92 (2H, br s), 3.46 (1H, dd, *J* = 11.0 Hz, 8.0 Hz), 3.53 (1H, dd, *J* = 10.5 Hz, 3.0 Hz), 4.04 (2H, s), 4.49 (1H, ddd, *J* = 8.5 Hz, 8.5 Hz, 4.0 Hz), 5.45 (1H, ddd, *J* = 8.5 Hz, 1.5 Hz, 1.5 Hz), 7.34-7.43 (6H, m), 7.62-7.66 (4H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.0, 19.2, 26.8, 66.3, 68.0, 69.1, 122.2, 127.6, 129.7, 133.5, 133.6, 135.52, 135.53, 139.5; IR (neat): 3361.5 (br m), 2929.9 (m), 2856.5 (m), 1471.8 (w), 1427.4 (m), 1389.4 (w), 1362.0 (w), 1109.3 (s), 1070.1 (s), 1028.0 (m), 823.9 (m), 740.0 (m), 700.9 (s), 614.9 (w), 503.9 (s), cm^{-1}. HRMS-(ESI+) for $C_{22}H_{34}NO_3Si$ [M+NH_4]: calculated: 388.2299, found: 388.2303. $[\alpha]^{25}_D$ = +13.7 (*c* = 2.85, CHCl*3*, *l* = 50 mm).

Proof of Stereochemistry.

The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic

material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.

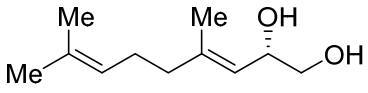


racemic

derived from reaction product

authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.849	MM	0.0588	44.90338	12.72177	3.85554
2	25.138	MM	0.1499	1119.74133	124.50630	96.14446



(*S,E*)-4,8-dimethylnona-3,7-diene-1,2-diol. The diboration was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (75.0 mg, 499 μmol), $Pt(dba)_3$ (13.4 mg, 15.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (16.3 mg, 18.0 μmol), and $B_2(pin)_2$ (133.1 mg, 524.1 μmol) in tetrahydrofuran (5.0 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (20-40% ethyl acetate/hexanes, R_f = 0.13 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil that was inseparable from pinacol (80.4 mg, 9.7:1 product:pinacol = 82%). ^{1}H NMR (500 MHz, CDCl3): δ 1.58 (3H, s), 1.66 (3H, s), 1.69 (3H, s), 1.99-2.02 (2H, m), 2.06-2.10 (2H, m), 3.46 (1H, dd, *J* = 11.0 Hz, 8.0 Hz), 3.53 (1H, dd, *J* = 11.0 Hz, 4.0 Hz), 4.46 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 3.5 Hz), 5.05 (1H, t, *J* = 6.0 Hz), 5.13 (1H, d, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, CDCl3): δ 16.8, 17.7, 25.6, 26.3, 39.5, 66.4, 69.4, 123.0, 123.7, 131.9, 141.3; IR (neat): 3349.0 (br m), 2967.7 (w), 2916.0 (m), 2857.6 (w), 1444.1 (w), 1377.9 (w), 1074.75 (m), 1021.0 (m) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{19}O$ [M+H-H_2O]: calculated: 167.1436, found: 167.1442. $[\alpha]^{25}_D$ = +25.9 (*c* = 0.33, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry.

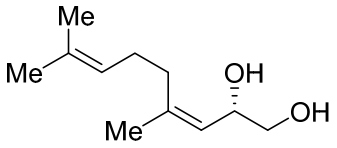
The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic p-toluenesulfonic acid to afford the acetonide for GLC analysis as shown below. The analogous racemic material was prepared by mixing approximate equimolar amounts of the product made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral GLC (β-Dex 120, Supelco, 90 °C for 5 min, ramp 2 °C/min to 160 °C, 20 psi, s/r = 35:1) - analysis of (E)-4-(2,6-dimethylhepta-1,5-dien-1-yl)-2,2-dimethyl-1,3-dioxolane.

mixture of products from **(*R*,*R*)-3.44** and **(*S*,*S*)-3.44**

derived from reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	34.664	BB	0.0776	21.40870	4.41401	2.19023
2	34.944	MM	0.1041	956.05499	153.13448	97.80977

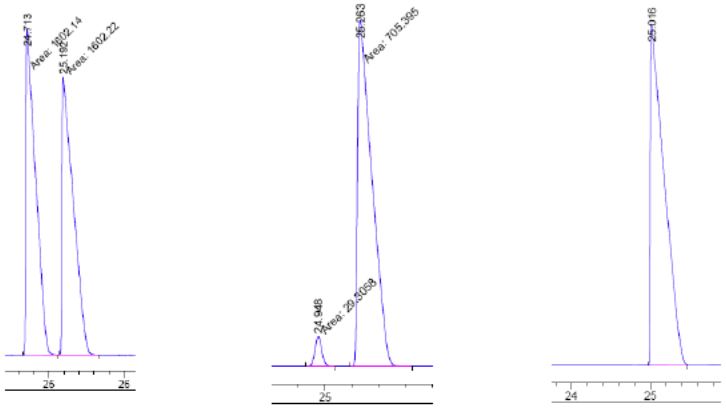


(*S*,*Z*)-4,8-dimethylnona-3,7-diene-1,2-diol. The diboration was performed according to the representative procedure with (*Z*)-4,8-dimethylnona-1,3,7-triene (30.0 mg, 199 μmol), $Pt(dba)_3$ (5.4 mg, 6.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (6.5 mg, 7.2 μmol), and $B_2(pin)_2$ (53.2 mg, 209 μmol) in tetrahydrofuran (2.0 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (20-50% ethyl acetate/hexanes, R_f = 0.24 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil that was inseparable from pinacol (40.7 mg, 2.2:1 product:pinacol = 86%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.59 (3H, s), 1.67 (3H, s), 1.73 (3H, d, *J* = 1.0 Hz), 1.99 (2H, br s), 2.02-2.13 (4H, m), 3.45 (1H, dd, *J* = 11.5 Hz, 8.0 Hz), 3.54 (1H, dd, *J* = 11.5 Hz, 4.0 Hz), 4.42 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 4.0 Hz), 5.06-5.10 (1H, m), 5.16 (1H, dd, *J* = 9.0 Hz, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.7, 23.4, 25.6, 26.5, 32.5, 66.6, 68.9, 123.7, 124.1, 132.6, 141.5; IR (neat): 3362.7 (br m), 2967.2 (m), 2917.8 (s), 2858.5 (m), 1668.5 (w), 1446.4 (m), 1376.4 (m), 1152.5 (w), 1075.0 (s), 1021.4 (s), 873.0 (m), 835.1 (m) cm^{-1}; HRMS-(ESI+) for $C_{11}H_{19}O$ [M+H-H_2O]: calculated: 167.1436, found: 167.1442. $[\alpha]^{25}_D$ = +13.3 (*c* =2.10, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry.

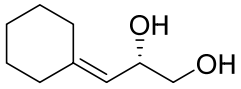
The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic *p*-toluenesulfonic acid. The acetonide was then subjected to ozonolysis/reduction, followed by acylation of the primary alcohol. The authentic material was prepared by acylation of (*S*)-isopropylideneglycerol, which was purchased from Aldrich.

Chiral GLC (β-Dex 120, Supelco, 60 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of (2,2-dimethyl-1,3-dioxolan-4-yl)methyl acetate.



racemic | derived from reaction product | authentic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.948	MM	0.0595	29.30579	8.21093	3.98881
2	25.263	MM	0.1234	705.39478	95.27135	96.01119

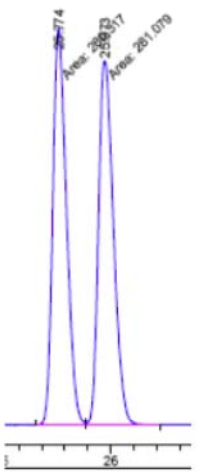


(*S*)-3-cyclohexylidenepropane-1,2-diol. The diboration was performed according to the representative procedure with allylidenecyclohexane (50.0 mg, 409 μmol), $Pt(dba)_3$ (11.0 mg, 12.3 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (13.4 mg, 14.7 μmol), and $B_2(pin)_2$ (109.1 mg, 429.6 μmol) in tetrahydrofuran (4.0 mL, 0.1 M). The crude reaction mixture was purified by column chromatography on silica gel (30-60% ethyl acetate/hexanes, R_f = 0.18 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a white solid (49.8 mg, 78%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.44-1.57 (6H, m), 2.07 (2H, t, *J* = 6.0 Hz), 2.14-2.21 (2H, m), 2.27 (2H, br s), 3.44 (1H, dd, *J* = 11.0 Hz, 8.0 Hz), 3.52 (1H, dd, *J* = 11.0 Hz, 3.5 Hz), 4.48 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 4.0 Hz), 5.06 (1H, d, *J* = 8.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 26.5, 27.9, 28.4, 29.5, 37.0, 66.7, 68.6, 119.9, 145.7; IR (neat): 3379.4 (br m), 2925.8 (s), 2853.2 (m), 1447.4 (w), 1070.8 (w), 1025.2 (w) cm^{-1}; HRMS-(ESI+) for $C_9H_{15}O$ [M+H-H_2O]: calculated: 139.1123, found: 139.1120. $[\alpha]^{25}_D$ = +9.46 (*c* = 1.51, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry.

The enantioselectivity was determined by treating the resulting 1,2-diol with 2,2-dimethoxypropane and catalytic p-toluenesulfonic acid to afford the acetonide for GLC analysis as shown below. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry be assigned by analogy.

Chiral GLC (β-Dex 120, Supelco, 90 °C for 5 min, ramp 3 °C/min to 160 °C, 20 psi, s/r = 35:1) - analysis of 4-(cyclohexylidenemethyl)-2,2-dimethyl-1,3-dioxolane.



racemic

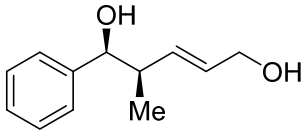
derived from
reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	25.720	BV	0.0524	30.27500	8.96470	2.80138
2	25.849	VB	0.0781	1050.44067	180.07285	97.19862

2.7.12 Representative Procedure for Diboration/Allylation/Oxidation with Cis-Dienes

To an oven-dried 6-dram vial with magnetic stir bar in the dry box was added $Pt(dba)_3$ (12.7 mg, 14.1 μmol), (*R,R*)-3,5-di-*i*-butylphenyl-TADDOLPPh (28.8 mg, 28.3 μmol), $B_2(pin)_2$ (119.7 mg, 471.2 μmol) and tetrahydrofuran (4.7 mL, [substrate] = 0.1 M). The vial was sealed with a polypropylene cap, removed from the dry box, and heated to 80 °C in an oil bath for 20 min. The vial was cooled to room temperature, returned to the dry box and charged with (*Z*)-penta-1,3-diene (32.0 mg, 471 μmol). The vial was sealed, removed from the dry box, and stirred at 60 °C for 12 h. The reaction mixture was then cooled to ambient temperature and the solvent was removed *in vacuo*. The vial was sealed, returned to the dry box and charged with dichloromethane (1.0 mL) and freshly distilled benzaldehyde (25.0 mg, 235 μmol). The reaction was allowed to stir at room temperature for 12 h at which time the reaction mixture was cooled to 0 °C (ice/water) and charged with tetrahydrofuran (2.0 mL), 3 M sodium hydroxide solution (2 mL), and 30 wt% hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 12 h at which time the vial was cooled to 0 °C (ice/water). Saturated aqueous sodium thiosulfate (2 mL) was carefully added dropwise. The reaction mixture was diluted with ethyl acetate and the aqueous and organic layers were separated. The aqueous layer was rinsed with ethyl acetate (3 x 15 mL), and the combined organics were dried over Na_2SO_4, filtered, and volatiles were removed *in vacuo*. The crude reaction mixture was purified on silica gel (30-60% ethyl acetate/hexanes, R_f = 0.23 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (32.6 mg, 72% yield).

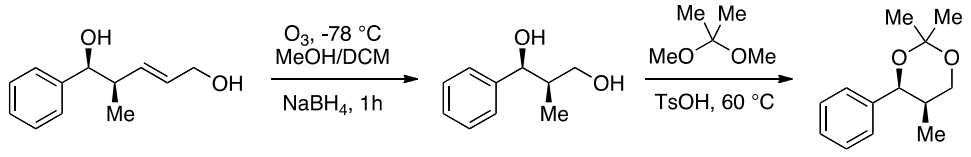
2.7.13 Characterization and Proof of Stereochemistry (Table 2.7)



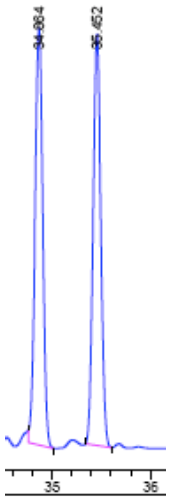
(4*R*,5*S*,*E*)-4-methyl-5-phenylpent-2-ene-1,5-diol. ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.01 (3H, d, *J* = 6.6 Hz), 1.23 (2H, br s), 2.56-2.60 (1H, m), 4.05 (2H, d, *J* = 3.6 Hz), 4.60 (1H, d, *J* = 5.4 Hz), 5.61-5.62 (2H, m), 7.26-7.30 (3H, m), 7.31-7.33 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.5, 43.4, 63.6, 77.6, 126.5, 127.5, 128.1, 130.1, 134.3, 142.6; IR (neat): 3355.9 (br m), 2967.3 (w), 2929.1 (w), 2873.0 (w), 1719.7 (w), 1452.3 (m), 1370.6 (w), 1259.5 (w), 1055.1 (w), 973.2 (s), 755.1 (m), 700.9 (s) cm^{-1}; HRMS-(ESI+) for $C_{12}H_{20}NO_2$ [M+NH_4]: calculated: 210.1494, found: 210.1492. $[\alpha]^{25}_D$ = -14.0 (*c* = 0.90, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry:

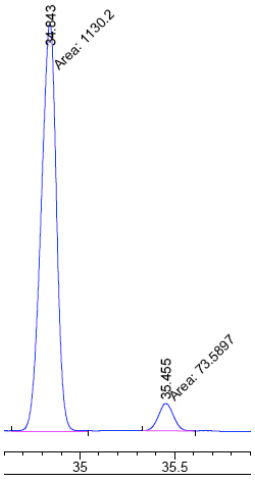
The enantioselectivity was determined by subjecting the 1,5-diol to ozonolysis/reduction, followed by acetonide protection (as shown below) for GLC analysis. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The major diastereomer was determined by measuring the coupling constant of the carbinol hydrogen in the six-membered ring ketal below by ^{1}H NMR: *J* = 4.0 Hz, proving *syn* stereochemistry.



Chiral GLC (β-Dex 120, Supelco, 90 °C for 5 min, ramp 2 °C/min to 150 °C, 20 psi, s/r = 35:1) - analysis of 2,2,5-trimethyl-4-phenyl-1,3-dioxane.



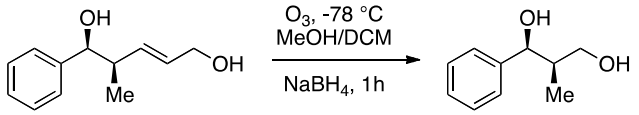
racemic



derived from reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	34.843	MM	0.0941	1130.20166	200.08630	93.88684
2	35.455	MM	0.0918	73.58967	13.36460	6.11316

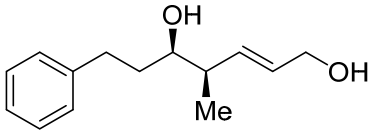
The absolute stereochemistry was determined by subjecting the 1,5-diol to ozonolysis/reduction. The specific rotation of the resulting 1,3-diol ($[\alpha]^{24}_D$ = -57.2 (*c* = 0.16, $CHCl_3$, *l* = 50 mm)) was compared to literature values ($[\alpha]^{24}_D$ = -51.6 (c = 0.15, $CHCl_3$)).[42]



$[\alpha]^{24}_D$ = -57.2 (c=0.16, $CHCl_3$)

The olefin geometry of the 1,5-diol was determined to be *trans* by measuring the coupling constants of the vinylic hydrogens from the ^{1}H NMR taken in benzene: ^{1}H NMR (500 MHz, C_6D_6): δ 0.97 (3H, d, *J* = 6.5 Hz), 2.42 (1H, ddq, *J* = 13.0 Hz, 13.0 Hz, 7.0 Hz), 3.79 (2H, dd, *J* = 5.5 Hz, 1.0 Hz), 4.38 (1H, d, *J* = 5.5 Hz), 5.44 (1H, dt, *J* = 16.0 Hz, 5.5 Hz, 5.5 Hz), 5.54 (1H, dd, *J* = 15.5 Hz, 7.5 Hz), 7.06-7.10 (1H, m), 7.18-7.23 (3H, m).

[42] Crimmins, M. T.; King, B. W.; Tabet, E. A.; Chaudhary, K. *J. Org. Chem.* **2001**, *66*, 894.



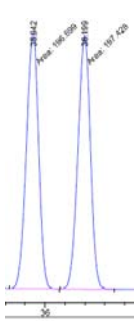
4*R*,5*R*,*E*)-4-methyl-7-phenylhept-2-ene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*Z*)-penta-1,3-diene (40.6 mg, 596 μmol), $Pt(dba)_3$ (16.1 mg, 17.9 μmol), (*R,R*)-3,5-di-*i*-butylphenylTADDOLPPh (36.5 mg, 35.8 μmol), $B_2(pin)_2$ (151.9 mg, 596.2 μmol) in tetrahydrofuran (6.0 mL, 0.1 M), freshly distilled hydrocinnamaldehyde (40.0 mg, 298 μmol) and dichloromethane (1.2 mL). The crude reaction mixture was purified on silica gel (30-50% ethyl acetate/hexanes, R_f = 0.19 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (45.9 mg, 70%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.02 (3H, d, *J* = 6.6 Hz), 1.64-1.70 (1H, m), 1.76-1.82 (1H, m), 2.30 (1H, dd, *J* = 12.0 Hz, 6.6 Hz), 2.63 (1H, ddd, *J* = 13.8 Hz, 9.6 Hz, 6.6 Hz), 2.83 (1H, ddd, *J* = 13.8 Hz, 9.6 Hz, 4.8 Hz), 3.50 (1H, ddd, *J* = 9.0 Hz, 5.4 Hz, 3.0 Hz), 4.11 (2H, d, *J* = 5.4 Hz), 5.61-5.71 (2H, m), 7.15-7.19 (3H, m), 7.23-7.29 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.7, 32.5, 35.9, 42.4, 63.6, 74.3, 125.9, 128.41, 128.44, 130.0, 134.5, 142.1 ; IR (neat): 3350.7 (br m), 3024.3 (w), 2920.9 (m), 2855.7 (w), 1718.7 (w), 1495.8 (w), 1453.3 (m), 1377.1 (w), 1315.7 (w), 1259.9 (w), 1066.4 (s), 1028.2 (s), 973.4 (m), 920.0 (w), 870.4 (w), 746.6 (m), 699.8 (s) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{24}NO_2$ [M+NH_4]: calculated: 238.1807, found: 238.1801. $[\alpha]^{25}_D$ = +26.5 (*c* = 0.98, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The enantioselectivity was determined by subjecting the 1,5-diol to ozonolysis/reduction, followed by acetonide protection. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The major

diastereomer was determined by measuring the coupling constant of the carbinol hydrogen in the six-membered ring ketal below by ^{1}H NMR: J = 3.5 Hz, proving *syn* stereochemistry. The absolute stereochemistry was assigned by analogy.

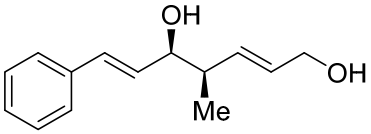
Chiral GLC (β-Dex 120, Supelco, 90 °C for 5 min, ramp 3 °C/min to 180 °C, 20 psi, s/r = 35:1) - analysis of 2,2,5-trimethyl-4-phenethyl-1,3-dioxane.



racemic

derived from reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	35.970	MM	0.0765	1128.57434	245.91464	94.05849
2	36.199	MM	0.0724	71.29002	16.40378	5.94151



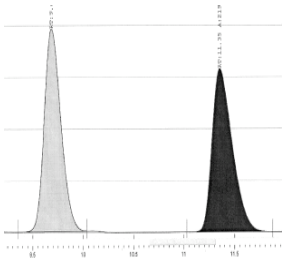
(2*E*,4*R*,5*R*,6*E*)-4-methyl-7-phenylhepta-2,6-diene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*Z*)-penta-1,3-diene (31.0 mg, 454 μmol), $Pt(dba)_3$ (12.2 mg, 13.6 μmol), (*R,R*)-3,5-di-*i*-butylphenylTADDOLPPh (27.8 mg, 27.2 μmol), $B_2(pin)_2$ (115.3 mg, 454.0 μmol) in tetrahydrofuran (4.5 mL, 0.1 M), freshly distilled cinnamaldehyde (30.0 mg, 227 μmol), and dichloromethane (0.9 mL). The crude reaction mixture was purified on silica gel (30-50% ethyl acetate/hexanes, R_f = 0.16 in 50% ethyl acetate/hexanes, stain in PMA) to afford a white solid (32.7 mg, 66%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.07 (3H, d, *J* = 6.6 Hz), 1.22 (2H, br s), 2.46-2.51 (1H, m), 4.12 (2H, d, *J* = 4.2 Hz), 4.20 (1H, dd, *J* = 5.4 Hz, 5.4 Hz), 5.69-5.76 (2H, m), 6.20 (1H, dd, *J* = 15.6 Hz, 6.6 Hz), 6.57 (1H, d, *J* = 15.6 Hz), 7.21-7.23 (1H, m), 7.29-7.33 (2H, m), 7.35-7.38 (2H, m); ^{13}C NMR (150 MHz, $CDCl_3$): δ 15.2, 42.5, 63.6, 76.0, 126.5, 127.7, 128.6, 129.8, 130.6, 131.4, 133.7, 136.7; IR (neat): 3362.1 (br m), 2957.9 (w), 2924.8 (m), 2869.3 (w), 2854.6 (w), 1715.4 (w), 1494.7 (w), 1450.5 (m), 1377.4 (w), 1070.1 (w), 968.8 (s), 750.0 (m), 695.1 (m); HRMS-(ESI+) for $C_{14}H_{22}NO_2$ [M+NH_4]: calculated: 236.1651, found: 236.1653. $[\alpha]^{25}_D$ = -17.4 (*c* = 0.70, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

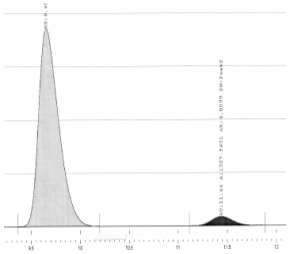
The enantioselectivity was determined by SFC analysis of the reaction product. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy. The olefin geometry of the 1,5-diol was determined to be *trans* by measuring the coupling constants of the vinylic hydrogens from the ^{1}H NMR taken in benzene: ^{1}H NMR (500 MHz, C_6D_6):

δ 1.01 (3H, d, *J* = 9.0 Hz), 2.29 (1H, ddd, *J* = 8.5 Hz, 8.5 Hz, 8.5 Hz), 3.83 (2H, d, *J* = 7.0 Hz), 3.97 (1H, ddd, *J* = 8.0 Hz, 2.0 Hz, 2.0 Hz), 5.53 (1H, dt, *J* = 20.0 Hz, 5.5 Hz, 5.5 Hz), 5.63 (1H, dd, *J* = 19.5 Hz, 9.0 Hz), 6.13 (1H, dd, *J* = 20.0 Hz, 7.0 Hz), 6.51 (1H, d, *J* = 20.0 Hz), 7.03-7.09 (1H, m), 7.11-7.13 (2H, m), 7.26-7.28 (2H, m).

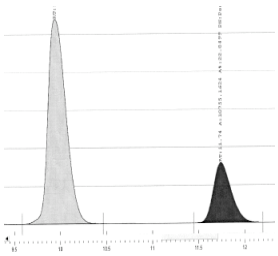
Chiral SFC (AD-H, Chiraldex, 5 mL/min, 5% MeOH, 100 bar, 35 °C) - analysis of reaction product.



racemic

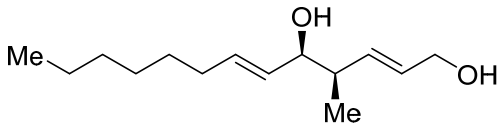


derived from reaction product



coinjection of diboration product + racemic

Peak No	% Area	Area	RT (min)	Height (mV)
1	95.1901	26272.8013	9.65	1850.4523
2	4.8099	1327.5631	11.44	86.6913

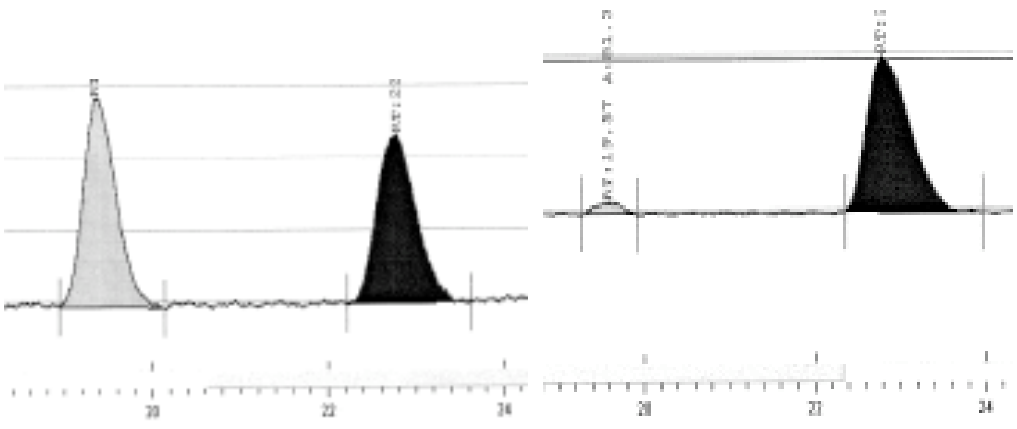


(2*E*,4*R*,5*R*,6*E*)-4-methyltrideca-2,6-diene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*Z*)-1,3-pentadiene (30.0 mg, 440 μmol), $Pt(dba)_3$ (11.8 mg, 13.2 μmol), (*R,R*)-3,5-di-*i*-butylphenylTADDOLPPh (27.0 mg, 26.4 μmol), $B_2(pin)_2$ (117.4 mg, 462.4 μmol) in tetrahydrofuran (4.4 mL, 0.1 M), freshly distilled nonenal (31.0 mg, 220 μmol) and dichloromethane (0.9 mL). The crude reaction mixture was purified on silica gel (25-40% ethyl acetate/hexanes, R_f = 0.37 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (32.7 mg, 66%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 6.5 Hz), 0.99 (3H, d, *J* = 7.0 Hz), 1.23-1.34 (6H, m), 1.47 (2H, br s), 2.02 (2H, dd, *J* = 14.0 Hz, 7.0 Hz), 2.36 (1H, ddd, *J* = 6.5 Hz, 6.5 Hz, 6.5 Hz), 3.95 (1H, br s), 4.11 (2H, br s), 5.42 (1H, dd, *J* = 15.5 Hz, 7.0 Hz), 5.62 (1H, dd, *J* = 15.5 Hz, 6.5 Hz), 5.66-5.72 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.3, 15.5. 22.8, 29.0, 29.4, 31.9, 32.5, 42.5, 64.0, 76.5, 130.3, 130.4, 133.7, 134.3; IR (neat): 3355.2 (m), 2924.7 (s), 2854.7 (m), 1456.9 (w), 1003.2 (m), 968.9 (s) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{30}NO_2$ [M+NH_4]: calculated: 244.2276, found: 244.2271. $[\alpha]^{25}_D$ = +12.7 (*c* = 0.54, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The enantioselectivity was determined by treating the 1,5-diol with benzoic anhydride and Et_3N to make the mono(benzoate) for SFC analysis. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

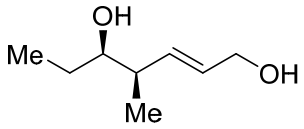
Chiral SFC (AD-H, Chiraldex, 3 mL/min, 3% MeOH, 100 bar, 35 °C) - analysis of the mono(benzoate) of the reaction product.



racemic

derived from reaction product

Peak No	% Area	Area	RT (min)	Height (mV)
1	4.3907	81.3506	19.57	3.7672
2	95.6093	1771.4541	22.78	50.2873

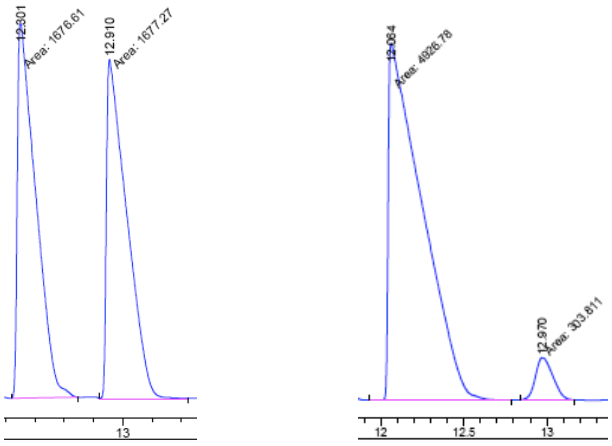


(4*R*,5*R*,*E*)-4-methylhept-2-ene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*Z*)-penta-1,3-diene (58.6 mg, 860 μmol), $Pt(dba)_3$ (23.2 mg, 25.8 μmol), (*R,R*)-3,5-di-*i*-butylphenylTADDOLPPh (52.7 mg, 51.6 μmol), $B_2(pin)_2$ (218.6 mg, 860.8 μmol) in tetrahydrofuran (2.9 mL, 0.3 M), freshly distilled propionaldehyde (25.0 mg, 430 μmol), and dichloromethane (1.7 mL). The crude reaction mixture was purified on silica gel (30-50% ethyl acetate/hexanes, R_f = 0.15 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (45.3 mg, 73%**).** ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (3H, t, *J* = 7.0 Hz), 1.00 (3H, d, *J* = 7.0 Hz), 1.32-1.41 (1H, m), 1.48-1.56 (1H, m), 1.69 (2H, br s), 2.25-2.31 (1H, m), 3.39 (1H, dddd, *J* = 4.5 Hz, 4.5 Hz 4.5 Hz, 4.5 Hz), 4.10 (2H, d, *J* = 4.5 Hz), 5.62-5.71 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 10.4, 14.3, 26.9, 41.7, 63.6, 76.4, 129.6, 135.1; IR (neat): 3333.4 (br m), 2962.8 (w), 2931.0 (w), 2874.7 (w), 1457.3 (w), 1376.1 (w), 1081.6 (w), 1022.8 (w), 1003.9 (m), 971.9 (s), 704.7 (w) cm^{-1}; HRMS-(ESI+) for $C_8H_{20}NO_2$ $[M+NH_4]$: calculated: 162.1494, found: 162.1499. $[\alpha]^{25}_D$ = +26.7 (*c* = 0.50, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The enantioselectivity was determined by subjecting the 1,5-diol to ozonolysis/reduction, followed by acetonide protection. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

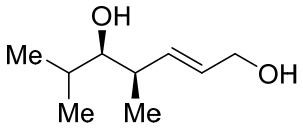
Chiral GLC (β-Dex 120, Supelco, 70 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) - analysis of 4-ethyl-2,2,5-trimethyl-1,3-dioxane.



racemic

derived from reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	12.064	MM	0.2343	4926.78467	350.49905	94.19166
2	12.970	MM	0.1209	303.81058	41.88768	5.80834

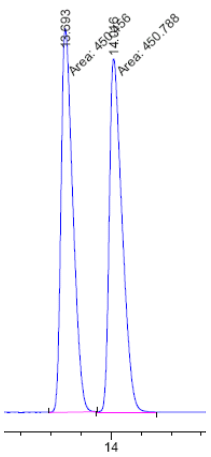


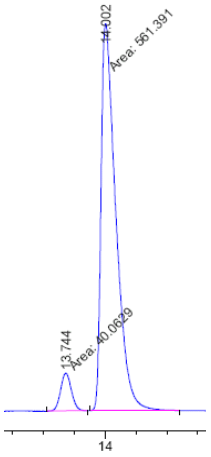
(4*R*,5*R*,*E*)-4,6-dimethylhept-2-ene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*Z*)-1,3-pentadiene (56.6 mg, 830 μmol), $Pt(dba)_3$ (22.4 mg, 24.9 μmol), (*R,R*)-3,5-di-*i*-butylphenylTADDOLPPh (50.9 mg, 49.8 μmol), $B_2(pin)_2$ (221.5 mg, 872.4 μmol) in tetrahydrofuran (8.3 mL, 0.1 M), freshly distilled isobutyraldehyde (30.0 mg, 415 μmol) and dichloromethane (1.6 mL). The crude reaction mixture was purified on silica gel (25-40% ethyl acetate/hexanes, R_f = 0.28 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (40.8 mg, 62%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.90 (6H, dd, *J* = 8.5 Hz, 6.5 Hz), 1.02 (3H, d, *J* = 8.0 Hz), 1.39 (2H, br s), 1.73 (1H, ddd, *J* = 33.0 Hz, 17.0 Hz, 8.5 Hz), 2.36 (1H, ddd, *J* = 15.5 Hz, 15.5 Hz, 7.7 Hz), 3.15 (1H, dd, *J* = 7.0 Hz, 7.0 Hz), 4.10 (2H, d, *J* = 5.5 Hz), 5.62-5.71 (2H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 14.1, 17.0, 19.7, 30.6, 39.3, 63.7, 79.8, 129.1, 135.8; IR (neat): 3330.8 (m), 2959.2 (m), 2924.8 (s), 1459.0 (m),1085.5 (m), 970.6 (s) cm^{-1}; HRMS-(ESI+) for $C_9H_{22}NO_2$ [M+NH_4]: calculated: 176.1650, found: 176.1649. $[\alpha]^{25}_D$ = +10.54 (*c* = 0.57, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

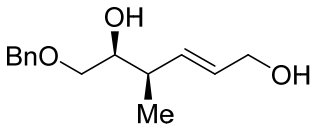
The enantioselectivity was determined by subjecting the 1,5-diol to ozonolysis/reduction, followed by acetonide protection. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral GLC (β-Dex 120, Supelco, 70 °C for 5 min, ramp 3 °C/min to 140 °C, 20 psi, s/r = 35:1) - analysis of 4-isopropyl-2,2,5-trimethyl-1,3-dioxane.





Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	13.744	MM	0.0813	40.06293	8.21339	6.66101
2	14.002	MM	0.1108	561.39135	84.41813	93.33899

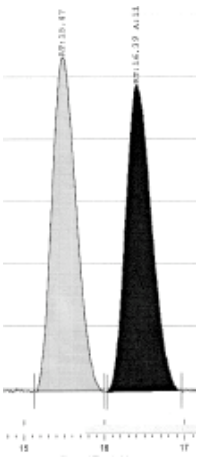


(4*R*,5*S*,*E*)-6-(benzyloxy)-4-methylhex-2-ene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*Z*)-1,3-pentadiene (30.0 mg, 440 μmol), $Pt(dba)_3$ (11.8 mg, 13.2 μmol), (*R,R*)-3,5-di-*i*-butylphenylTADDOLPPh (27.0 mg, 26.4 μmol), $B_2(pin)_2$ (117.4 mg, 462.4 μmol) in tetrahydrofuran (4.4 mL, 0.1 M), freshly distilled benzyloxyacetaldehyde (33.0 mg, 220.2 μmol) and dichloromethane (0.9 mL). The crude reaction mixture was purified on silica gel (35-50% ethyl acetate/hexanes, R_f = 0.19 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (37.5 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (3H, d, *J* = 7.0 Hz), 1.23 (2H, br s), 2.34 (1H, ddd, *J* = 20.5 Hz, 13.5 Hz, 7.0 Hz), 3.37 (1H, dd, *J* = 9.5 Hz, 7.5 Hz), 3.52 (1H, dd, *J* = 9.5 Hz, 3.0 Hz), 3.63 (1H, ddd, *J* = 8.0 Hz, 8.0 Hz, 3.5 Hz), 4.07 (2H, d, *J* = 4.5 Hz), 4.52 (2H, dd, *J* = 18.5 Hz, 11.5 Hz), 5.64-5.66 (2H, m), 7.26-7.36 (5H, m); ^{13}C NMR (100 MHz, $CDCl_3$): δ 15.9, 39.6, 63.6, 72.6, 73.4, 73.6, 127.6, 127.8, 128.5, 129.7, 134.1, 137.9; IR (neat): 3380.3 (s), 2924.6 (s), 2858.7 (s), 1719.1 (w), 1453.9 (m), 1078.9 (s), 974.3 (s), 698.6 (m) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{24}NO_2$ [M+NH_4]: calculated: 254.1756, found: 254.11755. $[\alpha]^{25}_D$ = +13.59 (*c* = 0.48, $CHCl_3$, *l* = 50 mm).

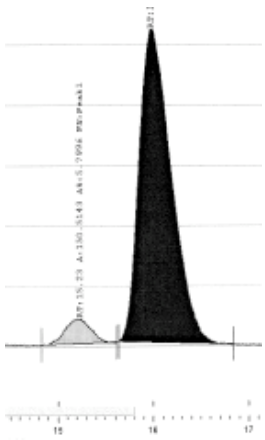
Analysis of Stereochemistry:

The enantioselectivity was determined SFC analysis of the reaction product. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

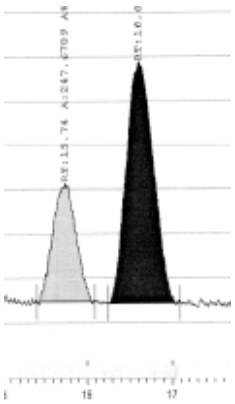
Chiral SFC (AD-H, Chiraldex, 100 bar, 5 mL/min, 4% MeOH, 35 °C)- analysis of reaction product.



racemic

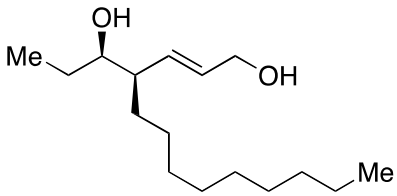


derived from reaction product



coinjection of diboration product + racemic

Peak No	% Area	Area	RT (min)	Height (mV)
1	5.7996	150.5143	15.23	8.1557
2	94.2004	2444.7506	15.98	103.8991



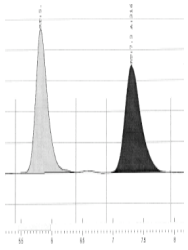
(4*R*,5*R*,*E*)-4-nonylhept-2-ene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*Z*)-trideca-1,3-diene (124.2 mg, 688.7 μmol), $Pt(dba)_3$ (18.6 mg, 20.7 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (32.9 mg, 41.3 μmol), $B_2(pin)_2$ (174.9 mg, 688.7 μmol) in tetrahydrofuran (2.3 mL, 0.3 M), distilled propionaldehyde (20.0 mg, 344.3 μmol), and dichloromethane (1.4 mL), followed by oxidation to afford an inseparable 1:1 mixture of the 1,2-diol and diboration/allylation product. 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 2h, 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 concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (20-35% ethyl acetate/hexanes, R_f = 0.33 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (61.7 mg, 70%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 6.5 Hz), 0.94 (3H, t, *J* = 7.5 Hz), 1.22-1.33 (14H, m), 1.48-1.62 (2H, m), 2.07-2.13 (1H, m), 3.38 (1H, ddd, *J* = 9.0 Hz, 5.5 Hz, 3.0 Hz), 4.12 (2H, dd, *J* = 6.0 Hz, 1.5 Hz), 5.47 (1H, dd, *J* = 15.5 Hz, 9.5 Hz), 5.67 (1H, dt, *J* = 15.5 Hz, 6.0 Hz, 6.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 10.4, 14.1, 22.7, 26.8, 27.4, 29.3, 29.59, 29.62, 29.7, 30.1, 31.9, 48.9, 63.6, 76.1, 131.4, 133.2; IR (neat): 3355.5 (br m), 2955.8 (w), 2922.5 (s), 2853.5 (m), 1463.3 (w), 1377.5 (w), 1078.2 (w), 1019.5 (w), 973.0 (m), 721.2 (w) cm^{-1};

HRMS-(ESI+) for $C_{16}H_{36}NO_2$ [M+NH_4]: calculated: 274.2746, found: 274.2751. $[\alpha]^{25}_D$ = -10.42 (*c* = 0.84, $CHCl_3$, *l* = 50 mm).

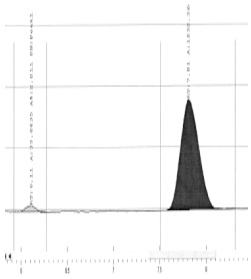
Analysis of Stereochemistry:

The enantioselectivity was determined by subjecting the 1,5-diol to ozonolysis/reduction. The resulting 1,3-diol was treated with benzoic anhydride and Et_3N to make the mono(benzoate) for SFC analysis. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

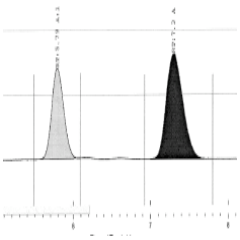
Chiral SFC (AD-H, Chiraldex, 5 mL/min, 5% MeOH, 100 bar, 35 °C) - analysis of 2-(1-hydroxypropyl)undecyl benzoate.



racemic

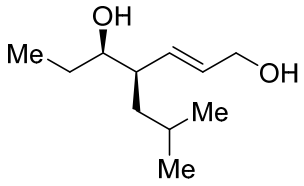


derived from reaction product



coinjection of diboration product + racemic

Peak No	% Area	Area	RT (min)	Height (mV)
1	2.811	35.6435	6.11	4.7413
2	97.189	1232.3661	7.81	89.8004



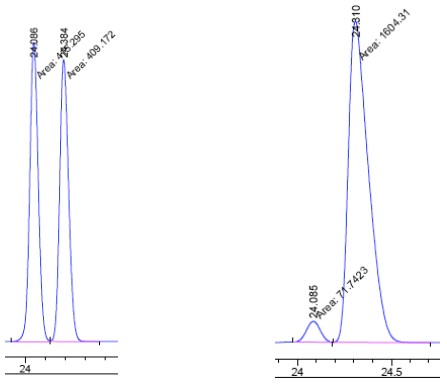
(4*R*,5*R*,*E*)-4-isobutylhept-2-ene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*Z*)-6-methylhepta-1,3-diene (75.9 mg, 688 μmol), $Pt(dba)_3$ (18.6 mg, 20.7 μmol), (*R,R*)-3,5-diethylphenylTADDOLPPh (32.9 mg, 41.3 μmol), $B_2(pin)_2$ (174.9 mg, 688.7 μmol) in tetrahydrofuran (2.3 mL, 0.3 M), distilled propionaldehyde (20.0 mg, 344 μmol), and dichloromethane (1.4 mL), followed by oxidation to afford an inseparable 1:1 mixture of the 1,2-diol and diboration/allylation product. 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 2h, after which time it was diluted with ethyl acetate, and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 x 10.0 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated in vacuo. The crude material was purified by column chromatography on silica gel (20-40% ethyl acetate/hexanes, R_f = 0.23 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (46.3 mg, 72%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.81 (3H, d, *J* = 6.6 Hz), 0.87 (3H, d, *J* = 6.6 Hz), 0.94 (3H, t, *J* = 7.2 Hz), 1.19-1.25 (2H, m), 1.26-1.33 (1H, m), 1.50-1.57 (2H, m), 1.73 (2H, br s), 2.22 (1H, dddd, *J* = 9.6 Hz, 9.6 Hz, 5.4 Hz, 5.4 Hz), 3.36 (1H, ddd, *J* = 8.4 Hz, 4.8 Hz, 3.0 Hz), 4.10 (2H, d, *J* = 5.4 Hz), 5.47 (1H, dd, *J* = 15.6 Hz, 9.6 Hz), 5.67 (1H, dt, *J* = 15.6 Hz, 6.0 Hz, 6.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$): δ 10.5, 21.4, 23.9, 25.3, 26.5, 39.2, 46.5, 63.5, 76.5, 131.3, 133.2; IR (neat): 3351.3 (br m), 2954.7 (m), 2927.4 (m), 2869.3 (w), 1464.6 (w), 1382.8 (w), 1367.0 (w), 1074.2 (m), 1021.7 (m), 972.6 (s), 869.9 (w), 828.3 (w) cm^{-1}; HRMS-(ESI+)

for $C_{11}H_{26}NO_2$ [M+NH_4]: calculated: 204.1964, found: 204.1970. $[\alpha]^{25}_D$ = -21.07 (*c* = 0.58, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The enantioselectivity was determined by subjecting the 1,5-diol to ozonolysis/reduction, followed by acetonide protection. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral GLC (β-Dex 120, Supelco, 70 °C for 5 min, ramp 2 °C/min to 150 °C, 20 psi, s/r = 35:1) - analysis of 4-ethyl-5-isobutyl-2,2-dimethyl-1,3-dioxane.



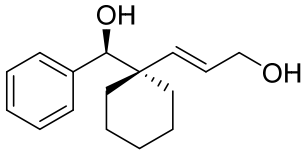
racemic derived from reaction product

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	24.085	MM	0.0856	71.74227	13.96429	4.28043
2	24.310	MM	0.1246	1604.31128	214.56406	95.71957

2.7.14 Representative Procedure for Diboration/Allylation/Oxidation with 4,4-Disubstituted Dienes

To an oven-dried 2-dram vial with magnetic stir bar in the glove box was added $Pt(dba)_3$ (13.4 mg, 15.0 μmol), (*R,R*)-3,5-di-iso-propylphenyl-TADDOLPPh (16.4 mg, 18.0 μmol), $B_2(pin)_2$ (133.1 mg, 524.1 μmol) and toluene (0.5 mL, [substrate] = 1.0 M). The vial was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C in an oil bath for 20 min. The vial was cooled to room temperature, returned to the glove box and charged with (*E*)-4,8-dimethylnona-1,3,7-triene (75.0 mg, 499 μmol). The vial was sealed, removed from the glove box, and stirred at 60 °C for 12 h. The reaction mixture was then cooled to ambient temperature, returned to the glove box and charged with freshly distilled cinnamaldehyde (66.0 mg, 499 μmol). The reaction was brought to the bench and heated to 60 °C in and oil bath and was allowed to stir for 24 h. The reaction mixture was then cooled to 0 °C (ice/water) and charged with tetrahydrofuran (2 mL), 3 M sodium hydroxide solution (2 mL), and 30 wt% hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 h, at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (2 mL) was carefully added dropwise. The reaction mixture was diluted with ethyl acetate (5 mL) and the aqueous and organic layers were separated. The aqueous layer was rinsed with ethyl acetate (3 x 15 mL), and the combined organics were dried over Na_2SO_4, filtered, and volatiles were removed *in vacuo*. The crude reaction mixture was purified by column chromatography on silica gel (20-35% ethyl acetate/ hexanes, R_f = 0.32 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (129.8 mg, 87%).

2.7.15 Characterization and Proof of Stereochemistry (Table 2.8)

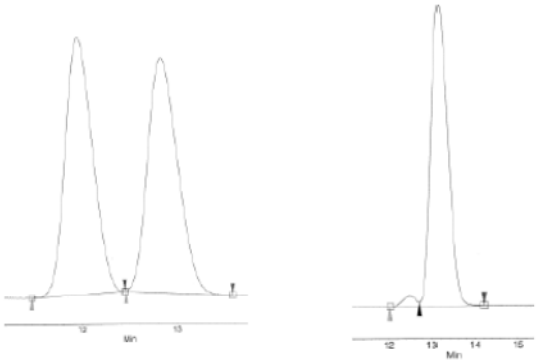


(*S,E*)-3-(1-(hydroxy(phenyl)methyl)cyclohexyl)prop-2-en-1-ol. The diboration was preformed according to the representative procedure with the following modifications: The diboration was carried out in tetrahydrofuran (2.5 mL) with allylidenecyclohexane (30.0 mg, 245 μmol), $Pt(dba)_3$ (6.7 mg, 7.4 μmol), (*R,R*)-3,5-di-*iso*-propylphenyl-TADDOLPPh (13.4 mg, 14.7 μmol), and $B_2(pin)_2$ (65.5 mg, 257 μmol) for 8 h at 60 °C. The reaction mixture was then cooled to ambient temperature and the solvent was removed *in vacuo*. The vial was sealed, returned to the glove box and charged with dichloromethane (0.5 mL) and freshly distilled benzaldehyde (27.4 mg, 257 μmol). The allylation was allowed to stir at rt for 14 h, at which time the reaction was subjected to the standard oxidation conditions. The crude material was purified by column chromatography on silica gel (20-35% ethyl acetate/hexanes, R_f = 0.33 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (37.5 mg, 62%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.05 (2H, m), 1.19-1.49 (8H, m), 1.82 (1H, s), 1.84 (1H, s), 4.12 (2H, d, *J* = 5.5 Hz), 4.29 (1H, s), 5.35 (1H, d, *J* = 16.5 Hz), 5.55 (1H, ddd, *J* = 16.5 Hz, 6.0 Hz, 6.0 Hz), 7.14-7.16 (2H, m), 7.17-7.24 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 22.0, 22.1, 26.2, 31.8, 33.1, 44.6, 64.0, 127.3, 127.4, 128.0, 131.5, 135.6, 140.8; IR (neat): 3364.6 (m), 2927.6 (s), 2853.5 (m), 1450.9 (m), 1156.5 (w), 1016.6 (m), 981.1 (m), 702.1 (s) cm^{-1}; HRMS-(ESI+) for $C_{16}H_{21}O$ [M+H-H_2O]: calculated: 229.1592, found: 229.1600. $[\alpha]^{25}_D$ = -53.17 (*c* = 0.40, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

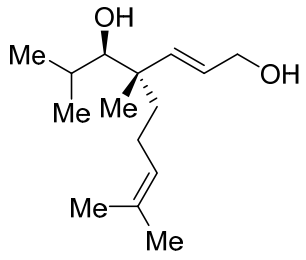
The enantioselectivity was determined SFC analysis of the reaction product. The analogous racemic material was prepared using PCy_3 as the achiral ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral SFC (AS-H, Chiraldex, 150 bar, 3 mL/min, 3% MeOH, 50 °C)- analysis of reaction product.



racemic reaction product

Start	Time	End	RT Offset	Quantity	Height	Area	Area
[Min]	[Min]	[Min]	[Min]	[% Area]	[µV]	[µV.Min]	[%]
12.03	12.49	12.72	0.00	2.89	176.8	61.8	2.891
12.72	13.13	14.21	0.00	97.11	4760.1	2077.4	97.109



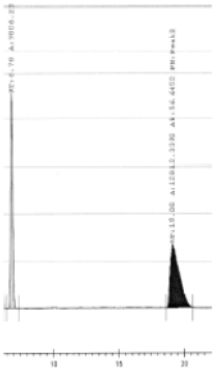
(4*S*,5*R*,*E*)-4,6-dimethyl-4-(4-methylpent-3-en-1-yl)hept-2-ene-1,5-diol. The diboration/allylation was performed according to the representative procedure with the following modifications: (*E*)-4,8-dimethylnona-1,3,7-triene (75.0 mg, 499 μmol), $Pt(dba)_3$ (13.4 mg, 15.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (16.4 mg, 18.0 μmol), $B_2(pin)_2$ (133.1 mg, 524.1 μmol) in toluene (0.50 mL, 1.0 M), and freshly distilled isobutyraldehyde (108.0 mg, 1.50 mmol). The crude material was purified by column chromatography on silica gel (20-35% ethyl acetate/hexanes, R_f = 0.38 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (69.6 mg, 58%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (3H, d, *J* = 7.0 Hz), 0.96 (3H, d, *J* = 7.0 Hz), 0.99 (3H, s), 1.35-1.44 (2H, m), 1.55 (3H, s), 1.64 (3H, s), 1.75-1.83 (1H, m), 1.85-1.94 (2H, m), 3.19 (1H, s), 4.12 (2H, d, *J* = 5.5 Hz), 5.05 (1H, t, *J* = 6.0 Hz), 5.58 (1H, ddd, *J* = 16 Hz, 5.5 Hz, 5.5 Hz), 5.69 (1H, d, *J* = 15.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 16.6, 17.6, 18.8, 22.7, 23.5, 25.6, 28.6, 38.5, 44.4, 63.9, 81.4, 124.8, 128.3, 131.3, 138.5; IR (neat): 3375.5 (m), 2964.6 (s), 2871.8 (m), 1465.2 (m), 1378.4 (m), 1077.2 (w), 980.1 (s) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{27}O$ [M+H-H_2O]: calculated: 223.2062, found: 223.2070. $[\alpha]^{25}_D$ = -3.80 (*c* = 1.21, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

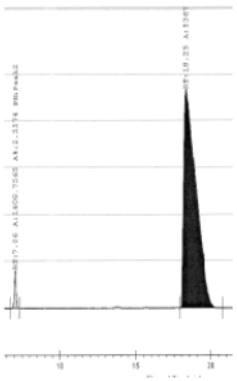
The enantioselectivity was determined by treating the 1,5-diol with benzoic anhydride and Et_3N to make the mono(benzoate) for SFC analysis. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-

propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral SFC (AD-H, Chiraldex, 100 bar, 4 mL/min, 4% MeOH, 35 °C)- analysis of (S,E)-4-((R)-1-hydroxy-2-methylpropyl)-4,8-dimethylnona-2,7-dien-1-yl benzoate.

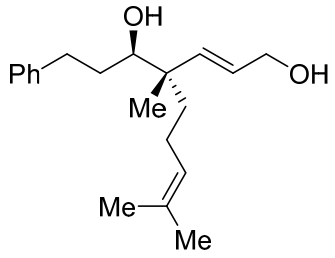


mixture of products from **(*R*,*R*)-3.44** and **(*S*,*S*)-3.44**



derived from reaction product using **(*R*,*R*)-3.44**

Peak No	% Area	Area	RT (min)	Height (mV)
1	2.5574	1408.7565	7.06	160.6432
2	97.4426	53676.012	18.25	934.6718



(4*S*,5*R*,*E*)-4-methyl-4-(4-methylpent-3-en-1-yl)-7-phenylhept-2-ene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (70.0 mg, 465 μmol), $Pt(dba)_3$ (12.6 mg, 14.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (15.2 mg, 16.7 μmol), $B_2(pin)_2$ (124.2 mg, 489.1 μmol) in toluene (0.45 mL, 1.0 M), and freshly distilled hydrocinnamaldehyde (62.5 mg, 465 μmol). The crude reaction mixture was purified on silica gel (30-60% ethyl acetate/hexanes) to afford an inseparable mixture of the product, pinacol, and 1,2-diol (152.6 mg). The mixture of diols was then dissolved in diethyl ether (3 mL), tetrahydrofuan (3 mL), and water (4 mL), and then cooled to 0 °C in an ice bath. $NaIO_4$ (521.8 mg, 2.44 mmol) was added and the reaction was allowed to warm to ambient temperature over 2h (oxidative cleavage of pinacol). The reaction mixture was quenched with saturated aqueous Na_2SO_3 (2 mL) 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 concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (40-60% ethyl acetate/hexanes, R_f = 0.33 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a white solid (101.9 mg, 72%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (3H, s), 1.21-1.38 (2H, m), 1.51-1.60 (1H, m), 1.54 (3H, s), 1.64 (3H, s), 1.74-1.81 (2H, m), 1.82- 1.90 (1H, m) 1.96 (2H, br s), 2.58 (1H, ddd, *J* = 14.0 Hz, 9.5 Hz, 7.0 Hz), 2.90 (1H, ddd, *J* = 14.0 Hz, 10.0 Hz, 5.0 Hz), 3.30 (1H, dd, *J* = 10.5 Hz, 1.5 Hz), 4.12 (2H, d, *J* = 4.0 Hz), 5.03 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.5 Hz), 5.57-5.65 (2H, m), 7.14-7.19 (3H, m), 7.22-7.27 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.4, 17.6, 22.7, 25.6, 32.9, 33.2, 37.6, 44.0, 63.7, 76.7, 124.6,

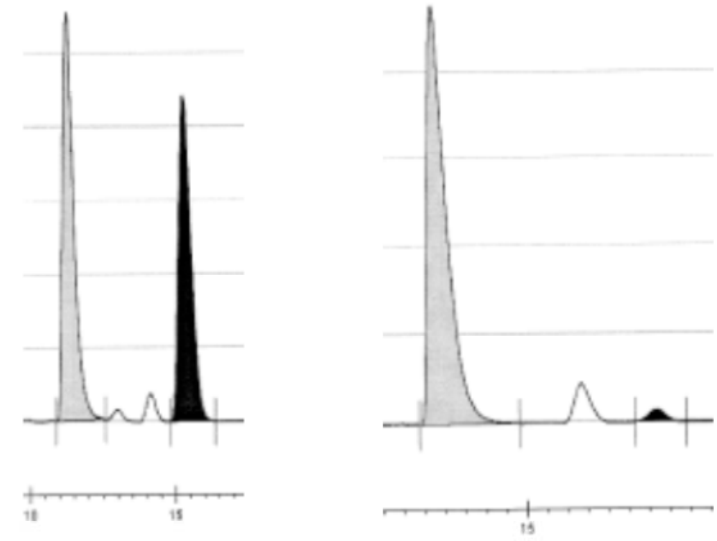
125.8, 128.3, 128.4, 129.4, 131.4, 137.9, 142.3; IR (neat): 3328.2 (br m), 3025.6 (w), 2963.6 (m), 2923.9 (m), 2857.1 (m), 1603.3 (w), 1495.8 (w), 1453.4 (m), 1377.8 (m), 1304.2 (w), 1153.2 (w), 1081.9 (m), 1065.7 (m), 1043.0 (m), 1008.1 (m), 977.7 (s), 935.2 (m), 838.0 (w), 747.6 (m), 699.0 (s) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{34}NO_2$ [M+NH_4]: calculated: 320.2590, found: 320.2598; $[\alpha]^{25}_D$ = +20.52 (*c* = 2.59, $CHCl_3$, *l* = 50 mm).

Proof of Stereochemistry:

The olefin geometry of the 1,5- diol was determined to be trans by measuring the coupling constants of the vinylic hydrogens from the ^{1}H NMR taken in pyridine: ^{1}H NMR (500 MHz, C_5D_5N): δ 1.19 (3H, s), 1.56 (3H, s), 1.67 (3H, s), 1.75 (2H, dd, *J* = 10.5 Hz, 8.5 Hz), 1.88-1.96 (1H, m), 2.00-2.08 (2H, m), 2.09-2.18 (1H, m) 2.83 (1H, ddd, *J* = 13.5 Hz, 10.0 Hz, 6.5 Hz), 3.24 (1H, ddd, *J* = 14.5 Hz, 10.5 Hz, 4.5 Hz), 3.66 (1H, dd, *J* = 10.0 Hz, 3.5 Hz), 4.49 (2H, d, *J* = 4.0 Hz), 5.21 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.5 Hz), 5.93 (1H, ddd, *J* = 16.0 Hz, 5.5 Hz, 5.5 Hz), 6.22 (1H, ddd, *J* = 16.0 Hz, 1.5 Hz, 1.5 Hz), 7.22-7.25 (2H, m), 7.29-7.34 (3H, m).

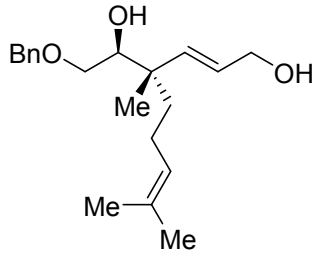
The enantioselectivity was determined by SFC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction.

Chiral SFC (AD-H, Chiraldex, 100 bar, 4 mL/min, 4% MeOH, 35 °C) - analysis of thereaction product.



mixture of products from **(*R*,*R*)-3.44** and **(*S*,*S*)-3.44**

derived from reaction product using **(*S*,*S*)-3.44**



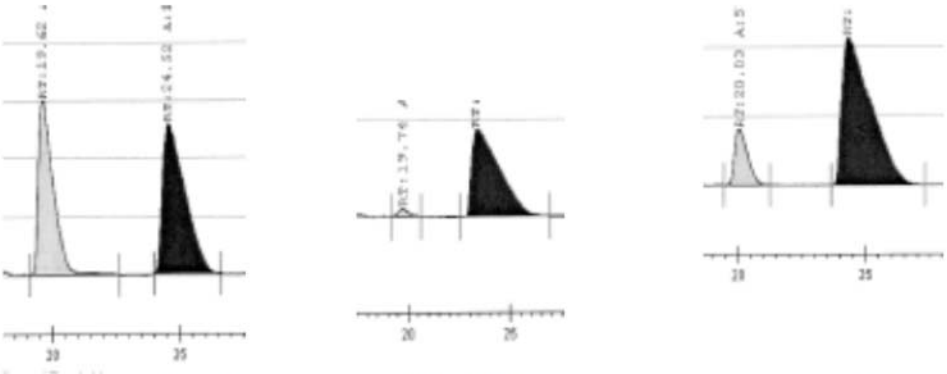
(4*S*,5*S*,*E*)-6-(benzyloxy)-4-methyl-4-(4-methylpent-3-en-1-yl)hex-2-ene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (75.0 mg, 499 μmol), $Pt(dba)_3$ (13.4 mg, 15.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (16.4 mg, 18.0 μmol), $B_2(pin)_2$ (133.1 mg, 524.1 μmol) in toluene (0.50 mL, 1.0 M), and freshly distilled benzyloxyacetaldehyde (75.0 mg, 499 μmol). The crude material was purified by column chromatography on silica gel (20-35% ethyl acetate/hexanes, R_f = 0.19 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (117.6 mg, 74%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.98 (3H, s), 1.33-1.46 (2H, m), 1.55 (3H, s), 1.64 (3H, s), 1.77-1.84 (1H, m), 1.87-1.94 (1H, m), 3.34 (1H, t, *J* = 9.5 Hz), 3.58 (1H, dd, *J* = 9.5 Hz, 2.5 Hz), 3.63 (1H, dd, *J* = 9.0 Hz, 2.5 Hz), 4.10 (2H, d, *J* = 5.5 Hz), 4.51 (2H, dd, *J* = 17.0 Hz, 12.0 Hz), 5.05 (1H, ddd, *J* = 6.0 Hz, 6.0 Hz, 1.5 Hz), 5.58 (1H, ddd, *J* = 16.0 Hz, 6.0 Hz, 6.0 Hz), 5.70 (1H, d, *J* = 16.0 Hz), 7.26-7.34 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.6, 18.7, 22.4, 25.6, 37.6, 41.9, 63.9, 71.0, 73.3, 75.7, 124.6, 127.66, 127.74, 128.4, 131.3, 137.3, 137.9; IR (neat): 3412.8 (m), 2921.9 (s), 2859.4 (m), 1453.6 (m), 1092.4 (s), 982.7 (m), 736.4 (m), 698.1 (s) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{34}NO_3$ [M+NH_4]: calculated: 336.2539, found: 336.2542. $[\alpha]^{25}_D$ = +7.63 (*c* = 0.72, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The enantioselectivity was determined by SFC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts

of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral SFC (AD-H, Chiraldex, 100 bar, 4 mL/min, 4% MeOH, 35 °C) - analysis of the reaction product.

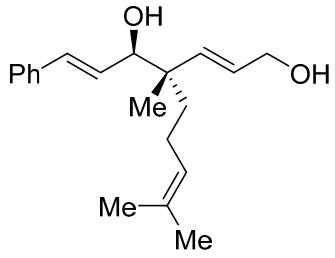


mixture of products from **(*R,R*)-3.44** and **(*S,S*)-3.44**

derived from reaction product using **(*R,R*)-3.44**

reaction product spiked with "rac"

Peak No	% Area	Area	RT (min)	Height (mV)
1	3.0359	1340.8172	19.74	41.1508
2	96.9641	42824.4476	23.33	451.6391



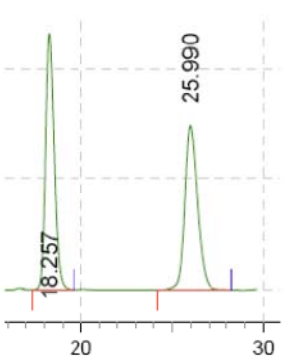
(2*E*,4*S*,5*R*,6*E*)-4-methyl-4-(4-methylpent-3-en-1-yl)-7-phenylhepta-2,6-diene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (75.0 mg, 499 μmol), $Pt(dba)_3$ (13.4 mg, 15.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (16.4 mg, 18.0 μmol), $B_2(pin)_2$ (133.1 mg, 524.1 μmol) in toluene (0.50 mL, 1.0 M), and freshly distilled cinnamaldehyde (66.0 mg, 499 μmol). The crude material was purified by column chromatography on silica gel (20-35% ethyl acetate/hexanes, R_f = 0.32 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (129.8 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.02 (3H, s), 1.40 (2H, t, *J* = 9.0 Hz), 1.55 (3H, s), 1.64 (3H, s), 1.82-1.96 (2H, m), 3.99 (1H, dd, *J* = 7.5 Hz, 1.0 Hz), 4.18 (2H, d, *J* = 4.5 Hz), 5.05 (1H, t, *J* = 7.0 Hz), 5.66-5.74 (2H, m), 6.19 (1H, dd, *J* = 16.0 Hz, 7.5 Hz), 6.56 (1H, d, *J* = 16.0 Hz), 7.21-7.24 (1H, m), 7.30 (2H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.5 Hz), 7.36 (2H, dd, *J* = 7.0 Hz, 1.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.6, 17.7, 22.7, 25.7, 37.8, 44.3, 63.8, 78.9, 124.6, 126.5, 127.7, 128.3, 128.6, 129.9, 131.4, 132.8, 136.7, 137.5; IR (neat): 3365.3 (m), 2923.9 (s), 2855.5 (m), 1448.9 (m), 1073.8 (m), 970.3 (s), 748.2 (m), 693.1 (m) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{27}O$ [M+H-H_2O]: calculated: 283.2062, found: 283.2055. $[\alpha]^{25}_D$ = +14.91 (*c* = 0.59, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

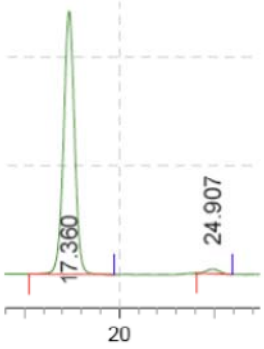
The enantioselectivity was determined by HPLC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-

propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

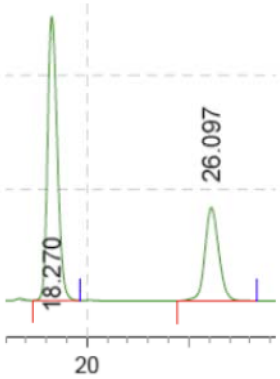
Chiral HPLC (AD-H, Chiraldex, 1 mL/min, 5% IPA, 254 nm) - analysis of the reaction product.



mixture of products from **(*R*,*R*)-3.44** and **(*S*,*S*)-3.44**

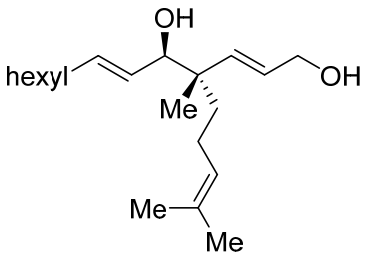


reaction product from **(*S*,*S*)-3.44**



reaction product spiked with "rac"

Retention Time	Area	Area %	Height	Height %
17.360	810071808	97.96	20281394	98.30
24.907	16853753	2.04	350658	1.70



(2*E*,4*S*,5*R*,6*E*)-4-methyl-4-(4-methylpent-3-en-1-yl)trideca-2,6-diene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (70.0 mg, 465 μmol), $Pt(dba)_3$ (12.6 mg, 14.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (15.2 mg, 16.7 μmol), $B_2(pin)_2$ (124.2 mg, 489.1 μmol) in toluene (0.45 mL, 1.0 M), and freshly distilled trans-2-nonenal (65.3 mg, 465 μmol). The crude material was purified by column chromatography on silica gel (30-60% ethyl acetate/hexanes, R_f = 0.37 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (107.7 mg, 75%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.86 (3H, t, *J* = 6.5 Hz), 0.95 (3H, s), 1.22-1.38 (10H, m), 1.55 (3H, s), 1.58 (2H, br s), 1.64 (3H, d, *J* = 1.0 Hz), 1.77-1.93 (2H, m), 2.02 (2H, ddd, *J* = 7.0 Hz, 7.0 Hz, 7.0 Hz), 3.76 (1H, d, *J* = 7.5 Hz), 4.16 (2H, dd, *J* = 3.0 Hz, 1.5 Hz), 5.05 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.5 Hz), 5.41 (1H, dddd, *J* = 15.0 Hz, 9.0 Hz, 1.5 Hz, 1.5 Hz), 5.61-5.69 (3H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 14.1, 17.5, 17.6, 22.58, 22.60, 25.6, 28.8, 29.1, 31.7, 32.4, 37.9, 43.7, 63.8, 79.1, 124.8, 128.5, 129.5, 131.2, 134.9, 137.9; IR (neat): 3348.7 (br w), 2959.4 (m), 2023.3 (m), 2854.5 (m), 1665.7 (w), 1455.3 (m), 1376.7 (m), 1302.5 (w), 1079.0 (m), 1004.8 (m), 970.9 (s) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{35}O$ [M+H–H_2O]: calculated: 291.2688, found: 291.2694; $[\alpha]^{25}_D$: -1.11 (*c* = 1.98, $CHCl_3$, *l* = 50 mm).

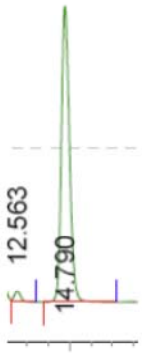
Analysis of Stereochemistry:

The enantioselectivity was determined by treating the 1,5-diol with benzoic anhydride and Et_3N to make the mono(benzoate) for HPLC analysis. The analogous

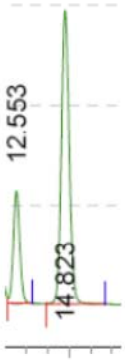
racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral HPLC (AD-H, Chiraldex, 1 mL/min, 1% IPA, 220 nm) - analysis of (S,E)-4-((R)-1-hydroxypropyl)-4,8-dimethylnona-2,7-dien-1-yl benzoate.

mixture of products from **(*R,R*)-3.44** and **(*S,S*)-3.44**



derived from reaction product using **(*R,R*)-3.44**



reaction product spiked with "rac"

Retention Time	Area	Area %	Height	Height %
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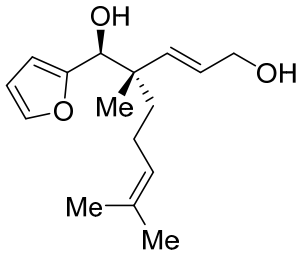
14.790	424218119	97.11	16172744	96.48



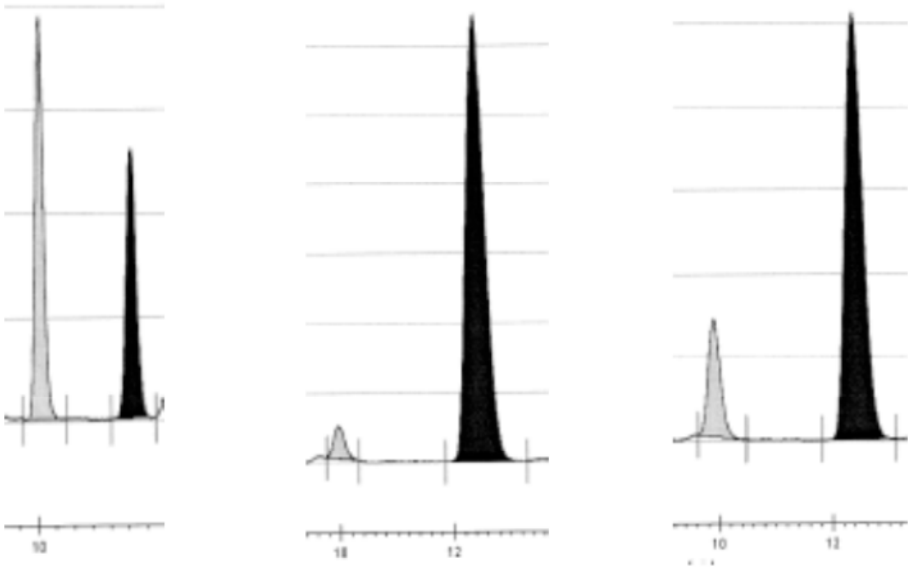
(4*S*,5*S*,*E*)-5-(furan-2-yl)-4-methyl-4-(4-methylpent-3-en-1-yl)pent-2-ene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (70.0 mg, 465 μmol), $Pt(dba)_3$ (12.6 mg, 14.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (15.2 mg, 16.7 μmol), $B_2(pin)_2$ (124.2 mg, 489.1 μmol) in toluene (0.45 mL, 1.0 M), and freshly distilled 2-furfural (44.8 mg, 465 μmol). The crude material was purified by column chromatography on silica gel (30-60% ethyl acetate/hexanes, R_f = 0.24 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, yellow oil (99.0 mg, 80%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.99 (3H, s), 1.23-1.31 (1H, m), 1.35-1.41 (1H, m), 1.54 (3H, s), 1.63 (3H, s), 1.85 (2H, ddd, *J* = 17.5 Hz, 17.5 Hz, 9.0 Hz), 2.11 (1H, br s), 2.40 (1H, br s), 4.13 (2H, d, *J* = 4.5 Hz), 4.45 (1H, s), 5.02 (1H, t, *J* = 7.0 Hz), 5.63-5.71 (2H, m), 6.20 (1H, d, *J* = 3.5 Hz), 6.31 (1H, dd, *J* = 3.0 Hz, 1.5 Hz), 7.33 (1H, dd, *J* = 1.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.6, 17.7, 22.6, 25.6, 37.5, 44.5, 63.7, 74.4, 107.8, 110.1, 124.6, 129.7, 131.4, 137.2, 141.5, 154.5; IR (neat): 3356.4 (m br), 2967.3 (m), 2921.9 (m), 2856.6 (m), 1665.2 (w), 1502.2 (w), 1452.5 (m), 1377.0 (m), 1277.4 (w), 1223.4 (w), 1146.9 (m), 1077.5 (m), 1050.5 (m), 1007.1 (s), 976.4 (s), 946.9 (w), 932.8 (w), 902.7 (w), 884.4 (w), 838.7 (w), 808.4 (m), 731.9 (s) cm^{-1}; HRMS-(ESI+): for $C_{16}H_{28}NO_3$ [M+NH_4]: calculated: 282.2069, found: 282.2080; $[\alpha]^{25}_D$ = +6.78 (*c* = 1.75, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The olefin geometry of the 1,5-diol was determined to be trans by measuring the coupling constants of the vinylic hydrogens from the ^{1}H NMR taken in benzene: ^{1}H NMR (500 MHz, C_6D_6): δ 1.04 (3H, s), 1.41-1.55 (2H, m), 1.53 (3H, d, *J* = 1.0 Hz), 1.64 (3H, d, *J* = 1.0 Hz), 1.96 (2H, ddd, *J* = 15.0 Hz, 15.0 Hz, 8.0 Hz), 2.43 (1H, br s), 3.93 (2H, d, *J* = 5.0 Hz), 4.42 (1H, s), 5.15 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.5 Hz), 5.54 (1H, m), 5.68 (1H, dd, *J* = 16.0 Hz, 1.0 Hz), 6.07 (1H, dd, *J* = 3.0 Hz, 1.5 Hz), 6.15 (1H, d, *J* = 3.0 Hz), 7.04 (1H, dd, *J* = 2.0 Hz, 1.0 Hz).

The enantioselectivity was determined by SFC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral SFC (AD-H, Chiraldex, 100 bar, 4 mL/min, 4% MeOH, 35 °C)- analysis of reaction product.

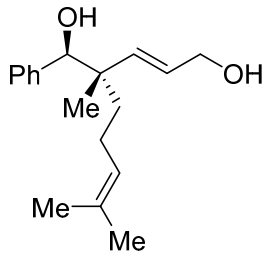


mixture of products from **(*R*,*R*)-3.44** and **(*S*,*S*)-3.44**

derived from reaction product using **(*R*,*R*)-3.44**

reaction product spiked with "rac"

Peak No	% Area	Area	RT (min)	Height (mV)
1	4.2533	648.2372	9.95	46.8904
2	95.7467	14592.4269	12.33	643.2522



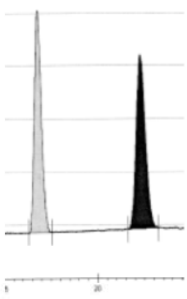
(4*S*,5*S*,*E*)-4-methyl-4-(4-methylpent-3-en-1-yl)-5-phenylpent-2-ene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (70.0 mg, 465 μmol), $Pt(dba)_3$ (12.6 mg, 14.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (15.2 mg, 16.7 μmol), $B_2(pin)_2$ (124.2 mg, 489.1 μmol) in toluene (0.45 mL, 1.0 M), and freshly distilled benzaldehyde (49.5 mg, 465 μmol). The crude reaction mixture was purified on silica gel (30-50% ethyl acetate/hexanes) to afford an inseparable mixture of the product and pinacol (160.2 mg). The mixture of diols was then dissolved in diethyl ether (3 mL), tetrahydrofuan (3 mL), and water (4 mL), and then cooled to 0 °C in an ice bath. $NaIO_4$ (521.8 mg, 2.440 mmol) was added and the reaction was allowed to warm to ambient temperature over 2h (oxidative cleavage of pinacol). The reaction mixture was quenched with saturated aqueous Na_2SO_3 (2 mL) 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 concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (40-60% ethyl acetate/hexanes, R_f = 0.28 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (111.5 mg, 87%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.22-1.30 (1H, m), 1.38-1.44 (1H, m), 1.53 (3H, s), 1.63 (3H, d, *J* = 1.0 Hz), 1.77-1.89 (2H, m), 4.15 (2H, m), 4.42 (1H, s), 5.02 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.0 Hz), 5.61 (1H, ddd, *J* = 15.5 Hz, 5.0 Hz, 5.0 Hz), 5.72 (1H, dd, *J* = 16.0 Hz, 1.0 Hz), 7.22-7.30 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.0, 17.6, 22.8, 25.7, 37.8, 44.8, 63.8, 80.5, 124.6, 127.51, 127.53, 128.0, 130.0, 131.3, 137.6, 140.6; IR (neat): 3376.9 (br s), 3085.8 (w), 3061.3 (w), 3028.8 (w), 2968.5 (s), 2922.4 (s), 2856.9 (s), 1666.4 (w),

1493.3 (w), 1452.8 (s), 1377.4 (m), 1195.6 (w), 1082.4 (m), 1046.0 (m), 1011.6 (s), 979.7 (s), 903.5 (w), 839.6 (w), 702.9 (s) cm^{-1}; HRMS-(ESI+) for $C_{18}H_{30}NO_2$ [M+NH_4]: calculated: 292.2277, found: 292.2271; $[\alpha]^{25}_D$ = -25.07 (*c* = 3.00, $CHCl_3$, *l* = 50 mm).

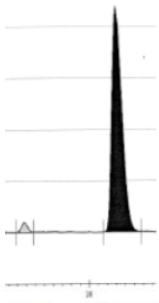
Analysis of Stereochemistry:

The enantioselectivity was determined by SFC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral SFC (AD-H, Chiraldex, 100 bar, 4 mL/min, 4% MeOH, 35 °C)- analysis of reaction product.



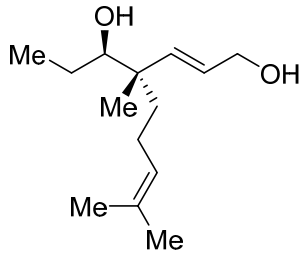
mixture of products from **(*R,R*)-3.44** and **(*S,S*)-3.44**



derived from reaction product using **(*R,R*)-3.44**

reaction product spiked with "rac"

Peak No	% Area	Area	RT (min)	Height (mV)
1	2.4924	221.3811	16.4	9.5035
2	97.5076	8660.7138	21.5	220.0133



(4*S*,5*R*,*E*)-4-methyl-4-(4-methylpent-3-en-1-yl)hept-2-ene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*E*)-4,8-dimethylnona-1,3,7-triene (70.0 mg, 465 μmol), $Pt(dba)_3$ (12.6 mg, 14.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (15.2 mg, 16.7 μmol), $B_2(pin)_2$ (124.2 mg, 489.1 μmol) in toluene (0.45 mL, 1.0 M), and freshly distilled propionaldehyde (27.0 mg, 465 μmol). The crude reaction mixture was purified on silica gel (30-60% ethyl acetate/hexanes) to afford an inseparable mixture of the product, pinacol, and 1,2-diol (129.4 mg). The mixture of diols was then dissolved in diethyl ether (3 mL), tetrahydrofuan (3 mL), and water (4 mL), and then cooled to 0 °C in an ice bath. $NaIO_4$ (521.8 mg, 2.440 mmol) was added and the reaction was allowed to warm to ambient temperature over 2h (oxidative cleavage of pinacol). The reaction mixture was quenched with saturated aqueous Na_2SO_3 (2 mL) 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 concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (40-60% ethyl acetate/hexanes, R_f = 0.24 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (70.7 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (3H, s), 0.96 (3H, t, *J* = 7.5 Hz), 1.16-1.26 (1H, m), 1.28-1.40 (2H, m), 1.51-1.59 (1H, m), 1.55 (3H, s), 1.64 (3H, d, 1.0 Hz), 1.75-1.83 (1H, m), 1.85-1.92 (1H, m), 2.03 (2H, br s), 3.17 (1H, dd, *J* = 10.0 Hz, 1.5 Hz), 4.12 (2H, d, *J* = 2.5 Hz), 5.05 (1H, ddd, *J* = 7.0Hz, 7.0 Hz, 1.5 Hz), 5.58-5.61 (2H, m); ^{13}C NMR (125 MHz, CDCl3): δ 11.5, 17.59 17.64, 22.7, 23.9, 25.6, 37.7, 44.0, 63.8,

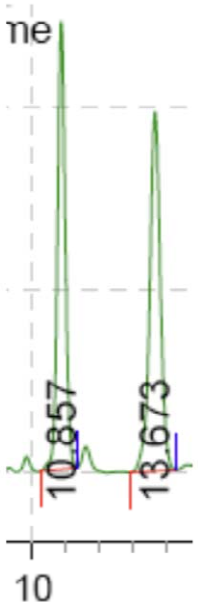
79.3, 124.7, 129.2, 131.3, 138.1; IR (neat): 3340.5 (br m), 2964.8 (m), 2927.6 (m), 2874.3 (m), 1665.2 (w), 1454.9 (m), 1377.5 (m), 1313.7 (w), 1243.7 (w), 1100.1 (m), 1047.7 (w), 974.5 (s) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{30}NO_2$ $[M+NH_4]$: calculated: 224.2277, found: 244.2274; $[\alpha]^{25}_D = +6.78$ (*c* = 1.75, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

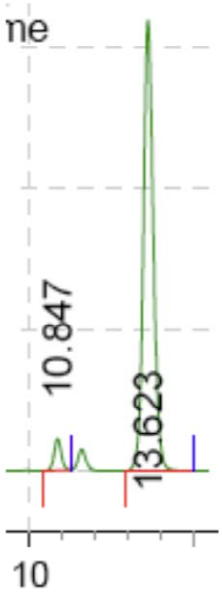
The olefin geometry of the 1,5-diol was determined to be trans by measuring the coupling constants of the vinylic hydrogens from the ^1H NMR taken in d6-benzene: ^1H NMR (500 MHz, C_6D_6): δ 0.89 (3H, s), 1.00 (3H, t, *J* = 7.5 Hz), 1.19 (1H, dddd, *J* = 14.5 Hz, 10.5 Hz, 7.5 Hz, 7.5 Hz), 1.31-1.44 (3H, m), 1.56 (3H, s), 1.68 (3H, s), 1.87-2.02 (2H, m), 3.03 (1H, dd, *J* = 10.5 Hz, 2.0 Hz), 3.84 (2H, d, *J* = 5.5 Hz), 5.19 (1H, ddd, *J* = 7.5 Hz, 7.5 Hz, 1.0 Hz), 5.44 (1H, ddd, *J* = 16.0 Hz, 5.0 Hz, 5.0 Hz), 5.52 (1H, d, *J* = 16.0 Hz).

The enantioselectivity was determined by treating the 1,5-diol with benzoic anhydride and Et_3N to make the mono(benzoate) for HPLC analysis. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

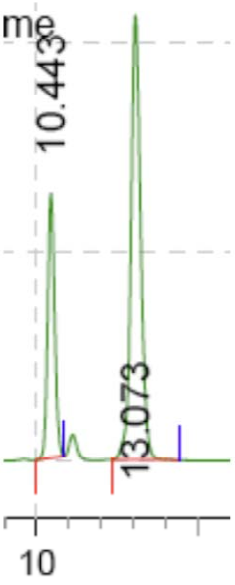
Chiral HPLC (AD-H, Chiraldex, 1 mL/min, 1% IPA, 220 nm) - analysis of (S,E)-4-((R)-1-hydroxypropyl)-4,8-dimethylnona-2,7-dien-1-yl benzoate.



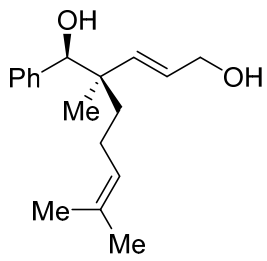
mixture of products from **(*R*,*R*)-3.44** and **(*S*,*S*)-3.44**



derived from reaction product using **(*R*,*R*)-3.44**



reaction product spiked with "rac"



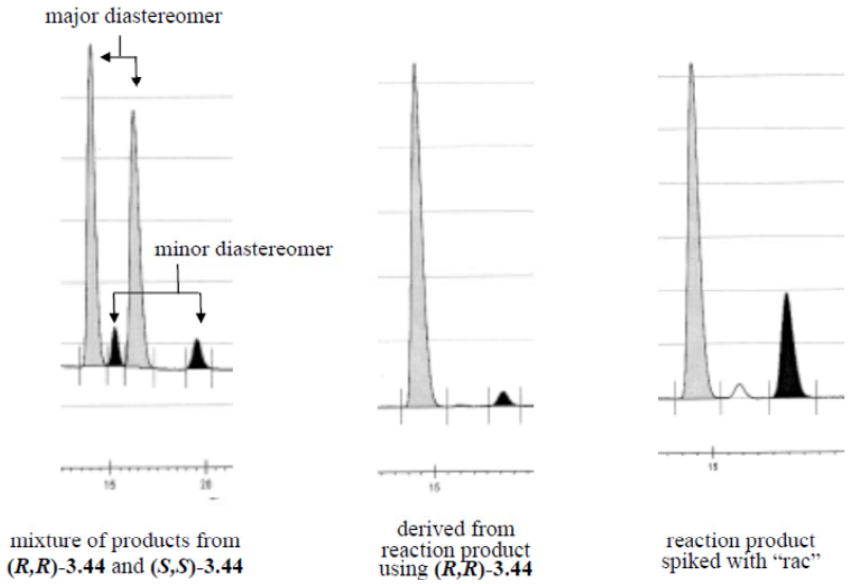
(4*R*,5*S*,*E*)-4-methyl-4-(4-methylpent-3-en-1-yl)-5-phenylpent-2-ene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*Z*)-4,8-dimethylnona-1,3,7-triene (70.0 mg, 465 μmol), $Pt(dba)_3$ (12.6 mg, 14.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (15.2 mg, 16.7 μmol), $B_2(pin)_2$ (124.2 mg, 489.1 μmol) in toluene (0.45 mL, 1.0 M), and freshly distilled benzaldehyde (49.5 mg, 465 μmol). The crude reaction mixture was purified on silica gel (30-50% ethyl acetate/hexanes) to afford an inseparable mixture of the product and pinacol (171.9 mg). The mixture of diols was then dissolved in diethyl ether (3 mL), tetrahydrofuan (3 mL), and water (4 mL), and then cooled to 0 °C in an ice bath. $NaIO_4$ (521.8 mg, 2.44 mmol) was added and the reaction was allowed to warm to ambient temperature over 2h (oxidative cleavage of pinacol). The reaction mixture was quenched with saturated aqueous Na_2SO_3 (2 mL) and the layers were separated. The aqueous layer was washed with ethyl acetate (3 x 10 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (40-60% ethyl acetate/hexanes, R_f = 0.33 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil as a mixture of diastereomers (108.0 mg, 85%, 9:1 dr). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.06 (3H, s), 1.32-1.39 (2H, m), 1.53 (3H, s), 1.63 (3H, s), 1.76-1.92 (2H, m), 2.15 (1H, br s), 4.12 (2H, d, *J* = 6.0 Hz), 4.42 (1H, s), 5.00 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.5 Hz), 5.55 (1H, ddd, *J* = 15.5 Hz, 5.5 Hz, 5.5 Hz), 5.66 (1H, dd, *J* = 16.0 Hz, 1.0 Hz), 7.22-7.30 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.6, 19.5, 22.8, 25.7, 36.5, 44.2, 63.9, 81.1, 124.7, 127.4, 127.5, 127.8, 129.4, 131.2, 136.9, 141.2; IR (neat): 3364.0 (m br), 3029.5 (w),

2967.0 (m), 2925.7 (m), 2857.2 (m), 1493.3 (w), 1452.1 (m), 1376.7 (m), 1197.7 (w), 1080.0 (m), 1044.6 (m), 1011.7 (s), 980.0 (s), 745.3 (m), 703.1 (s) cm^{-1}; HRMS-(ESI+) for $C_{18}H_{30}NO_2$ [M+NH_4]: calculated: 292.2277, found: 292.2278; $[\alpha]^{25}_D$ = -24.17 (*c* = 3.81, $CHCl_3$, *l* = 50 mm).

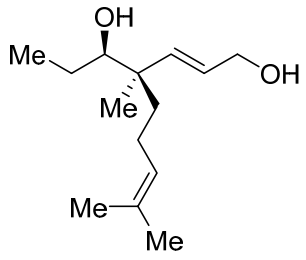
Analysis of Stereochemistry:

The enantioselectivity was determined by SFC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the product made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligand in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral SFC (AD-H, Chiraldex, 100 bar, 4 mL/min, 4% MeOH, 35 °C)- analysis of reaction product.



Peak No	% Area	Area	RT (min)	Height (nV)
1	96.1313	14209.2633	14.25	529.634
2	3.8687	571.8425	17.64	21.1354



(4*R*,5*R*,*E*)-4-methyl-4-(4-methylpent-3-en-1-yl)hept-2-ene-1,5-diol. The diboration/allylation was performed according to the representative procedure with (*Z*)-4,8-dimethylnona-1,3,7-triene (70.0 mg, 465 μmol), $Pt(dba)_3$ (12.6 mg, 14.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenylTADDOLPPh (15.2 mg, 16.7 μmol), $B_2(pin)_2$ (124.2 mg, 489.1 μmol) in toluene (0.45 mL, 1.0 M), and freshly distilled propionaldehyde (27.0 mg, 465 μmol). The crude reaction mixture was purified on silica gel (30-65% ethyl acetate/hexanes) to afford an inseparable mixture of the product, pinacol, and 1,2-diol (118.2 mg). The mixture of diols was then dissolved in diethyl ether (3 mL), tetrahydrofuan (3 mL), and water (4 mL), and then cooled to 0 °C in an ice bath. $NaIO_4$ (521.8 mg, 2.44 mmol) was added and the reaction was allowed to warm to ambient temperature over 2h (oxidative cleavage of pinacol). The reaction mixture was quenched with saturated aqueous Na_2SO_3 (2 mL) 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 concentrated *in vacuo*. The crude material was purified by column chromatography on silica gel (40-60% ethyl acetate/hexanes, R_f = 0.29 in 50% ethyl acetate/hexanes, stain in PMA) to afford the title compound as a clear, colorless oil (70.7 mg, 67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.95 (3H, t, *J* = 7.5 Hz), 1.00 (3H, s), 1.20 (1H, dddd, *J* = 14.5 Hz, 10.5 Hz, 7.5 Hz, 7.5 Hz), 1.38 (2H, t, *J* = 8.5 Hz), 1.52-1.60 (2H, m), 1.56 (3H, s), 1.81-1.90 (2H, m), 3.17 (1H, d, *J* = 10.5 Hz), 4.12-4.13 (2H, m), 5.06 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.0 Hz), 5.56-5.64 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 11.6, 17.6, 18.6, 22.6, 24.6, 25.7, 37.5, 43.9, 63.9, 80.0, 124.8, 128.8, 131.4, 137.6; IR (neat): 3353.8 (br m), 2965.9 (m), 2929.0 (m), 2874.7 (m), 1665.3 (w), 1455.1 (m),

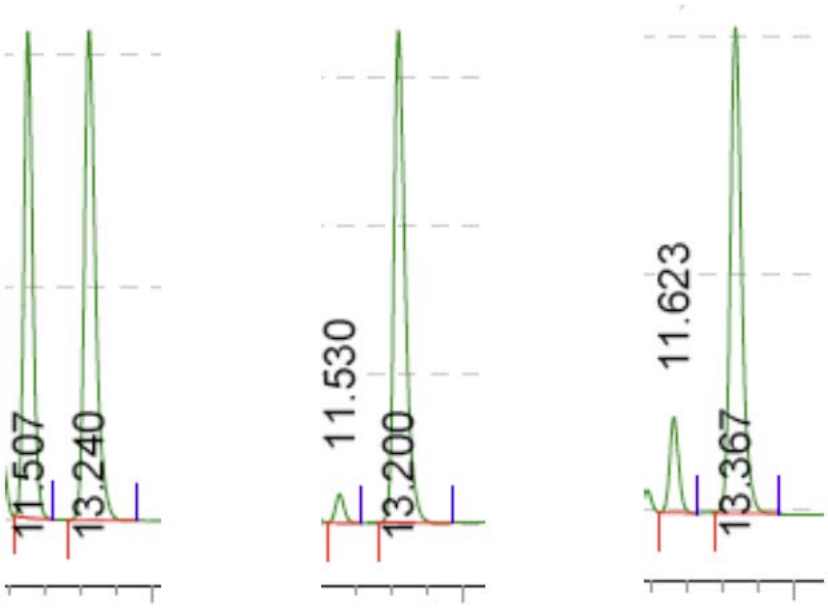
1376.7 (m), 1312.9 (w), 1242.1 (w), 1102.2 (m), 1047.6 (w), 1010.9 (m), 975.5 (s), 940.5 (w) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{30}NO_2$ [M+NH_4]: calculated: 244.2277, found: 244.2287. $[\alpha]^{25}_D$ = +22.17 (*c* = 1.52, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The olefin geometry of the 1,5-diol was determined to be trans by measuring the coupling constants of the vinylic hydrogens from the ^{1}H NMR taken in benzene: ^{1}H NMR (500 MHz, C_6D_6): δ 0.94 (3H, t, *J* = 7.5 Hz), 0.96 (3H, s), 1.12 (1H, dddd, *J* = 15.0 Hz, 11.0 Hz, 7.5 Hz, 7.5 Hz), 1.39-1.47 (3H, m), 1.56 (3H, s), 1.68 (3H, s), 1.94-1.98 (2H, m), 3.03 (1H, dd, *J* = 10.5 Hz, 1.5 Hz), 8.84-8.90 (2H, m), 5.20 (1H, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.0 Hz), 5.44 (1H, ddd, *J* = 16.0 Hz, 4.5 Hz, 4.5 Hz), 5.49 (1H, d, *J* = 16.5 Hz).

The enantioselectivity was determined by treating the 1,5-diol with benzoic anhydride and Et_3N to make the mono(benzoate) for HPLC analysis. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral HPLC (AD-H, Chiraldex, 1 mL/min, 1% IPA, 220 nm) - analysis of (R,E)-4-((R)-1-hydroxypropyl)-4,8-dimethylnona-2,7-dien-1-yl benzoate.



mixture of products from **(*R*,*R*)-3.44** and **(*S*,*S*)-3.44**

derived from reaction product using **(*R*,*R*)-3.44**

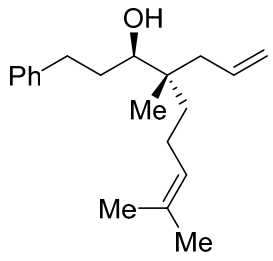
reaction product spiked with "rac"

Retention Time	Area	Area %	Height	Height %
11.530	27547574	4.29	1610403	5.49
13.200	613910926	95.71	27748826	94.51

2.7.16 Procedure for Diboration/Allylation/Protodeboronation Reaction Sequence (Scheme 2.21)

To an oven-dried 2-dram vial with magnetic stir bar in the glove box was added $Pt(dba)_3$ (13.4 mg, 15.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenyl-TADDOLPPh (16.3 mg, 18.0 μmol), $B_2(pin)_2$ (133.1 mg, 524.1 μmol) and toluene (0.5 mL, [substrate] = 1.0 M). The vial was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C in an oil bath for 20 min. The vial was cooled to room temperature, returned to the glove box and charged with (*E*)-4,8-dimethylnona-1,3,7-triene (75.0 mg, 499 μmol). The vial was sealed, removed from the glove box, and stirred at 60 °C for 12 h. The reaction mixture was then cooled to ambient temperature, returned to the glove box and charged with freshly distilled hydrocinnamaldehyde (67.0 mg, 499 μmol). The reaction was heated to 60 °C in and oil bath and was allowed to stir for 24 h. The reaction mixture was then cooled to ambient temperature, TBAF•nH_2O (521.9 mg, 2.00 mmol) was added and the vial was quickly sealed with a septum and purged with N_2. The reaction mixture was then transferred via syringe to a separate 25 mL flame-dried round-bottomed flask containing oven-dried 4 Å molecular sieves. The original vial was washed with toluene (2 x 1 mL), and the mixture was allowed to stir at rt for 10 min (to remove excess water from TBAF•nH_2O). The reaction mixture was then cannula transferred to an oven-dried scintillation vial fitted with a septum, and the flask was rinsed with toluene (2.5 mL, final [substrate] = 0.1 M). The reaction mixture was then heated to 60 °C in an oil bath for 6 h, at which time it was cooled to rt and the volatiles were removed *in vacuo* and the residue was filtered over a silica plug (10% ethyl acetate/hexanes). The crude material was then purified by column chromatography on silica gel (2-8% ethyl acetate/ hexanes, R_f = 0.33

in 10% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (105.8 mg, 74%, 5:1 terminal:internal alkene).

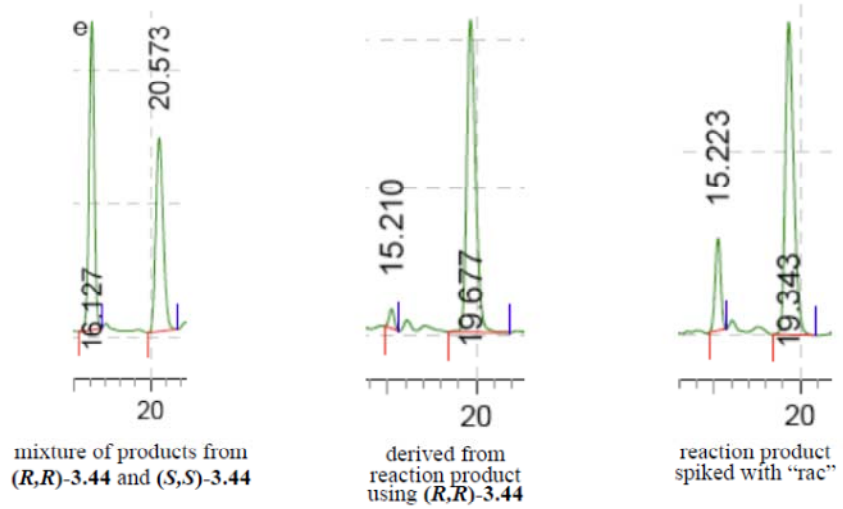


(3*R*,4*S*)-4-allyl-4,8-dimethyl-1-phenylnon-7-en-3-ol. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.84 (3H, s), 1.17-1.24 (2H, m), 1.32 (1H, ddd, *J* = 14.5 Hz, 14.5 Hz, 6.0 Hz) 1.51 (1H, br s), 1.57 (3H, s), 1.58-1.63 (1H, m), 1.65 (3H, s), 1.76-1.84 (1H, m), 1.86-1.94 (1H, m), 2.06 (1H, dd, *J* = 14.0 Hz, 7.0 Hz), 2.15 (1H, dd, *J* = 14.0 Hz, 8.0 Hz), 2.58 (1H, ddd, *J* = 16.0 Hz, 9.5 Hz, 6.5 Hz), 2.91 (1H, ddd, *J* = 14.5 Hz, 9.5 Hz, 4.0 Hz), 3.40 (1H, dd, *J* = 11.0 Hz), 5.01-5.09 (3H, m), 5.83 (1H, dddd, *J* = 17.0 Hz, 7.5 Hz, 7.5 Hz, 7.5 Hz), 7.15-7.20 (3H, m), 7.24-7.28 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.6, 20.3, 22.1, 25.7, 33.2, 33.4, 36.4, 40.3, 40.8, 76.7, 117.1, 124.8, 125.8, 128.4, 128.5, 131.3, 135.6, 142.4; IR (neat): 3444.9 (br w), 3063.0 (w), 3026.7 (w), 2924.6 (s), 2924.6 (s), 2859.0 (m), 1637.8 (w), 1602.7 (w), 1495.4 (w), 1454.2 (s), 1378.0 (m), 1076.7 (m), 1040.5 (m), 913.1 (m), 748.5 (m), 699.5 (s) cm^{-1}; HRMS-(ESI+) for $C_{20}H_{31}O$ [M+H]: calculated: 287.2375, found: 287.2377. $[\alpha]^{25}_{D}$ = +40.54 (*c* = 0.69, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The enantioselectivity was determined by HPLC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral HPLC (AD-H, Chiraldex, 1 mL/min, 0.5% IPA, 254 nm)- analysis of reaction product.

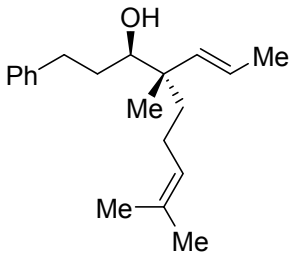


mixture of products from **(*R*,*R*)-3.44** and **(*S*,*S*)-3.44**

derived from reaction product using **(*R*,*R*)-3.44**

reaction product spiked with "rac"

Retention Time	Area	Area %	Height	Height %
15.210	1083144	3.39	54466	5.78
19.677	30853081	96.61	887157	94.22



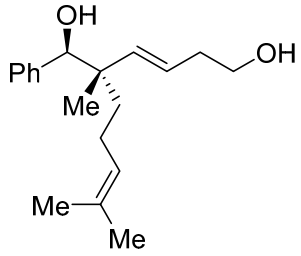
(3*R*,4*S*)-4,8-dimethyl-1-phenyl-4-((E)-prop-1-en-1-yl)non-7-en-3-ol. Purified by column chromatography on silica gel (2-8% ethyl acetate/hexanes, R_f = 0.38 in 10% ethyl acetate/hexanes, stain in PMA). ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.92 (3H, s), 1.20-1.27 (2H, m), 1.28- 1.35 (1H, m), 1.53-1.61 (1H, m), 1.55 (3H, d, *J* = 0.5 Hz), 1.65 (3H, d, *J* = 1.0 Hz), 1.75-1.81 (1H, m), 1.82-1.88 (1H, m), 2.59 (1H, ddd, *J* = 14.0 Hz, 10.0 Hz, 7.0 Hz), 2.92 (1H, ddd, *J* = 14.0 Hz, 10.5 Hz, 5.0 Hz), 3.24 (1H, dd, *J* = 10.5 Hz, 1.5 Hz), 5.05 (1H, ddd, *J* = 6.0 Hz, 6.0 Hz, 1.5 Hz), 5.31 (1H, dq, *J* = 15.5 Hz, 1.5 Hz), 5.48 (1H, dq, *J* = 15.5 Hz, 6.0 Hz), 7.13-7.21 (3H, m), 7.24-7.28 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.2, 17.6, 18.3, 22.8, 25.7, 32.8, 33.4, 37.8, 44.3, 76.6, 124.9,

125.7, 125.9, 128.3, 128.5, 131.3, 136.8, 142.6; HRMS-(ESI+) for $C_{20}H_{29}$ [M+H-H_2O]: calculated: 269.2269, found: 269.2260.

2.7.17 Procedure for Diboration/Allylation/Homologation/Oxidation Reaction Sequence (Scheme 2.22)

To an oven-dried 2-dram vial with magnetic stir bar in the glove box was added $Pt(dba)_3$ (13.4 mg, 15.0 μmol), (*R,R*)-3,5-di-*iso*-propylphenyl-TADDOLPPh (16.3 mg, 18.0 μmol), $B_2(pin)_2$ (133.1 mg, 524.1 μmol) and toluene (0.5 mL, [substrate] = 1.0 M). The vial was sealed with a polypropylene cap, removed from the glove box, and heated to 80 °C in an oil bath for 20 min. The vial was cooled to room temperature, returned to the glove box and charged with (*E*)-4,8-dimethylnona-1,3,7-triene (75.0 mg, 499 μmol). The vial was sealed, removed from the glove box, and stirred at 60 °C for 12 h. The reaction mixture was then cooled to ambient temperature, returned to the glove box and charged with freshly distilled benzaldehyde (53.0 mg, 499 μmol). The reaction was heated to 60 °C in and oil bath and was allowed to stir for 24 h. The reaction mixture was then cooled to ambient temperature and the vial cap was exchanged for a septum. After the vial was purged with N_2, tetrahydrofuran (2.5 mL) was added via syringe, followed by bromochloromethane (84 μL, 1.25 mmol). The reaction mixture was then cooled to -78 °C (dry ice/acetone) and *n*-BuLi (0.50 mL, 1.25 mmol, 2.48 M in hexane) was added dropwise under N_2. The reaction was allowed to stir at 78 °C for 10 min, and was then allowed to warm to rt and stir for 7 h. The reaction mixture was then transferred to a scintillation vial using tetrahydrofuran (2 x 1 mL) to rinse the reaction vial. The reaction mixture was then cooled to 0 °C (ice/water) and charged with 3 M sodium hydroxide solution (2 mL) and 30 wt% hydrogen peroxide (1 mL). The reaction was gradually

warmed to room temperature and allowed to stir for 4 h, at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (2 mL) was carefully added dropwise. The reaction mixture was diluted with ethyl acetate (5 mL) and the aqueous and organic layers were separated. The aqueous layer was rinsed with ethyl acetate (3 x 15 mL), and the combined organics were dried over Na_2SO_4, filtered, and volatiles were removed *in vacuo*. The crude reaction mixture was purified by column chromatography on silica gel (20-35% ethyl acetate/hexanes, R_f = 0.32 in 50% ethyl acetate/hexanes, stain in PMA) to afford a clear, colorless oil (119.5 mg, 83%).

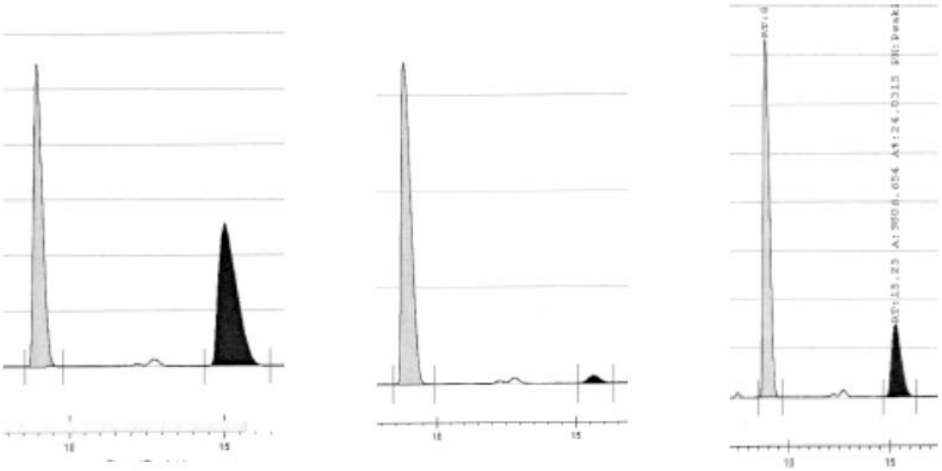


(1*S*,2*S*,*E*)-2-methyl-2-(4-methylpent-3-en-1-yl)-1-phenylhex-3-ene-1,6-diol. ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (3H, s), 1.21-1.28 (1H, m), 1.38-1.43 (1H, m), 1.53 (3H, s), 1.64 (3H, s), 1.84 (2H, ddd, *J* = 7.5 Hz, 7.5 Hz, 7.5 Hz), 2.33 (2H, ddd, *J* = 7.0 Hz, 7.0 Hz, 7.0 Hz), 3.58-3.67 (2H, m), 4.37 (1H, s), 5.03 (1H, t, *J* = 7.0 Hz), 5.37 (1H, ddd, *J* = 16.0 Hz, 7.0 Hz, 7.0 Hz), 5.55 (1H, d, *J* = 16.0 Hz), 7.22-7.30 (5H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 17.0, 17.6, 22.9, 25.7, 36.2, 37.9, 45.3, 61.8, 80.3, 124.7, 127.1, 127.4, 127.5, 130.0, 131.2, 139.1, 140.7; IR (neat): 3378.7 (m), 2966.2 (m), 2925.7 (s), 2855.9 (m), 1452.6 (m), 1376.7 (w), 1046.3 (s), 982.3 (m), 745.6 (m), 702.6 (s) cm^{-1}; HRMS-(ESI+) for $C_{19}H_{32}NO_2$ [M+NH_4]: calculated: 306.2433, found: 306.2419. $[\alpha]^{25}_D$ = -55.77 (*c* = 0.34, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

The enantioselectivity was determined by SFC analysis of the reaction product. The analogous racemic material was prepared by mixing approximate equimolar amounts of the products made using (*R,R*)-3,5-di-*iso*-propylTADDOLPPh and (*S,S*)-3,5-di-*iso*-propylTADDOLPPh as the ligands in the diboration reaction. The absolute stereochemistry was assigned by analogy.

Chiral SFC (AD-H, Chiraldex, 100 bar, 5 mL/min, 5% MeOH, 35 °C)- analysis of reaction product.



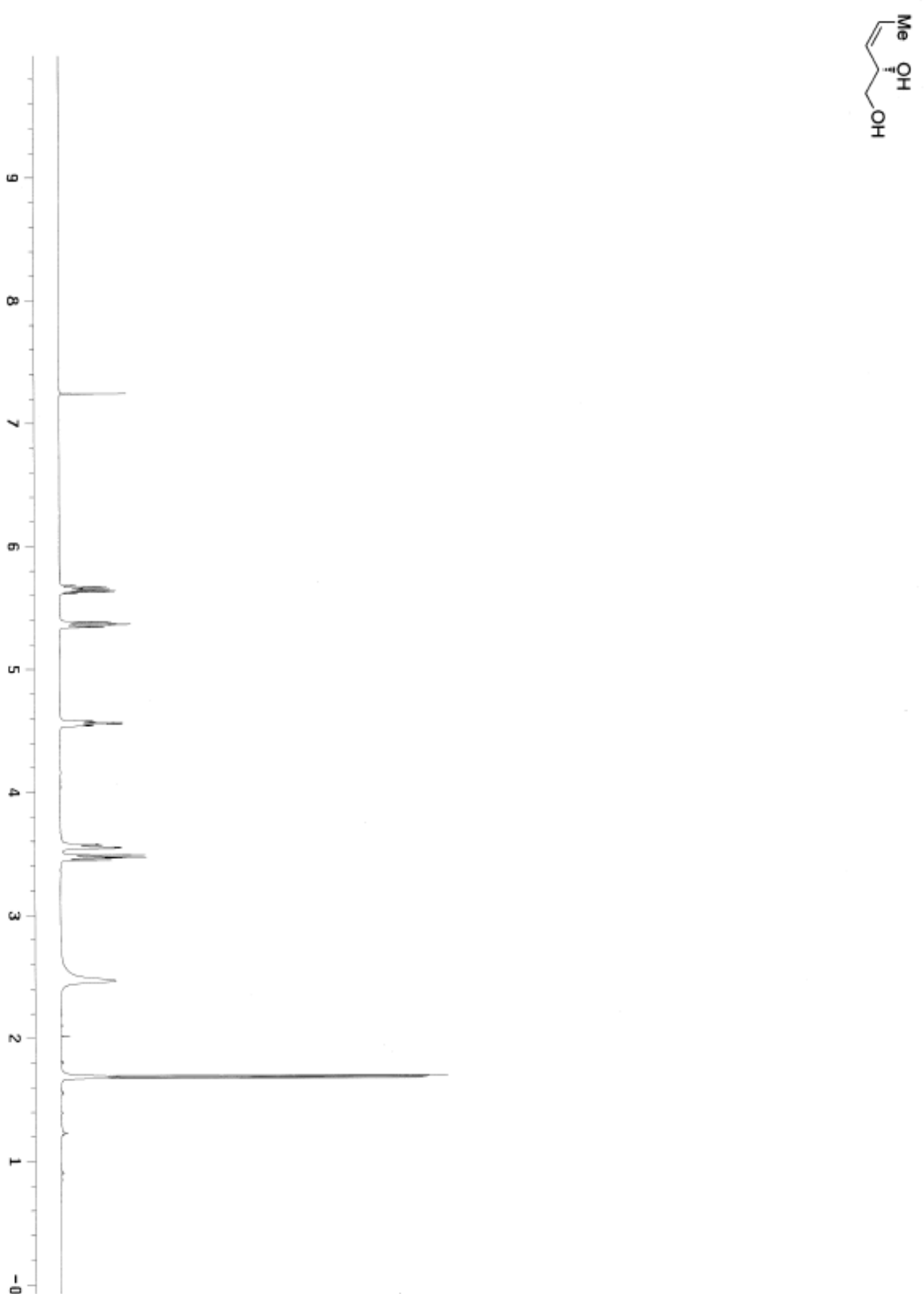
mixture of products from **(*R,R*)-3.44** and **(*S,S*)-3.44**

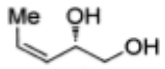
derived from reaction product using **(*S,S*)-3.44**

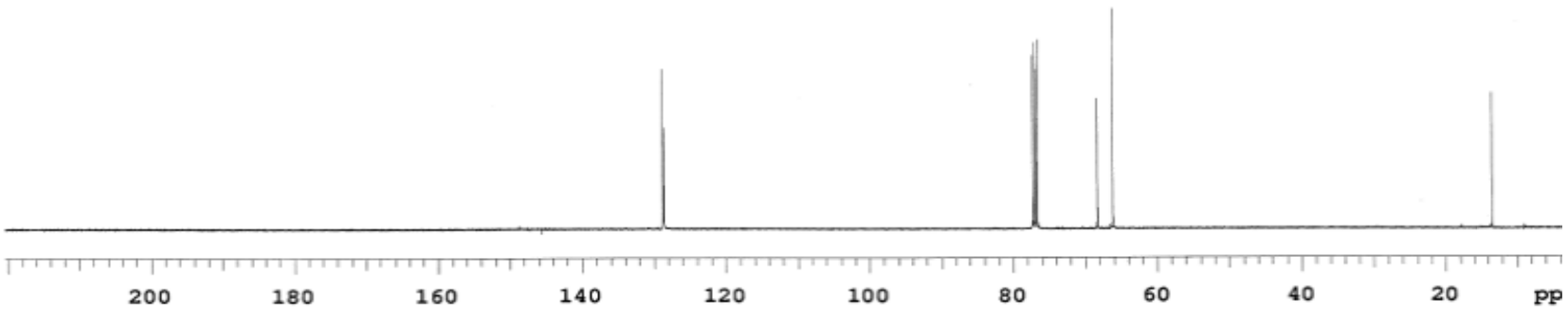
reaction product spiked with "rac"

Peak No	% Area	Area	RT (min)	Height (mV)
1	97.1166	39804.9326	8.8	1668.4574
2	2.8834	1181.817	15.65	40.7109

2.8 Representative NMR Spectra




Me
OH
OH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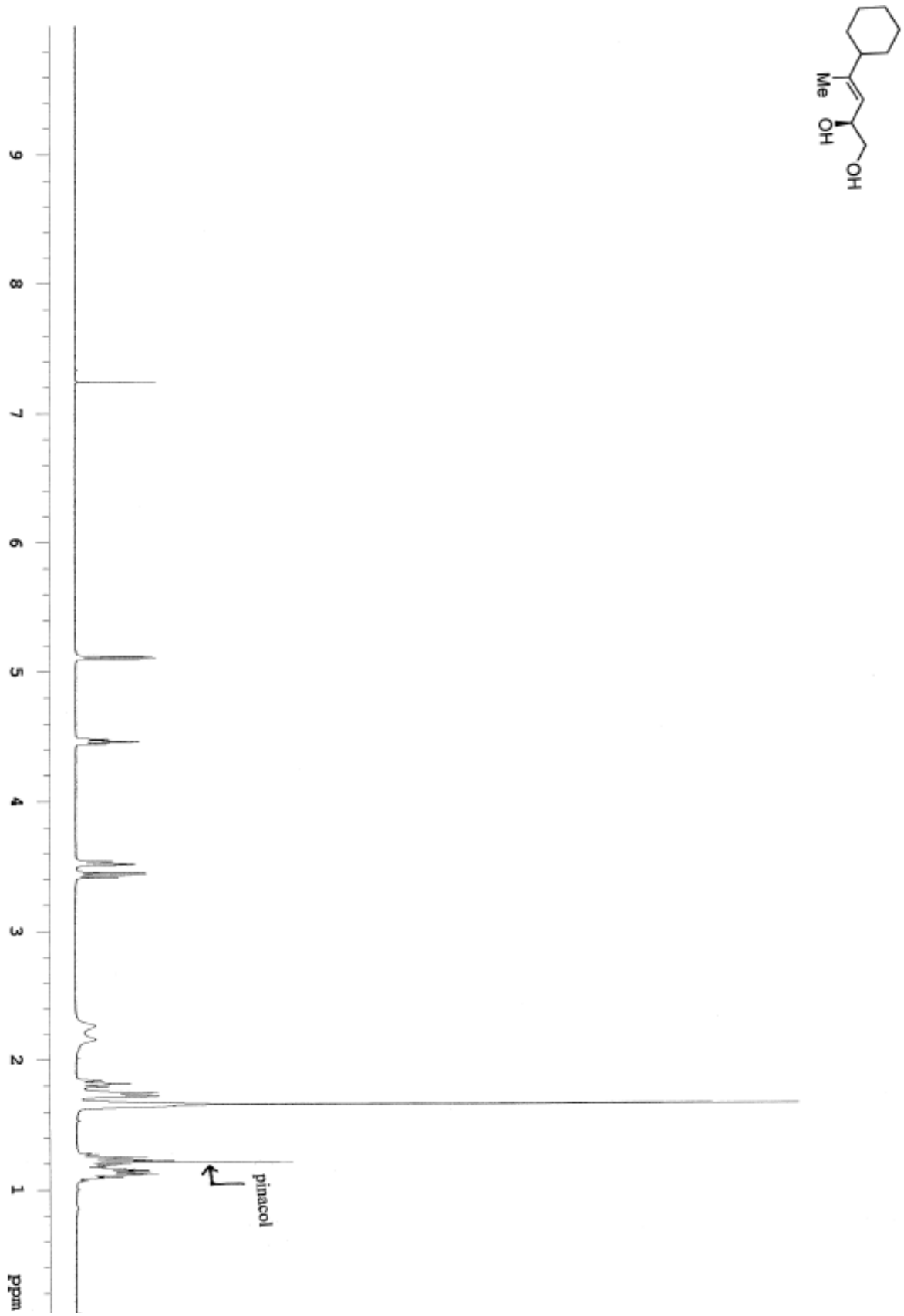
180
160
140
120
100
80
60
40
20
pp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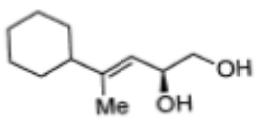
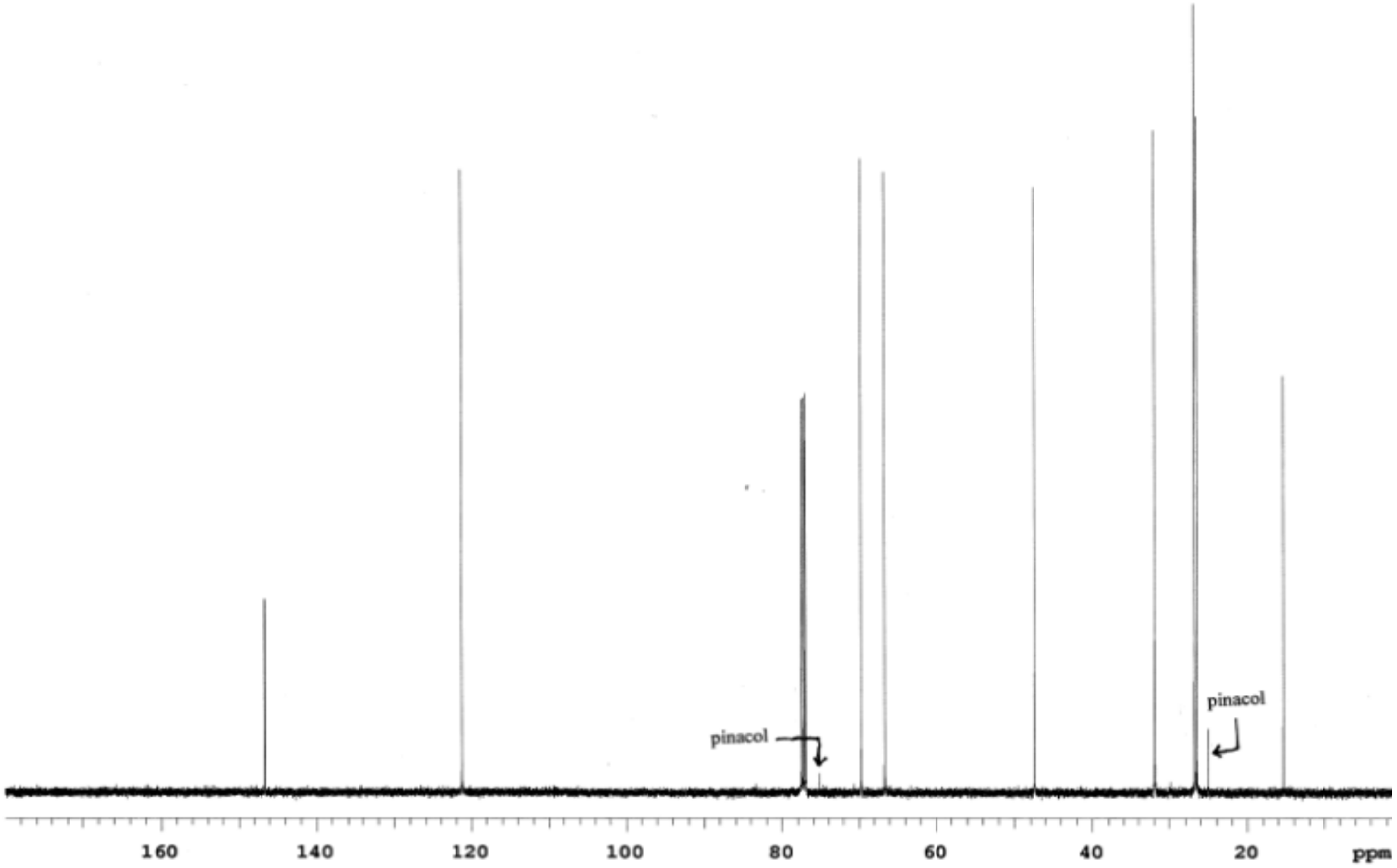
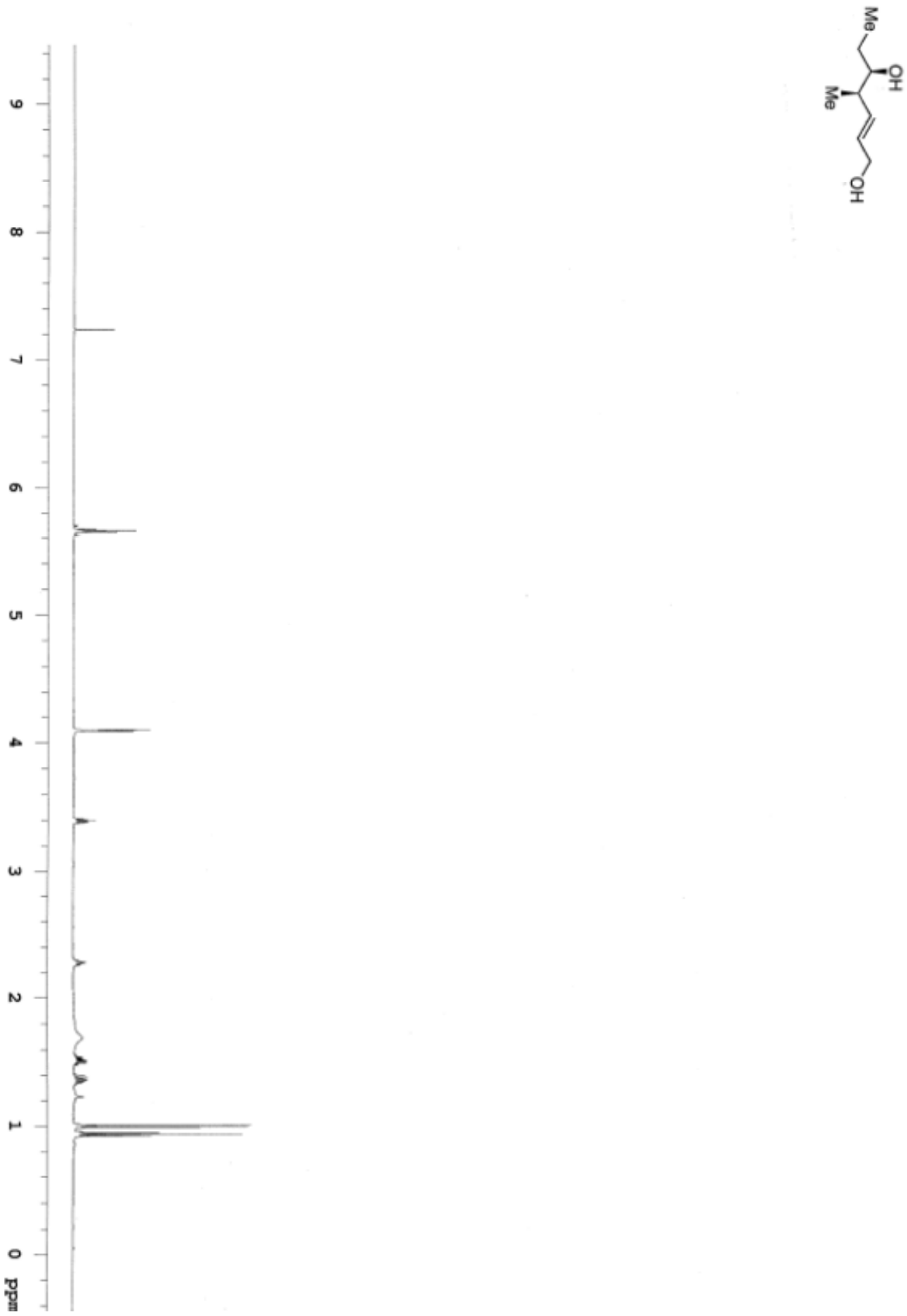
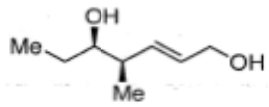
OH
pinacol
9
8
7
6
5
4
3
2
1
ppm


OH
Me
OH


pinacol
pinacol
160
140
120
100
80
60
40
20
ppm


Me
OH
Me
OH
9
8
7
6
5
4
3
2
1
0
ppm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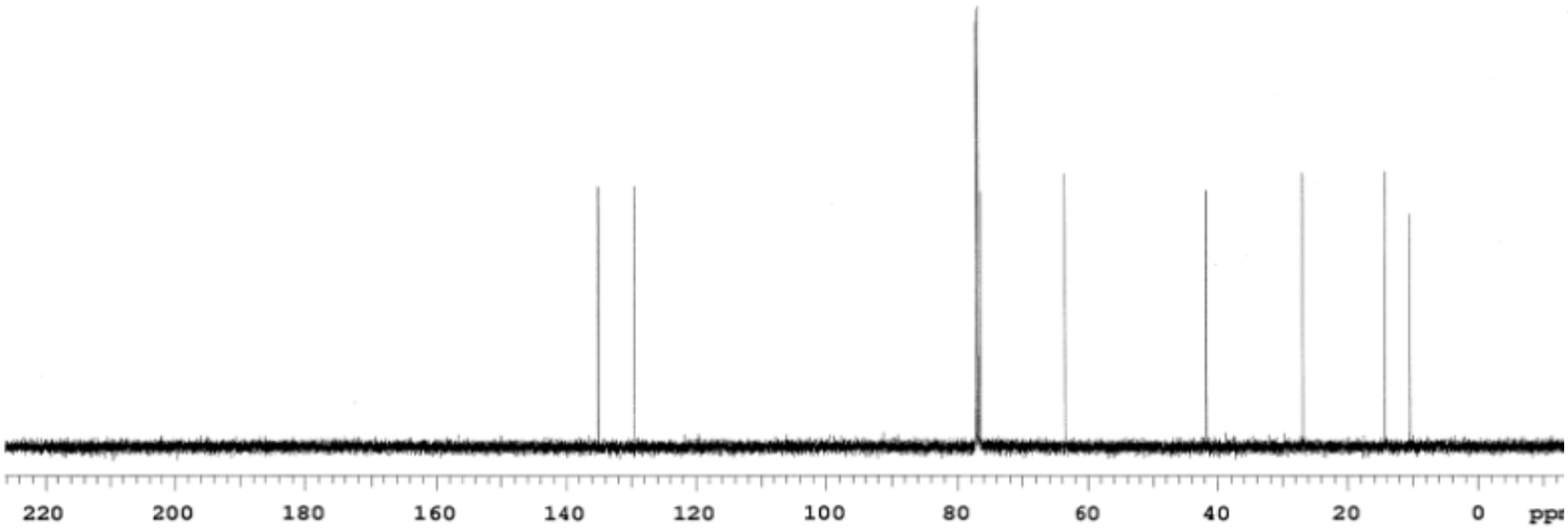
Me
OH
Me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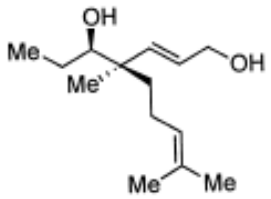
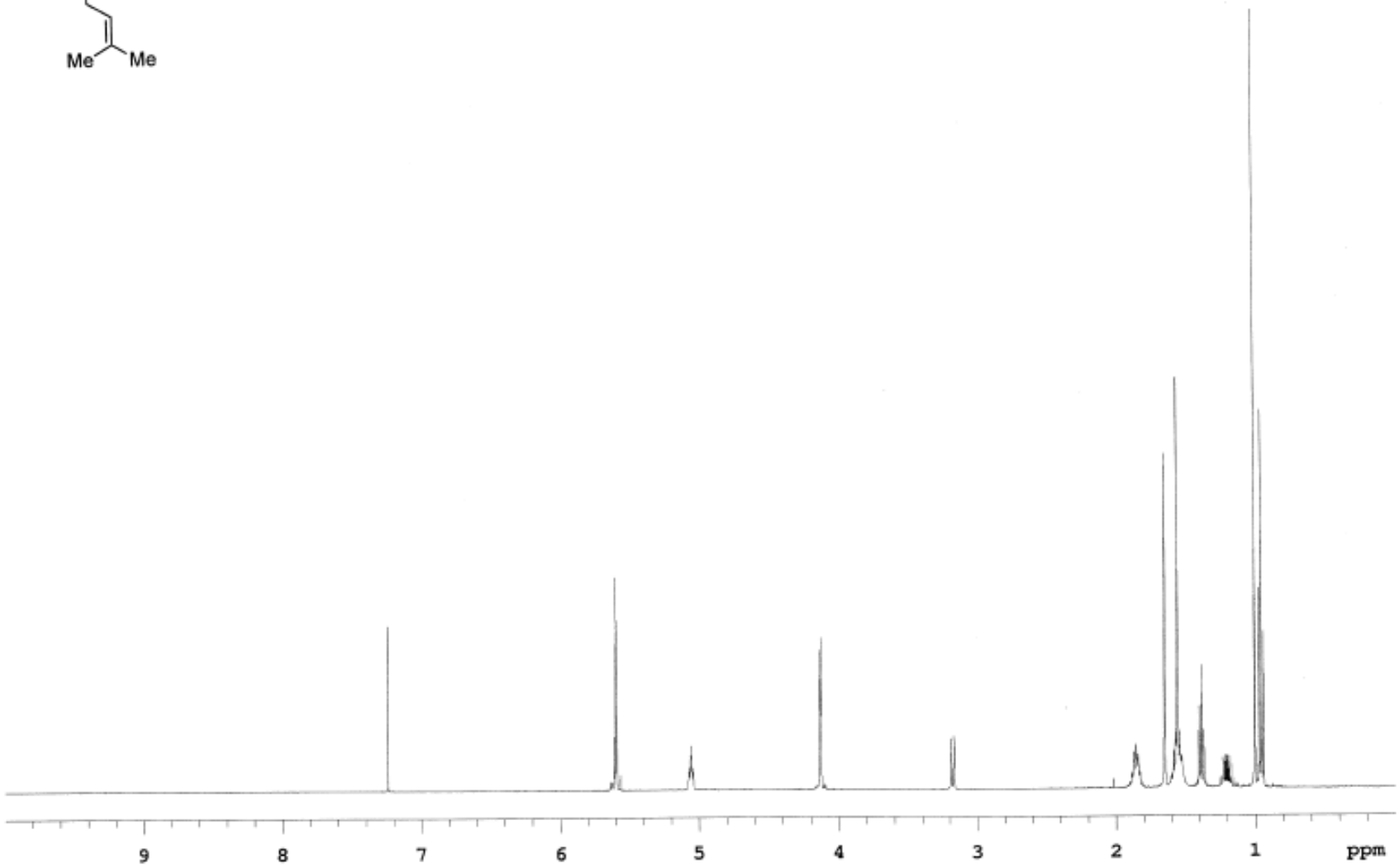
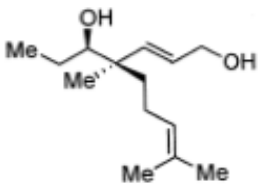
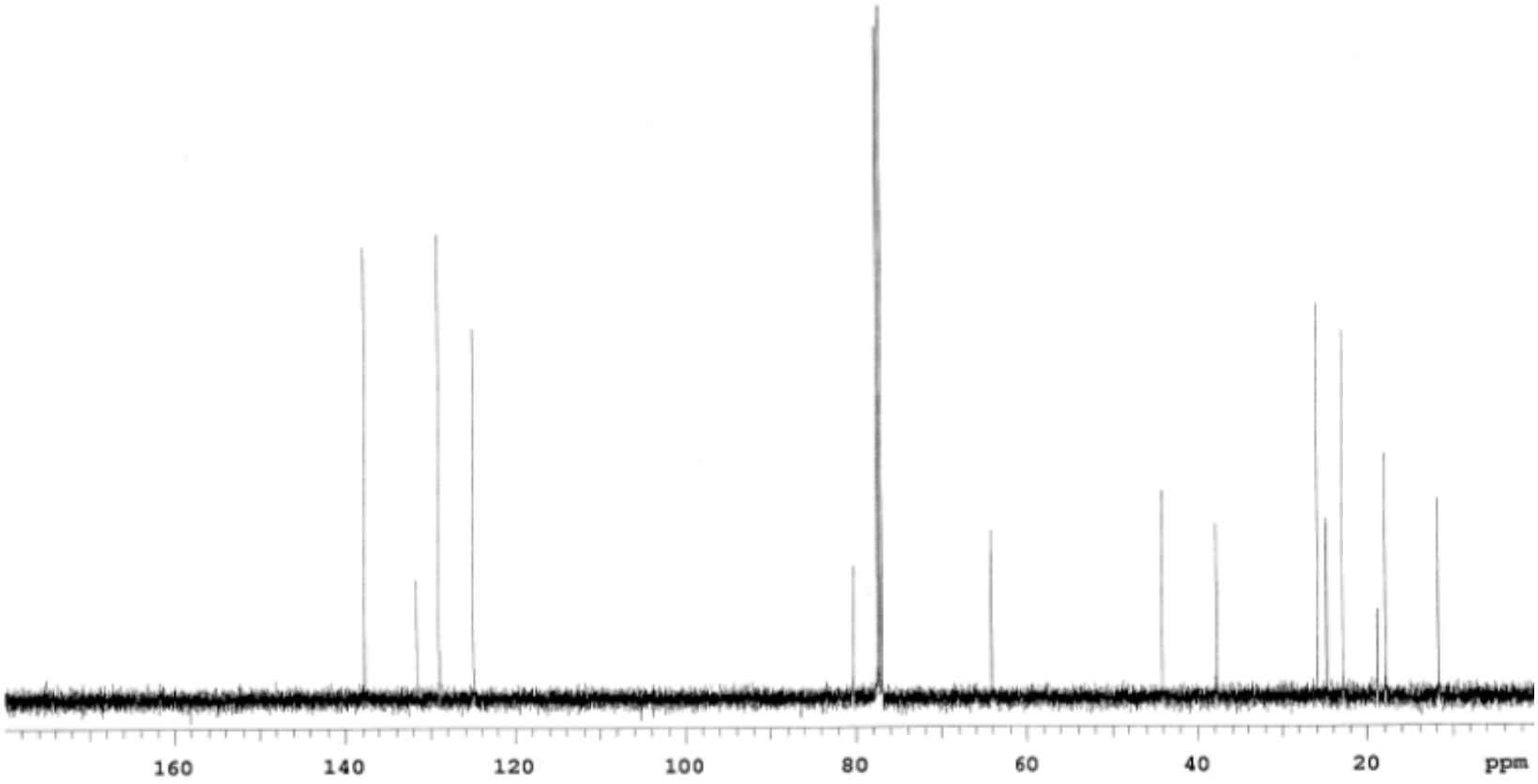
180
160
140
120
100
80
60
40
20
0
ppm


OH
Me
Me
OH
Me
Me


9
8
7
6
5
4
3
2
1
ppm


OH
Me
Me
OH
Me
Me


160
140
120
100
80
60
40
20
ppm

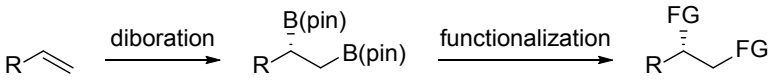
Chapter 3

Development and Scope of Selective Cross-Coupling of 1,2-Bis(Boronate) Esters: Application to Asymmetric Synthesis

3.1 Introduction

The enantioselective diboration of terminal alkenes discussed in chapter 1 successfully converts simple, achiral commodity chemicals into reactive chiral intermediates with excellent asymmetric control. While direct oxidation of the intermediate bis(boronate)esters delivers an attractive alternative to current asymmetric dihydroxylation reactions, a greater synthetic impact of this methodology remains embedded in the reactivity of the carbon-boron bonds. Subjection of the bis-boronate to reaction conditions for known transformations of carbon-boron bonds has the potential to generate a plethora of enantioenriched 1,2-difunctionalized products from a single α-olefin (Scheme 3.1).

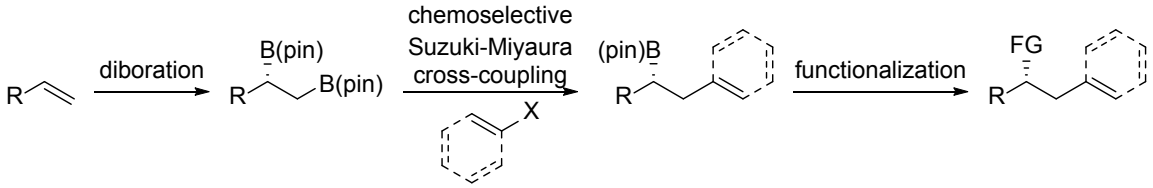
Scheme 3.1 Functionalization of Enantioenriched 1,2-Bis(boronate) Esters



A particularly appealing feature of the 1,2-bis(boronate) ester is that the boron atoms are bound to differentially substituted carbons, generating the possibility of chemoselective functionalization. Instead of converting both boronic acid pinacol esters into the same functional group, selective manipulation would enable two separate and distinct transformations and greatly expand the potential synthetic targets that are accessible from simple α-olefins. While any chemoselective transformation of 1,2-

bis(boronate) esters would be useful, direct carbon-carbon bond formation through Suzuki-Miyaura cross-coupling of the terminal boron moiety has the greatest potential impact for asymmetric synthesis (Scheme 3.2). Combined with enantioselective diboration, this would enable direct chain elongation of terminal alkenes while simultaneously establishing a highly versatile stereocenter poised for further functionalization.

Scheme 3.2 Selective Cross-Coupling of 1,2-Bis(boronate) Esters



Despite the vast attention in the catalysis community over the past several decades, Suzuki-Miyaura cross-coupling still suffers several limitations that render reactions of some substrates problematic. Unfortunately, the bis(boronate) ester derived from asymmetric diboration exhibits two of these inherent complications making it a challenging partner in cross-coupling. First, reactions of alkyl boronates proceed through the intermediacy of alkyl palladium intermediates. The latter compounds may engage in beta-hydride elimination thereby producing undesired byproducts. Secondly, boronic acid pinacol esters are less Lewis acidic than the majority of other boron analogues and this results in a more difficult transmetallation. Although developing the desired transformation appears daunting, the potential impact of the overall reaction sequence proved too great to ignore. Uncovering an operationally simple and robust reaction of this type would have a tremendous impact in the synthesis community and has the potential to revolutionize retrosynthetic analysis by offering unprecedented bond disconnections.

3.2 Background

In the 1970's, the field of organic chemistry experienced one of the most exciting advancements in the past century with the discovery of transition-metal catalyzed cross-coupling reactions. In 1972, Kumada[1] and Corriu[2] independently reported the bond forming reaction between aryl and vinyl electrophiles with Grignard reagents in the presence of a Ni(II) complex. Shortly after the initial reports, Murahashi demonstrated that palladium was also a suitable catalyst for this transformation.[3] By employing palladium complexes, the scope of the organometallic reagent expanded to include organozinc,[4] organolithium,[5] and organostannane[6] reagents. While the reactions vary in the organometallic nucleophile employed, the general mechanism remains the same (Scheme 3.3). The catalytic cycle begins with oxidative addition of palladium (0) into the aryl halide bond of the electrophile to generate palladium (II) intermediate **3.1**. At this point, transmetallation of the reactive organometallic reagent produces intermediate **3.3** which, upon reductive elimination, affords the carbon-carbon bond in the product **3.4**. While the extension of the organometallic reagents broadened the scope of nucleophiles in cross-coupling, the use of toxic and highly reactive reagents generates sensitive reactions that typically exhibit low functional group tolerance.

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[1] (a) Tamao, K.; Sumitani, K.; Kumada, M. *J. Am. Chem. Soc.* **1972**, *94*, 4374. (b) Tamao, K.; Zembayashi, M.; Kiso, Y.; Kumada, M. *J. Orgamnomet. Chem.* **1973**, *55*, C91.

[2] Corriu, R. J. P.; Masse, J. P. *J. Chem. Soc., Chem. Commun.* **1972**, 144.

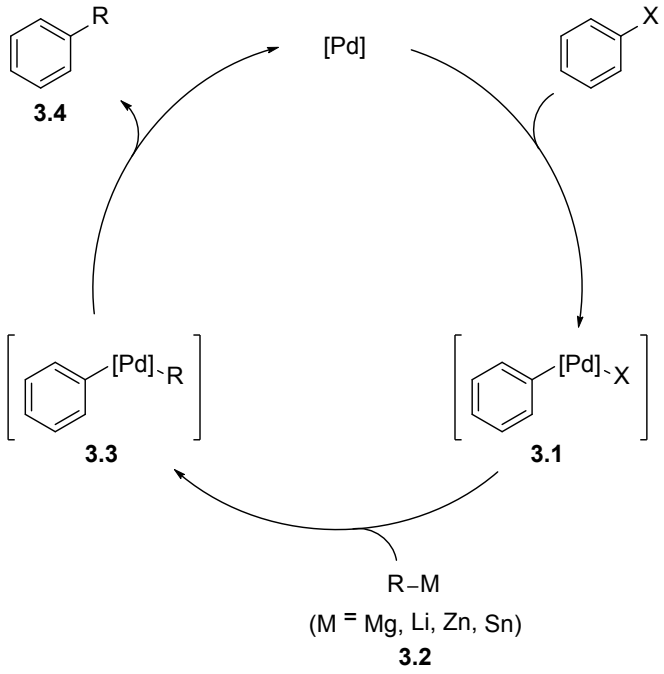
[3] Yamamura, M.; Moritani, I.; Murahashi, S. *J. Organomet. Chem.* **1975**, *91*, C39.

[4] (a) Negishi, E.; King, A. O.; Okukado, N. *J. Org. Chem.* **1977**, *42*, 1821. (b) King, A. O.; Okukado, N.; Negishi, E. *J. Chem. Soc., Chem. Commun.* **1977**, 683. (c) King, A. O.; Negishi, E. *J. Org. Chem.* **1978**, *43*, 358.

[5] Murahashi, S.; Yamamura, M.; Yanagisawa, K.; Mita, N.; Kondo, K. *J. Org. Chem.* **1979**, *44*, 2408.

[6] (a) Kosugi, M.; Simizu, Y.; Migita, T. *Chem. Lett.* **1977**, 1423. (b) Milstein, D.; Stille, J. K. *J. Am. Chem. Soc.* **1979**, *101*, 4992.

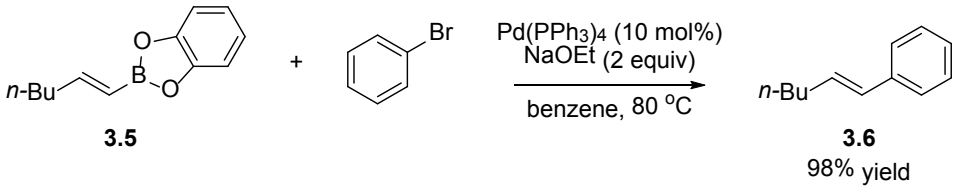
Scheme 3.3 General Mechanism for Palladium Catalyzed Cross-Coupling



Ultimately, many of the inherent limitations associated with cross-couplings of organometallic reagents were resolved with the development of reactions that employ less reactive organoboron and organosilicon[7] reagents. The use of organoboron reagents in palladium-catalyzed cross-coupling was first reported by Suzuki and Miyaura in 1979.[8] The seminal report revealed a phosphine-palladium catalyst for the successful bond formation between vinyl catechol boronates (derived from hydroboration of terminal alkynes) and aryl electrophiles (Scheme 3.4). This transformation required addition of an alkoxide base to promote transmetallation, but delivered the desired product **3.6** in excellent yield with low catalyst loading.

[7] Hatanaka, Y.; Hiyama, T. *J. Org. Chem.* **1988**, *53*, 918.
[8] Miayaura, N.; Suzuki, A. *J. Chem. Soc., Chem. Comm.* **1979**, 866.

Scheme 3.4 Seminal report of Suzuki-Miyaura cross-coupling

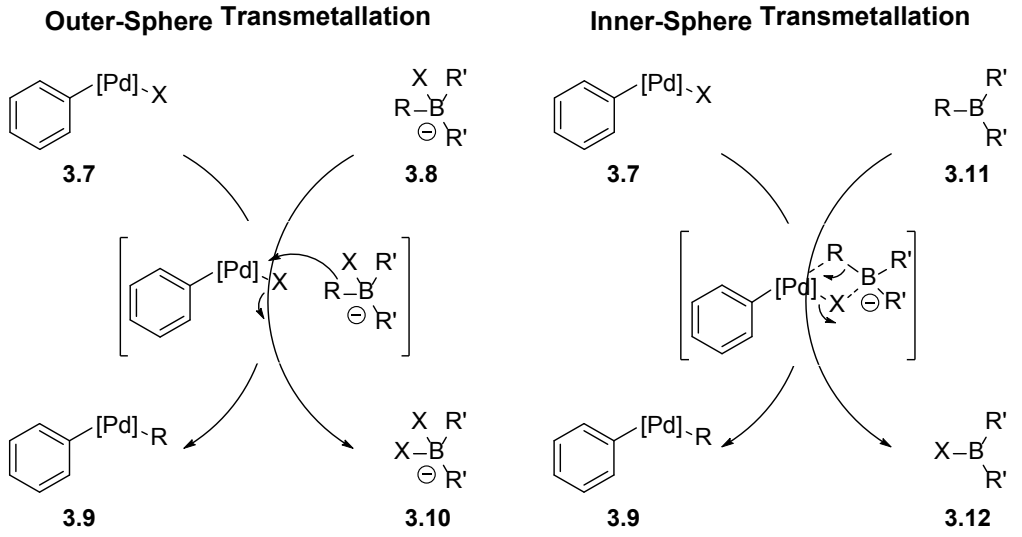


Since the initial discovery, the Suzuki-Miyaura cross-coupling has been extensively studied and is currently one of the most prominent carbon-carbon bond forming reactions employed in synthesis.[9] The ubiquitous acceptance of this reaction is due to the use of non-toxic organoboron reagents that are readily synthesized from a variety of precursors. With appropriate substitution, organoboron reagents can also be air and moisture stable making them ideal nucleophiles for cross-coupling reactions. The increased stability of organoboron reagents does, however, make them less reactive than other organometallic reagents such that they require external activation to promote transmetallation. Despite the extensive use of the Suzuki-Miyaura reaction, the exact mechanism for transmetallation is still under debate and is believed to occur through either an inner-sphere or an outer-sphere mechanism depending by case. The outer-sphere mechanism involves a reaction between a pre-formed borate species and a palladium(II) intermediate containing the corresponding halide leaving group (Scheme 3.5). Alternatively, the inner-sphere mechanism involves coordination of a ligand on palladium (II) to the empty p-orbital in the boron nucleophile. Coordination increases the electron density of the boron atom and effectively initiates the transmetallation process. While different mechanisms for activation are proposed, both pathways require borate

[9] Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron*, **2002**, *58*, 9633.

formation in order to promote transmetallation and ultimately generate the same intermediate **3.9** in the catalytic cycle.

Scheme 3.5 Possible Transmetallation Pathways for Organoboron Reagents

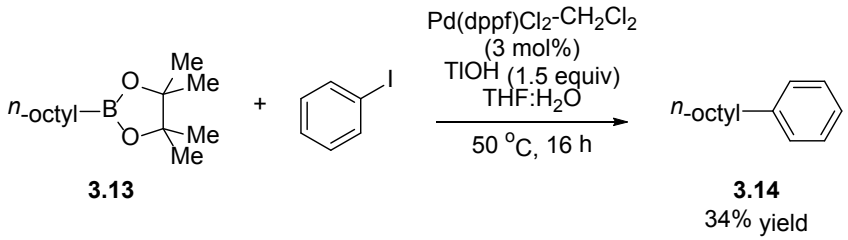


Regardless of which mechanism in Scheme 3.5 is the operative pathway for transmetallation, substitution on the boron atom has a direct effect on the efficacy of activation. While numerous organoboron derivatives have shown success as cross-coupling partners, a delicate equilibrium between reactivity and substrate stability is observed. Trialkylboranes are air and moisture sensitive, but participate in cross-coupling reactions with high levels of efficiency. Boronic acid pinacol esters are air and moisture stable, but due to the decreased Lewis acidity of the boron atom, are much harder to activate for transmetallation compared to analogous trialkyboranes. While the diminished reactivity has been addressed for vinyl and aryl pinacol boronates, cross-coupling of alkyl pinacol boronates remains challenging.

Cross-coupling of alkyl pinacol boronates, while uncommon in the literature, is not entirely unprecedented. The few examples known are generally less efficient relative

to the analogues aryl or vinyl nucleophiles and require toxic and strong bases in order to promote transmetallation. In 1989, Suzuki and Miyaura reported the first successful cross-coupling reaction with alkyl boronic acid esters (Scheme 3.6).[10] This transformation required super-stoichiometric amounts of toxic thallium(I) salts as well as highly activated aryl or vinyl electrophiles in order to obtain synthetically useful yields of the desired product. While pinacol esters could be used, the transformation was far less efficient compared to reactions where the more Lewis acidic catechol derivatives were employed.

Scheme 3.6 First Successful Cross-Coupling of Alkyl Boronates

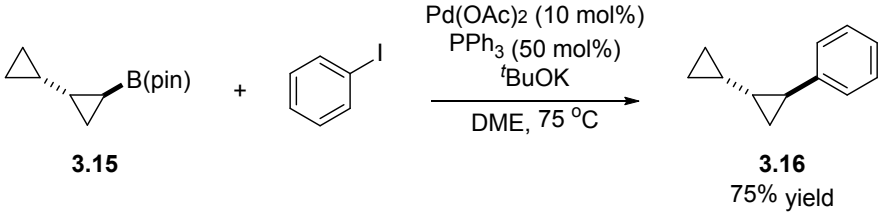


3.13 **3.14**
34% yield

The first example of cross-coupling of alkyl pinacol boronates without the use of highly toxic additives was reported by de Meijere and co-workers in 2001 (Scheme 3.7).[11] This transformation required high catalyst loadings and was only applicable to cyclopropyl pinacol boronates. While the scope of the cross-coupling reaction was limited, it was noted that the stereochemistry of the substrate was retained throughout the transformation.

[10] Sato, M.; Miyaura, N.; Suzuki, A. *Chem. Lett.* **1989**, 1405.
[11] Löhr, S.; Meijere, A. *Synlett*, **2001**, 489.

Scheme 3.7 Cross-Coupling of Cyclopropyl Pinacol Esters

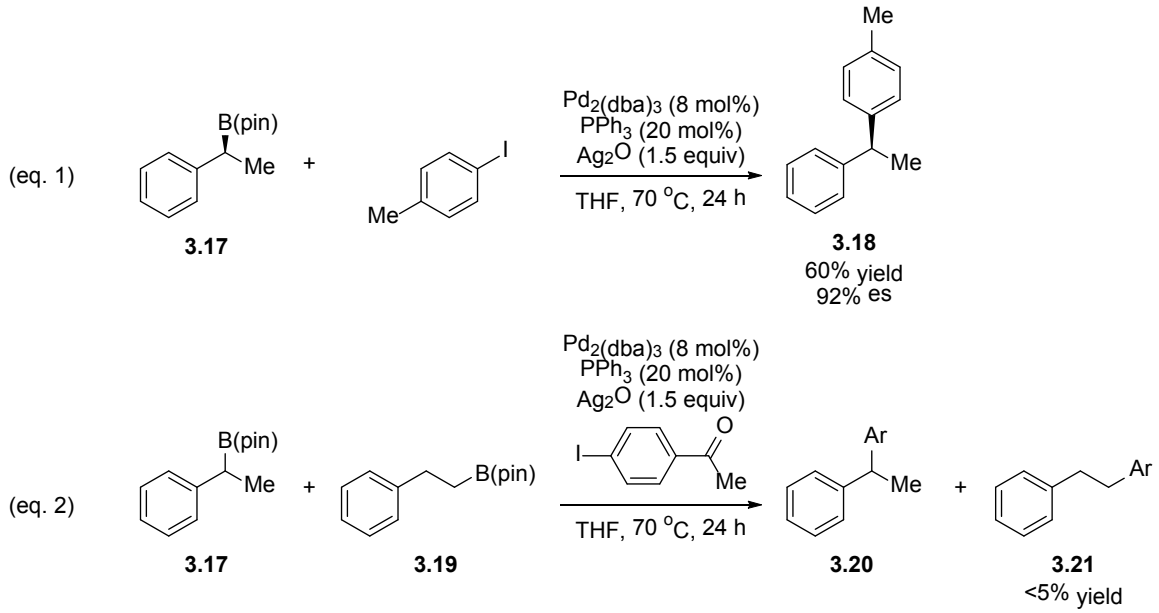


3.15 **3.16** 75% yield

Another unique substrate class that has been successfully employed in cross-coupling reactions is benzylic pinacol boronates.[12] Crudden and co-workers reported that commonly used bases such as Cs_2CO_3 or K_3PO_4 were ineffective at promoting transmetallation, but the desired product could be obtained when silver salts were employed. Importantly, the cross-coupled product was obtained with high levels of stereoretention when enantioenriched benzylic pinacol boronate substrates were used (Scheme 3.8, eq 1). Unfortunately, the increased reactivity observed with the addition of silver oxide was not observed with simple alkyl pinacol boronates. When both **3.17** and **3.19** were subjected to the reaction conditions, only the benzylic substituted product was obtained (Scheme 3.8, eq 2). Subjecting only **3.19** to the reaction conditions similarly failed to produce any desired product **3.21**, further demonstrating the inherent reactivity difference between benzylic and alkyl pinacol boronates in the cross-coupling reaction.

[12] (a) Imao, D.; Glasspoole, B. W.; Laberge, V. S. Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. (b) Glasspoole, B. W.; Oderinde, M. S.; Moore, B. D.; Antoft-Finch, A.; Crudden C. *Synthesis*, **2013**, *45*, 1759.

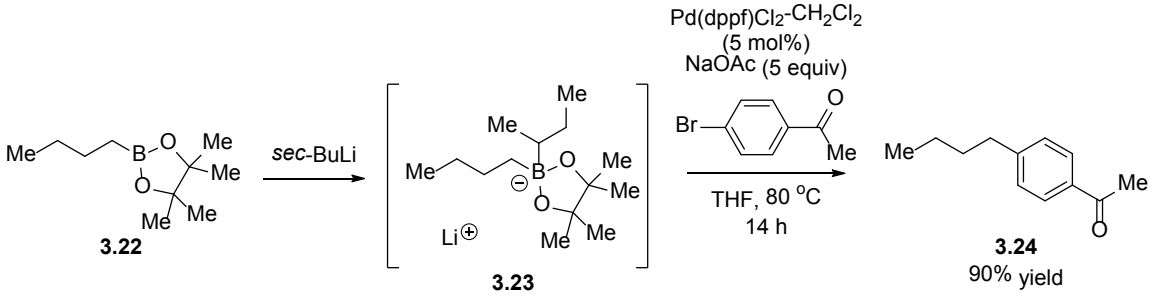
Scheme 3.8 Cross-Coupling of Benzylic Pinacol Boronates



Although simple alkyl pinacol boronates are substantially less reactive than cyclopropyl or benzylic derivatives, their use in cross-couplings has been accomplished without requiring the addition of highly toxic bases.[13] This transformation, reported by Falck and co-workers, requires pre-complexation of the primary boronate with sec-butyl lithium to form a tetrahedral borate intermediate (Scheme 3.9). Addition of the pre-formed borate to a solution of electrophile and palladium catalyst results in an effective carbon-carbon bond forming reaction. Importantly, the transmetallation proved to be chemoselective; the only product was derived from incorporation of the less hindered primary alkyl group. Although this reaction offered a significant advance regarding cross-couplings of alkyl pinacol esters, the requirement of a strong alkyl lithium base severely limited the overall substrate scope of the reaction.

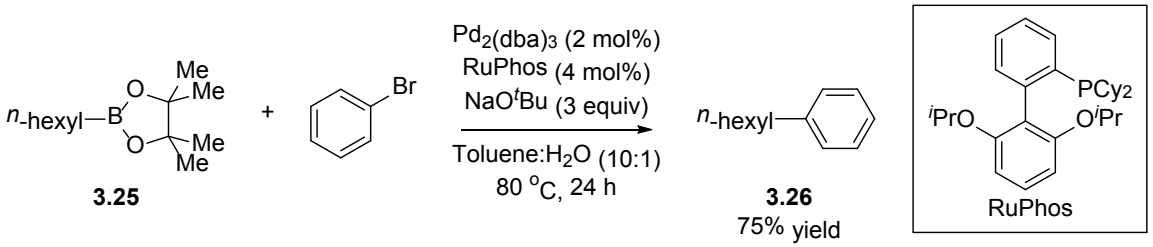
[13] Zou, G.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 5817.

Scheme 3.9 Cross-coupling of Alkyl Boronates through Preformed Borate Complexes



Recent advances in phosphine ligand design has improved reaction efficiency. With new ligands, the desired cross-coupling of alkyl boronate esters can be accomplished without requiring the use of toxic and strong bases. RuPhos, a monodentate phosphine ligand developed by Buchwald to increase reactivity of hindered aryl electrophiles, was recently shown to efficiently promote the cross-coupling of primary alkyl pinacol boronates and aryl bromides (Scheme 3.10).[14] This reaction requires excess pinacol boronate and extended reaction times, but it generates the desired product in excellent yield under relatively mild reaction conditions.

Scheme 3.10 Cross-Coupling of Primary Alkyl Pinacol Boronates

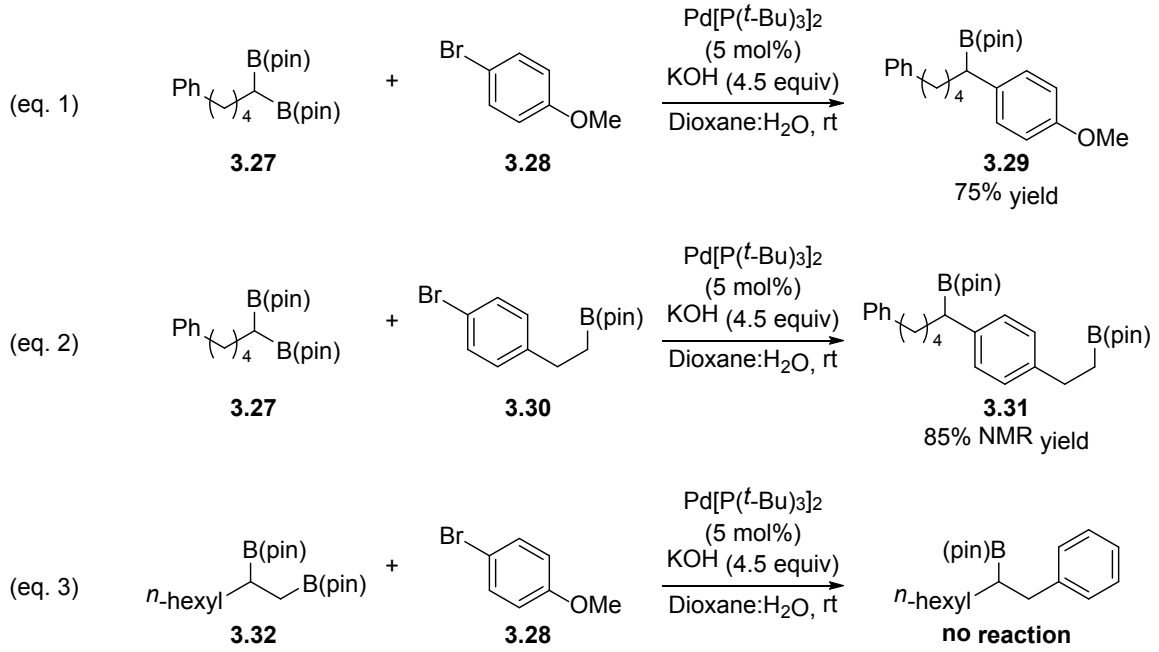


Suzuki-Miyaura cross-coupling of alkyl 1,1-diboronates with aryl bromides has also been reported (Scheme 3.11, eq 1).[15] This transformation is accomplished at room temperature and only requires the use of aqueous potassium hydroxide to promote

[14] Yang, C.-T.; Zhang, Z.-Q.; Tajuddin, H.; Wu, C.-C.; Liang, J.; Liu, J.-H.; Fu, Y.; Czyzeska, M.; Steel, P. G.; Marder, T. B.; Liu, L. *Angew. Chem. Int. Ed.* **2012**, *51*, 528.
[15] Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. *J. Am. Chem. Soc.* **2010**, *132*, 11033.

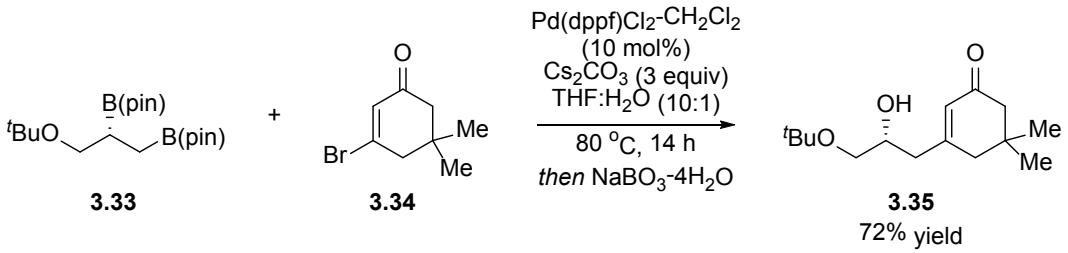
transmetallation. Interestingly, the 1,1-diboryl regioisomer was required for a successful cross-coupling reaction. Under identical reaction conditions, both a 1,2-bis(boronate)ester **3.32** (eq 3) and a terminal pinacol boronate **3.30** (eq 2) failed to participate in the reaction. The unique reactivity observed with the 1,1-diboronate was rationalized by a p-orbital overlap between the two germinal boron atoms. This orbital overlap decreases the energy of the LUMO through electron delocalization, and effectively lowers the energy associated with borate formation. The authors supported their hypothesis with DFT calculations as well as ^{11}B NMR analysis. The NMR experiments highlighted a dramatic increase in borate formation for the 1,1-diborylalkane at room temperature with potassium hydroxide compared to either the 1,2-regioisomer or the mono-borylalkane substrate.

Scheme 3.11 Cross-Coupling of Alkyl 1,1-Diboronates



Although cross-coupling of 1,2-bis(pinacolboronate)esters was not achieved by Shibata, a single example has been reported in the literature. In 2009, Hoveyda et al. reported a bis-copper-borylation of terminal alkynes to generate enantioenriched 1,2-bis(pinacolato)boronates.[16] To demonstrate the synthetic utility of this transformation, the authors subjected purified diboron **3.33** to cross-coupling conditions with β-bromoenone **3.34** (Scheme 3.12). In the presence of a commercial palladium catalyst the desired product **3.35** was obtained in 72% yield with complete retention of the secondary pinacol boronate stereochemistry.

Scheme 3.12 Cross-Coupling of Alkyl 1,2-Diboronates



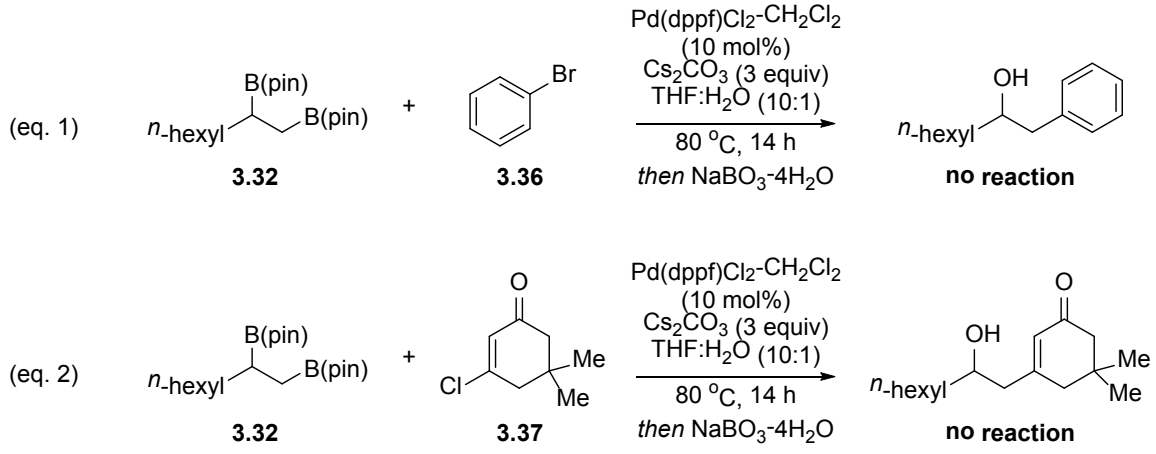
Suzuki-Miyaura cross-coupling has been extensively studied and utilized by the chemistry community since its discovery in 1979. Considering the vast attention the reaction has received, the limited literature precedence of successful cross-couplings of alkyl pinacol boronates serves to highlight the difficulty of the transformation. Developing a simple and efficient chemoselective cross-coupling of 1,2-bis(boronate)esters would therefore have an enormous impact in the field of synthetic chemistry as well as catalyst development.

[16] Lee, Y.; Jang, H.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 18234.

3.3 Development and Scope of a Regioselective Suzuki-Miyaura Cross-Coupling of Enantioenriched 1,2-bis(pinacolato)boronates[17]

Development of a general regioselective cross-coupling reaction of bis(boronate) esters began with investigating the conditions depicted in Scheme 3.12 utilized by Hoveyda and co-workers. Unfortunately, while these conditions successfully promoted the cross-coupling reaction between diboron **3.33** and β-bromoenone **3.34**, no desired product was observed when less functionalized reagents were used (Scheme 3.13, eq 1). These conditions were also unsuccessfully applied to the cross-coupling reaction between diboron **3.32** and β-chloroenone **3.37** (eq 2). While exact replication of the literature results was not investigated, it was apparent that the reaction conditions shown in Scheme 3.13 do not offer a general solution for regioselective cross-coupling of 1,2-bis(pinacolato)boroantes. In order to expand the scope of the reaction beyond highly functionalized substrates, new reaction conditions must be developed.

Scheme 3.13 Attempted Cross-Coupling Using $Pd(dppf)Cl_2$

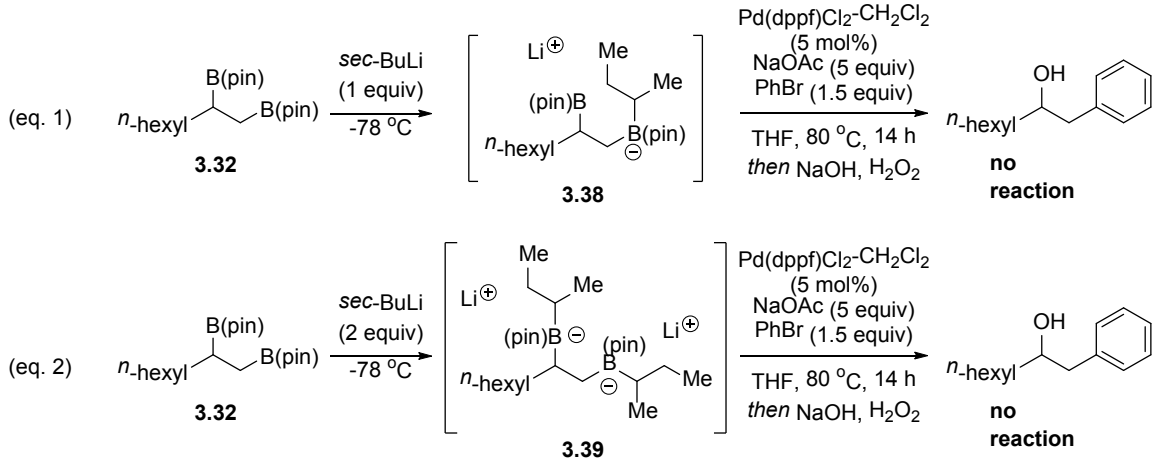


Selective cross-coupling of 1,2-bisboronates was also investigated using the preformed borate strategy developed by Falck. In hopes of a selective borate formation

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

with the less hindered primary boronic ester, this transformation was first attempted with equimolar amounts of diboron **3.32** and *sec*-butyl lithium (Scheme 3.14, eq 1). Under these reaction conditions, the desired cross-coupling product was not detected nor was the product derived from transmetallation of the internal boronic ester. The lack of reactivity observed may be explained through stabilization of the formed borate by the adjacent boron atom, which would effectively suppress transmetallation. In order to avoid this possible stabilization, the reaction was attempted with two equivalents of *sec*-butyl lithium to generate a highly energetic diborate intermediate. Following the observation made by Falck et al., only the primary alkyl group should participate in transmetallation resulting in a chemoselective transformation. Unfortunately, the diboron substrate was not stable to the strongly basic reaction conditions, even at cryogenic temperatures, and readily decomposed. The decomposition of an unfunctionalized diborylalkane highlights the necessity for uncovering milder reaction conditions if any useful functional group tolerance is to be observed.

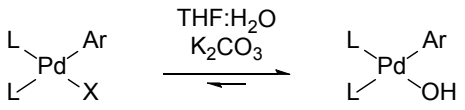
Scheme 3.14 Attempted Cross-Coupling Using Falck's Conditions



As anticipated at the onset of the project, the problematic step in the desired catalytic cycle appeared to be the transmetallation of the bis(boronate) ester. At this point in the reaction development we sought to simplify the model reaction even further and focus on uncovering conditions that efficiently promote transmetallation of alkyl boronic acid pinacol esters. Studying the reactivity of 1-octylB(pin) eliminates potential byproducts arising from complications with the internal boronate ester and focuses on identifying conditions that successfully promote transmetallation and suppress β-hydride elimination.

In attempts to identify the operative mechanism, Hartwig and co-workers performed a systematic analysis of the transmetallation in Suzuki-Miyaura cross-coupling (Scheme 3.5).[18] Their analysis uncovered the facile formation of a palladium(II) hydroxo species when the palladium(II) halide intermediate is in a basic biphasic reaction medium (Scheme 3.15). This palladium hydroxo species was determined to be the active intermediate, participating in an inner-sphere transmetallation under the reaction conditions employed. In order to promote an efficient transmetallation, the equilibrium between palladium(II)-halide (**3.40**) and palladium(II)-hydroxo (**3.41**) must favor the active species **3.41**. The equilibrium between the two species was found to be sensitive to the halogen, concentration of base, and ratio of aqueous and organic solvents used.

Scheme 3.15 Formation of Palladium Hydroxo Intermediate

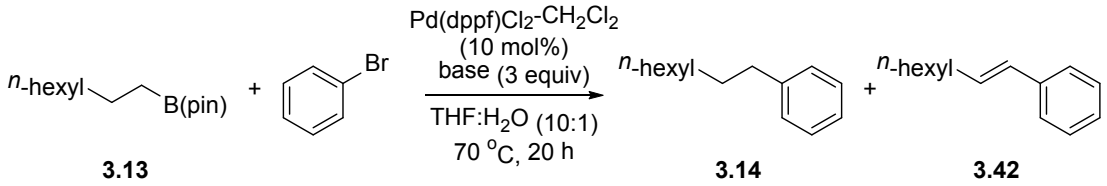


3.40 **3.41**

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

Inspired by the findings of Hartwig and co-workers, we decided to focus experimentation on identifying an optimal solvent, solvent ratio and base for the cross-coupling of 1-octylB(pin) and bromobenzene using a commonly employed commercial palladium(II) catalyst. A survey of bases was first performed, which exposed a strong influence of base on the efficiency of the reaction (Table 3.1). Weaker bases such as Cs_2CO_3 or fluoride (entries 1-5) were ineffective at promoting the desired transformation, while stronger hydroxide bases proved to be reactive. A counterion effect was observed among the hydroxide bases, with the highest conversion obtained from potassium hydroxide. While the result in entry 8 is far from optimal, the notable improvement in the reaction, while only altering a single variable, was encouraging.

Table 3.1 Optimization of Base for the Cross-Coupling of Alkyl Pinacol Boronates



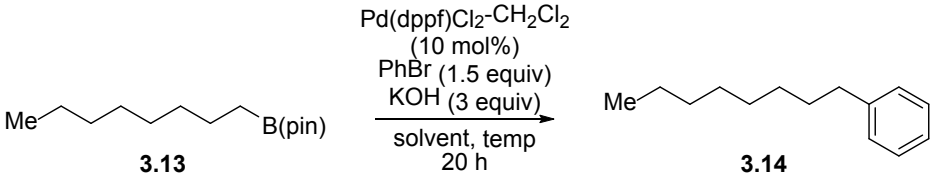
3.13 **3.14** **3.42**

entry	base	3.14 (%)[a]	3.42 (%)[a]
1	Cs_2CO_3	20	0
2	LiF	0	0
3	NaF	0	0
4	KF	<5	0
5	CsF	6	0
6	LiOH	41	<5
7	NaOH	51	<5
8	KOH	57	<5
9	$Ba(OH)_2$	38	<5
10	$Ca(OH)_2$	<5	0
11	nBu_4NOH	39	7
12	Et_3N	0	0

a) Percent $_{yield}$ of isolated material.

With the realization that hydroxide bases were required to promote transmetallation of alkyl boronates, and following the hypothesis that the reaction preceds through a palladium hydroxo intermediate, we hypothesized that the efficiency of the transformation could be improved by increasing the solubility of the base. Presumably, potassium hydroxide is predominately dissolved in the aqueous layer, while the desired transmetallation of the alkyl boronate with the palladium hydroxo intermediate occurs in the organic phase. Altering the properties of the reaction medium by changing the identity of the organic phase and ratio of organic and aqueous solvent directly affects the concentration of potassium hydroxide in both the organic and aqueous layers while potentially increasing the formation of the palladium hydroxo species. As anticipated, decreasing the polarity of the organic phase reduces the efficiency of the reaction, presumably through lowering the concentration of potassium hydroxide in the organic layer (Table 3.2). Unfortunately, the reaction is also negatively affected when highly polar organic solvents such as DMF or DMSO are used. While the solubility of potassium hydroxide is ultimately increased, the highly Lewis-basic nature of these solvents enables them to act as ligands and competitively coordinate to palladium. Changing the organic solvent from THF to dioxane resulted in similar conversion of reactants, but enabled the reaction to be performed at elevated temperatures (entries 7, 9, and 11). Additional manipulation of reaction solvent by decreasing the amount of water ultimately produced the most efficient conditions, promoting the desired reaction with 85% conversion of 1-octylB(pin) (entry 12). Importantly, the desired product was obtained cleanly with only trace amount of alkene arising from β-hydride elimination detected.

Table 3.2 Optimization of Solvent for the Cross-Coupling of Alkyl Pinacol Boronates

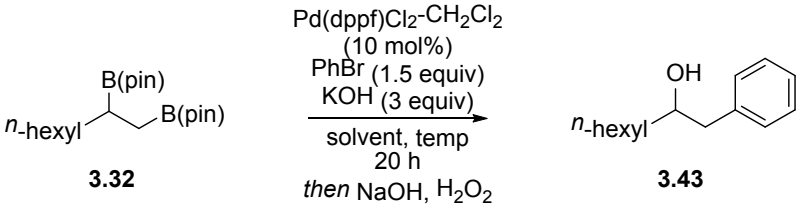


3.13 **3.14**

entry	solvent	temp (^{o}C)	3.14 (% conv)
1	Benzene:H_2O (10:1)	70	30
2	Benzene:H_2O (32:1)	70	39
3	DMF:H_2O (10:1)	70	<5
4	DMF:H_2O (32:1)	70	6
5	DMSO:H_2O (10:1)	70	19
6	DMSO:H_2O	70	<5
7	THF:H_2O (10:1)	70	57
8	THF:H_2O (32:1)	70	75
9	Dioxane:H_2O (10:1)	70	53
10	Dioxane:H_2O (32:1)	70	60
11	Dioxane:H_2O (10:1)	100	80
12	Dioxane:H_2O (32:1)	100	85

To determine if the observations discovered with the model substrate apply to the desired cross-coupling reaction, the cross-coupling of a 1,2-bis(boronate)ester was attempted using the improved conditions. Gratifyingly, the 1,2-bis(boronate)ester was completely consumed when subjected to the cross-coupling reaction with potassium hydroxide in dioxane/water; however, the desired product was only obtained in a 40% yield (Table 3.3, entry 1). Increasing the relative ratio of water, changing the organic solvent to THF, and decreasing the reaction temperature all proved beneficial. Ultimately, the desired product was obtained in an improved 62% yield while still maintaining complete conversion of the 1,2-bis(boronate)ester (entry 4).

Table 3.3 Initial Results for the Cross-Coupling of 1,2-Bis(Boronate) Esters

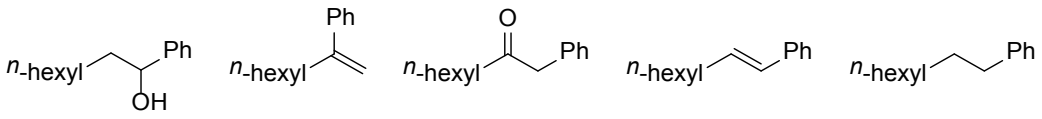


3.32 **3.43**

entry	solvent	temp (^{o}C)	conv (%)	yield **3.43** (%)
1	Dioxane:H_2O (32:1)	100	>98	40
2	Dioxane:H_2O (10:1)	100	>98	55
3	THF:H_2O (32:1)	70	>98	10
4	THF:H_2O (10:1)	70	>98	62

Although the desired homobenzylic alcohol was formed in a synthetically useful 62% yield, the discrepancy between consumption of starting material and isolated yield suggests possible competing byproduct formation. Thorough analysis of the crude reaction mixture revealed several byproducts including benzylic alcohol **3.44**, 1,1-disubstituted alkene **3.45**, ketone **3.46**, styrenyl derived alkene **3.42** and a fully saturated alkyl chain product **3.14** (Figure 3.1). Attempts to suppress formation of byproducts through altering the equivalence and identity of the base, reaction solvent, concentration and temperature of the reaction were unsuccessful. All modifications examined continued to produce one or more of the byproducts in unpredictable ratios, while leading to a decreased isolated yield of the desired alcohol **3.43**.

Figure 3.1 Byproducts Formed During Cross-Coupling of 1,2-Bis(boronate) Esters

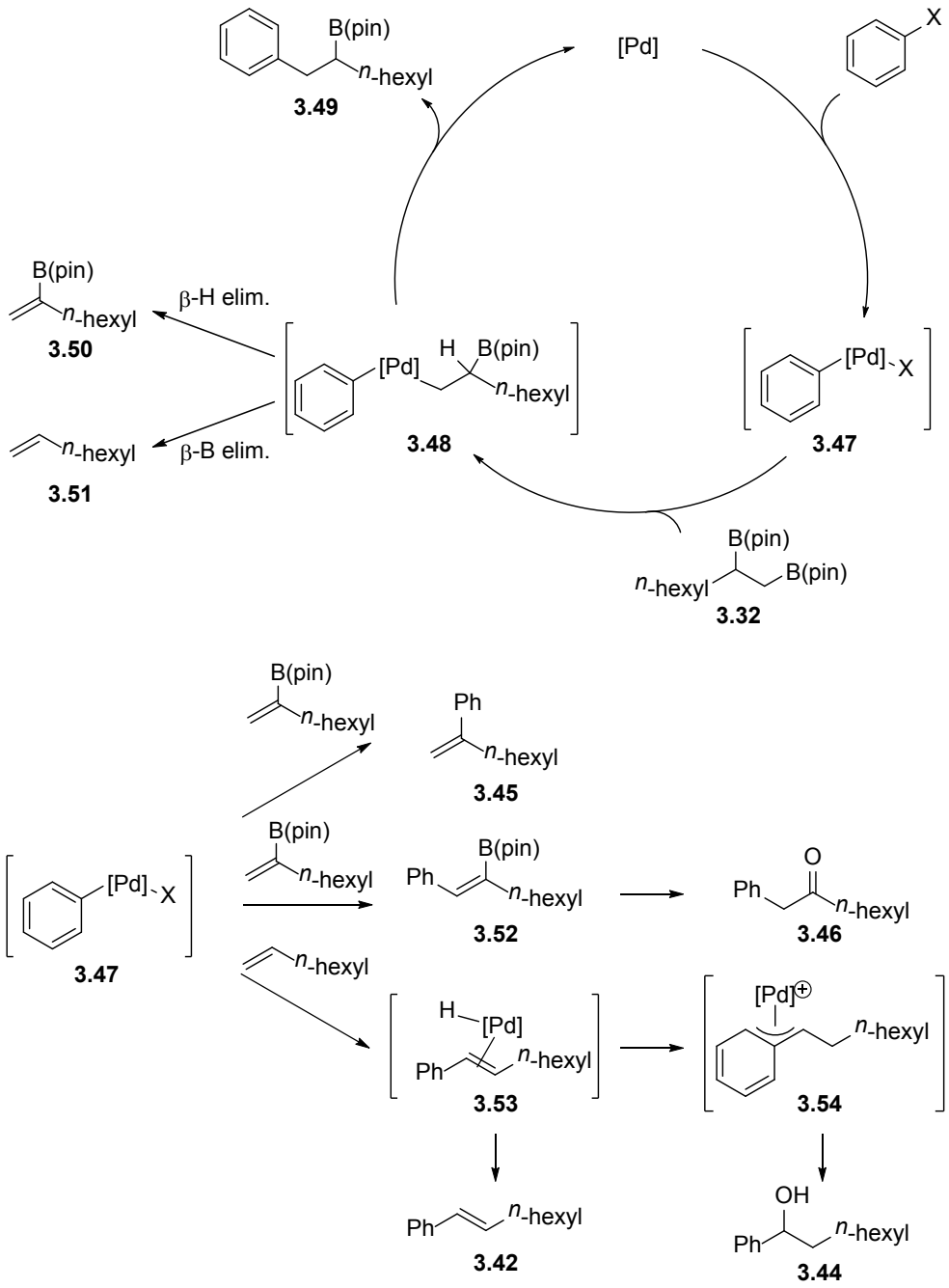


3.44 **3.45** **3.46** **3.42** **3.14**

While the exact mechanism for the formation of the byproducts was not investigated, plausible pathways are detailed in Scheme 3.16. Following transmetallation

with the bis(boronate) **3.32**, the palladium (II) intermediate **3.48** can undergo a productive reductive elimination generating the desired product **3.49**. Alternatively, intermediate **3.48** can undergo a β-hydride elimination event forming the internal vinyl boronate **3.50**, or it can participate in a formal β-boryl elimination generating 1-octene (**3.51**). The formed intermediates **3.51** and **3.50** can potentially interrupt the productive catalytic cycle through participation in Heck coupling reactions or an alternative Suzuki cross-coupling. Vinyl boronate **3.50** can undergo a more facile transmetallation, ultimately generating the observed 1,1-disubstited alkene **3.45** upon reductive elimination. Intermediate **3.47** can also participate in olefin insertion reactions with either 1-octene of vinyl boronate **3.50**, respectfully; this generates the styrenyl-derived alkene **3.42** or ketone **3.46** upon β-hydride elimination and oxidation of the reaction mixture. Formation of the benzylic alcohol **3.44** could arise through reinsertion of the palladium hydride intermediate **3.53** forming a stable π-benzyl intermediate **3.54**. External attack of hydroxide would ultimately generate the observed benzylic alcohol **3.44**. While merely speculative, the reaction pathways detailed in Scheme 3.16 offer plausible mechanisms for byproduct formation. However, if the described pathways are operative, then the formation of all six byproducts ultimately originate from complications with intermediate **3.48**. Following this hypothesis, complete byproduct suppression may be achievable through inducing a faster reductive elimination of intermediate **3.48** that outcompetes the undesired β-hydride or β-borylation elimination pathways.

Scheme 3.16 Plausible Mechanisms for the Formation of Byproducts



Reductive elimination is directly effected by the ligands on the metal with several ligand characteristics known to promote the process.[19] First, electron-withdrawing or π-acidic ligands reduce the electron density on the metal which effectively lowers the energy associated with gaining electrons during reductive elimination. Second, sterically cumbersome ligands generate a strained complex that releases energy upon reductively eliminating the substituents. Third, wide bite-angle bidentate ligands are known to promote reductive elimination by sterically forcing the participating substituents closer together, lowering the activation energy associated with the process.[20] With these steric and electronic characteristics in mind, a survey of phosphine ligands was performed to test the validity of the hypothesis described above (Table 3.4). Increasing the steric encumbrance by employing an isopropyl ferrocene-derived ligand in the cross-coupling led to an overall decrease in byproduct formation (entry 1 vs 2). Additional suppression of byproducts was observed when the cross-coupling was performed with larger bite angle ligands such as DPEphos and Xantphos (entries 3 and 4). An alternative approach to promote reductive elimination through employing Buchwald's hemi-labile biaryl ligands was simultaneously explored.[21] Although initially designed to extend catalyst life and promote cross-coupling of hindered aryl electrophiles, the Buchwald ligands proved vastly superior in the cross-coupling of 1,2-bis(boronate) esters, resulting in almost exclusive formation of the desired product (entries 5-7).

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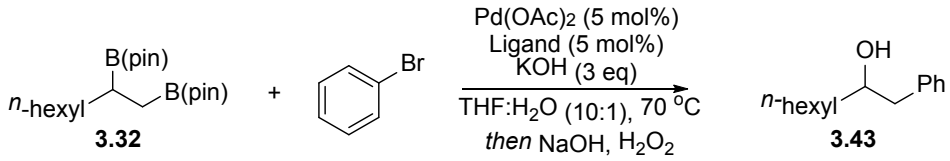
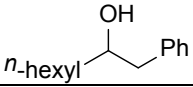
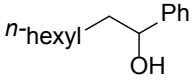
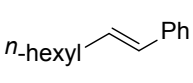
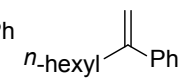
[19] (a) Brown, J. M. Cooley, N. A. *Chem. Rev.* **1988**, *88*, 1031. (b) Ozawa, F. In *Fundamentals of Molecular Catalysis*; Kurosawa, H.; Yamamoto, A.; Eds.; Elsevier: New York, 2013; Vol. *3*, p 479. (c) Hartwig, J. F. *Inorg. Chem.* **2007**, *46*, 1936. (d) Mann, G.; Shelby, Q.; Roy, A. H.; Hartwig, J. F. *Organometallics* **2003**, *22*, 2775. (e) Yamashita, M.; Vicario, J. V. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 16347. (f) Korenaga, T.; Abe, K.; Ko, A.; Maenishi, R.; Sakai, T. *Organometallics* **2010**, *29*, 4025.

[20] Birkholz, M.-N.; Freixa, Z.; Van Leeuwen, P. W. N. M. *Chem. Soc. Rev.* **2009**, *38*, 1099.

[21] (a) Barder, T; Walker, S.; Martinelli, J.; Buchwald, S. *J. Am. Chem. Soc.* **2005**, *127*, 4685. (b) Dreher, S.; Lim, S.; Sandrock, D.; Molander, G. *J. Org. Chem.* **2009**, *74*, 3626.

Table 3.4 Ligand Optimization for the Cross-Coupling of 1,2-Bis(Boronate) Esters



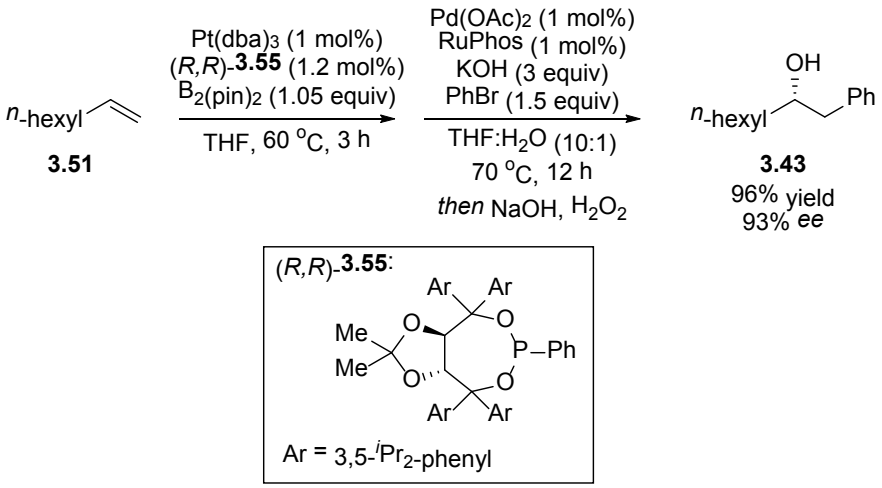
Ligand				
dppf	1.00	0.70	0.46	0.20
dippf	1.00	0.29	0.01	trace
Xant Phos	1.00	0.15	0.03	trace
DPE Phos	1.00	0.16	0.01	trace
dcpe	1.00	0.46	0.01	0.04
XPhos	1.00	0.17	0.05	trace
SPhos	1.00	0.02	trace	0.02
RuPhos	**1.00**	**0.01**	**trace**	**trace**

Product ratios were determined by ^{1}H NMR analysis on the crude reaction mixture

With an effective cross-coupling catalyst system identified, the feasibility of achieving a single-flask diboration/cross-coupling procedure was investigated. While a two-step procedure transforming a simple α-olefin into complex products such as **3.43** is synthetically impressive, a single-flask operation would eliminate the need to purify the intermediate, generate less waste and ultimately save time and money. To determine if the reagents for the individual steps would adversely react and suppress the cross-coupling, pre-complexed palladium/RuPhos, potassium hydroxide and bromobenzene were directly added to the crude diboration mixture and the reaction was diluted with tetrahydrofuran and water. Excitingly, upon oxidation the desired product **3.43** was obtained with comparable efficiency to the cross-coupling reactions performed with the purified bis(boronate) ester. Under the single-flask reaction sequence, the diboration and cross-coupling reactions could ultimately be performed with only 1 mol% of each catalyst generating the desired alcohol **3.43** in a 96% yield from the 1-octene (Scheme

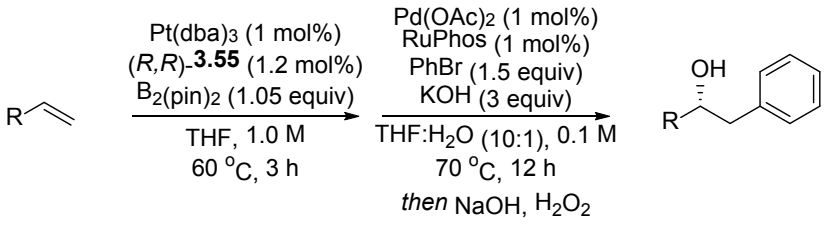
3.17). Importantly, the stereochemistry of the internal boronate ester was completely conserved throughout the reaction sequence.

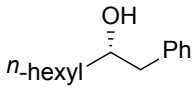
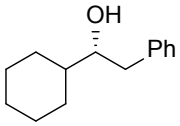
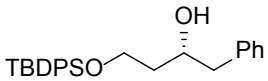
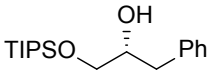
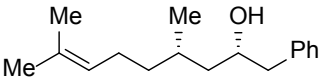
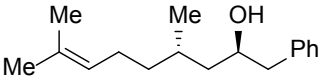
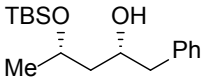
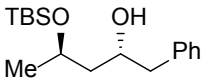
Scheme 3.17 One-Pot Diboration/Cross-Coupling Reaction



Once the optimized single-flask conditions were established, the scope of the diboration/cross-coupling (DCC) reaction was investigated. A variety of alkenes were examined in the DCC reaction with bromobenzene; this generated a diverse array of enantio-enriched homobenzylic alcohols (Table 3.5). Bis(boronate)esters generated from diboration of α-alkyl branched alkenes and alkenes containing silyl ethers were successfully cross-coupled, generating the desired products in excellent yield and enantioselectivity (entries 2-4). Interestingly, when examining homoallylic alcohols the TIPS protecting group (entry 4) proved paramount, with the TBS or TBDPS derivatives prone to elimination under the cross-coupling conditions. Alkenes containing alkyl- or oxygen-based β-stereocenters were also investigated and proved to be excellent substrates for the DCC reaction (entries 5-8). Diboration of these chiral substrates proceeds with catalyst control, generating the desired products in excellent yield and diastereomer ratios (17:1 to >20:1 dr).

Table 3.5 Alkene Substrate Scope for the Diboration/Cross-Coupling Reaction

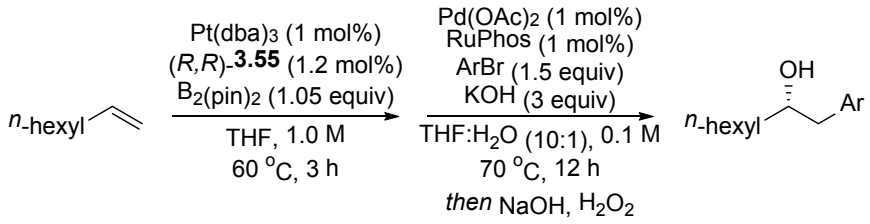


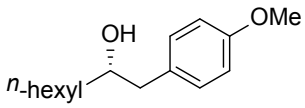
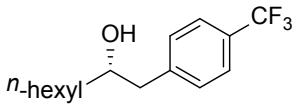
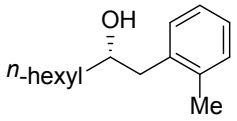
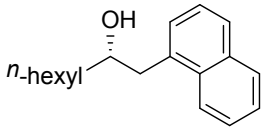
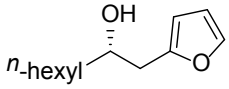
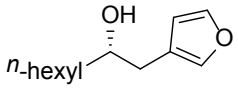
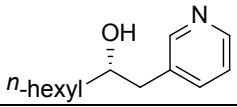
entry	product	yield (%)[a]	*ee* (%) or dr[b]
1		96	93
2		93	98
3		88	90
4[c]		62	89
5		97	>20:1
6[d]		96	>20:1
7		88	>20:1
8		94	17:1

[a] Percent yield of purified material. Value is average of two experiments. [b] *ee*(%) determined by GC or SFC analysis employing a chiral stationary phase. dr determined ^{1}H NMR. [c] (*R,R*)-1.46 ligand employed as chiral ligand in diboration. [d] (*S,S*)-**3.55** ligand employed as chiral ligand in diboration.

In addition to examining various alkenes, the scope of suitable electrophiles was also investigated. While bromobenzene proved to be the most efficient and highest yielding, other phenyl derived electrophiles can be used in the cross-coupling reaction but with varying success. Chlorobenzene was found to be an effective electrophile resulting in 88% yield of the desired product; however, iodobenzene and phenyltriflate proved to be significantly inferior leading to lower yields of the desired product (30% and 48% yield, respectively). Following this observation, only aryl bromide electrophiles were investigated (Table 3.6). The cross-coupling reaction tolerated both electron rich and electron poor aromatic electrophiles (entry 1 and 2) as well as sterically encumbered aryl bromides (entry 3 and 4). Notably, heteroaromatic electrophiles are also suitable substrates and furnish medicinally relevant compounds in synthetically useful yields with excellent enantiomeric excess (entries 5-7).

Table 3.6 Aryl Electrophile Substrate Scope for the Diboration/Cross-Coupling Reaction



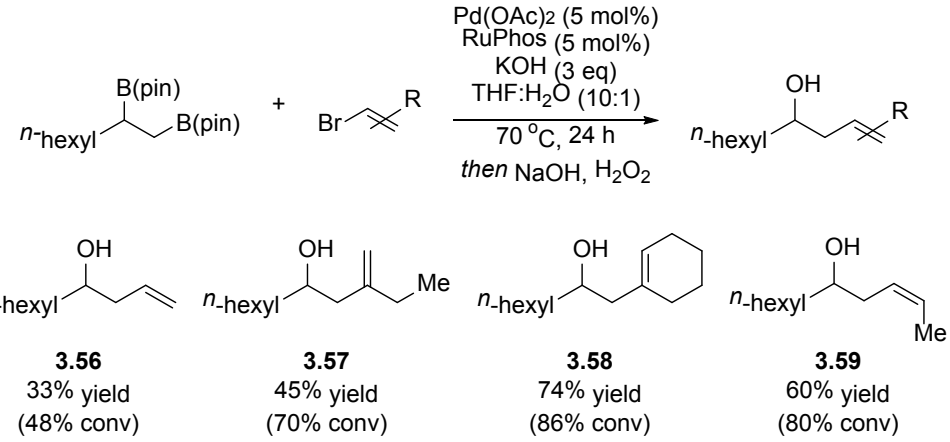
entry	product	yield (%)[a]	*ee* (%)[b]
1		96	93
2		93	98
3		88	90
4		90	90
5[c]		79	91
6[c]		63	92
7		86	95

[a] Percent yield of purified material. Value is average of two experiments. [b] Determined by SFC analysis employing a chiral stationary phase. [c] 1.0 equiv of LiCl was added.

Following the success of cross-coupling with various aryl electrophiles, the scope of the diboration/cross-coupling reaction was investigated to determine if vinyl electrophiles could be employed. Incorporation of vinyl halides in the DCC reaction would generate enantioenriched homoallylic alcohols from simple alkenes and could potentially have an even greater impact in the synthetic community compared to the homobenzylic products. Several vinyl bromides were examined under the optimized

conditions; however, even with higher catalyst loadings (5 mol%) and longer reaction times, the desired products were obtained in low isolated yields and with incomplete conversion of the bis(boronate)ester (Scheme 3.18).

Scheme 3.18 Cross-Coupling with Vinyl Bromides



3.56
33% yield
(48% conv)

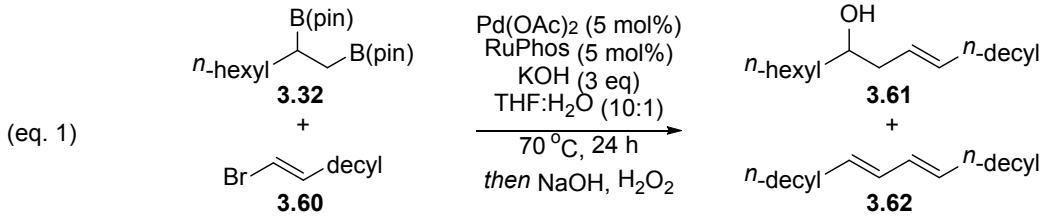
3.57
45% yield
(70% conv)

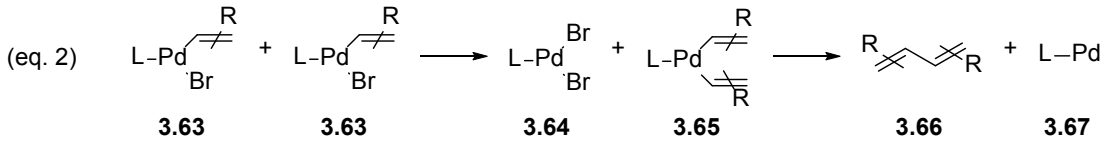
3.58
74% yield
(86% conv)

3.59
60% yield
(80% conv)

The reason for the discrepancy in reactivity between aryl and vinyl bromides remained elusive until the cross-coupling with *E*-1-bromo-1-dodecene was investigated. Analysis of the crude reaction mixture uncovered an internal diene byproduct (**3.62**), potentially arising from a disproportionation reaction between two palladium **3.63** intermediates, forming **3.64** and **3.65**. Reductive elimination of **3.65** would generate the observed diene **3.62** and a palladium(0) species that can reenter the catalytic cycle. The disproportionation event also generates an equivalent of dibromopalladium **3.64**, which is catalytically inactive. Eventually, if this side reaction continues to occur, the entirety of the palladium catalyst would be sequestered as the inactive **3.64** species.

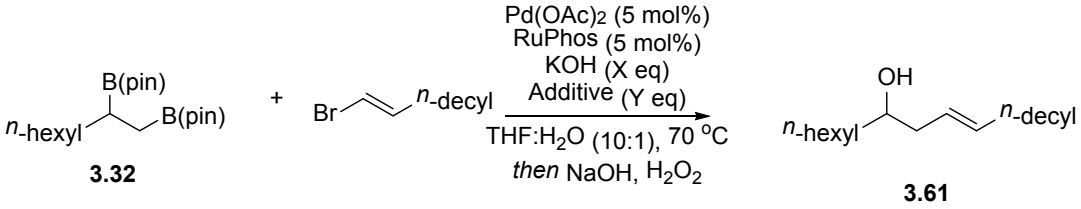
Scheme 3.19 Cross-Coupling with *E*-1-Bromo-1-Dodecene





In an effort to reintroduce intermediate **3.64** into the catalytic cycle, a small survey of mild reducing agents was performed. If palladium(0) could be regenerated *in situ* without affecting the desired cross-coupling reaction, yields might improve (Table 3.7). Of the reducing agents examined, ammonium formate proved the most effective, providing the closest correlation between conversion and isolated yield. Unfortunately, improving the yield of the reaction by altering the stoichiometry of reagents was only moderately effective and led to a maximum isolated yield of only 50%.

Table 3.7 Survey of Reducing Agents in Cross-Coupling with Vinyl Bromides



entry	additive (eq)	KOH (eq)	conv (%)[a]	yield (%)[b]
1	$NaHCO_2$ (1)	3	56	22
2	$KHCO_2$ (1)	3	65	21
3	NH_4HCO_2 (1)	3	34	31
4	NH_4HCO_2 (2)	3	0	-
5	NH_4HCO_2 (1)	6	65	48
6	NH_4HCO_2 (1)	9	90	53

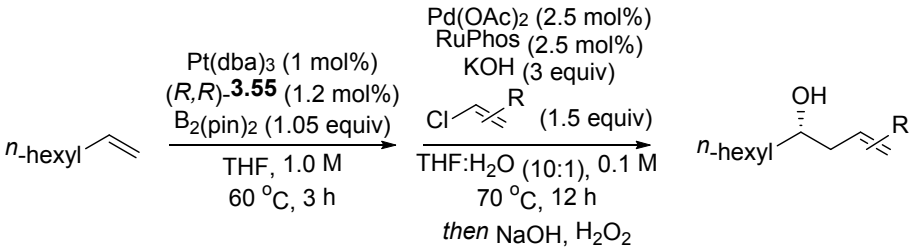
a) Determined by ^{1}H NMR analysis of crude reaction mixture.
b) Based on purified material.

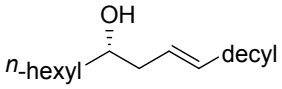
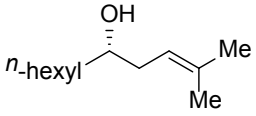
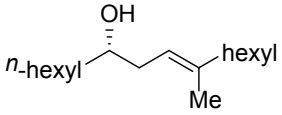
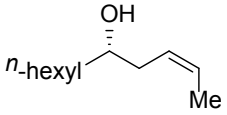
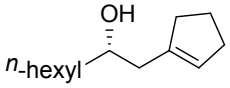
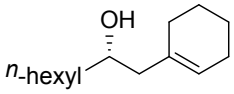
Although the data in Table 3.7 supported the hypothesis for how the diene byproduct **3.62** is formed, the addition of a formate salt to reduce the palladium(II)

dihalide byproduct is far from an ideal solution. A simpler and more attractive solution would be to disfavor the disproportionation reaction altogether. Considering that the disproportionation event may initiate through halogen-bridging between two palladium(II) species, changing the electrophile may have an impact on byproduct formation. Excitingly, when vinyl chlorides are employed as electrophiles, no dienes originating from homocoupling are observed. Instead, the corresponding homoallylic alcohols are generated in excellent yields and enantioselectivities (Table 3.8).

Enantioenriched homoallylic alcohols with substituted alkenes are typically synthesized through either carbonyl allylation or cross-metathesis reactions. These methods generally suffer poor control of the alkene geometry. An attractive feature of this methodology is the alkene geometry is established in the synthesis of the vinyl chloride substrate and is conserved throughout reaction. This enables the synthesis of configurationally defined homoallylic alcohols containing *cis* and *trans*-disubstituted, trisubstituted and cyclic alkenes.

Table 3.8 Vinyl Chloride Substrate Scope for the Diboration/Cross-Coupling Reaction



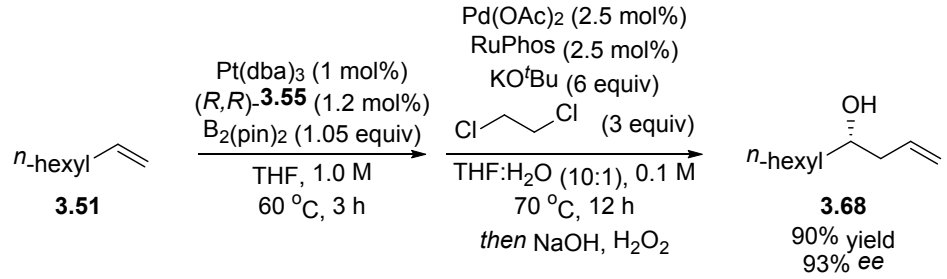
entry	product	yield (%)[a]	*ee* (%)[b]
1		92	93
2		92	93
3		90	93
4		86	93
5		90	92
6[c]		83	92

[a] Percent yield of purified material. Value is average of two experiments. [b] Determined by GC analysis of derivative employing a chiral stationary phase. [c] Vinyl bromide used as electrophile.

While synthesis of enantioenriched homoallylic alcohols bearing substituted alkenes are synthetically important, generating a product containing an α-olefin is particularly attractive for the DCC reaction since the product generated is also a suitable substrate. Iterative subjection of the product to additional DCC reactions would enable rapid access to 1,3-polyol motifs of any desired configuration while avoiding multiple functional group interconversions required with current synthetic methods. In order to achieve the goal of synthesizing a terminal alkene in a DCC reaction, the cross-coupling

would have to be performed using chloroethene as the electrophile. Unfortunately, chloroethene is an extremely toxic and carcinogenic gas and requires special apparatus to ensure adequate safety and ventilation. While it may be possible to use vinyl chloride gas in the cross-coupling directly, a safe and simple solution has been developed. Addition of 1,2-dichloroethane and potassium *tert*-butoxide to the cross-coupling reaction generates the desired terminal alkene product **3.68** in excellent yield and enantiomeric excess (Scheme 3.20).

Scheme 3.20 Synthesis of Terminal Alkenes



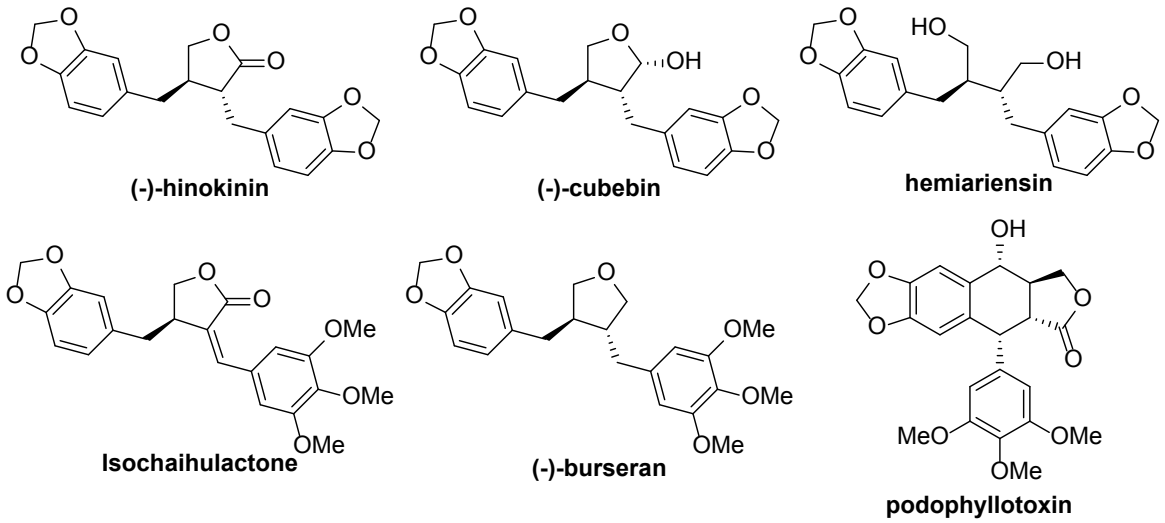
3.4 Application of Enantioselective Diboration/Cross-Coupling in Asymmetric Synthesis

Following the successful discovery of an efficient enantioselective diboration/cross-coupling cascade, the synthesis of biologically relevant compounds was investigated. This would demonstrate the potential impact that the reaction can have on the synthetic community. Through functionalization of commercially available α-olefins, the concise asymmetric synthesis of several compounds was achieved with high enantioselectivity.

The first synthetic target chosen was dibenzylbutyrolactone (-)-hinokinin (**3.72**), a member of the structurally diverse lignan natural product class (Figure 3.2). Lignans are a large family of secondary metabolites ubiquitous in the plant kingdom and display a

wide range of biological activity including antiviral, antimitotic, and anti-tumor properties.[22] While the exact biological function in plants remains elusive, the pharmacological application of lignans has long been established and even dates back to traditional folk remedies.[23] Specifically, (-)-hinokinin has recently been shown to noncompetitively inhibit dopamine and noradrenaline transport through allosterically modulating monoamine and GABA transporters.[24] Regulating the localized concentration of these neurotransmitters offers potential treatment for neurological disorders such as attention deficit hyperactivity disorder (ADHD) and other mental health conditions including substance abuse.

Figure 3.2 Select Examples of Biologically Active Lignans

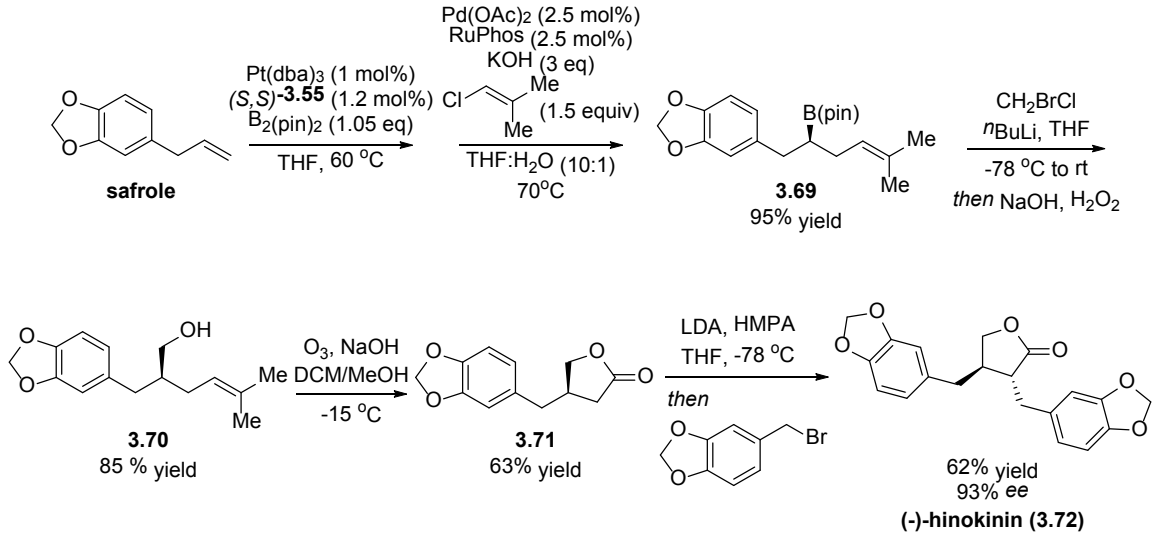


Starting from commercially available safrole, enantioselective diboration and selective cross-coupling with 1-chloro-2-methylprop-1-ene rapidly delivers homoallylic pinacol boronate **3.69** in excellent yield (Scheme 3.21). Methylene homologation and

[22] MacRae, W. D.; Towers, G. H. N. *Phytochemistry*, **1984**, *23*, 1207.
[23] Bett, W. R. *Practitioner*, **1951**, *166*, 77.
[24] Timple, J. M. V.; Mgalhaes, L. G.; Rezende, K. C. S.; Pereira, A. C.; Cunha, W. R.; Silva, M. L. A.; Mortensen, O. V.; Fontana, A. C. K. *J. Nat. Prod.* **2013**, *76*, 1889.

oxidative work-up affords chiral alcohol **3.70**. Upon subjection to ozonolysis under basic conditions, **3.70** undergoes olefin oxidation and cyclization to generate lactone **3.71**. Simple alkylation of the derived lithium enolate produces (-)-hinokin as a single diastereomer in 62% yield with excellent enantiopurity.

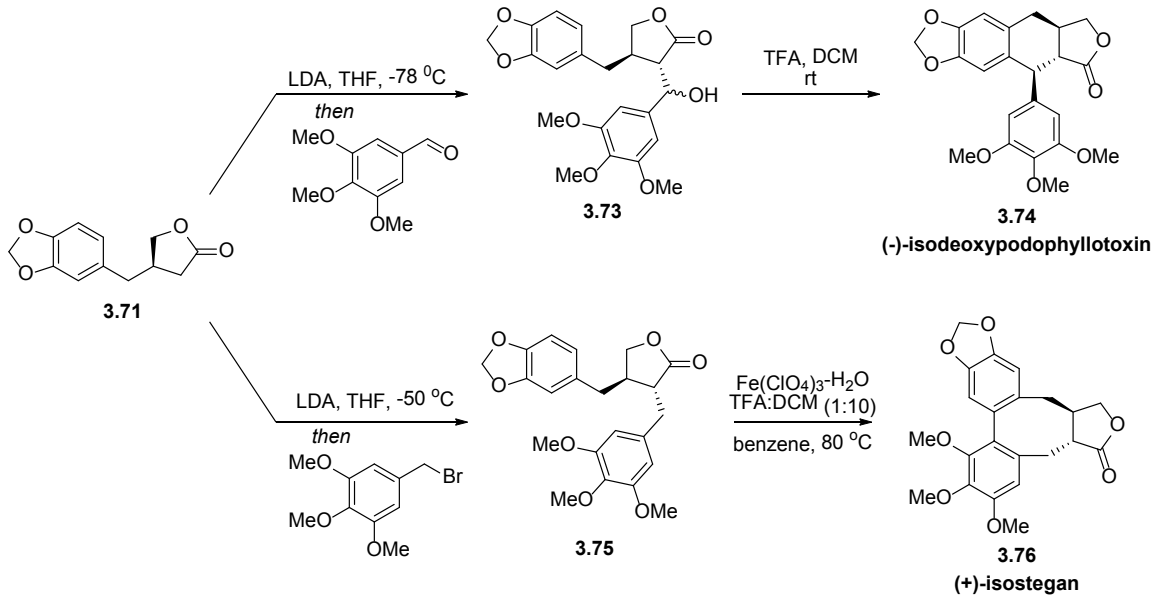
Scheme 3.21 Asymmetric Synthesis of (-)-Hinokinin



Several other lignan natural products can also be synthesized directly from the versatile lactone intermediate **3.71** (Scheme 3.22). Nishiyama and co-workers demonstrated that benzylic alcohol **3.73** undergoes facile cyclization under acidic conditions forming (-)-isodeoxypodophyllotoxin **3.74**.[25] Alternatively, treatment of lactone **3.75** with iron(III) perchlorate promotes oxidative cyclization generating (+)-isostegan as a single diastereomer.

[25] Itoh, T.; Chika, J.-I.; Takagi, Y.; Nishiyama, S. *J. Org. Chem.* **1993**, *58*, 5717.

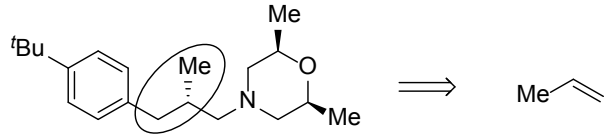
Scheme 3.22 Synthesis of Lignan Natural Products[25]



Another synthetic target that was particularly interesting was the pesticide (*S*)-fenpropimorph (Scheme 3.23). Fenpropimorph is a morpholine fungicide produced in excess of 40,000 tons per year and is used extensively worldwide to control the disease of cereal crops. [26] Although it is known that the *S*-enantiomer is more potent, fenpropimorph continues to be synthesized and used as the racemate due to inefficient and cost-prohibitive asymmetric routes.[27] Developing a concise, asymmetric synthesis of (*S*)-fenpropimorph would have a dramatic environmental impact by decreasing the amount of fungicide required to effectively protect crops. This would lower the annual production and decrease the amount of generated chemical waste.

[26] Himmele, W.; Pommer, E.-H. *Angew Chem.* **1980**, *92*, 176.
[27] Forsyth, S. A.; Gunaratne, H. Q. N.; McKeown, A.; Rooney, D. W.; Hardacre, C. *Org. Process Res. Dev.* **2006**, *10*, 94.

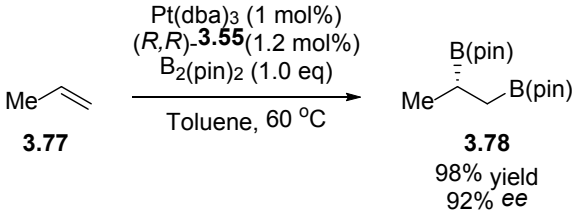
Scheme 3.23 (*S*)-Fenpropimorph



***S*-Fenpropimorph**

From a reaction development perspective, (*S*)-fenpropimorph is a particularly attractive target because the synthetic route would require asymmetric diboration of propene gas. Considering the low boiling point of propene gas (-47.6 ºC), it was unclear if propene would remain in solution at the 60 ºC reaction temperature required for an efficient diboration reaction. Furthermore, even if diboration can be promoted, will the transformation be stereoselective? To determine the feasibility of the desired diboration, roughly 4 equivalents of propene gas was subjected to the standard reaction conditions employing bis(pinacolato)diboron as the limiting reagent. Remarkably, after stirring at 60 ºC for 12 hours, the desired diboron **3.78** was produced in nearly quantitative yield. Even more importantly, the diboration of propene was stereoselective, generating the diboron **3.78** with 92% enantioselectivity (Scheme 3.24).

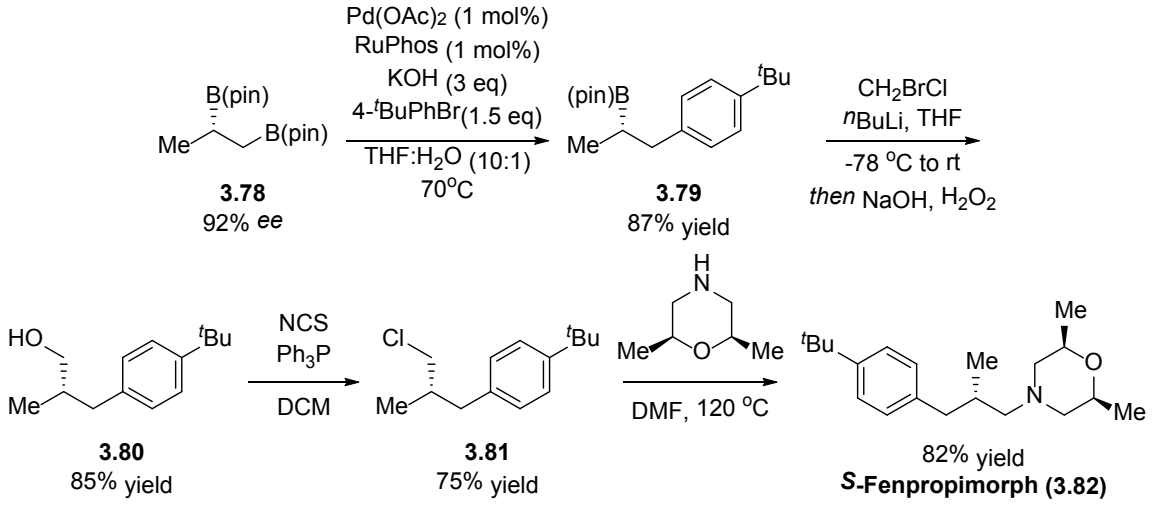
Scheme 3.24 Enantioselective Diboration of Propene Gas



With the successful enantioselective diboration of propene achieved, the concise synthesis of (*S*)-fenpropimorph was quickly completed (Scheme 3.25). Selective cross-coupling of diboron **3.78** with 1-bromo-4-(*tert*-butyl)benzene generated homobenzylic pinacol boronate **3.79**. Methylene homologation followed by oxidation produced primary

alcohol **3.80**, which was converted to the corresponding alkyl chloride **3.81**. Displacement with *syn*-3,5-dimethylmorpholine generates (*S*)-fenpropimorph **3.82** in high yield with complete conservation of enantiopurity. While the synthetic route depicted in Scheme 3.25 may not be currently ready to produce (*S*)-fenpropimorph on a 40,000 ton scale, the ability to convert propene gas into biologically important complex products serves to highlight the inevitable impact that the enantioselective diboration/cross-coupling cascade reaction will have on the synthetic community.

Scheme 3.25 Asymmetric Synthesis of (*S*)-Fenpropimorph



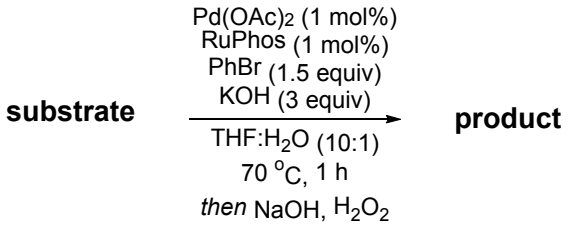
3.5 Mechanistic Investigation in the Regioselective Cross-Coupling of 1,2-Bis(boronate)Esters

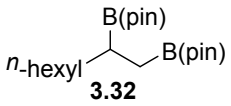
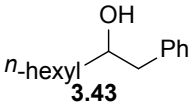
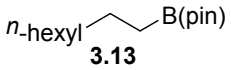
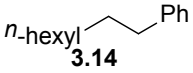
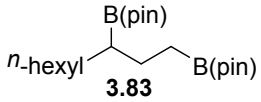
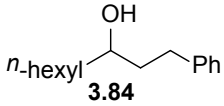
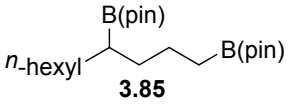
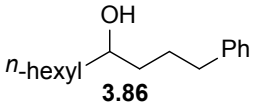
The universally high yields obtained for the single-flask diboration/cross-coupling reaction are both remarkable and unexpected. Suzuki-Miyaura cross-couplings of pinacol boronates do not generally proceed with such efficiency, and the few examples known employing alkyl nucleophiles are generally plagued with byproducts resulting in only moderate yields. While it is possible that the conditions developed are simply

superior at promoting the desired reaction, the reactivity difference observed between 1-octylB(pin) and 1,2-bis(boronate)esters during reaction development suggests a possible unique structural motif dependence.

To understand the increased reactivity of 1,2-bis(boronate)esters, the efficiency of other alkyl pinacol boronates under the optimized conditions must first be determined. Our investigation began with subjecting 1,2-bis(boronate) ester **3.32** to the optimized cross-coupling conditions with bromobenzene for 1 hour. Remarkably, the bis(boronate) was almost completely consumed (Table 3.9, entry 1). Interestingly, under identical conditions, only trace amount of product derived from cross-coupling with 1-octylB(pin) was detected (entry 2). Cross-coupling of a 1,3-bis(boronate) ester **3.83** (entry 3) and a 1,4-bis(boronate) ester **3.84** (entry 5) were also inefficient with only trace amount of products detected. The data in Table 3.9 clearly shows that not only the presence, but also location of the additional pinacol boronate is important in order to obtain an increase in reactivity

Table 3.9 Cross-Coupling of Alkyl Pinacol Boronates



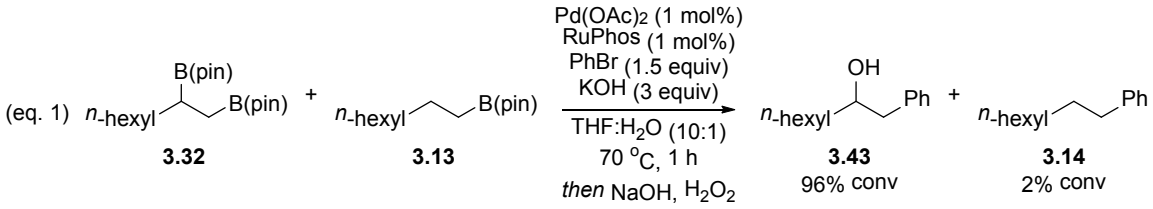
entry	substrate	product	conv (%)[a]
1	 **3.32**	 **3.43**	91
2	 **3.13**	 **3.14**	<5
3	 **3.83**	 **3.84**	<5
4[b]			31
5	 **3.85**	 **3.86**	9

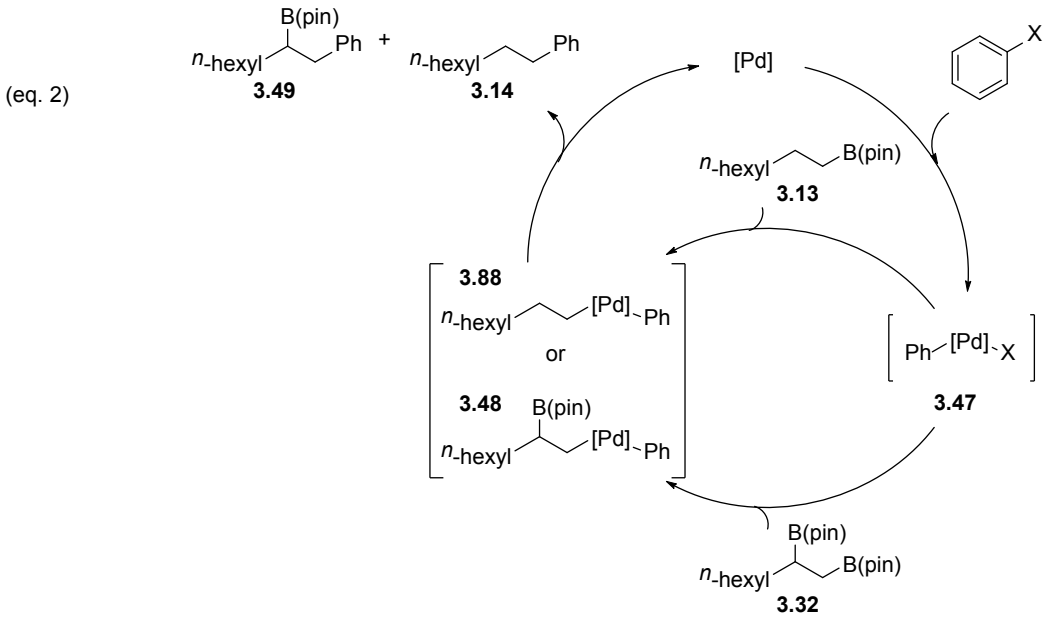
a) Determined by ^{1}H NMR analysis of the crude reaction mixture. b) 5 mol% $Pd(OAc)_2$/RuPhos exployed for 20 h

Presumably the nature of the boron transmetallation partner does not affect oxidative addition, so the enhanced reactivity observed with the 1,2-bis(boronate) ester arises either from a more facile transmetallation or a faster reductive elimination. To determine the origin of the enhanced reactivity, a direct competition experiment between 1-octylB(pin) **3.13** and 1,2-bis(boronate) **3.32** was performed (Scheme 3.26, eq 1). After 1 hour, the bis(boronate) was almost completely consumed while only trace amount of product derived from 1-octylB(pin) was detected. The results from the same-flask competition experiment are virtually identical to the separate flask experiments, which enables us to conclude that the increased reactivity of the 1,2-bis(boronate) is due to an enhanced transmetallation. If the two boron species underwent transmetallation with the

same efficacy, and the enhanced reactivity arose from a faster reductive elimination of the 1,2-bis(boronate), then the catalyst would eventually be sequestered as intermediate **3.88** resulting in a diminished conversion of the 1,2-bis(boronate) (eq 2).

Scheme 3.26 Direct Competition Experiment

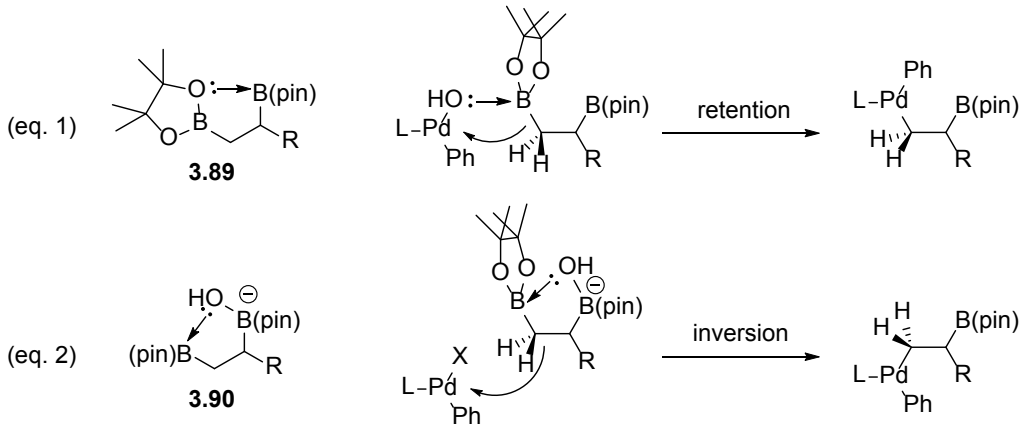




While it is clear that the presence of the vicinal pinacol boronate has a dramatic effect on the rate of transmetallation, the precise mechanistic rational is unknown. Of the possible explanations, the two most probable are detailed in Scheme 3.27. First, one of the pinacolato oxygen atoms can coordinate to the neighboring boron p-orbital, effectively increasing the Lewis acidity of the bonded boron moiety (**3.89**). The increased Lewis acidity would facilitate coordination with a palladium hydroxo species

and serve to promote transmetallation. Alternatively, hydroxide can simultaneously coordinate to both boron p-orbitals forming a stable bridged complex where the electron density is distributed across all three atoms (**3.90**). The differences between the two coordination pathways may appear subtle, but they have dramatically different consequences on transmetallation. The first route would involve a traditional inner-sphere transmetallation and should proceed with retention of configuration (eq 1). On the other hand, transmetallation involving the bridged complex **3.90** would occur through an outer-sphere pathway resulting in inversion of the carbon stereochemistry (eq 2).[28]

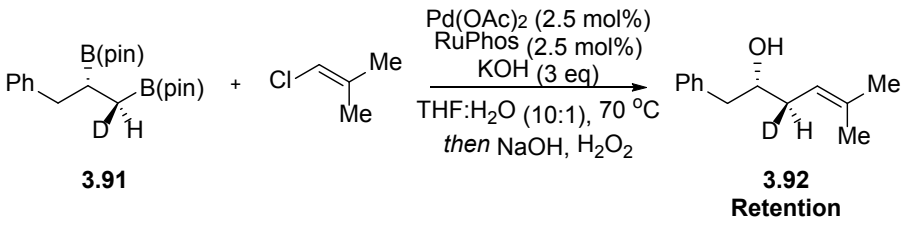
Scheme 3.27 Plausible Explanations for the Increased Reactivity in Transmetallation



To determine the operative transmetallation pathway, stereodefined deuterium-labeled bis(boronate) ester 3.91 was synthesized and subjected to the cross-coupling reaction (Scheme 3.28). Oxidative workup delivered homoallylic alcohol **3.92** as a single diastereomer which is consistent with retention of configuration. This experiment suggests that the enhanced reactivity observed with cross-coupling of 1,2-bis(boronate)esters is due internal Lewis acid activation (Scheme 3.27, eq. 1).

[28] For related cross-couplings that proceed with inversion of stereochemistry: (a) Ohmura, T.; Awano, T.; Suginome, M. *J. Am. Chem. Soc.* **2010**, *132*, 13191. (b) Lee, J. C. H.; McDonald, R.; Hall, D. G. *Nat. Chem.* **2011**, *3*, 894.

Scheme 3.28 Cross-Coupling with Stereodefined 1,2-Bis(boronate) ester



3.91 **3.92**
Retention

3.6 Conclusions

An efficient chemoselective cross-coupling of 1,2-bis(boronate)esters has been developed. This reaction, combined with asymmetric diboration, effectively converts simple terminal olefins into complex functionalized molecules using only commercial reagents in a single flask operation. To demonstrate the potential synthetic application of the developed reaction, several biologically relevant compounds were synthesized from unprecedented starting materials. In the course of developing the above described reaction, a novel structural characteristic of 1,2-bis(boronate) esters was uncovered where the adjacent pinacol ester moiety effectively increases the rate of transmetallation by enhancing the overall Lewis acidity of the boron nucleophile species. The observed rate enhancement is unique to 1,2-bis(boronate) esters but has the potential to be applied to alternative transformations involving transmetallation of organoboron compounds.

3.7 Supporting information

3.7.1 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.

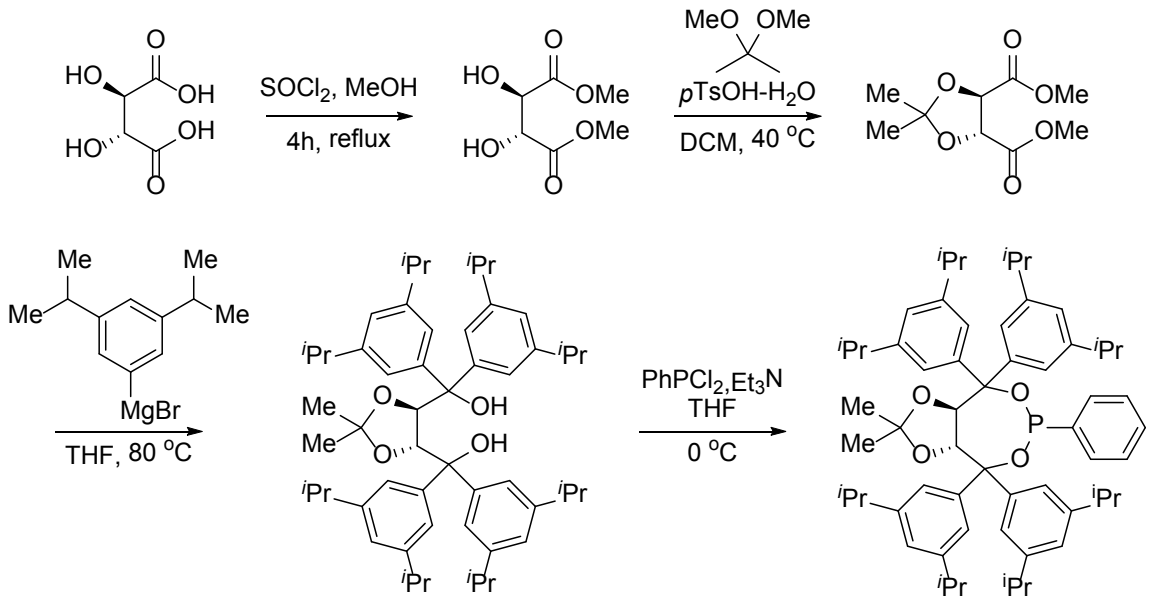
3.7.2 Preparation of Pt(dba)$_3$.

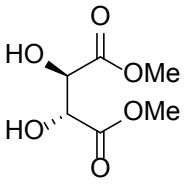
Tris(dibenzylideneacetone)platinum was prepared using the literature procedure[29] with slight modification but can also be purchased through Strem chemicals (order #: 78-1360). To a 3-neck 500-mL round-bottomed flask equipped with magnetic stir bar and reflux condenser was added dibenzylideneacetone (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 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.[30]

[29] Lewis, L. N.; Krafft, T. A.; Huffman, J. C. *Inorg. Chem.* **1992**, *31*, 3555.
[30] Sieber, J. D.; Morken, J. P. *J. Am. Chem. Soc.* **2008**, *130*, 4978.

3.7.3 Ligand Synthesis

(*R*,*R*)-3,5-di-*iso*-propylphenylTADDOLPPh was synthesized according to literature procedure,[31] but can also be purchased through Strem chemicals (order #: 15-1513).

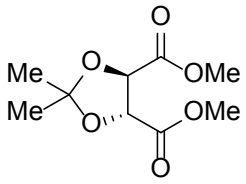




(2*R*,3*R*)-dimethyl 2,3-dihydroxysuccinate. A flame dried 2-neck round-bottomed flask with magnetic stir bar and condenser was charged with (*R*,*R*)-tartaric acid (30.0 g, 0.199 mol). The apparatus was purged with N_2, and methanol (95 mL) was added. The reaction flask was fitted with an outlet at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

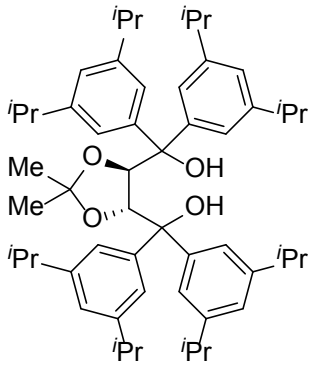
[31] Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. *Angew. Chem. Int. Ed.* **2012**, *51*, 521.

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.



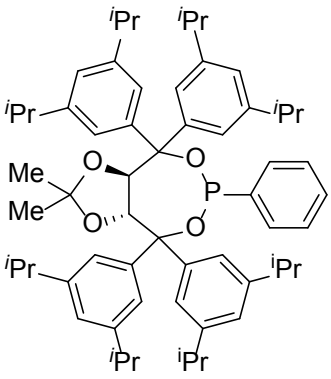
(4*R*,5*R*)-dimethyl 2,2-dimethyl-1,3-dioxolane-4,5-dicarboxylate. A 2-neck round-bottomed flask with magnetic stir bar and condenser was charged with (*R,R*)-dimethyl tartrate and *p*-toluenesulfonic acid monohydrate (18.9 g, 0.099 mol). The apparatus was purged with N_2, and the reaction was diluted with DCM (275 mL). 2,2-dimethoxypropane (156.0 mL, 1.298 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 (83% yield, 36.22 g). Spectral data are in accordance with the literature.[32]

[32] Kobayashi, Y.; Kokubo, Y.; Aisaka, T.; Saigo, K. *Tetrahedron: Asymmetry*, **2008**, *19*, 2536.



(*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[33] 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 as a white crystalline solid (20.1 g, 89% yield). Spectral data are in accordance with the literature.[31]

[33] Diemer, V.; Chaumeil. H.; Defoin, A.; Fort, A.; Boeglin, A.; Carré, C. *Eur. J. Org. Chem.* **2006**, *12*, 2727.



(*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, 4.78 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.[31]

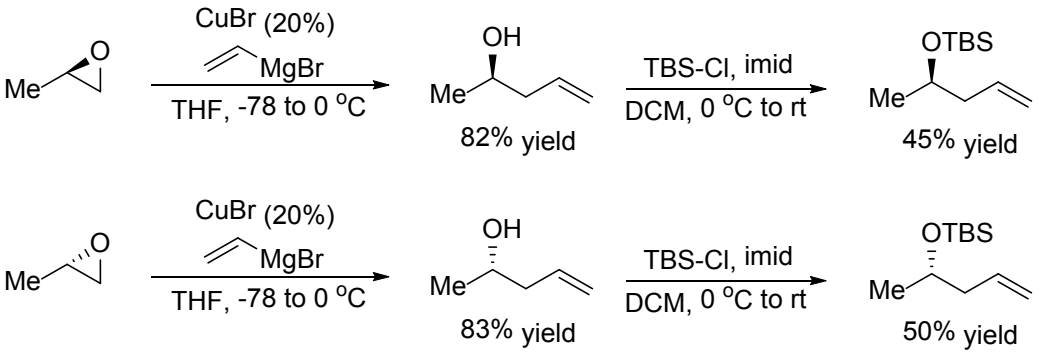
3.7.4 Preparation of Substrates

3.7.4.1 Synthesis of Alkenes

(Allyloxy)triisopropylsilane[34] and (but-3-en-1-yloxy)(tert-butyl)diphenylsilane[35] 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.[36] (*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

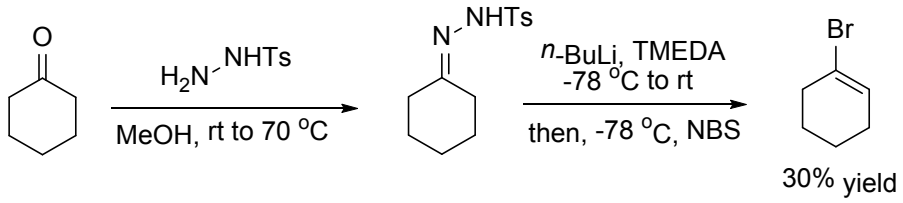
[34] Ziegler, D. T.; Steffens, A. M.; Funk, T. W. *Tet. Lett*. **2010**, *51*, 6726.
[35] Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. *J. Am. Chem. Soc.* **2009**, *131*, 13210.
[36] Coombs, J. R.; Haeffner, F.; Kliman, L. T.; Morken, J. P. *J. Am. Chem. Soc.* **2013**, *135*, 11222.

procedure[37] as shown below. (*S*)-2-Methyloxirane was prepared from (*rac*)-2-methyloxirane utilizing Jacobsen HKR according to the literature procedure[38]. All spectral data are in accordance with the literature.



3.7.5 Synthesis of Electrophiles

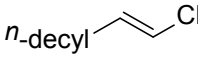
1-Bromocyclohex-1-ene. Prepared according to the literature procedure[39] as shown below. All spectral data are in accordance with the literature.



(*E*)-1-chlorododec-1-ene. The title compound was prepared according to the literature procedure[40] with slight modification. A flame-dried round-bottomed flask with magnetic stir bar was purged with N_2 and charged with 1-dodecyne (2.0 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

[37] Figueroa, R.; Hsung, R. P.; Guevarra, C. C. *Org. Lett.* **2007**, *9*, 4857.
[38] 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.
[39] Paquette, L. A.; Pegg, N. A.; Toops, D.; Maynard, G. D.; Rogers, R. D. *J. Am. Chem. Soc.* **1990**, *112*, 277.
[40] Ney, J. E.; Hay, M. B.; Yang, Q.; Wolfe, J. P. *Adv. Synth. Catal.* **2005**, *347*, 1614.

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).

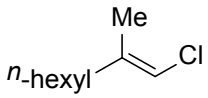


***E*)-1-chlorododec-1-ene.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.91 (1H, d, *J* = 13.0 Hz), 5.87 (1H, dt, *J* = 13.0 Hz, 7.0 Hz), 2.02 (2H, dt, *J* = 7.0 Hz, 7.0 Hz), 1.38-1.32 (2H, m), 1.30-1,24 (16H, m), 0.86 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 134.1, 116.6, 31.9, 30.9, 29.6, 29.5, 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[41] 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

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

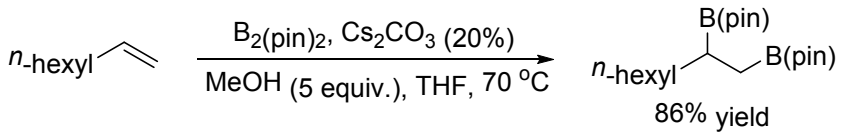
temperature. After stirring at room temperature for 10 min, the reaction was cooled to 0 ºC and 1-octyne (1.00 mL, 6.77 mmol) was added dropwise. The reaction was warmed to room temperature and stirred for 14 h. A solution of *N*-chlorosuccinamide (2.71 g, 20.3 mmol) in tetrahydrofuran (40 mL) was then 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).



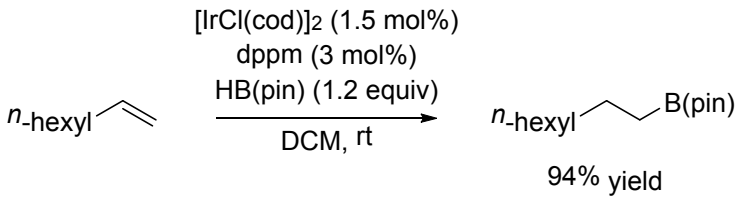
(*E*)-1-chloro-2-methyloct-1-ene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.76 (1H, d, *J* = 1.0 Hz), 2.03 (2H, t, *J* = 7.0 Hz), 1.74 (3H, d, *J* = 1.5 Hz), 1.39 (2H, tt, *J* = 7.5 Hz, 7.0 Hz), 1.30-1.22 (8H, m), 0.87 (3H, t, *J* = 7.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.9, 111.6, 37.1, 31.6, 28.8, 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}.

3.7.6 Synthesis of Alkyl Diboron Compounds

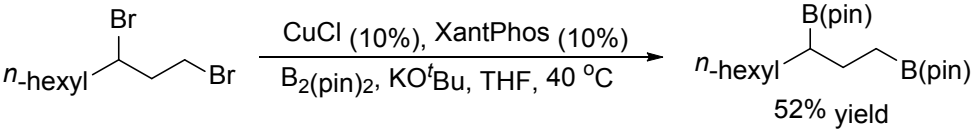
2,2'-(octane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Prepared according to the literature procedure[42] as shown below. All spectral data are in accordance with the literature.

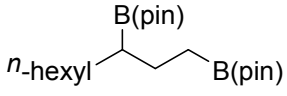


4,4,5,5-tetramethyl-2-octyl-1,3,2-dioxaborolane. Prepared according to the literature procedure[43] as shown below. All spectral data are in accordance with the literature.



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.[44]



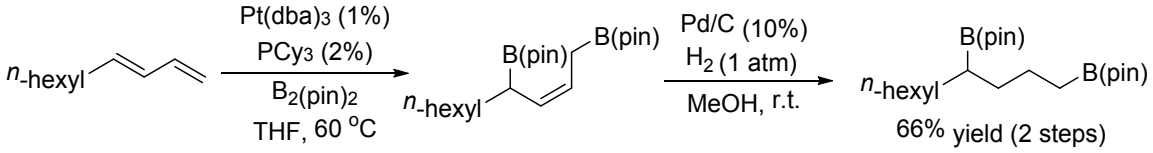


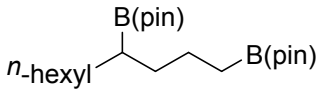
2,2'-(nonane-1,3-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.42-1.54 (2H, m), 1.31-1.40 (2H, m), 1.24-1.30 (8H, m), 1.22 (24H, s), 0.90-0.96 (1H, m), 0.86 (3H, t, *J* = 6.9 Hz), 0.70-0.82 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 82.8, 82.7, 31.8, 31.2, 29.6, 29.1, 25.4, 24.8, 24.8, 22.6, 14.1; IR (neat): 2977.2 (w), 2923.7 (m), 2854.9 (w),

[42] Bonet, A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyás, H.; Fernández, E. *Angew. Chem. Int. Ed.*, **2011**, *50*, 7158.
[43] Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron*, **2004**, *60*, 10695.
[44] Kubota, K.; Ito, H. *Org. Lett.*, **2012**, *14*, 890.

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 *via* a two-step sequence as shown below. *Trans*-1,3-decadiene was subjected to platinum catalyzed diboration according to the previously reported procedure.[45] The resulting unsaturated product was then hydrogenated to give the desired product.





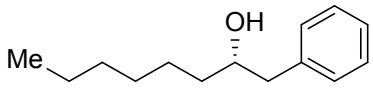
2,2'-(decane-1,4-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.29-1.44 (6H, m), 1.16-1.29 (32H, m), 0.91-0.99 (1H, m), 0.84-0.87 (3H, m), 0.72-0.77 (2H, m); ^{13}C NMR (125 MHz, $CDCl_3$): δ 82.7, 82.7, 34.1, 31.8, 31.2, 29.6, 29.2, 24.8, 24.8, 23.7, 22.6, 14.1; 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.

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

3.7.7 Representative 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, 1.5 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.

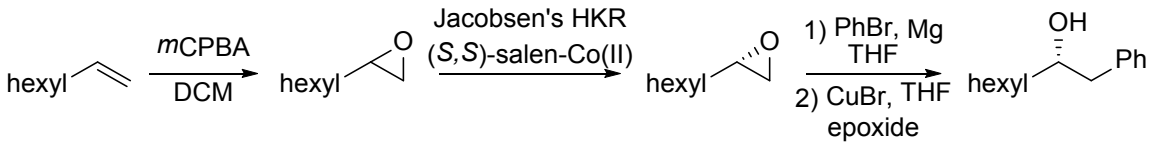
3.7.8 Characterization and Proof of Stereochemistry (Table 3.5, Table 3.6 and Table 3.8)



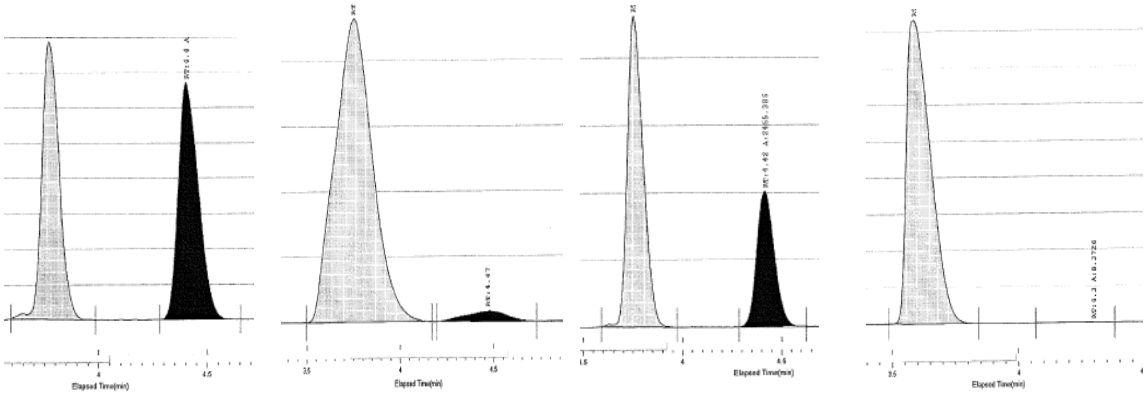
(*S*)-1-phenyloctan-2-ol.. Prepared according to the general procedure using octene (56.1 mg. 0.500 mmol) and bromobenzene (117.8 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the product as a colorless oil (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, dddd, *J* = 9.0 Hz, 9.0 Hz, 4.5 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:

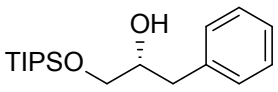


Chiral SFC (Chiracel, OD-H, 35 ^{o}C, 5 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of 1-phenyloctan-2-ol.



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	

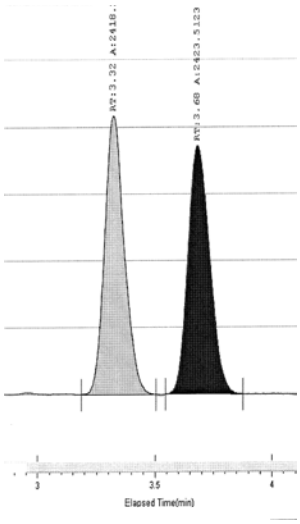


(*R*)-1-phenyl-3-((triisopropylsilyl)oxy)propan-2-ol. Prepared according to the general procedure using (allyloxy)triisopropylsilane (107.2 mg, 0.500 mmol) except (*R*,*R*)-diethylphenylTADDOPPh (8.0 mg, 10.0 µmol) was employed as the ligand. Diboration was carried out for 8 h at 60 ºC followed by cross-coupling, 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).

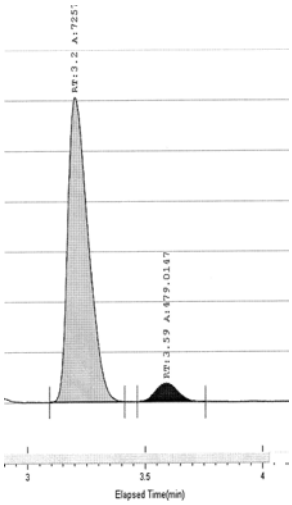
Analysis of Stereochemistry:

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 ^{o}C, 5 mL/min, 2% Isopropanol, 100 bar, 210-270nm) – analysis of 1-phenyl-3-((triisopropylsilyl)oxy)propan-2-ol.

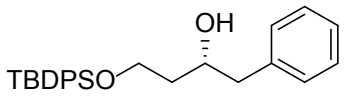


racemic



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	

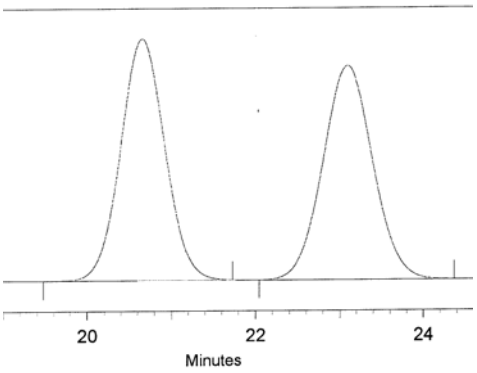


(*R*)-4-((*tert*-butyldiphenylsilyl)oxy)-1-phenylbutan-2-ol. Prepared according to the general procedure using (but-3-en-1-yloxy)(*tert*-butyl)diphenylsilane (155.3 mg, 0.500 mmol) and bromobenzene (117.8 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (5% 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, 135.5, 135.5, 133.1, 133.0, 129.8, 129.8, 129.4, 128.4, 127.7, 127.7, 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).

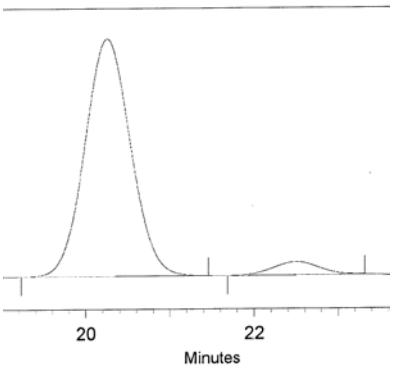
Analysis of Stereochemistry:

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.*

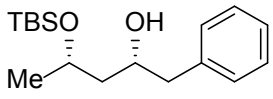


racemic



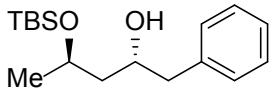
Diboration/cross -coupling product

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. $[\alpha]_D^{20}$ = +27.649 (*c* = 2.296, $CHCl_3$, *l* = 50 mm).

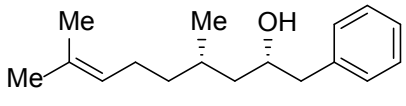
Analysis of Stereochemistry: *Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.*



(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. $[\alpha]_D^{20}$ = -13.090 (*c* = 1.255, $CHCl_3$, *l* = 50 mm).

Analysis of Stereochemistry:

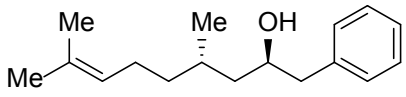
Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.



(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, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.0 Hz), 3.95 (1H, dddd, *J* = 8.5 Hz, 8.5 Hz, 4.5 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:

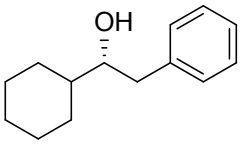
Diastereoselectivity was determined by ^{1}H NMR analysis of the crude reaction mixture.



(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, ddd, *J* = 7.0 Hz, 7.0 Hz, 1.5 Hz), 3.91 (1H, dddd, *J* = 8.0 Hz, 8.0 Hz, 3.5 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.

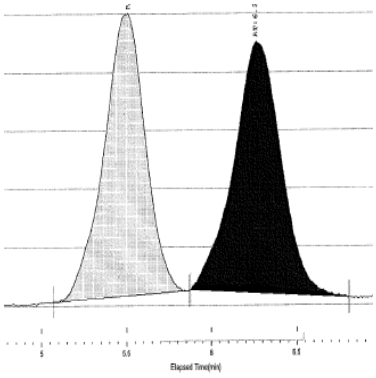


(*R*)-1-cyclohexyl-2-phenylethan-1-ol. Prepared according to the general procedure using vinyl cyclohexane (55.1 mg. 0.500 mmol) and bromobenzene (117.8 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the product 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), 1.91 (1H, ddd, *J* = 12.5 Hz, 1.5 Hz, 1.5 Hz), 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; $[\alpha]_D^{20}$ = +20.082 (*c* = 2.360, $CHCl_3$, *l* = 50 nm).

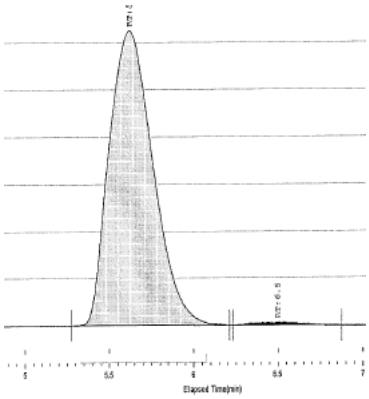
Analysis of Stereochemistry:

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.

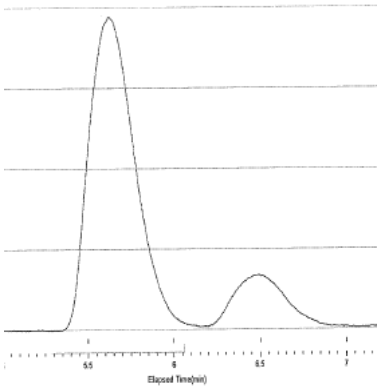
Chiral SFC (Chiracel, OD-H, 35 ^{o}C, 3 mL/min, 5% Isopropanol, 100 bar, 210-270nm) – analysis of 1-cyclohexyl-2-phenylethan-1-ol.



racemic

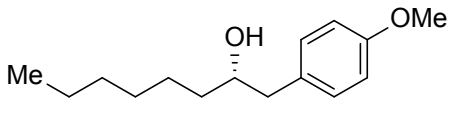


Diboration/cross -coupling product



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	

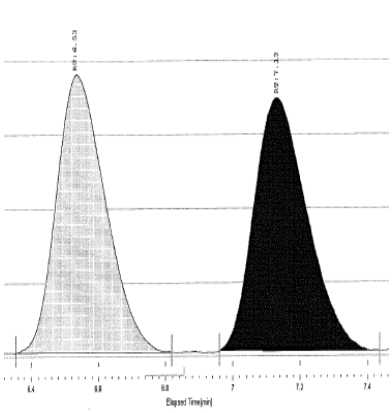


(*S*)-1-(4-methoxyphenyl)octan-2-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and 1-bromo-4-methoxybenzene (140.3 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (10-30% EtOAc/hexanes, stain with PMA) to afford the product 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).

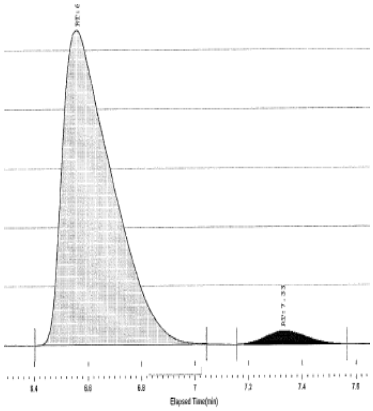
Analysis of Stereochemistry:

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.

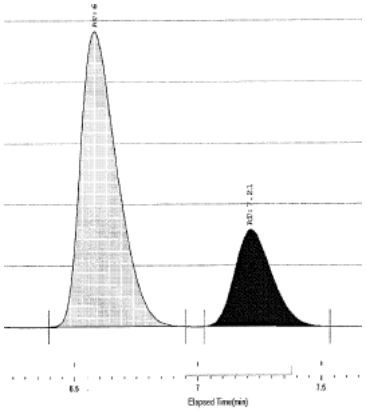
Chiral SFC (Chiracel, OD-H, 35 ^{o}C, 5 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(4-methoxyphenyl)octan-2-ol.



racemic

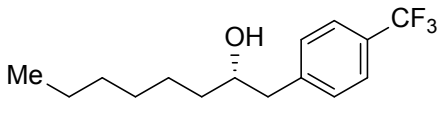


Diboration/cross-coupling product



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	

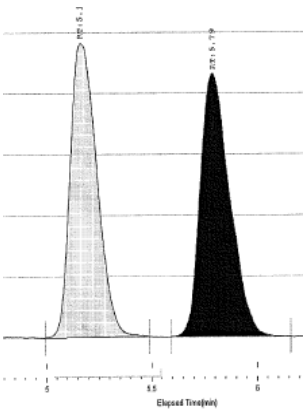


(*S*)-1-(4-(trifluoromethyl)phenyl)octan-2-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and 1-bromo-4-(trifluoromethyl)benzene (168.8 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (10-30% EtOAc/hexanes, stain with 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, dddd, *J* = 8.0 Hz, 8.0 Hz, 4.5 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).

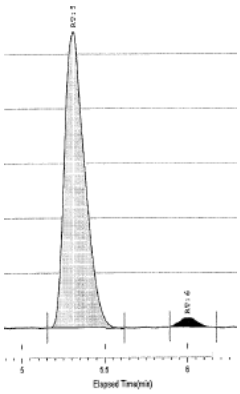
Analysis of Stereochemistry:

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.

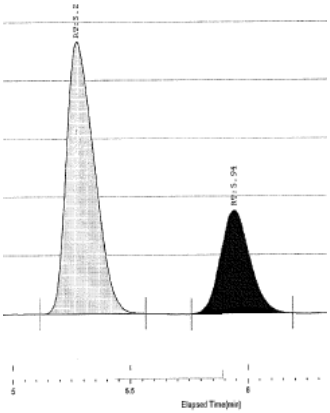
Chiral SFC (Chiracel, OD-H, 35 ^{o}C, 5 mL/min, 1% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(4-(trifluoromethyl)phenyl)octan-2-ol.



racemic

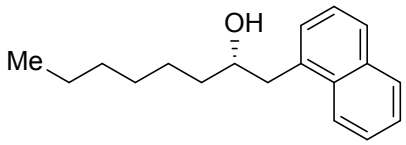


Diboration/cross-coupling product



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	

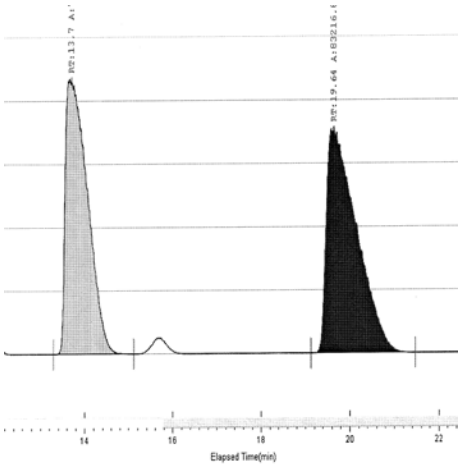


(*S*)-1-(naphthalen-1-yl)octan-2-ol. Prepared according to the general procedure using 1-octene (56.1 mg, 0.500 mmol) and 1-bromonaphthalene (155.3 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7% EtOAc/hexanes, stain with Seebach) to afford the product 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, dd, *J* = 8.3 Hz, 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. $[\alpha]_D^{20}$ = +18.458 (*c* = 2.412, $CHCl_3$, *l* = 50 mm).

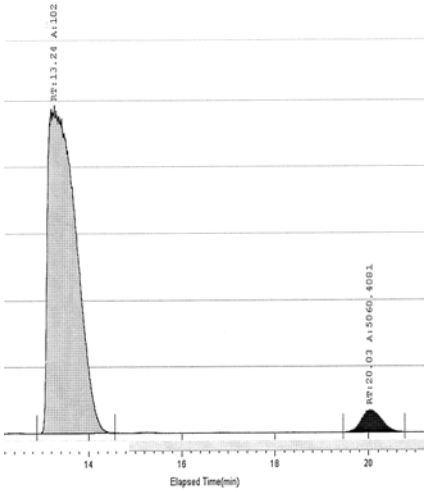
Analysis of Stereochemistry:

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 ^{o}C, 5 mL/min, 5% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(naphthalen-1 -yl)octan-2-ol.

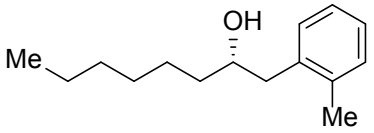


racemic



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	

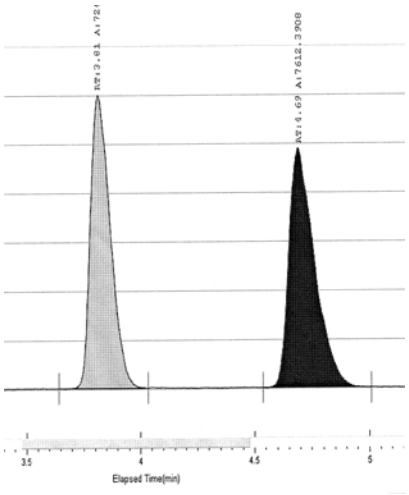


(*S*)-1-(*o*-tolyl)octan-2-ol. Prepared according to the general procedure using 1-octene (56.1 mg, 0.500 mmol) and 2-bromotoluene (128.3 mg, 0.750 mmol). The crude reaction mixture was purified on silica gel (7% EtOAc/hexanes, stain with PMA) to afford the product as a viscous oil (89.1 mg, 80%). ^{1}H 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. $[\alpha]_D^{20}$ = + 12.134 (*c* = 1.722, $CHCl_3$, *l* = 50 mm).

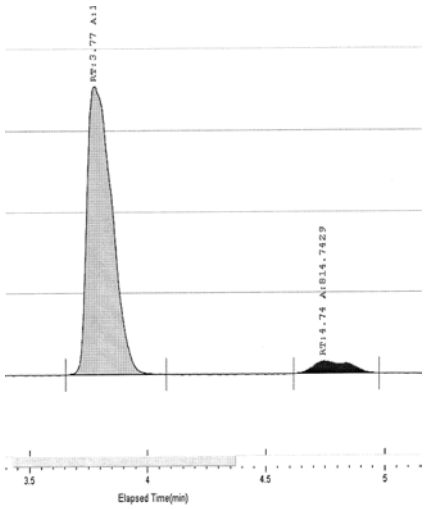
Analysis of Stereochemistry:

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.

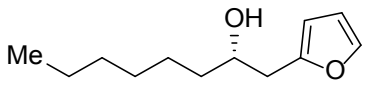


racemic



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	

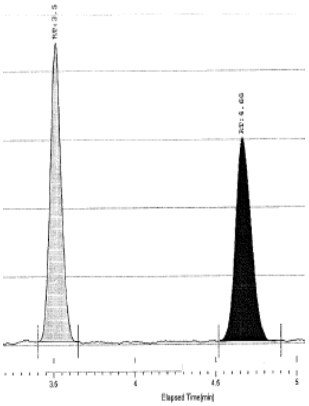


(S)-1-(furan-2-yl)octan-2-ol.. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and 2-bromofuran (110.2 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. Lithium chloride (21.2 mg, 0.50 mmol) was added for the cross-coupling. The crude reaction mixture was purified on silica gel (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).

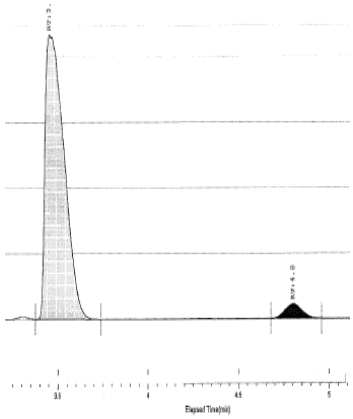
Analysis of Stereochemistry:

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.

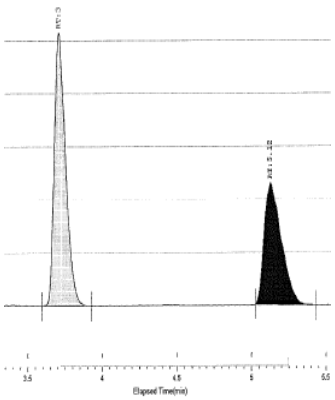
Chiral SFC (Chiracel, AD-H, 35 ^{o}C, 5 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(furan-2-yl)octan-2-ol.



racemic

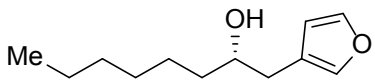


Diboration/cross-coupling product



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	

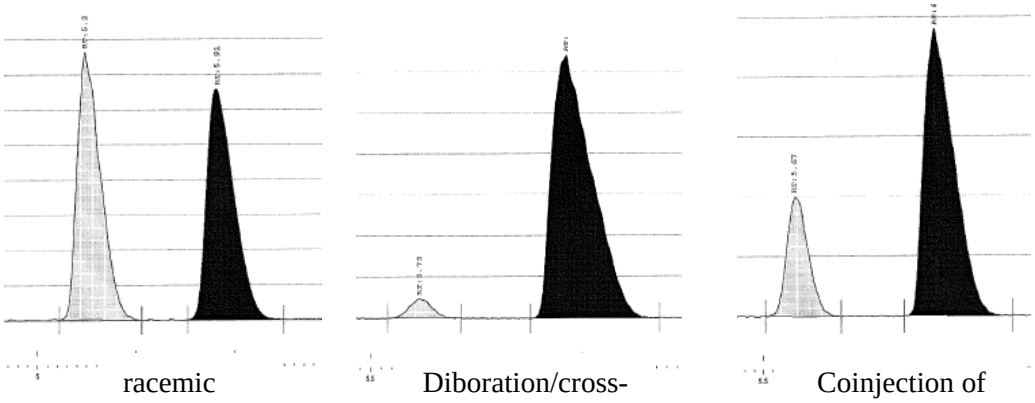


(*S*)-1-(furan-3-yl)octan-2-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and 3-bromofuran (110.2 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. Lithium chloride (21.2 mg, 0.50 mmol) was added for the cross-coupling. The crude reaction mixture was purified on silica gel (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.

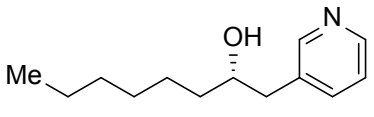


racemic

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	

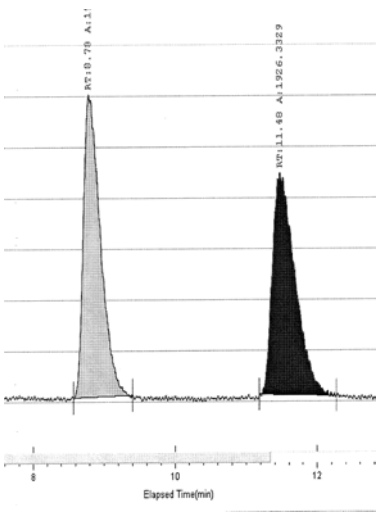


(*S*)-1-(pyridin-3-yl)octan-2-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and 3-bromopyridine (118.5 mg, 0.750 mmol) with 1 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (5% MeOH in ethyl acetate, stain with $KMnO_4$) to afford the product 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).

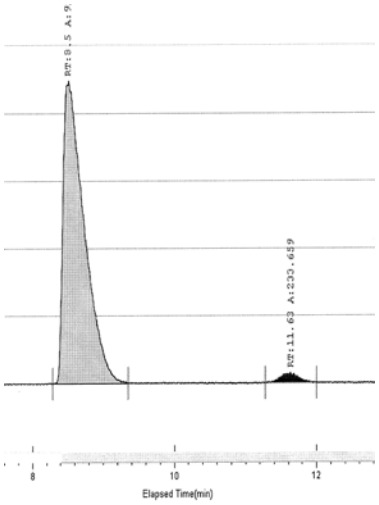
Analysis of Stereochemistry:

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 ^{o}C, 5 mL/min, 5% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(pyridin-3 -yl)octan-2-ol.

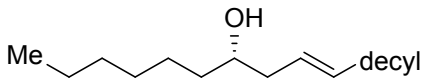


racemic



Diboration/cross-coupling product

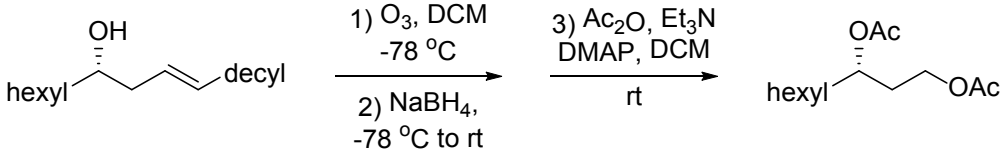
Peak No	% Area	Area	RT (min)
1	97.5218	9194.9843	8.5
2	2.4782	233.659	11.63
Total:	100	9428.6433	



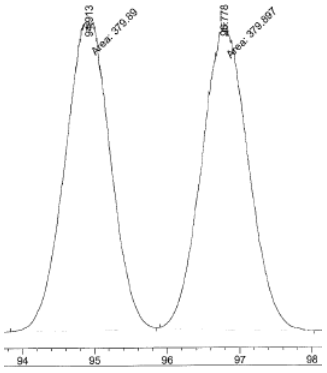
(*S*,*E*)-icos-9-en-7-ol.. Prepared according to the general procedure using 1-octene (56.1 mg, 0.500 mmol) and (*E*)-1-chlorododec-1-ene (151.7 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the product as 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, ddd, *J* = 14.0 Hz, 4.5 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:

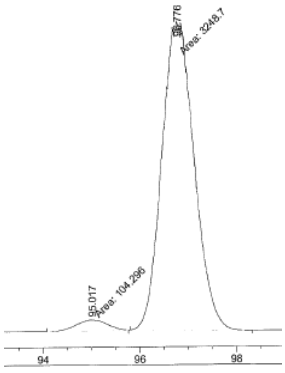
The title compound was converted to the corresponding bis-acetate as shown below. The resulting bis-acetate was compared to racemic material prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.



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.

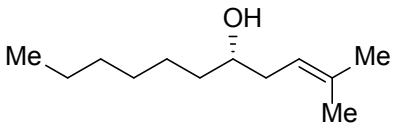


racemic



Diboration/cross-coupling product

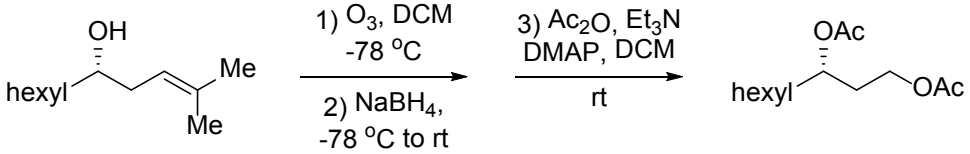
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	95.017	MM	0.7082	104.29550	2.45446	3.11052
2	96.776	MM	0.7742	3248.69800	69.93708	96.88948



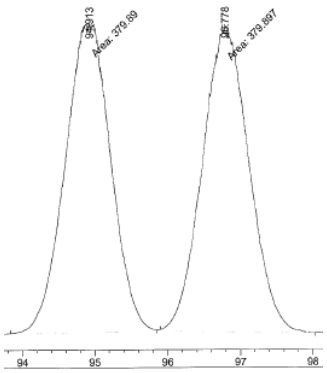
(*S*)-2-methylundec-2-en-5-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and 1-chloro-2-methylpropene (84.4 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the product as a colorless oil (84.9 mg, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.15 (1H, dddd, *J* =8.0 Hz, 8.0 Hz, 2.5 Hz, 1.0 Hz), 4.52 (1H, dddd, *J* = 11.5 Hz, 11.5 Hz, 7.0 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:

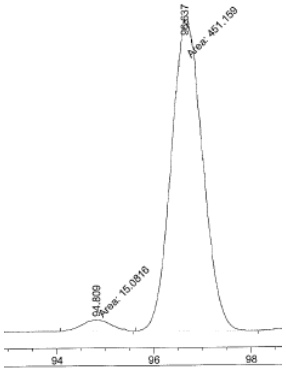
The title compound was converted to the corresponding bis-acetate as shown below. The resulting bis-acetate was compared to racemic material prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.



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.

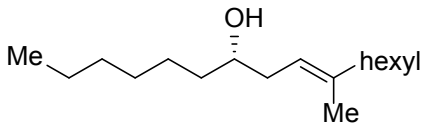


racemic



Diboration/cross-coupling product

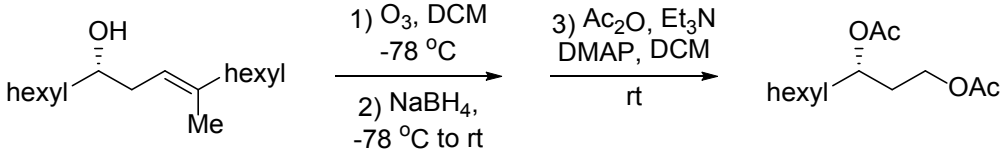
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	94.809	MM	0.6747	15.08162	3.72553e-1	3.23473
2	96.637	MM	0.7512	451.15884	10.01019	96.76527



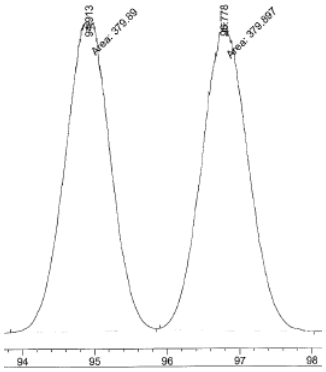
(*S*,*E*)-10-methylhexadec-9-en-7-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and (*E*)-1-chloro-2-methyloct-1-ene (120.5 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (5-10% EtOAc/hexanes, stain with PMA) to afford 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, 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; $[\alpha]_D^{20}$ = +5.193 (*c* = 0.770, $CHCl_3$, *l* = 50 nm).

Analysis of Stereochemistry:

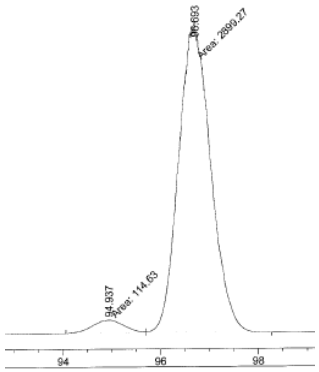
The title compound was converted to the corresponding bis-acetate as shown below. The resulting bis-acetate was compared to racemic material prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.



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.

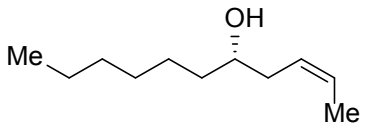


racemic



Diboration/cross-coupling product

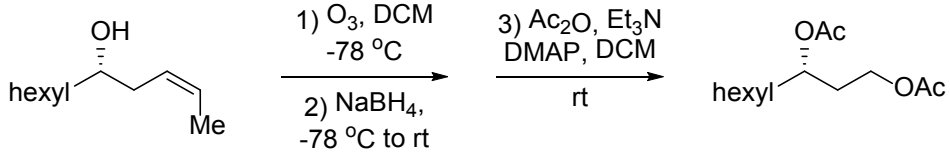
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	94.937	MM	0.7220	114.62968	2.64623	3.80337
2	96.693	MM	0.7502	2899.26758	64.40867	96.19663



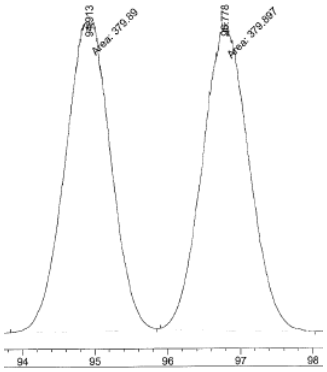
(*S*,*Z*)-undec-2-en-5-ol. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and (*Z*)-1-chloro-1-propene (57.4 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the product as 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, dddd, *J* = 12.0 Hz, 12.0 Hz, 6.0 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:

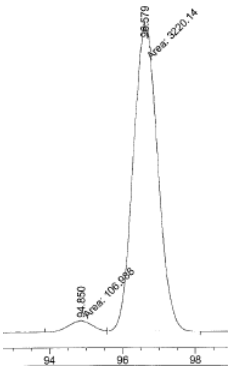
The title compound was converted to the corresponding bis-acetate as shown below. The resulting bis-acetate was compared to racemic material prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.



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.

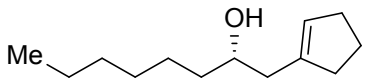


racemic



Diboration/cross-coupling product

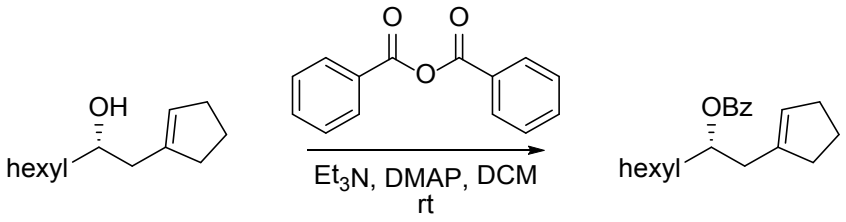
Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	94.850	MM	0.7143	106.98758	2.49647	3.21562
2	96.579	MM	0.7685	3220.13867	69.83436	96.78438



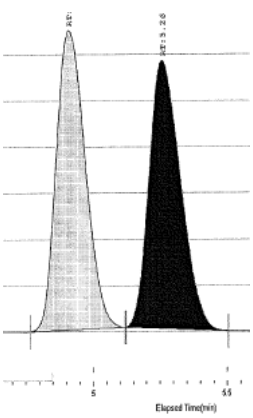
(*S*)-1-(cyclopent-1-en-1-yl)octan-2-ol. Prepared according to the general procedure with 1-octene (56.1 mg. 0.500 mmol) and 1-chlorocyclopent-1-ene (76.9 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7-10% EtOAc/hexanes, stain with PMA) to afford the 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; $[\alpha]_D^{20}$ = +7.183 (*c* = 0.863, $CHCl_3$, *l* = 50 nm).

Analysis of Stereochemistry:

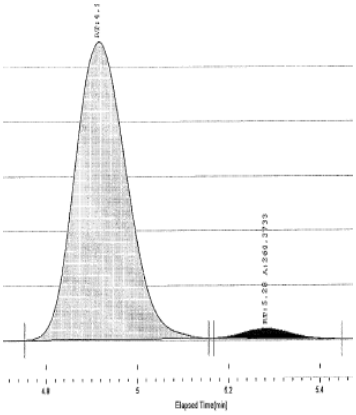
The title compound was converted to the corresponding benzoate as shown below. The resulting benzoate was compared to racemic benzoate prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.



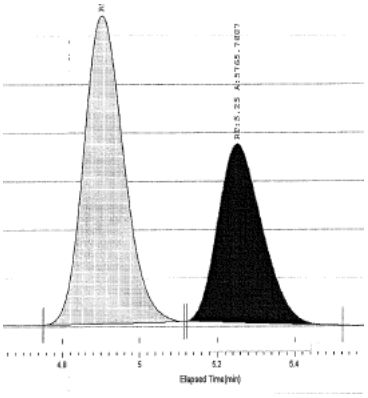
Chiral SFC (Chiracel, OD-H, 35 ^{o}C, 3 mL/min, 2% Isopropanol, 100 bar, 210-270nm) – analysis of 1-(cyclopent-1-en-1-yl)octan-2-yl benzoate.



racemic

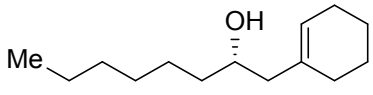


Diboration/cross-coupling



Coinjection of product + racemic

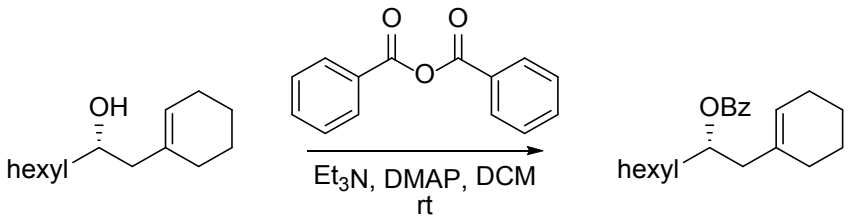
Peak No	% Area	Area	RT (min)
1	96.9859	8506.9002	4.91
2	3.0141	264.3733	5.28
Total:	100	8771.2735	



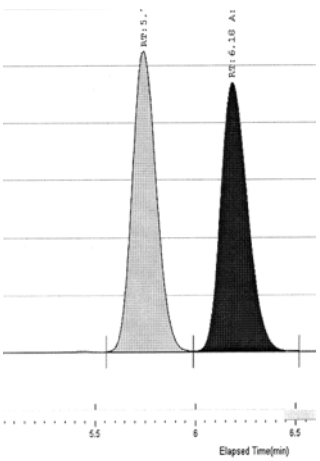
(*S*)-1-(cyclohex-1-en-1-yl)octan-2-ol.. Prepared according to the general procedure using 1-octene (56.1 mg. 0.500 mmol) and 1-bromocyclohexene (120.8 mg, 0.750 mmol) with 2.5 mol% Pd/RuPhos. The crude reaction mixture was purified on silica gel (7% EtOAc/hexanes, stain with PMA) to afford the product 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:

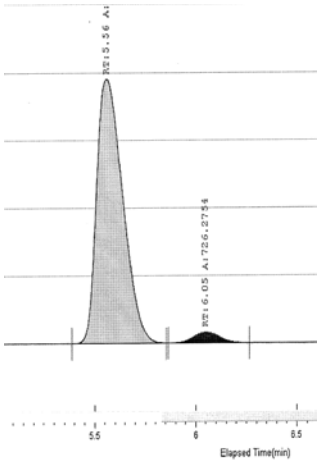
The title compound was converted to the corresponding benzoate as shown below. The resulting benzoate was compared to racemic benzoate prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.



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

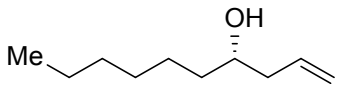


racemic



Diboration/cross-coupling product

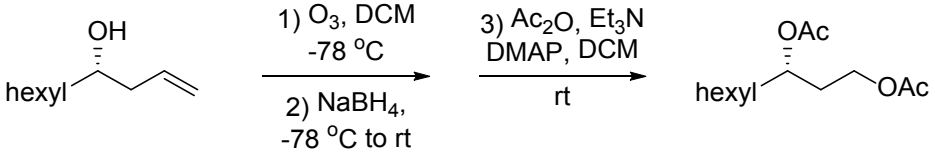
Peak No	% Area	Area	RT (min)
1	95.9963	17413.957	5.56
2	4.0037	726.2754	6.05
Total:	100	18140.2324	



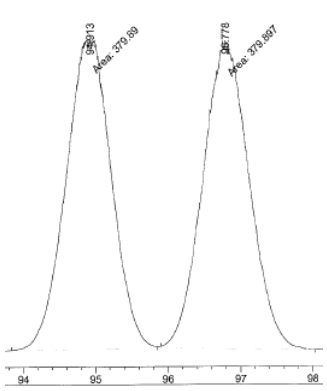
(S)-dec-1-en-4-ol. Prepared according to the general procedure with 1-octene (56.1 mg. 0.500 mmol) and 1,2-dichloroethane (0.12 mL, 1.50 mmol) with 2.5 mol% Pd/RuPhos, except potassium *tert*-butoxide (336.6 mg, 3.000 mmol) was used instead of potassium hydroxide. The crude reaction mixture was purified 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, ddd, *J* = 15.0 Hz, 7.0 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:

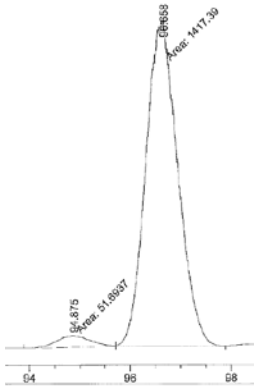
The title compound was converted to the corresponding bis-acetate as shown below. The resulting bis-acetate was compared to racemic bis-acetate prepared from diboration/cross-coupling employing PCy_3 as the ligand for diboration. Absolute stereochemistry was assigned by analogy.



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

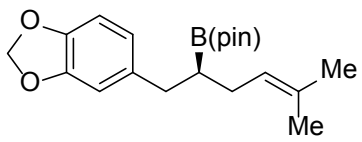


Diboration/cross-coupling product

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

3.7.9 Preparation of (-)-Hinokinin

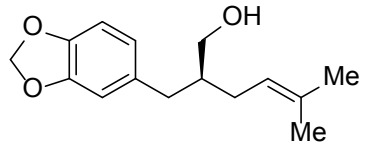
(*S*)-2-(1-(benzo[d][1,3]dioxol-5-yl)-5-methylhex-4-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To an oven-dried 16-mL vial with magnetic stir bar in the dry box was added $Pt(dba)_3$ (4.5 mg, 5.0 µmol), (*S*,*S*)-3,5-di-*iso*-propylphenyl-TADDOLPPh (5.5 mg, 6.0 µmol), $B_2(pin)_2$ (133.3 mg, 525 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, ddd, *J* = 7.5 Hz, 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, dddd, *J* = 15.0 Hz, 15.0 Hz, 7.5 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).

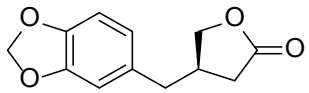
(*S*)-2-(benzo[d][1,3]dioxol-5-ylmethyl)-5-methylhex-4-en-1-ol. A flame-dried round bottom flask equipped with magnetic stir bar was charged with (*S*)-2-(1-(benzo[d][1,3]dioxol-5-yl)-5-methylhex-4-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (166 mg, 484 µmol). The flask was sealed with a septum and purged with N_2, and then diluted with tetrahydrofuran (4.8 mL, [substrate] = 0.1 M). Bromochloromethane (65 µL, 969 µmol) was added and the reaction was cooled to -78 ºC, followed by the dropwise addition of *n*-butyllithium (942 µmol) 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, dddd, *J* = 7.5 Hz, 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; $[\alpha]_D^{20}$ = -23.249 (*c* = 1.246, $CHCl_3$, *l* = 50 nm).

(*R*)-4-(benzo[d][1,3]dioxol-5-ylmethyl)dihydrofuran-2(3H)-one (Figure 6, compound 36). The title compound was prepared according to literature procedure[46] using (*S*)-2-(benzo[d][1,3]dioxol-5-ylmethyl)-5-methylhex-4-en-1-ol (76 mg, 306 μmol). The crude reaction mixture was purified on silica gel (20% EtOAc/hexanes, stain with PMA) to afford the title compound as a viscous oil (42.6 mg, 63% yield).



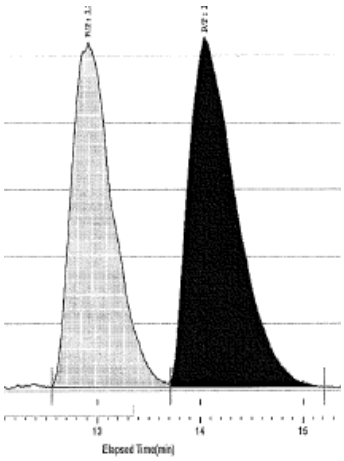
(*R*)-4-(benzo[d][1,3]dioxol-5-ylmethyl)dihydrofuran-2(3H)-one.. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.73 (1H, d, *J* = 7.5 Hz), 6.61 (1H, d, *J* = 1.5 Hz), 6.58 (1H, dd, *J* = 7.5 Hz, 1.5 Hz), 5.92 (2H, s), 4.31 (1H, dd, *J* = 9.5 Hz, 7.5 Hz), 4.00 (1H, dd, *J* = 9.5 Hz, 6.5 Hz), 2.77 (1H, dddd, *J* = 15.5 Hz, 15.5 Hz, 7.0 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; $[\alpha]_D^{20}$ = +2.375 (*c* = 0.685, $CHCl_3$, *l* = 50 nm).

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

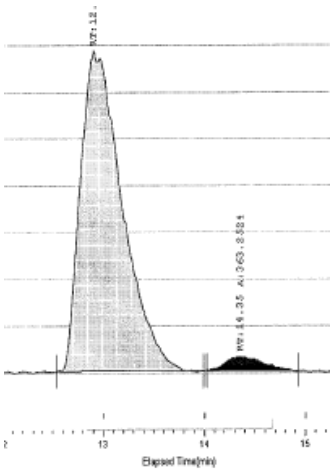
Analysis of Stereochemistry:

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.

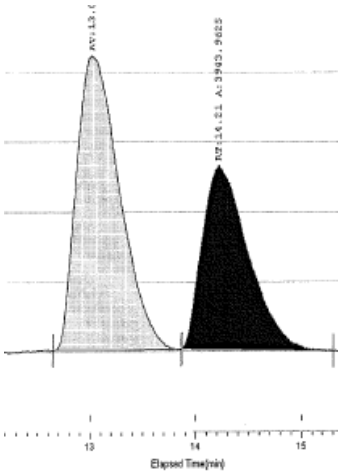
Chiral SFC (Chiracel, AD-H, 35 ^{o}C, 5 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of 4-(benzo[d][1,3]dioxol-5-ylmethyl)dihydrofuran-2(3H)-one.



racemic



Diboration/cross-coupling product

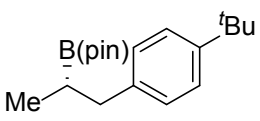


Coinjection of product + racemic

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

3.7.10 Preparation of (S)-(-)-Fenpopimorph

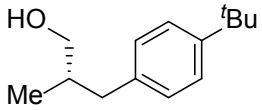
(*S*)-2-(1-(4-(tert-butyl)phenyl)propan-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To an oven-dried 16-mL vial with magnetic stir bar in the dry box was added (*S*)-2,2'-(propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (148 mg, 0.500 mmol), potassium hydroxide (84.2 mg, 1.50 mmol), 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, 1.42 mmol) was added and the reaction was cooled to -78 ºC, followed by the dropwise addition of *n*-butyllithium (0.55 mL, 1.33 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).

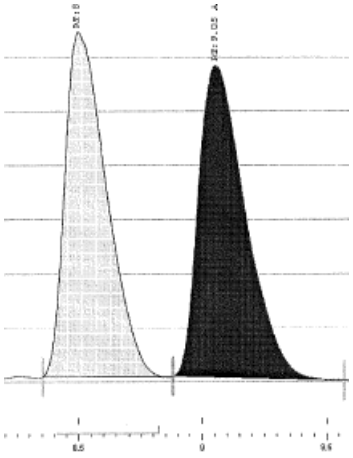


(*S*)-3-(4-(tert-butyl)phenyl)-2-methylpropan-1-ol. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (2H, d, *J* = 8.0 Hz), 7.10 (2H, d, *J* = 8.0 Hz), 3.53 (1H, dd, *J* = 11.0 Hz, 6.5 Hz), 3.46 (1H, dd, *J* = 10.5 Hz, 6.5 Hz), 2.70 (1H, dd, *J* = 13.5 Hz, 6.5 Hz), 2.40 (1H, dd, *J* = 13.5 Hz, 8.0 Hz), 1.93 (1H, dddd, *J* = 13.5 Hz, 13.5 Hz, 6.5 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).

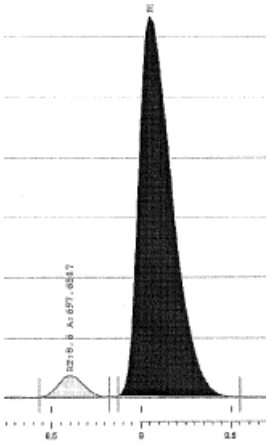
Analysis of Stereochemistry:

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.

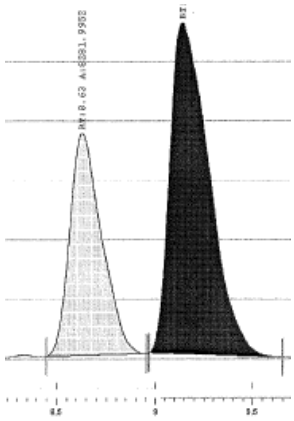
Chiral SFC (Chiracel, OD-H, 35 ^{o}C, 3 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of 3-(4-(tert-butyl)phenyl)-2-methylpropan-1-ol.



racemic



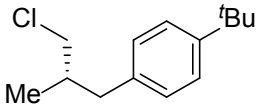
Diboration/cross-coupling product



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).

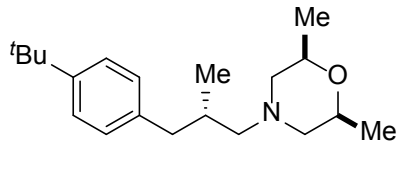


(*S*)-1-(tert-butyl)-4-(3-chloro-2-methylpropyl)benzene. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (2H, d, *J* = 8.5 Hz), 7.09 (2H, d, *J* = 8.5 Hz), 3.46 (1H, dd, *J* = 11.0 Hz, 5.0 Hz), 3.39 (1H, dd, *J* = 11.0 Hz, 6.0 Hz), 2.71 (1H, dd, *J* = 14.0 Hz, 7.0 Hz), 2.50 (1H, dd, *J* = 13.5 Hz, 7.0 Hz), 2.10 (1H, dddd, *J* = 14.0 Hz, 13.5 Hz, 7.0 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; $[\alpha]_D^{20}$ = +13.095 (*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[47] without modification. The

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

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).



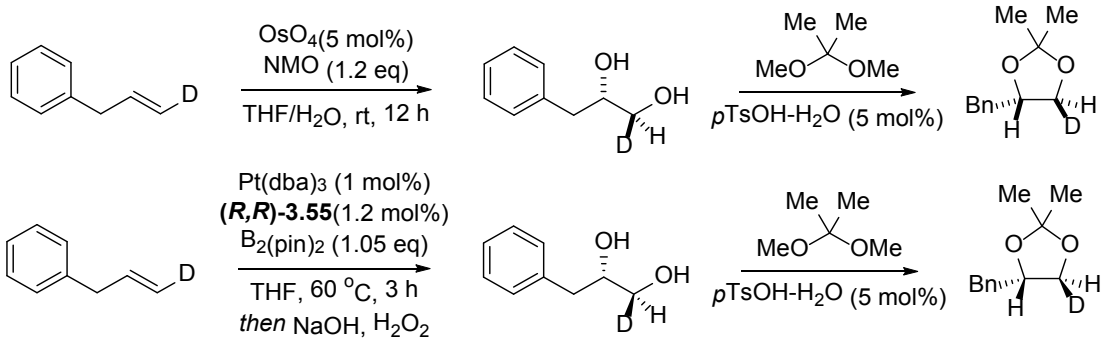
(*S*)-1-[3-(4-*tert*-Butylmethyl)-2-methyl]propyl-*cis*-3,5-dimethylmorpholine. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (2H, d, *J* = 8.0 Hz), 7.06 (2H, d, *J* = 8.0 Hz), 3.69-3.63 (2H, m), 2.75 (1H, dd, *J* = 13.5 Hz, 5.0 Hz), 2.70-2.64 (2H, m), 2.27 (1H, dd, *J* = 13.0 Hz, 8.0 Hz), 2.17 (1H, dd, *J* = 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; $[\alpha]_D^{20}$ = -1.213 (*c* = 0.824, $CHCl_3$, *l* = 50 nm).

3.7.11 Deuterium Labeled Studies

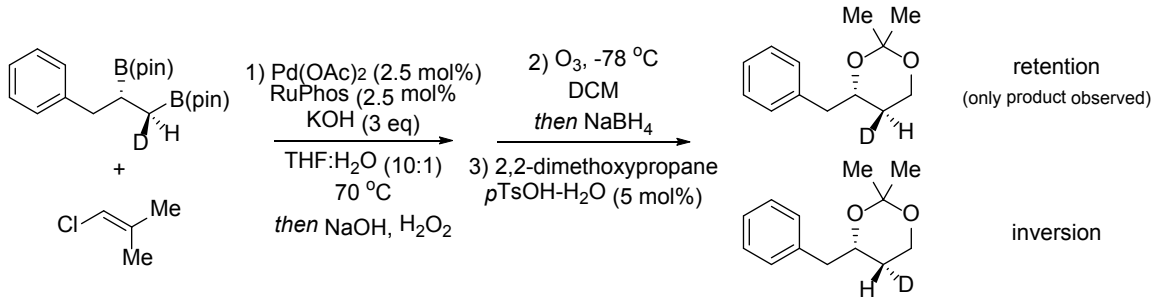
Hydroboration of 3-phenyl-1-propyne was performed according to the literature procedure[48] using AcOD as the deuterium source for boron/deuterium exchange. ^{1}H NMR showed 75% deuterium incorporation in the resulting alkene with geometry as shown. Syn-addition of bis(pinacolato)diboron in the platinum-catalyzed diboration of

[48] Ellis, N. M.; Molander, G. A. *J. Org. Chem.* **2008**, *73*, 6841.

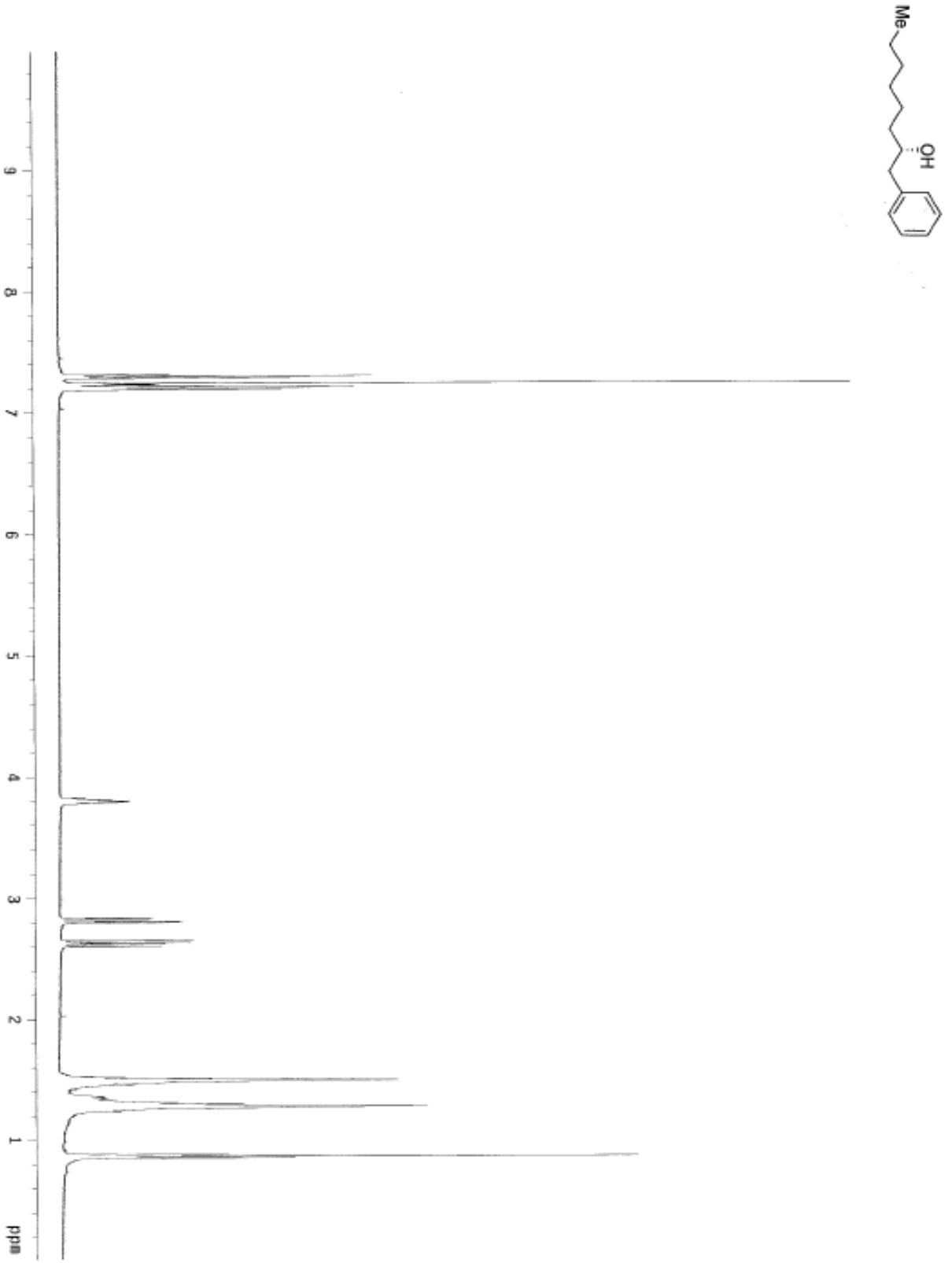
terminal alkenes was proven through comparison of acetonides derived from the 1,2-diol product of OsO_4 dihydroxylation. ^{1}H NMR of the resulting two acetonides were identical.

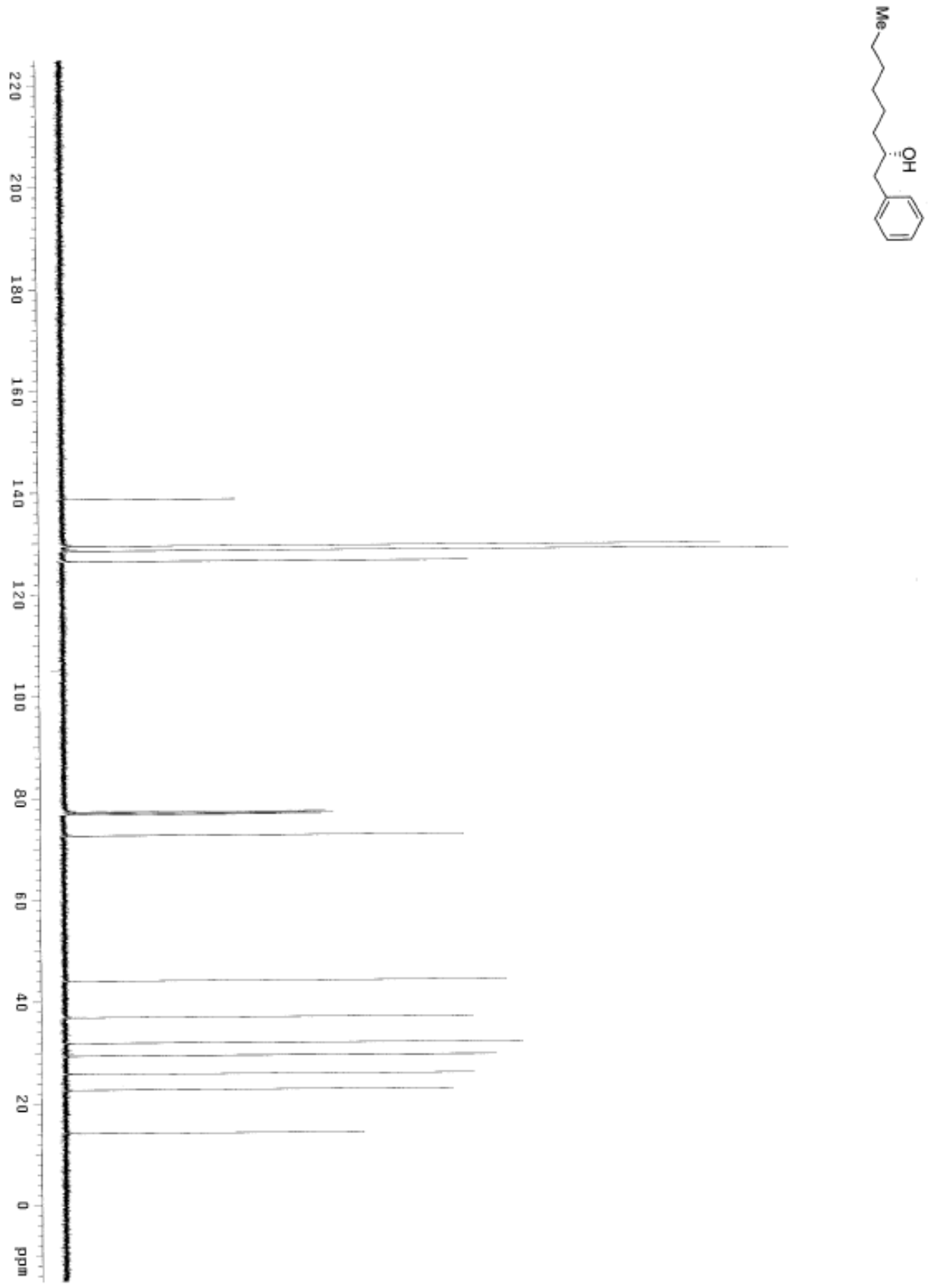


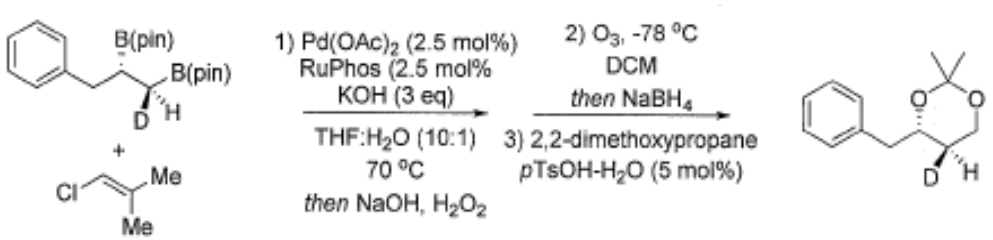
The stereochemical outcome of transmetallation in the palladium catalyzed cross-coupling was determined through ^{1}H NMR analysis of the 1,3-diol derived acetonide as described below. The resulting acetonide was compared to the analogous product employing allylbenzene as the substrate. ^{1}H NMR of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



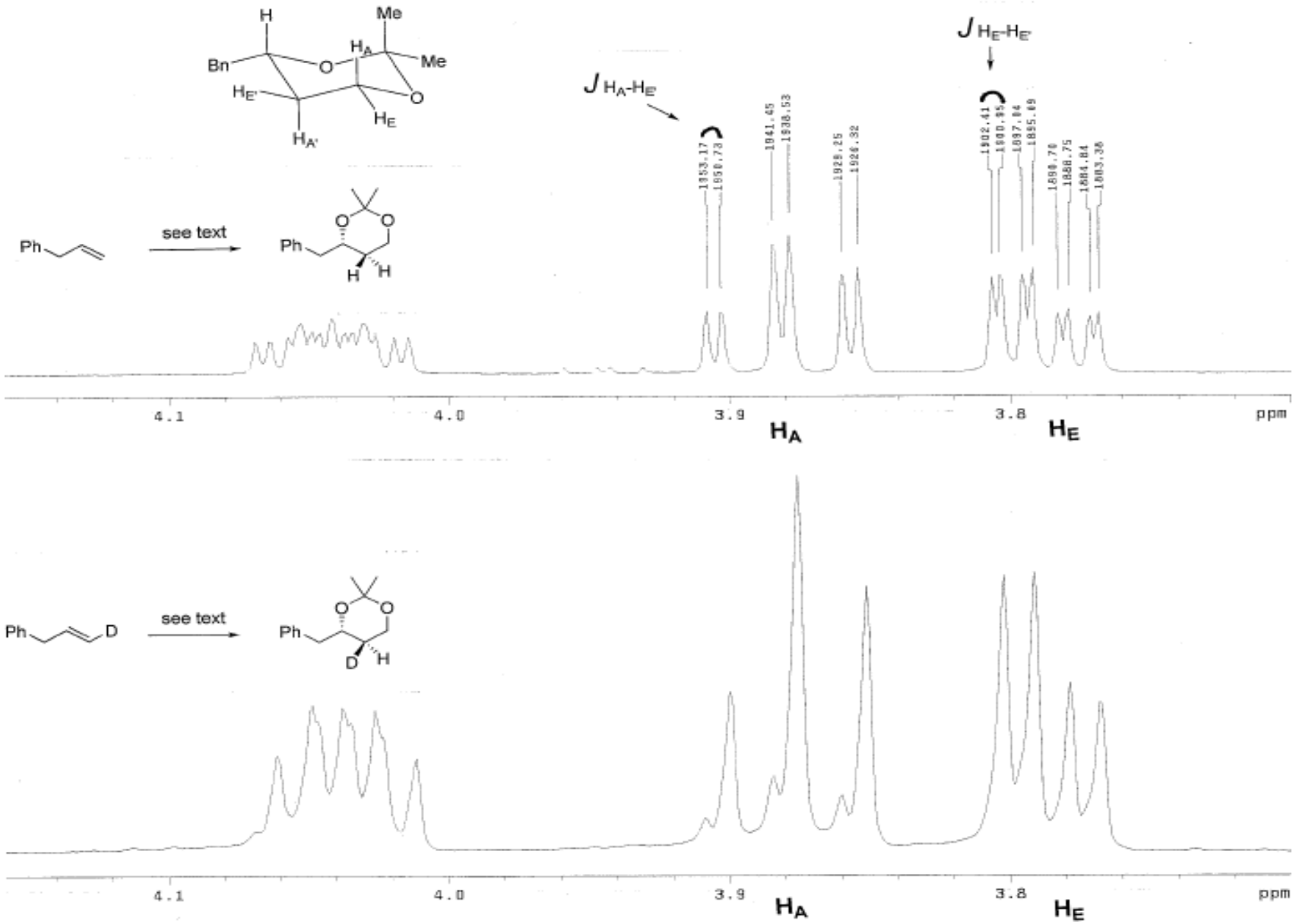
3.8 Representative NMR Spectra




Me
OH
220
200
180
160
140
120
100
80
60
40
20
0
ppm


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
O
H_A
Me
$H_{E'}$
O
H_E
$H_{A'}$
$J_{H_A-H_{E'}}$
$J_{H_E-H_{E'}}$
1953.17
1950.73
1941.45
1938.53
1928.25
1926.32
1902.41
1900.85
1897.84
1895.49
1890.76
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
Ph
O
O
D
H
4.1
4.0
3.9
3.8
ppm
H_A
H_E

Chapter 4

Direct Stereospecific Amination of Pinacol Boronates

4.1 Introduction

The methodologies described in the previous chapters enable the rapid enantioselective transformation of terminal olefins into complex chemical motifs. As illustrated in section 3.5, a variety of structurally diverse and biologically important compounds can be readily synthesized by combining the developed reactions with known transformations. While the syntheses of (-)-hinokinin and (*S*)-fenpropimorph (Scheme 4.1) effectively demonstrate the synthetic potential of asymmetric diboration/cross-coupling cascades, a more expansive application appeared possible. By transforming the carbon-boron bond in the DCC product into a carbon-nitrogen bond, a variety of enantioenriched substituted phenethylamines can be easily synthesized from previously unprecedented starting materials. These compounds are a commonly occurring class of metabolites present in plants and animals, and they exhibit a diverse array of biological activities including antiinflammatory[1], antiviral[2], and antitumor[3] as well as a plethora of neurological activities.[4] This high biological activity makes phenethylamines a commonly observed chemical motif in pharmaceuticals (Figure 4.1)

[1] Hwan, L. J.; San, A. C.; Sun, Y. B.; Suk, K. K.; Ae, L. Y.; Mi, W. S.; Joo, G. B.; Ig, C. S.; Ki-Baik, H. Eur. *J. Pharmacol.* **2012**, *687*, 28.

[2] Laconi, S.; Madeddu, M. A.; Pompei, R. Molecules 2011, 16, 3479.

[3] (a) Mukherjee, A.; Dutta, S.; Sanyal, U. *J. Exp. Biol.* **2007**, *26*, 489. (b) Carraro, F.; Naldini, A.; Pucci, A.; Locatelli, G. A.; Maga, G.; Schenone, S.; Bruno, O.; Ranise, A.; Bondavalli, F.; Brulo, C. *J. Med. Chem.* **2006**, *49*, 1549. (c) Guillard, J.; Decrop, M.; Gallay, N.; Espanel, C.; Boissier, E.; Herault, O.; Viaud-Massuard, M.-C. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1934.

[4] (a) Eshleman, A. J. Forster, M. J.; Wolfrum, K. M.; Johnson, R. A.; Janowsky, A.; Gatch, M. B. *Psychopharmacology* **2014**, *231*, 875. (b) Murnane, K. S.; Murai, N.; Howell, L. L.; Fantegrossi, W. E. *J. Pharmacol. Exp. Ther.* **2009**, *331*, 717. (c) Mottram, D. R.; Thakar, Y. *J. Pharm. Pharmacol.* **1984**, *36*,

Scheme 4.1 Applications of DCC Reaction in Asymmetric Synthesis

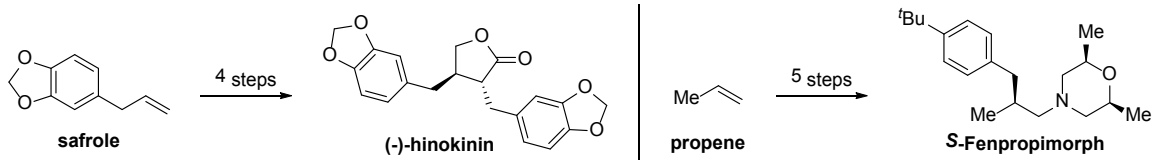
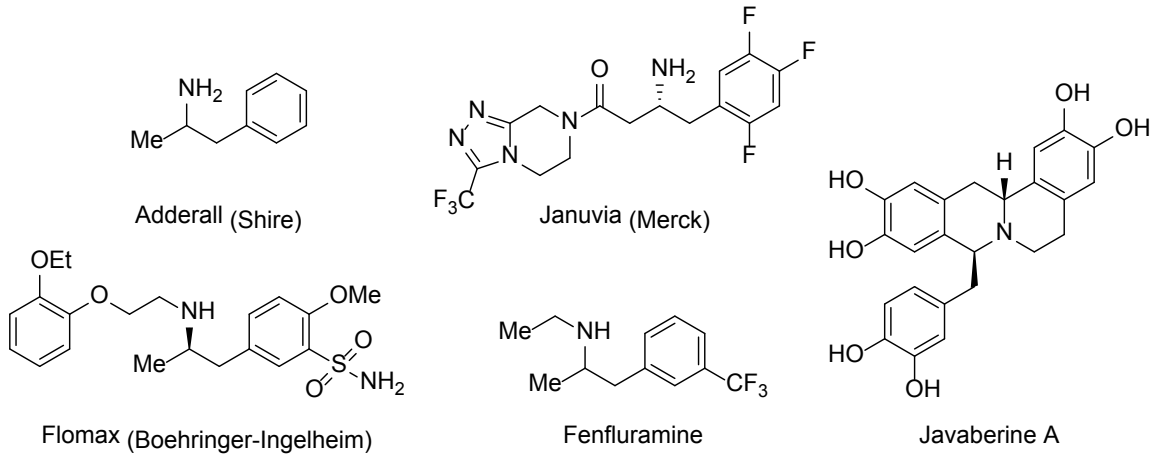


Figure 4.1 Select Examples of Phenethylamines in Pharmaceuticals



Unfortunately, a method for the direct conversion of pinacol boronates to amines was undeveloped. Current transformations of carbon-boron bonds into carbon-nitrogen bonds only apply to with highly electrophilic boron centers. Thus, for pinacol boronates to participate in known reactions, the boronate must first be converted into a reactive and unstable electrophilic borane. This requires multiple steps and often uses an excess of toxic reagents. In this chapter, the development of a new practical and scalable solution to directly transform pinacol boronates into amines will be discussed.

4.2 Background

The formation of amines from boranes was first developed in the 1960's and remains an important route for the synthesis of amines. Throughout the past several

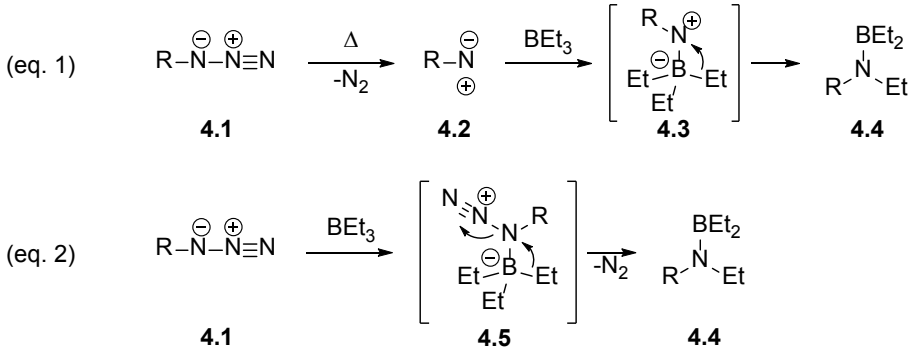
668. (d) Winter, J. C. *Psychopharmacology*, **1980**, *68*, 159. (e) Jones, C. N.; Howard, J. L.; McBennett, S. T. *Psychopharmacology*, **1980**, *67*, 111.

decades a variety of nitrogen-based reagents have been developed to promote the desired transformation. They exhibit the same general reactivity and contain a leaving group bound to a Lewis basic nitrogen atom.

4.2.1 Amination with Alkyl Azides

In 1971, the amination of triethylborane by organic azides was developed.[5] This transformation tolerated a variety of alkyl and aryl azides and offered a novel route for the synthesis secondary amines of type **4.4**. While thermal decomposition of organic azides is known, significant evolution of nitrogen gas was not observed under the reaction conditions in the absence of triethylborane. This effectively excludes a mechanism involving a nitrene intermediate (Scheme 4.2, eq 1). Instead, the authors propose that the reaction proceeds through reversible coordination of the azide with boron (Scheme 4.2, eq 2). Subsequent alkyl migration of intermediate **4.5** releases nitrogen and, upon solvolysis, generates the corresponding secondary amine **4.4**. Understanding the operative mechanism had an immense impact in the field of boron chemistry, and alkyl azides continue to be the most commonly employed reagent for the amination of carbon-boron bonds.

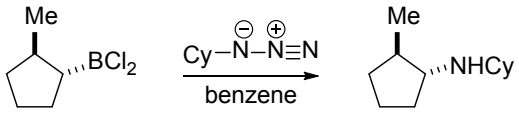
Scheme 4.2 Amination of Trialkylboranes with Organic Azides



[5] Suzuki, A.; Sono, S.; Itoh, M.; Brown, H. C.; Midland, M. M. *J. Am. Chem. Soc.* **1971**, *93*, 4329.

One drawback associated with the amination of triethylborane is that only one alkyl substituent participates in the migration event, despite addition of excess azide. Furthermore, if a differentially substituted organoboron reagent is used, a mixture of amine products originating from multiple migration pathways is observed. These two inherent limitations associated with trialkylboranes were eventually circumvented with the discovery that alkyl and aryl dichloroboranes also react with organic azides to generate amines.[6] In general, dichloroboranes exhibit higher reactivity than trialkylboranes, with the reaction even occurring at room temperature when less hindered boranes or azides were used. Importantly, the amination of alkyldichloroboranes was found to be stereospecific and proceeded with retention of configuration (Scheme 4.3).

Scheme 4.3 Amination of Alkyldichloroboranes with Organic Azides



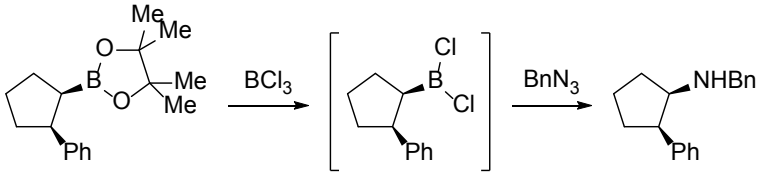
4.6 **4.7**

Unfortunately, while trialkylboranes and dichloroboranes react efficiently, more stable organoboron derivatives such as boronate esters fail to participate in amination with organic azides. In order to promote the desired transformation, the stable organoboron reagents must first be converted into reactive dichloroboranes. *In situ* generation of dichloroboranes from boronic esters can be accomplished by bubbling excess boron trichloride gas through the reaction mixture at cryogenic temperatures (Scheme 4.4).[7] Subsequent addition of an organic azide to intermediate **4.9** generates the

[6] (a) Brown, H. C.; Midland, M. M.; Levy, A. B. *J. Am. Chem. Soc.* **1973**, *95*, 2394. (b) Carboni, B.; Vaultier, M.; Carrié, R. *Tetrahedron Lett.* **1988**, *29*, 1279.
[7] Brown, H. C.; Salunkhe, A. M.; Argade, A. B. *Organometallics* **1992**, *11*, 3094.

desired amine **4.10** upon warming.[8] This two-step, single flask procedure effectively allows boronate esters to participate in reactions with azides to form amines, however, the use of toxic gas makes this reaction sequence unappealing and has prevented widespread use of this methodology.

Scheme 4.4 Amination of Pinacol Boronates through a Dichloroborane Intermediate

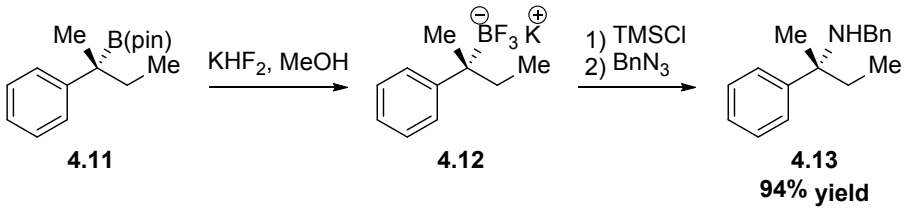


4.8 **4.9** **4.10**
63% yield

Alternatively, amination of boronate esters can be accomplished by first converting the stable ester into the corresponding potassium trifluoroborate salt.[9] Addition of $SiCl_4$ or TMSCl abstracts a fluoride from the stable salt generating a highly electrophilic difluoroborane. Similar to the dichloro analogues, this can undergo amination with organic azides (Scheme 4.5). Although this process requires two separate reactions, the intermediate trifluoroborate salts are both air and moisture stable, making them easier to handle compared to alkyldichloroborane variants. More importantly, this reaction sequence avoids using excess toxic trichloroborane gas, and makes the overall transformation more appealing.

[8] Hupe, E.; Marek, H.; Knochel, P. *Org. Lett.* **2002**, *4*, 2861.
[9] (a) Matteson, D. S.; Kim, G. Y. *Org. Lett.* **2002**, *4*, 2153. (b) Kim. B. J.; Matteson, D. S. *Angew. Chem. Int. Ed.* **2004**, *43*, 3056. (c) Bagutski, V.; Elford, T. G.; Aggarwal, V. K. *Angew. Chem. Int. Ed.* **2011**, *50*, 1080.

Scheme 4.5 Amination of Pinacol Boronates through a Potassium Trifluoroborate Intermediate

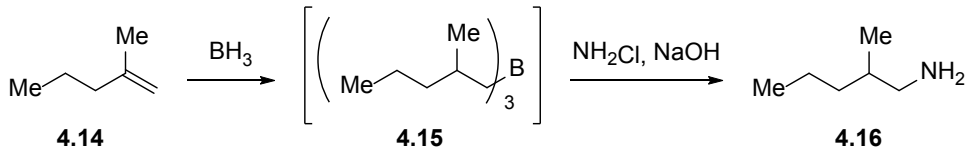


4.11 **4.12** **4.13**
94% yield

4.2.2 Amination with Chloramines

The conversion of trialkylboranes to amines has also been accomplished with chloramines.[10] Unlike amination with organic azides, two of the alkyl groups in the parent trialkylborane participate in the desired transformation, increasing the maximum theoretical yield to 66% (Scheme 4.6). Similar to reactions with organic azides, a complex mixture of products is obtained when differentially substituted trialkylboranes are used. This arises from the ability of each alkyl group to migrate. Chloramines are also effective in aminating other highly electrophilic boron analogues including dialkylborinic acids or esters.[11] This feature enables hindered alkenes, which typically only undergo hydroboration to the dialkylborane intermediate, to participate in amination.

Scheme 4.6 Amination of Trialkylboranes with Chloramine



4.14 **4.15** **4.16**
58% yield

Several major complications, however, are associated with the use of chloramines in the amination of alkylboron compounds. First, solutions of chloramine readily decompose, requiring fresh preparation each time the material is to be used. Secondly,

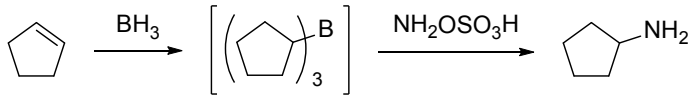
[10] Brown, H. C.; Heydkamp, W. R.; Breuer, E.; Murphy, W. S. *J. Am. Chem. Soc.* **1964**, *86*, 3565.
[11] Brown, H. C.; Kim, K.-W.; Srebnik, M.; Singaram, B. *Tetrahedron* **1987**, *43*, 4071.

the synthesis of chloramine is often inconsistent, requiring analysis of the reagent before use to determine the precise concentration of active species. Due to these inherent limitations with chloramine reagents, very few attempts to broaden the substrate scope or utilize the transformation in synthesis have been reported.

4.2.3 Amination with Hydroxylamines

The final class of reagents that have shown success at converting organoboron compounds into amines are hydroxylamine derivatives. Hydroxylamine-O-sulfonic acid, the first and most commonly employed reagent, was discovered concurrent to chloramine for its ability to convert trialkylboranes into the corresponding amines (Scheme 4.7).[10,12] While the two reagents deliver the desired amine products in similar yield, hydroxylamine-O-sulfonic acid is less reactive, requiring refluxing conditions and longer reaction times. The decreased reactivity, however, is offset by the tremendous advantage that hydroxylamine-O-sulfonic acid is a commercially available stable salt.

Scheme 4.7 Amination of Trialkylboranes with Hydroxylamine-O-Sulfonic Acid



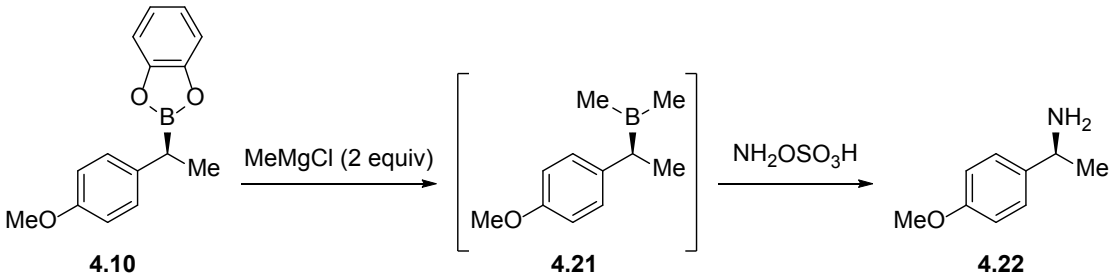
4.17 **4.18** **4.19** **59% yield**

While hydroxylamine-O-sulfonic acid is not reactive enough to convert boronate esters into amines directly, strategies have been developed that first convert the stable esters into more reactive analogues. Alkylcatecholboronates, obtained by asymmetric hydroboration with catechoborane, have been aminated successfully after being converted to the analogous trialkylborane with excess methyl magnesium chloride.[13]

[12] Rathke, M. W.; Inoue, N.; Varma, K. R.; Brown, H. C. *J. Am. Chem. Soc.* **1966**, *88*, 2870.
[13] Fernandez, E.; Hooper, M. W.; Knight, F. I.; Brown, J. M. *Chem. Commun.* **1997**, 174.

Addition of hydroxylamine-O-sulfonic acid generates the desired amine in moderate yield with complete retention of configuration, offering a practical approach for the synthesis of enantioenriched benzylic amines.

Scheme 4.8 Amination of Alkylcatecholboronates with Hydoxylamine



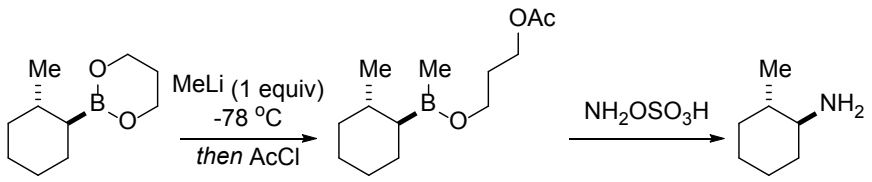
4.10 **98% *ee***

4.21

4.22 **56% yield** **98% *ee***

Boronate esters derived from 1,3-propanediol can be converted to amines using a similar strategy.[14] However, instead of using excess Grignard reagent, this substrate class requires only equimolar addition of methyl lithium to produce the corresponding borinic acid **4.24** upon acylation of the free alcohol intermediate (Scheme 4.9). The resulting borinic acid **4.24** is more Lewis acidic than the boronate ester, and is able to undergo amination upon addition of hydroxylamine-O-sulfonic acid.

Scheme 4.9 Amination of Boronate Esters with Hydroxylamine



4.23

4.24

4.25

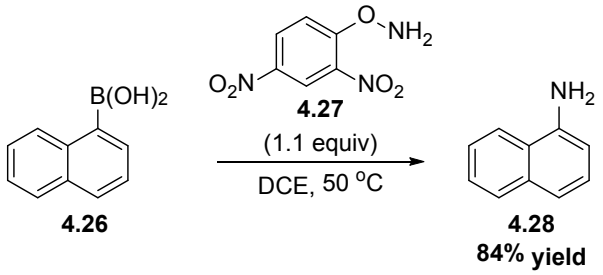
Recently, the direct amination of aryl boronic acids has been accomplished using a highly functionalized hydroxylamine derivative (Scheme 4.10).[15] This reaction

[14] (a) Brown, H. C.; Kim, K.-W.; Cole, T. E.; Singaram, B. *J. Am. Chem. Soc.* **1986**, *108*, 6761. (b) Fernandez, E.; Maeda, K.; Hooper, M. W.; Brown, J. M. *Chem.-Eur. J.* **2000**, *6*, 1840.

[15] Zhu, C.; Li, G.; Ess, D. H.; Falck, J. R.; Kürti, L. *J. Am. Chem. Soc.* **2012**, *134*, 18253.

tolerates a wide range of electron rich, electron poor and sterically encumbered aryl substrates and delivers the corresponding aniline derivatives in moderate to excellent yields under relatively mild reaction conditions. While this transformation offers a significant improvement over current methods, the reaction is limited by the specialized reagent, which requires a several step synthesis from commercial reagents.

Scheme 4.10 Amination of Aryl Boronic Acids with Hydroxylamine Derivative

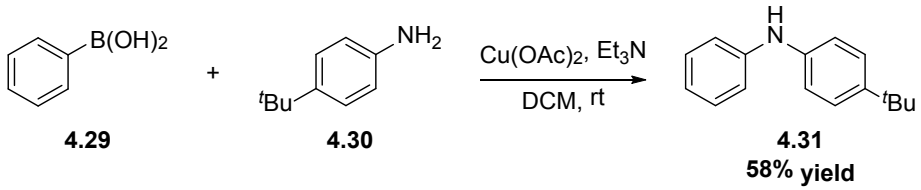


4.2.4 Copper-Catalyzed Amination

The Chan-Lam-Evans coupling is a copper-catalyzed method for the conversion of arylboronic acids into anilines. This transformation, first disclosed in 1998, requires stoichiometric cupric acetate and an amine base such as triethylamine or pyridine (Scheme 4.11).[16] The reaction tolerates a range of electron-rich and electron-poor arylboronic acid substrates, but is sensitive to steric encumberance adjacent to the boron atom. Impressively, a wide range of amine substrates are suitable cross-coupling partners, including primary and secondary amines, anilines, amides, imides, ureas, sulfonamides and carbamates.

[16] (a) Chan, D. M. T.; Monaco, K. L.; Wang, R.-P.; Winters, M. P. *Tetrahedron Lett.* **1998**, *39*, 2933. (b) Lam, P. Y. S.; Clark, C. G.; Saubern, S.; Adams, J.; Winters, M. P.; Chan, D. M. T.; Combs, A. *Tetrahedron Lett.* **1998**, 39, 2941. (c) Evans, D. A.; Katz, J. L.; West, T. R. *Tetrahedron Lett.* **1998**, *39*, 2937.

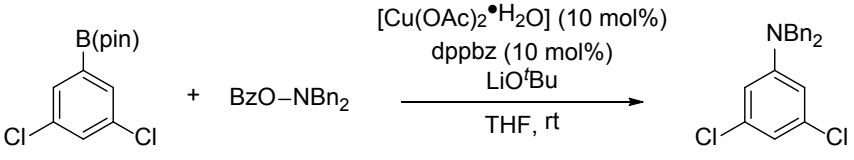
Scheme 4.11 Copper-Mediated Amination of Aryl Boronic Acids



4.29 + **4.30** → **4.31**, **58% yield**

Since its discovery, the Chan-Lam-Evans coupling has received significant attention from the chemistry community. This has led to the development of catalytic variants. Moreover, the substrate scope of the reaction has been expanded to include boronate esters. By employing O-benzoylhydroxylamines, Miura and co-workers were able to aminate aryl pinacol boronates, generating a diverse array of disubstituted aniline derivatives (Scheme 4.12).[17]

Scheme 4.12 Copper-Catalyzed Amination of Aryl Pinacol Boronates

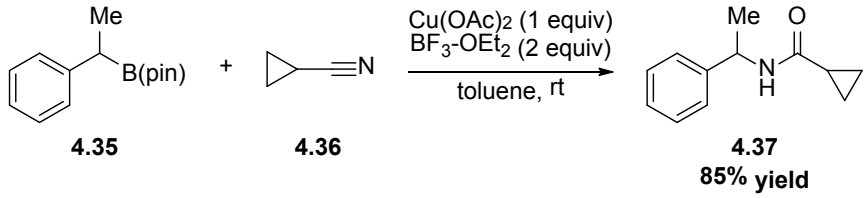


4.32 + **4.33** → **4.34**, **87% yield**

Alkyl potassium trifluoroborates have also been used successfully in copper mediated C-N bond forming reactions.[18] Interestingly, this transformation uses nitriles as the cross-coupling partner, and delivers the corresponding amide products (Scheme 4.13). The reaction is believed to proceed through a cation intermediate, resulting in racemization when enantioenriched alkylboron substrates are used.

[17] Matsuda, N.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem. Int. Ed.* **2012**, *51*, 3642.
[18] Cazorla, C.; Métay, E.; Andrioletti, B.; Lemaire, M. *Tetrahedron Lett.* **2009**, *50*, 6855.

Scheme 4.13 Copper Mediated Coupling of Alkylborons and Nitriles

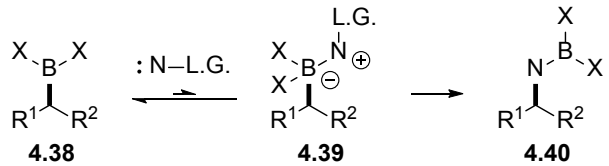


4.35 **4.36** **4.37**
85% yield

4.3 Development and Scope of Direct Stereospecific Amination of Pinacol Boronates[19]

The observed difference in reactivity of various organoboron compounds in the direct amination with previously described reagents can be explained by the Lewis acidity of the different boron atoms. All three classes of amine reagents that have been successfully employed in amination reactions contain a neutral, mildly Lewis basic nitrogen atom. While these reagents are able to coordinate to electron deficient substrates such as trialkylboranes and alkyldihaloboranes, the equilibrium for the coordination to less electrophilic pinacol boronates heavily favors the uncoordinated species **4.38** (Scheme 4.14). Even organic azides, which contain one of the most competent leaving groups, are unable to promote the desired amination because formation of the coordinated intermediate **4.39** is so unfavored. We hypothesized that a more Lewis-basic amine reagent might promote the necessary coordination, and, if attached to a suitable leaving group, enable direct amination of pinacol boronates.

Scheme 4.14 Amination of Organoboron Compounds

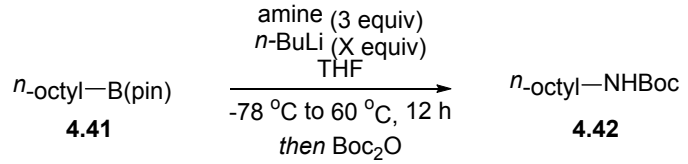


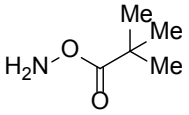
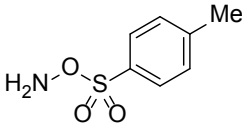
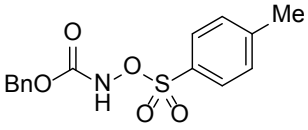
4.38 **4.39** **4.40**

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

To examine the validity of this hypothesis, the amination of octylB(pin) was attempted with hydroxylamine-O-sulfonic acid with both a neutral amine and an anionic amine. As expected from literature precedence, when equimolar equivalents of the hydroxylamine derivative and base were used, no desired amine was detected. Gratifyingly, when the reaction was performed with excess base, the desired product was observed, albeit in an unimpressive 9% yield. Having supported the hypothesis that direct amination of pinacol boronates can be accomplished with a more Lewis-basic reagent, we sought to improve on the low yield. One possible solution to improve the process could be to accelerate the necessary 1,2-migration by employing hydroxylamine derivatives with a more labile leaving group. Unfortunately, amine reagents possessing either a tosylate or carboxylate leaving group underwent decomposition upon deprotonation, presumably forming the nitrene *in situ*. Addition of a Cbz protecting group on nitrogen to stabilize the resulting anion proved futile, again showing visible decomposition of the reagent upon deprotonation. While milder reaction conditions and alternative leaving groups for these functionalized hydroxylamine derivatives might have been effective, the multi-step synthesis required to obtain these reagents was considered too detrimental. This feature would have possibly prevented the wide-spread utilization of the methodology and consequently no additional experimentation was performed.

Table 4.1 Amination of Alkyl Pinacol Boronates with Hydroxylamine Derivatives



entry	amine	*n*-BuLi (X equiv)	yield (%)[a]
1	NH_2OSO_3H	3	0
2	NH_2OSO_3H	6	9
3		3	0
4		3	0
5		3	0

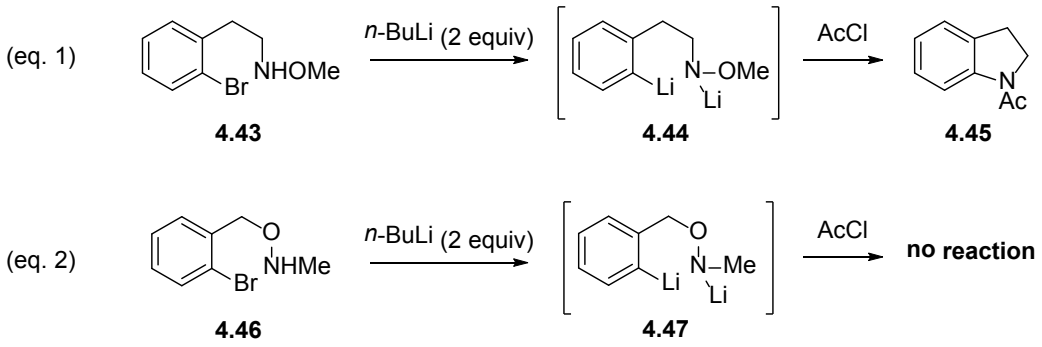
a) percent yield of purified material

In order to develop a direct amination reaction that would be more easily employed, we focused on utilizing commercially available reagents. Particularly appealing was O-methylhydroxylamine. In 1986, Beak and co-workers investigated the amination of organolithium reagents with alkoxyamines.[20] To determine if the reaction proceeds through a formal substitution event or through an intermediate nitrene, the authors conducted an endocyclic restriction test using aryl bromides **4.43** and **4.46** (Scheme 4.15). While the intermediate aryl lithiums from either substrate should participate if the reaction proceeds through nitrene insertion (eq 1 and 2), only the intermediate from **4.44** (eq 1) can adopt the appropriate geometry to displace the methoxide if the reaction proceeds through a formal substitution. As no reactivity was see with **4.46**, the authors were able to conclude that the amination of aryl lithiums with alkoxyamines occurs through direct displacement of the alkoxide. In the context of

[20] Beak, P.; Basha, A.; Kokko, B.; Loo, D. *J. Am. Chem. Soc.* **1986**, *108*, 6016.

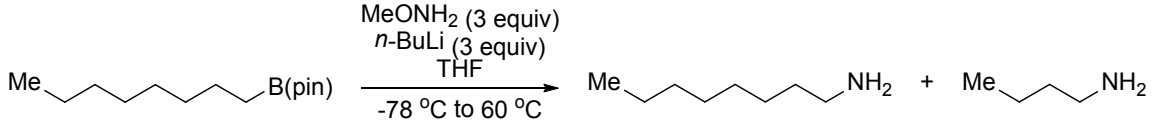
amination of pinacol boronates, this transformation offers potential solutions for two important obstacles. First, lithiated alkoxyamines are stable and do not undergo decomposition into nitrenes. Second, alkoxides are suitable leaving groups for the direct substitution with carbon nucleophiles.

Scheme 4.15 Amination of Aryl Lithiums with Alkoxyamines



Having established this understanding, the utilization of O-methylhydroxylamine for the amination of pinacol boronates was investigated. Excitingly, when octylB(pin) was added to a solution of lithiated O-methylhydroxylamine and heated, the desired amine was obtained. Unfortunately, thorough analysis of the reaction mixture uncovered butylamine as a byproduct, suggesting that direct substitution with the alkyllithium is competitive with deprotonation.

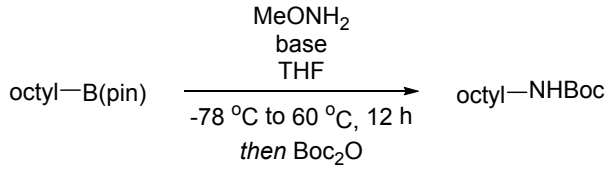
Scheme 4.16 Amination of OctylB(pin) with Lithiated Methoxyamine



As shown in Table 4.2, efforts to improve the reaction through altering the base were ineffective: the majority of the bases examined failed to produce the desired product. Some bases simply showed an inability to deprotonate O-methylhydroxylamine;

this suggests that formal deprotonation of the reagent is required to promote an efficient transformation. Of the bases examined that were able to deprotonate O-methylhydroxylamine, all produced analogous byproducts in greater quantities than reactions with *n*-butyllithium. We eventually found that while formation of the butylamine byproduct could not be avoided, synthetically useful yield of the desired amine could be obtained by adding an excess of reagents. Importantly, by directly protecting the amine product as the Boc-carbamate, the butylamine byproduct could be easily removed by column chromatography.

Table 4.2 Base Screen for Amination with Methoxyamine



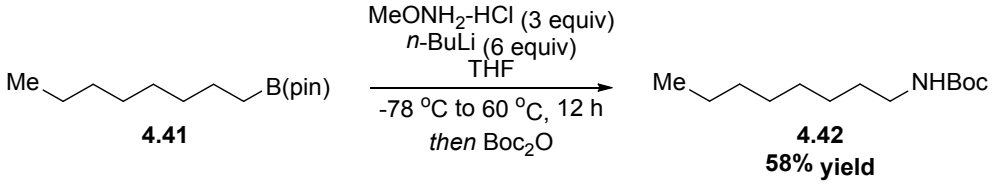
entry	$MeONH_2$ (equiv)	base (equiv)	yield (%)[a]
1	3.0	Li(O*t*Bu) (3.0)	<5
2	3.0	K(O*t*Bu) (3.0)	16
3	3.0	NaH (3.0)	<5
4	3.0	KH (3.0)	<5
5	3.0	vinylMgBr (3.0)	<5
6	3.0	*t*-BuLi (3.0)	54
7	3.0	*s*-BuLi (3.0)	39
8	3.0	*n*-BuLi (3.0)	84
9	2.0	*n*-BuLi (2.0)	72
10	1.0	*n*-BuLi (1.0)	41
11	3.0	MeLi (3.0)	48

a) Percent yield of isolated material

The direct amination of pinacol boronates can also be performed using the commercially available O-methylhydroxylamine hydrochloride salt directly. Addition of two equivalents of *n*-butyllithium is sufficient to free-base the hydrochloride salt and deprotonate the neutral amine, delivering the lithiated amination reagent (Scheme 4.17).

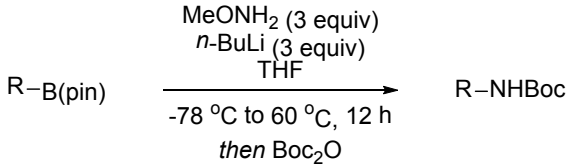
Unfortunately, due to the hydroscopic nature of the reagent, aminations employing the hydrochloride salt were erratic. In order to obtain reproducible results, the free base of the commercial salt was prepared and stored as a solution in tetrahydrofuran.

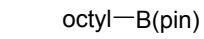
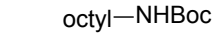
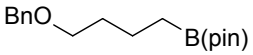
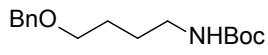
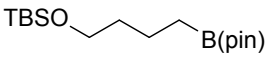
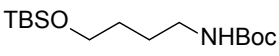
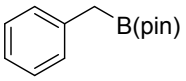
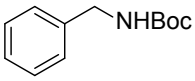
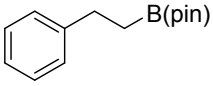
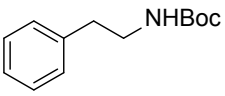
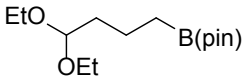
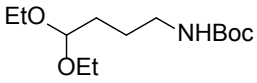
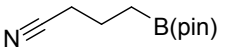
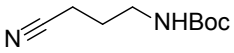
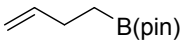
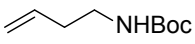
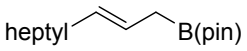
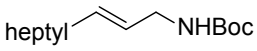
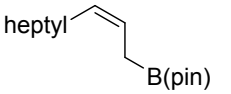
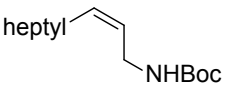
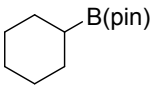
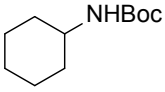
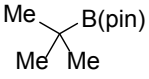
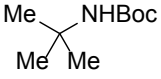
Scheme 4.17 Amination with Methoxyamine Hydrochloride Salt



With the optimized conditions established, the scope of the reaction was investigated. As shown in Table 4.3, the direct amination of pinacol boronates with lithiated methyoxyamine tolerated a range of functional groups including benzyl and silyl ethers, nitriles and acetals (entries 2, 3, 6 and 7). Alkenes, both remote and allylic, were well tolerated and were shown to be configurationally stable under the reaction conditions (entries 8-10). The transformation was also applicable to secondary pinacol boronates (entry 11); however, tertiary pinacol boronates failed to participate in the reaction and resulted in nearly quantitative recovery of the starting material (entry 12). Unfortunately, due to the highly basic reaction conditions, sensitive functional groups such as esters, amides and alkyl halides underwent side reactions with the lithiated amine and led to the formation of undesired byproducts (data not shown).

Table 4.3 Aliphatic Pinacol Boronate Substrate Scope



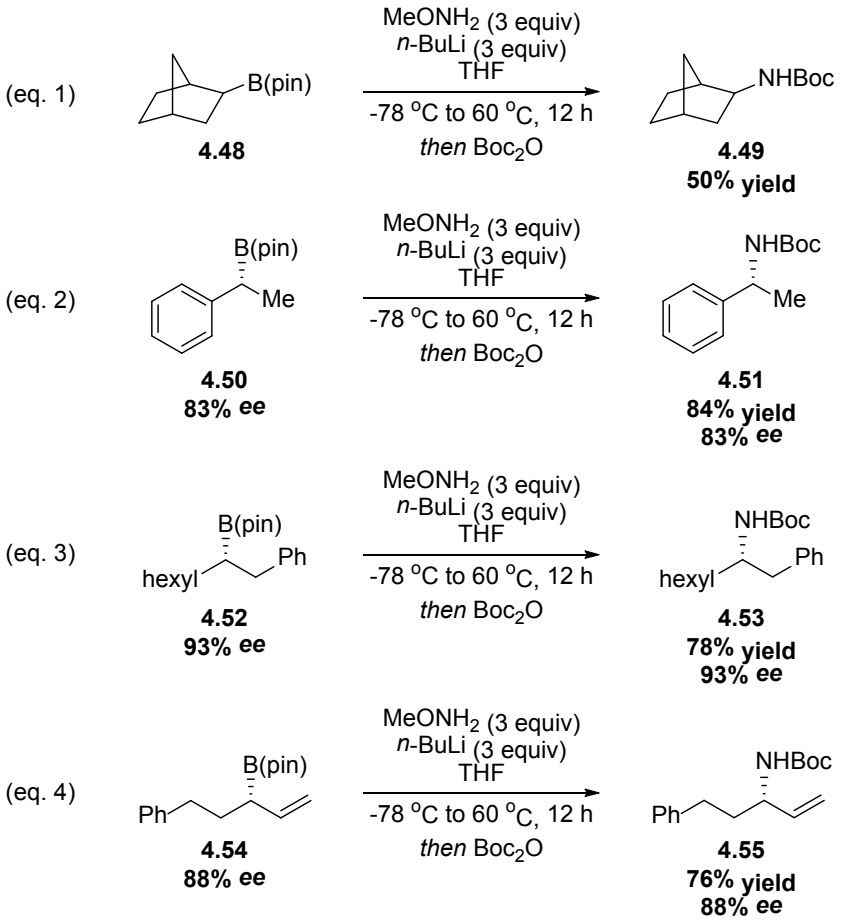
entry	substrate	product	yield (%)[a]
1			84
2			77
3			73
4			67[b]
5			77
6			67
7			36
8			68
9			82
10			81
11			68
12			<5

a) Percent yield of purified material - average of two experiments. b) An adiitional 15% yield of the bis(Boc)-protected amine was also isolated

Importantly, the amination of pinacol boronates was shown to be stereospecific and proceed with retention of configuration (Scheme 4.18). When *exo*-norbornyl boronate **4.48** was subjected to the reaction conditions, only *exo*-norbornyl amine **4.49** was produced (eq. 1). Similarly, when enantioenriched substrates were employed, the

corresponding amines were obtained with complete preservation of enantiomeric enrichment regardless of substitution [i.e. benzylic (eq. 2), alkyl (eq. 3) or allylic (eq. 4)].

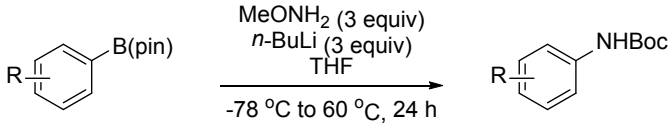
Scheme 4.18 Stereospecific Amination of Pinacol Boronates

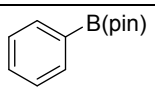
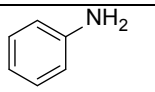
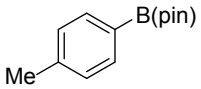
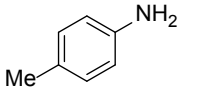
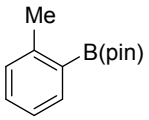
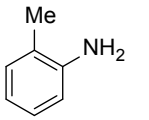
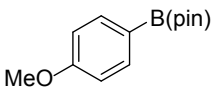
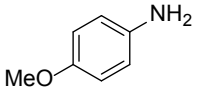
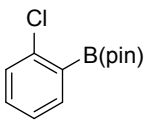
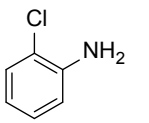
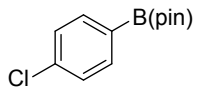
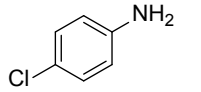
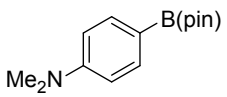
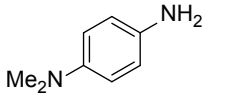
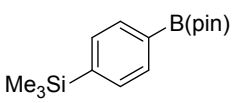
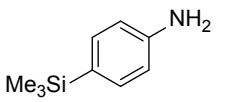
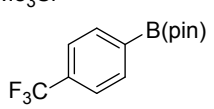
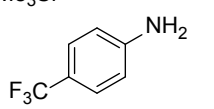
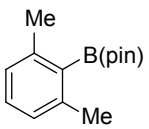
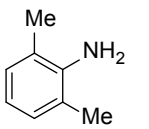
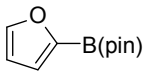
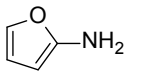
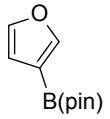
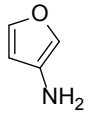
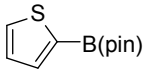
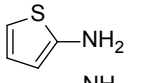
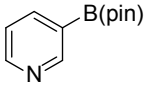
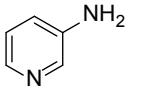


The amination of pinacol boronates with methoxyamine is not limited to aliphatic substrates. Although prolonged reaction times are required, aryl pinacol boronates undergo amination, which offers a convenient metal-free alternative to the Chan-Lam-Evans coupling (Table 4.4). Notably, all of the aniline analogues formed were separable from the butylamine byproduct on silica gel chromatography and could be isolated cleanly without protection. The reaction tolerated sterically encumbered substrates (entries 3 and 10) but proved to be sensitive to the electronic properties of the pinacol

boronates. While electron-rich aryl substrates reacted with excellent efficacy (entries 4 and 7), reactions of electron-poor substrates were significantly inferior (entries 5, 6 and 9). This difference in reactivity suggests that the slow step in the reaction sequence is likely the 1,2-metalate rearrangement, which can be completely suppressed through the incorporation of electron withdrawing groups. Additionally, heteroaromatic pinacol boronates failed to participate in amination with lithiated methoxyamine and suffered substrate decomposition under the reaction conditions

Table 4.4 Aryl Pinacol Boronate Substrate Scope



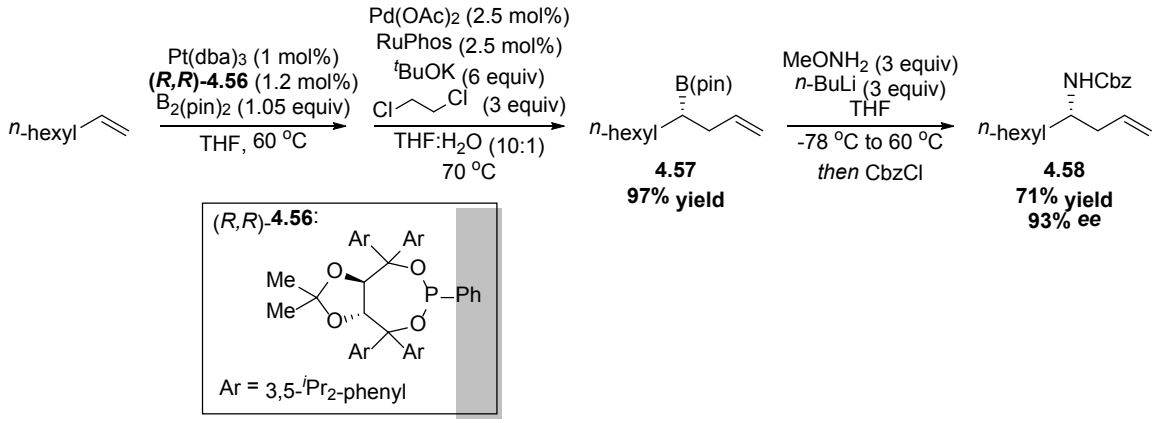
entry	substrate	product	yield (%)[a]
1			83
2			84
3			74
4			87
5			29
6			48
7			89
8			80
9			<5
10			71
11			<5
12			<5
13			<5
14			<5

a) Percent yield of purified material, average of two experiments.

4.4 Direct Amination of the Diboration/Cross-Coupling Cascade Products

Combined with enantioselective diboration/cross-coupling cascade, the direct amination of pinacol boronates offers a concise strategy for asymmetric amine synthesis. Specifically, cross-coupling of 1,2-dichloroethane with an *in situ* generated 1,2-bis(boronate)ester affords enantioenriched homoallylic boronate **4.57**, which can be subjected to amination conditions to generate the homoallylic amine **4.58** (Scheme 4.19). This two-step process is an operationally simple alternative to imine allylation and avoids complications with isolating pre-formed imines or generating them *in situ*. Additionally, the homoallylic amine product can be independently protected according to synthetic needs, while simultaneously avoiding the need to cleave chiral auxiliaries.

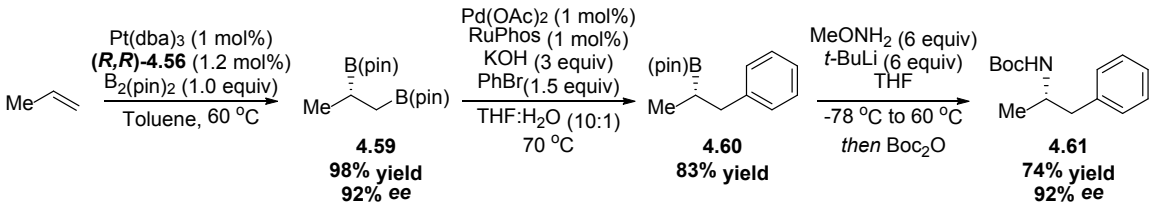
Scheme 4.19 Vinylogous Imine Allylation



In addition to forming important structural motifs, the combination of asymmetric diboration/cross-coupling cascades and direct amination enables the concise synthesis of numerous biologically active amines. In order to highlight the synthetic potential of the methodology, two medicinally relevant compounds were synthesized. Starting from propene gas, asymmetric diboration/cross-coupling quickly generates homobenzylic pinacol boronate **4.60** in excellent yield and enantioselectivity (Scheme 4.20). Direct

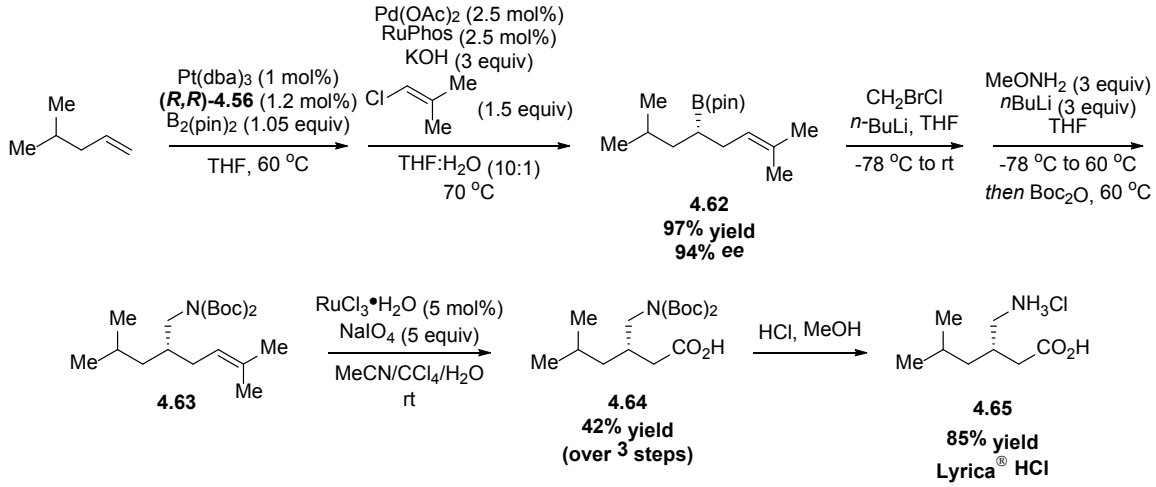
amination of **4.60** with lithiated methoxyamine delivers Boc-protected amphetamine **4.61**. This reaction sequence offers a novel and concise route to an important class of biologically active compounds using two catalytic methodologies and only commercial reagents.

Scheme 4.20 Synthesis of Boc-protected Amphetamine



The synthesis of Lyrica® hydrochloride salt was also accomplished using the previously discussed methodologies (Scheme 4.21). Asymmetric diboration/cross-coupling with 4-methyl-1-pentene quickly generates homoallylic pinacol boronate **4.62**. Matteson homologation followed by direct amination produces protected amine **4.63**. Oxidative cleavage of the olefin and deprotection of the amine affords the desired hydrochloride salt. While this reaction sequence may not be an improvement on the process-scale route for the synthesis of Lyrica® hydrochloride salt, it highlights the synthetic potential of the developed methodologies by offering novel alternative bond disconnections.

Scheme 4.21 Synthesis of Lyrica® Hydrochloride Salt



4.5 Conclusion

The direct stereospecific amination of pinacol boronates has been accomplished. This transformation utilizes commercially available reagents and tolerates a wide range of functional groups for both alkyl and aryl substrates. Combined with the previously discussed diboration/cross-coupling cascade, the concise synthesis of medicinally relevant amines can be quickly accomplished, offering an attractive alternative to current methods.

4.6 Experimental

4.6.1 General Information

^{1}H NMR spectra were recorded on either a Varian Gemini-400 (400 MHz), 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-400 (100 MHz), or a Varian Gemini-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). ^{11}B NMR spectra were recorded on a Varian Inova-500 (160 MHz) spectrometer. Chemical shifts are reported in ppm with an external standard (BF_3-OEt_2: 0.0 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, or phosphomolybdic acid (PMA) in ethanol. Analytical chiral supercritical fluid chromatography (SFC) was

performed on a Thar Supercritical Chromatograph equipped with an auto sampler and a Waters photodiode array detector with isopropanol as the modifier.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran 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. Di-*tert*-butyl dicarbonate was purchased from Oakwood Products, Inc. 2-Chlorophenylboronic acid pinacol ester and 4-trifluoromethylphenylboronic acid pinacol ester were purchased from Boron Molecular. 4-(trimethylsilyl)phenyl boronic acid pinacol ester was purchased from Acros Organics. 3-Cyano-1-propylboronic acid pinacol ester was purchased from Alfa Aesar. But-1-ene-4-boronic acid pinacol ester, benzylboronic acid pinacol ester and *tert*-butylboronic acid pinacol ester were purchased from Frontier Scientific, Inc. 4-Chlorophenylboronic acid pinacol ester, 4-(N,N-dimethylamino)phenylboronic acid pinacol ester, 4-methylphenylboronic acid pinacol ester, 4-methoxyphenylboronic acid pinacol ester, 2-phenylethylboronic acid pinacol ester and 2-methylphenylboronic acid pinacol ester were purchased from Combi-Blocks. All substrates were used without further purification.

4.6.2 Preparation of O-Methylhydroxylamine THF Solution.

O-Methylhydroxylamine THF solution was prepared using the literature procedure[21] with slight modification. A flame-dried, round bottom flask was charged with O-methylhydroxylamine hydrochloride (15 g, 0.18 mol) and sodium hydroxide (7.2 g, 0.18 mol). After the flask was purged with N_2, THF (30 mL) and one drop of water

[21] Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2003**, *125*, 16178.

were added. The mixture was vigorously stirred for 12 h. The supernatant was then transferred via syringe to another flame-dried, round bottom flask containing DRIERITE® (49 g). After vigorous stirring for 5 h, the supernatant was passed through a dried Schlenk-filter to a collection flask under an atmosphere of N_2 with THF washes (2 x 10 mL). The concentration of the O-methylhydroxylamine THF solution was determined by ^{1}H NMR spectroscopy utilizing toluene as the internal standard.

4.6.3 Preparation of Starting Materials.

4.6.3.1 Preparation of known boronic acid pinacol esters

The following boronic acid pinacol esters were prepared by the literature procedure: 4,4,5,5-tetramethyl-2-octyl-1,3,2-dioxaborolane[22], *tert*-butyldimethyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)silane[23], (*E*)-2-(dec-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[24], (*Z*)-2-(dec-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[25], 2-cyclohexyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[122], phenylboronic acid pinacol ester[26], 2-(2,6-dimethylphenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane[26], (*R*)-4,4,5,5-tetramethyl-2-(1-phenylethyl)-1,3,2-dioxaborolane ((*S*,*S*)-Me-DuPhos employed as ligand)[27], (*exo*)-2-(Bicyclo-[2,2,1]-hept-2-yl)-4,4,5,5-tetramethyl-[1,3,2]-dioxaborolane[22] and (*S*)-4,4,5,5-tetramethyl-2-(1-phenyloctan-2-yl)-1,3,2-dioxaborolane[28].

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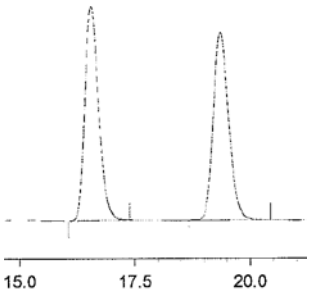
[22] Yamamoto, Y.; Fujikawa, R.; Umemoto, T.; Miyaura, N. *Tetrahedron*. **2004**, *60*, 10695
[23] Dreher, S. D.; Lim, S. E.; Sandrock, D. L.; Molander, G. *J. Org. Chem.* **2009**, *74* (10), 3626.
[24] Zang, P.; Roundtree, I. A.; Morken, J. P. *Org. Lett.* **2012**, *14* (6), 1416.
[25] Ely, R. J.; Morken, J. P. *J. Am. Chem. Soc.* **2010**, *132*, 2534.
[26] Morandi, S.; Caselli, E.; Forni, A.; Bucciarelli, M.; Torre, G.; Prati, F. *Tetrahedron Asymm.* **2005**, *16*, 2918.
[27] Noh, D.; Chea, H.; Ju, J.; Yun, J. *Angew. Chem. Int. Ed.* **2009**, *48*, 6062
[28] Manuscript for substrate is currently in preparation. For known methods to synthesize substrate, see Lee, Y.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2009**, *131*, 3160.

Proof of Stereochemistry:

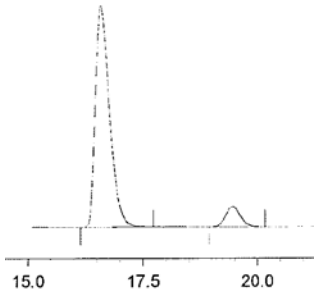
(R)-(1-phenylethyl)boronic acid pinacol ester

The enantiopurity of (*R*)-(1-phenylethyl)boronic acid pinacol ester was determined by oxidation with basic hydrogen peroxide to the corresponding alcohol and comparison to the commercially available racemic 1-phenylethanol.

Chiral HPLC (Chiracel OD-H, 0.5 mL/min, 5% isopropanol, 254 nm)



racemic



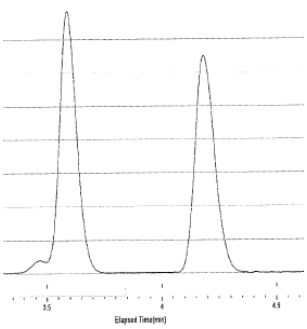
Amination substrate

Retention Time	Area	Area %
16.563	74777742	91.06
19.443	7342835	8.94

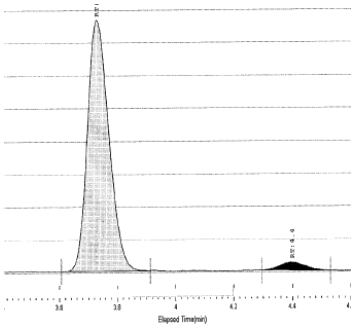
(S)-4,4,5,5-tetramethyl-2-(1-phenyloctan-2-yl)-1,3,2-dioxaborolane

The enantiopurity of (*S*)-4,4,5,5-tetramethyl-2-(1-phenyloctan-2-yl)-1,3,2-dioxaborolane was determined by oxidation with basic hydrogen peroxide to the corresponding alcohol and comparison to the oxidation product of racemic material.

Chiral SFC (Chiracel OD-H, 3% isopropanol, 5.0 mL/min, 100 bar, 35 °C, 254 nm



racemic

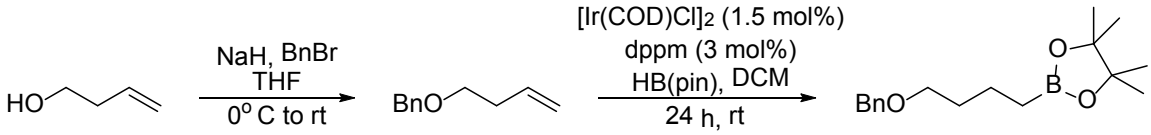


Amination substrate

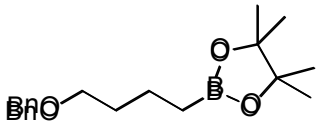
Peak No	% Area	Area	RT (min)
1	96.3362	1956.0671	3.73
2	3.6638	74.392	4.4

4.6.3.2 Preparation of New Boronic Acid Pinacol Esters

Preparation of 2-(4-(benzyloxy)butyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

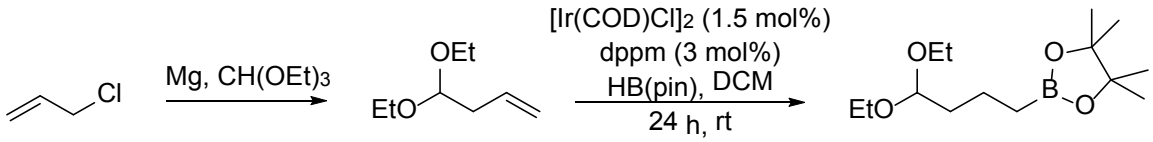


A flame-dried, round bottom flask was charged with $[Ir(COD)Cl]_2$ (77.1 mg, 0.115 mmol), diphenylphosphinomethane (88.3 mg, 0.230 mmol) and diluted with DCM (23 mL) in a dry box. Pinacolborane (1.18 g, 9.19 mmol) was added followed by ((but-3-en-1-yloxy)methyl)benzene[29] (1.24 g, 7.66 mmol). The flask was sealed and removed from the dry box. The reaction was stirred at room temperature for 24 h before being diluted with methanol (8 mL) and water (24 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 25 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (0.7% EtOAc in hexane, stain in $KMnO_4$) to provide the product as a clear, colorless liquid (0.986 g, 44%).



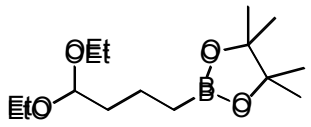
2-(4-(benzyloxy)butyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32-7.29 (4H, m), 7.27-7.23 (1H, m), 4.47 (2H, s), 3.45 (2H, t, *J* = 7.0 Hz), 1.64-1.57 (2H, m), 1.50-1.44 (2H, m), 1.22 (12H, s), 0.78 (2H, t, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.8, 128.3, 127.6, 127.4, 82.9, 72.8, 70.3, 32.6, 24.8, 20.6; IR (neat): 2933 (m), 2860 (m), 1370 (s), 1144 (s), 1101 (m), 735 (m), 697 (m) cm^{-1}; HRMS-(ESI+) for $C_{17}H_{28}BO_3$ [M+1]: calculated 291.2131, found: 291.2132.

Preparation of 2-(4,4-diethoxybutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.



[29] Cleary, P. A.; Woerpel, K. A. *Org. Lett.* **2005**, *7* (24), 5531.

A flame-dried, round bottom flask was charged with $[Ir(COD)Cl]_2$ (27.9 mg, 0.042 mmol), diphenylphosphinomethane (32.0 mg, 0.083 mmol) and diluted with DCM (8 mL) in a dry box. Pinacolborane (426.0 mg, 3.33 mmol) was added followed by 4,4-diethoxybut-1-ene[30] (400 mg, 2.78 mmol). The flask was sealed and removed from the dry box. The reaction was stirred at room temperature for 24 h before being diluted with methanol (3 mL) and water (9 mL). The layers were separated and the aqueous layer was extracted with diethyl ether (3 x 15 mL). The combined organics were dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (1% EtOAc in hexane, stain in $KMnO_4$) to provide the product as a clear, colorless liquid (413 mg, 55%).



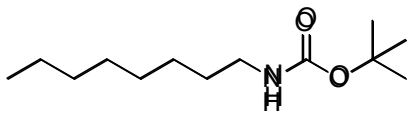
2-(4,4-diethoxybutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (500 MHz, $CDCl_3$): δ 4.46 (1H, t, *J* = 6.0 Hz), 3.61 (2H, dq, *J* = 16.5 Hz, 7.0 Hz), 3.46 (2H, dq, *J* = 16.5 Hz, 7.0 Hz), 1.62-1.58 (2H, m), 1.48-1.42 (2H, m), 1.22 (12H, s), 1.17 (6H, t, *J* = 7.0 Hz), 0.77 (2H, t, *J* = 8.0 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 102.8, 82.9, 60.7, 36.1, 24.8, 19.3, 15.3; IR (neat): 2976 (m), 2877 (w), 1372 (s), 1318 (m), 1145 (s), 1061 (m), 847 (w) cm^{-1}; HRMS-(ESI+) for $C_{14}H_{33}BNO_4$ $[M+NH_4]^+$: calculated 290.2502, found: 290.2497.

[30] Cloux, R.; Schlosser, M. *Helv. Chim. Acta* **1984**, *67*, 1470.

4.6.4 Representative Procedure for Amination of Aliphatic Boronic Acid Pinacol Esters.

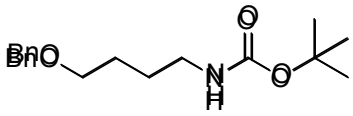
A flame-dried, round bottom flask equipped with a magnetic stir bar and septum was purged with N_2. After 5 min, O-methylhydroxylamine solution (0.48 mL, 1.25 mmol, 2.62 M in THF) was added and diluted with THF (4 mL). The reaction flask was cooled to -78° C in a dry ice/acetone bath. A solution of *n*-butyl lithium in hexanes (0.58 mL, 1.25 mmol, 2.14 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 octylboronic acid pinacol ester (100 mg, 0.416 mmol) and diluted with THF (1 mL) under N_2. The solution of boronic acid pinacol ester was then added dropwise to the solution of deprotonated O-methylhydroxylamine dropwise via syringe. The reaction flask was warmed to room temperature and then heated to 60° C. After stirring at 60° C for 12 h, the reaction flask was cooled to room temperature and Boc anhydride (0.31 mL, 1.33 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 *in vacuo* to give the crude reaction mixture.

4.6.5 Characterization of Aliphatic Substrate Products (Table 4.3)



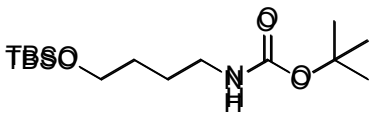
***tert*-Butyl octylcarbamate.** The amination was performed according to the general procedure with octylboronic acid pinacol ester (1.00 g, 4.16 mmol), O-methylhydroxyl amine (4.43 mL, 12.5 mmol, 2.82 M in THF), and *n*-butyl lithium (4.99 mL, 12.5 mmol, 2.5 M in

hexanes) in THF(51 mL, 0.08 M) with Boc anhydride (3.06 mL, 13.3 mmol) added after stirring at 60° C for 12 h. The crude reaction mixture was purified on silica gel (3-5% EtOAc/hexanes, stain with ninhydrin) to afford the product as a colorless oil (754 mg, 79% yield). Spectral data are in accordance with the literature.[31]

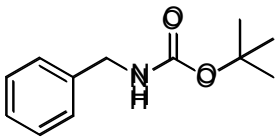


***tert*-Butyl (4-(benzyloxy)butyl)carbamate.** The amination was performed according to the general procedure with 2-(4-(benzyloxy)butyl)boronic acid pinacol ester (150 mg, 0.517 mmol), O-methylhydroxyl amine (0.59 mL, 1.55 mmol, 2.63 M in THF), and *n*-butyl lithium (0.62 mL, 1.55 mmol, 2.5 M in hexanes) in THF (6.4 mL, 0.08 M) with Boc anhydride (0.38 mL, 1.65 mmol) added after stirring at 60° C for 12 h. The crude reaction mixture was purified on silica gel (10% EtOAc/hexanes, stain with ninhydrin) to afford the product as a colorless oil (111 mg, 77% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34-7.29 (4H, m), 7.27-7.25 (1H, m), 4.62 (1H, br s), 4.47 (2H, s), 3.46 (2H, t, *J* = 6.5 Hz), 3.12 (2H, br d, *J* = 5.5 Hz), 1.65-1.60 (2H, m), 1.58-1.52 (2H, m), 1.42 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.9, 138.4, 128.3, 127.6, 127.5, 78.9, 72.9, 69.9, 40.3, 29.6, 28.4, 27.0; IR (neat): 3343 (br, w), 2928 (w), 2857 (w), 1692 (s), 1364 (m), 1167 (s), 1101 (m), 735 (m), 697 (m) cm^{-1}; HRMS-(ESI+) for $C_{16}H_{26}NO_3$ [M+H]: calculated: 280.1913, found: 280.1900.

[31] Hicks, J. D.; Hyde, A. M.; Cuezva, A. M.; Buchwald, S. C. *J. Am. Chem. Soc.* **2009**, *131*, 16720.



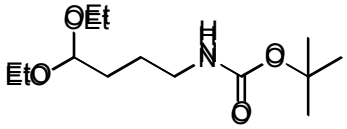
***tert*-Butyl (4-((tert-butyldimethylsilyl)oxy)butyl)carbamate.** The amination was performed according to the general procedure with *tert*-butyldimethyl(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)silane (150 mg, 0.477 mmol), O-methylhydroxyl amine (0.54 mL, 1.43 mmol, 2.63 M in THF), and *n*-butyl lithium (0.58 mL, 1.43 mmol, 2.45 M in hexanes) in THF (5.8 mL, 0.08 M) with Boc anhydride (0.35 mL, 1.53 mmol) added after stirring at 60° C for 12 h. The crude reaction mixture was purified on silica gel (3-10% EtOAc/hexanes, stain with ninhydrin) to afford the product as a colorless oil (106 mg, 73% yield). Spectral data are in accordance with the literature.[32]



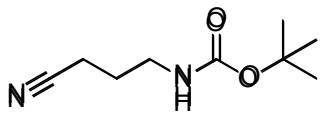
***tert*-Butyl benzylcarbamate.** The amination was performed according to the general procedure with benzylboronic acid pinacol ester (150 mg, 0.688 mmol), O-methylhydroxyl amine (0.73 mL, 2.06 mmol, 2.82 M in THF), and *n*-butyl lithium (0.83 mL, 2.06 mmol, 2.5 M in hexanes) in THF (8.6 mL, 0.08 M) with Boc anhydride (0.51 mL, 2.20 mmol) added after stirring at 60° C for 12 h. The crude reaction mixture was purified on silica gel (3-10% EtOAc/hexanes, stain with ninhydrin) to afford the desired product as a clear, colorless oil (89.7 mg, 67% yield) and the bis(boc)-protected benzylamine (31.5 mg, 15% yield). Spectral data of *tert*-butyl benzylcarbamate are in accordance with the literature.[33] Characterization of bis(boc)-protected benzylamine: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30-7.25 (4H, m), 7.23-7.19 (1H, m), 4.76 (2H, s), 1.43 (16H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.5, 138.5,

[32] McLaughlin, N. P.; Evans, P. *J. Org. Chem*. **2010**, *75*, 518.
[33] Chankeshwara, S. V.; Chakraborti, A. K. *Org. Lett.* **2006**, *8*, 3259.

128.2, 127.2, 127.0, 82.4, 49.5, 28.0; IR (neat): 2979 (w), 1698 (m), 1350 (m), 1223 (m), 1139 (s), 854 (m), 697 (m) cm^{-1}; HRMS-(ESI+) for $C_{17}H_{26}NO_4$ [M+H]: calculated: 308.1862, found: 308.1861.



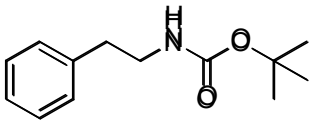
***tert*-Butyl (4,4-diethoxybutyl)carbamate**. The amination was performed according to the general procedure with 2-(4,4-diethoxybutyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (150 mg, 0.551 mmol), O-methylhydroxyl amine (0.63 mL, 1.65 mmol, 2.63 M in THF), and *n*-butyl lithium (0.68 mL, 1.65 mmol, 2.45 M in hexanes) in tetrahydrofuran (6.8 mL, 0.08 M) with Boc anhydride (0.41 mL, 1.76 mmol) added after stirring at 60° C for 12 h. The crude reaction mixture was purified on silica gel (10% EtOAc/hexanes, stain with ninhydrin) to afford the product as a colorless oil (96.3 mg, 67% yield). Spectral data are in accordance with the literature.[34]



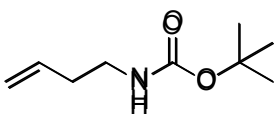
***tert*-Butyl (3-cyanopropyl)carbamate.** The amination was performed according to the general procedure with 3-cyano-1-propylboronic acid pinacol ester (150 mg, 0.769 mmol), O-methylhydroxyl amine (0.88 mL, 2.31 mmol, 2.63 M in THF), and *n*-butyl lithium (0.92 mL, 2.31 mmol, 2.5 M in hexanes) in THF (9.6 mL, 0.08 M) with Boc anhydride (0.57 mL, 2.46 mmol) added after stirring at 60° C for 12 h. The crude reaction mixture was purified on silica gel (10% EtOAc/hexanes, stain with ninhydrin) to afford the product as a clear, colorless oil (51.2 mg, 36% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.68 (2H, t, *J* = 7.0 Hz), 2.35 (2H, t, *J* =

[34] Nielsen, L.; Lindsay, K. B.; Faber, J.; Nielsen, N. C.; Skrydstrup, T. *J. Org. Chem.* **2007**, *72*, 10035.

7.5 Hz), 1.93 (2H, tt, *J* = 7.0 Hz, 7.0 Hz), 1.50 (9H, s); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.4, 119.2, 82.9, 44.9, 28.1, 25.1, 14.8; IR(neat): 2979 (w), 2927 (w), 1737 (m), 1696 (m), 1367 (m), 1142 (s), 1115 (s), 856 (w); HRMS-(ESI+) for $C_9H_{17}N_2O_2$ [M+H]: calculated: 185.1290, found: 185.1296.



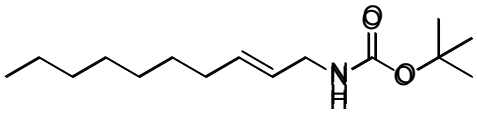
***tert*-Butyl phenethylcarbamate**. The amination was performed according to the general procedure with 2-phenylethylboronic acid pinacol ester (150 mg, 0.646 mmol), O-methylhydroxyl amine (0.74 mL, 1.94 mmol, 2.62 M in THF), and *n*-butyl lithium (0.84 mL, 1.94 mmol, 2.3 M in hexanes) in THF (8 mL, 0.08 M) with Boc anhydride (0.46 mL, 2.07 mmol) added after stirring at 60° C for 12 h. The crude reaction mixture was purified on silica gel (5% EtOAC/hexanes, stain with ninhydrin) to afford the product as a white solid (110.1 mg, 77% yield). Spectral data are in accordance with the literature.[35]



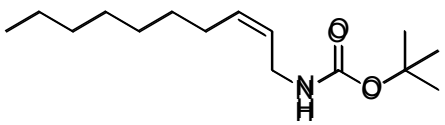
***tert*-Butyl but-3-en-1-ylcarbamate.** The amination was performed according to the general procedure with but-1-ene-4-boronic acid pinacol ester (150 mg, 0.824 mmol), O-methylhydroxyl amine (0.88 mL, 2.47 mmol, 2.82 M in THF), and *n*-butyl lithium (1.04 mL, 2.47 mmol, 2.37 M in hexanes) in THF (10.3 mL, 0.08 M) with Boc anhydride (0.61 mL, 2.64 mmol) added after stirring at 60° C for 12 h. The crude reaction mixture was purified on silica gel (5% EtOAc/hexanes, stain with ninhydrin) to afford the desired product as an inseperable

[35] Caddick, S.; Haynes, A. K. de K.; Judd, D. B.; Williams, M. R. V. *Tetrahedron Lett.* **2000**, *41*, 3513.

mixture with butylcarbamate (118.9 mg, 4.1:1 product:butylcarbamate, 68% yield). Spectral data are in accordance with the literature.[36]



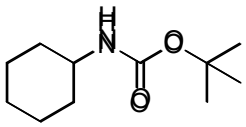
(*E*)-*tert*-Butyl dec-2-en-1-ylcarbamate. The amination was performed according to the general procedure with (*E*)-2-(dec-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (150 mg, 0.563 mmol), O-methylhydroxyl amine (0.64 mL, 1.69 mmol, 2.63 M in THF), and *n*-butyl lithium (0.67 mL, 1.69 mmol, 2.5 M in hexanes) in THF (7.0 mL, 0.08 M) with Boc anhydride (0.41 mL, 1.80 mmol) added after stirring at 60° C for 12 h. The crude reaction mixture was purified on silica gel (5% EtOAc/hexanes, stain with ninhydrin) to afford the desired product as a clear, colorless oil (117.8 mg, 82% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.56 (1H, dt, *J* = 15.0 Hz, 6.5 Hz), 5.40 (1H, dt, *J* = 15.0 Hz, 6.5 Hz), 4.49 (1H, s), 3.65 (2H, br s), 1.97 (2H, dt, *J* = 6.5 Hz, 6.5 Hz), 1.42 (9H, s), 1.33-1.30 (2H, m), 1.28-1.23 (8H, m), 0.85 (3H, t, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7, 133.2, 126.2, 79.1, 42.6, 32.1, 31.9, 29.5, 29.3, 29.1, 28.4, 22.6, 14.1; IR(neat): 3349 (br, m), 2924 (s), 2856 (m), 1693 (s), 1505 (m), 1390 (w), 1247 (m), 1169 (s), 1046 (m), 967 (m), 865 (w), 779 (w); HRMS-(ESI+) for $C_{15}H_{30}NO_2$ [M+H]: calculated: 256.2277, found: 256.2279.



(*Z*)-*tert*-Butyl dec-2-en-1-ylcarbamate. The amination was performed according to the general procedure with (*Z*)-2-(dec-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (150 mg,

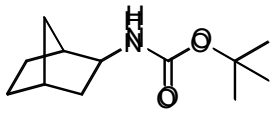
[36] Boyle, T. P.; Bremner, J. B.; Coates, J. A.; Keller, P. A.; Pyne, S. G. *Tetrahedron*, **2005**, *61*, 7271.

0.563 mmol), O-methylhydroxyl amine (0.65 mL, 1.69 mmol, 2.62 M in THF), and *n*-butyl lithium (0.74 mL, 1.69 mmol, 2.3 M in hexanes) in THF (7.0 mL, 0.08 M) with Boc anhydride (0.41 mL, 1.80 mmol) added after stirring at 60° C for 12 h. The crude reaction mixture was purified on silica gel (5% EtOAc/hexanes, stain with ninhydrin) to afford the desired product as a clear, colorless oil (115.7 mg, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.49 (1H, dt, *J* = 10.5 Hz, 7.0 Hz), 5.36 (1H, dt, *J* = 10.5 Hz, 6.5 Hz), 4.43 (1H, br s), 3.74 (2H, s), 2.03 (2H, dt, *J* = 7.0 Hz, 7.0 Hz), 1.42 (9H, s), 1.33-1.29 (2H, m), 1.27-1.21 (8H, m), 0.86 (3H, t, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.8, 133.3, 125.7, 79.2, 37.6, 31.8, 29.5, 29.2, 29.1, 28.4, 27.3, 22.6, 14.1; IR(neat): 3343 (br, w), 2925 (m), 2855 (m), 1691 (s), 1507 (m), 1248 (m), 1168 (s), 724 (w) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{30}NO_2$ [M+H]: calculated: 256.2277, found: 256.2276.

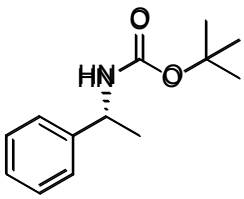


***tert*-Butyl cyclohexylcarbamate**. The amination was performed according to the general procedure with cyclohexylboronic acid pinacol ester (150 mg, 0.714 mmol), O-methylhydroxyl amine (0.81 mL, 2.14 mmol, 2.63 M in THF), and *n*-butyl lithium (0.86 mL, 2.14 mmol, 2.5 M in hexanes) in THF (8.8 mL, 0.08 M) with Boc anhydride (0.53 mL, 2.28 mmol) added after stirring at 60° C for 12 h. The crude reaction mixture was purified on silica gel (3-5% EtOAc/hexanes, stain with ninhydrin) to afford the product as a colorless oil (96.5 mg, 68% yield). Spectral data are in accordance with the literature.[37]

[37] Sarkar, A.; Roy, S. R.; Parikh, N.; Chakraborti, A. K. *J. Org. Chem.* **2011**, *76*, 7132.



***Exo-tert*-Butyl-2-norbornylcarbamate.** The amination was performed according to the general procedure with (*exo*)-2-norbornylboronic acid pinacol ester (150 mg, 0.675 mmol), O-methylhydroxyl amine (0.77 mL, 2.03 mmol, 2.63 M in THF), and *n*-butyl lithium (0.83 mL, 2.03 mmol, 2.43 M in hexanes) in THF (8.4 mL, 0.08 M) with Boc anhydride (0.50 mL, 2.16 mmol) added after stirring at 60° C for 12 h. The crude reaction mixture was purified on silica gel (5% EtOAc/hexanes, stain with ninhydrin) to afford the product as a white solid (71.2 mg, 50% yield). Spectral data are in accordance with the literature.[38]



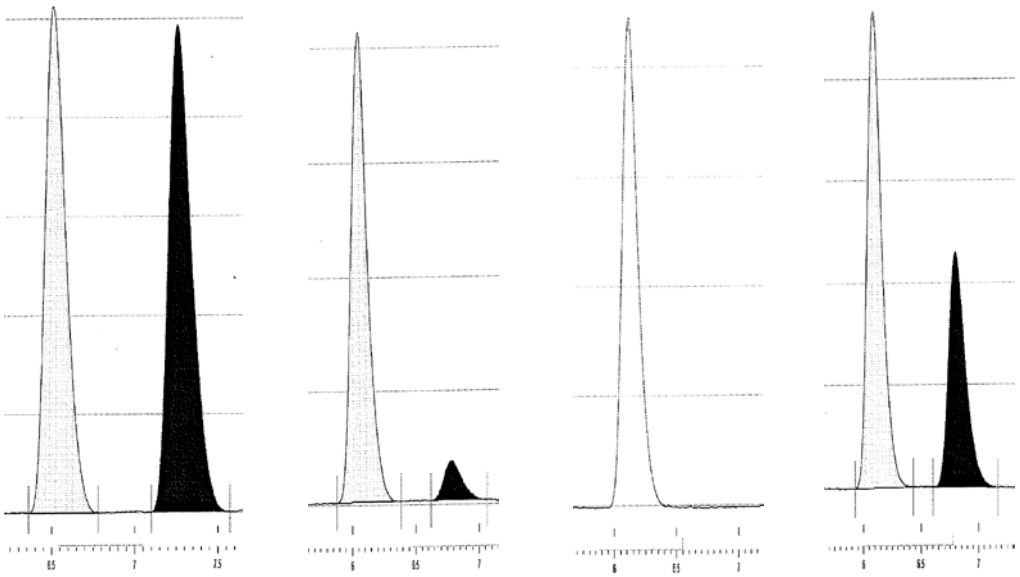
(*R*)-*tert*-Butyl-(1-phenylethyl)carbamate. The amination was performed according to the general procedure with (*R*)-(1-phenylethyl)boronic acid pinacol ester (150 mg, 0.646 mmol), O-methylhydroxyl amine (0.74 mL, 1.94 mmol, 2.63 M in THF), and *n*-butyl lithium (0.80 mL, 1.94 mmol, 2.45 M in hexanes) in THF (8.1 mL, 0.08 M) with Boc anhydride (0.48 mL, 2.01 mmol) added after stirring at 60° C for 12 h. The crude reaction mixture was purified on silica gel (3-5% EtOAc/hexanes, stain with ninhydrin) to afford the product as a white solid (120.2 mg, 84% yield). Spectral data are in accordance with the literature.[37] $[\alpha]_D^{20}$ = 45.139 (*c* = 0.701, $CHCl_3$, *l* = 50 nm).

[38] Zhou, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 12220.

Proof of Stereochemistry:

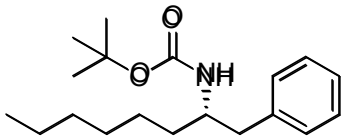
The resulting Boc-protected amine was compared to the racemic carbamate prepared from Boc-protection of commercially available α-methylbenzylamine. The authentic sample was prepared from Boc-protection of commercially available (*R*)-α-methylbenzylamine.

Chiral SFC (Chiracel OD-H, 2% isopropanol, 3.0 mL/min, 100 bar, 35 °C, 254 nm) – anaylsis of the tert-butyl-(1-phenylethyl)carbamate.



racemic | Amination product | authentic | Coinjection of amination product + racemic

Peak No	% Area	Area	RT (min)
1	91.5719	1834.7564	6.04
2	8.4281	168.868	6.78

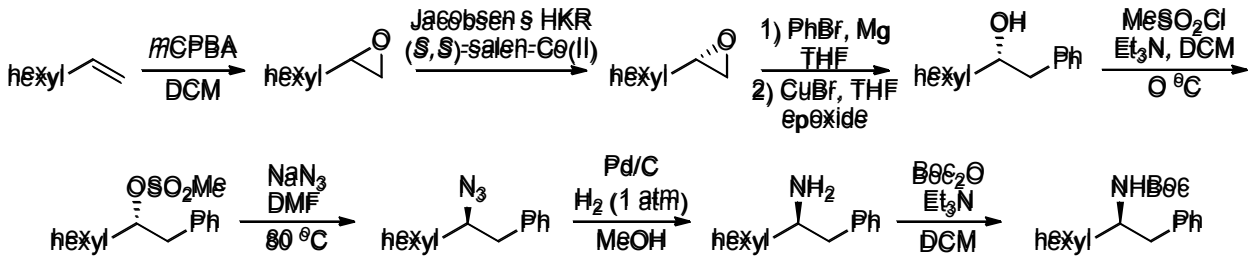


(*S*)-tert-butyl (1-phenyloctan-2-yl)carbamate. The amination was performed according to the general procedure with (*S*)-4,4,5,5-tetramethyl-2-(1-phenyloctan-2-yl)-1,3,2-dioxaborolane (100 mg, 0.32 mmol), O-methylhydroxyl amine (0.46 mL, 0.95 mmol, 2.06 M in THF), and n-butyl lithium (0.45 mL, 0.95 mmol, 2.1 M in hexanes) in THF (4.0 mL, 0.08 M) with Boc anhydride (0.23 mL, 1.01 mmol) added after stirring at 60° C for 12 h. The crude reaction mixture was purified on silica gel (3-5% EtOAc/hexanes, stain with ninhydrin) to afford the product as a white solid (72.5 mg, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.33-7.29 (2H, m), 7.25-7.19 (3H, m), 4.32 (1H, br s), 3.83 (1H, br s), 2.79 (2H, br s), 1.50- 1.47 (2H, m), 1.44 (9H, s), 1.31-1.27 (8H, m), 0.89 (3H, t, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.5, 138.4, 129.5, 128.2, 126.2, 78.9, 51.6, 41.4, 34.2, 31.7, 29.1, 28.4, 25.9, 22.5, 14.0; IR(neat): 3369 (w), 2927 (m), 2855 (m), 1686 (s), 1522 (m), 1365 (m), 1171 (s), 1045 (w), 699 (m); HRMS-(ESI+) for $C_{19}H_{32}NO_2$ [M+H]: calculated: 306.2433, found: 306.2432. $[\alpha]_D^{20}$ = -12.744 (c = 1.475, $CHCl_3$, l = 50 nm).

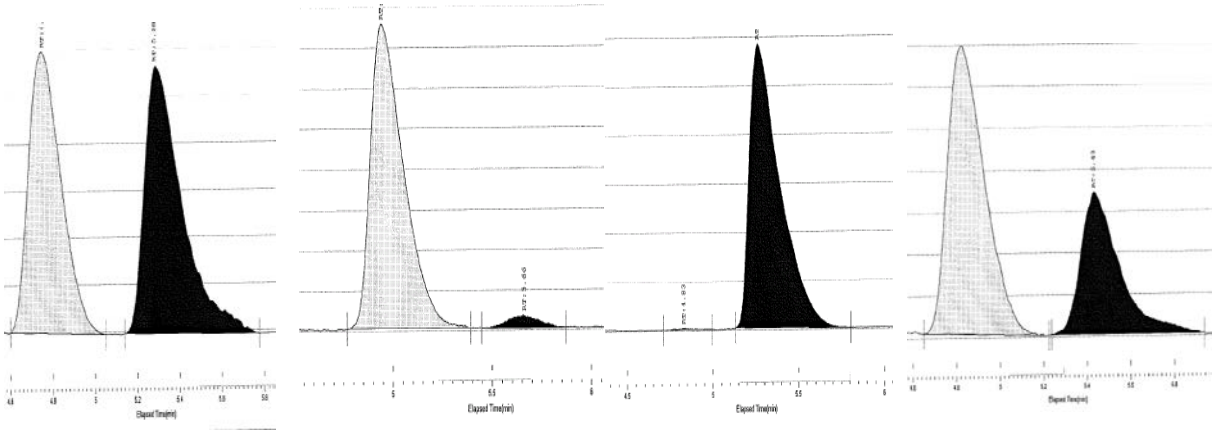
Proof of Stereochemistry:

The resulting Boc-protected amine was compared to the racemic carbamate. The authentic sample was prepared using Jacobsen's hydrolytic kinetic resolution[39], stereoretentive ring-opening of the epoxide, followed by inversion of the stereocenter as shown below.

[39] 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.



Chiral SFC (Chiracel OD-H, 1% isopropanol:hexane (1:1, v:v), 7.0 mL/min, 100 bar, 35 °C, 254 nm) – anaylsis of the tert-butyl (1-phenyloctan-2-yl)carbamate.



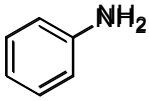
racemic | Amination product | authentic | Coinjection of amination product + racemic

Peak No	% Area	Area	RT (min)
1	96.3992	1742.2868	4.94
2	3.6008	65.0806	5.66

4.6.6 Representative Procedure for Amination of Aryl Boronic Acid Pinacol Esters.

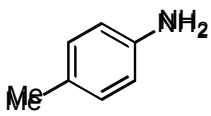
A flame-dried, round bottom flask equipped with a magnetic stir bar and septum was purged with N_2. After 5 min, O-methylhydroxylamine solution (0.48 mL, 1.25 mmol, 2.62 M in THF) was added and diluted with THF (4 mL). The reaction flask was cooled to -78° C in a dry ice/acetone bath. A solution of *n*-butyl lithium in hexanes (0.58 mL, 1.25 mmol, 2.14 M) was added dropwise and the reaction was stirred at -78° C for 30 min. A separate flame-dried conical flask was charged with phenylboronic acid pinacol ester (150 mg, 0.416 mmol) and diluted with THF (1 mL) under N_2. The solution of boronic acid pinacol ester was then added dropwise to the solution of deprotonated O-methylhydroxylamine dropwise via syringe. 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 diluted with 15 mL of H_2O. The layers were separated and the aqueous layer was neutralized with 3 M HCl. The aqueous layer was then extracted with EtOAc (3 x 20 mL), the combined organics were dried over Na_2SO_4, filtered, and concentrated *in vacuo* to afford the crude reaction mixture.

4.6.7 Characterization of Aryl Substrate Products (Table 4.4Table 4.3)

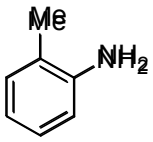


Aniline. The amination was performed according to the general procedure with phenylboronic acid pinacol ester (150 mg, 0.735 mmol), O-methylhydroxyl amine (0.84 mL, 2.21 mmol, 2.63 M in THF), and *n*-butyl lithium (0.88 mL, 2.21 mmol, 2.5 M in hexanes) in THF (9.2 mL, 0.08 M). The crude reaction mixture was purified on silica gel (25% EtOAc/hexanes, stain with ninhydrin) to afford

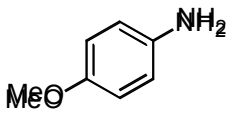
the product as a clear, colorless oil (63.6 mg, 83% yield). Spectral data are in accordance with the literature.[40]



***p*-Toluidine.** The amination was performed according to the general procedure with 4-methylphenylboronic acid pinacol ester (150 mg, 0.688 mmol), O-methylhydroxyl amine (0.73 mL, 2.06 mmol, 2.82 M in THF), and *n*-butyl lithium (0.83 mL, 2.06 mmol, 2.5 M in hexanes) in THF (8.5 mL, 0.08 M). The crude reaction mixture was purified on silica gel (10% EtOAc/hexanes, stain with ninhydrin) to afford the product as a clear, colorless oil (62.1 mg, 84% yield). Spectral data are in accordance with the literature.[40]



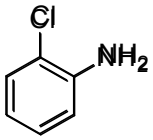
***o*-Toluidine.** The amination was performed according to the general procedure with 2-methylphenylboronic acid pinacol ester (150 mg, 0.688 mmol), O-methylhydroxyl amine (0.73 mL, 2.06 mmol, 2.82 M in THF), and *n*-butyl lithium (0.91 mL, 2.06 mmol, 2.27 M in hexanes) in THF (8.5 mL, 0.08 M). The crude reaction mixture was purified on silica gel (10% EtOAc/hexanes, stain with ninhydrin) to afford the product as a clear, colorless oil (54.7 mg, 74% yield). Spectral data are in accordance with the literature.[40]



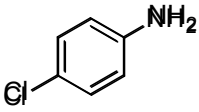
***p*-Methoxyaniline.** The amination was performed according to the general procedure with 4-methoxyphenylboronic acid pinacol ester (150 mg, 0.641 mmol), O-methylhydroxyl amine (0.68 mL, 1.92 mmol, 2.82 M in THF),

[40] Xu, H. J.; Liang, Y. F.; Cai, Z. Y.; Qi, H. X.; Yang, C. Y.; Feng, Y. S. *J. Org. Chem*. **2011**, *76*, 2296.

and *n*-butyl lithium (0.77 mL, 1.92 mmol, 2.5 M in hexanes) in THF (8.0 mL, 0.08 M). The crude reaction mixture was purified on silica gel (25% EtOAc/hexanes, stain with ninhydrin) to afford the product as a clear, colorless oil (68.8 mg, 87% yield). Spectral data are in accordance with the literature.[41]

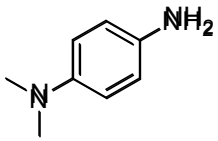


2-Chloroaniline. The amination was performed according to the general procedure with 4-chlorophenylboronic acid pinacol ester (100 mg, 0.419 mmol), O-methylhydroxyl amine (0.44 mL, 1.26 mmol, 2.82 M in THF), and *n*-butyl lithium (0.55 mL, 1.26 mmol, 2.27 M in hexanes) in THF (5.2 mL, 0.08 M). The crude reaction mixture was purified on silica gel (15% EtOAc/hexanes, stain with ninhydrin) to afford the product as a gray solid (15.6 mg, 29% yield). Spectral data are in accordance with the literature.[41]

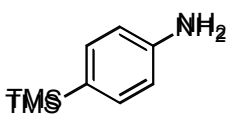


4-Chloroaniline. The amination was performed according to the general procedure with 4-chlorophenylboronic acid pinacol ester (150 mg, 0.629 mmol), O-methylhydroxyl amine (0.67 mL, 1.89 mmol, 2.82 M in THF), and *n*-butyl lithium (0.75 mL, 1.89 mmol, 2.5 M in hexanes) in THF (7.8 mL, 0.08 M). The crude reaction mixture was purified on silica gel (15% EtOAc/hexanes, stain with ninhydrin) to afford the product as a gray solid (38.7 mg, 48% yield). Spectral data are in accordance with the literature.[41]

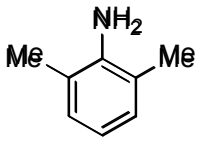
[41] Takasaki, M.; Motoyama, Y.; Higashi, K.; Yoon, S. H.; Mochida, I.; Nagashima, H. *Org. Lett.* **2008**, *10*, 1601.



***N,N*-Dimethyl-*p*-phenylenediamine.** The amination was performed according to the general procedure with 4-(N,N-dimethylamino)phenylboronic acid pinacol ester (150 mg, 0.607 mmol), O-methylhydroxyl amine (0.69 mL, 1.82 mmol, 2.63 M in THF), and *n*-butyl lithium (0.73 mL, 1.82 mmol, 2.5 M in hexanes) in THF (7.6 mL, 0.08 M). The crude reaction mixture was purified on silica gel (50-100% EtOAc/hexanes, stain with ninhydrin) to afford the product as a gray solid (73.7 mg, 89% yield). Spectral data are in accordance with the literature.[42]



4-(Trimethylsilyl)aniline. The amination was performed according to the general procedure with 4-(trimethylsilyl)phenylboronic acid pinacol ester (150 mg, 0.543 mmol), O-methylhydroxyl amine (0.62 mL, 1.63 mmol, 2.63 M in THF), and *n*-butyl lithium (0.65 mL, 1.63 mmol, 2.5 M in hexanes) in THF (6.8 mL, 0.08 M). The crude reaction mixture was purified on silica gel (10% EtOAc/hexanes, stain with ninhydrin) to afford the product as a clear, colorless oil (72.0 mg, 80% yield). Spectral data are in accordance with the literature.[43]



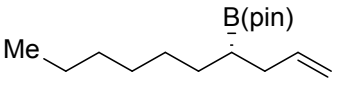
2,6-Dimethylaniline. The amination was performed according to the general procedure with 2,6-dimethylphenylboronic acid pinacol ester (150 mg, 0.646 mmol), O-methylhydroxyl amine (0.69 mL, 1.94 mmol, 2.82 M in THF), and *n*-butyl lithium (0.79 mL, 1.94 mmol, 2.45 M in hexanes) in THF (8.1 mL, 0.08 M). The crude reaction mixture was purified on silica gel (5 to 10% EtOAc/hexanes, stain

[42] Lee, S.; Jorgensen, M.; Hartwig, J. F. *Org. Lett.* **2001**, *3*, 2729.
[43] Lothian, A. P.; Ramsden, C. A.; Shaw, M. M.; Smith, R. G. *Tetrahedron* **2011**, *67*, 2788.

with ninhydrin) to afford the product as a yellow oil (55.6 mg, 71% yield). Spectral data are in accordance with the literature.[44]

4.6.8 Application of Direct Amination

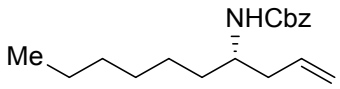
4.6.8.1 Vinylogous Imine Allylation



(*S*)-2-(dec-1-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-*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 1-octene (56.1 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 *tert*-butoxide (336.6 mg, 3.000 mmol), $Pd(OAc)_2$/RuPhos (added as a 1:1 solution in THF (0.018 M); 0.70 mL for 2.5 mol%), tetrahydrofuran (3.35 mL, [substrate] = 0.1 M; 10:1 THF:H_2O).. The vial was sealed, removed from the dry box, and 1,2-dichloroethane (0.12 mL, 1.50 mmol) and H_2O (sparged with N_2 for 30 min, 0.45 mL) were 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 (30 mL) and water (20 mL). The 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 condensed. The crude reaction mixture was purified on

[44] Vo, G. D.; Hartwig, J. F. *J. Am. Chem. Soc.* **2009**, *131*, 11049.

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, dddd, *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, dddd, *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).



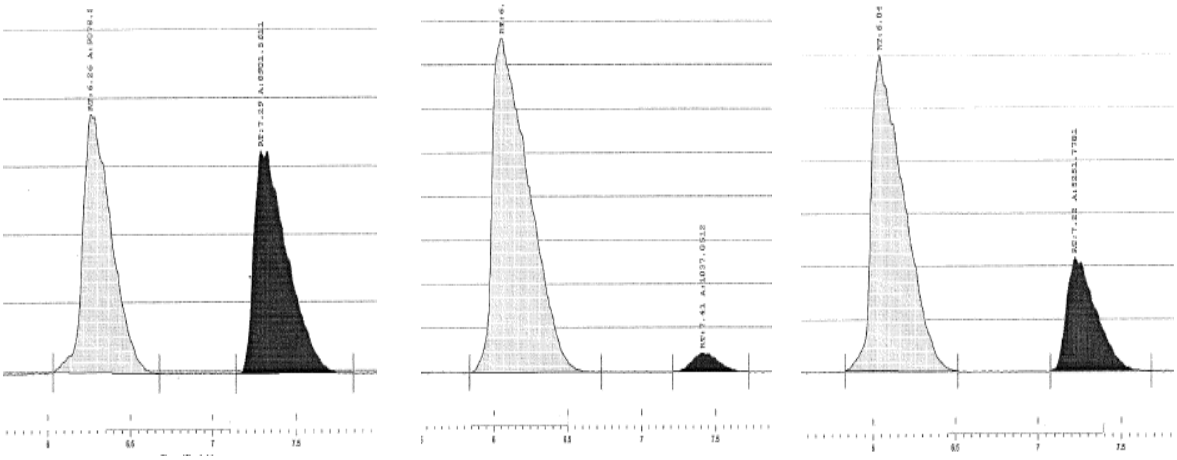
Benzyl (*S*)-dec-1-en-4-ylcarbamate. The title compound was prepared from (*S*)-2-(dec-1-en-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (115 mg, 0.432 mmol) according to representative procedure without modification. After stirring at 60° C for 12 h, the reaction flask was cooled to room temperature 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, dddd, *J* = 16.5 Hz, 9.0 Hz, 7.0 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, ddd, *J* = 13.0 Hz, 6.5 Hz, 6.5 Hz), 2.17 (1H, ddd, *J* = 13.5 Hz, 6.5 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; $[\alpha]_D^{20}$ = -19.967 (c = 1.392, $CHCl_3$, l = 50 nm).

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 oC, 4 mL/min, 3% Isopropanol, 100 bar, 210-270nm) – analysis of Benzyl (S)-dec-1-en-4-ylcarbamate.



racemic

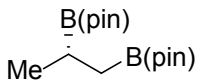
Diboration/cross -coupling product

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	

4.6.8.2 Preparation of tert-butyl (S)-(1-phenylpropan-2-yl)carbamate.

(*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 roughly 1 mL (*d*=0.614 g/ml at -47.8 ºC, roughly 14.5 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).

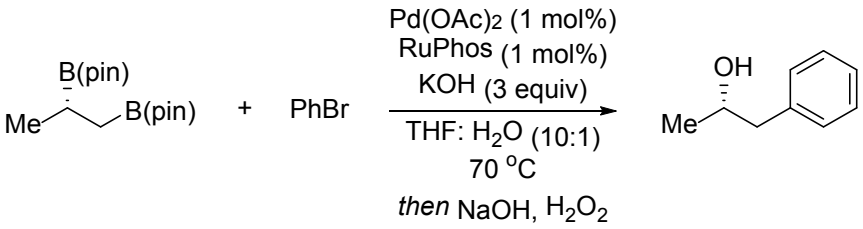


(*S*)-2,2'-(propane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.20 (24H, s), 1.25-1.13 (1H, m), 0.97 (3H, d, *J* = 7.0 Hz), 0.88 (1H, dd, *J* = 15.5 Hz, 8.5 Hz), 0.76 (1H, dd, *J* = 15.5 Hz, 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): δ 82.8, 82.7, 24.82, 24.77, 24.72, 24.67, 24.55, 18.3; IR(neat): 2977 (m), 2871 (w), 1461 (w), 1370 (s), 1311 (s), 1217 (m),

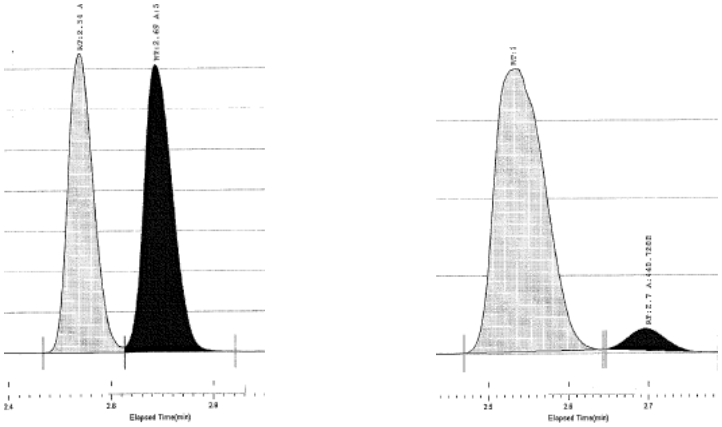
1193 (s), 968 (m) cm^{-1}; HRMS-(ESI+) for $C_{15}H_{30}B_2O_4$ [M+H]: calculated: 297.2408, found: 297.2415; $[\alpha]_D^{20}$ = +2.239 (*c* = 1.250, $CHCl_3$, *l* = 50 nm).

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.



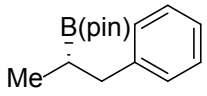
racemic

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 (4.28 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 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

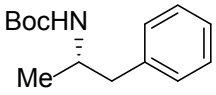
(3 x 20 mL). The combined organics were dried over Na_2SO_4, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (2-5% EtOAc/hexanes, stain with PMA) to afford the product as a viscous oil (102.3 mg, 83% yield).



(*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, 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, ddq, *J* = 14.0 Hz, 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 representative procedure 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, 2.63 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, 2.67 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).

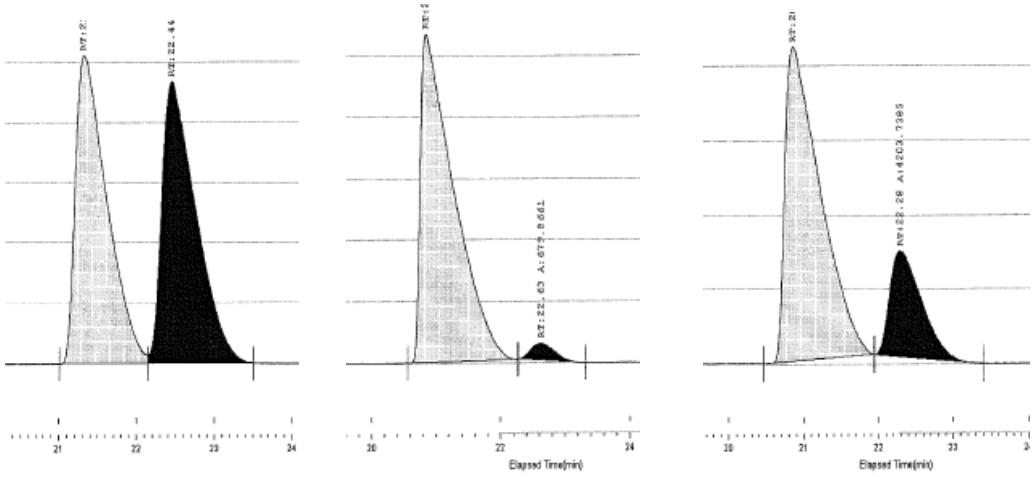


***tert*-butyl (*S*)-(1-phenylpropan-2-yl)carbamate.** ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.28-2.35 (2H, m), 7.21-7.15 (3H, m), 4.37 (1H, br s), 3.90 (1H, br s), 2.82 (1H, dd, *J* = 13.0 Hz, 5.0 Hz), 2.64 (1H, dd, *J* = 13.0 Hz, 7.0 Hz), 1.41 (9H, s), 1.06 (3H, d, *J* = 6.5 Hz); ^{13}C NMR (125 MHz, $CDCl_3$): 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 ^{o}C, 1.5 mL/min, 1% Isopropanol:Hexanes (1:1), 100 bar, 210-270nm) – analysis of tert-butyl (1-phenylpropan-2-yl)carbamate.



racemic

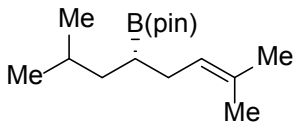
amination product

Coinjection of product + racemic

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

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

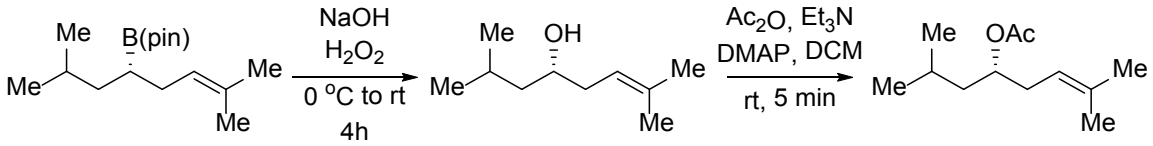
(*S*)-2-(2,7-dimethyloct-6-en-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To an oven-dried 16-mL vial with magnetic stir bar in the dry box was added $Pt(dba)_3$ (4.5 mg, 5.0 µmol), (*R,R*)-3,5-di-isopropylphenyl-TADDOLPPh (5.5 mg, 6.0 µmol), $B_2(pin)_2$ (133.3 mg, 525 µmol) and tetrahydrofuran (0.5 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, 1.5 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).



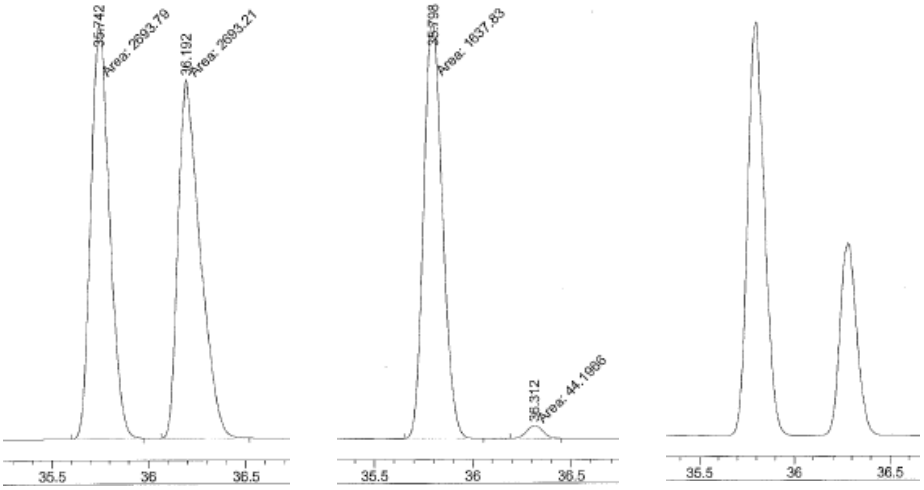
(*S*)-2-(2,7-dimethyloct-6-en-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. ^{1}H NMR (500 MHz, $CDCl_3$): δ 5.09 (1H, ddd, *J* = 7.5 Hz, 7.0 Hz, 1.0 Hz), 2.07-1.97 (2H, m), 1.64 (3H, d, *J* = 1.0 Hz), 1.58 (3H, s), 1.53 (1H, dddd, *J* = 13.5 Hz, 13.5 Hz, 6.5 Hz. 6.5 Hz), 1.33 (1H, ddd, *J* = 13.5 Hz, 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.

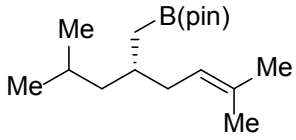


Chiral GLC (β-dex, Supelco, 50 ºC for 5 min, 2 ºC/min ramp to 180 ºC, 20 psi) – analysis of 2,7-dimethyloct-6-en-4-yl acetate.



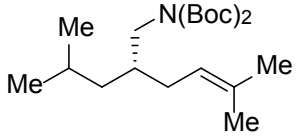
racemic | Diboration/cross -coupling product | Coinjection of product + racemic

Peak #	RetTime [min]	Type	Width [min]	Area [pA*s]	Height [pA]	Area %
1	35.798	MM	0.1125	1637.83179	242.60904	97.37242
2	36.312	MM	0.0974	44.19661	7.56519	2.62758

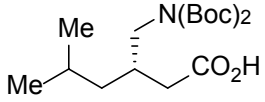


(*S*)-2-(2-isobutyl-5-methylhex-4-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. A flame-dried round bottom flask equipped with magnetic stir bar was charged with (*S*)-2-(2,7-dimethyloct-6-en-4-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (130 mg, 0.488 mmol). The flask was sealed with a septum and 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.



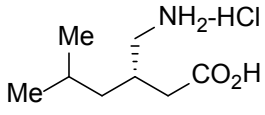
***bis*-Boc-(*S*)-2-isobutyl-5-methylhex-4-en-1-amine.** The title compound was prepared according to literature procedure[19**Error! Bookmark not defined.**] without modification. After stirring at 60 ºC for 18 h, di-*tert*-butyl dicarbonate (0.68 mL, 2.97 mmol, 6.1 equiv) was added. The reaction stirred 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[45] without modification from *bis*-Boc-(*S*)-2-isobutyl-5-methylhex-4-en-1-amine (assumed

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

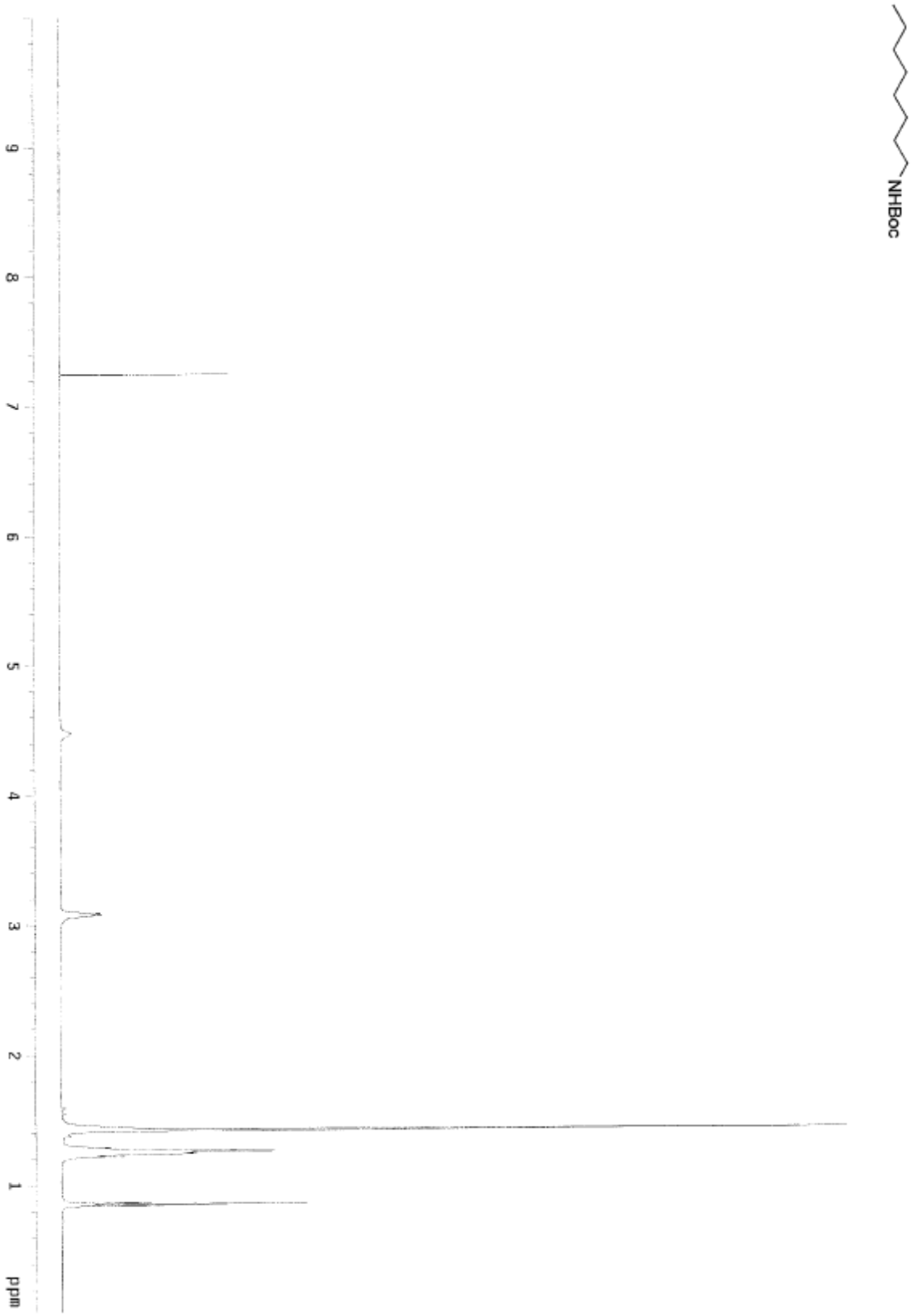
0.488 mmol). The crude reaction mixture was purified on silica gel (15% ethyl acetate in hexanes with 0.25% AcOH, stain with ninhydrin) to afford the title compound with >95% purity as a colorless oil (79.6 mg, 45% yield) . ^{1}H NMR (500 MHz, $CDCl_3$): δ 3.54 (1H, dd, *J* = 14.0 Hz, 5.0 Hz), 3.48 (1H, 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.

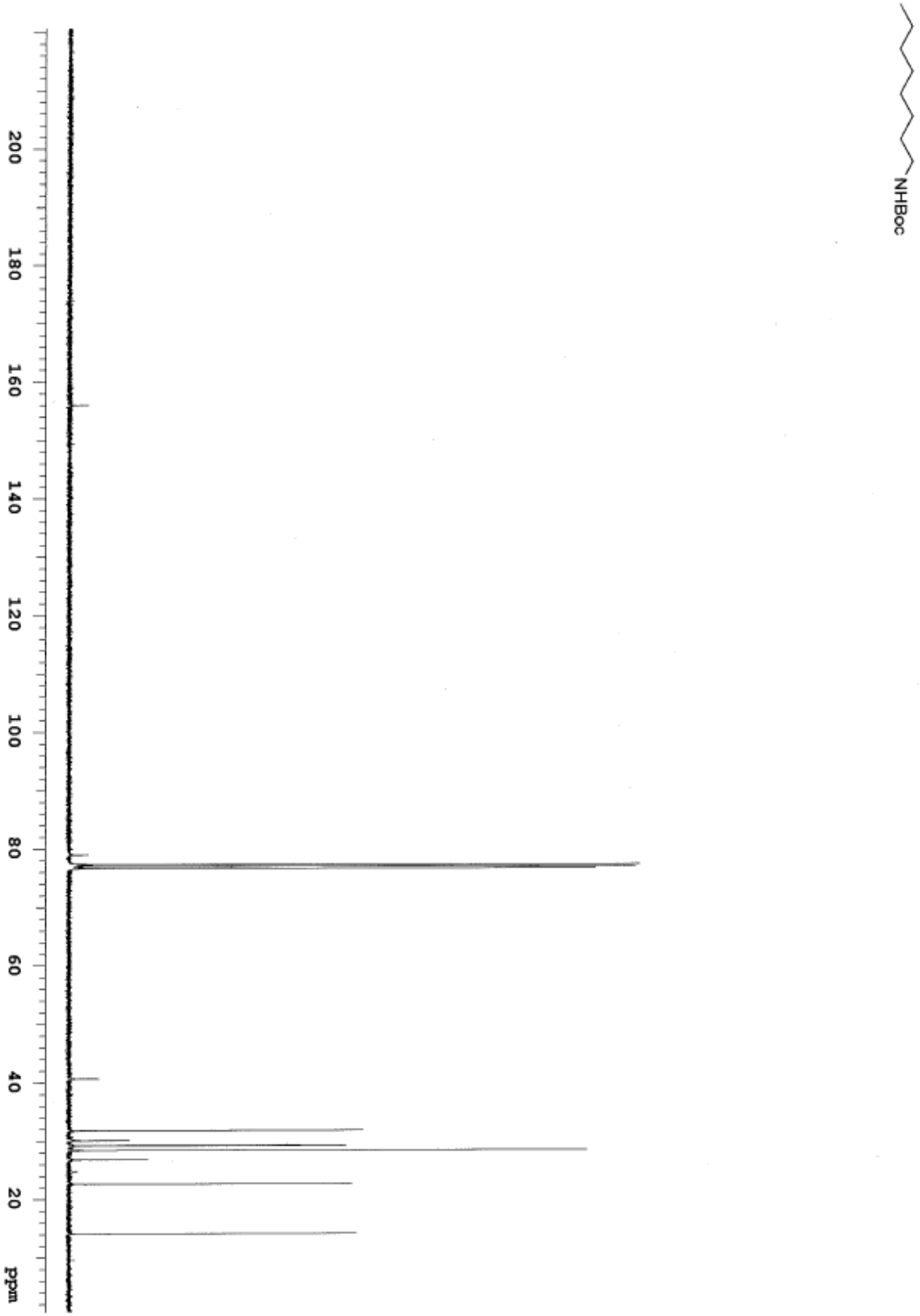


(*S*)-(+)-Pregabaline Hydrochloride. A flame-dried round bottom flask with magnetic stir bar was charged with *bis*-Boc-(*S*)-2-isobutyl-5-methylhex-4-en-1-amine (79.6 mg, 221 μmol) and hydrogen chloride in methanol (1.7 mL, 10 equiv., [HCl] in MeOH = 1.25 M). The reaction stirred at room temperature 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. 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.[46] $[\alpha]_D^{20}$ = +10.640 (*c* = 1.050, H_2O, *l* = 50 nm); lit.: +11.2 (*c* = 1.19, H_2O).

[46] Yu, H.J; Shao, C.; Cui, Z.; Feng, C. G.; Lin, G. Q. *Chem. Eur. J.* **2012**, *18*, 13274.

4.7 Representative NMR Spectra




NHBoc
200
180
160
140
120
100
80
60
40
20
ppm