Platinum-Catalyzed Enantioselective Diboration of Terminal Alkenes and Vinyl Boronates: Construction of Multiborylated Compounds for Asymmetric Synthesis

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Boston College

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PLATINUM-CATALYZED ENANTIOSELECTIVE DIBORATION OF TERMINAL ALKENES AND VINYL BORONATES: CONSTRUCTION OF MULTIBORYLATED COMPOUNDS FOR ASYMMETRIC SYNTHESIS

a dissertation

by

JOHN RYAN COOMBS

Submitted in partial fulfillment of the requirements

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PLATINUM-CATALYZED ENANTIOSELECTIVE DIBORATION OF TERMINAL ALKENES AND VINYL BORONATES: CONSTRUCTION OF MULTIBORYLATED COMPOUNDS FOR ASYMMETRIC SYNTHESIS

by

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Dissertation Advisor:

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ABSTRACT: This dissertation will discuss in depth four main projects pertaining to the synthesis and utility of organoboronates for the construction of enantioenriched small molecules. First, reaction optimization and substrate scope expansion of the platinumcatalyzed enantioselective diboration of alkenes are reported. Based on extensive experimental and computational mechanistic analysis, a preliminary stereochemical model is also proposed. A practical boron-Wittig reaction is presented in which synthetically challenging di- and trisubstituted vinyl boronates can be accessed in a highly stereoselective fashion from readily available starting materials. The enantioselective diboration of cis- and trans-vinyl boronates furnished novel 1,1,2tris(boronate) esters in up to 95:5 er. The intermediate tris(boronate) esters were employed successfully in deborylative alkylations to furnish enantioenriched internal vicinal bis(boronates) in excellent diasteoselectivity. In the final chapter, an enantioselective palladium-catalyzed intramolecular Suzuki-Miyaura coupling between allyl boronates and aryl electrophiles is disclosed. The newly developed transformation provides enantioenriched 5, 6, and 7-membered carbocycles in up to 93:7 er.

Dedicated to:

My parents, Lorie and John Coombs, for their unwavering love and support, and for their priceless lessons throughout the years.

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LIST OF ABBREVIATIONS

| Å: angstrom | cod: 1,5-cyclooctadiene |
|---|---|
| Ac: acetyl | conv: conversion |
| Acac: acetylacetonyl | Cy: cyclohexyl |
| Ad: adamantyl | d: day(s) |
| Aliquat 336: trioctylmethylammonium chloride | DART: direct analysis in real time |
| atm: atmosphere(s) | dba: dibenzylideneacetone |
| AQN: anthraquinone | DCC: diboration/cross-coupling |
| B ₂ (cat) ₂ : bis(catecholato)diboron | DCE: dichloroethane |
| B ₂ (pin) ₂ : bis(pinacolato)diboron | DCM: dichloromethane |
| 9-BBN: 9-borabicylco[3.3.1]nonane | DFT: density functional theory |
| BHT: 2,6-di- <i>t</i> -butyl-4-methylphenol | DHQ: dihydroquinine |
| BINAP: 2,2'-bis(diphenylphosphino)- | DHQD: dihydroquinidine |
| Bn: benzyl | DI: deionized |
| cat: catechol | DME: dimethoxyethane |
| CBz: carboxybenzyl | DMF: <i>N</i> , <i>N</i> -dimethylformamide |

| dmpd: 2,4-dimethylpenane-2,4-diol | GLC: gas-liquid chromatography |
|--|--|
| DMPU: 1,3-dimethyl-3,4,5,6-tetrahydro- 2(1H)-pyrimidinone | h: hour(s) |
| DMSO: dimethyl sulfoxide | HOMO: highest occupied molecular orbital |
| dppb: 1,1'-bis(diphenylphosphino) butane | HPLC: high performance liquid chromatography |
| dppf: 1,1'-bis(diphenylphosphino) ferrocene | HRMS: high resolution mass spectrometry |
| dppm: 1,1'-bis(diphenylphosphino) methane | Hz: hertz |
| dppp: 1,1'-bis(diphenylphosphino) propane | IPA: isopropanol |
| dr: diastereomeric ratio | IR: infrared spectroscopy |
| ee: enantiomeric excess | KIE: kinetic isotope effect |
| elim: elimination | LDA: lithium diisopropylamide |
| eq: equation(s) | LiTMP: lithium 2,2,6,6- tetramethylpiperidide |
| equiv: equivalent(s) | LUMO: lowest unoccupied molecular orbital |
| er: enantiomeric ratio | M: molar |
| ESI: electrospray ionization | MALDI: matrix-assisted laser desorption/ionization |
| EtOAc: ethyl acetate | MeCN: acetonitrile |
| GC: gas chromatography | min: minutes |
| | |

| MOP: 2-(diphenylphosphino)-2'- methoxy-1,1'-binaphthyl |
|---|
| MS: molecular sieves |
| MTBE: methyl <i>t</i> butyl ether |
| nbd: norbornadiene |
| NHC: N-heterocyclic carbine |
| NMO: <i>N</i> -methylmorpholine <i>N</i> -oxide |
| NMR: nuclear magnetic resonance |
| npg: neopentylglycol |
| NR: no reaction |
| PHAL: phalazine |
| pin: pinacol |
| PMA: phosphomolybdic acid |
| ppm: parts per million |
| |
| PYR: pyrimidine |
| PYR: pyrimidine Quinap: 1-(2-diphenylphosphino-1- naphthyl)isoquinoline |

RCM: ring-closing metathesis

RPKA: reaction progress kinetic analysis

rr: regioisomeric ratio

RT: room temperature

SAD: Sharpless asymmetric dihydroxylation

salen: bis(salicylidine)ethylenediamine

SES: 2-(trimethylsilyl)ethanesulfonyl

SFC: supercritical fluid chromatography

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

TBAF: tetrabutylammonium fluoride

tbc: 4-*t*-butylcatechol

TBDPS: *t*-butyldiphenylsilyl

TBS: *t*-butyldimethylsilyl

Tces: trichloroethoxysulfonyl

temp: temperature

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

Tf: trifluoromethanesulfonyl

THF: tetrahydrofuran

TLC: thin layer chromatography

TMEDA: *N*,*N*,*N*',*N*'- tetramethylenediamine

TMS: trimethylsilyl

tol: toluene

Ts: *p*-toluenesulfonyl

UV: ultraviolet

xylyl: dimethylphenyl

y: yield

ZACA: zirconium-catalyzed asymmetric carboalumination

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Chapter 1

Asymmetric Synthesis by Catalytic Enantioselective Functionalizations of Terminal Unactivated Alkenes

1.1. Introduction

The catalytic enantioselective reactions of monosubstituted alkenes offer singular opportunities for strategic chemical synthesis. These reactions can facilitate both hydrocarbon chain-extension and functional group installation simultaneously, and in a stereoselective fashion. As substrates, terminal alkenes are amongst the most attractive of starting materials for chemical synthesis. They are readily available from large scale industrial processes and they may be accessed on smaller scale by a number of efficient, catalytic and highly selective processes. In addition to ready availability, the reactivity characteristics of alkenes render them ideal functional groups for strategic chemical synthesis. They are relatively non-polar and hence inert to all but the strongest of bases. Moreover, their reluctance to engage with many common oxidants, reductants, and nucleophiles allows polar functionality (i.e. halides, alcohols, ketones, esters, etc.) to be manipulated in their presence. Coupled with this general inertness, however, is a crucial feature: under specialized reaction conditions, alkenes may be transformed, often with exquisite levels of chemoselectivity, into a range of functionalized products.

Considering the remarkable properties of terminal alkenes and the utility of their asymmetric transformations, it may seem surprising that so little progress has been charted in regards to their efficient catalytic asymmetric transformation. However, there are well-founded reasons that selective transformations that apply to this functional group have been slow to emerge. This review surveys the challenges associated with stereocontrol in reactions of α -olefins and documents the techniques that are currently available to synthetic chemists for the asymmetric transformation of this substrate class in useful levels of selectivity (> ca. 80% *ee*). For reasons that will be delineated below, we restrict the discussion to transformations that apply to aliphatic alkenes and do not include the many reactions that apply only to electronically biased alkenes (i.e. styrenes, dienes, enynes, enones), or that require the presence of chelating groups, directing groups, or other auxiliary functionality.

1.2. Background

Enantioselective transformations of unactivated alkenes are most often accomplished with transition metal catalysts. For these types of reactions quadrant diagrams can simplify stereochemical analysis and provide insight into the stereochemical outcome. In these diagrams, a chiral ligand attached to a reaction center provides a non-symmetric environment where steric encumbrance (shaded quadrant) guides reaction of the substrate. In the examples below, stereochemistry-determining olefin insertion into an M-A bond is depicted as a prototypical elementary catalytic step that might control enantioselectivity. As depicted in Scheme 1.1, a significant obstacle to controlling the selectivity in reactions of terminal alkenes arises because in many olefin insertion reactions, bond formation occurs by 1,2-insertion of the alkene into the M-A bond. In this mode, in contrast to reactions of *cis*, *trans*, and trisubstituted alkenes, the steric bias provided by the ligand framework is remote from the prochiral carbon atom of the substrate and prospects for effective stereocontrol are diminished. In contrast, asymmetric reactions of functionalized terminal alkenes are often more successful, in part because the substrate functionality turns over the regioselectivity of insertion reactions thereby positioning the prochiral carbon of the alkene much closer to the chiral ligand (2,1-insertion). For example, π -benzyl and π -allyl stabilization of organometallics turns over the insertion regiochemistry of styrenes and dienes and hence highly selective hydro- and difunctionalizations of these substrates are well developed. Similarly, chelation can turn over the regiochemistry of vinyl acetate and allyl alcohol insertions. The end result of these features is that the many excellent enantioselective reactions that apply to styrenes, dienes, and heteroatom-functionalized terminal alkenes, often give achiral linear products or are non-selective with common aliphatic terminal olefins.

Scheme 1.1. Possible Insertion Pathways for Terminal Olefins.



1.3. Asymmetric Hydrofunctionalizations of Unactivated Terminal Alkenes

1.3.1. Asymmetric Hydrosilylation. The catalytic hydrosilylation of 1-alkenes has been well-studied, and many transition metals have been utilized to date, including platinum, palladium, nickel, rhodium, and even a number of lanthanides.¹ In almost all cases, hydrosilylation of unactivated 1-alkenes proceeds with high anti-Markovnikov selectivity via a Chalk-Harrod-type mechanism (or closely related variants thereof) to provide achiral 1-silylalkanes (Scheme 1.2, cycle I).² In such a mechanism, oxidative addition with a hydrosilane furnishes coordinatively unsaturated complex **A**, followed by coordination of an alkene substrate to generate intermediate **B**. Subsequently, hydrometallation provides alkyl-silyl complex **C** after a 1,2-insertion. Finally, reductive elimination delivers 1-silylalkane **E** and regenerates the active catalyst. Alternatively, an alkene insertion into the M-Si bond (i.e. silylmetallation) has been suggested, most notably under Rh(I) or Co(III) catalyst systems (cycle **II**).^{2b,3} In this variant, a 2,1-migratory insertion mode results in generation of complex **D**, followed by reductive elimination to form the hydrosilylation product **E**.

¹ Marciniec, B.; Maciejewski, H.; Pietraszuk, C.; Pawluc, P. *Hydrosilylation: A Comprehensive Review on Recent Advances*; Marciniec, B., Ed.; Springer: New York, 2008.

² (a) Chalk, A. J.; Harrod, J. F. J. Am. Chem. Soc. **1965**, 87, 16. (b) Duckett, S. B.; Perutz, R. N. Organometallics **1992**, 11, 90.

³ (a) Schroeder, M. A.; Wrighton, M. S. J. Organomet. Chem. **1977**, 128, 345. (b) Bergens, S. H.; Noheda, P.; Whelan, J.; Bosnich, B. J. Am. Chem. Soc. **1992**, 114, 2128. (c) Brookhart, M.; Grant, B. E. J. Am. Chem. Soc. **1993**, 115, 2151.

Scheme 1.2. Proposed Mechanisms for Transition Metal-Catalyzed Hydrosilylation.



In 1991, Hayashi and co-workers reported the first and only catalytic asymmetric hydrosilylation of aliphatic terminal alkenes (Scheme 1.3).⁴ With only 0.2 mol % of a palladium salt in conjunction with the chiral monodentate phosphine MeO-MOP, various terminal alkenes underwent hydrosilylation with trichlorosilane. These reactions provide 2-silylalkanes in high yields and >80:20 regioselectivity in most cases (hindered terminal alkenes resulted in lower regioisomeric ratios). The silylalkanes generated could be oxidized *in situ* under Tamao-Fleming oxidation conditions (hydrogen peroxide in the presence of an anionic fluoride source) to generate 2-alkanols in >94% *ee*.

⁴ Uozumi, Y.; Hayashi, T. J. Am. Chem. Soc. 1991, 113, 9887.



Scheme 1.3. Catalytic Hydrosilylation of Terminal Alkenes Developed by Hayashi.

While the authors give little mechanistic insight into the origin of the surprisingly high regioselectivity, they suggest that the high reactivity arises because the monodentate ligand allows 16-electron palladium(II) intermediate access to а [PdH(SiCl₃)L(CH₂=CHR)], bearing a coordination site for olefin binding and activation. Indeed, reactions conducted in the presence of chelating bis(phosphine) ligands such as BINAP did not provide hydrosilylation products even when conducted at elevated temperatures.⁴ Furthermore, the authors suggest that the MOP ligand accelerates reductive elimination relative to β -hydride elimination when compared to other monodentate ligands such as triphenylphosphine or tri-o-tolylphosphine; this feature minimizes olefin isomerization during the course of the hydrosilylation. Lastly, it was

found that the methoxy group at the 2'-position of the binaphthyl moiety is not imperative for high regioselectivity, since varying this group (Et-MOP, *i*-PrO-MOP) provided similar levels of regio- and enantioselectivity (Scheme 1.4).⁵ A crystal structure of $[PdCl_2\{(R)-MeO-MOP\}_2]$ indicates that the substituent at the 2' position is far removed from the palladium center (Figure 1.1).

Scheme 1.4. Comparison of X-MOP Ligands Varying Substitution at the 2'-Naphthyl Position.



⁵ Uozumi, Y.; Kenji, K.; Hayashi, T.; Yanagi, K.; Fukuyo, E. Bull. Chem. Soc. Jpn. 1995, 68, 713.

Figure 1.1. Crystal Structure of [PdCl₂{(*R*)-MeO-MOP}₂] (Side View).



1.3.2. Asymmetric Hydroformylation. Due to its superb atom economy, fast reaction rates, and high turnover numbers, transition metal-catalyzed hydroformylation of alkenes has become one of the largest and most successful catalytic commodity chemical manufacturing processes, producing millions of tons of achiral aldehydes annually.⁶ Despite many decades of advancements to efficiently produce linear aldehydes from inexpensive petroleum feedstocks, methods of generating the chiral α -branched isomer with high regio- and enantioselectivity have not been well developed. Considering the abundance of biologically active compounds that may be derived from nonracemic chiral

⁶(a) *Rhodium Catalyzed Hydroformylation*; Claver, C.; van Leeuwen, P. W. N. M., Eds.; Kluwer Academic Publishers: Doordrecht, Netherlands, 2000. (b) Franke, R.; Selent, D.; Börner, A. *Chem. Rev.* **2012**, *112*, 5675.

aldehydes, the ability to directly provide α -chiral aldehydes from terminal alkenes in an enantioselective manner would be an appealing transformation.

Highly successful asymmetric and branch-selective hydroformylations of electronically activated terminal olefins or those containing chelating groups have been reported with a number of transition metals,⁷ but most notably with Rh(I).⁸ As stated above, generation of the branched isomer from aliphatic terminal alkenes under similar catalyst systems have been met with limited success, a result which can be explained by considering the mechanism for hydroformylation (Scheme 1.5).⁹ Subsequent to regiodetermining olefin insertion, Rh-complex **B** or **B'** may be generated from precursor Rh-alkene complex **A**. Coordination of CO and migratory insertion provides acyl complex **C** or **C'**. Finally, oxidative addition of H₂ followed by reductive elimination provides branched product **D** or linear product **D'** with concomitant regeneration of the rhodium catalyst. When intermediate **B** is stabilized by the substitution pattern on the

⁷ Besides Rh, Pt(II)-catalyzed asymmetric hydroformylation of activated alkenes is particularly successful. For early examples: (a) Consiglio, G.; Nefkens, S. C. A.; Borer, A. Organometallics 1991, 10, 2046. (b) Stille, J. K.; Su, H.; Brechot, P.; Parrinello, G.; Hegedus, L. S. Organometallics 1991, 10, 1183. (c) Consiglio, G.; Nefkens, S. C. A. Tetrahedron: Asymmetry 1990, 1, 417. (d) Kollár, L.; Kégel, T.; Bakos, J. J. Organomet. Chem. 1993, 453, 155. (e) Kollár, L.; Sandor, P.; Szalontai, G. J. Mol. Catal. 1991, 67, 191. (f) Tóth, I.; Guo, I. Hanson, B. E. Organometallics 1993, 12, 848. (g) Gladiali, S.; Fabbri, D.; Kollár, L. J. Organomet. Chem. 1995, 491, 91. (h) Bandini, A. L.; Banditelli, G.; Cesorotti, E.; Minghetti, G.; Nowogrocki, G.; Wignacourt, J. P. Inorg. Chem. 1992, 31, 391. (i)Pottier, Y. Mortreux, A.; Petit, F. J. Organomet. Chem. 1989, 370, 333. (j) Naili, S.; Carpentier, J.-F.; Agbossou, F.; Mortreux, A.; Nowogrocki, G.; Wignacourt, J. P. Organometallics 1995, 14, 401. (k) Parrinello, G.; Stille, J. K. J. Am. Chem. Soc. 1987, 109, 7122. (l) Consiglio, G.; Kollár, L.; Köllár, R. J. Organomet. Chem. 1990, 396, 375. (m) Kollár, L.; Consiglio, G.; Pino, P. J. Organomet. Chem. 1987, 330, 305. (n) Haelg, P.; Kollár, P.; Consiglio, G.; Pino, P. J. Organomet. Chem. 1987, 330, 305. (n) Haelg, P.; Kollár, P.; Flowers, L. I. J. Chem. Soc., Chem. Commun. 1982, 473. (p) Scrivanti, A.; Beghetto, V.; Bostianini, A.; Matteoli, U.; Menchi, G. Organometallics 1996, 15, 4687.

⁸For reviews on Rh-catalyzed asymmetric hydroformylations, see: (a) Klosin, J.; Landis, C. R. *Acc. Chem. Res.* **2007**, *40*, 1251. (b) van Leeuwen, P. W. N. M.; Kamer, P. C. J.; Claver, C.; Pámies, O.; Diéguez, M. *Chem. Rev.* **2011**, *111*, 2077. (c) Fernández-Pérez, H.; Etayo, P.; Panossian, A.; Vidal-Ferran, A. *Chem. Rev.* **2011**, *111*, 2119.

⁹ (a) Torrent, M.; Solá, M.; Frenking, G. *Chem. Rev.* **2010**, *100*, 439. (b) Nozaki, K.; Ojima, I. In *Catalytic Asymmetric Synthesis*; 2nd ed.; Ojima, I.; Ed.; Wiley-VCH: New York, 2000, p 429.

alkene (for example, when R=Ph, a stable π -benzyl intermediate is formed), branched product **D** is preferred and unfavorable steric interactions between the substrate and the metal center are overridden. However, with aliphatic alkenes, little to no stabilization effect exists and intermediate **B'** predominates. Thus, linear product **D'** is favored so as to avoid steric interactions that are created in **B**.

Scheme 1.5. Catalytic Cycle for Rh-Catalyzed Olefin Hydroformylation.



Developed by Takaya, Nozaki, and co-workers in 1997, phosphine-phosphite derived BINAPHOS 1.1 was the first ligand used for a highly enantioselective hydroformylation of aliphatic terminal alkenes (Scheme 1.6).¹⁰ Although synthetically useful levels of enantioselectivity were achieved for 1-hexene (82% ee) and 1-butene (83% ee), the undesired linear isomer predominated (1:3 branched:linear), a problem that is compounded by the fact that similar chemical and physical properties of the two isomers render purification difficult. Through extensive theoretical studies, it was later determined that facial selectivity of the olefin is mainly dictated by the absolute configuration of the phosphine group (occupying the equatorial site), while the phosphite unit (apical site) has a significant impact on the *degree* of enantioselectivity that is observed.^{6b,11,12} The favored conformation of the intermediate $RhH(CO)_2[(R,S)-$ BINAPHOS] along with quadrant representations of the two possible hydroformylation paths are provided in Figure 1.2 (S = pro-S quadrant; R = pro-R quadrant). Calculations predict that pathway II is highly favored over pathway I and, as indicated by the quadrant diagrams, insertion into the pro-R face of the olefin is preferred. It is concluded that for high stereoselectivity, Rh-diphosphane catalysts require (1) equatorial-apical specific coordination containing chirality at the apical position to enhance diastereoisomeric ligand-substrate interactions, (2) two stereogenic centers which discriminate against competing equatorial-apical pathways, and (3) a rigid catalyst that enhances stereoinduction on the substrate.¹¹

¹⁰ Nozaki, K.; Sakai, N.; Tetsuo, N.; Higashijima, T.; Mano, S.; Horiuchi, T.; Takaya, H. *J. Am. Chem. Soc.* **1997**, *119*, 4413.

¹¹ Aguado-Ullate, S.; Saureu, S.; Guasch, L.; Carbó, J. J. Chem. Eur. J. 2012, 18, 995.

¹² Note that calculations were performed with Styrene and (*E*)-2-butene: Gleich, D.; Schmid, R.; Herrmann, W. A. *Organometallics* **1998**, *17*, 2141.



Scheme 1.6. Rh-Catalyzed Hydroformylation of Alkenes by Tanaka et. al.

Figure 1.2. Favored Catalyst Conformation and Quadrant Diagrams Showing Preferred Olefin Binding Modes. (S = pro-S substituent location; R = pro-R substituent location)



In 2012, Clark and Cobey developed the first example of asymmetric hydroformylation in which electronically unbiased alkenes provided mainly branched

isomer in high levels of enantioselectivity (Scheme 1.7).¹³ For example, in the presence of bobphos and Rh(acac)(CO)₂ as the precatalyst, 1-hexene underwent hydroformylation in 93% ee and in a 3:1 branched:linear ratio. While low reaction temperatures and turnover numbers resulted in incomplete conversion and long reaction times (21-66 hours), the Clark system is a fundamentally important advance likely to lead to refined systems.

Scheme 1.7. Branched-Selective Rh-Catalyzed Hydroformylation of Alkenes Reported by Clark and Cobey.



1.3.3. Asymmetric Hydroamination. Although asymmetric intramolecular hydroaminations of functionalized terminal alkenes have been well-studied. intermolecular variants that involve reaction of unactivated alkenes are lacking.¹⁴ While iridium(I),¹⁵ gold(I),¹⁶ and platinum(II)¹⁷ complexes are known to catalyze intermolecular

¹³ Noonan, G. M.; Fuentes, J. A.; Cobley, C. J.; Clarke, M. L. Angew. Chem. Int. Ed. 2012, 51, 2477.

¹⁴ For general review on catalytic hydroamination reactions, see: (a) Brunet, J. J.; Neilbecker, D. In Catalytic Heterofunctionalization; Togni, A., Grützmacher, H., Eds.; Wiley-VCH: Weinheim, Germany, 2001, p 91. (b) Beller, M.; Seayad, J.; Tillack, A.; Jiao, H. Angew. Chem. Int. Ed. 2004, 43, 3368. (c) Müller, T. E.; Hultzsch, K. C.; Yus, M.; Foubelo, F.; Tada, M. Chem. Rev. 2008, 108, 3795.

¹⁵ Sevov, C. S.; Jianrong, Z.; Hartwig, J. F. J. Am. Chem. Soc. 2014, 136, 3200.

Markovnikov hydroamination, the low reactivity of unactivated 1-alkenes necessitates use of harsh reaction conditions and often occurs with poor substrate scope. Such limitations render asymmetric variants difficult to develop. Nonetheless, in 2009, Widenhoefer and co-workers reported an asymmetric gold(I)-catalyzed Markovnikovselective intermolecular hydroamination of unactivated alkenes with imidazolidin-2-ones (Scheme 1.8).¹⁸ The process employed a bis(gold) phosphine complex bearing a chiral bidentate ligand 1.2 in combination with a catalytic amount of AgOTf to provide good yields of the alkylated ureas in 71-78% ee. While superstoichiometric amounts of olefin were required for complete conversion, the inexpensive nature of many alkenes negates this problem. While the authors do not provide a mechanistic evaluation, enantioselective functionalizations of C=C π -bonds with chiral bis(gold)phosphine complexes have ample precedent.¹⁹ Thus, the reaction may proceeds by an outer sphere nucleophilic attack of the external urea on Au-activated alkene, followed by internal proton transfer. Of note, critical control experiments were performed which excluded the possibility of Ag or acid-catalyzed pathways for olefin hydroamination.

¹⁶For early examples, see: (a) Zhang, J.; Yang, C.-G.; He, C. J. Am. Chem. Soc. 2006, 128, 1798. (b) Liu, X.-Y.; Li, C.-H.; Che, C.-M. Org. Lett. 2006, 8, 2707. (c) Giner, X.; Nájera, C. Org. Lett. 2008, 10, 2919. (d) For a review, see: Corma, A.; Leyva-Pérez, A.; Sabater, M. J. Chem. Rev. 2011, 111, 1657.

¹⁷ For an early example, see: Karshtedt, D.; Bell, A. T.; Tilley, T. D. J. Am. Chem. Soc. **2005**, *127*, 12640. ¹⁸ Zhang, Z.; Lee, S. D.; Widenhoefer, R. A. J. Am. Chem. Soc. **2009**, *131*, 5372.

¹⁹ For comprehensive reviews of C-C bond functionalization with chiral bis(gold)phosphine complexes, see: (a) Widenhoefer, R. A. *Chem. Eur. J.* **2008**, *14*, 5382. (b) Bongers, N.; Krause, N. *Angew. Chem. Int. Ed.* **2008**, *47*, 2178.

Scheme 1.8. Widenhoefer's Gold(I)-Catalyzed Hydroamination of Terminal Alkenes with Cyclic Ureas.



Note: Absolute configuration not disclosed in orginal report.

1.3.4. Asymmetric C-H Bond Additions of Pyridines to Alkenes. The synthesis of chiral compounds containing pyridine moieties is of significant importance for synthetic chemists considering their prevalence in a wide array of natural products, pharmaceutically relevant and biologically active small compounds, and chiral ligands.²⁰ Asymmetric C-H additions of pyridines to alkenes remains underexplored despite a number of successful racemic variants.²¹ In 1994, Rodewald and Jordan reported an enantioselective C-H alkylation of pyridines utilizing a chiral zirconocene-based catalyst

²⁰ (a) Michael, J. P. *Nat. Prod. Rep.* **2005**, *22*, 627. (b) Arena, C. G.; Arico, G. *Curr. Org. Chem.* **2010**, *14*, 546. (c) Bull, J. A.; Mousseau, J. J.; Pelletier, G.; Charette, A. B. *Chem. Rev.* **2012**, *112*, 2642.

²¹ For asymmetric C-H alkylation of arenes and heteroarenes with activated olefins, see: (a)Thalji, R. K.; Ellman, J. A.; Bergman, R. G. J. Am. Chem. Soc. 2004, 126, 7192. (b) Wilson, R. M.; Thalji, R. K.; Bergman, R. G.; Ellman, J. A. Org. Lett. 2006, 8, 1745. (c) Zheng, J.; You, S.-L. Angew. Chem. Int. Ed. 2014, 126, 13460. (d) Lee, P.-S.; Yoshikai, N. Org. Lett. 2015, 17, 22. (e) Filloux, C. M.; Rovis, T. J. Am. Chem. Soc. 2015, 137, 508.

1.3.²² However, low yields due to poor catalyst turnover, and only moderate enantioselectivities were reported for unactivated monosubstituted alkenes (Scheme 1.9).

Scheme 1.9. Zirconium-catalyzed C-H Addition of 2-Picoline to 1-Octene Reported by Rodewald and Jordan.



Improving upon this work, Hou and co-workers recently reported a highly enantioselective C-H bond addition of pyridines to alkenes by employing chiral half-sandwich scandium dialkyl precatalyst **1.4** (Scheme 1.10).²³ High yields and excellent branched selectivity were obtained in the enantioselective reaction between unactivated α -olefins and 2-substituted pyridines. The novel catalyst retains a monocyclopentadienyl ligand that bears a tethered chiral binaphthyl backbone; the chiral element serves to block one of the two possible olefin binding modes and results in facially selective 1,2-insertion of the Sc-pyridyl bond to alkene (Figure 1.3). Unfortunately, reactions of unsubstituted pyridine and quinolones did not occur, most likely due to enhanced coordination to the metal center, which may poison the catalyst by inhibiting olefin coordination.

²² Rodewalkd, S.; Jordan, R. F. J. Am. Chem. Soc. 1994, 116, 4491.

²³ Song, G.; O, W. W. N., Hou, Z. J. Am. Chem. Soc. 2014, 136, 12209.

Scheme 1.10. Hou and Co-Workers' Asymmetric C-H Bond Addition of Pyridines to Alkenes.



Figure 1.3. Proposed Stereochemical Model for Olefin Coordination in Asymmetric C-H Addition of Pyridines to 1-Alkenes.



1.4 Asymmetric Difunctionalizations of Unactivated Terminal Alkenes

1.4.1. Asymmetric Dihydroxylation. Developed in 1980, the Sharpless asymmetric dihydroxylation (SAD) is one of the most broadly used and well-studied olefin difunctionalizations in organic synthesis.²⁴ Early variants by Sharpless and co-workers necessitated stoichiometric amounts of both a chiral quinuclidine-based ligand and expensive and toxic OsO₄. Furthermore, initial osmylation conditions provided diminished enantioselectivities for unactivated terminal olefins. Building on early findings by Sharpless that chiral quinuclidine- and amine-based ligands can both accelerate reaction rate and control facial selectivity during oxidation of the olefin,²⁵ Hirama reported the first highly enantioselective dihydroxylation of unactivated terminal

 ²⁴ (a) Hentges, S. G.; Sharpless, K. B. J. Am. Chem. Soc. 1980, 102, 4263. (b) For a review, see: Kolb, H. C.; Van Nieuwenhze, M. S.; Sharpless, K. B. Chem. Rev. 1994, 94, 2483.

²⁵ Previous to an asymmetric variant, Criegee discovered that pyridine can significantly accelerate reaction rates of OsO_4 with olefins. However, a seminal report by Sharpless suggested that chiral pyridine derivatives provided little to no enantioinduction due to low binding affinity of pyridine for OsO_4 : (a) Criegee, R. Justus Liebigs Ann. Chem. **1936**, 522, 75. (b) Criegee, R. Angew. Chem. **1938**, 51, 519.
olefins by utilizing chiral *N*,*N*'-dineohexyl-2,2'-bypyrrolidine **1.5**.²⁶ For example, 1-heptene could be dihydroxylated to generate the vicinal 1,2-diol in 90% yield and 91% *ee* (Scheme 1.11). However, the strongly binding bidentate nature of the ligand appeared to inhibit hydrolysis of the osmium(VI) glycolate product thereby inhibiting ligand and osmium turnover. Thus, the Hirama example necessitates stoichiometric amounts of both OsO₄ and chiral ligand in addition to an external oxidant.^{24b}

Scheme 1.11. Early Reports of a Highly Enantioselective Dihydroxylation of Terminal Alkenes as Reported by Hirama.



In 1988, Sharpless and Jacobsen demonstrated the first catalytic dihydroxylation of alkenes by employing *N*-methylmorpholine *N*-oxide as a co-oxidant.²⁷ In this process, lower enantioselectivities were observed compared to the stoichiometric variant due to a secondary competing and nonselective catalytic cycle.²⁸ This alternate mechanism could be avoided by performing the reaction with $K_3Fe(CN)_6$ as a stoichiometric reoxidant

²⁶ Oishi, T.; Hirama, T. J. Org. Chem. 1989, 54, 5834.

²⁷ Jacobsen, E. N.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. J. Am. Chem. Soc. **1988**, 110, 1968.

²⁸ Wai, J. S. M.; Markó, I.; Mungall, W. S.; Schröder, G.; Sharpless, K. B. J. Am. Chem. Soc. **1989**, 111, 1123.

under biphasic conditions.²⁹ By 1996, with an effective and reliable catalytic system in hand, the Sharpless lab had tested over 500 different ligands, ultimately discovering that easily accessible dihydroquinidinyl- and dihydroquininyl-based ligands, (DHQD)₂AQN and (DHQ)₂AQN, provided high enantioselectivities for a broad range of olefin Importantly, terminal unactivated olefins were found to undergo substrates. dihydroxylation with moderate to good levels of enantioinduction (Scheme 1.12).³⁰ Diphenylpyrimidine-based ligand, [(DHQD)₂PYR], was also found to be highly selective with unactivated terminal alkenes, especailly those with α -branching. Important to note, is that while "AD-mix" catalysts derived from phthalazine-based ligands [(DHQD)₂PHAL or (DHQ)₂PHAL] outperform most catalyst/ligand combinations for most alkene classes, "AD-mix" underperforms for unactivated terminal alkenes and the pyrazine catalysts are generally superior.

²⁹ Kwong, H.-L.; Sorato, C.; Ogini, Y.; Chen, H.; Sharpless, K. B. Tetrahedron Lett. 1990, 31, 2999.

³⁰ Becker, H.; Sharpless, K. B. Angew. Chem. Int. Ed. Engl. 1996, 35, 448.

| R | K ₃ Fe(CN) ₆ (3 equ K ₂ CO ₃ (3 equiv 0.4% K ₂ OsO ₂ (Ol 1% ligand | $ \stackrel{\text{liv.)}}{} \stackrel{\text{OH}}{} \stackrel{\text{OH}}{ \stackrel{\text{OH}}{} \stackrel{\text{OH}}{} \stackrel{\text{OH}}{} \stackrel{\text{OH}}{ \stackrel{\text{OH}}{} \stackrel{\text{OH}}{} \stackrel{\text{OH}}{ \stackrel{\text{OH}}{} \stackrel{\text{OH}}{} \stackrel{\text{OH}}{ \stackrel{\text{OH}}{} \stackrel{\text{OH}}{ \stackrel{\text{OH}}{} \stackrel{\text{OH}}{ \stackrel{\text{OH}}{} \stackrel{\text{OH}}{ \stackrel{\text{OH}}{ \stackrel{\text{OH}}{} \stackrel{\text{OH}}{ \stackrel{\text{OH}}}{ \stackrel{\text{OH}}{ \text{O$ | | | | |
|---|--|--|---|--|--|--|
| | | | | | | |
| | ee values (%) | | | | | |
| Olefin | [(DHQD) ₂ AQN] | [(DHQD) ₂ PYR] | AD-mix-β | | | |
| n-butyl | 87 (<i>R</i>) | 87 (<i>R</i>) | 80 (<i>R</i>) | | | |
| n-octyl | 92 (<i>R</i>) 87 (S) [(DHQ) ₂ AQN] | 89(<i>R</i>) 76 (<i>S</i>) [(DHQ) ₂ PYR] | 84 (<i>R</i>) 80 (<i>S</i>) (AD-mix-α) | | | |
| \bigcirc | 86 (<i>R</i>) | 96 (<i>R</i>) | 88 (<i>R</i>) 86 (<i>S</i>) (AD-mix-α) | | | |
| Me Me Me | | 92 (<i>R</i>) 87 (S) [(DHQ) ₂ PYR] | 64 (<i>R</i>) 66 (<i>S</i>) (AD-mix-α) | | | |
| CI | 90 (<i>S</i>) | 53 (S) | 63 (S) 54 (R) | | | |
| $\begin{array}{c ccccccccccccccccccccccccccccccccccc$ | | | | | | |
| AQN | PYR | PHAL (ligand substituent for AD-mix) | | | | |
| (ligand core of AD mix R) | | $H_{3}CO$ H_{3 | | | | |
| | R $Olefin$ $n-butyl$ $n-octyl$ $n-octyl$ Cl Cl Cl Cl Cl Cl Cl C | $\begin{array}{c c} & & & & & & & & & & & & & & & & & & &$ | $\begin{array}{c c} & \begin{array}{c} K_{3}Fe(CN)_{6} (3 equiv.) \\ K_{2}CO_{3} (3 equiv.) \\ 0.4\% K_{2}OSO_{2}(OH)_{4} \\ 1\% \mbox{ ligand } \\ 1\% \mbox{ ligand } \\ \hline 0 \mbox{ lefin } \\ \hline 16 \mbox{ loop}(HQD)_{2}AQN] \\ \hline 0 \mbox{ lefin } \\ \hline 0 \mbox{ lefin } \\ \hline (DHQD)_{2}AQN] \\ \hline 0 \mbox{ lefin } \\ \hline (DHQD)_{2}AQN] \\ \hline 0 \mbox{ lefin } \\ \hline (DHQD)_{2}AQN] \\ \hline 0 \mbox{ loop}(R) \\ \hline 0 \mbox{ so } \\ \hline 0 \mbox{ loop}(R) \\ \hline 0 \mbox{ so } \\ \hline 0 \mbox{ loop}(R) \\ \hline 0 \mbox{ loop}(R) \\ \hline 0 \mbox{ so } \\ \hline 0 \mbox{ loop}(R) \\ \hline 0 \mbox{ loop}(R) \\ \hline 0 \mbox{ so } \\ \hline 0 \mbox{ loop}(R) \\ \hline 0 \mbox{ loop}(R) \\ \hline 0 \mbox{ so } \\ \hline 0 \mbox{ loop}(R) \\ \hline 0 loop$ | | | |

Scheme 1.12. Sharpless Asymmetric Dihydroxylation of Terminal Alkenes.

1.4.2. Asymmetric Epoxidations. Although many highly stereoselective epoxidation methods have been developed, the majority of these are only effective with electronically-biased or functionalized alkenes.³¹ Selective epoxidation of unfunctionalized substrates are generally limited to alkenes that are di- and trisubstituted with selective reactions of unfunctionalized terminal alkenes being quite scarce. In addition to the recurring challenge associated with poor facial selectivity with terminal olefins, the lower HOMO energy of monosubstitued alkenes relative to their more substituted counterparts often leads to diminished reactivity of 1-alkenes towards electrophilic oxidants. Without practical and scalable methodology in hand for this challenging substrate class, production processes for nonracemic terminal epoxides rely on nonselective olefin epoxidation followed by Co(III)/salen-catalyzed hydrolytic kinetic resolution.³² While this process is highly practical with inexpensive substrates, for more precious alkene starting materials resolution processes may be too costly.

In 2006, Strukul reported that use of 2 mol % of Pt-complex **1.6** along with environmentally benign hydrogen peroxide furnished enantiomerically enriched terminal epoxides in good yields and moderate levels of enantioselectivity (Scheme 1.13).³³ Reactions of 1,4-dienes resulted in complete regioselectivity for the terminal double bond with excellent enantioinduction—an important breakthrough considering most chiral metal-based catalysts favor epoxidation of the more electron-rich substituted double

³¹ For helpful reviews, see: (a) Xia, Q.-H.; Ge, H.-Q.; Ye, C.-P.; Liu, Z.-M.; Su, K.-X. *Chem. Rev.* **2005**, *105*, 1603. (b) De Faveri, G.; Ilyashenko, G.; Watkinson, M. *Chem. Soc. Rev.* **2011**, *40*, 1722. (c) Zhu, Y.; Wang, Q.; Cornwall, R. G.; Shi, Y. *Chem. Rev.* **2014**, *134*, 8199.

³² (a) Tokunaga, M.; Larrow, J. F.; Kakiuchi, F.; Jacobsen, E. N. *Science* **1997**, *277*, 936. (b) Robinson, D. E. J. E.; Bull, S. D. *Tetrahedron Asymmetry* **2003**, *14*, 1407.

³³ Colladon, M.; Scarso, A.; Sgarbossa, P.; Michelin, R. A.; Strukul, G. J. Am. Chem. Soc. 2006, 128, 14006.

bond. Although the mechanistic details surrounding catalysis were not completely elucidated, the authors suggest that the pentafluorophenyl ligand renders the catalyst electron-deficient such that it activates the alkene for nucleophilic epoxidation, presumably by outer-sphere attack of peroxide on the metal-olefin complex. It was also speculated that the C_6F_5 group may enhance steric interactions between the substrate and the rigid chiral ligand.³⁴

Scheme 1.13. Pt-Catalyzed Asymmetric Epoxidation of Alkenes Developed by Strukul.



³⁴ Pizzo, E.; Sgarbossa, P.; Scarso, A.; Michelin, R. A.; Strukul, G. Organometallics 2006, 25, 3056.

Prior to Strukul's report, Katsuki and co-workers realized some success with di- μ oxo titanium(salen) complex **1.7** and hydrogen peroxide as the oxidant.³⁵ While initial studies only surveyed a limited range of substrates, further examination found that a broad array of terminal olefins underwent asymmetric epoxidation with good to excellent enantioselectivity (Scheme 1.14).³⁶ Notably, α -branched terminal olefins, a substrate class that was not examined by Strukul, provided the highest levels of enantioenrichment. Lastly, use of competition experiments that employ 1,6-dienes showed that the terminal alkene is more reactive and generated the terminal epoxide in moderate to high regioselectivity.

Scheme 1.14. Katsuki's Ti(salen)-Catalyzed Asymmetric Epoxidation of Terminal Alkenes.



³⁵ The enantioselective epoxidation of 1-octene was reported utilizing 1 mol% **1.7** (70% y, 82% *ee*). However, no other unactivated terminal alkenes were investigated: Matsumoto, K.; Sawada, Y.; Saito, B.; Sakai, K.; Katsuki, T. *Angew. Chem. Int. Ed.* **2005**, *44*, 4935.

³⁶ Sawada, Y.; Matsumoto, K.; Katsuki, T. Angew. Chem. Int. Ed. 2007, 46, 4559.

1.4.3. Asymmetric Chlorohydrin Synthesis. The enantioselective synthesis of chlorohydrins from terminal olefins represents a rare and powerful example in which both olefinic carbons can be differentially functionalized in a single step. Early findings by Bäckvall noted that the key to the catalytic synthesis of chlorohydrin from ethylene with Pd(II) salts was the use of an aqueous media containing high concentrations of Cl⁻ and $CuCl_2$ (>2.5 M and >3 M, respectively).³⁷ At low concentrations of Cl⁻ and CuCl₂ (<1.0 M for both), the Wacker reaction product (i.e acetaldehyde) was observed. However, later studies by Henry suggested that employment of an appropriate Pd(II) catalyst [i.e. PdCl₃(pyridine)] would allow for measurable chlorohydrin formation even at Cl⁻ concentrations as low as 0.2M.³⁸ Thus, in 1998, Henry and co-workers documented a Pd(II)-catalyzed asymmetric chlorohydrin synthesis with chiral bimetallic Pd-species **1.8** (Scheme 1.15).³⁹ With this complex, Unfunctionalized terminal olefins were converted to the derived chlorohydrin products with high enantioenrichement, albeit as a mixture of regioisomers. Comparatively, allyl ethers provided the product in much higher regioisomeric selectivity for the terminal chloride product, and in similar levels of enantioselectivity. Notably, only 5-20% of the total product consisted of aldehyde and ketone by-products. A significant amount of effort has been spent on determining the mechanism of oxypalladation in Wacker-type processes.⁴⁰ Through numerous mechanistic studies performed by Henry and others, it is *generally* accepted that under

³⁷ Bäckvall, J. E.; Åkermark, B.; Ljunggren, S. O. J. Am. Chem. Soc. 1979, 101, 2411.

³⁸ (a) Francis, J. W.; Henry, P. M. J. Mol. Catal. A: Chem. **1995**, 99, 77. (b) Lai, J.-Y.; Wang, F.-S.; Guo, G.-Z.; Dai, L.-X. J. Org. Chem. **1993**, 58, 6944.

³⁹ El-Qisairi, A.; Hamed, O.; Henry, P. M. J. Org. Chem. 1998, 63.

⁴⁰ For comprehensive reviews, see: (a) Keith, J. A.; Henry, P. M. Angew. Chem. Int. Ed. 2009, 48, 9038.
(b) McDonald, R. I.; Liu, G.; Stahl, S. S. Chem. Rev. 2011, 111, 2981.

conditions with high Cl⁻ concentrations, *trans*-hyxdroxypalladation via an outer-sphere nucleophilic attack is the operative pathway. Alternatively, inner-sphere *cis* addition is favored with low Cl⁻ concentrations.⁴¹ With the stereochemical outcome of the Wacker process being sensitive to catalyst structure and reaction conditions, a complete understanding of the stereochemical features of the Henry process is not currently established.⁴²

Scheme 1.15. Pd(BINAP)-Catalyzed Chlorohydrin Synthesis from Terminal Alkenes as Documented by Henry.



⁴¹ For selected examples, see: (a) Gregor, N.; Zaw, K.; Henry, P. M. *Organometallics* **1984**, *3*, 1251. (b) Francis, J. W.; Henry, P. M. *Organometallics* **1991**, *10*, 3498. (c) Hamed, O.; Thompson, C.; Henry, P. M. *J. Org. Chem.* **1997**, *62*, 7082. (d) Keith, J. A.; Nielsen, R. J.; Oxgaard, J.; Goddard, W. A. J. Am. Chem. Soc. **2007**, *129*, 12342.

⁴² (a) Comas-Vives, A.; Stirling, A.; Lledós, A.; Ujaque, G. *Chem. Eur. J.* 2010, *16*, 8738. (b) Angerson, B. J.; Keith, J. A.; Sigman, M. S. *J. Am. Chem. Soc.* 2010, *132*, 11872. (c) Kóvacs, G.; Stirling, A.; Lledós, A.; Ujaque, G. *Chem. Eur. J.* 2012, *18*, 18. (d) Stirling, A.; Nair, N. N.; Lledós, A.; Ujaque, G. *Chem. Soc. Rev.* 2014, *43*, 4940. (e) For an extensive review, see: Kočovský, P.; Bäckvall, J. E. *Chem. Eur. J.* 2015, *21*, 36.

In an important advance, Henry found that by simply varying conditions from chloride- to a bromide-containing medium, enantiomerically enriched vicinal dibromides could be accessed rather than the expected bromohydrin products (results not shown).⁴³ Only allyl ethers and α , β -unsaturated esters were investigated making it unclear whether this alternate mode of reactivity arises from electronic factors, or whether this process would also apply to unfunctionalized terminal alkenes.

1.4.4. Asymmetric Aziridination. The asymmetric aziridination of unactivated olefins is particularly difficult not only because of low reactivity of the substrate, but also due to the difficulty of finding highly reactive nitrene sources that are both accessible and easily deprotected.⁴⁴ Iminoiodane derivates such as PhI=NTs have been proven useful for Cu-catalyzed asymmetric aziridinations of electronically activated olefins or those bearing proximal polar functionality.⁴⁵ However, low reactivity with unfunctionalized terminal olefins suggests that a secondary binding interaction might be necessary to enhance reaction rates via induced intramolecularity.⁴⁶ Atom-economic azide derivatives were studied by many to provide an alternate efficient route to metal nitrene

⁴³ El-Qisairi, A. K.; Qaseer, H. A.; Katsigras, G.; Lorenzi, P.; Trivedi, U.; Tracz, S.; Hartman, A.; Miller, J. A.; Henry, P. M. *Org. Lett.* **2003**, *5*, 439.

⁴⁴ Degennaro, L.; Trinchera, P.; Luisi, R. Chem. Rev. 2014, 114, 7881.

⁴⁵ For early examples, see: (a) Li, Z.; Conser, K. R.; Jacobsen, E. N. J. Am. Chem. Soc. 1993, 115, 5326. (b)
Evans, D. A.; Faul, M. M.; Bilodeau, M. T.; Anderson, A.; Barnes, D. M. J. Am. Chem. Soc. 1993, 115, 5328. (c) Sanders, C. J.; Gillespie, K. M.; Bell, D.; Scott, P. J. Am. Chem. Soc. 2000, 122, 7132.

⁴⁶ (a) Fruit, C.; Müller, P. *Tetrahedron: Asymmetry* 2004, *15*, 1019. (b) Wang, X.; Ding, K. *Chem. Eur. J.*2006, *12*, 4568. (c) Anada, M.; Tanaka, M.; Washio, T.; Yamawaki, M.; Abe, T.; Hashimoto, S. *Org. Lett.*2007, *9*, 4559.

intermediates.⁴⁷ Still, harsh conditions are often needed for both azide decomposition and *N*-deprotection, hindering development of asymmetric variants.⁴⁸

In 2009, Zhang *et. al.* developed Co(II) porphyrin-based catalyst **1.9** that performed asymmetric aziridination of unactivated terminal alkenes under mild temperatures (Scheme 1.16).⁴⁹ In part, the key to their success was utilization of trichloroethoxysulfonyl azide (TcesN₃) as a highly reactive and easily accessible nitrene source. Although isolated yields were low despite a large excess of alkene in relation to azide, Zhang's report represented the first highly asymmetric aziridination for this substrate class. Furthermore, an operationally simple precipitation/filtration procedure was developed for recovery of the catalyst.

⁴⁷ For a review, see: Driver, T. G. Org. Biomol. Chem. **2010**, *8*, 3831.

⁴⁸(a) Li, Z; Quan, R. W.; Jacobsen, E. N. J. Am. Chem. Soc. **1995**, 117, 5889. (b) Bergmeier, S. C.; Seth, P.

P. Tetrahedron Lett. 1999, 40, 6181. (c) Katsuki, T. Chem. Lett. 2005, 1304.

⁴⁹ Subbarayan, V.; Ruppel, J. V.; Zhu, S.; Perman, J. A.; Zhang, X. P. Chem. Commun. **2009**, 4266.

| R (5 equiv.) | + TcesN ₃ C ₆ H ₅ | 5% 1.9 ₅CI, 4 A MS | * NTces N | O I ₃ -S-OCH ₂ CO O TcesN ₃ | CI3 |
|-----------------|---|------------------------------|-----------|---|-----|
| entry | product | temp. (^o C) | yield (%) | ee (%) | [α] |
| 1 ^a | n-butyl ≁ NTces | 40 | 42 | 91 | (+) |
| 2 ^a | <i>n</i> -hexyl | 40 | 30 | 90 | (+) |
| 3 | Bn * NTces | 0 | 26 | 94 | (+) |

Scheme 1.16. Enantioselective Aziridination of Terminal Alkenes with TcesN₃.

a) Performed with 5% $Pd(OAc)_2$ as and additive. Note: Absolute configuration not disclosed in original report.



Building on Zhang's precedence, the Katsuki group also reported a mild Ru(CO)(salen)-catalyzed asymmetric aziridination of unactivated terminal olefins utilizing 2-(trimethylsilyl)ethanesulfonyl azide (SESN₃) as a nitrene source (Scheme 1.17).⁵⁰ Employing 3 mol % of complex **1.10** and equimolar amounts of azide and alkene provided high yields and excellent enantioselectivities for a variety of terminal alkenes.

⁵⁰ Kim, C.; Uchida, T.; Katsuki, T. Chem. Commun. 2012, 48, 7188.

Importantly, Katsuki's report provided an expanded substrate scope that included nonconjugated dienes, bromide and ether-containing alkenes, as well as α -branched olefins. Of note, the aziridine protecting group was easily removed through use of tris(dimethylamino)sulfonium difluorotrimethylsilicate (TASF).



Scheme 1.17. Katsuki's Ru(salalen)-Catalyzed Aziridination of Terminal Alkenes.

Note: Absolute configuration not disclosed in the original report.

1.4.5. Asymmetric Cyclopropanation. The catalytic asymmetric cyclopropanation of alkenes represents one of the most general methods of accessing chiral cyclopropane units, a motif which is present in a number of natural or synthetic pharmaceutically

relevant compounds.⁵¹ Since the seminal report by Nozaki and Noyori,⁵² many reliable asymmetric transition metal-catalyzed processes have been developed for cyclopropane synthesis.⁵³ Impressively, unactivated terminal alkenes have been found to undergo selective transition metal-catalyzed cyclopropanation with many stabilized diazo compounds. Effective catalysts have been developed that are based on Co(II),⁵⁴ Cu(I),⁵⁵ Ru(II),⁵⁶ Rh(II),⁵⁷ and Ir(III)⁵⁸ complexes (major contributions are summarized in Scheme 1.18). The body of work in this field is large compared to that of other asymmetric transformations of terminal alkenes, and thus only a few key examples will be discussed in detail.

⁵¹ (a) Carson, C. A.; Kerr, M. A. Chem. Soc. Rev. 2009, 38, 3051. (b) Reissig, H. U.; Zimmer, R. Chem. Rev. 2003, 103, 1151.

⁽a) Nozaki, H.; Takaya, H.; Noyori, R. Tetrahedron Lett. 1965, 6, 2563. (b) Nozaki, H.; Takaya, H.; Moriuti, S.; Noyori, R. Tetrahedron 1968, 24, 3655.

⁵³ For a recent review, see: Bartoli, G.; Bencivenni, G.; Dalpozzo, R. Synthesis **2014**, 46, 979.

⁵⁴ Zhu, S.; Xu, X.; Perman, J. A.; Zhang, P. J. Am. Chem. Soc. **2010**, 132, 12796.

⁵⁵ (a) Lo, M. M.-C.; Fu, G. C. J. Am. Chem. Soc. 1998, 120, 10270. (b) Minuth, T.; Boysen, M. M. K. *Synthesis* **2010**, 2799. ⁵⁶ Hoang, V. D. M.; Reddy, P. A. N.; Kim, T.-J. *Tetrahedron Lett.* **2007**, *48*, 8014.

⁵⁷ (a) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. J. Am. Chem. Soc. 1996, 118, 6897. (b) Lindsay, V. N. G.; Lin, W.; Charette, A. B. J. Am. Chem. Soc. 2009, 131, 16383. (c) Chuprakov, S.; Kwok, S. W.; Zhang, L.; Lercher, L.; Fokin, V. V. J. Am. Chem. Soc. 2009, 131, 18034. (d) Lindsay, V. N. G.; Nicolas, C.; Charette, A. B. J. Am. Chem. Soc. 2011, 133, 8972.(e) Marcoux, D.; Azzi, S.; Charette, A. B. J. Am. Chem. Soc. 2009, 131, 6970. (f) Grimster, N.; Zhang, L.; Fokin, V. V. J. Am. Chem. Soc. 2010, 132, 2510. (g) Qin, C.; Boyarskikh, V.; Hansen, J. H.; Hardcastle, K. I.; Musaev, D. G.; Davies, H. M. L. J. Am. Chem. Soc. 2011, 133, 19198. (h) Lindsay, W. N. G.; Fiset, D.; Gritsch, P. J.; Azzi, S.; Charette, A. B. J. Am. Chem. Soc. 2013, 135, 1463.

⁵⁸ Suematsu, H.; Kanchiku, S.; Uchida, T.; Katsuki, T. J. Am. Chem. Soc. 2008, 130, 10327.

Scheme 1.18. Selected Examples of Asymmetric Transition Metal-Catalyzed Olefin Cyclopropanation with 1-Hexene.



While many methods are available for the generation of thermodynamically stable *trans*-disubstituted⁵⁵ and trisubstituted cyclopropanes,^{54,57} synthesis of *cis*-disubstituted cyclopropane derivatives in high diastereo- and enantioselectivity is still challenging. In

2008, Katsuki and co-workers reported an asymmetric iridium-catalyzed *cis*-selective cyclopropanation of nonconjugated olefins (Scheme 1.19).⁵⁸ Employing 1 mol% of aryliridium-salen complex **1.11** in the presence of ethyl α -diazoacetate and a large excess of olefin furnished *cis*-disubstituted cyclopropanes in high yields and excellent enantioselectivities. Of note, subsequent manipulation of the pendant ester moiety provides a straightforward method for chain extension or functional group installation.



Scheme 1.19. Katsuki's Ir-Catalyzed Asymmetric Cyclopropanation of Alkenes.

Although the authors state that a detailed mechanism of the stereochemical control is unclear, they do provide a stereochemical model based on crystal structures of the catalyst and with the help of density functional theory calculations. It is likely that the diazo precursor replaces a weakly bound methanol at the apical position to provide

the corresponding Ir-carbenoid intermediate displayed in Figure 1.4. With the $C_{carbene}$ - C_{ester} bond bisecting two Ir-N vectors, olefin is favored to attack the carbenoid carbon from the least hindered side over the downward naphthalene ring via a perpendicular, side-on approach. Subsequently, a counter-clockwise rotation of the olefin positions the substitutent away from the ester moiety of the carbenoid, leading to formation of the major isomer. Note that a clockwise rotation is unfavored due to development of steric repulsion between the olefin substituent and the basal salen ligand.

Figure 1.4. Stereochemical Model for the Ir-Salen Catalyzed Cyclopropanation of Alkenes Proposed by Katsuki.



In 2010, the Zhang group reported on a highly versatile chiral cobalt(II) porphyrin complex **1.12** that was found to catalyze the asymmetric cyclopropanation of a variety of activated and unactivated alkenes with *tert*-butyl α -cyanodiazoacetate as the carbene source (Scheme 1.20).⁵⁴ High enantioinduction and *E*-selectivity was achieved for all

substrates.⁵⁹ Unlike most metal-catalyzed carbene transfer methodologies, the reaction proceeded efficiently with olefin as the limiting reagent. Furthermore, the reaction is performed under solvent-free conditions and does not require slow addition of the diazoacetate.⁶⁰ Through appropriate reagent choice, either the ester group or the cyano group could be reduced chemoselectively with complete preservation of stereochemistry.

Scheme 1.20. Zhang's Co-catalyzed Asymmetric Cyclopropanation and Subsequent Chemoselective Reduction Sequences.



 ⁵⁹ For a detailed mechanistic study pertaining to the Co(II) porphyrin-catalyzed cyclopropanation, see: Dzik, W. I.; Xu, X.; Zhang, X. P.; Reek, J. N. H.; de Bruin, B. J. Am. Chem. Soc. 2010, 132, 12796.
 ⁶⁰ Slow diazoalkane addition is often required in order prevent formation of carbene dimerization byproducts typically observed at high concentrations of diazoalkane: Dörwald, F. Z. Metal Carbenes in Organic Synthesis; Wiley-VCH: Weinheim, Germany, 1999, p 116.

1.4.6. Asymmetric Carboalumination. In 1995, Negishi and co-workers described a zirconium-catalyzed asymmetric carboalumination (ZACA) of monosubstituted alkenes, adding to the list of stereoselective C-C bond-forming reactions available for this challenging substrate class (Scheme 1.21).⁶¹ Subsequent to treatment of the olefin starting material with 8 mol % of (-)-(NMI)₂ZrCl₂ and equimolar amounts of trimethylaluminum, the carboaluminated products could be oxidized in situ to provide β methyl primary alcohols in good yield and moderate enantioselectivity. Initially, extending the methodology to include other trialkylaluminum reagents resulted in low enantioselectivity. However, upon further evaluation, a dramatic solvent effect was observed and high enantioinduction was eventually obtained when using 1,1dichloroethane in place of 1,2-dichloroethane for other trialkylaluminum reagents (Scheme 1.22).⁶² While the authors do not offer a mechanistic rationale for this useful result, they have noted that use of more polar solvents suppresses carbometallation pathways involving metallacycles that are observed with reactions performed in hexanes. Through the principle of statistical enantiomeric amplification,⁶³ asymmetric carboalumination has been utilized for the syntheses of highly enantioenriched deoxypolypropionates via a one-pot tandem ZACA/Pd-catalyzed vinylation process.⁶⁴

⁶¹ Kondakov, D. Y.; Negishi, E. J. Am. Chem. Soc. 1995, 117, 10771.

⁶² Kondakov, D. Y.; Negishi, E. J. Am. Chem. Soc. 1996, 118, 1577.

⁶³ Statistical enantiomeric amplification is a principle which predicts, through the mass action law, that a combination of two compounds with low enantiomeric excess can generate a new compound containing two chiral centers in much greater enantiomeric excess (i.e. two chiral species of 80% *ee* can theoretically generate a new compound in 97.6% *ee* at the expense of lower yields). See: Negishi, E. *Dalton Trans.* **2005**, 827.

⁶⁴ (a) Tan, Z.; Negishi, E. Org. Lett. 2001, 3, 3253. (b) Negishi, E.; Tan, Z.; Liang, B.; Novak, T. Proc. Natl. Acad. Sci. 2004, 101, 5782. (c) Magnin-Lachaux, M.; Tan, Z.; Liang, B.; Negishi, E. Org. Lett. 2004, 6, 1425. (d) Novak, T.; Tan, Z.; Liang, B.; Negishi, E. J. Am. Chem. Soc. 2005, 127, 2838. (e) Liang, B.;



Scheme 1.21. Zr-Catalyzed Asymmetric Methylalumination Documented by Negishi.

Scheme 1.22. Zr-catalyzed asymmetric carboalumination as documented by Negishi.



Novak, T.; Tan, Z.; Negishi, E. J. Am. Chem. Soc. 2006, 128, 2770. (f) Xu, S.; Lee, C.-T.; Wang, G.; Negishi, E. Chem. Asian, J. 2013, 8, 1829.

1.5. Conclusion

Simple α -olefins are extremely abundant and accessible from both large-scale industrial and smaller-scale synthetic processes, making them ideal substrates for asymmetric catalysis. Despite recent advances in catalytic olefin functionalization, highly asymmetric transformations of terminal aliphatic olefins are still lacking. Additional progress needs to be made in developing chiral ligands and catalyst systems that control both alkene facial selectivity and olefin insertion modes for this challenging substrate class. Nonetheless, recent approaches have led to the development of unique and highly versatile catalysts that promote selective reactions for both activated and unactivated olefins alike, bringing new hope for the discovery of more strategic and concise methods for chemical synthesis. In this context, the following chapter will discuss the development and optimization of the first highly asymmetric diboration of unactivated olefins.

Chapter 2

Optimization, Scope and Mechanism of the Platinum-Catalyzed Enantioselective Alkene Diboration

2.1. Introduction

Asymmetric catalysis has revolutionized the field of organic chemistry over the past 50 years. Due to the never-ending advancements of asymmetric catalysis, highly functionalized chiral molecules can now be accessed in a single step from simple prochiral starting materials, thereby streamlining drug and natural product syntheses. As demonstrated by most of the examples described in Chapter 1, a single catalytic transformation provides access to a very specific functionality pattern. Thus, synthesis of a similar product bearing slightly different functionality would require the development of an entirely new catalyst system and reaction conditions. However, similar to the above-described epoxidation methods, a more powerful reaction would be one that provides access to a single enantioenriched intermediate that could then be transformed into a diverse range of functionalized products in a one-pot procedure. In this context, our research group has been interested in the enantioselective dimetallation of unsaturated substrates, which generates a reactive bis(metallate) intermediate for subsequent functionalization (Scheme 2.1).

Scheme 2.1. Asymmetric Dimetallation of Terminal Alkenes Provides Access to an Array of Functionalized Products.



Development of a practical asymmetric dimetallation reaction necessitates the construction of a C-M bond that can partake in a wide array of stereospecific transformations in a mild and efficient manner. Numerous dimetallation reactions have been reported to date that involve the use of disilanes, silylboranes, silylgermanes, distannanes, and borylstannanes.¹ Unfortunately, reactions of silicon-, tin-, and germanium-carbon bonds are limited to protonation, oxidation, and (in some cases) cross-coupling reactions. Furthermore, in addition to high toxicity, the respective dimetallation

¹ (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. (d) Burks, H. E.; Morken, J. P. Chem. Commun. 2007, 4717.

reagents are typically expensive or difficult to access. In contrast, organoboronates are known to participate in oxidation, amination, halogenation, sulphination and phosphination, as well as a number of C-C bond forming reactions (i.e. cross-coupling, homologation, and carbonylation).² Most of these transformations proceed with high levels of stereospecificity. In addition, bis(boronate) reagents are commercially available, inexpensive, and non-toxic when compared to the above-mentioned dimetallating reagents. In many cases, both the diboron starting material and the bis(boronate) products are air- and moisture-stable and can be isolated by simple chromatographic methods. For these reasons, the Morken group has largely focused on the development of highly appealing and broadly applicable asymmetric *diborations* of alkenes and other unsaturated systems. In this chapter, I will describe the development and optimization of the enantioselective Pt-catalyzed diboration of monosubstituted alkenes. In addition, a thorough mechanistic evaluation will be discussed in depth.

2.2. Background

2.2.1 History of Alkene Diboration. The first catalytic reaction relating to the addition of a diboron reagent across a C-C π -bond involved the diboration of terminal alkynes with 3 mol% Pt(PPh₃)₄ and bis(pinacolato) diboron [B₂(pin)₂] to access 1,2-vinylic bis(boronates) **2.1** and was reported by Suzuki and Miyaura in 1993 (Scheme 2.2).^{3,4} In the years following, alkyne diboration was also mechanistically investigated

² Brown, H. C.; Singaram, B. Pure Appl. Chem. 1987, 59, 879.

³ Schlesinger and co-workers previously reported reaction of tetrahalodiboranes with unsaturated C-C bonds, but the reagents and products were difficult to handle, limiting practical utility. Thus, diboration

by Marder, Norman, Smith, and Iverson.⁵ Although their products were achiral, this pioneering work eventually led to the development of novel catalytic systems that could be applied to alkene diboration, arguably a more synthetically appealing process as the reaction generates a valuable stereocenter. Unfortunately, phosphine-based Pt(0) catalysts were found to be incompetent for alkene diboration, presumably due to slow alkene insertion into a Pt-B bond, which limited catalyst turnover. Additionally, Rh(I) catalysts were briefly examined but initially suffered from β -hydride elimination resulting in formation of alkenyl and alkyl boronate byproducts.⁶

Scheme 2.2. First Catalytic Diboration of a Carbon-Carbon π -Bond.



The first example of a catalytic diboration of olefins was reported by Baker, Marder, and Wescott in 1995.⁶ Use of a phosphine-Au(I) catalyst in combination with bis(catecholato) diboron [B₂(cat₂)] provided 1,2-bis(boronate) esters **2.2** in high conversion after 48 hours at 80 °C (Scheme 2.3). Only styrene and its derivatives were

remained dormant for another four decades: Ceron, P.; Finch, A.; Frey, J.; Kerrigan, J.; Parsons, T.; Urry, G.; Schlesinger, H. I. J. Am. Chem. Soc. 1959, 81, 6368.

⁴ Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. J. Am. Chem. Soc. 1993, 115, 11018.

⁵ (a) Lesley, G.; Nguyen, P.; Taylor, N. J.; Marder, T. B.; Scott, A. J.; Clegg, W.; Norman, N. C. *Organometallics* **1996**, *15*, 5137. (b) Iverson, C. N.; Smith, M. R., III, *Organometallics* **1996**, *15*, 5155.

⁶ Baker, R. T.; Nguyen, P. Marder, T. B.; Westcott, S. A. Angew. Chem. Int. Ed. 1995, 34, 1336.

competent substrates in this seminal paper, with unactivated olefins providing little-to-no reactivity.

Scheme 2.3. First Catalytic Diboration of Terminal Alkenes Reported by Baker, Marder, and Westcott.



In 1996, Miyaura and co-workers investigated the diboration of 1,3-dienes under both phosphine- and phosphine-free Pt(0) catalysis, finding that high catalytic activity was achieved with Pt(dba)₂ (*vide infra*).⁷ Thus, it was reasoned that phosphine-free conditions might allow for more facile olefin insertion into a B-Pt bond. With these reports in hand, Miyaura and Smith independently discovered phosphine-free Ptcatalyzed alkene diborations that performed with high efficiency under mild conditions (Scheme 2.4). Miyaura's conditions employed $B_2(pin)_2$ in the presence of 3 mol% Pt(dba)₂ to furnish 1,2-diborylalkanes in high yields, albeit a large excess of olefin was required (eq. 1).⁸ Smith and Iverson utilized 3 mol% Pt(COD)₂ and a more reactive

⁷ Ishiyama, T.; Yamamoto, M.; Miyaura, N. Chem. Commun. 1996, 2073.

⁸ Ishiyama, T.; Yamamoto, M.; Miyaura, N. Chem. Commun. 1997, 689.

diboron reagent, $B_2(cat)_2$, which allowed the reaction to proceed at room temperature and without the need for excess olefin (eq. 2). 9

Scheme 2.4. Phosphine-Free Pt-Catalyzed Diboration of Terminal Olefins Independently Reported Independently by Miyaura and Smith.



While these results were promising, development of a Pt-catalyzed enantioselective variant was expected to be challenging considering chiral phosphinebased ligands would seemingly inhibit alkene diboration. Subsequently, in 1998, Marder and Norman reported the first diastereoselective diboration of styrenes using conditions similar to Miyaura's, but in conjunction with chiral diboron reagents (Scheme 2.5).¹⁰ A variety of chiral diol ligands were investigated, with the optimal diboron 2.3 only providing low to moderate diastereoselectivities of 1,2-bis(boronate) products 2.4. Notably, terminal aliphatic alkenes were not investigated.

 ⁹ Iverson, C. N.; Smith, M. R., III, Organometallics **1997**, *16*, 2757.
 ¹⁰ Marder, T. B.; Norman, N. C.; Rice, C. R. Tetrahedron Lett. **1998**, *39*, 155.

Scheme 2.5. Diastereoselective Diboration of Terminal Alkenes Employing Chiral Diborons.



The desire to unveil a more active alkene diboration catalyst that could be rendered chiral prompted a reinvestigation into the use of Rh(I) salts.¹¹ In 1998, reports by Marder and co-workers suggested that competitive β -hydride elimination with Rh(I)-catalysts could be suppressed by the use of the appropriate catalyst structure.^{11a} Thus, 4 mol% [(acac)Rh(dppm)] successfully catalyzed the diboration between B₂(cat)₂ and a variety of terminal and 1,2-disubstituted styrene derivatives obtaining bis(boronate) esters **2.5** in high yields and with minimal byproduct formation (Scheme 2.6).

¹¹ (a) Dai, C.; Robins, E. G.; Scott, A. J.; Clegg, W.; Yufit, D. S.; Howard, J. A. K.; Marder, T. B. *Chem. Commun.* **1998**, 1983. (b) Nguyen, P.; Coapes, R. B.; Woodward, A. D.; Taylor, N. J.; Burke, J. M.; Howard, J. A. K.; Marder, T. B. *J. Organomet. Chem.* **2002**, *652*, 77.

Scheme 2.6. Rh(I)-catalyzed Diboration of Syrenyl Derivatives Reported by Marder and Co-Workers.



Building on prior work, the Morken lab reported the first catalytic enantioselective alkene diboration in 2003.¹² Employment of a Rh(I)/(*S*)-Quinap catalyst system with B₂(cat)₂ efficiently promoted the diboration of a variety of activated and unactivated alkenes, including 1,2-disubstituted and trisubstituted alkenes. The bis(boronate) products could be oxidized *in situ* to generate enantioenriched 1,2-diols in a one-pot sequence. Unfortunately, low enantoinduction was observed for most terminal alkene substrates, with the exception of those bearing quaternary centers adjacent to the π -system (Scheme 2.7). In addition to lowering the overall cost of asymmetric diboration, developing a general catalyst system that is effective for a broad range of terminal aliphatic olefins would greatly improve the synthetic utility of this methodology.

¹² (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.

Scheme 2.7. Morken and Co-Workers' Rh-Catalyzed Asymmetric Diboration of Terminal Alkenes.



2.2.2. Development of a Pt-Catalyzed Enantioselective Alkene Diboration. The Pt-catalyzed diboration of 1,3-dienes with $B_2(pin)_2$ was initially disclosed by Miyaura and co-workers in 1996.⁷ Further investigations showed that regioselectivity of the diboration was highly influenced by the ligand employed.⁸ For example, in the diboration of *trans*-1,3-pentadiene with 3 mol% Pt(PPh₃)₄, (*Z*)-1,4-bis(boronate) ester 2.6 was generated exclusively in 84% yield. However, in the absence of a phosphine-based ligand, 1,2-bis(boronate) ester 2.7 was isolated in 92% yield as the sole product (Scheme 2.8).



Scheme 2.8. Pt-Catalyzed 1,4- and 1,2-Diboration of 1,3-Dienes Reported by the Miyaura Group.

Inspired by Miyaura's results, the Morken group reported a highly enantioselective Pt-catalyzed 1,4-diboration of *trans*-1,3-dienes with the use of 3 mol% Pt(dba)₃ and 6 mol% of a monodentate TADDOL-derived phosphonite (R,R)-2.8; this generates 1,4-diols 2.12 in excellent yield and enantioselectivity after oxidation of the intermediate 1,4-bis(boronate) esters 2.11 (Scheme 2.9, eq. 1).¹³ Notably, some chiral phosphine-based ligands delivered regioisomeric mixtures of 1,4- and 1,2-diboration products. Considering Miyaura's initial findings, it was important to conclude if the 1,2-bis(boronate) byproduct was a result of background reaction with ligand-free Pt(dba)₃ or if the Pt-ligand complex was capable of promoting 1,2-diboration for 1,2-diol product 2.14 with employment of chiral ligand (R,R)-2.9, confirming that the Pt-ligand complex effectively catalyzed a net 1,2-addition of B₂(pin)₂ across the terminal alkene (Scheme

¹³ Burks, H. E.; Kliman, L. T.; Morken, J. P. J. Am. Chem. Soc. 2009, 131, 9134.

2.9, eq. 2).¹⁴ More recently, *cis*- and 4,4-disubstituted 1,3-dienes were also found to undergo 1,2-diboration/oxidation in moderate to high regioselectivity and in excellent enantioselectivity to generate a variety of 1,2-diols **2.16** (Scheme 2.9, eq. 3).¹⁵

Scheme 2.9. Pt-Catalyzed Enantioselective Diboration of 1,3-dienes with Chiral TADDOL-Derived Ligands.



¹⁴ Kliman, L. T. Ph.D. Thesis, Boston College, Chestnut Hill, MA, 2011. P. 314.

¹⁵ Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. Angew. Chem. Int. Ed. 2012, 51, 521.

The above-mentioned results suggest that the internal alkene of the 1,3-diene moiety might not be necessary for reactivity in cases where 1,2-diboration was observed. Thus, it was reasoned that a Pt-catalyzed asymmetric diboration of simple 1-alkenes would be feasible with use of an appropriate TADDOL-derived phosphonite- or phosphoramidite-based ligand. In 2009, the Morken group reported that employment of 3 mol% Pt(dba)₃ and 6 mol% of phosphonite (*R*,*R*)-2.10 provided 1,2-diols in high yields and excellent levels of enantioselectivity upon oxidation with H₂O₂ (Scheme 2.10).¹⁶ While the initial report proved to be appealing enough to be adopted for asymmetric natural product syntheses,¹⁷ significant improvements pertaining to substrate scope, selectivity, and reaction optimization were clearly warranted. Furthermore, a more thorough mechanistic evaluation would provide useful insight for designing an improved process.

¹⁶ Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. J. Am. Chem. Soc. 2009, 131, 13210.

¹⁷ (a) Matsumoto, K.; Koyachi, K.; Shindo, M. *Tetrahedron* **2013**, *69*, 1043. (b) Geerdink, D.; ter Horst, B.; Lepore, M.; Mori, L.; Puzo, G.; Hirsch, A. K. H.; Gilleron, M.; de Libero, G.; Minnaard, A. *Chem. Sci.* **2013**, *4*, 709.

Scheme 2.10. Seminal Report on the Pt-Catalyzed Enantioselective Diboration of Terminal Alkenes.¹⁶



2.2.3. Recent Notable Advancements in Alkene Diboration. Recently, Fernandez and co-workers reported the first transition-metal free diboration of unactivated alkenes. Use of a Lewis base catalyst along with various diboron reagents promoted 1,2-diboration of terminal alkenes in moderate to high yields (Scheme 2.11).¹⁸ The overall transformation is a rare example in which a nominally nucleophilic reagent efficiently reacts with a nucleophilic, electron-rich alkene. Unfortunately, screening an array of chiral alcohols as an activator failed to provide high levels of enantioinduction.¹⁹ The

¹⁸ Bonet, A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyás, H.; Fernández, E. Angew. Chem. Int. Ed. **2011**, 50, 7158.

¹⁹ Bonet, A.; Sole, C.; Gulyás, H.; Fernández, E. Org. Biomol. Chem. **2012**, 10, 6621.

Morken group has recently extended this concept by demonstrating a hydroxyl-directed diastereoselective diboration of homoallylic and (bis)homoallylic alcohols.²⁰

Scheme 2.11. Lewis Base-Promoted Diboration of Alkenes Reported by Fernández.

$$R = alkyl, aryl$$

$$R = alkyl,$$

In 2013, Nishiyama and co-workers reported a chiral Rh(Phebox) complex 2.17 that is capable of catalyzing diboration of a variety of activated and unactivated terminal alkenes in good yields and high enantiomeric excess (Scheme 2.12).²¹ Employing 1 mol% 2.17 and 5 mol% NaOtBu efficiently catalyzed the net addition of B₂(pin)₂ across an olefin, providing enantioenriched vicinal 1,2-diols upon oxidation with NaBO₃. Due to the fact that the reaction is base-promoted, the authors conclude that either σ -bond metathesis or transmetallation is involved in forming a Rh(III)-boryl species **A** from Rh(III)-OtBu intermediate **C**, followed by Rh-B bond alkene insertion to form **B** (Scheme 2.13).

²⁰ Blaisdell, T. P.; Caya, T. C.; Zhang, L.; Sanz-Marco, A.; Morken, J. P. J. Am. Chem. Soc. **2014**, 136, 9264.

²¹ Toribatake, K.; Nishiyama, H. Angew. Chem. Int. Ed. **2013**, 52, 11011.

Scheme 2.12. Nishiyama's Rh(phebox)-Catalyzed Asymmetric Diboration/Oxidation of Terminal Alkenes.



Scheme 2.13. Proposed Catalytic Cycle for Rh-Catalyzed Asymmetric Diboration.



2.3 Optimization of the Pt-Catalyzed Enantioselective Diboration of Monosubstituted Alkenes²²

2.3.1. Optimization of Ligand and Ligand Synthesis. At the point of joining the project, fellow graduate students Dr. Laura T. Kliman and Dr. Scott N. Mlynarski had already tested numerous TADDOL-derived phosphoramidite- and phosphonite-based ligands, as well as solvents for the reaction. Initial efforts focused on expansion of this screening, with emphasis on ligands bearing meta-substitution on the ligand backbone. A sample of this ligand/solvent screen is provided in Table 2.1. In the enantioselective diboration of 1-octene, toluene and THF solvents could both be used with similar efficacy and were better than other solvents with respect to reactivity and enantioselectivity (entries 2-6). With no significant trend observed with solvent effects, efforts were shifted towards optimizing the ligand structure. A strong correlation was observed with respect to the size of the *meta*-substituent, with larger groups providing higher levels of enantioselectivity for 1,2-diol 2.18 (entries 1,2,7 and 10). Unfortunately, it was found that increasing the ligand bulk to R=tBu resulted in lower yields and diminished enantioselectivity (entry 9). Screening various phosphoramidite-derived ligands did not reveal ligands with improved yield or selectivity compared to phophonites (entries 11-17).

²² Coombs, J. R.; Haeffner, F.; Kliman, L. T.; Morken, J. P. J. Am. Chem. Soc. 2013, 135, 11222.
| <i>n</i> -hexyl | 3% 6% (F B ₂ (pin) ₂ TH then № | Pt(dba) ₃ ?,R)-Ligand (1.05 equiv.) F, 60 °C NaOH/H ₂ O ₂ | OH -hexyl 2.18 | .ОН (<i>R,R</i>)-L | Ar Ar O O Ar igand R | P-R' |
|-----------------|---|---|----------------------------------|-------------------------|----------------------------------|-----------------|
| entry | ligand | R | R' | solvent | yield (%) ^b | er ^c |
| 1 | 2.19 | н | Ph | toluene | 24 | 80:20 |
| 2 | 2.8 | Me | Ph | toluene | 81 | 92:8 |
| 3 | 2.8 | Me | Ph | THF | 84 | 95:5 |
| 4 | 2.8 | Me | Ph | 1,4-dioxane | 74 | 91:9 |
| 5 | 2.8 | Me | Ph | diethyl ether | 73 | 63:37 |
| 6 | 2.8 | Me | Ph | ethyl acetate | 65 | 94:6 |
| 7 | 2.10 | Et | Ph | toluene | 84 | 96:4 |
| 8 | 2.10 | Et | Ph | THF | 83 | 96:4 |
| 9 | 2.20 | <i>t</i> -Bu | Ph | toluene | 74 | 90:10 |
| 10 | 2.21 | OMe | Ph | toluene | 69 | 90:10 |
| 11 | 2.22 | Н | NMe ₂ | toluene | 68 | 84:16 |
| 12 | 2.23 | Н | NEt ₂ | toluene | 35 | 70:30 |
| 13 | 2.9 | Me | NMe ₂ | toluene | 77 | 90:10 |
| 14 | 2.9 | Me | NMe ₂ | THF | 73 | 89:11 |
| 15 | 2.24 | Me | N(CH ₂) ₄ | toluene | 76 | 91:9 |
| 16 | 2.25 | <i>t</i> -Bu | NMe ₂ | toluene | 40 | 78:22 |
| 17 | 2.25 | <i>t</i> -Bu | NMe ₂ | THF | 34 | 88:12 |

Table 2.1. Ligand Optimization for the Diboration of 1-Octene.^a

a) Reactions were conducted at 0.1 M substrate concentration for 12 h. b) Yield refers to isolated yield of the purified reaction product. c) Enantiomeric ratio determined on the derived acetonide by chromatography with a chiral stationary phase.

Upon joining the project, it was reasoned that a ligand with steric bulk in between R = Et [(R,R)-2.10] and R = t-Bu [(R,R)-2.20] might provide enhanced enantioinduction. Thus, upon employment of the 3,5-diisopropylphenyl-substituted ligand (R,R)-2.26 in place of the previously optimal ligand (R,R)-2.10, comparable enantioselectivity and

yield were observed for the diboration/oxidation of 1-octene (Table 2.2). More significantly, this ligand provided noticeable improvement in enantioselectivity in the diboration/oxidation of styrene when compared to (R,R)-2.10. While the newly tested ligand did not provide dramatically improved results, the enantioselectivities were *consistently* higher when compared to those obtained with (R,R)-2.10. Subsequent studies revealed that, at lower Pt/ligand loadings and lower Pt-ligand ratios, (R,R)-2.26 provided reproducibly high selectivity whereas (R,R)-2.10 provided lower and more variable results (i.e., with 1 mol% Pt(dba)₃ and 1.2 mol% (R,R)-2.10, reaction with 1-octene occurs in 72-90% *ee*; *vide infra*). Although the origin of variability is unknown, (R,R)-2.26 was reliable and consistent, and was therefore employed for the remainder of the study.

Table 2.2. Comparison of (R,R)-2.10 and (R,R)-2.26 in the Diboration/Oxidation of 1-

Octene and Styrene.

| R' | 3% 6% (F B ₂ (pin); TH <i>then</i> I | Pt(dba) ₃ R,R)-Ligand 2 (1.05 equiv.) F, 60 °C; NaOH/H ₂ O ₂ | OH R'OH | Me ∖ Me´ (<i>R,R</i>)- | Ar Ar O O O O O O O O O O O O O O O O O | |
|-------|---|--|-----------------|--------------------------------|---|-----------------|
| entry | ligand | R | R' | solvent | yield (%) ^b | er ^c |
| 1 | 2.10 | Et | <i>n</i> -hexyl | toluene | 84 | 96:4 |
| 2 | 2.10 | Et | <i>n</i> -hexyl | THF | 83 | 96:4 |
| 3 | 2.26 | <i>i</i> -Pr | <i>n</i> -hexyl | toluene | 84 | 97:3 |
| 4 | 2.26 | <i>i</i> -Pr | <i>n</i> -hexyl | THF | 83 | 97:3 |
| 5 | 2.10 | Et | Ph | THF | 84 | 93:7 |
| 6 | 2.26 | <i>i</i> -Pr | Ph | THF | 82 | 95:5 |

a) Reactions were conducted at 0.1 M substrate concentration for 12 h. b) Yield refers to isolated yield of the purified reaction product. c) Enantiomeric ratio determined on the derived acetonide by chromatography with a chiral stationary phase.

In order to enhance the utility of the method, improvements were made on the synthesis of (R,R)-2.26. Upon addition of four equivalents of Grignard 2.28 to 2.27, (R,R)-TADDOL 2.29 was synthesized in high efficiency and with clean conversion to the desired product (Scheme 2.14). In order to separate the product from a problematic unknown impurity, isolation of 2.29 and other TADDOL derivatives was typically achieved utilizing a tedious silica gel purification.^{15,16} Furthermore, inefficient separation resulted in low yields or necessitated multiple purifications, limiting the production of ligands on a large scale. Instead, it was found that purification by recrystallization in

methanol allowed for a reliable and rapid isolation of (R,R)-2.26 in high yield and excellent purity on a decagram scale. Due to these efforts, both (R,R)- and (S,S)-2.26 are now available for purchase from Strem Chemicals (Order numbers: 15-1513 and 15-1514, respectively).



Scheme 2.14. Optimization of Ligand Synthesis for Large-Scale Production

2.3.2. Optimization of Pt(0) Source, Catalyst Loading, and Catalyst Activation. Historically, Pt(0) sources are almost always employed as precursors for Pt-catalyzed diboration. Identification of an easily accessible and stable Pt(0) precursor is imperative if Pt-catalyzed asymmetric diboration is to be used routinely. In terms of practicality, dibenzylideneacetone-based Pt(0) complexes are readily accessed in a simple, moistureinsensitive and drybox-free one-pot synthesis from dba and K₂PtCl₄.²³ The resulting complexes are also thermally stable and are insensitive to air and moisture. While

²³ (a) Lewis, L. N.; Krafft, T. A.; Huffman, J. C. Inorg. Chem. 1992, 31, 3555. (b) Maitlis, P. M.; Moseley, K. Chem. Commun. 1971, 982. (c) Moseley, K. Maitlis, P. M. J. Chem. Soc. Chem. Commun. 1974, 169.

 $Pt(dba)_3$ can be isolated via simple washing of the solid precipitate from the resulting reaction mixture, $Pt_2(dba)_3$ requires recrystallization from THF/methanol. Norbornenebased Pt(0) complexes such as $Pt(nbe)_3$ also efficiently catalyze asymmetric diboration; however, synthesis of $Pt(nbe)_3$ is a two-step process involving stoichiometric amounts of Li(0) under air- and moisture-free conditions.²⁴

With 1-tetradecene as a probe substrate, various Pt(0) precursors were compared for the Pt-catalyzed enantioselective diboration.²⁵ Reaction rates were analyzed by reaction calorimetry under standard reaction conditions with (*R*,*R*)-2.26 (Figure 2.1). The results suggest that the nature of the precatalyst has little effect on the reactivity and selectivity, with $Pt(dba)_3$, $Pt_2(dba)_3$, and $Pt(nbe)_3$ all displaying similar levels of efficacy. Interestingly, all three complexes provide complete conversion at 60 °C with 1.0 M alkene concentration in just 3 hours, suggesting that catalyst loading and reaction times could be improved. Overall, $Pt(dba)_3$ was chosen as the optimal precatalyst since it is the most conveniently prepared out of the three. Additionally, $Pt(dba)_3$ is now commercially available from Strem Chemicals (Product number: 78-1360).

²⁴ Crascall, L. E.; Spencer, J. L.; Doyle, R. A.; Angelici, R. J. *Olefin Complexes of Platinum*, in *Inorganic Synthesis: Reagents for Transition Metal Complex and Organometallic Syntheses*; Vol. 28; Angelici, R. J., ed.; John Wiley & Sons, Inc.: Hoboken, NJ, USA, 1990, p 127.

²⁵ Employment of PtCl₂ with (*R*,*R*)-2.26 in the diboration of 1-tetradecene provided the corresponding diol in 38% y and 38% *ee*.

Figure 2.1. Comparison of Pt(0) Precatalysts in the Pt-Catalyzed Diboration of 1-Tetradecene



Reaction rates with $Pt(nbe)_3$, $Pt_2(dba)_3$, and $Pt(dba)_3$. Reactions employed 1 mol% Pt, 1.2 mol% (*R*,*R*)-2.26 and 1.2 equiv. $B_2(pin)_2$. Initial [tetradecene] = 1.0 M.

Early into the reaction optimization, it was determined that reaction concentration could be increased significantly. As depicted in Table 2.3, an increase in initial olefin concentration from 0.1 M to 2.0 M did not noticeably affect isolated yield or enantioselectivity. Nonetheless, an alkene concentration of 1.0 M was selected as the optimal condition due to poor solubility of the diboron reagent before and during catalyst pre-complexation.

| | | | | [olefin] (M) | Yield(%) | e.r. |
|-----------------|--|--|-------------------------------|--------------|----------|------|
| | | 3% Pt(dba)₃ | | 0.10 | 83 | 94:6 |
| <i>n</i> -hexyl | + B ₂ pin ₂ (1.05 equiv.) | 6% (R , R)-2.10 THF, 60 °C then NaOH/H ₂ O ₂ | OH <i>n</i> -hexyl 2.18 | 0.30 | 84 | 95:5 |
| | | | | 0.75 | 90 | 95:5 |
| | | | | 1.0 | 90 | 95:5 |
| | | | | 1.5 | 86 | 94:6 |
| | | | | 2.0 | 83 | 94:6 |

Table 2.3. Preliminary Optimization of Substrate Concentration

With the optimal Pt(0) precatalyst and a preliminary concentration screen in hand, efforts were focused on lowering catalyst loading and ligand-metal ratio (Table 2.4). Improving upon the initially reported conditions, catalyst loading could be decreased from 3 mol% to 0.5 mol% without significant effect on enantioselectivity and yield (entry 1 vs. entry 2). Lowering the catalyst loading even further to 0.2 mol% resulted in diminished yield, although enantioselectivity remained unaffected (entry 3). Upon further examination, ligand-metal ratio could be decreased from 2:1 to 1:1 with minimal loss of enantioinduction, although yield begins to suffer slightly (entries 4-7). When the ligand-metal ratio is less than 1:1, a drop in enantioselectivity observed—likely the result of competitive background diboration by a phosphonite-free Pt complex (entries 8 and 9). Interestingly, a decrease in yield is also observed when the ligand-metal ratio is below 1:1. Analysis of the crude reaction mixture revealed significant byproduct formation related to competing β -hydride elimination and olefin isomerization pathways (i.e. internal alkenes). Considering that 1 mol% of a 1.2:1 ligand-Pt complex resulted in consistently high yield and selectivity, these conditions were adopted for further studies (entry 6). Notably, minor oxidation of the ligand batch is common during the course of ligand synthesis. Thus, a 1.2:1 ligand-metal ratio ensures that enough unoxidized ligand is available in order to prevent background phophonite-free Pt-catalyzed diboration.

| <i>n</i> -hexyl | 1% 1.2% B ₂ (pin) ₂ THF <i>then</i> N | Pt(dba) ₃ (<i>R</i>,<i>R</i>)-2.26 (1.05 equiv.) ⁷, 60 °C; aOH/H₂O₂ | OH n-hexyl OH 2.18 | Me Me Ar = | Ar Ar O O Ar Ar = 3,5-di <i>i</i> propylp (<i>R</i>,<i>R</i>)-2.26 | '−Ph henyl |
|-----------------|---|---|--------------------------|------------------|--|---------------|
| entry | Pt(dba) ₃ (mol %) | (<i>R</i>,<i>R</i>)-2.26 (mol %) | [octene] (M) | time (h) | yield (%) | er |
| 1 | 3.0 | 6.0 | 0.1 | 3 | 89 | 97:3 |
| 2 | 0.5 | 1.0 | 1.0 | 11 | 88 | 96:4 |
| 3 | 0.2 | 0.4 | 1.0 | 28 | 60 | 96:4 |
| 4 | 3.0 | 3.6 | 0.1 | 1 | 88 | 98:2 |
| 5 | 3.0 | 3.0 | 0.1 | 3 | 75 | 86:14 |
| 6 | 1.0 | 1.2 | 1.0 | 3 | 82 | 97:3 |
| 7 | 1.0 | 1.0 | 1.0 | 3 | 66 | 94:6 |
| 8 | 1.0 | 0.75 | 1.0 | 3 | 39 | 80:20 |
| 9 | 1.0 | 0.5 | 1.0 | 3 | 30 | 64:36 |

Table 2.4. Optimization of Catalyst Loading and Ligand-Metal Ratio

Following optimization of reaction conditions, ³¹P and ¹H NMR experiments were performed in order to provide a better understanding how the catalyst was activated. In 1997, Pringle reported that addition of phosphites to $Pt(nbe)_3$ resulted in a rapid displacement of the norbornene ligand at room temperature.²⁶ For comparison, addition of (*R*,*R*)-2.10 or (*R*,*R*)-2.26 to $Pt(dba)_3$ at room temperature does not result in a

²⁶ Cobley, C. J.; Pringle, P. G. Inorg. Chim. Acta. 1997, 265, 107.

substantial change in the ³¹P NMR after one hour, suggesting that dba is still bound to the metal center.²⁷ In the procedure described above, catalyst activation is required before addition of substrate. In the activation step, 1 mol% Pt(dba)₃ and 1.2 mol% of the phosphonite ligand are stirred in the presence of 1.05 equivalents of $B_2(pin)_2$ at 80 °C for 20-30 minutes. Without this pre-complexation step, diminished yields and reduced enantiomeric ratios are observed. As noted above, without formation of the proper chiral Pt-ligand complex for asymmetric alkene diboration, olefin isomerization and hydroboration byproducts are observed in addition to generation of racemic product resulting from background diboration. To simulate catalyst activation chemistry, a similar "activation" reaction was analyzed by ¹H NMR in d_8 -THF. Reaction of Pt(dba)₃ with 1.2 equivalents of (R,R)-2.26 and excess B₂(pin)₂ provided >95% conversion to 2.30 after 30 minutes (Scheme 2.15). Importantly, observation of the 1,4-diboration product is consistent with reports by Marder on the conjugate borylation of α,β -unsaturated esters and ketones.²⁸ Overall, this finding is significant since it is expected that **2.30** would bind to Pt(0) with less efficiency when compared to dba.²⁹ Thus, conjugate borylation

²⁷ Upon complexation of phosphonite-based ligands with Pt, a color change from purple to yellow is typically observed. However, no color change was observed upon mixing $Pt(dba)_3$ and (R,R)-2.10 or (R,R)-2.26 at room temperature.

 ²⁸ (a) Lawson, Y. G.; Lesley, M. J. G.; Marder, T. B.; Norman, N. C.; Rice, C. R. *Chem. Commun.* 1997, 2051. (b) Bell, N. J.; Co, A. J.; Cameron, N. R.; Evans, J. S. O.; Marder, T. B.; Duin, M. A.; Elsevier, C. J.; Bauscherel, X.; Tulloch, A. A. D.; Tooze, R. P. *Chem. Commun.* 2004, 1854.

²⁹ (a) Amatore, C.; Jutland, A.; Khalil, F.; M'Barki, M. A.; Mottier, L. Organometallics 1993, *12*, 3168. (b) Amatore, C.; Broeker, G.; Jutland, A.; Khalil, F. J. Am. Chem. Soc. 1997, *119*, 5176. (c) Amatore, C.; Jutland, A. Coord. Chem. Rev. 1998, *178-180*, 511. (d) Stahl, S. S.; Thorman, J. L.; de Silba, N.; Guzei, I. A.; Clark, R. W. J. Am. Chem. Soc. 2002, *125*, 12. (e) Amatore, C.; Carre, E.; Jutland, A.; Medjour, Y. Organometallics 2002, *21*, 4540. (f) Popp, B. V.; Thorman, J. L.; Morales, C. M.; Landis, C. R.; Stahl, S. S. J. Am. Chem. Soc. 2004, *126*, 14832. (g) Fairlamb, I. J. S.; Kapdi, A. R.; Lee, A. F.; Org. Lett. 2004, *6*, 4435. (h) Mace, Y.; Kapdi, A. R.; Fairlamb, J. S.; Jutland, A. Organometallics 2006, *25*, 1795. (i) Fairlamb, I. J. S. Org. Biomol. Chem. 2008, *6*, 3645. (j) Buchner, M. R.; Belchars, B.; Wahl, B.; Ruhland, K. Organometallics 2013, *32*, 1643.

provides a reasonable mechanism for removal of dba in order to allow for coordination of a phosphonite ligand and generation of the active chiral catalyst.

Scheme 2.15. Catalyst Activation Experiment

Analysis of the reaction mixture from Scheme 2.14 by ³¹P NMR reveals the formation of a new phosphorous-bound compound with broad resonances and coupling to platinum: ³¹P{¹H} NMR (THF) δ 200.0 ppm (¹*J*_{P-Pt} = 1980 Hz); (*R*,*R*)-2.26 δ = 158.1 ppm, (s). The observed broadening of the ligand resonance is consistent with the ligand being bound to a Pt-boryl complex. Coupling between ³¹P and the boron quadrupole in metal-boryl complexes has been reported by many to result in observable broadening of signals.³⁰ Importantly, the fact that a 1.2:1.0 ligand: metal ratio was used and that free unbound ligand is still observed suggests generation of a monoligated Pt-bis(boryl) complex [LPt(B(pin))₂]. Upon addition of 1-tetradecene to the reaction mixture at room temperature, the resonance at 200.0 ppm disappears and generation of a new Pt-boryl complex with broadened ³¹P resonances is observed: ³¹P{¹H} NMR (THF) δ 152.3 ppm (¹*J*_{P-Pt} = 2715 Hz).

³⁰ (a) Ishiyama, T.; Matsuda, N.; Miyaura, N.; Suzuki, A. J. Am. Chem. Soc. **1993**, *115*, 11018. (b) Iverson, C. N.; Smith, M. R. J. Am. Chem. Soc. **1995**, *117*, 4403. (c) Sagawa, T.; Asano, Y.; Ozawa, F. Organometallics **2002**, *21*, 5879. (d) Braunschweig, H.; Leech, R.; Rais, D.; Radacki, K.; Uttinger, K. Organometallics **2008**, *27*, 418.

2.3.3. Drybox-Free Procedure and Oxidation. Of high interest was the possibility of performing Pt-catalyzed diboration without the use of a drybox. Purified TADDOLderived phosphonite ligands are sufficiently stable in air and moisture for extended periods of time. To highlight this fact, pure crystalline (R,R)-2.26 was exposed to air for over a month, at which point <3% oxidation was observed by ¹H and ³¹P NMR. After about 3 months, only 5% oxidation of the ligand was detected, without further degradation or byproducts being observed. Of importance, dissolving (R,R)-2.26 in diethyl ether for 1 hour resulted in 12% oxidation, suggesting that the ligand is prone to rapid oxidation when in solution. Likewise, $Pt(dba)_3$ and $B_2(pin)_2$ are also sufficiently stable to air and moisture. Thus, it was reasoned that the Pt-catalyzed diboration/oxidation procedure could be performed without the use of a drybox. To test this, $Pt(dba)_3$, (*R*,*R*)-2.26, and $B_2(pin)_2$ were weighed into vial that was open to the atmosphere. The cap was then sealed with a septum cap and purged with N₂, followed by addition of dry THF. After heating the reaction mixture to 80 °C for 30 minutes, the vial was cooled to room temperature and charged with alkene. The vial was purged once more with N₂ and allowed to stir at room temperature for 3 hours. As shown in Scheme 2.15, comparable yields and enantiomeric ratios are obtained for drybox and drybox-free diboration procedures after oxidation (Scheme 2.16).³¹

³¹ Employing 1-hexene with 3 mol% (R,R)-2.10 and 6 mol% Pt(dba)₃ for 12 h at 60 °C under air resulted in 58% yield and 82:18 er.



Scheme 2.16. Comparison of Drybox and Drybox-Free Diboration/Oxidation Procedures

After complete optimization of diboration/oxidation conditions, minimal byproduct formation and clean NMR spectra brought into question the discrepancy in isolated yields. Analysis of crude diboration reaction mixtures showed <3% reaction byproducts; however, the isolated yields were typically between 80 and 90%. To determine the fate of the remaining mass balance, reactions were examined in more detail. As depicted in Scheme 2.16, 1,2-bis(boronate) **2.32** could be isolated with high purity in 95% yield (eq 1).³² However, upon subjection of **2.32** to basic oxidation, 1,2-diol **2.31** is obtained in 87% yield. While the isolated yield for this transformation is higher than the yield of a single-pot diboration/oxidation procedure (82% yield, Scheme 2.17, eq 2), it could be concluded that oxidation is not a quantitative process. Of note, performing neutral oxidation and oxidation with NaBO₃ did not improve isolated yields. Although some loss in yield can be attributed to oxidative workup, a two-step single-pot oxidation/diboration procedure was still adopted to survey substrate scope due to ease of isolation and characterization of the derived 1,2-diols.

³² Rapid silica gel chromatography was performed using a short column. Longer purifications led to degradation of the 1,2-bis(boronate) **2.32** on silica gel and loss of product.



Scheme 2.17. Isolated Yield for Diboration and Yield Upon Oxidative Workup.

2.4 Scope of the Pt-Catalyzed Enantioselective Diboration²²

2.4.1. Aliphatic Alkenes. With optimal conditions fully established, the scope of Pt-catalyzed enantioselective diboration with aliphatic alkenes was examined (Table 2.5). Overall, high enantioselectivities were obtained with linear alkenes as well as with α - and β -branched substrates (entries 1-4). Notably, sterically encumbered olefins suffer from lower reactivity, but moderate yields can still be obtained with increased catalyst loading (3 mol% Pt and 3.6 mol% (*R*,*R*)-2.26, entry 5). Functional group tolerance was also tested. For example, oxygenation at the homoallylic position did not significantly affect reactivity and selectivity compared to unfunctionalized alkenes (entry 8). TBDPS-protected allyl alcohol also provided high yields of the desired 1,2-diol, however elevated catalyst loading was required and slightly diminished enantioselectivity was observed (entry 9). Of note, carbonyls are known to participate in some diboration reactions, and have the ability to coordinate to metal centers.³³ To our delight, ketone-, ester-, and

³³ (a) Laitar, D. S.; Tsui, E. Y.; Sadighi, J. P. J. Am. Chem. Soc. **2006**, 128, 11036. (b) Zhao, H.; Dang, L.; Marder, T. B.; Lin, Z. J. Am. Chem. Soc. **2008**, 130, 5586. (c) McIntosh, M. L.; Moore, C. M.; Clark, T. B. Org. Lett. **2010**, 12, 1996.

amide-containing substrates were all well tolerated, providing high yields and excellent enantiomeric ratios (entries 10-12).

| | 1% Pt(dba)₃ 1.2% (R,R)-2.26 B₂(pin)₂ (1.05 equiv. | .) <u>о</u> н | |
|-----------------|---|------------------------|-----------------|
| | R [™] THF, 60 °C, 3 h <i>then</i> NaOH, H ₂ O ₂ | R | |
| entry | substrate | yield (%) ^b | er ^c |
| 1 | <i>n</i> -hexyl | 81 | 96:4 |
| 2 | <i>n</i> -dodecyl | 82 | 96:4 |
| 3 | Me Me | 78 | 98:2 |
| 4 | Cy | 81 | 96:4 |
| 5 ^d | t-Bu | 53 | 93:7 |
| 6 | Ph | 85 | 97:3 |
| 7 | Ph | 78 | 96:4 |
| 8 | TBDPSO | 91 | 95:5 |
| 9 ^e | TBDPSO | 85 | 90:10 |
| 10 | Me | 53 | 94:6 |
| 11 ^e | MeO | 78 | 96:4 |
| 12 ^e | Et ₂ N | 73 | 96:4 |

Table 2.5. Diboration of Aliphatic 1-Alkenes with Pt(dba)₃ and (*R*,*R*)-2.26.^a

a) Reactions were conducted at 1.0 M concentration for 3 h. b) Refers to isolated yield of the purified reaction product. (c) Enantiomeric ratio determined on the derived acetonide by chomatography with a chiral stationary phase. (d) 3.0% Pt(dba)₃ and 3.6% (*R*,*R*)-2.26 was employed for 12 h. e) Oxidation with H_2O_2 at pH = 7.

As noted in Chapter 1, the Sharpless asymmetric dihydroxylation (SAD) is one of the most widely utilized asymmetric transformations for terminal alkenes. More electron-rich substrates are more activated for osmium-catalyzed dihydroxylations, and therefore more substituted olefins typically react with faster rates compared to less substituted olefins. Conversely, Pt-catalyzed diboration is highly sensitive to sterics and substitution on the olefin. For example, subjection of 1,5-diene **2.33** to Pt-catalyzed asymmetric diboration results in high regioselectivity for the least hindered, monosubstituted olefin (Scheme 2.18). After oxidation, 1,2-diol **2.34** is obtained in high yield and enantioselectivity with no detection of the other regiosomer by ¹H and ¹³C NMR (eq 1). In contrast, subjecting diene **2.33** to SAD conditions furnishes a 5:1 regioisomeric mixture of diols **2.35** and **2.34** in moderate yield (eq 2).³⁴

Scheme 2.18. Comparison of Pt-Catalyzed Alkene Diboration/Oxidation to SAD.



³⁴ Xu, D.; Crispino, G. A.; Sharpless, K. B. J. Am. Chem. Soc. 1992, 114, 7570.

2.4.2. Aromatic Alkenes. As described in Chapter 1, in the context of transitionmetal catalysis, π -benzyl stabilization can alter regiochemistry of olefin migratory insertion when comparing aromatic alkenes to aliphatic alkenes.³⁵ For this reason, it is common for a transition-metal catalyzed transformation to exhibit vastly different levels of enantioinduction for these substrate classes. To verify whether a deviating reaction manifold exists with Pt-catalyzed diboration, various styrene derivatives were examined and results are provided in Table 2.6. Utilizing the same conditions employed for aliphatic terminal alkenes, ortho, meta, and para-substituted styrenes undergo diboration with high efficiency (entries 2-4). Notably, electron-rich styrenes generate product in high enantiomeric ratios (entry 5), while electron-deficient styrenes reacted with slightly diminished enantiocontrol and required elevated catalyst loading (entries 7 and 8). Nonetheless, a similarly high level of enantioinduction with identical facial selectivity implies that olefin insertion modes are analogous for both styrenes and aliphatic substrates. Unfortunately, o-methoxy styrene and vinyl pyridines provided low yields of the desired product or inconsistent results, suggesting that polar functionality in close proximity to the metal center could inhibit catalyst turnover and diminish facial differentiation (entries 9-11).

³⁵ (a) Becker, Y.; Stille, J. K. J. Am. Chem. Soc. **1978**, 100, 845. (b) Hölscher, M.; Franciò, G.; Leitner, W. Organometallics **2004**, 23, 5606. (c) Urkalan, K. B.; Sigman, M. S. Angew. Chem. Int. Ed. **2009**, 48, 3146. (d) Werner, E. W.; Urkalan, K. B.; Sigman, M. S. Org. Lett. **2010**, 12, 2848. (e) Edwards, D. R.; Hleba, Y. B.; Lata, C. J.; Calhoun, L. A.; Crudden, C. M. Angew. Chem. Int. Ed. **2007**, 46, 7799.



Table 2.6. Diboration of Aromatic Alkenes with Pt(dba)₃ and (R,R)-2.26.^a

a) Reactions were conducted at 1.0 M concentration for 3 h. b) Refers to isolated yield of the purified reaction product. c) Enantiomeric ratio determined on the derived acetonide by chomatography with a chiral stationary phase. d) 3.0% Pt(dba)₃ and 3.6% (*R*,*R*)-2.26 was employed for 12 h.

2.4.3. Chiral Substrates. Considering drug targets and late-stage intermediates in natural product synthesis typically contain multiple stereogenic centers, the effect of substrate chirality on asymmetric Pt-catalyzed diboration is important to investigate.

Thus, alkenes containing α - and β -hydrocarbon and oxygenated stereocenters were employed under standard conditions for the Pt-catalyzed diboration with both enantiomers of TADDOL-derived ligand (R,R)-2.26 (Table 2.7). A chiral olefin substrate bearing a β -methyl stereocenter provided the desired 1,2-diols in high diastereoselectivities and good yields regardless of the enantiomer of ligand employed, indicating high catalyst control (entries 1 and 2). With α -methyl stereocenters, double diastereodifferentiation is observed depending on the combination of the ligand and the substrate; however, high levels of diastereoselectivity are still achieved in the mismatched scenario (12:1 dr versus 20:1 dr, entries 3 and 4). A similar match/mismatched scenario is observed with α -oxygenated stereocenters, which provided markedly low diastereoselectivity in combination with (R,R)-2.26 (1.4:1 dr, entry 5), but excellent diastereoselectivity with (S,S)-2.26 (20:1 dr, entry 6). In contrast, high diastereometric ratios are observed with β -oxygenated stereocenters, regardless of the absolute configuration of the ligand (entries 7 and 8). Importantly, other groups have noted similarly high levels of diastereoselectivity when utilizing Pt-catalyzed diboration on enantioenriched intermediates during their total synthesis efforts.¹⁷



Table 2.7. Diboration of Chiral Substrates with Pt(dba)₃ and (R,R)-2.26.^a

a) Unless otherwise noted, reactions were conducted at 1.0 M substrates concentration for 3 h at 60 °C. Yield refers to isolated yield of the purified reaction product. Diastereomeric ratio determined by ¹H NMR analysis. b) 3.0% Pt(dba)₃ and 3.6 mol% (*R*,*R*)- or (*S*,*S*)-2.26 was employed at 60 °C for 12 h.

2.4.4. Unreactive and Problematic Substrates. Despite elevated reaction temperatures and increased catalyst loadings, 1,2-disubstituted alkenes provided no observable reaction (Figure 2.2). For example, both *cis*- and *trans*- internal alkenes, as well as more strained cyclic olefins and aromatic variants, provided no desired product (2.36-2.40). Aliphatic 1,1-disubstituted olefin 2.41 did not provide desired product under any circumstances. Interestingly, however, α -methylstyrene 2.42 provided low yields of the desired product with employment of chiral TADDOL-derived ligand (*R*,*R*)-2.8 at increased catalyst loadings, albeit in low enantiomeric ratios and as a mixure with hydroboration and β -hydride elimination byproducts. Overall, it is likely that more sterically encumbered disubstituted alkenes lower the rate of olefin binding and/or insertion, and limit catalyst turnover (*vide infra*). These observations are in line with Miyaura's findings during development of a racemic Pt(dba)₂ catalyzed diboration of terminal alkenes with B₂(pin)₂ (Scheme 2.4, eq 1).⁸



Figure 2.2. Disubstituted Alkenes in Pt-Catalyzed Asymmetric Diboration

In addition to more substituted alkenes providing no or low reactivity, the presence of an alkyne was found to inhibit the reaction of terminal alkenes (Scheme 2.19). For example, employment of enyne **2.43** provided no desired diboration product, with only starting material observed at the end of the reaction (eq 1). A 1:1 mixture of 1-tetradecene and 1-tetradecyne also provided no reaction (eq 2). It is possible that the more π -acidic alkyne binds tightly to the Pt center and inhibits oxidative addition of the diboron and/or alkene binding. Also of note, employment of an unprotected alcohol **2.44** resulted in no observable diboration/oxidation product, and instead only hydroboration occured to furnish terminal alcohol **2.45** (eq 3).



Scheme 2.19. Problematic Functionalities for Pt-Catalyzed Asymmetric Diboration

2.5 Mechanistic Analysis of the Pt-Catalyzed Enantioselective Diboration²²

2.5.1. Reaction Progress Kinetic Analysis. A more thorough understanding of the reaction mechanism can unveil useful modifications to the system if it becomes necessary, and will provide a better understanding and direction for those looking to utilize Pt-catalyzed diboration in the future. Note that mechanistic analysis was performed based on the assumption that the catalytic cycle proceeds through the following well-precedented steps: (1) Insertion of a Pt(0) complex into the B-B bond of $B_2(pin)_{2,3}^{36,4,5a,30b}$ (2) Insertion of the olefin into a Pt-B bond, and (3) reductive elimination

³⁶ (a) Ishiyama, T.; Matsuda, N.; Murata, M.; Ozawa, F.; Suzuki, A.; Miyaura, N. *Organometallics* **1996**, *15*, 713. (b) Clegg, W.; Lawlor, F. J.; Marder, T. B.; Nguyen, P.; Norman, N. C.; Orpen, A. G.; Quayle, M. J.; Rice, C. R.; Robins, E. G.; Scott, A. J.; Souza, F. E. S.; Stringer, G.; Whittell, G. R. *J. Organomet. Chem.* **1998**, *550*, 183.

to deliver 1,2-diboron product and regenerate the active catalytic Pt-species.^{37,5b} To determine how the reaction rate is affected by reaction conditions and reagent concentrations, reaction progress kinetic analysis (RPKA) was performed on the diboration of 1-tetradecene. Experiments were monitored by reaction calorimetry, which allows for a non-intrusive and highly accurate method for determining reaction rate over the course of an entire reaction.³⁸ Although reaction calorimetry does not provide structural information during the course of the experiment, reaction heat output at any given time during the reaction is directly proportional to reaction rate at that point. Importantly, under the optimized conditions, Pt-catalyzed asymmetric diboration is a highly efficient reaction with minimal byproduct formation (<5% of the total conversion), thus ruling out the possibility of excess heat being generated from non-innocent side reactions.

As represented by the heat flow versus time graph in Figure 2.3, diboration of 1tetradecene with $B_2(pin)_2$ under standard conditions ([alkene] = 1.0 M, [$B_2(pin)_2$]= 1.05 M, 1 mol% Pt, 1.2 mol% (**R**,**R**)-2.26) reached full conversion within 3 hours.³⁹ As displayed in Figure 2.3A, plotting reaction rate versus [alkene] indicates that, although not exactly zero order (i.e. fractional order), the reaction rate does not change significantly over the first 60-80% of the reaction. Furthermore, increasing the concentration of both diboron and alkene to 1.5 M does not noticeably affect the rate of reaction when compared to standard conditions at any point in the reaction. For example,

³⁷ Thomas, R. L.; Souza, F. E. S.; Marder, T. B. J. Chem. Soc., Dalton Trans. 2001, 1650.

³⁸ For a review on reaction progress kinetic analysis with reaction calorimetry, see: Blackmond, D. G. *Angew. Chem. Int. Ed.* **2005**, *44*, 4302.

³⁹ GC analysis with dodecane as an internal standard verified this reaction rate.

under both of the experiments plotted in Figure 2.3A, reaction rates are nearly identical for all concentration values at or below 1.0 M, suggesting that catalyst decomposition and product inhibition do not occur over the course of the reaction.



Figure 2.3. RPKA of the Catalytic Enantioselective Diboration of 1-Tetradecene.

(A) Absolute reaction rate versus [substrates]. [Alkene] = $[B_2(pin)_2]$ for both 1.0 M (red) and 1.5 M (blue) reactions with 1.0 mol% Pt(dba)₃ and 1.2 mol% (*R*,*R*)-**2.26**. (B) Absolute reaction rate versus [substrates] for reactions with 1.0 mol% Pt(dba)₃ and 1.2 mol% (*R*,*R*)-**2.26** (red), and with 2.0 mol% Pt(dba)₃ and 2.4 mol% (*R*,*R*)-**2.26** (blue). (C) Heat flow versus time of normal diboration reaction conditions (red) and with 50% excess $B_2(pin)_2$ (blue). (D) Heat flow versus time of normal diboration reaction conditions (red), with 25% excess alkene (green), and with 0.7 M alkene (blue).

In order to determine the rate dependency on catalyst concentration, catalyst loading was doubled when compared to standard conditions (2 mol% Pt, 2.4 mol% (**R**,**R**)-2.26 versus 1 mol% Pt, 1.2 mol% (**R**,**R**)-2.26), leading to a 2-fold increase in the reaction rate (Figure 2.3B). Such a trend indicates that the reaction is first-order in catalyst concentration. A heat flow versus time profile for reaction with 50% excess $B_2(pin)_2$ suggests a slight positive order dependency on diboron concentration (Figure 2.3C). Note that the reaction is not first order in diboron, but instead fractional order, considering that an increase in diboron concentration by 50% does not result in a 50% enhancement in reaction rate. Heat flow versus time profiles also indicate that increased alkene concentration does not affect reaction rate at early stages of the reaction, but results in an increase in heat output towards the end of the reaction (Figure 2.3D). This observation is likely due to isomerization of the terminal alkene to internal alkenes once the diboron starting material is mostly consumed, which is an exothermic process. Analysis of the crude ¹H NMR indicates that both desired product and 2-tetradecene are A separate experiment indicates that after consumption of $B_2(pin)_2$, present. isomerization of 1-tetradecene to 2-tetradecene was found to occur within 3 hours. A decrease of initial 1-tetradecene concentration to 0.7 M results in an overall heat output of 70% of the heat output for standard reaction conditions, with the initial rate being Important to note, reaction rate quickly drops off at lower nearly identical. concentrations of both alkene and diboron, indicating that saturation kinetics is operative for the majority of the reaction, but rate eventually becomes dependent on limiting reagent towards the end of the reaction.

Overall, the data suggest that under standard reaction conditions, Pt-catalyzed diboration with $Pt(dba)_3$ and (\mathbf{R},\mathbf{R}) -2.26 is close to zero-order in both substrates and first-order in Pt. Thus, the turnover-limiting step must be one which involves an intermediate Pt-complex that is pre-loaded with alkene and diboron. Based on studies from other groups on the elementary mechanistic steps of Pt-catalyzed diboration, as well as the observations obtained from kinetic analysis, a plausible mechanism is provided in

Scheme 2.20. Diboration of $Pt(dba)_3$ in the presence of (\mathbf{R},\mathbf{R}) -2.26 during precomplexation allows for generation of active catalyst **A**. Oxidative addition of $B_2(pin)_2$ to an $L_nPt(0)$ complex to **B** is fast, followed by a rapid and (likely) reversible olefin binding to generate intermediate **C** (i.e. the olefin-bound complex **C** is strongly favored over **B**). Subsequently, based on the zero-order dependency of both substrates, the turnover-limiting step must be (1) migratory insertion to generate intermediate **D** or (2) reductive elimination to generate 1,2-bis(boronate) product and regenerate active catalyst **A** (with migratory insertion being reversible).⁴⁰ Note that it is conceivable for olefin coordination to precede oxidative addition of B₂(pin)₂.

⁴⁰ For examples of β-boryl eliminations: (a) Miyaura, Z.; Suzuki, A. J. Organomet. Chem. 1981, 213, C53.
(b) Marciniec, B.; Pietraszuk, C. Organometallics 1997, 16, 4320. (c) Lam, K. C.; Lin, Z.; Marder, T. B. Organometallics 2007, 26, 3149.





2.5.2. Natural Abundance ¹³C Kinetic Isotope Effects. Despite efforts towards identifying catalytic intermediates and catalyst resting states via NMR spectroscopy, no useful information was obtained. As an alternative, we considered that natural abundance ¹³C kinetic isotope effect (KIE) analysis developed by Singleton might provide insight into whether migratory insertion or reductive elimination is turnover-limiting.⁴¹ For simplicity of ¹³C NMR analysis, allylbenzene was used as a substrate,⁴² and two diborations were performed using standard conditions on a 1.5 g scale. Both reactions

⁴¹ (a) Singleton, D. A.; Thomas, A. A. J. Am. Chem. Soc. **1995**, 117, 9357. (b) Frantz, D. E.; Singleton, D. A.; Snyder, J. P. J. Am. Chem. Soc. **1997**, 119, 3383.

⁴² Initial studies were attempted with 1-tetradecene, but ¹³C NMR analysis was difficult due to similarities in peak resonances.

were stopped prematurely at 81 ± 3 and $83 \pm 3\%$ conversion, and the starting material was recovered. As shown in Scheme 2.21, moderate and observable ${}^{12}C/{}^{13}C$ KIEs were detected at both olefinic carbons of the recovered starting material, while the benzylic and aromatic carbons displayed negligible isotope effects. Such an observation indicates that migratory insertion of the olefin into a Pt-B bond ($C \rightarrow D$, Scheme 2.20) is the first irreversible step in the catalytic cycle and is therefore stereochemistry-determining as well. If migratory insertion were rapid and reversible, reductive elimination would then be turnover-limiting and stereocontrolling, and thus only one of the olefinic carbons would display an observable KIE (the olefinic carbon at which reductive elimination occurs). The size of the ${}^{12}C/{}^{13}C$ KIEs were found to be comparable with those of other processes in which migratory insertion is rate-limiting, including Ziegler-Natta polymerization of 1-hexene.⁴³

⁴³ (a) Landis, C. R.; Rosaaen, K. A.; Udden, J. J. Am. Chem. Soc. **2002**, 124, 12062. See also: (b) Vo, L. K.; Singleton, D. A. Org. Lett. **2004**, *6*, 2469.

Scheme 2.21. Natural Abundance ¹³C KIE Analysis for Pt-Catalyzed Diboration of Allylbenzene.



2.5.3. Insights into Regioselectivity of Olefin Insertion. Considering migratory insertion was found to be turnover-limiting and stereochemistry-determining, discerning the regioselectivity of olefin insertion is essential for development of a stereochemical model. The two possible modes of insertion are presented in Scheme 2.22, the general concept of which was described in further detail in Chapter 1. Upon binding the alkene, olefin insertion could position Pt at the more-hindered internal olefinic carbon $(\mathbf{E} \rightarrow \mathbf{F})$ or at the less-hindered terminal olefinic carbon $(\mathbf{G} \rightarrow \mathbf{H})$. Despite the seemingly unfavorable steric interactions that might arise from a 2,1-insertion mode $(\mathbf{E} \rightarrow \mathbf{F})$, such a pathway can explain two interesting features that exist in Pt-catalyzed alkene diboration: (1) High enantioinduction for terminal aliphatic olefins (a relatively rare class of substrates for

successful asymmetric catalysis) might be a result of the ligand being positioned in closer proximity to the prochiral carbon of the olefin; and (2) Similarly high levels of enantioinduction for aliphatic substrates and those with π -benzyl stabilization capabilities that are biased towards formation of **F** (i.e. styrenes) might be the result of a similar insertion mode. In other words, if 1,2-insertion occurred with aliphatic alkenes, one might expect different selectivities with aromatic alkenes that favor formation of **F**.

Scheme 2.22. Possible Migratory Insertion Modes of a Pt-B Bond into an Alkene.



Important insights were initially obtained when attempting to perform diboration on 1,1-disubstituted alkene 2.47 under standard conditions with (R,R)-2.10 (Scheme 2.23). Although no diboration product was observed, full conversion to a mixture of hydroboration products (2.48 and 2.49) and vinyl boronate 2.50 was observed. Formation of byproduct 2.50 is likely the result of a rare 2,1-migratory insertion in which a tertiary C-Pt bond is formed (intermediate I), followed by a β -hydride elimination. Formation of byproducts 2.48 and 2.49 also suggest that a Pt-H insertion into an alkene can position the Pt at either the terminal carbon (forming intermediate J and generating 2.48 after reductive elimination) or the internal carbon (forming intermediate K and

generating L after chain-walking resulting from a series of β -hydride eliminations and reinsertions). While not conclusive, the fact that byproducts derived from the generation of a more hindered tertiary Pt-C bond are observed upon insertion into 1,1-alkenes suggests that an internal 2,1-insertion mode for Pt-catalyzed diboration of terminal alkenes is plausible. Furthermore, other group 10 metal-catalyzed reactions have been previously reported that undergo similar internal insertion modes.⁴⁴



Scheme 2.23. Attempted Pt-Catalyzed Enantioselective Diboration of 2.47.

⁴⁴ (a) Coapes, R. B.; Souza, F. E. S.; Thomas, R. L.; Hall, J. J.; Marder, T. B. *Chem. Commun.* 2003, 614.
(b) Hada, M.; Tanaka, Y.; Ito, M.; Murukami, M.; Amii, H.; Ito, Y.; Nakatsuji, H. *J. Am. Chem. Soc.* 1994, *116*, 8754.

To provide more conclusive evidence for regioselectivity of olefin insertion, vinyl cyclopropane 2.51 was subjected to conditions for catalytic enantioselective diboration/oxidation (Scheme 2.24). Interestingly, ring-opened 1,5-diol 2.52 was obtained as the exclusive reaction product.⁴⁵ Thus, it is reasonable to conclude that the product is furnished via generation of an internal Pt-C bond $(M \rightarrow N)$, followed by cyclopropane ring opening $(N \rightarrow O)$ and reductive elimination. This finding is consistent with an analogous ring-opening pathway reported by Miyaura during the diboration of methylene cyclopropanes, in which rupture of an α -cyclopropyl organoplatinum complex was observed.⁴⁶ Similar cyclopropane ruptures promoted by adjacent C-M bonds have also been observed in Pd-catalyzed hydrostannation⁴⁷ and Rh-catalyzed hydrosilylation⁴⁸ reactions. Notably, ring-opening did not occur under similar conditions for vinyl boronate diboration (See Chapter 4, Schemes 4.16 and 4.18 compound 4.63), suggesting that the vinyl cyclopropane moiety would be stable under Pt(0)/Pt(II) catalysis if a 1,2insertion were operative.

⁴⁵ Generation of the 1,5-bis(boronate) prior to oxidation was also verified by ¹³C NMR, ¹H NMR, and mass spectroscopy.

⁴⁶ Ishiyama, T.; Momota, S.; Miyaura, N. *Synlett* **1999**, 1790.

⁴⁷ Lautens, M.; Meyer, C.; Lorenz, A. J. Am. Chem. Soc. **1996**, 118, 10676.

⁴⁸ Bessmertnykh, A. G.; Blinov, K. A.; Grishin, Y. K.; Donskaya, N. A.; Tveritinova, E. V.; Yurieva, N. M.; Beletskaya, I. P. *J. Org. Chem.* **1997**, *62*, 6069.



Scheme 2.24. Pt-Catalyzed Diboration of Vinyl Cyclopropane 2.51.

Additional evidence for the 2,1-insertion mode to provide an internal Pt-C bond was provided with density functional theory (DFT) calculations using a simplified ligand structure (i.e. an ethylene glycol-derived methyl phosphonite in place of (\mathbf{R} , \mathbf{R})-2.26) and propene as the substrate. Four possible alkene binding modes exist for the bis(boryl)Pt-propene complex prior to migratory insertion, and are provided in Figure 2.4. For example 2.53 and 2.55 are rotational isomers with the alkene bound to the complex through the *Re* face (eq 1 and 3), while 2.54 and 2.56 are rotational isomers with the alkene bound to the complex through the *Si* face (eq 2 and 4). DFT calculations indicate that all four isomeric complexes are within 1.3 kcal/mol of each other. Further optimization of each transition state conformation reveals that olefin insertion occurs in conjunction with rotation of the boryl ligand, which allows for a pinacol oxygen to coordinate immediately with the Pt center (2.57-2.60). The pinacol oxygen donation to Pt ensures that the metal center remains coordinatively saturated throughout the insertion process, a feature that

has been analogously calculated by Morokuma in the case of ethylene insertion.⁴⁹ Of the four possibilities calculated, it was found that both pathways in which a secondary Pt-C bond is formed ($2.53 \rightarrow 2.57$ and $2.54 \rightarrow 2.58$) are lower in energy than the pathways that lead to terminal Pt-C bond formation ($2.55 \rightarrow 2.59$ and $2.56 \rightarrow 2.60$).

Figure 2.4. Relative Energetics of Migratory Insertion for Bis(boryl)platinumpropene Complexes (Calculations performed at 333K with values in kcal/mol relative to **2.56**).



⁴⁹ Cui, Q.; Musaev, D. G.; Morokuma, K. Organometallics **1997**, *16*, 1355.

Figure 2.5 depicts the two lowest energy pathways and their respective transition state geometries for each regioisomer. It is evident from calculations that olefin insertion leading to an internal Pt-C bond is favored by nearly 2 kcal/mol. While the origin of the preference for regioselectivity of olefin insertion is not entirely clear, it is possible that the larger coefficient of the alkene HOMO exists on the terminal olefinic carbon, which has sufficient overlap with the empty *p*-orbital on boron in the transition state. Similar interactions have been calculated for Pd-catalyzed alkyne silastannation, which is also proposed to proceed via an insertion that generates an internal C-Pd bond.⁵⁰

⁵⁰ (a) Hada, M.; Tanaka, Y.; Ito, M; Murakami, M.; Amii, H.; Ito, Y.; Nakatsuji, H. J. Am. Chem. Soc. **1994**, *116*, 8754. For related studies: (b) Ohmura, T.; Oshima, K.; Taniguchi, H.; Suginome, M. J. Am. Chem. Soc. **2010**, *132*, 12194. (c) Sagawa, T.; Ohtsuki, K.; Ishiyama, T.; Ozawa, F. Organometallics **1998**, *17*, 5630. (d) Sagawa, T.; Sakamoto, Y.; Tanaka, R.; Katayama, H.; Ozawa, F. Organometallics **2003**, *22*, 4433.

Figure 2.5. Energy Profile for the Migratory Insertion of **2.53** and **2.56** to Provide **2.57** and **2.60** with Calculated Transition State Structures



2.5.4. Proposed Catalytic Cycle. With a more thorough understanding of the reaction kinetics and regiochemistry of migratory insertion, we have proposed a detailed catalytic cycle for the Pt-catalyzed asymmetric diboration of terminal alkenes (Scheme 2.25). The active Pt(0)/L* catalyst (**P**) is accessed from Pt(dba)₃ by diboration of dba, which lowers the π -acidity of the precatalyst ligand and allows the chiral ligand to bind to the metal center. Subsequently, oxidative addition of **P** with B₂(pin)₂ to form **Q** is fast,
followed by a rapid and reversible olefin coordination that favors **R**. Next, turnoverlimiting and stereodefining migratory insertion occurs to access **S**, furnishing an internal Pt-C bond and placing the chiral element close to the prochiral carbon of the olefin. Lastly, reductive elimination provides the desired 1,2-bisboronate product **T** and regenerates active catalyst **P**.



Scheme 2.25. Proposed Catalytic Cycle for Pt-Catalyzed Diboration

2.6 Model for Stereoselectivity for Pt-Catalyzed Enantioselective Diboration of Alkenes²²

With convincing data suggesting a 2,1-migratory insertion that is rate-limiting and stereochemistry determining, our focus was geared towards evolving a stereochemical

model for Pt-catalyzed asymmetric diboration. Despite significant time and effort spent towards isolating a crystal of a monoligated Pt-bis(boryl) complex for crystal structure analysis, all attempts failed. A variety of crystallization methods with numerous TADDOL-derived ligands were performed with limited success. Fortunately, treatment of xylyl-TADDOL-derived phenylphosphonite ligand (R,R)-2.8 with PtCl₂ in CDCl₃ provided bis-ligated Pt-complex 2.61 in quantitative yield after stirring at room temperature for 18 hours followed by warming to 40 °C for 2 hours (Scheme 2.26). Crystal structure analysis indicated that two ligands were bound to the Pt center in a *trans* configuration and with similar conformations. While it is evident from ³¹P NMR analysis that the active catalyst for Pt-catalyzed asymmetric diboration is a monoligated Ptbis(boryl) complex (See discussion in section 2.3.2), bis-ligated Pt-complex 2.61 provides information of the steric influence that the aryl moiety on the TADDOLbackbone has on the Pt center. For example, if the orientation of the ligand in complex **2.61** remains consistent with the orientation of the ligand in the monoligated Pt-bis(boryl) intermediate involved in the catalytic cycle, it would be possible to gain useful stereochemical insight.



Scheme 2.26. Preparation of Pt(II)-Ligand Complex 2.61 and X-Ray Crystal Structure.

Figure 2.6A and 2.6B depicts a truncated crystal structure of complex **2.61** with one of the TADDOL-derived phosphonite ligands removed. Assuming that the conformation of the ligand persists upon insertion of Pt into the B-B bond of $B_2(pin)_2$, coordination of a monosubstituted alkene could occur in a fashion depicted in Figure 2.6C. Such an orientation is consistent with observations that insertion provides the internal Pt-C bond, and also provides the experimentally observed enantiomer of product.

Close examination of this proposed binding mode indicates that the alkene substituent is positioned upwards to minimize steric interactions with a TADDOL aryl ring. Indeed, X-ray analysis suggests a pseudo-equatorial aryl ring sits directly below the alkene coordination site, which likely strongly influences olefin facial selectivity. Interestingly, increasing the size of the meta substitutents on the aryl ring would likely serve to rigidify the ligand conformation by preventing bond rotation of the aryl ring, while also increasing the energy difference in olefin binding modes (*Re* face versus *Si* face).

Figure 2.6. Front view (A) and Side View (B) of Complex **2.61** with Ligand Removed and Stereochemical Model in Enantioselective Alkene Diboration (C).



2.7 Conclusion

We have optimized reaction conditions for the Pt-catalyzed enantioselective diboration of terminal alkenes. Catalyst loadings could be reduced to as low as 0.2

mol% Pt(dba)₃ and 0.4 mol% (**R**,**R**)-2.26 without diminishing enantiomeric excess. Importantly, the reaction can be performed with commercially available reagents without the use of a drybox. Furthermore, the scope and limitations of the methodology has been described in depth. Lastly, kinetic experiments and detailed mechanistic analysis indicates that the reaction occurs by a stereochemistry-determining olefin 2,1-insertion the generates an internal C-Pt bond. Although a preliminary stereochemical model has been proposed, future efforts should focus on isolation of important intermediate Pt-complexes involved in the catalytic cycle and more extensive crystal structure analysis. Importantly, this newly optimized method has already found use in tandem diboration/crosscoupling (DCC) sequences,⁵¹ and holds hope of being useful in other tandem diboration/functionalization processes in order to access a variety of synthetically challenging enantioenriched products.

⁵¹ Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. Nature 2014, 505, 386.

2.8. Experimental

2.8.1. General Information.

¹H NMR spectra were measured using a Varian Unity Inova 500 MHz or a Varian Gemini 400 MHz spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CHCl₃: 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) or a Varian Gemini 400 MHz (100 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl₃: 77.00 ppm). ${}^{31}P{}^{1}H{}NMR$ (162 MHz) were recorded on a Varian Unity Inova 500 MHz spectrometer. Chemical shifts are reported for ³¹P NMR spectra using phosphoric acid as an external standard (H_3PO_4 : 0.0 ppm). Infrared (IR) spectra were recorded on a Bruker α -P Spectrometer. Frequencies are reported in wavenumbers (cm⁻¹) as follows: strong (s), broad (br), medium (m), and weak (w). High resolution mass spectrometry (HRMS) was performed at Boston College, Chestnut Hill, MA. Elemental analysis on all platinum pre-catalysts was performed by ICP Optical Emission Spectroscopy.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO₂, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography was performed on 25 μ m silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm), phosphomolybdic acid (PMA), and potassium permanganate (KMnO₄). 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 gas-liquid chromatography (GLC) was also performed on an Agilent Technologies 6850 Series chromatograph with a flame ionization detector, and a Supelco β -Dex 120 column with helium as the carrier gas. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar Supercritical Chromatograph equipped with an auto sampler and a Waters photoiodide array detector with isopropanol as the modifier. Analytical chiral high-performance liquid chromatography (HPLC) was performed on an Agilent Technologies 1120 compact LC or an Agilent Technologies 1220 Infinity LC chromatograph equipped with a UV detector and a Daicel Chiracel-OD-H column.

Reaction calorimetry was carried out in a SuperCRC reaction calorimeter in a glass, septum-cap vial equipped with a magnetic stir bar. The calorimeter measures the heat released or consumed in a sample vessel compared with that from a reference compartment over the course of the reaction.

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 sparged with N₂ before use. Triethylamine was distilled from calcium hydride. Potassium tetrachloroplatinate(II) was purchased from Acros Organics. Dibenzylideneacetone was purchased from Oakwood Chemicals. 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. Methanol and sulfuric acid were purchased from Fisher Scientific, Inc. and used without further purification. Diethylamine was purchased from Alfa Aesar and used without further purification. 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide Advanced purchased from was ChemTech and used without further purification. 5-Hexenoic acid, 2-methyl-1,5hexadiene, and 1,2:5,6-Di-O-isopropylidene-D-mannitol were purchased from TCI America and used without further purification. Tert-butyldiphenylsilyl chloride, tetrabutylammonium chloride, imidazole, bromochloromethane, methyl lithium (1.0 M in tetrahydrofuran), methyltriphenylphosphonium bromide, potassium tert-butoxide, p*m*-anisaldehyde, *p*-tolualdehyde, o-tolualdehyde, *m*-tolualdehyde, anisaldehyde, cyclopropanecarboxaldehyde, sodium (meta)periodate and N_N-diisopropylethylamine were purchased from Aldrich and used without further purification. Norbornene, cyclohexene, 2-octene, indene, hept-6-en-1-ol, 1-tetradecene, 1-octene, 4,4-dimethyl-1pentene, 4-phenyl-1-butene, vinyl cyclohexane, 3,3-dimethyl-1-butene, allylbenzene, styrene, 4-(trifluoromethyl)styrene, 3-(trifluoromethyl)styrene were purchased from Aldrich and were sparged with N₂ and distilled prior to use.

2.8.2. Preparation of Pt(0) Sources.

2.8.2.1. Preparation of Pt(dba)₃. Tris(dibenzylideneacetone)platinum(0) was prepared using the literature procedure with slight modification.⁵² To a three-neck 500 mL round-bottomed flask equipped with a 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). Salts were dissolved in methanol and the solution was warmed to 70 °C 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), and the mixture was gently warmed until all solids dissolved. The three-neck round-bottomed flask was charged with the potassium tetrachloroplatinate solution 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 500 mL roundbottomed flask and concentrated by rotary evaporation to half the volume. The reaction mixture was filtered on a Büchner funnel and the remaining solids were washed with copious amounts of water and methanol until no yellow dibenzylideneacetone crystals were visible. The resulting solid was placed under high vacuum for 24 h to remove residual methanol and water, to give the product as a dark brown solid (7.09 g, 47% yield). Anal Calc'd for C₅₁H₄₂O₃Pt: 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).

⁵² Lewis, L.N.; Krafft, T.A.; Huffman, J.C. Inorg. Chem. 1992, 31, 3555.

2.8.2.2. Preparation of $Pt_2(dba)_3$. Tris(dibenzylideneacetone)diplatinum(0) was prepared using the literature procedure.⁵² To a two-neck 25 mL round-bottomed 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 mL) was added and the solution was warmed to 70 °C in an oil bath until the solids dissolved (5 minutes). To a separate 50 mL pearshaped flask was added potassium tetrachloroplatinate (500 mg, 1.20 mmol) and water (6.3 mL), and the mixture gently warmed until all 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 500 mL round-bottomed 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 was dissolved in hot tetrahydrofuran (100 mL) and filtered. The filtrate was concentrated to a volume of 10 mL using rotary evaporation followed by the slow addition of methanol (12 mL). 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 the product as a black crystalline solid (348.9 mg, 53%). Anal Calc'd for C₅₁H₄₂O₃Pt₂: 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).

2.8.2.3. Preparation of Pt(nbe)₃. Tris(norbornene)platinum(0) was prepared using the literature procedure.⁵³ A flame-dried 100 mL three-neck round-bottomed flask equipped with magnetic stir bar and addition funnel was charged with finely powdered PtCl₂(COD) (3.50 g, 9.35 mmol) and freshly sublimed norbornene (7.00 g, 74.3 mmol) under N2. 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 washed with dry and degassed hexane (3 x 100 mL). The combined hexanes extracts were filtered through a plug of alumina and the filtrate was evaporated in vacuo to give the product as an off-white solid which was used without further purification (1.67 g, 52%). Anal Calc'd for $C_{21}H_{30}Pt$: C, 52.82; H, 6.33. Found: C, 52.84; H, 6.29.

⁵³ Reagents for Transition Metal Complex and Organometallic Syntheses. *Inorganic Syntheses*; Angelici, R.J., Ed.; Wiley: New York, 1990; Vol. 28; p 127.

2.8.3. Ligand Synthesis.

Preparation of 1-bromo-3,5-di-iso-propylbenzene

1-bromo-3,5-di-*iso*-propylbenzene was prepared according to the literature procedure from 2,6-di-*iso*-propylaniline as shown below.⁵⁴



Preparation of (R,R)-3,5-diisopropylphenylTADDOL.

(R,R)-3,5-Di-*iso*-propylphenylTADDOL was prepared according to the literature procedure with slight modification.⁵⁵ To a flame-dried 500 mL two-neck round-bottomed flask equipped with magnetic stir bar and reflux condenser was added crushed magnesium turnings (4.10 mg, 169 mmol) under N₂. The apparatus was flame-dried again, followed by addition of a single crystal of I₂ along with tetrahydrofuran (175 mL). To a separate flame dried 250 mL round-bottomed flask was added 1-bromo-3,5-di-*iso*propylbenzene (33.7 g, 140 mmol) (which was prepared according to the literature procedure from 2,6-di-*iso*-propylaniline as shown above) and tetrahydrofuran (175 mL). The resulting solution was slowly added to the magnesium mixture at room temperature *via* cannula transfer. The reaction was heated to reflux at 80 °C in an oil bath for 3 h, at

⁵⁴ Diemer, V.; Chaumeil, H.; Defoin, A.; Fort, A.; Boeglin, A.; Carré, C. Eur. J. Org. Chem. 2006, 12,

^{2727.}

⁵⁵ Seiber, J.D.; Morken, J.P. J. Am. Chem. Soc. **2008**, 130, 4978.

which time the reaction was cooled to 0 °C, and a solution of (4R,5R)-dimethyl 2,2dimethyl-1,3-dioxolane-4,5-dicarboxylate (6.13 g, 28.1 mmol) in tetrahydrofuran (10.0 mL) was added slowly *via* syringe. The reaction was allowed to reflux at 80 °C for 12 h, after which it was cooled to 0 °C and quenched with saturated aqueous NH₄Cl (100 mL). The organic and aqueous layers were separated and the aqueous layer was further extracted with ethyl acetate (3 x 70 mL). The combined organics were dried over Na₂SO₄, filtered, and concentrated *in vacuo*. The crude material was purified by recrystallization from methanol (50 mL). The crystallized solid was isolated by filtration, washed with cold methanol, and dried under vacuum to afford the product as a white solid (20.1 g, 89.2%).



(*R*,*R*)-3,5-di-*iso*-propylphenylTADDOL. ¹H NMR (500 MHz, CDCl₃): 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, dq, *J* = 7.0 Hz, 7.0 Hz), 2.81 (4H, dq, *J* = 7.0 Hz, 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); ¹³C NMR (125 MHz, CDCl₃): δ 23.9, 24.0, 24.0, 24.4,

27.0, 30.3, 34.2, 34.3, 78.5, 81.2, 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 C₅₅H₇₈O₄Na [M+Na]: calculated 825.5792, found: 825.5770. $[\alpha]_D^{25} = +19.88$ (c = 0.97, CHCl₃, l = 50 mm) *Preparation of (R,R)-di-iso-propylphenylTADDOLPPh*.

To a flame dried 150 mL round bottom flask equipped with magnetic stir bar was added (R,R)-3,5-diisopropylphenylTADDOL (3.50g, 4.36 mmol) and tetrahydrofuran (44.0 mL) under N₂. Triethylamine (2.06 mL, 14.8 mmol) was added via syringe and the reaction mixture was cooled to 0 °C in an ice bath. Dichlorophenylphosphine (0.650 mL, 4.79 mmol) was added dropwise via syringe at 0 °C. The reaction was warmed to room temperature and was allowed to stir for 2 h. The reaction was diluted with Et₂O, filtered quickly through celite and concentrated *in vacuo*. The crude material was purified by silica gel chromatography (2% ethyl acetate in hexanes, with 1% Et₃N to prevent hydrolysis) to afford the product as a white solid (3.65g, 92.0 %).



MHz, CDCl₃): δ 23.9, 23.9, 24.0, 24.1, 24.2, 28.0, 34.0, 34.1, 34.2, 34.4, 82.8, 82.8, 83.2, 83.4, 83.8, 83.9, 84.3, 84.3. 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; ³¹P NMR (202 MHz, CDCl₃): δ 155.4; 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. [α]_D²⁵ = -50.40 (*c* = 0.34, CHCl₃, *l* = 50 mm).

2.8.4. Preparation of Terminal Alkenes.

A. The following 1-alkenes were prepared by Wittig olefination of the commercially available aldehydes with methyltriphenylphosphonium bromide and potassium tertbutoxide in tetrahydrofuran: *p*-methoxystyrene,⁵⁶ *m*-methoxystyrene,⁵⁷ *p*-methylstyrene,⁵⁸ *o*-methylstyrene,⁵⁸ *m*-methylstyrene.⁵⁸ Spectral data are in accordance with the literature references.

The following 1-alkenes were prepared by the literature procedure: allyloxy(*tert*-butyl)diphenylsilane,¹⁶ (but-3-enyloxy)(*tert*-butyl)diphenylsilane.¹⁶ Spectral data are in accordance with the literature references.

B. Preparation of (S)-4,8-dimethylnona-1,7-diene. The title compound was synthesized by Wittig olefination of commercially available (*S*)-3,7-dimethyloct-6-enal.

Me Me (S)-4,8-dimethylnona-1,7-diene (Table 4.11, entry 9). ¹H NMR (500 MHz, CDCl₃): δ 0.86-0.88 (3H, d, J = 7.0 Hz); 1.09-1.61 (1H, m), 1.29-1.36 (1H, m), 1.45-1.52 (1H, m), 1.58 (3H, s), 1.66 (3H, s), 1.83-1.90 (1H, m), 1.92-2.01 (2H, m), 2.03-2.08 (1H, m), 4.94-4.99 (2H, m), 5.06-5.09 (1H, m), 5.76 (1H, dddd, J = 17.5 Hz, 10.5 Hz, 7.5 Hz, 7.5 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 17.7, 19.3, 25.6, 25.7, 32.4, 36.6, 41.3, 115.4, 124.8, 131.1, 137.7; IR (neat): 2955.0 (m),

⁵⁶ Alacid, E.; Nájera, C.; J. Org. Chem. 2009, 74, 2321.

⁵⁷ Deguest, G.; Bischoff, L.; Fruit, C.; Marsais, F.; Org. Lett. 2007, 9, 1165.

⁵⁸ Smith, C. R.; RajanBabu, T. V.; *Tetrahedron*, **2010**, *66*, 1102.

2923.3 (s), 2853.8 (m), 1724.5 (w), 1458.7 (w), 1376.7 (w), 1272.0 (w) cm⁻¹; HRMS-(ESI+) for $C_{11}H_{21}$ [M+H]: calculated: 153.1643, found: 153.1639.

C. Preparation of oct-7-en-2-one. The title compound was synthesized as shown below.⁵⁹ The spectral data was in accordance with the literature reference.⁵⁹



D. Preparation of methyl hept-6-enoate. The title compound was prepared by esterification of hept-1-enoic acid with MeOH and catalytic concentrated H₂SO₄, as shown below.⁵⁹ The spectral data was in accordance with the literature reference.⁵⁹



E. Preparation of N,N-diethylhept-6-enamide. The title compound was synthesized as shown below to afford a clear, pale yellow liquid.⁶⁰

⁵⁹ Rosillo, M.; Arnaiz, E.; Abdi, D.; Blanco-Urgoiti, J.; Dominguez, G.; Perez-Castells, J.; *Eur. J. Org. Chem.* **2008**, *23*, 3917.

⁶⁰ Buswell, M.; Fleming, I.; Ghosh, U.; Mack, S.; Russell, M.; Clark, B. P.; *Org. Biomol. Chem.* **2004**, *2*, 3006.



N,N-diethylhept-6-enamide. ¹H NMR (500 MHz, CDCl₃): δ 1.07 (3H, t, J = 7.0 Hz), 1.14 (3H, t, J = 7.0 Hz), 1.41 (2H, tt, J = 8.0, 8.0 Hz), 1.64 (2H, tt, J = 7.5, 7.5 Hz), 2.05 (2H, dt, J = 7.0, 7.0 Hz), 3.27 (2H, q, J = 7.0 Hz), 3.34 (2H, q, J = 7.0 Hz), 4.91 (1H, dd, J =10.0, 1.0 Hz), 4.98 (1H, dd, J = 17.5, 1.5 Hz), 5.78 (1H, dddd, J = 17.0, 10.0, 6.5, 6.5Hz); ¹³C NMR (125 MHz, CDCl3): δ 13.1, 14.4, 24.9, 28.7, 32.9, 33.6, 40.0, 41.9, 114.4, 138.6, 172.0; IR (neat): 2972.5 (w), 2931.2 (w), 1636.8 (s), 1458.6 (m), 1426.3 (m), 1378.9 (w), 1362.5 (w), 1260.3 (w), 1222.3 (w), 1140.7 (w), 1096.7 (w), 1071.6 (w), 907.4 (m), 792.6 (w) cm⁻¹; HRMS-(ESI+) for C₁₁H₂₂NO [M+H]: calculated: 184.1701, found: 184.1710.

F. Preparation of (S)-2,2-dimethyl-4-vinyl-1,3-dioxolane. The title compound was synthesized as shown below.⁶¹ The spectral data was in accordance with the literature reference.⁶¹



⁶¹ Racha, S.; Mallela, S. S. P.; Elie, A. Syn. Commun. 1989, 19, 3077.

G. Perparation of vinvlcvclopropane. The title compound was synthesized from cyclopropanecarboxaldehyde by the Conia-Dauben modification of the Wittig reaction, as shown below.⁶² The spectral data was in accordance with the literature.⁶³

$$\bigvee_{H}^{O} \xrightarrow{Ph_{3}P^{+}CH_{3}Br^{-}}_{Sodium t-amylate}$$

2.8.5. Representative Procedure for Alkene Diboration/Oxidation.

To an oven-dried vial equipped with a magnetic stir bar in air was added $Pt(dba)_3$ (6.9 mg, 7.6 µmol), (R,R)-3,5-diisopropylphenyl-TADDOLPPh (8.3 mg, 9.2 µmol), and $B_2(pin)_2$ (203.7 mg, 802.0 µmol). The vial was sealed with a septum cap and purged with N₂. Tetrahydrofuran (0.76 mL, 1.0 M) was added via syringe, and the vial was heated to 80 °C in an oil bath for 30 minutes. The vial was then cooled to room temperature and charged with freshly distilled and deoxygenated 1-tetradecene (150.0 mg, 763.8 µmol). After purging once more with N₂, the vial was stirred at 60 °C for 3 hours. The reaction mixture was cooled to 0 °C (ice/water) and charged with 3 M sodium hydroxide (2 mL), followed by dropwise addition of 30% hydrogen peroxide (1 mL). The reaction was gradually warmed to room temperature and stirred 4 hours at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate (4 mL) was added dropwise over 5 minutes. The reaction mixture was diluted with ethyl acetate and the

 ⁶² Tsunoda, T.; Hudlicky, T. *Synlett.* **1990**, *6*, 322.
⁶³ Schrumpf, G. *Tetrahedron Lett.* **1970**, 2571.

aqueous and organic layers were separated. The aqueous layer was further extracted with ethyl acetate (3 x 15 mL), and the combined organics were dried over Na₂SO₄, filtered, and concentrated by rotary evaporation. The crude reaction mixture was purified on silica gel (30-70% ethyl acetate in hexanes) to afford the product as a white solid (148.0 mg, 84% yield).

2.8.6. Full Characterization and Proof of Stereochemistry.

(S)-octane-1,2-diol. The diboration was performed OH ,OH Me. according to the general procedure with 1-octene (84.6 mg, 763 μ mol), Pt(dba)₃ (6.9 mg, 7.6 μ mol), (*R*,*R*)-3,5-diisopropylphenylTADDOLPPh (8.3 mg, 9.2 μ mol), and B₂(pin)₂ (203.7 mg, 802.0 μ mol) in tetrahydrofuran (0.76 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate in hexanes, stain in KMnO₄) to afford the product as a white solid (91.5 mg, 82% yield). Spectral data and optical rotation are in accordance with the literature.^{64,65} HRMS-(ESI+) for C₈H₁₉O₂ [M+H]: calculated: 147.1385, found: 147.1380.

Proof of Stereochemistry:

The 1,2-diol was treated with 2,2-dimethoxypropane and catalytic 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 tetroxide and 4-

 ⁶⁴ Emmanuvel, L.; Shaikh, T. M. A.; Sudalai, A. Org. Lett., 2005, 7, 5071.
⁶⁵ Kliman, L. T.; Mlynarski, S. N.; Morken, J. P. J. Am. Chem. Soc. 2009, 131, 13210.

methylmorpholine N-oxide. The authentic (S)-isomer was prepared from the Sharpless asymmetric dihydroxylation of 1-octene utilizing AD-mix- α .⁶⁶



Chiral GLC (β -dex, Supelco, 100 °C, 20 psi, s/r = 35:1)- analysis of the acetonide of octane-1,2-diol.



⁶⁶ Jacobsen, E. N.; Marko, I.; Mungall, W. S.; Schroeder, G.; Sharpless, K. B. J. Am. Chem. Soc., **1988**, 110, 1968.

OH (S)-tetradecane-1,2-diol. The diboration was performed according to the general procedure with 1-tetradecene (150.0 mg, 763.8 µmol), Pt(dba)₃ (6.9 mg, 7.6 µmol), (*R*,*R*)-3,5-diisopropylphenyl-TADDOLPPh (8.3 mg, 9.2 µmol), and B₂(pin)₂ (203.7 mg, 802.0 µmol) in tetrahydrofuran (0.76 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate in hexanes, stain in KMnO₄) to afford the product as a white solid (148.0 mg, 84% yield). Spectral data are in accordance with the literature.⁶⁷ HRMS-(ESI+) for C₁₄H₃₄NO₂ [M+NH₄]: calculated: 248.2590, found: 248.2580. $[\alpha]_D^{20} = -1.261$ (*c* = 1.015, CHCl₃, *l* = 50 mm).

Analysis of Stereochemistry:

The 1,2-diol was treated with 2,2-dimethoxypropane and catalytic toluenesulfonic acid (below). The resulting ketal was compared to the racemic ketal of octane-1,2-diol prepared from dihydroxylation of 1-tetradecene with osmium tetroxide and 4-methylmorpholine N-oxide. The absolute stereochemistry was assigned by analogy.

⁶⁷ Stallforth, P.; Adibekian, A.; Seeberger, P.H. Org. Lett. 2008, 10, 1573.

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



| 1 | 82.234 | MM | 0.2410 | 37.99389 | 2.62780 | 3.59826 |
|---|--------|----|--------|------------|----------|----------|
| 2 | 82.909 | MM | 0.2981 | 1017.90234 | 56.91163 | 96.40174 |

#



mg, 644 µmol), Pt(dba)₃ (5.8 mg, 6.4 µmol), (*R*,*R*)-3,5-di-*iso*-propylphenylTADDOLPPh (7.0 mg, 7.7 µmol), and B₂(pin)₂ (171.7 mg, 676.3 µmol) in tetrahydrofuran (0.64 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate in hexanes, stain in KMnO₄) to afford the product as a clear, colorless oil that could not be separated from pinacol (145.9 mg, 1:1.3 product:pinacol = 78% yield). Spectral data are in accordance with the literature.^{12b}

Analysis of Stereochemistry:

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

Chiral GLC (β -dex, Supelco, 90 °C, 20 psi, s/r = 35:1)- analysis of 4,4-dimethylpentane-1,2-diol.



OH (*S*)-1-cyclohexylethane-1,2-diol. The diboration was performed according to the general procedure with vinyl cyclohexane (100.0 mg, 907.4 µmol), Pt(dba)₃ (8.1 mg, 9.1 µmol), (*R*,*R*)-3,5-diisopropylphenylTADDOLPPh (9.9 mg, 11 µmol), and B₂(pin)₂ (258.8 mg, 1.019 µmol) in tetrahydrofuran (0.91 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate in hexanes, stain in KMnO₄) to afford the product as a clear, colorless oil (107.6 mg, 82% yield). Spectral data and optical rotation are in accordance with the literature.^{68,65} [M+H]: calculated: 145.1229, found: 145.1222.

Proof of Stereochemistry:

The 1,2-diol was treated with 2,2-dimethoxypropane and catalytic ptoluenesulfonic acid. The resulting ketal was compared to the racemic ketal of 1cyclohexylethane-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 .

⁶⁸ 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, s/r = 35:1) – analysis of the acetonide of 1cyclohexylethane-1,2-diol.



(S)-3,3-dimethylbutane-1,2-diol. The diboration was performed OH .OH Me according to the general procedure with 3,3-dimethylbut-1-ene (50.0 Me Мe 594.1 (16.0)17.8 µmol), $Pt(dba)_3$ umol), (R,R)-3,5mg, mg, diisopropylphenylTADDOLPPh (19.4 mg, 21.4 µmol), and B₂(pin)₂ (158.4 mg, 623.8 µmol) in tetrahydrofuran (0.59 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate in hexanes, stain in KMnO₄) to afford a clear, colorless oil that was inseparable from pinacol (69.6 mg, 1:1 product:pinacol, 50% yield). Spectral data and optical rotation are in accordance with the literature.^{65, 68} [M+H]: calculated: 119.1072, found: 119.1074.

Analysis 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 °C, 20 psi, s/r = 35:1) – analysis of 3,3-dimethylbutane-1,2-diol.



OH (S)-4-phenylbutane-1,2-diol. The diboration was performed according to the general procedure with 4-phenyl-1-butene (88.3 mg, 668 µmol), Pt(dba)₃ (6.0 mg, 6.68 µmol), (*R*,*R*)-3,5-diisopropylphenyl-TADDOLPPh (7.3 mg, 8.0 µmol), and B₂(pin)₂ (178.2 mg, 701.6 µmol) in tetrahydrofuran (0.67 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30- 70% ethyl acetate in hexanes, stain in KMnO₄) to afford the product as a clear, colorless oil (86.6 mg, 78% yield). Spectral data are in accordance with the literature.⁶⁹ HRMS-(ESI+) for C₁₀H₁₅O₂ [M+H]: calculated: 167.1072, found: 167.1080. $[\alpha]_D^{20} = -13.294$ (*c* = 1.050, CHCl₃, *l* = 50 mm).

Proof of stereochemistry:

The 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 .

⁶⁹ Stead, D.; O'Brien, P.; Sanderson, A.; Org. Lett., 2008, 10, 1409.

Chiral GLC (β -dex, Supelco, 90 °C, 20 psi, s/r = 35:1) – analysis of the acetonide of 4-phenylbutane-1,2-diol.



| racemic | | diboration product | | authentic | | |
|-------------|------------------|--------------------|----------------|----------------|----------------|-----------|
| Peak # | RetTime [min] | Туре | Width [min] | Area [pA*s] | Height [pA] | Area % |
| 1 | 51.224 | MM | 0.3009 | 44.65959 | 2.47390 | 3.11345 |



Analysis 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 absolute stereochemistry was assigned by analogy.

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



OH
TBDPSO(R)-3-(tert-butyldiphenylsilyloxy)propane-1,2-diol.Thediboration was performed according to the general procedure with

allyloxy(*tert*-butyl) diphenylsilane (66.7 mg, 224 μ mol), Pt(dba)₃ (6.1 mg, 6.7 μ mol), (*R*,*R*)-3,5-diisopropylphenylTADDOLPPh (7.4 mg, 8.1 μ mol), and B₂(pin)₂ (60.0 mg, 236 μ mol) in tetrahydrofuran (0.22 mL, 1.0 M). The crude reaction mixture was purified on silica gel (20-30% ethyl acetate in hexanes) to afford the product as a white solid (59.5 mg, 80% yield). R_f = 0.39 (50% ethyl acetate/hexane, stain in KMnO₄). Spectral data and optical rotation are in accordance with the literature.⁶⁵

Analysis of Stereochemistry:

The title compound was compared to racemic 3-(*tert*-butyldiphenylsilyloxy)propane-1,2-diol prepared by silyl protection of glycerol, as shown below. Absolute stereochemistry was assigned by analogy.

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



| Retention Time | Area | Area % | Height | Height % |
|----------------|-----------|--------|----------|----------|
| 14.410 | 58717514 | 9.26 | 1876785 | 11.27 |
| 16.740 | 575118998 | 90.74 | 14775893 | 88.73 |

OH (*S*)-4-(*tert*-butyldiphenylsilyloxy)butane-1,2-diol. The diboration was performed according to the general procedure with (but-3-enyloxy)(*tert*-butyl)diphenylsilane (200.0 mg, 644.1 µmol), Pt(dba)₃ (5.8 mg, 6.4 µmol), (*R*,*R*)-3,5-diisopropylphenylTADDOLPPh (7.0 mg, 7.7 µmol), and B₂(pin)₂ (171.1 mg, 676.3 µmol) in tetrahydrofuran (0.64 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-60% ethyl acetate in hexanes) to afford the product as a clear, colorless oil that could not be separated from pinacol (350.9 mg, 1:1 product:pinacol, 91% yield). R_f = 0.26 (50% ethyl acetate/hexane, stain in KMnO₄). Spectral data and optical rotation are in accordance with the literature.⁶⁵ HRMS-(ESI+) for C₂₀H₂₉O₃Si [M+H]: calculated: 345.1886, found: 345.1878.

Analysis of Stereochemistry:

The title compound was compared to racemic 4-(*tert*-butyldiphenylsilyloxy)butane-1,2-diol prepared from treatment of allylbenzene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The absolute stereochemistry was assigned by analogy.
Chiral HPLC (Chiracel OD-H, 2.0% IPA, 1.5 mL/min, 220 nm)-analysis of 4-(tertbutyldiphenylsilyloxy)butane-1,2-diol.



(S)-7,8-dihydroxyoctan-2-one. The diboration was OH OH. Me. performed according to the general procedure with oct-7-enmg, 792.4 μ mol), Pt(dba)₃ (7.1 mg, 7.9 2-one (100.0 umol). (R.R)-3.5diisopropylphenylTADDOLPPh (8.6 mg, 9.5 µmol), and B₂(pin)₂ (211.3 mg, 832.0 µmol) in tetrahydrofuran (0.79 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-85% ethyl acetate in hexanes) to afford a clear, colorless oil (73.2mg, 58% yield). ¹H NMR (500 MHz, CDCl₃): δ 1.30-1.36 (1H, m), 1.38-1.46 (3H, m), 1.53-1.62 (2H, m), 2.11 (3H, s), 2.43 (2H, t, J = 7.5 Hz), 3.41 (1H, dd, J = 11.0, 7.5 Hz), 3.62 (1H, dd, J = 11.0, 7.5 Hz), 3.64 (1H, dd, Jdd, J = 11.0, 3.0 Hz), 3.68-3.72 (1H, m); ¹³C NMR (125 MHz, CDCl₃): δ 23.5, 25.0, 29.9, 32.8, 43.5, 66.7, 71.9, 209.2; IR (neat): 3398.9 (br s), 2926.2 (s), 2858.8 (m), 1706.4 (s), 1459.5 (w), 1408.9 (w), 1363.0 (m), 1163.4 (w), 1054.2 (m), 599.8 (w) cm⁻¹; HRMS-(ESI+) for C₈H₁₇O₃ [M+H]: calculated: 161.1178, found: 161.1180. $[\alpha]_D^{20} =$ $+2.769 (c = 0.650, CHCl_3, l = 50 mm).$

Analysis 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 7,8-dihydroxyoctan-2-one prepared from treatment of oct-7-en-2-one with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The absolute stereochemistry was assigned by analogy.

Chiral GLC (β -dex, Supelco, 70 °C for 5 min, ramp 2 °C/min to 180 °C, 20 psi, s/r = 35:1) – analysis of the acetonide of 7,8-dihydroxyoctan-2-one.



Analysis 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 methyl 6,7-dihydroxyheptanoate prepared from treatment of hept-6-enoate with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The absolute stereochemistry was assigned by analogy.

⁷⁰ Chen, A.; Xu, J.; Chiang, W.; Chai, C. L. L.; *Tetrahedron*, **2010**, *66*, 1489.

Chiral GLC (β -dex, Supelco, 70 °C for 5 min, ramp 2 °C/min to 180 °C, 20 psi, s/r = 35:1) – analysis of the acetonide of methyl 6,7-dihydroxyheptanoate.



Me. (S)-N,N-diethyl-6,7-dihydroxyheptanamide. The OH OH Me. diboration was performed according to the general procedure with N,N-diethylhept-6-enamide (150.0 mg, 818.4 µmol), Pt(dba)₃ (7.3 mg, 8.2 μ mol), (*R*,*R*)-3,5-diisopropylphenylTADDOLPPh (8.9 mg, 9.8 μ mol), and B₂(pin)₂ (218.2 mg, 859.3 µmol) in tetrahydrofuran (0.82 mL, 1.0 M). The crude reaction mixture was purified on silica gel (0-10% methanol in dichloromethane, stain in KMnO₄) to afford the product as a clear, colorless oil (135.4 mg, 76% yield). ¹H NMR (500 MHz, CDCl₃): δ 1.06 (3H, t, 7.5 Hz), 1.13 (3H, t, J = 7.5 Hz), 1.34-1.47 (4H, m), 1.55-1.69 (2H, m), 2.28 (2H, t, J = 7.0 Hz), 3.26 (2H, q, J = 7.0 Hz), 3.31 (2H, q, J = 7.0 Hz), 3.40 (1H, dd, J = 11.0, 6.5 Hz), 3.58 (1H, dd, J = 11.5, 3.0 Hz), 3.68-3.70 (1H, m); ¹³C NMR (125 MHz, CDCl₃): δ 13.0, 14.5, 24.9, 25.2, 32.6, 32.8, 40.2, 42.0, 66.8, 71.8, 172.4; IR (neat): 3393.3 (br m), 2971.3 (w), 2933.4 (m), 2870.7 (w), 1617.1 (s), 1459.9 (m), 1433.1 (m), 1310.3 (m), 1265.0 (w), 1142.1 (w), 1096.9 (m), 1072.4 (m), 1052.3 (m), 606.3 (w) cm^{-1} ; HRMS-(ESI+) for C₁₁H₂₄NO₃ [M+H]: calculated: 218.1756, found: 218.1760. $[\alpha]_D^{20} = -4.374 \ (c = 1.015, \text{CHCl}_3, l = 50 \text{ mm}).$

Analysis 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 methyl *N*,*N*-diethyl-6,7-dihydroxyheptanamide prepared from treatment of *N*,*N*-diethylhept-6-enamide with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The absolute stereochemistry was assigned by analogy.

Chiral GLC (β -dex, Supelco, 140 °C for 60 min, ramp 1 °C/min to 180 °C, 20 psi, s/r = 35:1) – analysis of the acetonide of N,N-diethyl-6,7-dihydroxyheptanamide.



| Peak | RetTime | Туре | Width | Area | Height | Area |
|--------|------------------|--------------|--------|----------------------|-----------------------|---------------------|
| # | [min] | | [min] | [pA*s] | [pA] | % |
| 1 2 | 96.348 96.760 | MF FM | 0.1891 | 4.80400 121.74680 | 4.23356e-1 9.55517 | 3.79610 96.20390 |

(S)-5-methylhex-5-ene-1,2-diol. The diboration was performed OH .OH according to the general procedure with 2-methylhexa-1,5-diene Мe (75.0)779.9 µmol), $Pt(dba)_3$ (7.0)7.8 µmol), (R,R)-3,5mg, mg, diisopropylphenylTADDOLPPh (8.5 mg, 9.4 µmol), and B₂(pin)₂ (207.9 mg, 818.9 µmol) in tetrahydrofuran (0.8 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-50% ethyl acetate in hexanes) to afford the product as a clear, colorless oil (84.3 mg, 83% yield). Rf = 0.13 (50% ethyl acetate in hexane, stain in KMnO₄) ¹H NMR $(400 \text{ MHz}, \text{CDCl}_3)$: δ 1.56-1.60 (2H, m), 1.72 (3H, s), 2.01 (2H, br s), 2.07 (1H, dddd, J= 7.5, 7.5, 7.5, 7.5 Hz), 2.17 (1H, dddd, J = 7.5, 7.5, 7.5, 7.5 Hz), 3.45 (1H, dd, J = 11.0, 8.0 Hz), 3.65 (1H, d, J = 11.0 Hz), 3.69-3.73 (1H, m), 4.70 (1H, s), 4.72 (1H, s); ¹³C NMR (125 MHz, CDCl3): 8 22.3, 31.0, 33.8, 66.7, 72.0, 110.4, 145.4; IR (neat): 3363.6 (s), 3074.1 (w), 2929.6 (s), 1649.6 (w), 1447.6 (s), 1375.0 (m), 1333.5 (w), 1100.2 (m), 1053.3 (s), 886.0 (s) cm⁻¹; HRMS-(ESI+) for $C_7H_{15}O_2$ [M+H]: calculated: 131.1072, found: 131.1075. $[\alpha]_D^{20} = -2.714$ (*c* = 1.665, CHCl₃, *l* = 50 mm).

Analysis of Stereochemistry:

The enantiopurity was determined by treating the resulting 1,2-diol with 2,2dimethoxypropane and catalytic *p*-toluenesulfonic acid. The racemic material of 5methylhex-5-ene-1,2-diol was prepared using PCy3 as the achiral ligand in the diboration reaction. Absolute stereochemistry was assigned by analogy.

Chiral GLC (β -Dex, Supelco, 70 °C for 5 min, ramp 3 °C/min to 120 °C, 20 psi, s/r = 35:1) – analysis of the acetonide.



| Peak | RetTime | туре | Width | Area | Height | Area |
|------|---------|------|--------|-----------|----------|----------|
| # | [min] | | [min] | [pA*s] | [pA] | 8 |
| | | | | | | |
| 1 | 17.910 | BB | 0.0577 | 10.21409 | 2.72514 | 3.12745 |
| 2 | 18.247 | BB | 0.0759 | 316.38113 | 61.59937 | 96.87255 |

OH (S)-1-phenylethane-1,2-diol. The diboration was performed according to the general procedure with styrene (80.0 mg, 768 µmol), Pt(dba)₃ (6.9 mg, 7.7 µmol), (R,R)-3,5-diisopropylphenylTADDOLPPh (8.4 mg, 9.2 µmol), and B₂(pin)₂ (204.8 mg, 806.5 µmol) in tetrahydrofuran (0.77 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate/hexanes, stain in KMnO₄) to afford the product as a white solid (90.6 mg, 85% yield). Spectral data and optical rotation are in accordance with the literature.⁶⁸ HRMS-(ESI+) for C₈H₉O₁ [M-H₂O+H]: calculated: 121.0653, found: 121.0657.

Proof of stereochemistry:

The resulting 1,2-diol was treated with 2,2-dimethoxypropane and catalytic ptoluenesulfonic acid. The resulting ketal was compared to the racemic ketal of 1phenylethane-1,2-diol prepared from treatment of styrene with osmium tetraoxide and 4methylmorpholine *N*oxide.The authentic (*R*)-isomer was prepared from the Sharpless asymmetric dihydroxylation of vinyl cyclohexane utilizing AD-mix- β . Chiral GLC (β -dex, Supelco, 140 °C, 20 psi, s/r = 35:1) – analysis of the acetonide of 1phenylethane-1,2-diol.



Me OH OH OH OH F OH Performed according to the general procedure with 2-methylstyrene

(79.0 mg, 668 µmol), Pt(dba)₃ (6.0 mg, 6.7 µmol), (*R*,*R*)-3,5diisopropylphenylTADDOLPPh (7.3 mg, 8.0 µmol), and B₂(pin)₂ (178.2 mg, 701.6 µmol) in tetrahydrofuran (0.67 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate in hexanes) to afford the product as a white solid (84.4 mg, 83% yield). Spectral data and optical rotation are in accordance with the literature.⁷¹ HRMS-(ESI+) for C₉H₁₆NO₂ [M+NH₄]: calculated: 170.1181, found: 170.1187. $[\alpha]_D^{20} =$ +58.769 (*c* = 1.555, CHCl₃, *l* = 50 mm).

Analysis 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-(2-methylphenyl)ethane-1,2-diol prepared from treatment of *o*-methylstyrene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The absolute stereochemistry was assigned by analogy.

⁷¹ Kadyrov, R.; Koenigs, R. M.; Brinkmann, C.; Voigtlaender, D.; Rueping, M. Angew. Chem. Int. Ed. **2009**, 48, 7556.

Chiral GLC (β -dex, Supelco, 140 °C, 20 psi, s/r = 35:1) – analysis of the acetonide of 1-(2-methyl-phenyl)ethane-1,2-diol.



racemic

diboration product

| " [| |
|-----------------------------------|---------------|
| 1 13.548 MM 0.0996 70.32373 11.76 | 5942 12.06705 |

(S)-1-(3-methylphenyl)ethane-1,2-diol. OH The diboration was ,OH Me. performed according to the general procedure with 3methylstyrene (79.0 mg, 668 μ mol), Pt(dba)₃ (6.0 mg, 6.7 μ mol), (R,R)-3,5diisopropylphenylTADDOLPPh (7.3 mg, 8.0 µmol), and B₂(pin)₂ (178.2 mg, 701.6 µmol) in tetrahydrofuran (0.67 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate in hexanes) to afford the product as a clear, colorless oil (85.2 mg, 84% yield). $R_f = .20$ (40% ethyl acetate in hexanes, stain in KMnO₄); ¹H NMR (500 MHz, CDCl₃): δ 2.16 (1H, br s), 2.34 (3H, s), 2.57 (1H, br s), 3.65(1H, dd, J =11.0 Hz, 8.0 Hz), 3.74 (1H, dd, J = 11.5, 3.5 Hz), 4.77 (1H, dd, J = 8.5 Hz, 3.5 Hz), 7.09-7.16 (3H, m) 7.23 (1H, dd, J = 7.5, 7.5 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 21.4, 68.1, 74.7, 123.1, 126.7, 128.5, 128.8, 138.3, 140.4; IR (neat): 3346.7 (br s), 2921.3 (w), 1454.6 (w), 1075.5 (s), 1029.0 (s), 786.5 (m), 702.6 (s), 444.4 (w) cm⁻¹; HRMS-(ESI+) for C₉H₁₆NO₂ [M+NH₄]: calculated: 170.1181, found: 170.1184. $[\alpha]_D^{20} = +58.750$ (c = 0.290, CHCl₃, 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-(3-methylphenyl)ethane-1,2-diol prepared from treatment of 3-methylstyrene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The absolute stereochemistry was assigned by analogy.

Chiral GLC (β -dex, Supelco, 140 °C, 20 psi, s/r = 35:1) – analysis of the acetonide of 1-(3-methyl-phenyl)ethane-1,2-diol.





(*R*,*R*)-3,5-diisopropylphenylTADDOLPPh (7.3 mg, 8.0 µmol), and B₂(pin)₂ (178.2 mg, 701.6 µmol) in tetrahydrofuran (0.67 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate in hexanes, stain in KMnO₄) to afford a clear, colorless oil (78.1 mg, 77% yield). Spectral data and optical rotation are in accordance with the literature.⁷² HRMS-(ESI+) for C₉H₁₆NO₂ [M+NH₄]: calculated: 170.1181, found: 170.1187. [α]_D²⁰ = +50.480 (*c* = 2.060, CHCl₃, *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-(4-methylphenyl)ethane-1,2-diol prepared from treatment of *p*-methylstyrene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The absolute stereochemistry was assigned by analogy.

⁷² Wang, L.; Nakamura, S.; Ito, Y.; Toru, T. *Tetrahedron: Asymm.* **2004**, *15*, 3059.

Chiral GLC (β -dex, Supelco, 140 °C, 20 psi, s/r = 35:1) – analysis of the acetonide of 1-(4-methylphenyl)ethane-1,2-diol.



racemic

diboration product

| Peak | RetTime | туре | Width | Area | Height | Area |
|------|---------|------|--------|------------|-----------|----------|
| # | [min] | | [min] | [pA*s] | [pA] | 8 |
| | | | | | | |
| 1 | 13.664 | MM | 0.1032 | 195.53534 | 31.57282 | 6.40929 |
| 2 | 14.171 | MM | 0.1292 | 2855.27393 | 368.32419 | 93.59071 |

MeO (*S*)-1-(3-methoxyphenyl)ethane-1,2-diol. The diboration was methoxystyrene (30.0 mg, 223 µmol), Pt(dba)₃ (6.0 mg, 6.7 µmol), (*R*,*R*)-3,5diisopropylphenylTADDOLPPh (7.3 mg, 8.0 µmol), and B₂(pin)₂ (59.4 mg, 234 µmol) in tetrahydrofuran (0.22 mL, 1.0 M). The crude reaction mixture was purified on silica gel (20-75% ethyl acetate in hexanes, stain in KMnO₄) to afford a clear, colorless oil (27.9 mg, 75% yield). Spectral data and optical rotation are in accordance with the literature.⁷¹ HRMS-(ESI+) for C₉H₁₆NO₃ [M+NH₄]: calculated: 186.1130, found: 186.1122. $[\alpha]_D^{20} =$ +39.358 (*c* = 2.070, CHCl₃, *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-(3-methoxyphenyl)ethane-1,2-diol prepared from treatment of 3-methoxystyrene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The absolute stereochemistry was assigned by analogy.

Chiral GLC (β -dex, Supelco, 140 °C, 20 psi, s/r = 35:1) – analysis of the acetonide of 1-(3-methoxyphenyl)-ethane-1,2-diol.



racemic

diboration product

| Peak # | RetTime [min] | Туре | Width [min] | Area [pA*s] | Height [pA] | Area % |
|-----------|------------------|------|----------------|----------------|----------------|-----------|
| | | | | | | |
| 1 | 29.157 | MM | 0.2147 | 51.57898 | 4.00369 | 8.87792 |
| 2 | 30.770 | MM | 0.2250 | 529.40173 | 39.21622 | 91.12208 |



µmol), (*R*,*R*)-3,5-di-*iso*-propylphenylTADDOLPPh (**L8**) (8.1 mg, 8.94 µmol), and B₂(pin)₂ (198.7 mg, 782.5 µmol) in tetrahydrofuran (0.75 mL, 1.0 M). The crude reaction mixture was purified on silica gel (20-80% ethyl acetate/hexanes, stain in KMnO₄) to afford a white solid (90.2 mg, 72% yield). Spectral data and optical rotation are in accordance with the literature.⁷³ HRMS-(ESI+) for C₉H₁₁O₂ [M+H-H₂O]: calculated: 151.0759, found: 151.0762. [α]_D²⁰ = +48.369 (*c* = 1.075, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

The resulting 1,2-diol was compared to the racemic sample of 1-(4methoxyphenyl)ethane-1,2-diol prepared from treatment of 4-methoxystyrene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The absolute stereochemistry was assigned by analogy.

⁷³ Peach, P.; Cross, D. J.; Kenny, J. A.; Mann, I.; Houson, I.; Campbell, L.; Walsgrove, T.; Wills, M. *Tetrahedron* **2006**, *62*, 1864.

Chiral SFC (Chiracel AD-H, 5% MeOH, 5 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of 1-(4-methoxyphenyl)-ethane-1,2-diol.





racemic

diboration product

| Peak No | % Area | Area | RT (min) | Height (mV) | K' |
|---------|---------|------------|----------|-------------|--------|
| 1 | 94.4322 | 22871.8001 | 9.77 | 1225.916 | 0.0145 |
| 2 | 5.5678 | 1348.5343 | 10.76 | 91.1619 | 0.0159 |
| Total: | 100 | 24220.3344 | | | |

^{OH} F_3C (*S*)-1-(3-(trifluoromethyl)phenyl)ethane-1,2-diol. The diboration was performed according to the general procedure with 3-(trifluoromethyl)styrene (100.0 mg, 574.3 µmol), Pt(dba)₃ (5.2 mg, 5.7 µmol), (*R*,*R*)-3,5-diisopropylphenylTADDOLPPh (6.3 mg, 6.9 µmol), and B₂(pin)₂ (153.1 mg, 603.0 µmol) in tetrahydrofuran (0.57 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate in hexanes, stain in KMnO₄) to afford the product as a white solid (70.7 mg, 60% yield). Spectral data and optical rotation are in accordance with the literature.⁷⁴ IR (neat): 3370.7 (br s), 2926.2 (w), 1451.3 (w), 1329.0 (s), 1164.5 (m), 1123.6 (s), 1173.2 (m), 804.1 (w), 703.2 (w) cm⁻¹. HRMS-(ESI+) for C₉H₁₃F₃NO₂ [M+NH₄]: calculated: 224.0898, found: 224.0899. [α]_D²⁰ = +37.917 (*c* = 0.250, CHCl₃, *l* = 50 mm).

Analysis 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-(3-(trifluoromethyl)phenyl)ethane-1,2-diol prepared from treatment of 3-(trifluoromethyl)styrene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The absolute stereochemistry was assigned by analogy.

⁷⁴ Ohkuma, T.; Utsumi, N.; Watanabe, M.; Tsutsumi, K.; Arai, N.; Murata, K. Org. Lett. 2007, 9, 2565.

Chiral GLC (β -dex, Supelco, 140 °C, 20 psi, s/r = 35:1) – analysis of the acetonide of 1-(3-(trifluoro-methyl)phenyl)ethane-1,2-diol.



racemic

diboration product

| Peak # | RetTime [min] | туре | Width [min] | Area [pA*s] | Height [pA] | Area % |
|-----------|------------------|------|----------------|----------------|----------------|-----------|
| | 7.056 | BB | 0.0536 | 112.27570 | 33.10232 | 8.78842 |
| 2 | 7.432 | BB | 0.0583 | 1165.26562 | 306.69888 | 91.21158 |



diboration was performed according to the general procedure with 4-(trifluoromethyl)styrene (34.8 mg, 200.0 µmol), Pt(dba)₃ (5.4

The

mg, 6.0 μmol), (*R*,*R*)-3,5-diisopropylphenylTADDOLPPh (6.5 mg, 7.2 μmol), and B₂(pin)₂ (53.3 mg, 210. μmol) in tetrahydrofuran (0.20 mL, 1.0 M). The crude reaction mixture was purified on silica gel (0-60% ethyl acetate in hexanes) to afford a clear, colorless oil (30.4 mg, 74% yield). R_f = 0.18 (40% ethyl acetate in hexanes, stain in KMnO₄);¹H NMR (500MHz, CDCl₃): δ 1.96 (1H, br s), 2.59 (1H, br s), 3.63 (1H, dd, *J* = 11.5, 8.5 Hz), 3.80 (1H, dd, *J* = 11.5, 3.0 Hz), 4.89 (1H, dd, *J* = 8.5, 3.5 Hz), 7.49 (2H, d, *J* = 8.0 Hz), 7.61 (2H, d, *J* = 8.0 Hz); ¹³C NMR (125 MHz, CDCl₃): δ 67.9, 74.0, 125.1 (q), 125.4, 125.5, 130.3 (q), 144.4; IR (neat): 3396.7 (br m), 3317.0 (br m), 2926.6 (w), 1406.8 (w), 1322.5 (s), 1231.0 (w), 1173.8 (s), 125.8 (s), 1093.6 (m), 1064.9 (s), 1033.4 (m), 1017.0 (m), 895.3 (m), 837.7 (s), 762.2 (w), 681.8 (w), 636.0 (w), 607.3 (m), 523.1 (m), 429.3 (w) cm⁻¹. HRMS-(ESI+) for C₉H₁₃F₃NO₂ [M+NH₄]: calculated: 224.0898, found: 224.0906. [α]_D²⁰ = +30.564 (*c* = 1.265, CHCl₃, *l* = 50 mm).

Analysis 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-(3-(trifluoromethyl)phenyl)ethane-1,2-diol prepared from treatment of 4-(trifluoromethyl)styrene with osmium tetraoxide and 4-methylmorpholine *N*-oxide. The absolute stereochemistry was assigned by analogy.

Chiral GLC (β -dex, Supelco, 140 °C, 20 psi, s/r = 35:1) – analysis of the acetonide of 1-(4-(trifluoro-methyl)phenyl)ethane-1,2-diol.



racemic

diboration product

| Peak # | RetTime [min] | Туре | Width [min] | Area [pA*s] | Height [pA] | Area % |
|-----------|------------------|--------|----------------|----------------|----------------|-----------|
| | 8.169 | MM | 0.0667 | 21.98512 | 5.49291 | 9.43729 |
| 2 | 8.715 | MM | 0.0723 | 210.97491 | 48.62221 | 90.56271 |

(2S,4S)-4,8-dimethylnon-7-ene-1,2-diol. The diboration Me Me ОН OH was performed according to the general procedure with Me (S)-4,8-dimethylnona-1,7-diene (100.0 mg, 656.7 µmol), Pt(dba)₃ (5.9 mg, 6.6 µmol), (R,R)-3,5-diisopropylphenylTADDOLPPh (7.2 mg, 7.9 µmol), and B₂(pin)₂ (175.1 mg, 689.5 µmol) in tetrahydrofuran (1.3 mL, 0.5 M). The crude reaction mixture was purified on silica gel (20-40% ethyl acetate in hexanes) to afford the product as a clear, colorless oil (97.7 mg, 80% yield). $R_f = 0.32$ (50% ethyl acetate in hexane, stain in KMnO₄). ¹H NMR (500 MHz, CDCl₃): δ 0.92 (3H, d, J = 6.5 Hz), 1.09-1.16 (1H, m), 1.28-1.42 (3H, m), 1.58 (3H, s), 1.66 (3H, s), 1.53-1.61 (1H, m), 1.88-2.02 (2H, m), 3.38 (1H, dd, J =11.0, 8.0 Hz), 3.62 (1H, dd, J = 11.0, 3.0 Hz), 3.77-3.82 (1H, m), 5.05-5.08 (1H, m); ¹³C NMR (125 MHz, CDCl₃): δ 20.1, 25.3, 25.7, 29.2, 29.4, 36.7, 40.5, 66.9, 70.5, 124.6, 135.3; IR (neat): 3363.4 (m), 2954.5 (m), 2924.6 (s), 2872.2 (m), 1457.4 (m), 1376.9 (s), 1145.0 (m), 1110.0 (m), 1063.3 (s), 1031.9 (m), 949.9 (w), 884.8 (w) cm⁻¹; HRMS-(ESI+) for C₁₁H₂₃O₂ [M+H]: calculated: 187.1698, found: 187.1693. $[\alpha]_D^{20} = -4.866$ (*c* = 3.435, CHCl₃, l = 50 mm). The diastereometric ratio was determined by ¹H NMR spectroscopy. The relative stereochemistry was assigned by analogy.

Me Me OH (2*R*,4*S*)-4,8-dimethylnon-7-ene-1,2-diol. The diboration was performed according to the representative procedure with (*S*)-4,8-dimethylnona-1,7-diene (100.0 mg, 656.7 μ mol), Pt(dba)₃ (5.9 mg, 6.6 μ mol), (*S*,*S*)-3,5-diisopropylphenylTADDOLPPh (7.2 mg, 7.9 μ mol), and B₂(pin)₂ (175.1 mg, 689.5 μ mol) in tetrahydrofuran (1.3 mL, 0.5 M). The crude reaction mixture was

purified on silica gel (20-40% ethyl acetate in hexanes) to afford a clear, colorless oil that could not be separated from pinacol (88.8 mg, 73% yield). R_f = 0.36 (50% ethyl acetate in hexanes, stain in KMnO₄); ¹H NMR (500 MHz, CDCl₃): δ 0.89 (3H, d, *J* = 7.0 Hz), 1.02-1.12 (1H, m), 1.14-1.23 (1H, m), 1.27-1.34 (1H, m), 1.42-1.48 (1H, m), 1.57 (3H, s), 1.59-1.68 (1H, m), 1.65 (3H, s), 1.90-2.02 (2H, m), 2.32 (2H, br s), 3.38 (1H, ddd, *J* = 11.0, 7.5, 1.0 Hz), 3.59 (1H, d, *J* = 11.0 Hz), 3.76-3.81 (1H, m), 5.05-5.08 (1H, m); ¹³C NMR (125 MHz, CDCl₃): δ 17.6, 19.1, 25.4, 25.7, 28.7, 37.8, 40.2, 67.4, 70.1, 124.6, 131.3; IR (neat): 3363.1 (s), 2926.6 (s), 2872.6 (m), 1457.0 (m), 1377.0 (s), 1145.1 (m), 1065.3 (s), 1027.0 (m), 973.0 (m), 949.8 (m), 736.4 (m) cm⁻¹; HRMS-(ESI+) for C₁₁H₂₃O₂ [M+H]: calculated: 187.1698, found: 187.1703. $[\alpha]_D^{20} = +2.930$ (*c* = 5.740, CHCl₃, *l* = 50 mm). The diasteriomeric ratio was determined by ¹H NMR spectroscopy. The relative stereochemistry was assigned by analogy.

Spectral data are in accordance with the literature.⁷⁵ HRMS-(ESI+) for $C_{10}H_{21}O_2$ [M+H]: calculated: 173.1542, found: 173.1539. [α]_D²⁰ = -9.284 (*c* = 1.025, CHCl₃, *l* = 50 mm).

Proof of stereochemistry:

The relative configuration was assigned by comparison of the ¹³C NMR and ¹H NMR spectrum with that reported in the literature.⁷⁵

Me (2*R*,3*S*)-3,7-dimethyloct-6-ene-1,2-diol. The diboration was me (*R*,3*S*)-3,7-dimethyloct-6-ene-1,2-diol. The diboration was performed according to the general procedure with (*S*)-3,8dimethylnona-1,7-diene (50.0 mg, 362 µmol), Pt(dba)₃ (9.7 mg, 11 µmol), (*S*,*S*)-3,5diisopropylphenylTADDOLPPh (11.8 mg, 13.0 µmol), and B₂(pin)₂ (96.0 mg, 378.0 µmol) in tetrahydrofuran (0.35 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-65% ethyl acetate in hexanes) to afford a clear, colorless oil that could not be separated from pinacol (43.0 mg, 69% yield). R_f = 0.35 (50% ethyl acetate in hexanes, stain in KMnO₄). The diasteriomeric ratio was determined by ¹H NMR spectroscopy. Spectral data are in accordance with the literature.⁷⁵ HRMS-(ESI+) for C₁₀H₂₁O₂ [M+H]: calculated: 173.1542, found: 173.1541. [α]_D²⁰= -14.893 (*c* = 1.045, CHCl₃, *l* = 50 mm).

Proof of stereochemistry:

The relative configuration was assigned by comparison of the ¹³C NMR and ¹H NMR spectrum with that reported in the literature.⁷⁵

⁷⁵ Miyazawa, M.; Marumoto, S.; Masuda, A.; Kano, H.; Takechi, H. J. Agric. Food Chem. 2009, 57, 7800.

(*R*)-1-((*R*)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol. The dibor-ation was performed according to the general procedure with Me_{Me}^{+} (*S*)-2,2-dimethyl-4-vinyl-1,3-dioxolane (60.0 mg, 468.1 µmol), Pt(dba)₃ (12.6 mg, 14.0 µmol), (*R*,*R*)-3,5-diisopropylphenylTADDOLPPh (15.3 mg, 16.9 µmol), and B₂(pin)₂ (124.8 mg, 491.5 µmol) in tetrahydrofuran (0.46 mL, 1.0 M). The crude reaction mixture was purified on silica gel (50-80% ethyl acetate in hexanes, stain in KMnO₄) to afford the product as a clear, colorless oil (41.8 mg, 55% yield). The diasteriomeric ratio was determined by ¹H NMR spectroscopy. Spectral data are in accordance with the literature.⁷⁶ HRMS-(ESI+) for C₁₀H₂₁O₂ [M+H]: calculated: 173.1542, found: 173.1541. [α]_D²⁰ = +1.791 (*c* = 0.335, CHCl₃, *l* = 50 mm).

Proof of stereochemistry:

The relative configuration was assigned by comparison of the ¹³C NMR and ¹H NMR spectrum with that reported in the literature.⁷⁶

(S)-1-((R)-2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol. The dibor-ation was performed according to the general procedure with (S)-2,2-dimethyl-4-vinyl-1,3-dioxolane (60.0 mg, 468 µmol), Pt(dba)₃ (12.6 mg, 14.0 µmol), (S,S)-3,5-diisopropylphenylTADDOLPPh (15.3 mg, 16.9 µmol), and B₂(pin)₂ (124.8 mg, 491.5 µmol) in tetrahydrofuran (0.46 mL, 1.0 M). The

crude reaction mixture was purified on silica gel (50-80% ethyl acetate/hexanes, stain in

⁷⁶ Cren, S.; Wilson, C.; Thomas, N.R.; Org. Lett. , **2005,** 7, 3521.

KMnO₄) to afford the product as a clear, colorless oil (38.7 mg, 51% yield). The diasteriomeric ratio was determined by ¹H NMR spectroscopy. Spectral data are in accordance with the literature.⁷⁷ HRMS-(ESI+) for C₇H₁₅O₄ [M+H]: calculated: 163.0970, found: 163.0972. [α]_D²⁰ = +12.6082 (*c* = 0.720, CHCl₃, *l* = 50 mm).

Proof of stereochemistry:

The relative configuration was assigned by comparison of the ¹³C NMR and ¹H NMR spectrum with that reported in the literature.⁷⁷

(2S,4R)-4-((tert-butyldimethylsilyl)oxy)pentane-1,2-diol. The ΟН TBSO .OH Me dibor-ation was performed according to the general procedure with (R)-tert-butyldimethyl(pent-4-en-2-yloxy)silane (120.2 mg, 600.0 µmol), Pt(dba)₃ (5.4 mg, 6.0 µmol), (R,R)-3,5-diisopropylphenylTADDOLPPh (6.5 mg, 7.2 µmol), and $B_2(pin)_2$ (160.0 mg, 630.0 µmol) in tetrahydrofuran (0.60 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate/hexanes, stain in PMA) to afford the product as a clear, colorless oil that could not be separated from pinacol (174.9 mg, 1:0.885 product:pinacol = 86% vield). The diasteriomeric ratio was determined by 1 H NMR spectroscopy. Spectral data are in accordance with the literature.^{78 13}C NMR (125 MHz, CDCl₃): δ 68.9, 67.3, 67.1, 40.1, 25.7, 22.8, 17.9, -4.6, -5.1; IR (neat): 3382.0 (br m), 2929.9 (m), 2857.4 (m), 1462.9 (w), 1375.2 (m), 1254.2 (m), 1106.1 (s), 1032.2 (s), 834.1 (s), 773.7 (s), 664.8 (w) cm⁻¹; HRMS-(ESI+) for $C_{11}H_{27}O_3Si$ [M+H]: calculated: 235.1730, found: 235.1723. $[\alpha]_D^{20} = -24.307$ (*c* = 3.233, CHCl₃, *l* = 50 mm).

⁷⁷ Wroblewski, A.E.; Karolczak, W.; *Tetrahedron*, **2003**, *59*, 6075.

⁷⁸ Kumar, P.; Gupta, P.; Vasudeva Naida, S.; Chem. Eur. J. 2006, 12, 1397.

Proof of stereochemistry:

The relative configuration was assigned by comparison of the ¹³C NMR and ¹H NMR spectrum with that reported in the literature.⁷⁸

(2R,4R)-4-((tert-butyldimethylsilyl)oxy)pentane-1,2-diol. The TBSO OH ,OH Me dibor-ation was performed according to the general procedure with (R)-tert-butyldimethyl(pent-4-en-2-yloxy)silane (120.2 mg, 600.0 μ mol), Pt(dba)₃ (5.4 mg, 6.0 μ mol), (S,S)-3,5-diisopropylphenylTADDOLPPh (6.5 mg, 7.2 μ mol), and $B_2(pin)_2$ (160.0 mg, 630.0 µmol) in tetrahydrofuran (0.60 mL, 1.0 M). The crude reaction mixture was purified on silica gel (30-70% ethyl acetate/hexanes, stain in PMA) to afford the product as a clear, colorless oil that could not be separated from pinacol (167.8 mg, 1:0.676 product:pinacol = 89% vield). The diasteriomeric ratio was determined by 1 H NMR spectroscopy. Spectral data are in accordance with the literature.^{79 13}C NMR (125 MHz, CDCl₃): δ 71.5, 69.5, 66.8, 41.9, 25.8, 24.4, 17.9, -3.9, -4.9; IR (neat): 3380.2 (br m), 2929.5 (m), 2857.0 (m), 1462.6 (w), 1373.5 (m), 1253.9 (m), 1150.0 (m), 1037.9 (m), 833.6 (s), 773.9 (s), 664.8 (w) cm⁻¹; HRMS-(ESI+) for $C_{11}H_{27}O_3Si$ [M+H]: calculated: 235.1730, found: 235.1727. $[\alpha]_D^{20} = -25.027$ (*c* = 3.210, CHCl₃, *l* = 50 mm).

Proof of stereochemistry:

The relative configuration was assigned by comparison of the ¹³C NMR and ¹H NMR spectrum with that reported in the literature.⁷⁸

⁷⁹ Kumar, P.; Gupta, P.; Vasudeva Naida, S.; *Chem. Eur. J.* **2006**, *12*, 1397.

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HO OH pent-2-ene-1,5-diol. The oxidation was performed on 2,2'-(pent-2-ene-1,5-diyl)bis(4,4,5,5-tetramethyl-1,3,2-di-oxaborolane) according to the general procedure for oxidation of 1,2-diols. The crude reaction mixture was purified on silica gel (0-10% methanol in ethyl acetate, stain in PMA) to afford a clear, colorless oil (78.0 mg, 64% yield, *trans:cis* isomer = 3.8:1). ¹H NMR (500 MHz, CDCl₃): *Z***-isomer**: δ 5.85 (1H, dt, J = 11.0 Hz, 7.0 Hz), 5.59 (1H, dt, J = 11.0 Hz, 8.0 Hz), 4.14 (2H, d, J = 7.0 Hz), 3.68-3.64 (2H, t, overlaps with *E*-isomer), 2.36 (2H, dt, J = 7.0 Hz, 7.0 Hz), 1.22 (1H, br s); *E***-isomer**: δ 5.72 (1H, dt, J = 5.5 Hz, 15 Hz), 5.67 (1H, dt, J = 6.5 Hz, 15.0 Hz), 4.10 (2H, d, J = 5.5 Hz), 3.66 (2H, t, J = 6.5 Hz), 2.31 (2H, dt, J = 6.5 Hz, 6.5 Hz), 1.84 (1H,

br s); ¹³C NMR (125 MHz, CDCl₃): **mixture of isomers** δ 132.1, 131.5, 129.6, 128.7, 63.5, 61.8, 61.2, 57.8, 35.5, 30.5; HRMS-(ESI+) for C₅H₁₄NO₂ [M+NH₄]: calculated: 120.1025, found: 120.1021.

2.8.7. Catalyst Activation Experiments.

To an oven-dried J. Young tube in the dry box was added $Pt(dba)_3$ (20.0 mg, 22.3 μ mol) and d⁸-THF (1.0 mL). The tube was capped and removed from the dry box. The solution was analyzed by ¹H NMR, and the tube was returned to the dry box. (*R*,*R*)-3,5-diethylphenyl-TADDOLPPh (21.3 mg, 26.7 μ mol) was added, and the tube was sealed and removed from the dry box. After again analyzing the solution by ¹H NMR, the tube was returned to the dry box, and B₂(pin)₂ (28.3 mg, 111 μ mol) was added. The tube was once again removed from the glovebox and analyzed by ¹H NMR. The reaction mixture was then heated in the J. Young tube to 80 °C in an oil bath for 30 minutes. The tube was cooled to room temperature, and analyzed by ¹H NMR, indicating full consumption of dibenzylideneacetone and formation of 2-((1,5-diphenyl-1-(pinacolborolanyl)penta-1,4-dien-3-yl)oxy)-pinacolborolane.

2.8.8. Calorimeter Experiments.

Representative procedure for diboration reactions in calorimeter studies.

To an oven-dried reaction calorimeter vial equipped with a magnetic stir bar was added Pt(dba)₃ (6.9 mg, 7.6 μ mol), (*R*,*R*)-3,5-diethylphenyl-TADDOLPPh (8.3 mg, 8.0 μ mol), and B₂(pin)₂ (203.7 mg, 802.1 μ mol) on the benchtop. The vial was sealed with a

septum cap and purged with N₂. Tetrahydrofuran (0.8 mL, 1.0 M) was then added via syringe under N2. The N2 line was removed and the reaction mixture was heated to 80 °C in an oil bath for 20 minutes. The reaction mixture was cooled to room temperature and placed in the Omnical SuperCRC calorimeter. To the reference vial was added tetrahydrofuran (0.8 mL) and $B_2(pin)_2$ (203.7 mg, 802.1 µmol). The reference vial was then placed in the calorimeter. 1-Tetradecene (194 µL, 764 µmol) was taken up in a 250 μ L gas-tight glass syringe, and the syringe was placed into the sample syringe inlet. Another sample of 1-tetradecene (194 µL, 764 µmol) was taken up in a separate 250 µL gas-tight glass syringe, and the syringe was placed into the reference syringe inlet. The system was then thermostated to 60 °C and was allowed to stand for 1 hour to reach thermal equilibrium. The reaction was initiated by addition of 1-tetradecene to both the reaction vial and the reference vial simultaneously and all at once via microsyringe, with minimal disturbance of the calorimeter. The microsyringe was not removed from the vial. The top of the calorimeter was then fully insulated, and the reaction was allowed to run without disturbance until the heat evolved from the reaction returned to baseline. After the reaction was complete and the instrument was re-equilibrated, a correction factor to account for heat flow lag of the instrument was performed. Data from the calorimeter was then analyzed using Microsoft Excel.

2.8.9. Determination of ¹²C/¹³C Kinetic Isotope Effect^{80,81}

2.8.9.1. Sample Collection for Determination of ¹²C/¹³C Kinetic Isotope Effect

To an oven-dried 50 mL round-bottomed flask equipped with a magnetic stir bar in the dry box was added Pt(dba)₃ (115 mg, 127 μ mol), (*R*,*R*)-3,5-di-*iso*-propylphenyl-TADDOLPPh (138 mg, 152 µmol), B₂(pin)₂ (3.87 g, 15.2 mmol), and tetrahydrofuran (12.7 mL, 1.0 M). The vial was sealed with a septum, taped, and brought out of the dry box. The reaction mixture was heated to 80 °C in an oil bath for 25 minutes. The flask was cooled to room temperature and brought back into the dry box. To the reaction flask was added distilled and degassed allylbenzene (1.50 g, 12.7 mmol). The flask was sealed once more, taped, brought out of the dry box, and then allowed to stir at 60 °C for 55 minutes. The progress of the reaction was previously monitored by ¹H NMR spectroscopy. The reaction mixture was cooled to 0 °C (ice/water) and charged with 3 M sodium hydroxide (45 mL), and 30% hydrogen peroxide (20 mL). The reaction was gradually warmed to room temperature and allowed to stir for 3 hours at which time the vial was cooled to 0 °C (ice/water) and saturated aqueous sodium thiosulfate was added dropwise over 5 minutes. 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 Na₂SO₄, filtered, and concentrated by rotary evaporation. The conversion was determined by ¹H NMR to be

⁸⁰ Singleton, D. A.; Thomas, A. A. J Am. Chem. Soc. 1995, 117, 9357.

⁸¹ For Similar analyses, see: a) Frantz, D. E.; Singleton, D. A.; Snyder, J.P. J. Am. Chem. Soc. **1997**, *119*, 3383. b) Denmark, S. E.; Bui, T. J. Org. Chem. **2005**, 70, 10393. c) Edwards, D. R.; Montoya-Perez, P.; Crudden, C. M. Org. Lett. **2007**, *9*, 5481. d) Gao, R.; Yi, C. S. J. Org. Chem. **2010**, *75*, 3144.

 $83 \pm 3\%$. The resulting residue was purified on silica gel (0-65% ethyl acetate in hexanes) to yield 247 mg of recovered starting material. Labeled as **Trial 1**.

This process was repeated with a second sample from the same source of starting material. This reaction proceeded to $81\% \pm 3\%$ completion, and 274 mg of starting material was recovered. Labeled as **Trial 2**.

2.8.9.2. ¹³C NMR Measurements.

Purified samples of the recovered starting material (allylbenzene) and standard allylbenzene (from commercial source) were analyzed individually by ¹³C NMR spectroscopy, following Singleton's protocol. The spectra were acquired using a Varian Unity Inova 500 MHz spectrometer (125 MHz, CDCl₃) at 25 °C with inverse-gated decoupling and acquisition time of 4.920 s collecting 300000 points. T1 values were determined prior to the acquisitions, and delays of 125 s (125s > 8 x T1, with the exception of C4, which had a T1 of 23.8 s) were utilized between pulses. Three independent acquisitions were obtained for each sample (~10 hour acquisition time). Each spectrum was manually integrated three times to ensure integration accuracy, utilizing minimal baseline and phase correction.

The integration of the recovered starting material in comparison to the standard (commercial source of allyl benzene) for **Trial 1** and **Trial 2** are provided in Table S1. Table S2 contains the relative integration of the "enriched" sample (recovered starting material) to the "unreacted" or standard sample. This value is determined by R/R_0 , where R = "enriched" integration and $R_0 =$ "unreacted" integration. The calculated ¹²C/¹³C
isotope effects, as obtained using equation (1), are provided in Table S3. Standard deviations were determined following reported procedures.⁸⁰

$$KIE = \frac{\ln(1-F)}{\ln[(1-F)R/R_0]}$$
(1)

F = percent conversion of the substrate during diboration reaction (determined by ¹H NMR spectroscopy)



Table S1. Average integrations for **Trial 1** and **Trial 2** for the diboration/oxidation of allylbenzene. The starting material was recovered after the reaction was run to $83.6\pm3\%$ and $81.4\%\pm3\%$ completion, respectively.

| - | C1 | C2 | C3 | C4 | C5 | C6 | C7 |
|--|---------|--------|---------|--------|---------|---------|------------|
| ¹³ C NMR δ (125 MHz, CDCl ₃) | 115.59 | 137.34 | 40.15 | 139.86 | 128.48 | 128.29 | 125.96 |
| Control ^a - Spec. #1 | 1047.18 | 920.98 | 1104.33 | 520.28 | 1988.43 | 1970.72 | 1000 (std) |
| Spec. #2 | 1049.67 | 921.61 | 1109.63 | 520.75 | 1998.67 | 1966.12 | - |
| Spec. #3 | 1046.87 | 914.97 | 1106.77 | 521.03 | 1986.10 | 1968.78 | - |
| Control Avg. | 1047.91 | 919.19 | 1106.92 | 520.69 | 1991.07 | 1968.54 | 1000 (std) |
| Std. Dev. ^b | 1.878 | 3.240 | 2.611 | 1.954 | 6.918 | 2.496 | - |
| Enriched Trial 1 ^a | | | | | | | |
| Spec. #1 | 1069.92 | 943.65 | 1108.20 | 517.27 | 1991.45 | 1971.82 | 1000 (std) |
| Spec. #2 | 1069.73 | 944.42 | 1109.69 | 516.43 | 1986.42 | 1966.35 | - |
| Spec. #3 | 1068.08 | 939.36 | 1107.94 | 521.09 | 1982.43 | 1966.00 | - |
| Enriched Avg. | 1069.24 | 942.48 | 1108.61 | 518.26 | 1986.77 | 1968.06 | 1000 (std) |
| Std. Dev. ^b | 1.878 | 3.563 | 1.834 | 2.894 | 6.704 | 3.573 | - |
| Enriched Trial 2 ^a | | | | | | | |
| Spec. #1 | 1070.48 | 940.89 | 1108.65 | 519.79 | 1987.91 | 1968.93 | 1000 (std) |
| Spec. #2 | 1070.45 | 939.23 | 1005.69 | 523.00 | 1991.41 | 1969.40 | - |
| Spec. #3 | 1067.76 | 937.67 | 1113.31 | 523.28 | 1988.09 | 1972.99 | - |
| Enriched Avg. | 1069.76 | 939.26 | 1109.22 | 522.02 | 1989.14 | 1970.44 | 1000 (std) |
| Std. Dev. ^b | 2.196 | 1.501 | 3.660 | 2.018 | 2.833 | 3.284 | - |

a) Each spectrum was integrated three times. The average value is provided. b) The standard deviation is from all integrated spectra (three for each run).

| | C1 | C2 | C3 | C4 | C5 | C6 | C7 |
|--|--------------|--------------|--------------|--------------|--------------|--------------|--------|
| ¹³ C NMR δ (125 MHz, CDCl ₃) | 115.59 | 137.34 | 40.15 | 139.86 | 128.48 | 128.29 | 125.96 |
| Control/Enriched | 1.0204 | 1.0253 | 1.0015 | 0.9951 | 0.9978 | 0.9998 | 1.0000 |
| (R/R ₀) - Trial 1 | | | | | | | |
| Std. Dev. | ±0.0025 | ±0.0052 | ± 0.0029 | ± 0.0067 | ± 0.0048 | ± 0.0022 | - |
| Control/Enriched | 1.0207 | 1.0218 | 1.0022 | 1.0026 | 0.9990 | 1.0010 | 1.0000 |
| (R/R ₀) - Trial 2 | | | | | | | |
| Std. Dev. | ± 0.0028 | ± 0.0040 | ± 0.0041 | ± 0.0054 | ± 0.0038 | ± 0.0021 | - |

 Table S2. Relative integrations of Trial 1 and Trial 2 for the diboration/oxidation of allylbenzene.

Table S3. Calculated ${}^{12}C/{}^{13}C$ kinetic isotope effects for the diboration/oxidation of allylbenzene.

| | C1 | C2 | C3 | C4 | C5 | C6 | C7 |
|--|--------------|--------------|--------------|--------------|--------------|---------|--------|
| ¹³ C NMR δ (125 MHz, CDCl ₃) | 115.59 | 137.34 | 40.15 | 139.86 | 128.48 | 128.29 | 125.96 |
| KIE (83.6 ± 3% | 1.0113 | 1.0140 | 1.0008 | 0.9973 | 0.9988 | 0.9999 | 1.0000 |
| conv) - Trial 1 | | | | | | | |
| Std. Dev. | ±0.0018 | ± 0.0032 | ± 0.0016 | ± 0.0037 | ± 0.0027 | ±0.0012 | - |
| KIE (81.4 ± 3% | 1.0123 | 1.0130 | 1.0013 | 1.0015 | 0.9994 | 1.0006 | 1.0000 |
| conv) - Trial 2 | | | | | | | |
| Std. Dev. | ± 0.0020 | ± 0.0027 | ±0.0024 | ± 0.0032 | ±0.0022 | ±0.0012 | - |

Figure S1. ${}^{12}C/{}^{13}C$ kinetic isotope effects for each trial of the diboration/oxidation of allylbenzene.









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|----------|-----|------------|
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Chapter 3

Synthesis of Vinyl Boronates from 1,1-Bis(boronates) and Aldehydes: A Practical Boron-Wittig Reaction

3.1. Introduction

Vinyl boronate esters are important and widely used functional motifs in organic synthetic chemistry. In general, they have superb chemical stability and low toxicity when compared to other vinyl metal reagents. A vast array of boronate precursors are commercially available or easily accessible, making synthesis and utility of vinyl boronates highly appealing to synthetic chemists (Scheme 3.1A). Furthermore, their ability to participate in many mild and efficient transformations such as Suzuki-Miyaura couplings,¹ Chan-Lam couplings,² Hayashi-Miyaura conjugate additions,³ and Petasis reactions,⁴ to name a few, demonstrates their versatility as intermediates for drug and natural product synthesis (Scheme 3.1B).

Despite the abundance of reports over the past 50 years regarding the synthesis of vinyl boronate esters from alkynes and alkenes, their synthesis from other readily available reagents is lacking (*vide infra*). In addition, while the production of 1,2-

¹ (a) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457. (b) Suzuki, A. *J. Organomet. Chem.* **1999**, *576*, 147. (c) Lennox, A. J.; Lloyd-Jones, G. C. *Chem. Soc. Rev.* **2014**, *43*, 314.

² (a) Shade, R. E.; Hyde, A. M.; Olsen, J.-C.; Merlic, C. A. J. Am. Chem. Soc. **2010**, 132, 1202. (b) Winternheimer, D. J.; Merlic, C. A. Org. Lett. **2010**, 12, 2508.

³ (a) Takaya, Y.; Ogasawara, M.; Hayashi, T. *Tetrahedron Lett.* **1998**, *39*, 8479. (b) Takaya, Y.; Senda, T.; Kurushima, H.; Ogasawara, M.; Hayashi, T. *Tetrahedron: Asymmetry* **1999**, *10*, 4047.

⁴ (a) Candeias, N. R.; Montalbano, F.; Cal, P. M. S. D.; Gois, P. M. P. *Chem. Rev.* **2010**, *110*, 6169. (b) de Graaff, C.; Ruijter, E.; Orru, R. V. A. *Chem. Soc. Rev.* **2012**, *41*, 3969.

disubstituted vinyl boronates in a stereoselective fashion has seen much success throughout the years, highly regio- and stereoselective syntheses of tri- and 1,1disubstituted vinyl boronates is a continuing challenge. In this chapter, I will present the development of a practical and highly stereoselective boron-Wittig reaction between 1,1disubstituted bis(boronate) esters and aldehydes to furnish di- and trisubstituted vinyl boronates. The transformation represents a transition-metal free substitute to alkyne hydroboration that might otherwise suffer from low stereo- or regiocontrol.

Scheme 3.1.



3.2 Background

3.2.1. Representative Syntheses of 1,2-Disubstituted Vinyl Boronate Esters. The earliest routes to vinyl boronate esters relied mostly on the synthesis of organometallic intermediates and subsequent treatment with an electrophilic borate ester.⁵ For example, in 1966, Hunter and Woods described the synthesis of 2-methyl-2,4-pentanediol derived vinyl boronate **3.3** via a transmetallation between vinyl Grignard **3.2** and borate ester **3.1** (Scheme 3.2).⁶ The reaction provided moderate yields of the desired products, but required cryogenic temperatures and the intermediacy of a reactive and functional group intolerant organometallic reagent.





A more convenient approach would involve the hydroboration of alkynes with a disubstituted borane. In 1966, Woods and Strong reported on a *cis* hydroboration of 1-heptyne with 4,4,6-trimethyl-1,3,2-dioxaborinane **3.4** to provide vinyl boronate **3.5** in

⁵ (a) Mattesson, D. S. Acc. Chem. Res. **1970**, *3*, 186. (b) Schaumber, G. D.; Dobovan, S. J. Organomet. Chem. **1969**, *20*, 261. (c) Mattesson, D. S.; Thomas, J. R. J. Organomet. Chem. **1970**, *24*, 262. (d) Pastro, D. J.; Chow, J.; Arora, S. K. Tetrahedron **1969**, *25*, 1557.

⁶ Woods, W. G.; Bengelsdorf, I. S.; Hunter, P. L. J. Org. Chem. 1966, 31, 2766.

69% yield (Scheme 3.3, eq 1).⁷ Unfortunately, **3.4** was found to be a slow hydroborating reagent, requiring high temperatures and long reaction times for complete consumption of the starting material. Subsequently, Brown and Gupta reported on a more reactive hydroboration reagent, catecholborane [HB(cat)], which was capable of hydroborating various terminal alkynes in high yields and high regioselectivity for the terminal vinyl boronate **3.6** under milder conditions (Scheme 3.3, eq 2).⁸ Notably, only *cis*-hydroboration occurred such that the *trans* product were formed in high stereoselectivity and yields, and in moderate to excellent regiocontrol.

Scheme 3.3. Early Example of Alkyne Hydroboration Reported by Woods and Brown.



Since these seminal reports, more stable hydroborating reagents such as pinacolborane [HB(pin)] have also emerged, and have been employed successfully with

⁷ Woods, W. G.; Strong, P. L. J. Am. Chem. Soc. 1966, 88, 4667.

⁸ (a) Brown, H. C.; Gupta, S. K. J. Am. Chem. Soc. 1972, 94, 4370. (b) Brown, H. C.; Gupta, S. K. J. Am. Chem. Soc. 1975, 97, 5249.

activated and unactivated terminal alkynes. In 1992, Knochel reported that 2 equivalents of HB(pin) could be utilized to efficiently hydroborate a variety of terminal alkynes at room temperature in just 2 hours (Scheme 3.4, eq 1).⁹ Building on this finding, Srebnik and Pereira established that only one equivalent of HB(pin) in the presence of a catalytic amount of Schwartz's reagent was effective enough to achieve full conversion to the desired 1,2-disubstituted vinyl boronate **3.10** in high yields, and in excellent regio- and stereoselectivity (Scheme 3.4, eq 2).¹⁰ The reaction proceeds through hydrozirconation of the alkyne to access **3.12** followed by a σ -bond metathesis to regenerate the zirconium catalyst and afford the product. More recently, a similar strategy has been developed that employs catalytic dicyclohexylborane in place of Schwartz's reagent in order to promote a hydroboration followed by a boron to boron alkenyl group transfer.¹¹ Of note, unlike catechol-derived boronate esters, the pinacol-derived variants are air and moisture stable, and thus purification and subsequent transformations are more easily performed on products derived from HB(pin).

⁹ Tucker, C. E.; Davidson, J.; Knochel, P. J. Org. Chem. 1992, 57, 3482.

¹⁰ Pereira, S.; Srebnik, M. Organometallics **1995**, 14, 3127.

¹¹ Shirakawa, K.; Arase, A.; Hoshi, M. Synthesis 2004, 1814.

Scheme 3.4. Hydroboration of Terminal Alkynes with HB(pin) Reported by Knochel, Srebnik and Periera.



A number of methodologies pertaining to the synthesis of *cis* 1,2-disubstituted vinyl boronates have also emerged over the past few decades,¹² many of which are noncatalytic procedures relying on stoichiometric quantities of strong base or acid.¹³ Notably, in 2000, Miyaura and co-workers presented an unprecedented one-step synthesis of *cis* vinyl boronate esters from alkynes using HB(pin) or HB(cat) in the presence of a Rh(I) or Ir(I) catalyst and excess triethylamine (Scheme 3.5).^{14,15} The key to the turnover in selectivity is best explained by a close examination of the catalytic cycle.

¹² (a) Mirzayans, P. M.; Pouwer, R. H.; Williams, C. M.; Bernhardt, P. V. *Tetrahedron* **2009**, *65*, 8297. (b) Barbeyron, R.; Benedetti, E.; Cossy, J.; Vasseur, J. J.; Arseniyadis, S.; Smietana, M. *Tetrahedron* **2014**, *70*, 8431.

 ¹³ (a) Roush, W. R.; Ando, K.; Powers, D. B.; Palkowitz, A. D.; Halterman, R. L. J. Am. Chem. Soc. 1990, 112, 6339. (b) Ramachandran, P. V.; Pratihar, D.; Biswas, D. Chem. Commun. 2005, 1988. (c) Molander, G. A.; Ellis, N. M. J. Org. Chem. 2008, 73, 6841.

¹⁴ Ohmura, T.; Yamamoto, Y.; Miyaura, N. J. Am. Chem. Soc. 2000, 122, 4990.

¹⁵ More recently, a Ru-catalyzed *trans* hydroboration has been described: Gunanathan, C.; Hölscher, M.; Pan, F.; Lietner, W. J. Am. Chem. Soc. **2012**, 134, 14349.

Coordination of a M-P(*i*Pr)₃ complex to the alkyne followed by C-H bond insertion and hydride transfer results in generation of the vinylidene complex **3.16**. Metal-vinylidene formation is proposed to be highly favored with employment of electron-donating monodentate phosphine ligands and various Rh, Ru, and Ir complexes, as previously reported by a number of groups.¹⁶ Subsequently, oxidative addition of the borane generates metal-vinylidene 3.17, and a 1,2-migration of the boronate moiety to the α position furnishes intermediate **3.18**. Finally, reductive elimination provides the product (Z)-3.13 and regenerates the catalyst. Other groups have proposed that rather than a boryl migration from 3.17, a hydride insertion occurs to furnish 3.19, followed by reductive elimination to generate the B-C bond (see dashed arrows).¹⁷ Miyaura suggests that high stereoselectivity for the *cis* product is the result of a stereospecific formation of thermodynamically stable (E)-3.18, which is further favored with a large phosphine ligand bound to the metal center. Note that the excess triethylamine suppresses initial oxidative addition of the catalyst with the borane starting material, which would lead to *cis*-hydroboration and formation of *trans* vinyl boronate product (*E*)-3.13.

¹⁶ (a) Wolf, J.; Werner, H.; Serhadli, O.; Ziegler, M. L. *Angew. Chem. Int. Ed.Engl.* **1983**, *22*, 414. (b) Alonso, F. J. G.; Hohn, A.; Wolf, J.; Otto, H.; Werner, H. *Angew. Chem. Int. Ed. Engl.* **1985**, *24*, 406. (c) Wakatsuki, Y.; Yamazaki, H.; Kumegawa, N.; Satoh, T.; Satoh, J. Y. J. Am. Chem. Soc. **1991**, *113*, 9604. (d) Grünwald, C.; Gevert, O.; Wolf, J.; González-Herrero, P.; Werner, H. Organometallics **1996**, *15*, 1960. (e) Katayama, H.; Ozawa, F. Organometallics **1998**, *17*, 5190.

¹⁷ Cid, J.; Carbó, J. J.; Fernández, E. Chem.—Eur. J. **2012**, 18, 1512.



Scheme 3.5. Trans-Hydroboration of Terminal Alkynes Reported by Miyaura.

Recently, numerous vinyl boronate syntheses from alkene starting materials have also been developed, most often by means of a cross metathesis between a terminal olefin and a vinyl boronate.¹⁸ In 2013, Schrock and Hoveyda disclosed a highly *cis*-selective Mo-catalyzed cross metathesis between terminal olefins and vinyl boronate **3.20** (Scheme

¹⁸ (a) Blackwell, H. E.; O'Leary, D. J.; Chatterjee, A. K.; Washenfelder, R. A.; Bussmann, D. A.; Grubbs, R. H. J. Am. Chem. Soc. 2000, 122, 58. (b) Morrill, C.; Grubbs, R. H. J. Org. Chem. 2003, 68, 6031. (c) Morrill, C.; Funk, T. W.; Grubbs, R. H. Tetrahedron Lett. 2004, 45, 7733. (d) Funk, T. W.; Efskind, J.; Grubbs, R. H. Org. Lett. 2005, 7, 187. (e) McNulty, L.; Kohlbacher, K.; Borin, K.; Dodd, B.; Bishop, J.; Fuller, L.; Wright, Z. J. Org. Chem. 2010, 75, 6001. (f) Hemelaere, R.; Carreaux, F.; Carboni, B. J. Org. Chem. 2013, 78, 6786.

3.6).¹⁹ In addition to unactivated alkenes and styrenes, 1,3-dienes also were competent under the reaction conditions. Importantly, this transformation represents a rare example of accessing *cis* vinyl boronates **3.22** via a one-pot protocol using readily available alkene starting materials.

Scheme 3.6. Hoveyda and Schrock's Cis-Selective Cross Metathesis of **3.20** and Various Alkenes.



3.2.2. Representative Syntheses of 1,1-Disubstituted Vinyl Boronate Esters. The

construction of 1,1-disubstituted vinyl boronate esters remains a significant challenge in organic synthesis, especially with unactivated or electronically unbiased substrates.²⁰ Alkyne hydroboration proceeds in an *anti*-Markovnikov fashion to provide the above-

¹⁹ Kiesewetter, E. T.; O'Brien, R. V.; Elsie, C. Y.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. **2013**, 135, 6026.

²⁰ (a) Takahashi, K.; Ishiyama, T.; Miyaura, N. J. Organomet. Chem. 2001, 47, 625. (b) Takagi, J.;
Takahashi, K.; Ishiyama, T.; Miyaura, N. J. Am. Chem. Soc. 2002, 124, 8001. (c) Moran, W. J.; Morken, J.
P. Org. Lett. 2006, 8, 2413. (d) Jang, H.; Zhugralin, A. R.; Lee, Y.; Hoveyda, A. H. J. Am. Chem. Soc.
2011, 133, 7859. (e) Meng, F., Jung, B., Haeffner, F.; Hoveyda, A. H. Org. Lett., 2013, 15, 1414. (f) Guan,
W., Michael, A. K.; McIntosh, M. L.; Koren-Selfridge, L.; Scott, J. P.; Clark, T. B. J. Org. Chem. 2014, 79, 7199. (g) Jang, H., Jung, B.; Hoveyda, A. H. Org. Lett., 2014, 16, 4658. (h) Semba, K.; Shinomiya, M.; Fujihara, T.; Terao, J.; Tsuji, Y. Chem. Eur. J. 2013, 19, 7125.

mentioned 1,2-disubstituted alkenyl boronates in high regioselectivity. Thus, early protocols required a transmetallation between alkenyllithium or –magnesium reagents and an electrophilic boron source (i.e. a trialkyl borate).²¹ Unfortunately, these routes suffer from inherent limitations, most notably a limited substrate scope due to the high reactivity of the organometallic starting materials. Miyaura borylations between alkenyl halides and $B_2(pin)_2$ have also been reported;²² however, the overall process still necessitates the synthesis of 2-halo-1-olefins, and is therefore a multistep procedure typically requiring the use of an electrophilic halide source.²³

In 2010, Hoveyda and co-workers reported a novel Ni-catalyzed α -selective hydroalumination of aryl- and alkyl-substituted terminal alkynes (Scheme 3.7).^{23d} The internal vinylaluminums **3.23** could be generated directly from treatment of an alkyne with 1.3 equivalents of diisobutylaluminum hydride (dibal-H) in the presence of 3 mol% Ni(dppp)Cl₂. Importantly, in situ subjection of **3.23** to 3.0 equivalents of methoxy(pinacolato)borane [MeOB(pin)] provides the corresponding α -vinyl boronates **3.24** in moderate to high yields and excellent regioselectivity. Of note, 2-halo-1-alkenes could also be furnished in high yields and regioselectivity by substituting MeOB(pin) with *N*-bromo- or *N*-iodosuccinimide.

²¹ For a review, see: Miyaura, N.; Maruoka, K. In *Synthesis of Organometallic Compounds*; Wiley: Chichester, UK, 1997; p. 345.

²² Takagi, J.; Takahashi, K.; Ishiyama, T.; Miyaura, N. J. Am. Chem. Soc. 2002, 124, 8001.

²³ For examples, of 2-halo-1-alkene syntheses, see: (a) Spaggiari, A.; Vaccari, D.; Davoli, P.; Torre, G.; Prati, F. J. Org. Chem. 2007, 72, 2216. (b) Wang, C.; Tobrman, T.; Xu, Z.; Negishi, E. Org. Lett. 2009, 11, 4092. (c) Pan, J.; Wang, X.; Zhang, Y.; Buchwald, S. L. Org. Lett. 2011, 13, 4974. (d) Gao, F.; Hoveyda, A. H.; J. Am. Chem. Soc. 2010, 132, 10961.



3.2.3. Representative Syntheses of Trisubstituted Vinyl Boronate Esters. Despite a plethora of important natural products and pharmaceutical targets containing trisubstituted alkenes, there is still no general and practical procedure for the synthesis of trisusbstituted vinyl boronate esters.²⁴ As represented in Scheme 3.8, traditional methods pertaining to hydroboration of internal alkynes bearing sterically similar substituents suffer from low regioselectivity, and the resulting regioisomers are often difficult to separate.^{8,9,25}

Scheme 3.8. Brown's Hydroboration of Internal Alkyne 3.25 (Ref. 8).



²⁴ (a) Morrill, C.; Funk, T. W.; Grubbs, R. H. *Tetrahedron Lett.* **2004**, *45*, 7733. (b) Yuan, W.; Ma, S. *Adv. Synth. Catal.* **2012**, *354*, 1867.

 ²⁵ (a) He, X.; Hartwig, J. F. J. Am. Chem. Soc. 1996, 118, 1696. (b) Konno, T.; Chae, J.; Tanaka, T.;
 Ishihara, T.; Yamanaka, H. Chem. Commun. 2004, 690. (c) Semba, K.; Fujihara, T.; Terao, J.; Tsuji, Y.
 Chem. Eur. J. 2012, 18, 4179.

Even more challenging is the *E*-selective construction of trisubstituted vinyl boronates, of which no widely applicable example currently exists.²⁶ In 2013, the Fürstner lab reported a *trans* hydroboration of internal cyclic and acyclic alkynes. For example, treatment of 5-decyne with 1.2 equivalents of HB(pin) in the presence of 5% $[Cp*Ru(MeCN)_3]PF_6$ generates *trans* trisubstituted vinyl boronate **3.28** in good yield and excellent stereoselectivity (Scheme 3.9, eq 1). Unfortunately, employment of unsymmetric internal alkyne **3.29** provides the corresponding products **3.30** and **3.31** in moderate yield but in low regioisomeric ratios (Scheme 3.9, eq 2).

Scheme 3.9. Fürstner's Trans-Hydroboration of Internal Alkynes.



3.2.4. *History of the Boron-Wittig Reaction.* A more promising strategy for synthesis of highly substituted vinyl boronates would be one that involves a stereoselective olefination between two readily accessible conjunctive partners, with one

²⁶ Sundararaju, B.; Fürstner, A. Angew. Chem. Int. Ed. 2013, 52, 14050.

of the reagents bearing a boronate ester moiety.²⁷ One such example with high potential is the boron-Wittig reaction, which was initiated by Pelter and Matteson in the 1970's.²⁸ As displayed in Scheme 3.10, bis(boryl)methane 3.32 can undergo lithiation with the addition of lithium tetramethylpiperidide (LiTMP) at -78 °C to form 3.33. Subsequently, addition of a carbonyl electrophile results in intermediate 3.34, which undergoes an in situ boron-oxygen elimination to provide vinyl boronate **3.35**. Unfortunately, although the one-pot boron-Wittig reaction/oxidation procedure to furnish aldehyde homologation products 3.36 was studied in depth, the intermediate vinyl boronates 3.35 were rarely isolated due to the hydrolytic instability of the ethylene glycol-derived boronate motif. Thus, although the author suggested that the *trans* isomer was favored under the reaction conditions, stereoselectivity values were not thoroughly provided. Furthermore, in addition to the instability of bis(boryl) methane 3.32, its preparation is not trivial, requiring a multi-step synthesis that employs stoichiometric equivalents Li(0).^{28d} Of note, with the exception of a singular example of a reaction between a substituted 1,1bis(boronate) ester and an aldehyde, generation of tri- or tetrasubstituted vinyl boronates were not investigated by Matteson.^{28c}

²⁷ For examples other than the boron-Wittig reaction, see: (a) Takai, K.; Shinomiya, N.; Kaihara, H.; Yoshida, N.; Moriwake, T. *Synlett* **1995**, 963. (b) Guan, W.; Michael, A. K.; McIntosh, M. L.; Koren-Selfridge, L.; Scott, J. P.; Clark, T. B. *J. Org. Chem.* **2014**, *79*, 7199.

²⁸ (a) Matteson, D. S.; Moody, R. J.; Jesthi, P. K. J. Am. Chem Soc. 1975, 97, 5608. (b) Matteson, D. S.; Jesthi, P K. J. Organomet. Chem. 1976, 110, 25. (c) Matteson, D. S.; Moody, R. J. J. Am. Chem. Soc. 1977, 99, 3196. (d) Matesson, D. S.; Moody, R. J. Organometallics 1982, 1, 20. (e) Pelter, A.; Buss, D.; Colclough, E.; Singaram, B. Tetrahedron 1993, 49, 7077.

Scheme 3.10. Boron-Wittig Reaction Developed by Matteson and Co-Workers.



In 2010, Shibata and co-workers reported an extension of Matteson's work utilizing substituted 1,1-bis(boronate) ester **3.37** and phenyl ketones, which furnished various tetrasubstituted vinyl boronates **3.38** in high yields and excellent *E*-selectivity (Scheme 3.11, eq 1).²⁹ Interestingly, 2,2-diborylethylsilane **3.39** could also be employed as a coupling partner with various phenyl ketones to afford allylsilanes **3.40** (Scheme 3.11, eq 2).³⁰ Shibata's examples represent a rare and powerful method of accessing air and moisture stable tetrasubstituted vinyl boronates in high regio- and stereoselectivity. Unfortunately, synthesis of trisubstituted vinyl boronates was never investigated by either Matteson or Shibata.

²⁹ Endo, K.; Hirokami, M.; Shibata, T. *J. Org. Chem.* **2010**, *75*, 3469. Two dialkyl ketones (3-methylbutan-2-one and 1-cyclohexylethan-1-one) were also investigated, but significant differences in sterics between the alkyl substituents on the ketone were required for high stereoselectivity.

³⁰ Dialkyl ketones afforded complex crude reaction mixtures: Endo, K.; Sakamoto, A.; Ohkubo, T.; Shibata, T. *Chem. Lett.* **2011**, *40*, 1440.

Scheme 3.11. Boron-Wittig Reaction to Generate Tetrasusbstituted Vinyl Boronates.



The ability to conveniently access substituted 1,1-bis(boronate) esters would greatly improve the utility and practicality of the boron-Wittig reaction. For example, Shibata's route to these useful synthons entailed a Rh-catalyzed double hydroboration of terminal alkynes, which often suffered from monoborylation/reduction byproducts **3.42** and inherently prevented access to substrates bearing branching at the 2-position (Scheme 3.12, eq 1).³¹ Furthermore, only aryl acetylenes were extensively studied. Recently, much focus in our laboratory has been spent on the synthesis and utility of geminal bis(boronates).³² In this context, a large-scale preparation of **3.43** has been described and, with employment of alkylation reaction conditions developed by Matteson, construction of substituted variants (**3.44**) is now simple and straightforward (Scheme

³¹ Endo, K.; Hirokami, M.; Shibata, T. Synlett 2009, 1331.

³² (a) Sun, C.; Potter, B.; Morken, J. P. J. Am. Chem. Soc. 2014, 136, 6534. (b) Hong, K.; Liu, X.; Morken,

J. P. J. Am. Chem. Soc. 2014, 136, 10581. (c) Potter, B.; Szymaniak, A. A.; Edelstein, E. K.; Morken, J. P. J. Am. Chem. Soc. 2014, 136, 17918.

3.12, eq 2).^{28d} Other methods to access geminal bis(boronate) esters have also been developed over the past few years, including a Cu-catalyzed borylation of geminal dibromides,^{3232b,33} and a geminal diborylation of *N*-tosylhydrazones (Scheme 3.12, eq 3 and 4).³⁴

2.5% [RhCl(cod)]₂ B(pin) <u>6% DPPB</u> ____B(pin) (1) HB(pin) DCE, RT B(pin) 3.41 3.42 (2.4 equiv.) 26-68% y 3.41 1.7:1.0-4.7:1.0 3.41:3.42 B(pin) B(pin) LiTMP, 0 °C, 5 min (2) Br B(pin) B(pin) THF, RT 3.43 3.44 10% Cul B(pin) Br LiOMe (2.5 equiv.) $B_2(pin)_2$ (3)DMF, RT B(pin) R 3.45 (2 equiv.) B(pin) B₂(pin)₂ (1.2 equiv.) NaH (1.2 equiv.) **NNHTs** (4) toluene, 110 °C B(pin) toluene, RT 3.46

Scheme 3.12. Syntheses of Substituted 1,1-Bis(boronate) Esters.

With reliable methods for geminal bis(boronate) syntheses in hand, we reasoned that the boron-Wittig reaction could provide a highly general route to a variety of air and moisture stable vinyl(boronate) esters. As depicted in Scheme 3.13, through the use of

³³ Ito, H.; Kubota, K. Org. Lett. 2012, 134, 10693.

³⁴ Li, H.; Shangguan, X.; Zhang, Z.; Huang, S.; Zhang, Y.; Wang, J. Org. Lett. 2014, 16, 448.

the appropriate aldehyde in conjunction with substituted 1,1-bis(boronates) **3.47**, synthetically useful di- and trisubstituted vinyl boronates **3.48-3.50** bearing various substitution patterns could potentially be furnished. Additionally, the described methodology has the potential to be highly stereoselective and would bypass inherent regioselectivity issues that plague other protocols. More specifically, the overall transformation would represent a transition-metal-free alternative to alkyne hydroboration methodologies, and also uses readily available starting materials.

Scheme 3.13. Potential Method for Accessing Structurally Diverse Vinyl Boronates.



3.3. Development of a Practical and General Boron-Wittig Reaction for Access to Structurally Diverse Vinyl Boronates.³⁵

3.3.1. Synthesis of 1,2-Disubstituted Vinyl Boronates via the Boron-Wittig

Reaction. Considering Matteson's early success developing the boron-Wittig reaction between bis(boryl)methane **3.32** and aldehydes, optimal conditions for a similar reaction

³⁵ Coombs, J. R.; Zhang, L.; Morken, J. P. Org. Lett. 2015, 17, 1708.

employing bis(boryl)methane **3.43** were quickly realized (Table 3.1). Lithiation of **3.43** was found to occur in just 5 minutes at 0 °C. Subsequently, hexanal was added to the reaction mixture dropwise at 0 °C, and the reaction was allowed to warm to room temperature. To our delight, full conversion to the desired product was achieved within 1.5 hours, providing the vinyl boronate in moderate yield and excellent stereoselectivity (entry 1). Lowering the temperature to -78 °C for 4 hours provided slightly enhanced yields and stereoselectivity (entry 2). Additionally, lower temperature had a more pronounced effect on selectivity values when employing cinnamaldehyde as the electrophile (93:7 *E:Z* at room temperature versus >97:3 at -78 °C; entries 3 and 5). Thus, although high levels of stereoselectivity can still be obtained at ambient temperatures, allowing for shorter reaction times, conditions in which aldehyde is added at -78 °C were selected for further studies (entry 5). Importantly, a workup was not necessary, and only a short plug of silica gel was required for isolation of pure vinyl boronate products.

| | 0 B | (pin) L | LiTMP (1.2 equiv.) THF, 0 °C, 5 min | • | ,B(pin) |
|-------|-----------------|---|--|-----------|----------|
| R | H (1.: | [∼] B(pin) 3.43 2 equiv.) | <i>then</i> aldehyde THF, temp. | - R´ → | |
| entry | R | temp. (^o C) | time (h) | yield (%) | E:Z |
| 1 | <i>n</i> -hexyl | 0 °C-RT | 1.5 | 74 | 97:3 |
| 2 | <i>n</i> -hexyl | -78 °C | 4.0 | 80 | >97:3 |
| 3 | Ph | 0 °C-RT | 1.5 | 83 | 92.6:7.4 |
| 4 | Ph | O°C | 4.0 | 60 | 93.5:6.5 |
| 5 | Ph | -78 °C | 4.0 | 71 | >97:3 |

Table 3.1. Temperature Screen for Boron-Wittig Reaction of 3.43 with Aldehydes.

With a simple and effective procedure already providing high yields and excellent stereoselectivity, the substrate scope was investigated and is provided in Table 3.2. Moderate to high yields and excellent stereoselectivities were obtained with linear aldehydes (entries 1 and 2). While α -branches on the aldehyde are tolerated under the reaction conditions and excellent selectivity for the *trans* isomer is observed (entry 3), yield begins to suffer with bulkier substitutents (entry 4). Benzaldehyde could also be employed and provide the *trans*-styrenyl boronate in moderate yields and as a single isomer (entry 5).

| R H | B(pin) LiTMP (1.2 + B(pin) THF, 0 °C 3.43 <i>then</i> ald (1.2 equiv.) THF, -78 | 2 equiv.) <u>2, 5 min</u> ehyde °C, 4 h | B(pin) |
|-------|--|--|--------|
| entry | product | yield (%) ^a | E:Z |
| 1 | Me B(pin) | 63 | 97:3 |
| 2 | <i>n</i> -pentyl B(pin) | 80 | >97:3 |
| 3 | B(pin) | 79 | >97:3 |
| 4 | Me Me Me | 48 | >97:3 |
| 5 | Ph B(pin) | 76 | >97:3 |

Table 3.2. Synthesis of trans-Vinyl Boronates via the Boron-Wittig Reaction.^a

a) Results are an average of two experiments. Yield represents isolated yield after purification by silica gel chromatography.

1,3-Dienes are important motifs that are commonly found in biologically active natural products and drug targets. Of interest was the possibility of extending the boron-Wittig reaction to α,β -unsaturated aldehydes in order to access synthetically challenging dienyl boronates (Table 3.3). Under the optimized boron-Wittig conditions, acrolein provided the corresponding 1,3-dienyl boronate in 59% yield and in >97:3 *E*:*Z* (entry 1). Various substitutions at the α - and β - position of the electrophile were also well tolerated, furnishing the corresponding products in high yields and stereoselectivities (entries 2-5). Synthetically challenging trienyl and enynyl vinyl boronates could also be generated in

similar efficacy and selectivities (entries 6 and 7). Notably, Michael addition of the nucleophile was not detected under any circumstance.

| R H | B(pin) LiTMP (1.2 + B(pin) THF, 0 °C, 3.43 then alder (1.2 equiv.) THF, -78 ° | equiv.) <u>5 min</u> hyde C, 4 h | B(pin) |
|-------|--|---|--------|
| entry | product | yield (%) ^a | E:Z |
| 1 | B(pin) | 59 | >97:3 |
| 2 | Me B(pin) | 87 | >97:3 |
| 3 | Ph B(pin) | 71 | >97:3 |
| 4 | Me B(pin) | 80 | >97:3 |
| 5 | Me B(pin) | 91 | >97:3 |
| 6 | Me B(pin) | 81 | >97:3 |
| 7 | <i>n</i> -pentyl | 76 | 97:3 |

Table 3.3. Boron-Wittig Reaction with **3.43** and α,β -Unsaturated Aldehydes.^a

a) Results are an average of two experiments. Yield represents isolated yield after purification by silica gel chromatography.

3.3.2. Synthesis of 1,1-Disubstituted Vinyl Boronates via the Boron-Wittig

Reaction. While we were pleased to find a highly general and practical method for accessing 1,2-disubstituted vinyl and dienyl boronates, our efforts quickly shifted towards accessing more challenging substitution patterns. In theory, it is possible that a boron-Wittig reaction between substituted 1,1-bis(boronate) esters and formaldehyde would provide a simple protocol for constructing 1,1-disubstituted vinyl boronates. Unfortunately, such a transformation was only moderately effective. Considering

formaldehyde is only available as an aqueous solution, in situ generation of the electrophile was required. In this context, Lewis acid promoted degradation of 1,3,5-trioxane is known to occur efficiently with TiCl₄ at -20 °C. Unfortunately, employing similar conditions in the presence of lithiated bis(boronate) **3.52** resulted in no reaction (Scheme 3.14, eq 1). It is likely that TiCl₄ made a stable complex with THF rather than promoting trioxane rupture.³⁶ As an alternative approach, formaldehyde was generated by treatment of paraformaldehyde with catalytic *p*-toluenesulfonic acid (*p*TsOH) at 80 °C, which was transferred via cannula to a solution of **3.52** at -78 °C (Scheme 3.14, eq 2). While a moderate yield of the desired 1,1-vinyl boronate **3.53** was obtained, the reaction setup was impractical and non-ideal.

Scheme 3.14. Synthesis of 1,1-Vinyl Boronate 3.53 from 3.51 and Formaldehyde.



³⁶ TiCl₄ has been reported to form a stable solvate with THF [TiCl₄(THF)₂]: (a) Sobota, P.; Utko, J.; Janas, Z.; *J. Organomet. Chem.* **1986**, *316*, 19. (b) Sobota, P.; Utko, J. *Polymer Commun.* **1988**, *29*, 144.

Lastly, it was reasoned that addition of a lithiated bis(boronate) to a geminally dihalogoenated electrophile might result in nucleophilic substitution followed by a B-X elimination. Excitingly, addition of dibromomethane to 1.1 equivalents of lithiated 1,1-bis(boronate) **3.52** led to moderate yields of **3.53** (Table 3.4, entry 1). While the reaction did not benefit from excess electophile (entries 2-4), substituting dibromomethane with diiodomethane facilitated reaction of **3.51** to furnish **3.53** cleanly in 87% yield (entry 5). Thus, addition of 2.0 equivalents of diiodomethane was selected for further evaluation.

Table 3.4. Optimization of 1,1-Disubstituted Vinyl Boronate Synthesis.

| B(pi PhB 3.51 | n) 8(pin) | THF, LiTMP | B(pin) R ⊕ B(pin) 3.52 | | bhile iv.) 50 °C Pr 2 hr | B(pin) |
|---------------------|--------------|--------------|------------------------------|--------------|-----------------------------------|--------|
| | entry | electrophile | equiv. | conv. (%) | yield (%) | |
| | 1 | CH_2Br_2 | 1.0 | ^a | 65 | |
| | 2 | CH_2Br_2 | 2.0 | 80 | 68 | |
| | 3 | CH_2Br_2 | 10.0 | 80 | 65 | |
| | 4 | CH_2Br_2 | solvent | | no rxn | |
| | 5 | CH_2I_2 | 2.0 | >95 | 87 | |
| | 6 | CH_2I_2 | solvent | | no rxn | |

a) 1.1 equivalents of **3.51** was employed for this reaction.

As depicted in Table 3.5, various straight-chained 1,1-bis(boronate) esters provided the corresponding products in moderate to high yields (entries 1-3). Additionally, β - and α -branched 1,1-bis(boronate) esters could be employed successfully under the optimized reaction conditions (entries 4 and 5). Note that the presence of a quaternary center adjacent to the geminal bis(boronate) moiety inhibited reaction (entry 6). Overall, this strategy provides an appealing complement to allene protoborylation and alkyne hydrometallation/borylation methods.^{20d,g,h,23d}

| | | € CH₂l₂ |
|--------|--|--|
| s(pin) | THF, LITMP | (2.0 equiv.) B(pin) |
| B(pin) | 0 °C, 5 min. R 🗇 B(pin) | 0 °C to 60 °CR |
| | | THF, 2 hr |
| entry | product | yield (%) ^a |
| | B(pin) | |
| 1 | | 87 |
| | | |
| 0 | B(pin |) 70 |
| 2 | Me | 78 |
| _ | B(pi | n) |
| 3 | TBSO | 84 |
| | | |
| 4 | | 73 |
| | B(pin) | |
| F | | 04 |
| 5 | \int | 04 |
| | | |
| | B(pin) | |
| 6 | IVIE | (30) ^b |
| | ivie ' Me | |
| | B(pin) B(pin) entry 1 2 3 4 5 5 6 | $\begin{array}{c} B(pin) \\ B(pin) \\ B(pin) \\ \hline 0 \ ^{\circ}C, \ 5 \ min. \\ \hline \\ B(pin) \\ \hline \\ entry \\ \hline \\ \\ entry \\ \hline \\ \\ B(pin) \\ \hline \\ \\ \hline \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ $ |

Table 3.5. Synthesis of 1,1-Disubstituted Vinyl Boronates.

a) Results are an average of two experiments. Yield represents isolated yield after purification by silica gel chromatography. b) Value in parentheses represents conversion. Yield not determined.

3.3.3. Synthesis of Trisusbstituted Vinyl Boronates via the Boron-Wittig Reaction. To address the regioselectivity challenges associated with synthesis of trisubstituted vinyl boronates via current methods, we considered a boron-Wittig reaction between substituted geminal 1,1-bis(boronates) and aldehydes. Treatment of pinacolderived bis(boronate) **3.51** with LiTMP at 0 °C in THF and then addition of *n*-hexanal resulted in full conversion, with Z trisubstituted vinyl boronate **3.54** being favored slightly (Table 3.6, entry 1). Lowering the reaction temperature to -78 °C for 4 hours led to formation of **3.54** in 88% yield and in a synthetically useful diastereomeric ratio favoring the *cis* isomer (entry 2). Unfortunately, addition of Lewis acids (entries 3-5), additives that coordinate cations (entries 6 and 7), or employment of mixed solvent systems (entries 8-10) did not beneficially alter stereoselectivity. Additionally, although less polar solvents were found to turn over selectivity to favor the *E* isomer, all attempts to improve diastereomeric ratios to synthetically valuable levels failed (entries 11-15).

| | B(pin) | | B(p | in) |
|----------------|--|----------------------|-----------------------------|---------------------|
| | | LiTMP, 0°C, 5 min, | | ్ష <i>n</i> -pentyl |
| | * B(pin) | then hexanal, | | 5 |
| | 3.51 | additive, -78ºC, 4 h | 3.54 | |
| entry | solvent | addidtive | conversion (%) ^b | Z:E ^c |
| 1 ^d | THF | | >95 | 69:31 |
| 2 | THF | | >95 (88% y) | 88:12 |
| 3 | THF | ZnCl ₂ | >95 | 70:30 |
| 4 | THF | MgBr ₂ | <5 | |
| 5 | THF | nBu₄Cl | 90 | 63:27 |
| 6 | THF | DMPU | >95 | 81:19 |
| 7 | THF | 12-C-4 | >95 | 85:15 |
| 8 | THF/CH ₂ Cl ₂ (1:1 |) | <15 | |
| 9 | THF/MeCN (1:1) |) | >95 | 86:14 |
| 10 | THF/dioxane (10: | 1) | >95 | 85:15 |
| 11 | toluene | | >95 | 38:62 |
| 12 | cyclohexane | | <5 | 32:68 |
| 13 | diethyl ether | | >95 | 32:68 |
| 14 | diethyl ether | ZnCl ₂ | >95 | 48:52 |
| 15 | diethyl ether | <i>n</i> Bu₄Cl | >95 | 32:68 |

Table 3.6. Optimization of Boron-Wittig Conditions to Generate Trisubstituted Vinyl Boronates.

a) Reaction employed LiTMP (1.0 equiv.), **3.51** (1.0 equiv.), hexanal (1.2 equiv.) and additive (1.0 equiv.). b) Conversion refers to consumption of **3.51** and was determined by ¹H NMR analysis of the crude reaction mixture. c) *E*:*Z* ration was dermined by ¹H NMR analysis of the crude reaction mixture. d) Reaction run from 0 °C to RT for 1.5 h.

Interestingly, employment of alternative boronate esters dramatically altered stereoselection (Scheme 3.15). For example, with neopentylglycolato (npg) derived 1,1-bis(boronate) **3.55**, trisubstituted vinyl boronate **3.57** could be accessed in a 77:23 *Z:E* ratio and in 90% conversion. Fortunately, employing dimethylpenanediolato (dmpd)
derived bis(boronate) **3.56** resulted in generation of vinyl boronate **3.58** in 81% yield in a 27:73 *Z*:*E* ratio. Note that although a less polar medium (diethyl ether in place of THF) resulted in a reversal in stereoselectivity with employment of pinacol-derived boronate esters (Table 3.6, entry 13), diminished *E*-selectivity was observed when employing dmpd-derived boronate esters.





A variety of aldehydes were tested in combination with either pinacolato- or dmpd-derived geminal bis(boronate) esters for the construction of trisubstituted vinyl boronates (Table 3.7). As suggested above, using hexanal as the electrophile, both *E*- and *Z*-isomers could be furnished in good yields and with synthetically useful diastereomeric ratios simply by varying the boronate ester diol moiety (entries 1 and 2). A similar reversal in diastereoselectivity can be observed with β -branched aldehydes (entries 3 and 4). Increasing the steric influence of the aldehyde by means of α -branching resulted in a predominance of the *E*-isomer regardless of whether **3.51** or **3.56** is employed (entries 5-8), although **3.56** still provides enhanced stereoselectivity (entry 5 vs enty 6). Importantly, bis(boronate) esters bearing bulky substitutuents also favor *E*-isomer formation regardless of the size of the aldehyde (entries 9-12). Note that dmpd-derived bis(boronate) esters bearing bulky substituents suffer from low conversion, presumably due to slow lithiation (entry 10). Overall, the substrate screen suggests that employing large boronate substitutuents (\mathbb{R}^1) or large aldehyde substituents (\mathbb{R}^2) lead to formation of the *trans* vinyl boronates, whereas small boronates in combination with linear aldehydes tend to favor formation of *cis* vinyl boronates (entries 1,3, and 13).

While stereoselectivity is only moderate for construction of trisubstituted vinyl boronates in some select cases, it is worth noting that the boron-Wittig reaction bypasses regioselectivity issues associated with other methods for accessing similar motifs. For example, employment of bis(boronate) **3.51** with aldehyde **3.59** furnishes trisubsituted vinyl boronate **3.60** (Scheme 3.16, eq 1), while the combination of bis(boronate) **3.61** and aldehyde **3.62** provides the respective regioisomer **3.63** (eq 2). Thus, the boron-Wittig reaction allows access to both regioisomers of product in high yield and with excellent stereoselectivity simply by employing the appropriate coupling partners. In addition to the difficulty of accessing the *E*-product, synthesis of regioisomer **3.63** would be highly disfavored via existing hydroboration methodologies.

| DI | 0 | LiTMP (1.2 equiv.) | L | ВГ |
|--------------------|-----------|---|-------------------|-----------------------------|
| | + 1 | $\xrightarrow{\text{IHF, 0 °C, 5 min.}} \mathbb{R}^{1}$ | \mathbb{R}^2 | $R^1 \xrightarrow{R^2} R^2$ |
| R ^{1°} BL | R^{2} H | then aldehyde | H | н Н |
| | | THF, -78 °C, 4 h <i>E</i> -pi | roduct | Z-product |
| entry | L | major product | yield (%) | E:Z |
| | | B(pin) | | |
| 1 | pin | Ph | 88 | 12:88 |
| | | n-pentyl | | |
| 0 | dura a d | B(dmpd) | 04 | 70.07 |
| 2 | ampa | Ph | 81 | 73:27 |
| | | B(pin) | | |
| 3 | pin | Ph | 93 | 26:74 |
| | | i-Bu | | |
| 4 | dmpd | B(dmpd) | 81 | 78.22 |
| | ampa | Ph i-Bu | 01 70.22 | |
| 5 | nin | B(pin) | 89 | 61.39 |
| U | piii | Ph /-Pr | 00 | 01.00 |
| 6 | dmpd | B(dmpd) | 82 | 95.5 |
| • | | Ph /-Pr | | |
| 7 | pin | B(pin) | 85 | 96:4 |
| | F | Ph t-Bu | | |
| 8 | pin | B(pin) | 93 | 90:10 |
| - | F | Ph | | |
| 9 | pin | B(pin) | 83 | 86 [.] 14 |
| Ū | P | Cy /-Pr | | |
| | | B(dmpd) | (10) ^b | >97:3 |
| 10 | dmpd | i-Pr Cy | (25) ^c | >97:3 |
| | | B(nin) | (50) ^a | -97.5 |
| 11 | pin | <i>n</i> -pentyl | 65 | >97:3 |
| | | t-Bu B(nin) | | |
| 12 | pin | \sim Ph | 88 | >97:3 |
| | | t-Bu´ 🏏 🗸 t-Bu´ B(nin) | | |
| | | | | |
| 13 | pin | Ph´ ✓ | 95 | 83:17 |
| | | | | |
| | | М́е | | |

Table 3.7. Scope of Boron-Wittig Reaction for Trisubstituted Vinyl Boronates.^a

a) Results are an average of two experiments. Yield represents isolated yields of purified product. b) Lithiation performed at 0 $^{\circ}$ C for 5 min. c) Lithiation at 0 $^{\circ}$ C for 30 min. d) Lithiation at 0 $^{\circ}$ C for 2 h. Values in parenthases represent conversions.

Scheme 3.16. Synthesis of Regioisomers **3.60** and **3.63** via the Boron-Wittig Reaction.



3.3.4. Gram-Scale Synthesis of Di- and Trisubstituted Vinyl Boronates.

Since the boron-Wittig reaction makes use of commercially available or readily accessible starting materials and does not require the use of costly transition-metals, extending the methodology to a large-scale operation is highly appealing and practical. To examine this, 1,2-disubstituted, 1,1-disubstituted, and trisubstituted vinyl boronates (3.64, 3.53 and 3.60, respectively) were synthesized on gram scale (Scheme 3.17). In all three cases, high yields and excellent isomeric purity could be obtained when using a slight excess of base and electrophile.

Scheme 3.17. Gram-Scale Synthesis of Vinyl Boronates.



3.3.5. Efforts to Understand Stereoinduction in the Synthesis of 1,2-Disubstituted and Trisubstituted Vinyl Boronates. To uncover the origin of stereoselectivity for the boron-Wittig reaction, a number of experiments were conducted. Preliminary studies were performed to determine the rate-limiting step of the reaction. As depicted in Scheme 3.18, upon addition of hexanal to lithiated bis(boronate) **3.52** at -78 °C in THF, followed by addition of benzaldehyde at -78 °C, exclusive formation of vinyl boronate **3.54** was observed (eq 1). Similar results were obtained when using Et₂O as the solvent in place of THF (eq 2). Thus, the data suggest that addition of **3.52** to the electrophile is complete at -78 °C, before warming the reaction mixture to room temperature. The data also indicate that addition of the carbanion to the aldehyde is irreversible under the reaction conditions.

Scheme 3.18.



It was important to understand if B-O elimination was occurring at lower temperatures or upon warming the reaction mixture to room temperature. Thus, efforts to trap the intermediate prior to B-O elimination were attempted by treatment of the reaction mixture with TBSOTf at -78 °C (Scheme 3.19). Interestingly, when the reaction was performed in Et₂O, a 74:16 diastereomeric mixture of an unknown intermediate was obtained along with a 69:31 *E*:*Z* isomeric mixture of vinyl boronate product **3.54** (eq 1). An attempt to purify and isolate the intermediate by silica gel chromatography resulted only in isolation of vinyl

The results of the attempted isolation, along with ¹H NMR boronate **3.54**. analysis, suggest that the intermediate is likely 4-membered boracycle 3.65 or the ring-opened intermediate **3.66**. It is reasonable to conclude that **3.65** and **3.66** are thermally and/or hydrolytically unstable and undergo rapid B-O elimination on silica gel. Future studies should focus on further isolation and characterization of this intermediate. Conversely, no intermediates were observed when the same reaction was conducted with THF as the solvent (eq 2). The combined results from Scheme 3.18 and 3.19 obtained with Et₂O as the solvent indicate that addition of **3.52** to the electrophile is irreversible. Subsequently, B-O elimination of **3.65** or **3.66** to furnish vinyl boronate **3.54** is rate-limiting. Of note, since B-O elimination occurs in full conversion at -78 °C in THF, relative rates of nucleophilic attack and B-O elimination cannot be elucidated for this system. Furthermore, while B-O elimination might indeed be rate-limiting, stereoselectivity could still be predetermined by a least-hindered approach of the nucleophile to the electrophile to irreversibly form stable intermediates A or B, which lack the ability to undergo bond rotation (eq 3).



Scheme 3.19. Standard Boron-Wittig Conditions with Addition of TBSOTF.

In trying to understand the reaction mechanism, further experimental complications arise when delving into possible modes of B-O elimination.³⁷ As depicted in Scheme 3.20, a direct *syn* elimination from **C** or **D** leads to formation of *trans* vinyl boronate **E** or *cis* vinyl boronate **F**, respectively. Conversely, a deborylation/bond rotation to form **G** or **H** and subsequent *anti* elimination could result in the opposite stereoisomer of product relative to *syn* elimination. To

³⁷ For an in depth mechanistic discussion for the boron-Wittig reaction, see: Pelter, A.; Buss, D.; Colclough, E.; Singaram, B. *Tetrahedron* **1993**, *49*, 7077.

further complicate the scenario, rapid interconversion between carbanion **G** and **H** might take place. With this knowledge in hand, no conclusion can be made on the mode of elimination or origin of stereoselectivity based on the current data. Future studies should focus on low temperature ¹¹B and ¹H NMR analysis of the reaction mixture. Additionally, computational experiments should provide useful insight into the reaction mechanism.



Scheme 3.20. Possible Elimination Pathways for the Boron-Wittig Reaction.

3.3.6. Future Directions. Despite significant progress in improving the stereoselectivity for synthesis of vinyl boronates, further examination of alternative electrophiles still needs to be conducted. For example, geminal 1,1-dibromide **3.67** in combination with bis(boronate) ester **3.43** or **3.51** resulted in an isomeric mixture of the desired vinyl boronate products **3.68** and **3.70**, respectively, along with elimination byproduct **3.69** (Scheme 3.21, eq 1 and 2). Additional optimization of conditions with geminal dibromides, or employment of alternative electrophiles such as amides or sulfonamides, could result in improved or complementary selectivities and further expand the substrate scope.



Scheme 3.21. Initial Results for Boron-Wittig Reaction with Geminal Dibromides.

Use of alternative nucleophilic partners should also be examined in depth. For example, silaboronate **3.72** could be accessed efficiently and in high yield via a Cu-catalyzed borylation of (chloromethyl)trimethylsilane **3.71** (Scheme 3.22). Employment of **3.72** under standard boron-Wittig reaction conditions with hexanal lead to exclusive Si-O elimination product **3.73** in a 64:36 *Z:E* ratio. A similar finding was reported by Matteson and co-workers when investigating the reactivity of lithiated silaboronates in 1983.³⁸ Nonetheless, the slight predominance of *Z*-isomer suggests that a complementary methodology to the above-described boron-Wittig reaction with bis(boronate) esters might be possible upon further optimization. In addition, it would be interesting to test other geminal 1,1-metalloboronate derivatives under similar lithiation/Wittig-type processes in the future.

Scheme 3.22. Boron Wittig Reaction with Silaboronate **3.72**.



Lastly, applying the boron-Wittig reaction towards the synthesis of a natural product should highlight the power of this methodology. In Kishi's total synthesis of palytoxin reported in 1989, it was noted that terminal alkyne hydroboration on intermediate **3.74** failed due to other side reactions occurring between catecholborane and

³⁸ Matteson, D. S.; Majumdar, D. Organometallics 1983, 2, 230.

a tethered urethane group (Scheme 3.23).³⁹ Instead, late-stage failure was circumvented by using Matteson's boron-Wittig reaction between aldehyde **3.75** and lithiated bis(boryl)methane **3.33**, providing *trans* vinyl boronate **3.76** in moderate stereoselectivity. Thus, the newly developed boron-Wittig reaction would allow for an alternative for alkyne hydroboration on similar late stage intermediates, while also providing vinyl boronate products with higher stability and stereoselectivity compared to previously optimal boron-Wittig conditions.





Total synthesis of natural products containing trisubsituted olefins should also demonstrate the power of the boron-Wittig reaction over other methodologies. Recently,

³⁹ Armstrong, R. W.; Beau, J.-M.; Cheon, S. H.; Christ, W. J.; Fujioka, H.; Ham, W.-H.; Hawkins, L. D.; Jin, H.; Kang, S. H.; Kishi, Y.; Martinelli, M. J.; McWhorter, W. W., Jr.; Mizuno, M.; Nakata, M.; Stutz, A. E.; Talamas, F. X.; Taniguchi, M.; Tino, J. A.; Ueda, K.; Uenishi, J.; White, J. B.; Yonaga, M. J. Am. Chem. Soc. **1989**, *111*, 7525.

our group reported a concise total synthesis of (+)-discodermolide 3.77 utilizing a Nicatalyzed hydroboration of 1,3-diene 3.78 as a key step to construct the *cis* trisubstituted olefin at the C_{13} - C_{14} position in excellent stereoselectivity (Scheme 3.24, eq 1).⁴⁰ Previously, Novartis reported a decagram synthesis of 3.82 in which construction of the trisubstituted olefin fragment suffered from a low-yielding Wittig-Zhao olefination between aldehyde **3.80** and **3.81** (eq 2).⁴¹ Instead, one could imagine a boron-Wittig reaction between between aldehyde **3.84** and dmpd-derived bis(boronate) ester **3.85** to provide vinyl boronate **3.86**, presumably in high *trans* selectivity. Iodination of **3.86** would deliver vinyl iodide 3.82, while a Matteson homologation would furnish allyl boronate **3.79**. Thus, the boron-Wittig reaction could provide an alternative method for accessing the complex trisubstituted olefin motif in an efficient manner, and would perhaps allow for synthesis of other analogues for drug screening.

Scheme 3.24. Potential Application for the Boron-Wittig Reaction for Synthesis of 3.77.

 ⁴⁰ Yu, Z.; Ely, R. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 9632.
 ⁴¹ Arimoto, H.; Kaufman, M. D.; Kobayashi, K.; Qui, Y.; Smith, A. B. III. *Synlett.* **1998**, 765.



3.4. Conclusion

To summarize, a boron-Wittig reaction that utilizes readily available and stable geminal bis(boronates) has been described. The overall transformation represents an efficient and practical method for generating highly complex vinyl boronates that would be difficult to access via other available transformations. Additionally, the described methodology is amenable to large-scale operations and does not require the use of expensive transition metals. Overall, the boron-Wittig reaction should have a significant impact on the synthesis of natural products or drug candidates that contain challenging and highly substituted alkene units.

3.5. Experimental

3.5.1. General Information.

¹H NMR spectra were measured using a Varian Gemini-500 (500 MHz) spectrometer or a Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CHCl₃: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, pent= pentet, sept = septet, br = broad, m = multiplet), and coupling constants (Hz). ¹³C{¹H}NMR spectra were measured using a Varian Inova 500 (126 MHz) or Varian VNMRS 400 (100 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl₃: 77.0 ppm). ¹¹B{¹H}NMR spectra were measured using a Varian Inova 500 (160 MHz) spectrometer. Chemical shifts are reported in ppm using boron trifluoride as the external standard (BF₃·Et₂O: 0.0 ppm). Infrared (IR) spectra were measured using a Bruker α-P Spectrometer. Frequencies are reported in wavenumbers (cm⁻¹) as follows: strong (s), broad (br), medium (m), and weak (w). High-resolution mass spectrometry (HRMS) was performed at the chemistry department at Boston College, Chestnut Hill, MA.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO₂, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography was performed on 25 μ m silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm), phosphomolybdic acid

(PMA), potassium permanganate (KMnO₄), and Seebach's "magic" stain⁴² (phosphomolybdic acid, Ce(SO₄)₂, sulfuric acid). Analytical chiral gas-liquid chromatography (GLC) was also performed on an Agilent Technologies 6850 Series chromatograph with a flame ionization detector, and a Supelco β –Dex 120 column with helium as the carrier gas. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar Supercritical Fluid Chromatograph equipped with auto sampler and a Waters photodiode array detector with methanol as the modifier.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran, dichloromethane, toluene, and diethyl ether were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after being purged with argon. Dimethylformamide was dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC). Triethylamine was purchased from Aldrich and refluxed over calcium hydride prior to use. Copper iodide was purchased from Strem Chemicals and used as received. Triphenyl phosphate, lithium methyloxide, 3-phenylpropionaldehyde, hexanal, benzaldehyde, and crotonaldehyde were purchased from Alfa Aesar and used as received. B₂(pin)₂ was obtained from AllyChem and recrystallized from pentane prior to use. Pinacol borane was purchased from BASF and distilled prior to use. Bromine was purchased from Acros and used as received. All other reagents were obtained from Aldrich or Fisher and used as received.

⁴²Seebach, D. Helv. Chim. Acta. 1987, 70, 448.

Method A:



The 1,1-diboronates were prepared according to the literature procedure.^{32b} To a stirred solution of triphenyl phosphite (1.50 equiv) in anhydrous DCM (1 M) at -78°C under N₂ was added bromine (1.30 equiv) dropwise. Freshly distilled triethylamine (3.00 equiv) and aldehyde (1.00 equiv) were added at -78°C. The reaction mixture was allowed to warm to room temperature and stirred for 2 hours. Upon completion, the solvent was evaporated in vacuo and the crude reaction mixture was purified on silica gel (100% hexanes) to afford the 1,1-dibromide.

In the glove box, an oven-dried 100 mL round-bottom flask with a magnetic stir bar was charged with CuI (0.10 equiv), LiOMe (2.50 equiv) and $B_2(pin)_2$ (1.90 equiv). The flask was sealed with a rubber septum, removed from the glove box, and DMF (0.5 M) was added under N₂. After stirring at room temperature for 10 min, a solution of 1,1-dibromide (1.00 equiv) in DMF was added via syringe at room temperature. The reaction mixture was allowed to stir at room temperature for 12 hours. Upon completion, 40 mL DI water was added, and extracted with hexane (3x40 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The 1,1-

diboronate products were isolated after SiO₂ chromatography, unless otherwise noted.

Method B:



The 1,1-diboronates were prepared according to the literature procedure.³⁴ A 6-dram vial with magnetic stir bar was charged with aldehyde (1.00 equiv.) and tosylhydrazine (1.00 equiv), and methanol (5 mL) was added. The mixture was stirred at room temperature. N-Tosylhydrazone precipitated after 15 minutes or longer and the reaction was monitored by TLC analysis (spot of the carbonyl compound). The precipitate was then collected, washed with pentane (5 mL \times 3), and dried under vacuum.

In the glove box, an oven-dried 6-dram vial with a magnetic stir bar was charged with *N*-tosylhydrazone (1.00 mmol, 1.00 equiv.), NaH (1.20 mmol, 1.20 equiv.), and toluene (8 mL). The mixture was stirred at room temperature for 1 hour. Next, $B_2(dmpd)_2$ (1.20 mmol, 1.20 equiv) in toluene was added, and the vial was sealed, removed from the glovebox and heated at 110°C for 12 hours. Upon completion, the reaction mixture was allowed to cooled to room temperature, and Et₂O (10 mL) and H₂O (10 mL) were added. The mixture was stirred vigorously for 10 minutes. After separation of the organic layer, the aqueous layer was extracted with Et₂O (2x5 mL). The combined organic layers were washed with saturated brine (10 mL) and dried over anhydrous Na₂SO₄. After the solvent was evaporated, the crude product was purified by silica gel chromatography.

Method C:

$$R \xrightarrow{B(pin)} + H-B(pin) \xrightarrow{Pt(dba)_3 (3\%)} R \xrightarrow{B(pin)} B(pin)$$
(1.2 equiv.)

To an oven-dried 2-dram vial equipped with a stir bar in a glovebox was added Pt(dba)₃ (3 mol%) followed by THF (1.0 M in vinyl boronate). To the reaction mixture was added pinacolborane (1.20 equiv.) followed by vinyl boronate (1.00 equiv.). The reaction vessel was sealed with a polypropylene cap, brought out of the glovebox, and the reaction mixture was allowed to stir at 70 °C for 15 hours. Upon completion, the solvent was evaporated in vacuo and the crude reaction mixture was purified on silica gel to afford the 1,1-diboronate.

3.5.3. Preparation of Geminal Bis(boronate) Esters.

2,2'-(3-phenylpropane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-B(pin) B(pin) B(p

21.8 mmol), $B_2(pin)_2$ (4.20 g, 16.5 mmol), (3,3-dibromopropyl)benzene (2.43 g, 8.70 mmol) and DMF (15 mL). The crude reaction mixture was purified by column chromatography on silica gel (3% ethyl acetate/hexanes) to afford the desired product as a white solid (2.23 g, 69%). All spectral data are in accord with the literature.^{32b}

2,2'-(cyclohexylmethylene)bis(4,4,5,5-tetramethyl-1,3,2-

B(pin) B(pin) A) utilizing

dioxaborolane). Prepared according to the general procedure (Method A) utilizing CuI (309 mg, 1.62 mmol), LiOMe (1.54 g, 40.5 mmol),

 $B_2(pin)_2$ (7.80 g, 30.8 mmol), (dibromomethyl)cyclohexane (3.24 g, 16.2 mmol) and DMF (30 mL). The crude reaction mixture was purified by column chromatography on silica gel (3% ethyl acetate/hexanes) to afford the desired product as a white solid (3.74 g, 67%). All spectral data are in accord with the literature.^{32a}

 $B_2(pin)_2$ (3.20 g, 12.6 mmol), 1,1-dibromo-2,2-dimethylpropane (1.54 g, 6.60 mmol) and DMF (15 mL). The crude reaction mixture was purified by column chromatography on silica gel (3% ethyl acetate/hexanes) to afford the desired product as a white solid (1.39 g, 65%). All spectral data are in accord with the literature.³⁴



tosylhydrazine (1.86 g, 10.0 mmol), and methanol (5 mL). The precipitate was collected, washed with pentane, and dried under reduced pressure to afford 4-N'-(3-phenylpropylidene)toluenesulfono- hydrazide as a white solid, which was used in the

following step without further purification.

The second step of the general procedure (Method B) was performed utilizing the above-synthesized N'-(3-phenylpropylidene)toluenesulfonohydrazide (605 mg, 2.00 mmol), NaH (57.6 mg, 2.40 mmol), B₂(dmpd)₂ (677 mg, 2.40 mmol), and toluene (5.0 mL). The crude reaction mixture was purified by column chromatography on silica gel (2.5% ethyl acetate/hexanes) to afford the desired product as a white solid (632 mg, 79%). ¹H NMR (500 MHz, CDCl₃): δ 7.24 (2H, t, *J*= 7.5 Hz), 7.20 (2H, d, *J*= 7.0 Hz), 7.13 (1H, t, *J*= 7.5 Hz), 2.55 (2H, t, *J*= 8.0 Hz), 1.79-1.72 (2H, m), 1.75 (2H, s), 1.31 (24H, s), 0.47 (1H, t, *J*= 7.5 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 144.2, 128.7, 128.0, 125.1, 69.9, 48.9, 39.0, 31.9, 31.8, 28.6; IR (neat): 2072.7 (m), 2931.9 (w), 2862.8 (w), 1495.4 (w), 1453.8 (m), 1355.8 (s), 1300.5 (m), 1255.8 (m), 1196.1 (s), 1140.0 (w), 770.5 (w), 699.1 (w) cm⁻¹; HRMS-(DART) for: C₂₃H₃₉B₂O₄ [M+H]⁺: calculated: 401.3034, found: 401.3048.

2,2'-(cyclohexylmethylene)bis(4,4,6,6-tetramethyl-1,3,2-

B(dmpd) B(d

tosylhydrazine (1.86 g, 10.0 mmol), and methanol (5 mL). The precipitate was collected, washed with pentane, and dried under reduced pressure to afford N'- (cyclohexylmethylene)-4-toluenesulfonohydrazide as a white solid, which was used in the following step without further purification.

The second step of the general procedure (Method B) was performed utilizing the

above-synthesized *N'*-(cyclohexylmethylene)-4-toluenesulfonohydrazide (561 mg, 2.00 mmol), NaH (57.6 mg, 2.40 mmol), B₂(dmpd)₂ (677 mg, 2.40 mmol), and toluene (5.0 mL). The crude reaction mixture was purified by column chromatography on silica gel (2.5% ethyl acetate/hexanes) to afford the desired product as a white solid (646 mg, 85%). ¹H NMR (500 MHz, CDCl₃): δ 1.74 (4H, s), 1.78-1.66 (2H, m), 1.65-1.54 (4H, m), 1.32-1.20 (4H, m), 1.14-1.03 (1H, m), 0.91-0.83 (2H, m), 0.29 (1H, d, *J*= 10.0 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 69.8, 49.1, 35.7, 25.5, 21.9, 31.8, 26.9, 26.7; IR (neat): 2973.1 (m), 2918.2 (s), 2849.1 (w), 1446.0 (w), 1365.5 (s), 1293.1 (s), 1197.8 (s), 1139.9 (w), 770.2 (w) cm⁻¹; HRMS-(DART) for: C₂₁H₄₁B₂O₄ [M+H]⁺: calculated: 379.3191, found: 379.3206.

((5,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-

TBSO B(pin) B(pin) **yl)pentyl)-oxy**)(*tert*-butyl)dimethylsilane. Prepared according to the general procedure (Method C) utilizing (*E*)-*tert*-butyldimethyl((5-(4,4,5,5- tetramethyl-1,3,2-dioxaborolan-2-yl)pent-4-en-1-yl)oxy)silane (400.0 mg, 1.225 mmol), pinacolborane (188 mg, 1.47 mmol), Pt(dba)₃ (33.0 mg, 36.8 µmol) and THF (1.20 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (456 mg, 82%). ¹H NMR (500 MHz, CDCl₃): δ 3.57 (2H, t, *J*= 6.5 Hz), 1.57-1.47 (4H, m), 1.35-1.26 (2H, m), 1.22 (12H, s), 1.21 (12H, s), 0.87 (9H, s), 0.71 (1H, t, *J*= 7.5 Hz), 0.02 (6H, s); ¹³C NMR (126 MHz, CDCl₃): δ 82.8, 63.4, 33.0, 28.8, 26.0, 25.6, 24.8, 24.5, 18.3, -5.3; IR (neat): 2977.2 (w), 2929.2 (w), 2857.3 (w), 1462.9 (w), 1359.2 (m), 1309.4 (s), 1263.3 (m), 1215.0 (w), 1139.6 (s), 1098.2 (s), 969.1 (m), 834.6 (s), 773.9 (m), 667.0 (w) cm⁻¹; HRMS-(DART) for: C₂₃H₄₉B₂O₅Si [M+H]⁺: calculated: 455.3535, found: 455.3551.

2,2'-(2-cyclohexylethane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-B(pin)B(pin) dioxaborolane). Prepared according to the general procedure (Method C) utilizing (*E*)-2-(2-cyclohexylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (500 mg, 2.12 mmol), pinacolborane (325 mg, 2.54 mmol), Pt(dba)₃ (57.0 mg, 63.5 mol) and THF (2.10 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (473 mg, 61%). All spectral data are in accord with the literature.⁴³

3.5.4. Representative Procedure for Preparation of 1,2-Disubtituted Vinyl Boronates.



In the glove box, an oven-dried 2-dram vial with a magnetic stir bar was charged with LiTMP (0.30mmol, 1.2 equiv), sealed with a septum cap, and removed from the glovebox. The reaction vial was cooled to 0°C, and THF (0.30 mL), followed by a solution of bis(4,4,5,5-tetramethyl- 1,3,2-dioxaborolan-2-yl)methane (0.30 mmol, 1.2 equiv) in THF (0.60 mL) were added. The reaction vial was allowed to stir for 5 minutes

⁴³ Lee, S.; Li, D.; Yun, J. *Chem. Asian J.* **2014**, *9*, 2440.

at 0°C. Then the reaction vial was cooled to -78°C, and a solution of aldehyde (0.25 mmol, 1.0 equiv) in THF (0.30 mL) was added. The reaction vial was allowed to stir at - 78°C for additional 4 hours. Upon completion, the reaction mixture was concentrated under reduced pressure. The 1,2-disubtituted-vinyl boronates products were isolated by SiO₂ chromatography.

3.5.5. Full Characterization of 1,2-Disubtituted Vinyl Boronates.

(*E*)-4,4,5,5-tetramethyl-2-(prop-1-en-1-yl)-1,3,2-dioxaborolane. Me B(pin) Prepared according to the representative procedure utilizing LiTMP (162 mg, 1.10 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (268 mg, 1.00 mmol), acetaldehyde (5M solution in THF, 0.22 mL, 1.10 mmol), and THF (4.0 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (106 mg, 63%). ¹H NMR (500 MHz, CDCl₃): δ 6.64 (1 H, dq, J = 18.5, 6.5 Hz), 5.45 (1H, d, J =18.0 Hz), 1.84 (1H, d, J = 6.0 Hz), 1.25 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 149.6, 82.9, 24.7, 21.6; All additional data are in accord with the literature.³⁸



(E)-2-(hept-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-

dioxaborolane. Prepared according to the representative procedure utilizing LiTMP (44.2 mg, 0.300 mmol), bis(4,4,5,5-tetramethyl-1,3,2dioxaborolan-2-yl)methane (80.4 mg, 0.300 mmol), hexanal (30.0 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2.5% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (47.6 mg, 85%). ¹H NMR (500 MHz, CDCl₃): δ 6.63 (1H, dt, *J*= 18.0, 6.0 Hz), 5.42 (1H, d, *J*= 18.0 Hz), 2.14 (2H, q, *J*= 6.5 Hz), 1.42 (2H, pent, *J*= 7.0 Hz), 1.32-1.18 (4H, m), 1.26 (12H, s), 0.88 (3H, t, *J*= 7.0 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 154.8, 83.0, 35.8, 31.4, 27.9, 24.8, 22.5, 14.0; IR (neat): 2977.4 (m), 3959.2 (m), 2926.6 (m), 2857.6 (w), 1630.0 (s), 1466.7 (w), 1397.9 (s), 1360.3 (s), 1234.6 (w), 1215.4 (w), 1145.3 (s), 998.8 (m), 972.4 (m), 896.5 (w), 850.4 (m) cm⁻¹; HRMS-(DART) for: C₁₃H₂₆B₁O₂ [M+H]⁺: calculated: 225.2026, found: 225.2037.

(*E*)-2-(2-cyclohexylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane B(pin)Prepared according to the representative procedure utilizing LiTMP (44.2 mg, 0.300 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (80.4 mg, 0.300 mmol), cyclohexanecarbaldehyde (28.0 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (47.2 mg, 80%). All spectral data are in accord with the literature.⁴⁴

Me B(pin) Me Me B(pin) Me Me B(pin) Me Me dioxaborolane. Prepared according to the representative procedure utilizing LiTMP (44.2 mg, 0.3 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) methane (80.4 mg, 0.3 mmol), pivalaldehyde (21.5 mg, 0.250 mmol), and THF (1.2 mL).

⁴⁴ Yoshida, H.; Kageyuki, I.; Takaki, K. Org. Lett. 2014, 16, 3512.

The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (25.1 mg, 48%). All spectral data are in accord with the literature.¹¹

(E)-4,4,5,5-tetramethyl-2-styryl-1,3,2-dioxaborolane. Prepared according to the representative procedure utilizing LiTMP (44.2 mg, 0.300 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (80.4 mg, 0.300 mmol), benzaldehyde (26.5 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (43.7 mg, 76%). All spectral data are in accord with the literature.⁴³

(E)-2-(buta-1,3-dienyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Prepared according to the representative procedure utilizing LiTMP (44.2 mg, 0.300 mmol), bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methane (80.4 mg, 0.300 mmol), acrylaldehyde (14.2 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (26.8 mg, 59%). ¹H NMR (500 MHz, CDCl₃): 6.98 (1H, dd, *J*= 17.5 Hz, 10.5 Hz), 6.39 (1H, dt, *J*= 16.5 Hz, 11.0 Hz), 5.55 (1H, d, *J*= 17.5 Hz), 5.36 (1H, d, *J*= 17.0 Hz), 5.23 (1H, d, *J*= 10.0 Hz), δ 1.25 (12H, s); ¹³C NMR (100 MHz, CDCl₃): δ 150.4, 139.0, 121.2, 83.4, 25.0; IR (neat): 2978.3 (m), 1634.4 (m), 1592.3 (m), 1371.8 (s), 1337.5 (s), 1320.5 (s), 1221.5 (m), 1142.5 (m), 1106.4 (s), 969.7 (m), 913.0 (m) cm⁻¹; HRMS-(DART) for: $C_{10}H_{18}B_1O_2$ [M+H]⁺: calculated: 181.1400, found: 181.1392.

4,4,5,5-tetramethyl-2-((1*E*,3*E*)-penta-1,3-dienyl)-1,3,2dioxaborolane. Prepared according to the representative procedure utilizing LiTMP (44.2 mg, 0.300 mmol), bis(4,4,5,5-tetramethyl-1,3,2dioxaborolan-2-yl)methane (80.4 mg, 0.300 mmol), (*E*)-but-2-enal (17.5 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (42.2 mg, 87%). ¹H NMR (500 MHz, CDCl₃): δ 6.95 (1H, dd, *J*= 18.0 Hz, 11.0 Hz), 6.12 (1H, t, *J*= 14.5 Hz), 5.84-5.91 (1H, m), 5.38 (1H, d, *J*= 17.5 Hz), 1.76 (3H, d, *J*= 7.0 Hz), 1.24 (12H, s); ¹³C NMR (100 MHz, CDCl₃): δ 150.4, 134.3, 134.0, 83.2, 24.9, 18.4; IR (neat): 2978.0 (m), 1645.7 (m), 1603.6 (m), 1392.9 (m), 1378.2 (m), 1350.7 (s), 1319.5 (m), 1264.3 (m), 1106.4 (s), 1006.4 (m), 969.8 (m), 848.6 (m) cm⁻¹; HRMS-(DART) for: C₁₁H₂₀B₁O₂ [M+H]⁺: calculated: 195.1556, found: 195.1556.

(*E*)-4,4,5,5-tetramethyl-2-(4-methylpenta-1,3-dienyl)-1,3,2-Me B(pin) dioxaborolane. Prepared according to the representative procedure utilizing LiTMP (44.2 mg, 0.300 mmol), bis(4,4,5,5-tetramethyl-1,3,2dioxaborolan-2-yl)methane (80.4 mg, 0.300 mmol), 3-methylbut-2-enal (21.0 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (41.6 mg, 80%). ¹H NMR (500 MHz, CDCl₃): δ 7.23 (1H, dd, *J*= 18.0 Hz, 11.5 Hz), 5.91 (1H, d, *J*= 11.0 Hz), 5.38 (1H, d, *J*= 17.0 Hz), 1.82 (3H, s), 1.79 (3H, s), 1.25 (12H, s); ¹³C NMR (100 MHz, CDCl₃): δ 146.3, 140.7, 128.0, 83.2, 26.4, 24.9, 19.0; IR (neat): 2977.8 (m), 2928.6 (m), 1640.9 (m), 1602.8 (m), 1378.7 (m), 1356.7 (s), 1332.8 (s), 1313.8 (m), 1143.9 (s), 999.5 (m), 970.1 (m), 851.0 (m) cm⁻¹; HRMS-(DART) for: C₁₂H₂₂B₁O₂ [M+H]⁺: calculated: 209.1713, found: 209.1714.

4,4,5,5-tetramethyl-2-((1*E*,3*E*)-3-methylpenta-1,3-dienyl)-1,3,2-Me H_{Me} dioxaborolane. Prepared according to the representative procedure utilizing LiTMP (44.2 mg, 0.300 mmol), bis(4,4,5,5-tetramethyl-1,3,2- dioxaborolan-2yl)methane (80.4 mg, 0.300 mmol), (*E*)-2-methylbut-2-enal (21.0 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (47.5 mg, 91%). ¹H NMR (500 MHz, CDCl₃): δ 7.02 (1H, d, *J*= 18.5 Hz), 5.76 (1H, q, *J*= 7.0 Hz), 5.42 (1H, d, *J*= 18.0 Hz), 1.74 (3H, d, *J*= 7.0 Hz), 1.72 (3H, s), 1.26 (12H, s); ¹³C NMR (100 MHz, CDCl₃): δ 154.7, 136.3, 131.9, 83.2, 25.0, 14.4, 11.5; IR (neat): 2978.0 (m), 2928.7 (w), 1607.7 (m), 1458.6 (m), 1397.8 (m), 1378.5 (s), 1340.1 (m), 1144.2 (s), 1110.3 (m), 1033.9 (m), 993.2 (m), 900.4 (m) cm⁻¹; HRMS-(DART) for: C₁₂H₂₂B₁O₂ [M+H]⁺: calculated: 209.1713, found: 209.1707.



Me

4,4,5,5-tetramethyl-2-((1E,3E)-4-phenylbuta-1,3-dien-1-yl)-

1,3,2-diox-aborolane. Prepared according to the representative procedure utilizing LiTMP (44.2 mg, 0.300 mmol), bis(4,4,5,5-tetramethyl-1,3,2dioxaborolan-2-yl) methane (80.4 mg, 0.300 mmol), cinnamaldehyde (33.0 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2.5% ethyl acetate/hexanes) to afford the desired product as a clear, pale yellow oil (47.3 mg, 74%). ¹H NMR (500 MHz, CDCl₃): δ 6.43 (2 H, d, J = 7.5 Hz), 7.32 (2H, t, J= 7.5 Hz), 7.25 (1H, t, J= 7.5 Hz), 7.18 (1H, dd, J= 18.0, 10.5 Hz), 6.85 (1H, dd, J= 15.0, 10.0 Hz), 6.70 (1H, d, J= 15.0 Hz), 5.68 (1H, d, J= 18.0 Hz), 1.30 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 149.8, 136.8, 136.1, 130.6, 128.6, 128.1, 126.8, 83.2, 24.8; IR (neat): 3023.7 (w), 2977.6 (m), 2929.5 (w), 1623.2 (m), 1603.4 (s), 1389.7 (m), 1448.0 (w), 1358.6 (s), 1322.5 (s), 1260.0 (s), 1143.6 (s), 1006.6 (m), 969.9 (m), 850.2 (m), 748.3 (w), 691.0 (m), 643.7 (w) cm⁻¹; HRMS-(DART) for: $C_{16}H_{22}B_1O_2$ [M+H]⁺: calculated: 257.1713, found: 257.1712.

2-((1E,3E)-hepta-1,3,5-trien-1-yl)-4,4,5,5-tetramethyl-

`B(pin) 1,3,2-diox-aborolane. Prepared according to the representative procedure utilizing LiTMP (44.2 mg, 0.300 mmol), bis(4,4,5,5tetramethyl-1,3,2-dioxaborolan-2-yl) methane (80.4 mg, 0.300 mmol), a 5:1 mixture of (2E)-hexa-2,4-dienal and (2E,4Z)-hexa-2,4-dienal (24.0 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, pale yellow oil (41.6

mg, 76%). ¹H NMR (500 MHz, CDCl₃): δ 7.01 (1H, dd, *J*= 17.5, 10.0 Hz), 6.32 (1H, dd, *J*= 14.5, 10.5 Hz), 6.20-6.04 (2H, m), 5.81 (1H, dq, *J*= 14.0, 7.0 Hz), 5.50 (1H, d, *J*= 18.0 Hz), 1.79 (3H, d, *J*= 6.5 Hz), 1.27 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 150.0, 136.7, 132.5, 131.9, 131.5, 83.1, 24.8, 18.4; IR (neat): 2977.7 (w), 2930.7 (w), 1615.5 (m), 1584.4 (m), 1358.0 (s), 1320.0 (s), 1270.0 (m), 1214.1 (w), 1142.1 (s), 1106.6 (w), 1008.1 (s), 970.0 (m), 848.7 (m), 645.4 (w) cm⁻¹; HRMS-(DART) for: C₁₃H₂₂B₁O₂ [M+H]⁺: calculated: 221.1713, found: 221.1716.

(E)-4,4,5,5-tetramethyl-2-(non-1-en-3-ynyl)-1,3,2-

B(pin) **n**-pentyl **dioxaborolane.** Prepared according to the representative procedure utilizing LiTMP (44.2 mg, 0.300 mmol), bis(4,4,5,5-tetramethyl-1,3,2dioxaborolan-2-yl)methane (80.4 mg, 0.300 mmol), oct-2-ynal (31.0 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (48.7 mg, 78%). ¹H NMR (500 MHz, CDCl₃): δ 6.40 (1H, d, *J*= 18.5 Hz), 5.89 (1H, d, *J*= 18.0 Hz), 2.30 (2H, dt, *J*= 7.0 Hz, 1.5 Hz), 1.48-1.54 (2H, m), 1.23-1.36 (16H, m), 0.87 (3H, t, *J*= 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 130.5, 95.5, 83.6, 81.0, 31.2, 28.4, 25.0, 24.9, 22.4, 19.7, 14.2; IR (neat): 2977.8 (m), 2931.5 (m), 2209.2 (w), 1599.8 (s), 1387.0 (m), 1346.8 (s), 1323.3 (s), 1271.0 (m), 1199.0 (m), 1141.5 (s), 980.9 (m), 969.5 (m), 849.8 (m) cm⁻¹; HRMS-(DART) for: C₁₅H₂₆B₁O₂ [M+H]⁺: calculated: 249.2026, found: 249.2031.

3.5.6. Representative Procedure for Preparation of 1,1-Disubtituted Vinyl Boronates. Method A (with diiodomethane):

$$\begin{array}{c} \text{B(pin)} \\ \text{B(pin)} \\ \text{B(pin)} \\ \end{array} \xrightarrow{\begin{array}{c} \text{LiTMP, THF,} \\ 0^{\circ}\text{C, 5 min} \\ 0^{\circ}\text{C-60^{\circ}\text{C, 2h}} \\ \end{array}} \xrightarrow{\begin{array}{c} \text{B(pin)} \\ \text{B(pin)} \\ \end{array}}$$

In the glove box, an oven-dried 2-dram vial with magnetic stir bar was charged with LiTMP (0.200 mmol, 1.00 equiv), sealed with a septum cap, and removed from the glovebox. The reaction vial was cooled to 0°C, and THF (0.30 mL), and solution of 1,1-diboronate (0.200 mmol, 1.00 equiv) in THF (0.6 mL) were added. The reaction mixture was allowed to stir for 5 minutes at 0°C. Next, a solution of diiodomethane (0.400 mmol, 2.00 equiv) in THF (0.4 mL) was added dropwise at 0°C. The reaction vial was allowed to warm to 60°C and stir for additional 2 hours. Upon completion, the reaction mixture was concentrated under reduced pressure. The 1,1 disubtituted-vinyl boronate products were isolated by SiO₂ chromatography.

Method B (with formaldehyde):



In the glove box, an oven-dried 2-dram vial with magnetic stir bar was charged with LiTMP (29.4 mg, 0.200 mmol, 1.00 equiv), sealed with a septum cap, and removed from the glovebox. The reaction vial was cooled to 0°C, and THF (0.3 mL), and solution of 2,2'-(3-phenylpropane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (74.4 mg,

0.200 mmol) in THF (0.6 mL) were added. The reaction mixture was allowed to stir for 5 minutes at 0°C. Then, formaldehyde,⁴⁵ which was generated by heating a 2-dram vial with paraformaldehyde (60.0 mg, 2.00 mmol, 10.0 equiv) and *p*-toluenesulfonic anhydride (9.8 mg, 0.03 mmol, 0.15 equiv) at 85 °C, was carried by a slow N₂ stream and bubbled through the reaction mixture at -78 °C for 4 hours. Upon completion, the reaction mixture was concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (25.8 mg, 50%). All spectral data are in accord with the literature.⁴⁶

3.5.7. Full Characterization of 1,1-Disubtituted Vinyl Boronates



lane. Prepared according to the representative procedure (Method A) utilizing LiTMP (29.4 mg, 0.200 mmol), 2,2'-(3-phenylpropane-1,1-

4,4,5,5-tetramethyl-2-(4-phenylbut-1-en-2-yl)-1,3,2-dioxaboro-

diyl)bis(4,4,5,5- tetramethyl-1,3,2-dioxaborolane) (74.4 mg, 0.200 mmol), diiodomethane (107 mg, 0.400 mmol), and THF (0.9 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (44.9 mg, 87%). All spectral data are in accord with the literature.⁴⁶

⁴⁵ Schlosser, M., Jenny, T.; Guggisberg, Y. Synlett, **1990**, 11, 704.

⁴⁶ Ganić, Adnan, and Andreas Pfaltz, Chem. Eur. J. 2012, 18, 6724.

B(pin)

2-(1-cyclohexylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Prepared according to the representative procedure (Method A) utilizing LiTMP (29.4 mg, 0.200 mmol), 2,2'-(cyclohexylmethylene)bis(4,4,5,5-

tetramethyl-1,3,2 -dioxaborolane) (70.0 mg, 0.200 mmol), diiodomethane (107 mg, 0.400 mmol), and THF (0.9 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (40.3 mg, 85%). All spectral data are in accord with the literature.³⁸

2-(hept-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane.

^{B(pin)} Me Prepared according to the representative procedure (Method A) utilizing LiTMP (29.4 mg, 0.200 mmol), 2,2'-(hexane-1,1-diyl)bis(4,4,5,5- tetramethyl-1,3,2-dioxaborolane) (67.6 mg, 0.200 mmol), diiodomethane (107 mg, 0.400 mmol), and THF (0.9 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (35.3 mg, 78%). ¹H NMR (500 MHz, CDCl₃): δ 5.73 (1H, d, *J*= 3.0 Hz), 5.56 (1H, s), 2.11 (2H, t, *J*= 7.5 Hz), 1.39 (2H, p, *J*= 7.5 Hz), 1.30-1.22 (16H, m), 0.86 (3H, t, *J*= 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 128.8, 83.5, 35.5, 31.7, 29.1, 24.9, 22.8, 14.2; IR (neat): 2978.1 (m), 2958.9 (m), 2926.9 (m), 1425.9 (m), 1368.7 (s), 1343.7 (m), 1306.2 (s), 1204.7 (m), 1141.3 (s), 970.4 (m), 860.5 (m), 737.9 (m) cm⁻¹; HRMS-(DART) for: C₁₃H₂₆B₁O₂ [M+H]⁺: calculated: 225.2026, found: 225.2034.

tert-butyldimethyl((5-(4,4,5,5-tetramethyl-1,3,2-

TBSO

 $|_{B(pin)}$ dioxaborolan-2-yl)hex-5-en-1-yl)oxy)silane. Prepared according to the representative procedure (Method A) utilizing LiTMP (29.2 mg, 0.200 mmol), ((5,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)pentyl)oxy)(tertbutyl)dimethylsilane (90.9 mg, 0.200 mmol), diiodomethane (107 mg, 0.400 mmol), and THF (1.3 mL). The crude reaction mixture was purified by column chromatography on silica gel (2.5% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (57.0 mg, 84%). All spectral data are in accord with the literature.^{20h}

2-(3-cyclohexylprop-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaboro- $H_{B(pin)}$ **lane.** Prepared according to the representative procedure (*Method A*) utilizing LiTMP (29.2 mg, 0.200 mmol), 2,2'-(2-cyclohexylethane-1,1-diyl)bis(4,4,5,5tetra-methyl-1,3,2-dioxaborolane) (72.8 mg, 0.200 mmol), diiodomethane (107 mg, 0.400 mmol), and THF (1.3 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (36.1 mg, 72%). All spectral data are in accord with the literature.¹²

3.5.8. Representative Procedure for Preparation of Trisubtituted Vinyl Boronates.



In the glove box, an oven-dried 2-dram vial with a magnetic stir bar was charged with LiTMP (0.300 mmol, 1.20 equiv), sealed with a cap with a septum, and removed from the glovebox. The reaction vial was cooled to 0°C, and THF (0.30 mL), and solution of 1,1-diboronate (0.300 mmol, 1.20 equiv) in THF (0.60 mL) was added. The reaction vial was allowed to stir for 5 minutes at 0°C. Then the reaction vial was cooled to -78°C, and a solution of aldehyde (0.250 mmol, 1.00 equiv) in THF (0.30 mL) was added. The reaction vial was added to stir at -78°C for additional 4 hours. Upon completion, the reaction mixture was concentrated under reduced pressure. The trisubtituted vinyl boronate products were isolated by silica gel chromatography.

3.5.9. Full Characterization of Trisubtituted Vinyl Boronates.



phenylpropane-1,1-diyl) bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (112 mg, 0.300 mmol), hexanal (25.0 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2.5% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (72.2 mg, 88%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.26 (2H, t, *J*= 8.0 Hz), 7.19 (2H, d, *J*= 7.5 Hz), 7.16 (1H, t, *J*= 7.5 Hz), 6.32 (1H, t, *J*= 7.0 Hz), 2.65 (2H, t, *J*= 7.5 Hz), 2.44 (2H, t, *J*= 7.5 Hz), 2.02 (2H, q, *J*= 7.5 Hz), 1.33-1.22 (6H, m), 1.26 (12H, s), 0.88 (3H, t, *J*= 7.0 Hz); ¹³C NMR
(126 MHz, CDCl₃): δ (major isomer) 146.9, 142.7, 128.6, 128.1, 125.5, 83.0, 36.4, 31.7, 30.6, 28.7, 28.4, 24.7, 22.5, 14.0; IR (neat): 2976.3 (w), 2956.3 (w), 2925.6 (m), 2857.5 (w), 1628.3 (w), 1453.8 (m), 1408.4 (m), 1377.5 (s), 1348.8 (s), 1300.9 (s), 1143.7 (s), 965.6 (w), 856.4 (m), 747.0 (m), 697.3 (s) cm⁻¹; HRMS-(DART) for: C₂₂H₃₅B₁O₂ [M]⁺: calculated: 342.2730, found: 342.2747. (*Note: The olefin geometry was assigned based on analogy to compounds*).

(E)-4,4,6,6-tetramethyl-2-(1-phenylnon-3-en-3-yl)-1,3,2-B(dmpd) dioxaborinane. Prepared according to the representative procedure utilizing LiTMP (35.4 mg, 0.240 mmol), 2,2'-(3-

phenylpropane-1,1-diyl)bis(4,4,6,6-tetramethyl-1,3,2-dioxaborinane) (96.1 mg, 0.240 mmol), hexanal (20.0 mg, 0.200 mmol), and THF (0.96 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (55.4 mg, 81%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.28-7.14 (5H, m), 5.90 (1H, t, *J* = 7.0 Hz), 2.65 (2H, t, *J*= 8.0 Hz), 2.35 (2H, t, *J*= 8.0 Hz), 2.27 (2H, q, *J*= 7.0 Hz), 1.84 (2H, d, *J*= 3.0 Hz), 1.38-1.23 (6H, m), 1.37 (12H, s), 0.89 (3H, t, *J*= 7.0 Hz); ¹³C NMR (126 MHz, CDCl₃): δ (major + minor isomers) 143.5, 143.4, 143.3, 143.1, 128.6, 128.5, 128.1, 128.1, 125.4, 125.3, 70.5, 70.2, 48.8, 39.5, 37.3, 36.7, 31.9, 31.9, 31.8, 31.6, 30.8, 30.7, 29.8, 29.1, 28.4, 22.6, 22.6, 14.1, 14.0; IR (neat): 3025.5 (w), 2972.5 (m), 2923.8 (m), 2855.7 (m), 1672.7 (w), 1495.2 (w), 1453.7 (w), 1384.8 (s), 1366.9 (s), 1323.0 (m), 1257.7 (s), 1169.0 (s), 1204.7 (m), 1098.1 (w), 771.1 (w), 746.2 (w), 697.8 (s) cm⁻¹; HRMS-(DART) for: C₂₁H₃₄B₁O₂

[M+H]⁺: calculated: 329.2652, found: 329.2660.

Determination of Stereochemistry:

The olefin geometry was determined by 2D NMR (NOESY).



(Z)-4,4,5,5-tetramethyl-2-(6-methyl-1-phenylhept-3-en-3-yl)-B(pin) 1,3,2-dioxaborolane. Prepared according to the representative Me procedure utilizing LiTMP (44.2 mg, 0.300 mmol), 2,2'-(3-Мe phenylpropane -1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (112 mg, 0.300 mmol), 3-methylbutanal (21.5 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (72.4 mg, 92%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.28-7.14 (5H, m), 6.33 (1H, t, J= 7.0 Hz), 2.65 (2H, t, J= 7.5 Hz), 2.44 (2H, t, J= 8.5 Hz), 1.94 (2H, t, J= 7.0 Hz), 1.66-1.55 (1H, m), 1.26 (12H, s), 0.88 (6H, d, J= 6.5 Hz); ¹³C NMR (126 MHz, CDCl₃): δ (major + minor isomers) 145.8, 145.5, 142.8, 128.6, 128.1, 125.5, 125.4, 83.0, 82.8, 40.1, 39.1, 37.6, 37.0, 36.3, 30.7, 29.0, 28.3, 24.8, 24.8, 22.6, 22.3; IR (neat): 2976.0 (m), 2953.6 (m), 2929.0 (m), 2867.8 (w), 1628.1 (w), 1495.2 (w), 1453.6 (m), 1407.8 (s), 1378.0 (s), 1350.8 (s), 1268.7 (w), 1142.5 (s), 1030.9 (m), 857.0 (m), 696.7 (s) cm⁻¹; HRMS-(DART) for: $C_{20}H_{32}B_1O_2$ [M+H]⁺: calculated: 315.2495, found: 315.2498. (*Note: The olefin geometry was assigned based on analogy*).



mmol), 2,2'-(3-phenylpropane-1,1-diyl)bis(4,4,6,6-tetramethyl-1,3,2-dioxaborinane) (96.0 mg, 0.240 mmol), 3-methylbutanal (17.3 mg, 0.200 mmol), and THF (0.96 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (52.9 mg, 81%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.29-7.14 (5H, m), 5.92 (1H, t, *J*= 7.5 Hz), 2.67 (2H, t, *J*= 8.0 Hz), 2.37 (2H, t, *J*= 8.0 Hz), 2.18 (2H, t, *J*= 8.0 Hz), 1.83 (2H, s), 1.70-1.54 (1H, m), 1.37 (12H, s), 0.87 (6H, s, *J*= 7.0 Hz); ¹³C NMR (126 MHz, CDCl₃): δ (major + minor isomers) 143.5, 143.3, 142.1, 141.8, 128.6, 128.5, 128.1, 128.1, 125.4, 125.3, 70.5, 70.2, 48.8, 39.8, 39.6, 37.5, 37.3, 36.6, 31.9, 31.8, 30.8, 29.2, 28.5, 22.7, 22.4; IR (neat): 3025.6 (m), 2972.3 (m), 2927.1 (m), 2867.7 (w), 1627.5 (w), 1495.5 (w), 1453.6 (m), 1384.2 (s), 1316.3 (m), 1301.6 (m), 1281.8 (m), 1204.5 (s), 1097.9 (w), 770.4 (w), 746.0 (w), 698.1 (m) cm⁻¹; HRMS-(DART) for: C₂₁H₃₇B₁N₁O₂ [M+NH₄]⁺: calculated: 346.2917, found: 346.2926. (*Note: The olefin geometry was assigned based on analogy*).



(dmpd)B

Me

(*E*)-4,4,5,5-tetramethyl-2-(5-methyl-1-phenylhex-3-en-3-yl)-1,3,2-dioxaborolane. Prepared according to the representative procedure utilizing LiTMP (44.2 mg, 0.300 mmol), 2,2'-(3-

phenylpropane -1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (112 mg, 0.300 mmol), isobutyraldehyde (18.0 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (66.9 mg, 89%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.27-7.24 (2H, m), 7.20-7.14 (3H, m), 5.74 (1H, d, J=9.5 Hz), 2.98-2.91 (1H, m), 2.67 (2H, t, J= 7.5 Hz), 2.36 (2H, t, J= 8.5 Hz), 1.28 (12H, s), 0.91 (6H, d, J= 6.5 Hz); (minor isomer) 7.27-7.24 (2H, m), 7.20-7.14 (3H, m), 6.10 (1H, d, J= 9.5 Hz), 2.67 (2H, t, J= 7.5 Hz), 2.63-2.56 (1H, m), 2.45 (2H, t, J= 8.0 Hz), 1.26 (12H, s), 0.88 (6H, d, J= 6.5 Hz); ¹³C NMR (126 MHz, CDCl₃): δ (major + minor isomers) 154.4, 153.4, 142.7, 142.7, 128.7, 128.6, 128.1, 128.0, 125.5, 125.4, 83.0, 82.8, 38.8, 36.9, 36.8, 30.7, 29.7, 27.4, 24.8, 24.8, 23.4, 22.6; IR (neat): 2975.5 (m), 2960.9 (m), 2928.6 (m), 2865.6 (w), 1630.2 (w), 1495.5 (w), 1453.7 (m), 1405.3 (s), 1371.6 (m), 1290.7 (s), 1261.2 (s), 1142.9 (s), 966.5 (m), 863.3 (m), 747.2 (w), 698.1 (s) cm⁻¹; HRMS-(DART) for: $C_{19}H_{30}B_1O_2$ [M+H]⁺: calculated: 301.2339, found: 301.2334. (*Note: The olefin* geometry was assigned based on analogy).

(E)-4,4,6,6-tetramethyl-2-(5-methyl-1-phenylhex-3-en-3-yl)-

Me 1,3,2-dioxaborinane. Prepared according to the representative

procedure utilizing LiTMP (35.3 mg, 0.240 mmol), 2,2'-(3-phenylpropane -1,1-diyl) bis(4,4,6,6-tetramethyl-1,3,2-dioxaborinane) (96.0 mg, 0.240 mmol), isobutyraldehyde (14.4 mg, 0.200 mmol), and THF (0.96 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (57.3 mg, 91%). ¹H NMR (500 MHz, CDCl₃): δ 7.26 (2H, t, *J*= 8.0 Hz), 7.19 (2H, d, *J*= 7.0 Hz), 7.16 (1H, t, *J*= 7.5 Hz), 5.65 (1H, d, *J*= 9.0 Hz), 2.96-2.90 (1H, m), 2.65 (2H, t, *J*= 8.5 Hz), 2.32 (2H, t, *J*= 9.0 Hz), 1.84 (2H, s), 1.37 (12H, s), 0.93 (6H, d, *J*= 6.5 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 150.7, 143.3, 128.6, 128.0, 125.3, 70.5, 48.8, 39.3, 37.2, 31.9, 29.5, 24.5; IR (neat): 2972.0 (m), 2924.6 (m), 2864.5 (w), 1626.6 (w), 1453.6 (w), 1389.1 (s), 1355.8 (s), 1304.3 (s), 1254.0 (s), 1204.0 (s), 1098.7 (w), 769.9 (w), 746.4 (w), 697.9 (m); HRMS-(DART) for: C₂₀H₃₁B₁O₂ [M]⁺: calculated: 314.2417, found: 314.2412.

Determination of Stereochemistry:

The olefin geometry was determined by 2D NMR (NOESY).





(*E*)-2-(1,4-diphenylbut-1-en-2-yl)-4,4,5,5-tetramethyl-1,3,2dioxa-borolane. Prepared according to the representative procedure utilizing LiTMP (44.2 mg, 0.300 mmol), 2,2'-(3-

phenylpropane -1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (112 mg, 0.300

mmol), benzaldehyde (26.5 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (75.0 mg, 90%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.34-7.15 (11H, m), 2.80 (2H, dd, *J*= 10.5, 7.0 Hz), 2.69 (2H, dd, *J*= 10.0, 7.5 Hz), 1.32 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ (major isomer) 142.6, 142.4, 137.8, 128.8, 128.5, 128.2, 128.1, 127.1, 125.6, 83.4, 36.0, 31.3, 24.8; IR (neat): 3024.9 (w), 2976.9 (m), 2929.6 (w), 1616.4 (w), 1493.4 (m), 1446.3 (m), 1404.7 (s), 1371.4 (s), 1349.4 (s), 1210.9 (m), 1141.6 (s), 963.4 (m), 923.8 (m), 749.5 (s), 697.3 (s), 473.4 (w) cm⁻¹; HRMS-(DART) for: C₂₂H₂₈B₁O₂ [M+H]⁺: calculated: 335.2182, found: 335.2197. (*Note: The olefin geometry was assigned based on analogy*).

(E)-2-(1-cyclohexyl-3-methylbut-1-enyl)-4,4,5,5-tetramethyl-(pin)B Me Me 1,3,2-dioxaborolane. Prepared according to the representative procedure 2,2'utilizing LiTMP (44.2)mg, 0.300 mmol), (cyclohexylmethylene)bis(4,4,5,5- tetramethyl-1,3,2-dioxaborolane) (105.0 mg, 0.300 mmol), isobutyraldehyde (18.0 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (59.3 mg, 85%). ¹H NMR (500 MHz, CDCl₃): δ 5.55 (1H, d, J= 9.0 Hz), 2.69-2.76 (1H, m), 1.96 (1H, t, J= 12.0 Hz), 1.64-1.72 (4H, m), 1.27 (12H, m), 1.11-1.17 (2H, m), 0.93 (6H, d, *J*= 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 148.4, 83.0, 44.5, 33.5, 30.4, 27.0, 26.5, 25.0, 23.9; IR (neat): 2976.4 (m), 2922.7 (m), 2851.5 (m), 1404.0 (m), 1370.6 (m), 1346.0 (m), 1329.9 (m), 1256.8 (s),

983.8 (m), 714.3 (m) cm⁻¹; HRMS-(DART) for: $C_{17}H_{32}B_1O_2$ [M+H]⁺: calculated: 279.2495, found: 279.2504. (*Note: The olefin geometry was assigned based on analogy*).

(E)-2-(2,2-dimethylnon-3-en-3-yl)-4,4,5,5-tetramethyl-1,3,2-B(pin) , n-pentyl Me dioxaborolane. Prepared according to the representative procedure Me Me utilizing LiTMP (44.2 mg, 0.300 mmol), 2,2'-(2,2-dimethylpropane-1,1-diyl) bis(4,4,5,5tetramethyl-1,3,2-dioxaborolane) (97.2 mg, 0.300 mmol), hexanal (25.0 mg, 0.250 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (45.5 mg, 65%). ¹H NMR (500 MHz, CDCl₃): δ 5.78 (1H, t, J= 7.0 Hz), 2.07 (2H, q, J= 7.0 Hz), 1.22-1.36 (18H, m), 1.04 (9H, s), 0.86 (3H, t, J= 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 136.0, 83.3, 35.2, 32.2, 31.8, 30.6, 30.1, 25.2, 22.7, 14.3; IR (neat): 2956.9 (m), 2928.1 (m), 2860.3 (m), 1465.3 (m), 1413.1 (m), 1388.8 (s), 1370.9 (m), 1327.9 (s), 1290.8 (m), 1213.4 (s), 1108.6 (m), 862.4 (m) cm⁻¹; HRMS-(DART) for: $C_{17}H_{34}B_1O_2$ [M+H]⁺: calculated: 281.2652, found: 281.2666. (*Note: The* olefin geometry was assigned based on analogy).



phenylpropane-1,1-diyl) bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (111.6 mg, 0.3 mmol), (*E*)-but-2-enal (17.5 mg, 0.25 mmol), and THF (1.2 mL). The crude reaction

mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (70.2 mg, 94%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.16-7.30 (5H, m), 6.78 (1H, d, *J*= 11.0 Hz), 6.36-6.41 (1H, m), 5.89 (1H, dq, *J*= 14.0 Hz, 7.0 Hz), 2.69 (2H, t, *J*= 7.0 Hz), 2.56 (2H, t, *J*= 7.0 Hz), 1.80 (3H, d, *J*= 7.0 Hz), 1.25 (12H, s); ¹³C NMR (100 MHz, CDCl₃): δ 145.5, 142.8, 134.0, 128.8, 128.3, 127.7, 125.7, 83.3, 36.8, 31.0, 25.0, 18.8; IR (neat): 2976.8 (m), 2930.6 (m), 1640.8 (m), 1594.1 (m), 1406.8 (m), 1379.5 (m), 1371.3 (s), 1345.1 (s), 1301.2 (m), 1213.8 (s), 866.8 (m), 856.1 (m), 675.2 (m) cm⁻¹; HRMS-(DART) for: C₁₉H₂₈B₁O₂ [M+H]⁺: calculated: 299.2182, found: 299.2183. (*Note: The olefin geometry was assigned based on analogy*).

(pin)B Me (E)-2-(5,5-dimethyl-1-phenylhex-3-en-3-yl)-4,4,5,5-Me tetramethyl-1,3,2-dioxaborolane. Prepared according to the

representative procedure utilizing LiTMP (35.4 mg, 0.240 mmol), 2,2'-(3-phenylpropane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (89.3 mg, 0.240 mmol), pivalaldehyde (17.2 mg, 0.200 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (54.5 mg, 87%). ¹H NMR (500 MHz, CDCl₃): δ 7.22-7.26 (2H, m), 7.12-7.16 (3H, m), 5.74 (1H, s), 2.66 (2H, t, *J*= 8.0 Hz), 2.33 (2H, t, *J*= 8.0 Hz), 1.30 (12H, s), 1.03 (9H, s); ¹³C NMR (100 MHz, CDCl₃): δ 151.6, 142.7, 128.8, 128.3, 125.7, 83.6, 40.7, 36.9, 34.1, 30.6, 25.0; IR (neat): 2977.2 (m), 2951.9 (m), 1453.7 (m), 1406.6 (m), 1371.0 (s), 1330.8 (m), 1270.2 (m), 1205.5 (s), 1141.1 (m), 965.0 (m), 860.7 (m), 697.9 (m) cm⁻¹; HRMS-(DART) for: $C_{20}H_{32}B_1O_2$ [M+H]⁺: calculated: 315.2495, found: 315.2511.

Determination of Stereochemistry:

The olefin geometry was determined by 2D NMR (NOESY).



(E)-2-(2,2-dimethyl-6-phenylhex-3-en-3-yl)-4,4,5,5-

Me Me Me

tetramethyl-1,3,2-dioxaborolane. Prepared according to the representative procedure utilizing LiTMP (35.4 mg, 0.240

mmol), 2,2'-(2,2-dimethylpropane-1,1-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (77.8 mg, 0.240 mmol), 3-phenylpropanal (26.8 mg, 0.200 mmol), and THF (1.2 mL). The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (55.2 mg, 88%). ¹H NMR (500 MHz, CDCl₃): δ 7.23-7.26 (2H, m), 7.13-7.17 (3H, m), 5.86 (1H, t, *J*= 8.0 Hz), 2.65 (2H, t, *J*= 8.0 Hz), 2.40 (2H, q, *J*= 8.0 Hz), 1.28 (12H, s), 1.05 (9H, s); ¹³C NMR (100 MHz, CDCl₃): δ 142.5, 135.1, 128.6, 128.4, 125.8, 83.3, 37.0, 35.4, 34.2, 30.5, 25.2; IR (neat): 2976.6 (m), 2950.0 (m), 1454.0 (m), 1412.9 (m), 1388.7 (m), 1378.9 (m), 1325.3 (s), 1291.3 (m), 1268.1 (m), 1141.8 (s), 1108.6 (m), 974.1 (m), 697.8 (m) cm⁻¹; HRMS-(DART) for: C₂₀H₃₂B₁O₂ [M+H]⁺: calculated: 315.2495, found: 315.2506. (*Note: The olefin geometry was assigned based on analogy*).

3.5.10. Gram-Scale Synthesis of Vinyl Boronates.

Me B(pin) (E)-2-(but-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. To an oven-dried 250 mL round-bottomed flask equipped with a

stirbar was added lithium tetramethylpiperidide (LiTMP, 2.33 g, 15.8 mmol), and the flask was sealed and brought out of the glovebox. To the reaction flask was added THF (40 mL), and the solution was cooled in an ice bath to 0 °C. Once the solution was solution of 4,4,5,5-tetramethyl-2-((4,4,5,5-tetramethyl-1,3-dioxolan-2cooled. а yl)methyl)-1,3,2-dioxaboro- lane (3.85 g, 14.4 mmol) in THF (17 mL) was added dropwise, and the reaction mixture was allowed to stir at 0 °C for 5 minutes. Next, propionaldehyde (1.13 mL, 15.8 mmol) was added dropwise at 0 °C, and the mixture was allowed to stir at this temperature for an additional 3 hours. After completion, the reaction mixture was warmed to room temperature, diluted with diethyl ether (50 mL) and run through a pad of silica gel (100% diethyl ether). The resulting mixture was concentrated under reduced pressure and purified using silica gel comlumn chromatography (2.5% ethyl acetate/hexane) to provide the title compound as a clear, colorless oil as a 97:3 mixture of E:Z isomers (1.99 g, 76%). All spectral data are in accord with the literature.⁴⁷ Note: The addition of propionaldehyde can also be performed at -78 °C to provide higher E:Z ratios (99:1).

⁴⁷ Bruckner, R.; Burghart-Stoll, H. Org. Lett. 2011, 13, 2730.

(pin)B Me Me Me

(E)-2-(5,5-dimethyl-1-phenylhex-3-en-3-yl)-4,4,5,5tetramethyl-1,3,2-dioxaborolane. To an oven-dried 50 mL

round-bottomed flask equipped with a stirbar was added lithium

tetramethylpiperidide (LiTMP, 972 mg, 6.60 mmol), and the flask was sealed and brought out of the glovebox. To the reaction flask was added THF (15 mL), and the solution was cooled in an ice bath to 0 °C. Once the solution was cooled, a solution of 2,2'-(3-phenylpropane-1,1-diyl) bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (2.23 g, 6.00 mmol) in THF (5.0 mL) was added dropwise, and the reaction mixture was allowed to stir at 0 °C for 5 minutes. Next, the reaction mixture was cooled to -78 °C, and pivaldehyde (569 mg, 6.60 mmol) was added dropwise. The reaction mixture was allowed to stir at -78 °C for 4 hours. After completion, the reaction mixture was warmed to room temperature, diluted with diethyl ether (50 mL) and run through a pad of silica gel (100% diethyl ether). The resulting mixture was concentrated under reduced pressure and purified using silica gel column chromatography (2 % ethyl acetate/hexane) to provide the title compound as a clear, colorless oil (1.78 g, 95%).

B(pin) dioxaborolane. To an oven-dried 100 mL round-bottomed flask equipped with a stirbar was added lithium tetramethylpiperidide (LiTMP, 971 mg, 6.60 mmol), and the flask was sealed and brought out of the glovebox. To the reaction flask was added THF (10 mL), and the solution was cooled in an ice bath to 0 °C. Once the solution was cooled, a solution of 2,2'-(3-phenylpropane -1,1-diyl)bis(4,4,5,5tetramethyl-1,3,2- dioxaborolane) (2.23 g, 6.00 mmol) in THF (15 mL) was added dropwise, and the reaction mixture was allowed to stir at 0 °C for 5 minutes. Next, diiodomethane (3.23 g, 12.0 mmol) in THF (5.0 mL) was added dropwise at 0 °C, and the mixture was allowed to stir at this temperature for an additional 15 minutes. Next, the reaction mixture was allowed to warm to 60 °C and stir for 2 hours. After completion, the reaction mixture was cooled to room temperature, diluted with diethyl ether (50 mL) and run through a pad of silica gel (100% diethyl ether). The resulting mixture was concentrated under reduced pressure and purified using silica gel comlumn chromatography (2 % ethyl acetate/hexane) to provide the title compound as a clear, colorless oil (1.28 g, 83%). All spectral data are in accord with the literature.⁴⁶

3.5.11. Attempt at Trapping Boron-Wittig Intermediate.



In the glove box, an oven-dried 2-dram vial with a magnetic stir bar was charged with LiTMP (35.3 mg, 0.240 mmol), sealed with a cap with a septum, and removed from the glovebox. The reaction vial was cooled to 0°C, and Et₂O (0.24 mL), and solution of 1,1-diboronate **3.51** (89.3 mg, 0.240 mmol) in Et₂O (0.48 mL) was added. The reaction vial was allowed to stir for 5 minutes at 0°C. Then the reaction vial was cooled to -78°C, and a solution of aldehyde (20.0 mg, 0.200 mmol) in Et₂O (0.24 mL) was added. The reaction

vial was allowed to stir at -78°C for 4 hours. Next, TBSOTf (0.055 mL, 0.240 mmol) was added at -78 °C and the reaction was allowed to stir for an additional hour. Upon completion, the reaction mixture was concentrated under reduced pressure. Crude ¹H NMR shows the presence of **3.54** along with a diastereomeric mixture of an unknown compound consistent with **3.65 or 3.66**. Purification by silica gel column chromatography resulted in only isolation of vinyl boronate **3.54**, with the unknown intermediate being converted to **3.54** during attempted isolation. See ¹H NMR for further analysis.

3.5.12. Boron-Wittig Reaction with Geminal Dibromides.



In the glove box, an oven-dried 2-dram vial with a magnetic stir bar was charged with LiTMP (44.2 mg, 0.300 mmol), sealed with a cap with a septum, and removed from the glovebox. The reaction vial was cooled to 0°C, and THF (0.45 mL), and solution of 1,1-diboronate **3.43** (80.4 mg, 0.300 mmol) in THF (0.45 mL) was added. The reaction vial was allowed to stir for 5 minutes at 0°C. Next, a solution of dibromide **3.67** (69.5 mg, 0.250 mmol) in THF (0.30 mL) was added. The reaction vial was allowed to stir at 0 °C for 1.5 hours. Upon completion, the reaction mixture was concentrated under reduced pressure. Crude ¹H NMR shows the presence of **3.68** along with byproduct **3.69**, both

matching spectral data previously reported in the literature, 48,49 with a 41% overall conversion of dibromide **3.67**. No further purification was performed.



In the glove box, an oven-dried 2-dram vial with a magnetic stir bar was charged with LiTMP (44.2 mg, 0.300 mmol), sealed with a cap with a septum, and removed from the glovebox. The reaction vial was cooled to 0°C, and THF (0.45 mL), and solution of 1,1-diboronate **3.51** (111.1 mg, 0.300 mmol) in THF (0.45 mL) was added. The reaction vial was allowed to stir for 5 minutes at 0°C. Next, a solution of dibromide **3.67** (69.5 mg, 0.250 mmol) in THF (0.30 mL) was added. The reaction vial was allowed to stir at 0 °C for 1.5 hours. Upon completion, the reaction mixture was concentrated under reduced pressure. Crude ¹H NMR shows the presence of **3.70** along with byproduct **3.69**, matching spectral data previously reported in the literature,⁴⁹ with a 49% overall conversion of dibromide **3.67**. No further purification was performed.

 ⁴⁸ Takai, K.; Kunisada, Y.; Tachibana, Y.; Yamaji, N.; Nakatani, E. *Bull. Chem. Soc. Jpn.* **2004**, *77*, 1581.
⁴⁹ Pinhey, J. T.; Stoermer, M. J. J. Chem. Soc., Perkin Trans. 1 **1991**, 2455.

3.5.13. Boron-Wittig Reaction with Trimethylborylmethane 3.72.



trimethyl((4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)methyl)silane. In SiMe₃ B(pin) the glovebox, an oven-dried 2-dram vial with a magnetic stir bar was charged with CuI (19.0 mg, 0.100 mmol) followed by LiOMe (114 mg, 3.00 mmol). The reaction vessel was sealed with a septum cap and brought out of the glovebox, at which point DMF (1.0 mL) was added. The reaction mixture was allowed to stir at room temperature for 2 minutes, at which point B₂(pin)₂ (508 mg, 2.00 mmol) as a solution in DMF (2.0 mL) was added. Next, (chloromethyl)trimethylsilane (0.28 mL, 3.0 mmol) was added dropwise under N₂, and the reaction mixture was allowed to stir at 60 °C for 24 hours. The vial was cooled to room temperature and diluted with Et₂O (10 mL), and the crude mixture was passed through a pad of celite with a layer of silica gel on top. The mother liquor was concentrated in vacuo, diluted with hexanes (10 mL) and DI H_2O (20 mL) was added. The aqueous layer was washed with hexanes (2x20 mL), and the organic layers were collected and washed with DI H_2O (2x20 mL). The organic layer was dried over Na₂SO₄, filtered, and concentrated under reduced pressure to provide the title compound as a clear, colorless oil (351 mg, 82%). No further purification was required. All spectral data are in accord with the literature.³⁸



magnetic stir bar was charged with LiTMP (44.2 mg, 0.300 mmol), sealed with a cap with a septum, and removed from the glovebox. The reaction vial was cooled to 0°C, and THF (0.45 mL), and solution of 1,1-silaboronate **3.72** (64.3 mg, 0.300 mmol) in THF (0.45 mL) was added. The reaction vial was allowed to stir for 10 minutes at 0°C. Next, the reaction vessel was cooled to -78 °C a solution of hexanal (25.0 mg, 0.250 mmol) in THF (0.30 mL) was added. The reaction vial was allowed to stir at -78 °C for 4 hours, at which point the reaction mixture was concentrated under reduced pressure. Crude ¹H NMR shows the presence of the title compound, as verified by spectral data previously reported in the literature.^{28b,38} Crude ¹H NMR indicated close to 55% conversion of **3.72**, with the title compound being formed exclusively in a 64:36 *Z:E* ratio. No further purification was performed.





































Chapter 4

Pt-Catalyzed Enantioselective Diboration of Vinyl Boronates and Utility of 1,1,2-Tris(boronate) Esters

4.1. Introduction

In recent years, polyborylated compounds have found increasing utility as conjunctive reagents in natural product and drug synthesis.¹ Importantly, they can either be furnished or transformed in an asymmetric and catalytic fashion. In some cases, multiborylated reagents can be constructed and employed in one-pot tandem processes, allowing access to complex chiral products from readily available reagents in a simple and efficient manner (*vide infra*).

As addressed in Chapters 2 and 3, the Morken group has been largely involved in the synthesis and utility of 1,2-bis(boronate) and, more recently, 1,1-bis(boronate) compounds. Of interest was the distinctive reactivity of these unique motifs, the basis of which is due to the ability of three-coordinate boron to participate in chelation or accept electrons and stabilize adjacent charge buildup. For example, vicinal bis(boronates) have enhanced efficiency in cross-coupling reactions due to internal chelation of a pinacol oxygen to the internal boronate moiety, increasing the Lewis acidity of the terminal unit

¹ For key examples, see: (a) Ferris, G. E.; Hong, K.; Roundtree, I. A.; Morken, J. P.; *J. Am. Chem. Soc.* **2013**, *135*, 2501. (b) Matsumoto, K.; Koyachi, K.; Shindo, M. *Tetrahedron* **2013**, *69*, 1043. (c) Gerrdink, D.; ter Horst, B.; Lepore, M.; Mori, K.; Puzo, G.; Hirsch, A. K. H.; Gilleron, M.; de Libero, G.; Minnaard, A. *Chem. Sci.* **2013**, *4*, 709. (d) Burns, M.; Essafi, S.; Bame, J. R.; Bull, S. P.; Webster, M. P.; Balieu, S.; Dale, J. W.; Butts, C. P.; Harvey, J. N.; Aggarwal, V. K. *Nature* **2014**, *513*, 183. (e) Yu, Z.; Ely, R. J.; Morken, J. P. *Angew. Chem. Int. Ed.* **2014**, *53*, 9632.

(A, Scheme 4.1A). On the other hand, geminal bis(boronates) deborylate under mild conditions with Lewis bases to generate stabilized α -boryl anions, which undergo alkylation with various carbon-based electrophiles (**B** and **C**, Scheme 4.1A).

It was reasoned that 1,1,2-tris(boronate) esters might profit from both of these aspects in order to furnish internally chelated α -boryl anion **D** (Scheme 4.1B). More so, the chelation might provide enhanced rigidity and organization in order to promote highly stereoselective transformations. In this chapter, the Pt-catalyzed asymmetric diboration of vinyl boronates to access enantioenriched 1,1,2-tris(boronate) esters will be presented. Additionally, a highly stereoselective deborylative alkylation of this novel motif with various alkyl electrophiles will be described in depth. Preliminary investigation into other C-C bond-forming reactions with tris(boronates) is also briefly discussed.

Scheme 4.1.

A) Reactivity Features of Bis(boronate) Esters:



B) Potential Reactivity Features of Chiral Tris(boronates):


4.2. Background

4.2.1. Enhanced Reactivity of Vicinal Bis(boronate) Esters. Suzuki-Miyaura cross-coupling has arguably been one of the most extensively studied and utilized C-C bond-forming reactions ever since its initial discovery in 1979.² Nonetheless, a significant limitation is the difficulty of balancing reactivity and stability of the organoboronate substrate. For example, while trialkylboranes have been shown to participate in a variety of cross-coupling reactions in an efficient manner, they are air and moisture sensitive. Conversely, alkyl boronate esters are stable under ambient conditions, but are comparatively harder to activate for transmetallation. The first successful Suzuki-Miyaura coupling utilizing pinacol-derived alkyl boronates was reported in 1989 and necessitated stoichiometric amounts of toxic thallium hydroxide and highly activated aryl iodides in order to obtain low to moderate yields of coupled product (Scheme 4.2, eq 1).³ The overall transformation was less effective than when more Lewis acidic catechol-based boronates were utilized. Pre-activation of primary alkyl boronate esters with alkyl lithium reagents to form a reactive borate complex 4.4 has also been reported to effectively promote transmetallation for Pd-catalyzed cross-coupling; however, substrate scope is limited (eq 2).⁴ Since then, specialized or activated nucleophiles such as cyclopropyl- and benzylic pinacol-derived boronate esters have been

² Miyaura, N.; Suzuki, A. J. Chem. Soc., Chem. Comm. 1979, 866.

³ Sato, M.; Miyaura, N.; Suzuki, A. Chem. Lett. **1989**, 1405.

⁴ Zou, G.; Falck, J. R. *Tetrahedron Lett.* **2001**, *42*, 5817.

employed as well, and react efficiently to provide high yields of the coupled products under mild conditions.⁵



Scheme 4.2. Early Examples of Suzuki Couplings with Alkyl Boronate Esters

Recently, new monodendate phosphine-based ligands have been developed by Buchwald, which have been shown to efficiently promote Suzuki-Miyaura couplings between primary pinacol-derived alkyl boronate esters and a variety of aryl electrophiles.⁶ For example, a highly general sp^3 - sp^2 coupling was achieved when employing 4 mol% RuPhos with 2 mol% Pd₂(dba)₃ and 3 equivalents of NaO*t*Bu at 80

⁵ (a) Löhr, S.; Meijere, A. *Synlett* **2001**, 489. (b) Imao, D.; Glasspoole, B. W.; Laberge, V. S.; Crudden, C. M. *J. Am. Chem. Soc.* **2009**, *131*, 5024. (c) Glasspoole, B. W.; Oderinde, M. S.; Moore, B. D.; Antoff-Finch, A.; Crudden, C. *Synthesis* **2013**, *45*, 1759.

⁶ For a review on Buchwald ligands, see: Sclummer, B.; Scholz, U. Adv. Synth. Catal. 2004, 346, 1599.

^oC.⁷ While the reaction requires a slight excess of boronate equivalents and extended reaction times, the coupled products could be furnished under mild conditions and in high yield.

Scheme 4.3. Suzuki Coupling Between Primary Alkyl Boronates and Aryl Electrophiles Reported by Marder and Liu.



In 2014, Morken and co-workers described a tandem asymmetric alkene diboration/cross-coupling (DCC) method which provided access to chain-extended enantioenriched monoborylated products **4.8** (Scheme 4.4).^{8,9} Complete regioselectivity for the terminally cross-coupled product is observed when employing a variety of aryl and vinyl electrophiles. Interestingly, utilizing just 1 mol% Pd(OAc)₂ and 1 mol% RuPhos with KOH as the base, cross-coupled product **4.14** could be obtained in high conversion from bromobenzene and bis(boronate) **4.10** in 1 hour at 70 °C (Scheme 4.5A, entry 1). Conversely, under otherwise identical conditions, primary alkyl boronate **4.11**

⁷ 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.

⁸ Mlynarski, S. N.; Schuster, C. H.; Morken, J. P. Nature 2014, 505, 386.

⁹ For related cross-coupling reactions, see: (a) Morgan, J. B.; Felix, J.; Nepveux, V.; Morken, J. P. Org. Lett. **2004**, *6*, 131. (b) Lee, Y.; Hoveyda, A. H. J. Am. Chem. Soc. **2009**, 131, 18234.

provided <5% conversion of the coupled product **4.15** (entry 2). Moreover, 1,3- and 1,4bis(boronates) (**4.12** and **4.13**) proved to be less efficient under the reaction conditions (entries 3 and 4). A direct competition experiment between monoboronate **4.11** and 1,2bis(boronate) **4.10** suggests markedly enhanced reactivity for the vicinal boronate substrate (i.e. a >50-fold rate increase) (Scheme 4.5B). The combined data suggest that the rate of transmetallation for 1,2-bis(boronates) is accelerated when compared to monoborylated substrates.

Scheme 4.4. Morken's Asymmetric Diboration/Cross-Coupling (DCC) Sequence.





Scheme 4.5. Comparison of Efficacy of Various Boronates in Pd-Catalyzed Coupling.



Coupling between deuterium-labelled bis(boronate) **4.18** and chloroalkene **4.19** furnishes cross-coupled product **4.20** exclusively, indicating that transmetallation occurs with complete retention of configuration (Scheme 4.6). The result is most consistent with an inner-sphere transmetallation pathway. Thus, it is proposed that the adjacent boronate moiety could function as a Lewis acid, facilitating internal coordination of a neighboring pinacolato oxygen and therefore increasing the Lewis acidity of the terminal boronate (**A**). The result is a more reactive boronate species for highly efficient transmetallation,

perhaps via association of a Pd(hydroxide) complex with internally chelated structure **A** (i.e. via **E**).



Scheme 4.6. Cross Coupling with Stereodefined 1,2-Bis(boronate) Ester 4.18.

4.2.2. Enhanced Reactivity of Geminal Bis(boronate) Esters. Recently, Shibata and co-workers described a Suzuki-Miyaura cross-coupling between 1,1-bis(boronates) **4.21** and aryl bromides to generate benzylic boronates **4.22** under rather mild conditions (Scheme 4.7, eq 1).¹⁰ Efficient transmetallation could be achieved at room temperature utilizing aqueous potassium hydroxide as the base. In contrast, primary alkyl boronate **4.24** and 1,2-bis(boronate) ester **4.10** did not deliver any coupled product under the same conditions (eqs 1 and 2). With insights from computational and ¹¹B NMR analysis, the authors suggest that 1,1-bis(boronate) esters benefit from *p*-orbital overlap between both

¹⁰ Endo, K.; Ohkubo, T.; Hirokami, M.; Shibata, T. J. Am. Chem. Soc. 2010, 132, 11033.

of the geminal boronate moieties, thus lowering the LUMO by electron delocalization. The result is a decrease in energy associated with coordinating a Lewis base for borate complex formation.



Scheme 4.7. Suzuki Coupling of 1,1-Bis(boronates) Reported by Shibata.

Since Shibata's discovery, the Morken group has reported an enantiotopic-groupselective Suzuki reaction between 1,1-bis(boronates) and various sp^2 -hybridized electrophiles.¹¹ For example, 5 mol% Pd(OAc)₂ and 10 mol% TADDOL-derived phosphoramidite (*R*,*R*)-4.28 promotes an efficient coupling between geminal diborons 4.26 and aryl halides at room temperature to provide benzylic boronates 4.27 in high levels of enantioinduction (Scheme 4.8, eq 1). Vinyl electrophiles 4.29 were also

¹¹ (a) Sun, C.; Potter, B.; Morken, J. P. J. Am. Chem. Soc. **2014**, 136, 6534. (b) Potter, B.; Szymaniak, A. A.; Edelstein, E. K.; Morken, J. P. J. Am. Chem. Soc. **2014**, 136, 17918.

competent under similar reaction conditions with 1 mol% Pd-complex **4.30**, furnishing chiral allyl boronates **4.31** in high yields and enantioselectivity (eq 2). While an exact model for transmetallation is still unclear, ¹⁰B isotopic labelling studies indicate inversion of configuration at the carbon center occurs with both classes of electrophile; thus, a mechanism involving the formation of an "ate" complex and subsequent attack of an electrophilic Pd-center is plausible.



Scheme 4.8. Morken's Enantiotopic-Group-Selective Coupling of 1,1-Bis(boronates).

In addition to their enhanced susceptibility for transmetallation in Pd-catalyzed Suzuki reactions, 1,1-bis(boronate) esters also readily undergo deborylation under transition-metal free conditions. For example, in 2014, Morken and co-workers reported a deborylative alkylation between 1,1-bis(boronate) esters **4.26** and various sp^3 -

hybridized carbon-based electrophiles **4.32** to provide alkyl boronates **4.33** in high yields (Scheme 4.9).^{12,13} Interestingly, metal alkoxides were nucleophilic enough to promote the reaction even at room temperature—much milder conditions than what is required for deborylation of simple monoborylated alkanes. The origin of this unique reactivity lies in the ability of three-coordinate boron to stabilize negative charge at the α -carbon. Indeed, ¹³C NMR studies suggest that deborylative alkylation proceeds via generation of a full-fledged anionic intermediate **B** from borate **F**, which is stabilized through delocalization of electron density into the empty *p*-orbital of the adjacent boronate (**C**).





4.2.3. Potential Synthetic Applications of 1,1,2-Tris(boronate) Esters. As

described in Scheme 4.1, 1,1,2-tris(boronate) esters might benefit from analogous reactivity of both vicinal and geminal bis(boronate) esters (see Scheme 4.1, structure **D**), and might therefore be suitable candidates for highly stereoselective transformations. If

¹² Hong, K.; Liu, X.; Morken, J. P. J. Am. Chem. Soc. 2014, 136, 10581.

¹³ For related reactions, see: (a) Matteson, D. S.; Moody, R. J. *Organometallics* **1982**, *1*, 20. (b) Wommack, A. J.; Kingsbury, J. S. *Tetrahedron Lett.* **2014**, *55*, 3163.

this is the case, Suzuki coupling or deborylative alkylation of enantioenriched 1,1,2tris(boronate) esters **4.34** would furnish internal 1,2-bis(boronate) esters (**4.35-4.38**), presumably in high regio- and stereoselectivity (Scheme 4.10). Notably, with the exception of an expensive and non-ideal Rh-catalyzed asymmetric diboration of internal alkenes, there is no known method for constructing enantioenriched internal 1,2bis(boronates).¹⁴ As explained in Chapter 2, Pt-catalyzed asymmetric diboration suffers from low reactivity with internal alkene substrates.¹⁵ Development of a new strategy for accessing this challenging motif is clearly warranted.

Scheme 4.10. Potential for 1,1,2-Tris(boronate) Esters as Substrates for C-C Bond Forming Transformations.



Despite their synthetic potential, few methods are available for accessing 1,1,2tris(boronate) esters, and they are not general. For example, in 2002, Marder reported a

¹⁴ (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.

¹⁵ Coombs, J. R.; Haeffner, F.; Kliman, L. T.; Morken, J. P. J. Am. Chem. Soc. 2013, 135, 11222.

Rh-catalyzed diboration of catechol-derived vinyl boronate **4.39** in order to furnish 1,1,2-tris(boronate) **4.40**, along with a mixture of β -hydride elimination and hydroboration byproducts **4.41** and **4.42** (Scheme 4.11).¹⁶ Only styrenylboronate esters were investigated and their utility and reactivity was not evaluated.

Scheme 4.11. Rh-Catalyzed Diboration of Vinyl Boronate 4.39.



Considering that vinyl boronates are readily available and inexpensive starting materials (see Chapter 3), we reasoned that asymmetric diboration of these compounds would provide a simple route for constructing enantioenriched 1,1,2-tris(boronates) (Scheme 4.12). Indeed, Pt-catalyzed diboration of more activated π -systems such as alkynes,¹⁷ imines,¹⁸ dienes,¹⁹ and α , β -unsaturated carbonyls²⁰ are known to occur under mild conditions and in an efficient manner. Thus, despite the above-mentioned

¹⁶ Nguyen, P.; Coapes, R. B.; Woodward, A. D.; Taylor, N. J.; Burke, J. M.; Howard, J. A. K.; Marder, T. B. *J. Organomet. Chem.* **2002**, *652*, 77.

 ¹⁷ (a) Lesley, G.; Nguyen, P.; Taylor, N. J.; Marder, T. B.; Scott, A. J.; Clegg, W.; Norman, N. C. *Organometallics* 1996, *15*, 5137. (b) Iverson, C. N.; Smith, M. R., III, *Organometallics* 1996, *15*, 5155.
¹⁸ Hong, K.; Morken, J. P. J. Am. Chem. Soc. 2013, *135*, 9252.

¹⁹ (a) Kliman, L. T.; Mlynarski, S. N.; Ferris, G. E.; Morken, J. P. Angew. Chem. Int. Ed. **2012**, *51*, 521. (b) Hong, K.; Morken, J. P. J. Org. Chem. **2011**, *76*, 9102. (c) Burks, H. E.; Kliman, L. T.; Morken, J. P. J. Am. Chem. Soc. **2009**, *131*, 9134. (d) Schuster, C. H.; Li, B.; Morken, J. P. Angew. Chem. Int. Ed. **2011**, *50*, 7906.

²⁰ Lawson, Y. G.; Lesley, M. J. G.; Norman, N. C.; Rice, C. R.; Marder, T. B. Chem. Commun. 1997, 2051.

limitations of the Pt-catalyzed asymmetric diboration system in the context of internal alkene reactivity, it is plausible that the olefin of a vinyl boronate might be pre-activated or electronically biased for Pt binding and insertion, thereby making them competent substrates.²¹

Scheme 4.12. Potential Route to Enantioenriched 1,1,2-Tris(boronate) Esters.

$$R \xrightarrow{B(OR)_2} + B_2(OR')_2 \xrightarrow{\text{cat. Pt/L}^*} R \xrightarrow{B(OR')_2} B(OR)_2$$

4.3. Development of Pt-Catalyzed Enantioselective Diboration of Vinyl Boronates²²

Prior to ligand screening, it was important to test whether or not diboration could occur with nonligated Pt. Thus, *trans*-vinyl boronate **4.43** was treated with 1.05 equivalents of $B_2(pin)_2$ in the presence of 3 mol% Pt(dba)₃ at 60 °C for 13 hours (Table 4.1, entry 1). Full conversion was observed, furnishing racemic 1,1,2-tris(boronate) **4.44** cleanly in 81% yield. To our delight, employing (*R*,*R*)-**4.45** provided the product in high yield and in a low but measureable enantiomeric ratio (entry 2). Interesting, the *cis*-vinyl boronate **4.43** provided the opposite enantiomer of product in markedly higher enantiomeric ratios, albeit in moderate yield (entry 3). Contrary to what is observed for

²¹ Notably, Hayashi and co-workers recently reported that vinyl boronates were suitable Michael acceptors and can be applied to Rh-catalyzed conjugate addition reactions with arylboroxines: Sasaki, K.; Hayashi, T. *Angew. Chem. Int. Ed.* **2010**, *49*, 8145.

²² Coombs, J. R.; Zhang, L.; Morken, J. P. J. Am. Chem. Soc. 2014, 136, 16140.

Pt-catalyzed diboration terminal alkenes, the diboration of **4.43** benefitted from increased ligand-to-metal ratios as evident by a slight enhancement in enantioselectivity (entry 4). Subsequently, various TADDOL-derived ligands bearing substitution at the *meta* position of the aryl ring were examined under the reaction conditions. Increasing the steric bulk of the ligand from R = Et (**4.45**) to R = i-Bu (**4.47**) provided enhanced enantiomeric ratios (94:6 er, entry 7), but at the price of reactivity. Unfortunately, an even bulkier ligand, (*R*,*R*)-**4.48**, resulted in diminished enantioselectivity (entry 8). Phosphoramidite (*R*,*R*)-**4.49** was also examined but gave low conversions to the desired product (entry 9).





Additional screening of conditions was performed with (R,R)-4.47 in an effort to improve reactivity (Table 4.2). Surprisingly, low conversion issues were not improved with prolonged reaction times. Only a slight increase in conversion was observed after 2 days at 60 °C (55% vs 50%, entry 2 vs. entry 1). Notably, *cis* vinyl boronate 4.50 suffered from similarly low levels of conversion over the same time period (entry 3). It became apparent that increasing the rate of diboration versus the rate of catalyst inhibition would be necessary to obtain higher conversions (*vide infra*). Indeed, increasing the reaction temperature from 60 °C to 70 °C led to full conversion and moderate yield of 4.44, albeit in reduced enantiomeric ratio (entry 4). Additionally, Pt loading could be increased 2-fold to provide tris(boronate) 4.44 in higher yield and with moderate enantioinduction (entry 5). Likewise, high yield and good selectivity was obtained when employing *cis* vinyl boronate 4.50 under these reaction conditions (entry 6).

Table 4.2. Additional Screening of Conditions for Enantioselective Diboration of with *Cis* Vinyl Boronates.

| B(pin) R + | | + (1. | B ₂ (pin) ₂ 05 equiv.) | X% Pt(X% (R,f THF, tem | dba) ₃ ₹)-4.47 p., 48 h | B(pin) R B(pin) B(pin) | |
|----------------|---|--------------------------------|---|--------------------------------------|---|---|-----------------------|
| R = R = | = <i>n</i> -hexyl; = Bn; 4.50 | 4.43 | | | | R = <i>n</i> -hexy R = Bn; 4. | /l; 4.44 51 |
| entry | R | Pt(dba) ₃ (mol%) | ligand (mol%) | temp. (^o C) | conv. (%) | yield (%) | er |
| 1 ^a | <i>n</i> -hexyl | 3.0 | 6.0 | 60 | 50 | 46 | 94:6 |
| 2 | <i>n</i> -hexyl | 3.0 | 6.0 | 60 | 55 | 50 | 94:6 |
| 3 | Bn | 3.0 | 6.0 | 60 | 52 | 40 | 95:5 |
| 4 | <i>n</i> -hexyl | 3.0 | 6.0 | 70 | 100 | 71 | 90:10 |
| 5 | <i>n</i> -hexyl | 6.0 | 9.0 | 60 | 100 | 81 | 91:9 |
| 6 | Bn | 6.0 | 9.0 | 60 | 100 | 84 | 94:6 |

a) Reaction run for 14 h.

The reason for the diminution in reaction rate over time seems to be most consistent with catalyst degradation. For example, directly after precomplexation of a mixture of 9 mol% (*R*,*R*)-4.47 and 6 mol% Pt(dba)₃ in the presence of B₂(pin)₂, a monoligated Pt-catalyst is observed by ³¹P NMR analysis: ³¹P{¹H} NMR (THF) δ 201.0 ppm (¹J_{P-Pt} = 1615 Hz). As expected, a significant amount of unbound ligand is also present initially ((*R*,*R*)-4.47 δ = 158.8 ppm). Addition of vinyl boronate 4.50 to the precomplexation mixture did not result in a significant change in ratio of active catalyst to free ligand, although generation of a new Pt-boryl complex which is suggestive of olefin binding or insertion was observed in minor amounts: ³¹P{¹H} NMR (THF) δ

142.3 ppm. Upon heating the reaction mixture to 60 °C for 14 hours, ³¹P NMR revealed that the free ligand had been completely consumed and a substantial amount of a Pt-phosphorus species consistent with a doubly-ligated Pt-complex had been generated: ³¹P{¹H} NMR (THF) δ 124.7 ppm (²J_{P-P} = 38.3 Hz, ¹J_{P-Pt} = 4748.9 Hz); 70.4 ppm (²J_{P-P} = 39.0 Hz, ¹J_{P-Pt} = 4022.8 Hz). Meanwhile, a reduction in the peak corresponding to the catalytically active Pt-complex at 201 ppm is observed. The studies suggest that the active monoligated Pt-complex can be converted to inactive bis-ligated complex over time. Note that olefin binding to a bis-ligated d⁸ 16-electron Pt(boryl)-complex [i.e. PtL₂(B(OR)₂)₂] is expected to be largely uphill in energy, and therefore is unlikely to partake in diboration.²³ Thus, with longer reaction times, a 2:1 ligand:metal ratio might eventually result in complete consumption of active catalyst and prevent a productive reaction from occurring.

With promising results in hand, a variety of *cis*-vinyl boronates were tested under the optimized conditions (Scheme 4.13). Notably, although high yields and good enantioselectivities were obtained with the benzyl substituted vinyl boronate (4.51), low and often inconsistent enantioselectivities were observed for other substrates (4.52, 4.53 and 4.44).

²³ Addition of excess ligand or employment of bidentate phosphine ligands have been shown to inhibit Ptcatalyzed diboration: (a) see ref. 16[a]. (b) Ali, H. A.; Aziz, A. E. A. A.; Goldberg, I.; Srebnik, M. *Organometallics* **2002**, *21*, 4533.



Scheme 4.13. Initial Substrate Scope with Cis-Vinyl Boronates.

We reasoned that the poor and variable selectivity could originate from interconversion of the *cis*-vinyl boronate starting material to the more thermodynamically stable *trans* isomer over the course of the reaction. If isomerization were possible, diboration of the *trans*-vinyl boronate would result in formation of the opposite enantiomer of product, drastically reducing enantiomeric ratios (Scheme 4.14, eq 1). Interestingly, although *cis*-vinyl boronate **4.43** was found to be thermally stable under the reaction temperatures, addition of 6 mol% Pt(dba)₃ resulted in considerable isomerization after just 12 hours (eq 2). Furthermore, ¹H NMR analysis of the reaction mixture verified that isomerization of the starting material occurs as the reaction proceeds.

Scheme 4.14. Isomerization Issues with Cis Vinyl Boronates.



With these new insights in hand, it was clear that either inhibiting or outcompeting isomerization by increasing reaction rate would be necessary. Conversely, optimizing conditions around the thermodynamically favored *trans*-vinyl boronate would circumvent issues of isomerization. Despite testing a variety of Pt-based precatalysts and solvents, isomerization could not be fully prevented. Thus, to enhance the reaction rates even further, $B_2(cat)_2$ was employed in place of $B_2(pin)_2$ followed by transesterification with pinacol upon completion of the reaction (Scheme 4.15). With employment of the more reactive diboron source, ^{17a} full conversion and moderate yield of tris(boronate) **4.44** was observed, with a slight predominance of the opposite enantiomer typically obtained when employing $B_2(pin)_2$.



Scheme 4.15. Pt-Catalyzed Asymmetric Diboration of **4.43** with B₂(cat)₂.

Considering that the *trans*-isomer of vinyl boronate **4.43** already favored the same enantiomer of product observed when $B_2(cat)_2$ was utilized in combination with *cis* vinyl boronate **4.43**, efforts were refocused towards optimizing the reaction conditions around the *trans* isomer of starting material. As depicted in Table 4.3, by employing $B_2(cat)_2$ with 5 mol% Pt(dba)₃ and 10 mol% (*R*,*R*)-**4.47**, tris(boronate) product could be furnished in high conversions, albeit in moderate yields and enantioselectivity (88:12 er, entry 1). For comparison, utilizing $B_2(pin)_2$ resulted in a markedly reduced enantiomeric ratio (68:32 er), and was slightly less reactive under identical reaction conditions (entry 2). A quick ligand screen determined that smaller ligands [i.e. (*R*,*R*)-**4.45**] resulted in no improvement in selectivity (entry 3), while a larger ligand [(*R*,*R*)-**4.9**] provided the highest levels of enantioinduction (95:5 er, entry 4). Increasing the bulk of the ligand past R = *i*Pr led to similar enantioselectivity but required longer reaction times (entry 5).

With optimal ligand (R,R)-4.9 in hand, an extensive evaluation of catalyst loading, ligand:metal ratio, reagent stoichiometry, and temperature was performed, the highlights of which are provided in the latter half of Table 4.3. Employing 6 mol% Pt(dba)₃ and 9 mol% (R,R)-4.9 at 60 °C generated tris(boronate) 4.52 with full

conversion and in moderate yield (entry 6). Interestingly, 4-*tert*-butylcatechol derived diboron $[B_2(tbc)_2]$ provided an efficient reaction, but furnished the desired product in lower selectivity (91:9 er, entry 7). Overall, it was important to reduce catalyst and ligand loading to a practical and operationally appealing level. Thus, optimal conditions were determined to be those which employed 3 mol% Pt(dba)₃, 6 mol% (*R*,*R*)-4.9, and 2.0 equivalents of $B_2(cat)_2$ at 70 °C for 24 hours. Subsequent to treatment of the crude reaction mixture with pinacol, 1,1,2-tris(boronate) 4.52 could be furnished in 70% isolated yield and in 92:8 er (entry 8).

| | | | | | | Ligand: Ar | Ar |
|----------------|--|---|-----------------------------------|---|-----------|---|-------|
| <i>i-</i> Bu | —————————————————————————————————————— | Pt(dba) ₃ , Ligand B ₂ (OR) ₂ (1.2 equiv.) <u>THF, 60 °C, 24 hr</u> <i>then</i> pinacol RT, 14 hr | | B(pin) <i>i</i> -Bu B(pin) B(pin) 4.52 | | $Me \qquad PX \\ Me \qquad PX \\ O'' \qquad O' \\ Ar \qquad Ar \\ Ar = \begin{cases} \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\ \\$ | |
| Entry | R | ligand | diboron | cat. (%) Pt/L | con (% | v. yield) (%) | er |
| 1 | <i>i</i> Bu | 4.47 | B ₂ (cat) ₂ | 5/10 | 81 | 50 | 88:12 |
| 2 ^b | <i>i</i> Bu | 4.47 | B ₂ (pin) ₂ | 5/10 | 72 | 2 49 | 68:32 |
| 3 | Et | 4.45 | B ₂ (cat) ₂ | 5/10 | 78 | 3 43 | 89:11 |
| 4 | <i>i</i> Pr | 4.9 | B ₂ (cat) ₂ | 5/10 | 80 |) 51 | 95:5 |
| 5 ^c | <i>t</i> Bu | 4.48 | B ₂ (cat) ₂ | 5/10 | 90 |) 48 | 94:6 |
| 6 | <i>i</i> Pr | 4.9 | B ₂ (cat) ₂ | 6/9 | >9 | 8 56 | 94:6 |
| 7 | <i>i</i> Pr | 4.9 | B ₂ (tbc) ₂ | 6/9 | >9 | 8 70 | 91:9 |
| 8 ^e | <i>i</i> Pr | 4.9 | B ₂ (cat) ₂ | 3/6 | >9 | 8 70 | 92:8 |

Table 4.3. Development of Catalytic Enantioselective Vinyl Boronate Diboration.^a

a) Conditions: Pt(dba)₃, ligand, and B₂(OR)₂ preheated to 80 ^oC for 30 min. prior to addition of substrate. b) The transesterification step was omitted from this experiment. c) Reaction run for 48 h. d) tbc = 4-*tert*-butylcatechol. e) Reaction at 70 ^oC. for 24 h utilizing 2.0 equivalents B₂(cat)₂

4.4. Scope of Pt-Catalyzed Enantioselective Diboration of Vinyl Boronates²²²

The substrate scope for the catalytic enantioselective diboration of vinyl boronates was explored and is provided in Scheme 4.16. In addition to the product obtained from the test substrate (4.52), phenyl-containing tris(boronate) esters 4.51 and 4.55 could be furnished in good yields and high enantiomeric ratios. Various tris(boronates) containing linear hydrocarbon chains could also be generated with high enantioinduction (4.52, 4.56-**4.60**). Notably, 1,1,2-tris(boronate) **4.44** could be synthesized on a larger scale without negatively affecting yield and selectivity (1 mmol scale, 75% y, 93:7 er). Importantly, substrates containing alkyl chloride, bromide, and protected alcohol functionality were well tolerated under the reaction conditions (4.53, 4.56-4.59). Substrates bearing trisubstituted olefins also underwent diboration efficiently without competing olefin diboration or other side reactions being observed (4.60). Unfortunately, styrenyl and α substututed vinyl boronates were slow to react and/or suffered from diminished selectivity (4.61-4.63). The broad scope clearly reveals the enhanced reactivity for diboration of vinyl boronates when compared to simple internal alkenes in Pt-catalyzed diboration. When *trans*-2-octene was employed under the reaction conditions, no desired product was isolated and only starting material was observed by ¹H NMR. Lastly, it is important to mention that all of the tris(boronates) generated were sufficiently stable on silica gel to be isolated cleanly and with minimal degradation. The products could also be stored ambient conditions for long time periods without any noticeable decomposition.



Scheme 4.16. Scope of the Catalytic Enantioselective Diboration of Vinyl Boronates.^a

a) Unless otherwise noted, reactions performed on 0.300 mmol scale employing 2.0 equiv. of $B_2(cat)_{2.}$ Each entry represents an average outcome of two experiments. Isolated yields are provided. b) Experiment performed with 1.2 equivalents of $B_2(cat)_2$ instead of 2.0 equivalents. c) Reaction run on 1.0 mmol scale with 1.2 equivalents of $B_2(cat)_2$. d) Reaction run at 100 °C for 24 hours.

In order to survey the synthetic utility of 1,1,2-tris(boronates), a reliable and practical method for generation of racemic product needed to be developed. As previously stated, there is no reported protocol for accessing this novel motif. Unfortunately, metal-free diboration conditions developed by Fernandez²⁴ provided no desired product when employing vinyl boronate **4.43**, with only 1,2-bis(boronate) **4.10** being observed (Scheme 4.17). Considering the reaction employs a Lewis base and a proton source, it is likely that bis(boronate) **4.10** resulted from a tandem diboration/protodeboronation sequence.

Scheme 4.17. Attempts at Metal-Free Diboration of Vinyl Boronates.



Fortunately, treatment of various vinyl boronates with 1.05 equivalents of $B_2(pin)_2$ and 2% Pt(dba)₃ at 60 °C for 12 hours provided a general method for furnishing racemic tris(boronates) in high yields. A small sample of results is provided in Scheme 4.18. Of note, the reaction can be performed on a large scale: subjecting 9.0 mmol of vinyl boronate 4.43 to 1.05 equivalents of $B_2(pin)_2$ and 1 mol% Pt(dba)₃ provided 3.7 g (83% yield) of the corresponding 1,1,2-tris(boronate) 4.44 in just 12 hours.

²⁴ Bonet. A.; Pubill-Ulldemolins, C.; Bo, C.; Gulyás, H.; Fernández, E. Angew. Chem. Int. Ed. 2011, 50, 7158.



Scheme 4.18. Scope of the Racemic Pt-Catalyzed Diboration of Vinyl Boronates.

a) Reaction performed on 9.0 mmol scale of vinyl(boronate) with 1 mol% $Pt(dba)_3$ to yield 3.7g of the tris(boronate).

Despite low conversions, the ability to furnish tris(boronate) **4.63** under both asymmetric and racemic conditions provides important insight into the mode of migratory insertion for vinyl boronate diboration. Similar to analysis performed for terminal alkene diboration (see Chapter 2, Scheme 2.24),¹⁵ an insertion which places Pt

adjacent to the cyclopropyl moiety (i.e. **G**) would result in cyclopropane rupture, followed by reductive elimination to generate **H** (Scheme 4.19, eq 1). However, this product is not observed by ¹H and ¹³C NMR. Instead, the results are most consistent with a migratory insertion to furnish α -boryl organoplatinum compex **I**, followed by reductive elimination to provide tris(boronate) **4.63** (eq 2). The regioselectivity for insertion is not surprising, as it is well-known that α -boryl substitution provides stability to adjacent carbon-metal bonds.^{10,25}

Scheme 4.19. Analysis of Insertion Modes for Pt-Catalyzed Diboration of Vinyl Boronates.



²⁵ (a) Nakamyura, M.; Hara, K.; Hatakeyama, T.; Nakamura, E. Org. Lett. 2001, 3, 3137. (b) Nakamura, M.; Hatakeyama, T.; Hara, K.; Fukudome, H.; Nakamura, E.; J. Am. Chem. Soc. 2004, 126, 14344. (c) Hatakeyama, T.; Nakamura, M.; Nakamura, E. J. Am. Chem. Soc. 2008, 130, 15688. (d) Endo, K.; Hirokkami, M.; Shibata, T. Synlett 2009, 1331.

4.5. Synthetic Utility of Pt-Catalyzed Enantioselective Diboration of Vinyl Boronates: Deborylative Alkylation²²

In order to demonstrate the utility of chiral 1,1,2-tris(boronate) esters, deborylative alkylation conditions similar to those utilized for geminal bis(boronate) esters were examined (Table 4.4).¹² If operative, such a route would provide a general method for accessing internal 1,2-bis(boronate) esters, or internal vicinal diols upon in situ oxidation. To our delight, reaction of tris(boronate) 4.44 with allyl chloride in the presence of 4 equivalents of NaOtBu in THF at room temperature provided a 4.5:1 syn:anti diastereomeric mixture of the corresponding 1,2-bis(boronate) (entry 1). A focused solvent screen showed that non-polar solvents provided higher diastereomeric ratios for the syn product, while use of polar solvents resulted in no desired product (entries 2-6). In order to study reaction efficiency, dodecyl bromide was used as the electrophile in place of allyl chloride (entry 7). It was discovered that 3.0 equivalents of base provided slightly diminished conversion, while 5.0 and 6.0 equivalents of base resulted in similarly high efficacy after 14 hours (entries 8-10). Finally, increasing the amount of tris(boronate) employed from 1.3 to 1.5 equivalents resulted in full conversion, high yield, and excellent diastereoselectivity for the desired product (entry 11). Notably, use of KOtBu instead of NaOtBu provided nearly identical results (entry 12 and 13). A screen of additional alkoxide bases, solvent mixtures, and temperatures resulted in no improvement in yield and/or diastereoselectivity (data not shown).

| | B(pin) B(pin) + B(pin) | | R-X | 1) Base solvent, RT, 14 h 2) NaOH, H ₂ O ₂ | | | B(pin) |
|---|------------------------------|------------------|---------------------|--|--------------|-----------------|---------------------------|
| <i>n</i> -nexyl [*] 4.44 | | | КХ | | | <i>n</i> -hexyl | B(pin) |
| entry | solvent | base (equiv.) | electophile | triboron (equiv.) | yield (%) | conv. (%) | dr (<i>syn:anti</i>) |
| 1 ^a | THF | 4.0 | allyl chloride | 1.3 | 93 | | 4.5:1 |
| 2 ^a | hexane | 4.0 | allyl chloride | 1.3 | 87 | | 11:1 |
| 3 ^a | toluene | 4.0 | allyl chloride | 1.3 | 88 | | 11:1 |
| 4 | MeCN | 4.0 | allyl chloride | 1.3 | | | |
| 5 | pyridine | 4.0 | allyl chloride | 1.3 | | | |
| 6 | DMSO | 4.0 | allyl chloride | 1.3 | | | |
| 7 | toluene | 4.0 | <i>n-</i> dodecylBr | 1.3 | | 82 | >20:1 |
| 8 | toluene | 3.0 | <i>n</i> -dodecylBr | 1.3 | | 72 | >20:1 |
| 9 | toluene | 5.0 | <i>n</i> -dodecylBr | 1.3 | | 92 | 20:1 |
| 10 | toluene | 6.0 | <i>n</i> -dodecylBr | 1.3 | | 93 | 20:1 |
| 11 | toluene | 5.0 | <i>n</i> -dodecylBr | 1.5 | 93 | >98 | 18:1 |
| 12 ^b | toluene | 5.0 | <i>n</i> -dodecylBr | 1.3 | | 90 | 16:1 |
| 13 ^b | toluene | 5.0 | <i>n</i> -dodecylBr | 1.5 | | >95 | 16:1 |

| <i>Table 4.4.</i> Optimization of 1,1,2-Tris(boronate | e) Deborylative Alkylation Conditions. |
|---|--|
|---|--|

a) Due to high volatility of the electrophile, conversions could not be determined.

b) KOtBu employed as base instead of NaOtBu.

With optimized conditions in hand, various electrophiles were examined in combination with chiral tris(boronate) ester **4.44** as the nucleophile (Table 4.5). For simplicity of analysis, an *in situ* oxidative workup was conducted on the bis(boronate) products in order to furnish the corresponding vicinal diols. In all cases, the *syn* diastereomer predominated and high yields were obtained for an array alkyl halides. In addition to linear aliphatic alkyl bromides (entries 1-3), iodomethane provided high yields and excellent diastereomeric ratios (entry 4). More hindered primary electrophiles

also reacted with outstanding efficiency and selectivity (entry 5). Although more reactive electrophiles such as allyl chloride and benzyl chloride gave slightly diminished diastereoselectivity, the corresponding syn 1,2-diols could be furnished in exceptional yields (entry 6 and 7). Interestingly, employing bromo(chloro)alkanes resulted in excellent chemoselectivity for the bromide, leaving the alkyl chloride moiety untouched (entry 8). Finally, it is important to note that in addition to primary aliphatic bromides, secondary electrophiles were competent under the reaction conditions and provided the *syn* diol exclusively and in good yield (entry 9). Currently, it is unknown whether deborylative alkylation proceeds with inversion or retention of stereochemistry at the electrophilic carbon center.



Table 4.5. Scope of the Electrophile in the Deborylative Alkylation of Tris(boronates).

a) Reactions performed with 0.25 mmol substrate and 5.0 equiv. of NaO*t*Bu. b) Styrene is a minor side product. c) lodomethane employed. d) Allyl chloride employed. e) Benzyl chloride employed. f) Reaction exclusively at the bromide; displacement of the chloride was not detected.

Various 1,1,2-tris(boronate) esters were also tested utilizing (3bromopropyl)benzene **4.67** as the electrophile (Table 4.6). In addition to straight-chained aliphatic tris(boronates) (entry 1), benzyl and β -substituted nucleophiles were also competent under the reaction conditions (entries 2 and 3). Substrates bearing silyl ether functionality and those containing other points of unsaturation within the molecule were also well tolerated, with high diastereoselectivities and yields being observed in all cases (entries 4 and 5).



Table 4.6. Scope of the Nucleophile in the Deborylative Alkylation of Tris(boronates).

Overall, deborylative alkylation of tris(boronates) provides a complementary route to alkene diboration for accessing challenging internal vicinal bis(boronates). For example, employment of allyl chloride in conjunction with tris(boronate) **4.51** provides access to an internal bis(boronate) **4.68** bearing a terminal olefin for further elaboration (Scheme Scheme 4.20, eq 1). Conversely, **4.68/4.69** would be inaccessible by diboration of 1,4-diene precursor **4.70** since the terminal olefin moiety would preferentially react over the internal alkene (eq 2).¹⁵ It is important to note that the one-pot deborylative

a) Reactions performed with 0.25 mmol substrate and 5.0 equiv. of NaOtBu.

alkylation/oxidation sequence occurs without racemization (see **4.51**, Scheme 4.16 for comparison).

Scheme 4.20. Comparison of Tris(boronate) Deborylative Alkylation Versus Alkene Diboration.



Considering vinyl boronates bearing tethered alkyl halides are competent substrates for asymmetric diboration, it is possible to develop an intramolecular deborylative alkylation to form cyclic 1,2-bis(boronates). As shown is Table 4.6, five-, six-, and seven-membered rings can all be accessed from alkyl bromide or chloride containing 1,1,2-tris(boronates). Although only moderate yields are observed, the reaction occurs with exclusive formation of the *anti* diastereomer. Thus, a one-pot deborylative alkylation/oxidation of enantioenriched tris(boronate) **4.56** generates *anti* 1,2-cyclohexanediol **4.73** in high yields and in excellent diastereo- and enantioselectivity (Scheme 4.21, eq 1). Moreover, deborylative alkylation followed by a one-pot double Matteson homologation/oxidation sequence provides access to synthetically challenging

anti-1,2-bis(hydroxymethyl)-cyclohexane **4.74** in moderate yield and excellent diastereocontrol (eq 2). This protocol represents a novel synthetic route to access cyclic *anti*-bis(boronates) that are otherwise inaccessible from alkene diboration and other borylation methodologies.

| B(pin) | | | NaO <i>t</i> Bu (5 equiv.) _O H | | | |
|--------|---------------------------|-------------|---|--------------------|----------|--|
| X | $\sim \sqrt{\frac{1}{2}}$ | B(pin) | toluene, rt, 1 | <u>4 h</u> ┌ ∕ | · | |
| · | (*)n | ∐ B(pin) | <i>then</i> NaOH, ⊢ | |)nOH | |
| entry | n | × | product | vield (%) | dr | |
| | | ~ | product | J iola (70) | <u> </u> | |
| 1 | 1 | CI | OH | 44 | >20:1 | |
| 2 | 1 | Br | ОН | 36 | >20:1 | |
| 3 | 2 | Cl | ,,,OH | 67 | >20:1 | |
| 4 | 2 | Br | ОН | 62 | >20:1 | |
| 5 | 3 | Br | ОН | 58 | >20:1 | |

Table 4.7. Scope of the Intramolecular Deborylative Alkylation of Tris(boronates).

Scheme 4.21. Transformations of Cyclic Anti-1,2-Bis(boronate) esters.



Based on our knowledge of stereochemical outcome in the deborylative alkylation of 1,1,2-tris(boronate) esters, a working stereochemical model has been proposed Importantly, deborylation occurs under much milder conditions (Scheme 4.22). compared to what is required for 1,1-bis(boronates).¹² Such an observation is consistent with chelation of the pinacol oxygen of one of the geminal boron atoms to the internal boronate, enhancing its Lewis acidity and hence its proclivity for activation by an Upon preliminary examination, it is reasonable to consider that external base. intermolecular alkylations occur via a least-hindered approach of the electrophile to structure F, in order to furnish K; however, the product configuration experimentally observed from an intramolecular reaction is inconsistent with this analysis since syn stereoisomer L would be expected from chelated intermediate F. Instead, a leasthindered approach of the electrophile to nonchelated intermediate J seems to be consistent with the stereochemical outcome of both inter- and intramolecular alkylations. It is thus proposed that an interaction of the electron rich C-B σ -bond with the adjacent C=B π -bond would result in enhanced nucleophilicity of the π -bond and facilitate reaction with the electrophile. The stereochemistry of the experimentally obtained products from inter- and intramolecular processes is consistent with this model (i.e. M and N). Importantly, similar orbital interactions have been suggested to rationalize the stereoselectivity of reactions of allylsilanes, allylstannanes, and allyl boronates.²⁶

²⁶ (a) Fleming, I.; Lawrence, N. J. *Tetrahedron Lett.* **1988**, *29*, 2073. (b) Fleming, I.; Lawrence, N. J. *Tetrahedron Lett.* **1988**, *29*, 2077. (c) Fleming, I.; Lawrence, N. J. *J. Chem. Soc., Perkin Trans. 1* **1992**, 3309. (d) Pelz, N. F.; Morken, J. P. *Org. Lett.* **2006**, *8*, 4557. (e) Kyne, R. E.; Ryan, M. C.; Kliman, L. T.; Morken, J. P. *Org. Lett.* **2010**, *12*, 3796.



Scheme 4.22. Plausible Stereochemical Model for Deborylative Alkylation.

Further utility of vinyl boronate diboration was investigated by targeting a natural product for asymmetric total synthesis. Of interest was accessing diol **4.78**, which can be converted to *exo*-brevicomin²⁷ via a known one-pot Wacker oxidation/cyclization process (Scheme 4.23).²⁸ Synthesis of **4.78** is not trivial considering oxidation of *trans*-alkenes in the presence of a terminal alkene is not highly regioselective. Thus, construction of the targeted diol previously required multiple steps and a series of protection/deprotection

²⁷ Silverstein, R. M.; Brownlee, R. G.; Bellas, T. E.; Wood, D. L.; Browne, L. E. *Science* **1968**, *159*, 889.

²⁸ For synthesis of *exo*-Brevicomin using an intramolecular double Wacker oxidation, see: (a) Byrom, N. T.; Grigg, R.; Kongkathip, B.; Reimer, G.; Wade, A. R. J. Chem. Soc., Perkin Trans. 1 1984, 1643. (b) Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. *Tetrahedron Lett.* 1986, 27, 3535. (c) Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. J. Chem. Soc., Chem. Commun. 1988, 356. (d) Page, P. C. B.; Rayner, C. M.; Sutherland, I. O. J. Chem. Soc., Perkin Trans. 1 1990, 1375. (e) Mayer, S. F.; Mang, H.; Steinreiber, A.; Saf, R.; Faber, K. Can. J. Chem. 2002, 80, 362.

sequences. Alternatively, using the boron-Wittig reaction discussed in Chapter 3,²⁹ vinyl boronate **4.76** could be accessed from readily available **4.75** and propionaldehyde on a multigram scale in good yield and excellent stereoselection. Subsequently, asymmetric diboration generates tris(boronate) **4.77**, followed by deborylative alkylation and oxidation to afford diol **4.78** in good yield and high diastereo- and enantioselectivity. Preliminary attempts at a Cu-catalyzed Wacker oxidation/cyclization resulted in *exo*-brevicomin low yield. The low yield was determined to be due to product volatility. As described above, others have reported moderate yields with careful isolation techniques utilizing a similar procedure. Overall, this approach represents one of the shortest enantioselective routes to the target molecule.

Scheme 4.23. Synthesis of Exo-Brevicomin.



²⁹ Coombs, J. R.; Zhang, L.; Morken, J. P. Org. Lett. 2015, 17, 1708.

4.6. Synthetic Utility of Pt-Catalyzed Enantioselective Diboration of Vinyl Boronates: Additional Transformations

4.6.1. Pd-Catalyzed Suzuki Coupling of 1,1,2-Tris(boronates). Of interest was extending the utility of 1,1,2-tris(boronates) to additional useful C-C bond forming Considering the previous success in Pd-catalyzed cross-coupling of 1,2reactions. bis(boronate) esters, we reasoned that the products from vinyl boronate diboration could be employed in a similar reaction as a new route for accessing internal 1,2-bis(boronates). Preliminary optimization focused around a rigorous ligand screening with tris(boronate) **4.44** as the test substrate and bromobenzene as the electrophile (Table 4.8). Ligands developed by Buchwald and co-workers were initially tested, but provided the desired coupled product 4.81 in minor amounts along with a mixture of byproducts (4.79, 4.80, and **4.14**) (entries 1 and 2). While the exact mechanism for byproduct formation has not been fully investigated, they seemingly arise from a successful transmetallation followed by β -boryl elimination or protonation of a Pd-C bond. Overall, while electron deficient phosphines resulted in significant generation of side products and incomplete conversion (entries 3 and 4), electron-rich ligands led to increased formation of the desired product **4.81** (entries 5-10). Bulkier ligands gave better results, delivering **4.81** as the major compound in moderate diastereoselectivity favoring the *anti* diol (entries 8-10). Unfortunately, over longer reaction times, the byproduct to desired product ratio increased suggesting that 4.81 was being consumed by a subsequent transmetallation process (entry 9 vs entry 10). Furthermore, the syn diastereomer seemingly degraded faster than the anti-product as the reaction proceeded. Thus, reactions with high
conversions to product **4.81** led to lower diastereoselectivity, while reactions with significant byproduct formation resulted in high *anti* selectivity.

| | | 1) Pd(| OAc) ₂ (5%) | hexyl | he | он _{куl} Он | |
|--|----------------------------------|-------------------------------|--|-------------------|-------|-------------------------|--|
| B(人 | pin) B(pin) | Liga √ ^{Br} KOH (| and (5%) 4.0 equiv.) | 4.79 | | 4.80 | |
| hexyl B(pin) + B(pin) 6(pin) + (1.1 equ | | quiv.) THF/H | I ₂ O (10:1) C, 3 hrs DH, H ₂ O ₂ | OH hexyl Ph he | | OH exyl Ph OH | |
| | | | | 4.14 | | 4.81 | |
| entry | ligand | 4.79 | 4.80 | 4.14 | 4.81 | anti:syn ^a | |
| 1 | Ruphos | 0.49 | 1.00 | 0.32 | 0.09 | >20:1 | |
| 2 | XPhos | 1.00 | 0.74 | 0.25 | 0.27 | ~5:1 | |
| 3 ^b | PPh_3 | 0.61 | 1.00 | trace | | | |
| 4 ^b | CyPPh ₂ | 1.00 | 0.58 | | 0.08 | >20:1 | |
| 5 | Cy ₂ PPh | 1.00 | 0.41 | trace | 0.25 | >20:1 | |
| 6 | PCy ₃ | 1.00 | 0.20 | trace | 0.30 | ~20:1 | |
| 7 | ⁱ Pr ₃ P | 1.00 | 0.24 | | 0.43 | 11:1 | |
| 8 | ^t Bu ₂ PPh | 1.00 | 0.15 | trace | 0.93 | 4:1 | |
| 9 | ^t Bu₃P | 0.54 | 0.23 | 0.04 | 1.00 | 4:1 | |
| 10 ^{b,c} | ^t Bu₃P | 0.34 | 0.06 | trace | 1.00 | 2.2:1 | |
| 11 | ⁿ Bu ₃ P | 1.00 | 0.95 | | trace | | |

Table 4.8. Ligand Screen for Pd-Catalyzed Cross-Coupling of 4.44.

a) Diastereoselectivity of **4.81**. b) Incomplete conversion. c) Reaction time = 30 minutes.

Subsequently, examination of various bases and base loading was conducted utilizing di(*tert*-butyl)phenylphosphine as the optimal ligand (Table 4.9). Reactions with more equivalents of base suffered from increased byproduct formation, likely resulting

from an enhanced rate of transmetallation (entries 2 and 3). Overall, 3.0 equivalents of KOH provided 4.81 as the major product in moderate yield, albeit in low diastereoselectivity (entry 4). Similar efficacy and selectivity was observed with 3.0 equivalents of NaOH or LiOH (entries 7 and 8). Notably, at lower loadings, these bases suppressed formation of byproduct **4.80** and **4.14** completely. Unfortunately, no reaction was observed when employing metal carbonates as the base (entries 10 and 11).

 \sim

| | | | 1) P ^t B Ba | d(OAc) ₂ (u ₂ PPh (5 ^c se (X equ | 5%) %) iv.) | hexyl | he | ОН exyl ОН |
|------------------|--------------------------------|--------------|------------------------------|--|-------------------|---------|-----------------------|-----------------------|
| | B(pin) | ∽ Br | TH | F/H ₂ O (10 | D:1) | 4.79 | | 4.80 |
| hexvl´ | └B(pin |) + | <u> </u> | 0 °C, 3 hr | s > | | | ОН |
| ···· · | ∣ B(pin) | | (۷ | паоп, п | 202 | UF L | 1 Ph hov | Ph |
| | 4.44 | (1.1 equiv.) | | | | hexyl | | OH |
| | | | | | | 4.14 | | 4.81 |
| entry | base | base equiv. | 4.79 | 4.80 | 4.14 | 4.81 | anti:syn ^a | yield 4.81 (%) |
| 1 | KOH | 4.00 | 1.00 | 0.15 | trace | 0.93 | 4:1 | |
| 2 | KOH | 10.0 | 1.00 | 0.63 | 0.28 | 0.18 | >20:1 | |
| 3 | KOH | 7.0 | 1.00 | 0.58 | 0.17 | 0.34 | 14:1 | |
| 4 | KOH | 3.0 | 0.61 | | | 1.00 | 2.6:1 | 54 |
| 5 ^b | КОН | 3.0 | 1.00 | 0.02 | | 0.35 | >20:1 | |
| 6 ^{b,c} | КОН | 2.0 | 1.00 | | | 0.49 | >20:1 | |
| 7 | NaOH | 3.0 | 0.62 | | | 1.00 | 2.8:1 | 55 |
| 8 | LiOH | 3.0 | 0.77 | | | 1.00 | 3.3:1 | |
| 9 | NH ₄ OH | (1.5M) | 0.59 | 0.34 | 0.54 | 1.00 | 2.5:1 | |
| 10 | K ₂ CO ₃ | 3.0 | | | | | | NR |
| 11 | Cs_2CO_3 | 3.0 | | | | | | NR |

Table 4.9. Base Screen for Pd-Catalyzed Cross-Coupling of 4.44.

a) Diastereoselectivity of **4.81**. b) Performed with ^tBu₃P (5 mol%). c) Unknown byproducts present.

Currently, the best conditions are those which employ 5% Pd(OAc)₂ with 5% di(adamantyl)(*n*-butyl)phosphine and 3 equivalents of NaOH at 70 °C (Scheme 4.24, eq 1). After 3 hours, **4.81** can be furnished in 70% yield, albeit in low diastereoselectivity for the *anti*-isomer. Notably, 4-bromoanisole also gave promising results when di(*tert*-butyl)phenylphosphine was employed, generating diol **4.82** in high yield and moderate *anti* selectivity (eq 2). Future studies should focus on increasing stereoinduction, perhaps through the use of chiral phosphine ligands. In addition, it would be interesting to investigate a Pd-catalyzed coupling of tris(boronates) with vinyl and allyl electrophiles.





4.6.2. Boron-Wittig Reaction of 1,1,2-Tris(boronate) Esters. Considering the successful development of a boron-Wittig reaction between geminal bis(boronates) and

aldehydes described in Chapter 3, it was reasoned that 1,1,2-tris(boronates) might benefit from similar reactivity. Upon treatment of enantioenriched tris(boronate) **4.44** with LiTMP for 5 minutes followed by addition of benzaldehyde, bis(boronate) **4.83** could be isolated in good yield and exceptional stereoselectivity for the *trans* isomer (Scheme 4.25). The product bears both an allylic and vinylic boronate which can be utilized for further functional group installation and chain extension. Notably, oxidative workup of **4.83** generates synthetically challenging α -hydroxy ketone **4.84**, which can be isolated in high yield and with complete conservation of stereochemistry. Overall, the diboration/boron-Wittig sequence provides complex multiborylated products that would be inaccessible by other routes such as enantioselective allene diboration.³⁰ Future work in this area should include expansion of substrate scope and investigation into additional transformations of the products.

Scheme 4.25. Boron-Wittig/Oxidation of Tris(boronate) Ester 4.44.



³⁰ For examples of terminal allene diboration and utility of vinylic/allylic bis(boronates), see: (a) Pelz, N.
F.; Woodward, A. R.; Burks, H. E.; Sieber, H. E.; Morken, J. P. J. Am. Chem. Soc. 2004, 126, 16328. (b)
Woodward, A. R.; Burks, H. E.; Chan, L. M.; Morken, J. P. Org. Lett. 2005, 7, 5505. (c) Sieber, J. D.;
Morken, J. P. J. Am. Chem. Soc. 2006, 128, 74. (d) Pelz, N. F.; Morken, J. P. Org. Lett. 2006, 8, 4557. (e)
Burks, H. E.; Liu, S.; Morken, J. P. J. Am. Chem. Soc. 2007, 129, 8766.

4.7. Efforts Toward Extending Pt-Catalyzed Additions Across Functionalized Alkenes

4.7.1. Pt-Catalyzed Diboration of Functionalized Alkenes. Following the development of an asymmetric diboration of vinyl boronates, a preliminary screening of various functionalized alkenes was performed (Scheme 4.26). Unfortunately, little to no reaction was observed when attempting to diborate vinyl chloride 4.85, nitro alkene 4.86, vinyl silanes 4.87 and 4.88, or dihydropyran 4.89. Additionally, dienyl boronate 4.90 provided no desired product, although steric effects might be the reason for low reactivity. Overall, a more rigorous examination of diboration conditions and substrates needs to be conducted before declaring the above-mentioned functionalities as incompetent reaction partners. For example, utilizing a more reactive diboron source such as $B_2(cat)_2$ in place of $B_2(pin)_2$, as well as increasing reaction times and temperatures, might result in enhanced conversions. Considering the numerous methodologies available pertaining to C-B bond functionalization, asymmetric diboration of any of the above-mentioned substrates might provide a route for accessing a variety of important and synthetically challenging enantioenriched small molecules. Thus, further investigation into this area is clearly warranted.

Scheme 4.26. Attempts Toward Pt-Catalyzed Diboration of Various Functionalized Alkenes.



4.7.2. Pt-Catalyzed Hydrometallation of Vinyl Boronates. As described in depth above, the synthesis and utility of 1,1-bis(boronate) esters has progressed significantly over recent years. Despite such advancements, the construction of geminal 1,1silaboronates has been examined in far less detail.³¹ Furthermore, only one report for the generation of enantioenriched aliphatic 1,1-silaboronates exists to date, and relies on the use of pyrophoric *s*BuLi and an expensive silaboronation reagent.^{32,33} Nonetheless, these motifs have been shown to be competent partners in Zweifel olefinations that furnish synthetically challenging enantioenriched allylsilanes.³² Yet to be discovered is whether or not geminal silaboronates can participate in a variety of other C-C bond-forming

 ³¹ (a) Shimizu, M.; Kurahashi, T.; Kitagawa, H.; Shimono, K.; Hiyama, T. J. Organomet. Chem. 2003, 686, 286. (b) Shimizu, M.; Kurahashi, T.; Kitagawa, H.; Hiyama, T. Org. Lett. 2003, 5, 225. (c) Li, H.; Shangguan, X.; Zhang, Z.; Huang, S.; Zhang, Y.; Wang, J. Org. Lett. 2013, 16, 448.
 ³² Aggarwal, V. K.; Binanzer, M.; de Ceglie, C.; Gallanti, M.; Glasspoole, B. W.; Kendrick, S. J. F.;

³² Aggarwal, V. K.; Binanzer, M.; de Ceglie, C.; Gallanti, M.; Glasspoole, B. W.; Kendrick, S. J. F.; Sonawane, R. P.; Vázquez-Romero, A.; Webster, M. P. *Org. Lett.* **2011**, *13*, 1490.

³³ The synthesis of enantioenriched 1,1-silaboronates via a Cu-catalyzed protoborylation of β -(silyl)styrenes has been described: Meng, F.; Jang, H.; Hoveyda, A. H. *Chem. Eur. J.* **2013**, *19*, 3204.

reactions, including Matteson homologations, deborylative alkylations, desilylative alkylations, Hiyama couplings, and Suzuki couplings, to name a few. If such processes can occur with high levels of stereospecificity, then geminal silaboronates can provide synthetic chemists with a method for accessing an array of enantioenriched organoboronates and organosilanes from a single building block.

We considered that a Pt-catalyzed asymmetric hydrosilylation of vinyl boronates might provide access to geminal 1,1-silaboronates in an efficient and practical manner. After an extensive ligand screen and optimization of the silane, it was determined that employment of 6 mol% (R,R)-4.91 in conjunction with 3 mol% Pt(dba)₃ and 1.2 equivalents of dimethylphenylsilane provides hydrosilylation product 4.92 in high yield and moderate enantiomeric ratios (Scheme 4.27). Notably, exceptional regioselectivity is observed, with exclusive C-Si bond formation occuring at the carbon bearing the boronate moiety. Further modification of reaction conditions to improve selectivity is ongoing. Subsequently, substrate scope and product utility should be investigated in depth.



Scheme 4.27. Pt-Catalyzed Asymmetric Hydrosilylation of Vinyl Boronates.

In addition to hydrosilylation, Pt-catalyzed hydroboration of vinyl boronates can also be performed as another method for accessing geminal 1,1-bis(boronate) esters. For example, treatment of vinyl boronate **4.93** with 1.2 equivalents of pinacolborane and 3% Pt(dba)₃ provides bis(boronate) **4.94** in high yield after 15 hours at 70 °C (Scheme 4.28). Since the reaction is unoptimized, it would be interesting to see if catalyst loading could be reduced to more operationally practical levels. Interestingly, a similar Rh-catalyzed double hydroboration of alkynes has been developed by Shibata and co-workers; however, high catalyst loadings are required and the product is often formed along with a mixture of monoborylation/reduction byproducts (see Chapter 3, Scheme 3.12, eq 1).^{25d}

Scheme 4.28. Pt-Catalyzed Hydroboration of Vinyl Boronates.



4.8. Conclusion

The synthesis of enantioenriched 1,1,2-tris(boronate) esters can be achieved via a Pt-catalyzed asymmetric diboration of vinyl boronates. Furthermore, synthetic utility of this novel motif has been demonstrated via a variety of C-C bond-forming reactions, most notably an inter- and intramolecular deborylative alkylation, which provides an array of 1,2-bis(boronates) in high diastereoselectivity. Future studies should focus on optimization of cross-coupling conditions and development of other useful applications herein described. Furthermore, enantioselective Pt-catalyzed hydro- and dimetallations of additional functionalized alkenes should be investigated in greater detail.

4.9. Experimental

4.9.1. General Information.

¹H NMR spectra were measured using a Varian Gemini-500 (500 MHz) spectrometer or a Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CHCl₃: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, pent= pentet, sept = septet, br = broad, m = multiplet), and coupling constants (Hz). ¹³C{¹H}NMR spectra were measured using a Varian Inova 500 (126 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl₃: 77.0 ppm). ³¹P{¹H}NMR spectra were measured using a Varian Inova 500 (202 MHz) spectrometer. Chemical shifts are reported in ppm using phosphoric acid as the external standard (H₃PO₄: 0.0 ppm). Infrared (IR) spectra were measured using a Bruker α -P Spectrometer. Frequencies are reported in wavenumbers (cm⁻¹) as follows: strong (s), broad (br), medium (m), and weak (w). High-resolution mass spectrometry (HRMS) was performed at the chemistry department at Boston College, Chestnut Hill, MA.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO₂, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography was performed on 25 μ m silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm), phosphomolybdic acid

(PMA), potassium permanganate (KMnO₄), and Seebach's "magic" stain³⁴ (phosphomolybdic acid, Ce(SO₄)₂, sulfuric acid). Analytical chiral gas-liquid chromatography (GLC) was also performed on an Agilent Technologies 6850 Series chromatograph with a flame ionization detector, and a Supelco β –Dex 120 column with helium as the carrier gas. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar Supercritical Fluid Chromatograph equipped with auto sampler and a Waters photodiode array detector with methanol as the modifier.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran, dichloromethane, toluene, and diethyl ether were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after being purged with argon. Dimethylformamide was dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC). Triethylamine was purchased from Aldrich and refluxed over calcium hydride prior to use. Schwartz's reagent, phenyldichlorophosphine, and sodium *tert*-butoxide were purchased from Strem Chemicals and used as received. 3-Phenyl-1-propyne, imidazole, ethynylcyclohexane, and 1-bromo-2-methylpropane purchased from Alfa Aesar and used as received. B₂(pin)₂ was obtained from AllyChem and recrystallized from pentane prior to use. Dibenzylideneacetone and 1-bromo-6-chlorohexane were purchased from Oakwood and used as received. *tert*-Butylchlorodiphenylsilane was purchased from Gelest and used as

³⁴ Seebach, D.; Imwinkelried, R.; Stucky, G. Helv. Chim. Acta. 1987, 70, 448.

received. Pinacol borane was purchased from BASF and distilled prior to use. 5-Chloro-1-pentyne was purchased from Chemsampco and used as received. Iodomethane was purchased from Acros and used as received. All other reagents were obtained from Aldrich or Fisher and used as received.

4.9.2. Preparation of Pt(dba)₃ and Phosphonite Ligands.

Tris(dibenzylideneacetone)platinum(0) was prepared according to the literature procedure.³⁵ All spectral data and elemental analysis were in accordance with the literature.

TADDOL-derived Ligands were prepared according to the general reaction scheme shown below. All spectral data were in accordance with the literature.³⁵



³⁵ Coombs, J.R.; Haeffner, F.; Kliman, L.T.; Morken, J.P. J. Am. Chem. Soc. **2013**, 135, 11222.

4.9.3. Preparation of Vinyl Boronate Starting Materials.

Unless otherwise noted, vinyl boronate starting materials were prepared according to the general method shown below.

General procedure for vinyl boronate synthesis

$$R + HB(pin) + HB(pin) + B(pin) + B(pi$$

To an oven-dried 2-dram vial equipped with magnetic stir bar in the glovebox was added alkyne (1.10 equiv.) and pinacol borane (1.00 equiv.), followed immediately by Schwartz's reagent (0.10 equiv.). The vial was sealed with a polypropylene cap, taped, and removed from the glovebox. The mixture was heated in an oil bath to 60 $^{\circ}$ C for 14 hours, at which point it was cooled to room temperature. The pure vinyl(boronate) products were isolated after SiO₂ gel chromatography, unless otherwise noted.

The following starting materials were purchased from Aldrich and used without further purification: (*E*)-1-octen-1-ylboronic acid pinacol ester, (*E*)-4-(*tert*-butyldimethylsiloxy)-1-buten-1-ylboronic acid pinacol ester, (*E*)-6-chloro-1-hexen-1-ylboronic acid pinacol ester, (*E*)-2-cyclopropylvinylboronic acid pinacol ester, and (*E*)-2-phenylvinylboronic acid pinacol ester.

 $\begin{array}{c} (E)-4,4,5,5-tetramethyl-2-(4-methylpent-1-en-1-yl)-1,3,2-\\ Me & \\ B(pin) & \\ Mixed aboro-lane. \\ Prepared according to the general procedure \\ utilizing pinacolborane (1.28 g, 10.0 mmol), Schwartz' reagent (258 mg, 1.00 mmol), and \\ 4-methylpent-1-yne (904 mg, 11.0 mmol). \\ The crude material was purified (SiO_2, 3% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (1.74 g, 83%). \\ All spectral data are in accordance with the literature. \\ \begin{array}{c} 36 \end{array}$

(*E*)-4,4,5,5-tetramethyl-2-(3-phenylprop-1-en-1-yl)-1,3,2-B(pin) dioxaboro-lane. Prepared according to the general procedure utilizing pinacolborane (1.28 g, 10.0 mmol), Schwartz' reagent (258 mg, 1.00 mmol), and 3-phenyl-1-propyne (1.28 g, 11.0 mmol). The crude material was purified (SiO₂, 3% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (1.94 g, 79%). All spectral data are in accordance with the literature.³⁷

B(pin) (E)-4,4,5,5-tetramethyl-2-(4-phenylbut-1-en-1-yl)-1,3,2dioxaboro-lane. Prepared according to the general procedure

utilizing pinacolborane (1.28 g, 10.0 mmol), Schwartz' reagent (258 mg, 1.00 mmol), and 4-phenyl-1-butyne (1.56 g, 12.0 mmol). The crude material was purified (SiO₂, 3% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (2.07 g, 80%). All spectral data are in accordance with the literature.³⁶

Cl______B(pin) (E)-2-(5-chloropent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2dioxaboro-lane. Prepared according to the general procedure utilizing pinacolborane

³⁶ Yoshida, H.; Kageyuki, I.; Takaki, K. Org. Lett. 2014, 16, 3512.

³⁷ Shimizu, H.; Igasrashi, T.; Miura, T.; Murakami, M. Angew. Chem. Int. Ed. 2011, 50, 11465.

(1.28 g, 10.0 mmol), Schwartz' reagent (258 mg, 1.00 mmol), and 5-chloropent-1-yne (1.13 g, 11.0 mmol). The crude material was purified (SiO₂, 3% ethyl acetate in hexane) to give the desired product as a white solid (1.87 g, 81%). All spectral data are in accordance with the literature.³⁶

(*E*)-2-(5-bromopent-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-Br∖ ≪ ∠B(pin) dioxaboro-lane. To a solution of pent-4-yn-1-ol (1.26 g, 15.0 mmol) in dry dichloromethane (20 mL) were added the tetrabromomethane (7.46 g, 22.5 mmol) and the triphenylphosphine (5.90 g, 22.5 mmol). The mixture was stirred at room temperature for 1 hour. The reaction mixture was directly distilled under vacuum to afford the 5bromopent-1-yne as clear, colorless oil (2.05 g, 93%), which was used in the subsequent step without further purification. Next, (*E*)-2-(5-bromopent-1-en-1-yl)-4,4,5,5tetramethyl-1,3,2-dioxaborolane was prepared according to the general procedure utilizing pinacolborane (1.28 g, 10.0 mmol), Schwartz' reagent (258 mg, 1.00 mmol), and 5-bromopent-1-yne (1.62 g, 11.0 mmol). The crude material was purified (SiO₂, 3% ethyl acetate in hexane) to give the desired product as a white solid (1.32 g, 48%). ¹H NMR (500 MHz, CDCl₃): δ 6.55 (1H, dt, J=18.0, 6.5 Hz), 5.47 (1H, d, J=17.5 Hz), 3.38 (2H, t, J=7.0 Hz), 2.29 (2H, q, J=7.0 Hz), 1.96 (2H, pent, J=7.0 Hz), 1.24 (12H, s); ¹³C NMR (100 MHz, CDCl₃): δ152.1, 83.3, 34.2, 33.3, 31.3, 24.9; IR (neat): 2911.4 (m), 1638.1 (m), 1397.6 (m), 1361.5 (s), 1320.1 (s), 1217.1 (s), 1002.0 (m), 969.4 (m), 849.1 (m); HRMS-(DART+) for $C_{10}H_{21}B_1Br_1O_2$ [M+H]⁺: calculated: 275.0818, found: 275.0819.

(E)-2-(6-bromohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-B(pin) Br' dioxabor-olane. To a solution of hex-5-yn-1-ol (1.47 g, 15.0 mmol) in dry dichloromethane (20 mL) were added the tetrabromomethane (7.46 g, 22.5 mmol) and the triphenylphosphine (5.90 g, 22.5 mmol). The mixture was stirred at room temperature for 1 hour. The reaction mixture was directly distilled under vacuum to afford the 6bromohex-1-yne as clear, colorless oil (2.39 g, 99%), which was used in the subsequent step without further purification. Next, (*E*)-2-(6-bromohex-1-en-1-yl)-4,4,5,5tetramethyl-1,3,2-dioxaborolane was prepared according to the general procedure utilizing pinacolborane (1.92 g, 15.0 mmol), Schwartz' reagent (387 mg, 1.50 mmol), and 6-bromohex-1-yne (2.66 g, 16.5 mmol). The crude material was purified (SiO₂, 3% ethyl acetate in hexane) to give the desired product as a white solid (2.17 g, 50%). ¹H NMR (500 MHz, CDCl₃): δ 6.58 (1H, dt, J= 17.5, 7.0 Hz), 5.43 (1H, d, J= 17.5 Hz), 3.38 (2H, t, J= 7.0 Hz), 2.16 (2H, q, J= 7.5 Hz), 1.85(2H, pent, J= 7.0 Hz), 1.56 (2H, pent, J= 7.0 Hz), 1.24 (12H, s); ¹³C NMR (100 MHz, CDCl₃): δ 153.6, 83.3, 34.7, 33.6, 32.1, 26.7, 24.7; IR (neat):2977.5 (m), 2933.9 (m), 1638.1 (s), 1359.5 (s), 1318.5 (s), 1164.4 (s), 994.8 (m), 969.5 (m), 848.8 (m); HRMS-(DART+) for $C_{12}H_{23}B_1Br_1O_2$ [M+H]⁺: calculated: 289.09745, found: 289.0980.

Br (E)-2-(7-bromohept-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dio-xaborolane. To a solution of hept-6-yn-1-ol (1.68 g, 15.0 mmol) in dry dichloromethane (20 mL) were added the tetrabromomethane (7.46 g, 22.5 mmol) and the triphenylphosphine (5.90 g, 22.5 mmol). The mixture was stirred at room temperature for 1 hour. The solvent was removed under reduced pressure. A solution of hexane/ethyl acetate (9:1) was added and the resulting precipitate was filtered and washed abundantly. The filtrate was evaporated and the crude material was purified by silica gel chromatography (SiO₂, 100% hexane) to give 7-bromohept-1-yne as a clear, colorless oil (2.18 g, 83%), which was used in the subsequent step without further purification. Next, (*E*)-2-(7-bromohept-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane was prepared according to the general procedure utilizing pinacolborane (1.08 g, 8.47 mmol), Schwartz's reagent (218 mg, 0.847 mmol), and 7-bromohept-1-yne (1.63 g, 9.32 mmol). The crude material was purified (SiO₂, 3% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (1.85 g, 72%). ¹H NMR (500 MHz, CDCl₃): δ 6.59 (1H, dt, *J*= 17.5, 6.5 Hz), 5.41 (1H, d, *J*= 17.5 Hz), 3.37 (2H, t, *J*= 6.5 Hz), 2.14 (2H, q, *J*= 7.0 Hz), 1.83 (2H, pent, *J*= 7.0 Hz), 1.44-1.41 (4H, m), 1.24 (12H, s); ¹³C NMR (100 MHz, CDCl₃): δ 154.2, 83.2, 35.7, 33.9, 32.8, 27.9, 27.5, 25.0; IR (neat): 2977.9 (m), 2931.6 (m), 1638.3 (s), 1361.3 (s), 1318.9 (s), 1144.6 (s), 997.2 (m), 970.5 (m), 849.4 (m); HRMS-(DART+) for C₁₃H₂₅B₁Br₁O₂ [M+H]⁺: calculated: 303.1131, found: 303.1134.

TBSO *tert*-butyldimethyl(pent-4-yn-1-yloxy)silane. To an oven-dried 100 mL round-bottomed flask was added imidazole (4.41 g, 64.2 mmol) followed by CH₂Cl₂ (9.0 mL). To the flask was added pent-4-yn-1-ol (2.21 mL, 23.8 mmol) and the reaction mixture was allowed to stir at room temperature for 5 minutes. To the flask was added *tert*-butyldimethylsilyl chloride (4.96 g, 35.7 mmol) in one portion. The flask wash flushed with nitrogen and the reaction mixture was allowed to stir at room temperature for 18 hours, at which point the mixture was diluted with deionized H₂O (20 mL) and CH₂Cl₂ (20 mL). The crude mixture was extracted with CH₂Cl₂ (3x20 mL), and the organics were combined, dried over Na_2SO_4 , filtered, and concentrated under reduced pressure. The crude material was purified (SiO₂, 3% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (3.54 g, 75%). All spectral data are in accordance with the literature.³⁸

TBSO (E)-tert-butyldimethyl((5-(4,4,5,5-tetramethyl-1,3,2dioxaboro-lan-2-yl)pent-4-en-1-yl)oxy)silane. Prepared according to the general procedure utilizing pinacolborane (640 mg, 5.00 mmol), Schwartz' reagent (129 mg, 0.500 mmol), and tert-butyldimethyl(pent-4-yn-1-yloxy)silane (1.09 g, 5.50 mmol). The crude material was purified (SiO₂, 3% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (1.32 g, 81%). All spectral data are in accordance with the literature.³⁹

TBDPSO (but-3-yn-1-yloxy)(*tert*-butyl)diphenylsilane. To an oven-dried 100 mL round-bottomed flask was added imidazole (1.09 g, 16.0

mmol) followed by CH_2Cl_2 (20.0 mL). To the flask was added but-3-yn-1-ol (0.610 mL, 8.06 mmol) and the reaction mixture was allowed to stir at room temperature for 5 minutes. To the flask was added *tert*-butyl(chloro)diphenylsilane (2.31 mL, 8.88 mmol) in one portion. The flask wash flushed with nitrogen and the reaction mixture was allowed to stir at room temperature for 18 hours, at which point the mixture was diluted with deionized H₂O (20 mL) and CH₂Cl₂ (20 mL). The crude mixture was extracted with CH₂Cl₂ (3x20 mL), and the organics were combined, dried over Na₂SO₄, filtered, and

³⁸ Kleinbeck, F.; Toste, F.D. J. Am. Chem. Soc. 2009, 131, 9178.

³⁹ Varseev, G.N.; Maier, M.E. Angew. Chem. Int. Ed. 2006, 45, 4767.

concentrated under reduced pressure. The crude material was purified (SiO₂, 3% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (2.28 g, 92%). All spectral data are in accordance with the literature.⁴⁰

(E)-tert-butyldiphenyl((4-(4,4,5,5-tetramethyl-1,3,2-∠B(pin) TBDPSO[^] dioxaboro-lan-2-yl)but-3-en-1-yl)oxy)silane. Prepared according to the general procedure utilizing pinacolborane (640 mg, 5.00 mmol), Schwartz' reagent (129 mg, 0.500 mmol), and (but-3-yn-1-yloxy)(tert-butyl)diphenylsilane (1.70 g, 5.50 mmol). The crude material was purified (SiO₂, 2.5% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (1.98 g, 91%). ¹H NMR (500 MHz, CDCl₃): δ 7.67 (4H, d, J= 6.5 Hz), 7.44-7.36 (6H, m), 6.60 (1H, dt, J= 18.0, 7.0 Hz), 5.49 (1H, d, J= 18.0 Hz), 3.74 (2H, t, J= 7.0 Hz), 2.44 (2H, q, J= 7.0 Hz), 1.26 (12H, s), 1.05 (9H, s); ¹³C NMR (126 MHz, CDCl₃): δ 150.6, 135.6, 133.9, 129.5, 127.6, 83.0, 62.9, 39.2, 26.8, 24.7, 19.2; IR (neat): 2976.6 (w), 2930.8 (w), 2857.8 (w), 1639.1 (m), 1472.0 (w), 1388.7 (s), 1359.1 (s), 1144.1 (s), 1107.6 (s), 996.3 (m), 849.3 (m), 822.6 (m), 737.6 (s), 612.8 (m), 504.3 (s) cm⁻¹; HRMS-(DART) for: $C_{26}H_{38}BO_3Si [M+H]^+$: calculated: 437.2683, found: 437.2696.

undec-10-ynal. A 50-mL flame-dried round-bottomed flask was charged with a solution of Dess-Martin periodinane (6.36 g) in 20 mL of dichloromethane and then cooled in an ice bath. To the reaction vessel was added undec-10-yn-1-ol (2.87 mL, 15.0 mmol), dropwise over 1 min. The reaction was allowed to stir for 5 min at 0 °C, at which point the reaction vessel was allowed to stir for an additionally

⁴⁰ Greshock, T.J.; Johns, D.M.; Noguchi, Y.; Williams, R.M. Org. Lett. 2008, 10, 613.

3 hours at room temperature. The reaction mixture was washed with saturated NaHCO₃, and concentrated under vacuum. The crude was purified by silica gel chromatography (3% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (1.98 g, 80%). All spectral data are in accordance with the literature.⁴¹



12-methyltridec-11-en-1-yne. A solution of *n*-butyllithium in hexanes (2.48 M, 5.40 mL, 13.4

mmol, 2.0 equiv.) was added dropwise via syringe to a stirred suspension of 2propyltriphenylphosphonium bromide (5.16 g, 13.4 mmol) in tetrahydrofuran (40 mL) at -78 °C. After completion of the addition, the cooling bath was removed and the reaction vessel was placed in an ice bath. The mixture was allowed to stir for 1 hour at 0 °C. The dark red solution that formed was cooled to -78 °C and undec-10-ynal (1.12 g, 6.70 mmol) was added dropwise via syringe over 5 minutes. The reaction mixture was stirred for 1 hour at -78 °C, at which point the vessel was placed in an ice bath. The mixture was allowed to stir for an additional 2 hours at 0 °C. The product mixture was diluted sequentially with saturated ammonium chloride solution (10 mL) and water (30 mL). The diluted product mixture was transferred to a separatory funnel and extracted with ether (3x40 mL). The organic layers were combined and the combined layers were dried over sodium sulfate. The dried solution was filtered and the filtrate was concentrated. The residue obtained was purified by silica gel chromatography (100% hexanes) to afford the

⁴¹ Pelletier, G.; Bechara, W. S.; Charette, A. B. J. Am. Chem. Soc. 2010, 132, 12817.

desired product as a clear, colorless oil (847.5 mg, 66%). All spectral data are in accordance with the literature.⁴²

Me B(pin) (E)-4,4,5,5-tetramethyl-2-(12-methyltrideca-1,11-dien-1-yl)-Me 1,3,2-dioxaborolane. Prepared according to the general

procedure utilizing pinacolborane (640 mg, 5.00 mmol), Schwartz' reagent (129 mg, 0.500 mmol), and 12-methyltridec-11-en-1-yne (1.70 g, 5.50 mmol). The crude material was purified (SiO₂, 2.5% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (1.37 g, 86%). All spectral data are in accordance with the literature. ¹H NMR (500 MHz, CDCl₃): δ 6.61 (1H, dt, *J*= 18.0, 6.5 Hz), 5.40 (1H, d, *J*= 17.5 Hz), 5.10 (1H, tt, *J*= 6.0, 1.5 Hz), 2.11 (2H, q, *J*= 7.0 Hz), 1.93 (2H, q, *J*=6.5 Hz), 1.66 (3H, s), 1.57 (3H, s), 1.40-1.36 (2H, m), 1.24-1.22 (22H, m); ¹³C NMR (100 MHz, CDCl₃): δ 154.8, 131.1, 124.9, 82.9, 35.8, 29.8, 29.5, 29.3, 29.2, 28.2, 28.0, 25.7, 24.8, 24.7, 17.6; IR (neat): 2977.3 (m), 2923.8 (m), 2853.7 (m), 1637.9 (m), 1360.3.5 (s), 1317.2 (s), 1144.6 (s), 970.6 (m), 849.4 (m); HRMS-(DART+) for C₂₀H₃₈B₁O₂ [M+H]⁺: calculated: 321.2965, found: 321.2961.

(E)-2-(2-cyclohexylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizingpinacolborane (1.28 g, 10.0 mmol), Schwartz' reagent (258 mg, 1.00 mmol), andethynylcyclohexane (1.19 g, 11.0 mmol). The crude material was purified (SiO₂, 3%ethyl acetate in hexane) to give the desired product as a white solid (2.00 g, 85%). Allspectral data are in accordance with the literature.³⁶

⁴² Li, L.; Herzon, S.B. J. Am. Chem. Soc. **2012**, 134, 17376.

4.9.4. Representative Procedure for Pt-catalyzed Vinyl Boronate Diboration.

General procedure for racemic Pt-catalyzed vinyl(boronate) diboration

$$R \xrightarrow{B(pin)} + B_2(pin)_2 \xrightarrow{Pt(dba)_3 (2\%)} R \xrightarrow{B(pin)} B(pin)$$

To an oven-dried 2-dram scintillation vial equipped with a magnetic stirbar in the glovebox was added $Pt(dba)_3$ (0.02 equiv.) and $B_2(pin)_2$ (1.05 equiv.), followed by THF (1.0 M in vinyl(boronate)). The mixture was allowed to stir at room temperature for 2 minutes, at which point the vinyl(boronate) (1.00 equiv.) was added all at once. The vial was sealed with a polypropylene cap, taped, brought outside of the glovebox, and heated in an oil bath at 60 °C for 13 hours. The resulting mixture was cooled to room temperature and concentrated under reduced pressure to give the crude material, which was subsequently purified using SiO₂ gel column chromatography.

General procedure for asymmetric Pt-catalyzed vinyl(boronate) diboration

$$R \xrightarrow{B(\text{pin})} + B_2(\text{cat})_2 \xrightarrow{3\% \text{Pt}(\text{dba})_3}{6\% (R,R)-4.9} \xrightarrow{\text{pinacol}} RT \xrightarrow{B(\text{pin})}{R} \xrightarrow{\overline{B}(\text{pin})}{B(\text{pin})}$$

To an oven-dried 2-dram vial equipped with a magnetic stirbar in the glovebox was added $Pt(dba)_3$ (0.03 equiv.), (*R*,*R*)-4.9 (0.06 equiv.), and $B_2(cat)_2$ (1.20 or 2.00 equiv.), followed by THF (1.0 M in vinyl(boronate)). The vial was sealed with a

polypropylene cap, taped, brought outside of the glovebox, and heated to 80 °C for 25 minutes (Caution: While we have not experienced any explosions, this reaction involves heating of a closed system, and therefore appropriate safety measures should be followed). Over this period, the mixture turned from a deep purple solution to a pale yellow solution. The mixture was cooled to room temperature and brought into the glovebox, at which point the vinyl(boronate) (1.00 equiv.) was added all at once. The vial was sealed with a polypropylene, taped, brought outside of the glovebox, and heated to 60 °C for 24 hours. The resulting mixture was cooled to room temperature and brought back into the glovebox, at which point pinacol (7.2 equiv.) was added all at once. The vial was sealed, taped, brought out of the glovebox, and allowed to stir at room temperature for 14 hours. The resulting mixture was cooled to room temperature, concentrated under reduced pressure, and subsequently purified via SiO₂ gel column chromatography to provide the pure diboration products (Note: All tris(boronates) tested are adequately stable to SiO₂ gel column chromatography with minimal degradation observed).

4.9.5. Representative Procedure for Deborylative Alkylation of 1,1,2-Tris(boronate) Esters.

General procedure for deborylative alkylation/oxidation of 1,1,2-tris(boronate)esters



To an oven-dried 2-dram vial equipped with a magnetic stirbar in the glovebox was added 1,1,2-tris(boronate) (1.50 equiv.) and NaOtBu (5.0 equiv.), followed by toluene (0.22 M in tris(boronate)). The mixture was allowed to stir at room temperature for 3-5 minutes, at which point alkyl halide (1.00 equiv.) was added dropwise. The reaction vessel was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at room temperature for 14-18 hours. The reaction mixture was then transferred to a 6-dram vial and diluted with THF (2 mL). The crude mixture was cooled to 0 °C and 3M NaOH (1.5 mL) was added, followed by 30% H₂O₂ (1.0 mL), dropwise. The reaction mixture for 4 hours. The reaction mixture was cooled to 0 °C and saturated aq. Na₂S₂O₃ (1.5 mL) was added dropwise. The reaction mixture was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and

concentrated under reduced pressure. The pure diol products were isolated after SiO₂ chromatography, unless otherwise noted.

General procedure for deborylative cyclization/oxidation of 1,1,2-tris(boronate)esters



To an oven-dried 2-dram vial equipped with a magnetic stirbar in the glovebox was added 1,1,2-tris(boronate) (1.00 equiv.) and NaOtBu (5.0 equiv.), followed by toluene (0.22 M in tris(boronate)). The reaction vessel was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at room temperature for 14-18 hours. The reaction mixture was then transferred to a 6-dram vial and diluted with THF (2 mL). The crude mixture was cooled to 0 °C and 3M NaOH (1.5 mL) was added, followed by 30% H₂O₂ (1.0 mL), dropwise. The reaction mixture was allowed to warm to room temperature, and was allowed to stir at room temperature for 4 hours. The reaction mixture was cooled to 0 °C and saturated aq. Na₂S₂O₃ (1.5 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The pure diol products were isolated after SiO₂ chromatography, unless otherwise noted.



(**R**,**R**)-**4.9** (16.4 mg, 0.0180 mmol), methylpent-1-en-1-yl)-1,3,2-dioxaboro-lane (63.1 mg, 0.300 mmol), and THF (0.30 mL), followed by pinacol (425.3 mg, 3.600 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (96.1 mg, 70%). ¹H NMR (500 MHz, CDCl₃): δ 1.57-1.53 (1H, m), 1.42-1.31 (2H, m), 1.20-1.12 (37 H, m), 0.84 (3H, d, *J*= 6.0 Hz), 0.81 (3H, d, *J*= 6.5 Hz), 0.78 (1H, d, *J*= 9.5 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 82.9, 82.8, 82.8, 43.2, 27.2, 25.2, 25.0, 24.9, 24.8, 24.8, 23.7, 22.6; IR (neat): 2976.3 (m), 2952.2 (m), 1378.8 (m), 1369.8 (m), 1344.7 (s), 1307.1 (s), 1165.4 (s), 968.6 (m), 848.4 (m) cm⁻¹; HRMS-(DART) for: C₂₄H₄₈B₃O₆ [M+H]⁺: calculated: 465.3730, found: 465.3726. [α]_D²⁰= -12.351 (*c* = 0.340, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for racemic vinyl boronate diboration utilizing (*E*)-4,4,5,5-tetramethyl-2-(4-methylpent-1-en-1-yl) -1,3,2- dioxaborolane and Pt(dba)₃ as the catalyst. The title compound was subjected to the general procedure for deborylative alkylation with (3-bromopropyl)benzene followed by oxidation to give (4S,5S)-7-methyl-1- phenyloctane-4,5-diol. Further analysis of

stereochemistry was performed on (4S,5S)-7-methyl-1-phenyloctane-4,5-diol. Absolute stereochemistry was assigned by analogy (see **4.56** and **4.57**).

Chiral SFC (Chiracel OD-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (4S,5S)-7-methyl-1-phenyloctane-4,5-diol





Racemic Material

Standard Conditions

| Peak No | % Area | Area | RT (min) | Peak No | % Area | Area | RT (min) |
|---------|---------|------------|----------|---------|---------|------------|----------|
| 1 | 49.9449 | 9624.4423 | 12.76 | 1 | 7.5755 | 1025.0807 | 12,56 |
| 2 | 50.0551 | 9645.6814 | 14.05 | 2 | 92.4245 | 12506.4458 | 13.45 |
| Total: | 100 | 19270,1237 | | Total: | 100 | 13531.5265 | |



(*R*,*R*)-4.9 (16.4 mg, 0.0180 mmol), B₂(cat)₂ (85.6 mg, 0.360 mmol), (*E*)-4,4,5,5tetramethyl-2-(3-phenylprop-1-en-1-yl)-1,3,2-dioxaborolane (73.2 mg, 0.300 mmol), and THF (0.30 mL), followed by pinacol (255.2 mg, 2.160 mmol). The crude material was purified (SiO₂, 5-7% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (121.5 mg, 81%). ¹H NMR (500 MHz, CDCl₃): δ 7.23-7.17 (4H, m), 7.10 (1H, tt, *J*= 6.5, 2.0 Hz), 2.80 (1H, dd, *J*= 13.5, 7.0 Hz), 2.71 (1H, dd, *J*= 13.5, 8.5 Hz) 1.68 (1H, dt, *J*= 7.0, 9.0 Hz), 1.23 (24 H, s), 1.13 (6H, s), 1.10 (6H, s), 0.85 (1H, d, *J*= 9.0 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 142.7, 129.3, 127.8, 125.3, 82.8, 82.8, 82.8, 39.2, 25.0, 24.9, 24.8, 24.8, 24.6, 24.6; IR (neat): 2976.6 (m), 2929.1 (w), 1454.9 (w), 1369.8 (s), 1350.4 (s), 1309.6 (s), 1264.6 (m), 1213.7 (w), 1140.0 (s), 969.6 (m), 850.4 (m), 744.7 (w), 699.7 (w), 669.9 (w) cm⁻¹; HRMS-(DART) for: C₂₇H₄₆B₃O₆ [M+H]⁺: calculated: 499.3574, found: 499.3592. [α]_D²⁰= -15.837 (*c* = 0.500, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for racemic vinyl boronate diboration utilizing (*E*)-4,4,5,5-tetramethyl-2-(3-phenylprop-1-en-1-yl)-1,3,2-dioxaborolane and Pt(dba)₃ as the catalyst. The title compound was subjected to protodeboronation as shown below to give (*R*)-2,2'-(3-phenylpropane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Further analysis of stereochemistry

was performed on (R)-2,2'-(3-phenylpropane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Absolute stereochemistry was assigned by analogy (see **4.56** and **4.57**).



Chiral SFC (Chiracel OD-H, 5% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2,2'-(3-phenylpropane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)



| Peak No | % Area | Area | RT (min) | Peak No | % Area | Area | RT (min) |
|---------|---------|-----------|----------|---------|---------|-----------|----------|
| 1 | 49.9915 | 4695.5075 | 3.1 | 1 | 6.0939 | 140.4854 | 3.1 |
| 2 | 50.0085 | 4697.1091 | 4.02 | 2 | 93.9061 | 2164.8638 | 3.99 |
| Total: | 100 | 9392.6166 | | Total: | 100 | 2305.3492 | |

(R)-2,2',2''-(4-phenylbutane-1,1,2-trivl)tris(4,4,5,5-tetra-B(pin) B(pin) methyl-1,3,2-dioxaborolane). Prepared according to the B(pin) general procedure utilizing Pt(dba)₃ (8.1 mg, 0.0090 mmol), (*R*,*R*)-**4.9** (16.4 mg, 0.0180 mmol), B₂(cat)₂ (85.6 mg, 0.360 mmol), (E)-4,4,5,5-tetramethyl-2-(4-phenylbut-1-en-1yl)-1,3,2-dioxaboro-lane (77.5 mg, 0.300 mmol), and THF (0.30 mL), followed by pinacol (255.2 mg, 2.160 mmol). The crude material was purified (SiO₂, 5-7% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (121.5 mg, 81%). ¹H NMR (500 MHz, CDCl₃): δ 7.26-7.22 (2H, m), 7.17 (2H, d, *J*= 7.0 Hz), 7.13 (1H, t, J= 7.5 Hz), 2.66 (1H, ddd, J= 13.5, 10.5, 6.5 Hz), 2.52 (1H, ddd, J= 13.5, 11.0, 6.5 Hz), 1.80-1.70 (2H, m), 1.47-1.43 (1H, m), 1.24-1.21 (36H, m), 0.94 (1H, d, *J*= 10.0 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 143.7, 128.4, 128.1, 125.2, 82.8, 82.8, 82.8, 35.7, 35.3, 25.1, 25.0, 24.8, 24.7, 24.7, 24.6; IR (neat): 2977.2 (m), 2929.6 (w), 1496.1 (w), 1455.9 (w), 1378.0 (s), 1370.1 (s), 1348.3 (s), 1312.2 (s), 1267.6 (m), 1214.4 (w), 1141.0 (s), 969.4 (m), 849.0 (m), 699.4 (w) cm⁻¹; HRMS-(DART) for: C₂₈H₄₈B₃O₆ [M+H]⁺: calculated: 513.3730, found: 513.3751. $[\alpha]_D^{20} = -20.472$ (*c* = 0.969, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for racemic vinyl boronate diboration utilizing (E)-4,4,5,5-tetramethyl-2-(4-phenylbut-1-en-1-yl)-1,3,2-dioxaboro-lane and Pt(dba)₃ as the catalyst. The title compound was subjected to protodeboronation to give (R)-2,2'-(4-phenylbutane-1,2-diyl)bis(4,4,5,5-tetramethyl-

1,3,2-dioxaborolane). Further analysis of stereochemistry was performed on this product. Absolute stereochemistry assigned by analogy (see **4.56** and **4.57**).

Chiral SFC (Chiracel OD-H, 1% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2,2'-(4-phenylbutane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)



Standard Conditions





| Peak No | % Area | Area | RT (min) | Peak No | % Area | Area | RT (min) |
|---------|---------|-----------|----------|---------|---------|-----------|----------|
| 1 | 49.6317 | 4046.2516 | 7.58 | 1 | 94.1875 | 8351.9413 | 7.37 |
| 2 | 50.3683 | 4106.2983 | 8.35 | 2 | 5.8125 | 515.4178 | 8.32 |
| Total: | 100 | 8152.5499 | | Total: | 100 | 8867.3591 | |

(R)-2,2',2''-(octane-1,1,2-triyl)tris(4,4,5,5-tetramethyl-B(pin) Me B(pin) 1,3,2-dioxaborolane). Prepared according to the general B(pin) procedure utilizing Pt(dba)₃ (8.1 mg, 0.0090 mmol), (*R*,*R*)-4.9 (16.4 mg, 0.0180 mmol), $B_2(cat)_2$ (85.6 mg, 0.360 mmol), (E)-1-octen-1-ylboronic acid pinacol ester (71.8 mg, 0.300 mmol), and THF (0.30 mL), followed by pinacol (255.2 mg, 2.160 mmol). The crude material was purified (SiO₂, 5-7% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (115.6 mg, 78%). ¹H NMR (500 MHz, CDCl₃): δ 1.44-1.36 (2H, m), 1.35-1.28 (2H, m), 1.27-1.16 (43H, m), 0.86-0.82 (4H, m); ¹³C NMR (126 MHz, CDCl₃): δ 82.7, 82.6, 82.6, 33.4, 31.8, 29.6, 28.6, 25.0, 24.9, 24.8, 24.7, 24.6, 22.6, 14.1; IR (neat): 2976.0 (m), 2924.6 (m), 2855.2 (w), 1466.8 (w), 1370.1 (s), 1346.7 (s), 1306.2 (s), 1262.4 (s), 1213.3 (w), 1136.1 (m), 876.3 (m), 712.9 (w) cm⁻¹; HRMS-(DART) for: $C_{26}H_{52}B_{3}O_{6}$ [M+H]⁺: calculated: 493.4043, found: 493.4062. [α]_D²⁰ = -23.179 (c = 1.025, CHCl₃, l = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for racemic vinyl boronate diboration utilizing (*E*)-1-octen-1-ylboronic acid pinacol ester and Pt(dba)₃ as the catalyst. The title compound was subjected to the general procedure for deborylative alkylation with (3-bromopropyl)benzene followed by oxidation as shown below to give (4S,5S)-1-phenylundecane-4,5-diol. Further analysis of stereochemistry was performed on (4S,5S)-1-phenylundecane-4,5-diol. Absolute stereochemistry was assigned by analogy (see **4.56** and **4.57**).



Chiral SFC (Chiracel OD-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (4S,5S)-1-phenylundecane-4,5-diol



Racemic Material

Standard Conditions

| Peak No | % Area | Area | RT (min) | Peak No | % Area | Area | RT (min) |
|---------|---------|-----------|----------|---------|---------|-----------|----------|
| 1 | 50.6383 | 3071.2958 | 16.08 | 1 | 10.7066 | 825.3601 | 15.53 |
| 2 | 49.3617 | 2993.8709 | 32.44 | 2 | 89.2934 | 6883.5181 | 29.79 |
| Total: | 100 | 6065.1667 | | Total: | 100 | 7708.8782 | |



(**R**,**R**)-4.9 (16.4 mg, 0.0180 mmol), B₂(cat)₂ (142.7 mg, 0.600 mmol), (*E*)-2-(6-chlorohex-1-enyl)-4,4,5,5-tetramethyl-1,3,2 -dioxaborolane (72.9 mg, 0.300 mmol), and THF (0.30 mL), followed by pinacol (425.3 mg, 3.600 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (114.3 mg, 76%). ¹H NMR (500 MHz, CDCl₃): δ 3.49 (2H, t, *J*= 7.0 Hz), 1.74-1.70 (2H, m), 1.46-1.31 (5H, m), 1.20-1.18 (36H, m), 0.83 (1H, d, *J*= 9.5 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 83.0, 83.0, 82.9, 45.4, 33.1, 32.6, 26.2, 25.2, 25.1, 25.0, 24.9, 24.8, 24.9; IR (neat): 2976.1 (m), 2928.2 (m), 1460.9 (w), 1370.1 (m), 1348.7 (m), 1303.3 (s), 1262.4 (m), 1136.0 (s), 968.6 (m), 846.5 (m) cm⁻¹; HRMS-(DART) for: $C_{24}H_{47}B_3Cl_1O_6 [M+H]^+$: calculated: 499.3340, found: 499.3344. [α]_D²⁰ = -16.084 (*c* = 0.470, CHCl₃, *l* = 50 mm).

Analysis and Proof of stereochemistry:

Racemic compound was prepared according to the general procedure for racemic vinyl boronate diboration utilizing (*E*)-2-(6-chlorohex-1-en-1-yl)-4,4,5,5-tetramethyl- 1,3,2- dioxaborolane and Pt(dba)₃ as the catalyst. The title compound was subjected to the general procedure for deborylative cyclization followed by oxidation to give (1*S*,2*S*)- cyclohexane-1,2-diol. Absolute configuration of stereochemistry was assigned by

comparing the prepared (1*S*,2*S*)-cyclohexane-1,2-diol with an authentic sample purchased from Fluka.



Chiral GLC (β-dex 225, Supelco, 100 °C for 5 min, ramp 3 °C/min to 160 °C, 20 psi) – analysis of (1S,2S)-cyclohexane-1,2-diol

Racemic Material

Standard Conditions





| Peak RetTime Type | Width | Area | Height | Area | | | | | |
|-------------------|--------|------------|----------|----------|----------------|------------|------------|----------|----------|
| # [min] | [min] | [pA*s] | [PA] | 98 | Peak RetTime 7 | Cype Width | Area | Height | Area |
| | | | | | # [min] | [min] | [pA*s] | [pA] | 40 |
| 1. 14.427 MM | 0.1997 | 556.62695 | 46.46300 | 49.97651 | 1 | | | | |
| 2 15.122 MM | 0.2298 | 557.15027 | 40.40024 | 50.02349 | 1 14.327 1 | M 0.2887 | 1120.20935 | 64.67873 | 94.74193 |
| Totals : | | 1113.77722 | 86.86324 | | 2 15.404 № | MM 0.1941 | 62.17039 | 5.33910 | 5.25807 |

Authentic Material



| Peak RetT # [mi | ime Type n] | Width [min] | Area [pA*s] | Height [pA] | Area % |
|--------------------|----------------|----------------|----------------|----------------|-----------|
| | | | | | |
| 1 14. | 326 MM | 0.2958 | 1112.23303 | 62.67395 | 99.69204 |
| 2 15. | 461 MM | 0.1717 | 3.43582 | 3.33552e-1 | 0.30796 |
| | | | | | |
| Totals : | | | 1115.66886 | 63.00751 | |

B(pin) (*R*)-2,2',2''-(6-bromohexane-1,1,2-triyl)tris(4,4,5,5-Br $\xrightarrow{B(pin)}$ B(pin) tetramethyl-1,3,2-dioxaborolane). Prepared according to the general procedure utilizing Pt(dba)₃ (8.1 mg, 0.0090 mmol), (*R*,*R*)-4.9 (16.4 mg, 0.0180 mmol), B₂(cat)₂ (142.7 mg, 0.6000 mmol), (*E*)-2-(6-bromohex-1-en-1-yl)-4,4,5,5tetramethyl-1,3,2-dioxaborolane (71.8 mg, 0.300 mmol), and THF (0.30 mL), followed by pinacol (425.3 mg, 3.600 mmol). The crude material was purified (SiO₂, 5-7% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid, which coeluted with B₂(pin)₂ (135.1 mg, product: B₂(pin)₂ = 1.00:0.26, 74%). ¹H NMR (500 MHz, CDCl₃): δ 3.38 (2H, t, 6.5 Hz), 1.87-1.76 (2H, m), 1.50-1.30 (5H, m), 1.23-1.18 (36H, m), 0.84 (1H, d, *J*= 10.0 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 82.8, 82.8, 82.7, 34.0, 33.1,
32.3, 27.3, 25.0, 25.0, 24.9, 24.8, 24.7, 24.6; IR (neat): 2976.4 (m), 2930.2 (w), 1461.3 (w), 1369.4 (s), 1347.1 (s), 1304.5 (s), 1267.1 (s), 1213.4 (m), 1137.7 (s), 968.9 (m), 848.8 (m), 644.6 (w), 578.2 (w) cm⁻¹; HRMS-(DART) for: $C_{24}H_{47}B_3BrO_6$ [M+H]⁺: calculated: 543.2835, found: 543.2855. [α]_D²⁰ = -16.415 (*c* = 2.975, CHCl₃, *l* = 50 mm).

Analysis and Proof of stereochemistry:

Racemic compound was prepared according to the general procedure for racemic vinyl boronate diboration utilizing (E)-2-(6-bromohex-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and Pt(dba)₃ as the catalyst. The title compound was subjected to the general procedure for deborylative cyclization followed by oxidation to give (1S,2S)-cyclohexane-1,2-diol. Absolute configuration of stereochemistry was assigned by comparing the prepared (1S,2S)-cyclohexane-1,2-diol with an authentic sample purchased from Fluka.



Chiral GLC (β -dex 225, Supelco, 100 °C for 5 min, ramp 3 °C/min to 160 °C, 20 psi) – analysis of (1S,2S)-cyclohexane-1,2-diol

Racemic Material





| Peak RetTime Type # [min] | Width [min] | Area [pA*s] | Height [pA] | Area % | Peak # | RetTime [min] | Туре | Width [min] | Area [pA*s] | Height [pA] | Area % |
|------------------------------|----------------|----------------|----------------|-----------|-----------|------------------|------|----------------|----------------|----------------|-----------|
| | | | | | | | | | | | |
| 1 14.427 MM | 0.1997 | 556.62695 | 46.46300 | 49.97651 | , 1 | 14.702 | MM | 0.1368 | 149.13812 | 18.17207 | 93.07457 |
| 2 15.122 MM | 0.2298 | 557.15027 | 40.40024 | 50.02349 | 2 | 15.492 | MM | 0.0809 | 11.09697 | 2.28523 | 6.92543 |
| | | | | | | | | | | | |
| Totals : | | 1113.77722 | 86.86324 | | Total | ls : | | | 160.23509 | 20.45730 | |

Authentic Material



| Peak RetTime Type | Width Area | Height | Area |
|-------------------|-------------------|------------|----------|
| # [min] | [min] [pA*s] | [pA] | de . |
| | | | |
| 1 14.326 MM | 0.2958 1112.23303 | 62.67395 | 99.69204 |
| 2 15.461 MM | 0.1717 3.43582 | 3.33552e-1 | 0.30796 |
| | | | |
| Totals : | 1115.66886 | 63.00751 | |

(R)-tert-butyldimethyl(3,4,4-tris(4,4,5,5-tetramethyl-1,3,2-B(pin) B(pin) TBSO dioxa-borolan-2-yl)butoxy)silane. Prepared according to the B(pin) general procedure utilizing Pt(dba)₃ (8.1 mg, 0.0090 mmol), (*R*,*R*)-4.9 (16.4 mg, 0.0180 mmol), B₂(cat)₂ (85.6 mg, 0.360 mmol), (E)-4-(tert-butyldimethylsiloxy)-1-buten-1ylboronic acid pinacol ester (93.7 mg, 0.300 mmol), and THF (0.30 mL), followed by pinacol (255.2 mg, 2.160 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (135.4 mg, 80%). ¹H NMR (500 MHz, CDCl₃): δ 3.63 (1H, dt, J= 6.0, 10.5 Hz), 3.53 (1H, dt, J= 6.0, 10.5 Hz), 1.76-1.69 (1H, m), 1.65-1.59 (1H, m), 1.32-1.18 (37H, m), 0.86 (9H, s), 0.80 (1H, d, J= 8.5 Hz), 0.02 (6H, s); ¹³C NMR (126 MHz, CDCl₃): δ 82.7, 82.7, 82.7, 63.2, 36.4, 26.1, 25.1, 25.0, 24.9, 24.7, 24.7, 24.6, 18.4, -5.1; IR (neat): 2976.8 (m), 2929.5 (m), 2857.2 (w), 1470.1 (w), 1369.6 (s), 1347.5 (s), 1305.9 (s), 1256.4 (m), 1214.7 (m), 1138.8 (s), 1091.2 (s), 1005.4 (m), 846.5 (s), 835.0 (s), 775.0 (m), 668.7 (w), 578.1 (w) cm⁻¹; HRMS-(DART) for: $C_{28}H_{58}B_{3}O_{7}Si [M+H]^{+}$: calculated: 567.4231, found: 567.4257. $[\alpha]_{D}^{20} = -11.340$ (*c* = 2.155, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for racemic vinyl boronate diboration utilizing (E)-4-(*tert*-butyldimethylsiloxy)-1-buten-1-ylboronic acid pinacol ester and Pt(dba)₃ as the catalyst. The title compound was subjected to the general procedure for deborylative alkylation with (3-bromopropyl)benzene followed by oxidation to give (3S,4S)-1-((tert-butyldimethylsilyl)oxy)-7-phenylheptane-3,4-diol.

Further analysis of stereochemistry was performed on (3S,4S)-1-((tertbutyldimethylsilyl)oxy)-7-phenylheptane-3,4-diol. Absolute stereochemistry was assigned by analogy (see **4.56** and **4.57**).

Chiral SFC (Chiracel OD-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (3S,4S)-1-((tert-butyldimethylsilyl)oxy)-7-phenylheptane-3,4-diol



| Peak No | % Area | Area | RT (min) | Peak No | % Area | Area | RT (min) |
|---------|---------|------------|----------|---------|---------|-----------|----------|
| 1 | 50.5769 | 14000.6213 | 53.66 | 1 | 18.6821 | 1814.0332 | 54.6 |
| 2 | 49.4231 | 13681.2508 | 58.31 | 2 | 81.3179 | 7895.9517 | 58.54 |
| Total: | 100 | 27681.8721 | | Total: | 100 | 9709.9849 | |

(R)-tert-butyldiphenyl(3,4,4-tris(4,4,5,5-tetramethyl-1,3,2-B(pin) B(pin) TBDPSO dioxa-borolan-2-yl)butoxy)silane. Prepared according to B(pin) the general procedure utilizing $Pt(dba)_3$ (8.1 mg, 0.0090 mmol), (*R*,*R*)-4.9 (16.4 mg, 0.0180 mmol), B₂(cat)₂ (142.7 mg, 0.6000 mmol), (E)-tert-butyldiphenyl((4-(4,4,5,5tetramethyl-1,3,2-dioxaboro-lan-2-yl)but-3-en-1-yl)oxy)silane (130.9 mg, 0.300 mmol), and THF (0.30 mL), followed by pinacol (425.3 mg, 3.600 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid, which co-eluted with $B_2(pin)_2$ (203.1 mg, product: $B_2(pin)_2 =$ 1.0:0.66, 79%). ¹H NMR (500 MHz, CDCl₃): δ 7.66 (4H, dd, J= 7.5, 1.5 Hz), 7.39-7.32 (6H, m), 3.71 (1H, dt, J= 5.5, 10.0 Hz), 3.63 (1H, dt, J= 6.0, 9.5 Hz), 1.89-1.76 (2H, m), 1.40-1.33 (1H, m), 1.21 (12H, s), 1.19 (12H, s), 1.13 (6H, s), 1.12 (6H, s), 1.02 (9H, s), $0.81 (1H, d, J = 8.5 Hz); {}^{13}C NMR (126 MHz, CDCl_3); \delta 135.5, 135.5, 129.2, 127.4, 82.7)$ 82.7, 82.7, 63.8, 36.1, 25.0, 24.9, 24.9, 24.7, 24.7, 24.6, 19.2; IR (neat): 2977.0 (m), 2930.9 (m), 2858.0 (w), 1469.3 (w), 1348.4 (s), 1308.7 (s), 1279.6 (s), 1213.6 (w), 1139.7 (s), 1124.4 (s), 1109.7 (s), 969.2 (m), 849.0 (m), 742.3 (w), 703.1 (m), 578.7 (w), 505.6 (w) cm⁻¹; HRMS-(DART) for: $C_{38}H_{62}B_{3}O_{7}Si [M+H]^{+}$: calculated: 691.4544, found: 691.4555. $[\alpha]_D^{20} = -7.697$ (*c* = 1.190, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for racemic vinyl boronate diboration utilizing (E)-*tert*-butyldiphenyl((4-(4,4,5,5-tetramethyl-1,3,2-dioxaboro-lan-2-yl)but-3-en-1-yl)oxy)silane and Pt(dba)₃ as the catalyst. The title

compound was subjected to the general procedure for deborylative alkylation with (3bromopropyl)benzene followed by oxidation to give (3S,4S)-1-((tertbutyldiphenylsilyl)oxy)-7-phenylheptane-3,4-diol. Further analysis of stereochemistrywas performed on <math>(3S,4S)-1-((tert-butyldiphenylsilyl)oxy)-7-phenylheptane-3,4-diol.Absolute stereochemistry was assigned by analogy (see **4.56** and **4.57**).

Chiral SFC (Chiracel OD-H, 20% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (3S,4S)-1-((tert-butyldiphenylsilyl)oxy)-7-phenylheptane-3,4-diol



Racemic Material

Standard Conditions

| Peak No | % Area | Area | RT (min) | Peak No | % Area | Area | RT (min) |
|---------|---------|------------|----------|---------|---------|------------|----------|
| 1 | 49.4598 | 25730.5679 | 10.07 | 1 | 82.9705 | 31147.197 | 9.98 |
| 2 | 50.5402 | 26292.634 | 11.67 | 2 | 17.0295 | 6392.8934 | 11.78 |
| Total: | 100 | 52023,2019 | | Total: | 100 | 37540.0904 | |

(R)-tert-butyldimethyl((4,5,5-tris(4,4,5,5-tetramethyl-B(pin) TBSO, B(pin) 1,3,2-dioxa-borolan-2-yl)pentyl)oxy)silane. Prepared B(pin) according to the general procedure utilizing $Pt(dba)_3$ (8.1 mg, 0.0090 mmol), (*R*,*R*)-4.9 (16.4 mg, 0.0180 mmol), B₂(cat)₂ (85.6 mg, 0.360 mmol), (E)-tert-butyldimethyl((5-(4,4,5,5-tetramethyl-1,3,2-dioxaboro-lan-2-yl)pent-4-en-1-yl)oxy)silane (97.9 mg, 0.300 mmol), and THF (0.30 mL), followed by pinacol (255.2 mg, 2.160 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (123.6 mg, 71%). ¹H NMR (500 MHz, CDCl₃): δ 3.56 (2H, t, J= 7.0 Hz), 1.62-1.54 (1H, m), 1.49-1.30 (4H, m), 1.21 (18H, s. overlap), 1.21(18H, s, overlap), 0.87 (9H, s), 0.88-0.86 (1H, overlaps), 0.02 (6H, s); ¹³C NMR (126 MHz, CDCl₃): δ 82.7, 82.7, 64.1, 32.3, 29.6, 26.0, 25.0, 24.9, 24.8, 24.6, 24.6, 24.6, 18.4, -5.2; IR (neat): 2976.8 (m), 2929.5 (m), 2857.1 (w), 1470.4 (w), 1369.7 (s), 1345.8 (s), 1308.6 (s), 1266.0 (m), 1214.4 (m), 1140.3 (s), 1100.5 (m), 1005.4 (w), 969.8 (m), 836.0 (s), 775.1 (m), 669.3 (w) cm⁻¹; HRMS-(DART) for: $C_{29}H_{60}B_3O_7Si [M+H]^+$: calculated: 581.4388, found: 581.4391. $[\alpha]_D^{20} = -15.094$ (*c* = 1.060, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for racemic vinyl boronate diboration utilizing), (*E*)-*tert*-butyldimethyl((5-(4,4,5,5-tetramethyl-1,3,2-dioxaboro-lan-2-yl)pent-4-en-1-yl)oxy)silane and Pt(dba)₃ as the catalyst. The title compound was subjected to the general procedure for deborylative alkylation with (3-bromopropyl)benzene followed by oxidation to give (<math>4S,5S)-1-((tert-

butyldimethylsilyl)oxy)-8-phenyloctane-4,5-diol. Further analysis of stereochemistry was performed on (4S,5S)-1-((tert-butyldimethylsilyl)oxy)-8-phenyloctane-4,5-diol. Absolute stereochemistry was assigned by analogy (see **4.56** and **4.57**).

Chiral SFC (Chiracel OD-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (4S,5S)-1-((tert-butyldimethylsilyl)oxy)-8-phenyloctane-4,5-diol



Racemic Material

Standard Conditions

| Peak No | % Area | Area | RT (min) | Peak No | % Area | Area | RT (min) |
|---------|---------|------------|----------|---------|--------|------------|----------|
| 1 | 50.5133 | 5681.8675 | 19.03 | 1 | 7.614 | 2081.9541 | 18.84 |
| 2 | 49.4867 | 5566.3938 | 23.85 | 2 | 92.386 | 25261.846 | 22.17 |
| Total: | 100 | 11248.2613 | | Total: | 100 | 27343.8001 | |

(R)-2,2',2''-(12-methyltridec-11-ene-1,1,2-triyl(4,4,5,5-B(pin) Me B(pin) tetramethyl-1,3,2-dioxaborolane). Prepared according to the B(pin) general procedure utilizing Pt(dba)₃ (8.1 mg, 0.0090 mmol), (*R*,*R*)-**4.9** (16.4 mg, 0.0180 mmol), B₂(cat)₂ (142.7 mg, 0.600 mmol), (E)-4,4,5,5-tetramethyl-2-(12-methyltrideca-1,11-dien-1-yl)-1,3,2-dioxaborolane (96.1 mg, 0.300 mmol), and THF (0.30 mL), followed by pinacol (425.3 mg, 3.600 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane, UV/magic stain) to give the desired product as a clear colorless oil (118.3 mg, 69%). ¹H NMR (500 MHz, CDCl₃): δ 5.08 (1H, tt, J= 7.0, 1.5 Hz), 1.93-1.89 (2H, m), 1.66 (3H, s), 1.57 (3H, s), 1.40-1.17 (52H, m), 0.84 (1H, d, *J*= 8.5 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 131.2, 125.2, 82.9, 82.9, 82.8, 33.6, 30.2, 30.1, 29.7, 29.6, 28.8, 28.3, 25.9, 25.2, 25.1, 25.0, 24.9, 24.8, 24.7, 17.8; IR (neat): 2976.6 (m), 2924.5 (m), 2854.1 (m), 1462.4 (m), 1369.5 (m), 1345.6 (s), 1306.2 (m), 1139.3 (s), 849.3 (m), 756.2 (m) cm⁻¹; HRMS-(DART) for: $C_{32}H_{63}B_3O_6$ [M+H]⁺: calculated: 575.4826, found: 575.4853. $[\alpha]_D^{20} = -16.084$ (*c* = 0.470, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for racemic vinyl boronate diboration utilizing (E)-4,4,5,5-tetramethyl-2-(12-methyltrideca-1,11- dien-1-yl)-1,3,2-dioxaborolane and Pt(dba)₃ as the catalyst. The title compound was subjected to the general procedure for deborylative alkylation with (3-bromopropyl)benzene followed by oxidation to give (4*S*,5*S*)-15-methyl-1- phenylhexadec-14-ene-4,5-diol. Further analysis of stereochemistry was performed on (4*S*,5*S*)-15-methyl-1-

phenylhexadec-14-ene-4,5- diol. Absolute stereochemistry was assigned by analogy (see **4.56** and **4.57**).

Chiral SFC (Chiracel AD-H, 10% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (4S,5S)-15-methyl-1-phenylhexadec-14-ene-4,5-diol.



Racemic Material

Standard Conditions

| Peak No | % Area | Area | RT (min) | Peak No | % Area | Area | RT (min) |
|---------|---------|------------|----------|---------|---------|------------|----------|
| 1 | 48.3725 | 7800.5002 | 17.95 | 1 | 5.6631 | 792,8513 | 17.98 |
| 2 | 51.6275 | 8325.4009 | 19.76 | 2 | 94.3369 | 13207.5682 | 19.36 |
| Total: | 100 | 16125.9011 | | Total: | 100 | 14000.4195 | |



0.0180 mmol), B₂(cat)₂ (142.7 mg, 0.600 mmol), (*E*)-4,4,5,5-tetramethyl-2-styryl-1,3,2dioxaborolane (69.1 mg, 0.300 mmol), and THF (0.30 mL), followed by pinacol (425.3 mg, 3.600 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (68.7 mg, 47%). ¹H NMR (500 MHz, CDCl₃): δ 7.19-7.12 (4H, m), 7.02-6.99 (1H, m), 2.64 (1H, d, *J*= 12.5 Hz), 1.42 (1H, d, *J*= 12.5 Hz), 1.21 (6H, s), 1.20 (6H, s), 1.13 (6H, s), 1.11 (6H, s), 0.92 (6H, s), 0.90 (6H, s); ¹³C NMR (100 MHz, CDCl₃): δ 145.5, 128.7, 128.0, 124.8, 83.2, 83.2, 82.8, 25.0, 24.8, 24.6, 24.5, 24.4; IR (neat): 2978.3 (m), 1370.2 (m), 1309.1 (s), 1263.8 (m), 1214.3 (w), 1137.7 (s), 968.0 (m), 908.3 (m), 846.5 (m), 739.4 (s), 668.9 (m) cm⁻¹; HRMS-(DART) for: C₂₆H₄₄B₃O₆ [M+H]⁺: calculated: 485.3417, found: 485.3431. [α] α ²⁰ = -9.267 (*c* = 0.650, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for racemic vinyl boronate diboration utilizing (E)-4,4,5,5-tetramethyl-2-styryl-1,3,2- dioxaborolane and Pt(dba)₃ as the catalyst. The title compound was subjected to protodeboronation to give (R)-2,2'-(1-phenylethane-1,2-diyl)bis(4,4,5,5-tetramethyl- 1,3,2-dioxaborolane). Further analysis of stereochemistry was performed on (R)-2,2' -(1-phenylethane-1,2-

diyl)bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolane). Absolute stereochemistry was assigned by analogy (see **4.56** and **4.57**).

Chiral SFC (Chiracel OD-H, 3% IPA, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2,2'-(1-phenylethane-1,2-diyl)bis(4,4,5,5-tetramethyl-1,3,2- dioxaborolane)



| Peak No | % Area | Area | RT (min) | Peak No | % Area | Area | RT (min) |
|---------|--------|------------|----------|---------|---------|------------|----------|
| 1 | 50,088 | 6747.9698 | 3.29 | 1 | 34.3608 | 4061,1813 | 3.03 |
| 2 | 49.912 | 6724.2719 | 3.56 | 2 | 65.6392 | 7758.0581 | 3.3 |
| Total: | 100 | 13472.2417 | | Total: | 100 | 11819.2394 | |

(R)-2,2',2''-(2-cyclohexylethane-1,1,2-triyl)tris(4,4,5,5-B(pin) B(pin) tetramethyl-1,3,2-dioxaborolane). Prepared according to the B(pin) general procedure utilizing Pt(dba)₃ (8.1 mg, 0.0090 mmol), (*R*,*R*)-**4.9** (16.4 mg, 0.0180 mmol), B₂(cat)₂ (142.7 mg, 0.600 mmol), (E)-2-(2-cyclohexylvinyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (70.8 mg, 0.300 mmol), and THF (0.30 mL), followed by pinacol (425.3 mg, 3.600 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (24.3 mg, 17%). ¹H NMR (500 MHz, CDCl₃): δ 1.78-1.57 (5H, m), 1.35-1.30 (2H, m), 1.27-1.02 (42H, m), 0.85-0.79 (1H, m); ¹³C NMR (100 MHz, CDCl₃): δ 82.9, 82.8, 82.8, 42.6, 33.9, 30.6, 27.4, 27.3, 27.1, 25.5, 25.3, 25.0, 24.9, 24.8, 24.6; IR (neat): 3026.4 (w), 2925.1 (m), 2858.3 (m), 1495.6 (m), 1453.9 (m), 1099.6 (m), 1063.4 (m), 1030.9 (m), 747.3 (m), 699.2 (s) cm⁻¹; HRMS-(DART) for: $C_{26}H_{50}B_3O_6 [M+H]^+$: calculated: 491.3887, found: 491.3905.

Cl B(pin) B(pin)

Pt(dba)₃ (26.9 mg, 0.030 mmol), $B_2(pin)_2$ (799.9 mg, 3.150 mmol), (*E*)-2-(5-chloropent-1-en- 1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaboro-lane (691.6 mg, 3.000 mmol), and THF (3.00 mL). The crude material was purified (SiO₂, 5% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (767.1mg, 58%). ¹H NMR (500 MHz, CDCl₃): δ 3.50 (2H, t, *J*= 7.0Hz), 1.87-1.80 (1H, m), 1.74-1.67 (1H, m), 1.59-1.51 (2H, m), 1.37-1.32 (1H, m), 1.26-1.21 (36H, m), 0.84 (1H, d, *J*= 10.0 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 83.0, 83.0, 45.9, 32.3, 30.9, 25.2, 25.1, 25.1, 25.0, 24.9, 24.8; IR (neat): 2976.9 (m), 1370.1 (m), 1347.4 (m), 1307.4 (s), 1264.8 (m), 1164.5 (m), 1137.1 (s), 1108.0 (m), 847.4 (m), 699.1 (m) cm⁻¹; HRMS-(DART) for: C₂₃H₄₅B₃Cl₁O₆ [M+H]⁺: calculated: 485.3184, found: 485.3181.

B(pin) Br B(pin) B(pin)

Pt(dba)₃ (26.9 mg, 0.030 mmol), B₂(pin)₂ (799.9 mg, 3.150 mmol), (*E*)-2-(5-bromopent-1- en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaboro-lane (824.9 mg, 3.000 mmol), and THF (3.00 mL). The crude material was purified (SiO₂, 5% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (528.9 mg, 36%). ¹H NMR (500 MHz, CDCl₃): δ 3.35 (2H, t, *J*= 7.5 Hz), 1.94-1.87 (1H, m), 1.81-1.74 (1H, m), 1.54-1.49 (2H, m), 1.35-1.30 (1H, m), 1.23-1.18 (36H, m), 0.81 (1H, d, *J*= 10.0 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 83.0, 83.0, 45.8, 32.5, 32.2, 25.2, 25.2, 25.1, 25.0, 24.9, 24.8; IR (neat): 2976.6 (m), 1369.5 (m), 1346.5 (m), 1306.5 (s), 1263.8 (m), 1213.5 (m), 1137.3 (s), 968.6 (m), 847.8 (m) cm⁻¹; HRMS-(DART) for: C₂₃H₄₅B₃Br₁O₆ [M+H]⁺: calculated: 529.2679, found: 529.2669.



utilizing Pt(dba)₃ (26.9 mg, 0.030 mmol), B₂(pin)₂ (799.9 mg, 3.150 mmol), (E)-2-(7-

bromohept-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dio-xaborolane (909.1 mg, 3.000 mmol), and THF (3.00 mL). The crude material was purified (SiO₂, 5% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (1.027g, 60%). ¹H NMR (500 MHz, CDCl₃): δ 3.36 (2H, t, *J*= 7.5 Hz), 1.81 (2H, pent, *J*= 7.0 Hz), 1.42-1.31 (7H, m), 1.19-1.18 (36H, m), 0.82 (1H, d, *J*= 10.5 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 82.9, 82.9, 34.2, 33.1, 32.9, 28.6, 27.9, 25.2, 25.1, 25.0, 24.9, 24.9, 24.8; IR (neat): 2976.5 (m), 2929.4 (m), 1464.7 (w), 1369.5 (m), 1346.0 (m), 1306.2 (s), 1265.9 (m), 1139.2 (s), 1108.1 (m), 969.2 (m), 848.6 (m) cm⁻¹; HRMS-(DART) for: C₂₅H₄₉B₃Br₁O₆ [M+H]⁺: calculated: 557.2992, found: 557.3019.

4.9.7. Characterization and Proof of Stereochemistry of Deborylative Alkylation Products.

Note: For analysis of diastereoselectivity, see ¹H NMR spectra in the Spectral Data section



1,3,2-dioxaborolane) (147.6 mg, 0.3000 mmol), 1-bromododecane (49.8 mg, 0.200 mmol), sodium *tert*-butoxide (96.1 mg, 1.00 mmol) and toluene (1.30 mL). The crude material was purified (SiO₂, 20% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (58.6 mg, 93%). ¹H NMR (500 MHz, CDCl₃): δ (major

isomer) 3.44-3.36 (2H, m), 1.98 (2H, br s), 1.52-1.40 (7H, m), 1.38-1.20 (25H, m), 0.90-0.86 (6H, m); ¹³C NMR (126 MHz, CDCl₃): δ (major isomer) 74.5, 33.6, 31.9, 31.8, 29.7, 29.6, 29.6, 29.6, 29.3, 29.3, 25.7, 25.6, 22.7, 22.6, 14.1, 14.1; IR (neat): 3336.9 (br), 2952.6 (m), 2914.2 (s), 2847.0 (s), 1466.3 (s), 1415.2 (w), 1378.1 (w), 1142.1 (m), 1117.1 (m), 1100.3 (m), 1016.7 (m), 850.4 (w), 720.9 (m), 660.7 (w) cm⁻¹; HRMS-(DART) for: C₂₀H₄₁O [M+H-H₂O]⁺: calculated: 297.3157, found: 297.3145.

1-phenyldecane-3,4-diol. Prepared according to the ŌН Me ∠Ph general procedure for deborylative alkylation utilizing ŌН racemic 2,2',2"-(octane-1,1,2-trivl)tris(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (147.6 mg, 0.3000 mmol), (2-bromoethyl)benzene (37.0 mg, 0.200 mmol), sodium tert-butoxide (96.1 mg, 1.00 mmol) and toluene (1.30 mL). The crude material was purified (SiO₂, 20% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (60.4 mg, 80%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.29 (2H, t, J= 8.0 Hz), 7.23-7.18 (4H, m), 3.46-3.42 (2H, m), 2.85 (1H, ddd, J= 14.0, 9.5, 6.0 Hz), 2.71 (1H, ddd, J= 14.0, 9.5, 7.0 Hz) 2.11 (1H, br s), 1.99 (1H, br s), 1.86-1.74 (2H, m), 1.54-1.23 (10H, m), 0.88 (3H, t, J= 6.5 Hz); ¹³C NMR (126 MHz, CDCl₃): δ (major isomer) 141.9, 128.4, 125.9, 74.6, 73.8, 35.3, 33.6, 32.0, 31.7, 29.3, 25.5, 22.6, 14.1; IR (neat): 3360.9 (br), 3063.1 (w), 3026.7 (w), 2926.9 (s), 2856.5 (s), 1603.5 (w), 1496.1 (m), 1176.7 (w), 1130.5 (s), 925.5 (w), 747.4 (m), 724.3 (s) cm⁻¹; HRMS-(DART) for: C₁₆H₂₅O [M+H- H_2O]⁺: calculated: 233.1905, found: 233.1904.

1-phenvlundecane-4,5-diol. Prepared according to OH Me the general procedure for deborylative alkylation Ph ŌΗ utilizing racemic 2,2',2"-(octane-1,1,2-trivl)tris(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (147.6 mg, 0.3000 mmol), (3-bromopropyl)benzene (39.8 mg, 0.200 mmol), sodium tertbutoxide (96.1 mg, 1.00 mmol) and toluene (1.30 mL). The crude material was purified (SiO₂, 20% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (41.8 mg, 79%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.32-7.29 (2H, m), 7.22 (2H, d, J= 7.0 Hz), 3.48-3.40 (2H, m), 2.73-2.63 (2H, m), 2.05 (1H, br s), 1.98 (1H, br s), 1.91-1.82 (1H, m), 1.79-1.70 (1H, m), 1.63-1.42 (6H, m), 1.37-1.27 (6H, m), 0.92 (3H, t, J= 5.0 Hz); ¹³C NMR (126 MHz, CDCl₃): δ (major isomer) 142.2, 128.4, 128.3, 125.8, 74.5, 74.3, 35.8, 33.6, 33.2, 31.8, 29.3, 27.4, 25.6, 22.6, 14.1; IR (neat): 3326.9 (br), 3062.1 (w), 3026.9 (w), 2918.3 (s), 2851.8 (s), 1605.3 (w), 1494.5 (m), 1456.4(m), 1334.5 (m), 1286.4 (m), 1226.0 (w), 1067.1 (m), 1019.7 (m), 938.4 (w), 854.6 (m), 746.3 (s), 719.5 (s), 695.9 (s), 491.6 (m) cm⁻¹; HRMS-(DART) for: $C_{17}H_{29}O_2$ $[M+H]^+$: calculated: 265.2168, found: 265.2168.

Ne Ne Ne Ne for deborylative alkylation utilizing racemic 2,2',2"-(octane-1,1,2-triyl)tris(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (147.6 mg, 0.3000 mmol), (3bromopropyl)benzene (39.8 mg, 0.200 mmol), sodium *tert*-butoxide (96.1 mg, 1.00 mmol) and toluene (1.30 mL). The crude material was purified (SiO₂, 20% ethyl acetate in hexane, UV/magic stain) to give the desired product as a clear, colorless oil (41.8 mg, 79%). All spectral data are in accordance with the literature.⁴³ HRMS-(DART) for: $C_9H_{19}O[M+H-H_2O]^+$: calculated: 143.1436, found: 143.1442.

2-methylundecane-4.5-diol. Prepared according to the OH Me general procedure for deborylative alkylation utilizing Me Me ŌΗ racemic 2,2',2"-(octane-1,1,2-trivl)tris(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (147.6 mg, 0.3000 mmol), 1-bromo-2-methylpropane (27.4 mg, 0.200 mmol), sodium tertbutoxide (96.1 mg, 1.00 mmol) and toluene (1.30 mL). The crude material was purified (SiO₂, 20% ethyl acetate in hexane, UV/magic stain) to give the desired product as a clear, colorless oil (34.4 mg, 85%). ¹H NMR (500 MHz, CDCl₃): δ 3.48 (1H, dt, J= 9.0, 4.5 Hz), 3.37-3.34 (1H, m), 2.20 (2H, br s), 1.86-1.78 (1H, m), 1.51-1.20 (12H, m), 0.94 (3H, s, J=7.0 Hz), 0.92 (3H, d, J=6.5 Hz), 0.88 (3H, t, J=6.0 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 75.0, 72.5, 42.7, 33.6, 31.8, 29.3, 25.6, 25.0, 23.7, 22.6, 21.7, 14.0; IR (neat): 3363.2 (br), 2954.8 (s), 2927.4 (s), 2858.6 (s), 1466.9 (m), 1382.9 (w), 1367.2 (w), 1147.6 (w), 1066.5 (m), 843.5 (w) cm⁻¹; HRMS-(DART) for: $C_{12}H_{25}O [M+H-H_2O]^+$: calculated: 185.1905, found: 185.1904.

Me undec-1-ene-4,5-diol. Prepared according to the general procedure for deborylative alkylation utilizing racemic 2,2',2"-(octane-1,1,2-triyl)tris(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (147.6 mg, 0.3000 mmol), allyl chloride (15.3 mg, 0.200 mmol), sodium *tert*-butoxide (96.1 mg, 1.00 mmol) and toluene (1.30 mL). The crude material was purified (SiO₂, 20% ethyl acetate in hexane, UV/magic stain) to give the desired product as a clear, colorless oil

⁴³ Li, X.; Tanasova, M.; Vasileiou, C.; Borhan, B. J. Am. Chem. Soc. 2008, 130, 1885.

(34.7 mg, 93%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 5.85 (1H, ddt, *J*= 17.5, 10.5, 7.5 Hz), 5.17-5.14 (2H, m), 3.51-3.43 (2H, m), 2.38-2.32 (1H, m), 2.26-2.20 (3H, m), 1.53-1.42 (3H, m), 1.37-1.25 (7H, m), 0.87 (3H, t, *J*= 7.0 Hz); ¹³C NMR (126 MHz, CDCl₃): δ (major isomer) 134.5, 118.1, 73.9, 73.3, 38.3, 33.5, 31.8, 29.3, 25.6, 22.6, 14.0; IR (neat): 3376.1 (br), 3077.3 (w), 2954.8 (s), 2926.9 (s), 2857.1 (s), 1641.4 (w), 1458.7 (m), 1433.6 (m), 1285.7 (w), 1128.9 (w), 1062.5 (m), 996.1 (m), 913.1 (m), 870.4 (w) cm⁻¹; HRMS-(DART) for: C₁₁H₂₃O₂ [M+H]⁺: calculated: 187.1698, found: 187.1692.

1-phenvlnonane-2,3-diol. Prepared according to the ОH Me general procedure for deborylative alkylation utilizing ŌН racemic 2,2',2"-(octane-1,1,2-triyl)tris(4,4,5,5-tetramethyl-1,3,2-dioxaboro-lane) (147.6 mg, 0.3000 mmol), benzyl chloride (25.3 mg, 0.200 mmol), sodium tert-butoxide (96.1 mg, 1.00 mmol) and toluene (1.30 mL). The crude material was purified (SiO₂, 20% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (42.6 mg, 90%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.32 (2H, t, J= 8.0 Hz), 7.26-7.23 (3H, m), 3.68 (1H, dt, J= 8.5, 4.5 Hz), 3.49 (1H, dt, J= 8.5, 4.5 Hz), 2.90 (1H, dd, J= 13.5, 4.5 Hz), 2.75 (1H, dd, J= 13.5, 9.0 Hz), 2.09 (1H, br s), 1.97 (1H, br s), 1.59-1.23 (10H, m), 0.87 (3H, t, J=7.0 Hz); ¹³C NMR (100 MHz, CDCl₃); δ (major isomer) 138.1, 129.4, 128.6, 126.6, 75.0, 73.6, 40.3, 33.7, 31.8, 29.3, 25.6, 22.6, 14.1; IR (neat): 3379.6 (br), 3062.4 (w), 2953.6 (s), 2925.7 (s), 2856.0 (s), 1603.8 (w), 1495.7 (m), 1454.9 (m), 1179.7 (w), 1128.8 (m), 1060.7 (m), 747.7 (m), 699.3 (s) 514.4 (w) cm⁻¹; HRMS-(DART) for: $C_{15}H_{23}O[M+H-H_2O]^+$: calculated: 219.1749, found: 219.1751.

1-chlorotetradecane-7.8-diol. Prepared OH Me accord-ing to the general procedure for CI ŌΗ utilizing deborylative alkylation racemic 2,2',2"-(octane-1,1,2-triyl)tris-(4,4,5,5tetramethyl-1,3,2-dioxaborolane) (147.6 mg, 0.3000 mmol), 1-bromo-6-chlorohexane (39.9 mg, 0.200 mmol), sodium tert-butoxide (96.1 mg, 1.00 mmol) and toluene (1.30 mL). The crude material was purified (SiO₂, 20% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (43.0 mg, 81%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 3.53 (2H, t, J= 7.0 Hz), 3.42-3.38 (2H, m), 2.07 (1H, br s), 2.00 (1H, s), 1.78 (2H, dt, J= 14.0, 7.0 Hz), 1.52-1.25 (18H, m), 0.88 (3H, t, J= 7.0 Hz); ¹³C NMR (126 MHz, CDCl₃): δ (major isomer) 74.5, 74.4, 45.1, 33.6, 33.5, 32.5, 31.8, 29.3, 28.9, 26.8, 25.6, 25.5, 22.6, 14.0; IR (neat): 3337.8 (br), 2928.4 (s), 2854.7 (s), 1463.4 (m), 1408.1 (w), 1377.5 (w), 1284.1 (w), 1135.0 (m), 1009.7 (m), 724.8 (m), 652.1 (m) cm^{-1} ; HRMS-(DART) for: $C_{14}H_{28}ClO$ [M+H-H₂O]⁺: calculated: 247.1829, found: 247.1820.



1-phenylhex-5-ene-2,3-diol. Prepared according to the general procedure for deborylative alkylation utilizing racemic 2,2',2"-(3-phenylpropane-1,1,2-triyl)tris(4,4,5,5-tetramethyl-1,3,2-dioxabor-

olane) (149.4 mg, 0.3000 mmol), allyl chloride (15.3 mg, 0.200 mmol), sodium *tert*butoxide (96.1 mg, 1.00 mmol) and toluene (1.30 mL). The crude material was purified (SiO₂, 20% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (32.1 mg, 83%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.33-7.30 (2H, m), 7.25-7.22 (3H, m), 5.85 (1H, ddt, *J*= 17.5, 10.5, 7.5 Hz), 5.17-5.13 (2H, m), 3.72 (1H, dt, J= 8.5, 4.0 Hz), 3.57 (1H, dt, J= 8.5, 4.0 Hz), 2.90 (1H, dd, J= 14.0, 5.0 Hz), 2.78 (1H, dd, J= 14.0, 9.0 Hz), 2.41-2.29 (2H, m), 2.13 (1H, br s), 2.01(1H, br s); ¹³C NMR (100 MHz, CDCl₃): δ (major isomer) 138.3, 134.6, 129.6, 128.8, 126.8, 118.4, 74.6, 72.4, 40.4, 38.6; IR (neat): 3377.7 (br), 2919.4 (m), 1495.1 (m), 1454.0 (m), 1434.0 (m), 1077.0 (m), 1041.6 (s), 994.8 (m), 914.0 (s), 868.8 (m), 745.1 (m), 698.2 (s) cm⁻¹; HRMS-(DART) for: C₁₂H₁₅O [M+H-H₂O]⁺: calculated: 175.1123, found: 175.1122. The relative configuration (*syn* diol) was assigned by comparing the ¹H and ¹³C NMR spectra of the prepared sample of the title compound with the spectra of *syn*-1-phenylhex-5-ene-2,3-diol previously reported in the literature.⁴⁴



1,6-diphenylhexane-2,3-diol. Prepared according to the general procedure for deborylative alkylation utilizing racemic 2,2',2"-(3-phenylpropane-1,1,2-triyl) tris(4,4,5,5-

tetramethyl-1,3,2-dioxaborolane) (149.4 mg, 0.3000 mmol), (3-bromopropyl)benzene (39.8 mg, 0.200 mmol), sodium *tert*-butoxide (96.1 mg, 1.00 mmol) and toluene (1.30 mL). The crude material was purified (SiO₂, 20% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (46.5 mg, 88%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.31-7.17 (10H, m), 3.67 (1H, dt, *J*= 9.0, 4.5 Hz), 3.50 (1H, dt, *J*= 8.5, 4.5 Hz), 2.86 (1H, dd, *J*= 14.0, 5.0 Hz), 2.73 (1H, dd, *J*= 14.0, 9.0 Hz), 2.70-2.60 (2H, m), 2.04 (2H, br s), 1.89-1.80 (1H, m), 1.76-1.67 (1H, m), 1.64-1.54 (2H, m); ¹³C NMR (100 MHz, CDCl₃): δ (major isomer) 142.4, 138.2, 129.6, 128.9, 128.6, 128.5, 126.8, 126.0, 75.1, 73.5, 40.4, 36.0, 33.4, 27.6; IR (neat): 3377.7 (br), 2976.8 (m), 2924.6

⁴⁴ Jiao, P.; Kaasaki, M.; Yamamoto, H. Angew. Chem. Int. Ed. 2009, 48, 3333.

(m), 1312.7 (m), 1264.9 (s), 1137.9 (s), 969.7 (m), 844.5 (m) cm⁻¹; HRMS-(DART) for: $C_{18}H_{21}O [M+H-H_2O]^+$: calculated: 253.1592, found: 253.1587.

Me OH Me OH Me OH Me OH Tracemic 2,2',2"-(4-methylpentane-1,1, 2-trivl)tris(4,4,5,5-

tetramethyl-1,3,2-dioxaborolane) (139.2 mg, 0.3000 mmol), (3-bromopropyl)benzene (39.8 mg, 0.200 mmol), sodium *tert*-butoxide (96.1 mg, 1.00 mmol) and toluene (1.30 mL). The crude material was purified (SiO₂, 20% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (33.6 mg, 71%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.28-7.25 (2H, m), 7.18-7.15 (3H, m), 3.46 (1H, dt, J= 8.5, 4.0 Hz), 3.37 (1H, dt, J= 8.5, 4.5 Hz), 2.69-2.58 (2H, m), 2.04 (1H, br s), 1.92(1H, br s), 1.85-1.74 (2H, m), 1.72-1.66 (1H, m), 1.58-1.43 (2H, m), 1.39 (1H, ddd, J= 14.5, 10.0, 5.0 Hz), 1.91 (1H, ddd, J= 13.0, 9.5, 3.5 Hz), 0.92 (3H, d, J= 7.0 Hz), 0.89(3H, d, J= 6.5 Hz); ¹³C NMR (100 MHz, CDCl₃): δ (major isomer) 142.4, 128.6, 128.5, 126.0, 75.0, 72.7, 42.9, 36.0, 33.8, 27.6, 24.7, 23.9, 21.9; IR (neat): 3363.5 (br), 2951.6 (m), 2927.7 (m), 2866.8 (m), 1495.9 (m), 1453.4 (m), 1142.1 (m), 1064.1 (m), 1030.3 (m), 746.9 (m), 697.3 (s), 489.6 (m) cm⁻¹; HRMS-(DART) for: C₁₅H₂₃O [M+H-H₂O]⁺: calculated: 219.1749, found: 219.1951.



15-methyl-1-phenylhexadec-14-ene-4,5-diol . Prepared according to the general procedure for deborylative

alkylation utilizing racemic 2,2',2"-(12-methyltridec-11-ene-1,1,2-triyl)tris(4,4,5,5tetramethyl-1,3,2- dioxaborolane) (172.3 mg, 0.3000 mmol), (3-bromopropyl)benzene (39.8 mg, 0.200 mmol), sodium *tert*-butoxide (96.1 mg, 1.00 mmol) and toluene (1.30 mL). The crude material was purified (SiO₂, 20% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid (46.3 mg, 67%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.27-7.24 (2H, m), 7.17-7.14 (3H, m), 5.10 (1H, tt, *J*= 7.0, 1.5 Hz), 3.43-3.36 (2H, m), 2.68-2.58 (2H, m), 1.94 (2H, q, *J*= 6.5 Hz), 1.85-1.77 (1H, m), 1.72-1.67 (4H, m), 1.65-1.35 (7H, m), 1.30-1.26 (12H, m); ¹³C NMR (100 MHz, CDCl₃): δ (major isomer) 142.4, 131.3, 128.6, 128.5, 126.0, 125.1, 74.7, 74.5, 36.0, 33.8, 33.4, 30.1, 29.8, 29.7, 29.7, 29.5, 28.2, 27.6, 25.9, 25.8, 17.9; IR (neat): 3385.0.3 (br), 2925.0 (s), 2854.0 (m), 1603.3 (m), 1496.1 (m), 1454.0 (m), 1376.7 (w), 1313.2 (m), 1069.5 (m), 1030.1 (m), 747.9 (m), 698.8 (m), 558.2 (w) cm⁻¹; HRMS-(DART) for: C₂₃H₃₇O [M+H-H₂O]⁺: calculated: 329.2844, found: 329.2846.



1-((*tert***-butyldimethylsilyl)oxy)-7-phenylheptane-3,4-diol.** Prepared according to the general procedure for deborylative alkylation utilizing racemic *tert*-

butyldimethyl(3,4,4-tris-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)butoxy)silane (169.9 mg, 0.3000 mmol), (3-bromopropyl)benzene (39.8 mg, 0.200 mmol), sodium *tert*butoxide (96.1 mg, 1.00 mmol) and toluene (1.30 mL). The crude material was purified (SiO₂, 20% ethyl acetate in hexane, UV/magic stain) to give the desired product as a clear, colorless oil (61.2 mg, 94%). Diastereoselectivity was determined by SFC (see spectral data section). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 7.27 (2H, t, *J*= 7.5 Hz), 7.19-7.16 (3H, m), 3.90-3.82 (2H, m), 3.68 (1H, dt, J= 3.0, 7.5 Hz), 3.57 (1H, d, J= 7.5 Hz), 3.45 (1H, dt, J= 11.0, 5.5 Hz), 2.65 (1H, dt, J= 6.5, 8.5 Hz), 2.60 (1H, d, J= 5.5 Hz), 1.90-1.63 (4H, m), 1.58-1.51 (2H, m), 0.90 (9H, s), 0.09 (6H, s); ¹³C NMR (126 MHz, CDCl₃): δ (major isomer) 142.4, 128.4, 128.3, 125.7, 74.2, 74.1, 62.0, 35.9, 35.1, 33.1, 27.6, 25.8, 18.1, -5.6, -5.6; IR (neat): 3402.9 (br), 3026.6 (w), 2950.8 (s), 2928.2 (s), 2856.8 (s), 1496.3 (w), 1471.0 (m), 1462.1 (m), 1361.2 (w), 1254.3 (s), 1090.6 (br), 1005.9 (m), 938.0 (m), 834.9 (s), 776.8 (s), 747.9 (m), 698.6 (m), 663.6 (w) cm⁻¹; HRMS-(DART) for: C₁₁H₂₃O [M+H]⁺: calculated: 339.2356, found: 339.2345.

2-methyldecane-3,4-diol. Prepared according to the OH Me general procedure for deborylative alkylation utilizing Me ŌH Me racemic 2,2',2"-(octane-1,1,2-triyl)tris-(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (147.6 mg, 0.3000 mmol), 2-bromopropane (24.6 mg, 0.200 mmol), sodium tert-butoxide (96.1 mg, 1.00 mmol) and toluene (1.30 mL). The crude material was purified (SiO₂, 20% ethyl acetate in hexane, UV/magic stain) to give the desired product as a clear, colorless oil (28.5 mg, 76%). ¹H NMR (500 MHz, CDCl₃): δ (major isomer) 3.59 (1H, dt, J= 8.0, 4.5 Hz), 3.13 (1H, t, J= 5.0 Hz), 2.14 (1H, br s), 1.79 (1H, sept, J= 7.0 Hz), 1.50-1.25 (10H, m), 0.96 (3H, d, J=7.0 Hz), 0.93 (3H, d, J=6.5 Hz), 0.88 (3H, t, J=7.0 Hz); ¹³C NMR (126 MHz, CDCl₃): δ (major isomer) 79.0, 71.9, 33.9, 31.8, 30.1, 29.3, 25.6, 22.6, 19.7, 17.0, 14.0; IR (neat): 3378.4 (br), 2956.6 (s), 1926.6 (s), 2871.7 (s), 2857.2 (s), 1466.4 (m), 1383.5 (w), 1366.6 (w), 1176.9 (w), 1063.2 (m), 998.9 (m), 725.5 (w) cm⁻¹; HRMS-(DART) for: $C_{11}H_{23}O[M+H-H_2O]^+$: calculated: 171.1749, found: 171.1751.

anti-cyclopentane-1,2-diol. Prepared according to the general procedure for OH OH deborvlative cyclization/oxidation utilizing racemic 2,2',2"-(5chloropentane-1,1,2-triyl)tris(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (96.9 mg, 0.2000 mmol). 2,2',2"-(5-bromopentane-1,1,2-triyl)tris(4,4,5,5tetramethyl-1.3.2or dioxaborolane) (105.8 mg, 0.2000mmol), sodium tert-butoxide (96.1 mg, 1.00 mmol) and toluene (0.87 mL). The crude material was purified (SiO₂, 50% ethyl acetate in hexane, magic stain) to give the desired product as a white solid (9.0 mg, 44% from chloro-1,1,2tris(boronate)esters, 7.4 mg, 36% from bromo-1,1,2- tris(boronate)esters). All spectral data are in accordance with the literature.⁴⁵ The relative configuration (anti diol) was assigned by comparing the ¹H and ¹³C NMR spectra of the prepared sample of the title compound with the spectra of anti-cyclopentane-1,2-diol previously reported in the literature.45

anti-cyclohexane-1,2-diol. Prepared according to the general procedure for OH OH deborylative cyclization/oxidation utilizing 2,2',2"-(6racemic chlorohexane-1,1,2-triyl)tris(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (99.7 mg, 0.2000 2,2',2"-(6-bromohexane-1,1,2-triyl)tris (4,4,5,5-tetramethyl-1,3,2mmol), or dioxaborolane) (111.4 mg, 0.2000mmol), sodium tert-butoxide (96.1 mg, 1.00 mmol) and toluene (0.87 mL). The crude material was purified (SiO₂, 50% ethyl acetate in hexane, magic stain) to give the desired product as a white solid (15.6 mg, 67% from chloro-1,1,2-tris(boronate)esters, 14.4 mg, 62% from bromo-1,1,2- tris(boronate)esters). All spectral data are in accordance with the literature.⁴⁵ The relative configuration (*anti* diol)

⁴⁵ Muller, C.E.; Wanka, L.; Jewell, K.; Schreiner, P.R. *Angew. Chem. Int. Ed.* **2008**, *47*, 6180.

was assigned by comparing the ¹H and ¹³C NMR spectra of the prepared sample of the title compound with the spectra of *anti*-cyclohexane-1,2-diol previously reported in the literature.⁴⁵

OH anti-cycloheptane-1,2-diol. Prepared according to the general procedure OH for deborylative cyclization/oxidation utilizing racemic 2,2',2"-(7bromoheptane-1,1,2-triyl)tris(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (113.4 mg, 0.2000mmol), sodium *tert*-butoxide (96.1 mg, 1.00 mmol) and toluene (0.87 mL). The crude material was purified (SiO₂, 50% ethyl acetate in hexane, magic stain) to give the desired product as a white solid (15.1 mg, 58%). All spectral data are in accordance with the literature.⁴⁵ The relative configuration (*anti* diol) was assigned by comparing the ¹H and ¹³C NMR spectra of the prepared sample of the title compound with the spectra of *anti*-cyclohexane-1,2-diol previously reported in the literature.⁴⁵

4.9.8. Additional transformations of 1,1,2-Tris(boronate) Esters.

Procedure for deborylative cyclization/homologation/oxidation of 2,2',2"-(6-chlorohexane-1,1,2-triyl)tris(4,4,5,5-tetramethyl-1,3,2-dioxaborolane)





chlorohexane-1,1,2-triyl)tris(4,4,5,5-tetramethyl-1,3,2-dioxaborolane) (99.7 mg, 0.2000 mmol) and sodium *tert*-butoxide (96.1 mg, 1.00 mmol), followed by toluene (0.87 mL). The reaction vessel was sealed with a polypropylene cap, taped, and brought out of the glovebox where it was allowed to stir at room temperature for 14 hours. The reaction mixture was pushed through a silica gel plug with diethyl ether, and the obtained crude was used in next step without future purification.

To an oven-dried 2-dram vial equipped with a septum cap was added the crude material followed by THF (2.0 mL), and the flask cooled to 78°C. To the reaction vial was added bromochloromethane (28 μ L, 0.44 mmol) and *n*-BuLi (0.18 mL, 0.44 mmol), sequentially. After 10 min, the cooling bath was removed and the contents stirred for 12 h. The reaction mixture was then transferred to a 6-dram vial and diluted with THF (2 mL). The crude mixture was cooled to 0 °C and 3M NaOH (1.5 mL) was added, followed by 30% H₂O₂ (1.0 mL), dropwise. The reaction mixture was allowed to warm to room temperature, and was allowed to stir at room temperature for 4 hours. The reaction mixture was cooled to 0 °C and saturated aq. Na₂S₂O₃ (1.5 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure and purified by silica gel chromatography (50% ethyl acetate in hexane) give the desired product as a colorless oil (10.4 mg, 36% yield). All spectral data are in accordance with the

literature.⁴⁶ The relative configuration (*anti*) was assigned by comparing the ¹H and ¹³C NMR spectra of the prepared sample of the title compound with the spectra of *anti*-cyclohexane-1,2-diyldimethanol previously reported in the literature.⁴⁶

4.9.9. Procedures for the Formal Synthesis of exo-Brevicomin.

B(pin) 4,4,5,5-tetramethyl-2-((4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)methyl)-B(pin) 1,3,2-diox-aborolane. To an oven-dried 150 mL round-bottomed flask equipped with a stirbar was added copper(I) iodide (571 mg, 3.00 mmol) and lithium methoxide (3.42 g, 90.0 mmol) in the glovebox. The flask was sealed with a septum, brought out of the glovebox, and DMF (40 mL) was added. To the stirring mixture under nitrogen was added a solution of bis(pinacolato)diboron (15.2 g, 60.0 mmol) in DMF (20 mL total, with washings), resulting in a dark black solution. Next, to the stirring solution was added dibromomethane (4.17 mL, 60.0 mmol), dropwise. The reaction mixture was allowed to stir at room temperature for 24 hours, at which point the mixture was diluted with diethyl ether (40 mL) and run through a layer of celite. The resulting solution was concentrated under reduced pressure, and the resulting residue was diluted with hexane (50 mL) and washed with deionized H₂O (3 x 50 mL). The organic layers were combined, dried over sodium sulfate, filtered and concentrated under reduced pressure to

⁴⁶ Zhang, X.; Huang, K.; Hou, G.; Cao, B.; Zhang, X. Angew. Chem. **2010**, *122*, 6565.

provide the title compound as a clear, colorless oil (5.99 g, 75%). No further purification was necessary. All spectral data are in accordance with the literature.⁴⁷

(E)-2-(but-1-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. B(pin) Me[^] To an oven-dried 250 mL round-bottomed flask equipped with a stirbar was added lithium tetramethylpiperidide (LTMP, 2.33 g, 15.8 mmol), and the flask was sealed and brought out of the glovebox. To the reaction flask was added THF (40 mL), and the solution was cooled in an ice bath to 0 °C. Once the solution was cooled, a solution of 4,4,5,5-tetramethyl-2-((4,4,5,5-tetramethyl-1,3-dioxolan-2-yl)methyl)-1,3,2-diox-aborolane (3.85 g, 14.4 mmol) in THF (17 mL) was added dropwise, and the reaction mixture was allowed to stir at 0 °C for 5 minutes. Next, propionaldehyde (1.13 mL, 15.8 mmol) was added dropwise at 0 °C, and the mixture was allowed to stir at this temperature for an After completion, the reaction mixture was warmed to room additional 3 hours. temperature, diluted with diethyl ether (50 mL) and run through a pad of silica gel (100% diethyl ether). The resulting mixture was concentrated under reduced pressure and purified using silica gel comlumn chromatography (2.5% ethyl acetate in hexane) to provide the title compound as a clear, colorless oil as a 97:3 mixture of E:Z isomers (1.99 g, 76%). All spectral data are in accordance with the literature.⁴⁸ Note: The addition of propionaldehyde can also be performed at -78 $^{\circ}$ C to provide higher E:Z ratios (99:1).

 ⁴⁷ Hong, K.; Liu, X.; Morken, J.P. J. Am. Chem. Soc. 2014, 136, 10581.
⁴⁸ Bruckner, R.; Burghart-Stoll, H. Org. Lett. 2011, 13, 2730.

(R)-2,2',2''-(butane-1,1,2-triyl)tris(4,4,5,5-tetramethyl-1,3,2-B(pin) B(pin) Me dioxaboro-lane). Prepared according to the general procedure in a B(pin) 15 mL pressure vessel utilizing Pt(dba)₃ (80.8 mg, 0.0900 mmol), (*R*,*R*)-4.9 (165 mg, 0.1800 mmol), $B_2(cat)_2$ (1.43 g mg, 6.00 mmol), (E)-2-(but-1-en-1-yl)-4,4,5,5tetramethyl-1,3,2-dioxaborolane (546 mg, 3.00 mmol), and THF (3.0 mL), followed by pinacol (4.25 g, 36.0 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane, UV/magic stain) to give the desired product as a white solid, which co-eluted with $B_2(pin)_2$ (1.46 g, product: $B_2(pin)_2 = 1.00:0.75, 77\%$). ¹H NMR (500 MHz, CDCl₃): δ 3.63 (1H, dt, J= 6.0, 10.5 Hz), 3.53 (1H, dt, J= 6.0, 10.5 Hz), 1.76-1.69 (1H, m), 1.49-1.38 (2H, m), 1.33-1.16 (37H, m), 0.89-0.85 (4H, m); ¹³C NMR (126 MHz, CDCl₃): δ 82.7, 82.6, 26.0, 25.0, 24.8, 24.8, 24.6, 24.6, 13.2; IR (neat): 2977.2 (m), 2930.6 (w), 1464.5 (w), 1370.3 (s), 1348.3 (s), 1306.6 (s), 1278.7 (s), 1212.6 (w), 1139.2 (s), 1123.7 (s), 969.1 (m), 848.8 (s), 835.0 (s), 668.4 (w), 555.3 (w) cm⁻¹; HRMS-(DART) for: $C_{22}H_{44}B_{3}O_{6}[M+H]^{+}$: calculated: 437.3417, found: 437.3420. $[\alpha]_{D}^{20} = -14.107$ (c = 1.015, $CHCl_{3}, l = 50 \text{ mm}$).

Me (3*S*,4*S*)-non-8-ene-3,4-diol. Prepared according to the general procedure for deborylative alkylation utilizing (*R*)-2,2',2"-(butane-1,1,2-triyl)tris(4,4,5,5-tetramethyl-1,3,2-dioxaboro-lane) (218.0 mg, 0.5000 mmol), 5-bromopent-1-ene (62.1 mg, 0.417 mmol), sodium *tert*-butoxide (200 mg, 2.08 mmol) and toluene (2.20 mL). The crude material was purified (SiO₂, 30% ethyl acetate in hexane, UV/magic stain) to give the desired product as a clear, colorless oil, which co-eluted with pinacol (166.6 mg, product:pinacol = 1.00:3.31, 73%). All spectral data are in accord with the literature.⁴⁹ HRMS-(DART) for: $C_9H_{19}O_2 [M+H]^+$: calculated: 159.1385, found: 159.1385. $[\alpha]_D^{20} = -16.200 \ (c = 1.695, CHCl_3, l = 50 \text{ mm}).$

Analysis of stereochemistry:

Racemic compound was prepared according to the same procedure utilizing racemic 2,2',2"-(butane-1,1,2-triyl)tris(4,4,5,5-tetramethyl-1,3,2-dioxaboro-lane) and 5bromopent-1-ene. Further analysis of stereochemistry was performed on non-8-ene-3,4diol. Absolute stereochemistry was assigned by comparing the specific rotation of the title compound to that of (3R,4R)-non-8-ene-3,4-diol.⁴⁹ Diastereoselectivity was determined by both GLC (14:1 *syn:anti*) and ¹H NMR (16:1 *syn:anti*) analysis.

⁴⁹ Page, P.C.B.; Rayner, C.M.; Sutherland, I.O. J. Chem.Soc. Perkin Trans. I. 1990, 5, 1375.

Chiral GLC (β -dex 225, Supelco, 100 °C for 5 min, ramp 3 °C/min to 160 °C, 20 psi) – analysis of (3S,4S)-non-8-ene-3,4-diol





Racemic Material

Standard Conditions

| Peak # | RetTime [min] | Туре | Width [min] | Area [pA*s] | Height [pA] | Area % | Peak # | RetTime [min] | Туре | Width [min] | Area [pA*s] | Height [pA] | Area % |
|-----------|------------------|------|----------------|----------------|----------------|-----------|-----------|------------------|------|----------------|----------------|----------------|-----------|
| | | | | | | | | | | | | | |
| 1 | 19.981 | MF | 0.3543 | 248.50932 | 11.69048 | 50.13722 | 1 | 20.201 | MM | 0.1734 | 47.68409 | 4.58331 | 10.48614 |
| 2 | 21.065 | FM | 0.4503 | 247.14902 | 9.14740 | 49.86278 | 2 | 20.909 | MM | 0.4881 | 407.05023 | 13.89834 | 89.51386 |
| Tota | ls : | | | 495.65834 | 20.83788 | | Total | .s : | | | 454.73433 | 18.48165 | |



| Peak # | RetTime [min] | Туре | Width [min] | Area [pA*s] | Height [pA] | Area % |
|-----------|------------------|------|----------------|----------------|----------------|-----------|
| | | | | | | |
| 1 | 20.201 | MM | 0.1734 | 47.68409 | 4.58331 | 9.78884 |
| 2 | 20.909 | MM | 0.4881 | 407.05023 | 13.89834 | 83.56141 |
| 3 | 23.286 | MM | 0.2578 | 32.39273 | 2.09410 | 6.64975 |
| | | | | | | |
| Total | s: | | | 487.12706 | 20.57575 | |

Standard Conditions-Analysis of Diastereoselectivity

4.9.10. Representative Procedure for Pd-Catalyzed Suzuki Coupling of 1,1,2-

Tris(boronates).





1-phenyloctane-1,2-diol. In the glovebox in a 2-dram oven-dried vial was added tris(boronate) ester 4.44 (73.8 mg, 0.150 mmol)

followed by NaOH (12.0 mg, 0.300 mmol), THF (0.77 mL) and Pd(OAc)₂/Ad₂PnBu (added as a 1:1 solution in THF (0.035 M); 0.14 mL). Next, bromobenzene (15.7 mg, 0.100 mmol) was added to the reaction vessel, and the vial was sealed with a septum cap and brought out of the glove box. To the vial was added DI H₂O (sparged with N₂) under N₂ through the septum cap. The vial was heated to 70 °C and was allowed to stir for 3 hours. The reaction mixture was transferred to a 6-dram vial, cooled to 0 °C and charged with 3 M NaOH (1.5 mL), and 30% H₂O₂ (1 mL). The reaction was gradually warmed to room temperature and allowed to stir for 4 hours at which time the vial was cooled to 0 °C. To the vial was added saturated aqueous sodium thiosulfate (2 mL) dropwise over 5 minutes. The reaction mixture was diluted with ethyl acetate (3x10 mL) and the combined organics were dried over Na₂SO₄, filtered, and concentrated. The crude reaction mixture was purified by column chromatography (0-

30% ethyl acetate in hexanes) to provide the title product as a clear, colorless oil (16.7 mg, 75%). Spectral data are in accordance with the literature values.⁵⁰ ¹H NMR (500 MHz, CDCl₃): δ (*anti*-diol) δ 7.38-7.33 (4H, m), 7.32-7.29 (1H, m), 4.69 (1H, d, *J*= 4.5 Hz), 3.84 (1H, dt, *J* = 8.0, 4.0 Hz), 1.50-1.22 (10 H, m), 0.92-0.82 (3H, m); (*syn*-diol) δ 7.38-7.33 (4H, m), 7.32-7.29 (1H, m), 4.45 (1H, d, *J*= 6.5 Hz), 3.84 (1H, ddd, *J* = 8.5, 6.5, 3.5 Hz), 1.50-1.22 (10 H, m), 0.92-0.82 (3H, m); ¹³C NMR (125 MHz, CDCl₃): (*syn*-and *anti*-diol) δ 141.2, 140.4, 128.5, 128.4, 128.1, 127.9, 126.8, 77.9, 77.1, 76.0, 75.2, 32.7, 31.8, 31.7, 31.7, 29.7, 29.2, 29.2, 25.8, 25.6, 22.6, 22.5, 14.0; IR (neat): 3414.3 (br s), 2953.5 (m), 2923.9 (s), 2855.3 (m), 1494.5 (w), 1378.2 (w), 1076.8 (w), 1055.5 (w), 1026.8 (w), 760.6 (w), 700.8 (s) cm⁻¹.

4.9.11. Boron-Wittig Reaction of 1,1,2-Tris(boronate) Esters



added (R)-2,2',2"-(octane-1,1,2-trivl)tris (4,4,5,5-tetramethyl-1,3,2-

dioxaborolane) (73.8 mg, 0.150 mmol), and THF (0.25mL). The reaction vessel was

glovebox

was

⁵⁰ Bellucci, G.; Chiappe, C.; Cordoni, A. Tetrahedron: Asymmetry 1996, 7, 197.

sealed with a septum cap, taped, and brought out of the glovebox where it was cooled to 0 °C. A solution of LiTMP (22.1mg in 0.44mL THF) was added dropwise by syringe and the reaction mixture was allowed to stir at 0 °C for 5 minutes. Next, to the reaction vessel was added a solution of benzaldehyde (10.6 mg in 0.11mL THF) dropwise, and the reaction mixture was allowed to warm to 60 °C and stir for additional 2 hours. After completion, the reaction mixture was concentrated under reduced pressure and purified by silica gel chromatography (2% ethyl acetate in hexane) to give the desired product as a colorless oil (35.0 mg, 77%). ¹H NMR (500 MHz, CDCl₃): δ 7.29 (2H, d, *J*= 7.5 Hz), 7.21 (2H, t, J=7.0 Hz), 7.13 (1H, tt, J=7.5, 1.5 Hz), 6.86 (1H, s), 1.99 (1H, t, J=8.0 Hz), 1.70-1.65 (1H, m), 1.57-1.52 (1H, m), 1.36-1.21 (32H, m), 0.85 (3H, t, J= 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 139.8, 138.8, 128.3, 127.9, 126.7, 83.6, 83.3, 32.0, 30.7, 29.6, 29.5, 25.1, 25.0, 24.9, 22.9, 14.3; IR (neat): 2977.5 (m), 2925.9 (m), 2855.4 (m), 1465.2 (m), 1388.6 (m), 1370.5 (m), 1304.6 (s), 1252.3 (m), 1141.8 (s), 966.5 (m), 858.5 (m), 696.2 (m) cm⁻¹; HRMS-(DART) for: $C_{27}H_{45}B_2O_4$ [M+H]⁺: calculated: 455.3504, found: 455.3518.

Me (S)-3-hydroxy-1-phenylnonan-2-one. To a 6-dram vial equipped with a magnetic stirbar was added (S,E)-2,2'-(1-phenylnon-1-ene-2,3-diyl)bis(4,4,5,5-tetra-

methyl-1,3,2-dioxaborolane) (35.0 mg, 0.077 mmol), and THF (2.0 mL). Then the reaction mixture was cooled to 0 °C and pH 7.0 buffer (2.0 mL) was added, followed by 30% H₂O₂ (1.0 mL) dropwise. The reaction mixture was allowed to warm to room temperature, and was allowed to stir at room temperature for 18 hours. The reaction
mixture was cooled to 0 °C and saturated aq. Na₂S₂O₃ (1.5 mL) was added dropwise. The reaction mixture was allowed to warm to room temperature and the aqueous layer was extracted with ethyl acetate (3 x 20 mL). The combined organic layers were dried over Na₂SO₄, filtered, and concentrated under reduced pressure and purified by silica gel chromatography (5% ethyl acetate in hexane) to give the desired product as a colorless oil (13.6 mg, 85%). ¹H NMR (500 MHz, CDCl₃): δ 7.32 (2H, tt, *J*= 7.0, 1.5 Hz), 7.26 (1H, tt, *J*= 7.0, 1.5 Hz), 7.18 (2H, d, *J*= 8.5 Hz), 4.27 (1H, dt, *J*= 7.0, 3.5 Hz), 3.79 (1H, d, *J*=15.5 Hz), 3.74(1H, d, *J*= 15.5 Hz), 3.33 (1H, d, *J*= 4.0 Hz), 1.88-1.82 (1H, m), 1.60-1.53 (1H, m), 1.40-1.21 (8H, m), 0.87 (3H, t, *J*= 7.0 Hz); ¹³C NMR (100 MHz, CDCl₃): δ 210.0, 133.2, 129.6, 129.0, 127.5, 76.2, 45.1, 33.8, 31.8, 29.2, 24.9, 22.7, 14.2; IR (neat): 3470.6 (br), 2953.6 (m), 2925.1 (m), 2856.0 (m), 1709.7 (s), 1495.6 (m), 1454.4 (m), 1060.8 (m), 1043.9 (m), 1031.6 (m), 756.5 (m), 723.7 (m), 698.4 (s) cm⁻¹; HRMS-(DART) for: C₁(H₂)O₂[M+H]⁺: calculated: 235.1698, found: 235.1701.

Analysis of stereochemistry:

Racemic compound was prepared according to the same procedure utilizing racemic 2,2',2''-(octane-1,1,2-triyl)tris (4,4,5,5-tetramethyl-1,3,2-dioxaborolane) and benzaldehyde. Further analysis of stereochemistry was performed on (*S*)-3-hydroxy-1-phenylnonan-2-one. Absolute stereochemistry was assigned by analogy.

Chiral SFC (Chiracel AD-H, 3% MeOH, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-3-hydroxy-1-phenylnonan-2-one



| Peak No | % Area | Area | RT (min) | Peak No | % Area | Area | RT (min) |
|---------|---------|-------------------------|----------|---------|--------|-----------|----------|
| 1 | 51.5227 | 5761.4879 | 8.28 | 1 | 95.331 | 14034.101 | 7.8 |
| 2 | 48.4773 | 5420.9404 11182.4283 | | 2 | 4.669 | 687,351 | 10.76 |
| Total: | 100 | | | Total: | 100 | 14721.452 | |

4.9.12. Pt-Catalyzed Hydrometallation of Vinyl Boronates.



dimethyl(phenyl)(3-phenyl-1-(4,4,5,5-tetramethyl-1,3-dioxo-

lan-2-yl)propyl)silane. To an oven-dried 2-dram scintillation vial ŚiMe₂Ph equipped with a magnetic stirbar in the glovebox was added $Pt(dba)_3$ (8.1 mg, 9.00 μmol), (*R*,*R*)-4.91 (10.2 mg, 18.0 μmol) and HSiMe₂Ph (49.1 mg, 0.360 mmol), followed by THF (0.30 mL). The vial was sealed with a polypropylene cap, taped, brought outside of the glovebox, and heated to 80 °C for 25 minutes (Caution: While we have not experienced any explosions, this reaction involves heating of a closed system, and therefore appropriate safety measures should be followed). Over this period, the mixture turned from a deep purple solution to a pale yellow solution. The mixture was cooled to room temperature and brought into the glovebox, at which point vinyl boronate 4.54 (73.2 mg, 0.300 mmol) was added all at once. The vial was sealed with a polypropylene, taped, brought outside of the glovebox, and heated to 60 °C for 24 hours. The resulting mixture was cooled to room temperature, concentrated under reduced pressure. Analysis of the crude reaction mixture indicated >98% conversion and >98% yield of the desired product (tetrachlorethane was used as an internal standard). Subsequently, the product was purified via SiO₂ gel column chromatography (2% ethyl acetate in hexanes) to provide the pure title product 4.92 with minimal product degradation. All spectral data are in accordance with the literature.³²

Analysis of stereochemistry:

Racemic compound was prepared according to the same procedure utilizing tricyclohexylphosphine as the ligand. Further analysis of stereochemistry was performed on silaboronate **4.92**. Absolute stereochemistry has not yet been determined.

Chiral SFC (Chiracel OD-H, 1% IPA, 2.5 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of **4.92**.





Racemic Material

Standard Conditions

| Peak No | % Area | Area | RT (min) | Peak No | % Area | Area | RT (min) |
|---------|---------|-----------|----------|---------|---------|------------|----------|
| 1 | 49.8959 | 1833.2597 | 11,96 | 1 | 14.3457 | 2662.0743 | 12,23 |
| 2 | 50,1041 | 1840,9071 | 12.83 | 2 | 85.6543 | 15894.5569 | 12.96 |
| Total: | 100 | 3674.1668 | | Total: | 100 | 18556.6312 | |



TBSOB(pin)((5,5-bis(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-B(pin)yl)pentyl)-oxy)(*tert*-butyl)dimethylsilane. To an oven-dried

2-dram vial equipped with a stir bar was in a glovebox was added Pt(dba)₃ (33.0 mg, 36.8 μ mol) followed by THF (1.2 mL). To the reaction mixture was added pinacolborane (188 mg, 1.47 mmol) followed by vinyl boronate **4.93** (400.0 mg, 1.225 mmol). The reaction vessel was sealed with a polypropylene cap, brought out of the glovebox, and the reaction mixture was allowed to stir at 70 °C for 15 hours. Upon completion, the solvent was evaporated in vacuo. The crude reaction mixture was purified by column chromatography on silica gel (2% ethyl acetate/hexanes) to afford the desired product as a clear, colorless oil (456 mg, 82%). ¹H NMR (500 MHz, CDCl₃): δ 3.57 (2H, t, *J*= 6.5 Hz), 1.57-1.47 (4H, m), 1.35-1.26 (2H, m), 1.22 (12H, s), 1.21 (12H, s), 0.87 (9H, s), 0.71 (1H, t, *J*= 7.5 Hz), 0.02 (6H, s); ¹³C NMR (126 MHz, CDCl₃): δ 82.8, 63.4, 33.0, 28.8, 26.0, 25.6, 24.8, 24.5, 18.3, -5.3; IR (neat): 2977.2 (w), 2929.2 (w), 2857.3 (w), 1462.9 (w), 1359.2 (m), 1309.4 (s), 1263.3 (m), 1215.0 (w), 1139.6 (s), 1098.2 (s), 969.1 (m), 834.6 (s), 773.9 (m), 667.0 (w) cm⁻¹; HRMS-(DART) for: C₂₃H₄₉B₂O₅Si [M+H]⁺: calculated: 455.3535, found: 455.3551.





















































Chapter 5

Enantioselective Carbocycle Formation via an Intramolecaular Pd-Catalyzed Allyl-Aryl Cross-Coupling¹

5.1. Introduction

For well over a century, organic chemists have been inspired by the abundance of highly complex molecules that nature constructs. Indeed, the most sought-after transformations are those which furnish motifs commonly found in medicinally important or biologically active natural products. For example, nature often forges stereodefined carbocycles of varying ring sizes in order to access rigid molecules with well-defined geometries, and thus their synthesis by man has quickly gained significant attention as well. Asymmetric Diels-Alder reactions² and Robinson annulations³ provide reliable and efficient routes to 6-membered carbocycles, but generation of larger ring systems and medium-sized rings with certain substitution patterns continues to be a challenging feat. One of the most common catalytic methods for carbo- and heterocycle formation is ring closing metathesis (RCM).⁴ Impressively, employment of enantiopure Mo- or Ru-based

¹ This work was accomplished in collaboration with Dr. Christopher H. Schuster. For more details, see: Schuster, C. H. Ph. D. Thesis, Boston College, Chestnut Hill, MA, 2014, p. 281.

 ² For useful reviews on asymmetric Diels-Alder reactions, see: (a) Kagan, H. B.; Riant, O. *Chem. Rev.* 1992, 92, 1007. (b) Dias, L. C. *J. Braz. Chem. Soc.* 1997, *8*, 289. (c) Jiang, X.; Wang, R. *Chem. Rev.* 2013, 113, 5515.
³ For a recent review on asymmetric Robinson annulations, see: Yang, X.; Wang, J.; Li, P. *Org. Biomol. Chem.* 2014, 12, 2499.

⁴ For backing examples and useful reviews, see: (a) Grubbs, R. H. *Handbook of Metathesis*; Wiley-VCH: Weinheim, Germany, 2003, p. 18. (b) Schrock, R. R.; Hoveyda, A. H. *Angew. Chem. Int. Ed.* **2003**, *42*,

RCM catalysts (i.e. **5.2** and **5.6**) has provided useful routes to enantioenriched cyclic compounds via kinetic resolutions of chiral dienes,⁵ or via desymmetrization of trienes (Scheme 5.1).⁶

Scheme 5.1. Enantioselective Construction of Carbo- and Heterocycles via Ring Closing Metathesis.



Perhaps a more modular and well-precedented method for stereoselective carbocycle formation is the enantioselective intramolecular Heck reaction.⁷ The first

^{4592. (}b) Hoveyda, A. H.; Zhugralin, A. R. *Nature* **2007**, *450*, 243.(c) Hoveyda, A. H. *J. Org. Chem.* **2014**, *79*, 4763.

⁵ Alexander, J. B.; La, D. S.; Cefalo, D. R.; Hoveyda, A. H.; Schrock, R. R. J. Am. Chem. Soc. **1998**, 120, 4041.

⁶ (a) Seiders, T. J.; Ward, D. W.; Grubbs, R. H. *Org. Lett.* **2001**, *3*, 2335. (b) Malcolmson, S. J.; Meek, S. J.; Sattely, E. S.; Schrock, R. R.; Hoveyda, A. H. *Nature* **2008**, *456*, 933.

examples of such a transformation were independently reported by Overman and Shibasaki in 1989.⁸ For example, Shabasaki utilized 9 mol% of chiral ligand (*R*)-BINAP and 3 mol% $Pd(OAc)_2$ along with silver carbonate as a base to provide *cis*-decalin **5.9** from symmetrical triene **5.8** in moderate yield. Although enantioselectivity was low, this demonstrated for the first time that a Heck cyclization could be rendered asymmetric with the use of an appropriate ligand. Shortly afterwards, Overman and co-workers employed chiral bidentate ligand (*R*,*R*)-DIOP in conjunction with $Pd(OAc)_2$ and trimethylamine to efficiently furnish spirocycle **5.11** in similarly low levels of enantioinduction after two sequential Heck cyclizations (via **5.12**). Nonetheless, the generation of a highly complex and challenging all-carbon quaternary center demonstrates the powerful potential of the intramolecular Heck reaction in natural product synthesis.

⁷ For useful reviews, see: (a) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945. (b) Funk, T. W.; Berlin, J. M.; Grubbs, R. H. *J. Am. Chem. Soc.* **2006**, *128*, 1840. (c) McCartney, D.; Guiry, P. J. *Chem. Soc. Rev.* **2011**, *40*, 5122.

⁸ (a) Carpenter, N. E.; Kucera, D. J.; Overman, L. E. J. Org. Chem. **1989**, *54*, 5846. (b) Sato, Y.; Sodeoka, M.; Shibasaki, M. J. Org. Chem. **1989**, *54*, 4738.

3% Pd(OAc)₂ CO₂Me 9% (R)-BINAP MeO₂C 6% cyclohexene PPh₂ (1)PPh₂ Ag₂CO₃ (2 equiv.) Ĥ NMP, 60 °C 5.9 5.8 74% y (R)-BINAP 73:27 er 10% (R,R)-DIOP PPh₂ Ph₂P 10% Pd(OAc)₂ .OTf 40% PPh₃ Ο O (2) Et₃N (2.0 equiv.) Ме Mé benzene. RT. 2 h (R.R)-DIOP C 5.10 via: 5.11 >90% y dL_n 72.5:27.5 er 5.12 О

Scheme 5.2. Asymmetric Intramolecular Heck Cyclizations Independently Reported by Shibasaki and Overman.

Since these initial findings, Shibasaki and co-workers have improved upon their conditions for *cis*-decalin formation through use of vinyl triflate **5.13** in place of the vinyl iodide **5.8**.⁹ Additionally, an extensive solvent and base screen provided the optimal system which is represented in Scheme 5.3. Shibasaki's efforts in this area allowed them to report the first asymmetric total synthesis of (+)-vernolepin **5.15**,¹⁰ and later spawned an array of related reports pertaining to the asymmetric construction of natural products containing fused bicyclic 5-6 and 5-5 ring systems.¹¹

⁹ Kondo, K.; Sodeoka, M.; Mori, M.; Shibasaki, M. Tetrahedron Lett. 1993, 4219.

¹⁰ Ohrai, K.; Kondo, K.; Sodeoka, M.; Shibasaki, M. J. Am. Chem. Soc. 1994, 116, 11737.

¹¹ For selected examples, see: (a) Sato, Y.; Mori, M.; Shibasaki, M. *Tetrahedron Lett.* **1992**, *33*, 2593. (b) Sato, Y.; Mori, M.; Shibasaki, M. *Tetrahedron: Asymmetry* **1995**, *6*, 757. (c) Kagechika, K.; Shibasaki, M.

Scheme 5.3. Shibasaki's Improved Conditions for cis-Decalin Formation.



As represented in Scheme 5.4, an inherent feature in Heck reactions is that carbopalladation proceeds in a *syn* fashion across a π -system. Subsequently, *syn* β -hydride elimination generates a Pd-hydride species and furnishes the coupled product. Considering the geometric requirement for *syn* elimination, employment of cyclic alkenes prevents β -hydride elimination from occurring at the newly formed C-C bond, and destruction of the precious stereocenter can be averted. In other words, although alkyl palladium intermediate **5.16** contains three β -hydrogens, only H_a is in the proper orientation to partake in elimination and thus only product **5.17** is furnished.

J. Org. Chem. **1991**, *56*, 4093. (d) Oshima, T.; Kagechika, K.; Adachi, M.; Sodeoka, M.; Shibasaki, M. J. Am. Chem. Soc. **1996**, *118*, 7108. (e) Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron Lett.* **1993**, *34*, 4965. (f) Sato, Y.; Nukui, S.; Sodeoka, M.; Shibasaki, M. *Tetrahedron* **1994**, *50*, 371.



Scheme 5.4. Requirements for β-Hydride Elimination in Pd-Catalyzed Heck Reactions.

In contrast to what is observed when cyclic alkenes are employed as coupling partners, formation of an exocyclic alkyl palladium species adjacent to a tertiary center can result in achiral regioisomeric products. A powerful example of this occurrence has been reported by Tietze and co-workers, who revealed that Heck cyclization of **5.20** performed under both neutral and cationic conditions generated a mixture of the desired chiral product **5.21** and an achiral byproduct **5.22** (Scheme 5.5, eq 1).¹² Such results can be traced back to issues associated with a non-selective β -hydride elimination. Subsequent to carbo-palladation, bond rotation of the alkyl palladium intermediate can result in *syn* β -hydride elimination of any of the four available β -hydrogens. Furthermore, the eliminated HPdX species has a propensity to partake in additional alkene insertion/elimination sequences. Instead, a silyl group was installed in order to

¹² (a) Tietze, L. F.; Schimpf, R. Angew. Chem. Int. Ed. **1994**, 33, 1089. (b) Tietze, L. F.; Thede, K.; Schimpf, R.; Sannicoló, F. Chem. Commun. **2000**, 583. (c) Tietze, L. F.; Modi, A. Eur. J. Org. Chem. **2000**, 1959.

direct elimination. Utilization of allylsilane **5.23** was found to provide the desired coupled product **5.24** in high yield and in excellent enantioselectivity when employing chiral ligand (R)-BINAP. While the exact mode of silyl elimination is unknown, the results clearly indicate that a highly asymmetric and regioselective intramolecular coupling can be accomplished with use of the appropriate directing group. Consequently, the Tietze group has reported a total synthesis of naturally occurring norsesquiterpene **5.25** in three steps from exocyclic olefin **5.24**.¹³

Scheme 5.5. Tietze's Intramolecular Heck Cyclizations with Unfunctionalized Alkenes and Allyl Silanes.



¹³ Tietze, L. F.; Raschke, T. Synlett 1995, 597.
Despite the above-mentioned advancements in carbocycle formation via the asymmetric intramolecular Heck reaction, significant limitations still exist. While allcarbon quaternary centers can be efficiently forged without an opportunity for racemization and unwanted β -elimination byproduct formation, generation of stereodefined tertiary centers is still largely restricted to cyclic olefin substrates. Indeed, Tietze's directing group strategy is a powerful solution to these issues, but an alternate and more general method is still warranted. It was considered that development of an enantioselective intramolecular cross-coupling reaction would provide an improved route for accessing challenging carbocycles containing enriched tertiary stereocenters. More specifically, employment of an allyl-metal species bearing a tethered sp^2 -hybridized electrophile (i.e. A) might provide cyclized product (B). Importantly, the resulting product would be difficult to access via a traditional Heck reaction due to the aforementioned isomerization issues. While this methodology could potentially provide a straightforward method for accessing a variety of carbon-based skeletons often found in nature, the furnished exocyclic olefin can also be employed in numerous transformations to generate more complex molecules. Herein, the development and scope of an enantioselective intramolecular Suzuki-Miyaura cross-coupling reaction between aryl halides and tethered allyl boronates will be discussed in detail.

Scheme 5.6. Proposed Asymmetric Intramolecular Aryl-Allyl Coupling to Generate Enantioenriched Carbocylic Products.



5.2. Background

5.2.1. Suzuki-Miyaura Couplings with Allylic Boronate-Based Nucleophiles.

Allylmetal reagents are valuable nucleophilic partners in cross-coupling reactions. Under the appropriate conditions, use of nonsymmetric allyl fragments provides an opportunity to furnish a C-C bond at one of two possible sites, potentially in a highly regio- and enantioselective manner. Additionally, the resulting products contain an olefin for further chain extension or functional group installation.

In comparison to other allylmetal reagents, allyl boronates are particularly useful due to their chemical stability, functional group tolerance, and ease of preparation.^{14,15}

¹⁴ For selected examples of cross-coupling between aryl electrophiles and allyl boronates, see: (a) Nilsson, K.; Hallberg, A. Acta Chem. Scand. **1987**, 41b, 569. (b) Occhiato, E. G.; Trabocchi, A.; Guarna, A. J. Org. Chem. **2001**, 66, 2459. (c) Kotha, S.; Behera, M.; Shah, V. R. Synlett **2005**, 1877. (d) Rossi, E.; Abbiati, G.; Canevari, V.; Celentano, G.; Magri, E. Synthesis **2006**, 299. (e) Gerbino, D. C.; Mandolesi, S. D.; Schalz, H.-G.; Podestá, J. C. Eur. J. Org. Chem. **2009**, 3964. (f) Glasspoole, B. W.; Ghozati, K.; Moir, J. W.; Crudden, C. M. Chem. Commun. **2012**, 48, 1230. (g) Farmer, J. L.; Hunter, H. N.; Organ, M. G. J. Am. Chem. Soc. **2012**, 134, 17470. (h) Yang, Y.; Buchwald, S. L. J. Am. Chem. Soc. **2013**, 135, 10642. (i) Chausset-Boissarie, L.; Ghozati, K.; LaBine, E.; Chen, J. L.-Y.; Aggarwal, V. L.; Crudden, C. M. Chem. Eur. J. **2013**, 19, 17698.

¹⁵ For coupling with allyl electrophiles, see: (a) Flegeau, E. F.; Schneider, U.; Kobayashi, S. *Chem. Eur. J.* **2009**, *15*, 12247. (b) Zhang, P.; Brozek, L. A.; Morken, J. P. J. Am. Chem. **2010**, *132*, 10686. (c) Zhang, P.;
Le, H.; Kyne, R. E.; Morken, J. P. J. Am. Chem. Soc. **2011**, *133*, 9716. (d) Jiménez-Aquino, A.; Flegeau, E.
F.; Schneider, U.; Kobayashi, S. Chem. Commun. **2011**, *47*, 9456. (e) Brozek, L. A.; Ardolino, M. J.;
Morken, J. P. J. Am. Chem. Soc. **2011**, *133*, 16778. (f) Le, H. Kyne, R. E.; Brozek, L. A.; Morken, J. P. *Org. Lett.* **2013**, *15*, 1432. (g) Le, H.; Batten, A.; Morken, J. P. *Org. Lett.* **2014**, *16*, 2096. (h) Ardolino, M. J.;
Morken, J. P. J. Am. Chem. Soc. **2014**, *136*, 7092.

The first example of allyl boronate esters being utilized in a coupling reaction was described by Hallberg in 1987.^{14a} The authors were under the assumption that the terminal alkene would participate in a Heck reaction without participation of the boronate moiety, considering alkyl boronates were known to be less reactive under Pd-catalyzed coupling conditions. Instead, employment of allyl boronate **5.26** with iodobenzene and triethylamine as a base furnished allyl benzene along with a mixture of additional deborylated products **5.27-5.29** (Scheme 5.7, eq 1). A cleaner reaction performed with NaOMe as the base and THF as the solvent afforded allylbenzene exclusively. Nonetheless, a nearly two-fold excess of boronate **5.26** was required for just 50% conversion of the electrophile.

Scheme 5.7. Hallberg's Seminal Report on Allyl Boronate Coupling.



Perhaps due to the dismal results provided in the seminal report presented above, Suzuki-Miyaura couplings employing allyl boronates remained unexplored for the next 9 years. In 1996, Kalinin and co-workers presented a Pd-catalyzed Suzuki-Miyaura coupling between allyl boronate **5.30** and iodobenzene to provide allyl benzene in excellent yield and with no other deborylated byproducts observed (Scheme 5.8, eq 1).¹⁶ Employing bromobenzene as the electrophile provided product as well, longer reaction times are required for just 40% yield of the desired coupled product. The high efficiency of the reaction under such mild conditions is likely due to the use of a relatively reactive methanol-derived allyl boronate **5.30**.

In 2001, Occhiato and co-workers examined the efficiency of various boronate nucleophiles with vinyl triflate **5.31**. Despite incomplete conversion, coupled product **5.32** was obtained cleanly when employing pinacol-derived allyl boronate **5.26** under the reaction conditions described in Scheme 5.8 (eq 2).^{14b} Subsequently, other groups eventually followed suit with reports of success using allyl boronate coupling partners. For example, under almost identical conditions to Occhiato, the Rossi group described a highly efficient synthesis of **5.34** from reaction between indole triflate **5.33** and allyl boronate **5.26** (eq 3).^{14c}

¹⁶ Kalinin, V. N.; Denisov, F. S.; Bubnov, Y. N. Mendeleev Communications 1996, 206.

Scheme 5.8. Early Examples of Suzuki-Miyaura Coupling Between Allyl Boronates and sp^2 Electrophiles Reported by Kalinin, Occhiato and Rossi.



It wasn't until a 2006 report by Szabó and coworkers that the first examples of substituted allylic nucleophiles being exploited as competent coupling partners emerged. For example, it was discovered that coupled products **5.36** were obtained from a reaction between various linear allyl boronic acids **5.35** and aryl electrophiles (Scheme 5.9, eq 1). Notably, although two possible products can theoretically arise from such a scenario, only the branched regioisomer resulting from a γ -selective coupling is observed. Interestingly, reversal of the nature of the coupling partners resulted in a vastly different outcome in regioselectivity, with linear adduct **5.41** now being favored (eq 2 vs. eq 3). Thus, the authors conclude that while reaction with phenyl boronic acid **5.38** and **5.37**

proceeds via the interemediacy of Pd-allyl species **5.39**, the reaction between iodobenzene and allyl boronic acid **5.42** does not occur from a similar Pd-allyl intermediate. Instead, it is suggested that high γ -selectivity is likely the consequence of a regioselective carbo-palladation to form intermediate **5.43**, followed by a Pd-mediated β boryl elimination. Such a conclusion would be consistent with the findings of Hallberg and Nilsson almost 20 years prior (see Scheme 5.7).^{14a}

Scheme 5.9. y-Selective Allyl-Aryl Coupling and Mechanistic Studies by Szabó.



To complement Szabó's findings, Organ and co-workers described an α -selective coupling between various aryl electrophiles and prenyl boronate **5.44** to provide linear products **5.46** in high yield and excellent regiocontrol (Scheme 5.10, eq 1).^{14g} The key to

this unique regioselectivity is employment of a sterically bulky NHC-based Pd-PEPPSI catalyst **5.45**. Interestingly, use of Pd(PPh₃)₄ resulted in a reversal of selectivity to provide the γ -isomer **5.50** as the major coupled product (eq 2). Whereas S_E2' transmetallation is possible with Pd(PPh₃)₄, mechanistic experiments utilizing **5.45** seem to point toward S_E2 transmetallation of the nucleophile to form σ -allyl intermediate **5.51**, followed by a rapid reductive elimination with limited σ - π - σ interconversion occurring beforehand (eq 3).



Scheme 5.10. Organ's α-Selective Allyl-Aryl Coupling with Prenyl Boronate 5.44.

Impressively, Buchwald recently reported that excellent α - or γ -regioselective prenylation of aryl electrophiles could be achieved with the appropriate choice of ligand (Scheme 5.11).^{14h} For example, coupling between aryl bromide **5.53** and pinacol-derived prenyl boronate **5.44** with dialkylbiaryl phosphine **5.54** resulted in nearly exclusive γ -selectivity to produce **5.55** (eq 1), while *t*BuXPhos (**5.57**) provided almost complete α -

selectivity to produce **5.56** (eq 2). High yields could be obtained under mild conditions for both catalytic systems, representing an ideal regiodivergent reaction set. Similar to Organ's findings, the authors propose that generation of the γ -product is typically favored with most ligands, but the bulkiness of **5.57** prevents the formation of the branched σ allyl species necessary for γ -selective coupling.

Scheme 5.11. Buchwald's Regiodivergent Routes to Linear and Branched Allyl-Aryl Adducts.



Internal allyl boronates have also been utilized successfully in intramolecular allyl-aryl couplings. In 2012, Crudden discovered that γ -selective adducts were favored

in moderate to high regioselectivity for a variety of racemic internal allyl boronates (Scheme 5.12, eq 1).^{14f} Shortly afterwards, Aggarwal and Crudden collaborated to report a similar catalytic system utilizing enantiomerically enriched allyl boronates in conjunction with various aryl iodides.¹⁴ⁱ Importantly, the resulting coupled products could be isolated in moderate yield, high regioisomeric ratios and often in excellent retentive stereospecificity (eq 2).



Scheme 5.12. Enantiospecific γ -Selective Coupling of Internal Allyl Boronates.

Mechanistic studies suggest that γ -selective transmetallation is operative, followed by reductive elimination, which outcompetes isomerization to the π -allyl intermediate. Upon further inspection of stereochemical outcome, it was determined that the reaction proceeds via a *syn*-S_E2' transmetallation. For example, (*R*,*E*)-**5.65** generates (*S*,*E*)-**5.66** under the reaction conditions, whereas (*R*,*Z*)-**5.67** provides (*R*,*E*)-**5.68** (Scheme 5.13). Thus, the authors propose that the transmetallation pathway is an intramolecular process likely involving a B-O-Pd linkage as suggested in structure \mathbf{C} .¹⁷

Scheme 5.13. Insights into Transmetallation for Allyl-Aryl Coupling Reported by Crudden and Aggarwal.



Despite significant interest in Pd-catalyzed Suzuki coupling between aryl electrophiles and allyl boronates over the past decade, only one enantioselective variant exists to date. In 2006, Miyaura and co-workers discovered that an electron-rich and bulky Josiphos derivative **5.70** could be utilized to promote a highly regioselective coupling of various aryl bromides and *trans*-crotyl trifluoroborate **5.69** (Scheme 5.14).¹⁸ Notably, moderate to good enantiomeric ratios were obtained in all cases. Vinyl halides

¹⁷ Similar transmetallation pathways have been proposed previously: (a) Matos, K.; Soderquist, J. A. *J. Org. Chem.* **1998**, *63*, 461. (b) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. Eur. J.* **2011**, *17*, 2492. (c) Carrow, B. P.; Hartwig, J. F. *J. Am. Chem. Soc.* **2011**, *133*, 2116. (d) Lennox, A. J. J.; Lloyd-Jones, G. *Angew. Chem. Int. Ed.* **2013**, *52*, 7362.

¹⁸ Yamamoto, Y.; Takada, S.; Miyaura, N. Chem. Lett. 2006, 35, 1368.

were also efficient substrates under the reaction conditions, providing similar results to aryl electrophiles.

Scheme 5.14. Miyaura's Enantioselective Allyl-Aryl Coupling with Crotyl Trifluoroborate **5.69**.



By comparing the reaction rates between various *p*-substituted aryl bromides and crotyl boronate **5.69**, a Hammett plot was produced.¹⁹ Interestingly, a negative ρ -value of -0.7 was acquired, corresponding to a positive charge buildup in the turnover-limiting step. Thus, the authors suggest that the rate-determining step is halide abstraction of Pdcompex **5.72** to form cationic intermediate **5.73** (Scheme 5.15, eq 1). Next, S_E2' transmetallation is stereodetermining and occurs via an open transition state (**5.74**). Lastly, a rapid reductive elimination from **5.75** generates the γ -coupled product, outcompeting π -allyl isomerization. Notably, cationic Pd-intermediate **5.76** was synthesized and employed in a reaction with crotyl boronate **5.69** under the optimized cross-coupling conditions (eq 2). Although enantioselectivity was not provided, similar yields and regioisomeric ratios were obtained when compared to when Josiphos

¹⁹ Yamamoto, Y.; Takada, S.; Miyaura, N. Organometallics 2009, 28, 152.

derivative **5.70** was employed with the corresponding aryl bromide. The results indicated that cationic Pd-complex **5.73** is a plausible intermediate in the catalytic cycle.



Scheme 5.15. Mechanistic Studies of Miyaura's Enantioselective Allyl-Aryl Coupling.

5.2.2. Intramolecular Examples of Suzuki-Miyaura Cross-Couplings. All previous Suzuki-Miyaura couplings discussed thus far have been intermolecular variants. Even rarer couplings are those performed intramolecularly, in which an electrophile and a boron-based nucleophile are tethered together within a single molecule. In terms of utility of boronate esters in such reactions, only sp^2-sp^2 Suzuki-Miyaura couplings have been reported in the literature. For example, the Zhu group showed that macrocycle 5.79 can be generated as a single atropisomer in moderate yield from an intramolecular coupling between the pinacol-derived aryl boronate ester and the aryl iodide moiety of substrate 5.78.²⁰ Unfortunately, even with extensive optimization of catalyst sources, ligands, solvents, and reaction temperature, stoichiometric amounts of Pd are required for

²⁰ Jia, Y.; Bois-Choussy, M.; Zhu, J. Org. Lett. 2007, 9, 2401.

full conversion. More recently, Zhu and others have reported similar macrocyclization strategies, in which catalyst turnover is achieved, to access synthetically challenging and complex natural products.²¹



Scheme 5.16. Intramolecular Suzuki-Miyaura Coupling Reported By Zhu.

Some success has also been realized with intramolecular Suzuki-Miyaura coupling between alkyl boranes and aryl or vinyl halides. In 1989, Miyaura and Suzuki reported a one-pot 9-BBN hydroboration/cross-coupling reaction to afford 5- and 6- membered carbocycles.²² For instance, 1-allyl-2-bromobenzene **5.80** can undergo hydroboration followed by sp^3-sp^2 Suzuki-Miyaura coupling to access indane **5.81** in good yield (Scheme 5.17, eq 1). Since this seminal report, other groups have utilized

²¹ (a) Jia, Y.; Bois-Choussy, M.; Zhu, J. Angew. Chem. Int. Ed. 2008, 47, 4167. (b) Wang, Z.; Bois-Choussy, M.; Jia, Y.; Zhu, J. Angew. Chem. Int. Ed. 2010, 49, 2018. (c) Coste, A.; Bayle, A.; Marot, J.; Evano, G. Org. Lett. 2014, 16, 1306. For earlier related examples, see: (d) Carbonnelle, A.-C.; Zhu, J. Org. Lett. 2000, 2, 3477. (e) Kaiser, M.; Siciliano, C.; Assfalg-Machleidt, I.; Groll, M.; Milbradt, A. G.; Moroder, L. Org. Lett. 2003, 5, 3435. (f) Lepine, R.; Zhu, J. Org. Lett. 2005, 7, 2981.

²² Miyaura, N.; Ishiyama, T.; Sazaki, H.; Ishikawa, M.; Sato, M.; Suzuki, A. J. Am. Chem. Soc. **1989**, 111, 314.

similar protocols in order to generate complex polycyclic natural products.²³ A notable example was reported by Halcomb during the final steps in the synthesis of (+)-phomactin A **5.83**.²⁴ Subsequent to hydroboration with 1.5 equivalents of 9-BBN, the vinyl iodide moiety of **5.82** undergoes a transannular cyclization with the generated alkylborane (eq 2). In addition to 6.0 equivalents of toxic Tl_2CO_3 , stoichiometric amounts of Pd and AsPh₃ are once again necessary. Following an *in situ* global TBAF deprotection, the natural product was furnished in moderate yields over two steps.

Scheme 5.17. One-Pot Hydroboration Cross-Coupling Procedure.



Despite its potential synthetic applications, an intramolecular coupling utilizing less reactive sp^3 -hybridized alkyl boronate esters has never been accomplished. Even more surprisingly, allyl boronates have never been employed in intramolecular Suzuki-

²³ (a) Miyaura, N.; Ishikawa, M.; Suzuki, A. *Tetrahedron Lett.* 1992, 33, 2571. (b) Soderquist, J. A.; León, G.; Colberg, J. C.; Martínez, I. *Tetrahedron Lett.* 1995, 36, 3119. (c) Chemler, S. R.; Danishefsky, S. J. Org. Lett. 2000, 2, 2695.

²⁴ Mohr, P. T.; Halcomb, R. L. J. Am. Chem. Soc. 2003, 125, 1712.

Miyaura couplings of any fashion. Indeed, allylsilanes,^{12,13} allylstannanes,²⁵ and allylindium²⁶ reagents have all been utilized successfully in analogous intramolecular couplings to form carbo- or heterocyclic products. However, out of all of these examples, only those reported by Tietze have been rendered asymmetric (See Scheme 5.5). Thus, an enantioselective coupling that engages stable allyl boronate coupling partners is clearly warranted.

5.3. Development of an Asymmetric Intramolecular Pd-Catalyzed Allyl-Aryl Cross-Coupling²⁷

5.3.1. Substrate Preparation. A limiting factor in the development of an intramolecular allyl-aryl Suzuki-Miyaura coupling is the ability to access a molecule containing both nucleophilic and electrophilic moieties. Indeed, many methods for installing allyl boronates involve the intermediacy of highly reactive organometallics which cannot be accessed in the presence of alkenyl or aryl halides.²⁸ Thus, relatively neutral functionality and conditions would be required to install the allyl boronate

²⁵ For selected examples involving allylstannanes, see: (a) Trost, B. M.; Walchi, R. J. Am. Chem. Soc. **1987**, 109, 3487. (b) Grigg, R.; Sansano, J. M. J. Tetrahedron **1996**, 52, 13441.

²⁶ For selected examples involving allylindiums, see: (a) Seomoon, D.; Lee, K.; Kim, H.; Lee, P. H. *Chem. Eur. J.* **2007**, *13*, 5197. (b) Lee, K.; Kim, H.; Mo, J.; Lee, P. H. *Chem. Asian J.* **2011**, *6*, 2147.

²⁷ Schuster, C. H.; Coombs, J. R.; Kasun, Z. A.; Morken, J. P. Org. Lett. **2014**, *16*, 4420.

²⁸ For selected examples from allyl magnesiums, see: (a)Brown, H. C.; Singh, S. M.; Rangaishenvi, M. V. J. Org. Chem. **1986**, 51, 3150. (b)Althaus, M.; Mahmood, A.; Suárez, J. R.; Thomas, S. P.; Aggarwal, V. K. J. Am. Chem. Soc. **2010**, 132, 4025. (c) Clary, J. W.; Rettenmaier, T. J.; Snelling, R.; Bryks, W.; Banwell, J.; Wipke, N. T.; Singaram, B. J. Org. Chem. **2011**, 76,9602. From allyl electrophiles: (d) Dutheuil, G.; Selander, N.; Szabó, K. J.; Aggarwal, V. K. Synthesis **2008**, 2293. (e) Guzman-Martinez, A.; Hoveyda, A. H. J. Am. Chem. Soc .**2010**, 132, 10634. (f) Larsson, J. M.; Szabó, K. J. J. Am. Chem. Soc. **2013**, 135, 443.

moiety.²⁹ Furthermore, an ideal methodology for allyl boronate synthesis should be cost efficient, utilizing cheap starting materials and catalysts. It was considered that various allyl boronates **5.87** could eventually be accessed from allyl alcohol **5.84**.³⁰ Chlorination of **5.84** can be accomplished with SOCl₂ in just 30 minutes at room temperature. The resulting product is a mixture of regioisomers **5.85** and **5.86**, which was obtained cleanly in varying regioisomeric ratios and in moderate to good yields after a short silica gel column. Fortunately, the Morken lab has developed a borylation of allyl electrophiles which uses equimolar amounts of B₂(pin)₂ and 1 mol% PdCl₂ (Scheme 5.18).³¹ The overall transformation is a simple, regioconvergent method for accessing pure terminal allyl boronates **5.87** as the exclusive regioisomer in moderate to high yields. Most importantly, the resulting allyl boronates are sufficiently stable to air and moisture to be purified by simple chromatographic methods.

Scheme 5.18. Synthesis of Starting Materials 5.87 for Intramolecular Suzuki Coupling.



²⁹ For selected examples from 1,3-dienes, see: (a) Wu, J. Y.; Moreau, B.; Ritter, T. J. Am. Chem. Soc. 2009, 131, 12915. (b) Ely, R. J.; Morken, J. P. J. Am. Chem. Soc. 2010, 132, 2534. From olefins: (c) Kiesewetter, E. T.; O'Brian, R. B.; Yu, E. C.; Meek, S. J.; Schrock, R. R.; Hoveyda, A. H. J. Am. Chem. Soc. 2013, 135, 6026.

³⁰ See experimental section for a more detailed synthesis of allyl boronate starting materials and precursors.

³¹ Zhang, P.; Roundtree, I. A.; Morken, J. P. Org. Lett. 2012, 14, 1416.

5.3.2 Optimization of Intramolecular Coupling Conditions with Bidentate Ligands. Considering earlier findings by Miyaura and co-workers with intermolecular Miyaura-Suzuki couplings,¹⁹ we reasoned that an intramolecular asymmetric variant might proceed via a cationic palladium intermediate. Thus, a bidentate chiral ligand could facilitate binding of the tethered olefin of the allyl boronate motif (5.88), followed by S_E2' transmetallation to access palladacycle 5.89 (Scheme 5.19). Thus, the chiral ligand would ideally induce a stereoselective transmetallation to furnish an enantioenriched C-Pd bond. Subsequently, it was reasoned that a rapid reductive elimination similar to what is observed by Miyaura and others would provide the desired carbocycle 5.90. In other words, stereochemistry would be set during transmetallation, and a fast and stereospecific reductive elimination would outcompete σ - π - σ isomerization which could result in racemization.

Scheme 5.19. Proposed Asymmetric Intramolecular Miyaura-Suzuki Coupling



Initial attempts at an asymmetric intramolecular coupling are described in Table 5.1, utilizing allyl boronate **5.91** as a test substrate. Preliminary investigation focused on the use of various bidentate chiral phosphine-based ligands. While high levels of

conversion and clean reactions were obtained, low enantioselectivity was achieved in all cases. Interestingly, despite Miyaura's success with intermolecular aryl-allyl coupling when utilizing JosiPhos derived ligands,¹⁸ employment of a similar ligand structure resulted in a nearly racemic reaction. Similarly, although Tietze reported moderate enantioinduction when employing (*S*)-BINAP in a Pd-catalyzed intramolecular Heck reaction,¹² low selectivities were obtained for this system. Chirality at the phosphorus center of the ligand also provided essentially no improvement in enantiomeric ratios. Overall, the best results with bidentate ligands were attained with Me-DuPhos, albeit only providing marginally enhanced levels of enantioinduction (57:43 er). It should be noted that without a ligand present, only starting material is recovered with no noticeable background reaction taking place.



Table 5.1. Screening of Chiral Bidentate Ligands in Intramolecular Allyl-Aryl Coupling.

Additional attempts at enhancing enantioinduction were performed with Me-DuPhos, but were more or less fruitless (Scheme 5.20). For example, the use of 3.0 equivalents of cesium fluoride in place of potassium hydroxide provided similar results, however with decreased efficiency. After extensive optimization, the highest enantioselectivities were achieved with cesium fluoride under anhydrous conditions, giving only a slight enhancement in selectivity (59:41 er).

Scheme 5.20. Optimal Results with Bidentate Ligands for Intramolecular Allyl-Aryl Coupling.



It was important to determine why bidentate ligands with vastly different structures all provided similarly poor levels of enantioinduction. To determine the origin of such observations, the catalytic cycle was considered (Scheme 5.21). It was considered that oxidative addition of **5.91** and intramolecular olefin binding provides borate intermediate **5.94**. Similar to what is observed with Miyaura's intermolecular system, it is feasible that subsequent transmetallation is highly regioselective and is stereochemistry-determining. Thus, formation of palladacycle **5.95** occurs in a stereoselective fashion; however, unlike Miyaura's observations, π - σ - π isomerization (via **5.96**) could compete with reductive elimination, resulting in racemization of the Pd-C bond.³² Alternatively, low selectivities could originate from poor facial selectivity during transmetallation (i.e. to either **5.95** or **5.97**), followed by a rapid stereospecific reductive elimination.³³

³² Isomerization through this pathway requires the intermediacy of a primary η^1 -allyl intermediate **5.121**. See scheme 5.24 for a more in depth discussion of requirements for π - σ - π isomerization.

³³ For studies on allyl-Pd intermediates, see: (a) Jolly, P. W. Angew. Chem. Int. Ed. **1985**, 24, 283. (b) Trost, B. M.; Van Vranken, D. L. Chem. Rev. **1996**, 96, 395. (c) Pregosin, P. S.; Salzmann, R. Coord. Chem. Rev. **1996**, 155, 35.



Scheme 5.21. Proposed Catalytic Cycle for Intramolecular Allyl-Aryl Coupling.

Judging by the extensive bidentate ligand screen that was already performed, it was postulated that both improving stereoinduction during transmetallation and inhibiting allyl isomerization might be a challenging task. Indeed, with bidentate ligands, allyl isomerization is already likely suppressed due to the high energy η^3 -bound Pd(II) intermediate **5.96** that is required for such a pathway to occur.^{33a} While high energy 18-electron complexes have been noted in intermolecular processes^{15b,c,e,f} and when employing nickel catalysts,³⁴ accessing such an intermediate in the current Pd-catalyzed

³⁴ (a) Kurosawa, H.; Ohnishi, H.; Emoto, M.; Chatani, N.; Kawasaki, Y.; Murai, S.; Ikeda, I. *Organometallics* **1990**, *9*, 3038. (b) Rufinska, A.; Goddard, R.; Weidenthaler, C.; Bühl, M.; Pörschke, K.-R. Organometallics **2006**, *25*, 2308.

intramolecular system is unprecedented and might be problematic. For comparison, employing Ni(cod)₂ instead of Pd(OAc)₂ under otherwise identical conditions results in markedly enhanced levels of enantioselectivity (80:20 er vs. 59:41 er, Scheme 5.22). Thus, while it is possible that the mode of selectivity varies between the two systems, the fact that 18-electron metal-allyl species are more easily accessed with Ni can be a significant factor. Unfortunately, further optimization of a Ni-catalyzed intramolecular coupling was met with limited success due to low reactivity. In order to proceed forward, it was instead considered that developing a system that promotes a stereoconvergent allyl isomerization might remedy issues associated with a non-selective transmetallation.

Scheme 5.22. Ni-Catalyzed Intramolecular Allyl-Aryl Coupling.



5.3.3. Additional Optimization with Monodentate Ligands. We reasoned that employing monodentate ligands might facilitate allyl isomerization since the resulting 16electron π -allyl intermediate (i.e. 5.96) would be lower in energy when compared to the analogous bidentate 18-electron species. As presented in Table 5.2, various chiral monodentate phosphine-based ligands were surveyed using 5.91 as a test substrate. Although BINOL-derived phosphoramidites 5.98-5.101 all provided low enantiomeric ratios, using TADDOL-derived phosphonite 5.102 resulted in significant improvement in selectivity. In addition, TADDOL-derived phosphoramidite **5.103** led to similar levels of enantioinduction.

Table 5.2. Screening of Chiral Monodentate ligands in Intramolecular Allyl-Aryl Coupling.



A more extensive screen of TADDOL-derived ligands was performed and is provided in Table 5.3. Dimethylamino-based phosphoramidite ligands provided comparable or slightly improved enantiomeric ratios when compared to the corresponding phenyl phosphonites (entries 2 and 3 vs. entries 4 and 5). Increasing the bulk of the aryl group on the TADDOL backbone resulted in an enhancement in selectivity (entries 4-6), with R = tBu (5.106) yielding similar results to when $R = SiMe_3$ (5.107). Next, the amino substituent of the phosphoramidite ligand was varied. While the pyrrolidine-derived TADDOL 5.108 provided nearly identical results to 5.106 (entry 7), even a slight increase in the size of the amino moiety led to significant diminishment in enantioselectivity (etnries 8-11). Additionally, when phosphite 5.113 was employed, a racemic mixture of coupled product 5.92 was obtained (entry 12). Overall, a clear trend exists in which ligands bearing bulkier TADDOL backbones and smaller amino groups are required for enhanced enantioinduction. It is important to note that although 5.107 and 5.108 led to the highest enantioselectivities, further optimization with these ligands gave comparable or slightly diminished selectivities when compared to reactions employing 5.106; thus, phosphoramidite 5.106 was selected for further studies. To our delight, in essentially all cases in which phosphoramidite-based ligands were utilized, full and clean conversion to the desired coupled product was realized.



Table 5.3. Additional Screening of TADDOL-Derived Ligands.

a) The (S,S)-enantiomer of the TADDOL backbone was employed.

Additional reaction conditions were examined in an attempt to improve selectivity and efficiency (Table 5.4). A brief base screen revealed CsF as optimal (entry 1), with all other bases providing the product in markedly lower enantiomeric ratios (entries 2-8). At this point, the marked variance in selectivity with different bases is perplexing, but suggests that other roles in addition to boron activation are operative. Furthermore, while use of both polar and nonpolar solvents led to an effective coupling reaction, THF furnished the desired product in the highest enantiomeric ratios (entries 9-13). Nonpolar solvents appear to have a detrimental effect on selectivity.

| | Br 5.91 | 5% B(pin) <u>7%</u> base | Pd(OAc) ₂ (<i>R</i>,<i>R</i>)-5.106 (3.0 equiv.) solvent 0 °C, 14 h | 5.92 |
|----------------|--------------------------------|--------------------------------|--|-------|
| entry | base | solvent | conv. (%) | er |
| 1 | CsF | THF | >98 | 84:16 |
| 2 | KF | THF | 24 | 76:24 |
| 3 | TBAF | THF | >98 | 46:54 |
| 4 | КОН | THF | >98 | 80:20 |
| 5 ^a | KO <i>t</i> Bu | THF | complex mixture | |
| 6 | KOAc | THF | <5 | |
| 7 | K ₃ PO ₄ | THF | >98 | 56:44 |
| 8 | Cs_2CO_3 | THF | >98 | 68:32 |
| 9 | CsF | MeCN | >98 | 61:39 |
| 10 | CsF | EtOAc | 74 | 83:17 |
| 11 | CsF | dioxane | >98 | 83:18 |
| 12 | CsF | toluene | >98 | 74:26 |
| 13 | CsF | hexane | >98 | 74:26 |

Table 5.4. Base and Solvent Screen for Intramolecular Allyl-Aryl Coupling.

a) No desired product by ¹H NMR.

Of immediate interest was uncovering methods of facilitating π - σ - π isomerization. Notably, previous reports by Trost³⁵ and Togni³⁶ suggested that π -allyl interconversion could be promoted with the addition of tetra-alkyl ammonium salts. Strongly coordinating counterions have the ability to act as a labile ligand in the case of Pd-allyl complexes during intermolecular aminations or etherifications. For instance, upon addition of a Lewis base (X⁻) to chiral Pd-allyl complex **5.114**, a stable four-coordinate 16-electron η^1 intermediate **5.115** is formed (Scheme 5.23). Subsequently, loss of the counterion allows for generation of a stereoinverted Pd-allyl complex **5.116**, which is favored over its stereoisomer **5.114** due to the facial preference dictated by the chiral ligand bound to the metal. Thus, in the event of a nonselective transmetallation, addition of the appropriate coordinating additive can allow for equilibration or stereoconvergence of π -allyl species **5.114** and **5.116**.

Scheme 5.23. Effects of Counterion for π -Allyl Interconversion.



As stated above, such observations have been reported in intermolecular variants of Pd-catalyzed nucleophilic additions to allyl electrophiles. Still unknown is whether

³⁵ Trost, B. M.; Toste, F. D. J. Am. Chem. Soc. 1999, 121, 4545.

³⁶ Burckhardt, U.; Baumann, M.; Togni, A. Tetrahedron: Asymmetry 1997, 8, 155.

the same concept can be applied to systems in which both the electrophilic and nucleophilic coupling partners are bound to the metal. For example, Amatore and Jutland have found that the addition of a strong Lewis base can promote reductive elimination in Suzuki-Miyaura cross-coupling reactions.³⁷ In the case of an intramolecular allyl-aryl coupling, a nonselective transmetallation would lead to σ -allyl complexes **5.117** and **5.118** (Scheme 5.24). The addition of a counterion could promote the isomerization of both isomers to 8-membered palladacycle **5.121**, with the potential to eventually equilibrate to the favored diastereomer (**5.117** or **5.118**) prior to reductive elimination. Alternatively, based on Amatore and Jutland's findings, the added Lewis base could promote reductive elimination prior to the completion of allyl equilibration, leading to diminished enantioselectivities of coupled product **5.92**. Therefore, selection of an additive which promotes isomerization but does not facilitate a premature reductive elimination is exceptionally imperative. Such a delicate balance between the two possible pathways might help explain some of the anomalies observed in Table 5.4.

³⁷ (a) Amatore, C.; Jutand, A.; Le Duc, G. *Chem. Eur. J.* **2011**, *17*, 2492. (b) Amatore, C.; Jutand, A.; Le Duc., G. *Angew. Chem. Int. Ed.* **2012**, *51*, 1379.

Scheme 5.24. Effect of Lewis Base on Allyl Isomerization in Intramolecular Allyl-Aryl Coupling.



With the above-mentioned concerns under consideration, various Lewis base additives were surveyed in the Pd-catalyzed asymmetric intramolecular allyl-aryl coupling reaction (Table 5.5). To our delight a noticeable elevation in enantioselectivity was observed with tetrabutylammonium chloride and bromide (entries 1 and 2). All other additives led to lower or unchanged selectivity values compared to when no additive was employed (entries 3-10). Interestingly, addition of lithium bromide resulted in no reaction (entry 7). It is likely that a salt metathesis occurred between lithium bromide and cesium fluoride to generate lithium fluoride, resulting in consumption of the base.

| B | B(pin) | 5% Pd(OAc) ₂ 7% (<i>R</i> , <i>R</i>)-5.106 CsF (3.0 equiv.) | |
|-------|-----------------------|---|-------|
| | 5.91 | THF, 70 °C, 14 h | 5.92 |
| entry | additive | conv. (%) | er |
| 1 | NBu ₄ Cl | 70 | 90:10 |
| 2 | NBu ₄ Br | 78 | 87:13 |
| 3 | NBu ₄ I | >98 | 57:43 |
| 4 | NBu ₄ OAc | >98 | 78:22 |
| 5 | Ph ₃ PMeBr | 35 | 76:24 |
| 6 | LiCl | >98 | 85:15 |
| 7 | LiBr | <2 | |
| 8 | CsCl | >98 | 82:18 |
| 9 | Ph ₂ MeP=O | >98 | 83:17 |
| 10 | NEt ₃ | >98 | 84:16 |

Table 5.5. Survey of Lewis Base Additives in Intramolecular Allyl-Aryl Coupling.

An additional screening of tetra-alkylammonium chlorides was performed and the results are presented in Table 5.6. It was discovered that both smaller and larger ammonium chloride additives resulted in diminished selectivities (entries 2-4). Various solvents were also re-examined under the coupling conditions employing tetrabutylammonium chloride. Unfortunately, although conversions were fully restored, acetonitrile and other etheral solvents provided no improvements when compared to THF (entries 5-8). It was considered that the use of aryl bromide **5.91** resulted in the generation of bromide salts as the reaction proceeds. Thus, given the fact that chloride

salts gave enhanced selectivities in comparison to bromide based additives, aryl chloride **5.122** was investigated under the reaction conditions. To our delight, high enantioselectivities were realized even without the addition of a Lewis base (entry 9). Additionally, elevated levels of enantioinduction could be obtained with the addition of tetrabutylammonium chloride (entry 10). Overall, however, it became apparent that additives having a beneficial impact on enantioselectivity also led to incomplete conversions. Thus, employment of aryl chlorides without additive in THF was selected as the optimal conditions.

Table 5.6. Additional Examination of Tetra-Alkyl Ammonium Additives.

| | X | B(pin) | 5% Pd(OAc) ₂ <u>7% (<i>R</i>,<i>R</i>)-5.106</u> CsF (3.0 equiv.) additive (1.5 equiv.) | | |
|-------|----|---|---|-----------|-------|
| | | X = Br; 5.91 X = Cl; 5.122 | solvent, 70 °C, 14 h | 5.92 | |
| entry | Х | additive | solvent | conv. (%) | er |
| 1 | Br | NBu ₄ CI | THF | 70 | 90:10 |
| 2 | Br | NEt ₄ Br | THF | >98 | 81:19 |
| 3 | Br | N(tetradecyl) ₄ Me | aCI THF | >98 | 78:22 |
| 4 | Br | Aliquat 336 | THF | >98 | 68:32 |
| 5 | Br | NBu ₄ Cl | dioxane | >98 | 84:16 |
| 6 | Br | NBu ₄ CI | MeCN | >98 | 72:28 |
| 7 | Br | NBu ₄ Cl | Me-THF | >98 | 86:14 |
| 8 | Br | NBu ₄ Cl | MTBE | >98 | 80:20 |
| 9 | CI | | THF | >98 | 90:10 |
| 10 | CI | NBu ₄ Cl | THF | 45 | 93:7 |

5.3.4. Scope of the Pd-Catalyzed Enantioselective Intramolecular Allyl-Aryl Coupling. Subsequent to optimization, the scope of the enantioselective intramolecular allyl-aryl coupling was investigated in depth (Table 5.7). Notably, the unsubstituted test substrate 5.91 provided a moderate yield of carbocycle 5.92 and in high enantioselectivity. It is important to note that the ¹H NMR yield is excellent (90%), and the drop in the isolated yield is consistent with product volatility. A variety of substitution is well tolerated under the optimized reaction conditions. For example, a *meta*-methylated substrate furnishes carboxycle 5.123 in enhanced selectivity and in moderate isolated yield. Employment of *ortho*-methylated substrates results in reduced enantioinduction, however selectivity can be partially restored with the addition of tetrabutylammonium chloride (5.124). The drop in selectivity for substrates bearing *ortho* substitution is likely due to an increase in the rate of reductive elimination in relation to allyl isomerization.

Both electron-rich (5.125) and electron-deficient (5.126) substrates can be crosscoupled effectively, with electron-poor substrates necessitating the use of tetrabutylammonium chloride in order to obtain high enantioselectivity. Notably, disubstituted arenes are also well tolerated, with dioxolane-bearing substrates providing high enantiomeric ratios in moderate yield (5.127). Substitution on the allyl boronate portion of the substrate does not affect reaction efficiency, although selectivity suffers slightly (5.128). Lastly, changing the tether length between the nucleophilic and electrophilic partners results in generation of 6- and 7-membered carbocycles (5.129 and 5.130, respectively). Considering allyl isomerization requires the intermediacy of 9- and 10-membered palladacycles for products **5.129** and **5.130**, the fact that even the slightest enantioinduction is observed is somewhat surprising. Importantly, the carbocyclic products are generated as a single regioisomer, with no α -isomer being observed in any case.



Table 5.7. Scope of the Pd-Catalyzed Enantioselective Intramolecular Coupling.^a

a) Yield refers to isolated yield of purified material and is an average of two experiments. b) Yield determined by ¹H NMR using 1,3,5-trimethoxybenzene as and internal standard. c) Selectivity obtained with NBu₄Cl (1.5 equiv.).

To provide support for the proposed reaction pathway, various test substrates were synthesized which contained altered nucleophilic and electrophilic components If the stereodetermining step in the intramolecular coupling is (Scheme 5.25). transmetallation as described by Miyaura,¹⁹ then the geometry of the allyl boronate moiety should have a significant effect on the stereochemical outcome of the reaction. Instead, employment of the Z-allyl boronate 5.131 under the optimized reaction conditions provided almost identical levels of enantioinduction when compared to the corresponding *E*-allyl boronate (eq. 1 vs. eq. 2). Furthermore, swapping the position of the electrophilic and nucleophilic components in the test substrate (5.132-5.134) resulted in the same enantiomer of product, albeit in slightly varied levels of enantioselectivity (eq. 3, 4, and 5).Considering the likelihood of obtaining similar levels of enantioinduction during the transmetallation step with vastly different substrates is low, it is likely that allyl equilibration of the transmetallated intermediates results in stereoconvergence to a single palladacycle species. Subsequently, reductive elimination controls the product configuration and generates carbocycle 5.92.



Scheme 5.25. Examination of Alternate Substrate Configurations.^a

a) Yields determined by ¹H NMR versus internal standard.

5.4. Conclusion

To summarize, the development of the first example of an enantioselective intramolecular Suzuki-Miyaura coupling between aryl electrophiles and allyl boronates has been described. The methodology displays a wide scope, generating various substituted carbocycles in moderate to good levels of enantioselectivity and with excellent regioselectivity. Furthermore, a variety of nucleophilic and electrophilic
patterns can be utilized to access the desired carbocylces in similar levels of enantioinduction, uncovering a novel mode of stereoselectivity through allyl equilibration. Future studies should focus on enhancing stereoselectivities, testing additional electrophiles such as vinyl halides, and applying the methodology to natural product total synthesis.

5.5. Experimental

5.5.1. General Information.

¹H NMR spectra were measured using a Varian Gemini-500 (500 MHz) spectrometer or a Varian Inova-500 (500 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CHCl₃: 7.26 ppm). Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, p = pentet, br = broad, m = multiplet, app = apparent), and coupling constants (Hz). ¹³C{¹H}NMR spectra were measured using a Varian Inova 500 (126 MHz) spectrometer. Chemical shifts are reported in ppm with the solvent resonance as the internal standard (CDCl₃: 77.0 ppm). ³¹P{¹H}NMR spectra were measured using a Varian Inova 500 (202 MHz) spectrometer. Chemical shifts are reported in ppm using phosphoric acid as the external standard (H₃PO₄: 0.0 ppm). Infrared (IR) spectra were measured using a Bruker α -P Spectrometer. Frequencies are reported in wavenumbers (cm⁻¹) as follows: strong (s), broad (br), medium (m), and weak (w). High-resolution mass spectrometry (HRMS) was performed at Boston College, Chestnut Hill, MA.

Liquid chromatography was performed using forced flow (flash chromatography) on silica gel (SiO₂, 230 x 450 Mesh) purchased from Silicycle. Thin layer chromatography was performed on 25 μ m silica gel glass backed plates from Silicycle. Visualization was performed using ultraviolet light (254 nm), phosphomolybdic acid (PMA), potassium permanganate (KMnO₄), and Seebach's "magic" stain (phosphomolybdic acid, Ce(SO₄)₂, sulfuric acid). Analytical chiral gas-liquid chromatography (GLC) was also performed on an Agilent Technologies 6850 Series

chromatograph with a flame ionization detector, and a Supelco β –Dex 120 column with helium as the carrier gas. Optical rotations were measured on a Rudolph Analytical Research Autopol IV Polarimeter. Analytical chiral supercritical fluid chromatography (SFC) was performed on a Thar Supercritical Chromatograph equipped with auto sampler and a Waters photodiode array detector with methanol as the modifier.

All reactions were conducted in oven- or flame-dried glassware under an inert atmosphere of nitrogen or argon. Tetrahydrofuran, dichloromethane and diethyl ether were purified using Pure Solv MD-4 solvent purification system, from Innovative Technology, Inc., by passing the solvent through two activated alumina columns after being purged with argon. Dimethylformamide was dispensed from a Glass Contour Solvent Purification System (SG Water, USA LLC). Triethylamine was purchased from Aldrich and refluxed over calcium hydride prior to use. Palladium acetate ($Pd(OAc)_2$), rhodium cyclooctadiene chloride dimer ($[RhCl(COD)]_2$), phosphorus trichloride, and triisopropyl phosphine were purchased from Strem Chemicals and used as received. Catechol borane, (*R*,*R*)-tartaric acid, 2,2'-bipyridine, and 3,5-ditertbutylbromobenzene were purchased from Alfa Aesar and used as received. B₂(pin)₂ was obtained from AllyChem and recrystallized from pentane prior to use. 2-Iodobromobenzene and 2-Iodochlorobenzene were purchased from Matrix Scientific and used as received. All other reagents were obtained from Aldrich or Fisher and used as received.

5.5.2. Preparation of Phosphoramidite Ligands.

TADDOL ligands were prepared according to the general reaction scheme shown below. All spectral data are in accordance with the literature.³⁸



5.5.3. Representative Procedures for Preparation of Starting Materials.

Unless otherwise noted, allyl boronate starting materials were prepared according to the general method shown below.



³⁸ Pelz, N. F.; Woodward, A. R.; Burks, H. E.; Sieber, J. D.; Morken, J. P. J. Am. Chem. Soc. **2004**, *126*, 16328.

General procedure for aldehyde synthesis³⁹



To a flame-dried round-bottomed flask equipped with magnetic stir bar in the glovebox was added $Pd(OAc)_2$ (0.02 equiv.). The flask was removed from the glovebox, charged with tetrabutylammonium chloride (1.00 equiv.) and sodium bicarbonate (2.50 equiv.) and sealed with a septum. The flask was evacuated and back-filled with nitrogen (3x) followed by addition of dimethylformamide (0.5 M). After stirring at room temperature for 10 minutes, aryl iodide (1.00 equiv.) followed by allyl alcohol (1.50 equiv.) were added and the resulting mixture was heated to 40 °C for 12 hours. The resulting dark reaction mixture was cooled to room temperature, diluted with diethyl ether (50 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic layers washed with a 50/50 water/brine solution (2 x 50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The pure aldehyde products were isolated after SiO₂ chromatography unless otherwise noted.

³⁹ Kuwabe, S.; Torraca, K. E.; Buchwald, S. L. J. Am. Chem. Soc. 2001, 123, 12202.

General procedure for allylic alcohol synthesis



To a flame-dried round-bottomed flask equipped with magnetic stir bar under nitrogen was added vinyl magnesium bromide (1.0 M in THF, 2.00 equiv.). The solution was cooled to 0 $^{\circ}$ C (ice/water bath) and treated dropwise with aldehyde (0.5 M in THF, 1.00 equiv.). After stirring at room temperature for 1 hour, the resulting yellow solution was returned to 0 $^{\circ}$ C and excess vinyl magnesium bromide was carefully quenched with water (5 mL) followed by addition of saturated aqueous ammonium chloride (20 mL). The resulting mixture was diluted with ethyl acetate (50 mL) and water (20 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The pure allylic alcohol products were isolated after SiO₂ chromatography.

General procedure for allylic chloride synthesis



To a flame-dried round-bottomed flask equipped with magnetic stir bar under nitrogen was added thionyl chloride (10.00 equiv.). The flask was cooled to 0 °C (ice/water bath) and an outlet line was installed in order to allow continuous nitrogen flow from the inlet through the outlet line which was bubbled through a 90/10 saturated aqueous sodium bicarbonate/water solution. Allylic alcohol (0.25 M in DCM, 1.00 equiv.) was then added dropwise and stirred at 0 °C for 30 minutes. After stirring at room temperature for 2 hours, the reaction mixture was diluted with DCM and poured over solid ice (75 mL) in a separatory funnel. The layers were separated and the aqueous layer was extracted with DCM (3 x 50 mL). The combined organic layers were washed with brine (75 mL), dried over sodium sulfate, filtered and concentrated under reduced pressure. The resulting crude material was purified *via* SiO₂ chromatography to give a mixture of internal and terminal chloride products.

General procedure for allyl-boronate synthesis⁴⁰



To an oven-dried vial equipped with magnetic stir bar in the glovebox was added $PdCl_2$ (0.01 equiv.) followed by $B_2(pin)_2$ (1.00 equiv.) and THF (1.0 M). The resulting mixture was stirred for approximately 1 minute followed by addition of allyl chloride (mixture of

⁴⁰ Zhang, P.; Roundtree, I. A.; Morken, J. P. Org. Lett. 2012, 14, 1416.

regioisomers, 1.00 equiv.). The vial was sealed with a cap, removed from the glovebox and heated to 60 °C for 12 hours with vigorous stirring. After cooling to room temperature, the reaction mixture was passed through a plug of SiO₂, eluding with 10% ethyl acetate in hexane (200 mL). The resulting solution was concentrated under reduced pressure to give the crude material which was subsequently purified via SiO₂ chromatography. (NOTE: the allyl-boronate products suffer slow decomposition on SiO₂ and purification is best carried out in an expedient fashion.)

5.5.4. Preparation of Starting Materials.

3-(2-bromophenyl)propanal. Prepared according to the general procedure utilizing $Pd(OAc)_2$ (47.6 0.212 mg, mmol), tetrabutylammonium chloride (2.95 g, 10.6 mmol), sodium bicarbonate (2.23 g, 26.5 mmol), dimethylformamide (21 mL), 2-bromoiodobenzene (1.36 mL, 10.6 mmol), and allyl alcohol (1.10 mL, 15.9 mmol). The crude material was purified (SiO₂, 6% ethyl acetate in hexane) to give the desired product as a clear, yellow oil (1.99 g, 88%). $R_f = 0.29$ (5% ethyl acetate in hexane, UV/magic stain). All spectral data are in accordance with the literature.³⁹



5-(2-bromophenyl)pent-1-en-3-ol. Prepared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 18.7 mL, 18.7 mmol), 3-(2-bromophenyl)propanal (1.99 g,

9.34 mmol), and THF (19 mL). The crude material was purified (SiO₂, 12% ethyl acetate

in hexane) to give the desired product as a clear, slightly yellow oil (1.94 g, 86%). $R_f = 0.24$ (10% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.53 (1H, dd, J = 7.8, 1.0 Hz), 7.26-7.21 (2H, m), 7.07-7.04 (1H, m), 5.93 (1H, ddd, J = 17.1, 10.3, 5.9 Hz), 5.28 (1H, ddd (app dt's), J = 17.1, 1.5, 1.5 Hz), 5.16 (1H, ddd (app dt's), J = 10.3, 1.5, 1.5 Hz), 4.17 (1H, ddd (app q), J = 6.4 Hz), 2.88 (1H, ddd, J = 13.7, 9.3, 5.9 Hz), 2.81 (1H, ddd, J = 13.7, 9.3, 6.9 Hz), 1.91-1.80 (2H, m), 1.73 (1H, br s); ¹³C NMR (126 MHz, CDCl₃): δ 141.2, 140.8, 132.8, 130.4, 127.6, 127.4, 124.4, 115.0, 72.4, 36.9, 32.0; IR (neat): 3359.9 (br), 3066.8 (w), 2931.3 (m), 2864.0 (m), 1643.6 (w), 1566.8 (w), 1470.6 (s), 1438.7 (m), 1045.4 (m), 1022.1 (s), 990.6 (m), 923.6 (s), 748.9 (s), 658.5 (m) cm⁻¹; HRMS-(DART) for: C₁₁H₁₂Br [M+H-H₂O]⁺: calculated: 223.0122, found: 223.0118.

(*E*)-1-bromo-2-(5-chloropent-3-en-1-yl)benzene. Prepared according to the general procedure utilizing thionyl chloride (2.27 mL, 31.3 mmol), 5-(2-bromophenyl)pent-1-en-3-ol (750 mg, 3.11 mmol), and DCM (12.4 mL). The crude material was purified (SiO₂, 2% ethyl acetate in hexane) to give the desired product as a 10:1 mixture of the title compound: 1-bromo-2-(3chloropent-4-en-1-yl)benzene (clear, colorless oil (650.4 mg, 81%). R_f = 0.78 (10% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): (major isomer) δ 7.54 (1H, dd, *J* = 8.3, 1.0 Hz), 7.26-7.19 (2H, m), 7.07 (1H, ddd (app dt's), *J* = 7.3, 7.3, 2.0 Hz), 5.84 (1H, dt's, *J* = 15.2, 6.9, 6.9 Hz), 5.66 (1H, dtt's, *J* = 15.2, 6.9, 6.9, 1.5, 1.5 Hz), 4.04 (2H, d, *J* = 6.8 Hz), 2.84 (2H, t, *J* = 7.3 Hz), 2.40 (2H, dt's (app q), *J* = 7.8 Hz); (minor isomer) δ 7.54 (1H, d, J = 8.3 Hz), 7.26-7.19 (2H, m), 7.10-7.05 (1H, m), 5.96 (1H, ddd, J = 17.1, 10.3, 7.8 Hz), 5.32 (1H, d, J = 17.1 Hz), 5.19 (1H, d, J = 10.3 Hz), 4.38 (1H, ddd (app q), J = 7.8 Hz), 2.95 (1H, ddd, J = 13.7, 9.3, 5.9 Hz), 2.89-2.82 (1H, m), 2.18-2.08 (2H, m); ¹³C NMR (126 MHz, CDCl₃): (both isomers (one overlapping signal)) δ 140.6, 140.1, 138.2, 134.5, 132.9, 132.8, 130.5, 130.4, 127.9, 127.7, 127.5, 127.4, 126.8, 124.4, 116.9, 62.2, 45.2, 37.9, 35.5, 33.1, 32.1; IR (neat): 3054.3 (w), 3037.0 (w), 3011.4 (w), 2950.5 (m), 2931.3 (m), 2860.6 (w), 1665.2 (m), 1592.5 (w), 1566.8 (m), 1470.6 (s), 1438.7 (s), 1249.7 (m), 1023.5 (s), 965.1 (s), 747.9 (s), 676.1 (s), 657.4 (s), 444.3 (m) cm⁻¹; HRMS-(DART) for: C₁₁H₁₂Br [M+H-HCl]⁺: calculated: 223.0122, found: 223.0121.

(E)-2-(5-(2-bromophenyl)pent-2-en-1-yl)-4,4,5,5-Br tetramet- hyl-1,3,2-dioxaborolane. Prepared according to

the general procedure utilizing PdCl₂ (4.2 mg, 0.024 mmol), B₂(pin)₂ (599.6 mg, 2.36 mmol), THF (2.4 mL), and (*E*)-1-bromo-2-(5-chloropent-3-en-1-yl)benzene (10:1 with regio-isomeric allyl chloride, 612.9 mg, 2.36 mmol). The crude material was purified (SiO₂, 4% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (538.0 mg, 65%). R_f = 0.36 (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.51 (1H, d, *J* = 7.8 Hz), 7.23-7.19 (2H, m), 7.06-7.01 (1H, m), 5.55-5.43 (2H, m), 2.77 (2H, t, *J* = 7.8 Hz), 2.30 (2H, dt (app q), *J* = 5.9 Hz), 1.65 (2H, d, *J* = 6.8 Hz), 1.25 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 141.4, 132.7, 130.4, 129.5, 127.4, 127.2, 125.9, 124.5, 83.1, 36.4, 32.8, 24.8; IR (neat): 3057.0 (w), 2977.3 (m),

2930.1 (m), 2862.4 (w), 1664.3 (w), 1591.9 (w), 1469.8 (m), 1438.8 (m), 1359.7 (s), 1323.1 (s), 1271.9 (m), 1213.7 (m), 1164.4 (m), 1142.3 (s), 1022.7 (m), 966.1 (s), 846.6 (s), 747.4 (s), 657.5 (m), 444.9 (w) cm⁻¹; HRMS-(DART) for: $C_{17}H_{25}BBrO_2$ [M+H]⁺: calculated: 351.1131, found: 351.1136.

3-(2-chlorophenyl)propanal. Prepared according to the general procedure utilizing $Pd(OAc)_2$ (44.9 mg, 0.20 mmol), tetrabutylammonium chloride (2.78 g, 10.0 mmol), sodium bicarbonate (2.10 g, 25.0 mmol), dimethylformamide (20 mL), 2-chloroiodobenzene (1.22 mL, 10.0 mmol), and allyl alcohol (1.02 mL, 15.0 mmol). The crude material was purified (SiO₂, 6% ethyl acetate in hexane) to give the desired product as a clear, slightly yellow oil (1.5592 g, 92%). $R_f = 0.40$ (10% ethyl acetate in hexane, UV/magic stain). All spectral data are in accordance with the literature.³⁹

5-(2-chlorophenyl)pent-1-en-3-ol. Prepared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 8.00 mL, 8.00 mmol), 3-(2-chlorophenyl)propanal (674.5 mg, 4.00 mmol), and THF (8.0 mL). The crude material was purified (SiO₂, 12% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (675 mg, 86%). $R_f = 0.22$ (10% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.34 (1H, dd, J = 7.8, 1.5 Hz), 7.25 (1H, dd, J = 7.8, 2.0 Hz), 7.18 (1H, ddd (app dt's), J = 7.8, 7.8, 1.5 Hz), 5.28

(1H, ddd (app dt's), J = 17.1, 1.5, 1.5 Hz), 5.15 (1H, ddd (app dt's), J = 10.3, 1.0, 1.0 Hz), 4.16 (1H, ddd (app q), J = 5.9 Hz), 2.88 (1H, ddd, J = 13.7, 9.3, 6.5 Hz), 2.80 (1H, ddd, J = 13.7, 9.8, 6.9 Hz), 1.91-1.80 (2H, m), 1.75 (1H, br s); ¹³C NMR (126 MHz, CDCl₃): δ 140.8, 139.5, 133.9, 130.4, 129.5, 127.3, 126.8, 115.0, 72.5, 36.7, 29.5; IR (neat): 3374.8 (br), 3072.8 (w), 2929.1 (m), 2863.2 (w), 1643.6 (w), 1571.6 (w), 1474.3 (s), 1443.0 (m), 1133.3 (w), 1051.5 (s), 1031.5 (m), 990.9 (m), 923.9 (s), 750.2 (s), 679.7 (m) cm⁻¹; HRMS-(DART) for: C₁₁H₁₂Cl [M+H-H₂O]⁺: calculated: 179.0628, found: 179.0631.

(E)-1-chloro-2-(5-chloropent-3-en-1-yl)benzene. Prepared CI CI according to the general procedure utilizing thionyl chloride (2.27 mL, 31.1 mmol), 5-(2-chlorophenyl)pent-1-en-3-ol (750 mg, 3.11 mmol), and DCM (12.4 mL). The crude material was purified (SiO₂, 2% ethyl acetate in hexane) to give the desired product as a 9:1 mixture of the title compound: 1-chloro-2-(3-chloropent-4-en-1-yl)benzene (clear, colorless oil (650.4 mg, 81%)). $R_f = 0.77$ (10% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): (major isomer) δ 7.35 (1H, d, J = 7.8 Hz), 7.22-7.20 (2H, m), 7.18-7.13 (1H, m), 5.84 (1H, dt's, J = 15.2, 6.9, 6.9 Hz), 5.66 (1H, dt's, J = 15.2, 7.3, 7.3 Hz), 4.04 (2H, d, J = 7.3 Hz), 2.84 (2H, t, J = 7.3 Hz), 2.40 (2H, dt's (app q), J = 7.3 Hz); (minor isomer) δ 7.35 (1H, d, J = 7.8 Hz), 7.27-7.25 (1H, m), 7.18-7.13 (2H, m), 5.96 (1H, ddd, J = 16.6, 10.3, 8.3 Hz), 5.32 (1H, d, J = 16.6 Hz), 5.19 (1H, d, J = 10.3 Hz), 4.37 (1H, ddd (app q), J = 6.9 Hz), 2.96 (1H, ddd, J = 14.2, 8.8, 6.4 Hz), 2.89-2.82 (1H, m), 2.17-2.11 (2H, m); ¹³C NMR (126 MHz, CDCl₃): (both isomers) δ 138.9, 138.4, 138.2, 134.6, 133.9, 133.9, 130.5, 130.4, 129.6, 129.5, 127.7, 127.4, 126.8, 126.7, 126.7, 116.8, 62.2, 45.1, 37.8, 32.9, 32.0, 30.5; IR (neat): 3063.8 (w), 3035.5 (w), 2933.5 (m), 2861.0 (w), 1665.3 (w), 1593.9 (w), 1571.8 (w), 1474.2 (s), 1441.7 (s), 1349.0 (w), 1250.1 (s), 1122.7 (w), 1069.0 (w), 1051.3 (s), 1036.2 (s), 965.6 (s), 749.3 (s), 675.2 (s), 445.4 (m) cm⁻¹; HRMS-(DART) for: C₁₁H₁₂Cl [M+H-HCl]⁺: calculated: 179.0628, found: 179.0620.

(E)-2-(5-(2-chlorophenyl)pent-2-en-1-yl)-4,4,5,5-tetrame-B(pin) CI thyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizing $PdCl_2$ (3.8 mg, 0.021 mmol), $B_2(pin)_2$ (544.7 mg, 2.15 mmol), THF (2.1 mL), and (E)-1-chloro-2-(5-chloropent-3-en-1-yl)benzene (9:1 with regioisomeric allyl chloride, 500 mg, 2.15 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (525.7 mg, 80%). $R_f = 0.36$ (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.32 (1H, dd, J = 7.8, 1.0 Hz), 7.20 (1H, dd, J = 7.8, 2.0 Hz), 7.16 (1H, ddd (app dt's), J = 7.8, 7.8, 2.0 Hz), 7.11 (1H, ddd (app dt's), J = 7.8, 7.8, 2.0 Hz), 5.58-5.42 (2H, m), 2.77 (2H, t, J = 7.8 Hz), 2.31 (2H, dt's (app q), J = 5.9 Hz), 1.65 (2H, d, J = 6.8 Hz)Hz), 1.25 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 139.7, 133.9, 130.4, 129.6, 129.3, 127.0, 126.5, 125.8, 83.1, 33.8, 32.6, 24.7; IR (neat): 3059.8 (w), 2978.3 (m), 2931.5 (m), 1641.2 (w), 1572.0 (w), 1473.9 (m), 1443.2 (m), 1361.1 (s), 1326.0 (s), 1272.7 (m), 1214.3 (w), 1143.6 (s), 1051.7 (w), 967.3 (s), 882.3 (w), 847.9 (s), 750.4 (s), 675.7 (m),

578.5 (w) cm⁻¹; HRMS-(DART) for: C₁₇H₂₅BClO₂ [M+H]⁺: calculated: 307.1636, found: 307.1631.

sodium bicarbonate (5.25 g, 62.5 mmol), dimethylformamide (50 mL), 2-chloro-1-iodo-4-methylbenzene (6.31 mL, 25.0 mmol), and allyl alcohol (2.55 mL, 37.5 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane) to give the desired product as a clear, slightly yellow oil (2.20 g, 48%). $R_f = 0.40$ (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 9.82 (1H, s), 7.18 (1H, d, *J*= 1.0 Hz), 7.12 (1H, d, *J*= 8.0 Hz), 6.99 (1H, dd, *J*= 8.0, 1.5 Hz), 3.02 (2H, t, *J* = 7.5 Hz), 2.77 (2H, td, *J* = 7.5, 7.5, 1.0 Hz), 2.30 (3H, s) ; ¹³C NMR (126 MHz, CDCl₃): δ 201.2, 137.9, 134.7, 133.4, 130.2, 130.0, 127.7, 43.6, 25.7, 20.6; IR (neat): 2923.8 (w), 2821.7 (w), 2722.7 (w), 1722.8 (s), 1610.3 (w), 1494.3 (s), 1446.8 (m), 1406.4 (m), 1214.7 (w), 1052.6 (s), 878.3 (s), 818.9 (s), 687.3 (m), 563.8 (m), 409.9 (m) cm⁻¹; HRMS-(DART) for: C₁₀H₁₀CIO [M-H]⁺: calculated: 181.0420, found: 181.0426.



5-(2-chloro-4-methylphenyl)pent-1-en-3-ol. Prepared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 11.0 mL, 11.0 mmol), 3-(2-chloro-4-

methylphenyl)propanal (1.00 g, 5.74 mmol), and THF (11.0 mL). The crude material

was purified (SiO₂, 10% ethyl acetate in hexane) to give the desired product as a clear, slightly yellow oil (1.05 g, 91%). $R_f = 0.31$ (10% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.17 (1H, d, *J*= 1.0 Hz), 7.12 (1H, d, *J*= 7.5 Hz), 6.99 (1H, dd, *J*= 8.0, 1.0 Hz), 5.92 (1H, ddd, *J*= 16.5, 10.0, 6.0 Hz), 5.27 (1H, ddd (app dt's), *J* = 17.0, 1.5, 1.5 Hz), 5.15 (1H, ddd (app dt's), *J* = 11.0, 1.0, 1.0 Hz), 4.15 (1H, ddd (app q), *J* = 6.5 Hz), 2.83 (1H, ddd, *J*= 15.0, 9.0, 6.0 Hz), 2.76 (1H, ddd, *J*= 14.5, 9.5, 7.0 Hz), 2.30 (3H, s), 1.86-1.81 (2H, m), 1.77 (1H, br s); ¹³C NMR (126 MHz, CDCl₃): δ 140.8, 137.3, 136.2, 133.5, 130.1, 129.9, 127.6, 114.9, 72.5, 36.9, 29.0, 20.6; IR (neat): 3348.7 (br), 2979.6 (s), 2923.4 (m), 2864.6 (m), 1610.5 (s), 1494.6 (m), 1452.4 (m), 1425.5 (m), 1311.6 (s), 1180.4 (s), 1109.5 (s), 1109.5 (s), 1048.3 (s), 990.4 (s), 923.1 (m), 820.2 (s), 687.4 (m) cm⁻¹; HRMS-(DART) for: C₁₂H₁₄Cl [M+H-H₂O]⁺: calculated: 193.0784, found: 193.0774.

Me C_I (*E*)-2-chloro-1-(5-chloropent-3-en-1-yl)-4-methylbenzene Prepared according to the general procedure utilizing thionyl chloride (3.44 mL, 47.5 mmol), 5-(2-chloro-4-methylphenyl)pent-1-en-3-ol (1.00 g, 4.75 mmol), and DCM (14.4 mL). The crude material was purified (SiO₂, 2% ethyl acetate in hexane) to give the desired product as a 6.7:1 mixture of the title compound: 2chloro-1-(3-chloropent-4-en-1-yl)-4-methylbenzene (997 mg, 90%)). R_f = 0.38 (4% DCM in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): (major isomer) δ 7.16 (1H, s), 7.06 (1H, d, *J*= 7.5 Hz), 6.98 (1H, d, *J*= 7.0 Hz), 5.81 (1H, dt's, *J* = 15.5, 6.5, 6.5 Hz), 5.64 (1H, dt's, *J* = 15.0, 7.0, 7.0 Hz), 4.02 (2H, d, *J* = 7.0 Hz), 2.77 (2H, t, *J* = 7.5 Hz), 2.40 (2H, dt's (app q), J = 7.0 Hz), 2.29 (3H, s); (minor isomer) δ 7.16 (1H, s), 7.12 (1H, d, J = 7.5), 7.07-6.97 (1H, m), 5.93 (1H, ddd, J = 17.0, 10.0, 8.0 Hz), 5.29 (1H, d, J = 16.5 Hz), 5.17 (1H, d, J = 10.0 Hz), 4.34 (1H, ddd (app q), J = 7.5 Hz), 2.89 (1H, ddd, J = 14.5, 9.0, 6.5 Hz), 2.83-2.76 (1H, m), 2.29 (3H, s), 2.16-2.06 (2H, m); ¹³C NMR (126 MHz, CDCl₃): (both isomers, one overlapping signal) δ 138.3, 137.7, 137.4, 135.7, 135.2, 134.8, 133.6, 133.5, 130.3, 130.2, 130.1, 129.9, 127.6, 127.5, 126.7, 116.8, 62.3, 45.2, 37.9, 32.5, 32.1, 30.1, 20.7; IR (neat): 3033.1 (w), 2924.7 (m), 2831.3 (w), 1665.8 (w), 1610.1 (w), 1494.1 (s), 1441.2 (m), 1250.1 (m), 1214.6 (w), 1049.7 (s), 966.0 (s), 930.9 (w), 875.0 (s), 817.9 (s), 686.6 (s), 573.2 (m), 446.5 (w) cm⁻¹; HRMS-(DART) for: C₁₂H₁₄Cl [M+H-HCl]⁺: calculated: 193.0784, found: 193.0788.



according to the general procedure utilizing PdCl₂ (7.0 mg, 0.039 mmol), B₂(pin)₂ (997 mg, 3.93 mmol), THF (3.9 mL), and (*E*)-2-chloro-1-(5-chloropent-3-en-1-yl)-4-methylbenzene (6.67:1 with regioisomeric allyl chloride, 900 mg, 3.93 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (1.08 g, 85%). R_f = 0.42 (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.14 (1H, s), 7.08 (1H, d, *J* = 7.5 Hz), 6.96 (1H, d, *J* = 7.5, 1.0 Hz), 5.53-5.42 (2H, m), 2.72 (2H, t, *J* = 8.0 Hz), 2.30-2.26 (2H, m), 2.28 (3H, s), 1.65 (2H, d, *J* = 6.5 Hz), 1.25 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 136.9, 136.5, 133.5, 130.1, 129.8, 129.7, 127.3, 125.7, 83.1, 33.4, 32.8, 24.7, 20.6; IR (neat):

2977.8 (m), 2928.3 (w), 2862.9 (w), 1610.5 (w), 1451.3 (w), 1360.2 (s), 1325.1 (s), 1272.4 (w), 1214.2 (w), 1164.8 (s), 1050.1 (w), 1004.5 (s), 882.2 (m), 847.2 (m), 818.1 (m), 686.3 (w), 673.9 (w), 575.9 (w), 449.9 (w) cm⁻¹; HRMS-(DART) for: $C_{18}H_{27}BClO_2$ $[M+H]^+$: calculated: 321.1793, found: 321.1797.

NH₂ 2-chloro-3-methylaniline. To a solution of 2-chloro-1-methyl-3nitrobenzene (5.00 g, 29.1 mmol) in ethanol (48 mL) was added Fe(0) CI Me (4.88g, 87.4 mmol) and conc. HCl (2.43 mL) at room temperature. The reaction mixture was heated to reflux for 1.5 hours and then cooled to room temperature. The solvent was removed under reduced pressure and the residue was diluted with sat. aq. NH₄Cl and extracted with ethyl acetate (3 x 75 mL). The organic layers were combined and washed with DI H₂O (75 mL), brine (75 mL), dried over sodium sulfate, and concentrated under reduced pressure. The crude material was purified (SiO₂, 5% ethyl acetate in hexane) to give the product as a clear, yellow oil (2.78g, 67%). ¹H NMR (500 MHz, CDCl₃): δ 6.96 (1H, dd (app t), J= 8.0 Hz), 6.65-6.63 (2H, m), 4.07 (2H, br s), 2.35 (3H, s); ¹³C NMR (126 MHz, CDCl₃): § 143.0, 136.8, 126.7, 120.3, 119.8, 113.3, 20.4; IR (neat): 3471.2 (br), 3381.2 (br), 3060.8 (w), 3026.1 (w), 2979.9 (w), 2950.3 (w), 1611.3 (s), 1469.5 (s), 1313.1 (m), 1167.7 (w), 1095.2 (w), 1048.0 (s), 943.9 (w), 764.9 (s), 708.5 (m), 598.2 (s) cm⁻¹; HRMS-(DART) for: C₇H₉ClN [M]⁺: calculated: 142.0424, found: 142.0426.

CI equipped with a magnetic stir bar was added 2-chloro-3-methylaniline (2.25 Me

g, 15.9 mmol), followed by DI H₂O (41 mL) and conc. HCl (8.1 mL). The reaction mixture was cooled to 0 °C (ice/water bath) and treated dropwise with a solution of sodium nitrite (1.42 g, 20.6 mmol) in DI H₂O (10 mL), maintaining the reaction temperature to less than 10 °C. After completing addition, the reaction mixture was allowed to stir at 0 °C for 30 minutes. To the mixture was added dropwise a solution of potassium iodide (4.22 g, 25.4 mmol) in DI H_2O (10 mL). The mixture rapidly turned to a deep black solution. After the addition was complete, the mixture was heated to $60 \,^{\circ}\text{C}$ and allowed to stir for 1 h. The cooled solution was washed with 10% sodium bicarbonate (50 mL), 1M sodium thiosulfate (50 mL), 10% hydrochloric acid (50 mL), water (50 mL), and brine (50 mL). The organic layer was dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified (SiO2, 100% hexanes), to give the product as a clear, slightly yellow oil (2.51 g, 63%). ¹H NMR (500 MHz, CDCl₃): δ 7.70 (1H, d, J= 8.0 Hz), 7.20 (1H, d, J= 8.0 Hz), 6.86 (2H, t, J = 7.5 Hz), 2.45 (3H, s); ¹³C NMR (126 MHz, CDCl₃): δ 138.1, 137.9, 137.7, 130.6, 127.7, 98.9, 22.4; IR (neat): 3052.6 (w), 2977.9 (w), 2952.1 (w), 2921.9 (w), 1579.0 (w), 1441.0 (s), 1398.7 (s), 1375.9 (m), 1251.6 (w), 1179.5 (w), 1090.7 (m), 1048.1 (s), 893.9 (s), 828.3 (s), 716.7 (s), 697.8 (s), 556.3 (m) cm⁻¹; HRMS-(DART) for: $C_7H_6ClI[M]^+$: calculated: 251.9203, found: 251.9213.



5-(2-chloro-3-methylphenyl)pent-1-en-3-ol To a flame-dried round-bottomed flask equipped with magnetic stir bar in the glovebox was added $Pd(OAc)_2$ (71.3 mg, 0.32 mmol). The flask

was removed from the glovebox, charged with tetrabutylammonium chloride (5.29 g, 19.0 mmol) and sodium bicarbonate (3.33 g, 39.7 mmol) and sealed with a septum. The flask was evacuated and back-filled with nitrogen (3x) followed by addition of dimethylformamide (32 mL). After stirring at room temperature for 10 minutes, 2-chloro-1-iodo-3-methylbenzene (2.50 g, 9.90 mmol) followed by allyl alcohol (2.16 mL, 31.7 mmol) were added and the resulting mixture was heated to 40 °C for 12 hours. The resulting dark reaction mixture was cooled to room temperature, diluted with diethyl ether (50 mL) and water (50 mL) and the layers separated. The aqueous layer was extracted with diethyl ether (3 x 50 mL) and the combined organic layers washed with a 50/50 water/brine solution (2 x 50 mL). The organic layer was dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude reaction mixture was partially purified using flash chromatography (SiO₂, 10% ethyl acetate in hexane) to give a clear, yellow oil (crude, 1.21 g) which was used in the next step without any further purification.

The title compound was prepared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 13.3 mL, 13.3 mmol), 3-(2-chloro-3-methylphenyl)propanal (1.21 g, 6.63 mmol), and THF (13.3 mL). The crude material was purified (SiO₂, 10% ethyl acetate in hexane) to give the desired product as a clear, slightly yellow oil (1.12 g, 54% over 2 steps). $R_f = 0.37$ (10% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.40-7.05 (3H, m), 5.93 (1H, ddd, J = 17.0, 11.0, 6.5 Hz), 5.28 (1H, ddd (app dt's), J = 17.0, 1.5, 1.5 Hz), 5.15 (1H, ddd (app dt's), J = 10.5, 1.5, 1.5 Hz), 4.14 (1H, ddd (app q), J = 6.0 Hz), 2.89 (1H, ddd, J = 14.5,

9.5, 6.0 Hz), 2.81 (1H, ddd, J= 14.0, 9.5, 6.5 Hz), 2.39 (3H, s), 1.91-1.80 (2H, m), 1.66 (1H, br s); ¹³C NMR (126 MHz, CDCl₃): δ 140.9, 139.6, 136.6, 134.2, 128.7, 127.9, 126.1, 114.9, 72.5, 36.7, 30.0, 20.8; IR (neat): 3334.1 (br), 2979.4 (w), 2925.2 (w), 2862.9 (w), 1466.2 (m), 1453.7 (m), 1419.2 (m), 1380.5 (w), 1166.6 (w), 1043.2 (s), 989.5 (s), 922.4 (s), 770.2 (s), 725.1 (s) cm⁻¹; HRMS-(DART) for: C₁₂H₁₂Cl [M+H-H₂O]⁺: calculated: 191.0628, found: 191.0626.

(E)-2-chloro-1-(5-chloropent-3-en-1-yl)-3-methylbenzene. CI Prepared according to the general procedure utilizing thionyl CI Me chloride (2.53)mL, 34.5 mmol), 5-(2-chloro-3methylphenyl)pent-1-en-3-ol (734 mg, 3.48 mmol), and DCM (12.4 mL). The crude material was purified (SiO₂, 2% ethyl acetate in hexane) to give the desired product as a 6.7:1 2-chloro-1-(3-chloropent-4-en-1-yl)-3mixture of the title compound: methylbenzene (655 mg, 82%)). $R_f = 0.38$ (4% DCM in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): (major isomer) δ 7.11-7.04 (3H, m), 5.85 (1H, dt's, J = 15.0, 7.0, 7.0 Hz), 5.66 (1H, dt's, J = 15.5, 7.0, 7.0 Hz), 4.04 (2H, d, J = 7.0 Hz), 2.84 (2H, t, J = 7.0 Hz, 2.42-2.37 (2H, m), 2.40 (3H, s); (minor isomer) δ 7.11-7.04 (3H, m), 5.95 (1H, ddd (app dt's), J = 16.5, 10.0, 10.0 Hz), 5.31 (1H, d, J = 17.0 Hz), 5.19 (1H, d, J = 10.5Hz), 4.37 (1H, ddd (app q), J = 7.5 Hz), 2.96 (1H, ddd (app dt's), J = 15.0, 9.0, 9.0 Hz), 2.89-2.83 (1H, m), 2.40 (3H, s), 2.16-2.11 (2H, m); ¹³C NMR (126 MHz, CDCl₃): (both isomers) § 139.1, 138.6, 138.3, 136.8, 136.6, 134.9, 134.2, 134.2, 129.0, 128.8, 128.0, 127.8, 126.6, 126.2, 126.1, 116.8, 62.4, 45.2, 37.8, 33.5, 32.0, 31.1, 20.8, 20.8; IR (neat):

3054.7, (w), 2951.7 (m), 2858.6 (w), 1665.6 (w), 1466.7 (s), 1453.9 (s), 1439.9 (m), 1249.7 (m), 1044.8 (s), 965.2 (s), 771.4 (s), 679.0 (m), 630.0 (s), 566.0 (w) cm⁻¹; HRMS-(DART) for: $C_{12}H_{14}Cl [M+H-HCl]^+$: calculated: 193.0784, found: 193.0785.

(*E*)-2-(5-(2-chloro-3-methylphenyl)pent-2-en-1-yl)-4,4,5,5tetramethyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizing PdCl₂ (5.1 mg, 0.029 mmol), B₂(pin)₂ (726 mg, 2.86 mmol), THF (2.9 mL), and (*E*)-2-chloro-1-(3-chloropent-4-en-1-yl)-3-methylbenzene (6.7:1 with regio-isomeric allyl chloride, 655 mg, 2.86 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (789 mg, 86%). $R_f = 0.38$ (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.07-7.04 (3H, m), 5.54-5.43 (2H, m), 2.78 (2H, t, *J* = 8.0 Hz), 2.38 (3H, s), 2.30 (2H, dt's (app q), *J* = 6.5 Hz), 1.65 (2H, d, *J* = 6.0 Hz), 1.25 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 139.9, 136.3, 134.2, 129.8, 128.4, 127.8, 125.9, 125.6, 83.1, 34.4, 32.6, 24.7, 20.8; IR (neat): 2977.6 (m), 2930.3 (s), 1466.8 (w), 1359.3 (s), 1323.6 (s), 1213.8 (s), 1164.8 (s), 1107.7 (m), 882.7 (w), 846.6 (m), 770.6 (m), 724.2 (s), 673.7 (s) cm⁻¹; HRMS-(DART) for: C₁₈H₂₇BClO₂ [M+H]⁺: calculated: 321.1793, found: 321.1785.



sodium bicarbonate (1.56 g, 18.6 mmol), dimethylformamide (15 mL), 1-chloro-2-iodo-

4-methoxybenzene (2.00 g, 7.45 mmol), and allyl alcohol (0.76 mL, 11.2 mmol). The crude material was purified (SiO₂, 20% ethyl acetate in hexane) to give the desired product as a clear, slightly yellow oil (1.25 g, 84%). $R_f = 0.49$ (30% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 9.82 (1H, s), 7.23 (1H, d, J= 9.0 Hz), 6.78 (1H, d, J= 2.0 Hz), 6.70 (1H, dd, J= 8.5, 3.0 Hz), 3.77 (3H, s), 3.01 (2H, t, J = 7.5 Hz), 2.78 (2H, t, J = 7.5 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 200.9, 158.3, 138.8, 130.0, 125.0, 116.0, 113.1, 55.3, 43.3, 26.3; IR (neat): 3003.4 (w), 2938.8 (w), 2836.1 (w), 2723.9 (w), 1721.6 (s), 1597.3 (m), 1575.8 (m), 1476.3 (s), 1408.5 (m), 1298.2 (s), 1278.3 (s), 1241.1 (s), 1191.1 (s), 1021.7 (s), 868.8 (w), 805.4 (m), 630.9 (s), 858.7 (w) cm⁻¹; HRMS-(DART) for: $C_{10}H_{15}CINO_2$ [M+NH₄]⁺: calculated: 216.0791, found: 216.0788.



5-(2-chloro-5-methoxyphenyl)pent-1-en-3-ol. Prepared according to the general procedure utilizing vinyl magnesium

methoxyphenyl)propanal (1.20 g, 6.04 mmol), and THF (12.0 mL). The crude material was purified (SiO₂, 10% ethyl acetate in hexane) to give the desired product as a clear, slightly yellow oil (1.22 g, 89%). $R_f = 0.22$ (10% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.23 (1H, d, J= 9.0 Hz), 6.79 (1H, d, J= 3.0 Hz), 6.69 (1H, dd, J= 3.0, 8.5 Hz), 5.92 (1H, ddd, J= 16.5, 10.0, 5.5 Hz), 5.27 (1H, ddd (app dt's), J = 17.0, 1.5, 1.5 Hz), 5.16 (1H, ddd (app dt's), J = 10.5, 1.5, 1.5 Hz), 4.16 (1H, ddd (app q), J = 6.5 Hz), 3.77 (3H, s), 2.83 (1H, ddd, J = 14.0, 9.5, 6.5 Hz), 2.75 (1H, ddd, J= 14.0, 9.5, 6.5 Hz), 1.90-1.79 (2H, m), 1.69 (1H, br s); ¹³C NMR (126 MHz, CDCl₃): δ 158.3, 140.8, 140.4, 130.0, 125.3, 115.9, 115.0, 112.8, 72.4, 55.4, 36.7, 29.8; IR (neat): 3360.6 (br), 3003.1 (w), 2936.2 (m), 2864.5 (s), 2836.7 (s), 1597.0 (m), 1575.3 (m), 1476.0 (s), 1419.8 (s), 1277.2 (s), 1161.7 (s), 1023.3 (s), 923.9 (m), 855.2 (s), 631.7 (s), 460.6 (s) cm⁻¹; HRMS-(DART) for: C₁₂H₁₄ClO [M+H-H₂O]⁺: calculated: 209.0733, found: 209.0731.

(E)-1-chloro-2-(5-chloropent-3-en-1-yl)-4-methoxyben-MeO CI CI Prepared according to the general procedure zene. utilizing thionyl chloride (3.52 mL, 48.5 mmol), 5-(2-chloro-5-methoxyphenyl)pent-1en-3-ol (1.10 g, 4.85 mmol), and DCM (16 mL). The crude material was purified (SiO₂, 2% ethyl acetate in hexane) to give the desired product as a 5:1 mixture of the title compound: 1-chloro-2-(3-chloropent-4-en-1-yl)-4-methoxybenzene (clear, colorless oil (1.08 g, 91%)). R_f = 0.65 (10% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): (major isomer) δ 7.23 (1H, d, J = 8.5 Hz), 6.84 (1H, d, J = 3.5 Hz), 6.70 (1H, dd, J = 8.5, 3.0 Hz), 5.83 (1H, dt's, J = 15.0, 7.0, 7.0 Hz), 5.66 (1H, dtt's, J = 15.0, J)7.5, 7.5, 1.0, 1.0 Hz), 4.03 (2H, d, J = 7.0 Hz), 3.78 (3H, s), 2.78 (2H, t, J = 8.0 Hz), 2.38 (2H, dt's (app q), J = 7.0 Hz); (minor isomer) δ 7.24 (1H, d, J = 8.5 Hz), 6.79 (1H, d, J =3.5 Hz), 6.71 (1H, dd, J= 8.5, 3.5 Hz), 5.94 (1H, ddd, J = 17.0, 10.0, 7.5 Hz), 5.31 (1H, ddd (app dt's), J = 17.0, 1.0, 1.0 Hz), 5.18 (1H, d, J = 10.5 Hz), 4.36 (1H, ddd (app q), J = 7.5 Hz), 3.79 (3H, s), 2.89 (1H, ddd, J = 13.5, 9.5, 6.0 Hz), 2.83-2.76 (1H, m), 2.17-2.07 (2H, m); ¹³C NMR (126 MHz, CDCl₃): (both isomers) δ 158.3, 158.2, 139.8, 139.4,

138.2, 134.6, 130.2, 130.0, 126.8, 125.3, 116.9, 116.1, 116.0, 115.9, 113.0, 112.8, 62.2, 55.4, 45.2, 37.7, 36.6, 33.2, 31.9, 30.8; IR (neat): 3003.5 (w), 2939.1 (w), 2836.7 (w), 2723.3 (w), 1723.4 (s), 1597.8 (m), 1576.2 (m), 1477.5 (s), 1420.4 (m), 1356.3 (m), 1299.0 (m), 1279.1 (s), 1063.9 (m), 1022.5 (m), 936.3 (w), 870.0 (m), 631.3 (m) cm⁻¹; HRMS-(DART) for: $C_{12}H_{14}Cl_2O [M]^+$: calculated: 244.0422, found: 244.0422.



according to the general procedure utilizing PdCl₂ (5.3 mg, 0.030 mmol), B₂(pin)₂ (259 mg, 3.00 mmol), THF (3.0 mL), and (*E*)-1-chloro-2-(5-chloropent-3-en-1-yl)-4methoxybenzene (5:1 with regio-isomeric allyl chloride, 733 mg, 3.00 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (917 mg, 91%). R_f = 0.47 (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.21 (1H, d, *J*= 9.0 Hz), 7.75 (1H, d, *J* = 3.0 Hz), 6.66 (1H, dd, *J*= 9.0, 3.5 Hz), 5.54-5.42 (2H, m), 3.77 (3H, s), 2.72 (2H, t, *J* = 8.0 Hz), 2.29 (2H, dt's (app q), *J* = 7.5 Hz), 1.65 (2H, d, *J* = 7.0 Hz), 1.24 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 158.1, 140.7, 129.8, 129.6, 125.8, 125.3, 115.8, 112.5, 83.1, 55.4, 34.1, 32.6, 24.7; IR (neat): 2977.8 (m), 2935.2 (m), 2837.8 (w), 1397.3 (w), 1575.7 (w), 1476.4 (s), 1360.4 (s), 1325.3 (s), 1275.2 (m), 1240.5 (s), 1162.2 (m), 1143.6 (s), 1108.5 (m), 1026.6 (s), 881.9 (m), 846.9 (w), 631.3(w) cm⁻¹; HRMS-(DART) for: C₁₈H₂₆BClO₃ [M]⁺: calculated: 336.1664, found: 336.1679.

5-chloro-6-iodobenzo[d][1,3]dioxole. To an oven-dried 250 mL RBF equipped with a stir bar added was а solution of 5chlorobenzo[d][1,3]dioxole (2.00 g, 12.8 mmol) in acetonitrile (60 mL). To the flask was added trifluoroacetic acid (2.90 g, 25.4 mmol) followed by N-iodosuccinimide (8.60 g, 38.2 mmol), and the mixture was allowed to stir in the dark at room temperature under nitrogen for 24 hours. The dark brown solution was concentrated under reduced pressure and the crude residue was purified (SiO₂, 0-4% ethyl acetate in hexane) to give the desired product as a slightly yellow oil (1.80 g, 50%). $R_f = 0.52$ (5% ethyl acetate in hexane, UV/magic stain). All spectral data are in accordance with the literature.⁴¹



3-(6-chlorobenzo[d][1,3]dioxol-5-yl)propanal. Prepared according to the general procedure utilizing Pd(OAc)₂ (28.6 mg, 0.128 mmol), tetrabutylammonium chloride (1.77 g, 6.37 mmol),

sodium bicarbonate (1.34 g, 15.9 mmol), dimethylformamide (20 mL), 5-chloro-6iodobenzo[d][1,3]dioxole (1.80 g, 6.37 mmol), and allyl alcohol (0.65 mL, 9.6 mmol). The crude material was purified (SiO₂, 6% ethyl acetate in hexane) to give the desired product as a clear, slightly yellow oil (771 mg, 57%). $R_f = 0.42$ (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 9.81 (1H, t, *J*= 1.5 Hz), 6.82 (1H, s), 6.71 (1H, s), 5.94 (2H, s,), 2.96 (2H, t, *J* = 7.5 Hz), 2.74 (2H, td, *J* = 7.0, 7.0, 1.5 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 201.1, 146.8, 146.7, 130.9, 125.2, 110.0, 109.9, 101.7, 43.8, 26.1; IR (neat): 2898.4 (w), 2826.2 (w), 2726.4 (w), 1721.7 (s), 1503.7 (s),

⁴¹ Xiong, C.; Changgeng, Q.; Haixiao, Z. PCT Int. Appl., 2008115719, 25 Sep 2008.

1477.2 (s), 1413.2 (m), 1237.7 (s), 1160.0 (w), 1119.7 (s), 1035.4 (s), 931.7 (s), 863.3 (m), 838.6 (m), 433.0 (w) cm⁻¹; HRMS-(DART) for: $C_{10}H_{10}ClO [M]^+$: calculated: 212.0240, found: 212.0237.



5-(6-chlorobenzo[d][1,3]dioxol-5-yl)pent-1-en-3-ol. Prepared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 7.2 mL, 7.2 mmol), 3-(6-

chlorobenzo[d][1,3]dioxol-5-yl)propanal (765 mg, 3.60 mmol), and THF (36 mL). The crude material was purified (SiO₂, 10% ethyl acetate in hexane) to give the desired product as a clear, slightly yellow oil (726 mg, 84%). $R_f = 0.24$ (10% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 6.81 (1H, s), 6.71 (1H, s), 5.96-5.87 (1H, m), 5.93 (2H, s), 5.26 (1H, ddd (app dt's), J = 17.5, 1.0, 1.0 Hz), 5.14 (1H, ddd (app dt's), J = 11.0, 1.0, 1.0 Hz), 4.13 (1H, ddd (app q), J = 6.0 Hz), 2.76 (1H, ddd, J = 14.5, 8.5, 6.5 Hz), 2.69 (1H, ddd, J = 14.5, 9.0, 6.5 Hz), 1.82-1.76 (2H, m), 1.73 (1H, br s); ¹³C NMR (126 MHz, CDCl₃): δ 146.6, 146.4, 140.8, 132.4, 125.1, 114.9, 109.8, 109.8, 101.5, 72.3, 36.9, 29.4; IR (neat): 3378.6 (br), 2894.8 (m), 1503.1 (s), 1477.2 (s), 1412.4 (m), 1232.9 (s), 1158.3 (w), 1117.8 (s), 1037.6 (s), 992.1 (m), 931.8 (s), 861.5 (m), 837.2 (m), 722.4 (w), 692.1 (w) cm⁻¹; HRMS-(DART) for: C₁₂H₁₃CIO₃ [M]⁺: calculated: 240.0553, found: 240.0557.



(E)-5-chloro-6-(5-chloropent-3-en-1-yl)benzo-[d][1,3]-

dioxole. Prepared according to the general procedure

utilizing thionyl chloride (2.19 mL, 30.1 mmol), 5-(6-chlorobenzo-[d][1,3]dioxol-5yl)pent-1-en-3-ol (726 mg, 3.01 mmol), and DCM (8.5 mL). The crude material was purified (SiO₂, 2% ethyl acetate in hexane) to give the desired product as a 11:1 mixture of the title compound: 5-chloro-6-(3-chloropent-4-en-1-yl)benzo[d][1,3]dioxole (701 mg, 90%)). $R_f = 0.28$ (4% DCM in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): (major isomer) δ 6.82 (1H, s), 6.66 (1H, s), 5.94 (2H, s), 5.81 (1H, dt's, J = 15.0, 7.0, 7.0Hz), 5.64 (1H, dtt's, J = 15.0, 7.5, 7.5, 1.0, 1.0 Hz), 4.03 (2H, d, J = 7.0 Hz), 2.72 (2H, t, J = 7.5 Hz), 2.33 (2H, dt's (app q), J = 7.0 Hz); (minor isomer) δ 6.82 (1H, s), 6.72 (1H, s), 5.96-5.89 (1H, m), 5.95 (2H, s), 5.30 (1H, d, J = 17.0 Hz), 5.18 (1H, d, J = 10.5 Hz), 4.34 (1H, ddd (app q), J = 8.0 Hz), 2.84 (1H, ddd, J = 14.0, 8.5, 5.5 Hz), 2.77-2.70 (1H, m), 2.12-2.02 (2H, m); ¹³C NMR (126 MHz, CDCl₃): (both isomers) δ 146.7, 146.7, 146.6, 146.5, 138.3, 134.5, 131.9, 131.3, 126.8, 125.3, 125.2, 116.9, 110.0, 109.9, 109.8, 109.8, 101.6, 101.5, 62.2, 45.2, 37.9, 32.9, 32.2, 30.5; IR (neat): 2897.5 (w), 1502.8 (m), 1475.8 (s), 1412.2 (m), 1232.3 (s), 1170.4 (w), 1117.5 (m), 1037.3 (s), 965.3 (m), 933.8 (s), 860.9 (m), 839.4 (m), 722.6 (w), 677.0 (m), 438.2 (w) cm⁻¹; HRMS-(DART) for: $C_{12}H_{12}ClO_2 [M]^+$: calculated: 258.0214, found: 258.0215.



The crude material was purified (SiO₂, 5% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (797 g, 84%). $R_f = 0.30$ (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 6.79 (1H, s), 6.65 (1H, s), 5.90 (2H, s), 5.50-5.45 (1H, m) 5.43-5.37 (1H, m), 2.64 (2H, t, J = 7.5 Hz), (2H, dt's (app q), J = 8.0 Hz), 1.62 (2H, d, J = 7.0 Hz), 1.22 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 146.4, 146.2, 132.8, 129.5, 125.9, 125.1, 109.9, 109.7, 101.4, 83.2, 33.7, 32.8, 24.7; IR (neat): 2977.8 (w), 2929.2 (w), 1503.8 (m), 1476.7 (s), 1358.0 (s), 1324.0 (s), 1233.3 (s), 1165.0 (m), 1143.0 (s), 1116.5 (s), 1037.8 (s), 1004.5 (s), 966.8 (s), 935.0 (s), 845.7 (s), 722.6 (w), 693.2 (w), 674.3 (w), 438.1 (w) cm⁻¹; HRMS-(DART) for: C₁₈H₂₄BClO₄ [M]⁺: calculated: 350.1456, found: 350.1458.

3-(2-chloro-5-(trifluoromethyl)phenyl)propanal. Prepared according to the general procedure utilizing Pd(OAc)₂ (22.5 mg, 0.100 mmol), tetrabutylammonium chloride (1.39 g, 5.00 mmol), sodium bicarbonate (1.05 g, 12.5 mmol), dimethylformamide (10 mL), 4-chloro-3-iodobenzotrifluoride (0.78 mL, 5.00 mmol), and allyl alcohol (0.51 mL, 7.50 mmol). The crude material was purified (SiO₂, 6% ethyl acetate in hexane) to give the desired product as a clear, slightly yellow oil (922.5 mg, 78%). R_f = 0.42 (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 9.82 (1H, d, *J* = 1.0 Hz), 7.51 (1H, d, *J* = 1.5 Hz), 7.46 (1H, d, *J* = 8.3 Hz), 7.41 (1H, d, *J* = 8.8 Hz), 3.10 (2H, t, *J* = 7.3 Hz), 2.83 (2H, t, *J* = 7.3 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 200.1, 139.1, 137.6, 130.1, 129.4 (q, *J*_{C-F} = 32.4 Hz), 127.3 (q, *J*_{C-F} = 3.8 Hz), 124.6 (q, *J*_{C-F} = 3.8 Hz), 123.6 (q, *J*_{C-F} = 271.8 Hz), 43.0, 26.0; IR (neat): 2942.7 (w), 2901.9 (w), 2826.4 (w), 2728.2 (w), 1724.5 (s), 1610.3 (m), 1583.2 (w), 1412.4 (m), 1325.2 (s), 1276.6 (m), 1165.4 (s), 1119.2 (s), 1080.9 (s), 1056.0 (s), 904.1 (s), 825.5 (s), 728.7 (m), 507.5 (m), 458.1 (m), 439.6 (m), 386.3 (w) cm⁻¹; HRMS-(DART) for: $C_{10}H_7ClF_3O$ [M-H]⁺: calculated: 235.0138, found: 235.0140.

5-(2-chloro-5-(trifluoromethyl)phenyl)pent-1-en-3-ol. OH Pre- F_3C pared according to the general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 31.0 mL, 31.0 mmol), 3-(2-chloro-5-(trifluoromethyl)phenyl)propanal (3.6552 g, 15.5 mmol), and THF (30 mL). The crude material was purified (SiO₂, 12% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (3.6363 g, 90%). $R_f = 0.26$ (10% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.51 (1H, d, J = 2.0 Hz), 7.45 (1H, d, J = 8.3 Hz), 7.39 (1H, d, J = 8.3 Hz), 5.92 (1H, ddd, J = 17.1, 10.3, 6.4 Hz), 5.28 (1H, d, J = 17.1 Hz), 5.17 (1H, d, J = 10.3 Hz), 4.17 (1H, ddd (app q), J = 6.4 Hz), 2.96-2.90 (1H, m), 2.87-2.81 (1H, m), 1.96-1.77 (3H, m); ¹³C NMR (126 MHz, CDCl₃): δ 140.6, 137.7, 137.7, 129.9, 129.2 (q, $J_{C-F} = 32.4$ Hz), 127.2 (q, $J_{C-F} = 3.8$ Hz), 124.2 (q, $J_{C-F} = 3.8$ Hz), 123.8 $(q, J_{C-F} = 271.8 \text{ Hz}), 115.3, 72.4, 36.3, 29.5; \text{ IR (neat)}: 3348.4 (br), 3082.8 (w), 2937.1$ (w), 2870.9 (w), 1644.9 (m), 1482.4 (m), 1412.0 (m), 1362.2 (s), 1274.4 (m), 1166.2 (s), 1121.0 (s), 1080.3 (s), 1042.0 (s), 990.0 (m), 924.9 (s), 823.9 (s), 730.3 (m), 513.3 (m), 441.0 (m), 385.7 (m) cm⁻¹; HRMS-(DART) for: $C_{12}H_{11}ClF_3$ [M+H-H₂O]⁺: calculated: 247.0501, found: 247.0504.



(E)-1-chloro-2-(5-chloropent-3-en-1-yl)-4-

(trifluoromet- hyl)benzene. Prepared according to the CI general procedure utilizing thionyl chloride (8.36 mL, 115 mmol), 5-(2-chloro-5-(trifluoromethyl)phenyl)pent-1-en-3-ol (2.8113 g, 10.7 mmol), and DCM (45 mL). The crude material was purified (SiO₂, 2% ethyl acetate in hexane) to give the desired product as a 10:1 mixture of the title compound: 1-chloro-2-(3-chloropent-4-en-1-yl)-4trifluoromethyl)benzene (clear, colorless oil (2.1999 g, 72%). $R_f = 0.51$ (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): (major isomer) δ 7.51-7.38 (3H, m), 5.81 (1H, dt's, J = 15.1, 6.8, 6.8 Hz), 5.65 (1H, dtt's, J = 15.1, 6.8, 6.8, 1.5, 1.5 Hz), 4.02 (2H, dd, J = 6.8, 1.0 Hz), 2.88 (2H, t, J = 7.3 Hz), 2.41 (2H, dt's (app q), J =7.3 Hz); (minor isomer) δ 7.51-7.38 (3H, m), 5.94 (1H, ddd, J = 17.1, 10.2, 7.8 Hz), 5.32 (1H, ddd (app dt's), J = 17.1, 1.0, 1.0 Hz), 5.21 (1H, d, J = 9.8 Hz), 4.37 (1H, ddd (app q), J = 7.8 Hz), 3.03-2.97 (1H, m), 2.93-2.86 (1H, m), 2.16-2.11 (2H, m); ¹³C NMR (126 MHz, CDCl₃): (major isomer) δ 139.9, 133.7, 130.0, 129.2 (q, $J_{C-F} = 32.4$ Hz), 127.4, 127.2 (q, $J_{C-F} = 3.8$ Hz), 124.3 (q, $J_{C-F} = 3.8$ Hz), 123.8 (q, $J_{C-F} = 271.8$ Hz), 117.1, 44.9, 32.9, 31.6; IR (neat): 3039.3 (w), 2946.3 (m), 2866.1 (w), 1666.7 (w), 1609.5 (w), 1412.5 (m), 1325.3 (s), 1275.9 (m), 1166.7 (s), 1121.5 (s), 1080.0 (s), 1047.6 (m), 966.5 (m), 894.8 (m), 825.4 (s), 679.5 (m), 514.3 (w), 442.3 (w) cm⁻¹; HRMS-(DART) for: $C_{12}H_{11}ClF_{3}[M-Cl]^{+}$: calculated: 247.0501, found: 247.0508.



Prepared according to the general procedure utilizing PdCl₂ (10.6 mg, 0.060 mmol), B₂(pin)₂ (1.52 g, 6.00 mmol), THF (6.0 mL), and (*E*)-1-chloro-2-(5-chloropent-3-en-1-yl)-4-(trifluoromethyl)benzene (10:1 with regio-isomeric allyl chloride, 1.699 g, 6.00 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane) to give the desired product as a clear, colorless and viscous oil (1.96 g, 87%). R_{*f*} = 0.35 (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.46-7.41 (2H, m), 7.37 (1H, dd, *J* = 8.3, 2.0 Hz), 5.54-5.48 (1H, m), 5.45-5.40 (1H, m), 2.81 (2H, t, *J* = 7.8 Hz), 2.32 (2H, dtd's (app dq), *J* = 7.8, 7.8, 7.8, 1.5 Hz), 1.64 (2H, d, *J* = 7.3 Hz), 1.24 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 140.7, 137.7, 129.8, 129.0 (q, *JC-F* = 33.4 Hz), 128.8, 127.2 (q, *JC-F* = 3.8 Hz), 126.6, 123.9 (q, *JC-F* = 3.8 Hz), 123.9 (q, *JC-F* = 271.9 Hz), 83.2, 33.8, 32.3, 24.6; IR (neat): 2979.7 (m), 2932.5 (w), 2868.1 (w), 1609.2 (w), 1480.9 (w), 1453.9 (w), 1326.6 (s), 1166.6 (m), 1127.1 (s), 1082.3 (s), 967.3 (m), 847.0 (m), 824.9 (m), 674.0 (w), 513.3 (w) cm⁻¹; HRMS-(DART) for: C₁₈H₂₄BClF₃O₂ [M+H]⁺: calculated: 375.1510, found: 375.1519.

OH Cl ClCl minutes, the reaction mixture became a slightly cloudy brown color and began to reflux. After refluxing under the heat of the reaction approximately 10 minutes, the reaction was returned to reflux for an additional 30 minutes, and the resulting light brown mixture was cooled to 0 °C (ice/water bath) and treated dropwise with a solution of 3-(2chlorophenyl)propanal (1.03 g, 6.10 mmol) in THF (12 mL). After stirring at room temperature for 1 hour, the resulting brown, cloudy mixture was returned to 0 °C and excess Grignard reagent was carefully quenched with water (5 mL) followed by addition of saturated aqueous ammonium chloride (20 mL). The resulting mixture was diluted with ethyl acetate (50 mL) and water (20 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified (SiO₂, 12% ethyl acetate in hexane) to give the desired product as a clear, slightly yellow oil (1.1141 g, 87%). $R_f = 0.23$ (10% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.35 (1H, d, J = 7.8 Hz), 7.25 (1H, d, J= 7.3 Hz), 7.19 (1H, dd (app t), J = 7.3 Hz), 7.14 (1H, ddd (app dt's), J = 7.8, 7.8, 1.5 Hz), 5.01 (1H, s), 4.90 (1H, s), 4.13 (1H, dd (app t), J = 6.9 Hz), 2.85 (1H, ddd, J = 13.7, 10.8, 5.9 Hz), 2.76 (1H, ddd, J = 13.7, 10.3, 6.4 Hz), 1.95-1.81 (2H, m), 1.77 (3H, s), 1.70 (1H, br s); ¹³C NMR (126 MHz, CDCl₃): δ 147.2, 139.6, 133.9, 130.4, 129.5, 127.3, 126.8, 111.2, 75.3, 34.7, 29.8, 17.6; IR (neat): 3352.6 (br), 3070.8 (w), 2940.4 (w), 2865.2 (w), 1650.7 (w), 1474.2 (m), 1443.0 (m), 1168.3 (w), 1051.6 (m), 1028.4 (m), 901.5 (m), 749.4 (s), 680.1 (m), 554.0 (w), 452.8 (w) cm⁻¹; HRMS-(DART) for: $C_{12}H_{14}Cl$ [M+H-H2O]⁺: calculated: 193.0784, found: 193.0790.



(*E*)-1-chloro-2-(5-chloro-4-methylpent-3-en-1-yl)benzene.

Prepared according to the general procedure utilizing thionyl chloride (2.84 mL, 39.4 mmol), 5-(2-chlorophenyl)-2-methylpent-1-en-3-ol (830.4 mg, 3.94 mmol), and DCM (20 mL). The crude material was purified (SiO₂, 2% ethyl acetate in hexane) to give the desired product as a 5:1 mixture of the title compound: 1-chloro-2-(3-chloro-4-methylpent-4-en-1-yl)benzene (clear, colorless oil, 758.7 mg, 84%). $R_f =$ 0.48 (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): (major isomer) δ 7.36-7.32 (1H, m), 7.20-7.12 (3H, m), 5.60 (1H, t, J = 7.3 Hz), 4.01 (2H, s), 2.79 (2H, t, J = 7.3 Hz), 2.37 (2H, dt's (app q), J = 7.3 Hz), 1.67 (3H, s); (minor isomer) δ 7.36-7.32 (1H, m), 7.26-7.22 (1H, m), 7.20-7.12 (2H, m), 5.05 (1H, s), 4.94 (1H, q, J = 1.0 Hz), 4.40 (1H, dd (app t), J = 7.7 Hz), 2.92-2.84 (1H, m), 2.81-2.74 (1H, m), 2.19-2.11 (2H, m), 1.85 (3H, d, J = 1.0 Hz); ¹³C NMR (126 MHz, CDCl₃): (both isomers, one overlapping signal) δ 144.1, 139.0, 138.4, 133.9, 132.8, 130.5, 130.5, 129.6, 129.4, 129.3, 127.7, 127.4, 1126.8, 126.7, 114.4, 66.0, 52.2, 36.2, 33.1, 31.1, 28.1, 17.1, 14.0; IR (neat): 3064.4 (w), 2944.9 (w), 2861.4 (w), 1474.2 (m), 1442.0 (m), 1263.1 (m), 1122.6 (w), 1051.5 (m), 1036.8 (m), 909.3 (w), 749.8 (s), 679.6 (s), 455.9 (w), 443.4 (w) cm⁻¹; HRMS-(DART) for: $C_{12}H_{14}Cl [M-Cl]^+$: calculated: 193.0784, found: 193.0788.



the general procedure utilizing PdCl₂ (5.8 mg, 0.033 mmol), B₂(pin)₂ (840.8 mg, 3.31 mmol), THF (3.3 mL), and (*E*)-1-chloro-2-(5-chloro-4-methylpent-3-en-1-yl)benzene

(5:1 with regio-isomeric allyl chloride, 758.7 mg, 3.31 mmol). The crude material was purified (SiO₂, 5% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (1.0045 g, 95%). $R_f = 0.40$ (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.32 (1H, dd, J = 7.8, 1.5 Hz), 7.21 (1H, dd, J = 7.8, 2.0 Hz), 7.16 (1H, ddd (app dt's), J = 7.3, 7.3, 1.5 Hz), 7.11 (1H, ddd (app dt's), J = 7.3, 7.3, 2.0 Hz), 5.18 (1H, t, J = 6.9 Hz), 2.74 (2H, t, J = 7.8 Hz), 2.31 (2H, dt's (app q), J = 7.8 Hz), 1.67 (2H, s), 1.61 (3H, s), 1.25 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 139.9, 133.9, 132.9, 130.5, 129.3, 127.1, 126.5, 123.0, 83.1, 33.9, 28.3, 24.7, 17.8; IR (neat): 3070.6 (w), 2977.3 (m), 2931.9 (w), 2864.3 (w), 1475.0 (s), 1440.3 (s), 1372.1 (m), 1324.3 (m), 1147.8 (m), 1052.2 (w), 966.6 (w), 850.9 (w), 751.0 (m), 673.6 (m) cm⁻¹; HRMS-(DART) for: C₁₈H₂₇BClO₂ [M+H]⁺: calculated: 321.1793, found: 321.1794.

H 4-(2-chlorophenyl)butanal. Prepared according to the general procedure utilizing Pd(OAc)₂ (46.5 mg, 0.21 mmol), tetrabutylammonium chloride (22.88 g, 10.4 mmol), sodium bicarbonate (2.18 g, 25.9 mmol), dimethylformamide (21 mL), 2-chloroiodobenzene (2.47 g, 10.4 mmol), and but-3-en-1-ol (1.12 g, 15.5 mmol). The crude material was purified (SiO₂, 6% ethyl acetate in hexane) to give the desired product as a 11:1 mixture of the title compound: 3-(2-chlorophenyl)butanal (clear, slightly yellow oil (1.64 g, 87%)). $R_f = 0.40$ (10% ethyl acetate in hexane, UV/magic stain). All spectral data are in accordance with the literature.³⁹



^{OH} general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 18.0 mL, 18.0 mmol), 4-(2-chlorophenyl)butanal (1.64 g, 8.99 mmol), and THF (50 mL). The crude material was purified (SiO₂, 10% ethyl acetate in hexane) to give the desired product as a 15:1 mixture of the title compound: 5-(2-chlorophenyl)hex-1-en-3-ol (clear, slightly yellow oil (1.80 g, 87%)). $R_f = 0.39$ (10% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.33 (1H, dd, J = 7.5, 1.5 Hz), 7.22-7.11 (3H, m), 5.87 (1H, ddd, J = 17.0, 10.5, 6.5 Hz), 5.23 (1H, ddd (app dt's), J = 17.5, 1.5, 1.5 Hz), 5.11 (1H, ddd (app dt's), J = 10.0, 1.5, 1.5 Hz), 4.14 (1H, ddd (app q), J =6.5 Hz), 2.76 (2H, t, J = 7.5Hz), 1.80-1.56 (5H, m); ¹³C NMR (126 MHz, CDCl₃): δ 141.0, 139.8, 133.9, 130.3, 129.4, 127.2, 126.7, 114.8, 73.0, 36.5, 33.3, 25.5; IR (neat): 3356.1 (br), 3069.5 (w), 2932.2 (m), 2863.2 (m), 1474.2 (s), 1460.4 (m), 1317.0 (w), 1276.3 (w), 1109.3 (w), 1053.1 (s), 990.5 (s), 922.8 (s), 750.3 (s), 679.1 (m), 456.4 (w) cm⁻¹; HRMS-(DART) for: C₁₂H₁₄Cl [M+H-H₂O]⁺: calculated: 193.0784, found: 193.0781.

6-(2-chlorophenyl)hex-1-en-3-ol. Prepared according to the

(*E*)-1-chloro-2-(6-chlorohex-4-en-1-yl)benzene. Prepared according to the general procedure utilizing thionyl chloride (3.44 mL, 47.5 mmol), 6-(2-chlorophenyl)hex-1-en-3-ol (1.00 g, 4.75 mmol), and DCM (13.4 mL). The crude material was purified (SiO₂, 2% DCM in hexane) to give the desired product as a 40:8:1 mixture of the title compound: 1-chloro-2-(4-chlorohex-5-en-1-yl)benzene: (*E*)-1-chloro-2-(6-chlorohex-4-en-2-yl)benzene (691 mg, 59%)). $R_f = 0.56$ (5% DCM in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): (major isomer) δ 7.34 (1H, dd, *J*= 8.0, 1.0 Hz), 7.24-7.12 (3H, m), 5.81 (1H, dt's, *J* = 15.0, 6.5, 6.5 Hz), 5.66 (1H, dtt's, *J* = 15.5, 7.0, 7.0, 1.0, 1.0 Hz), 4.05 (2H, d, *J* = 7.5 Hz), 2.74 (2H, t, *J* = 8.0 Hz), 2.15 (2H, dt's (app q), *J* = 7.0 Hz), 1.77-1.72 (2H, m); (minor isomer) δ 7.35-7.26 (1H, m), 7.24-7.12 (3H, m), 5.89 (1H, ddd, *J* = 16.5, 9.5, 8.0 Hz), 5.27 (1H, dd, *J* = 17.0, 1.0 Hz), 5.14 (1H, d, *J* = 10.0 Hz), 4.38 (1H, ddd (app q), *J* = 7.5 Hz), 2.77 (2H, t, *J* = 7.5 Hz), 1.93-1.72 (4H, m); ¹³C NMR (126 MHz, CDCl₃): (both major isomers) δ 139.7, 139.4, 138.5, 135.4, 133.9, 133.5, 130.4, 130.3, 129.5, 129.5, 127.4, 127.3, 126.8, 126.7, 126.5, 116.6, 62.8, 45.4, 37.8, 33.0, 32.9, 31.6, 28.8, 26.6; IR (neat): 3065.2 (w), 2015.7 (w), 2932.9 (m), 2862.8 (w), 1665.4 (w), 1571.6 (w), 1474.1 (s), 1442.4 (s), 1249.5 (m), 1122.9 (w),1076.9 (s), 965.8 (s), 928.0 (s), 750.2 (s), 679.0 (s), 458.7 (w), 441.6 (w) cm⁻¹; HRMS-(DART) for: C₁₂H₁₄Cl [M+H-HCl]⁺: calculated: 193.0784, found: 193.0778.



(E)-2-(6-(2-chlorophenyl)hex-2-en-1-yl)-4,4,5,5-tetra-

methyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizing PdCl₂ (16.9 mg, 0.0955 mmol), B₂(pin)₂ (2.43 mg, 9.55 mmol), THF (9.6 mL), and (*E*)-1-chloro-2-(6-chlorohex-4-en-1-yl)benzene (5:1 with regio-isomeric allyl chloride, 2.06 g, 9.55 mmol). The crude material was purified (SiO₂, 0-10% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (2.32 g, 79%). $R_f = 0.35$ (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.32 (1H, dd, *J* = 7.5, 1.5 Hz), 7.21 (1H, dd, *J* = 7.5, 2.0 Hz), 7.16 (1H, ddd
(app td's), J = 7.5, 7.5, 1.0 Hz), 7.11 (1H, ddd (app td's), J = 7.5, 7.5, 2.0 Hz), 5.53-5.39 (2H, m), 2.71 (2H, t, J = 8.0 Hz), 2.06 (2H, dt's (app q), J = 7.0 Hz), 1.70-1.64 (4H, m),(2H, m), 1.25 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 140.2, 139.9, 130.4, 130.2, 129.4, 127.0, 126.6, 125.5, 83.1, 33.0, 32.3, 29.5, 24.8; IR (neat): 2977.7 (w), 2928.5 (w), 2860.1 (w), 1473.9 (m), 1442.5 (w), 1359.6 (s), 1323.4 (s), 1272.1 (m), 1213.7 (w), 1143.0 (s), 1052.5 (m), 965.8 (s), 883.1 (w), 846.2 (s), 780.9 (s), 675.2 (m), 578.0 (w), 457.9 (w) cm⁻¹; HRMS-(DART) for: C₁₈H₂₇BClO₂ [M+H]⁺: calculated: 321.1793, found: 321.1786.

OH 5-(2-chlorophenyl)pent-4-yn-1-ol. Prepared according to the literature procedure⁴² utilizing CuI (28.6 mg, 0.150 mmol), PdCl₂(PPh₃)₂ (105.3 mg, 0.150 mmol), triethylamine (12.5 mL), 2-chloroiodobenzene (0.61 mL, 5.00 mmol), and pent-4-yn-1-ol (0.56 mL, 6.00 mmol). The crude material was purified (SiO₂, 20% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (924.1 mg, 95%). $R_f = 0.29$ (25% ethyl acetate in hexane, UV/KMnO₄). All spectral data are in accordance with the literature.⁴²



5-(2-chlorophenyl)pentan-1-ol. To a 50 mL round-bottomed flask equipped with magnetic stir bar was added PtO₂ (22.7 mg,

0.100 mmol) followed by methanol (20 mL) and 5-(2-chlorophenyl)pent-4-yn-1-ol (973.3 mg, 5.00 mmol). The flask was sealed with a septum and a three-way inlet equipped with

⁴² Gericke, K. M.; Chai, D. I.; Lautens, M. *Tetrahedron* **2008**, *64*, 6002.

vacuum line and hydrogen balloon was added. The flask was briefly evacuated until the reaction mixture began to boil, then backfilled with hydrogen. After repeating this sequence three additional times, the reaction mixture was vigorously stirred under positive hydrogen pressure (balloon) at room temperature for 24 hours. The resulting dark reaction mixture was diluted with 25% ethyl acetate in hexane (20 mL) and eluted through a small plug of SiO₂ with additional 25% ethyl acetate in hexane (150 mL). The resulting clear, colorless solution was concentrated under reduced pressure. The crude material was purified (SiO₂, 20% ethyl acetate in hexane) to give the desired product and a small amount (>5%) of inseparable de-chlorinated by-product. $R_f = 0.30$ (25% ethyl acetate in hexane). ¹H NMR (500 MHz, CDCl₃): δ 7.33 (1H, dd, J = 7.8, 1.0 Hz), 7.21 (1H, dd, J = 7.8, 2.0 Hz), 7.17 (1H, ddd (app dt's), J = 7.3, 7.3, 1.5 Hz), 7.12 (1H, ddd)(app dt's), J = 7.3, 7.3, 2.0 Hz), 3.65 (2H, t, J = 6.9 Hz), 2.74 (2H, t, J = 7.8 Hz), 1.69-1.59 (4H, m), 1.53 (1H, br s), 1.47-1.41 (2H, m); ¹³C NMR (126 MHz, CDCl₃): δ 140.0, 133.8, 130.3, 129.4, 127.1, 126.6, 62.8, 33.5, 32.5, 29.5, 25.5; IR (neat): 3324.8 (br), 3063.4 (w), 3017.3 (w), 2931.5 (s), 2859.2 (m), 1594.0 (w), 1571.5 (w), 1473.3 (s), 1441.9 (m), 1069.9 (s), 1049.8 (s), 1031.4 (s), 746.9 (s), 678.8 (s), 456.9 (m), 444.0 (m) cm^{-1} ; HRMS-(DART) for: $C_{11}H_{14}Cl$ [M+H-H₂O]⁺: calculated: 181.0784, found: 181.0775.

5-(2-chlorophenyl)pentanal. Prepared according to the H literature procedure.⁴³ To a 50 mL round-bottomed flask

⁴³ Hoover, J. M.; Stahl, S. S. J. Am. Chem. Soc. 2011, 133, 16901.

equipped with magnetic stir bar was added tetrakis(acetonitrile) copper(I) hexafluorophosphate (37.3 mg, 0.100 mmol) followed by acetonitrile (2 mL). To the resulting clear, colorless solution was added 2.2²-bipyridine (15.6 mg, 0.100 mmol) as a solution in acetonitrile (2 mL), resulting in immediate formation of a brown reaction mixture. TEMPO (15.6 mg, 0.100 mmol) as a solution in acetonitrile (2 mL) was added followed by N-methylimidazole (16.4 mg, 0.200 mmol) as a solution in acetonitrile (2 mL). After stirring at room temperature open to air for approximately 5 minutes, 5-(2chlorophenyl)pentan-1-ol (397.4 mg, 2.00 mmol) was added as a solution in acetonitrile (2 mL). The resulting brown reaction mixture was vigorously stirred at room temperature open to air until the reaction became blue/green in color and TLC analysis indicated consumption of starting material (5 hours). The reaction mixture was concentrated under reduced pressure, and the resulting residue was taken up in 10% ethyl acetate in hexane (10 mL) and eluted through a short plug of SiO₂ with additional 10% ethyl acetate in hexane solution (150 mL). The resulting clear, slightly yellow solution was concentrated under reduced pressure and the crude material was purified (SiO2, 6% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (385.6 mg, 98%). $R_f = 0.27$ (5% ethyl acetate in hexane, UV/KMnO₄). ¹H NMR (500 MHz, CDCl₃): δ 9.83 (1H, s), 7.40 (1H, d, J = 7.3 Hz), 7.28-7.23 (2H, m), 7.20 (1H, ddd (app dt's)), J = 7.8, 7.8, 2.0 Hz), 2.82 (2H, t, J = 7.8 Hz), 2.54 (2H, t, J = 6.8 Hz), 1.81-1.71 (4H, m); ¹³C NMR (126) MHz, CDCl₃): δ 201.4, 138.5, 132.9, 129.4, 128.5, 126.4, 125.8, 42.7, 32.3, 28.2, 20.7; IR (neat): 3063.5 (w), 2935.7 (m), 2862.9 (w), 2822.0, (w), 2718.3 (w), 1722.4 (s), 1594.1 (w), 1571.5 (w), 1474.0 (m), 1442.8 (m), 1072.7 (m), 1050.7 (m), 1030.9 (m), 751.4 (s), 678.8 (m), 459.9 (w) cm⁻¹; HRMS-(DART) for: $C_{11}H_{14}ClO [M+H]^+$: calculated: 197.0733, found: 197.0738.

7-(2-chlorophenyl)hept-1-en-3-ol. Prepared according to the OH general procedure utilizing vinyl magnesium bromide (1.0 M in THF, 7.80 mL, 7.80 mmol), 5-(2-chlorophenyl)pentanal (761.2 mg, 3.87 mmol), and THF (8.0 mL). The crude material was purified (SiO₂, 12% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (692.8 mg, 80%). $R_f = 0.28$ (10% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.33 (1H, dd, J = 6.4, 1.5 Hz), 7.21 (1H, dd, J = 7.8, 2.0 Hz), 7.17 (1H, ddd (app dt's), J = 6.8, 6.8, 1.5 Hz), 7.12 (1H, ddd (app dt's), J = 7.3, 7.3, 2.0 Hz), 5.87 (1H, ddd, J = 17.1, 10.3, 6.4 Hz), 5.22 (1H, ddd (app dt's), J = 17.1, 1.5, 1.5 Hz), 5.11 (1H, ddd (app dt's), J = 10.3, 1.5, 1.5Hz), 4.12 (1H, ddd (app q), J = 6.4 Hz), 2.75-2.72 (2H, m), 1.70-1.38 (7H, m); ¹³C NMR (126 MHz, CDCl₃): δ 141.2, 140.0, 133.8, 130.2, 129.4, 127.1, 126.6, 114.6, 73.1, 36.7, 33.5, 29.6, 25.1; IR (neat): 3361.9 (br), 3068.9 (w), 2933.6 (m), 2859.9 (m), 1643.7 (w), 1571.6 (w), 1474.0 (m), 1442.4 (m), 1131.2 (w), 1051.3 (m), 1032.1 (m), 990.6 (m), 921.4 (m), 750.1 (s), 680.2 (w) cm⁻¹; HRMS-(DART) for: C₁₃H₂₁ClNO [M+NH₄]⁺: calculated: 242.1312, found: 242.1311.



chloride (2.13 mL, 29.2 mmol), 7-(2-chlorophenyl)hept-1-en-3-ol (655.7 mg, 2.92

mmol), and DCM (12 mL). The crude material was purified (SiO₂, 2% ethyl acetate in hexane) to give the desired product as a 5:1 mixture of the title compound: 1-chloro-2-(5chlorohept-6-en-1-yl)benzene (clear, colorless oil, 619.0 mg, 87%). $R_f = 0.51$ (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): (major isomer) δ 7.34 (1H, dd, J = 7.8, 1.0 Hz), 7.22-7.16 (2H, m), 7.13 (1H, ddd (app dt's), J = 7.8, 7.8, 2.0 Hz), 5.78 (1H, dt's, J = 15.2, 6.4, 6.4 Hz), 5.63 (1H, dtt's, J = 15.2, 7.3, 7.3, 1.5, 1.5 Hz), 4.03 (2H, dd, J = 6.4, 1.0 Hz), 2.74 (2H, t, J = 7.8 Hz), 2.12 (2H, dt (app q), J = 7.3 Hz), 1.68-1.61 (2H, m), 1.48 (2H, tt's (app q), J = 7.3 Hz); (minor isomer) δ 7.34 (1H, dd, J =7.8, 1.0 Hz), 7.22-7.11 (3H, m), 5.89 (1H, ddd, J = 17.1, 10.3, 8.3 Hz), 5.26 (1H, d, J = 17.1, 10.3, 10.2, 10.2, 10.2, 10.2, 10.2, 10.2, 10.2, 10.2, 10.2, 10.2, 10.2, 10.2, 10.2, 10.2, 10.2, 10.2, 10. 16.6 Hz), 5.14 (1H, d, J = 9.8 Hz), 4.35 (1H, ddd (app q), J = 7.3 Hz), 2.76-2.72 (2H, m), 1.93-1.80 (2H, m), 1.70-1.45 (4H, m); ¹³C NMR (126 MHz, CDCl₃): (both isomers) δ 140.0, 139.8, 138.7, 135.8, 133.9, 133.9, 130.3, 130.3, 129.5, 129.4, 127.2, 127.2, 126.7, 126.7, 126.1, 116.4, 63.0, 45.4, 38.0, 33.4, 33.4, 31.8, 29.2, 29.1, 28.5, 26.2; IR (neat): 3064.8 (w), 3016.2 (w), 2932.6 (m), 2858.7 (m), 1737.4 (w), 1665.6 (w), 1595.0 (w), 1571.5 (w), 1474.0 (m), 1441.9 (m), 1348.6 (w), 1249.8 (m), 1052.1 (w), 966.3 (m), 750.8 (s), 678.9 (m) cm⁻¹; HRMS-(DART) for: $C_{13}H_{16}Cl_2$ [M]⁺: calculated: 242.0629, found: 242.0628.



(*E*)-2-(7-(2-chlorophenyl)hept-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane. Prepared according to

the general procedure utilizing $PdCl_2$ (4.2 mg, 0.024 mmol), $B_2(pin)_2$ (606.9 mg, 2.39 mmol), THF (2.4 mL), and (*E*)-1-chloro-2-(7-chlorohept-5-en-1-yl)benzene (5:1 with

regio-isomeric allyl chloride, 581.2 mg, 2.39 mmol). The crude material was purified (SiO₂, 6% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (604.4 mg, 76%). $R_f = 0.40$ (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.32 (1H, dd, J = 7.8, 1.5 Hz), 7.20 (1H, dd, J = 7.8, 2.0 Hz), 7.16 (1H, ddd (app dt's), J = 7.3, 7.3, 1.5 Hz), 7.11 (1H, ddd (app dt's), J = 7.3, 7.3, 2.0 Hz), 5.46 (1H, dt's, J = 15.2, 7.8, 7.8 Hz), 5.39 (1H, dt's, J = 15.2, 6.9, 6.9 Hz), 2.71 (2H, t, J = 7.8 Hz), 2.03 (2H, dt's (app q), J = 6.9 Hz), 1.64 (2H, d, J = 6.9 Hz), 1.62-1.58 (2H, m), 1.42 (2H, tt's (app p), J = 7.8 Hz), 1.24 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 140.3, 133.9, 130.6, 130.3, 129.3, 127.0, 126.6, 125.0, 83.1, 33.4, 32.5, 29.3, 29.2, 24.7; IR (neat): 3061.1 (w), 2978.1 (m), 2928.6 (m), 2857.6 (w), 1474.1 (m), 1442.6 (m), 1359.0 (s), 1325.4 (s), 1272.4 (w), 1144.3 (s), 966.7 (s), 846.9 (m), 750.4 (s), 676.4 (w) cm⁻¹; HRMS-(DART) for: Cl₁₉H₂₉BClO₂ [M+H]⁺: calculated: 335.1949, found: 335.1945.

H 1-(but-3-yn-1-yl)-2-chlorobenzene. Prepared according to the literature procedure.⁴⁴ To a flame-dried 250 mL round-bottomed flask equipped with magnetic stir bar was added K₂CO₃ (1.382 g, 10.0 mmol). The flask was sealed with a septum and evacuated, then back-filled with nitrogen (3x). Dry methanol (25 mL) was added, followed by 3-(2-chlorophenyl)propanal (843.1 mg, 5.00 mmol) as a solution in dry methanol (12.5 mL), and diethyl (1-diazo-2oxopropyl)phosphonate (Ohira-Bessman reagent 1.321 g, 6.00 mmol) as a solution in dry methanol (12.5 mL). The resulting cloudy, yellow reaction mixture was stirred at room

⁴⁴ Gung, B. W.; Dickson, H. Org. Lett. 2002, 4, 2517.

temperature for 12 hours. The reaction was diluted with diethyl ether (75 mL) and 5% aqueous sodium bicarbonate and the layers separated. The aqueous layer was extracted with diethyl ether (2 x 50 mL) and the combined organic layers were washed with brine (75 mL), dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified (SiO₂, 100% hexane) to give the desired product as a clear, colorless oil (548.6 mg, 67%). $R_f = 0.55$ (100% hexane, UV/KMnO₄). ¹H NMR (500 MHz, CDCl₃): δ 7.36 (1H, dd, *J* = 7.8, 1.5 Hz), 7.29 (1H, dd, *J* = 7.3, 2.0 Hz), 7.21 (1H, ddd (app dt's), *J* = 7.3, 7.3, 1.5 Hz), 7.18 (1H, ddd (app dt's), *J* = 7.3, 7.3, 2.0 Hz), 2.98 (2H, t, *J* = 7.3 Hz), 2.53 (2H, dt's, *J* = 7.3, 7.3, 2.9 Hz), 1.99 (1H, t, *J* = 2.9 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 137.8, 133.9, 130.7, 129.5, 127.9, 126.7, 83.4, 69.0, 32.6, 18.6; IR (neat): 3300.0 (m), 2362.7 (w), 2322.4 (w), 1474.7 (w), 1444.3 (w), 1053.3 (w), 1038.7 (w), 750.0 (s), 637.6 (m) cm⁻¹; HRMS-(DART) for: C₁₀H₁₀Cl [M+H]⁺: calculated: 165.0471, found: 165.0469.

(Z)-2-(4-(2-chlorophenyl)but-1-en-1-yl)-4,4,5,5-tetramethyl-1, 3,2-dioxaborolane. Prepared according to the literature procedure.⁴⁵ To an oven-dried scintillation vial in the glovebox equipped with magnetic stir bar was added chloro(1,5-cyclooctadiene)rhodium(I) dimer (19.3 mg, 0.039 mmol), triisopropylphosphine (25.1 mg, 0.157 mmol), cyclohexane (7.0 mL), triethylamine (0.37 mL, 2.62 mmol), and catecholborane (0.28 mL, 2.62 mmol). The reaction mixture was stirred for 30 minutes followed by addition of 1-(but-3-yn-1-yl)-2-chlorobenzene (516.7

⁴⁵ Ohmura, T.; Yamamoto, Y.; Miyaura, N. J. Am. Chem. Soc. 2000, 122, 4990.

mg, 3.14 mmol). After stirring at room temperature for 2 hours, pinacol (463.5 mg, 3.92 mmol) was added in one portion and the vial was removed from the glovebox and stirred at room temperature for 12 hours. The resulting dark reaction mixture was diluted with 10% ethyl acetate in hexane (10 mL) and eluted through a short plug of SiO₂ with additional 10% ethyl acetate in hexane (150 mL). The resulting clear, yellow solution was concentrated under reduced pressure and the crude material was purified (SiO₂, 5% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (>40:1 Z:E, 586.8 mg, 77%). $R_f = 0.37$ (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.33 (1H, dd, J = 7.8, 1.5 Hz), 7.23 (1H, dd, J = 7.3, 2.0 Hz), 7.17 (1H, ddd (app dt's), J = 7.3, 7.3, 1.5 Hz), 7.12 (1H, ddd (app dt's), J = 7.8, 7.8, 2.0 Hz), 6.48 (1H, dt's, J = 13.7, 6.9, 6.9 Hz), 5.38 (1H, dt's, J = 13.7, 1.0, 1.0 Hz), 2.84-2.81 (2H, m),2.76-2.71 (2H, m), 1.25 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 153.3, 139.4, 134.0, 130.6, 129.3, 127.2, 126.5, 82.8, 33.5, 32.2, 24.8; IR (neat): 3066.8 (w), 2978.5 (m), 2929.9 (w), 2862.2 (w), 1628.6 (m), 1474.4 (w), 1439.5 (m), 1422.5 (m), 1321.4 (m), 1261.7 (s), 1144.3 (s), 1053.4 (w), 968.8 (w), 749.2 (s), 677.8 (w) cm⁻¹; HRMS-(DART) for: C₁₆H₂₃BClO₂ [M+H]⁺: calculated: 293.1480, found: 293.1478.

(Z)-2-(5-(2-chlorophenyl)pent-2-en-1-yl)-4,4,5,5-tetrameth-B(pin) yl-1,3,2-dioxaborolane. To a flame-dried 50 mL roundbottomed flask equipped with magnetic stir bar under nitrogen was added (Z)-2-(4-(2chlorophenyl)but-1-en-1-yl)-4,4,5,5-tetramethyl-1, 3,2-dioxaborolane (522.5 mg, 1.79 mmol), followed by THF (18 mL) and bromochloromethane (0.15 mL, 2.32 mmol). The resulting clear, colorless solution was cooled to -78 °C (dry ice/acetone bath) and treated dropwise with *n*-butyllithium (2.5 M in hexane, 0.93 mL, 2.32 mmol). After stirring at -78 °C for 20 minutes, the cooling bath was removed and the reaction mixture was allowed to slowly warm to room temperature and stirred an additional 3 hours. The resulting slightly cloudy reaction mixture was cooled to 0 °C (ice/water bath) and water (10 mL) was slowly added. The mixture was diluted with ethyl acetate (50 mL) and additional water (20 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 30 mL) and the combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified (SiO₂, 6% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (339.6 mg, 62%). $R_f = 0.35$ (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.33 (1H, dd, J = 7.8, 1.5, Hz), 7.23 (1H, dd, J = 7.3, 1.5 2.0 Hz), 5.58-5.52 (1H, m), 5.48-5.42 (1H, m), 2.78 (2H, t, J = 7.8 Hz), 2.36 (2H, dt's (app q), J = 7.8 Hz), 1.67 (2H, d, J = 7.8 Hz), 1.24 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 139.7, 133.9, 130.4, 129.3, 128.3, 127.2, 126.6, 125.3, 83.2, 33.5, 27.1, 24.7; IR (neat): 3059.7 (w), 2978.2 (m), 2930.9 (w), 2864.6 (w), 1473.9 (w), 1443.5 (w), 1324.7 (s), 1272.5 (w), 1214.1 (w), 1143.8 (s), 1052.6 (w), 967.8 (w), 882.9 (w), 847.3 (w), 749.1 (m) cm⁻¹; HRMS-(DART) for: $C_{17}H_{25}BClO_2$ [M+H]⁺: calculated: 307.1636, found: 307.1645.



5-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pent-1en-3-ol. To a flame-dried two-neck 250 mL round-bottomed flask equipped with magnetic stir bar in the glovebox was added sodium

hydride (576.0 mg, 24.0 mmol). The flask was sealed with septa, removed from the glovebox and equipped with a reflux condenser. THF (50 mL) was added and the resulting mixture was cooled to 0 °C (ice/water bath). To the cooled, stirring mixture was added 5-(2-bromophenyl)pent-1-en-3-ol (2.900 g, 12.0 mmol) as a solution in THF (10 mL). The resulting slightly yellow reaction mixture was then removed from the bath, warmed to room temperature, then heated to 80 °C in an oil bath. After 2.5 hours the resulting yellow-orange reaction mixture was cooled to room temperature, then to -78 °C (dry ice/acetone bath) and treated dropwise with *n*-butyllithium (2.51 M in hexane, 5.3 mL, 13.2 mmol), resulting in a slight darkening of the reaction mixture. After stirring for approximately 5 minutes at -78 °C, 2-isopropoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (3.93 mL, 19.2 mmol) was added dropwise. The reaction was stirred at -78 °C for an additional 10 minutes, then warmed to room temperature. After 2 hours, the reaction was cooled to 0 °C (ice/water bath) and slowly quenched with the dropwise addition of water (6 mL). The reaction was diluted with ethyl acetate (75 mL) and additional water (50 mL) and the layers separated. The aqueous layer was extracted with ethyl acetate (3 x 50 mL) and the combined organic layers were dried over sodium sulfate, filtered and concentrated under reduced pressure. The crude material was purified (SiO₂, 20% ethyl acetate in hexane) to give the desired product as an inseparable mixture of the title compound and proto-debrominated starting material (5:1 respectively), (clear, slightly yellow, viscous oil, 2.8722 g, 83%). $R_f = 0.28$ (25% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.81 (1H, d, J = 6.9 Hz), 7.37 (1H, ddd (app dt's), J = 7.8, 7.8, 1.5 Hz), 7.24-7.18 (2H, m), 5.89 (1H, ddd, J = 17.1, 10.5, 5.4 Hz), 5.25 (1H, ddd (app dt's), J = 17.1, 1.5, 1.5 Hz), 5.08 (1H, ddd (app dt's), J = 10.7, 1.5, 1.5 Hz), 4.11-4.07 (1H, m), 3.04-2.93 (3H, m), 1.90-1.76 (2H, m), 1.37 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 148.8, 141.1, 136.4, 131.2, 129.3, 125.2, 113.9, 83.8, 71.5, 40.7, 31.2, 24.9, 24.6; IR (neat): 3445.3 (br), 3067.2 (w), 2978.2 (m), 2931.0 (w), 2868.6 (w), 1644.3 (w), 1599.5 (m), 1568.8 (w), 1442.0 (m), 1381.1 (s), 1346.8 (s), 1311.7 (s), 1144.5 (s), 1071.4 (m), 861.6 (m), 661.1 (m) cm⁻¹; HRMS-(DART) for: C₁₇H₂₄BO₂ [M+H-H₂O]⁺: calculated: 271.1869, found: 271.1871.

(*E*)-2-(2-(5-chloropent-3-en-1-yl)phenyl)-4,4,5,5-

B(pin) tetramethyl-1,3,2-dioxaborolane. Prepared according to the general procedure utilizing thionyl chloride (1.10 mL, 15.0 mmol), 5-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pent-1-en-3-ol (as a 5:1 mixture with proto-debrominated material described above) (432.3 mg, 1.50 mmol), and DCM (6.0 mL). The crude material was purified (SiO₂, 6% ethyl acetate in hexane) to give the desired product as a 9:1 mixture of the title compound: 2-(2-(3-chloropent-4-en-1-yl)phenyl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (clear, colorless oil, 368.8 mg, 80%). $R_f = 0.38$ (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): (major isomer) δ 7.81 (1H, d, *J* = 7.3 Hz), 7.36 (1H, dd (app t), *J* = 7.3 Hz), 7.21 (1H, dd (app t), *J* = 7.3 Hz), 7.17 (1H, d, *J* = 7.3 Hz), 5.86 (1H, ddd, *J* = 14.4, 7.1, 6.9 Hz), 5.65 (1H, ddd, J = 7.3 Hz), 5.65 (1H, ddd, J = 14.4, 7.1, 6.9 Hz), 5.65 (1H, ddd, J = 7.3 Hz), 5.65 (1H, ddd, J = 14.4, 7.1, 6.9 Hz), 5.65 (1H, ddd, J = 7.3 Hz), 5.65 (1H, ddd, J = 14.4, 7.1, 6.9 Hz), 5.65 (1H, ddd, J = 7.3 Hz), 7.17 (1H, dz) = 7.3 Hz), 5.86 (1H, ddd, J = 14.4, 7.1, 6.9 Hz), 5.65 (1H, ddd, J = 7.3 Hz), 5.65 (1H, ddd), J = 7.3 Hz), 5.6

J = 14.2, 7.1, 6.9 Hz), 4.05 (2H, d, J = 7.3 Hz), 2.98 (2H, t, J = 7.8 Hz), 2.34 (2H, dt's (app q), J = 7.8 Hz), 1.36 (12H, s); (minor isomer) δ 7.84-7.78 (1H, m), 7.39-7.32 (1H, m), 7.24-7.14 (2H, m), 5.97 (1H, ddd, J = 17.1, 10.3, 8.3 Hz), 5.30 (1H, d, J = 17.1 Hz), 5.17 (1H, d, J = 10.3 Hz), 4.41 (1H, ddd (app q), J = 7.3 Hz), 3.10-2.92 (2H, m), 2.14-2.06 (2H, m), 1.36 (12H, s); ¹³C NMR (126 MHz, CDCl₃): (both isomers) δ 148.5, 148.0, 138.8, 136.4, 136.2, 135.7, 131.0, 130.9, 129.4, 129.2, 126.0, 125.4, 125.2, 116.3, 83.5, 83.4, 63.0, 45.5, 41.4, 35.7, 35.3, 33.0, 24.9, 24.9; IR (neat): 3065.6 (w), 2977.4 (m), 2932.4 (m), 2867.3 (w), 1664.7 (w), 1599.3 (m), 1569.1 (w), 1488.3 (m), 1441.5 (s), 1380.5 (s), 1344.6 (s), 1311.5 (s), 1261.7 (s), 1213.8 (m), 1142.9 (s), 1115.2 (s), 1075.5 (s), 1039.7 (m), 962.0 (s), 862.0 (s), 759.9 (s), 673.5 (s) cm⁻¹; HRMS-(DART) for: C₁₇H₂₅BClO₂ [M+H]⁺: calculated: 307.1636, found: 307.1636.

(18.3 mg, 0.150 mmol). The flask was sealed with a septum, evacuated, and back-filled with nitrogen followed by addition of DCM (7.5 mL), triethylamine (0.63 mL, 4.50 mmol), and acetic anhydride (0.28 mL, 3.00 mmol). 5-(2-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)pent-1-en-3-ol (as a 5:1 mixture with proto-debrominated material described above) (432.3 mg, 1.50 mmol) as a solution in DCM (7.5 mL). After stirring at room temperature for 3 hours, TLC analysis indicated consumption of starting material and the reaction mixture was diluted with DCM (20 mL) and water (20 mL).

The layers were separated and the aqueous layer was extracted with DCM (3 x 25 mL). The combined organic layers were dried over sodium sulfate, filtered, and concentrated under reduced pressure. The crude material was purified (SiO₂, 8% ethyl acetate in hexane) to give the desired product as a clear, colorless oil (437.2 mg, 88%). $R_f = 0.24$ (5% ethyl acetate in hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.79 (1H, d, J = 7.3 Hz), 7.35 (1H, dd (app t), J = 7.3 Hz), 7.20-7.16 (2H, m), 5.86 (1H, ddd, J = 17.1, 10.3, 6.4 Hz), 5.34 (1H, ddd (app q), J = 5.9 Hz), 5.28 (1H, d, J = 17.1 Hz), 5.19 (1H, d, J = 10.8 Hz), 2.96-2.86 (2H, m), 2.08 (2H, s), 1.96-1.84 (2H, m), 1.35 (12H, s); ¹³C NMR (126 MHz, CDCl₃): δ 170.3, 148.6, 136.6, 136.3, 131.0, 129.2, 125.2, 116.4, 83.4, 74.9, 37.4, 31.7, 24.9, 24.8, 21.2; IR (neat): 3066.0 (w), 2977.8 (m), 2934.7 (w), 1371.2 (s), 1345.2 (s), 1312.8 (s), 1233.3 (s), 1144.1 (s), 1110.7 (m), 1079.8 (m), 1021.5 (s), 962.5 (m), 861.5 (m), 755.8 (m), 661.2 (s) cm⁻¹; HRMS-(DART) for: C₁₉H₃₁BNO₄ [M+NH₄]⁺: calculated: 348.2346, found: 348.2362.

5.5.5. Representative Procedure for Intramolecular Coupling.



To an oven-dried 2-dram vial equipped with magnetic stir bar in the glovebox was added (R,R)-5.106 (0.07 equiv.), followed by cesium fluoride (3.00 equiv.), 1,3,5-trimethoxy benzene (internal standard, 10.0 mg), substrate (1.00 equiv.) and Pd(OAc)₂ (0.05 equiv.)

as a solution in THF (0.2 M in substrate) resulting in a yellow-orange reaction mixture. The vial was sealed with a cap, removed from the glovebox and heated to 70 °C with vigorous stirring for 14 hours. The resulting grey, cloudy reaction mixture was cooled to room temperature, diluted with diethyl ether (2 mL) and passed through a short plug of SiO₂, eluding with additional diethyl ether (10 mL). The resulting clear, yellow solution was concentrated under reduced pressure and the crude reaction material analyzed for conversion and yield by ¹H NMR analysis. The pure cyclized products were isolated after SiO₂ chromatography.

5.5.6. Full Characterization and Proof of Stereochemistry.

(*R*)-1-vinyl-2,3-dihydro-1*H*-indene. Prepared according to the general procedure utilizing (*R*,*R*)-5.106 (17.3 mg, 0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (*E*)-2-(5-(2-chlorophenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (76.7 mg, 0.250 mmol), Pd(OAc)₂ (2.8 mg, 0.0125 mmol), and THF (1.25 mL). The crude material was purified (SiO₂, 100% pentane) to give the desired product as a clear, colorless oil (27.5 mg, 76%). R_f = 0.34 (100% hexane, UV/KMnO₄). ¹H NMR (500 MHz, CDCl₃): δ 7.27-7.25 (1H, m), 7.20-7.17 (3H, m), 5.89 (1H, ddd, *J* = 17.1, 9.3, 8.3 Hz), 5.18 (1H, dd, *J* = 17.1, 1.0 Hz), 5.12 (1H, dd, *J* = 9.8, 1.0 Hz), 3.78 (1H, ddd (app q), *J* = 8.3 Hz), 2.99-2.86 (2H, m), 2.36 (1H, dddd (app dtd's), *J* = 11.7, 7.8, 7.8, 3.9 Hz), 1.88 (1H, dddd (app dq's), *J* = 12.7, 8.8, 8.8, 8.8 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 145.6, 143.9, 141.1, 126.5, 126.2, 124.4, 124.3, 114.8, 49.8, 33.1, 31.6; IR (neat): 3070.7 (w), 2954.6 (m), 2939.3 (m), 2926.2 (m), 2848.2 (m), 1638.4 (w),

1474.6 (m), 1457.7 (m), 1437.5 (w), 991.7 (m), 913.0 (s), 768.2 (m), 742.2 (s) cm⁻¹; HRMS-(DART) for: $C_{11}H_{13}$ [M+H]⁺: calculated: 145.1017, found: 145.1024. [α]_D²⁰ = -69.233 (*c* = 1.360, CHCl₃, *l* = 50 mm).

Proof of stereochemistry:

The title compound was subjected to tandem ozonolysis/reduction as shown below to give (*S*)-(2,3-dihydro-1*H*-inden-1-yl)methanol and the specific rotation was measured $([\alpha]_D^{20} = -11.452 \ (c = 0.550, \text{ benzene}, l = 50 \text{ mm})$. This value was compared to the known literature value⁴⁶ ($[\alpha]_D^{20} = -14.3$ (benzene, 85% *ee* material) for (*S*)-(2,3-dihydro-1*H*-inden-1-yl)methanol.



Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (*E*)-2-(5-(2-chlorophenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and Pd(dppf)Cl₂ as the pre-catalyst.

⁴⁶ Caro, Y.; Torrado, M.; Masaguer, C. F.; Raviña, E. *Tetrahedron Asymm.* **2003**, *14*, 3689.

Chiral GLC (β -dex, Supelco, 80 °C for 5 min, ramp 1 °C/min to 150 °C, 20 psi) – analysis of 1-vinyl-2,3-dihydro-1H-indene.



Racemic Material



| Peak # | RetTime [min] | Туре | Width [min] | Area [pA*s] | Height [pA] | Area ۶ | Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|-----------|------------------|--------|----------------|----------------|----------------|-----------|-----------|------------------|--------|----------------|----------------|----------------|-----------|
| | 27.702 | MF | 0.1490 | 277.63089 | 31.05866 | 49.77444 | | 27.782 | MM | 0.1311 | 81.24442 | 10.32570 | 90.02868 |
| 2 | 28.116 | FM | 0.1676 | 280.14709 | 27.85743 | 50.22556 | 2 | 28.199 | MM | 0.1293 | 8.99840 | 1.15978 | 9.97132 |
| Total | .s : | | | 557.77798 | 58.91609 | | Tota | ls : | | | 90.24282 | 11.48548 | |





(R)-6-methyl-1-vinyl-2,3-dihydro-1H-indene. Prepared according Me to the general procedure utilizing (R,R)-5.106 (17.3 mg, 0.0175 (E)-2-(5-(2-chloro-4mmol), cesium fluoride (113.9 mg, 0.750 mmol), methylphenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborol-ane (80.2 mg, 0.250 mmol), Pd(OAc)₂ (2.8 mg, 0.0125 mmol), and THF (1.25 mL). The crude material was purified (SiO₂, 100% pentane) to give the desired product as a clear, colorless oil (27.0) mg, 68%). $R_f = 0.38$ (100% hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.13 (1H, d, J=7.5 Hz), 6.98 (1H, d, J=11.5 Hz), 6.97 (1H, s), 5.85 (1H, ddd (app dt's), J = 17.0, 8.5, 8.5 Hz), 5.16 (1H, d, J = 17.0 Hz), 5.09 (1H, d, J = 10.0 Hz), 3.72 (1H, ddd (app q), J = 8.5 Hz), 2.99 (1H, ddd, J = 15.0, 9.0, 3.5 Hz), 2.83 (1H, ddd (app dt's), J =15.5, 8.0, 8.0 Hz), 2.36-2.30 (1H, m), 2.33 (3H, s), 1.85 (1H, dddd (app dq's), J = 12.5, 8.5, 8.5, 8.5 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 145.8, 141.3, 140.9, 135.8, 127.3, 125.0, 124.1, 114.7, 49.8, 33.3, 31.2, 21.2; IR (neat): 3004.3 (w), 2922.8 (s), 2855.7 (m), 1732.8 (w), 1612.5 (m), 1491.0 (s), 1452.4 (m), 1439.4 (m), 1230.3 (w), 1119.4 (w), 1037.3 (s), 911.4 (s), 885.6 (w), 808.4 (s), 687.3 (w), 447.8 (w), 422.7 (w) cm⁻¹; HRMS-(DART) for: C₁₂H₁₅ [M+H]⁺: calculated: 159.1174, found: 159.1177. [α]_D²⁰ = -73.635 (*c* = 0.535, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (E)-2-(5-(2-chloro-4-methylphenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxa-borolane and Pd(OAc)₂ / PCy₃ as the pre-catalyst. The title compound was subjected to tandem ozonolysis/reduction as shown below to give (*S*)-(6-methyl-2,3-dihydro-1H-inden-1-yl)methanol. Further analysis of stereochemistry was performed on (*S*)-(6-methyl-2,3-dihydro-1H-inden-1-yl)methanol. Absolute stereochemistry was assigned by analogy.

Chiral SFC (Chiracel OJ-H, 3% IPA/hexane, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (S)-(6-methyl-2,3-dihydro-1H-inden-1-yl)methanol



Racemic Material

Standard Conditions

| Peak No | % Area | Area | RT (min) | Peak No | % Area | Area | RT (min) |
|---------|---------|-----------|----------|---------|---------|-----------|----------|
| 1 . | 48.9441 | 2975.2647 | 6.59 | 1 | 7.4501 | 313.4004 | 6.61 |
| 2 | 51.0559 | 3103.6356 | 8.28 | 2 | 92.5499 | 3893.2675 | 8.28 |
| Total: | 100 | 6078.9003 | | Total: | 100 | 4206.6679 | |

(R)-7-methyl-1-vinyl-2,3-dihydro-1H-indene. Prepared according to the general procedure utilizing (R,R)-5.106 (17.3 mg, 0.0175 mmol), cesium Ńе fluoride (113.9 mg, 0.750 mmol), (E)-2-(5-(2-chloro-3-methylphenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (80.2 mg, 0.250 mmol), Pd(OAc)₂ (2.8 mg, 0.0125 mmol), and THF (1.25 mL). The crude material was purified (SiO₂, 100% pentane) to give the desired product as a clear, colorless oil (28.9 mg, 73%). $R_f = 0.36$ (100% hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.10-7.06 (2H, m), 6.96-6.95 (1H, m), 5.87 (1H, ddd, J = 17.0, 10.0, 8.0 Hz), 4.97-4.90 (2H, m), 3.82 (1H, ddd (app td's), J = 8.0, 8.0, 2.0 Hz), 3.00 (1H, ddd (app dt's), J = 16.5, 9.0, 9.0 Hz), 2.82 (1H, ddd, J = 16.0, 9.0, 3.0 Hz) 2.33 - 2.25 (1H, m), 2.26 (3H, s), 1.94 (1H, dddd (appddt's), J = 13.0, 5.5, 3.0, 3.0 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 143.9. 143.4, 140.0, 134.8, 127.5, 126.9, 121.9, 113.3, 48.3, 32.5, 31.2, 18.8; IR (neat): 3017.9 (w), 2939.6 (m), 2847.7 (m), 1633.9 (w), 1596.6 (w), 1474.6 (m), 1459.4 (m), 1377.6 (w) 991.9 (m), 908.6 (s), 811.1 (s), 686.1 (m) 603.5 (w) cm⁻¹; HRMS-(DART) for: $C_{12}H_{15}$ [M+H]⁺: calculated: 159.1174, found: 159.1176. $[\alpha]_D^{20} = -7.307$ (*c* = 0.950, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (E)-2-(5-(2-chloro-3-methylphenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and Pd(dppf)Cl₂ as the pre-catalyst. The title compound was subjected to tandem hydroboration/oxidation as shown below to give (R)-2-(7-methyl-2,3-dihydro-1H-inden-1-yl)ethanol. Further analysis of stereochemistry was

performed on (R)-2-(7-methyl-2,3-dihydro-1H-inden-1-yl)ethanol. Absolute stereochemistry was assigned by analogy.



Chiral SFC (Chiracel OJ-H, 3% IPA/hexane, 3 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2-(7-methyl-2,3-dihydro-1H-inden-1-yl)ethanol.



Racemic Material



Standard Conditions

| Peak No | % Area | Area | RT (min) | Peak No | % Area | Area | RT (min) |
|---------|---------|-----------|----------|---------|---------|------------|----------|
| 1 | 50.4504 | 2741.4917 | 19.14 | 1 | 32.1948 | 6062.9513 | 20.61 |
| 2 | 49.5496 | 2692.5384 | 20.6 | 2 | 67.8052 | 12769.151 | 21.92 |
| Total: | 100 | 5434.0301 | | Total: | 100 | 18832.1023 | |

(*R*)-5-methoxy-1-vinyl-2,3-dihydro-1H-indene. Prepared

according to the general procedure utilizing (R,R)-5.106 (17.3 mg, 0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (E)-2-(5-(2-chloro-5-methoxyphenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (84.2 mg, 0.250 mmol), Pd(OAc)₂ (2.8 mg, 0.0125 mmol), and THF (1.25 mL). The crude material was purified (SiO₂, 100% pentane) to give the desired product as a clear, colorless oil (40.2 mg, 77%). $R_f = 0.18$ (100% hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 7.05 (1H, d, J=8.0 Hz), 6.90 (1H, s), 6.74 (1H, dd, J=8.5, 2.5 Hz), 5.84 (1H, ddd, J=17.5, 10.0, 8.5 Hz), 5.12 (1H, ddd (app dq's), J = 17.0, 1.0 Hz), 5.07 (1H, ddd (app dq's), J = 10.0, 1.0 Hz), 3.80 (3H, s), 3.70 (1H, ddd (app q), J = 8.0 Hz), 2.91 (1H, ddd, J = 15.5, 8.5, 3.5 Hz), 2.84 (1H, ddd (app dt's), J = 16.0, 8.0, 8.0 Hz), 2.34 (1H, ddd (app dtd's), J = 12.5, 8.0, 8.0, 4.0 Hz), 1.86 (1H, dddd (app dq's), J = 12.5, 8.5, 8.5, 8.5 Hz); ¹³C NMR (126) MHz, CDCl₃): δ 159.0, 145.5, 141.6, 137.8, 124.8, 114.4, 112.0, 109.9, 55.4, 49.0, 33.5, 31.8; IR (neat): 3077.1 (w), 2996.4 (w), 2940.1 (m), 2833.3 (w), 1605.4 (m), 1584.9 (w), 1487.5 (s), 1378.3 (m), 1253.6 (m), 1240.7 (s), 1118.1 (s), 1032.9 (s), 991.9 (m), 864.9 (s), 839.9 (m), 806.6 (m), 697.8 (w), 627.1 (w), 435.7 (m) cm⁻¹; HRMS-(DART) for: $C_{12}H_{15}O[M+H]^+$: calculated: 175.1123, found: 175.1127. $[\alpha]_D^{20} = -83.999$ (c = 1.040, $CHCl_{3}, l = 50 \text{ mm}$).

Analysis of stereochemistry:

MeO.

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (*E*)-2-(5-(2-chloro-5-methoxy-phenyl)pent-2-en-1-yl)-4,4,5,5-

tetramethyl-1,3,2-dioxa-borolane and $Pd(dppf)Cl_2$ as the pre-catalyst. Absolute stereochemistry was assigned by analogy.

Chiral GLC (β -dex, Supelco, 90 °C for 5 min, ramp 1 °C/min to 140 °C, 20 psi) – analysis of (R)-5-methoxy-1-vinyl-2,3-dihydro-1H-indene.



Racemic Material

Standard Conditions

| Peak # | RetTime [min] | Туре | Width [min] | Area [pA*s] | Height [pA] | Area % | Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|-----------|------------------|------|----------------|----------------|----------------|-----------|-----------|------------------|------|----------------|----------------|----------------|-----------|
| | | | | | | | | | | | | | |
| 1 | 50.442 | MM | 0.1567 | 285.71756 | 30.39396 | 50.00391 | 1 | 50.199 | MM | 0.2294 | 2294.41724 | 166.71036 | 89.76009 |
| 2 | 50.910 | MM | 0.1585 | 285.67285 | 30.03251 | 49.99609 | 2 | 50.897 | MM | 0.1855 | 261.74902 | 23.51253 | 10.23991 |
| | | | | | | | | | | | | | |
| Total | s: | | | 571.39041 | 60.42647 | | Tota. | ls : | | | 2556.16626 | 190.22289 | |



(*R*)-5-vinyl-6,7-dihydro-5H-indeno[5,6-d][1,3]dioxole. Prepared accord-ing to the general procedure utilizing (*R*,*R*)-5.106 (17.3 mg, 0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (*E*)-2-(5-

(6-chlorobenzo[d][1,3]dioxol-5-yl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2dioxaborolane (87.7 mg, 0.250 mmol), Pd(OAc)₂ (2.8 mg, 0.0125 mmol), and THF (1.25 mL). The crude material was purified (SiO₂, 100% pentane) to give the desired product as a clear, colorless oil (25.4 mg, 54%). $R_f = 0.08$ (100% hexane, UV/magic stain). ¹H NMR (500 MHz, CDCl₃): δ 6.69 (1H, s), 6.61 (1H, s), 6.74 (1H, dd, J = 8.5, 2.5 Hz), 5.91 (2H, dd, J= 3.5, 1.0 Hz), 5.80 (1H, ddd, J = 17.0, 10.0, 8.0 Hz), 5.12 (1H, ddd (app dq's), J = 17.0, 1.0 Hz), 5.06 (1H, ddd (app dq's), J = 9.0, 1.0 Hz), 3.64 (1H, ddd (app q), J = 8.0 Hz), 2.83 (1H, ddd, J = 15.0, 8.0, 3.5 Hz), 2.76 (1H, ddd (app dt's), J = 15.5, 9.0, 9.0 Hz), 2.33 (1H, ddd (app dtd's), J= 12.0, 7.0, 7.0, 3.5 Hz), 1.86 (1H, dddd (app dq's), J = 13.0, 8.5, 8.5, 8.5 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 146.7, 146.4, 141.4, 138.5, 136.6, 114.7, 105.0, 105.0, 100.9, 49.7, 33.6, 31.4; IR (neat): 3076.4 (w), 2929.0, m), 2850.1 (m), 1768.3 (w), 1637.7 (w), 1470.6 (s), 1351.5 (m), 1294.2 (s), 1268.1 (s), 1170.5 (s), 1038.1 (s) 992.7 (m), 940.0 (s), 913.4 (s), 855.8 (s), 823.1 (m), 775.1 (w), 682.1 (w), 419.2 (m) cm⁻¹; HRMS-(DART) for: $C_{12}H_{12}O_2[M+H]^+$: calculated: 188.0837, found: 188.0834. $[\alpha]_D^{20} = -69.201$ (*c* = 0.590, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (*E*)-2-(5-(6-chlorobenzo[d][1,3]dioxol-5-yl)pent-2-en-1-yl)-4,4,5,5-

tetramethyl-1,3,2-dioxaborolane and Pd(dppf)Cl₂ as the pre-catalyst. The title compound was subjected to tandem hydroboration/oxidation as shown below to give (R)-2-(6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-5-yl)ethanol. Further analysis of stereochemistry was performed on (R)-2-(6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-5-yl)ethanol. Absolute stereochemistry was assigned by analogy.



Chiral SFC (Chiracel ODR-H, 1% IPA/hexane, 2 mL/min, 100 bar, 35 °C, 210-270 nm) – analysis of (R)-2-(6,7-dihydro-5H-indeno[5,6-d][1,3]dioxol-5-yl)ethanol.



Racemic Material

| Peak No | % Area | Area | RT (min) |
|---------|---------|------------|----------|
| 1 | 48.9109 | 7937.4771 | 4.86 |
| 2 | 51.0891 | 8290.9498 | 5.13 |
| Total: | 100 | 16228.4269 | |

Standard Conditions

| Peak No | % Area | Area | RT (min) |
|---------|---------|------------|----------|
| 1 | 91.3767 | 14223.3138 | 4.93 |
| 2 | 8.6233 | 1342.274 | 5.31 |
| Total: | 100 | 15565.5878 | |

 $F_{3}C$ (*R*)-5-(trifluoromethyl)-1-vinyl-2,3-dihydro-1*H*-indene. Prepared according to the general procedure utilizing (*R*,*R*)-5.106 (17.3 mg,

0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (E)-2-(5-(2-chloro-5-(trifluoromethyl)phenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (93.7)mg, 0.250 mmol), Pd(OAc)₂ (2.8 mg, 0.0125 mmol), and THF (1.25 mL). The crude material was purified (SiO₂, 100% pentane) to give the desired product as a clear, colorless oil (30.7 mg, 58%). $R_f = 0.64$ (100% hexane, UV/KMnO₄). ¹H NMR (500 MHz, CDCl₃): δ 7.48 (1H, s), 7.43 (1H, dd, J = 7.8, 1.0 Hz), 7.24 (1H, d, J = 7.8 Hz), 5.84 (1H, ddd, J = 17.1, 10.3, 7.8 Hz), 5.17 (1H, ddd (app dt's), J = 17.1, 1.0, 1.0 Hz), 5.14 (1H, ddd (app dt's), J = 10.3, 1.0, 1.0 Hz), 3.79 (1H, ddd (app q), J = 8.3 Hz), 2.99 (1H, ddd, J = 15.7, 8.8, 3.4 Hz), 2.91 (1H, ddd (app dt's), J = 16.1, 8.3, 8.3 Hz), 2.40 8.3, 8.3, 8.3 Hz); ¹³C NMR (126 MHz, CDCl₃): δ 149.7, 144.7, 140.1, 129.1 (q, J_{C-F} = 32.4 Hz), 124.5 (q, *J*_{C-F} = 272.8 Hz), 124.5, 123.4 (q, *J*_{C-F} = 3.8 Hz), 121.3 (q, *J*_{C-F} = 3.8 Hz), 115.7, 49.6, 33.1, 31.4; IR (neat): 3079.6 (w), 2939.1 (m), 2858.8 (w), 1433.4 (w), 1333.1 (s), 1290.3 (m), 1121.9 (s), 1061.1 (m), 992.2 (w), 918.6 (m), 889.8 (m), 851.1 (w), 830.1 (m) cm⁻¹; HRMS-(DART) for: $C_{12}H_{12}F_3 [M+H]^+$: calculated: 213.0891, found: 213.0890. $[\alpha]_D^{20} = -40.342$ (*c* = 0.960, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (E)-2-(5-(2-chloro-5-(trifluoromethyl)phenyl)pent-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and Pd(dppf)Cl₂ as the pre-catalyst. Absolute stereochemistry was assigned by analogy.

Chiral GLC (β -dex, Supelco, 80 °C for 5 min, ramp 1 °C/min to 150 °C, 20 psi) – analysis of 5-(trifluoromethyl)-1-vinyl-2,3-dihydro-1H-indene.



Racemic Material

Standard Conditions

| Peak | RetTime | Туре | Width | Area | Height | Area | Peak | RetTime | Type | Width | Area | Height | Area |
|-------|---------|------|--------|------------|----------|----------|-------|---------|------|--------|-----------|----------|----------|
| # | [min] | | [min] | [pA*s] | [pA] | 8 | # | [min] | | [min] | [pA*s] | [pA] | olo |
| | | | | | | | | | | | | | |
| 1 | 31.621 | MM | 0.1899 | 534.93860 | 46.93755 | 50.03403 | 1 | 31.517 | MM | 0.1879 | 482.38672 | 42.79670 | 76.41761 |
| 2 | 32.796 | MM | 0.2010 | 534.21088 | 44.30485 | 49.96597 | 2 | 32.793 | MM | 0.1489 | 148.86403 | 16.66365 | 23.58239 |
| Total | ls : | | | 1069.14948 | 91.24239 | | Total | s: | | | 631.25075 | 59.46035 | |

(*R*)-1-(prop-1-en-2-yl)-2,3-dihydro-1*H*-indene. Prepared according to the general procedure utilizing (*R*,*R*)-5.106 (17.3 mg, 0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (*E*)-2-(5-(2-chlorophenyl)-2-

methylpent-2-en-1-yl)-4,4,5, 5-tetramethyl-1,3,2-dioxaborolane (80.2 mg, 0.250 mmol), Pd(OAc)₂ (2.8 mg, 0.0125 mmol), and THF (1.25 mL). The crude material was purified (SiO₂, 100% pentane) to give the desired product as a clear, colorless oil (31.5 mg, 80%). $R_f = 0.43$ (100% hexane, UV/KMnO₄). ¹H NMR (500 MHz, CDCl₃): δ 7.26-7.22 (1H, m), 7.20-7.11 (3H, m), 4.86-4.85 (1H, m), 4.84-4.83 (1H, m), 3.87 (1H, dd (app t), J =8.3 Hz), 2.98 (1H, ddd, J = 15.7, 8.8, 4.4 Hz), 2.89 (1H, ddd (app dt's), J = 15.7, 7.8, 7.8 Hz), 2.32-2.25 (1H, m), 2.02-1.94 (1H, m), 1.66 (3H, s); ¹³C NMR (126 MHz, CDCl₃): δ 147.3, 145.2, 144.3, 126.5, 126.1, 124.5, 124.3, 111.6, 53.3, 31.7, 31.2, 19.2; IR (neat): 3069.8 (w), 3021.2 (w), 2957.4 (m), 2944.1 (m), 2848.0 (w), 1644.2 (m), 1477.0 (m), 1457.1 (m), 1437.0 (w), 1373.5 (w), 891.1 (s), 742.2 (s) cm⁻¹; HRMS-(DART) for: C₁₂H₁₅ [M+H]⁺: calculated: 159.1174, found: 159.1176. [α]p²⁰ = -25.425 (c = 1.050, CHCl₃, l = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (*E*)-2-(5-(2-chlorophenyl)-2-methylpent-2-en-1-yl)-4,4,5,5-tetramethyl -1,3,2-dioxaborolane and Pd(dppf)Cl₂ as the pre-catalyst. Absolute stereochemistry was assigned by analogy.

Chiral GLC (β -dex, Supelco, 80 °C for 5 min, ramp 1 °C/min to 150 °C, 20 psi) – analysis of 1-(prop-1-en-2-yl)-2,3-dihydro-1H-indene.



| Peak | RetTime | Туре | Width | Area | Height | Area | Peak | RetTime | Type | Width | Area | Height | Area |
|-------|---------|------|--------|-----------|----------|----------|------|---------|------|--------|-----------|----------|----------|
| # | [min] | | [min] | [pA*s] | [pA] | 40 | # | [min] | | [min] | [pA*s] | [pA] | do |
| | | | | | | | | | | | | | |
| 1 | 35.674 | MM | 0.1485 | 188.77815 | 21.18037 | 50.03820 | 1 | 35.566 | MM | 0.1400 | 59.57478 | 7.09374 | 23.28648 |
| 2 | 36.332 | MM | 0.1475 | 188.48993 | 21.30090 | 49.96180 | 2 | 36.185 | MM | 0.1511 | 196.25943 | 21.64572 | 76.71352 |
| Total | s: | | | 377.26808 | 42.48127 | | Tota | ls : | | | 255.83421 | 28.73946 | |

(*R*)-1-vinyl-1,2,3,4-tetrahydronaphthalene. Prepared according to the general procedure utilizing (*R*,*R*)-5.106 (17.3 mg, 0.0175 mmol), cesium fluoride (113.9 mg, 0.750 mmol), (*E*)-2-(6-(2-chlorophenyl)hex-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (80.2 mg, 0.250 mmol), Pd(OAc)₂ (2.8 mg, 0.0125 mmol), and THF (1.25 mL). The crude material was purified (SiO₂, 100% pentane) to give the desired product as a clear, colorless oil (21.8 mg, 55%). $R_f = 0.38$ (100% hexane, UV/magic stain). All spectral data are in accordance with the literature.⁴⁷ HRMS-(DART) for: C₁₂H₁₅[M+H]⁺: calculated: 159.1174, found: 159.1181. $[\alpha]_D^{20} = -21.636$ (*c* = 0.610, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (E)-2-(6-(2-chlorophenyl)hex-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and Pd(dppf)Cl₂ as the pre-catalyst. Absolute stereochemistry was assigned by analogy.

⁴⁷ Namba, K.; Yamamoto, H.; Sasaki, I.; Mori, K.; Imagawa, H.; Nishizawa, M. Org. Lett. **2008**, *10*, 1767.

Chiral GLC (β -dex, Supelco, 80 °C for 5 min, ramp 1 °C/min to 150 °C, 20 psi) – analysis of (R)-1-vinyl-1,2,3,4-tetrahydronaphthalene.



Racemic Material

Standard Conditions

| Peak # | RetTime [min] | Туре | Width [min] | Area [pA*s] | Height [pA] | Area % | Peak # | RetTime [min] | Type | Width [min] | Area [pA*s] | Height [pA] | Area % |
|-----------|------------------|------|----------------|----------------|----------------|-----------|-----------|------------------|------|----------------|----------------|----------------|-----------|
| | | | | | | | | | | | | | |
| 1 | 43.994 | MF | 0.1618 | 289.61905 | 29.82614 | 50.56328 | 1 | 43.503 | MM | 0.3270 | 3059.74146 | 155.95407 | 85.77616 |
| 2 | 44.533 | FM | 0.1613 | 283.16623 | 29.25908 | 49.43672 | 2 | 44.390 | MM | 0.2460 | 507.38211 | 34.37797 | 14.22384 |
| Total | s: | | | 572.78528 | 59.08522 | | Tota | ls : | | | 3567.12357 | 190.33204 | |



according to the general procedure utilizing (R,R)-5.106 (17.3 mg, 0.0175

mmol), cesium fluoride (113.9 mg, 0.750 mmol), (*E*)-2-(7-(2chlorophenyl)hept-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (83.7 mg, 0.250 mmol), Pd(OAc)₂ (2.8 mg, 0.0125 mmol), and THF (1.25 mL). The crude material was purified (SiO₂, 100% pentane) to give the desired product as a clear, colorless oil (21.6 mg, 50%). $R_f = 0.40$ (100% hexane, UV/KMnO₄). ¹H NMR (500 MHz, CDCl₃): δ 7.14-7.12 (2H, m), 7.11-7.09 (2H, m), 6.16 (1H, ddd, *J* = 17.6, 10.3, 6.4 Hz), 5.12 (1H, ddd (app dt's), *J* = 10.3, 1.5, 1.5 Hz), 4.92 (1H, d, *J* = 17.6 Hz), 3.64-3.61 (1H, m), 2.88-2.83 (1H, m), 2.81-2.76 (1H, m), 1.96-1.84 (2H, m), 1.81-1.69 (2H, m), 1.68-1.58 (2H, m); ¹³C NMR (126 MHz, CDCl₃): δ 144.0, 142.8, 141.1, 129.7, 128.1, 126.1, 125.9, 114.4, 48.8, 36.2, 33.2, 28.9, 28.0; IR (neat): 3071.2 (w), 3014.7 (w), 2922.5 (s), 2852.5 (m), 1639.3 (w), 1489.4 (w), 1474.1 (w), 1444.7 (w), 1053.1 (w), 1001.2 (w), 913.6 (m), 746.8 (s) cm⁻¹; HRMS-(DART) for: C₁₃H₁₇ [M+H]⁺: calculated: 173.1330, found: 173.1331. [α]_D²⁰= -6.752 (*c* = 0.385, CHCl₃, *l* = 50 mm).

Analysis of stereochemistry:

Racemic compound was prepared according to the general procedure for intramolecular coupling utilizing (*E*)-2-(7-(2-chlorophenyl)hept-2-en-1-yl)-4,4,5,5-tetramethyl-1,3,2-dioxaborolane and Pd(dppf)Cl₂ as the pre-catalyst. Absolute stereochemistry was assigned by analogy.

Chiral GLC (β -dex, Supelco, 80 °C for 5 min, ramp 1 °C/min to 150 °C, 20 psi) – analysis of 5-vinyl-6,7,8,9-tetrahydro-5H-benzo[7] annulene.



Racemic Material

Standard Conditions

| RetTime Type [min] | Width Area [min] [pA*s] | Height Area [pA] % | Peak # | RetTime [min] | Туре | Width [min] | Area [pA*s] | Height [pA] |
|----------------------------|--|------------------------------------|-----------|------------------|--------------|----------------|------------------------|----------------------|
| 1 53.774 MM 2 54.663 MM | 0.2081 1084.78577 0.2209 1072.73657 | 86.89310 50.279 80.92230 49.720 | 1 1 2 | 53.786 54.632 | MM MM | 0.1567 | 207.83444 345.63385 | 22.09879 33.50714 |
| : | 2157.52234 | 167.81540 | Tota | ls : | | | 553.46829 | 55.60593 |






