Investigation of Boron Carboxylates and Phosphates as Catalysts for Homoallylation of Aldehydes

Senior Thesis

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by
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ABSTRACT

Investigation of Boron Carboxylates and Phosphates as Catalysts for Homoallylation of Aldehydes

A thesis presented to the Department of Chemistry
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Waltham, Massachusetts

By Ashley Klein

Allyl- and crotylboration of aldehydes is a useful and interesting transformation, due to predictable stereochemical outcomes which can be understood through cyclohexane chair-like transition state models. We have recently found that cyclopropanated allyl- and crotylboronate reagents react through transition states analogous to allylation; in an equally predictable manner, they stereoselectively deliver structural motifs which were difficult to access through previous methods. Although this reaction was originally promoted by stoichiometric amounts of PhBCl₂, we have recently found that boron carboxylates can catalyze homoallylation by a ligand exchange mechanism. Herein, we report further explorations in this mode of catalysis, using chiral and achiral ligands including carboxylates and phosphates.
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CHAPTER I

Introduction
The allylation and crotylation of aldehydes and ketones have been studied in great detail due to the versatility of the alkene functional group. The alkene formed from these reactions can participate in various synthetically useful transformations, such as epoxidation, olefin metathesis, and oxidative cleavage. Allyl Grignard and allyl lithium reagents may be used as the nucleophile in such reactions. Unfortunately, substituted allyl groups present the additional problem of predicting which end of the reagent reacts. As we can see below, allylation of aldehyde 1 with allyl reagent 2 can result in the mixture of allylation products 3, 4, and 5 due to the poor regioselectivity (Scheme 1).\textsuperscript{1,2} However, this overactivity can be controlled by changing the metal to those with a stronger metal-carbon bond, such as silanes and boronates.

Alllylic silanes react with carbonyl compounds in the presence of a Lewis acid while undergoing allylic inversion. This contrasts the general mixture of products obtained from using Grignard or lithium reagents. These allyl silanes are not Lewis acidic enough to activate the carbonyl; thus, they require an additional Lewis acid promoter. This leads to open transition state
where both $E$ and $Z$ allyl silanes will react to give the syn product 8 (Scheme 2). However, allylic boronates are sufficiently Lewis acidic to react through a closed chair-like, or Zimmerman-Traxler transition state 11 (Scheme 3). The chair transition state allows one to accurately predict regio- and stereocultural outcomes. This transition state favors orientation of the compounds that minimize axial interactions. The Roush allylation exemplifies a more complex case where additional attractive interactions lead to a favored transition state which involves addition of the $Si$ face, as opposed to $Re$ face addition (Scheme 4).

**Scheme 3.** Zimmerman-Traxler transition state for allylation

![Scheme 3](image)

**Scheme 4.** Roush allylation stereoselectivity model

![Scheme 4](image)
In contrast to allylation, homoallylation reactions have not been readily studied despite their synthetic utility (Scheme 5).\textsuperscript{13-14} Substituted homoallylation reagents using magnesium and lithium react with aldehydes to give $\sim 1:1$ diastereomeric mixtures. However, Mori and Tamaru developed a nickel-catalyzed reductive homoallylation reaction with dienes. Its utility can be seen in the formal synthesis of the C1-C9 fragment 17 of Amphidinolide C (Scheme 6).\textsuperscript{15}

**Scheme 5.** Synthetic utility of the homoallylation reaction in natural products\textsuperscript{13-14}

![Diagram showing synthetic utility of homoallylation in natural products](image)

This seems like a promising reaction, but it results in poor regioselectivity with simple homoallylation substrates. This method can be used to synthesize 1,3-\textit{anti}-homocrotylated products, but the homocrotylated \textit{syn} products are not accessible with this method (Scheme 7).\textsuperscript{16}

**Scheme 6.** Synthetic utility of the Tamaru reaction for homoallylation\textsuperscript{15}

![Diagram showing synthetic utility of Tamaru reaction](image)
**Scheme 7.** Limitations of the Tamaru reaction\(^\text{16}\)

The scope of the asymmetric reaction is limited to 2,5-aryl-substituted products making it a poor option for asymmetric transformations (Scheme 8).\(^\text{17-22}\)

It was predicted that the use of cyclopropanated analogues of allylboration reagent \(^\text{28}\) could overcome the stereoselectivity issues because the mechanism would be predicted to be

**Scheme 8.** Summary of the limitations with current homoallylation methods\(^\text{17-22}\)

Current Limitations

Asymmetric Routes are Long

very similar to the allylation mechanism. If the reaction proceeds through the Zimmerman-Traxler transition state, then it should be possible to synthesize bishomoallylic alcohol products with high diastereoselectivity (Scheme 9).\(^\text{23-24}\)
Reagents similar to 28 were not completely unknown prior to research in the Krauss group. Binger and Hill synthesized various cyclopropanated analogs of allylboration reagents that are not stable at moderate temperature and rearrange to homoallylboranes. The reagents most likely rearrange by a concerted mechanism involving the Lewis acidic boron center. These rearrangements do not seem to proceed through a radical mechanism because they can be inhibited by Lewis bases and are stereospecific. Luck and Young synthesized a stannane that is more stable than the Binger and Hill boranes. However, the stannane is a weaker nucleophile than the allyl stannane and does not homoallylate aldehydes either thermally or in the presence of BF$_3$·Et$_2$O (Scheme 10).

Studies in the Krauss group started with cyclopropylcarbinyiboronate 36. The stable and easily handled cyclopropylcarbinyiboronate 36 reacted with hydrocinnamaldehyde 37 to test for conditions for homoallylation. Heating up the boronate and aldehyde in various organic solvents
did not result in a successful reaction. Moreover, the addition of strong Lewis acids causes a rapid ring opening of the boronate while leaving the aldehyde unchanged. However, switching to a weaker Lewis acid or Brønsted acid results in no ring opening but no aldehyde consumption. The first success came when BCl$_3$ was found to promote the desired reaction, although with side products. It was hypothesized that disproportionation of the BCl$_3$ could result in a cationic boron species, which is a strong enough Lewis acid to promote the reaction. In search of milder conditions, PhBCl$_2$ was explored as a promoter. However, no conversion of aldehyde was observed. The addition of a catalytic amount of silver trifluoroacetate allowed for a successful reaction, albeit with inconsistent results. Hydrolysis of the pinacol group and condensation of 1,3-propanediol resulted in a much more reactive boronate 39 that much more consistently underwent homoallylation with a stoichiometric amount of PhBCl$_2$ (Scheme 11).
To test whether the homoallylation proceeds through a Zimmerman-Traxler transition state under these conditions, homocrotylation reagents were synthesized. Excitingly, the reaction of the *cis* boronate 40 with hydrocinnamaldehyde 37 yielded the 1,3-anti-methyl-substituted bishomoallylic alcohol 41. Conversely, the *trans* boronate reagent afforded the *syn* diastereomer. The high diastereo- and regioselectivity suggests that this reaction does go through a chair-like transition state (Scheme 12).\(^{23}\) Moreover, the methyl stereocenter in the *cis* boronate retained its stereochemistry in the homoallylation product; thus, it acts somewhat as a chiral auxiliary. Thus, asymmetric routes to these *cis* and *trans* boronates would allow for asymmetric homocrotylation.

*Scheme 12. Zimmerman-Traxler models for substituted homoallylboration reagents*\(^{23}\)

Due to the need to use a stoichiometric amount of strongly Lewis acidic PhBCl\(_2\), improvements to this reaction were explored. Naturally, milder promoters that could be used in catalytic amounts were investigated. Expanding on the observation that silver trifluoroacetate with PhBCl\(_2\) successfully promoted the reaction, boron tris(trifluoroacetate) was studied as a possible catalyst. It was discovered that 15 mol % of boron tris(trifluoroacetate) (B(OTFA))\(_3\)^{29}
effectively promoted the homoallylation reaction faster than the stoichiometric PhBCl₂. As with the PhBCl₂ promoter, it was observed that coordinating solvents resulted in a poor yield due to the formation of side products. NMR experiments and DFT calculations suggest ligand exchange as a possible mechanism (Scheme 13). Exchange of diol and OTFA ligands between 39 and B(OTFA)₃ produces 42. 42 can then react with aldehyde to afford product 43. Trifluoroacetates then exchange with the propanediol ligand on the next catalytic equivalent of 39 to regenerate 42.

**Scheme 13.** Proposed ligand exchange catalytic cycle

![Scheme 13](image)

We looked to further research boron carboxylates and phosphates as possible catalysts for homoallylation due to the electronic and steric tenability of the ligands. This should allow the reaction to become asymmetric by using a chiral catalyst.
CHAPTER II

Synthesis and effectiveness of boron carboxylates and boron phosphates as catalysts in the homoallylboration reaction
We looked to further explore boron carboxylates and phosphates as possible catalysts for homoallylation. Syntheses of the boron phosphates and carboxylates were achieved using carboxylic or phosphoric acids to protonate hydrides from BH$_3$·DMS, evolving hydrogen gas.

**Scheme 14.** Synthesis of boron biscarboxylates

Due to the insolubility of many of these carboxylic acids and phosphates in non-coordinating solvents, these reactions were run in either diethyl ether or tetrahydrofuran. This resulted in boron carboxylate products that were complexed to solvent (45, Scheme 14). The mechanism of this transformation is thought to begin with coordination of the borane to either the carbonyl oxygen or the carboxylic acid oxygen (Scheme 15).$^{27-29}$ All attempts at synthesizing boron triscarboxylates failed. It has been shown that the rate of hydrogen gas

**Scheme 15.** Possible mechanisms for forming boron carboxylates$^{27-29}$
evolution decreases as more hydrides are replaced by carboxylates. Thus, it was not too surprising that the major species formed was boron bis-carboxylates as opposed to boron triscarboxylates. Furthermore, unhindered, electron-rich acids tended to form anhydrides. This is caused by an intermolecular reaction between boron carboxylate 46 to form dimer 47 (Scheme 16).\textsuperscript{27-29} This obstacle was overcome by slow addition of a dilute solution of borane to a very concentrated solution of acid. Another side reaction that occurred was reduction of the carboxylic acids, for which BH\textsubscript{3} is commonly used. The reaction of carboxylic acid with borane, under sufficiently warm enough conditions, can form boron carboxylate 46, which can also be viewed as the acetoxy borane resonance structure 50 with subsequent steps forming the cyclic 51. Hydrolysis of 51 would form the alcohol. Resonance structure 50 essentially acts as an activated ester due to \(\pi\)-donation of the acetoxy oxygen to the boron atom (Scheme 17).\textsuperscript{27-29} This
reduction can be avoided by running the reaction at a sufficiently cold temperature. This optimal temperature varies depending on the acid used. As discussed, there is a conflict that can be seen

\textit{Scheme 17.} Reduction of carboxylic acid to alcohol$^{27-29}$

between the desired process of evolving hydrogen, which requires higher temperatures for each successive carboxylate and reduction and anhydride formation, which are suppressed at lower temperatures. This conflict explains the impossibility of isolating the boron triscarboxylate and the variability in optimal temperatures for each acid.

Since these boron carboxylates are air and moisture sensitive, purification methods are limited to recrystallization, which was never successful in our hands. Characterization methods are also limited in that the boron-hydride bond was not easy to reliably see or quantitate and the NMR spectra of the carboxylic acid, and the mono- di- and tricarboxylates differ only very subtly. Moreover, the desired compounds either were not able to ionize or were not stable for mass spectrometry. The above methods to avoid byproducts, anhydride and alcohol, allow us to synthesize the product with up to 90% purity. However, we needed to use some indirect methods to better assess whether we successfully formed the boron carboxylate. To start with, we expect a change in chemical shift in $^1$H, $^{13}$C, and potentially other nuclei within the starting acid when a bond is formed to boron, but these chemical shift changes do not distinguish between formation of the desired product and the byproducts described above. To test whether this change in
chemical shift is due to coordination and not the formation of other byproducts, we perform a water test where we add three equivalents of deuterated water ($\text{D}_2\text{O}$) to one equivalent of product in the NMR tube in order to hydrolyze the product back to the starting acid (Scheme 18).

**Scheme 18.** Hydrolysis of boron carboxylate with addition of $\text{D}_2\text{O}$

![Scheme 18](image)

Additionally, we perform a ligand exchange experiment where we add one equivalent of boronate 39 to one equivalent of product in deuterated chloroform ($\text{CDCl}_3$). Many of these boron

**Scheme 19.** $^1\text{H}$ NMR of ligand exchange experiment

![Scheme 19](image)
biscarboxylates are insoluble in CDCl$_3$, with most NMRs being performed in deuterated acetonitrile (CD$_3$CN). Thus, a quick positive indicator of a successful reaction is when the product, that is initially insoluble in CDCl$_3$, solubilizes after the addition of boronate. Moreover, the addition of the boronate to a boron carboxylate or phosphate should cause ligand exchange to occur. These ligand exchange species can then be detected using $^1$H and $^{11}$B NMR (Scheme 19).

The major purpose for further exploring boron carboxylates and phosphates is to develop a chiral catalyst that can successfully catalyze an asymmetric homoallylboration reaction. As chiral reagents are typically expensive, we sought to narrow down the chemical field by identifying a structure-activity relationship between the boron carboxylate and the ability to catalyze homoallylboration. After synthesizing and testing a number of potential catalysts, we found that only very electron deficient boron carboxylates, such as 52a, were catalytically active (Scheme 20). This is not too surprising considering the electron deficiency of boron.

**Scheme 20.** Reactivity of boron carboxylates as homoallylboration catalysts

<table>
<thead>
<tr>
<th>CATALYST</th>
<th>YIELD</th>
<th>CATALYST</th>
<th>YIELD</th>
</tr>
</thead>
<tbody>
<tr>
<td>((\text{O}_2\text{N})\text{O})(\text{BH} \cdot \text{THF}) 52(a)</td>
<td>68%</td>
<td>((\text{O}_2\text{N})\text{O})(\text{BH} \cdot \text{THF}) 52(e)</td>
<td>NR</td>
</tr>
<tr>
<td>((\text{O}_2\text{N})\text{CF}_2)(\text{BH} \cdot \text{THF}) 52(b)</td>
<td>23%</td>
<td>((\text{O}_2\text{Me})\text{O})(\text{BH} \cdot \text{THF}) 52(f)</td>
<td>NR</td>
</tr>
<tr>
<td>((\text{F}_2\text{F})\text{O})(\text{BH} \cdot \text{THF}) 52(c)</td>
<td>15%</td>
<td>((\text{Ph} \text{O})\text{O})(\text{BH} \cdot \text{THF}) 52(g)</td>
<td>NR</td>
</tr>
<tr>
<td>((\text{O}_2\text{O})\text{BH} \cdot \text{THF}) 52(d)</td>
<td>NR</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
tris(trifluoroacetate) (See Chapter 1, Scheme 13). Although not surprising, this did suggest that development of chiral carboxylate catalysts could be challenging, as most easily accessible acids that exhibit point chirality are aliphatic and would not be sufficiently electron poor.

Having found 52a to be catalytically active, we decided to test its functional group tolerance in homoallylation. 52a was able to successfully catalyze the reaction in the presence of TBS silyl ether and benzyl ether protecting groups, which are moderately to severely unstable in the presence of our most commonly used activator, PhBCl2. Homoallylation of aldehyde 53

**Scheme 21.** Tolerance of synthetically useful functional groups

![Scheme 21](image)

produced the bishomoallylic alcohol 54 in 47% yield and reaction with aldehyde 55 produced the homoallylic product 56 in 51% yield. In the case of acetonide-protected aldehyde 57, GC/MS of the crude product showed the correct mass of bishomoallylic alcohol 58 but the product was too unstable on silica to purify by flash column chromatography. In the future, it might be worth...
trying to purify this compound using deactivated silica or using a basic additive to the eluent (Scheme 21).

**Exploration of Boron Phosphate Catalysts**

We decided to explore whether boron phosphates would be viable for catalyzing this reaction due to phosphoric acids having similar electronic properties to carboxylic acids. Syntheses of the boron phosphates were also achieved using phosphoric acids to protonate hydrides from BH₃-DMS, evolving hydrogen gas (Scheme 22).

**Scheme 22.** Synthesis of boron phosphates

\[
\text{RO}_2\text{P(OH)} \xrightarrow{\text{BH}_3 \cdot \text{DMS (1.6 eq)} \text{ Et}_2\text{O}} \left(\text{RO}_2\text{P} \cdot \text{BH} \cdot \text{Et}_2\text{O}\right)_2
\]

In agreement with the above trend, the electron deficient boron bisphosphate 60 was able to catalyze homoallylboration, albeit in poor yield, whereas boron bisphosphate 59 was unsuccessful (Scheme 23).

**Scheme 23.** Exploring boron phosphates as homoallylboration catalysts
With this proof of principle that boron phosphates can catalyze homoallylboration, we decided to explore chiral analogs for asymmetric catalysis. We sought to synthesize boron bisphosphates that exhibit axial chirality because the electronic and steric properties of the ligands are easily tunable. We decided to target chiral phosphate \( 69 \) because it is both chiral and extremely electron poor due to the nitro functional groups. First, \((S)\)-BINOL \( 61 \) was protected with a methoxymethyl acetal (MOM) to give \( 62 \) in 74% yield. Protected \((S)\)-BINOL \( 62 \) underwent ortho-iodination to produce diiodide \( 63 \) in 83% yield. Attempted Suzuki couplings of diiodide \( 63 \) and boronic acid \( 64 \) were extremely sluggish and yielded no more than trace amounts of \( 65 \) (Scheme 24). \(^{31-33}\) Unable to successfully use this Suzuki coupling, we decided to switch the Scheme 24. First approach towards synthesizing phosphate ligands \(^{31-33}\)

boronic acid and halide coupling partners. In this way, \((S)\)-BINOL \( 61 \) was again protected as methoxymethyl ether. Ortho-lithiation and trapping with triethyl borate afforded diboronic acid.
in 85% crude yield. However, 66 appeared to be a complex mixture according to $^1$H NMR, and attempts at recrystallization failed. We hypothesized crude 66 was a mixture of boronic acid dimers or oligomers formed by dehydration. This was likely the case, as crude 66 underwent a Suzuki coupling with aryl bromide 67. Without further purification, the MOM protecting group was subsequently removed to give diol 68 in 63% yield over three steps. Diol 68 then reacts with POCl$_3$ to give phosphate 69 in 94% yield (Scheme 25). The $^1$H NMR spectrum of crude 69 looked clean, but became very complex after silica gel chromatography. Literature precedent suggested that running this extremely acidic compound on the column can lead to deprotonation of the acid, resulting in a mixture of metal phosphate salts derived from metal impurities
commonly found in the silica gel. Washing this material with 1 M HCl and then azeotroping with toluene protonated these metal salts, affording pure 69.34

In conclusion, sufficiently electron poor boron carboxylates and phosphates are viable catalysts for homoallylation of aldehydes. The dinitro boron biscarboxylate 52a can even tolerate synthetically useful protecting groups in homocrotylation. In the future, a chiral boron bisphosphate will be synthesized from the reaction of chiral phosphate 69 with BH3-DMS and then tested as a catalyst for homoallylation. Through the route depicted in Scheme 25, many chiral phosphates can be synthesized with different electronic and steric properties.
Experimental Section

General Experimental Methods. Reactions were conducted in flame- or oven-dried glassware under a nitrogen atmosphere and were stirred magnetically. The phrase concentrated refers to removal of solvents by means of a rotary evaporator attached to a Welch 1400 oil pump (bled to 5-300 mm Hg as needed). The phrase pumped refers to removal of residual solvent under full vacuum from a Welch 1400 oil pump. Flash chromatography was performed on silica gel 60 (230-400 mesh). Analytical thin layer chromatography (TLC) was performed using SiliaPlate TLC glass backed extra hard layer (60 Å, Cat# TLG-R10011B-323). TLC Plates were analyzed by short wave UV illumination or vanillin stain (15 g vanillin in 250 mL ethanol and 2.5 mL concentrated sulfuric acid) and heating on a hot plate. $^1$H, $^{31}$P, $^{19}$F, $^{11}$B, and $^{13}$C NMR spectra were obtained on a 400 MHz spectrometer in CDCl$_3$ with tetramethylsilane as an internal standard unless specifically indicated. Chemical shifts are reported in $\delta$ (ppm downfield from tetramethylsilane) if taken in CDCl$_3$ or were referenced to the residual solvent peak if taken in other solvents. $^{31}$P NMR spectra were referenced to phosphoric acid as an external standard, $^{11}$B NMR spectra were referenced to BF$_3$•OEt$_2$ as an external standard, and $^{19}$F NMR spectra were referenced to trifluoroacetic acid as an external standard. Coupling constants are reported in Hz with multiplicities denoted as s (singlet), d (doublet), t (triplet), q (quartet), p (pentet), m (multiplet) and br (broad). GC/MS spectra were obtained on an Agilent 7890 GC spectrometer with a 5975C VL MSD Triple-Axis Defector. IR spectra were recorded on a Varian 640-IR FT-IR spectrometer and are reported in wavenumbers (cm$^{-1}$). Achiral liquid chromatography mass spectrometry (LC-MS) was performed on a Waters S3 Acquity UPLC system coupled to a photodiode array detector and micromass ZQ4000 single quadrupole mass spectrometer, using a reversed phase column (reversed-phase C18 columns, 150 x 2.0 mm, 1.7 μm). Reagents were obtained from commercial vendors.
**General Experimental Procedure for the Synthesis of bishomoallyl alcohols.** To a solution of catalyst (15 mol %) in anhydrous CH₂Cl₂ (1 mL) in an oven dried 10 mL round bottom flask was added boronate (3.0 equiv). The solution was stirred in the glovebox for 1 minute. Aldehyde (1.0 equiv) was added and the reaction was stirred at room temperature. After TLC analysis showed consumption of aldehyde, the reaction was quenched with 3 M NaOH, and the mixture was extracted with EtOAc three times. The organic layers were then combined, dried over MgSO₄, filtered, and concentrated. The crude reaction mixture was purified by flash column chromatography (EtOAc/hexanes or EtOAc/toluene for benzyl protected products) to yield the desired product.

**Scale, weights, yields, and references listing spectral data for reactions producing known compounds.** 38⁵⁵ (0.186 mmol scale, 26.0 mg, 68%), 54⁵⁰ (0.332 mmol scale, 35.0 mg, 47%).

**1H NMR** 5.65 (ddd, J = 17.3, 10.3, 8.2 Hz, 1H), 5.03 (app d, J = 17.6, 1H), 4.95 (app d, J = 10.4, 1H), 3.70–3.63 (m,1H), 3.59 (d, J = 3.44 Hz, 1H), 3.57 (d, J = 3.44 Hz, 1H), 3.37 (dd, J = 10.0, 8.0 Hz, 1H), 2.48–2.37(m,1H), 1.46-1.39(m,1H), 1.30–1.23 (m,1H), 1.02 (d, J = 6.8, 3H), 0.84 (s, 9H), 0.06 (s,6H); IR (neat) 2954, 2929, 2858, 1463, 1255, 1107, 100, 912, 836, 778; [α]D = -4.7⁰ mL/(dm*g) (c = 5.93 mg/mL in CH₂Cl₂).

**Bis(2,4-Dinitrobenzoyl) Borane 52a.** To a 10 mL oven-dried Schlenk flask was added 2,4-dinitrobenzoic acid (0.500 g, 2.36 mmol) and Et₂O (6.00 mL) in a 10 mL schlenk flask. This solution was cooled to 0 °C and BH₃-DMS (0.130 mL, 1.26 mmol) was added. A formation of a
white precipitation was observed and the reaction continued stirring at 0 °C for 2 hours. The solvent was pumped at 0 °C to give the ether complex of 52a as a white solid: $^1$H NMR (CD$_3$CN) δ 8.67 (s, 2H), 8.52 (d, $J = 8.4$ Hz, 2H), 8.05 (d, $J = 8.4$ Hz, 2H), 3.51 (br s, 4H), 1.16 (br s, 6H), (singlets at 3.51 and 1.16 correspond to the complexed ether, singlet at 10.52 is unreacted dinitrobenzoic acid); $^{13}$C NMR (CD$_3$CN) δ 132.7(2C), 128.8(2C), 120.6 (2C); $^{11}$B NMR (CD$_3$CN) 4.40.

**Bis(4-nitro-2-(trifluoromethyl)benzoyl) Borane 52b.** To a 10 mL oven dried Schlenk flask was added 4-nitro-2-(trifluoromethyl)benzoic acid (0.500 g, 2.13 mmol) and THF (3.00 mL). BH$_3$-DMS (0.092 g, 1.21 mmol) was slowly added at room temperature. This was left to stir for 2 hours. The reaction was pumped to give a yellow powder: $^1$H NMR (CD$_3$CN) 8.57 (d, $J = 8.8$ Hz, 1H), 8.50 (dd, $J = 8.8$ Hz, 8.4 Hz, 1H), 8.03 (d, $J = 8.4$ Hz, 1H); $^{11}$B NMR 2.42.

**Bis(2,3,4,5,6-pentafluorobenzoyl) Borane 52c.** To a 10 mL oven-dried Schlenk flask was added 2,3,4,5,6-pentafluorobenzoic acid (0.500 g, 2.36 mmol) and THF (1.00 mL). This was cooled to 0 °C. BH$_3$-DMS (0.017 mL, 0.210 mmol) in THF (4.00 mL) was added to the reaction. The reaction was left to stir for 4 hours, warmed to room temperature, and then left to stir for another 2 hours. The reaction was pumped: $^{19}$F NMR (CD$_3$CN) -138.8 (2F), -149.8, -161.1 (2F); $^{11}$B NMR 1.54.

**Boron bis(benzoate) 52d.** To a 10 mL oven-dried Schlenk flask was added 4-methoxybenzoic acid (1.00 g, 8.29 mmol) and THF (1.00 mL). This was cooled to -20 °C. BH$_3$-DMS (0.390 mL, 4.10 mmol) in THF (4.00 mL) was slowly added to the reaction. The reaction was left to stir for
3 hours. The reaction was pumped at -20 °C to give a white powder: $^1$H NMR 8.24-8.14 (m, 2H), 7.64 (t, $J = 7.6$ Hz, 1H), 7.49 (t, $J = 7.6$ Hz, 2H); $^{11}$B NMR 3.29.

**Bis(2,6-dimethylbenzoyl) Borane 52e.** To a 10 mL oven-dried Schlenk flask was added 2,6-dimethyl benzoic acid (0.250 g, 1.66 mmol) and THF (0.600 mL). This was cooled to 0 °C. BH$_3$-DMS (0.090 mL, 0.945 mmol) in THF (2.00 mL) was added slowly to the reaction. The reaction was left to stir for 2 hours, warmed to room temperature, and then left to stir for another 2 hours. The reaction was pumped to give a white powder: $^1$H NMR 7.26 (t, $J = 7.6$ Hz, 1H), 7.08 (d, $J = 7.6$ Hz, 2H), 2.51 (s, 6H); $^{11}$B NMR 3.12.

**Bis(4-methoxybenzoyl) Borane 52f.** To a 10 mL oven-dried Schlenk flask was added 4-methoxybenzoic acid (1.00 g, 6.57 mmol) and THF (1.00 mL). This was cooled to 0 °C. BH$_3$-DMS (0.320 mL, 3.30 mmol) in THF (4.00 mL) was slowly added to the reaction. The reaction was left to stir for 1 hour, warmed to room temperature, and then left to stir for another 2 hours. The reaction was pumped to give a white powder: $^1$H NMR 8.22 (d, $J = 8.6$ Hz, 2H), 6.94 (d, $J = 8.6$ Hz, 2H); $^{11}$B NMR 3.29.

**Bis(1-phenylcyclopropanecarboxylate) Borane 52g.** To a 10 mL oven-dried Schlenk flask was added 1-phenylcyclopropanecarboxylic acid (0.250 g, 1.54 mmol) and CH$_2$Cl$_2$ (0.50 mL). This was cooled to -20 °C. BH$_3$-DMS (0.052 mL, 0.514 mmol) in CH$_2$Cl$_2$ (4.00 mL) was added slowly to the reaction. The reaction was left to stir for 4 hours, warmed to room temperature, and then left to stir for another 2 hours. The reaction was pumped to give a clear oil: $^1$H NMR 7.27 (m, 5H), 1.68 (dd, $J = 6.4$, 3.6 Hz, 2H), 1.25 (br s, 2H); $^{11}$B NMR 2.29.
(1S,2S)-1,2-bis(2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol. To a 2 L round bottom flask with a stir bar was added D-mannitol (40 g, 220 mmol) and anhydrous acetone (800 mL). To this was added a 1 M solution of ZnCl₂ in diethyl ether (460 mL, 460 mmol). This was allowed to stir at room temperature for 22 hours. The reaction was cooled to 0 °C. A solution of K₂CO₃ (120 g, 869 mmol) in H₂O (120 mL) was added to the vigorously stirring reaction. This was filtered, extracted with CH₂Cl₂ (2 x 500). The organic layers were basified with NH₄OH and were then concentrated. The solid was dissolved in CH₂Cl₂, washed with H₂O (200 mL), dried with MgSO₄, filtered, and concentrated. The crude material was then recrystallized using Hexanes and CH₂Cl₂ to give the product as a white solid in 58% yield: ¹H NMR 4.21-4.08 (m, 4H), 3.99-3.94 (m, 4H), 3.73 (d br, J = 6.8 Hz, 2H), 1.40 (s, 6H), 1.34 (s, 6H). ¹H NMR spectral data are consistent with literature values.³⁶

(R)-2,2-dimethyl-1,3-dioxolane-4-carbaldehyde 57. To a 50 mL round bottom flask with a stir bar was added (1S,2S)-1,2-bis(2,2-dimethyl-1,3-dioxolan-4-yl)ethane-1,2-diol (2.00 g, 7.62 mmol), CH₂Cl₂ (6.00 mL), and saturated NaHCO₃ (1.00 mL). To this suspension was slowly added NaIO₄ (3.26 g, 15.2 mmol). This was left to stir at room temperature for 2 hours. The suspension was filtered and concentrated. This was then purified by distillation under reduced pressure (15 mmHg, 75 °C) to yield the product as a clear oil in 34% yield: ¹H NMR 9.72 (d, J = 2.0 Hz, 1H), 4.38 (td, J = 6.4 Hz, 1.6 Hz, 1H), 4.17 (dd, J = 8.8, 7.6 Hz, 1H), 4.10 (dd, J = 8.8, 4.8 Hz, 1H), 1.49 (s, 3H), 1.42 (s, 3H). ¹H NMR spectral data are consistent with literature values.³⁶
**Bis(diphenyl phosphate) Borane 59.** To a 10 mL oven-dried Schlenk flask was added diphenyl hydrogen phosphate (0.100 g, 0.400 mmol) and CH$_2$Cl$_2$ (1.00 mL). This was cooled to 0 °C. BH$_3$-DMS (0.017 mL, 0.210 mmol) in CH$_2$Cl$_2$ (4.00 mL) was added to the reaction. The reaction was left to stir for 4 hours, warmed to room temperature, and then left to stir for another 2 hours. The reaction was concentrated to give a white powder: $^1$H NMR 7.13-7.00 (m, 10H); $^{31}$P NMR -19.5; $^{11}$B NMR -2.92.

**Bis(bis(4-nitrophenyl)phosphate) Borane 60.** To a 10 mL oven-dried Schlenk flask was added bis(4-nitrophenyl) hydrogen phosphate (0.100 g, 0.294 mmol) and THF (0.50 mL). This was cooled to 0 °C. BH$_3$-DMS (0.016 mL, 0.167 mmol) in THF (4.00 mL) was added slowly to the reaction. The reaction was left to stir for 4 hours, warmed to room temperature, and then left to stir for another 2 hours. The reaction was concentrated to give a white powder: $^1$H NMR (CD$_3$CN) 8.22 (d, $J$ = 8.0 Hz, 4H), 8.02 (d, $J$ = 9.6 Hz, 4H); $^{31}$P NMR -21.7; $^{11}$B NMR -2.49; $^{13}$C NMR 126.8 (4C), 126.5 (4C), 122.0 (2C), 121.9 (2C).

**(S)-2,2’-bis(methoxymethoxy)-1,1’-binaphthyl 62.** To a flame-dried 250 mL round bottom flask with a stir bar was added (S)-1,1’-binaphthyl-2,2’-diol (61, 5.00 g, 17.46 mmol) and THF (75 mL, 0.2 M). The reaction was cooled to 0 °C. A 6-% NaH dispersion in mineral oil (1.54 g, 38.4 mmol) was added in 5 portions. The reaction mixture was warmed to room temperature and the yellow solution was allowed to stir for 30 minutes. A 6.5 M MOMCl solution (3.09 g, 38.4 mmol) in THF was added. This was allowed to stir for 5 hours. The reaction was quenched with water (50 mL) and the aqueous phase was extracted with Et$_2$O (2 x 50 mL). The combined organic fractions were washed with 1 M NaOH (100 mL) and saturated aqueous NaCl (100 mL).
The organic phase was dried with MgSO₄, filtered, concentrated, and purified from hexanes and a minimum amount of EtOAc to yield the product as a white crystalline solid in 74% yield (4.8 g): ¹H NMR 7.95 (d, J = 9.2 Hz, 2H), 7.87 (d, J = 8.4 Hz, 2H), 7.57 (d, J = 9.2 Hz, 2H), 7.34 (t, J = 6.4 Hz, 2H), 7.22 (t, J = 7.2 Hz, 2H), 7.15 (d, J = 8.4 Hz), 5.02 (dd, J = 42, 6.8 Hz, 4H), 3.14 (s, 6H). ¹H NMR spectral data are consistent with literature values. ³³

(S)-3,3’-diido-2,2’-bis(methoxymethoxy)-1,1’-binaphthyl 63. To a flame-dried 250 mL round-bottom flask with a stir bar was added (S)-2,2’-bis(methoxymethoxy)-1,1’-binaphthyl (62, 3.70 g, 9.88 mmol) and THF (100 mL). The reaction mixture was cooled to -78 °C and 2.5 M n-BuLi in hexanes (14.8 mL, 34.6 mmol) was added dropwise over 10 minutes. The yellow solution was stirred for 30 minutes, warmed to 0 °C and stirred for an additional 1 hour. During this time, the solution turned brown. The reaction mixture was again cooled to -78 °C, and a solution of 1M I₂ in THF (37.0 mL, 37.0 mmol) was transferred via cannula. After stirring for 20 minutes, the tan reaction mixture was warmed to 0 °C and left to stir for an additional 30 minutes. The reaction was then quenched with saturated aqueous Na₂SO₃ (150 mL) and extracted with Et₂O (3 x 100 mL). The combined organic fractions were washed with water (250 mL) and brine (250 mL), dried with MgSO₄, filtered, and concentrated. The crude product was purified by column chromatography (7:1 hexanes/EtOAc) followed by recrystallization from hexanes and a minimum amount of EtOAc to give the product as a yellow crystalline solid in 83% yield (5.13 g): ¹H NMR 8.54 (s, 2H), 7.77 (d, J = 8.4 Hz, 2H), 7.42 (t, J = 7.2 Hz, 2H), 7.30 (t, J = 7.6 Hz, 2H), 7.17 (d, J = 8.4 Hz, 2H), 4.75 (dd, J = 46, 5.2 Hz, 4H), 2.60 (s, 6H). ¹H NMR spectral data are consistent with literature values. ³³
(S)-3,3’-bis(dihydroxyborane)-2,2’-bis(methoxymethoxy)-1,1’-binaphthyl 66. To a 500 mL oven-dried three-neck flask equipped with a N₂-inlet and a stir bar was added dry Et₂O (300 mL) and TMEDA (5.42 mL, 36.2 mmol). To this was added 2.5 M n-BuLi in hexanes (15.0 mL, 37.5 mmol). The solution was stirred for 30 minutes at room temperature. (S)-2,2’-bis(methoxymethoxy)-1,1’-binaphthyl (62, 4.76 g, 12.7 mmol) was added in 1 portion. This was allowed to stir for 3 hours. The light brown reaction mixture was cooled to -78 °C and B(OEt)₃ (13.3 mL, 78.3 mmol) was added via syringe over 10 minutes. The solution was warmed to room temperature and was allowed to stir overnight. The reaction mixture was cooled to 0 °C and 1 M HCl (150 mL) was added. The reaction mixture was left to stir for 2 hours. The phases were separated and the organic phase was washed twice with 1 M HCl (100 mL) and brine (100 mL), dried over Na₂SO₄, and concentrated to give a white solid in 85% crude yield (4.98 g): ¹H NMR 8.6 (s, 2H), 7.99 (d br, J = 8.0 Hz, 2H), 7.45 (td, J = 6.8, 2.8 Hz, 2H), 7.35 (td, J = 7.6, 2.8 Hz, 2H), 7.20 (d, J = 8.4 Hz, 2H), 4.40 (dd, J = 19, 5.2 Hz, 4H), 3.05 (s, 6H).

(S)-3,3’-bis(2,4-dinitrophenyl)-1,1’-binaphthyl-2-2’-diol 68. Degassed dioxane (6 mL) and degassed water (2 mL), were added to a mixture of 1-bromo-2,4-dinitrobenzene (67, 0.346 g, 1.40 mmol), crude (S)-3,3’-bis(dihydroxyborane)-2,2’-bis(methoxymethoxy)-1,1’-binaphthyl (0.200 g, 0.433 mmol), barium hydroxide octahydrate (0.402 g, 1.27 mmol), and Pd(PPh₃)₄ (0.050 g, 0.043 mmol) under nitrogen. The reaction mixture was heated to 70 °C for 48 hours and was then cooled to room temperature. The dioxane was removed and the residue was redissolved in CH₂Cl₂, washed with 1 M HCl (50 mL), dried over Na₂SO₄, and concentrated. Without further purification, 12 M HCl (4.6 mL) and dioxane (50 mL) were added to the crude material. This was heated to 60 °C and was allowed to stir overnight. The reaction material was
washed with saturated aqueous NaHCO₃ (50 mL), brine (50 mL), dried with MgSO₄, filtered, and concentrated. The crude product was purified by column chromatography (95:5 toluene/EtOAc) to give the product as a yellow/orange solid in 62% yield (0.502 g) over 2 steps: 

\textsuperscript{1}H NMR (CD₃CN) 8.78 (s, 2H), 8.60 (d, \( J = 7.2 \) Hz, 2H), 8.15 (s, 2H), 8.02 (d, \( J = 8.0 \) Hz, 2H), 7.91 (s, 2H), 7.48-7.38 (m br, 4H), 7.11 (s, 2H); \textsuperscript{13}C NMR (CD₃CN) 150.4 (2C), 149.3 (2C), 147.4 (2C), 139.0 (2C), 134.3 (4C), 130.8 (4C), 129.4 (2C), 128.7 (2C), 128.2 (2C), 127.7 (2C), 124.5 (2C), 124.0 (2C), 119.7 (2C), 112.7 (2C); exact mass calculated for [M-H] (C₃₂H₁₇N₄O₁₀) requires \( m/z \) 617.09, found \( m/z \) 617.23.

**Chiral Phosphate Ligand 69.** To a 25 mL flask with a stir bar was added (S)-3,3'-bis(2,4-dinitrophenyl)-1,1'-binaphthyl-2-2'-diol (68, 0.250 g, 0.404 mmol). This was dissolved in pyridine (5.00 mL). POCl₃ (0.075 mL, 0.808 mmol) was added to the reaction dropwise with rapid stirring. This was left to stir at room temperature overnight. H₂O (8.50 mL) was added to the reaction and this was left to stir for 1 hour. The reaction was diluted with CH₂Cl₂ (10 mL). Pyridine was removed by washing twice with 1 M HCl (30 mL). This was then dried with Na₂SO₄. The crude material underwent flash column chromatography (1:20 MeOH/CH₂Cl₂). This pure material was then washed twice with 1 M HCl (20 mL) and azeotroped with toluene (5 mL) to give pure material as a yellow solid in 94% yield (0.259 mg): \textsuperscript{1}H NMR ((CD₃)₂SO) 8.75 (s, 2H), 8.63 (dd, \( J = 8.4, 2.4 \) Hz, 2H), 8.27 (s, 2H), 8.14 (d, \( J = 8.0 \) Hz, 2H), 8.03 (d, \( J = 8.8 \) Hz, 2H), 7.56 (t, \( J = 7.2 \) Hz, 2H), 7.46 (t, \( J = 6.8 \) Hz, 2H), 7.25 (d, \( J = 8.4 \) Hz, 2H); \textsuperscript{13}C NMR ((CD₃)₂SO) 148.5 (2C), 147.0 (2C), 137.9 (2C), 136.3 (2C), 134.6 (2C), 132.2 (2C), 131.2 (2C), 130.5 (2C), 129.8 (2C), 129.5 (2C), 138.4 (2C), 126.9 (2C), 126.6 (2C), 125.0 (2C), 121.6 (2C), 120.5 (2C); \textsuperscript{3}P NMR ((CD₃)₂SO) 10.1; IR 1526, 1342, 1018, 725; exact mass calculated for [M+H] (C₃₂H₁₈N₄O₁₂P) requires \( m/z \) 681.07, found \( m/z \) 681.33.
$^{11}\text{B} \quad 52\text{a}$

CD$_3$CN, 128 MHz
CD$_3$CN, 128 MHz
CD$_3$CN, 380 MHz
CDCl₃, 128 MHz
CDCl₃, 128 MHz
$\left( \begin{array}{c} \text{PhO} \\ \text{PhO} \\
\end{array} \right) \text{PO} \text{O} \text{BH}_2$

$^1\text{H}$

CDCl$_3$, 400 MHz
$\overset{31p}{\text{PhO}}$ $\overset{59}{\text{PO}}$ $\overset{59}{\text{PO}}$ $\overset{\text{BH}}{\text{O}}$

CDCl$_3$, 160 MHz
$^{11}\text{B}$

CDCl$_3$, 128 MHz
$\text{ArO} - \text{P} - \text{O}\cdot\text{BH} \cdot \text{THF}$

$\text{Ar} = \begin{array}{c}
\text{H} \\
\text{H}
\end{array}$

$\text{CD}_3\text{CN}, 400 \text{ MHz}$
$^{13}$C

CD$_3$CN, 100 MHz
$^{31}_P$ Ar = \( \text{ArO} \quad \text{ArO} \)

CD$_3$CN, 160 MHz
$^{11}$B

$\left( \begin{array}{c}
\text{ArO} \\
\text{ArO} \\
\text{ArO}
\end{array} \right)_{2} \cdot \text{BH} \cdot \text{THF}$

$^{11}$B

CD$_3$CN, 128 MHz
CD$_3$CN, 400 MHz
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