ASYMMETRIC INTRAMOLECULAR HYDROBORATION VIA A UNIQUE CHIRAL CHLOROBORANE

Breanna N. von Dollen

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ASYMMETRIC INTRAMOLECULAR HYDROBORATION VIA A UNIQUE CHIRAL CHLOROBORANE

BY

BREANNA VON DOLLEN

A DISSERTATION SUBMITTED IN PARTIAL FULFILLMENT OF THE REQUIREMENTS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY

MAJOR: ORGANIC CHEMISTRY

UNIVERSITY OF MEMPHIS

DECEMBER 2023
DEDICATION

My children, Aubrie and Anakin.

My husband, James.

With prayer and hard work, You can accomplish anything!
ACKNOWLEDGEMENTS

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I would also like to acknowledge my children, Aubrie and Anakin von Dollen, for their encouragement. I hope that my achievements will give you the confidence to pursue your own dreams. Your smiling faces make every day worth it.

Lastly and most importantly, I want to give glory to God for the opportunity and ability to fulfil my goals. I want to recognize that I could not have achieved anything without the strength and guidance from the Lord Jesus. Philippians 4:13 – “I can do all things through Christ which strengthened me.” It may not always come in the form that you expect, but God always has a plan. May the Lord bless you.
ABSTRACT

A novel enantiomerically pure, internally coordinated alkylchloroborane monomer was synthesized using commercially available materials. The applications of this unique chiral borane (11A) were explored. It was known that H. C. Brown had developed a chloro-derivative of his monoalkyl borane (IpcBCl(OR)) and was able to convert symmetrical epoxides into chlorohydrins with reasonable ee’s. For example, Brown obtained the chlorohydrin from cyclohexene oxide with a 35% ee. It was unclear if this novel chiral chloroborane would generate chlorohydrins or simply alcohols since there is still a hydrogen present unlike Brown’s chloroborane. The application of the chiral chloroborane for reduction of ketones was also explored because boranes are known to readily reduce aldehydes and ketones to their corresponding alcohols. Dipinylchloroborane is well-known for an asymmetric reaction reducing ketones or aldehydes with good ee’s (84-98%). Lastly, The hydroboration of 1,4-dienes using a chloride/hydride exchange wherein only the intramolecular step creates a new chiral center was explored. Early results indicate this approach has three benefits: for R = methyl, (a) the process is regioselective, forming 1,4-diols in a 17:1 ratio; (b) the intramolecular process gives better asymmetric induction (84% ee). This approach should significantly augment the few existing routes to non-racemic 1,4-dioxygenated intermediates. Many pharmaceuticals require precise placement of functional groups, with most common of these groups being oxygen, therefore, having a method for effectively forming chiral 1,4-diols would be beneficial.
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LIST OF ABBREVIATIONS

9-bbn 9-Borabicyclo[3.3.1]nonane

AMU atomic mass unit

bp boiling point

CCB chiral chloroborane

DCM dichloromethane

DME dimethoxyethane

DMF dimethylformamide

ee enantiomeric excess

EWG electron withdrawing group

GC gas chromatography
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Full Form</th>
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<tbody>
<tr>
<td>GC-MS</td>
<td>gas chromatography- mass spectroscopy</td>
</tr>
<tr>
<td>HBcat</td>
<td>catecholborane</td>
</tr>
<tr>
<td>HBPin</td>
<td>pinacolborane</td>
</tr>
<tr>
<td>HPLC</td>
<td>high-performance liquid chromatography</td>
</tr>
<tr>
<td>Hz</td>
<td>Hertz</td>
</tr>
<tr>
<td>MCPBA</td>
<td>meta-chloroperoxybenzoic acid</td>
</tr>
<tr>
<td>MHz</td>
<td>Mega Hertz</td>
</tr>
<tr>
<td>mp</td>
<td>melting point</td>
</tr>
<tr>
<td>MTO</td>
<td>methyltrioxorhenium</td>
</tr>
<tr>
<td>NME</td>
<td>nopyl methyl ether</td>
</tr>
<tr>
<td>NME-OH</td>
<td>nopyl methyl ether alcohol</td>
</tr>
<tr>
<td>NMR</td>
<td>nuclear magnetic resonance</td>
</tr>
<tr>
<td>PMA</td>
<td>phosphomolybdic acid</td>
</tr>
<tr>
<td>ppm</td>
<td>part per million</td>
</tr>
<tr>
<td>RT</td>
<td>retention time</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>TLC</td>
<td>thin layer chromatography</td>
</tr>
<tr>
<td>TMA</td>
<td>4,6,8-trimethylazulene</td>
</tr>
<tr>
<td>TMEDA</td>
<td>tetramethylethylenediamine</td>
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CHAPTER 1: INTRODUCTION

Hydroboration/oxidation is a useful synthetic tool discovered by H.C. Brown in the mid 1950’s that allows for high regiochemical and stereochemical control of the synthesis of alcohols from alkenes, later winning a Nobel Prize (1979) for this body of work. Boranes react with non-aromatic carbon-carbon double bonds to very selectively produce, after oxidation, anti-Markovnikov alcohols derived from a strictly syn addition of H and B. Regiochemically, this reaction (Figure 1) consists of the addition of a boron-hydrogen bond across a carbon-carbon double bond, with the hydride going to the more substituted carbon. These boranes are typically oxidized to alcohols with alkaline hydrogen peroxide. During oxidation, the syn stereochemistry is entirely retained, if dioxygen is excluded.\textsuperscript{1–3}

\begin{figure}[h]
\centering
\includegraphics[width=\textwidth]{hydroboration_oxidation.png}
\caption{Hydroboration/oxidation mechanism}
\end{figure}
The parent borane, BH₃, exists as the B₂H₆ dimer in the absence of Lewis base donors. Diborane is unreactive in hydroboration unless moderately-coordinating Lewis bases (ethers and sulfides) are present to convert the dimer into two molecules of BH₃•L. However, it is necessary that the coordination be weak enough that an equilibrium with free borane exists, and more strongly coordinating Lewis bases (amines and phosphines) form complexes that are unreactive in hydroboration except at elevated temperatures. Diborane is typically made by reacting four equivalents of boron trifluoride with three equivalents of sodium borohydride (Figure 2). Diborane is a toxic and pyrophoric gas, but can be dissolved into various solvents (THF or dimethyl sulfide) to make it easier to use and make it reactive toward hydroboration. These solutions are commercially available from several suppliers. The borane-methyl sulfide complex is more stable than the THF complex, as the THF complex slowly ring-opens to butoxyborane species and must be refrigerated for long-term storage. In contrast, borane-methyl sulfide can be made and handled as the highly-concentrated (10 M) solvent-free 1:1 addition compound. Commercially, this complex may contain ~ 5% excess methyl sulfide present in solution, but this can be removed by bulb-to-bulb vacuum distillation. Conveniently, dimethyl sulfide does not interfere with the hydrogen peroxide oxidation of organoboranes.

![Figure 2: Diborane synthesis](image)

Hydroboration of carbon-carbon double and triple bonds are often very fast reactions, sometimes even faster than borane reactions with some other functional groups, which can allow hydroboration to be selective tool with a good functional group tolerance. Halogens
and alkoxy groups, as in p-chlorostyrene and p-methoxystyrene, as well as several other functional groups are generally inert.\textsuperscript{9–13} Aldehyde, ketone and carboxylic acid carboxyls, on the other hand, are highly reactive with boranes, and their reduction would compete with hydroboration, but conversion of these groups to acetals, ketals, or esters generally protects them under hydroboration conditions. Hydroboration has proven to be a useful synthetic tool that has been utilized for various chemical innovations. For example, hydroboration is involved in the key step for the total synthesis of (+)-muricadinin (Figure 3).\textsuperscript{14}

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{figure3.png}
\caption{Synthesis of (+)-muricadinin}
\end{figure}

Other reaction types

Boranes can also perform reduction reactions, converting aldehydes, ketones, epoxides, and carboxylic acids into their corresponding alcohols (Figure 4). Such reductions are often referred to as "hydroborations" of carbonyl groups, but here they will be referred to as "reductions", and the term "hydroboration" used only for reactions with alkenes.
Boranes can be reacted with alcohols to form dialkoxy boranes which are typically poor hydroborating agents. However, the dialkoxy borane catecholborane or HBCat, produced from the reaction of catechol with borane, is somewhat more reactive than other dialkoxyboranes. Hydroboration of alkenes with catecholborane exhibits enhanced regioselectivity but does require high temperature (100°C), but alkynes react at somewhat lower temperature (70°C). Dialkoxy boranes such as HBcat and HBPin (pinacolborane) have proven to be useful in metal catalyzed hydroboration.

In recent years, metal-catalyzed hydroborations have been studied, which typically use dialkoxyboranes that are not directly reactive with alkenes. These reactions are catalyzed by rhodium, iridium, or palladium complexes as well as catalysts containing earth-abundant metals like copper or cobalt. These metal-catalyzed hydroborations differ in regiochemistry, in that they do not always give the anti-Markovnikov product. Both metal types allow for highly regio- and enantio-selective hydroboration for di-substituted alkenes.

**Figure 4: Borane reduction reactions**
but may give either Markovnikov or anti-Markovnikov products depending on the particular system. This dissertation does not involve any metal-catalyzed hydroboration

Regiochemistry

Most alkenes undergoing hydroboration consume all the available B-H bonds, giving the corresponding trialkyl borane, except when the alkene is significantly hindered, in which case it forms a dialkyl or monoalkyl borane. When a terminal alkene undergoes hydroboration, the boron atom will quite selectively attach at the terminal position over the more substituted position (typical ratio ~ 16:1). This distribution is unaffected by branching of the alkyl substituents (steric effect), however, aryl groups (electronic effect) can alter this distribution, increasing placement at the more substituted carbon. Substituents on the ring can further impact this distribution, with electron withdrawing groups increasing the placement at the nonterminal carbon. This trend persists for internal alkenes; however, there is little regiochemical control in an internal alkene that is equally substituted, even when the substituents vary in steric (Figure 5).

![Figure 5: Selectivity of equally substituted internal alkenes](image)

However, electronegative groups can affect the direction of the hydroboration addition. Studies have shown that alkoxy substituents on aryl alkenes will favor the placement of boron on the more substituted carbon unlike chlorine, which will follow the normal trend of placement on the less substituted carbon (Figure 6).
Figure 6: Effects of EWG on hydroboration of aryl alkenes

It is important to note that beta-elimination followed by re-hydroboration can occur when a β leaving group is present, but in ring-opening of epoxides, the chlorohydrin can be obtained in solvents like ethyl ether. \(^{31}\)

The issues related to selectivity that occurs in boranes from their multifunctionality, their small steric requirements, the formation of cyclic intermediates and the effects of nearby directive groups can be addressed by using different borane derivatives such as mono and dialkylboranes. Thexylborane is a monoalkyl borane made from the hydroboration of 2,3-dimethyl-2-butene and can be used to obtain high regioselectivity by utilizing its steric bulk. It can stop at monohydroboration with hindered alkenes, but a mixture of products is formed with less substituted alkenes. \(^{32}\)

Figure 7: Sterically hindered alkenes

The regiochemical control and can be improved by using haloboranes or more hindered boranes, such as a dialkylborane (disiamylborane or 9-BBN) or the monoalkyl borane, thexylborane. \(^{33}\) Dialkylboranes can be used to obtain more regiocontrol of hydroboration of the less hindered alkenes. For example, the borane intermediate from the hydroboration of 2-methyl-2-butene (disiamylborane) is a sterically bulky dialkylborane that
can undergo hydroboration with other alkenes, providing higher selectivity for the anti-Markovnikov product than borane itself, even in the presence of directing groups.\textsuperscript{32,34}

9-BBN is another interesting dialkylborane formed from the hydroboration of 1,5-cyclooctadiene. Although it is somewhat less reactive than disiamylborane, it is stable in dry air and has a high thermal stability. It’s thermal stability allows higher temperatures to be employed in special cases and ultimately provides a higher regioselectivity than disiamylborane. Unlike monoalkyl boranes, 9-BBN necessarily stops at the monohydroboration product to produce a vinyl borane from acetylenes.

Alkyl and aryl boranes can be useful in many different reactions after hydroboration occurs other than just creating alcohols. Once the boron is in place, it is a handle for a chemist to manipulate. It can be converted into different functional groups such as amines, ketones, aldehydes, or it can be used to form new carbon-carbon bonds. Further derivatizing after oxidizing to the alcohol can also be accomplished for example creating methyl ethers. The retention of configuration after derivatizing is what makes boron chemistry an extremely useful tool for synthetic chemistry.

**Intramolecular hydroboration**

In cases where multiple double bonds are present, intramolecular hydroboration reactions are possible that can deviate from regiochemical expectations based only on intermolecular reactivity. For appropriate dienes, a second, intramolecular hydroboration can form cyclic organoboranes. Where possible, these favor the formation of five-membered rings. In cases where this isn’t possible, six-membered rings are favored over others, all things otherwise being equal. This is demonstrated in the hydroboration-oxidation products of 1,5-hexadiene (69% 1,6 diol, 22% 1,5 diol, and 9% 2,5 diol); however, when independent
(entirely intermolecular) hydroboration of the same diene occurs, the usual ratio is observed leading to the following products: 88% 1,6-diol, 11% 1,5 diol, and 0.4% 2,5 diol (Figure 8).

Figure 8: Intramolecular versus intermolecular hydroboration scheme

The favoring of the formation of five-membered boracycles is further demonstrated with 1,4-pentadiene which produces 62% of the 1,4-diol, while only 38% of the 1,5 diol is formed (Figure 6). Like in the reactions above, many cyclic organoboranes occur spontaneously, but some can be forced by simply heating. 1,5-Cyclooctadiene is an interesting example of this phenomena, were heating is used to shift the equilibrium to favor only the desired isomer (9-BBN), mentioned above (Figure 7). 9-BBN is very useful for hydroboration, although it is large molecule, the groups are “tied back” making it less hindered than other boranes such as disiamylborane.

Another important derivative of borane that has been developed and provides high regioselectivity is monochloroborane (BH₂Cl). Chloroborane can be made in several ways: (a) from the distribution reaction of diborane with boron trichloride etherate or (b) borane-
THF with HCl, or (c) reaction of borane with carbon tetrachloride or (d) the disproportionation reaction of BCl$_3$•SMe$_2$ with BH$_3$•SMe$_2$. Since the ethyl ether derivative (BH$_2$Cl•OEt$_2$) is more reactive, a simpler synthesis has been developed in which lithium borohydride is reacted with boron trichloride in ethyl ether. Borane dimethyl sulfide and trichloroborane dimethyl sulfide have been used to make chloroborane dimethyl sulfide complexes which significantly improves the ease of synthesis. This hydroborating reagent requires low temperature for high selectivity but does give selectivity like 9-BBN.$^{15}$

Intramolecular hydroboration is of great interest due to its ability to increase regiochemical control. There are two possible approaches to intramolecular HB: (a) heteroatom-directed and (b) hydroboration of dienes. For the first type, it has been explored using heteroatom directing groups, such as phosphines or amines, and activated boranes (boranes that contain a good leaving group);$^{39-43}$ however, the exact mechanism has not been determined.$^{44}$ In recent years, alcohol containing alkenes have been suggested to undergo direct intramolecular hydroboration when using activated boranes; however detailed study has not been done.$^{44}$

Asymmetric hydroboration, first done by H. C. Brown, was one of the earliest methods for preparing non-racemic alcohols. In 1961 he developed a dialkylborane, (-)-diisopinocampheylborane, symbolized as (Ipc)$_2$BH, from hydroboration of alpha-pinene with BH$_3$. This gave good asymmetric selectivity with alkenes that were less sterically hindered. For instance, this alkyl borane obtained 60-93% ee alcohols with cis-disubstituted alkenes. He went on to develop a mono-alkyl version (IPC)BH$_2$ of this borane from (Ipc)$_2$BH. The mono-alkyl borane could not be made directly, because $\alpha$-pinene reacts to form a dialkylborane. So instead IpcBH$_2$ was synthesized by reacting (IPC)$_2$BH with TMEDA. The strong nitrogen boron coordination resulted in loss of a molecule of $\alpha$-pinene, giving (IPBCBH$_2$)•TMEDA. A subsequent reaction with boron trifluoride etherate precipitates...
(BF$_3$)$_2$•TMEDA, leaving IPCBH$_2$ in solution, which exists mainly as a dimer. The mono-alkyl borane IPCBH$_2$ provided higher enantiomeric excess (65-92 % ee) with more hindered trans- and tri-substituted alkenes than did (IPC)$_2$BH. There have since been other chiral boranes developed, of which nearly all derived their chirality from hydroboration of an alkene from the chiral pool. Selected chiral boranes are shown in Figure 9. For example, Masamune’s C$_2$-chiral borane, which uniformly gives higher enantioselectivity for all alkene types except 1,1-disubstuted, requires a lengthy synthesis, making it much less practical to use. Asymmetric hydroboration has been very useful for the synthesis of several compounds and natural products.$^{45–48}$

![Chiral Boranes](image.png)

**Figure 9: Known chiral boranes**

Although hydroboration has been extensively studied, including several intramolecular examples, *intramolecular asymmetric* reactions of dienes have not been examined. This would require a chiral borane that could do two hydroborations. To obtain regiochemical control of these reactions, the first double bond would need to be terminal and not produce a chiral center. The second hydroboration is now intramolecular, taking advantage of boron’s favoring of a five-membered boracycle. This means these reactions would require either 1,4 or 1,5 dienes (Figure 10). The first hydroboration would occur on the less substituted terminal alkene and the second would occur on the less substituted carbon of the internal alkene. It would be expected to produce mostly 1,4 diols when the second alkene is equally substituted on the 4th and 5th carbon of the 1,4 diene due the aforementioned five membered ring.
formation. Only 1,4 diols are expected when the 5\textsuperscript{th} carbon is more substituted. The 1,5 dienes should follow the same trend and produce mostly 1,5 diols. Brown’s mono-alkyl borane, (IPC)BH\textsubscript{2}, should be capable of these reactions, but this has not been studied. A hydroborating agent of this type would provide both regiochemical and stereochemical control, which is very important for synthesis, especially in pharmaceuticals.\textsuperscript{46–49}

![Figure 10: 1,4- and 1,5-Diene substitution patterns and major hydroboration/oxidation products](image)

A novel chloroborane

A novel mono-alkyl crystalline chiral chloroborane (6) has been synthesized in two simple steps from commercially available materials (Figure 11). This chiral borane has many advantages over the previous ones. Since it is prepared in solvent-free form, it can be used in any non-reactive solvent. The internal coordination appears to stop the hydroboration at the monoalkyl borane stage, promotes crystallinity and prevents dimerization. Its ease of synthesis makes it more practical for lab use, including NMR solvents (CDCl\textsubscript{3}, C\textsubscript{6}D\textsubscript{6}, etc.). Nearly all previous chiral boranes were obtained as solutions in ether solvents.
**Figure 11: Chiral chloroborane**

This new chiral borane reagent (6) is unique in two respects (Figure 12). First, it contains an internal ether that coordinates to the boron. Internal coordination favors formation of the mono-alkylborane, which Brown was unable to do efficiently with α-pinene.49 This also has the advantage that the methoxy group acts as a sensitive \(^1\)H NMR reporter of the boron environment. The methoxy group is deshielded by coordination to boron, and the resonance in nopol methyl ether is shifted downfield by 0.49 ppm upon reaction with BH\(_2\)Cl•SMe\(_2\). Upon subsequent hydroboration of alkenes, the methoxy group shifts upfield by 0.3-0.35 ppm due to an increase in steric environment and/or a decrease the Lewis acidity at the boron. In many cases, after reaction with a prochiral alkene, a separate methoxy signal is observed for each diastereomer, integration of which reveals what the enantioselectivity would be after oxidation (see Table 1).

**Figure 12: Chiral chloroborane synthesis**

Secondly, the boron bears both hydrogen and chlorine atoms. The hydrogen provides for hydroboration and reduction reactions, while the chlorine allows for easy
nucleophilic substitutions at boron. The latter are useful for intramolecular asymmetric hydroborations, unprecedented in literature.

If the internal coordination is involved in the transition state of the hydroboration, this borane might show different degrees of asymmetric induction in different solvents. The chloroborane was tested in a variety of otherwise unreactive solvents (Error! Reference source not found.) using ethylidene cyclohexane as the alkene. The product, 1-cyclohexylethanol, was obtained with the same enantiomeric excess (69 ± 3% ee) within experimental error. This suggests that the internal coordination, while valuable for synthetic and NMR reporting purposes, plays no role in the actual hydroboration step and might make the reagent less reactive in hydroboration than comparable reagents lacking internal coordination. Comparable reagents are hardly available, and no such studies have been attempted. However, the reactivity and asymmetric induction of the chiral chloroborane has been determined for a variety of alkenes and has proven to be similar to Brown's IPCBH$_2$ reagent, generally giving poorer induction for cis alkenes but better for trans- and tri-substituted alkenes. Where directly comparable, the observed degrees of asymmetric induction were, on average, 87% of the ee's observed with the IPCBH$_2$ reagent.$^{50}$

This work explores a further application of this unique chiral borane (1). The first application is for hydroboration of 1,4-dienes using a chloride/hydride exchange in which only the intramolecular step creates a new chiral center (Figure 13). Early results indicate that this approach has three benefits: for R = methyl, (a) the process is quite regioselective, preferentially forming 1,4-diols in a 17:1 ratio; (b) the intramolecular process gives better asymmetric induction (84% ee) than intermolecular reactions. Results with a range of 1,4-dienes will be presented. It is anticipated that this approach will significantly augment the relatively few existing routes to non-racemic 1,4-dioxygenated intermediates. Many
pharmaceuticals require precise placement of functional groups, with the most common of these groups being oxygen, therefore, having a method for effectively forming chiral 1,4-diols would be beneficial.

![Figure 13: Intramolecular asymmetric hydroboration of sulcatone derived diene](image)

The chiral borane may also be useful in reactions with epoxides. There has been previous work with chiral chloroboranes that formed chlorohydrins with some regioselectivity. The previous work with halo derivatives of Brown's boranes and the asymmetric induction was rather low. Our chiral chloroborane has the potential to form these chlorohydrins with more selectivity. The chiral chloroborane contains both hydrogen and chlorine, therefore the chiral chloroborane could either form a chlorohydrin or simply reduce the epoxide, and it is unclear which to expect. All other asymmetric epoxide openings used chloroboranes without a hydride on boron. Furthermore, as mentioned above boranes can undergo reduction reactions with aldehyde and ketone carbonyls as well as hydroboration. Therefore, the chiral borane should be able to reduce aldehydes, and ketones into their corresponding chiral alcohols.
Prior to the discovery of the chloroborane 6, only one internally-coordinated borane was known. Borane 9 was prepared from the hydroboration of allyl methyl sulfide with BH$_3$•S(CH$_3$)$_2$ (Figure 14). Note that this is a rare example of a terminal alkene stopping at the monohydroboration stage, no doubt the result of the strong internal coordination. Remarkably, 9 is a distillable liquid, and is active in hydroboration. Chiral borane-sulfide complex 10 was reported after the discovery of chloroborane 6, but offers no advantages.

*Figure 14: Examples of internally coordinated boranes*
CHAPTER 2: INTERNALLY COORDINATED CHIRAL HALOBORANES

Applications of the chiral chloroborane that was described earlier will be further explored in this chapter, which recounts work from our 2022 paper “A Crystalline, Internally-Coordinated Chloroborane for Asymmetric Hydroboration”, *Tetrahedron* 2022, 108, 132654. The following information comes almost entirely from that paper. The preparation of the various internally-coordinated haloboranes, their evaluation, and the use of chloroborane 6 in the hydroboration of simple mono-alkenes described in this paper were taken from the dissertation of Dr. Charles Garner, which was almost entirely unpublished previously (Figure 15). While this chapter contains much material from that dissertation, it also describes improvements in the borane synthesis, hydroboration of a few other alkenes and determining the NMR differences in hydroboration products, work done by Breanna von Dollen.

![Figure 15: various internally coordinated chiral boranes attempted compared to previously known a chiral boranes](image)

In exploring internally-coordinated pinene-based haloborane reagents, we chose to study both ethers and sulfides, and chloro- and bromo-boranes. Reagents 11A-11B were made in two steps from commercially-available materials. Commercially-available nopol (12, ~ 92% ee) was first converted to the corresponding methyl ether (13) (Figure 16). This was easily accomplished on large scale (3 mole) using a phase-transfer method. A small amount of remaining nopol was easily removed by treating with 5 mol % of LAH prior to vacuum (~ 5 mmHg) distillation. This routinely provided nopol methyl ether in 86% yield.
and > 99% purity. The sulfide (14) required to make 11C-11D was made in two steps, first converting nopol to the known\textsuperscript{55} tosylate 15, followed by reaction with sodium methanethiolate to give sulfide 15 in an overall yield of 66%.

\[ (-)-\text{nopol (12)} \rightarrow \text{OH} \xrightarrow{(\text{MeO})_2\text{SO}_2/\text{DCM}} 50\% \text{aq NaOH} \xrightarrow{\text{cat. Bu}_4\text{N HSO}_4} \text{TsCl} \xrightarrow{\text{pyr/DCM}} 79\% \text{CH}_3\text{SNa} \xrightarrow{\text{DMF}} 86\% \text{distilled} \xrightarrow{\text{83\% OTs}} \text{L = O (13)} \xrightarrow{\text{L = S (14)}} \text{L = S (14)} \]

Figure 16: Scheme for synthesis of nopyl methyl ether and nopyl methyl sulfide

Boranes 11A-11D were made by reaction of the ether or the sulfide with either monochloroborane-methyl sulfide\textsuperscript{56,57} or mono-bromoborane methylsulfide.\textsuperscript{57} These haloboranes are available commercially or can be made by a redistribution reaction (Figure 17, Eqn. 1) of the boron trihalide-methyl sulfide with slightly less than two equivalents of borane-methyl sulfide, catalyzed by a few mol% (relative to BH\textsubscript{3}•SMe\textsubscript{2}) of lithium borohydride. Whether purchased commercially or not, \textsuperscript{11}B NMR reveals that chloroborane-methyl sulfide exists as an equilibrium mixture containing no more than 73% BH\textsubscript{2}Cl•SMe\textsubscript{2},\textsuperscript{58} with the remainder (ideally) equally divided between BH\textsubscript{3}•SMe\textsubscript{2} and BHCl\textsubscript{2}•SMe\textsubscript{2}, giving a K\textsubscript{eq} of 29 (Figure 17 ,Eqn. 2). This distribution assumes the ideal overall hydride-to-chloride ratio of 2:1; we have observed the commercial material to be somewhat hydride-rich. The same equilibrium and with identical proportions is observed by \textsuperscript{11}B NMR for mono-bromoborane-methyl sulfide. Fortunately, in the preparation of the internally-coordinated boranes 11A-11D, it appears\textsuperscript{58} that redistribution occurs under the reaction conditions, and product yields sometimes exceed the amount of BH\textsubscript{2}X•SMe\textsubscript{2} initially present. Thus, the concentration of these haloboranes was
calculated irrespective of the equilibrium, with BH₂Cl•SMe₂ at 9.1-9.6 M,⁵⁷ and BH₂Br•SMe₂ at 9.1 M.⁵⁷

\[
2 \text{BH₃•SMe₂} + BX₃•SMe₂ \xrightarrow{\text{neat}} 3 \text{BH₂X•SMe₂} \quad (\text{Eqn. 1})
\]

\[
\text{BH₃•SMe₂} + BHX₂•SMe₂ \xleftrightarrow{K = 29} 2 \text{BH₂X•SMe₂} \quad (\text{Eqn. 2})
\]

Figure 17: Synthesis of haloboranes and the equilibrium composition based on boron NMR

The boranes 11A-11D were prepared by addition of 1 equivalent of ether 13 or sulfide 14 to an equimolar amount of either BH₂Cl•SMe₂ or BH₂Br•SMe₂ in DCM or ether followed by application of vacuum until a solid resulted (Figure 18). Recrystallization was done in hydrocarbon solvent (originally hexanes or cyclohexane), typically with a hot filtration by cannula using a Kramer⁵⁹ filter. The bromo ether 11B was obtained in only 36% yield, reflecting perhaps the greater tendency of bromoboranes to cleave ethers.⁶⁰ The other three boranes were obtained in 50-64% yield. The chloroboranes 11A and 11C were contaminated with dichlorides, though much less for the ether 16 (2%) than for the sulfide 17 (20%). Interestingly, the ethers 11A and 11B gave NMR spectra consistent with a single stereoisomer or rapid averaging of stereoisomers, but the sulfides 11C and 11D gave three sets of ¹³C resonances at room temperature. This was attributed to a slow equilibration of stereoisomers at the boron and sulfur stereocenters, probably requiring dissociation of the stronger B-S bond. Apparently, the weaker B-O bond of the ether complexes rapidly averaged these structures. Heating chloro-sulfide 11C to 90 °C (toluene-₈₁) gave a ¹³C spectrum with only a single set of resonances. In all four cases, the B-H coupling was unresolved in the ¹¹B spectrum, but revealed as an increase in width at half-height of 48-101 Hz when ¹H-decoupled versus ¹H-coupled spectra were compared.
These four boranes were tested in the asymmetric hydroboration/oxidation of ethylidenecyclohexane. Studies of the hydroboration mechanism have predominantly concluded that prior dissociation of the borane-Lewis base bond is required. On this basis, the ethers would presumably be more reactive than the sulfides by virtue of the weaker B-O bond, but no effort was made to measure differences in reaction rates. In all cases, after oxidation, in addition to the desired alcohol, the nopol-derived alcohols 18 and 19 were formed; by virtue of the extra oxygen atom, 18 was readily separable from the desired alcohols by column chromatography. Sulfide 19 had nearly identical mobility on silica as the desired alcohols, but this separation problem was remedied by adding a small amount of AgNO₃-treated silica to the top of the column, which we found to bind sulfides very strongly. The product from the bromo ether 11B was contaminated with ether-cleavage products 20 and 21. All of these chiral boranes 11A-11D gave 1-cyclohexylethanol that had within experimental error the same enantiomeric excess (69% ± 3% ee), measured using an NMR chiral shift reagent (Figure 19). Thus, neither the strength of the internal coordination (S > O) nor the 16% difference in the halogen's covalent radii (Cl 1.02 pm, Br 1.20 pm) had a significant effect on the degree of asymmetric induction. For reasons of yield and simplicity of synthesis, the chloro ether 11A was chosen for further study.
Figure 19: Reaction of ethyldenecyclohexane with internally coordinated ether and sulfide haloboranes

An optimized synthesis of chloroborane 11A was developed. Monochloroborane methyl sulfide was suspended in hexanes or (preferably) cyclopentane, ether 13 was added, and the temperature was raised to distill off a mixture of dimethyl sulfide and solvent (Figure 20). It is important that the reaction mixture not exceed ~ 80 °C, making cyclopentane (BP 49 °C) superior to the higher-boiling hexanes (BP 68 °C). After distillation slowed, vacuum was applied to remove remaining solvent, the product crystallized, and recrystallization under inert atmosphere was done in hexanes or preferably in cyclopentane. Borane 11A was obtained in 69-90% yield as large plates. NMR showed this product to be solvent free, and the only contaminant to be approximately 2% of dichloroborane 16. The X-ray structure of 11A revealed an axial chlorine and other features consistent with a boron-centered anomeric effect. Variable temperature $^{13}$C NMR revealed this stereoisomer to be in rapid equilibrium at room temperature with ~ 8% of a minor stereoisomer taken to be that with an equatorial chlorine, with an activation barrier of 14-15 Kcal/mol, which is likely the strength of the B-O dative bond (see Supplemental Material for more details). Chloroborane 11A appears to be stable to dry oxygen in both the crystalline state and in solution; there were no changes observed when dry O$_2$ was bubbled through an NMR sample for 1 h. This borane is, however, water-sensitive and quickly becomes sticky if handled in moist air.
Chloroborane 11A has several advantageous properties. The recrystallization in its preparation improves the reagent's enantiomeric purity from the 92% ee of nopol to 100% ee.\(^5\) Because it is obtained solvent-free, subsequent studies can easily be carried out in any non-reactive solvent (no OH, SH or C=O), including deuterated NMR solvents (e.g., CDCl\(_3\), C\(_6\)D\(_6\)). The internal coordination appears to entirely prevent equilibration of the reagent with RBH\(_2\) and RBCl\(_2\) species, as has been observed for IPCBHCl,\(^6\) a similar but intermolecularly-coordinated chloroborane. Interestingly, the methoxy group in chloroborane 11A acts as a reporter in the \(^1\)H NMR, sensitive to both the Lewis acidity of the boron and the diastereomeric environment created upon reaction with prochiral alkenes. Formation of the chloroborane results in the methoxy group of methyl ether 13 (\(\delta\) 3.32 ppm in CDCl\(_3\)) shifting 0.47 ppm downfield in 11A (to \(\delta\) 3.79), reflecting the electron-withdrawing nature of coordination to the Lewis-acidic boron. Upon subsequent hydroborations, the methoxy resonance shifts upfield by 0.03 - 0.35 ppm, and often shows separate methoxy singlets for each diastereomer; selected examples are given in Table 1. Interestingly, in all these cases, the major diastereomer also has the more upfield methoxy resonance. Integration of these peaks provides the diastereomeric excess, which becomes the enantiomeric excess after oxidation to the alcohols. We find CDCl\(_3\) to provide better resolution of the diastereomeric signals than does C\(_6\)D\(_6\). In CDCl\(_3\), both of the OCH\(_2\) protons (3.94 and 4.18 ppm) are downfield of the OCH\(_3\) group (\(\delta\) 3.79), as expected. Interestingly, benzene solvent has a
strong upfield shifting effect in borane-Lewis base complexes,\textsuperscript{57} and in C\textsubscript{6}D\textsubscript{6} one of the O-CH\textsubscript{2} protons in 11A is upfield ($\delta$ 2.84) of the methoxy group ($\delta$ 3.01). This tends to interfere with the diastereotopic methyl resonances. In the $^{11}$B NMR spectrum, at 80.2 MHz ($^1$H = 250 MHz), the $^{11}$B resonance showed no resolvable coupling, but exhibited a half-height width of 358 Hz when proton-decoupled, and 452 Hz when proton-coupled. At 195.2 MHz ($^1$H = 600 MHz), a broad doublet was observed with $^1$J\textsubscript{1H-11B} of about 95 Hz.

Table 1: \textit{NMR shifts and diastereomeric excess of the dialkylchloroborane intermediates before oxidation versus enantiomeric after oxidation.} \textsuperscript{a} Percent de determined from $^1$H NMR of OCH\textsubscript{3} resonance. \textsuperscript{b} Percent ee determined by chiral shift NMR analysis of the alcohol after oxidation

<table>
<thead>
<tr>
<th>Alkene</th>
<th>methoxy chemical shift (CDCl\textsubscript{3})</th>
<th>$\Delta\delta$</th>
<th>% de\textsuperscript{a}</th>
<th>% ee\textsuperscript{b}</th>
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</thead>
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<tr>
<td>methyl ether 13</td>
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<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
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<td>N/A</td>
<td>N/A</td>
</tr>
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<td>1-nonene</td>
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<td>N/A</td>
<td>N/A</td>
<td>N/A</td>
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<td>3.76</td>
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<td>Cyclohexene</td>
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<td>3.64</td>
<td>0.02</td>
<td>76</td>
</tr>
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<tr>
<td>Cyclohexene</td>
<td>3.44</td>
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<td>62</td>
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<tr>
<td>2-Methylpropene</td>
<td>3.49</td>
<td>3.58</td>
<td>0.09</td>
<td>62</td>
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The internal coordination present in chloroborane 11A could be expected to decrease its reactivity relative to intermolecularly-coordinated alkylchloroboranes, but this has not been studied. However, we find it to be more than sufficiently reactive in hydroboration. While directly comparable kinetics have not been done, reactions of IPCBHC• diethyl ether with 2-methyl-2-butene at room temperature gives\(^6\) an estimated second-order rate constant only about ten times larger than chloroborane 11A gives with ethylidenecyclohexane.\(^5\)

To probe the response of the borane to solvent polarity and Lewis basicity, the hydroboration of ethylidenecyclohexane was performed with chloroborane 11A in eight solvents of varying polarity and Lewis basicity. Even dimethyl sulfide could be used as solvent; basic hydrogen peroxide oxidizes boranes to alcohols much faster than it converts sulfides to sulfoxides.\(^6\) The result, within experimental error, was that the asymmetric induction (67.5 ± 1.3% ee) was not a function of solvent (Table 2).

<table>
<thead>
<tr>
<th>Solvent</th>
<th>% ee</th>
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<tr>
<td>cyclohexane</td>
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</tr>
<tr>
<td>CCl(_4)</td>
<td>65</td>
</tr>
<tr>
<td>benzene</td>
<td>69</td>
</tr>
<tr>
<td>toluene</td>
<td>67</td>
</tr>
<tr>
<td>CH(_2)Cl(_2)</td>
<td>68</td>
</tr>
<tr>
<td>ether</td>
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<td>THF</td>
<td>67</td>
</tr>
<tr>
<td>Me(_2)S</td>
<td>67</td>
</tr>
</tbody>
</table>

The reactivity and asymmetric induction observed in reactions of chloroborane 11A with a wide variety of alkenes (Table ) were studied under standardized conditions (typically 1.2 M borane in toluene). While the more reactive alkenes gave complete reaction in a few hours or less at room temperature, the least reactive (1-phenylcyclopentene) required ~ 5 days to
approach completion. We found that using an excess (1.5 - 2 equiv) of the borane gave faster reactions, with GC yields of 91-100% at 24 h. In one case (entry 3) we found that using excess alkene gave a better result (38% ee) than using excess borane (14% ee); the cause for this is unclear. To see if this was a general effect, we studied the use of excess olefin for the alkenes in entries 1, 4, 8, 12, 15 and 19, but there was no difference in the % ee. In two cases (entries 13 and especially 17), the dialkylchloroborane intermediate was susceptible to retro-hydroboration-rehydroboration, leading to multiple products. Performing these reactions at 0 °C for 24 h eliminated this problem.

Figure 21: Possible rationalization of asymmetric induction observed

The efficiency of chloroborane 11A is much the same as that of Brown's IPCBH₂ reagent, generally poor for cis alkenes but better for trans- and tri-substituted alkenes. Hydroboration/oxidation with this reagent consistently adds the OH group to the re face of the alkene. This is consistent with approach of the alkene to the face of the borane opposite the ether group and with the now-trigonal boron oriented as it was in the coordinated form (Figure 21; R₁ represents the pinyl group). However, this could simply be a coincidence, because after correcting for (-)-nopol having the opposite configuration as that of the (+)-α-pinene Brown used, we observe the same sense of asymmetric induction as IPCBH₂ provides. This suggests that the internal coordination in 11A does not greatly change the active conformation of the borane from that of IPCBH₂. Norbornene (entry 8) is an exception, both in terms of the high asymmetric induction (82% ee) for a cis-alkene and its absolute configuration (OH added to si face). This absolute configuration was confirmed by single
crystal x-ray of the dialkylchloroborane intermediate before oxidation. Where directly comparable, the observed degrees of asymmetric induction for 11A are similar to those reported for Brown's mono-pinyl borane, averaging 87% of the ee's observed with the IPCBH$_2$ reagent. The product obtained from (E)-3-methyl-3-hexene (entry 13), (3R,4S)-(+) -4-methyl-3-hexanol is the naturally-occurring diastereomer and enantiomer of the pheromone of the ant Tetramorium impurum Foerster, whose synthesis was previously reported in four steps in 17% overall yield.
Table 3: Reaction times, yields and enantiomeric purities for reaction of chloroborane IIA with alkenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>alkene</th>
<th>Equiv.(^a) borane</th>
<th>Reaction Time (h)</th>
<th>alcohol product</th>
<th>% GC Yield(^d) (isolated)(^j)</th>
<th>Absolute Config.(^h)</th>
<th>% ee</th>
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<td>0.75</td>
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<td>S</td>
<td>9(^d)</td>
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<td>S</td>
<td>14(^e)</td>
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<td>19(^d)</td>
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Table 3 continued: Reaction times, yields and enantiomeric purities for reaction of chloroborane II\textsubscript{A} with alkenes

<table>
<thead>
<tr>
<th>Entry</th>
<th>alkene</th>
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<th>alcohol product</th>
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<td>1.7</td>
<td>24</td>
<td>91</td>
<td>1R,2R\textsuperscript{c}</td>
<td>29\textsuperscript{e}</td>
<td></td>
</tr>
<tr>
<td>17</td>
<td></td>
<td>2.0\textsuperscript{g}</td>
<td>24\textsuperscript{b}</td>
<td>96</td>
<td>1R,2R\textsuperscript{c}</td>
<td>62\textsuperscript{d}</td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td>1.8</td>
<td>24</td>
<td>99</td>
<td>1R,2S</td>
<td>74\textsuperscript{f}</td>
<td></td>
</tr>
<tr>
<td>19</td>
<td></td>
<td>1.2</td>
<td>2</td>
<td>99</td>
<td>R</td>
<td>67\textsuperscript{d}</td>
<td></td>
</tr>
</tbody>
</table>
Table 3 continued: Reaction times, yields and enantiomeric purities for reaction of chloroborane II A with alkenes (a) Neat olefins were treated with the specified number of equiv. of 1.2 M chloroborane 1 in toluene at 25 °C for the specified period of time before oxidation. (b) 1.2 M chloroborane 1 in CH2Cl2 was used. (c) absolute configuration determined by the method of Trost, et al. Enantiomeric purities were determined using (d) the NMR chiral shift reagent Eu(hfc)3, or capillary GC analysis of the derived (e) (+)-mandelate or (f) (-)-MTPA esters. (g) reaction done at 0 °C to suppress rearrangement of the borane intermediate. (h) Absolute configuration determined by the sign of the optical rotation. (i) GC yield by internal standard method, rounded to two significant figures. (j) Isolated yield, rounded to two significant figures.

One advantage that chiral reagents have over catalytic asymmetric reactions is that diastereomeric, rather than enantiomeric, products are formed. This allows for the possibility of diastereomeric purification before oxidation, and this would result in products of higher optical purity afterwards. This has been demonstrated previously for Brown's mono-pinyl70,71 and di-pinyl71 boranes. We studied the feasibility of using recrystallization of five intermediates prior to oxidation as a way to improve the diastereomer ratio. These could be done either of two ways, either as the dialkylchloroborane or as the derived ethanolamine complexes.72 The latter have the advantage of being entirely air- and water-stable, and are an option if the dialkylchloroborane happens to give unsuitable (e.g., fibrous) crystals. Despite their air-stability, the ethanolamine complexes undergo oxidation to alcohols readily. We found that four of the five intermediates chosen for this study gave diastereomeric purities of > 95% ee in 38-63% yields after three recrystallizations or less (Table 4).

Table 4: Results of recrystallization to improve the intermediate (borane % de/alcohol % ee)

<table>
<thead>
<tr>
<th>Alkene</th>
<th>No recryst</th>
<th>one recryst</th>
<th>Two recryst</th>
<th>Three recryst</th>
<th>% yield</th>
<th>% ee</th>
<th>% yield</th>
<th>% ee</th>
<th>% yield</th>
<th>% ee</th>
<th>% ee method</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-phenylcyclopentene</td>
<td>92 (isol)</td>
<td>73.5</td>
<td>84 (GC)</td>
<td>96.8</td>
<td>76</td>
<td>99.2</td>
<td>64</td>
<td>99.8</td>
<td></td>
<td></td>
<td>(-)-MTPA/GC</td>
</tr>
<tr>
<td>1-methylcyclohexene</td>
<td>98 (GC)</td>
<td>68</td>
<td>ND</td>
<td>ND</td>
<td>47</td>
<td>ND</td>
<td>38</td>
<td>99.1</td>
<td></td>
<td></td>
<td>(-)-mandelate/GC</td>
</tr>
<tr>
<td>2,3,3-trimethyl-1-butene</td>
<td>96 (GC)</td>
<td>38</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>44</td>
<td>95.4</td>
<td></td>
<td></td>
<td>(+)-mandelate/GC</td>
</tr>
<tr>
<td>ethylidenecyclohexane</td>
<td>99 (GC)</td>
<td>67</td>
<td>ND</td>
<td>ND</td>
<td>21</td>
<td>84</td>
<td>ND</td>
<td>ND</td>
<td></td>
<td></td>
<td>(-)-MTPA/GC</td>
</tr>
<tr>
<td>norbornene</td>
<td>100 (GC)</td>
<td>82</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>ND</td>
<td>56</td>
<td>96.5</td>
<td></td>
<td></td>
<td>CS/NMR</td>
</tr>
</tbody>
</table>

Yields are overall from chloroborane II A. Recrystallized as the ethanolamine complex. % ee determined by chiral shift NMR using Eu(hfc)3. ND: value not determined.
Intramolecular hydroborations of dienes have shown enhanced regio- and stereoselectivity over intermolecular hydroborations, yet asymmetric variations have not been explored. In theory, reactions of IPCBH$_2$ with dienes could proceed as intramolecular hydroborations, but this appears to not have been reported. Given that the chloride in chloroborane 11A is easily replaced with hydride, this reagent is also well-suited for intramolecular asymmetric hydroborations. Reaction with (E)-1,4-hexadiene proceeds to the dialkylchloroborane by reaction at the less-substituted alkene, forming no new chiral centers (Figure 22). Subsequent treatment with commercially-available NaEt$_3$BH replaces chloride with hydride, and the dilute (0.11 M) mixture was allowed to stand 24 h. After oxidation, (S)-1,4-hexanediol 22 (84% ee) predominated in a 17:1 ratio over 1,5-hexanediol 23 (70% ee), consistent with the known preference for boron to form five-membered rings over six-membered. The observed absolute configuration is the same (re face) as that for the intermolecular reaction. This same diene is easily converted to (4S,5R)-5-deutero-1,4-hexanediol in 84% ee by simply using the commercially-available LiBEt$_3$D in the chloride-replacement step. Two other 1,4-dienes were studied and gave diols (24, 25) of similar enantiomeric purities (74% and 69% ee, resp.). No attempt was made to determine the absolute configuration of the latter two diols.
In summary, the chiral chloroborane 11A is easily made in crystalline and enantiomerically-pure form, is stable to oxygen (though not water) and is one of the very few boranes available in solvent-free form. This reagent gives alcohols of predictable stereochemistry in reasonably good percent enantiomeric excess, especially for trans-disubstituted and trisubstituted alkenes. The dialkylchloroborane intermediates (or derived ethanolamine complexes) can be recrystallized to higher percent diastereomeric excess (before oxidation) and percent enantiomeric excess (after oxidation). This reagent is also well-suited for the asymmetric intramolecular hydroboration of appropriate 1,4-dienes with control of regiochemistry, even in cases where intermolecular hydroboration would have low regioselectivity. Further studies of intramolecular asymmetric hydroboration follow.

Figure 22: preliminary results of intramolecular asymmetric hydroboration

In summary, the chiral chloroborane 11A is easily made in crystalline and enantiomerically-pure form, is stable to oxygen (though not water) and is one of the very few boranes available in solvent-free form. This reagent gives alcohols of predictable stereochemistry in reasonably good percent enantiomeric excess, especially for trans-disubstituted and trisubstituted alkenes. The dialkylchloroborane intermediates (or derived ethanolamine complexes) can be recrystallized to higher percent diastereomeric excess (before oxidation) and percent enantiomeric excess (after oxidation). This reagent is also well-suited for the asymmetric intramolecular hydroboration of appropriate 1,4-dienes with control of regiochemistry, even in cases where intermolecular hydroboration would have low regioselectivity. Further studies of intramolecular asymmetric hydroboration follow.
CHAPTER 3: DESIGN AND PREPARATION OF 1,4-DIENES

DESIGN OF DIENES

Before studying intramolecular hydroboration, access to the appropriate 1,4-dienes was required. The 1,4-substitution pattern is critical for intramolecular asymmetric hydroboration. To have the asymmetric induction to be entirely intramolecular, the first hydroboration has to occur on a terminal alkene so no chiral center is formed. A non-terminal alkene would create a chiral center in the first hydroboration, which is undesirable for two reasons. First, we believe that intramolecular processes would give higher levels of asymmetric induction than intermolecular reactions. Second, if both hydroborations create chiral centers, this would lead to a mixture of diastereomers and complicate the determination of enantiomeric excesses. It is 1,4-dienes that, given equal substitution on the 4- and 5-carbons, have the possibility of forming either five- or six-membered boracycles (Figure 23). Intramolecular hydroboration strongly favors the formation of a five-membered ring and this can be taken advantage of to selectively make 1,4-diols even when the second double bond is equally substituted. Unfortunately, practically none of the desired dienes were commercially available. Because all the desired dienes could be made using the same phosphonium salt, we chose the Wittig olefination of aldehydes and ketones make our 1,4-dienes.
Figure 23: Dienes versus undesired dienes and their products

MAKING THE PHOSPHONIUM SALT

All the 1,4-dienes we required could be made from the same phosphonium salt, 3-butenyltriphenylphosphonium bromide (26)\textsuperscript{76} made by reaction of triphenylphosphine with 4-bromo-1-butene (Figure 24). This bromobutene was commercially available at moderate
cost ($70/100g). The reaction with triphenylphosphine was slow even at the reflux temperature of toluene (∼ 110 °C) and the reaction required at least 3 days to reach completion even using high concentrations (i.e., a minimal amount of solvent). These reactions were run in toluene at a reactant concentration ranging from 1.1 to 1.4 M, and usually with a small excess (1.02 to 1.07 equiv.) of the butenyl bromide. Despite being run under inert atmosphere, these reactions inevitably turned orange or even darker, but the color remained in the supernatant rather than in the desired product, which precipitated from solution and was isolated simply by filtration. Yields ranged from 66 to 91%. It is important to do the reaction at reflux (∼ 110 °C); one reaction allowed to go for 7 days at 80-90 °C gave only 66% yield, and 15% of triphenylphosphine was recovered from the supernatant. This phosphonium salt does not appear to be hygroscopic.

\[
\begin{align*}
\text{Br} & \quad + \quad \text{PPh}_3 \\
\text{toluene} & \quad \text{reflux} \\
\text{Br} & \quad \text{PPh}_3
\end{align*}
\]

\[
\%
\]

\[
26
\]

Figure 24: Synthesis of Wittig salt

MAKING DIENES

The ideal type of diene for our purposes would be those made from aldehydes, because the resulting 1,4-dienes would be equally substituted at the interior double bonds, and thus suited to demonstrate the selectivity for 1,4- over 1,5-diols. However, this also raises the necessity of obtaining such dienes in either pure (E) or (Z) form. The Wittig reaction is inherently Z selective unless lithium bases are used, and we initially planned to perform a "typical" Wittig reaction to get Z isomers, and to use the Schlosser modification to make the E dienes.

The generalized Wittig reaction is shown below (Figure 25). The critical variables are (a) type of base used. Options are butyllithium, or another organolithium, or sodium or
potassium hydride. Sodium or potassium bases favor intermediate B and lead preferentially to the (Z) alkene. Lithium bases stabilize intermediates A and B, slowing the elimination rate and even allowing for equilibration between the two diastereomers via the ylide. Because intermediate A is of lower energy, equilibration favors the (E) alkene. Thus, organolithium bases favor the (E) isomer. (b) The time the base is allowed to react with the phosphonium salt. This only applies to the hydride bases, because organolithiums react very rapidly even at low temperatures. (c) The temperatures and period of time allowed after addition of the aldehyde or ketone component. The extent to which the diastereomeric intermediates equilibrate and/or lose triphenylphosphine oxide to form dienes depends on the times and temperatures involved.

Figure 25: Generalized Wittig reaction

The choice of base is the most critical aspect of Wittig reactions. Sodium and potassium hydride are completely insoluble in any solvent they do not react with and are much slower to form ylide than soluble bases. In this work, when using sodium or potassium hydride, reaction times of overnight to one week were employed, typically in DME. Our early work was with dienes formed from benzaldehyde, and in this case, we observed an
equilibration of 1,4-dienes with 1,3-dienes. This is believed to have occurred via the pentadienyl anion E (Figure 26), which is apparently formed in the presence of excess base. Protonation at the end of the reaction can produce four 1,3-dienes, and in the worst cases all of these have been observed by GC-MS. Avoidance of excess base is difficult to achieve using the hydride bases, as these come as dispersions in mineral oil or paraffin, the concentration of which is only approximate. To minimize this problem, we allowed the reactions to warm to only about 0 °C before quenching. This avoided the equilibration issue, but gave only low yields of diene, presumably because intermediates C and D (Figure 25) had only partially eliminated triphenylphosphine oxide. Later it was discovered that this 1,4-versus 1,3- equilibration was only a problem for aryl dienes from benzaldehyde and possibly from acetophenone, because only these dienes can stabilize a pentadienyl anion with resonance with the aromatic ring.

Figure 26: Presence of excess base leads to isomerization

Butyl-Aryl exchange

Butyllithium as base had another complication: butyl-aryl exchange in the phosphonium salt. Butyllithium can act as a nucleophile to give a penta-coordinate phosphorus (Figure 27), which can eliminate phenyllithium (more stable than butyllithium), and the resulting
butylated phosphonium salt can transfer butyl to the carbonyl compound. This produces an impurity that is evident in the GC-MS as a closely-eluting peak with a mass two units greater than the desired diene, and entirely inseparable by any preparative means.

Figure 27: butyl-aryl exchange in the phosphonium salt

We could avoid the problem shown in Figure 27 by using tert-butyllithium. While tert-butyl-aryl exchange might still occur, the tert-butyl group has no α-hydrogens that could lead to an undesired ylide. However, our yields of dienes were still low. This is thought to be due to incomplete elimination of triphenylphosphine oxide, though a few experiments with longer reaction times did not yield significantly higher yields. Despite the low yields, the dienes were, however, easily purified by simply passing through a column of silica gel using hexanes solvent.
E/Z stereochemistry

A. From aldehydes, giving dienes with a disubstituted internal double bond. As expected, dienes with a disubstituted internal double bond exhibited mainly the (Z) stereochemistry when made using sodium hydride. The stereochemistry was determined by the vinyl-vinyl (H\textsubscript{a}-H\textsubscript{b}) coupling constant, with the Z isomer's J value being distinctly less (~11 Hz) than that of the E stereoisomer (~16 Hz) (Figure 28).

\begin{figure}[ht]
\centering
\includegraphics[width=0.8\textwidth]{figure28}
\caption{Example of stereochemistry determination by the vinyl-vinyl (H\textsubscript{a}-H\textsubscript{b}) coupling constant}
\end{figure}

B. From unsymmetrical ketones, giving dienes with a trisubstituted internal double bond. Unsymmetrical ketones will give E and Z isomers in Witting reactions, but in these cases the selectivity for the Z isomer is less. This is because sterically there is less difference between two alkyl groups in the vicinity of the carbonyl group than there is between a hydrogen and an alkyl group as in aldehydes. In these cases, the presence of E and Z isomers can be inferred from the proton NMR spectrum or GC-MS chromatogram, but assigning the stereochemistry is much more difficult. For methyl ketones, the long-range coupling constants (\textsuperscript{4}J\textsubscript{H-CH\textsubscript{3}}) across the double bond do not yield distinctive differences in the proton NMR spectrum. However, there do appear to be predictable chemical shift differences. For dienes made from methyl ketones, using the chemical shift prediction feature of the ChemDraw application, there is a consistent 0.13 to 0.15 ppm downfield shift of the methyl resonance in the E isomers (Error! Reference source not found.).
The Schlosser modification has only one deviation from the normal Wittig reaction. After cooling the solution to \(-78^\circ C\) and adding the ketone/aldehyde the solution is allowed to stir (0.5 h), then methanol (10mL) is added the solution at \(-78^\circ C\) and the resulting mixture is gradually warmed to room temperature for about 0.5 h by removing a dry ice–acetone bath. The reaction was then worked up in the same manner as the previous reaction. In our hands, using benzaldehyde, this modification did not provide the desired stereochemistry efficiently. We then studied the use of other bases.

**Separating E and Z Isomers**
Dienes made from unsymmetrical ketones would exist as a mixture of E and Z isomers, which after hydroboration would have two chiral centers (28, 29, 31-33; Figure 30). This will lead to a mixture of diastereomers which would make the percent enantiomeric excess analysis much more difficult. The remaining dienes from symmetrical ketones (27, 30, 34; Figure 30) do not form multiple chiral centers and therefore do not have an E/Z issue.

The 4-tert-butylcyclohexyl diene (27; Figure 30) is a special case, the only diene being chiral. Although hydroboration does not create a second chiral center, two diastereomers are formed, having axial and equatorial isomers. Thus, two chiral diastereomeric products are formed.

It would have been ideal to make each E and Z isomer separately. However, since we were unable to synthesize or purchase each isomer in pure form, we planned to separate the isomers after they had been synthesized. These isomers are very similar to each other, so it would be impossible to separate using typical separation methods such as distillation. Crystallization was also excluded, as the dienes are in every case (except 27) liquids. We would need to use a method that would take advantage of the small difference in the molecules' steric of the internal double bond. This would have to be either a reaction that would favor the more- or less-hindered double bond, or a separation method that was sensitive to the E/Z nature of the double bonds. Initially, epoxidation was considered, since it preferentially occurs at the more substituted double bond. We thought to preferentially epoxidize the less hindered Z alkene and then separate the desired E compound by silica gel chromatography. Alternatively, one might be able to use "silver nitrate chromatography", in which the silver ion reversibly coordinates with carbon-carbon double bonds. Less-hindered double bonds coordinate more strongly with silver, and travel more slowly as a result.
Figure 30: Chiral diol product from corresponding diene

The E and Z isomers were originally planned to be separated using silver nitrate chromatography on the radial chromatotron; however, the attempts to make silver nitrate plates were ineffective. The plates were made using the same recipe from the manual with the addition of silver nitrate dissolved in the water to make a 10% solution. In nearly all attempts, the silica layers cracked as they dried. One plate was successfully dried and used to attempt to separate the isomers. Using 10% silver nitrate TLC plates, it was determined that the isomers should be separable from each other; unfortunately, the silver nitrated RC plate did not show any separation. The plate was tested to see if it could separate beta-pinene from 3-
carene and it was again unsuccessful, but there did seem to a slight degree of separation. A commercial plate that was made by dipping a RC plate in 10% silver nitrate was tested, but this seemed to give less separation. It was then attempted to make a 20% silver nitrate plate, and after several attempts a plate was obtained that did not crack during drying, but the silica layer detached from the glass support while in use.

Since the silver nitrated method did not work in our hands, the next attempt was to separate the E and Z isomers by selectively reacting the more substituted but less-hindered Z carbon-carbon double bond (Figure 31) via epoxidation. This was attempted with MCPBA, which is known to react more rapidly with more-substituted double bonds. The goal was to react only (or mostly) the Z isomer to form the epoxide, and then it would be easy to separate the very nonpolar diene from the epoxide by silica gel chromatography in 100% hexanes. The results from this reaction (Error! Reference source not found.) demonstrated that the E isomer reacted a little faster than the Z, but there was not enough difference in the reactivities, as evidenced by the very small change in the (Z/E) ratio. Therefore, this method would not allow us to purify either isomer.

Figure 31: E and Z isomers could potentially be separated by selectively reacting the more substituted but less-hindered Z carbon-carbon double bond
Since our efforts to separate the E/Z isomers were unsuccessful, we looked again at the possible products that could form from each isomer (Figure 32) to determine how best to avoid the anticipated mixture of stereoisomers. After examining the products that could be formed, we determined that due to the syn nature of the hydroboration, any given diene diastereomer would produce a mixture of only two diol diastereomers rather than four; see Figure 33 for all possible stereoisomers and Figure 32 for only those which hydroboration could form. Because the E/Z diastereomers of each diene will presumably be formed in unequal amounts, if all four diol stereoisomers were to be separable, we could hope to identify each peak as arising from the major or minor diene by comparing the sum of two peaks to the fraction of each diene present (Figure 34). This means we might be able to avoid the need for E/Z separation because the diastereomers would possibly be separated by, say, chiral GC, giving two peaks on an achiral column and ideally four peaks using a chiral GC column.

Table 5: E/Z separation via MCPBA GC results (80°C to 220°C at 15 °C/min)

<table>
<thead>
<tr>
<th>time</th>
<th>Z/std</th>
<th>E/std</th>
<th>Z/E</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>10.9</td>
<td>2.6</td>
<td>4.3</td>
</tr>
<tr>
<td>0.5</td>
<td>9.7</td>
<td>2.1</td>
<td>4.6</td>
</tr>
<tr>
<td>2.25</td>
<td>8.7</td>
<td>2</td>
<td>4.4</td>
</tr>
<tr>
<td>3*</td>
<td>6.6</td>
<td>1.4</td>
<td>4.6</td>
</tr>
<tr>
<td>3.3*</td>
<td>5</td>
<td>0.9</td>
<td>5.4</td>
</tr>
</tbody>
</table>

* extra MCPBA added

Figure 32: Possible products from each isomer derived from unsymmetrical alkenes
Figure 33: The only isomers that could form due to the syn addition of hydroboration

Figure 34: Theoretical separation of chiral diol diesteromers via chiral GC

Although the diene synthesis was complicated by the issues mentioned above, several were able to be purified and the E/Z ratio determined. The dienes are shown below including the yield and E/Z ratio. 

Reference source not found.
<table>
<thead>
<tr>
<th>Diene</th>
<th>Structure</th>
<th>E/Z ratio</th>
<th>Yield</th>
<th>base</th>
<th>Compound #</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-tert-butyl cyclohexanone</td>
<td><img src="image1" alt="Structure" /></td>
<td>n/a</td>
<td>16 - 22 %</td>
<td>t-butyl Li</td>
<td>27</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>n-butyl Li</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>12 – 65 %</td>
<td></td>
<td></td>
</tr>
<tr>
<td>sulcatone</td>
<td><img src="image2" alt="Structure" /></td>
<td>50:50</td>
<td>20 %</td>
<td>t-butyl Li</td>
<td>28</td>
</tr>
<tr>
<td>acetophenone</td>
<td><img src="image3" alt="Structure" /></td>
<td>60:40</td>
<td>72 %</td>
<td>t-butyl Li</td>
<td>29</td>
</tr>
<tr>
<td></td>
<td></td>
<td>70:30</td>
<td>8.4%</td>
<td>n-butyl Li</td>
<td></td>
</tr>
<tr>
<td>cycloheptanone</td>
<td><img src="image4" alt="Structure" /></td>
<td>n/a</td>
<td>46-52 %</td>
<td>n-butyl Li</td>
<td>30</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>45 %</td>
<td>t-butyl Li</td>
<td></td>
</tr>
<tr>
<td>phenyl diene</td>
<td><img src="image5" alt="Structure" /></td>
<td>13:87</td>
<td>16 %</td>
<td>KH</td>
<td>31</td>
</tr>
<tr>
<td></td>
<td></td>
<td>17:83</td>
<td>70 %</td>
<td>NaH</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>78:21</td>
<td>82 %</td>
<td>n-butyl Li</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>63:37</td>
<td>6.8 %</td>
<td>t-butyl Li</td>
<td></td>
</tr>
<tr>
<td>tert-butyl diene</td>
<td><img src="image6" alt="Structure" /></td>
<td>87:13</td>
<td>16 %</td>
<td>t-butyl Li</td>
<td>32</td>
</tr>
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<td><img src="image7" alt="Structure" /></td>
<td>53:47</td>
<td>16 %</td>
<td>t-butyl Li</td>
<td>33</td>
</tr>
<tr>
<td>DCK</td>
<td><img src="image8" alt="Structure" /></td>
<td>n/a</td>
<td>39 %</td>
<td>n-butyl Li</td>
<td>34</td>
</tr>
</tbody>
</table>
The dienes above were all successfully synthesized despite the challenges that limited the yields. The NMR of each diene allowed us to determine the E/Z ratio based either on the cis or trans $^3J$ value or on the Chemdraw predicted chemical shift or the E and Z isomers respectively. The NMR spectra for the dienes were all very similar in the double bond region due to the similarity in this part of the structure. This makes the identification of the presence of the correct diene pattern simple. While the long-range coupling can causes some variations, the general peak patterns for a few hydrogens are consistent across all the dienes. The terminal CH$_2$ hydrogens are the farthest upfield alkene protons both appearing as doublets of quartets with the trans hydrogens having a larger doublet coupling (Figure 35). The CH hydrogen (C) is the farthest downfield alkene proton and appears as a double double triplet. For ketone derived olefins, the hydrogen on the internal alkene (F) forms a triplet, but when derived from an aldehyde it is a doublet of triplets in the E isomer. The CH$_2$ between the double bonds forms, to a first approximation, a triplet. Although there is some change in the shift for these peaks, as well as long range couplings, there is not overlap from other parts of the molecule. This means these are diagnostic for the presence of the desired dienes.

![Figure 35: NMR patterns for dienes](image-url)

Though some of these were mixtures of E and Z isomers, with the desired dienes in hand we proceeded to the asymmetric intramolecular hydroborations.

CHAPTER 4: ASYMMETRIC INTRAMOLECULAR HYDROBORATION
Synthesis of the Chiral Chloroborane

The chiral chloroborane \(6\) is synthesized in a two-step, high-yield procedure that uses the commercially available materials nopol\(^{78}\) (7) and BH\(_2\)Cl•SMe\(_2\).\(^{79}\) The first step in this synthesis is making the methyl ether (8) from (−)-nopol (7), which is inexpensive, only slightly more expensive than the pinenes. The large-scale synthesis of nopyl methyl ether (NME) from nopol employed phase-transfer catalysis. This phase transfer reaction allows for the use of an aqueous base in a mixed water/dichloromethane system. The methylation proceeds to 95-98% completion, and vacuum distillation from a small quantity of lithium aluminum hydride (LAH) removes any unreacted nopol or water that may be present.

The second step of the process requires BH\(_2\)Cl•SMe\(_2\). We chose to make it by equilibrating BH\(_3\)•SMe\(_2\) with BCl\(_3\)•SMe\(_2\),\(^{80}\) but this reaction does not go to completion, yielding at equilibrium approximately 72% BH\(_2\)Cl•SMe\(_2\) contaminated with 14% BHCl\(_2\)•SMe\(_2\) and 14% BH\(_3\)•SMe\(_2\), giving an equilibrium constant of about 26 (Figure 36). It should be noted that this equilibrium is present irrespective of the method used to prepare the material. The \(^{11}\)B NMR of the commercially available (Aldrich) BH\(_2\)Cl•SMe\(_2\) (Figure 37, Spectrum 1) revealed this material to be somewhat hydride-rich. Using the Aldrich material, crystallization of the crude product \(6\) was often difficult. Therefore, a "homemade" material (Figure 38, Spectrum 2) was made, and this BH\(_2\)Cl•SMe\(_2\) at equilibrium (catalyzed by LiBH\(_4\), still required ~300 hrs) was slightly chloride-rich; it consisted of 11.8% BHCl\(_2\)•SMe\(_2\), 9.5% BH\(_3\)•SMe\(_2\), and 78.7% BH\(_2\)Cl•SMe\(_2\). It is not clear why this batch had a more favorable

\[
\text{BCl}_3\cdot\text{SMe}_2 + 2\, \text{BH}_3\cdot\text{SMe}_2 \rightarrow 3\, \text{BH}_2\text{Cl}\cdot\text{SMe}_2
\]

\[
2\, \text{BH}_2\text{Cl}\cdot\text{SMe}_2 \leftrightarrow \text{BHCl}_2\cdot\text{SMe}_2 + \text{BH}_3\cdot\text{SMe}_2
\]

*Figure 36: synthesis of BH\(_2\)Cl•SMe\(_2\)*
amount of BH$_2$Cl•SMe$_2$. The homemade BH$_2$Cl•SMe$_2$ did provide crystals when reacted with NME (5).

**Figure 37**: $^{11}$B NMR of the commercially available (Aldrich) BH$_2$Cl•SMe$_2$

**Figure 38**: $^{11}$B NMR of the homemade BH$_2$Cl•SMe$_2$
To make the chloroborane (6), nopyl methyl ether (NME, 5) was added dropwise to the rapidly-stirring, warm (35°C) mixture of BH₂Cl•SMe₂ and hexane as an immiscible suspension (Figure 39). The hexanes (BP = 69 °C) are then distilled off, carrying away dimethyl sulfide and the mixture becomes homogeneous. After removal of remaining volatiles under vacuum, crystallization of the chloroborane from the viscous crude product can then typically be induced with dry ice. This reaction worked very well initially using commercial materials and homemade NME, but in subsequent reactions the crystallization failed. Using homemade chloroborane, the crystallization was again successful on a small scale. Attempts at a larger scale reaction were unsuccessful. It was observed in all unsuccessful attempts that the mixture foamed at the end of the distillation and then turned a faint brown. It was suspected that this occurred because the chloroborane may decompose at the higher internal temperatures near the end of the distillation. To prevent this, a somewhat lower-boiling solvent, cyclopentane (BP = 50 °C), was used to replace the hexanes. This change did improve the results, producing crystals in good yield (76%).

**Figure 39: Synthesis of the chiral chloroborane**

Initially the chiral chloroborane was stored in a Teflon capped vial in the refrigerator, but over time the chloroborane tended toward a brown liquid despite our attempts to protect it from moisture. It was evident that the storage of the chiral chloroborane would need to be
improved because, although it is not oxygen-sensitive, it is highly water-sensitive. It was found that storing it in a Teflon-capped vial in a glove box, rather than in the refrigerator, seems to increase its shelf life significantly. Over time the crystals would again become sticky after opening the vial several times, so ultimately it was decided to store the chiral chloroborane (CCB), in about 200 mg portions.

The chloroborane was then studied for its application in the asymmetric hydroboration of 1,4-dienes. Since the second hydroboration would be intramolecular and should also favor the formation of 5-membered rings, it should presumably provide better regioselectivity and higher asymmetric induction than if two intermolecular hydroborations had occurred (Figure 40). This hypothesis is supported by the preliminary data in Chapter 2.

![Figure 40: Intermolecular hydroboration results of 1,4-diene](image)

Each of the alkenes chosen would first react at the less substituted double bond and the boron would be on the terminal carbon. The chlorine would be exchanged for a hydrogen by using lithium triethylborohydride (“Super Hydride®”) and then an intramolecular hydroboration would occur (Figure 41). The methyl cyclopropyl (33) and the dicyclopentyl (34) dienes were included in this study because it is known that cyclopropyl rings will ring open in the presence of some transition metals, so they may not be a candidate for certain metal-catalyzed hydroborations. The sulcatone diene (28) is also very interesting because it is...
expected to intramolecularly hydroborate one internal double bond without disturbing the other equally substituted internal alkene. This selectivity would not be possible via intermolecular hydroboration (Figure 41), including in metal-catalyzed reactions.

![Figure 41: Intramolecular hydroboration of sulcatone derived diene](image)

Each of the dienes was reacted with one equiv of chiral chloroborane in dry DME and allowed to stir at room temperature in a 1 M solution for an hour. The solution was then further diluted to 0.5 M in order to favor intramolecular reactions. Finally, 1 equiv of Super Hydride® (LiEt₃BH) was added. The mixtures were then allowed to stir overnight. The following day, the reactions were oxidized using 2.5 equiv of 3 M KOH, 1 ml ethanol, and excess (> 5 equiv) of 30 % hydrogen peroxide. The yields for the chiral diols ranged from 23 - 86 % (Table 7), which might be attributed to the somewhat uncertain concentration of commercial Super Hydride®. Diols were isolated by radial chromatography. In the chromatographic purification of the diols, we found it convenient to add a little Disperse Blue 14, which is significantly less polar than any of the diols. This way, fractions were collected only after the blue color had eluted, minimizing the amount of TLC work that would need to be done.
Table 7: The yields for the non-racemic diols

<table>
<thead>
<tr>
<th>Non-racemic diols</th>
<th>Diol derived from</th>
<th>Structure</th>
<th>Compound #</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>4-tert-butyl cyclohexanone</td>
<td><img src="image" alt="Structure" /></td>
<td>27B</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>sulcatone</td>
<td><img src="image" alt="Structure" /></td>
<td>28B</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>acetophenone</td>
<td><img src="image" alt="Structure" /></td>
<td>29B</td>
<td>53</td>
</tr>
<tr>
<td></td>
<td>cycloheptanone</td>
<td><img src="image" alt="Structure" /></td>
<td>30B</td>
<td>43</td>
</tr>
<tr>
<td></td>
<td>benzaldehyde</td>
<td><img src="image" alt="Structure" /></td>
<td>31B</td>
<td>68</td>
</tr>
<tr>
<td></td>
<td>pivaldehyde</td>
<td><img src="image" alt="Structure" /></td>
<td>32B</td>
<td>86</td>
</tr>
<tr>
<td></td>
<td>methyl cyclopentyl ketone</td>
<td><img src="image" alt="Structure" /></td>
<td>33B</td>
<td>23</td>
</tr>
<tr>
<td></td>
<td>dicyclopropyl ketone</td>
<td><img src="image" alt="Structure" /></td>
<td>34B</td>
<td>45</td>
</tr>
</tbody>
</table>
For comparison, racemic diols were made from each of the dienes. They were made using BH$_3$•SMe$_2$ followed by standard oxidation. However, in the case of the sulcatone-derived diene, only two equivalents of hydride could be tolerated, otherwise the third double bond would likely react. In this case we used BH$_2$Cl•SMe$_2$. Diols were isolated by radial chromatography. In the chromatographic purification of the diols, we again used the Disperse Blue 14, to minimize the amount of TLC that would need to be done. The yields after purification were 18 - 88% (Table 8).
<table>
<thead>
<tr>
<th><strong>Diol derived from</strong></th>
<th><strong>Structure</strong></th>
<th><strong>Compound #</strong></th>
<th><strong>Yield</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td>4-tert-butyl cyclohexanone</td>
<td><img src="image1" alt="Structure" /></td>
<td>27C</td>
<td>46</td>
</tr>
<tr>
<td>sulcatone</td>
<td><img src="image2" alt="Structure" /></td>
<td>28C</td>
<td>18</td>
</tr>
<tr>
<td>acetophenone</td>
<td><img src="image3" alt="Structure" /></td>
<td>29C</td>
<td>72</td>
</tr>
<tr>
<td>cycloheptanone</td>
<td><img src="image4" alt="Structure" /></td>
<td>30C</td>
<td>65</td>
</tr>
<tr>
<td>benzaldehyde</td>
<td><img src="image5" alt="Structure" /></td>
<td>31C</td>
<td>86</td>
</tr>
<tr>
<td>pivaldehyde</td>
<td><img src="image6" alt="Structure" /></td>
<td>32C</td>
<td>43</td>
</tr>
<tr>
<td>methyl cyclopropyl ketone</td>
<td><img src="image7" alt="Structure" /></td>
<td>33C</td>
<td>47</td>
</tr>
<tr>
<td>dicyclopropyl ketone</td>
<td><img src="image8" alt="Structure" /></td>
<td>34C</td>
<td>88</td>
</tr>
</tbody>
</table>
DETERMINING ENANTIOMERIC EXCESS VIA CHIRAL GC

Analyzing 1,4-diols is significantly more difficult than analyzing 1,2- or 1,3-diols, because many of the methods for determining ee’s, such as making boronate\textsuperscript{83–85} or phosphate\textsuperscript{86} esters, even chiral shift/NMR, form cyclic compounds with the alcohols. For 1,4-diols, this would form a 7-membered ring, which is less favored than making five- or six-membered rings. The modest difference in reactivity between primary and secondary alcohols makes derivatizing the secondary alcohol with a chiral reagent, without also (or even preferentially) reacting the primary alcohol a challenge.

Alcohols are known to often exhibit broad peaks in gas chromatography due to significant and non-ideal hydrogen bonding to the stationary phase, especially in aged columns. This would be especially problematic on a chiral GC column, since the cyclodextrin stationary phases present extensive hydrogen bonding possibilities. In addition, chiral GC columns are much more limited in maximum temperature (~ 220 °C) than are achiral columns (≥ 300 °C), making elution of compounds more difficult. Given that we were looking for peaks that would be very close to each other, it was assumed that direct analysis of the diols on a chiral GC column was not feasible. To avoid this issue and hopefully increase the likelihood of observing separation of enantiomers, we anticipated that the chiral diols would need to be converted into derivatives that would maintain the stereochemical integrity but with lesser H-bonding options. It was also desirable to make the molecule smaller if possible, because smaller molecules have shorter retention times and less retention on GC columns. A general rule for chiral GC analyses is that enantiomer separations are rarely observed for elution temperatures above 200 °C.\textsuperscript{87}

LACTONE DERIVATIVES

\(\gamma\)-Lactones were chosen as attractive derivatives for chiral GC analysis, both in having significantly less hydrogen bonding, and being prepared in one step by 1,4-diol oxidation
chemistry (Figure 42). In addition, chiral lactones are present in many natural products, suggesting that our chiral chloroborane could be useful for synthesizing non-racemic lactones. The racemic diols were converted to lactones first to determine if these derivatives would be uniformly separable on a chiral GC column.

![Figure 42: Oxidation of primary versus secondary alcohol of 1,4-diols to form lactones](image)

Several methods to make lactones were evaluated. A method that would work on a small scale (~ 10 mg of diol) without isolation of the lactone was desired. It was critical that the $1^\circ$ alcohol oxidize first, giving a two diastereomers of a lactol that would further oxidize to the desired lactone (Figure 42). Reactions that oxidize the $2^\circ$ alcohol would give a ketal (as two diastereomers) that is unable to oxidize further (Figure 42). Initially, pyridinium chlorochromate (PCC) on Celite® was studied, but we found this to be slow, even with excess reagent, and to give multiple products. The Stahl oxidation$^{88}$ (a Cu(I)-TEMPO-catalyzed aerobic oxidation) appeared to give no products by GC-MS. Silver carbonate on Celite® (the Fétizon oxidation)$^{89}$ was slow and incomplete even at high temperatures; 120 °C overnight with 1.5 equiv of the silver salt was only about 15% complete. A reaction with an N-halo reagent$^{90}$ (trichlorocyanuric acid) gave selective oxidation at the $2^\circ$ alcohol, leading to ketal formation. Finally, the TEMPO-catalyzed diacetoxyiodobenzene (PhI(OAc)$_2$) oxidation$^{91}$ was found to cleanly make the desired lactones, the only major contaminant after filtration through silica being iodobenzene (Figure 43).
Once the lactones were made, a subset of five lactones were tested on several different chiral GC columns (Table 9: Subset of five lactones were tested on several different chiral GC columns (Table 9). The first column tested, a Restek Rt-b-DEXsa, showed separation of diastereomers for one lactone (Comp 27D) but no separation of enantiomers. It also had possible separation of enantiomers for one lactone (compound 28D). It was unable to separate the other lactone enantiomers or even diastereomers. The best column was CycloSil-B column, showing separation of diastereomers for two lactones (Comp27D and 29D) but no separation of their enantiomers. It also showed possible separation of enantiomers for two other lactones (compound 30D and 34D). Ultimately it was determined that the lactones would not provide sufficient separation to determine the enantiomeric excess.

Figure 43: TEMPO-catalyzed diacetoxyiodobenzene (PhI(OAc)_2) oxidation of 1,4 diol to from desired lactone
Table 9: Subset of five lactones were tested on several different chiral GC columns

<table>
<thead>
<tr>
<th># R group carbons</th>
<th># R group carbons</th>
<th>lactone</th>
<th>MF/MW</th>
<th>Restek Rt-β-DEXsa</th>
<th>Cyclosil-B</th>
</tr>
</thead>
<tbody>
<tr>
<td>27D</td>
<td>10</td>
<td><img src="Image1.png" alt="Image" /></td>
<td>C_{14}H_{24}O_{2} 224.34</td>
<td>20.85 (0.160) 22.45 (0.171) only diastr sepn</td>
<td>14.84 (0.083) 15.13 (0.116) only diastr sepn</td>
</tr>
<tr>
<td>28D</td>
<td>8</td>
<td><img src="Image2.png" alt="Image" /></td>
<td>C_{12}H_{29}O_{2} 196.29</td>
<td>poss enantiomers (same areas) 12.31 (0.078) 13.02 (0.075) other diastr? 13.15 (0.089) if so, 30:70 diastr</td>
<td>8.13? (0.077) lactone not so cleanly formed but corresponds to this chrom</td>
</tr>
<tr>
<td>29D</td>
<td>8</td>
<td><img src="Image3.png" alt="Image" /></td>
<td>C_{12}H_{14}O_{2} 190.24</td>
<td></td>
<td>10.13 (0.098) 10.31 (0.080) only diastr sepn</td>
</tr>
<tr>
<td>30D</td>
<td>7</td>
<td><img src="Image4.png" alt="Image" /></td>
<td>C_{11}H_{10}O_{2} 182.26</td>
<td>15.39 (0.135)</td>
<td>10.34 (0.116)</td>
</tr>
<tr>
<td>34D</td>
<td>7</td>
<td><img src="Image5.png" alt="Image" /></td>
<td>C_{11}H_{10}O_{2} 180.25</td>
<td>12.44 (0.091)</td>
<td>7.63 (0.057) 7.71 (0.056) enantiomers separated</td>
</tr>
</tbody>
</table>

THF DERIVATIVES

The next derivative attempted was the tetrahydrofuran (THF) derivatives. The THF derivatives were slightly smaller than the lactones since the carbonyl is no longer present. It should also be less polar and hopefully have less overall affinity for the column than the lactones. Again, the racemic diols were initially converted to the corresponding THFs (27G - 34G). The THF derivatives were made by selective tosylation of the 1° alcohol using dibutyltin oxide as a catalyst.\(^2\) Then treatment with sodium hydride gave the THF by an intramolecular Sn2 reaction (Figure 44). The product was analyzed by GC-MS to determine purity and presence of product. The presence of a base peak of 71 AMU peak in the mass...
spectrum signified that the THF had been successfully synthesized. This peak was present in all the THF samples and typically they looked very pure by GC-MS.

\[
\text{Figure 44: Synthesis of THF derivatives}
\]

The samples were then analyzed on a CycloSil-B chiral GC column, which had been the most effective of the three columns we evaluated the lactones on. The results for the THF derivatives were not as clear as for the lactones. Although the GC-MS looked very pure, the GC showed several potential product peaks present, and it was unclear which peaks corresponded to the THF enantiomers. To help make this distinction, the corresponding non-racemic chiral diols (27F – 34F) were converted to THF’s using the same procedure. They also all contained the 71 AMU base peak in the mass spectra and looked very pure by GC-MS. However, again the chiral GC was not clear if there was any separation of enantiomers when the spectra for the racemic and non-racemic chiral THFs were compared. It was again determined that this would not be a useful derivative for separating enantiomers.

**DIMETHYL ETHER DERIVATIVE**

There was one more derivative attempted for the diols in an effort to use chiral GC to determine the ee’s. The racemic cycloheptanone diol was methylated to form a dimethyl ether. (DME). The DME derivative (30E) were made by deprotonation of the alcohols using sodium hydride, followed by treatment with dimethyl sulfate. The product was analyzed by GC-MS to determine purity and the presence of product. The GC-MS showed a large peak with the largest mass peak of 114 and a base peak of 74.
The sample was then analyzed on a CycloSil-B chiral GC column. The GC chromatogram contained four peaks that were of similar area but the retention times were too far apart to be consistent with separation of enantiomers.

DETERMINING ee’s via chiral shift NMR

Since the ee’s could not be determined via GC, a new method had to be developed. Initially, chiral HPLC was considered, but since a normal-phase HPLC instrument was not readily available, it was decided that chiral shift NMR would be the next method used to determining ee’s of the diols.

A sample of the racemic cycloheptyl diol (30C) was placed in an NMR tube with an equimolar amount of dry tris-[3-(heptafluoropropyl hydroxyl methylene)-d-camphorato] europium (III) [Eu (hfc)3]. The mixture (30H) was sonicated before obtaining NMR. The peaks had not resolved, so the solution was passed through a small Celite column, but again the peaks did not resolve. The solution was then passed through a small silica column. This time the solution, although still transparent, became pinkish rather than brightly yellow and the peaks did resolve. This method was repeated for the chiral diol (30B), however, the peaks (30I) did not resolve.

DETERMINING ee’s via chiral derivatization and NMR

Since the chiral shift NMR was inconclusive, a new method for determining ee’s was needed. A literature method using 2-formylphenyl boronic acid with the chiral amine ((S)-α-methylbenzylamine) (Figure 45) was shown to provide EEs by NMR for several diols.
Although the paper only showed results for a single not-very-representative 1,4 diol (1,1'-bi(2-naphthol)) (Figure 46), this method was attempted with all the racemic diols (27J - 34J).\textsuperscript{93,94} The racemic diols were reacted with 1 equiv (or a slight excess) of the boronic acid and chiral amine. A molecular sieve was added to each reaction to remove any water. The NMR spectra was obtained the following day. The NMR spectra did have sharp peaks but also some broad humps in the spectra in the range in where a quartet for each enantiomer should have been.
The reaction was repeated with a few variables tested: time, temperature, and amine solution. Racemic cycloheptyl diol (30C) was used for all of these reactions. Using the same equivalents as above, one was reacted in an ice bath, one was heated to 40°C, one was only allowed to stir for 10 minutes, and one was made by adding the amine directly rather than using the 0.21 M amine in CDCl₃ solution. The spectra for the four experiments were essentially identical to the original spectrum.

The paper suggested that low temperature NMR might help resolve peaks by shifting the equilibrium. This was attempted with the original NMR sample of the racemic cycloheptyl diol (30C). The spectra were obtained at 0 °C, -20 °C, -40 °C, and -55 °C. As the temperature was lowered, two quartets (5.42 and 5.31 ppm) (Error! Reference source not found.) of equal height began to resolve. This was consistent with the paper for the region for the hydrogen on the tertiary carbon adjacent to the nitrogen (Figure 47). Two singlets of equal area also began to resolve (8.13 and 7.89 ppm) (Error! Reference source not found.) and this was consistent with paper for the region for the hydrogen on the secondary carbon adjacent to the nitrogen. The resolution was best at -40°C so the experiment was repeated with the chiral diol. The singlets and quartets again resolved and were not of equal area. The ee was determined to be 50%. This method, however, was not successful for all the diols.

![Figure 47: Diagnostic NMR patterns and chemical shifts of diesteramers](image-url)
Figure 48: $H_2CH$ region of NMR of racemic cycloheptyl diol (30J) at various temperatures; from top to bottom, temperatures are -55, -40, -20, 0, and 25°C.
Figure 49: Aromatic region of NMR of racemic cycloheptyl diol (30J) at various temperatures; from top to bottom, temperatures are -55, -40, -20, 0, and 25°C

DETERMINING EES VIA CHIRAL HPLC

Chiral HPLC has the potential to separate the chiral diols. Using a reverse phase HPLC with a cellulose based chiral column (CHIRALCEL® OD-H) and a refractive index detector, we could hope to determine the ee’s for the chiral diols if they are able to be eluted quickly enough with 10% or less isopropanol in hexanes and are separated by the column. If the diols cannot be used, the previously mentioned lactones would be a good candidate. Again, they are smaller and less polar than the diols which could allow for better separation.

CHAPTER 5: REDUCTION OF EPOXIDES, ALDEHYDES, AND KETONES
Epoxides

Asymmetric reductions of aldehydes and ketones is an important reaction for the synthesis of chiral alcohols from prochiral compounds. Often chiral alcohols are building blocks for biologically active compounds. For chemists to synthesize complex molecules with specific stereocenters, reliable methods for converting available carbonyls to chiral alcohols are necessary. Another valuable reaction is the conversion of epoxides to chlorohydrins. Chlorohydrins are important for the synthesis of marine products as well as in organic transformations. Unfortunately, this conversion often has low enantioselectivity.

B-halo derivatives of H. C. Brown’s chiral boranes were demonstrated to be able to absorb. The dialkyl halo-derivatives (IPC₂BCl) gave products with ee’s in the range of 22-95% with various epoxides (Figure 50). The mono-alkyl B-chloro derivative (IpcBCl(OR)), most like our chiral chloroborane, was able to convert cyclohexene oxide into its corresponding chlorohydrin with a 35% ee (Figure 50). It was not clear whether our chiral chloroborane, having both hydride and chloride on boron, would convert the epoxides into chlorohydrins or simply reduce them to alcohols.

![Chemical structures]

Figure 50: The results of mono-alkyl B-chloro derivative (IpcBCl(OR)) and the chiral chloroborane reaction with cyclohexene oxide

64
We selected four symmetrical epoxides that were either commercially available or easy to make using hydrogen peroxide and a methyltrioxorhenium catalyst (Figure 51). The procedure to react epoxides with our chiral chloroborane was adapted from Brown’s paper. The chiral chloroborane was cooled to -78°C and treated with 1 equiv of epoxide and allowed to slowly warm to room temperature overnight. The products were analysed by GC-MS. The GC-MS data showed that the chlorohydrin was successfully synthesized except for the product (37A) from cis-stilbene epoxide (37). For cyclohexene oxide (35), there was a peak at 8.3 min with a 91% match to the chlorohydrin (35A). The mass spectra had molecular ion of 134 and MI+2 of 136 with a ratio of 3:1 which is consistent with the presence of a chlorine. The cyclooctene oxide (36) did not have a database match to product, but a peak at 11.3 min. had a MI of 144 and a MI +2 of 146 with a ratio of 3:1 which is consistent with a loss of water from the chlorohydrin (36A). The norborene oxide (37) had a large peak at 10.0 min that had a MI of 111, which was consistent with a loss of Cl (37A).

![Figure 51: Selected symmetrical epoxides](image)

The determination of the % ee's using a Restek GC chiral column was largely successful. While the yields were reasonable (46-86%), the enantiomeric purities were poor. The highest ee that was obtained was for cyclohexene oxide (35), forming trans-2-chlorocyclohexanol (35A) in 18% ee. This was lower than what Brown was able to obtain with his mono-alkyl chloro-derivative (35% ee).97 The remaining epoxides were essentially
racemic (Figure 52), though we were unable to easily determine the % ee for the chlorohydrin from the cis-stilbene epoxide. Ultimately, it was determined our chloroborane is a poor reagent for making chlorohydrins from symmetrical oxides.

![Figure 52: Chlorhydrin ee results determined using Restek GC chiral column](image)

Boranes are known to readily reduce aldehydes and ketones to their corresponding alcohols. In fact, there is a well-known asymmetric reaction with dipinylchloroborane to reduce ketones or aldehydes good ee’s (84-98%), which suggests a similar application of our chiral chloroborane. We chose ketones (Figure 53) that would probe the rate of hydroboration versus reduction as well as the possibility of oxygen-directed hydroboration.

The ketones were all reacted using the same method. The chloroborane was dissolved in DME to make a 0.3 M solution. The temperature was then lowered to -78°C and equimolar amount of the ketone was slowly added to the cold, stirring solution. After an hour, the solution was oxidized using the same method as previously discussed. The products were purified via a radial chromatography and analyzed by GC-MS. The GC-MS for the isophorone reaction showed an 89% match to the expected reduction product (39A). The
mass spectrum had a MI of 140 with a base peak of 125. Acetophenone (40) was reacted with both the CCB and with borane. Both GC-MS spectra showed a product match for corresponding alcohol (40A or 40B). For both reactions there was a peak at 8.9 min with 95% match, a MI of 122, MI +1 of 123, a base peak of 79. The 2,2,2-trifluoroacetophenone reduction product (41) had a peak at 8.6 min. with a MI of 176, a base peak of 79, and a large mass peak of 107 which is consistent with the reduction product. The sulcatone reaction GC-MS spectra had a peak with an 81% match to the reduction product (42) with a MI of 128, a base peak of 41, and a large 95 mass peak. Lastly, the 6H2O (43) mass spectrum had a peak with a MI of 140 which is consistent with the reduction product. These results do not show any C=C hydroboration products or oxygen-directed hydroboration products.

![Figure 53: Ketones selected for Reduction](image)

We attempted to determine the ee’s of the alcohol products via chiral GC, but unfortunately enantiomers of only two of the alcohols, 1-Phenylethanol and 2,2,2-trifluoro-1-Phenylethanol (40A and 41A) were separated on the chiral column (Figure 54). The ee’s of the two alcohols were extremely low, only 8 and 13% ee. Chiral shift NMR was again attempted for the remaining alcohol products, but it was not clear enough to determine ee’s. It
was concluded that our chiral chloroborane is not useful for the intermolecular reduction of aldehydes and ketones.

\[ \begin{align*}
39 & \quad \text{24\% yield} \\
40 & \quad \text{8\% ee, 67\% yield} \\
41 & \quad \text{13\% ee, 61\% yield} \\
42 & \quad \text{20\% yield} \\
43 & \quad \text{5\% yield}
\end{align*} \]

*Figure 54: results from reduction with chiral chloroborane*

The results from this body of work demonstrate several characteristics of the CCB. When a carbonyl and a non-terminal alkene are both present, the CCB favors reduction over hydroboration. However, it would be of interest to repeat this experiment with aldehydes and ketones that also have terminal carbon-carbon double bonds. The CCB can be used to make racemic chlorohydrins and favors this over simply reducing the oxide to an alcohol.

**CONCLUSION**

The non-conjugated 1,4-dienes needed for this study were able to be successfully synthesized, although the yields were not able to be consistently improved. Varying the base and the temperature was able to impact the E/Z ratio and yield. The diene structures and E/Z ratio were confirmed and determined using NMR. The dienes were used to evaluate the intramolecular asymmetric hydroboration. The diol products from both reactions were
confirmed using GC-MS and NMR. Determining the ee’s for the alcohols posed several issues. Alcohols will generally tail in most types of chromatography, so the diols were derivatized in three ways, but they were still not able to be separated on chiral GC. Two NMR methods were also attempted, but again unfortunately did not provide the ee determination for most of the diols. HPLC could be the key to determining the ee’s, either of the diols or their corresponding lactones. This will require a normal phase HPLC with a chiral column and an RI detector for the diols. Based on the data that has been collected, the CCB is still very promising for intramolecular asymmetric hydroboration. Once a method for determining ee’s is determined, it would of interest to determine the temperature and concentration dependence of the chiral induction for these intramolecular hydroboration. It would also be interesting to determine whether IPCBH$_2$ could do intramolecular asymmetric hydroboration.

CHAPTER 6: EXPERIMENTAL

Reactants and reagents were purchased from Sigma-Aldrich, Acros Organics, Fisher and other common vendors and, unless noted otherwise, were used without further purification. Diethyl ether, tetrahydrofuran and 1,2-dimethoxyethane were purchased from Fisher, dried over molecular sieves, and stored under nitrogen prior to use. All Wittig and hydroboration procedures were carried out under argon or nitrogen atmosphere, using a glove box for transfer of solids, and standard cannula and Schlenk techniques for liquids. Proton and carbon NMR spectra were obtained with a JEOL 400 MHz spectrometer. Chemical shifts were referenced to residual solvent peaks.99
Gas-chromatography-mass spectrometry was done on a Hewlett-Packard GCD equipped with a 20 m x 0.15 mm Restek RTxi-5ms capillary column using helium carrier at 15 psi with an inlet temperature of 250 °C.

Synthesizing nopol methyl ether (7)

(1R,5S)-2-(2-methoxyethyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene (7)

A 2 L flask fitted with a reflux condenser and overhead stirring was charged with NaOH (116.99 g, 2.9 mol, 5 equiv) and an equal mass of water and cooled to room temperature. Then 100 ml of nopol (0.58 mol) and 115 ml of DCM were added to the flask with 3.97 g of Bu₄NHSO₄ (11.7 mmol, 2 mol%). The solution was stirred vigorously for 15 min before being placed in a water bath at 20 °C. Then using an addition funnel, 1 equiv dimethyl sulfate (55 ml, 0.58 mol) was slowly dripped into the stirring solution. The solution was checked for completion via TLC using 15% EtOAc in hexanes and PMA stain. The reaction mixture was also analysed by GC by diluting a drop of the organic phase with DCM, and drying with MgSO₄ prior to analysis. The methyl ether eluted slightly earlier than the alcohol. Since the alcohol was still present, the solution was stirred an additional 30 minutes before slowly adding 30 ml of concentrated ammonium hydroxide followed by an hour of stirring. The solution was then partitioned between 100 ml hexanes and 150 ml of H₂O. The organic phase was extracted three times and combined. The combined organic phases were washed with a brine solution and dried over K₂CO₃, filtered and concentrated. The pale-yellow solution was vacuum distilled (~ 5 torr) from LAH (58 mmol, 2.2 g, 1 mol%). The distillate was collected, giving the desired product (67.547 g, 374.7 mmol, 64.6%). The product was stored over K₂CO₃ in an argon-filled flask in the refrigerator. Yields for this reaction ranged from 64-80 %. The proton NMR was consistent for nopyl methyl ether.
\(^1\)H NMR (CDCl\(_3\), 600 MHz): \(\delta\) 0.83 (s, 3H), 1.16 (d, 1H, \(J = 8.5\) Hz), 1.27 (s, 3H), 2.03 (td, 1H, \(J = 5.6, 1.5\) Hz), 2.05-2.10 (m, 1H), 2.15-2.29 (m, 4H), 2.35 (dt, 1H, \(J = 8.5, 5.6\) Hz), 3.32 (s, 3H), 3.34-3.42 (m, 2H), 5.26 (tq, 1H, \(J = 2.9, 1.5\) Hz).

Synthesizing chiral chloroborane (6)

An oven-dried argon-filled 100 ml flask fitted with stir bar and septum was fitted with a distillation head and receiver and charged with chloroborane-methyl sulfide complex (3.0 g, 2.8 mL, 9.56 molar, 27 mmol, 1.1 equiv) and dry cyclopentane (16 mL). The two-phase mixture was stirred rapidly and warmed to 35 °C in an oil bath. Nopryl methyl ether (7) (5.0 mL, 1 equiv, 25 mmol) was added dropwise added between 35 and 40°C in oil bath. The bath was warmed to 70-80 °C to distill SMe\(_2\) and cyclopentane. The distillation head was quickly swapped for a fritted vacuum adapter. The residue was swirled under pump vacuum (< 2 mmHg) for 5 min, then the viscous liquid was left under argon overnight. The mixture crystallized overnight and was recrystallized by dissolving all but a single crystal in dry cyclopentane (21 mL) at ~ 45 °C. The solution was then allowed to cool slowly to room temperature. The crystals were washed with cold cyclopentane and then dried under vacuum. The product (4.86 g, 86% yield) was then stored in Teflon capped vials in ~100 mg portions in a glove box. This material was obtained as white plates, mp 84-86.5 °C (sealed capillary). Calculated for C\(_{12}\)H\(_{22}\)BClO: C 63.06, H 9.70, Cl 15.51; found: C 62.90, H 9.72, Cl 15.43. It was pure by proton NMR.

IR (soln in CDCl\(_3\)): 2465 (strong, B-H). MS (70 eV): 228 (M+), 193, 105, 79 (base). \([\alpha]_D^\text{D}: -30.1^\circ (c = 14.2, \text{CCl}_4)\).

\(^1\)H NMR (600 MHz, CDCl\(_3\)): 0.83 (d, \(J = 9.1\) Hz, 1H), 1.15 (s, 3H), 1.23 (s, 3H), 1.52-1.61 (m, 2H), 1.64 (br d, \(J = 13.8, 1H\)), 1.80 (t, \(J = 5.7\) Hz, 1H), 1.86-2.18 (m, 3H), 2.26 (br t,
11.0 Hz, 1H), 2.44 dtd, J = 9.6, 6.2, 1.8 Hz, 1H), 3.79 (s, 3H), 3.96 (br s), 4.23 (br t, J = 10.3, 1H).

$^{13}$C NMR (150.8 MHz, CDCl$_3$): 22.9, 28.5 (v br), 29.5, 30.1, 35.5, 38.3, 39.2 (v br), 40.7, 42.8, 47.5, 66.8 (br), 79.4 (br). $^{11}$B NMR (192.5 MHz, CDCl$_3$): 14.8 (br d, J = 96 Hz).

$^{11}$B NMR (80.2 MHz, CDCl$_3$): 14.4 ppm (br s; half-height width 358 Hz proton-decoupled, 452 Hz proton-coupled). This contained about 2% of the dichloroborane complex 16, evident as a small methoxy singlet at 3.97 ppm, but more evident as $^{13}$C NMR peaks for the oxygen-bound carbons at 62.9 and 83.2 ppm.

Synthesizing dienes

3-Butenyltriphenylphosphonium bromide (26)

To a 250 mL round-bottom flask with a stir bar was added triphenylphosphine (10.763 g, 41.0 mmol) and toluene (30 mL), and the flask was sealed with a septum. Using a needle through the septum, an inert atmosphere was established using two vacuum/argon cycles. Then 4-bromo-1-butene (4.6 mL, 45 mmol, 1.1 equiv) was added by syringe and the transparent colorless solution was heated to 100 °C for 3 days, during which the solution took on an orange color and a powdery solid formed. After cooling to room temperature, the solid was isolated by vacuum filtration, and washed with hexanes. After oven drying (120 °C) to constant weight, 3-butenyltriphenylphosphonium bromide (15 g, 91.2%) was obtained.

$^1$H NMR (CDCl$_3$, 400 MHz): δ 2.32-2.40 (m, 2H), 3.74-3.81 (m, 2H), 4.90 (d, 1H, J = 10.3 Hz), 5.99 (d, 1H, J = 17.0 Hz), 6.01 (ddt, 1H, J = 17.0, 10.4, 6.4 Hz), 7.68-7.76 (m, 6H), 7.77-7.90 (m, 9H).

$^{31}$P NMR (CDCl$_3$, 161.4 MHz): δ 24.71 (s)
(R,S)-1-(but-3-en-1-ylidene)-4-(tert-butyl)cyclohexane (27)

An oven dried 50 mL recovery flask with a stir bar was cooled under vacuum. Then 2.0974 g (5.4 mmol) of 3-butenyltriphenylphosphonium bromide was added, and the flask was put under argon using 1 vacuum/argon cycle. Then about 10 mL of dry DME was added, giving a white suspension. The stirring mixture was cooled to -78 °C followed by the addition of n-butyllithium (2.28 M in ether, 2.2 mL, 4.9 mmol, 0.91 equiv) dropwise. Each drop made a dark brown spot. The solution became a light pale orangish color after all the butyllithium was added. The mixture was allowed to warm slowly to room temperature (~ 60 min) and then was allowed to stir at room temperature for 1 hour. The solution was a deeper orange color after being at room temperature for an hour. The mixture was cooled to -78 °C again, and 1 equivalent of 4-(tert-butyl) cyclohexanone (0.83 g, 5.4 mmol) was added as a solution in ether. The red color faded slightly after the addition of ketone to a lighter orange color but did not disappear. The mixture was stirred overnight. The next day, 1 mL of water was added to quench any remaining ylide. Rotary evaporation was used to remove the DME. The product was swirled with hexanes (15 mL) forming a beige suspension. It was then filtered thru Celite to give a yellow-orange filtrate. The solution was purified via radial chromatography. The yield was 0.4480 g (44 %). The product was analysed by GC-MS, $^1$H NMR, and $^{13}$C NMR. The GC-MS temperature program was 35 °C hold 4 min, then to 240 °C at 20 °C/min, hold 4 min.

$^1$H NMR (CDCl$_3$, 400 MHz): δ 0.86 (s, 9 H), 0.89-1.08 (m, 3 H), 1.16 (tt, 1 H, J = 11.9, 3.0 Hz), 1.69 (bt, 1H, 13.1 Hz), 1.82-1.89 (m, 2 H), 2.02 (br t, 1 H, 13.9), 2.26 (br dq, 1 H, J = 13.5, 2.5 Hz), 2.64 (br dq, 1 H, J = 13.8, 2.6 Hz), 2.76 (br t, 1 H, J = 6.8 Hz), 4.95 (br dd, 1 H, J = 10.1, 1.4 Hz), 5.03 (br dq, 1 H, J = 17.1, 1.6 Hz), 5.10 (br t, 1 H, J = 7.5 Hz), 5.8 (ddt, 1 H, 16.9, 10.4, 5.9 Hz).
$^{13}$C NMR (CDCl$_3$, 100.1 MHz): $\delta$ 27.9, 28.5, 28.6, 29.3, 37.1, 48.8, 114.2, 117.9, 138.0, 141.0.

GC-MS: RT 11.86 min, MI 193, base of 57 (t-butyl group), 135 (diene without t-butyl).

(E/Z)-5,9-dimethyl-1,4,8-decatriene (28)

A 100 mL recovery flask fitted with a stir bar and a septum was charged with 6.0 g (15 mmol) of 3-butenyltriphenylphosphonium bromide. The air was removed by vacuum, and nitrogen carefully admitted. About 40 mL of ether was added via cannula. The flask was cooled to -78 °C. Then tert-butyllithium (8.7 mL, 1.9 M, 16.5 mmol, 1.1 equiv) was added via syringe, creating a yellow color that gradually deepened to a reddish-brown as the mixture was allowed to slowly warm to about 0 °C. Then it was re-cooled to -78 °C, before adding 2.45 mL (16.1 mmol, 1.1 equiv) of sulcatone via syringe. The reaction did not show any immediate color change, and even with gradually warming to +5 °C, the reaction mixture stayed a dark reddish-brown. Once the reaction had reached +5 °C, 1 ml of saturated NH$_4$Cl solution was added. The mixture was filtered, rinsed with hexanes, and then concentrated by rotary evaporation. A little 4,6,8-trimethylazulene (TMA) was added to the crude product. The product was purified by passage through silica gel (~ 30 g) using only hexanes. It is convenient to add a little TMA, which is significantly more polar than any of the dienes. This way, fractions were collected until the purple color began to elute, minimizing the amount of TLC work that would need to be done. A yield of 500 mg (20%) of product was obtained as a colorless oil. The product showed only one spot on TLC, but two peaks on GC-MS. GC-MS program was 80 °C hold 2 min at 20 °C/min to 300 °C hold 4 min.

GC-MS: RT 10.02 min, MI 164, base of 69, 54 peak; RT: 10.16 min. MI 164, base of 69, 54 peak. The isomers were in a 50:50 ratio.
1H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.61 (bs, 6 H), 1.69 (bs, 3 H), 1.72 (q, 4 H, $J = 1.2$ Hz), 2.75 (t, 2 H, $J = 6.8$ Hz), 4.95 (ddt, 1 H, $J = 17.2, 1.8, 0.9$ Hz), 5.01 (ddt, 1 H, 10.2, 3.4, 1.4, Hz), 5.08 – 5.14 (m, 1 H), 5.14 – 5.19 (m, 1 H), 5.75 – 5.86 (m, 1 H).

13C NMR (CDCl$_3$, 100.1 MHz): $\delta$ 13.9, 17.7, 25.70, 25.74, 33.3, 38.3, 42.7, 62.9, 75.5, 124.60, 124.70, 131.5.

(E)-hexa-2,5-dien-2-ylbenzene (29)

A 100 mL recovery flask fitted with a stir bar and a septum was charged with 6.0 g (15.1 mmol) of 3-butenyltriphenylphosphonium bromide. The air was removed by vacuum, and nitrogen carefully admitted. About 40 mL of dry ether was added via cannula. The flask was cooled to -78 °C. Then tert-butyllithium (8.7 mL, 1.9 M, 16.5 mmol) was added via syringe, creating a yellow color that gradually deepened to a reddish-brown as the mixture was allowed to slowly warm to about 0 °C. Then it was re-cooled to -78 °C, before adding 1.94 mL (16.1 mmol) of acetophenone via syringe. The reaction did not show any immediate color change, but with gradually warming to +5 °C, the acetophenone reaction lost almost all its color. Once the reaction had reached +5 °C, 1 ml of saturated NH$_4$Cl solution was added to the reaction. The crude product was then filtered, rinsed with hexanes, then concentrated by rotary evaporation, added a little TMA, then purified by passage through silica gel (~ 30 g) using only hexanes. The acetophenone product had two high-Rf spots (~ 0.75 and 0.65) visible on TLC (100% hexanes), but hardly separated on the column. The organic factions were combined and concentrated by rotary evaporation to give 270 mg of slightly purple liquid. GC-MS program was 100 °C hold 3 min then at 7 °C/min to 200 °C. The spectrum showed isomers in a 60:40 ratio, resp. Proton NMR showed 57:43 ratio of isomers with the major isomer being Z.

GC-MS: RT 6.39 min, MI 158, base of 128, 54 peak; RT: 8.45 min, MI 158, base of 128, 54, in a 60:40 ratio, resp.
$^1$H NMR (CDCl$_3$, 400 MHz): δ 2.06 (q, 3 H, J = 1.2 Hz), 2.72 (tdq, 2 H, J = 6.8, 1.7, 1.4 Hz), 4.97 (dq, 1 H, J = 10.1, 1.7 Hz), 5.02 (dq, 1 H, J = 17.2, 1.8 Hz), 5.49 (tq, 1 H, J = 7.5, 1.4 Hz), 5.76 – 5.86 (m, 1 H), 7.17 – 7.27 (m, 5 H).

but-3-en-1-ylidenecycloheptane (30)

A 100 mL recovery flask fitted with a stir bar and a septum was charged with 3.22 g (8.1 mmol) of 3-butenyltriphenylphosphonium bromide. The air was removed by vacuum, and argon carefully admitted. About 15 mL of ether was added via cannula. The flask was cooled to 10 °C, then tert-butyllithium (4.7 mL, 1.9 M, 8.9 mmol) was added via syringe, creating a yellow color that gradually deepened to a reddish-brown as the mixture was allowed to slowly warm to room temperature. Then it was re-cooled to 10 °C, before adding 0.96 ml (8.1 mmol) of cycloheptanone via syringe. The reaction did not show any immediate color change, but was gradually warmed to room temperature for about 2 hrs, by which time the reaction lost almost all its color. After 2 hours, 1 ml of saturated NH$_4$Cl solution was added to the reaction. The mixture was filtered, rinsed with hexanes, then concentrated by rotary evaporation. A small amount of TMA was added before purifying by passage through silica gel (~ 30 g) using only hexanes. The product had two high-$R_f$ spots (~ 0.75 and 0.65) that were visible on TLC (100% hexanes). The organic factions were combined and concentrated via rotary evaporation to give 542 mg of slightly purple liquid. The product was analyzed by GC-MS (60 °C, hold 3 then at 20 °C/min to 240, hold 4).

GC-MS: RT 7.92 min, MI 150, base of 81.

$^1$H NMR (CDCl$_3$, 400 MHz): δ 1.47-1.52 (m, 4 H), 1.54 -1.59 (m, 4 H), 2.20-2.24 (m, 4 H), 2.73 (br t, 2 H, J = 6.7 Hz), 4.94 (dq, 1 H, J = 10.1, 1.9 Hz), 5.02 (dq, 1 H, J = 17.1, 1.8 Hz), 5.17 (tt, 1 H, J = 7.3, 1.2 Hz), 5.81 (ddt, 1 H, J = 17.0, 10.1, 6.1 Hz).
$^{13}$C NMR (CDCl$_3$, 100.1 MHz): $\delta$ 142.6, 137.6, 121.9, 114.1, 37.9, 32.1, 30.0, 29.1, 27.1

(Z)-penta-1,4-dien-1-ylbenzene (31)

made using n-butyl lithium

An oven-dried 50 mL recovery flask fitted with a large football stir bar was cooled under vacuum. Then 1.0017 g (2.52 mmol) of 3-butenyltriphenylphosphonium bromide were added, and the flask was put under argon using one vacuum/argon cycle. About 10 mL of dry DME was added, giving a white suspension. The stirring mixture was cooled to -78 °C followed by the addition of n-butyl lithium (2.28 M in ether, 1.0 mL, 2.3 mmol, 0.9 eq.) dropwise. Each drop made a dark brown color. The solution became a light pale orangish color after all of the n-butyl lithium was added. The mixture was allowed to warm slowly to room temperature over an hour period. The solution then stirred at room temperature for another hour. The solution became a deeper orange color. The mixture was cooled to -78 °C again followed by the addition of benzaldehyde (0.25 mL, 2.54 mmol, 1.0 eq.) was added dropwise. The red color faded slightly to a lighter orange color but did not disappear after the addition of benzaldehyde. The mixture was allowed to warm from -78 °C to about 0 °C, then the bath was entirely removed, and the mixture allowed to stir overnight. The solution was quenched using 1 mL of water. The DME was removed via rotary evaporation. The product was then extracted 3 times with 15 mL portions of hexanes. The combined organic extracts were filtered through Celite to give a yellow-orange filtrate. The product was purified using radial chromatography (100% hexanes) to give 0.3016 g (82 % yield), and analysed by GC-MS (program 35 °C hold 4 min then 20 °C /min to 240 °C hold 2 min). The spectrum showed four additional peaks with the correct mass. This probably corresponds to the E and Z isomers for the conjugated (1,3-diene) product. The proton NMR had an E/Z ratio of 20:80.
\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 3.10\) (ddq, 2 H, \(J = 7.6, 5.9, 1.7\) Hz), \(5.09\) (dq, 1 H, \(J = 10.2, 1.6\) Hz), \(5.16\) (dq, 1 H, \(J = 17.2, 1.7\) Hz), \(5.74\) (dt, 1 H, \(J = 11.6, 7.7\) Hz), \(5.94\) (ddt, 1 H, \(J = 17.0, 10.2, 6.0\) Hz), \(6.56\) (br d, 1 H, \(J = 11.5\) Hz), 7.21 -7.40 (m, 5 H).

GC-MS: RT: 10.21 min, MI 144, base of 128; RT 10.41 min, MI 144, base of 128; RT: 10.67 min, MI 144, base of 128; RT: 10.81 min, MI 144, base of 128.

\((Z)\)-penta-1,4-dien-1-ylbenzene (31)

Made using NaH

An oven-dried 50 mL recovery flask fitted with a septum was charged with 641 mg NaH (60% in oil). This corresponds to 385 mg of NaH (16.0 mmoles). This was washed three times with pentane, then 6.36 g (16.0 mmoles) of 3-butenyltriphenylphosphonium bromide was quickly added with a stir bar and was septum sealed. Then about 30 mL of dry ether were added by cannula. After stirring for about 70 hours at room temperature, benzaldehyde was added (1.5 mL, 14.8 mmol, 0.92 equiv) and put in the sonicator. The previously quite viscous suspension was now very easily stirred. The flask was removed from the sonicator after about 10 minutes, and put it under nitrogen and stirred. After 24 hours, the supernatant became orange. The reaction was quenched by the addition of 0.5 mL of water. The solution was then allowed to stir for about 10 minutes before being filtered through Celite on a fritted funnel and washed well with hexanes. The yellow filtrate was concentrated and then passed through 28 g of silica gel using hexanes, collecting usual ~ 10 mL test tube fractions. The fractions were analyzed by GC (column 12 m x 0.2 mm HP-5, 100 °C to 190 °C at 15 °C/min, ). The combined fractions had a yield of 1.5 g (70 %) of product. The product was analyzed by proton NMR which showed about 95:5 cis:trans isomer ratio. The
GC-MS (60 °C hold 3 at 15 °C/min to 190 °C hold 4) revealed 3-4 peaks with the correct weight that correspond to the conjugated isomers, with a purity of 78%.

GC-MS: RT: 7.79 min, MI 144, base 128; RT: 8.08 min, MI 144, base 128; RT: 8.35 min, MI 144, base 128; RT: 8.49 min, MI 144, base 128; RT: 8.68 min, MI 144, base 128.

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta\) 3.10 (ddq, 2 H, J = 1.6, 5.9, 7.6 Hz), 5.09 (br dd, 1 H, J = 10.1, 1.2 Hz), 5.15 (br dd, 1 H, J = 17.4, 1.6 Hz), 5.74 (dt, 1 H, J = 11.5, 7.6 Hz), 5.89-5.99 (m, 1 H), 6.55 (br d, 1 H, J = 11.6 Hz), 7.21 -7.39 (m, 5 H).

(E)-6,6-dimethylhepta-1,4-diene (32)

An oven dried 50 mL recovery flask was charged with 3.97 g (10.1 mmol) of the 3-butynyltriphenylphosphonium bromide, a stir bar was added and sealed with a septum. Air was removed using one careful vacuum/N\(_2\) cycle. Then approx. 25 mL of ether were added by cannula, and with stirring the flask was cooled to –78 °C. Once cooled, 5.3 mL of tert-butyl lithium (1.9 M, 10.1 mmol, 1 equiv) was added via syringe. The suspension gradually became an orange-brown. The solution was allowed to warm to -20 °C before being re-cooled to -78 °C. After cooling, pivaldehyde (1.09 mL, 10.7 mmol) was added via syringe. There was no change in color, even as it was allowed to warm gradually (20-30 min) to -20°C, at which point 0.5 mL of saturated ammonium chloride solution was added. Orange brown still persisted for a while, but essentially lost all color at some point as it warmed up. The mixture was filtered through celite and concentrated by rotary evaporation to about 2 or 3 ml. The crude product was analyzed by GC-MS (35 °C hold 4 min then at 10 °C/min to 110°C). The chromatogram showed peaks at 5.69 and 6.15, 60% and 33% of the total, resp. These had the correct masses (124). On the GC using 40 to 90 @ 7 (12m x 0.25 mm, H\(_2\) carrier), peaks at 2.03 (pivaldehyde), 2.42 (77%, E diene), 2.63 (12.5%, Z diene). A little TMA was added to each of the product, and it was purified on ~ 25 g of silica gel in the
"filtration column", collecting what eluted in a series of 100 mL pear flasks. The diene eluted while TMA was still 2-3 cm from the bottom. For the tert-butyl diene, the major isomer (2.42 min) was the E isomer, based on the proton NMR coupling constant of 15.7 Hz. The E:Z ratio was 90:10 by proton NMR. The diene-containing "fractions" were combined to give only about 200 mg (16% yield) of diene. The product was stored in freezer.

GC-MS: RT 5.68 min (87%), MI 124, base of 54, 57 peak; RT: 6.15 min (13%), MI 124, base of 55, 57 peak.

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 0.99 (s, 9H), 2.73 (br td, 2H, $J = 6.4, 0.8$ Hz), 4.95-5.03 (m, 2 H), 5.31 (dt, 1 H, $J = 6.5, 15.7$ Hz), 5.47 (br d, 1 H, 15.7 Hz), 5.83 (ddt, 1 H, $J = 17.2, 10.3, 6.4$ Hz).

(Z)-hexa-2,5-dien-2-ylcyclopropane (33)

An oven dried 50 mL recovery flask was charged with 3.97 g (10.1 mmol) of the 3-butenyltriphenylphosphonium bromide, a stir bas was added and sealed with a septum. Air was removed using one careful vacuum/N$_2$ cycle. Then approx. 25 mL of ether were added by cannula, and with stirring flask was cooled to $-78^\circ$C. Once cooled, 5.3 mL of tert-butyllithium (1.9 M, 10.1 mmol) was added via syringe. The suspension gradually became an orange-brown. The solution was allowed to warm to -20 °C before being re-cooled to -78 °C. After cooling, methyl cyclopropyl ketone (MCK) (1.09 mL, 10.7 mmol, 1.06 equiv) was added via syringe. There was no change in color, even as it was allowed to warm gradually (20-30 min) to -20 C, at which point 0.5 mL of saturated ammonium chloride solution was added. Orange brown still persisted for a while, but essentially lost all color at some point as it warmed up. The mixture was filtered through celite in a disposable plastic funnel and concentrated by rotary evaporation to about 2 or 3 mL. The following day GC-MS was done on the crude product (35 °C hold 4 min then at 10 °C/min to 110°C). The spectrum for the
MCK reaction showed peaks at 3.60 min (ketone, 38% of total), 9.06 min (diene, 31% of total), 9.15 min (diene, 24% of total). A little TMA was added to the product, and it was purified on ~ 25 g of silica gel, collecting what eluted in a series of 100 mL pear flasks. The diene eluted while TMA was still 2-3 cm from the bottom. The peak first isomer (4.66 min) was only a little larger than the second-eluting isomer (4.75 min). The diene-containing fractions were combined to give only about 200 mg (16% yield) of diene. The product was stored in freezer.

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 0.40-0.44\) (m, 2 H), \(0.50-0.55\) (m, 2 H), \(0.56-0.62\) (m, 1 H), \(1.43\) (br q, 3 H, J = 1.2 Hz), \(2.89\) (ddq, 2 H, J = 1.3, 6.7, 7.9 Hz), \(4.94 \text{–} 4.98\) (m, 1 H), \(5.03\) (dq, 1 H, J = 16.9, 1.8 Hz), \(5.21 \text{–} 5.24\) (m, 1 H), \(5.73 \text{–} 5.89\) (m, 1 H).

GC-MS: RT 9.06 min (53%), MI 123, base of 79, 41 peak; RT: 9.15 min (47%), MI 123, base of 79, 41 peak.

penta-1,4-diene-1,1-diyldicyclopropane (34)

An oven-dried 50 ml flask was charged with a stir bar and 3.709 g of 3-butenyltriphenylphosphonium bromide (9.336 mmol) and 12 ml of dry DME. The flask was cooled to -78°C via dry ice and acetone and then butyllithium (4.1 ml of 2.28 M, 9.3 mol, 1 equiv) was dripped in slowly. The solution was then allowed to warm to room temperature over about 1 hr. The solution became greenish black. The solution was then cooled again to -78°C via dry ice and acetone and dicyclopropyl ketone (DCK, 1.1 mL, 9.3 mol) was added dropwise and then allowed to warm overnight. The following day, the now-black solution was quenched with 3 ml of DI water before removing the DME via rotary evaporation. The resulting liquid was extracted three times with 5 ml portions of hexanes. The product was concentrated and purified using a column with TMA to mark the elution and eluting with 100% hexanes. When the TMA began to come off, the collection was stopped. This eluate
was then concentrated to 238.9 mg (13 % yield) and an inhibitor was added before storing in the refrigerator. The product was analyzed by proton NMR.

$^1$H NMR (CDCl$_3$, 400 MHz): δ 0.30-0.34 (m, 2 H), 0.48-0.53 (m, 2 H), 0.61-0.66 (m, 2 H), 0.70-0.77 (m, 2 H), 0.93-0.96 (m, 2 H, 6.7 Hz), 2.90 (br t, 2 H, J = 6.8 Hz), 4.95 (br dq, 1 H, J = 1.6, 10.1 Hz), 5.01 (dq, 1 H, J = 1.7, 17.1 Hz), 5.13 (br t, 1 H, J = 7.3 Hz), 5.83 (ddt, 1 H, J = 6.2, 10.1, 17.0 Hz)

Synthesizing chiral diols

An oven-dried 25 ml recovery flask was tared and fitted with a stir bar and septum outside of the glove box, then inside a glove box was charged with about 1.64 mmol of chloroborane 7. The flask was re-weighed outside of the box to get an accurate mass of the borane, which was about 374 mg. The flask was placed under inert atmosphere and dissolved in about 1.64 ml of dry ether followed by an equimolar amount of diene (1.6 mmol) via syringe to the stirring solution. The solution is allowed to stir for 2 hrs. Then an additional 1.4 ml ether is added before the addition of 1 equiv super hydride (1.64 ml, 1 M in THF) to give a final borane concentration of 0.35 M. The solution is then allowed to stir overnight. The following day, the product is oxidized using the usual method 2.5 equiv 3 M KOH (4.0 mmol), 1 ml of EtOH, followed by 1 mL H$_2$O$_2$ (10 mmol, 6 equiv) added rapidly dropwise while in a water bath. The solution is allowed to stir at room temp for about 5 minutes. The solution then undergoes a water work up and concentration. The product is purified using radial chromatography. The product is collected and concentrated. The product is confirmed by proton NMR.

1-(4-(tert-butyl)cyclohexyl)butane-1,4-diol (27b)

Yield: 57%
\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 0.82\) (s, 9 H), \(0.89\) (s, 1 H), \(0.94\)-1.07 (m, 5 H), \(1.20\) (s, 1 H), \(1.41\)-1.51 (m, 1 H), \(1.61\)-1.73 (m, 5 H), \(1.75\)-1.84 (m, 3 H), \(3.35\)-3.39 (m, 1 H), \(3.61\)-3.71 (m, 2 H).

5,9-dimethyldec-8-ene-1,4-diol (28b)
Yield: 80%

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 0.86\) (dd, 3 H, \(J = 3.5, 6.8\) Hz), \(1.09\)-1.19 (m, 1 H), \(1.35\)-1.45 (m, 4 H), \(1.57\) (d, 3 H, \(J = 0.7\)), \(1.64\) (d, 3 H, \(J = 1.2\) Hz), \(1.65\)-1.68 (m, 2 H), \(2.01\) (s, 1 H), \(2.78\) (br s, 1 H), \(2.95\) (s, 3 H), \(2.43\)-2.52 (m, 1 H), \(3.59\) (br dd, 1 H, \(J = 6.1, 10.8\) Hz), \(3.67\) (br dd, 1 H, \(J = 5.6, 10.72\)), \(5.06\) (tdq, 1 H, \(J = 7.20, 1.3\) Hz).

\(^13\)C NMR (CDCl\(_3\), 100.1 MHz): \(\delta 13.9, 17.7, 25.7, 29.8, 31.4, 33.2, 38.2, 42.7, 63.0, 75.5, 124.6, 131.5\).

5-phenylhexane-1,4-diol (29b)
Yield: 53%

\(^1\)H NMR (CDCl\(_3\), 400 MHz): \(\delta 1.27\) (q, 3 H, \(J = 7.0\) Hz), \(1.36\)-1.53 (m, 1 H), \(1.53\)-1.88 (m, 3 H), \(2.27\) (br s, 2 H), \(2.78\) (dq, 1 H, \(J = 15.1, 7.2\) Hz), \(3.57\)-3.73 (m, 3 H), \(7.20\)-7.35 (m, 5 H).

1-cycloheptylbutane-1,4-diol (30b)
Yield: 43%

83
$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.20-131 (m, 2 H), 1.34-1.46 (m, 4 H), 1.47-1.59 (m, 5 H), 1.60-1.74 (m, 6 H), 3.35 (br s, 2 H), 3.43 (dd, 1 H, $J = 2.63, 4.66, 9.31$ Hz), 3.57 (dt, 1 H, $J = 6.24, 10.6$ Hz), 3.66 (dt, 1 H, $J = 5.56, 10.6$ Hz).

5-phenylpentane-1,4-diol (31b)
Yield: 68%

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 1.48-1.63 (m, 3 H), 1.67-1.76 (m, 3 H), 2.74-2.83 (m, 2 H), 2.47 (br s, 2 H), 3.83-3.89 (m, 2 H), 4.66 (dd, 1 H, $J = 5.32, 7.66$), 7.16-7.30 (m, 5 H).

6,6-dimethylheptane-1,4-diol (32b)
Yield: 86%

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 0.95 (s, 9 H), 1.36 (br d, 2 H, 3.5 Hz), 1.44-1.61 (m, 2 H), 1.67 (p, 2 H, $J = 6.40$), 2.61 (s, 2 H), 3.60-3.70 (m, 2 H), 3.75-3.88 (m, 1 H).

$^{13}$C NMR (CDCl$_3$, 100.1 MHz): $\delta$ 29.0, 30.20, 30.34, 36.6, 51.4, 63.0, 69.6.

5-cyclopropylhexane-1,4-diol (33b)
Yield: 23%

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 0.05-0.06 (m, 3 H), 0.09-0.14 (m, 2 H), 0.16-0.22 (m, 1 H), 0.37-0.44 (m, 1 H), 0.45-0.88 (m, 3 H), 0.92 (br d, 3 H, 2.0 Hz), 3.31 (br s, 2 H), 3.50-3.60 (m, 2 H), 3.62-3.68 (m, 1 H).

$^{13}$C NMR (CDCl$_3$, 100.1 MHz): $\delta$ 3.2, 4.6, 6.0, 14.4, 29.4, 31.8, 42.7, 62.9, 76.1.

5,5-dicyclopropylpentane-1,4-diol (34b)
Yield: 45%
Synthesizing racemic diols

An oven-dried 25 mL recovery flask fitted with stir bar was placed under nitrogen. Then 3 mL of dry DME were added by syringe. Then about 1.5 mmol of the diene followed by 2 equiv of borane methyl sulfide (10 M) were added to the flask. A little bubbling was observed, and some warming was noticed. The reaction was allowed to stir overnight and oxidized the following day using the normal procedure: 2.5 equiv of 3 M KOH (4.0 mmol), then 1 mL of EtOH, followed by 1 mL of H2O2 (10 mmol, 6 equiv) were added rapidly dropwise while in a water bath. The reaction was then allowed to stir for about 10 minutes before transferring to a separatory funnel using 15 mL of saturated NaCl solution and 15 mL of ethyl acetate. The solution was extracted three times with ~ 15 mL portions of EtOAc. The organic layers were combined, dried with MgSO4, filtered and concentrated. The diols were purified using radial chromatography: 4 mm plate, loaded in 50% EtOAc, used a little disperse blue (it moves faster than the diols); eluted with 50% ethyl acetate in hexanes, then 70% then 85% then 100% EtOAc. The diols were then analyzed by proton NMR and they matched the NMRs for the chiral diols. The GC-MS was also matched that of the chiral diols.

Yield: 46 %

1H NMR (CDCl3, 400 MHz): δ 0.13-0.24 (m, 5 H), 0.40-0.54 (m, 4 H), 0.64-0.76 (m, 2 H), 1.59-1.68 (m, 1 H), 1.70-1.79 (m, 2 H), 1.80-1.88 (m, 1 H), 2.32 (s, 2 H), 3.64-3.75 (m, 3 H),

13C NMR (CDCl3, 100.1 MHz): δ 2.3, 2.9, 3.2, 3.7, 10.5, 13.5, 29.4, 32.3, 43.6, 52.8, 63.3.
For the sulcatone racemic diol, 1 equivalent of chloroborane was used in place of borane in order to limit hydroboration of the distal equally-substituted diene.

Yield: 18%

5-phenylhexane-1,4-diol (29c)
Yield: 72%

1-cycloheptylbutane-1,4-diol (30c)
Yield: 65%

5-phenylpentane-1,4-diol (31c)
Yield: 86%

5,9-dimethyl-deca-9-ene-1,4-diol (32c)
Yield: 43%

5-cyclopropylhexane-1,4-diol (33c)
Yield: 47%

5,5-dicyclopentane-1,4-diol (34C)
Yield: 88%

Synthesizing lactone derivatives (27D-34D)

The procedure for preparing γ-lactones was derived from the literature. A 2-mL GC vial was charged with about 8 to 15 mg of the diol, TEMPO (2-3 mg, 0.0141 mmol, 0.2 equiv), and PhI(OAc)₂ (50-60 mg, 0.130 mmol, 2.1 equiv). A flea stir bar and 0.5 mL of dry DCM were added, and the vial was capped and allowed to stir overnight. The reaction was checked by TLC for the absence of diol and hemi-ketal (formed by oxidation of the 2° alcohol). The reaction mixture was passed through a 3-cm column of silica in a pipette and then rinsed with two 1 ml portions of DCM. The sample was analyzed by GC-MS using a 20
m x 0.15 m Restek Rtx-5sil-ms column and the following temperature program: 100 °C, hold 3 min then at 20/min to 260, hold 1. A base peak of 85 is diagnostic for a γ-lactone ring. The products were then analyzed on various chiral GC columns, with little success. For the Restek Rt-β-DEXsa column, the program 160 °C to 220 °C at 5 °C/min was used. For the Cyclosil-B column, the program 180 °C to 220 °C at 2 °C/min was used.

5-(4-(tert-butyl)cyclohexyl)dihydrofuran-2(3H)-one (27D)

GC-MS: two peaks of about equal size: earlier-eluting: 10.71 min: M+ 224, 85 (base) and 57; later-eluting: 10.86 min: M+ not evident, 156, 85 (base), 57. These peaks correspond to the diastereomers (axial and equatorial at the cyclohexane ring).

Restek Rt-β-DEXsa: RT: 20.85 min (peak width 0.160 min), RT: 22.45 min (peak width 0.171 min). Only the diastereomers were separated.

Cyclosil-B: RT: 14.84 min (peak width 0.083 min), RT: 16.13 min (peak width 0.116 min). Only the diastereomers were separated.

5-(6-methylhept-5-en-2-yl)dihydrofuran-2(3H)-one (28D)

GC-MS: RT 9.11 min., 125 peak, base of 41, peak for 85; RT 8.89 min, base of 85.

Restek Rt-β-DEXsa: possible separation of enantiomers. The peaks had same areas. RT: 12.31 min (peak width 0.078 min), RT: 13.02 min (peak width 0.075 min). RT: 13.15 min (peak width 0.089 min). The last peak could possibly be the other diastereomer (30:70 ratio).

Cyclosil-B: RT: 8.13 min (peak width 0.077 min). Neither enantiomers or diastereomers were separated.
5-(1-phenylethyl)dihydrofuran-2(3H)-one (29D)

GC-MS: RT: 9.44 min MI not present, 190, base of 85, 57, 105 peak.

Cyclosil-B: RT: 10.13 min (peak width 0.098 min), RT: 10.31 min (peak width 0.080 min). Only the diastereomers were separated.

5-cycloheptyldihydrofuran-2(3H)-one (30D)

GC-MS program was (80 °C hold 3 min then 3 °C/min to 220 hold 4) was used for this lactone.

GC-MS: RT: 10.64 Mi 153, base of 85, peak for 97

Restek Rt-β-DEXsa: RT: 15.39 min. (peak width 0.135 min). The enantiomers were not separated.

Cyclosil-B: RT: 10.34 min (peak width 0.116 min). The enantiomers were not separated.

5-(dicyclopropylmethyl)dihydrofuran-2(3H)-one (34D)

GC-MS: RT 8.77 min., MI 95, base of 95

Restek Rt-β-DEXsa: RT: 12.44 min. (peak width 0.091 min). The enantiomers were not separated.

Cyclosil-B: RT: 7.63 min. (peak width 0.057 min) and RT: 7.71 min. (peak width 0.056 min). The enantiomers were separated.
Synthesizing dimethyl ethers

A septum-capped 1-dram vial was fitted with a flea stir bar and charged with about 10 mg of a 1,4-diol (0.050 to 0.063 mmol), 0.5 mL of dry DMF, and NaH (~10 mg, 0.42 mmol, 7-8 equiv). Finally, via syringe 21 µL (0.22 mmol, 3.5 to 4.4 equiv.) of dimethyl sulfate was added to the solution. The solution was stirred for 30 minutes, before a drop of water was cautiously added (foams up). Then 0.5 mL of hexanes were added to the solution and allowed to stir for a few minutes. The capped vial was shaken. The phases were allowed to separate before extracting twice with hexanes. The organic phases were dried via a pipette column filled with sodium sulphate. The column was rinsed with another 0.5 mL portion of hexanes. The clear solution was analysed by GC-MS, (80°, hold 3 then 20°/min to 260°) to determine purity and the presence of product. The sample was then analysed by a CycloSil-B chiral column on the GC using the program 160, ramp at 4°C/min to 220 °C hold 5 min.

(1,4-dimethoxybutyl)cycloheptane (30e)
GC-MS: did not give masses consistent with the dimethyl ether

Synthesizing Tetrahydrofuran Derivatives

All the THF derivatives were made using the following method. A septum-capped 1-dram vial fitted with a flea stir bar was charged with about 10 mg of a 1,4-diol (0.050 to 0.063 mmol), 0.5 mL of dry DMF, and a spec of dibutyltin oxide. Then added 1 equivalent of triethylamine and 1 equivalent tosyl chloride (1 M). The solution was stirred for 30 minutes, before adding ~ 10 mg of NaH. It was then stirred for another 30 minutes. The initially clear solution became yellow. Then cautiously add a drop of water (will foam up), followed by 0.5 mL of hexanes. The mixture was stirred a few minutes more. Then the capped vial was shaken before letting the phases separate. The aq phase was yellow and the organic was clear. The organic layer was removed via a pipette and dried though a pipette drying column.
containing sodium sulphate. The extraction was repeated with another 0.5 mL of hexanes and
the column was rinsed with another 0.5 mL of hexanes. The clear solution was analysed by
GC-MS, (80°, hold 3 then 20°/min to 260°C) to determine purity and presence of product.
The presence of a 71 peak is diagnostic of the presence of a THF being present. The sample
was then analyzed by a CycloSil-B chiral column on the GC.

non-racemic 2-(4-(tert-butyl)cyclohexyl)tetrahydrofuran (27F)

GC-MS RT: 9.6 min. small peak 138, base: 71, peak for 57, RT: 9.8 min large peak 210,
base:71, peak for 57, RT: 11.29 min. small peak: 101, base: 71, peak at 57, and RT: 10.36
min. large peak: M+ not present, 199, base 91

Chiral GC: 9.36 min, (area 1496), (width 0.083); RT: 9.60 min, (area 1599), (width 0.073);
RT: 10.21 min, (area 4998), (width 0.121). RT: 10.47 min, (area 6070), (width 0.084).
Possible enantiomer separation. Chiral GC program was 200°C, ramp at 2°C/min to 220 °C
hold 2.

racemic 2-(4-(tert-butyl)cyclohexyl)tetrahydrofuran (27G)

GC-MS RT: 9.6 min. small MI:138, base: 71, peak for 57, RT: 9.8 min large peak MI:210,
base: 71, peak for 57, RT: 11.29 min. small MI:101, base: 71, peak for 57, and RT: 10.36
min. large peak M+ not present, 199, base 91

Chiral GC: RT: 9.32 min, (area 8926), (width 0.099); RT: 9.55 min, (area ), (width 0.028);
RT: 10.16 min, (area 7410), (width 0.118). Possible enantiomer separation. Chiral GC
program was 200°C, ramp at 2°C/min to 220 °C hold 2.

Non-racemic 2-(6-methylhept-5-en-2-yl)tetrahydrofuran (28F)

GC-MS: RT 8.4 min. M+ not present, 110 (sulcatone with loss of THF), peak 71, base 41,
RT 8.5 min. M+ not present, 114, peak 71, base 41.
Chiral GC: RT: 5.59 min, (area 5811), (width 0.055); RT: 5.65 min, (area 5049), (width 0.060). Some diastereomer separation possible. Chiral GC program was 200°C, ramp at 2°C/min to 220 °C hold 2.

racemic 2-(6-methylhept-5-en-2-yl)tetrahydrofuran (28G)
GC-MS: RT 7.0 min. MI 111 (sulcatone with loss of THF), peak 71, base 41, RT 8.5 min. M⁺ not present, 114, peak 71, base 41

Chiral GC: RT: 6.56 min, (area 2234). No separation. Chiral GC program was 200°C, ramp at 2°C/min to 220 °C hold 2.

Non-racemic 2-(1-phenylethyl)tetrahydrofuran (29F)
There are two peaks for the E and Z isomer and 3 small non-product peaks.

GC-MS: RT:8.4 largest peak M⁺ not present, 116, base of 71 RT: 8.5 large peak M⁺ not present, 114, base of 71, RT:9.74 small peak M⁺ not present, 118, base: 71 peak for 105 RT: 9.78 small peak M⁺ not present, 118, base 71 peak for 105 RT: 10.37 large peak M⁺ not present, 92, base 91

Chiral GC: RT: 6.56 min, (area 1263), (width 0.049 min). No separation. Chiral GC program was 200°C, ramp at 2°C/min to 220 °C hold 2.

racemic 2-(1-phenylethyl)tetrahydrofuran (29G)
There are two peaks for the E and Z isomer and three small non-product peaks.

GC-MS: RT:8.4 largest peak M⁺ not present, 116, base of 71 RT: 8.5 large peak M⁺ not present, 114, base of 71, RT:9.74 small peak M⁺ not present, 118, base: 71 peak for 105 RT:
9.78 small peak M+ not present, 118, base 71 peak for 105 RT: 10.37 min large peak M+ not present, 92, base 91

Chiral GC: RT: 4.86 min, (area 4139), (width 0.052). 4.94 min, (area 5143), (width 0.050). Possible enantiomer separation. Chiral GC program was 190°C, ramp at 1°C/min to 205 °C hold 2

Non-racemic 2-cycloheptyltetrahydrofuran (30F)
GC-MS: RT 8.32 min largest peak M+ not present, 97, base: 71 RT: 9.78 min MI: 127, base: 71, peak for 97 RT: 10.37 min. large peak M+ not present, 199, base 91

Chiral GC: RT: RT: 6.54 min, (area 5981), (width 0.36); RT: 6.68 min, (area 11798), (width 0.077); RT: 6.90 min, (area 7808), (width 0.081). Possible enantiomer separation. Chiral GC program was 200°C, ramp at 2°C/min to 220 °C

Racemic 2-cycloheptyltetrahydrofuran (30G)
GC-MS: RT 8.31 largest peak M+ not present, 81, base 71 peak RT: 10.36 large peak M+ not present, base 91

Chiral GC: RT: RT: 6.540 min, (area 1892), (width 0.47); RT: 6.68 min, (area 4034), (width 0.047); RT: 6.90 min, (area 2520), (width 0.064). Possible enantiomer separation. Chiral GC program was 200°C, ramp at 2°C/min to 220 °C

Non-racemic 2-neopentyltetrahydrofuran (32F)
There are two peaks for the E and z isomer as well as several other peaks that contain 71 peaks
GC-MS: RT 6.92 min. large peak M+ not present, 116, base 57, 71 Rt 6.96 M+ not present, 109, base 57, peak 71 several other small peaks that some contain 71 peaks

Chiral GC: RT: 10.03 min, (area 3224), (width 0.148). No separation. Chiral GC program was 200°C, ramp at 2°C/min to 220 °C
The epoxides were all made using the same method of methyltrioxorhenium (MTO)/H₂O₂. A 4 dram vial was charged with MTO (.7 to .9 mol%), 1 equiv alkene, and 0.12 equiv pyridine. Just enough DCM was added to make a 2 M solution of alkene. Lastly 1.4 equiv of 30% H₂O₂ was added to the solution. The reaction was stirred rapidly at room temp, giving a distinct yellow color. The norbornene and cyclooctene reactions became warm. After about 2 hrs, a few drops of the lower (DCM) phase was passed through a few cm of anhydrous Na₂SO₄ in a filter pipette into a GC vial. The product was then analyzed by TLC in 5% EtOAc/hexanes. When the reaction reached completion, the product was worked up by passing the DCM phase through anhydrous Na₂SO₄ in filter pipettes. The resulting solution was concentrated via rotary evaporation.
The method used to react with our chiral chloroborane was taken from Brown’s paper. The chiral chloroborane in DCM was cooled to -78°C and treated with 1 equiv of epoxide, allowed to slowly warm to room temperature overnight, then quenched with water. The solution was worked up by adding solid sodium chloride and extracted 3 times with ethyl acetate. Blue dye is often used to help see the barrier of the organic and water layer. It was noted that the blue dye turned green. It was ultimately determined that the water layer had a pH of 1. The organic layer was combined, dried, and concentrated using rotary evaporation. The product was purified using radial chromatography. It was loaded with 20% ethyl acetate in hexanes. The product was then found by TLC, combined, and concentrated. The product was analysed by GC-MS. The ee’s were to be determined using a Chiral Restek GC column. It was determined from GC-MS data, program 40°C hold 3 min then 15°C/min to 220°C, that the chlorohydrin was successfully synthesized except for cis-stilbene. The chiral GC using H₂ gas carrier and a program of 100°C at 10°C/min to 200°C.

(1R,2R)-2-chlorocyclohexan-1-ol (35A)

The yield was 0.1356 g (59 %)
The mass spec library had a 91% match to the chlorohydrin product.

GC-MS: RT 8.3 min, MI: 134 and M+2 of 136 with a ratio of 3:1, and base of 57.

Chiral GC: RT 7.7 min, 26807 area, RT 7.8 min, 38752 area, 18 % ee

(1R,2R)-2-chlorocyclooctan-1-ol (36A)

The yield was 0.0633 g (44.5 %).
GC-MS: RT 11.3 min, M⁺ not present, 144 and 146 in a 1:3 ratio consistent with a loss of water from the chlorohydrin. A base of 57.

Chiral GC: RT 9.7 min, 65356 area, RT 9.8 min, 67975 area, 2 % ee

(2R,3R)-3-chlorobicyclo[2.2.1]heptan-2-ol
The yield was 0.1108 g (85.99 %)

GC-MS: RT 10.0 min, M⁺ not present, 111 consistent with a loss of Cl, and base of 79.

Chiral GC: RT 10.1 min, 26366 area, RT 10.2 min, 27734 area, 2.5% ee

reduction of ketones and aldehyde (39a-43a)

The ketones were all reacted using the same method. An oven-dried flask was charged with the chiral chloroborane (0.55 mmol) and filled with argon. The CCB was dissolved in 1.8 ml of DME to make a 0.3 M solution. The temperature was then lowered to -78°C and equimolar amount of the ketone or aldehyde was slowly added to the cold, stirring solution. After an hour, the solution was oxidized using the same method as previously discussed (excess ethanol (1 ml), 2.5 equiv of 3 M KOH solution, and excess 30% H₂O₂ (1 ml)). Solid sodium chloride was added to the solution and it was extracted 3 times with DCM. The organic layers were combined and concentrated. The solution was analyzed by TLC in 20% ethyl acetate in hexanes. The products were purified via a radial chromatography. The product was purified on the RC by loading at 20% ethyl acetate in hexanes. The gradient was made using 100 ml each of 20%, 30%, 50%, and 100% ethyl acetate in hexanes. The product was analyzed by GC-MS using the program 40°C hold for 3 min. then 15°C to 240°C. The ee’s were determined using a chiral Restek GC column and H₂ carrier gas.
3,5,5-trimethylcyclohex-2-en-1-ol (39A)
The GC-MS for the isophorone reaction showed an 89% match to the expected reduction product. The chiral GC was ran using the program 100°C at 10°C/min to 200°C.
The yield was 18.5 mg, (24.3 %)
GC-MS: RT 9.3 min, MI: 140 and base of 125.

1-phenylethan-1-ol (40A or 40B)
Acetophenone was reacted with both the CCB and with borane. Both GC-MS spectra showed a product match of 95% for corresponding alcohol for both reactions. The Chiral GC showed a broad peak that did not separate. The chiral GC was ran using the program 140°C at 2°C/min to 170°C.
Non-racemic alcohol:
The yield was 45 mg, (67 %)
ee was 8 %
GC-MS: RT 8.9 min, a MI of 122 and a base peak of 79.
Chiral GC: RT: 5.51 min (area 5656) (width 0.060), RT: 6.50 min (area 137502) (width 0.111).
racemic alcohol
GC-MS: RT 8.9 min, a MI of 122 and a base peak of 79.

2,2,2-trifluoro-1-phenylethan-1-ol (41)
The yield was 10 mg, (6.1 %)
ee was 13 %
GC-MS: RT 8.6 min MI: 176, base of 79, and a large mass peak of 107 loss of CF₃.

Chiral GC: RT: 12.424 in (area 5544) (width 0.118), 14.86 min (area 20373) (width 0.231).
The chiral GC was ran using the program 120°C at 2°C/min to 240°C.

6-methylhept-5-en-2-ol (42)
The sulcatone reaction GC-MS spectra had a peak with an 81% match to the reduction product with a MI of 128, a base peak of 41, and a large 95 mass peak. The chiral GC was ran using the program 120°C at 2°C/min to 240°C.
The yield was 12.2 mg, (20.4 %)

GC-MS: RT 7.8 min, MI: 128 and base of 41

Chiral GC: RT: 5.20 min (area 2177) (width 0.65), 5.65 min (area 42698) (width 0.72)

4,4-dimethylhept-6-yn-2-ol (43)
Yield 6.2 mg (4.6 %)

GC-MS: RT 8.9 min, MI: 140 and base of 125

Chiral GC: RT 6.21 min (area 3857) (width 0.09), 6.759 min (area 5469) (width 0.1). The chiral GC was ran using the program 120°C at 2°C/min to 240°C.
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APPENDIX 1: [TITLE]

1. Nopyl methyl ether proton (8) NMR

2. Chiral chloroborane (6) proton NMR