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RHODIUM-CATALYZED HYDROBORATION OF 1,1-DISUBSTITUTED ALKENES

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RHODIUM-CATALYZED HYDROBORATION OF 1,1-DISUBSTITUTED ALKENES

by

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Rhodium-Catalyzed Hydroboration of 1,1-Disubstituted Alkenes

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Enantioselective rhodium-catalyzed hydroboration is becoming an increasingly important asymmetric transformation of alkenes based upon the utility of the organo boranate ester intermediate. The newly acquired asymmetric C-B bond can be converted to C-O, C-N, C-C bonds and the organo borante can be coupled to SP2 hybridized halogen bonds, all with retention of configuration. Catalyzed hydroboration of 1,1-disubstituted alkenes are an especially challenging substrate class for this enantioselective transformation. The difficulty for catalysts to distinguish between the two enantiotopic faces of the olefin is one of the major issues that have to be overcome to achieve a desirable level of enantioselectivity. Rhodium catalyzed hydroboration of the 1,1-disubstituted alkenes gives the expected *anti*-Markovnikov's regio-chemistry products in high yields. Herein is reported our groups progress in the rhodium catalyzed hydroboration of the 1,1-disubstituted allyl sulfonamide substrate class utilizing monodenate ligands with our best results to date being with sulfonamide **25** and $Rh(nbd)_2BF_4$, **L6f** and pinacol borane (99% yield, 67.7% ee).

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i. Acknowledgements

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ii: Index of Schemes

iii. Index of Tables

iv: List of Abbreviations

9-BBN	9-Borabicyclo(3.3.1)nonane
BINAP	2,2'-*Bis*(diphenylphosphino)-1,1'-binaphthyl
Bn	Benzyl
Bu	Butyl
ca.	Circa
Calcd.	Calculated
CatBD	Deutero Catecholborane
CatBH	Catecholborane
COD	Cyclooctadiene
Cy	Cyclohexyl
DCE	Dichloroethane
DCM	Dichloromethane
de	Diastereomeric excess
DMAP	4-Dimethylaminopyridine
DMF	N,N-Dimethylformamide
DMS	Dimethyl sulfide

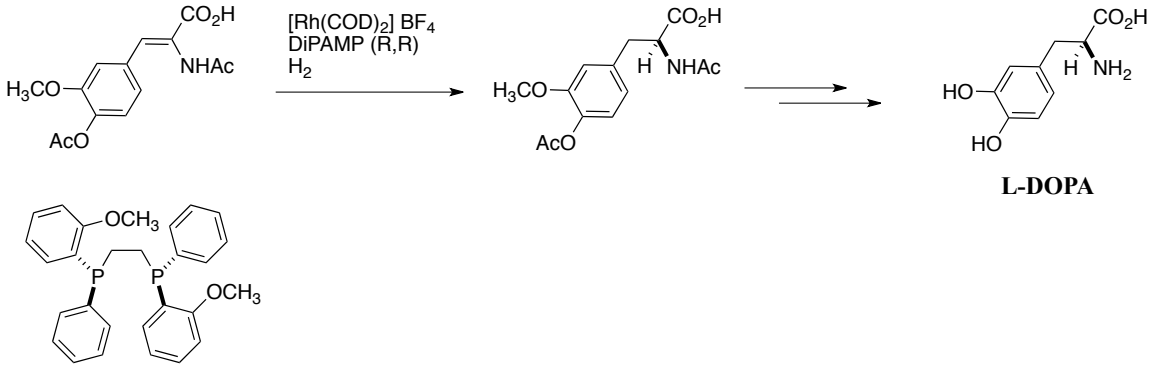
DPPB	Butane-1,4-diylbis(diphenylphosphane)
ee	Enantiomeric excess
Et	Ethyl
EtOH	Ethanol
Eq.	Equivalents
FAB	tris(pentafluorophenyl)boron
GC	Gas Chromatography
HPLC	High Pressure Liquid Chromatography
Hz	Hertz
LDA	Lithium diisopropylamide
M	Molarity
Me	Methyl
MeOH	Methanol
Min	Minute
nbd	Norbornadienyl
NMR	Nuclear Magnetic Resonace
PinBH	Pinacolborane

Pr	Propyl
Py	Pyridine
Rac	Racemic
r.t.	Room temperature
S.M.	Starting Material
TBDMS	Tertbutyldimethyl silyl
TBDPS	Tertbutyldiphenyl silyl
TES	Triethyl silyl
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
TMDB	4,4,6-Trimethyl-1,3,2-dioxyborinane
TMS	Trimethylsilyl
UV	Ultraviolet

Chapter 1: Introduction

1.1 Establishment of Enantioselective Catalysis

Pharmaceutical companies spend billions of dollars each year in the development of possible new drug candidates. According to FDA regulation, they are required to test each potential enantiomer individually for pharmacologic activity, the pharmacokinetic profile, and toxicology.[1] The ability to make enantiomerically pure compounds from prochiral starting material is an extremely attractive path to achieving this goal, because both enantiomers should theoretically be able to be synthesized from common starting material. Enantioselective catalysis is an increasing important approach to this goal, and a vast amount of research is being done in both industrial and academic laboratories. One of most influential industrially breakthroughs came in the 1960's when the enantioselective rhodium-catalyzed hydrogenation of alkenes was used in the Monsanto process in the development for the commercial preparation of L-DOPA. This research effort culminated in a process for highly enantioselective production of the amino acid of up to 97% ee (**Scheme 1.1**).[2,3]



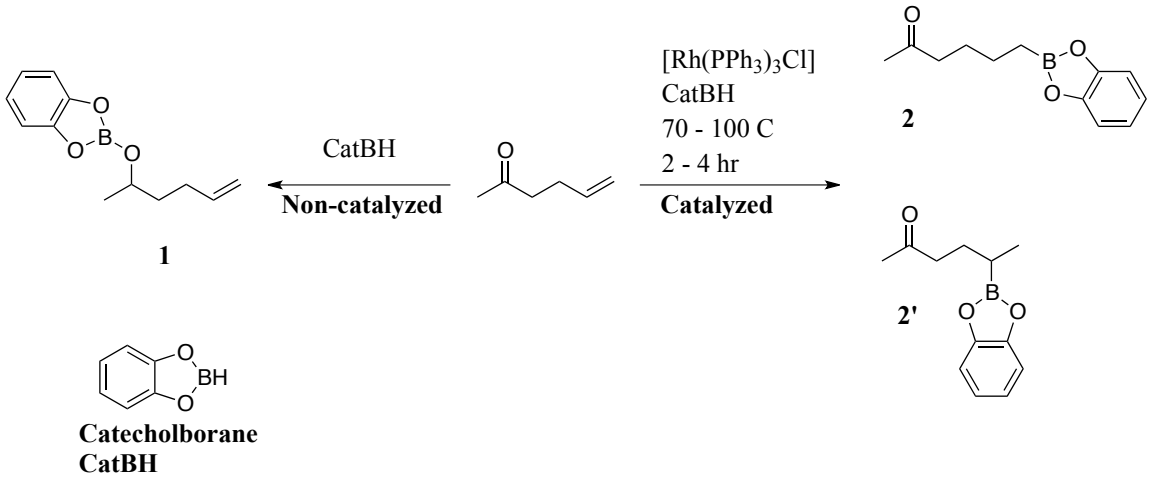
Scheme 1.1: Rhodium catalyzed hydrogenation in the Mansanto process of L-DOPA[2,3]

Until the development of the rhodium catalyzed asymmetric hydrogenation used in the synthesis of L-DOPA, transition metal catalyzed enantioselective reactions did not garner much attention.Few examples of enantioselective catalytic reactions had been achieved which did not invoke the use of an enzymatic process.[4] Academically, the extent of enantioselective catalytic transformations has gathered an immense amount of attention since the development of rhodium catalyzed asymmetric hydrogenation. A large number of asymmetric transformations have been developed, many of which have become standard practice in organic synthesis including: dihydroxylation,[5] epoxidation,[6,7] Aldol condensations,[8,9,10] and cycloadditions,[11,12,13] to name just a few. A number of asymmetric transformations have been developed with organic catalysts, *e.g.,* iminium catalysis, enamine catalysis and counterion catalysis,[14] while among the transition metal catalysts developed, rhodium,[15] palladium[16] and copper[17] play particularly important roles. Enantioselective transition metal catalysis has received much attention the past few decades for many different reasons. In the better cases, reactions proceed with low catalyst loading, high selectivity and a versatile reaction scope with a single metal precursor; some of these features are present in rhodium-catalyzed hydrogentations,[2,3] carbonylations[18] and hydroborations (*vide infra*).

1.2 Development of Enantioselective Catalyzed Hydroboration

In 1985 Männing and Nöth reported the first rhodium catalyzed hydroboration of various unsaturated substrates ranging from cyclic alkenes, to terminal alkenes and alkynes.[19] The catalyzed hydroboration of terminal alkenes with catecholborane (CatBH)

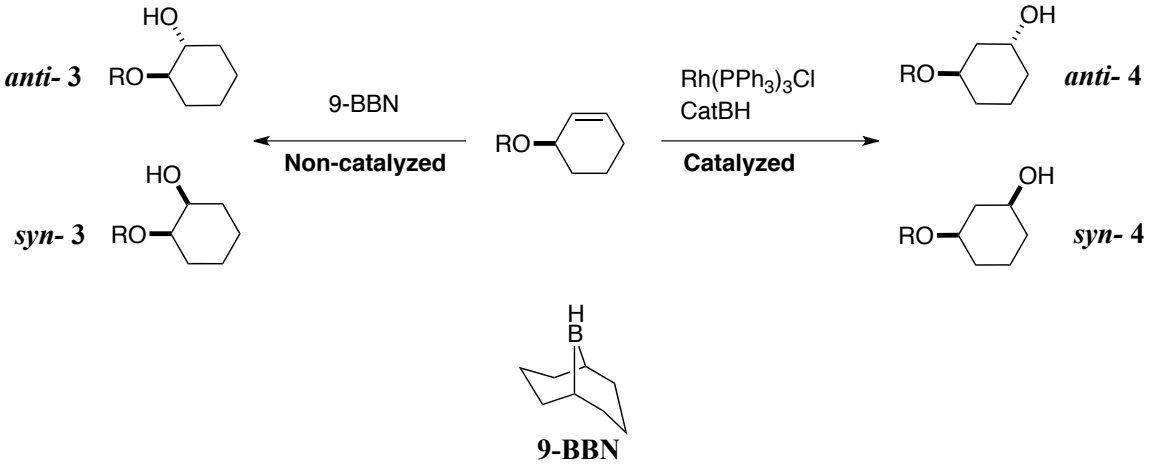
gives the *anti*-Markovnikov regioselectivity as does the non-catalyzed reaction with BH_3-THF. However the catalyzed reaction shows increased functional group tolerance (**Scheme 1.2**).[15] Since the use of Wilkinson's catalyst ([$Rh(PPh_3)_3Cl$]) and CatBH gives the same *anti*-Markovnikov product as the non-catalyzed reaction with BH_3-THF with terminal alkenes, the exploration of internal alkenes was a logical next step in the development of this transformation.



Scheme 1.2: First reported catalyzed hydroboration of alkenes; **Non-catalyzed** reaction gives quantitative reduction of carbonyl group; the **Catalyzed** reaction gives an 83:17 (**2**:**2'**) ratio of hydroboration product to reduction (53.8% yield).

In 1988 Evans *et. al.* discovered that a carbonyl directing group within the substrate could be used to control the regioselectivity of the catalyzed hydroboration.[20] They also demonstrated on a variety of functionalized alkene derivatives, including allylic alcohols, alkyl ethers and silyl ethers appended to acyclic or cyclic alkenes, a reversal in the regioselectivity between the non-catalyzed (proximal product, **3**) and catalyzed (distal product, **4**) reactions. While the regioselectivity of the catalyzed and

non-catalyzed reaction are complementary, the diastereoselectivity in one case was found to be the same; both reaction conditions favor the *anti*- product formation (**Scheme 1.3**).



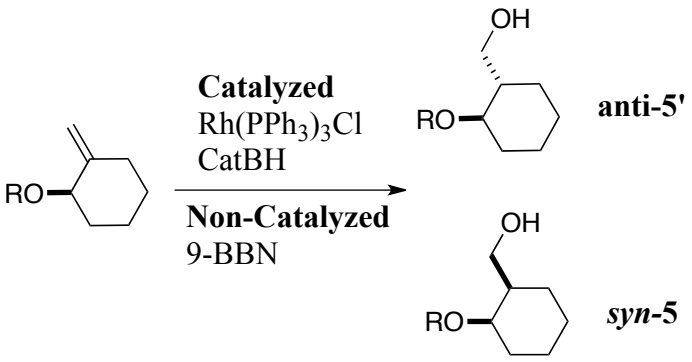
Scheme 1.3: Non-catalyzed vs. catalyzed hydroboration of cyclic alkenes

Table 1: Yields and selectivities of the catalyzed hydroboration vs. non-catalyzed hydroboration of cyclic alkenes

R	Conditions	Yield (%)	*anti*- 3	*syn*- 3	*anti*- 4	*syn*- 4
H	Catalyzed	84	18	1	72	9
	Non-catalyzed	86	83	2	5	10
CH_2Ph	Catalyzed	87	7	8	72	13
	Non-catalyzed	73	68	0	13	19
$Si(CH_3)_2t$-Bu	Catalyzed	79	2	1	86	11
	Non-catalyzed	70	74	0	13	13

Evans and co-workers further expanded on the utility of the directed catalyzed hydroboration of allyl functionized substrates. Using an exocyclic 1,1-disubstituted alkene, they demonstrated that under catalyzed reaction conditions diastereoselectivity

(*syn*) could be achieved while the non-catalyzed reaction of 9-BBN is almost completely non-selective (**Scheme 1.4**).



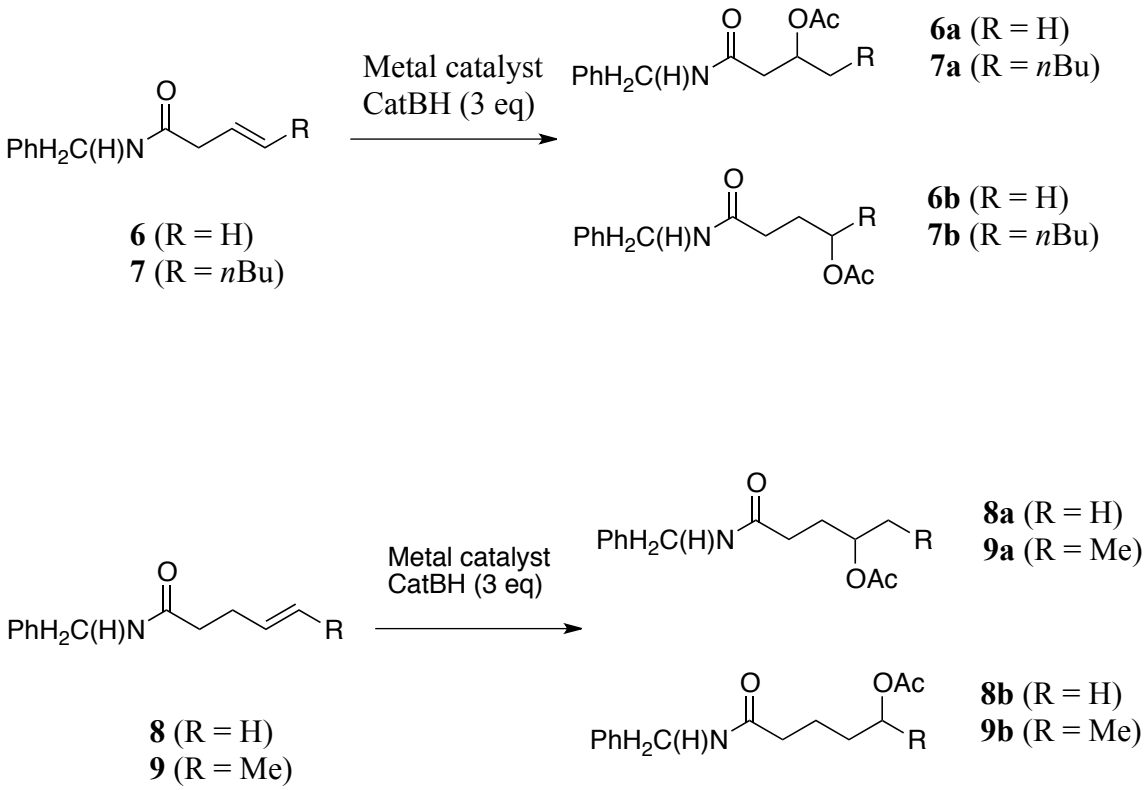
Scheme 1.4: Catalyzed and non-catalyzed reactions; 3eq of borane, 3 mol% $Rh(PPh_3)_3Cl$

Table 2: Yield and selectivity of catalyzed vs. non-catalyzed hydroboration of 1,1-disubstituted exocyclic alkenes

R	**Conditions**	**Yield (%)**	***syn*-5**	***anti*-5'**
H	Catalyzed	93	90	10
	Non-catalyzed	83	50	50
$Si(CH_3)_2t$-Bu	Catalyzed	88	96	4
	Non-catalyzed	81	39	61

Evans *et. al.* also showed that amides could direct regioselectivity in the reactions of alkenes with high selectivity (**Scheme 1.5**).[21] Both (*E*)-beta, gamma- and (*E*)-gamma, delta-disubstituted alkenes as well as the corresponding terminal alkenes were shown to

be suitable substrates. This directing group was not only capable of directing the rhodium catalyzed hydroboration, but also provided a strong chelation to iridium; the latter catalyzed hydroboration with even greater control over the regioselectivity.



Scheme 1.5: Benzyl amide directed rhodium and iridium catalyzed hydroboration of (*E*) β,γ- and γ,δ-unsaturated 1,2-disubsubstituted and mono-substituted alkenes

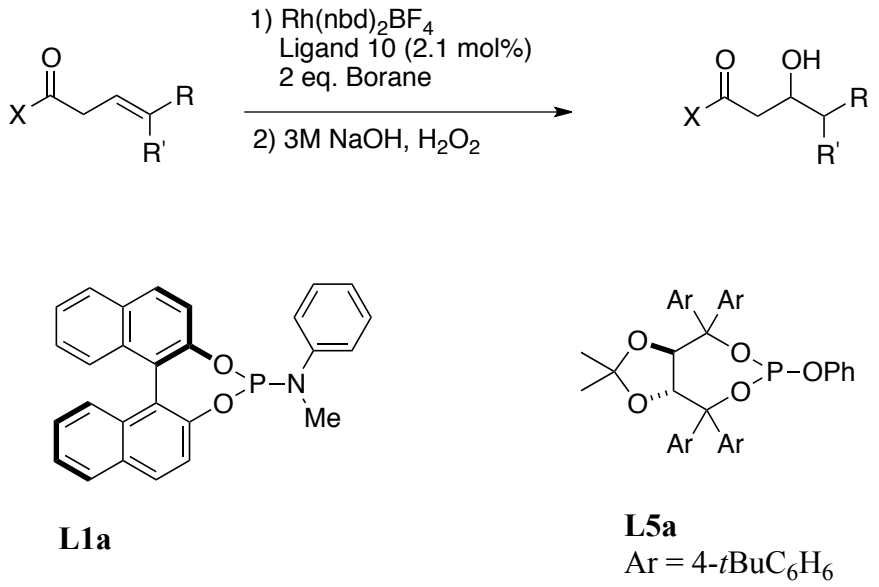
Table 3: Yields and regioselectivities for amide-directed catalyzed hydroboration. [Rh = Rh(nbd)(diphos-4)BF_4; Ir = Ir(cod)(PCy_3)PF_6) *Ratio for γ : δ : ε

Substrate	Catalyst	Yield (%)	a : b
6	Rh	NA	NA
6	Ir	78	1 : 1
7	Rh	74	20 : 1
7	Ir	73	>99 : 1
8	Ir	78	1 : 3
9	Rh	NA	70 : 20 : 10*
9	Ir	78	99 : 1

The recent development of simple enantiopure phosphite and phosphoramidite mono-dentate ligands showed that a chiral environment can be achieved around the metal via ligand complexation, and in turn transfer the chirality via the metal complex to newly formed covalent bonds.[22] With the high level of success that these chiral monodentate ligands achieve in rhodium-catalyzed asymmetric hydrogenation, the Takacs group applied them to the problem of rhodium-catalyzed asymmetric hydroboration. Initially these ligands were used in conjunction with cationic rhodium(I) and neutral rhodium(I) chloride catalyst precursors for the catalytic asymmetric hydroboration (CAHB) of styrene and a variety of *ortho*-, *meta*- and *para*-substituted derivatives. It was found that these catalysts efficiently control the stereochemistry in the reactions of such substrates to give high levels of enantioselectivity.[23]

Exploring the finding that the mono-dentate ligands create a highly efficient chiral pocket and taking queue from advantage of the fact that amide's are capable of

controlling the regioselectivity of various olefinic substituted substrates, the Takacs group was able to apply the same concept and develop the enantioselective hydroborations of beta, gamma-unsaturated amides and -Weinreb amides (**Scheme 1.6**).[24,25,26] The regio- and enantioselective control of this reaction has been attributed to a couple of key factors. The essential aspects of this control include the need of a strongly chelating metal complex between the directing group and alkene, and the creation of a specific chiral environment around the metal center itself. Unlike with the styrene substrates for which both cationic rhodium(I) and neutral rhodium(I) chloride catalyst precursors were both capable of high levels of enantioselective catalysis, the amide directed catalysts gave significantly lower levels of enantioselectivity and slower conversion with the rhodium(I) chloride metal precursor. This makes sense when explained mechanistically (*vide infra*) as chelating the substrate to the metal requires an open coordination site on rhodium(I) (also referred to as two-point binding); recall it is this chelate that is used to rationalize the observed regioselectivity, and is now also used to rationalize the enantioselectivity for the directed reaction.



Scheme 1.6: If X = N(H)(Ph) PinBH is borane source; if X = N(Me)(OMe) TMDB is used as borane source

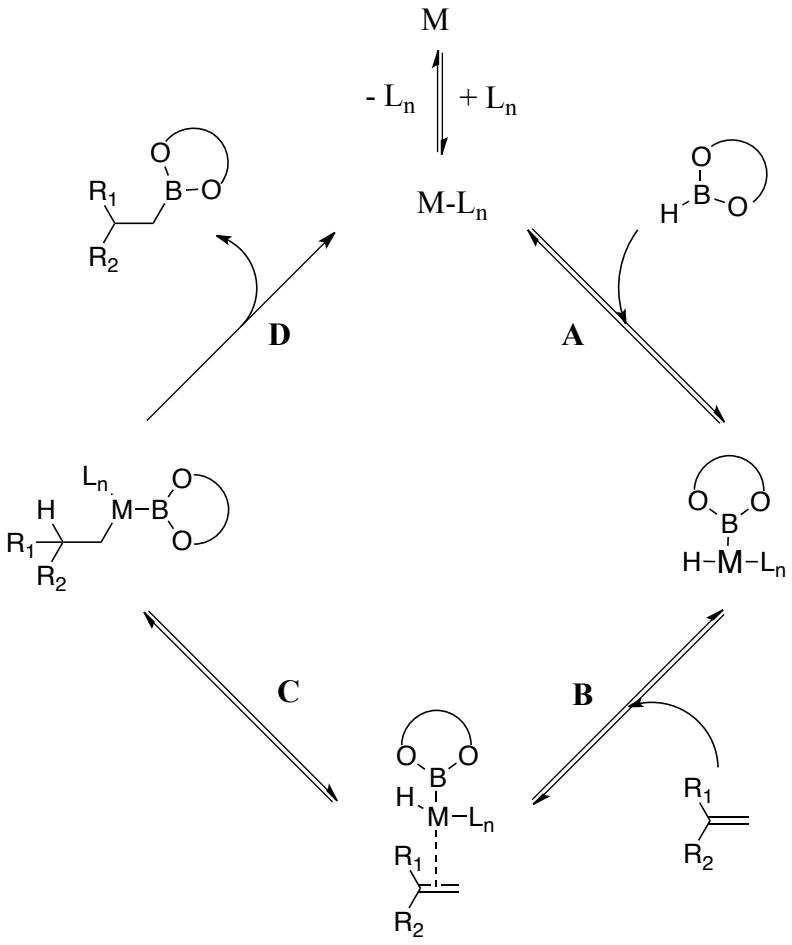
Table 4: Yields and enantioselectivities of various directed catalytic hydroborations

X	R	R'	Ligand	Yield (%)	% ee
N(H)(Ph)	CH_2CH_3	H	L1a	81	99
	H	CH_2CH_3	L1a	83	99
	*i*Pr	H	L1a	76-80	93
	CH_2CH_2Ph	H	L1a	76-80	99
	nC_4H_9	Me	L5a	79	98
	Me	nC_4H_9	L5a	80	96
N(Me)(OMe)	nC_4H_9	H	L1a	77	92
	C_2H_5	H	L1a	73	97
	H	C_2H_5	L1a	72	97

1.3 Discussion of Possible Mechanism for Transition Metal Catalyzed Hydroboration

While two-point binding substrates, specifically amides and Weinreb amides, are currently necessary to achieve highly enantioselective hydroborations of substrates other than vinyl arenes, in principle, the directing group is superfluous in the catalyzed hydroboration reaction of simple alkene substrates. There are four essential steps required to achieve the metal catalyzed hydroboration cycle in the generally accepted reaction mechanism; they are (**A**) oxidative addition of the metal into the B-H bond, (**B**) coordination of the metal complex with the alkene, (**C**) migratory insertion of the alkene into the metal hydride bond creating an alkyl metal bond, and (**D**) reductive elimination of the metal producing the final alkyl boronate ester product and regenerating the metal catalyst (**Scheme 1.7**).

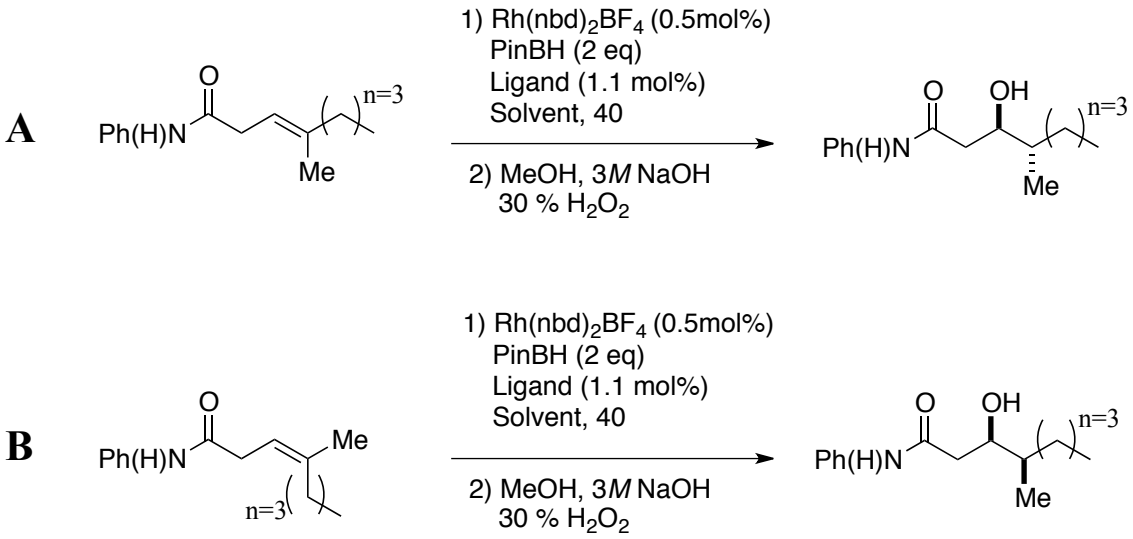
There is currently some debate over the order of addition of the hydride and borane in the literature. Evans *et. al.* have done some elaborate deuterium labeling studies on non-directed substrates using Wilkinson's catalyst and CatBD and demonstrated that in simple alkyl substrates there are mixed deuterium products formed.[27] This would lead to the conclusion that under certain conditions the borane could be added prior to the hydride, leading to the migratory insertion (step **C**) into the metal borane bond. This also suggests that that under the same conditions the migratory insertion (step **C**) could be reversible within the proposed catalytic cycle.



Scheme 1.7: Proposed transition metal catalyzed hydroboration of simple alkenes

The deuterium labeled mechanistic investigations have been done on simple alkyl and vinyl arene substrates and have not taken into account how the directing group of the amide or Weinreb amide moiety could effect the catalytic cycle. The catalytic cycle for the directed catalytic cycle is proposed to undergo a very similar reaction pathway with the stereospecificity of the two point binding metal in the reaction being the major difference. In the case of the trisubstituted alkene both (*E*) and (*Z*) alkenes give high enantioselectivities, but with the complementary diastereoselectivity; (*E*) gives rise to the

anti-product and (*Z*) gives rise to the *syn*-product (**Scheme 1.8**). These selectivities are due to the *syn* addition of the borane and the hydrogen (**Table 4**). Since these reactions occur with high yields, are highly regio- and enantioselective, the directing group may prevent the hydride insertion step from being reversible, otherwise epimerization could occur and the stereospecific products would not be observed.

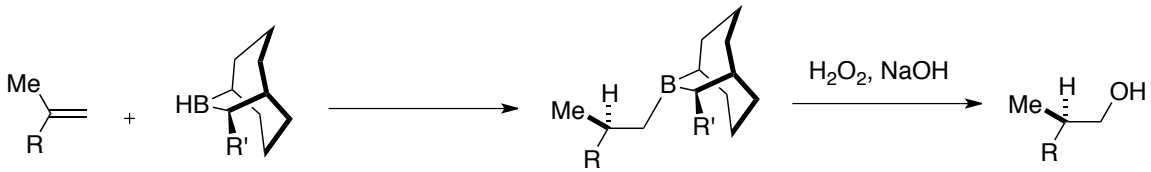


Scheme 1.8: Enantioselective hydroboration of (*E*) and (*Z*) trisubstituted alkenes giving rise to complimentary diastereomers. **A)** *Anti*-diastereomer (3R,4S) 79% yield, 98% ee. **B)** *Syn*-diastereomer (3R,4R) 80% yield, 96% ee.

1.4 Previous Attempts of Enantioselective Hydroboration of 1,1-Disubstituted Alkenes

The Takacs group has made great progress with the directed enantioselective catalytic hydroboration over the past 5 years, and there is still more that needs to be explored. The common theme for enantioselective hydroboration to date is the need of polar functional

directing groups to control the regio- and stereochemistry of the reaction. For this reason one avenue to explore is the scope of potentially new polar- functional groups, as well as non-polar functional groups (non-chelating) within the substrate. While exploring new functional groups is indeed needed, another aspect of the substrate that has yet to have been sufficiently researched is the 1,1-substitution pattern of disubstituted alkenes. The 1,1-disubstituted alkene moiety have been a challenge for other types of enantioselective catalysis. For example, conditions for asymmetric epoxidation, after much research solutions, have been found for the latter and high enantioselectivity (99% ee) has been achieved.[28] There has been some success in the enantioselective hydroboration of the 1,1-disubstituted alkenes but they rely upon the use of a stoichiometric chiral borane (**Scheme 1.8**).[29] Although good enantioselectivity can be achieved (92% ee), only one substrate achieves an enantiomeric excess of greater than 80% (**Table 5**, **Entry 5**). In addition to the limited substrate scope, and the use of stoichiometric amount of the chiral borane reagent, some other major drawbacks to this method are little functional group tolerance, and the synthesis of the chiral boranes



10 R' = Ph
11 R' = $SiMe_3$

Scheme 1.9: Stoichiometric asymmetric hydroboration of 1,1-disubstituted alkenes

Table 5: Yield and enantioselectivity of 1,1-disubstituted alkenes with chiral alkylboranes

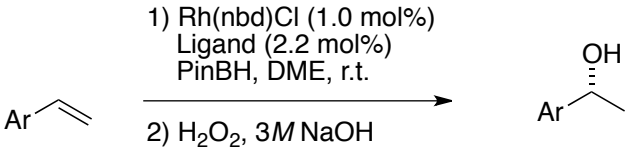
Entry	R	Borane	Yield (%)	% ee
1	Et	10	83	28
2	Et	11	87	40
3	*i*Pr	10	97	38
4	*i*Pr	11	82	52
5	*t*Bu	10	84	92
6	*t*Bu	11	60	56
7	Ph	10	95	78
8	Ph	11	83	66

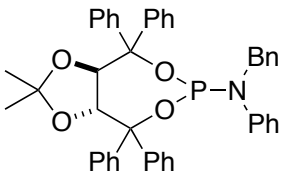
The research herein describes endeavors to improving the scope of enantioselective rhodium catalyzed hydroboration of 1,1-disubstituted alkenes utilizing monodentate ligands while exploring diverse allylic functional groups. While no satisfactory solution (< 90% ee) to this challenge has been found some encouraging leads have been identified. It is expected that these will set the stage for continued investigation.

Chapter 2: Functional Group Reactivity and Compatibility

2.1 Investigation of Alkyl 1,1-disubstituted Alkenes

Vinyl arenes are the most widely studied substrates for catalyzed asymmetric hydroboration (CAHB). They have been shown to afford high levels of enantioselectivities with a variety of ligands, boranes and catalyst reagents. They give predominantly the secondary alkyl borane product, which is complementary to the observed regioselectivity in the non-catalyzed hydroboration. Our group has previously investigated the use of monodentate phosphite and phosphoramidite ligands for the rhodium-catalyzed CAHB of vinyl arenes and has been able to achieve high levels of enantioselectivity with styrene derived *para*-substituted substrates (**Scheme 2.1**).[30]





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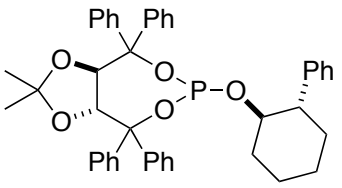

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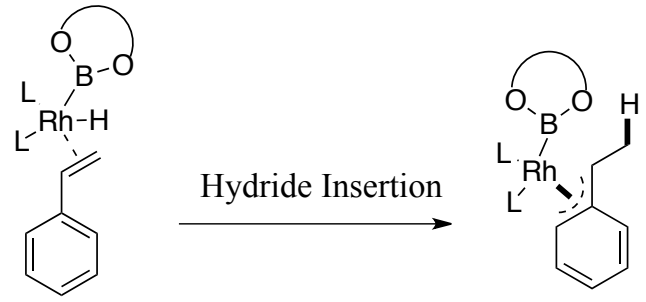
Scheme 2.1: Enantioselective hydroboration of styrene derived *para*-substituted vinyl arenes with monodentate TADDOL derived phosphite and phosphoramidites

Table 6: Yield and enantioselectivity of *para* substituted vinyl arenes

Ligand	Ar = *p*C_6H_4	Yield (%)	% ee	Ligand	Ar = *p*C_6H_4	Yield (%)	% ee
12	*p*OMe	71	93	13	*p*OMe	67	94
12	*p*CH_3	62	92	13	*p*CH_3	60	93
12	C_6H_5	78	95	13	C_6H_5	82	96
12	*p*CF_3	63	90	13	*p*CF_3	62	90
12	*p*Cl	77	91	13	*p*Cl	77	94
12	*p*F	79	95	13	*p*F	72	95

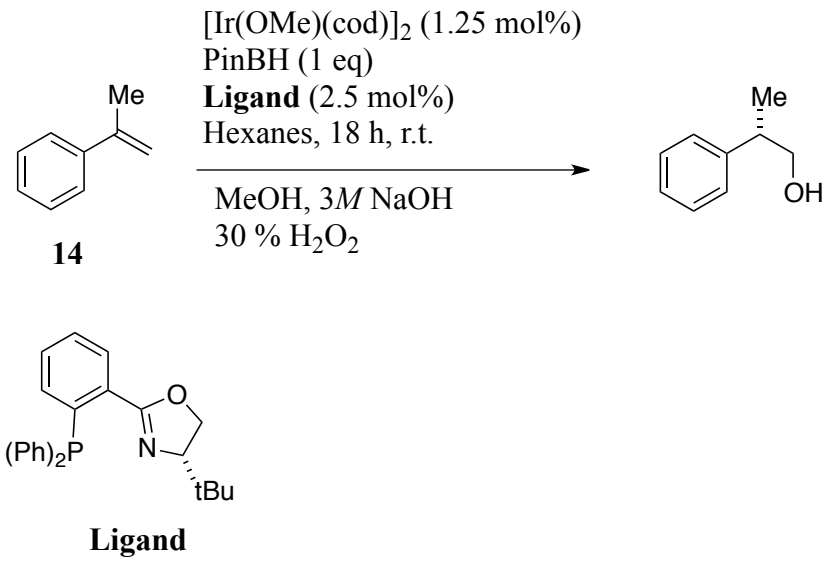
The success of enantioselective catalysis with vinyl arenes has been proposed to be partly due to an interaction between the metal and the pi system of the aromatic ring that has the ability to create a π-benzyl complex (**Scheme 2.2**).[31] This π-benzyl complex is used to account for the complementary Markovnikov regioselectivity of catalyzed hydroboration forming the branched or benzyl boronate over the linear product.



Scheme 2.2: Formation of alkyl rhodium π-benzyl complex after hydride insertion

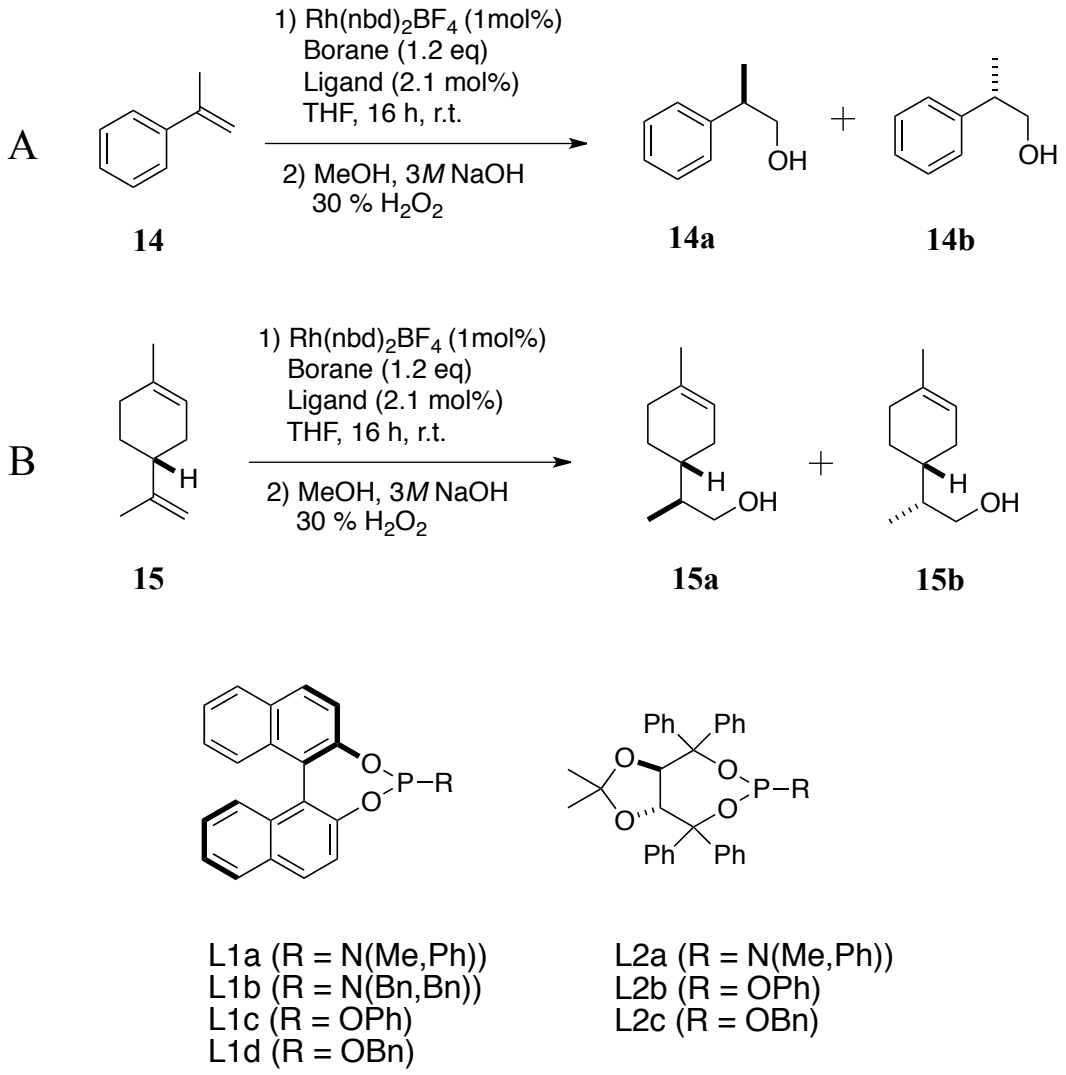
A logical progression for the study of 1,1-disubstited alkenes lacking a polar directing group would be to begin with the vinyl arene α-methylstyrene (**14**). Like many

vinyl arene substrates, **14** has been rather extensively studied with a variety of different catalytic systems. The best results with this type of substrate has been reported recently by Mazet *et. al*. utilizing an iridium catalyst $[Ir(OMe)(cod)]_2$ and a bidentate P,N-ligand **L7** (**99% yield, 92% ee** (S)) (**Scheme 2.3**).[32]



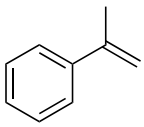
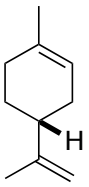
Scheme 2.3: Catalytic enantioselective hydroboration of vinylarene **14** (**99% yield, 92% ee**)

R-(+)-limonene (**15**) is also a well studied though it has proven to be a rather challenging substrate. Thus far, the best results achieved with the use of the stoichiometric chiral borane **10** giving an 88:12 mixture of *cis*-**15a** and *trans*-**15b**. Continuing the theme of our group while developing reaction conditions for these 1,1-disubstituted substrates, chiral monodentate ligands **L1a-L2b** were employed.



Scheme 2.4: (A) Reaction conditions for rhodium catalyzed hydroboration of α-methyl styrene; **(B)** Reaction conditions for rhodium catalyzed hydroboration of R-(+)-limonene

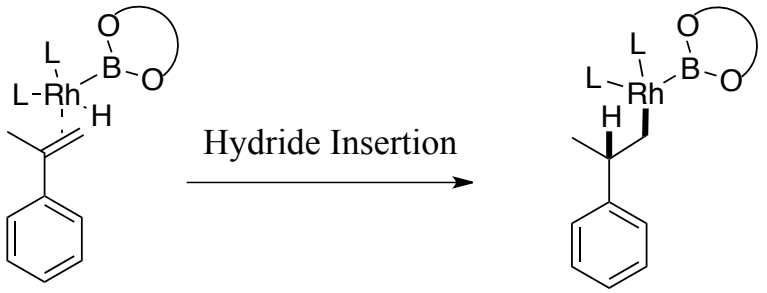
Table 7: Yields and selectivity of alkyl substrates **14** and **15**

 **14**			 **15**		
Ligand	**Yield (%)**	**% ee**	**Ligand**	**Yield (%)**	**% ee**
L1a	96	33	L1a	85	25
L1c	Trace	NA	L1b	85	20
L2a	97	48	L1c	34	20
L2b	32	35	L1d	30	37
			L2a	99	30
			L2b	85	28
			L2c	99	25

Substrates **14** and **15** exhibit a range of reactivity with the catalyst depending upon the ligand scaffold utilized; the low yields range around 30%, while in other cases, yields as high as the upper 90% range are obtained. The level of enantioselectivity for the two substrates also differs with ligand with the highest levels of enantioselectivity of **14** being accomplished with **L2a** (**97% yield, 48% ee**) and of **15** with **L1d** (**30% yield, 37% ee**).

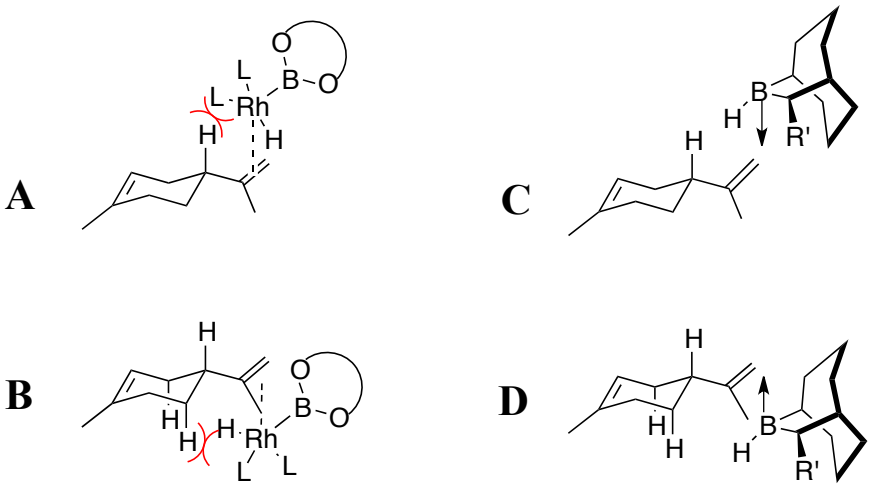
The alkyl substrates **14** and **15**, lacking any polar functional groups, have individually unique results based upon the ligand employed. The expected *anti*-Markovnikov regiochemistry product of **14** highlights it's difference in the catalytic hydroboration with other styrene derivatives. As previously postulated, a π-benzyl

complex may play a major role of the reaction of styrene (**Scheme 2.2**), but it is formed after the initial hydride insertion to the terminal carbon. **14** could potentially enjoy the same stabilizing π-benzyl effect but that complex follows hydride insertion. It is found that instead, the alkyl metal bonds is formed on the terminal carbon producing the linear product and no branched product is observed (**Scheme 2.5**).



Scheme 2.5: Proposed alkyl rhodium complex of α-substituted vinyl arene after hydride insertion

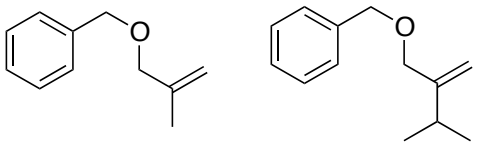
15 is an interesting alkyl substrate for different reasons; it has multiple alkenes and a preexisting stereocenter. The preexisting stereocenter within **15** creates a sense facial selectivity control since it promotes the coordination to the alkene based on the steric environment the molecule presents to the catalyst (**Scheme 2.5**). This stereocenter is expected to influence the stereochemical course of the reaction.



Scheme 2.6: Steric hindrance in facial selectivity of R-(+)-limonene **(A)** Catalyzed approach to make *trans* product **15b (B)** Catalyzed approach to make *cis* product **15a (C)** Chiral organoborane approach to make *trans*-**15b (D)** Chiral organoborane approach to make *cis*-**15a**

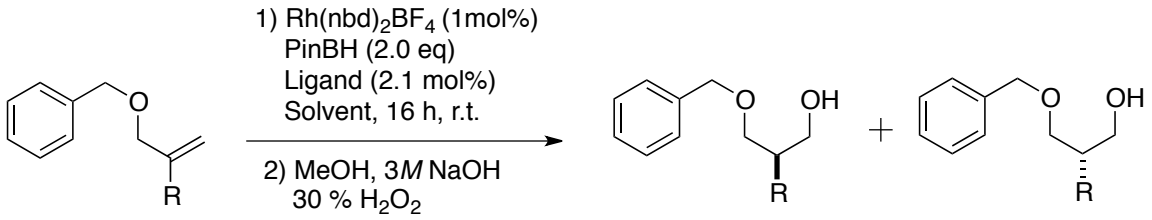
2.2 Investigation of Benzyl Ether 1,1-disubstituted Alkenes

As stated earlier, Evans *et. al.* was able to demonstrate that with an exocyclic 1,1-disubstituted alkene system, a variety of ether substrates gave products with high diastereoselectivity (**Figure 1.3 and 1.4**). To expand upon these initial findings, a variety of truncated versions of the Evans substrate, that is, acyclic 1,1-disubstituted alkenes bearing an allyl benzyl ether group were explored. A series of benzyl ethers with increasing steric bulk on the alkene were investigated (**Figure 2.7**). As with the alkyl substrates, a set of monodentate ligands with the phosphite and phosphoramidite were used to examine this functional group.

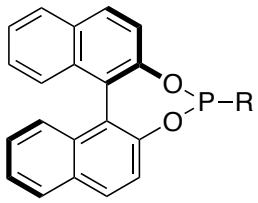


16 **17**

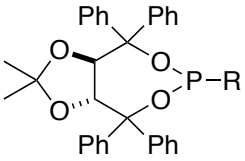
Scheme 2.7: Benzyl ether substrates with varying vinyl steric bulk



16 R = Me
17 R = *i*Pr



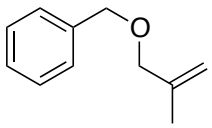
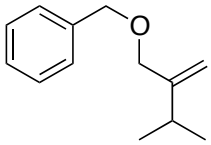
L1a (R = N(Me,Ph))
L1b (R = N(Bn,Bn))
L1c (R = OPh)



L2a (R = N(Me,Ph))
L2b (R = OPh)
L2c (R = OBn)

Scheme 2.8: Representative conditions for the enantioselective hydroboration of bezyl ethers

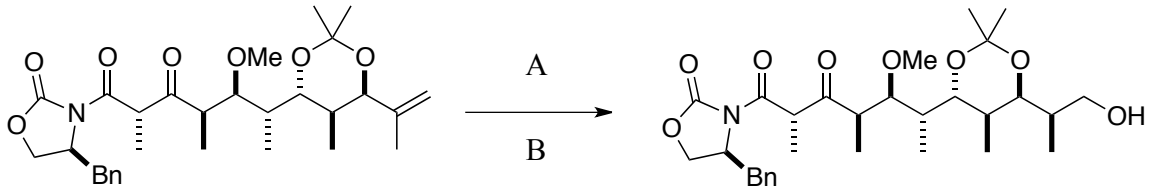
Table 8: Yields and selectivity of benzyl ether functionalized 1,1-disubstituted alkenes

 **16**			 **17**		
Ligand	**Yield (%)**	**% ee**	**Ligand**	**Yield (%)**	**% ee**
L1a	35	5	L1a	26	0
L1b	84	5	L1c	29	15
L1c	22	1	L2a	30	15
L2a	64	1	L2c	57	20
L2b	70	17			
L2c	99	25			

Low to high levels of reactivity is achieved with the benzyl ether functional group with the methyl substituent being relatively more reactive then the isopropyl. This result is expected since the bulky nature of the substituent would hinder the approach of the catalyst and possibly make the coordination more difficult to achieve. The low levels of enantioselectivity for both ether substrates suggests the comparative bulk between the two substituents has only a minor influence on catalysts selectivity for the systems examined. The next section investigates similar substrates with different substituents on the oxygen atom.

2.3 Investigation of Allylic Acetal 1,1-Disubstituted Alkenes

To further probe the importance of the sterics, the nature of the ether was changed. Literature precedent guided our selection of substrates. A large sterically encumbered, diastereomerically pure substrate **18**, prepared enroute to lonomycin A, was studied by Evans *et. al.* It was demonstrated that the steric effects remote to the alkene can in fact play a significant role in determining the diastereoselectivity of CAHB (**Scheme 2.8**).[21]

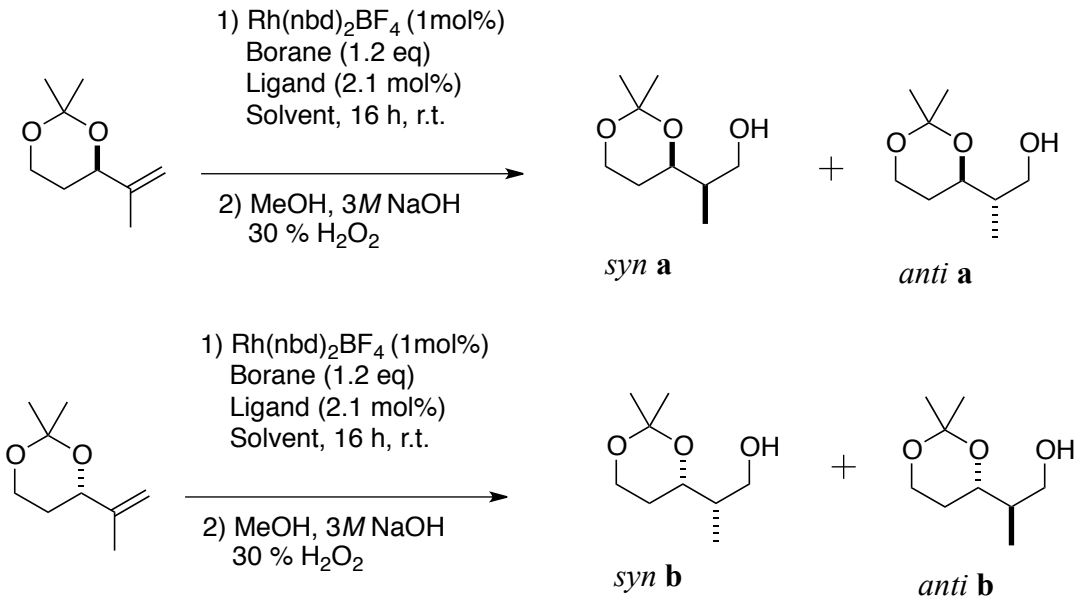


18 *syn* product

Scheme 2.9: (**A**) $Rh(PPh_3)_3Cl$, CatBH (62% yield, 94:6 *syn* : *anti*); (**B**) 9BBN (84% yield, 8:92 *syn* : *anti*)

Given the *syn* preference for the CAHB and the *anti* selectivity for the bulky alkyl 9-BBN reaction, it was envisioned that a chiral catalysts might be able to overcome the steric bias of the substrate to create the new chiral center independent of the pre-existing stereocenter. Allylic dimethyl acetal **19** lacks the chiral methyl within the six member dimetthyl acetal ring that the similar **18** has present. When rhodium (I) tetrafluoroborate and the chiral monodentate ligands were employed, only low levels of enantioselectivity was observed while a slight to moderate level of the *syn* : *anti* ratio still existed (**Table 9**). The preexisting allylic stereocenter in **19** seems to still have an influence the

diastereoselectivity of the reaction and, like **15,** when using 9-BBN the borane approaches the less sterically hindered face of the alkene, giving rise to a high level of the expected *anti*-**19** diastereomer product (90:10).



Scheme 2.10: Representative reaction conditions for the dimethyl acetal substrate (**19**)

Table 9: Yield and selectivity of allylic dimethyl acetal functionalized 1,1-disubstituted substrate. *Non-catalyzed 9BBN borane reaction

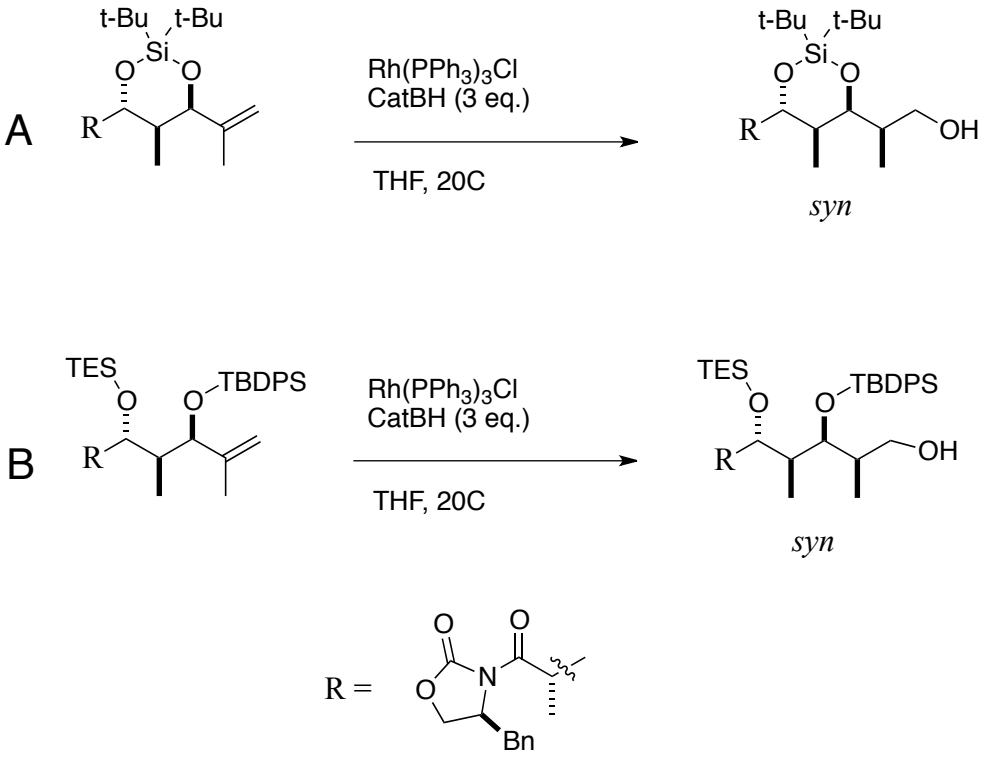
Ligand	**Yield (%)**	**a : b**	***syn* : *anti***
L1b	21	60 : 40	52 : 48
L1c	39	57 : 43	54 : 46
L2b	76	53 : 47	74 : 26
NA*	90	0	10 : 90

By investigating the racemic acetal starting material, rather then the individual enantiopure (R) and (S) compounds, it allows for both of the enantiomers to be studied

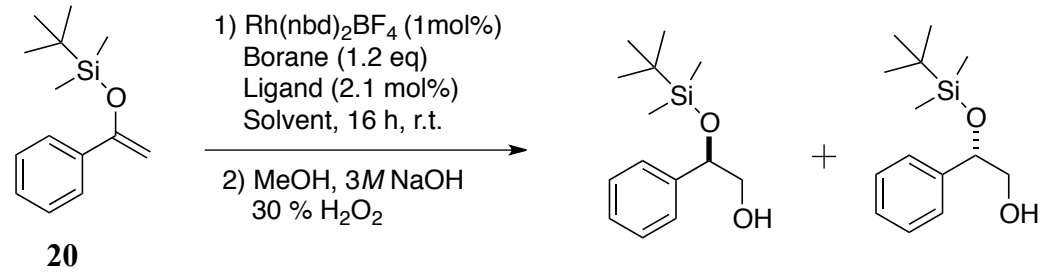
simultaneous and in turn doubling the amount of data that can be obtained with one reaction. It is also interesting to notice that the selectivity of the catalytic reaction changes between the two ligand backbones. The biaryl ligands give a slightly more diastereoselectivity preference, while the TADDOL ligand gives an excess of syn over anti rather than diastereoselective selectivity. The most noticeable difference between the acetal substrate studied by Evans *et. al.* and the acetal **19** studied here is the missing methyl group adjacent to the allylic oxygen. This significant change lowers the *anti*-selectivity of 9-BBN of **19** and this missing chiral methyl could as well be the cause for the lower enantioselectivity in the catalyzed variant.

2.4 Investigation into a Silyl Enol Ether: A Different 1,1-Disubstituted Alkene

To continue our investigation of the role that the ether may play, enol ethers were also studied to get a better understanding of the location this functional group may need to be for optimization. While not directly relevant to the question, 1,3-silyl ethers, similar to the acetal substrate, have been previously studied and they demonstrated that the bulk of the silyl ether has a substantial role for diasteroselectivity of the catalyzed hydroboration reaction (**Scheme 2.11**). The silyl enol ether **20** differs from those substrates described in Scheme 2.11 since there is no preexisting stereocenters. However, the steric bulk electronic effect of the electron rich silyl enol ether double bond could both have major influences the overall reactivity of this type of alkene.



Scheme 2.11: A) 97% yield, 73:27 *syn*: *anti*; **B)** 91% yield, 93:7 *syn*: *anti*



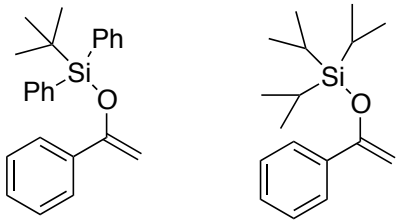
20

Scheme 2.12: Representative reaction conditions for silyl enol ether (**20**)

Table 10: Yields and selectivity for silyl enol ether functionalized 1,1-disubstituted alkene (**20**); *Yields taken of the organoborane ester

Ligand	Yield (%)*	% ee
L1a	13	21
L1b	22	35.5
L2a	49	27
L2c	37	11
L2d	64	37

As it turns out the reactivity of the silyl enol ether was poor, giving low to moderate yields of the boronate ester. Despite the low reactivity, the most problematic issue with these substrates is the incompatibility with the work up of the reaction. During the oxidation of the boronate ester to the alcohol under the standard basic conditions the TBDMS silyl group has a tendency to migrate between the two alcohols. For this reason other silyl groups were also examined with the hope that migration could be prevented. However, these substrates proved to be even less reactive; no conversion to the organobornate ester was observed. This could be due to sterics of the TBDPS and TIPS silyl groups shielding the alkene from the approaching metal complex.



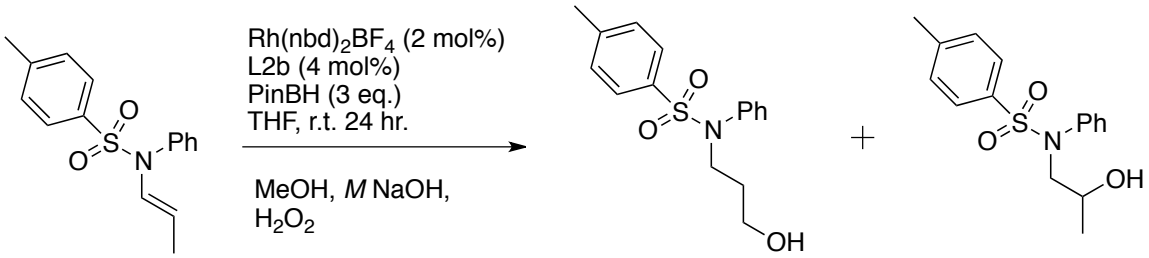
21a **21b**

Scheme 2.13: Silyl enol ether substrates that demonstrated no reactivity in the catalyzed hydroboration

The inability of very bulky silyl compounds to react can be explained by the difficulty of the metal complex to approach the alkene and therefore the coordination could be a very weak interaction if any at all occurs. Sterics will affect both reactivity and selectivity.

2.5 Investigation of Allylic Sulfonamide Functionalized 1,1-Disubstituted Alkenes

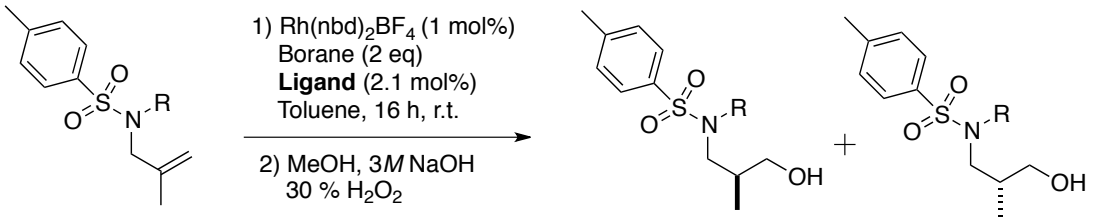
The Takacs group has investigated enamine derivatives in the rhodium catalyzed enantioselective hydroboration. For example, the vinyl sulfonamide **21** was found to undergo competing rhodium-catalyzed alkene isomerization. The major product was formed after the double bond had migrated to the end of the alkyl chain prior to hydroboration. After oxidative workup, the terminal alcohol was obtained (**Scheme 2.12)**.



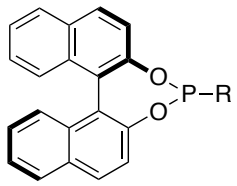
Scheme 2.14: Representative reaction conditions for hydroboration of allylic sulfonamide (90:10; 1°: 2°)

The 1,2-disubstituted vinyl sulfonamide system was also briefly studied. Since the alkene migrates to the terminal position under catalytic conditions the linear 1° product is an issue. The 1,1-disubstituted alkene allylic sulfonamides do not have the same migration issue since the terminal alkene is unable to migrate under the catalytic

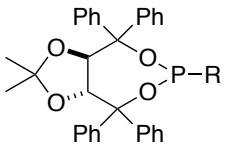
conditions. The 1,1-disubstituted sulfonamide substrates **23** and **24** are similar to the allylic acetal substrates with respect to the position of the functional group, but may be influenced by the sulfone functionality, which may act as a directing group.



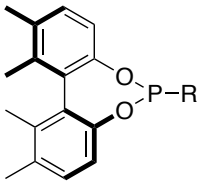
23 (R = Et)
24 (R = Cy)



L1a (R = N(Me,Ph))
L1b (R = N(Bn,Bn))
L1c (R = OPh)



L2a (R = N(Me,Ph))
L2b (R = OPh)
L2c (R = OBn)



L6a (R = OPh)
L6b (R = OBn)
L6c (R = N(Me,Ph))
L6d (R = N(Bn,Bn))
L6e (R = N(S)-Bis(1-Phenylethyl)
L6f (R = N(R)-Bis(1-Phenylehtyl)

Scheme 2.15: Optimized reaction conditions for allylic sulfonamide derivatives

Scheme 2.15 lists some optimized reaction conditions for the enantioselective reaction of the sulfonamide substrates with the best results being achieved on **25** with **L6f** (**91% yield, 67.7% ee, Table 11**). The conditions used here, after some reaction optimization, differ from the typical conditions used for ethers, acetal and alkyl substrates. These promising results reported within our group has been partially attributed to the steric effects from the alkyl group on the sulfonamide, and partially to a weak

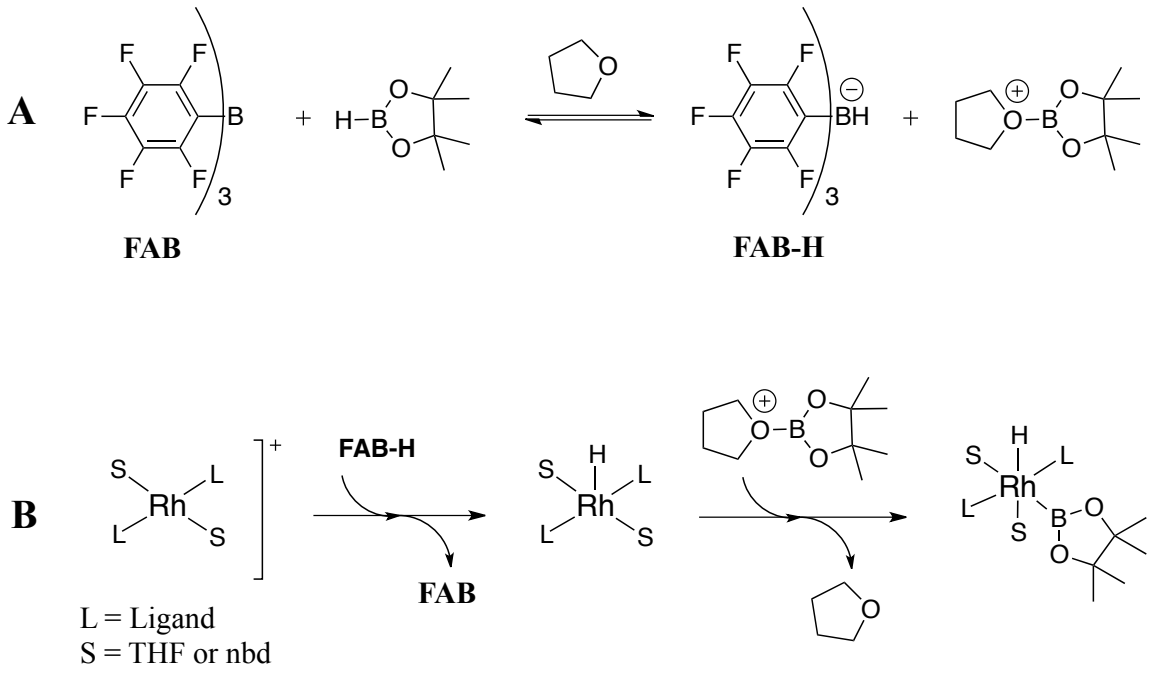
coordination between the alkene and polar S=O bond. While these reasons may be true, the change in solvent also plays a significant role.

Table 11: Yields and enantioselectivity for the CAHB of allylic sulfonamides (**R = Et (23), Cy (24)**) in toluene

Ligand	**R**	**Yield (%)**	**% ee**	**Ligand**	**R**	**Yield (%)**	**% ee**
L1a	Et	52	11	L1a	Cy	61	3
L1b	Et	71	1	L1b	Cy	42	18
L1c	Et	64	30	L1c	Cy	75	33
L2a	Et	99	10	L2a	Cy	30	5
L2b	Et	61	9	L2b	Cy	12	15
L2c	Et	99	23	L2c	Cy	76	9
L6a	Et	99	47	L6a	Cy	77	57
L6b	Et	99	6	L6b	Cy	68	17
L6c	Et	99	53	L6c	Cy	43	41
L6d	Et	99	23	L6d	Cy	73	39
L6e	Et	99	55	L6e	Cy	99	45
				L6f	Cy	91	67.7

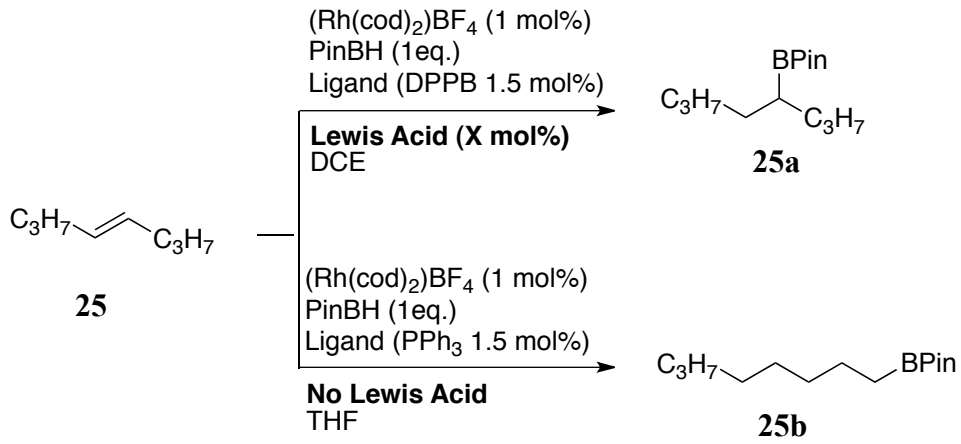
One potential difference that could account for the solvent effects may be how the different solvents interact with the borane and effect its oxidative addition to rhodium. There is some evidence in the literature to support this idea. Ether solvents, like THF and DME, are known to form fairly stable Lewis acid-base coordination complexes with boranes. In fact, BH_3 is usually purchased as a complex with either an ether or sulfide

complex (BH_3-THF or BH_3-$S(Me)_2$). Crudden *et. al.* investigated the role of the Lewis acids on the catalytic hydroboration. They proposed a change in the oxidative addition of borane to account for some interesting results they obtained (**Scheme 2.15**).[33]



Scheme 2.16: A) Hydride abstraction from pinBH by FAB **B)** Proposed oxidative addition in the presence of Lewis acid

Although the stabilized borenium ion was not isolated by Crudden *et. al.,* similar structures have been investigated Gevorgyan and Stephan.[34,35] The proceeding steps in the proposed catalytic cycle for hydroboration remain the same. A key observation is the Lewis acid effect is only seen in a non-coordinating solvent (**Table 12).** This study suggests that the oxidative addition could be directly related to the coordination of the solvent to the borane (**Scheme 2.17**).

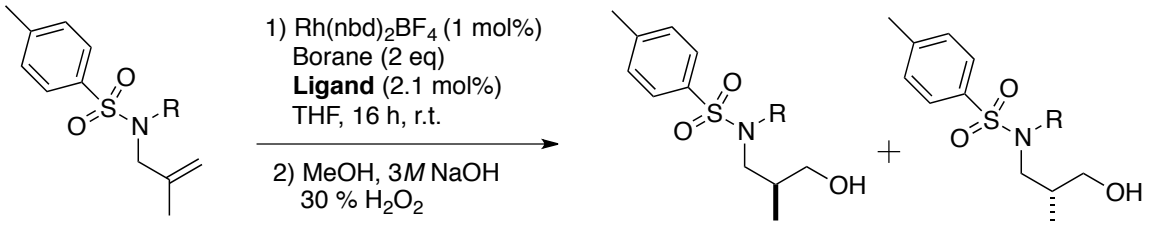


Scheme 2.17: Hydroboration of (E)-4-Octene (**25a : 25b branched:linear**) other possible positions of product are minor

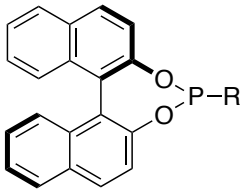
Table 12: Lewis acid additives for the regio-selective catalyzed hydroboration

Ligand	Solvent	Lewis Acid (X mol %)	Yield (%)	Ratio 25a :25b
PPh_3	THF	None	95	1 : 99
PPh_3	DCE	$Sc(OTf)_3$ (2)	65	75 : 16
DPPB	DCE	$Sc(OTf)_3$ (2)	92	73 : 10
DPPB	DCE	FAB (2)	94	91 : 2

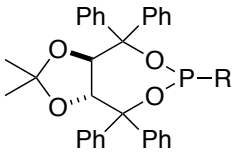
If the solvent played a major role in the oxidative addition step in the B-H bond, it would be expected to be universal throughout all the different substrates. So to test this hypothesis, the reactions of a series of allylic sulfonamides and ligands were compared in THF versus toluene. If the yield and selectivity did not change with otherwise identical conditions, it would mean that the solvent has little influence on the reaction. Comparing the results in Table 11 to those in Table 13, finds that the selectivity and yield? increases in toluene.



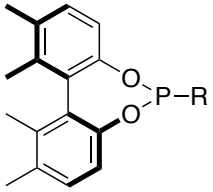
23 (R = Et)
24 (R = Cy)



L1a (R = N(Me,Ph))
L1b (R = N(Bn,Bn))
L1c (R = OPh)



L2a (R = N(Me,Ph))
L2b (R = OPh)
L2c (R = OBn)



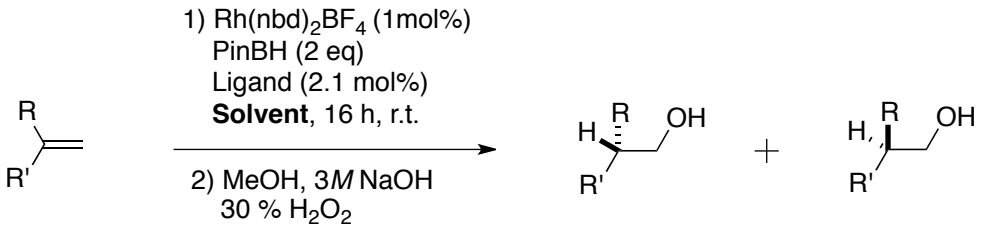
L6a (R = OPh)
L6b (R = OBn)
L6c (R = N(Me,Ph))
L6d (R = N(Bn,Bn))
L6e (R = N(S)-Bis(1-Phenylethyl)
L6f (R = N(R)-Bis(1-Phenylehtyl)

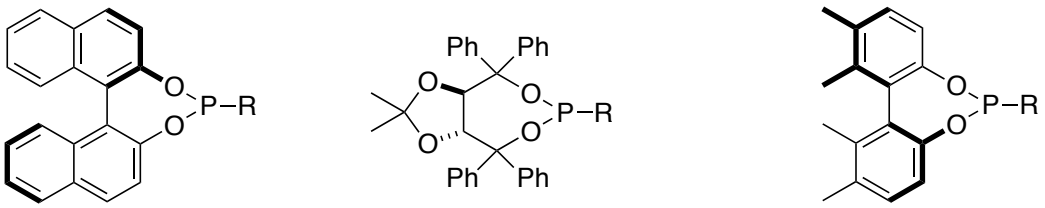
Scheme 2.18: Reaction conditions for allylic sulfonamide utilizing THF as coordinating solvent

Table 13: Solvent effect on the rhodium catalyzed hydroboration of allylic sulfonamides **23** and **24** in THF

Ligand	**R**	**Yield (%)**	**% ee**	**Ligand**	**R**	**Yield (%)**	**% ee**
L1a	Et	91	21	L1a	Cy	61	3
L1b	Et	99	1	L1b	Cy	42	18
L1c	Et	58	35	L1c	Cy	47	43
L2a	Et	99	10	L2a	Cy	30	5
L2b	Et	12	15	L2b	Cy	12	15
L6a	Et	58	35	L6a	Cy	47	43
L6b	Et	99	47	L6b	Cy	48	0
L6c	Et	45	0	L6c	Cy	47	0
L6d	Et	43	20	L6d	Cy	48	33
				L6e	Cy	96	0

Since changing from a coordinating solvent (**THF**) to a non-coordinating solvent (**toluene**) improves the selectivity of the reaction, investigations were done to determine if this change was universal throughout the scope of 1,1-disubstituted alkenes. **Table 14** illustrates that the change of solvent to toluene for a number of substrates. There is no universal improvement for these substrates suggesting that there are more important underlying aspects to the reaction to achieve useful levels of enantioselectivity.





L1a (R = N(Me,Ph))
L1b (R = N(Bn,Bn))
L1c (R = OPh)

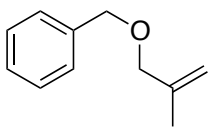
L2a (R = N(Me,Ph))
L2c (R = OBn)

L6a (R = OPh)
L6c (R = N(Me,Ph))
L6d (R = N(Bn,Bn))

Scheme 2.19: General reaction conditions for enantioselective hydroboration of the 1,1-disubstituted alkenes

With **Table 14** giving a direct comparison between the benzyl ether **16** and sulfonamide **24** while changing the solvent, it is observed that the reactivity between the two is different. The solvent has a larger effect on the sulfonamide then it does the ether, however, the effect is mostly noticed in the reactivity. The selectivity within the same class of functional group in either solvent is fairly similar. The best case for the sulfonamide class takes place in toluene with substrate **25**, and ligand **L6f (67.7 ee, 91% yield**). The best case for the benzyl ether incidentally is the same in both THF and toluene, substrate **16**, ligand **L2c (99% yield, 25% ee**), and this suggests that the solvent may only have a major effect when in the presence of polar functional groups.

Table 14: Direct comparison of various substrates with non-coordinating solvent



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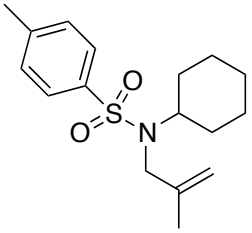
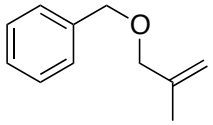
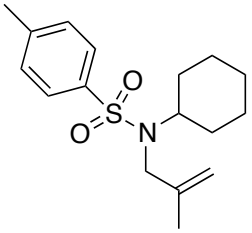


24

Solvent	L	Yield (%)	% ee	Solvent	L	Yield (%)	% ee
Toluene	L1a	15	6	Toluene	L1a	61	3
Toluene	L1b	32	6	Toluene	L1b	42	18
Toluene	L1c	22	1	Toluene	L1c	75	33
Toluene	L2a	40	13	Toluene	L2a	30	5
Toluene	L2c	99	25	Toluene	L2c	76	39
Toluene	L6a	45	21	Toluene	L6a	77	57
Toluene	L6c	28	16	Toluene	L6c	43	41
Toluene	L6d	29	1	Toluene	L6d	73	39



16



24

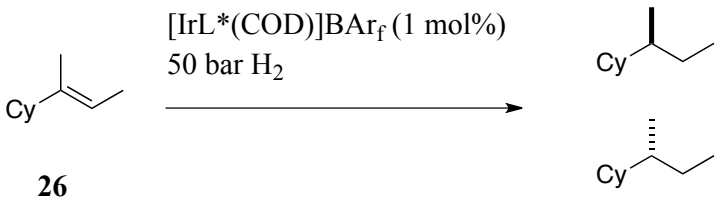
Solvent	L	Yield (%)	% ee	Solvent	L	Yield (%)	% ee
THF	L1a	35	5	THF	L1a	91	21
THF	L1b	84	5	THF	L1b	99	1
THF	L1c	22	1	THF	L1c	58	35
THF	L2a	64	1	THF	L2a	99	10
THF	L2c	99	25	THF	L2c	58	35

Perhaps the biggest challenge in trying to perform enantioselective catalysis on 1,1-disubstituted systems is that, as stated by Aggarwal, this substitution pattern is "barely" prochiral.[36] This transfer of chirlaity is difficult to achieve specifically if one substituent is a methyl, since the source of the chirlaity is being inserted onto the methylidene, one carbon removed from the stereogenic center made in the reaction. In our attempt make the enantiotopic faces of the alkene distinctly different from each other we have looked at two varying methods, changing the relative bulk of the substituents of the 1,1-disubstituted alkene is varied and also the nature of the functional group is changed.

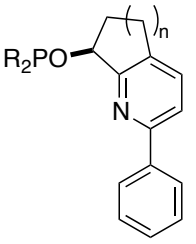
Our studies on different functional groups have led to few definitive conclusions to be drawn. However, it seems that within the limits we have thus far explored, changing the relative bulk of the substituents of the 1,1-disubstituted alkene does not seem to have a big effect on the level of facial selectivity.

Chapter 3: Ligand Effect in Enantioselective Rhodium Catalyzed Hydroboration

In 2006 Andreas Pfaltz and co-workers recently demonstrated that iridium catalyzed enantioselective hydrogenation could be achieved without the need of the typical carbonyl directing group on the substrate (**Scheme 3.1**).[37] He attributed the ability to perform the asymmetric transformation to the use of bicyclic, bidentate P,N ligands (**L8-L10)**. (*E*)-but-2-en-2-ylcyclohexane (**26**) was chosen because it would lack any functionality capable of influencing the reaction other than by steric effects, so the enantioselectivity would be completely controlled by the catalyst complex alone. Its hydrogenation was achieved with high levels of enantioselectivity (**L8, 62% yield, 92% ee**). Examining the proposed mechanisms for iridium catalyzed hydrogenation and the rhodium catalyzed hydroboration they seem to share a strikingly similar catalytic cycle, and therefore the efficient enantioselective hydroborations of substrates lacking a directing group should, in principle, also be viable.



26



Ligand
n = 1
L8 (R = *t*Bu)
L9 (R = *o*Tol)
n = 2
L10 (R = *o*Tol)

Ligand

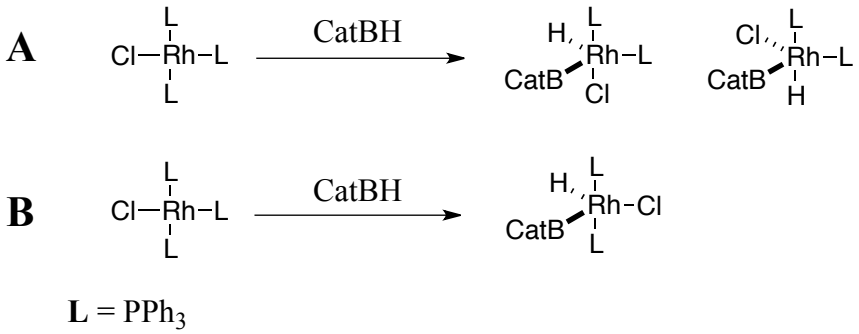
L8 (83% ee)
L9 (92% ee)
L10 (34% ee)

Scheme 3.1: Non-directed iridium catalyzed enantioselective hydrogenation

Table 15: Yields and enantioselectivity of non-directed iridium catalyzed hydrogenation

Ligand	Yield (%)	% ee
L8	71	83
L9	62	92
L10	78	34

Perhaps the most obvious difference between the bidentate ligands that Pfaltz *et. al.* have utilized to achieve the enantioselective hydrogenation, and the monodentate ligands that our group use for hydroboration, is only one bi-dentate ligand is involved in forming the topography of the chiral pocket whereas two monodentate ligands are needed to achieve the same effect. Nonetheless, monodentate ligands though have been shown now to be capable of comparable selectivities to bi-dentate ligands.[38] One downside to using monodentate ligands over bi-dentate ligands is that the former have more rotational and conformational flexibility and as such it is more difficult to predict potential conformations. This difficulty is amplified by the fact that multiple rhodium(III) complexes can be envisioned for this reaction (**Scheme 3.2**).[15,39] The choice of the Rh(I) counterion is another potentially complicating feature. For example, starting with Wilkinson's catalyst, the chloride stays tightly bonded to the catalyst under most conditions. In contrast, $Rh(nbd)_2BF_4$ adds an open coordination site that is likely filled by solvent, alkene or excess ligand.



Scheme 3.2: A) Potential *cis* binding geometries of rhodium(III) of Wilkinson's catalyst **B)** Potential *trans* binding geometries of rhodium(III) of Wilkinson's catalyst

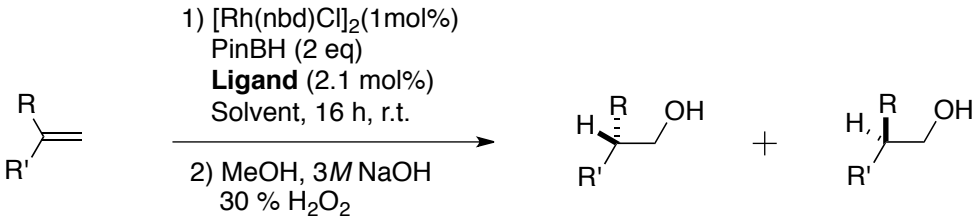
Crystal structures have been obtained of various Rh(I)-ligand complexes but whether or not the crystal structures represent the active catalyst is unclear.[40] Computational studies are currently underway to try to elucidate which bonding geometry could account for the active catalyst complex. (Takacs group, unpublished results).

Lacking a sound way to characterize the chiral pocket and optimize its topography for 1,1-disubstituted alkenes, a screening approach was adopted. The approach focused on changing two features of the ligand, the ligand back bone and the nature of the phosphorus center (i.e., phosphite or phosphoramidite).

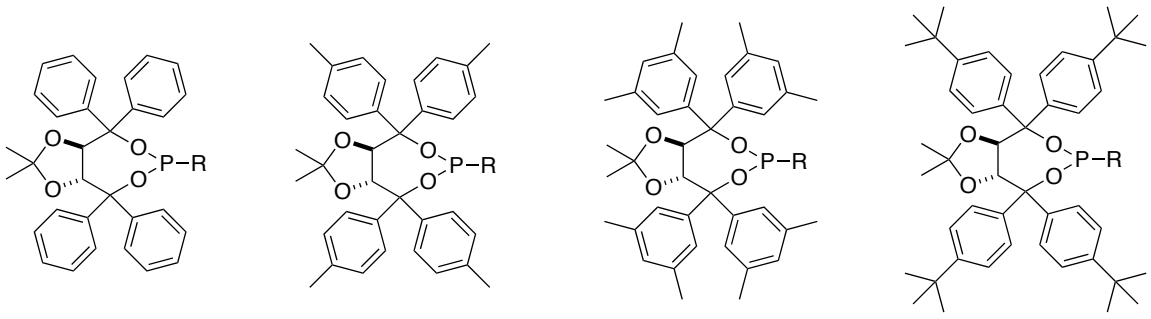
3.1 Exploration into changing topography of the ligand backbone

The topography of TADDOL ligand backbone is easily changed in subtle ways by changing the nature of the aryl groups.[41] Previous results have shown that by making subtle substitutions to the aryl groups on the TADDL ligands different results can be obtained while holding the phosphorus constant.[24,25] By changing the aryl groups on the

TADDOL backbone along with changing the electronics of the phosphorous center, a large library of ligands begins to unfold; in essence our ligand optimization is amenable to a combinatorial approach.



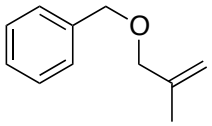
Scheme 3.3: General reaction conditions for the enantioselective catalyzed hydroboration of 1,1-disubstituted alkenes



L2c (R = OPh) **L3** (R = OPh) **L4** (R = OPh) **L5** (R = OPh)

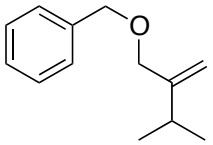
Scheme 3.4 The selected changes made to the aryl backbone of the TADDOL ligands

Table 16: TADDOL derived ligand results for various substrates



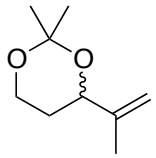
16

L	Yield (%)	%ee
L2b	84	5
L3a	59	1
L4a	99	3
L5a	99	20



17

L	Yield (%)	% ee
L2b	84	7
L3a	93	20
L4a	75	21
L5a	61	18



19

L	Yield (%)	% de*
L2b	76	6
L3a	99	5
L4a	99	1
L5a	99	10

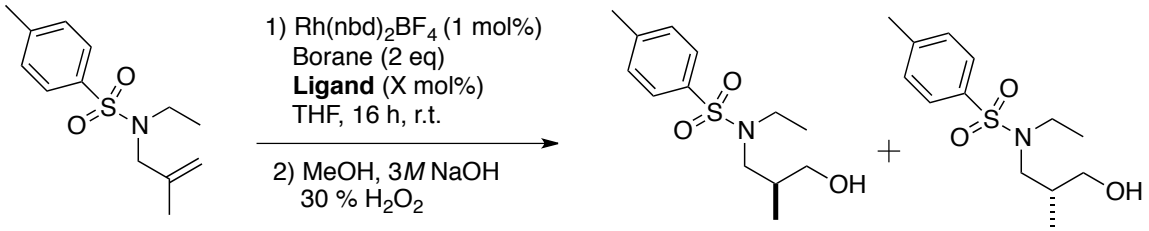
***de** is diastereomeric excess

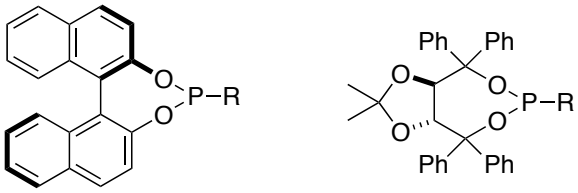
The subtle modifications in the topography of the TADDOL-derived ligands have only a minor effect on the overall reactivity and selectivity of the catalyst. The sensitivity of the reactions seems to be more dependent upon the substrate and backbone of the

ligand rather than the substitution of the aryl groups. The metal ligand complexes that give low selectivity with one class of ligand tend to give low selectivity throughout the whole class of the ligands with only minor differences.

3.2 Ligand Equivalents Needed for Catalytic Selectivity

TADDOL derived monodentate ligands are one of the commonly used subclasses of monodentate ligands. A different class of ligands, the biaryls (**Scheme 3.4**), has been referred to as a privileged class of ligand, this is due to the fact that this backbone has shown a great versatility throughout many different reactions.[42] This biaryl backbone has been utilized as both bidentate phosphite ligand, and as monodentate ligands. These biaryl ligands *a priori* have proven to give consistently positive results for the directed CAHB reaction. The directing group likely occupies one of the coordination sites within the metal catalyst and the lack of a directing group in the current series of substrates therefore presumably creates an open coordination site. With "neutral" Rh(I) catalyst precursors such as $[Rh(cod)Cl]_2$, it is presumed that chloride ion occupies that site. For "cationic" Rh(I) catalyst precursors such as $Rh(nbd)_2BF_4$, it is presumed that site is vacant or occupied by solvent, alkene or excess ligand. It was previously found that 2.1 mol% equivalents of ligand was the optimal amount for the directed CAHB of β,γ-unsaturated amides (**Scheme 1.6**). The directed CAHB was indeed sensitive to the number of equivalents of ligand and excess ligands lower the reactivity and selectivity of the reaction. For a substrate lacking a strong directing group (**Scheme 3.5)** varying the number of equivalents of ligands in the case of $Rh(nbd)_2BF_4$ finds little improvement with 3 equivalents and significantly diminished reactivity with 4 equivalents.





L1a (R = N(Me,Ph))
L1b (R = N(Bn,Bn))

L2a (R = N(Me,Ph))
L2b (R = OPh)

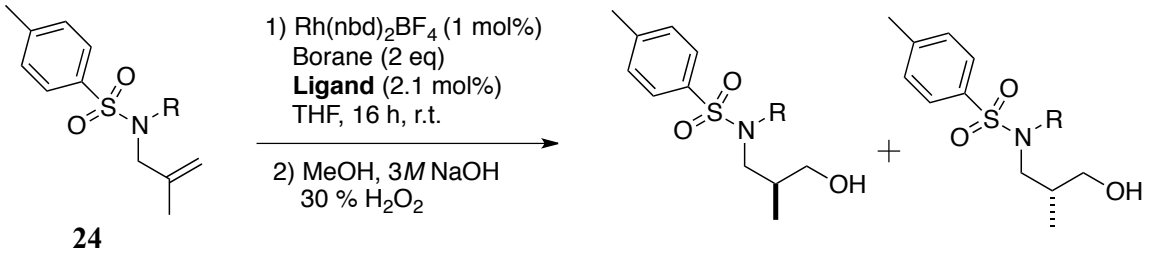
Scheme 3.5: General reaction scheme for variability in ligand equivalents for sulfonamide functionalized 1,1-disubstituted alkenes

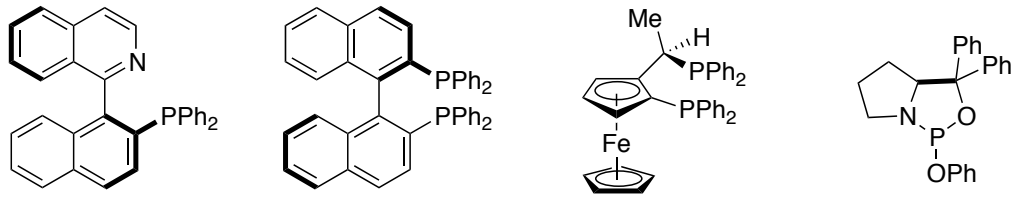
Table 17: Experimental data for equivalents of ligand required for enantioselective catalysis

Ligand	X mol %	Yield (%)	% ee
L1a	2.1	61	3
L1b	2.1	42	18
L2a	2.1	30	5
L2b	2.1	12	15
L1a	3	30	5
L1b	3	34	1
L2a	3	99	1
L2b	3	59	2
L1a	4	0	NA
L1b	4	0	NA
L2a	4	99	1
L2b	4	6	19

3.3 Other Ligands Screened

To assess the possibility that the monodentate ligands are incapable of achieving a sufficient chiral pocket without the aid of a directing group, some common commercially available bi-dentate ligands and monodentate ligand **L11** were screened against a several of the 1,1-disubstituted alkene substrates. The results obtained with sulfonamide **24** are typical (**Table 18**) and suggest that the Josiphos and **L11** scaffolds hold some promise and should be investigated further.





Quinap Binap (R,S)-JOSIPHOS **L11**

Scheme 3.6: Additional ligand exploration for cyclohexyl sulfonamide **24**, a 1,1-disubstituted alkene

Table 18: Additional ligands yields and selectivity for 1,1-disubstituted alkene **24**

Ligand	**Yield (%)**	**% ee**
Quinap	< 10	1
Binap	84	15
(R,S)-Josiphos	73	51
L11	99	51

3.4 Conclusions in the Ligand Effects in the Enantioselectivity

Comparing all the data between the different ligands it is evident that controlling the topography around the metal is better accommodated by the monodentate ligands

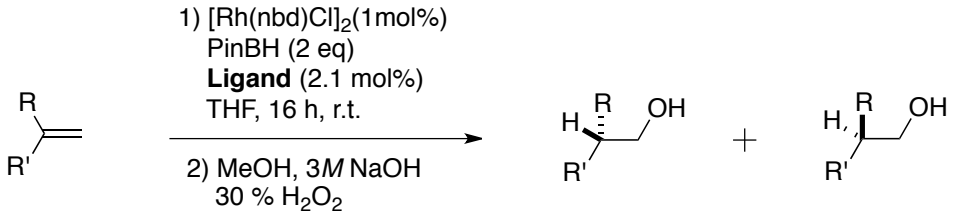
generally gave higher enantioselectivity then the commercially available bi-dentate ligands explored in this study. The best results generally being obtained with the biaryl ligands. While the study was intended to screen substrates lacking a directing group capable of two-point binding, several sulfonamides were included in the study and turned out to be among the more successful substrates. The data cannot rule out its participation as a two-point binding substrate.

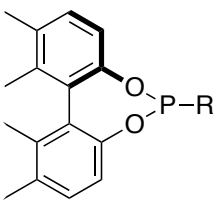
Chapter 4: Contribution of the Metal Source

Rhodium metal precursors have given the best results within the Takacs group for the directed CAHB or two-point binding substrates, although it is not the only metal being investigated for this transformation; iridium,[43] and copper[44] have also garnered some attention while palladium has thus far been principally used to effect diboration reactions.[45]

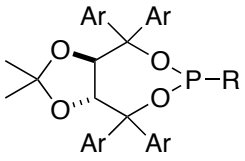
4.1 Rhodium Chloride Precursor Investigation

As discussed above, revisiting the mechanism with Wilkinson's catalyst [$Rh(PPh_3)_3Cl$] and CatBH, it is anticipated that the chloride ion remains bound to rhodium as one of the ligands. This is thought to be detrimental to the directed rhodium CAHB, because it occupies a coordination site that is needed for the two-point binding substrates. The cationic rhodium species that our group has shown to be an efficient metal precursor [$Rh(nbd)_2BF_4$] has the norbornadiene as dissociative ligands that can be either bound to the metal, displaced by the coordinated directing group or consumed via hydroboration. Having previously discussed that many of the 1,1-substrates under question do not have the strong directing group ability like the amide moiety, it then begs to question if the chloride ion could have a productive role if there was no strong directing group. To investigate this idea, a rhodium metal precursor with a chlorine ligand were explored ([$Rh(nbd)Cl]_2$) with a group of previously descried ligands, which should give a broad scope of both the backbone and the nature of the phosphorus group, and a variety of the 1,1-disubstituted substrates (**Scheme 4.1**).

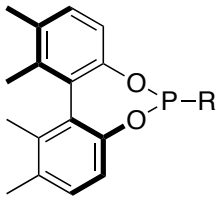




L1a (R = N(Me,Ph))
L1b (R = N(Bn,Bn))
L1c (R = OPh)



L2a (R = N(Me,Ph))
L2c (R = OPh)
L4a (R = OPh)
(Ar = (3',5'-DiMe)C_6H_3

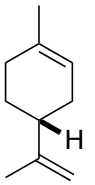


L6b (R = OBn)
L6c (R = N(Me,Ph))
L6d (R = N(Bn,Bn))
L6e (R = (S)-Bis(1-Phenylethyl)

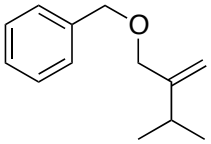
Scheme 4.1: Using the neutral Rh(I) catalyst precursor, $[Rh(nbd)Cl]_2$

Table 20 illustrates the results obtained with ($[Rh(nbd)Cl]_2$ used as the catalyst precursor. Slightly higher enantioselectivity is found for the all alkyl substrate **15** (**L1a, 52% yield, 42 ee**) compared to the cationic rhodium(I) tetrafluoroborate precursor (**L2a, 99% yield, 30 ee**). A similar small improvement was found for the benzyl ether substrate **17** (**L4a, 72% yield, 33% e**e with Rh(I)Cl and **L2c, 57% yield, 20% ee** for $Rh(I)BF_4$). Note that these best cases for each catalyst precursor require different ligands. Thus these modest improvements cannot solely be attributed to the catalyst precursor. The results obtained with the sulfonamide substrate **24** are generally, but not exclusively, showed both lower reactivity and selectivity completely across the scope of the monodentate ligands explored using the Rh(I)Cl catalyst precursor. This may be taken as evidence that the sulfonamide can act as a two-point binding substrate when an open coordination site is available.

Table 20: Selected results by substrate (Alkyl **15**; Benzyl Ethers **16**, **17**; Sulfonamide **24**) with $[Rh(nbd)Cl]_2$ metal precursor

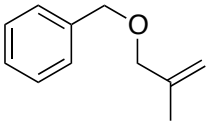


15



17

Ligand	Yield (%)	% ee	Ligand	Yield (%)	% ee
L1a	52	46	L1c	72	5
L1b	22	36	L2b	57	17
L2a	99	24	L4a	72	33



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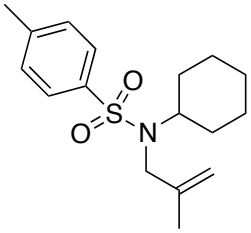
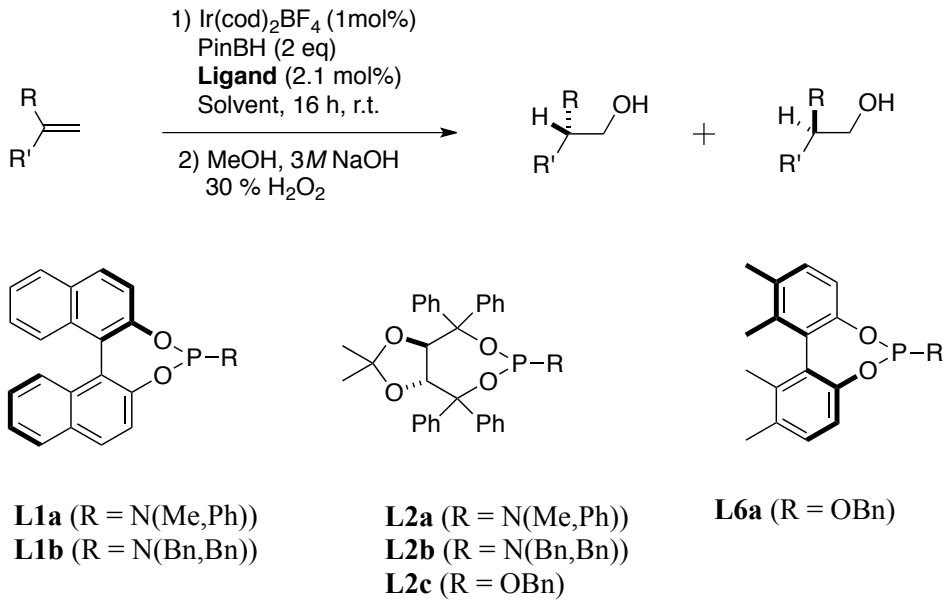


24

Ligand	Yield (%)	% ee	Ligand	Yield (%)	% ee
L1a	55	10	L1a	5	9
L1b	40	9	L1b	NR	NA
L1d	88	1	L2a	13	9
L2b	47	19	L2c	37	5
L6b	95	9	L6b	99	11
L6c	15	23	L6c	14	5
L6d	36	7	L6d	20	31
L6e	60	1	L6e	66	11

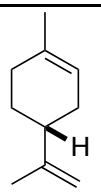
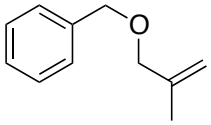
4.2 Iridium Metal Precursor Investigation

Iridium shares many characteristics with rhodium and has also been employed, albeit much less frequently, for the catalytic hydroboration of alkenes. Iridium was also part of the initial investigation of this reaction by Evans *et. al.* and more recently been shown to be successful with α-substituted vinyl arenes by Mazet *et. al*.[32] Just as with the rhodium catalyst precursor, iridium can be commercially purchased as the neutral chloride or as the cationic tetrafluoroborate salt. Both precursors were screened with substrates **15** and **16**. Neutral iridium chloride was for all intents and purposes completely non-reactive, giving only trace amounts of product even for the most successful ligands that was employed for the rhodium equivalent. The complementary cationic iridium metal precursor, $Ir(cod)_2BF_4$, demonstrated greater reactivity then the neutral iridium chloride, though its enantioselectivity was very low. The most encouraging results were obtained with the alkyl substrate **15** (**L6b, 37% yield, 33% ee**).



Scheme 4.2: Representative cationic iridium tetrafluoroborate [$Ir(cod)_2BF_4$] metal precursor reaction conditions

Table 21: Selected alkenes for the $Ir(cod)_2BF_4$ catalyzed hydroboration

 **15**			 **16**		
Ligand	**Yield (%)**	**% ee**	**Ligand**	**Yield (%)**	**% ee**
L1a	NR	NA	L1a	NR	NA
L1b	18	25	L1b	26	5
L2a	25	13	L2a	81	13
L2b	54	9	L2b	86	13
L2c	7	21	L2c	81	5
L6b	37	33	L6b	73	5

Both iridium metal precursors exhibited lower yields and selectivity's then their rhodium counterparts throughout the substrate scope. The best results obtained with the iridium metals are with alkyl substrate **15** (**L6b, 37% yield, 33% ee**).

4.3 Conclusions in the Effect of the Transition Metal

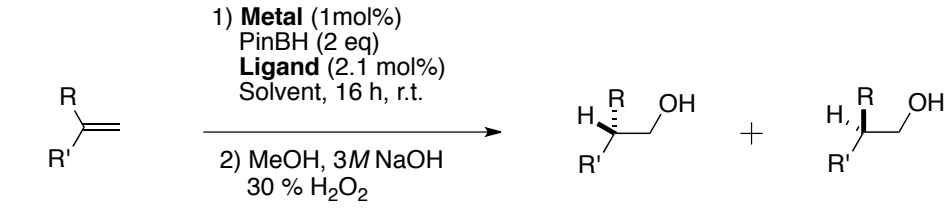
Even though other metal sources are available to achieve this catalytic transformation, the cationic rhodium(I) tetrafluoroborate, $Rh(nbd)_2BF_4$, was found to be the most general catalyst precursor for the enantioselective catalyzed hydroboration of the series of 1,1-disubstituted alkenes studied in this thesis. Modest success was achieved

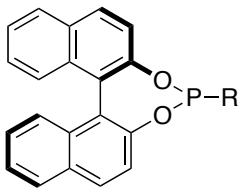
with the neutral rhodium(I) chloride, $[Rh(nbd)Cl]_2$, although its reactivity and selectivity throughout the range of monodentate ligands utilized in this study are lower on average. The most encouraging results obtained using it was with alkyl substrate **15** (**52% yield, 42% ee**). In comparison, the two iridium(I) catalyst precursors were relatively less reactive to unreactive.

Chapter 5: Concluding Remarks

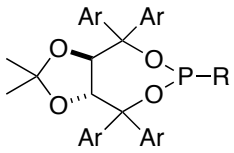
The catalyzed enantioselective hydroboration reaction is currently limited in to certain vinyl arenes and certain two-point binding substrates. To expand its scope, the reactions of several 1,1-disubstitued alkenes, including simple alkyl derivatives (e.g., **14** and **15**), benzyl ethers (e.g., **16** and **17**), allylic acetal **20**, silyl enol ether **21** and the more complex sulfonamide substrates (e.g., **24** and **25**), were investigated in this thesis. The investigations proceeded by exploring the reaction variables thought to be most important in the catalytic cycle that could be independently controlled; these included the ligands, catalyst precursor and to a lesser extent the solvent. To assess the viability of the substrates two classes of monodentate ligands were primarily investigated utilizing a combinatorial chemistry approach to examine these ligand scaffolds. The TADDOL-derived carbon centered chiral ligands and biaryl-derived axial chiral ligands. Alongside studying the different ligand topographies, the electronic effect of the phosphorus center (i.e., comparing phosphite and phosphoramidite derivatives) was also probed. Finally, the transition metal source for the catalyst complex was studied with differing starting catalyst precursors, including cationic rhodium(I) tetrafluoroborate, neutral rhodium(I) chloride and their iridium counterparts.

The 1,1-disubstituted alkenes studied within this thesis have differing degrees of reactivity and enantioselectivity with the most promising substrates having the most polar functional group, sulfonamide's **24** and **25**. A summary of the best reactivity and selectivity for the studied substrates are listed in **Table 21**.

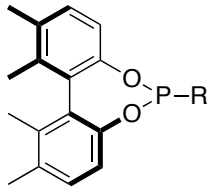




L1a (R = N(Me,Ph))
L1b (R = N(Bn,Bn))
L1d (R = OBn)



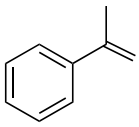
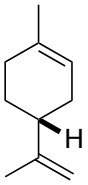
L2a (R = N(Me,Ph))
L2b (R = N(Bn,Bn))
L2c (R = OPh)
L2d (R = OBn)
L4a (R = OPh)
(Ar = (3',5'-DiMe)C_6H_3

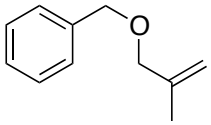


L6a (R = OPh)
L6c (R = N(Me,Ph))
L6e (R = N(S)-Bis(1-Phenylethyl)
L6f (R = N(R)-Bis(1-Phenylethyl)

Figure 5.1: General reaction scheme for enantioselective hydroboration of 1,1-disubstituted alkenes

Table 22: Most promising results for enantioselective hydroboration of various 1,1-disubstituted alkenes studied in this report

 **14**				 **15**			
Metal	**L**	**Yield (%)**	**% ee**	**Metal**	**L**	**Yield (%)**	**% ee**
$Rh(nbd)_2BF_4$	L2a	97	48	$Rh(nbd)_2BF_4$	L1d	30	37
$[Rh(cod)Cl]_2$	L2b	32	35	$[Rh(cod)Cl]_2$	L1a	52	46



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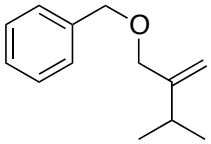
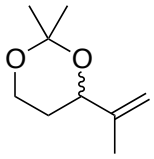


17

Metal	L	Yield (%)	% ee	Metal	L	Yield (%)	% ee
$Rh(nbd)_2BF_4$	L2c	99	25	$Rh(nbd)_2BF_4$	L2c	57	20
$[Rh(cod)Cl]_2$	L6c	15	23	$[Rh(cod)Cl]_2$	L4a	72	33



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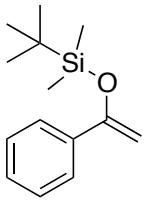
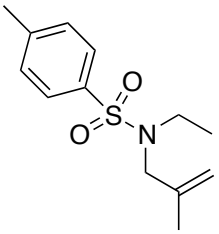
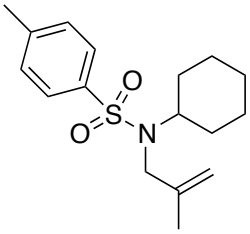


20

Metal	L	Yield (%)	% de	Metal	L	Yield (%)	% ee
$Rh(nbd)_2BF_4$	L1b	21	20	$Rh(nbd)_2BF_4$	L1b	22	35
$Rh(nbd)_2BF_4$	L2b	76	6	$Rh(nbd)_2BF_4$	L2d	64	37



23



24

Metal	L	Yield (%)*	% ee	Metal	L	Yield (%)*	% ee
$Rh(nbd)_2BF_4$	L6c	99	53	$Rh(nbd)_2BF_4$	L6a	77	57
$Rh(nbd)_2BF_4$	L6e	99	55	$Rh(nbd)_2BF_4$	L6f	91	67.7

*Results in toluene

For each individual functionalized 1,1-disubstituted alkene independent reaction conditions are necessary to achieve the highest levels of enantioselectivity and reactivity. Nonetheless, the monodentate ligands featured in this study were generally more effective than Quinap, BINAP and Josiphos, the bidentate ligands reported to be the most effective ligands for the reactions of vinyl arene substrates. The rhodium(I) catalyst precursors demonstrated more general utility then their iridium counterparts. Overall, the results of these studies changing the ligand, catalyst precursor and 1,1-disubstituted alkene substrate gave few useful trends for further optimizing the catalyst.

The enantioselective hydroboration of sulfonamide derivative **24** using the biaryl monodentate derived ligand ((S)-(Biphep-N-(R)-(Bis-1-Phenylethyl)) and cationic rhodium(I) tetrafluoroborate, $Rh(nbd)_2BF_4$, achieved up to 91% yield and 67.7% ee. While this is still only moderate and not up to the typical 90% ee benchmark, it is still comparable to the best examples in the literature for similar 1,1-disubstituted alkenes using asymmetric catalysis or stoichiometric chiral borane reagents.

Chapter 6: Experimental Data

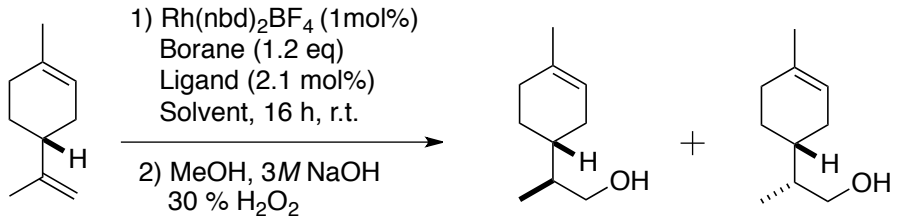
General Procedures. Air-sensitive reactions were carried out under an atmosphere of nitrogen. All catalytic hydroboration reactions were assembled inside a nitrogen-filled glove box then brought outside the glove box to be stirred. Tetrahydrofuran was freshly distilled from benzophenone and sodium metal. Dichloromethane was freshly distilled from calcium hydride. When indicated, solvents were degassed by three freeze pump thaw cycles under vacuum. Substrates synthesized by flash chromatography were done using EMD Silica Gel 60 Geduran®. Thin layer chromatography analysis was performed on Analtech Silica Gel HLF (0.25 mm) precoated analytical plates and visualized using short wavelength UV light, iodine stain or vanillin stain. HPLC analysis was performed using ISCO model 2360 HPLC and Chiral Technologies, Inc. chiral HPLC columns (chiralpak AS-H, chiralpak AD, chiralpak OD, chiralpak IC or chiralpak IB). Data were recorded and analyzed with ChromPerfect chromatography software (version 5.1.0). Chiral capillary GC analysis was performed on Shimadzu GC 14APFSC with J&W Scientific 30.om x 0.25 mm ID Cyclosil β column, or Varian 25.0 x 0.25 mm CP-Chiralsil Dex CB column. NMR spectra were recorded on 300, 400 or 600 MHz Bruker Avance NMR spectrometers-using residue $CHCl_3$ (δ 7.27 ppm ^{1}H and δ 77.0 ppm ^{13}C) for reference. Peaks are reported as s (singlet), d (doublet), t (triplet), q (quartet), dd (doublet of doublets), or m (unresolved multiplet) or combinations thereof.

Representative Procedure for the Enantioselective Catalyzed Hydroboration

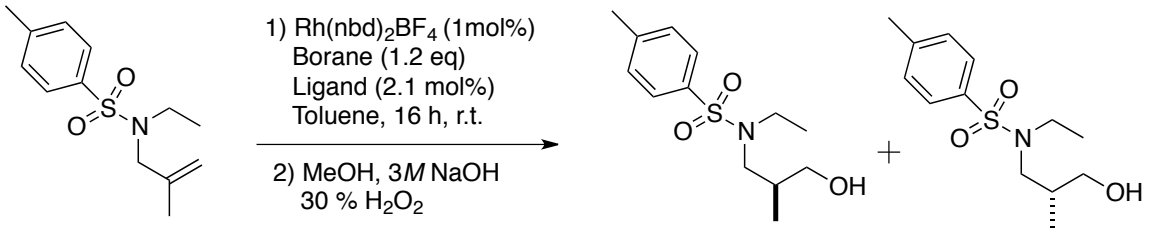
In a nitrogen filled glove box, a stock solution of $Rh(nbd)_2BF_4$ (1 mol%) in 1.0 ml DCM was prepared. Then a 0.1 ml aliquot of the metal containing solution was transferred to individual 8.0 ml vials to which several glass stirring beads had previously been added. These vials were then dried under vacuum (3 times) so all the DCM had evaporated and the glass beads could roll freely inside the vial. The residual $Rh(nbd)_2BF_4$ was then diluted with 0.1 ml of the appropriate solvent. In separate 8.0 ml vials a stock solution of ligand (2.1 mol %) in the corresponding solvent (1.2 ml) was prepared and 0.1 ml aliquots were added to the vial containing the $Rh(nbd)_2BF_4$ solution. These $Rh(nbd)_2BF_4$ and ligand solutions were permitted to stir for approximately 1 hr to permit the metal-ligand complex to form. To this metal-ligand complex a solution of the substrate under investigation (0.4 mmol) was added; the resulting mixture was stirred for approximately 15 min. The borane source (varying equivalents) diluted in the proper solvent was then added to this solution and the vials were brought outside the glovebox to be stirred for the corresponding time in a circular shaker. After reaction, the reaction mixture was quenched by the addition of MeOH (0.6 ml), 3 *M* NaOH (0.8 ml) and 30% H_2O_2 (0.1 ml) (added in the stated order), then stirred for a minimum of 30 min. The reactions were extracted with DCM (3X 2ml) and the combined organics dried and concentrated in vacuo. The yield was determined by NMR using an internal standard (mesitylene resonance at δ 6.8 ppm).

Note: Due to the preliminary nature of the investigations described in this study, many of the reaction products are known compounds. A few are unknown in the literature but

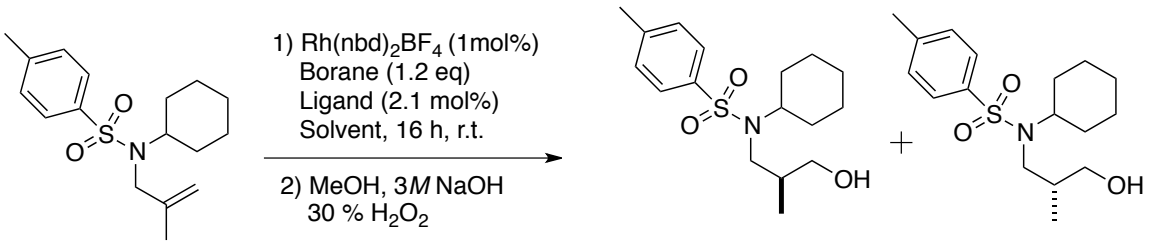
easily identified by their ^{1}H and ^{13}C NMR spectra; these were not fully characterized for elemental composition as would be required for journal publication.



Preparation of 2-((R)-4-methylcyclohex-3-en-1-yl)propan-1-ol. Using the general procedure, the enantioselective catalyzed hydroboration of (R)-(+)-limonene (136 mg, 0.99 mmol) affords a mixture of diastereomers as colorless oil. The spectra are in congruence with reported literature information.[46] Spectral data: ^{1}H-NMR (400 MHz, $CDCl_3$), δ 5.39-5.37 (m, 1H), δ 3.67-3.62 (dd, J = 10.6, 5.1 Hz, 1H), δ 3.52-3.47 (dd, J = 10.6, 4 Hz, 1H), δ 2.02-1.91 (m, 2H), δ 1.87-1.65 (m, 2H), δ 1.62 (s, 3H), δ 1.60-1.54 (m, 2H), δ 1.48 (s, 1H), δ 1.36-1.30 (m, 1H), δ 0.95-0.93 (d, J = 6.5 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$), δ 133.9, δ120.6, δ 66.4, δ 40.2, δ 35.2, δ 30.7, δ 27.7, δ 27.2, δ 23.4, δ 13.2.

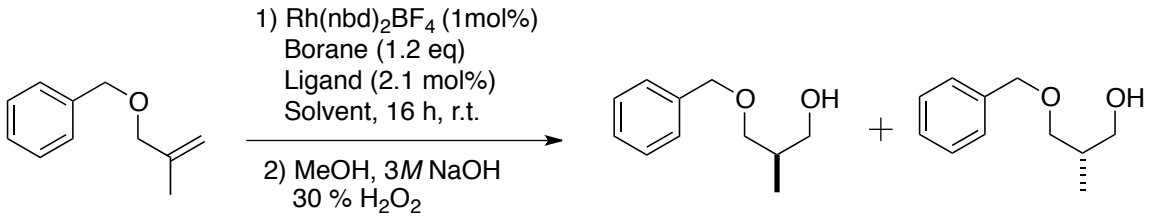


Preparation of *N*-ethyl-*N*-(3-hydroxy-2-methylpropyl)-methylbenzenesulfonamide. Using the general procedure, the enantioselective catalyzed hydroboration of *N*-ethyl-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (101 mg, 0.4 mmol) affords the title compound as a colorless oil oil. Spectral data: ^{1}H-NMR (400 MHz, $CDCl_3$), δ 7.73-7.31 (d, J = 8.4 Hz, 2H),), δ 7.32-7.30 (d, J = 8.4 Hz, 2H)**,** δ 3.88 (m, 1H), δ 3.52 (m, 1H), δ 3.33 (m, 2H), δ 3.16 (m, 1H), δ 2.73 (dd, J = 8.7, 5.5 Hz, 1H), δ 2.46 (s, 3H), δ 1.90 (m, 1H), δ 1.10 (t, J = 7.5 Hz, 3H), δ 0.98 (d, J = 6.8 Hz, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$), δ 143.8, δ 136.7, δ 130.0, δ 127.3, δ 63.7, δ 50.7, δ 44.0, δ 35.0, δ 21.8, δ 14.6, δ 14.0.

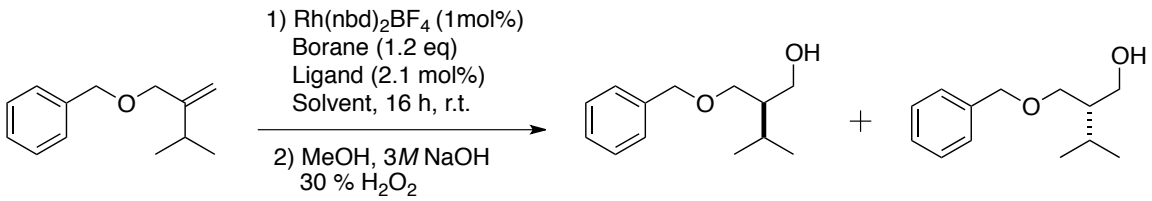


Preparation of *N*-cyclohexyl-*N*-(3-hydroxy-2-methylpropyl)-4-methylbenzenesulfonamide. Using the general procedure, enantioselective catalyzed hydroboration of *N*-cyclohexyl-4-methyl-*N*-(2-methylallyl)benzenesulfonamide (123 mg, 0.4 mmol) affords the title compound as a colorless oil: R_f = 0.5 (50 % EtOAc/Hex) shows a single spot. Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$), δ 7.69-7.67 (d, J = 8.4

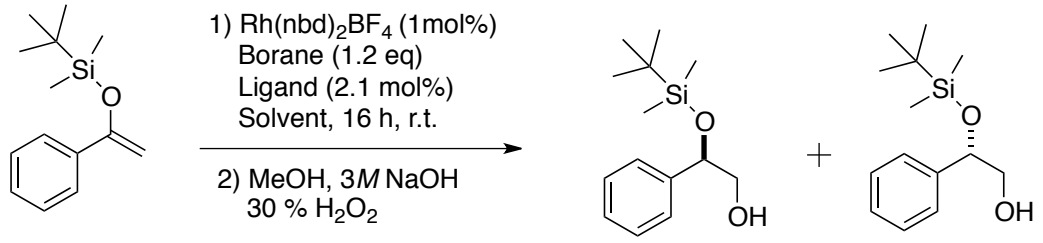
Hz, 2H)**,**), δ 7.29-7.27 (d, J = 8.4 Hz, 2H)**,** δ 3.97-3.93 (dd, J = 11.6, 3.5 Hz, 1H), δ 3.59-3.52 (m, 2H), δ 3.36-3.28 (dd, J = 4.7, 10.5 Hz, 1H), δ 2.88-2.79 (dd, J = 9.4, 5.5 Hz, 1H), δ 2.62 (m, 1H), δ 2.42 (s, 3H), δ 1.98 (m, 1H), δ 1.92-1.0 (m, 10H), δ 0.99-0.96 (d, J = 6.7 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ 143.3, δ 138, δ 129.8, δ 126.6, δ 63.5, δ 58.4, δ 46.8, δ 36.3, δ 33.9, δ 30.6, δ 26.1, δ 25.3, δ 21.5, δ 14.7.



Preparation of 3-(benzyloxy)-2-methylpropan-1-ol. Using the general procedure, enantioselective catalyzed hydroboration of (((2-methylallyl)oxy)methyl)benzene (97 mg, 0.6 mmol) affords the title compound as a colorless oil. Its spectra are in congruence with reported literature information.[47] Spectral data: ^{1}H-NMR (400 MHz, $CDCl_3$), δ 7.23-7.36 (m, 5H)**,** δ 4.50 (s, 2H), δ 3.60 (dd, J = 10.8, 4.9 Hz, 1H), δ 3.57 (dd, J = 10.8, 6.3 Hz, 1H), δ 3.51 (dd, J = 9.1, 7.9 Hz, 1H), δ 3.42 (dd, J = 9.1, 7.8 Hz, 1H), δ 2.70 (brs, 1H), δ 1.98-2.10 (m, 1H), δ 0.89 (d, J = 7.3 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ 138.0, δ 128.4, δ 127.8, δ 127.6, δ 75.3, δ 73.4, δ 67.7, δ 35.5, δ 13.4.



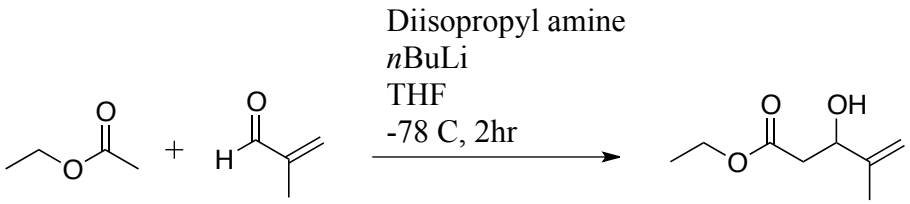
Preparation of 2-((benzyloxy)methyl)-3-methylbutan-1-ol. Using the general procedure, enantioselective catalyzed hydroboration of ((3-methyl-2-methylenebutoxy)methyl)benzene) (91.0 mg, 0.48 mmol) affords the title compound as a colorless oil. Its spectra are in congruence with reported literature information.[48] Spectral data: ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.38-7.30 (m, 5H), δ 4.53 (d, J = 11.9 Hz, 1H), δ 4.48 (d, J = 11.9 Hz, 1H), δ 3.80-3.72 (m, 2H). δ 3.71 (dd, J = 4.0, 9.2 Hz, 1H), δ 3.58 (t, J = 8.5, 1H), δ 1.80-1.70 (m, 1H), δ 1.67-1.59 (m, 1H), δ 0.91 (d, J = 7.0, 3H), δ 0.89 (d, J = 7.0, 3H) ^{13}C-NMR (100 MHz, $CDCl_3$): δ 138.6, δ 128.3, δ 127.8, 127.5, δ 73.5, 72.7, δ 64.7, δ 46.4, δ 26.5, δ 20.2, δ 20.1.



Preparation of 2-((*tert*-butyldimethylsilyl)oxy)-2-phenylethanol. Using the general procedure, enantioselective catalyzed hydroboration of *tert*-butyldimethyl((1-phenylvinyl)oxy)silane (143 mg, 0.4 mmol) affords the title compound as a clear oil. Spectral data: ^{1}H-NMR ($CDCl_3$, 400 MHz): δ 7.3-7.2 (m, 5H), δ 4.8-4.7 (dd, J = 7.0, 4.7 Hz, 1H), δ 3.6-3.5 (m, 2H), δ 2.0 (dd, J = 7.7, 5.3 Hz,1H), δ 0.9 (s, 9H), δ 0.09 (s, 3H), δ -

0.07 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 142.3, δ 128.2, δ 127.6, δ 126.2, δ 75.8, δ 68.9, δ 25.8, δ 18.2, δ -4.5, δ -4.9.

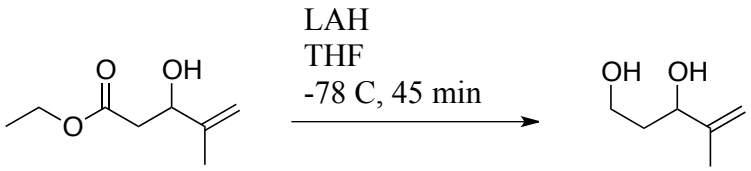
Synthesis of Dimethyl Acetal (19)



28

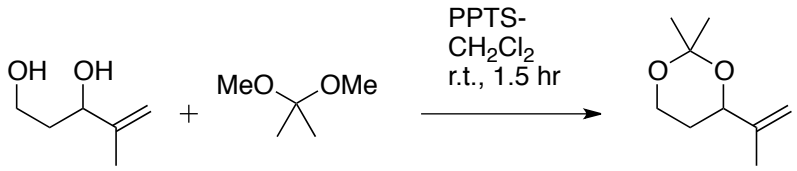
Preparation of ethyl 3-hydroxy-4-methylpent-4-enoate (28). (28). To a cooled (-78 °C) solution of diisopropylamine (5.8 ml, 41.3 mmol) in dry THF (130 ml) was dropwise added *n*BuLi (17 ml, 42.5 mmol, 2.5 M,). The resulting solution was stirred (30 min) and then ethyl acetate (4.05 ml, 41.2 mmol) was slowly added at -78 °C. The resulting mixture was stirred for another 30 min and then a solution of methacrylaldehyde in THF (1.7 ml, 20.6 mmol, 3.0 M) was dropwise added over 15 min. The resulting mixture was stirred at -78 °C (2 h) and then brought to room temperature and quenched by the addition of saturated aqueous NH_4Cl (100 ml). The resulting biphasic mixture was extracted with ether (3 x 75 ml), dried over anhydrous magnesium sulfate and the volatiles removed under vacuum. The crude residue was purified via column chromatography (25% EtOAc / 75% Hexanes) to yield the title compound (**28**) as yellow oil (3.01 g, 92% yield). Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$), δ 4.99 (s, 1H)**,** δ 4.84 (s, 1H), δ 4.27 (t, J = 5.3 Hz, 1H), δ 3.82-3.77 (q, J = 7.1 Hz, 2H), δ 3.19 (brs, 1H), δ 1.80-1.73 (m, 2H), δ 1.71 (s, 3H), δ 1.26-1.21 (t, J = 7.1 Hz, 2H), δ 1.92-1.0 (m, 10H), δ

0.99-0.96 (t, J = 7.1 Hz, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ 171.3, δ 147.3, δ 110.5, δ 75.3, δ 60.4, δ 36.5, δ 18.1, δ 14.1.



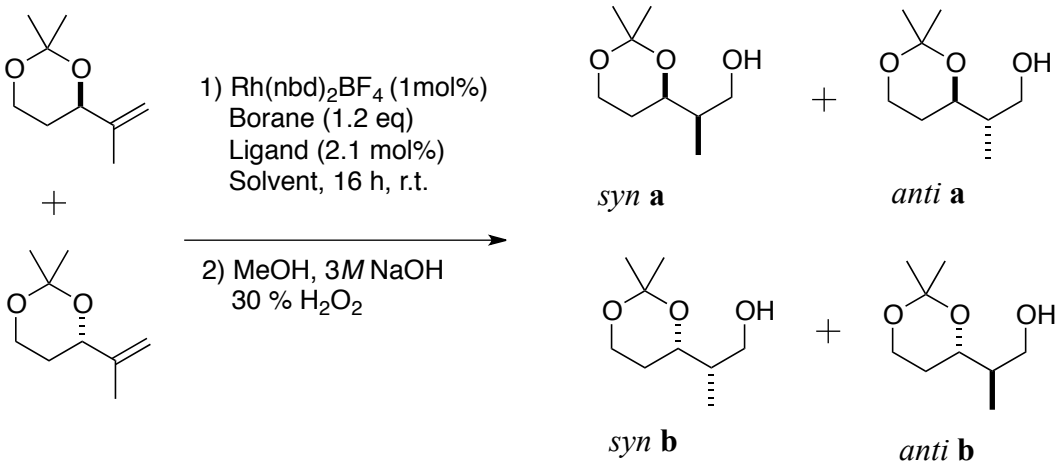
28 **29**

Preparation of 4-methylpent-4-ene-1,3-diol (29). LAH (0.88 g, 23.2 mmol) is diluted in dried THF (50 ml), and the suspension was cooled to (-78 °C). Ester **28** (2.0 g, 12.6 mmol) is diluted in dry THF (10 ml) and added dropwise to the cold (-78 °C) mixture over the course of 10 min. The resulting mixture was kept at -78 °C for 45 min before being brought to room temperature and quenched by the careful addition sequentially of H_2O (5 ml), NaOH (10 ml, 3 M) then again with H_2O (40 ml). The resulting suspension was stirred (approximately 2 h); the mixture turns milky white. The mixture was then extracted (4 x 50 mL of EtOAc) and the combined organics dried over magnesium sulfate. The volatiles removed via rotovap and the reisdue purified via flash chromatography (30% EtOAc/ 70% Hexanes) to yield the title compound **29** as a clear oil (0.9 g, 66.8% yield). Spectral data: ^{1}H-NMR (400 MHz, $CDCl_3$), δ 5.04 (s, 1H)**,** δ 4.89 (s, 1H), δ 4.34-4.31 (t, J = 6 Hz, 1H), δ 3.90-3.80 (m, 2H), δ 2.54 (brs, 2H), δ 1.85-1.81 (m, 2H), δ 1.75 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$), δ 147.3, δ 110.6, δ 75.6, δ 61.4, δ 36.5, δ 18.2.



29 **19**

Preparation of 2,2-dimethyl-4-(prop-1-en-2-yl)-1,3-dioxane (19). To a solution of dry DCM (40 ml) and diol (**29**) (500 mg, 4.3 mmol) was added 2,2-dimethoxypropane (13.2 ml, 107.6 mmol) and PPTS (54.0 mg 0.215 mmol, 5 mol%). The resulting mixture was stirred for 1.5 h and then quenched by the addition of saturated aqueous $NaHCO_3$ (40 ml). The resulting biphasic mixture was extracted with EtOAc (3 x 25 mL), the combined organics washed with brine (50 mL) and then dried (anhydrous magnesium sulfate) and concentrated. The crude residue was purified via flash chromatography (50% EtOAc / 50% Hexanes) to yield the title compound **20** (420 mg, 84.2% yield) as a colorless oil. Spectral data: ^{1}H-NMR (300 MHz, $CDCl_3$), δ 5.02 (s, 1H)**,** δ 4.87 (s, 1H), δ 4.32-4.28 (dd, J = 11.89, 2.35 Hz, 1H), δ 4.08-3.99 (td, J = 11.9, 2.77 Hz, 1H), δ 3.91-3.85 (ddd, J = 11.67, 5.48, 1.69 Hz, 1H), δ 1.76 (s, 3H), δ 1.50 (s, 3H), δ 1.44 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$), δ 145.4, δ 110.9, δ 98.4, δ 72.2, δ 59.9, δ 30.0, δ 29.9, δ 19.2, δ 18.3.

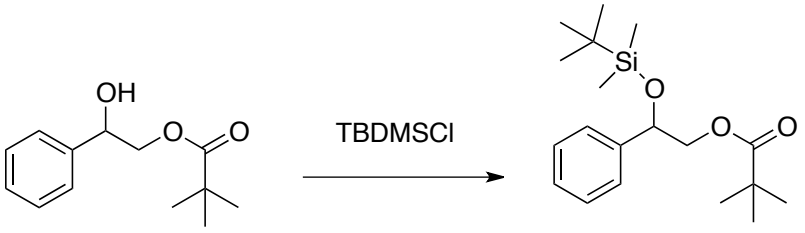


Preparation of 2-(2,2-dimethyl-1,3-dioxan-4-yl)propan-1-ol. Using the general procedure described above, enantioselective catalyzed hydroboration of 2,2-dimethyl-4-(prop-1-en-2-yl)-1,3-dioxane (125 mg, 0.8 mmol) affords a mixture of diastereomers as a colorless oil. The spectra are in congruence with reported literature information.[49] Spectral data: ^{1}H NMR (600 MHz, $CDCl_3$) δ 4.16 (ddd, J = 12.0, 4.0, 2.5 Hz, 1H), δ 4.02-3.98 (dt, J = 11.5, 2.5 Hz, 2H), δ 3.92-3.87 (ddd, J = 11.5, 5.5, 2.5 Hz, 2H), δ 3.85-3.82 (ddd, J = 11.5, 5.5, 2.5 Hz,1H), δ 3.75-3.72 (ddd, J = 11.5, 5.5, 2.5 Hz, 1H), δ 3.64 (m, 2H), δ 3.01 (brs, 1H), δ 2.75 (brs, 1H), δ 1.92-1.89 (m, 1H), δ 1.79-1.67 (m, 3H), δ 1.53 (s, 3H), δ 1.50 (s, 3H), δ 1.42 (s, 3H), δ 1.41 (s, 3H), δ 0.94 (d, J = 7.0 Hz, 3H), δ 0.97 (d, J = 7.0Hz, 3H). ^{13}C NMR (150 MHz, $CDCl_3$) δ 98.5, 98.37, δ 77.3, 77.1, δ 76.8, 75.1, δ 72.5, δ 67.6, δ 65.6, δ 60.4, δ 60.0, 59.9, δ 40.46, δ 38.97, δ 30.0, 29.9, δ 29.5, δ 26.5, δ 21.0, δ 19.3, 19.1, δ 14.2, δ 12.8, 11.6.

Determination of Regio-Chemistry for Silyl Alcohol (20)

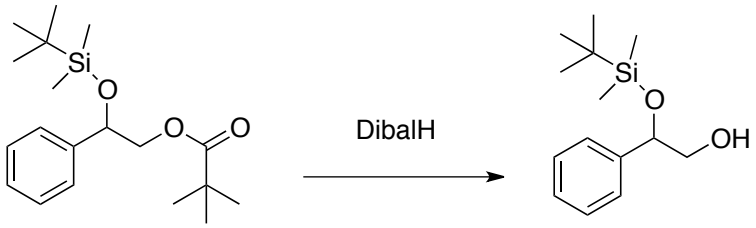
30 **31**

Preparation of 2-hydroxy-2-phenylethyl pivalate (31). To a solution of dry DCM and 1-phenylethane-1,2-diol (**30**) (1.28 g, 8.75 mmol) is added pyridine (9 ml, 111 mmol). The resulting solution was cooled (0 ^{o}C, 10 min) after which pivaloyl chloride (1.07 ml, 8.75 mmol) was added dropwise over 10 min. The resulting mixture was then warmed to room temperature and stirred for an additional 5 h before the volatiles were evaporated via rotovap and the crude mixture diluted with toluene to azeotropically remove the pyridine; repeat the latter 3 times. The residue was purified by flash chromatography (25% EtOAc/75% Hexanes) to yield **31** (1.4 g, 74%) as a clear oil: Spectral data: ^{1}H-NMR ($CDCl_3$, 300 MHz): δ 7.2-7.4 (m, 5H), δ 4.9 (dd, J = 7.7, 3.8 Hz, 1H), δ 4.25 (dd, J = 11.5, 3.8 Hz, 1H), δ 4.18 (dd, J = 11.5, 7.7 Hz, 1H), δ 2.62 (brs, 1H), δ 1.19 (s, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$): δ 178.9, δ 140.4, δ 128.2, δ 121.7, δ 126.4, δ 72.8, δ 69.4, δ 27.5



31 **32**

Preparation of 2-((tert-butyldimethylsilyl)oxy)-2-phenylethyl pivalate (32). To a solution of imidazole (149.7 mg, 2.2 mmol) in DMF (2 ml) was slowly added **31** (250 mg, 1.1 mmol). A solution of tert-butyldimethylsilyl chloride (331.5 mg, 2.2 mmol) in DMF (2 ml) was then added drop wise over 10 minutes. The mixture was stirred at room temperature overnight and then diluted with water (10 ml) and extracted with EtOAc (3 x 10 ml). The combined organics were dried over anhydrous magnesium sulfate and concentrated in vacuo. The resulting crude residue was purified via flash chromatography (10% EtOAc/ 90% Hexanes) to yield the title compound **32** as a colorless oil (292mg, 79%) used directly in the next reaction.



32 **33**

Preparation of 2-((tert-butyldimethylsilyl)oxy)-2-phenylethanol (33). To a cooled (-78 ^{o}C) solution of **32** (300 mg, 0.79 mmol) in dry DCM (10ml) was slowly added DibalH (1.0 M in THF, 1.1ml). After 10 minutes of stirring at -78 ^{o}C the reaction mixture was brought 0 ^{o}C and then a saturated solution of aqueous sodium sulfate decahydrate (6 ml) was slowly added. The solution was then brought to room temperature and stirred for 1 hour before being further diluted with water and extracted with EtOAc (3 x 10 ml). The combined organics were washed with brine, dried over magnesium sulfate and concentrated in vacuo. The residue was purified by flash chromatography (10% EtOAc/

90% Hexanes) to yield the title compound **20** as a colorless oil (179.5 mg, 90%): Spectral data: ^{1}H-NMR ($CDCl_3$), 400 MHz) δ 7.3-7.2 (m, 5H), δ 4.8-4.7 (dd, J = 7.0, 4.7 Hz, 1H), δ 3.6-3.5 (m, 2H), δ 2.0 (dd, J = 7.7, 5.3 Hz,1H), δ 0.9 (s, 9H), δ 0.09 (s, 3H), δ -0.07 (s, 3H). ^{13}C-NMR (100 MHz, $CDCl_3$): δ 142.3, δ 128.2, δ 127.6, δ 126.2, δ 75.8, δ 68.9, δ 25.8, δ 18.2, δ -4.5, δ -4.9.This compound was used as a standard to identify a byproduct formed in the enantioselective hydroboration of silyl enol ether **20**.

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