REACTIVITY AND STEREOCONTROL OF BOROHYDRIDE REDUCTIONS MEDIATED BY DIHYDROGEN BONDING AND THE UTILITY OF CHIRAL LITHIUM AMINOBOROHYDRIDES AS ASYMMETRIC REDUCING AGENTS

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A DISSERTATION

Submitted to
Michigan State University
in partial fulfillment of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

Department of Chemistry

1999

ABSTRACT

REACTIVITY AND STEREOCONTROL OF BOROHYDRIDE REDUCTIONS MEDIATED BY DIHYDROGEN BONDING AND THE UTILITY OF CHIRAL LITHIUM AMINOBOROHYDRIDES AS ASYMMETRIC REDUCING AGENTS

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The effects of dihydrogen bonding were probed to gain an understanding of how this unconventional type of hydrogen bond influence the reactivity and stereocontrol of borohydride reductions. Studies of the reductions using AM1 semiempirical calculations, FTIR, NMR, gas chromatography, and liquid chromatography provided detailed information of rates and stereochemistry of the reduction products. The results of this study showed that hydrogen bonding between a hydroxyl site and a borohydride ion can be exploited to direct the delivery of hydride in ketone reductions. Reductions of 2-hydroxycycloalkanones with tetrabutylammonium borohydride in non hydrogen bonding solvents such as dichloromethane and ortho dichlorobenzene takes place > 100 times faster than reduction of the corresponding simple cycloalkanones, and yield predominately the trans diol. Strong hydrogen

bonding reagents inhibit the substrate-BH_4^- interaction, causing a decrease in rate and stereoselectivity. These results appear to be the first recognized examples of reactivity control via hydridic to protonic dihydrogen bonds.

A second aspect of this dissertation involves a study of lithium aminoborohydrides as potential reagents for asymmetric reduction of ketones. Lithium aminoborohydrides can be conveniently synthesized from any primary or secondary amine. Alkylamine groups may be introduced sequentially to provide wide structural variances thus allowing control of the steric and electronic environments of these reagents. This feature makes lithium aminoborohydrides potential candidates for asymmetric reducing agents. However, the lack of conformational rigidity of these chiral reagents in solution afforded only low to moderate asymmetric induction when used to reduce acetophenone. The details of this study will be presented in chapter 4 of this dissertation.

ACKNOWLEDGEMENTS

The author wishes to thank Mrs. Jackie Kellyman and The Dow Chemical Company for providing me the wonderful opportunity to pursue this Ph.D. degree. The author also wishes to express sincere thanks to Professor James Jackson for graciously receiving me into his research group, for his guidance, and dedication as the major advisor of this work. To his wife Mary, the author wishes to express an immeasurable amount of appreciation for her steadfast love, support, and priceless encouragement especially through some of the rough times. Finally, the author gives thanks to God for His grace and sustaining Power through out this graduate school process.

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INTRODUCTION

The reactivity and stereochemistry in borohydride reactions can be dramatically influenced by a relatively new phenomenon known as dihydrogen bonding. For instance, a dihydrogen bonding interaction between a hydroxyl site and a borohydride ion can be exploited to direct the delivery of hydride in ketone reductions. Reduction of α-hydroxy cycloalkanones in non-hydrogen-bonding solvents such as dichloromethane and o-dichloro-benzene takes place > 100 times faster than reduction of the simple ketone, and yields predominantly the trans diol product. Infrared studies verify that stereocontrol and rate enhancement are caused by the directing effect of the -OH group via dihydrogen bonding with BH_4^-, as opposed to reaction of the -OH with borohydride followed by intramolecular carbonyl reduction in a covalent $ROBH_3$ complex. AM1 semiempirical calculations agree that both pre-complexes and transition structures favor hydride delivery to the -OH substituted face of the substrate. These results appear to be the first recognized example of reactivity control via hydridic to protonic dihydrogen bonding.

The research described in this dissertation uses spectroscopic, chromatographic, and theoretical calculation studies to demonstrate the hydridic to protonic interaction of BH_4^- with -OH and to show that this interaction enhances reaction rate and directs the hydride stereoselectively during ketone reduction.

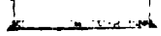
Since the concept of dihydrogen bonding has only been recently described, a brief literature review of this unconventional type of hydrogen bonding will be given in chapter 1 as well as a review of substituent-directed stereoselective reduction.

1.1 Dihydrogen Bonding - A Literature Review

Conventional hydrogen bonds are formed between a proton donor, such as an OH or NH group, and a proton acceptor, such as an oxygen or nitrogen lone pair[1] which acts as a weak base component. Metal atoms in complexes[2,3,4,5,6] and π-bonds[7] have also been shown to act as weak proton acceptors.

A wide variety of element-hydrogen (E-H) sigma bonds (E = transition metal or Boron), were found by Crabtree et al.[8,9,10,11] and Morris and co-workers[12,13] to act as unexpectedly efficient hydrogen bond acceptors toward conventional proton donors, such as O-H and N-H groups. The resulting E-H···H-X systems have been characterized with H···H contacts of 1.75 - 1.9 Å and bond strengths of 3-7 kcal mol^{-1} which lie in the range found for conventional hydrogen bonds. This new H···H interaction was termed Dihydrogen bonding by Crabtree.[11]

The presence of hydrogen bonds between a transition metal hydride and a hydrogen bond donor containing an O-H or an N-H has been established intramolecularly by Morris and Crabtree and intermolecularly by Crabtree in the solid state[14,15] and Epstein and Berke in solution.[16] Such hydrogen bonds have also been studied by theoretical calculations.[9,14,17,18,19,20,21]



1.1.1 Transition Metal Dihydrogen Bonds: Intramolecular Examples

Two early examples of M-H bonds acting as proton acceptors were reported in 1990 by Caulton et al.[22] and Bau, Milstein, and Koetzle[23] (Figure 1.1).

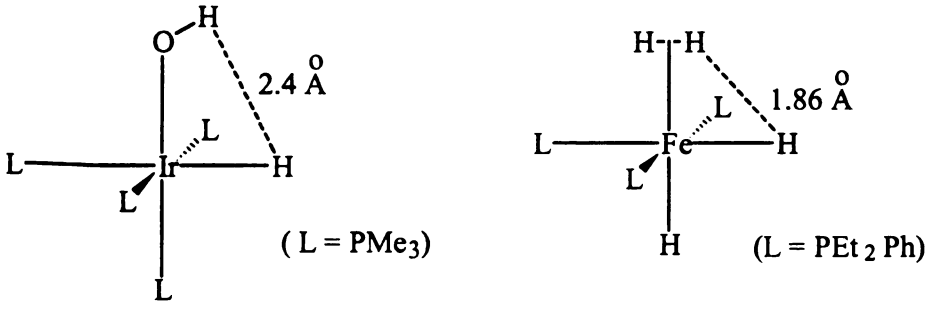
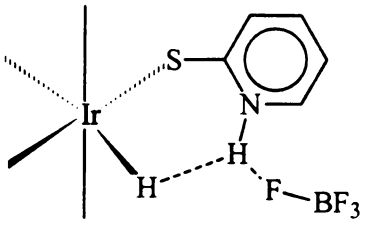


Figure 1.1 Two early examples of complexes showing dihydrogen bond interaction with H···H distances determined by neutron diffraction studies.

In the neutron diffraction structure of $[Ir(PMe_3)_4(H)(OH)]^+$ by Bau, Milstein, and Koetzle, a H···H distance of 2.4 Å was found between the OH proton and the Ir-H hydride.[23] A significant feature of the structure of $[Ir(Pme_3)_4(H)(OH)]^+$ shows the O-H group eclipsing the hydride ligand, with a smaller than usual Ir-O-H angle of 104.4°, suggestive of an attractive interaction between the H atom on the

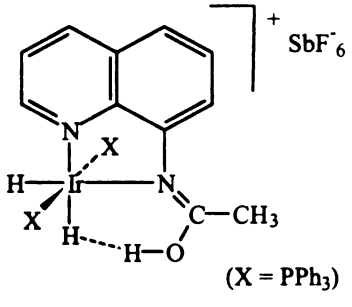
hydroxyl group and the electron-rich hydride ligand. However, a H···H distance of 2.4 Å is too long for this interaction to be considered a normal hydrogen bond. The neutron diffraction structure of $[Fe(H)_2(H_2)(PEt_2Ph)_4]$ showed a close contact of 1.862 Å between one of the H_2 protons and the hydrogen of a cis Fe-H group. The fact that the H_2 ligand adopts a conformation in which the H-H bond is coplanar with and parallel to the cis Fe-H bond prompted the authors to termed this a "cis effect" but Morris indicated that this could also be attributed to an intramolecular dihydrogen bond.[13]

Morris and co-workers and Crabtree et al. independently discovered a series of Ir-H···H-N species simultaneously. Morris and co-workers showed that reversible protonation of a pendant pyridyl group can switch intramolecular N-H···H-M hydrogen bonding on and off.[12] They have also reported the preparation and characterization of an iridium (III) complex **1** containing a unique bifurcated dihydrogen bonding interaction.[24]



1

Crabtree reported evidence for an Ir-H···H-O hydrogen bond via an iridium - iminol tautomer complex **2**[8] with a calculated H···H distance in the hydrogen bond of 1.58 Å.



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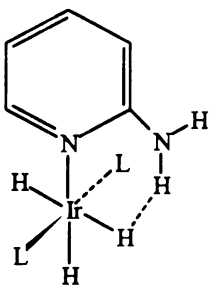
Crabtree compared the barrier for bond rotation in complexes **3** and **4** to gain information about the hydrogen bond strength of an H···H bond versus a conventional H···F hydrogen bond.[10]



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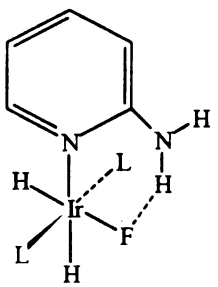
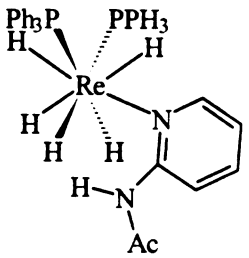


4

Variable temperature NMR was used to determine the barrier of rotation about the C-NH_2 which represents the sum of the intrinsic rotation barrier and H-bond strength. The barrier of rotation for **3** was found to be 10.8 ± 0.2 kcal mol^{-1}. Since the intrinsic rotation is known to be about 6-7 kcal mol^{-1} this means that the H-bond strength is approximately 4.3 kcal mol^{-1}. The barrier for **4** was found to be 11.0 ± 0.2 kcal mol^{-1} with a H-bond strength of approximately 4.5 kcal mol^{-1}. This work showed that the dihydrogen bond strength fall in the same range as that of conventional hydrogen bonds.

Hydride rotational fluxionality in $ReH_5(PPh_3)_2L$ (**5**, L = N-acetyl-2-aminopyridine) is affected by intramolecular Re-H···H-N dihydrogen bonding.[25]



5

The presence of a M-H···H-OH dihydrogen bond also facilitates proton transfer. Crabtree has shown via variable temperature NMR studies, that the OH and MH protons exchange readily with a $\Delta G^{\ddagger}$ of 15 kcal mol^{-1} for **6**. It was proposed[26] that proton transfer from the acidic iminol OH group (initiated by dihydrogen bonding) to the basic hydride leads to a dihydrogen complex, which undergoes rotation[27] about the M-(H_2) bond, followed by back transfer of a proton (Figure 1.2).

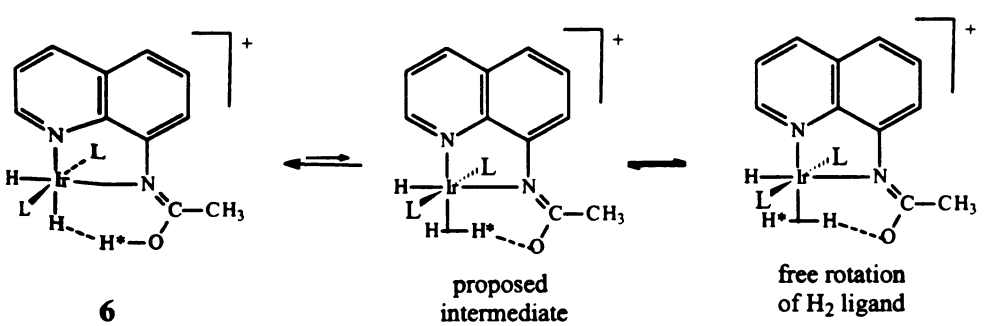
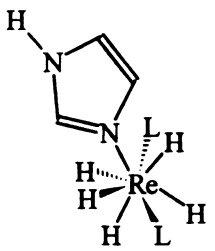


Figure 1.2. Proton exchange reaction facilitated by dihydrogen bonding.

1.1.2 Transition Metal Dihydrogen Bonds: Intermolecular Examples

Are intermolecular N-H···H-M bonds possible?

Crabtree proposed to answer this question by definitively characterizing such a system. He approached the problem by conducting a neutron diffraction study on complex **7** in which proton donor (D) and acceptor (A) are covalently linked.



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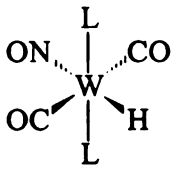
The imidazole ligand acts as the proton donor (D) N-H function. X-ray crystallography[15] showed that the D-A molecules line up head to tail in the lattice, but the H···H distances are all > 2.4 Å and thus are too long to be hydrogen bonds. However the crystals contained free imidazole (from an impurity in the recrystallization solvent) which was strongly hydrogen bonded to a $ReH_5(PPh_3)_2(L)$ molecule with the closest H···H contact being 1.7 Å. Strong hydrogen

bonding (estimated strength ≅ 5.3 kcal mol^{-1}) was also confirmed by IR studies.[26]

Shubina et al. experimentally addressed the problem of intermolecular X-H···H-M hydrogen bonding in solution.[16] A series of tungsten monohydrides **8** were systematically studied in solution in the presence of acidic alcohols (phenol, hexafluoro-



8

2-propanol, and perfluoro-2-methyl-2-propanol). They reported IR and NMR spectroscopic evidence for intermolecular W-H···H-O dihydrogen bonding.

The chemical and spectroscopic properties of polyhydride complexes exhibiting quantum mechanical exchange coupling J_{ab} between adjacent hydride sites a and b has been extensively studied.[28,29,30,31,32,33,34,35,36] Chaudret et al. showed that hydrogen bonding to $Cp^*(PCy_3)RuH_3$ leads

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in solution to an enhancement of the exchange coupling to this complex and have suggested that exchange couplings are good sensors for the establishment of hydrogen bonds. They discovered that the spectroscopic properties as well as the reactivity of hydride complexes could be modified by dihydrogen bonding.[37,36,38]

1.1.3 B-H···H-NH Dihydrogen Bond Examples

The Cambridge Crystallographic Database (CSD) was searched by Crabtree et al. for close intermolecular B-H···H-N contacts of which 26 were found[17] (18 were amine-boranes) in the range of 1.7 - 2.2 Å. These distances are less than the Van der Waals radius for H, which indicate the presence of an attractive interaction. Examination of these compounds indicated an N-H···HB angle (ψ) of 117-171° (average 149°) and a B-H···HN angle (θ) of 90°-171° (average 120°), but in the majority of examples, θ = 95-120° (Figure 1.3).

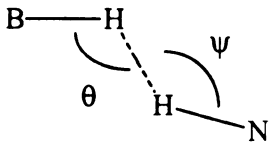

Figure 1.3. Typical geometry for dihydrogen bond in amine boranes: $\theta = 95\text{-}120°, \psi = 117\text{-}171°$.

Just as conventional hydrogen bonds cause deviation in simple properties such as boiling point, dihydrogen bonds demonstrate their existence by a significant deviation in melting point. The difference in melting point between BH_3NH_3 (+104°C) and the isoelectronic ethane molecule (-181°C) is as large as 285°C. Since BH_3NH_3 lacks lone pairs it cannot form conventional hydrogen bonds, and therefore dihydrogen bonds must be present. One may argue that BH_3NH_3 has a considerable dipole moment unlike ethane, but the polar but nonbonding CH_3F and the isoelectronic CH_4 have essentially the same melting point despite a large difference in dipole moment. This N-H···H-B dihydrogen bond interaction has been confirmed and characterized by crystallographic methods,[17,26] and by theoretical calculations.[17,19,21,26,39]

Jackson et al. demonstrated using ab initio calculations, X-ray crystallography, and IR and NMR

spectroscopic studies that the hydridic hydrogen in the BH_4^- anion can serve as the electron donors in dihydrogen bonding. Figure 1.4 shows X-ray crystal structures for the hydrogen bonded compounds $NaBH_4.2H_2O$ and guanidine borohydride.[40]

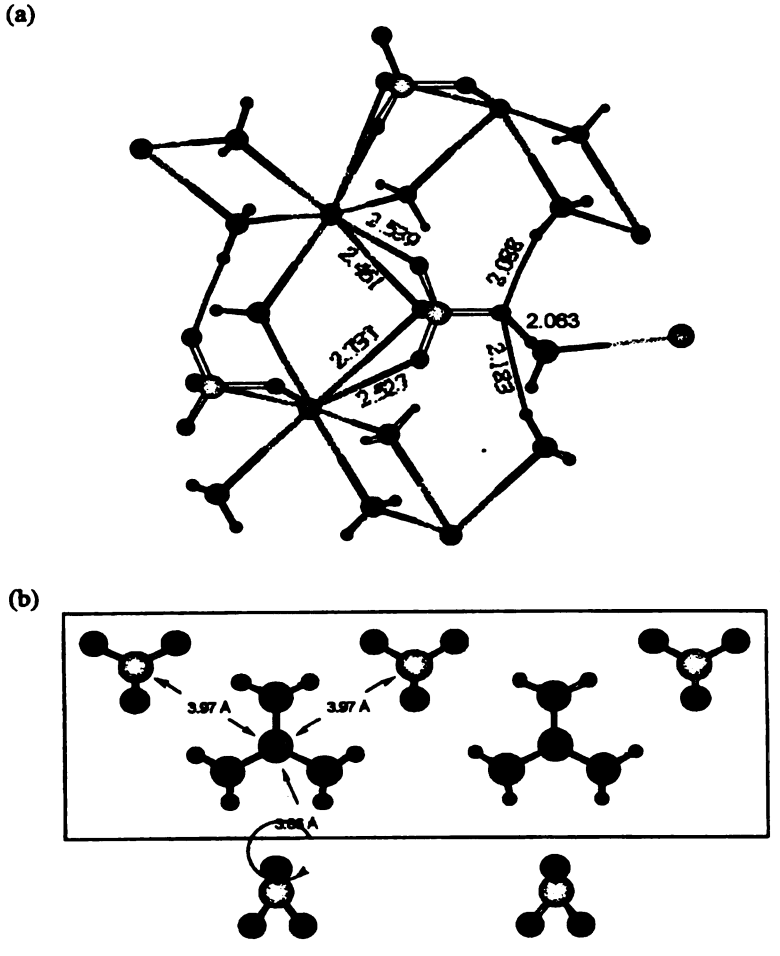

Figure 1.4. (a) X-ray structure of $NaBH_4.2H_2O$. (b) X-ray structure of guanidinium borohydride

The sodium borohydride dihydrate contains four hydridic (B-H) and four protonic (O-H) hydrogens

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which suggest a one to one interaction. However, as illustrated in Figure 1.4a, three of the four B-H sites are occupied via binding to Na^+ ions, but the fourth B-H site has three of the four unique O-H bonds converging on it. The H-H contacts (after correction for the apparent shortening of X-H bonds typical of X-ray diffraction studies) were estimated at 1.86, 1.86, and 1.99 Å. The neutron diffraction structure of $NaBD_4.D_2O$ confirmed these data showing in this case D-D distances of 1.79, 1.86, and 1.94 Å. These distances are over 1/2 Å shorter than the 2.4 Å sum of the Van der Waals radii denoting strong dihydrogen bonding interaction.

Guanidinium borohydride was used to probe the BH_4^- ion's potential to form multi-point dihydrogen bonding interactions. As shown in Figure 1.4b, the X-ray structure confirms the expected two point contact between guanidinium edge hydrogens and the BH_4^- ion.

Further evidence of dihydrogen bonding between BH_4^- and conventional proton donors was demonstrated using IR solution studies. In nonpolar organic

solvents, O-H and N-H vibrational bands are shifted to lower frequencies with greater integrated intensities when exposed to BH_4^- salts, just as they are with Cl^-, Br^-, and I^- salts or neutral donors such as pyridine. Figure 1.5 shows a shift in the N-H stretching frequency of pyrrole with traditional hydrogen bonding reagents such as tetrabutylammonium halides as well as with the non traditional dihydrogen bonding tetrabutylammonium borohydride. It was also shown via chemical shift variations and NOE experiments using ^1H NMR that the N-H and O-H protons of pyrrole and water are in contact with those of BH_4^- in C_6D_6 and CD_3CN solutions respectively[41] again confirming dihydrogen bonding.

Jackson suggested that this new phenomenon has interesting implications for the rational assembly of materials. The concept of using dihydrogen bonding as chemical "basting stitches", weak associations that organize and hold a molecular structure's form while it is more firmly sewn together, using dihydrogen bonding is being explored in Jackson's group. It is known that these systems can lose H_2 leaving Lewis acidic and basic

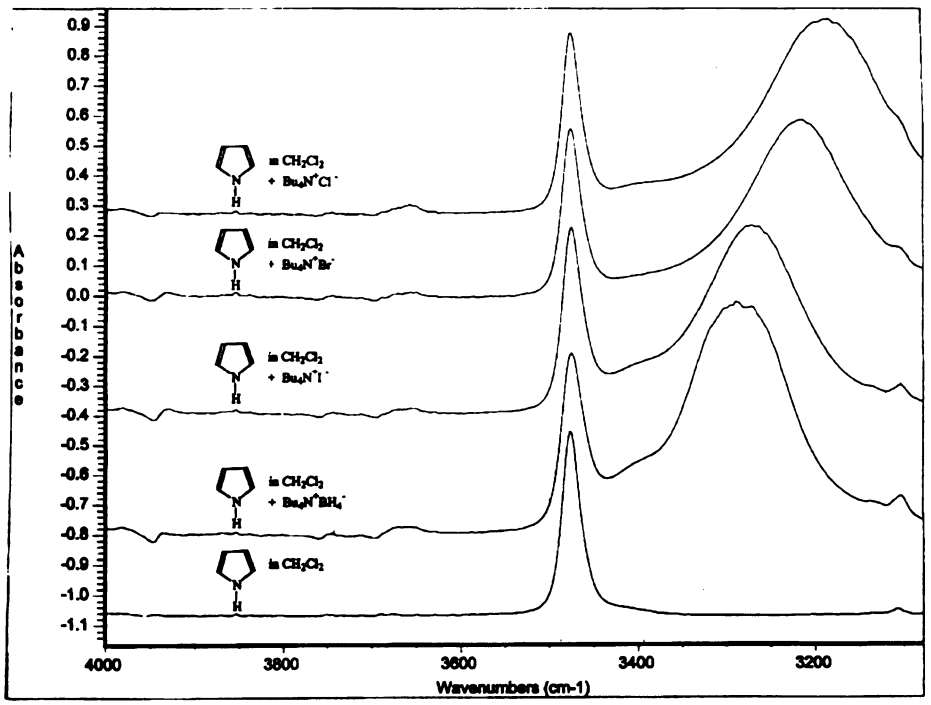


Figure 1.5. IR Studies: N-H stretch region of pyrrole hydrogen bonding to quaternary ammonium halide salts and dihydrogen bonding to tetra-butylammonium borohydride in dichloromethane solvent.

Sites in close proximity which can combine via Covalent bonds, potentially reflecting the Connectivity of the original network.[26,42] Figure 1.6 (a and b) show how these systems lose H_2.

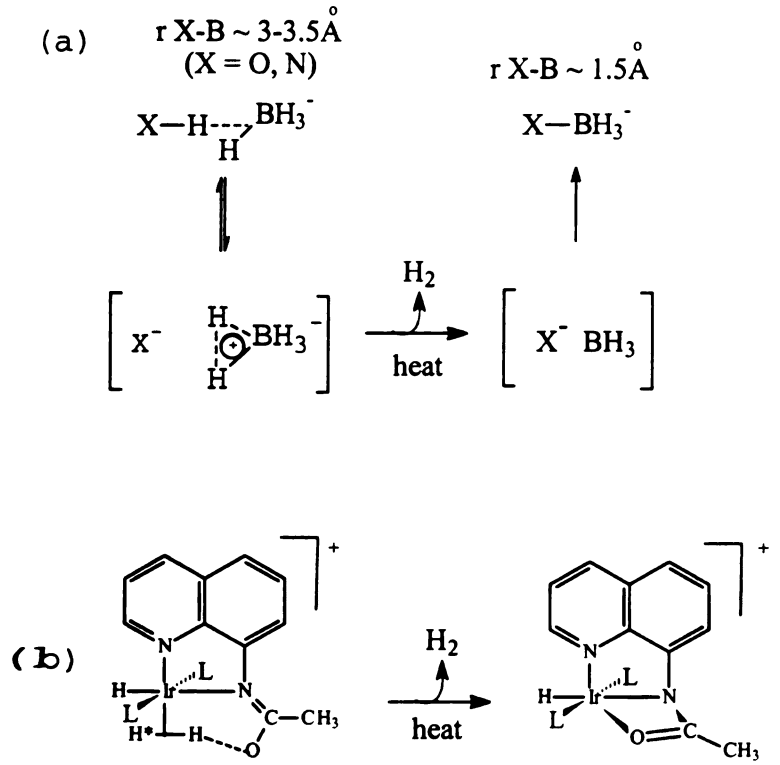


Figure 1.6. (a) Loss of H_2 based on the known BH_4^- hydrolysis mechanism.[43] (b) Thermolysis of iridium complex with loss of H_2 via transmetalation.[26]

More recently N-[2-(6-aminopyridyl)]-acetamidine cyanoborohydride was synthesized demonstrating the ability of $CNBH_3^-$ to form dihydrogen bonds resulting in the formation of the dimer-type structure shown in Figure 1.7.[43]

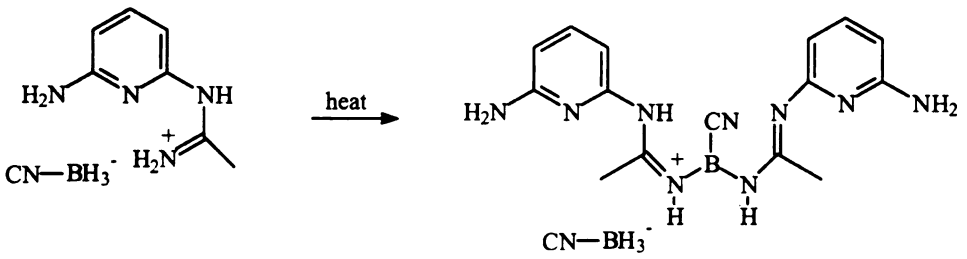


Figure 1.7. Dimer structure prepared from N-[2-(6-Aminopyridyl)]-acetamidine cyanoborohydride resulting from dihydrogen bonding of $CNBH_3^-$.

As shown in this literature review there is significant crystallographic and spectroscopic evidence for the existence of dihydrogen bonding. However, there have been no studies reported to date showing the role of this new type of unconventional hydrogen bond in directing chemical reactivity in solution.

We have demonstrated a substantial attraction between the -OH group of appropriately designed hydroxyketones and an approaching BH_4^- ion in the borohydride reduction of ketones by both product stereochemistry and reaction rate enhancement relative to the unsubstituted ketone.[44] The details of this study will be presented in Chapter 2.

1.2

1.2 Substituent directed stereoselective reduction - A Review

The origin and magnitude of the stereoselectivity in the reduction of chiral carbonyl compounds continues to be an area of theoretical and practical study. Significant efforts have concentrated on the 1,2 asymmetric induction that occurs in the hydride addition to a carbonyl group adjacent to an asymmetric center (Figure 1.8). Cram's rule was formulated to rationalize the results of nucleophilic addition to aldehydes and ketones containing no polar groups.[45] The most stable transition state conformation **9** arises from the minimization of the interaction between the largest group (R_L) and the carbonyl group, which is coordinated to the incoming reagent. The addition of the nucleophile then occurs preferentially on the side of the smallest substituent (R_s). The outcome of Cram reduction of ketone **9** to alcohol **10** is illustrated in Figure 1.8.

The results for reduction of α-halo aldehydes and ketones were anomalous and led to the dipolar

model formulated by Conforth[46] as illustrated by **11**, in which the dipoles due to the carbonyl group and the carbon-halogen bond were in an antiperiplanar arrangement. The incoming hydride then attacks from the less-hindered side of the ketone leading to alcohol **12**. When the α-substituent is an alcohol, alkoxy, or amino group there is a possibility of chelation with the metal cation associated with the hydride reagent. Cram proposed a cyclic or chelate model to cover these cases.[47] The chelating group X and the carbonyl group are eclipsed, coordinating to the metal (M), and reduction occurs from the less-hindered side. Cram's chelate model has been used to rationalize diastereoselectivity in reduction of ketones such as **13**.

Karabatsos proposed an alternative model.[48] Calculations suggested that the most favored conformation **15** would have the medium-sized group (R_m) of ketone eclipsing the carbonyl group, and addition of the hydride would occur from the side of the less bulky substituent (R_s) to give alcohol **16**.

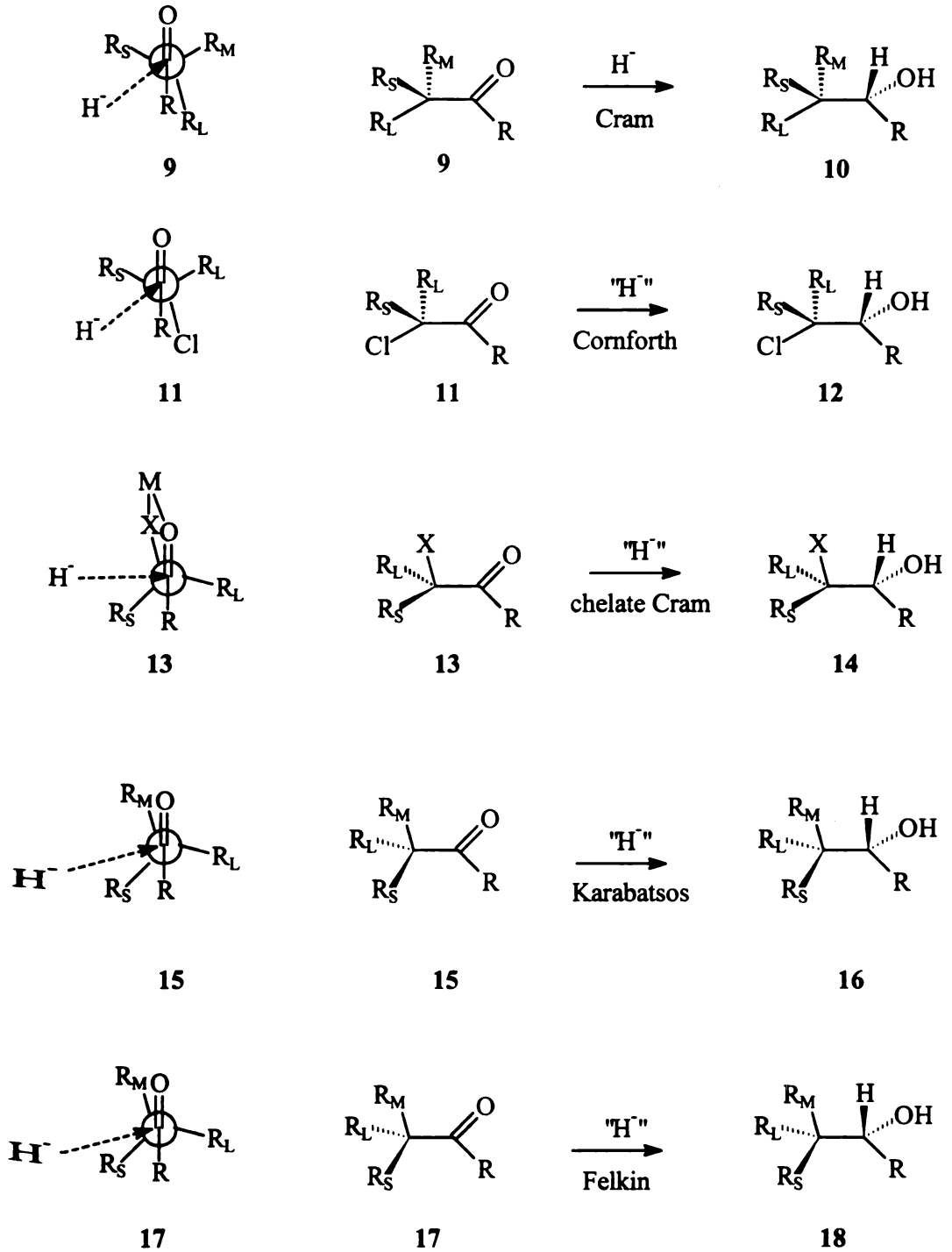


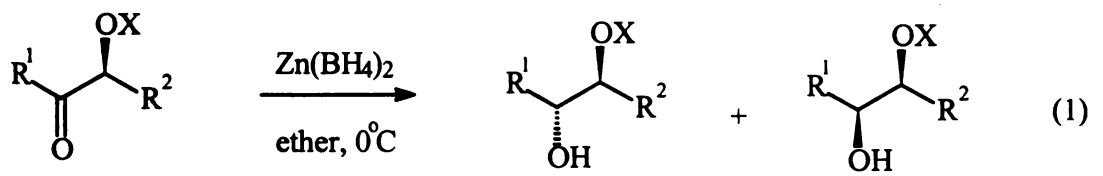
Figure 1.8. 1,2 asymmetric induction in hydride addition to carbonyl compounds flanked by an asymmetric center.

The most widely accepted model for the interpretation of 1,2-asymmetric induction in nucleophilic reactions with carbonyl compounds was proposed by Felkin.[49] Felkin directed attention to the structure of the transition state which he assumed to be very similar to the substrate. Felkin found that the transition state energies were minimized as a consequence of the anti arrangement of the bond forming to the incoming nucleophile and the bond between the adjacent carbon and the largest or most electronegative group. The nucleophile was assumed to attack perpendicular to the carbonyl group plane (plane bisecting the carbon-oxygen double bond) however, this angle of approach was later revised to the Burgi-Dunitz trajectory[50,51] derived from crystallographic studies which placed the incoming nucleophile much closer to the substituent (R_s) as illustrated in **17**. The Felkin model was successfully applied to reduction of both acylic and cyclic ketones with and without an adjacent polar substituent and supported by ab initio calculations.[52]

The requirements in modern total synthesis to produce single diastereoisomers[53] has prompted an

explosive growth in the development of reliable methods for the diastereoselective reduction of carbonyl compounds in a wide range of acyclic systems.[54]

Nakata et al. reported the reduction of α-hydroxy ketones **19** to the corresponding erythro-diols **20** by zinc borohydride[55,56,57] (eq 1) and examined the relationship between the substitution pattern of the α-hydroxy ketones and the stereoselectivity of the reduction. The results are summarized in Table 1.1.



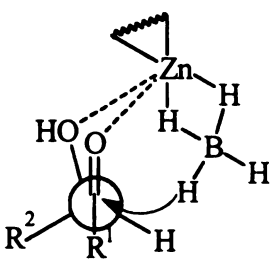
19 erythro - **20** threo - **21** (1)

Reduction is presumed to proceed through the Cram chelate transition state **22.**

Table 1.1: Reduction of α-Hydroxy Ketones **19**

Entry	Comp'd	R^1	R^2	X = H[a] erythro:threo	X = TBDPS[b,c] erythro:threo
1	**19a**	$n\text{-}C_5H_{11}$	CH_3	77:23	39:61
2	**19b**	$n\text{-}C_4H_9$	$n\text{-}C_2H_5$	89:11	14:86
3	**19c**	$n\text{-}C_3H_7$	$n\text{-}C_3H_7$	>99:1	14:86
4	**19d**	C_2H_5	$n\text{-}C_4H_9$	87:13	7:93
5	**19e**	CH_3	CH_3	85:15	2:98
6	**19f**	$i\text{-}C_3H_7$	$n\text{-}C_5H_{11}$	85:15	54:46
7	**19g**	CH_3	$i\text{-}C_3H_7$	96:4	4:96
8	**19h**	Ph	CH_3	98:2	9:91
9	**19i**	CH_3	Ph	90:10	24:76

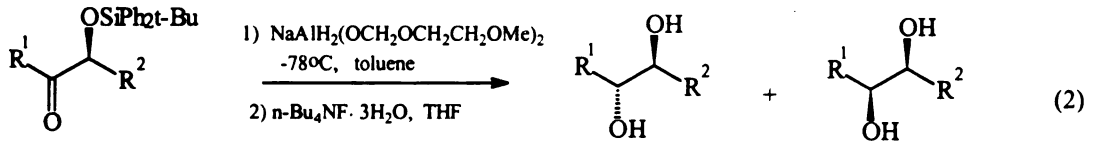
[a] Reduction with $Zn(BH_4)_2$ [b] Reduction with sodium bis (2-methoxy)aluminum hydride (Vitride) [c] TBDPS = t-butyldiphenylsilyl)oxy.



22

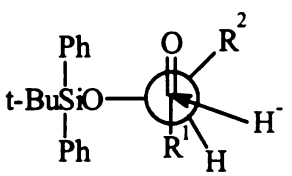
Silylation with the α-(t-butyldiphenylsilyl)oxy (TBDPS) group gave the protected derivatives **23** which were reduced by Vitride at -78°C preferentially

to the threo products **21** (Table 1.1) presumably via a Felkin open-chain transition state **24.**



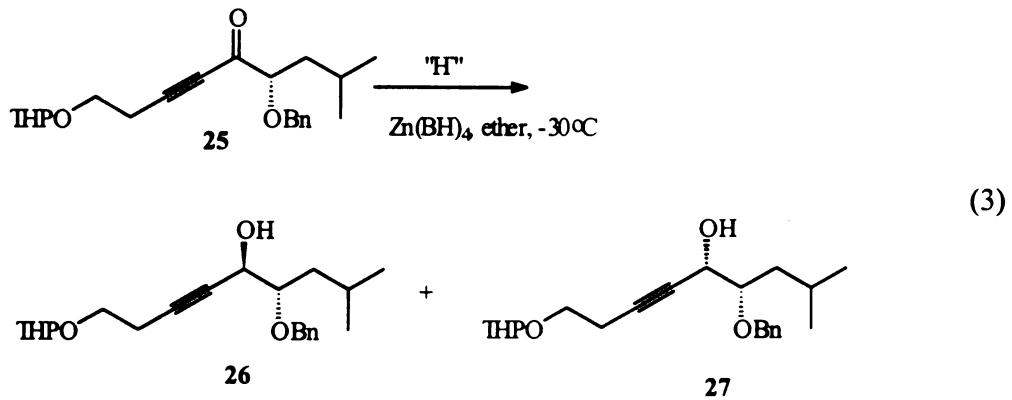
(2)

23 erythro -**20** threo -**21**



24

Takahashi et al. reported analogous results for reduction of the α-benzyloxy nonynone **25** (eq 3).[58] The erythro isomer **26** was produced by zinc borohydride (95:5), presumably via chelation control, and K-selectride (having low coordinating ability) gave the threo Felkin product **27** (90:10). The lithium aluminum hydride (LAH) reduction of α-alkoxy enone **28** also favored the erythro product **29** via chelation to the benzyloxy group (eq 4) while the TBDPS ether prevented chelation so that reduction occurred via an open transition state to



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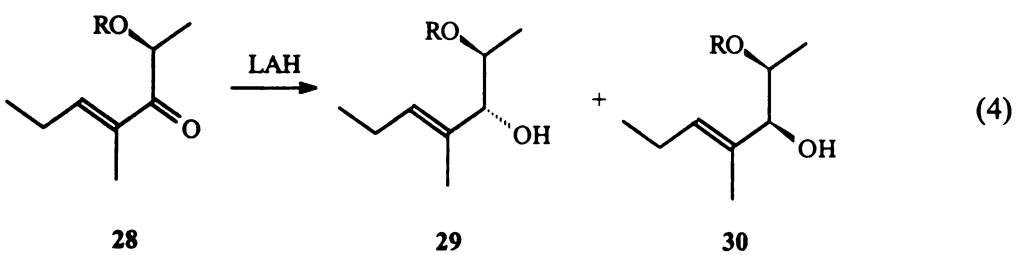
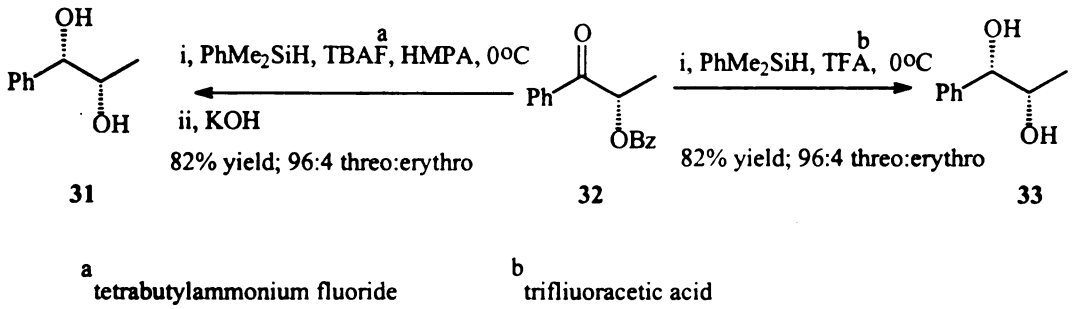


(4)

R = CH_2OBn, ether, -10°C	98 : 2
R = t- $BuPh_2Si$, THF, -20°C	5 : 95

give the threo-alcohol **30** (95:5).[59]

Hydrosilylation provided a novel alternative reduction of α-benzyloxy ketones **32** with tunable diastereoselectivity (scheme 1).

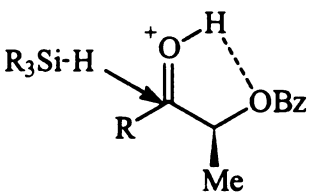


31 **32** **33**

[a] tetrabutylammonium fluoride [b] trifliuoracetic acid

Scheme 1

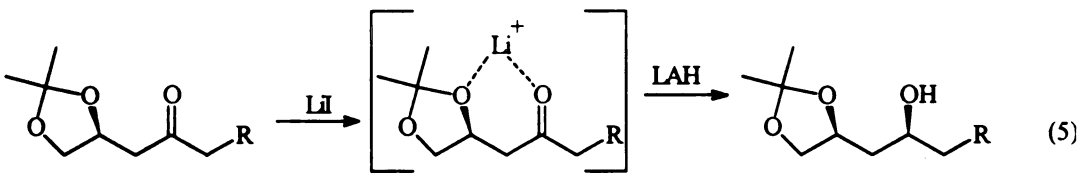
Fluoride-catalyzed reduction with phenyldimethylsilane in HMPA provided the threo-alcohol **31** with high selectivity (87:13 - 96:4).[60] The absence of a coordinating cation and the bulkiness of the reducing species combined to favor the Felkin model for these reductions. Conversely, reduction in trifluoroacetic acid (TFA) proceeded via a proton-bridged Cram cyclic transition state **34** to give the erythro product **33** (84:16 - 99:1) after basic hydrolysis.[61]



34

The stereocontrolled formation of 1,3-diols is of great interest to synthetic chemists since the

1,3-polyhydroxylated chain forms the basic skeleton of polyene and polyol macrolide antibiotics.[62] Consequently, highly diastereoselective methods for reducing β-hydroxy ketones to either of the possible diastereomers have been developed. The β-alkoxy-directed diastereoselective reduction of acyclic β-alkoxy ketones with LAH in the presence of lithium iodide in ether was reported by Mori et al.[63] and found to provide syn-1,3 diol derivatives with high diastereoselection (eq 5). The reductions



(5)

35 **36** **37**

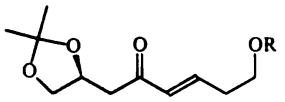
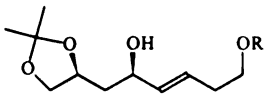
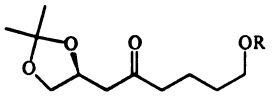
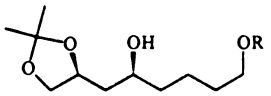
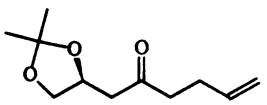
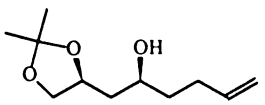
syn:anti 95:5

of β-alkoxy ketones **38**, **39**, and **40** with LAH in the presence of LiI are summarized in Table 1.2. In all cases the major products were found to possess a syn-relationship between the newly formed hydroxy group and the β-alkoxy group of the 1,3-dioxolane ring.

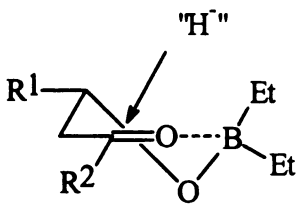
Highly selective asymmetric induction can be achieved in the reduction of acyclic β-hydroxy-ketones via boron chelates. Narasaka[64] reported a highly diastereoselective method for reducing β-hydroxyketones to either of the possible diastereoisomers. The syn isomer was produced by attack of an external hydride reagent on a six membered chelate such as **44**, the conformation of which was governed by the substituent at the alcohol center. Conversely, intramolecular delivery of hydride from a group bound to the alcohol via a chair transition state **45** gave the anti diastereo-isomer. The combination of trialkylboranes and sodium borohydride in THF at -100°C was the first highly syn selective method of this type. This was later refined by using alkoxydialkylboranes to chelate the β-hydroxyketones **46** and conducting the reduction at -70°C in THF-methanol (eq 6).[65] The syn 1,3-diols **47** were preferred by 98:2.

Intramolecular hydrosilylation of the carbonyl group of β-silyoxy ketones **48** via the boat-like transition state **49** induced by tin(IV) chloride

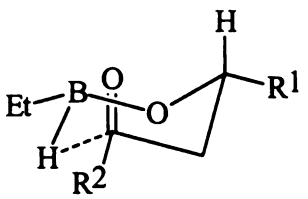
Table 1.2: Reduction of β-Alkoxy Ketones by LAH/LiI Method in Ether Solvent

β-alkoxy ketone	Product	temp (°C)	syn :anti	yield (%)
 **38**	 **41**	-100	96 : 4	98
 **39**	 **42**	0	93 : 7	90
		-78	95 : 5	98
		0	74 : 26	80[a]
 **40**	 **43**	-78	95 : 5	98
		-78	82 : 18	98[a]

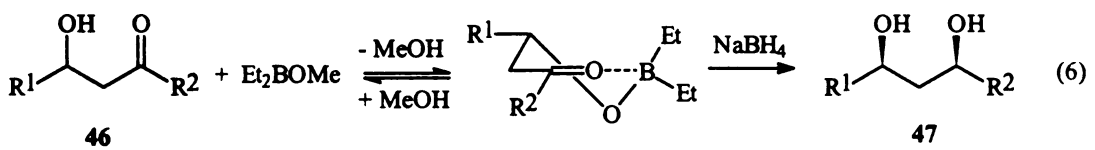
[a] Reductions were carried out ether solvent in the absence of LiI



44

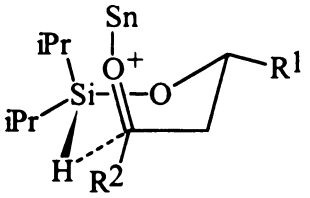


45



46 **47** (6)

catalysis (coordination of tin to carbonyl oxygen) at -80°C in dichloromethane generated the anti-1,3-diol **50** after desilylation with stereoselectivity >95% (eq 7).[66]



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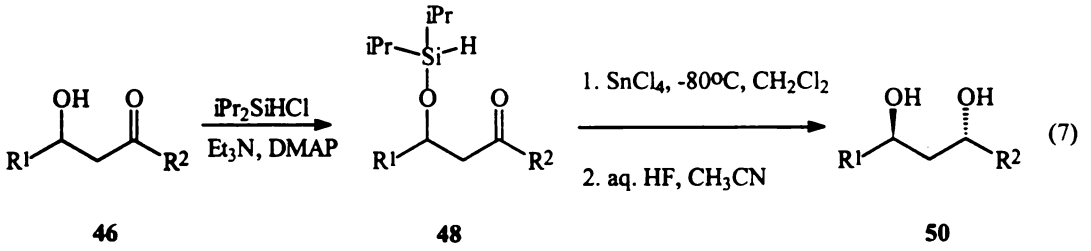
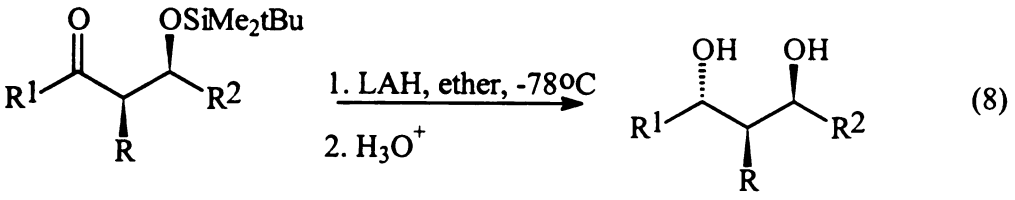
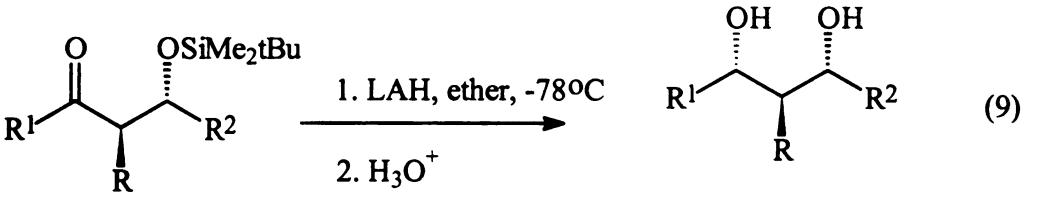


46 **48** **50** (7)

Reduction of TBDMS ethers of α-substituted-β-hydroxy ketones **51** and **53** with LAH in ether at -78°C proceeded with high 1,2 anti distereo-selectivity (>96:4) to give the corresponding

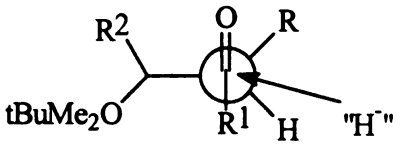


51 52 (8)



53 54 (9)

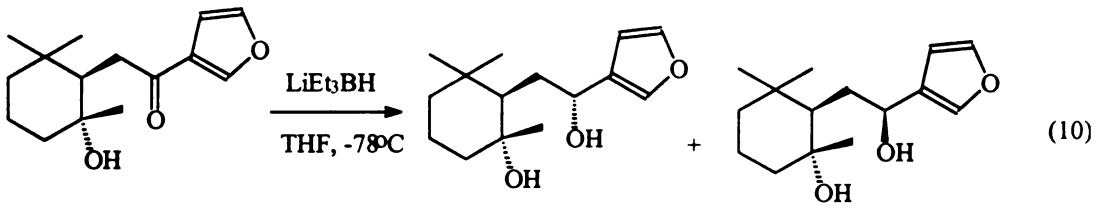
syn,anti and anti,anti-1,3-diols **52** and **54** after acidic hydrolysis (eq 8 and 9).[67] The stereochemistry presumably results from a chelation-free Felkin transition state **55** with the bulky trialkylsilyloxy group in the perpendicular position.



55

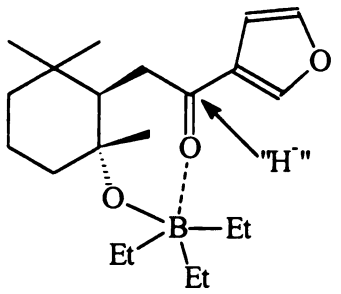
Examples of asymmetric induction from more remote hydroxyl groups in the reduction of

hydroxyketones are rare. However the correct choice of reducing agent allowed complete diastereo-selectivity to be achieved in the reduction of γ-hydroxy ketone **56** in a synthesis of ancistrofuran (eq 10).[68]



56 **57** **58** (10)

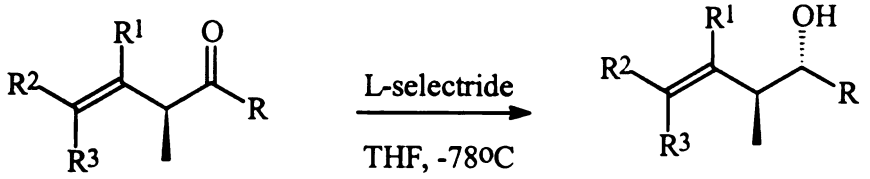
Reduction of **56** with $LiAlH_4$, $ZnBH_4$, and $NaBH_4$ all yielded mixtures of the diols **57** and **58**.[68] However reduction with two equivalents of $LiEt_3BH$ yielded diol **57** as the only product. The authors proposed that the basis for this remarkable high degree of stereoselectivity in the reduction is due to initial reaction of the reducing agent with the tertiary alcohol and subsequent chelation to the carbonyl to yield the cyclic structure **59.** However, given the fact that $R\text{-}O\text{-}BEt_3^-$ has a full coordination sphere, one may question the validity of boron forming a fifth bond. Attack of hydride from a second



59

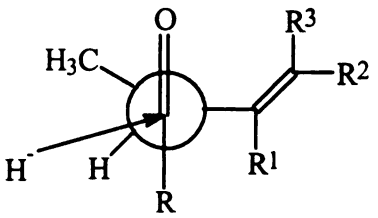
equivalent of the reducing agent then occurred from the less-hindered β-face.

The olefinic linkage in enantiomerically pure α-methyl-β,γ-unsaturated ketones **60** exerted a powerful influence on their reduction with L-selectride, particularly when R^1 was a trimethylsilyl group.[69] As illustrated in eq 11 the anti homoallylic alcohols **61** were formed with uniformly excellent stereoselectivity (>93:7) via a Felkin transition state **62** in which the double bond occupied the perpendicular position.



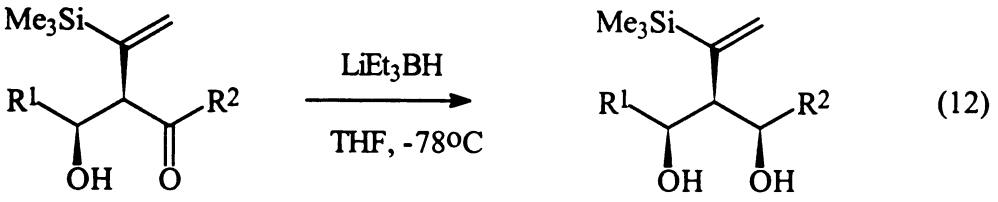
(11)

60 **61**



62

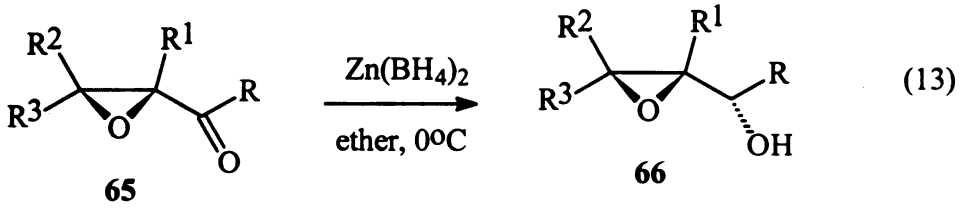
Suzuki et al.[70] reported the reduction of α-vinyl-β-hydroxy ketones **63** and demonstrated that despite the presence of the β-OH group (which can facilitate a chelation mediated transition state) the extremely large steric bias posed by the TMS-bearing vinyl group[71,72,73] strongly favored the Felkin type transition state to give the 1,2-syn-diols **64**.



(12)

63 **64**

Zinc borohydride was effective for the reduction of α,β-epoxy ketones **65** to the corresponding anti-α,β-epoxy alcohols **66** in ether at 0°C irrespective of the substituents on the epoxide (eq 13).[74]



65 **66**

(13)

The authors rationalized the selectivity by intramolecular hydride delivery from a five-membered zinc chelate avoiding the epoxide ring. Kishi reported the steroselective reduction of γ,σ-epoxy ketones **67** with LAH and di-2(o-toluidino-methyl)-pyrrolidine in ether at -78°C which gave the desired

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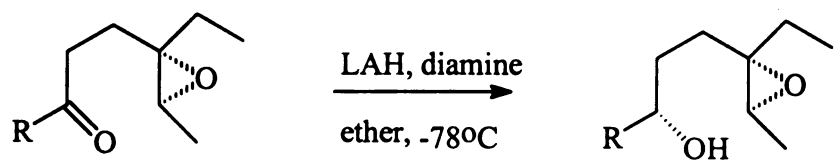
cis-epoxy alcohols **68** with a selectivity of 10:1 (eq 14).[75]

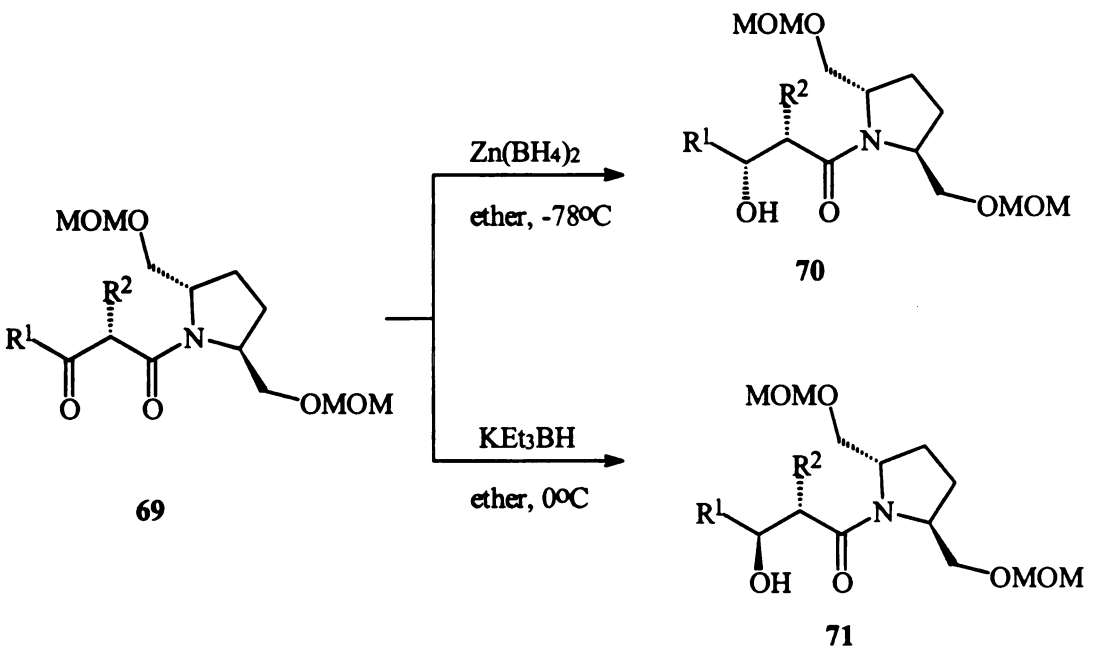


67 **68** (14)

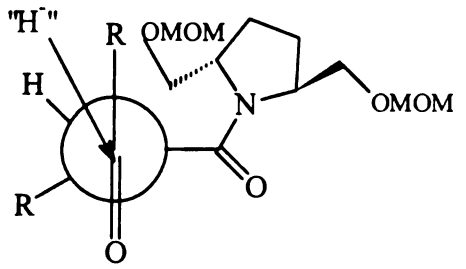
α-alkyl-β-keto acid derivatives are readily available and the syn α-alkyl-β-hydroxy acid structure is often encountered in a variety of natural products. The stereoselective reduction of α-alkyl-β-keto acid derivatives also represents an attractive alternative to stereoselective aldol condensation.[76] Yamaguchi et al. developed complementary methods for production of either diastereoisomer of α-alkyl-β-hydroxy amides from the corresponding α-alkyl-β-keto amides **69**

(scheme 2).[77] Zinc borohydride in ether at -78°C gave the syn isomer **70** with excellent selectivity (≥97:3) in high yield via a metal chelated transition state. A Felkin transition state **72** with the amide in the perpendicular position accounted for reduction with

potassium triethylborohydride in ether at 0°C to give the stereochemically pure anti diasteroisomer **71**. The combination of these methods with asymmetric acylation provided an effective solution to the asymmetric problems in the formation of aldol products (scheme 2).[78,79] In contrast to the case of potassium triethyl-borohydride, the reduction of α-methyl-β-keto amides with zinc borohydride was



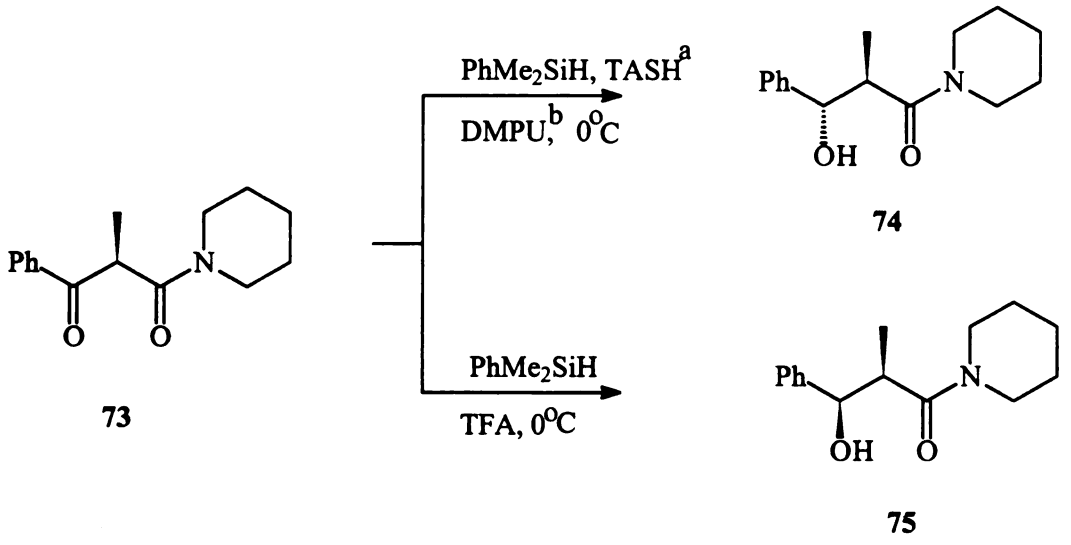
Scheme 2



72

highly syn selective when the ketone was aromatic or α,β-unsaturated, but less selective in aliphatic cases.[54] Hydrosilylation also provided diastereo-control in the reduction of α-substituted-β-keto amides (scheme 3). The fluoride-mediated reaction was anti selective (≥98:2) while the reduction in trifluoroacetic acid favored formation of the syn isomer (≥98:2)[80] with no loss of optical purity. The hydrosilane based reductions are remarkable in light of the extremely mild reaction conditions and easy handling of commercially available hydrosilanes and provide an alternative efficient approach to aldols of both threo and erythro configurations.

Diastereomerically pure syn- and anti-β-alkylthioalcohols **77** and **79** are useful synthetic intermediates for the preparation of geometrically pure alkenes[81,82,83] or single diastereoisomers of epoxides.[84,85,86] Reduction of β-keto sulfides **76**



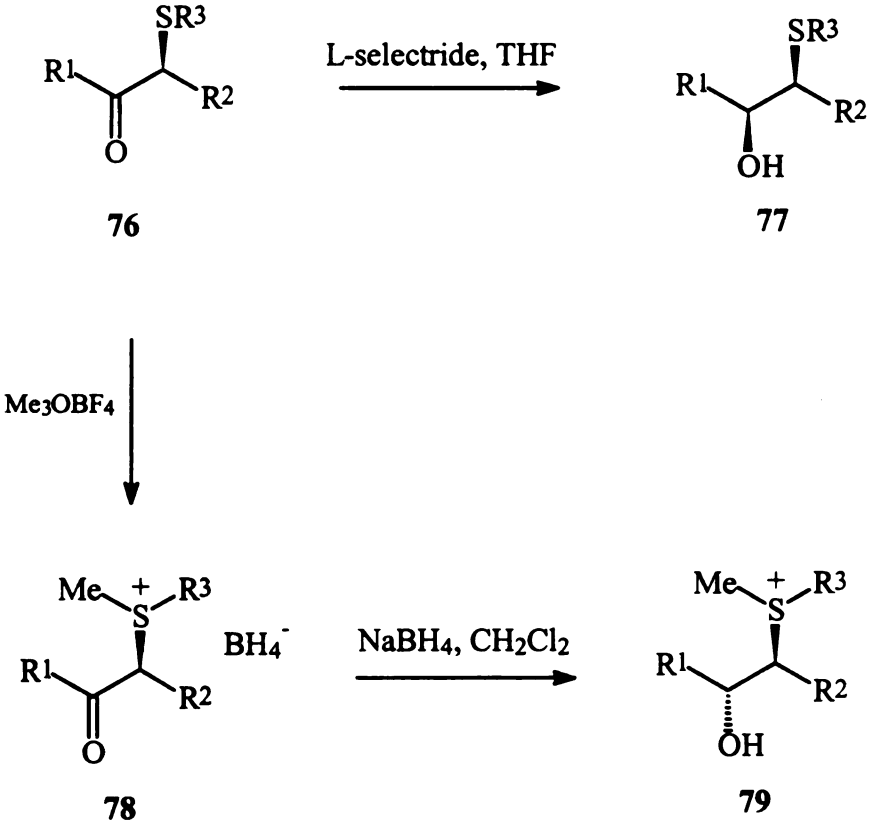
[a] tris(diethylamino)sulfonium difluorotrimethylsilicate (used a fluoride source).

[b] 1.3-dimethyl-3,4,5,6-tetrahydro-2-(1H)-pyrimidinone

Scheme 3

with L-selectride in THF gave the syn-β-hydroxy sulfides **77** via α Felkin transition state.[87] The selectivity was good (≥92:8) unless the acyl group was branched. However, in the $Zn(BH_4)_2$ reduction, expected to give anti selectivity, excellent results

were obtained only in limited cases. The solution for the formation of the anti diastereoisomer **79** was reduction of the sulfonium salts **78**, (prepared by methylation of the β-keto sulfides **76**) with sodium borohydride in dichloromethane (scheme 4). The sulfonium salt **78** is hypothesized to be in its most stable conformation **80** in which the carbonyl and the

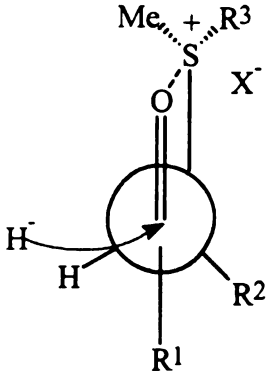


76 **77** **78** **79**

Scheme 4

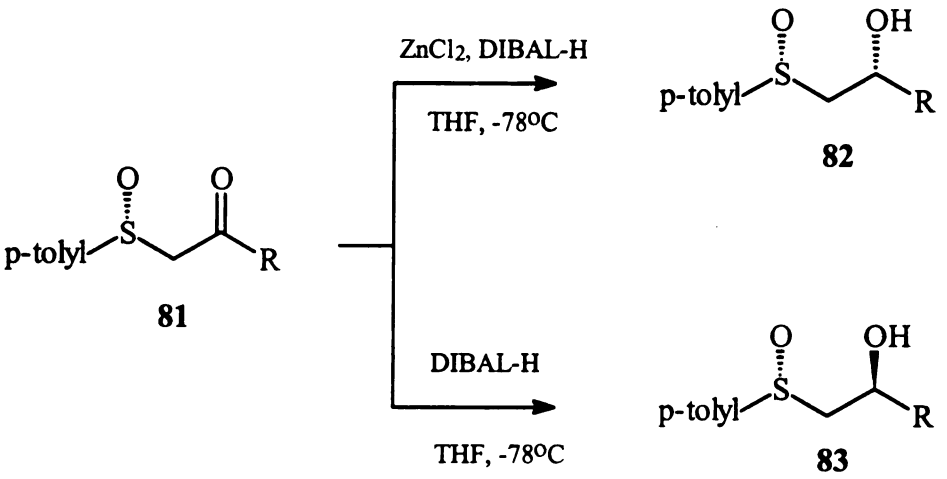
sulfonium groups are eclipsed due to the charge attraction between these closely located functional

groups. Therefore, the hydride anion may attack the ketone from the less hindered side producing the anti-**79**.[88]



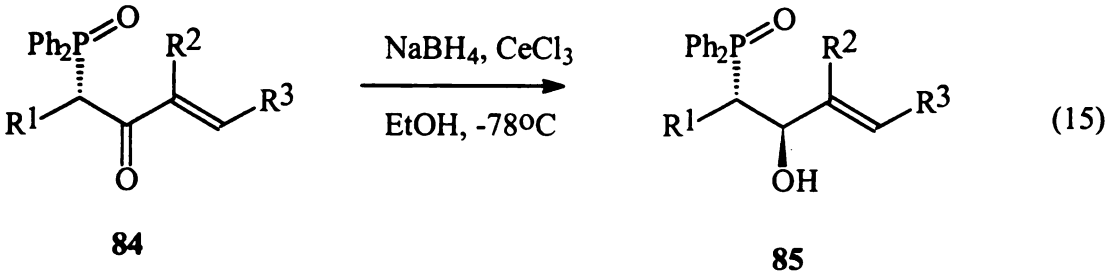
80

The stereocontrolled reduction of optically pure β-keto sulfoxides **81** with DIBAL-H (anti selective **82**, ≥93:7) or DIBAL-H in the presence of zinc chloride (syn selective **83**, >95:5) provided an entry to enantiomerically pure alcohols after desulfurization (scheme 5).[89,90] The formation of the syn isomer **82** is presumably due to the initial complexation of the β-keto-sulfoxide moiety with $ZnCl_2$ and the subsequent attack of a hydride from DIBAL on the less hindered side of the chelated species.



Scheme 5

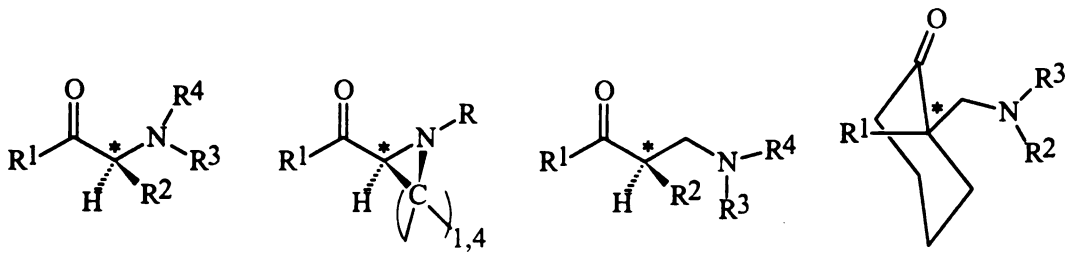
Geometrically pure alkenes were generated by Horner-Wittig elimination of stereochemically pure β-hydroxy diphenylphosphine oxides available from reduction of the corresponding β-keto phosphine oxides.[91] Reduction with typical reducing agents was generally syn selective according to the Felkin model however, in the presence of cerium chloride, sodium borohydride reduced sterically hindered α′-diphenylphosphinoyl enones **84** to the anti-alcohols **85** exclusively, presumably via a chelated transition state (eq 15).[92]



84 **85** (15)

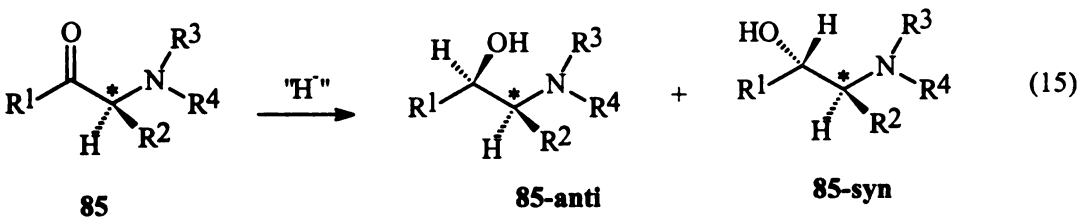
Diastereocontrolled reduction of amino ketones represents an attractive route to amino alcohols. The production by synthetic methods of chiral amino alcohols and the isolation of their enantiomeric and/or diastereomeric forms are of great importance in pharmacological research on anaesthetics, analgesics, etc.[93]

The α- and β-aminocarbonyl systems with the chiral center in the α-position such as **85-88**, generally prefer syn-attack by hydride (with respect to the amine group) to give the anti product regardless of the reducing agent employed with the exception of α-chiral α-amino carbonyl substrates bearing a tertiary amino group preferring anti-attack which appears to be associated with steric hindrance.[93]



85 86 87 88

Reduction of aminocarbonyl compounds **85** has been widely investigated, due to the pharmacological relevance of amino alcohols **85-anti** as ephedrine-like systems (eq 15). The stero-chemical behavior of **85** bearing primary or secondary amino groups produced the anti-isomer predominantly except when R^2 = CH_2OH or CH_2NH_2 group bonded to the chiral center (Table 1.3).



85 **85-anti** **85-syn** (15)

In the latter cases, the stereoselectivity is much lowered and highly dependent on temperature variations.[94,95] The situation is more complex with tertiary amino derivatives: syn-attack, in general, is still favored, but a high number of cases exist

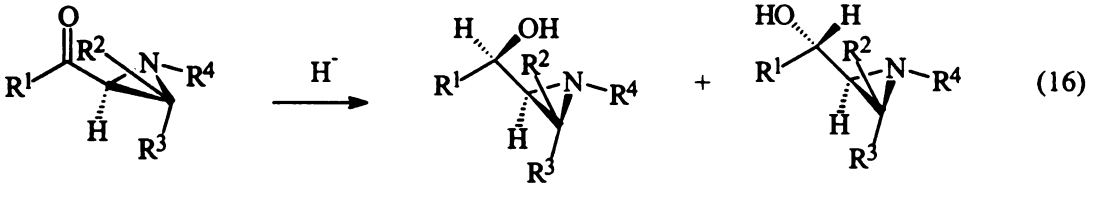
in which anti-attack is favored or even quantitative. The possibility of anti-attack increases with increasing steric hindrance of the amine moeity.

The reduction of acylaziridines **86** (eq 16) show a strong influence of the reducing agent on the stereochemistry of the reaction (Table 1.4). In the $LiAlH_4$ reductions, the attack is typically predominant from the syn-direction and sometimes stereospecific, with an exception for the more rigid polycyclic system **86** (R^1-R^2 = -$(CH_2)_3$-). In the reductions with borohydrides, the syn-attack showed a general increase and, in some cases, is predominant.

Rigid cyclic amino systems **89-93**, show a complex sterochemical behavior due to strong effects of both reducing agent type and amino substrate structure.

Table 1.3. Reduction of α-chiral Acyclic α-Amino **85**.[93]

Amino Ketone **85**							
R^1	R^2	R^3	R^4	Reducing agent	Solvent	Temp °C	anti:syn ratio
C_6H_5	CH_3	H	H	$LiAlH_4$	$(C_2H_5)_2O$	r.t.	95:5
C_6H_5	CH_2NH_2	H	H	$NaBH_4$	C_2H_5OH	r.t.	50:50
C_6H_5	CH_2OH	H	H	$NaBH_4$	C_2H_5OH	reflux	56:44
C_6H_5	CH_3	H	C_6H_5-CH_2	$NaBH_4$	CH_3OH	r.t.	100:0
C_6H_5	CH_3	CH_3	CH_3	$NaBH_4$	C_2H_5OH	reflux	1:1
C_6H_5	CH_3	CH_3	$C_6H_5CH_2CH_2$	$NaBH_4$	DMF		100:1
C_6H_5	CH_3	CH_3	$C_6H_5(CH_2)_3$	$NaBH_4$	CH_3OH	r.t.	84:16
C_6H_5	CH_3	CH_3	$C_6H_5(CH_2)_3$	$LiAl(OtBu)_3$	THF		0:100
C_6H_5	C_6H_5	CH_3	C_6H_5	$LiAlH_4$	$(C_2H_5)_2O$	r.t.	75:25
C_6H_5	C_6H_5	-$(CH_2)_7$-	-$(CH_2)_7$-	$LiAlH_4$	$(C_2H_5)_2O$	r.t.	53:47
C_6H_5	C_6H_5	n-C_3H_7	n-C_3H_7	$LiAlH_4$	$(C_2H_5)_2O$	r.t.	34:66
C_6H_5	C_6H_5	i-$C_3H_7CH_2$	i-$C_3H_7CH_2$	$LiAlH_4$	$(C_2H_5)_2O$	r.t.	0:100



(16)

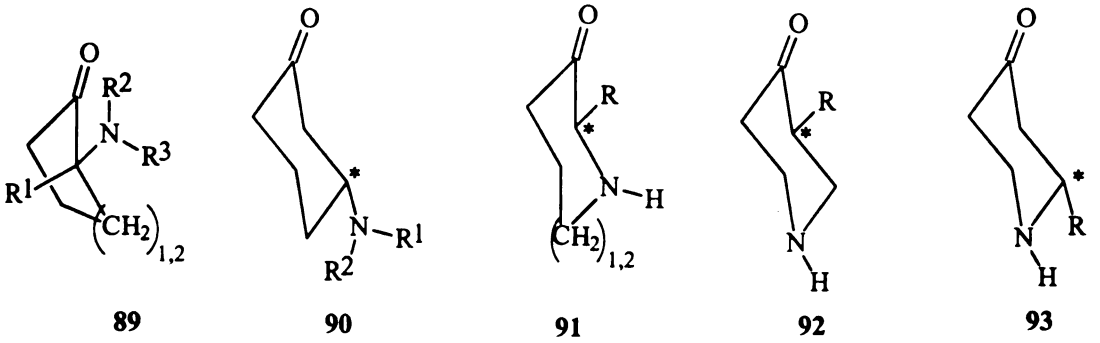
86 **86-anti** **86-syn**

In the reduction of 2-aminocycloalkanones **89** (eq 17), both ring size and the nature of the reducing agent appear to be important. In most cases reduction of aminocyclopentanones (**89**, n=1) afforded preferentially the anti-diastereomer, whereas aminocyclohexanones (**89**, n=2), on the other hand afforded preferentially the syn-diasteromer (Table 1.5). Also phenylcyclohexanone (**89,** n=2; $R^1 = C_6H_5$), bearing a primary or secondary amino group gives only the syn-diastereomer **89-syn** (eq 18).[96,97]

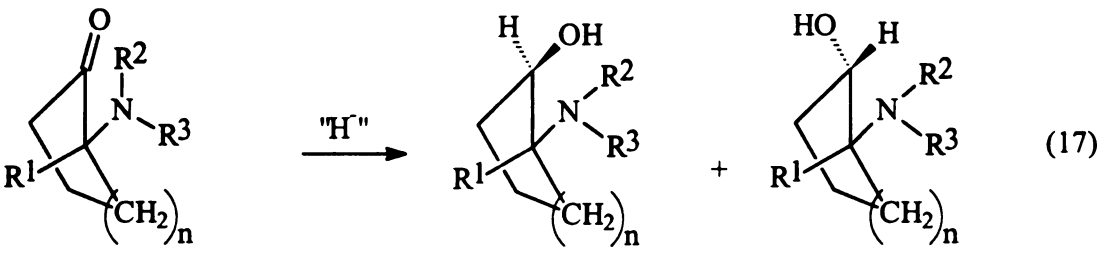
In the group of 3-piperidones (**91**, n = 2), the oxobenzomorphanes and their quaternary ammonium salts behave differently: anti-attack largely predominants in reduction of the free base, but syn-attack largely predominates in reduction of quaternary ammonium salt.[93] The type of substrate has a profound effect on stereoselectivity of reducing agents in the case of 4-piperidone systems **93.** β-substituents in the axial position with respect to the carbonyl group undergo predominant syn-attack, even by reagents usually preferring anti-attack.

Table 1.4. Reduction of Acylaziridines **86**.[99,100,101,102,103,104]

Acylaziridines **86**							
R^1	R^2	R^3	R^4	Reducing agent	Solvent	Temp °C	Anti:Syn ratio
CH_3	H	H	t-C_4H_9	$LiAlH_4$	$(C_2H_5)_2O$	r.t.	40:60
C_6H_5	H	H	CH_3	$LiAlH_4$	$(C_2H_5)_2O$	r.t.	93:7
C_6H_5	H	H	CH_3	$(CH_3)_4NBH_4$	i-C_3H_7OH	r.t.	12:88
C_6H_5	H	H	t-C_4H_9	$LiAlH_4$	$(C_2H_5)_2O$	r.t.	94:6
C_6H_5	H	H	t-C_4H_9	$NaBH_4$	CH_3OH	r.t.	30:70
C_6H_5	C_6H_5	H	c-C_6H_{11}	$LiAlH_4$	$(C_2H_5)_2O$ or C_6H_6	r.t.	100:0
C_6H_5	C_6H_5	H	c-C_6H_{11}	$NaBH_4$	CH_3OH	r.t.	65:35
-$(CH_2)_3$	-$(CH_2)_3$	H	t-C_4H_9	$LiAlH_4$	$(C_2H_5)_2O$	r.t.	47:53
-$(CH_2)_3$	-$(CH_2)_3$	H	t-C_4H_9	$NaBH_4$	CH_3OH	r.t.	95:5
CH_3	H	CH_3	CH_3	$LiAlH_4$	$(C_2H_5)_2O$	r.t.	74:26
CH_3	H	CH_3	CH_3	$NaBH_4$	CH_3OH	r.t.	57:43
CH_3	H	t-C_4H_9	CH_3	$LiAlH_4$	$(C_2H_5)_2O$	r.t.	61:39
CH_3	H	t-C_4H_9	CH_3	$NaBH_4$	CH_3OH	r.t.	86:14
C_6H_5	H	C_6H_5	c-C_6H_{11}	$LiAlH_4$ or C_6H_6	$(C_2H_5)_2O$	r.t.	100:0
C_6H_5	H	C_6H_5	c-C_6H_{11}	$NaBH_4$	CH_3OH	r.t.	85:15
C_6H_5	CH_3	CH_3	H	$NaBH_4$	CH_3OH	r.t.	9:91



89 90 91 92 93



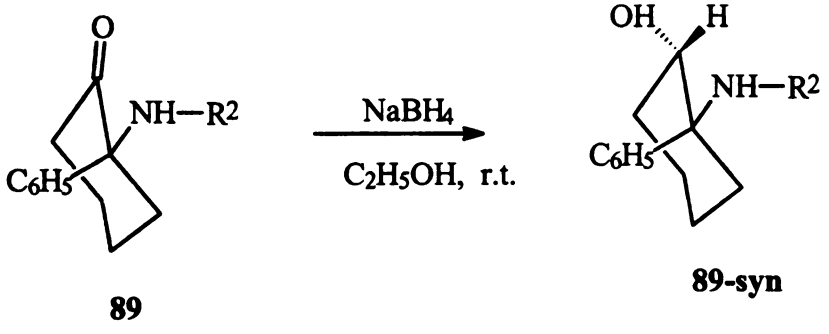
89 89-anti 89-syn (17)

For reductions of 3,5-bridged bicyclic 4-Piperidone derivatives **94** using $NaBH_4$ in methanol, the steroselectivity appears to be determined by the relative size of the ring with anti:syn ratios for n = 1,2,3 of 91:9, 38:62, and 5: 95 respectively.[98]

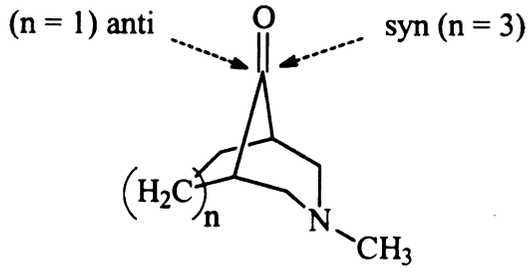
Cyclohexanone derivatives **95** with an axial aminomethyl group prefers anti-attack, whereas equatorial derivatives are not significantly steroselective.

Table 1.5. Reduction of 2-Aminocyclopentanones and 2-Aminocyclohexanones **89** (R^1=H; n = 1,2)to Alcohols **89-anti,syn**.[93]

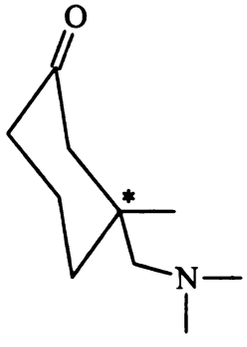
Amino Ketone **89**						
n	R^2	R^3	Reducing agent	Solvent	Temp °C	anti:syn ratio
1	CH_3	CH_3	$NaBH_4$	THF	r.t.	80:20
1	CH_3	CH_3	KBH_4	C_2H_5OH		42:58
1	$-(CH_2)_5-$	$-(CH_2)_5-$	$LiBH_4$	C_2H_5OH		84:16
1	$-(CH_2)_5-$	$-(CH_2)_5-$	$LiBH_4$	THF	r.t.	100:0
2	CH_3	CH_3	$NaAlH_4$	C_5H_5N		68:32
2	CH_3	CH_3	$LiBH_4$	C_6H_6		15:85
2	n-C_3H_7	n-C_3H_7	$NaBH_4$	C_5H_5N		11:89
2	CH_3	c-C_6H_{11}	$NaBH_4$	C_2H_5OH	reflux	20:80
2	$-(CH_2)_5-$	$-(CH_2)_5-$	$NaAlH_4$	THF		62:38
2	$-(CH_2)_5-$	$-(CH_2)_5-$	$NaBH_4$	C_5H_5N		11:89
2	$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$	$NaBH_4$	C_2H_5OH	r.t.	59:41
2	$-(CH_2)_2O(CH_2)_2-$	$-(CH_2)_2O(CH_2)_2-$	$NaBH_4$	C_5H_5N	r.t.	15:85



89 **89-syn** (18)



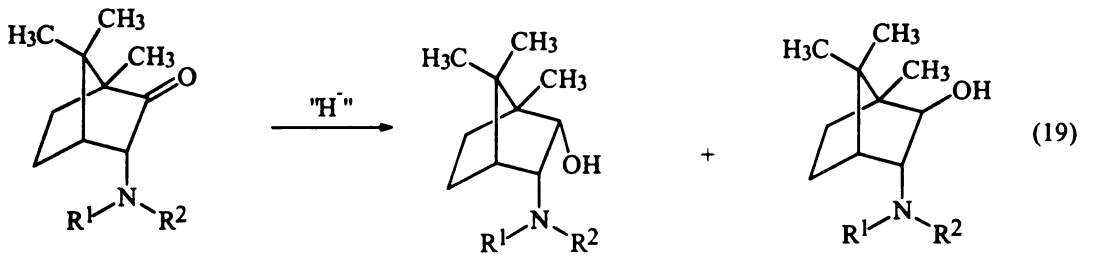
94



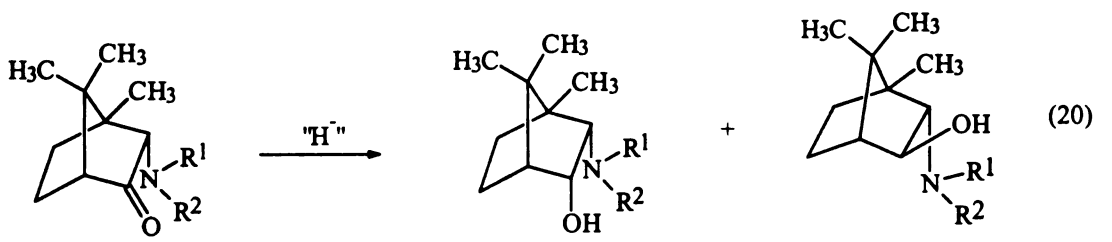
95

Aminobornanones **96** and **98** give predominantly the isomers **97** (en) and **99** (en) respectively when reduced with LAH (eq 19 and 20). On the contrary sodium/ethanol produced the opposite results giving the **97** (ex) and **99** (ex) respectively. The authors concluded that, in hydride reduction of these systems, the attack from the opposite side with respect to the amino group is preferred regardless of it's endo or exo-position contrary to sodium/ethanol which prefer endo-attack. A series of

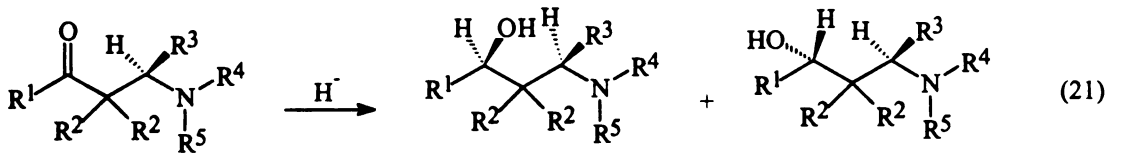
β-asymmetric β-amino ketones **100** (eq 21) has been investigated and the sterochemical model for hydride reduction has been studied.



96 **97 (en)** **97 (ex)**



98 **99 (en)** **99 (ex)**

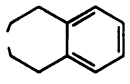


100 **101-anti** **101-syn**

In LAH reductions the stereochemical behavior of substrates with a primary or secondary amino group

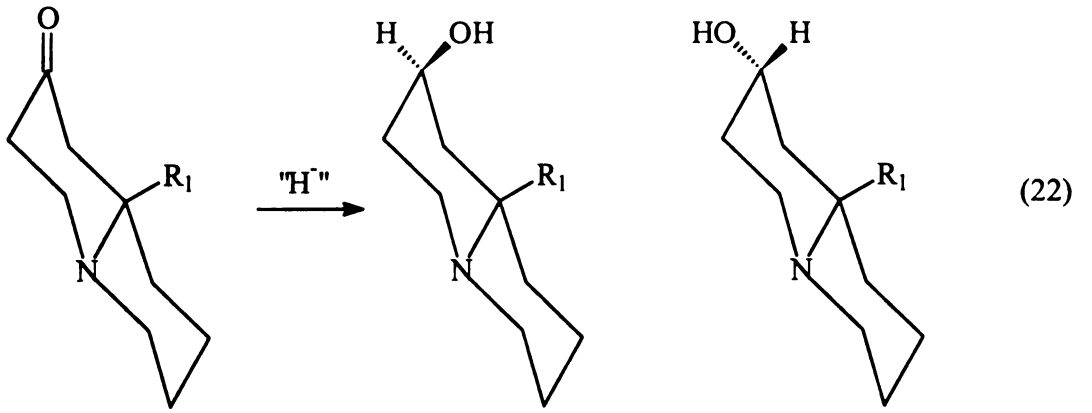
differs from that of the tertiary derivatives. Primary and secondary keto bases are reduced non-stereoselectively, whereas tertiary keto bases show a moderate preference for syn-attack (Table 1.6).

Table 1.6. Lithium Aluminum Hydride Reduction of β-Chiral β-Aminopropiophenones **100**.[114,115]

Aminopropiophenone **100**					
R^1	R^2	R^3	R^4	R^5	anti:syn ratio
C_6H_5	H	C_6H_5	H	H	57:43
CH_3, C_2H_5	H	C_6H_5	H	CH_3, C_2H_5	~50:50
t-C_4H_9, C_6H_5	H	C_6H_5	H	2-naphthyl	~50:50
CH_3, C_6H_5	H	CH_3, C_6H_5	CH_3	CH_3	25:75 - 34:66
CH_3, i-C_3H_7	H	CH_3, C_6H_5	-$(CH_2)_5$-	attached to R^4	23:77 - 40:60
CH_3, i-C_3H_7	H	C_6H_5		attached to R^4	28:72 - 50:50
CH_3, C_6H_5	CH_3	CH_3, C_6H_5	-$(CH_2)_5$-	attached to R^4	24:76 - 45:55

The stereochemical results of reductions of the azabicycloketones **102** (eq 22) are similar to those obtained with the analogous derivatives **92** and indicate a large preference for anti-attack by most reducing agents (see Table 1.7). Cyanoethyl-cyclohexanones **104** are reduced with hydride to give the corresponding alcohols **105** (eq 23), with a

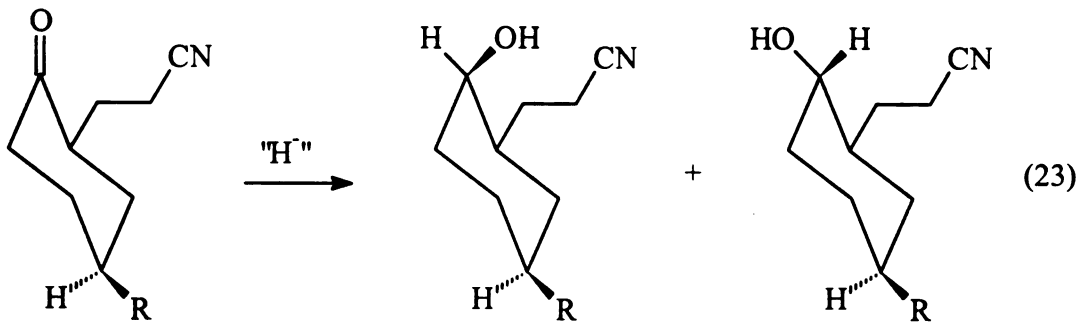
preference for the syn-diastereomer (i.e. equatorial -OH) with **105** anti:syn ratios ranging from 36:64 to 20:80.[118]



102 **103-anti** **103-syn** (22)

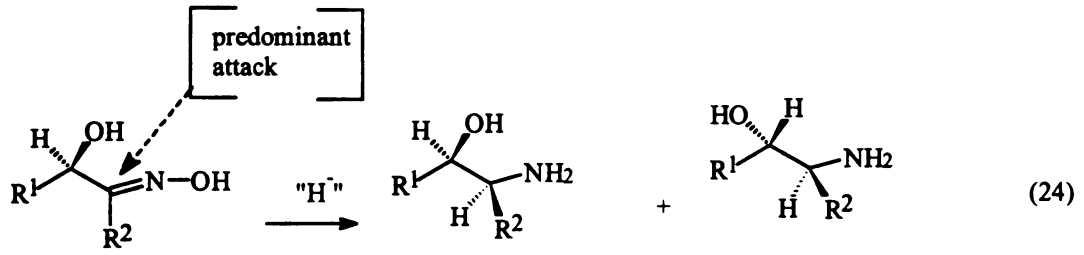
Table 1.7. Reduction of Azabicycloketone **102**[116,117].

Azabicycloketone **102**				
R^1	Reducing Agent	Solvent	Temp°C	anti:syn ratio
H	$LiAlH_4$	$(C_2H_5)_2O$	r.t.	~7:93
H	$NaBH_4$	CH_3OH	r.t.	~7:93
H	Na	C_2H_5OH	reflux	~7:93

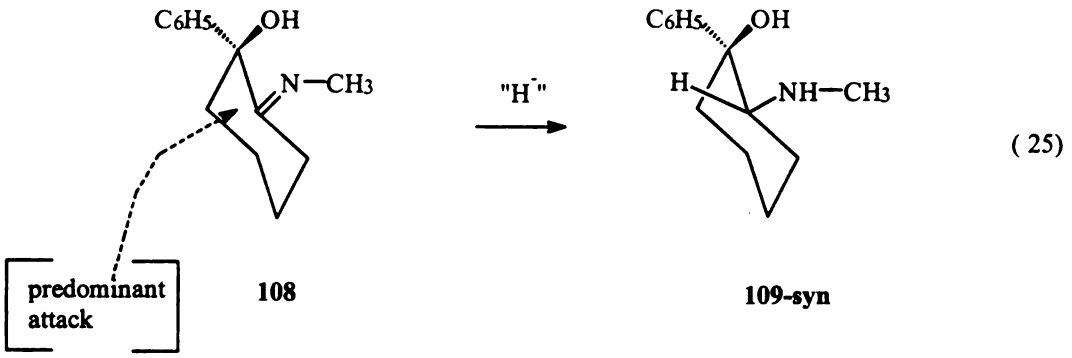


104 **105-anti** **105-syn** (23)

Hydroxyoximes **106** give amino alcohols **107**[45] on reduction with various reducing agents (eq 24). Reduction appear to take place with attack from the opposite side with respect to the hydroxy group showing a preference for the anti-diastereomer (**107** anti:syn ratio = 10:1). In contrast, reduction of the hydroxyimine **108** gives only one diastereomer **109-syn**[97] deriving from attack of the hydride on the same side with respect to the hydroxyl group (eq 25).



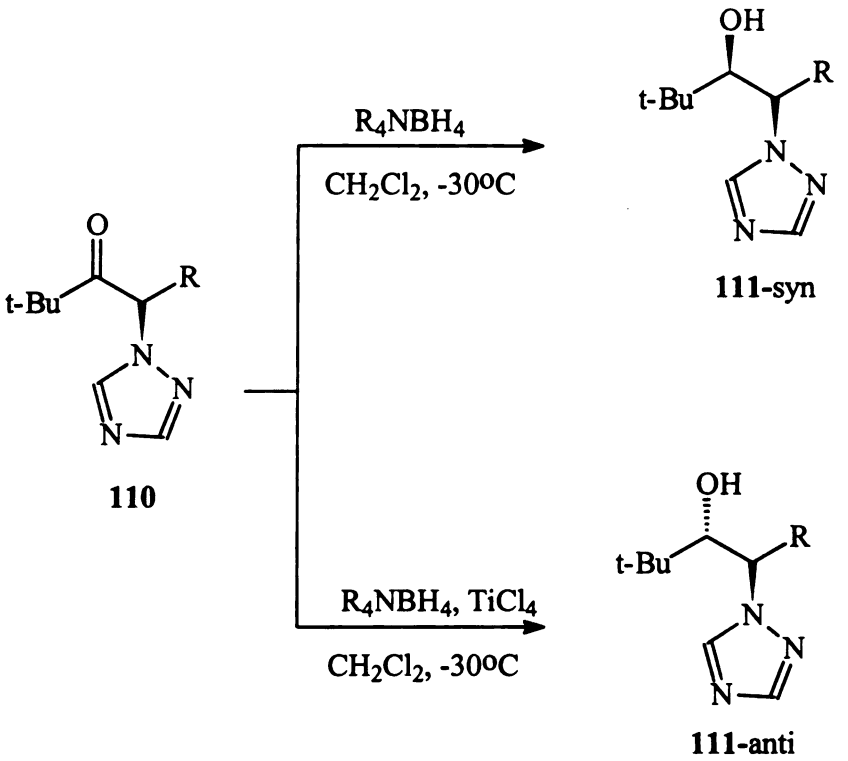
106 **107-anti** **107-syn** (24)



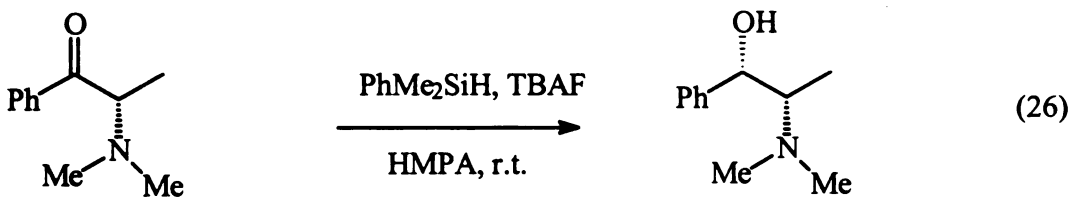
(25)

In contrast to α-amino ketones in which stereoselectivity was rare[119] with conventional hydride reagents, α-triazolyl ketones **110** were reduced in high stereoselectivity by tetra-alkylammonium borohydrides to the syn-alcohols **111**-syn in dichloromethane or to the anti isomers **111**-anti when titanium tetrachloride was added (scheme 6).[120]

Hydrosilylation of α-amino ketones **112** and **114** showed very high levels of selectivity in either direction depending on the reaction conditions (eq 26 and 27). The syn product **113** was the exclusive product of the fluoride-catalyzed reduction[60], while trifuoroacetic acid catalysis generated the anti-isomer **138.**[61]



Scheme 6



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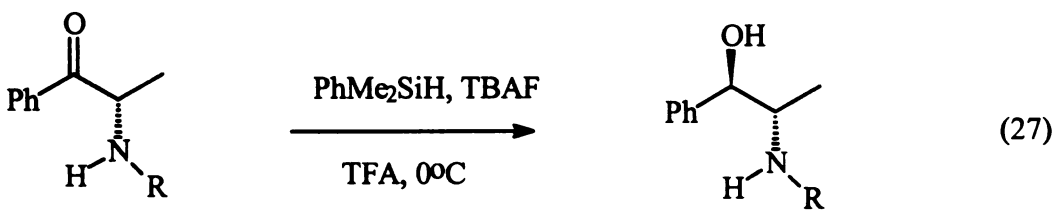
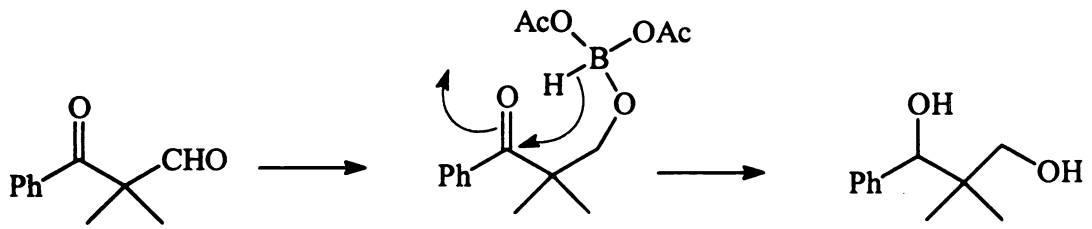


(27)

Several studies have been reported in the literature on face stereoselective reduction of hydroxy-aldehydes and ketones with tetraalkyl-ammonium triacetoxyborohydride. During a study on the chemoselective reduction of aldehydes, Gribble et al.[121] reported the reduction of the keto-aldehyde **116** shown in Figure 1.9 with $n\text{-}Bu_4NBH(OAc)_3$ and postulated an intramolecular hydride delivery[122] as illustrated by intermediate **117** in Figure 1.9.



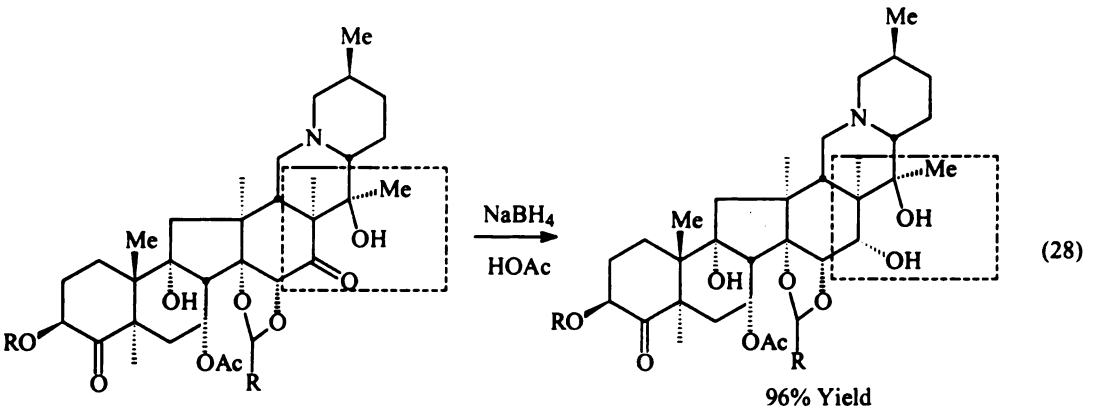
116 **117** **118**

Figure 1.9. Intramolecular hydride delivery during the reduction of the phenylketoaldehyde **116** with tetrabutylammonium triacetoxyborohydride in benzene solvent.

Several workers, beginning with Saksena, have implicated this type of intermediate in apparent intramolecular, hydroxyl-directed ketone reductions (eq 28-31).[123,124,125]

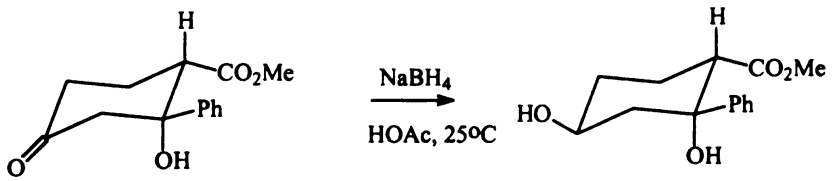
Evans reported studies on the hydroxyl-directed hydride reduction of acylic β-hydroxy ketones using the reducing agent $Me_4NBH(OAc)_3$ (eq 32).[126,127] The range of acylic hydroxy ketones studied by Evans et al. is summarized in Table 1.8.[126] As illustrated in Table 1.8 these reductions exhibit both good levels of reaction diastereoselection and a good degree of generality. It is significant that both the anti and syn aldol adducts (Table 1.8 entries 2 and 3) also exhibit high levels of anti reduction. This suggests that the asymmetric induction from the distal hydroxy-bearing stereocenter overrides the proximal α-methyl stereocenter in either configuration.

The sterochemical course of these reductions is consistent with a mechanistic postulate first suggested by Gribble[122] and may be rationalized via the transition states illustrated in scheme 7. Ligand exchange between substrate hydroxy and the reactive borohydride ligands affords an intermediate substrate-bound alkoxydiacetoxy borohydride which is a stronger hydride donor than the parent borohydride[134,135] and more importantly capable of intramolecular hydride delivery for stereoselective reduction.



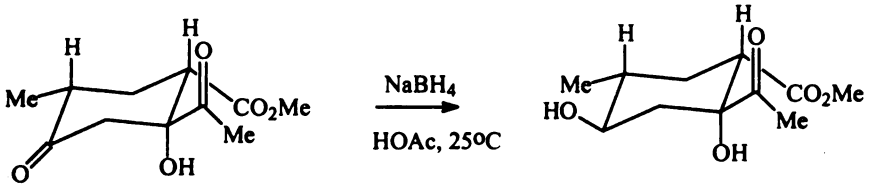
96% Yield

119 120 (28)



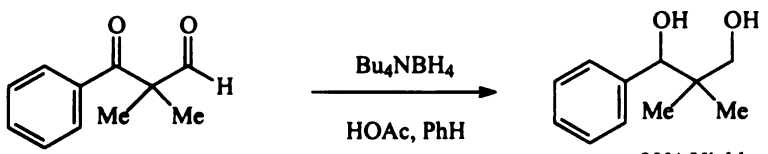
80% Yield

121 122 (29)



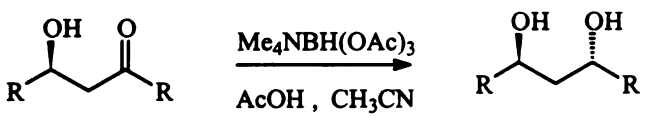
57% Yield

123 124 (30)



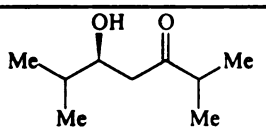
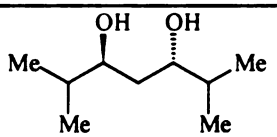
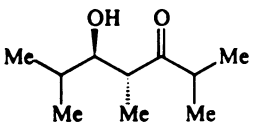
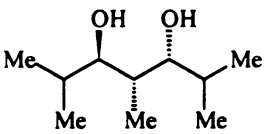
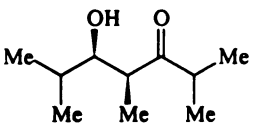
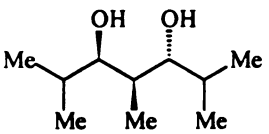
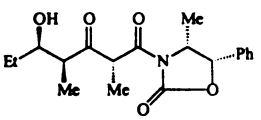
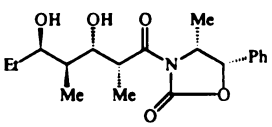
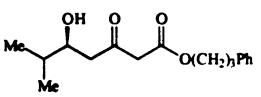
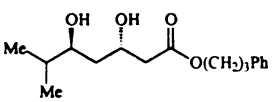
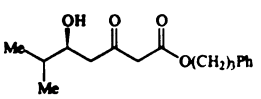
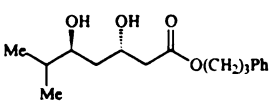
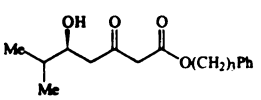
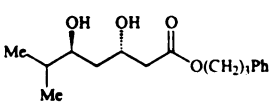
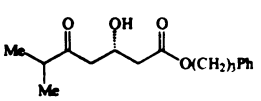
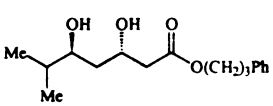
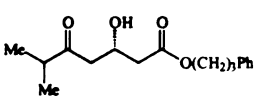
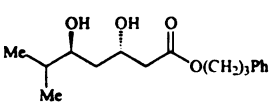
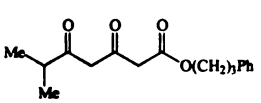
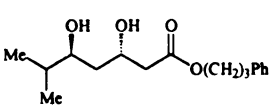
80% Yield

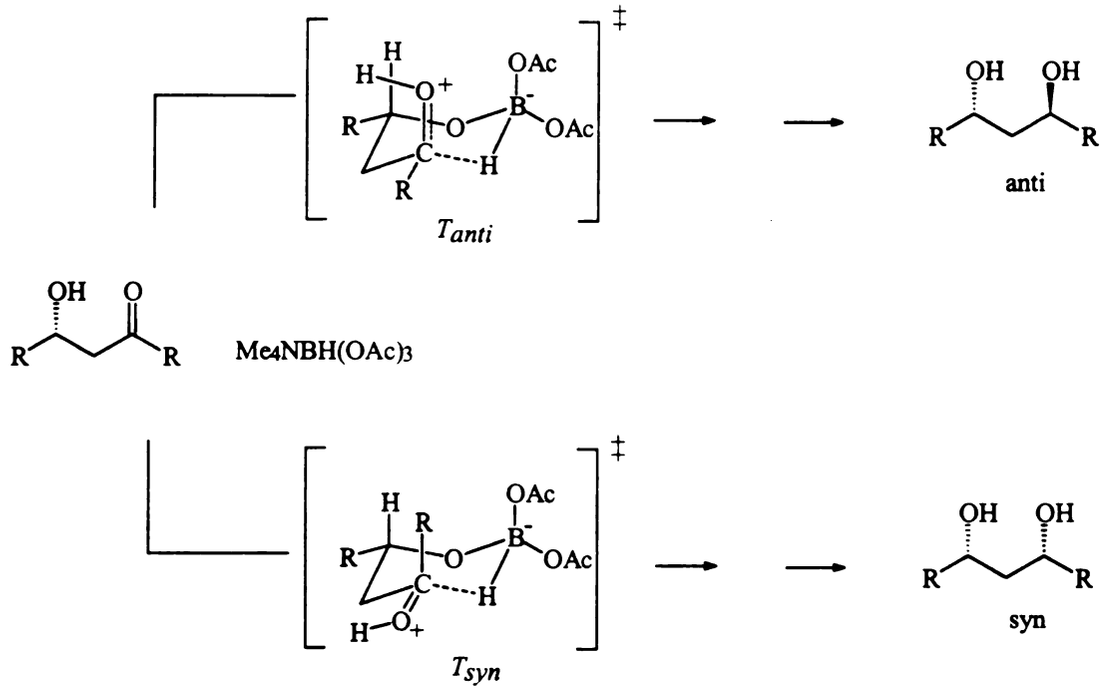
125 126 (31)



(32)

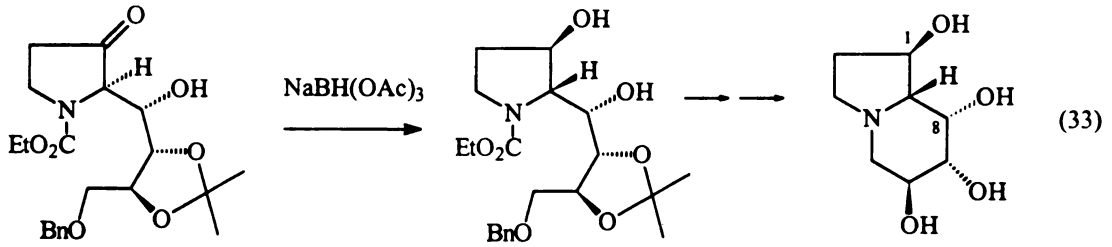
Table 1.8. Diasteroselective Hydroxy Ketone Reduction with $Me_4NBH(OAc)$.[126,128,129,130,131,132,133]

Entry	Reactant	Product	Time (Temp)	Ratio Anti:Syn	Percent Yield
1			5h (-20°C)	96:4	86
2			18h (-20°C)	98:2	92
3			18h (-20°C)	98:2	84
4			30m(+25°C)	>98.2	99
5			18h (-40°C)	95:5	92
6			3h (+25°C)	92:8	89
7			30 min(+25°C)	87:13	78
8			18h (-40°C)	95:5	90
9			18h (+25°C)	89:11	83
10			6h (+25°C)	92:8	69

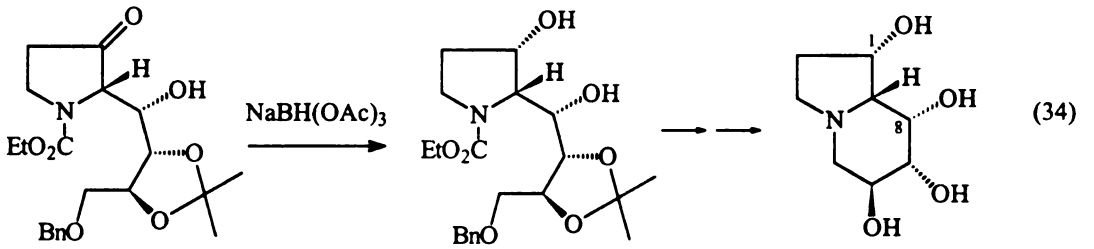


Scheme 7

Thompson et al. employed a hydroxy-directed ketone reduction using $NaBH(OAc)_3$ in the synthesis of 1,8,8a-triepicastanospermine **129** and 8-epicastanospermine **132**.[136] The stereoselective reduction of the heterocyclic-derived aldol adducts **127** and **130** using $NaBH(OAc)_3$, to produce the diol intermediates **128** and **131** (eq 33 and 34) were key steps in the introduction of the C-1 OH in **129** and **132.**

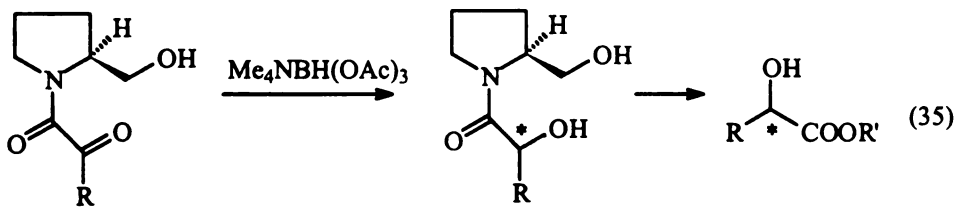


127 128 129 (33)



130 131 132 (34)

Pansare reported studies on a stereodivergent approach to α-hydroxy acids involving substrate directed reduction of α-keto amides using tetramethyl ammonium triacetoxyborohydride (eq 35).[137]



133 134 (2S,2'R) 135 (2S,2'S) 136 (R=Ph,R'=H) 137 (R=R'=CH_3) (35)

They employed a chiral α-keto amide **133** bearing a pendant hydroxyl functionality that could be utilized as a directing group. The treatment of **133** with $Me_4NBH(OAc)_3$ using dimethyl ether gave **134** and **135** as a 18/1 mixture of diastereomers. The observed diastereoselectivity is consistent with a transition state assembly as depicted in figure 1.10.

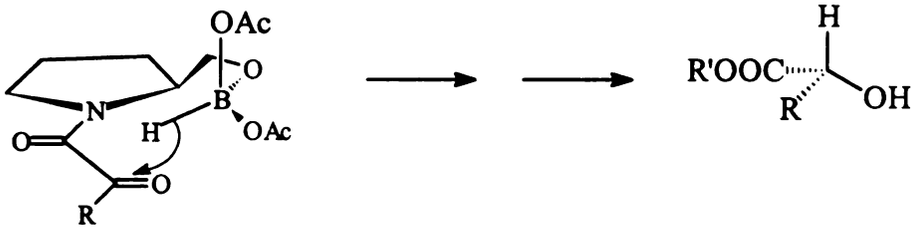


Figure 1.10. Transition state for $Me_4NBH(OAc)_3$ reduction of **133.**

Assuming a coplanar syn amide-anti α-dicarbonyl conformation, intramolecular reduction from the Si-face of the ketone generates mandelic acid with "R" configuration.

Several examples of stereoselective hydroxy-directed reductions of α-hydroxyketones have also been reported (Figure 1.11).[138,139,140]

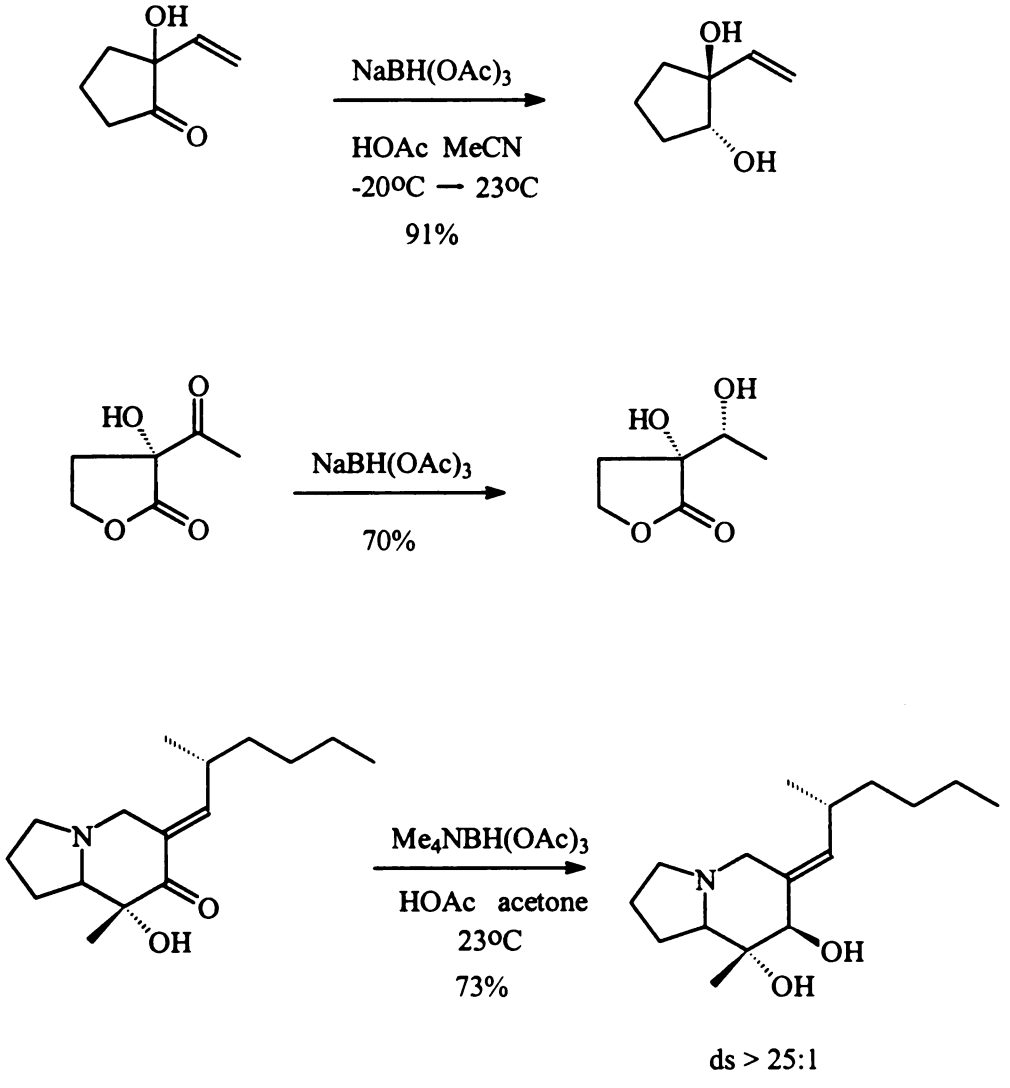


Figure 1.11. Examples of stereoselective hydroxy-mediated α-hydroxyketones.

This review provides only a glimpse of the vast amount of information in the chemical literature involving steroselective reductions. No information was reported employing dihydrogen bonding as a means of enhancing reaction rates or influencing the stereochemistry of reductions. However, we have discovered that dihydrogen bonding has a profound influence on reaction rate and stereoselectivity of borohydride reductions. The results of this work will be presented in chapter 2.

CHAPTER 2

2.1 Reactivity and Stereocontrol in Borohydride Reductions of Ketones Mediated by Dihydrogen Bonding.

Several reports of hydrogen bonding between hydridic and protonic hydrogen centers ("dihydrogen bonding") have explored the structural and electronic characteristics of these interactions,[9,26] demonstrated their significance in both intra- and intermolecular examples,[9,26,141] and developed estimates of the associated energetics.[142,19,20] Of particular interest is the work concerning borohydrides; the stability of these salts in water and other hydroxylic solvents has been known for six decades, and they are among the most common and versatile reducing agents in the organic chemist's toolbox.

In 1994 Jackson et al. structurally examined the $HOH\cdots BH_4^-$ hydrogen bonds in $NaBH_4 \cdot 2H_2O$, concluding that the three close H···H contacts (neutron diffraction internuclear distances 1.79, 1.86, and 1.94 from $NaBD_4 \cdot 2D_2O$) could only be properly understood as true hydrogen bonds, with substantial charge transfer and interpenetration of the Van der Waals surfaces.[143] Having also observed clear hydrogen bonding behavior in solution IR

experiments, we then sought a simple example of a reactivity effect due to such associations. To study face selection in a typical borohydride reaction--ketone reduction mediated by dihydrogen bonding we have chosen to use reduction of α and β-hydroxyalkanones in non hydrogen bonding solvents as the test reaction.

2.1.1 α-Hydroxyketones

The substrates, 2-hydroxycyclobutanone **136,** and 2-hydroxycyclopentanone **138,** (Figure 2.1), were selected with the guidance of AM1 calculations and simple structural models. A particularly important feature is that intramolecular hydrogen bonding between -OH and carbonyl moieties is geometrically impossible in these constrained frameworks. Directing or rate effects, then, could not arise from simple activation of the carbonyl group via intramolecular hydrogen bonding. The relative rigidity of these cyclic ketones also avoids conformational complexity.

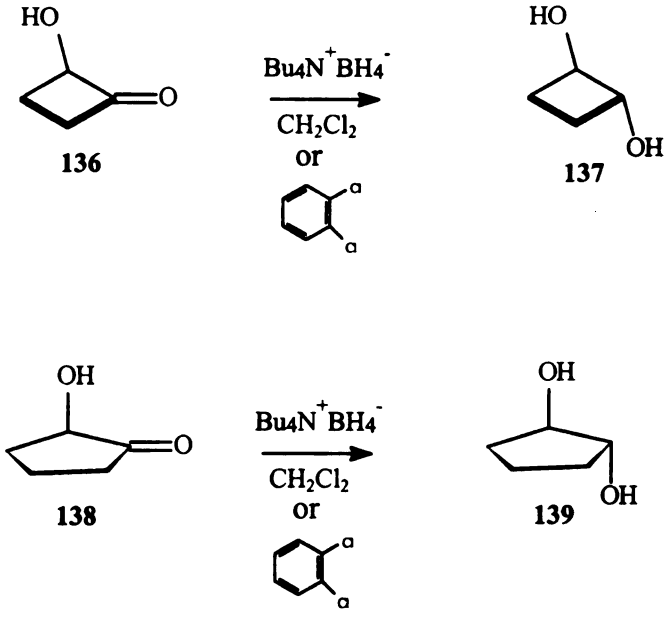


Figure 2.1. 2-hydroxycyclobutanone **136,** and 2-hydroxycyclopentanone **138** reduction using TBABH.

The chlorinated hydrocarbon solvent and the borohydride's tetrabutylammonium countercation were also chosen to be incapable of hydrogen bonding to either borohydride or substrate.

It is important to rule out a process in which an initial reaction of BH_4^- with the -OH site is followed by intramolecular hydride delivery, as is the case with the triacetoxyborohydride reductions previously mentioned. Fortunately, it is easy to observe by FTIR that hydrogen bonding of -OH to BH_4^- occurs prior to reduction, and that there is no depletion of the -OH absorption band or H_2 evolution

during the course of the reaction. This finding mirrors the behavior of the -OH group of cyclopentanol. When cyclopentanone was reduced with $Bu_4N^+BH_4^-$ (TBABH) in the presence of cyclopentanol, no reaction of the OH group was observed during the course of 32 hrs! (Figure 2.2)

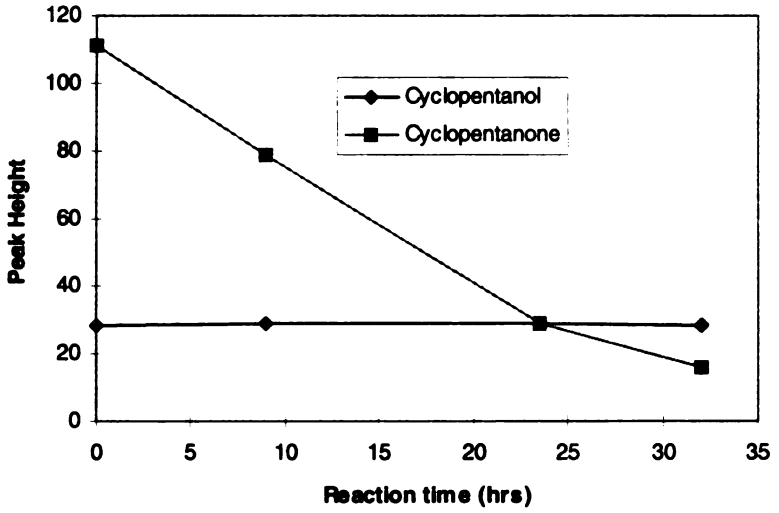
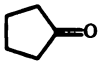


Figure 2.2. Reduction of cyclopentanone in the presence of cyclopentanol with TBABH using dichloromethane as solvent.

Table 2.1 summarizes the results of **136** and **138,** and the corresponding unhydroxylated ketone reference compounds.

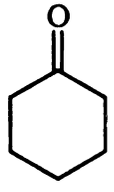
Table 2.1. Reduction Results of **136** and **138,** and the Corresponding Unsubstituted Ketones Reference Compounds.

Substrate	Solvent	Rxn Rate($t_{1/2}$)	Cis diol	Trans diol
	DCB[a]	2 hrs		
136	DCB	< 1 min	0.1	99.9
	DCB	17 hrs		
138	DCB	7 min	1.4	98.6
138	CH_2Cl_2	8 min	0.1	99.9

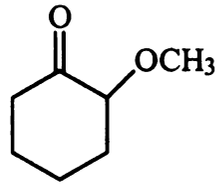
[a] 1,2 dichlorobenzene

As seen in Table 2.1 the reduction of **136** and **138** gave almost exclusively the trans diol product. This finding demonstrates that the hydride is delivered from the -OH substituted face of the substrate. A sursprising result was the extent of reaction rate enhancement cause by the α-hydroxy group. Strikingly, compounds **136** and **138** reacted >100 times faster than the corresponding simple cycloalkanones. This large rate increase cannot be explained on the basis of an inductive effect by the α-substituent alone. It is known that α-substitution by an electron withdrawing group does accelerate ketone reduction.[144] Thus, reactivity of

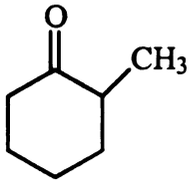
α-substituted benzyl phenyl ketones by $NaBH_4^-$ in 2-propanol increases in the order of H < OH < OMe with reduction rates of 2.69 x 10^3, 98.6 x 10^3, and 238.6 x 10^3 liter mol^{-1} sec^{-1} respectively. Presumably the electron withdrawing nature of the substituent facilitates the nucleophilic attack of BH_4^- on the carbonyl carbon. However, reduction rates are less sensitive to α-substituents in saturated cyclohexanones **139-141** as shown by the $t_{1/2}$ data in Table 2.2.



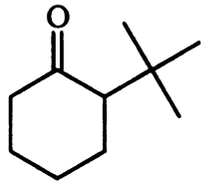
139



140



141



142

Table 2.2. Reduction Rate Data for Cyclohexanones.

Substrate	Reaction Rate $t_{1/2}$(Hrs)
139	22
140	21
141	24
142	35

Unlike the benzyl phenyl ketones, the rates for α-methoxycyclohexanone **140** and cyclohexanone **139** were essentially the same, while the methyl and t-butyl groups in **141** and **142** slightly slowed the reaction as expected($t_{1/2}$ decreased by factors of 1.1 and 1.5 for methyl and t-butyl respectively).

Both the stereochemical outcome and the rate acceleration induced by the presence of the -OH group in **136** and **138** are consistent with a large enhancement (a factor of >100) in the rate of attack by borohydride on the carbonyl face syn to the -OH group. In non hydrogen bonding solvents, the dihydrogen bonding interaction between BH_4^- and the α-hydroxy group facilitates delivery of the hydride to produce (after hydrolysis) the trans diol product (Figure 2.3).

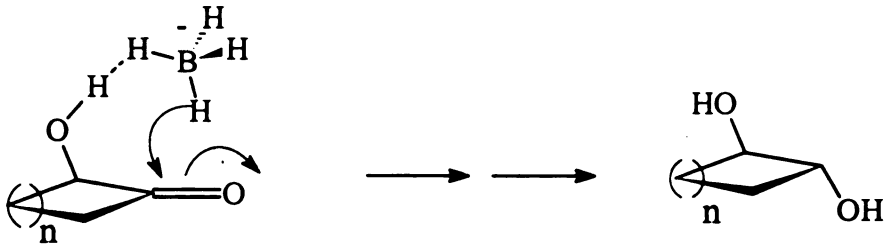


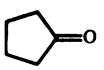
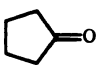
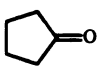
Figure 2.3. Dihydrogen bonding interaction of BH_4^- with α-hydroxy substituent in α-hydroxy-cycloalkanones

The above picture predicts a loss of rate and stereodirecting effects when an added hydrogen bonding reagents, such as an alcohol, interacts with -OH, C=O, and BH_4^- fragments. The trans:cis diol ratio decreased from 332:1 to 22:1 when methanol was added but the reduction rate increased at least 8-fold as seen in Table 2.3, entries 3 and 4 decreasing the half-life from 8 min to < 1 min. Unlike other alcohols, methanol's acidity leads to loss of H_2 and formation of the $CH_3O_nBH_{4-n}^-$ species which is known to be more reactive than BH_4^-.[145,146] The hydroxylic solvent can accelerate reductions of simple ketones by hydrogen bonding

Table 2.3: Reduction Summary of α-Hydroxy-Cyclopentanone.

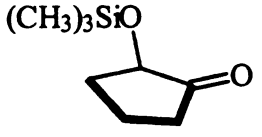
Substrate = 0.25M

TBABH = 0.25M

Entry	Substrate	Solvent	Additive (conc)	$t_{1/2}$	Cis diol	Trans diol
1		CH_2Cl_2		17 hrs		
2		CH_2Cl_2	TBABr (0.35M)	13 hrs		
3		CH_3OH		20 min		
4	**138**	CH_2Cl_2		8 min	0.3	99.7
5	**138**	CH_2Cl_2	CH_3OH (15.5M)	< 1 min	4.4	95.6
6	**138**	CH_2Cl_2	t-amyl (0.9M)	30 min	8.0	92.0
7	**138**	CH_2Cl_2	TBABr (0.25M)	30 min	6.5	93.4
8	**138**	CH_2Cl_2	TBABr (0.25M)		20.1	79.9
9	**138**	CH_2Cl_2	TBAC (0.25M)	57 min	20.3	79.7
10	**138**	CH_2Cl_2	TBAF (0.25M)	120 min	55.0	45.0
11	**143**	CH_2Cl_2		6 Hrs	39.0	61.0

to the carbonyl group and stabilization of the developing negative charge during hydride delivery. Thus, even for e.g. unhydroxylated cyclopentanone

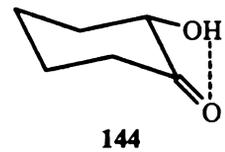
(Table 2.3, entries 1 and 3) addition of methanol accelerates reduction ca. 50-fold ($t_{1/2}$ = 17 hrs vs. 20 min). The bulky t-amyl alcohol (Table 2.3, entry 6) which hydrogen bonds but does not react with the borohydride, causes the expected decrease in rate ($t_{1/2}$ of **138** from 8 to 30 min) and regioselectivity, decreasing the trans:cis ratio from 322:1 to 12:1. Tetrabutylammonium halides-fluoride (TBAF), chloride (TBAC), and bromide (TBABr)- also inhibit the reaction, presumably by competing with borohydride for hydrogen bonding to the substrate's hydroxyl group. As shown in entries 7 - 10 in Table 2.3, the stronger the hydrogen bonding nature of the reagent (TBAF > TBAC > TBABr), the greater the effect on the rate with ($t_{1/2}$ = 120 min, 57 min, and 20 min respectively) and stereoselectivity (trans:cis ratios of 0.8:1, 3.9:1, and 14.4:1 respectively). Further evidence that the -OH group is key to the rate enhancement and stereocontrol is provided by the trimethylsilyl ether **143.**



143

Here, the BH_4···OH- interaction (and hence any directing effect) is turned off, while the reaction half-life was increased from 8 min for **138** to 6 hrs for **143** (Table 2.3, entries 4 and 11).

In 2-hydroxycyclohexanone **144,** the -OH group caused a 300-fold rate increase ($t_{1/2}$ = 4 min for **144** and 22 hrs for **139**) over simple cyclohexanone **139**, but essentially no stereoselectivity was observed in the cyclohexanediol product (49:51 cis/trans). This can be explained in terms of the chair structure of **144,** in which the equatorial -OH activates



144

the coplanar carbonyl group through intramolecular hydrogen bonding, without inducing a significant facial directing effect on the BH_4-. Thus, results for the reduction of **144** give further credibility to the claim that in the conformationally rigid systems **136** and **138**, where intramolecular hydrogen bonding

is not possible, the stereocontrol and rate enhancement are caused by the directing effect of the -OH group via dihydrogen bonding with BH_4-.

Figure 2.4 summarizes the results of semiempirical AM1 calculations on BH_4^- reduction of **136**. Consistent with the experimental findings, the hydrogen bonded complexes are substantially lower in energy than the "Van der Waals" minimum located for approach to the unsubstituted face. The energetic preference for the -OH face also appears in the calculated transition structures for hydride transfer. For reference, the complexation energy and barrier for hydride delivery to the simple ketones are comparable to those for attack on the unhydroxylated face.

2.1.2 β-Hydroxyketones

To expand our study we looked at hydroxyl-directed stereodirecting and rate effects of β-hydroxy cyclic ketones (Table 2.4). No significant directing effects or rate enhancement were found when 2,2,4,4-tetrametyl-3-hydroxy-1-cyclobutanone **145** and 3-hydroxy-1-indanone **146** reacted with TBABH (Table 2.4 entries 1 and 2). However, 4_{ax}-hydroxy-2-

adamantanone **147** does show rate and stereodirecting effects like those found in **136** and **138,** albeit weaker. The locked chair conformation of **147** forces the axial -OH closer to the carbonyl group which should place the dihydrogen bonded BH_4^- in an ideal location for effective hydride delivery to the carbonyl carbon. As seen in Table 2.4 entries 3 and 4 a 150 fold rate enhancement was observed for **147** compared to the unhydroxlated adamantanone **148** ($t_{1/2}$ = of 0.9 hrs and 147 hrs respectively). The reduction of **147** shows the predicted preference for the trans diol but the stereoselectivity was observed to a lesser extent compared to **136** and **138** with a 20/80 cis/trans ratio for **146** compared to 1/99 cis/trans ratio for **136** and **138**. The stereoselectivity for **147** was complicated by epimerization which presumably occurs via a retro-aldol ring opening; rotation of the aldehyde group and subsequent recyclization then gives the epimer (scheme 8).[147] To determine if epimerization was occuring the 4_{eq}-hydroxy adamantanone isomer **149** was prepared and reduced under equivalent conditions as **147**. If no epimerization occurs, only the trans diol **150** and the equatorial cis diol **151** should be

produced (scheme 9). However if epimerization occurs at C-4 in **149** then the axial cis diol **152** would be formed(scheme 8). Indeed when reduction of **149** was carried out under the same reaction condition as **147** a significant amount of **152** was formed (Table 2.4 entry 5). The rate of reduction for **149** was also significantly increased compared to **148** (Table 2.4 entries 5 and 4). Unlike **147** in which the -OH group is in the axial position for which effective hydride delivery via dihydrogen bonding is possible, the equatorial -OH in **149** can not direct hydride delivery and therefore the observed rate enhancement can not be attributed to dihydrogen bonding interaction between BH_4^- and -OH unless epimerization occurs.

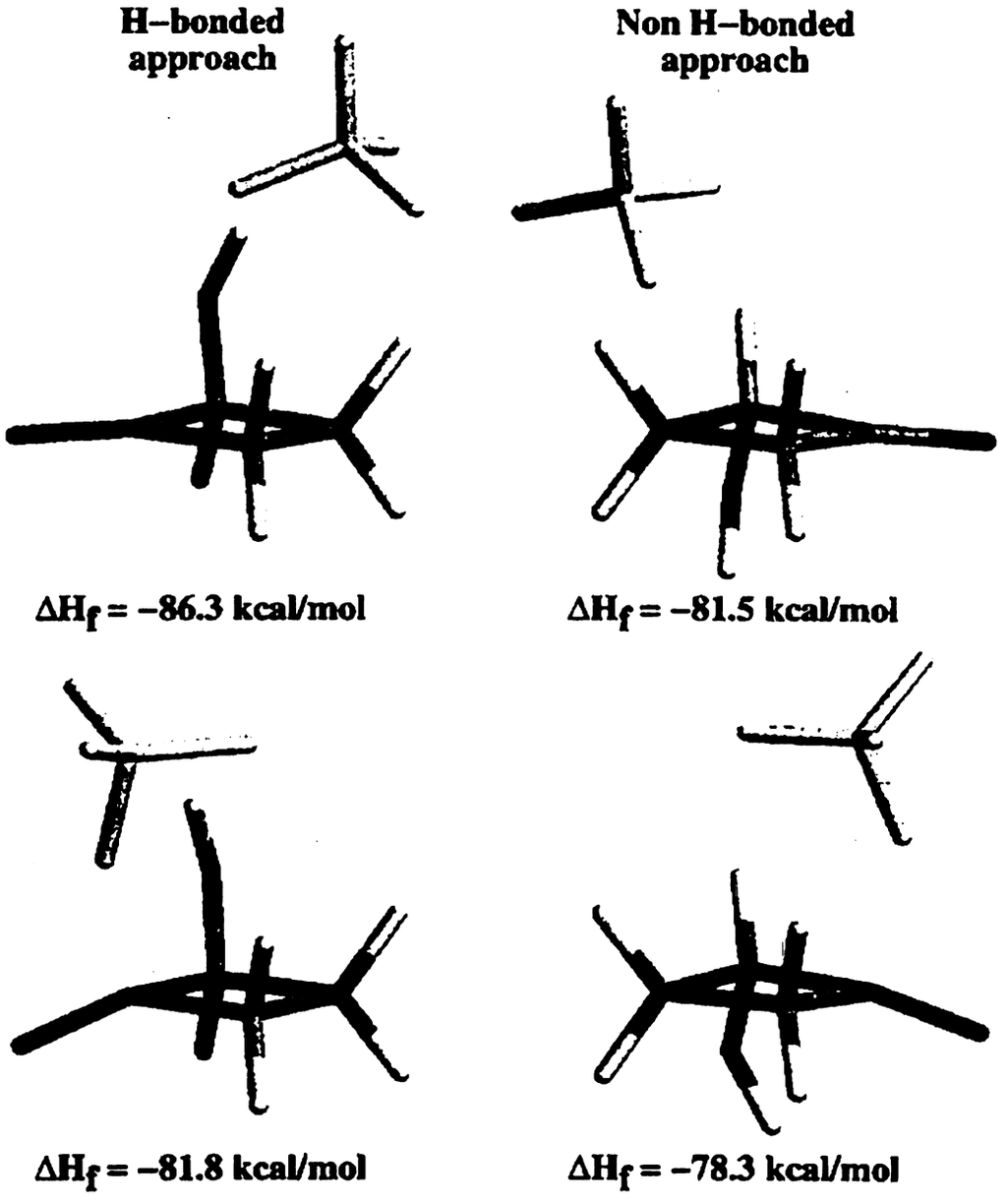
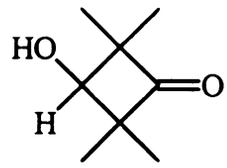
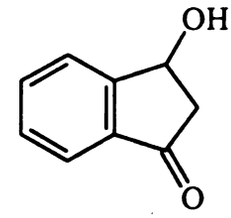


Figure 2.4. Dihydrogen-bonded directed borohydride delivery: AM1 Semiemperical calculated structures and energies.



145

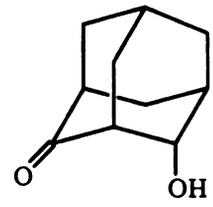


146

Table 2.4: Reduction of β-Hydroxy Cyclic Ketones.

Entry	Substrate	Solvent	$T_{1/2}$ (hrs)	Cis diol	Trans diol
1	**145**	CH_2Cl_2	10	41	59
2	**146**	CH_2Cl_2	4	60	40
3	**147**	CH_2Cl_2	0.9	20[a]	80
4	**148**	CH_2Cl_2	147		
5	**149**	CH_2Cl_2	1.5	17[b]/33[a]	50
6	**150**	CH_2Cl_2			

[a] Cis diol **152** [b] Cis diol **151**



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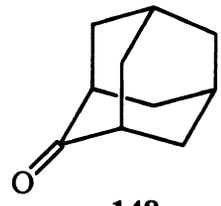

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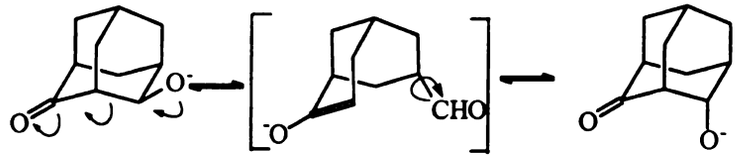
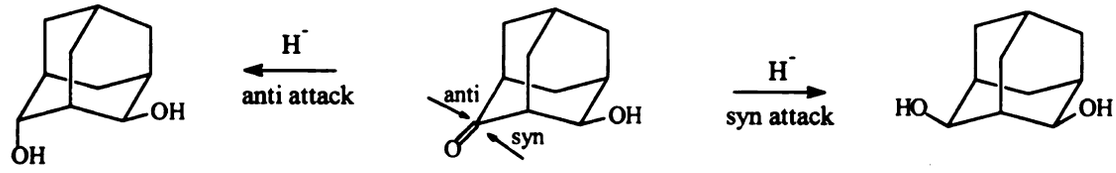
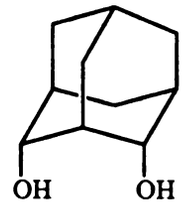


Scheme 8



150 149 151

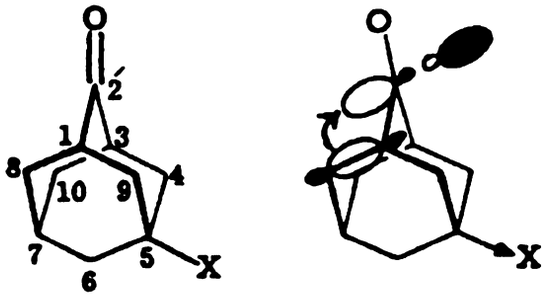
Scheme 9



152

The rate effect and the moderate preference for the trans diol for the reduction of **149** may also be rationalized based on Cieplak's theory of charge transfer stabilization of the transition state.[148] Le Noble et al. employed Cieplak's theory in their study of the effects of substituent modification on face selection in the reduction of 5-substituted 2-adamantanones.[149] They found it possible to account for their experimental observations by assuming that the transition states were stabilized by hyperconjugative donation of electrons into the σ^* orbital of the newly forming or breaking bond by the antiperiplanar vicinal bonds. When two of these vicinal bonds are adjacent to an electron withdrawing substituent as in **153,** they are rendered electron poor by it; the two transition states are then unequal in energy, and as a result a rate effect is induced and syn attack as in **154** is favored (with a reported E/Z diol ratio of 58/42 when X = OH).[149] However the rate enhancement caused by this phenomenon were all less than a factor of 10 whereas for the case of **147** and **149** in our study the rate was increased by factors of 150 and 100 respectively. In light of the large rate

enhancement for **149** it seems reasonable that an electronic inductive effect from the 4_{eq}-OH in **149** as well as epimerization to the axial **147** and subsequent hydride reduction may both be contributing to rate enhancement and stereoselectivity. Indeed, recovered starting material for experiments starting with **149** showed the presence of some **147** in addition to the reduced products.

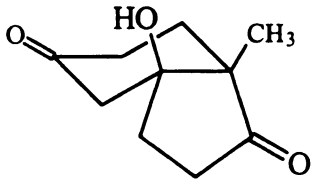


153 **154**

Although complicated by epimerization and electronic effects, the reduction results of **147** showed that the proximity of the directing group to the carbonyl functionality is crucial for rate enhancement and stereoselectivity for α and β-hydroxy cycloketones, which may explain why the β-hydroxyketones **145** and **146** showed no significant rate or stereodirecting

effect. Since these rings are relatively flat and rigid, the dihydrogen bonded BH_4^- is presumably positioned out of range for effective hydride delivery to the carbonyl carbon.

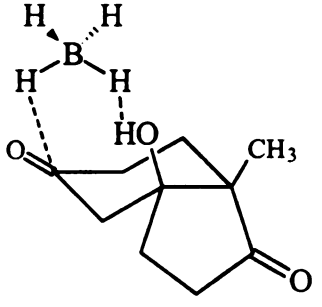
To further demonstrate this point the bicyclic β-hydroxy-diketone 1S,6S-1-hydroxy-6-methyl-bicyclo[4.3.0]nona-3,7-dione **155** was studied.



155

The reduction of **155** with the -OH group positioned in a 1,3 relationship to both the cyclohexyl and the cyclopentyl carbonyl groups further illustrates the differences in the stereodirecting and rate effects of the 3-hydroxycyclohexanone ring in which the chair conformation positions the OH closer to the cyclohexyl carbonyl than the relatively flat 3-hydroxycyclopentyl carbonyl. Based on the reaction results of **145, 146** and **147** one would expect the carbonyl on the cyclohexanone ring to be reduced in preference to the carbonyl on the cyclopentanone ring in **155**. The reaction was

carried out using one hydride equivalent of TBABH in dichloromethane as solvent. The addition of the TBABH caused a shift of approximately 7 cm^{-1} in the -OH and the carbonyl vibrational stretching frequencies on the cyclohexanone ring (from 3597 to 3590 cm^{-1} and 1750 to 1743 cm^{-1} respectively) which indicates an interaction of BH_4^- with the -OH and the carbonyl site on the cyclohexanone ring as shown in **155A.**



155A

The fact that there was no shift in the carbonyl frequency for the cyclopentanone ring indicates that the dihydrogen bonded BH_4^- is too distant to interact simultaneously with the -OH and the cyclopentanone carbonyl group. This preference is manifested in the reactivity results as shown in figure 2.5.

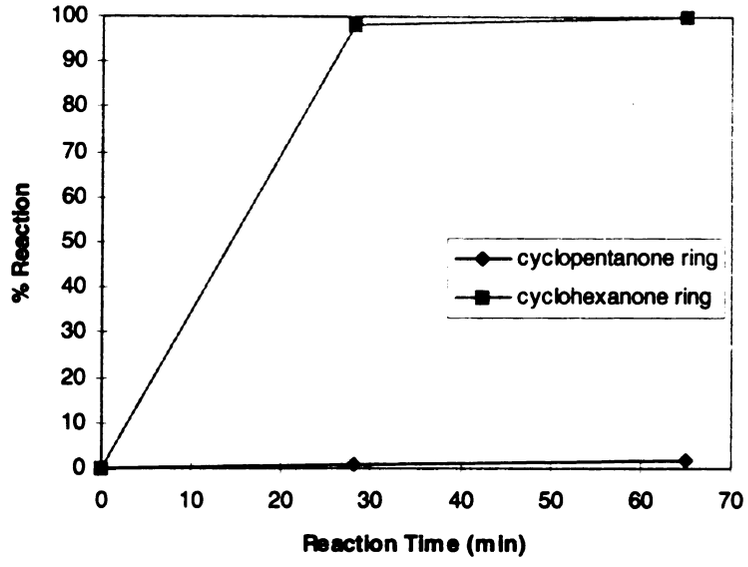
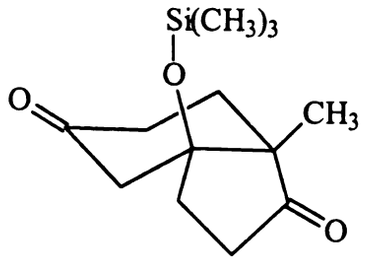


Figure 2.5. Reduction of **155** Using One Equivalent of BH_4^- in Dichloromethane Solvent.

The results in figure 2.5 clearly show that the carbonyl on the cyclohexanone ring is preferentially reduced under these conditions. When the -OH substituent on **155** was trimethylsilylated to **156**, thus turning off any directing effect, no rate enhancement was observed relative to the simple 5/6 monocylic ketones and furthermore the reactivity was reversed so that the reduction of the cyclopentanone carbonyl was preferred (figure 2.6), consistent with the relative reactivities of the simple 5- and 6-membered cycloalkanones.



156

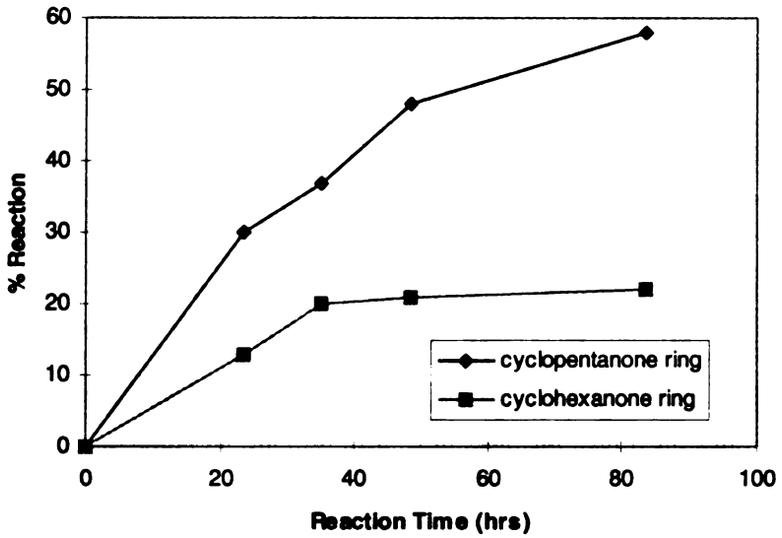
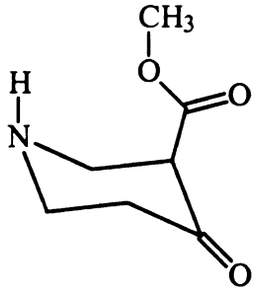


Figure 2.6. Reduction of **156** using one equivalent of BH_4^- in dichloromethane solvent.

The silylated compound **156** did not show a shift in the carbonyl vibrational frequency for either the cyclohexanone or the cyclopentanone rings (vibrational frequencies for the cyclohexanone and cyclopentanone rings were 1750 and 1723 cm^{-1} respectively before and after TBABH addition).

Compound **157** was used to study rate effects of BH_4^- using an amine functionality as the directing group. AM1 geometry optimization calculations



157

favor the ester group being in the axial position which allows the -NH site to direct the BH_4^- (via dihydrogen bonding) to the ester carbonyl. As shown in figure 2.7 the ester functionality was reduced in preference to the ketone. However this rate enhancement can not be totally attributed to the -NH directing BH_4^- to the ester carbonyl because this compound is capable of assuming a conformation **158** that is capable of forming an intramolecular hydrogen bond between the -NH site and the ester carbonyl oxygen which would also cause an increase in reduction rate. Probably both effects are in operation here.

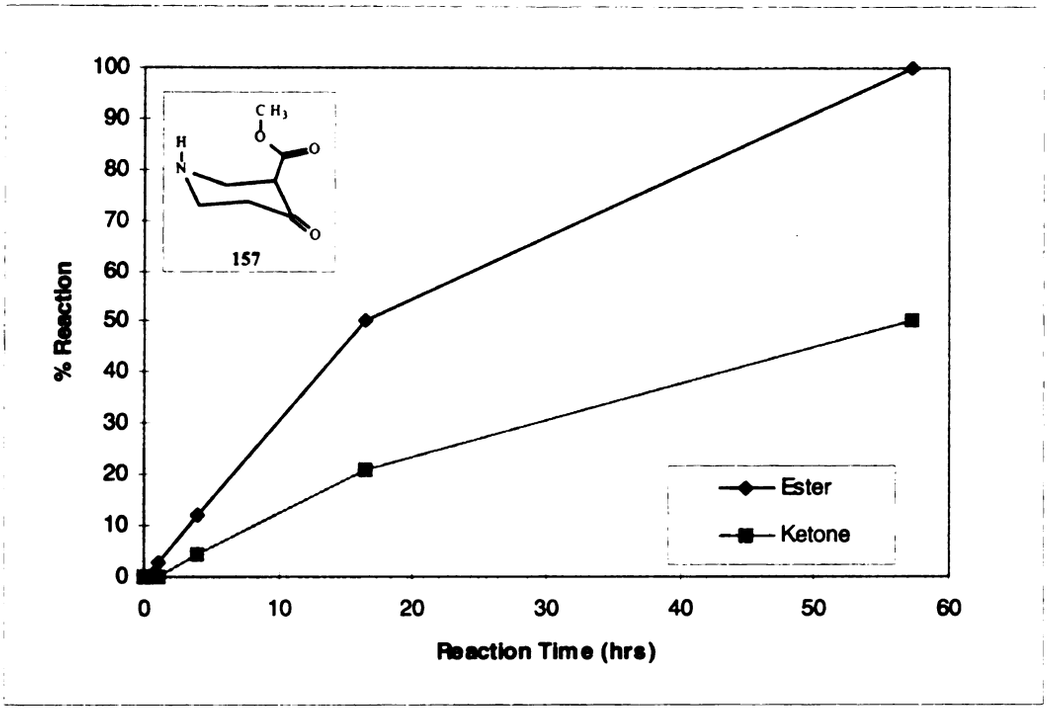
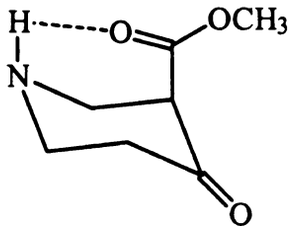


Figure 2.7. Rate comparison of Ester & Ketone functionalities in the reduction of methyl 4-oxo-3-piperidine carboxylate **157** with 2 equivalents of TBABH in dichloromethane.



158

We believe the results presented herein represent the first recognized instance of a directing effect specifically mediated by dihydrogen bonding. Such interactions must have exerted influences in numerous previous studies, but their

contributions have been undetectable in the context of a given substrate, or have been muddied by the presence of hydrogen bonding solvents, Lewis acidic counterions, or other stereochemical biases. The strength of the facial preference, however, suggests that this class of directing effect may offer some useful stereo- and regiocontrol of reactions involving hydride reagents.

CHAPTER 3

3.1 Asymmetric Reduction Using Chiral Hydride Reagents.

Asymmetric reduction of prochiral ketones using chiral hydride reagents has provided an efficient tool for the synthesis of optically active alcohols[150,151] which are considered one of the most important classes of substrates.[152] Lithium aluminum hydride (LAH), $NaBH_4$, and BH_3:THF complexes have been modified with optically active ligands to achieve the delivery of hydride selectively to one face of the prochiral ketones. In general, the chiral hydride reagent is generated in situ by reaction of a suitable metal hydride with chiral ligands such as alkaloids,[153] sugar derivatives,[154] amino alcohols,[155] chiral oxazolines,[156] tartaric acid derivatives,[157] chiral amines,[158] chiral amineboranes,[159] and chiral diols.[160]

During the past two decades there have been many papers describing research on the enantioselective reduction of ketones by a wide variety of chiral hydride reagents thus a brief review of this area is in order. For clarity the

review is arranged according to the chiral hydride reagent type.

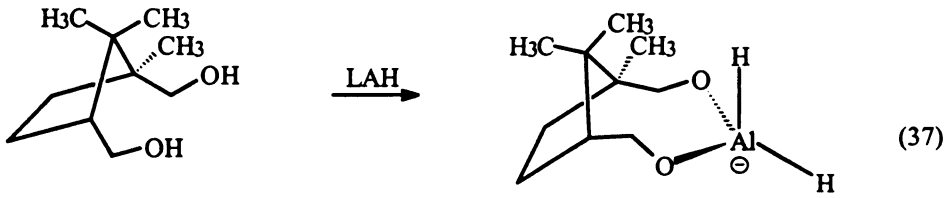
3.1.1 Chiral Aluminum Hydride Reagents

Chiral lithium aluminum alkoxy hydrides were first studied by Bothner-By over 4 decades ago.[161] He utilized an LAH/Camphor complex which precipitated many studies to determine methods of increasing the stereoselectivity of the reductions.[162] The studies showed that stereoselectivity is dependent on the temperature, solvent, substrate, the LAH:ligand ratio and the ligand used. Poor stereoselectivity resulted due to the disportionation of the chiral alkoxy ligands which generated more than one hydride species in solution (eq 36). Primary alcohols such as

$$2LiAl(OR)H_3 \longrightarrow LiAl(OR)_2H_2 + LiAlH_4 \qquad (36)$$

ethanol and 2-propanol have been used to convert the chiral alkoxy ligand into the trisalkoxy hydride form which is known to be more stable to

disproportionation.[163,164,165] When (+)-1,2,2-trimethyl-1,3-bis(hydroxymethyl)cyclopentane **159** is reacted with LAH, two hydrides remain, one hindered (syn) and one unhindered (anti) hydride (eq 37).

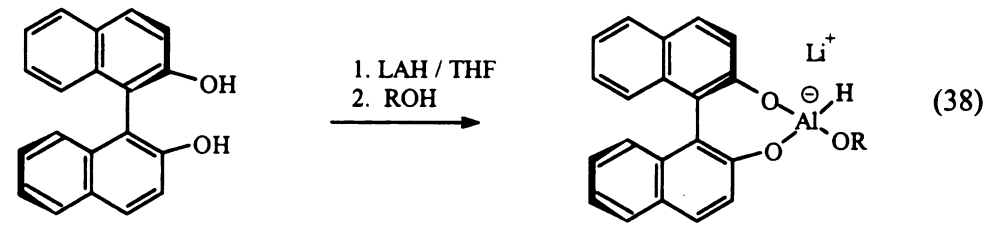


(37)

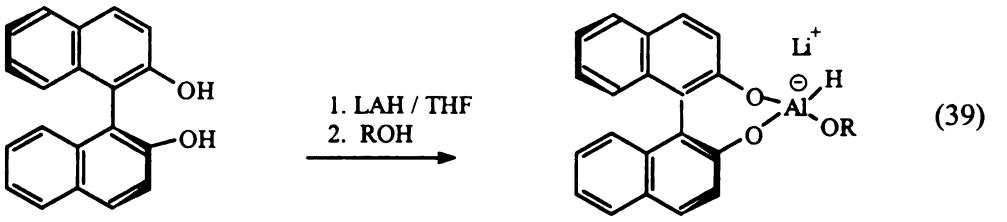
159 **160**

The effect of replacing the less hindered hydride with an achiral alcohol in the reduction of acetophenone was studied by Johnson and Klein.[166] The addition of the achiral alcohol increased the optical yield but, the best case gave only 18% ee.

Noyori has devised a chiral hydride reagent (BINAL-H) (R)-**162** and its enantiomer (S)-**162** by the modification of LAH with equimolar amounts of (R)- or (S)-[1,1'-binaphthyl]-2,2'-diol **161** and a simple alcohol (eq 38 & 39).[167,168]



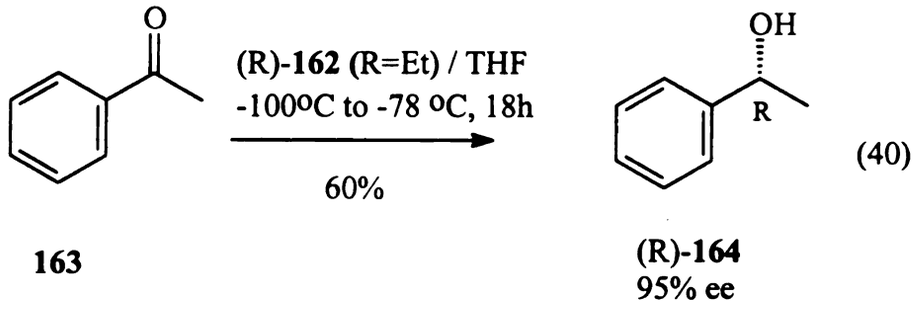
(R)-**161** (R)-**162** (38)



(S)-**161** (S)-**162** (39)

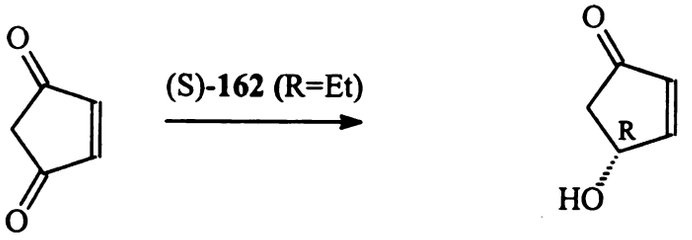
R = Me, Et, CH_2CF_3, etc

The reducing agents **162** exhibit high enantioface-differentiating ability in the reduction of diverse unsaturated carbonyl compounds such as aromatic ketones, alkynlic ketones, olefinic ketones, and aldehydes, etc. Reduction of acetophenone with (R)-**162** (R = Et) under the conditions described in eq 40 gave the corresponding (R)-**164** in 95% ee.



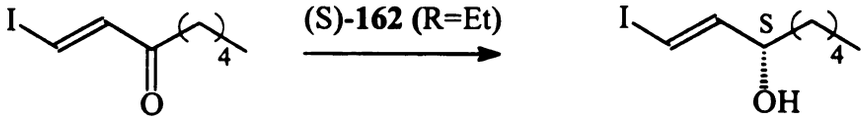
When R in (R)-**162** was changed from Et to CH_2CF_3, the %ee of **164** decreased from 95% to 42% and the absolute configuration was inverted to the (S)-**164.**

Noyori's BINAL-H reagent **162** has also been successfully used to synthesize building blocks of prostaglandins (PG). 4-Hydroxy-2-cyclopenten-1-one (**166**) and compound **168,** which are part of a three component coupling process[169] in PG synthesis, have been prepared in 94% ee and 97% ee respectively by reducing the corresponding enones with (S)-**162** (R = Et) (eq 42 and 43).



(42)

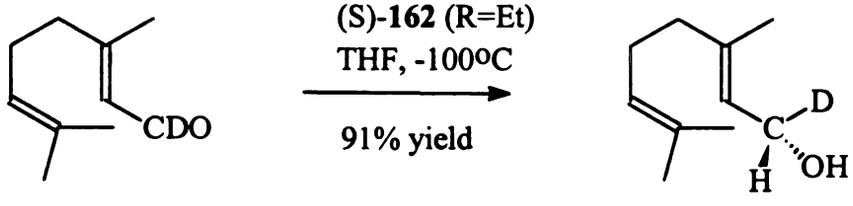
165 **166**



(43)

167 **168**

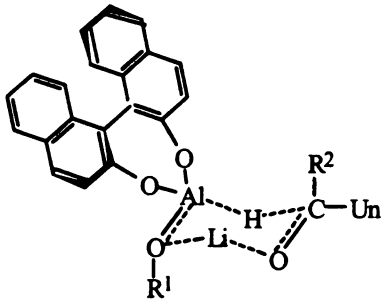
Noyori's BINAL-H reagent has also successfully reduced deuterated aldehydes. Geranial-1-d(3,4-dimethyl-2,6-octadienal[1-^{2}H]), **169** has been reduced to geraniol-1-d **170** in 91% yield and 84% ee (eq 44).[168]



(44)

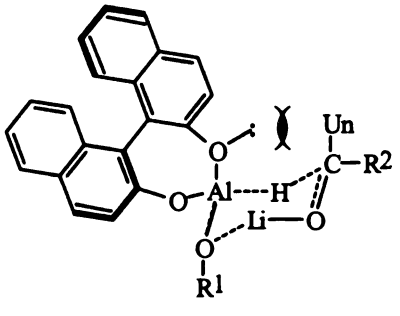
169 **170**

A six-membered transition state model **171** has been proposed to account for the observed stereoselectivity in ketone reduction.



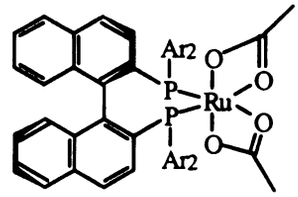
171

Equatorial unsaturated (Un) and axial saturated groups (R) attached to the carbonyl function are differentiated based on their electronic nature. The alternative diastereomeric transition state is unfavorable due to the interaction of an oxygen lone pair and the unsaturated group (**172**).



172

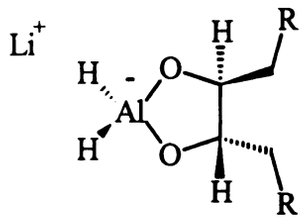
Noyori has also developed a BINAP-Ru complex **173** for the enantioselective hydrogenation of carbonyl compounds.



173

No more will be said about **173** here, this research has been thoroughly reviewed by Noyori.[170,171,172]

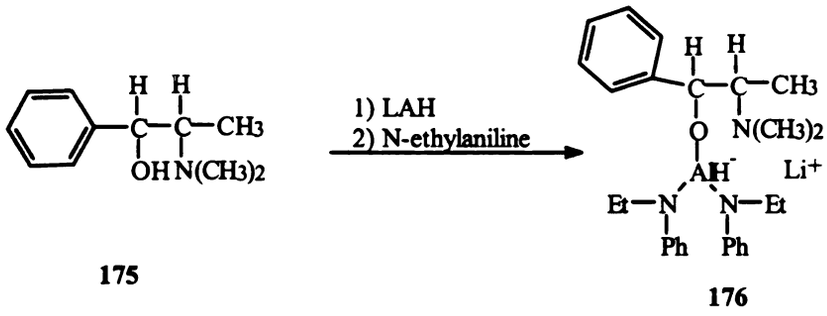
Seebach and co-workers discovered that the N- and O-substituted chiral diols prepared from tartaric acid and maleic acid were effective as chiral ligands in the reduction of aryl alkyl ketones. The diol is reacted with LAH to form the proposed cyclic structure **174.** The optical yields were in the range of 0.8% to 45% ee except for the reduction of 1-(2,4,6-trimethylphenyl)-1-ethanone which gave 87% ee using **174** (R = pyrrolidine).



R = $N(Me)_2$, pyrrolidine, piperdine, $NMe(C_8H_{17})$, NMePh, $NMe(EtO)_3Me$, OMe, OPh, etc.

174

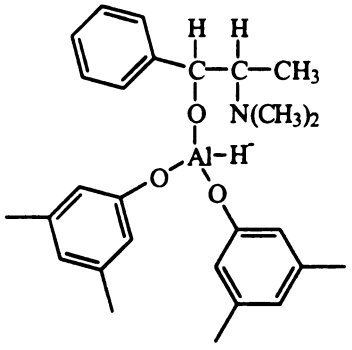
The reduction of α,β-unsaturated ketones using a chiral complex **176** prepared from LAH, (-)-N-methylephedrine **175**, and N-ethylaniline (eq 45) gave their corresponding allylic alcohols in high optical (78-98% ee) and chemical (92-100%) yields.



175 **176** (45)

Vigneron and Bloy studied the reduction of α,β-acetylenic ketones with the chiral complex [LAH:N-methylephedrine:3,5-dimethyphenol] **177**

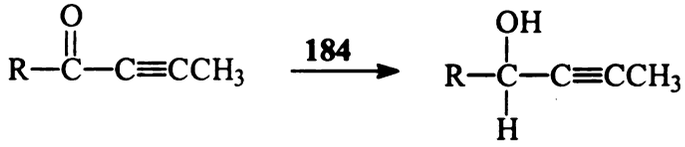
which provided propargylic carbinols with 75 to 90% ee.[173]

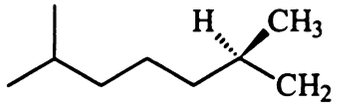
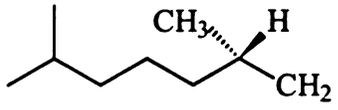
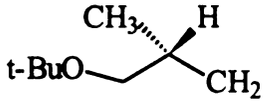
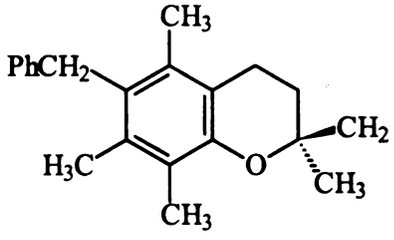
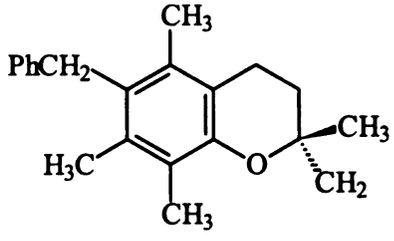


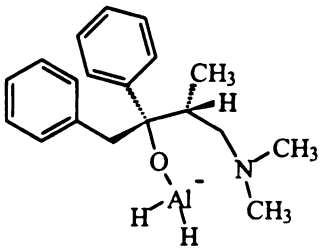
177

The use of various LAH /carbinolamines complexes as chiral reducing agents have been extensively studied by Cohen et al.[174] Asymmetric reduction of the α,β-acetylenic ketones **178** - **183** (Table 3.1) using the Mosher-Yamaguchi (LAH - Darvon alcohol complex) **184** at -70°C produced mainly the (R)-carbinols in 62-99% yield and 34-90% ee.

Table 3.1: Asymmetric LAH Reduction of α,β-Acetylenic Ketones

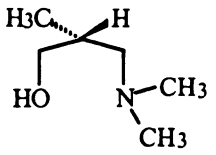


Substrate	R	%R	%S	%ee	% Yield
178	$(CH3)_2CHCH_2$	91	9	82	99
179		82	18	64	78
180		55	45	10	84
181		93	7	86	94
182		67	33	34	87
183		95	5	90	93

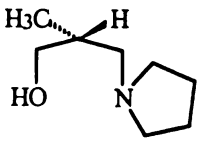


184

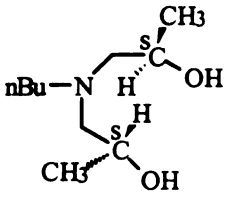
This effect of remote chiral centers was studied by Morrison et al. using the substituted aminodiols **187-190** with different chirality α to the nitrogen.[175] The authors found that all chiral centers have an additive effect on asymmetric induction and centers as far away as those in **188** can induce a small (~10% ee) excess of one enantiomer. The results are shown in Table 3.2. Aminodiol **190** containing all three chiral centers of the (S)-configuration gave the highest optical yield in contrast to **189** (one (R)-chiral center, two (S)-chiral centers) which has a lower optical yield. The authors proposed a transition structure **191** where the tertiary nitrogen coordinates with the Li^+ cation which in turn coordinates with the carbonyl oxygen of the ketone.



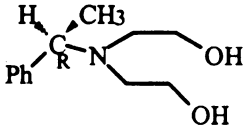
185



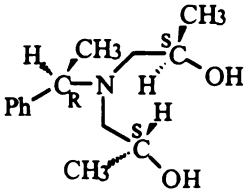
186



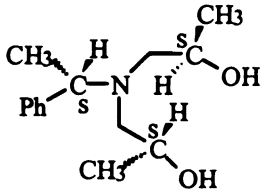
187



188



189

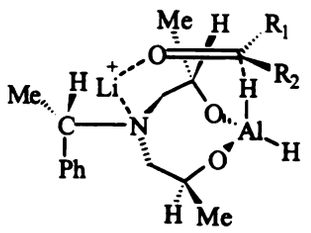


190

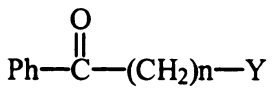
Yamaguchi and Kabuto studied the effect of substituents and the number of methylene groups in the reduction of ketones **192.**[176] When n = 2 or 3, the stereoselectivity of the reduction increased when Y = OMe or NMe_2 but decreased when Y = SH. This can be rationalized by the hard/soft acid/base concept where the hard Li^+ cation will complex with the hard oxygen and nitrogen but not with the soft sulfur. As the ability of Li^+ to chelate increases, the transition state become more rigid which causes greater asymmetric induction.

Table 3.2. Reduction of Acetophenone and Propiophenone Using LAH Complexed with Substituted 1,2-Aminodiols.

Reducing Agent	Ketone	% Yield	%ee (Config. of Alcohol)	Authors' Comments
LAH:**187**	Acetophenone	85	44(R)	Induction by carbinol centers
LAH:**187**	Propiophenone	85	57(R)	
LAH:**188**	Acetophenone	87	10(S)	Induction by chiral center next to N
LAH:**188**	Propiophenone	97	10(S)	
LAH:**189**	Acetophenone	90	35(R)	carbinol center induction opposed by that of chiral center next to N
LAH:**189**	Propiophenone	88	19(R)	
LAH:**190**	Acetophenone	98	82(R)	carbinol center induction reinforced by that of chiral center next to N
LAH:**190**	Propiophenone	98	77(R)	

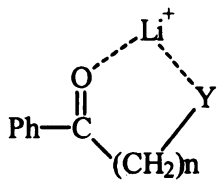


191



192

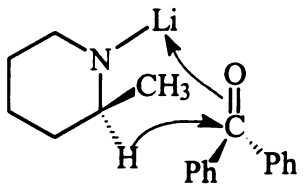
The value of n is related to the stability of the cyclic transition state, when n = 2 or 3, a 5- or 6-member ring is formed as shown by the transition structure **193.**



193

The reduction of diaryl ketones was reported by Cervinka et al. using an asymmetric Meerwein-Pondorf-Verley reduction.[177] The reaction is based on the transfer of a hydride from the lithium salts of secondary amines to ketones.[178] The mechanism of hydride transfer using the lithium salt of

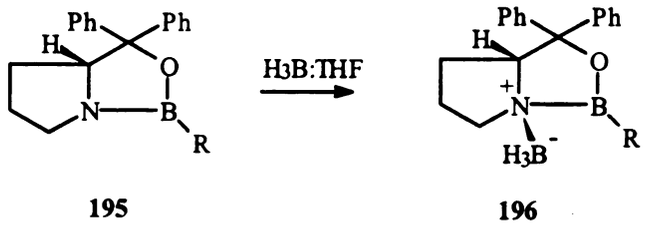
(S)-(+)-2-methyl piperdine is illustrated in the structure **194.**



194

3.1.2. Borane Reagents

Corey and co-workers have published several papers on the catalytic reduction of ketones using oxazaborolidines.[179,180,181,182,183,184] Chiral oxazaborolidines **195** are known to induce a highly enantioselective catalytic reduction of ketones as borane is used as a source of hydrogen. Formation of the borane adduct **196** has been proposed to be the first step in the mechanism of the catalysis (eq 46).[179] The catalyst (S)-**195** has been tested in the reduction of several ketones, the results are summarized in Table 3.3.

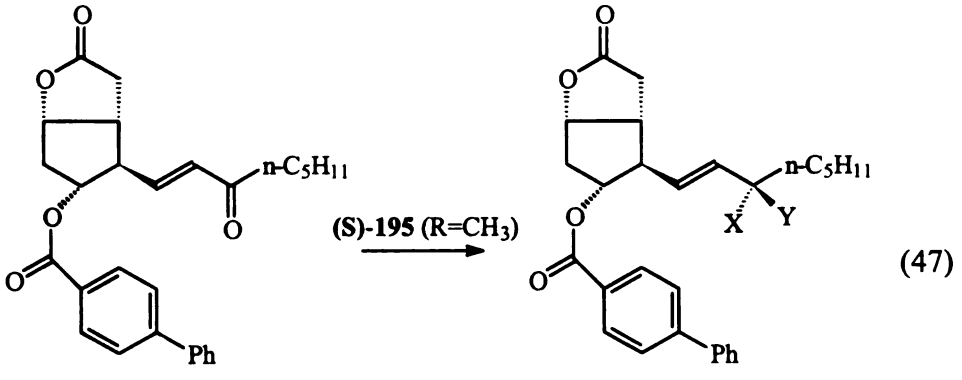


195 196 (46)

Table 3.3. Borane Reduction of Ketones Catalyzed by (S)-**195**.[179,180]

Oxazabolidine Catatylsis	Ketone	equiv (BH_3)	equiv (**195**)	reaction temp°C	config of product (%ee)
(S)-**195** (R=H)	$C_6H_5COCH_3$	1	0.1	25	R(97)
(S)-**195** ($R=CH_3$)	$C_6H_5COCH_3$	0.6	0.1	2	R(96)
(S)-**195** (R=H)	$C_6H_5COC_2H_5$	0.6	0.05	25	R(90)
(S)-**195** ($R=CH_3$)	$C_6H_5COC_2H_5$	0.6	0.1	-10	R(96)
(S)-**195** (R=H)	t-$BuCOCH_3$	0.6	0.05	25	R(92)
(S)-**195** ($R=CH_3$)	t-$BuCOCH_3$	0.6	0.1	-10	R(97)
(S)-**195** (R=H)	α-tetralone	0.6	0.05	25	R(89)
(S)-**195** ($R=CH_3$)	α-tetralone	0.6	0.1	-10	R(84)
(S)-**195** (R=H)	$C_6H_5COCH_2Cl$	0.6	0.05	25	S(97)
(S)-**195** ($R=CH_3$)	$C_6H_5COCH_2Cl$	0.6	0.1	32	S(95)

The power of Corey's catalytic enantio-selective reduction in synthesis is illustrated by the examples which follow. The Corey method has been used in controlling the C-15 sterochemistry in prostaglandin (PG) synthesis.[180] The chiral ester lactone **197**, a standard intermediate in PG synthesis, underwent selective reduction of the keto group upon treatment with 0.6 equivalents of borane in THF at 23°C for 2 min in the presence of 10 mol % of (S)-**195** (R=CH_3) as catalyst to give 15-R alcohol **198** and 15-S diastereomer **199** in a ratio of 91:9 (eq 47).



(47)

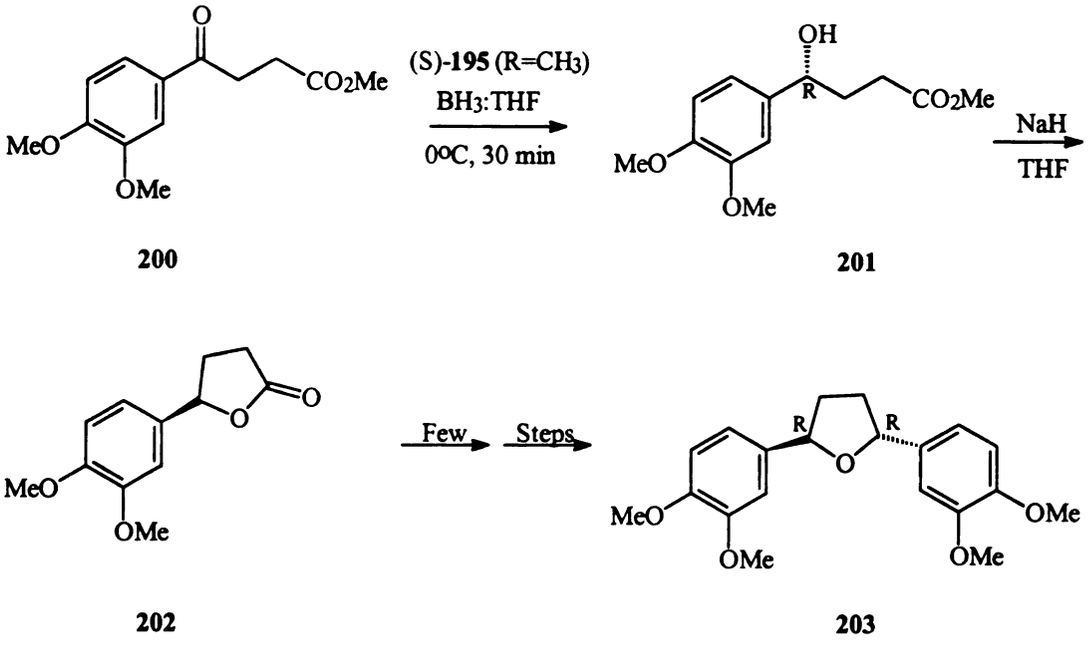
197

(R)-198 X=H, Y=OH
(S)-199 X=OH, Y=H

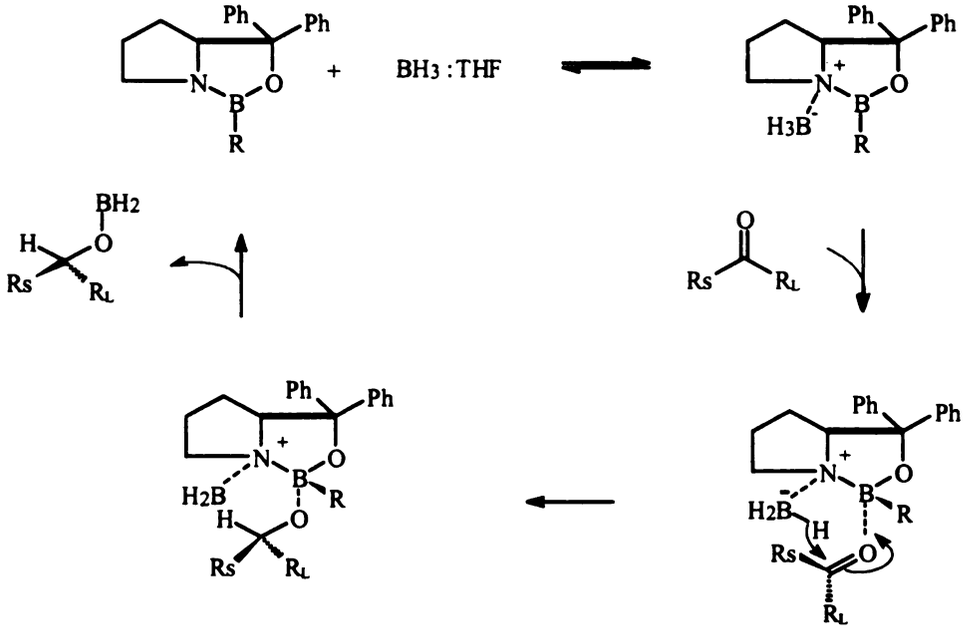
Under the same conditions but with the enantiomer of **195** as catalyst the opposite stereochemical preference was observed with the 15-S diastereomer **199** predominating in a ratio of 90:10.

Corey reported the first enantioselective route to chiral trans-2,5-diarylfurans[180] which are known to be potent antagonists of platelet activating factors.[185] Reduction of 3-(3,4-dimethoxy-benzoyl)propionate **200** with 0.6 equivalents of borane and 2 mol% of (S)-**195** ($R=CH_3$) as catalyst at 0°C for 30 min was selective for the keto function and produced the corresponding secondary alcohol **201** (98% yield and 95% ee). The alcohol **201** was treated with NaH in THF producing the (R)-lactone **202** which was subsequently converted to the (2R,5R)-diarylfuran product **203** (scheme 10).

The mechanism of the oxazaborolidine catalyzed reduction has been proposed by Corey et al. and is shown in Scheme 11.[179] The oxazaborolidine catalyst



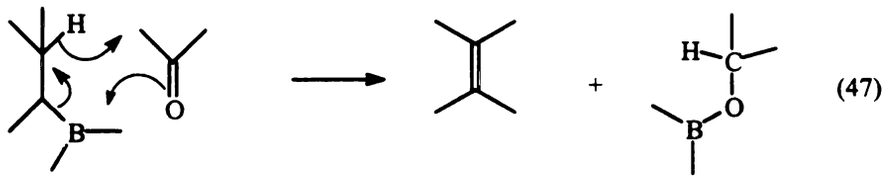
Scheme 10



Scheme 11

behaves like an enzyme in the sense that it binds with the ketone and with the borane forming a complex that can hydride transfer via a six-membered transition state uniting both reducing agent and carbonyl substrate.[186] After the reaction is complete, it releases them and itself becomes free.

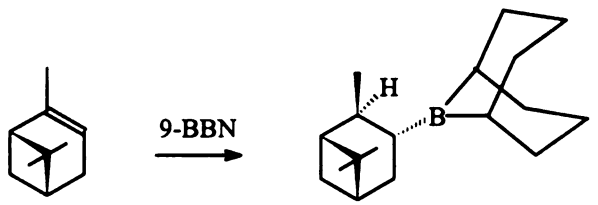
Trialkylboranes also embody many desirable features as reducing agents. Organoboranes are readily prepared and are tolerant of many functional groups. They do not possess an active hydrogen on boron therefore the reductions involve a Meerwein-Ponndorf-Verley type of process in which the hydrogen β to the boron is transferred to the carbonyl carbon as depicted in eq 47. Again, a six-membered transition state is involved.



(47)

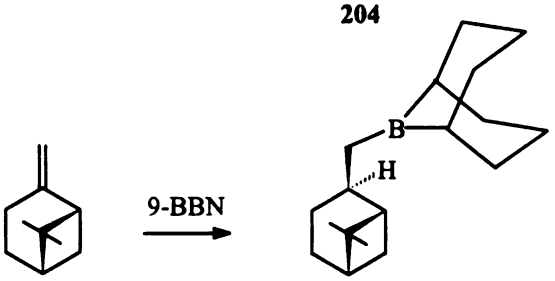
The ability to create the reducing agent by hydroboration of an olefin allows one to incorporate

a number of structural and electronic features into the reducing agent. High stereo- and regio-specificity can be achieved in hydroborations with 9-borabicyclo[3.3.1]nonane (9-BBN) and therefore optically active terpenes such as α-pinene and β-pinene can be transformed into the optically active reducing agents **204** ((R)-Alpine-Borane)and **205** (eq 48 & 49).[187,188]



(48)

204



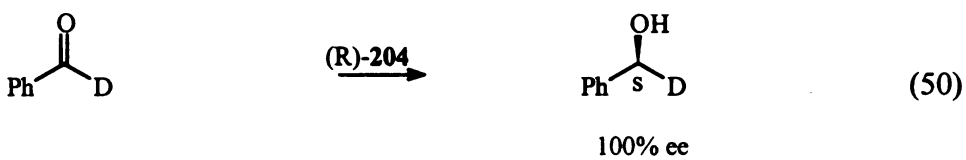
(49)

205

Like other trialkylboranes,[189] the Alpine-Borane is virtually inert to various functional groups but very effective in transferring the β-hydride to one

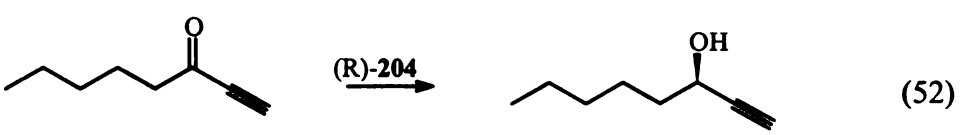
of the prochiral faces of a labeled aldehyde (eq 50)[187] and acetylenic ketones (eq 51 & 52).[190,191]

A six-membered ring boat like transition state **206** has been proposed for the reduction in which the large appendage of a carbonyl group lies in the equatorial position to avoid steric interaction with the methyl group of the reagent. This model also fulfills the observation that a syn-planar B-C-C-H arrangement of the reagent leads to a faster rate of reduction.[192,193]

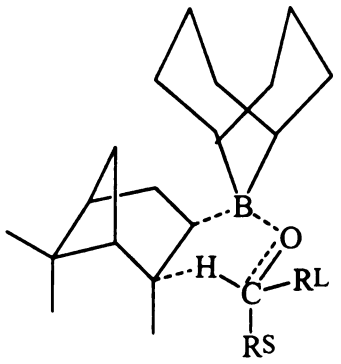


100% ee (50)

99% ee (51)

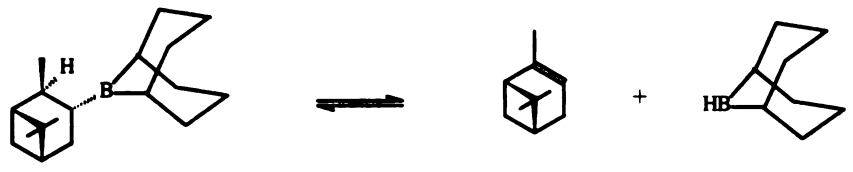


94% ee (52)



206

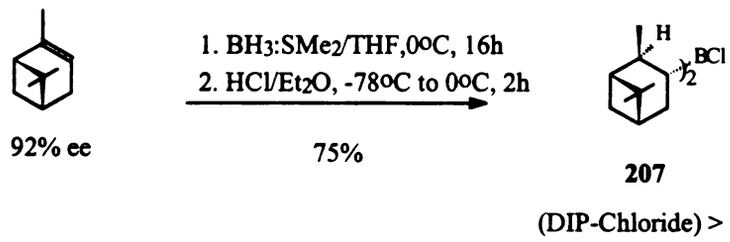
Alpine-Borane is not suitable for the reduction of aliphatic and aromatic ketones under normal conditions. This is due to a side reaction caused by the reduction of the substrate by 9-BBN formed via a slow unimolecular dissociation of Alpine-Borane **204** (eq 53).[193]



204 (53)

One of the drawbacks of using Alpine-Borane is that it is not very reactive toward ketones.

Increasing the Lewis acidity of the boron would however increase the reactivity. In this regard, Brown investigated a variety of dialkylhaloboranes, the best of which was the chlorodisopino-campheylborane (DIP-Chloride) **207** (synthesized via eq 54).[194]



(54)

207

(DIP-Chloride) > 99% ee

DIP-Chloride is a good chiral reducing agent for aromatic alkyl and α-tertiary alkyl ketones. Placement of the halogen atom on the boron makes it more Lewis acidic resulting in an increase in reactivity toward carbonyl compounds. A variety of ketones have been reduced to optically active alcohols in high selectivity using **207** (figure 3.1).

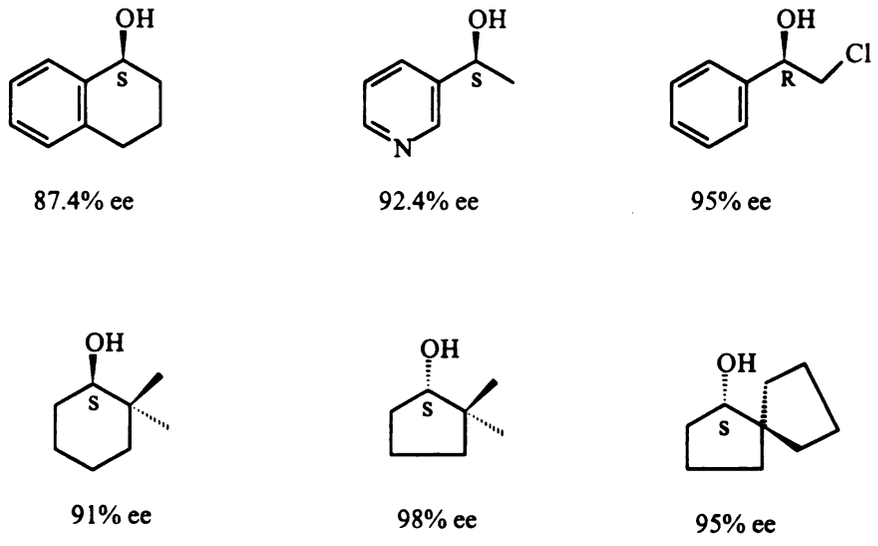


Figure 3.1. Optically active alcohol products from the reduction of their corresponding ketones using **207** as reducing agent.

The mechanism for DIP-Chloride is similar to that proposed by Midland for Alpine-Borane (see transition structure **206**).[194]

3.1.3. Aminoborohydride Reagents

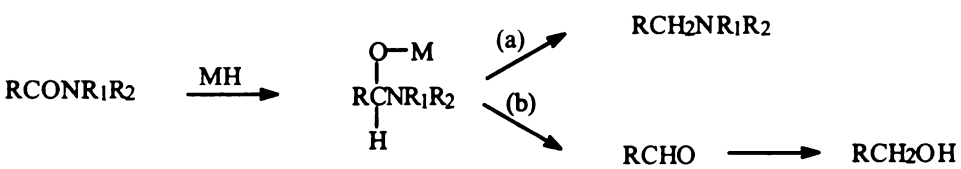
The replacement of one or more of the hydrides on borohydride with other substituents can either increase (electron donating groups, i.e., alkyl,[195] alkoxy,[196] alkylamino)[159,197] or temper (electron withdrawing groups i.e., CN,[198] O_2CR)[199,124] the hydride delivering ability of the resulting reagent.

(Alkylamino)borohydrides offer useful characteristics as versatile reducing agents. Due to the lower electronegativity of nitrogen compared to oxygen (3.07 vs. 3.50),[200] better donation of the lone pair of electrons toward boron from nitrogen should occur. This combination suggests that aminoborohydrides should demonstrate considerable enhancement of hydride delivering ability compared to either borohydride or alkoxy derivatives.[201] This was demonstrated by Hutchins et al. with the synthesis of sodium dimethylaminoborohydride and the study of its reduction characteristics (eq 55).[159]

$$Me_2NH{:}BH_3 \xrightarrow[THF,\ 1h]{NaH,\ 25^oC} Na^+\,[H_3BHMe_2]^- \qquad (55)$$

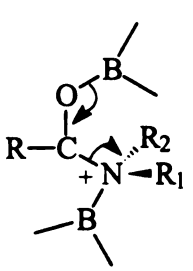
As expected, sodium dimethylaminoborohydride showed enhanced reducing ability. In addition to reducing aldehydes and ketones to the corresponding alcohols, it was also effective in converting esters to alcohols and primary amides to amines. Tertiary amides were reduced to either alcohols or amines, depending on the steric requirements of the amide

group. The mechanism of the tertiary amide reduction presumably involves an initial attack by hydride at the carbonyl followed by either displacement of the oxygen functionality (carbon-oxygen bond cleavage) by a second hydride to give an amine or carbon-nitrogen bond cleavage releasing an aldehyde that is reduced to an alcohol (eq 56).



(56)

The authors proposed that the second cleavage reaction (path b) may require, or be enhanced by, complexation with a boron species (i.e. **208**) to augment the leaving ability of the amine.



208

As the N substituents become larger, such complexation is resisted and hydride substitution (path a) favorably competes to afford the amine. Reductions with the sodium aminoborohydrides were not facile and required long reaction times and harsh conditions.

Singaram et al.[197,202] reported the first synthesis of lithium aminoborohydrides ($LiABH_3$) which are more reactive than the sodium derivatives. $LiABH_3$ are a relatively new class of powerful, selective, air stable reducing agents that reproduce virtually all of the transformations for which lithium aluminum hydride is used (figure 3.2) $LiABH_3$'s can be synthesized in situ from any primary or secondary amine. A significant advantage of $LiABH_3$ over lithium aluminum hydride is that, once the $LiABH_3$ has been formed in situ, no precautions to exclude air need be taken when the reduction is done. Furthermore, alkylamine groups may be introduced sequentially so that the corresponding mono-, di-, and triaminoborohydrides are conceptually available with wide structural variances thus allowing control of the steric and electronic environments of these reagents.

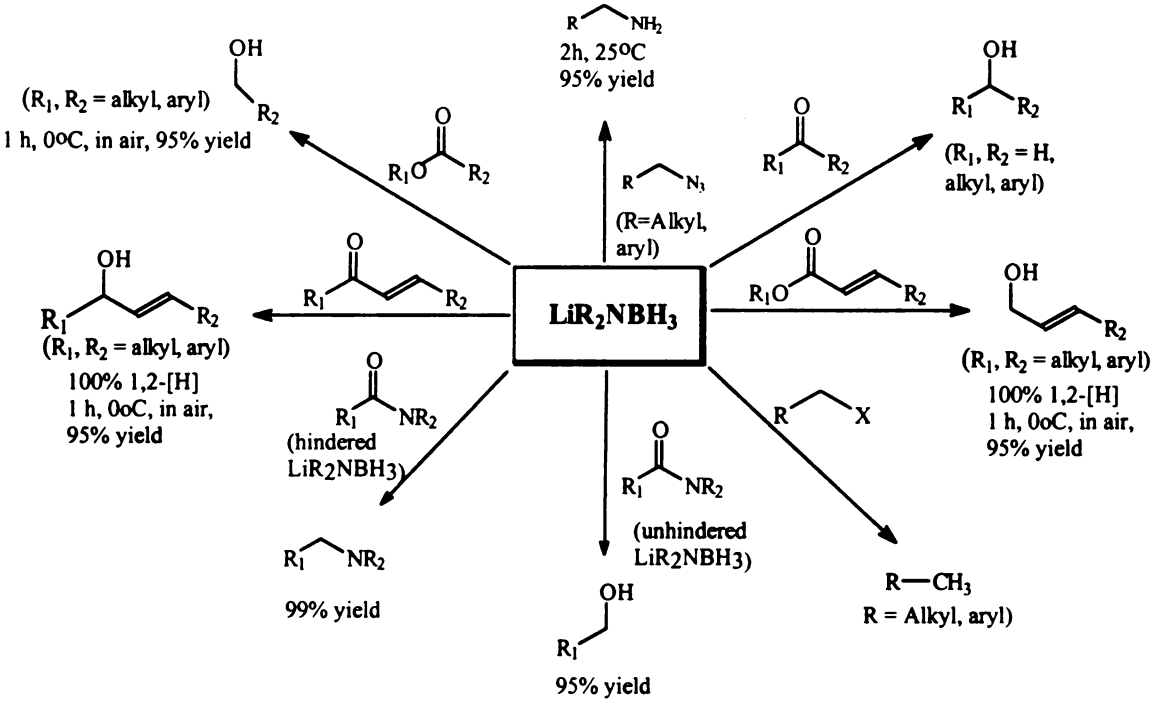


Figure 3.2. Representative functional groups reduced by $LiABH_3$

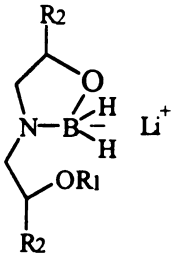
We are interested in exploring the use of optically active lithium aminoborohydrides. Consequently the focus of the second aspect of this research is to study the utility of chiral lithium aminoborohydrides as potential asymmetric reducing agents for ketone reductions. The results of this work will be described in Chapter 4.

CHAPTER 4

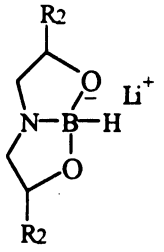
4.1 Asymmetric Reduction of Ketones using $LiABH_3$ as Reducing Agents

Sodium aminoborohydrides were first synthesized by Hutchins by deprotonating a pre-formed secondary amine-borane with sodium hydride. [159] Singaram and co-workers have published several papers describing the preparation and uses of lithium aminoborohydrides.[197,202,203,204,205,206] These compounds were described as safe and powerful reducing agents, comparable to lithium aluminum hydride , yet selective in their reducing properties. $LiABH_3$ reduce esters, lactones, and anhydrides to the corresponding alcohols, while carboxylic acids are not reduced. Although these new reducing agents have been extensively studied, the chemistry of chiral members of this class has only been briefly examined.

Kagan[207] investigated the use of mono and dialkoxyaminoborohydrides of types **209** and **210** and found that this class of reducing agents reacted with acetophenone to afford 1-phenylethanol in good chemical yields but low ee's (Table 4.1).

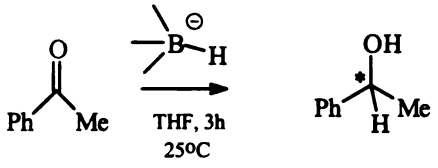


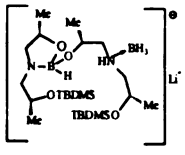
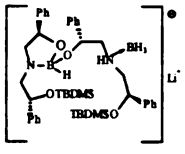
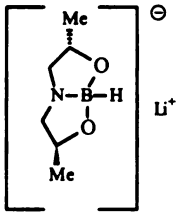
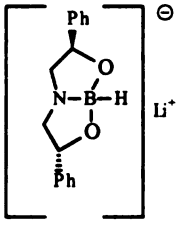
209



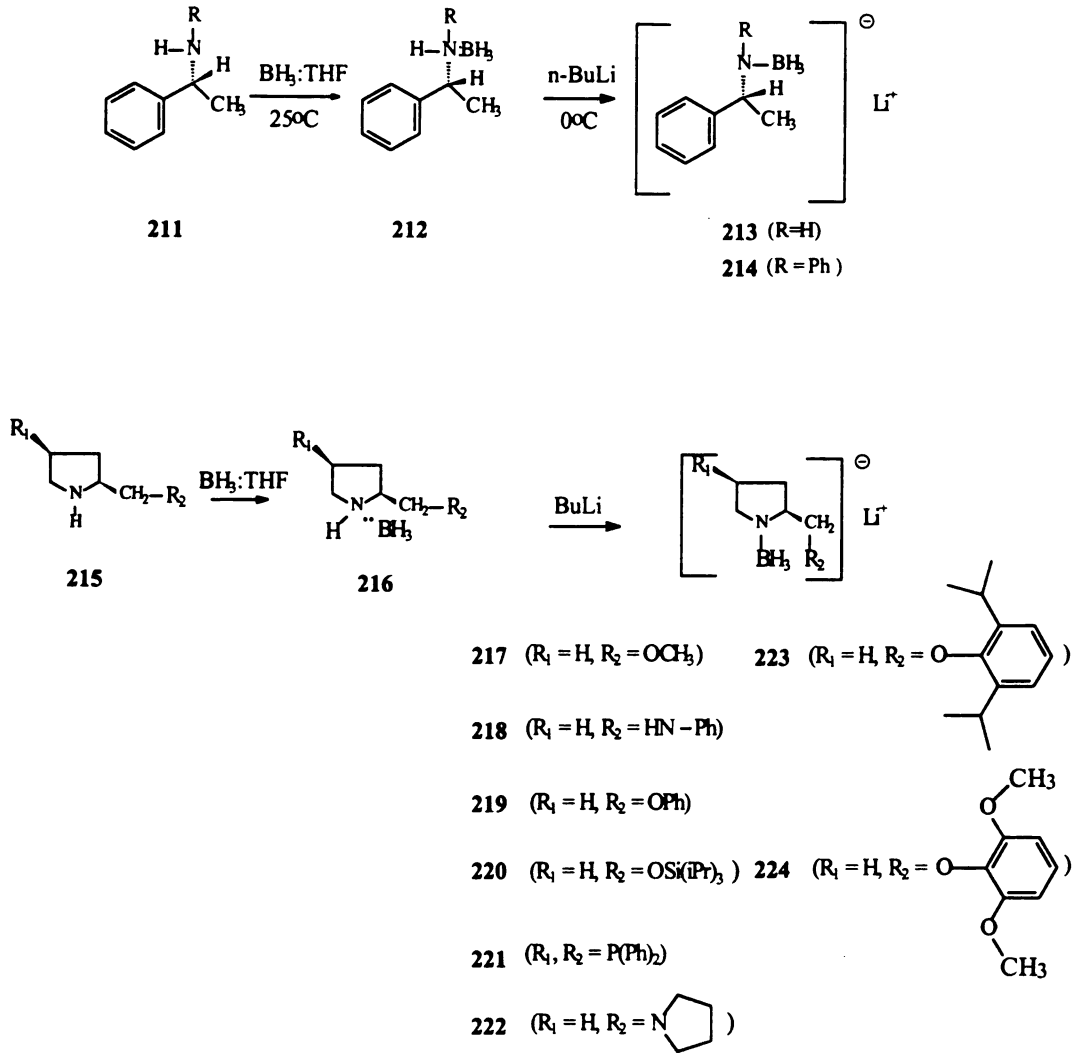
210

Table 4.1. Reduction of Acetophenone Using Mono and Dialkoxyaminoborohydrides as Reducing Agents.[159]



Reducing Agent				
Equivalents	1.1	1.1	1.1	1.8
% Yield	95	85	93	90
% ee	6(R)	8(R)	9(R)	5(R)

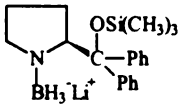
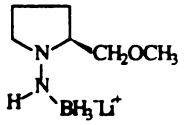
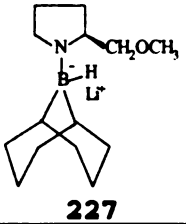
We have investigated a variety of optically active lithium aminoborohydride compounds as potential chiral reducing agents. The reducing reagents were prepared using Singaram's procedure[197] as illustrated in scheme 12.



Scheme 12

The chiral reagents were evaluated by the reduction of acetophenone under a variety of experimental conditions. The R/S enantiomer ratio were determined using a chiral LC column (see experimental). The results are summarized in Table 4.2.

Table 4.2. Asymmetric Reductions of Acetophenone.

Entry	Reducing Agent	Reagent equiv	Solvent	Temp°C	%ee[1]	Config	% Yield[2]
1	**213**	1.2	THF	25	8.7	R	95.7
2	**214**	1.2	THF	25	0		77.6
3	**216** (R_1 = H; R_2 = OCH_3)	1.2	THF	25	0		>98.0
4	**216** (R_1 = H; R_2 = OCH_3)	1.2	Toluene	25	0		>98.0
5	**217**	1.0	THF	25	11.0	R	98.6
6	**217**	1.2	Hexane	25	14.6	R	>98.0
7	**217**	1.2	Toluene	25	25.0	R	>98.0
8	**217**	1.2	Toluene	55	28.7	R	>98.0
9	**217**	1.2	Toluene	-78	21.0	R	>98.0
10	**218**	1.1	THF	25	1.7	R	>94.0
11	**219**	1.2	THF	25	11.5	R	>95.0
12	**220**	0.6	THF	25	0		>95.0
13	**220**	0.6	THF	-20	0		>95.0
14	**221**	1.2	THF	25	12.0	S	>95.0
15	**222**	1.2	THF	15	17.8	R	>95.0
16	**223**	1.2	Toluene	25	4.4	S	>95.0
17	**223**	1.2	Toluene	90	5.3	S	>95.0
18	**224**	1.2	Toluene	25	30.0	S	>95.0
19	 **225**	0.6	THF	25	5.0	S	>95.0
20	 **226**	1.2	THF	25	0		94.2
21	 **227**	1.1	THF	25	0		96.3

[1] %ee determined by chiral LC (see experimental section for details)
[2] Yield based on acetophenone

Unlike the structurally rigid borane and modified chiral LAH reagents previous discussed, the $LiABH_3$ reagents are not conformationally rigid in solution. This presents a challenge in constructing chiral $LiABH_3$ reagents capable of efficient asymmetric reduction of prochiral ketones. Introducing bulky substituents on the chiral amine has little effect on % ee due presumably to the high degrees of freedom of bond rotation in the reagent. As illustrated in figure 4.1 the bonds in the aminoborohydride reagents are free to rotate which is a characteristic not conducive to efficient asymmetric induction. Compounds **213** and **214** are examples of the type of $LiABH_3$ reagents illustrated in figure 4.1. As seen in Table 4.2 (entries 1 & 2), the reduction of acetophenone using **213** and **214** gave very low to no asymmetric induction (8.7 and 0% ee of the 1-phenylethanol respectively).

Mukaiyama and Asami studied the asymmetric reduction of various ketones with LAH modified with chiral diamines derived from (S)-proline. They found that a chiral reagent **228** formed in situ from LAH and the chiral diamine

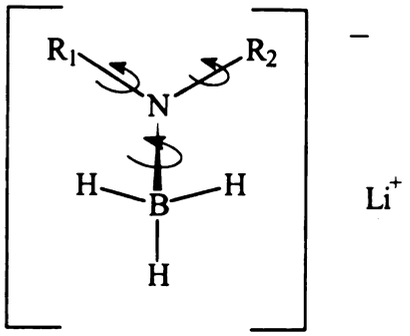
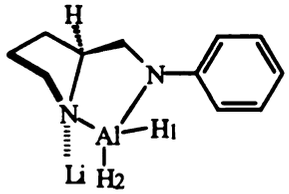


Figure 4.1. Illustration of bond rotations in Chiral $LiABH_3$ reducing agent.

(S)-2-(anilininomethyl)pyrroline is an efficient reducing agent for the reduction of acetophenone, affording (S)-1-phenylethanol in 92% ee.[152]



228

The authors assumed that the high selectivity was accountable by considering the following factors:

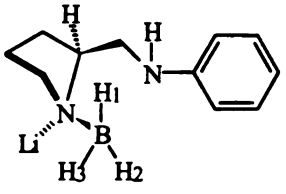
1) the complex **228** is extremely rigid with cis-fused 5-membered bicyclic structure, and

2) the reactivity of the two diastereotopic hydrogen atoms contained in this chiral hydride reagent is significantly different
3) the lithium cation, presumably coordinated to the nitrogen atoms on the pyrrolidine ring and/or the side chain, directs the approach of the ketone.

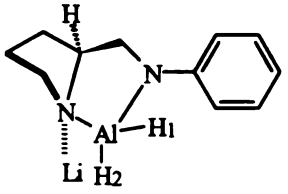
Based on the assumption that a conformationally restricted ring complex, constructed between the chiral ligand and reducing reagent, would create an effective chiral environment for asymmetric induction, we subsequently examined the use of chiral reagents **216** - **227** derived from (S)-prolinol (Table 4.2).

In contrast to the asymmetric reduction of acetophenone with chiral modified lithium aluminum hydride (LAH) reagents such as **228** where high ee's had been obtained, the asymmetric reduction using chiral $LiABH_3$ reagents had only low to moderate success. A maximum ee of only 30% was obtained using reagent **224** (Table 4.2, entry 18).

The difference in enantioselectivity of the $LiABH_3$ reagents compared to the modified LAH reagents can be attributed to the inability of the $LiABH_3$ reagent to form a rigid ring complex creating a chiral environment for efficient asymmetric induction. This is illustrated in the $LiABH_3$ reagent **218** and the modified LAH reagent **228.**



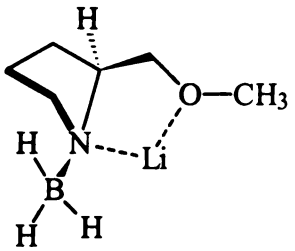
218



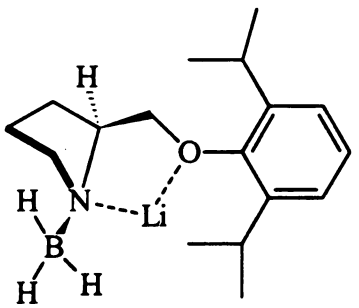
216

In **228** the reactivity of the two hydrogens is remarkably different. It is plausible that only H_2 is delivered in the reduction step, as H_1 is sterically hindered by the pyrrolidine ring and N-phenyl substituent. In contrast, the hydrogens in **218** are equivalent due to rotation of the boron bond. Since this structure is not rigid in solution, asymmetric induction is minimal. The reduction of acetophenone with **218** (Table 4.2, entry 10) and **228**[152] afforded 1-phenylethanol in 1.7 and 92% ee respectively.

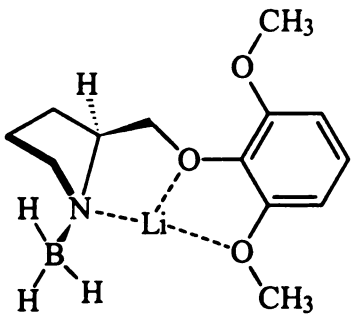
The influence of reaction temperature and solvent on the optical yield in the asymmetric reduction of acetophenone was examined using **217** as the chiral reducing agent (Table 4.2, entries 5-9). The effect of solvent is significant, and toluene was found to be the solvent of choice. The effect of solvent is consistent with the findings of Mukaiyama and Asami that the lithium cation (complexed to nitrogen on the pyrrolidine ring and the heteroatom on the side chain) directs the approach of the ketone. Figure 4.2 illustrates how lithium is complexed in the $LiABH_3$ reagents. The use of THF as a solvent gave a lower %ee than hexane and toluene. THF may complex the lithium cation which interferes with its ability to coordinate the ketone and direct it's approach for reduction. Hexane and toluene in contrast are not coordinating solvents and therefore do not complex with the lithium cation. The reduction of acetophenone with the amineborane **216** (Table 4.2, entries 3&4) also show the importance of the lithium cation in asymmetric reduction. When the lithium cation is absent (as in **216)** the %ee drops from a maximum of 28.7 to 0% (Table 4.2, entries 4 & 8) using toluene as a solvent.



217 (%ee = 28.7 (R)



223 (%ee - 4.4 (S)



224 (%ee = 30.0 (S)

Figure 4.2. Lithium aminoborohydride chiral reducing agents illustrating the potential complexation of lithium cation. The %ee values are taken from Table 4.2, entries 9, 16, & 18).

The effect of temperature was also studied and showed no significant effect. As seen in Table 4.2, entries 7-9, reductions of acetophenone carried out at 55, 25, and -78°C afforded 1-phenylethanol with similar results of 28.7, 25.0, and 21% ee's respectively.

In conclusion, lithium aminoborohydrides are a new class of powerful yet selective reducing agents that reproduce, in air, virtually all of the transformations for which LAH is now used but without the safety hazards associated with LAH. The reagents can be conveniently prepared from a variety of primary and secondary amines. The use of chiral amines can be used to prepare chiral $LiABH_3$ reducing agents but due to the apparent lack of conformational rigidity of these chiral reagents in solution, only low to moderate ee's were achieved when acetophenone was reduced to 1-phenylethanol.

CHAPTER 5

5.1 Experimental Section Borohydride Reductions Mediated by Dihydrogen Bonding.

General

All reagents were obtained from commercial suppliers and used without further purification. Reduction reactions were monitored by FTIR. IR spectra were obtained on a Perkin-Elmer 1600 FTIR spectrometer and were examined using NaCl solution cells with a path length of 0.1 or 1.0 mm.

Gas Chromatography Analyze the Silylated DIOL Product to Determine CIS:Trans Ratios.

Gas chromatography analyses were performed on a Hewlett Packard 5890 Series II Gas chromatograph.

Column: DBS, 30m x 50mm thin film (Durabond ® from J&W Scientific)

Injection temp: 275°C

Detector temp 300°C

Initial temp: 100°C

Ramp: 20°C/min

Final temp: 280°C

Carrier Gas: Helium

Detector: FID

Silylation Conditions. Chlorotrimethylsilane (1ml) was added to a stirred solution of the alcohol or diol (50 mg) in dry pyridine (5ml). The solution was allowed to stand for 15 min at room temperature and then poured into water and extracted with dichloromethane. The extract was washed with saturated aqueous sodium hydrogen carbonate. The dichloromethane layer was separated, washed with water and dried over $MgSO_4$. After filtration to remove $MgSO_4$ the dichloromethane was removed under vacuum and the trimethylsilyl derivatives were analyzed directly by gas chromatography.

Reductions with Tetrabutylammonium Borohydride. The following general procedure was employed for the reductions discussed in this work.

To a solution of the carbonyl compound (0.0025 mol) in 10 ml of dichloromethane was added as a solid in a single portion 0.0025 mol of tetrabutylammonium borohydride. The reaction vessel was stoppered and shaken and the homogeneous solution was allowed to stand for 0.25 - 147 hours. The reaction was quenched by the addition of 20 ml of 3% hydrogen peroxide followed by 10 ml of 10%

sodium hydroxide and the mixture was stirred for 1 - 2 hours. The layers were separated and the aqueous phase was extracted with three 30-ml portions of dichloromethane. The combined organic solutions were extracted with 20 ml of saturated sodium sulfite, dried over anhydrous magnesium sulfate, and concentrated under reduced pressure (Note, the diol products **137** and **139** are very water soluble and therefore difficult to extract into the organic phase). The crude product was taken up in anhydrous diethyl ether, the insoluble tetrabutylammonium salts were removed by filtration, and the ether solvent was evaporated.

Preparation of 2-hydroxycyclobutanone (136).[209] In a 250 ml, three-neck flask fitted with a magnetic stirring bar, a dropping funnel, a nitrogen bubbler and a reflux condenser was placed 115 ml reagent grade methanol. Dry oxygen-free nitrogen was vigorously bubbled through the methanol for one hour. Then 15 g (0.065 mole) of 1,2 bis(trimethylsilyloxy)-cyclobutene (purchased from Aldrich) was transferred under nitrogen to the addition funnel and added dropwise to the stirred methanol for 24 hours. The methanol and

methoxytrimethylsilane were removed under reduced pressure, and the residual 2-hydroxycyclobutanone was distilled through a short-path still as a colorless liquid, b.p. 52-57°C (0.1mm.), (3.2g, 57%): IR 3583, 3435, 1783 cm^{-1}; (lit. [209] IR 1780 cm^{-1}) ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.9 (1H, m, C-2), 2.69 (2H, m), 2.4 (1H, m), 1.8 (1H, m); $^{13}C\{^{1}H\}$ NMR (300 MHz, $CDCl_3$) δ 209.00, 105.93, 93.80, 81.80, 71.06, 38.77, 31.11, 28.87, 28.14, 24.04, 21.46. Anal. Calcd for $C_4H_6O_2$: C, 55.8; H, 7.0. Found: C, 54.0; H, 7.20.

Preparation of 2-hydroxycyclopentanone (138). This procedure involved an acyloin condensation in which chlorotrimethylsilane was used as a trapping agent and was based on the organic synthesis preparation used to prepare **136** above.

A. 1,2-bis(trimethylsilyloxy)cyclopentene. A 1 liter, three-neck flask was fitted with a mechanical stirrer, a dropping funnel, a nitrogen bubbler and a reflux condenser and maintained under an oxygen-free, nitrogen atmosphere. The flask was charged with 300g of reagent grade toluene (dried over $MgSO_4$) and 15g of freshly cut sodium (weighed under

nitrogen and transferred under toluene to the reaction flask). The temperature was slowly increased to 110°C The stirrer was operated at full speed to disperse the sodium. After the sodium was fully dispersed the stirrer was adjusted to 384 rpm. A mixture of 75g (0.69 mole) chlorotrimethylsilane, 24g (0.15 mole) dimethyl glutarate in 50 ml toluene was added over 3 hours. After reacting for 12 hours the contents of the reactor was cooled and filtered through a 75-mm. coarse glass filter. The precipitate was washed several times with anhydrous ether. Toluene was removed under reduced pressure and the crude 1,2-bis (trimethylsilyloxy)cyclopentene was distilled as above, b.p. 44°C (0.21 mm), (24.8g, 67.6%);

B. 2-hydroxycyclopentanone (138). In a 250 ml, three-neck flask fitted with a magnetic stirring bar, a dropping funnel, a nitrogen bubbler and a reflux condenser was placed 115 ml reagent grade methanol. Dry oxygen-free nitrogen was vigorously bubbled through the methanol for one hour. Then 24 g (0.1 mole) of 1,2-bis(trimethylsilyloxy)cyclopentene was transferred under nitrogen to the addition funnel and added

dropwise to the stirred methanol for 2 hours at room temperature. The methanol and methoxytrimethylsilane were removed under reduced pressure, and the residual 2-hydroxycyclopentanone was distilled as above, (7.5g, 75%) was collected: IR 3556, 1743 cm^{-1} (lit.[210] IR 3450, 1749 cm^{-1}); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.96 (1H, br, C-2), 2.00-1.26 (6H, m, remaining cyclopentyl); $^{13}C\{^{1}H\}$ NMR (300 MHz, $CDCl_3$) δ 216.00, 114.58, 87.89, 75.88, 34.10, 34.04, 33.38, 32.84, 30.68, 28.65, 22.99, 16.73, 16.67. Anal. Calcd for $C_5H_8O_2$: C, 60.00; H, 8.10. Found: C, 61.00; H, 7.77.

Reduction of 2-hydroxycyclopentanone (138). The reduction of **138** was carried out based on the general reduction procedure described above. The resulting diol product was compared against cis and trans cyclopentanediol standards purchased from The Aldrich Chemical Company.

Preparation of 2-hydroxycyclohexanone (144). 2-hydroxycyclohexanone was prepared by treating hydroxy cyclohexanone dimer (Adipoin purchased from Aldrich) with dilute (5 %) HCl. In a 250 ml, three-

neck flask fitted with a magnetic stirring bar and a reflux condenser were added 20 ml of 5% aqueous HCl and 0.37g (0.0016mol) of adipoin. The reaction was allowed to run for 1 hour, afterwhich dichloromethane was added to extract the 2-hydroxycyclohexanne product. The dichloromethane phase was washed with water and subsequently dried over $MgSO_4$. The solvent was removed under vacuum yielding 0.3g (81% yield) of the 2-hydroxy-cyclohexanone product: IR 3489cm^{-1} and 1716 cm^{-1} (lit.[210] IR 3484 and 1715 cm^{-1}); ^1H NMR (300 MHz, $CDCl_3$) δ 4.13 (1H, t, C-2), 2.59-1.42 (8H, m, remaining cyclohexyl) $^{13}C\{^1H\}$ NMR (300 MHz, $CDCl_3$) δ 211.3, 39.5, 36.8, 27.6, 23.4 (lit. [211] ^{13}C 211.0, 39.5, 36.8, 27.5, 23.5); Anal. Calcd for $C_6H_{10}O_2$: C, 63.1; H, 8.1. Found: C, 63.2; H, 8.7.

Preparation of 2,2,4,4 tetramethyl-3-hydroxycyclobutanone (145). In a 250 ml, three-neck flask fitted with a magnetic stirring bar and a reflux condenser were added 20 ml of dichloromethane, 5.1g (0.0357mol) of 2,2,4,4 tetramethyl-cyclobutanedione, and 2.4g (0.009 mol) of tetrabutylammonium borohydride. The reaction was

allowed to run for 19 hours, afterwhich 6.0 g of 6.25N HCl was added and the mixture was stirred for 30 min. The dichloromethane phase was washed with water and subsequently dried over $MgSO_4$. The solvent was removed under vacuum yielding 0.4g (7.8% yield) of the 3-hydroxy-2,2,4,4 teramethyl cyclobutanone product: IR 3610, 1777, 1716 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 3.90 (1H, s, C-3) 1.21 (6H, s, 2 methyls), 1.19 (6H, s, 2 methyls); $^{13}C\{^1H\}$ NMR (300 MHz, $CDCl_3$) δ 222, 65.80, 59.94, 23.06, 17.11, 15.25; Anal. Calcd for $C_8H_{14}O_2$: C, 67.6; H, 9.9. Found: C, 65.8; H, 9.7.

Preparation of 3-hydroxy-1-indanone (146). In a 250 ml, three-neck flask fitted with a magnetic stirring bar and a reflux condenser were added 20 ml of dichloromethane, 2.0g (0.0135mol) of 1,3 indandione, and 0.87g (0.0034 mol) of tetrabutylammonium borohydride. The solution was allowed to stand for 1 week, afterwhich 1.0 g of 6.25N HCl was added and the mixture was stirred for 30 min. The dichloromethane phase was washed with water and subsequently dried over $MgSO_4$. The solvent was removed under vacuum yielding 0.74g (37% yield) of the 3-hydroxy-1-indanone product: IR 3590, 1723

cm-$^{-1}$ (lit[212] IR 3590, 1717 cm-$^{-1}$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.72-7.44 (4H, aromatic) 5.40 (1H, dd, *J* 6.6 and *J* 2.8), 3.10 (1H, m,)3.07 (1H, dd, *J* 7 and *J* 7, 2.57 (1H, dd, *J* 8.8 and *J* 3.8) (lit[212] ^{1}H NMR 7.9-7.3 (4 H,m), 5.3 (1H, dd, *J* 7 and *J* 3), 2.98 (1H, dd, *J* 19 and *J* 7), 2.48 (1H, dd, *J* 19 and *J* 3) $^{13}C\{^{1}H\}$ NMR (300 MHz, $CDCl_3$) δ 155.3, 136.4, 135.4, 129.5, 126.0, 123.3, 68.6, 47.2; Anal. Calcd for $C_9H_8O_2$: C, 73.0; H, 5.4. Found: C, 72.7; H, 5.7.

Preparation of 4-hydroxy-2-adamantanone (147 & 149).[147] The axial and equatorial isomers of 4-hydroxy-2-adamantanone were prepared via the rearrangement reaction of 4-oxahomoadamantan-5-one in hot 50% sulfuric acid.

Preparation of 4-oxahomoadamantan-5-one. Admantanone (12g) was added during 30 min to a stirred solution of 30% hydrogen peroxide (9g) in t-butyl alcohol (50 ml) containing selenium dioxide (0.5g) while the temperature was kept at approximately 80°C. After an additional 1.5 hrs at this temperature the solution was poured into cold

water and the mixture was saturated with sodium chloride and extracted with dichloromethane (3 x 100 ml). The extract was washed with water, dried, and concentrated, to yield the lactone (12.3g, 93%): ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.48 (1H, br,), 3.07 (1H, t, *J* 5.6), 2.54 (1H, s), 2.11 - 1.26 (11H, m, remaining homoadamantyl) (lit.[147] ^{1}H NMR 4.48 (1H, m,), 3.06 (1H, m, C-6), 2.1-1.7 (12H, m, remaining homoadamantyl).

Rearrangement of 4-oxahomoadamantan-5-one in 50% Sulfuric Acid. A solution of the 4-oxahomoadamantan-5-one (6.0g) in 50% v/v sulfuric acid (200 ml) was stirred at 90°C for 5 hrs. The cooled solution was poured into cold water and neutralized with 50% sodium hydroxide. The mixture was extracted with chloroform (4 x 50ml) and the extract was washed with 10% aqueous sodium chloride and dried. Evaporation gave a white solid (4.30g, 71.7%). The solids were dissolved in acetone and placed on a column of silica gel. Elution with ether-acetone (10:1) gave starting material, followed by 4_{eq}-hydroxyadamantan-2-one **(149)**, IR 3597, 1716 cm^{-1} (lit.[147] 3350, 1724, and

1710 cm-^{1}); ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.94 (1H, m,), 2.60 (1H, br, s), 2.47 (1H,br, s) 2.31 - 1.60 (10H, m, remaining adamantyl) (lit.[147] ^{1}H NMR 3.98, (1H,m), 2.75 (1H, br, s), 2.62 (1H, br, s), 2.45 - 1.5 (10H, m, remaining adamantyl).

Further elution of the column gave 4_{ax}-hydroxyadamantan-2-one **(147)** IR 3597, 1723 cm^{-1} (lit.[147] IR 3400, 1725, 1710 cm-^{1}); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.25 (1H, s, C-4), 2.62 (1H, br s, C-3), 2.47 (1H, br, s, C-1), 240-1.82 (10H, m, remaining adamantyl) (lit.[147] ^{1}H NMR 4.28 (1H, m), 2.65 (1H, br, s), 2.47 (br, s) 2.37 - 1.8 (10H, m, remaining adamantyl).

Reduction of 4-hydroxy-2-adamantanones (147 & 149). The reductions were carried out based on the general reduction method described above. The diol products were silylated (see silylation procedure described above) and the resultant disilylated products were analyzed directly according to the GC conditions described above: (G.C. retention time of the silylated diol: adamantanone-2_{ax}-4_{ax}-diol, 17.214 min., adamantanone-2_{eq}-4_{eq}-diol, 17.425 min.,

adamantanone-2_{ax}-4_{eq}-diol, 17.544 min.); ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.02 (1H, s,), 3.90 (1H,s,) (4.02 & 3.90 represent C-2 & C-4 hydrogens), 2.4-1.4 (11H, m, remaining adamantyl);

Reduction of 1S,6S-1-hydroxy-6-methyl bicyclo[4.3.0]nona-3,7-dione (155). The reduction of **155** was carried out using one hydride equivalent of tetrabutylammonium borohydride in dichloromethane solvent (see the general procedure described for the reductions discussed in this work): IR 3597, 1742 cm^{-1}; $^{13}C\{^{1}H\}$ NMR (300 MHz, $CDCl_3$) δ 220.3, 78.3, 65.7, 59.0, 52.9, 44.3, 34.5, 33.1, 30.9, 27.6, 19.7, 17.6, 13.6.

Reduction of 1S,6S-1-trimethylsilyloxy-6-methyl bicyclo[4.3.0]nona-3,7-dione (156). The reduction of **156** was carried out using one equivalent of tetrabutylammonium borohydride in dichloromethane solvent. (see the general procedure described for the reductions discussed in this work): IR 1743, 1723 cm^{-1}; $^{13}C\{^{1}H\}$ NMR (300 MHz, $CDCl_3$) δ 217.9, 148.8, 124.1, 59.1, 53.4, 50.4, 36.6, 33.7, 29.1, 24.2, 19.8, 13.6, 2.1.

Reduction of methyl-4-oxo-3-piperdine carboxylate (157). The reduction of **157** was carried out according to the general procedure described above. The ester and keto functionality's were followed by FTIR: IR 1743 (ester functionality), 1723 (keto functionality), and 1655 cm^{-1} (H-bonded ester functionality).

5.2 Experimental Section for lithium amino-borohydride study

General Methods

All reagents were obtained from commercial suppliers and used without further purification.

Liquid Chromatography (Analyze the 1-Phenylethanol Product to Determine Percent Enantiomeric Excess). Liquid chromatography analyses were performed using a Hitachi L-4200 UV-Vis detector and a Hitachi D-2500 chromato-integrator:

Column: Chiralcel OJ

Eluent: 95% Hexane / 5% 2-propanol

Flow rate : 1.5 ml/min

Wavelength: 214 nm

Sample size: 20 µl

Reductions with $LiABH_3$. The chiral amine reducing agent was generated in-situ. The following general procedure was employed for the reduction of acetophenone using $LiABH_3$.

To a 250 ml flask equipped with a condenser, nitrogen blanket, and magnetic stirrer were added 120 mm of a chiral amine (from which the $LiABH_3$ was prepared in situ), and 10 ml of anhydrous THF. 12 ml of 1.0M (120 mm) BH_3:THF complex was added over a 30 min period via syringe through a rubber septum at 25°C. The solution was stirred for 1 hr at 25°C. The reaction mixture was charged dropwise with n-butyllithium (2.5M, 4.6 ml, 120 mm) via syringe through a rubber septum at 0°C over a 15 min period. The reaction mixture was stirred for an additional 30 min at 0°C and allowed to come to room temperature. The reaction mixture was charged with acetophenone (1.5g, 125 mm) in a single portion. The reaction mixture was stirred at 25°C for an additional 2 hrs. The reaction mixture was quenched by the slow addition of 6.25N HCl (8 ml, 480 mm).

The aqueous and organic layers were separated and the aqueous fraction extracted with Et_2O (2 x 25 ml). The combined ethereal fractions were washed with water (3 x 10 ml) and dried over $MgSO_4$. The solvent was removed at 25°C under reduced pressure to yield the (R),(S)-1-phenylethanol product. The percent enantiomeric excess was determine via a chiral liquid chromatographic column (see liquid chromatography method above).

Preparation of the Chiral Amines used to make $LiABH_3$ Reducing Agents employed in this Study. [208] The following general procedure was employed for the preparation of chiral amines **219, 220, 223,** and **224**. Chiral amines **217, 218, 221,** and **222** were purchased from The Aldrich Chemical Company.

To a solution of triphenylphosphine (3.83g, 14.6 mmol) in 40 ml of anhydrous THF at 0°C was added diethyl azodicarboxlate (2.30 ml, 14.6 mmol) dropwise. The mixture was stirred at 0°C for 30 min then brought to room temperature. (S)-1-BOC-2-pyrrolidinemethanol (1.96g, 9.75 mmol) and 14.6 mmol of either phenol, 2,6-diisopropylphenol, or 2,6-dimethoxyphenol were added to the reaction vessel,

and the mixture was stirred for 16 hrs. Solvent was removed under reduced pressure, and the residue was diluted with hexane and stirred for 30 min. The resulting precipitate was filtered and washed with hexane. The hexane was removed under reduced pressure.

To a solution of the compound from above (1.39 mmol) in dichlormethane (2ml) at 0°C was added trifluoroacetic acid (2 ml). The mixture was stirred at this temperature for 40 min, allowed to reach room temperature, and stirred for an additional 30 min. Saturated K_2CO_3 was added, and the product was extracted with dichloromethane (3 x 10 ml). The organic layer was dried over $MgSO_4$. The solvent was removed under reduced pressure. The product was used without further purification for the in situ preparation of the $LiABH_3$ reducing agent and subsequent reduction of acetophenone via the general method described above.

Preparation of Chiral Amine (219). The preparation of **219** was carried out according to the general procedure described above. 2.0 g of **219**

(unpurified) were collected for a yield of 81%: IR 3363, 1609, 1493 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.33-6.85 (5H, m, aromatic) 3.97 (1H, m), 3.61 (2H, m), 3.11 (2H, m), 1.92 (2H, m), 1.67 (2H, m); $^{13}C\{^{1}H\}$ NMR (300 MHz, $CDCl_3$) δ 159.08, 129.48, 121.03, 114.78, 46.32, 27.90, 24.97; GC/MS m/z (relative intensity) 237 (3), 205 (2), 168 (13), 138 (6), 84 (100), 70 (35); Anal. Calcd for $C_{11}H_{15}NO$: C, 74.5; H, 8.5; N, 7.9. Found: C, 73.5; H, 7.0; N, 7.7.

Preparation of Chiral Amine (220). The preparation of **220** was carried out by the silylation of (S)-(+)-2-pyrrolidinemethanol with excess chlorotriisopropyl silane in the presence of pyridine using dichloromethane as solvent. ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.8 (2H, br, s), 3.7 (1H, m), 3.3-2.9 (4H, m), 1.82 (2H, m), 1.09 (21H, m); $^{13}C\{^{1}H\}$ NMR (300 MHz, $CDCl_3$) δ 64.90, 60.01, 46.26, 24.93, 18.01, 11.99; GC/MS m/z (relative intensity) 257 (1), 214 (26), 170 (3), 128 (1), 103 (2), 70 (100), 59 (9); Anal. Calcd for $C_{14}H_{31}NOSi$: C, 65.3; H, 12.1; N, 5.4. Found: C, 61.6; H, 11.1; N, 4.8.

Preparation of Chiral Amine (223). The preparation of **223** was carried out according to the general procedure described above. 2.3 g of **223** (unpurified) were collected for a yield of 63%: IR 3605 cm^{-1}; ; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.73-7.07 (3H, m, aromatic), 4.02 (1H, m), 3.93 (2H, m), 3.33 (2H, m), 2.10-1.90 (4H, m) 1.13-1.18 (14H, m); $^{13}C\{^{1}H\}$ NMR (300 MHz, $CDCl_3$) δ 153.05, 141.60, 125.07, 124.16, 58.75, 45.72, 27.81, 26.64, 24.06, 23.92; GC/MS m/z (relative intensity) 261 (0.5), 216 (0.5), 163 (0.5), 133 (0.5), 115 (0.5), 70 (100), 56 (5.3); Anal. Calcd for $C_{17}H_{27}NO$: C, 78.1; H, 10.4; N, 5.4. Found: C, 67.4; H, 8.9; N, 4.6.

Preparation of Chiral Amine (224). The preparation of **224** was carried out according to the general procedure described above. 0.75 g of **224** were collected for a yield of 23%: IR 3664, 3355 cm^{-1}; ^{1}H NMR (300 MHz,$CDCl_3$) δ 7.06-6.58 (3H, m, aromatic), 4.19 (2H, m) 4.07 (1H, m) 3.86 (6H, m, methoxy groups), 3.58 (2H, m), 2.13 (2H, m), 1.46 (2H, m); $^{13}C\{^{1}H\}$ NMR (300 MHz, $CDCl_3$) δ 153.63, 125.01, 105.24, 59.17, 56.26, 24.57; GC/MS m/z (relative

intensity) 237 (5), 205 (2), 168 (13), 138 (6), 84 (100), 70 (34); Anal. Calcd for $C_{13}H_{19}NO_3$: C, 65.8; H, 8.1; N, 5.9. Found: C, 54.3; H, 7.0; N, 4.8 (All three elements are approximately 17% below expected values. Could have contaminants from the silica gel column used to purify sample).

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