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C_2-SYMMETRIC LEWIS ACID CATALYSTS:

The Role of Imidazole in the Stereoselective Hydrosilylation of Carbonyl Compounds

By

FRANK JERRY LARONDE, B. Sc.

A Thesis

Submitted to the School of Graduate Studies

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C_2-Symmetric Lewis Acid Catalysts:

The Role of Imidazole in the Stereoselective Hydrosilylation of Carbonyl Compounds

To Eudora Lambert and Franklin

and Theresa LaRonde

DOCTOR OF PHILOSOPHY (2000) McMaster University

(Chemistry) Hamilton, Ontario

TITLE: C_2-Symmetric Lewis Acid Catalysts:
The Role of Imidazole in the Stereoselective
Reduction of Carbonyl compounds

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ABSTRACT

The demand for functionalized materials of high optical purity has led to an intense research effort in asymmetric synthesis. Much of the attention has focused on the application of chiral main group and transition metal complexes to promote enantioselective transformations. The successful development of asymmetric catalysts is an iterative, multistep, process involving ligand design, catalyst synthesis, and substrate screening. In order to facilitate this process, new ligands, which are easily prepared and modified, must be advanced. In the realm of tetradentate ligands, the classical example is Jacobsen's salen complexes.

The ligands introduced here contain an imidazole moiety, which for years have been utilized by organic chemists as additives when protecting alcohols with silicon reagents. We advance here novel ligands that allow for enantioselective hydrosilylation of ketones. In particular we take advantage of the high reactivity of pentacoordinate silicon species. Initially, we provide evidence for pentacoordination of hydridosilicon compounds by imidazole, histidine, and C_2-symmetric imidazole ligands. We subsequently show that these species can be used for the reduction of carbonyl compounds; in the case of histidine and a C_2-symmetric ligand reduces enantioselectively. The lack of reactivity of chiral C_2 symmetric *N,N'*-bis(*N*-methyl-2-methylene-imidazole)-1,2-cylcohexanediamine derivatives prompted us to look at the metal binding properties of these ligands, and their

subsequent use as enantioselective reduction catalysts. Thus the second phase of this work involved the study of the complexation of these tetradentate ligands with metal species. The copper complex of the achiral *N*,*N*'-bis(*N*-methyl-2-methylene-imidazole)-1,2-ethanediamine and chiral *N*,*N*'-bis(*N*-methyl-2-methylene-imidazole)-1,2-cyclohexyldiamine were prepared and characterized by electrospray mass spectrometry and X-ray crystallography. The titanium adduct of two chiral cyclohexyl diamine ligands was utilized as catalyst for the enantioselective hydrosilylation of ketones. This reaction may or may not involve the intermediacy of pentacoordinate silicon compounds. The rhodium complex of these ligands was then utilized for the hydrostanylation of aldehydes.

The third part of this thesis involved preliminary work on developing a catalyst for the polymerization of alkoxysilane. Recent reports of an enzyme responsible for assembling the silicate surfaces of a marine sponge, prompted us to explore the possibility of our ligand system being utilized for the polymerization of alkoxysilanes.

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LIST OF ABBREVIATIONS

AcOH	Acetic acid
Ala	Alanine
Asp	Aspartic Acid
Bn	Benzyl
Boc	Butoxycarbonyl
bs	Broad signal (^{1}H NMR)
^{13}C NMR	C-13 Nuclear Magnetic Resonance Spectroscopy
CI	Chemical Ionization
d	Doublet (^{1}H NMR)
dd	Doublet of Doublets (^{1}H NMR)
dt	Doublet of Triplets (^{1}H NMR)
DCC	Dicyclohexylcarbodiimide
DCM	Dichloromethane
DIPEA	Diisopropylethylamine
DMAP	4-Dimethylaminopyridine
DMF	Dimethylformamide
EDAC-HCl	1-(3-(Dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride
e.e.	Enantiomeric Excess

EI	Electron Impact Mass Spectrometry
ES	Electrospray Mass Spectrometry
EtOH	Ethanol
Gln	Glutamine
Glu	Glutamic acid
Hb	Hemoglobin
His	Histidine
HPLC	High Performance Liquid Chromatography
HRMS	High Resolution Mass Spectrometry
^{1}H NMR	Proton Nuclear Magnetic Resonance Spectrometry
h	Hours
Im	Imidazole
IR	Infrared Spectroscopy
m	Multiplet (^{1}H NMR)
Mb	Myoglobin
Me	Methyl
MeOH	Methanol
m.p.	Melting point
MS	Mass Spectrometry
NH_3	Ammonia
NMI	*N*-methylimidazole
MTPA-Cl	α-Methoxy-α-(trifluoromethyl)phenylacetyl chloride)

ppm	Parts per million
Pro	Proline
Pyr	Pyridine
q	quartet (^{1}H NMR)
s	singlet (^{1}H NMR)
Ser	Serine
^{29}Si NMR	Silicon-29 Nuclear Magnetic Resonance Spectrometry
t	Triplet (^{1}H NMR)
TBAF	Tetrabutylammonium fluoride
TBS	tertiary-Butyldimethylsilyl
TBSCl	tertiary-Butyldimethylchlorosilane
TBDMS	tertiary-Butyldimethylsilyl
TFA	trifluoroaceticacid
THF	Tetrahydrofuran
Thr	Threonine
TLC	Thin Layer Chromatography
TMEDA	*N,N,N',N'*-Tetramethylethylenediamine

Preface and Objectives

The rational design of selective receptors and catalysts remains a challenge for both chemists and biochemists alike. In contrast, nature has produced enzymes that catalyze a huge array of reactions with exquisite selectivity and antibodies that bind virtually any molecule with high affinity. Nature has solved many of the complex problems associated with molecular recognition and catalysis by generating and screening large libraries of proteins, either on an evolutionary time scale or over the course of a few weeks during immune response. It is therefore wise in the development of novel catalytic systems that one looks to nature for guidance. In this light, Platz[1], and later Evans[2] have utilized the semi-corrin architecture as a guide to the development of C_2 symmetric oxazoline complexes that possess the ability to catalyze a host of chemical transformations with high enantioselection. Our interest in the development of enantioselective catalysts lies within the realm of silicon chemistry. In particular, the utility of the diverse properties of imidazole is exploited in the development of catalytic systems that allow for the enantioselective hydrosilylation of carbonyl compounds.

Therefore, in light of the previous discussion, it is pertinent that we begin our quest by evaluating nature's use of the imidazole moiety. In chapter 2 we will evaluate the properties of imidazole that account for its multifunctional role.

Chapter 3 will be concerned with the utility of imidazole in silicon chemistry, focussing on the propensity of silicon to become hypervalent. This will present past accounts of the preparation, structure and reactivity of extracoordinate silicon compounds. Chapter 4 will review the use of C_2-symmetric ligands in stereoselective organic transformations. Chapter 5 will outline our work on the use of lithium-imidazolide as catalyst to effect hypercoordination at a silicon center, allowing for the reduction of ketones. The amino acid histidine is utilized for the enantioselective reduction of these ketones. Chapter 6 will address the question of the use of novel C_2-symmetric imidazole bis-imine complexes. Chapters 7 and 8 will summarize our reduction results and propose a mechanism by which these reductions occur respectively. Moreover, the lack of reactivity of newly developed C_2 symmetric imidazole bis-amine complexes in these enantioselective reductions has led to the application of these ligands to metal based hydrosilylation and allylstanylation reactions. The use of these novel C_2-symmetric ligands as metal binders will be described in Chapter 9. Chapter 10 will illustrate the use of diamine titanium complexes for the enantioselective hydrosilylation of ketones and α-haloketones. Chapter 11 will focus on our work concerning the enantioselective allyl stannylation of aldehydes. Chapter 12 will show our preliminary work on the development of an enzyme mimic, which may allow for polymerization of alkoxysilanes. Finally some conclusions and experiments that might be conducted from the developments outlined in this thesis will be addressed in chapter 13.

Imidazole has proved to be an excellent activator of silicon in protecting group chemistry. However, it has never been shown, if activation of a hydridosilane by

imidazole would possess reductive potential. Thus, our objective in this thesis is to evaluate the ability of imidazole to activate hydrosilicates, which in turn allows for the reduction of carbonyl species. We would also like to render this reduction process enantioselective. We would also like to evaluate the use of C_2-symmetric systems (that have been shown to be very fruitful in transition metal based catalytic systems) bearing the imidazole moiety to confer selection in this reduction process. Moreover, we want to evaluate the use of these C_2-symmetric ligands in transition metal based hydrosilylation processes.

---

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Chapter 1

Imidazole in Biological Systems

1.1 INTRODUCTION

The imidazole ring, as a histidine moiety, and the benzimidazole ring, particularly as its 5, 6-dimethyl derivative, function as ligands toward transition metal ions in a variety of biologically important molecules including iron-heme systems, vitamin B_{12} and its derivatives, and several metalloproteins[1]. Of the amino acid-bound Cu (II) in human blood plasma, more than 98% occurs in histidine complexes, and most of this is in mixed ligand complexes involving oxygen donation from other amino acid ligands[2]. The imidazole ring is also known to function in biological systems as a nucleophile or as proton-transfer reagent. Four systems are outlined below that illustrate the diverse utility of imidazole in biological systems. We will examine imidazole as a metal binder (carboxypeptidase A, and carbonic anhydrase enzymes), a metal protector (porphyrin system), and as a nucleophile and temporary reservoir of protons for subsequent transfer to another substrate (proton transfer agent, with the catalytic triad of serine protease enzymes).

1.2 IMIDAZOLE AS A METAL BINDER

Carboxypeptidase stands as an example of a class of metalloenzyme where the imidazole moiety seems to serve mainly in holding a metal ion, zinc, in the correct topology in the active site of the enzyme. This class of proteins catalyzes the hydrolysis of the C-terminal residue of polypeptides[3]. Carboxypeptidases, like all enzymes, are highly specific for the chemical identities of the substances whose reaction they catalyze. The side chain specificity of the various carboxypeptidases are listed in **Table 1. 1**.

Table 1. 1: Specificities of Various Exopeptidases[1]

Enzyme	Source	Specificity[a]
Carboxypeptidase A	Bovine pancreas	R_n =Arg, Lys, Pro; R_{n-1} /= Pro
Carboxypeptidase B	Bovine pancreas	R_n = Arg, Lys; R_{n-1} /= Pro
Carboxypeptidase C	Citrus leaves	All free C-terminal residues; pH optimum = 3.5
Carboxypeptidase Y	Yeast	All free C-terminal residues; slow with R_n=Gly

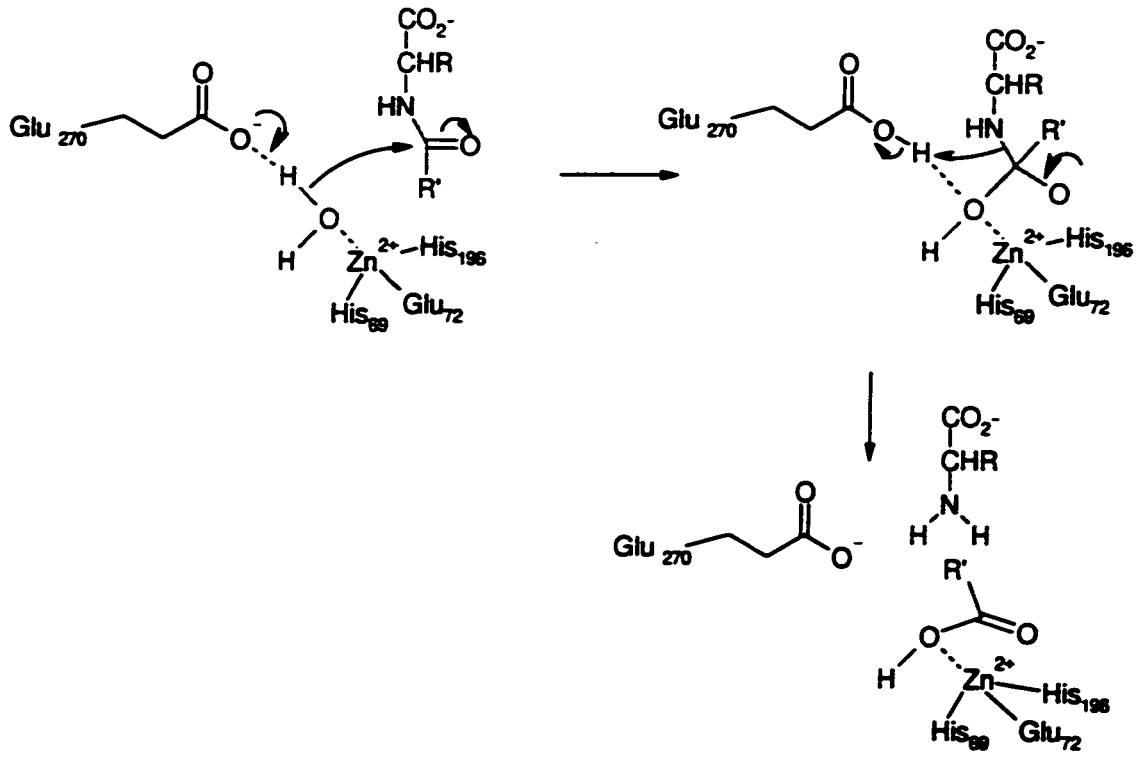
The chemical analysis of carboxypeptidase A failed to show the involvement of the imidazole residue, in the form of histidine, in the binding of the zinc ion[4]. On the other hand, the results of X-ray diffraction study of the crystalline enzyme[5] in conjunction with amino acid sequence[6] indicated that the zinc ion is bonded to two histidyl and one glutamic acid residues about 25 Å from the amino terminus. Specifically, in bovine pancreatic carboxypeptidase A it was found that His_{69}, His_{196}, and Glu_{72}, of the 307 amino acid single polypeptide chain protein[7] are the residues responsible for the binding (**Scheme 1. 1**).

The proposed mechanism by which carboxypeptidase A hydrolyzes the carboxyl terminal amino acid residue of peptides is illustrated **Scheme 1. 1**. The X-ray structure[5] indicates the presence of a bound water molecule within the active site as diagrammed below.

In the active site of the enzyme, the Glu_{270} side chain is deprotonated. This residue acts as a general base, and a general acid catalyst. This mechanistic proposal shows a synchronous attack of the bound water molecule by the carboxylate ion of Glu_{270}, and an attack of the water onto the C terminal amide bond. Subsequent collapse of the resulting tetrahedral intermediate releases the C-terminus amino acid. The polypeptide chain coordinated to the zinc ion via carboxylate oxygen is displaced upon coordination of water.

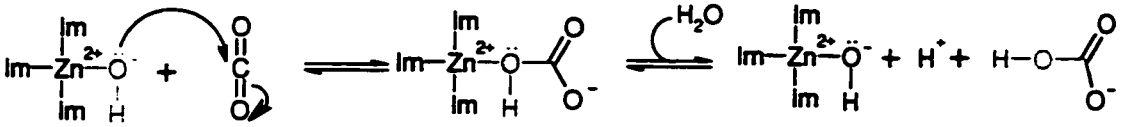
Other metal ions may be substituted for the zinc ion in carboxypeptidase, sometimes resulting in increases of the peptidase and esterase activities observed for the native zinc enzyme[8]. The order of peptidase activity for metallocarboxypeptidases is Co(II) > Zn(II) > Ni(II) > Mn(II). For esterase activity the order is Mn(II) > Cd (II) > Co (II) > Zn (II) > Hg (II) > Ni(II) > Pb (II). The incorporation of metal ions that appear in the latter list and not in the former yields a protein that is inactive as a peptidase. The Cu (II) substituted protein is inactive in both reactions, although both kinds of substrates are bound.[9]

Scheme 1. 1: Proposed Mechanism for Carboxypeptidase A



Another example of the utility of imidazole in binding an essential Lewis acidic metal needed for catalysis in biological systems is that of carbonic anhydrase. This enzyme is responsible for the conversion of carbon dioxide to carbonic acid. The enzyme contains a Zn^{+2} ion essential for its activity, that is implicated in the enzymes catalytic mechanism **(Scheme 1. 2)**.

Scheme 1. 2: Catalytic cycle of carbonic anhydrase



Im = Imidazole

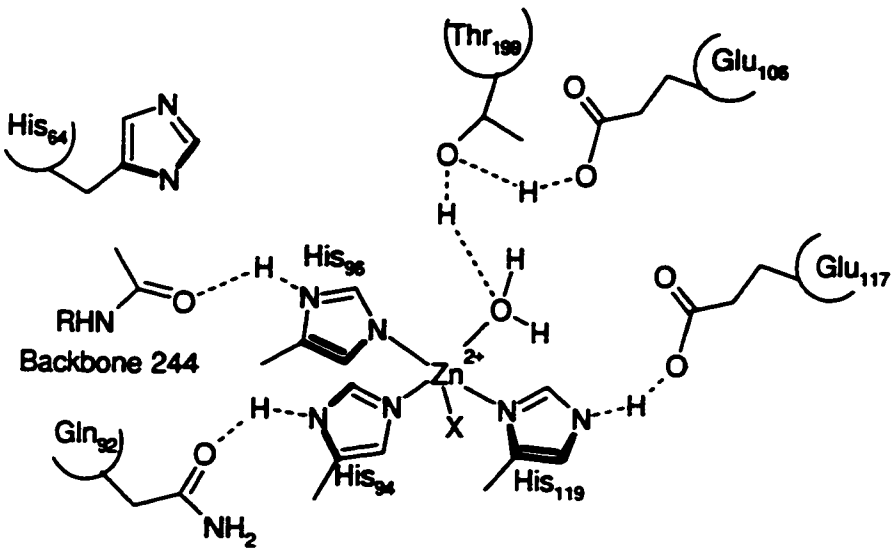
(1) The crystal structure of human carbonic anhydrase[10] reveals that three His side chains and a water molecule tetrahedrally coordinate about a Zn^{+2} ion. The Zn^{+2}-polarized

water ionizes in a process facilitated through general base catalysis by either Glu 106 or Glu 117.

(2) The resulting Zn^{+2} bound HO^- nucleophilically attacks the nearby enzymatically bound CO_2, thereby converting it to HCO_3^-.

(3) The binding to the Zn^{+2} and ionization of another molecule of water then regenerates the catalytic site, possibly before the departure of the HCO_3^- ion, so as to form a transient 5-coordinate Zn^{+2} complex.

Figure 1. 1: Active site of human carbonic anhydrase[11]

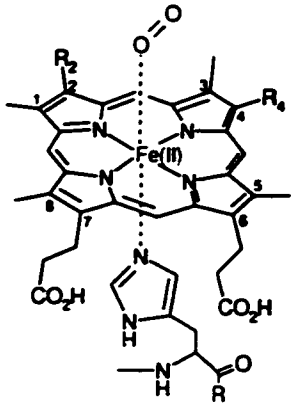


This example illustrates the retention of the Lewis acidity of metal ions bound to three imidazole moieties. This is a very important consideration needed for the development of catalytic systems where one has to retain the Lewis acidity of bound metal within an active complex. The importance of this example will make itself clear as the reader examines chapter 10 and chapter 11.

1.3 IMIDAZOLE AS A METAL PROTECTOR

The classic example of biological histidine-metal interaction is, of course, the case of hemoglobin[12] and the related myoglobin[13] and erythrocruorin[14]. X-ray structures have in each case revealed bonding of one histidine residue to the porphyrin iron. It is believed that oxygen binding converts Fe (II) from high spin to low spin that leads to movement of the iron which initially is as much as 0.8 Å out of the porphyrin plane to a position in the plane of the nitrogen atoms[15]. The current interpretation of cooperative O_2 binding by hemoglobin envisages this movement as the triggering event, which by pulling on the bound histidine results in conformational changes that are transmitted between sub-units leading to an increasing avidity to bind oxygen.

Figure 1. 2: A Structural Glossary for the Hemes

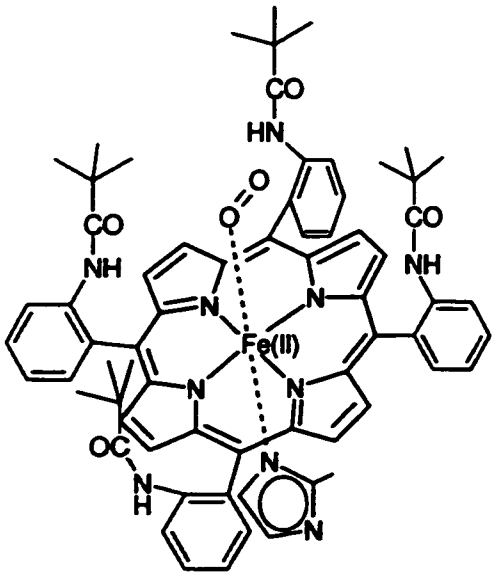


Protoheme	R2, R4 = -CH=CH_2
Synonyms	Fe(II), heme; Fe (III), hematin
Mesoheme	R_2, R_4 = CH_2CH_3
Deuteroheme	R2, R4 = H
Pyroheme	R2, R4 = C2H5, H for CH2CH2CO2H at 6
Heme a_2	R2= -CH=CH2, R4 = -CHOHCH3
Heme C	R2, R4 = -C(SMe)HCH3
Heme A	R2 = CH(OH)CH2CH(CH3)(CH2)3CH(CH3)2 R4 = -CH=CH2 CH3 at 8 = -CH=O

The imidazole binding not only modulates the O_2-binding affinity of heme, but also makes O_2 binding possible[1]. Fe(II) heme by itself is incapable of binding O_2 reversibly. Rather, in the presence of O_2, it autooxidizes irreversibly to the Fe (III) form through the intermediate formation of a complex consisting of an O_2 bridging the Fe atoms of two hemes.

This reaction can be inhibited by derivatizing the heme with bulky groups that sterically prevent the close face-to-face approach of two hemes. Such "picket fence" Fe(II)-porphyrin complexes (**Scheme 1. 3**), which James Collman first synthesized, bind O_2 reversibly[16].

Figure 1. 3: Picket fence porphyrin



The backside of this porphyrin is unhindered and is complexed with a substituted imidazole in a manner similar to that in myoglobin (Mb) and hemoglobin (Hb). In fact, O_2 affinity for the picket-fence complex is similar to that of myoglobin. Thus, the polypeptide chain, specifically histidine, of Mb and Hb functions to prevent the autooxidation of oxyheme by surrounding it, a metal protector.

1.4 NUCLEOPHILIC CHARACTER AND PROTON PUMP ACTIVITY OF IMIDAZOLE

An important example of the general base (nucleophilic character)-general acid character of imidazole comes from a diverse group of proteolytic enzymes known as serine proteases (**Table 1. 2**). These enzymes are so-named because they have a common catalytic mechanism characterized by the possession of a reactive serine residue[3].

Table 1. 2: A Selection of Serine Proteases[1, 17]

Enzyme	Source	Function
Trypsin	Pancreas	Digestion of proteins
Chymotrypsin	Pancreas	Digestion of proteins
Elastase	Pancreas	Digestion of proteins
Thrombin	Vertebrate serum	Blood clotting
Plasmin	Vertebrate serum	Dissolution of blood clots
Kallikrein	Blood and tissues	Control of blood flow
Complement C1	Serum	Cell lysis in the immune response
Acrosomal protease	Sperm acrosome	Penetration of the ovum
Lysosomal protease	Animal cells	Cell protein turnover
Cocoonase	Moth larvae	Dissolution of cocoon after metamorphosis
α-Lytic protease	Bacillus soroangium	Possibly digestion
Proteases A and B	Streptomyces griseus	Possibly digestion
Subtilisin	Bacillus subtilis	Possibly digestion

X-ray structural analysis and primary structure determinations of bovine chymotrypsin, bovine trypsin, and porcine elastase have shown extensive active site homologies among the various serine proteases, indicating that they all have the same catalytic mechanism[1, 18]. The proposed catalytic mechanism of action is depicted below for chymotrypsin (**Scheme 1. 3**)[19].

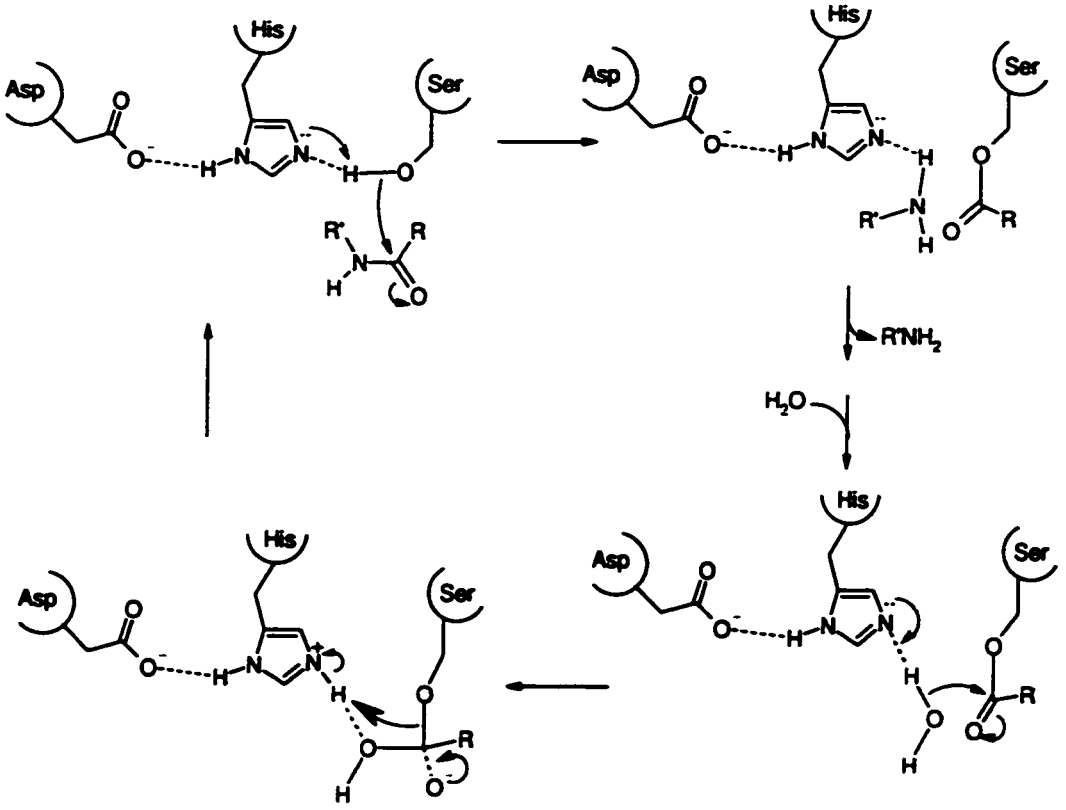
After chymotrypsin binds substrate to form the Michaelis complex, the serine residue nucleophilically attacks the peptide's carbonyl group to form a tetrahedral intermediate. X-ray studies indicate that serine 195 is ideally positioned to carry out this nucleophilic attack[20]. The imidazole ring of histidine 57 takes up the liberated proton thereby forming an imidazolium ion (general base catalysis). The process is aided by the polarizing effect of the unsolvated carboxylate ion of aspartic acid 102, which is hydrogen bonded to the N1 proton of the imidazole ring of histidine 57.

Indeed the replacement of trypsin's aspartic 102 with asparagine, by site directed mutagenesis, leaves the enzyme's K_m substantially unchanged at neutral pH[21]. Neutron diffraction studies have demonstrated that aspartic acid 102 remains a carboxylate ion rather than abstracting a proton from the imidazolium ion[22].

The transient tetrahedral species decomposes to the acyl-enzyme intermediate under the driving force of proton donation from N(3) of histidine 57 (general acid catalysis). The amine leaving group ($R'NH_2$, the new *N*-terminal portion of the cleaved polypeptide chain) is released from the enzyme and replaced by a water molecule from the solvent. The acyl-enzyme intermediate is extremely sensitive to hydrolytic cleavage. Despite this instability, the X-ray structure of elastase's acyl-enzyme intermediate has been reported at –55 °C[20].

The deacylation step proceeds largely through the reversal of the previous steps, with release of the carboxylate product and the concomitant regeneration of the enzyme. In this process water is the attacking nucleophile and serine 195 is the leaving group.

Scheme 1. 3: Proposed catalytic activity for chymotrypsin (Serine Proteases)



These examples demonstrate the general utility of imidazole in biological systems. This was illustrated in three general categories: (1) carboxypeptidases and carbonic anhydrase demonstrated the metal binding properties of imidazole; (2) the porphyrins indicated the metal protecting activity; and (3) serine proteases exemplify the utility of imidazole as a general acid-general base (nucleophilic reagent) catalyst. This thesis will display to the reader how each of these aforementioned motifs has been transferred to the chemical laboratory.

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Chapter 2

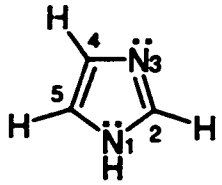
Properties of Imidazole

2.1 Introduction

The structural features associated with imidazole or the 1, 3-diazole ring, which allows for its diverse chemical properties, must be discussed briefly. The parent molecule falls in the class of the aromatic heterocycles and its unique structural features are best discussed with reference to pyridine and pyrrole, to both of which imidazole is structurally related.

2.2 Aromaticity of the Imidazole Ring

Aromaticity in completely conjugated monocyclic systems requires a planar array of atoms with $4n + 2$ π electrons[1]. The possibility for aromaticity in imidazole can be recognized if imidazole is considered to be constructed from: (a) a trigonal nitrogen (sp^2) with two electrons in the unhybridized *p* orbital (N-1, "pyrrole nitrogen"); (b) a trigonal nitrogen, with a single electron in a hybrid orbital and a lone pair of electrons in a *p* orbital (N-3, "pyridine nitrogen"); and (c) three trigonal carbons each with one electron in a *p* orbital. An aromatic sextet is then available.



Imidazole is indeed generally regarded as being aromatic. The molecule is planar, as anticipated for an aromatic system[2]. From Dewar's definition of aromaticity the resonance energy of imidazole is calculated to be 15.4 kcal/mol[3]. The same method yields resonance energies of 20.0, 20.9, and 8.5 kcal/mol for benzene, pyridine, and pyrrole, respectively[3]. Similarly, the resonance energies of benzimidazole (30.9 kcal/mol) and naphthalene (30.5 kcal/mol) are comparable. Empirical resonance energies for imidazole, derived from thermochemical data, range from 12 to 32 kcal/mol depending on the assumptions taken[4].

The net charges on the nitrogen atoms found for pyrrole[5], pyridine[6], and imidazole[6b] have been calculated using *ab initio* methods and are documented in **Table 2. 1.**

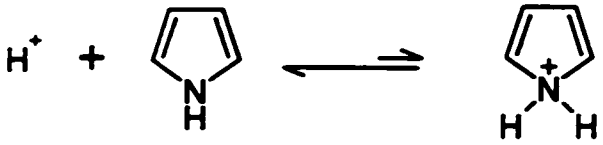
Table 2. 1: Calculated Net Charges at Nitrogen Atoms Contained in Pyridine, Imidazole, and Pyrrole

Heterocycle	σ	π
Pyridine	-0.22	-0.01
Imidazole		
N-3	-0.16	-0.10
N-1	-0.84	+0.40
Pyrrole	-0.75	+0.34

From comparison of the values presented in **Table 2. 1**, the N-3 nitrogen of imidazole is aptly termed the pyridine nitrogen and the N-1 nitrogen is properly called the pyrrole nitrogen. The pyridine nitrogens display fractional negative σ and π electronic charges,

indicating that this nitrogen is a modest σ acceptor and a weak π acceptor. What is also evident from **Table 2. 1** is the two-way charge transfer at the pyrrole nitrogen. The pyrrole nitrogen donates substantial fractional electronic charge to the π system but withdraws an even greater amount of charge from the σ orbital. These calculations indicate that the σ electrons of pyrrole and imidazole are strongly delocalized and polarized about the rings.

A crucial structural feature with respect to the most available coordination site of imidazole is simplified when the aromatic nature of the molecule is accepted. There is only one pair of electrons distinguished as an unshared pair, the pair on the N-3.



Equation 2.1

The π electrons of N-1 are part of the aromatic sextet, and therefore are unavailable for coordination. Bonding of a proton or metal ion at N-1 is expected to be unfavorable since the aromatic nature of the ring would be compromised. The basicity of this site cannot be measured, since protonation at carbon intervenes with a pKa of –3.8.[7]

It has been estimated that the equilibrium constant for the reaction that appears in **Equation 2.1** is 10^{-10} (pKa = -10).[8] The pyrrole nitrogen of imidazole must be of lower basicity than pyrrole, because of the additional electron-withdrawing effect of the pyridine nitrogen. Therefore, a neutral imidazole molecule only possesses a single energetically favorable coordination site, the unshared pair of electrons on N-3. Structures **1** and **2** are of very high energy.

Figure 2. 1: High-energy coordination site on imidazole

1 2

The transfer of the N-1 proton to N-3 would be very favorable energetically, and species such as 1 and 2 would not be expected to be observable. Instead, the aromatic cations, structures 3 and 4, are expected to be observable, and in fact can be isolated.

Figure 2. 2: Representative stable coordination sites displayed by imidazole

3 4

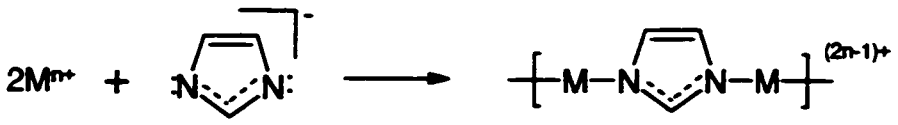
The distinction between N-1 and N-3 nitrogens is lost in the protonated imidazolium cation 3. Since this cation is symmetrical, H-4 and H-5 are equivalent, and a single peak appears in the proton NMR spectrum. A single average peak for the H-4 and H-5 protons also persists into basic solutions of neutral imidazole because of proton exchange reactions between N-1 and N-3. In aqueous solutions tautomeric equilibration of the nitrogen bound hydrogen occurs without disruption of the aromaticity. The predominant exchange reaction in acidic solution is:

$$ImH^+ \underset{k_2}{\overset{k_1}{\rightleftharpoons}} Im + H^+ \quad \textbf{Equation 2.2}$$

And in basic solution it is:

$$Im + H_2O \underset{k_4}{\overset{k_3}{\rightleftharpoons}} ImH^+ + HO^- \quad \textbf{Equation 2.3}$$

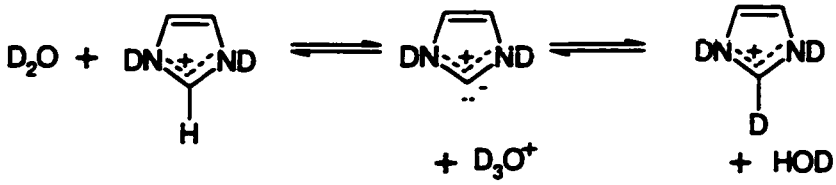
In addition to protonation at N-3 with pK_a = 7.1 (25 °C at 0.2 ionic strength) to give the imidazolium cation, neutral imidazole undergoes deprotonation at N-1 in strongly basic solutions with reported pK_a values from 14.2 to 14.6[9].



Equation 2.4

The resulting anionic imidazole, also aromatic, possesses two equivalent sites for coordination and is a potential bridging ligand (**Equation 2.4**)[10].

Although never a major component of the mixture in aqueous solution at equilibrium, the ylide formed by deprotonation of the imidazolium ion at C-2 can play a significant role in the chemistry of imidazole. The exchange of proton at C-2 in imidazole in aqueous solution is quite rapid (**Equation 2.5**)[6].

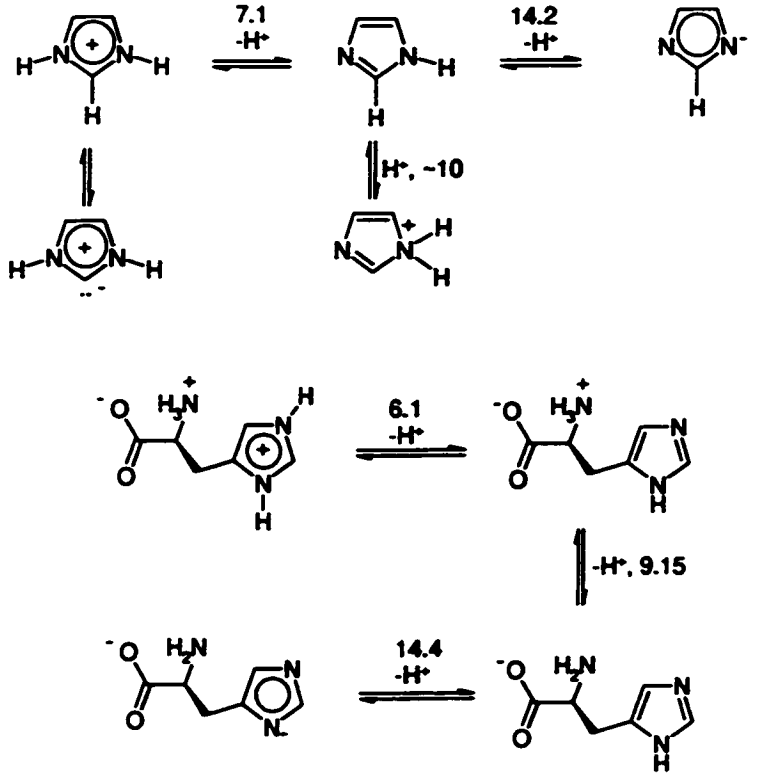


Equation 2.5

The half-life for incorporation of deuterium from D_2O at 65 °C and pD 6.9 is 109 min[11]. The pH-rate profiles for both imidazole and 1-methylimidazole[12] indicate that the ylide is the reactive species in the exchange process. Proton-exchange processes at C-2 or 1,3-dialkylimidazolium ions have been studied and found to occur via ylide intermediates[13]. The most stable ylide is formed by deprotonation at C-2, which is bonded to two positively charged nitrogens. The 4(5) position adjacent to a single nitrogen is less acidic[11]. Figure 2. 3 summarizes the protonation equilibria for imidazole and gives similar data for histidine. As noted in Figure 2. 3, imidazole and therefore histidine are

amphoteric, being moderately strong organic bases capable of accepting protons at N-3 as well as weak acids capable of loss of a proton from N-1.

Figure 2. 3: Protonation Equilibria for Imidazole and Histidine



2.3 IMIDAZOLE-METAL COMPLEXES

As noted previously, imidazole and similarly histidine are amphoteric and in solutions near neutrality, the unprotonated imidazole molecule usually functions as a ligand via the unshared electrons on N-3. These two important characteristics of imidazole play a large role in its chemistry.

Representative logarithms of stability constants for complexation of metal ions with ammonia, imidazoles, pyridine, and histidine are listed in **Table 2. 2.** In order to maintain consistent conditions when comparing stabilities of a single ligand with a

variety of metal ions, the work of Bjerrum was used for ammonia and most pyridine constants.[14]

Table 2. 2: Logarithms of Stability Constants[15]

Ligand	H^+	Co(II)	Ni(II)	Cu(II)	Zn(II)	Cd(II)	Hg(II)	Cu(I)	Ag(I)	Ref
NH_3[a]	K_1 9.33	2.11	2.80	4.15	2.37	2.65	8.8	5.9	3.2	17a
	K_2	1.63	2.24	3.50	2.44	2.10	8.7	4.9	3.8	
	K_3	1.05	1.73	2.89	2.50	1.44	1.0			
	K_4	0.76	1.19	2.13	2.15	0.93				
4-MI[b]	K_1 7.69			4.13	2.44					17b
	K_2			3.49	2.53					
	K_3			2.87	2.64					
	K_4			2.0	2.4					
Im[c]	K_1 7.11	2.45	3.0	4.20	2.52	2.80		5.8	3.1	6
	K_2	1.9	2.5	3.42	2.32	2.10	16.7	5.2	3.8	
	K_3	1.4	2.0	2.88	2.32	1.55				
	K_4		1.5	2.1	2.0	1.1				
Pyr[d]	K_1 5.21	1.15	1.78	2.41	0.88	1.30	5.1	3.2	2.0	17c, d
	K_2	0.55	1.22	1.88	0.47	0.84	4.9	3.4	2.2	
	K_3	-0.3	0.3	1.14	0.15	0.36	0.3			
	K_4		-0.3	0.60	-0.2	-0.2				
His[c,e]	K_1 9.15	6.9	8.7	10.1	6.6	5.4				17e, f
	K_2 6.10	5.5	6.9	8.0	5.5	4.3	21			

[a]All values in 2M NH_4NO_3 ($\mu = 2$) and 30 °C, except Hg (II) and Cu(I) which are at 20 °C. [b]At 25 °C and $\mu = 0.16$ ionic strength. [c] "Consensus" values near 0.2 ionic strength and 25 °C. [d]Except for Cu (I) all values at 25 °C and $\mu = 0.5$; Cu (I) at 20 °C and $\mu = 0.15$. [e] At 25 °C and $\mu = 0.10$:

The values for ammonia are measured at greater ionic strength and temperature than the constants for the other ligands in **Table 2. 2.** The ionic strength dependence on the stability constants is slight, and the 5 °C greater temperature is a constant difference in comparing ammonia with other ligands. For the ligands described above, the usual stability order, [16] Mn (II) < Fe (II) < Co (II) <Ni (II) < Cu (II) < Zn (II), is found. Changes in vibrational frequencies found in infrared spectra have been interpreted to give the same stability order.[17]

A comparison of stability constants among ligands requires some recognition of their differences in basicity. The precise dependence of stability constants on ligand

basicity varies among families of ligands and also from ligand to ligand. **Table 2. 2** shows that stability constants for divalent transition metal ions are slightly greater for imidazole than NH_3 despite the 170 times greater basicity of the latter. If σ-bonding ability were the sole factor in determining stability constants, the values of NH_3 would be appreciably greater than those for imidazole. The relatively strong binding of the weaker base imidazole to metal ions may be partly due to the greater π-acceptor properties of imidazole over ammonia, which permit it to accept electronic charge from *d* orbitals on the metal ion.

The importance of π-acceptor qualities in strengthening the bonding of imidazole to metal ions may be further supported by noting that though 4-methylimidazole is nearly a four times stronger base than imidazole, it binds to Cu (II) and Zn (II) less strongly. This inversion in order in pKa and log K_1 for the two imidazoles may be accounted for by the hyperconjugative or inductive effect of the methyl group, which reduces the π-acceptor capability of the imidazole ring.[18, 19] Significant π-acceptor properties remain for 4-methylimidazole, as the stability constants for Cu (II) and Zn (II) are nearly identical with those for NH_3, while the latter ligand binds protons over 40 times more strongly.

As pointed out in **Table 2. 1,** the π-acceptor capability of pyridine is greater than that of imidazole, and, for most of the metal ions of **Table 2. 2,** the stability constants for pyridine are greater than the basicity difference values would suggest when comparing it to imidazole. Furthermore, the nearly constant difference in log K_1 between imidazole

and NH_3 does not carry over to pyridine, where the differences with both of the other two metal ligands varies with the metal ion.

The first four ligands of **Table 2. 2** are arranged in order of decreasing basicity, which is also the order of increasing π-acceptor capability. The latter feature seemingly dominates the former with Ru (II). Estimates of the stability constant for formation of complexes of imidazole, NH_3, and pyridine with pentaaamineruthenium (II) have been made from kinetic data.[20] The stability order pyridine > Im > NH_3 stands in striking contrast to the order Im > NH_3 > pyridine found with the first row transition metal series. The greater stability constant of Ru / pyridine interaction can be attributed to the exceptional π-donor ability of Ru(II).[21]

2.3.1 Dynamics of Imidazole-Metal Interaction

The kinetics of acid catalyzed aquation of $[(NH_3)_5ImRu]^{2+}$ have been studied[20] and compared with similar acid-mediated cleavage of ligand from $[(NH_3)_6Ru]^{2+}$ and $[(NH_3)_5PyRu]^{2+}$.[22] The imidazole complex is labile in comparison with both the ammonia and pyridine analogs (**Table 2. 3**).

Table 2. 3: Equilibrium constants measured for acid catalyzed substitution of the various heterocyclic bases

$$[(NH_3)_5RuB]^{2+} + H_3O^+ \underset{}{\overset{k_1}{\rightleftharpoons}} [NH_3)_5RuH_2O]^{2+} + BH^+$$

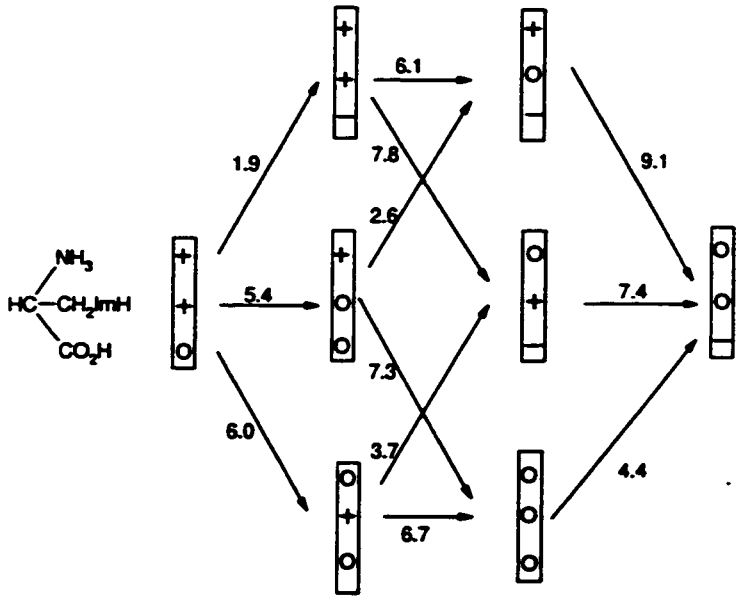
Base (B)	k_1, $M^{-1}s^{-1}$ (at $\mu = 1.0$)
Ammonia	20×10^{-5}
Pyridine	5.4×10^{-5}
Imidazole	3380×10^{-5}

Part of this lability may be ascribed to the relatively poor π-acceptor properties of imidazole as compared to pyridine. It is known that in the pyridine series the rate of aquation decreases as the pyridine is substituted by electron-withdrawing groups[22]. However, the fact that imidazole cleavage is about 170 times faster than cleavage of ammonia (no π-acceptor ability) indicates that other factors must also come into play. The imidazole-ruthenium bond seems to be somewhat kinetically labile since imidazole is lost in preference to ammonia by at least 10:1 from $[(NH_3)_5ImRu]^{2+}$, while pyridine is eliminated from $[(NH_3)_5PyRu]^{2+}$ at only about two times the rate.[22]

2.4 Histidine Complexes

The importance of histidine interactions with transition metal ions in biological systems has been recognized for quite some time. The imidazole nitrogens of histidine residues provide one of the primary means by which metal ions may be bound to proteins as depicted in Chapter 1. The carboxyl group (pKa = 1.9), the imidazole nitrogen (pKa = 6.1), and the amino nitrogen (pKa = 9.1) become available for complexation as the pH increases. A complete ionization scheme for histidine is shown in **Figure 2.4**.

Figure 2. 4: Complete protonation equilibria for histidine[23]



Histidine deprotonation scheme near 25 °C and μ = 0.15. Signs indicate charges on ammonium, imidazole, and carboxylic acid groups respectively. Predominant deprotonation equilibria are across the top of the figure.

The pKa value anticipated for a histidyl residue in a polypeptide chain is shown at the bottom, center of **Figure 2.4**, where for the (0 + 0) → (0 0 0) deprotonation of the imidazolium group from an otherwise uncharged molecule, the pKa is 6.7. This value is within the range commonly observed for histidyl residues titrated normally in proteins.

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Chapter 3

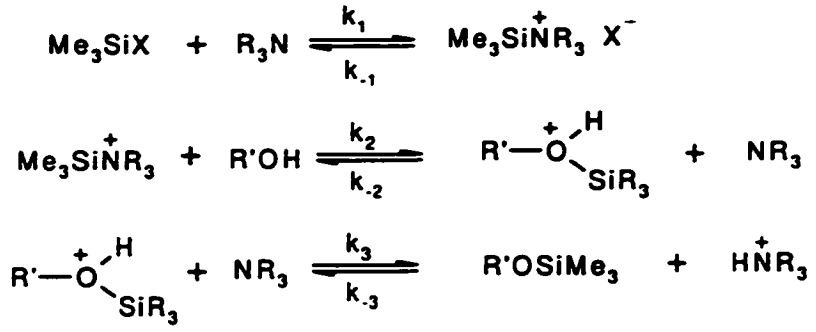
Hypervalent Silicon Chemistry

3.1 Imidazole in Silicon Chemistry

It has been known for a number of years that imidazole, and related aromatic amines, promote the silylation of alcohols, thiols, ketones, and other labile compounds[1]. Three different mechanisms were originally postulated for the role of these amine-assisted silylations. The first assigns the role of the amine to that of a proton acceptor, facilitating reaction by driving the equilibrium towards the product side (acid mop).

The second mechanism[2] involves a pre-equilibrium quaternization of the amine by the electrophilic silane. The quaternized aminosilane then becomes the active silylating species, being attacked by the alcohol, or other nucleophile, in a rate determining bimolecular displacement (**Scheme 3.1**).

Scheme 3. 1: Pre-equilibrium quaternization mechanism for silylation of alcohols



The third mechanism[3] is kinetically equivalent to that shown in **Scheme 3.1.** However, the formation of a five coordinate silyl species that is a molecular adduct between the silane and amine is postulated to be the initial step. The rate-determining step involves the attack of the alcohol on the five coordinate silicon species.

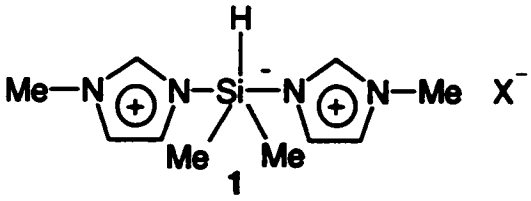
There is now a considerable body of evidence that rules out the amine as a simple proton acceptor, and shows its intimate involvement in the reaction. For example, Chaudhary and Hernandez[4] showed that a mixture of triethylamine and 4-dimethylaminopyridine (DMAP) promoted the silylation of alcohols by *t*-butylchlorodimethylsilane (TBDMS). The silylation was quantitative in the presence of catalytic amounts of DMAP, but did not proceed in its absence, despite the presence of stoichiometric amounts of triethylamine or pyridine.

These observations were taken as evidence for the mechanism outlined in **Scheme 3.1.** The pre-equilibrium mechanism is established for aminosilane solvolysis,[5] in which the initial step is protonation of aminosilane. Moreover, Frye *et al.*[6] showed that the alcoholysis of chlorosilanes is accelerated according to the nucleophilicity of the added amine and is unrelated to its pKa. In a detailed discussion, the mechanistic evidence was reviewed and the mechanism in **Scheme 3.1** was strongly supported.

The mechanism involving five and six coordinate silicon intermediates was proposed by Corriu[7] and is supported by conductivity measurements and kinetic data. However, as mechanisms two and three are kinetically indistinguishable, it is important to establish the nature of the species present in silylation reactions.

There is now a large body of evidence, which will be described below that outlines the great strides that have been made to support mechanism 3 in these nucleophilic substitution reactions. A number of pentacoordinate species of silicon have been isolated and completely characterized. For instance, Bassindale *et al.*[8] isolated pentacoordinate imidazole species 1, which suggests the intermediacy of related pentacoordinate silicon species in the silylation of alcohols.

Figure 3. 1: Isolated pentacoordinate bis-*N*-methyl imidazole dimethylsilane species



1

This chapter will briefly outline the strides that have been made to establish the intermediacy (or transitory nature) of extracoordinate species in nucleophilic substitution reactions at a silicon center.

3.2 History

Compounds of silicon with coordination number greater than four have been known since the beginning of the 19th century, when Gay-Lussac[9] and H. Davy[10] first observed, independently, the formation of the $[SiF_6]^{2-}$ ion and of the adduct of SiF_4 with ammonia.

An important aspect of the chemistry of hypervalent silicon compounds, which has stimulated the interest of researchers in the past 20-30 years, is the fact that these compounds behave very differently from their tetracoordinate analogues.[11] A driving

force for the studies of extracoordinate compounds arises from the widespread use of (catalytic) nucleophilic activation in the application of organosilicon compounds in organic synthesis[12].

The purpose of this chapter is to familiarize the readers with the chemistry of hypervalent silicon. Therefore the preparation, structural characteristics, and reactivity of hypervalent silicon compounds will be outlined below, stressing the utility of hydridosilicates with respect to their applications to organic synthesis. Then, the nucleophilic activation of silicon by imidazole to give extracoordinate silicon, a central theme of this thesis, will be described in further detail in later chapters.

3.3 Preparation of Pentacoordinate Silicon Compounds

Penataoordinate silicon compounds can be prepared according to the following general methods:

(1) By the addition of an anion to an organosilane or to a spirosilane to give an anionic pentacoordinate silicon complex.

(2) By inter- or intramolecular coordination of a neutral donor to silicon, giving a neutral silicon complex,

(3) By addition to an organosilane of a bidentate or multidentate ligand that may or may not be charged. For example, addition of triethanolamine to a trifunctional silane to give silatranes, or by tris-(2-amino-ethyl)amine to give triazasilatranes.

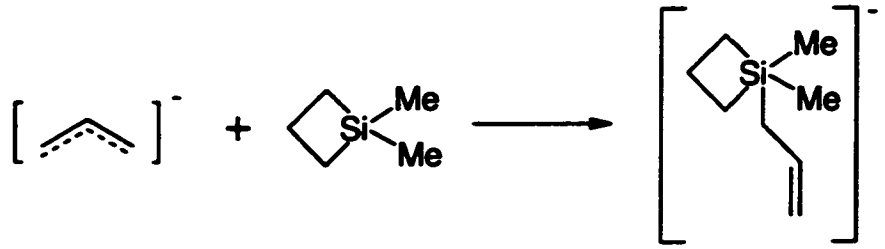
Specific examples of these methods of preparation are discussed in more detail below.

3.3.1 Coordination of Anions to Tetracoordinate Silicon Compounds

3.3.1.1 Fluoride Donation to an Organosilane

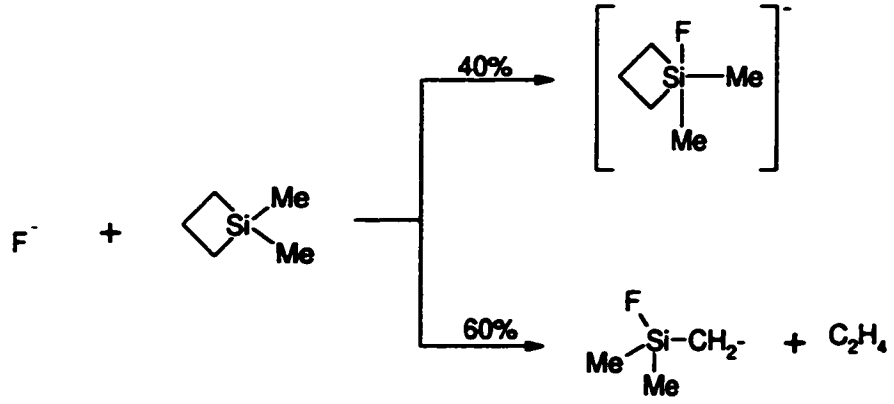
The fluorosilanes SiF_4, $RSiF_3$ (R = Me, Ph), and Ph_2SiF_2 react with tetraalkylammonium fluorides in a 1:1 ratio to yield stable ionic compounds.[13] NMR[13,14] and vibrational spectroscopic data[15] strongly suggest that anions in these compounds are pentacoordinate at silicon. Attempts to isolate trialkyl- and triaryl-substituted complexes by this method were not successful. In 1981, Damrauer *et al.* reported[16] that, in the gas phase, a large number of organic pentacoordinate silicon anions, including one with five carbon substituents, could be generated cleanly by the addition of anions to cyclic or acyclic silanes (**Scheme 3.2**).

Scheme 3. 2: Penta-organofunctional silicon species



The need to reinvestigate the dynamic behavior of pentacoordinate silicon species led Damrauer and Danahey[17] to prepare stable and nonhygroscopic pentacoordinate organofluorosilicates, so that subsequent NMR studies could be carried out without ambiguity.

Scheme 3. 3: Fluoride donation to dimethylsilacyclobutane



They found that the presence of 18-crown-6 ether greatly stabilizes potassium salts of pentacoordinate fluorosilicates [R_nSiF_{5-n}] (n= 1-3). Shortly after, this method was used to prepare other organotetra- and diorganotrifluorosilicates ([$RSiF_4$][18] and R_2SiF_3],[19] respectively) as their 18-crown-6 potassium salts and also the triaryldifluorosilicate ([$Ph_2(\alpha Np)SiF_2$]$^-$[$S(NMe_2)_3$]$^+$)[20].

3.3.1.2 Alkoxide Donation to an Organosilane

The use of potassium ion complexed by 18-crown-6 ethers as counterions to stabilize pentacoordinate anionic silicates, as developed by Damrauer and Danahey,[17] has been extended to the preparation of alkoxy- and aryloxysilicates. The phenylmethoxysilicates, **2** were isolated by Corriu[21] as white crystalline powders (**Scheme 3.6**). In analogous reactions, the salts of [$MeSi(OEt)_4$]$^-$ and [$PhSi(OCH_2CF_3)_4$]$^-$[22] were similarly isolated, the former arising from aryl-silicon bond cleavage (**Scheme 3.5**). In the case of the [$Si(OR)_5$]$^-$ series, the formation of pentacoordinate oxysilicates in solution was inferred from the upfield shift of the ^{29}Si NMR resonances.

Scheme 3. 4: Pentacoordinate silicon generated by methoxide donation

$$Ph_nSi(OMe)_{4-n} + MeO^-[K,18\text{-crown-6}]^+ \longrightarrow Ph_nSi(OMe)_{5-n}]^-[K, 18\text{-crown-6}]^+$$

(n = 1-3) **2**

Scheme 3. 5: Pentacoordinate silicon generated by ethoxide donation

$$MePhSi(OEt)_2 + EtO^-[K, 18\text{-crown-6}]^+ \longrightarrow [MeSi(OEt)_4]^-[K, 18\text{-crown-6}]^+$$

The direct reaction of alkoxy (or aryloxy) silanes with the corresponding potassium alkoxide (or aryloxide) afforded the anionic pentacoordinate hydridosilicates[23] $[HSi(OR)_4]^-$ in good yield, even in the absence of crown ether (**Scheme 3.6**).

Scheme 3. 6: General method for generation of pentacoordinate silicon via alkoxide donation

$$HSi(OR)_3 + ROK \xrightarrow[DMF]{THF\ or} [HSi(OR)_4]^-K^+$$

(R = Me, Et, n-Bu, i-Pr, Ph)

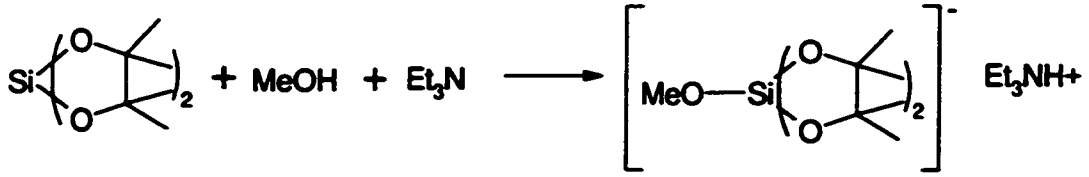
3.3.1.3 Coordination of an Anion to a Spirosilane

Few examples of the formation of pentacoordinate silicon derivatives from spirosilanes are presented in the literature. In 1961 Muller and Heinrich[24] presented evidence for the formation of the silicates **5** and **6** isolated from the reaction of the corresponding spirosilane with lithium and sodium methoxide, respectively. A decade later, Frye[25] found that simple amines were sufficiently basic to afford similar silicates.

Figure 3. 2: Spiro-pentacoordinate silanes

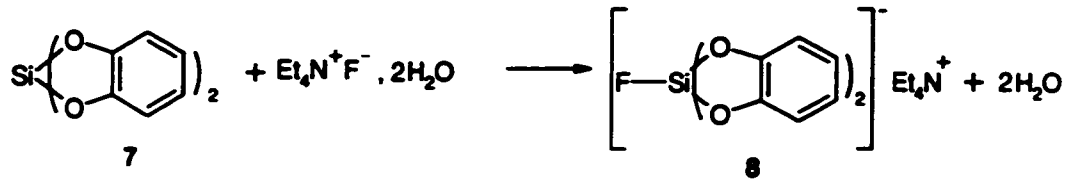
5 **6**

Scheme 3. 7: Synthesis of spiro-pentacoordinate silanes



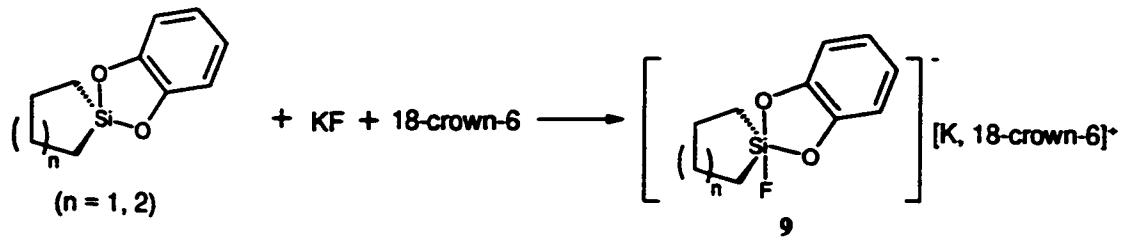
This method for preparation of pentacoordinate silicates has not been extensively developed[26] since only spirosilicates derived from sterically encumbered 1,2-diols can be prepared. Holmes *et al.*[27] synthesized tetraethylammonium bis(1,2-benzenediolato)-fluorosilicate, **8** by reaction of the corresponding spirosilane with $Et_4N^+F^-$ **(Scheme 3.8).** They have also reported the reaction of some spirosilanes with potassium fluoride in the presence of 18-crown-6 ether to give new pentacoordinate cyclic organofluorosilicates**(Scheme 3.9).**[28] While these catechol-derived compounds undergo extracoordination without difficulty, spirosilane **10** has an exceptional ability to coordinate a further ligand including organic, fluoride, hydride, and neutral donors **(Scheme 3.10).**[29]

Scheme 3. 8: Pentacoordinate bis-catechol fluorosilanes



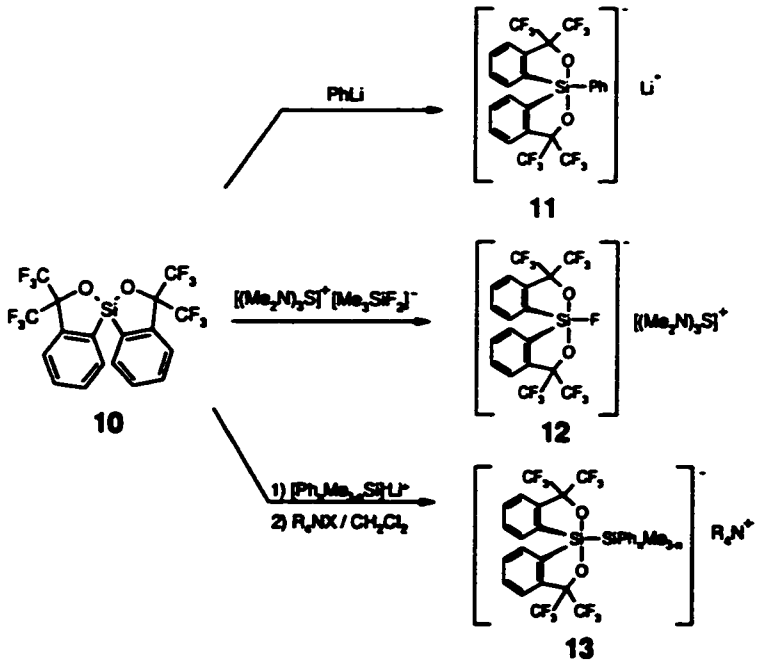
7 **8**

Scheme 3. 9: Pentacoordinate spiro silicon species of dialkyldialkoxy silane generated by fluoride donation



9

Scheme 3. 10: Pentacoordinate silane generated from bis-[α, α-bis(trifluoromethyl)-benzenemetananolato] ligand and nucleophile donor

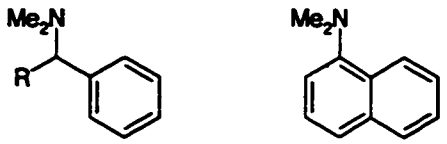


3.3.2 DONOR TO AN ORGANOSILANE

3.3.2.1 Intramolecular Donation to an Organosilane

A conceptually different way of achieving pentacoordination in silicon species is to prepare tetraorganosilicon compounds in which the silicon center may become pentacoordinate by intramolecular coordination. van Koten *et al.*[30] first used this concept, in their design of ligands **14**[30] and **15**[31].

Figure 3. 3: Intramolecular donors

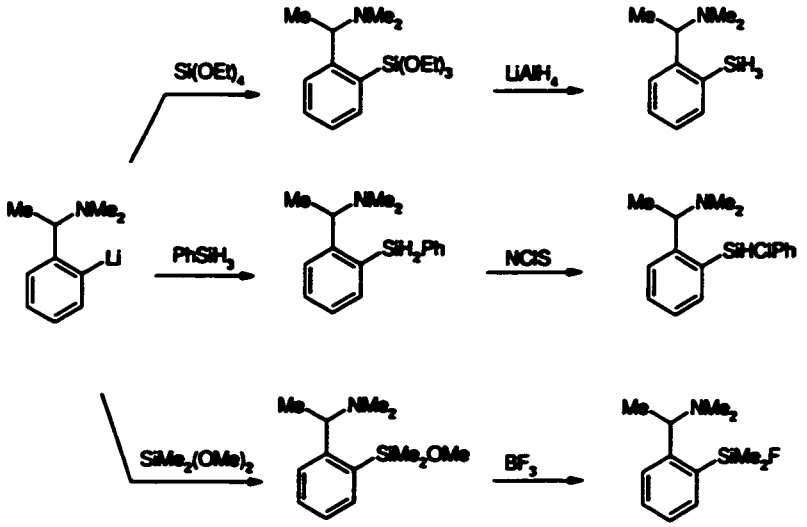


14
a : R = H
b : R = Me

15

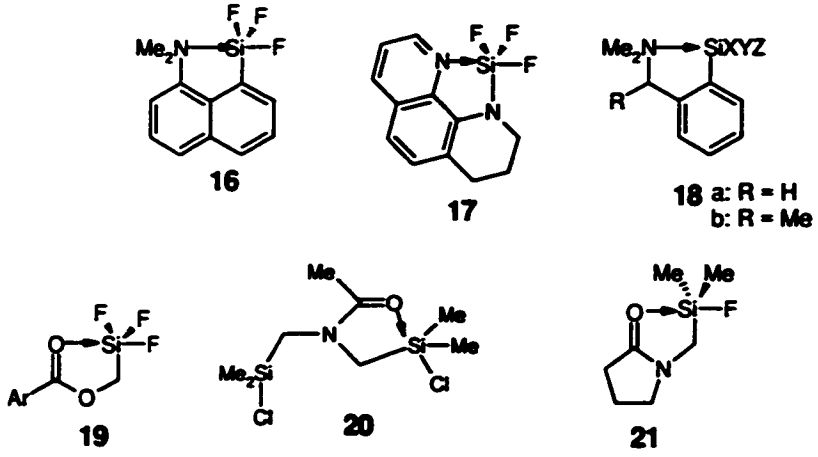
The preparation of silicon compounds containing such ligands is quite straightforward. The presence of the dimethylamino group facilitates the lithiation of these ligands in a single position (ortho lithiation from **14**, para-lithiation from **15**).[32] Further reaction of these lithio derivatives with a functional organosilane affords the corresponding organosilane (**Scheme 3.11**) containing the appropriate spatial arrangement needed for intramolecular coordination of the Me_2N group.[33]

Scheme 3. 11: Preparation of pentacoordinate silicon using intramolecular donors



The rigid geometry of structures **16**[34] and **17**[35] facilitates intramolecular extracoordination from the donor group. The donor group is always held in close proximity to the silicon center. Intramolecular coordination is also possible with ligands for which there exists a favorable conformation allowing interaction between the Si-center and the donor atom, as depicted in compounds **18**[36], **19**[37], **20**[38], **21**[39]. In these cases, the extent of extracoordination is dependent on the remaining substituents on the silicon atom. It may be inferred from crystallographic data (i.e., donor atom to silicon distance) or by solution phase silicon NMR data.

Figure 3. 4: Pentacoordinate silicon generated by intramolecular ligand donors



3.3.3 SUBSTITUTION IN A TRIFUNCTIONAL ORGANOSILANE

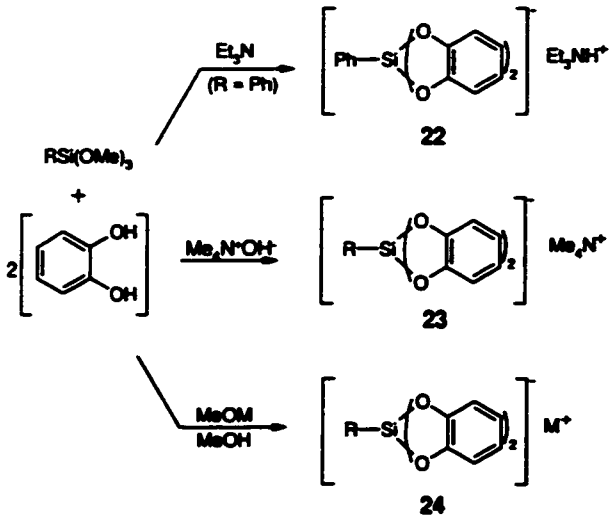
3.3.3.1 Substitution by Bidentate Ligand

Extracoordinate structures in which oxygen is directly bonded to silicon within a cyclic bidentate ligand have been known since Frye[40] found that $PhSi(OMe)_3$ reacts with catechol in the presence of triethylamine to give **22** quantitatively. Subsequently, Boer and coworkers[41] determined the structure of the tetramethylammonium salt, confirming the presence of a pentacoordinate silicon species. This reaction is quite general. It was shown that trialkoxysilanes $RSi(OMe)_3$, when placed in the presence of catechol and bases such as tetraalkylammonium hydroxide or sodium or potassium methoxide, formed pentacoordinate silicon species **23** and **24** (**Scheme 3.12**).[42]

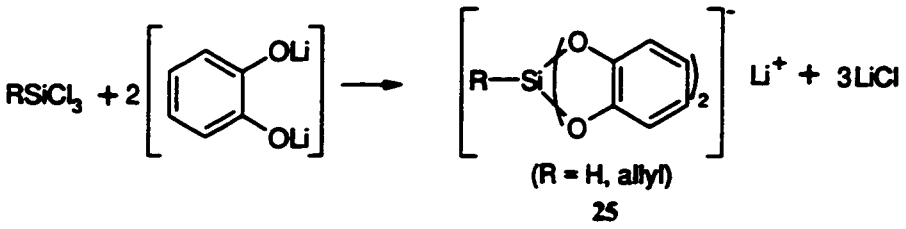
Related extracoordinate species have also been prepared from trichlorosilane and alkali metal catecholates (**Scheme 3.13**)[43]. These complexes were synthesized as their lithium salts, but could not be isolated. However, the potassium and

tetramethylammonium salts of the allylsilicate were prepared and isolated as crystalline solids.[44]

Scheme 3. 12: Catechol silanes



Scheme 3. 13: Allyl or hydrido bis(catechol) silanes

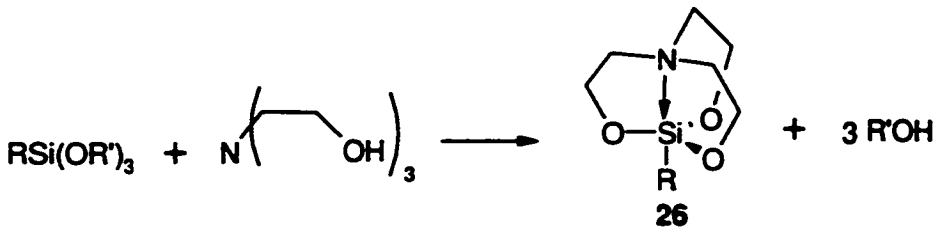


3.3.3.2 Substitution by Trialkanolamines

3.3.3.2.1 Preparation of Silatranes

Frye and coworkers[45] first reported the reaction of triethanolamine, and other trialkanolamines of suitable structure, with trifunctional silanes to yield monomeric silicon compounds **26** to which a pentacoordinate structure was assigned from physical and chemical evidence.

Scheme 3. 14: Preparation of silatranes



26

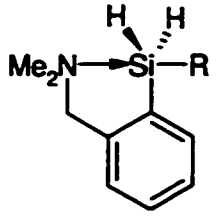
The structure was later confirmed by X-ray crystallographic analysis by Boer *et al.*[46] Subsequently, Frye and coworkers[47] described the preparation and chemistry of silatranes bearing halo, acyloxy, siloxy, and hydroxy substituents at the apical silicon site, which exhibited some unusual properties. Voronkov and coworkers,[48] since that time, have published numerous papers on the structure, method of preparation, and also chemical and biological properties of this class of compounds.[49]

3.4 Structure of Pentacoordinate Silicon Compounds

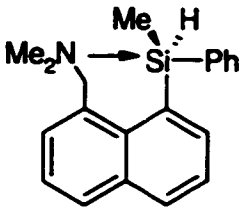
3.4.1 Structures of Pentacoordinate Hydridosilanes

Of particular relevance to this thesis is the occurrence of pentacoordinate silicon species which contain hydrogen functionality. The X-ray structures of **27**,[36] **28**,[50] and **29**[50], show a significant amount of Si-N bonding, the geometry around the silicon center being trigonal bipyramidal (TBP). The donor nitrogen atom is found in the axial position. Interestingly, and important for mechanistic considerations, the hydrogen atoms were found to occupy equatorial sites in all cases. The placement of hydrogen atoms in the equatorial site was also observed by Ebsworth *et al.* in compound **30**.[51]

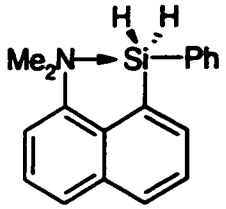
Figure 3. 5: Pentacoordinate Hydridosilanes



27 a: R = αNp
b: R = Ph

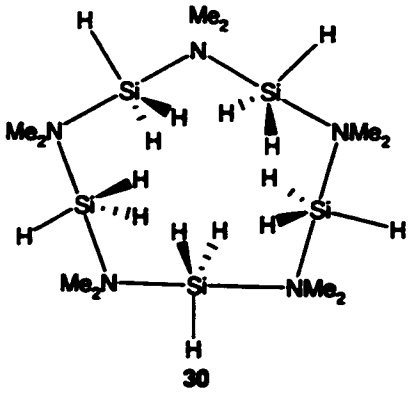


28



29

Figure 3. 6: Pentasilazane



30

As with many nucleophilic substitution at silicon, the entry of the donor atom is always axial irrespective of the nature of the substituents at silicon (halogen, oxygen, or hydrogen). This is supported by calculations[52] that show this geometry of attack to be preferred, even for the nucleophilic substitution process that occurs with retention of configuration at silicon atom centers.

It should also be noted that bonds from pentacoordinate silicon to other substituents are lengthened by comparison with the normal tetracoordinate distance. This is illustrated by the molecular structure of compound **20**[38] in which the $Si_{(1)}$-$Cl_{(1)}$ bond length (2.35 Å) is 15% longer than that of $Si_{(2)}$-$Cl_{(2)}$ bond at tetracoordinate silicon (2.05 Å).

3.5 Reactivity of Pentacoordinate Hydridosilicon Compounds

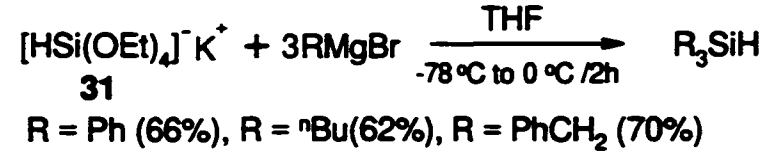
3.5.1 Pentacoordinate Alkoxyhydridosilicates

Pentacoordinate hydridosilicates have been postulated as reactive intermediates in the reduction of carbonyl compounds with hydrosilanes in the presence of fluoride or alkoxide ion.[53] The reactivity of isolated species $[HSi(OEt)_4]^-K^+$ and $[H_2Si(O^iPr)_3]^-K^+$ were studied in detail.[54,55,56] The reactions that can be performed with these reagents are much more varied than those that can be run with the analogous $HSi(OR)_3$, since they can behave as electrophilic reagents, basic reagents, reducing reagents, and SET reagents (see below).

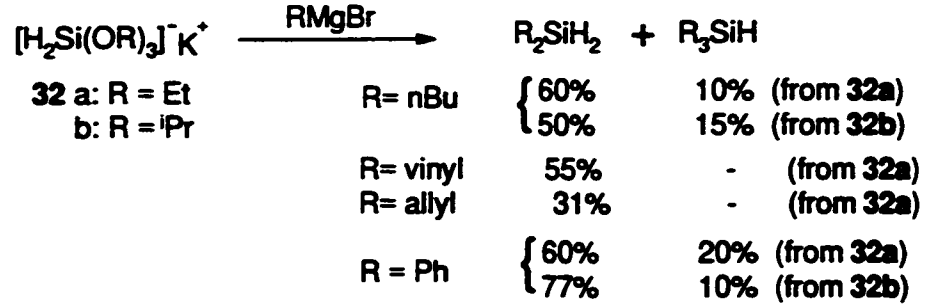
3.5.2 Reaction with Grignard Reagents

The electrophilic nature of the silicon atom in pentacoordinate hydridosilicates was demonstrated in the reactions of Grignard reagents. **31** reacted quite readily with a slight excess of Grignard reagent at low temperature to give trialkylsilanes R_3SiH.[55b] Similarly, dihydridosilicates **32a** and **32b** underwent nucleophilic displacement at silicon with Grignard reagents to give a mixture of diorganosilanes R_2SiH_2 and triorganosilanes R_3SiH.[55c,d] This reaction took place under mild conditions with **32a**, but higher temperatures were needed in the case of **32b**. Moreover, the formation of R_2SiH_2 provides good chemical evidence for the structure of **32a** that has not been isolated because of fast redistribution reactions[55d].

Scheme 3. 15: Reaction of pentacoordinate silicon with Grignard reagents



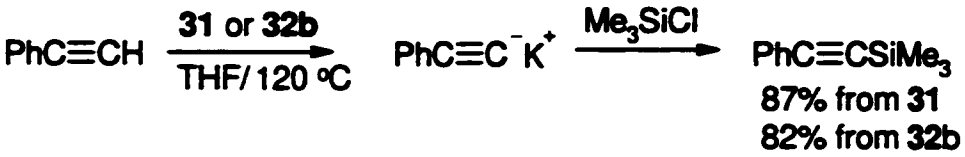
Scheme 3. 16: Reaction of Grignard reagents with pentacoordinate silicon II



3.5.3 Basic Reactions

31 and **32b** can sometimes exhibit properties of a base. Reaction with phenylacetylene in THF, for example, gave potassium acetylide that was trapped with Me_3SiCl.[55] In a similar way **31**, as shown by the recovery of Ph_3CCD in 35% yield after deuterolysis, effected the metalation of Ph_3CCH.[55]

Scheme 3. 17: Basic properties of pentacoordinate silicon

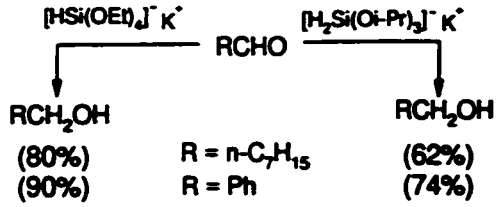


3.5.4 Reduction of Carbonyl Compounds

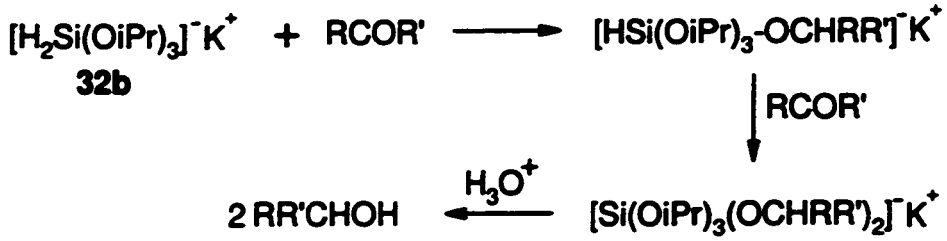
Hydridosilicates **31** and **32b** were found to reduce aldehydes and ketones in the absence of a catalyst and under very mild conditions.[55] Yields of primary and secondary alcohols were generally high. Lower yields were obtained in the case of $PhCOCH_3$ with both reducing agents because of partial enolization of the ketone. Note also that the

reduction of benzophenone gave only benzhydrol; no trace of the blue ketyl radical was detected and no benzopinacol was isolated. It is thus clear that the reduction proceeds by an ionic pathway. With dihydridosilicate **32b** both hydrogen atoms are utilized in the reduction of carbonyl compounds, probably in successive steps.

Scheme 3. 18: Reduction of ketones with pentacoordinate silanes



Scheme 3. 19: Reaction of dihydridosilicate with carbonyl compounds

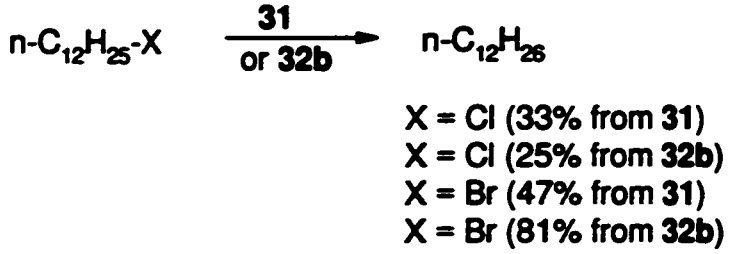


Species such as **31** also possess the ability to reduce esters to alcohols with good yields and amides to aldehydes.[12c] Under the same conditions, triethoxysilane and triisopropoxysilane were found to be completely unreactive. The high reactivity of these species strongly supports the involvement of pentacoordinate silicates as reactive species in the case of reduction of carbonyl compounds by $HSi(OEt)_3$ in the presence of alkoxide or fluoride ions.

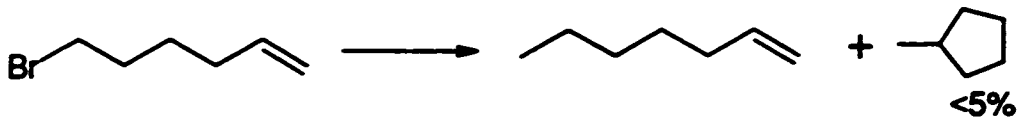
3.5.5 Reactions with Organic Halides

Pentacoordinate hydrosilanes **31** and **32b** are capable of reducing alkyl halides to the corresponding alkanes,[55] under the same conditions $HSi(OEt)_3$ is unreactive. In order to probe the mechanism of the reaction, the reduction of 6-bromo-1-hexene was conducted, and it was found that, in both cases, 1-hexene was the major product. Less than 5% of methyl cyclopentane was isolated. These results suggest that a hydride transfer process is operating in the reduction of primary alkyl halides, rather than a SET mechanism.

Scheme 3. 20: Nucleophilic substitution of alkylhalides with pentacoordinate silicon



Scheme 3. 21: Reaction of 43 with 6-bromo-1-hexene



3.5.6 Role of Pentacoordinate Intermediates in Hydrolysis Reactions of Organic Silicates

In the past two decades there has been an increase in the amount of interest shown in the sol-gel process.[57,58] The process provides a means for a practical route for the generation of advanced materials for structural, electrical, and optical applications. The key reaction in this process for developing silica particles involves the hydrolysis of an

organic silicate, usually $Si(OMe)_4$ or $Si(OEt)_4$. In basic conditions, two mechanisms have been proposed[59]. The first is an S_N2 reaction induced by HO^- (Scheme 3.22). The second involves a nucleophilic substitution reaction assisted by a nucleophile, with formation of an intermediate (or transitory) pentacoordinate silicon species (**Scheme 3.24**).

Scheme 3. 22: Proposed mechanisms of hydrolysis of alkoxysilanes

Hydrolysis

$$HO^- + (RO)_3SiOR \xrightarrow{slow} (RO_3)SiOH + RO^-$$

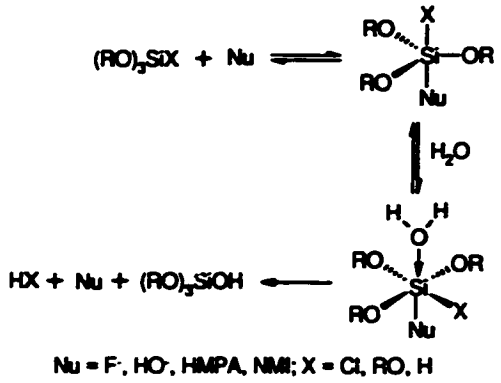
$$RO^- + H_2O \xrightarrow{fast} ROH + HO^-$$

Condensation

$$(RO)_3SiOH + HO^- \xrightarrow{fast} (RO)_3SiO^- + H_2O$$

$$(RO)_3SiO^- + (RO)_4Si \xrightarrow{slow} (RO)_3SiOSI(OR)_3 + RO^-$$

Scheme 3. 23 Proposed mechanisms of hydrolysis of alkoxysilanes II



In order to investigate the possible role of pentacoordinate anionic silicon species in the sol-gel process, the hydrolysis and gel times of the isolated pentaalkoxysilicates $[Si(OR)_5]^-$ [K, 18-crown-6]$^+$ (R = Me, Et, Ph) were studied[60] and compared to the hydrolysis and gel times of $Si(OR)_4$ and $Si(OR)_4$ / ROK (10%, R = Me, Et, Ph). The tetravalent silicon derivatives $(SiOR)_4$ (R = Me, Et, Ph) were found to hydrolyze with

difficulty under neutral conditions. However, when a catalytic amount of ROK was added, the rate of hydrolysis increased dramatically. Even more rapid hydrolysis was observed with silicates $[Si(OR)_5]^-$ [K, 18-crown-6]$^+$. The results of the study are summarized in **Table 3.1**.

It can be seen quite readily that these results cannot be interpreted as a base-catalyzed hydrolysis process. Indeed, if that were the case one would expect PhO^- to react more slowly than EtO^-, since the former is less basic. These results show the greater susceptibility of isolated pentacoordinate silicates to hydrolysis; which in turn suggests that RO^- acts as a coordinating nucleophile in these reactions. However, during the hydrolysis of $Si(OR)_4$ and $[Si(OR)_5]^-$[K, 18-crown-6]$^+$, it did not prove possible to isolate any intermediate. Therefore, no real proof of the proposed mechanism was obtained. In order to shed some light on the mechanism under operation here, the hydrolysis of $HSi(OR)_3$ (R = Me, Et, ^{n}Bu, *i*-Pr, Ph) in neutral and basic conditions was compared to that of the preformed pentacoordinate silicon derivatives $[HSi(OR)_4]^-K^+$. The presence of the SiH bond helps in following the course of the reaction by virtue of the prominent band in the IR spectrum and the possibility of observing hydrogen gas evolution during the reaction. The hydrolysis reactions were studied in dilute solutions in THF. The results of these studies are tabulated in **Table 3.1** and **Table 3.2**. The hydrolysis of the tetracoordinate $HSi(OR)_3$ (R = Me, Et, ^{n}*Bu*, *i*-Pr, Ph) is slow in neutral or acidic conditions. The IR spectra of the hydrolysis products showed that the Si-H bond was still present in all cases except for $HSi(OPh)_3$. This points to the fact that hydrolysis of Si-OR bonds occurs before hydrolysis of Si-H bonds. Moreover, the

hydrolysis of trialkoxysilane was increased upon addition of 10% of the corresponding potassium alkoxide (aryloxide).

Table 3. 1: Hydrolysis of $Si(OR)_4$ and $[Si(OR)_5]^-$ in THF at ambient temperature[61]

Entry	Silicate	Reaction time	Physical Appearance
1	$Si(OMe)_4$	5 days	Viscous liquid
2	$Si(OMe)_4$ + 10% MeOK	7 h	Liquid + solid
3	$[Si(OMe)_5]^-[K, 18\text{-crown-6}]^+$	<1 min	White precipitate
4	$Si(OEt)_4$	7 days	Liquid
5	$Si(OEt)_4$ + 10% EtOK	4 h	Liquid
6	$[Si(OEt)_5]^-[K, 18\text{-crown-6}]^+$	2-3 h	Early stage of gelation
7	$Si(OPh)_4$	5 days	Early stage of gelation
8	$Si(OPh)_4$ + 10% PhOK	40 min	White precipitate
9	$[Si(OPh)_5]^-[K, 18\text{-crown-6}]^+$	< 1 min	Gel

The hydrolysis of pentacoordinate hydridosilicates (**Table 3.1, Table 3.2**) was very fast except when the R group was isopropyl. The formation of a gel was always observed irrespective of the nature of the R group. In all cases of hydrolysis in basic solution, immediate evolution of hydrogen gas was found, and the IR of the gel indicated the absence of Si-H bonds in the products.

Table 3. 2: Hydrolysis of $HSi(OR)_3$ and $[HSi(OR)_4]^-K^+$ in THF at ambient temperature[61]

Entry	Silane	Reaction time	Physical properties	Si-H bond: $\nu(cm^{-1})$
1	$HSi(OMe)_3$	5 days	Liquid + gel	2254
2	$[HSi(OMe)_4]^-K^+$	< 1 min	Powder	No Si-H
3	$HSi(OEt)_3$	5 days	Viscous liquid	2252
4	$HSi(OEt)_3$ + EtOK (10%)	1 h	Gel	No Si-H
5	$[HSi(OEt)_4]^-K^+$	13 min	Gel	No Si-H
6	$HSi(O^nBu)_3$	5 days	Liquid	2245
7	$HSi(O^nBu)_3$ + ^{n}BuOK (10%)	15 h	Gel	No Si-H
8	$[HSi(O^nBu)_4]^-K^+$	2 h	Gel	No Si-H
9	$HSi(O^iPr)_3$	5 days	Liquid	2238
10	$HSi(O^iPr)_3$ + ^{i}PrOK (10%)	7 days	Viscous liquid	No Si-H
11	$[HSi(O^iPr)_4]^-K^+$	30 h	Gel	No Si-H
12	$HSi(OPh)_3$	7 days	Gel	2243 (very weak)
13	$HSi(OPh)_3$ + PhOK (10%)	20 min	Gel	No Si-H
14	$[HSi(OPh)_4]^-K^+$	3 min	Gel	No Si-H

Therefore, one can conclude that the hydrolysis reaction proceeds by a nucleophilic rather than base-catalyzed process. This point is illustrated by the fact that phenoxide is a weaker base than ethoxide, however hydrolysis occurs 6 times as fast with phenoxide as compared to ethoxide. The nucleophilic displacement takes place on a pentacoordinate silicon species and results in the formation of a hexacoordinate intermediate (or transition state) by coordination of a molecule of water.

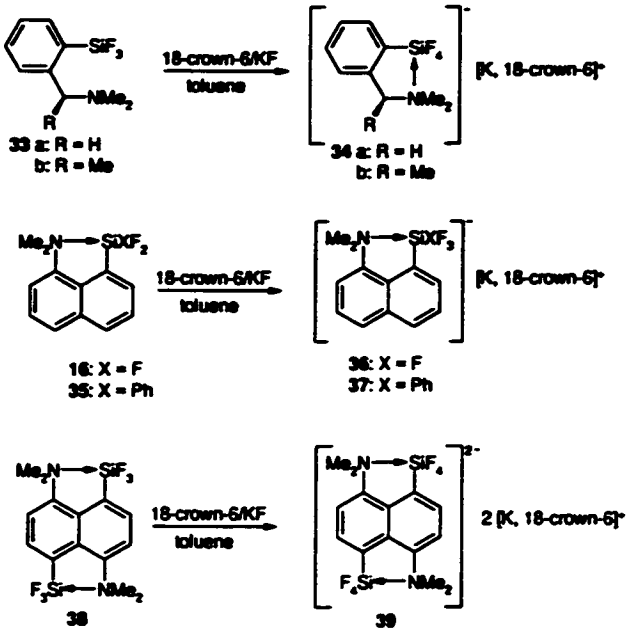
3.6 Aptitude of Pentacoordinate Silicon Compounds To Become Hexacoordinate: Structure-Reactivity Relationships

Pentacoordinate anionic and neutral silicon species have been shown to be able to undergo facile nucleophilic substitution at silicon by strong nucleophiles.[12c] Hexacoordinate silicon species have been frequently reported as intermediates or

transition states in these reactions.[12,62] In order to obtain information about the involvement of these species in the reactivity of pentacoordinate silicon compounds, a range of pentacoordinate models have been prepared in which hexacoordination may be achieved by intramolecular donation.

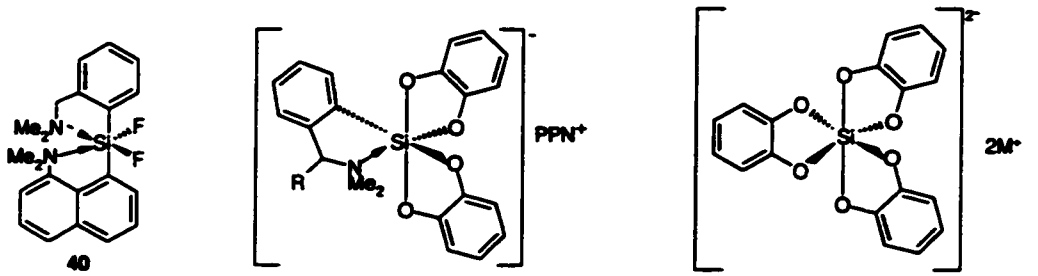
Hexacoordinate fluorosilicates, **34a, 34b, 36, 37** and **39**, were synthesized in high yields from the corresponding pentacoordinate fluorosilanes by reaction with 1 equivalent of 18-crown-6/ KF[63] (**Scheme 3.24**). Interestingly, **16** reacts with KF, even in the absence of crown ether, to give a stable salt with spectroscopic characteristics identical to those of the crown salt. It was also observed that whereas F^- coordination takes place with pentacoordinate di- and trifluorosilanes to give the corresponding hexacoordinate silicates, the pentacoordinate monofluorosilicates do not react.

Scheme 3. 24: Hexacoordinate silicon species



The hexacoordinate nature of these compounds was determined unambiguously by ^{29}Si and ^{19}F NMR data.[63] The X-ray crystal structure was obtained for **36**. The complex was found to exhibit a slightly distorted octahedral geometry in which the four Si-F bonds are approximately the same length (1.65- 1.68 Å), the shortest being the Si-F bond opposite the Si-N coordinate bond. The Si-N bond length in **36** (2.21 Å) is short compared to the values reported for the neutral hexacoordinate difluorosilane **40** (2.59-2.81 Å):[64] The bond is even shorter than the neutral pentacoordinate starting material **16** (2.31 Å).

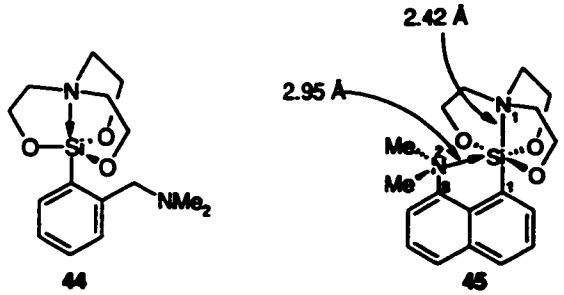
Figure 3. 7: Hexacoordinate silicon species II



The crystal structure of bis-(1,2-benzene-diolato)silicate **41** was determined.[63] The structure shows that the anion adopts an octahedral geometry very similar to that of **36**. **41** thus more closely resembles a hexacoordinate species than a pentacoordinate one, since the lengths of the six Si-O bonds in the anionic hexacoordinate silicon complex **43d**[65] are very close to those in **41** (between 1.765 and 1.813 Å, average of 1.784 Å). The short Si-N distance of 2.15 Å illustrates the electrophilic character of hexacoordinate silicon species.

To obtain additional information about the ability of pentacoordinate silicon species to become hexacoordinated, the structures of other pentacoordinate silicon species have been examined. The molecular structures of **44** and **45**, which might also become hexacoordinated by intramolecular coordination, have been determined[66].

Figure 3. 8: Hexacoordinate silatrane species

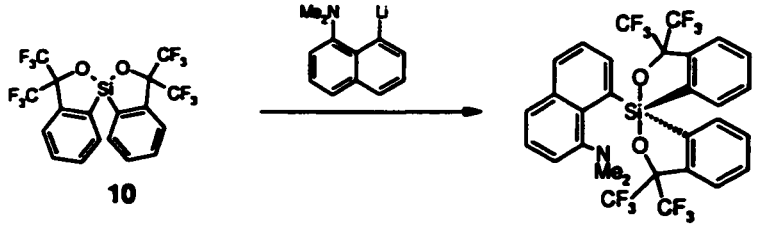


The X-ray structure analysis of **44** has shown that the nitrogen atom is not coordinated to the silicon atom. In contrast, the structure of silatrane **45** is not so clear-cut. In solution, the ^{1}H-NMR spectrum exhibits a sharp singlet for the NMe_2 protons. The ^{29}Si chemical shift in solution appears at δ = -70.76 ppm, downfield from that of 1-naphthylsilatrane (δ = -80.49 ppm). These results indicate that the silicon atom remains pentacoordinated in solution. By contrast, the X-ray crystal structure analysis reveals a hexacoordinate silicon center for **45**. The length of the Si-N(2) bond (2.95 Å) indicates a weak interaction between the silicon and nitrogen atoms, imposed by the rigid geometry of the 8-(dimethylamino)-1-napthyl group. These results indicate the difficulty that silatranes have in becoming hexacoordinate, presumably because the rigidity of the silatrane cage is not conducive to hexacoordination.

Compound **46** was prepared by the reaction of the corresponding lithio derivative with spirosilane **10**. The solution ^{29}Si NMR shift of 58 (δ = - 74.3 ppm) corresponds to a

pentacoordinate silicon atom. The absence of observed diastereotopism in the ^1H NMR spectrum of the NMe_2 group indicates the lack of coordination of this group to the silicon atom. It is significant to note that, whereas silane **10** readily coordinates a further ligand easily to provide pentacoordinate complexes, no case is known where **10** forms hexacoordinated compound by the addition of nucleophiles.

Scheme 3. 25: Synthesis of hexacoordinate silicon Specie 46



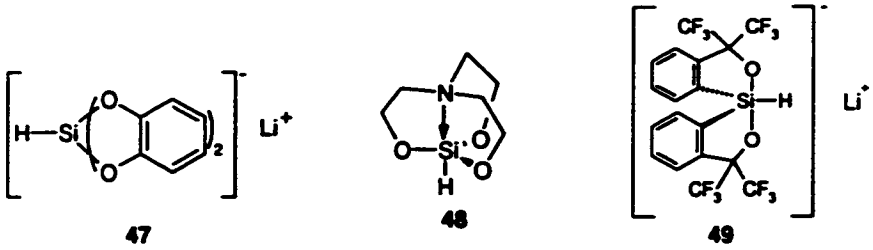
10 **46**

A parallel exists between the aptitude of pentacoordinate species to become hexacoordinated and the reactivity of these species. For example, there is a dramatic difference in the reactivity between the pentacoordinate hydridosilanes **47**, **48**, and **49** toward carbonyl compounds. Bis(1,2-benzenediolato)hydridosilicate **47** reduces aldehydes and ketones easily in the absence of any catalyst. Hydrosilatrane reduces carbonyl compounds,[67] but the reaction conditions are more severe, requiring heating (35 °C to 140 °C) and long reaction times (22-44 h). The pure lithium salt of **49**, as well as the corresponding tetrabutylammonium salt, have been found to reduce aldehydes only slowly.

The reactivity of **47** towards carbonyl compounds can be rationalized by the formation of a hexacoordinate intermediate via coordination of the oxygen of the carbonyl to the silicon, facilitating the transfer of hydride anion to the carbonyl carbon. This hypothesis is supported by the ready hexacoordination of compound **41**. In contrast,

the formation of a hexacoordinate intermediate by coordination of the oxygen of the carbonyl group to the silicon atom in **48** and **49** is much less likely, as the structural study of silatranes **44** and **45** and NMR study of **47** has shown.

Figure 3. 9: Pentacoordinate Hydridosilanes



47 **48** **49**

3.7 CONCLUSION

It is generally accepted today that most nucleophilic substitution reactions at silicon occur through a pentacoordinate intermediate (or transition state). These species are far more reactive than their tetracoordinate partners. It is for this reason that controlled substitution at a trisubstituted silicon (e.g. trichloromethylsilane) is quite difficult.[68] In these pentacoordinate species, there is a TBP arrangement of ligands around silicon, the silicon-ligand bond length is increased from its tetracoordinate parent, the silicon atom center becomes more electrophilic, and the ligands take on a more nucleophilic character. The unique reactivity displayed by these species has fostered great interest in their study as outlined above. This thesis builds on the existing understanding of the utility of imidazole in the generation of these pentacoordinate species. In particular, pentacoordinate hydridosilanes are prepared *in situ* from lithium imidazolides, which are used in the subsequent reduction of carbonyl species. Chiral imidazole ligands are developed that confer enantioselection to these reductions.

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Chapter 4

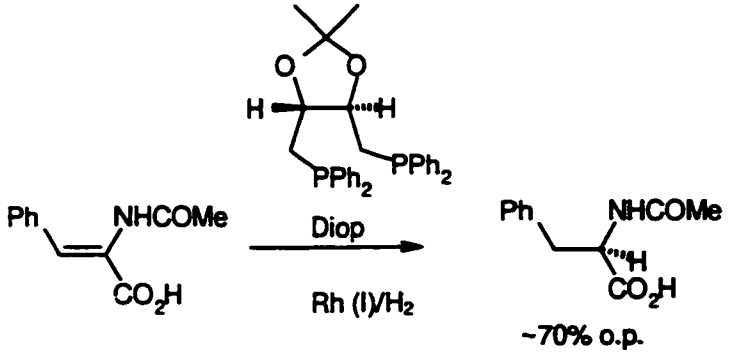
C_2-Symmetric Auxiliaries in Organic Synthesis

4.1 INTRODUCTION

The development of asymmetric catalysts has led many workers to consider the C_2-architecture as a beneficial structural motif for chiral induction. The presence of a C_2-symmetry axis within the chiral auxiliary can serve the very important function of dramatically reducing the number of possible competing transition states.[1] In other words, a reagent experiences the same chiral environment, independent of its trajectory of approach.[2]

The introduction of a C_2-chiral auxiliary can be traced back to Kagan,[2,3] who introduced the Diop ligand (Scheme 4.1).

Scheme 4. 1: Catalytic stereoselective reduction using DIOP

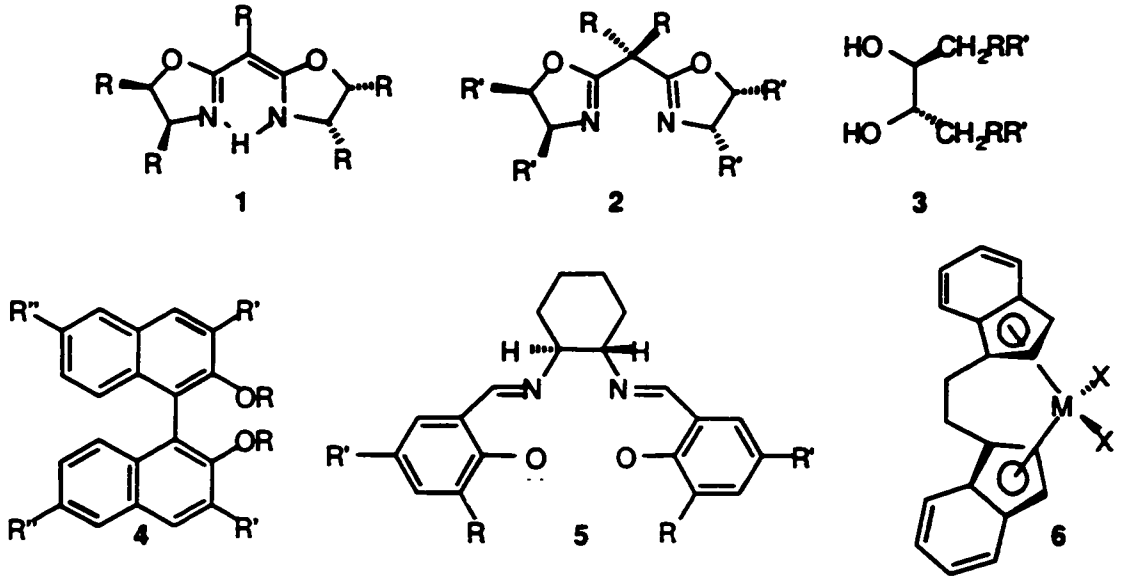


In the years that followed, a large number of ligands have been constructed with this symmetry axis (see Appendix to Chapter 4). We have constructed and describe in the following chapters, C_2-symmetric ligands containing the imidazole moiety. The utilization of this symmetry element in ligand design warrants a brief discussion of its application in asymmetric transformations. More particularly, and relevant to this thesis, the utility of these ligands in hydrosilylation/reduction of ketones will be discussed.

4.2 STRUCTURAL MOTIFS BEARING A C_2-SYMMETRY AXIS

There are five general structural motifs, bearing the C_2-symmetry axis, which have been widely adopted by workers for a number of different organic transformations (**Figure 4.1**). Each of these motifs has been employed in a wide variety of synthetic methods. In all cases, the ligand design, the choice of metal species, and also the substrate are key to obtaining maximal enantioselection.

Figure 4. 1: C_2-Symmetric ligands



4.2.1 C_2-Symmetric Semi-Corrins (1) and Bisoxazoline complexes (2) and Relatives

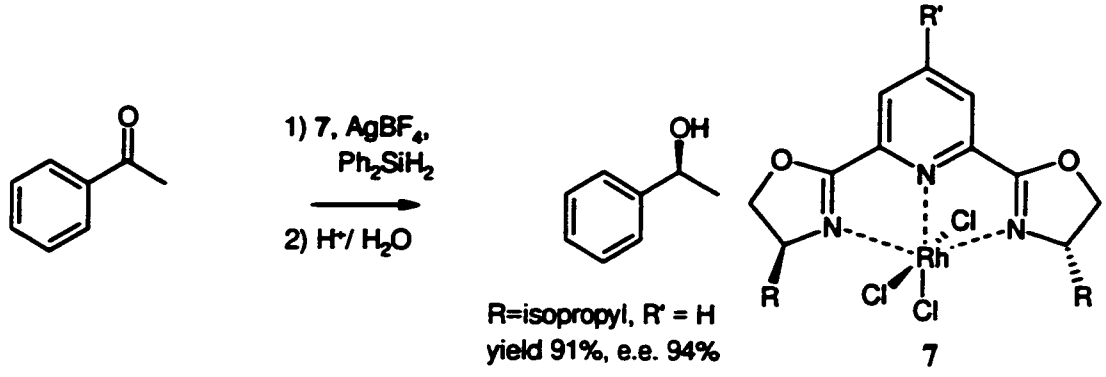
Pfaltz *et al.*[4] first reported the synthesis and utility of semicorrin ligands such as **1**. These species are a class of bidentate nitrogen ligands, inspired by the structures of corrinoid and porphinoid metal complexes, which in nature play a fundamental role as biocatalysts. Semicorrins were originally prepared as intermediates in the synthesis of corrinoid and hydroporphinoid compounds.[5,6] The semicorrins **1** possess a number of structural features that make them ideally suited as ligands for the stereocontrol of metal-catalyzed reactions. First, the geometry of the vinylogous amidine system is ideal for coordinating a metal ion. Accordingly, semicorrins form a variety of metal complexes with metal ions such as Co(II), Rh(I), Ni(II), Pd(II) or Cu(II).[7,8] Depending on the metal ion, the ligand structure, and the reaction conditions, either mono- or bis (semicorrinato) complexes are obtained. These metal systems have provided asymmetric environments from which a variety of stereoselective reactions have been carried out with good efficiency and excellent facial selectivity (See Appendix to Chapter 4, **Table A4.1**, Entry 1A).

A major drawback of the semicorrin architecture is that the preparation of the ligands involves a multi-step synthesis[4b] and only one enantiomer is generally available.[9] This has led to construction of structural analogues of semicorrins, bisoxazolines **2**. The development of these ligands has allowed for flexibility in ligand design, convenient synthesis and availability of ligands in both enantiomeric forms. Thus, a great range of structurally diverse bis(oxazoline) ligands have been introduced (Table A4.1, **Entries 1B-1C**). In general, bis(oxazoline) ligands (**1B-1C**) with a one-carbon spacer between

the oxazoline rings are most frequently utilized. These ligands form six-membered metal chelates and the substituents on the ring are close to the metal center. These ligands have been successfully applied in catalytic asymmetric carbon-carbon bond formation reactions such as the aziridination of olefins and imines, Diels-Alder reactions, hetero-Diels-Alder reactions, Mukaiyama aldol reactions and nucleophilic addition reactions to aldehydes with good to excellent enantioselectivity. For a given asymmetric process, both the choice of the substituents on the ligand and the metal are critical to optimum enantioselectivity.

The Rh(III) complex 7 (**Scheme 4.2**), after treatment with $AgBF_4$, proved to be efficient for the enantioselective hydrosilylation of ketones[10]. Bolm and coworkers have described a series of related oxazoline metal complexes.[11]

Scheme 4. 2: Hydrosilylation of ketones using rhodium complex of 2,6-bis(oxazolinyl)pyridine

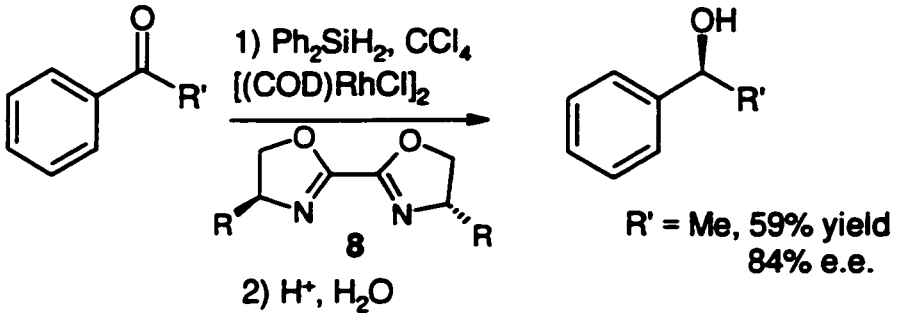


A number of substrate ketones were reduced with enantioselection ranging from 27-96% depending on the steric bulk around the ketone. Predictably, the bulkier the ketone the higher the enantiomeric excess. The ability to tune the electronics of the system, and thus affect the selectivity, was studied by varying R'. This work demonstrated that as the

electronics of the system changes the reaction conditions must also change to optimized the e.e. It was observed that electron donating groups at R', increased the e.e.'s of the resulting alcohol.

Helmchen *et al.*[12] prepared a series of differently substituted bioxazolines and analogous bithiazolines, which they employed in the rhodium-catalyzed enantioselective hydrosilylation of acetophenone (Scheme 4.5).

Scheme 4. 3: Hydrosilation of ketones using rhodium catalyst 8

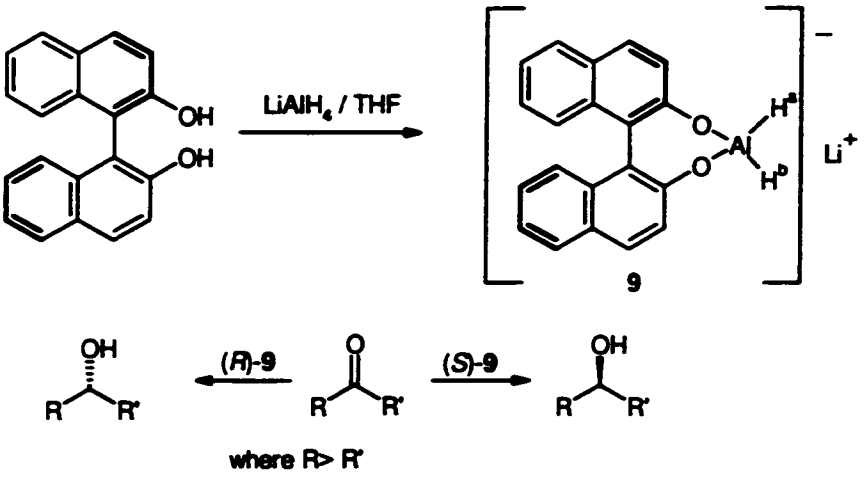


As in previous studies, it was noted that both the choice of substituent on the ligand and the structure of the substrate itself played critical roles in determining the enantioselection. Although screening of various Rh-, Ru-, and Ir- bis(oxazoline) complexes did not reveal any apparent affinity toward molecular hydrogen, it was found that the (bisoxazoline)iridium(I) complexes, prepared *in situ* from [Ir(COD)Cl]$_2$ and **8**, catalyzed the reduction of ketones using 2-propanol as a hydride donor. The best selectivity was observed in the reduction of isopropyl phenyl ketone using **8** (R' = isopropyl, 91% e.e. at 70% conversion, 88% e.e. at 93% conversion).[13]

4.2.2 Binaphthylic C_2-Symmetric Derivatives

The synthesis of binapthyl system **4** was first reported by Pummerer *et al.*[14] Subsequent workers have described similar syntheses[15] and resolutions[16] of these complexes. The drawback to these systems has been the subsequent need to resolve the species into the respective enantiomers (some of these are now commercially available). The best synthesis to date directly affords optically active **4** (where R=R'=R''=H) in e.e.s of 96%.[17] Moreover, the structural diversity in this ligand system is less rich than that of the oxazoline architecture (**Table A4.2**). However, ligands with this general architecture have been utilized in a number of asymmetric transformations (**Table A4.2**), including reductions, Diels-Alder and hetero-Diels-Alder reactions, hydrogenations, nucleophilic addition to aldehydes, isomerizations, and polymerizations with good to excellent enantioselectivity. In a particular case of relevance the reaction of optically pure [1,1'-binaphthyl]-2,2'-diol with $LiAlH_4$ (LAH) in a ratio of 1:1 (**Scheme 4. 4**) provides an adduct in which the two atoms H_a and H_b are homotopic. Therefore the successive reaction with an achiral ketone gives rise to the same reducing species in the solution of BINAL-H.

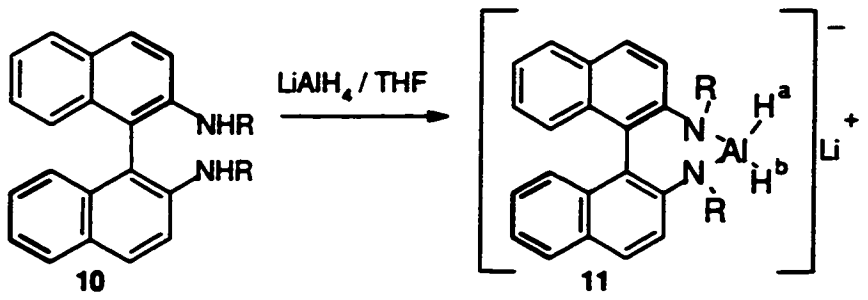
Scheme 4. 4: Reduction of ketones by BINAL-H



When such a reagent is employed in the enantioselective reduction of alkyl aryl ketones, the corresponding secondary alcohols are obtained in e.e.s of up to 100%.[18,19] It is worth noting that the reduction reaction with (*R*)-BINAL produced (*R*)-enriched alcohols, whilst the reaction with (*S*)-BINAL produced the (*S*) enantiomer.

Hashimoto *et al.*[20] have reported the use of a catalytic system derived from the treatment of pure diamine **10** with equimolar amounts of LAH in THF solution. They proposed structure **11** as the catalytically active species. Reduction of alkyl phenyl ketones produced non-uniform results.

Scheme 4. 5: Proposed Homogeneous complex for asymmetric reduction

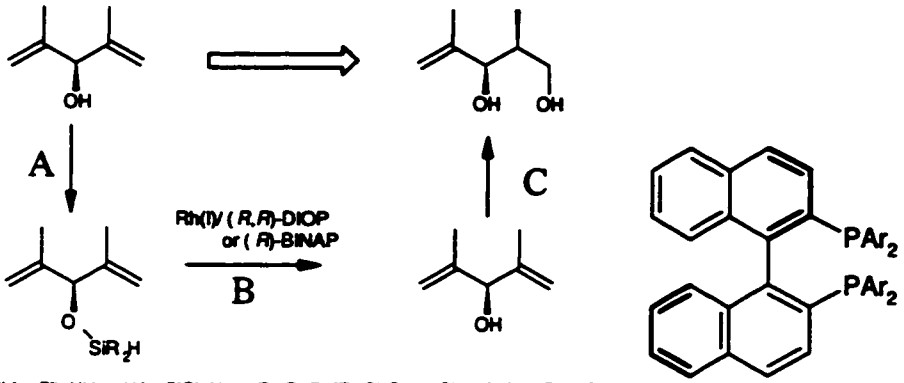


R = H, Me, Et, *i*-Bu, Bn

For example (*R*)-**11a** (R=H) gives secondary alcohols with an *R* absolute configuration, whereas (*R*)-**11b-e** (i.e. Me, Et, i-Bu, Bn repectively) gives *S*-alcohols. The highest e.e. (82%) was obtained with *R*-**11c** (R = Et); when the steric bulk of the alkyl group in the chiral amine ligand becomes smaller or larger than that of an ethyl group, the selectivity drops. Finally, the degree of asymmetric induction also depends on the steric bulk of the alkyl group in alkyl phenyl ketone; the best result was obtained with isopropyl phenyl ketone.

The intramolecular hydrosilylation of alkenes by dialkyl or diaryl- hydridosilane-protected homoallylalcohols, [i.e. $R_2HSiOCH_2CH_2CH{=}CH_2$] was reported by Tamao *et al.*[29] (**Scheme 4.6**) to give β-diols. For the HMe_2Si derivative, the use of (*R*)-BINAP as ligand displayed higher enantiomeric purity than (*R,R*)-DIOP. In contrast, for the HPh_2Si derivative, (*R,R*)-DIOP was a better ligand than (*R*)-BINAP.

Scheme 4. 6: Hydrosilylation of ketones catalyzed by 1 and 11



A: $(HMe_2Si)_2NH$ or HAr_2SiCl, NH_3, Et_2O. B: $[RhCl(CH_2{=}CH_2)_2]_2$/2(*R,R*)-DIOP or (*R*)-BINAP (2 mol%), $ClCH_2CH_2Cl$. C: 30% H_2O_2, KF, $KHCO_3$, MeOH, THF.

BINAP

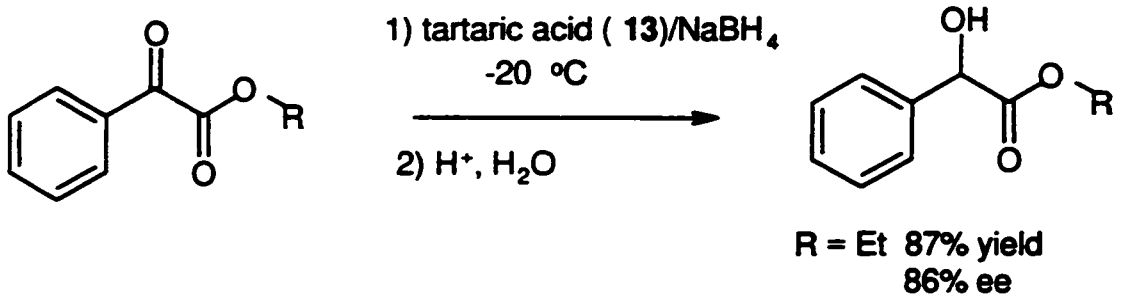
4.2.3 C_2-SYMMETRIC TADDOL DERIVATIVES

Another C_2-symmetric ligand that has gained popularity in asymmetric transformations is the α,α,α',α'-tetraaryl-1,1,3-dioxolan-4,5-dimethanol (TADDOL) 3 and derivatives. They are prepared from commercially available tartrate ester acetals and Grignard reagents.[21] Depending on the aldehyde or ketone from which the tartrate acetal precursors are formed, the molecules have C_2 or C_1 symmetry. Most TADDOL's have the tendency to form clathrates with various guest molecules, for example, CCl_4[22] and other solvents,[22b,23] carbonyl compounds,[24] alcohols,[25] and amines.[26] This property must be kept in mind not only when preparing and purifying them, but also when isolating products from TADDOL-mediated reactions.[21a] TADDOLs have proven to be useful in stoichiometric and catalytic enantioselective reactions, such as the reductions of ketones,[27] epoxidation, oxidation, nucleophilic addition to aldehydes, Wittig reaction, hydrogenations, Diels-Alder cycloadditions, hetero Diels-Alder reactions, ene reactions, hydrosilylations,[28, 29] and hydroborations.

Yatagai *et al.* have reported[27] that tartaric acid (13) reduces α-keto esters enantioselectively in the presence of $NaBH_4$. This system displayed poor reactivity toward simple ketones: upon exposure of the above system to acetophenone at room temperature for 120 h, only 28% yield and 0.2% ee was noted. However, the introduction of a functional group on the α-carbon of acetophenone raised the enantiomeric excess in the reduction of those substrates in the order of Cl<OH<OMe. In the case of α-methoxyacetophenone the optical yield was raised to 84% e.e. from 2%. These effects of the functional groups suggest that their affinities to a sodium or boron

atom enable the ketone to chelate to the reductant, and to facilitate the hydride-transfer and enantiotopic face selection by chirally modified $NaBH_4$.

Scheme 4. 7: Reduction of Ketones Catalyzed by Sodium Borohydride/Tartaric Acid System



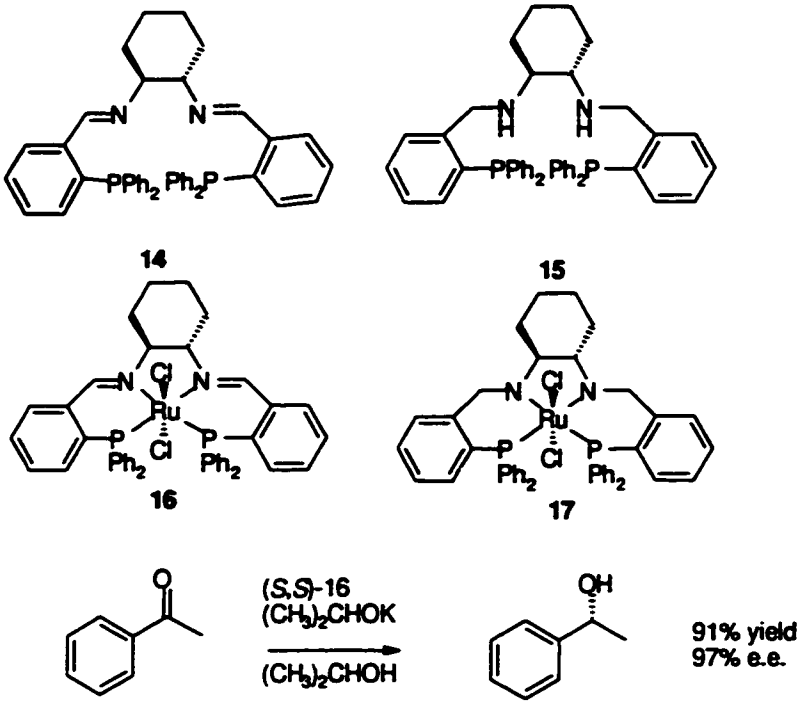
4.2.4 C_2-Symmetric Jacobsen's Salen Derivatives

In the realm of tetradentate ligands, the classic C_2-symmetric example is the salen complex of type **5**, which serves as a workhorse in inorganic chemistry and forms complexes with most *d*-block elements. Many contributions, especially those related to the Mn(III) complexes of these species, have arisen through the elegant work of Jacobsen and coworkers.[30,31] The successful application of chiral transition metal-based salen complexes in asymmetric epoxidation, aziridination and epoxide opening clearly demonstrate the exceptional ability of these chiral organic ligands when bound to the appropriate metal center. These complexes are synthesized by condensation of either optically pure 1,2-diaminocyclohexane or 1,2-diamino-1,2-diphenylethane and substituted salicylaldehyde derivatives. As a result of the simple synthetic sequences that lead to these compounds, the tuning of the metal species bound within the center of this

ligand can be easily achieved by choice of the appropriate derivatives of the salicylaldehyde precursor.[32]

Modification of this general structure by Noyori *et al.* [33] has provided N_2P_2 (**14**) and $P_2(NH)_2$ (**15**) ligands which have two soft phosphorus atoms and two hard nitrogen atoms.[34] The Ru (II) complexes **16** and **17** catalyzed hydrogen transfer processes. The (*S,S*) enantiomer produced *R* alcohol. In these cases, it appears that electron-donating groups placed on the substrate ketone reduce the enantioselection of the reaction.

Scheme 4. 8: Hydrogen transfer catalyzed by 15 and 16



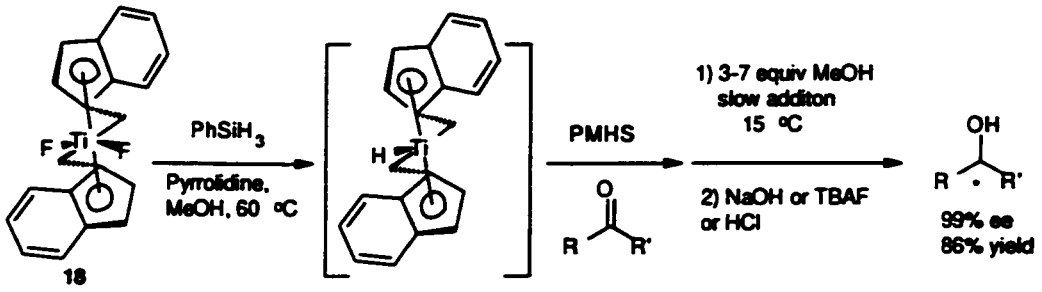
4.2.5 C_2-Symmetric Metallocene (Ansa-Metallocene)Derivatives

Chiral *ansa*-metallocenes have proved to be useful for a number of catalyzed enantioselective reactions. Many contributions, especially with regard to structure-

property relations for metallocene-catalyzed olefin polymerizations, have arisen from the work of Rausch and coworkers.[35] Rausch developed a stereoselective synthesis for racemic, C_2-symmetric *ansa*-metallocenes, which avoids the formation of the achiral *meso*-isomer. A major drawback of these catalytic species is their sensitivity to air and moisture.

Buchwald and Yun[36] have reported the asymmetric hydrosilylation of ketones utilizing bridged titanocene complex **17**. They found that the addition of primary amines and alcohols increased the efficiency with which the hydrosilylation occurred.

Scheme 4. 9: Hydrosilylation of ketones catalyzed by a titanocene catalyst



Moreover, it was noted that the use of different alcohol additives did not affect the enantioselectivity of the process. This was in contrast to the imine hydrosilylation, for which different amine additives produced secondary amine products with varying levels of enantiomeric excess.[37] It was also noted that sterically demanding ketones produced product alcohols in greater enantiomeric excess.

4.3 CONCLUSIONS

The presence of a C_2-symmetric axis in a chiral auxiliary or in catalyst design has been demonstrated to be quite successful in conferring facial selectivity to reactions. We have

focussed here on the hydrosilylation and reduction processes utilizing C_2-symmetry in catalyst design. As one will notice from the discussion, many factors are involved in development of a catalytic system that provides high enantioselection. It is in this light, that the lessons of nature can be used in order to fashion systems that can be utilized for a particular situation.

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Appendix to Chapter 4

C_2 Symmetric Catalyst in Organic Synthesis

A4.1 C_2-SYMMETRIC SEMI-CORRINS AND BISOXAZOLINE COMPLEXES

Pfaltz *et al.*[1] have reported the synthesis of C_2-symmetric semicorrins (**1A**), a class of bidentate nitrogen ligands derived from pyroglutamic acids. Semicorrins form stable chelate complexes with a variety of metal ions such as Co(II), Rh(I), Ni(II), Pd(II) or Cu(II). The use of copper semicorrinato complexes allowed efficient control of the enantioselective cyclopropanation of olefins with diazo compounds, where the highest e.e.s were obtained with bulky R groups (Table A4.1).

Cobalt semicorrin complexes were found to catalyze the reduction of electrophilic double bonds using sodium borohydride as reducing agent. In the presence of 0.1-1 mol % catalyst, formed *in situ* from $CoCl_2$ and semicorrin ligand, α,β-unsaturated carboxylic esters were reduced to the corresponding saturated esters in high yield and excellent enantioselectivity (**Table A4.1**, Entry 1A). Semicorrins give the best enantioselectivity for Cu (97% e.e.) and Co (99% e.e.)-mediated reactions.

In recent years, there has been an intense investigation into the use of bis(oxazoline) based chiral auxiliary ligands, which are structural analogs of semicorrins. The development of routes to these ligands allowed for flexibility in ligand design, convenient synthesis and availability of ligands in both enantiomeric forms. Thus, a great deal of structural diversity has been introduced to bis(oxazoline) ligands (**Table A4.1**).

Bis(oxazoline) ligands (**1B-1C**) with a one-carbon spacer between the oxazoline rings are most frequently utilized. These ligands form six-membered metal chelate rings and the substituents on the ring are close to the metal centre. These ligands have been successfully used as catalysts in asymmetric allylic substitutions,[2] allylic oxidations,[3,4] aziridination of olefins,[5] and imines,[6] cyclopropanations,[7,8,9,10,11] glyoxylate-ene reactions,[12] Michael addition reactions,[13] Diels-Alder reactions[14,15,16,17,18,19,20] hetero Diels-Alder reactions,[21,22,23] free radical additions[24,25], Mukaiyama aldol reactions,[26,27] nucleophilic addition reactions to aldehydes,[28,29] and imines,[30] reduction of ketones,[31] reduction of α, β-unsaturated amides[32] and esters, and aldol reactions[26,33]. In all of the asymmetric processes, both the choices of substituents on the ligand and the metal are critical to optimum enantioselection. Ligand **1D** forms five-membered chelate structures and was synthesized for hydrosilylation[34] and hydrogenation reactions[35].

Ligand **1E** was introduced by Masamune and co-workers and was utilized for asymmetric cyclopropanation reactions.[36] Ligand **1F** containing a two-carbon spacer forms seven membered chelates and was designed for cylcopropanation reactions.[37] Ligand **1G** was utilized in the preparation of cationic aqua complexes for enantioselective

Diels-Alder reactions.[19] Tridentate ligand **1H** was designed for hydrosilylation reactions.[38] Ligands **1I** and **1J** were designed for catalytic cyclopropanation reactions.[39,40,41] These ligands afford oxazoline rings that are held in nine-membered metal chelates. Asymmetric allylic substitution was achieved with ligand **1K**.[42]

A4.2 BINAPHTHYLIC C_2-SYMMETRIC DERIVATIVES

Biaryl molecules have been studied extensively. Increased hindrance to rotation at the pivotal 1,1'-bond can make these molecules resolvable as optically active enantiomers. The structural diversity in this ligand system is less rich than that of the oxazoline architecture (**Table A4.2**).

The rigid structure and the C_2-symmetry of the chiral binaphthylic metal complexes have been used in many asymmetric reactions with high enantioselectivity. Enantioselective reductions utilizing aluminum salts of the binaphthol ligand **14** occur with up to 100% e.e. (**2A**[43], **2B**[44]). It is worth noting that the reduction reaction with (*R*)-BINAL produced (*R*)-enriched alcohols, while the reaction with (*S*)-BINAL produced the (*S*)-enantiomer. Ligand **2A** has been used for a variety of asymmetric transformations: addition to aromatic aldehydes, hydrocyanation,[45] reduction of imines,[46] asymmetric Diels-Alder,[47] hetero Diels-Alder,[48] and ene reactions.[49] **2A** has also been employed in stereoselective polymerizations,[50] and asymmetric Ullman coupling reactions.[51] Potassium salts have been utilized for asymmetric Michael addition.[52] *In situ* generation of chiral Lewis acids by the addition of ethylaluminum dichloride, diethylaluminum chloride, or titanium (IV) chloride to compound **2A** catalyzed asymmetric Diels-Alder

reactions.[53] Organoaluminum reagent (*R*)- and (*S*)-**14d** was utilized for hetero Diels-Alder reactions.[54,55,56] A boron reagent derived from **2C** (R = H) was utilized for Diels-Alder[57] and hetero Diels-Alder reactions.[58]

Ligand **2D** was designed for the asymmetric hydrogenation of prochiral acids and esters,[59] asymmetric alkylation of racemic allylic substrates,[60] alkylation of aldehydes,[61] and asymmetric hydroboration of olefins.[62] The potassium salts derived from ligand **2E** have been developed for asymmetric Michael reactions,[63] and as initiators for anionic polymerization of methacrylic acid esters.[50]

Ligand **2C** was applied to asymmetric hydrogenation,[64,65,66,67,68,69,70] asymmetric isomerization of double bonds,[71,72] asymmetric hydroboration,[73] and enantioselective desilylation.[74] Ligand **2F** was utilized for the enantioselective reduction of ketones,[75] hydrogenation reactions,[76] asymmetric lactone synthesis,[77] alkylation of aromatic aldehydes,[78] and asymmetric glyoxylate-ene reactions.[79] Ligand **2G** has been exploited in the asymmetric hydrogenation of α-acylaminoacrylic acids.[80]

A4.3 C_2-SYMMETRIC TADDOL DERIVATIVES

Another C_2-symmetric ligand which has gained popularity in asymmetric transformations is the α,α,α',α'-tetraaryl-1,1,3-dioxolan-4,5-dimethanol (TADDOL) **21**. It has proved to be a useful catalyst in stoichiometric and catalytic enantioselective reactions, such as reductions of ketones,[81] epoxidation,[82] oxidation,[83,84,87] nucleophilic addition to aldehydes,[85,86,87,88,89] Wittig reactions,[90] hydrogenations,[91,92,93,94,95,96] Diels-Alder cycloadditions,[97,98] hetero Diels-Alder reactions,[99] ene reactions,[100] hydrosilylations,[101,102] and hydroborations.[103] Seebach and co-workers have performed

extensive studies on TADDOL-titanium catalyzed additions of dialkylzinc reagents to aliphatic and aromatic aldehydes. The efficiency of this catalyst was found to depend on the bulkiness of the α-substituents in the dioxolane dimethanols, in the following order; H<alkyl<Ph< β-naphthyl. When the steric hindrance becomes too large, as in the α-naphthyl derivative, the rate and the enantioselectivity of the reaction decrease. Seebach also reported that an excess amount of Ti(O-*i*-Pr)$_4$ is necessary to achieve high enantioselectivity.[104]

A4.4 C_2 SYMMETRIC METALLOCENE (*ANSA*-METALLOCENE) DERIVATIVES

The development of chiral transition metal complexes as catalysts for stereoselective organic transformations is being widely pursued.[105] This work stemmed from the original work of Ziegler and Natta who discovered the utility of early transition metals in the polymerization of olefins.[106] Chiral bridged-metallocenes (known as *ansa*-metallocenes) of group IV transition metals have been applied to a variety of synthetic transformations. These include olefin hydrogenations,[107] epoxidations,[108] isomerizations,[109] hydrooligomerizations,[110] and cyclopolymerization reactions,[111] olefin-pyridine couplings,[112] imine hydrogenations,[113] enamine hydrogenations,[114] Diels-Alder reactions,[115] allylic amine synthesis,[116] allylic alcohol synthesis,[117] carbomagnesation reactions,[118] hydrosilylation of ketones,[119] kinetic resolution of pyrans,[120] and dehydrogenative phenylsilane oligomerizations.[121] However, practical application of *ansa*-metallocene catalysts and reagents is hindered by the fact that current *ansa*-

metallocene syntheses, which are based on salt elimination of reactions between MCl_x compounds and biscyclopentadienyl dianion reagents, are inefficient (30–40%).

A4.5 C_2-Symmetric Jacobsen's Salen Derivatives

Building on the work of Kochi[122] and Borrows[123] in the 1980s, who used achiral manganese salen catalysts for epoxidations, Jacobsen reported in 1990 that unfunctionalized alkenes could be epoxidized with high enantioselectivities using chiral manganese salen catalysts.[124] Ever since that discovery, a number of workers have modified the salen architecture to furnish new ligand systems. The systems developed were utilized in a number of asymmetric transformations. These include the utility of **4A** and **4B** in asymmetric epoxidation,[125,126] addition to aldehydes[127] and ring opening of epoxides[128]. **4A** was also utilized in the asymmetric hetero-Diels-Alder reaction.[129] **4C** and **4D** were designed for asymmetric alkene aziridination reactions.[130] The ruthenium-catalyzed asymmetric reduction of ketones was accomplished with ligands **4E** and **4F**.[131] It is interesting to note that asymmetric ligand **4G**, produced e.e.s of up to 86% in the epoxidation of unfunctionalized olefins.[132]

A4.6 Miscellaneous

There are a number of C_2-symmetric ligands, which have been utilized in asymmetric transformations, that do not fall into the general motifs presented above. These have been presented in **Table A4.6**. These have been used for hydrogenation of enamides,[96] hetero-Diels-Alder reactions,[133] addition to aldehydes,[134,135] hydrogenation,[136] Diels-Alder[137], reduction of ketones,[138,139] and the cyclopropanation of allylic alcohols.[140]

Table A4. 1: Semicorrins and Bisoxazoline; Reaction type and Best Optical Yield

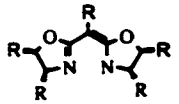
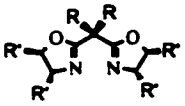
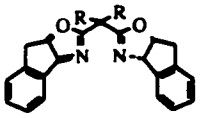
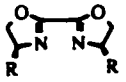
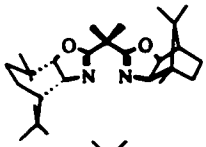
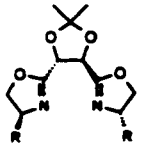
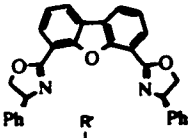
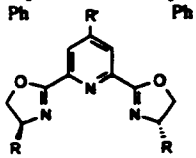
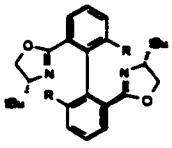
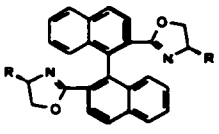
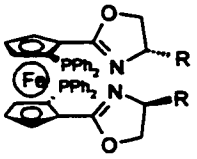
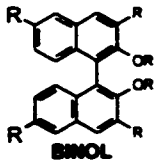
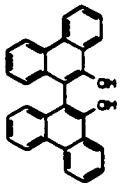
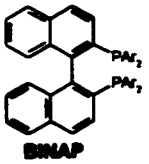
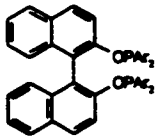
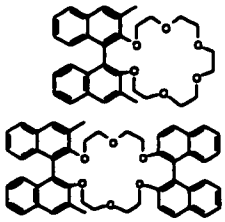
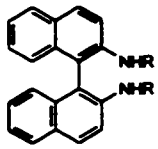
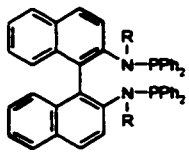
Entry	Chiral catalyst	Reaction		e.e.	Ref
1A		/Cu	cyclopropanation of olefins	97	8
		/Co	reduction of a,b-unsaturated amides	99	25
		/Co	reduction of a, b-unsaturated esters	96	25
1B		/Cu	cyclopropanation of olefins	92	11
		/Cu	aziridination of olefins	97	5
		/Cu	Aldol reaction	99	22
		/Cu	heteroDiels-Alder	99	23
		/Cu	Michael additon reaction	99	13
		/Fe	Diels-Alder reaction	86	11
		/Ti	hydrosilylation of ketones	85	31
		/Cu	glyoxalate-ene reaction	97	12
1C		/Cu	heteroDiels-Alder	98	23b
		/Ni	hetertoDiels-Alder	96	23b
		/Cu	Diels-Alder Reaction	99	18
1D		/Ir	transfer hydrogenation of ketones	91	11
		/Pd	allylic alkylation	77	11
		/Rh	hydrosilylation	84	26
1E		/Cu	cyclopropanation	90	36
1F		/Cu	cyclopropantation	89	37
1G		/Co	enantioselective Diels-Alder	>99	19
1H		/Rh	hydrosilylation of ketones with Ph_2SiH_2	99	38b
		/Rh	allyl transfer to aldehydes	77	29
		/Cu	asymmetric Diels-Alder	96	17b
1I		/Cu	catalytic cyclopropanation reaction	92	41a
1J		/Cu	catalytic cyclopropanation reaction	97	41b
1K		/Pd	asymmetric allylic substitution	99	42

Table A4. 2: Binaphthyl derivatives; Reaction type and Best Optical Yield

Entry	Chiral catalyst		Reaction	ee	Ref
2A	 BINOL	/Al	hetero Diels-Alder reaction	97	48c
		/B	Diels-Alder reaction	>98	48c
		/K	Michael addition reaction	99	52
		/LiAlH4	reduction of ketones	100	43b
		/Ti	Diels-Alder reaction	98	53
		/Zn	asymmetric ene reaction	>90	49
		/Ti	hydrocyanation of aldehydes	82	45
		/Zr	reduction of imines	91	46
2B		/LiAlH4	reduction of ketones	98	44
2C	 BINAP	/Rh	isomerization of allylamines	99	43c
		/Ru	hydrogenation of b-functionalized ketones	>99	43c
		/Ru	hydrogenation of acrylic acid deriv.	>99	43c
		/Ru	hydrogenation of allylic alcohols	99	43c
		/Rh	hydroboration of olefins	96	62
2D		/Rh	hydrogenation of unsaturated acid and esters	76	59
		/Pd	alkylation of racemic allylic substrates	69	60
2E		/K	Michael reaction	99	63
		K/ Li	polymerization of methacrylic acid esters	90	50
2F		/Ti	asymmetric glyoxylate-ene reaction	>99	79
		/LiAlH4	reduction of aromatic ketones	82	75
			synthesis of lactones	58	77
		/Zn	alkylation of aromatic aldehydes	70	78
		/Rh	hydrogenation of a-acyaminoacrylic acids	95	76
2G		/Rh	hydrogenation of a-acylaminoacrylic acids	95	80

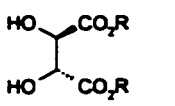
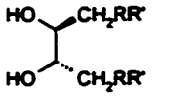
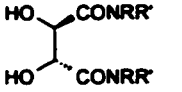
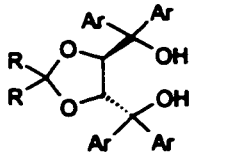
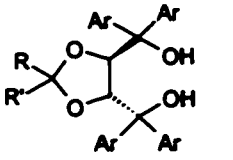
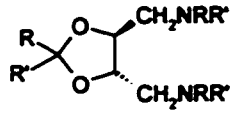
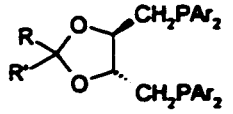
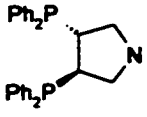
Entry	Chiral catalyst		Reaction	ee	Ref
3A		/NaBH4	reduction of ketones	86	81
		/Ti	epoxidation of allylic alcohols	>98	82b
			oxidation of sulfides	97	83
			addition of Me_3SiCN to aldehydes	91	85
			photooxidation of olefins to epoxyalcohols	72	84
		crys. chiral host	Wittig reaction with cyclohexanones	57	90
		/Raney-Ni-NaBr	hydrogenation of β-functionalized ketones	92	91
3B		/$EtAlCl_2$	Diels-Alder reaction	98	53
3C		/$B(OMe)_3$	Diels-Alder reaction	92	98
		/B-allyl	allylboration of aldehydes	97	86
3D		/Ti	hetero Diels-Alder	97	99
3E		/$Ti(OR)_2Cl_2$	addition of MeLi to aldehydes	90	87
		/$Ti(OR)_2Cl_2$	addition of Me_3SiCN to aldehydes	96	98
		/$Ti(OR)_2Cl_2$	intramolecular ene reaction	>98	100
		/$CpTiCl_3$	addition of M-allyl to aldehydes	97	88
		/Ti	alcoholysis of thioesters (kinetic resolution)	92	87
			Diels-Alder reaction	94	96
			addition of Et_2Zn to aldehydes	99	89
			2 + 2 cycloaddition reaction	>98	98b
3F		/OsO_4	dihydroxylation of olefins	90	87
3G		/Rh	hydrosilylation of ketoesters	85	101
		/Rh	hydrogenation of enamides	94	94
		/Rh	hydroboration of olefins	82	103
		/Rh	intramolecular hydrosilylation of olefins	93	102
		/Ir	hydrogenation of imines	70	95
		/Rh	hydrogenation of aminoketones	95	96
3H		/Rh	hydrogenation of enamides	100	92

Table A4. 4: C_2 symmetric Metallocene derivatives; Reaction type and Best Optical Yield

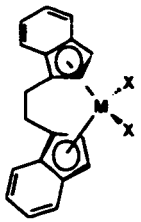
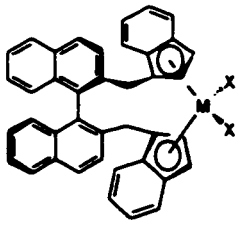
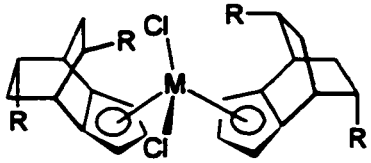
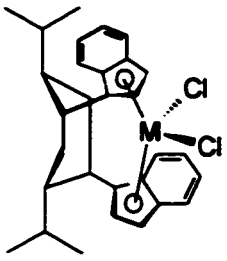
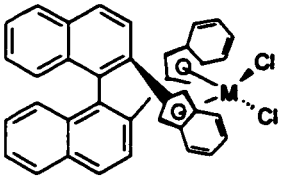
Entry	Chiral catalyst	Reaction		ee	Ref
4A		/Ti	epoxidation of olefins	–	108
		/Ti	reduction of imines	99	107d
		/Ti	hydrogenation of imines	84	107c
		/Ti	hydrosilylation of ketones	97	119b
		/Ti	allylation of aldehydes	55	117a
		/Ti	Diels-Alder reaction	95	115b
		/Ti	hydrogenation of enamines	98	114
		/Ti	isomerization of alkenes	80	109
		/Ti	hydrogenation of olefins	>99	107b
		/Zr	carbomagnesation	98	118
		/Zr	hydrogenation of olefins	63	107a
		/Zr	oligomerization of phenylsilane	—	121a
		/Zr	synthesis of allylic amines	99	116
		/Zr	olefin insertion reactions	>98 (de)	112
		/Zr	kinetic resolution of pyrans	>99	120
4B		/Ti	epoxidation of alkenes	22	108a
4C		/Ti	hydrosilylation of Aryl alkyl ketones	13	119a
4D		/Ti	hydrosilylation of Aryl alkyl ketones	20	119
4E		/Ti	hydrosilylation of Aryl alkyl ketones	40	119
		/Ti	epoxidation of alkenes	16	108b
4F		/Ti	addition to aldehydes	99	117b
		/Zr	Diels-Alder reaction	91	115a

Table A4. 5: Salen Derivatives; Reaction type and Best Optical Yield

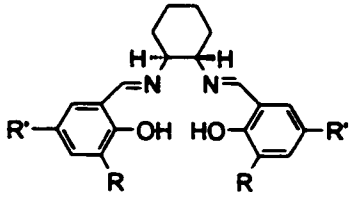
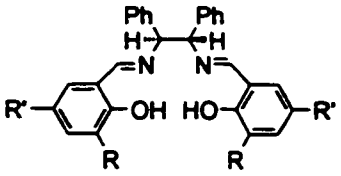
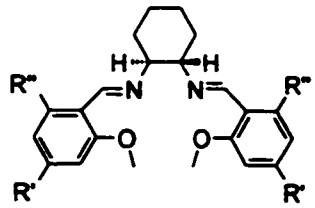
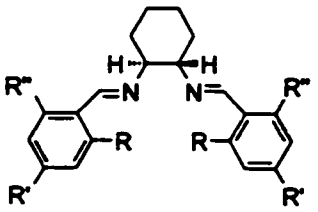
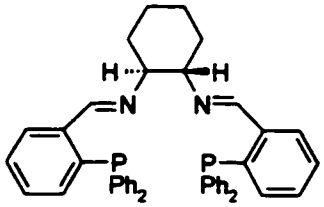
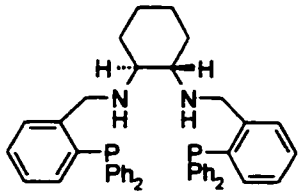
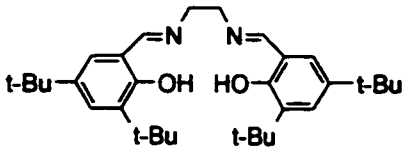
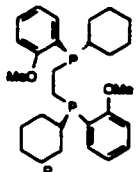
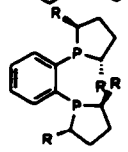
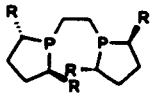
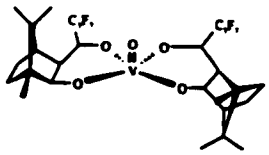
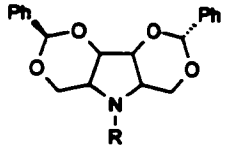
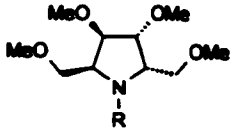
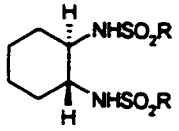
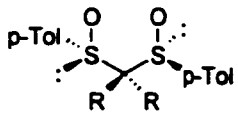
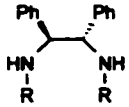
Entry	Chiral catalyst		Reaction	ee	Ref
5A		/Mn	epoxidation of olefins	88	125
		/Cr	hetero-Diels-Alder	99	129
		/Ti	addition of Me_3SiCN to aldehydes	86	127
		/Co	ring opening of α-chloro epoxides	96	128
5B		/Mn	epoxidation of olefins	93	124a
5C		/Cu	alkene aziridination	90	130
5D		/Cu	alkene aziridination	>98	130
5E		/Ru	reduction of aromatic ketones	18	131
5F		/Ru	reduction of aromatic ketones	97	131
5G		/Mn	epoxidation of olefins	86	132

Table A4. 6: Miscellaneous C_2 Symmetric systems

Entry	Chiral catalyst		Reaction	ee	Ref
6A		/Rh	hydrogenation of enamides	97	97
6B	 DUPHOS	/Rh	hydrogenation of α, β–unsaturated esters	99	136b
		/Ag	allylation of aldehydes	48	61
6C		/Rh	hydrogenation of α, β–unsaturated esters	99	117
6D		/Rh	reduction of ketones	95	138
6E			Hetero-Diels-Alder reaction	85	133
6F			addition of Et_2Zn to aldehydes	42	134
6G			addition of Et_2Zn to aldehydes	82	135
6H		/Ti	reduction of aldehydes	99	135
		/Zn	cyclopropanation of allylic alcohols	82	140
6I		/Fe	asymmetric Diels-Alder	56	137
6J		/Ru	hydrogenation of b-functionalized ketones	>99	138c
		/Ru	hydrogenation of acrylic acid deriv.	>99	136a
		/Ru	hydrogenation of allylic alcohols	99	136b
		/Rh	isomerization of allylamines	99	136b
		/Rh	reduction of ketones	99	136b
		/Rh	hydroboration of olefins	96	52
		/Pd	alkylation of racemic allylic substrates	69	60
		/Ag	allylation of aldehydes	96	134

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Chapter 5

Stereoselective Reduction of Ketones by Histidine-Alkoxysilane Complexes: The Role of Imidazole in Nucleophilic Substitution at Silicon *

5.1 ABSTRACT

The reduction of carbonyl compounds with transient, hypervalent silicon hydrides is described. Trialkoxysilanes, upon activation by a catalytic amount of lithium imidazolide or the mono or dilithium salt of histidine, but not by neutral imidazole or histidine, reduced the carbonyl groups of various ketones, forming the corresponding silyl ethers, which were cleaved upon workup. Enantiomerically enriched product alcohols were recovered in good to excellent yield (70-95%) with e.e.'s ranging from 5-75% with catalysis by histidine derivatives.

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5.2 INTRODUCTION

Simple hydrosilanes may be used as mild reducing agents for carbonyl compounds. They offer some distinct advantages over traditional metal hydrides. For instance, unlike most hydride reducing agents, these compounds are stable in water at neutral pH. Their activity is normally unleashed by transition metal catalysts, in which case the reduction can be enantioselective with appropriate chiral ligands on the transition metal.[1] The hydrosilanes also readily react with acidic or basic catalysis.

A conceptually different way to activate hydrosilanes is to form extracoordinate, usually pentacoordinate, hydrosiliconates. The hydride in these compounds is a much more nucleophilic reducing agent than in the analogous tetracoordinate silanes.[2,3] The traditional method to prepare extracoordinate hydrosilanes involves adding an alkoxide to a trifunctional hydrosilane, typically a trialkoxysilane. The pentacoordinate compounds formed from catechol are particularly easy to prepare.[4] These and related compounds[5,6,7,8,9,10] cleanly reduce carbonyl and α,β-unsaturated carbonyl compounds[4,11] preferentially in a 1,2-fashion.

Hosomi *et al.*[10] and Kagan and coworkers[12], respectively, demonstrated that extracoordinate hydrosilanes, formed from chiral diols or β-aminoalcohols, reduce ketones enantioselectively. For instance, the reduction of acetophenone to (*R*)-1-phenethyl alcohol by a mixture of $HSi(OEt)_3$ and a catalytic amount of (*S*)-prolinol occurred with 52% e.e.[10]

Imidazole and its derivatives play a special role in organosilicon chemistry. They activate silicon to nucleophilic attack with unique efficiency and are frequently employed

as catalysts, for instance, in the preparation of silyl ethers from alcohols.[13] Bassindale *et al.* [14] have established the pentacoordinate nature of the interaction between *N*-methylimidazole (NMI) and chlorodimethylsilane (DMCS) using ^{29}Si NMR.

We were interested to examine with what efficiency imidazole could be used to facilitate the extracoordination of hydrosilanes to give compounds that would subsequently reduce carbonyl groups. We were additionally interested to discover if imidazole derivatives from the chiral pool, in particular histidine, would influence the stereoselectivity of the reduction. We report herein the use of catalytic amounts of lithium imidazolides (Li-IM) and the mono- (Li-His) and di-lithium salts of histidine (Li_2-His) to form extracoordinate silanes that not only reduce ketones, but do so stereoselectivley with only catalytic amount of the amino acid.

5.3 Results and Discussion

Extracoordinate hydrosilanes **1** (**Scheme 5. 1**), were prepared *in situ* by mixing lithium imidazolide or the mono- or di-lithium salts of histidine with trialkoxysilane **2** in tetrahydrofuran (THF) solution. The extracoordinate nature of the resulting silicon species was demonstrated by the change in ^{29}Si NMR shifts upon mixing of the reagents (**Table 5. 1**), consistent with the work of Bassindale[14]. Note that the pentacoordinate systems derived from the mono- and dianions of histidine were identical by ^{29}Si NMR: hexacoordinate systems were not observed. This suggests a coincidental chemical shift for two different species, either mono or bidentate, or more likely the preferred formation of one isomeric structure (**Table 5. 1**).

Table 5. 1: ^{29}Si NMR chemical shifts of products of hydrosilane: imidazolide reactions

Entry	$HSiR_3$	Solvent	^{29}Si NMR (δ ppm) Silane	L	Silane + L
1	$HSiMe_2Cl$	$CHCl_3$:hexane	12	NMI	-81[a]
5	$HSi(OEt)_3$	THF	-59	Li-IM	-83
2	$HSi(OMe)_3$	THF/ TMEDA (30:1)	-56	Li-IM	-79
3	$HSi(OMe)_3$	THF/ TMEDA (30:1)	-56	Li-His	-79
4	$HSi(OMe)_3$	THF/ TMEDA (30:1)	-56	Li_2-His	-79

[a] Reported by Bassindale *et al.*[14] and subsequently remeasured by us.

Neither imidazole nor histidine catalysed the reaction between $HSi(OMe)_3$ and acetophenone: starting materials were recovered. However, ketone reduction took place at 0 °C over 24 hours when catalysed by imidazolide or histidyl anions, via a pentacoordinate species (**Scheme 5. 1**). A preliminary screening of the reaction conditions necessary to effect reduction was performed with lithium imidazolide and acetophenone **3** as a model system, and THF as the solvent (**Table 5. 2**). The reaction occurs more readily at 0 °C than at –78 °C in accordance with the results by Kagan *et al.*[12] They found that reaction of pentacoordinate hydrosilicates generated by chiral lithium alkoxides showed no reactivity at –78 °C, but mixing the components at that temperature and then warming to room temperature overnight gave, after aqueous workup, the corresponding 1-phenethyl alcohol. Also in accord with the results obtained by Kagan *et al.*, is the use of TMEDA as cosolvent increased the yield of hydrosiliconate reductions, presumably by changing the aggregation behaviour of the organolithium salts (**Table 5.2**).

Scheme 5. 1: Proposed mechanism of the reduction process with di-lithium salt of histidine

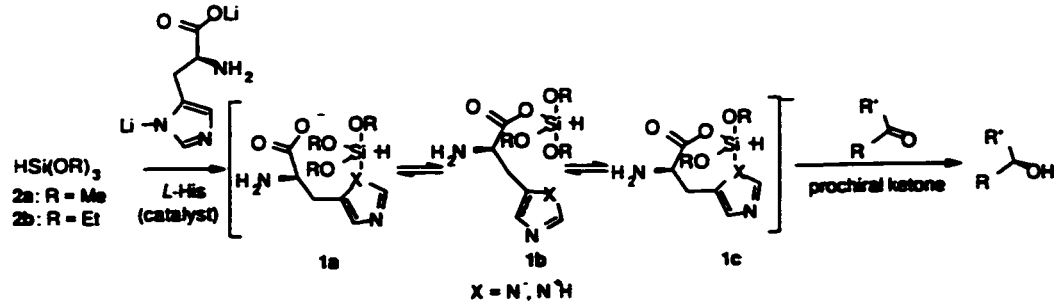

Table 5. 2: Effect of TMEDA as additive for the reduction of acetophenone

Entry	Solvent	$(RO)_3SiH$	Conditions [a]	Yield (%)[b]
1	THF	$(EtO)_3SiH$ (2a)	6h, 0 °C then r.t. 17h	20
2	THF/TMEDA (30:1)	2a	6h, 0 °C then r.t. 17h	41
3	THF/TMEDA (30:1)	2a	6h, -78 °C then r.t. 17h	35
4	THF/TMEDA (30:1)	2a	12h, 0 °C	65

[a] 10 mol % of lithium imidazolide as catalyst and 1 eq of silane 2. [b] Isolated yield after column chromatography on silica gel (pentane/ether = 3:1).

The enantioselective reduction of a variety of ketones was examined in Table 5.3 using conditions optimized for the reduction of acetophenone (THF/TMEDA) with the di-lithium salt of *L*-histidine as catalyst (10 mol%); the results are presented in **Table 5. 3**. It is noteworthy with this system that, in accord with the system described by Kagan *et al.*,[12], steric effects play a much more important role than electronic effects in determining the degree of enantioselection.

In the reduction of the acetophenone series, with the different steric requirements of the phenyl and methyl groups, it is not surprising that a reasonable level of stereoselectivity is observed. Pertinent to the discussion of the structure of the

intermediate is the observation that as the distal group on the acetophenone becomes more electron donating, the preference for facial reduction of the ketone increases *p*-OMe (70) > *p*-Me (40) > *p*-H (26). Enantioselection is also observed in the benzophenone derivatives, where the only element for steric differentiation is far removed from the centre to be reduced. To a smaller degree, electronic effects appear to operate here as well. Somewhat surprisingly, different facial selectivity is observed in the reduction of the analogous compounds 4-phenyl-2-butanone, *trans*-4-phenyl-3-buten-2-one, and 4,7-dimethylindanone.

Table 5. 3: Reduction of different ketones [a]

Entry	Ketone	$(RO)_3SiH$	Yield (%)[b]	e.e.(%)[c]
1	Acetophenone	$(EtO)_3SiH$ (**2a**)	70	26 (*S*)
2	Acetophenone	$(MeO)_3SiH$ (**2b**)[f]	85	N.M.[d]
2	Acetophenone	$(MeO)_3SiH$ (**2b**)	85	N.M.[d]
3	Benzophenone	**2b**	90	N.A.[e]
4	4,7-dimethyl-indanoneindanone	**2b**	66	30 (*R*)
5	4-phenyl-2-butanone	**2b**	91	28 (*R*)
6	*trans*-4-phenyl-3-buten-2-one	**2b**	78	70 (*S*)
7	4-(trifluoromethyl)acetophenone	**2b**	86	30 (*S*)
8	4-methyl-acetophenone	**2b**	80	40 (*S*)
9	4-methoxy-acetophenone	**2b**	89	70 (*S*)
10	4-(trifluoromethyl)benzophenone	**2b**	95	30 (*S*)
11	4-methyl-benzophenone	**2b**	82	5 (*S*)
12	4-methoxy-benzophenone	**2b**	78	5 (*S*)
13	Phenylacetone	**2b**	90	N.M.

[a] All reactions were conducted with 10 mol % of the di-lithium salt of *L*-histidine as catalyst and 1 eq of silane in THF/TMEDA = 30:1 solution. All reactions were run at 0 °C for 24 h. [b] Isolated yields, after chromatography on silica gel (pentane/ether=3:1). [c] Measured by ^1H NMR analysis of the Mosher ester of the corresponding alcohols.[15] Also measured by ^{19}F NMR of Mosher ester. Absolute configuration assigned from optical rotation of alcohol. [d] Not measured. [e] Not applicable. [f] Only monoanion of histidine added.

Imidazole is commonly used to activate silicon to nucleophilic attack when good leaving groups such as chloride are involved. With poorer leaving groups, such as hydride in the cases cited above, more powerful silanucleophiles are required, such as imidazolide or the histidyl dianion. While structural studies are ongoing, it is premature to predict the exact nature of the active intermediate. However, the facts give the same chemical shift in the ^{29}Si NMR of the active complex and that the mono- and dianion of histidine reduce acetophenone with the same enantioselectivity strongly suggests that a single structure either monodentate structures **1a**, **1b** or bidentate structures **1c** is involved in both cases. These and related studies will form the basis of future reports.

5.4 CONCLUSION

We have shown that lithium-imidazolide can act as an effective catalyst for the hydrosilylation of ketones. More specifically, we have demonstrated that a pentacoordinate silicon species results from the addition of lithium imidazolide to trialkoxysilanes, creating a transient (or intermediary) in the reduction process. Moreover, we have shown that when the lithium salt of histidine is utilized, chiral induction is noted in these reductions.

5.5 EXPERIMENTAL

5.6.1 Reagents and Physical Methods

The following materials were obtained from Aldrich and were used without further purification: acetophenone, benzophenone, *n*-butyllithium (2M solution in cyclohexane), chlorodimethylsilane, 4,7-dimethyl-1-indanone, 4-phenyl-2-butanone, dimethylformamide, absolute ethanol, *L*-histidine, imidazole, 4-methoxyacetophenone, 4-methoxybenzophenone, (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl (+)), 4-methylacetophenone, 4-methylbenzophenone, *N*-methylimidazole, *trans*-4-phenyl-3-buten-2-one, sodium borohydride, sodium sulfate, *N,N,N',N'*-tetramethylethylenediamine (TMEDA), triethoxysilane, 4-(trifluoromethyl)acetophenone, trimethoxysilane and 4-(trifluoromethyl)benzophenone.

^{1}H NMR spectra were recorded on a Bruker AC-200 (at 200-MHz for protons) Fourier transform spectrometer. ^{13}C and ^{29}Si-NMR were performed on a Bruker AC-200 (50.32 and 39.7 MHz for carbon and silicon, respectively) or a Bruker AC-300 (at 75.44 MHz and 59.60 MHz for carbon and silicon, respectively). Chemical shifts are reported either with respect to tetramethylsilane as an external standard for ^{29}Si, set to 0 ppm, or $CDCl_3$ as an internal standard for protons, set at 7.24 ppm. Coupling constants (*J*) are recorded in Hertz (Hz). The abbreviations s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, are used to report spectra.

Electron impact (EI) and chemical ionization (CI, NH_3) mass spectra were recorded at 70 eV with a source temperature of 200 °C on a VG analytical ZAB-R mass

spectrometer equipped with a VG 11-250 data system. High resolution mass spectral (HRMS) data were obtained using the EI method. Infrared spectra were run as KBr pellets or as liquid films on NaCl discs (as indicated) on a Perkin-Elmer 283 spectrometer or on a BIORAD FTS-40 spectrometer as a neat film.

All solvents were thoroughly dried before use: acetonitrile was dried over P_2O_5; THF was dried from K/benzophenone. All reactions were carried out in dry apparatus under a nitrogen atmosphere with the use of septa and syringes for the transfer of reagents.

5.6.2 ***Typical Experimental Procedure (example acetophenone):***

Triethoxysilane 2a and especially trimethoxysilane 2b are rather toxic compounds and therefore care must be taken in their handling. Both are available commercially (Aldrich) and can be handled without problems via syringe techniques. To a dry 100 mL round-bottomed flask flushed with nitrogen was added *L*-histidine (50 mg, 0.3 mmol) and THF (30 mL). At ambient temperature *n*-butyl lithium (2M, 0.32 mL, 0.6 mmol) was added slowly and the resulting suspension was stirred for 30 min. The reaction mixture was cooled to 0 °C and TMEDA (1.0 mL, 6 mmol) was added and stirring was continued for 10 min, then trimethoxysilane (0.38 mL, 3 mmol) was added and the mixture was stirred for an additional 10 min. Finally acetophenone (0.35 mL, 3 mmol) was added and the reaction mixture was kept at 0 °C for 24 h. The reaction was quenched by the addition of sodium hydrogen carbonate (0.1 M, 20 mL) and stirred vigorously for 30 min at room temperature. The biphasic system was transferred to a separatory funnel and extracted with ether (3 * 40 mL). The ether was removed without drying and the resulting crude product was purified

by column chromatography on silica gel eluting with pentane/ether (3:1), to give (*S*)-phenethyl alcohol (0.31 g, 85%) as a colorless liquid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.56 (d, 3H, J = 6.5 Hz, PhCH(OH)C*H*$_3$), 2.76 (bs, 1H, PhCH(O*H*)CH_3), 4.94 (q, 1H, J = 6.5 Hz, PhC*H*(OH)CH_3), 7.32-7.45 (m, 5H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.97, 69.99, 125.24, 127.14, 128.24, 145.75; FTIR (neat, KBr disc) ν (cm^{-1}) 3364, 3065, 3031, 2974, 2929, 1603, 1494, 1452, 1371, 1287, 1204, 1077, 1030, 1011, 900, 762, 700, 607, 541; MS (EI) m/z (%): 122 (M^+, 10), 121 (40), 104 (68), 79 (28), 57 (7), 43 (100); (CI) m/z (%): 140 (M^+ + 18, 17), 122 (100), 105 (41), 78 (2), 52 (1), 44(1).

4-Trifluoromethylphenethylalcohol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.46 (d, 3H, J = 6.5 Hz, CF_3-PhCH(OH)C*H*$_3$), 2.33 (bs, 1H, CF_3-PhCH(O*H*)CH_3), 4.90 (q, 1H, J = 6.5 Hz, CF_3-PhC*H*(OH)CH_3), 7.43 (d, J = 8.1 Hz, CF_3-Ph-*H*), 7.61 (d, J = 8.1 Hz, CF_3-Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 25.25, 69.73, 121, 125.40, 125.59, 149.65; FTIR (neat, KBr disc) ν (cm^{-1}) 3623, 3375, 2979, 2934, 2880, 1925, 1806, 1680, 1622, 1452, 1417, 1373, 1328, 1206, 1167, 1125, 1091, 1070, 1017, 901, 843, 738, 631, 607; MS (EI) m/z %: 190 (M^+, 5), 175 (40), 159(2), 145 (7), 128 (5), 127 (30), 109 (3), 95 (5), 77(8), 69 (5), 51 (8), 43 (100); (CI) m/z (%):190 (M^+, 37), 168(45), 135 (100), 76 (61), 52 (19), 44 (16).

4-(Methyl) phenethylalcohol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (d, 3H, J = 6.4 Hz, CH_3-PhCH(OH)C*H*$_3$), 1.87 (bs, 1H, CH_3-PhCH(O*H*)CH_3), 2.33 (s, 3H, C*H*$_3$-PhCH(OH)CH_3), 4.84 (q, 1H, J = 6.4 Hz, CH_3-PhC*H*(OH)CH_3), 7.14 (d, J = 8.0 Hz,

CH_3-Ph-*H*), 7.24 (d, *J* = 8.0 Hz, CH_3-Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 21.06, 25.04, 70.20, 125.32, 129.13, 137.10, 142.85; FTIR (neat, KBr disc) ν (cm^{-1}) 3623, 3376,3023, 2972, 2927, 2872, 1904, 1669, 1612, 1515, 1451, 1371, 1284, 1202, 1181, 1120, 1075, 1011, 899, 818, 728; MS (EI) m/z (%): 136 (M^+, 62), 135 (M^+-1, 100), 109 (67), 94 (16), 77 (25), 65 (13), 45 (11), 43 (47); (CI) m/z (%): 136(M^+, 13), 135(M^+ -1, 100).

4-Methoxyphenethylalcohol: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.41 (d, 3H, *J* = 6.4 Hz, CH_3O -PhCH(OH)C*H*$_3$), 2.64 (bs, 1H, CH_3O-PhCH(O*H*)CH_3), 3.74 (s, 3H, C*H*$_3$O - PhCH(OH)CH_3), 4.76 (q, 1H, *J* = 6.4 Hz, CH_3O -PhC*H*(OH)CH_3), 6.85 (d, *J* = 8.0 Hz, CH_3O-Ph-*H*), 7.25 (d, *J* = 8.0 Hz, CH_3O-Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.88, 55.09, 69.61, 113.62, 126.53, 138.00, 158.70; FTIR (neat, KBr disc) ν (cm^{-1}) 3409, 2969, 2932, 2838, 1613, 1587, 1514, 1463, 1370, 1327, 1291, 1249, 1176, 1118, 1087, 1072, 1036, 1008, 899, 833, 809, 738, 585, 550; MS (EI) m/z (%):152 (M^+, 6), 135 (37), 109 (78), 105 (50), 84 (17), 77 (74), 51 (42), 43 (100).

Diphenylcarbinol: ^1H NMR ($CDCl_3$, 200 MHz) δ 2.19 (bs, 1H, PhCH(O*H*)Ph), 5.84 (s, 1H, PhC*H*(OH)Ph), 7.24-7.39 (m, 10H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 75.96, 126.46, 127.35, 128.31, 143.69; FTIR (neat, KBr disc) ν (cm^{-1}) 3390, 3086, 3061, 3028, 1598, 1495, 1454, 1395, 1350, 1317, 1290, 1269, 1181, 1085, 1034, 1018, 926, 912, 852, 754, 736, 700, 654; MS (EI) m/z: 184 (M^+, 38), 167 (53), 152 (7), 105 (100), 79 (52), 77 (60), 51 (41); (CI) m/z (%): 184 (M^+, 8), 167 (100), 135 (4), 105 (4), 78 (1).

1-(4-Trifluoromethylphenyl)-1-phenylcarbinol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.87 (s, 1H, CF_3-PhC*H*(OH)Ph), 7.24-7.36 and 7.47-7.60 (m, 9H, CF_3-Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 75.71, 125.24, 126.58, 127.73, 128.55; FTIR (neat, KBr disc) ν (cm^{-1}) 3384, 3067, 3034, 2959, 2929, 2874, 1669, 1620, 1606, 1495, 1453, 1415, 1327, 1276, 1163, 1124, 1068, 1041, 1019, 864, 841, 807, 750, 736, 701; MS (EI) m/z (%): 252 (M^+, 33), 235 (67), 183 (10), 173 (29), 145(17), 127 (24), 105 (100), 79 (86), 51 (46); (CI) m/z: HR-MS (CI) m/z (%): 269 (M^++17, 1), 252 (M^+, 25), 235 (100), 181(3), 173(3), 145 (2), 117 (4), 105 (14), 78 (7), 58 (2), 52 (1).

1-(4-Methylphenyl)-1-phenylcarbinol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.30 (s, 3H, C*H*$_3$-PhCH(OH)Ph), 5.75 (s, CH_3-PhC*H*(OH)Ph), 7.08-7.35 (m, 9H, CH_3-Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 21.07, 76.03, 126.43, 126.48, 127.39, 128.39, 129.13, 140.93, 143.92; FTIR (neat, KBr disc) ν (cm^{-1}) 3536, 3384, 3088, 3062, 3030, 2958, 2924, 2871, 1660, 1604, 1514, 1494, 1453, 1412, 1382, 1319, 1279, 1176, 1114, 1078, 1037, 1018, 944, 912, 861, 843, 799, 777, 735, 700; MS (EI) m/z (%):198 (M^+, 53), 181 (100), 165 (10), 152 (6), 119 (78), 105 (73), 91 (59), 77 (69), 51 (31), 43 (15); (CI) m/z (%): 198 (M^+, 6), 181 (100), 119 (5), 105 (5), 91(3), 77(1), 65 (1).

1-(4-Methoxyphenyl)-1-phenylcarbinol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.31 (bs, 1H, CH_3O-PhCH(O*H*)Ph), 3.79 (s, 3H, C*H*$_3$O -PhCH(OH)Ph), 5.80 (s, 1H, CH_3O -

PhC*H*(OH)Ph),7.10 (d, 2H, *J* = 8.0 Hz, CH_3O-Ph-*H*), 7.23-7.40 (m, CH_3O-Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 55.25, 75.76, 113.83, 126.37, 127.38, 127.89, 128.40, 136.13, 143.98, 159; FTIR (neat, KBr disc) ν (cm^{-1}) 3414, 3064, 3031, 3005, 2959, 2934, 2839, 1612, 1587, 1513, 1454, 1384, 1303, 1252, 1174, 1113, 1078, 1036, 915, 843, 806, 782, 739, 700, 649, 628; MS (EI) m/z (%): 214 (M^+, 51), 197 (100), 165 (5), 135 (28), 115 (5), 109 (75), 77 (38), 51 (18), 43 (8); (CI) m/z (%): 214 (M^+, 5), 197 (100), 135 (5), 105 (5), 94 (2), 65 (1), 44 (1).

4,7-Dimethyl-1-indanol: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.84 (bs, 1H, PhCH(O*H*)R), 1.97-2.11 (m, 1H, PhCH(O*H*)$CH_2C\mathit{H}_2$), 2.25 (s, 3H, Ph-$C\mathit{H}_3$), 2.30-2.44 (m, 1H, PhCH(O*H*)$C\mathit{H}_a$ H_bCH_2), 2.39 (s, 3H, Ph- $C\mathit{H}_3$), 2.67-2.81 (ddd, *J* = 3.2 Hz, 8.9 Hz, 16.43 Hz, PhCh(OH)$CH_2C\mathit{H}_aC\mathit{H}_b$), 3.00 (dd, *J* = 8.3 Hz, 16.3 Hz, PhCH(OH)$CH_2C\mathit{H}_aC\mathit{H}_b$), 5.26 (dd, 1H, *J* = 2.0 Hz, 6.5 Hz, PhC*H*(OH)R), 6.94 (d, 1H, *J* = 7.6 Hz, Ph-*H*), 7.01 (d, 1H, *J* = 7.6 Hz, , Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 17.93, 18.58, 28.79, 34.66, 75.59, 128.14, 129.45, 139.40, 132.17, 142.52, 142.68; FTIR (neat, KBr disc) ν (cm^{-1}) 3297, 3037, 2961, 2923, 2858, 1496, 1454, 1402, 1379, 1338, 1158, 1067, 1048, 979, 928, 891, 808; MS (EI) m/z (%): 162 (M^+, 62), 145 (100), 129 (23), 119 (15), 115(20), 103(6), 91 (23), 77 (20), 65 (14), 55(29), 41 (15); (CI) m/z (%): 162 (8), 145 (100), 129 (3), 119 (1), 105 (1), 91 (1), 65 (0.5).

1-Phenyl-3-butanol: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.32 (d, 3H, *J* = 6.2 Hz, $PhCH_2CH_2CH(OH)C\mathit{H}_3$) 1.80- 1.92 (m, 2H, $PhCH_2C\mathit{H}_2CH(OH)CH_3$), 2.12 (bs, 1H,

$PhCH_2CH_2CH(OH)CH_3$), 2.80 (sept,2H, J = 7.9 Hz, $PhCH_2CH_2$ $CH(OH)CH_3$), 3.91 (sex, 1H, $PhCH_2CH_2CH(OH)CH_3$), 7.24-7.43 (m, 5H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.45, 32.03, 40.71, 67.33, 125.70, 142.01; FTIR (neat, KBr disc) ν (cm^{-1}) 3064, 3028, 2966, 2929, 1604, 1496, 1455, 1375, 1261, 1126, 1029, 955, 908, 856, 800, 746, 699; MS (EI) m/z (%): 150 (M^+, 9), 132 (44), 117 (80), 91 (100), 77 (27), 65 (26), 45 (71); (CI) m/z (%): 168 (M^+ + 16, 100), 152 (M^+, 55), 132 (40), 117 (12), 108 (11), 91 (16), 65(5); HR-MS (EI) m/z: Calcd. for $C_{10}H_{14}O$: 150.0903. Found: 150.0902.

Trans-4-Phenyl-3-buten-2-ol: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.38 (d, 3H, J = 6.4 Hz, $PhCHCHCH(OH)CH_3$), 2.26 (bs, 1H, $PhCHCHCH(OH)CH_3$), 4.48 (dp, 1H, J = 0.9 Hz, 6.3 Hz, $PhCHCHCH(OH)CH_3$), 6.26 (dd, 1H, J = 6.3 Hz, 16.0 Hz, $PhCHCHCH(OH)CH_3$), 6.56 (d, 1H, J = 16.0 Hz, $PhCHCH(OH)CH_3$), 7.20-7.41 (m, 5H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.27, 68.68, 126.34, 127.47, 128.44, 129.16, 133.51, 136.61; FTIR (neat, KBr disc) ν (cm^{-1}) 3362, 3062, 3028, 2974, 2928, 2873, 1950, 1879, 1807, 1719, 1658, 1599, 1579, 1495, 1450, 1369, 1295, 1141, 1067, 968, 943, 877, 826, 750, 694; MS (EI) m/z (%): 148 (M^+, 63), 131 (66), 115 (26), 105 (100), 91 (49), 77 (37), 55 (15), 43 (71); (CI) m/z (%): 149 (3), 148 (1), 131 (100), 105(2), 91 (3), 78 (2), 55 (3), 43 (1).

1-Phenylpropan-2-ol: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.16 (d, J = 6.18, 3H, $PhCH_2CH(OH)CH_3$), 2.20 (bs, 1H, $PhCH_2CH(OH)CH_3$), 2.61 (dd, J = 11.8, J = 7.3, 1H, $PhCH_aH_bCH(OH)CH_3$); 2.70 (dd, J = 11.8, J = 7.4, 1H, $PhCH_aH_bCH(OH)CH_3$), 3.93 (m,

1H, $PhCH_2CH(OH)CH_3$), 7.29-7.07 (m, 5H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 22.60, 45.63, 68.74, 126.29, 127.36, 128.66, 129.00, 138.50.

1, 1-diphenylpropan-2-ol: ^1H NMR ($CDCl_3$, 200 MHz) δ 2.42 (d, J = 6.08, 3H, $Ph_2CHCH(OH)CH_3$), 2.89 (bs, 1H, $Ph_2CHCH(OH)CH_3$), 5.03 (d, J = 8.8, 1H, $Ph_2CHCH(OH)CH_3$), 5.78 (dq, J = 8.8, J = 6.1, 1H, $Ph_2CHCH(OH)CH_3$), 8.65-8.38 (m, 10H, $Ph_2CHCH(OH)CH_3$); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 14.02, 60.60, 70.03, 126.53, 126.88, 128.62, 128.85, 141.49, 142.49 ; MS (EI) m/z (%): 196, 195, 183, 168, 152, 128, 115, 91, 77, 65, 43; (CI) m/z (%): 230 (M^+ + 18 , 100), 212 (M^+ , 3), 195 (20), 183 (3), 167 (42), 152 (10), 128 (3), 115 (4), 105 (3), 91 (7), 76 (3).

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[15] **General experimental procedure for preparation of Mosher esters** (for (*S*)-1-phenylethanol)): (*S*)-1-phenylethanol (2 mg, 0.02 mmol) and MTPA-Cl (+) (4 μL, 0.02 mmol) were mixed with carbon tetrachloride (3 drops) and dry pyridine (3 drops). The reaction mixture was allowed to stand in a stoppered flask for 12 h at ambient temperature. Water (1 mL) was added and the reaction mixture transferred to a separatory funnel and extracted with ether (20 mL). The ether solution, after washing successively with HCl (1M, 20 mL), saturated sodium carbonate solution (20 mL), and water (20 mL) was dried with sodium sulfate, filtered and solvent was removed *in vacuo*. The residue was dissolved in deuterated chloroform for NMR analysis. The integration(s) of the hydrogen on the carbon bearing the hydroxyl group was used as a measure to assess the enantioselection. Also arrived at fluorine analysis of the Mosher ester. Dale, J. A.; Dull, D. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543.

Chapter 6

Stereoselective Reduction of Ketones by Bis-imidazole Ligand 1-Alkoxysilane Complexes: The Role of Imidazole in Nucleophilic Substitution at Silicon (Part B)

6.1 ABSTRACT

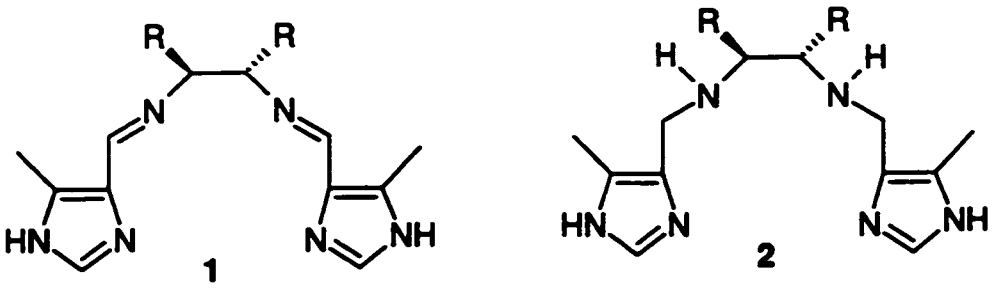
The reduction of carbonyl compounds with transient, hypervalent silicon hydrides is described. Trialkoxysilanes, upon activation by a catalytic amount of bis imidazole ligand **1**, reduced the carbonyl groups of various ketones. Enantiomerically enriched product alcohols were recovered in poor to excellent yield (20 - 91%) with e.e.'s ranging from 5-40%.

6.2 INTRODUCTION

One of the fundamental operations in organic synthesis remains the stereoselective reduction of carbonyl groups.[1] In a process related to that reported by Kagan and coworkers[2] and Hosomi *et al.*,[3] using hydrosilanes as the stoichiometric reductant and amino acid anions as the catalytic source of chirality, we demonstrated that a variety of ketones were reduced in good to excellent yield and with moderate stereoselectivity.[4] This process reduces the amount of chiral catalyst needed and utilizes catalysts from the chiral pool that can be exploited directly in their commercially available form. Our interest lies in the examination of the efficiency with which imidazole could be utilized to

facilitate the extracoordination[5] of hydrosilanes to produce species that would subsequently reduce carbonyl compounds. In particular, it was our objective to examine the ability of chiral imidazole species to confer stereoselectivity to the reduction. With this in mind we undertook the synthesis of compounds with the general structure displayed in **Figure 6. 1.**

Figure 6. 1: Bis-imidazole ligands



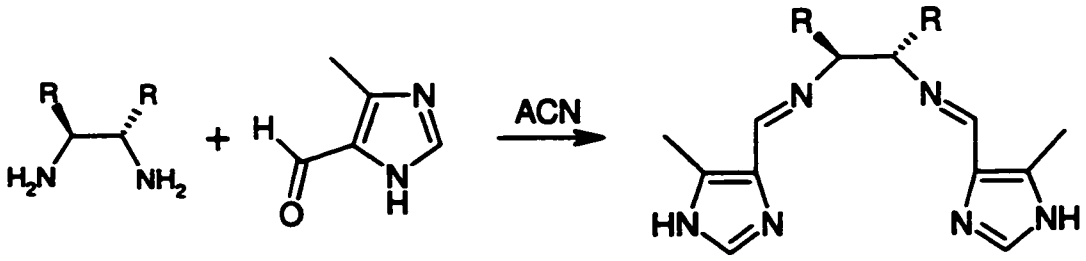
These structures contain a C_2-symmetry axis. The presence of this symmetry axis can serve the very important function of dramatically reducing the number of possible competing transition states.[6] Simply, the reagent and substrate experience the same chiral environment, independent of their trajectory of approach[7]. A number of workers have reported the successful application of reagents possessing a C_2-symmetry axis to confer chiral information to their reduction processes.[8,9,10,11,12] We wondered if such C_2-symmetric structures would further enhance the stereoselectivity of reduction.

We report herein our ongoing examination of imidazole derivatives from the chiral pool to transfer chiral information in the reduction of ketones.

6.3 Results and Discussion

Ligand **1** was readily prepared by Schiff base condensation of commercially available 4-methyl-5-imidazolecarboxaldehyde (2 equivalents) with *S,S*-1,2-diphenylethylenediamine in acetonitrile (**Scheme 6. 1**). The bisimine precipitated out of solution allowing the easy separation of the desired material (92-99%).

Scheme 6. 1: Synthesis of bis-imidazole ligand 1



1a: R = Ph

The extracoordinate hydrosilane **3** or **4** was prepared *in situ* by mixing the di-lithium salt of **1**, generated *in situ*, with trialkoxysilane **2** in tetrahydrofuran (THF) solution. The extracoordinate nature of the resulting silicon species was elucidated by an upfield ^{29}Si NMR shift upon mixing of these reagents (**Table 6.1**).

Table 6. 1: ^{29}Si NMR chemical shifts of silicon-imidazolide interaction

Entry	$HSiR_3$	Solvent	^{29}Si NMR (δ p.p.m.) Silane	Silane + L
1	$HSi(OMe)_3$ (2)	THF:TMEDA (30:1)	-56	-78

Subsequent addition of the ketone to the pentacoordinate species at 0 °C for 24 hours provided the necessary conditions to effect the reduction. A systematic screening of ketones was made with the di-lithium salt of 1 (5 mol %); the results are listed in **Table 6.2.**

Table 6. 2: Reduction of different ketones [a]

Entry	Ketone	$(RO)_2SiH$	Yield (%)[b]	e.e.(%)[c]
1	Acetophenone	$(MeO)_2SiH$ (2a)	70	26 (S)
2	4-(Trifluoromethyl)acetophenone	2a	91	23 (R)
3	4-Methyl-acetophenone	2a	73	22 (R)
4	4-Methoxy-acetophenone	2a	63	34 (S)
5	4-(Trifluoromethyl)benzophenone	2a	86	0 (S)
6	4-Methyl-benzophenone	2a	25	40 (S)
7	4-Methoxy-benzophenone	2a	20	5 (S)
8	4-Phenyl-2-butanone	2a	87	0
9	*trans*-4-Phenyl-3-buten-2-one	2a	91	23 (S)
10	Napthone	2a	58	34 (S)
11	Tetralone	2a	23	3 (S)

[a] All reactions were conducted with 5 mol % of the di-lithium salt of 1 as catalyst and 1 eq. of silane in THF/TMEDA = 30:1 solution. All reactions were run at 0 °C for 24 h. [b] Isolated yields, after chromatography on silica gel (pentane/ether=3:1). [c] Measured by ^1H NMR analysis of the Mosher ester of the corresponding alcohols.[13] Also measured by ^{19}F NMR of Mosher ester. Absolute configuration assigned from optical rotation of alcohol.

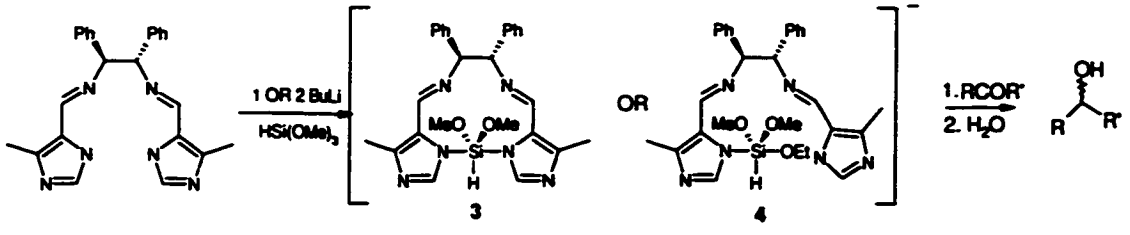
In examining the results presented in Table 6. 2, it is apparent that steric effects play a large role in the reduction process; the greater the steric demand around the ketone the less the yield of the product alcohol (comparing entries 1-2 with entries 10-11).

The enantioselectivity exhibited by this system is quite low. In the reduction of the acetophenone series, with the different steric requirements of the phenyl and methyl groups, it is not surprising that some level of stereoselectivity is observed, but what we found surprising is the low level of induction. Pertinent to the discussion of the structure of the intermediate is the observation that as the distal group on the acetophenone becomes more electron donating, the preference for facial reduction of the ketone increases: *p*-OMe (34) > *p*-Me (22) ~ *p*-CF_3 (23). Enantioselection, as expected, is quite

low in the benzophenone derivatives, where the only element for steric differentiation is far removed from the center to be reduced. To a larger degree, electronic effects appear to operate here as well. Somewhat surprisingly, different facial selectivity is observed in the reduction of the analogous compounds 4-phenyl-2-butanone, *trans*-4-phenyl-3-buten-2-one, tetralone, and naphthone (entries 8-11).

From the observations made above, a speculation of the mechanism of action is warranted. The intermediacy of a pentacoordinated silicon species, **3** or **4** must be included in the mechanistic discussion of the process owing to the upfield ^{29}Si NMR shift observed for this species (Table 6. 1). Moreover, in examining the ^{13}C NMR for the intermediate structure, there appears to be the loss of alkoxide from the parent silicon species. Based on these data, structure **3** is suggested to be the catalytically active species in this process. One consequence of this mechanism is that the alkoxide released from the initial process may act as a catalytic activator promoting achiral reduction, reducing the overall enantioselectivity of the process. Another difference in the selectivity with these catalysts, when compared to the amino acid derivatives, may be the large distance between the center of chemistry, the silicon, and the chirality which is relatively remote.

Scheme 6. 2: Proposed mechanism of the reduction process



A more complete description of the mechanistic implication of the imidazole-mediated reductions will be reserved for future communications from this laboratory.

6.4 CONCLUSIONS

The use of catalytic amounts of 1 (R = Ph) in the reduction protocol proved to be quite efficient in the reduction process, but produced lower *e.e.'s* than the histidyl anions previously reported by us.[4] Stereoselective hydrosilylation mediated by imidazole promoted activation of alkoxysilane was applied to a variety of ketones. The full scope of this procedure [4,14] has not been completely mapped out. The implication that the C_2-symmetric ligands promoted the reduction suggest that imidazole is participating in the reduction with histidine. This process and the mechanistic implications suggested by these results will form the subject of future communication.

6.5 EXPERIMENTAL

The following materials were obtained from Aldrich and were used without further purification: acetophenone, benzophenone, *n*-butyllithium (2M solution in cyclohexane), chlorodimethylsilane, naphthone, tetralone, 4-phenyl-2-butanone, dimethylformamide, absolute ethanol, *L*-histidine, imidazole, 4-methoxyacetophenone, 4-methoxybenzophenone, (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl (+)), 4-methylacetophenone, 4-methylbenzophenone, *N*-methylimidazole, *trans*-4-phenyl-3-buten-2-one, sodium borohydride, sodium sulfate, *N,N,N',N'*-

tetramethylethylenediamine (TMEDA), triethoxysilane, 4-(trifluoromethyl)acetophenone, trimethoxysilane and 4-(trifluoromethyl)benzophenone.

^{1}H NMR spectra were recorded on a Bruker AC-200 (at 200-MHz for protons) Fourier transform spectrometer. ^{13}C and ^{29}Si-NMR were performed on a Bruker AC-200 (50.32 and 39.7 MHz for carbon and silicon, respectively) or a Bruker AC-300 (at 75.44 MHz and 59.60 MHz for carbon and silicon, respectively). Chemical shifts are reported either with respect to tetramethylsilane as an external standard for ^{29}Si, set to 0 ppm, or $CHCl_3$ as an internal standard for protons, set at 7.24 ppm. Coupling constants (*J*) are recorded in Hertz (Hz). The abbreviations s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, are used to report spectra.

Electron impact (EI) and chemical ionization (CI, NH_3) mass spectra were recorded at 70 eV with a source temperature of 200 °C on a VG analytical ZAB-R mass spectrometer equipped with a VG 11-250 data system. High resolution mass spectral (HRMS) data were obtained using the EI method. Infrared spectra were run as KBr pellets or as liquid films on NaCl discs (as indicated) on a Perkin-Elmer 283 spectrometer or on a BIORAD FTS-40 spectrometer as a neat film.

All solvents were thoroughly dried before use: acetonitrile was dried over P_2O_5; THF was dried from K/benzophenone. All reactions were carried out in dry apparatus under a nitrogen atmosphere with the use of septa and syringes for the transfer of reagents.

6.5.1 *N,N'*-bis(4-methyl-5-imidazole carboxaldehyde)-1*S*,2*S*- diphenyl-ethanediamine (1):

To a dry 100 ml round-bottomed flask flushed with nitrogen was added 4-methyl-5-imidazolecarboxaldehyde (0.52 g, 4.71 mmol), 1*S*,2*S*-(-)-1,2-diphenylethylenediamine (0.5 g, 2.35 mmol), and acetonitrile (50 ml). The resulting solution was stirred overnight at ambient temperature, during which time the product precipitated out of solution. The product was filtered, washed with acetonitrile and dried under vacuum to yield 0.92 g (99%) (m.p. 145-146 °C). ^{1}H NMR ($CDCl_3$-MeOD, 500 MHz) δ 2.19 (s, 6H, IM-C*H*$_3$), 4.63 (s, 2H, PhC*H*N), 7.10-7.33 (m, 10H, Ph-H), 7.56 (s, 2H, IM-*H*), 7.97 (s, 2H, N=C*H*); ^{13}C NMR ($CDCl_3$-MeOD, 500 MHz) δ 11.98, 12.14, 81.06, 126.88, 127.11, 128.10, 128.44, 128.50, 128.60, 136.32, 141.36, 150.97; FTIR (KBr disc): ν (cm^{-1}) 3396, 3190, 3119, 3068, 2924, 2861, 1642, 1603, 1494, 1453, 1394, 1353, 1244, 1116, 1047, 1027, 954, 816, 765, 701; MS (EI) m/z (%): 396 (M^+, 1), 287 (4), 262 (0.5), 198 (100), 194 (45), 165 (6), 116 (18), 91 (41), 77 (29), 43 (72); MS (CI) m/z (%): 414 (M^++18, 1), 396 (M^+, 2), 393 (23), 305 (9), 288(9), 249 (2), 223 (8), 200 (38), 146 (9), 129 (15), 106 (100), 79 (44), 43 (32).

6.5.2 General Procedure for Reduction (example acetophenone):

Trimethoxysilane 2b is a rather toxic compound and therefore care must be taken in its handling. It is available commercially (Aldrich) and can be handled without problems via syringe techniques. To a dry 100 ml round-bottomed flask flushed with

nitrogen was added 1 (40 mg, 0.10 mmol) and THF (30 ml). The mixture was cooled to –78 °C before the slow addition *n*-butyl lithium (1.6 M, 0.20 ml, 0.2 mmol). The resulting reaction mixture was stirred at –78 °C for 5 min and then allowed to warm up to 0 °C. TMEDA (1.0 ml, 6 mmol) was added and the mixture was stirred for 10 min, then trimethoxysilane (0.38 ml, 3 mmol) was added and stirring continued for additional 10 min. Finally acetophenone (0.35 mL, 3 mmol) was added and the reaction mixture was kept at 0 °C for 24 h. The reaction was quenched by the addition of sodium hydrogen carbonate (0.1 M, 20 mL) and the mixture was stirred vigorously for 30 min at room temperature. The biphasic system was transferred to a separatory funnel and extracted with ether (3 * 40 ml). The ether was removed without drying and the resulting crude product was purified by column chromatography on silica gel eluting with pentane/ether (3:1), to give (*S*)-phenethyl alcohol (0.31 g, 85%) as a colorless liquid. Spectral analysis was conducted and provided the same information presented in Chapter 5.

1, 2, 3, 4-Tetrahydro-1-naphthol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.92-2.09 (m, 4H), 2.27 (bs, 1H, O*H*), 2.64-2.87 (m, 2H), 4.75 (m, 1H, C*H*OH), 7.07-7.44 (m, 4H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 18.76, 29.17, 32.21, 68.02, 126.05, 127.43, 128.55, 128.87, 137.00, 138.78; FTIR (neat, KBr disc) ν (cm^{-1}) 3399, 3063, 3022, 2934, 2866, 2839, 1684, 1605, 1490, 1454, 1341, 1283, 1067, 1037, 1002, 963, 774, 739; MS (EI) m/z (%): 148 (M^+, 35), 147 (33), 131 (100), 130 (98), 120 (76), 119 (68), 115 (28), 105 (44), 91 (85), 77 (24), 65 (26), 51 (29), 41 (17); (CI) m/z (%):148 (M^+, 53), 147 (20), 131 (100), 130 (69), 120 (26),

119 (36), 105 (21), 91 (33), 78 (4), 65 (7).

1-Phenyl-1-butanol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.91 (t, J = 7.1 Hz, 3H, PhCHOHCH$_2$CH$_2$C*H$_3$*), 1.15-1.47 (m, 2H, PhCHOHCH$_2$C*H$_2$*CH$_3$); 1.60-1.80 (m, 2H, PhCHOHC*H$_2$*CH$_2$CH$_3$); 2.08 (bs, 1H, O*H*), 4.64 (t, J = 6.4 Hz, PhC*H*OH), 2.27-7.31 (m, 5H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 13.88, 18.97, 41.21, 74.33, 125.85, 127.37, 128.34, 144.95; FTIR (neat, KBr disc) ν (cm^{-1}) 3387, 3064, 3031, 2960, 2933, 2873, 1494, 1455, 1380, 1310, 1200, 1105, 1062, 1028, 962, 904, 858, 762, 700; MS (EI) m/z (%): 150 (M^+, 6), 133 (6), 107 (100), 91 (9), 79 (70), 63 (3), 49 (31); (CI) m/z (%): 168 (M^+ + 18,3), 150 (M^+, 58), 133 (100), 107 (7), 91 (40), 77 (9), 43 (7); HR-MS (CI) m/z: Calcd. for $C_{10}H_{14}O$: 150.0903. Found: 150.0947.

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[13] **General experimental procedure for preparation of Mosher esters** – These analysis was conducted as outlined in Chapter 5.

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Chapter 7

Stereoselective Reduction of Ketones Using Extracoordinate Silicon: C_2-Symmetric Ligands*

7.1 ABSTRACT

Several C_2-symmetric diimidazole ligands were prepared by forming amides or imines from suitably functionalized imidazole derivatives. Extracoordinate silanes were formed by the addition of imidazolide anions to trialkoxysilanes; neutral imidazoles did not lead to observable extracoordination as judged by ^{29}Si NMR. The extracoordinate hydrosilanes enantioselectively reduce prochiral ketones with good yield and moderate to good stereoselectivity (up to 70 % e.e.). However, the induction observed with these C_2-symmetric ligands was comparable to that observed with catalysis by simple amino acids. The mechanistic implications of these observations are discussed.

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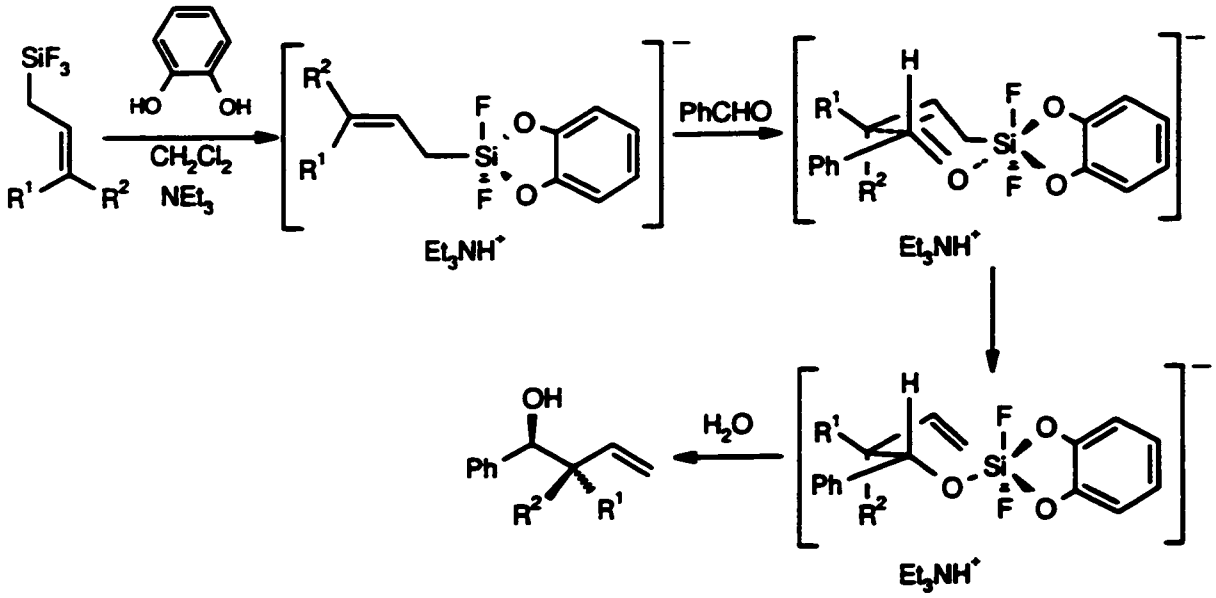
7.2 INTRODUCTION

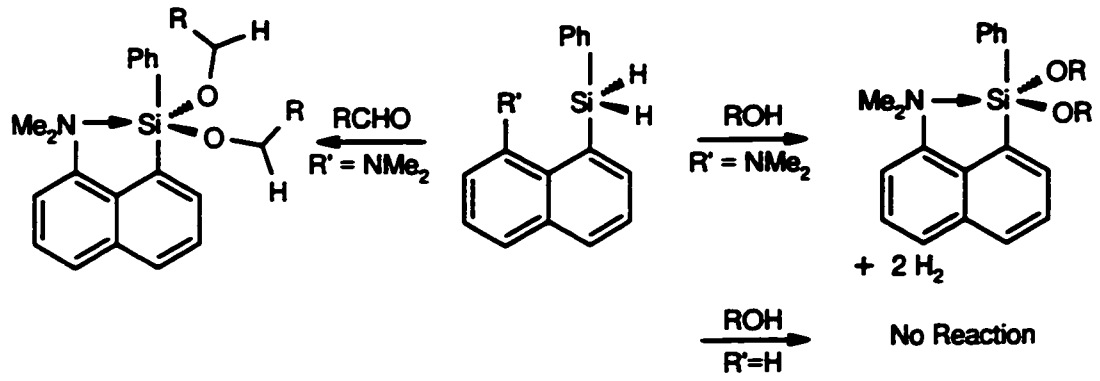
Over the past two decades, a much deeper understanding of the mechanisms of reactions at silicon has evolved. In particular, the importance of extracoordinate species has become very clear in nucleophilic substitution processes at silicon.[1] Upon expansion from 4- to 5-coordination, silicon becomes much more susceptible to further nucleophilic attack. At the same time, the ligands attached to silicon become more nucleophilic.

These effects have been most profitably exploited in the reactions of hydrosilanes and allylsilanes. For example, Kira and coworkers have demonstrated the diastereoselective allylation of aldehydes using pentacoordinate silanes (**Scheme 7.1**).[2] The pentacoordinate silicon likely undergoes further expansion to the hexacoordinate system that, in analogy to the Zimmerman-Traxler transition state of the aldol reaction, reacts intramolecularly to form the homoallylic alcohol. In analogy, Corriu and coworkers demonstrated that hydrosilanes, extracoordinate by virtue of an intramolecular dative bond, are rather reactive to alcoholysis, whereas the 4-coordinate analogues are relatively unreactive (R=H), particularly at neutral pH (**Scheme 7. 2**).[3]

Scheme 7. 1: Zimmerman-Traxler transition state of the allyl-transfer reactions



Scheme 7. 2: Change in reactivity of pentacoordinate silicon species



Many catalysts are known to activate silicon to nucleophilic substitution via extracoordinate intermediates. The best known, especially among organic chemists, is

fluoride, which is routinely used to remove silyl protecting groups.[4] However, many other silaphilic compounds including a variety of nitrogen heterocycles are almost as effective in this role.[5] Imidazole, in particular, is frequently used to facilitate nucleophilic substitution at chlorosilanes in the preparation of silyl ethers.[6]

The ability to activate hydrosilanes to reaction, using an organic catalyst to form an extracoordinate complex, provides a synthetic opportunity; one may use a variety of triggers to stimulate selective reactions, including those that can provide chiral induction. Some examples of this approach are known. For instance, Fujita and Hiyama demonstrated that the intramolecular reduction of ketones, likely via bidentate intermediates, occurs stereoselectively.[7] Schiffers and Kagan have described the use of the monoanion of enantiopure binaphthol as both an activator of hydrosilanes and as a chiral steering group in the reduction of ketones such as acetophenone (e.e. 61%).[8] Hosomi and coworkers showed that dianions of β-diols and β-aminoalcohols may be used in a similar fashion (e.e. 22-49%, yield 44-99%).[9]

We have been interested in the development of imidazole ligands that will activate organosilanes to nucleophilic substitution and, simultaneously, provide a chiral environment for the process. Recently, we published our first experiments in the utilization of histidine derivatives for the stereoselective reduction of carbonyl groups.[10] In this paper, we compare those results with the reductions of ketones catalyzed by C_2-symmetric dihistidine derivatives and a series of related C_2-symmetric ligands not derived from the chiral pool.

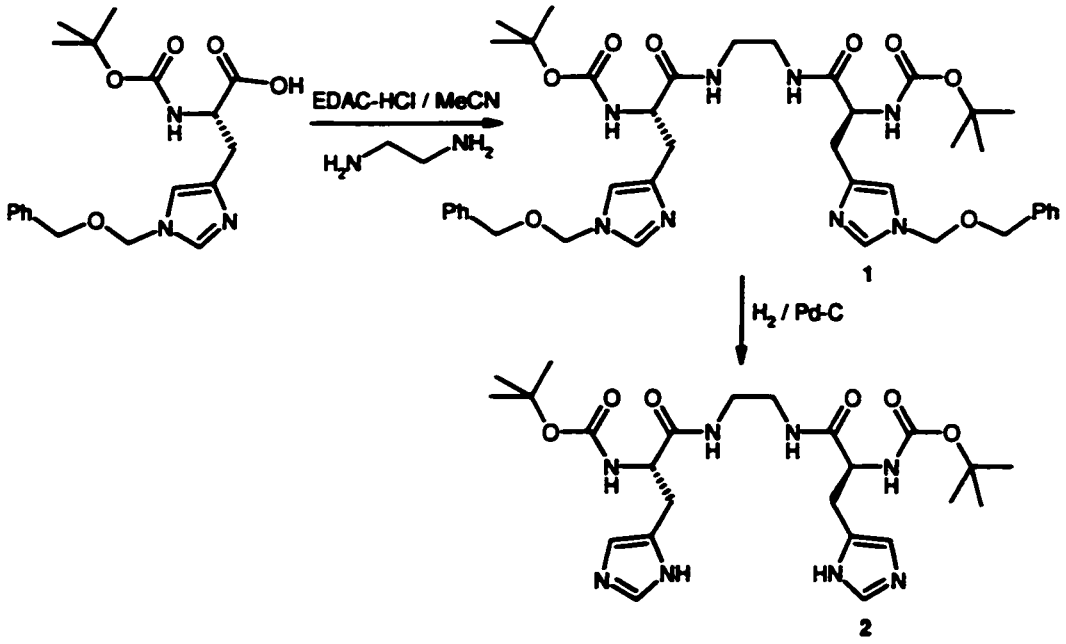
7.3 RESULTS

The syntheses of all of the ligands described below involved the condensation of ethylene diamine and related derivatives with suitably functionalized imidazoles. Two different reactions were used for attachment, amidation and imine formation.

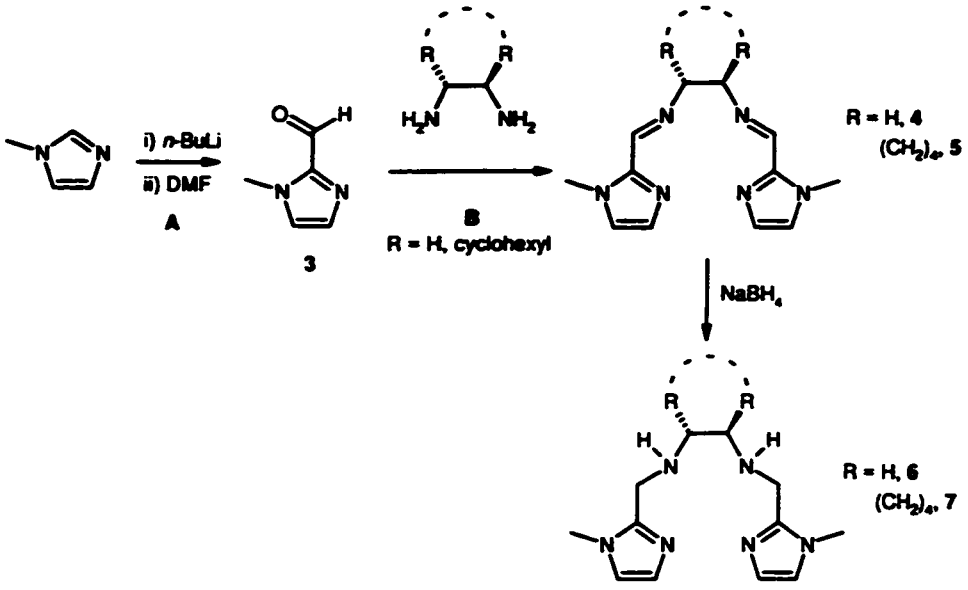
The preparation of the dihistidyl ligand **1** involved EDAC-HCl coupling of ethylene diamine and the commercially available *N*-α-*t*-BOC-π-*N*-benzyloxymethyl-*L*-histidine in acetonitrile. This reaction is quite elegant, in that the initially insoluble histidine derivative is made soluble with the addition of the diamine; during the course of the reaction the product precipitates out of solution. The urea that develops during the course of the reaction is soluble in acetonitrile. Therefore, the product could be obtained by filtration and washing with cold solvent. The free diimidazole **2** was accessible by hydrogenation of **1** using a Pd-C catalyst (**Scheme 7. 3**).

The remaining diimidazole derivatives were prepared from imidazole carboxaldehydes. These are either commercially available or can be readily prepared from the anionic carbonylation of imidazoles using DMF. Thus, *N*-methylimidazole can be converted to **3** (**Scheme 7. 4A**).

Scheme 7. 3: Synthesis of Bis-histidine ligand 2

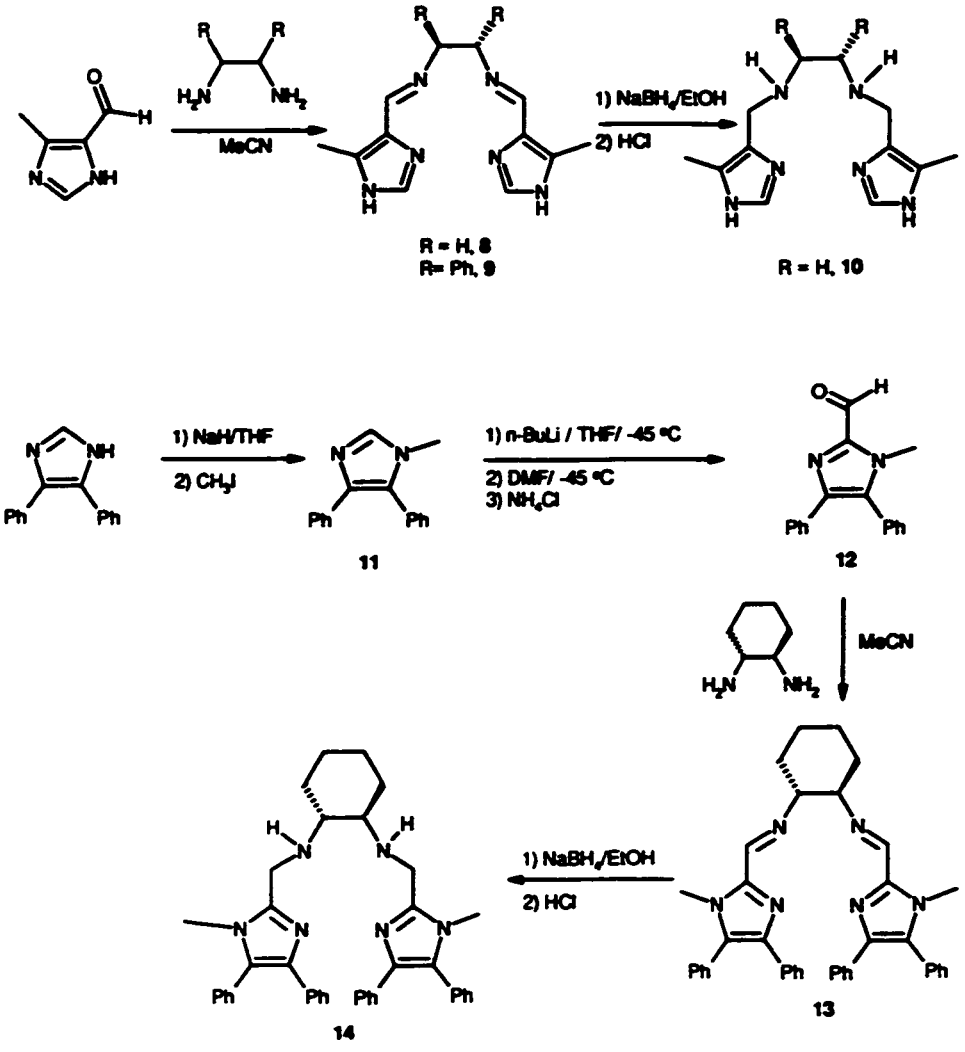


Scheme 7. 4: Synthesis of bis-imidazole ligands 4 and 5



Transformation of the imidazole derivatives to the C_2-symmetric ligands simply involved reaction with ethylenediamine derivatives to give **4** and **5**. The Schiff base could be used directly as a ligand or converted by borohydride reduction into the diamine derivatives **6**, **7** (**Scheme 7. 4B**). In an analogous fashion, a variety of other C_2-symmetric diimidazole derivatives were prepared (**8-10**, and **13**, **14**, **Scheme 7. 5**).

Scheme 7. 5: Synthesis of bis-imidazole ligands 10 and 14



7.5.1 The Question of Extracoordination

^{29}Si NMR is extremely sensitive to the degree of coordination at silicon. Bassindale and coworkers, for instance, have extensively used ^{29}Si NMR to examine the conditions under which an expansion of coordination from 4 to 5 occurs at silicon: an approximately 30 ppm upfield shift normally accompanies this change.[11] We therefore used ^{29}Si NMR to examine the circumstances under which the ligands described above would induce extracoordination.

Neutral imidazole derivatives, including some commercially available imidazole derivatives and those described above that we prepared, were not sufficiently nucleophilic to induce observable coordination expansion with triethoxysilane as the functional hydrosilane. In all cases, the ^{29}Si NMR chemical shifts were unchanged from approximately -59 ppm (**Table 7. 1**). However, extracoordination readily occurred with the more potent nucleophiles, the imidazolide anions. While the presence of TMEDA improved the yields of the reduction products described below, it did not affect the ^{29}Si NMR chemical shifts (**Table 7. 1**). In some cases, both one and two equivalents, respectively, of base were added. The ^{29}Si NMR data was shown to be independent of the number of equivalents of base added.

Table 7. 1: ^{29}Si NMR chemical shifts of products of hydrosilane: imidazolide reactions

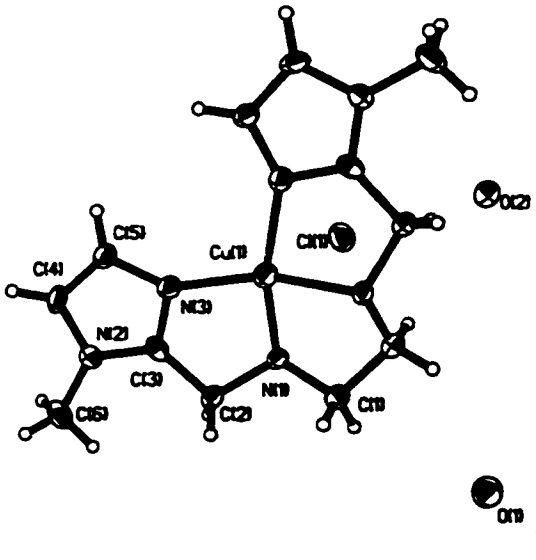
Entry	$HSiR_3$	Solvent	Silane	L[a]	$HSiR_3$ + L
1	$HSiMe_2Cl$	$CHCl_3$:hexane	12	NMI	-81[b]
2	$HSi(OEt)_3$	THF	-59	Li-Im	-83
3	$HSi(OMe)_3$	THF/ TMEDA (30:1)	-56	Li-Im	-79
4	$HSi(OMe)_3$	THF/ TMEDA (30:1)	-56	Li-His	-79
5	$HSi(OMe)_3$	THF/ TMEDA (30:1)	-56	Li_2-His	-79
6	$HSi(OEt)_3$	THF/ TMEDA (30:1)	-59	Li-2	-78
7	$HSi(OEt)_3$	THF/ TMEDA (30:1)	-59	Li_2-2	-78
8	$HSi(OEt)_3$	THF/ TMEDA (30:1)	-59	Li-9	-79
9	$HSi(OEt)_3$	THF/ TMEDA (30:1)	-59	Li_2-9	-79

[a] Li implies monoanion, Li_2 the dianion of the ligand formed by deprotonation of the NH of the imidazole ring.

[b] Reported by Bassindale *et al.*[5] and subsequently remeasured by us.

All attempts to crystallize extracoordinate silicon compounds, to determine their detailed structure, have been fruitless to date. However, it was possible to form a copper complex **15** from **10** and determine the crystal structure.[12] The copper ion is found within the body of the ligand (Figure 7. 1). Four short in-plane bonds (1.9370-1.9903 Å) are formed between copper and all four nitrogen atoms N(2), N2(A), N(3), and N3(A) of the tetradentate ligand. This structure suggests that it is reasonable for one or more of the chain- or ring-bound nitrogen ligands in **10** to bind to a silicon atom in extracoordinate complexes derived from, **10** and other diimidazole ligands.

Figure 7. 2: ORTEP drawing of the structure of 15.



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7.5.2 Reduction

Extracoordinate hydrosilanes are more reactive towards a variety of electrophiles than their 4-coordinate counterparts (e.g., **Scheme 7. 2**). It was noted above that none of the neutral imidazole derivatives induced observable extracoordination of triethoxysilane (or trimethoxysilane). It was not surprising, therefore, that when these mixtures were exposed to ketones such as acetophenone, no reaction was observed to occur.

By contrast, when activated by catalytic amounts of imidazolide anions, triethoxysilane efficiently reduced a variety of ketones. We chose acetophenone as a test ketone for the comparison of the yields and enantioselectivities of reductions with various C_2-symmetric imidazolides (**Table 7. 2**): the enantioselectivity was determined, once the products were converted to the Mosher esters, using the relative areas of the two product enantiomers in the ^{1}H NMR and ^{19}F NMR. Note that, as was observed with the NMR

data, the enantioinduction was independent of the number of equivalents of base added to the imidazole catalyst.

The role of simple amino acids in inducing enantioselective reduction was also investigated. Histidine, an imidazole-containing amino acid, and phenylalanine were both examined in this regard. As can be seen, the simple amino acids lead to lower induction than the bidentate di-imidazole derivatives.

Table 7. 2: Reduction of Acetophenone by $HSi(OEt_3)$ in the Presence of Imidazolide Anions

Entry	Imidazolide	Mol% imidazolide	Yield	e.e. (product configuration)
1	Li-**2**	5	55	56 (*S*)
2	$HSi(OMe)_3$	100	0	-
3	Li-**9**	5	70	26 (*S*)
4	Li_2-**9**	5	73	30 (*S*)
5	Li-His[a]	10	75	26 (*S*)
6	Li_2-His	10	85	26 (*S*)
7	Li-Phe	100	71	25 (*S*)

[a] $HSi(OMe)_3$ was used for the reduction.

Several other ketones were reduced by $HSi(OEt)_3$ in the presence of catalytic amounts of histidyl mono- or dianions. The yields and enantioselectivities are shown in **Table 7. 3.** The yields of reduction are quite reasonable in all cases favouring, with one exception, the *S*-alcohol. Among the acetophenones that were reduced, there is a correlation between the observed e.e. and the electron density of the ketone: electron donors led to higher induction (entries 2-5). By contrast, the benzophenone derivatives gave poor

e.e.'s, the magnitudes of which improved with electron donating groups (entries 7-9). Perhaps it is surprising that there is any induction at all in the case of the benzophenones, as there is no source of steric discrimination at the ketone centre. Instead, it is the interaction of the chiral ligand with a prochiral electronic environment that leads to enantioinduction.

Table 7. 3: Reduction of different ketones [a]

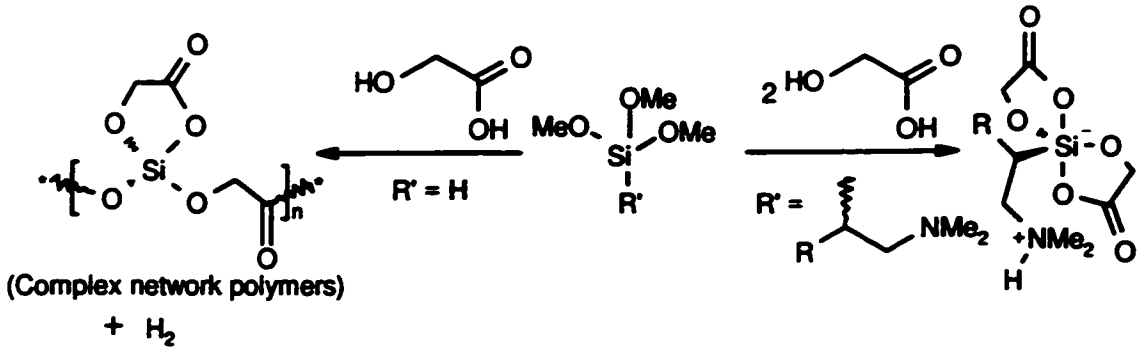
Entry	Ketone	$(RO)_3SiH$	Yield (%)[b]	e.e.(%)[c]
1	Acetophenone	$(EtO)_3SiH$	70	26 (*S*)
2	Acetophenone	$(MeO)_3SiH$[d]	85	26 (*S*)
3	4-(trifluoromethyl)acetophenone	$(MeO)_3SiH$	86	30 (*S*)
4	4-methylacetophenone	$(MeO)_3SiH$	80	40 (*S*)
5	4-methoxyacetophenone	$(MeO)_3SiH$	89	70 (*S*)
6	Benzophenone	$(MeO)_3SiH$	90	N.A.[e]
7	4-(trifluoromethyl)benzophenone	$(MeO)_3SiH$	95	30 (*S*)
8	4-methylbenzophenone	$(MeO)_3SiH$	82	5 (*S*)
9	4-methoxybenzophenone	$(MeO)_3SiH$	78	5 (*S*)
10	4,7-dimethyl-1-indanone	$(MeO)_3SiH$	66	30 (*R*)
11	4-phenyl-2-butanone	$(MeO)_3SiH$	91	28 (*R*)
12	*Trans*-4-phenyl-3-buten-2-one	$(MeO)_3SiH$	78	70 (*S*)
13	Phenylacetone	$(MeO)_3SiH$	90	N.M.[f]

[a] All reactions were conducted with 10 mol % of the di-lithium salt of *L*-histidine as catalyst and 1 eq of silane in THF/TMEDA = 30:1 solution. All reactions were run at 0 °C for 24 h. [b] Isolated yields, after chromatography on silica gel (pentane/ether=3:1). [c] Measured by ^1H NMR analysis of the Mosher ester of the corresponding alcohols. Also measured by ^{19}F NMR of Mosher ester. Absolute configuration assigned from optical rotation of alcohol. [d] One equivalent of histidine monoanion was added. [e] Not applicable. [f] Not measured.

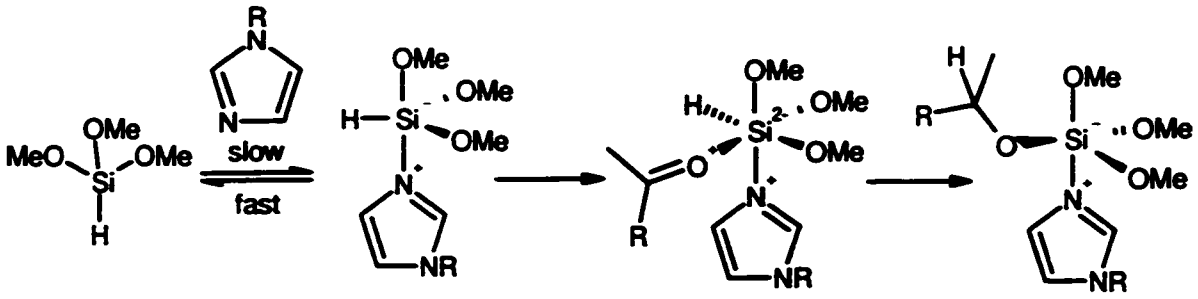
7.4 Discussion

The facility of trialkoxysilanes to undergo extracoordination lies between that of trialkyl- and trihalosilanes.[13] While even weakly coordinating bidentate nucleophiles, such as α-hydroxyacids (**Scheme 7. 6A**,[14] B[15]), react with hydrotrialkoxysilanes to rapidly lead to new alkoxysilanes via nucleophilic substitution, only with more powerful *mono*dentate nucleophiles will extracoordination result. Consistent with this, triethoxysilane neither displayed any evidence of extracoordination nor of reactivity towards ketones in the presence of any of the neutral imidazole derivatives we examined. The absence of reactivity likely reflects a low rate of addition of the imidazole to give the generally more reactive pentacoordinate species **16** (or a low equilibrium constant).

Scheme 7. 6: Extracoordination facilitated by α-hydroxyacids



Scheme 7. 7: Reduction profile initiated by imidazole



16

Triethoxysilane readily underwent coordination expansion with the different imidazolide anions that we used, as was clearly shown by ^{29}Si NMR. Predictably, these intermediates efficiently converted ketones to alkoxysilanes. This result suggests the most important difference between imidazoles and imidazolides occurs in the formation of **16** rather than in subsequent reactions (**Scheme 7.7**). Similarly, mono- and dianions of histidine and the monoanion of phenylalanine induced both extracoordination and reduction of acetophenone.

While little structural information for the reactive extracoordinate silanes is available, it is useful to try to develop a model that explains the observed stereoselectivity in reduction. Several factors contribute to our understanding of this picture:

i) imidazoles are not sufficiently active nucleophiles to form extracoordinate compounds from $HSi(OEt)_3$;

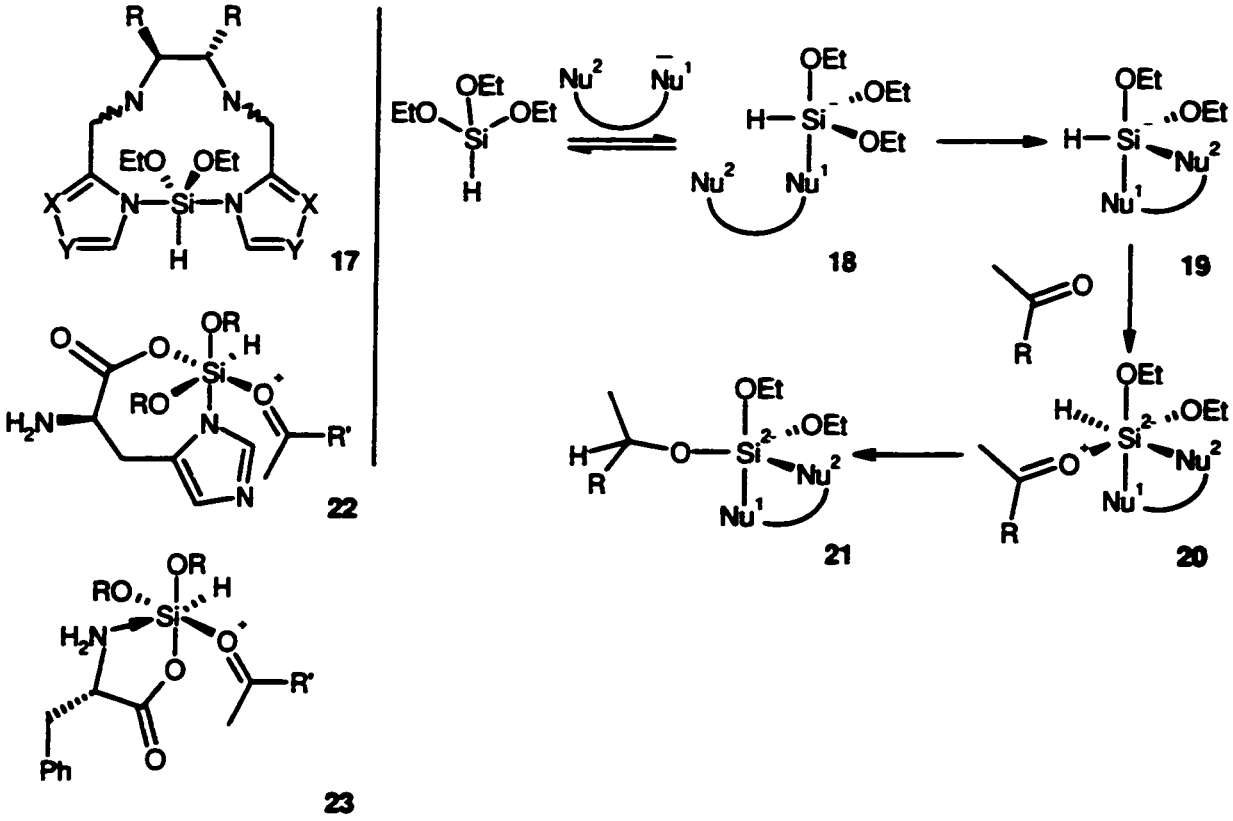
ii) the crystal structure of **15**;

iii) pentacoordinate silanes are known to possess more electronegative ligands and greater receptivity towards nucleophiles than the analogous 4-coordinate silanes;

iv) the absence of differences in the ^{29}Si NMR spectra and reactivity of the monoanion and dianions derived from **2**, **9** and of histidine.

From the crystal structure of copper compound **15** we learn that all four nitrogens are, in principle, available for binding to silicon. However, it is unlikely that such tetradentate bonding is occurring at silicon - it would involve exchange of all the alkoxy groups by nitrogen. However, this datum shows that *trans*-diimidazole binding, as in **17**, is structurally reasonable. Imidazoles will not activate $HSi(OEt)_3$ to extracoordination. However, once an imidazolide (or carboxylate, see below) anion adds to give a pentacoordinate silane, either nucleophilic substitution **18** or further complexation to give a bidentate system **19** could occur (**Scheme 7. 8**). This would explain the absence of difference between mono- and dianion catalysts: in either case once extracoordinate silicon is formed, substitution/nucleophilic addition is facilitated. That is, $HSi(OEt)_3$ is converted to **19**, which subsequently undergoes addition of the ketone **20** and then internal hydrogen transfer, **21**. One of our future objectives is to examine the nucleophilic substitution of such compounds (e.g., $RR'SiX_2 \rightarrow$ **18** $\rightarrow$ **19**, **Scheme 7. 8**) using different leaving groups than OEt to determine if this hypothesis is viable.

Scheme 7. 8: Proposed reaction mechanism observed for reductions initiated by C_2 bis-imidazole ligands and amino acids



In such a model, the chiral environment is provided by a single stereogenic centre (histidine **22**, phenylalanine **23**) or a pair of stereogenic centres (**17**, **Scheme 7. 8**). We speculate, based on known trends of reactivity of extracoordinate silanes, that the major intermediates are more likely to have the bidentate structures shown, with axial imidazole or carboxylate groups, respectively, although we are currently focussing on better characterized materials that will hopefully address this question explicitly. Note that other structural isomers (other equatorial/axial *cis* and equatorial/equatorial *cis*, etc) may also be energetically reasonable. This model would predict that the single stereogenic centre of the histidine and phenylalanine-complexed silane more efficiently transfers chiral information than the more distal pair of chiral centres in the C_2-symmetric ligands. Designing ligands in which the

centres of chirality are located closer to the central silicon atom using C_2-systems will be the focus of future reports from this laboratory.

7.5 Experimental Section

7.5.1 Reagents and Physical Methods

The following materials were obtained from Aldrich and were used without further purification: acetophenone, benzophenone, *n*-butyllithium (2M solution in cyclohexane), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDAC-HCl), chlorodimethylsilane, 4,7-dimethyl-1-indanone, dimethylformamide, absolute ethanol, *L*-histidine, imidazole, 4-methoxyacetophenone, 4-methoxybenzophenone, (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl (+)), 4-methylacetophenone, 4-methylbenzophenone, *N*-methylimidazole, 4-phenyl-2-butanone, *trans*-4-phenyl-3-buten-2-one, sodium borohydride, sodium sulfate, *N,N,N',N'*-tetramethylethylenediamine (TMEDA), triethoxysilane, 4-(trifluoromethyl)acetophenone, trimethoxysilane and 4-(trifluoromethyl)benzophenone.

^{1}H NMR spectra were recorded on a Bruker AC-200 (at 200-MHz for protons) Fourier transform spectrometer. ^{13}C and ^{29}Si-NMR were performed on a Bruker AC-200 (50.32 MHz and 39.7 for carbon and silicon, respectively) or a Bruker AC-300 (at 75.44 MHz and 59.60 MHz for carbon and silicon, respectively), respectively. Chemical shifts are reported either with respect to tetramethylsilane as an external standard, set to 0 ppm, or $CHCl_3$ as an internal standard, set at 7.24 ppm. Coupling constants (J) are recorded in

Hertz (Hz). The abbreviations s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, are used to report spectra.

Electron impact (EI) and chemical ionization (CI, NH_3) mass spectra were recorded at 70 eV with a source temperature of 200 °C on a VG analytical ZAB-R mass spectrometer equipped with a VG 11-250 data system. High resolution mass spectral (HRMS) data were obtained using the EI method. Infrared spectra were run as KBr pellets or as liquid films on NaCl discs (as indicated) on a Perkin-Elmer 283 spectrometer or on a BIORAD FTS-40 spectrometer as a neat film.

All solvents were thoroughly dried before use: acetonitrile was dried over P_2O_5; THF was dried from Na/benzophenone. All reactions were carried out in dry apparatus under a nitrogen atmosphere with the use of septa and syringes for the transfer of reagents.

7.5.2 General Procedure for the Data Reported in Table 7. 1

To a dry 25 ml round-bottomed flask flushed with nitrogen was added *L*-histidine (0.23 g, 1.5 mmol) and THF (15 ml). At ambient temperature *n*-butyl lithium (1.1 ml, 1.5 mmol, 1.4 M solution in hexane) was added slowly and the resulting suspension was stirred for 20 min at room temperature, cooled to 0 °C and TMEDA (0.5 ml) was added. The mixture was stirred for an additional 10 min, after which time trimethoxysilane (0.20 ml, 1.5 mmol) was added. The system was stirred for 10 min at 0 °C. A 3 ml aliquot was taken and placed into a 5 mm NMR tube where it was placed in the probe tuned for ^{29}Si

for analysis. Variable temperature NMR was conducted on these samples. Data obtained from analysis are shown in Table 1.

Bis(*N*-BOC-*N'*-benzyloxymethylhistidine)ethylenediamide 1:

To a dry 50 ml round-bottomed flask flushed with nitrogen was added *N*-α-*t*-BOC-*N*-π-benzyloxymethyl-*L*-histidine (0.62 g, 1.66 mmol) and acetonitrile (12 ml). To this heterogeneous mixture was added ethylenediamine (0.06 ml, 0.83 mmol). This produced a homogenous colourless solution, which was cooled to 0 °C, before the addition of EDAC-HCl (0.33g, 1.74 mmol). The mixture was stirred for 30 min at 0 °C, at which time the cooling bath was removed. The mixture was allowed to stir overnight at ambient temperature. Within 3 h of stirring at room temperature, the product began to precipitate out of solution. The product was collected by filtration and washed with cold acetonitrile, dissolved in chloroform (30 ml) and washed with water (3 x 10 ml) and brine (2 x 10 ml). The organic layer was dried with sodium sulfate, filtered, and solvent was removed *in vacuo* to produce 0.58 g (91%) of the desired product (m.p. 175-176 °C).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.39 (s, 18 H, *t*-Bu), 3.05 (m, 4H, CH_2-Im), 3.14 (bs, 4H, PhCH_2OCH_2), 4.30 (dd, J = 7.2 Hz, 7.4 Hz, α-CH), 4.48 (s, 4H, PhCH_2OCH_2), 5.30 (s, 4H, HN (CH_2)$_2$NH), 5.53 (d, J = 8.1 Hz, N*H*-*t*-BOC), 6.51 (bs, 2H, *H*N(CH_2)$_2$N*H*), 6.85 (s, 2H, Im-H), 7.30-7.31 (m, 10 H, Ph-H), 7.48 (s, 2H, Im-H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 178.85, 171.60, 155.49, 138.29, 135.97, 129.15, 128.69, 128.36, 128.08, 127.40, 80.28, 73.11, 69.98, 54.00, 39.29, 28.27, 26.87; FTIR (KBr disc): ν (cm^{-1}) 3332, 3090, 2998, 2914, 2879, 2805, 2679, 2056, 1679, 1665, 1544, 1522, 1503, 1368, 1233, 1085,

1074, 922; Electro-spray MS (MeOH/AcCN/H_2O) m/z (%) 775 (M^+, 20), 655 (3), 555 (3), 388 (100), 360 (23), 91 (15).

Bis(*N*-BOC-histidine)ethylenediamide 2

To a dry 100 ml round-bottomed flask equipped with a three necked inlet adapter, flushed with nitrogen, was added **1** (0.70 g, 0.90 mmol), Pd/C (10 % Pd, 100 mg) and 80% aqueous acetic acid (40 ml). The solution was evacuated several times (5) with a water aspirator and hydrogen was put into the system via a balloon. After final evacuation and inoculation with hydrogen gas, the system was allowed to stir overnight over a blanket of hydrogen gas supplied by two filled balloons. Filtration of the reaction mixture over a bed of Celite was followed by the evaporation of the solid yellow residue. The product was recrystallized using methanol and acetonitrile (by solvating of the product in the minimum amount of methanol followed by the slow addition of the poor solvent acetonitrile until near the crystallization point). The product was obtained after placing the system into the fridge overnight (0.4g, 83%, m.p. 283-284 °C dec.).

^{1}H NMR (MeOD, 200 MHz) δ 1.17 (s, 18H, *t*-Bu), 2.96 (m, 4H, CH_2-Im), 3.04 (s, 4H, HN (CH_2)$_2$NH), 4.05 (m, 2H, α-CH), 6.76 (s, 2H, Im-H), 7.65 (s, 2H, Im-H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 180.21, 174.32, 157.55, 135.95, 134.03, 80.82, 56.10, 40.03, 28.64; FTIR (KBr disc): ν (cm^{-1}) 3446, 3190, 3012, 2928, 2795, 2495, 1658, 1591, 1565, 1510, 1351, 1315, 1035, 1008, 811; Electro-spray MS (MeOH/AcCN/H_2O) m/z (%) 535 (M^+, 100), 435 (12), 335 (5), 198 (2), 180 (8), 167.9 (60).

_N_-Methyl-2-imidazolecarboxaldehyde 3

To a 50 ml round-bottomed flask flushed with N_2 was added *N*-methylimidazole (0.3 g, 3.65 mmol) and THF (20 ml). To this stirring solution was added *n*-butyllithium (2.6 ml, 1.4 M solution in hexane, 3.65 mmol), dropwise. The resulting yellow-red solution was stirred for 3 h at ambient temperature. Dimethylformamide (0.28 ml, 3.65 mmol) was added, at which time a white precipitate formed. The reaction mixture was stirred for 12 h at room temperature, and then quenched by an aqueous solution of saturated NH_4Cl (20 ml). After evaporation to dryness under reduced pressure the residue was dissolved in chloroform, which was washed several times with water. The chloroform solution was dried over sodium sulfate and the solvent was removed under reduced pressure to give a yellow solid. The product was purified on a silica gel column (flash chromatography) eluting with $CHCl_3$: MeOH (9:1, R_f = 0.9). Yield, 0.34 g (85%); m.p. 36.1-36.8 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.89 (s, 3H, N-C*H*$_3$), 7.01 (s, 1H, C*H*=CH), 7.13 (s, 1H, CH=C*H*), 9.67 (s, 1H, C*H*O); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 34.66, 127.15, 131.20, 143.46, 181.82; FTIR (KBr disc): ν (cm^{-1}) 3141, 9098, 1670, 1511, 1490, 1460, 1422, 1383, 1334, 1297, 1154, 1046, 920, 897, 802, 772, 698, 685, 422; MS (EI) m/z: 111 (M^++1, 52), 110 (M^+, 100), 82 (68), 66 (2), 54 (42), 42 (25).

Preparation of the Bis-Imine Derived from _N_-Methyl-2-imidazolecarboxaldehyde 4

To 3 (0.25 g, 2.2 mmol) in acetonitrile (5 ml) was added ethylenediamine (0.08 ml, 1.1 mmol). The resulting system was allowed to stir at ambient temperature for 24 h. The product crystallized out of solution to yield 0.26 g (95%) of the desired bis-imine.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.48 (s, 4H, C*H*$_2$), 4.45 (s, 6H, N-C*H*$_3$), 7.44 (s, 2H, C*H*=CH), 7.58 (s, 2H, CH=C*H*), 8.83 (s, 2H, *H*C=N); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 34.58, 61.23, 124.20, 128.33, 142.28, 153.56; FTIR (KBr disc): ν (cm^{-1}) 3132, 3107, 2952, 2909, 2887, 2851, 1655, 1641, 1523, 1479, 1440, 1415, 1366, 1326, 1289, 1230, 1151, 11021, 959, 928, 836, 786, 713, 692, 560, 482, 425; MS (EI) m/z: 111 (M^++1, 52), 244 (M^+, 3), 149 (40), 134 (11), 122 (38), 111 (36), 95 (83), 84 (87), 68 (6), 49 (100), 42 (64); (CI) m/z: 245 (M^++1, 100), 149 (13), 136 (7), 122 (9), 109 (11), 95 (15), 84 (13), 71 (9); Electro-spray MS (MeOH/AcCN/H_2O) m/z (%) 245 (M^+, 40), 195 (10), 162 (10), 136 (100), 110 (5), 95 (40), 83 (15).

Preparation of the Chiral Bis-Imine Derived from *N*-Methyl-2-imidazolecarboxaldehyde, 5

To 3 (0.39 g, 3.50 mmol) and acetonitrile (5 ml) was added *R,R*-1,2-diaminocyclohexane (0.2 g, 1.75 mmol), which was allowed to stir at ambient temperature for 24 h. The solvent was removed, and ^{1}H-NMR analysis showed complete conversion to the desired product. Yield 0.57 g (98%) after filtration; m.p. 94.7-95.7 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.36 (m, 2H), 1.57 (m, 6H), 3.17 (m, 2H), 3.78 (s, 6H, N-C*H*$_3$), 6.74 (s, 2H, Im-*H*), 6.91 (s, 2H, Im-*H*), 8.12 (s, 2H, N=C*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.06, 32.63, 35.19, 74.49, 124.46, 128.61, 142.88, 151.91; MS (EI) m/z (%): 299 (M^+ + 1, 100), 298 (M^+, 31), 216 (22), 203 (74), 191 (51), 160 (22), 134 (36), 109 (50), 95 (79), 93 (57), 54 (31), 42 (66); (CI) m/z (%): 299 (M^+ + 1, 100), 207 (13), 109 (10), 83 (13).

Preparation of 6 from 4

To $NaBH_4$ (0.15 g, 4.09 mmol) in ethanol (5 ml) was added 4 (0.40 g, 1.63 mmol) in ethanol (5 ml). After stirring the reaction mixture for 2 h at ambient temperature, the mixture was cooled to 0 °C and HCl (12 M, 3 ml) was added dropwise with stirring. The solvent was removed *in vacuo*, after which time CH_2Cl_2 was added and the system was stirred for 2 h to help extract the product. The resulting system was filtered and the desired product was obtained after removal of the solvent under reduced pressure and was recrystallized from ether/methanol. Yield 0.39 g (96%); m.p. 250-251 °C.

^{1}H NMR (D_2O, 200 MHz) δ 3.40 (s, 4H, C*H*$_2$), 3.83 (s, 6H, N-C*H*$_3$), 4.56 (s, 4H, N-C*H*$_2$) 7.41 (s, 4H, C*H*=C*H*); ^{13}C NMR (D_2O ($CDCl_3$ as std.), 200 MHz) δ 38.60, 43.38, 48.51, 123.99, 129.21, 141.67; FTIR (KBr disc): ν (cm^{-1}) 3341, 3316, 3106, 3085, 1604, 1564, 1528, 1457, 1424, 1394, 1335, 1292, 1197, 1135, 1091, 1039, 960, 765, 692, 473; MS (EI) m/z: 248 (M^+-1, 6), 137 (10), 124 (55), 95 (100), 81 (10), 55 (9), 43 (18); (CI) m/z 249 (M^+, 100), 155 (19), 124 (29), 96 (40), 83 (8); Electro-spray MS (MeOH/AcCN/$H_2$0) m/z (%) 249 (M^+, 50), 176 (15), 167 (20), 155 (40), 137 (5), 125 (22), 95 (100), 83 (20); MS/MS (on mass 249): 249 (70), 177 (10), 167 (100), 137 (20), 95 (30).

Preparation of the Chiral amine Derived from *N*-Methyl-2-imidazolecarboxaldehyde, 7

To $NaBH_4$ (0.16 g, 4.38 mmol) and ethanol (5 ml) was added 5 (0.58 g, 1.75 mmol) in ethanol (5 ml). After stirring the reaction mixture for 2 h at ambient temperature, the reaction was cooled to 0 °C and HCl (12 M, 3 ml) was added dropwise

with stirring. The solvent was removed *in vacuo*, after which time CH_2Cl_2 was added and the system was stirred for 2 h to help extract the product. After filtration the solvent was removed under reduced pressure. The resulting solid was recrystallized from ether/methanol. Yield 0.58 g (98%); m.p. 234-236 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.81 (m, 2H), 2.24 (m, 4H), 2.70 (m, 2H), 3.28 (m, 2H), 3.76 (s, 6H, N-C*H*$_3$), 4.15 (d, 2H, J = 14.5 Hz, N-C*H*$_a$), 4.35 (d, 2H, J = 14.5 Hz, N-C*H*$_b$), These signals reflect the geminal coupling between the methylene protons alpha to imidazole species, 7.15 (s, 2H, Im-*H*), 7.25 (s, 2H, Im-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.61, 29.22, 36.07, 39.03, 61.31, 120.41, 125.89, 141.61; FTIR (KBr disc): ν (cm^{-1}) 3467, 3230, 3147, 3081, 2940, 2865, 2638, 2374, 2052, 1605, 1535, 1495, 1449, 1387, 1321, 1279, 1126, 1105, 992, 934, 863, 770, 699; MS (EI) m/z (%): 302 (M^+, 4), 191 (7), 112 (36), 95 (100), 42 (23); (CI) m/z (%): 303 (M^+ + 1, 100), 248 (6), 112 (46), 95 (54), 46 (29).

Preparation of the Bis-Imine Derived from 4-methyl-5-imidazolecarboxaldehyde, 8

To a dry 100 ml round-bottomed flask flushed with nitrogen was added 4-methyl-5-imidazolecarboxaldehyde (2 g, 18.16 mmol), ethylenediamine (0.61 ml, 9.08 mmol), and acetonitrile (20 ml). The resulting mixture (the aldehyde is not fully soluble) was stirred overnight at ambient temperature. The white precipitate that formed, which was distinctly different than the starting aldehyde, was filtered and washed with cold acetonitrile. This produced 2.2 g (95%) of the desired material (m.p. 145-146 °C).

^{1}H NMR (MeOD, 200 MHz) δ 2.30 (s, 6H, Im-C*H*$_3$), 3.84 (s, 4H, N (C*H*$_2$)$_2$N), 7.60 (s, 2H, Im-H), 8.22 (s, 2H, N=C*H*); ^{1}H NMR ($CDCl_3$-MeOD, 200 MHz) δ 1.98 (s, 6H, Im-C*H*$_3$), 2.28 (s, 4H, N (C*H*$_2$)$_2$N), 7.53 (s, 2H, Im-H), 8.16 (s, 2H, N=C*H*); ^{13}C NMR ($CDCl_3$-MeOD, 200 MHz) δ 11.18, 60.84, 116.35, 136.40, 136.52, 152.14; FTIR (KBr disc): ν (cm^{-1}) 3088, 2982, 2916, 2862, 2841, 2557, 1890, 1642, 1578, 1454, 1242, 1165, 1005, 956, 844, 642; MS (EI) m/z (%): 245 (M^++1, 35), 137 (37), 122 (100), 95 (36), 68 (16), 54 (13), 43 (55); MS (CI) m/z (%): 245 (M^++1, 100), 137 (6), 122 (11); MS-High Resolution m/z: calcd. for mass $C_{12}H_{16}N_6$ (M^+); 244.1425 amu; found: 244.1436.

Preparation of *N,N'*-Bis (4-methyl-5-imidazolide)-1*S*,2*S*-diphenylethanediamine, 9

To a dry 100 ml round-bottomed flask flushed with nitrogen was added 4-methyl-5-imidazolecarboxaldehyde (0.52 g, 4.71 mmol) and 1*S*,2*S*-(-)-1,2-diphenylethylenediamine (0.5 g, 2.35 mmol), and acetonitrile (50 ml). The resulting solution was stirred overnight at ambient temperature, during which time the product precipitated out of solution. The product was filtered, washed with acetonitrile and dried under vacuum to yield 0.92 g (99%) of the desired product (m.p. 145-146 °C).

^{1}H NMR ($CDCl_3$-MeOD, 500 MHz) δ 2.19 (s, 6H, Im-C*H*$_3$), 4.63 (s, 2H, PhC*H*N), 7.10-7.33 (m, 10H, Ph-H), 7.56 (s, 2H, Im-*H*), 7.97 (s, 2H, N=C*H*); ^{13}C NMR ($CDCl_3$-MeOD, 500 MHz) δ 11.98, 12.14, 81.06, 126.88, 127.11, 128.10, 128.44, 128.50, 128.60, 136.32, 141.36, 150.97; FTIR (KBr disc): ν (cm^{-1}) 3396, 3190, 3119, 3068, 2924, 2861, 1642, 1603, 1494, 1453, 1394, 1353, 1244, 1116, 1047, 1027, 954, 816, 765, 701; MS (EI) m/z (%): 396 (M^+, 1), 287 (4), 262 (0.5), 198 (100), 194 (45), 165 (6), 116 (18), 91 (41), 77

(29), 43 (72); MS (CI) m/z (%): 414 (M^++18, 1), 396 (M^+, 2), 393 (23), 305 (9), 288(9), 249 (2), 223 (8), 200 (38), 146 (9), 129 (15), 106 (100), 79 (44), 43 (32).

Preparation of *N,N'*-Bis(4-methyl-5-imidazolide)ethanediamine, 10

To a dry 50 ml round-bottomed flask flushed with nitrogen was added sodium borohydride (0.20 g, 5.12 mmol) and ethanol (5 ml). To this stirring suspension was added the bis-imine of 10 in ethanol (20 ml). After 2 h stirring at ambient temperature, the reaction mixture was cooled to 0 °C and 3 ml of HCl (12 M) was added dropwise with stirring. The solvent was reduced *in vacuo* after which time methylene chloride (100 ml) was added and the system was stirred for 2h to extract the product. The product was filtered, to produce 0.5g (98%) of a pale yellow solid (m.p. 249-251 °C).

^{1}H NMR (D_2O, 200 MHz) δ 2.25 (s, 6H, Im-CH_3), 3.41 (s, 4H, N (CH_2)$_2$N), 4.33 (s, 4H, NCH_2-Im), 8.54 (s, 2H, Im-H); MS (EI) m/z (%): 248 (M^+, 1), 189 (3), 176 (4), 137 (2), 125 (7.5), 95 (100), 82 (16), 68 (7.5), 42 (43); MS (CI) m/z (%): 249 (M^++1, 7.1), 189 (10), 177 (17), 155 (91), 124 (11), 95 (77), 83 (64), 61 (100), 44 (21); Electro-spray MS (MeOH/AcCN/$H_2$0) m/z (%) 249 (M^++1, 93), 167 (5), 155 (100), 95 (98), 61 (20); Electro-spray MSMS (MeOH/AcCN/$H_2$0) m/z (%) 155 (100), 138 (5), 95 (24), 61 (40).

***N*-Methyl-4,5-diphenylimidazole, 11**

To a suspension of 4,5-diphenylimidazole (5.0 g, 22.70 mmol) in THF (20 ml) was added NaH (1.0 g, 24.97 mmol, 60 % NaH in mineral oil). The resulting blue-green solution was stirred for 3 h at room temperature, cooled to 0 °C and MeI (0.71 ml, 22.70 mmol) was added dropwise. After the solution was stirred overnight the white powder,

which deposited during the course of the reaction, was collected by filtration and washed with water (2 ml), ethanol (2 ml) and then ether (3 ml). The white powder was recrystallized from $CHCl_3$/ether to give colourless crystals. Yield 4.1 g (77%); m.p. 159-160 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.48 (s, 3H, N-CH_3), 7.12-7.53 (m, 11H, N-CH + H_{arom}); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 32.15, 126.27, 126.58, 128.09, 128.56, 128.96, 130.64, 134.62, 137.90, 138.22; FTIR (KBr disc): ν (cm^{-1}) 3115, 3077, 3043, 1964, 1884, 1762, 1699, 1639, 1601, 1507, 1444, 1368, 1249, 1194, 1070, 1021, 951, 917, 821, 773, 737, 720, 701, 647, 564; MS (EI) m/z: 234 (M^+, 100), 218 (14), 190 (7), 165 (57), 139 (3), 117 (7), 103(6), 89(16), 63 (12), 49(24); (CI) m/z: 235 (M^+, 100), 165 (5).

_N_-methyl-4,5-diphenyl-2-imidazolecarboxaldehyde, 12

To a suspension of *N*-methyl-4,5-diphenylimidazole (1 g, 4.27 mmol) in THF (20 ml) was added *n*-BuLi (3.4 ml, 5.12 mmol, 1.6 M in hexanes) with stirring at -45 °C. After the resulting yellow-brown solution was stirred for 3h, dry DMF (0.46 ml, 5.97 mmol) was added to the solution at -78 °C. After stirring overnight at -45 °C and warming to room temperature, the reaction mixture was quenched by the addition of an aqueous solution of saturated NH_4Cl (30 ml). The organic solvents were removed under reduced pressure, and the residue was dissolved in $CHCl_3$; the resulting solution was washed with water several times. The $CHCl_3$ was dried using Na_2SO_4 and the solvent was removed *in vacuo* to give a yellow solid. The product was purified utilizing column

chromatography on silica gel by eluting with $CHCl_3$:MeOH (95:5) (R_f= 0.94). Yield: 0.9 g (82%); m.p. 138-140 °C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.70 (s, 3H, N-C*H*$_3$), 7.09-7.38 (m, 10H, Ph-*H*), 9.92 (s, 1H, CHO); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 32.15, 126.27, 126.58, 128.09, 128.56, 128.96, 130.64, 134.62, 137.90, 138.22; FTIR (KBr disc): ν (cm^{-1}) 3060, 3030, 2946, 2831, 2820, 1689, 1601, 1503, 1473, 1453, 1304, 1231, 1191, 1128, 1074, 1054, 1027, 963, 941, 919, 852, 823, 770, 725, 670, 678, 608, 527, 509; MS (EI) m/z (%): 234 (M^+, 100), 218 (14), 190 (7), 165 (57), 139 (3), 117 (7), 103(6), 89(16), 63 (12), 49(24); MS (CI) m/z (%): 235 (M^+, 100), 165 (5).

Preparation of the Bis-Imine Derived from *N*-methyl-4,5-diphenyl-2-imidazolecarboxaldehyde, 13

To a dry 50 ml round-bottomed flask flushed with nitrogen was added *N*-methyl-4,5-diphenyl-2-imidazolecarboxaldehyde (4.60 g, 17.51 mmol), 1*R*,2*R*-diaminocyclohexane (1.00 g, 8.76 mmol) and acetonitrile (20 ml). The resulting suspension was stirred at room temperature overnight (12 h). The yellow aldehyde dissolved quickly and the immediate appearance of a fluffy colourless material was observed. This material was filtered, and washed with cold acetonitrile to produce 5.2 g (98%) of the desired material (m.p. 185-186 °C).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.49 (m, 2H, Cy-*H*), 1.83 (m, 4H, 6H, Cy-*H*), 3.35 (m, 2H, Cy-*H*), 3.77 (s, 6H, N-C*H*$_3$), 7.14-7.39 (m, 20H, Ph-*H*), 8.39 (s, 2H, N=C*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.27, 32.91, 33.46, 74.91, 77.20, 126.43, 126.76, 128.01,

128.73, 128.85, 129.98, 130.68, 132.86, 134.14, 138.45, 142.66, 152.66; FTIR (KBr disc): ν (cm^{-1}) 3420, 3064, 3026, 2934, 2853, 1646, 1603, 1504, 1466, 1385, 1360, 1308, 1134, 1073, 1028, 966, 939, 920, 876, 833, 773, 722, 698, 543, 501; MS (EI) m/z (%): 602 (M^+, 7), 355 (91), 312 (9), 261 (53), 247 (92), 178 (91), 118 (100), 103 (93), 41 (39); MS (CI) m/z (%): 603 ($M^+ + 1$, 17), 359 (9), 303 (100), 235 (32), 209 (8), 165 (3), 95 (34), 46 (18).

Preparation of the Chiral amine Derived from *N*-Methyl-4,5-diphenyl-2-imidazolecarboxaldehyde, 14

To a dry 100 ml round-bottomed flask flushed with nitrogen was added sodium borohydride (0.83 g, 21.90 mmol) and ethanol (15 ml). To this stirring suspension was added the bis-imine **13** in ethanol (15 ml). After 24 h stirring at ambient temperature, the reaction mixture was cooled to 0 °C and 3 ml of HCl (12 M) was added dropwise with stirring until the system was acidic. The solvent was reduced *in vacuo* after which time it was taken up into a methanol/water (20 :1) mixture and neutralized with aqueous KOH. The solvent was again removed under reduced pressure. The resulting pale yellow residue was taken up into chloroform (50 ml) and washed several times with water (4 x 20 ml) and brine (1 x 10 ml). The organic layer was dried with sodium sulfate, filtered and solvent was removed *in vacuo*. The product was purified through silica gel chromatography eluting with chloroform:methanol (95:5) R_f= 0.2. This produced 4.9 g (92%) the desired product as a yellow meringue (m.p. 81-82 °C).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.35 (m, 4H, Cy-H), 1.81 (m, 2H, Cy-H), 2.27 (m, 2H, Cy- H), 2.83 (m, 2H, Cy-H), 3.38 (s, 6H, N-CH_3), 3.96 (d, J= 14.2 Hz, 2H, NH-C$H_a$$H_b$Im), 4.27 (d, J= 14.2 Hz, 2H, NH-C$H_a$$H_b$Im), 7.08-7.37 (m, 20H, Ph-H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.75, 31.06, 43.26, 50.08, 61.28, 125.99, 126.58, 127.93, 128.30, 128.80, 129.57, 130.67, 134.50, 136.17, 146.02; FTIR (KBr disc): ν (cm^{-1}) 3298, 3057, 2927, 2854, 1603, 1503, 1461, 1445, 1405, 1326, 1225, 1113, 1072, 1055, 1026, 986, 966, 917, 772, 698, 669; MS (EI) m/z (%): 606 (M^+, 1), 360 (4), 343 (2), 262 (21), 248 (100), 178 (13), 165 (32), 103 (64), 77 (39); MS (CI) m/z (%): 606 (M^+, 2), 343 (4), 247 (100), 178 (9), 165 (8), 103 (63), 77 (15); Electro-spray MS (MeOH/AcCN/H_2O) m/z (%) 607 (M^++1, 5), 361 (10), 304 (15), 247 (22), 117(32), 64 (12), 42 (100); Electro-spray MSMS (MeOH/AcCN/H_2O) m/z (%) 607 (M^++1, 100), 481 (5), 373 (8), 247 (50).

Preparation of the Copper Complex, 15

10 (0.02 g, 0.01 mmol) was allowed to dissolve in methanol (5 ml) before the addition of anhydrous K_2CO_3 (0.02 g, 0.02 mmol) and $CuCl_2$·$2H_2O$ (0.01 g, 0.01 mmol). After stirring the resulting system at ambient temperature for 4 h, the solid was filtered off and the clear blue solution was layered with diethyl ether. After 2 weeks bluish-purple crystals were isolated. Yield 0.010 g (40%).

FTIR (KBr disc): ν (cm^{-1}) 3421, 3186, 3135, 3106, 2927, 1641, 1508, 1455, 1290, 1174, 999, 936, 802, 512, 423; Electro-spray MS (MeOH/AcCN/H_2O) m/z (%) 310 (M^+, 100),

281 (12), 261 (5), 210 (3), 181 (5), 155 (70), 140 (18), 125 (22), 95 (18), 39 (28); MS/MS (on mass 310): 310 (15), 281 (40), 267 (5), 254 (30), 215 (5), 200 (100), 186 (7), 171 (4).

7.5.3 Reductions

7.5.3.1 General Procedure for Reducing Acetophenone Using C_2-Symmetric Dimidazoles

Note: Triethoxysilane and especially trimethoxysilane are rather toxic compounds and therefore care must be taken in their handling. Both are available commercially (Aldrich) and can be handled without problems via syringe techniques.

To a dry 100 ml round-bottomed flask flushed with nitrogen was added **1** (40 mg, 0.10 mmol) and THF (30 ml). The mixture is cooled to –78 °C before the slow addition *n*-butyl lithium (1.6 M, 0.20 ml, 0.2 mmol). The resulting reaction mixture was stirred at –78 °C for 5 min and then allowed to warm up to 0 °C. TMEDA (1.0 ml, 6 mmol) was added and stirred for 10 min, then trimethoxysilane (0.38 ml, 3 mmol) was added and reaction stirred for an additional 10 min. Finally acetophenone (0.35 ml, 3 mmol) was added and the reaction mixture was kept at 0 °C for 24 h. The reaction was quenched by the addition of sodium hydrogen carbonate (0.1 M, 20 ml) and stirred vigorously for 30 min at room temperature. The biphasic system was transferred to a separatory funnel and extracted with ether (3 * 40 ml). The ether was removed without drying and the resulting crude product was purified by column chromatography on silica gel eluting with pentane/ether (3:1), to give (S)-phenethyl alcohol (0.26 g, 70%) as a colorless liquid.

The experiment was repeated with: i) **2** using only one equivalent of BuLi, ii) **9** using one or two equivalents of BuLi, iii) Histidine using one or two equivalents of BuLi, iv)

Phenylalanine using one equivalent of BuLi. For yields and stereoselectivity, see **Table 7. 2**; for spectral data, see the following experimental procedure.

7.5.3.2 General Procedure for Reduction Using Simple Amino Acids

Shown for acetophenone: To a dry 100 ml round-bottomed flask flushed with nitrogen was added *L*-histidine (50 mg, 0.3 mmol) and THF (30 ml). At ambient temperature *n*-butyllithium (2M, 0.32 ml, 0.6 mmol) was added slowly and the resulting suspension stirred for 30 min. The reaction mixture was cooled to 0 °C and TMEDA (1.0 ml, 6 mmol) was added. After stirring for 10 min trimethoxysilane (0.38 ml, 3 mmol) was added and reaction stirred for an additional 10 min. Finally acetophenone (0.35 ml, 3 mmol) was added and the reaction mixture was kept at 0 °C for 24 h. The reaction was quenched by the addition of sodium hydrogen carbonate (0.1 M, 20 ml) and stirred vigorously for 30 min at room temperature. The biphasic system was transferred to a separatory funnel and extracted with ether (3 x 40 ml). The ether was removed without drying and the resulting crude product was purified by column chromatography on silica gel eluting with pentane/ether (3:1), to give (*S*)-phenethyl alcohol (0.31 g, 85%) as a colourless liquid.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.56 (d, 3H, J = 6.5 Hz, PhCH(OH)C*H*$_3$), 2.76 (bs, 1H, PhCH(O*H*)CH_3), 4.94 (q, 1H, J = 6.5 Hz, PhC*H*(OH)CH_3), 7.32-7.45 (m, 5H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.97, 69.99, 125.24, 127.14, 128.24, 145.75; FTIR (neat, KBr disc) ν (cm^{-1}) 3364, 3065, 3031, 2974, 2929, 1603, 1494, 1452, 1371, 1287, 1204, 1077, 1030, 1011, 900, 762, 700, 607, 541; MS (EI) m/z (%): 122 (M^+, 10), 121 (40), 104

(68), 79 (28), 57 (7), 43 (100); (CI) m/z (%): 140 (M^+ + 18, 17), 122 (100), 105 (41), 78 (2), 52 (1), 44(1).

4-Trifluoromethylphenethylalcohol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.46 (d, 3H, *J* = 6.5 Hz, CF_3-PhCH(OH)C*H*$_3$), 2.33 (bs, 1H, CF_3-PhCH(O*H*)CH_3), 4.90 (q, 1H, *J* = 6.5 Hz, CF_3-PhC*H*(OH)CH_3), 7.43 (d, *J* = 8.1 Hz, CF_3-Ph-*H*), 7.61 (d, *J* = 8.1 Hz, CF_3-Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 25.25, 69.73, 121, 125.40, 125.59, 149.65; FTIR (neat, KBr disc) ν (cm^{-1}) 3623, 3375, 2979, 2934, 2880, 1925, 1806, 1680, 1622, 1452, 1417, 1373, 1328, 1206, 1167, 1125, 1091, 1070, 1017, 901, 843, 738, 631, 607; MS (EI) m/z %: 190 (M^+, 5), 175 (40), 159(2), 145 (7), 128 (5), 127 (30), 109 (3), 95 (5), 77(8), 69 (5), 51 (8), 43 (100); (CI) m/z (%):190 (M^+, 37), 168(45), 135 (100), 76 (61), 52 (19), 44 (16).

4-(Methyl) phenethylalcohol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.45 (d, 3H, *J* = 6.4 Hz, CH_3-PhCH(OH)C*H*$_3$), 1.87 (bs, 1H, CH_3-PhCH(O*H*)CH_3), 2.33 (s, 3H, C*H*$_3$-PhCH(OH)CH_3), 4.84 (q, 1H, *J* = 6.4 Hz, CH_3-PhC*H*(OH)CH_3), 7.14 (d, *J* = 8.0 Hz, CH_3-Ph-*H*), 7.24 (d, *J* = 8.0 Hz, CH_3-Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 21.06, 25.04, 70.20, 125.32, 129.13, 137.10, 142.85; FTIR (neat, KBr disc) ν (cm^{-1}) 3623, 3376,3023, 2972, 2927, 2872, 1904, 1669, 1612, 1515, 1451, 1371, 1284, 1202, 1181, 1120, 1075, 1011, 899, 818, 728; MS (EI) m/z (%): 136 (M^+, 62), 135 (M^+-1, 100), 109

(67), 94 (16), 77 (25), 65 (13), 45 (11), 43 (47); (CI) m/z (%): 136(M^+, 13), 135(M^+ -1, 100).

4-Methoxyphenethylalcohol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.41 (d, 3H, J = 6.4 Hz, CH_3O -PhCH(OH)C*H*$_3$), 2.64 (bs, 1H, CH_3O-PhCH(O*H*)CH_3), 3.74 (s, 3H, C*H*$_3$O - PhCH(OH)CH_3), 4.76 (q, 1H, J = 6.4 Hz, CH_3O -PhC*H*(OH)CH_3), 6.85 (d, J = 8.0 Hz, CH_3O-Ph-*H*), 7.25 (d, J = 8.0 Hz, CH_3O-Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.88, 55.09, 69.61, 113.62, 126.53, 138.00, 158.70; FTIR (neat, KBr disc) ν (cm^{-1}) 3409, 2969, 2932, 2838, 1613, 1587, 1514, 1463, 1370, 1327, 1291, 1249, 1176, 1118, 1087, 1072, 1036, 1008, 899, 833, 809, 738, 585, 550; MS (EI) m/z (%):152 (M^+, 6), 135 (37), 109 (78), 105 (50), 84 (17), 77 (74), 51 (42), 43 (100).

Diphenylcarbinol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.19 (bs, 1H, PhCH(O*H*)Ph), 5.84 (s, 1H, PhC*H*(OH)Ph), 7.24-7.39 (m, 10H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 75.96, 126.46, 127.35, 128.31, 143.69; FTIR (neat, KBr disc) ν (cm^{-1}) 3390, 3086, 3061, 3028, 1598, 1495, 1454, 1395, 1350, 1317, 1290, 1269, 1181, 1085, 1034, 1018, 926, 912, 852, 754, 736, 700, 654; MS (EI) m/z: 184 (M^+, 38), 167 (53), 152 (7), 105 (100), 79 (52), 77 (60), 51 (41); (CI) m/z (%): 184 (M^+, 8), 167 (100), 135 (4), 105 (4), 78 (1).

1-(4-Trifluoromethylphenyl)-1-phenylcarbinol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 5.87 (s, 1H, CF_3-PhC*H*(OH)Ph), 7.24-7.36 and 7.47-7.60 (m, 9H, CF_3-Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 75.71, 125.24, 126.58, 127.73, 128.55; FTIR (neat, KBr disc) ν (cm^{-1}) 3384, 3067, 3034, 2959, 2929, 2874, 1669, 1620, 1606, 1495, 1453, 1415, 1327, 1276, 1163, 1124, 1068, 1041, 1019, 864, 841, 807, 750, 736, 701; MS (EI) m/z (%): 252 (M^+, 33), 235 (67), 183 (10), 173 (29), 145(17), 127 (24), 105 (100), 79 (86), 51 (46); (CI) m/z: HR-MS (CI) m/z (%): 269 (M^++17, 1), 252 (M^+, 25), 235 (100), 181(3), 173(3), 145 (2), 117 (4), 105 (14), 78 (7), 58 (2), 52 (1).

1-(4-Methylphenyl)-1-phenylcarbinol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.30 (s, 3H, C*H*$_3$-PhCH(OH)Ph), 5.75 (s, CH_3-PhC*H*(OH)Ph), 7.08-7.35 (m, 9H, CH_3-Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 21.07, 76.03, 126.43, 126.48, 127.39, 128.39, 129.13, 140.93, 143.92; FTIR (neat, KBr disc) ν (cm^{-1}) 3536, 3384, 3088, 3062, 3030, 2958, 2924, 2871, 1660, 1604, 1514, 1494, 1453, 1412, 1382, 1319, 1279, 1176, 1114, 1078, 1037, 1018, 944, 912, 861, 843, 799, 777, 735, 700; MS (EI) m/z (%):198 (M^+, 53), 181 (100), 165 (10), 152 (6), 119 (78), 105 (73), 91 (59), 77 (69), 51 (31), 43 (15); (CI) m/z (%): 198 (M^+, 6), 181 (100), 119 (5), 105 (5), 91(3), 77(1), 65 (1).

1-(4-Methoxyphenyl)-1-phenylcarbinol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.31 (bs, 1H, CH_3O-PhCH(O*H*)Ph), 3.79 (s, 3H, C*H*$_3$O -PhCH(OH)Ph), 5.80 (s, 1H, CH_3O -PhC*H*(OH)Ph),7.10 (d, 2H, *J* = 8.0 Hz, CH_3O-Ph-*H*), 7.23-7.40 (m, CH_3O-Ph-*H*); ^{13}C

NMR ($CDCl_3$, 200 MHz) δ 55.25, 75.76, 113.83, 126.37, 127.38, 127.89, 128.40, 136.13, 143.98, 159; FTIR (neat, KBr disc) ν (cm^{-1}) 3414, 3064, 3031, 3005, 2959, 2934, 2839, 1612, 1587, 1513, 1454, 1384, 1303, 1252, 1174, 1113, 1078, 1036, 915, 843, 806, 782, 739, 700, 649, 628; MS (EI) m/z (%): 214 (M^+, 51), 197 (100), 165 (5), 135 (28), 115 (5), 109 (75), 77 (38), 51 (18), 43 (8); (CI) m/z (%): 214 (M^+, 5), 197 (100), 135 (5), 105 (5), 94 (2), 65 (1), 44 (1).

4,7-Dimethyl-1-indanol: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.84 (bs, 1H, PhCH(O*H*)R), 1.97-2.11 (m, 1H, PhCH(O*H*)$CH_2C\mathit{H_2}$), 2.25 (s, 3H, Ph-$C\mathit{H_3}$), 2.30-2.44 (m, 1H, PhCH(O*H*)$C\mathit{H_a}$ H_bCH_2), 2.39 (s, 3H, Ph- $C\mathit{H_3}$), 2.67-2.81 (ddd, J = 3.2 Hz, 8.9 Hz, 16.43 Hz, PhCh(OH)$CH_2C\mathit{H_a}C\mathit{H_b}$), 3.00 (dd, J = 8.3 Hz, 16.3 Hz, PhCH(OH)$CH_2C\mathit{H_a}C\mathit{H_b}$), 5.26 (dd, 1H, J = 2.0 Hz, 6.5 Hz, PhC*H*(OH)R), 6.94 (d, 1H, J = 7.6 Hz, Ph-*H*), 7.01 (d, 1H, J = 7.6 Hz, , Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 17.93, 18.58, 28.79, 34.66, 75.59, 128.14, 129.45, 139.40, 132.17, 142.52, 142.68; FTIR (neat, KBr disc) ν (cm^{-1}) 3297, 3037, 2961, 2923, 2858, 1496, 1454, 1402, 1379, 1338, 1158, 1067, 1048, 979, 928, 891, 808; MS (EI) m/z (%): 162 (M^+, 62), 145 (100), 129 (23), 119 (15), 115(20), 103(6), 91 (23), 77 (20), 65 (14), 55(29), 41 (15); (CI) m/z (%): 162 (8), 145 (100), 129 (3), 119 (1), 105 (1), 91 (1), 65 (0.5).

1-Phenyl-3-butanol: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.32 (d, 3H, J = 6.2 Hz, $PhCH_2CH_2CH(OH)C\mathit{H_3}$) 1.80- 1.92 (m, 2H, $PhCH_2C\mathit{H_2}CH(OH)CH_3$), 2.12 (bs, 1H,

$PhCH_2CH_2CH(OH)CH_3$), 2.80 (sept,2H, J = 7.9 Hz, $PhCH_2CH_2$ $CH(OH)CH_3$), 3.91 (sex, 1H, $PhCH_2CH_2CH(OH)CH_3$), 7.24-7.43 (m, 5H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.45, 32.03, 40.71, 67.33, 125.70, 142.01; FTIR (neat, KBr disc) ν (cm^{-1}) 3064, 3028, 2966, 2929, 1604, 1496, 1455, 1375, 1261, 1126, 1029, 955, 908, 856, 800, 746, 699; MS (EI) m/z (%): 150 (M^+, 9), 132 (44), 117 (80), 91 (100), 77 (27), 65 (26), 45 (71); (CI) m/z (%): 168 (M^+ + 16, 100), 152 (M^+, 55), 132 (40), 117 (12), 108 (11), 91 (16), 65(5); HR-MS (EI) m/z: Calcd. for $C_{10}H_{14}O$: 150.0903. Found: 150.0902.

Trans-4-Phenyl-3-buten-2-ol: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.38 (d, 3H, J = 6.4 Hz, $PhCHCHCH(OH)CH_3$), 2.26 (bs, 1H, $PhCHCHCH(OH)CH_3$), 4.48 (dp, 1H, J = 0.9 Hz, 6.3 Hz, $PhCHCHCH(OH)CH_3$), 6.26 (dd, 1H, J = 6.3 Hz, 16.0 Hz, $PhCHCHCH(OH)CH_3$), 6.56 (d, 1H, J = 16.0 Hz, $PhCHCHCH(OH)CH_3$), 7.20-7.41 (m, 5H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.27, 68.68, 126.34, 127.47, 128.44, 129.16, 133.51, 136.61; FTIR (neat, KBr disc) ν (cm^{-1}) 3362, 3062, 3028, 2974, 2928, 2873, 1950, 1879, 1807, 1719, 1658, 1599, 1579, 1495, 1450, 1369, 1295, 1141, 1067, 968, 943, 877, 826, 750, 694; MS (EI) m/z (%): 148 (M^+, 63), 131 (66), 115 (26), 105 (100), 91 (49), 77 (37), 55 (15), 43 (71); (CI) m/z (%): 149 (3), 148 (1), 131 (100), 105(2), 91 (3), 78 (2), 55 (3), 43 (1).

1-Phenylpropan-2-ol: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.16 (d, J = 6.18, 3H, $PhCH_2CH(OH)CH_3$), 2.20 (bs, 1H, $PhCH_2CH(OH)CH_3$), 2.61 (dd, J = 11.8, J = 7.3, 1H,

$PhCH_aH_bCH(OH)CH_3$); 2.70 (dd, J = 11.8, J = 7.4, 1H, $PhCH_aH_bCH(OH)CH_3$), 3.93 (m, 1H, $PhCH_2CH(OH)CH_3$), 7.29-7.07 (m, 5H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 22.60, 45.63, 68.74, 126.29, 127.36, 128.66, 129.00, 138.50.

1, 1-diphenylpropan-2-ol: ^1H NMR ($CDCl_3$, 200 MHz) δ 2.42 (d, J = 6.08, 3H, $Ph_2CHCH(OH)CH_3$), 2.89 (bs, 1H, $Ph_2CHCH(OH)CH_3$), 5.03 (d, J = 8.8, 1H, $Ph_2CHCH(OH)CH_3$), 5.78 (dq, J = 8.8, J = 6.1, 1H, $Ph_2CHCH(OH)CH_3$), 8.65-8.38 (m, 10H, $Ph_2CHCH(OH)CH_3$); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 14.02, 60.60, 70.03, 126.53, 126.88, 128.62, 128.85, 141.49, 142.49 ; MS (EI) m/z (%): 196, 195, 183, 168, 152, 128, 115, 91, 77, 65, 43; (CI) m/z (%): 230 (M^+ + 18 , 100), 212 (M^+ , 3), 195 (20), 183 (3), 167 (42), 152 (10), 128 (3), 115 (4), 105 (3), 91 (7), 76 (3).

General experimental procedure for preparation of Mosher esters (for (*S*)-1-phenylethanol)): (*S*)-1-phenylethanol (2 mg, 0.02 mmol) and MTPA-Cl (+) (4 ml, 0.02 mmol) were mixed with carbon tetrachloride (3 drops) and dry pyridine (3 drops). The reaction mixture was allowed to stand in a stoppered flask for 12 h at ambient temperature. Water (1 ml) was added and the reaction mixture transferred to a separatory funnel and extracted with ether (20 ml). The ether solution, after washing successively with HCl (1M, 20 ml), and saturated sodium carbonate solution (20 ml), and water (20 ml) was dried with sodium sulfate, filtered and solvent was removed *in vacuo*. The residue was dissolved in deuterated chloroform for NMR analysis. The integration(s) of

the hydrogen on the carbon bearing the hydroxyl group was used as a measure to assess the enantioselection.

7.6 CONCLUSIONS

In summary, we have demonstrated the use of lithium imidazolides as activators for trialkoxysilane towards the reduction of carbonyl species. We have introduced a new C_2 symmetric ligand that also affects the reduction. The mechanistic implications of these reductions were outlined, suggesting bidentate structures. Our ongoing investigation of the true nature of the reactive transition (or intermediate) state will form the basis of future communications.

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Containing Bidentate 1,2-Diolato(2-) Ligands Derived from α-Hydroxycarboxylic Acids, Acetohydroximic Acid, and Oxalic Acid: New Results in the Chemistry of Pentacoordinate Silicon, in Auner, N.; Weiss, J., (eds.), *Organosilicon Chemistry: from molecules to materials II (Proceedings of the Munich Silicon Days, 1994)*, VCH: Weinheim, 1996, p. 427, 447, 453.

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Chapter 8

Imidazole Mediated Hydrosilylation of Ketones: Mechanistic Implications

8.1 ABSTRACT

Lithium salts of imidazolide-containing ligands and amino acids are shown to activate trialkoxysilane towards pentacoordination. The semi-empirical method, using AM1 basis set, was used to calculate the relative orientation of the ligands around silicon. ^{13}C NMR was utilized to establish the displacement of methoxide from silicon by the various ligands. The mechanistic implications of these observations are discussed. Binding of α-aminoacids to the silicon center seems to involve the α-amino and the carboxylate functionalities. In this mode, the 'R' group of the amino acid essentially sweeps around one face of the hexacoordinate transition state, causing the incoming ketone to orient itself in such a manner as to minimize the interaction with the 'R' group of the amino acid. This model predicts that bulkier and more flexible R groups should have a greater influence over stereochemical control than the tightness of binding around the reactive center. It is in this way we account for the equality of enantiomeric excess (e.e.) observed with histidine (26% ee) and phenylalanine (25% ee), and the decrease in e.e. observed in the case of proline (16% ee) and alanine (<1% ee).

8.2 INTRODUCTION

The major reason for the great interest in the chemistry of hypervalent silicon species originates in mechanistic studies performed on the racemization[1], hydrolysis[2] and alcoholysis[3] of tetracoordinate chlorosilanes. These reactions have been shown to be activated by particular nucleophilic reagents[4], and kinetic data have established that the rate laws in all cases are very similar and involve two molecules of silaphilic nucleophilic reagent (**Scheme 8. 1**).[5] These "silaphiles" or "silicophiles" are molecules that have a special affinity for silicon, and usually possess electron-rich oxygen or nitrogen ligands,[6] such as hexamethylphosphoric triamide (HMPA), Ph_3PO, RCO_2^-, *N,N*-dimethylaminopyridine (DMAP),[7] imidazole, *N*-methylimidazole (NMI), *N,N*-dimethylpropyleneurea (DMPU), *N,N*-dimethylethyleneurea (DMEU), *N*-methylpyrrolidinone (NMP), dimethylformamide (DMF)[8], dimethylsulfoxide (DMSO)[9] and fluoride.

Scheme 8. 1: Equation for rate of racemization and hydrolysis at silicon

$$v_{rac} = [R_1R_2R_3Si\text{-}Cl][Nu]^2$$

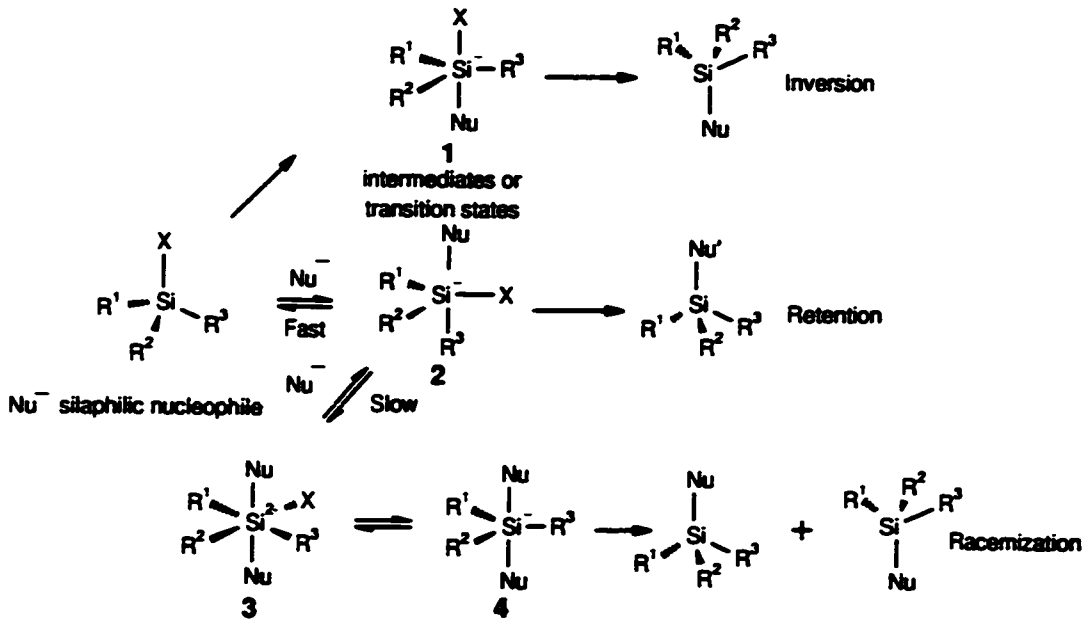
$$v_{water} = k'_{water}\,[R_1R_2R_3Si\text{-}Cl][H_2O][Nu]$$

Nu = Nucleophilic catalyst, v_{rac} = rate of reaction racemization
V_{water} = rate of hydrolysis

Thermodynamic properties of these processes have been evaluated.[5] The enthalpic and entropic parameters were evaluated to be -40 to -60 kcal/ mol and < 3 e. u., respectively. These features point to a mechanism that is predominantly controlled by the entropy of activation. The mechanism proposed[10] (**Scheme 8. 2**) involves an initial and

reversible attack of the activating nucleophilic catalyst on the substrate to provide pentacoordinate silicon intermediate **1** or **2**. This is followed by a rate determining second attack of the same nucleophile in the case of racemization and by reaction with a molecule of the incoming nucleophile which substitutes the Si-X bond in the case of "nucleophile assisted" nucleophilic substitution at silicon.

Scheme 8. 2: Mechanism of nucleophilic substitution at silicon



The mechanistic implications of this process are the following:

(1) The pentacoordinate silicon species **1** and **2** must react faster with nucleophiles than the starting tetracoordinate silane, since there is acceleration of the racemization and of the hydrolysis of chlorosilanes in the presence of nucleophilic catalyst even if the silicon species **1** and **2** are negatively charged[8].

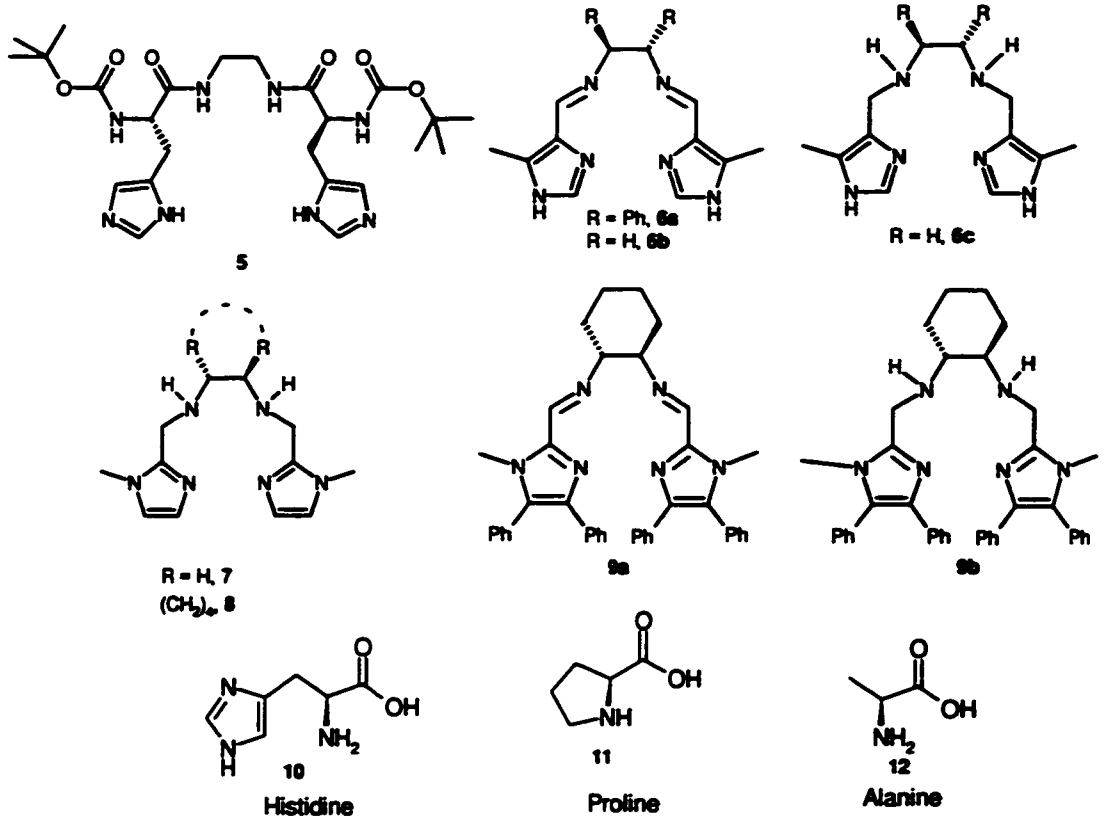
(2) The rate-determining step involves the nucleophilic attack on a pentacoordinate silicon atom via a hexacoordinate intermediate (or transition state).

We have previously reported the utility of the anion of imidazole to activate trialkoxysilanes for subsequent reduction of carbonyl compounds.[11] In particular, we have noted the utility of anion salts of histidine, and other amino acids, to facilitate nucleophilic substitution as well as to promote reduction with facial selectivity. We report herein our ongoing investigation of this reductive system and the mechanistic implications of each of the aforementioned systems in light of nucleophilic substitution at silicon.

8.3 RESULTS

We have reported previously the synthesis and reductive potential of histidine, phenylalanine as well as the novel *N,N'*-bis(5-methyl-4-methylene-imidazole)-1,2-bisphenylethanediimine ligand (**Table 8. 1**).[11] The elucidation of the propensity of each of these reagents to effect extracoordination at silicon utilizing ^{29}Si NMR has also been reported.

Figure 8. 1: Chiral imidazole and amino acid derivatives



8.3.1 Reduction

The previously reported yields and facial selectivity of amino acid and ligand based systems are listed in **Table 8. 1**. As noted previously **5, 6b,** and **10-12,** exhibit low enantioselectivity toward reduction of acetophenone. The yields of reduction as noted are quite reasonable favouring the *S*-alcohol in all cases. When considering the mechanism of this process, one must note that as the size of the *R* group of the amino acid becomes smaller as the enantioselection becomes smaller. In addition, as the complexity (greater the steric requirement for incoming nucleophile) of the bidentate ligand increases the enantioselection increases.

Table 8. 1: Reduction of acetophenone by $HSi(OEt_3)$ in the presence of imidazolide anions

Entry	Imidazolide	Mol% imidazolide	Yield	e.e. (product configuration)
1	Li-5	5	55	56 (S)
2	Li-6a	5	70	26 (S)
3	Li_2-6a	5	73	30 (S)
4	Li-His[a]	10	75	26 (S)
5	Li_2-His	10	85	26 (S)
6	Li-Phe	100	71	25 (S)
7	Li_2-Pro	10	50	15 (S)
8	Li_2-Ala	10	38	<1(-)

[a] $HSi(OMe)_3$ was used for the reduction.

Surprisingly, it was found that although extracoordination at silicon is facilitated by the bis-lithium salts of ligands **7**, **8** and **9b**, subsequent addition of ketone produced no product alcohol. This may be due to the reduced Lewis acidity of silicon species associated with the strong electron rich environment.

8.6.2 ^{13}C NMR Analysis

^{13}C NMR analysis of the intermediate pentacoordinate silicon species obtained for the bis-lithium salt of histidine and the mono-lithium salt of **6c** displayed 2 peaks in the region of methoxide in THF-d_8 solvent (**Table 8. 2**). We attribute one to an extracoordinate silicon species ($[HSiL_2(OMe)_2]^-$) and the extra peak to methoxide released during the reaction. The starting material peak is 1-2 ppm upfield from the ones observed for the ligand silicon mixture. This supports our previous hypothesis that the nature of the intermediate species must be bidentate in nature.

Table 8. 2: Selected ^{13}C NMR peaks for intermediate in imidazole mediated hydrosilylation of ketones

Entry	Imidazolide	Species	^{13}C NMR (ppm)[a]
1	None	LiOMe	50.22
2	None	$(MeO)_3SiH$	49.98
3	Li_2-His	$(MeO)_3SiH$	51.33, 50.67
4	Li-**6b**	$(MeO)_3SiH$	51.35, 50.45

[a] Measured relative to THF upfield pentet set at 67.57.

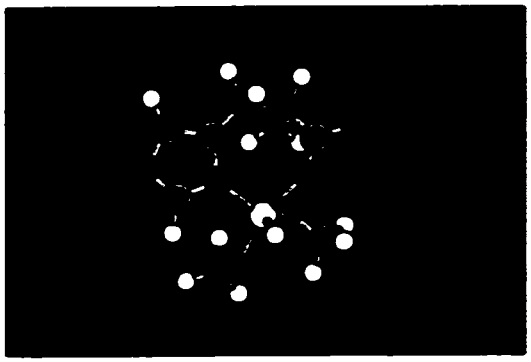
The peak at 50.67 and 50.45 ppm, found respectively in entries 3 and 4 **Table 8. 2**, is attributed to lithium methoxide release. The peak at 51.33 ppm, results from the conversion at silicon from tetracoordinate to pentacoordinate, as the bidentate ligand displaces one of the methoxy groups on $HSi(OMe)_3$.

8.6.3 Molecular Modeling Calculations

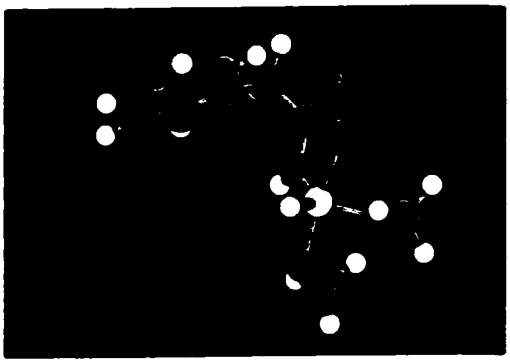
Molecular modeling calculations of the various pentacoordinate silicon species are presented in **Figure 8. 2.** These calculations were conducted using semi-empirical methods utilizing the AM1 basis sets. The AM1 basis set was utilized in order to maintain consistency among previous calculations done for hypervalent silicon species.[12]

Figure 8. 2: The optimized geometry of the various pentacoodinated silicon intermediates

A)

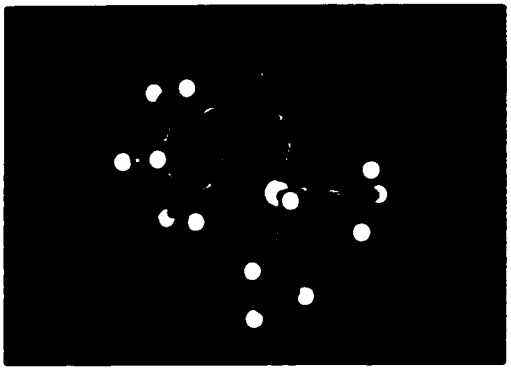


13a

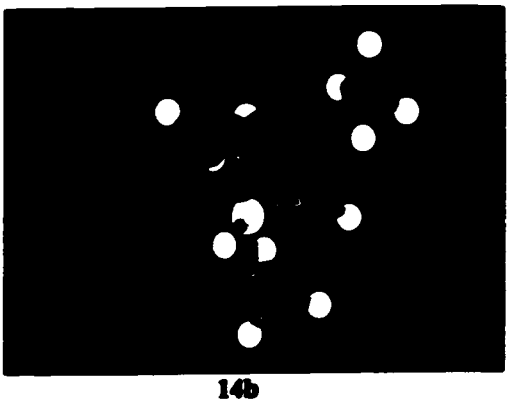


13b

B)

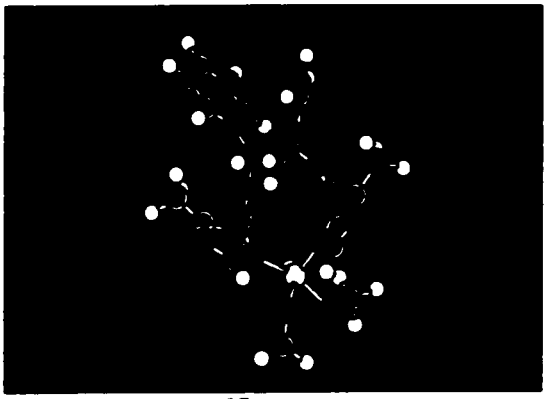


14a

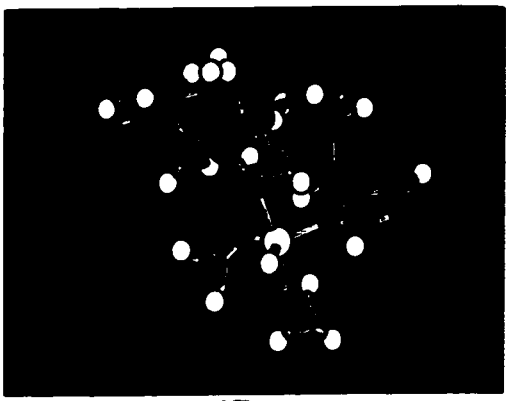


14b

C)



15a

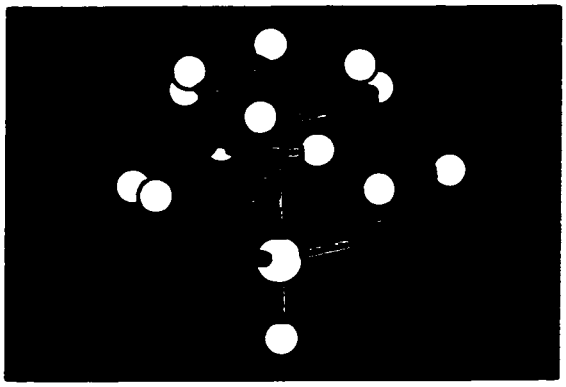


15b

Semi-empirical calculations using the AM1 basis set and restricted trigonal bipyramidal geometry around silicon: (13a) His; (13b) Phe; (14a) Pro, (14b) Ala; (15a) bis-imine ligand 6a; (15b) bis His ligand 5. Note: Hydrogens (white); Carbons (light blue); Nitrogens (dark blue); Oxygen (red); Silicon (central white)

These optimized geometries can give us some idea as to the arrangement of ligands around silicon. It should be noted in the ligands where both carboxylate and amine are available to bind to silicon, that the carboxylate always adopts the axial position and the nitrogen the equatorial one. This is consistent with the findings of Tacke and coworkers.[13] This can been seen quite readily if one examines the interaction of histidine dianion (**13a**), the dianion of proline (**13b**), the dianion of phenylalanine (**14a**), and dianion of alanine (**14b**). However, when two imidazole units are the ligating partners, one adopts the axial and the other the equatorial position. Moreover, in all cases the hydrogen atoms are found to occupy equatorial sites. This result is consistent with the observation of Boyer *et al.*[14], Corriu and coworkers[15] and Ebsworth *et al.*[16]

Figure 8. 3: The Optimized Geometry of Hydridosilatrane



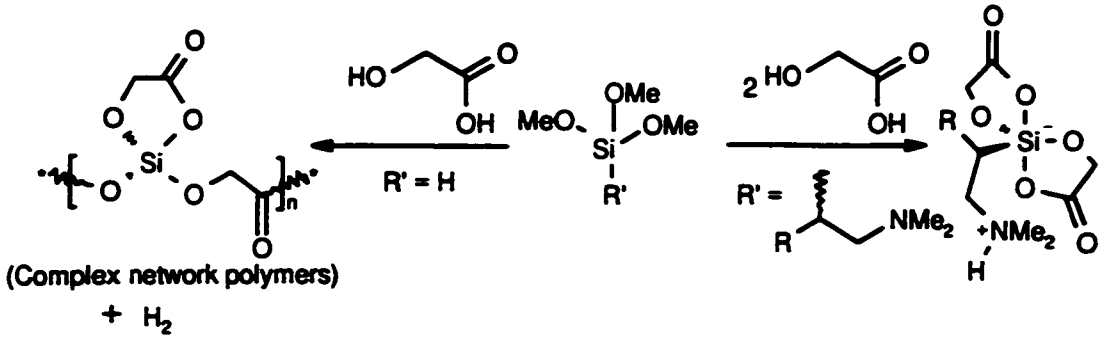
We feel confident that these structural arrangements are viable: This basis set correctly produces the analogous geometric arrangement of ligands for hydridosilatrane, as confirmed by X-ray crystallographic analysis[17,18]. However, we are less confident in the bond lengths determined by this method of calculation. In most silatranes that have

been studied the Si-N distance lies between 2.0 and 2.2 Å. This calculation produced Si-N bond length of 2.6 Å.

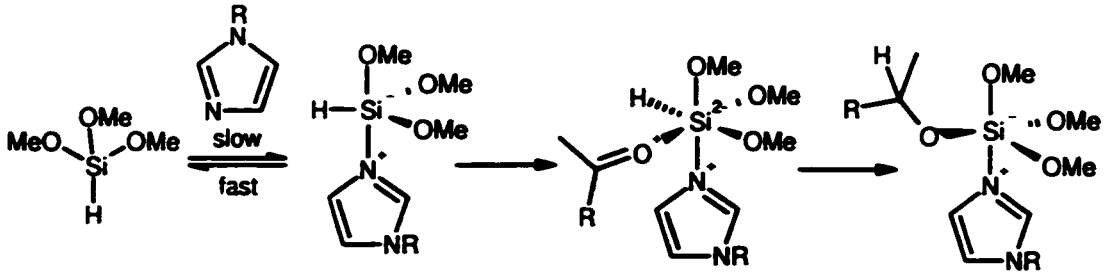
8.4 DISCUSSION

The facility of trialkoxysilanes to undergo extracoordination lies between that of trialkyl- and trihalosilanes.[19] While even weakly coordinating bidentate nucleophiles, such as α-hydroxyacids (**Scheme 8. 3A**,[20] **B**[21]), react with hydrotrialkoxysilanes to rapidly lead to new alkoxysilanes via nucleophilic substitution, only with more powerful *mono*dentate nucleophiles will extracoordination result. Consistent with this, triethoxysilane neither displayed any evidence of extracoordination nor of reactivity towards ketones in the presence of any of the neutral imidazole derivatives that we examined. The absence of reactivity likely reflects a low rate of addition (or a low equilibrium constant) of the imidazole to give the generally more reactive pentacoordinate species **16**.

Scheme 8. 3: Extracoordination facilitate by α-hydroxyacids



Scheme 8. 4: Reductions initiated by imidazole



Triethoxysilane readily underwent coordinate expansion with the different, more nucleophilic, imidazolide anions that we used, as was clearly shown by ^{29}Si NMR. Predictably, these intermediates efficiently converted ketones to alkoxysilanes. This suggests the most important difference between imidazoles and imidazolides occurs in the formation of **16** rather than in subsequent reactions (**Scheme 8. 4**). This is consistent with the thermodynamic findings found by Corriu *et al.*[5c] and is quite consistent with his proposed mechanism of nucleophilic substitution at silicon. Similarly, mono- and dianions of histidine and the monoanion of phenylalanine induced both extracoordination and reduction of acetophenone.

While little structural information for the reactive extracoordinate silanes is available, we have previously put forth a model that would account for the observed stereoselectivity in reduction. Here we seek to build on this model. Several factors contribute to our understanding of this picture:

i) imidazoles are not sufficiently active nucleophiles to form extracoordinate compounds from $HSi(OR)_3$;

ii) the crystal structures of copper complex of **7** and **8**.

iii) molecular modelling calculations.

iv) pentacoordinate silanes are known to possess more electronegative ligands and greater receptivity towards nucleophiles than the analogous 4-coordinate silanes; the more electronegative the substituent, the greater its apicophilicity.

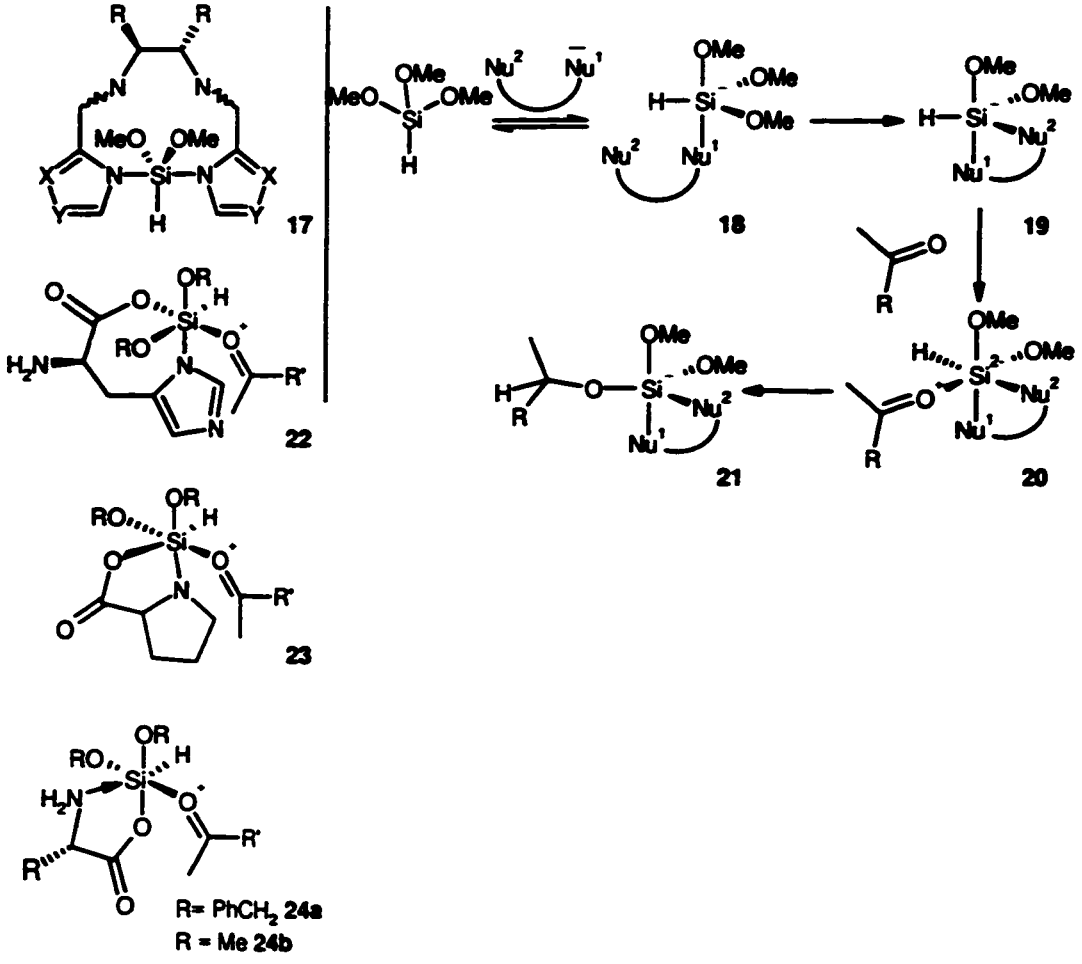
v) the absence of differences in the ^{29}Si NMR spectra and reactivity of the monoanion and dianions derived from **5**, **6a** and **6b**, and of histidine.

vi) The presence of an additional ^{13}C NMR signal in the methoxide of the postulated five coordinate silicon species.

From the crystal structure of copper compounds **7** and **8** we learn that all four nitrogens are, in principle, available for binding to silicon. However, it is unlikely that such tetradentate bonding is occurring at silicon in reduction involving **6b** - it would involve exchange of all the alkoxy groups by nitrogen. However, these data shows that *trans*-diimidazole binding, as in **17**, is structurally reasonable in the case of bidentate ligands **5** and **6a**. The additional methoxide peak in the ^{13}C NMR also supports this structure. Imidazoles will not activate $HSi(OEt)_3$ to extracoordination. However, once an imidizolide (or carboxylate, see below) anion adds to give a pentacoordinate silane, either nucleophilic substitution **18** or further complexation to give a bidentate system **19** could occur (**Scheme 8. 5**). This would explain the absence of difference between mono- and dianion catalysts: in either case once extracoordinate silicon is formed, substitution/nucleophilic addition is facilitated. That is, $HSi(OEt)_3$ is converted to **19**, which subsequently undergoes addition of the ketone **20** and then internal hydrogen transfer, **21**. The catalytic nature of this process, as well as the diminished facial selectivity, can be appreciated if one realises that either the chiral alcohol,

the bidentate ligand, or methoxide can act as leaving groups, and subsequently activate another tetracoordinate silicon species. Nucleophilic substitution/reduction initiated by the chiral product alcohol might confer the opposite enantiosense to the resulting alcohol than the ligand, and obviously reduction activated by the achiral alkoxide would lead to racemic product: both of these processes lead to a diminished enantioselectivity.

Scheme 8. 5: Proposed reaction mechanism observed for reductions initiated by C_2 bis-imidazole ligands and amino acids



In such a model, the chiral environment is provided by a single stereogenic center (histidine **22**, proline **23**, and phenylalanine or alanine **23**) or a pair of stereogenic centers (ligands **5** or

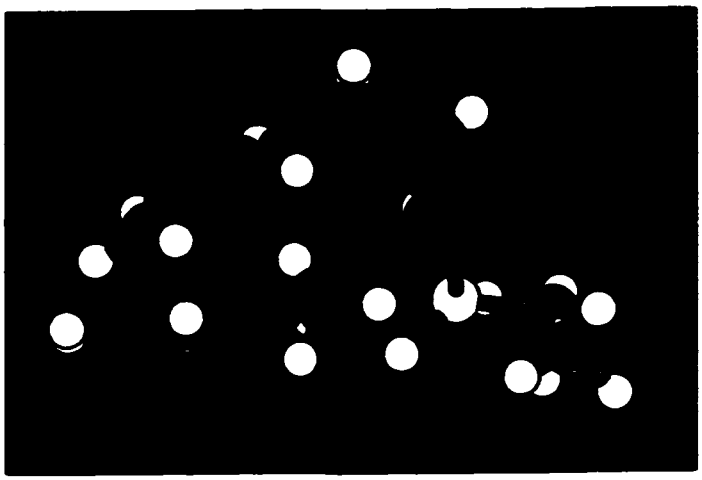
6a, **17**, **Scheme 8. 5**). We speculate, based on known trends of reactivity of extracoordinate silanes and the ^{13}C NMR results obtained by us, that the major intermediates are more likely to have the bidentate structures shown, with axial imidazole or carboxylate groups. Semi-empirical calculations have suggested, and crystal structures support, that the most thermodynamically favored species are the ones where the carboxylate group adopts an axial position and the imidazole, the equatorial position. However, the stereochemical non-rigidity of pentacoordinate silicon compounds[22] must be appreciated here as well. This can flip carboxyl and imidazole group between axial and equatorial positions through the Berry pseudorotation process.[23] Calculations only point to a global minimum structure in a vacuum. This fact is apparent when one examines the ^{29}Si-NMR spectra of these species at variable temperatures. At 0 °C there are two peaks associated with pentacoordinated silicon species, at -78.98 and –79.83 ppm, respectively. These peaks persist until –100 °C at which point only one peak appears at –79.25 ppm. We attribute then the peak at –80 ppm to the species with the carboxyl group axial and the imidazole species in the equatorial position, **13a**. Under the reaction conditions generally used in the reductions described above, both species are present.

This model predicts that the single stereogenic centre of the histidine and phenylalanine-complexed silanes would more efficiently transfer chiral information than the more distal pair of chiral centres in the C_2-symmetric ligands.

The *S*-alcohol is always the preferred product in the reductions catalyzed by either the bidentate ligands or the amino acids. The above observation can be accounted for if one takes a look at the molecular modelling analysis of the hexacoordinate species

believed to be involved in this reduction process. We believe that the approach of the incoming ketone may be controlled by π-stacking interactions. The ketone must interact with the silicon centre in the equatorial plane adjacent to the hydrogen to be delivered. The π-stacking system essentially turns the face of the ketone towards the hydrogen to be delivered. Thus, stereocontrol is conferred through π-stacking interactions in the histidine and phenylalanine case and the bidentate ligands (depicted for phenylalanine below).

Figure 8. 4: Approach of ketone to Phe-Si(OMe)$_2$H species controlled by π-stacking

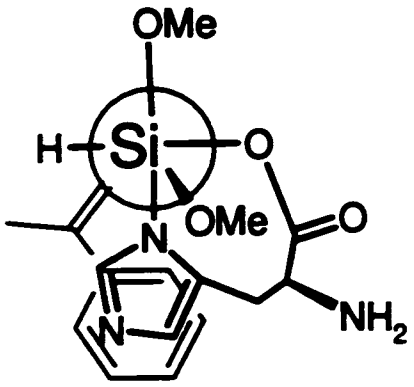


Note: Hydrogens (white); Carbons (light blue); Nitrogens (dark blue); Oxygen (red); Silicon (central white).

The enantioselection observed for proline and alanine are 15%, and <1%, respectfully, much lower than the examples given above. These results are consistent with the model above: very little stereodiscrimination will result with proline and alanine as activating chiral ligands, since no such π-stacking interactions would exist. The facial selectivity in proline should only arise from steric factors.

Mechanistically, one could interpret the stereochemical results obtained from the reductions catalyzed by histidine in two ways. As noted in chapter 2, two distinct binding modes of histidine are possible: binding of the pyrrole nitrogen of imidazole and the carboxylate or the binding of the α-amino group and the carboxylate to the silicon center. If the former mode of binding is the correct one, then the preferential reactive intermediate must involve axial imidazole binding and equatorial carboxylate binding (**Figure 8.5**). AM1 calculations predicted the opposite mode of binding. However, as noted earlier, these calculations may point to a global minimum, which may or may not be the mode of binding involved in the reduction process.

Figure 8. 5: Newman projection of the proposed hexacoordinate transition state

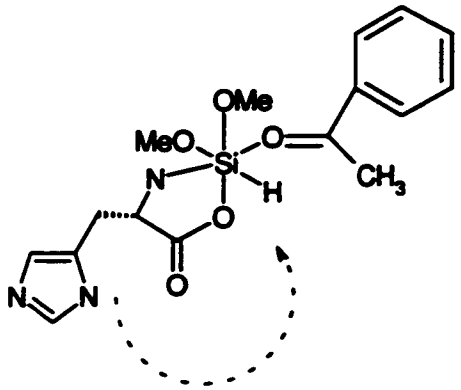


In this mode of binding, π-stacking interactions are again invoked to account for stereodiscrimination. The approach of the ketone is controlled by the amine, which occupies one face of the silicon center. Thus as diagrammed above, approach of the ketone must occur on the opposite side of the amine function, and π-stacking interactions further control the manner in which the ketone approaches the silicon center. Thus,

delivery of the hydride must occur on the *re* face of the ketone. If this model is correct, then bulking up the amine group should lead to greater stereocontrol.

The latter mode of binding seems to account for all the stereochemical outcomes of each of the amino acids considered. In this mode, the R group of the amino acid essentially sweeps around one face of the hexacoordinate transition state. This causes the incoming ketone to orient itself in such a manner as to minimize the interaction with the R group. Again delivery of the hydride must occur on the re face of the ketone.

Figure 8. 6: Proposed hexacoordinate silicon transition state



First, this mode of binding predicts that the stereochemical outcome of the reductions with histidine should be independent of the number of equivalents (1 or 2) of base added. Secondly, it predicts that the size and relative flexibility of the R group will control the stereochemical outcome of the reaction. This explains the observed equal selectivity of the reductions carried out with phenylalanine and histidine. If this model is correct the bulkiness of the R group is vital to the stereocontrol observed.

8.5 CONCLUSION

We have noted the utility of lithium imidazolide as a nucleophilic activator of silicon. The pentacoordinate silicon so produced is more reactive than its tetracoordinate counterpart, and thus subsequent complexation of carbonyl compounds lead to intramolecular hydride transfer. This produces product alcohols which display enantiopreferences, in this case for *S*-alcohols. A model is put forth which accounts for the reduction process, and observable spectroscopic measurements. The observation that the various pentacoordinate species produced exhibit almost identical upfield ^{29}Si NMR shifts and the appearance of methoxide in ^{13}C NMR analysis allowed for the elucidation of these reactive intermediates. Molecular modeling calculations support the findings of the preference for the *S*-alcohol. This preference may or may not involve π-stacking interactions. As outlined above, it would seem more likely that the binding of amino acids to silicon involves the α-amino group and also the carboxylate function, and stereodiscrimination results from an orientation that minimizes steric interactions. This mode of binding accounts for all the spectroscopic measurements made. The true nature of these reactive intermediates will not be appreciated until the isolation and crystal structure analysis is performed. These studies are on the way and will form the subject of future communication from the laboratory.

8.6 Experimental Section

8.6.1 Reagents and Physical Methods

The following materials were obtained from Aldrich and were used without further purification: acetophenone, benzophenone, *n*-butyllithium (2M solution in cyclohexane), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDAC-HCl), chlorodimethylsilane, 4,7-dimethyl-1-indanone, dimethylformamide, absolute ethanol, THF-d_8, *L*-histidine, *L*-proline, *L*-alanine, imidazole, 4-methoxyacetophenone, 4-methoxybenzophenone, (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl (+)), 4-methylacetophenone, 4-methylbenzophenone, *N*-methylimidazole, 4-phenyl-2-butanone, *trans*-4-phenyl-3-buten-2-one, sodium borohydride, sodium sulfate, *N*,*N*,*N'*,*N'*-tetramethylethylenediamine (TMEDA), triethoxysilane, 4-(trifluoromethyl)acetophenone, trimethoxysilane and 4-(trifluoromethyl)benzophenone.

^{1}H NMR spectra were recorded on a Bruker AC-200 (at 200-MHz for protons) Fourier transform spectrometer. ^{13}C and ^{29}Si-NMR were performed on a Bruker AC-200 (50.32 MHz and 39.7 for carbon and silicon, respectively) or a Bruker AC-300 (at 75.44 MHz and 59.60 MHz for carbon and silicon, respectively), respectively. ^{1}H chemical shifts are reported either with respect to tetramethylsilane as an external standard, set to 0 ppm, or $CHCl_3$ as an internal standard, set at 7.24 ppm. ^{13}C chemical shifts are reported either with respect to $CDCl_3$ as an internal standard, set at 7.24 or THF-d_8 as an internal standard set at 67.57 ppm. Coupling constants (J) are recorded in Hertz (Hz). The abbreviations s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, are used to report spectra.

Electron impact (EI) and chemical ionization (CI, NH_3) mass spectra were recorded at 70 eV with a source temperature of 200 °C on a VG analytical ZAB-R mass spectrometer equipped with a VG 11-250 data system. High resolution mass spectral (HRMS) data were obtained using the EI method. Infrared spectra were run as KBr pellets or as liquid films on NaCl discs (as indicated) on a Perkin-Elmer 283 spectrometer or on a BIORAD FTS-40 spectrometer as a neat film.

All solvents were thoroughly dried before use: acetonitrile was dried over P_2O_5; THF was dried from Na/benzophenone. All reactions were carried out in dry apparatus under a nitrogen atmosphere with the use of septa and syringes for the transfer of reagents.

Molecular modelling calculations were performed with the Hyper-Chem 5 modelling package, using semi-empirical methods. AM1 basis functions were used with a constrained trigonal bipyramidal geometry for all calculations involving the extracoordinate silicon species.

8.6.2 General Procedure for the Data Reported in Table 8. 1

8.6.2.1 General Procedure for Reduction with ligand 6a:

*Triethoxysilane **2a** and especially trimethoxysilane **2b** are rather toxic compounds (causing corneal damage in particular) and therefore care must be taken in their handling. Both are available commercially (Aldrich) and can be handled without problems via syringe techniques.* To a dry 100 ml round bottom flask flushed with nitrogen was added 1 (40 mg, 0.10 mmol) and THF (30 ml). The mixture was cooled to

–78 °C before the slow addition *n*-butyl lithium (1.6M, 0.20 ml, 0.2 mmol). The resulting reaction mixture was stirred at –78 °C for 5 min and then allowed to warm up to 0 °C. TMEDA (1.0 ml, 6 mmol) was added and stirred for 10 min, then trimethoxysilane (0.38 ml, 3 mmol) was added and reaction stirred for an additional 10 min. Finally acetophenone (0.35 mL, 3 mmol) was added and the reaction mixture was kept at 0 °C for 24 h. The reaction was quenched by the addition of sodium hydrogen carbonate (0.1 M, 20 mL) and stirred vigorously for 30 min at room temperature. The biphasic system was transferred to a separatory funnel and extracted with ether (3 x 40 ml). The ether was removed without drying and the resulting crude product was purified by column chromatography on silica gel eluting with pentane/ether (3:1), to give (*S*)-phenethyl alcohol (0.31 g, 85%) as a colourless liquid.

8.6.2.2 General Procedure for Reduction with amino acids:

To a dry 100 ml round-bottomed flask flushed with nitrogen was added *L*-histidine (50 mg, 0.3 mmol) and THF (30 ml). At ambient temperature *n*-butyllithium (2M, 0.32 ml, 0.6 mmol) was added slowly and the resulting suspension stirred for 30 min. The reaction mixture was cooled to 0 °C and TMEDA (1.0 ml, 6 mmol) was added. After stirring for 10 min trimethoxysilane (0.38 ml, 3 mmol) was added and reaction stirred for an additional 10 min. Finally acetophenone (0.35 ml, 3 mmol) was added and the reaction mixture was kept at 0 °C for 24 h. The reaction was quenched by the addition of sodium hydrogen carbonate (0.1 M, 20 ml) and stirred vigorously for 30 min at room temperature. The biphasic system was transferred to a separatory funnel and

extracted with ether (3 x 40 ml). The ether was removed without drying and the resulting crude product was purified by column chromatography on silica gel eluting with pentane/ether (3:1), to give (*S*)-phenethyl alcohol (0.31 g, 85%) as a colourless liquid. ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.56 (d, 3H, J = 6.5 Hz, PhCH(OH)C*H*$_3$), 2.76 (bs, 1H, PhCH(O*H*)CH_3), 4.94 (q, 1H, J = 6.5 Hz, PhC*H*(OH)CH_3), 7.32-7.45 (m, 5H$_{arom}$); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.97, 69.99, 125.24, 127.14, 128.24, 145.75; FTIR (neat, KBr disc) ν (cm^{-1}) 3364, 3065, 3031, 2974, 2929, 1728, 1603, 1494, 1452, 1371, 1287, 1204, 1077, 1030, 1011, 900, 762, 700, 607, 541; MS (EI) m/z (%): 122 (M^+, 10), 121 (40), 104 (68), 79 (28), 57 (7), 43 (100); (CI) m/z (%): 140 (M^+ + 18, 17), 122 (100), 105 (41), 78 (2), 52 (1), 44(1).

8.6.3 General Procedure for the Data Reported in Table 8. 2

To a dry 10 ml vial, fitted with a septum, flushed with nitrogen was added *L*-histidine (0.23 g, 1.5 mmol) and THF-d_8 (2 ml). At ambient temperature *n*-butyl lithium (1.1 ml, 1.5 mmol, 1.4 M solution in hexane) was added slowly and the resulting suspension was stirred for 20 min at room temperature, cooled to 0 °C and TMEDA (0.5 ml) was added. The mixture was stirred for an additional 10 min, after which time trimethoxysilane (0.20 ml, 1.5 mmol) was added. The system was stirred for 10 min at 0 °C. The resulting mixture was filtered through a dry glass wool-plugged Pasteur pipette into a dry 10 ml NMR tube under nitrogen. The resulting solution was analysed by ^{13}C NMR analysis. The data obtained from analysis are shown in **Table 8. 2**.

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Chapter 9

Copper (II) Complexes of *N*-Methyl Imidazole Amines: Synthesis and Crystal Structure*

9.1 ABSTRACT

The ligand *N,N'*-bis(*N*-methyl-2-methylene-imidazole)-1,2-ethanediamine **2** and chiral (*R,R*) *N,N'*-bis(*N*-methyl-2-methylene-imidazole)-1,2-cyclohexanediamine **3** were prepared from the $NaBH_4$ reduction of the corresponding bis-imine analogues. Reaction with copper (II) chloride hydrate afforded the complexes **4** and **5**, which were characterized by electrospray MS, IR, and X-ray crystallography. In complex **4** and **5**, the square pyramidal copper (II) is in-plane coordinated in a tetradentate fashion by ligand **2** and **3**, with the chloride ion in a pseudo apical position. The basal plane of the square pytamid is slightly distorted toward tetrahedral geometry. The secondary amines remain protonated upon complexation.

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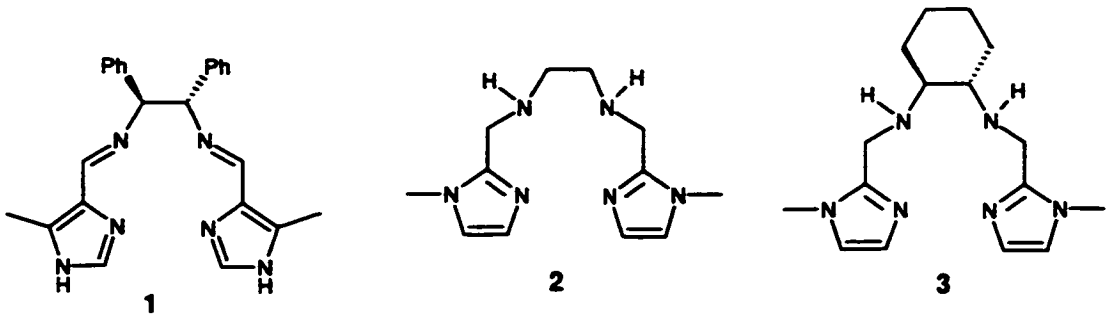
9.2 INTRODUCTION

Many hydrolytic enzymes (phosphoesterases, peptidases) contain metal centers within their active site. These metals are usually supported by amino-acid side chain ligands (e.g., His-imidazole, Asp/Glu-carboxylate, Lys-ammonium, etc.). We are interested in developing new catalytic systems that mimic the catalytic principles displayed in nature.[1] In these systems, the ligand should play a dual role, as a support for the reactions taking place at the bound metal center and as a source of chirality, so that the catalyzed reactions can be enantioselective. A further objective is to choose a ligand system, the reactivity of which can be easily tuned.

We have been examining ligands derived from imidazole and, by extension, histidine derivatives. For example, the simple imidazole anion has been shown to be a good activator of hydrosilanes toward the reduction of carbonyl compounds.[2] A related bidentate structure, **1** has been shown to induce reduction of ketones stereoselectively.[3] In this case, silicon occupies a position between the two imidazole rings: when introduced as a protecting group, imidazole groups frequently activate silicon.[4] Other related C_2-symmetric ligands are also of use in the ligand-accelerated reduction of carbonyl groups using hydrosilanes.[4]

Figure 9. 1: Bis-Imidazole Ligands



It is our interest to extend these studies to transition metal complexes. Enzymes frequently use multiple binding sites on metals to constrain transition state geometries of the reactions catalysed by the metal centers. We describe below the synthesis and characterization of a much simpler system that possess two imidazole and two amine ligands. In order to focus only on the metal binding properties of the imidazole group, and not the proton pump characteristics, the *N*-methyl derivative was used.[5] Chirality is provided, in one case, by the use of C_2-symmetric enantiopure bis-imidazoles **3**. Krämer *et al.*[6] have previously noted that related derivatives, in which two imidazole groups are sterically organized by a metal ion, may mimic the activity of imidazole in such enzymes as ribonuclease A.[7] We report herein the synthesis and crystal structure of *N,N'*-bis(*N*-methyl-2-methyleneimidazole)-1,2-ethanediamine copper (II) complex **4**, and *N,N'*-bis(*N*-methyl-2-methyleneimidazole)-1,2-cyclohexanediamine copper (II) complex **5**.

9.3 EXPERIMENTAL SECTION

9.3.1 Reagents and Physical Methods

The following materials were used without further purification: *N*-methylimidazole, butyllithium (2M, hexane), absolute ethanol, dimethylformamide, sodium borohydride and sodium sulfate (all from Aldrich); copper(II) chloride hydrate (BDH).

All solvents were thoroughly dried before use. Acetonitrile was dried over P_2O_5; THF was dried from K/benzophenone. All reactions were carried out in dry apparatus under a N_2 atmosphere with the use of septa and syringes for the transfer of reagents.

^1H and ^{13}C NMR spectra were recorded on a Bruker AC-200 (at 200-MHz for protons and at 50.32 MHz for carbon). Chemical shifts are reported with respect to $CHCl_3$ as an internal standard, set at 7.24 ppm.

Electron impact (EI) and chemical ionization (CI, NH_3) mass spectra were recorded at 70 eV with a source temperature of 200°C on a VG analytical ZAB-R mass spectrometer equipped with a VG 11-250 data system. High resolution mass spectral (HRMS) data were obtained using the EI method. Infrared spectra were run as KBr pellets or as liquid films on NaCl discs (as indicated) on a Perkin-Elmer 283 spectrometer or on a BIORAD FTS-40 spectrometer as a neat film.

_N_-Methyl-2-imidazolecarboxaldehyde 6

To a 50 ml round-bottomed flask flushed with N_2 was added *N*-methylimidazole (0.3g, 3.65 mmol) and THF (20 ml). To this stirring solution was added *n*-butyllithium (2.6 ml, 1.4 M solution in hexane, 3.65 mmol), dropwise. The resulting yellow-red solution was stirred for 3h at ambient temperature. Dimethylformamide (0.28 ml, 3.65 mmol) was added at this time; a white precipitate formed. The reaction mixture was stirred for 12 h at room temperature, and then quenched by an aqueous solution of saturated NH_4Cl (20 ml). The reaction mixture was evaporated to dryness under reduced pressure and the residue was dissolved in chloroform, which was washed several times with water. The chloroform solution was dried over sodium sulfate and the solvent was removed under reduced pressure to give a yellow solid. The product was purified on a silica gel column (flash chromatography) eluting with $CHCl_3$: MeOH (9:1, r.f. = 0.9). Yield: 0.34 g (85%), m.p. 36.1-36.8°C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.89 (s, 3H, N-C*H*$_3$), 7.01 (s, 1H, C*H*=CH), 7.13 (s, 1H, CH=C*H*), 9.67 (s, 1H, C*H*O); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 34.66, 127.15, 131.20, 143.46, 181.82; FTIR (KBr disc): ν (cm^{-1}) 3141, 9098, 1670, 1511, 1490, 1460, 1422, 1383, 1334, 1297, 1154, 1046, 920, 897, 802, 772, 698, 685, 422; MS (EI) m/z: 111 (M^++1, 52), 110 (M^+,100), 82 (68), 66 (2), 54 (42), 42(25); MS-High Resolution m/z: calcd. for mass $C_5H_6N_2O$; 110.0452 amu; found: 110.0480.

Preparation of the Bis-Imine Derived from *N*-Methyl-2-imidazolecarboxaldehyde 7

To **6** (0.25 g, 2.2 mmol) in acetonitrile (5 ml) was added ethylenediamine (0.08 ml, 1.1 mmol). The resulting system was allowed to stir at ambient temperature for 24 h. The product crystallized out of solution to yield 0.26 g (95%) of the desired bis-imine (m.p. 94.7-95.7°C).

^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.48 (s, 4H, C*H*$_2$), 4.45 (s, 6H, N-C*H*$_3$), 7.44 (s, 2H, C*H*=CH), 7.58 (s, 2H, CH=C*H*), 8.83 (s, 2H, *H*C=N); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 34.58, 61.23, 124.20, 128.33, 142.28, 153.56; FTIR (KBr disc): ν (cm^{-1}) 3132, 3107, 2952, 2909, 2887, 2851, 1655, 1641, 1523, 1479, 1440, 1415, 1366, 1326, 1289, 1230, 1151, 11021, 959, 928, 836, 786, 713, 692, 560, 482, 425; MS (EI) m/z: 111 (M^++1, 52), 244 (M^+, 3), 149 (40), 134 (11), 122 (38), 111 (36), 95 (83), 84 (87), 68 (6), 49 (100), 42 (64); (CI) m/z: 245 (M^++1, 100), 149 (13), 136 (7), 122 (9), 109 (11), 95 (15), 84 (13), 71 (9); Electro-spray MS (MeOH/AcCN/H_2O) m/z (%) 245 (M^+, 40), 195 (10), 162 (10), 136 (100), 110 (5), 95 (40), 83 (15).

Preparation of 2 from 7

To $NaBH_4$ (0.15 g, 4.09 mmol) in ethanol (5 ml) was added **7** (0.4g, 1.63 mmol) in ethanol (5 ml). After stirring the reaction mixture for 2 h at ambient temperature, the reaction was cooled to 0 °C and HCl (12 M, 3 ml) was added dropwise with stirring. The solvent was removed *in vacuo* after which time CH_2Cl_2 was added and the system was stirred for 2 h to help extract the product. The resulting system was filtered and the

desired product was obtained after removal of the solvent under reduced pressure and was recrystallized from ether/methanol. Yield 0.39g (96%).

^{1}H NMR (D_2O, 200 MHz) δ 3.40 (s, 4H, C*H*$_2$), 3.83 (s, 6H, N-C*H*$_3$), 4.56 (s, 4H, N-C*H*$_2$) 7.41 (s, 4H, C*H*=C*H*); ^{13}C NMR (D_2O ($CDCl_3$ as std.), 200 MHz) δ 38.60, 43.38, 48.51, 123.99, 129.21, 141.67; FTIR (KBr disc): ν (cm^{-1}) 3341, 3316, 3106, 3085, 1604, 1564, 1528, 1457, 1424, 1394, 1335, 1292, 1197, 1135, 1091, 1039, 960, 765, 692, 473; MS (EI) m/z: 248 (M^+-1, 6), 137 (10), 124 (55), 95 (100), 81 (10), 55 (9), 43 (18); (CI) m/z 249 (M^+, 100), 155 (19), 124 (29), 96 (40), 83 (8); Electro-spray MS (MeOH/AcCN/$H_2$0) m/z (%) 249 (M^+, 50), 176 (15), 167 (20), 155 (40), 137 (5), 125 (22), 95 (100), 83 (20); MS/MS (on mass 249): 249 (70), 177 (10), 167 (100), 137 (20), 95 (30).

9.3.2 Preparation of the Chiral Bis-Imine Derived from N-Methyl-2-imidazolecarboxaldehyde 8

To **6** (0.39 g, 3.50 mmol) and acetonitrile (5 ml) was added *R,R*-1,2-diaminocyclohexane (0.2 g, 1.75 mmol), which was allowed to stir at ambient temperature for 24 h. The solvent was removed, and ^{1}H-NMR analysis showed complete conversion to the desired product. Yield 0.57 g (98%) after filtration; m.p. 94.7-95.7°C.

^{1}H NMR ($CDCl_3$, 200 MHz) δ 0.88 (m, 4H), 1.21 (m, 4H), 2.69 (m, 2H), 3.27 (s, 6H, N-C*H*$_3$), 6.25 (s, 2H, im-*H*), 6.41 (s, 2H, im-*H*), 7.66 (s, 2H, N=C*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.30, 31.90, 34.37, 73.70, 123.81, 127.85, 142.04, 151.21; MS (EI) m/z (%): 299 (M^+ + 1, 100), 298 (M^+, 31), 216 (22), 203 (74), 191 (51), 160 (22), 134 (36), 109 (50), 95 (79), 93 (57), 54 (31), 42 (66); (CI) m/z (%): 299 (M^+ + 1, 100), 207 (13), 109

(10), 83 (13); MS-High Resolution m/z: calcd. for mass $C_{16}H_{23}N_6$ (M^+ +1); 299.2012 amu; found: 299.1984.

9.3.3 Preparation of the Chiral amine Derived from *N*-Methyl-2-imidazolecarboxaldehyde 3

To $NaBH_4$ (0.16 g, 4.38 mmol) and ethanol (5 ml) was added **8** (0.58g, 1.75 mmol) in ethanol (5 ml). After stirring the reaction mixture for 2 h at ambient temperature, the reaction was cooled to 0 °C and HCl (12 M, 3 ml) was added dropwise with stirring. The solvent was removed *in vacuo* after which time CH_2Cl_2 was added and the system was stirred for 2 h to help extract the product. After filtration the solvent was removed under reduced pressure. The resulting solid was recrystallized from ether/methanol. Yield 0.58g (98%).

^1H NMR ($CDCl_3$, 200 MHz) δ1.81 (m, 2H), 2.24 (m, 4H), 2.70 (m, 2H), 3.28 (m, 2H), 3.76 (s, 6H, N-C*H*$_3$), 4.15 (d, 2H, J = 14.5 Hz, N-C*H*$_a$), 4.35 (d, 2H, J = 14.5 Hz, N-C*H*$_b$), These signals are geminal coupling between the methylene protons alpha to imidazole species, 7.15 (s, 2H, im-*H*), 7.25 (s, 2H, im-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.61, 29.22, 36.07, 39.03, 61.31, 120.41, 125.89, 141.61; MS (EI) m/z (%): 302 (M^+, 4), 191 (7), 112 (36), 95 (100), 42 (23); (CI) m/z (%): 303 (M^+ + 1, 100), 248 (6), 112 (46), 95 (54), 46 (29); MS-High Resolution m/z: calcd. for mass $C_{16}H_{26}N_6$ (M^+); 302.2250 amu; found: 302.2219.

Preparation of the Copper Complex 4

Compound **2** (0.02 g, 0.01 mmol) was allowed to dissolve in methanol (5 ml) before the addition of anhydrous K_2CO_3 (0.02 g, 0.02 mmol) and $CuCl_2 \cdot 2H_2O$ (0.01 g, 0.01 mmol). After stirring the resulting system at ambient temperature for 4 h, the solid was filtered off and the clear blue solution was layered with diethyl ether. After 2 weeks bluish-purple crystals were isolated. Yield 0.01 g (40%).

FTIR (KBr disc): ν (cm^{-1}) 3421, 3186, 3135, 3106, 2927, 1641, 1508, 1455, 1290, 1174, 999, 936, 802, 512, 423; Electro-spray MS (MeOH/AcCN/H_2O) m/z (%) 310 (M^+, 100), 281 (12), 261 (5), 210 (3), 181 (5), 155 (70), 140 (18), 125 (22), 95 (18), 39 (28); MS/MS (on mass 310): 310 (15), 281 (40), 267 (5), 254 (30), 215 (5), 200 (100), 186 (7), 171 (4).

Preparation of the Copper Complex 5

Compund **3** (0.02 g, 0.01 mmol) was allowed to dissolve in methanol (5 ml) before the addition of anhydrous K_2CO_3 (0.02 g, 0.02 mmol) and $CuCl_2 \cdot 2H_2O$ (0.01 g, 0.01 mmol). After stirring the resulting system at ambient temperature for 4 h, the solid was filtered off and the clear blue solution was layered with diethyl ether. After 2 weeks bluish-purple crystals were isolated. Yield 0.01 g (40%).

FTIR (KBr disc): ν (cm^{-1}); 3425, 3178, 3130, 3100, 2928, 1639, 1510, 1452, 1280, 1170; Electro-spray MS (MeOH/AcCN/H_2O) m/z (%): 364 (M^+, 100), 269 (20), 182 (23), 175 (32).

X-ray data collection, structure solution and refinement

Single crystals of 4 were obtained and a structure determined. For relevant data can be found in **Table 9. 1.** Data collection was performed on a P4 Siemens/Syntex diffractometer, equipped with a Siemens SMART IK CCD area detector controlled by SMART,[8] and a rotating anode emitting Kα radiation monochromatized (0.7103 Å) by a graphite crystal. The crystal to detector distance was typically 5 cm. Processing of the raw data was completed using SAINT,[9] which applied Lorentz and polarization corrections to the three dimensionally integrated diffraction spots. Scaling of the integrated data was completed with SADABS,[10] which applies decay corrections, and an empirical absorption correction based on intensity ratios redundant reflections. XPREP[11] was used to confirm the unit cell dimensions and the crystal lattice. A solution was found using direct methods of SHELXTL™ Version 5 and refined by full-matrix least squares against F^2 (SHELXTL™ Version 5).

All calculations were performed on a Silicon Graphics, Inc., Model 4600PC workstation using the SHELXTL™ Version 5[11] determination package for structure solution, refinements and molecular graphics.

No absorption correction was performed. Anisotropic thermal parameters were used for all non-hydrogen atoms. Figure 9.2 shows the ORTEP diagram of 4 and 5 with 50% probability ellipsoids. In **Figure 9. 2** no disordered solvent molecules are represented.

Single crystals of **5** were obtained and a structure determined. For relevant data see **Table 9.1** and **Table B9.2.**

Table 9. 1: X-ray crystallographic information for **4** and **5**

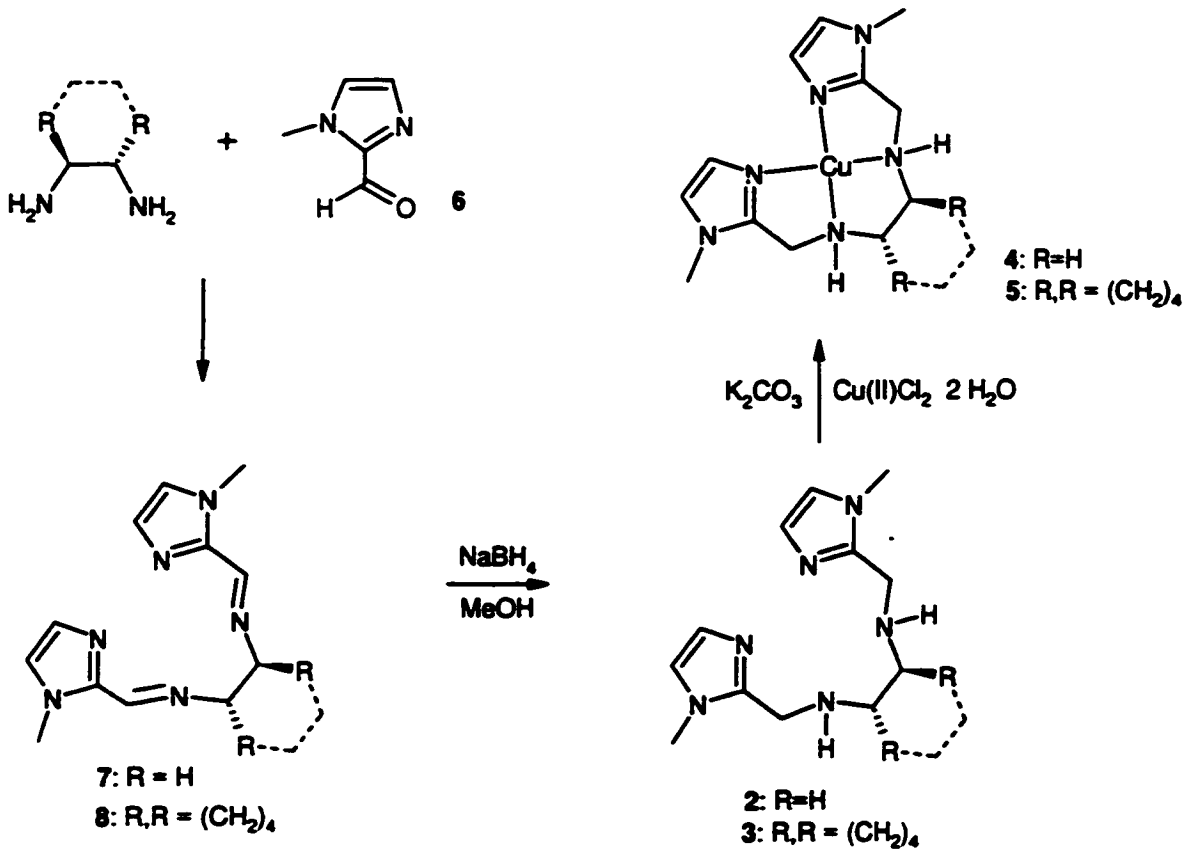
Crystal Parameters	4	5
Formula	$C_{12}H_{22.67}Cl_2CuN_6O_{1.33}$	$C_{16}H_{32}C_{12}CuN_6O_3$
Formula Weight	406.80	490.92
Temperature (K)	299(2)	299(2)
Radiation wavelength, Mo Kα (Å)	0.71073	0.71073
Crystal system	Monoclinic	Orthorhombic
Space group	C2/c	P2(1)2(1)2(1)
a (Å)	9.4799(14	8.1347(5)
b (Å)	14.879(2)	20.6673(4)
c (Å)	12.945(2)	25.30750(10)
α (°)	90°	90°
β (°)	108.565(4)°	90°
γ (°)	90°	90°
Volume ($Å^3$)	1731.0(5)	4254.8(3) $Å^3$
Z	4	8
D_c(g cm^{-3})	1.561	1.533
Absorption coefficient (mm^{-1})	1.583	1.308
Crystal size (mm)	.06 x .13 x .24 mm^3	.04 x .06 x .26 mm^3
Theta range for Data collection(°)	2.65 to 27.61	1.27 to 21.97°
Reflections collected	7780	25324
Independent reflections	1991 [R(int) = 0.1035]	5215 [R(int) = 0.1266]
R	0.0573	0.0574
R_w	0.1211	0.1077
Goodness of fit	0.902	0.956
Largest diff. peak and hole	0.654 and -0.386 e.$Å^{-3}$	0.338 and -0.287 e.$Å^{-3}$

9.4 RESULTS AND DISCUSSION:

9.4.1 Synthesis and characterization

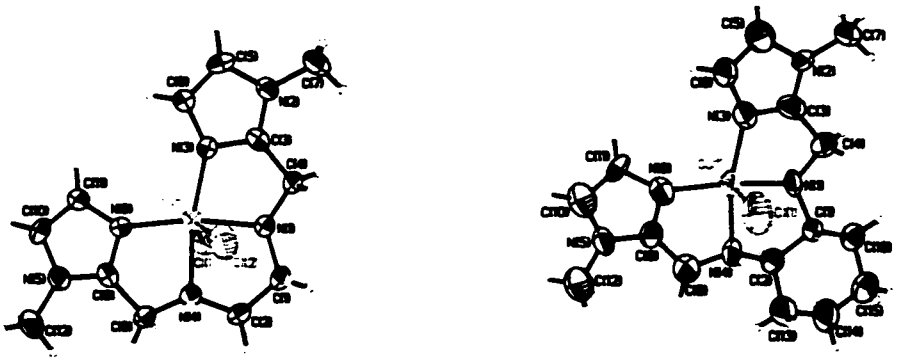
N-Methyl-2-imidazolecarboxaldehyde **6** was synthesized by the classical method; base deprotonation of imidazole followed by addition of dimethylformamide. Note that the lithium salt of the carbinolamine precipitates from the THF solution and can be isolated if the reaction is not worked up under aqueous conditions. Ligand **2** was readily prepared by condensation of *N*-methyl-2-imidazolecarboxaldehyde (2 equivalents) with ethylenediamine in acetonitrile to give the **7**, followed by reduction of the diimine with $NaBH_4$ (Scheme 1). The Schiff base **7** could be isolated and was quite air stable and, therefore, characterization was straightforward. The analogous enantiopure ligand **3** was also readily prepared in 85-90% yield.

Scheme 9. 1: Synthetic procedure used to obtain 4 and 5



The copper complexes **4** and **5** were prepared by the reaction **2** and **3**, respectively, with copper (II) chloride in methanol in the presence of excess potassium carbonate. Bluish-purple crystals of **4** and **5** were grown by slow diffusion of ether in a methanol solution of the complex. Electro-spray mass spectrometry, infrared spectroscopy and X-ray crystallography (Table 9. 1) were used to elucidate the structures of **4** and **5**. The bis-*N*-methylimidazole ligands **2 and 3** form 1:1 complexes with Cu^{2+} with a tetradentate in-plane co-ordination in the solid state. Relevant bond lengths and angles are shown in the Appendix. Cu sits on a crystalographic 2 fold axis.

Figure 9. 2: Crystal structure of 4 and 5: 50% probability ellipsoids with non-hydrogen atoms labelled

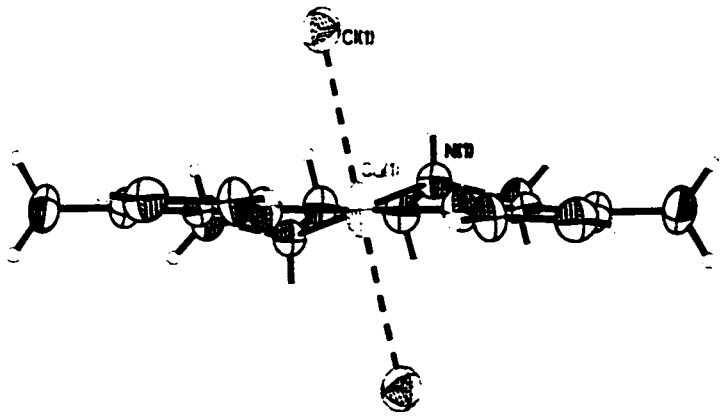


4 5

In both structures, the copper ion has a square pyramidal geometry allocated within the body of the ligand. Four short in-plane bonds (1.9370-1.9903) are formed between copper and all nitrogen atoms N(2), N2(A), N(3), and N3(A) of the tetradentate ligand **2** and **3**. The crystallographic data support the contention that N(2) and N(2A) seem to retain their sp^3 hybridization upon binding in the complex.

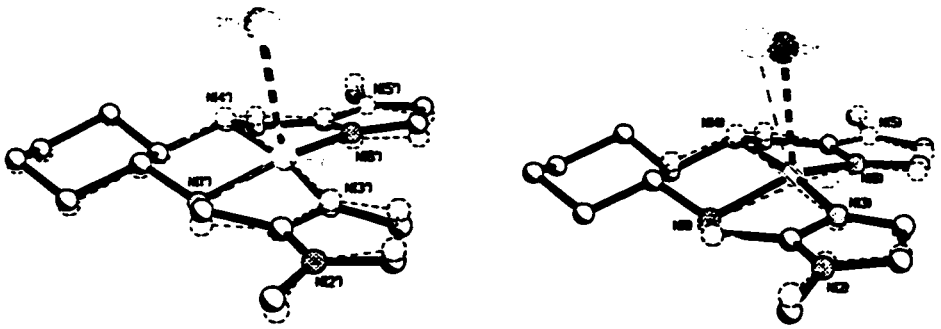
Atomic coordinates and isotropic thermal parameters are listed in **Table A9.2** for **4**. The copper ion is square-pyramidally coordinated, and sits on a crystallographic special position (two-fold axis). The basal plane of the square pyramid is slightly distorted towards tetrahedral geometry (**Figure 9.3**).

Figure 9. 3: Basal plane of the square pyramid looking down the C_2 axis



Atomic coordinates and isotropic thermal parameters are listed in **Table B9.2** for **5**. The unit cell contains two independent molecules of **5**. In order to access the chirality in these systems the Flack parameter was analyzed for the *S,S* and *R,R* isomer. Scrutiny of this parameter depicted that the chirality of the starting cyclohexyldiamine adduct was retained utilizing the reaction conditions that produced initially the chiral ligand and subsequently the copper complex. Similar to the molecule above there are two moles of chloride for each copper ion. Moreover, the square-pyramidal structure of **5** is closely related to that of **4**, with very similar bond distances and angles at the metal center. The similarities of these two structures are noted if one inspects **Figure 9.4**. **Figure 9.4a** depicts the closeness of fit between the two independent cyclohexyl molecules present in the crystal packing of **5**.

Figure 9. 4: The superposition of the two independent cyclohexyl copper adducts (A) and cyclohexyl adduct onto the ethylene diamine adduct (B)



A) B)

The closeness of fit accessed through correlation of N1, N2, N3, N4, N5, N6 to N1', N2', N3', N4', N5', and N6' shows a route mean square (RMS) deviation between the relative position of these atoms of 0.0893 Å. **Figure 9.4B** depicts the closeness of fit between the achiral ethylene diamine nitrogens and chiral cyclohexyldiamine complex of 0.236 Å. Moreover, Cu1-Cu1' and Cl1-Cl1', in comparison with the cyclohexyl species, deviate from each other by 0.042 Å and 0.157 Å, respectively. The same comparison between Cu1-Cu1 and Cl1-Cl1, in the comparison of cyclohexyl and ethylenediamine chelates, produced deviations of 0.236 Å and 0.696 Å respectively. The same comparison between Cu1-Cu1 and Cl1-Cl1, in the comparison of the cyclohexyl and ethylenediamine chelates, produced deviation of 0.236 Å and 0.696 Å respectively.

Electrospray mass spectral analysis of **4** and **5** did not reveal a molecular ion peak at 312 and 366 respectively, suggesting the lack of secondary amine hydrogens. One would expect to see significant 156 and 183 peaks (doubly charged species are found at half

mass) if these species contained protonated nitrogens. Contradicting this contention is the significant NH stretch (3421 cm^{-1}) in the infrared spectrum, which hints at the difference in structure between the solution and solid phases.

We suggest that the C_2-cyclohexane ligand will exert an influence over the efficiency of binding of additional ligands at copper or other metals bound to this and related ligands. Structural details of **5** suggest that the ring is in an excellent position to exert an influence on organic reactions catalyzed by the metal center. A number of chiral ligands with the same general structure as **5**, chelated to various metals, are currently under investigation in our laboratory in this context, for their ability to catalyze Lewis acid-promoted reactions (Diels-Alder, ene, aldol, etc.), hydrosilylation, and reductions, and will form the basis for future communications.

9.5 CONCLUSION

Reaction with copper (II) chloride hydrate with ligands **2** and **3** afforded the complexes **4** and chiral **5**, which were characterized by electrospray MS, IR, and X-ray crystallography. In complex **4** and **5**, the square pyramidal copper (II) is in-plane co-ordinated in a tetradentate fashion by ligand **2** and **3**, with the chloride ion in a pseudo apical position. The secondary amines remain protonated upon complexation. We are especially encouraged by the formation of chiral metal complex **5**, and believe that subsequent metal complexes derived from this and related ligands should confer stereoselection in the reactions that they may catalyze.

Appendix to Chapter 9

Crystal Data Collection Tables for 4 and 5

Table A9. 1: Crystal data and structure refinement for 4.

Identification code	45	
Empirical formula	C12 H22.67 Cl2 Cu N6 O1.33	
Formula weight	406.80	
Temperature	299(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	C2/c	
Unit cell dimensions	a = 9.4799(14) Å	α= 90°.
	b = 14.879(2) Å	β= 108.565(4)°.
	c = 12.945(2) Å	γ = 90°.
Volume	1731.0(5) $Å^3$	
Z	4	
Density (calculated)	1.561 Mg/m^3	
Absorption coefficient	1.583 mm^{-1}	
F(000)	841	
Crystal size	.06 x .13 x .24 mm^3	
Theta range for data collection	2.65 to 27.61°.	
Index ranges	-12<=h<=12, -19<=k<=17, -16<=l<=16	
Reflections collected	7780	
Independent reflections	1991 [R(int) = 0.1035]	
Completeness to theta = 27.61°	98.6 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	1991 / 0 / 107	
Goodness-of-fit on F^2	0.902	
Final R indices [I>2sigma(I)]	R1 = 0.0573, wR2 = 0.1211	
R indices (all data)	R1 = 0.1875, wR2 = 0.1466	
Largest diff. peak and hole	0.654 and -0.386 $e.Å^{-3}$	

Table A9. 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 6. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cu(1)	5000	1229(1)	2500	52(1)
N(1)	5205(5)	2200(2)	1499(3)	34(1)
N(2)	7095(5)	417(3)	480(3)	37(1)
N(3)	5858(5)	467(3)	1643(3)	37(1)
C(1)	5479(6)	3050(3)	2132(4)	39(2)
C(3)	6434(6)	958(3)	1004(4)	31(1)
C(4)	6308(6)	1949(3)	955(4)	41(2)
C(5)	6956(6)	-454(3)	794(4)	41(2)
C(6)	6182(6)	-412(4)	1511(4)	40(2)
C(7)	7839(6)	691(4)	-307(5)	51(2)
Cl(1)	1622(2)	1770(1)	1028(1)	59(1)
O(1)	0	2742(4)	2500	78(2)
O(2)	0	383(10)	2500	65(8)

Table A9. 3: Bond lengths [Å] and angles [°] for 4.

Cu(1)-N(3)	1.937(4)
Cu(1)-N(3)#1	1.937(4)
Cu(1)-N(1)	1.990(4)
Cu(1)-N(1)#1	1.990(4)
N(1)-C(1)	1.484(6)
N(1)-C(4)	1.482(5)
N(2)-C(3)	1.331(6)
N(2)-C(5)	1.377(6)
N(2)-C(7)	1.469(6)
N(3)-C(3)	1.343(6)
N(3)-C(6)	1.367(6)
C(1)-C(1)#1	1.513(8)
C(3)-C(4)	1.480(7)
C(5)-C(6)	1.356(6)
N(3)-Cu(1)-N(3)#1	108.3(2)
N(3)-Cu(1)-N(1)	84.61(15)
N(3)#1-Cu(1)-N(1)	160.61(17)
N(3)-Cu(1)-N(1)#1	160.61(17)
N(3)#1-Cu(1)-N(1)#1	84.61(15)
N(1)-Cu(1)-N(1)#1	87.0(2)
C(1)-N(1)-C(4)	116.7(4)
C(1)-N(1)-Cu(1)	107.2(3)
C(4)-N(1)-Cu(1)	110.9(3)
C(3)-N(2)-C(5)	108.3(4)
C(3)-N(2)-C(7)	126.4(4)
C(5)-N(2)-C(7)	125.3(4)
C(3)-N(3)-C(6)	106.9(4)
C(3)-N(3)-Cu(1)	111.2(3)
C(6)-N(3)-Cu(1)	141.6(3)
N(1)-C(1)-C(1)#1	108.2(3)
N(2)-C(3)-N(3)	109.6(4)
N(2)-C(3)-C(4)	128.7(4)
N(3)-C(3)-C(4)	121.7(4)
C(3)-C(4)-N(1)	106.8(4)
C(6)-C(5)-N(2)	106.4(4)
C(5)-C(6)-N(3)	108.8(4)

Symmetry transformations used to generate equivalent atoms:

#1 -x+1,y,-z+1/2

Table A9. 4: Anisotropic displacement parameters ($Å^2 x\ 10^3$) for 4. The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cu(1)	80(1)	33(1)	60(1)	0	48(1)	0
N(1)	38(3)	30(3)	38(3)	-1(2)	15(2)	-3(2)
N(2)	37(3)	40(3)	40(3)	-2(2)	19(2)	-1(2)
N(3)	51(3)	28(3)	39(3)	3(2)	22(3)	1(2)
C(1)	48(4)	25(3)	47(4)	4(3)	19(3)	0(3)
C(3)	23(3)	44(4)	26(3)	-2(3)	6(3)	3(3)
C(4)	52(4)	28(3)	52(4)	2(3)	28(3)	2(3)
C(5)	46(4)	27(4)	51(4)	-6(3)	15(3)	8(3)
C(6)	52(4)	33(3)	41(4)	2(3)	26(3)	1(3)
C(7)	50(4)	60(4)	53(4)	-3(3)	32(4)	5(3)
Cl(1)	57(1)	66(1)	60(1)	-16(1)	27(1)	-6(1)
O(1)	106(6)	43(4)	114(6)	0	74(5)	0
O(2)	62(15)	30(11)	80(15)	0	-10(11)	0

Table A9. 5: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 4.

	x	y	z	U(eq)
H(1C)	4309	2255	969	41
H(1A)	5230	3560	1641	47
H(1B)	6521	3094	2563	47
H(4A)	5978	2151	204	49
H(4B)	7264	2223	1326	49
H(5A)	7321	-969	560	49
H(6A)	5916	-901	1857	47
H(7A)	7783	1333	-391	76
H(7B)	7357	411	-997	76
H(7C)	8864	510	-46	76

Table A9. 6: Torsion angles [°] for 4.

N(3)-Cu(1)-N(1)-C(1)	-148.5(4)
N(3)#1-Cu(1)-N(1)-C(1)	78.4(6)
N(1)#1-Cu(1)-N(1)-C(1)	14.0(2)
N(3)-Cu(1)-N(1)-C(4)	-20.0(4)
N(3)#1-Cu(1)-N(1)-C(4)	-153.1(5)
N(1)#1-Cu(1)-N(1)-C(4)	142.5(4)
N(3)#1-Cu(1)-N(3)-C(3)	178.1(4)
N(1)-Cu(1)-N(3)-C(3)	12.9(4)
N(1)#1-Cu(1)-N(3)-C(3)	-51.9(7)
N(3)#1-Cu(1)-N(3)-C(6)	-8.3(6)
N(1)-Cu(1)-N(3)-C(6)	-173.5(7)
N(1)#1-Cu(1)-N(3)-C(6)	121.7(7)
C(4)-N(1)-C(1)-C(1)#1	-164.0(5)
Cu(1)-N(1)-C(1)-C(1)#1	-38.9(6)
C(5)-N(2)-C(3)-N(3)	-0.5(6)
C(7)-N(2)-C(3)-N(3)	179.1(5)
C(5)-N(2)-C(3)-C(4)	178.9(6)
C(7)-N(2)-C(3)-C(4)	-1.5(9)
C(6)-N(3)-C(3)-N(2)	0.3(6)
Cu(1)-N(3)-C(3)-N(2)	176.1(3)
C(6)-N(3)-C(3)-C(4)	-179.2(5)
Cu(1)-N(3)-C(3)-C(4)	-3.3(6)
N(2)-C(3)-C(4)-N(1)	168.1(5)
N(3)-C(3)-C(4)-N(1)	-12.5(7)
C(1)-N(1)-C(4)-C(3)	144.8(5)
Cu(1)-N(1)-C(4)-C(3)	21.6(5)
C(3)-N(2)-C(5)-C(6)	0.5(6)
C(7)-N(2)-C(5)-C(6)	-179.0(5)
N(2)-C(5)-C(6)-N(3)	-0.4(6)
C(3)-N(3)-C(6)-C(5)	0.1(6)
Cu(1)-N(3)-C(6)-C(5)	-173.7(5)

Symmetry transformations used to generate equivalent atoms:
#1 -x+1,y,-z+1/2

Table B9. 1: Crystal data and structure refinement for 5.

Identification code	p212121	
Empirical formula	C16 H32 Cl2 Cu N6 O3	
Formula weight	490.92	
Temperature	299(2) K	
Wavelength	0.71073 Å	
Crystal system	Orthorhombic	
Space group	P2(1)2(1)2(1)	
Unit cell dimensions	a = 8.1347(5) Å	α= 90°.
	b = 20.6673(4) Å	β= 90°.
	c = 25.30750(10) Å	γ = 90°.
Volume	4254.8(3) $Å^3$	
Z	8	
Density (calculated)	1.533 Mg/m^3	
Absorption coefficient	1.308 mm^{-1}	
F(000)	2056	
Crystal size	.04 x .06 x .26 mm^3	
Theta range for data collection	1.27 to 21.97°.	
Index ranges	-8<=h<=8, -21<=k<=20, -26<=l<=26	
Reflections collected	25324	
Independent reflections	5215 [R(int) = 0.1266]	
Completeness to theta = 21.97°	100.0 %	
Absorption correction	None	
Refinement method	Full-matrix least-squares on F^2	
Data / restraints / parameters	5215 / 0 / 487	
Goodness-of-fit on F^2	0.956	
Final R indices [I>2sigma(I)]	R1 = 0.0574, wR2 = 0.1077	
R indices (all data)	R1 = 0.1379, wR2 = 0.1299	
Absolute structure parameter	0.03(3)	
Extinction coefficient	0.00034(18)	
Largest diff. peak and hole	0.338 and -0.287 $e.Å^{-3}$	

Table B9. 2: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 5. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
Cu(1)	1348(2)	5403(1)	1078(1)	66(1)
Cl(1)	3921(5)	5132(2)	1710(1)	88(1)
N(1)	-105(11)	5887(4)	1584(3)	52(3)
N(2)	-1565(12)	4272(5)	1925(4)	52(3)
N(3)	65(11)	4648(5)	1314(4)	55(3)
N(4)	2482(10)	6248(4)	1000(3)	50(2)
N(5)	3580(13)	5629(5)	-320(4)	54(3)
N(6)	2177(11)	5230(6)	357(4)	58(3)
C(1)	796(13)	6456(5)	1773(4)	47(3)
C(16)	-219(12)	6937(5)	2089(4)	53(3)
C(15)	811(15)	7547(5)	2203(4)	66(4)
C(14)	1442(18)	7856(6)	1699(5)	86(4)
C(13)	2509(14)	7357(6)	1371(5)	77(4)
C(2)	1468(14)	6777(5)	1272(4)	49(3)
C(3)	-785(16)	4798(6)	1744(5)	57(4)
C(4)	-764(16)	5454(5)	1988(4)	71(4)
C(5)	-1213(15)	3763(6)	1578(5)	68(4)
C(6)	-172(16)	4013(6)	1211(5)	63(4)
C(7)	-2738(13)	4211(5)	2368(4)	67(4)
C(8)	2947(14)	5748(6)	167(5)	46(3)
C(9)	2936(14)	6381(6)	438(5)	73(4)
C(10)	3241(15)	4997(7)	-432(6)	66(4)
C(11)	2369(14)	4751(6)	-23(5)	51(3)
C(12)	4546(15)	6067(5)	-642(4)	76(4)
Cu(1')	3678(2)	374(1)	988(1)	52(1)
Cl(1')	803(3)	264(2)	1572(1)	64(1)
N(1')	3332(10)	1322(3)	803(3)	44(2)
N(2')	1284(13)	667(5)	-356(4)	55(3)
N(3')	2760(10)	240(5)	279(3)	42(3)
N(4')	4555(10)	717(4)	1684(3)	46(3)
N(5')	6587(13)	-844(5)	1793(4)	55(3)
N(6')	4824(11)	-401(5)	1230(4)	53(3)
C(1')	3262(12)	1679(5)	1299(4)	40(3)
C(16')	3379(13)	2426(4)	1233(4)	49(3)
C(15')	3371(15)	2758(5)	1753(5)	64(4)
C(14')	4802(15)	2522(6)	2101(4)	73(4)
C(13')	4675(13)	1762(6)	2179(4)	57(4)
C(2')	4684(13)	1461(5)	1648(4)	48(3)
C(3')	2024(15)	763(6)	104(5)	47(4)
C(4')	1923(13)	1363(5)	449(4)	52(3)

Table B9. 3: Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for 5 cont.. U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(5')	1621(16)	42(7)	-506(5)	66(4)
C(6')	2553(15)	-228(6)	-113(5)	56(4)
C(7')	315(15)	1142(5)	-670(4)	69(4)
C(8')	5806(14)	-292(6)	1630(5)	43(3)
C(9')	6024(12)	363(5)	1858(4)	55(3)
C(10')	6031(16)	-1310(6)	1470(6)	64(4)
C(11')	4966(15)	-1057(6)	1124(5)	58(4)
C(12')	7786(13)	-892(6)	2207(5)	70(4)
Cl(2)	6892(17)	7188(6)	384(4)	143(3)
Cl(2A)	4266(13)	7928(4)	28(3)	143(3)
O(1)	6844(18)	6816(8)	986(7)	100(3)
O(3)	6545(11)	6548(5)	1233(4)	100(3)
O(4)	6740(30)	7267(12)	601(8)	100(3)
Cl(2')	-4049(5)	1907(2)	-5(1)	104(1)
O(1')	-1588(15)	2357(5)	606(4)	102(3)
O(2')	-1220(60)	1260(40)	1669(19)	102(3)
O(3')	-1114(17)	1651(14)	1694(6)	102(3)
O(4')	-1260(30)	1999(12)	1353(11)	102(3)
O(5')	-1490(20)	2474(9)	862(7)	102(3)

Table B9. 4: Bond lengths [Å] and angles [°] for 5.

Cu(1)-N(3)	1.970(10)
Cu(1)-N(6)	1.977(9)
Cu(1)-N(4)	1.985(8)
Cu(1)-N(1)	2.010(8)
Cu(1)-Cl(1)	2.693(4)
N(1)-C(4)	1.462(12)
N(1)-C(1)	1.466(11)
N(2)-C(3)	1.338(12)
N(2)-C(5)	1.401(13)
N(2)-C(7)	1.479(12)
N(3)-C(3)	1.325(13)
N(3)-C(6)	1.353(13)
N(4)-C(9)	1.495(13)
N(4)-C(2)	1.532(11)
N(5)-C(8)	1.358(13)
N(5)-C(10)	1.365(12)
N(5)-C(12)	1.449(12)
N(6)-C(8)	1.331(12)
N(6)-C(11)	1.389(13)
C(1)-C(16)	1.519(12)
C(1)-C(2)	1.533(13)
C(16)-C(15)	1.540(13)
C(15)-C(14)	1.516(14)
C(14)-C(13)	1.582(14)
C(13)-C(2)	1.490(13)
C(3)-C(4)	1.491(14)
C(5)-C(6)	1.359(14)
C(8)-C(9)	1.477(14)
C(10)-C(11)	1.354(14)
Cu(1')-N(6')	1.951(9)
Cu(1')-N(3')	1.963(9)
Cu(1')-N(4')	2.028(8)
Cu(1')-N(1')	2.034(7)
N(1')-C(4')	1.458(11)
N(1')-C(1')	1.457(11)
N(2')-C(3')	1.325(13)
N(2')-C(5')	1.373(12)
N(2')-C(7')	1.489(12)
N(3')-C(3')	1.313(12)
N(3')-C(6')	1.395(13)
N(4')-C(9')	1.468(11)
N(4')-C(2')	1.544(12)
N(5')-C(10')	1.343(14)
N(5')-C(8')	1.369(13)
N(5')-C(12')	1.434(13)
N(6')-C(8')	1.311(11)
N(6')-C(11')	1.386(12)
C(1')-C(2')	1.523(13)

C(1')-C(16')	1.555(13)
C(16')-C(15')	1.485(12)
C(15')-C(14')	1.537(14)
C(14')-C(13')	1.586(15)
C(13')-C(2')	1.483(12)
C(3')-C(4')	1.520(14)
C(5')-C(6')	1.370(14)
C(8')-C(9')	1.481(13)
C(10')-C(11')	1.338(13)
Cl(2)-O(4)	0.58(2)
Cl(2)-O(1)	1.71(2)
Cl(2)-Cl(2A)#1	2.208(15)
Cl(2A)-Cl(2)#2	2.208(15)
O(1)-O(3)	0.870(18)
O(1)-O(4)	1.35(2)
O(1')-O(5')	0.70(2)
O(2')-O(3')	0.81(7)
O(2')-O(4')	1.72(9)
O(3')-O(4')	1.13(3)
O(4')-O(5')	1.59(3)

N(3)-Cu(1)-N(6)	108.5(5)
N(3)-Cu(1)-N(4)	166.7(4)
N(6)-Cu(1)-N(4)	84.8(4)
N(3)-Cu(1)-N(1)	83.7(4)
N(6)-Cu(1)-N(1)	151.5(4)
N(4)-Cu(1)-N(1)	84.2(4)
N(3)-Cu(1)-Cl(1)	93.8(3)
N(6)-Cu(1)-Cl(1)	104.2(3)
N(4)-Cu(1)-Cl(1)	83.1(3)
N(1)-Cu(1)-Cl(1)	100.5(3)
C(4)-N(1)-C(1)	116.5(8)
C(4)-N(1)-Cu(1)	110.9(7)
C(1)-N(1)-Cu(1)	108.3(6)
C(3)-N(2)-C(5)	107.4(10)
C(3)-N(2)-C(7)	129.4(11)
C(5)-N(2)-C(7)	122.9(11)
C(3)-N(3)-C(6)	108.1(10)
C(3)-N(3)-Cu(1)	109.9(10)
C(6)-N(3)-Cu(1)	141.8(10)
C(9)-N(4)-C(2)	115.4(9)
C(9)-N(4)-Cu(1)	111.8(6)
C(2)-N(4)-Cu(1)	109.4(6)
C(8)-N(5)-C(10)	106.6(11)
C(8)-N(5)-C(12)	127.1(12)
C(10)-N(5)-C(12)	126.2(13)
C(8)-N(6)-C(11)	105.6(10)
C(8)-N(6)-Cu(1)	110.4(9)
C(11)-N(6)-Cu(1)	143.8(11)
N(1)-C(1)-C(16)	115.2(9)
N(1)-C(1)-C(2)	104.7(8)
C(16)-C(1)-C(2)	110.2(9)
C(1)-C(16)-C(15)	109.8(9)

C(14)-C(15)-C(16)	111.7(10)
C(15)-C(14)-C(13)	110.6(10)
C(2)-C(13)-C(14)	107.5(10)
C(13)-C(2)-N(4)	110.2(9)
C(13)-C(2)-C(1)	114.2(9)
N(4)-C(2)-C(1)	104.8(8)
N(3)-C(3)-N(2)	109.8(11)
N(3)-C(3)-C(4)	123.2(12)
N(2)-C(3)-C(4)	127.0(12)
N(1)-C(4)-C(3)	105.7(9)
C(6)-C(5)-N(2)	105.6(12)
N(3)-C(6)-C(5)	109.0(11)
N(6)-C(8)-N(5)	111.2(11)
N(6)-C(8)-C(9)	122.8(12)
N(5)-C(8)-C(9)	125.8(13)
C(8)-C(9)-N(4)	106.3(10)
C(11)-C(10)-N(5)	107.8(12)
C(10)-C(11)-N(6)	108.8(12)
N(6')-Cu(1')-N(3')	110.6(4)
N(6')-Cu(1')-N(4')	81.2(4)
N(3')-Cu(1')-N(4')	167.6(4)
N(6')-Cu(1')-N(1')	158.2(4)
N(3')-Cu(1')-N(1')	82.7(4)
N(4')-Cu(1')-N(1')	84.9(3)
C(4')-N(1')-C(1')	118.0(8)
C(4')-N(1')-Cu(1')	107.9(6)
C(1')-N(1')-Cu(1')	107.2(6)
C(3')-N(2')-C(5')	107.0(11)
C(3')-N(2')-C(7')	127.6(11)
C(5')-N(2')-C(7')	125.3(12)
C(3')-N(3')-C(6')	106.0(10)
C(3')-N(3')-Cu(1')	111.5(8)
C(6')-N(3')-Cu(1')	142.5(10)
C(9')-N(4')-C(2')	117.3(8)
C(9')-N(4')-Cu(1')	111.9(7)
C(2')-N(4')-Cu(1')	108.7(6)
C(10')-N(5')-C(8')	104.9(11)
C(10')-N(5')-C(12')	128.6(12)
C(8')-N(5')-C(12')	126.4(11)
C(8')-N(6')-C(11')	105.5(10)
C(8')-N(6')-Cu(1')	113.1(9)
C(11')-N(6')-Cu(1')	141.4(10)
N(1')-C(1')-C(2')	108.6(9)
N(1')-C(1')-C(16')	114.1(9)
C(2')-C(1')-C(16')	108.1(9)
C(15')-C(16')-C(1')	111.2(8)
C(16')-C(15')-C(14')	111.0(9)
C(15')-C(14')-C(13')	109.6(9)
C(2')-C(13')-C(14')	107.6(9)
C(13')-C(2')-C(1')	113.4(10)
C(13')-C(2')-N(4')	111.4(9)
C(1')-C(2')-N(4')	106.2(9)
N(3')-C(3')-N(2')	112.4(11)

N(3')-C(3')-C(4')	120.2(11)
N(2')-C(3')-C(4')	127.0(12)
N(1')-C(4')-C(3')	105.2(8)
N(2')-C(5')-C(6')	107.0(11)
C(5')-C(6')-N(3')	107.5(12)
N(6')-C(8')-N(5')	111.9(10)
N(6')-C(8')-C(9')	122.1(12)
N(5')-C(8')-C(9')	126.1(12)
N(4')-C(9')-C(8')	103.9(9)
C(11')-C(10')-N(5')	109.7(12)
C(10')-C(11')-N(6')	108.1(11)
O(4)-Cl(2)-O(1)	44(3)
O(4)-Cl(2)-Cl(2A)#1	131(4)
O(1)-Cl(2)-Cl(2A)#1	113.1(9)
O(3)-O(1)-O(4)	160(2)
O(3)-O(1)-Cl(2)	159.1(18)
O(4)-O(1)-Cl(2)	17.6(11)
Cl(2)-O(4)-O(1)	118(4)
O(3')-O(2')-O(4')	33(3)
O(2')-O(3')-O(4')	124(5)
O(3')-O(4')-O(5')	178(3)
O(3')-O(4')-O(2')	23(2)
O(5')-O(4')-O(2')	155(3)
O(1')-O(5')-O(4')	122(3)

Symmetry transformations used to generate equivalent atoms:
#1 x+1/2,-y+3/2,-z #2 x-1/2,-y+3/2,-z

Table B9. 5: Anisotropic displacement parameters ($Å^2$x 10^3)for 5. The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2a^{*2}U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
Cu(1)	90(1)	53(1)	56(1)	-13(1)	24(1)	-12(1)
Cl(1)	94(2)	113(3)	59(2)	5(2)	-1(2)	24(2)
N(1)	70(7)	54(7)	32(6)	-7(5)	20(5)	0(5)
N(2)	66(7)	36(7)	53(7)	-18(5)	21(6)	-16(6)
N(3)	65(6)	54(8)	46(7)	2(6)	11(6)	-2(6)
N(4)	59(6)	60(7)	31(6)	-10(5)	3(5)	-3(5)
N(5)	61(7)	60(8)	41(7)	3(6)	15(7)	3(7)
N(6)	56(7)	65(9)	53(7)	3(7)	12(5)	0(6)
C(1)	55(8)	44(8)	43(7)	-9(6)	12(6)	-9(6)
C(16)	47(7)	53(9)	59(9)	-13(6)	4(6)	12(6)
C(15)	74(9)	50(9)	75(10)	-15(7)	4(8)	19(7)
C(14)	107(11)	77(10)	74(10)	-17(8)	21(11)	4(9)
C(13)	92(10)	65(10)	73(10)	-10(8)	25(8)	-7(8)
C(2)	58(7)	36(8)	53(8)	-11(6)	13(7)	4(7)
C(3)	63(9)	58(11)	48(9)	17(8)	-7(7)	-17(8)
C(4)	111(11)	39(9)	62(8)	-8(7)	15(8)	-18(8)
C(5)	56(8)	77(11)	73(10)	-2(9)	11(9)	3(8)
C(6)	76(10)	56(11)	59(10)	-12(8)	24(8)	1(7)
C(7)	91(9)	44(9)	65(9)	3(7)	23(8)	-14(7)
C(8)	49(9)	54(11)	36(9)	-3(8)	-4(7)	3(7)
C(9)	70(10)	84(12)	66(10)	-10(9)	4(8)	-12(8)
C(10)	49(9)	78(13)	71(10)	7(9)	7(8)	27(8)
C(11)	67(8)	32(9)	54(8)	-21(8)	-3(7)	9(7)
C(12)	81(10)	90(12)	58(9)	11(8)	7(8)	10(8)
Cu(1')	60(1)	42(1)	53(1)	1(1)	-10(1)	-1(1)
Cl(1')	62(2)	77(2)	53(2)	4(2)	-7(2)	-21(2)
N(1')	43(5)	33(6)	55(6)	11(5)	3(5)	-11(4)
N(2')	62(7)	48(8)	55(8)	-2(6)	8(7)	-3(7)
N(3')	47(6)	34(7)	45(6)	2(6)	1(5)	10(5)
N(4')	48(5)	45(7)	45(6)	11(5)	5(5)	-4(5)
N(5')	59(7)	44(8)	63(8)	-5(6)	27(7)	1(7)
N(6')	63(6)	37(7)	60(7)	-2(6)	-3(6)	4(6)
C(1')	28(6)	42(8)	50(8)	-1(6)	-1(6)	4(5)
C(16')	76(8)	25(7)	47(7)	0(5)	-6(7)	-8(6)
C(15')	71(9)	27(7)	92(10)	7(7)	15(9)	27(7)
C(14')	70(9)	78(12)	71(10)	-31(8)	-10(8)	-1(8)
C(13')	40(7)	77(10)	55(9)	-14(7)	-7(6)	5(7)
C(2')	50(7)	41(9)	53(9)	-1(6)	11(6)	-8(6)
C(3')	61(9)	56(11)	24(8)	4(7)	-11(7)	-9(8)
C(4')	71(9)	37(9)	49(8)	12(6)	-20(7)	1(6)
C(5')	69(9)	87(13)	42(8)	-22(8)	0(8)	-1(9)
C(6')	62(8)	51(10)	56(9)	-18(9)	10(7)	-9(7)
C(7')	83(9)	64(10)	60(9)	12(7)	-21(8)	-10(7)
C(8')	57(8)	16(8)	57(8)	-4(7)	1(7)	-6(7)

C(9')	45(7)	56(9)	63(8)	32(7)	-9(6)	14(8)
C(10')	62(9)	47(10)	85(10)	22(9)	13(9)	23(8)
C(11')	51(8)	47(10)	75(10)	5(8)	1(8)	-5(7)
C(12')	52(8)	77(11)	81(10)	20(8)	12(8)	5(7)
Cl(2)	224(8)	124(5)	80(5)	-1(4)	19(5)	-100(5)
Cl(2A)	224(8)	124(5)	80(5)	-1(4)	19(5)	-100(5)
Cl(2')	153(4)	71(3)	88(3)	-7(2)	36(3)	-20(2)

Table B9. 6: Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for 5.

	x	y	z	U(eq)
H(1B)	-977	6036	1394	63
H(4C)	3442	6216	1183	60
H(1A)	1722	6311	1991	57
H(16D)	-565	6742	2419	64
H(16E)	-1195	7055	1891	64
H(15B)	143	7857	2394	79
H(15C)	1736	7431	2426	79
H(14B)	2104	8231	1786	103
H(14C)	519	8000	1486	103
H(13C)	2852	7549	1039	92
H(13D)	3484	7237	1569	92
H(2A)	548	6898	1042	59
H(4A)	-1866	5585	2089	85
H(4B)	-72	5458	2300	85
H(5A)	-1609	3341	1595	82
H(6A)	301	3784	933	76
H(7A)	-2792	4613	2557	100
H(7B)	-2376	3875	2603	100
H(7C)	-3807	4105	2233	100
H(9A)	2139	6668	276	88
H(9B)	4012	6582	419	88
H(10B)	3553	4774	-736	79
H(11D)	1966	4331	0	61
H(12A)	4837	5857	-967	114
H(12B)	5527	6185	-455	114
H(12C)	3913	6448	-717	114
H(1'B)	4234	1460	623	52
H(4'C)	3764	633	1929	55
H(1'A)	2227	1575	1478	48
H(16A)	4382	2533	1045	59
H(16B)	2457	2577	1024	59
H(15A)	2338	2673	1931	76
H(15D)	3464	3221	1700	76
H(14A)	4760	2736	2441	88
H(14D)	5840	2630	1934	88
H(13A)	5599	1607	2385	69
H(13B)	3668	1653	2364	69
H(2'A)	5718	1572	1471	57
H(4'A)	1981	1752	235	63
H(4'B)	903	1369	648	63
H(5'A)	1280	-160	-815	79
H(6'A)	2972	-647	-108	68

H(7'A)	245	1543	-481	104
H(7'B)	-770	975	-730	104
H(7'C)	848	1214	-1004	104
H(9'A)	6082	345	2240	66
H(9'B)	7016	566	1724	66
H(10A)	6338	-1743	1484	77
H(11A)	4418	-1281	859	69
H(12D)	8155	-1332	2235	105
H(12E)	7303	-759	2535	105
H(12F)	8705	-617	2126	105

Table B9. 7: Torsion angles [°] for 5.

N(3)-Cu(1)-N(1)-C(4)	23.3(8)
N(6)-Cu(1)-N(1)-C(4)	140.9(9)
N(4)-Cu(1)-N(1)-C(4)	-151.3(8)
Cl(1)-Cu(1)-N(1)-C(4)	-69.4(7)
N(3)-Cu(1)-N(1)-C(1)	152.3(7)
N(6)-Cu(1)-N(1)-C(1)	-90.1(11)
N(4)-Cu(1)-N(1)-C(1)	-22.3(7)
Cl(1)-Cu(1)-N(1)-C(1)	59.6(7)
N(6)-Cu(1)-N(3)-C(3)	-167.1(7)
N(4)-Cu(1)-N(3)-C(3)	10(2)
N(1)-Cu(1)-N(3)-C(3)	-13.5(7)
Cl(1)-Cu(1)-N(3)-C(3)	86.6(7)
N(6)-Cu(1)-N(3)-C(6)	18.9(14)
N(4)-Cu(1)-N(3)-C(6)	-163.5(14)
N(1)-Cu(1)-N(3)-C(6)	172.5(13)
Cl(1)-Cu(1)-N(3)-C(6)	-87.4(13)
N(3)-Cu(1)-N(4)-C(9)	-163.0(14)
N(6)-Cu(1)-N(4)-C(9)	14.6(7)
N(1)-Cu(1)-N(4)-C(9)	-139.0(7)
Cl(1)-Cu(1)-N(4)-C(9)	119.6(7)
N(3)-Cu(1)-N(4)-C(2)	-33.9(19)
N(6)-Cu(1)-N(4)-C(2)	143.7(7)
N(1)-Cu(1)-N(4)-C(2)	-10.0(6)
Cl(1)-Cu(1)-N(4)-C(2)	-111.3(6)
N(3)-Cu(1)-N(6)-C(8)	175.3(7)
N(4)-Cu(1)-N(6)-C(8)	-4.1(7)
N(1)-Cu(1)-N(6)-C(8)	63.5(12)
Cl(1)-Cu(1)-N(6)-C(8)	-85.6(7)
N(3)-Cu(1)-N(6)-C(11)	-11.2(13)
N(4)-Cu(1)-N(6)-C(11)	169.3(13)
N(1)-Cu(1)-N(6)-C(11)	-123.1(13)
Cl(1)-Cu(1)-N(6)-C(11)	87.8(13)
C(4)-N(1)-C(1)-C(16)	-64.0(13)
Cu(1)-N(1)-C(1)-C(16)	170.3(7)
C(4)-N(1)-C(1)-C(2)	174.8(9)
Cu(1)-N(1)-C(1)-C(2)	49.0(10)
N(1)-C(1)-C(16)-C(15)	-173.0(9)
C(2)-C(1)-C(16)-C(15)	-54.8(12)
C(1)-C(16)-C(15)-C(14)	57.0(12)
C(16)-C(15)-C(14)-C(13)	-57.8(14)
C(15)-C(14)-C(13)-C(2)	56.3(14)
C(14)-C(13)-C(2)-N(4)	-174.7(8)
C(14)-C(13)-C(2)-C(1)	-57.1(13)
C(9)-N(4)-C(2)-C(13)	-71.1(11)
Cu(1)-N(4)-C(2)-C(13)	161.8(8)
C(9)-N(4)-C(2)-C(1)	165.6(9)
Cu(1)-N(4)-C(2)-C(1)	38.5(9)
N(1)-C(1)-C(2)-C(13)	-177.3(9)

C(16)-C(1)-C(2)-C(13)	58.3(13)
N(1)-C(1)-C(2)-N(4)	-56.6(10)
C(16)-C(1)-C(2)-N(4)	178.9(8)
C(6)-N(3)-C(3)-N(2)	0.4(13)
Cu(1)-N(3)-C(3)-N(2)	-175.7(7)
C(6)-N(3)-C(3)-C(4)	177.6(11)
Cu(1)-N(3)-C(3)-C(4)	1.5(13)
C(5)-N(2)-C(3)-N(3)	-1.6(13)
C(7)-N(2)-C(3)-N(3)	-175.5(10)
C(5)-N(2)-C(3)-C(4)	-178.6(11)
C(7)-N(2)-C(3)-C(4)	7.5(19)
C(1)-N(1)-C(4)-C(3)	-150.5(9)
Cu(1)-N(1)-C(4)-C(3)	-26.1(11)
N(3)-C(3)-C(4)-N(1)	16.9(15)
N(2)-C(3)-C(4)-N(1)	-166.4(11)
C(3)-N(2)-C(5)-C(6)	2.1(13)
C(7)-N(2)-C(5)-C(6)	176.5(10)
C(3)-N(3)-C(6)-C(5)	1.0(13)
Cu(1)-N(3)-C(6)-C(5)	175.1(9)
N(2)-C(5)-C(6)-N(3)	-1.9(13)
C(11)-N(6)-C(8)-N(5)	1.7(13)
Cu(1)-N(6)-C(8)-N(5)	177.6(7)
C(11)-N(6)-C(8)-C(9)	175.8(10)
Cu(1)-N(6)-C(8)-C(9)	-8.2(13)
C(10)-N(5)-C(8)-N(6)	-2.3(13)
C(12)-N(5)-C(8)-N(6)	-177.6(10)
C(10)-N(5)-C(8)-C(9)	-176.2(11)
C(12)-N(5)-C(8)-C(9)	8.5(19)
N(6)-C(8)-C(9)-N(4)	19.5(14)
N(5)-C(8)-C(9)-N(4)	-167.2(10)
C(2)-N(4)-C(9)-C(8)	-146.5(9)
Cu(1)-N(4)-C(9)-C(8)	-20.6(11)
C(8)-N(5)-C(10)-C(11)	2.0(13)
C(12)-N(5)-C(10)-C(11)	177.3(10)
N(5)-C(10)-C(11)-N(6)	-1.0(13)
C(8)-N(6)-C(11)-C(10)	-0.4(13)
Cu(1)-N(6)-C(11)-C(10)	-174.0(9)
N(6')-Cu(1')-N(1')-C(4')	160.0(9)
N(3')-Cu(1')-N(1')-C(4')	30.5(6)
N(4')-Cu(1')-N(1')-C(4')	-149.5(6)
N(6')-Cu(1')-N(1')-C(1')	-72.0(12)
N(3')-Cu(1')-N(1')-C(1')	158.4(7)
N(4')-Cu(1')-N(1')-C(1')	-21.6(6)
N(6')-Cu(1')-N(3')-C(3')	-178.2(7)
N(4')-Cu(1')-N(3')-C(3')	-16.0(19)
N(1')-Cu(1')-N(3')-C(3')	-16.0(7)
N(6')-Cu(1')-N(3')-C(6')	4.7(12)
N(4')-Cu(1')-N(3')-C(6')	167.0(13)
N(1')-Cu(1')-N(3')-C(6')	166.9(12)
N(6')-Cu(1')-N(4')-C(9')	24.6(6)
N(3')-Cu(1')-N(4')-C(9')	-138.6(14)
N(1')-Cu(1')-N(4')-C(9')	-138.6(6)
N(6')-Cu(1')-N(4')-C(2')	155.6(7)

N(3')-Cu(1')-N(4')-C(2')	-7.6(18)
N(1')-Cu(1')-N(4')-C(2')	-7.6(6)
N(3')-Cu(1')-N(6')-C(8')	163.4(7)
N(4')-Cu(1')-N(6')-C(8')	-12.8(7)
N(1')-Cu(1')-N(6')-C(8')	38.2(14)
N(3')-Cu(1')-N(6')-C(11')	-17.0(13)
N(4')-Cu(1')-N(6')-C(11')	166.7(12)
N(1')-Cu(1')-N(6')-C(11')	-142.3(12)
C(4')-N(1')-C(1')-C(2')	168.8(8)
Cu(1')-N(1')-C(1')-C(2')	47.0(9)
C(4')-N(1')-C(1')-C(16')	-70.6(11)
Cu(1')-N(1')-C(1')-C(16')	167.5(6)
N(1')-C(1')-C(16')-C(15')	-177.6(9)
C(2')-C(1')-C(16')-C(15')	-56.8(12)
C(1')-C(16')-C(15')-C(14')	58.2(13)
C(16')-C(15')-C(14')-C(13')	-58.0(12)
C(15')-C(14')-C(13')-C(2')	57.4(12)
C(14')-C(13')-C(2')-C(1')	-60.1(11)
C(14')-C(13')-C(2')-N(4')	-179.7(8)
N(1')-C(1')-C(2')-C(13')	-176.2(9)
C(16')-C(1')-C(2')-C(13')	59.6(11)
N(1')-C(1')-C(2')-N(4')	-53.7(10)
C(16')-C(1')-C(2')-N(4')	-177.9(8)
C(9')-N(4')-C(2')-C(13')	-74.2(11)
Cu(1')-N(4')-C(2')-C(13')	157.7(7)
C(9')-N(4')-C(2')-C(1')	161.9(8)
Cu(1')-N(4')-C(2')-C(1')	33.9(9)
C(6')-N(3')-C(3')-N(2')	3.2(13)
Cu(1')-N(3')-C(3')-N(2')	-175.0(7)
C(6')-N(3')-C(3')-C(4')	176.4(9)
Cu(1')-N(3')-C(3')-C(4')	-1.7(13)
C(5')-N(2')-C(3')-N(3')	-2.8(14)
C(7')-N(2')-C(3')-N(3')	179.3(10)
C(5')-N(2')-C(3')-C(4')	-175.5(11)
C(7')-N(2')-C(3')-C(4')	6.5(18)
C(1')-N(1')-C(4')-C(3')	-157.6(9)
Cu(1')-N(1')-C(4')-C(3')	-36.0(9)
N(3')-C(3')-C(4')-N(1')	26.3(13)
N(2')-C(3')-C(4')-N(1')	-161.5(10)
C(3')-N(2')-C(5')-C(6')	1.2(14)
C(7')-N(2')-C(5')-C(6')	179.2(10)
N(2')-C(5')-C(6')-N(3')	0.6(14)
C(3')-N(3')-C(6')-C(5')	-2.2(13)
Cu(1')-N(3')-C(6')-C(5')	174.9(9)
C(11')-N(6')-C(8')-N(5')	0.0(12)
Cu(1')-N(6')-C(8')-N(5')	179.7(6)
C(11')-N(6')-C(8')-C(9')	178.8(9)
Cu(1')-N(6')-C(8')-C(9')	-1.5(12)
C(10')-N(5')-C(8')-N(6')	-0.2(12)
C(12')-N(5')-C(8')-N(6')	177.5(9)
C(10')-N(5')-C(8')-C(9')	-179.0(10)
C(12')-N(5')-C(8')-C(9')	-1.3(16)
C(2')-N(4')-C(9')-C(8')	-155.4(8)

Cu(1')-N(4')-C(9')-C(8')	-28.9(9)
N(6')-C(8')-C(9')-N(4')	20.6(13)
N(5')-C(8')-C(9')-N(4')	-160.8(9)
C(8')-N(5')-C(10')-C(11')	0.3(12)
C(12')-N(5')-C(10')-C(11')	-177.3(10)
N(5')-C(10')-C(11')-N(6')	-0.3(13)
C(8')-N(6')-C(11')-C(10')	0.2(12)
Cu(1')-N(6')-C(11')-C(10')	-179.4(9)
O(4)-Cl(2)-O(1)-O(3)	117(7)
Cl(2A)#1-Cl(2)-O(1)-O(3)	-117(5)
Cl(2A)#1-Cl(2)-O(1)-O(4)	126(5)
Cl(2A)#1-Cl(2)-O(4)-O(1)	-81(5)
O(3)-O(1)-O(4)-Cl(2)	-112(7)
O(2')-O(3')-O(4')-O(5')	29(90)
O(3')-O(2')-O(4')-O(5')	-178(6)
O(3')-O(4')-O(5')-O(1')	-36(89)
O(2')-O(4')-O(5')-O(1')	-10(7)

Symmetry transformations used to generate equivalent atoms:
#1 x+1/2,-y+3/2,-z #2 x-1/2,-y+3/2,-z

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Chapter 10

Stereoselective Reduction of Ketones with Triethoxysilane Catalysed by Chiral *N,N'*-bis(*N*-methyl-2-methylene-imidazole)-1,2-cyclohexanediamine Titanium Complex 1

10.1 ABSTRACT

Chiral bis-imidazole titanium complexes, in the presence of triethoxysilane, catalyzed the enantioselective reduction of ketones. The catalyst was prepared from chiral *N,N'*-bis(*N*-methyl-2-methylene imidazole)-1,2-cyclohexanediamine, butyllithium and titanium salts. The reductions produced alcohols in good to excellent yield (60-99%), with facial selectivity ranging from fair to excellent (28-99%).

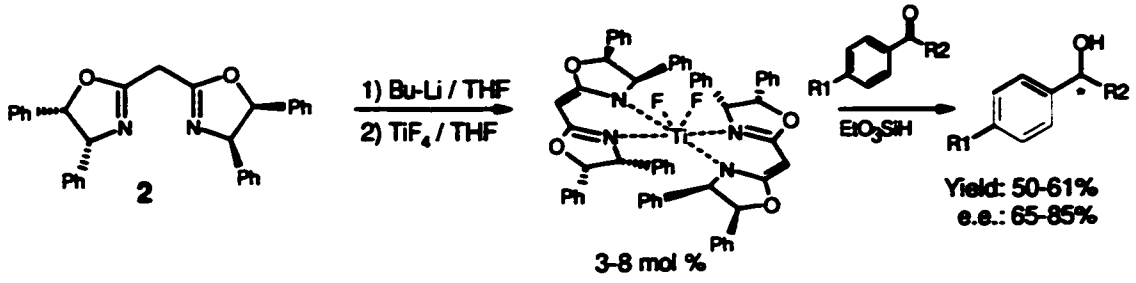
10.2 INTRODUCTION

The enantioselective reduction of carbonyl compounds is an important and widely utilized methodology for the preparation of key intermediates for the synthesis of drugs and biologically active compounds.[1] Corey's oxazaborolidine **2** and related compounds have played a decisive role in these chirotechnologies.[2] Recently, Buchwald has shown that chiral titanium metallocenes were able to catalyze the enantioselective hydrosilylation of ketones and imines with high e.e.'s.[3] For these reactions enantiomerically pure titanocene complexes were necessary. In spite of the recently

reported methodology to prepare the chiral C_2-metallocene complexes in high diastereomeric ratios,[4] a resolution process is still needed to access the enantiomerically pure metal complex.[5] More recently, Cozzi *et al.* have demonstrated that Evan's chiral bis-oxazoline titanium complexes also catalyze these transformations.[6] The ease with which these chiral metal ligands are synthesized and their commercial availability, in enantiopure form, suggests their use in asymmetric transformations.

Cozzi *et al.*[6] utilized the procedure of Nakamura and coworkers[7] to generate their catalyst *in situ*. They reasoned that, since the titanium complexes were generated utilizing a 2:1 molar ratio of the methylene bis-oxazoline and a titanium salt, the catalytic species should have an octahedral structure as shown in **Figure 10. 1**.

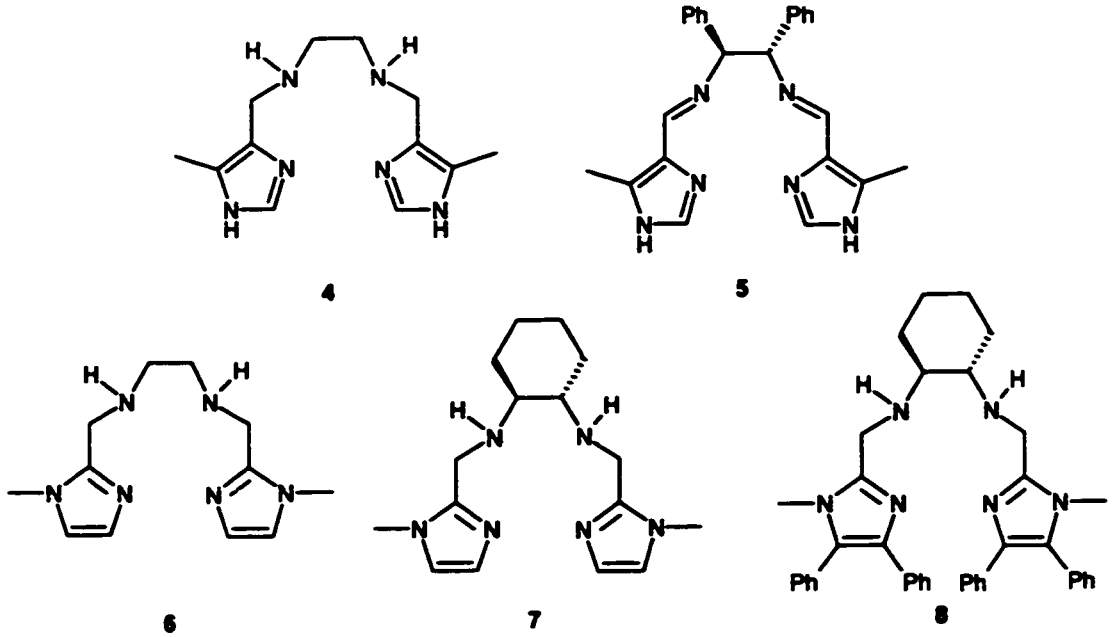
Figure 10. 1: Enantioselective Reduction by a Methylene bis-Oxazoline Titanium Complex



We have recently reported the synthesis and characterization of bis-imidazole complexes **4-8**[8] **(Figure 10. 2)**. Compound **5** was shown to catalyze the reduction of ketones with poor facial selectivity utilizing the imidazole species as a sila-nucleophile.[9] These transformations are believed to occur through a pentacoordinate silicon-imidazolide species, which is subsequently complexed by the carbonyl species. Reduction of the carbonyl species with stereo-discrimination then occurs through an

intramolecular hydride transfer process. Compounds **6-8**, when exposed to the same reaction conditions as **5**, showed no capacity to reduce ketones. This may be a consequence of a reduced Lewis acidity of the silicon nucleus situated within the body of these ligands. Ligands such as these lend themselves to transition metal binding[10].

Figure 10. 2: Bis-imidazole Ligands

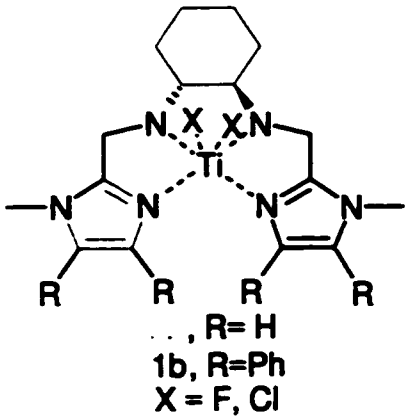


It is well known that the Lewis acidity of a given metal is reduced by heteroatom ligands such as oxygen and nitrogen (when compared to halogens, for instance). One of the concerns of metal-ligand complexes derived from **6-8**, is the possibility of reduced Lewis acidity of the complexed metal. However, the report of Cozzi *et al.*[6] encouraged us to attempt Lewis acid mediated reduction of carbonyl compounds with titanium complexes of **7** and **8**. We report herein a method for the enantioselective titanium-catalyzed hydrosilylation of ketones and α-haloketones.

10.3 Results and Discussion

The reduction process involves the treatment of C_2-symmetric chiral bis-imidazole **7** or **8** with *n*-BuLi at –78 °C, followed by the addition of a titanium salt to produce **1** (**Figure 10. 3**). We speculate that **1** has the structure displayed below, based on the X-ray crystal structures obtained from the copper chloride salt of **1a** and its ethylene diamine achiral parent.[11]

Figure 10. 3: Hypothetical structure of catalytic species involved in the hydrosilylation process

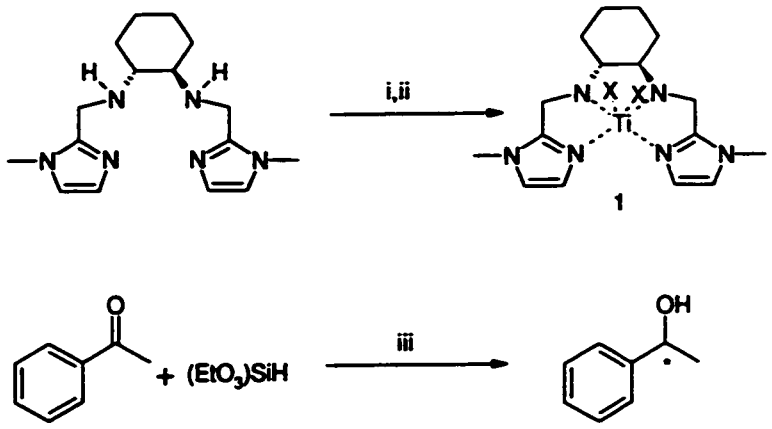


The titanium complex, thus produced, was treated with triethoxysilane leading to a new catalytic system for the hydrosilylation of ketones and α-halo ketones. A preliminary screening of the reaction conditions necessary to effect reduction was performed with acetophenone and triethoxysilane, and 5 mol % of various titanium complexes of **7** (**Table 10. 1**).

Table 10. 1: Enantioselective reduction of acetophenone catalyzed by titanium complex 1

			1a		1b	
Entry	TiX_4	Conditions	Yield %	e.e. %	Yield %	e.e. %
1	$TiCl_4$	Ambient temp., 24 h, $(EtO)_3SiH$	2	-	-	-
2	$TiCl_4$	Ambient temp., 4d. , $(EtO)_3SiH$	30	-	-	-
3	$TiCl_4$	65 °C, 24 h, $(EtO)_3SiH$	75	40 (S)	-	-
4	TiF_4	Ambient temp., 24h.,	42	47 (S)	-	-
5	TiF_4	40 °C, 24 h, $(EtO)_3SiH$	50	33 (S)	62	22
6	TiF_4	55 °C, 24 h, $(EtO)_3SiH$	65	38 (S)	65	9
7	TiF_4	65 °C, 24 h, $(EtO)_3SiH$	70	52 (S)	92	5
8	TiF_4	65 °C, 24 h, $(EtO)_3SiH$, 4Å, m.s.	92	44 (S)	-	-

As can be seen from **Table 10. 1**, the best results were obtained with TiF_4. It is worthwhile to note that, as the temperature of the reaction increases and contrary to intuition, the e.e. also increases. These results are not unfounded as evidenced in the cited papers.[12] As a result, subsequent hydrosilylation was performed with 5 mol % the catalyst **1** prepared from commercially available TiF_4 and ligand **7** (**Scheme 10.1**). These hydrosilylations were best carried out at 55 °C over 24 hours. These reaction conditions produced (*S*)-1-phenylethan-1-ol[3a] in 65% yield and 52% e.e.

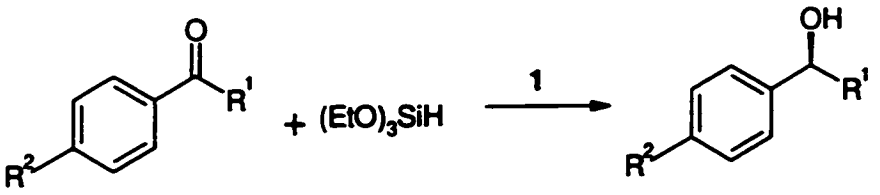


Scheme 10. 1: Reagents and conditions: (i) BuLi, THF; (ii) TiX_4, THF; (iii) 1 (5 mol %), 55 °C.

A systematic screening of ketones was made by selection of the best conditions for reduction; the results are listed in **Table 10. 2** and **Table 10. 3**. This reaction displays chemoselectivity. Only carbonyl reduction is observed in the presence of an α,β-unsaturated ketone (entry 3, **Table 10. 3**), or α-bromoketones (entries 9-12, **Table 10. 2**). Neither 1,4-conjugate addition product, nor nucleophilic displacement of bromide was observed.

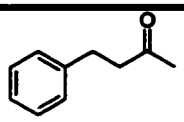
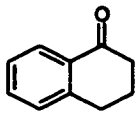
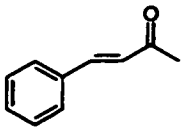
Structurally related ketones are reduced with the same degree of enantioselction. This is quite apparent when one compares the results of the acetophenone series to the α-bromoacetophenone series (entries 1-3 and 9-12, **Table 10. 2**). In addition, electronic factors seem to greatly influence the amount of stereoselectivity observed. As one decreases the electron density present on the carbonyl carbon, the e.e. increases; that is, electron poor ketones display greater enantioselection (Entries 1-4, **Table 10.2**). This is revealed in each of the classes of ketones investigated.

Table 10. 2: Enantioselective reduction of ketones and α-haloketones using $HSi(OEt)_3$ and 1



Entry	R^1	R^2	1a		1b	
			Yield %	e.e.%	Yield %	e.e.%
1	Me	H	65	52 (S)	65	42 (S)
2	Me	Me	99	48 (S)	65	38 (S)
3	Me	OMe	83	28 (S)	54	51 (S)
4	Me	CF_3	99	85 (S)	60	57 (S)
5	Pr	Me	86	47 (S)	86	50 (S)
6	CH_2Br	H	79	>99 (R)	52	>99 (R)
7	CH_2Br	Me	61	87 (R)	61	85 (R)
8	CH_2Br	OMe	63	95 (R)	89	87 (R)
9	CH_2Br	Cl	97	85 (R)	97	47 (R)

Table 10. 3: Enantioselective reduction of ketones using $HSi(OEt)_3$ and 1

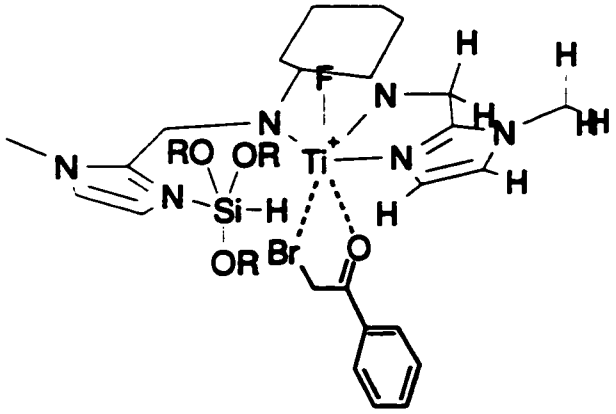
Entry	Ketone	1a		1b	
		Yield %	e.e.%	Yield %	e.e.%
1		72	64 (S)	96	22 (S)
2		66	66 (S)	94	46 (S)
3		60	65 (S)	80	26 (S)

At the present time, we can only speculate about the mechanism of this reaction. In particular, we are unable to definitely demonstrate that the reduction is due to the formation of an active titanium (III)[3a,b] or titanium (IV) species.[13] We speculate that this

process may involve the nucleophilic activation of silicon by fluoride or that of imidazole. However, the enantio-induction that we observe must involve reaction occurring in a chiral environment. Therefore, it is likely that the titanium complex **1** steers the ketone and allows for approach of the alkoxysilane in a facial manner.

Based on the X-ray structural analysis of the copper chloride salt of 1a and also molecular modeling calculations we speculate that the geometry of the ligand around the metal center takes on the orientation depicted below (**Figure 10. 4**).

Figure 10. 4: Optimized Geometry of *N*-methylimidazole amines Titanium Complex

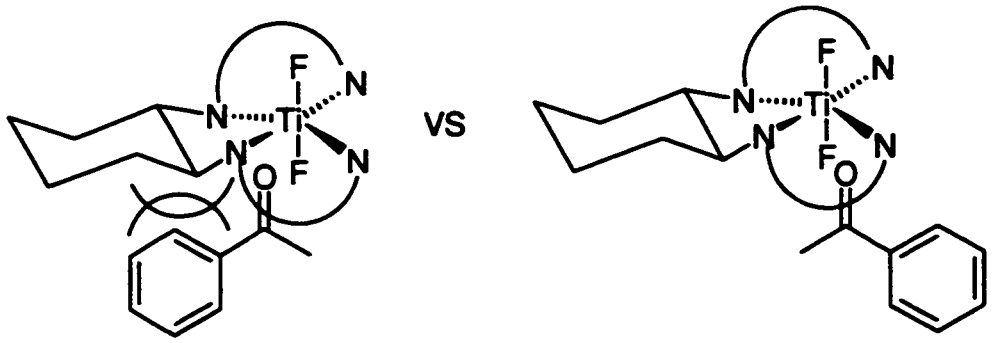


2

The incoming ketone can complex either from the top or under side of the titanium-ligand complex, but in doing so will orient itself so as to minimize steric interaction. Thus, as can be imagined from structure **2**, the ketone will bind in order that the phenyl group from the ketone and the cyclohexyldiamine group on the ligand are far removed from one another (**Figure 10.5**). Upon complexation of the carbonyl species, one of the imidazole moieties is displaced from the metal center, which subsequently coordinates a

trialkoxysilane. The extracoordinate species thus produced delivers its hydride on the *re* face of the ketone, producing the *S* alcohols observed.

Figure 10. 5: Orientation of incoming ketone to titanium center



The decrease of enantioselection observed for reductions performed with 3 may be due to the increased steric demand around titanium upon ketone complexation. Since it is known that imidazole is a quite labile ligand,[14,15] it is conjectured that release of both of the ligated bis-phenyl imidazole complexes relaxes the activated carbonyl ligand-imidazole complex and thus opens up two different paths by which silane could approach.

The increased enantioselection observed for α-bromoketones is consistent with tighter binding of the ketone to the catalytic titanium center resulting from chelation of the halogen. Obviously, the bidentate chelation of the ketone would result in a highly rigid ligand-titanium-ketone interaction, during the reduction step.

10.4 CONCLUSION

We have developed a new ligand system, in which bound metal species retain enough Lewis acidic character to activate carbonyl species to reduction. Furthermore, we have demonstrated that the titanium complex 1 can reduce ketones and α-haloketones

enantioselectively. It is shown that there is less facial selectivity experienced by ketones that are exposed to the more bulky titanium complex **1b** than the less bulky analogue **1a**.

10.5 EXPERIMENTAL

10.5.1 Reagents and Physical Methods

The following materials were obtained from Aldrich and were used without further purification: acetophenone, benzophenone, *n*-butyllithium (2M solution in cyclohexane), 4-methoxyacetophenone, 4-methoxybenzophenone, (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl (+)), 4-methylacetophenone, 4-methylbenzophenone, *N*-methylimidazole, 4-phenyl-2-butanone, *trans*-4-phenyl-3-buten-2-one, sodium sulfate, triethoxysilane, 4-(trifluoromethyl)acetophenone, 4-(trifluoromethyl)benzophenone.

^{1}H NMR spectra were recorded on a Bruker AC-200 (at 200-MHz for protons) Fourier transform spectrometer. ^{13}C and ^{29}Si-NMR were performed on a Bruker AC-200 (50.32 and 39.7 MHz for carbon and silicon, respectively) or a Bruker AC-300 (at 75.44 MHz and 59.60 MHz for carbon and silicon, respectively). Chemical shifts are reported either with respect to tetramethylsilane as an external standard for ^{29}Si, set to 0 ppm, or $CHCl_3$ as an internal standard for protons, set at 7.24 ppm. Coupling constants (*J*) are recorded in Hertz (Hz). The abbreviations s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, are used to report spectra.

Electron impact (EI) and chemical ionization (CI, NH_3) mass spectra were recorded at 70 eV with a source temperature of 200 °C on a VG analytical ZAB-R mass

spectrometer equipped with a VG 11-250 data system. High resolution mass spectral (HRMS) data were obtained using the EI method. Infrared spectra were run as KBr pellets or as liquid films on NaCl discs (as indicated) on a Perkin-Elmer 283 spectrometer or on a BIORAD FTS-40 spectrometer as a neat film.

All solvents were thoroughly dried before use: acetonitrile was dried over P_2O_5; THF was dried from Na/benzophenone. All reactions were carried out in dry apparatus under a nitrogen atmosphere with the use of septa and syringes for the transfer of reagents.

10.6.2 General Procedure for Reduction with ligand 1

To a dry 10 mL round-bottomed flask flushed with nitrogen was added **1** (0.03g, 0.05 mmol) and THF (1.5 mL). This solution was cooled to –78 °C and then *n*-butyllithium (0.06 mL, 1.6M solution in hexanes, 0.1 mmol) was added dropwise. The resulting yellow-orange solution was stirred for 5 min at –78 °C, and then warmed to 0 °C for 15 min. To this yellow solution was added TiF_4 (6 mg, 0.05 mmol) all at once and the mixture was vigorously stirred until complete dissolution of the salt had occurred. The resulting yellow mixture was stirred for 60 min at room temperature and then triethoxysilane (0.38 mL, 2.06 mmol) and acetophenone (0.12 mL, 1.02 mmol) were added. The solution was stirred at 55 °C, and product development was monitored by TLC. The reaction mixture was diluted with ethyl acetate (5 mL) and carefully made basic with 1M sodium hydroxide. The solid was separated by filtration and the organic phase collected. The aqueous phase was extracted with ethyl acetate (3 x 10 mL). The organic layers were combined, dried over

sodium sulfate, then concentrated to give the crude product which was purified by column chromatography eluting with pentane: ether (9:1). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 1.56 (d, 3H, J = 6.5 Hz, PhCH(OH)C*H*$_3$), 2.76 (bs, 1H, PhCH(O*H*)CH$_3$), 4.94 (q, 1H, J = 6.5 Hz, PhC*H*(OH)CH$_3$), 7.32-7.45 (m, 5H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 24.97, 69.99, 125.24, 127.14, 128.24, 145.75; FTIR (neat, KBr disc) ν (cm^{-1}) 3364, 3065, 3031, 2974, 2929, 1728, 1603, 1494, 1452, 1371, 1287, 1204, 1077, 1030, 1011, 900, 762, 700, 607, 541; MS (EI) m/z (%): 122 (M^+, 10), 121 (40), 104 (68), 79 (28), 57 (7), 43 (100); (CI) m/z (%): 140 (M^+ + 18, 17), 122 (100), 105 (41), 78 (2), 52 (1), 44(1).

2-Bromoacetophenone: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 2.69 (bs, 1H, O*H*), 3.69-3.45 (m, 2H, C*H*$_2$Br), 4.90 (dd, J = 3.5 Hz, J = 8.6 Hz, 1H, PhC*H*(OH)), 7.36 (s, 5H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 40.12, 73.78, 125.95, 128.43, 128.65, 140.31; FTIR (neat, KBr disc) ν (cm^{-1}) 3474, 3064, 3035, 2955, 2930, 2862, 1966, 1901, 1730, 1689, 1599, 1494, 1451, 1287, 1077, 971; MS (EI) m/z %: 202 (M^++2, 2), 200 (M^+, 2), 185 (5), 183 (5), 121 (5), 107 (100), 91 (10), 79 (78), 51 (29); (CI) m/z (%): 220 (M+20, 22), 218 (M+18, 22), 202 (M^++2, 52), 200 (M^+, 55), 185 (77), 183 (83), 161 (29), 137 (18), 120 (22), 107 (89), 91 (68), 77 (100), 43 (40).

4'-Chloro-2-bromo-acetophenone: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 3.01 (bs, 1H, O*H*), 3.33-3.83 (m, 2H, C*H*$_2$Br), 4.86 (dd, J = 3.7 Hz, J= 8.3 Hz, 1H, 1H, PhC*H*(OH)), 7.17-7.27 (m 4H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 39.52, 72.91, 127.27, 128.67, 134.01, 138.74;

FTIR (neat, KBr disc) ν (cm^{-1}) 3413, 2978, 2930, 2895, 1492, 1392, 1168, 1105, 1084, 967, 793; MS (EI) m/z %: 221 (M^+ -13, 24), 219 (M^+-15, 100), 217 (M^+-17, 83), 155 (8), 141 (50), 113 (13), 91 (10), 77 (25), 51 (10), 43 (11); (CI) m/z (%): 236 (M^++2, 17), 234 (M^+, 70), 232 (M^+-2, 55), 221 (25), 219 (100), 217 (72), 198 (15), 154 (25), 138 (45), 94 (93), 76 (53), 44 (12); HR-MS (CI) m/z: Calcd. for C_8H_8OClBr: 233.9434. Found: 233.9447.

4'-Methoxy-2-bromo-acetophenone: ^1H NMR ($CDCl_3$, 200 MHz) δ 2.87 (bs, 1H, CHO*H*), 3.59-3.79 (m, 2H, CHOHCH_2Br), 3.93 (s, 3H, CH_3O), 4.96 (m, 1H, C*H*OH), 7.42 (d, J = 7.9 Hz, Ph-*H*), 7.02 (d, J = 7.9 Hz, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 40.07, 55.24, 73.40, 114.02, 127.18, 132.48, 159.62; FTIR (neat, KBr disc) ν (cm^{-1}): 3491, 3030, 2841, 2051, 1906, 1750m 1604, 1514, 1461, 1028, 975, 836; MS (EI) m/z %: 232 (M^++2, 18), 230 (M^+, 23), 215 (76), 213 (77), 169 (17), 151 (18), 137 (100), 109 (68), 94 (22), 77 (25), 63 (18), 51 (15), 43 (15); (CI) m/z (%): 232 (M^++2, 10), 230 (M^+, 10), 215 (100), 213 (100), 169 (28), 151 (7), 137 (65), 109 (10), 94 (7), 77 (4), 63 (5), 43 (1); HR-MS (CI) m/z: Calcd. for $C_9H_{11}O_2Br$: 229.9859. Found: 229.9842.

1, 2, 3, 4-Tetrahydro-1-naphthol: ^1H NMR ($CDCl_3$, 200 MHz) δ 1.92-2.09 (m, 4H), 2.27 (bs, 1H, O*H*), 2.64-2.87 (m, 2H), 4.75 (m, 1H, C*H*OH), 7.07-7.44 (m, 4H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 18.76, 29.17, 32.21, 68.02, 126.05, 127.43, 128.55, 128.87, 137.00, 138.78; FTIR (neat, KBr disc) ν (cm^{-1}) 3399, 3063, 3022, 2934, 2866, 2839, 1684, 1605, 1490, 1454, 1341, 1283, 1067, 1037, 1002, 963, 774, 739; MS (EI) m/z (%): 148 (M^+, 35),

147 (33), 131 (100), 130 (98), 120 (76), 119 (68), 115 (28), 105 (44), 91 (85), 77 (24), 65 (26), 51 (29), 41 (17); (CI) m/z (%):148 (M^+, 53), 147 (20), 131 (100), 130 (69), 120 (26), 119 (36), 105 (21), 91 (33), 78 (4), 65 (7).

1-Phenyl-1-butanol: ^1H NMR ($CDCl_3$, 200 MHz) δ 0.91 (t, J = 7.1 Hz, 3H, $PhCHOHCH_2CH_2CH_3$), 1.15-1.47 (m, 2H, $PhCHOHCH_2CH_2CH_3$); 1.60-1.80 (m, 2H, $PhCHOHCH_2CH_2CH_3$); 2.08 (bs, 1H, O*H*), 4.64 (t, J = 6.4 Hz, Ph*CH*OH), 2.27-7.31 (m, 5H, Ph-*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 13.88, 18.97, 41.21, 74.33, 125.85, 127.37, 128.34, 144.95; FTIR (neat, KBr disc) ν (cm^{-1}) 3387, 3064, 3031, 2960, 2933, 2873, 1494, 1455, 1380, 1310, 1200, 1105, 1062, 1028, 962, 904, 858, 762, 700; MS (EI) m/z (%): 150 (M^+, 6), 133 (6), 107 (100), 91 (9), 79 (70), 63 (3), 49 (31); (CI) m/z (%): 168 (M^+ + 18,3), 150 (M^+, 58), 133 (100), 107 (7), 91 (40), 77 (9), 43 (7); HR-MS (CI) m/z: Calcd. for $C_{10}H_{14}O$: 150.0903. Found: 150.0947.

All other spectral information of the compounds described here and general experimental procedure for preparation of Mosher esters are as outlined in Chapter 5.

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Chapter 11

Enantioselective Allylation of Aldehydes Catalyzed by Chiral *N,N'*-bis(*N*-methyl-2-methylene-4,5-bisphenyl-imidazole)-1,2-cyclohexanediamine Rhodium (III) Complexes

11.1 ABSTRACT

Chiral bis-imidazole rhodium (III) complexes catalyze the enantioselective allylation of aldehydes by allyltributyltin. The pre-catalyst was prepared from chiral *N,N'*-bis(*N*-methyl-2-methylene-4,5-bisphenylimidazole)-1,2-cyclohexanediamine, potassium carbonate and rhodium (III) chloride trihydrate. The rhodium (III) complex thus produced showed no activity in an allyl transfer process in the presence of the allyltin reagent. However, when silver tetrafluoroborate was added to the pre-catalyst, the resulting system becomes an efficient catalyst for the allyl transfer process. The reductions produced homo-allyl alcohols with good to excellent yield (67-97%), with poor facial selectivity (8-10% e.e.). This outlines our ongoing investigation of the catalytic ability of bound metal species to our tetradentate nitrogen ligand system.

11.2 INTRODUCTION

The development of chiral Lewis acid catalysts, particularly those used for carbon-carbon bond forming reactions, is very challenging for organic chemists.[1] It is relatively difficult to generate highly Lewis acidic catalysts that possess chirality associated with heteroatoms (e.g., chiral amines or alcohols). While reactions that can be promoted by stoichiometric quantities of Lewis acids are rather numerous, those that require only catalytic quantities are much more rare.

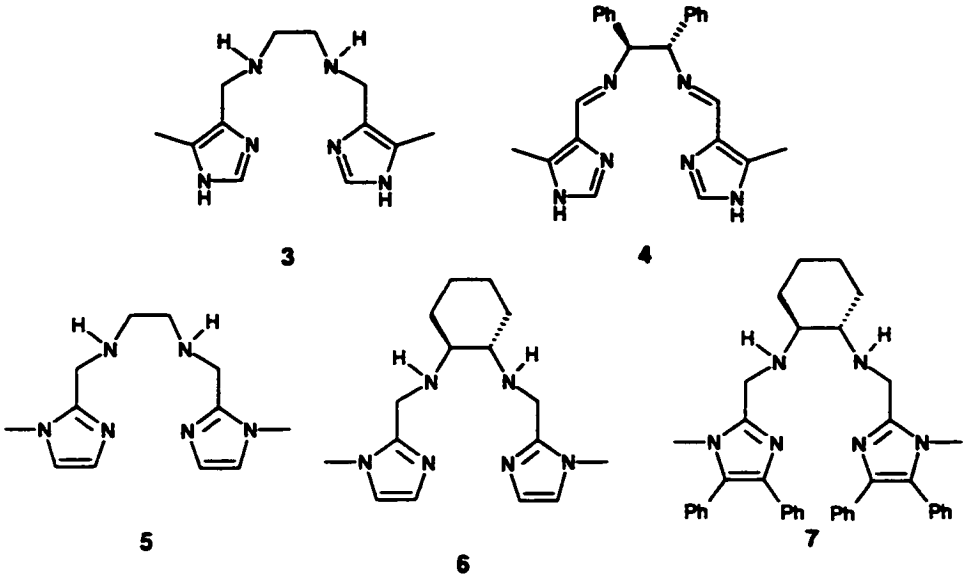
The asymmetric allylation of carbonyl compounds is a valuable means of constructing chiral functionalized structures. A number of chiral allylmetal reagents have been designed and synthesized.[2] The application of these allylmetal systems to the allylation process generally requires stoichiometric amounts of Lewis acid catalysts.[3] Processes that require only catalytic amounts chiral Lewis acid catalysts include chiral (acyloxy)borane (CAB) complexes with allylsilanes[4] or allylstannanes,[5] binaphthol-derived chiral titanium complexes with allylstannanes,[6] or allylsilanes,[7] and BINAP-derived chiral silver complexes with allylstannanes[8].

It is relatively obvious that the key to the development of chiral Lewis acid catalysts is the choice of the central metal and the design of the asymmetric ligand that houses that metal. Traditional Lewis acid catalysts, such as aluminum, boron, tin, and titanium are extremely moisture sensitive, and are known to form oligomers in solution. Moreover, chiral complexes are generally generated *in situ*, so that a variety of species with varying Lewis acid strengths and enantioselection are present. This makes it difficult to develop selective processes. Conversely, transition metal complexes can form

single, well-defined species that are generally not moisture sensitive.[9] This is the focus of this study.

We recently reported the synthesis and characterization of bis-imidazole complexes 3-7 (**Figure 11. 1**). Species 4 was shown to catalyze the reduction of ketones by $HSi(OEt)_3$ with poor facial selectivity. The mechanism involves the generation of a penta-coordinate hydrido-silicon species, which is believed to coordinate to ketones, delivering its hydride via an intra-molecular pathway. Subjecting ligands 6 and 7 to the same reaction conditions for reduction using trimethoxysilane was fruitless. No product alcohol was obtained even in the presence of stoichiometric quantities of ligand. However, these ligands lend themselves quite readily to the complexation of transition metals (both early and late).[10] Herein, we present an examination of the enantioselective allylation of aldehydes with allyltributylstannane catalyzed by a new air-stable rhodium (III) complex 2.

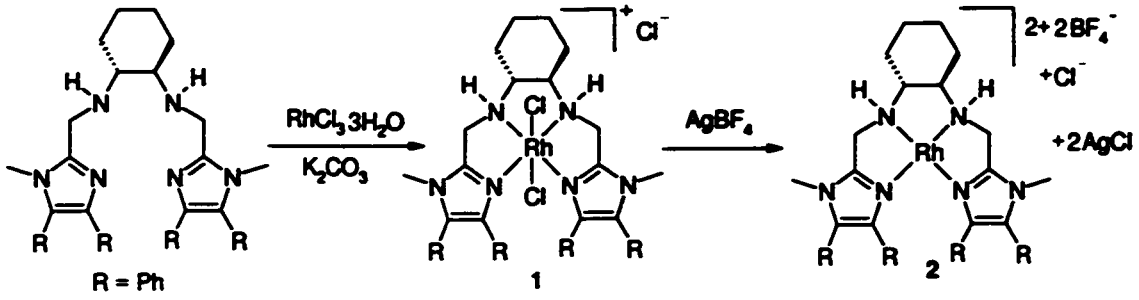
Figure 11. 1: Bis-imidazole Ligands



11.3 Results and Discussion

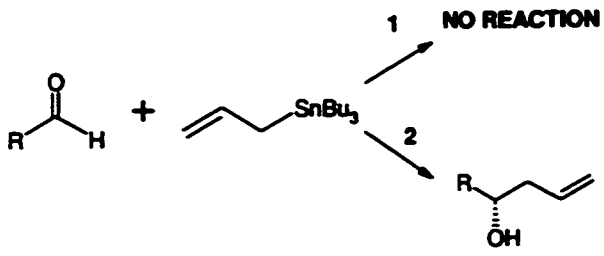
Complex 1 was quite easily synthesized by the mixing of equimolar amounts of commercially available rhodium (III) chloride hydrate, and 2.2 equivalents of potassium carbonate in ethanol. The complex thus formed is sufficiently air stable that purification by silica gel chromatography is possible (**Scheme 11. 1**). Although, no crystallographic data has been obtained, we propose structure 1 as the precatalyst, based on the X-ray crystal structures obtained from the copper chloride salt of **6** and its ethylene diamine achiral parent[11] and NMR, IR and mass spectral data of 1. The C_2-symmetry of the ligand has been lost upon complexation of the metal. This can be seen if one examines the ^{1}H NMR of 1 (described in the experimental). This implies that the coordination of the ligand is not bound in the equatorial plane of the rhodium.

Scheme 11. 1: Bis-Imidazole Rhodium Complexes



The optimization of the allylation reaction was carried out with benzaldehyde and allyltributylstannane in the presence of 5 mol% of the (*S*,*S*)-1 or 2 as the chiral catalyst (**Scheme 11. 2**).

Scheme 11. 2: Optimization of the allyl-transfer process



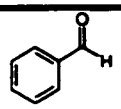
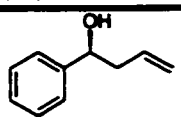
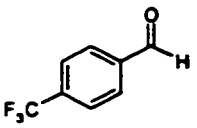
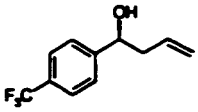
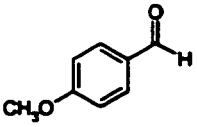
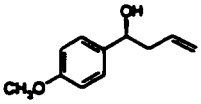
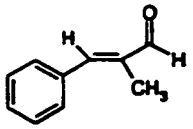
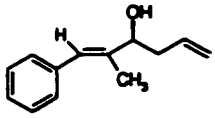
The absolute configuration of the known allylated product was determined by comparison of its optical rotation with literature values.[12] Exposing benzaldehyde and allyltributylstannane to complex 1 provided no reaction after 7 days at room temperature. However, after treatment of 1 with silver tetrafluoroborate for 1 hour (noting the precipitation of AgCl) as described by Nishiyama *et al.*,[13] reduction proceeded efficiently at room temperature. However, poor selectivity was noted in all solvents tested. Methylene chloride provided a system that displayed very little stereo-discrimination (e.e. 2%). This is entry 4 (**Table 11.1**). Although the reaction was accelerated in the presence of 4 Å molecular sieves, the enantiomeric excess of the product did not change (**Table 11. 1**, entries 2 and 3).

Table 11. 1: Asymmetric allylation of benzaldehyde with rhodium complexes

Entry	Catalyst	Solvent	Conditions	Yield (%)	e.e. (%)
1	1	THF	Ambient temp., 4 d.	0	-
2	2	THF	Ambient temp., 4 d.	65	9 S
3	2	THF	Ambient. Temp., 4 Å m.s., 4 d.	97	10 S
4	2	CH_2Cl_2	Ambient. Temp., 4 Å m.s., 4 d.	95	2 S

Table 11. 2 summarizes the results obtained from the allylation reaction utilizing allyltributylstannane and catalyst 2 with a variety of aldehydes.

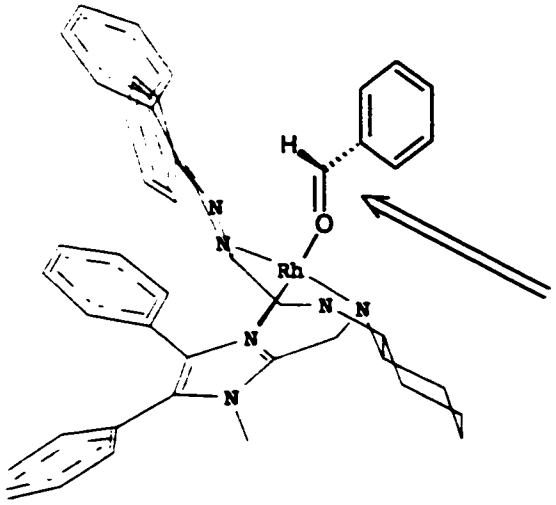
Table 11. 2: Asymmetric allylation of aldehydes catalyzed by 2

Entry	Ketone	Product	Yield (%)	e.e. (%)	Configuration
1			97	10	S
2			78	10	S
3			67	6	S
4			85	8	-

These reactions are high yielding but display poor facial selectivity. This may be a result of residual silver species activating the carbonyl species outside of the rhodium center.

Based on the X-ray structural analysis of the copper chloride salt of **1a** and also molecular modeling calculations we speculate now on the geometry of the transition state that accounts for the observed stereochemical outcome of the reaction (**Figure 11. 2**). The ketone approaches the activated rhodium complex in such a manner as to avoid steric interaction of the phenyl groups with the metal ligands. The allylstannane approaches the carbonyl *si*-face because the *re*-face is shielded by the phenyl substituents of the imidazole ring.

Figure 11. 2: Proposed Transition State of Allylation Process



Rhodium complex **1** possesses a striking resemblance to Wilkinson's catalyst ($(Ph_3P)_3RhCl$). Although **1** proved not to be active for the allylation reactions that formed the basis for this paper, it may possess the ability to catalyze the hydrosilylation of alkenes, enantioselectively. An examination of this possibility is currently underway in our laboratories.

11.4 CONCLUSION

Enantiopure, tetraamine ligands bind effectively to Rh(III). Cationic complexes derived from the ligand are sufficiently electrophilic to act as Lewis acids that catalyze the enantioselective addition of allyltributylstannane to aldehydes. Application of these ligands to other transition metal based catalytic processes will form the basis of future reports.

11.5 EXPERIMENTAL

11.5.1 Reagents and Physical Methods

The following materials were obtained from Aldrich and were used without further purification: acetophenone, benzophenone, benzaldehyde, 4-trifluorotolualdehyde, 4-methoxybenzaldehyde, *trans*-4-phenyl-2-methyl-2-butenal, dodecanal, (*S*)-(+)-α-methoxy-α-(trifluoromethyl)phenylacetyl chloride (MTPA-Cl (+)), pyridine, silver tetrafluoroborate, rhodium (III) chloride trihydrate, potassium carbonate, 4Å molecular sieves.

^{1}H NMR spectra were recorded on a Bruker AC-200 (at 200-MHz for protons) Fourier transform spectrometer. ^{13}C NMR was performed on a Bruker AC-200 (at 50.32 MHz) or a Bruker AC-300 (at 75.44 MHz) Fourier transform spectrometer. ^{1}H chemical shifts are reported either with respect to tetramethylsilane as an external standard, set to 0 ppm, or $CDCl_3$ as an internal standard, set at 7.24 ppm. ^{13}C chemical shifts are reported with respect to $CDCl_3$ as an internal standard, set at 77. Coupling constants (J) are recorded in Hertz (Hz). The abbreviations s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, are used to report spectra.

Electron impact (EI) and chemical ionization (CI, NH_3) mass spectra were recorded at 70 eV with a source temperature of 200 °C on a VG analytical ZAB-R mass spectrometer equipped with a VG 11-250 data system. High resolution mass spectral (HRMS) data were obtained using the EI method. Infrared spectra were run as KBr pellets or as liquid films on NaCl discs (as indicated) on a Perkin-Elmer 283 spectrometer or on a BIORAD FTS-40 spectrometer as a neat film.

All solvents were thoroughly dried before use: acetonitrile was dried over P_2O_5; THF was dried from Na/benzophenone. All reactions were carried out in dry apparatus under a nitrogen atmosphere with the use of septa and syringes for the transfer of reagents.

11.5.2 Preparation of 1

To a dry 25 mL round bottomed flask flushed with nitrogen was added 7 (0.12 g, 0.20 mmol), potassium carbonate (0.06 g, 0.42 mmol), EtOH (15 mL), and $RhCl_3$ hydrate (0.1g, 0.19 mmol). The system was stirred under nitrogen under reflux for 2 h. The resulting mixture was filtered and was washed with THF (10 ml). The solvent was removed *in vacuo*. The crude product was purified using column chromatography eluting with $CHCl_3$: MeOH (9:1, R_f = 0.85) to produce 0.12g (80%) of an orange powder. ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.65 (bs, 1H, N-H), 7.39-6.77 (m, 20H, Ph-H), 5.08 (m, 1H, Cy-H), 4.98 (m, 1H, Cy-H), 4.27 (m, 1H, Cy-H), 4.17 (m, 1H, Cy-H), 3.92 (d, J = 15.5 Hz, 1H, Cy–H), 3.64 (m, 1H, Cy-H), 3.54 (s, 3H, NCH_3), 3.38 (s, 3H, N-CH_3), 2.59 (q, J = 11.9 Hz, 1H, Cy-H), 2.41 (d, J = 11.6Hz, 1H, Cy-H), 1.76 (d, J = 11.20, 2H, Cy-H), 1.17 (t, J = 6.8 Hz, 2H, Cy-H), 1.24 (q, J = 12.4 Hz, 1H, Cy-H); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 23.95, 24.33, 28.63, 30.75, 33.00, 45.71, 51.12, 58.14, 68.55, 70.57, 126.10, 126.86, 127.51, 127.59, 127.67, 127.81, 128.27, 128.33, 128.42, 128.68, 129.20, 130.40, 130.57, 131.01, 131.21, 132.09, 139.12, 148.99, 149.49; FTIR (neat, KBr disc) ν (cm^{-1}) 3424.6, 3056, 2935, 2854, 1640, 1602, 1505, 1445, 1426, 1027, 785, 700; Electro-spray MS (positive) m/z %: 779.2 (M^+ + 1, 100) .

11.5.3 Typical Experimental for Allylation (example benzaldehyde)

To a dry 25 mL round-bottomed flask flushed with nitrogen was added 1 (0.02g, 0.025 mmol), silver tetrafluoroborate (0.01g, 0.05 mmol), molecular sieves (250 mg), and THF (15 mL). The system was stirred for 1 h at room temperature. To this stirring mixture was added benzaldehyde (0.05 g, 0.5 mmol) and allyltributyltin (0.23 mL, 0.77 mmol). The resulting system was stirred at ambient temperature for 4 days. The system was quenched with an aqueous solution of sodium bicarbonate (1M, 5 mL) and filtered. The aqueous layer was extracted with ether (3 x 10 mL). The combined organic fractions were washed with sodium bicarbonate (1M, 3 x 10 mL), 1M HCl (3 x 10 mL) and water (3 x 10 mL). The solvent was removed under reduced pressure. The crude product was purified by silica gel chromatography eluting with pentane: ether (9:1). ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.26-7.12 (m, 5H, Ph-*H*), 5.81-5.60 (m, 1H, C*H*=CH_2), 5.10-5.00 (m, 2H, CH=CH_2), 4.60 (t, *J* = 6.5 Hz, 1H, C*H*(OH)), 2.41(t, *J* = 6.5 Hz, 2H, CH_2CH=CH_2), 2.32 (bs, 1H, O*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 26.69, 65.66, 117.97, 125.72, 127.33, 128.22, 134.39, 143.84; FTIR (neat, KBr disc) ν (cm^{-1}) 3388, 3078, 3032, 2927, 1642, 1494, 1454, 1048, 916, 758, 700; MS (EI) m/z %:148 (M^+, 1), 131 (M^+-17, 5), 107 (100), 79 (75), 41 (33); (CI) m/z (%): 166 (M^+ + 18, 27), 148 (M^+, 70), 131 (M^+ - 17, 100), 94 (5), 77 (2), 41 (1); HR-MS (CI) m/z: Calcd. for $C_{10}H_{12}O$: 131.0846. Found: 131.0861.

1-(4-Trifluoromethylphenyl)-3-buten-1-ol: ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.50 (d, J = 8.3, 2H, Ph-H), 7.35 (d, *J* = 8.3, 2H, Ph-H), 5.75-5.58 (m, 1H, C*H*=CH_2), 5.09-5.02 (m,

2H, CH=C*H*$_2$), 4.68 (t, *J* = 6.4 Hz, 1H, C*H*OH), 2.43-2.31 (m, 2H, C*H*$_2$CH=CH$_2$); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 34.11, 72.56, 118.96, 125.25, 126.06, 133.67, 147.80; FTIR (neat, KBr disc) ν (cm^{-1}) 3388, 3082, 2984, 2927, 1643, 1622, 1418, 1328, 1166, 1126, 1068, 1018, 922, 843, 607; MS (EI) m/z %: 216 (M^+, 1), 199 (M^+ + 17, 30), 175 (100), 147 (18), 127 (100), 95 (6), 77 (15), 41 (27); (CI) m/z (%): 234 (M^+ + 18, 8), 216 (M^+, 18), 199 (M^+ + 17, 30), 166 (16), 127 (100), 94 (6), 78 (6), 52 (14); HR-MS (CI) m/z: Calcd. for $C_{11}H_{10}F_3$: 199.0721. Found: 199.0735.

***1-(4-Methoxyphenyl)-3-buten-1-ol*:** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 6.52 (d, *J* = 8.3, 2H, Ph-H), 6.12 (d, *J* = 8.3, 2H, Ph-H), 5.11-4.94 (m, 1H, C*H*=CH$_2$), 4.45-4.34 (m, 2H, CH=C*H*$_2$), 3.89 (t, *J* = 6.5 Hz, 1H, C*H*OH), 3.05 (s, 3H, OC*H*$_3$), 1.74 (m, 2H, C*H*$_2$CH=CH$_2$), 1.35 (bs, 1H, CHO*H*); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 26.80, 55.22, 72.96, 113.75, 118.09, 127.03, 134.58, 136.04, 151.20; FTIR (neat, KBr disc) ν (cm^{-1}) 3421, 3077, 2959, 2927, 1612, 1514, 1464, 1249, 1037, 832; MS (EI) m/z %: 178 (M^+, 3), 177 (M^+ - 1, 6), 161 (M^+ - 17, 7), 137 (100), 109 (38), 77 (31), 41 (42); (CI) m/z (%): 178 (M^+, 4), 161 (M^+-17, 100), 137 (13), 94 (1); HR-MS (CI) m/z: Calcd. for $C_{11}H_{13}O_2$: 161.0976. Found: 161.0966.

***Trans-1-Phenyl-2-methyl-1, 5-hexadien-3-ol*:** ^{1}H NMR ($CDCl_3$, 200 MHz) δ 7.36-7.16 (m, 5H, Ph-H), 6.52 (s, 1H, PhC*H*=CMeR), 5.90-5.73 (m, 1H, RC*H*=CH$_2$), 5.22-5.11 (m, 2H, RCH=C*H*$_2$), 4.21 (t, J = 6.5 Hz, C*H*OH), 2.46-2.37 (m, 2H, RC*H*$_2$CH=CH$_2$), 1.87 (s, 3H, PhCH=CC*H*$_3$R); ^{13}C NMR ($CDCl_3$, 200 MHz) δ 13.64, 40.09, 76.55, 117.94,

125.73, 126.40, 128.06, 128.94, 134.51, 137.54, 139.49; FTIR (neat, KBr disc) ν (cm^{-1}) 3389, 3079, 3025, 3924, 2859, 1642, 1601, 1493, 1445, 1047, 916, 749, 700; MS (EI) m/z %: 171 (M^+-17, 100), 147 (40), 129 (51), 115 (9), 91 (25), 41 (25); (CI) m/z (%): 188 (M^+, 5), 171 (M^+-17, 100), 147 (15), 129 (24), 91 (8), 69 (2), 41 (3); HR-MS (CI) m/z: Calcd. for $C_{13}H_{15}O$: 171.1165. Found: 171.1174.

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Chapter 12

Synthesis and Structure of a Silicatein Bio-mimetic

12.1 Abstract

The synthesis and characterization of a silicatein bio-mimetic is reported. A four-step synthetic process is described where the compound is synthesized on a solid support. The treatment of the N^{α}-t-BOC protected amino acid peptide bound resin with acetic acid, allows for the removal of the peptide from the resin without cleaving the BOC protecting group. The methodology can be applied to the development of a combinatorial library.

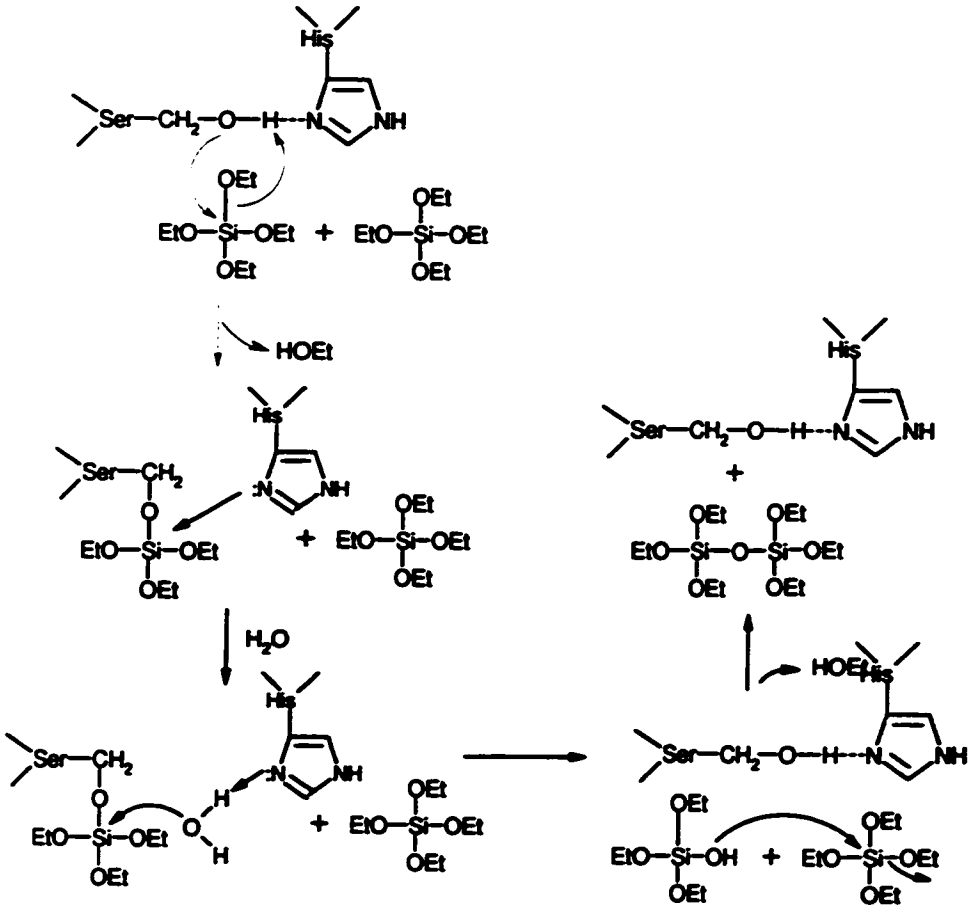
12.2 Introduction

Silicon is the second most abundant element in the earth's crust.[1] There is evidence to suggest that silicon is essential to the normal growth and biological function of a diverse number of plant, animal, and microbial systems.[2] DeLaRocha *et al.*[3c] and others have studied marine organisms that produce large masses of silica containing structures and have probed the mechanism by which living things process silicon. However, the mechanism by which living things metabolize silicon is still not well understood.[3] Hildebrand *et al.*[4] recently characterized the cDNAs coding for a family of

silicon transporters in diatoms and showed that the transporters are likely trans-membrane proteins.

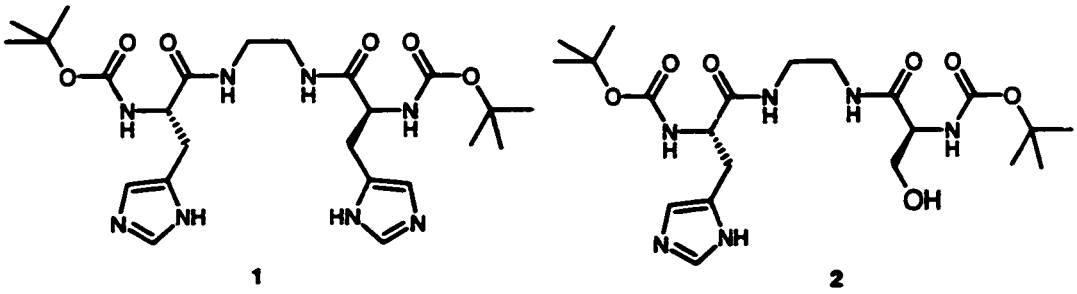
Cha *et al.* have found that the marine sponge, *Tehya aurantia* produces silica needles (1-2 mm in length and 2 μm in diameter) that constitute 75% of the dry weight of the organism and that each of the filaments contained a central axial filament of protein.[5] The protein, for which the name *Silicatein* was coined, was noted to consist of 3 similar units. The silicatein α subunit (the subunit comprises 70% of the mass of the filament) and its cloned cDNA have been characterized.[5] These studies indicated sequence homology to the cathepsin L subfamily of the papain family of proteolytic enzymes. More recently, these workers have shown that at neutral pH, the silicatein filament catalyzes the *in vitro* polymerization of silica and silsesquioxanes from tetraethoxysilane, and organically modified triethoxysilanes. They suggested a possible mechanism for catalysis, based on the amino acid side chain that is prevalent in these proteolytic enzymes. The mechanism invokes a catalytic triad consisting of serine, histidine, and glutamic acid.[6]

Scheme 12. 1: Proposed mechanism for condensation of triethoxysilane catalyzed by silicatein



We have been involved in the design and synthesis of ligands for hydrosilylation reactions. We have reported that an ethylene diamine linked bis-histidine ligand 1 (**Figure 12. 1**) was catalytically active in the hydrosilylation of ketones with triethoxysilane. We felt that a simple modification of our synthesis of ligand 1 would lead to a ligand that contains the serine and the histidine partners needed to mimic the activity of silicatein. We report herein, the synthesis and characterization of a silicatein bio-mimetic 2 (**Figure 12. 1**).

Figure 12. 1: Histidine containing ligands



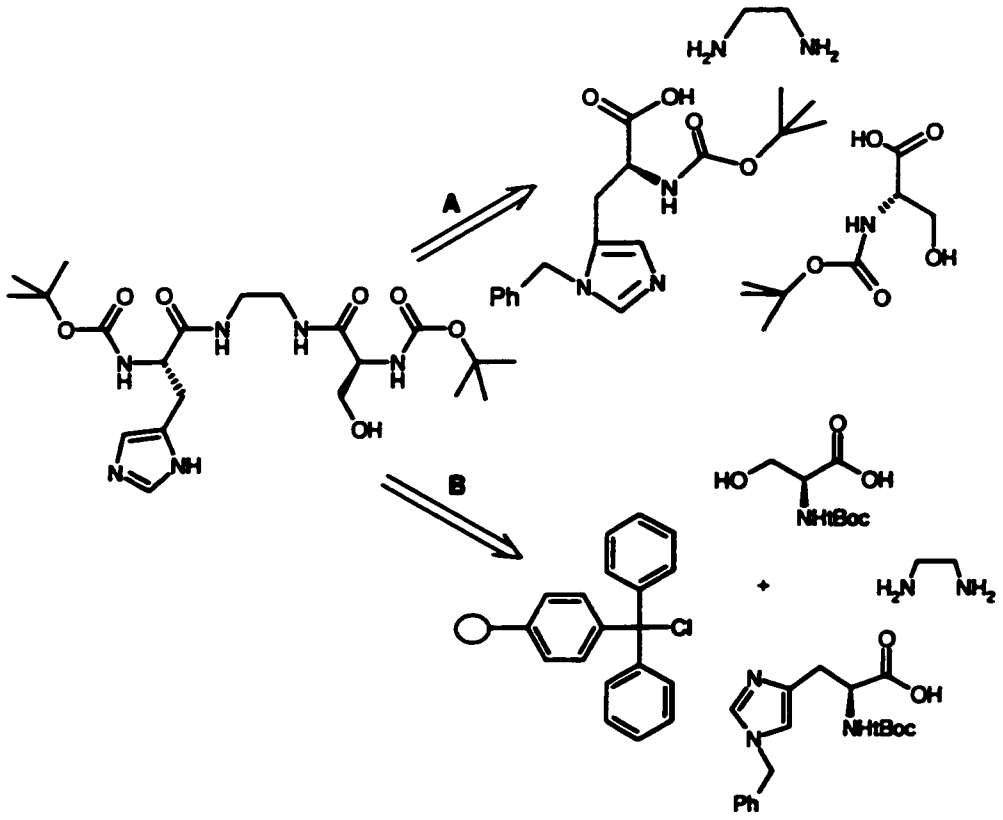
1 2

12.3 Results and Discussion

The retrosynthetic analysis of **2** is presented **Scheme 12. 2.** One could envision either the solution or solid support method as feasible methodologies to arrive at our target molecule. Path B was chosen for two different reasons. First, it is unknown how the length of the tether between the two amino acids will affect the catalytic performance of **compound 2.** The development of a solid support methodology can lend itself quite nicely to the development of a combinatorial library of this class of compounds, in which the tether length is varied. Moreover, the addition of an excess of reagent encourages the necessary peptide coupling reaction to proceed to completion. Secondly, mono-substitution of a symmetric bis-functional compound is quite difficult[7] in solution. In fact, attempts to control mono-substitution of ethylene diamine with *N*-α-*t*-BOC-*N*-π-benzyl-*L*-histidine proved to be quite problematic even with a ratio of ethylenediamine to amino acid of 1:10. Solid support synthesis allows for this needed monosubstitution, through the utility of the support material as a protecting group for one of the functionalites. The entropic penalty that would result from two of the support materials

becoming attached prevents the double substitution of the symmetric bis-functional compounds. Thus, method B was utilized in the synthesis of compound **2**.

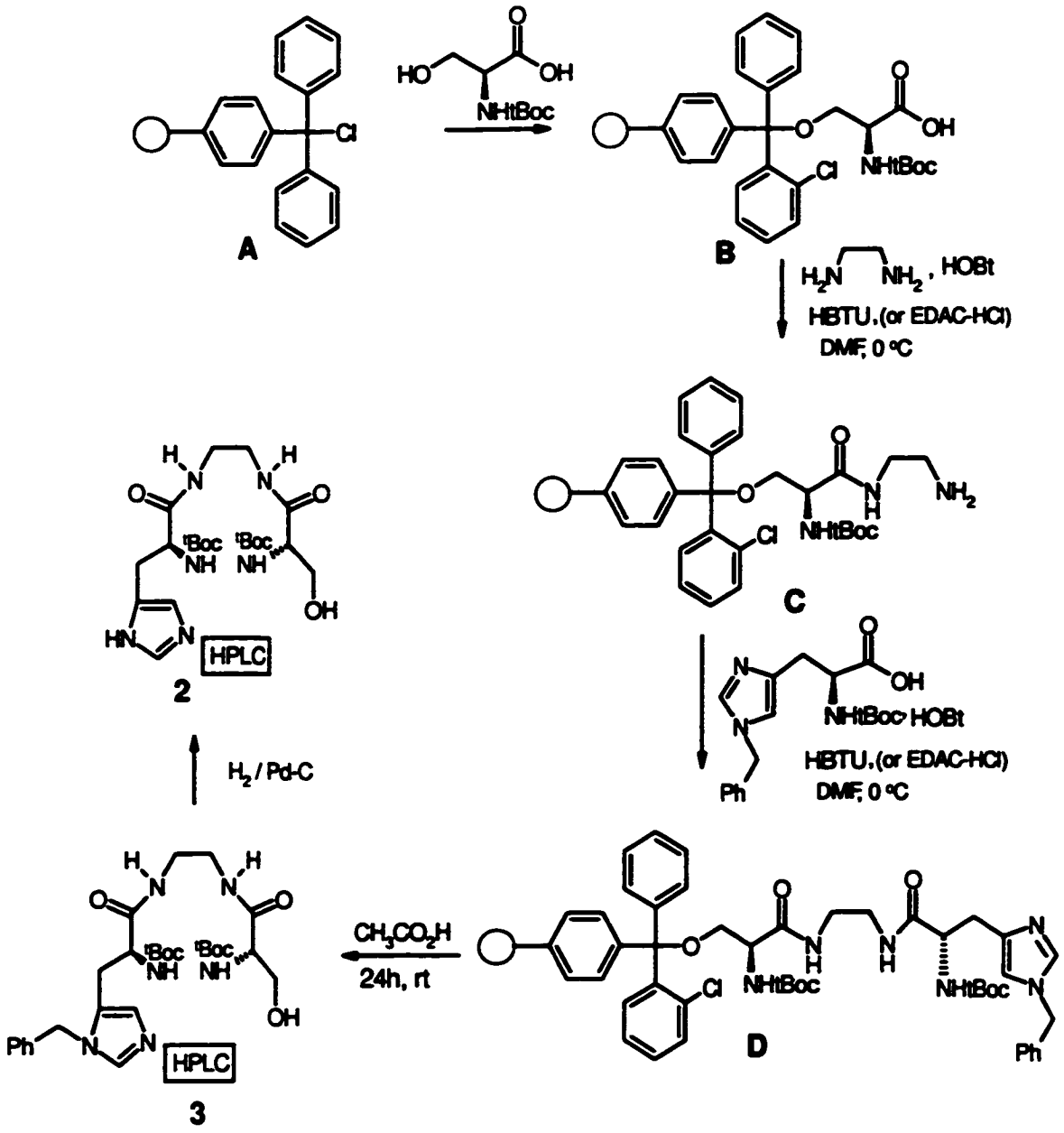
Scheme 12. 2: Retrosynthetic analysis of 2



We decided that the *t*-BOC protecting groups present on the α-amino acid should remain to adequately mimic the polypeptide chain present in the catalytic sites of proteins when examining the reactivity as a catalyst.

The synthesis of the ligand was carried out by solid phase synthetic methods. The synthetic scheme appears in **Scheme 12.3**. The synthesis begins with the attachment of N^{α}-*t-BOC-L*-serine to a trityl resin, **A**.[8] The attachment was made according to the procedure of Fyles and Leznoff.[9]

Scheme 12. 3: Preparation of Silicatein bio-mimetic



Treatment of commercially available trityl chloride resin with N^{α}-*t*-BOC-*L*-serine in DCM/pyridine solution produced **B** (**Scheme 12. 3**). This attachment proceeded quite readily. One must be careful in the washing of the reacted resin to ensure that all

unreacted starting material is removed. This is quite problematic in subsequent steps in the reaction sequence. Subsequent treatment of the resin-grafted serine with ethylenediamine in the presence of EDAC-HCl and coupling additive HOBt in DMF at 0 °C led to the attachment of this unit to the amino acid, producing the desired species, **C**. An excess of ethylenediamine can be used in the place of the base *N*-methylmorpholine, and coupling proceeds just as smoothly. Finally, treatment of **C** with *N*-α-*t*-BOC-*N*-π-benzyl-*L*-histidine under the same coupling reaction conditions described above produced the desired material **D**, which was subsequently removed from the solid support, by treatment of the resin bound peptide with acetic acid for 24 hours. The desired product 3 was purified using preparative HPLC.

Characterization of the material obtained in each coupling step was performed before subsequent reaction was undertaken. The characterization of **B** was done by FTIR analysis. The diagnostic peaks are the carbonyl and hydroxyl stretches (Figure 12. 2Error! Reference source not found. and Figure 12. 3). This ensured that the serine was attached to the hydroxyl function of its R group instead of carboxyl attachment.

Figure 12. 2: FTIR spectrum of Trityl resin

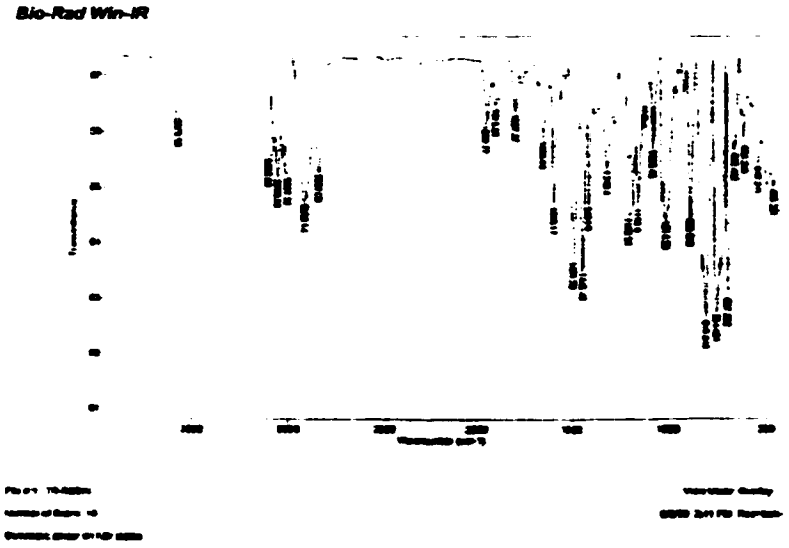
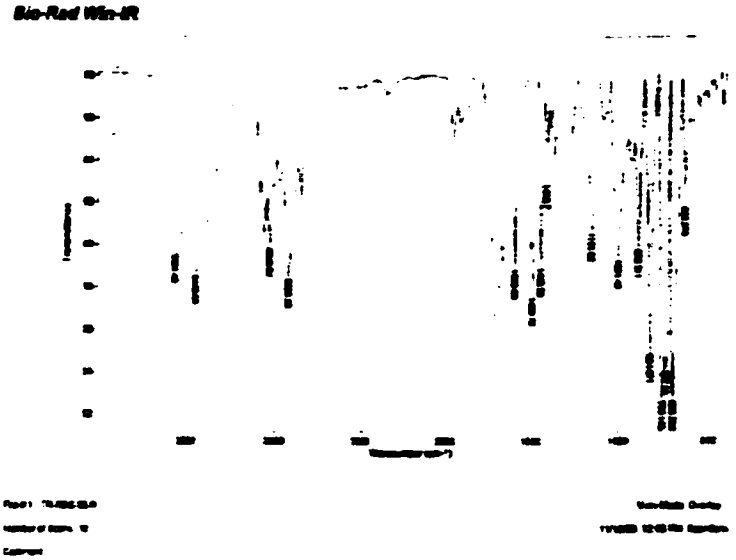


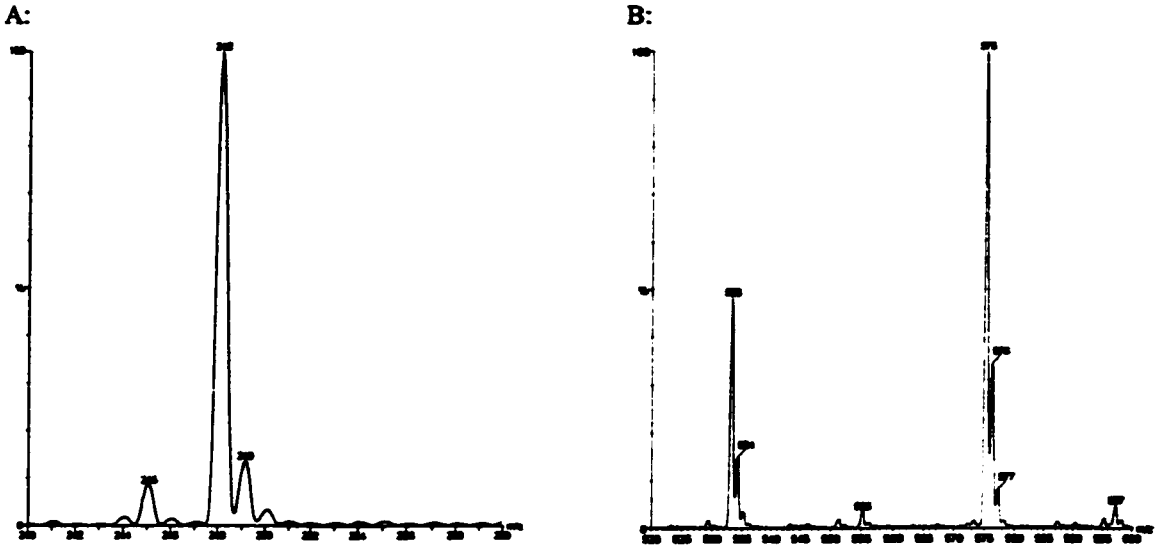
Figure 12. 3: FTIR of Serine bound Trityl resin



In order to ensure the coupling of the ethylenediamine moiety to the bound serine amino acid, a number of tests were done. FTIR analysis and positive ninhydrin tests were consistent with this attachment. In addition, at this point in this sequence, it is necessary

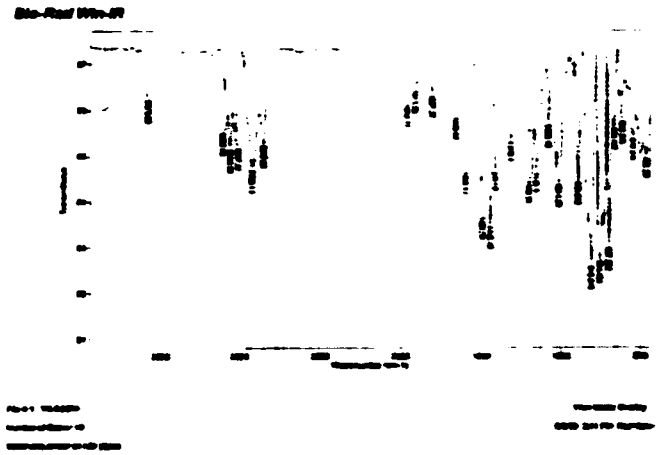
to ensure that the desired material needed for the subsequent coupling is in hand. Removal of the peptide from the solid support was achieved through treatment of the resin with acetic acid for 24 h. This led to the release of peptide from the support; confirmation of its structure was made by electro-spray mass spectroscopy (**Figure 12. 4A**).

Figure 12. 4: Electro-spray mass spectrum of Serine-ethylene diamine couple (A) and Silicatein mimetic (B)



It is worth noting that removal of the peptide from the resin with acetic acid did not lead to deprotection of the *t*-BOC protecting group at the α-amino position. The desired pre-silicatein bio-mimetic 3 was cleaved from the resin by treatment with glacial acetic acid solution for 24 h, and its presence confirmed by electro-spray mass spectrometry (**Figure 12. 4B**). The crude compound 3 was purified using HPLC.

Figure 12. 5: FT-NMR of Pre-Silicatein Bio-mimetic



The method described above is quite costly. Therefore, it is proposed that a methodology which does not involve the removal of the peptide from resin be developed. This may involve the use of commercially available *O*-benzyl-*L*-serine. This would allow attachment to the resin at the *N*-α position, and coupling can be achieved as described above. The final deprotection step would involve the removal of the benzyl group from the resin.

12.4 CONCLUSION

We have presented here the straightforward synthesis and structural characterization of a potential catalyst for the polymerization of alkoxysilanes. The synthesis involved simple solid phase peptide synthesis. The catalytic ability of this species will be the focus of future reports from this laboratory.

12.5 Acknowledgements

We thank Dr. Brian McCarry for the use of his HPLC instrument. Special thanks must be extended to Susan Ackloo and Julie Batoia for their patience in the instruction and aid with running of the HPLC.

12.6 EXPERIMENTAL

12.6.1 Reagents and Physical Methods

The following materials were obtained from the indicated suppliers and were used without any further purification. Aldrich: pyridine, *N*-hydroxybenzotriazole (HOBt), *N*-methylmorphline (NMM), ethylenediamine (EDA), 1-(3-(dimethylamino)propyl)-3-ethylcarbodiimide hydrochloride (EDAC-HCl), dimethylformamide (DMF), absolute ethanol, methylene chloride (DCM), ethanol (EtOH) (95%), and acetic acid Novabiochem: Trityl chloride resin (2.06 mmol / g loading); Sigma Aldrich: *N*-α-*t*-BOC-*L*-serine, *N*-α-*t*-*BOC*-*N*-π-benzyl-*L*-histidine; .

^{1}H NMR spectra were recorded on a Bruker AC-200 (at 200-MHz for protons) Fourier transform spectrometer. ^{13}C was performed on a Bruker AC-200 at 50.32 MHz or a Bruker AC-300 at 75.44 MHz. ^{1}H chemical shifts are reported either with respect to tetramethylsilane as an external standard, set to 0 ppm, or $CDCl_3$ as an internal standard, set at 7.24 ppm. ^{13}C chemical shifts are reported either with respect to $CDCl_3$ as an internal standard, set at 7.24 ppm. Coupling constants (J) are recorded in Hertz (Hz).

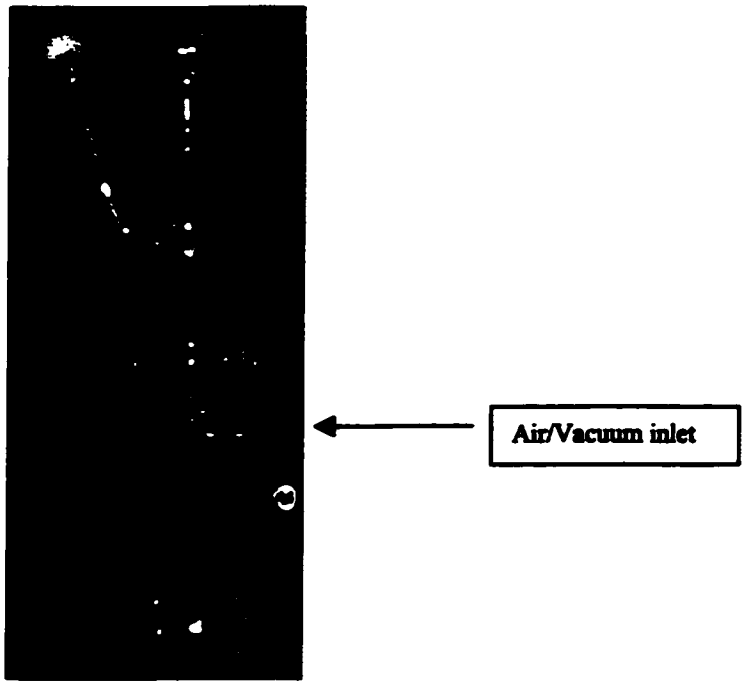
The abbreviations s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublets, dt = doublet of triplets, m = multiplet, are used to report spectra.

Electron impact (EI) and chemical ionization (CI, NH_3) mass spectra were recorded at 70 eV with a source temperature of 200 °C on a VG analytical ZAB-R mass spectrometer equipped with a VG 11-250 data system. High resolution mass spectral (HRMS) data were obtained using the EI method. Infrared spectra were run as KBr pellets or as liquid films on NaCl discs (as indicated) on a Perkin-Elmer 283 spectrometer or on a BIORAD FTS-40 spectrometer as a neat film.

Reverse phase high performance liquid chromatography (RP-HPLC) was performed with a HP-1090 liquid chromatograph instrument using a 4.6 mm X 250 cm column (5 μ reverse phase VYDAC-C_{18}). Elution was performed using gradient elution profile at a rate of 1 ml/ min.

All solvents were thoroughly dried before use: acetonitrile was dried over P_2O_5; DMF was dried over KOH and then freshly distilled; pyridine was kept over KOH before use. All reactions were carried out in dry vessel, fitted with a frit and an air inlet valve (see Figure 12. 6), under a nitrogen/argon atmosphere with the use of septa and syringes for the transfer of reagents.

Figure 12. 6: Reaction vessel where solid phase synthesis was conducted



12.6.2 Polymer-bound N-α-t-BOC-L-serine (side chain O-linked) B

To a dry reaction vessel purged with nitrogen was added trityl chloride resin A (0.5 g of a 2.06 mmol/g loaded polystyrene resin, 1.03 mmol) and DCM (15 ml). The resulting system was allowed to mix by supplement of nitrogen through the air intake valve for 20 min. The nitrogen was taken away and a vacuum line was used to remove the DCM. This was repeated 3 times with DCM and then once with pyridine (15 ml). Pyridine (15 ml), DCM (20 ml), and *N*-α-*t*-BOC-*L*-serine (1.05 g, 5.13 mmol) was then added and the resulting system was mixed for 4 d at ambient temperature. The resulting amino-acid bound resin was washed by the above procedure one time with pyridine (15 ml) and then three times in succession with

DMF (20 ml), DCM (20 ml) and MeOH (20 ml). Finally the system was washed one more time with DCM and left under vacuum to dry for 20 min.

FTIR (KBr disc): ν (cm^{-1}) 3564 (OH), 3447 (OH), 3027, 2923, 1758(C=O), 1716 (C=O), 1669, 1607.

12.6.3 Polymer-bound N-α-t-boc-L-serine- EDA C

To a dry reaction vessel purged with nitrogen was added **B** (0.49 g of a 1.00 mmol) and DMF (15 ml). The resulting system was allowed to mix by supplement of nitrogen through the air intake valve for 15 min. The nitrogen was taken away and a vacuum line was used to remove the DMF. This was repeated 3 times after which DMF (10 ml) and ethylenediamine (0.33 ml, 5 mmol) were added. The system was cooled to 0 °C. To the reaction vessel was added previously mixed HOBt (0.68g, 5 mmol), EDAC-HCl (0.96 g, 5 mmol), and NMM (0.55 ml, 5 mmol) in DMF (30 ml). The resulting system was mixed at 0 °C for 24 h. The system was worked up as described above with successive washings with DMF (20 ml), DCM (20 ml), MeOH (20 ml) and finally with DCM (20 ml) after which time the resin was allowed to dry for 20 min. The resin exhibited a positive ninhydrin test. Although the FTIR spectrum of the original resin was morphologically different than the product, no distinct new absorption bands were present.

FTIR (KBr disc): ν (cm^{-1}) 3430, 3064, 3026, 2924, 2854, 1658.

12.6.4 Deprotection of N-α-t-BOC-L-serine- EDA peptide from Resin

To a dry 25 ml screw top vial was added C (0.15 g, 0.3 mmol) and acetic acid (15 ml). The resulting mixture was stirred at ambient temperature for 24 h. The resin was filtered and washed 3 times successively with acetic acid (3 ml), acetonitrile (3 ml) methanol (3 ml), ethanol (3 ml). The solvent from the combined filtrate was removed under reduced pressure, and the resulting yellow oil was submitted for electro-spray mass spectrometry.

Electro-spray MS (CI) m/z (%): 248 (M^++1,100).

12.6.5 Polymer-bound N-α-t-BOC-L-serine-EDA-N-α-t-BOC-Nπ-benzyl-L-histidine D

To a dry reaction vessel purged with nitrogen was added C (0.49 g of a 1.00 mmol) and DMF (15 ml). The resulting system was allowed to mix by supplement of nitrogen through the air intake valve for 15 min. The nitrogen was taken away and a vacuum line was used to remove the DMF. This was repeated 3 times after which DMF (20 ml), *N*-α-*t*-BOC-*N*-π-benzyl-*L*-histidine (1.2 g, 3.5 mmol), HOBt (0.47 g, 3.5 mmol), and NMM (0.38 ml, 3.5 mmol) were added. The resulting system was cooled to 0 °C before the slow addition of EDAC-HCl (0.67 g, 3.5 mmol). The system was mixed at 0 °C for 24 h, after which point it was allowed to warm up to ambient temperature and allowed to react for an additional 24 h. The system was worked up as outlined above. The resin exhibited a negative ninhydrin test. The deprotection of the resulting peptide was conducted as outlined in 12.6.4.

Electro-spray MS (CI) m/z (%): 575 (M^+ + 1, 100).

12.6.6 Ninhydrin Test[10]

Ninhydrin Test solutions:
Reagent 1: Ninhydrin (0.5 g) dissolved in ethanol (10 ml)
Reagent 2: Phenol (80 g) in ethanol (2 ml)
Reagent 3: Potassium cyanide (2 ml of 0.01 stock solution, made from 33 mg KCN in 50 ml water) diluted to 100 ml with pyridine.

To a vial containing a small portion of washed and dried resin was 1 drop of each of the above reagents. The mixture was gently heated with a heat gun. A straw yellow colored solution and no coloration of the beads indicated a negative test (no primary amines). A positive test was indicated by a deep blue/ purple color of the resin.

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Chapter 13

Conclusion and Future Work

CONCLUSION

We have developed a number of catalytic systems that can be utilized in hydrosilylation and allylstannylation reactions. Our work has focussed on the use of imidazole derivatives as all-purpose ligating species. We have used the lessons of nature to control the design of our catalytic systems. For example, imidazole is utilized as a nucleophile in the initial stage of this work, mimicking its actions in serine proteases.

The nucleophilic character of imidazole allowed for the activation of alkoxyhydridosilanes to the corresponding pentacoordinate species which subsequently reduced ketones. The amino acid histidine was used to provide a chiral environment around the imidazole and, thus, the activated silicon species so that enantioselectivity is conferred in these reductions.

In order to investigate the utility of C_2-symmetric systems, derived from histidine and other systems, to provide facial selectivity to the reductions, we undertook the design and synthesis of novel imidazole containing ligands containing this symmetry axis. Reductions were conducted with one of these species. The

compounds showed a distinct lack of chiral induction, possibly because the ligand held the silicon atom remote from the stereogenic centers. However, the reactivity shown by these species and the known biological use of imidazole as metal binders (e.g. porphyrins and carbonic anhydrase) led to the study of the metal chelating abilities of these ligands. Copper complexes of a chiral and an achiral representative of the ligands were synthesized and characterized by X-ray diffraction methods. Subsequent treatment of the chiral ligands with titanium and rhodium salts led to active catalyst systems, which were used for hydrosilylation and allylstannylation of carbonyl compounds, respectively. The hydrosilylation process proved to be quite fruitful in that it produced alcohols in high enantiomeric excess. The allylstannylation process gave alcohols in high yield, but poor facial selectivity was observed.

A tangentially related project also involved alkoxysilanes and imidazole. The general acid/general base activity of imidazole was used to advantage in the development of a active catalyst site mimic of a protein which has been shown to polymerize alkoxysilanes. This led to the design and application of a solid phase method to obtain a serine/histidine partner shown to be essential for the catalytic activity of the protein coined silicatein. This method should lead to the development of a combinatorial library of serine/histidine partners, allowing for the optimization of catalytic ability of the resulting peptide.

In short we have taken the lessons taught by nature to develop species that exploit the diverse properties of imidazole. We have taken advantage of imidazole's nucleophilic character, metal protecting/binding ability, and proton pump activity. It

would be wise for future researchers to further utilize lessons of nature in their design and synthesis of catalytic systems.

FUTURE WORK

The work presented in this thesis lends itself to numerous areas of development. For example, in studying the mechanism of action in our pentacoordinate silicon system, initially examined with $(EtO)_3SiH$, we began to study the activity of chlorohydridosilanes. These species showed varied reactivity depending on the amount of activator added. With catalytic amounts of the dianion of histidine, it was found that the homoaldol product resulted. With the addition of stoichiometric amounts of $HSiCl_3$, the reduction product was predominant as in the case with the alkoxysilane. A full investigation of the reaction profile of various silicon hydride donors should be undertaken.

With the development of the novel C_2-symmetric imidazole ligands, the exploration of their utility in asymmetric transformations can be quite fruitful. For example, we have already shown that the titanium adducts of these ligands can be utilized as catalysts for Mukiyama aldol reactions. These species may be used for catalytic hetero-Diels-Alder transformations. The placement of various metal species within these ligands can lead to a study of various asymmetric organic transformations as was presented in chapter 4. For example, the copper complexes developed in chapter 9 have not been tested for catalytic ability. These may lend themselves to asymmetric Diels-Alder reactions. Epoxidations may be achieved with manganese as the central metal. Ruthenium may be used in asymmetric reductions. The rhodium species can be used for

hydrosilylation of alkenes (a substitute for Wilkinson's catalyst). In summary, there are a number of areas that can be explored utilizing the ligands developed here.

Finally, it is still left to explore the full activity of the silicatein mimic. If species of the type described in chapter 13 can be utilized in the polymerization of alkoxysilanes, one can envision their use in the synthesis of stereoregular silicones. The methodologies developed in chapter 13 and also the suggestions made in chapter 13 involving the testing of catalytic activity of these species on the polystyrene beads, should lead to combinatorial assessment of the activity of the silicatein mimic. Once the species with the optimal activity is assessed, one can make use of these species in the development of silicones with unique properties, such as isotactic silicones.