12-2011

The Design, Synthesis and Application of a Novel Class of N-Heterocyclic Carbene Catalysts

Abigail Lynn Hubbard
University of Arkansas, Fayetteville

THE DESIGN, SYNTHESIS AND APPLICATION OF A NOVEL CLASS OF *N*-HETEROCYCLIC CARBENE CATALYSTS

THE DESIGN, SYNTHESIS AND APPLICATION OF A NOVEL CLASS OF *N*-HETEROCYCLIC CARBENE CATALYSTS

A dissertation submitted in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy in Chemistry

By

Abigail Hubbard
Kent State University
Bachelor of Science in Chemistry, 2007

December 2011
University of Arkansas

ABSTRACT

A copper carbenoid representative of a novel class of *N*-heterocyclic carbene (NHC) catalysts has been synthesized. This compound was characterized by X-ray crystallography and was found to confirm the rationale of our synthetic design: The C_2-symmetric structure places four stereocenters in close proximity (<5Å) to the reactive site of the carbene via a *trans*-annular gearing effect. The copper carbenoid was found to catalyze the hydrosilylation of prochiral ketones with superb selectivity in high yield.

This dissertation is approved for recommendation
to the Graduate Council.

Dissertation Director:

_____

Dr. Robert E. Gawley

Dissertation Committee:

_____

Dr. Neil Allison

_____

Dr. James Hinton

_____

Dr. Mathias McIntosh

DISSERTATION DUPLICATION RELEASE

I hereby authorize the University of Arkansas Libraries to duplicate this dissertaion when needed for research and/or scholarship.

Agreed _____
Abigail Hubbard

Refused _____
Abigail Hubbard

AKNOWLEDGEMENTS

I would like to thank Professor Gawley for his guidance and mentorship, which were the cornerstone of this work, and for his truly exceptional dedication to his work and students, which will serve as my definition of the gold standard long after I leave this lab. I extend my gratitude to all the members of the Gawley Group with whom I've had the privilege of sharing a bench, especially Beng: Thank you so much for your friendship; it has made all the difference. Lastly, a sincere thank you to the chemists who have taken me into their labs and provided me with a truly unique graduate education: Professors Oliver Reiser and Kirsten Zeitler of the Universität Regensburg, and Professors Peter Steel and Chris Fitchett of the University of Canterbury.

DEDICATION

To my ever-loving husband, Adam: Your support has been my port in many a storm. I promise I will never get another PhD.

TABLE OF CONTENTS

CHAPER I: LIST OF FIGURES

CHAPTER I: LIST OF SCHEMES

CHAPTER I: LIST OF TABLES

CHAPTER II: LIST OF FIGURES

CHAPTER II: LIST OF SCHEMES

CHAPTER II: LIST OF TABLES

CHAPTER III: LIST OF FIGURES

CHAPTER III: LIST OF SCHEMES

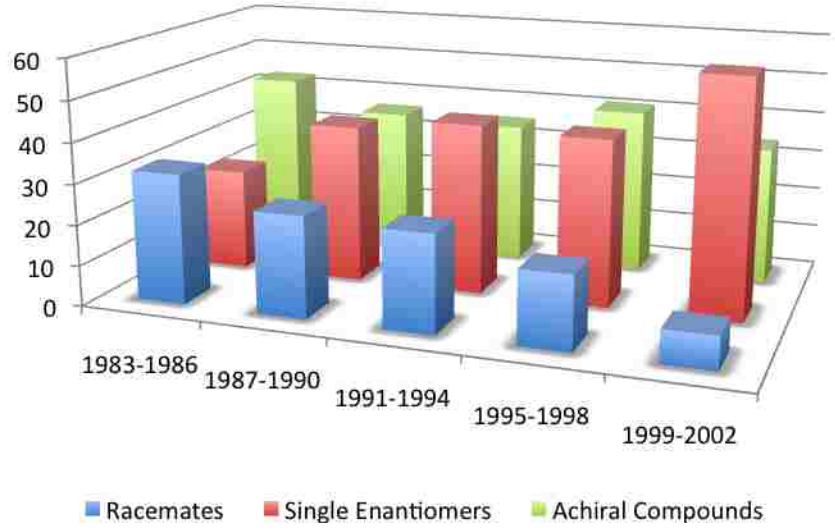
CHAPTER III: LIST OF TABLES

Chapter I: Design and Synthesis

Introduction

Perhaps the single most challenging task facing the synthetic organic chemist today is the efficient and cost-effective synthesis of enantiopure compounds. The paramount importance of chirality in synthesis is rooted in the fact that the physiological and/or pharmacological activity of a compound is often determined by its interaction with chiral receptors in the body. It is now a standard requirement for all new drugs to be characterized as single enantiomers[1] and the FDA has not approved the use of a drug in its racemic form in over a decade. Figure 1.1 illustrates graphically the total number of pharmaceuticals approved worldwide as racemates, single enantiomers or achiral compounds, respectively, and aptly depicts the sharp decline in the prevalence of racemic drugs. Historical precedent - founded on such sobering events as the thalidomide tragedy - and modern day drug development, in which numerous enantiomeric pharmaceuticals have been shown to display drastically different physiological activity (dexfenfluramine, dextromethorphan, Ritalin),[2] speak to the need for improved asymmetric methodology. Tedious processes and processes with very poor atom economy, such as preparative chiral stationary phase chromatography and diastereomeric crystallization, remain linchpins in present day drug development. The use of chiral catalysts and auxillaries represent a superior tool available to the scientific community for achieving asymmetric syntheses.

Figure 1.1: Number of drugs approved worldwide as racemates, single enantiomers or achiral compounds.[2]

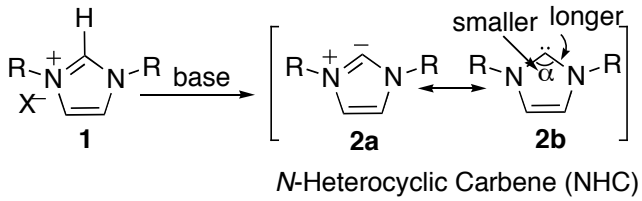


N-Heterocyclic carbenes (NHCs) and their organometallic complexes have risen to prominence in recent years, in part due to their broad utility in the catalysis of numerous bond forming reactions.[3] The field of NHC catalysis has evolved rapidly and a variety of practical uses in synthetic chemistry have been developed.[4]

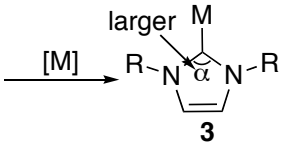
Carbenes are divalent carbons with an electron sextet; they were first reported by Buchner and Curtius as early as 1885 as hypothetical intermediates in decomposition of diazomethane.[5] The existence of this important class of compounds was confirmed by Wanzlick and Schoner[6] and, independently, Ofele[7] in 1968. Although poorly understood at the time, thiazolylidenes were being used for the homodimerization of aldehydes as early as 1943, in what is very probably the first example of NHC organocatalysis.[8] It was not until the synthesis of an isolable, crystalline NHC by Arduengo in 1991, however, that the field of NHC catalysis gained serious traction in the scientific community. The use of NHCs as ligands in catalysis –

or as organocatalysts themselves - is a focal point of investigation because NHCs are electron rich, nucleophilic and structurally unique.

Scheme 1.1: NHC generation by azolium deprotonation and notable structural features.[9]



N-Heterocyclic Carbene (NHC)

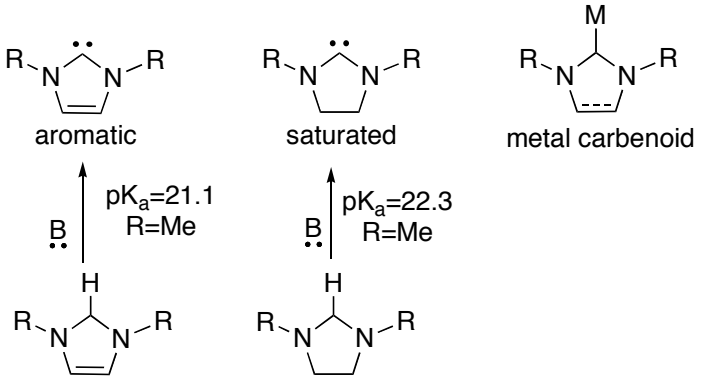


metal carbenoid

NHCs are arguably the most stable carbenes accessible to the scientific community. This unique attribute is owing to a number of factors: Firstly, the most widely used NHCs are designed with large *N*-substituents (R groups, Scheme 1.1) to provide for shielding of the carbene. The immediate precursors to many of the useful NHC catalysts contain *N,N'*-diarylimidazolium and -imidazolinium rings (R=Ar, Scheme 1.1). Secondly and more critically, the lone pair electrons on nitrogen are delocalized into the empty p orbital of the sp^2 hybridized carbene (see structure **2a**). The contribution of resonance structure **2a** is apparent in the high degree of nucleophilicity of most NHC ligands, which is notable in that carbenes are generally quite electron poor. The structural attributes of NHCs, as compared with their azolium precursors (**1**), are more in line with resonance structure **2b**. Lengthening of the C2-heteroatom bonds and larger bond angle α are both indicative of increased σ-bond character.[9]

Removal of the C-2 proton of an imidazolium results in the formation of a carbene and retention of aromaticity, deprotonation of an imidazolinium affords a saturated carbene, and complexation of either with a metal affords a metal carbenoid (Figure 1.2). The C2 proton of an imidazolium is therefore more easily removed than the corresponding hydrogen in an imidizolinium.[9] Consideration of the electronic attributes of each structure can prove useful in the rational design of an NHC catalyst for a given application. For example, the empty p-orbital of an aromatic carbene allows for strong back bonding when bound to a metal, while saturated heterocycles lack comparable capacity for this interaction and therefore tend to be more labile ligands.

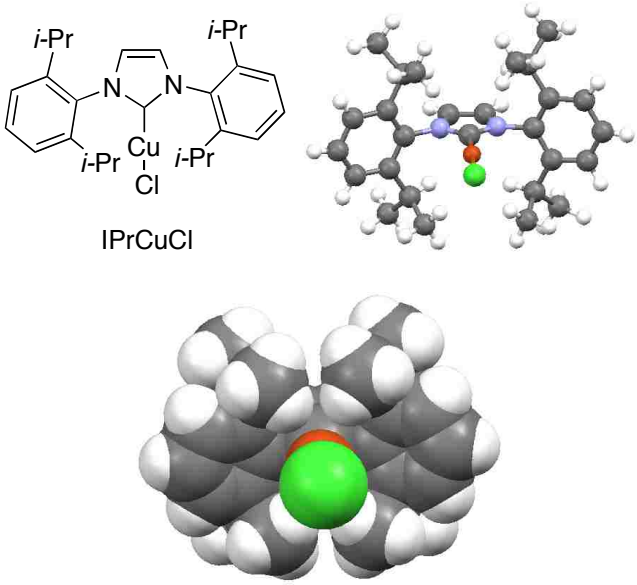
Figure 1.2: Notable electronic features of imidazolium- and imidazolinium-based carbenes



One of the most versatile imidazolium NHCs is the *N,N'*-bis(2,6-diisopropylphenyl)imidazol-2-ylidine (IPr) ligand, in which 2,6-diisopropylphenyl groups comprise the aryl substituent on the heterocycle.[10] The X-ray crystal structure of the IPrCuCl complex is displayed in Figure 1.3, in both wire and space-filling representations. It can be seen that the four methyls of the isopropyl groups are in close proximity to the copper atom, with an average distance of 3.840 Å. One can reasonably speculate that when the IPr NHC is

used as a free carbene (organocatalyst), the catalyst-coordinated reactant would be in approximately the same place as the copper, while in metal-mediated catalysis, the position of the reactant would be approximately in the position of the chlorine atom, which is ~4.8 Å distant from the four methyl groups. Analysis of the crystal structure of CuIPr led us to speculate that an NHC with stereogenicity incorporated at the location of the isopropyl methine could produce a compound with a well-formed chiral pocket around the catalytic reactive site. Should such a compound retain the synthetic versatility and ease-of-use of its achiral prototype, it could represent a valuable contribution to the field of enantioselective NHC catalysis.

Figure 1.3. The crystal structure of IPrCuCl.[10]

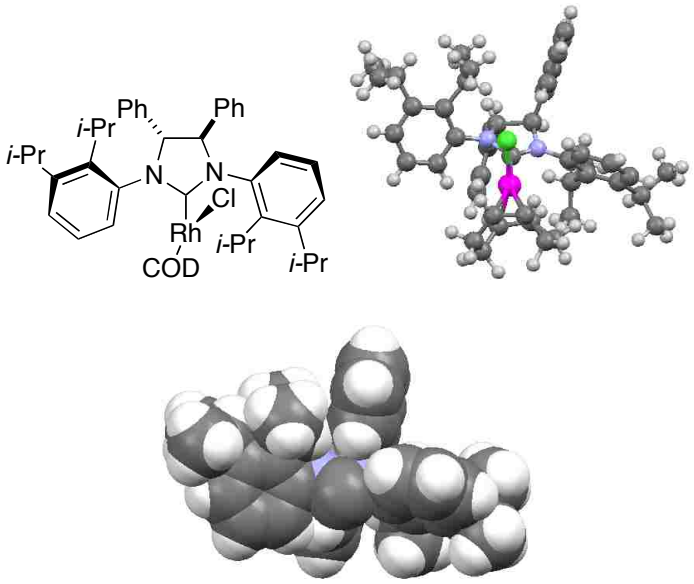


IPrCuCl

The formation of a similar chiral pocket in the saturated imidazolinium series can be obtained via placement of the two phenyls on the backbone of a saturated heterocyclic ring. The gearing effect induced by the phenyl substituents forces ortho-substituted phenyl rings to

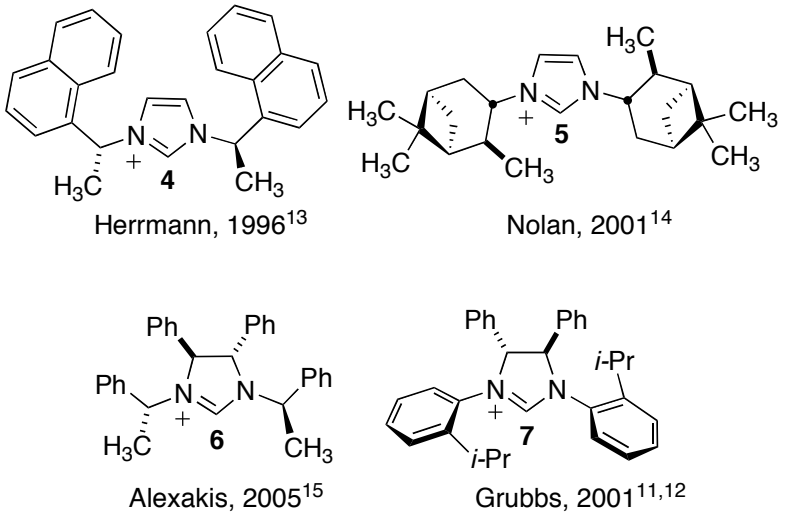
reside orthogonal to the plane of the heterocycle, with the substituents pointed away from the phenyl groups on the imidazolinium backbone.[11,12] The X-ray crystal structure of one such geared compound is shown in Figure 1.4, revealing the anti orientation of phenyl and isopropyl groups. The complex lacks C_2-symmetry due to the other ligands on the metal, so the *N*-aryl rings are not symmetrically disposed in this structure.

Figure 1.4. Crystal structure of a saturated NHC with a chiral backbone and "geared" unsymmetrical *N*-aryl groups. In the space-filling representation (bottom), only the NHC ligand is shown, and the gearing effect of the phenyl groups can be seen clearly.[12]



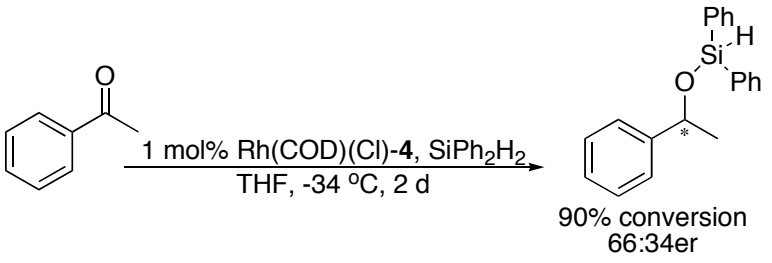
Although a number of chiral, C_2-symmetric imidazoliums and imidazoliniums have been reported (selected examples illustrated in Figure 1.5)[11-15] enantioselectivities are often moderate and none of the reported C_2-symmetric ligands have replaced 2-(isopropyl)aryl groups with stereogenic groups in either an imidazolium or imidazolinium NHC precursor.

Figure 1.5. C_2-symmetric imidazoliums and imidazoliniums.



Imidazolium salt **4** was used to generate both iron and rhodium based carbenoids, which were found to be remarkably stable at temperatures up to 100 °C. Both metal carbenoids were screened in the hydrosilylation of acetophenone with diphenylsilane. The ferrocenyl-based complex yielded racemic silyl ether in low yield while the rhodium carbenoid achieved good conversion but only very modest enantioselectivty (Scheme 1.2).[13]

Scheme 1.2. Asymmetric hydrosilylation of acetophenone with Rh(COD)(Cl)-**4**

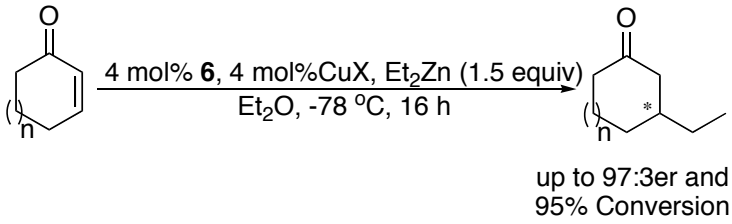


Nolan's C_2-symmetric imidazolium **5** and its analogs (compounds possessing chiral alkyl substituents on the nitrogen) were used in the synthesis of ruthenium-based cyclopentadienyl

complexes (Cp*Ru(Cl)-**5**) and characterized by solution calorimetry and X-ray diffraction. An application of these complexes in any enantioselective reaction has yet to be reported.[14]

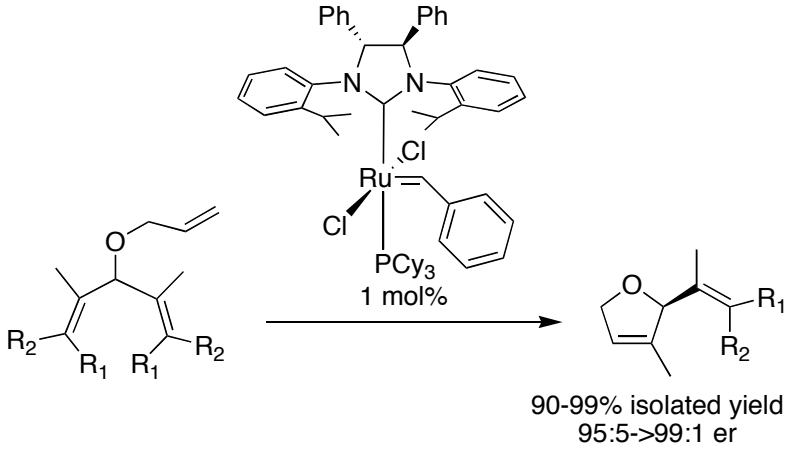
Imidazolinium **6** was metallated in situ with a variety of copper (I) and (II) salts and applied to the catalysis of conjugate additions with diethyl zinc (Scheme 1.3). The transformation required extensive optimization and had a limited substrate scope, but excellent conversion and enantioselectivity were observed in some cases. The silver carbenoid of **6** was found to have superior reactivity relative to the free carbene.[15]

Scheme 1.3: Conjugate reduction catalyzed by imidazolinium **6**



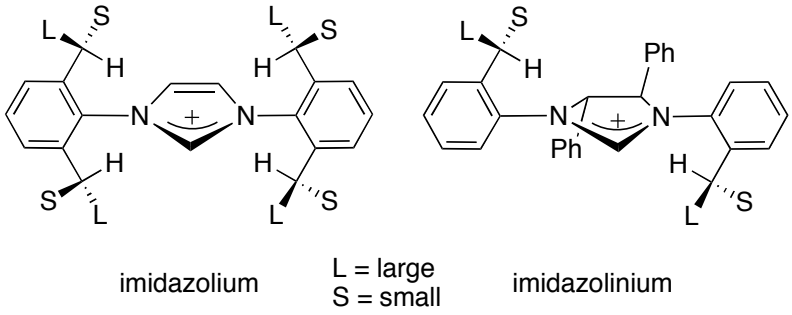
The greatest success story in the field of NHC catalysis is of course that of Grubbs et al. The details of this work alone have filled many of dissertations unto themselves, and will therefore be touched upon only briefly herein. By incorporation of imidazolinium **7**, as well as other similar chiral NHC precursors, into ruthenium-based catalysts for olefin metathesis, asymmetric variants of these important transformations were achieved. One general example of ring closing metathesis is depicted below in Scheme 1.4.[11,12,16]

Scheme 1.4: Asymmetric ring closing metathesis



It can thus be seen that while the potential of chiral C_2-symmetric NHC ligands in asymmetric catalysis has been well-established, it is far from fully developed. A design in which the stereogenic center is γ to the annular nitrogen could produce an NHC that retains the synthetic versatility of the *N*-aryl NHC ligands[17] and simultaneously place the reactive site in a chiral pocket. This design could place two or more stereogenic centers in close proximity to the putative carbene site, whereby large groups would occupy diagonally opposite quadrants around the carbene (Figure 1.6). We therefore decided to investigate the preparation of such species, characterize them structurally by X-ray crystallography, and test their activity in enantioselective hydrosilylation.

Figure 1.6: Design prototype for new chiral C_2-symmetric NHCs



In summary, the development of new chiral C_2-symmetric NHC ligands for application in asymmetric catalysis was the foremost goal of my doctoral research. In particular, we hoped to develop chiral analogs of the widely used, air and moisture stable copper carbenoid, CuIPr. An NHC ligand exhibiting this novel structural motif, with a stereocenter incorporated at the position of the isopropyl methine (γ to the heterocyclic nitrogen), has yet to be reported in the literature.

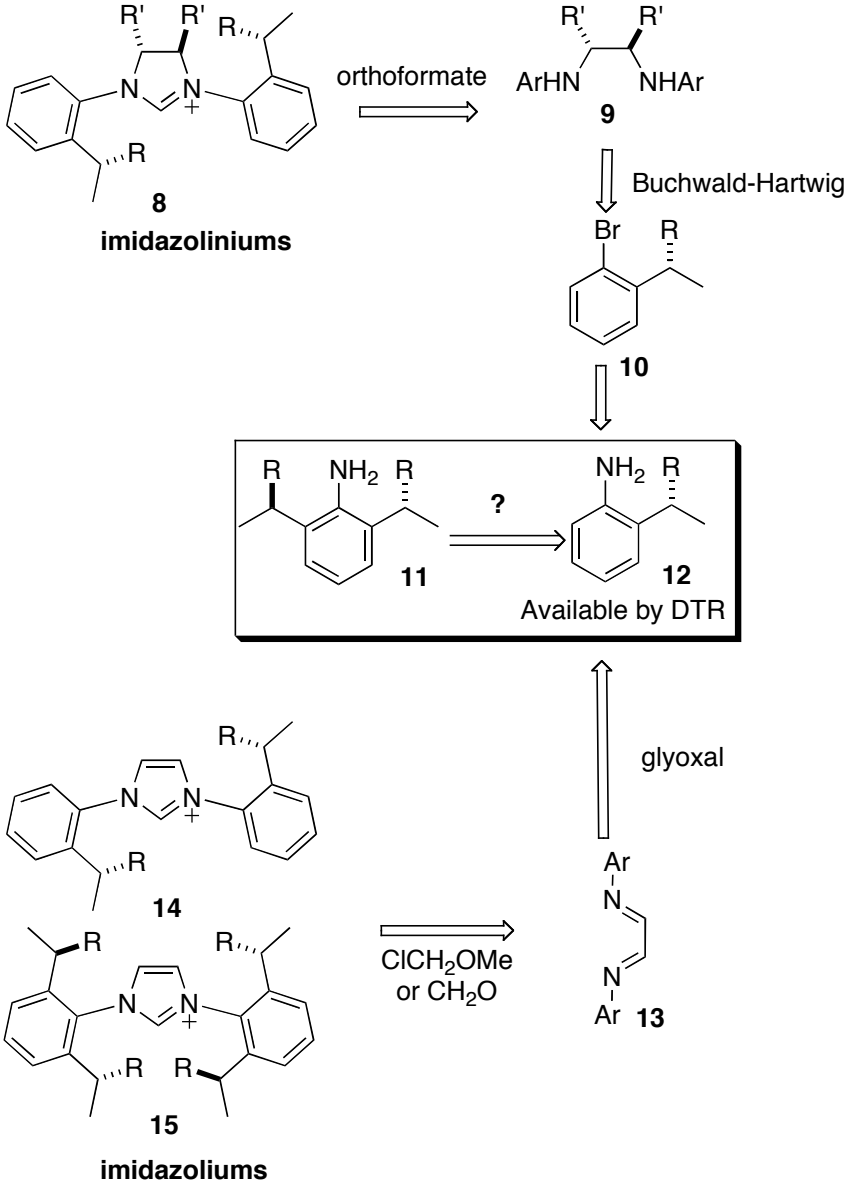
Results and Discussion

Design and Synthesis of CuPhEt

The design envisioned for chiral, C_2-symmetric imidazoliums and imidazoliniums is shown in Scheme 1.5, along with the retrosynthetic plans for their preparation. Cyclization of diamine **9** with an orthoformate afforded imidazolinium **8**, whereas cyclization of a diimine, **13**, with a formaldehyde equivalent afforded the imidazoliums **14** and **15**. The plan for the preparation of geared imidazoliniums involved Buchwald-Hartwig coupling of an orthosubstituted aryl bromide such as **10** with 1,2-diphenylethylenediamine. The aryl bromide was to be synthesized by Sandmeyer substitution of a 2-substituted aniline, **12**, which is available by dynamic thermodynamic resolution (DTR).[18] The diimine precursor, **13**, of the imidazoliums **14** and **15** was prepared by condensation of anilines **11** or **12** with glyoxal. A route to access enantioenriched 2,6-disubstituted anilines, such as **11**, is absent from the literature and required investigation.

Notably, work related to the synthesis of compounds representative of imidazolinium **8** (R, R'=Ph) and imidazolium **14** (R=TMS) was carried out by a former student, Dr. Daniel Eddings, before my work on this project began. While the synthesis of these compounds will not be discussed in detail, it is summarized here because my work does include some characterization and application of these NHC-precursors.

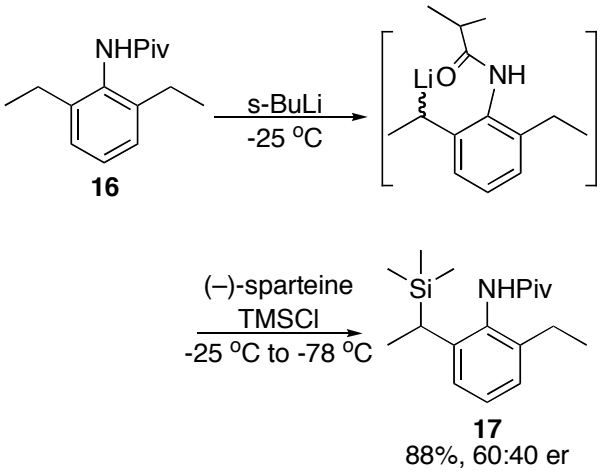
Scheme 1.5: Retrosynthetic plan for the preparation of C_2-symmetric imidazolium and imizolinium salts



Significant efforts were focused on the synthesis of an enantioenriched 2,6-disubstituted aniline compound for use as the starting material in the synthesis of an unsaturated chiral NHC. It was found that the use of 2,6-diethylaniline as a substrate complicated the introduction of the stereogenic center via a dynamic thermodynamic resolution procedure

developed by Beak and Basu.[18] Although the 2,6-compound can be successfully silylated via this protocol (88% isolated yield), the enantiomer ratio is poor (Scheme 1.6). Various reaction conditions were probed for optimization. The best results (60:40 er) were obtained with the published warm-cool temperatures and MTBE as solvent. As this reaction protocol proceeds smoothly with a number of monosubstituted pivalamides, it can be inferred that the second alkyl arm in some way disrupts resolution of the lithiated intermediate by (–)-sparteine.

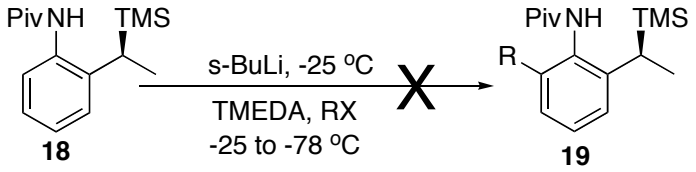
Scheme 1.6: Attempting the DTR of 2,6-Diethylpivanilide



A second related reaction scheme is depicted in Scheme 1.7. It was hypothesized that if a 2-substituted pivanilide, tertiary at the benzylic position, were employed as a starting material, the most probable site of lithiation would be at the 6-position. To test this possibility, the selectively silylated product of the Beak protocol with 2-ethylaniline (**18**) was used as the starting material for a second lithiation reaction. Subsequent quench with an alkyl halide as the electrophile should then yield the desired enantioenriched 2,6-substituted aniline. Unfortunately, no reaction was observed under a large variety of reaction conditions. The

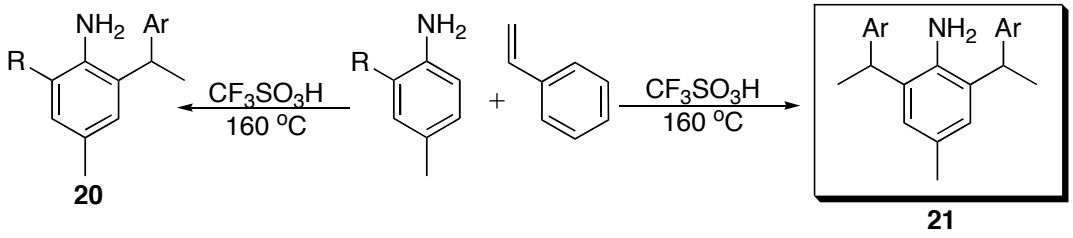
reaction conditions summarized in Table 1.1 were also applied to compound **18** and no conversion of starting material was observed in any case.

Scheme 1.7: Attempting lithiation of the 6-position.



An alternate procedure for the ortho-alkylation of anilines was developed by Coates et al[19] and is depicted in Scheme 1.8. In an approach sequentially similar to that described above, it was hoped that the stereocenter could be successfully incorporated into the 2-substituted compound and Coates' hydroarylation procedure then applied to obtain the desired enantioenriched 2,6-substituted aniline compound.

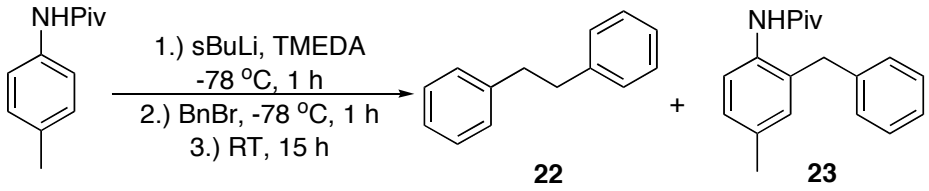
Scheme 1.8: Friedel Crafts-type alkylation of the 6-position



Since the Coates procedure requires that the para-position be blocked, my efforts were concentrated on the synthesis of 2-benzyl-4-methylaniline for use as a starting material in these studies. We again attempted to employ lithium chemistry to benzylate 4-methylpivalamide. To decide upon the optimal reaction solvent, the lithiation was carried out in tetrahydrofuran,

diethyl ether and methyl tert-butyl ether (MTBE) and subjected to a deuterated quench (D_2O, CD_3OD). As told by these results, it was concluded that deprotonation is most efficient in MTBE (Scheme 1.9).

Scheme 1.9: Initial reaction conditions for synthesis of 2-Benzyl-4-methylpivanilide



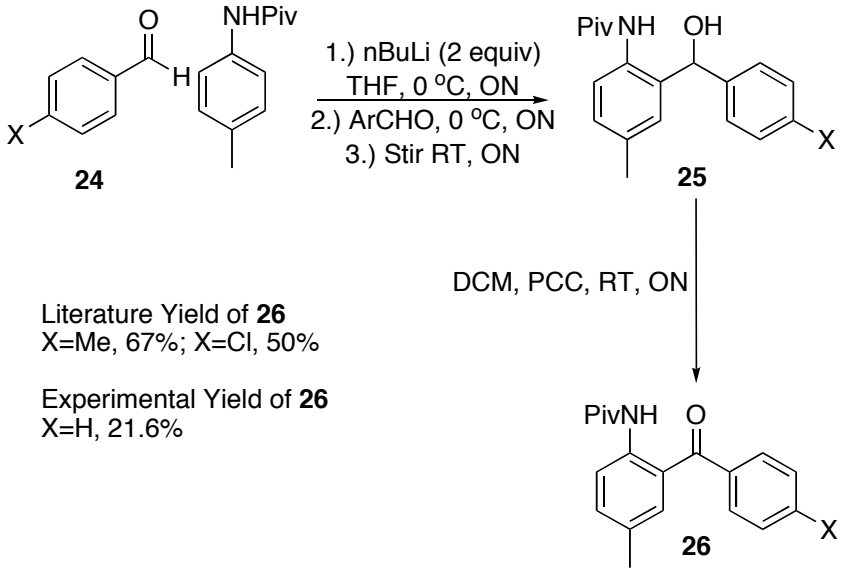
Because of the propensity of benzyl bromide to undergo reactions proceeding via free radical mechanisms, diphenylethane (**22**) was observed as a coupling byproduct. Attempts to optimize this reaction were extensive and are summarized in Table 1.1. In addition to an exhaustive amount of variation in the reaction conditions, benzyl chloride, benzoyl chloride, benzaldehyde, and benzyl mesylate and tosylate were all tested as potential electrophiles. Surprisingly, starting material was recovered intact when the organolithium was quenched with benzaldehyde or benzoyl chloride, while benzyl mesylate and tosylate effectively consumed the starting material but yielded complex reaction mixtures. In many cases, two additional unknown byproducts were formed. These were never identified as they were found to decompose upon purification via column chromatography. The best results obtained were~40% to the desired product and ~30% to diphenylethane (Entry 8).

Table 1.1: Reaction conditions investigated (Scheme 9)

Entry	Conditions	Solvent	Conversion to **22**	Conversion to **23**
1	Scheme 8	MTBE	33.40%	trace
2	sBuLi , 0 ^{o}C, 2 h; BnBr , 0 ^{o}C, 30 m; RT, 2 h	MTBE	13.30%	0%
3	sBuLi, 0 ^{o}C, 2 h; BnBr (≥3 equiv) 0 ^{o}C, 30 m; RT, 2 h	MTBE	33.60%	38.40%
4	nBuLi 0 ^{o}C, 2 h; BnBr (≥3 equiv) 0 ^{o}C, 30 m; RT, 2 h	THF	29.40%	0.00%
5	sBuLi 0 ^{o}C, 2 h; BnBr (≥3 equiv) 0 ^{o}C, 30 m, RT, ON	MTBE	30.20%	18.90%
6	nBuLi , 0 ^{o}C, 2 h; BnBr (≥3 equiv) 0 ^{o}C, 30 m; RT, ON	THF	26.40%	0%
7	sBuLi, -78 ^{o}C, 2 h; BnBr (≥3 equiv) , 78 ^{o}C, 30 m; RT, 2 h	MTBE	19.10%	0%
8	sBuLi, 0 ^{o}C, 2 h; BnBr (≥3 equiv) TMEDA, 0 ^{o}C, 30 m; RT, 2 h	MTBE	28.90%	44.40%
9	nBuLi, 0 ^{o}C, 2 h; BnBr (≥3 equiv) TMEDA, 0 ^{o}C,, 30 m; RT, 2 h	THF/Ether	40.90%	0%

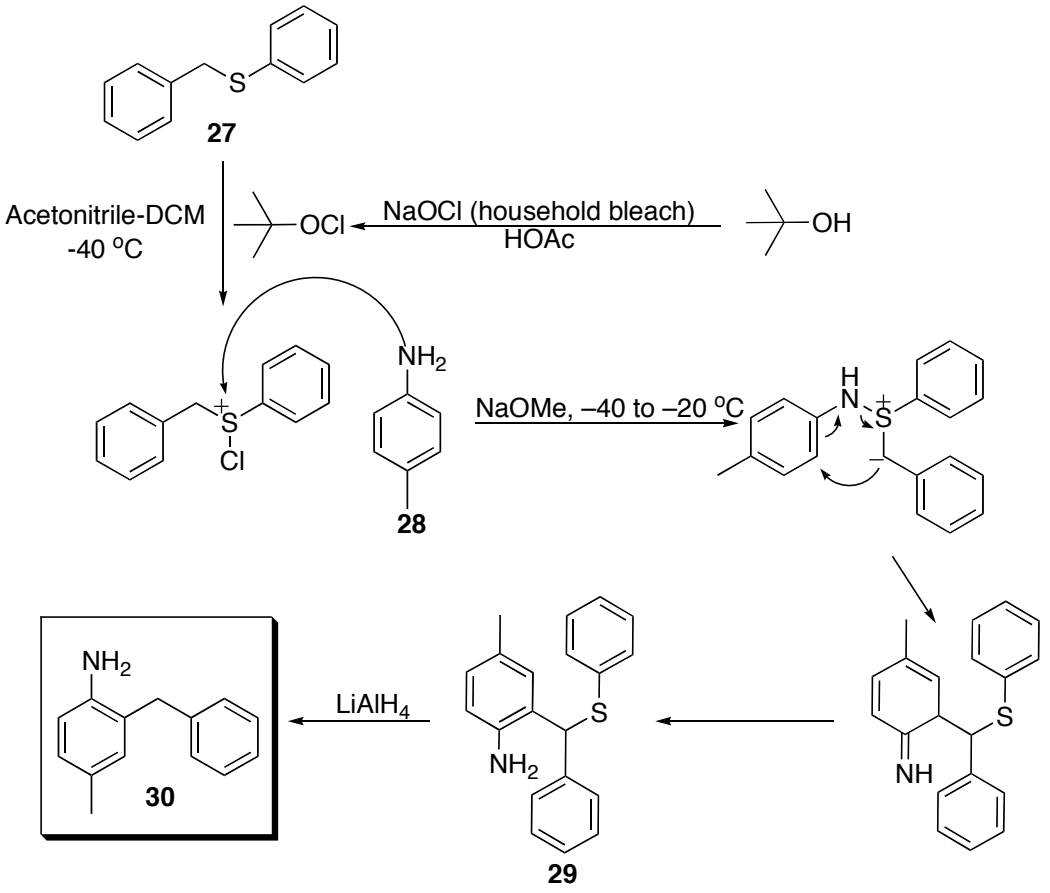
Alternate syntheses for 2-benzyltoluidine were sought. Two reaction protocols applicable to the desired compound were investigated. A reaction for the conversion of 4-methylpivalamide to the corresponding benzyl alcohol by reaction of the lithiated starting material with various benzaldehyde derivatives followed directly by in situ oxidation to yield the ketone compound has been reported by Tsai et al[20] and is depicted in Scheme 1.10. Reduction of **26** would yield the desired pivanilide of 2-benzyltoluidine, **23**.

Scheme 1.10: Alternate approach from the method of Tsai et al



Alternatively, a methodology for the benzylation of pivalamides developed by Gassman and Drewes,[21] involving the generation of the aza-sulfonium salt upon reaction with phenyl benzyl sulfide and consequent rearrangement, rearomatization, and desulfurization, is depicted in Scheme 1.11. It was found that, in addition to avoiding lengthening the synthesis with an additional reduction step, the reaction protocol of Gassman and Drewes was superior in terms of yield and convenience.

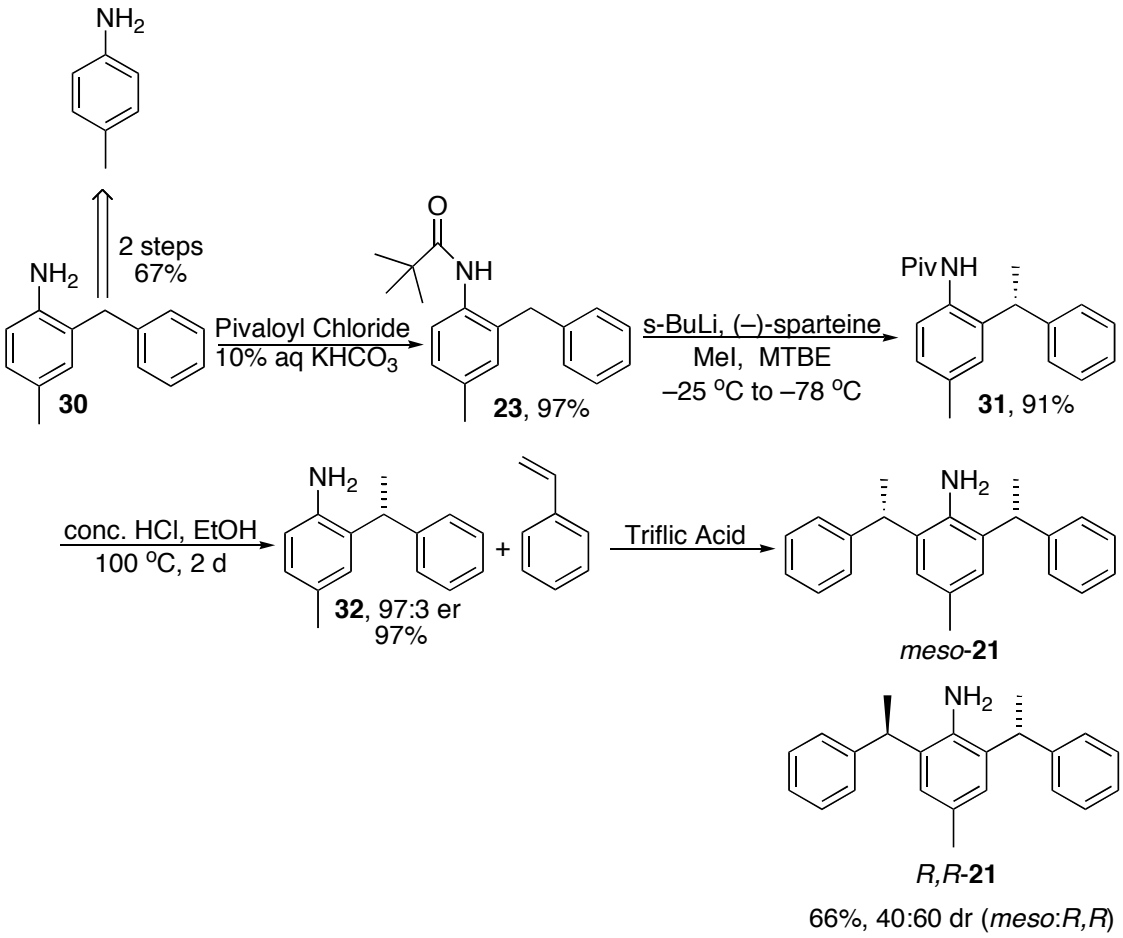
Scheme 1.11: Alternate approach using the method of Gassman and Drewes



The Gassman and Drewes protocol yields 2-benzyltoluidine (**30**) in 67% over two steps (Scheme 1.12). Compound **30** undergoes acylation at nitrogen with pivloyl chloride smoothly and in excellent yield. The pivanilide **23** was then enantioselectively methylated by DTR and hydrolyzed to yield the free aniline **31** in good yield (88%, 2 steps) and excellent enantioselectivity (97:3er). Friedel Crafts-type alkylation of the 6-position, according to the Coates protocol, was then carried out. The resultant reaction mixture was difficult to purify due to the formation of styrene oligomers, but allowed for isolation of the desired 2,4,6-trisubstituted aniline in moderate yield (66%) after somewhat tedious chromatographic

separation. The reaction mixture was found to display a slight diastereomeric preference for the chiral *R,R*-**21** stereoisomer (60:40 dr, *R,R*:*meso*).

Scheme 1.12: Asymmetric synthesis of **21**

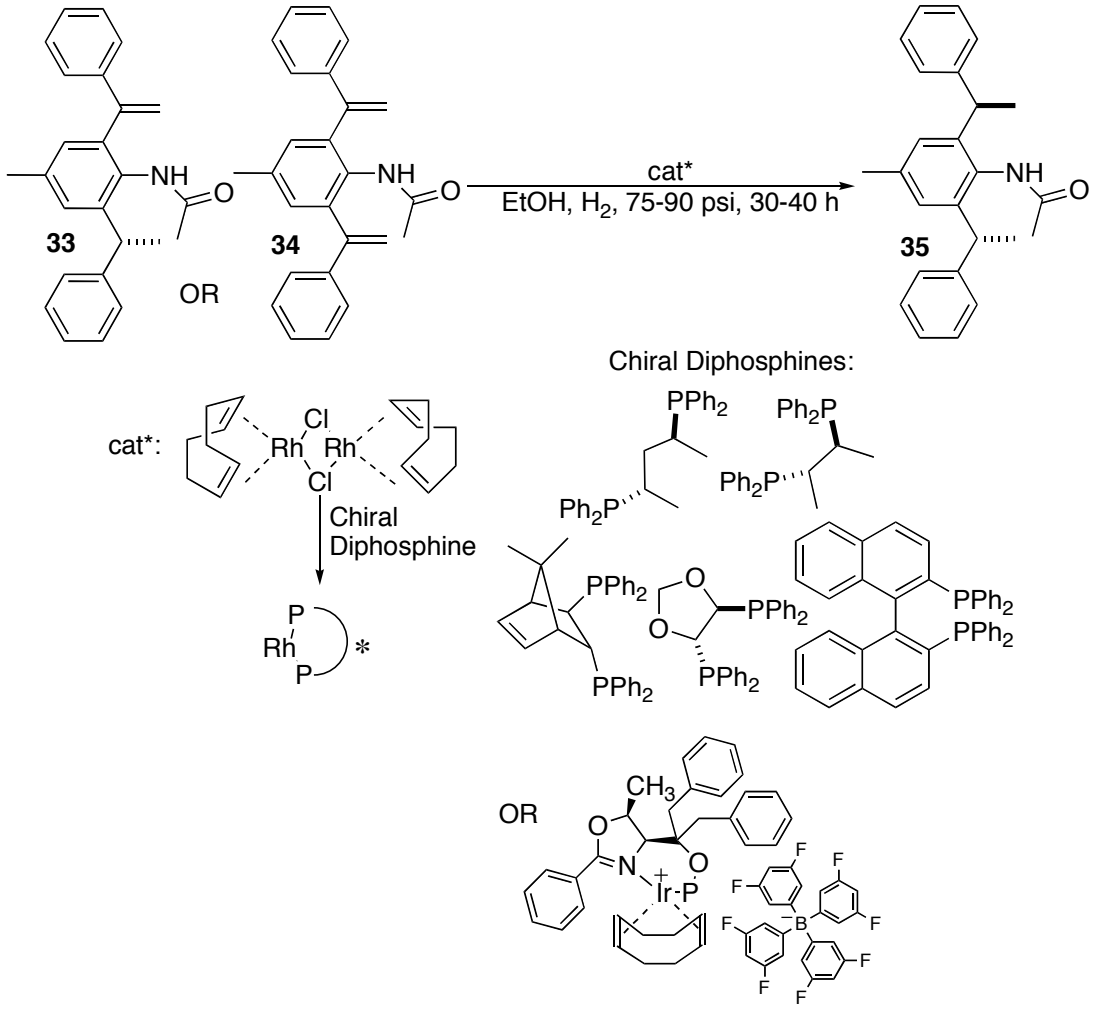


Compound **21** was found to be problematic in that both nitrogen and the benzylic hydrogens are quickly oxidized in air. More critically, the diastereomers were found to be inseparable by column chromatography, although the *meso* compound may be separated by successive recrystallization from ethanol, providing for isolation of the chiral diastereomer in low yield (<10%).[22] An alternate protocol for the separation of the diastereomers of **21** was sought.

Semi-preparative HPLC, crystallization of the hydrochloride salt, and use of gravity column chromatography were extensively investigated with no success. It was ultimately found that the diastereomers could be partially separated using radial chromatography with a gradient solvent system. Improved, but still incomplete, separation could be achieved by acylation of the aniline nitrogen with benzyl chloroformate.

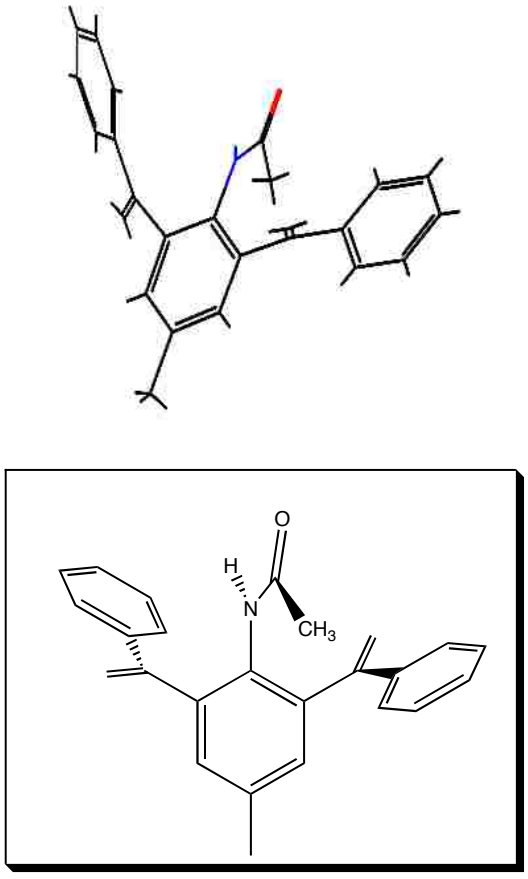
Because the extremely tedious diastereomer separation in the synthetic plan reduces the utility of the catalyst, even if it were to exhibit phenomenal catalytic activity, an alternate route to the chiral diastereomer of **21** was sought. Asymmetric hydrogenation of **33** or **34** would greatly reduce the length of the synthesis as well as eliminating the need to separate diastereomers.

Scheme 1.13: Attempts at asymmetric hydrogenation



In order to achieve asymmetric induction in the hydrogenation, the chiral catalyst must coordinate the olefin such that only one face is exposed to hydrogen. Substrates containing a primary aniline moiety are often acylated to provide an anchor for the chiral catalyst: The hydrogenation is rendered enantioselective via simultaneous coordination of the olefin and the oxygen of the acylated nitrogen. The lowest energy conformer of **34** was determined by molecular mechanics and is shown below in Figure 1.7.

Figure 1.7: Low energy confomer of **34**



Initial investigation into this transformation utilized chiral diphosphine rhodium catalysts generated in situ from the Rh(COD)(Cl) dimer and corresponding diphosphine (See experimental). We discovered that these catalytic systems are significantly less active than Pd/C: Reaction conditions were optimized and found to require longer times, higher pressure, and the application of heat to achieve full conversion. The results of the reduction of diolefin **33** and enantioenriched alkene **34** are displayed below in Table 1.2.

Table 1.2: Results of investigation into asymmetric hydrogenation

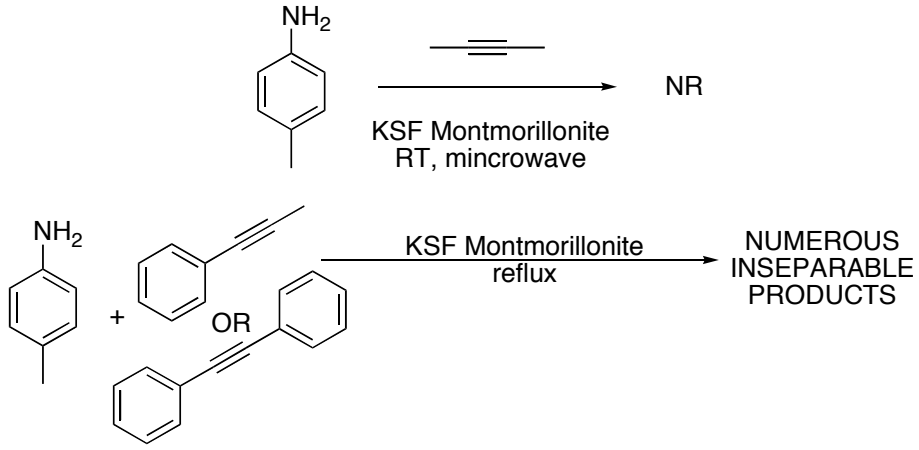
Substrate	Diphosphine	dr (*meso*:*R,R*+*S,S*)	er
34	DIOP	55:45	50:50
34	CHIRAPHOS	60:40	50:50
34	SKEWPHOS	55:45	50:50
34	NORPHOS	65:35	50:50
34	BINAP	60:40	50:50
33	DIOP	55:45	97:3
33	CHIRAPHOS	60:40	97:3
33	SKEWPHOS	55:45	97:3
33	NORPHOS	68:32	97:3
33	BINAP	60:40	97:3
34	Ir-COD*	70:30	50:50

Asymmetric hydrogenation with the chiral rhodium-diphosphine systems yielded low diastereoselectivity and no enantioselectivity. Despite these disappointing results, a more thorough survey of the literature revealed that the production of *gem*-1,1-diaryl-methine containing stereocenters via hydrogenation is historically problematic. Recent developments in this area have shown that a new class of iridium catalysts are capable of achieving excellent enantioselectivities with substrates closely resembling our own.[23] Because these catalysts are difficult to access synthetically, our investigation was limited to the commercially available iridium catalyst shown above in Scheme 1.13. While this substrate also failed to yield sufficient dia- and enantioselectivity, further investigation into the application of this class of catalysts in our system is warranted and is underway.

$[(N,P)^*Ir(COD)]^+[BAr_F]^-$ catalysts have achieved very high enantioselectivies in the hydrogenation of the olefins with *gem*-1,1-diaryl substituents. The two aryl groups may differ by as little as a *para*-methyl group and still undergo reduction of the olefin with excellent selectivity, but the role of the other olefin terminus is of great importance in achieving enantiodifferentiation. With this in mind, the synthesis of an analog of **33** containing

trisubstituted double bonds was investigated. It was hoped that a 2-butyne, methyl phenylacetylene, or 1,2-diphenylacetylene would undergo efficient and selective alkylation in the presence of acidic surface catalyst, KSF Montmorillonite. Found to be insufficiently reactive, 2-butyne was failed to give product even when microwaved for extended periods of time (the boiling point of 2-butyne is 27 ºC, precluding high temperature reflux). Methyl phenylacetylene and 1,2-diphenylacetylene, on the other hand, react quickly and indiscriminately, yielding a mixture of regioisomers and polymeric byproducts.

Scheme 1.14: Synthesis of trisubstituted *gem*-diaryl olefin starting materials

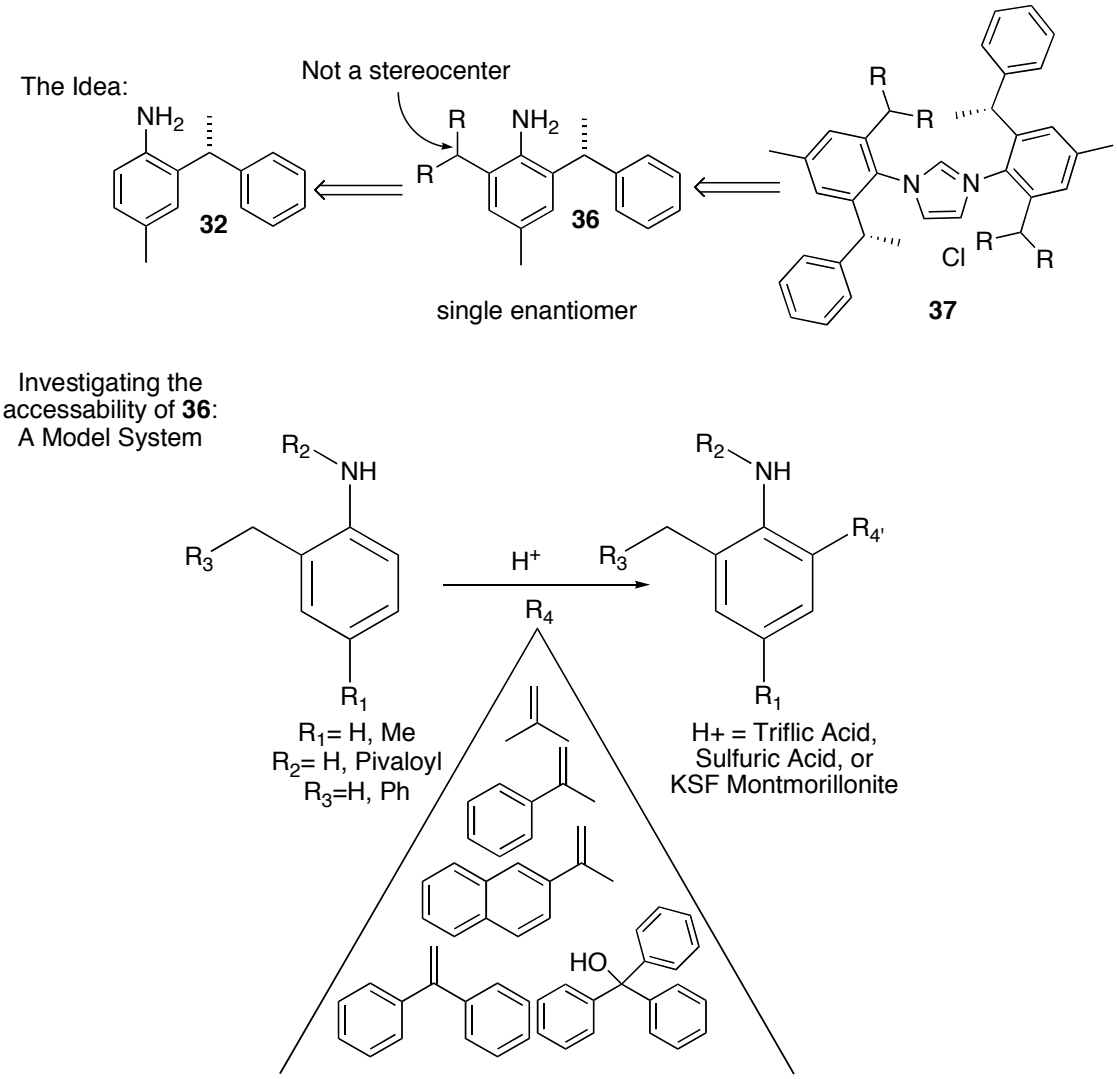


To the extent that time and resources had permitted, the possibility of asymmetric hydrogenation was exhausted at this point. We instead decided to pursue the synthesis 2,6-disubstituted anilines lacking C_2-symmetry. Since DTR can be employed to install one stereocenter and consequent alkylation of the 6-position via Friedel-Crafts type chemistry with styrene or phenylacetylene was successful, it was hoped that this reaction sequence may also be used to yield "non-diastereomeric" 2,6-disubstituted aniline precursors (Scheme 1.15). The starting materials and substrates investigated are briefly summarized below. Considering that

the free amine may actually serve to deactivate the aromatic system under acidic conditions, both the aniline and the pivanilide structures were investigated as starting materials. Starting materials with and without the *p*-position blocked were studied; it was determined that none of the protocols investigated were regioselective and a methyl group in the 4-position was a necessity. The 2-position was substituted with either a methyl or benzyl group.

Triphenylmethanol cannot be forced to react, even under the harshest conditions employed. Diphenylethylene did not react with the starting material under any conditions, but yielded dimeric and polymeric products with strong acid and reflux conditions. Phenylpropene and 2-naphthylpropene reacted with 2,4-dimethylaniline and 2,4-dimethylpivanilide to give the desired product in good yield with minimal dimeric or polymeric byproducts when mild acid (KSF Montmorillonite) was used. This positive result was negated, however, with 2-benzyl-substituted starting material because hydroarylation was not selective for the nitrogen bearing phenyl group. Isobutene was extremely reactive and generated multitudinous byproducts even at decreased temperature and pressure. This course of investigation was thus abandoned.

Scheme 1.15: Synthesis of non-diastereomeric 2,6-disubstituted anilines



Fortuitously, an opportunity for collaboration with Drs. Chris Welch and Regina Black of Merck arose. The separation of all three stereoisomers of **21** (*S,S*, *R,R*, and *meso*) on preparative chiral stationary phase SFC was confirmed with a small batch sample. The preparation of compound **21** as a mixture of all three stereoisomers was accomplished by di-*ortho* substitution of toluidine with either phenylacetylene followed by reduction, or styrene,

according to protocols published by Tarantola[24] and Coates[19] respectively (Scheme 1.16). Although lengthier by one step, the Tarantola route was found to be a higher yielding and cleaner way to access compound **21** as a mixture of a chiral racemate and a *meso* diastereomer. This mixture was separated via stacked injection into a semi-preparative chiral stationary phase SFC column (Figure 1.8).

Each of the stereoisomers were independently analyzed: It was found that the first to elute was (+)-**21**, the second (–)-**21** and the third was the optically inactive *meso* **21**. Subsequent XRD analysis of the copper carbenoid, prepared from (+)-**21**, revealed it to be the (*S,S)* enantiomer.

Scheme 1.16. Syntheses of **21** as a Mixture of Stereoisomers

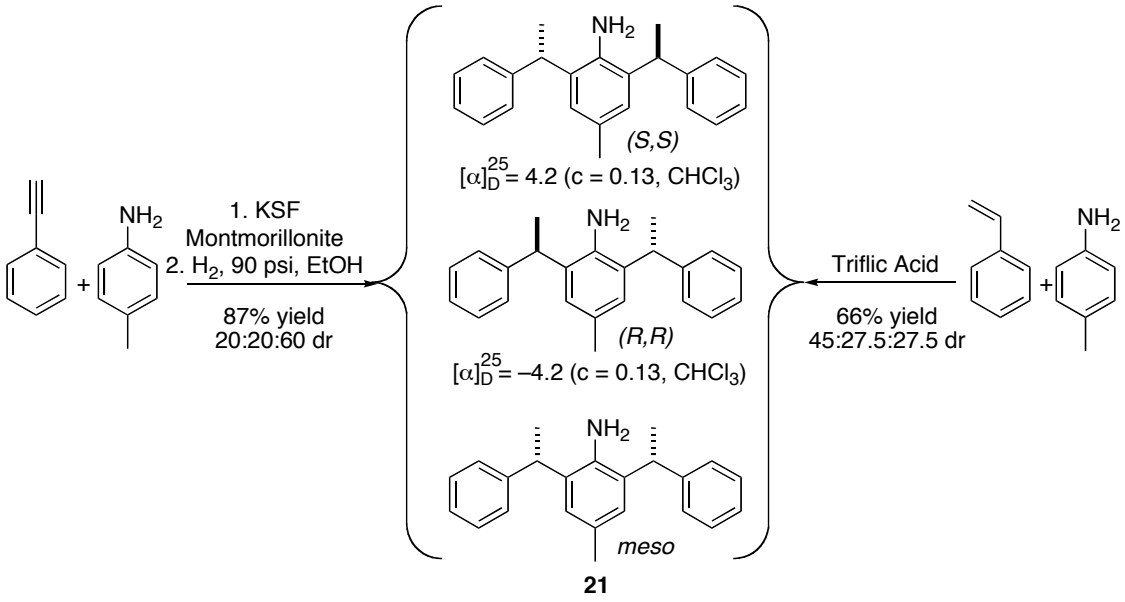
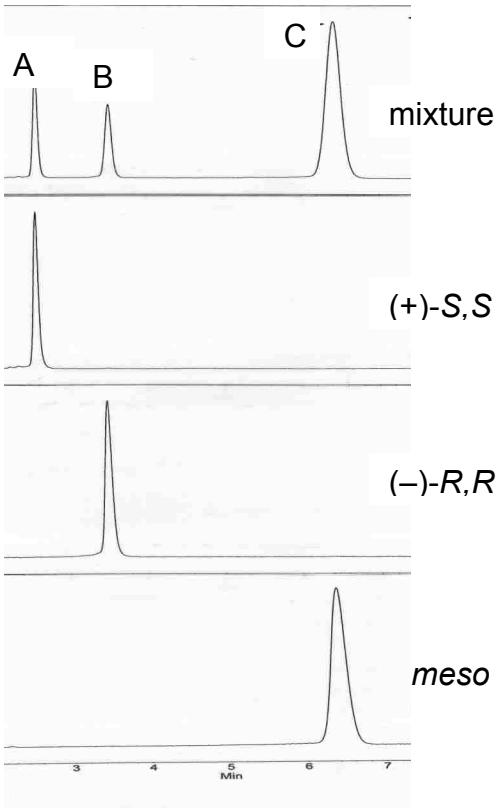
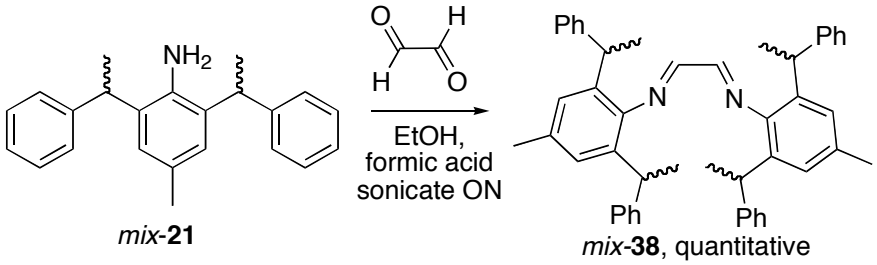


Figure 1.8: Analytical results of the preparative separation of the stereoisomers of **21**



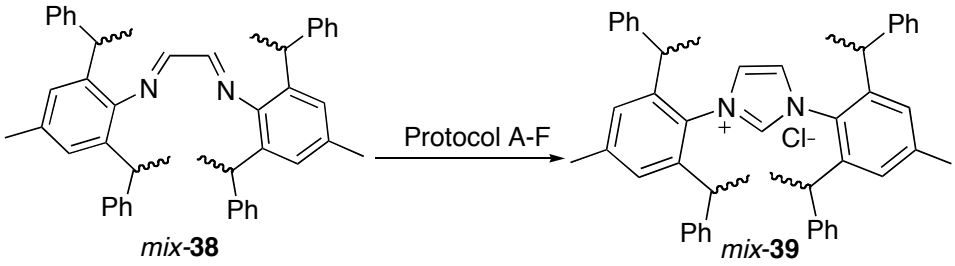
The rest of the synthesis was optimized with either compound *mix*-**21 (**mixture of all 3 stereoisomers) or with *meso*-**21**, as it has no potential in asymmetric catalysis, before being carried out with enantiopure **21**. Aniline *mix*-**21** was condensed with glyoxal in quantitative yield to give diimine *mix*-**38** (Scheme 1.17). The cyclization and purification of this product, however, was not straightforward and required extensive optimization.

Scheme 1.17: Glyoxal condensation of *mix*-**21**



Initial attempts to achieve ring closure were carried out with diimine *mix*-**21** according to the original procedure published by Arduengo (Protocol A, Scheme 1.18).[25] When this protocol failed to achieve any conversion of the starting material, a rigorous search of the literature was conducted to locate every published protocol for the ring closure of diimines yielding imidazolium salts. Of particular note is Protocol B, which was shown to effectively yield an extremely bulky 2,6-terphenyl substituted imidazolium salt.[26] The feasibility of this transformation suggests there is no steric basis for the failure of compound **38** to undergo ring closure.

Scheme 1.18: Cyclization of *mix*-**38**



1 : 1

mix-38 —(Cl, O; 40 °C, 16 h, THF)→

Protocol A - Diimine (1eq) and chloromethyl methyl ether (1equiv) were combined in THF under N_2 and stirred at 40 °C for 16 h. Product collect by flitration.[25]

1 : 20

mix-38 —(Cl, O; 40 °C, 1 h, MeCN)→

Protocol B - Diimine (1equiv) and chloromethyl methyl ether (20equiv) were stirred for 5-10 m before the addition of MeCN. Resultant solution stirred for one hour before the removal of all volatiles. The product was washed first with water, then with diethyl ether. Recrystallized from acetone.[26]

1 : 10

mix-38 —(Cl, O; 40 °C, 1 h, H_2O, THF)→

Protocol C - Diimine (1equiv) and chloromethyl methyl ether (10 equiv) and water (0.5 equiv) were stirred in THF at 40 °C for 18hr before the removal of all volatiles. Residue was extracted with DCM and purified via trituration b/t EtOAc and DCM.[27]

1 : 1.5 : 1.5

mix-38 —(HO(CH(H)O)$_n$H; O; HCl,4M; 40 °C, 24 h, toluene)→

Protocol D - Diimine (1 equiv) was added to a solution of paraformaldehyde (1.5 equiv) in toluene at 40 °C. Reaction vessel was purged with N_2 for 5-10min before dropwise addition of HCl in dioxane (4M, 1.5 equiv). Stirred 24 h before isolation by filtration and washed with THF. Dissolved in DCM and washed with water before purification by recrytallization from DCM and pentane.[15]

1 : 1.1 : 2.1

mix-38 —(AgOTf, Cl, O, O; 50 °C, 20 h, DCM, dark)→

Protocol E - Diimine (1 equiv) and silver triflate (1.1 equiv) were combined in freshly distilled DCM and chloromethyl pivolate (2.1 equiv) was added. Reaction solution was stirred in the dark for 20 h at 50 °C. Purified via column chromatography.[28]

0.9 : 1

mix-38 —(+N=Cl)→

Protocol F -Dimethyldiamine (1 equiv) was dissolved in dichloromethane in an ice bath and acetyl chloride (1equiv) was added dropwise. The diimine (0.9 eq) was added to the resultant suspension in a single portion. The reaction vessel was removed from the ice bath and allowed to warm to room temperature before removal of volatiles and recrystallization from dichloromethane and ethyl acetate[29]

Table 1.3: Summary of Ring Closing Investigation

	Protocol	Changes to protocol*	unreacted SM?	*mix*-**39** Formation?
1	A	None; KI	0 (w/ KI)	N
2	B	None; KI	0	Y
3	C	None; KI	0	N
4	D	None	0	Y
5	E	None; KI	0	N
6	F	None	0	N

Consumption of the diimine starting material was monitored by TLC while conversion to product was indicated by the presence of the diagnostic imidazolium proton at C-2 in the ^{1}H NMR spectra. The products of the reactions in which the diimine was consumed but the imidazolium was not produced were not identified. In the first round of reactions, literature protocols A-F were employed without alteration. In the second round, a stoichiometric amount of potassium iodide was added to protocols A, B, C, and E. It was hoped that the in situ formation of iodo methyl alkyl ethers would lead to improved reactivity.

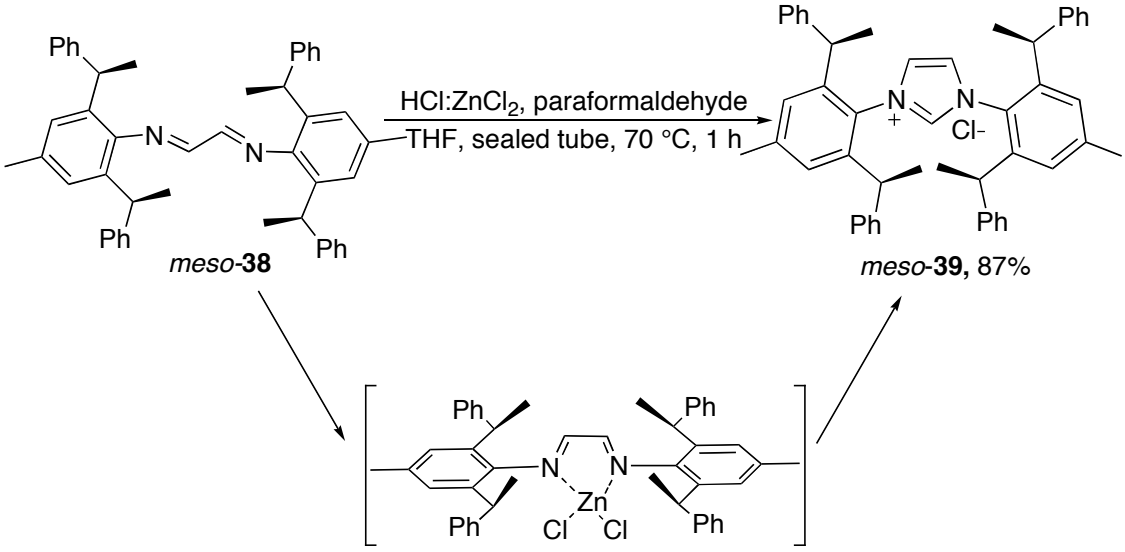
The formation of imidazolium choride, *mix*-**39** was observed when the diimine was subjected to Protocol B, in which a twenty-fold excess of chloromethylethyl ether was employed, and in Protocol D, in which para-formaldehyde was used as the cyclizing reagent in conjunction with HCl-Dioxane (4M). The imidazolium proton was absent from the crude NMR spectra of reactions subjected to Protocols A, C, E and F. The addition of an iodide salt to protocol A did force conversion of the diimine although no product formation was observed.

Purification of the crude reactions mixtures showing the presence of product was difficult. The product was found to be unstable on silica and alumina. Innumerable attempts at

purification by recrystallization from dichloromethane, hexanes, petroleum ether, diethyl ether, tetrahydrofuran and ethyl acetate solvent systems were unsuccessful.

Fortunately, it was subsequently discovered that minimal revisions to a cyclization protocol by Markó[30] provided for isolation of pure imidazolium chloride in 87% yield after recrystallization (Scheme 1.19). This protocol utilizes zinc (II) chloride as a stoichiometric additive, which is known to coordinate to diimines in a square planar arrangement. Markó et al have proposed that the zinc chloride serves to facilate cyclization to the imidazolium, presumably by coordinating the diimine in the reactive s-cis conformation.

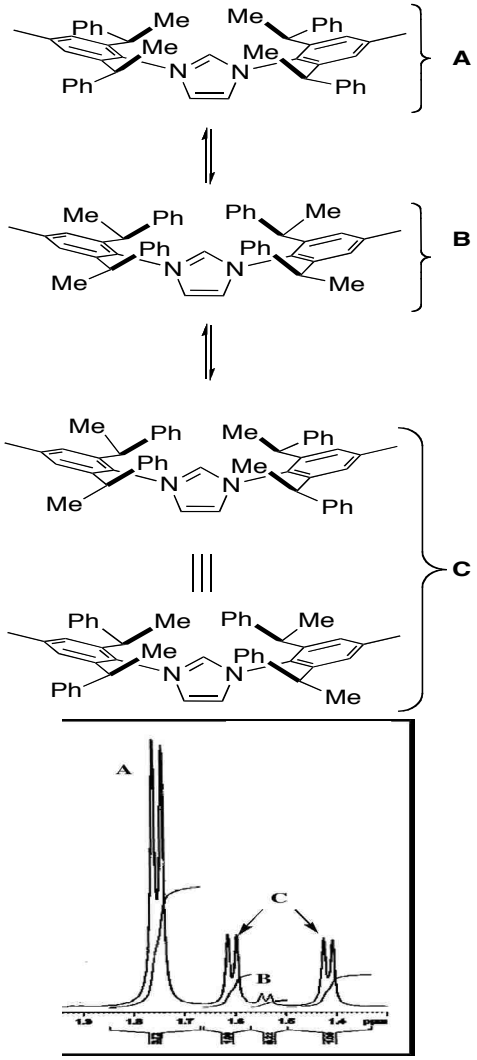
Scheme 1.19: Optimized diimine cyclization



When *meso*-**38** was condensed and cyclized, some interesting stereochemical features were discovered in the characterization of *meso*-**39**: The NMR spectra exhibited quadrupling of the aliphatic signals. Further consideration of this phenomenon led us to conclude that *meso*-**39** exists as a mixture of three rotamers (Figure 1.9). We hypothesize that conformer A

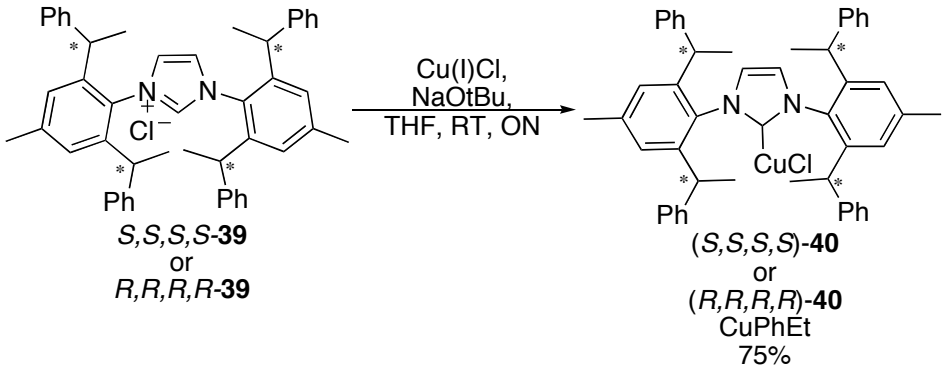
is the most highly populated species: one can imagine that the cyclization of the diimine to the imidazolium is facilitated by a conformation which places the forming imidazole carbon in the least sterically hindered environment. Rotation around both *N*-aryl bonds would give conformer B, likely the least populated species because carbon 2 is in a highly crowded environment in the midst of four bulky phenyl groups. Rotation around only one of the rightmost *N*-aryl bonds of A or B gives compound C. The two depictions of compound C are identical, however the methyl groups γ to the heterocyclic nitrogen are diastereotopic, resulting in their non-equivalence in the proton NMR spectrum.

Figure 1.9: Rotamers of *meso*-**39**



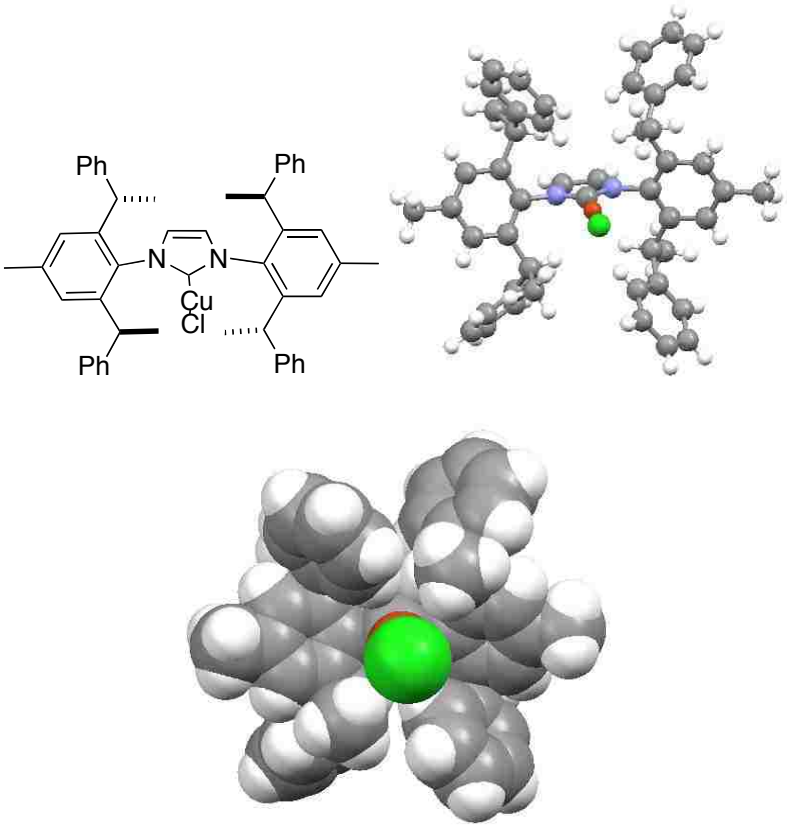
Imidazolium chlorides (*R*,*R*,*R*,*R*)-**39** and (*S*,*S*,*S*,*S*)-**39** were then synthesized according to the optimized reaction protocols and subjected to metallation in the presence of copper (I) chloride and NaO*t*-Bu (Scheme 1.20). Copper carbenoids (*R*,*R*,*R*,*R*)-**40** and (*S*,*S*,*S*,*S*)-**40** were obtained in good yield via this protocol.

Scheme 1.20: Synthesis of Copper Carbenoid CuPhEt, **40**



Crystals of (*S*,*S*,*S*,*S*)-CuPhEt suitable for X-ray diffraction were grown by slow diffusion of hexanes into ether. The monoclinic crystal ($\beta = 115.097°$) was determined to have the C_2 space group; a final R factor of 0.0438 was obtained. The crystal structure is presented in Figure 1.10. The Flack Parameter was refined to a value of zero, establishing the absolute configuration as (*S*,*S*,*S*,*S*). We were pleased to observe the formation of a chiral pocket at the site of the putative carbene. CuPhEt successfully places four stereocenters in close proximity to the C-2 reactive site and the crystal structure of the copper carbenoid reveals a nicely formed chiral pocket, which serves to confirm the rationale of our synthetic design. To our knowledge, CuPhEt represents the first example of a structural gearing effect induced not by placement of bulky substituents on the backbone of a saturated imidazolinium but via trans-annular steric interaction of bulky substituents γ to nitrogen in an unsaturated imidazolium.

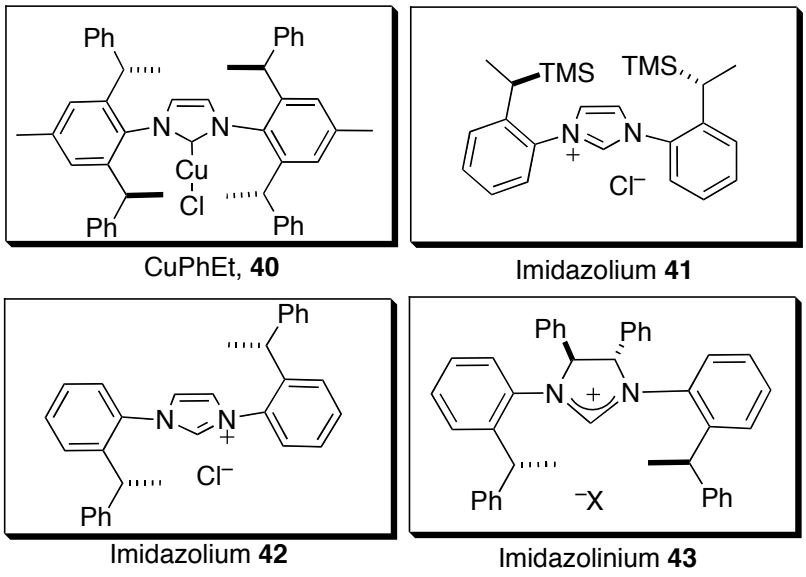
Figure 1.10: Crystal structure of (*S*,*S*,*S*,*S*)-CuPhEt



Preliminary Investigation into the Catalytic Activity of the γ NHC Ligands*

The metallation of CuPhEt proceeded smoothly and in good yield, indicating that imidazolium **39** is reasonably stable in the presence of base. This, unfortunately, was not the case with other members of the γ*-NHC family, shown below in Figure 1.11. Geared imidazolinium **43** and singly substituted imidazoliums **41** and **42** were found to decompose when subjected to the reaction protocol depicted in Scheme 1.20. The silver carbenoid derived from **42** was generated from the corresponding imdazolium chloride by using silver oxide as both the base and the metal source.[31] This protocol is attractive for its use of such mild conditions, but the product was obtained only in very low yield (<10%).

Figure 1.11: γ*-NHC Precursors and metal carbenoids



CuPhEt, **40**

Imidazolium **41**

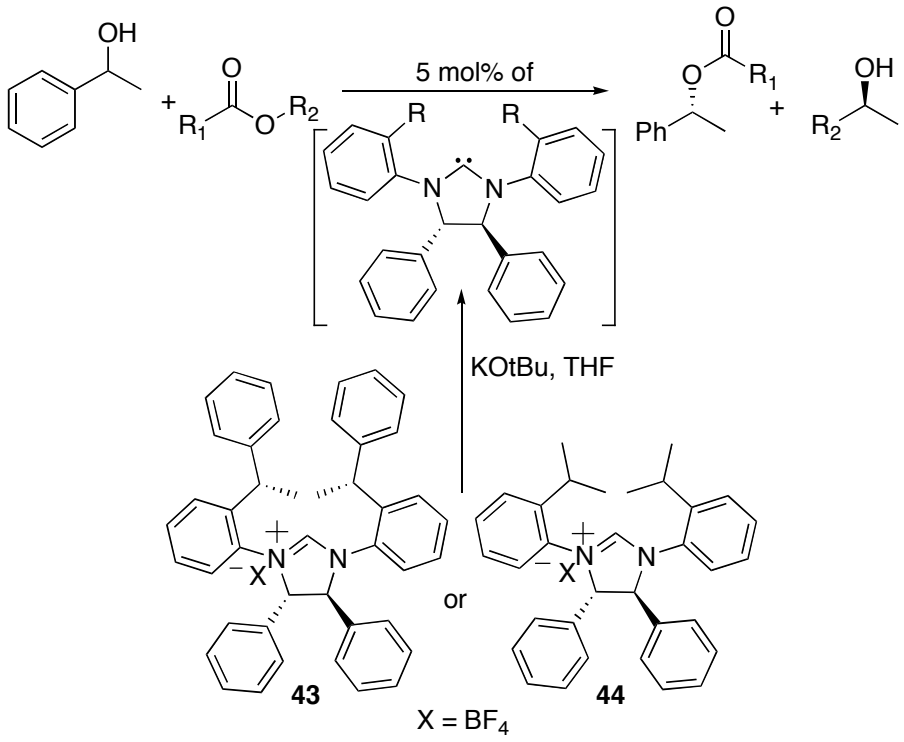
Imidazolium **42**

Imidazolinium **43**

There is some precedent for the organocatalytic application of NHC-precursors via in situ generation of the carbene, although most examples utilize imidazolium salts rather than those

with an unsaturated backbone. A number of reactions were investigated to test the potential catalytic application of the chiral imidazolium salts **41** and **42** and the geared imidazolinium **43**. A portion of this work pertaining to the organocatalytic applications of **43** as well as preliminary investigation into the catalytic activity of CuPhEt **40** are detailed below.

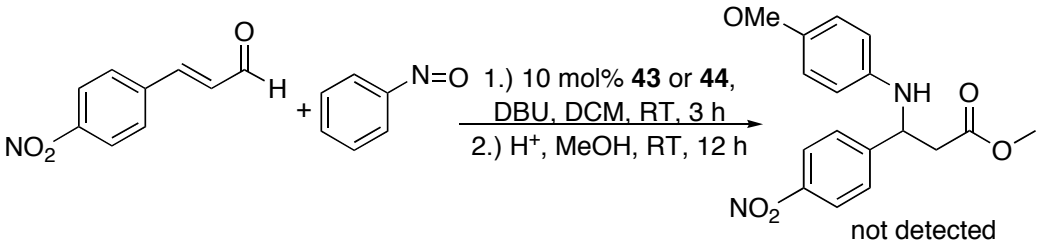
Scheme 1.21: Organocatalytic asymmetric transesterification



The reaction depicted in Scheme 1.21 was reported to be successful with unsaturated imidazolium salts[32] and has not been investigated with the use of saturated analogs. Methyl acetate, vinyl acetate, and phenyl benzoate were used as substrates to probe the catalytic activity of imidazoliniums **43** and **44**. Only with the use of methyl acetate was an isolatable amount of product formed (11.2% yield). Unfortunately the product was not optically active.

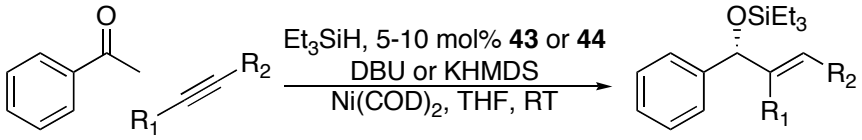
Furthermore, ^{1}HNMR spectra of the "carbene" solution revealed a loss of symmetry, indicating decomposition of the imidazolium salts in the presence of KOtBu.

Scheme 1.22: Organocatalytic synthesis of phenylisoxazolidin-5-ones



The reaction depicted in Scheme 1.22 was carried with achiral imidazolium and imidazolinium-based organocatalysts,[33] although the yield decreased with use of the saturated heterocycle. The reaction was investigated to find if it could be rendered enantioselective with the use of a chiral NHC precursor. It proceeds via the reaction of an enal with nitrosobenzene followed by acid-catalyzed esterification and Bamberger-type rearrangement of the *N*-phenylisoxazolidinone to the corresponding *N*-protected ß-amino acid ester. In the literature, KOtBu was used to generate the carbene, but as this base had been found to decompose compounds **43** and **44**, DBU was used instead. Attempts with both imidazoliniums led to complex reaction mixtures, the purification of which was not attempted.

Scheme 1.23: Asymmetric reductive silylation

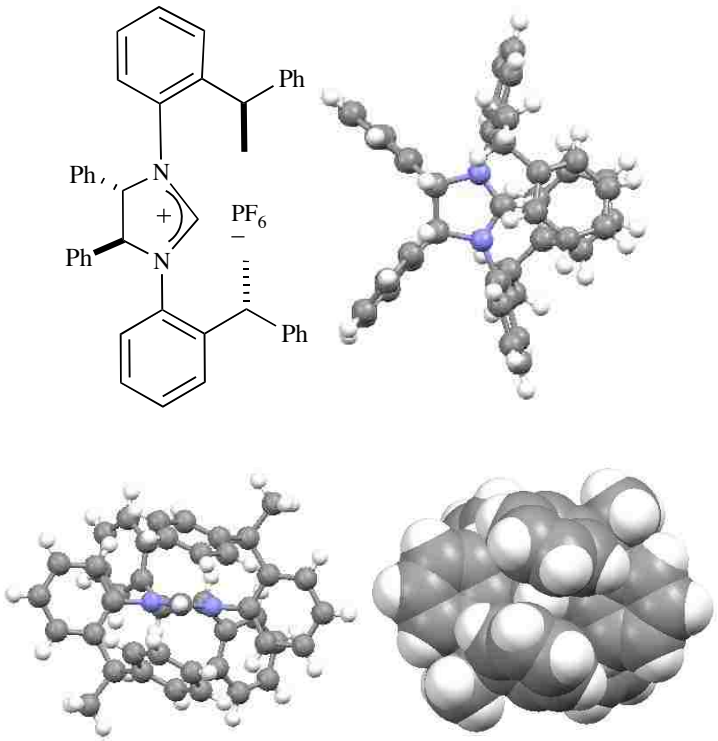


The reaction depicted in Scheme 1.23 was reported to proceed with moderate to good enantioselectivity using saturated imidazolium salts,[34] and thus is very promising for a potential application of compounds **43** and **44**. In the literature, KOtBu was used to generate the carbene in situ. This reaction was investigated with both KHMDS and DBU as base. Unfortunately only starting material was recovered with the use of either base and either imidazolium salt. Alkyne substrates investigated were diphenylacetylene and methylphenylacetylene. As this reaction is particularly oxygen sensitive due to the use of the Ni (0) $(COD)_2$ compound, it is likely that the reaction was being quenched by air before it could proceed. Although Schlenk-techniques were employed, reagent transfer was still problematic. The reaction was again investigated using compound **43** and using a glove box for reagent transfer. Despite these additional precautions the same results were obtained. My speculation is that the quality of the Ni (0) $(COD)_2$ co-catalyst was in both cases at least partially oxidized, as indicated by its coloration. (According to EROS the chemical should be yellow in color;[35] the supply used in Regensburg was black and the supply bought new was brown.)

While the successful application of imidazolinium **43** as an asymmetric organocatalyst remains an elusive goal, we were pleased to observe the formation of a chiral pocket in its crystal structure. Crystals of **43** suitable for XRD were grown by slow diffusion of dichloromethane into pentane. The monoclinic crystal ($\beta = 94.5024°$) was determined to have the P21 space group and a final R factor of 0.0433 was obtained. The crystal structure is shown in Figure 1.12. The Flack Parameter was refined to a value of zero, providing confirmation of the absolute configuration as the (*S,S,R,R*) enantiomer. The phenyl groups of the *ortho*-aryl substituent are geared to the front of the imidazolinium ring to avoid steric

interaction with the phenyl groups of the imidazolinium backbone, thereby blocking two faces of the carbene center. These results indicate that continued investigation into the organocatalytic application of **43** may be warranted.

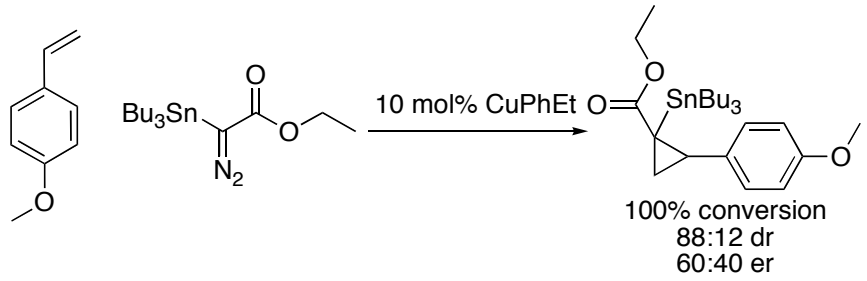
Figure 1.12: Crystal structure of **43**



CuPhEt was originally designed for application in asymmetric cyclopropanations. This transformation was chosen for its high synthetic utility and the limited number of asymmetric variants currently in the literature. Furthermore, the CuIPr has exhibited unique reactivity in the cyclopropanation of olefins with diazoacetate esters: it suppresses the dimerization of ethyl diazoacetate (EDA), thereby eliminating lengthy (up to 3d) syringe-pump additions from the synthetic protocol[36] and has been shown to effectively catalyze cyclopropanations of (tributylstannyl)-diazoacetate esters with high diastereoselectivity.[37] Much to our

disappointment, it was discovered that while CuPhEt indeed catalyzes the transformation and even suppresses the dimerization of diazoacetate ester, it does so with poor diastereo- and enantioselectivity. Similar results were obtained with both ethyldiazoacetate (EDA) and (tributylstannyl)ethyldiazoacetate. These results strongly suggest that the CuNHC-catalyzed cyclopropanation with diazoacetate esters *does not* take place on the metal center. Since this is of course a critical feature to the successful application of CuPhEt as a chiral catalyst, we began to investigate the literature for a transformation with a well characterized catalytic cycle.

Scheme 1.24: Application of CuPhEt to the cyclopropanation of p-methoxystyrene



Conclusions

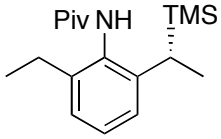
The synthesis of CuPhEt **40** and other members of the γ* family of NHC ligands presented many challenges. Nonetheless, their structural attributes beautifully exemplified the envisioned design. While our search for application for CuPhEt and NHC-precursors **41**, **42** and **43** was not immediately successful, more positive efforts to this end are detailed in the next chapter of this dissertation.

Experimental:

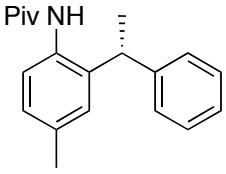
General: All reagents and solvents were used as received, unless indicated below. Diethyl ether (Et_2O), *t*-butyl methyl ether (MTBE), and tetrahydrofuran (THF) were distilled from Na/benzophenone ketyl under N_2 immediately prior to use. Toluene was dried over CaH_2 followed by distillation and stored over 3 Å molecular sieves. Methylene chloride was distilled from CaH_2 under N_2 immediately prior to use. *N,N,N',N'*-tetramethylethylenediamine (TMEDA) was vacuum distilled from CaH_2 and stored over 4 Å molecular sieves. (–)-Sparteine was vacuum distilled over CaH_2 and stored over 4 Å molecular sieves. Solutions of *s*-BuLi in cyclohexane were titrated against *N*-pivaloyl-*o*-benzaniline. ^{1}H NMR spectra were obtained at 300 or 400 MHz in $CDCl_3$ unless otherwise noted. Coupling constants (J), are reported in Hz. Supercritical fluid chromatography was used to determine enantiomer ratios on a Daicel Chiracel OD-H column or a Whelk-O column using absolute ethanol as modifier.

General Procedure for Dynamic Thermodynamic Resolution: To an oven dried, Argon purged, 250 mL round bottom flask was added the pivanilide **16** or **23** (14.6 mmol) in 120 mL of freshly distilled MTBE or Et_2O and cooled to –25 °C. Some crystallization occurs. To this was added dropwise 35 mL of 1.4 M *s*-BuLi in cyclohexane (49.0 mmol). After 2 h, (–)-Sparteine (50.0 mmol) was added, stirred 45 min, then rapidly cooled to –78 °C. After 30 m, the electrophile (TMSCl or MeI, 29.5 mmol) was added and stirred 16 h. The reaction was quenched with 15 mL of MeOH followed by 15 mL of water and warmed to room temperature. The contents were transferred to a separatory funnel, diluted with 50 mL of water, and washed 3 × 25 mL of EtOAc. The combined organic layers were washed with 3 ×

20 mL of 5% H_3PO_4, 3 × 20 mL of brine, dried over $MgSO_4$, filtered and concentrated in vacuo to give a pale tan oil which was used without further purification for subsequent reactions (89-99%yield). An analytical sample was prepared by radial chromatography on silica, eluting with 95% hexanes/4.5% EtOAc/0.5% NH_4OH followed by recrystallization via slow evaporation of hexanes. Procedure revised from the published protocol.[18]

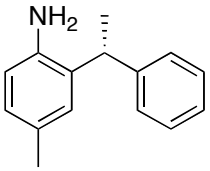


***N*-(2-ethyl-6-(1-((*R*)-trimethylsilyl)ethyl)phenyl)pivalamide 17:** DTR carried out in freshly distilled MTBE. ^{1}H NMR ($CDCl_3$): -0.0 (9H,s), 1.2 (3H, t, J=7.5), 1.3 (3H, d, J=7.5), 1.4 (9H, s), 2.3 (1H, q, J=7.5), 2.5 (2H, q, J=7.5), 6.7 (1H, bs), 7.0 (2H, m), 7.2 (1H, t, J=7.6). ^{13}C NMR ($CDCl_3$): -2.8 (CH_3), 14.7 (CH_3), 15.7 (CH_3), 23.6 (CH), 25.5 (CH_2), 28.0 (CH_3), 39.4 (C), 124.9 (2-CH), 127.7 (CH), 131.9 (C), 141.5 (C), 144.0 (C), 176.6 (C). MS (CI/MH+): 306. Anal calcd for $C_{18}H_{31}NOSi$: C, 70.76; H, 10.23. Found: C, 70.62; H, 10.26. SFC er: 60:40



***N*-(4-methyl-2-((*R*)-1-phenylethyl)phenyl)pivalamide – 31**: DTR carried out in freshly distilled MTBE. ^{1}H NMR ($CDCl_3$): ^{1}H NMR ($CDCl_3$): 1.3 (9H, s), 1.7 (3H, d, J=7.2), 2.4 (3H, s), 4.1 (1H, q, J=7.2), 6.3 (1H, dd, J=1.5, 7.5), 6.6-6.7 (2H, m), 7.1 (1H, m), 7.2-7.3 (4H, m). ^{13}CNMR ($CDCl_3$): 22.0 (CH_3), 24.6 (CH_3), 40.4 (CH), 116.4 (CH), 118.9 (CH), 126.6 (CH), 127.4 (CH), 127.6 (CH), 128.9 (C), 129.9 (C), 144.5 (C), 145.8 (C). MS (CI/MH+): 296. Anal calcd for $C_{20}H_{25}NO$: C, 81.31; H, 8.53. SFC er: 97:3

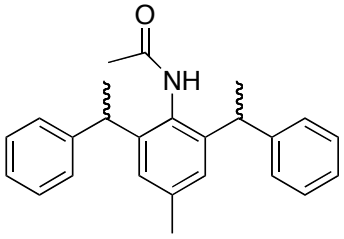
General Procedure for Pivanilide Hydrolysis: To a 100mL round bottom flask equipped with a stir bar was added the pivanilide (2.88 mmol), absolute ethanol (30 mL) and concentrated hydrochloric acid (30 mL). The reaction solution was fitted with a condenser and refluxed at 100 °C for 2 d after which time the reflux condenser was replaced with a distillation short path and the reaction volume was reduced to approximately 5mL. The crude reaction solution was then cooled to room temperature, diluted with diethyl ether and neutralized with potassium hydroxide. The organic layer was extracted thrice with diethyl ether (10 mL) and washed with distilled water before drying over $MgSO_4$. The reaction solution was filtered and concentrated in vacuo to give the corresponding anilide.



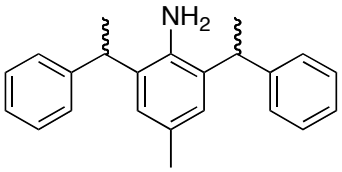
4-methyl-2-((*R*)-1-phenylethyl)benzenamine– **32**: ^{1}H NMR ($CDCl_3$): ^{1}H NMR ($CDCl_3$): 1.7 (3H, d, J=7.2), 2.4 (3H, s), 3.5 (2H, s), 4.1 (1H, q, J=7.2), 6.3 (1H, dd, J=1.5, 7.5), 6.6-6.7 (2H, m), 7.1 (1H, m), 7.2-7.3 (4H, m). ^{13}CNMR ($CDCl_3$): 22.0 (CH_3), 24.6 (CH_3), 40.4 (CH), 116.4 (CH), 118.9 (CH), 126.6 (CH), 127.4 (CH), 127.6 (CH), 128.9 (C), 129.9 (C), 144.5 (C), 145.8 (C). MS (CI/MH+): 212. SFC er: 97:3.[19]

General Procedure for Asymmetric Hydrogenation: The cyclooctadiene rhodium chloride dimer (56.6 μmol) and chiral diphosphine (56.6 μmol), or the $[(N,P)*Ir(COD)]^+[BAr_F]^-$ catalyst, were dissolved in anhydrous EtOH under inert atmosphere and stirred for 15 m. To the resultant bright orange slurry was added the substrate (**33** or **34**, 0.283 mmol**)** and reaction vessel was thrice purged with hydrogen before being pressured to 100 psi. The reaction

solution was heated to 100 °C in a Parr shaker for 1-2 d before filtering through a plug of silica. The reaction solutions were analyzed by GCMS and chiral stationary phase SFC.

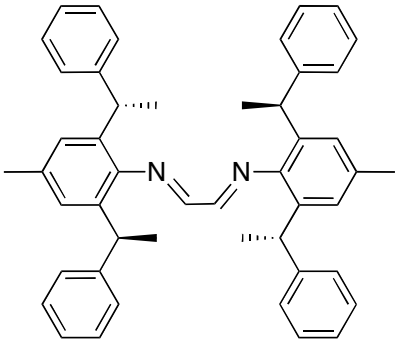


***N*-(4-methyl-2,6-bis(1-phenylethyl)phenyl)acetamide – 35**: ^{1}HNMR ($CDCl_3$): 1.7 (6H, d, J=6.5), 2.0 (3H, s), 2.3 (3H, s), 3.7 (2H, q, J=6.5), 6.8 (1H, s), 6.85 (2H, s), 7.25 (10H, m). ^{13}CNMR ($CDCl_3$): 21.8, 23.8, 24.1, 41.8, 126.7, 126.9, 128.6, 128.9, 129.0, 139.0, 139.4, 145.8, 170.9. This mixture of stereoisomeric pivanilides was not further characterized.

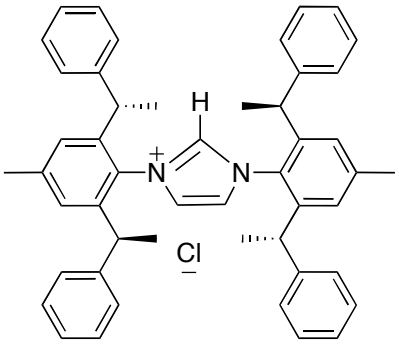


4-methyl-2,6-bis(1-phenylethyl)benzenamine (mixture of stereoisomers)-21: A 25 mL round bottom flask equipped with a stir bar was charged with toluidine (10.0 mmol), KSF montmorillonite (1.0 g), and phenyl acetylene (40.0 mmol). The round bottom was fitted with a reflux condenser and the heterogeneous slurry was refluxed with vigorous stirring at 140 °C for 8 h. The reaction vessel was allowed to cool to room temperature before dilution with ethyl acetate and filtration. The solvent was removed from the mother liquor under reduced pressure and the resultant red oil was purified via column chromatography with 50:50 dichloromethane and hexanes. The product (4-methyl-2,6-bis(1-phenylvinyl)benzenamine) was obtained as an off-white solid in 88% yield. ^{1}H NMR ($CDCl_3$): 2.2 (3H, s), 3.3 (2H, s), 5.3 and 5.7 (4H, dd), 6.9 (2H, s), 7.1-7.4 (10H, m). ^{13}C NMR ($CDCl_3$): 20.5, 116.2, 126.5, 127.8, 128.3, 128.7, 131.0, 139.3, 139.9, 147.5.[24] A Parr shaker was charged with 4-methyl-2,6-bis(1-phenylvinyl)benzenamine (8.8mmol), 10w/w% Pd/C (0.88mmol), and absolute ethanol

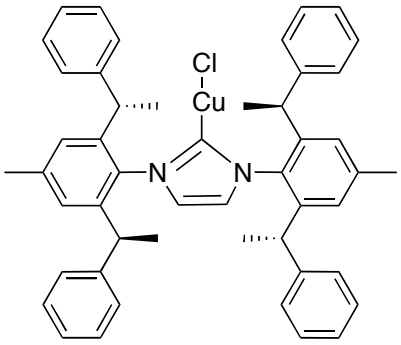
(25 mL). The shaker was thrice purged with hydrogen before it was pressurized to 90 psi and shaken overnight. The black hetergeneous solution was filtered and the solvent removed from the mother liquor under reduced pressure to give compound **21** in nearly quantitative yield (99%) with a diastereomer ratio of 60:20:20. Spectra were in agreement with previously published data.[19] Separated on a Chiral Technologies Chiralcel OJ-H, 20x250mm. Conditions: 40% (MeOH+0.2%DEA)/CO_2, 50ml/min, 140bar outlet, 220nm, feed concentration=100mg/ml in 1:1 MeOH/CH_2Cl_2, injection volume=1mL by stacked preparative processing (30 injections in total). Conditions as above; injection interval=5.5min.



N,N'-Bis-[4-methyl-2,6-bis((*S,S)*-1-phenylethyl)phenyl]-ethane-1,2-diylidenediimine-38: To a 25 mL round bottom flask was added chiral or meso aniline **21** (5.80 mmol) in 3 mL EtOH. To this was added 40% glyoxal (2.9 mmol) and one drop of formic acid. The reaction mixture was sonicated overnight at room temperature. The contents were then filtered to give a bright yellow solid. The mother liquor was concentrated and recrystallized from ethanol. These combined batches yielded the product diimine **38** quantitatively (2.88 mmol) as a single diastereomer. ^{1}HNMR ($CDCl_3$): 1.6 (12H, d, J=6.3), 2.3 (6H, s), 4.0 (4H, q, J=6.5), 7.0 (s, 4H), 7.2 (m, 20H), 7.4 (s, 2H). ^{13}CNMR ($CDCl_3$): 21.4, 22.1, 39.1, 125.9, 126.2, 127.8, 128.6, 134.5, 146.6, 164.0. $[\alpha]_D$ = 66.3, (c = 1.76, dichloromethane). ESI-FTMS Calc. $[M+H]^+$ $C_{48}H_{49}N_2$= 653.38957. Found $[M+H]^+$=653.38923.



1,3-Bis-[2,6-(*S*,*S*)-(1-phenyl-ethyl)-phenyl]-1*H*-imidazolium chloride-39: The following procedure is a revision of the protocol published by Markó et al.[30] A solution of zinc (II) chloride and paraformaldehyde in concentrated hydrochloric acid was prepared ($ZnCl_2$:p-formaldehyde:HCl=1:1:2, ~4.2M in paraformaldehyde). A test tube with a screw cap was charged with the diimine (**38**, 0.31 mmol) in freshly distilled THF (8 mL) under inert atmosphere and was treated with the acid solution (0.372 mmol paraformaldehyde, 1.2 equiv). The reaction solution was then heated to 70 °C in the sealed tube for 1h before cooling to room temperature and removal of the solvent in vacuo. The resultant residue was then dissolved in dichloromethane (2 mL) and washed with water (3x1 mL) and saturated $NaHCO_3$ (1x1 mL) before drying over $MgSO_4$, filtration and removal of the solvent in vacuo. The off white solid was then recrystallized from diethyl ether and dichloromethane. ^{1}HNMR ($CDCl_3$): 1.4 (6H, d, J=6.7), 1.6 (6H, d, J=6.7), 2.3 (6H, s), 3.75 (2H, q, J=6.6), 3.85 (2H, q, J=6.6), 6.5 (2H, s), 6.7 (4H, d, J=7.5), 6.9 (2H, s), 7.0-7.5 (18H, m), 11.6 (1H, s). ^{13}CNMR ($CDCl_3$): 21.8, 21.85, 22.7, 38.5, 40.0, 124.3, 126.5, 126.8, 127.1, 127.6, 127.8, 128.3, 128.5, 129.1, 141.3, 141.9, 142.8, 143.5, 145.6. ESI-FTMS Calc. [M^+] $C_{49}H_{49}N_2$=665.38957. Found [M^+]=665.38957. Single Diastereomer.



Copper carbenoid (*S,S,S,S*)-CuPhEt **40**: A 25mL round bottom flask equipped with a stir bar was charged with Cu(I)Cl (0.25 mmol) and sodium tert-butoxide (0.25 mmol). The reaction vessel was sealed under inert atmosphere and a

solution of (*S,S,S,S*)-**39** (0.25 mmol, 175.1 mg) in freshly distilled THF (3 mL) was added. The reaction was stirred overnight at room temperature before being filtered through a plug of celite. The celite was rinsed with dichloromethane and the combined organic layers were concentrated en vacuo. The resulting beige solid was recrystallized from dichlormethane and hexanes to give CuPhEt as a white solid (0.19 mmol, 143.1 mg, 75%). ^{1}HNMR ($CDCl_3$): 1.25 (6H, d, J=8.0), 1.4 (6H, d, J=8.0), 2.15 (6H, s); 3.65 (m, overlapping quartets, J=5.3); 6.3 (2H, s), 6.6-7.3 (m, 24H). ^{13}CNMR ($CDCl_3$): 21.7, 21.9, 22.7, 38.0, 39.6, 123.0, 126.0, 126.5, 127.0, 127.5, 128.0, 129.1, 133.2, 140.5, 142.3, 144.0, 144.3, 145.9, 181.2. ESI-FTMS Calc $[M^+]$ $C_{49}H_{48}CuN_2$=727.31135 Found $[M^+]$=727.31176. XRD analysis of CuPhEt resulted in refinement of the Flack Parameter to a value of zero, providing confirmation of the absolute configuration as (*S,S,S,S*).

Chapter II: Application to Enantioselective Hydrosilylation

Introduction

Our decision to pursue asymmetric hydrosilylation was guided by the high industrial and academic utility of this transformation. Although asymmetric hydrogenation has been employed in the reduction of numerous functionalities with excellent chemo- and enantioselectivity, notably with the advent of BINAP-based catalytic systems developed by Noyori et al,[38] high yield and selectivity in asymmetric hydrogenation often require a high degree of catalyst-substrate specificity and large catalyst libraries are frequently required for optimization.[38] The asymmetric hydrosilylation of prochiral ketones yielding enriched silylethers or alcohols is an attractive alternative to asymmetric hydrogenation, employing affordable and easy-to-handle silane reagents rather than expensive precious metal catalysts, and occurring under very mild conditions.[39]

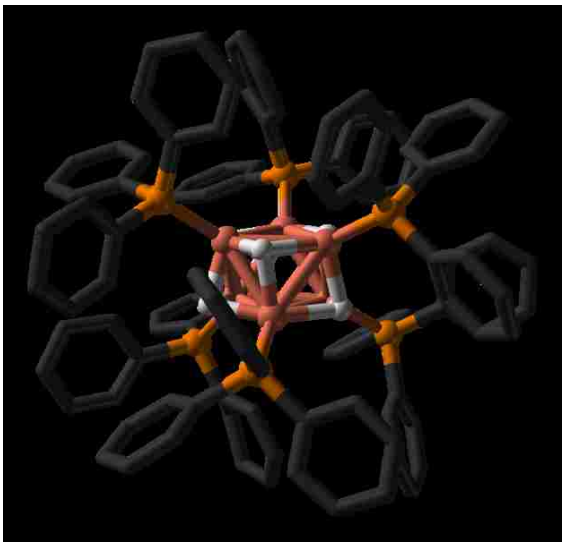
The first catalytic ketone hydrosilylation was affected with tris (triphenylphosphine) rhodium chloride (Wilkinson's Catalyst) in 1972; this transformation has since become an important route to access the silyl ether and alcohol functionalities. Over the same period of time, silanes have emerged as an important class of protecting group for alcohols, fortuitously making the products of ketone hydrosilylation - before hydrolysis - useful in their own right. Furthermore, hydrosilylation generally occurs under mild reaction conditions, which avoid over-reduction of the substrate, and utilizes affordable and easy-to-handle reagents.[40]

Historically, most hydrosilylation catalysts have been developed as complexes of group 9 metals like rhodium and iridium, but recent advances have shown group 11 metals to be attractive alternatives.[41] In particular, stabilized copper hydride species are powerful reducing

agents for numerous reductive transformations, among them hydrosilylation of ketones.[42] The first copper(I)-catalyzed reduction of acetophenone was achieved with diphenyl silane nearly twenty-five years ago,[43] although it was not known at the time that Cu-H is the likely active catalyst for the transformation.

Despite the fact that they were first reported in 1844, copper hydrides were widely considered to be of little use as reagents in organic reactions until the early 2000s.[44] Stryker et al was the first to demonstrate the utility of these species with the application of thermally stable, hexameric $[(PPh_3)CuH]_6$ in the highly regioselective conjugate reduction of α,β-unsaturated ketones and aldehydes.[45] Notably, Stryker's reagent was first synthesized and characterized by Osborn et al in 1971.[46] The crystal structure is depicted below in Figure 2.1.

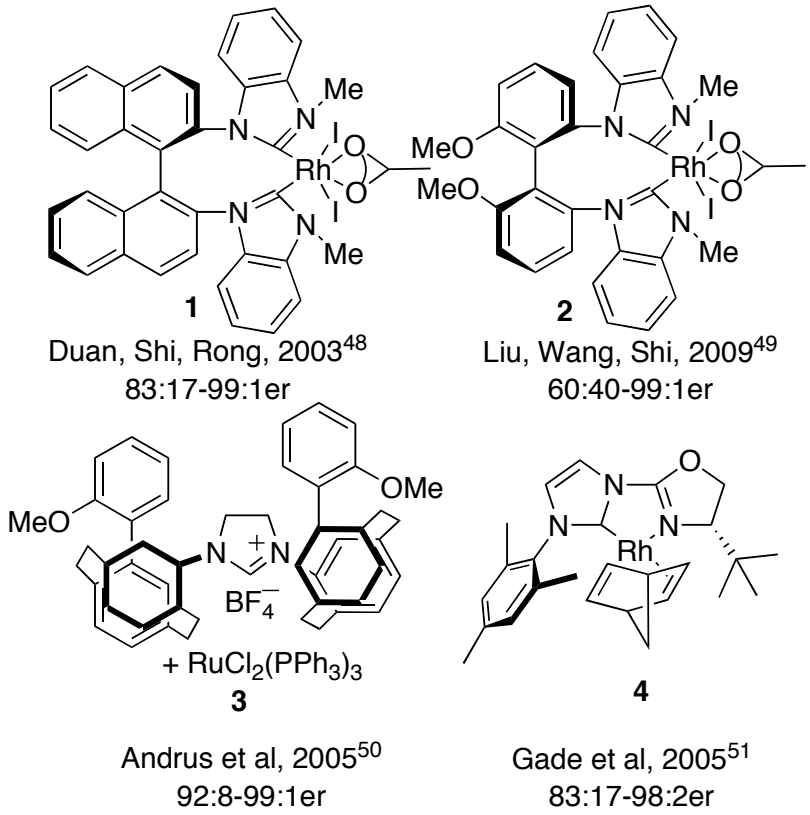
Figure 2.1: XRD structure of Stryker's Reagent / Osborn Complex / $[(PPh_3)CuH]_6$ [46]



Tertiary phosphines have been widely employed as ligands in hydrosilylation catalysts, particularly chiral ones, owing to their highly tunable steric and electronic properties.

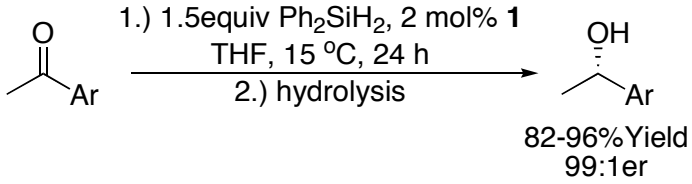
Comparable in their attributes but much less extensively employed are *N*-heterocyclic carbene ligands.[47] To date, only a handful of chiral NHC catalysts have been employed in the enantioselective hydrosilylation of prochiral ketones; key examples are depicted in Figure 2.2.

Figure 2.2: Selected chiral NHC hydrosilylation catalysts



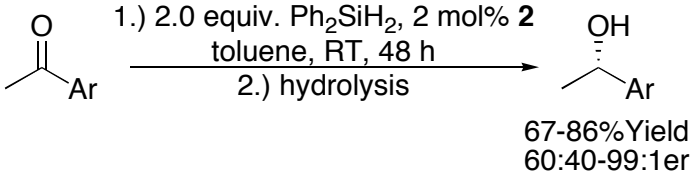
Rhodium carbenoid **1** is derived from 1,1'-binaphthalenyl-2,2'-diamine (BINAM) and possesses axial chirality. It was applied in the hydrosilylation of methyl aryl ketones and achieved excellent yield and enantioselectivity with this class of substrates (Scheme 2.1). Dialkyl ketone 2-nonanone was reduced in 86% yield in 83:17er.[48]

Scheme 2.1: Hydrosilylation of methyl aryl ketones with **1**



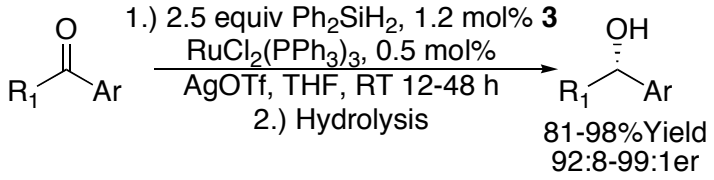
Rhodium carbenoid **2** is closely related to **1**, derived from (*R*)-6,6′-dimethoxybiphenyl-2,2′-diamine rather than BINAM. The selectivity of hydrosilylation catalyzed by carbenoid **2** was found to be highly dependent on solvent choice, with toluene giving the best results (Scheme 2.2). Acetophenone was reduced in just 77:23 er under optimized conditions, while electron deficient aryl methyl ketones were reduced with much better selectivity (up to 99:1er). Dialkyl ketones were not included in the substrate scope. Notably, the activity of the palladium bound variants of **1** and **2** include the oxidative kinetic resolution of alcohols, the conjugate addition of arylboronic acids to cyclic enones and the arylation of *N*-tosylamines with arylboronic acids.[49]

Scheme 2.2: Hydrosilylation of methyl aryl ketones with **2**



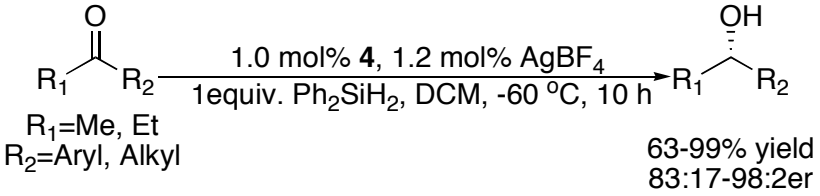
When paracyclophane imidazolium **3** was applied to asymmetric hydrosilylation it was found to give diphenyl silyl ethers in consistently excellent yield and selectivity (Scheme 2.3). Lower enantiomer ratios were obtained with substrates bearing an electron deficient aryl group or an alkyl substituent bulkier than methyl (R_1=Et, iPr, sBu, Cy).[50] The addition of catalytic tris(triphenylphosphine)ruthenium chloride and stoichiometric silver triflate was required for optimal yield and selectivity, so the active catalytic species in this transformation is not obvious.

Scheme 2.3: Hydrosilylation of alkyl aryl ketones with **3**



While many aryl alkyl ketones can be reduced with excellent enantioselectivity using NHC hydrosilylation catalysts **1**, **2** and **3**, the rhodium complex **4** developed by Gade is notable in that it can achieve moderate enantioenrichment in the hydrosilylation of dialkyl ketones as well. For all of the great many compounds developed as catalysts in this field, the enantioselective reduction of linear ketones remains an elusive goal: The best selectivity with which the silylether of 2-butanone can be obtained was achieved with **4** at just 83:17 er.[51] Before the publication of this work, a TADDOL based catalyst developed by Seebach et al held the record for the most selective hydrosilylaltion of 2-butanone, achieving 78:22 er.[52]

Scheme 2.4: Hydrosilylation of alkyl aryl and dialkyl ketones with **4**



The CuIPr NHC (Figure 1.3) has shown promise in the hydrosilylation of a wide variety of ketones; furthermore, the catalytic cycle has been studied in detail.[53-55] Since the γ* metal bound NHCs and NHC precursors can be considered chiral analogs of the CuIPr, with stereocenters incorporated at the location of the isopropyl methine, we have assessed the potential of our catalysts in asymmetric hydrosilylation by analogy. The generally accepted catalytic cycle (Scheme 2.5) proceeds via the formation of a copper hydride followed by coordination of the ketone and sigma bond metathesis.[54] Remarkably, formation of the copper hydride as the active catalytic species, marked by color change of the reaction solution from colorless to bright yellow, is supported by XRD characterization (Figure 2.3). The crystal structure depicts the copper hydride as a dimer.[55]

Scheme 2.5: Proposed catalytic cycle of NHC-catalyzed hydrosilylation of ketones.

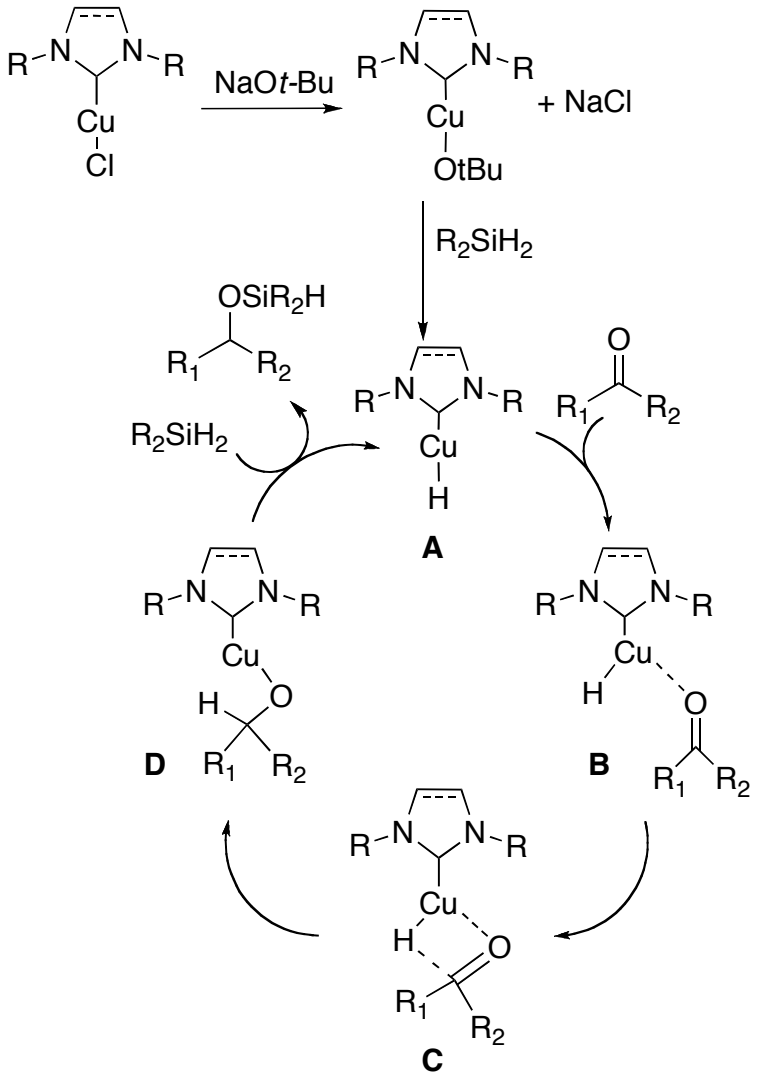
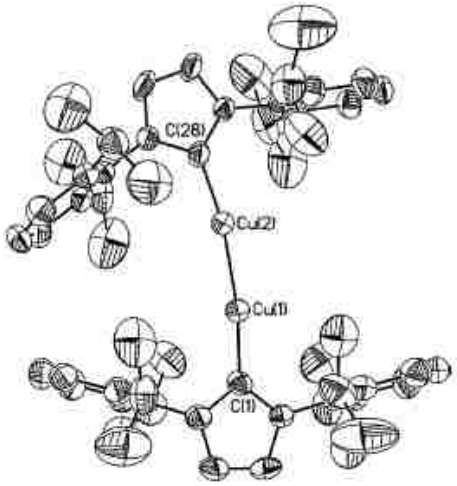


Figure 2.3: Crystal structure of a dimeric (carbene) copper (I) hydride



A

The stereo determining step of the catalytic cycle depicted in Scheme 2.5 is hydride delivery to the carbonyl, occuring from intermediate C to intermediate D. If the γ* NHCs follow a similar mode of reactivity, the chirality of the silyl ether will be determined within a chiral pocket. The existing experimental evidence supporting the mechanism of NHC-copper hydride catalyzed hydrosilylation led us to speculate that this transformation provides the best opportunity for showcasing the potential selectivity of our newly developed class of NHC ligands.

In summary, the CuIPr is an effective hydrosilylation catalyst, via in situ formation of the corresponding copper hydride as the active catalytic species. Copper hydrides are known to be powerful reducing agents. The generation of a copper hydride bound to a chiral NHC has the potential to be a versatile and effective catalyst for reductive asymmetric transformations. The potential substrate scope of a reagent of this kind is vast, including the possibility of not just the hydrosilylation of prochiral ketones, but also imines, α,β-unsaturated carbonyl compounds, and alkynes.

Results and Discussion

Our investigation into the design and synthesis of novel C_2-symmetric NHC ligands led to the disclosure of four new NHC precursors and metal carbenoids, which are depicted in Figure 1.11 (p37). Of these, three served to confirm the feasibility of the design motif, as judged by the observation of a well-formed chiral pocket in the crystal structure. With these compounds in hand, we set out to test this new class of NHCs in an enantioselective hydrosilylation (Scheme 6). There is precedent for the in-situ formation of the copper carbenoid,[53] so imidazolinium **43** and imidazolium **42** – for which we lack efficient metallation procedures – were investigated in this manner.

Scheme 2.6. Hydrosilylation of acetophenone

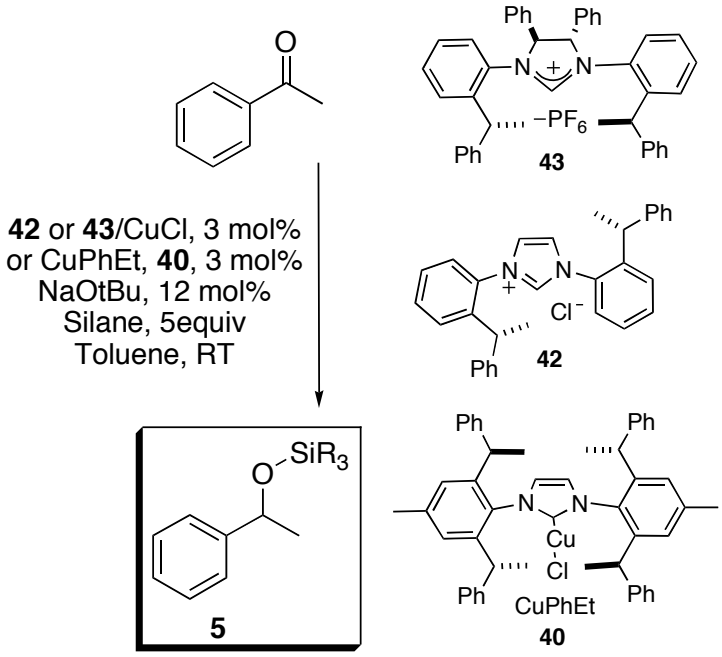
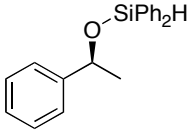
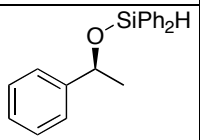
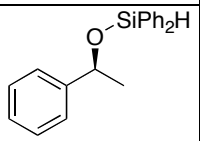


Table 2.1. Hydrosilylation of acetophenone

Catalyst	Time (h)	Silane	Product	%conversion*	er (*S*:*R*)
43	24	Ph_2SiH_2		29	60:40
42	4	Ph_2SiH_2		95	73:27
CuPhEt **40**	0.75	Ph_2SiH_2		100	98:2

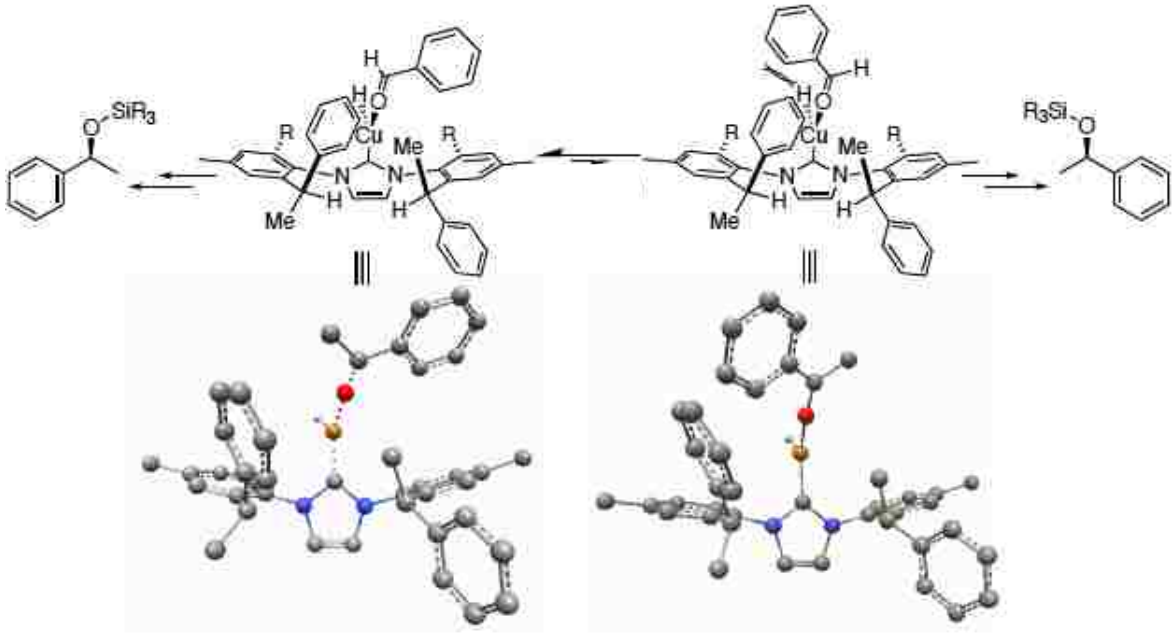
*Determined by GC

Imidazolinium **43** was found to be the least effective in the hydrosilylation of acetophenone, achieving only minimal conversion to the silylether after 24h. The enantioselectvity of the transformation was very poor. Unsaturated imidazoliums **42** and CuPhEt were found to give nearly quantitative conversion to the silylether at room temperature in 4 and <1h, respectively. And while **42** yields the product with only very moderate enantioenrichment, CuPhEt provides for isolation of nearly enantiopure silylether. The absolute configuration of the silylether was determined by coinjection of an enantiopure authentic sample and found to be *S* when using the *R*,*R*,*R*,*R* stereoisomer of CuPhEt.

In order to obtain better insight into the steric course for the hydrosilylation of acetophenone catalyzed by *R*,*R*,*R*,*R*-CuPhEt, a DFT minimization (B3LYP 3-21g-d) was carried out on intermediate **B** of the catalytic cycle (Scheme 2.5) using the PQS ab-initio molecular modeling software.[56] The minimized structure is detailed in Figure 2.4, with two of the *ortho* N-aryl substituents drawn as R groups for clarity. In the lowest energy conformation, the copper, the hydride, and the carbonyl of acetophenone lie in a common plane, and more critically, this

plane is roughly orthogonal to the plane of the heterocycle. Recalling that CuPhEt has C_2-symmetry, examination of the minimized structures reveals that the phenyl group of acetophenone preferentially resides in the less crowded upper right quadrant and thereby exposes the *Re* face of the carbonyl to the hydride. Delivery of the hydride in this manner would lead to formation of the *S*-enantiomer of the silyl ether, as is observed experimentally. The relative energy between these two intermediates was found to be a 3.6 kcal/mol.

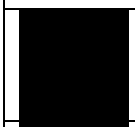
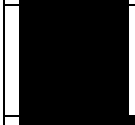
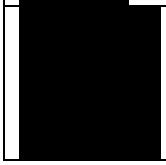
Figure 2.4. DFT Minimization of Intermediate **B**



Encouraged by the high degree of stereoinduction observed in the CuPhEt catalyzed hydrosilylation of acetophenone, we decided to investigate this transformation in more detail. We first investigated the variation of the silane reagent. Results are summarized in Table 2.2. We discovered that dihydrosilanes are more reactive than triethylsilane, as indicated by more rapid consumption of the ketone, and serve to significantly increase the selectivity of the

transformation. Similar results have been observed with chiral BINAP-copper (I) catalysts used for hydrosilylation.[57] Incredibly, the use of either diphenyl- or diethyl silane, rather than triethyl silane, provided for an increase in the enantiomer ratio of the silyl ether of 2-butanone to 98:2er! Also notable is the chemoselectivity of the CuPhEt catalyst. The use of a dihydrosilane reagent could feasibly lead to formation of the dialkoxy silane products, but di-*sec*-butoxysilanes were not detected.

Table 2.2: Investigating the role of the silane reagent on yield and selectivity.

Product	Reaction Time (h)	%Conversion*	er (S:R)
	1.5	100	85:15
	0.5	100	98:2
	0.5	100	98:2

*GC conversions

These results reveal that the minimizations depicted in Figure 2.4 represent little more than a useful predictive model for the observed selectivity of CuPhEt-catalyzed hydrosilylation. This model is fundamentally flawed for lack of inclusion of the silane. The effect this reagent has on the rate and selectivity of the transformation indicate that it is intimately involved in the transition state.

The reaction conditions were optimized, along with a procedure for recovery of CuPhEt (of which we have a very limited supply, due to necessity of a preparative chiral separation in its synthesis). The optimized reaction conditions are detailed below in Scheme 2.7. Less volatile ketone substrates (Entries 1-6, Table 2.3) were hydrosilylated with diethylsilane, providing for

easy removal of excess silane during work up and eliminating the need for purification of the product. To prevent loss of product by evaporation, the more volatile dialkyl ketones (Entries 7-11, Table 2.3) were converted to diphenylsilyl ethers instead.

Scheme 2.7: CuPhEt catalyzed hydrosilylation of prochiral ketones.

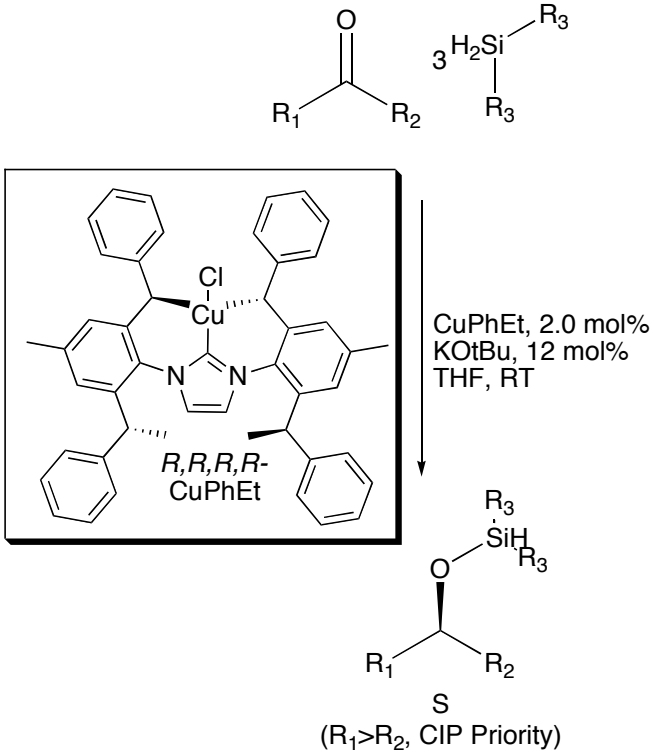
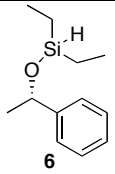
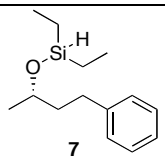
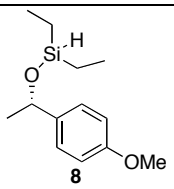
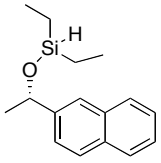
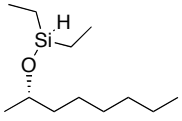
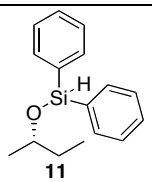
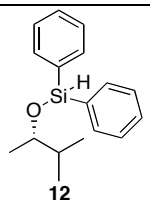
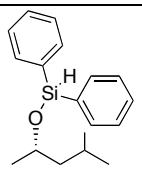
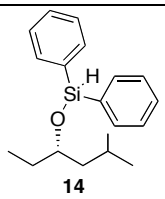
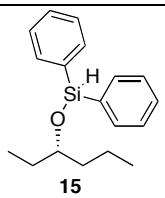


Table 2.3: Scope of (*R,R,R,R*)-CuPhEt catalyzed hydrosilylation.

Entry	Product	%conversion (Isolated Yield)	er (*S:R*)	Time (h)
1	 **6**	100 (90)	99:1	0.75
2	 **7**	100 (81)	98:2	0.75
3	 **8**	100 (85)	97:3	1
4	 **9**	100 (92)	99:1	1
5	 **10**	100 (77)	97:3	0.75
6	 **11**	100 (69)	98:2	0.5

7	 **12**	100 (88)	99:1	0.5
8	 **13**	100 (74)	96:4	0.5
9	 **14**	100 (77)	96:4	0.75
10	 **15**	100 (77)	95:5	0.75

CuPhEt shows remarkable reactivity and selectivity in the hydrosilylation of a variety of aryl alkyl ketones and, more notably, simple linear ketones. Of particular note, 2-butanone (entry 6) and 3-hexanone (entry 10) are respectively reduced in 98:2 and 95:5er! To the best of our knowledge, the selectivity we observe with this class of substrates is unprecedented, and it is achieved in less than an hour under very mild reaction conditions.

The absolute configuration of the silyl ethers derived from acetophenone, 2-butanone, methyl isopropyl ketone, and 2-octanone was assigned by CSP-GC coinjection of an authentic enantiopure silyl ether, or by hyrolysis of the silyl ether to the corresponding alcohol and comparison of optical rotation with an authentic sample. The configuration of the silylethers was in all cases found to be *S* via hydride addition to the *Re* face of the ketone using (*R,R,R,R*)-CuPhEt. For those samples for which an authentic enantiopure silane or alcohol was not available, absolute configuration was assigned by analogy. Further investigation into the mechanism of CuPhEt-catalyzed hydrosilylation, particularly the role of the silane in the transformation, is ongoing.

Conclusions

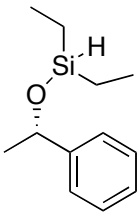
Copper carbenoid CuPhEt has been synthesized and its activity in the hydrosilylation of prochiral ketone substrates has been investigated. CuPhEt exhibits extraordinary reactivity and enantioselectivity in this transformation, most notably in the reduction of simple dialkyl ketones. To the best of our knowledge, the selectivity reported herein is unmatched by any synthetically accessible asymmetric hydrosilylation or hydrogenation catalyst reported to date.

Experimental

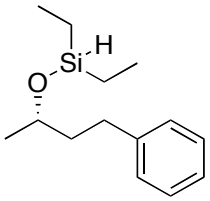
General: All reagents and solvents were used as received, unless indicated below. Tetrahydrofuran (THF) was distilled from Na/benzophenone ketyl under N_2 immediately prior to use. Toluene was dried over CaH_2 followed by distillation and storage over 3 Å molecular sieves. Diethyl silane and diphenyl silane were distilled prior to use. ^{1}H NMR spectra were collected at 300 or 400 MHz in $CDCl_3$ unless otherwise noted. Coupling constants (J), are reported in Hz. Chiral stationary phase gas chromatography (CSP-GC) was used to determine enantiomer ratios on a β-Dex column.

General Procedure for Hydrosilylation (adapted from the procedure of Nolan et al[53]): To an oven dried vial fitted with a septum screw cap and purged with argon was added copper carbenoid CuPhEt (0.020 mmol) and freshly sublimed potassium *tert*-butoxide (0.012 mmol) in freshly distilled THF (2 mL). The cloudy white reaction solution was stirred for 10 min at room temperature before addition of the silane (3.0 mmol). An immediate color change to bright yellow was observed and the reaction was stirred for an additional 20 min before addition of the ketone (1.0 mmol). Solid ketones were added as concentrated solutions in THF. The reaction progress was monitored by GC or TLC. Upon completion (or observation of the cessation of product formation) the reaction solution was treated with charcoal and filtered through a plug of celite. The celite plug was rinsed with ethyl acetate and the combined organic layers were concentrated under reduced pressure. The residue was analyzed on a β-DEXcst (14% cyanopropylphenyl/ 86% dimethyl polysiloxane) by CSP-GC. All of the diethylsilyl ethers (compounds **6**-**10**) were separated using the following temperature program: 50 °C/1 m/ 2 °C per min/150 ºC/30 m. Diphenyl silylethers (**11**-**15**) were separated isothermally at 27 °C.

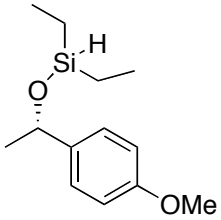
General Procedure for Catalysts Recovery: Charcoal and celite from the post-work up hydrosilylation reaction were placed in a sealed Erlenmeyer flask with DCM (5 mL). The heterogeneous solution was sonicated for 2-6 h,filtered and concentrated under reduced pressure. The resultant residues were accumulated from several reactions (3+) before recrystallization from diethyl ether. The recycled CuPhEt was obtained as a nearly 1:1 mixture of the copper carbenoid and it's corresponding imidazolium chloride salt.



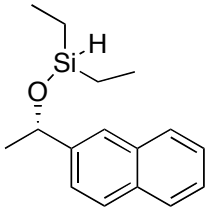
((*S*)-1-phenylethoxy)triethylsilane – 6: ^{1}HNMR: 0.65 (4H, qd, J_3=7.84, J_1=2.35), 0.95 (3H, t, J=7.87), 1.03 (3H, t, J=7.87), 1.51 (3H, d, J=6.41), 4.47 (1H, q, J=2.44), 4.92 (1H, q, J=6.44), 7.23-7.41 (5H, m). ^{13}CNMR: 5.46 ($2CH_2$), 6.70 ($2CH_3$), 26.43 (CH_3), 72.44 (CH), 125.37 (CH), 127.00 (2CH), 128.18 (2CH), 145.94 (C). Anal calcd for $C_{12}H_{20}SiO$: C, 69.17; H, 9.67. Found: C, 69.30; H, 9.00. er (*S*:*R*) = 99:1; RT_R=39.3, RT_S=41.9



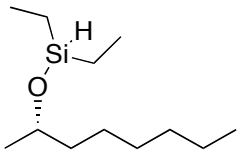
((*S*)-4-phenylbutan-2-yloxy)diethylsilane – 7: ^{1}HNMR: 0.73 (4H, m), 1.06 (6H, td, , J_3=7.81, J_1=2.78), 1.27 (3H, d, J=6.14), 1.83 (2H, m), 2.73 (2H, m), 3.91 (1H, sextet, J=6.24), 4.53 (1H, q, J=2.42), 7.19-7.38 (5H, m). ^{13}CNMR: 5.63 ($2CH_2$), 6.80 ($2CH_3$), 23.41 (CH_3), 32.17 (CH_2), 41.09 (CH_2), 69.95 (CH), 125.69 (CH), 128.36 (2CH), 142.46 (C). Anal calcd for $C_{14}H_{24}SiO$: C, 71.12; H, 10.23. er (*S*:*R*) = 98:2; RT_R=51.0, RT_S=52.1



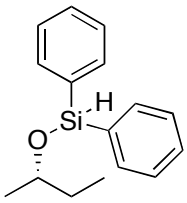
((*S*)-1-(4-methoxyphenyl)ethoxy)triethylsilane – 8: ^{1}HNMR: 0.54 (4H, qd, J_3=8.02, J_1=2.34), 0.83 (3H, t, 7.76), 0.90 (3H, t, 7.76), 1.37 (3H, d, 6.41), 3.72 (3H, s), 4.33 (1H, quintet, J=2.43), 4.75 (1H, q, J=6.46), 6.78 (2H, d, J=8.39), 7.18 (2H, d, 8.39). ^{13}CNMR: 5.45 ($2CH_2$), 6.70 ($2CH_3$), 26.33 (CH_3), 55.21 (CH_3), 72.09 (CH), 113.50 (CH), 126.60 (CH), 138.09 (C), 158.59 (C). Anal calcd for $C_{13}H_{22}SiO_2$: C, 65.50; H, 9.30. Found: C, 64.81; H, 9.28. er (*S*:*R*) = 97:3; RT_R=54.6, RT_S=55.9



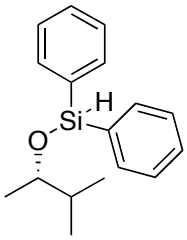
((*S*)-1-(naphthalen-3-yl)ethoxy)diethylsilane – 9: ^{1}HNMR: 0.60-0.78 (4H, qd, J_3=7.86, J_1=2.39), 0.96 (3H, t, J=8.05), 1.05 (3H, t, 8.05), 1.58 (3H, t, J=6.19), 4.50 (1H, quintet, J=2.19), 5.07 (1H, q, J=6.28), 7.43-7.56 (3H, m), 7.80-7.90 (4H, m). ^{13}CNMR: 5.48 ($2CH_2$), 6.74 ($2CH_3$), 26.38 (CH_3), 72.59 (CH), 123.69, 124.03, 125.54, 125.95, 127.66, 127.95, 132.77, 133.30, 143.39. Anal calcd for $C_{16}H_{22}SiO$: C, 74.36; H, 8.48. Found: C, 82.78; H, 7.08. er (*S*:*R*) = 99:1; RT_R=59.3, RT_S=61.4



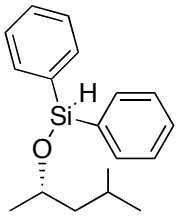
((*S*)-octan-2-yloxy)diethylsilane – 10: ^{1}HNMR: 0.67 (4H, qd, J_3=7.99, J_1=2.11), 0.90 (3H, m), 1.01 (6H, t, J=7.39), 1.18 (3H, d, J=6.59), 1.23-1.51 (10H, m), 3.80 (1H, sextet, J=5.75), 4.44 (1H, quintet, J=2.34). ^{13}CNMR: 5.58 ($2CH_2$), 6.724 ($2CH_3$), 14.09 (CH_3), 22.64 (CH_2), 23.41 (CH_3), 25.75 (CH_2), 29.32 (CH_2), 31.87 (CH_2), 39.40 (CH_2), 70.57 (CH).). Anal calcd for $C_{12}H_{29}SiO$: C, 66.59; H, 13.04. Too volatile for CA. er (*S*:*R*) = 97:3; RT_R=30.3, RT_S=32.2



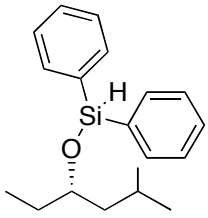
((*S*)-*sec*-butoxy)diphenylsilane – 11: ^{1}HNMR: 0.82 (3H, t, J=7.52), 1.11 (3H, d, J=6.49), 1.46 (2H, m), 3.82 (1H, sextet, J=5.92), 5.38 (1H, s), 7.25-7.37 (6H, m), 7.51-7.61 (4H, m). ^{13}CNMR: 10.11 (CH_3), 22.75 (CH_3), 32.02 (CH_2), 72.34 (CH), 127.95, 130.16, 134.68, 134.70. Anal calcd for $C_{16}H_{20}SiO$: C, 74.95; H, 7.86. Found: C, 75.01; H, 7.83. er (*S*:*R*) = 98:2; RT_R=20.7, RT_S=20.9



((*S*)-3-methylbutan-2-yloxy)diphenylsilane – 12: ^{1}HNMR: 0.99 (6H, overlapping doublets, J=6.41), 1.22 (3H, d, J=6.29), 1.80 (1H, m, J=6.85), 3.83 (1H, quintet, J=5.93), 5.54 (1H, s), 7.40-7.50 (m, 6H), 7.67-7.76 (4H, m). ^{13}CNMR: 18.11 (CH_3), 18.28 (CH_3), 19.81 (CH_3), 35.21 (CH), 75.58 (CH), 127.96, 130.17, 134.70, 134.74. Anal calcd for $C_{17}H_{22}SiO$: C, 75.50; H, 8.20. Found: C, 75.83; H, 8.48. er (*S*:*R*) = 99:1; RT_R=21.2, RT_S=21.9

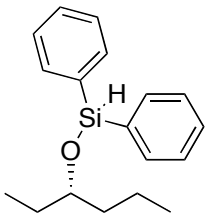


((*S*)-4-methylpentan-2-yloxy)diphenylsilane – 13: ^{1}HNMR: 0.92 (3H, d, J=6.60), 0.95 (3H, d, J=6.60), 1.29 (3H, d, 6.04), 1.32(1H, m – overlapping with previous), 1.66 (1H, m), 1.87 (1H, m, J=6.60), 4.14 (1H, sextet, J=5.60), 5.57 (1H, s), 7.40-7.60 (6H, m), 7.68-7.82 (4H, m). ^{13}CNMR: 22.28 (CH_3), 23.31 (CH_3), 23.81 (CH_3), 24.61 (CH), 48.72 (CH_2), 69.22 (CH), 128.01, 130.24, 134.74 , 134.75. Anal calcd for $C_{18}H_{24}SiO$: C, 76.00; H, 8.50. Found: C, 75.86; H, 8.34. er (*S*:*R*) = 96:4; RT_R=25.0, RT_S=27.0



((*S*)-5-methylhexan-3-yloxy)diphenylsilane – 14: ^{1}HNMR: ^{1}HNMR: 0.88 (9H, m, overlapping signals), 1.28 (1H, m), 1.58 (3H, m), 1.78 (1H, m, J=6.53), 3.86 (1H, m), 5.52 (1H, s), 7.37-7.50 (6H, m), 7.65-7.73 (4H, m). ^{13}CNMR:

9.77 (CH_3), 22.11 (CH_3), 23.42 (CH_3), 24.42 (CH), 30.15 (CH_2), 45.79 (CH_2), 74.09 (CH), 127.91, 130.15, 134.74. Anal calcd for $C_{19}H_{26}SiO$: C, 76.45; H, 8.78. Found: C, 76.24; H, 8.40. er (*S*:*R*) = 96:4; RT_R=22.1, RT_S=23.3



((*S*)-hexan-3-yloxy)diphenylsilane – 15: ^{1}HNMR: 0.91 (6H, m), 1.56 (6H, m), 3.83 (1H, quintet, J=6.02), 5.54 (1H, s), 77.40-7.50 (6H, m), 7.67-7.74 (4H, m). ^{13}CNMR: 9.91 (CH_3), 14.19 (CH_3), 18.76 (CH_2), 29.73 (CH_2), 38.70 (CH_2), 75.91 (CH), 128.11, 130.28, 134.77. Anal calcd for $C_{18}H_{24}SiO$: C, 76.00; H, 8.50. Found: C, 75.83; H, 8.48. er (*S*:*R*) = 95:5; RT_R=24.6, RT_S=25.4

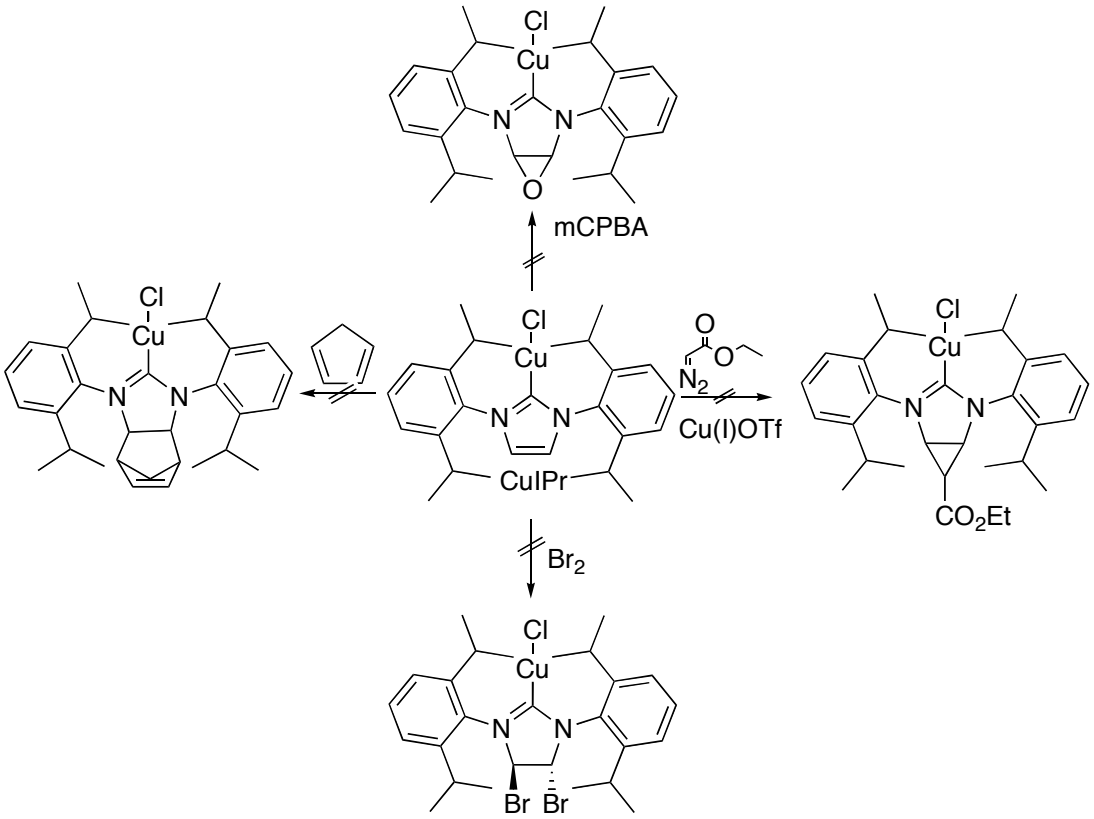
Chapter III: Miscellaneous Research

A.) *Post Synthetic Modification of CuIPr*

My research began at the Universität Regensburg with an investigation into the backbone reactivity of the CuIPr copper carbenoid (Figure 1.3). Such post-synthetic modification to an NHC has yet to be reported and is thus of interest for novelty's sake, but furthermore, it could serve as a new means of introducing stereogenic centers to the catalyst.

Bromination, epoxidation, cyclopropanation and [4+2] cycloaddition to the backbone *pi* bond of CuIPr were investigated under a variety of conditions (Scheme 3.1). Although none of these reactions proved successful, their failure served to demonstrate the highly robust nature of this compound. Under very harsh conditions, for example a high pressure reaction at 250 bar/100 ºC/ 72 h or in a microwave in THF at 150 ºC/1 h, the compound was recovered intact.

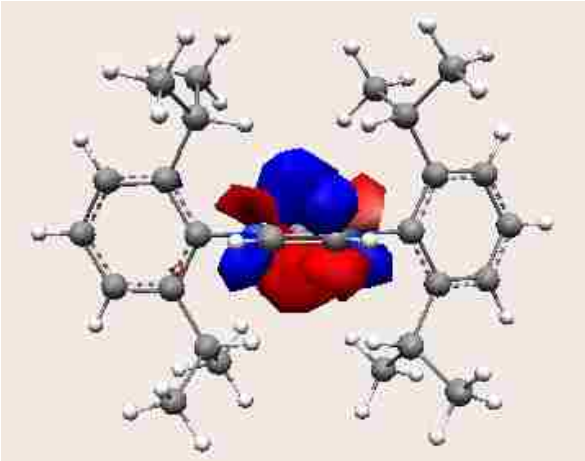
Scheme 3.1: Attempts at Post-Synthetic Modification of the CuIPr



To gain further insight into the above results, molecular modeling calculations were conducted. The initial question to be addressed was if the HOMO of compound CuIPr lies on the backbone *pi* orbital of interest. Furthermore we were curious to assess the potential reactivity at this site by comparison of the HOMO-LUMO gap of CuIPr with that of other dienophiles known to be highly reactive. Calculations were carried out on the Titan modeling program with the B3LYP DFT method and 3-21G** basis set. It was found that the HOMO of the CuIPr does in fact lie on the backbone *pi* bond and that its reactivity, as judged by the HL gap, was comparable to that of other dienophiles known to be highly reactive, namely maleic anhydride and methyl acrylate.

The HOMO orbital of CuIPr is illustrated in Figure 3.1. These results strongly suggest that it is the steric bulk of the compound which prohibits reactivity at the desired site.

Figure 3.1: HOMO and LUMO orbitals of the CuIPr

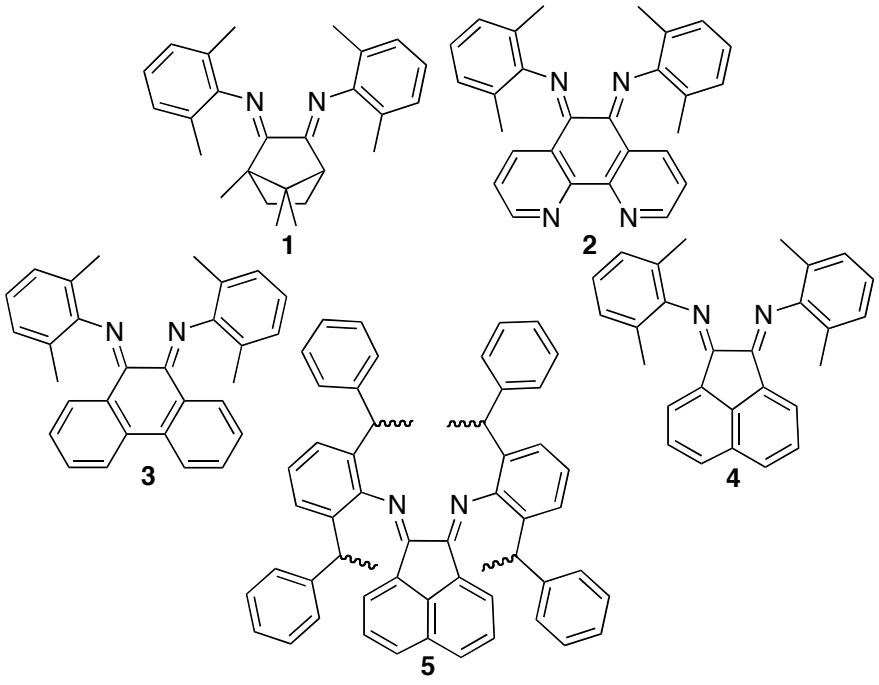


The CuIPr was shown to effectively catalyze cyclopropanation reactions while suppressing the dimerization of ethyldiazoacetate (EDA) by Fructos and Nolan.[36] My host laboratory, the Reiser group at the University of Regensburg, has reported the cyclopropanation of aromatic heterocycles such as pyrroles and furans using a copper bis(oxazoline) catalyst.[58] The reaction is widely used in the Reiser group despite the lengthy syringe pump additions required to prevent the dimerization of EDA. One final investigation into the reactivity of CuIPr entailed its use as a catalyst for the cyclopropanation of methyl furan-2-carboxylate. The decomposition of EDA was confirmed by the presence of fumarate in the reaction solution, however only the furan starting material was recovered.

B.) Investigating the Synthesis of Novel Diimines

I received a fellowship to travel to the University of Canterbury to study X-ray crystallography in the summer of 2009. My original proposal entailed the characterization of CuPhEt and the other γ* ligands by XRD, however these compounds were not yet available when my fellowship commenced. As a result I worked instead on the synthesis of novel diimines and their subsequent crystallographic characterization. This class of compounds was chosen for their novelty and for the fact that they are likely to be highly crystalline. The compounds chosen as targets are depicted in Figure 3.2.

Figure 3.2: EAPSI Target Molecules for XRD Characterization

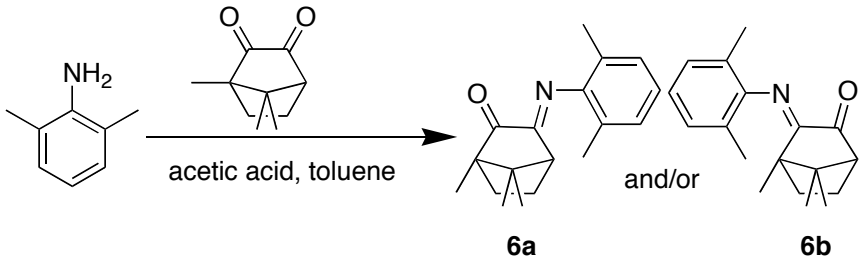


Compounds **1-5** are unique as diimines, but could also be cyclized to yield imidazolium salts or reduced and cyclized to yield imidazoliniums. The derivatization of the imidazolium or imidazolinium backbone in this manner has been little exploited in NHC chemistry and has

tremendous potential to provide a wide range of novel, structurally diverse NHC precursors. 2,6-Xylidene was chosen as the starting material for compounds **1-4** to mimick the 2,6-substitution of the *N*-aryl substituents on CuPhEt.

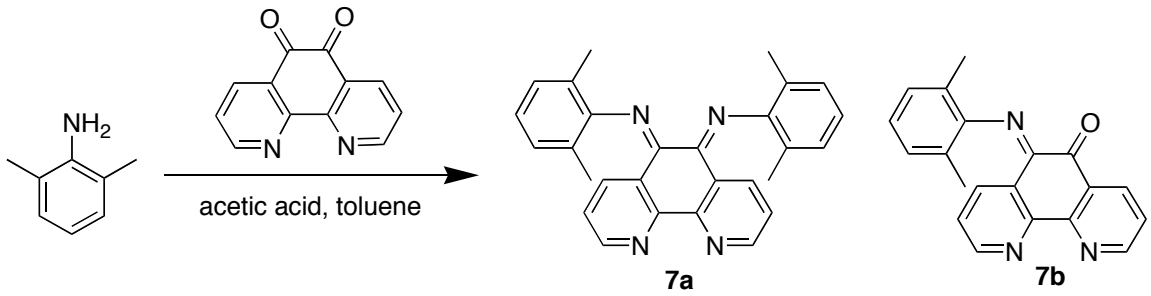
We surmised that camphor-backboned target **1** may be derived from the condensation product of 2,6-xylidene with camphor 3-quinone. The condensation was carried out in toluene and acetic acid under a variety of reaction conditions (Scheme 3.2). Even under extended reflux conditions, only one equivalent of xylidene could be forced to react. The identity of the regioisomer was not confirmed.

Scheme 3.2: Condensation with Camphor-3-Quinone



The synthesis of compound **2** was similarly envisaged from the condensation of xylidene with phenanthroline quinone, depicted below in Scheme 3. Phenanthroline quinone was prepared according to an unpublished procedure.[59] The condensation was carried out in toluene and acetic acid under a variety of conditions. The phenanthroline quinone was completely consumed in all cases and numerous products were formed. Small amounts of both the monocoupled and desired products could be identified in the mass spectrum, however the scheme was abandoned due to time constraints and the complexity of the reaction mixture.

Scheme 3.3: Condensation with phenanthroline quinone



The diimine preceding target **3** is the condensation product of xylidene with phenanthrene quinone. The desired diimine could not be generated. Despite extended purging with nitrogen, a cycloannulated product , **8b**, was obtained via an unknown oxidative process. Various reaction conditions were employed in attempts to either: A.) Force the coupling of a second equivalent of xylidene or B.) Promote a second oxidative cyclization by exposing the reaction to air. The phenanthrene quinone was completely consumed in all cases and the unidentified byproducts were removed via column chromatography. Results are summarized in Scheme 3.4 and Table 3.1. The crystal structure of **8b** is depicted below in Figure 3.3.

Scheme 3.4: Attempts at optimizing the condensation with phenanthrene quinone

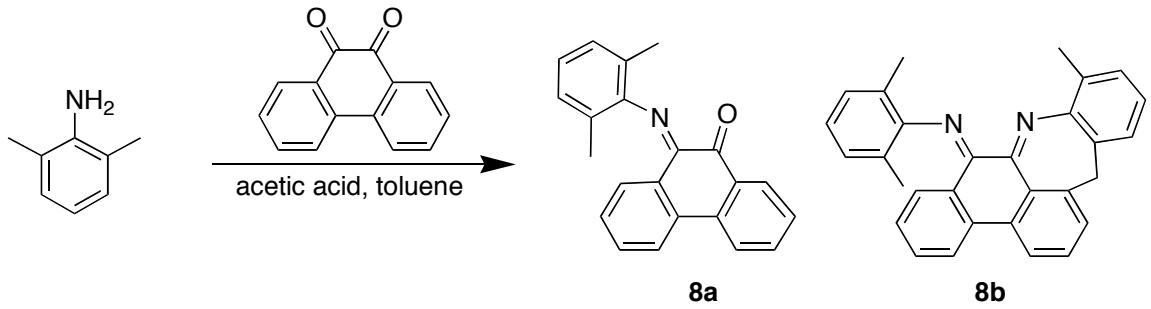
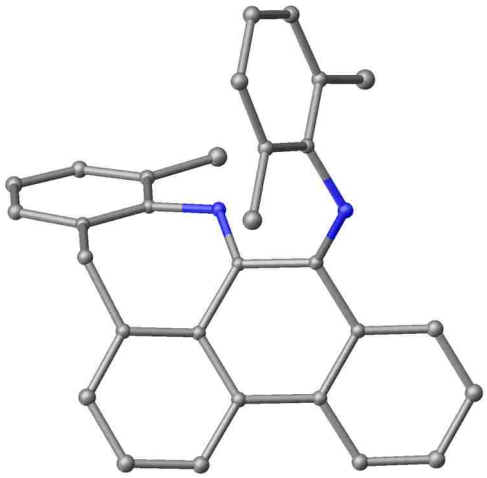


Table 3.1: Results of Scheme 3.4

Reaction Conditions	% Conversion	% **8a**	% **8b**
100 °C, 3 h, Sealed tube	100	11	not isolated
100 °C; 15 h; Sealed tube	100	10	15
140 °C, 15 h, reflux	100	7	27
140 °C, 15 h, reflux, open to air	100	not isolated	20

Figure 3.3: XRD Structure of **8b**



Condensation with acenaphthene quinone was carried out in toluene and acetic acid according to the published procedure.[60] It proceeds smoothly without need for optimization, although it was found that refluxing conditions provide for a higher yield. In addition to the use of 2,6-xylidene, the condensation of *mix*-**21** with acenaphthene quinone was also investigated; the ring-closure and metallation of this diimine would yield a particularly rigid NHC due to the effects of π-stacking. Acenaphthenquinone was completely consumed in all cases and the unidentified

byproducts were removed via column chromatography and/or recrystallization. The results are summarized in Scheme 3.5 and Table 3.2.

Scheme 3.5: Condensation with acenaphthenquinone

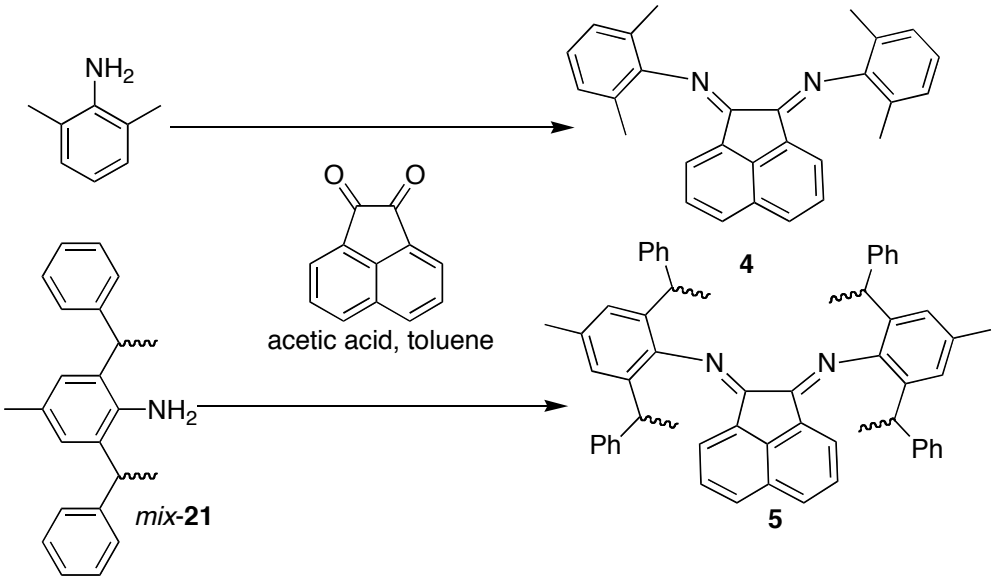


Table 3.2: Results of Scheme 5

Reaction Condition	Substrate	%Conversion	%Product
100 °C, 3 h, Sealed tube	xylidene	100	56
100 °C; 15 h; Sealed tube	xylidene	100	75
140 °C, 15 h, reflux	xylidene	100	87
100 °C, 15 h, Sealed tube	*mix*-**21**	100	35
140 °C, 15 h, reflux	*mix*-**21**	100	46

C.) Attempts at the Dynamic Thermodynamic and Catalytic Dynamic Resolution of Derivatives of 1,2,3,4-Tetrahydroisoquinoline and the Ethylene Ketal of 4-Boc-piperidone

While waiting for the return the 2,6-disubstituted aniline (Chapter 1, *mix*-**21**) sent to Merck for separation, work commenced on an alternate project investigating the scope of the catalytic dynamic resolution discovered and developed by my fellow graduate student, Timothy Beng. His work in this area has focused primarily on the resolution of Boc-piperidine. In efforts to expand the utility of this novel transformation, its application to a number of 1,2,3,4-tetrahydroisolquinoline (THIQ) derivatives, shown below in Scheme 3.6, was investigated. Because this structural motif is found in numerous alkaloids and other natural products, a protocol for the enantioselective functionalization of the benzylic position α to nitrogen is highly desirable.

Scheme 3.6: Investigating the resolution of THIQ

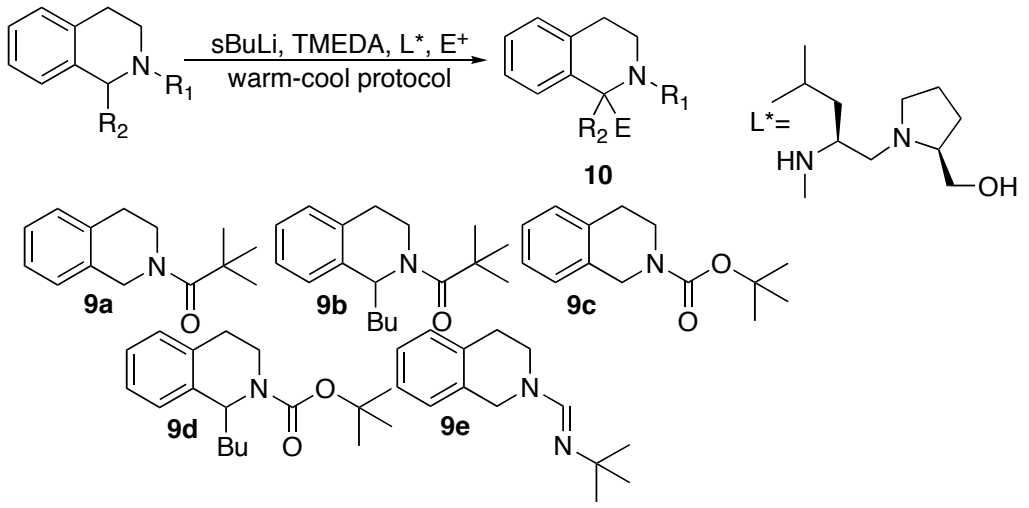


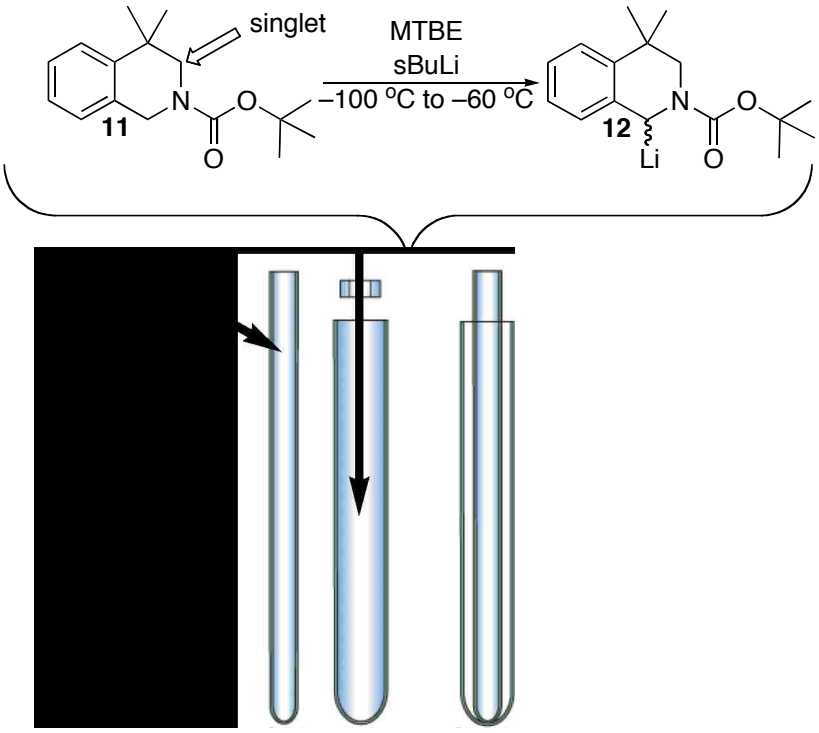
Table 3.3: Attempts at the DTR and CDR of various THIQ derivatives

Substrate	Conditions	solvent	Electrophile	er
9a	Scheme 3.6	Et_2O	PhCNO	55:45
9a	"	MTBE	PhCNO	52:48
9a	"	Et_2O	TMSCl	58:42
9a	"	MTBE	TMSCl	56:44
9a	"	Et_2O	BuBr	55:45
9a	"	MTBE	BuBr	56:44
9b	"	Et_2O	MeI	60:40
9b	"	MTBE	MeI	59:41
9c	"	Et_2O	PhCNO	58:42
9c	"	MTBE	PhCNO	53:47
9c	"	Et_2O	TMSCl	55:45
9c	"	MTBE	TMSCl	55:45
9c	"	Et_2O	BuBr	56:44
9c	"	MTBE	BuBr	57:43
9d	"	Et_2O	MeI	60:40
9d	"	MTBE	MeI	62:38
9e	*tert*-BuLi	Et_2O	TMSCl	~60:40
9e	"	MTBE	TMSCl	~60:40
9e	"	Et_2O	MeI	~60:40
9e	"	MTBE	MeI	~60:40

When substrate **9a** failed to react with substantial enantioselectivity under a number of conditions, we sought to increase the barrier to inversion by substitution of the nitrogen with a bulkier group, and to this end prepared pivanilide **9c** and formamidine **9d**. These substrates again failed to undergo efficient resolution. In a final attempt at modification of the system, the benzylic position of the Boc- and Piv-protected THIQ was alkylated with butylbromide to yield substrates **9b** and **9c**, respectively, so that deprotonation occurs at a teritiary carbon to yield a quaternary stereogenic center. Unfortunately, the system continued to exhibit very poor selectivity.

It is likely that the small enantiomeric excess observed in the products is attributable to thermodynamics, and to glean more detail on the energetics of the THIQ system, low-temperature NMR experiments were commenced. The substrate for these experiments, the 4,4-dimethyl substituted Boc-THIQ, was generously provided by collaborators in the Coldham group. By blocking the benzylic position β to nitrogen, the non-benzylic methylene may be observed as a singlet.

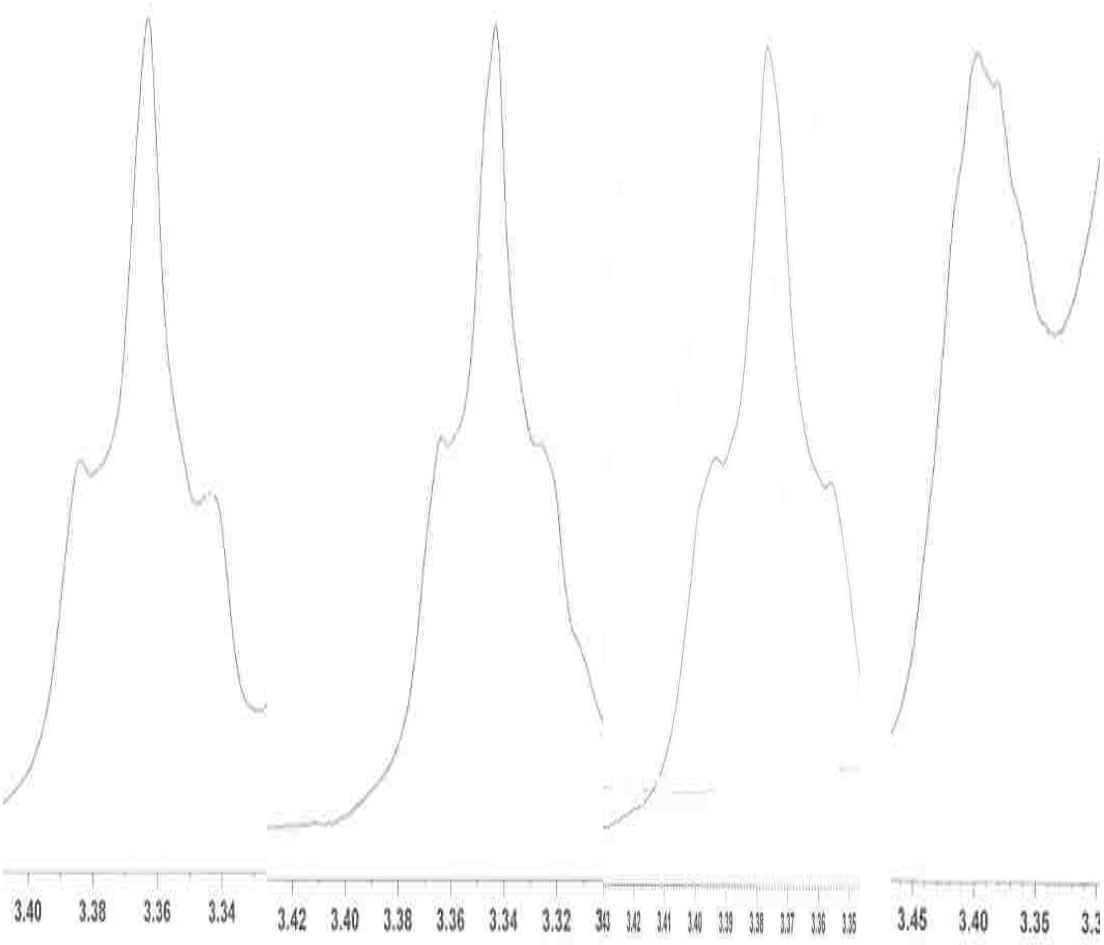
Figure 3.4: THIQ lithiation low temperature NMR experiments



Compound **11** was deprotonated with sec-BuLi in MTBE (perhaps notably in the absence of TMEDA) and the carbanion was observed in the proton NMR spectra at temperatures varying from -100 to -60°C. The spectra are shown in Figure 3.5. Even at the –100 °C, complete

resolution of the carbanion signal was not observed. While these experiments provided only preliminary data and further study of this system is warranted, the results are indicative of a very high energy barrier to inversion.

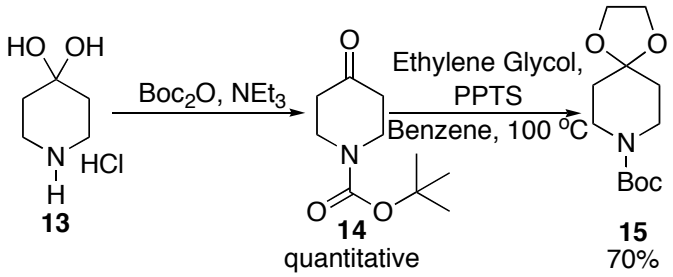
Figure 3.5: Low temperature NMR spectra



Our focus next shifted to the resolution of the ethylene ketal of 4-Boc-piperidone, **15**, which is prepared in two steps from the hydrochloride hydrate of 4-piperidone. The introduction of

functionality in the 4-position of the piperidine ring would allow for the use the CDR or DTR protocol, if successful, in the synthesis of a number of important compounds such as pipecolic acid.

Scheme 3.7: Preparation of the ethylene ketal of 4-Boc-Piperidone



The results of this investigation are briefly summarized in Scheme 3.8 and Table 3.4 below. A brief survey of these results highlights reproducibility issues; however, we were pleased to observe selectivities up to 93:7 er using a stoichiometric amount of the chiral ligand. Catalytic dynamic resolution failed; racemic product was obtained in every case.

Scheme 3.8: DTR and CDR of **15**

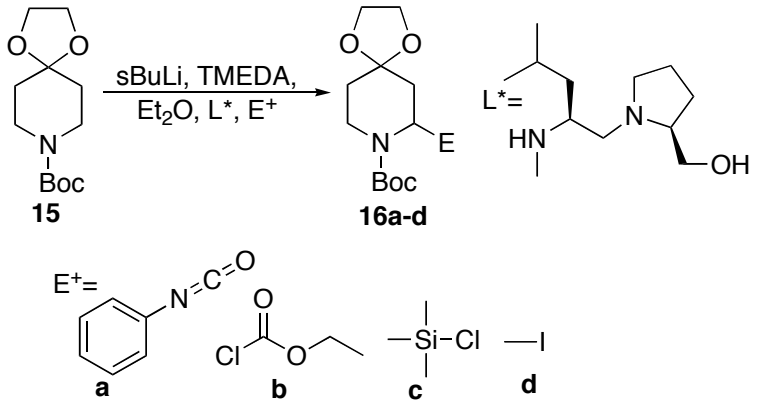
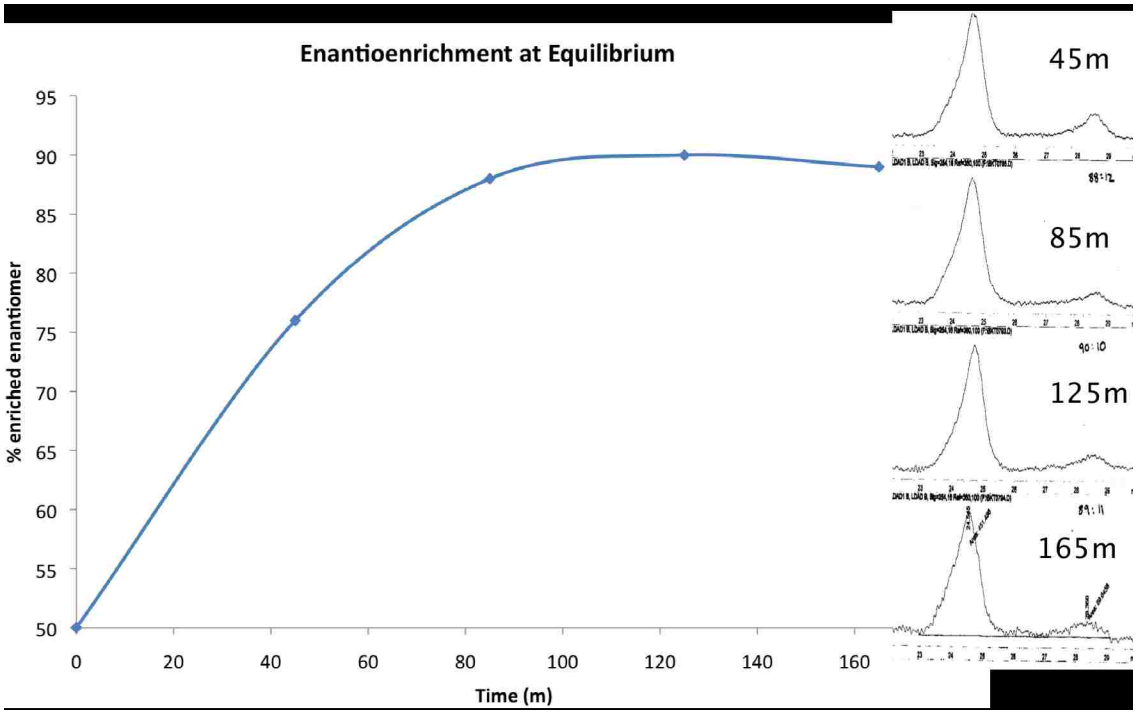


Table 3.4: Investigating the DTR and CDR of **15**

Electrophile	Equiv. L*	Equil. T (^{o}C)	% Conversion	er
a	1	-30	60	90:10
a	1	-45	69	88:12
a	1	-20	70	50:50
a	0.1	-30	75	50:50
a	0.1	-45	50	50:50
b	1	-30	87	75:25
b	1	-45	94	88:12
b	1	-20	70	93:7
b	1	-35	100	90:10
b	1	-35	88	60:40
b	0.1	-20	95	50:50
b	0.1	-30	85	50:50
b	0.1	-40	90	50:50
b	0.1	-45	100	50:50
c	1	-20	82	55:45
c	1	-20	90	55:45
c	1	-35	86	90:10
d	1	-20	77	60:40
d	1	-20	100	80:20

Preliminary kinetic studies were also carried out to probe the inconsistencies observed in the enantiomer ratio of the products obtained from DTR. The resolution with stoichiometric chiral ligand was allowed to equilibrate for 45, 85, 125, and 165 m, before addition of phenyl isocycanate and analysis of the enantioenrichment of the product obtained. Enantiomer ratios were found to level off around 90:10.

Figure 3.6: Enantioenrichment vs. time at equilibrium for ketal DTR



It is important to note that the results reported above are somewhat eclipsed by Beng's more recent results, in which enantioselectivities of up to 98:2er were observed consistently. The underlying reason of the irreproducibility observed in this investigation is not well understood. Subsequent kinetic studies by Beng also strongly suggest that high rate of racemization in this system precludes the use of substoichiometric amounts of chiral ligand.

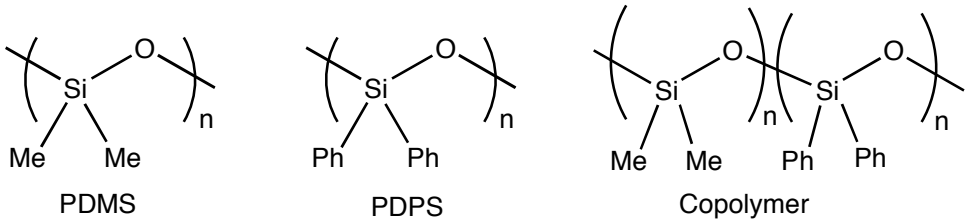
D.) NHC-Catalyzed Oxidation of Diphenylsilane: A Facile Synthesis of Octaphenylcyclotetra(siloxane)

Introduction

Over the course of our investigation into the hydrosilylation of prochiral ketones, a unique application of the CuIPr N-heterocyclic carbene (NHC) to the oxidation of diphenylsilane was discovered. The transformation was carried out open to air at room temperature, yielding octaphenylcyclotetra(siloxane) quantitatively in one hour. This preparation constitutes a significant improvement over existing methods for the preparation of this compound. The diphenylsilanone tetramer is the precursor to a number of industrially significant polymers.

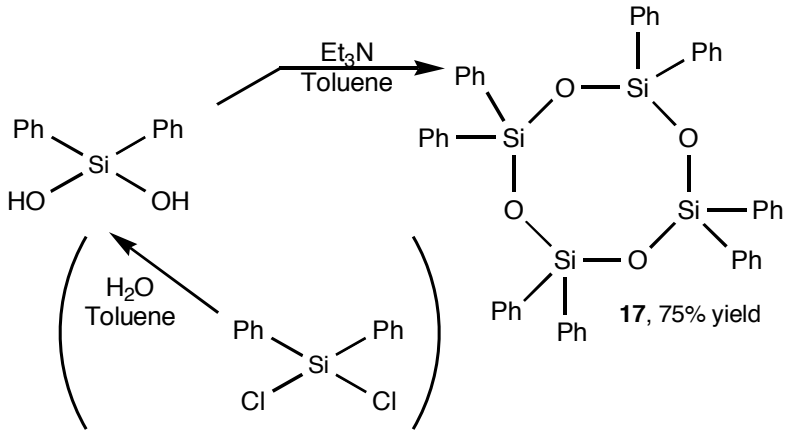
Siloxane polymers can be synthesized as fluids, gels, elastomers and resins and have a wide variety of applications in both industry and academia.[61] Straight chain poly(dimethylsiloxane) (PDMS) is a representative silicone with a number of useful properties including high gas permeability, a small dielectric constant, a very flexible backbone and general chemical and physiological inertness.[62] Replacement of the methyl groups of PDMS with alternate organic substituents is of interest because it allows for fine-tuning of the properties of the polymer.[63] Octaphenylcyclotetra(siloxane), or $(Ph_2SiO)_4$, is a common reagent for the introduction of the diphenylsiloxane moiety into a variety of copolymers, or it can be polymerized independently to yield polydiphenylsiloxane (PDPS). Recent work has shown that incorporation of diphenylsiloxane groups into polyimidesiloxane (PIS) polymers provided for significantly improved compatibility between the segments of the copolymer and allowed for manipulation of the thermal stabilities and mechanical properties.[64]

Figure 3.7. Representative Siloxane Polymers



Most of the previously published syntheses of octaphenylcyclotetra(siloxane), **17**, require lengthy reaction times and high temperatures.[65] These syntheses, as well as the typical industrial preparation of **17**, involve either the hydrolysis of diphenyldichlorosilanes or diphenyldialkoxysilanes. The general reaction is depicted in Scheme 3.9, with the best-reported reaction conditions included.[66]

Scheme 3.9. Prior Synthesis of Compound **17**.

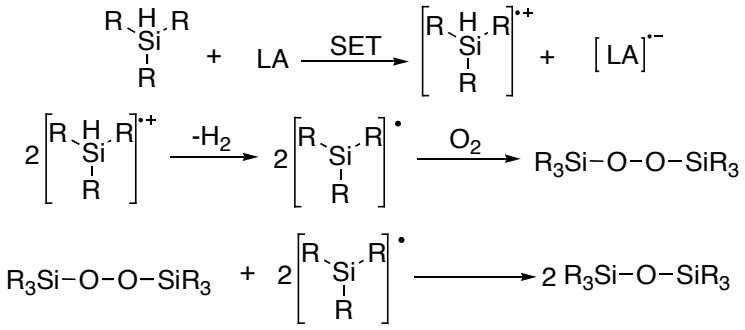


In addition to their application in polymer chemistry, silanols such as the one depicted in Scheme 3.9 are useful in their own right as reagents in cross coupling reactions.[67] Strict pH control prevents self-condensation to disiloxanes and higher order oligomers.[68] Although still

widely prepared by the hydrolysis of the chlorosilanes, recent efforts have focused on the metal-catalyzed conversion of organosilanes to silanols. A number of promising systems employing rhenium, ruthenium, iridium, and silver have been developed,[69] most of which employ water or hydrogen peroxide as the oxygen source. Comparatively few methods employing molecular oxygen have been reported.[70]

Diorganotellurides have been shown to catalyze the formation of silanols from a variety of organosilanes with molecular oxygen, using a photosensitizer and light. While the mechanism of this transformation has not been fully elucidated, the necessity of light and a photosensitizer suggest singlet oxygen may be playing a role.[71] A number of Lewis acids have also been shown to catalyze the formation of disiloxanes from the organosilane and oxygen, including $CuCl_2$-$2H_2O$, $Cu(OTf)_3$, $NbCl_5$, Bi $(OTf)_3$, $SbCl_3$, $InCl_3$ and $InBr_3$. The reaction is thought to proceed via single electron transfer (SET) from the silane to the lewis acid, followed by homolytic cleavage of the Si-H bond causing generation of hydrogen gas. A neutral silicon radical is subsequently formed, which reacts with molecular oxygen to give the disiloxane (Scheme 3.10).[72]

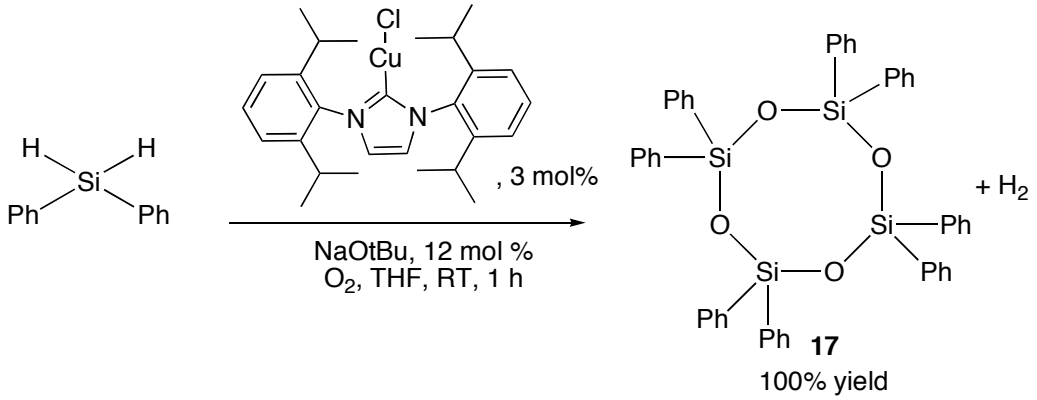
Scheme 3.10: Lewis acid catalyzed disiloxane formation by SET



Results and Discussion

The copper *N,N'*-bis(2,6-diisopropylphenyl)imidazol-2-ylidine (CuIPr) NHC is an air and moisture stable catalyst that has been applied in a wide variety of reactions,[53] but its application to silane oxidation has not, to our knowledge, been reported previously. During an investigation into the NHC-CuH mediated hydrosilylation of ketones, we observed the formation of a highly crystalline byproduct when rigorous exlusion of air was neglected. Indeed, our first observation of the byproduct occurred upon its precipitation from the crude hydrosilylation reaction mixture as a diamond shaped crystal over 2 cm in length! Upon isolation and characterization, we discovered it to be octaphenylcyclotetra(siloxane), **17**. Formation of the siloxane tetramer can be avoided by carrying out hydrosilylation under inert atmosphere. Alternatively, siloxane **17** can be obtained exclusively by omitting addition of the ketone and merely stirring diphenylsilane and NaO*t*-Bu in THF containing 3 mol percent CuIPr-Cl, open to air, under which conditions diphenyl silane is completely consumed in 1h at room temperature and siloxane **17** is produced quantitatively (Scheme 3.11). The vigorous evolution of gas, likely hydrogen, was observed.

Scheme 11: NHC-Catalyzed oxidation of Diphenylsilane



The identity of siloxane **17** was established by NMR, XRD, and combustion and melting point analysis. Very high quality colorless cubic crystals were obtained by slow diffusion of hexanes into dichloromethane at low temperature. The triclinic unit cell (a = 10.726Å. b = 10.7624 Å, c = 19.125 Å, α = 83.694°, β = 83.026°, γ = 76.213°) was determined to have the P1 space group, and after refinement, a final R value of 0.0402 was obtained. Our crystal structure is illustrated in Figure 3.8; it is in complete agreement with that previously reported.[65,66]

Figure 3.8: XRD structure of compound **17**

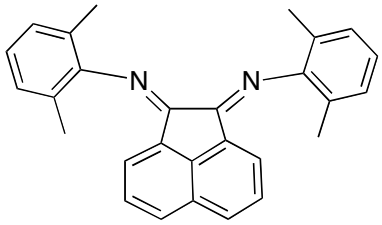
It is likely that when the CuIPr is first treated with a *tert*-butoxide base it forms the copper alkoxide, which then reacts with the silane to give the corresponding copper hydride. The formation of the IPr copper hydride in this manner is supported by its previously reported activity.[53] Notably, copper (I) hydride complexes have been reported to catalyze silicon-oxygen bond formation between organosilanes and alcohols.[73]

However, as this transformation proceeds smoothly even under anhydrous conditions, it apparently employs dioxygen as a reactant. The mechanism of the CuIPr-catalyzed formation of **17** is not obvious; there is precedence for the coordination of both molecular oxygen[74] and organosilanes[75] to NHCs. Nonetheless, it is likely that the catalytic cycle yields diphenylsilanediol, which then undergoes self-condensation to yield **17**.

In summary, an extremely facile synthesis of octaphenylcyclotetra(siloxane) was discovered and, perhaps more notably, an interesting mode of reactivity for the CuIPr NHC. The new synthesis of siloxane **17** provides a significant improvement over those currently in the literature and may be adaptable to a larger scale.

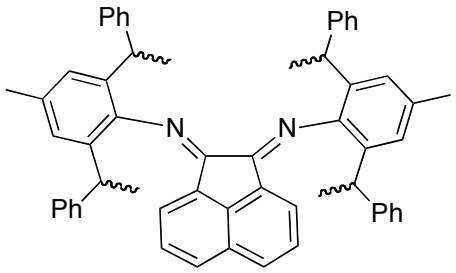
Experimental

General: All reagents and solvents were used as received, unless indicated below. Tetrahydrofuran (THF) was distilled over Na/benzophenone ketyl under N_2 immediately prior to use. ^{1}H NMR spectra were obtained at 300 or 400 MHz in $CDCl_3$ unless otherwise noted. Coupling constants (J), are reported in Hz. X-ray diffraction was carried out on a Bruker SMART X2S. The CuIPr was prepared according to literature methods.[14]

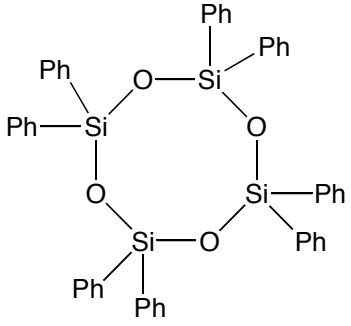


(11*E*)-*N*-((*E*)-1-(2,6-dimethylphenylimino)acenaphthylen-2(1*H*)-ylidene)-2,6-dimethylbenzenamine – 4: To a test tube equipped with a stir bar and screw cap was added freshly distilled xylidene (12.1 mmol), acenaphthenequinone (5.8 mmol) and freshly distilled toluene (6.8 mL). The reaction vessel was thrice purged with nitrogen and sealed. Acetic acid (9.9 mL) was added and the tube was heated to 100 °C for 15 h. (Alternatively, for improved yield, the reaction was carried out in a round bottom flask equipped with a stir bar and reflux condenser, and refluxed at 140 °C for 15 h.) The reaction solution was allowed to cool to room temperature and was washed with saturated $NaHCO_3$ to neutral pH. The organic layer was separated and the aqueous layer was washed with DCM (3 x 10mL). The combined organic extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The crude reaction mixture was purified by column chromatography with 98:2, petroleum ether: ethyl acetate as the eluant and recrystallized from DCM and pentane to yield the product as a bright red crystalline solid (5.0mmol, 87%). ^{1}HNMR ($CDCl_3$): 2.15 (12H, s), 6.72 (2H, d, J=5.6), 7.16 (2H, m), 7.18 (4H, m), 7.20 (2H, t, J=7.6), 7.90 (2H, d, J=6.8). Crystals for XRD of

this compound were grown by slow diffusion of DCM into pentane. This compound was not further characterized.



(26*E*)-*N*-((*E*)-1-(4-methyl-2,6-bis(1-phenylethyl)phenylimino)acenaphthylen-2(1*H*)-ylidene)-4-methyl-2,6-bis(1-phenylethyl)benzenamine, mixture of stereoisomers – 5: ^{1}HNMR ($CDCl_3$): 1.24 (12H, t), 2.08 (6H, s), 4.19 (4H, q), 6.6-8.8 (26H). Calculated $[M+H]^+$ for $C_{58}H_{52}N_2$: 777.41305. Found: 777.4184. This compound was not further characterized.



Octaphenylcyclotetrasiloxane - 17: To a scintillation vial equipped with a stir bar was added CuIPr (14.6mg, 0.030mmol), sodium *tert*-butoxide (11.5mg, 0.12mmol) and THF (5mL). The reaction vessel was left open to air. The heterogeneous solution was stirred for 10 m before addition of diphenyl silane (0.186mL, 1.0mmol). An immediate color change to bright yellow was observed and stirring was continued for 1h, over which time the reaction solution darkened significantly. The reaction solution was then treated with charcoal, run through a plug of silica and celite, and recrystallized from dichloromethane and hexanes. The resultant highly crystalline white solid was isolated by filtration (0.25mmol, 0.197g, 100%). ^{1}HNMR ($CDCl_3$): 7.23 (16H, t, J=7.33), 7.39 (8H, tt, J=7.49), 7.53 (16H, dd, J=7.33). ^{13}C NMR ($CDCl_3$): 127.63 (CH), 130.04 (C), 134.40 (CH). Anal calcd for $C_{48}H_{40}O_4Si_4$: C, 72.68; H, 5.08. Found: C, 72.62; H, 5.00.

References:

1. (a) Food and Drug Administration, 1992, Policy Statement for the Development of New Stereoisomeric Drugs. *US Food and Drug Administration Regulatory Guidance*; www.fda.gov/cder/guidance/stereo.htm. (b) Gawley, R. E.; Aubé, J. *Principles of asymmetric synthesis*, Pergamon: Oxford, U.K.; Tarrytown, N.Y., **1996**.

2. (a) Rouhi, A. *Chem. Eng. News* **2003**, *81*, 56-61. (b) Shimazawa, R.; Nagai, N.; Toyoshima, S.; Okuda, H. *J. Health Sci.* **2008,** *54*, 23-29. (c) Caner, H.; Groner, E.; Levy, L.; Agranat, I. *Drug Discovery Today* **2004**, *9*, 105-110.

3. (a) Nolan, S. P. *Eur. J. Inorg. Chem.* **2009**, 1664. (b) Jones, W. *J. Am. Chem. Soc.* **2009**, *131*, 15075-15077.

4. (a) Herrmann, W. *Angew. Chem. Int. Ed.* **2002**, *41*, 1290-1309. (b) Enders, D.; Balensiefer, T. *Acc. Chem. Res.* **2004**, *37*, 534-541. (c) Crudden, C. M.; Allen, D. P. *Coord. Chem. Rev.* **2004**, *248*, 2247-2273. (d) Cesar, V.; Bellemin-Laponnaz, S.; Gade, L. H. *Chem. Soc. Rev.* **2004**, *33*, 619-636. (e) Bantreil, X.; Broggi, J.; Nolan, S. P. *Annu. Rep. Prog. Chem., Sect. B: Org. Chem.* **2009**, *105*, 232-263; (f) Diez-Gonzalez, S.; Marion, N.; Nolan, S.P. *Chem. Rev.* **2009**, *109*, 3612-3676

5. Buchner, E.; Curtius, T. *Chem. Ber.* **1885**, *8*, 2377.

6. Wanzlick, H.W.; Schönherr, H.J. *Angew. Chem. Int. Ed. Engl.* **1968**, 141-142.

7. Öfele, K. *J. Organomet. Chem.* **1968**, *12*, 42-43

8. Ukai, T.; Tanaka, S.; Dokawa, S. *J. Pharm. Soc., Jpn.* **1943**, *63*, 296.

9. Droge, T.; Glorius, F. *Angew. Chem. Int. Ed.* **2010**, *49*, 6940-6952.

10. Kaur, H.; Zinn, F.; Stevens, E.; Nolan, S.P. *Organometallics* **2004,** *23*, 1157-1160.

11. Seiders, T.; Ward, D.; Grubbs, R. *Org. Lett.* **2001**, *3*, 3225-3228.

12. Funk, T. W.; Berlin, J. M.; Grubbs, R. *J. Am. Chem. Soc.* **2006**, *128*, 1840-1846.

13. Herrmann, W. A.; Goossen, L. J.; Köcher, C.; Artus, G. R. J. *Angew. Chemie Int. Ed.* **1996**, *35*, 2805-2807.

14. Huang, J.; Jafarpour, L.; Hillier, A. C.; Stevens, E. D.; Nolan, S. P. *Organometallics*, **2001**, *20*, 2878-2882.

15. Winn, C. L.; Guillen, F.; Pytkowicz, J.; Roland, S.; Mangeney, P.; Alexakis, A. *J. Organomet. Chem.* **2005**, *690*, 5672-5695.

16. Perry, M.; Burgess, K. *Tetrahedron: Asymmetry* **2003,** *14*, 951-961.

17. Luan, X.; Mariz, R.; Gatti, M.; Costabile, C.; Poater, A.; Cavallo, L.; Linden, A.; Dorta, R. *J. Am. Chem. Soc.* **2008**, *130*, 6848-6858.

18. (a) Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1996**, *118*, 1575-1576; (b) Thayumanavan, S.; Basu, A.; Beak, P. *J. Am. Chem. Soc.* **1997**, *119*, 8209-8216

19. Cherian, A.; Domski, G.; Rose J.; Lobkovsky, E.; Coates, G. *Org. Lett.* **2005**, *7*, 5135-5137

20. Tsai, S. C.; Liu, S. T. *J. Chin. Chem. Soc.* **1991**, *38*, 39-45.

21. Gassman, P. G.; Drewes, H. R. *J. Am. Chem. Soc.* **1978,** *100,* 7600-7610.

22. Email correspondence with Dr. Anna Cherian

23. Tolstoy, P.; Engman, M.; Paptchikhine, A.; Bergquist, J.; Church, T.; Leung, A.; Andersson, P. G. *J. Am. Chem. Soc.* **2009**, *131*, 8855-8860.

24. Arienti, A.; Bigi, F.; Maggi, R.; Marzi, E.; Moggi, P.; Rastelli, M.; Sartori, G.; Tarantola, F. *Tetrahedron* **1997**, *53*, 3795-3804.

25. (a) Arduengo, A.J. *Acc. Chem. Res.* **1999**, *32*, 913. (b) Lee, K.; Brown, K.; Hird, A. W.; Hoveyda, A. H. *J. Am. Chem. Soc.* **2006**, *128*, 7182-7184.

26. Belokon, Y.; Grachev, A.; Maleev, V.; Khrustalev, V.; Peregudov, A.; North, M. *Tetrahedron-Asymmetry* **2008,** *19*, 756-760.

27. Lillo, V.; Prieto, A.; Bonet, A.; Diaz-Requejo, M.; Ramirez, J.; Perez, P.; Fernandez, E. *Organometallics* **2009,** *28*, 659-662.

28. Dyson, G.; Frison, J.; Simonovic, S.; Whitwood, A.; Douthwaite, R. *Organometallics* **2008,** *27*, 281-288.

29. Tominaga, S.; Oi, Y.; Kato, T.; An, D.; Okamoto, S. *Tet. Lett.* **2004,** *45*, 5585-5588.

30. Berthon-Gelloz, G.; Siegler, M.; Spek, A.; Tinant, B.; Reek, J.; Marko, I. *Dalton Trans.* **2010,** *39*, 1444-1446.

31. Wang, H.; Lin, I. *Organometallics* **1998,** *17*, 972-975.

32. Kano, T.; Sasaki, K.; Maruoka, K. *Org. Lett.* **2005,** *7*, 1347-1349.

33. Seayad, J.; Patra, P.; Zhang, Y.; Ying, J. *Org. Lett.* **2008,** *10*, 953-956.

34. Chaulagain, M. R.; Sormunen, G. J.; Montgomery, J. *J. Am. Chem. Soc.* **2007**, *129*, 9568-9569.

35. Wender, P. A.; Smith, T. E.; Zuo, G.; Duong, H. A.; Louie, J. Bis(1,5-cyclooctadiene)nickel(0). In *Encyclopedia of Reagents for Organic Synthesis*, John Wiley & Sons, Ltd: **2001**.

36. Fructos, M.; Belderrain, T.; Nicasio, M.; Nolan, S.; Kaur, H.; Diaz-Requejo, M.; Perez, P. *J. Am. Chem. Soc.* **2004,** *126*, 10846-10847.

37. Gawley, R.; Narayan, S. *Chem. Commun.* **2005**, 5109-5111.

38. (a) Noyori, R. *Acta. Chem. Scand.* **1996**, *50*, 380-390. (b) Genet, J.P. In *Reductions in Organic Synthesis*, Abdel-Magid, A.F., Ed.; ACS Symposium Series, 641; American Chemical Society: Washington D.C., **1996**, 31-51. (c) Morris, R.H. *Chem. Soc. Rev.* **2009**, *38*, 2282-2291.

39. (a) Ojima, I.; Li, Z.; Zhu, I. *The Chemistry of Organosilicon Compounds*, ed. Patai, S. and Rappoport, Z. Wiley, New York, **1998**. (b) Troegel, D.; Stohrer, J. *Coord. Chem. Rev.* **2011**, *255*, 1440-1459.

40. (a) Noyori, R. *Acta. Chem. Scand.* **1996**, *50*, 380-390. (b) Genet, J.P. In *Reductions in Organic Synthesis*, Abdel-Magid, A.F., Ed.; ACS Symposium Series, 641; American Chemical Society: Washington D.C., **1996**, 31-51. (c) Morris, R.H. *Chem. Soc. Rev.* **2009**, *38*, 2282-2291.

41. (a) Ojima, I.; Nihonyanagi, M.; Nagai, Y. *Bull. Chem. Soc. Jap.* **1972**, *45*, 3506-3506. (b) Marciniec, B.; Maciejewski, H.; Pietraszuk, C.; Pawluc, P. *Hydrosilylation. A Comprehensive Review on Recent Advances*, ed. B. Marciniec, Springer, **2008**.

42. Diez-Gonzalez, S.; Nolan, S. *Acc. Chem. Res.* **2008,** *41*, 349-358.

43. (a) Lipshutz, B.; Keith, J.; Papa, P.; Vivian, R. *Tet. Lett.* **1998,** *39*, 4627-4630. (b) Lipshutz, B.; Chrisman, W.; Noson, K.; Papa, P.; Sclafani, J.; Vivian, R.; Keith, J. *Tetrahedron* **2000,** *56*, 2779-2788. (c) Lipshutz, B.; Servesko, J.; Taft, B. *J. Am. Chem. Soc.* **2004,** *126*, 8352-8353. (d) Lipshutz, B.; Servesko, J.; Petersen, T.; Papa, P.; Lover, A. *Org. Lett.* **2004,** *6*, 1273-1275. (e) Lipshutz, B.H.; Frieman, B.A. *Angew. Chem. Int. Ed.* **2005**, *44*, 6345-6348.

44. Ojima, I.; Nihonyanagi, M.; Nagai, Y. *Chem. Commun.* **1972**, *45*, 938.

45. (a) Wurtz, A. *Ann. Chim. Phys.* **1844,** *11*, 250-252 (b) Boeckman, R.K.; Michalak, R. *J. Am. Chem. Soc.* **1974**, *96*, 1623-1625 (b) Semmelhack, M.F.; Stauffer, R.D. *J. Org.*

Chem. **1975**, *40*, 3619-3621 (c) Brunner, H.; Miehling, W. *J. Organomet. Chem*. **1984**, *275*, 17-21.

46. Chen, J.; Daeuble, J.; Stryker, J. *Tetrahedron* **2000,** *56*, 2789-2798.

47. Bezman, S.A.; Churchill, M.R.; Osborn, J.A. *J. Am. Chem. Soc.* **1971**, *93*, 2063-2065.

48. Nolan, S. P. *N-Heterocyclic carbenes in synthesis.* Wiley-VCH; John Wiley distributor: Weinheim Chichester, **2006**.

49. Duan, W.; Shi, M.; Rong, G. *Chem. Commun.* **2003**, 2916-2917.

50. Liu, L.; Wang, F.; Shi, M. *Organometallics* **2009,** *28*, 4416-4420.

51. Song, C.; Ma, C.; Ma, Y.; Feng, W.; Ma, S.; Chai, Q.; Andrus, M.B. *Tet. Lett.* **2005**, *46*, 3241-3244.

52. (a) Cesar, V.; Bellemin-Laponnaz, S.; Wadepohl, H.; Gade, L. *Chem. Eur. J.* **2005,** *11*, 2862-2873. (b) Gade, L. H.; César, V.; Bellemin-Laponnaz, S. *Angew. Chem. Int. Ed.* **2004**, *43*, 1014-1017.

53. Heldmann, D. K.; Seebach, D. *Helv. Chim. Acta* **1999**, *82*, 1096-1110.

54. (a) Diez-Gonzalez, S.; Scott, N.; Nolan, S.P. *Organometallics* **2006,** *25*, 2355-2358. (b) Díez-González, S.; Kaur, H.; Zinn, F. K.; Stevens, E. D.; Nolan, S. P. *J. Org. Chem.* **2005**, *70*, 4784-4796.

55. Mankad, N.P; Laitar, D.S.; Sadighi, J.P. *Organometallics*, **2004**, *23*, 3369-3371.

56. Lorenz, C.; Schubert, U. *Chem. Ber.* **1995**, *128*, 1267-1269.

57. Baker, J.;Wolinski, K.; Janowski, T.; Saebo, S.; Füsti-Molnár, L.; Magyarfalvi, G.; Pulay, P. PQS version 4.0, Parallel Quantum Solutions, LLC, Fayetteville, Arkansas, http://www.pqs-chem.com.

58. Issenhuth, J.; Dagorne, S.; Bellemin-Laponnaz, S. *Adv. Synth. Catal.* **2006,** *348*, 1991-1994.

59. Bohm, C.; Schinnerl, M.; Bubert, C.; Zabel, M.; Labahn, T.; Parisini, E.; Reiser, O. *Eur. J. Org. Chem.* **2000,** 2955-2965.

60. Courtesy of Dr. Chris Fitchett.

61. Cherian, A.; Rose, J.; Lobkovsky, E.; Coates, G. *J. Am. Chem. Soc.* **2005,** *127*, 13770-13771.

62. a.) Clarkson, S.; Semlyen, J. *Siloxane Polymers*, PTR Prentice Hall, New Jersey, **1993** b.) Brandt, P.J.A; Elsbernd, C.L.S.; Patel, N.; York, G.; McGrath, J.E. *Polymer* **1990,** *31*, 180-190.

63. Morariu, S.; Brunchi, C. E.; Cazacu, M.; Bercea, M. *J. Chem. Eng. Data* **2011,** *56*, 1468-1475.

64. Li, H.; Zhang, J.; Xu, R.; Yu, D. *J. Appl. Polym. Sci.* **2006,** *102*, 3848-3856.

65. Liaw, W.; Chen, K. *J. Polym. Res.* **2007,** *14*, 5-21.

66. (a) Burkhard, C.A.; Decker, B.F.; David, H. *J. Am. Chem. Soc.* **1945**, *67*, 2173-2174. (b) Deka, K.; Sarma, J. R.; Baruah, J.B. *Inorg. Chem. Commun.* **2005**, *8*, 1082-1084. (c) Yang, M.H.; Chou, C.Y.; Lin, C. *J. Chin. Chem. Soc.* **1995**, *42*, 923-928.

67. Luo, M.; Yan, B. *Tet. Lett.* **2009**, *50*, 5208-5209.

68. (a) Denmark, S. E., Sweis, R. F. In *Metal-Catalyzed Cross-Coupling Reactions*; Meijere, de A., Diederich, F., Eds.; Wiley-VCH: Weinheim, Germany, **2004**; Vol. 1, Chapter 4. (b) Hirabayashi, K., Nishihara, Y., Mori, A., Hiyama, T. *Tetrahedron Lett.* **1998**, 39, 7893– 7896. (c) Hirabayashi, K., Kawashima, J., Nishihara, Y., Mori, A., Hiyama, T. *Org. Lett.* **1999**, 1, 299– 301. (d) Denmark, S. E., Wehrli, D. *Org. Lett.* **2000**, 2, 565– 568

69. (a) Rochow, E. G., Gilliam, W. F. *J. Am. Chem. Soc.* **1941**, 63, 798– 800. (b) Sauer, R. O. *J. Am. Chem. Soc.* **1944**, 66, 1707– 1709

70. (a) Adam, W., Mitchell, C. M., Saha-Mller, C. R., Weichold, O. *J. Am. Chem. Soc.* **1999**, 121, 2097– 2103. (b) Adam, W., Saha-Mller, C. R., Weichold, O. *J. Org. Chem.* **2000**, 65, 2897– 2899. (c) Tan, H., Yoshikawa, A., Gordon, M. S., Espenson, J. H. *Organometallics* **1999**, 18, 4753– 4757. (d) Ison, E. A., Corbin, R. A., Abu-Omar, M. M. *J. Am. Chem. Soc.* **2005**, 127, 11938– 11939. (e) Corbin, R. A., Ison, E. A., Abu-Omar, M. M. *Dalton Trans.* **2009**, 2850– 2855. (f) Lee, M., Ko, S., Chang, S. *J. Am. Chem. Soc.* **2000**, 122, 12011– 12012 (g) Mori, K., Tano, M., Mizugaki, T., Ebitani, K., Kaneda, K. *New J. Chem.* **2002**, 26, 1536– 1538. (h) Lee, Y., Seomoon, D., Kim, S., Han, H., Chang, S., Lee, P. H. *J. Org. Chem.* **2004**, 69, 1741– 1743. (i) Mitsudome, T., Arita, S., Mori, H., Mizugaki, T., Jitsukawa, K., Kaneda, K. *Angew. Chem., Int. Ed.* **2008**, 47, 7938– 7940

71. Minisci, F., Recupero, F., Punta, C., Guidarini, C., Fontana, F., Pedulli, G. F. *Synlett* **2002**, 1173– 1175

72. Okada, Y., Oba, M., Arai, A., Tanaka, K., Nishiyama, K., Ando, W. *Inorg. Chem.* **2010**, 49, 383– 385

73. Sridhar, M.; Ramanaiah, B.C.; Narsaiah, C.; Swamy, M.K.; Mahesh, B.; Reddy, M.K.K. *Tet. Lett.* **2009**, *50*, 7166-7168.

74. Baruah, J. B., *Catalysts for silane and silanol activation*, ACS Symposium Series, **2007**, 964, *Science and Technology of Silicones and Silicone-Modified Materials*, 69-80. American Chemical Society.

75. Popp, Brian V.; Wendlandt, Johanna E.; Landis, Clark R.; Stahl, Shannon S. *Angew. Chem. Int. Ed.* **2007**, 46, 601-604.

76. Xiong, Y.; Yao, S.; Driess, M. *J. Am. Chem. Soc.* **2009**, 131, 7562– 7563.