UNIVERSITY OF OKLAHOMA

GRADUATE COLLEGE

LIGAND ASSISTED COPPER CATALYZED C-H AMINATIONS

A DISSERTATION

SUBMITTED TO THE GRADUATE FACULTY

in partial fulfillment of the requirements for the

Degree of

DOCTOR OF PHILOSOPHY

By

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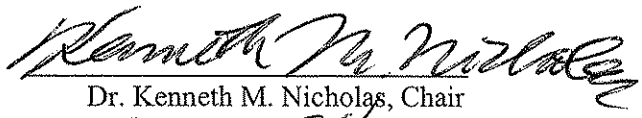
Norman, Oklahoma
2010

LIGAND ASSISTED COPPER CATALYZED C-H AMINATION

A DISSERTATION APPROVED FOR THE
DEPARTMENT OF CHEMISTRY AND BIOCHEMISTRY

BY



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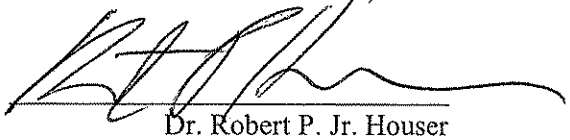

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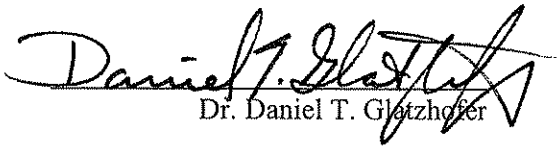

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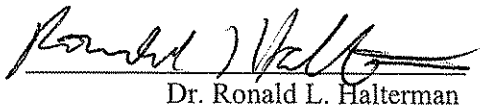

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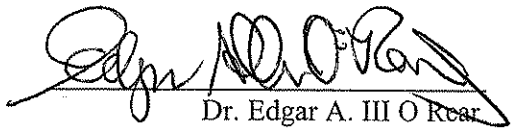

Dr. Edgar A. III O Rear

Acknowledgement

This is by far the most important part of my doctoral thesis. Chemists often define their achievements in terms of the number of novel reactions they have invented. Yet, I realize that my greatest achievements have been the professional and personal relationships I have developed throughout my graduate career. So it is with tremendous gratitude that I write these acknowledgements to show my appreciation to some of the people who have helped me throughout the years.

I must thank the most important people in my life, my family. I am nothing without them. My sister, Indu Prava Barman, is my biggest pillar of support. She truly believes that her brother will win a Noble Prize in future. My mother, Japamala Barman, is the backbone of our family. She has sacrificed everything to ensure that we would always be able to strive for our goals. I need to thank her for developing my insatiable passion for pursuing knowledge. She deserves this Ph.D. as much as I do. My father, Santosh Kumar Barman is my role model in life. He has taught me the value of honesty, hard work and humanity. I would like to thank my wife Piali Barman, always been willing to support me, especially during the toughest days of graduate school. She always knows when I needed to hear words of encouragement. I could not imagine living a single day of my life without her support and guidance. Her presence helped me to stay calm during my general exam. I talked so much about the chemistry at home; she thinks that she can now even teach organic chemistry despite being a well-qualified engineer. I would like to thank my extended family, especially my brother-in-law Dr. Pritam Das and my sister-in-law Siuli Das. I could not finish my graduate studies without a generous moral support from my mother-in-law Madhumati Das and my father-in-law Dr.

Sukhamoy Das. They have always trust on me. I only hope that they realize how much I love them too.

How do I even begin to thank my adviser Dr. Nicholas? I have known Dr. Nicholas for a long time now, and I have never had any difficulties to say anything to him. So it is ironic that I am having difficulty expressing my gratitude. How can I thank a person who has done everything in his power to make sure that I succeed in life? I am getting emotional just thinking about it. Intellectually, Dr. Nicholas has been an ideal advisor. I met him in February 2007, when I looking forward to move out of University of Missouri. Perhaps, I knew about the famous "Nicholas reaction" but I was not sure that he was the inventor of that famous reaction. Dr. Nicholas is the most down-to-earth, genius on the planet. There is no doubt in my mind that I will be a student of Dr. Nicholas throughout my life. As an advisor, he has always encouraged me to explore my ideas, and he has always guided me in the right direction. The world knows, Dr. Nicholas as a prolific, brilliant organometallic chemist. And he is by far the most hard working person I know. Dr. Nicholas is also an amazing friend. He has always been there to congratulate me on the happiest days of my life, and he has always been the first one to console me up on the most difficult days of my research. I am able to sit here today and write my acknowledgements because of Dr. Nicholas's support. Although the occasion of my thesis defense marks the end of my time as a member of Dr. Nicholas's group, it also marks the beginning of a lifelong friendship.

I specially thanks to my all-present and past co-workers as well. They are very talented chemists and even better people. And of course, I must thank the humble John Hallren, my best undergraduate student and my partner for the making various ligands. Having a supportive colleague like John Hallren and Dr. Alex John can make a significant difference in graduate school.

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Abstract

The presence of nitrogen in amino functional groups found in many useful natural and synthetic products makes their preparation valuable to chemicals and materials production, biology and medicinal chemistry. Their importance has inspired chemists to design a variety of methodologies for C-H bond activation essential for building amino functional groups. Transition metal-mediated nitrenoid transfer reactions are important chemical processes in which hydrocarbons are transformed to nitrogen containing compounds via direct C-N bond formation. A variety of transition metal catalysts have been developed for the oxidative functionalization of carbon–hydrogen bonds. Although general methods for intramolecular C–H bond amination are relatively new, they have already found application in the preparation of a variety of natural product targets. The objectives of our project are to discover efficient nitrenoid sources for catalytic C–H amination with inexpensive copper complexes as catalysts, and to evaluate the scope and selectivity and mechanism in amination reactions.

Several classes of ligands, including α-amino acids, diamines, diphosphines, bis-oxazolines, and diimines, support efficient copper-catalyzed intermolecular amination of benzylic hydrocarbons by anhydrous chloramine-T. The initial synthetic study of the reactions revealed ligand-accelerated catalysis with significant sensitivity to the electronic character of the substrates and ligands. Intermolecular reaction with various benzylic hydrocarbons gives tosyl-protected amines that can be isolated with moderate to excellent yields and that cleave easily to produce the corresponding free amine. Catalysts derived from homochiral ligands, particularly chiral diimines, and effect amino-

sulfonation of benzylic hydrocarbon with low to moderate enantioselectivity. The low enantioselectivity led us to study the mechanism of the amination reaction.

The mechanism of hydrocarbon amination by chloramine-T derivatives catalyzed by (diimine) copper complexes has been investigated. Isotopic effects, stereochemical studies and the electronic nature of the transition state are used to probe the mechanism of the reaction. A kinetic isotope effect of 4.6 was found in the amination of α-D(H)-cumenes catalyzed by [(diimine)Cu(solv)]Z. Amination of the isomeric substrates *cis*- and *trans*-4-t-butyl-1-phenylcyclohexanes with 4-Me-$C_6H_4SO_2NNaCl$ (chloramine-T) or 4-NO_2-$C_6H_4SO_2NNaCl$ (chloramine-N) catalyzed by [(diimine)Cu(CH_3CN)]PF_6 produced in all cases an approximately 1:1 mixture of the corresponding *cis*- and *trans*-4-t-butyl-1-phenyl-1-sulfonaminocyclohexanes. Amination of the radical-clock substrate 1-phenyl-2-benzylcyclopropane with chloramine-T/(diimine)Cu(CH_3CN)]PF_6 gave a mixture of ring-opened and cyclopropylmethylamino derivatives. Together these results are most consistent with a stepwise insertion of an N-Ts unit into the C-H bond, via carbon radicals, and a secondary contribution from a concerted insertion pathway. B3LYP and CASSCF computations (in collaboration with P. Liu and Prof. K. Houk) suggest that the C-H insertion step involves the reaction of the hydrocarbon with a Cu-imido (nitrene) complex, [(diimine)Cu=NSO_2R]$^+$. The ground state triplet of the Cu-imido complex is calculated to be more stable than singlet complex. The reaction of each complex with hydrocarbon showed that the C-H insertion transition state for the triplet is lower in energy than the singlet. The triplet reacts by a stepwise H-atom abstraction, while the singlet would react by a concerted C-H insertion. These results and kinetic

isotope effect calculations for the singlet (2.9) and triplet (4.8) pathways, respectively, agree with the experimental observations (4.6) and point to a major role for the triplet complex in the stepwise, non-stereoselective insertion pathway.

The discovery of the ligand assisted copper catalyzed intramolecular reaction was another aspect of our amination project. Metal nitrenes for use in C-H insertion reactions were obtained from carbamates in the presence of iodosyl benzene and a Cu(I) ligand complex. The intramolecular C-H amination reaction proceeds smoothly catalyzed by Cu(I)-diimine complexes in moderate to excellent yield. This new methodology allows the amination of benzylic, and aliphatic tertiary, and secondary C-H bonds. The intramolecular reaction provides an interesting route to various substituted oxazolidinones and oxathiazinanes via formation of five-membered and six-membered rings respectively. Employing homochiral diimine ligands affords oxazolidinones and oxathiazinanes with modest enantioselectivity. The development, scope, and limitations of the reactions are discussed herein.

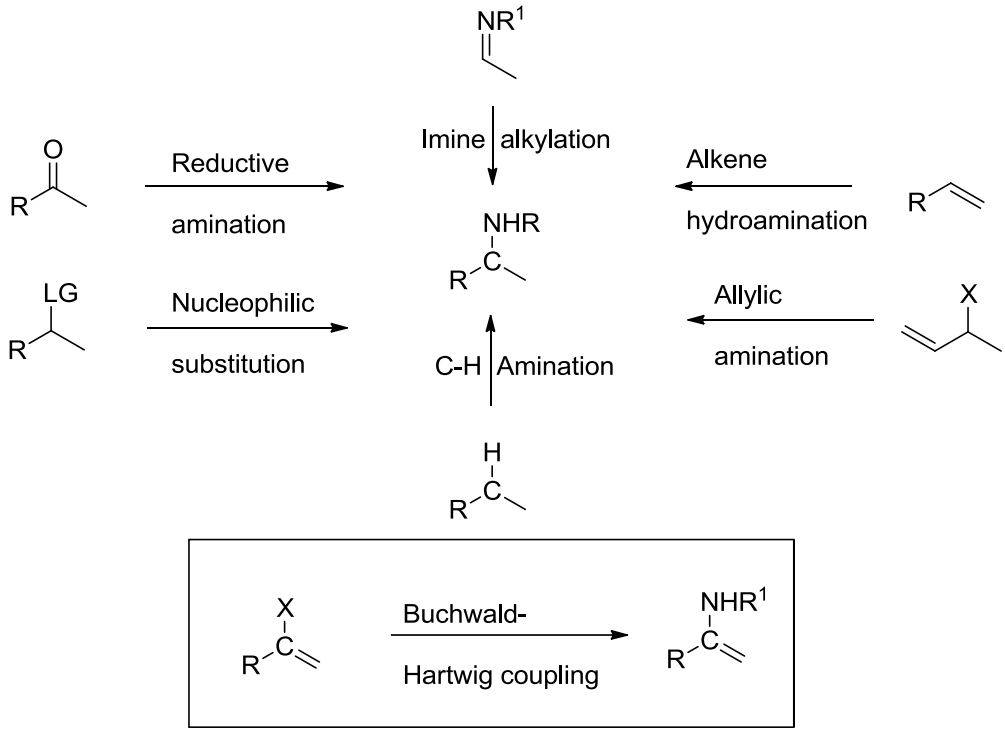
CHAPTER ONE

A Brief History of Amination

1.1 Background and Introduction

Nitrogen is a key atom in nature, found in natural product families such as amino acids, alkaloids, porphyrins and penicillins, where it is incorporated via biosynthetic pathways by enzyme catalyzed condensation reactions with pre-installed oxygen functionality. Moreover, synthetic drugs generally contain more nitrogen than natural products .[1] The nitrogen atom in an amine acts as a hydrogen bond donor when protonated. Amines can acts as hydrogen bond acceptors. Thus the amine group strongly influences the interaction between the medicinal agent and its target. The pK_as of amines are often in the range of physiological pH (7.4 outside the blood vesicle and 5.7 inside the blood vesicle), a physical property essential for improving the bio-reactivity of drugs.[2a] Because the ubiquitous presence of the amine functionality in natural products and the key role it plays in many biologically active compounds, the formation of C-N bonds is of great importance in organic synthesis.[2c,d]

In the synthesis of natural products, bioactive compounds or materials C–N bond forming methodologies are among the most intensively investigated fields. The classical C-N bond formation reactions are nucleophilic displacement of a leaving group and reduction of imines that are formed by condensation of a carbonyl group with primary or secondary amine. Newly discovered transition metal promoted,[3] modern amination methods include Buchwald–Hartwig C–N coupling,[4] hydroamination,[5] allylic amination[6] and diamination[7] of olefins (Scheme 1).

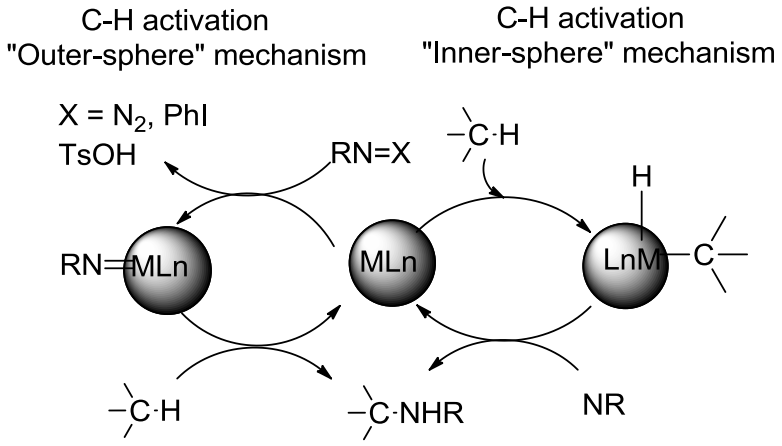


Scheme 1: C-N bond formation reactions

The fundamental question is whether transition metal complexes could help to replace the hydrogen by an amino group. Such a C–H functionalization process could offer unique opportunities compared to those involving a pre-installed functional group. The bond dissociation energies of typical carbon–hydrogen bonds are between 85 and 105 kcal/ mol and this is the very significant challenge in this area. In physiological processes, the oxygenases enzymes could selectively break C–H to form hydroxylation products but a direct nitrogen transfer has not been found in any biosynthetic pathway so far. Several transition metal catalyzed C–H activation/functionalization reactions allow the selective installation of the carbon–nitrogen bond.

1.2 General mechanisms for transition metal catalyzed C–H bond functionalization

Transition metal catalysts have been developed for the oxidative functionalization of carbon–hydrogen bonds to produce aminated products. All of these catalysts promote the same general transformations (C–H/C–N) and operate within two very different mechanistic manifolds. These two mechanisms are referred to as ‘inner-sphere’ and ‘outer-sphere’ and are shown below (Scheme 2).[8]

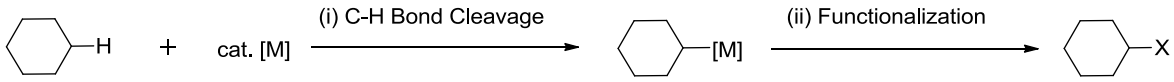


Scheme 2: General mechanisms of C–H amination

1.2.1 Inner-sphere mechanism

The ‘inner-sphere’ C–H bond functionalization mechanism goes through two discrete mechanistic steps: (1) cleavage of a C-H bond to form a transition metal alkyl/aryl species and (2) functionalization of the transition metal alkyl/aryl species by reaction with a nucleophile at the metal center (Scheme 3). The important feature of this ‘inner sphere’ mechanism is the formation of a discrete organometallic intermediate and the structural and electronic feature of this intermediate influence the regio- and

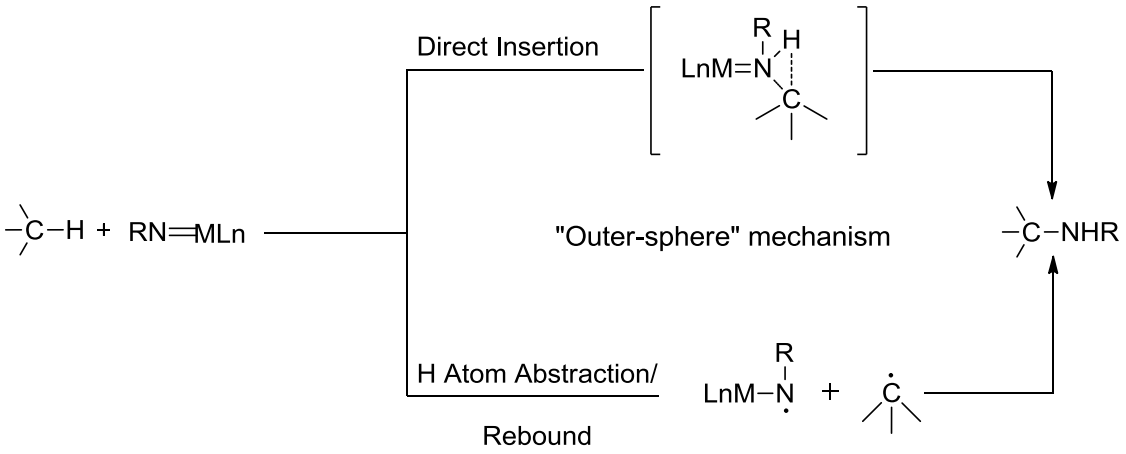
stereoselectivity of C-H functionalization.



Scheme 3: Inner-sphere mechanism

1.2.2 Outer-sphere mechanism

The 'outer-sphere' mechanisms for C–H bond functionalization are being compared to those in biological enzyme-catalyzed oxidation reactions. These processes proceed through (1) formation of a high oxidation state metal complex containing an activated metal imido species followed by (2) reaction of the imido species with a C–H bond (Scheme 4). This latter step can proceed by either direct insertion or H-atom abstraction/radical rebound. The important point of the outer-sphere mechanism is that the alkane/arene substrate does not interact directly with the transition metal center. In Scheme 4, the transformations involve buildup of radical and/or cationic character at carbon, and therefore typically show high selectivity for weaker allylic or benzylic C–H bonds. In this review we will stress this 'outer sphere' mechanism.



Scheme 4: Outer-sphere mechanism

1.3 General challenges for transition metal catalyzed C–H bond functionalization

The four major challenges associated with transition metal catalyzed C–H bond transformation reaction are:

(a) Reactivity

(b) Chemoselectivity

(c) Regioselectivity

(d) Stereoselectivity

1.3.1 Reactivity

Generally, most oxidation reactions are thermodynamically downhill[9] but there is a large kinetic barrier for this C–H bond cleavage. Transition metal catalysts increase the rates of reactions of C–H bonds by many more orders of magnitude than any other conventional method.

1.3.2 Chemoselectivity

The ability to stop functionalization at the required oxidation state represents a major challenge. The over-oxidation of the functionalized products is often highly thermodynamically downhill.[9] The over-oxidation could be avoided by:

(1) Running reactions to low conversion

(2) Utilizing large excesses of substrate to oxidant

(3) Carrying out intramolecular, rather than intermolecular, C-H bond activation.

1.3.3 Regioselectivity

There are many different types of carbon–hydrogen bonds presents in complex organic molecules. So regioselectively functionalizing a single C–H bond within a complex structure remains a challenge.[10] The number of approaches could be done to address this regioselectivity issue:

(1) The use of substrates containing weaker or activated C–H bonds

(2) The use of coordinating ligands within a substrate as directing groups,

(3) Carrying out intramolecular functionalization reactions via formation of a five or six-membered transition states,

(4) The use of supramolecular chemistry to position a specific C–H bond near the active site of the catalyst

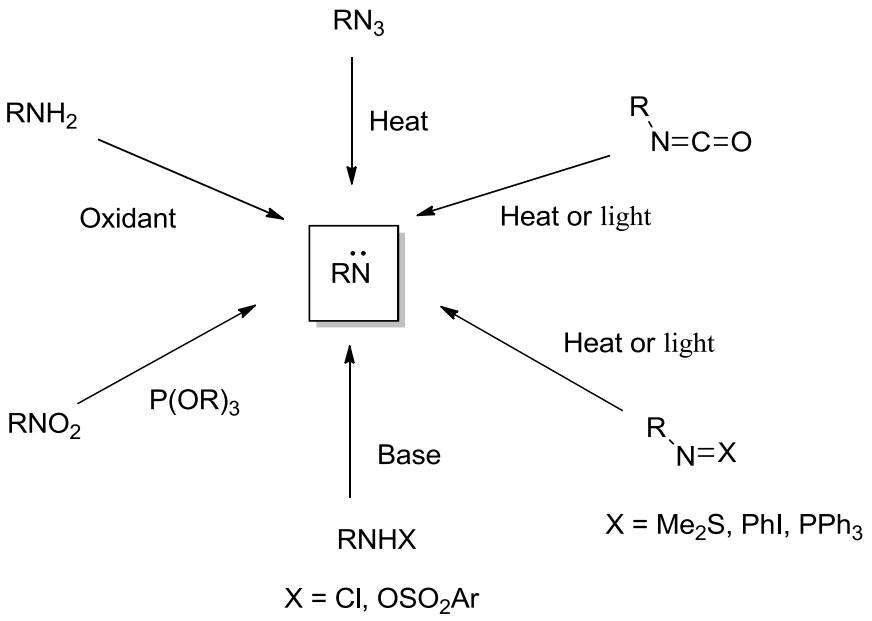
(5) The use of the ligated transition metal complex to control selectivity

1.3.4 Stereoselectivity

The generation of new stereogenic centers using C-H bond activation in a highly diastereoselective and/or enantioselective fashion represents an emerging challenge. Of these, the stereoselectivity issue has been the least explored. The stereoselectivity issue could be handled by using substrates that contains pre-installed stereocenters or chiral auxiliaries or by using chiral transition metal complexes to control the enantioselectivity.[11]

1.4.1 Nitrene formation reaction

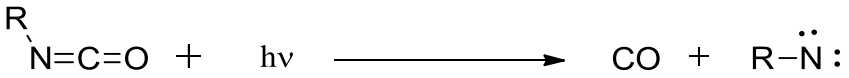
A nitrene (R-N:) is the nitrogen analogue of a carbene. The nitrogen atom in nitrene has six electrons available and is therefore considered an electrophile. The singlet with two paired sets of free electrons on the nitrogen, or the triplet with one pair and two electrons of parallel spins might be a priori of a ground state for a nitrene.[12] A nitrene is a reactive intermediate and is involved is many chemical reactions and, as such, cannot be isolated. They are formed as reactive intermediates as shown in scheme 5.



Scheme 5: Nitrene formation reactions

1.4.1.1 Decomposition of isocyanates[13]

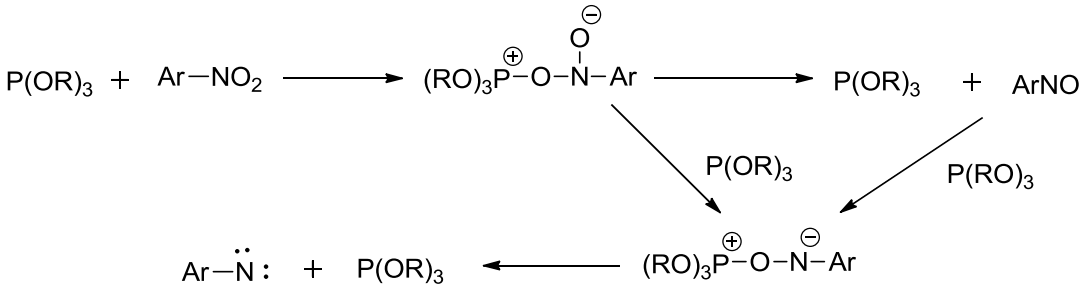
The nitrene could form from isocyanates with the expulsion of carbon monoxide, analogous to carbene formation from ketenes (scheme 6).



Scheme 6: Decomposition of isocyanates

1.4.1.2 Nitrene from nitro groups[14]

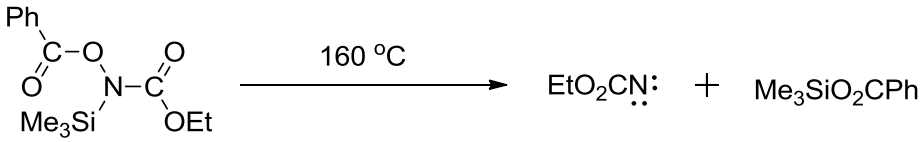
The aryl nitro compounds could rearrange to form aryl nitrenes in presence of phosphite (Scheme 7).



Scheme 7: Nitrene from nitro groups

1.4.1.3 Deoxysilylation of Organosilylated Hydroxylamine Derivatives[15]

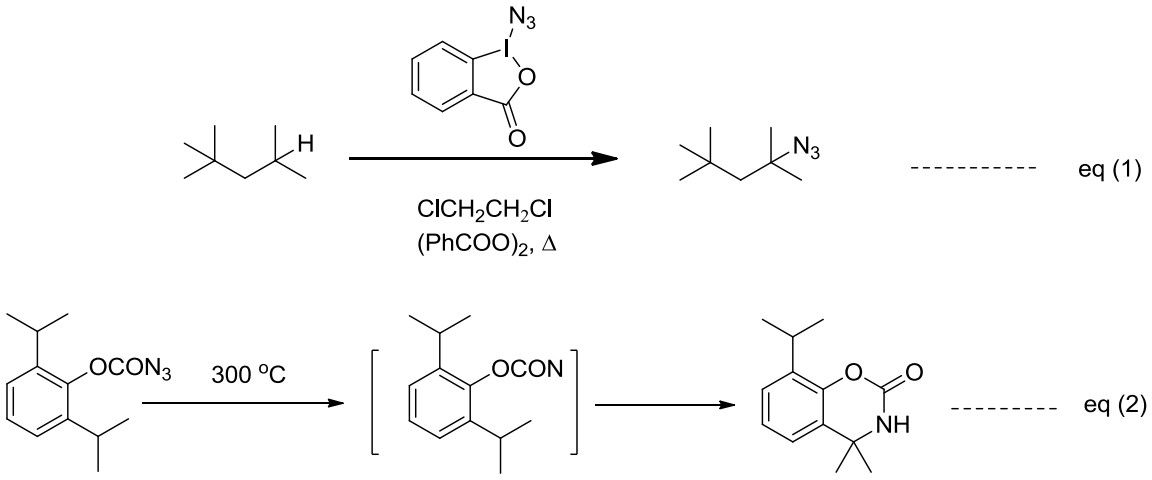
Thermolysis of organosilylated hydroxylamines ($EtO_2CN(OR')SiR_3$) in the presence of nitrene trapping agents has given products consistent with deoxysilylation; leading to EtO_2CN: (Scheme 8).



Scheme 8: Deoxysilylation of Organosilylated Hydroxylamine Derivatives

1.4.1.4 Thermolysis or photolysis of azides

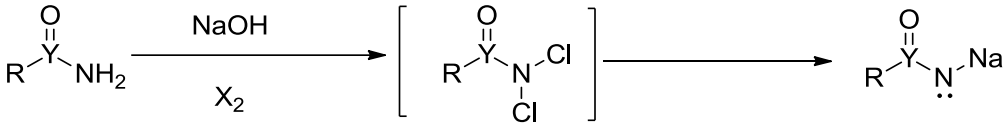
The decomposition of an azide forms the nitrene. The sulfonyl azide could photochemically decompose and form nitrene. This sulfonyl nitrene undergoes C-H insertion reaction. Hydrocarbons can also undergo radical aziridation at high temperatures with the somewhat more stable hypervalent iodo reagent (equation 1).[16] In the case of the 2,6-di-isopropylphenyl azidoformate the derived nitrene inserts into the reactive tertiary C-H bond to give benzoxazinone (equation 2).[17]



Scheme 9: Thermolysis of azides

1.4.1.5 Preparation from Carbamate or Sulfamate ester[18]

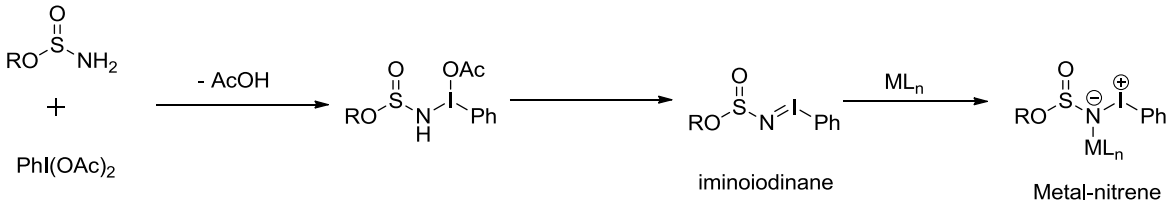
Sulfamate and carbamate esters can form from in-situ generated nitrene when reacted with commercially available bleach (Sodium hypochlorite) (Scheme 10). These nitrenes can undergo C-H bond activation/ aziridination to form environmental friendly sodium chloride as a by-product. The commercially available chloramine-T is made from toluene sulfonamide.



Scheme 10: Preparation of haloamine

1.4.1.6 Metal-Nitrene formation

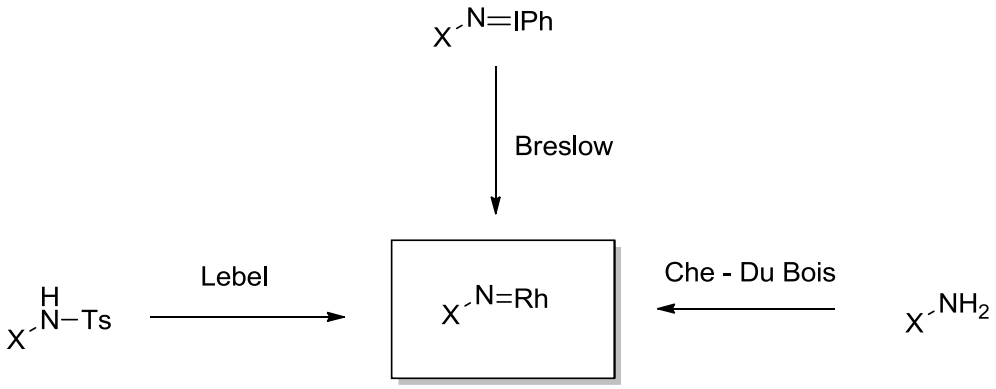
Imido metal complexes are classified as those species that contain the M=NR unit (M=metal). The R group can be hydrogen, alkyl, aryl, alkoxy, or trimethyl-silane, singly bonded to the nitrogen atom. The M-NR moieties of a complex are termed transition metal-imido or -nitrene, depending on whether the nitrogen is electron rich or electron deficient. The sulfamates or sulfonamides can react with hypervalent iodine and form imino-iodinanes (scheme 11). [19]When this imino-iodinane reacts with a suitable transition metal, it potentially forms a metal nitrene as an intermediate.



Scheme 11: Metal nitrene formation

Scheme 12 shows routes to common Rhodium nitrene intermediates. The generally applicable procedure, pioneered by Breslow, [20(a,b)] was to use hypervalent iodine. Che[11(c)] and Du Bois[11 (d,e)] discovered an improved process, in which the iodinane is generated in situ, thereby opening up the chemistry to a range of primary amide and sulfonamide substrates. The mechanistic studies indicate that Rh-nitrenes form during the

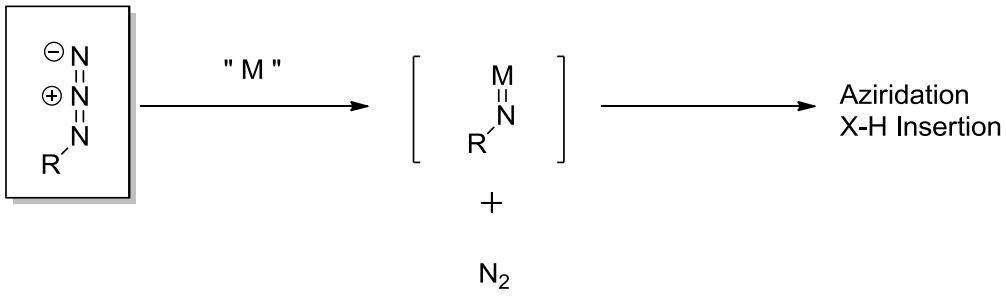
C-H bond activation process. One of the major drawbacks associated with the use of hypervalent iodine reagents is the generation of a stoichiometric amount of iodobenzene. Lebel[11(f)] showed, a rhodium-catalyzed decomposition of N-tosyl-oxy-carbamates to produce metal nitrenes, which undergo either C-H insertion or aziridination reactions with high yields and chemoselectivity. In their control experiments they showed that both the rhodium catalyst and the base are required for N-tosyl-oxy-carbamates to react. Coordination of the rhodium dimer with N-tosyl-oxy-carbamates is required prior to deprotonation with the base that leads to the active species. This approach also has great synthetic potential.



Scheme 12: General ways for making rhodium nitrene

More recently, there have been reports on the activation of azide derivatives with transition-metal complexes.[21] In contrast to the well-defined reactivity of diazo compounds with transition-metal complexes, examples of such reactions with azides are scarce. Some studies for the activation of acyl azides with transition-metal complexes shows the formation of nitrene species, which could undergo aziridination and C–H insertion reactions (scheme 13). The reaction with alkyl azides in the presence of a transition metal supposedly involves the loss of nitrogen and formation of a metal nitrene

complex.



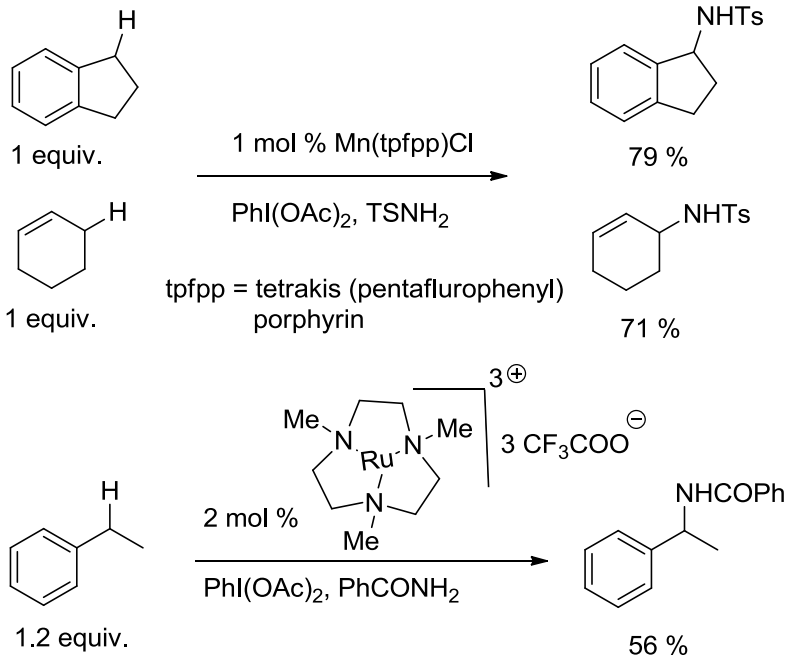
Scheme 13: Metal nitrene from azides

1.4.2. Intermolecular amination

Intermolecular transition metal catalyzed C–H amination reactions are more challenging, and they have been far more extensively investigated than their intramolecular counterparts. A high degree of chemo- and regio-selectivity was achieved by the intramolecular insertion of nitrene complex. In the intramolecular C–H activation, the chelation effect brings the metal into the vicinity of the C–H bond to be cleaved. There are some challenges associated with intermolecular amination e.g. over oxidation, formation of metal nitrene and regio-selectivity. The over-oxidation could be minimized by using excess equivalent of substrates. The regio-selectivity could be addressed by the amination of activated C–H bonds, i.e. benzylic and allylic C-H bonds, which displays higher reactivity vis-a`-vis the electrophilic metallonitrene. Despite significant work in this area, the scope of intermolecular C–H amination reactions generally remains limited to the functionalization of highly activated benzylic or allylic C–H bonds. Here we are discussing some well-established methods of intermolecular C-H amination.

1.4.2.1. Che's Amination

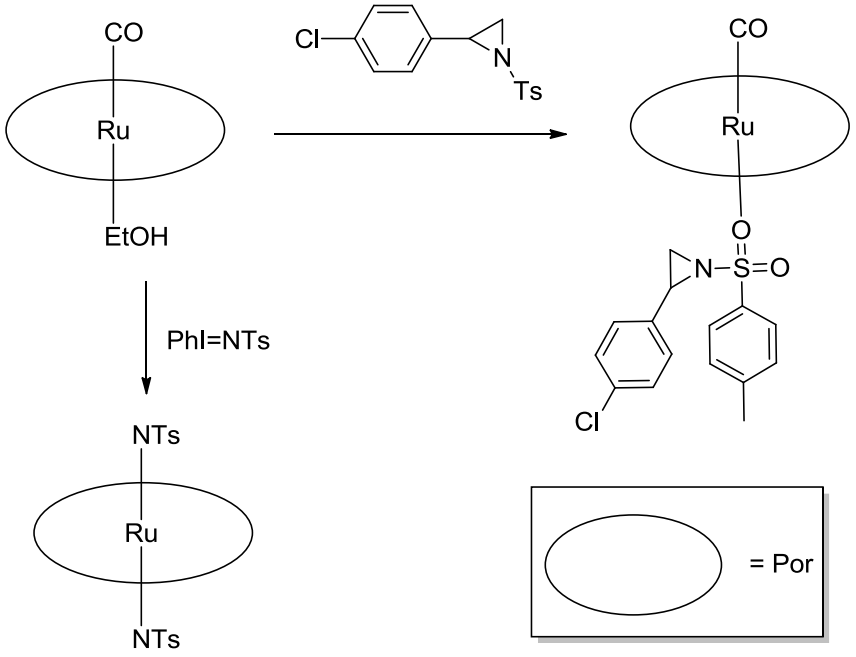
The first intermolecular amination using imino-iodinanes was established with ruthenium and manganese meso-tetrakis(pentafluorophenyl)porphyrin complexes and afforded N-substituted amides with a very high turnover number (2600) . The amination of hydrocarbons (Scheme 14) is shown below.[22]



Scheme 14: Ruthenium and manganese-catalyzed amination

In their following work Che's group investigated the nitrogen group-transfer reactions (Scheme 15) with PhI=NTs and varieties of hydrocarbons and alkenes catalyzed by chiral metalloporphyrins [Mn(Por)(OH)(MeOH)] and [Ru(Por)(CO)(EtOH)]. The isolation of the aziridination- and amidation-active chiral imido ruthenium porphyrin [Ru(Por)$(NTs)_2$] and the ruthenium porphyrin aziridine adduct [Ru(Por)(CO)(TsAz)],TsAz=N-tosyl-2-(4-chlorophenyl)aziridine) with an oxygen bound rather than a nitrogen-bound aziridine ligand has provided useful insight into the

mechanism of asymmetric nitrogen-atom-transfer reactions catalyzed by [Ru(Por)(CO)(EtOH)].[23]



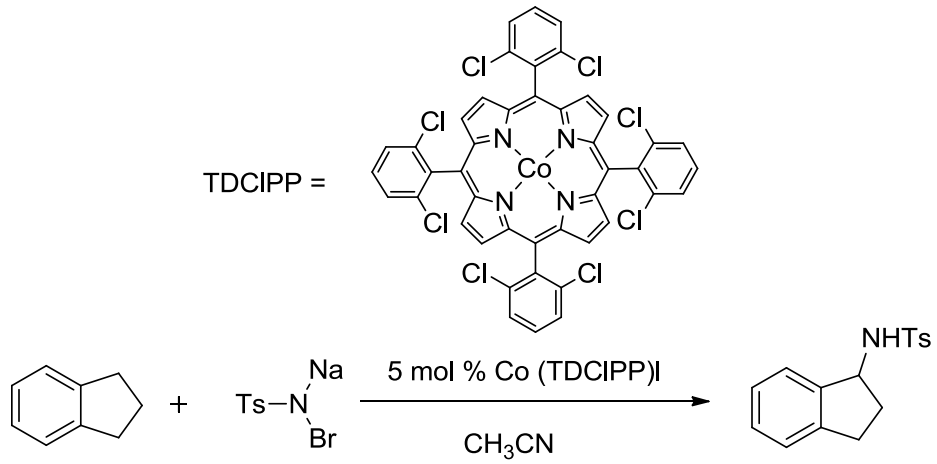
Scheme 15: Mechanism of asymmetric nitrogen-atom-transfer reactions

In their intermolecular amination reaction, Che's group showed that a diverse set of activated substrates, including adamantane, tetrahydrofuran, trans-3-hexene, ethylbenzene and cyclohexene, are aminated efficiently without the requirement for an excess of organic substrate relative to the oxidant. In presence of the chiral ruthenium porphyrin the hydrocarbons undergoes an enantioselective asymmetric amination (56 % ee) with iminoiodanes.

The notable limitation of this system is that large excesses of oxidant (PhI=NTs) relative to substrate are required in order to achieve good yields. The oxidant (PhI=NTs) produces stoichiometric amount of iodobenzene (PhI). The use of expensive ruthenium (Ru) and the synthesis of bulky porphyrins could be another limiting factor.

1.4.2.2. Zhang's Amination

The capability of cobalt-porphyrins [Co(TDClPP)] to catalyze intermolecular nitrene insertion of benzylic C–H bonds with bromamine-T at room temperature was shown by Zhang's group (Scheme 16).[24] Bromamine-T reacted with a limited number of benzylic hydrocarbons such as indane and 1,2,3,4-tetrahydronaphthalene, and produced good yields of amination products.

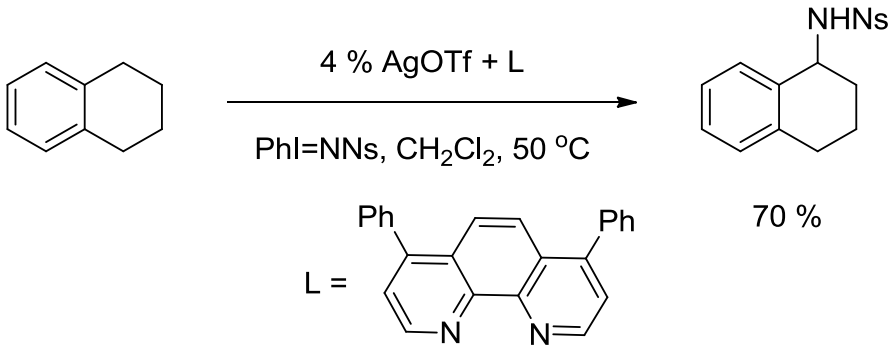


Scheme 16: Cobalt catalyzed amination

The biggest advantage of their method was the mild reaction condition, use of cheap cobalt as the transition metal, and the use of bromamine-T as the nitrene source. The bromamine-T produces environmentally friendly NaBr as the by-product. The limitations of their systems are the substrate scopes are really limited and synthesis of porphyrin. The use of 10:1 ratio of substrate to bromamine-T is also noteworthy. Although the reaction is really attractive but could not be useful for a total synthesis.

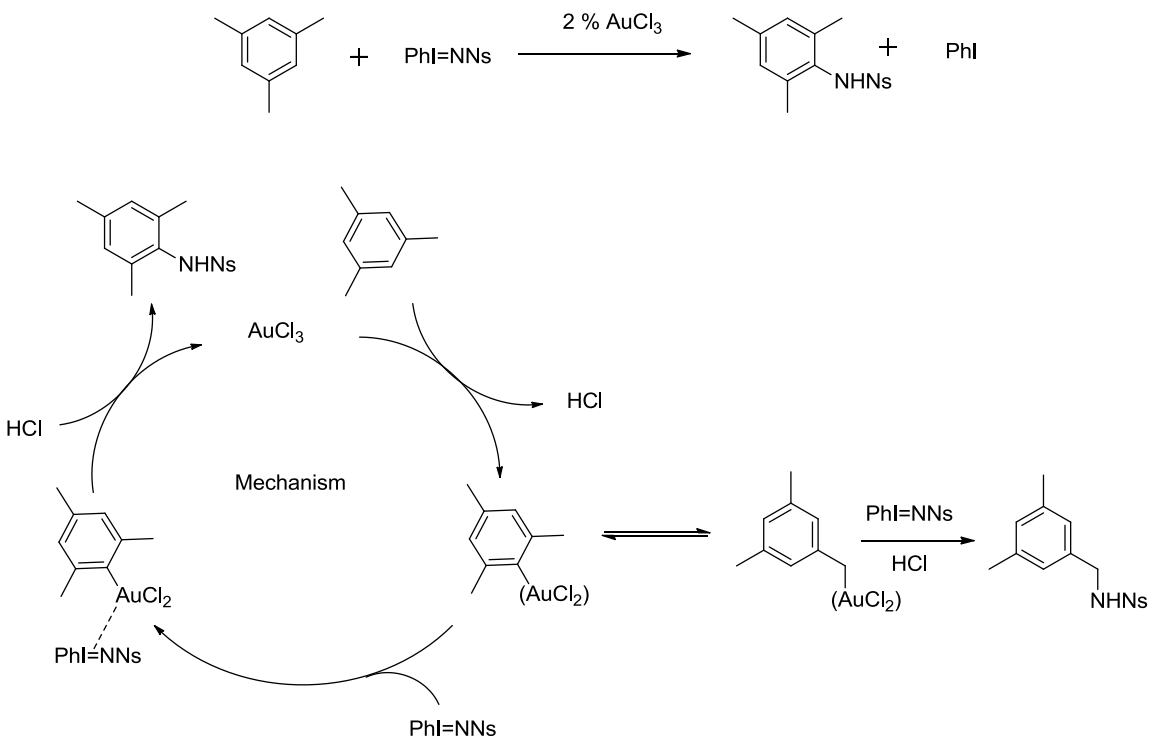
1.4.2.3. He's Amination

Silver (I) complexes with phenanthroline ligands react with PhI=NNs (NS= 4-nitrobenzenesulfonyl) and inserts nitrogen into benzylic position (Scheme 17).[25] The C-H functionalization with the disilver(I) catalyst $[Ag_2(tBu_3{}^tpy)_2(NO_3)](NO_3)]$ indicates that the dinuclear core catalyzes nitrene transfer oxidation chemistry in silver complexes. The significant limitation of this system is that it uses large excesses of substrate relative to PhI=NNs and thus would not be useful synthetically.



Scheme 17: Silver catalyzed amination

The gold-catalyzed nitrene insertion into aromatic and benzylic C-H bonds at room temperature was also reported with PhI=NNs and suitable hydrocarbons (Scheme 18).[26] It was hypothesized that the aryl gold(III) species is generated from the reaction of $AuCl_3$ and an aromatic C-H bond. The PhI=NNs was inserted into the aryl gold(III) center and reductive elimination makes the aminated product. In the presence of weak benzylic C-H bonds, it is suggested that gold(III) displaces a benzylic proton to form a carbon gold(III) bond via formation of aryl gold(III) in the first step followed by migration to the benzylic position.



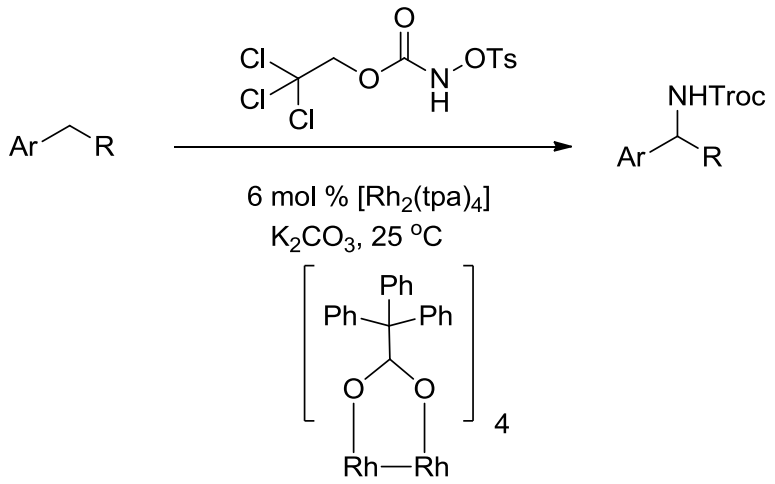
Scheme 18: Gold catalyzed amination reaction

1.4.2.4. Lebel's Amination

The most extensively studied intermolecular amination systems are with *troc-protected amines (Troc*=trichloro-ethoxycarbonyl*).*[23] They serve as a useful source of metal nitrenes from rhodium-catalyzed C-H activation. The N-Tosyloxycarbamates are stable and easy to prepare and handle and the reaction also works under mild reaction conditions. Intermolecular amination produces the Troc-protected amines (Scheme 19). The rhodium-catalyzed intermolecular C-H insertion with N-tosyloxycarbamates and aliphatic alkanes produces moderate to good yield (~87%) of trichloroethoxycarbonyl-protected amines. The amination reaction also showed excellent selectivity with aromatic alkanes. The potassium tosylate is the only stoichiometric byproduct produced in this reaction. The stereospecificity observed for the reaction with chiral substrates and the no

fragmentation with the "radical clock" substrate suggests that a singlet rhodium nitrene is the reactive intermediate. The singlet rhodium nitrene guides the C-H insertion step through a concerted reaction pathway.[27]

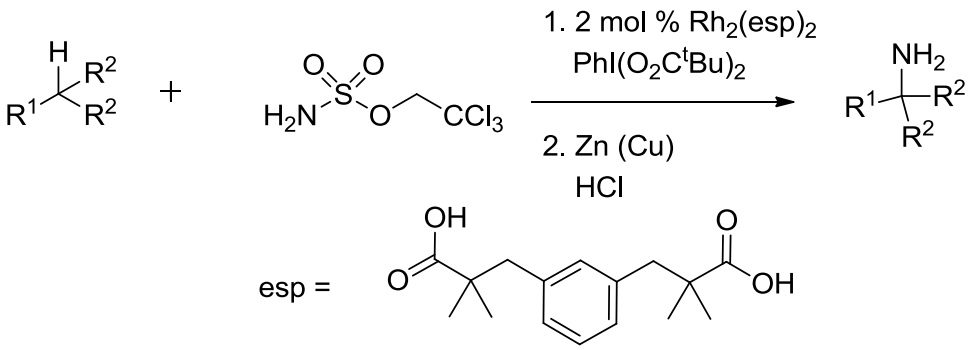
The use of N-tosyloxycarbamates and the formation of the less environmentally hazardous potassium tosylate are the advantages for this intermolecular amination. The limitation of this system is the use of five equivalents of substrate in order to achieve good yields. To use this methodology in total synthesis, it is important to minimize the use of substrate. The usage of expensive rhodium (Rh) and the synthesis of rhodium(II) triphenylacetate ligands could deter its use on an industrial scale.



Scheme 19: Rhodium catalyzed amination

1.4.2.5. Du-Bois's Amination

The di-Rh tetra-carboxylate ($Rh_2(esp)_2$)-catalyzed (esp= (α,α,α'α'-tetramethyl-1,3-benzenedipropionic acid) intermolecular C-H amination of various benzylic and 3° substrates in presence of $TcesNH_2$ ($TcesNH_2$=trichloroethylsulfamate)and an iodine (III) oxidant is one of the nice additions in this C-H activation (Scheme 20).[28]



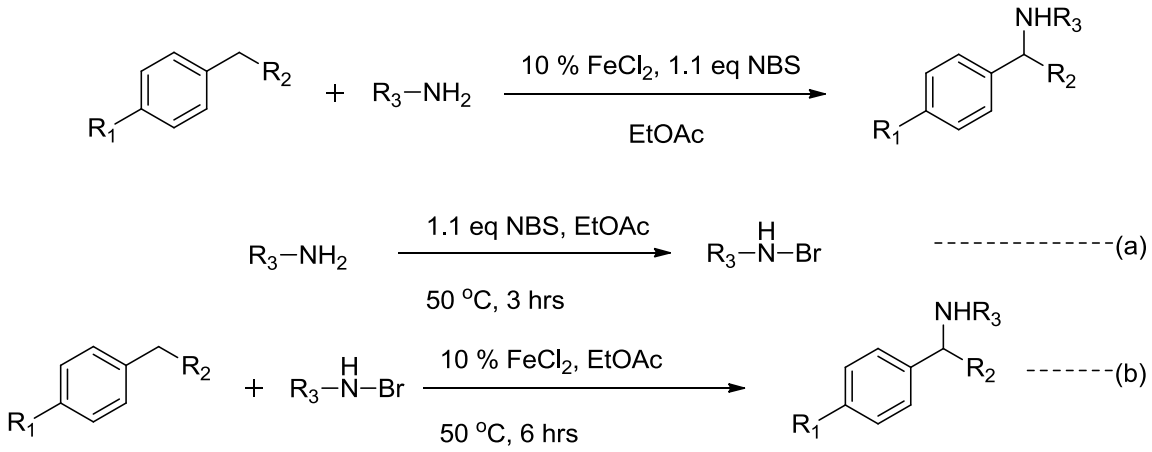
Scheme 20: Rhodium catalyzed amination by using Tces

The best part of the reaction is the use of more soluble $PhI(O_2C^tBu)_2$ than insoluble $PhI(OAc)_2$. A significant limitation of this system is the use of 2 equivalent of oxidant ($PhI(O_2C^tBu)_2$) relative to substrate are required in order to achieve good yields. Tertiary substrates used as the solvent could react with the nitrene. The oxidant (PhI=NTces) produces the stoichiometric amount of iodobenzene (PhI). The use of expensive rhodium (Rh) and the synthesis of the esp ligands are other limitations.

1.4.2.6. Fu's Amination

Fu's group developed an efficient, inexpensive, and air-stable $FeCl_2$/NBS-mediated amidation of benzylic C-H bonds (Scheme 19). The NBS (N-bromosuccinimide) could react with the sulfonamide or carboxamide to produce N-bromosulfonamide or N-bromocarboxamide respectively (Scheme 21, equation a). The resulted N-bromosulfonamide could react with the $FeCl_2$ and form a metal nitrene complex (Scheme 21, equation b). This metal nitrene could insert into benzylic C-H bonds to form the amination products.[29]

An advantage of this NBS mediated aminations is the ability to run these reactions on the bench top without taking any precaution. The inexpensive and readily available catalyst-oxidant ($FeCl_2$/NBS) is an added advantage. The limitations of their system are the substrate scope is really limited and the creation of a radical intermediate. Although the reaction has lot of nice features, it will be very difficult to control the stereoselectivity on the benzylic carbon.

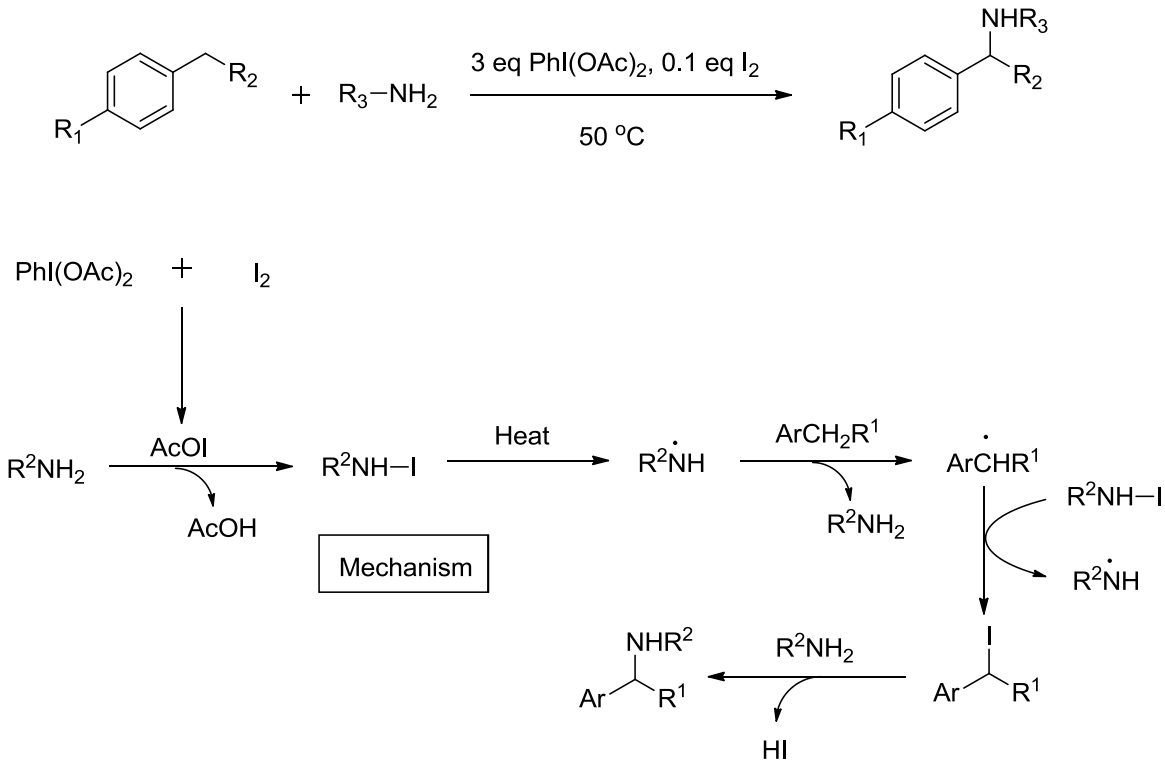


Scheme 21: Iron-catalyzed amination

1.4.2.7. Fan's Amination

Amination with a nitrene source but without using a transition metal catalyst is one of the recent developments in this field (Scheme 22).[30] Fan's group have developed a direct transitionmetal free amination of sp^3 C-H bonds with sulfonamides activated by the combination of iodobenzene diacetate and a catalytic amount of iodine. With this system, benzylic hydrocarbons are preferentially N-functionalized to afford amines, amino alcohol, α-, and β-aminoesters. Sulfonamidyl radicals, which are generated from the

reactions of sulfonamides with acetyl-hypoiodite, could be important intermediates for the amination reaction. A broad range of benzylic hydrocarbons are N-functionalized with this reaction.

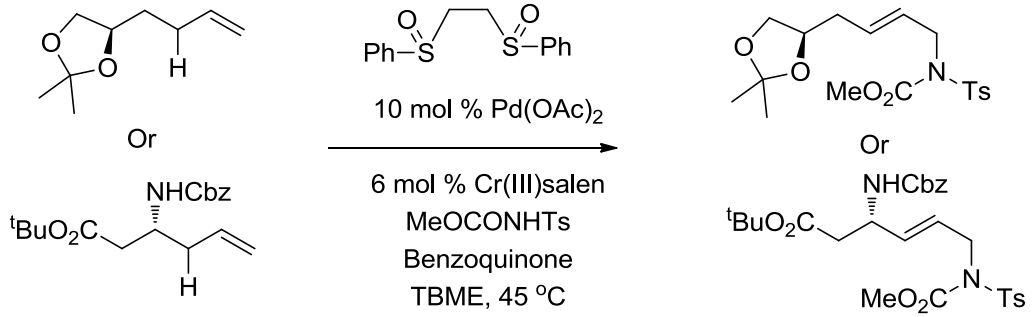


Scheme 22: Iodine catalyzed amination

The advantages of transition metal free aminations are its applicability in industry and its environmental friendliness. The limitations of their systems are the substrate scopes are limited to benzylic C-H and usage of a three-folds excess of substrate to tosylsulfonamide. The iodine-induced activation of the sp^3 C-H bonds with toluene showed expected benzylic sulfonamides and also unexpected aryl sulfonylimines. The secondary oxidation of the corresponding benzylic sulfonamides produces aryl sulfonylimines; so this system is not chemoselective.

1.4.2.8. White's Allylic Amination

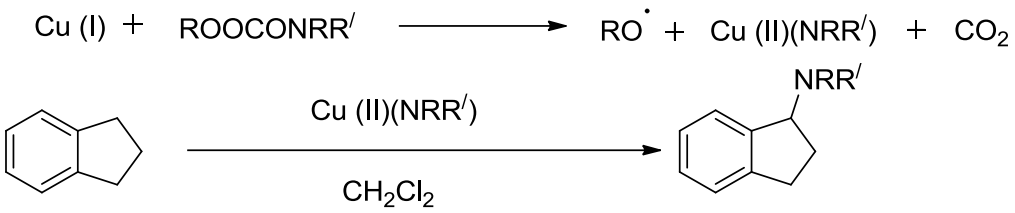
White's group demonstrated that the bis-sulfoxide/$Pd(OAc)_2$ catalyst promotes intermolecular allylic C-H amination of R-olefins with a N-tosyl carbamate nucleophile. (scheme 23).[31] In terms of regioselectivity, this procedure complements the former intramolecular version, wherein the internal nucleophilic delivery directs the substitution to the secondary allylic position. The allylpalladium intermediate, once again generated after Pd(II)–bis-sulfoxide-induced C–H cleavage, undergoes amination at the primary site and the final step was promoted by the Cr(III)salen complex in conjunction with benzoquinone.



Scheme 23: Allylic amination by using palladium

1.4.2.9. Katsuki's Amination

Katsuki's group used p-toluene sulfonamide as an aminating reagent for allylic and benzylic amination by using modified Kharash-Sosnovsky reaction condition.[32] The benzylic amination was done in presence of Cu(I) triflate and using t-butyl N(-p-toluenesulfonyl)peroxycarbamate as the oxidizing reagent. The reaction between Cu(II) and the alkyl peroxycarbamate could give an alkoxy radical and Cu(II)($NRR^{/}$) species which may effect the amination of allylic and benzylic position (Scheme 24).



Scheme 24: Copper catalyzed amination

A significant limitation of this system is that a large excess of substrate relative to aminating reagent are required in order to achieve good yields, and so it would not be very useful synthetically.

Katsuki's group also reported C-H amination by using the tetrabromo-substituted (salen) manganese(III) complex (Scheme 25).[33] The advantages of this amination are the abilities to achieve good to high enantioselectivity with a cheap transition metal and readily synthesizable ligands. The limitations of their systems are the limited substrate scope and the creation of phenyl iodide as a byproduct.

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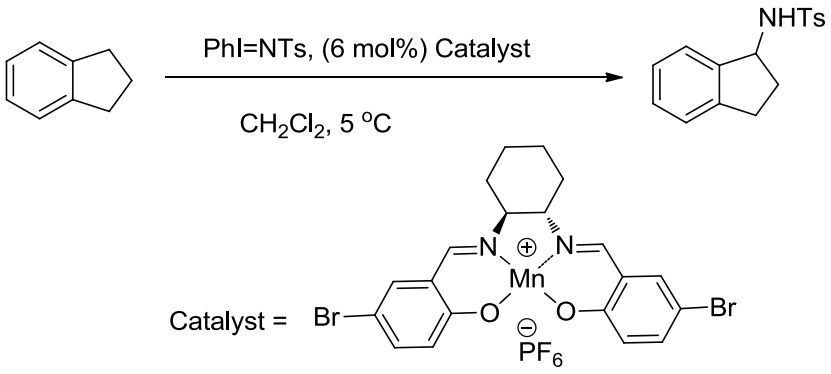
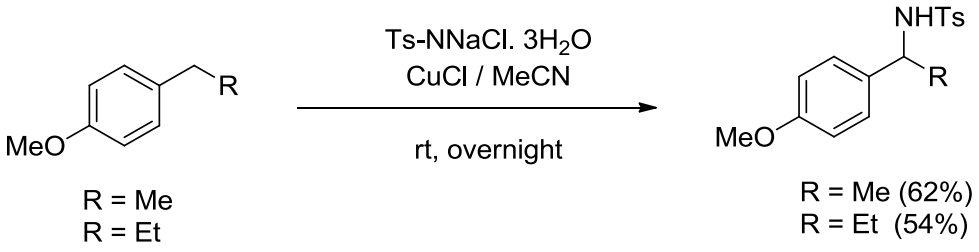


Scheme 25: Manganese catalyzed amination

1.4.2.10. Taylor's Amination

Taylor's group showed that amination of C–H bonds activated by ether oxygen atoms is facile with hydrated chloramine-T as nitrene source and copper (I) chloride in acetonitrile as catalyst. The activated benzylic positions were more likely to produce C-H amination product (scheme 26).[34] The limitations of their systems are limited substrate scopes and hydrated chloramine t was not a good aminating reagent as it produce more tosyl amide in the reaction.



Scheme 26: Copper catalyzed amination with haloamine

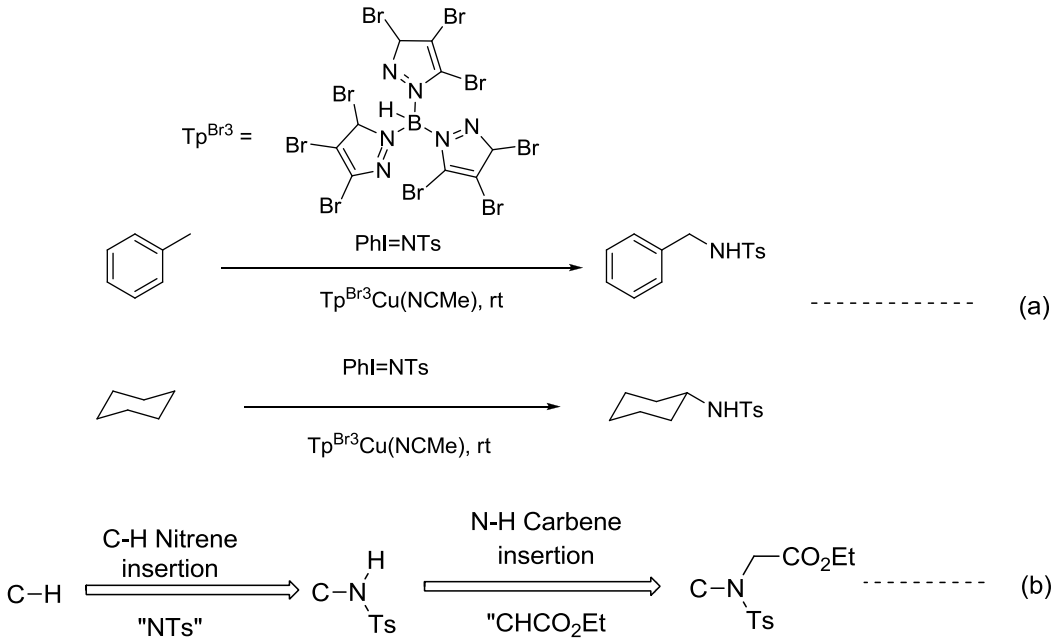
1.4.2.11. Perez's Amination

Perez and co-workers used the copper (I)-homoscorpionate $[Tp^{Br3}Cu(NCMe)]$[35(a)] complexes as catalysts for the amination of C-H bonds (Scheme 27, equation a) with imino-iodinane. They have discovered that the complex $Tp^{Br3}Cu(NCMe)$ catalyzes the insertion of a nitrene group into the carbon-hydrogen bond to diverse hydrocarbons e.g. cyclohexane, benzene, as well as into the primary C-H bonds of the methyl groups of toluene and mesitylene, in moderate to high yield.

The regio-selectivity of their amination follow the general trend; tertiary sites > secondary sites > primary sites. The significant limitation of this system is that large

excesses of substrate relative to stoichiometric oxidant (PhI=NTs) are required in order to achieve good yields and isolation of iodobenzene is produced in stoichiometric amounts. The consecutive nitrene and carbene insertions are also possible with the one-pot C-H amination and followed by carbene insertion (Scheme 27, equation b).

They have also studied the use of copper (I)-homoscorpionate [$Tp^{Br}_3Cu(NCMe)$] with inexpensive, commercially available chloramine-T for the intermolecular amination process. They also use this methodology for amination of toluene, mesitylene, and tetrahydropyran, etc. The significant limitation of this system is that large excesses of substrate relative to amination reagent are required in order to achieve good yields.



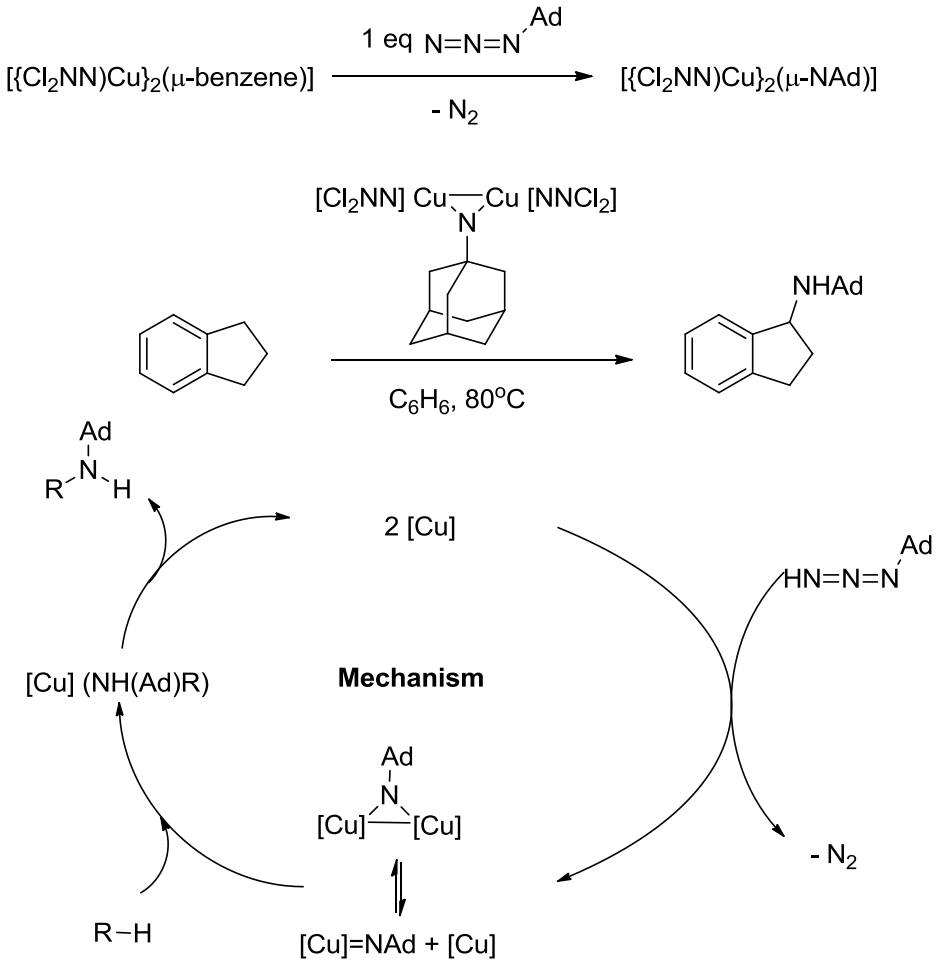
Scheme 27: Amination catalyzed by $Tp^{Br}_3Cu(NCMe)$

1.4.2.12. Warren's Amination

Warren's group has investigated the discrete dicopper nitrene intermediates, $[[Cu]_2(\mu\text{-NAd})]$;[36] ; reported to behave as nitrene source for the insertion into C-H bonds. The reaction of 1-adamantylazide (N_3Ad) with $[\{(Me_3NN)Cu\}_2(\mu\text{-toluene})]$ in diethyl ether produces green crystals $[\{(Me_3NN)Cu\}_2(\mu\text{-NAd})]$. This copper complex induces the C–H functionalization of various hydrocarbons with good yields. For a hydrocarbon with weaker benzylic C-H bonds, results suggests that nitrene C-H insertion is rate limiting than dissociation of a $[(Cl_2NN)Cu]$ fragment (Scheme 28).

The significant limitation of this system is that large excesses of substrate relative to $[[Cu]_2(\mu\text{-NAd})]$, are required in order to achieve good yields, and so it would not be useful synthetically.

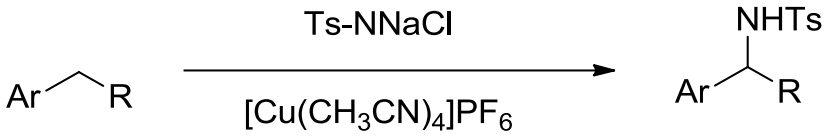
The complete active space self-consistent field (CASSCF)/MM hybrid methods was employed to calculate the energies of the $[(Cl_2NN)Cu{=}NAd]$ and it's C-H insertion transition state. The outcome of their calculation was finding the ground state to be a singlet. The singlet ground state of $[(Cl_2NN)Cu{=}NAd]$ is calculated to be 18 kcal/mol below that of the triplet state. The triplet state of $[(Cl_2NN)Cu{=}NAd]$ has a more linearly coordinated nitrene ligand and the singlet ground state has a bent nitrene coordination. This bent arrangement of the nitrene ligand permits the access of a wider array of hydrocarbon substrates at the copper–nitrene active intermediate.



Scheme 28: Copper catalyzed amination with adamantyl azide

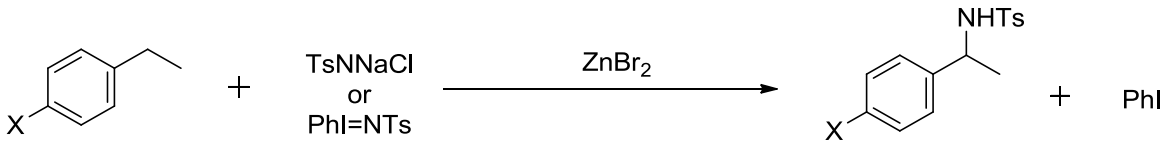
1.4.2.13. Nicholas's Amination

Benzylic hydrocarbons are selectively converted to the corresponding sulfonamides by the $[Cu(CH_3CN)_4]PF_6$-catalyzed reaction with anhydrous $TolSO_2NNaCl$ (chloramine-T). Similarly, ethers are also α-amidated; olefins produce allyl sulfonamides. The study also showed that NaCl is the by-product generated in this case (scheme 29).[37]



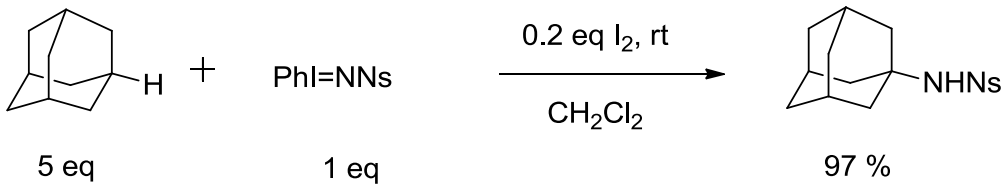
Scheme 29: Copper catalyzed amination with dry chloramine-T

Despite these significant achievements, improvements were needed in terms of efficiency and selectivity in order to dispose of a general method for intermolecular C–H amination. Our group is trying to develop new catalytic amination reactions using inexpensive N–reagents and catalysts. We found that benzylic and allylic hydrocarbons are selectively converted to the corresponding sulfonamides by a $ZnBr_2$–H_2O-catalyzed reaction with PhI=NTs (Scheme 30).[38]



Scheme 30: Zinc catalyzed amination

In their follow up study Lamar found[39] that 1°, 2°, and 3° benzylic substrates, along with some saturated and unsaturated hydrocarbons, can be aminated by the reaction of PhI=NNs catalyzed by inexpensive iodine (I_2). This is the first non-metal-catalyzed system utilizing imido-iodinane reagents to efficiently aminosulfonate benzylic hydrocarbons as well as saturated hydrocarbons (Scheme 31). It showed that it reacted with the unreactive adamantane. A limitation of this chemistry is that it uses an excess equivalent of the hydrocarbon over the amination reagent. This chemistry is more economical to run but could not be useful for the total synthesis of natural products.



Scheme 31: Amination using a catalytic amount of iodine

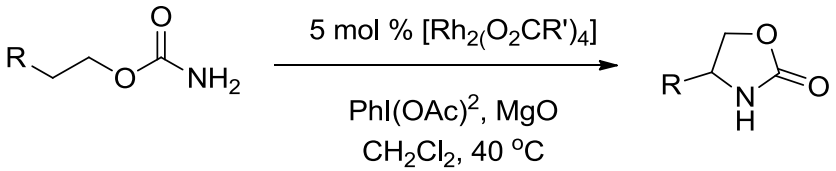
1.4.3. Intramolecular amination

Vicinal amino alcohols are common building blocks in both naturally occurring molecules and pharmaceutical agents. The large number of applications for β-hydroxy amines in synthetic, medicinal, materials, and coordination chemistry are the important factors for development of methods for their construction. To create the vicinal amino alcohols building blocks are the intramolecular C-H amination. The most synthetically useful recent developments in this C-H amination have involved intramolecular C–H insertion reactions. A number of groups have recognized the potential synthetic utility of this transformation and have begun to develop its scope. Herein we discuss some of the known intermolecular amination reactions.

1.4.3.1. Du-Bois et. al.

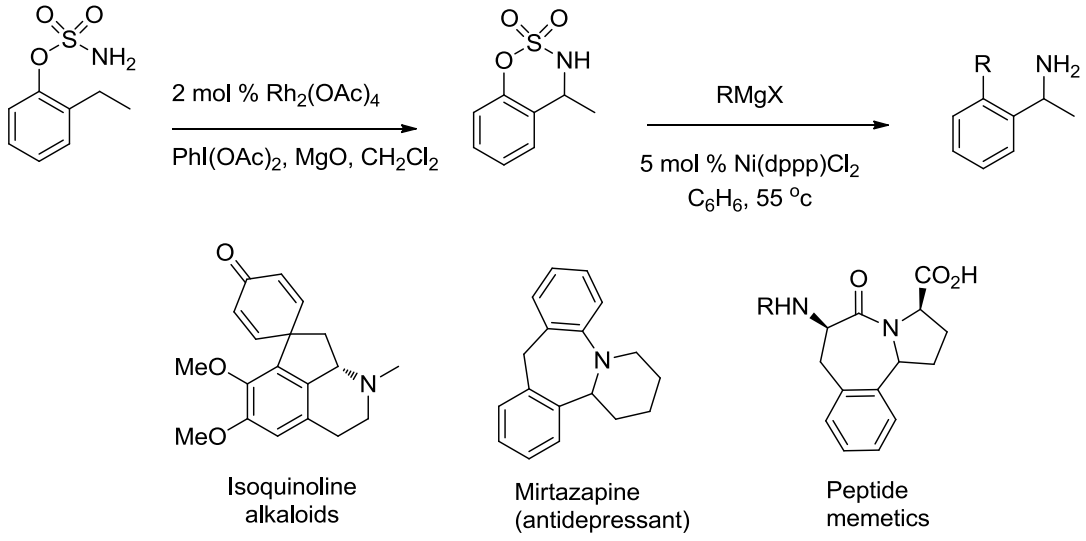
Based on Breslow's pioneering study of C-H activation,[11a] Espino and Du Bois developed selective insertions of nitrogen fragments into various C–H bonds. These C–H aminations involve the regio-selective internal delivery of a nitrene generated *in situ* by forming the imino-iodinane from a combination of iodobenzene di-acetate [$PhI(OAc)_2$] and MgO in the presence of a rhodium [Rh(II)] catalyst. The 1° carbamates are

transformed into oxazolidin-2-ones via C–H insertion at the β-position, whereas in the case of sulfamates, the reaction generally occurs at the γ-position, affording homologous 6-membered rings.[11d] Such findings serve to define a new, exceptionally versatile strategy for the preparation of 1,3-amino alcohols and related β-amino acids.[31]



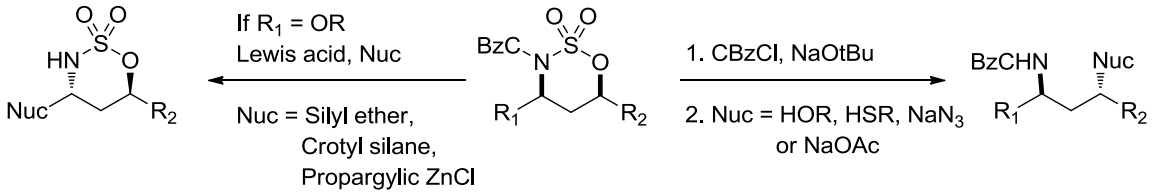
Scheme 32: Rhodium catalyzed intramolecular amination

Benzoxathiazine and related cyclic structures can serve as effective starting materials for cross-coupling reactions with Grignard reagents (Scheme 33).[11e] The combination of C-H amination and C-C bond formation are very important steps for preparation of various functionalized amines which constitute both natural and synthetic products.



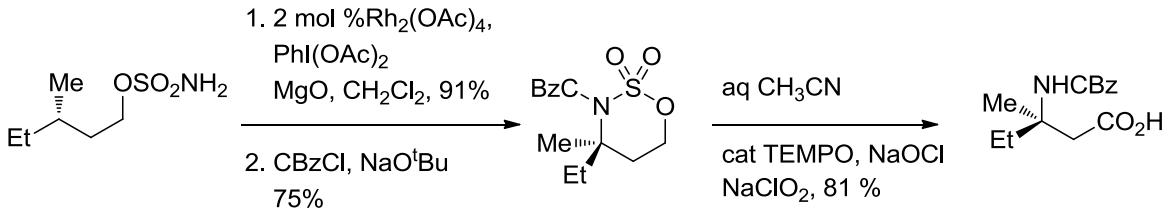
Scheme 33: Natural products from benzo-fused oxathiazinane heterocycles

These cyclic oxathiazinane products are synthetically useful intermediates. A N-, O-, or S-based nucleophile (e.g., amines, thiols, alcohols, H_2O, N_3^-, AcO^-) results in a nucleophilic ring opening to afford diverse 1,3-amino-functionalized products. In addition, the N,O-acetal products generated from C–N insertion serve as valuable precursors to iminium ions (via treatment with a Lewis acids), which can then undergo highly diastereoselective couplings with alkynyl zinc reagents, allyl silanes and silyl enol ethers (scheme 34).[11(d)]



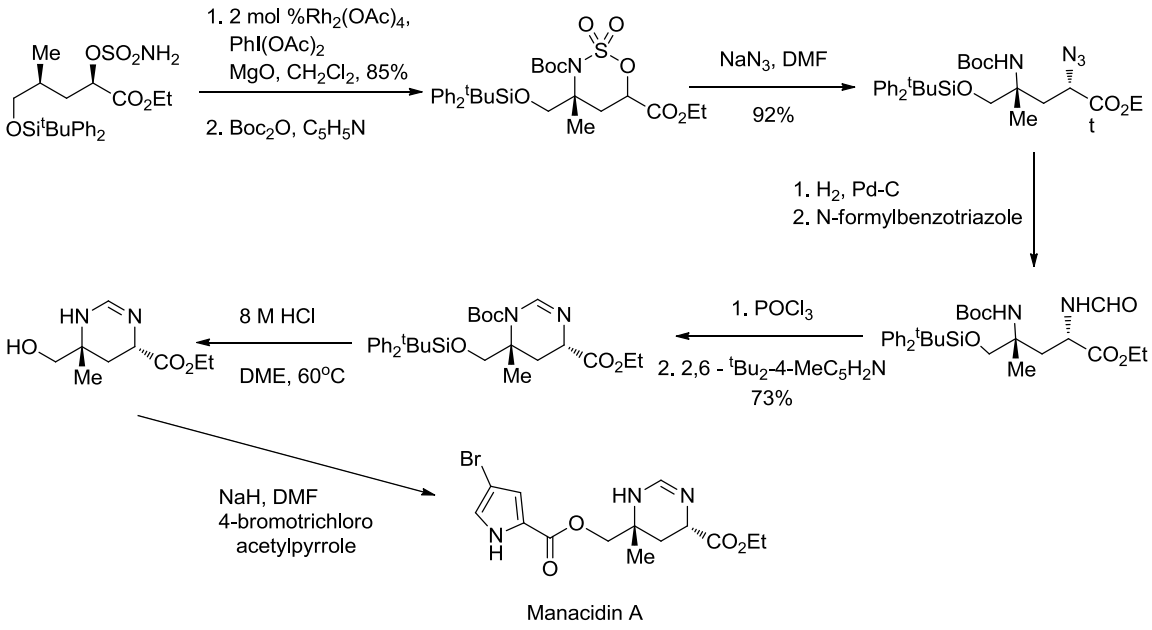
Scheme 34: Addition of nucleophile to the cyclic oxathiazinane

Du Bois's group has also achieved the oxathiazinane ring opening-oxidation and achieved the asymmetric synthesis of (R)-N-CBz-β-isoleucine (Scheme 35). One of the salient potentials of C-H insertion reaction is the synthesis of chiral β-amino acids and optically pure quaternary centers.[40]



Scheme 35: Oxathiazinane ring opening-oxidation

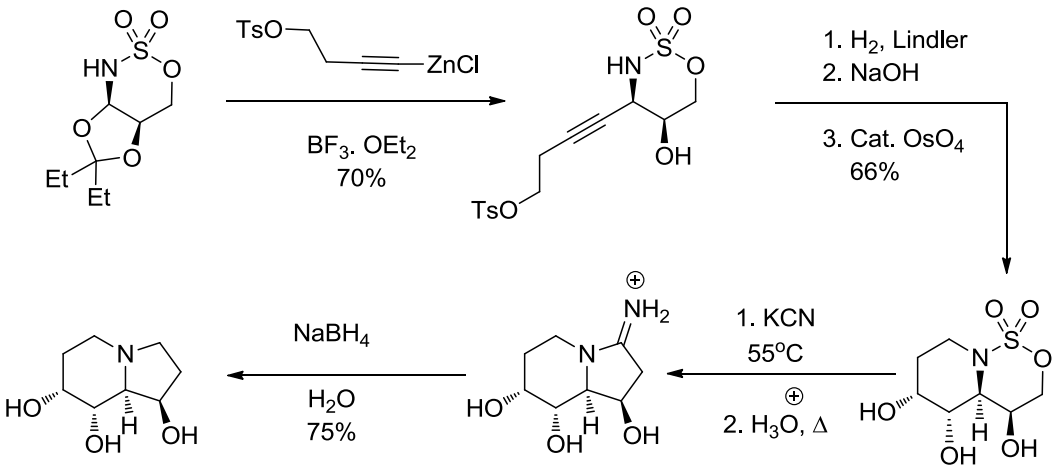
Bromopyrrole alkaloids are one of the main components in various marine natural products having potentially useful pharmacological activities e.g. α-adrenoreceptor blockers, seretonin antagonists, and actomyosin ATPase activators.[41] Oxidative C-H insertion of sulfamate esters with Rh catalysis occurs efficiently and with absolute retention of configuration at stereo defined tertiary centers. The product oxathiazinane was activated for nucleophilic ring opening to give 1,3-difunctionalized amine products. One application of this reaction sequence leads toward the synthesis of bromopyrrole alkaloids (Scheme 36).



Scheme 36: Preparation of bromopyrrole alkaloids

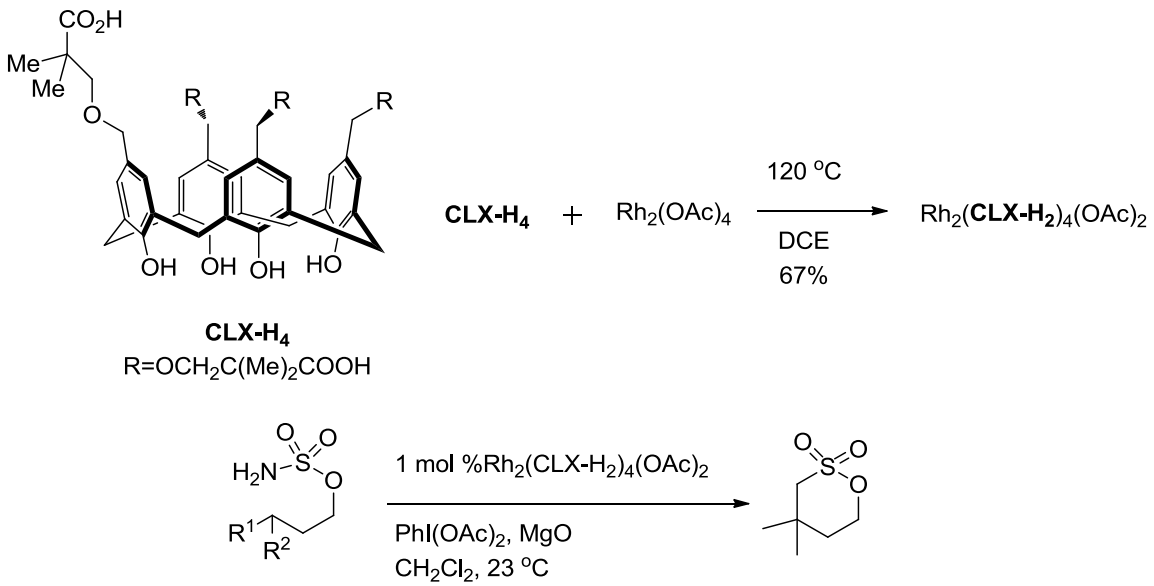
The oxathiazinane products isolated from N,O-acetals 1-5 are moderate electrophiles that undergo ring opening with agents e.g. CN^-, N_3^-, RS^-, and R_2NH. The potential of the alkynylated compounds are in the synthesis of poly-hydroxylated

indolizidines (scheme 37).[42]



Scheme 37: Synthesis of poly-hydroxylated indolizidine

Rhodium-catalyzed oxidative amination of saturated C–H bonds has advanced as one of the most important methods for the construction of stereoselective carbamine centers. The challenges associated with the design of a catalytic system being able to support a reactive oxidant that can discriminate between two hydrogen atoms on a prochiral methylene center are significant. Du-Bois's group has continued their studies towards new, robust catalyst systems capable of enhancing reaction yields and influencing product selectivity. The dinuclear Rh(II) catalyst, $Rh_2(esp)_2$ has enhanced the catalytic turnover number. Based on $Rh_2(esp)_2$ catalyst's crystal structure, they considered next generation catalyst designs using calixarane based platform where three or four carboxylate groups would be affixed to a common frame. The structure of the calixarane based ligand is shown below (scheme 38).[43]

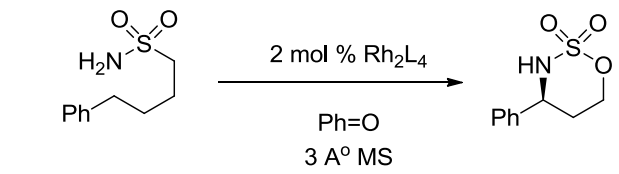


Scheme 38: Use of calixarane based ligands in amination

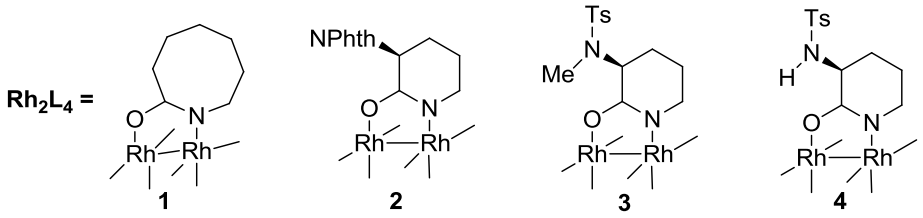
The two carboxylic acid groups which failed to adopt an equatorial mode of coordination instead occupy both axial sites along the Rh–Rh vector. The cis-equatorial sites along the Rh–Rh vector are absolutely necessary for getting stereoselectivity in the amination reaction.

The dirhodium tetracarboxylate complexes derived from α-amino acids shown poor enantiomeric results. Studies to evaluate % ee as a function of product conversion clearly established that the enantiomeric ratio was decreasing over the reaction time course. So the successful design was to change the lability of the bridging carboxylate groups. The carboxamidate groups increase the capacity of the dirhodium centers for back bonding to the π-acidic nitrene ligand, thus affording a more stable and potentially more discriminating oxidant. The resulting one-electron oxidation of rhodium when combined with $PhI(OAc)_2$ mixed-valent Rh^{2+}/Rh^{3+} dimer appears and the redox potential was measured as 11 mV. In order to promote nitrene-mediated insertion, it is important to

increase the redox potential of the catalytic reaction. The finding of the Du-Bois group is shown below (scheme 39).[44] The radical clock experiments shows no cyclopropane ring opening products obtained from the amination reaction and is consistent to a concerted, nitrene-type oxidation.



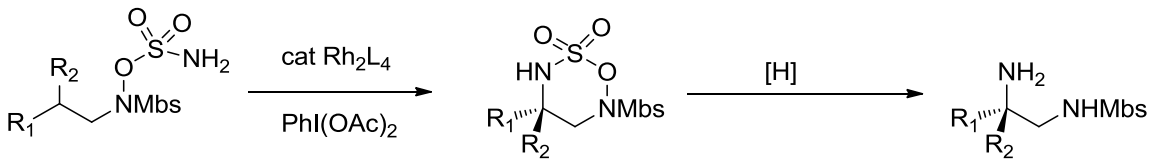
Rh_2L_4	E_{ox}	% yield	% ee
1	11 mv	≤ 5	-
2	120 mv	22	54
3	242 mv	≤ 5	nd
4	330 mv	85	92



Scheme 39: Designing of rhodium based ligands

With both carbamate and the sulfamates, it is recognized that the reaction takes place via a concerted insertion of a singlet metal bound nitrene, but a fast recombination of radical species.

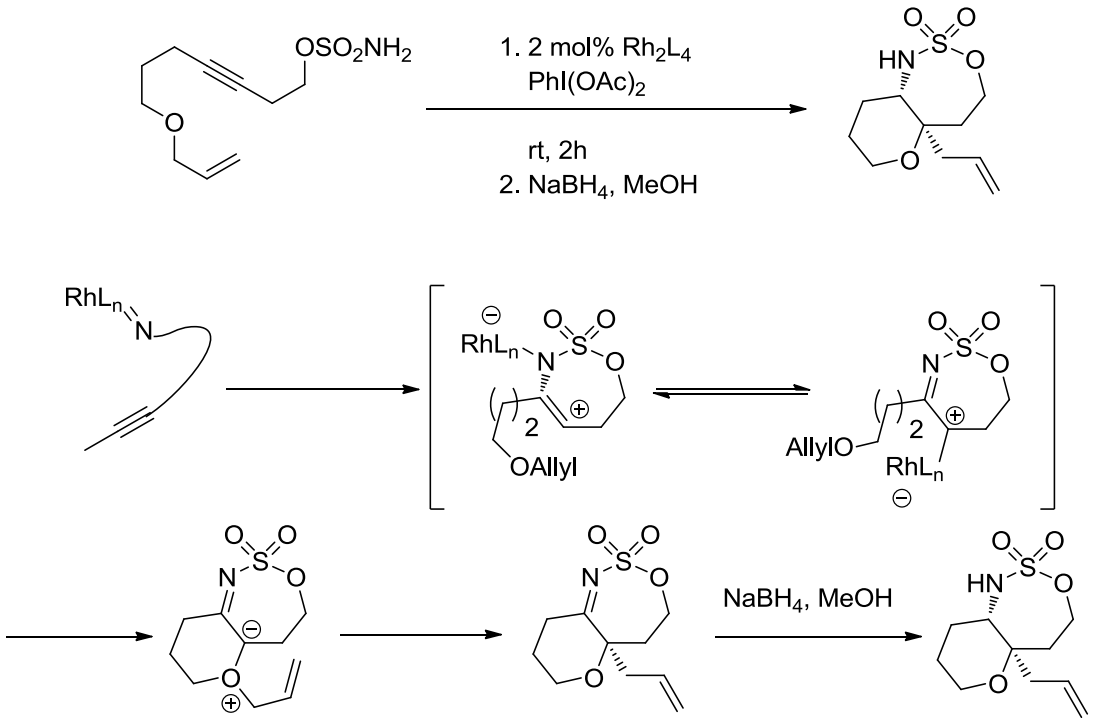
Vicinal diamines are one of the most important structural units in biological and medicinal molecules of interest. With the standard procedure to cyclize the sulfamate Du Bois's group created a unique method to create vicinal diamine (scheme 40). [11(e)]



Scheme 40: Preparation of vicinal diamines

1.4.3.2. Blakey et. al.

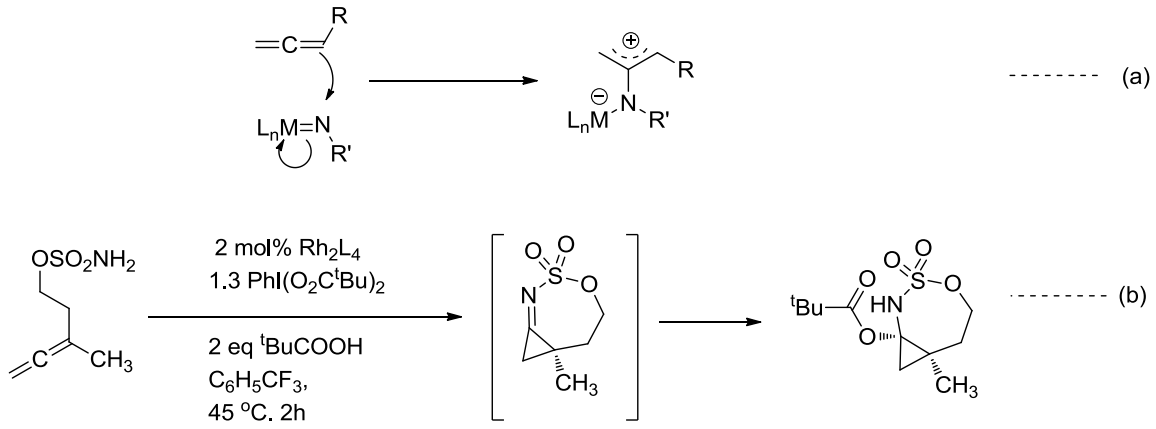
The development of a new metallonitrene/alkyne metathesis reaction is one of the most important applications of this intramolecular amination. Blakey's group discovered that metallonitrene species reacted with an alkyne, leading to a zwitterionic intermediate which undergoes a [1,3] metal shift to generate a new imine and a reactive metallocarbene to cascade into further C–C, C–O, or C–N bond-forming reactions (scheme 41).[45(a)]



Scheme 41: Metallonitrene/alkyne metathesis reaction

The interaction of a sulfamate ester derived metallonitrene with an allene generates a versatile intermediate. Electrophilic metallonitrene could react with an allene to generate a 2-amidoallylcation (1,3 dipole equivalent) and that could be useful for [4+3]

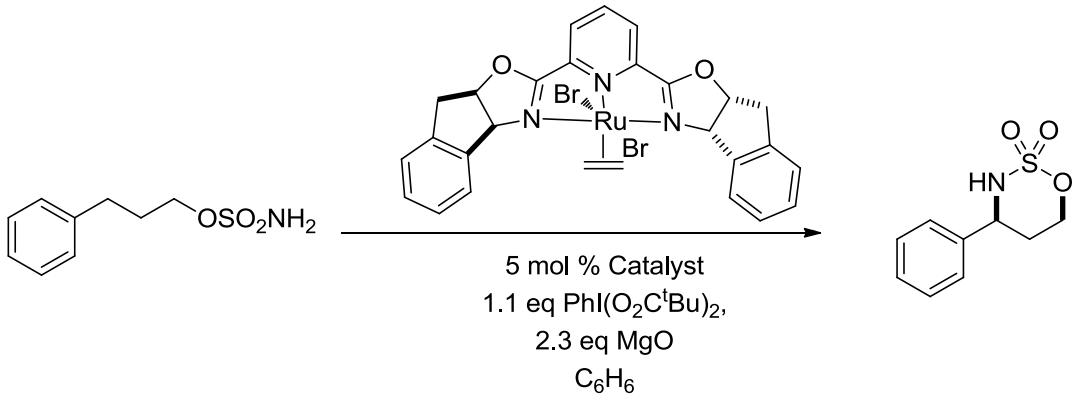
cycloaddition reactions [scheme 42(a)]. With the 2-amidoallylcation-like reactivity, 1,3 dipole equivalents are capable of rearranging to give highly substituted iminocyclopropanes or acting as novel dipolar species engaging external dipolarophiles.[39(b)] Under Du Bois's established reaction conditions the sulfamate ester of allene could form the strained cyclopropylimine that is subsequently trapped by the pivalic acid present in the reaction mixture to give N-sulfamoyl-O-pivaloylcyclopropylaminol [scheme 42(b)].



Scheme 42: Reaction of metallonitrene with allene

Despite the recent advances in rhodium chemistry, general methods for both enantioselective and intermolecular C-H amination remain elusive. Although Du Bois's chiral dirhodium (II) complexes have been developed as catalysts for highly enantioselective intramolecular metallocarbene reactions, their application to intermolecular C-H amination chemistry has yet to produce the same spectacular results. To date, the most effective protocol for asymmetric C-H amination requires the combination of enantioenriched sulfoxamines as chiral auxiliaries and a chiral dirhodium(II)catalyst.[39(c)] To address the challenge of catalytic asymmetric C-H

amination, Blakey and co-workers chose ruthenium(II)–pybox (pybox=pyridine bis-oxazoline) complexes as the catalyst (Scheme 43).[39(d)] The pybox ruthenium complex catalyzes the reaction conditions to allow asymmetric C-H amination of substrates with benzylic and allylic C-H bonds. Both electron-donating and electron-withdrawing substituents produce good yields and excellent enantioselectivities. The allylic amination reaction proceeds with complete selectivity for the C-H insertion product. The competing aziridination product, which is commonly generated when dirhodium(II) tetracarboxylate catalysts are used were not observed with their case.

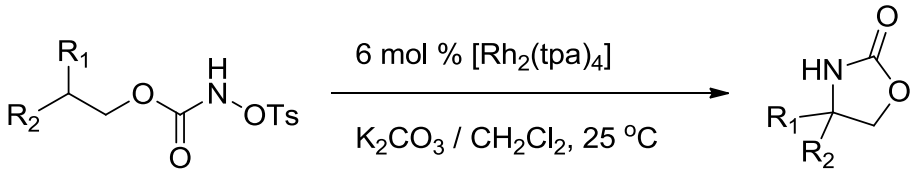


Scheme 43: Ruthenium pybox system

1.4.3.3. Lebel et. al.

Lebel's group studied the C-H amination with N-tosyloxycarbamates for forming metal nitrenes with rhodium. The intramolecular reaction gave oxazolidinones in good yields to form Troc-protected amines. Potassium tosylate was the only stoichiometric byproduct produced. Mechanistic studies suggested that a singlet rhodium nitrene was the reactive species and that the C-H insertion step proceeded via a concerted asynchronous transition state. This intramolecular amination also features novel syntheses of products with important biological activities, such as amantadine hydrochloride, memantine

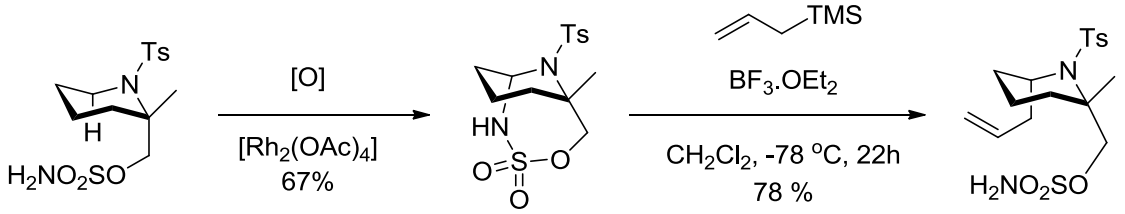
hydrochloride, and various benzhydrylamines (Scheme 44).[46]



Scheme 44: Amination of Troc-protected amines

1.4.3.4. Compain et. al.

It was evident that amination of tertiary C-H bonds is generally preferred to secondary C-H bonds, and electron-donating groups activating the α-C-H bond toward insertion. Amination reactions with sulfamate esters led to the formation of the corresponding six-membered ring insertion products, more rarely to five membered rings, whereas carbamates afforded only five membered rings. The highly favored formation of the oxathiazinane ring may be rationalized by the preferable geometry of the sulfur is planner and thus the N-S-O angle, which matches the metrical parameters of the heterocycle. There are additional factors influencing the regio-selectivity of the reaction. Copmain's group followed Du-Bois's chemistry for C-H amination in intramolecular way to form an unusual seven-membered ring.[47] These results opened the synthetic strategy for synthesis of poly-functionalized piperidines (scheme 45).



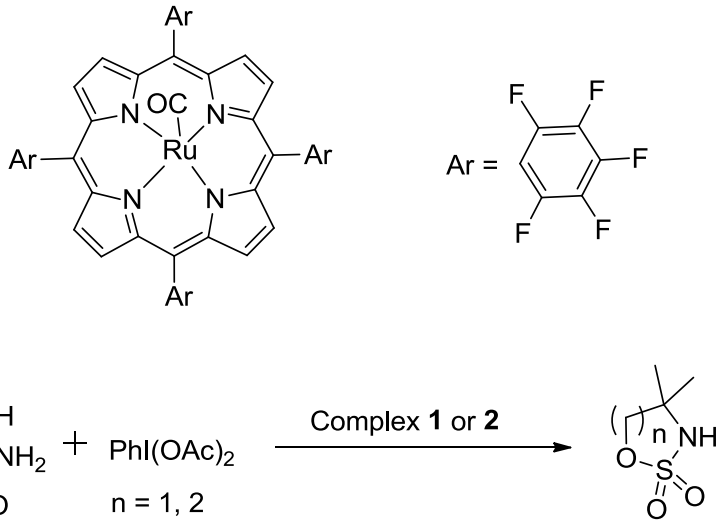
Scheme 45: Synthesis of poly-functionalized piperidines

In connection with the studies on carbohydrate mimics, the spiranic oxathiazolidine formed by regio-specific intramolecular C-H insertion into the pseudo anomeric bonds. The regio-selectivity of the amination reaction cannot be attributed solely to electronic factors but was influenced by conformational factors. The distinct regio-selectivity obtained in intramolecular amination with pyran and piperidine sulfamates series could be explained by conformational preferences which placed the nitrene center in a favorable position to the reacting C-H bond.

1.4.3.5. Che et. al.

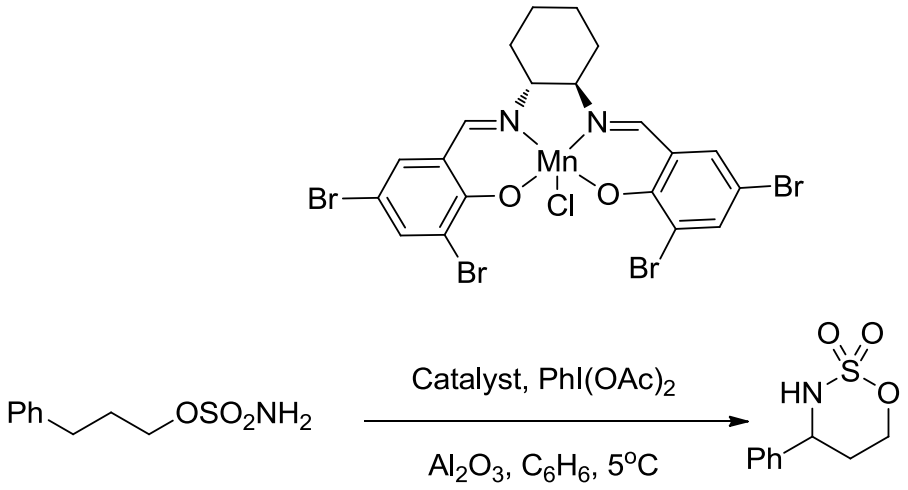
The electron-deficient ruthenium porphyrin [Ru(tpfpp)(CO)] catalyzed intramolecular amination reactions of saturated C-H bonds in presence of hypervalent iodine and Al_2O_3 as a base (scheme 46).[48(a)] They showed that this intramolecular amination worked for a wide variety of sulfonamides including, benzylic and tertiary C-H.

The sulfamate esters with $PhI(OAc)_2$, ruthenium porphyrin [Ru(tpfpp)(CO)] and Al_2O_3 reactions afforded cyclic sulfamidates with good to high yields and also very high ee. The main limitation of their chemistry was use of relatively expensive ruthenium as catalyst.



Scheme 46: Ruthenium catalyzed intramolecular amination

Ching-ming Che's group also explored the scope of these manganese (III) Schiff-base catalysts in intramolecular amidation reactions. They used hypervalent iodine and Al_2O_3 in presence of manganese(III) Schiff-base complexes to cyclize sulfamate and carbamate esters (scheme 47).[42(b)] The chiral metallo-salen catalyzed enantio-selective intramolecular amination of sulfamate esters that proceeded in moderate to good yields, substrate conversions, with exclusive cis-selectivity and with moderate to good enantio-selectivity. The sulfamate esters with electron-donating substituents showed a significant drop in enantio-selectivity. Kinetic experiments suggested that electron donating groups accelerate whereas electron-withdrawing groups retard the nitrogen atom insertion reaction. Enantiomerically pure sulfamate esters were reacted with chiral manganese (III) Schiff-base as catalyst under the same conditions gave the retention of the stereocenters product. This result indicates that the Mn(III)-catalyzed intramolecular amination reaction is stereospecific.



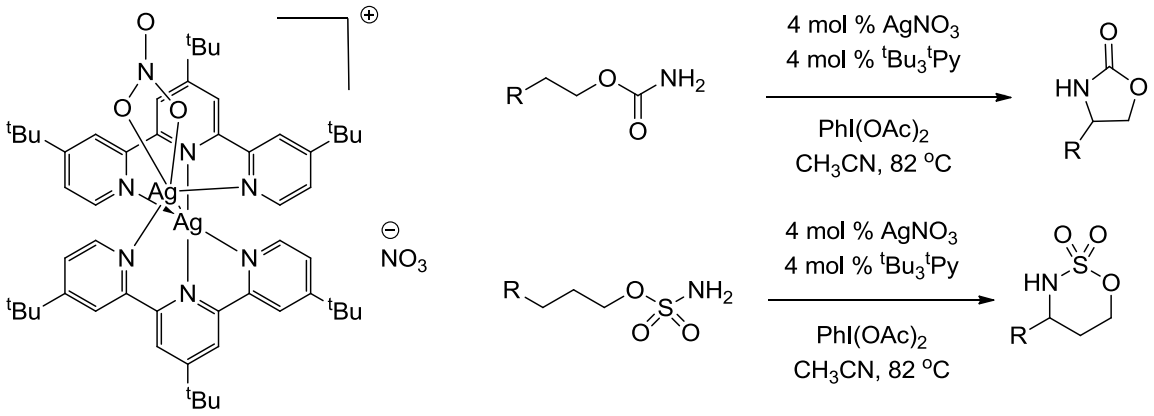
Scheme 47: Manganese catalyzed intramolecular amination

1.4.3.6. He et. al.

Despite extensive studies of rhodium catalyzed intramolecular aminations of C-H bonds, efficient and practical examples of such processes are limited. Chun-he's group reported that sulfamate and carbamete esters could undergo intramolecular amination with disilver(I) complex and hypervalent iodine [$PhI(OAc)_2$] (scheme 48).[49] The five- and six-membered ring insertion products were generated preferentially from carbamates and sulfamates, respectively. Good to excellent yields were observed with disilver(I) and 2 mol % of 4,4',4''-tri-tert-butyl-2,2':6',2''terpyridine (tBu_3^tpy) complex. In addition the disilver(I) catalyst successfully activates various types of the C-H bonds e.g. benzylic, 3^o and 2^o. The results suggest the involvement of silver–nitrene intermediate. Excess amounts of the ligand (10 equiv with respect to the silver catalyst) produced no reaction.

In their mechanistic study, the sulfamate substrate derived from (S)-2-methyl-1-butanol was used for the intramolecular C-H amination reaction. The product of this reaction showed the retention of configuration. This result indicates that the silver-

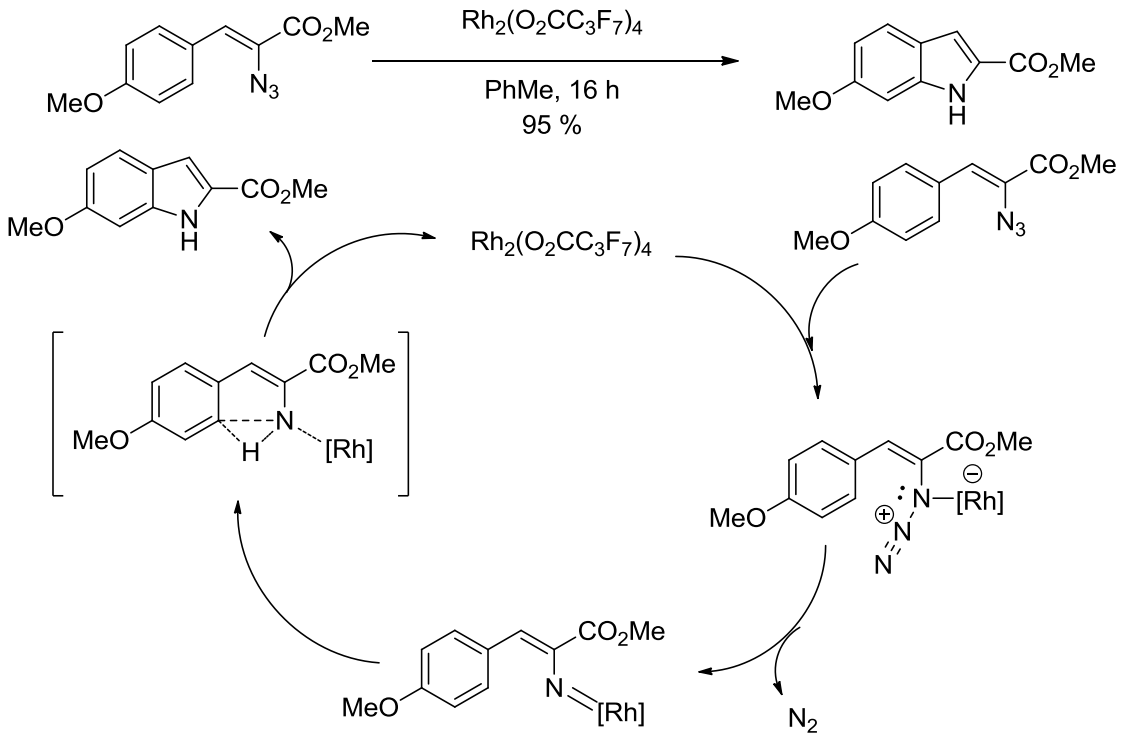
catalyzed intramolecular amination reaction is stereospecific and presumably concerted.



Scheme 48: Silver catalyzed intramolecular amination

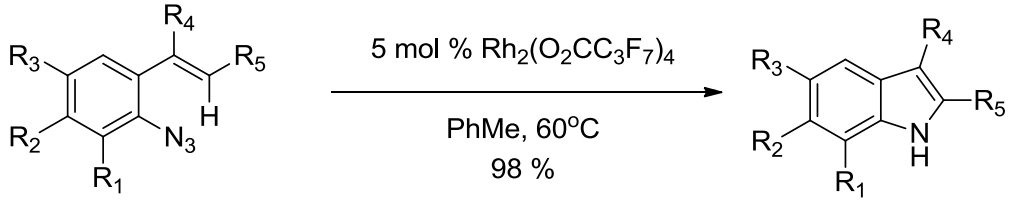
1.4.3.7. Driver et. al.

Recent intramolecular C-H amination reactions have emerged, especially devoted to the preparation of indoles via rhodium(II) decomposition of vinyl-azides and arylazides. The electron deficient rhodium(II) perfluorobutyrate converts vinyl azide to indole very effectively. In addition to indoles, a variety of aromatic N-heterocycles from vinyl azides was synthesized by using rhodium(II) perfluorobutyrateas a catalyst. In their mechanistic study, it was proposed that the dirhodium(II) carboxylate with the R-nitrogen of azide produces a rhodium nitrenoid, followed by a C-N bond formation could occur by a concerted insertion into an ortho C-H bond (scheme 49).[50]



Scheme 49: Preparation of indoles from arylazides

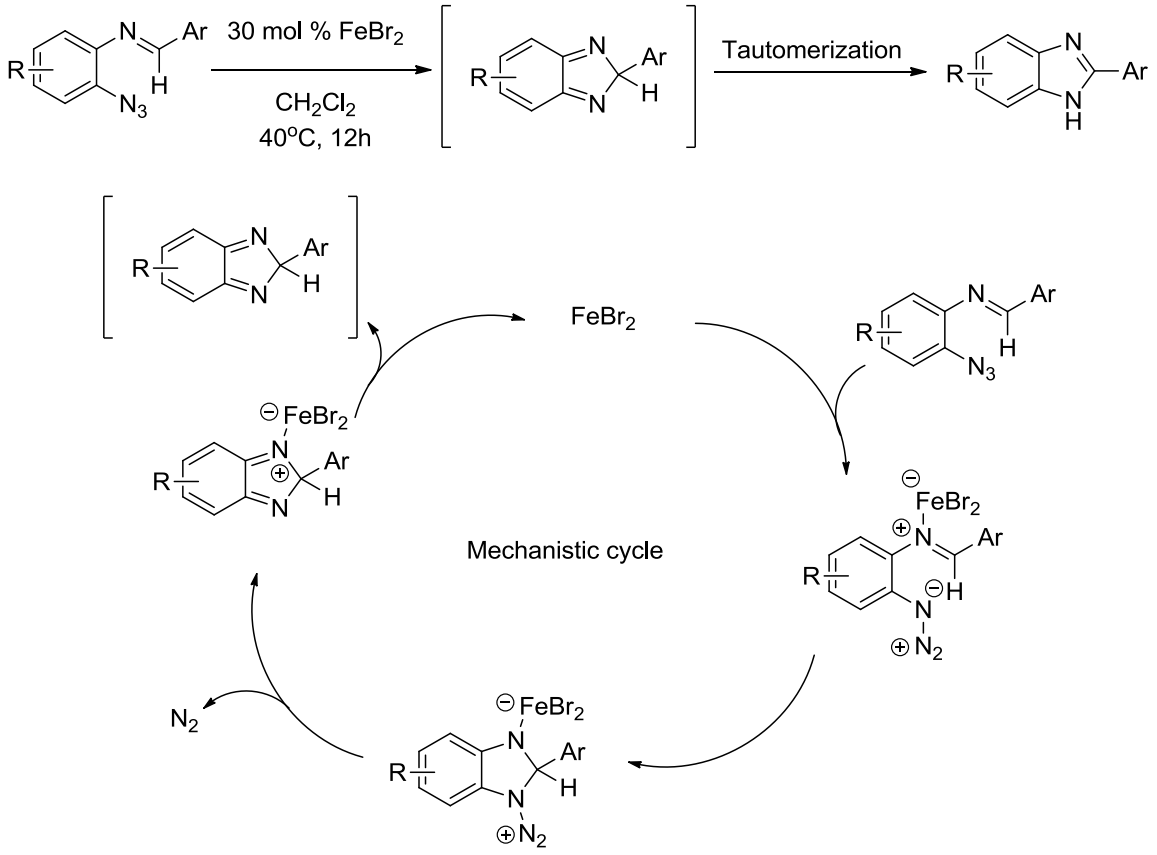
Dirhodium (II)-catalyzed intramolecular C-H aminations of arylazides also have been done (scheme 50).[51]



Scheme 50: C-H amination of arylazides

The aldimine, formed from the condensation of aromatic aldehyde and 2-azidoaniline, reacts with the transition metal to produce benzimidazole. It was showed that the ferrous bromide ($FeBr_2$) could effectively cyclize the aldimine to the benzimidazole. Higher yields of benzimidazole were obtained with more electron-

deficient aryl groups. The reactivity trends provide evidence for a Lewis acid-mediated mechanism: higher conversions were observed with electron-deficient imines and electron-rich azides. The coordination of iron (II) bromide to the imine nitrogen increases its electrophilicity to trigger nucleophilic attack by the azide. The tautomerization of the 2H-benzimidazole formed the 1H-benzimidazole (scheme 51).[52]



Scheme 51: Iron catalyzed preparation of indoles from arylazides

1.5 Conclusions

A high degree of chemo- and regio-selectivity can be assured by the intramolecular delivery of nitrene and but the intermolecular amination the discrimination between C–H bonds is much more challenging. In this amination process the metal does not insert directly in the substrate. Efficiency is also an issue to address due to the high reactivity of the metallo-nitrene, a drawback circumvented in intramolecular C–H amination wherein the reacting centers are in close proximity. The formation of products resulting from over-oxidation is also minimized in this intramolecular amination. Thus, the control of the chemo, regio and stereoselectivity are much better in intramolecular than intermolecular reactions.

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CHAPTER TWO

Cu-catalyzed, Enantioselective Intermolecular amination

2.1 Background and Introduction

The development of methods for the direct conversion of carbon-hydrogen bonds into carbon-nitrogen, bonds remains a critical challenge in organic chemistry. Mild and selective transformations of this type will undoubtedly find widespread applications, e.g. for the synthesis of pharmaceuticals, natural products, agro-chemicals, and polymers. Traditional approaches to amines rely heavily on pre-functionalized starting materials for installing the desired C-N bond. This makes the overall construction of such a molecule more expensive. Circumventing this issue will not only improve atom economy but also increase the overall efficiency of multistep synthetic sequences.

Direct C-H bond functionalization is limited by the fundamental challenges listed below:

(i) Very high dissociation energy of C-H bonds.

(ii) Site selectivity in multiple C-H bond-containing molecules needs to be controlled.

Transition metal complexes can react with C-H bonds to produce C-M bonds. The resulting C-M bonds are far more reactive than their C-H counterparts and can be converted to new functional groups under mild conditions. Selective functionalization of a single C-H bond within a complex molecule is the second most challenging job since the benzylic and tertiary C-H bonds are weaker than the primary, secondary or the aromatic C-H bonds.

In my chapter one, I have discussed thoroughly about various well established metal nitrene systems. But some improvements need to be made considering the following factors:

1. Most of the catalysts display a low catalytic activity with linear, non-activated hydrocarbons
2. Use of excess of olefin for the conversion of expensive or rare substrates
3. Use of PhINTs supposes the formation of iodobenzene as a byproduct, with the subsequent low values of the atomic selectivity[1] for this process.

Due to these reasons, in recent years chloramine-T (N-chloro-N-sodium-p-toluenesulfonamide) and related compounds have been screened as the nitrene source for C-H amination. The main advantage of these reagents is the formation of an alkaline halide as byproduct. With these ideas in mind, the design of an improved catalyst for the C-H amination reaction should meet the following requirement:

1. High performance for both activated and non-activated hydrocarbons
2. Use of less equivalent of olefin.

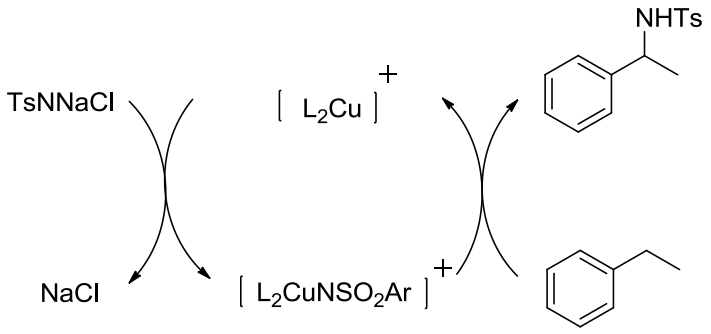
During my predoctoral research, I focused on using Cu-complexes as catalysts for the oxidative functionalization of carbon–hydrogen bonds. The first goal was to develop new environmentally friendly catalytic amination reactions using inexpensive aminating reagents and Cu catalysts. Secondly, we wanted to achieve enantioselectivity in intermolecular amination reactions.

2.2 Copper catalyzed C-H amination

In order to improve the scope of intramolecular C–H aminations, attention has recently been paid to the design of either new catalysts or nitrene precursors. Hypervalent

iodine-imido reagents (e.g. ArI=NZ) are popular and widely used for intermolecular amination. There are some limitations associated with the use of these hypervalent iodine reagents, including their instability and the generation of ArI as a byproduct. Hence some effort has been made to develop alternative nitrene sources for catalytic C–H amination. Chloramine-T and bromamine-T are considered to be greener (NaX by–product) and readily available, inexpensive nitrene sources.

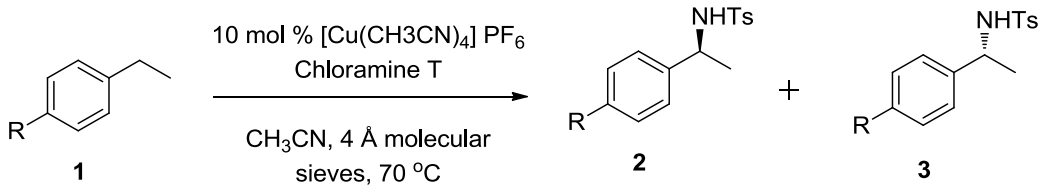
Our group is seeking to develop new catalytic amination reactions, which use inexpensive aminating reagents and catalysts. As noted earlier benzylic substrates could be efficiently aminated by anhydrous chloramine-T with commercially available $[Cu(CH_3CN)_4]PF_6$ as the catalyst (scheme 1).[2]



Scheme 1: General scheme for amination

High conversions and good yields of amination products were obtained by using 10 mol % of $[Cu(CH_3CN)_4]$-PF_6 catalyst in acetonitrile at 70 °C with a slight excess of chloramine-T and 4 Å molecular sieves. The functionalization of carbon–hydrogen bonds could generate new stereogenic centers potentially in a highly diastereoselective and/or enantioselective fashion. When a prochiral hydrocarbon (e.g. **1**) reacts with the aminating

reagent (chloramine T) and the achiral catalyst $Cu(CH_3CN)_4X$, two enantiomers are produced (isomers **2** and **3**) (scheme 2).



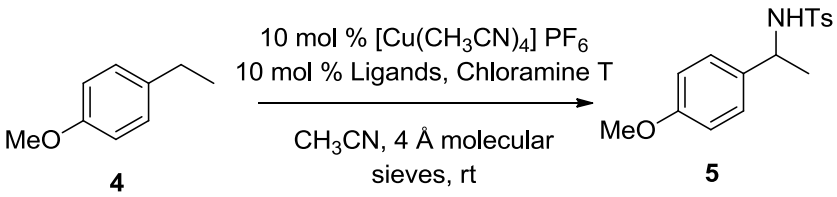
Scheme 2: Formation of stereoisomers

While this issue has been the least well explored to date, both substrate-based approaches (involving the use of substrates containing pre-installed stereocenters)[3] as well as catalyst-based approaches (involving the use of chiral ligands with transition metal to control the enantioselectivity of functionalization)[4] have been developed. As previously indicated, C–H activation is generally directed by the chelate effect, a strategy always applied in the intramolecular examples described so far. Allylic substrates provide a case of allowing selective catalytic intramolecular C–H activation–amination. Herein, we report our findings of ligand-assisted, Cu-catalyzed oxidative benzylic amination reactions and efforts to effect enantioselective variant.

2.3 Results and discussion

The major portion of this chapter is already published[4] and here we discuss the way we approached the solution for achieving our goal.

First we screened ligands for their effect on the activity of Cu-catalyzed amination, 4-ethylanisole was selected as a test substrate since its amination by chloramine-T (TsNNaCl) catalyzed by 'ligandless' $Cu(CH_3CN)_4PF_6$ (10 mol %) is slow at 20 ^oC (12 h, CH_3CN, <5% yield of product. Corresponding reactions were conducted in the presence of representative ligand types under the same conditions (1:1; ligand vs copper, Scheme 3), and the yield of the amination product sulfonamide was determined by NMR integration relative to starting material and/or isolation.



Scheme 3: Ligand assisted catalysis of benzylic amination

We established a typical reaction procedure by using commercial $[Cu(CH_3CN)_4]PF_6$ (0.01 eq), the ligand (0.01 eq), and dry CH_3CN added to a round-bottomed flask containing dry molecular sieves (4 Å) under argon. To the well-stirred suspension 4-ethyl anisole (1 eq) was added. Anhydrous chloramine-T (vacuum-dried over refluxing toluene; 1.3 eq) was added after one hour and the mixture was stirred at room temperature overnight. The mixture was then filtered through Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (4:1 hexane/ethyl acetate). The results are summarized in Table **1**.[5]

Table 1: Effect of ligands on the amination of 4-ethylanisole

Entry	ligands	Reaction time (hr)	% yield[a]
1	None	12	5
2	$P(OMe)_3$	16	68
3	PPh_3	16	62
4	$Ph_2PCH_2CH_2PPh_2$	16	66
5	$Me_2NCH_2CH_2NMe_2$	12	52
6	Phenanthroline	12	77
7	S-Proline	12	45
8	S-Lysine	12	67
9	S-Histidine	12	67
10	A	12	No reaction
11	B	12	No reaction
12	D	12	No reaction
13	G	12	No reaction

[a]Yield determined by NMR integration of reaction mixture; $TsNH_2$ is the only detected by-product.[6]

The Cu(I) catalyzed reaction exhibits significant acceleration of amination by adding ligands in the reaction (DPPE, TMEDA etc.). Moderate to excellent yields are obtained with several of these ligands, demonstrating ligand-assisted catalysis. It was found that 4-ethyl anisole reacted effectively with chloramine-T/$Cu(CH_3CN)_4PF_6$ in the presence of DPPE, TMEDA, tri-phenyl phosphine and with various amino acids. The reaction of 4-ethyl anisole with Cu(I) and the ligands bipyridine (entry 10), BINOL (entry 11), picolinic acid (entry 12) and salen[7] (entry 13), did not show any catalysis.

The primary focus of this project was to find suitable reaction conditions for getting maximum yield and enantioselectivity. The enantioselectivity could potentially be achieved by using chiral ligands. The chiral amino acids are the most common ligands in any synthetic organic lab. Therefore we started using the amino acids as potential bi-dentate ligands for the $[Cu(CH_3CN)_4]$-PF_6 complex.

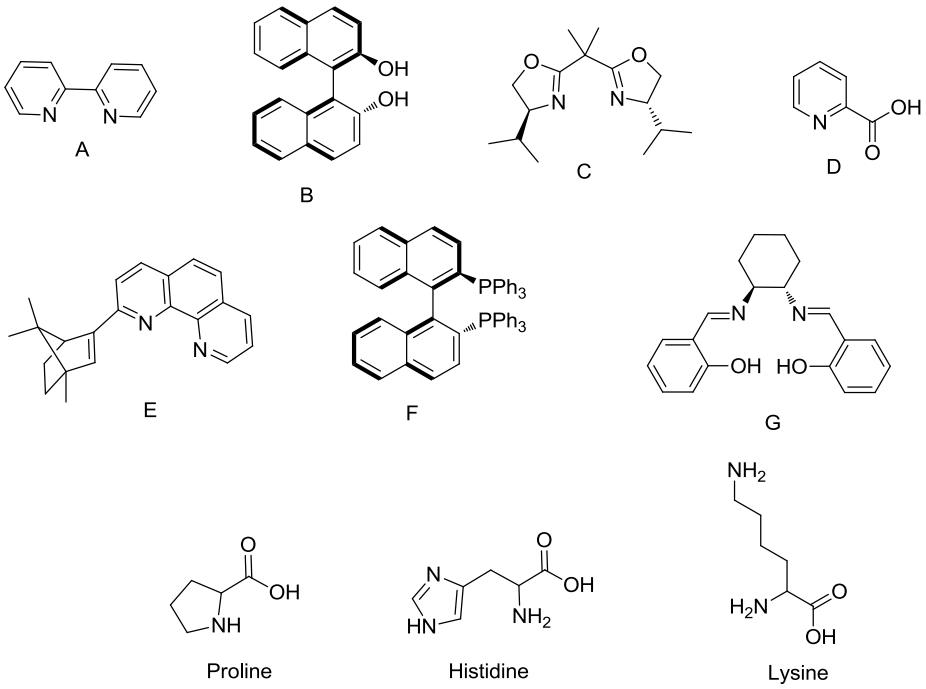


Figure 1: Ligands used in intermolecular amination

The optical purity of the isolated amination products was determined by polarimetry. In the polarimetric analysis, the products were dissolved in chloroform and the optical rotations were measured at 25 ^{o}C at the D-line of the sodium lamp (λ=589.3 nm). The sample containing x g/mL of the compound in a 1 dm tube produced a rotation of "X" unit in clockwise/anticlockwise direction. Percent of optical purity = (observed specific rotation)/(specific rotation of the pure enantiomer)$*$100%. In all cases examined, the products were formed with low enantiomeric induction (0-7% ee).

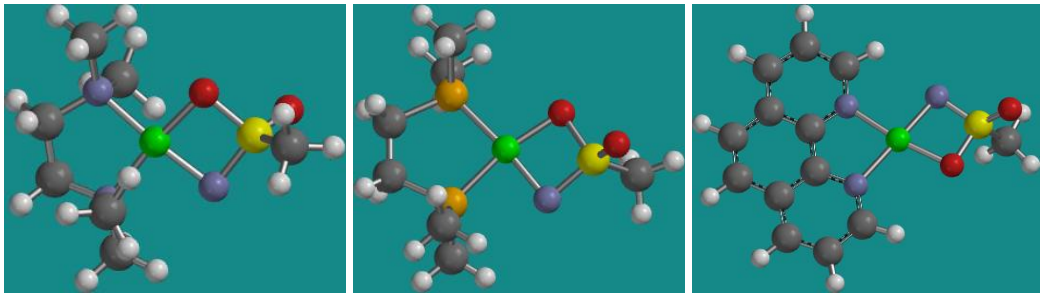
Chiral bisoxazoline ligands and phenanthroline[8] based ligands are either commercially available or easy to synthesize, will improve the enantioselectivity. The enantiomeric purity of the isolated amination products was determined by polarimetry and/or by chiral HPLC. The findings are shown below (table 2).

Table 2: Copper-catalyzed enantioselective amination

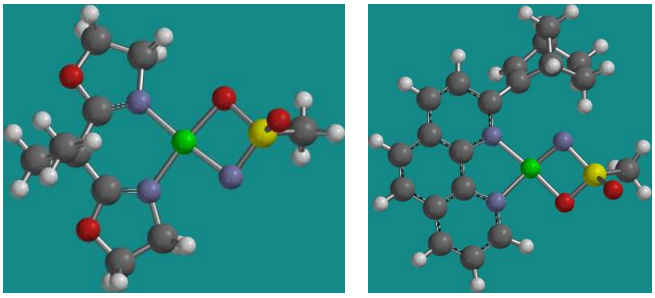
Entry	Ligand	% Yield	% ee
1	S-Histidine	67	3
2	S-Proline	45	4
3	**E**	68	12[a]
4	**C**	65	5

[a]Determined by HPLC on Chiralcel OJ column; 15% i-PrOH/85% hexane eluant

It is also evident that ligands with nitrogen and phosphorus atoms, coordinated with copper are effective for catalysis. Based on these findings, we considered next generation catalyst designs in which two nitrogen atoms of a ligand would be affixed to a common frame. From an architectural standpoint, devising nitrogen containing bidentate ligand for these types of monometallic structures offers an enticing challenge. The kinetic and theoretical studies by Jacobson[9] and Norrby[10], suggest that the aziridination reactions occur via a Cu(I)/Cu(III) cycle involving a Cu-imido complex LCu=NTs as the reactive intermediate. We did PM3 calculations on SPARTAN software for LCu-imido/nitrene intermediate. The bite angle to copper and ligand (L-Cu-L) is increasing gradually across the figure and it reflects the stereoselectivity. The modeling studies are shown below (Figure 2).



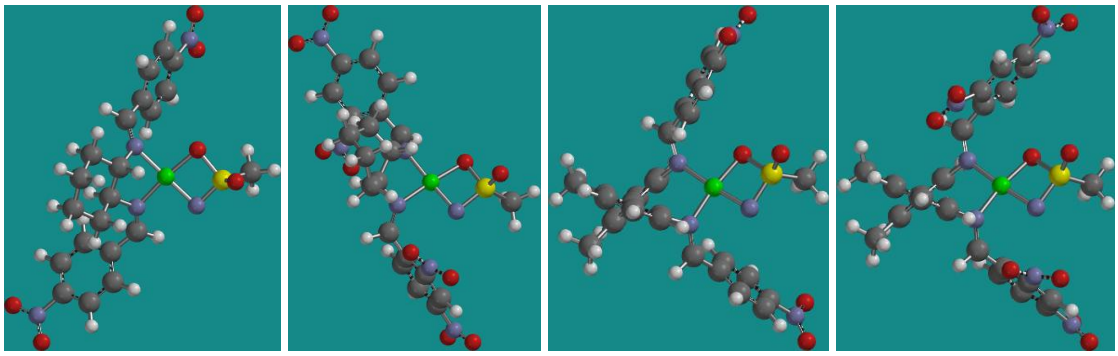
TMEDA Imido complex DPPE Imido complex Phenanthroline Imido complex



Cu Imido complex with **C** Cu Imido complex with **E**

Figure 2: Copper imido complex

The accessibility of diverse diimine ligands from primary diamines and aldehyde building blocks[11] facilitated an assessment of the electronic effects of the ligand on the catalytic activity. Therefore, we explored asymmetric C-H aminations with chiral Cu (Schiff base) complexes. The model studies for this copper imido schiff base complex are shown below (Figure 3). The bite angle of ligand and metal (L-Cu-L) is increasing and the angle between O-Cu-N is increasing from H5 to J2 (figure 4).



Cu Imido complex with **H5** | Cu Imido complex with **H6** | Cu Imido complex with **J1** | Cu Imido complex with **J2**

Figure 3: Copper imido schiff base complex

To prepare the diimine ligands, the aromatic aldehydes and diamines were mixed with dry $ClCH_2CH_2Cl$ in a dry flask containing anhydrous magnesium sulfate fitted with a reflux condenser and filled argon balloon. The reaction mixture was refluxed overnight and then filtered after cooling. The solvent was evaporated under reduced pressure and the crude product residue triturated with methanol to remove any unreacted starting materials. The purity of the compounds was determined by the NMR. The Schiff bases made by the above process were used for the following amination reactions.

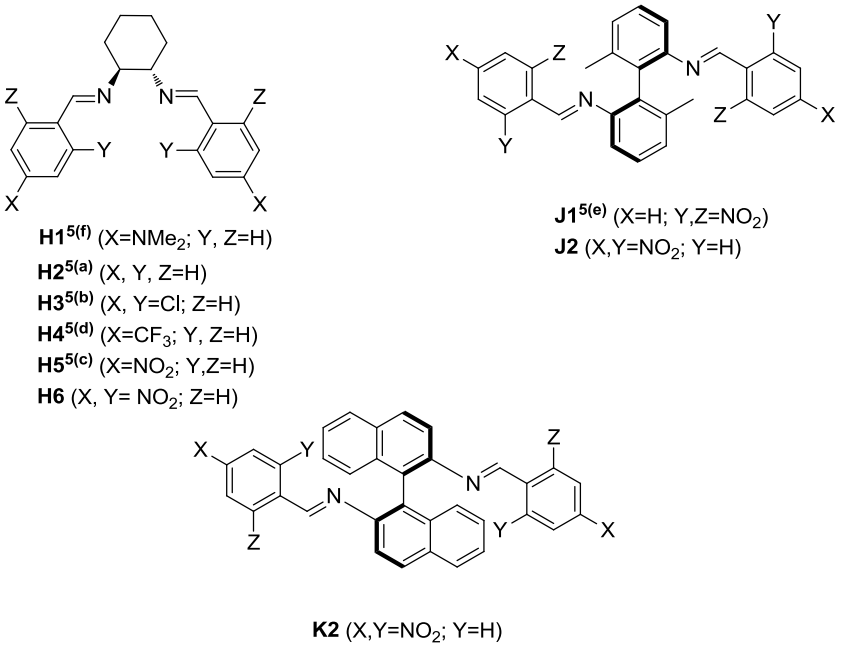


Figure 4: Schiff base ligands

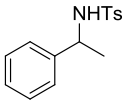
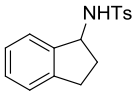
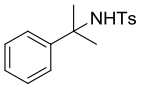
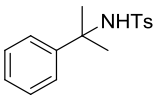
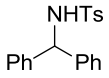
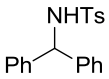
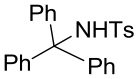
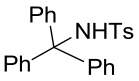
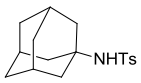
Corresponding reactions were conducted in the presence of representative ligand types under the same conditions (1:1; ligand vs copper), and the yield of the amination product sulfonamide was determined by isolation. The results are summarized in Table 3. It is shown that the electron deficiency of the schiff base ligand enhances the reactivity of the amination reaction.

Table 3: Effect of Schiff base ligands on the amination of 4-ethylanisole

Entry	ligands	Reaction time (hr)	% yield
1	**H1**	12	20
2	**H2**	12	56
3	**H3**	6	74
4	**H4**	6	81
5	**H5**	6	88
6	**H6**	6	92

To assess the ligand-assisted reaction's scope a survey of the catalytic amination of a set of benzylic substrates was carried out using ligands derived from the nitro-substituted diimine ligands H5 and H6. The reactions were conducted under the same conditions as established for 4-ethylanisole with chloramine T (CH_3CN, rt, 6–12 h, 0.1 equivalent $Cu(CH_3CN)_4PF_6$ / 0.1 equivalent ligand). The results are summarized in Table 4. All of the reported yields are based on isolated product. The ligands from cyclohexyl diimine (H5 and H6) are from the commercially available source. The enhanced activity of the diimine based catalysts was again indicated by the room temperature conversions of the starting material with the former catalysts versus the 60–70 ^oC required for reactions with $Cu(CH_3CN)_4PF_6$. Several secondary and tertiary benzylic hydrocarbons were thus aminated with moderate efficiency and good regioselectivity, with $TsNH_2$ as the only detected by-product. Diphenylmethane (entry 5, 6) and sterically crowded triphenylmethane (entry 7, 8) reacted with good efficiency. More impressively, the saturated substrate adamantane,[1] unreactive to chloramine-T/$[Cu(CH_3CN)_4]PF_6$ could; with modest yield.

Table 4: Substrate scope of L-assisted, Cu-catalyzed amination

Entry	Substrate	Ligand	Product	% Yield[a]
1	Ethylbenzene	**H6**		68
2	Indane	**H6**		66
3	Cumene	**H5**		62
4	Cumene	**H6**		67
5	Diphenylmethane	**H5**		64
6	Diphenylmethane	**H6**		65
7	Triphenylmethane	**H5**		59
8	Triphenylmethane	**H6**		62
9	Adamantane	**H6**		19

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[a]Isolated yield; by-product is TsNH2.

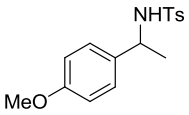
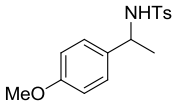
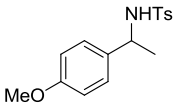
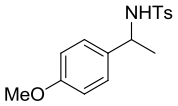
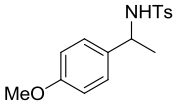
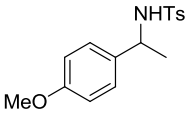
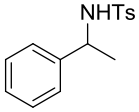
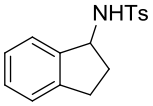
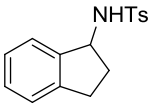
Having established the ability of several ligand-Cu systems to effectively catalyze benzylic amination by chloramine-T, homochiral ligands were selected and tested for their ability for enantioselective aminations of prochiral benzylic substrates. All reactions were conducted under the previously established conditions with 1:1 ligand/ $[Cu(CH_3CN)_4]$ PF_6. The optical purity of the isolated amination products was determined by polarimetry and/or by chiral HPLC and the results are shown in Table 5. Negligible to

low stereo-induction was also found in the reactions employing the diimine ligands derived from 1,2-cyclohexyldiamine (H5 and H6) and from more sterically hindered binaphthyldiamine (K2). So we can conclude that sterically demanding ligands from the 1,2-cyclohexyldiamine could not help us to achieve the goal. More substantial enantioselectivities were found employing the catalyst derived from the biphenyldiamine ligand J2, with 4-ethylanisole, ethylbenzene and indane; entry 8, 10 and 12 respectively. The PM3 calculation with J1 and J2 also suggest that the L-Cu–NTs species should look like an umbrella thus hinder the nitrene approach from various sides. The low enantioselectivities observed may reflect ineffective chirality transfer from the ternary LCu=NTs complex. This indicates a stepwise process for C–H cleavage and C–N bond formation.

Moreover the electron-rich 4-methoxy anisole reacts more efficiently than ethyl-benzene and indane. These results agree with the experimental evidences of amination efficiency (%yield) on the substrate. These suggest that the Cu-imido complex for amination reaction could be electrophilic in nature.

Often it is found that lower temperature has significant impact on the enantioselectivity. At -40 ^{o}C, however, the reaction was very slow and we did not achieve a good yield.

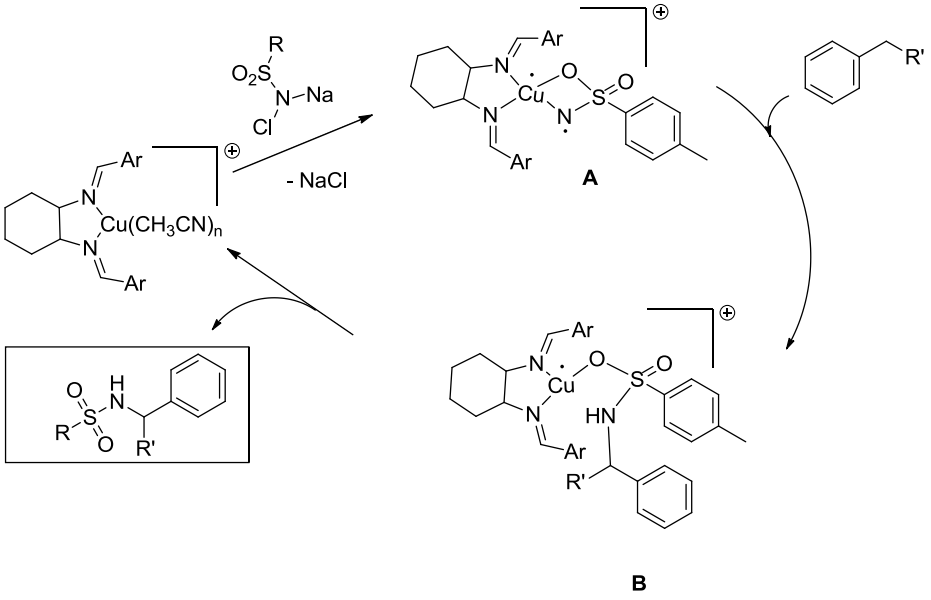
Table 5: Copper-catalyzed enantioselective amination

Entry	Substrate	Ligand	Product	% Yield	% ee[b]
1	4-Ethylanisole	**H5**		88	7
2	,,	**H6**		85	4
3	,,	**J1**		84	6
4	,,	**J2**		81	16
5	,,	**K2**		71	5
6	,,	**H4**		81	8
7	Ethylbenzene	**J2**		68	22
8	Indane	**F**		55	7[a]
9	,,	**J2**		66	28[a]

[a]Reaction in 1,2-dichloroethane showed the same yield and enantioselectivity.
[b]Determined by HPLC on Chiralcel OJ column; 15% i-PrOH/85% hexane eluant**.**

2.4 Conclusion

Although the enantioselectivities achieved in the Cu-catalyzed, ligand-assisted reactions are not very high, they strongly suggest that a chiral-Cu complex of a –NTs species is at least partly responsible for the C–H insertion and thus may be improved with more sterically hindered or chiral-inducing ligands. The modest enantioselectivities observed may reflect ineffective chirality transfer from the L-Cu–NTs complex and/or a stepwise process (radical formation) for C–H cleavage and C–N bond formation. The plausible mechanism is shown below (scheme 4).



Scheme 4: Plausible mechanistic pathway

2.5 Experimental

2.5.1 General Materials/Methods:

Acetonitrile was refluxed over and distilled from calcium hydride. Some of the hydrocarbon substrates were obtained commercially and distilled before use. $Cu(CH_3CN)_4PF_6$ was obtained commercially. NMR spectra were recorded on a Varian Mercury NMR spectrometer at 300 MHz for ^{1}H- and 75 MHz for ^{13}C-NMR spectra. All chemical shifts (ppm) reported are relative to the NMR solvent peak. Mass spectra were recorded on a Finnigan TSQ 700 mass spectrometer with an electron spray source. All of the catalytic reactions were carried out under a dry argon atmosphere.

2.5.2 Typical reaction procedure for benzylic amination

The commercially available $[Cu(CH_3CN)_4]$-PF_6 (28 mg, 0.073 mmol), the ligand (0.073 mmol), and 5 mL of dry CH_3CN were added to a round-bottomed flask containing dry molecular sieves (4 Å, ca. 200 mg) under argon. To the well-stirred suspension 4-ethyl anisole (0.10 mL, 0.73 mmol) was added. Anhydrous chloramine-T (vacuum-dried over refluxing toluene; 218 mg, 0.95 mmol) was added after one hour and the mixture was stirred at room temperature for 6 hrs to 12 hrs. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (4:1 hexane/ethyl acetate).

2.5.3 Typical reaction procedure for benzylic amination with amino acids as ligands

The $[Cu(CH_3CN)_4]$-PF_6, and the amino acids ligands (tyrosine, proline, methionine, histidine, cystine, phenylalanine, tryptophan, serine and lysine) complex was reacted with

4-ethyl anisole and anhydrous chloramine-T. The reaction was done on various temperature e.g 25 ^{o}C and 65 ^{o}C, for 6 hrs to 12 hrs. We did not see any C-H amination reaction with tyrosine, methionine, cystine, phenylalanine, tryptophan and serine as ligands. We the reactivity when we used proline, histidine, and lysine as ligands.

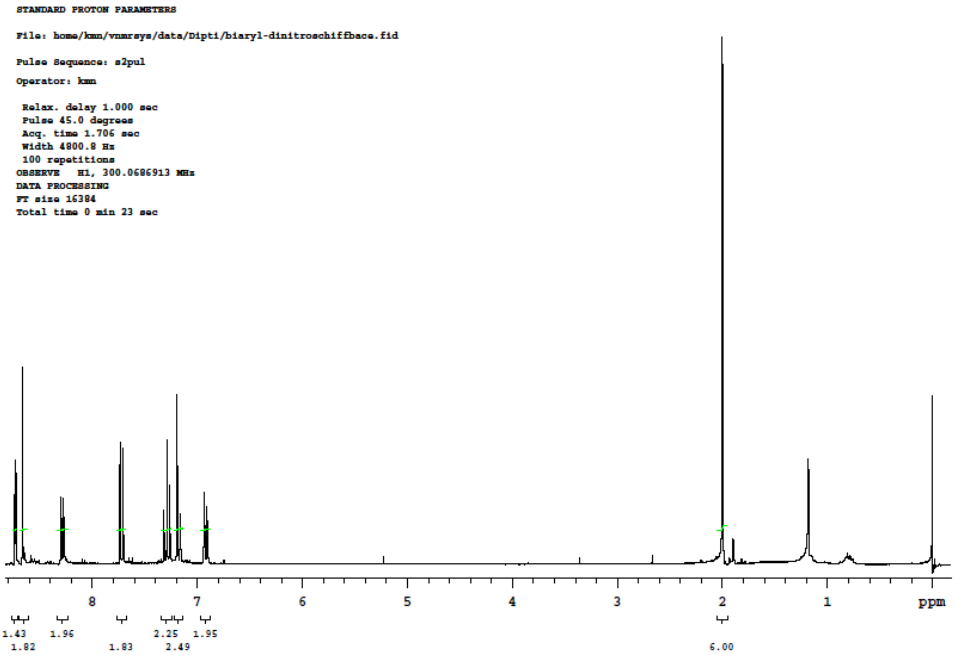
2.5.4 Computational Studies

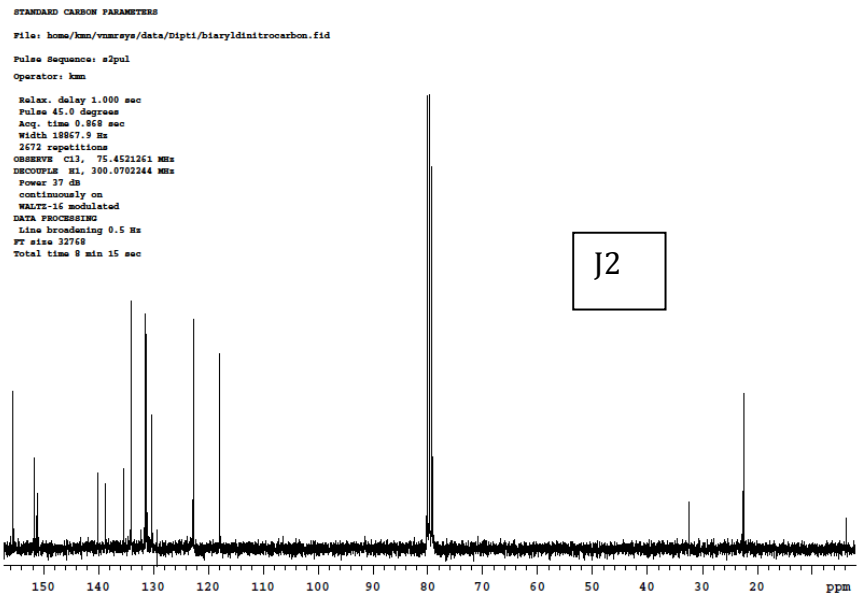
To understand the mechanism and concertedness of the Cu-catalyzed amination reactions of chloramine-T we have performed PM3 calculations. We focused on the C-H insertion reaction of the Cu-imido complex since this process is stereoselectivity-determining. The mechanisms of a related reaction thought to involve Cu-imido intermediates, Cu-catalyzed alkene aziridinations with PhI=NTs and TsN_3, have been investigated previously by both experiment and theory. Kinetic and theoretical studies by Jacobson and Norrby, suggest that the aziridination reactions occur via a Cu(I)/Cu(III) cycle involving a Cu-imido complex LCu=NTs as the reactive intermediate.

2.5.5 Representative Preparations of Schiff base ligands.

J2: 2,4-dinitrobenzaldehyde (96 mg, 0.49 mmol) and biphenyldiamine (52 mg, 0.244 mmol) were mixed with dry $ClCH_2CH_2Cl$ (5 mL) in a dry flask containing anhydrous magnesium sulfate fitted with a reflux condenser and filled argon balloon. The reaction mixture was refluxed overnight and then filtered after cooling. The solvent was evaporated under reduced pressure and the crude product residue triturated with methanol to remove any unreacted starting materials. The Schiff base thus produced had the following characteristics: Yield 88%, brown solid, m.p. 186 - 188°C, ^{1}H NMR ($CDCl_3$,

300 MHz) δ 8.73 (s, 1H), 8.66 (s, 1H), 8.28 (d, 2H, J=11.1 Hz), 7.72 (d, 2H, J=8.4), 7.28 (t, 2H), 7.18 (d, 2H, J=8.4), 6.92 (d, 2H, J=7.8), 1.99 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 152.9, 149.1, 148.4, 137.4, 136.1, 132.7, 131.4, 128.9, 128.7, 127.5, 126.6, 120.1, 115.2, 19.8. ESI-MS m/z 591.1 (M+Na).

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Operator: kmn
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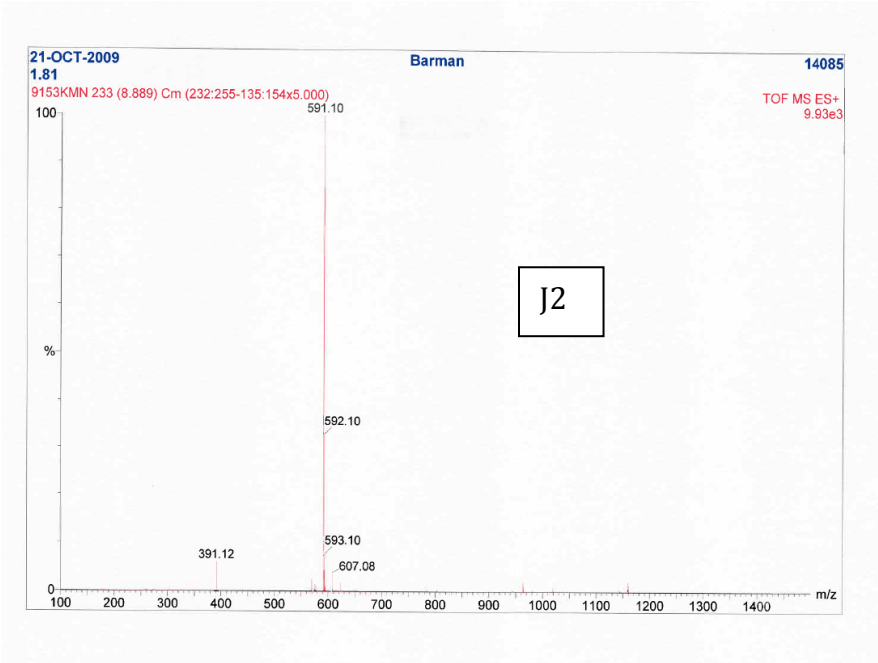
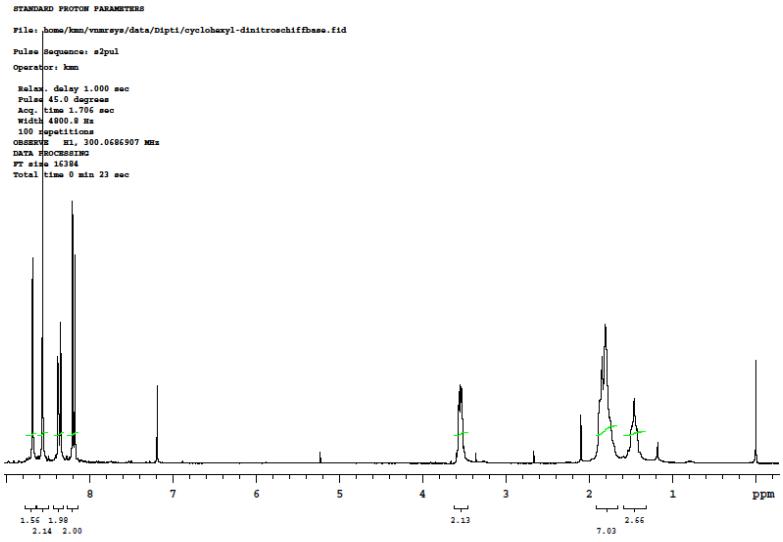
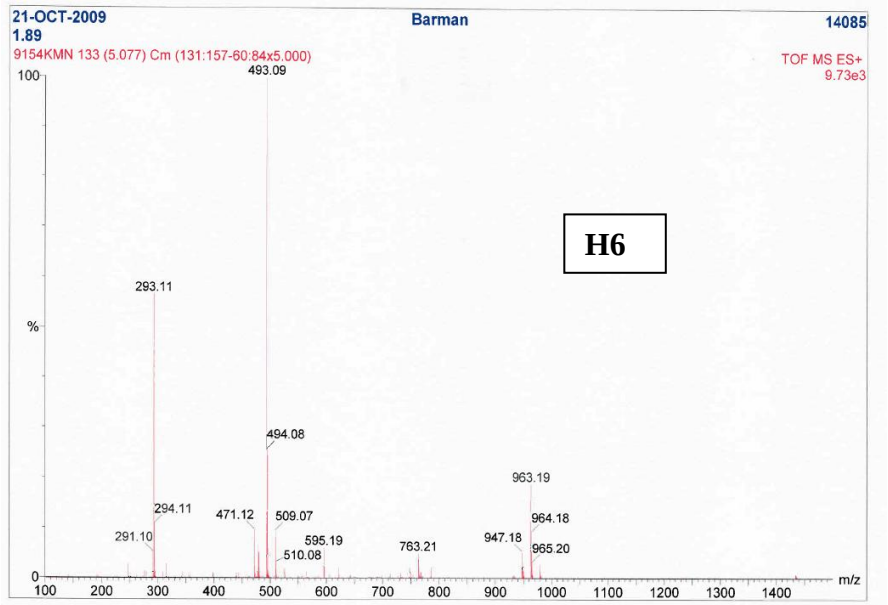
Pulse 45.0 degrees
Acq. time 0.868 sec
Width 18867.9 Hz
2672 repetitions
OBSERVE C13, 75.4521261 MHz
DECOUPLE H1, 300.0702244 MHz
Power 37 dB
continuously on
WALTZ-16 modulated
DATA PROCESSING
Line broadening 0.5 Hz
FT size 32768
Total time 0 min 15 sec
J2
150 140 130 120 110 100 90 80 70 60 50 40 30 20 ppm


21-OCT-2009
1.81
Barman
14085
9153KMN 233 (8.889) Cm (232:255-135:154x5.000)
TOF MS ES+
9.93e3
J2
100
%
0
591.10
592.10
593.10
391.12
607.08
100 200 300 400 500 600 700 800 900 1000 1100 1200 1300 1400 m/z

H6: 4-nitrobenzaldehyde (530 mg, 3.50 mmol) and trans-1,2-diaminocyclohexane (0.2 ml, 1.75 mmol) were combined as above. The Schiff base thus produced had the following characteristics: Yield 90%, brown solid, m.p. 186-188 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.73 (s, 1H), 8.61 (s, 1H), 8.41 (m, 1H), 8.24 (d, 1H, J=8.7), 3.60-3.57 (m, 2H), 1.91-1.85 (m, 4H), 1.51-1.49 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 154.9, 148.6, 148.3, 135.8, 131.5, 127.3, 119.8, 74.1, 32.3, 23.9. ESI-MS m/z 493.09 (M+Na).



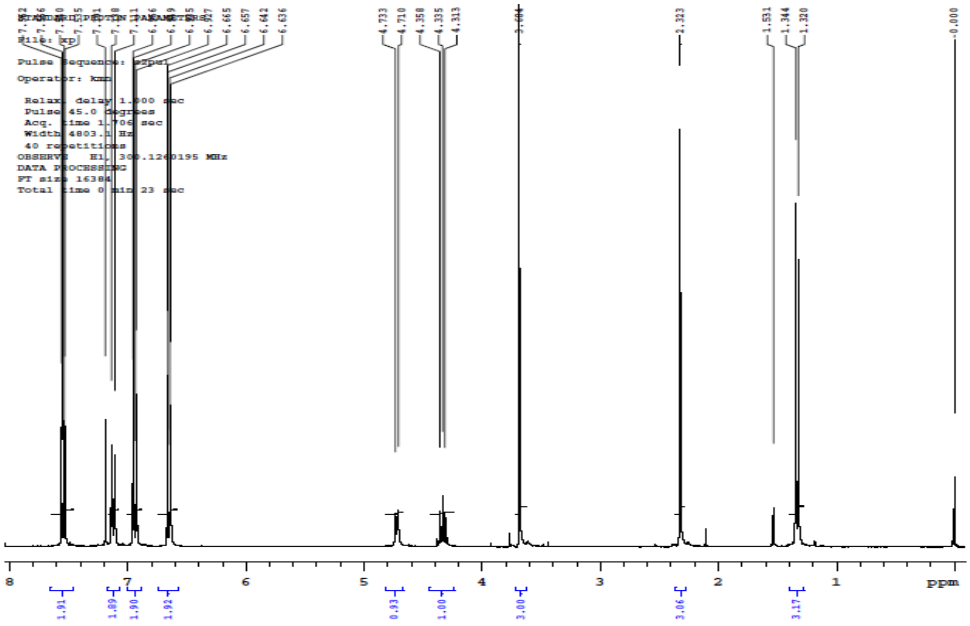


2.5.6 General amination procedure.

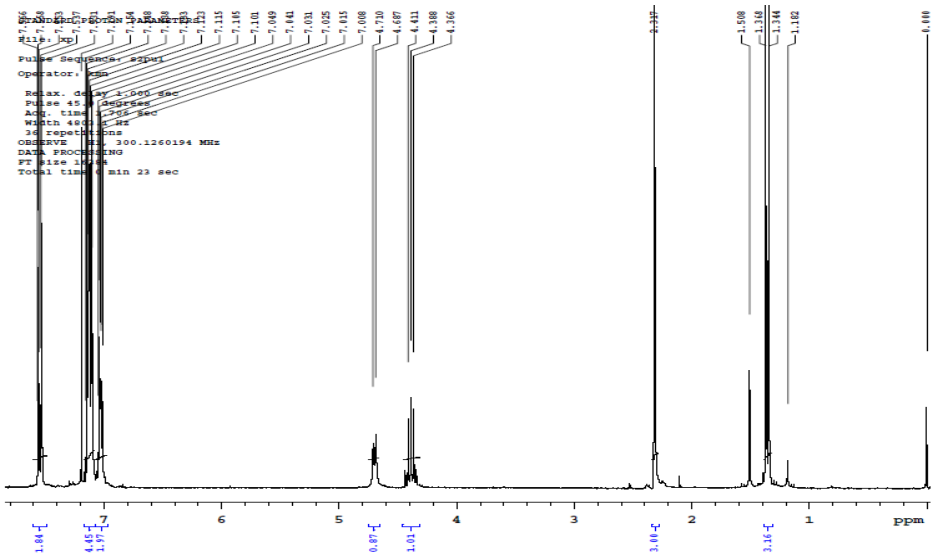
Commercial $Cu(CH_3CN)_4PF_6$ (28 mg, 0.073 mmol), the commercial/made ligand (0.073 mmol) and 5 mL of dry CH_3CN were added to a round bottom flask containing dry molecular sieves (4Å, ca. 200 mg) under argon. To the well-stirred suspension 4-ethyl anisole (0.10 ml, 0.73 mmol) was added. Anhydrous chloramine-T (vacuum-dried over refluxing toluene; 218 mg, 0.95 mmol) was added after one hour and the mixture was stirred at room temperature overnight. The mixture was filtered through Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (4:1 hexane:ethyl acetate).

Characterizational data for product sulfonamides (all compounds were previously reported).

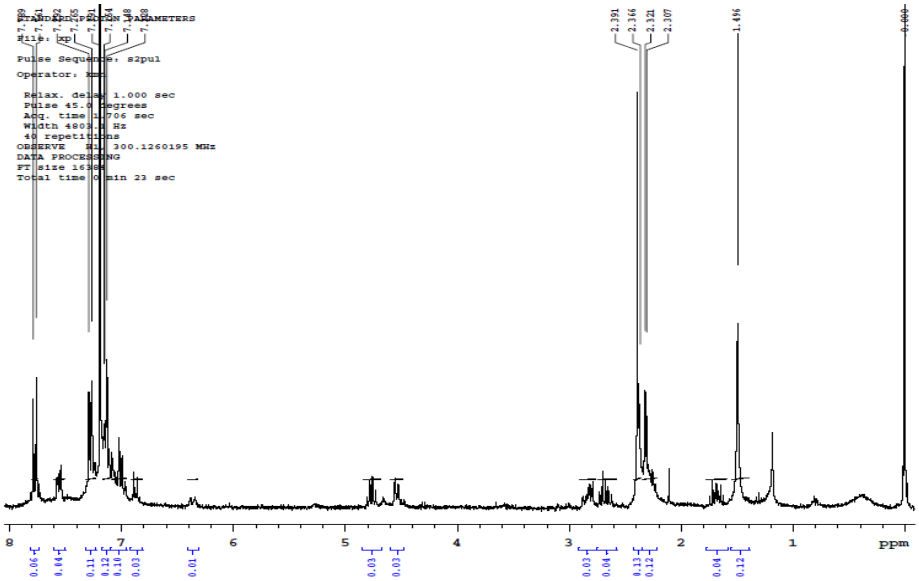
***N*-[1-(4-Methoxy-phenyl)-ethyl]-4-methyl benzenesulfonamide:**[12] white solid, m.p. 87 °C**.** ^{1}H NMR (CDCl3, 300 MHz) 7.64 (d, 2H, *J*=8.2 Hz), 7.21 (d, 2H, *J*=7.81 Hz), 7.04 (d, 2H, *J*=8.8 Hz), 6.7 (d, 2H, *J*=8.7 Hz), 4.84 (S, 1H), 4.44-4.39 (m, 1H), 3.77 (s, 3H), 2.40(s, 3H), 1.41 (d, 3H, *J*=6.91 Hz). ESI-MS m/z 328[M+Na^{+}, 100].



4-Methyl-*N*-(1-phenyl-ethyl)-benzenesulfonamide:[13] white solid, m.p. 78 °C ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.62 (d, 2H, J=10.2 Hz), 7.22-7.18 (m, 5H), 7.12-7.09 (m, 2H), 4.74 (br, 1H), 4.49-4.45 (m, 1H), 2.39 (s, 3H), 1.43 (d, 3H, J=6.6). ESI-MS m/z 298 [M+Na^{+}].



Indan-1-yl-4-methyl-benzenesulfonamide:[14] white solid, m.p. 140 °C ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, 2H, J=8.4 Hz), 7.35 (d, 2H, J=8.7 Hz), 7.23-7.07 (m, 4H), 4.86-4.80 (m,1H), 4.64 (d, 1H, J=9Hz), 2.91-2.86 (m, 1H), 2.80-2.72 (m, 1H), 2.46 (s, 3H), 2.41-2.29 (m, 1H), 1.82-1.69 (m, 1H). ESI-MS m/z 310 [M+Na^+].



Adamantan-1-yl-4-methyl-benzenesulfonamide:[15] ^{1}H NMR (300 MHz, CDCl3) δ 7.82 (d, 2H, J=8.4 Hz), 7.31 (d, 2H, J=7.8 Hz), 4.55 (s, 1H), 2.43 (s, 3H), 2.02 (br s, 3H), 1.79 (d, 6H, J=3 Hz), 1.63-1.56 (m, 6H).

4-Methyl-*N*-trityl-benzenesulfonamide:[16] ^{1}H NMR (300 MHz, CDCl3) δ 7.35−7.31 (m, 6H), 7.19-7.16 (m, 9H), 7.11 (d, 2H, J=8.4 Hz), 6.96 (d, 2H, J=8.5 Hz), 5.92 (s, 1H), 2.33 (s, 3H).

2-Cumyl benzenesulfonamide:[17] ^{1}H NMR (300 MHz, CDCl3) δ 7.59 (d, 2H, J=8.5 Hz), 7.34-7.31 (m, 2H), 7.21-7.15 (m, 5H), 5.24 (s, 1H), 3.39 (s, 3H), 1.64 (s, 6H).

***N*-benzhydryl-4-methylbenzenesulfonamide:**[10] ^{1}H NMR (300 MHz, CDCl3) δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.22-7.17 (m, 6H), 7.10-7.08 (m, 6H), 5.56 (d, *J* = 7.3 Hz, 1H), 5.35 (d, *J* = 7.3 Hz, 1H), 2.35 (s, 3H).

H1 N,N`-Bis (4-dimethyl phenyl) cyclohexane-1,2-diimine: ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.56 (s, lH), 7.84 (d, J = 15.4 Hz), 7.76 (d, J = 8.7 Hz), 6.76 (d, J= 8.7 Hz), 3.58 (s, lH), 3.2 (s, 6H), 2.07 (d, J=8.7) 1.92 (d, J=7.8), 1.68 (d, J=8.2), 1.58 (m, 2H), 1.38-1.12 (m, 4H).

H2 N,N`-Bis (4-methoxybenzylidene) cyclohexane-1,2-diimine: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (s, 2H), 7.54 (d, J=9), 6.82 (d, J=9 Hz), 3.78 (s, 6H), 3.42–3.27 (m, 2H), 1.20–1.97 (m, 8H).

H3; N,N`-Bis(2,4-dichlorobenzylidene)cyclohexane-1,2-diimine: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.57 (s, 1H), 8.52 (s, 1H), 7.98 (d, J=8.5 Hz), 7.86 (d, J=8.40Hz, 1H), 7.33 (d, J=1.9 Hz), 7.28 (d, J=1.92 Hz, 1H), 7.10- 7.22 (m, 2H,) 3.5-3.4 (m, 1H), 2.00-1.42 (m, 8H).

H4 N2-Bis(4-(trifluoromethyl)benzylidene)cyclohexane-1,2-diimine: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.22 (s, 2H), 7.69 (d, J=8.1, 4H), 7.57 (d, J=8.2, 4H), 3.50–3.4 (m, 2H), 1.98–1.768 (m, 6H), 1.57–1.46 (m, 2H).

J1 N,N`-Bis(4-nitrobenzylidene)-6,6-dimethylbiphenyl-2,2-diimine: ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.31 (s, 2H), 8.19 (d, J= 8.9 Hz, 4H), 7.62 (d, J= 8.7 Hz, 4H), 7.28 (t, J= 7.7 Hz, 2H), 7.18 (d, J=7.5 Hz, 2H), 6.89 (d, J= 7.8 Hz, 2H), 2.02 (s, 6H).

2.6 References:

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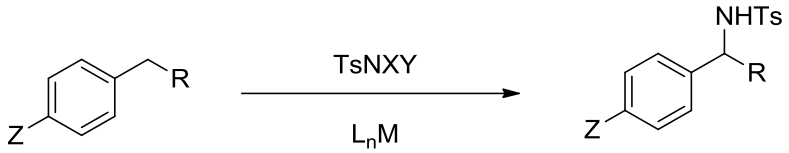
CHAPTER THREE

A Mechanistic Study of Ligand-Assisted, Copper-Catalyzed Benzylic Amination

3.1 Introduction

Amines and their derivatives are primary constituents in the preparation of a number of products, ranging from amino acids to polymeric chains. Among the several works on amination reported, the metal-free[1] and metal-based[2] procedures have gained considerable attention. Most of the recent works cited in the literature concentrates on the use of transition metal complexes as catalysts for C-H activation. The potentials of such catalysts lie in the ability to control the selectivity of the reaction, i.e., to induce some degree of enantio- or diastereomeric excess. Complexes of many transition metals have been found to catalyze such C-H amination reactions using several aminating reagents, most commonly imidoiodinanes (ArI=NZ), azides (Z-N_3) or haloamine derivatives (ZNNaX).



Scheme 1: Amination reaction with haloamine-T

The mechanism of aziridinations was studied by Jacobsen[3], Scott[4] and O'Brien[5] with moderate to excellent enantioselectivities as well as diastereoselectivities employing chiral metal complex catalysts. Some of these systems do not react stereospecifically, often producing cis/trans aziridine product mixtures, suggestive of a stepwise formation of the two C-N bonds. The stereoselectivity of C-H amination reactions has not been

investigated extensively.

There are some reports on intramolecular L_2Rh_2-[6] and Ru(pybox)-catalyzed[7] -catalyzed reactions, reagent-based $[ArS(O)(NSO_2Ar)NH_2]$/Rh-catalyzed[8]-catalyzed intermolecular reactions, and (salen)Mn-catalyzed[9] intermolecular aminations of benzylic substrates with moderate to high enantioselectivities. These stereoselectivity features are determined primarily by the nature of the reactive N-species that is involved in the step in which the C-N bond is formed.

For the most part the reactive intermediates in metal-catalyzed amination are unknown. It has been generally assumed that metal-imido (nitrene) complexes, LM=NZ, are the active N-transfer agents. Only in a few instances have structurally characterized imido-complexes been isolated and shown to effect aziridination or C-H insertions. Che and coworkers have investigated the reactions of isolable (porphyrin)$Ru(NSO_2R)_2$ complexes[10], which both aziridinate olefins and aminate hydrocarbon C-H bonds. Recently, Warren and coworkers reported on the C-H insertion reactivity of dinuclear $[(ketoiminato)Cu\text{-}N(adamantyl)]_2$[11]. In their following report in collaboration with Cundari, the kinetic isotope effects and correlations with C-H bond dissociation energies suggest that a monometallic LCu(NR) singlet diradical species is responsible for the C-H insertion[12].

Aside from the systems involving isolable metal-imido complexes, some insights have been gained from mechanistic probes of other metal-catalyzed aziridinations and aminations presumed to involve imido-metal intermediates. The radical clock experiments with rhodium catalyzed intramolecular amination shows no cyclopropane

ring opening products obtained from the amination reaction and is consistent to a electrophilic imido-Rh_2 complex which effects a concerted insertion.[13]

From mechanistic studies on copper-catalyzed aziridination, the general picture is less clear. Some Cu-catalyzed aziridinations using chiral ligands[4] achieve high enantioselectivities. The olefin stereochemistry is not always retained as expected for a concerted process. Computational studies of various imido-Cu complexes with different N-donor auxiliary ligands have mostly supported a ground state triplet state for such species. This triplet species reacts stepwise as a N-centered radical.[14]

An efficient system for benzylic amination was first developed employing anhydrous chloramine-T with commercial $[Cu(CH_3CN)_4]PF_6$ as catalyst.[15] Then our job became to identify suitable ligand partners for copper that could provide tailored catalytic activity and selectivity. Several ligand types, including phosphines, amines, α-amino acids and diimines (Schiff bases), were indeed found to enhance catalytic amination activity (ligand-accelerated catalysis) relative to without using any ligands. It was evident that the catalytic activity was increased with more electron deficient ligands and more electron rich substrates. This indicates an electrophilic aminating species, possibly $[L_2CuNSO_2Ar]^+$ created during the C-H bond activation process. A survey of the amination of prochiral benzylic substrates by chloramine-T catalyzed by complexes of *homochiral* aminoacids and diimines, however, achieved only low to modest enantioselectivities (0-35%).[16] These results caused us to consider further the identity of the aminating species in these reactions and the origin of its limited enantioselectivity. Further development of this intermolecular amination reaction requires an in-depth understanding of the reaction mechanisms. After going through all the ligand's scope the

obvious questions that came to our mind were:

1. What is the rate-determining step?
2. What is the reactive intermediate that effects C-H insertion?
3. How does this insertion take place, in a concerted or a stepwise manner?

To address these issues we have conducted a mechanistic study, including both experimental and computational probes, focusing on the crucial C-H insertion process. This study has already been published and here we describe the approaches and findings.[17]

3.2 Results and Discussion

The primary focus of our experimental mechanistic investigation is the C-H/C-N substitution process itself. The key questions are:

1. Is the substitution reaction rate-limiting?

2. Is the process concerted or step-wise?

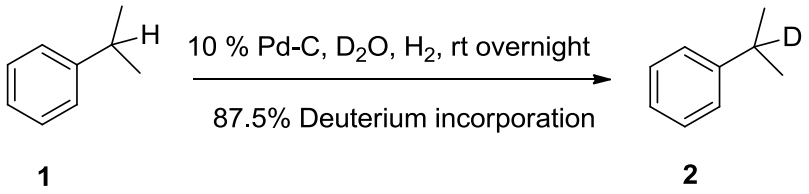
3. Is it stereoselective and, if so, in what sense, i.e. retention of configuration/inversion?

4. What is the active aminating agent?

3.2.1 Kinetic Isotope Effect

Our preliminary substrate and ligand-based reactivity survey showed significant electronic effects suggesting that the C-H insertion step could be rate-limiting. To address this issue further we prepared α- deuterio-cumene from cumene. The deuterium

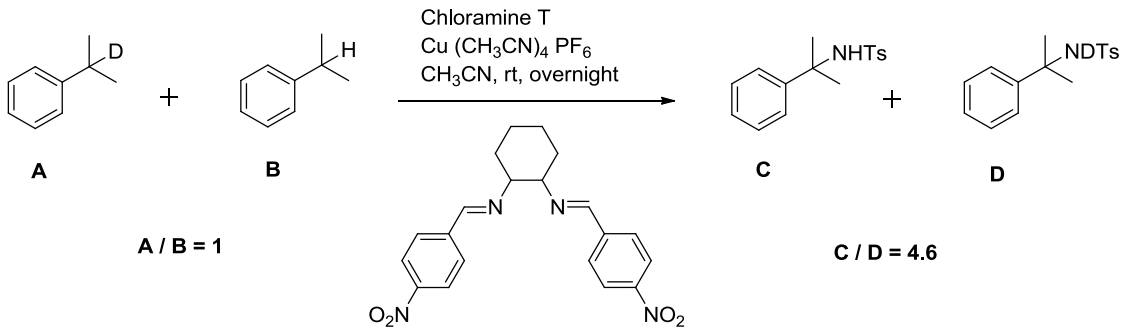
incorporation could be done in several ways. The recently developed chemoselective hydrogenation method, using heterogeneous palladium catalysts was found appropriate in this context. The cumene was stirred at room temperature with a catalytic amount of 10% Pd/C in D_2O under hydrogen baloon and the reaction process was followed by ^1H NMR spectroscopy (A small amount of aliquots was taken periodically in a sample vial and extracted with CH_2Cl_2/water and dried with dry Na_2SO_4. The solvent was removed by blowing N_2.). The gradual and continuous decrease in the signal intensity of the benzylic proton of cumene was observed throughout the reaction time, indicating the reaction of the Pd/C-catalyzed regioselective displacement of the hydrogen atom on the benzylic carbon by the deuterium atom. The procedure was modified from the previously reported preparation (scheme 1)[18]



Scheme 2: Preparation of Cumene-D

We carried out a competitive amination reaction between cumene and α-d1-cumene to determine the kinetic isotope effect (Scheme 3). A 1:1 mixture of the isotopomers **2**-H(D) was added to the preformed complex from diimine **3** and $[Cu(CH_3CN)_4]PF_6$ in CH_3CN (20 ^oC), followed by addition of anhydrous chloramine-T (0.8 equiv). We wanted to avoid H/D exchange in the product. (There is a possibility to get the deuterium exchange among the product C and D and the cumene could be removed by reduced pressure) After a minimum non-hydrolytic work up, GC-MS

analysis[19] of the reaction mixture showed the ratio of the product sulfonamides **C**-H/**D**-D and the isotope effect to be 4.6 at 40% conversion. The sizable primary k.i.e. indicates that C-H bond-breaking is substantially rate-limiting.



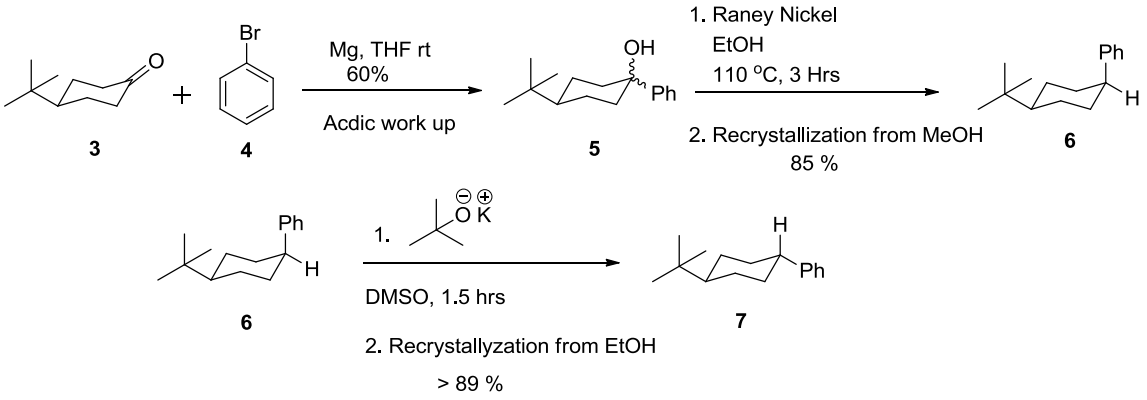
Scheme 3: Kinetic isotope experiments

3.2.2 Stereoselectivity Test

The stereochemical study of the C-H insertion of the nitrenoid species would give us some idea about the reaction pathway, e.g. a triplet pathway (stepwise reaction) or singlet pathway (concerted reaction). To probe the nature of the C-H insertion step, especially its concertedness, we examined the stereoselectivity of the Cu-catalyzed amination with a pair of diastereomeric hydrocarbon substrates, *cis*- (compound **6**) and *trans*-1-t-butyl-4-phenylcyclohexane (compound 7). A concerted insertion pathway is expected to be stereospecific, i.e. the respective isomeric substrates should produce opposite isomeric products with high selectivity.

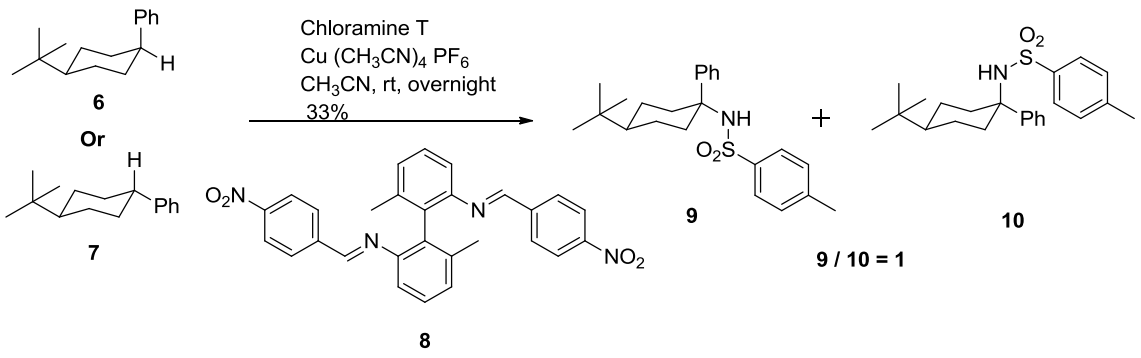
Cis- and trans- isomers of **6** were made by the following procedure (Scheme 4).[20] Commercially available 4-t-butyl cyclohexanone **3** was treated with phenyl magnesium bromide and form compound **5**. This compound **5** reacted with Raney nickel to produce mostly cis-1-t-butyl-4-phenylcyclohexane. After recrystallization from methanol, we

obtained cis-t-butyl-4-phenylcyclohexane (85% yield). Compound **6** reacted with potassium tert-butoxide in dimethyl sulfoxide (DMSO) to produce trans-**7**. The identification of *cis* and *trans* isomer was compared by tallying the tert-butyl group's NMR peak.



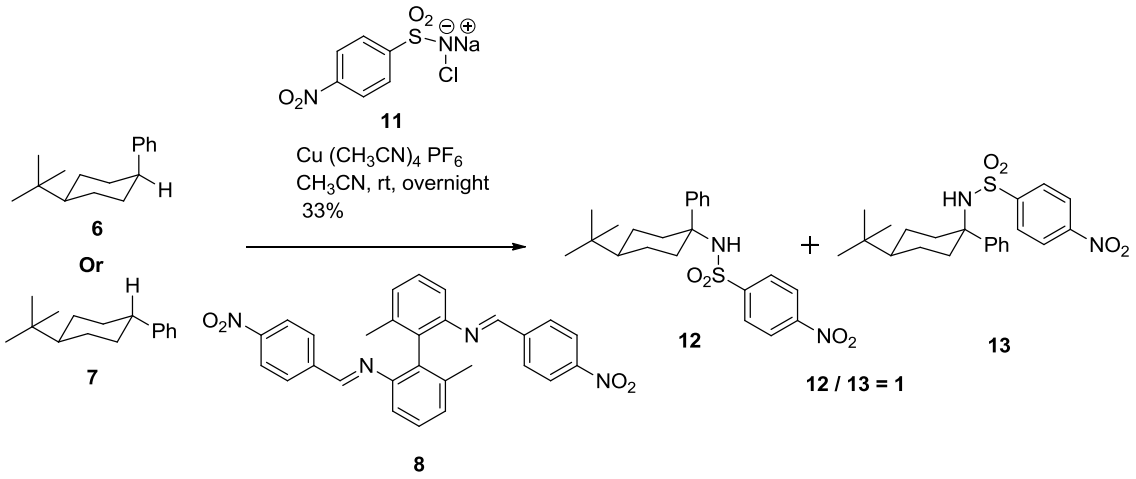
Scheme 4: Preparation of cis- and trans-1-t-butyl-4-phenylcyclohexane

Each substrate was separately treated with chloramine-T in the presence of the preformed catalyst from biphenyldiimine ligand **8** and $[Cu(CH_3CN)]_4PF_6$ under typical conditions. Chromatographic purification of the mixture from the reaction with cis-1-t-butyl-4-phenylcyclohexane (compound **6**) provided an inseparable mixture of the isomeric 1-t-butyl-4-phenyl-tosylamide-cyclohexanes (**9**-C/**10**-T, 33% yield) in a 1:1 ratio. Trans-1-t-butyl-4-phenylcyclohexane (compound **7**) was similarly aminated to give a nearly identical isomeric mixture of amination products **9**-C/**10**-T in 28% combined yield. These results strongly suggest the primary operation of a non-concerted process for the C-H insertion, likely proceeding through a common intermediate.



Scheme 5: Stereoselectivity Test with chloramine-T

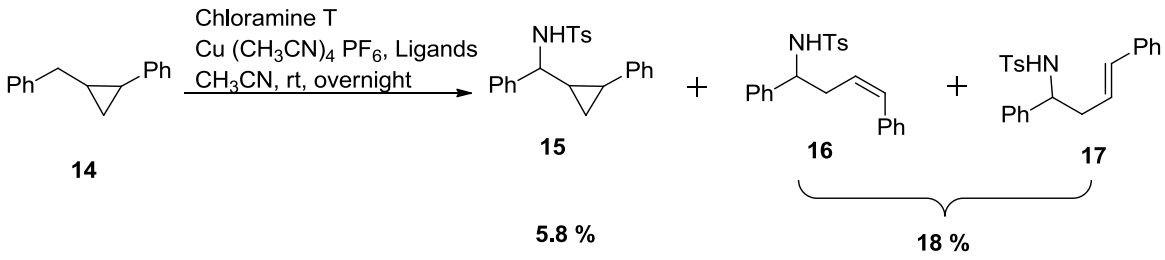
We wondered whether the electronic character of the aminating species could be sufficiently altered to affect the concertedness of the insertion step and hence its stereoselectivity. To test this idea the nosylamination of cis- and trans-1-t-butyl-4-phenylcyclohexane (**6**-C and **7**-T respectively) were examined using 4-O_2N-$C_6H_4SO_2NNaCl$ (Compound **11**), "chloramine-N"[21] (Scheme 6). Commercial $Cu(CH_3CN)_4PF_6$ (0.1 equivalent), the ligand **8** (0.1 equivalent) and 5 mL of dry CH_3CN were added to a round bottom flask containing dry molecular sieves under argon. To the well-stirred suspension cis- or trans-1-t-butyl-4-phenylcyclohexane (1 equivalent) was added into it. 4-O_2N-$C_6H_4SO_2NNaCl$ (1.3 equivalent) was added after one hour and the mixture was stirred at room temperature overnight. The mixture was then filtered through Celite and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (4:1 hexane:ethyl acetate). In this case an inseparable mixture of isomeric 4-t-butyl-1-phenyl-1-nosylcyclohexanes (9-C/9-T) was obtained (33% combined yield), still in a nearly 1:1 ratio. The rations of two products were confirmed by NMR integration. Clearly, the nosylamino transfer agent still effects C-H insertion primarily by a stepwise, non-stereoselective process.



Scheme 6: Stereoselectivity Test with chloramine-N

3.2.3 "Radical Clock" Experiment

The non-stereoselective feature of the C-H insertion suggested the possibility of a stereorandomizing carbon radical or carbocation intermediate during the amination process. We chose the compound **14** to test the validity of this hypothesis. We anticipated that if either a radical or a cation were generated at C-1, ring-opened amination products, e.g. N-(1,4-diphenylbut-3-enyl)-4-methylbenzenesulfonamide (compound **16**/**17**), would be produced via rapid ring opening of the intermediate.[22] Amination of compound **14** produced a mixture of cyclic sulfonamide (compound **15**) (6%) and ring-opened products **16**-C/**17**-T (18%). So we can conclude that the nitrenoid C-H insertion occurs stepwise and proceeds via H-atom (or hydride) abstraction to form the C-1 radical (or cation). The formation of ring-opened products cannot unambiguously differentiate radical from carbocation intermediates.



Scheme 7: Radical clock experiment

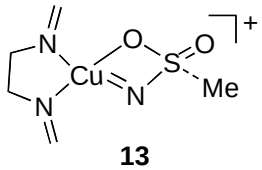
3.2.4 Computational Studies

In collaboration with Professor Kendall N. Houk's group (U.C.L.A.), we have performed DFT and CASSCF calculations on the mechanism of the Cu-catalyzed amination reactions of hydrocarbons with chloramine-T.

The mechanisms of a related reaction thought to involve Cu-imido intermediates, Cu-catalyzed alkene aziridinations with PhI=NTs and TsN_3, have previously been investigated by both experiment and theory. Kinetic and theoretical studies by Jacobson,[23] Norrby,[24] and Comba[25] suggest that the aziridination reactions occur via a Cu(I)/Cu(III) cycle involving a Cu-imido complex LCu=NTs as the reactive intermediate. On the other hand, alternative mechanisms involving Cu(II) active species were proposed by Pérez[26] and Vedernikov.[27] Cundari and coworkers suggest that the singlet-triplet gap is affected by the nitrene substituent. The singlet ground states are favored when aryl/alkyl groups are on the nitrene[28] while the triplet is favored with the hetero groups (like Chloramine-T) are on the nitrene.[29]

In this study, we investigated the structures and spin state of Cu-imido complexes and the C-H insertion transition state. *N*,*N*′-Dimethylene-1,2-ethylenediamine was used

as a model ligand and *N*-chloro-sodiomesylamide was used as an aminating reagent instead of chloramine-T in the calculations. Both the B3LYP[30] (Becke, three-parameter, Lee-Yang-Parr) and CASSCF[31] (complete active space self-consistent field) calculations suggest a triplet ground state for the Cu-imido complex. Single point CASSCF calculations on B3LYP predicted very similar singlet/triplet splitting. B3LYP calculations with a mixed basis set of LANL2DZ effective core potential basis set for Cu and 6-31G(d) for other atoms predict that the triplet complex is 5.8 kcal/mol more stable than the singlet complex. CASSCF geometry optimizations using CEP-31G(d) and LANL2DZ basis sets predict the triplet is 7.5 and 11.1 kcal/mol more stable than the singlet, respectively. This is in contrast to the CASSCF study by Cundari and coworkers on the (β-diketiminate)Cu-nitrene complexes, which predicts a singlet ground state.



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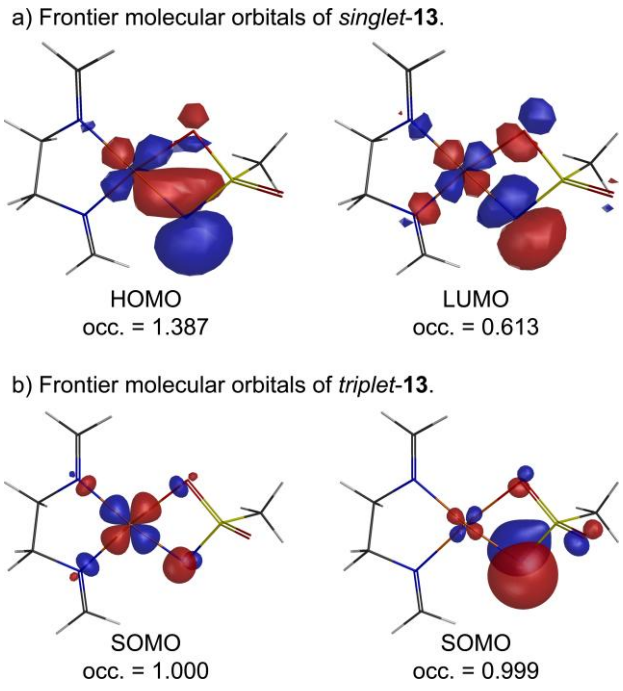


Figure 1. Frontier molecular orbitals of *singlet*- and *triplet*-13 from CASSCF calculations

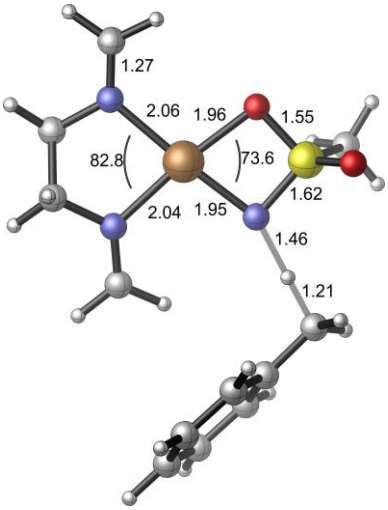
In the triplet C-H insertion transition state *triplet*-**TS14**, the toluene hydrogen approaches the perpendicular position of the imido-N, since the radical character is mainly located at the out-of-plane *p* orbital of the nitrogen. In contrast, in the singlet transition state, *singlet*-**TS14**, the toluene attacks the in-plane position of the Cu-imido complex.

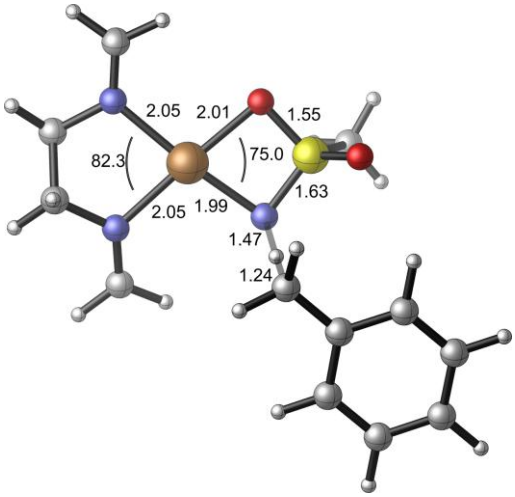
The CASSCF frontier molecular orbitals of the singlet and triplet Cu-imido complexes are shown in Figure 2. The two singly occupied orbitals in the triplet complex are the in-plane Cu d_{xy} orbital and the out-of-plane *p* orbital of the imido N, respectively (Figure 2b). These results suggest that the unpaired electrons of the triplet Cu-imido complex are mainly located on the imido N and Cu atoms, and that subsequent C-H insertion is most likely to occur at the imido N atom.

The triplet C-H insertion transition state is more stable than the singlet transition state. IRC (Intrinsic Reaction Coordinate) calculations on the singlet transitions state *singlet*-**TS14** leads directly to the amination product. In contrast, the triplet transition state *triplet*-**TS14** leads to a radical pair intermediate**.** This suggests the intermediate in the triplet C-H insertion is a carbon radical rather than a carbocation. Recombination of the radical pair may occur via multiple mechanisms:

(1) Spin crossover to form a singlet radical pair followed by rapid radical combination

(2) Intermolecular radical coupling.





$\Delta G^{\ddagger}$ = 10.2 kcal/mol

singlet-**TS14**

$\Delta G^{\ddagger}$ = 8.2 kcal/mol

triplet-**TS14**

Figure 2: Transition state structures of *singlet*- and *triplet*-TS14 from B3LYP calculations

The Gibbs free energy and enthalpy profiles for C-H insertion of toluene via singlet and triplet pathways were calculated at the B3LYP/LANL2DZ-6-31G(d) level and are shown in Figures 2 and 3, respectively. Transition states and intermediates in both profiles are with respect to the most stable triplet LCu-imido complex *triplet*-**13**. The spin crossover or radical terminations are shown with dashed lines.

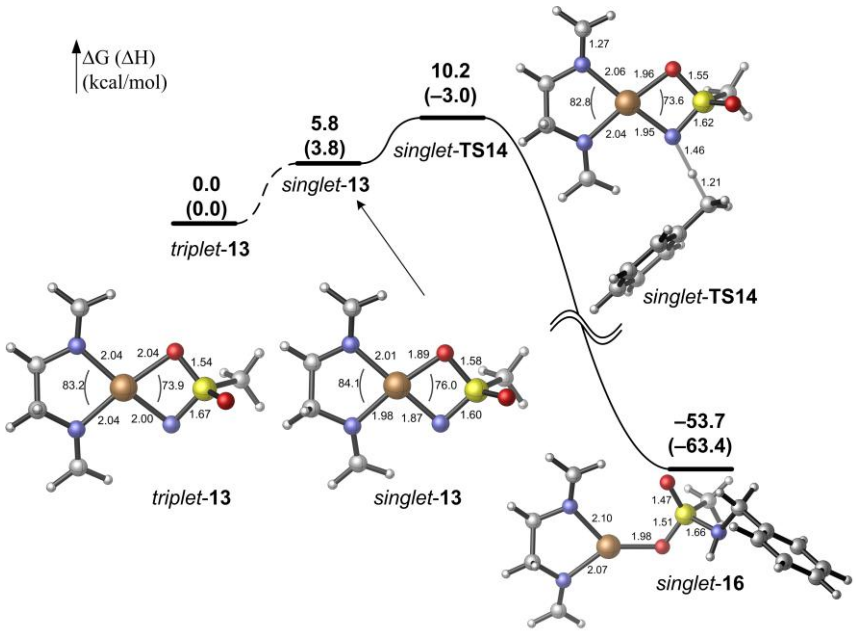


Figure 3: Potential energy profile for the singlet pathway

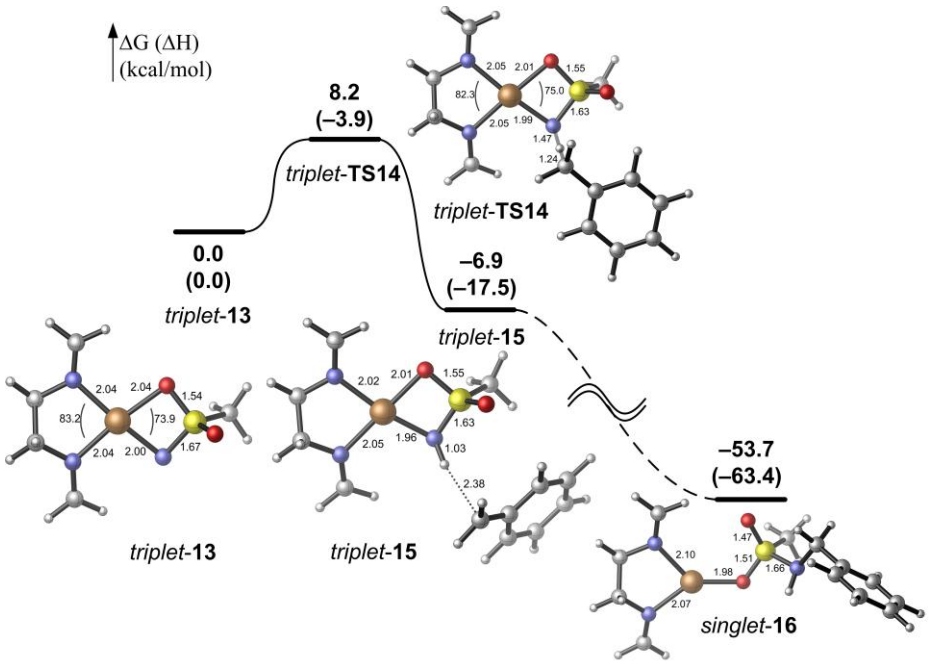
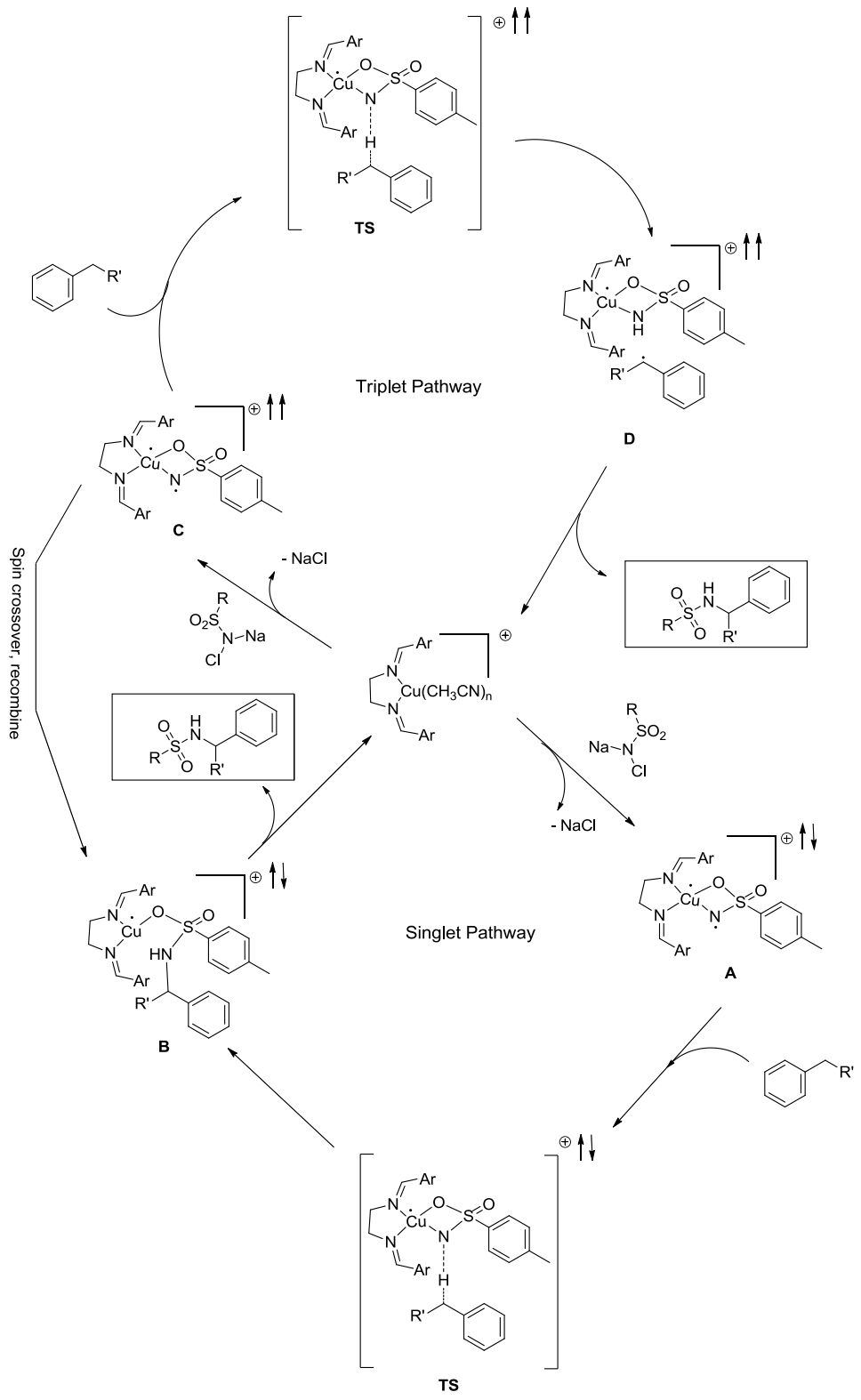


Figure 4: Potential energy profile for the triplet pathway

The k_H/k_D are calculated by the differences of the Gibbs free energies of the H/D-substituted transition states at 298K. Kinetic isotope effects (KIEs) on the C-H insertion of toluene were calculated at the B3LYP/LANL2DZ-6-31G(d) level. The resulting KIEs for the singlet and triplet pathways are 2.91 and 4.83, respectively. The experimentally observed KIE for the reaction with cumene is 4.6 (Scheme 2), in agreement with calculated KIE for the triplet pathway.

To study the electronic effects of substituents on the sulfonamide reagent, activation energies of the C-H insertion with two Cu-imido complexes, LCu-N-SO_2CH_3, and LCu-N-SO_2CF_3, were calculated using B3LYP. The results are given in Scheme 7. Both Cu-imido complexes have a triplet ground state. An electron-withdrawing group on the sulfonamide decreases the singlet/triplet gap of the Cu-imido complex from 5.8 kcal/mol for LCu-N-SO_2CH_3 to 2.3 kcal/mol for LCu-N-SO_2CF_3. Both complexes still prefer the triplet pathway in C-H insertion. The experimentally calculated KIE for the amination reaction with cumene is 4.6 (Scheme 3), in agreement with calculated KIE for the triplet pathway.

Based on these experimental and computational studies we propose the mechanistic pathways outlined in Scheme 8. In both singlet and triplet pathways the intermediate **A** and **C** respectively could form after the ligand exchange with copper complex and nitrene. The hydrocarbon was inserted in singlet and triplet pathways and form intermediate **B** and **D** respectively. The triplet intermediate **D** could undergo for a spin-flip and produce **B**. The reductive elimination of intermediate **B** and **D** produce the amination product. The rapid recombination of the radical pairs could explain the loss of carbon stereochemistry.



Scheme 8: Mechanistic cycle

3.3 Conclusion

Considering all the evidences, it appears that the triplet pathway dominates. The experimental observations from chapter one was showing low enantioselectivity. A substantial primary kinetic isotope effect, negligible diastereoselectivity, and the formation of ring-opened products with the cyclopropyl substrate together are indicative of a stepwise C-H insertion process. Computational study with reactive nitrene-species and hydrocarbon was pointing towards triplet (diimine)Cu(NZ) complex which acts as an N-centered radical, stepwise abstracting H-atom from substrate followed by radical rebound to make the C-N bond. A minor pathway involving concerted, stereoselective insertion via the singlet complex may also contribute. A primary kinetic isotope effect (KIE) was observed and calculations suggest that the KIE corresponds to the triplet C-H insertion transition state.

The DFT (Density functional theory) calculations on copper suggest a ground triplet state is common for these Cu-imido complexes. However, recent studies suggested that a biradical singlet could be the ground state for (β-diketiminate)Cu(NPh) and (β-diketiminate)Cu(NH) complexes. A recent DFT study on Ni-nitrene complexes by Cundari and coworkers suggest that the singlet-triplet gap is affected by the nitrene substituent. The singlet ground states are favored when aryl/alkyl groups are on the nitrene while the triplet is favored with the hetero groups (like Chloramine-T) are on the nitrene.

3.4 Experimental

General. Acetonitrile was refluxed over and distilled from calcium hydride. Some of the hydrocarbon substrates were obtained commercially and distilled before use. Commercial chloramine-T trihydrate was dried in a drying pistol over refluxing toluene under vacuum (0.1 mm) for 4-5 h; no thermal instability or decomposition was noted in any samples dried in this way. $Cu(CH_3CN)_4PF_6$ was obtained commercially. NMR spectra were recorded on a Varian Mercury NMR spectrometer at 300 MHz for ^{1}H- and 75 MHz for ^{13}C-NMR spectra. All chemical shifts (ppm) reported are relative to the NMR solvent peak. Electrospray (ESI) mass spectra were recorded on a Finnigan TSQ 700 mass spectrometer. GC-mass spectra (electron impact) were obtained on an Agilent bench-top HP6890/MSD5973. The following compounds were prepared by literature methods: diimine ligands **3** and **8**, N-chloro-N-sodio-4-nitro-benzenesulphonamide, cyclohexane derivatives 6-C and **7**-T, and cyclopropyl substrate **14**. .

3.4.1 Preparation of d_1-cumene

The procedure was modified from the previously reported preparation.[10] Commercially available cumene (2.0 mL, 19 mmol) was mixed with 10 wt % of Pd-C, 8 mL of D_2O and the reaction flask was fitted with two balloons full of hydrogen. The mixture was stirred overnight and then filtered through filter paper to remove the Pd-C. The reaction mixture was partitioned between ethyl acetate and water, the organic phase dried over $MgSO_4$, and concentrated by rotary evaporation. The deuterium content (87 %) of the recovered cumene was determined by ^{1}H NMR integration of the methyl groups to the tertiary hydrogen.

3.4.2 D-isotope effect determination

Commercial $Cu(CH_3CN)_4PF_6$ (19 mg, 0.049 mmol), diimine **3** (19 mg, 0.049 mmol) and 5 mL of dry CH_3CN were added to a round bottom flask containing dry molecular sieves (4Å, ca. 200 mg) under argon. To the well-stirred suspension the 1:1 mixture of cumene and deuterated cumene (68 µL, 0.49 mmol) was added. Anhydrous chloramine-T (89 mg, 0.39 mmol) was added after one hour and the mixture was stirred at room temperature overnight. The mixture was filtered through Celite to remove the precipitated copper salts and then analyzed by gas chromatography/mass spectrometry (GC-MS). The ratio of the d_0-product to the d_1-product (**Compound C**-H/**Compound D**-D) was 4.6 : 1.0.

3.4.3 Aminosulfonation of cis-1-t-butyl-4-phenylcyclohexane.

Commercial $Cu(CH_3CN)_4PF_6$ (28 mg, 0.073 mmol), diimine **8** (35 mg, 0.073 mmol) and 5 mL of dry CH_3CN were added to a round bottom flask containing dry molecular sieves (4Å, ca. 250 mg) under argon. To the well-stirred suspension was added *cis*-1-t-butyl-4-phenylcyclohexane[19] (**6**-C, 0.16 g, 0.73 mmol). Anhydrous chloramine-T (0.25 g, 1.1 mmol) was added to the reaction vessel after 30 min and the mixture stirred at room temperature overnight. The mixture was then filtered through Celite powder to remove insoluble metal-containing materials and the solvent was evaporated under reduced pressure. The crude residue was purified by preparative TLC (3:1 hexane:ethyl acetate). The ratio of the inseparable isomeric products **9**-T, **10**-C was determined by integration of the tertiary butyl group of each isomer (found 1.0:1.0). Combined yield: 9.3 mg (33%). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.96 (s, 1H), 7.88(d, 2H, J=8.1), 7.33-7.25

(m, 14H), 7.13 (d, 2H, J=8.1), 7.04 (d, 2H, J=8.4), 5.57 (s, 1H), 2.56 (d, 2H, J=12.9), 2.47 (s, 3H), 2.45(s, 3H), 2.22 (d, 2H,J=12), 1.93-1.62 (m, 8H), 1.3-1.09 (m, 6H), 0.95 (s, 9H), 0.90 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 167.0, 163.4, 146.9, 146.2, 142.9, 141.9, 140.6, 139.9, 129.5, 129.2, 128.8, 128.5, 127.7, 126.7, 126.2, 125.3, 59.6, 59.9, 47.5, 47.3, 38.63, 36.1, 32.6, 27.7, 23.2, 23.0, 22.8, 22.2, 21.7, 21.6. ESI-MS m/z 408.21 (M+Na) 449.21 (M+CH_3CN+Na).

3.4.4 Aminosulfonation of trans-1-t-butyl-4-phenylcyclohexane

Commercial $Cu(CH_3CN)_4PF_6$ (0.028 g, 0.073 mmol), diimine ligand **8** (35 mg, 0.073 mmol) and 5 mL of dry CH_3CN were added to a round bottom flask with dry molecular sieves (4Å, ca. 200 mg) under an argon atmosphere. *Trans*-1-t-butyl-4-phenylcyclohexane (**7**-T, 0.158 g, 0.73 mmol) was then added to the mixture. Anhydrous chloramine-T (251 mg, 1.1 mmol) was added after 30 min and the reaction mixture was stirred at room temperature overnight. The mixture was then filtered through Celite powder and the solvent was evaporated under reduced pressure. The crude residue was purified by preparative TLC (3:1 hexane:ethyl acetate). The yield of **9**-C/**10**-T: 8.0 mg, yield 28%, white solid. The ratio of the isomers was determined by integration of the tertiary butyl groups of each (found 1.0:1.0). ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.96 (s, 1H), 7.88(d, 2H, J=8.1), 7.33-7.25(m, 14H), 7.13 (d, 2H, J=8.1), 7.04 (d, 2H, J=8.4), 5.57 (s, 1H), 2.56 (d, 2H, J=12.9), 2.47 (s, 3H), 2.45(s, 3H), 2.22 (d, 2H, J=12), 1.93-1.62 (m, 8H), 1.3-1.09 (m, 6H), 0.95 (s, 9H), 0.90 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 167.0, 163.4, 146.9, 146.2, 142.9, 141.9, 140.6, 139.9, 129.5, 129.2, 128.8, 128.5, 127.7, 126.7, 126.2, 125.3, 59.6, 59.9, 47.5, 47.3, 38.6, 36.1, 32.6, 27.7, 23.2, 23.0, 22.8, 22.2, 21.7, 21.6. ESI-MS m/z 408.21 (M+Na), 449.21 (M+CH_3CN+Na).

3.4.5 Aminonosylation of trans-1-t-butyl-4-phenylcyclohexane.

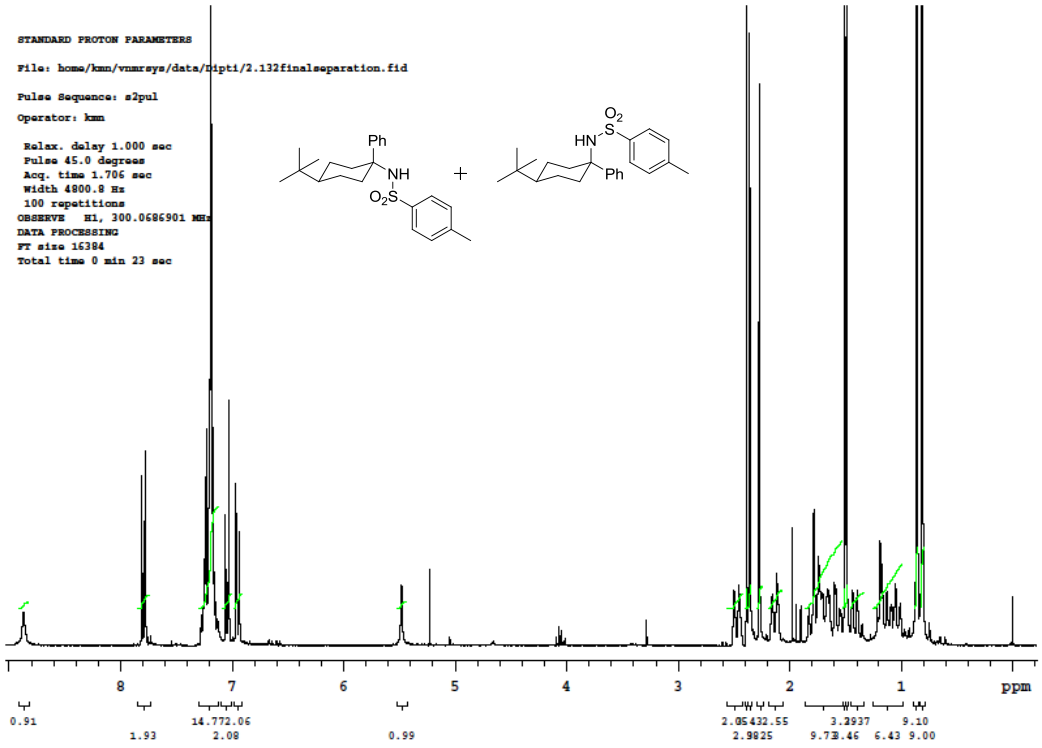
Commercial $Cu(CH_3CN)_4PF_6$ (10 mg, 0.025 mmol), diimine **7** (13 mg, 0.025 mmol) and 5 mL of dry CH_3CN were added to a round bottom flask containing dry molecular sieves (4Å, ca. 200 mg) under argon. To the well-stirred suspension *trans*-1-t-butyl-4-phenylcyclohexane (**7**-T, 55 mg, 0.25 mmol) was added. Anhydrous N-chloro-N-sodio-4-nitro-benzenesulphonamide (**11**, 80 mg, 0.31 mmol) was added into the reaction vessel after one hour and the mixture was stirred at room temperature overnight. The mixture was then filtered through Celite to remove the precipitated copper salts and the solvent was evaporated under reduced pressure. NMR analysis of crude product showed a 1:1 ratio of isomers from integration of the t-butyl protons. The isomers **12**-C, 13-T were separated by preparative TLC (3:1 hexane:ethyl acetate) but not stereochemically assigned. R_f (isomer 1) = 0.38; yield: 12 mg (12 %), white solid, mp 207-208 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.92(d, 2H, J=8.7), 7.33 (d, 2H, J=8.7), 7.11 (d, 2H, J=8.4), 7.04-6.97 (m, 3H), 4.80 (s, 1H), 2.76 (d, 2H, J=11.1), 1.75 (t, 2H, J=12.9), 1.58 (d, 2H, J=13.2), 0.91-0.78 (m, 3H), 0.634 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 147.7, 137.5, 135.2, 128.2, 128.1, 127.8, 127.6, 123.4, 60.9, 47.5, 38.3, 32.2, 27.3, 23.6. ESI-MS (m/z) 416.21 (M+Na). R_f (isomer 2) = 0.15; yield: 10 mg (10%); mp > 220 °C; ^1H NMR ($CDCl_3$, 300 MHz) δ 8.05 (d, 2H, J=8.7), 7.34-7.24 (m, 10H), 5.63 (s, 1H), 2.39 (d, 2H, J=12.9), 1.75-1.62 (m, 6H), 1.18-1.031 (m, 2H), 0.9 (s, 9H).

3.4.6 Aminonosylation of cis-1-t-butyl-4-phenylcyclohexane

The amination reaction of *cis*-1-t-butyl-4-phenylcyclohexane (6-C) was carried out in the same way as with the *trans* isomer. NMR analysis of crude product showed a 1:1 ratio of isomers **9**-C/**9**-T from the integration of the t-butyl proton peaks.

3.4.7 Amination of 1-benzyl-2-phenylcyclopropane

Commercial $Cu(CH_3CN)_4PF_6$ (9.0 mg, 0.024 mmol), diimine **7** (7.0 mg, 0.024 mmol) and 5 mL of dry CH_3CN were added to a round bottom flask containing dry molecular sieves (4Å, ca. 200 mg) under argon. To the well-stirred suspension was added 1-benzyl-2-phenylcyclopropane (**14**, 50 mg, 0.24 mmol). Anhydrous chloramine-T (94 mg, 0.36 mmol) was added to the reaction vessel after 30 min and the mixture was stirred at room temperature overnight. The mixture was then filtered through Celite and the solvent was evaporated under reduced pressure. The crude residue was purified by preparative TLC (3:1 hexane:ethyl acetate) to afford the cyclopropylmethyl amine derivative **15**; yield: 5 mg (6 %), white solid. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.66 (d, 2H, J=8.1), 7.26-7.17 (m, 5H), 7.12-6.96 (m, 5H), 6.57 (d, 2H, J=7.2), 4.96 (d, 1H, J=10.5), 4.87 (d, 1H, J=3), 4.61 (dd, 1H, J=4.5, J=5.1), 3.23-3.17 (m, 1H), 2.38 (s, 3H), 2.24-2.1 (m, 2H). ^{13}C NMR ($CDCl_3$, 75 MHz), δ 144.1, 139.0, 137.6, 136.2, 130.0, 128.6, 128.5, 128.4, 128.3, 127.1, 127, 126.7, 67.0, 58.6, 57.4, 38.4, 21.6. ESI-MS (m/z) 408.21 (M+Na). The NMR spectra for the isolated ring-opened products **12**-C and **12**-T (18 mg combined, 18% yield) were identical to those reported previously.[20]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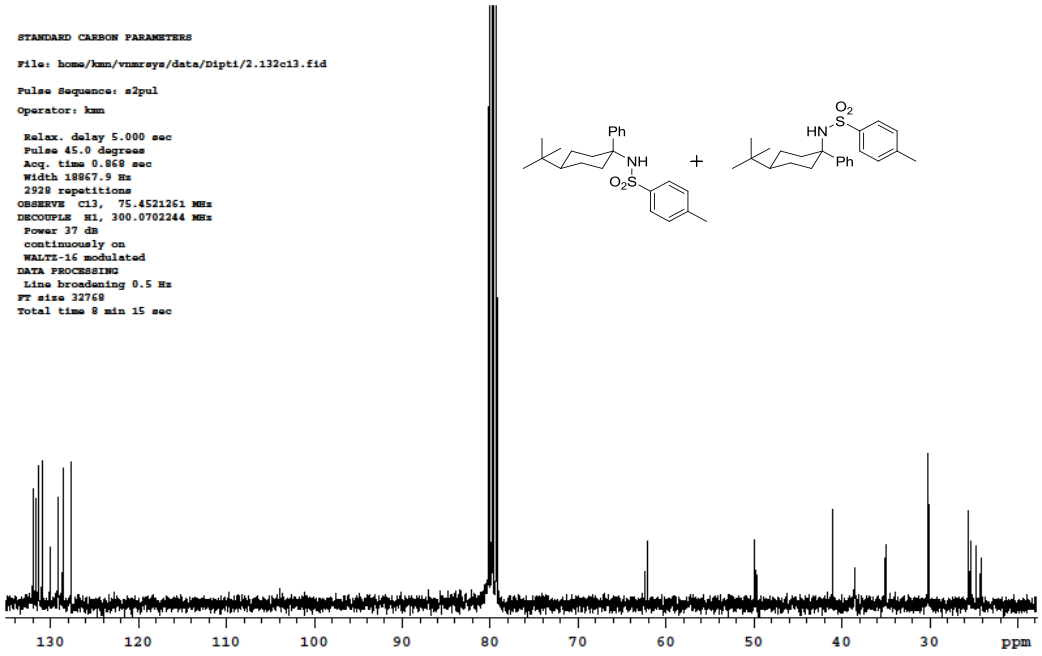
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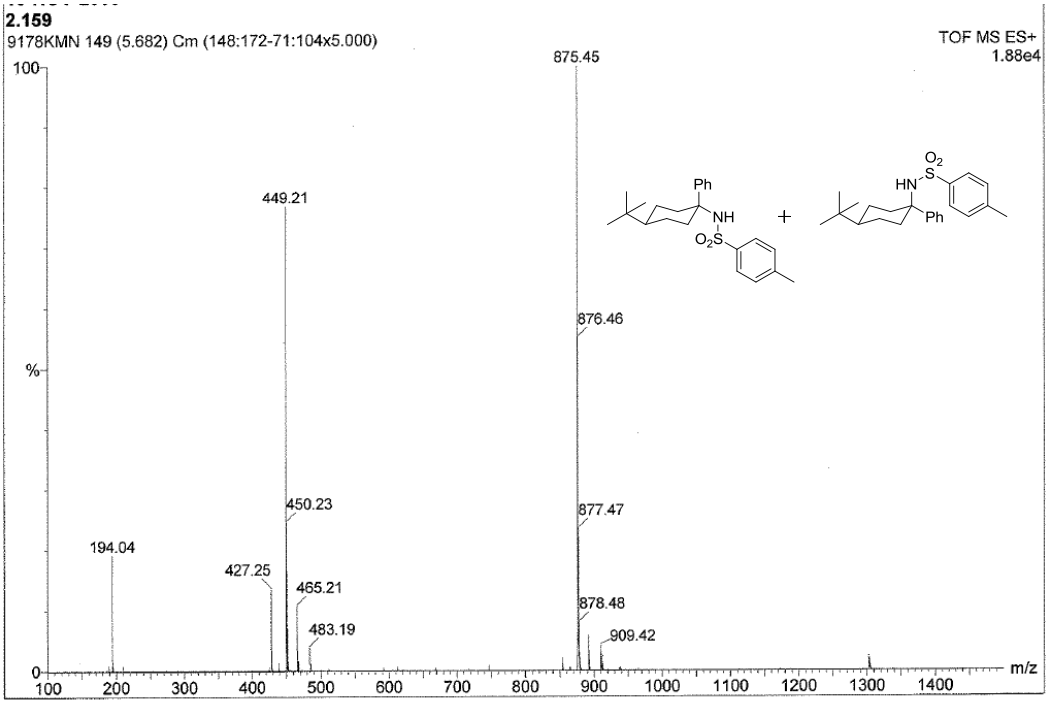
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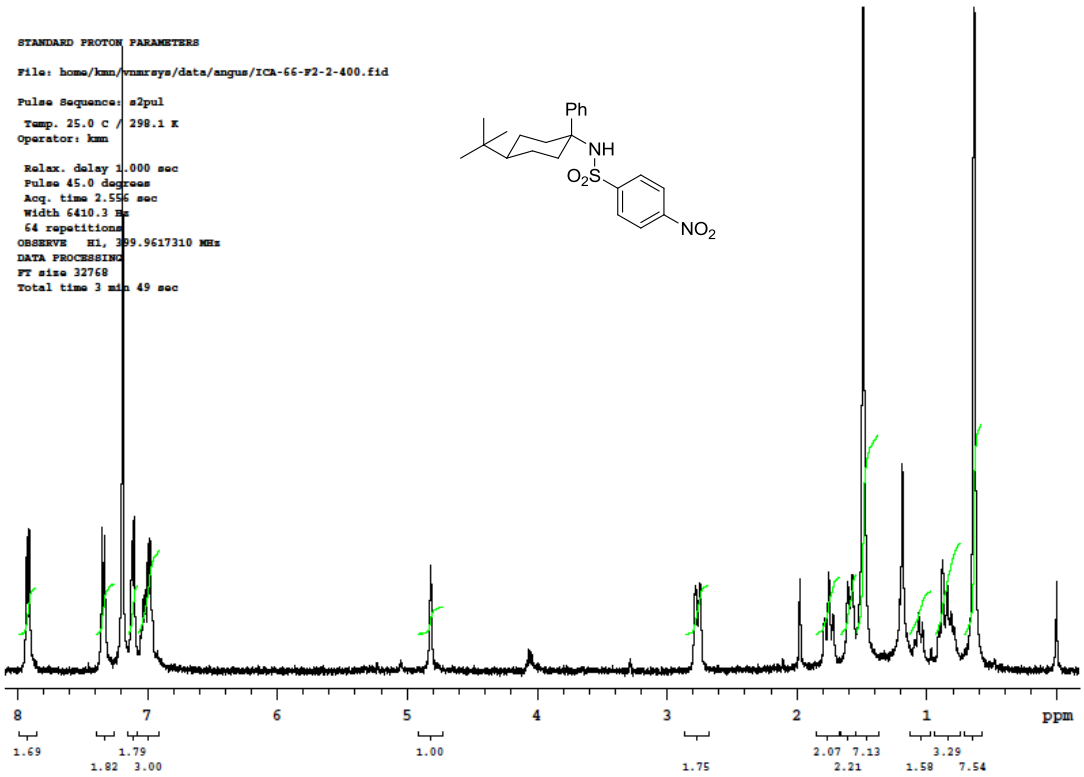
m/z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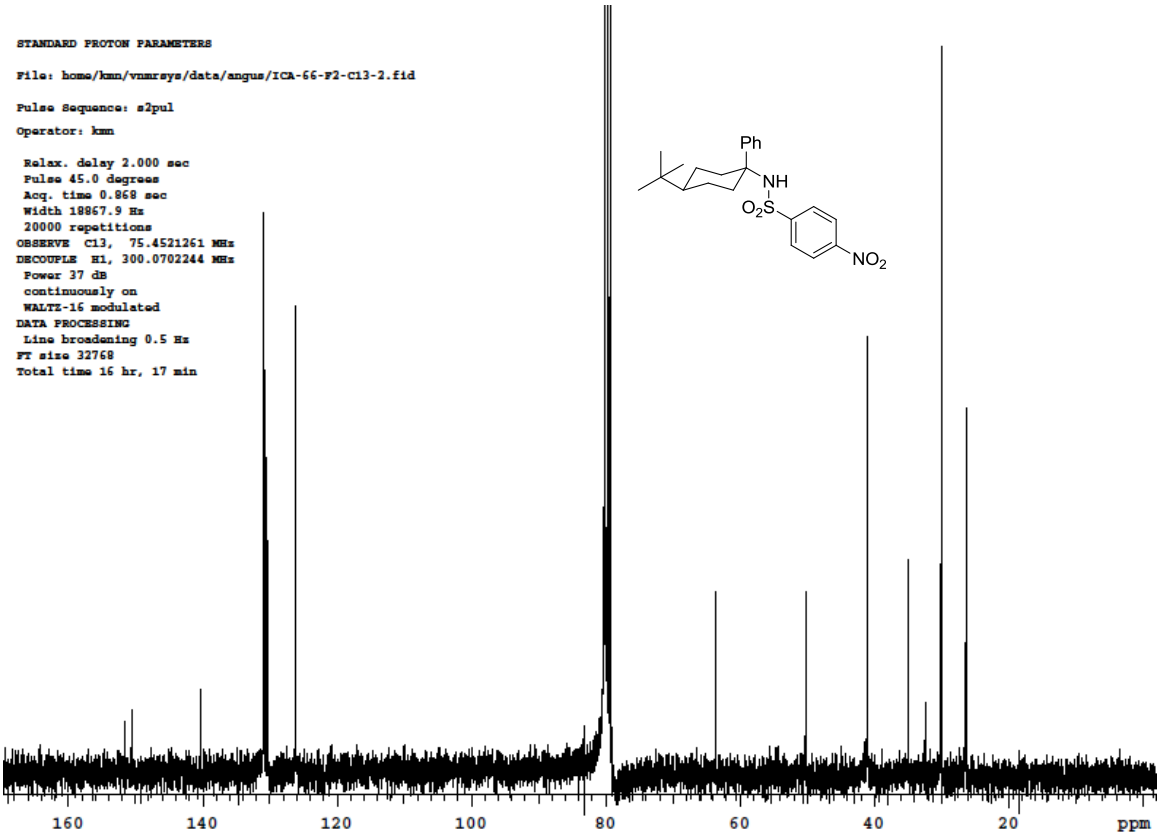
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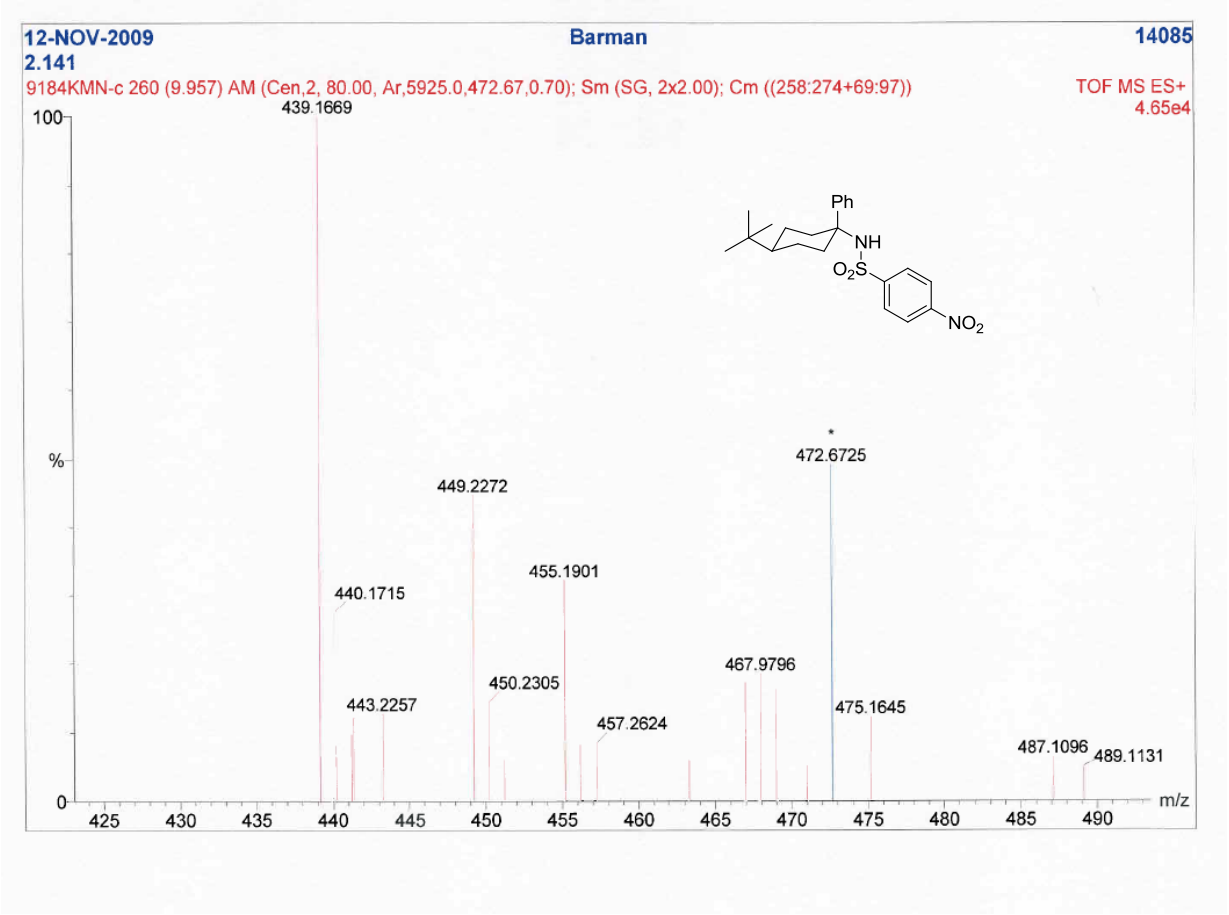
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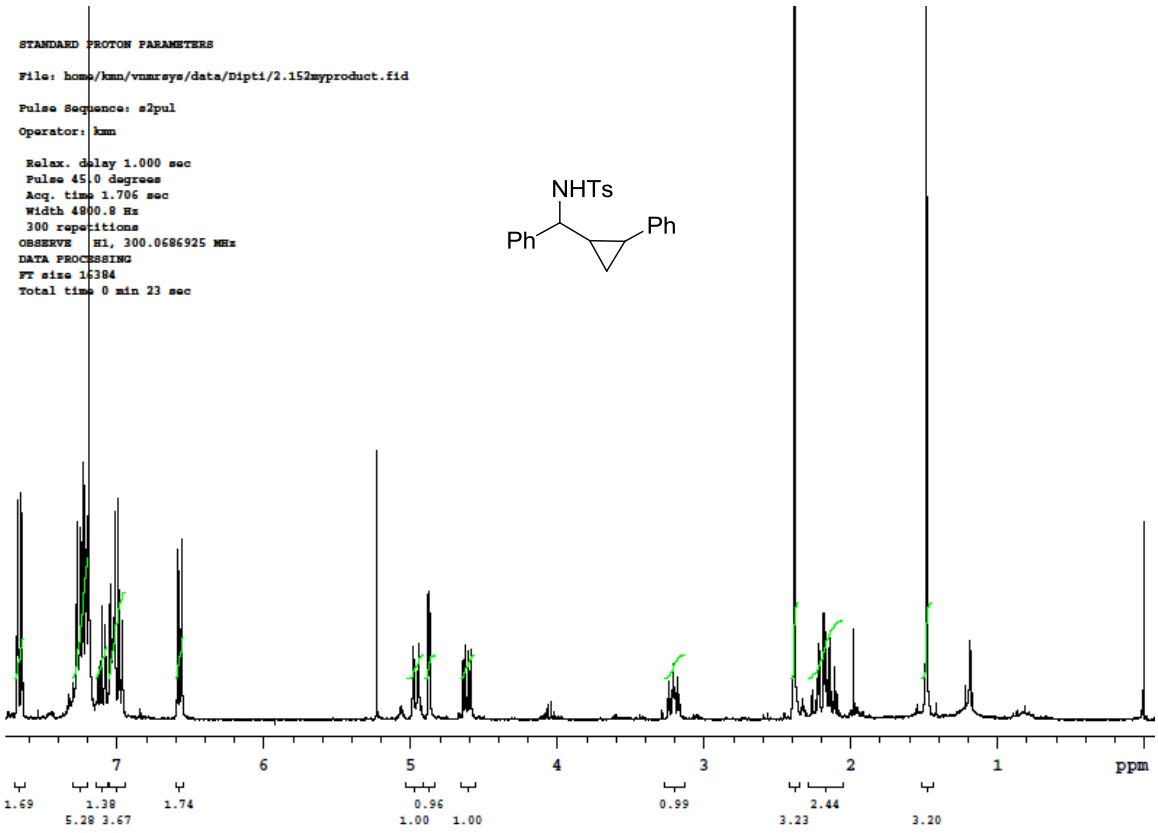
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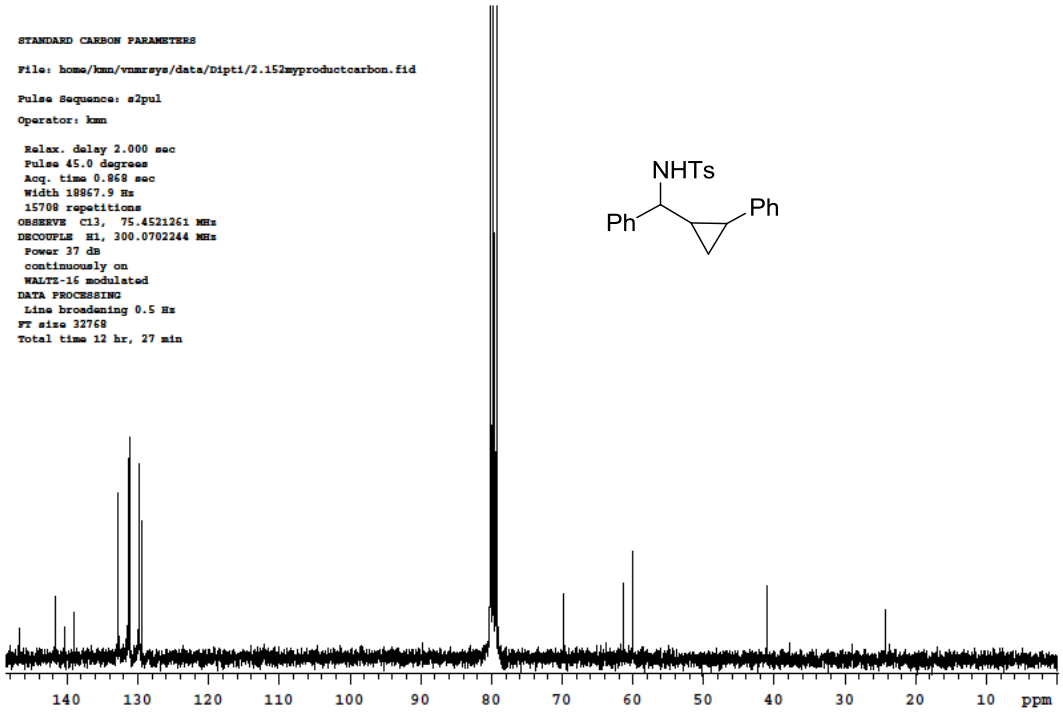
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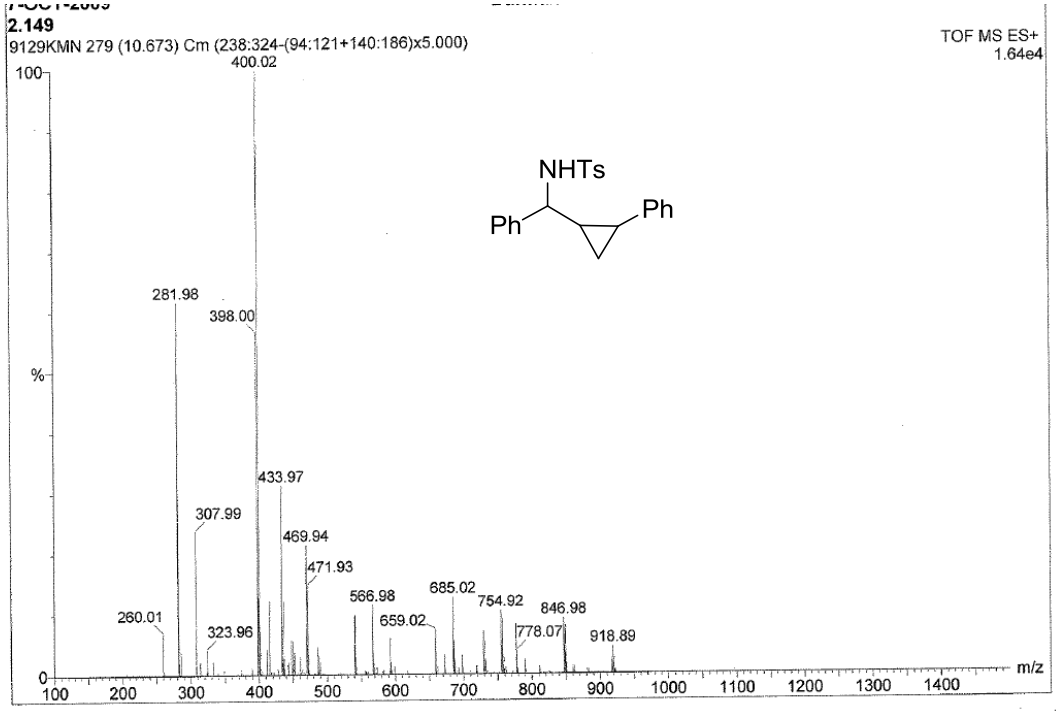
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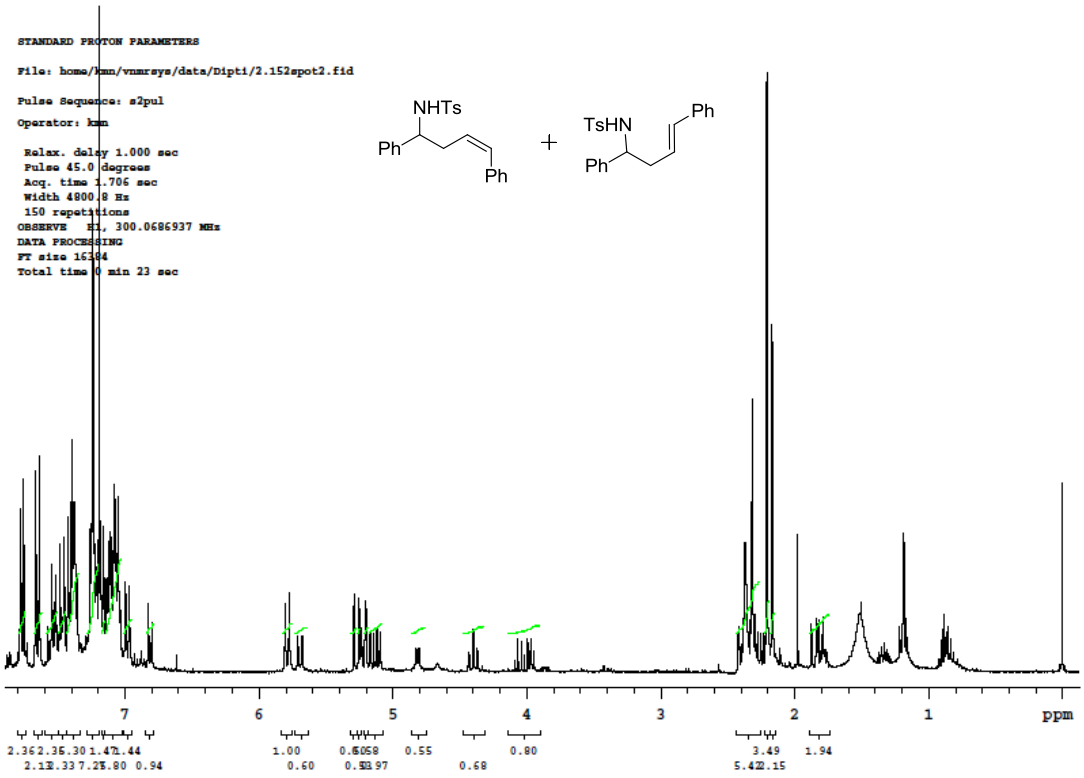
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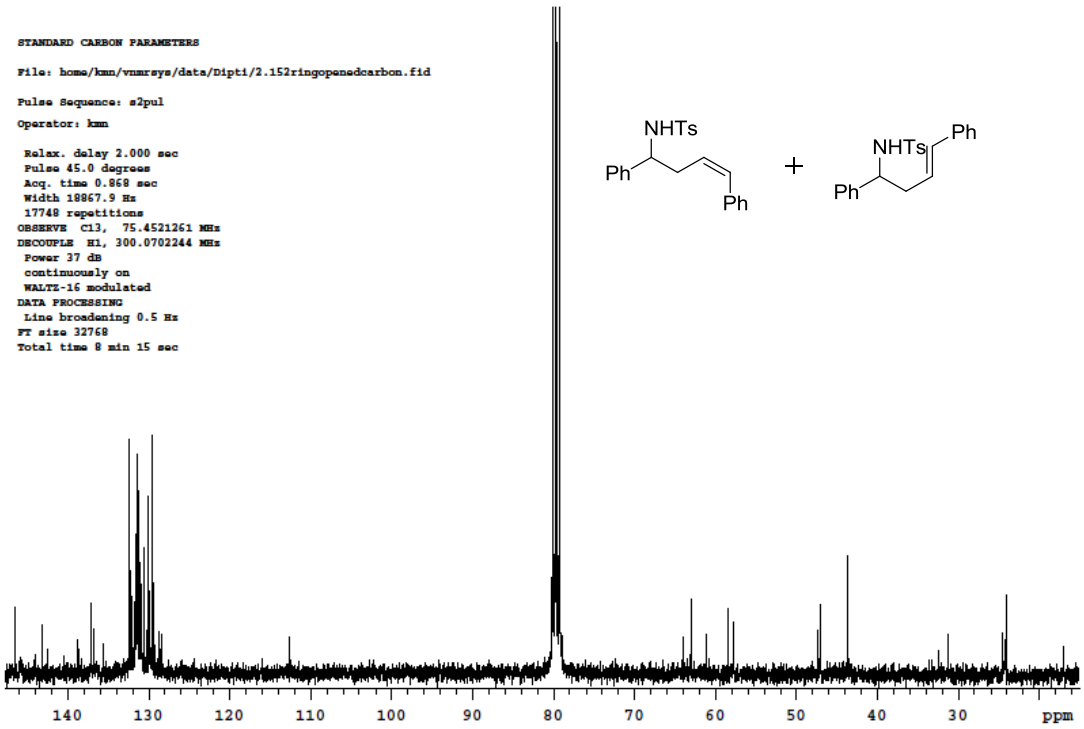
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3.5 References:

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[19] The isotopic pattern of molecular ions is different from the elemental pattern expected owing to the contributions from the organic groups attached. Therefore, even isotopes with such low natural abundance as ^{2}H, ^{13}C, ^{15}N and ^{18}O can bring about significant m+1and m+2 peaks. Mathematical correction equations to correct for such contributions using the known isotopic abundances of those isotopes have been used.

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CHAPTER FOUR

Copper Catalyzed, Enantioselective Intramolecular amination

4.1 Background and Introduction

Commonly used drugs are small organic molecules which activate/inhibit the function of a bio-molecule and results in a therapeutic benefit to the patient. Drug design is the inventive process of finding new medications based on the knowledge of the biological target. A major challenge in drug design is to economically synthesize molecules in large quantities. Therefore, new strategies for synthesis can not only evolve new synthetic methodologies but also making available new targets and materials.

Traditional ways of modification (e.g. oxidation/reduction, aromatic substitution, and nucleophilic/electrophilic attack) of an organic molecule (indicated by blue arrows) rely on the presence of reactive functional groups. Selective functionalizations of C–H bonds (red arrows) often have adjacent activating groups.[1]

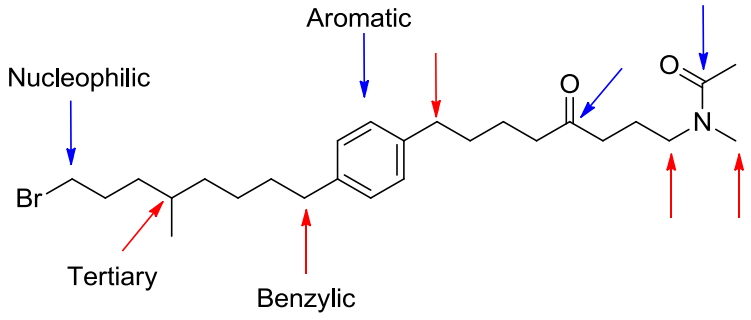
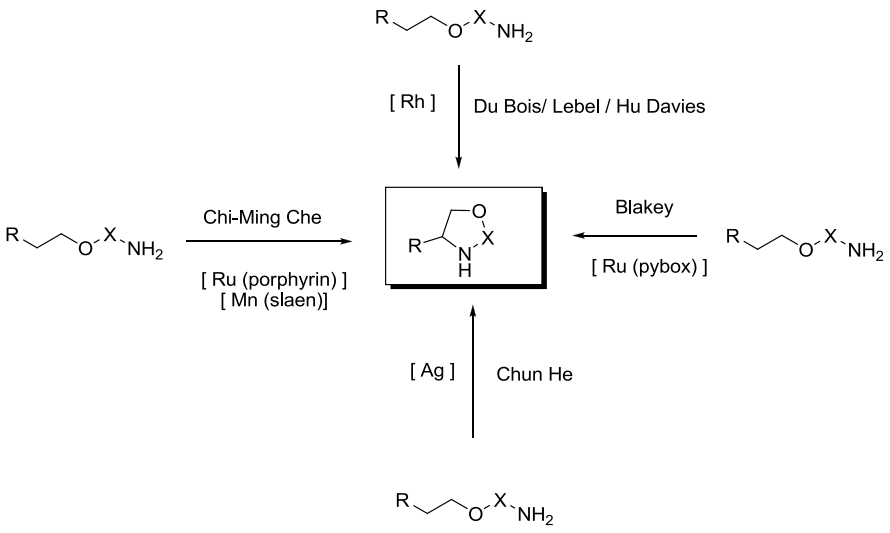


Figure 1: Synthesis by functional group modification (blue arrows) compared to C–H functionalization (red arrows)

The most synthetically useful recent developments in this field involve intramolecular C–H insertion reactions. Recent advancement in the intramolecular amination of C–H bonds has provided a unique opportunity for the synthesis of complex amine-derivatives.

In 1982, Breslow and Gellman[2] reported the use of Mn or Fe porphyrin catalysts for the amination of cyclohexane using PhI=NTs as a stoichiometric oxidant (~7% yield). While the subsequent work demonstrated that intramolecular variants of this transformation are more efficient. The survey of metal catalysts revealed that rhodium[3], ruthenium[4] and silver[5] (Scheme 1) are particularly effective, producing very high yield. The key transformation demonstrated the first uses of both the oxidant ($PhI(OAc)_2$) and catalyst system that have subsequently been widely applied in intramolecular amination reactions. Subsequent to this important methodological work, a number of groups have recognized the potential synthetic utility of this transformation and have begun to develop its synthetic scope[6].



Scheme 1: Types of intramolecular aminations

The use of carbamates as nitrene precursor has typically led to oxazolidinones via C–H insertion at the β-position, while in the case of sulfamates it inserts at the γ-position, affording homologous 6-membered rings. The six-member ring oxathiazinane formation is presumably favored by the elongated S-O and S-N bonds (1.58 Å) and the obtuse N-S-O angle (103°) of the sulfamate.[7]

Common building blocks for synthesizing antibiotics are derivatives of oxazolidinone. The first ever oxazolidinone drug was cycloserine (4-amino-1,2-oxazolidin-3-one), a second line drug against Tuberculosis.[8] Some of the important oxazolidinones are the latest generation of antibiotics, used against gram-positive pathogens e.g. Methicillin-resistant Staphylococcus aureus. There are several bacterial strains that became resistant to vancomycin, which triggered the need to develop a suitable oxazolidinone derivative. These oxazolidinone antibiotics are considered as a choice of last resort where every other antibiotic therapy has failed.

The intramolecular amination reaction facilitates production of oxazolidinones derivatives. The philosophy behind our approach is to begin with inexpensive starting materials and develop simple, safe, environmentally acceptable synthesis steps that would allow selectivity (chemo-, regio-, diastereo-, and enantio-), support atom economy and achieve high yield.

4.2 C-H Amination

As part of our ongoing project to discover and elucidate new C-H bond activation reactions of hydrocarbons catalyzed by non-precious metal catalysts, we focused first on the intermolecular amination of benzylic substrates by chloramines-T with copper

complexes. Diimine (Schiff base) ligands in combination with commercial $[Cu(CH_3CN)_4]PF_6$ were found to provide an efficient catalysis for the intermolecular benzylic C-H bond activation by anhydrous chloramine-T.

In order to improve the scope of the intramolecular C–H aminations, recently attention has been paid to the incorporation of new transition metal catalysts, designing of new ligands and designing of suitable nitrene precursors. Milder conditions, shorter reaction times, and a broader substrate scope still remain desirable synthetic improvements to these transition metal-catalyzed intramolecular C-H amination reactions.

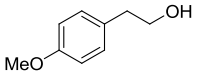
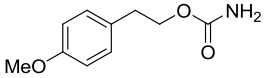
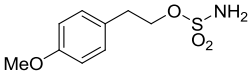
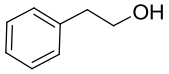
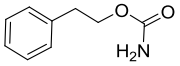
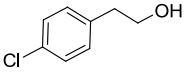
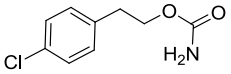
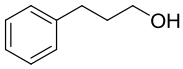
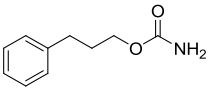
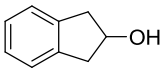
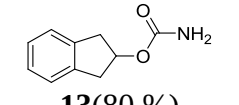
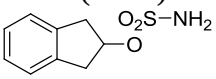
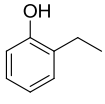
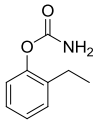
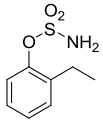
This part of the thesis has been submitted for publication. Here we are discussing in details about intramolecular amination reactions of carbamates and sulfamates by using $[Cu(CH_3CN)_4]PF_6$, Schiff base ligands and iodosylbenzene as oxidant.[9]

4.3 Preparation of Sulfamate and Carbamate Amination Substrates

Reported protocols for the synthesis of sulfamate esters, potential amination substrates, typically employ sulfamoyl chloride $[ClSO_2NH_2]$, a convenient reagent for preparative scale, made from commercially available, inexpensive $ClSO_2NCO$ and concentrated formic acid. The condensation reaction of $ClSO_2NH_2$ with most primary and secondary alcohols (pyridine, CH_2Cl_2) furnishes the target sulfamates with 85-95% yield. Similarly the synthesis of a typical propanamide is done via condensation reaction of the primary or secondary alcohol to trichloro isothiocyanate with 80-95% yield.The yield of the sulfamates and carbamates from the corresponding alcohols are shown in Table 1. ^{1}H-

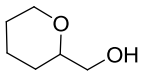
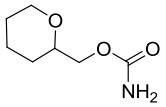
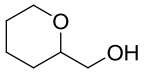
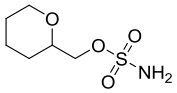
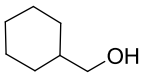
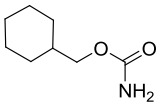
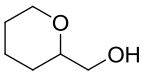
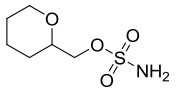
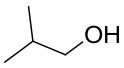
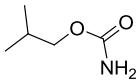
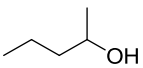
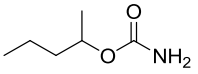
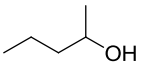
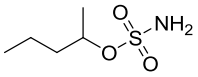
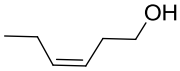
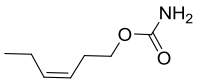
NMR analysis indicated that the product carbamates were formed in >95% purity and were thus used without further purification.

Table 1: Preparation of benzylic carbamates and sulfamates

Entry	Substrate	Carbamate/ Sulfamate substrate
1		 **1** (92 %)  **3** (85 %)
2		 **5 (**82%)
3		 **7** (88 %)
4		 **9** (85 %)
5		 **11** (82 %) **13**(80 %)  **15** (82 %)
6		 **17 (**96 %)  **19** (78 %)

A set of aliphatic tethered carbamates and sulfamates substrates was efficiently prepared (table 2) from the corresponding alcohols by reaction with trichloro- acetyl isocyanate (for carbamates) and chlorosulfonamide (for sulfamates), respectively.

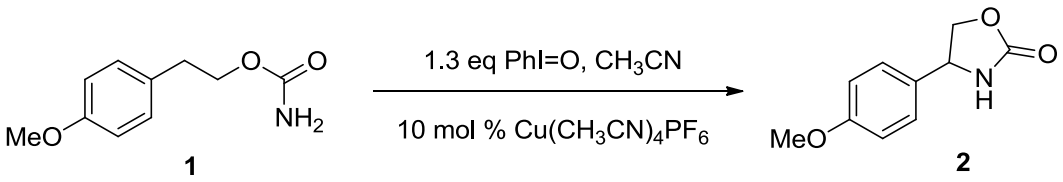
Table 2: Preparation of 2^o and 3^o carbamates and sulfamates

Entry	Substrate	Carbamate/ Sulfamate substrate
1		 **21(95%)**
2		 **23 (93%)**
3		 **24 (91%)**
4		 **26 (90%)**
5		 **28 (96%)**
6		 **30 (92%)**
7		 **32 (95%)**
8		 **34 (88%)**

4.4 Copper-Catalyzed Cycloamination Reactions

Initially, we tried to cyclize the sulfamates and the carbamates with iodobenzene di-acetate [$PhI(OAc)_2$] along with magnesium oxide (MgO) in the presence of copper(I) [$[Cu(CH_3CN)_4]PF_6$] catalyst. We expected that the oxidant will react with the carbamates *in-situ* and would form the imino-iodinane[10], which in turn would form the oxazolidinones in presence of copper catalyst. Inspite of several attempts using various solvents at various temperatures we did not witness any intramolecular amination product. So we decided to use a different oxidant than iodobenzene di-acetate ($PhI(OAc)_2$). We did not see any products with $PhI(OAc)_2$. Iodosylbenzene [PhIO] is an oxidant, which could react with the carbamates *in-situ* and form the imino-iodinane.[10] Compound **1** along with PhIO and prospective catalysts $Cu^{II}Cl_2$ and $[Cu^{I}(CH_3CN)_4]PF_6$ in various solvents were assessed. The results are summarized in table 3. We also tried to observe the solvents' effect for this intramolecular C-H activation. We used dichloroethane, acetonitrile and benzene as solvent (1.3 equivalent PhIO, 0.1 equivalent $Cu(CH_3CN)_4PF_6$ / 0.1 equivalent ligands 45 ^oC, 12 hr).

From this study, the combination PhIO/$[Cu(CH_3CN)_4]PF_6$ (10 mol%) in acetonitrile (45 ^oC, 12 hr) was found to be the most effective, providing a modest 26 % conversion to oxazolidinone **2** from **1** (Scheme 2). In the absence of the copper complex the oxazolidinone was not produced.

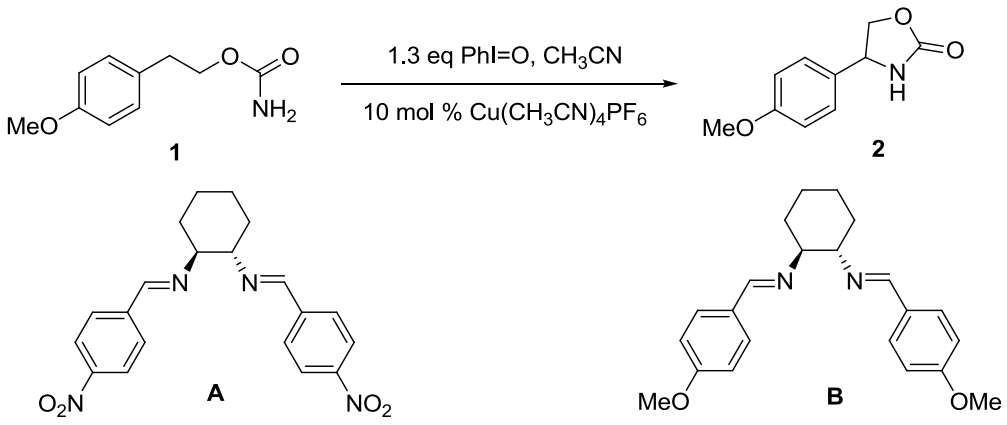


Scheme 2: Copper catalyzed intramolecular amination

Table 3:Solvent effect

Solvent effect	% of NMR yield
$(CH_2Cl)_2$	21
CH_3CN	67
C_6H_6	28

After achieving these modest yields, we decided to use ligands to try to improve the yield of oxazolidinone. Reactions of **1** were conducted in the presence of representative ligand types (scheme 3) under the same conditions as with the "unligated" $[Cu(CH_3CN)_4]PF_6$ (1:1 Cu : Ligand) and the yield of oxazolidinone **2** was determined by NMR integration and/or isolation; the results are summarized in Table 4. In the absence of the copper complex oxazolidinone was not produced. Substantial improvements in conversion and yield were found with phenanthroline and electron-poor diimine Schiff base ligand **A**, while PPh_3 and electron-rich Schiff base ligand **B** were less effective than the ligandless Cu catalyst. The accessibility of diverse diimine ligands from commercially available diamines and aldehyde building blocks provides a convenient set of ligands for catalyst tuning. Hence, we used these ligands in the follow-up studies.



Scheme 3: Ligand used for amination

Table 4:- Effect of ligands on the amination of 1

Ligand	Time (hr)	% of NMR Yield
None	12	26
PPh_3	12	15
Phenanthroline	12	48
B	12	15
A	12	62

We then treated carbamate ester (compound **1)** with PhIO in acetonitrile at 45^{o}C, in the presence of catalyst (10 mol%) and ligand A (10 mol%) to see it's reactivity over the time. We took aliquotes from the reaction flask over the time and removed the solvent in high vacuum pump and dissolved the crude reaction mixture in deuterated chloroform. The yield of oxazolidinone **2** was determined by NMR integration at various times (Figure 2). It was observed that the reaction achieved ~54 % yield of oxazolidinone in 5 hrs.

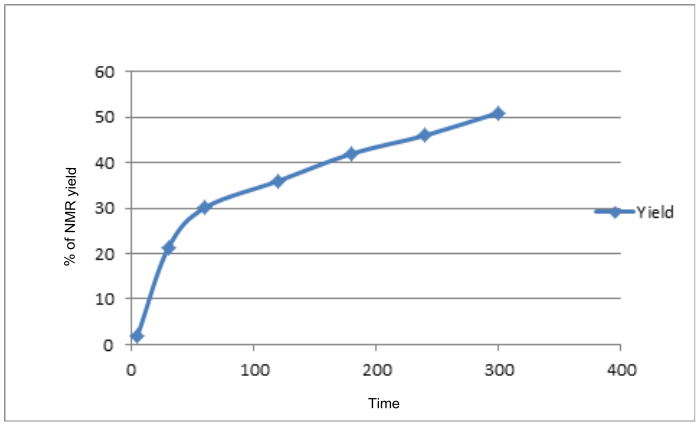
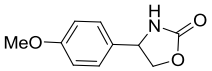
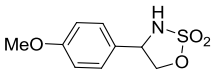
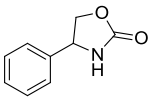
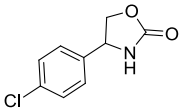
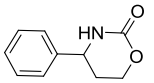
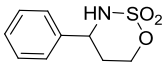
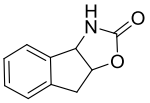
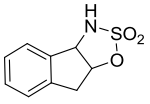
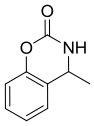
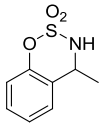


Figure 2: Product 2 formation over time

An assessment of the scope of the amination of benzylic substrates was then conducted with a set of representative sulfamates and carbamates using ligand **A** with $Cu(CH_3CN)_4PF_6$. The amination reactions were conducted under the same conditions established for the carbamate **1** (CH_3CN, rt, 6-12 hr, 0.1 equiv $Cu(CH_3CN)_4PF_6$ / 0.1 equiv L); the results are summarized in Table 5. In all cases, oxathiazinane heterocycles were formed exclusively and neither of the five-membered ring sulfamidates was obtained. Product ratios were determined by ^1H NMR analysis of the unpurified material. The yield of the sulfamates and the carbamates from the corresponding primary alcohol are given in the row 3 of table 3. All of the compounds were made before (except entry 1 and 3) and the ^1H-NMR was compared with the reported literatures.

Table 5:- Cu-catalyzed amination of benzylic substrates

Entry	Carbamate/ Sulfamate substrate	Cyclic product	Yield[a] (conv)[b]
1	**1**	 **2**	62 (67%)
2	**3**	 **4**	No reaction
3	**5**	 **6**	42 (44)
4	**7**	 **8**	32
5	**9**	 **10**	54 (57)
6	**11**	 **12**	56 (59)
7	**13**	 **14**	62 (68)
8	**15**	 **16**	70 (72)
9	**17**	 **18**	No reaction
10	**19**	 **20**	57 %

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[a] isolated yield after chromatography [b] conversion determined by NMR integration of substrate/product in the unpurified reaction mixture

Moderate to good yields of cyclized oxazolidinone amine derivatives were obtained with several substrates. Important features of the reactions include:

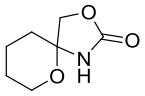
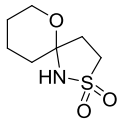
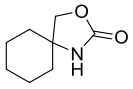
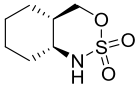
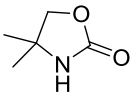
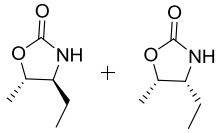
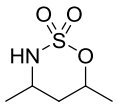
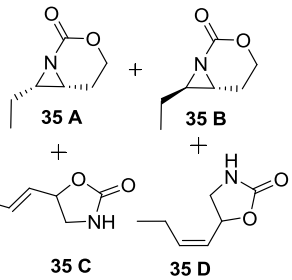
1) An increasing efficiency and conversion rate with more electron rich aromatic carbamates than electron poor counterparts (entries 1-3);
2) Failure of the sulfamate **3** to form the 5-membered product **4** (entry 1 vs. 4);
3) The longer chain derivatives **9** and **11** both readily form the six-membered products (entries 4);
4) The more constrained indane derivatives **13** and **15** both efficiently cyclized to the 5-membered products (entries 5);
5) Phenolic carbamate **17** failed to produce the 6-membered **18**, whereas ortho-substituted phenolic sulfamates **19** afforded the corresponding benzo-fused oxathiazinane heterocycle **20** with moderate efficiency.

The occasional divergent carbamate/sulfamate cyclization behavior (e.g. entries 1/2, 6/18) is probably a result of geometric differences between the trigonal carbamate and tetrahedral sulfamate functionalities. While the former provides a less strained 5-membered transition state and product, the latter is less strained for 6-membered ring formation.

As shown in the table 4, the electron poor ligand system facilitates the reaction and electron rich ligands shows poor yield. Thus different types of electron deficient Schiff's base ligands were tested. We observed that the product was obtained with a higher yield only when electron deficient aromatic aldehydes in the corresponding Schiff's base (compounds A).

In our intermolecular C-H amination reaction we observed that ligand assisted Cu-catalysis with chloramine-T has lower reactivity towards non-benzylic C-H bonds. Generally intramolecular reactions are entropically favored as the neucleophile is held in close proximity of the electrophile by connecting the carbon chain. In the intramolecular amination the corresponding carbamates and sulfamates were treated with $Cu(CH_3CN)_4PF_6$, the ligand **D** and PhIO in dry CH_3CN at 45^oC. The product was purified by column chromatography on silica gel. The results are shown below (table 4).

Table 6:- Cu-catalyzed amination of aliphatic substrates

Entry	Carbamate/ Sulfamate substrate	Cyclic product	% yield[a] (conv)[b]
1	**21**	 **22**	80 (86)
2	**23**		No reaction
3	**24**	 **25**	76 (79)
4	**26**	 **27**	5 (9)
5	**28**	 **29**	67 (72)
6	**30**	 **31 A** **31 B**	47 (52) A : B =2.21 : 1
7	**32**	 **33**	12 (20) Syn : Anti = 1.8 : 1
8	**34**	 **35 A** **35 B** **35 C** **35 D**	42 (51) A : B : C : D = 3.4:2.7:2.4:1

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[a] isolated yield after chromatography [b] conversion determined by NMR integration of substrate/product in the unpurified reaction mixture

Several substrates possessing secondary and tertiary C-H centers are cyclized effectively in the intramolecular amination reaction. The key features of these sets of reactions are:

1) C-H amination of tertiary aliphatic carbamates (entries 1,3,5) to form oxazolidinones; with very good efficiency
2) Less efficient amination of secondary C-H bonds with moderate to low yield (entries 4,6,7);
3) Selective formation of 5-membered (oxazolidinone) rings from carbamate precursors (entries 1,3,5,6);
4) Selective formation of 6-membered oxathiazinanes from sulfamate precursors (entries 4,7);
5) Modest diastereoselectivity in the cycloamination of substrates **30** and **32** (entries 6,7);
6) Competitive C-H amination and azirdination of olefinic substrate **34** with low stereoselectively (entry 8).

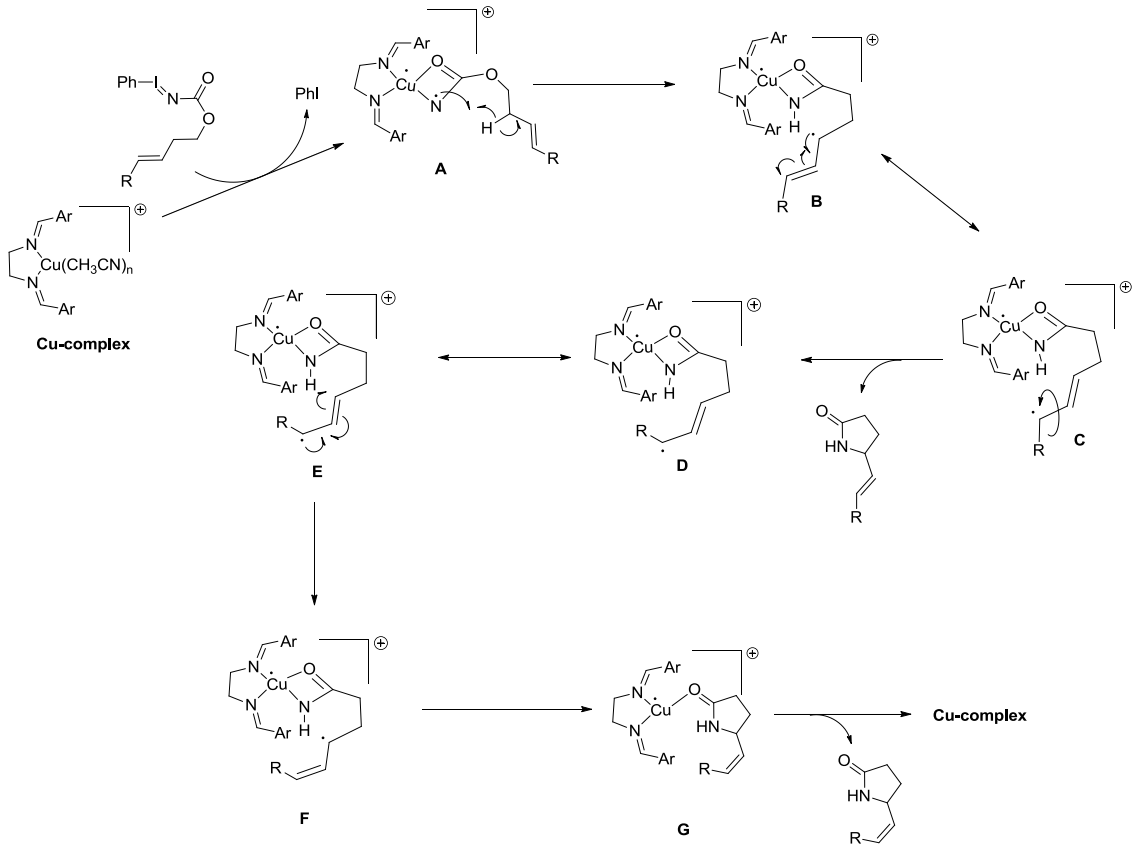
The regio- and diastereoselectivity of the Cu-catalyzed reactions are comparable to those found in other metal-catalyzed intramolecular aminations.[3, 5, 14] Comparing the information gathered from experiments with our catalyst system, a qualitative rate scale for C–H amination can be drawn as follows: $3^{o} > 2^{o} > 1^{o}$. This is matching with all other known system e.g. Rh, Ag and Ru[11]. Primary methyl C–H bonds are at the bottom end of the reactivity spectrum and, in fact, we did not witness any $–CH_3$ insertion. Two additional observations merit comment:

(1) General reactivity trends are similar to those observed in Rh-catalyzed carbenoid insertions[1]

(2) The substrate can influence product selectivity

This latter point has important mechanistic implications and provides the most compelling evidence for an active oxidant that is Cu-bound.

The lack of chemoselectivity observed for cyclization of the carbamate **34** (entry 8), however, contrasts with the corresponding Rh_2-[12] and Ag_2[5]-catalyzed reactions in which C-H amination predominates with preservation of the double bond geometry. The oxidation of cis- and trans-alkene derivatives with rhodium is stereospecific, as would be expected for a concerted, electrophilic oxidation process. In our case the imino-iodinane reacted with the olefin and formed the corresponding aziridine as well as the cyclized products. The *E/Z*-mixture obtained from **34** in the Cu-catalyzed reaction is indicative of a stepwise C-H insertion process. Our computational results from the corresponding intermolecular amination reactions support this stepwise insertion process with the primary reactive N-species proposed to be the triplet (diimine)Cu(NZ)$^+$ complex which reacts as an *N*-centered radical, abstracting a H-atom followed by radical rebound to make the C-N bond. The possible mechanism is shown below (scheme 4). The radical B can resonate into F. The competing allyl C-C rotation is the reason for transformation of cis and trans isomers.



Scheme 4: Mechanistic cycle for cyclization of the carbamate 34

Some of our previously made chiral schiff base ligands were tested for their ability to mediate enantioselective aminations of the prochiral benzylic substrates **1**, **13** and **15**. All reactions were conducted under the previously established conditions with 10 mole % of ligand copper catalyst (1:1 L*/Cu), 1.3 equivalents of PhIO, and CH_3CN as solvent at 45 ^oC. After doing a lot of trial and error, we saw chiralcell OJ-H column was showing two separate peaks for the two enantiomers for compound 14 and for compound 2 the chiralcell OD-H column was the best. The results are shown in Table 5. In each case a low but significant enantioselectivity was observed, comparable in magnitude to the corresponding Cu-catalyzed *inter*molecular reactions. These results reflect the ineffective stereoinduction by the L*Cu-imino-iodinane intermediate.

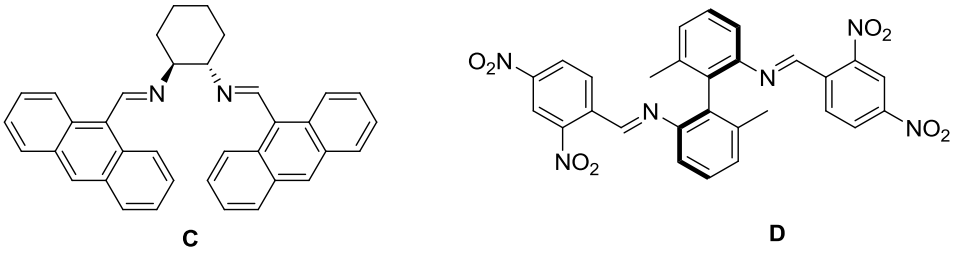
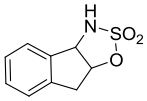
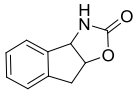
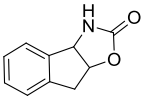
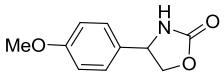


Figure 3: Chiral ligands used for enantioselective amination

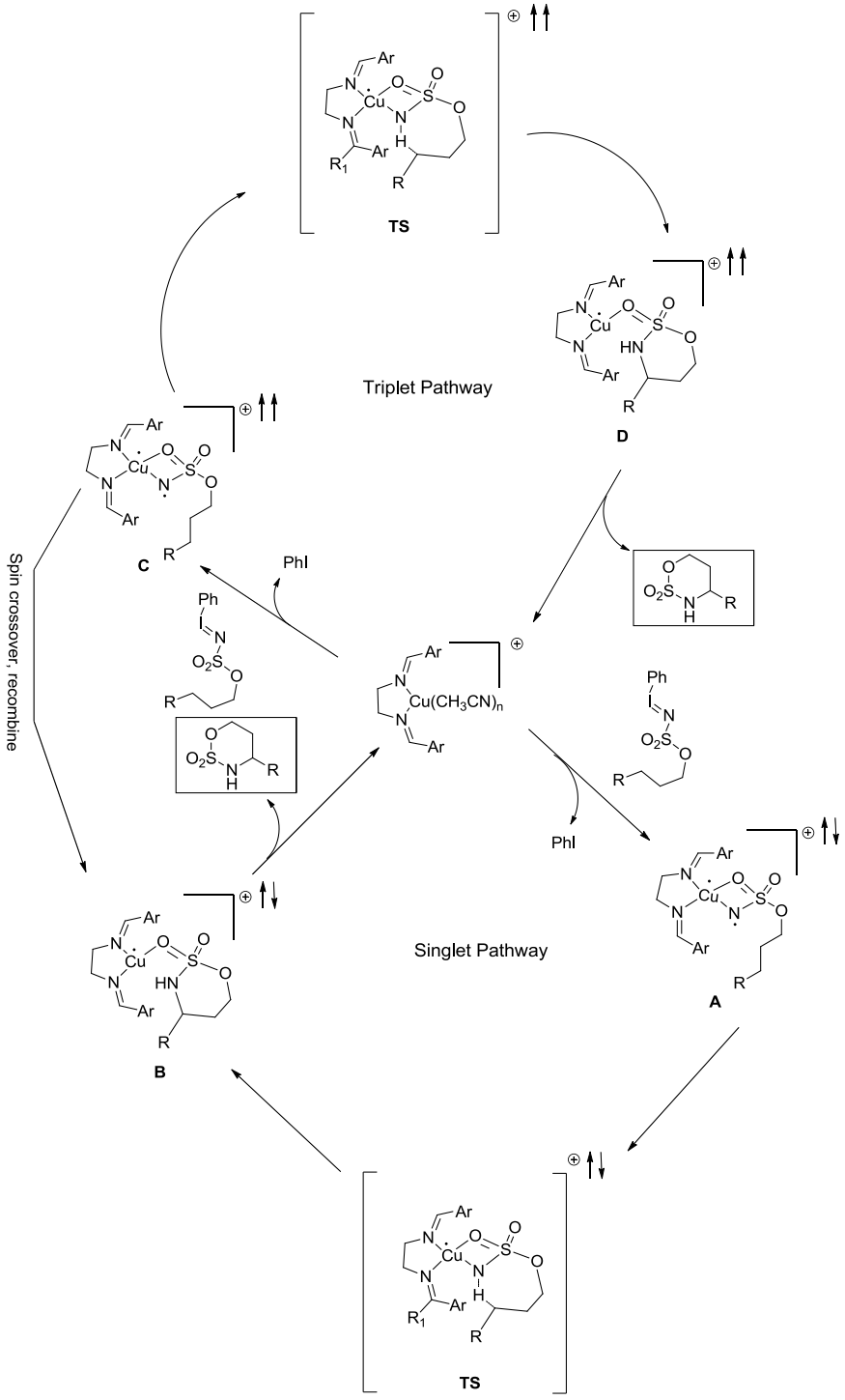
Table 7. Enantioselective amination with chiral diimines

Entry	Ligands	Product	% of ee
1	A		16 % [a]
2	D		13 % [b]
3	C		18 % [b]
4	A		14 % [a]

[a] Chiralcell OD-H column,10 % isopropanol:90 % hexane; [b] Chiralcell OJ-H column, 10 % isopropanol:90 % hexane[e]

We can propose a mechanistic cycle for intramolecular C-H amination (Scheme 6). In both singlet and triplet pathways the intermediate **A** and **C** respectively could form after the ligand exchange with copper complex and *in-situ* formed nitrene. The nitrogen could insert into the secondary or tertiary C-H in singlet and triplet pathways and form intermediate **B** and **D** respectively. The triplet intermediate **D** could change into **B**. The

intermediate **B** and **D** produce the amination product. The slow recombination of the radical pairs could explain the loss of carbon stereochemistry.



Scheme 5: Mechanistic cycle for intramolecular C-H amination

In summary, we have developed a catalytic method employing economical copper-diimine catalysts for the oxidative cyclization of carbamates and sulfamates to corresponding five- and six-membered N,O-heterocycles. Saturated substrates have low reactivity with chloramine-T/[Cu($CH_3CN)_4$]Z/ligand in intermolecular aminations but give moderate yields in intramolecular amination. Our results in terms of yield are comparable to those of Du Bois (Rhodium system), Chun He (Silver system), Blakey (Ruthenium pybox)[13] and Ching-ming Che (Ruthenium porphyrin and Manganese salen system). The hydrolytic convertibility of these products to 1,2- and 1,3-amino alcohol derivatives further amplifies their synthetic value and their valuable application in the stereoselective synthesis of complex molecules.

4.5 Conclusion

In conclusion, ligand-assisted copper catalysis is a useful methodology for C-H amination reactions. Schiff base ligands were stable, easy to prepare and handle and the reaction also preceded under much milder reaction conditions. The intramolecular reaction gave oxazolidinones or oxathiazinanes in good yields and the intermolecular version gave an efficient C-H amination. The purification of the intramolecular amination product was very easy to carry out because the starting material was the only impurity that was present after the reaction.

Copper-catalyzed intermolecular and intramolecular C–H amination represents a general method for the preparation of amine. Our interest in understanding reactivity trends and low enantioselectivity associated with this process has driven our efforts to dissect the reaction mechanism. A combination of data collected from the intermolecular amination by substrate probes and computational studies leads to the conclusion that the active oxidizing species is best described as a Cu-bound nitrene. Finally, the computational studies suggested that a triplet copper nitrene was the reactive species and that the C–H insertion is likely a stepwise, synchronous event.

4.6 Experimental procedure

4.6.1 General Materials/Methods:

Acetonitrile was refluxed over and distilled from calcium hydride. Some of the hydrocarbon substrates were obtained commercially and distilled before use. $Cu(CH_3CN)_4PF_6$ was obtained commercially. NMR spectra were recorded on a Varian Mercury NMR spectrometer at 300 MHz for ^{1}H- and 75 MHz for ^{13}C-NMR spectra. All chemical shifts (ppm) reported are relative to the NMR solvent peak. Mass spectra were recorded on a Finnigan TSQ 700 mass spectrometer with an electron spray source. All of the catalytic reactions were carried out under a dry argon atmosphere.

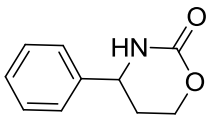
4.6.2 General Preparation of Carbamates.

A typical experimental procedure for making the carbamate is to dissolve the primary ethanol (32 mmol, 1 equivalents) in dry $ClCH_2CH_2Cl$ (12 mL) in a dry flask under an argon atmosphere. The trichloro isothiocyanate (42 mmol, 1.2 equivalent) was added slowly to the reaction mixture at 0^oC. The reaction was monitored by TLC until all the starting materials were consumed. After 5 hrs K_2CO_3 (0.35 mmol, 0.1 equivalent) was added and wait for 10 minutes and 12 ml of MeOH was added to it slowly with vigorous stirring. The reaction mixture was stirred for 16 hrs and poured into saturated NH_4Cl solution and extracted with CH_2Cl_2. The solvent was removed under vacuum and purity of the compounds was judged by the ^{1}H NMR.

4.6.3 General Preparation of Sulfamates

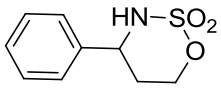
Formic acid (283 μL, 7.5 mmol, 2.5 equiv) was added to neat $ClSO_2NCO$ (653 μL, 7.5 mmol, 2.5 equiv) at 0 °C with vigorous stirring. The mixture became solidified. To the resulting white mass was added 5.0 mL of dry acetonitrile and the contents were then warmed to 23°C. After stirring for 5 h the solvent was removed under vacuum. In a separate flask the alcohol (3.0 mmol) was treated with NaH (3.5 mmol) in 10 mL of DMF. The resulting $ClSO_2NH_2$ was added to the mixture at 0 °C with vigorous stirring. The reaction was warmed to 23 °C and stirred at this temperature for 12 hrs. The reaction was quenched by the addition of 15 mL of H_2O and extracted with CH_3COOEt and saturated brine. The combined organic extracts were dried over $MgSO_4$, and concentrated under reduced pressure. The purity of the compound was judged by the ^1H NMR.

4.6.4 Catalyst screening reactions: Catalyst screening with the various ligands was performed with 10 mol% of $Cu(CH_3CN)_4PF_6$, 10 mol% of ligand B, 3-(4-methoxyphenyl) propanamide as substrate (1.0 equiv), and anhydrous Iodoso benzene (PhI=O; 1.3 equiv), with activated 4Å molecular sieves present in the reaction vessel. Reactions were carried out in CH_3CN while monitoring by TLC. The reaction mixture was filtered and concentrated under vacuum.

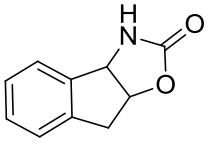


4-Phenyl-1,3-oxazinan-2-one:[3] ^1H NMR (300 MHz, $CDCl_3$) δ d 7.38 (d, *J* = 8.1Hz, 2H), 7.36-7.31 (m, 3H), 5.57 (s, 1H), 4.66 (t, *J* = 6.3 Hz, 1H), 4.29-4.33 (m,

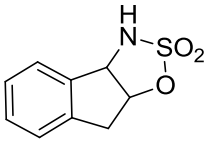
2H), 2.26 (m, 1H), 1.98 (m, 1H); *m/z* $C_{10}H_{12}NO_2$ (M+Na): 201.087



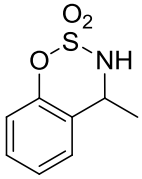
Compound 12:[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.41-7.34 (m, 5H), 4.88 (m, 2H), 4.66 (m, 1H), 4.34(d, 1H, J = 9.0), 2.29-2.23 (m, 1H), 2.02(m, 1H); m/z (M+Na): 236



Compound 14: [4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.35-5.25 (m, 5H), 6.53 (s, 1H), 5.42 (m, 1H), 5.16 (d, 1H, J = 7.2), 3.36-3.31 (m, 2H); MS m/z (M+Na): 198

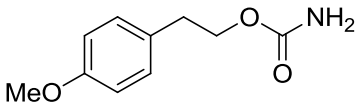


Compound 16:[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.34-7.19 (m, 4H), 5.46 (m, 1H), 5.24 (m, 1H), 4.50 (s, 1H), 3.47-3.33 (m, 2H); m/z (M+Na): 234

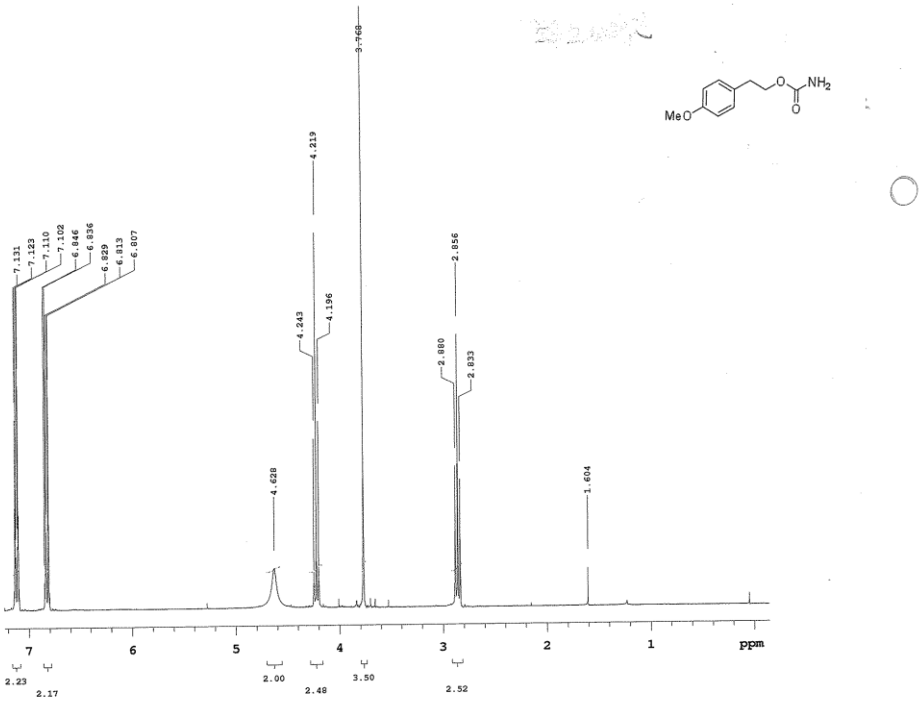


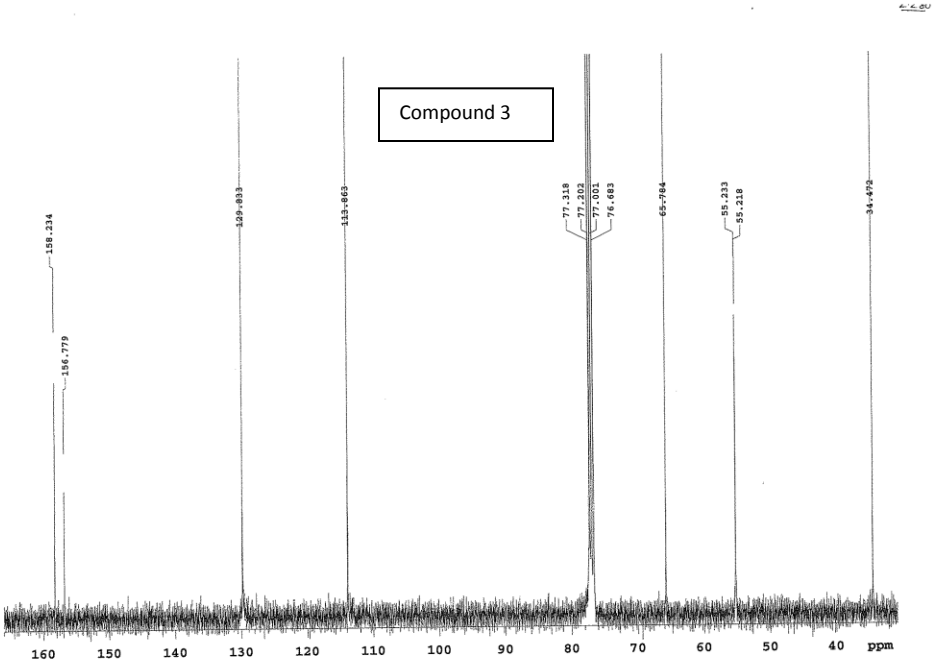
Compound 20:[4] ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.31 (dddd, 1H, *J* = 11.5, 6.5, 2.6, 0.6 Hz), 7.24-7.18 (m, 2H), 6.99 (dd, 1H, *J* = 8.3, 0.8 Hz), 4.90 (q, 1H, *J* = 7.0

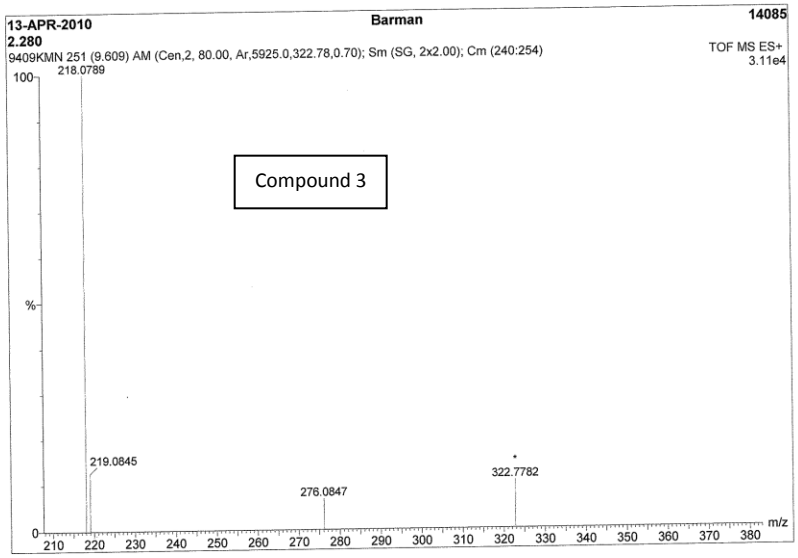
Hz), 4.58 (br s, 1H), 1.72 (d, 3H, *J* = 7.0 Hz); m/z (M+Na): 222

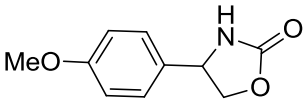


3-(4-methoxyphenyl)propanamide: ^{1}H NMR (300 MHz, $CDCl_3$) 7.12 (t, J= 2.4, 2H), 6.83 (dd, 2H, J= 3, 1.8), 4.63 (s, 1H), 4.22 (t, J= 7.2, 2 H), 3.77 (s, 3H), 2.86 (t, J= 7.2, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) d 158.2, 156.7, 129.8, 131.2, 113.8, 65.7, 55.2, 34.5; ESI-MS calc. m/z (M+Na) 218.0793, found 218.0789

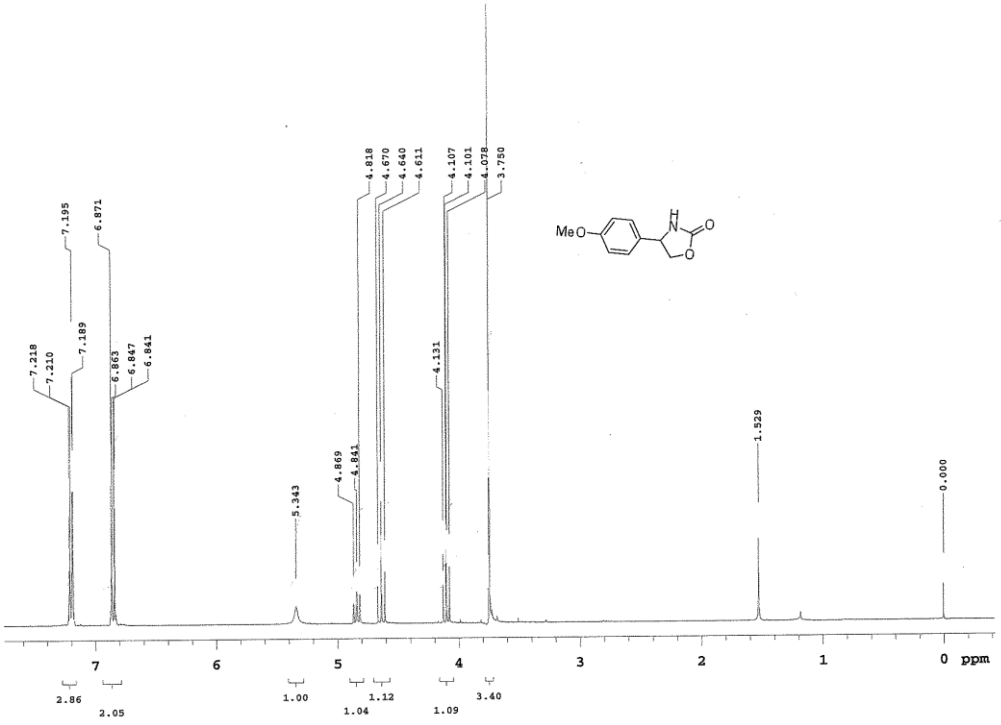


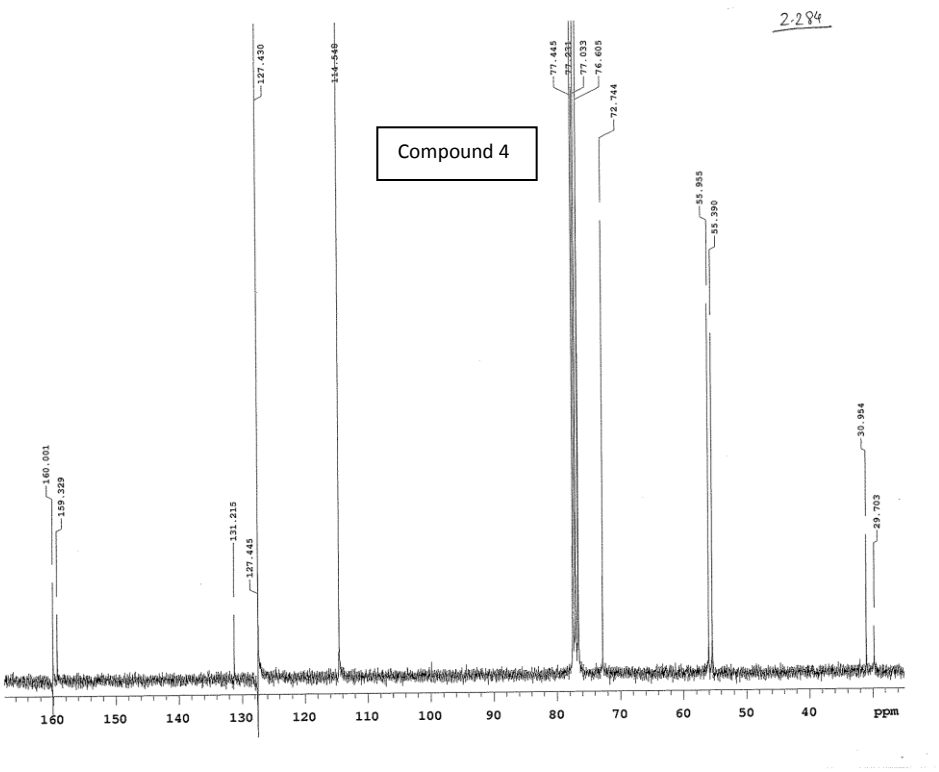

Compound 3
158.234
156.779
129.833
113.663
77.318
77.203
77.001
76.683
65.704
55.233
55.218
34.472
160 150 140 130 120 110 100 90 80 70 60 50 40 ppm

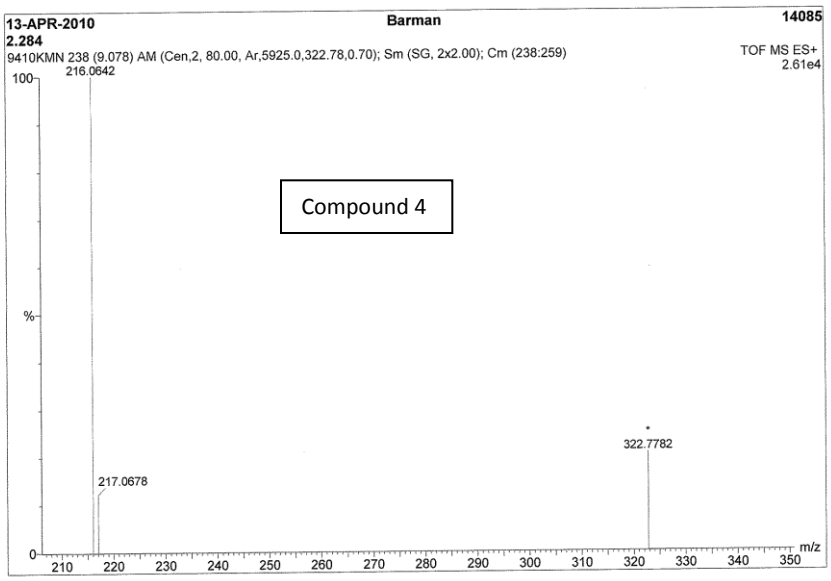

13-APR-2010
Barman
14085
2.280
9409KMN 251 (9.609) AM (Cen,2, 80.00, Ar,5925.0,322.78,0.70); Sm (SG, 2x2.00); Cm (240:254)
TOF MS ES+
3.11e4
100
218.0789
Compound 3
%
219.0845
276.0847
322.7782
0
210 220 230 240 250 260 270 280 290 300 310 320 330 340 350 360 370 380
m/z

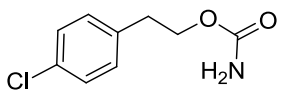


(4-methoxyphenyl oxazolidinone): White amorphous solid, R_f = 0.34, EtOAc/CH_2Cl_2 (1:4); ^{1}H NMR (300 MHz, $CDCl_3$) 7.2 (d, J= 6.3, 2 H), 6.86 (d, J= 8.7, 2H), 5.34 (s, 1H), 4.84 (t, J= 7.7, 1H), 4.64 (t, J= 8.8, 1H), 4.1 (t, J = 7.8, 1H), 3.75 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz), d 160.0, 159.3, 131.2, 127.4, 114.5, 72.7, 55.9, 30.9; ESI-MS calculated m/z (M+Na) 216.0636, found 216.0642.

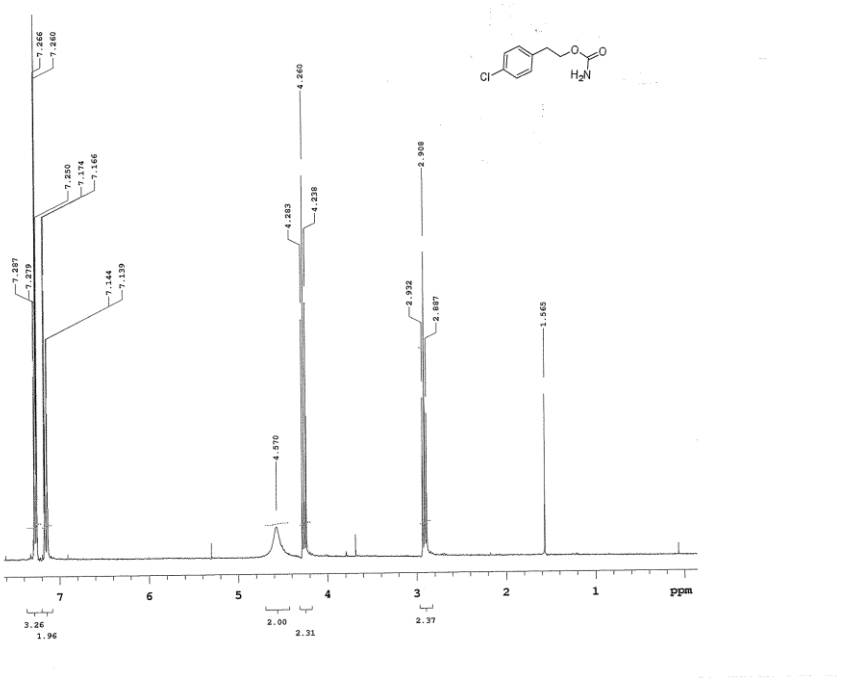


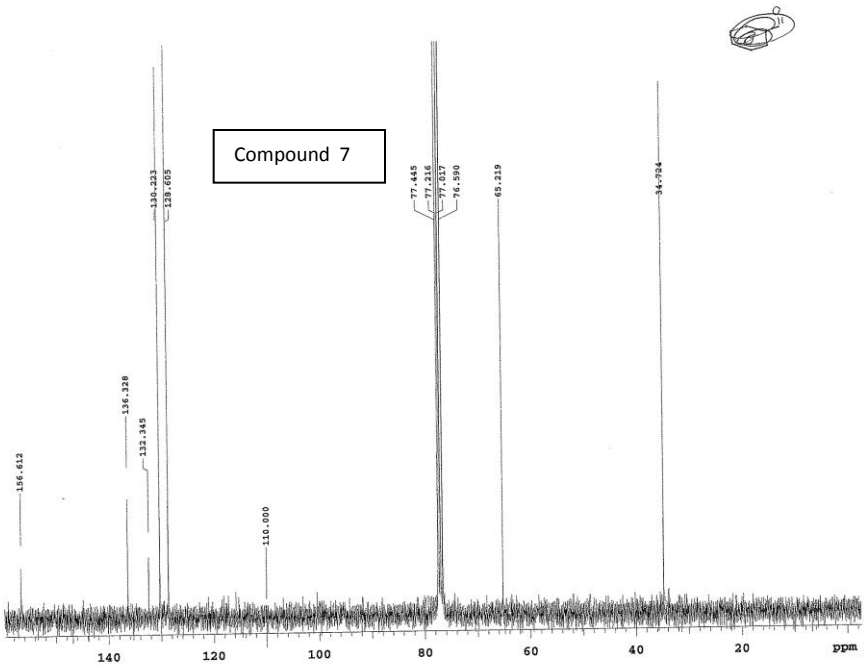

2.284
Compound 4
160.001
159.329
131.215
127.445
127.430
114.548
77.445
77.231
77.033
76.605
72.744
55.955
55.390
30.954
29.703
160
150
140
130
120
110
100
90
80
70
60
50
40
ppm

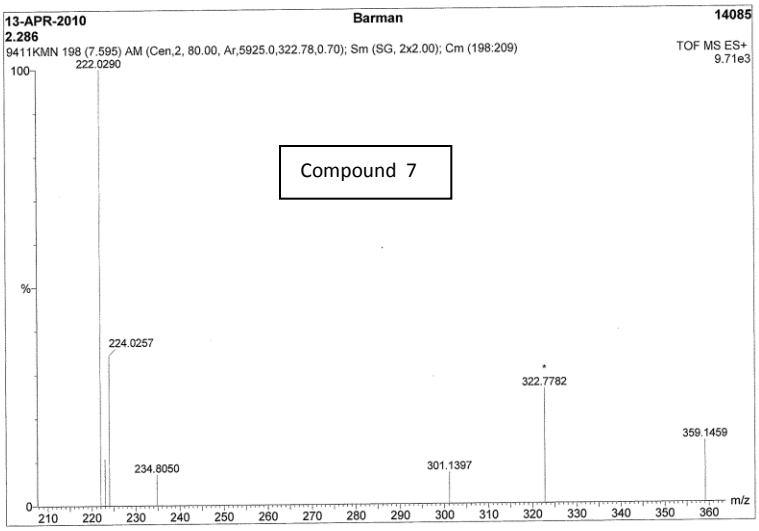

13-APR-2010
2.284
Barman
14085
9410KMN 238 (9.078) AM (Cen,2, 80.00, Ar,5925.0,322.78,0.70); Sm (SG, 2x2.00); Cm (238:259)
TOF MS ES+
2.61e4
Compound 4
216.0642
217.0678
322.7782
100
%
0
m/z
210
220
230
240
250
260
270
280
290
300
310
320
330
340
350

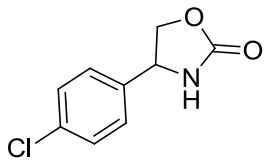


3-(4-chlorophenyl)propanamide : white solid, ^{1}H NMR (300 MHz, $CDCl_3$) 7.27 (d, J= 9, 2H), 7.16 (dd, J= 2.4, 1.5, 2H), 4.57 (s, 2H), 4.26 (t, J= 6.7, 2H), 2.91 (t, J= 6.7, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) d 156.6, 136.3, 132.3, 130.2, 128.6, 65.2, 34.7; ESI-MS calc. m/z (M+Na) 222.0298, found 222.0290

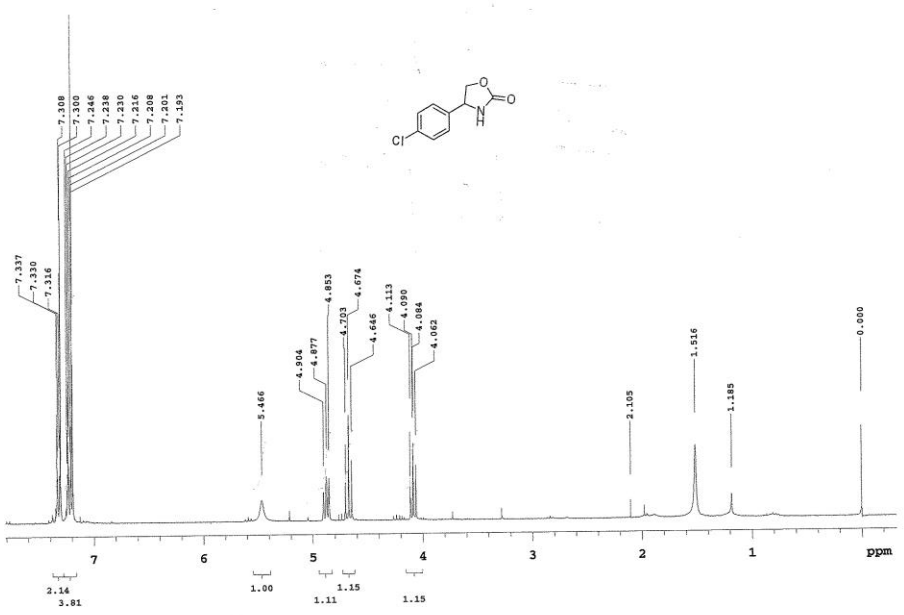


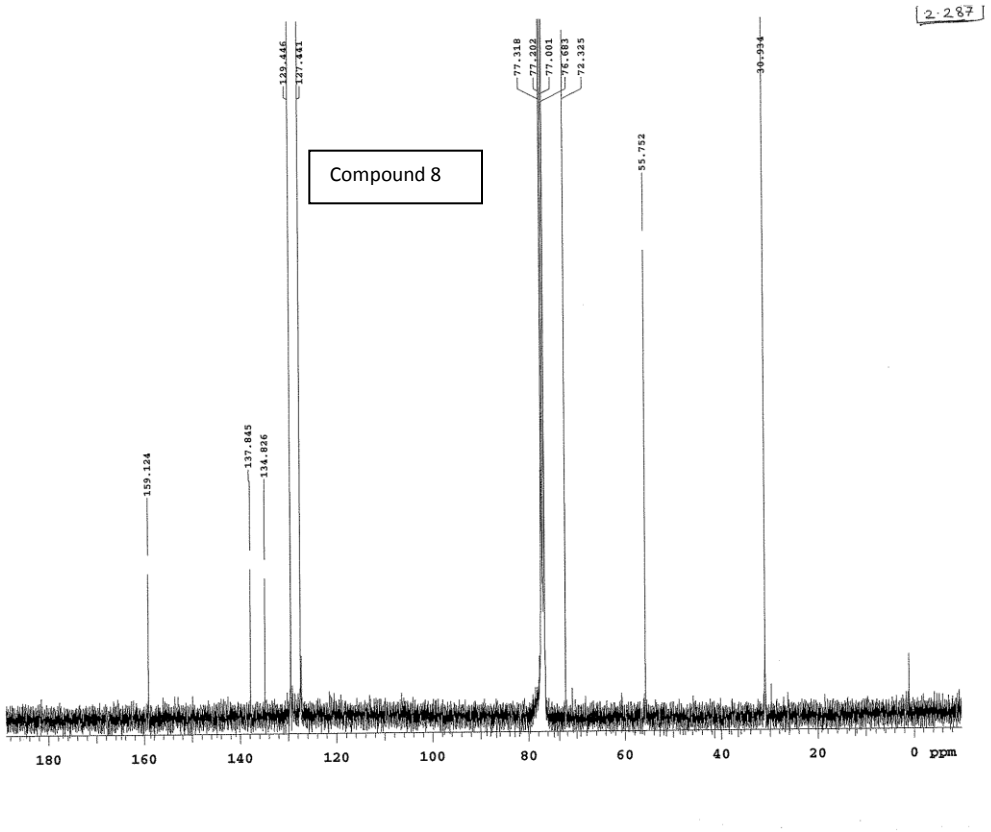

Compound 7
156.612
136.328
132.345
130.223
128.605
110.000
77.445
77.216
77.017
76.590
65.219
34.734
140
120
100
80
60
40
20
ppm

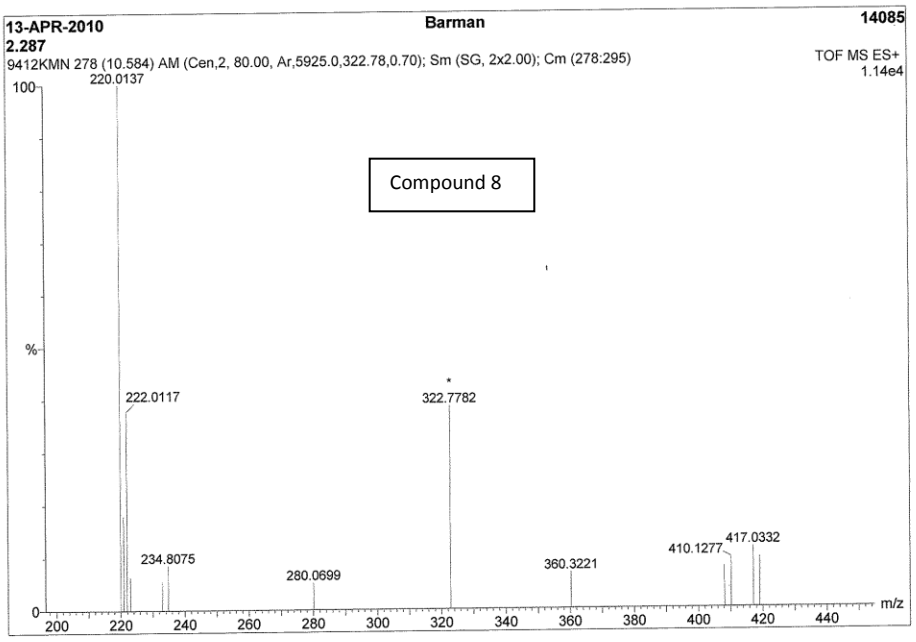

13-APR-2010
2.286
Barman
14085
9411KMN 198 (7.595) AM (Cen,2, 80.00, Ar,5925.0,322.78,0.70); Sm (SG, 2x2.00); Cm (198:209)
TOF MS ES+
9.71e3
Compound 7
222.0290
224.0257
234.8050
301.1397
322.7782
359.1459
100
%
0
m/z
210
220
230
240
250
260
270
280
290
300
310
320
330
340
350
360

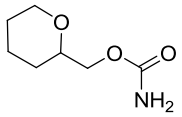


(4-chlorophenyl) oxazolidinone: white solid, R_f=0.24, EtOAc/CH_2Cl_2 (1:4). ^{1}H NMR (300 MHz, $CDCl_3$) 7.32 (d, J= 8.7, 2H), 7.24- 7.19 (m, 2H), 5.46 (S, 1H), 4.88 (t, J= 8.1, 1H), 4.67 (t, J= 8.4, 1H), 4.08 (dd, J=8.6, 6.9, 1H), ^{13}C NMR ($CDCl_3$, 75 MHz) d 159.1, 137.8, 134.8, 129.4, 127.4, 55.7, 30.9; ESI-MS calc. m/z (M+Na) 220.0141, found 220.0137.

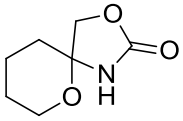



2.287
Compound 8
159.124
137.845
134.826
129.446
127.441
77.318
77.202
77.001
76.683
73.325
55.752
30.934
180
160
140
120
100
80
60
40
20
0 ppm

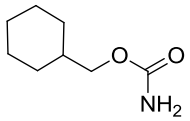




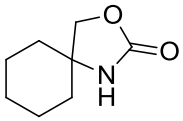
Compound 21:[14] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.7 (s, 2H), 4.11 (dd, 1H, *J* = 11.6, 3.1 Hz), 4.07–4.0 (m, 1H), 3.98 (dd, 1H, *J* =11.6, 7.2 Hz), 3.6–3.54 (m, 1H), 3.45 (dt, 1H, *J* = 11.4, 2.5 Hz), 1.94–1.85 (m, 1H), 1.67–1.46 (m, 4H), 1.4–1.28 (m, 1H) ppm; m/z (M+Na) $C_7H_{12}NO_3$ 158.0739 found 181.0740.



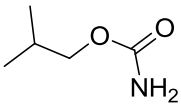
Compound 22:[14] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.98 (s, 1H), 4.32 (d, 1H, *J* = 9.3 Hz), 4.12 (d, 1H, *J* = 9.3 Hz), 3.83–3.71 (m, 2H), 1.89–1.7 (m, 4H), 1.66–1.56 (m, 2H) ppm; m/z (M+Na) $C_7H_{11}NO_3$ 157.07 found 180.07



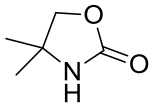
Compound 24:[14] ^{1}H NMR ($CDCl_3$; 300 MHz) δ 4.8 (s, 2H), 3.84 (d, 2H, *J* = 6.67Hz), 1.79–1.55 (m, 6H), 1.32–1.10 (m, 3H), 1.07–0.9 (m, 2H) ppm; m/z (M+Na) $C_8H_{14}NO_2$ 156.0946 found 179.0946.



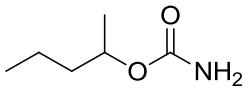
Compound 25:[14] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.65 (s, 1H), 4.09 (s, 2H), 1.72–1.34 (m, 10H) ppm; m/z (M+Na) $C_8H_{13}NO_2$ 155.09 found 178.09.



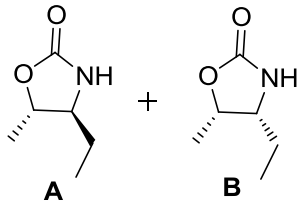
Compound 28:[5] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.64 (s, 1H), 3.84 (d, J= 7.2, 2H), 1.95–1.78 (m, 1H), 0.93 (d, J=6.6, 6H) ppm; m/z (M+Na) $C_5H_{11}NO_2$ 117.09 found 140.1.



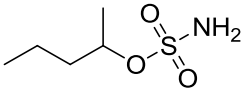
Compound 29:[5] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.7 (s, 1H), 4.08 (s, 2H), 1.36 (s, 6H,) ppm; m/z (M+Na) $C_5H_9NO_2$ 115.09 found 138.13.



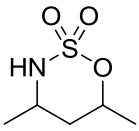
Compound 30:[5] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.83-4.76 (m, 1H), 4.58 (s, 1H), 1.62-1.51 (m, 1H), 1.49-1.3(m, 3H), 1.22(d, J= 6, 3H), 0.92(t, 3H) ppm; m/z (M+Na) $C_6H_{13}NO_2$ 131.07 found 154.08.



Compound 31:[5] Compound **A** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.8 (S, 1H), 4.4-4.2 (m, 1H), 3.32 (q, 1H, J =6.2), 1.47-1.61 (m, 1H), 1.38 (d, 3H, J = 6.2), 0.93 (t, 3H). Compond **B**[6] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 6.5 (S, 1H), 4.8-4.6 (m, 1H), 3.66 (dt, 1H, J = 4.8, J= 8.4), 1.59-1.44 (m, 1H), 1.34 (d, 3H, J =6.8), 0.95 (t, 3H).

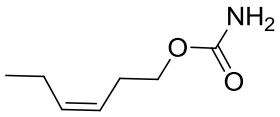


Compound 32:[5] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.9 (s, 2H), 4.73-4.62(m, 1H), 1.75-1.65(m, 2H), 1.61-1.5 (m, 2H), 1.39 (d, 3H, J=6), 0.92 (t, 3H, J=7.3).

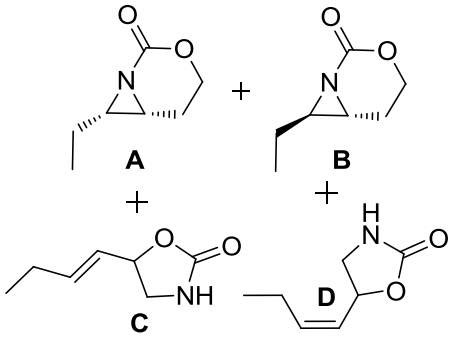


Compound 33:[5] *syn isomer*: ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.26 (m, 1H), 3.92 (d, J = 7.8, 1H), 3.82-3.71 (m, 1H), 1.82 (m, 1H), 1.47-1.36 (m, 1H), 1.4 (d, 3H, J = 7.8

Hz), 1.27 (d, 3H, J = 7.8 Hz) ppm; *anti isomer*:[7] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.07 (m, 1H), 4.44 (d, J = 8.0, 1H), 3.87-3.78 (m, 1H), 1.85 (m, 1H), 1.71 (m, 1H), 1.54 (d, 3H, J = 7.0), 1.45 (d, 1H, J = 7.0 Hz) ppm;



Compound 34:[15] ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.46(dd, 1H, J=6.8, J=10.1), 5.27 (dd, 1H, J=7.5, J=10.2), 5.1 (s, 1H), 4.03-3.96 (m, 2H), 2.33(q, 2H, J=7), 2.01 (m, 2H), 0.92 (t, 3H, J=7.6)



Compound 35:[15] Compound **A** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.39(m, 1H), 4.33 (m, 1H), 2.89 (m, 1H), 2.60 (m, 1H), 2.18 (ddt, 1H, J=14.7, J=6.9, J=1.9), 1.86 (m, 1H), 1.47 (m, 1H), 1.23 (1H, m), 1.10 (t, 3H, J=7.3)

Compound **B** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 4.40 (ddd, 1H), 4.29 (ddd, 1H, J=10.6, 4.2, 1.9), 2.60 (ddd, 1H, J=9.0,6.2, 3.3), 2.35 (ddt, 1H, J=14.6, 6.2, 1.9), 2.23 (m, 1H), 1.66 – 1.59 (m, 2H), 1.44 – 1.34 (m, 1H), 1.06 (t, 3H, J= 7.4).

Compound **C** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.78 (ddt, 1H), 5.41 (s, 2H, bs & ddt, J 15.3, 8.0,1.6), 4.51 (m, 1H), 4.38 – 4.33 (m, 1H), 4.04 (dd, 1H, J=8.5, J=7.0), 2.13 – 2.04(m, 2H), 1.01 (t, 3H, J=7.5)

Compound **D** ^{1}H NMR ($CDCl_3$, 300 MHz) δ 5.72 (s, 1H), 5.64 (ddt, 1H), 5.38 (ddt, 1H), 4.78 – 4.70 (m, 1H), 4.52 (m, 1H), 4.02 (dd, 1H), 2.19 – 2.00(m, 2H), 0.99 (t, 3H)

4.7 Reference:-

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[3] Espino, C. G.; Wehn, P. M.; Chow, J; Du Bois J. *J. Am. Chem. Soc.* **2001**, *123*, 6935–6936.

[4] Liang, J.-L.; Yuan, S.-X.; Huang, J.-S.; Yu, W.-Y.; Che, C.-M. *Angew. Chem., Int. Ed*. **2002**, *41*, 3465–3468.

[5] Cui, Y.; He, C. *Angew. Chem., Int. Ed*. **2004**, *43*, 4210–4212.

[6] Fruit, C.; Muller, P. *Helv. Chim. Acta* **2004**, *87*, 1607–1615.

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CHAPTER FIVE

Future directions

Computational and experimental results described earlier show that the primary reactive N-species in the copper-catalyzed aminations, the triplet (diimine)Cu(NZ) complex, acts as an N-centered radical and there is likely a minor pathway involving the singlet complex. The singlet insertion pathway is calculated to have a higher energy than the triplet pathway. To enhance the reaction stereoselectivity a goal could be to minimize the singlet/triplet energy gap. It was shown by various computational studies that triplet state for Cu-imido complex with a β-diketiminate ligand **19** is slightly favorable than singlet state. So if we can design some ligands involving the β-diketiminate core could be very effective.

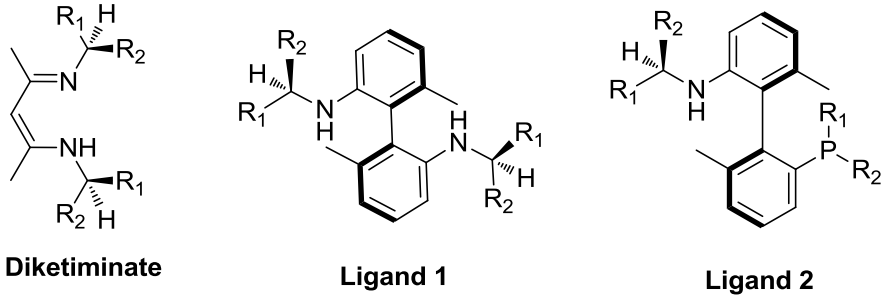
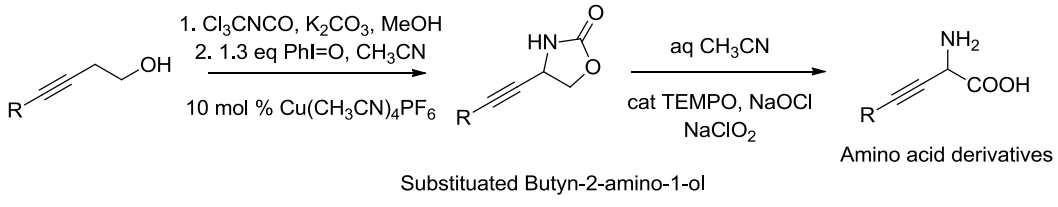


Figure 1: Future ligands

From our computational and experimental studies we observed that the Schiff base ligands derived from *N,N'*-dibenzylidene-1,2-cyclohexanediamine and chiral biaryldiamine ligands did not show effective chirality transfer in C-H amination. So we could design a ligand where we can have chirality closer to the amination site (ligand 1 and 2).

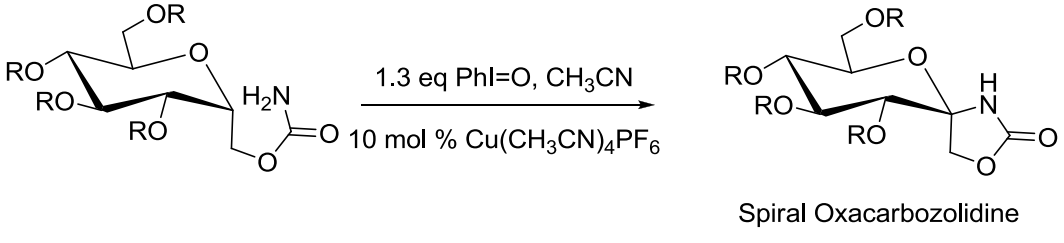
Another interesting and useful direction would be to develop applications of the Cu-mediated aminations in synthetic methodology and targeted total synthesis. For example, we could also utilize ligand-assisted, copper catalyzed intramolecular C-H amination to achieve the following goals:

1. Synthesis of α,β-unsaturated amino acids as potential catalytic irreversible enzyme inhibitors could be accomplished using this proposed intramolecular C-H amination methodology. A novel series of oxindole-type inhibitors of CDK_2[1] could also been synthesized with substituted-butyn-2-amino-1-ol with this novel methodology (Scheme 2).



Scheme 1: Formation of amino acid derivatives

2. Preparation of an oxathiazolidine derivative with copper-catalyzed intramolecular C-H amination could also be plausible. Oxothiazolidine is an excellent substrate of the enzyme; it may serve as an intracellular delivery system for cysteine and thus has potential as a therapeutic agent.[2]



Scheme 2: Formation of Spiral oxathiazolidine

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