The Sequential Insertion of Carbon Monoxide and Imines into Nickel-Carbon σ-Bonds: Synthesis, Reactivity and Multi-Component Couplings

A thesis submitted to McGill University in partial fulfillment of the requirements for the degree of Doctor of Philosophy

By

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Your file Votre référence
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This Thesis is dedicated to

The memory of my Father Ken Davis

my mother Claudette Davis

my sisters Vanessa and Jennifer

the other important people in my life who have had the

patience to help me see this through

ABSTRACT

The Sequential Insertion of Carbon Monoxide and Imines into Nickel-Carbon σ-Bonds: Synthesis, Reactivity and Multi-Component Couplings

The development of new methods of generating α-amino acid derivatives via multi-component reactions remains an important challenge. The primary goal of this study is to develop new transition metal-mediated routes to synthesize these α-amino acid derivatives using combinations of simple reagents, such as imines, carbon monoxide, acid chlorides and organotin reagents. The proposed approach requires the sequential insertion of imine and carbon monoxide into late transition-metal σ-bonds, as well as the further reactivity of the products.

In chapter 2, the ability of the nickel complex $L_2Ni(CH_3)N(R)=C(H)R'^+X^-$ (L_2 = chelating nitrogen ligands, X^- = non-coordinating counteranion) to mediate the insertion of imines is examined. Although $L_2Ni(CH_3)N(R)=C(H)R'^+X^-$ does not undergo direct imine insertion into the Ni-CH_3 bond, the addition of CO leads to the generation of the novel nickel complex $(L_2)Ni[\eta^2\text{-}CH(R')NRCOCH_3]^+X^-$ via the insertion of imine into the nickel-acyl bond of $L_2Ni(COCH_3)N(R)=C(H)R'^+X^-$. This demonstrates as proof of concept, that these nickel complexes can mediate the sequential insertion of CO and imine into nickel-methyl bonds, in direct analogy to well known CO/olefin insertions. Further reactivity studies have demonstrated that

the amide bound nickel chelates generated via the sequential insertion of CO and imines are generally inert towards subsequent migratory insertion with CO, imine and olefins (Chapter 3). These complexes are also inert towards auxiliary ligand exchange or amide de-chelation, with both mono- and bidenate nitrogen and phosphine ligands.

Studies involving the use of imines and alkenes as interchangeable insertion substrates, (Chapter 4) resulted in the first example of a metal mediated cyclocarbonylation incorporating imine as a formal insertion substrate. Based on these studies, one-pot sequential insertion cascade of CO, olefin, a second unit of CO, and imine was developed for the synthesis of 5 and 6 membered lactams. In addition, the competitive insertion propensity of imines and α-olefins was examined, and clear steric and electronic effects were identified.

The isoelectronic palladium-bound amide complexes, generated via the oxidative addition of N-acyl iminium salts (R(H)C=N(R')COR'') to $Pd_2(dba)_3 \cdot CHCl_3$ can undergo a Stille-tye coupling with organotin reagents to generate α-substituted amide derivatives (Chapter 5). This reactivity was extended into a convenient and general one-pot synthesis of α-substituted amides and N-protected amines by a palladium-catalyzed three-component coupling of imines, acid chlorides or chloroformates, and organotin reagents. Mechanistically, this process provides an oxidative addition/reductive elimination-based alternative to nucleophilic approaches to C-C bond formation with imines, in which the imines are activated towards addition to palladium by RCOCl.

Résumé

L'insertion Séquentielle de Monoxide de Carbone et D'imines dans les Liaisons Nickel-Carbone : Synthèse, Réactivité et Couplage à Plusieurs Composantes

Parmi les méthodes de synthèse disponibles pour la construction de dérivés d'acides aminés, il n'y existe toujours pas de protocol utilisant une approche à plusieurs composantes. Alors, le premier but de cette recherche est de développer une méthode, basée sur la chimie des métaux de transitions, qui permettra de fabriquer des dérivés d'acides aminés à partir de simples substrats tel qu'imines, monoxide de carbone, chlorures d'acide et dérivés organoétain. L'approche proposée requiert premièrement l'insertion séquentielle d'imine et de monoxide de carbon dans des liaisons sigma de complexes organométalliques suivie par la réaction du produit résultant.

Au chapitre 2, la capacité du complexe $L_2Ni(CH_3)N(R)=C(H)R'^+X^-$ (L2 = chélatants azotés, X^- = contre-anion non-coordinné) d'effectuer l'insertion d'imines est analysée. Bien que le complexe $L_2Ni(CH_3)N(R)=C(H)R'^+X^-$ n'effectue pas d'insertion d'imines dans le lien Ni-CH_3, avec l'introduction de monoxide de carbone dans le medium celui-ci réagit pour former un complexe nickel-acyl,

$L_2Ni(COCH_3)N(R)=C(H)R'^+X^-$, qui ensuite facilite l'insertion d'une imine pour ainsi produire le nouveau complexe $L_2Ni[\eta^2\text{-}CH(R')NRCOCH_3]^+X^-$. Cette observation appui l'hypothèse que ces complexes à base de nickel peuvent effectuer l'insertion séquentielle de monoxide de carbone et d'imines, et tire analogie des systèmes bien connus d'insertion séquentielle de monoxide de carbone et d'oléfin. Par contre, les études qui ont poursuivies démontrent que le chélate amide résultant de cette séquence d'insertions est généralement inerte à des insertions subséquentes soit d'une molécule de monoxide de carbone ou d'imine (chapitre 3). Ces complexes sont aussi inertes à l'échange de ligands auxiliaires ou à la dé-chélation de l'amide, que ce soit avec des ligands mono- ou bidendate à base d'azote ou de phosphore.

Au chapitre 4, l'insertion interchangeable entre une imine et une oléfine est analysée. De ces études a résulté un premier exemple de cyclocarbonylation favorisé par un métal de transition et utilisant une imine comme substrat. Alors, dérivée de ces études, une synthèse comportant, en une seule étape, l'insertion de monoxide de carbone, d'une oléfine, de monoxide de carbone et d'une imine en cascade fut développée pour ainsi fournir des lactames formées de cycles à 5 ou 6 atomes. La vitesse d'insertion relative entre imine et α-oléfine a aussi été examinée, pour lesquelles des influences électroniques et d'encombrements stériques sont identifiés.

Le complexe isoélectronique à base de palladium, produit par addition oxydative de sels *N*-acyl iminium (R(H)C=N(R')COR'' sur le $Pd_2(dba)_3*CHCl_3$, accélère les couplages de type Stille en réagissant avec des réactifs organoétain pour ainsi produire des dérivées d'amides α-substituées (chapitre 5). Cette réactivité fut mise à profit dans le développement d'une synthèse à trois composantes, en une

étape, d'amides α-substitués et d'amines protégées construits à partir d'imines, de chlorures d'acide ou de chloroformates et de dérivés organoétain. Ce cycle catalytique offre une alternative au mécanisme traditionnel de substitution nucléophilique pour la génération de liaisons carbone-carbone à partir d'imine et où ces dernières sont activées enves l'addition oxydative par le palladium via des chlorures d'acides.

Foreword

In accordance with guidline C of the "Guidelines for Thesis Preperation" (Faculty of Graduate Studies and Research), the following text is cited:

" As an alternative to the traditional thesis format, the dissertation can consist of a collection of papers that have a cohesive, unitary character making them report of a single program of research. The structure for the manuscript-based thesis must conform to the following:

Candidates have the option of including, as part of the thesis, the text of one or more papers submitted, or to be submitted for publication, or the clearly duplicated text (not the reprints) of one or more published papers. These texts must conform to the "Guidelines for Thesis Preparation" with respect to font size, line spacing and margin sizes and must be bound together as an integral part of the thesis. (Reprints of published papers can be included in the appendices at the end of the thesis).

The thesis must be more then a collection of manuscripts. All components must be integrated into a cohesive unit with a logical progression from one chapter to the next. In order to ensure that the thesis has continuity, connecting texts that provide logical bridges between the different papers are mandatory.

As manuscripts submitted for publication are frequently very concise documents, where appropriate, additional material must be provided (*e. g.* in appendices) in sufficient detail to allow a clear and precise judgement to be made of the importance and originality of the research reported in the thesis.

In general, when co-authored papers are included in a thesis the candidate must have made a substantial contribution to all papers included in the thesis. In addition, the candidate is required to make an explicit statement as to who contributed to such work and to what extent. This statement should appear in a single section entitled "Contribution of Authors" as a preface to the thesis. The supervisor must attest to the accuracy of this statement at the doctoral oral defense. Since the task of the examiners is made more difficult in these cases, it is in the candidate's interests to clearly specify the responsibilities of all authors of the co-authored papers.

When previously published copyright material is presented in a thesis, the candidates must obtain, if necessary, signed waivers from the co-authors and publishers and submit these to the thesis office with the final deposition"

This dissertation is written in the form of three papers. The papers each comprise one chapter in the main body of the thesis (chapters 2, 4, and 5) with general introduction to this work in the first chapter. An additional chapter elaborating on some

unpublished results makes up the third chapter, and conclusions in the sixth chapter. Following normal procedures, the papers have either been published, or are to be submitted in scientific journals. A list of papers are given below:

Chapter 2: "Sequential Insertion of Carbon Monoxide and Imines into Nickel-Methyl Bonds: A New Route to Imine Hydroacylation"; Jason L. Davis; Bruce A. Arndtsen. *Organometallics*, **2000**, *19*, 4657.

Chapter 4: "Generation of 5 and 6 Membered Lactams Via a Nickel Mediated CO, Olefin, CO, Imine, Insertion Cascade"; (to be submitted)

Chapter 5 "Imines in Stille-Type Cross-Coulping Reactions: A Multicomponent Synthesis of α-Substituted Amides."; Jason, L. Davis, Rajiv Dhawan, Bruce A. Arndtsen. *Angew. Chem. Int. Ed.* **2004**, *43*, 590.

Contributions of the Authors

All these papers include the research director, Professor Bruce A. Arndtsen, as co-author as all research was performed under his direction. Chapter 5 includes Rajiv Dhawan, a colleague and Ph.D. graduate of Dr. Arndtsen's laboratory, as co-author in acknowledgement of the his contributions towards the synthesis and isolation of the palladium-bound amide complex, and characterization of number of the amides synthesized in the work. Other then the aforementioned contributions, all of the work presented in this dissertation was initiated and performed by the author.

I hereby give a copyright clearance for the inclusion of the following papers, of which I am co-author, in the dissertation of Jason L. Davis.

"Sequential Insertion of Carbon Monoxide and Imines into Nickel-Methyl Bonds: A New Route to Imine Hydroacylation"

"Generation of 5 and 6 Membered Lactams Via a Nickel Mediated CO, Olefin, CO, Imine, Insertion Cascade"

"Imines in Stille-Type Cross-Coulping Reactions: A Multicomponent Synthesis of α-Substituted Amides."

_____ Date: _____

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Acknowledgments

I would like to start by first thanking Dr. Bruce Arndtsen for allowing me the opportunity to learn the craft of chemistry in his laboratory. I'd also like to thank the other chemistry faculty members for their various insights over my time in the department.

As amazing as it may sound, a lifetime of chemistry would never yield stronger bonds then those I formed with my lab mates and friends at McGill. I cannot imagine a better group of people with which to endure the trials of graduate school. Even with all the degrees of separation that life brings to us, I have only to invoke the thought of our evenings on a terrace somewhere, and I can smile.

I will not name names here for fear of leaving anyone out. Those who I count my friends, you know who you are and what you mean to me. I cannot thank you enough.

Lastly, I would like to thank all the people who have had the patience to help see this thesis through. Hilary and Libby, your support and understanding have made an impossible hill climbable, and I thank you. Recent events in my life have changed me on many levels and put a new perspective on the value of things, and what is truly important. With this in mind, I would like to again dedicate this thesis in memory of my father. Nothing was more important to him then all of his children's accomplishments, and I know he would have taken pride in this one.

TABLE OF CONTENTS

List of Equations

List of Schemes

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List of Abbreviations

OTf	SO_3CF_3
$BArF_4$	$(3,5\text{-}(CF_3)_2C_6H_3)_4B$
Bn	$\text{-}CH_2C_6H_5$
Tol	*p*- $C_6H_4CH_3$
Me	CH_3
Ph	C_6H_5
*i*Pr	$\text{-}CH(CH_3)_2$
*t*Bu	$\text{-}C(CH_3)_3$
bipy	2,2'-bipyridine
TMEDA	tetramethylethylenediamine
dppe	1,2-bis (diphenylphosphino)ethane
dppp	1,3-bis (dipenylphosphino)propane
phen	1,10-phenanthroline
bian	bis(aryl)acenaphthenequinonediimine

CHAPTER ONE

Introduction:

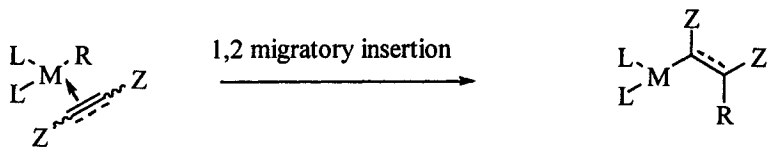
Synthesis of Small Organic Molecules Via Metal Mediated Insertion Chemistry

1.0 PERSPECTIVE

Transition metal catalyzed reactions have become a critical component in many industrial processes.[1-4] Reactions such as olefin polymerization,[1] hydroformylation,[2] Reppe carbonylation,[3] and numerous other commercial processes[4] are essential for generating basic products, such as plastics, solvents, and fuels. More recently, transition metal catalysts have served to fill an ever-increasing demand for new synthetic routes to pharmaceuticals and other biologically active molecules.[5] This has come, in part, as a result of the introduction of new catalysts capable of performing well-defined reactions under mild conditions. Increases in chemoselectivity, as well as the development of new ligands capable of highly enantioselective transformations, have provided a new generation of useful catalysts for synthetic organic chemists.

There are a wide variety of pathways by which transition metal catalysis can efficiently generate new products, though one of the most common involves the insertion of unsaturated substrates into metal-carbon bonds (Scheme 1.1).[6] By combining this process with other reaction steps (e.g. oxidative addition/reductive

elimination, further insertion, β-hydride elimination), a diverse variety of catalytic reactions can be envisioned.[6]



1.1 **1.2**

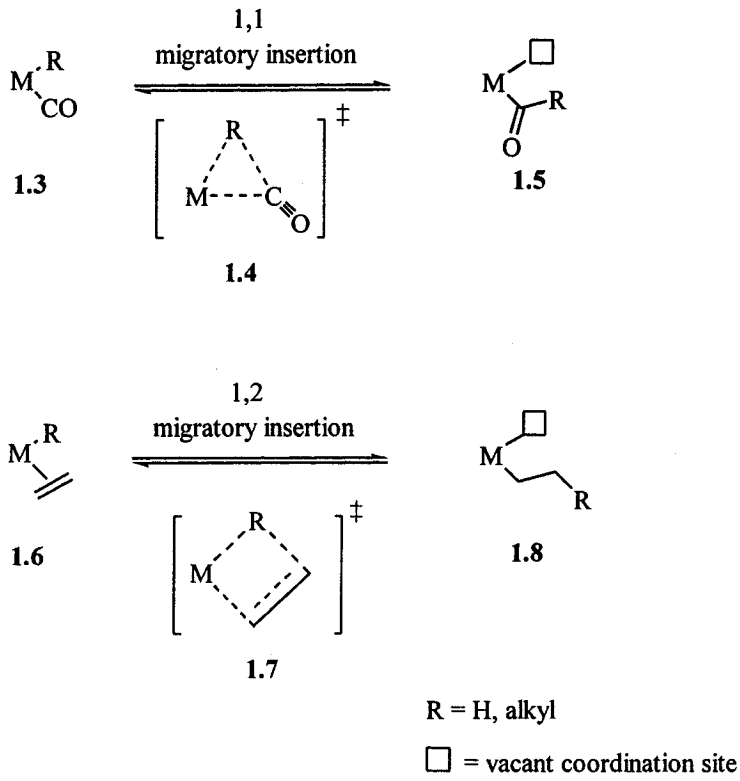
Scheme 1.1 Migratory insertion of unsaturated substrates

In an attempt to provide an overview of this area, a brief summary of the different types of substrates capable of undergoing migratory insertion will be discussed, along with their applications in small molecule synthesis. While many different metals have been used to mediate migratory insertion reactions, this introduction will concentrate primarily on the palladium and nickel-based systems relevant to those used in this thesis. In addition, the scope of insertion substrates will focus primarily on alkenes and alkynes, and some representative examples of their synthetic application. Finally, a more detailed examination of the factors influencing the well defined alkene insertion step in Heck coupling chemistry has been used as a representative example, and provides perspective for the imine insertion chemistry developed in the body of this thesis.

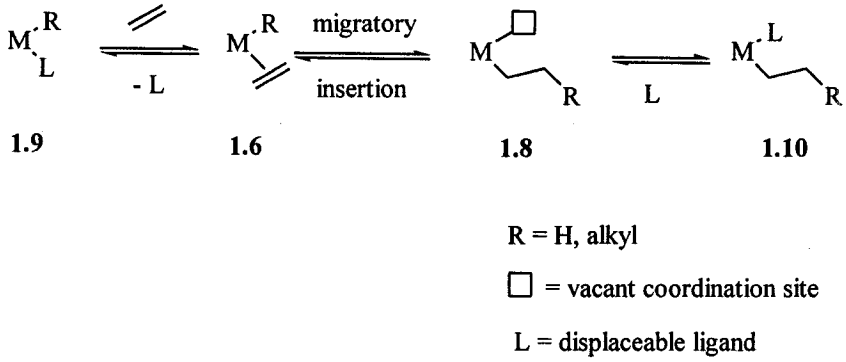
1.1 Insertion of Unsaturated Substrates Using Late Transition Metal Catalysts: General Mechanism

The most common substrates employed in migratory insertion reactions are hydrocarbon-based, such as alkenes, alkynes and carbon monoxide. Their low cost, availability, and molecular diversity make them excellent building blocks for small molecule formation. Combining these unsaturated units with other simple substrates can lead to the generation of highly functionalized products and a wide range of molecular diversity.[5b]

Migratory insertion typically involves the formal insertion of an unsaturated ligand (e.g. CO, RNC, olefins, alkynes) into a cis metal-ligand σ-bond. The insertion often proceeds via a migration of the ligand (R) to the metal-bound unsaturated species (Scheme 1.2). This insertion can occur in the 1,1 fashion, typical seen with CO and isonitriles, or the 1,2 fashion common to alkenes and alkynes. The insertion step is typically postulated to proceed via a concerted mechanism (**1.4**), where the electron density in the M-R σ-bond can be considered to interact with the π^* orbital of the unsaturated ligand.[6a] As such, the unsaturated system must be coordinated to the metal center prior to insertion. This is generally accomplished via an initial ligand substitution process (Scheme 1.3).



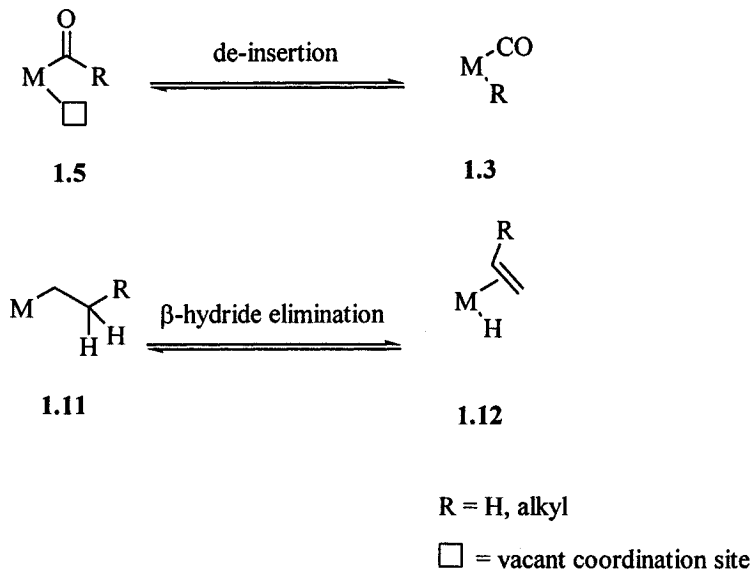
Scheme 1.2 General examples of 1,1 and 1,2 migratory insertion



Scheme 1.3 The role of ligands (L) in migratory insertion

Migratory insertion is typically an equilibrium process. Similar to insertion, de-insertion requires an available cis coordination site for migration to occur. This reaction with 1,2-insertion substrates (e. g. alkenes) usually involves

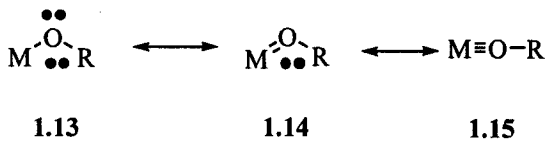
the formation of a metal hydride bond, and is referred to as β-hydride elimination. Here a β-hydrogen migrates to an available cis coordination site to form a new metal-hydride bond and regenerate the unsaturated ligand (Scheme 1.4).



Scheme 1.4 General mechanism for de-insertion and β-hydride elimination

The equilibrium between insertion and de-insertion is dependent on a number of factors, including the migratory aptitude of the R group, the presence of the ligands, the metal center, and the type of unsaturated species involved. For example, the typical order of migration for CO into a M-R bond is: R = Et > Me > $PhCH_2$ > vinyl > aryl > $ROCH_2$ > H > CF_3. Examples of heteroatom containing ligands (e.g. RO^- and R_2N^-) undergoing migration are rare.[6c] In addition, additives such as Lewis acids can accelerate insertion by several orders of magnitude (up to 10^8 in some cases).[7] In the case of alkenes, the insertion

aptitude is somewhat different in that hydride groups migrate the most readily, followed by significantly slower rates for alkyl, vinyl, and aryl groups.[6c] Again, alkoxy and amide ligands generally migrate with difficulty, as the extra lone pairs can often form additional bonds to the metal (Scheme 1.5).[6c]



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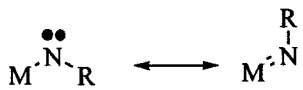
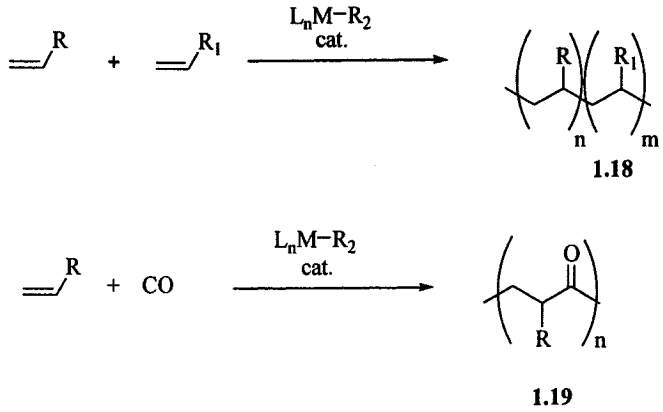


1.16 **1.17**

Scheme 1.5 Lone pair interactions reduce migratory aptitude

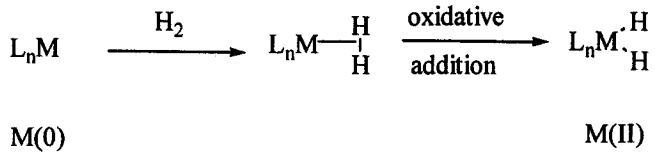
Alkenes and alkynes, in particular, have the ability to undergo multiple insertions, which results in oligomerization and polymerization processes. Similarly, different insertion substrates can undergo competitive migratory insertion to generate alternating, or block co-polymers (Scheme 1.6).[1]



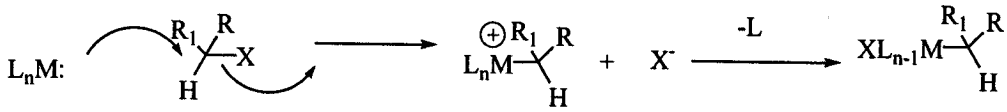
Scheme 1.6: General route to polymers via multiple insertion

The use of migratory insertion reactions to generate small molecules differs significantly from insertion polymerization catalysis in that what are typically referred to as the "initiation" and "termination" steps in polymer synthesis occur much more frequently relative to the insertion step.[4a,7] Thus, the catalyst must not only mediate the insertion step, but must also efficiently generate the prerequisite M-R bond necessary for the insertion, and readily release the product following insertion.

Oxidative addition is likely the most common method used in the formation of the M-R bonds required for insertion. This is usually achieved via either a formal oxidative addition across a sigma bond (*e.g.* H_2), as shown in Scheme 1.7, or an S_N2 mechanism common with polar substrates, shown in Scheme 1.8.[6] Once the M-R bond has been generated, coordination and then insertion of the unsaturated system can take place to form the new bond.

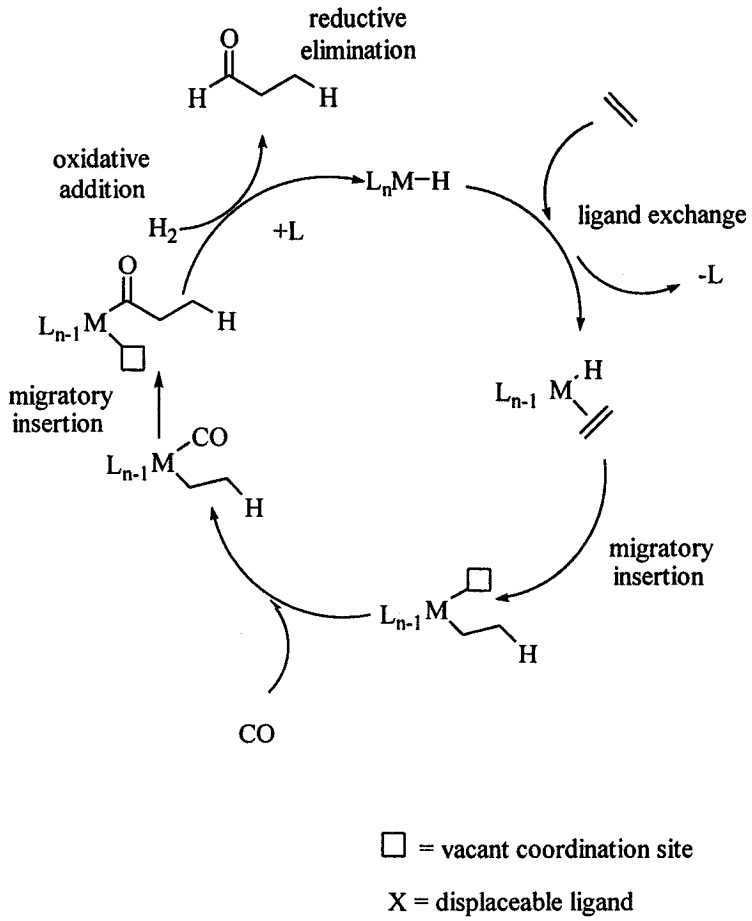


Scheme 1.7 Oxidative addition of non-polar substrates



Scheme 1.8 S_N2 type oxidative addition mechanism for polar substrates

There are a variety of methods by which the product of migratory insertion can be released from the metal (e.g. β-hydride elimination, electrophilic or nucleophilic attack, etc.). One of the most common involves reductive elimination, which is the reverse of oxidative addition. Reductive elimination represents the important final step in many catalytic cycles by which two σ-bonded ligands (L) can be released from the metal to form a new L-L σ-bond.[6b] The combination of an initial oxidative addition, followed by insertion and reductive elimination, represent the general steps found in many catalytic cycles (e.g. the catalytic hydroformylation of olefins).[6c]

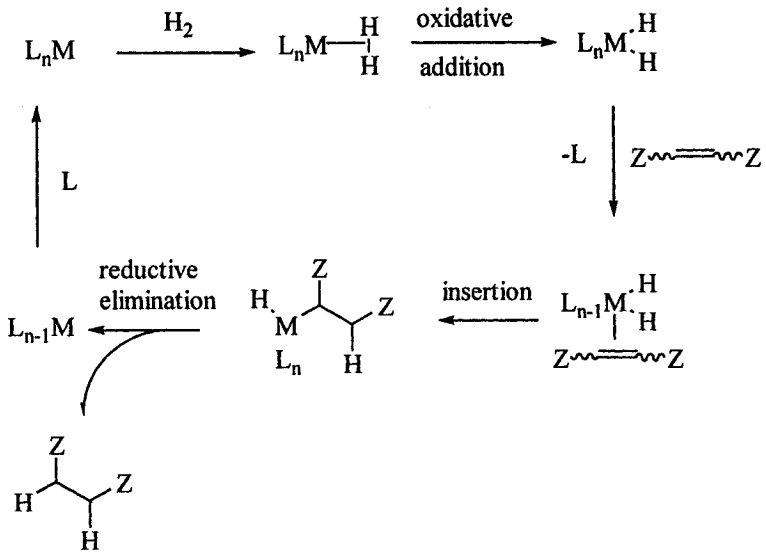


Scheme 1.9 General catalytic cycle for hydroformylation of olefins

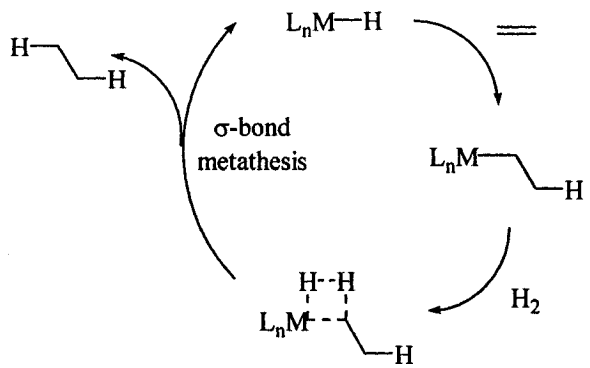
1.2 Hydrogenation of Alkenes and Alkynes

One of the earliest examples of a transition metal catalyzed reaction involving migratory insertion is the hydrogenation of alkenes and alkynes.[6,9,10] In this, hydrogen gas is used to generate metal-hydride complexes capable of inserting the double or triple bonds of alkenes and alkynes. In many catalytic systems, this is generally followed by a reductive elimination with a second metal-hydride bond to generate the hydrogenated product (Scheme 1.10).[6] An

alternative σ-bond metathesis mechanism has also been suggested for a number of catalytic systems (Scheme 1.11) Regardless of the mechanistic pathway, metal catalyzed hydrogenation can provide a mild and hetero-atom tolerant process for reducing unsaturated systems, and has been used in many natural product syntheses, as described in the following section.[10]



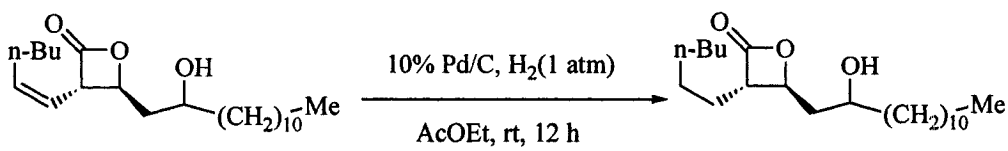
Scheme 1.10 General mechanism for alkene/alkyne hydrogenation



Scheme 1.11 General σ-bond metathesis mechanism for hydrogenation

1.2.1 Hydrogenation of Alkenes

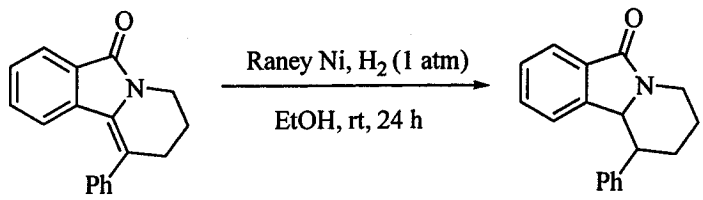
The hydrogenation of an alkene using a heterogeneous catalyst is one of the mildest and most frequently used methods for the reduction of a carbon-carbon double bond. In addition to simple hydrocarbons, reductions of this type have been performed selectively in the presence of functional groups, including acids, ketones, aldehydes, esters, amines, and nitriles.[9,10] A variety of late transition metals, such as palladium, nickel, platinum, rhodium, ruthenium, manganese and iron have all been successfully employed either individually, as alloys, or mixtures for the reduction of alkenes.[10] The amount and particle size of the catalyst used for these reductions can vary significantly, as can the composition of the solid support (e.g. carbon, barium sulfate, alumina, oxides).[9,10] Of these, palladium on charcoal, platinum oxide and Raney nickel have been used extensively, and are capable of hydrogenating most mono, di, and trisubstituted alkenes, regardless of the geometry about the double bond. The order of reactivity is generally Pd/C > Raney nickel > PtO_2 (Schemes 1.12 and 1.13).[9,11]



99%

1.21 **1.22**

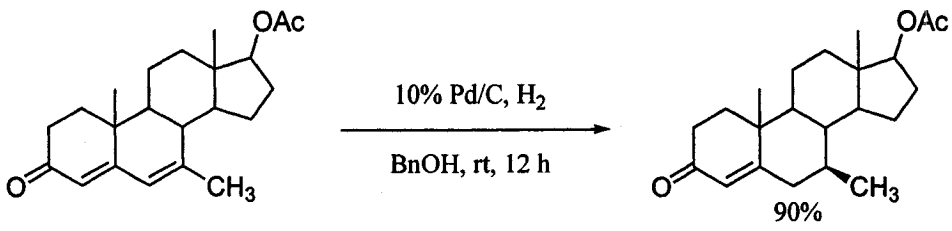
Scheme 1.12 Palladium catalyzed hydrogenation of alkenes



1.23 **1.24**

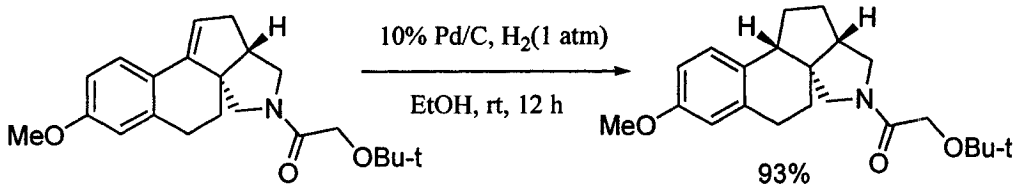
Scheme 1.13 Nickel catalyzed hydrogenation of alkenes

The heteroatom tolerant nature of these catalysts have made them extremely useful in the synthesis of complex and highly functionalized natural products.[5b,10] Existing stereocenters can also be used to direct selectivity during the formation of additional stereocenters. This has been demonstrated to be particularly effective with substrates containing fused ring systems, such as those found in steroids and their analogs (Scheme 1.14).[12] The selectivity observed in these hydrogenations results from the delivery of hydrogen to the sterically less hindered face of the molecule. Unfortunately, these cases are somewhat limited, and generally, the hydrogenation of less rigid substrates result in non-selective reductions.[13]



7-methyl-6-dehydrotestosterone
1.25

7-methyltestosterone
1.26



1.27

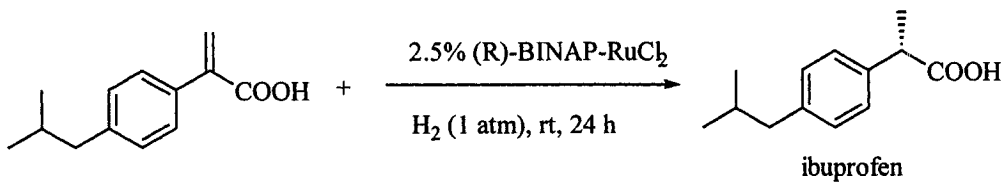
1.28

Scheme 1.14 Palladium catalyzed diastereoselective hydrogenations

The limitations associated with hydrogenation using heterogeneous catalysts has led to the development of a host of homogeneous catalysts capable of performing more mild and selective hydrogenations.[9,13] In particular, homogeneous catalysts have the potential for performing enantioselective hydrogenations. As with many metal catalyzed processes, stereocontrol is typically achieved by the use of chiral ligands.

The simplest alkene substrates capable of undergoing asymmetric hydrogenation are α-disubstituted olefins. Over the last ten to fifteen years, a range of metal complexes capable of performing asymmetric hydrogenations on this class of olefin have been developed.[13,14] Further refinement and application have provided systems capable of delivering the extremely high enantiomeric

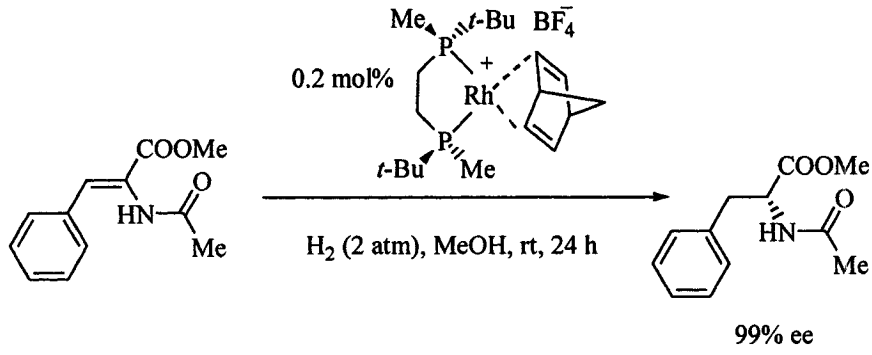
excesses required in pharmaceutically useful reactions, such as the synthesis of ibuprofen, illustrated in Scheme 1.15. [13]



1.29 **1.30**

Scheme 1.15 Ruthenium catalyzed asymmetric hydrogenation

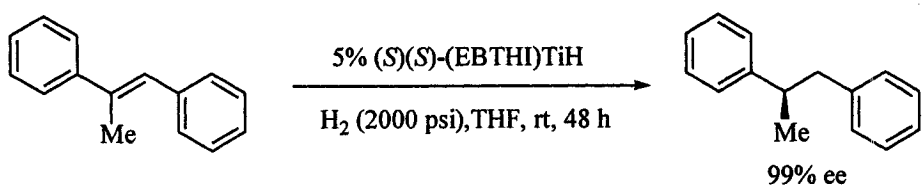
The development of homogeneous catalysts capable of inducing high levels of enantioselectivity in more sterically congested tri and tetra-substituted olefins has proven challenging. Initially, these systems required the judicious placement of chelating substituents capable of inducing the close metal-substrate interactions normally required for asymmetric induction (Scheme 1.16).[15] Using this chelation motif, a number of chiral cobalt, rhodium, and ruthenium complexes have been developed that are capable of inducing high levels of selectivity.[13-16] However, these systems demonstrate low levels of chiral induction when applied to unfunctionalized, or distally functionalized, olefins.[14a, 15]



1.31 **1.32**

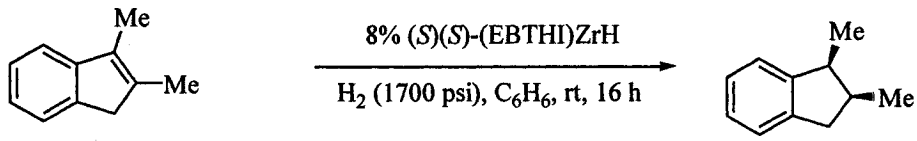
Scheme 1.16 Asymmetric hydrogenation of heteroatom substituted olefins

In an effort to develop chiral catalysts capable of selectively hydrogenating unfunctionalized trisubstituted olefins, a number of new catalysts have been developed.[13,14] For example, the chiral titanocene complex (EBTHI)TiH (EBTHI = ethylenebistetrahydroindenyl) has been shown by Buchwald and co-workers to mediate the hydrogenation of trisubstituted alkene **1.33** with high enantioselectivity (Scheme 1.17).[16a] The analogous zirconocene complex has been used for the selective hydrogenation of tetrasubstituted olefins.[16b] The later alkenes are particularly interesting, as their hydrogenation can lead to the formation of two new stereocenters. However, they also represent the least reactive olefins for hydrogenation, and development of a catalyst capable of selectively hydrogenating these sterically congested substrates represents a significant advance.



99% ee

1.33 **1.34**

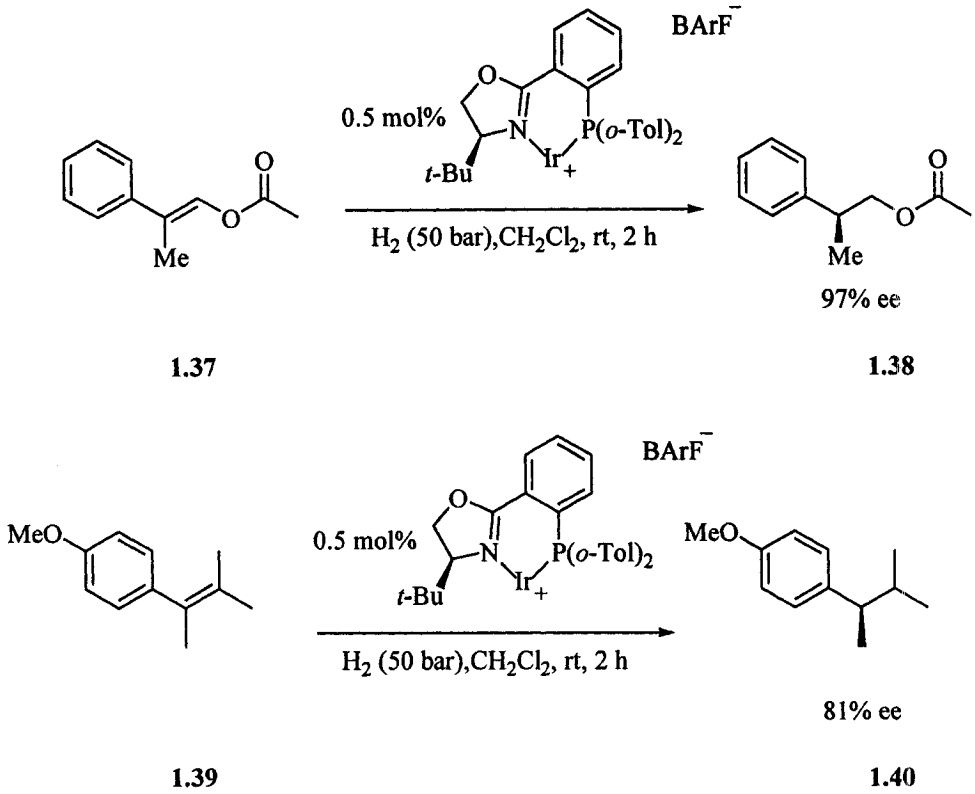


93% ee

1.35 **1.36**

Scheme 1.17 Asymmetric hydrogenation of tri and tetra substituted olefins

More recently, Pfaltz and co-workers have developed a number of chiral iridium complexes capable of hydrogenating both functionalized and unfunctionalized olefins with high levels of selectivity under mild conditions.[14a,14b,16c] These catalysts are also capable of selectively hydrogenating tetrasubstituted olefins with relatively good enantioselectivity (Scheme 1.18). In addition to these general examples, a range of other systems have demonstrated the ability to perform this transformation with varying degrees of success.[10,17]



1.37 1.38

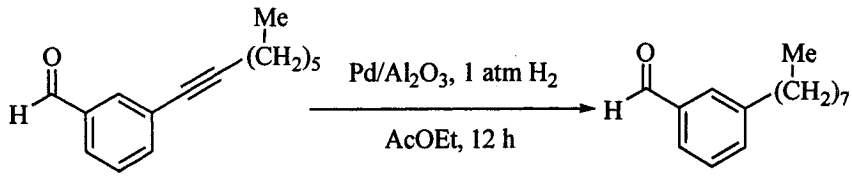
1.39 1.40

Scheme 1.18 Asymmetric hydrogenation using chiral iridium complexes

1.2.2 Hydrogenation of Alkynes

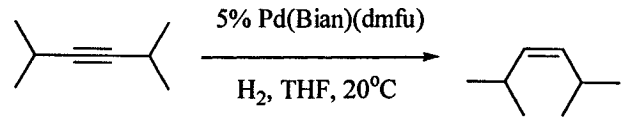
Similar to their alkene counterparts, alkynes can also undergo metal catalyzed hydrogenation reactions. While complete hydrogenation of alkynes to their saturated derivatives can be readily accomplished (Scheme 1.19),[18a] more mild versions of the catalysts used for alkene hydrogenations are often used to partially hydrogenate alkynes to alkenes (e.g. Lindlar catalyst: Pd on $CaCO_3$/5% $Pb(OAc)_2$).[19] In addition, many ligand systems can be used to control the nature of the cis/trans geometry in the product (Scheme 1.20).[18b,20] An example of this

is illustrated with the selective conversion of alkyne **1.43** to the cis alkene **1.44** in Scheme 1.20.



1.41 **1.42**

Scheme 1.19 Example of complete hydrogenation of alkynes



99.5%

1.43 **1.44**

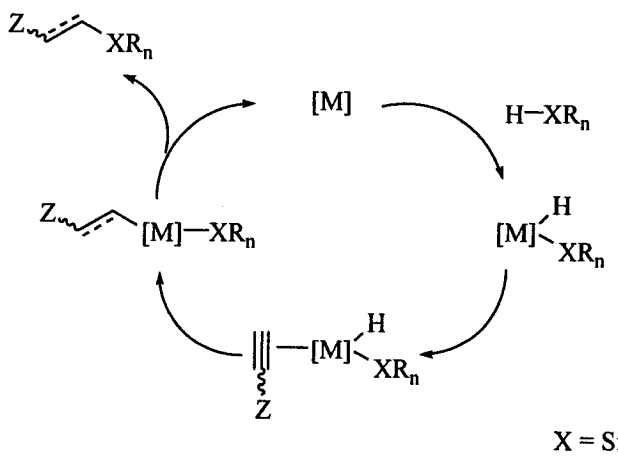
Bian =bis(aryl)acenaphthenequinonediimine
dmfu = dimethylfumerate

Scheme 1.20 Palladium catalyzed regioselective partial hydrogenation of alkynes

1.2.3 Hydrosilation and Hydroboration of Alkenes and Alkynes

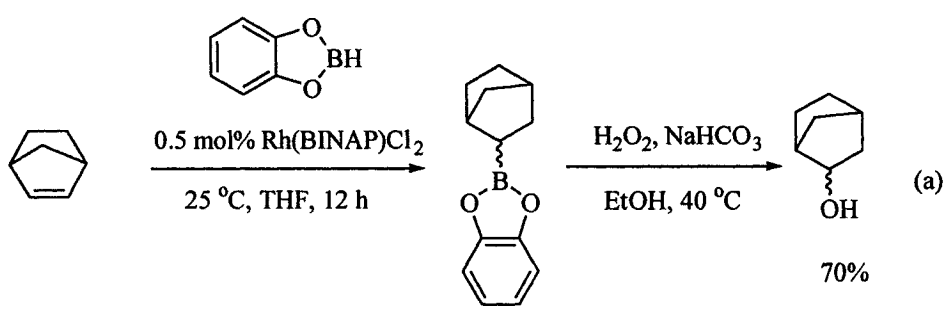
While transition metal catalyzed hydrogenation represents the simplest example of the application of migratory insertion reactions in catalysis, a number of other substrates are also capable of reducing alkenes and alkynes via an

analogous reaction. For example, the metal catalyzed hydrosilation[21] and hydroboration[22] of alkenes and alkynes has become an important method for the generation of synthetically useful building blocks. The general mechanism is similar to that described previously for hydrogenations, and typically involves initial oxidative addition of a hydrogen-boron or hydrogen-silyl bond to a metal center, followed by alkene or alkyne coordination, migratory insertion, and finally reductive elimination (Scheme 1.21).[22a] Alternatively, these reactions can also be achieved through a σ-bond metathesis mechanism analogous to that in Scheme 1.11.[23] In particular, the activation of Si-H bonds and unsaturated hydrocarbons towards σ-bond metathesis have been mediated by a number of electrophilic, high valent transition metal centers of the type $Cp^*_2MR_2$ (M = Ti, Zr, Hf; Cp^*_2 =C_5Me_5; R = H, alkyl, silyl)[24] (i.e. Scheme 1.22, b).

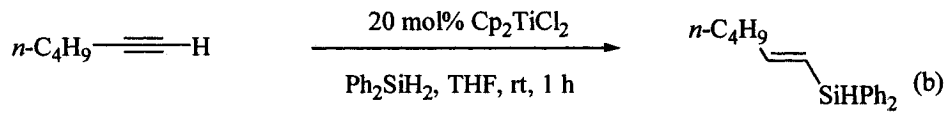


Scheme 1.21 General mechanism for hydrosilation and hydroboration

The products of hydroboration and hydrosilation can be readily converted to other synthetically useful functionalities. This feature has led to a broad range of applications and representative examples are given below (Scheme 1.22).[12b,12c]



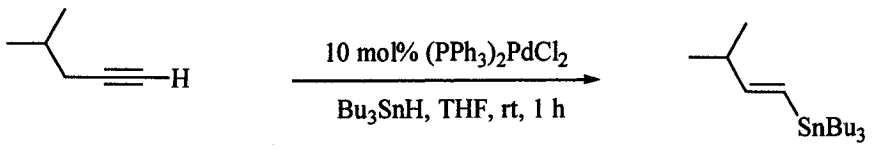
1.45 **1.46** **1.47**



1.48 **1.49**

Scheme 1.22 Examples of metal catalyzed hydroboration and hydrosilation

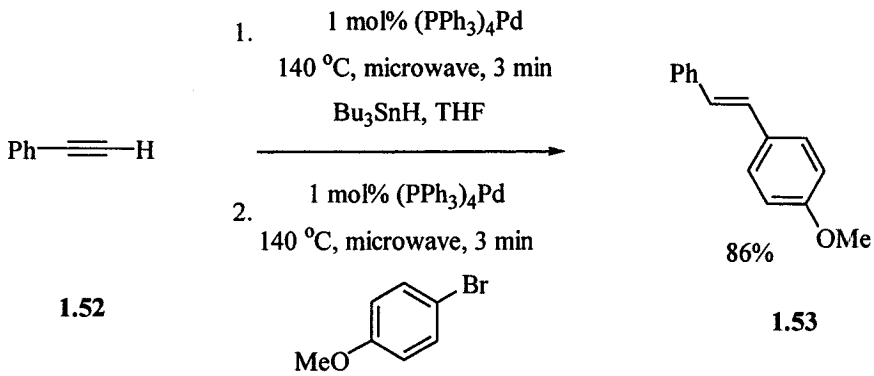
Metal catalyzed hydrostannylations of alkynes also proceed via a similar mechanism, and can be used to generate a variety of synthetically useful vinyl stannanes (Scheme 1.23).[22d] These building blocks have been utilized extensively in late transition metal catalyzed cross-coupling reaction (i.e. Stille couplings, Scheme 1.24).[22e]



90%

1.50 **1.51**

Scheme 1.23 Examples of metal catalyzed hydrostannylation



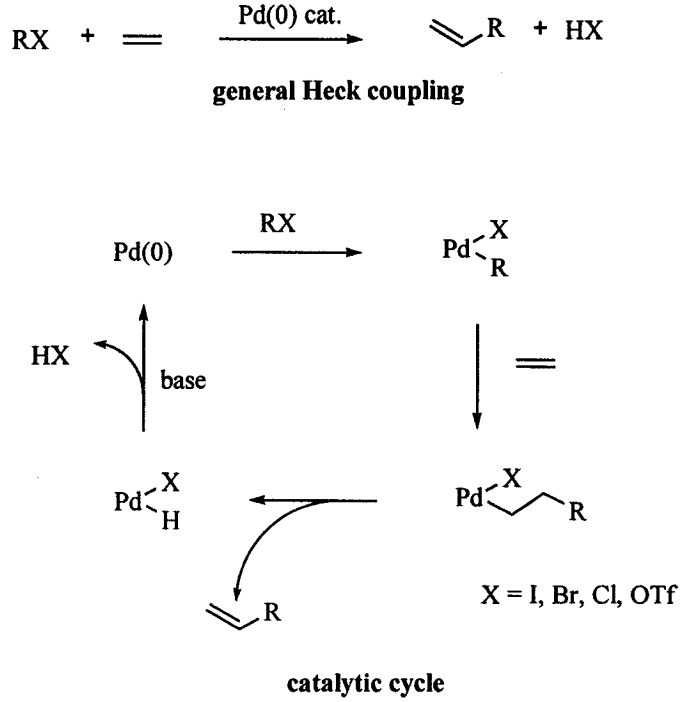
86%

1.52 **1.53**

Scheme 1.24 Example of one pot hydrostannylation/Stille couplings

1.3 C-C Bond Forming Reactions with Alkenes

The development of catalysts capable of performing alkene insertions into metal-carbon bonds has received a great deal of interest, as it provides a straight forward method to construct carbon-carbon bonds. While a wide range of catalytic processes involve this basic transformation, the Heck reaction (Scheme 1.25) has arguably become one of the most synthetically useful reactions of this type.[25,26,27] The subsequent sections involving metal catalyzed carbon-carbon bond formation will focus on providing a brief summary of Heck couplings, as well as some representative examples of their use in small molecule synthesis.



Scheme 1.25 General catalytic cycle of the Heck reaction

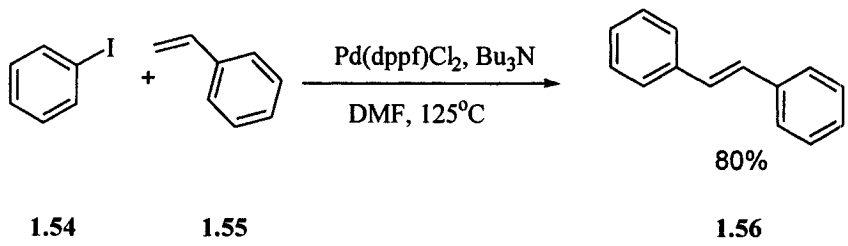
The Heck reaction is typically a palladium catalyzed process, though recently other metal complexes including those of cobalt,[25a,25b] copper,[25c] and nickel[25d] have also been used with varying degrees of success. Palladium catalysts are considered to mediate this reaction via the initial oxidative addition of R-X to Pd(0), followed by the formal insertion of an alkene into a palladium-carbon bond to form a new carbon-carbon bond. This is generally followed by a β-hydride elimination step, where the R-substituted alkene is generated. In addition, subsequent reductive elimination of a strong acid HX regenerates the Pd(0) source. This acid is generally removed from the reaction using a variety of

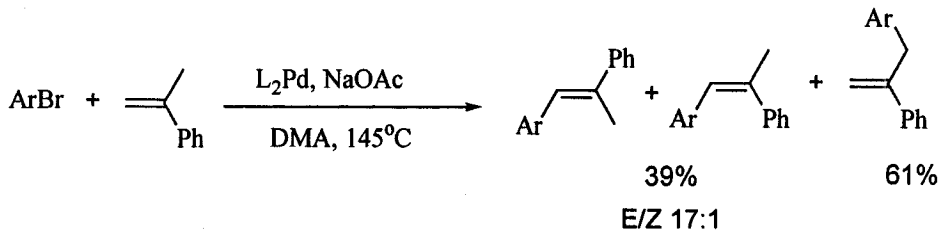
organic and inorganic bases, which serves to help drive the catalytic cycle (Scheme 1.25).[6]

While the Heck reaction can allow for the coupling of a wide range of R-X and alkene substrates, no truly general set of conditions for this process has yet emerged. In fact, recent reviews by both Overman[26] and Meijere[27] have referred to these conditions as "recipes" or "cocktails", from which no one optimal system exists. Nonetheless, the active catalyst is generally a relatively electron rich Pd(0) complex bearing mono or bidentate ligands, which help facilitate the initial oxidative addition step. The base used can vary dramatically, though the most common are trialkyl amines (e.g. triethylamine, diisopropylethylamine) or inorganic salts (e.g NaOAc, K_2CO_3). Similarly, a wide range of solvents have been used, including THF, toluene, dichloromethane, DMF, NMP and aqueous systems.[25-27] Many of these condition selections are substrate dependent, and, as such, have been used interchangeably as a method for optimization.

Perhaps the most significant area of catalyst modification has involved the ligands on the metal center.[25-28] Altering this component of the catalytic system can lead to dramatic changes in reactivity and selectivity. Phosphine-based ligands[28] have been the most extensively employed. These vary widely in their nature, from sterically bulky monodentate systems,[25f] to smaller bidentate ligands.[25g] More recently, non-phosphorous based ligands have also been used, and include phenanthrolines,[29a,b] carbene ligands[29c,d] and a large number of mixed P-N systems.[29e]

While the Heck reaction is quite efficient with simple α-olefins (Scheme 1.26)[25g], this is not necessarily the case with the more complex alkenes often employed in organic synthesis. As the complexity of the substitution pattern about the olefin is increased, a variety of selectivity issues must be addressed. Most importantly, these include regio- and stereo-control in both the olefin insertion, and the β-hydride elimination steps (Scheme 1.26).[25g] The products obtained from Heck couplings can often be influenced by a wide range of parameters, including solvent, temperature, ligand, base, and counterion. While any of the aforementioned variables can produce somewhat unpredictable results, extensive use of the reaction over the last fifteen years has shown that the desired coupling can eventually be achieved under the appropriate conditions.[25]

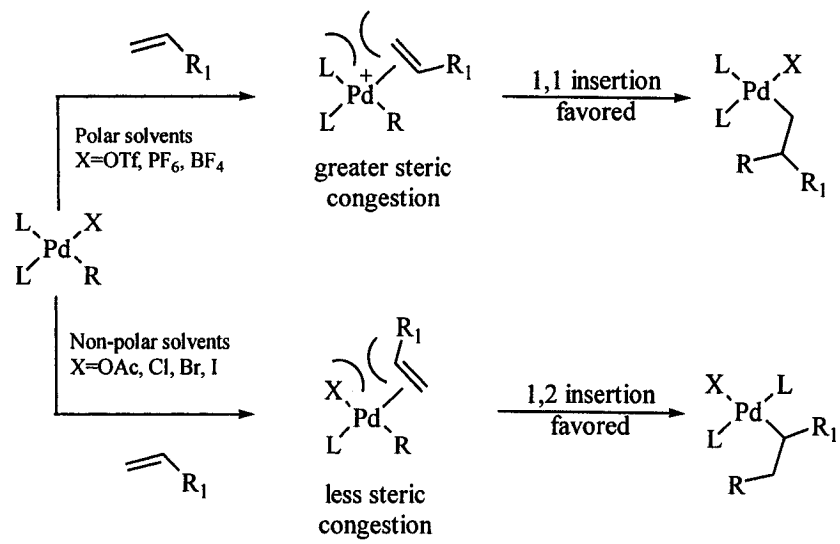




Scheme 1.26 General examples of Heck coupling and β-hydride elimination

1.31 Regioselectivity of the Insertion

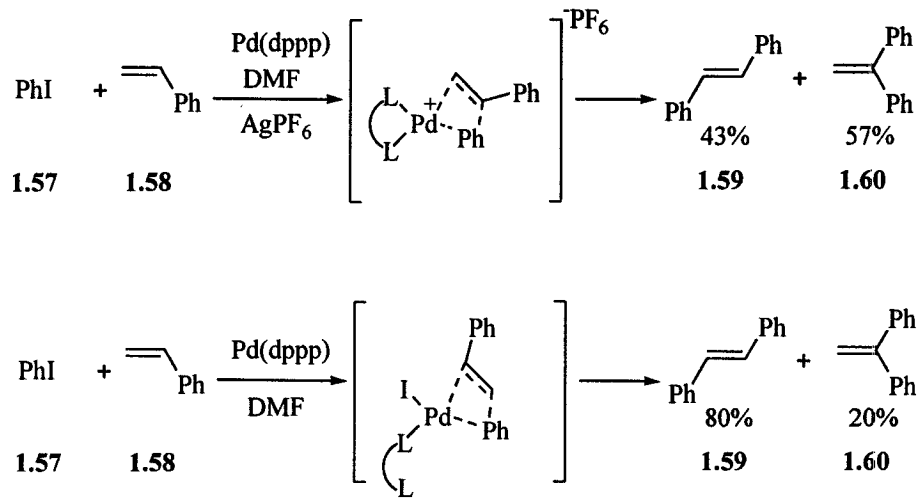
A wide range of different alkene substrates, have been used in Heck coupling reactions. Electron-deficient alkenes, such as acrylates, enones, and nitriles; unactivated alkenes like propylene, ethylene, and styrene, as well as electron-rich systems, (e.g. enol-ethers and enamides) are all potential Heck substrates. Not surprisingly, the nature of the substrate can dramatically affect the regioselectivity of insertion. For example, the insertion of electron-poor and unactivated alkenes is primarily sterically controlled, with insertion often proceeding in a 1,2 fashion (Scheme 1.27). Unfortunately, the insertion regioselectivity of electron-rich alkenes is less defined, and often mixtures of the two isomers are obtained.[28b] Not surprisingly, the nature of the substrate is not the only factor affecting insertion regioselectivity, and a number of other variables can also influence the product distribution.



As L becomes larger the amount of 1,1 insertion products increases

Scheme 1.27 Counterion effect on insertion regioselectivity

Studies done by Cabri et al.[25e] and Hayashi et al.[30] have demonstrated that the counterion appears to play an important role in determining the product distribution (Scheme 1.28). For instance, when strongly binding halide counterions are used, the mechanism is thought to proceed via an initial ligand (L) dissociation, followed by coordination and insertion of the alkene. This generally creates a sterically less demanding environment around the metal center during the insertion step. Conversely, weakly coordinating counterions, such as triflates, favor the formation of cationic intermediates. Here, the anion is the more readily displaced ligand and alkene insertion occurs under the continued influence of the neutral phosphine ligands, which remain bound throughout the catalytic cycle. Thus, in the palladium catalyzed phenylation of styrene in DMF with (dppp) as the ligand (dppp = 1,3-bis (diphenylphosphino)propane), strongly coordinating I^- and OAc^- counterions favored the formation of trans stilbene (**1.59**) over α-phenylstyrene (**1.60**, Scheme 1.28). More weakly coordinating anions, such as PF_6 and BF_4, yielded almost equivalent amounts of the two products (43% trans stilbene and 57% α-phenylstyrene).[31]



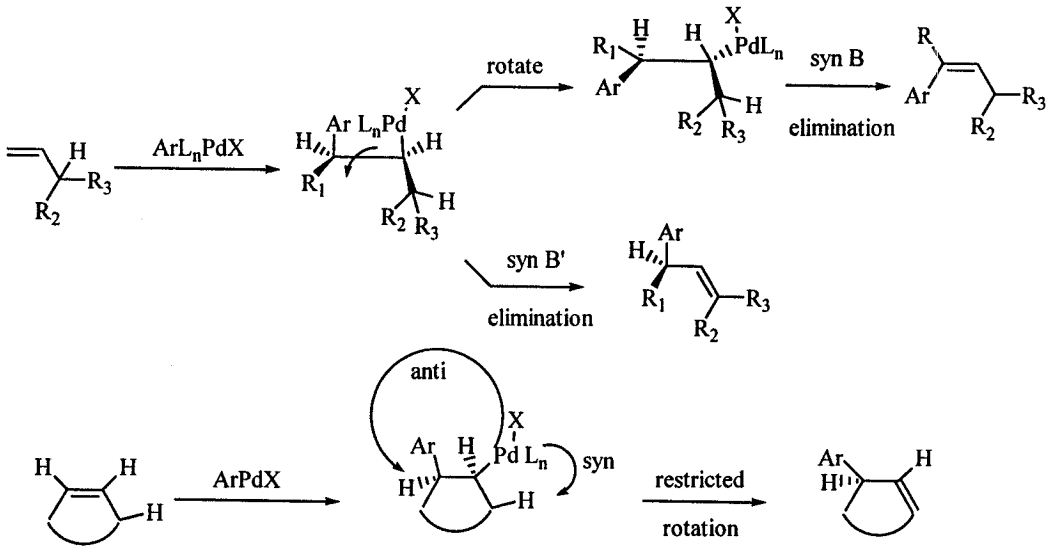
Scheme 1.28 Effects of counterion/solvent polarity on insertion regioselectivity

Further studies have demonstrated that solvent polarity can be used to further enhance this effect. Highly polar solvent systems (DMF/H_2O), which are capable of stabilizing the cationic palladium species, also favor the α-substituted product, while the less polar solvents (CH_2Cl_2) are more likely to generate neutral intermediates, and show good selectivity for substitution at the terminal position.[31]

1.32 Selectivity of the β-Hydride Elimination

β-hydride elimination is the critical final step in most Heck-type couplings. The execution of this step allows for the liberation of the product, as well as the regeneration of the catalyst. This step must also be considered in terms of the regio-isomer formed, particularly when there are multiple sites

capable of β-hydride elimination. The selectivity of this step is primarily governed by the relative ability of competing β-hydrogens to migrate to the palladium center upon alkene de-insertion. Since β-hydride elimination is considered to be a concerted reaction, the most important requirement associated with β-hydride elimination is a syn orientation with the metal center. If the β-hydrogens cannot attain this syn geometry, the elimination becomes extremely disfavored. Thus, the substrates ability to orient itself in this fashion, usually via rotation about a β-sigma bonds, largely determines where the β-hydride elimination is directed (Scheme 1.29). [28b, 6c]



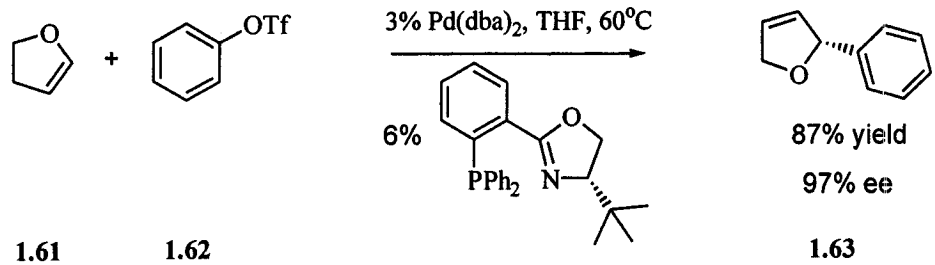
Scheme 1.29 Syn-orientation required for β-hydride elimination

Cyclic alkenes are particularly attractive Heck substrates, as they generally do not face the regio-selective issues associated with competitive β-hydride elimination. With cyclic olefins, the hydrogen present on the newly substituted

carbon is always anti with respect to the carbon-palladium bond, and thus cannot readily undergo β-hydride elimination. Thus, Heck couplings with cyclic alkenes can often lead to the formation of a single olefin product. This is critical in the development of asymmetric versions of Heck couplings (*vide infra*).

1.33 Asymmetric Induction

The number of natural products and bio-active pharmaceuticals containing one or more stereocenters has made the design of methods to selectively form chiral products an area of intense research. Thus, the development of asymmetric versions of the Heck coupling represents an important advance.[25h,26,27] As with hydrogenations, the enantioselective insertion of olefins in Heck reactions can be achieved using a wide range of chiral ligands.[28] However, because of the β-hydride elimination step, the potential for regenerating the sp^2 hybridized center, and thus destroying the newly formed chiral center, makes the design of enantioselective Heck reactions much more difficult. To prevent this, β-hydride elimination must preferentially occur away from the newly formed β-center. This usually restricts asymmetric Heck reactions to the use of cyclic alkenes, or the formation of quaternary centers, as it is only in these cases that β-hydride elimination can be directed away from the newly formed chiral carbon (Scheme 1.29).[28b] When these conditions are met, high levels of enantioselectivity can be achieved, as illustrated in Scheme 1.30.



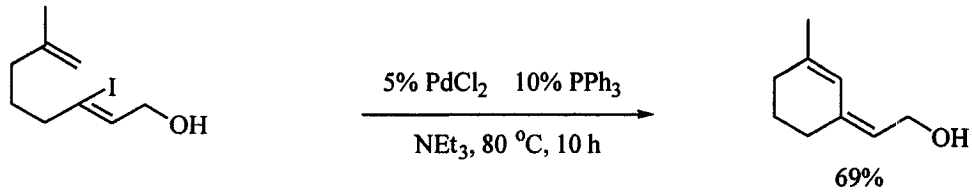
1.61 **1.62** **1.63**

Scheme 1.30 Asymmetric Heck coupling using chiral ligands

Despite these restrictions, asymmetric Heck chemistry has become an important method for the installation of stereocenters.[26] In particular, intramolecular Heck couplings have been used extensively to generate a wide range of fused chiral ring systems[13] and will be discussed in more detail in the next section.

1.4 Carbocyclizations

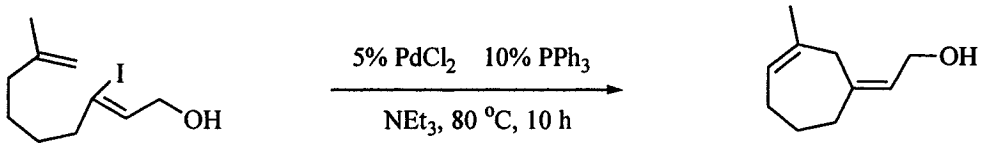
The initial success of metal catalyzed intermolecular Heck reactions were soon followed by the development of intramolecular versions capable of generating cyclic products.[26,32] These types of insertion-based cyclizations have been very effectively employed to generate simple 5, 6 and 7 membered rings (Scheme 1.31 and 1.32[33]), as well as more complex fused or functionalized heterocycles (Scheme 1.33).[34c] Examples of Heck cyclizations generating medium sized ring systems (eight through twelve-membered) in good yields are rare.[31,32,33]



69%

1.64 **1.65**

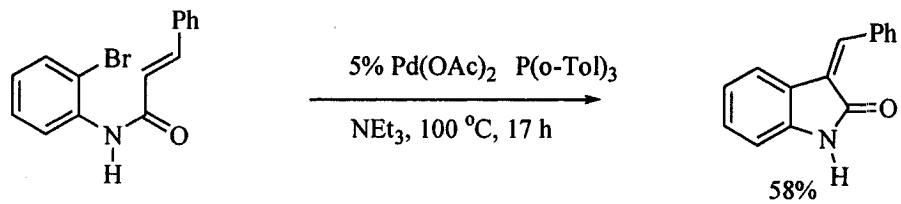
Scheme 1.31 Palladium catalyzed Heck six membered ring formation



68%

1.66 **1.67**

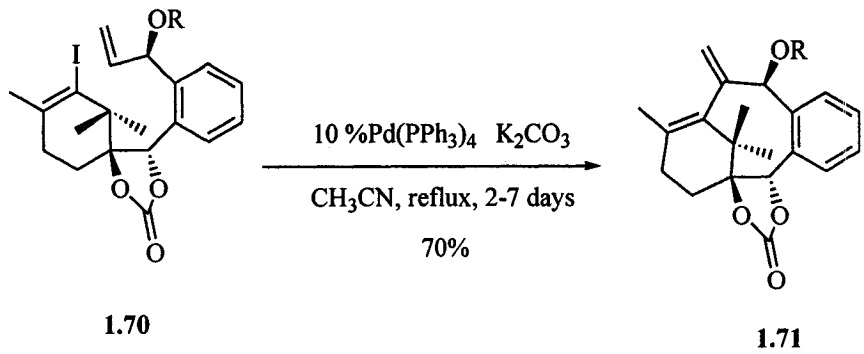
Scheme 1.32 Palladium catalyzed Heck seven membered ring formation



58%

1.68 **1.69**

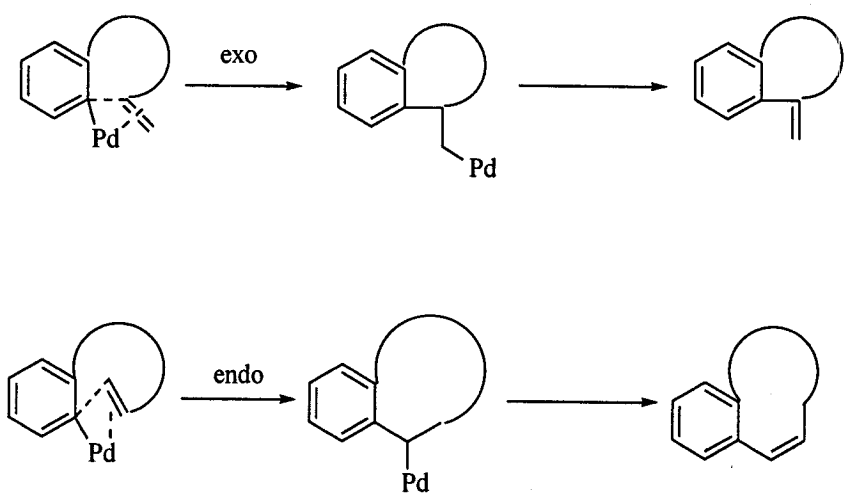
Scheme 1.33 Palladium catalyzed Heck hetero-cyclization



1.70 **1.71**

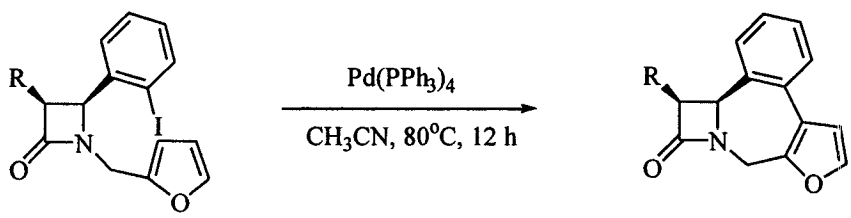
Scheme 1.34 Palladium catalyzed Heck medium ring closure

While the basic mechanism for the intramolecular insertion is similar to its intermolecular counterpart, several new selectivity issues can arise. In particular, the regioselectivity of the olefin insertion step becomes even more critical, as it now not only affects the substitution pattern of the product, but also determines the ring size.[25g] Thus, the ability to control the formation of either the *exo* or the *endo* insertion product (Scheme 1.35) is crucial, otherwise a mixture of products, or the undesired ring system may be formed.



Scheme 1.35 Regioselectivity determines ring size

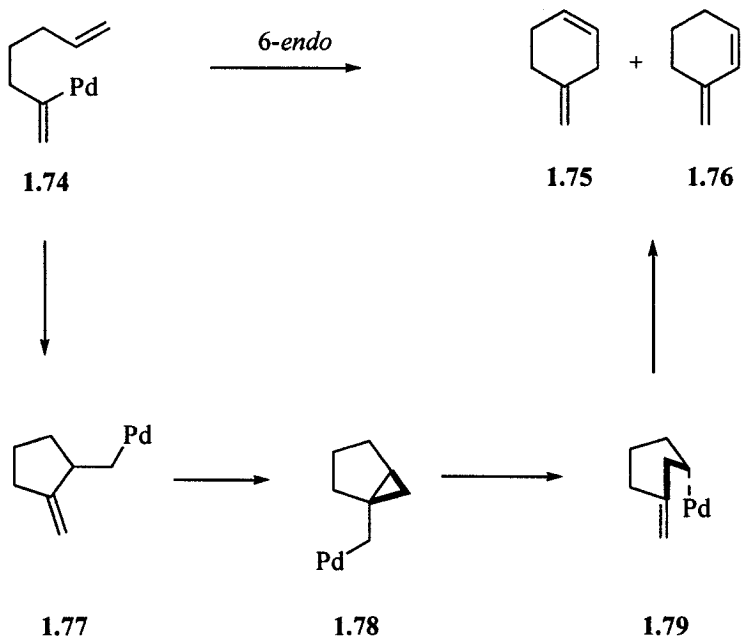
In general the *exo*-mode of cyclization is dominant for most simple ring systems, as it is far less sterically demanding for alkene insertion.[38] The formation of five membered ring systems is generally preferred, though examples of smaller three and four-membered cycles are also known.[39,40] The much less common *endo* mode requires that the olefin orient itself inside the tether during the formation of the intermediate π-complex. This typically requires a long or flexible tether between the alkene and Pd-carbon bond. It is this highly strained geometry which makes 6-*endo* cyclizations disfavored. Most examples of endo-mode cyclization involve constrained alkenes, or those with specific substitution patterns (Scheme 1.36[28b]).[13,34] It is also worthy to note that the endo-mode of cyclization dominates in medium size ring systems, which is in accordance with the absence of strong stereoelectronic effects.[34]



1.72 **1.73**

Scheme 1.36 Example of endo-mode Heck cyclization

Many of the cases where endo-mode cyclization products are observed actually undergo the more usual exo-mode cyclization, followed by a cyclopropanation, cyclopropylcarbinyl-to-homoallyl rearrangement, and subsequent β-hydride elimination (scheme 1.37).[33] Thus, even systems apparently exhibiting endo-mode selectivity do not necessarily procede via this pathway, and supporting mechanistic studies are required to confirm the true nature of the insertion selectivity.

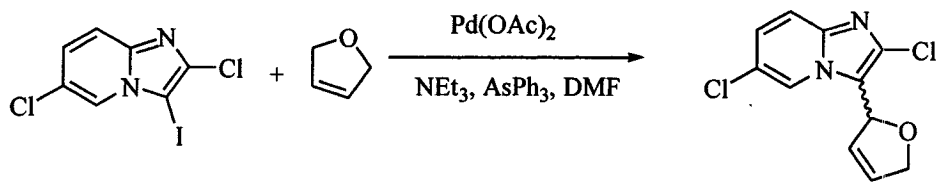


Scheme 1.37 Alternate route for 6-*endo* cyclization product formation

1.5 Heck Couplings in Synthesis

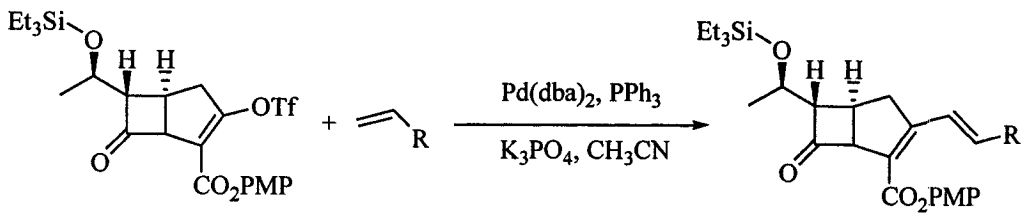
The versatility of the Heck reaction has led to a range of applications in the synthesis of natural products and pharmaceutically important small molecules

(representative examples are described in Scheme 1.38[33] and 1.39[41]). Heck couplings have also been used as key steps in the design of a number of complex total syntheses, and cascade reactions (Scheme 1.40), which have been the subject of several reviews.[26, 2, 34b]



1.80 **1.81**

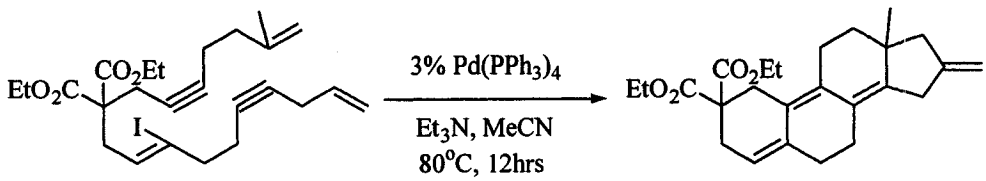
Scheme 1.38 Example of Heck coupling in anti-viral nucleosides



1.82 **1.83**

R=Ph, CO_2Me, CH_2OH, $CH(OEt)_2$, CH_2OAc, CH_2NHCO_2PMP

Scheme 1.39 Heck coupling used to generate β-lactam analogs



76%

1.84 **1.85**

Scheme 1.40 Palladium catalyzed cascade reaction to steroid cores

1.5 Transition Metal Mediated Imine Insertion

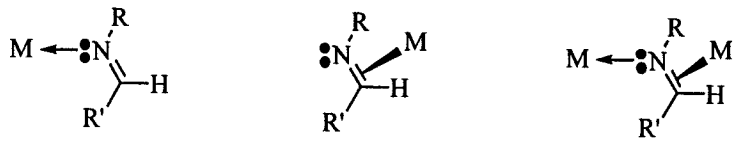
While the migratory insertion of unsaturated hydrocarbons into late transition metal-carbon bonds has been extensively employed in synthesis, examples of the analogous insertion reaction with hetero-atom containing substrates such as imines (R_2C=NR) are rare or often poorly defined.[42] Given the potential utility of the products, it is somewhat surprising that systems capable of generating new C-N bonds by imine insertion have received so little attention. In fact, until recently, the literature on imine insertion consisted almost entirely of studies involving metal-catalyzed imine hydrogenations, hydroborations or hydrosilations. [42]

1.5.1 Imine Insertion into Metal-Hydride Bonds

The insertion of imines into metal-hydride bonds has been proposed as a key step in the catalytic hydrogenation of imines with a variety of transition metal

complexes, including those with Ti,[42e,42h,43] Rh,[44] Ir,[45] Ru,[46] and several organolanthanide systems.[47] While mechanistic data on the imine insertion step is often unavailable, a number of well defined examples of imine insertion into transition metal-hydride bonds exist.[48,49] Though alkenes and imines are iso-electronic in nature, one significant difference regarding insertion propensity involves the presence of the lone pair of electrons on the nitrogen. This lone pair of electrons provides a potential sigma coordination mode, in addition to the π-coordination considered necessary for olefin insertion (Scheme 1.41). The presence of this alternate binding mode can complicate mechanistic studies.

pre-insertion coordination mode for olefins

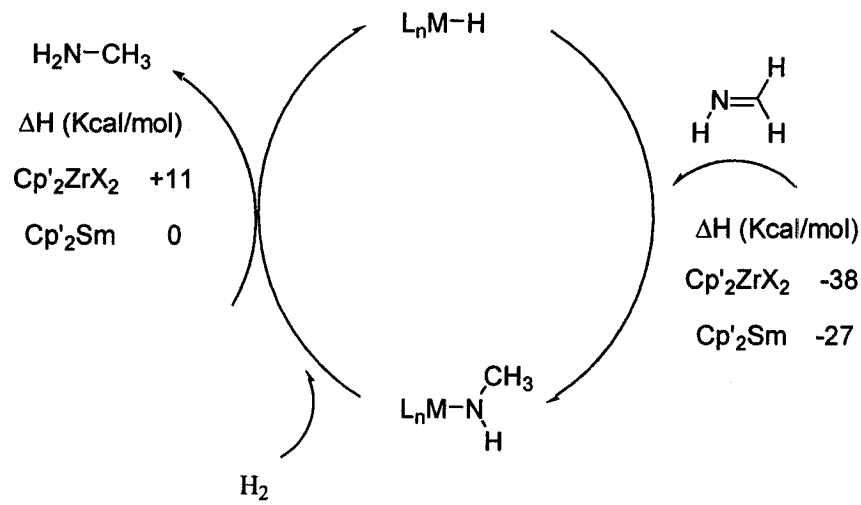


Scheme 1.41 Binding modes available for olefins vs. imines

From a simple enthalpy standpoint, early transition metals are known to form strong metal-nitrogen bonds, and thus offer a considerable driving force for imine insertion.[47] However, due to this, the liberation of the substrate from the metal center can present a significant problem. Despite this potential issue, a number of early transition metal complexes that can hydrogenate imines have been developed. For example, titanocene complexes have been used successfully

for both the hydrogenation and hydrosilation of imines (Scheme 1.17 and Scheme 1.46).[16a,16b,42e,f,h,i,43]

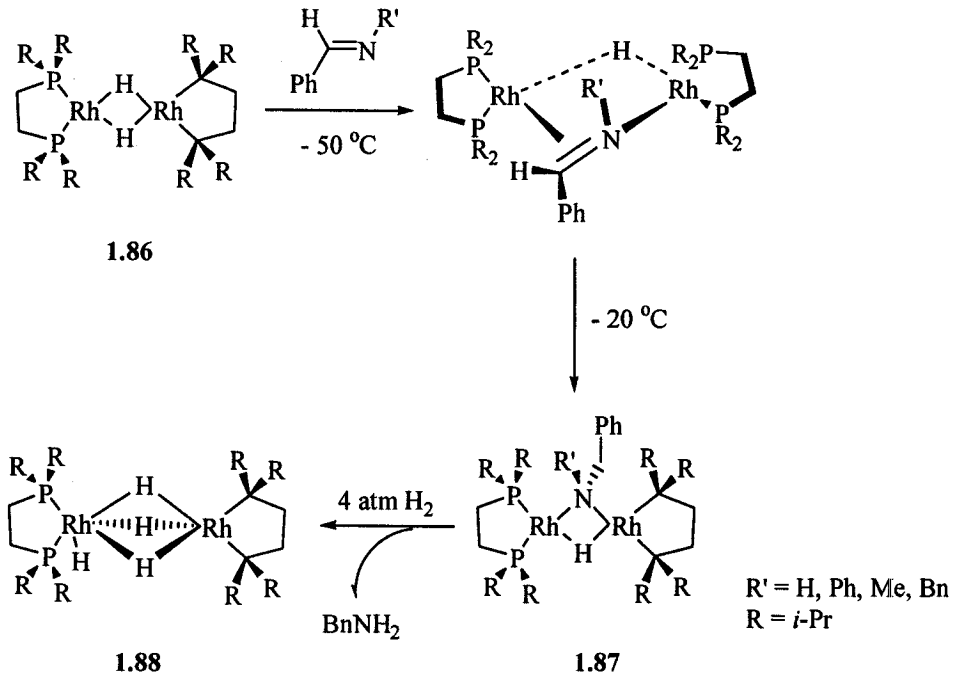
Marks and co-workers have also investigated a number of potential imine hydrogenation catalysts using organolanthanide complexes.[47] Simplified bond strength calculations for imine hydrogenation with early transition metal zirconium complexes, suggest imine insertion into the metal-hydride bond is highly exothermic.[47] The second step, however, involving product release becomes much more difficult due to the strength of the metal-nitrogen bond (Scheme 1.42).[47] However, similar calculations on the analogous samarium complex suggest a more kinetically favorable catalytic cycle might be possible, due to a less exothermic imine insertion.



Scheme 1.42 Enthalpy of imine hydrogenation using early metals

A range of late transition metal complexes have also been found to be active catalysts for the hydrogenation of imines.[13,48] In addition, the study of low

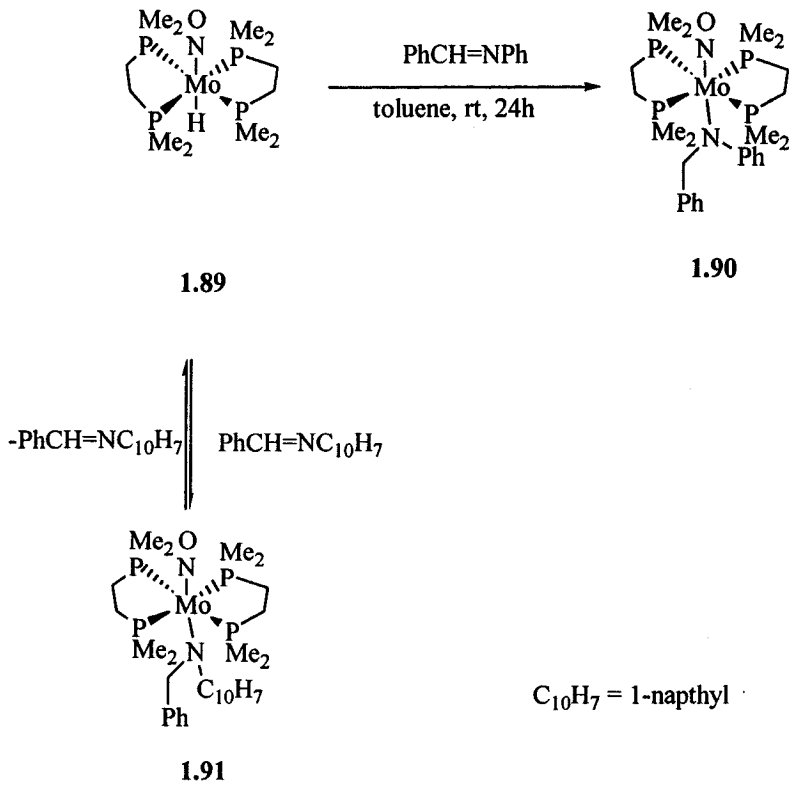
oxidation state metal-hydride complexes have led to a number of examples of imine insertion to form stable products.[48] Here, the σ-coordination of imines to a metal center can be exploited to achieve insertion. For example, Piers and Fryzuk demonstrated that imines undergo 1,2 insertion into the metal-hydride bonds of bridged rhodium dimers.[49] The postulated mechanism involves an initial σ-coordination of the imine to one of the rhodium centers, followed by a secondary π-coordination with the other metal center, and subsequent insertion into the rhodium-hydride bond (Scheme 1.43).



Scheme 1.43 Imine insertion via σ and π coordination

Recently, Berke and co-workers performed similar studies using a monomeric molybdenum-hydride complex, and were able to isolate and obtain X-ray crystal structures of the products of imine insertion.[50] This insertion was also

demonstrated to be reversible when a sterically bulky 1-naphthyl substituent was placed on the nitrogen, and species **1.89** and **1.91** were observed by ^{1}H NMR.



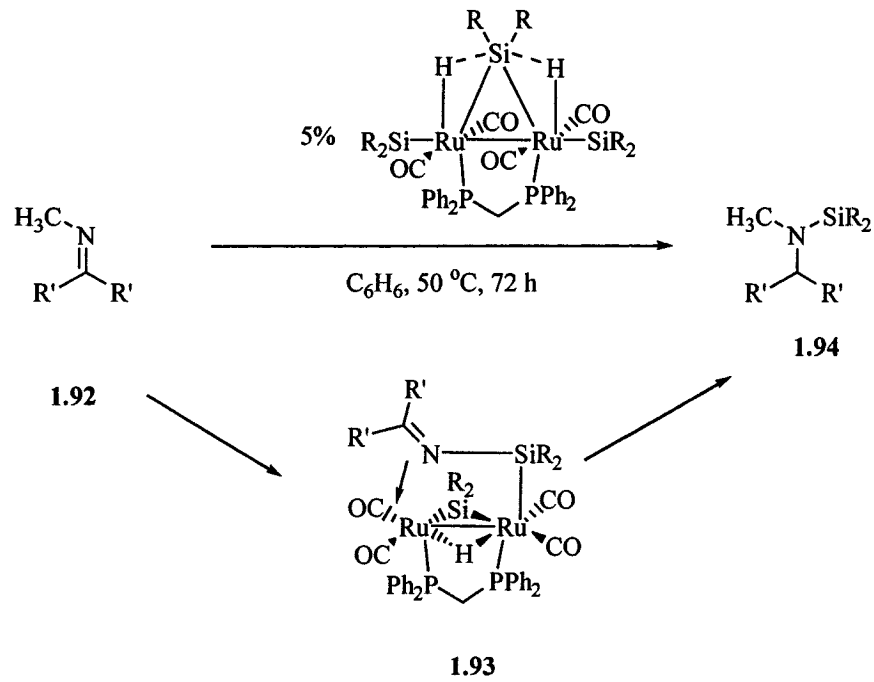
1.89 **1.90**

1.91

Scheme 1.44 Imine insertion into molybdenum-hydride bonds

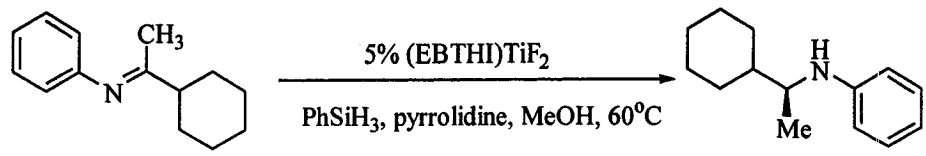
The catalytic hydrosilation of imines has also been postulated to proceed via imine insertion into metal-hydride bonds.[13,51,52] As with the transition metal catalyzed hydrogenation of imines, many examples of imine hydrosilation can be found in the literature.[13,32,52] Kira and co-workers have investigated the hydrosilation of imines using diruthenium complexes and characterized several intermediates (Scheme 1.45). Here, the nature of the intermediates suggest that

one metal center activates the Si-H bond for insertion, while the other occupies the lone pair of the imine prior to insertion into the metal-hydride bond.[51]



Scheme 1.45 Imine insertion for hydrosilation

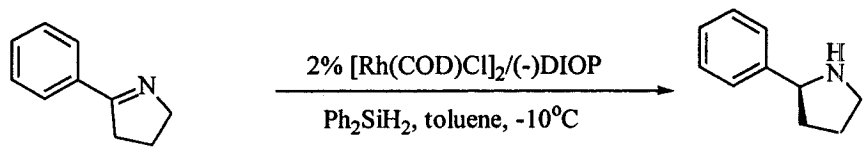
Several asymmetric versions of imine hydrogenations have also been developed.[13] It is interesting to note that many of the same catalytic systems used in asymmetric olefin hydrogenation and hydrosilation have also been used successfully for asymmetric imine hydrogenation and hydrosilation (Scheme 1.46 and 1.47).[32] Despite recent efforts, development of a general catalytic system for the asymmetric hydrosilation of imines remains a challenge, and continuing work towards this goal may bring further mechanistic insight.



99% ee

1.95 **1.96**

Scheme 1.46 Asymmetric hydrosilations of imines with early transition metal complexes



59% ee

1.97 **1.98**

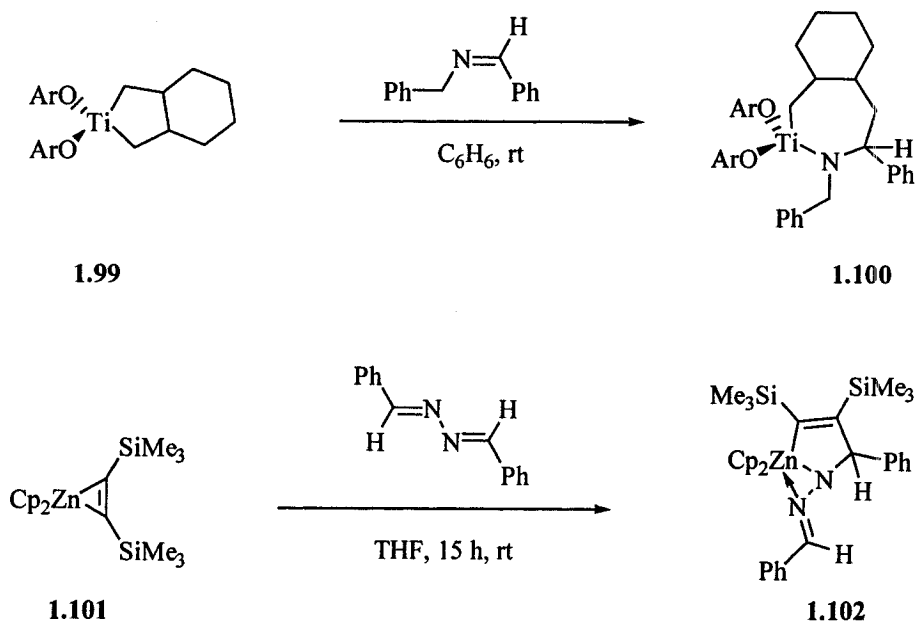
(-)DIOP=(*R*,*R*,)-(-)-P,P'-[2,2-dimethyl-1,3-dioxolane-4,5-diylbis(methylene)] bis(diphenylphosphane)

Scheme 1.47 Asymmetric hydrosilations of imines with late transition metal complexes

1.5.2 Imine Insertion into Early Tansition Metal-Carbon Bonds

While the insertion of olefins into metal-carbon bonds are well known, examples involving the analogous substrates containing carbon-nitrogen double bonds (*e.g.* imines) are rare. Only recently have a number of well defined examples appeared in the literature, and the majority of these are limited to the

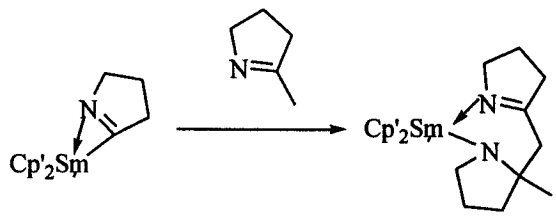
more electropositive early transition metals.[53,54] For example, a well defined 1,2 insertion of imines into titanium-carbon bonds has been observed by Rothwell and co-workers (**1.100**, Scheme 1.48). Here, the formation of a strong titanium-nitrogen bond serves as an excellent thermodynamic driving force for insertion. Similarly, Rosenthal and co-workers have also observed the insertion of an azine carbon-nitrogen double bond into zirconium-carbon bonds.[54]



Scheme 1.48 Imine insertion into early metal-carbon bonds

The samarium system developed by Marks and co-workers[47] proved capable of inserting imine not only into samarium-hydride bonds, but also samarium-carbon bonds (**1.103**). The insertion of imine leads to the formation of

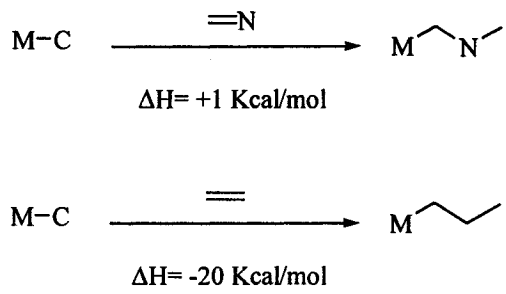
a robust chelate (**1.104**), with strong nitrogen-metal bonds that impedes further reaction (Scheme 1.49).



1.103 **1.104**

Scheme 1.49 Imine insertion into samarium metal-carbon bonds

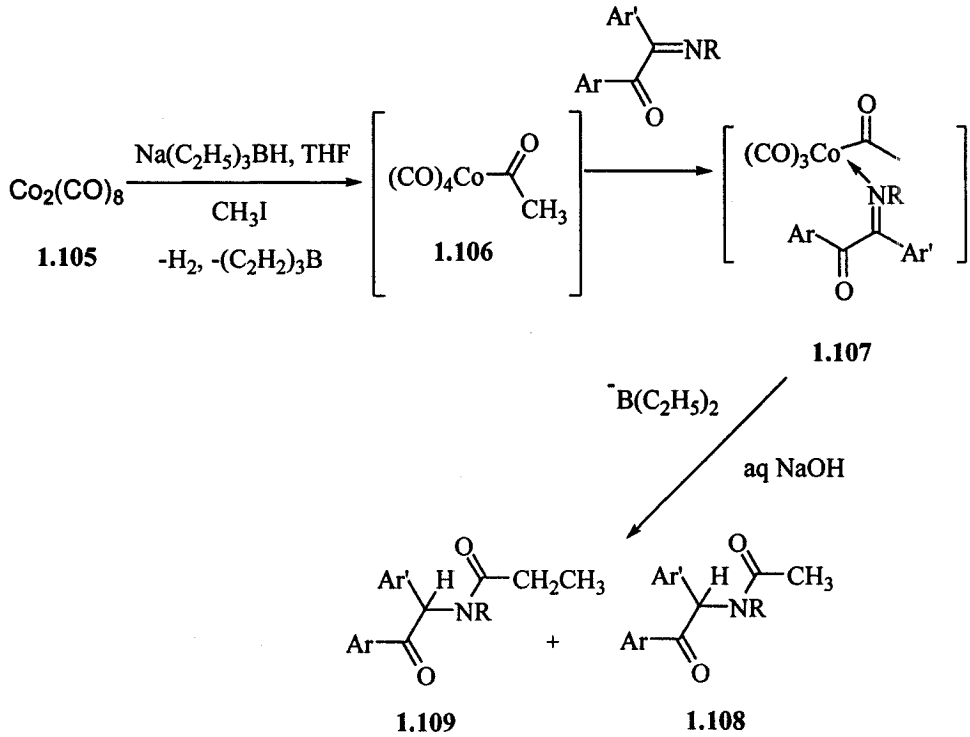
Unlike early transition metals, the ability of late transition metal catalysts to tolerate heteroatoms is well known. Nevertheless, examples of imine insertion into late transition metal-carbon bonds are rare.[56] When the enthalpy of imine insertion is compared to those observed for the much more common olefin insertion, a rationale for the lack of well defined examples of imine insertion into late transition metal-carbon bonds becomes more clear. Such a comparison using simple bond enthalpy calculations is summarized in Scheme 1.50. While olefin insertion is clearly exothermic (*ca.* –20 kcal/mol), imine insertion appears to be essentially thermoneutral (*ca.* +1 kcal/mol) when 72.8 and 147 kcal/mol are used as the average carbon-nitrogen single and double bond energies.[57] Thus, the driving force provided by the formation of the new C-N bond is not nearly as strong as the one associated with the C-C bond formed during olefin insertion. This lack of driving force may be the reason so few examples of imine insertion into late metal-carbon bonds exist.



Scheme 1.50 Estimated enthalpies of olefin vs. imine insertion into metal-carbon bonds

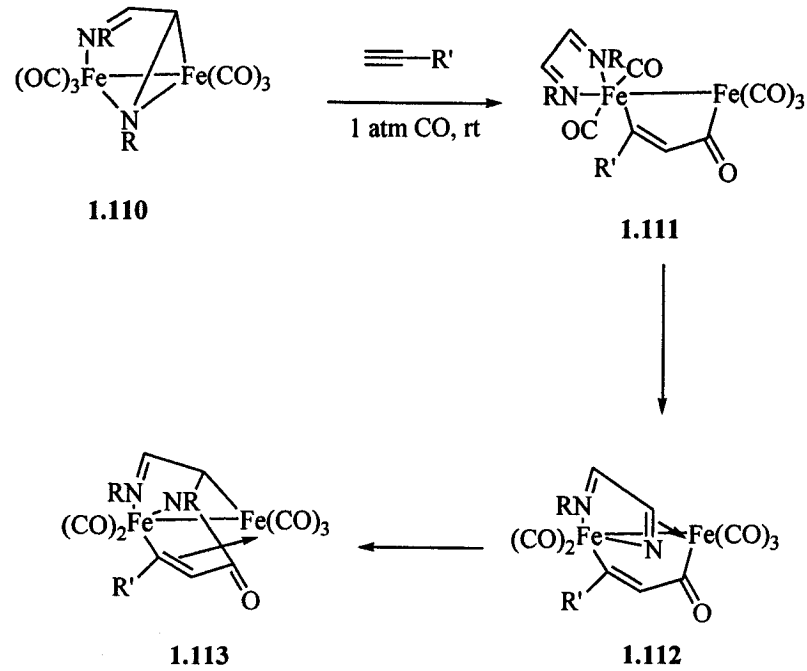
1.5.3 Literature Examples Consistent With Imine Insertion Using Late Transition Metals

Until recently, most reports suggesting imine insertion into a late metal-carbon bond contained little direct evidence supporting an imine insertion mechanism. For example, the hydro-acylation of imines by an *in situ* generated cobalt-acyl complex **(1.106)** can be considered to occur via imine insertion.[58] Though no direct evidence for a mechanistic pathway involving imine insertion is presented, it is possible that imine coordinates to the acyl-cobalt complex via CO displacement, followed by insertion, reductive cleavage, and hydrolysis to the amide (Scheme 1.51).



Scheme 1.51 Imine insertion into cobalt-acyl complexes

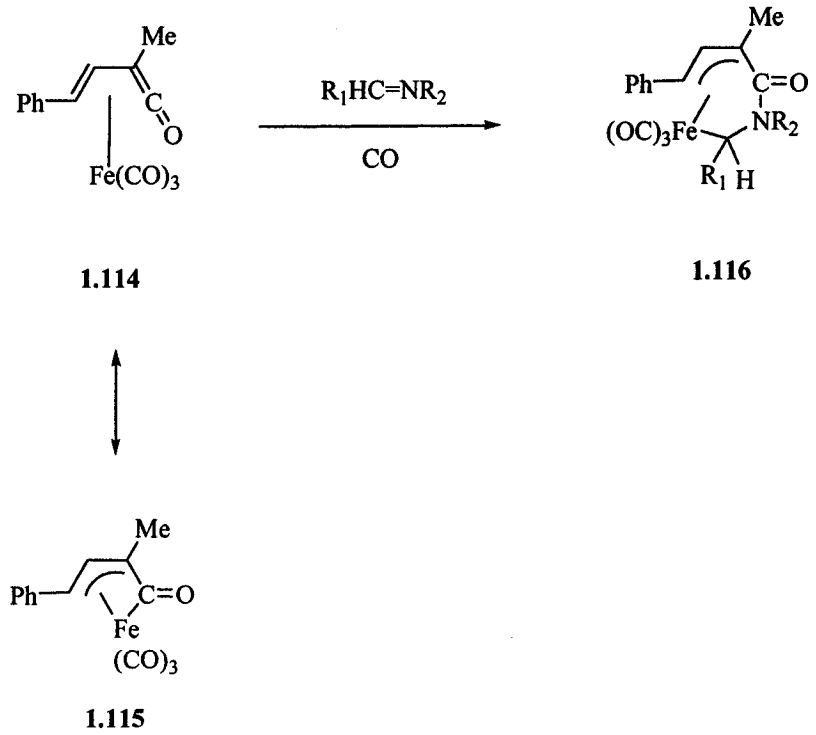
Also, the reaction of the iron complex $Fe_2(CO)_6$(R-DAB) [DAB = 1,4-diaza-1,3-butadiene; R = *i*-Pr, *c*-Hex] with methyl propionate is postulated to proceed via an imine insertion into an iron-acyl bond in the final step to yield the product **1.113** (Scheme 1.52).[59]



1.110 **1.111** **1.113** **1.112**

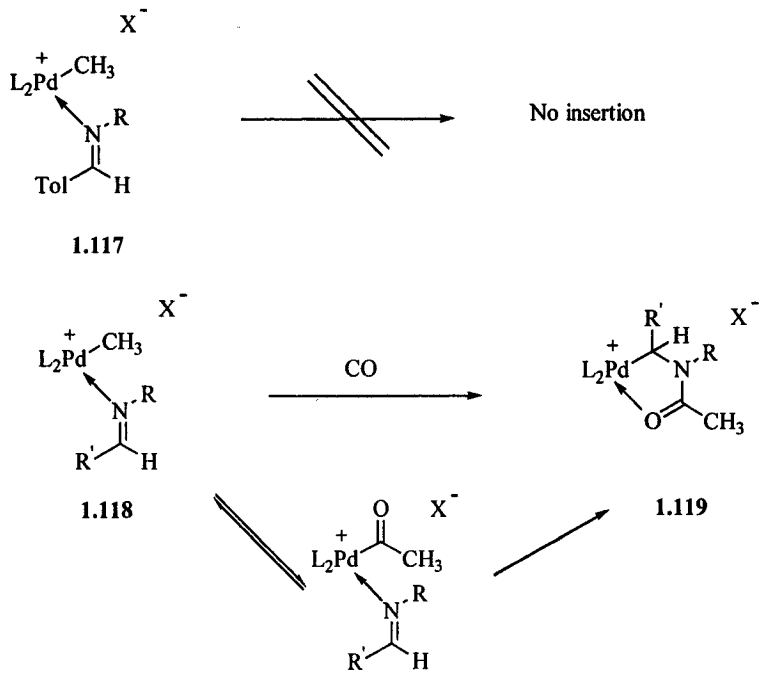
Scheme 1.52 Imine insertion into iron-acyl complexes

Hegedus *et al.*, have also suggested that the reaction of **1.114** with imine proceeds via a formal imine insertion into the metal-acyl bond of the η^3-allyl resonance form **1.115** (Scheme 1.53). Unfortunately, these highly electrophilic substrates may also react via nucleophilic attack by the imine nitrogen, and this has also been put forward as an alternative mechanism.[60]



Scheme 1.53 Imine insertion with iron-ketene complexes

Research done by our own group,[61] as well as Sen and co-workers,[62] described the first well defined examples of imine insertion into late transition metal-carbon bonds (Scheme 1.54). These systems utilized imine bound palladium-methyl complexes, which, in the presence of carbon monoxide, underwent sequential carbonylation followed by imine insertion.



L = bipy, dppe, bian, phen

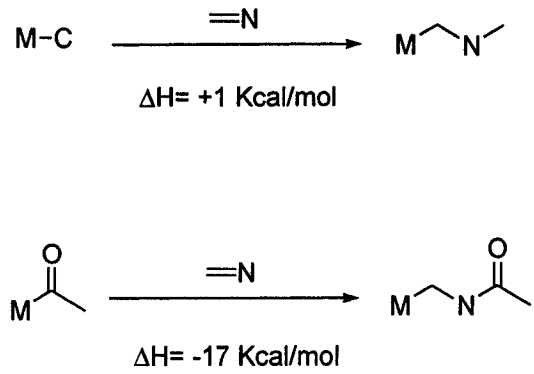
R = CH_3, $CH_2C_6H_5$, C_6H_5, C_6F_5, *p*-$CF_3C_6H_4$, *p*-$OCHC_6H_4$

R' = C_6H_5, C_6F_5, *p*-$CF_3C_6H_4$, *p*-$OCHC_6H_4$

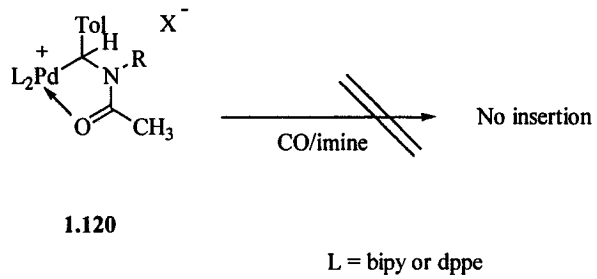
Scheme 1.54 Imine insertion into palladium-acyl complexes

Again, simple thermodynamic calculations provide some rationale for the increased insertion propensity displayed by imines in these systems (Scheme 1.55).[57] These calculations suggest that the strength of the resonance stabilized amide C-N bond generated by insertion into the metal-acyl ligand, can provide the required driving force for insertion. Indeed, the overall enthalpy of the imine insertion is close to that of olefin insertions. The formation of this amide bond is also likely responsible for the regioselectivity of insertion observed. The product **1.119**, (Scheme 1.54) immediately chelates to the metal center through the oxygen of the newly formed amide to generate a robust 5 membered metallacycle.

Chelation to the palladium center through the amide oxygen appears to be strong, and initial attempts to achieve subsequent insertion were unsuccessful (Scheme 1.56).[61,62]



Scheme 1.55 Enthalpies of imine insertion into M-carbon vs M-acyl bonds

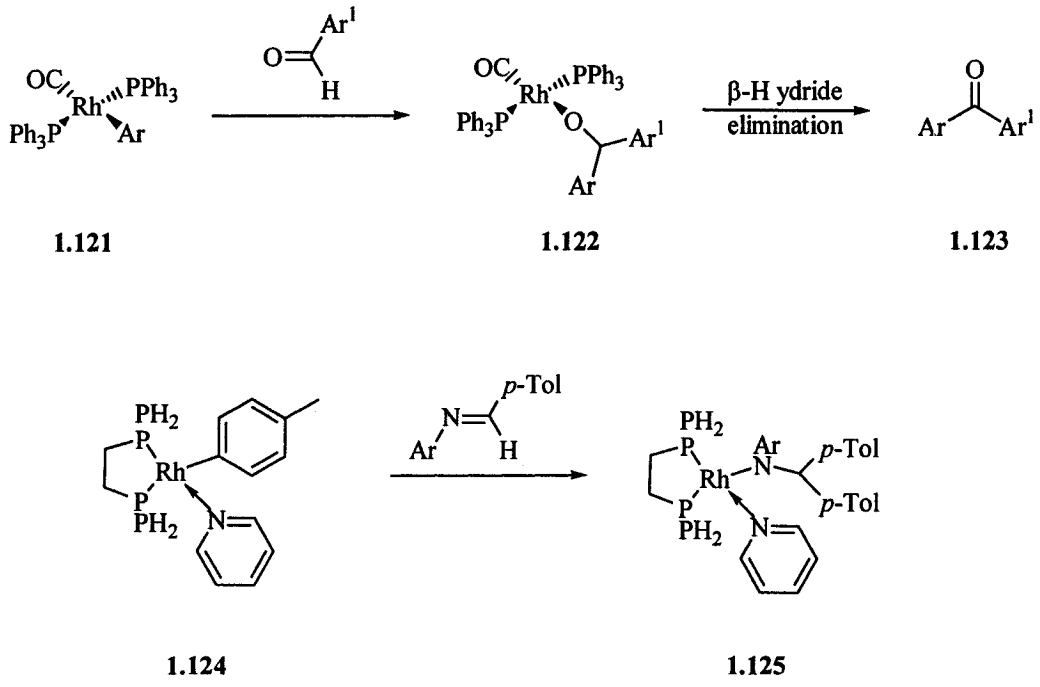


Scheme 1.56 Attempts at further CO/imine insertion

Density functional calculations carried out by Cavallo[64] provide further insite into the reaction mechanism. Using simplified imines and ligands, Cavallo found that imines display a significantly higher barrier to insertion into palladium-

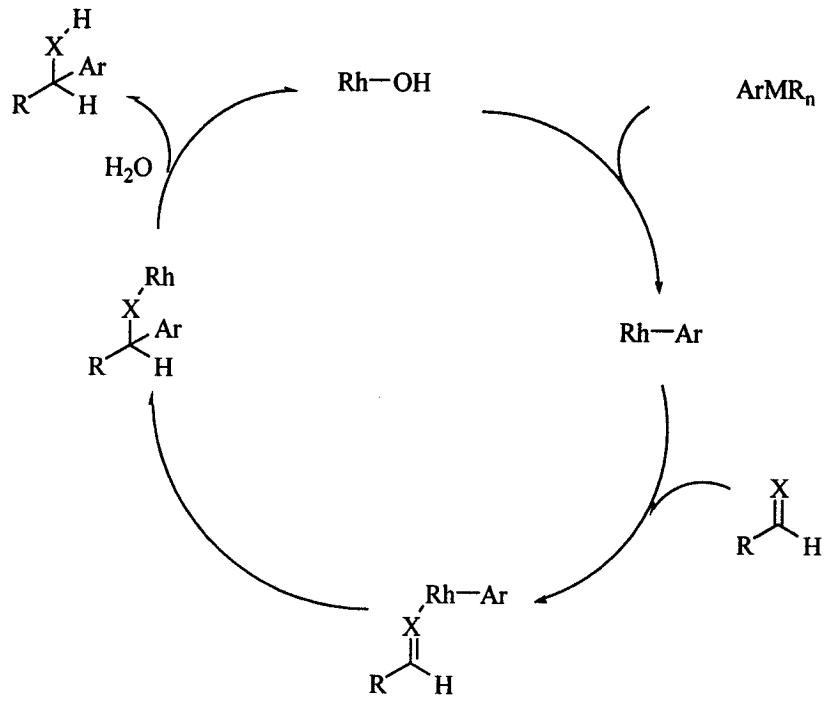
acyl bonds than those found for the analogous olefin insertion ($\Delta H^{\ddagger}$ = 22.2 Kcal mol^{-1} for H_2C=NH vs. $\Delta H^{\ddagger}$ = 16.6 Kcal mol^{-1} for CH_2=CH_2). Nevertheless, imine insertion is exothermic, with the driving force for the reaction appearing to be the formation of a very stable amide bond. These calculations also provide some mechanistic insight regarding the coordination mode of the imine during insertion. For example, attempts to optimize a geometry with a π-coordinated imine all converged to the σ-bond form observed experimentally. Only during the final stages of the path towards the transition state does the imine reorient itself into a π-coordinated geometry similar to those observed for ethane.[64] These calculations suggest a relatively concerted mechanism for imine insertion. Geometric analysis is consistent with an early transition state for insertion into the Pd-acyl bond, and the length of the Pd-C bond calculated in the transition state is stretched only 5% compared to the values obtained for the initial imine coordinated complex.

More recently, Hartwig reported the direct insertion of aldehydes and imines into rhodium-aryl bonds.[65,66] These examples differ from those observed previously in palladium-based systems in that imine insertion occurs without the initial insertion of CO. In addition, the regiochemistry of imine insertion is reversed, such that a new carbon-carbon bond is formed along with a formal rhodium-nitrogen or oxygen bond.



Scheme 1.57 Examples of imine and aldehyde insertion into Rh-C bonds

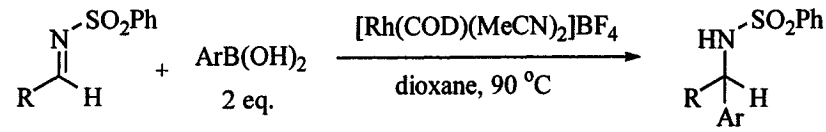
This rhodium-based insertion chemistry is directly related to the recently developed rhodium catalyzed coupling reactions of $R^1R^2C=X$ (X = O, NR) with organoboranes, organotins, and organosilanes (Scheme 1.58).[67] While the majority of these catalytic reactions involve aldehydes, more recently imines have been shown to be viable coupling partners, particularly N-sulfonyl aldimines.[68] These reactions proceed in excellent yield to give arylated products, such as those shown in the representative examples below (Scheme 1.59).[67]



M = $B(OR)_2$, SnR_3, SiR_3

X = O, NAr'

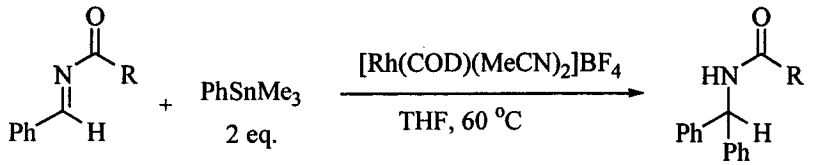
Scheme 1.58 General catalytic route for Rh catalyzed couplings



70-99%

1.126 **1.127**

R = Aryl,CH_2=CHPh, cyclohexyl



50-98%

1.128 **1.129**

R = Ph,$CO_2{}^tBu$, $SO_2C_6H_4CH_3$, $PO(OEt)_2$

Scheme 1.59 Examples of Rh catalyzed imine couplings

1.6 Overview of Thesis

The use of migratory insertion reactions as a method to form new carbon-carbon and/or carbon-heteroatom bonds continues to be an important area of investigation. While these transformations have been exploited extensively with alkenes and alkynes as detailed above,[26,27,34] the extrapolation of this chemistry to heteroatom-containing substrates such as imines remains a challenge. The study of late transition metal complexes capable of using imines as migratory insertion substrates could lead to solutions to these issues. Moreover, the development of new catalysts capable of using imines and alkenes as interchangeable insertion

substrates would represent a useful advance in this field of study. The previous investigations of palladium complexes has provided an excellent precedent for the insertion of imines into late transition metal-carbon bonds. Despite their lack of further reactivity, these examples confirm the viability of imines as insertion monomers. Further investigation of more reactive complexes may lead to the development of systems capable of performing useful transformations via imine migratory insertion.

Previous work has shown that nickel complexes are significantly more reactive towards the migratory insertion of alkenes than their palladium counterparts.[69,70] This higher intrinsic reactivity towards migratory insertion suggests nickel complexes would make excellent imine insertion candidates as well. The initial research described in this thesis (chapter 2) involves the development of a series of nickel complexes capable of mediating the sequential migratory insertion of CO and imines. Subsequent investigations will focus on the potential of these nickel-based CO/imine insertion products to undergo further reactions (chapter 3). Studies involving the use of imines and alkenes as interchangeable insertion substrates allows for the development of multi-component insertion cascades for the synthesis of lactams (chapter 4).

Finally, this thesis will describe our development of a novel method to use double-bonded electrophiles such as imines in Stille-type cross-coupling reactions, providing a multi-component route to prepare α-substituted amides from imines, acid chlorides and alkyl-tin reagents (chapter 5).

1.7 References

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CHAPTER TWO

Sequential Insertion of Carbon Monoxide and Imines into Nickel-Methyl Bonds: A New Route to Imine Hydroacylation

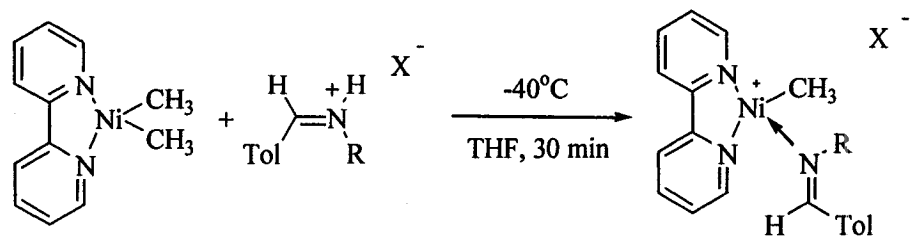
2.0 Introduction

The migratory insertion of imines into metal-acyl bonds provides a potential method to generate amides from simple and readily available R'(H)C=NR building blocks. However, while the insertion of carbon-containing unsaturated molecules (e. g., olefins or alkynes) has been explored extensively,[1-3] reports of heteroatom containing substrates (e.g., C=X; X = O, NR) undergoing analogous reactions are much less common.[4-7] Examples of the latter typically involve electropositive metal centers, which undergo insertion with a regio-chemistry to generate a robust M-X bond rather than a new nitrogen-carbon bond.[4,5] The development of late transition metal complexes that can tolerate functionality during insertion reactions suggests they might be prime candidates for insertion of substrates such as imines.[8-11] Recently, both we[12] and others[13] have demonstrated that palladium complexes of the form $L_2Pd(CH_3)(RN{=}C(H)R')^+X^-$ (L_2 = bidentate neutral ligand; R = alkyl, aryl; R' = aryl) can mediate the sequential insertion of carbon monoxide and imines to generate palladium-bound amides. These provide the first well-defined examples of imine insertion into a late metal-carbon bond.[6] In an

attempt to explore the scope of this reaction, as well as develop a metal complex capable of mediating imine insertion under more mild conditions, the synthesis and reactivity of the nickel complexes (bipy)Ni-$(CH_3)(RN{=}C(H)Tol)^+X^-$ (bipy = 2,2'-bipyridyl, Tol = *p*-$C_6H_4CH_3$) has been investigated. We report herein the first example of the sequential insertion of CO and imines into nickel-methyl bonds, which ultimately leads to a controlled, metal-mediated route to synthesize amides from imines.[14] Methods for the generation, characterization, and cleavage of the amide fragments from the nickel center, as well as a comparison of the relative rates of insertion to the analogous palladium complexes, are described in this chapter.

2.1 Results and Discussion

The reaction of $[R(H)N{=}CH(Tol)]^+X^-$ (**2.2a-h**) with (bipy)Ni$(CH_3)_2$ in THF at –40 °C results in the immediate liberation of methane and formation of the cationic nickel-imine complexes **2.3a-h** (Eq. 2.1).[15] Complexes **2.3a-h** can be isolated by precipitation with pentane, affording solids which are stable at room temperature under nitrogen. The ^1H and ^{13}C NMR for **2.3a-h** displays a downfield shift in the imine resonances upon coordination,[16] consistent with η^1-binding of the imine through the nitrogen.[12]



2.1 **2.2a-h** **2.3a-h**

Equation 2.1: Synthesis of cationic nickel-imine complexes

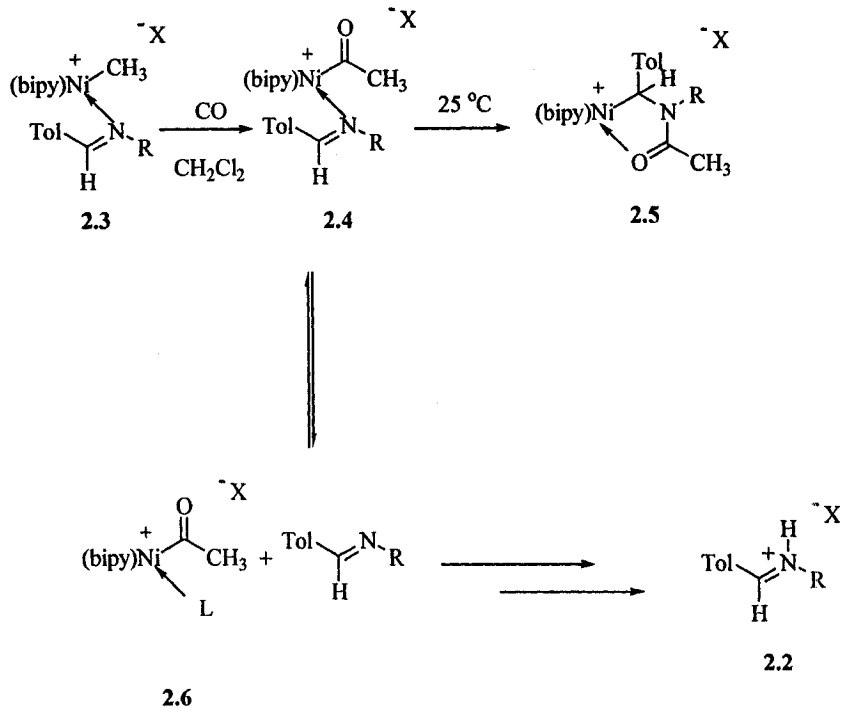
No evidence for imine insertion into the Ni-CH_3 bond of complexes **2.3a-h** was observed at ambient temperature, and heating to 70 °C resulted only in the decomposition of the complex to liberate free imine. Thus, similar to the analogous palladium complexes,[12] **2.3a-h** have a significant kinetic barrier to imine insertion into the nickel-alkyl bond. However, the exposure of complexes **2.3a-h** to 1 atm of carbon monoxide results in the rapid insertion of CO to form the nickel-acyl complexes **2.4a-h**. Unlike **2.3a-h**, nickel-acyl complexes react upon standing for several hours in CD_2Cl_2 solution, resulting in the formation of the product of imine insertion into the nickel-acyl bond (**2.5a-g**) (Scheme 2.1). The same reaction at 70 °C results in complete conversion to **2.5a-g** in under 30 min.

Table 2.1: Synthesis of Complexes **2.3a-h** and **2.5a-g**

entry	Imine	R	X	**2.3**[a]	**2.5**[b]
1	**2.2a**	Ph	PF_6	64%	90%
2	**2.2b**	CH_2Ph	PF_6	84%	95%
3	**2.2c**	Me	PF_6	92%	98%
4	**2.2d**	Me	SbF_6	86%	88%
5	**2.2e**	Me	BArf[c]	85%	91%
6	**2.2f**	Me	OTf	89%	36%
7	**2.2g**	^{i}Pr	PF_6	68%	25%
8	**2.2h**	^{t}Bu	PF_6	78%	--
9	**2.2i**	Me	Cl	82%[e]	--

[a] Isolated yields. [b] NMR yields. [c] BArf = $B(3,5\text{-}C_6H_3(CF_3)_2)_4$. [d] OTf = OSO_2CF_3. [e] Yield of $(bipy)Ni(CH_3)Cl$

Complexes **2.5a-g** have been characterized by ^{1}H and ^{13}C NMR, IR, and in the case of **2.4b**, X-ray structural analysis. In all cases, only one regioisomer of complexes **2.5a-g** is obtained, in which imine insertion has occurred to form an amide bond and a new nickel-carbon bond. The formation of a robust amide bond likely provides the driving force for imine insertion into the nickel-acyl bond, which does not exist in nickel-methyl complexes **2.3a-h**.

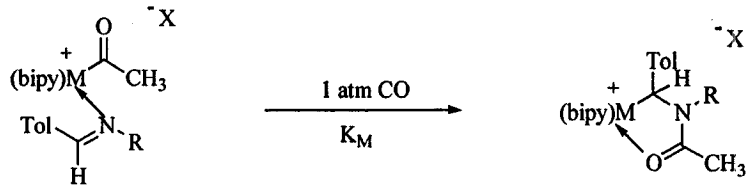


Scheme 2.1: Imine insertion into Nickel-acyl bonds

The yield of the imine insertion products is sensitive to the imine and couterion employed. Use of more strongly coordinating counteranions dramatically reduces the yield of **2.5** (Table 1, entries 6 and 9). In the case of the **2.3i**, the chloride counterion is found to coordinate preferentially over imine in both the nickel-methyl and nickel-acyl complexes, and no evidence for imine insertion is observed. Replacing the primary alkyl substituent on the imine nitrogen with a secondary *i*Pr substituent greatly reduces both the rate of insertion and the yield, while the N(*t*Bu)-substituted imine **2.1h** does not undergo insertion at all. Monitoring the reaction of **2.4g** by ^{1}H NMR (CD_2Cl_2) reveals the competitive formation of the protonated iminium salt **2.2g** in 21% yield in the product mixture and similar results were observed

with complex **2.4h** (40% iminium salt formation). Similarly, the use of a less basic *N*-phenyl-substituted imine in **2.3a** also leads to the low-yield formation of **2.2a** (6% yield) in addition to **2.5a**, as does the coordinating OTf$^-$ counterion in **2.4f** (**2.2f**: 42% yield). The generation of protonated iminium salts with less basic or more slowly inserting imines, or more strongly coordinating anions, implies that de-coordination of the imine to form (bipy)Ni(COCH$_3$)L$^+$ (L = CO, X) may lead to decomposition. Consistent with this observation, the addition of excess PhN=C(H)Tol to the reaction of **2.3a** with CO completely suppresses the formation of the protonated imine products and generates complex **2.5a** in quantitative yield.[17]

The insertion of imines into the nickel-acyl bond of **2.4a-g** occurs with a lower barrier than that of the analogous palladium complexes, which require prolonged heating at 70 °C. To quantify the influence of the metal center on insertion rates, the first-order rate constants for the insertion of imines with a number of isoelectronic nickel- and palladium-acyl complexes have been determined. As shown in Table **2.2**, the nickel complexes all display a ca. 4.3-5.5 kcal/mol lower barrier for imine insertion than the analogous palladium complexes.



2.4a-c (M = Ni); **2.7a-c** (M = Pd)

Table 2.2: Rates of Imine Insertion with **2.4a-c** and **2.6a-c**.

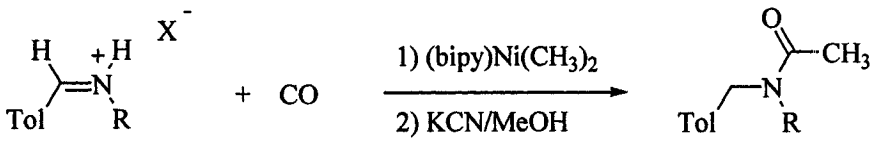
	R	k_{Ni}[a] ($10^{-3}s^{-1}$)	$\Delta G^{\ddagger}$ (40 °C) (kcal/mol)	K_{Pd}[b] ($10^{-4}s^{-1}$)	$\Delta G^{\ddagger}$ (90 °C) (kcal/mol)	$\Delta\Delta G^{\ddagger}$
a	Ph	1.5	22.7	0.84	28.2	5.5
b	$PhCH_2$	0.27	23.8	0.93	28.1	4.3
c	CH_3	0.89	23.1	2.3	27.4	4.3

[a] Rate of disappearance of **2.4a-c** at 40 °C in CD_2Cl_2. [b] Rate of disappearance of **2.7a-c** (X = BArf) at 90 °C in CD_2Cl_2.

The lower barrier to imine insertion with nickel complexes is not surprising and is similar to that observed in ethylene insertion into isolelectronic cationic nickel and palladium complexes.[19,20] It has been suggested that the more rapid insertion of olefins with first row transition metals may arise from either a weakened metal-olefin bond or perhaps a weaker metal-alkyl bond.[21] While we do not have sufficient evidence to distinguish between these possibilities for imine insertion, our data are consistent with a more labile imine σ-coordination in the nickel complexes. This is shown qualitatively by the rapid equilibrium coordination of imine in **2.3a-c** in acetonitrile solvent. In contrast to the behavior of palladium complexes **2.7a-c** in CD_3CN, where $(bipy)Pd(CH_3)(RN{=}C(H)Tol)^+X^-$ can be

clearly distinguished at ambient temperature by ^{1}H NMR,[12] the analogous equilibrium with nickel complexes **2.4a-c** and the solvated complex is much more rapid, resulting in broadened ^{1}H NMR resonances at temperatures down to –40 °C.

The sequential insertion of carbon monoxide and imine into the nickel-methyl bond of **2.3** allows the formation of nickel-bound amides under very mild conditions (i.e., ambient temperatures and 1 atm of CO). In addition, the amide ligand in **2.5a-c** can be readily cleaved from the nickel center, providing a metal mediated route to generate amides from imines and CO. Addition of KCN to a solution of **2.5a** in methanol results in the immediate generation of a colorless solution and cleavage of the organic fragment, possibly via a σ-bond metathesis mechanism with HCN. Removal of the solvent, followed by an ether extraction and acid wash with 10% HCl, provides amide **2.8a** in >95% yield (Eq. 2.2). A similar process can be performed with complexes **2.5b** and **2.5c**, in all cases leading to the production of amides in near-quantitative yields. Overall, this reaction represents a relatively straightforward two-step method to hydroacylate imines via the sequential insertion of carbon monoxide and imine into a nickel-methyl bond. (Eq. **2.2**). To our knowledge, the only other report of imine hydroacylation with carbon monoxide is that by Alper and co-workers,[14a-d] which utilizes cobalt carbonyl catalysts at elevated temperatures.



2.2a-c **2.8a-c**

Equation 2.2: Hydroacylation of Imines

2.2 Conclusions

In conclusion, we have presented the first example of imine insertion into a nickel-acyl bond to form the five-membered metallacycles **2.5a-g**. This sequential insertion of carbon monoxide and imine occurs with a significantly lower barrier with nickel-complexes **2.3a-g** than the isoelectronic palladium complexes and provides a new and controlled route to generate both nickel-bound and free amides. Considering that these amides are formed via the well defined insertion of imines into a Ni-C bond, the induction of asymmetry into this process, and the incorporation of other insertion monomers into the amide products, should prove to be viable extensions of this work. Studies directed towards the latter will be discussed in subsequent chapters.

2.3 Experimental Section

General

Unless otherwise noted, all manipulations were carried out under an inert atmosphere in a Vacuum Atmosphere 553-2 drybox or using standard Schlenk or vacuum line techniques. NMR spectra were obtained on 300MHz and 400MHz Varian machine. IR spectra were obtained on a Bruker IFS-48 spectrometer.

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Liquids were freeze-pump-thawed three times to de-gas before use. Diethyl ether was distilled from sodium benzophenone. Pentane, methylene chloride, and chlorobenzene were distilled from CaH_2. Deuterated solvents were dried as their protonated analogues, but were vacuum transferred from the drying agent. UHP grade carbon monoxide was obtained from Matheson. Imines were prepared by reaction of *p*-tolualdehyde and amine in diethyl ether at room temperature over $4A^{o}$ molecular sieves. (bipy)$NiMe_2$ was prepared via literature procedure.[22] Iminium salts were prepared via addition of 1.1 equiv. of anhydrous HCl in diethyl ether to the appropriate imine and pumped to dryness. 1 equiv. of the desired counterion salt (i.e. $AgPF_6$, NaBArf[23]) was added in CH_2Cl_2 and stirred for 4hrs. The precipitate was filtered off and the filtrate pumped to dryness and used without further purification.

[(bipy)Ni(CH_3)(PhN=C(H)Tol)]$^{+}PF_6^{-}$ (2.3a)

A typical procedure for the synthesis of complexes **2.3a-h** is as follows. (bipy)Ni(CH_3)$_2$ (75 mg, 0.307 mmol) was suspended in THF (10 mL) and cooled to -40 °C to give an intense dark green solution. In a separate vessel [Ph(H)N=C(H)Tol)]$^+PF_6^-$ (104 mg, 0.307 mmol) was dissolved in THF (10 mL) and cooled to –40 °C. The iminium salt was then added to the rapidly stirring solution of (bipy)Ni(CH_3)$_2$ over 3 minutes via pipette. Near the end of the addition the dark green solution changes to a deep red color. The solution is cooled to –40°C for 30 minutes and filtered through celite, and recrystallized from diethyl ether (50 mL) at –40 °C. After twelve hours the clear solvent mixture was decanted, the solid residue washed with pentane (3 x 5 mL), and then dried under vacuum to produce an orange powder (112 mg, 64% yield)

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 9.81 (d, 2H), 8.59 (s, 1H), 8.39 (d, 1H), 8.24-7.89 (m, 8H), 7.81 (m, 6H), 2.43 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 169.1, 157.2, 156.4, 153.1, 149.8, 147.1, 146.1, 140.6, 140.4, 132.1, 130.4, 130.0, 129.8, 129.3, 127.7, 127.2, 123.4, 122.5, 122.3, 21.8, -1.50.

IR (KBr): ν_{CN} = 1606 cm^{-1}

[(bipy)Ni(CH_3)($PhCH_2N$=C(H)Tol)]$^+PF_6^-$ (2.3b)

Yield : 84%

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 9.43 (d, 2H), 8.25 (s, 1H), 8.15 (d, 1H), 8.04-7.90 (m, 4H), 7.17 (m, 10H), 5.10 (m, 2H) 2.19 (s, 3H), 0.03 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 169.1, 157.2, 152.9, 149.2, 148.1, 145.1, 140.6, 140.4, 139.8, 135.6, 132.1 130.8, 130.3, 128.9, 128.3, 126.9, 122.9, 120.8, 68.2, 21.4, -2.00.

IR (KBr): ν_{CN} = 1608 cm^{-1}

Analysis. Calculated for $C_{26}H_{26}F_6N_3NiP$ (C 53.46%, H 4.49%, N 7.19%) Found (C 53.07%, H 4.52%, N 7.06%).

[(bipy)Ni(CH_3)(CH_3N=C(H)Tol)]$^+PF_6^-$ (2.3c)

Yield : 92%

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 9.39 (d, 2H), 8.41 (d, 1H), 8.39 (s, 1H), 8.15-8.10 (m, 5H), 7.67 (d, 1H), 7.59 (t, 1H) 7.49 (t, 1H), 7.39 (d, 1H), 3.9(s, 3H), 2.39 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 171.1, 156.2, 152.9, 149.2, 147.1, 144.1, 140.6, 139.8, 131.6, 130.1, 129.3, 127.9, 126.9, 122.9, 122.1, 50.2, 21.4, -2.00.

IR (KBr): ν_{CN} = 1608 cm^{-1}

[(bipy)Ni(CH_3)(CH_3N=C(H)Tol)]$^+SbF_6^-$ (2.3d)

Yield : 86%

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 9.39 (d, 2H), 8.41 (d, 1H), 8.39 (s, 1H), 8.15-8.04 (m, 4H), 7.67 (d, 1H), 7.59 (t, 1H) 7.49 (t, 1H), 7.39 (d, 1H), 3.9 (s, 3H), 2.39 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 171.1, 156.2, 152.9, 149.2, 147.1, 144.1, 140.6, 139.8, 131.6, 130.1, 129.3, 127.9, 126.9, 122.9, 122.1, 50.2, 21.4, -2.00.

IR (KBr): ν_{CN} = 1608 cm^{-1}

[(bipy)Ni(CH_3)(CH_3N=C(H)Tol)]$^+$BArf$^-$ (2.3e)

Yield : 85%

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 9.39 (d, 1H), 8.41 (d, 2H), 8.39 (s, 1H), 8.15-8.04 (m, 4H), 7.99-7.91 (m, 3H) 7.71-7.37 (m, 12H), 7.34 (d, 2H), 3.90 (s, 3H), 2.39 (s, 3H), 0.98 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 171.1, 162.9, 162.2, 161.4, 160.7, 156.7, 153.6, 149.4, 148.0, 144.9, 140.7, 140.4, 134.7, 130.6, 129.9, 129.3, 128.7, 127.7, 127.1, 124.1, 123.4, 122.1, 118.6, 117.5, 50.7, 21.3, -1.93.

IR (KBr): ν_{CN} = 1606 cm^{-1}

[(bipy)Ni(CH_3)(CH_3N=C(H)Tol)]$^+$OTf$^-$ (2.3f)

Yield : 89%

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 9.37 (d, 2H), 8.37 (d, 1H), 8.34 (s, 1H), 8.26 (t, 2H), 8.14 (t, 2H), 7.68 (d, 1H) 7.55 (t, 1H), 7.45 (t, 1H), 7.35 (d, 2H), 3.9.4 (s, 3H), 2.38 (s, 3H), 0.04 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 171.1, 156.6, 153.6, 149.2, 148.1, 144.9, 140.6, 140.4, 131.6, 130.6, 129.9, 127.9, 127.1, 124.1, 123.4, 52.9, 21.4, 1.16.

IR (KBr): $\nu_{CN} = 1606\ cm^{-1}$

[(bipy)Ni(CH_3)(iPrN=C(H)Tol)]$^+PF_6^-$ (2.3g)

Yield : 68%

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 9.50 (d, 2H), 8.41 (s, 1H), 8.36 (d, 1H), 8.15-8.02 (m, 4H), 7.68-7.49 (m, 2H) 7.38-7.25 (m, 3H), 4.38 (m, 1H), 2.39 (s, 3H), 1.84 (d, 3H), 1.65 (d, 3H), 0.04 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 168.1, 156.6, 153.6, 149.2, 147.2, 145.1, 140.6, 139.8, 131.6, 130.3, 129.9, 127.9, 127.3, 122.3, 122.1, 63.2, 24.9, 24.0, 21.6, -3.50.

IR (KBr): $\nu_{CN} = 1605\ cm^{-1}$

[(bipy)Ni(CH_3)(tBuN=C(H)Tol)]$^+$ PF_6^- (2.3h)

Yield : 78%

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 9.69 (d, 2H), 8.21 (s, 1H), 8.19 (d, 1H), 8.10-8.00 (m, 5H), 7.84-7.75 (m, 2H), 7.41-7.35 (m, 2H), 2.39 (s, 3H), 1.90 (s, 9H), 0.18 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 168.1, 149.2, 147.9, 148.1, 144.2, 140.8, 140.2, 131.8, 131.6, 131.0, 130.3, 130.0, 127.4, 127.2, 122.4, 122.3 65.4, 31.9, 21.4, -4.87.

IR (KBr): $\nu_{CN} = 1604\ cm^{-1}$

[(bipy)Ni[η^2-C(Tol)HN(Ph)COCH$_3$]]$^+$ PF$_6^-$ (2.5a)

A typical procedure for the synthesis of complexes **2.5a-g** is as follows. Complex **2.3a** (67.2 mg, 0.118 mmol) was dissolved in CH_2Cl_2 (15 mL) in a 100 mL reaction bomb. The solution was placed under 1 atm of CO and stirred for 5 minutes. Upon stirring, the solution changes from orange to deep red, and the bomb was then heated to 70 °C for 20 minutes. The solution was filtered through celite, added to 10 mL of pentane and cooled to – 40 °C overnight. The clear solvent mixture was decanted and the solid residue washed with pentane (3 x 5 mL) and then dried under vacuum to yield an orange powder (68.4 mg, 97% yield).

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 8.59 (d, 1H), 8.12 (t, 2H), 7.99-7.91 (m, 4H), 7.67 (t, 2H), 7.51 (d, 2H), 7.36-7.30 (m, 2H), 7.07 (d, 2H), 6.95 (d, 2H), 4.62 (s, 1H), 2.22 (s, 3H), 1.98 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 179.9, 157.2, 152.9, 150.1, 148.1, 140.1, 139.8, 138.6, 136.6, 129.8, 129.3, 128.9, 128.1, 126.9, 126.6, 126.1, 121.9, 121.2, 65.2, 21.4, 18.0.

IR (KBr): $\nu_{CO} = 1611\ cm^{-1}$

[(bipy)Ni[η^2-C(Tol)HN(CH_2Ph)$COCH_3$]]$^+$ PF_6^- (2.5b)

Yield: 95%

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 8.58 (d, 1H), 8.15 (t, 1H), 7.99-7.91 (m, 4H), 7.67-7.61 (m, 2H), 7.51-7.42 (m, 2H), 7.36-7.30 (m, 2H), 7.28-7.22 (m, 5H), 4.40 (d, 1H), 4.401 (d, 1H), 4.31 (s, 1H), 2.23 (s, 3H), 2.21 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 180.1, 155.1, 152.2, 150.9, 148.2, 140.8, 140.1, 138.6, 137.8, 134.6, 130.8, 129.3, 128.9, 128.3, 127.9, 127.1, 122.0, 121.4, 59.2, 51.1, 21.4, 19.0.

IR (KBr): ν_{CO} = 1605 cm^{-1}

Analysis. Calculated for $C_{27}H_{26}F_6N_3NiOP$ (C 52.97%, H 4.28%, N 6.86%) Found (C 52.65%, H 4.28%, N 7.16%).

[(bipy)Ni[η^2-C(Tol)HN(CH_3)$COCH_3$]]$^+$ PF_6^- (2.5c)

Yield: 98%

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 8.49 (d, 1H), 8.10-7.89 (m, 5H), 7.61-7.55 (m, 3H), 7.39 (t, 1H), 7.17 (d, 2H), 4.27 (s, 1H), 2.78 (s, 3H), 2.19 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 179.7, 155.7, 152.9, 150.2, 148.1, 140.5, 139.6, 138.6, 137.1, 130.1, 127.7, 127.0, 126.9, 121.9, 121.1, 62.4, 34.8, 21.4, 18.1.

IR (KBr): ν_{CO} = 1610 cm^{-1}

[(bipy)Ni[η^2-C(Tol)HN(CH_3)$COCH_3$]]$^+$ SbF_6^- (2.5d)

Yield: 88%

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 8.49 (d, 1H), 8.10-7.89 (m, 5H), 7.61-7.55 (m, 3H), 7.39 (t, 1H), 7.17 (d, 2H), 4.27 (s, 1H), 2.78 (s, 3H), 2.19 (s, 3H), 2.14 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 179.7, 155.7, 152.9, 150.2, 148.1, 140.5, 139.6, 138.6, 137.1, 130.1, 127.7, 127.0, 126.9, 121.9, 121.1, 62.4, 34.8, 21.4, 18.1.

IR (KBr): ν_{CO} = 1610 cm^{-1}

[(bipy)Ni[η^2-C(Tol)HN(CH_3)$COCH_3$]]$^+$ BArf$^-$ (2.5e)

Yield: 91%

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 8.49 (d, 1H), 8.10-7.55 (m, 13H), 7.53-7.39 (m, 7H), 7.27 (t, 1H), 7.17 (d, 2H), 4.21 (s, 1H), 2.75 (s, 3H), 2.18 (s, 3H), 2.11 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 179.6, 163.8, 162.2, 161.2, 160.5, 151.2, 148.2, 140.6, 139.8.1, 138.6, 136.4, 134.3, 129.4, 129.1, 128.9(q), 127.7, 127.1, 126.7, 122.5, 121.2,117.7, 63.2, 35.4, 21.4, 18.3.

IR (KBr): ν_{CO} = 1611 cm^{-1}

[(bipy)Ni[η^2-C(Tol)HN(CH_3)$COCH_3$]]$^+$ OTf$^-$ (2.5f)

Yield: 36%

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 8.49 (d, 1H), 8.19-7.89 (m, 5H), 7.61-7.55 (m, 3H), 7.39 (t, 1H), 7.17 (d, 2H), 4.32 (s, 1H), 2.81 (s, 3H), 2.21 (s, 3H), 2.17 (s, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 179.7, 155.7, 152.9, 151.2, 148.1, 140.5, 139.6, 138.6, 137.1, 130.1, 127.7, 127.0, 126.9, 121.9, 121.1, 62.4, 34.8, 21.4, 18.1.

IR (KBr): $\nu_{CO} = 1609\ cm^{-1}$

[(bipy)Ni[η^2-C(Tol)HN(^{i}Pr)COCH$_3$]]$^+$ PF$_6^-$ (2.5g)

Yield: 25%

^{1}H-NMR (270 MHz, CD_2Cl_2): δ 8.55 (d, 1H), 8.25 (d, 1H), 8.10-7.89 (m, 4H), 7.64-7.51 (m, 4H), 7.13-7.08 (m, 2H), 4.57 (s, 1H), 2.26 (s, 3H), 2.19 (s, 3H), 1.38 (d, 3H), 0.84 (d, 3H).

^{13}C NMR (75 MHz, CD_2Cl_2): δ 179.7, 155.8, 153.1 151.4, 148.7, 140.9, 140.6, 140.1, 136.1, 130.1, 127.8, 127.1, 126.0, 121.8, 121.3, 57.7, 21.6, 21.2, 20.6, 19.1.

IR (KBr): $\nu_{CO} = 1607\ cm^{-1}$

Cleavage of the Amide from 2.5

A typical procedure for the cleavage of the amide ligand from **2.5c** is as follows. Complex **2.5c** (16 mg, 0.03 mmol) was dissolved in 1 mL d_4-methanol. To this solution was added 4 mg KCN. The reaction solution

immediately turned colorless. ^{1}H NMR of reaction mixture reveals the formation of TolCH_2(Me)NCOMe (**2.6c**) in 95% yield (vs. Me_3SiPh internal standard). **2.6c** can be isolated by removal of the solvent in vacuo, dissolution of the resultant oil in 5 mL CH_2Cl_2 and washing with 10% HCl (25 mL). Evaporation of the CH_2Cl_2 solvent provides **2.6c** (4 mg, 80% yield). ^{1}H NMR (CD_2Cl_2): δ 7.20-7.00 (m, 4H), 4.45 (s, 2H), 2.90 (s, 3H), 2.38 (s, 3H).[3]

2.4 References

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(15) Wilke, G, Herrmann, G. *Angew. Chem., Int. Ed. Engl.* **1966**, *6*, 581.

(16) Complex **2.3 c**: ^{1}H NMR (CD_2Cl_2) δ 8.56 (s, =C(H)Tol), ^{13}C NMR δ 169.7 (s, =C(H)Tol). Free MeN=C(H)Tol: ^{1}H NMR (CD_2Cl_2) δ 8.42 (s, =C(H)Tol), ^{13}C NMR δ 160.6 (s, =C(H)Tol).

(17) The added PhN=C(Tol) does not significantly perturb the rate of formation of **2.5 a** suggestion that imine insertion is an intramolecular process from **2.4 a**. A manuscript describing the complete mechanistic details of imine insertion with the isoelectronic palladium complexes is currently in preparation.

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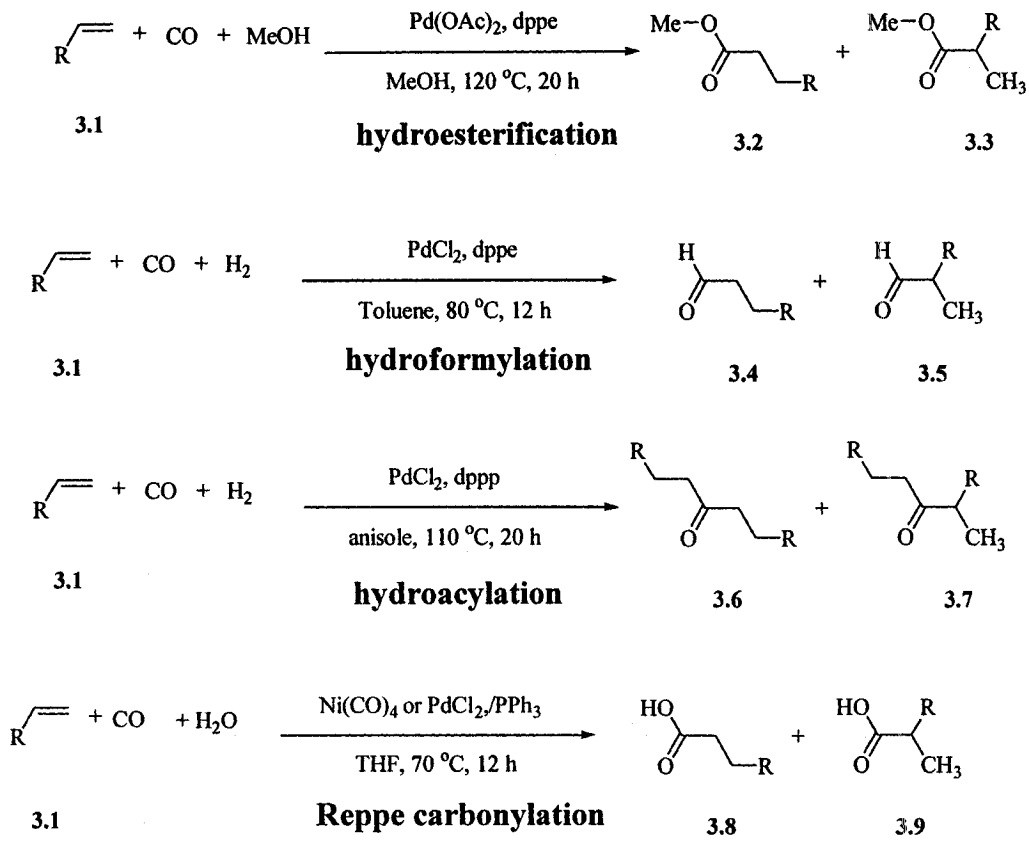
CHAPTER THREE

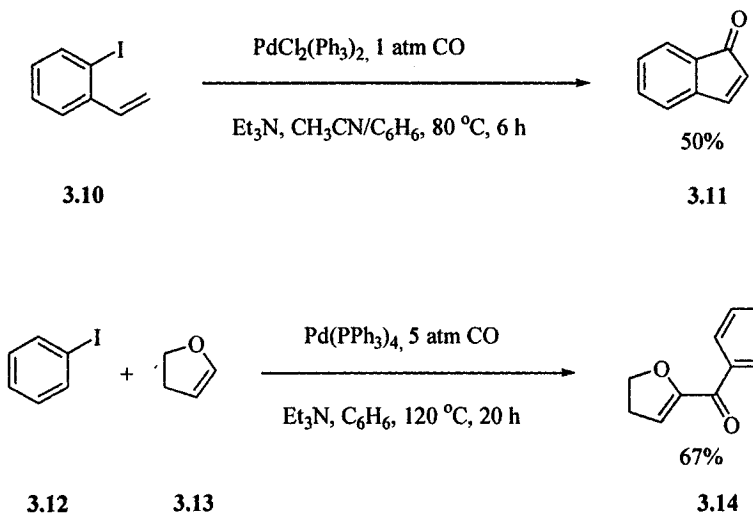
Investigating the Reactivity of Nickel Chelated Amide Complexes: $(L_2)Ni[n^2\text{-}CH(R`)NRCOR``]^+X^-$

3.0 Introduction

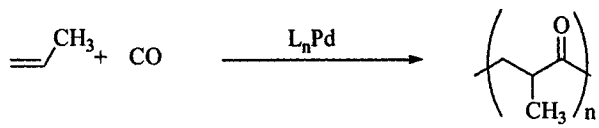
The metal mediated sequential insertion of carbon monoxide and olefins has been utilized effectively in a number of commercially important processes,[1,2] including hydroformylation,[3] hydroesterification,[4] hydroacylation,[5] and Reppe carbonylation (Scheme 3.1).[1a,6] In addition, the use of carbon monoxide insertion in palladium catalyzed Heck-type reactions can provide routes to a range of ketones and other carbonylated products (Eq. 3.1).[7] Alternatively, perfectly alternating insertion of CO/olefins into nickel and palladium-alkyl bonds can be used to generate a variety of polyketones with interesting material properties (e.g. Eq. 3.2).[2]



Scheme 3.1 General examples of hydroesterification, hydroformylation, hydroacylations and Reppe carbonylations.



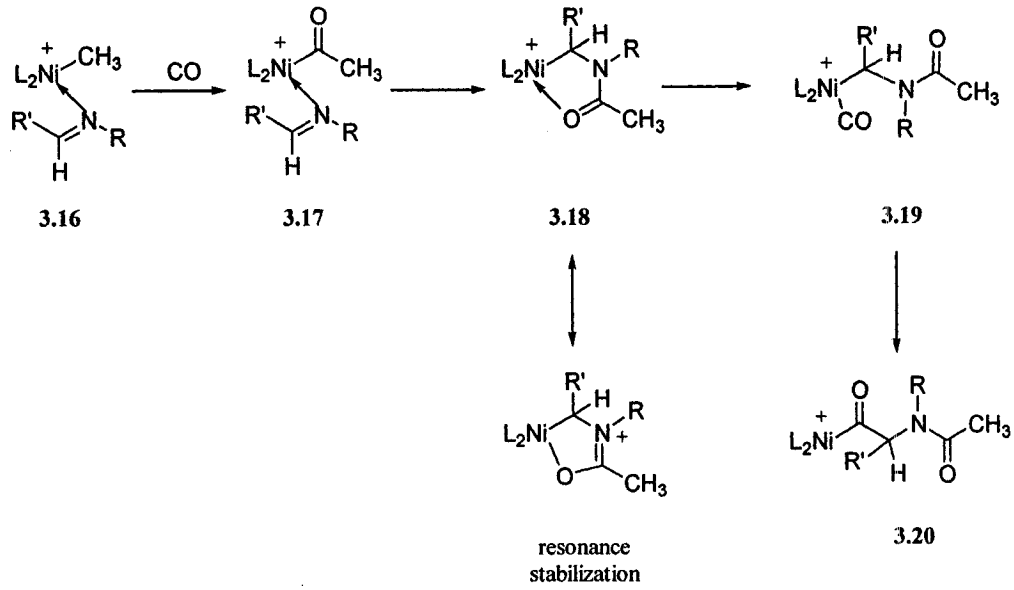
Equation 3.1 Synthesis of ketones via olefin/CO insertion



3.15

Equation 3.2 Palladium catalyzed co-polymerization of CO and propene

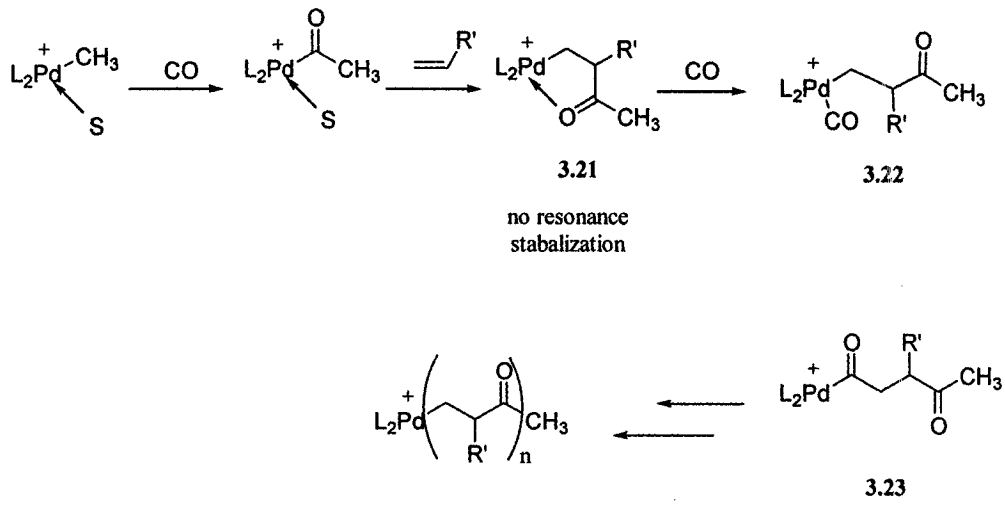
The analogous insertion of carbon monoxide and imines into the nickel-methyl bond of $[bipyNi(CH_3)(RN{=}C(H)R`)]^+X^-$ (bipy = 2,2'-bipyridyl, R = Me, Bn, Ph, *i*-Pr; R` = Tol, X = BArf, PF_6, SbF_6, OTf) has been examined in chapter 2, and demonstrated to provide a route to construct nickel-chelated amides **3.18** (Scheme 3.2). The ability to induce subsequent insertions of CO/imine into the nickel-carbon bond of **3.18** would provide a potentially powerful route to construct poly-amides bearing a peptide linkage in the backbone. Even the simple insertion of one additional molecule of carbon monoxide into **3.18** would generate a nickel-bound α-amido acyl complex **3.20**, which could presumably be employed to generate a range of α-amino acid based products.[9,10]



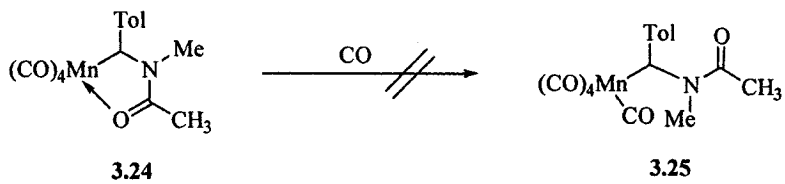
Scheme 3.2 Sequential CO/imine insertion with nickel complexes

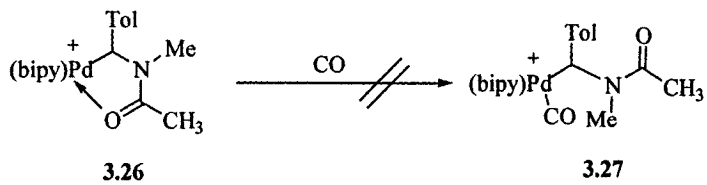
The product of the sequential insertion of carbon monoxide and imine into nickel-methyl complexes (**3.18**) is directly analogous to the palladium-chelated ketone intermediates observed in metal catalyzed alkene/CO alternating copolymerization (Scheme 3.3), suggesting that further insertions may be possible under the appropriate conditions. However, the chelation of the amide to the nickel center in complex **3.18** is resonance stabilized, in contrast to that of the ketone in **3.21**. As the first step in most migratory insertion systems involves the coordination of the substrate to the metal center, this could significantly slow or even prevent further insertions, by blocking the formation of an empty coordination site on nickel.[8,5,11] Indeed, similar work done by our group using analogous palladium and manganese complexes (Eq. 3.3), show no evidence for further insertion into the metal-

carbon bond of the chelated amide ligand. In addition, crystallographic data obtained on these complexes show distinctly longer C-O bonds and shorter C-N bonds consistent with increased metal-oxygen interaction.[12,13]



Scheme 3.3 Effects of resonance on chelate stabilization



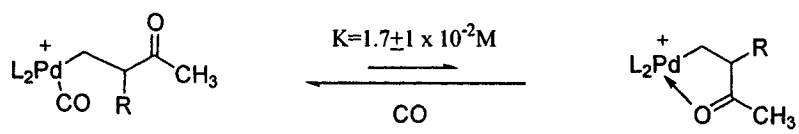


Equation 3.3 Analogous Pd and Mn metallacycles

Considering that Ni-ligand bonds are often weaker than those observed with palladium, as well as the potential utility of the products, we have undertaken a study of the general reactivity of complex **3.18** towards subsequent insertions of CO and imine. The results of these experiments are described in this chapter.

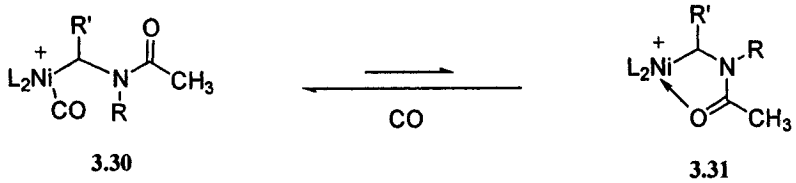
3.1 Effects of Carbon Monoxide Pressure and Temperature on the Reactivity of $(L_2)Ni[\eta^2\text{-}CH(R`)NRCOR``]^+X^-$

The palladium-chelated ketone complexes observed as intermediates in olefin/CO alternating co-polymerization, have been demonstrated to be in equilibrium with their non-chelated counterparts **3.28** in the presence of carbon monoxide, (Eq. 3.4)[14] which ultimately leads to insertion and co-polymerization. (Scheme 3.3). This CO coordinated complex is a critical intermediate for further insertion reactions.



3.28 **3.29**

Equation 3.4 Equilibrium for CO displacement of metal-chelate

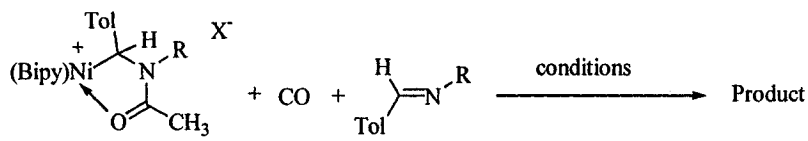


3.30 3.31

Scheme 3.4 Equilibrium for CO displacement of metal-chelate

In an effort to investigate an analogous reaction with the nickel chelated amide complexes, a series of experiments were carried out where complex **3.32** (50 mg) was placed under varying pressures of CO (from 1 atm to 60 atm) with various solvents and imines (Table 3.1). In all cases, removal of CO followed by immediate ^{1}H NMR analysis showed no evidence for the formation of **3.30** or any co-polymerization product, and in most cases the starting material **3.32** was recovered.

Table 3.1: Reaction of complex **3.32** with CO



3.32 10 equiv.

CO (atm)	Imine	X	Solvent	Temp	Product
1	Ph	BArF	CH_2Cl_2	70°C	**3.32**
1	Bn	BArF	CH_2Cl_2	70°C	**3.32**
1	Me	BArF	CH_2Cl_2	70°C	**3.32**
1	Me	SbF_6	CH_2Cl_2	70°C	**3.32**
1	Me	OTf	CH_2Cl_2	70°C	**3.32**

1	Me	BArF	CH_3CN	70°C	**3.32**
1	Me	BArF	CH_3CN	110°C	**3.32**
60	Me	BArF	CH_3CN	110°C	**3.32**
60	Me	BArF	CH_3CN	120°C	free imine + Ni(0)[a]

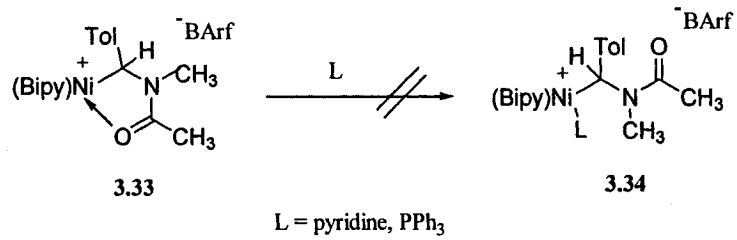
[a] Reaction is performed in the presence of 20-fold excess imine; BArF = $B(3,5\text{-}C_6H_3(CF_3)_2)_4$. OTf = OSO_2CF_3

This data suggests that the insertion of carbon monoxide into **3.32** does not occur readily under these conditions, or that the insertion is reversible and **3.30** rapidly undergoes decarbonylation upon removal of carbon monoxide to regenerate **3.32**. Under pressing conditions (60 atm CO, 120°C, 20 eq. imine), complex **3.32** does decompose, however, no evidence for the insertion of carbon monoxide or imine is observed. Though the products of decomposition could not be de-convoluted from the reaction mixture due to the large excess of imine present, the formation of a nickel metal precipitate was observed.

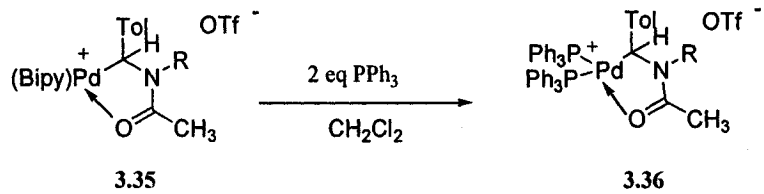
3.2 Reactivity Towards Ligand Substitution

The apparent lack of reactivity of the nickel complex **3.32** with CO prompted us to examine the potential of other strongly coordinating mono- and bi-dentate ligands to displace the amide chelation (Scheme 3.5). The addition of pyridine (16 mg, 0.21 mmol, 5 eq) to complex **3.33** (50 mg, 0.04 mmol) in dichloromethane showed no evidence for the desired open complex

3.34, even at temperatures up to 70°C. Instead, ^{1}H NMR analysis revealed only starting material and free ligand. The reaction of the even more strongly coordinating triphenylphosphine (52 mg, 0.21 mmol) with complex **3.33** (50 mg, 0.04 mmol) similarly showed no evidence for ligand displacement. The latter is somewhat surprising, given that the palladium analog (**3.35**), readily undergoes ligand exchange to give the bis-(triphenylphosphine) complex **3.36**.[15]



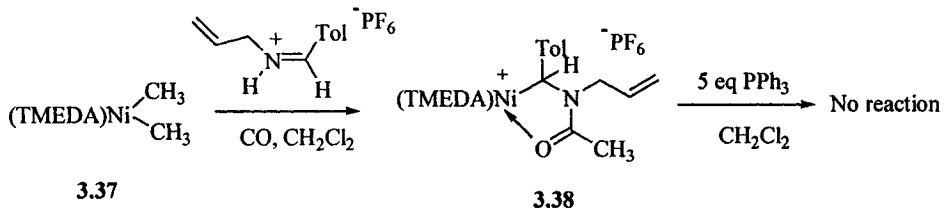
Scheme 3.5: Attempts at amide displacement using neutral ligands



Scheme 3.6: Reactivity of Ni and Pd metallacycles with phosphine ligands

One rationale for the lack of ligand exchange observed with the nickel complex **3.33** may involve the pairing of the softer phosphine ligand with a hard cationic nickel center, which may prefer to coordinate to the harder

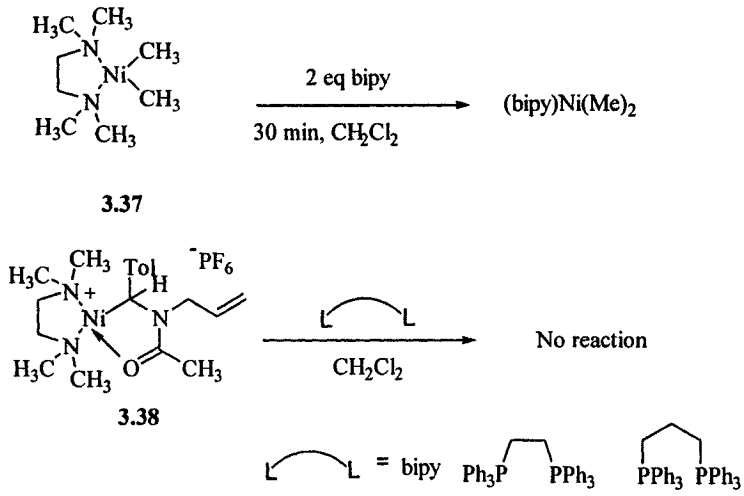
nitrogen-donor bipyridyl ligand. Indeed, even the tetramethylethylenediamine (TMEDA) substituted complex **3.38**, which can be prepared by the reaction of **3.37** and $(CH_2=CHCH_2(H)N=C(H)Tol)]^+PF_6^-$ and CO, is inert towards PPh_3.[16] However, this same complex, **3.38** is also unreactive towards substitution with 2,2'-bipyridyl. This contrasts with the behavior of $(TMEDA)NiMe_2$, which rapidly undergos reaction with bipy to form $(bipy)NiMe_2$ (Scheme 3.8).



Scheme 3.7: Reactivity of complex **3.37** with PPh_3

The inability to induce ligand exchange with either **3.33** or **3.38** suggests that not only does the nickel center strongly chelate to the amide oxygen, but that it is also kinetically inert towards substitution of the other donor ligands on the metal (Scheme 3.8). Even the addition of bi-dentate phosphine ligands to **3.38** (*e.g.* 1,2-bis (diphenylphosphino)ethane and 1,3-bis (diphenylphosphino)propane) does not displace either TMEDA or the amide ligand. Given the apparent ligand affinity of the nickel center in **3.33**, the generation of an empty coordination site for subsequent insertion substrates to

bind, via either the amide de-chelation or the displacement of the neutral nitrogen ligand, appears to be heavily disfavored.

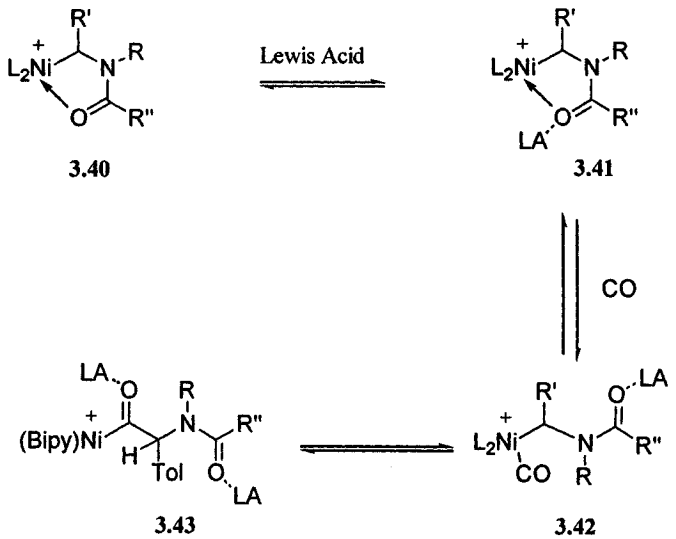


Scheme 3.8: Ligand exchange with cationic and neutral nickel complexes

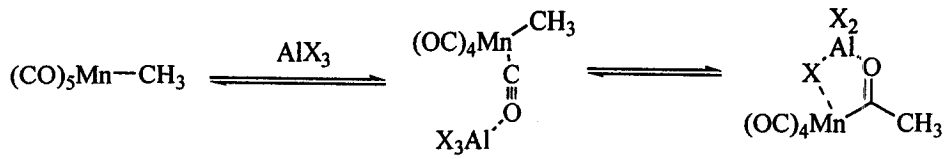
3.3 Reactivity of $(L_2)Ni[\eta^2\text{-}CH(R`)NRCOR``]^+X^-$ with Lewis Acids

The ability of Lewis acids to complex with carbonyl functional groups is well known,[5] and is commonly used to activate carbonyl systems towards nucleophilic attack.[17] By coordinating through the lone pair of electrons on the oxygen, Lewis acids effectively remove electron density from the system. Such an interaction with the amide ligand in compound **3.40** could potentially

weaken the chelation to the nickel center, (Scheme 3.9) resulting in an intermediate which more closely resembles the ketone-based chelates found in CO/olefin co-polymerization systems. In addition, Lewis acids have also been shown to enhance insertion rates of carbon monoxide.[18] For example, studies done by Shriver and co-workers demonstrate that the addition of AlX_3 (X = Cl, Br) to $CH_3Mn(CO)_5$ led to a dramatic increase in the rates of migratory insertion (ca. 10^8 rate enhancement) to form **3.45**. The increase in rates can be primarily attributed to the coordination of the Lewis acid to the oxygen of the CO ligand (Scheme 3.10). Once migratory insertion has occurred, the Lewis acid also plays a thermodynamic role by stabilizing the acyl group and occupying the vacant coordination site on the metal center.[15,19]



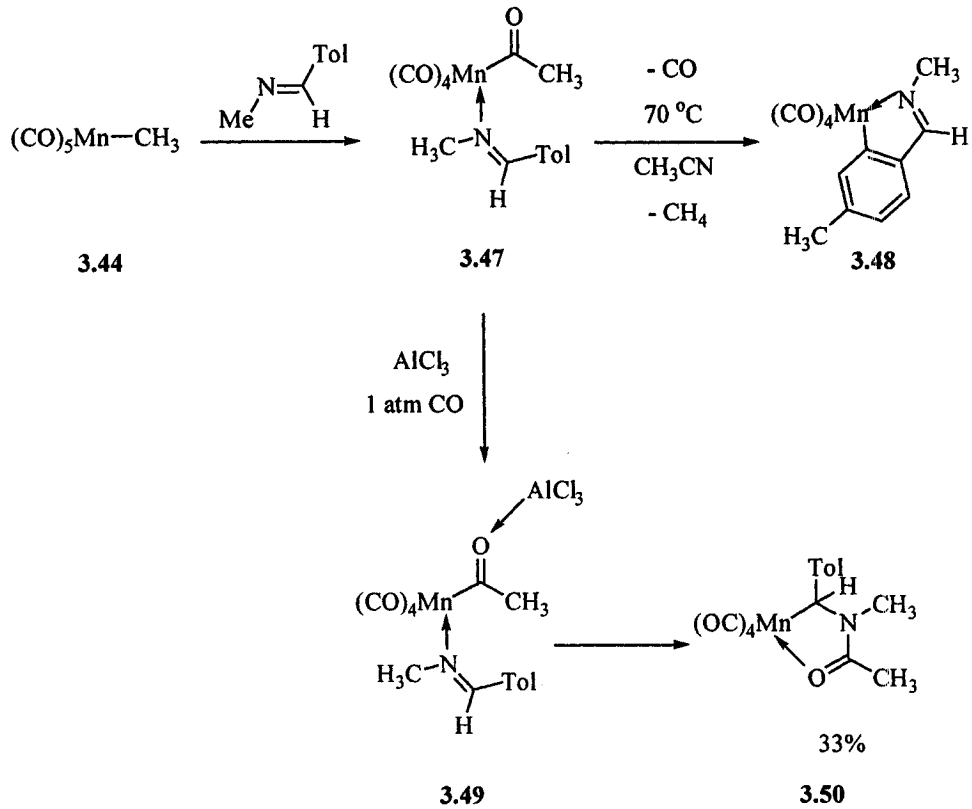
Scheme 3.9: Potential coordination of Lewis acid with the amide of **3.40**



3.44 **3.45** **3.46**

Scheme 3.10: Stabilization of metal acyl-species by Lewis acids

Similarly, our group has studied the effect of Lewis acids on the insertion of imine and carbon monoxide using manganese complexes.[13] Initial efforts to achieve sequential CO/imine insertion with neutral CH_3-$Mn(CO)_5$ complexes yielded instead the ortho-metallated product **3.48** and methane (Eq. 3.5). This suggests that the decarbonylation of **3.47**, followed by C-H bond activation, was occurring at a faster rate than imine insertion. However, when the reaction is performed in the presence of 1 equivalent of $AlCl_3$, the ortho-metallation pathway is completely blocked, and instead imine insertion occurs to form the manganese chelated amide **3.50** (Eq. 3.5). The $AlCl_3$ was postulated to both stabilize the Mn-acyl ligand as **3.49,** as well as facilitate imine insertion via activation of the electrophilic Mn-acyl carbonyl towards the nucleophilic imine.[13]

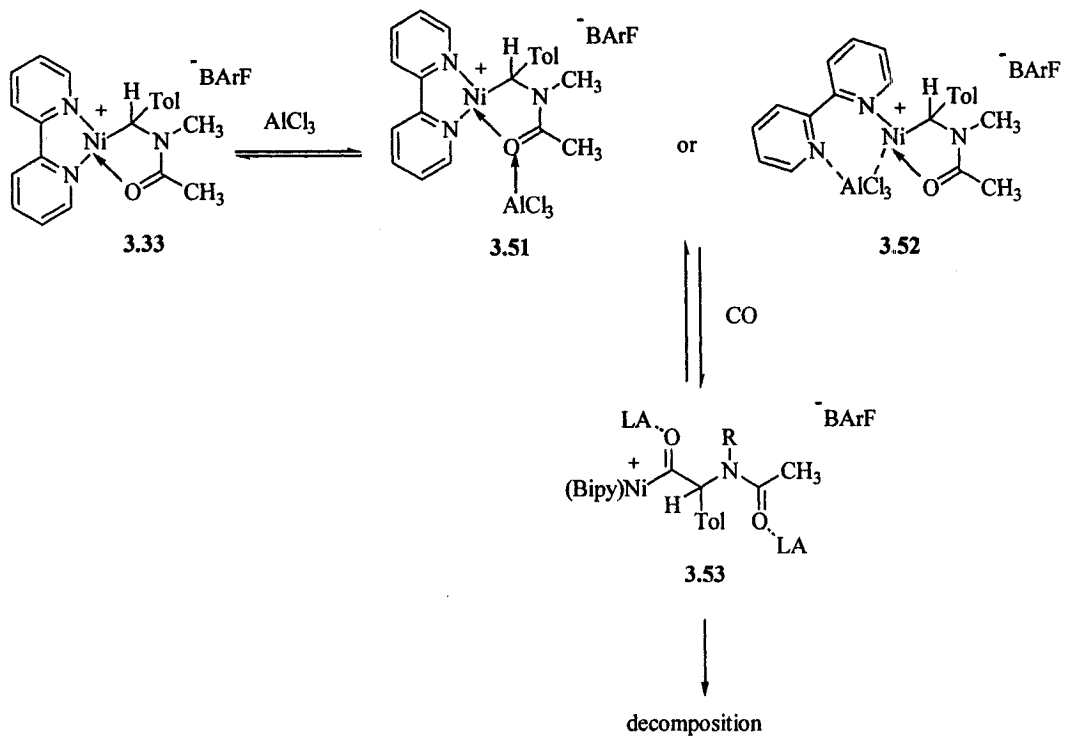


Equation 3.5: Effects of Lewis acid on imine insertion into Mn-acyl bonds

In light of all the above, we investigated the reactivity of nickel chelated amide complexes with various Lewis acids. The reaction of **3.33** (24 mg, 0.02 mmol) with $AlCl_3$ (2.5 mg, 0.02 mmol) was followed *in situ* by ^1H NMR. This showed the formation of a new product in approximately ~10% yield which is believed to be the Lewis acid coordinated complex (Scheme 3.11). This product contains a similar amide ligand to that in **3.33**, in which the ^1H NMR resonances for the $COCH_3$ (1.99 ppm) and $N(CH_3)$ (2.70 ppm) are shifted upfield from those observed in **3.33** (2.14 ppm and 2.78 ppm). While this is consistent with $AlCl_3$ binding to oxygen, it is possible that the Lewis acid may also bind to the bipyridyl ligand (**3.52**). We have previously

noted that with palladium, bipyridyl is more labile than the chelated amide, and the ^{1}H NMR **3.51** reveals a broadening and upfield shift of the bipyridyl resonances.

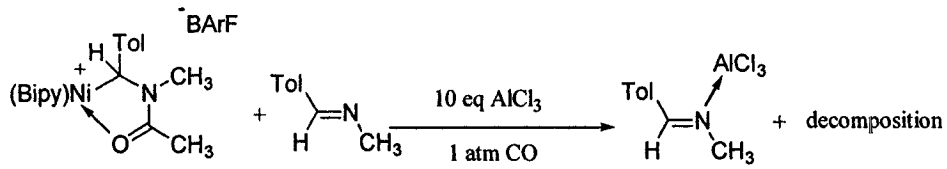
Allowing the reaction mixture to stand at room temperature overnight, resulted in no significant increase in the amount of **3.51**, suggesting a possible equilibrium between **3.33** and $AlCl_3$. Indeed, incremental addition of 2, 4, and finally 10 equivalents of $AlCl_3$ lead to complete conversion of **3.33** to the Lewis acid coordinated complex. This new complex displayed no evidence for decomposition or further reactivity in solution after several days. However, addition of 1 atm of CO to the reaction mixture led to the complete decomposition of complex **3.51** with no identifiable compounds formed.



Scheme 3.11: Activation of **3.33** with Lewis acids

While no identifiable products are observed upon addition of CO to **3.51**, the fact that it does react at all is distinct from our previous results. This increased reactivity of **3.51** towards CO suggests that an available binding site may be generated on the nickel center in the presence of $AlCl_3$. The exact role of $AlCl_3$ in the activation of complex **3.33** is unclear, and may involve either amide or 2,2'-bipyridyl de-chelation. The reason CO addition to **3.51** leads to decomposition is unclear. One possibility could be that $AlCl_3$ induces CO insertion to generate complex **3.53**. However, considering the rapid decomposition of **3.51** in the presence of CO, it is possible that the latter may not be stable under these reaction conditions.

In an attempt to trap any unstable intermediate, a similar reaction was performed in the presence of 2 equivalents of Tol(H)C=NCH$_3$ (Eq. 3.6). Unfortunately, this also led to complete decomposition of complex **3.33**, with no evidence for further insertions of imine or CO. Examination of the reaction mixture showed that imine had not been consumed, but had instead bound to $AlCl_3$. This same complex can be prepared by the addition of 1 equivalent of $AlCl_3$ to a solution of Tol(H)C=NCH$_3$, and displays characteristic downfield shifts in the =C(**H**) (8.91 ppm) and N(C**H**$_3$) (3.90 ppm) ^{1}H NMR signals. This strong coordination with the lone pair of imine is most likely inhibiting its ability to stabilize or interact with any unsaturated nickel complex generated.



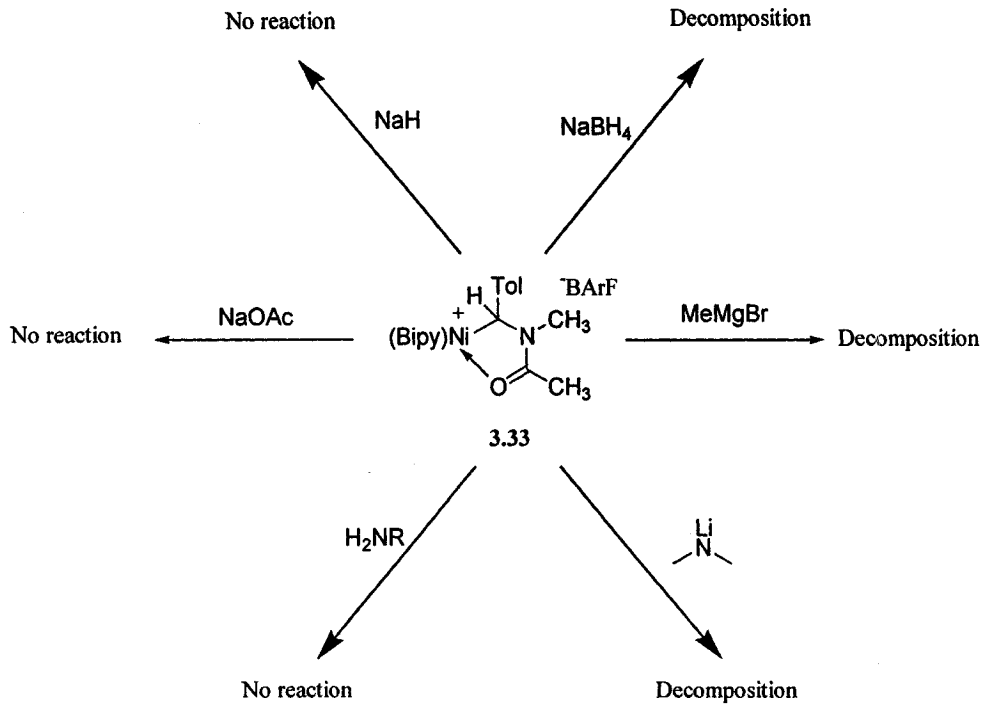
Equation 3.6: Reactivity of **3.33** in the presence of Lewis acid, imine and CO

In addition to $AlCl_3$, the more mild Lewis acid $InCl_3$ has also been examined. However, even with large excesses of $InCl_3$ (20 eq.), no interaction with complex **3.33** was observed by ^{1}H NMR analysis, and the addition of CO did not result in the subsequent decomposition displayed with $AlCl_3$. These results suggest that stronger Lewis acids are required to achieve the desired activation of complex **3.33**, and allow for further reactivity with CO.

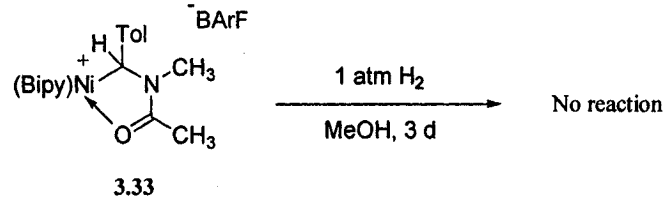
Unfortunately, in the case of $AlCl_3$, this Lewis acid is incompatible with the imines examined.

3.4 General Stability and Reactivity of $(L_2)Ni[\eta^2$-$CH(R`)NRCOR``]^+X^-$

In an effort to better understand the relative stability and reactivity of the nickel-chelated complexes (**3.33**), the reaction of this metallacycle with a variety of nucleophilic, electrophilic, and unsaturated substrates was examined. Complex **3.33** showed surprising stability towards most nucleophilic reagents, and in many cases the starting material was recovered (Scheme 3.12). Complex **3.33** was also unreactive towards hydrogenation and alcoholysis (Eq. 3.7).



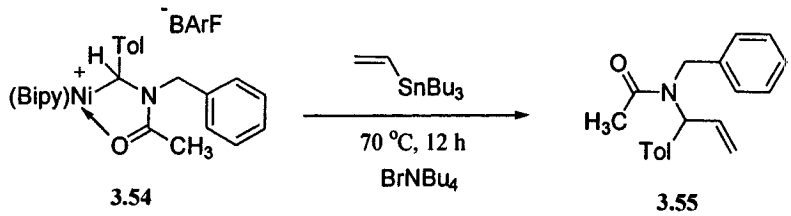
Scheme 3.12: Reactivity of **3.33** with nucleophiles



Equation 3.7: Reactivity of **3.33** under hydrogenation conditions

While complex **3.33** displayed little or no reactivity towards nucleophilic reagents, it was reactive towards Stille-type transmetallations with tributylvinylstannane. This is somewhat surprising given the apparent lack of vacant coordination sites on complex **3.33**. However, in the presence

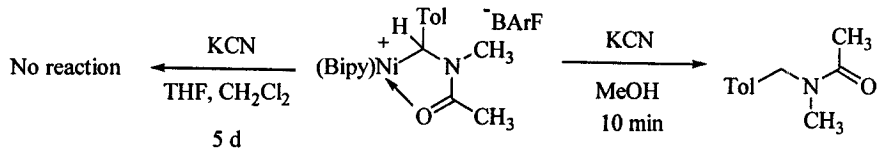
of Bu_4NBr,[20] complex **3.54** reacts smoothly to yield the α-vinyl amide **3.54** in 70% yield. This reactivity with organtin reagents will be described in more detail in Chapter 5.



3.54 3.55

Equation 3.8: Stille coupling with complex **3.54**

The amide ligand fragment can also be quantitatively cleaved with KCN in methanol (Eq. 3.9). This could involve the *in-situ* formation of HCN as the active substrate,[21] since no reaction is observed when KCN is used in non-protic solvents such as THF and dichloromethane.

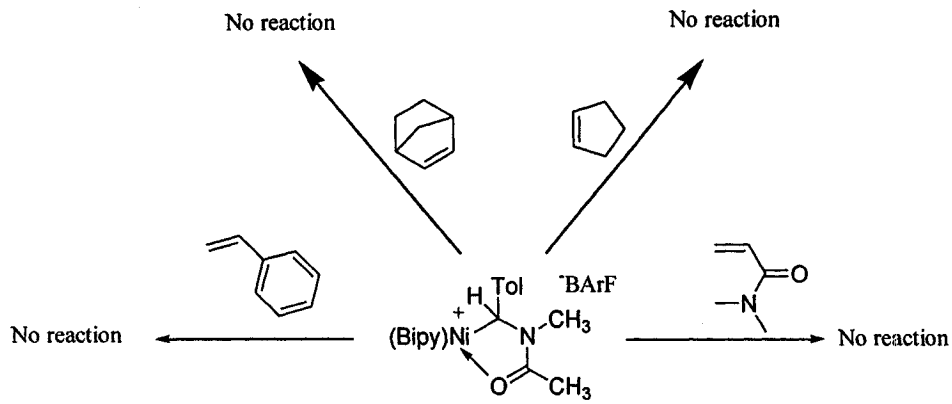


3.33 3.58

Equation 3.9: Reactivity of **3.33** with KCN

Finally, the reactivity of these nickel metallacycles with alkenes has been probed. While the insertion of alkenes into nickel and palladium-carbon bonds is well established with many systems,[14,22,23] **3.33** was found to be unreactive towards all alkenes. In all cases, **3.33** was recovered and no

reaction was observed (Scheme 3.13). This behavior is consistent with a lack of available coordination sites, preventing subsequent insertion.



3.33

Scheme 3.13: Reactivity of complex **3.33** with alkenes

3.5 Conclusions

These studies have demonstrated that the amide ligand in **3.32** is strongly chelated to the nickel center, and appears to inhibit the ability of these complexes to undergo subsequent insertion of CO or imine into the nickel-carbon bond. Strongly coordinating phosphine ligands were also unable to open the amide chelate, nor were they able to activate it towards further insertions. In addition, the other ligands on these chelated nickel complexes (e.g. bipy, TMEDA) are tightly bound, and do not undergo ligand exchange even in the presence of excess mono- or bidentate ligands.

Activation of the nickel-chelated amide complex **3.33** can be achieved using $AlCl_3$, and results in a dramatic increase in the reactivity of these

metallacycles towards CO. Though our attempts at further insertions of CO and imine were unsuccessful, this potential mode of activation is promising. Further investigation should be directed towards finding more compatible Lewis acid/imine pairings and achieving a better understanding of the nature of the interaction of the Lewis acid with these complexes.

While under most conditions these nickel chelated amides are inert to reaction, they do undergo coupling with tin reagents. This indicates that under the appropriate conditions, coordination sites can be made available for further reactions. The use of this observed transmetallation with organotin reagents as a route to construct amides (Chapter 5), as well as a study of the ability of alkenes to undergo migratory insertions in the presence of imines (Chapter 4), will be explored in more detail in following chapters.

3.6 Experimental Section

General

Unless otherwise noted, all manipulations were carried out under an inert atmosphere in a Vacuum Atmosphere 553-2 drybox or using standard Schlenk or vacuum line techniques. NMR spectra were obtained on 300MHz and 400MHz Varian machine. IR spectra were obtained on a Bruker IFS-48 spectrometer.

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Liquids were freeze-pump-

thawed three times to de-gas before use. Diethyl ether was distilled from sodium benzophenone. Pentane, methylene chloride and chlorobenzene were distilled from CaH_2. Deuterated solvents were dried as their protonated analogues, but were vacuum transferred from the drying agent. UHP grade carbon monoxide was obtained from Matheson. Imines were prepared by reaction of *p*-tolualdehyde and amine in diethyl ether at room temperature over 4A° molecular sieves. (bipy)$NiMe_2$ was prepared via a literature procedure.[24] Iminium salts were prepared via addition of 1.1 equiv. of anhydrous HCl in diethyl ether to the appropriate imine and pumped to dryness. 1 equiv. of the desired counterion salt (i.e. $AgPF_6$, NaBArf[25]) was added in CH_2Cl_2 and stirred for 4hrs. The precipitate was filtered off and the filtrate pumped to dryness and used without further purification.

Reaction of complex 3.32 with CO

The general procedure followed for all experiments in Table 3.1 performed under 1 atm of CO is as follows. Complex **3.32** (0.075 mmol) and 10 equivalents of the appropriate imine were dissolved in ~1 ml of deuterated solvent and the solution was placed under 1 atm of CO in a sealed NMR tube. The reaction was then heated for 24 hours and monitored by ^1H NMR. In all cases only starting material was observed.

Reactions performed at higher pressures of CO were performed in a Parr bomb as follows. Complex **3.32** (0.075 mmol) and 20 equivalents of

imine were dissolved in CH_3CN (15 mL) and place under CO in a Parr bomb. The reaction was then heated for 24 hours. The CO was removed, and the solvent pumped off under vacuum, followed by immediate analysis by ^1H NMR.

Reaction of [(bipy)Ni[η^2-C(Tol)HN(CH_3)$COCH_3$]]$^+$ BArF$^-$(3.33) with pyridine

To a solution of complex **3.33** (50 mg, 0.04 mmol) in CD_2Cl_2 (500 μL) was added pyridine (16 mg, 0.21 mmol, 5 eq) in an NMR tube. The reaction was monitored by ^1H NMR, and exhibited no discernable change in the resonances for **3.33**, even upon heating to 70°C for 12h.

Reaction of [(bipy)Ni[η^2-C(Tol)HN(CH_3)$COCH_3$]]$^+$ BArF$^-$(3.33) with PPh_3.

To a solution of complex **3.33** (50 mg, 0.04 mmol) in CD_2Cl_2 (500 μL) was added PPh_3 (52 mg, 0.21 mmol, 5 eq) in an NMR tube. The reaction was monitored by NMR and exhibited no discernable change in the ^1H resonances for **3.33** or ^{31}P NMR peaks of PPh_3 (-5 ppm) after 12 hours at room temperature.

Ligand Exchange with [(bipy)Ni[η^2-C(Tol)HN(CH_3)$COCH_3$]]$^+$ BArF$^-$ (3.33) and dppe.

To a solution of complex **3.33** (50 mg, 0.04 mmol) in CD_2Cl_2 (500 μL) was added (diphenylphosphino)ethane (83 mg, 0.21 mmol, 5 eq) in an NMR tube. The reaction was monitored by ^1H NMR and exhibited no discernable change after 12 hours at room temperature.

Ligand Exchange with [(bipy)Ni[η^2-C(Tol)HN(CH_3)$COCH_3$]]$^+$ $BArF^-$ (3.33) and dppp.

To a solution of complex **3.33** (50 mg, 0.04 mmol) in CD_2Cl_2 (500 μL) was added 1,3-bis(diphenylphosphino)propane (86 mg, 0.21 mmol, 5 eq) in an NMR tube. The reaction was monitored by ^1H NMR and exhibited no discernable change after 12 hours at room temperature.

(TMEDA)Ni[η^2-C(Tol)HN(CH_2=$CHCH_2$)$COCH_3$]]$^+PF_6^-$ (3.38)

200 mg (0.846mmol) of (TMEDA)$NiMe_2$ was dissolved in 10 ml of methylene chloride, and 1 equiv. of (CH_2=$CHCH_2$(H)N=C(H)Tol)]$^+PF_6^-$ dissolved in an additional 10 mL of methylene chloride was added drop wise to the stirring solution. The dark yellow solution rapidly turns a deep red color near the end of the addition to provide 170 mg (0.34 mmol) of the desired cationic nickel complex.

Yield: 40%, yellow solid

^{1}H-NMR (400 MHz, CD_2Cl_2): δ 9.38 (d, J = 11.6 Hz, 2H), 7.79 (s, 1H), 7.30 (d, J = 11.6 Hz, 2H), 5.78 (m, 1H), 5.21 (m, 2H), 4.61 (m, 1H), 4.41 (m, 1H), 2.33 (s, 3H), 2.25 (s, 3H), 2.22-2.01 (m, 10 H), 1.56 (s, 3H), -0.90 (s, 3H).
^{13}C NMR (400 MHz, CD_2Cl_2): δ 170.1, 135.9, 131.9, 128.8, 127.3, 122.5, 115.5, 64.2, 63.5, 63.1, 62.9, 62.4, 60.8, 60.1, 21.4, -1.5.

The complex $[(TMEDA)Ni(CH_3)(CH_2{=}CHCH_2N{=}C(H)Tol)]^+PF_6^-$ (160 mg, 0.32 mmol) was dissolved in CH_2Cl_2 (15 mL) in a 100 mL reaction bomb. The solution was placed under 1 atm of CO and stirred for 5 minutes. Upon stirring, the solution changes from yellow to brown, and the bomb was then heated to 70 °C for 12 hours. The solution was filtered through celite, added to 10 mL of pentane and cooled to – 40 °C overnight. The clear solvent mixture was decanted and the solid residue washed with pentane (3 x 5 mL) and then dried under vacuum to yield a yellow powder (80 mg, 49% yield).

^{1}H-NMR (400 MHz, CD_2Cl_2): δ 7.31 (br, 2H), 7.00 (d, J = 11.6 Hz, 2H), 5.27 (m, 1H), 5.11 (s, 1H), 5.01 (m, 2H), 3.15 (m, 2H), 2.31 (s, 3H), 2.30 (s, 3H), 2.29-2.10 (m, 4H), 2.05 (s, 3H), 2.00 (s, 3H), 1.80 (s, 3H), 1.56 (s, 3H).
^{13}C NMR (400 MHz, CD_2Cl_2): δ 179.9, 135.9, 131.9, 128.8, 127.3, 122.5, 115.5, 64.2, 63.5, 63.1, 62.9, 62.4, 60.8, 60.1, 35.8, 21.4, 18.1.

Reaction of $(TMEDA)Ni[\eta^2\text{-}C(Tol)HN(CH_2{=}CHCH_2)COCH_3]]^+PF_6^-$ (3.38) with PPh_3.

To a solution of complex **3.38** (20 mg, 0.04 mmol) in CD_2Cl_2 (500 μL) was added PPh_3 (52 mg, 0.21 mmol, 5 eq) in an NMR tube. The reaction was monitored by ^1H NMR and exhibited no discernable change after 12 hours at room temperature.

Reaction of (TMEDA)Ni[η^2-C(Tol)HN(CH_2=$CHCH_2$)$COCH_3$]]$^+PF_6^-$ (3.38) with dppe.

To a solution of complex **3.38** (20 mg, 0.04 mmol) in CD_2Cl_2 (500 μL) was added 1,2-bis-(phenylphosphino)ethane (83 mg, 0.21 mmol, 5 eq) in an NMR tube. The reaction was monitored by ^1H NMR and exhibited no discernable change after 12 hours at room temperature.

Reaction of (TMEDA)Ni[η^2-C(Tol)HN(CH_2=$CHCH_2$)$COCH_3$]]$^+PF_6^-$ (3.38) with dppp

To a solution of complex **3.38** (20 mg, 0.04 mmol) in CD_2Cl_2 (500 μL) was added 1,3-bis(diphenylphosphino)propane (86 mg, 0.21 mmol, 5 eq) in an NMR tube. The reaction was monitored by ^1H NMR and exhibited no discernable change after 12 hours at room temperature.

(bipy)Ni[η^2-C(H)TolN(CH_3)$COCH_3$]$^+BArf_4^-$ /$AlCl_3$ (3.51)

To a solution of (bipy)Ni[η^2-C(H)TolN(CH_3)$COCH_3$]$^+Barf_4^-$ (50 mg, 0.04 mmol) in dry CD_2Cl_2 (500 μL) was added $AlCl_3$ (54 mg, 2.1 mmol).

Allowing the mixture to stand overnight led to the postulated Lewis acid coordinated species, as observed by *in-situ* NMR analysis.

^{1}H NMR (300 MHz, CD_2Cl_2): δ 9.50-9.10 (br m, 1H), 8.66-8.52 (m, 2H), 8.03-7.95 (m, 1H), 7-68-7.66 (m, 12H), 7.31-7.23 (m, 4H), 7.25-7.20 (m, 2H), 7.17 (d, J = 11.0 Hz, 2H), 4.62 (s, 1H), 2.70 (s, 3H), 2.21 (s, 3H), 1.99 (s, 3H).

^{13}C NMR (300 MHz, CD_2Cl_2): δ 178.7, 159.5, 156.8, 148.9, 147.2, 139.9, 139.2, 138.6, 138.4, 136.1, 129.3, 127.9, 127.2, 124.1, 122.4, 69.8, 36.9, 22.5, 19.2.

Reaction of (bipy)Ni[η^2-C(H)TolN(CH_3)$COCH_3$]$^+$$Barf_4^-$ /$AlCl_3$ (3.51) with CO.

A solution of complex **3.51,** generated from the addition of $AlCl_3$ (54 mg, 2.1 mmol) to complex **3.33** (50 mg, 0.04 mmol) in CD_3CN (500 μL) in a J-Young NMR tube was placed under 1 atm of CO and monitored by ^{1}H NMR. After 12 hours at room temperature, the complex has decomposed completely to give a complex mixture of organic products.

Reaction of $AlCl_3$ and CO with complex 3.33 in the presence of excess imine

To a solution of (bipy)Ni[η^2-C(H)TolN(CH_3)$COCH_3$]$^+$$Barf_4^-$ (50 mg, 0.04 mmol) in dry CD_3CN (500 μL) in a J-Young NMR tube was added 2 equivalents of Tol(H)C=NCH_3 (11 mg, 0.08 mmol). The reaction mixture was shaken for 5 minutes and 2 eq of $AlCl_3$ (10 mg, 0.08 mmol) was added.

The reaction mixture was placed under 1 atm of CO and monitored by ^{1}H NMR. After 12 hours at room temperature complex **3.33** was consumed to give a complex mixture of products including the $AlCl_3$ bound imine adduct.

$(AlCl_3)N(CH_3)=C(H)Tol$

Addition of $AlCl_3$ (100 mg, 0.74 mmol) to a solution of $N(CH_3)=C(H)Tol$ (50 mg, 0.37 mmol) in CD_3CN (500 μL) in an NMR tube led to the immediate and quantitative formation of$(AlCl_3)N(CH_3)=C(H)Tol$, as chacterized by *in-situ* NMR.

^{1}H NMR (300 MHz, CD_3CN): δ 8.91 (s, 1H), 7.43 (d, J = 11.2 Hz, 2H), 7.10 (d, J = 11.2 Hz, 2H), 3.90 (s, 3H), 2.34 (s, 3H).

^{13}C NMR (300 MHz, CD_2Cl_2): δ 178.9, 136.4, 132.2, 128.8, 127.3, 55.6, 22.4.

Addition of $InCl_3$ and CO to complex 3.33

To a solution of (bipy)Ni[η^2-C(H)TolN(CH_3)$COCH_3$]$^+Barf_4^-$ (50 mg, 0.04 mmol) in dry CD_3CN (500 μL) in a J-Young NMR tube was added 20 equivalents of $InCl_3$ (177 mg, 0.80 mmol). The mixture was allowed to stand at room temperature for 1 hour and monitored by ^{1}H NMR. No discernable shifts in the resonances of **3.33** were observed. The reaction mixture was placed under 1 atm of CO and allowed to stand for 24 hours. No reaction was observed.

Reaction of 3.33 with $LiNMe_2$

To a solution of **3.33** (0.06 mmol) in THF (20 mL) was added $LiNMe_2$ (3 mg, 0.06 mmol). The yellow solution turns dark purple upon addition of the nucleophile, and a black precipitate forms. The solvent is removed under vacuum and ^1H NMR of the crude residue shows a complex mixture of products.

Reaction of 3.33 with MeMgBr

To a solution of **3.33** (0.06 mmol) in THF (20 mL) was added MeMgBr as a 1M solution in diethyl ether (0.06 μL, 0.06 mmol). The yellow solution turns dark red upon addition of the nucleophile and then becomes colorless along with the formation of a black precipitate. The solvent is removed under vacuum and ^1H NMR of the crude residue shows a complex mixture of products.

Reaction of 3.33 with $MeNH_2$

To a solution of **3.33** (0.06 mmol) in THF (20 mL) was added $MeNH_2$ as a 1M solution in THF (0.12 μL, 0.12 mmol). After stirring at room temperature for 12 hours the solvent is removed under vacuum and ^1H NMR of the crude residue shows unreacted starting materials.

Reaction of 3.33 with NaH

To a solution of **3.33** (0.06 mmol) in THF (20 mL) was added 5 eq of 60% NaH oil dispersion (10 mg, 0.30 mmol). After stirring at room temperature for 12 hours the solvent is removed under vacuum and ^{1}H NMR of the crude residue shows unreacted starting materials.

Reaction of 3.33 with NaOAc

To a solution of **3.33** (0.06 mmol) in THF (20 mL) was added 5 eq of NaOAc (24 mg, 0.30 mmol). The slurry was stirred at room temperature for 12 hours. The solvent was removed under vacuum and ^{1}H NMR of the crude residue showed unreacted starting materials.

Reaction of 3.33 with $NaBH_4$

To a solution of **3.33** (0.06 mmol) in THF (20 mL) was added 5 eq of $NaBH_4$ (20 mg, 0.30 mmol). The yellow solution turns colorless upon addition of the $NaBH_4$ along with the formation of a black precipitate. The solvent is removed under vacuum and ^{1}H NMR of the crude residue showed a complex mixture of products.

General procedure for the Hydrogenation of complex 3.33

Complex **3.33** (50 mg, 0.04 mmol) was dissolved in MeOH (20 mL) and placed under 1 atm of H_2 in a Shlenk flask. The yellow solution was stirred at room temperature for 72 hours under H_2 using a balloon. The solvent

was then removed under nitrogen to yield a yellow residue. ^{1}H NMR of the crude reaction mixture showed only unreacted starting material.

N(Bn)(C(H)(CH=CH$_2$)Tol)COCH$_3$ (3.55)

To a solution of complex **3.54** (100 mg, 0.08 mmol) was added $BrNBu_4$ (1 eq) and tributylvinyl tin (1.1 eq). The reaction mixture was left to stir at room temperature overnight. The solvent was evaporated *in vacuo* to provide a brown oil. The residue is then taken up in 50 mL of ethyl acetate. Tributyl tin chloride was removed by stirring with 25 mL of saturated KF solution and was accompanied by the immediate formation of a white solid. The solution was filtered through celite and extracted three times with 50 mL water/ethyl acetate. The organic layers were combined and dried over $MgSO_4$ and the solvent removed *in vacuo* to provide a viscous yellow/orange oil which was chromatographed on Silica Gel 60 using hexanes/ethyl acetate as eluent.

Yield: 70%, oil

^{1}H-NMR (400 MHz, $CDCl_3$ 25 °C): δ 7.30-7.01 (m, 9H), 6.42 (d, 1H, major), 5.96 (m, 1H), 5.50 (d, 1H, minor), 5.29(d, 1H), 5.19 (d, 1H, minor), 4.75 (d, 1H, minor), 4.55 (d, 1H, minor), 4.47 (d, 1H, minor), 4.34 (d, 1H, major), 2.32(s, 3H), 2.23(s, 3H, minor), 2.06 (s, 3H, major).

^{13}C NMR (400 MHz, $CDCl_3$): δ 171.8, 139.2, 138.2, 138.0, 137.9, 136.1, 135.8, 135.5, 129.8, 129.7, 128.2, 128.0, 127.8, 127.2, 126.5, 126.1, 118.9, 118.2, 64.1, 59.8, 49.6, 47.8, 22.3, 21.6.

$N(CH_3)(CH_2C_6H_4$-*p*-$CH_3)COCH_3$ (3.46)

To a solution of complex **3.33** in dry CH_2Cl_2 was added 5 ml of saturated KCN/methanol solution. The deep red solution immediately goes colorless to give the free acetamide. The solvent is then removed under reduced pressure and the residue taken up in 50 mL of ethyl acetate. The organic layer is washed with 10% HCl (2 x 100 mL), dried over Na_2SO_4 and the solvent removed under reduced pressure to yield a colorless oil.

Yield: 95%, oil

^{1}H NMR (300 MHz, CD_2Cl_2): δ 8.1.5-7.80 (m, 5H), 5.21 (s, 2H, major), 5.19 (s, 2H, minor), 3.59 (s, 3H, major), 3.55 (s, 3H, minor), 2.81 (s, 3H, major), 2.80 (s, 3H, minor), 2.20 (s, 3H).

^{13}C NMR (300 MHz, CD_2Cl_2): δ 169.8, 138.9, 135.9, 131.2, 128.8, 127.3, 50.2, 50.1, 47.8, 47.7, 21.1, 20.7.

General procedure for olefin insertion reactions with complex 3.33

To a solution of **3.33** (25 mg, 0.02 mmol) in dry CD_2Cl_2 was added 5 equivalents of the olefin. The yellow solution was shaken well and allowed to stand at room temperature for 24 hours. ^{1}H NMR revealed only unreacted starting materials in all cases.

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CHAPTER FOUR

Generation of 5 and 6 Membered Lactams Via a Nickel Mediated CO, Olefin, CO, Imine, Insertion Cascade

4.0 Introduction

Transition-metal mediated carbon-carbon and carbon-nitrogen bond forming reactions have become important fundamental transformations in synthesis.[1] In particular, reactions capable of incorporating unsaturated substrates via migratory insertion have been used extensively in synthetic organic chemistry, as well as polymer chemistry.[2] While metal catalyzed reactions involving the migratory insertion of alkenes are well known (e.g. olefin polymerization,[2] hydrogenation,[3] and Heck couplings[4]), examples involving heteroatom containing unsaturated substrates (e.g. imines and aldehydes) are less common.[6] Perhaps the most established of these is the catalytic hydrogenation of aldehydes and imines.[5] More recently, the rhodium catalyzed addition of organotin and organoborane reagents to imines and aldehydes has also been achieved.[7]

The extensive use of alkene insertion reactions in synthetic processes suggests that the analogous reaction with imines could provide an effective method for generating carbon-nitrogen bonds. However, until only recently, examples of even the stoichiometric insertion of imines into late metal-carbon

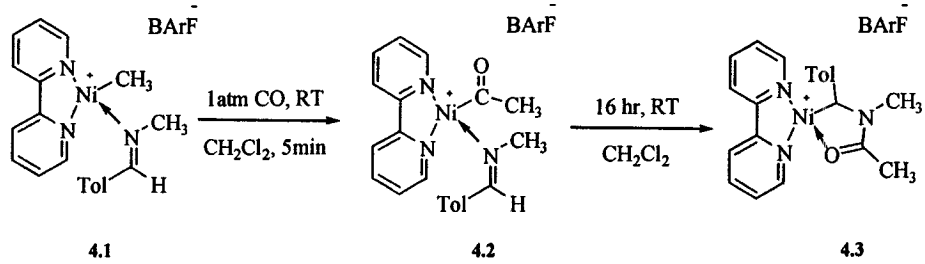
bonds in a fashion analogous to alkenes were rare.[6] This appears to be at least partially based upon thermodynamics, where the insertion of an imine into a metal-carbon bond to cleave a carbon-nitrogen π–bond, and the formation of a new carbon-nitrogen σ-bond is not expected to be nearly as exothermic as is observed with alkene insertion.* This significant difference in reactivity appears to be a key caveat in the development of systems capable of mediating migratory insertion with imines. Given the potential utility of this reaction, we were interested in exploring systems which would allow us to study the relative insertion propensities of imines and alkenes. To our knowledge, this fundamental comparison has not been previously explored, and thus could be critical in the development of synthetic processes that utilize both alkenes and imines as insertion substrates.

We[6b,6f,8] and others[6c] have recently demonstrated that CO and imines can undergo sequential migratory insertion into late transition metal-carbon bonds to yield products analogous to those of CO/alkene insertion. For example, imines readily undergo insertion into the *in-situ* generated nickel-acyl bond of **4.2** to form metal-chelated amides (Scheme 4.1).[8] Considering that these same nickel complexes have been demonstrated to readily undergo alkene insertion reactions, this system provides an intriguing opportunity to probe the relative insertion propensity of these two fundamental fragments. We report below the results of these efforts, which examine the steric, electronic, and regiochemical effects governing competitive insertion between α-olefins and imines. This information

has been subsequently used to design a nickel mediated four component insertion cascade to construct 5- and 6- membered lactams.

4.1 Results and Discussion

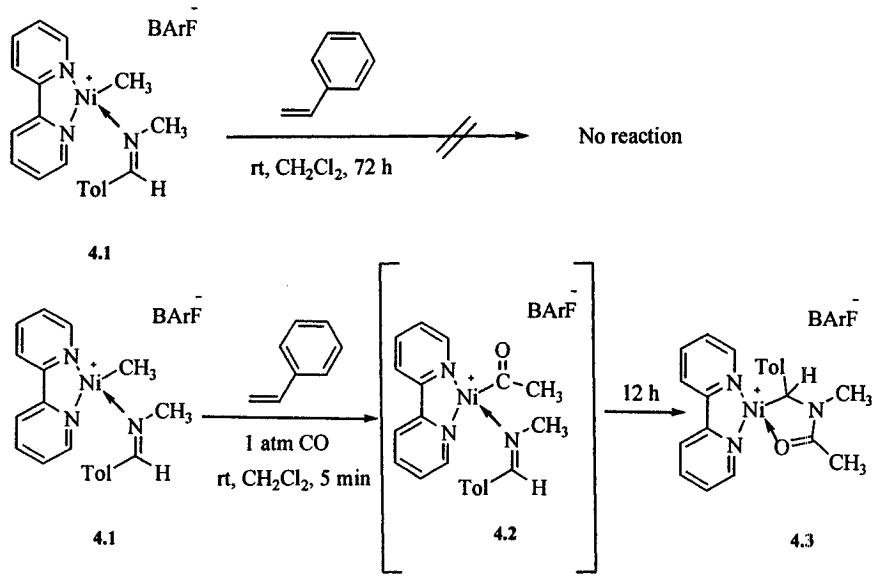
We have previously demonstrated that imines bound to nickel complexes of the type **4.1** (BArf = $B(3,5\text{-}C_6H_3(CF_3)_2)_4$, Tol = $p\text{-}C_6H_4CH_3$) do not undergo insertion directly into the nickel-methyl bond even at elevated temperature.[8] However, exposure of these complexes to 1 atm of carbon monoxide leads to the formation of the analogous Ni-acyl complex **4.2**, which can undergo imine migratory insertion into the Ni-$COCH_3$ bond to generate the stable metallacycle **4.3**. The kinetic barrier to this imine insertion ($\Delta G^{\ddagger}$ = 23 kcal/mol at 40 °C)[7] is significantly higher than that previously reported for alkene insertions into analogous nickel-carbon bonds (e.g. $\Delta G^{\ddagger}$ = 14 kcal/mol at -40°C for styrene).[9] This rate difference, as well as the prerequiste CO insertion, led us to question the ability of imines to undergo competitive insertion in the presence of olefins. However, migratory insertion is considered to be an intramolecular reaction from the coordinatively unsaturated substrate, and the basicity of the imine nitrogen should compete favorably with olefins for binding to the nickel center.



Scheme 4.1 Sequential insertion of CO and imine into nickel-alkyl bonds.

As an initial probe of this competition, 2 equivalents of styrene were added to the nickel-imine complex **4.1** (Eq. 4.1). While the analogous non-imine coordinated Ni-alkyl complexes are known to mediate the insertion of α-olefins very rapidly at ambient temperature,[9,10] complex **4.1** did not react with styrene after several days at room temperature, and no evidence for decomposition of complex **4.1** or olefin consumption was observed. This lack of reactivity and no visible signal broadening in the ^{1}H NMR spectrum, suggested that imine was remaining bound to the metal center during the reaction, effectively blocking olefin coordination for insertion. This is notable since previous studies have determined that the imines in these nickel complexes are relatively labile, and could be rapidly replaced by other nitrogen donors (e.g. other imines and CH_3CN) at room temperature.[8]

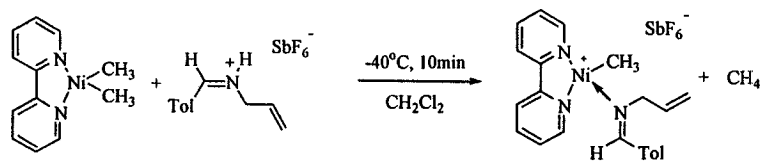
In an effort to initiate imine dissociation and subsequent insertion, carbon monoxide was added to the reaction mixture. In contrast to the above, this led to the rapid insertion of carbon monoxide to form **4.2**, which is subsequently converted quantitatively to the imine insertion product **4.3**, with no evidence for styrene insertion observed.



Equation 4.1 Competitive insertion of CO and imine into nickel-alkyl bonds in the presence of styrene.

The observation that the trans-disubstituted imine could undergo preferential insertion relative to an α-olefin into the nickel-carbon bond was somewhat surprising, given their typical relative insertion rates, though consistent with the stronger binding of the imine to nickel. We rationalized that introducing a tethered α-olefin into the system, which could undergo associative ligand substitution more readily than a free alkene, might allow for competitive insertion with imines. The alkene tethered imine complex can be prepared by the addition of the iminium salt $[CH_2{=}CHCH_2(H)N{=}CH(p\text{-}C_6H_4CH_3)]^+SbF_6^-$ (**4.5**) to $(bipy)Ni(CH_3)_2$ (**4.4**) (bipy =2,2'-bipyridyl) in CH_2Cl_2, which affords the deep red

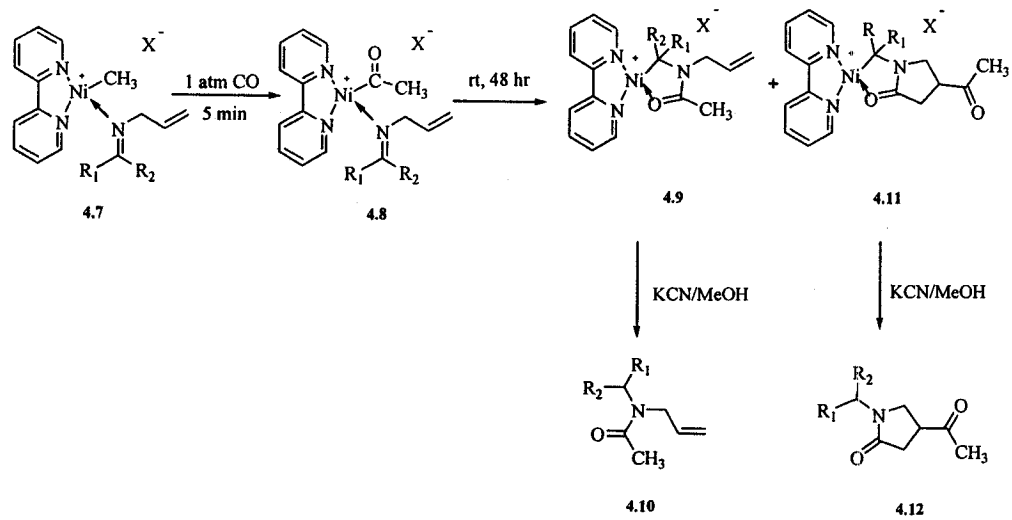
cationic complex **4.6**, along with the rapid liberation of methane. No evidence for olefin coordination or insertion was observed in **4.6**, and the ^{1}H and ^{13}C NMR spectra display downfield shifts in the imine resonances consistent with η^{1}-binding of the imine through the lone pair on nitrogen.[11] These complexes are stable at room temperature in solution, and can be isolated as solids under nitrogen. These species are however, thermally unstable, and upon heating undergo complex decomposition during which the signals in ^{1}H NMR associated with the olefin are consumed.



Scheme 4.2. Formation of imine bound cationic nickel species.

The addition of 1 atm of carbon monoxide to **4.6** in CD_2Cl_2 and monitoring the reaction by ^{1}H NMR shows the formation of the Ni-acyl complex **4.7** after 5 minutes ($NiCOCH_3$ at 2.60 ppm). This CO insertion initiates the competitive insertion of the olefin or imine unit into the newly generated nickel-acyl bond. After 48 hours, the product of imine insertion into the Ni-acyl bond **4.9,** as well as the bicyclic complex **4.11** (as a mixture of diastereomers) are observed in a 1:1 ratio. **4.11** represents the unusual product of the insertion cascade illustrated in Scheme 4.4, where olefin insertion into the Ni-acyl bond leads to the formation of a new Ni-alkyl bond, which can undergo insertion of a

second equivalent of CO, followed by cyclization via imine insertion. Consistent with our previous observations, the metal chelated amides are inert to further insertion. The addition of a KCN/MeOH solution readily cleaves the organic fragments from the metal center, affording the hydroacylated imine **4.10** and the lactam **4.12** in 41% and 41% yield, respectively.

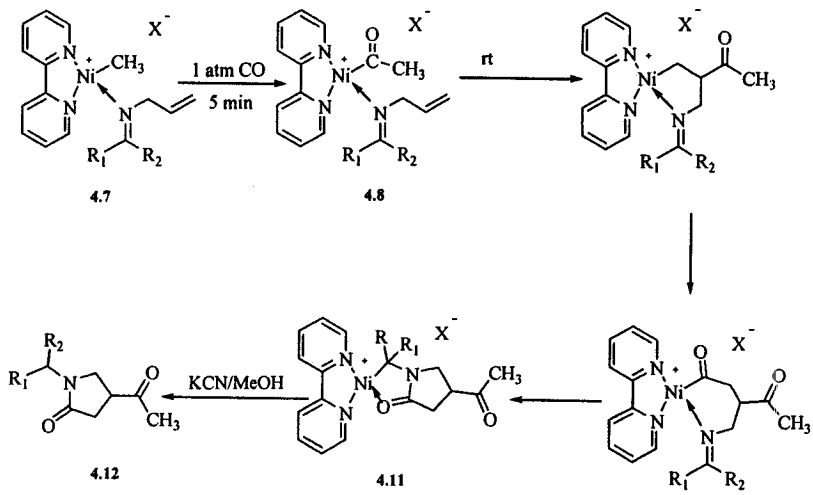


4.7 4.8 4.9 4.11 4.10 4.12

Scheme 4.3. Products of competitive insertion with CO and olefin tethered imines.

Carbon monoxide appears to play a critical role in this reaction as both an insertion monomer, and an initiator for imine and alkene insertion. As was previously demonstrated, imine insertion requires the formation of a nickel acyl ligand to be thermodynamically viable. The reason for alkene insertion occurring

only after CO insertion is less clear, though it may be due to the olefin being able to compete more favorably with imine for coordination to the Ni-acyl complex, perhaps by CO behaving as a ligand to initiate an associative exchange process. While no evidence for alkene coordination is observed, given the much faster rates of alkene insertion, even a small equilibrium should allow for it to compete with imine.



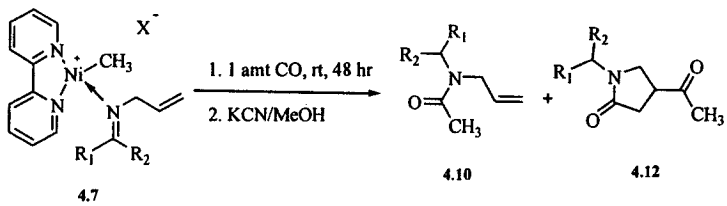
Scheme 4.4 Postulated insertion pathway for olefin tethered imines.

On the basis of this analysis, it was rationalized that modifying the ability of the imine to bind to the metal center should provide some degree of control over the relative insertion propensity of olefin and imine. For example, the use of electron-withdrawing substituents on the imine reduces its ability to bind to the metal center, and favors cyclization by initial olefin insertion to form product **4.12** (Table 1, entry b). Conversely, more electron rich imines favored the formation of the imine insertion product **4.10** (Table 1, entry c). The ratio of products is also affected by the ligands on the metal center, where increasing electron density

on the ligand (Table 1, entry d and e) favored lactam formation. The latter may result from the more electron rich metal center favoring coordination to the π-back bonding of the alkene. Use of the harder tetramethyethylenediamine yielded only the product of direct imine insertion (Table 1, entry f).

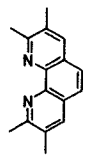
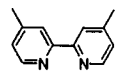
Product selectivity also exhibits strong steric trends. Not surprisingly, use of the more sterically encumbered trisubstituted imines derived from acetophenone and benzophenone greatly reduced its ability to compete for insertion with the alkene (Table 1, entry g and h). Nevertheless, these imines undergo intramolecular insertion at room temperature to form the lactam in good yield.

Table 4.1 Steric and electronic effects on competitive insertion



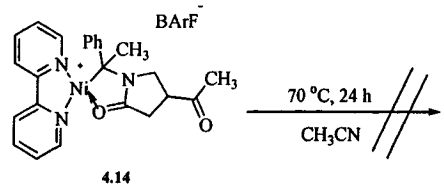
4.7 4.10 4.12

Entry	R^1	R^2	Ligand	4.10	4.12
a	H	p-$C_6H_4CH_3$	bipy	41%	41%
b	H	p-$C_6H_4CF_3$	bipy	--	78%
c	H	p-$C_6H_4OCH_3$	bipy	61%	21%

d	H	p-$C_6H_4CH_3$		10%	70%
e	H	p-$C_6H_4CH_3$		10%	70%
f	H	p-$C_6H_4CH_3$		93%	--
g	CH_3	Ph	bipy	--	75%
h	Ph	Ph	bipy	--	77%

[a] 0.85 mmol (bipy)Ni(Me)$_2$ 0.85 mmol BArF iminium salt, 1 atm CO, for 48 h at rt in CH_2Cl_2 bipy = 2,2'-bipyridyl.

While β-hydride elimination is often the final step in many insertion based cascade reactions, these metallacycles appear to be particularly resistant to further reaction even upon prolonged heating (Scheme 4.5).[13] This is presumably due to the restricted rotation induced by tight chelation to the amide oxygen, which may prevent the β-hydrogens from adopting the syn-orientation required for elimination to occur.[14]

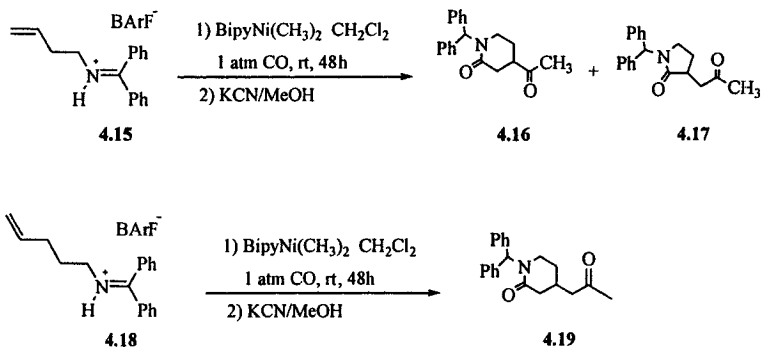


4.14

Scheme 4.5 Inability of complex **4.14** to undergo β-hydride elimination

Control over the relative rates of insertion provided an unusual route to synthesize substituted lactams using four distinct components (CO, olefin, CO,

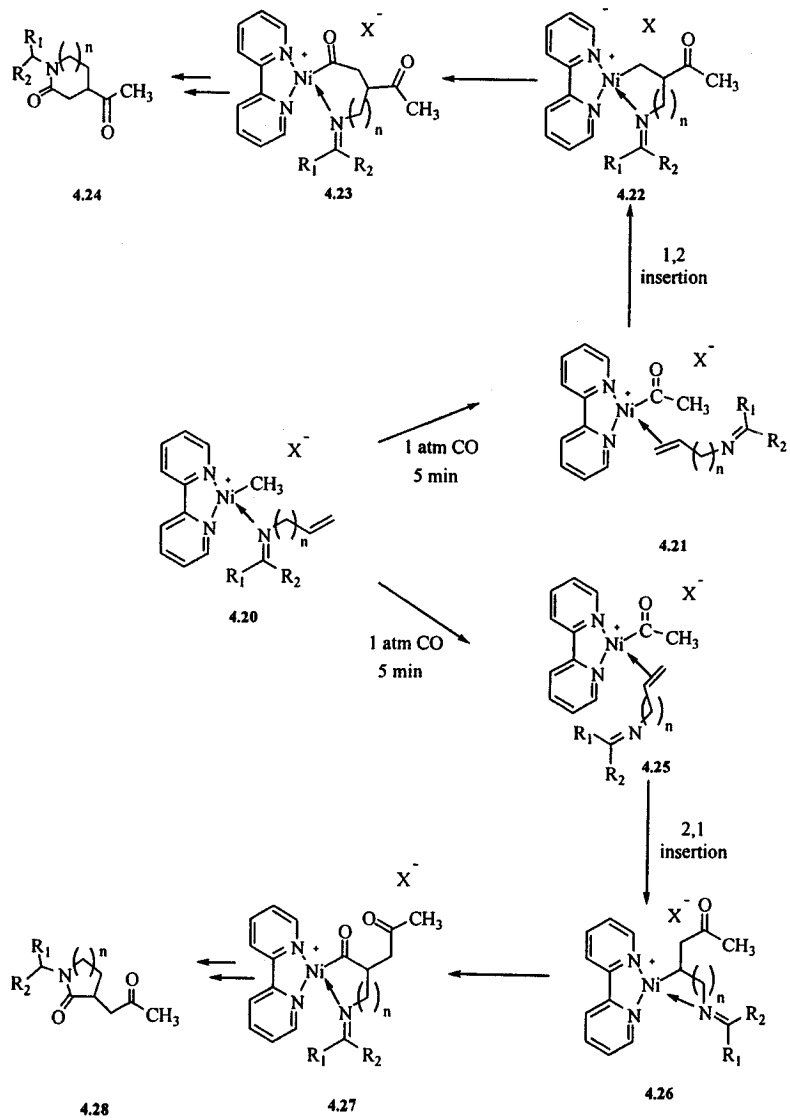
and imine). In an effort to further probe the generality of this insertion cascade, we have investigated the potential for generating larger ring systems. When the tether length was increased by one carbon, the expected six membered lactam (**4.16**) was formed in only 20% yield. The major product of the reaction (formed in 60% yield) was the five membered exo-cyclization product (**4.17**). Extension of the tether to 3 methylene units provided the six membered lactam (**4.19**) with almost complete selectivity (72% yield) and very little (<5%) of the seven membered lactam was observed.



Scheme 4.6 Synthesis of substituted lactams

The change in regioselectivity for the olefin insertion step appears to be directly related to the length of the tether, though the exact nature of the directing influences remain unclear. The *N*-allyl substituted imines show complete selectivity for the sterically less congested 1,2 insertion product. This selectivity may be a result of the sterically bulky imine unit directing the orientation of the initial olefin coordination prior to insertion. As the length of the tether is increased the steric interactions at the metal center should become less pronounced, and the selectivity reverts back to the favored 2,1 insertion products

(Scheme 4.7) more commonly found in systems bearing ligands with smaller bite angles, (e.g. 2,2'-bipyridyl).[15] While the selectivity of the olefin was reversed at longer tether lengths, the regiochemistry of imine insertion remained unchanged. In all cases, insertion occurs such that amide bond formation is conserved regardless of the regiochemistry of the olefin insertion or the sterics about the imine.



Scheme 4.7 Postulated insertion pathway for 1,2 and 2,1 insertion products

4.2 Conclusions

Overall, these provide the first examination of the relative insertion propensity of imines and alkenes under competitive conditions. In general, while the rate of imine insertion into nickel-carbon bonds is slow, this does not prevent them from competing for insertion into Ni-acyl bonds with α-olefins. The relative insertion propensity shows clear steric and electronic effects, and indicates that the superior coordinating ability of imines allows them to compete for insertion, despite the faster insertion rates of α-olefins. These effects can be used to direct the reaction towards either imine hydroacylation or cyclization to form the lactam. The latter has been used to design a novel nickel mediated one-pot insertion cascade of CO, olefin, a second unit of CO, and imine, to synthesize 5 and 6 membered lactams in good yield under mild conditions. Further investigation into the relative insertion propensity of imines with other types of unsaturated monomers, as well as studies directed towards the coupling of these cyclizations into catalytic reactions (e.g. cross-coupling), should further expand the scope and utility of this chemistry.

4.3 Experimental

General

Unless otherwise noted, all manipulations were carried out under an inert atmosphere in a Vacuum Atmosphere 553-2 drybox or using standard Schlenk or vacuum line techniques. NMR spectra were obtained on 300MHz and 400MHz Varian machine. IR spectra were obtained on a Bruker IFS-48 spectrometer.

Unless otherwise stated, all reagents were purchased from commercial sources and used without further purification. Liquids were freeze-pump-thawed three times to de-gas before use. Diethyl ether was distilled from sodium benzophenone. Pentane, methylene chloride and chlorobenzene were distilled from CaH_2. Deuterated solvents were dried as their protonated analogues, but were vacuum transferred from the drying agent. UHP grade carbon monoxide was obtained from Matheson. Imines were prepared by reaction of the aldehyde and amine in THF at room temperature over magnesium sulfate. Benzophenone derived imines were prepared by reacting benzophenone imine with the appropriate HCl salt of the amine at room temperature overnight in methylene chloride. The solution was then filtered and the solvent removed under vacuum to give the desired imine as a colorless oil. (bipy)$NiMe_2$ was prepared via literature procedure.[16] Iminium salts were prepared via addition of 1.1 equiv. of anhydrous HCl in diethyl ether to the appropriate imine and pumped to dryness, 1 equiv. of the desired counterion salt (i.e. $AgSbF_6$, NaBArf[17]) was added in CH_2Cl_2 and stirred for 4hrs. The precipitate was filtered off and the filtrate pumped to dryness and used without further purification.

General Procedure for the Cyclocarbonylation of Imines

(bipy)$NiMe_2$ (200 mg, 0.846 mmol) was dissolved in 10 ml of dry methylene chloride to give an intense blue-green solution. 1 equiv. of iminum salt was dissolved in an additional 10 mL of methylene chloride and added dropwise to a stirring solution of (bipy)$NiMe_2$. The solution rapidly turns a deep red color near the end of the addition to provide the cationic nickel complex. The addition is also accompanied by the evolution of methane. The solution was then transferred to a 300 mL bomb, frozen in a liquid nitrogen bath, and the atmosphere evacuated and replaced with 1 atm of carbon monoxide gas. The mixture is then allowed to warm to room temperature and stirred for 48 h. The organic products are then cleaved from the metal center by addition of a saturated solution of KCN/MeOH. This is accompanied by a rapid color change from deep red to pale yellow. The solvent is removed and the residue dissolved in methylene chloride, filtered through celite and the solvent removed again. The resulting oil is then dissolved in ethyl acetate, washed twice with 10% HCl solution, and purified by silica gel column chromatography. The products were identified by comparison of spectral data with those of the authentic materials where known (**4.12g**)[18], as well as spectral data [IR, NMR (^1H, ^{13}C)].

Procedure for the Synthesis of [(bipy)Ni(CH_3)(CH_2=$CHCH_2$N=(H)Tol]$^+SbF_6^-$

A typical procedure for the synthesis of complexes **4.6** is as follows. (bipy)Ni(CH_3)$_2$ (75 mg, 0.307 mmol) was suspended in THF (10 mL) and cooled to -40 °C to give an intense dark green solution. In a separate vessel [CH_2=$CHCH_2$(H)N=CH(*p*-$C_6H_4CH_3$)]$^+SbF_6^-$ (124 mg, 0.307 mmol) was dissolved in THF (10 mL) and cooled to –40 °C. The iminium salt was then added to the rapidly stirring solution of (bipy)Ni(CH_3)$_2$ over 3 minutes via pipette. Near the end of the addition the dark green solution changes to a deep red color. The solution is cooled to –40°C for 30 minutes and filtered through celite, and recrystallized from diethyl ether (50 mL) at –40 °C. After twelve hours the clear solvent mixture was decanted, the solid residue washed with pentane (3 x 5 mL), and then dried under vacuum to produce an orange powder (112 mg, 64% yield)

[(bipy)Ni(CH_3)(CH_2=$CHCH_2$N=(H)Tol]$^+SbF_6^-$ (4.6)

Synthesis of compound **4.6** was carried out via the general procedure given above and isolated for analysis by re-crystallization from dichloromethane and pentane.

Yield 66% isolated, yellow powder

^{1}H-NMR (400 MHz, CD_2Cl_2): δ 9.39 (d, *J* = 11.6 Hz, 2H), 8.40-8.35 (m, 2H), 8.15-8.01 (m, 4H), 7.63-7.54 (m, 2H), 7.41-7.30 (m, 3H), 6.50-6.36 (m, 1H), 5.61-5.54 (m, 1H), 5.36-5.30 (m, 1H), 4.65 (d, *J* = 7.2 Hz, 2H), 2.38 (s, 3H), 0.09 (s, 3H).

^{13}C NMR (400 MHz, CD_2Cl_2): δ 169.1, 157.2, 156.4, 153.1, 149.8, 147.1, 146.1, 141.1, 136.6, 134.0, 129.3, 128.2, 127.7, 127.2, 123.4, 122.5, 115.5, 63.5, 21.4, -1.5.

Analysis. Calculated for $C_{22}H_{24}F_6N_3NiSb$ (C 42.29%, H 3.87%, N 6.72%) Found (C 41.97%, H 3.77%, N 6.55%).

N-Allyl-N-(4-methyl-benzyl)-acetamide (4.10a):

Yield: 41% isolated, oil

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.20-7.00 (m, 4H), 5.81-5.65 (m, 1H), 5.24-5.04 (m, 2H), 4.75 (s, 2H, major), 4.43 (s, 2H, minor), 3.98 (d, 2H, J = 7.6 Hz, minor), 3.79 (d, 2H, J = 7.6 Hz, major), 2.38 (s, 3H, minor), 2.31 (s, 3H, major), 2.38 (s, 3H, minor), 2.36 (s, 3H, major).

^{13}C NMR (400 MHz, $CDCl_3$): δ 171.1, 169.8, 137.5, 137.3, 134.7, 133.2, 132.6, 129.8, 129.5, 128.5, 126.5, 117.7, 117.0, 50.8, 49.9, 48.0, 47.9, 21.8, 21.6, 21.4, 21.3.

IR (KBr): ν_{CO}: 1650 cm^{-1}

Analysis. Calculated for $C_{13}H_{17}NO$ (C 76.81%, H 8.43%, N 6.89%) Found (C 76.41%, H 8.72%, N 7.23%).

4-Acetyl-1-(4-methyl-benzyl)-pyrrolidin-2-one (4.12a):

Yield: 41% isolated, oil

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.20-7.02 (m, 4H), 4.39 (dd, J = 14.6 Hz, 8.3 Hz, 2H), 3.50-3.12 (m, 3H), 2.62 (d, J = 9.8 Hz, 2H), 2.34 (s, 3H), 2.18 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$): δ 206.1, 172.2, 137.7, 133.1, 129.7, 128.4, 47.3, 46.5, 43.5, 33.4, 28.6, 21.3.

IR (KBr): ν_{CO}: 1699 cm^{-1}

Analysis. Calculated for $C_{14}H_{17}NO_2$ (C 72.70%, H 7.41%, N 6.06%) Found (C 72.44%, H 7.85%, N 6.39%).

4-Acetyl-1-(4-trifluoromethyl-benzyl)-pyrrolidin-2-one (4.12b):

Yield: 78% isolated, oil

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.57 (d, 2H, 8.4 Hz), 7.35 (d, J = 8.4 Hz, 2H), 4.42 (d, J = 11.4 Hz, 2H), 3.45 (m, 1H), 3.40-3.20 (m, 2H), 2.63 (m, 2H), 2.19 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$): δ 206.0, 172.5, 140.3, 128.5, 128.4, 125.9, 125.8, 47.4, 46.3, 43.3, 33.2, 28.7

IR (KBr): ν_{CO}: 1699 cm^{-1}

Analysis. Calculated for $C_{14}H_{14}F_3NO_2$ (C 58.95%, H 4.95%, N 4.91%) Found (C 58.58%, H 5.21%, N 5.18%).

N-Allyl-N-(4-methoxy-benzyl)-acetamide (4.10c):

Yield: 61% isolated, oil

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.35 (d, J = 8.8 Hz, 2H, major), 7.18 (d, J = 8.8 Hz, 2H, minor), 6.78 (d, J = 9.6 Hz, 2H, minor), 6.62 (d, J = 9.6 Hz, 2H, major), 5.81-5.61 (m, 1H), 5.24-5.07 (m, 2H), 4.50 (s, 2H, major), 4.41 (s, 2H, minor), 3.96 (d, J = 5.2 Hz, 2H, minor), 3.79 (d, J = 5.2 Hz, 2H, major), 2.78 (s, 3H), 2.32 (s, 3H, minor), 2.21 (s, 3H, major)

^{13}C NMR (400 MHz, $CDCl_3$ 65 °C): δ 171.1, 171.0, 159.2, 159.1, 133.2, 132.7, 129.9, 128.7, 127.8, 127.5, 117.6, 116.9, 114.5, 114.1, 55.5, 55.4, 50.6, 49.9, 47.7, 47.6, 21.9, 21.7

IR (KBr): ν_{CO}: 1650 cm^{-1}

Analysis. Calculated for $C_{13}H_{17}NO_2$ (C 71.21%, H 7.81%, N 6.39%) Found (C 70.71%, H 8.15%, N 6.29%).

4-Acetyl-1-(4-methoxy-benzyl)-pyrrolidin-2-one (4.12c):

Yield: 21% isolated, oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.18 (d, J = 8.4 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.44 (d, 1H, J = 11.2 Hz, 2H), 4.32 (d, J = 11.2 Hz, 1H), 3.79 (s, 3H), 3.44 (m, 1H), 3.35 (m, 1H), 3.25 (m, 1H), 2.66 (m, 2H), 2.16 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$): δ 206.15, 171.1, 159.4, 129.7, 128.1, 114.3, 55.5, 47.3, 46.2, 43.5, 33.4, 28.7

IR (KBr): ν_{CO}: 1699 cm^{-1}

Analysis. Calculated for $C_{14}H_{17}NO_3$ (C 68.00%, H 6.93%, N 5.66%) Found (C 67.57%, H 7.15%, N 5.29%).

4-Acetyl-1-benzhydryl-pyrrolidin-2-one (4.12h):

Yield: 77% isolated, oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.20 (m, 6H), 7.20-7.08 (m, 4H), 6.57 (s, 1H), m, 3.45-3.35 (m, 1H), 3.33-3.19 (m, 2H), 2.71 (d, J = 11.6 Hz, 2H), 2.14 (s, 3H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 206.3, 172.5, 138.5, 138.2, 128.9, 128.8, 128.6, 128.5, 128.0, 127.9, 58.9, 45.3, 43.6, 33.5, 28.8.

IR (KBr): ν_{CO}: 1699 cm^{-1}

Analysis. Calculated for $C_{19}H_{19}NO_2$ (C 77.79%, H 6.53%, N 4.77%) Found (C 78.20%, H 7.02%, N 4.34%).

4-Acetyl-1-benzhydryl-piperidin-2-one (4.15):

Yield: 20% isolated, oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.15 (m, 11H), 3.19 (m, 1H), 3.00-2.81 (m, 2H), 2.69 (m, 2H), 2.19 (s, 3H), 2.08 (m, 1H), 1.85 (m, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 208.3, 168.7, 138.7, 138.4, 129.7, 128.7, 128.2, 128.0, 127.5, 60.0, 127.5, 45.7, 42.8, 33.9, 28.3, 25.3.

IR (KBr): ν_{CO}: 1699 cm^{-1}

Analysis. Calculated for $C_{20}H_{21}NO_2$ (C 78.15%, H 6.89%, N 4.56%) Found (C 78.27%, H 7.20%, N 4.34%).

1-Benzhydryl-3-(2-oxo-propyl)-pyrrolidin-2-one (4.16):

Yield: 60% isolated, oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.20 (m, 6H), 7.20-7.14 (m, H), 6.58 (s, 1H), 3.23-3.02 (m, 3H), 2.90 (m, 1H), 2.59 (m, 1H), 2.35 (m, 1H), 2.19 (s, 3H), 1.7 (m, 1H).

^{13}C NMR (400 MHz, $CDCl_3$ 65 °C): δ 207.1, 176.0, 138.8, 138.7, 129.1, 128.8, 128.7, 128.2, 127.9, 127.6, 59.1, 44.9, 42.9, 38.2, 30.4, 25.8.

IR (KBr): ν_{CO}: 1699 cm^{-1}

Analysis. Calculated for $C_{20}H_{21}NO_2$ (C 78.15%, H 6.89%, N 4.56%) Found (C 78.27%, H 7.20%, N 4.43%).

1-Benzhydryl-3-(2-oxo-propyl)-piperidin one (4.18):

Yield: 72% isolated, oil.

^{1}H-NMR (400 MHz, $CDCl_3$): δ 7.40-7.10 (m, 11H), 3.18-2.84 (m, 4H), 2.65 (m, 1H), 2.19 (s, 3H), 1.95 (m, 1H), 1.80 (m, 2H), 1.58 (m, 1H).

^{13}C NMR (400 MHz, $CDCl_3$): δ 207.7, 172.4, 139.1, 129.5, 128.9, 128.7, 128.6, 128.5, 127.6, 127.5, 60.3, 45.7, 44.4, 38.4, 30.6, 27.1, 22.7.

IR (KBr): ν_{CO}: 1699 cm^{-1}

Analysis. Calculated for $C_{21}H_{23}NO_2$ (C 78.47%, H 7.21%, N 4.36%) Found (C 78.11%, H 7.63%, N 4.22%).

4.4 References

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(11) complex **4.6** ^{1}H NMR (CD_2Cl_2) δ 8.40 (s, =C(H)Tol, ^{13}C NMR δ 169.1 (s, =*C*(H)Tol). Free imine: ^{1}H NMR (CD_2Cl_2) δ 8.27(s, =C(H)Tol, ^{13}C NMR δ 161.4 (s, =*C*(H)Tol).

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CHAPTER FIVE

Imines in Stille-Type Cross-Coulping Reactions: A Multicomponent Synthesis of α-Substituted Amides.

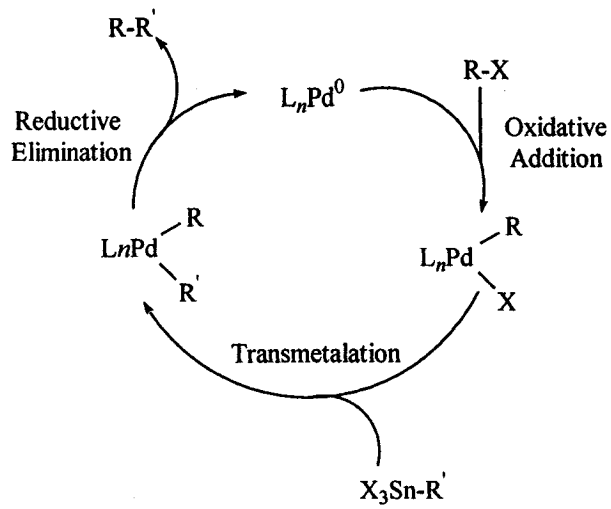
5.0 Preface

The investigations described in chapter 3 into the reactivity of the amide–chelated nickel complexes, indicated that these complexes were capable of undergoing transmetallation with organotin reagents to form amides. This chapter will describe the further development of this reaction with the analogous palladium complexes, generated by the oxidative addition of N-acyl iminium salts to Pd^0. This has been developed into a novel route to use imines in Stille-type cross coupling reactions. Overall, this provides a palladium catalyzed multicomponent coupling route to prepare α-substituted amides from imines, acid chlorides and organotin reagents.

5.1 Introduction

Palladium-catalyzed cross-coupling processes such as the Stille reaction have emerged as some of the more important methods for the construction of carbon–carbon bonds.[1-4] A useful feature of the Stille coupling is its use of non polar organostannanes, rather than nucleophilic agents, in reactions with organic halides. Organotin reagents are generally air and

moisture-stable, and they can be prepared with a diverse range of transferable substituents, many of which are less readily formed, or unavailable, within nucleophilic reagents (e.g. Grignard, organozinc and organolithium reagents). In addition, the lower reactivity of organotin reagents makes them easily handled and compatible with most functional groups, allowing their use on substrates without prior functional-group protection.[1] While Stille couplings with organotin reagents have been performed extensively with electrophilic compounds RX (organic halides and triflates, and related σ-bonded substrates),[2] one traditional limitation of this process is its inability to mediate similar reactions with a second important class of electrophiles: multiply bonded substrates $R_2C{=}X$ such as imines.[5] Carbon–carbon bond formation with imines is typically performed with nucleophilic agents and provides a useful method to construct α-substituted amines.[6] However, these reactions lack many of the features detailed above in the complementary Stille cross-coupling reactions. This limitation is of relevance, since α-substituted amines and amides are among the more common units in biologically relevant molecules, including α-amino acids, peptides, peptidomimetics, and β-lactam antibiotics.[7] We report below the development of a method to utilize multiply bonded substrates such as imines in cross-coupling reactions. This provides a palladium-catalyzed alternative to nucleophilic chemistry for the preparation of α-substituted amides, protected amines, and amino acid derivatives by a Stille-type coupling of imines with organotin reagents.[8]

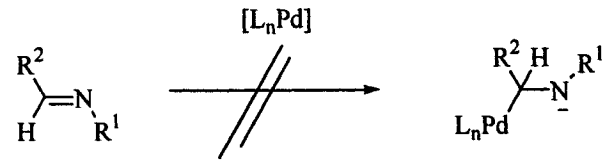


Scheme 5.1 General mechanism of Stille couplings.

5.2 Results and Discussion

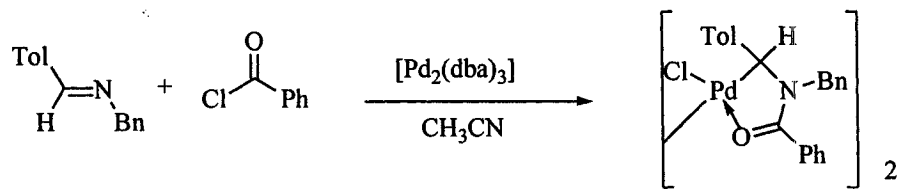
Analysis of a generalized mechanism for palladium catalyzed cross-coupling reactions (Scheme 5.1) reveals why imines and related substrates (aldehydes and ketones) have remained inappropriate as cross-coupling partners: imines have no demonstrated propensity to add directly to palladium to generate a Pd-C bond. This is likely due to the lack of stabilization of either the nitrogen anion or palladium cation shown in (Equation 5.1). This analysis suggests, however, that the addition of substrates that could neutralize the nitrogen anionic charge might provide a route to activate imines towards this transformation.[9] Indeed, we have recently observed that imines can undergo a catalyzed coupling with carbon monoxide and acid chlorides to generate 1,3-oxazolium-5-oxides (Münchnones),[10] a process that was postulated to proceed

by formation of palladium-chelated amides.[11] This indicates that the addition of acid chlorides to imines can convert the latter into a substrate capable of oxidative addition.[12,13]



5.1 **5.2**

Equation 5.1 Unfavorable oxidative addition of imines with palladium.

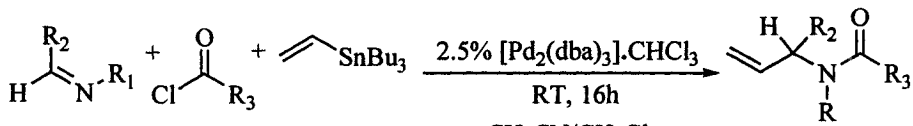


5.3 **5.4** **5.5**

Equation 5.2 Pd-C bond formation of N-acyl iminium salts with palladium.

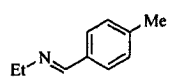
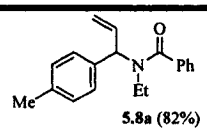
Stoichiometric control experiments (Eq. 5.2), where the mixing of Tol(H)C=NBn (Tol=4-$CH_3C_6H_4$), PhCOCl, and $[Pd_2(dba)_3]\cdot CHCl_3$ (dba=dibenzylideneacetone) leads to the quantitative formation of chelated product **5.5**. Notably, the ^1H NMR spectrum reveals reduction of the imine C=N bond upon addition to palladium (δ=5.06 ppm (s, C*H*Tol)), and ^{13}C

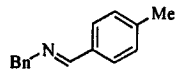
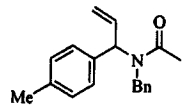
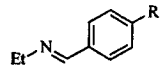
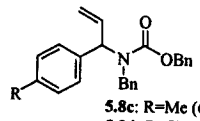
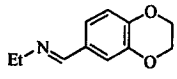
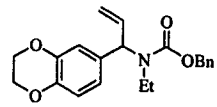
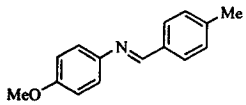
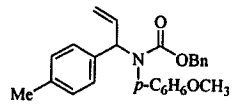
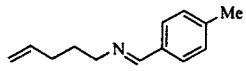
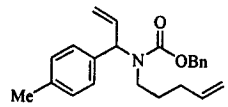
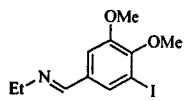
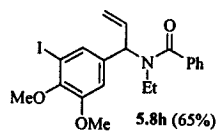
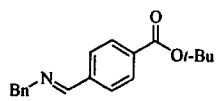
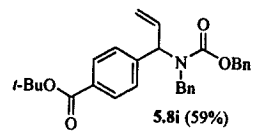
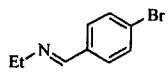
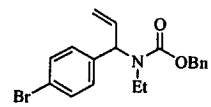
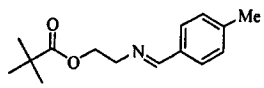
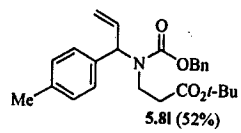
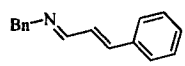
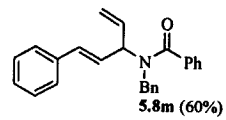
NMR data indicates that amide chelation has occurred to form a five-membered metallacycle (δ= 182.3 ppm (*C*OPh)).[14,15] Mass spectrometric data is consistent with the dimeric structure of **5.5**, likely formed through bridging chloro ligands to generate a pseudo-square-planar 16-electron palladium complex. The oxidative addition chemistry in Equation 5.2 suggested that this process might also be employed with imines in palladium-catalyzed carbon-carbon bond-forming reactions, provided the palladium–carbon-bonded intermediate **5.5** can be intercepted with transmetalation. This does turn out to be the case. The reaction of a solution of Tol(H)C=NEt, PhCOCl, and $Bu_3Sn(CH{=}CH_2)$ with 2.5 mol% $[Pd_2(dba)_3]\cdot CHCl_3$ results in the rapid disappearance of starting materials at ambient temperature. Workup of the reaction solution reveals that the clean coupling of the three reactants has occurred to form the vinyl-substituted amide **5.8a** in 82% yield (Table 5.1, entry 1).

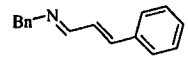
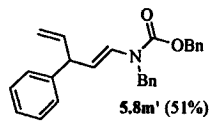


5.1 **5.6** **5.7** **5.8**

Table 5.1 Palladium-catalyzed synthesis of amides[a]

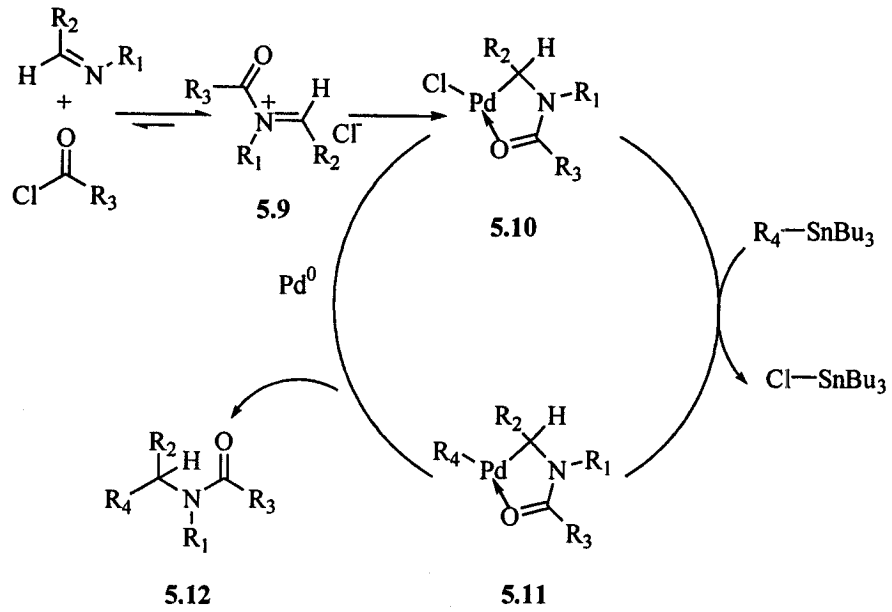
Entry	Imine	Acid Chloride	Product (yield)
1		PhCOCl	 **5.8a (82%)**

2		MeCOCl	 **5.8b** (78%)
3		BnOCOCl	 **5.8c**: R=Me (68%) **5.8d**: R=SMe (73%)
4		BnOCOCl	 **5.8e** (70%)
5		BnOCOCl	 **5.8f** (68%)
6		BnOCOCl	 **5.8g** (65%)
7		PhCOCl	 **5.8h** (65%)
8		BnOCOCl	 **5.8i** (59%)
9		BnOCOCl	 **5.8k** (62%)
10		BnOCOCl	 **5.8l** (52%)
11		PhCOCl	 **5.8m** (60%)

12[b]		BnOCOCl	 5.8m' (51%)

[a] Reaction conditions: 0.75 mmol imine, 0.75 mmol acid chloride. 0.75 mmol tributylvinyltin, 2.5 mol% $[Pd_2(dba_3)]\cdot CHCl_3$ for 16 h in 20 mL CH_3CN/CH_2Cl_2 (1:1). [b] in the presence of 0.75 mmol Bu_4NBr.

This palladium-catalyzed three-component coupling occurs under mild conditions and with high selectivity, considering that acid chlorides themselves are known to undergo cross-coupling reactions.[2] In examining the plausible mechanism (Scheme 5.2), we can attribute this selectivity to the equilibrium reaction of imine and acid chloride strongly favoring N-acyl iminium salt/α-chloroamide **5.9** formation, which undergoes selective addition to Pd(0).[13] This is facilitated by the ability of **5.9** to chelate to give **5.10**, allowing catalysis to proceed in the absence of the ligands often required to aid in oxidative addition.[2] Indeed, the addition of ligands significantly inhibits this coupling,[16] consistent with reports that suggest that an empty coordination site can facilitate transmetalation from tin.[17] As such, reaction with the organotin reagent can occur directly with the three-coordinate complex **5.10** to form **5.11**, which yields products by reductive elimination.[18] Overall, these multiple mechanistic steps create what is to our knowledge a unique method to utilize palladium-catalyzed cross-coupling chemistry to convert imines into α-substituted amides.

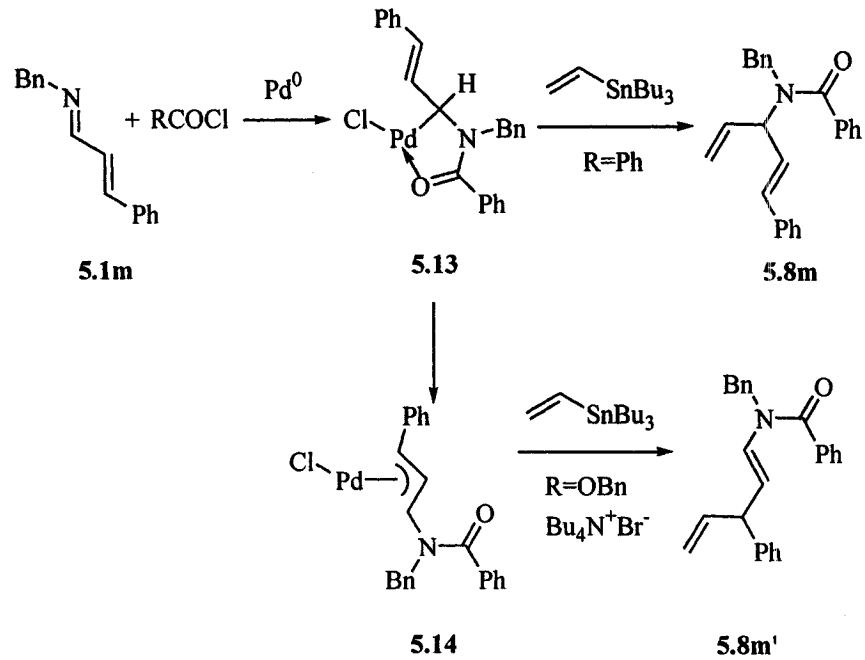


Scheme 5.2 Postulated mechanism for the palladium-catalyzed three component coupling.

Further investigation of this catalytic reaction shows it to have a good degree of generality. Thus both aryl and alkyl acid chlorides (Table 5.1, entry 2) can be employed to generate vinyl-substituted amides. Alternatively, acid chlorides can be replaced with chloroformates. This is somewhat surprising, since the iminium salt of a chloroformate does not oxidatively add to Pd(0) to form a stable product. This provides a catalytic method to convert imines directly into N-protected, α-substituted amine building blocks. As anticipated, the catalytic reaction shows tolerance to various functional groups (e.g. ethers, thioethers and esters; entries 3–5, 8, 10), although enolizable C-alkyl imines are not compatible with these coupling conditions.[19] This process is also amenable to substrates capable of undergoing other palladium-catalyzed reactions. Imines with terminal alkene substituents, which can undergo Heck

couplings with acid chlorides,[20] react exclusively at the imine carbon to form α-substituted carbamates (entry 6). Similarly, imines containing standard Stille coupling groups such as aryl bromides and electron-rich aryl iodides undergo preferential coupling as the iminium salt (entries 7 and 9). This selectivity can be attributed to the stabilizing effect of amide chelation in the product arising from oxidative addition of the iminium salt, which leads to the favored generation of **5.10** for transmetalation and coupling.

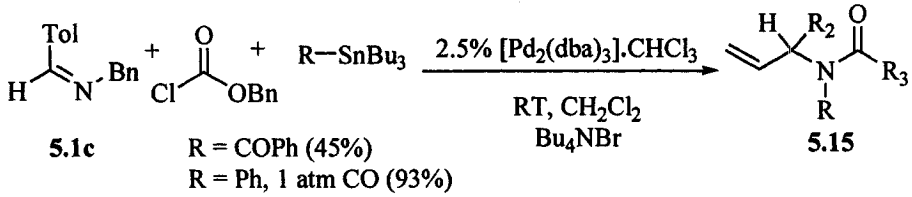
In addition to imines of aromatic aldehydes, α,β-unsaturated imines react with benzoyl chloride and tributylvinyltin to form α-substituted amides (**5.8m**, entry 11). Interestingly, replacement of the acid chloride with benzylchloroformate results in the generation of the Michael addition product **5.8m'** as well as **5.8m** (*ca.* 1:1 ratio). Based on the mechanism of this reaction, this would appear to result from the rearrangement of a chelated amide intermediate **5.13** to the π-allylic structure **5.14**, which can reductively eliminate at the remote carbon (Scheme 5.3). The addition of a weakly coordinating bromide source ($Bu_4N^+Br^-$), which can presumably accelerate an associative rearrangement mechanism relative to transmetalation,[21] results in the favored formation of the 1,4-addition product **5.8m'** (entry 12). This provides a useful catalyst-based method to control the regioselectivity of the addition to unsaturated imine substrates as opposed to nucleophilic approaches, which typically rely upon variation of the actual vinyl-transfer substrate.[22]



Scheme 5.3 Palladium-catalyzed vinylation of α,β-unsaturated imines

The use of organotin reagents also provides a route to incorporate substrates into the α-position beyond those accessible from nucleophilic sources. This is illustrated in Equation 5.3, where the palladium-catalyzed reaction of benzoyltributyltin[23] with imine and chloroformate leads to transfer of the benzoyl unit to the imine carbon and formation of **5.15**. Even more simplified, the intermediacy of Pd-C-bonded complexes suggests the possibility of incorporating insertion substrates into the overall catalytic process.[1] Thus, the catalytic coupling of Tol(H)C=NBn, BnOCOCl, and phenyltributyltin under one atmosphere of carbon monoxide yields the same product **5.15** in 51%yield.[11] Examination of the crude mixture revealed that the only starting materials present were free imine and phenyltributyltin. The addition of excess chloroformate (4 equiv) can thus be used to drive

conversion of the imine into **5.15** in 93% yield.[24] This represents a rare example of a selective four-component cross-coupling reaction, in this case from imine, chloroformate, phenyltin, and carbon monoxide, which allows for the construction of α-amido ketones. The latter are useful components for the synthesis of heterocycles[25] and as enzyme inhibitors.[26]

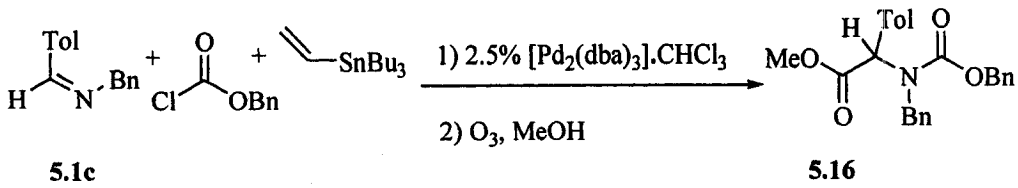


5.1c R = COPh (45%); R = Ph, 1 atm CO (93%) **5.15**

Equation 5.3 Synthesis of α-amido ketones

5.3 Conclusion

In conclusion, this study describes a convenient and general one-pot synthesis of α-substituted amides and N-protected amines by a palladium-catalyzed three-component coupling of imines, acid chlorides or chloroformates, and organotin reagents. Mechanistically, this process provides an oxidative addition/reductive elimination-based alternative to nucleophilic approaches to C-C bond formation with imines, in which the imines are activated towards addition to palladium by RCOCl.



5.1c 5.16

Equation 5.4 Synthesis of α-aryl glycine derivatives

Considering the utility of imine reduction products, as well as the generality and mild features of tin couplings, this chemistry could prove useful in the preparation of a range of α-substituted amine derivatives. One illustration of this is in Equation 5.4, where the palladium-catalyzed reaction of Tol(H)C=NBn, BnOCOCl, and tributylvinyltin followed by ozonolysis of the vinylic group under Marshall conditions[27] provides a simple two step route to diprotected α-arylglycine derivatives from airstable reagents and a commercially available catalyst.

5.4 Experimental Section

General Procedures

Unless otherwise noted, all manipulations were performed under an inert atmosphere in a vacuum atmosphere 553-2 dry box or by using standard Schlenk or vacuum line techniques. Tris(dibenzylideneacetone) dipalladium·chloroform was prepared according to literature procedures and used freshly recrystalized.[28] Carbon monoxide (99.99%) was purchased from Matheson and used as received. Imines[29] were prepared and freshly distilled

using literature procedures. All other reagents were purchased from Aldrich and used as received. Tetrahydrofuran (THF) was distilled from sodium/benzophenone ketyl under nitrogen. Acetonitrile and methylene chloride were distilled from CaH_2 under nitrogen. Deuterated solvents were dried as their protonoted analogues, but were transferred under vacuum from the drying agent, and stored over 3Å molecular sieves. ^1H, and ^{13}C NMR spectra were recorded on JEOL 270, Varian 300 and Varian 400 Spectrometers. Infrared spectra were recorded on a Nicolet Avatar Spectrometer.

Synthesis of 5.5

(*p*-$CH_3C_6H_4$)(H)C=NCH_2Ph (62.5 mg, 0.298 mmol) and benzoyl chloride (42.0 mg, 0.298 mmol) were dissolved in 10 mL of acetonitrile. $Pd_2(dba)_3{\cdot}CHCl_3$ (150.1 mg, 0.145 mmol) was added to this solution, and the mixture stirred 16h at ambient temperature. The solvent volume was reduced to 2 mL and diethyl ether (10 mL) was added and cooled to –40°C, resulting in the precipitation of the product **5.5** as a yellow solid (92% yield).

^1H NMR (CD_2Cl_2, 270 MHz): δ 7.70-7.42 (m, 5H), 7.40-7.26 (m, 3H), 7.20-7.05 (m, 4H), 7.04-6.94 (m, 2H), 5.06 (s, 1H), 4.28 (dd, 2H), 2.29 (s, 3H).

^{13}C NMR (CD_2Cl_2, 68 MHz): δ 182.3, 138.2, 136.6, 133.9, 132.3, 131.0, 130.3, 129.1, 128.7, 128.3, 128.1, 127.7, 127.5, 65.7, 52.3, 21.6.

IR (KBr): ν_{CO} : 1547 cm^{-1}.

Analysis: Calculated for $C_{22}H_{20}NOClPd$: C, 57.91; H, 4.42; N, 3.07; found: C, 58.24; H, 4.56; N, 3.01.

LRMS: Calc. for $C_{44}H_{40}N_2O_2Cl_3Pd_2$: 949.0; found: 949.4.

N-Ethyl-N-(1-p-tolyl-allyl)-benzamide (5.8a)

Yield: 82% isolated, oil

^{1}H-NMR (270 MHz, CD_3CN 80°C): δ 7.42 (m, 5H), δ 7.20 (4H, m), δ 6.25 (1H, m), δ 5.63 (broad d, 1H), δ 5.39 (d, 1H, 4Hz), δ 5.24 (d, 1H, 7Hz), δ 3.32 (q, 2H, 8Hz), δ 2.33 (s, 3H), δ 0.90 (t, 3H, 5Hz)

^{13}C NMR (68 MHz, CD_3CN 80°C): δ171.5, δ 138.1, δ 137.4, δ 136.6, δ 136.1, δ 129.1, δ 129.0, δ 128.4, δ 127.8, δ 126.2, δ 117.5, δ 62.9, δ 39.7, δ 20.0, δ 14.0

IR (KCl): ν_{CO}: 1635 cm^{-1}

HRMS. Calculated for $C_{19}H_{21}NO$: 279.16231; found: 279.16264

N-Benzyl-N-(1-p-tolyl-allyl)-acetamide (5.8b)

Yield: 78% isolated, white solid

^{1}H-NMR (270 MHz, CD_3CN, 80°C): δ 7.47-7.10 (m, 9H); 6.16-6.06(m, 1H); 6.02-5.84(s, 1H); 5.38-5.16(m, 2H); 4.60(d, 1H, 17Hz); 4.48(d, 1H, 17Hz); 2.30(s, 3H); 2.07(s, 3H).

^{13}C-NMR (68 MHz, CD_3CN, 80°C): δ 171.3; 139.4; 137.5; 136.9; 136.6; 129.3; 128.4; 128.3; 127.2; 126.8; 117.8; 63.4; 49.4; 21.9; 20.3.

IR (KBr): ν_{CO}: 1638 cm^{-1}

HRMS. Calculated for $C_{19}H_{21}NO$: 279.16231; found: 279.16206

Benzyl-(1-p-tolyl-allyl)-carbamic acid benzyl ester (5.8c)

Yield: 68% isolated, oil

^{1}H-NMR (400 MHz, $CDCl_3$ 65°C): δ 7.36-7.05 (m, 14H), δ 6.08 (m, 1H), δ 5.73 (br, 1H), δ 5.23 (d, 1H, 8Hz), δ 5.16 (d, 1H, 17 Hz), δ 5.16 (s, 2H), δ 4.55 (d, 1H, 17 Hz), δ 4.46 (d, 1H, 17Hz), δ 2.36 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$ 65°C): δ 156.6, δ 139.0, δ 137.1, δ 136.8, δ 136.5, δ 135.9, δ 129.1, δ 128.4, δ 128.2, δ 128.0, δ 127.9, δ 127.8, δ 127.5, δ 126.8, δ 118.1, δ 67.6, δ 63.1, δ 49.3, δ 21.2

IR (KBr): ν_{CO}: 1699 cm^{-1}

HRMS. Calculated for $C_{25}H_{25}NO_2$: 371.18853; found: 371.18747.

Ethyl-[1-(4-methylsulfanyl-phenyl)-allyl]-carbamic acid benzyl ester (5.8d)

Yield: 73% isolated, oil

^{1}H-NMR (400 MHz, $CDCl_3$ 65 °C): δ 7.35-7.28 (m, 5H), δ 7.22-7.16 (m, 4H), δ 6.12 (m, 1H), δ 5.73 (br, 1H), δ 5.32 (d, 1H, 8Hz), δ 5.23 (d, 1H, 17Hz), δ 5.17 (s, 2H), δ 3.25 (q, 2H, 8Hz), δ 2.48 (s, 3H), δ 0.97 (t, 3H, 9Hz)

^{13}C-NMR (101 MHz, $CDCl_3$, 65°C): δ 156.3; 137.9; 137.1; 136.9; 135.7; 128.5; 128.5; 128.0; 127.9; 127.0; 118.2; 67.4; 62.2; 40.3; 16.3; 15.2.

IR (KBr): ν_{CO}: 1699 cm^{-1}

HRMS. Calculated for $C_{20}H_{23}NO_2S$: 341.14495; found: 341.14336.

[1-(2,3-Dihydro-benzo[1,4]dioxin-6-yl)-allyl]-ethyl-carbamic acid benzyl ester (5.8e)

Yield: 70% isolated, oil

^{1}H-NMR (400 MHz, $CDCl_3$ 65°C): δ 7.40-7.25 (m, 5H), δ 6.82-6.71 (m, 3H), δ 6.09 (m, 1H), δ 5.70 (broad, 1H), δ 5.30 (d, 1H, 10Hz), δ 5.21(d, 1H, 17Hz), δ 5.17 (s, 2H), δ 4.22 (s, 4H), δ 3.23 (q, 2H, 8Hz), δ 0.96 (t, 3H, 9Hz)

^{13}C-NMR (101 MHz, CD_3CN, 20°C): δ 155.9; 143.7; 143.2; 137.6; 136.2; 133.3; 128.6; 128.0; 128.0; 120.9; 117.4; 117.2; 116.7; 66.8; 64.7; 64.6; 61.9; 40.1; 14.7

IR (KBr): ν_{CO}: 1699cm^{-1}

HRMS. Calculated for $C_{21}H_{23}NO_4$: 353.16271; found: 353.16147

(4-Methoxy-phenyl)-(1-p-tolyl-allyl)-carbamic acid benzyl ester (5.8f)

Yield: 68% isolated, oil

^{1}H-NMR (400 MHz, $CDCl_3$ 65°C): δ 7.60-7.41 (m, 3H), δ 7.20-7.08 (m, 6H), δ 6.94 (m, 2H), δ 6.76 (d, 2H), δ 6.10 (m, 1H), δ 5.91 (br, 1H), δ 5.32 (d, 1H, 17Hz), δ 5.27 (d, 1H, 8Hz), δ 5.13 (s, 2H), δ 3.78 (s, 3H), δ 2.34 (s, 3H)

^{13}C-NMR (101 MHz, $CDCl_3$, 20°C): δ 158.6; 155.8; 137.2; 137.0; 137.0; 136.1; 132.8; 130.7; 129.0; 128.3; 128.1; 127.7; 127.5; 118.2; 113.9; 67.3; 65.0; 55.6; 21.3,

IR (KBr): ν_{CO}: 1699 cm^{-1}

HRMS. Calculated for $C_{25}H_{25}NO_3$: 387.18334; found: 387.18385

Pent-4-enyl-(1-p-tolyl-allyl)-carbamic acid benzyl ester (5.8g)

Yield: 65% isolated, oil

^{1}H-NMR (400 MHz, $CDCl_3$ 65°C): δ 7.41-7.22 (5H, m), δ 7.20-7.03 (4H, m), δ 6.14 (m, 1H), δ 5.72 (br, 1H), δ 5.62 (m, 1H), δ 5.31 (d, 1H, 9Hz), δ 5.22 (d, 1H, 8Hz), δ 5.17 (s, 2H), δ 4.90 (2H, m), δ 3.18 (m, 2H), δ 2.35 (s, 3H), δ 1.89 (m, 2H), δ 1.61 (m, 1H), δ 1.38 (m, 1H)

^{13}C NMR (101 MHz, $CDCl_3$, 65°C): δ 156.4, δ 138.0, δ 137.2, δ 137.1, δ 136.8, δ 136.0, δ 129.2, δ 128.5, δ 128.0, δ 127.9, δ 127.8, δ 117.8, δ 114.8, δ 67.3, 62.5, δ 45.4, δ 31.4, δ 28.9, δ 21.3

IR (KBr): ν_{CO}: 1699 cm^{-1}

HRMS. Calculated for $C_{23}H_{27}NO_2$: 349.20418; found: 349.20450.

N-Ethyl-N-[1-(3-iodo-4,5-dimethoxy-phenyl)-allyl]-benzamide (5.8h)

Yield: 65% isolated, oil

^{1}H-NMR (400 MHz, $CDCl_3$ 65°C): δ 7.40-7.38 (m, 5H), δ 7.25 (s, 1H), δ 6.81 (s, 1H), δ 6.13 (m, 1H), δ 5.16 (br, 1H), δ 5.42 (d, 1H, 10Hz), δ 5.26 (d, 1H,

17Hz), δ 3.83 (s, 3H), δ 3.82 (s, 3H), δ 3.40 (m, 1H), δ 3.28(m, 1H), δ 1.6 (m, 3H)

^{13}C NMR (101 MHz, $CDCl_3$ 65°C): δ171.9, δ 152.7, δ 149.0, δ 137.2, δ 137.1, δ 134.8, δ 129.9, δ 129.4, δ 128.5, δ 126.4, δ 119.1, δ 113.2, δ 92.3, δ 62.5, δ 60.4, δ 56.3, δ 40.0, δ 14.7

IR (KBr): ν_{CO}: 1634 cm^{-1}

HRMS. Calculated for $C_{20}H_{22}NO_3I$: 451.06445; found: 451.06496

2,2-Dimethyl-propionic acid 4-[1-(benzyl-benzyloxycarbonyl-amino)-allyl]-phenyl ester (5.8i)

Yield: 59% isolated, oil

^{1}H-NMR (400 MHz, $CDCl_3$ 65°C): δ 7.45-7.06 (m, 12H), δ 7.96 (d, 2H), δ 6.05 (m, 1H), δ 5.71 (br, 1H), δ 5.25(d, 1H), δ 5.75 (d, 1H, 15Hz), δ 5.14 (s, 2H), δ 4.57 (d, 1H, 17Hz), δ 4.38 (d, 1H, 15Hz), δ 1.38 (s, 9H)

^{13}C NMR (101 MHz, $CDCl_3$ 65°C): δ176.7, δ 156.6, δ 150.6, δ 138.7, δ 136.8, δ 136.6, δ 135.5, δ 128.8, δ 128.3, δ 127.9, δ 127.8, δ 127.5, δ 126.9, δ 121.3, δ 118.4, δ 67.4, δ 62.7, δ 125.2, δ 49.2, δ 39.1, δ 27.1

IR (KBr): ν_{CO}: 1750 cm^{-1}, 1699 cm^{-1}

HRMS. Calculated for $C_{29}H_{31}NO_4$: 457.22531; found: 457.22297

[1-(4-Bromo-phenyl)-allyl]-ethyl-carbamic acid benzyl ester (5.8k)

Yield: 62% isolated, oil

^{1}H-NMR (400 MHz, $CDCl_3$ 65°C): δ 7.43 (d, 2H, 8Hz), δ 7.40-7.21 (m, 5H), δ 7.14 (d, 2H, 8Hz), δ 6.09 (m, 1H, 8Hz), δ 5.69 (br, 1H), δ 5.35 (d, 1H, 10Hz), δ 5.24 (d, 1H, 15Hz), δ 5.16 (s, 2H), δ 3.26 (q, 2H, 17Hz), δ 1.02 (t, 3H, 15Hz)

^{13}C NMR (101 MHz, $CDCl_3$ 65°C): δ156.1, δ 139.1, δ 136.9, δ 135.2, δ 131.5, δ 129.5, δ 128.5, δ 128.0, δ 127.9, δ 121.5, δ 118.6, δ 67.4, δ 62.2, δ 40.5, δ 15.2

IR (KBr): .CO: 1699 cm^{-1}

HRMS. Calculated for $C_{19}H_{20}NO_2Br$: 373.06774; found: 373.06736

2,2-Dimethyl-propionic acid 2-[benzyloxycarbonyl-(1-p-tolyl-allyl)-amino]-ethyl ester (5.8l)

Yield: 52% isolated, oil

^{1}H-NMR (400 MHz, $CDCl_3$ 65°C): δ 7.40-7.20 (m, 5H), δ 7.18-7.01 (m, 4H), δ 6.19 (m, 1H), δ 5.41 (br, 1H), δ 5.33 (d, 1H), δ 5.19 (d, 1H, 7Hz), δ 5.15 (s, 2H), δ 4.00-3.80 (m, 2H), δ 3.45-3.30 (m, 2H), δ 2.38 (s, 3H), δ 1.19 (s, 9H)

^{13}C NMR (101 MHz, $CDCl_3$ 65°C): δ 177.7, δ 156.0, δ 137.2, δ 137.1, δ 136.9, δ 136.1, δ 129.0, δ 128.3, δ 127.8, δ 127.7, δ 127.5, δ 117.4, δ 66.9, δ 62.7, δ 62.4, δ 44.2, δ 38.3, δ 26.4, δ 19.9

IR (KBr): ν_{CO}: 1749 cm^{-1}, 1699 cm^{-1}

HRMS. Calculated for $C_{25}H_{31}NO_4$: 409.22531; found: 409.22588

N-Benzyl-N-(3-phenyl-1-vinyl-allyl)-benzamide (5.8m)

Yield: 60% isolated, oil

^{1}H-NMR (400 MHz, CD_3CN 80°C): δ 7.58-7.20 (m, 15H), δ 6.45 (d, 1H, Hz), δ 6.30 (dd, 1H, 5Hz), δ 6.10 (m, 1H), δ 5.29-5.15 (m, 3H), δ 4.80 (d, 1H, 17Hz), δ 4.61 (d, 1H, 17Hz)

^{13}C NMR (101 MHz, CD_3CN 80°C): δ171.9, δ 139.2, δ 137.4, δ 136.8, δ 136.2, δ 132.7, δ 129.3, δ 128.5, δ 128.4, δ 128.2, δ 127.8, δ 127.5, δ 127.2, δ 126.7, δ 126.4, δ 116.8, δ 62.4, δ 47.5

IR (KBr): ν_{CO}: 1635 cm^{-1}

HRMS. Calculated for $C_{25}H_{23}NO$: 353.17796; found: 353.17712

Benzyl-(3-phenyl-penta-1,4-dienyl)-carbamic acid benzyl ester (5.8m')

Yield: 51% isolated, oil

^{1}H-NMR (400 MHz, CD_3CN 80°C): δ 7.38-6.91 (m, 15H), δ 6.01 (m, 1H), δ 5.28 (s, 2H), δ 5.40 (m, 1H), δ 5.05 (d, 1H, 17Hz), δ 4.95 (d, 1H, 17Hz), δ 4.83 (s, 2H), δ 4.09 (t, 1H, 6Hz)

^{13}C NMR (101 MHz, CD_3CN 80°C): δ154.2, δ 143.6, δ 141.2, δ 137.7, δ 136.8, δ 128.7, δ 128.5, δ 128.2, δ 128.0, δ 127.9, δ 127.8, δ 127.1, δ 126.8, δ 126.4, δ 117.1, δ 114.4, δ 113.2, δ 68.0, δ 50.1, δ 48.2

IR (KBr): ν_{CO}: 1701 cm^{-1}

HRMS. Calculated for $C_{26}H_{25}NO_2$: 383.18853; found: 383.18888

Synthesis of Benzyl-(2-oxo-2-phenyl-1-p-tolyl-ethyl)-carbamic acid benzyl ester (5.15)

(p-$CH_3C_6H_4$)(H)C=NCH_2Ph (157.5 mg, 0.75 mmol) and benzyl chloroformate (408 mg, 3.0 mmol) were dissolved in 10 mL of acetonitrile solution and stirred for 1 hour in a 50 mL reaction bomb. To this solution was added $Pd_2(dba)_3$•$CHCl_3$ (20 mg, 0.019 mmol). The solution was stirred until all the $Pd_2(dba)_3$•$CHCl_3$ was dissolved resulting in a clear yellow solution. $BrNBu_4$ (241 mg, 0.75 mmol) and tributylphenyltin (275 mg, 0.75 mmol) were dissolved in 10 mL of methylene chloride and added dropwise to the stirring yellow solution. The solution was degassed once and pressurized with CO (1 atm). The reaction mixture was left to stir at room temperature for 48 h. The solvent was evaporated in vacuo to provide a brown oil. The residue was then dissolved in 50 mL of ethyl acetate. Tributyltinchloride was removed by stirring with 25 mL of saturated KF solution, which resulted in the immediate formation of a white solid. The solution was filtered through celite and extracted three times with 50 mL water/ethyl acetate. The organic layers were combined and dried over $MgSO_4$ and the solvent removed in vacuo to provide a viscous yellow/orange oil which was chromatographed on Silica Gel 60 using hexanes/ethyl acetate as eluent.

Yield: 93% isolated, oil

^{1}H-NMR (400 MHz, $CDCl_3$ 65°C): δ 7.83 (br, 2H), δ 7.46-6.99 (m, 16H), δ 6.94 br, 2H), δ 5.14 (dd, 2H, 12Hz), δ 4.87 (d, 1H, 16Hz), δ 4.25 (d, 1H, 16Hz), δ 2.26 (s, 3H)

^{13}C NMR (101 MHz, $CDCl_3$ 65°C): δ197.2, δ 156.2, δ 138.4, δ 138.1, δ 136.6, δ 136.1, δ 132.9, δ 131.7, δ 131.2, δ 128.7, δ 128.5, δ 128.4, δ 128.0, δ 127.9, δ 127.8, δ 127.5, δ 126.9, δ 126.5, δ 67.1, δ 65.7, δ 49.1, δ 20.1

IR (KBr): ν_{CO}: 1704 cm^{-1},1699 cm-1

HRMS. Calculated for $C_{30}H_{27}NO_3$: 449.19909; found: 449.20122

(Benzyl-benzyloxycarbonyl-amino)-*p*-tolyl-acetic acid methyl ester from oxidation (5.16)

Yield: 68% isolated, oil

^1H-NMR (400 MHz, $CDCl_3$ 65°C): δ 7.38-6.91 (m, 14H), δ 5.71 (broad, 1H), δ 5.18 (dd, 2H, 5Hz), δ 4.65 (d, 1H, 17Hz), δ 4.22 (d, 1H, 17Hz), δ 3.61 (s, 3H), δ 2.31 (s, 3H)

^{13}C NMR (400 MHz, $CDCl_3$ 65°C): δ171.1, δ 156.6, δ 138.4, δ 136.1, δ 131.2, 128.7, δ 128.3, δ 128.0, δ 127.9, δ 127.8, δ 127.7, δ 127.5, δ 126.9, δ 126.5, δ 68.2, δ 63.8, δ 52.2, δ 49.6, δ 21.6

IR (KBr): ν_{CO}: 1649 cm^{-1},1699 cm^{-1}

HRMS. Calculated for $C_{25}H_{25}NO_4$: 403.17836; found: 403.17801

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CHAPTER SIX

Conclusions, Contributions to Original Knowledge, and Suggestions for Future Work

This chapter gives a brief summary of the results and conclusions presented in this thesis, as well as the contributions to original knowledge. These parallel the individual conclusions made in each chapter. Suggestions for future work are also provided.

6.0 Conclusions and Contributions to Knowledge

This body of work represents the first investigation of imine as a viable insertion substrate into nickel-carbon σ-bonds. The nickel complexes $L_2Ni(CH_3)N(R)=C(H)R'^{+}X^{-}$ with a range of substituents and counteranions have been synthesized and fully characterized. These complexes have been demonstrated to undergo the sequential insertion of carbon monoxide and imine to form the nickel-bound amide complex: $(L_2)Ni[\eta^2\text{-}CH(R')NRCOCH_3]^{+}X^{-}$. Kinetic studies demonstrated that the sequential insertion of carbon monoxide and imine occurs with a significantly lower barrier than isoelectronic palladium complexes, and provides a new and controlled route to generate nickel-bound amides. Further, a method for the cleavage of the nickel bound amide fragments has been developed which provides the product of imine hydroacylation.

Reactivity studies on these amide-bound nickel chelates show that they are generally inert towards the subsequent migratory insertion of CO, imines and olefins. These complexes are also inert towards auxiliary ligand exchange or amide de-chelation, with both mono- and bi-denate nitrogen and phosphine ligands. They do, however, show increased reactivity towards carbon monoxide in the presence of strong Lewis acids, which may weaken the amide ligand interactions with the nickel center.

Cationic nickel-imine complexes have also been found to undergo competitive insertion with imine tethered α-olefins in the presence of CO. Despite slower rates of insertion, imines are able to compete favorably for insertion with olefins. This is likely the result of the superior coordinating ability of imines, which prevents the faster rates of insertion displayed by olefins from dominating. Systems of this type were developed into the first example of a metal mediated cyclocarbonylation incorporating imine as a formal insertion substrate. This chemistry can be used to design a one-pot, nickel-mediated insertion cascade of four units (CO, olefin, a second unit of CO, and imine) to construct 5 and 6 membered lactams

Though attempts to induce subsequent insertion into the nickel carbon bond of the amide chelate $(L_2)Ni[\eta^2\text{-}CH(R')NRCOCH_3]^+X^-$ were unsuccessful, the complexes were able to undergo reductive coupling with organotin reagents. This reactivity was further developed with the analogous amide bound palladium chelates generated via the oxidative addition of N-acyl iminium salts $(R(H)C{=}N(R')COR'')^+Cl^-$ to $Pd_2(dba)_3{\bullet}CHCl_3$ into a

catalytic coupling capable of generating α-substituted amide derivatives. This reactivity was extended into a convenient and general one-pot synthesis of α-substituted amides and N-protected amines by a palladium-catalyzed three-component coupling of imines, acid chlorides or chloroformates, and organotin reagents.

6.1 Suggestions for Future Works

The strong chelation of the amide carbonyl to the nickel center represents a significant challenge in the development of catalytic systems involving the sequential insertion of CO and imine. Efforts toward the weakening of this chelation using strong Lewis acids were promising and further investigation in this direction is warranted. In particular, investigation of more oxophilic or imine compatible Lewis acids may produce a more controlled activation of the complex, and allow for further insertion. As well, increasing the lability of the other ligands on the metal center may provide an additional avenue by which vacant coordination sites can be generated.

Combining imine insertion with other unsaturated insertion substrates (*e.g.* alkynes, substituted alkenes and dienes) provides a wide range of potential coupling and zipper reactions. In addition, the development of more complex substrates, as well as the investigation of stereo- and regiochemical control, could lead to a number of total synthesis applications.

The catalytic coupling of imines with acid chlorides/chloroformates and organotin reagents represents a synthetically useful process with a number of potential extensions. The most attractive of these involves expanding the scope of the reaction to incorporate some of the other coupling partners currently used in synthesis (*e. g.* boronic acids/esters, organosilanes, and organo cuprates).