Imines in Copper-Catalyzed Cross-Coupling Reactions

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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Our file Notre référence
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To my family,

without whom this thesis would

never have been possible

ABSTRACT

Imines in Copper-Catalyzed Cross-Coupling Reactions

The purpose of this study was to develop new catalytic methods to mediate carbon-carbon bond forming reactions with imines under mild conditions and in a general manner. We found that copper catalysts were compatible in cross-coupling of a range of mild organometallic reagents, providing simple, efficient routes to α-substituted amides and amines.

Chapter 2 of this thesis describes a new copper-catalyzed multicomponent synthesis of α-substituted amides. This reaction was developed based upon previous work in this laboratory, which showed that palladium catalysts were competent in Stille-type cross-coupling of imines, acid chlorides, and organostannanes. While providing a mild method of generating the amide products, a more general procedure able to incorporate a wider range of organostannanes was sought. This chapter details the development of a copper-catalyzed protocol, which, as well as performing the cross-coupling under mild reaction conditions, proceeds with a diverse range of aryl-, heteroaryl-, and vinyl-substituted organostannanes and employs an inexpensive and readily available catalyst. Through this system, control over regioselectivity of addition to α,β-unsaturated imines is also possible.

Chapter 3 demonstrates that, in addition to organostannanes, other substrates are viable in copper-catalyzed cross-coupling with imines and acid chlorides. Herein, the coupling of terminal alkynes with imines and acid chlorides is described, leading to an efficient synthesis of tertiary propargylamides directly from simple starting materials. This synthesis incorporates a wide variety of substituted imines, acid chlorides/chloroformates, and terminal alkynes, providing a rapid synthesis of these useful building blocks (reaction completion in only 15 minutes). In addition, the process is shown to work with aza-aromatic heterocycles, such as pyridine, where the alkynylation occurs exclusively at the 2-position.

Chapter 4 describes the utility of these rapid multicomponent reactions, where the products are directly converted into oxazole heterocycles. Copper-catalyzed- and zinc-catalyzed protocols are developed for the synthesis of secondary propargylamides from silyl-imines, acid chlorides, and terminal alkynes. The secondary propargylamide products are then, in a one pot sequence, transformed into trisubstituted oxazoles.

Chapter 5 describes the development of an atom-economical, non-toxic alternative to the organotin coupling described in Chapter 2. This involves the use of tri- and tetraorgano-indium reagents, which can transfer all of their organic groups in a copper-catalyzed coupling with imines and acid chlorides. This reaction shows good functional group compatibility and

further expands the scope of α-substituted amides and *N*-protected amines that can be synthesized through mild copper catalysis.

Chapter 6 explores the enantioselective alkynylation of nitrogen-containing heterocycles. As described in Chapter 3, heterocycles such as pyridine can undergo copper-catalyzed 1,2-addition with terminal alkynes upon activation by chloroformates. As this process generates a stereocenter, it is possible to introduce enantio-control into the reactions by using a chiral copper catalyst. With ligands from the PINAP series, enantioselectivities of up to 84% can be induced in the coupling of nitrogen-containing heterocycles (e.g., quinoline), chloroformates, and terminal alkynes. This provides a mild and simple synthesis of chiral 2-alkynyl-1,2-dihydroquinolines directly from simple starting materials.

RÉSUMÉ

L'Utilisation d'Imine Comme Substrat en Couplages Croisés Médiés par le Cuivre

Le but de cette recherche était de développer des nouvelles méthodologies pour la formation de liaisons carbone-carbone, dont le couplage inclus une imine sous des conditions modérées et de façon générale. On a découvert que le cuivre peut faciliter ces réactions de couplage croisé avec divers réactifs organométalliques. Ces réactions fournissent des méthodes simples et efficaces pour la synthèse d'amines et d'amides α-substituées.

Le chapitre 2 décrit une nouvelle synthèse multicomposante d'amides α-substituées. Dans notre laboratoire, nous avons démontré que le palladium convient à la catalyse combinatoire d'imines, de chlorures d'acides et d'organostannanes. Même si cette réaction nous fournit une méthode rélativement douce de générer ces produits, on a poursuivi une synthèse encore plus générale. Ce chapitre décrit une nouvelle méthode catalytique, dont l'utilisation des sels de cuivre, qui nous offre une synthèse plus générale et en soit étant économique et facilement disponible.

Le troisième chapitre démontre la diversité des réactifs qui peuvent participer dans les réactions de couplage croisé avec les imines et les chlorure d'acides. En fait, des alcynes terminales peuvent réagir avec des imines et des chlorures d'acides, en présence de cuivre, afin de produire des amides propargyliques. Cette réaction, qui est terminée en une quinzaine de minutes, nous offre une synthèse rapide et efficace. De plus, la réaction n'est pas seulement limité aux imines, on peut aussi introduire des hétérocycles comme une pyridine.

Le chapitre 4 décrit l'utilité de ces réactions multicomposantes, avec lesquelles on peut convertir les produits directement en oxazoles. Ceci a été fournit par de développement de réactions catalysées par le cuivre et le zinc en employant les substrats suivants : des « silyl-imines », des chlorure d'acides et des alcynes. Les amides propargyliques secondaires produites par cette réaction ont été converties en oxazoles tri-substituées.

Le chapitre 5 implique une méthode alternative à celle décrite au chapitre 2. On décrit l'utilisation de réactifs organo-indium, qui font le transfer quantitatif de leur substituants dans la réaction catalysée par le cuivre avec les imines et les chlorure d'acides. Cette reaction démontre qu'une grande variété de réactifs y peuvent être incorporés.

Au chapitre 3, on a décrit la réaction entre une pyridine, une chlorure d'acide et une alcyne. Ce processus nous donne un carbone chirale, tout de même racémique. En y introduisant un ligand chiral, au chapitre 6, spécifiquement de la famille PINAP, nous avons réussi des énantiosélectivités jusqu'à 84%. Cette réaction nous donne une nouvelle synthèse d'amides propargyliques cycliques chirales provenant de réactifs simples et écononmiques.

Foreword

In accordance with guideline C of the "Guidelines for Thesis Preparation" (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 of which the student is an author or co-author. These papers must have a cohesive, unitary character making them a 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 than 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 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 in the thesis as to who contributed to such work and to what extent. This statement should appear in a single section entitled "Contributions 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 interest to specify the responsibilities of all the authors of the co-authored papers.

When previously published copyright material is presented in a thesis, the candidate must include signed waivers from the co-authors and publishers and submit these to the Thesis Office with the final deposition, if not submitted previously."

This dissertation is written in the form of four papers. The papers each comprise one chapter in the main body of the thesis (Chapters 2, 3, 4, and 5), with a general introduction to this work in the first chapter and conclusions in the seventh chapter. Following normal procedures, the papers have either been published in, submitted to, or to be submitted to scientific journals. A list of papers is given below:

Chapter 2: Daniel A. Black; Bruce A. Arndtsen* *Journal of Organic Chemistry* **2005**, *70*, 5133.
Copper-Catalyzed Cross-Coupling of Imines, Acid Chlorides, and Organostannanes: A Multicomponent Synthesis of α-Substituted Amides

Chapter 3: Daniel A. Black; Bruce A. Arndtsen* *Organic Letters* **2004**, *6*, 1107.
Copper-Catalyzed Coupling of Imines, Acid Chlorides, and Alkynes: A Multicomponent Route to Propargylamides

Chapter 4: Daniel A. Black; Bruce A. Arndtsen* *Tetrahedron* **2005**, *61*, 11317.
Metal-Catalyzed Multicomponent Syntheses of Secondary Propargylamides and Oxazoles from Silylimines, Acid Chlorides, and Alkynes

Chapter 5: Daniel A. Black; Bruce A. Arndtsen* *Organic Letters* **2006**, *8*, 1991.
General Approach to the Coupling of Organoindium Reagents with Imines via Copper Catalysis

Contributions of Authors

All of the papers in this thesis include the research director, Professor Bruce A. Arndtsen, as a co-author, since the work was done under his direction.

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

"Copper-Catalyzed Cross-Coupling of Imines, Acid Chlorides, and Organostannanes: A Multicomponent Synthesis of α-Substituted Amides"

"Copper-Catalyzed Coupling of Imines, Acid Chlorides, and Alkynes: A Multicomponent Route to Propargylamides"

"Metal-Catalyzed Multicomponent Syntheses of Secondary Propargylamides and Oxazoles from Silylimines, Acid Chlorides, and Alkynes"

"General Approach to the Coupling of Organoindium Reagents with Imines via Copper Catalysis"

Date:_____

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The love of a good woman... something that too many of us take for granted. Yael Pfeiffer, for everything that you are, and what we will be; I smile when I think of you, in love, respect, and appreciation. You don't know what you mean to me, your presence alone brightens my day and keeps me going. I love you.

Going through graduate school you meet many people, but I would have never imagined the quality of those that I have met here at McGill. This Chemistry Department is unparalleled in the wonderful folk that inhabit it, and many great friendships that will last a long time I have made here. I would like to

thank all who I count as friends here – you know who you are. Thanks for making the past five years of my life the best yet.

To my labmates of the past - Rajiv and Jason – thank you for making my time at McGill with you the most special time of my life. I will always cherish our time together, and I am sure that we will remain friends forever – or at least until Hell freezes over.

To all my current labmates, Daniel St. Cyr, Ali Siamaki, YingDong Lu, Carolyne Stafford, Ramsey Beveridge, Kraig Worrall, and Weijuan Jia, thanks for making our time in the lab together fun and exciting. I will never forget our laughs, even if they were often at each others' expense! Good luck to you all.

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The Copper-Catalyzed Coupling of Imines, Acid Chlorides and Alkynes: A Multicomponent Route to Propargylamides

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Metal-Catalyzed Multicomponent Syntheses of Secondary Propargylamides and Oxazoles from Silylimines, Acid Chlorides, and Alkynes

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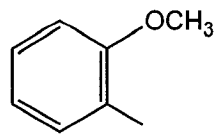
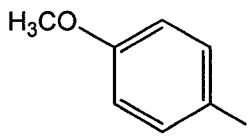
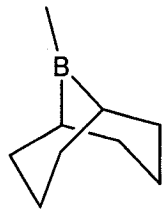
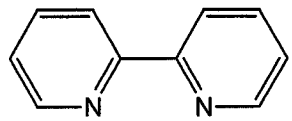
List of Abbreviations

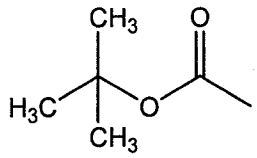
Ar	-aryl
Bn	$-CH_2C_6H_5$
Bu or ^{n}Bu	$-CH_2CH_2CH_2CH_3$
^{t}Bu	$-C(CH_3)_3$
^{i}Bu	$-CH_2CH(CH_3)_2$
^{s}Bu	$-CH(CH_3)(CH_2CH_3)$
$BF_3{\cdot}Et_2O$	-boron trifluoride diethyl etherate
Bu_3Sn	-tri(n-butyl)stannyl
Bu_3SnX	-tri(n-butyl)tin halide
DMSO	-dimethyl sulfoxide
Et	$-CH_2CH_3$
EWG	-electron withdrawing group
^{n}Hex	$-CH_2CH_2CH_2CH_2CH_2CH_3$
H_2O	-water
Me	$-CH_3$
NMR	-Nuclear Magnetic Resonance
OBz	$-OC(O)C_6H_5$
OMOM	$-OCH_2OCH_3$
OTf	$-OSO_2CF_3$
Ph	$-C_6H_5$
Pr	$-CH_2CH_2CH_3$
^{i}Pr	$-CH(CH_3)_2$
r.t. or RT	-room temperature
TMS	$-Si(CH_3)_3$
TBAT	-tetrabutylammonium triphenyldifluorosilicate
TBS	$-Si(CH_3)_2C(CH_3)_3$

^{o}An 

An or ^{p}An 

BBN 

bipy 

Boc 

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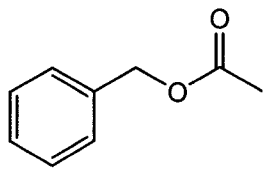
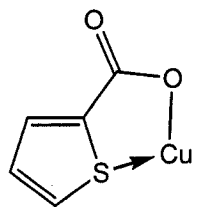
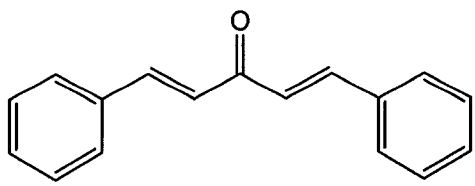
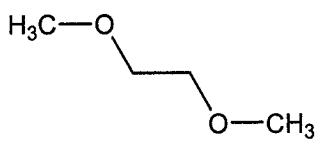
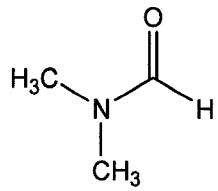
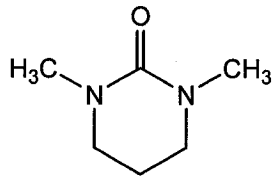
CBz 

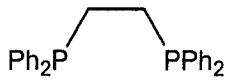
CuTC 

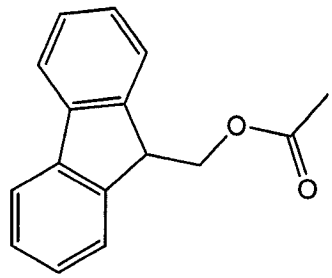
dba 

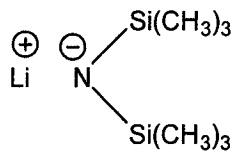
DME 

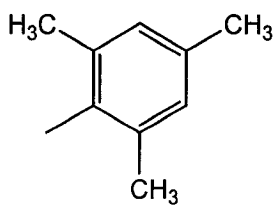
DMF 

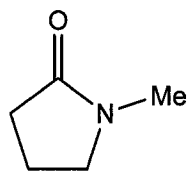
DMPU 

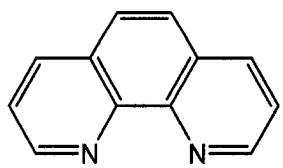
dppe 

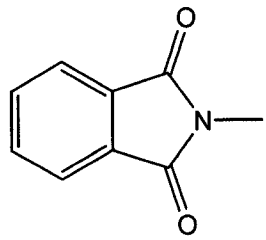
FMOC 

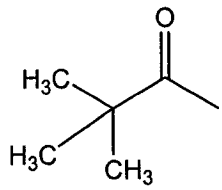
LiHMDS 

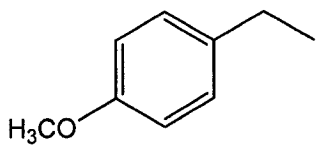
Mes 

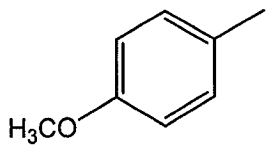
NMP 

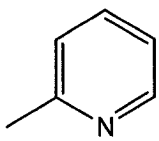
phen 

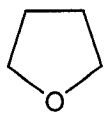
phthalimido 

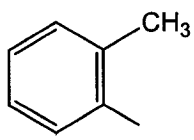
Piv 

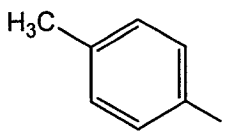
PMB 

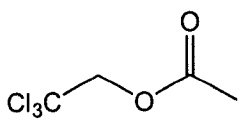
PMP 

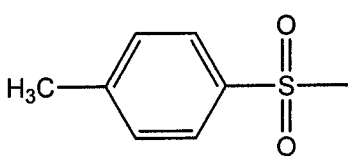
2-Py 

THF 

^{o}Tol 

Tol or ^{p}Tol 

TROC 

Ts 

CHAPTER ONE

Introduction:

Copper Catalysis in Cross-Couplings and Imine Additions

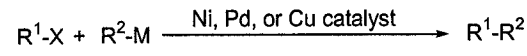
1.0 Perspective

The construction of carbon-carbon bonds is one of the fundamental reactions in organic synthesis. The past several decades have seen an expansive growth in the use of transition metal complexes to mediate such reactions.[1] The ability of metal complexes to perform a wide range of mechanistic processes, often under mild reaction conditions and with good substrate compatibility, are only some of their salient features. They also allow for the use of starting materials that are typically not considered viable with traditional nucleophile-electrophile approaches to carbon-carbon bond formation. In addition, metal-catalyzed reactions provide handles for stereo- and regio-control over organic products by modulation of the catalyst employed.

Of the metal complexes that are frequently used in catalytic carbon-carbon bond formation, those of the late transition metals have found widespread utility. For example, complexes of palladium, nickel, and copper are now routinely employed in a wide range of carbon-carbon bond forming processes, such as cross-coupling reactions,[2] Heck coupling reactions,[3] additions to carbon-heteroatom π-bonds,[4]

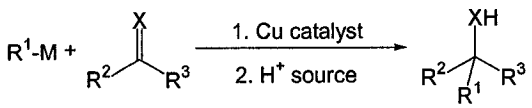
conjugate additions to α,β-unsaturated compounds,[5] cycloadditions,[6] oxidative homocouplings,[7] cyclopropanations,[8] and many more (Scheme 1.1). Due to its relevance, this introduction will focus on copper-catalyzed carbon-carbon bond forming reactions, with an emphasis on cross-coupling reactions and nucleophilic additions to imines.

Cross-Coupling Reactions



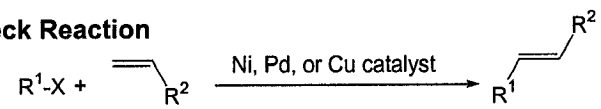
X = halide, sulfonate, etc.
M = Li, Mg, Zn, Cu, Si, B, Sn, etc.

Additions to C=X π-bonds



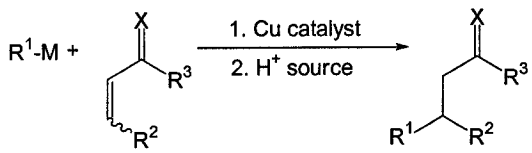
M = Li, Mg, Zn, etc.
X = NR, O, S

Heck Reaction



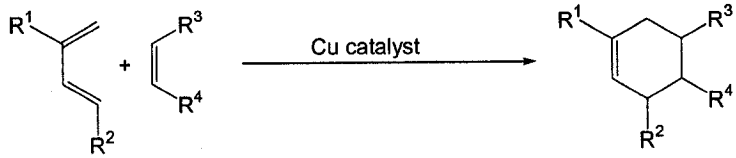
X = halide, pseudohalide, etc.

Conjugate Additions to α,β-Unsaturated Compounds

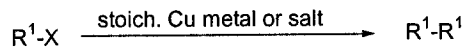


X = NR, O, S;
M = Zn, Cu, Mg, B, etc.

Cycloadditions

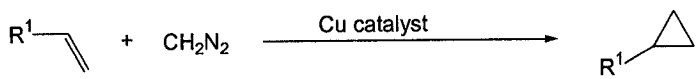


Oxidative Homocoupling



X = halide, pseudohalide

Cyclopropanations

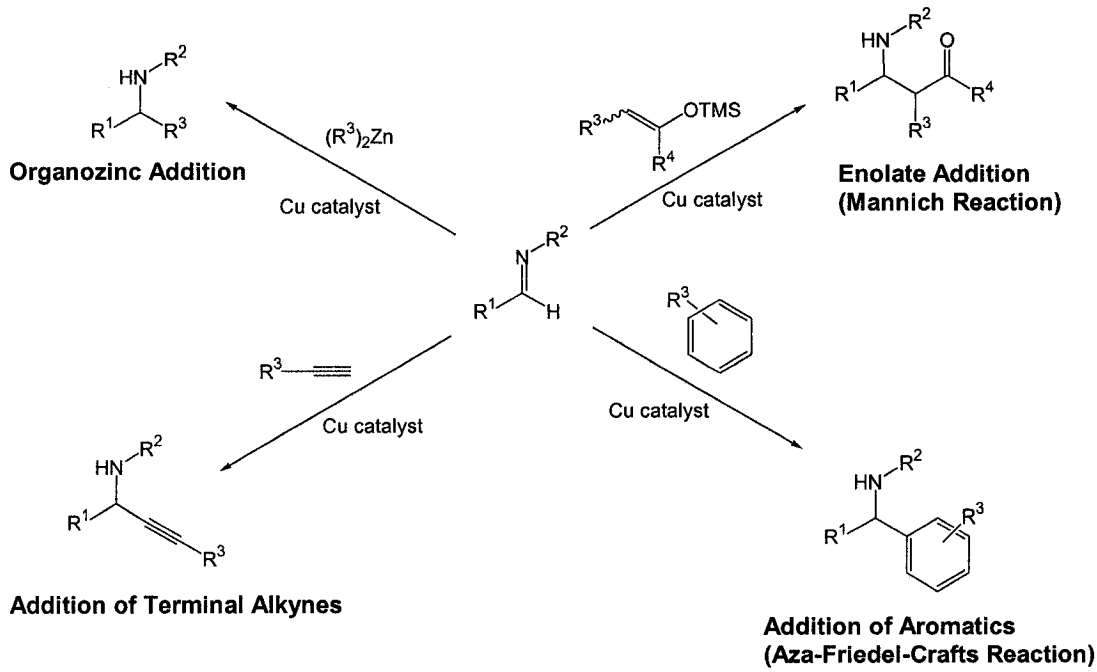


Scheme 1.1 Examples of late transition metal-catalyzed carbon-carbon bond forming transformations, continued.

Metal-catalyzed cross-coupling reactions (e.g., the Stille, Suzuki, and Sonogashira reactions) combine organic halides with organometallic reagents to generate new carbon-carbon bonds. Despite only having been developed over the past three decades, these reactions have found broad utility. While the most commonly employed catalysts in these couplings are those of palladium,[2] copper has been shown to efficiently mediate many of these transformations.[9] The range of transmetalating agents that copper can incorporate in cross-coupling is nearly as broad as those with palladium, and includes Grignard reagents, organo-stannanes, -lithiums, -zincs, -silanes, and -boranes. Furthermore, copper complexes can be used to generate organocuprates *in situ* from organic compounds with acidic carbon-hydrogen bonds, such as malonate derivatives and terminal alkynes, allowing their use in these cross-

coupling processes. This, coupled with the relatively low cost, availability, and air stability of copper catalysts makes them a potentially useful alternative to palladium catalysts. These reactions will be discussed extensively in Section 1.1 of this thesis.

Copper complexes are also frequently employed in the addition of organometallic reagents to carbon-heteroatom π-bonds. These catalysts have found wide application in nucleophilic addition to carbonyl-containing compounds (e.g., 1,4-additions), which will not be discussed in this thesis. However, copper-catalyzed addition to imines has also received significant attention.[10] The products resulting from addition to imines, α-substituted amine derivatives, are among the most widely observed structures found in biological systems. Copper complexes can often catalyze the formation of these products under mild reaction conditions and, through the use of chiral ligands, with high levels of enantiocontrol. For example, some of the most common copper-catalyzed enantioselective additions to imines include the additions of organozinc reagents,[11] terminal alkynes,[12] enolates (the Mannich reaction),[13] and aromatics (Aza-Friedel Crafts reaction)[14] (Scheme 1.2). These transformations, and others, will be further discussed in Section 1.2 of this introduction.

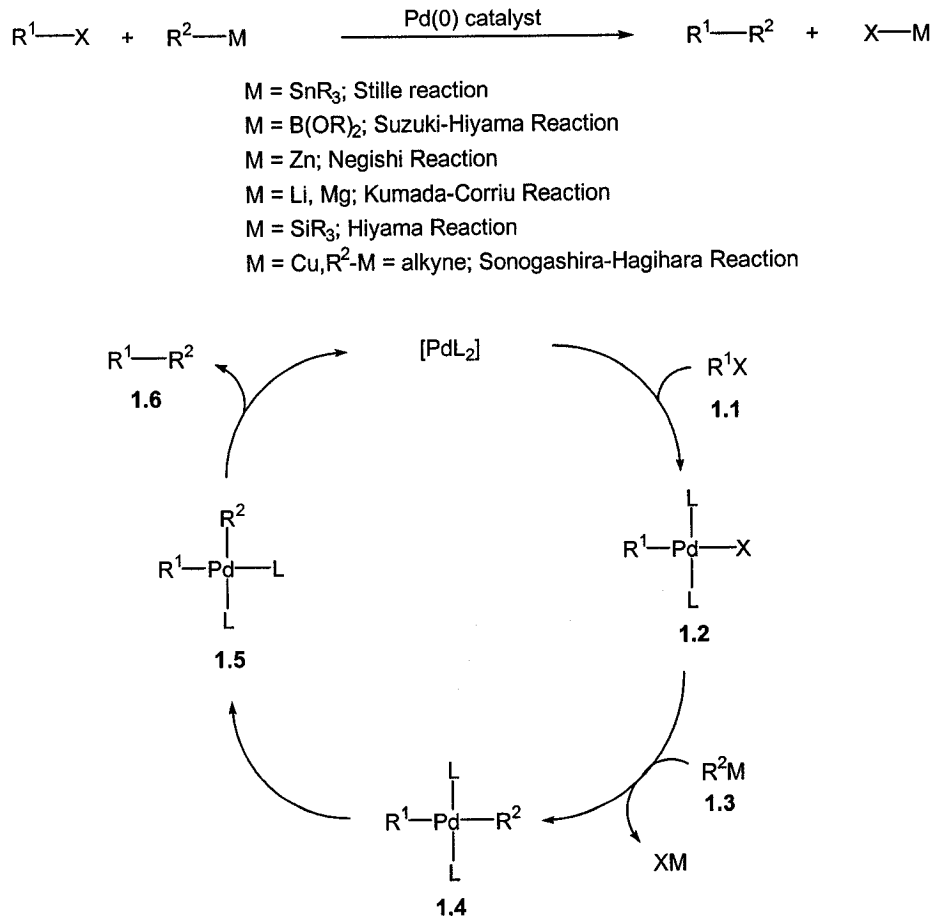


Scheme 1.2 Examples of copper-catalyzed carbon-carbon bond forming reactions with imines.

1.1 Copper Catalysis in Cross-Coupling Reactions

Metal-catalyzed cross-coupling reactions refer to a family of transformations in which an organic electrophile, typically an aromatic- or vinyl-halide, and an organometallic reagent (e.g., an organostannane or boronic acid), react with the aid of a transition metal catalyst to form a carbon-carbon bond between the organic fragments (Scheme 1.3).[2c] Palladium (0) sources are the most frequently employed catalysts in these transformations. Some of these palladium-catalyzed cross-coupling reactions include the Stille (organotin), Suzuki (organoborane), Sonogashira (alkyne),

Kumada-Corriu (organolithium or Grignard reagent), Negishi (organozinc), and Hiyama (organosilicon) reactions.



Scheme 1.3 Generalized mechanism of a palladium-catalyzed cross-coupling.

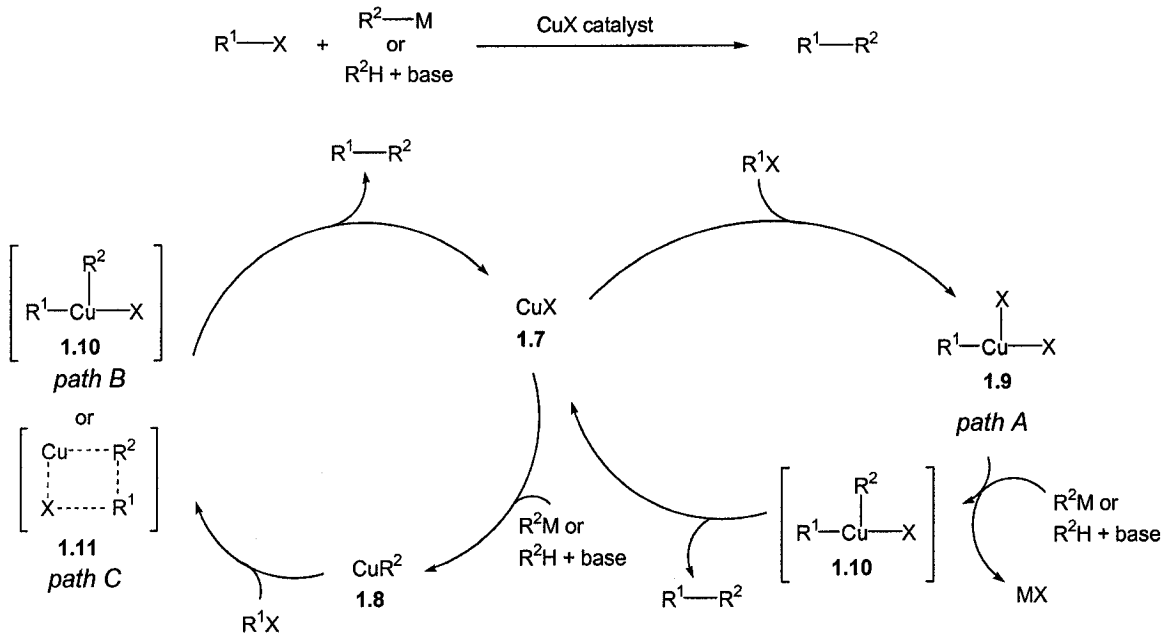
These cross-coupling reactions involve the use, or *in situ* generation, of a coordinatively unsaturated palladium (0) catalyst.[15] This complex is postulated to undergo an oxidative addition reaction with the organic halide **1.1** to provide intermediate **1.2**. The next step in the catalytic cycle involves transmetalation of the organometallic reagent with palladium to form a palladium complex with both organic fragments coordinated (**1.4**). After isomerization to **1.5**, a reductive

elimination occurs to release product **1.6** containing a new carbon-carbon bond and regenerate the Pd(0) catalyst.

Cross-coupling reactions offer many useful features that complement traditional nucleophile-electrophile approaches to carbon-carbon bond formation. One of these features is the ability to incorporate electrophiles that are not typically considered viable in coupling with strong nucleophiles without a catalyst. Some of the most common of these substrates include aromatic- and vinyl-halides. Cross-coupling protocols also commonly involve milder reaction conditions than standard nucleophile-electrophile chemistry, making them more functional group compatible. Additionally, the use of a metal catalyst often allows for greater control over product selectivity (e.g., regio- and enantioselectivity). Another useful feature of cross-coupling chemistry is that it allows for intermediary insertion processes, where species such as alkenes, alkynes, or carbon monoxide can insert into the metal-carbon bond of **1.2** before transmetalation. These features can be found not only in palladium-catalyzed cross-coupling reactions, but also in cross-couplings with other metal complexes, such as those of copper.

Most of the mechanistic evidence obtained to date indicates that copper complexes can take part in cross-coupling chemistry in a manner similar to palladium.[9] However, the oxidation states of the active species involved in the catalytic cycle differ: copper is proposed to cycle between +1 and (potentially) +3 (Scheme 1.4), whereas palladium typically cycles between 0 and +2. Furthermore, in copper's catalytic cycle, the ordering of the oxidative addition and transmetalation steps is unknown, and it is possible for CuX species **1.7** (path A) or R^2Cu species **1.8**

(path B) to undergo oxidative addition of an R^1X electrophile.[16] This results in significant questions as to whether copper salts do in fact cycle between oxidation states in their cross-coupling catalytic cycle. It has been suggested that copper simply undergoes a σ-bond metathesis reaction between the $[R^2Cu(L)]$ species formed after transmetalation and the organic halide R^1X (path C), resulting in carbon-carbon bond formation and regeneration of the copper catalyst.[16]



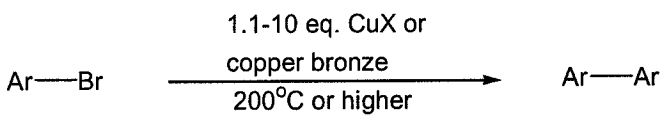
Scheme 1.4 Postulated mechanisms of copper-catalyzed cross-coupling reactions.

Copper-catalyzed cross-coupling reactions will be discussed in the first section of this introduction. These reactions will be organized based on the transmetalating agents used in the given processes, which include organotin reagents, organolithiums, Grignard reagents, organozinc species, organosilicon compounds, boron derivatives, as well as acidic methylene compounds and terminal acetylenes.

This thesis will describe the general classes of organic electrophiles with which the processes are compatible, as well as some of the significant advances made for each cross-coupling reaction. Also, while it is not truly a cross-coupling reaction, the copper mediated synthesis of biaryls from aromatic halides, known as the Ullmann reaction, is arguably the grandfather of modern cross-coupling, and as such will be discussed. The copper-catalyzed Heck reaction will also be mentioned.

1.1.1 The Ullmann Reaction

The Ullmann reaction, initially reported in 1901, has long been employed to construct biaryl systems.[17] This reaction involves reductive homocoupling of aromatic iodides or bromides (Scheme 1.5).

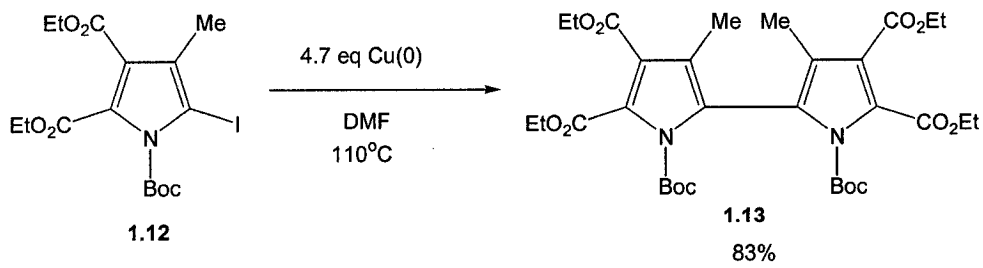


Scheme 1.5 The Ullmann Reaction.

The classic version of this reaction requires high temperatures (above 200°C) and stoichiometric copper salts, unless a stoichiometric quantity of reductant is present. The procedure has been extensively reviewed and considerable improvements have been made over the last century.[18] Ullmann couplings are typically activated by the presence of *ortho*-electron-withdrawing substituents, such

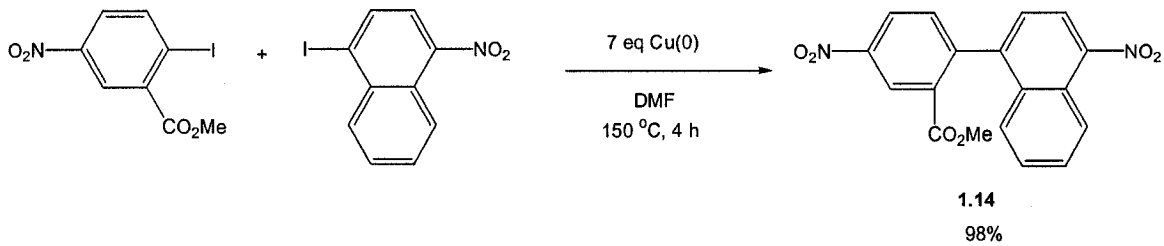
as nitro groups. Alternatively, under the classic conditions, substituents such as hydroxyl-, amino-, and carboxyl groups can slow down or even stop the desired reaction from occurring, due to competitive C-O, C-N, and C-C bond formation with these functional groups. In addition, sterics can influence the reaction when bulky groups are situated in the ortho position. Many of these hindrances have been alleviated through the use of modern Ullmann protocols.[18]

While this coupling continues to employ stoichiometric quantities of copper salts, it remains a useful protocol for biaryl synthesis. The improvements made to this reaction over the past century have allowed for its continued utility. For example, it has been noted that lower reaction temperature can be achieved with *N*,*N*-dimethylformamide (DMF) as solvent.[18] Also, utilization of an activated copper powder, generated from reduction of copper (I) iodide by potassium, allows the reaction to be conducted at or below 85°C. These improvements have permitted a wider functional group tolerance in Ullmann couplings, for example, where carboxyl groups are tolerated in the homocoupling of 2-iodopyrroles **1.12** (Scheme 1.6).[19]



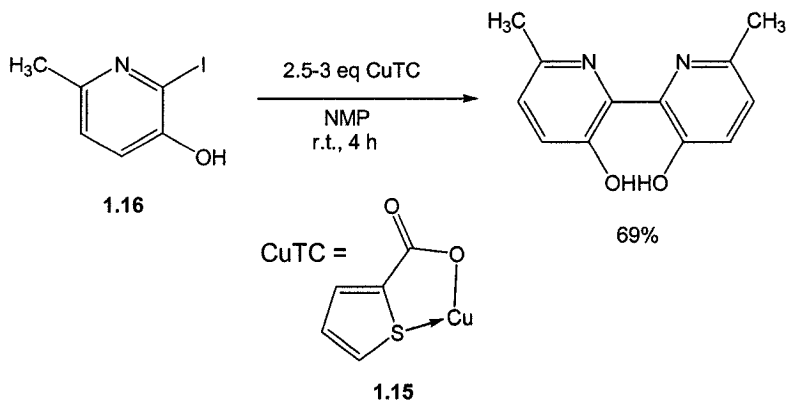
Scheme 1.6 Homocoupling of 2-iodopyrroles.

The coupling of unsymmetrical aromatic halides using the Ullmann reaction was a noteworthy step toward the generalization of this process, though a large excess of one organic halide was necessary to achieve a high yield. For example, Suzuki has shown that this process can be used to synthesize benzanthrones **1.14** (Scheme 1.7).[20]



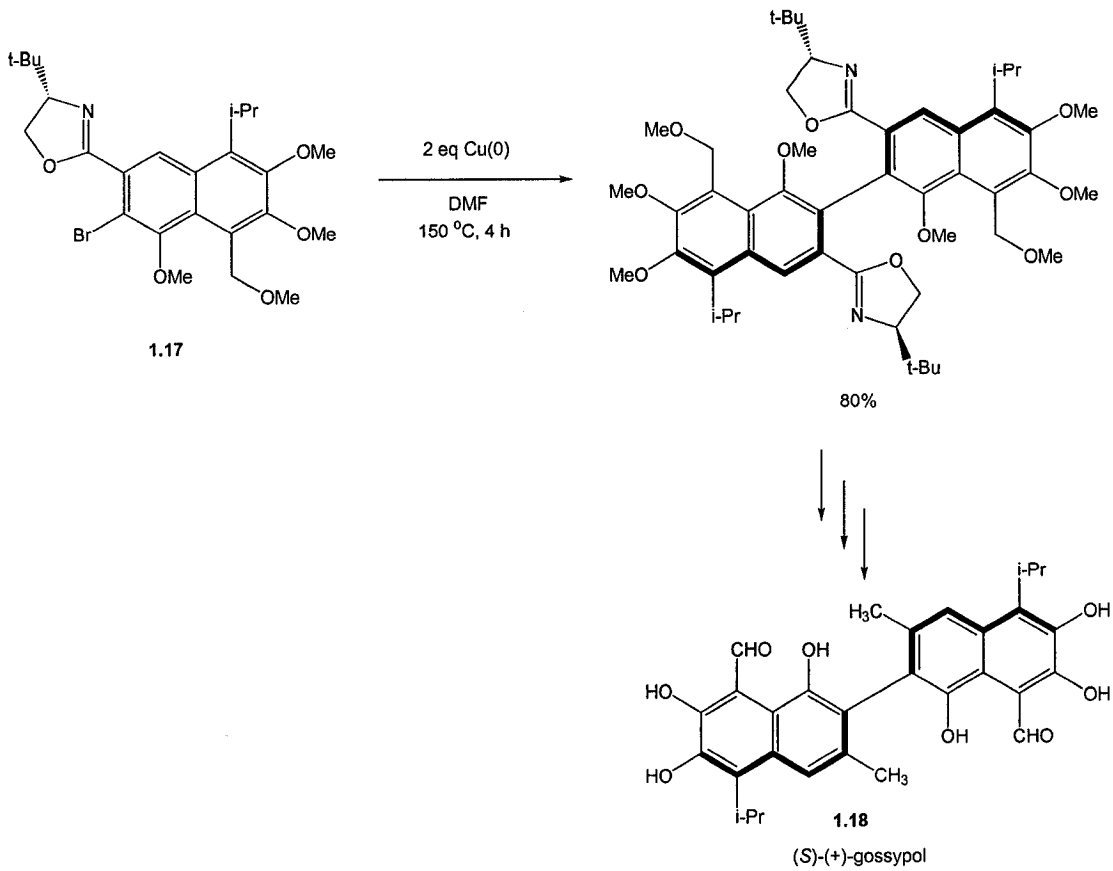
Scheme 1.7 Unsymmetrical Ullmann coupling.

A significant advance in developing a mild Ullmann protocol came from the use of copper (I) thiophene-carboxylate **1.15** (CuTC) as the copper source for this reaction. Liebeskind has shown that this copper salt will mediate Ullmann coupling at room temperature (Scheme 1.8).[21] The reason proposed for this significant increase in catalyst efficiency was that the carboxylate ligand acts to stabilize the oxidative addition product of the aromatic halide and CuTC. It has been theorized by Liebeskind that oxidative addition to Cu(I) salts is reversible, and that the presence of the stabilizing carboxylate group drives this equilibrium forward. Using this protocol allows the incorporation of hydroxyl groups into the coupling of 2-iodopyridines **1.16**.



Scheme 1.8 Copper (I) thiophene-carboxylate in Ullmann coupling.

When two aromatic moieties are coupled, there exists the possibility of generating axially chiral molecules. Meyers has reported that enantiomerically enriched biaryls can be formed using chiral oxazolines as auxiliaries. This has been used to produce diastereoselective Ullmann couplings of bromonaphthalenes **1.17**.[22] Chiral binaphthyl systems have been used extensively as ligands in asymmetric synthesis. This asymmetric Ullmann coupling was also employed in the first synthesis of (*S*)-(+)-gossypol (Scheme 1.9).[23]

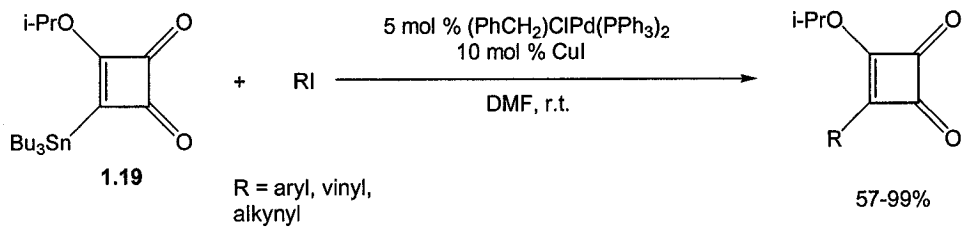


Scheme 1.9 Diastereoselective Ullmann coupling in the synthesis of (*S*)-(+)-gossypol.

1.1.2 Organotin Reagents in Cross-Coupling

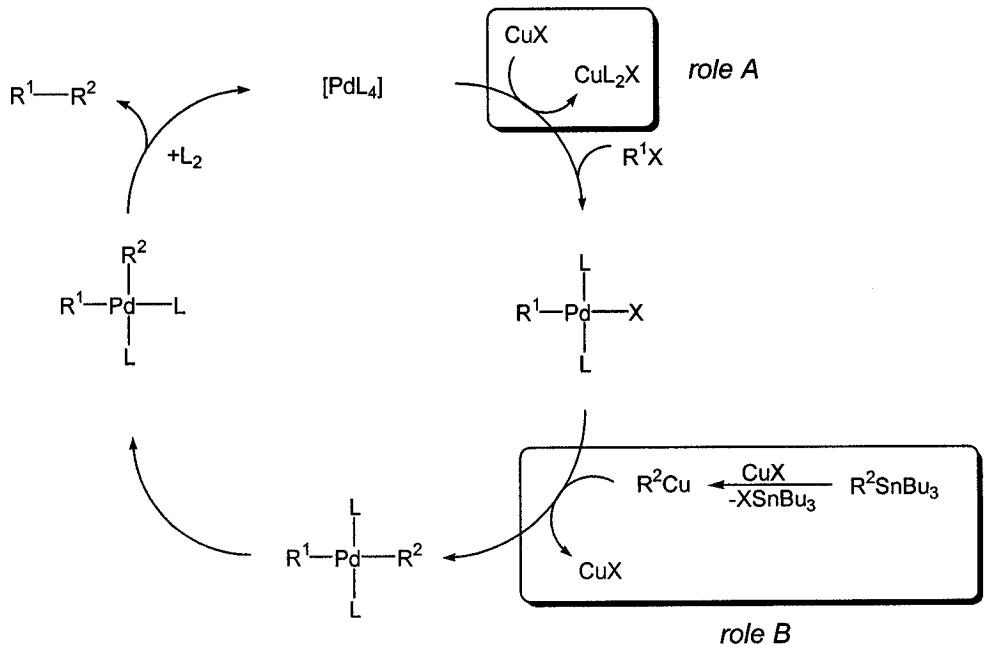
The palladium-catalyzed cross-coupling of organic electrophiles and organotin reagents, known as the Stille reaction, is an effective and mild methodology for the formation of carbon-carbon bonds.[24] The low nucleophilicity of organotin reagents renders these species versatile cross-coupling agents, which can often be employed in the presence of delicate functionality. Copper (I) salts have been

frequently used to accelerate otherwise sluggish Stille couplings, particularly for reactions involving geminally substituted alkenyltin compounds.[25] For example, Liebeskind has shown that stannylcyclobutenediones **1.19** will react with organic halides in the presence of 5 mol % Pd(0) catalyst with 10 mol % CuI (Scheme 1.10).[26] The same reaction in the absence of copper salts provides minimal product.



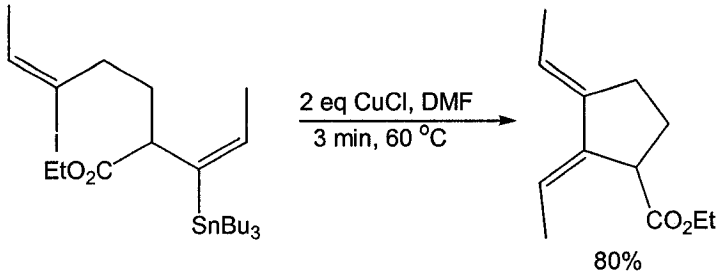
Scheme 1.10 Cross-coupling of stannylcyclobutenediones with organic halides.

There are two modes by which copper is hypothesized to catalyze these reactions.[25] The first is that copper acts as a scavenger of phosphine ligands, thus freeing coordination sites on the palladium metal center for oxidative addition and transmetalation (role A). The second, more widely accepted hypothesis is that copper can undergo transmetalation with the organostannane to form intermediate organocopper species (role B), which can more easily transmetalate to the palladium metal center (Scheme 1.11).



Scheme 1.11 Transmetalation of organotin reagents to copper salts and subsequent transmetalation to palladium.

In addition to accelerating palladium catalysis, copper salts can also mediate this type of cross-coupling without palladium. Piers, Liebeskind, Falck, and others have established copper complexes as viable replacements for palladium catalysts in Stille-type cross-coupling, in both intra- and intermolecular coupling of organostannanes with aromatic- and halides.[27] The first copper-catalyzed cross-coupling of organostannanes with vinylic halides was demonstrated by Piers in 1993, as shown in Scheme 1.12.[27a]



Scheme 1.12 Intramolecular coupling of alkenyliodide and alkenylstannane.

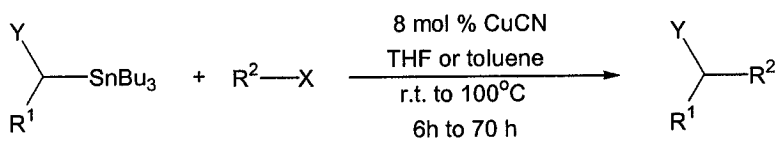
Mechanistically, this reaction was proposed to proceed via an initial transmetalation of the organotin reagent to the copper catalyst, followed by oxidative addition of the organic halide to generate a transient Cu (III) species.[9] This mechanism (Scheme 1.4, Path B) was shown in the introduction to this section. It is also possible that after the transmetalation step, the organocuprate undergoes a σ-bond metathesis with the organic halide (Scheme 1.4, Path C), generates the product, and regenerates a copper (I) halide back into the catalytic cycle.

Most copper-mediated cross-couplings employ stoichiometric quantities of copper catalyst. While the reaction in principle can be catalytic, the transmetalation between the organostannane and the copper species is thought to be reversible. Liebeskind has shown that the initial rate of these reactions is rapid, followed by a significant slowing as the reaction approaches 50% completion.[28] Also, the addition of one equivalent of the Bu_3SnX by-product at the start of this reaction resulted in almost no product formation. These observations are consistent with a reversible transmetalation of the organostannane to the copper catalyst, which is inhibited by increasing concentration of Bu_3SnX. As such, many copper-catalyzed cross-couplings

do not reach completion unless superstoichiometric quantities of copper salt is present.

The copper-catalyzed cross-coupling of organostannanes with organic halides is not limited to aromatic- and vinylic halides. In fact, a wide range of organic electrophiles such as enol-triflates, allylic halides, polymer-bound aryl iodides, and iodoalkynes are viable substrates under copper catalysis. Also, a number of organotin reagents, including aryl-, alkenyl- (including geminally substituted alkenes), heteroaryl-, and alkyl-substituted stannanes are compatible in this reaction.[27]

It has been found that a highly polar solvent is necessary for many of these reactions to proceed. This is postulated to be due to a greater propensity for transmetalation from the organostannane to the copper catalyst under polar conditions. However, the use of proximal coordinating groups (α-heteroatoms) on the organotin reagent **1.20** is thought to facilitate transmetalation, allowing for the use of catalytic quantities of copper catalyst (Scheme 1.13).[29] Falck has shown that these coordinating groups, particularly those of sulfur, allow more rapid cross-coupling with a number of R-X electrophiles in toluene.

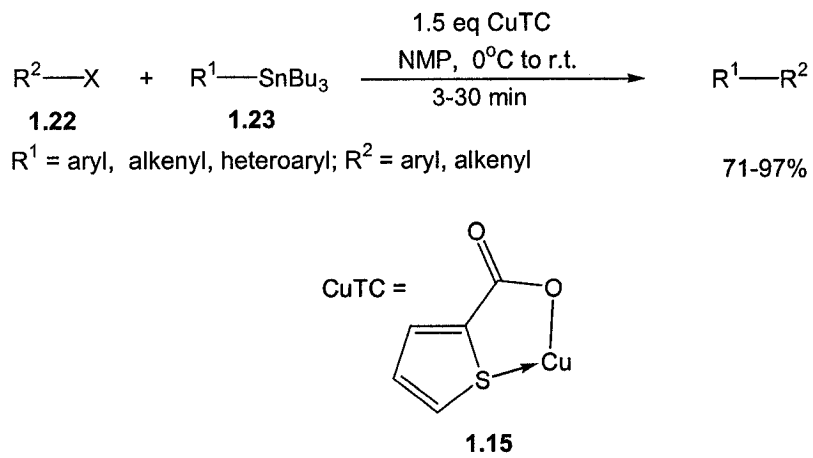


1.20 **1.21**

Y = OAc, OBz, OMOM, PhOC(S), $Ph_2P(O)$, phthalimide, etc.
R^1 = aryl, alkyl, alkenyl
R^2 = allyl, propargyl, aryl, benzoyl, acyl, PhOC(S), EtSC(O)

Scheme 1.13 Proximal coordinating groups on the organostannane in coupling.

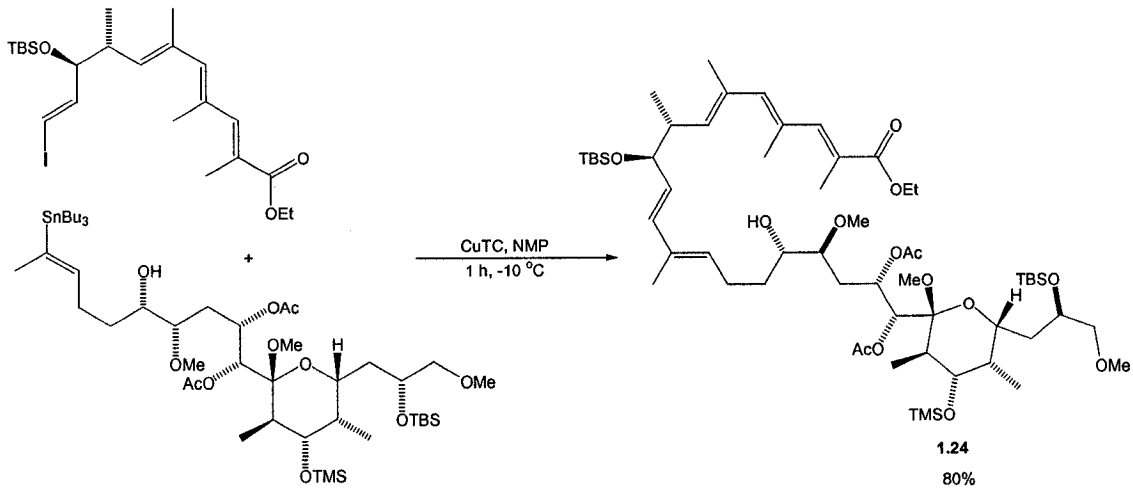
The copper (I) thiophene-2-carboxylate catalyst **1.15** (CuTC) developed by Liebeskind has provided a very useful protocol for copper-catalyzed cross-coupling of organostannanes with aryl and alkenyl iodides at room temperature.[28] While this process often involves the use of stoichiometric quantities of CuTC, due to the aforementioned reversible transmetalation between organostannane and the catalyst, it remains a useful method in complex organic synthesis due to the mild reaction conditions and high reaction rate. Liebeskind reported in 1996 that CuTC can cross-couple a wide range of aryl- and vinyl-iodides and bromides **1.22** with aromatic and vinylic organostannanes **1.23** at room temperature (Scheme 1.14).



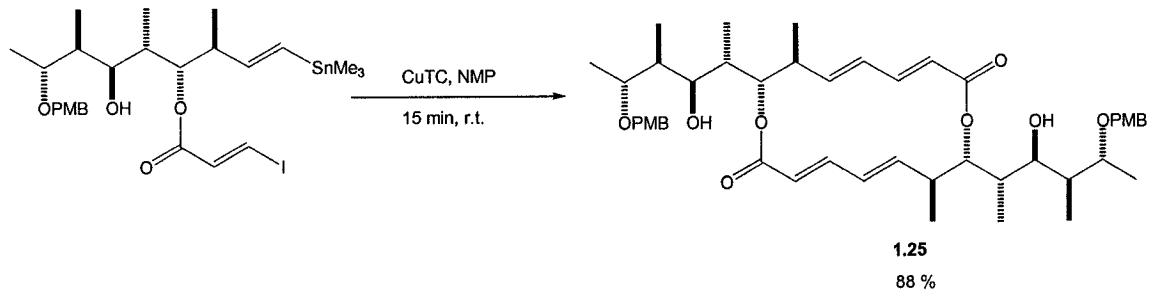
Scheme 1.14 Liebeskind's copper (I) thiophene-carboxylate catalyst in cross-coupling of organostannanes with organic halides.

CuTC has demonstrated the ability to mediate the coupling of a wide range of substituted alkenyl groups. Because of this, it has found extensive use in natural product synthesis (Schemes 1.15-1.17).[30] Some examples of this are in the total

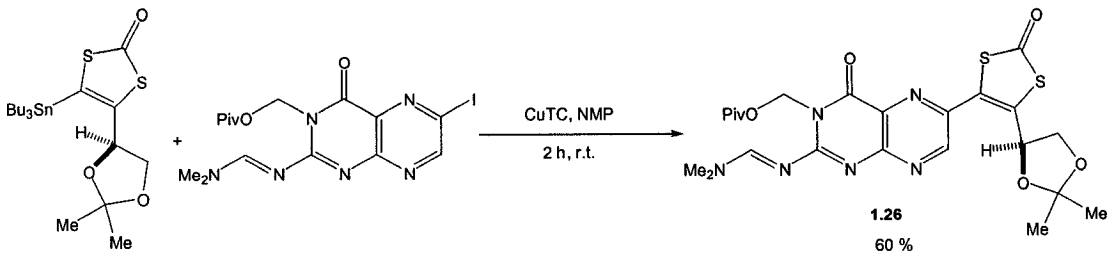
syntheses of apoptolidinone **1.24**, elaiolide **1.25**, and of the organic ligand of the molybdenum co-factor **1.26**.



Scheme 1.15 Intermediate in the synthesis of Apoptolidinone.



Scheme 1.16 Intermediate in the synthesis of Elaiolide.

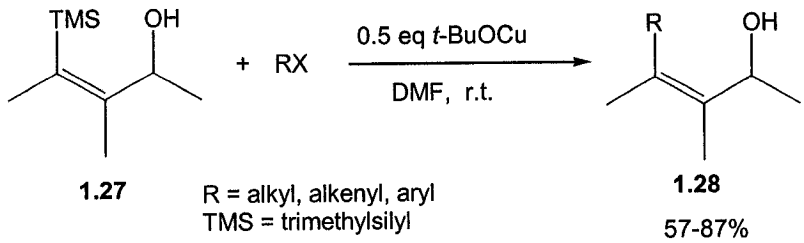


Scheme 1.17 Intermediate in the synthesis of the organic ligand of the molybdenum co-factor.

1.1.3 Organosilicon species

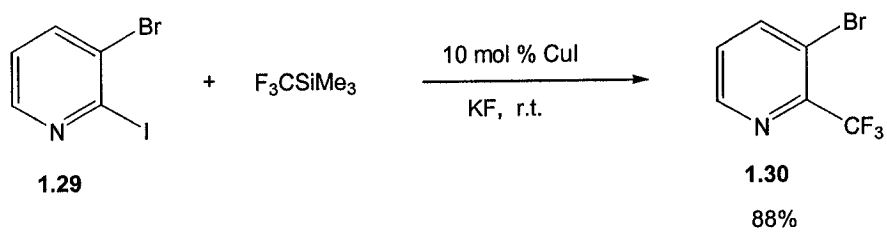
The palladium-catalyzed cross-coupling of organosilanes with organic halides, known as the Hiyama coupling, has been extensively explored.[31] The copper-catalyzed variant of this reaction is far less well known. These reactions typically employ stoichiometric quantities of copper (I) salts, despite the fact that the role of copper in these reactions is catalytic. This is postulated to be due to the reversible transmetalation of the organic fragment from silicon to copper, where build-up of silicon halide derivatives slows the transmetalation rate, in a manner similar to organotin reagents.[31b] Since 1979, a number of protocols have been reported for the coupling of organosilicon compounds with organic halides mediated by copper salts. Aryl-, vinyl-, and alkynyl silicon reagents have been successfully employed in copper-catalyzed cross-coupling reactions with a range of organic electrophiles, including alkyl- and aryl halides, -tosylates, and -triflates.[32]

Similar to organostannanes, an α-heteroatom (proximal coordinating group) on the organosilane has been proposed to accelerate transmetalation and allow for use of lower loadings of copper salt.[33] For example, neighbouring oxygen or nitrogen atoms in the form of hydroxyl- or pyridyl units can provide catalytic coupling with an allylic-, benzylic-, or primary alkyl halide (Scheme 1.18).



Scheme 1.18 Cross-coupling of organic halides and alkenyl silanes.

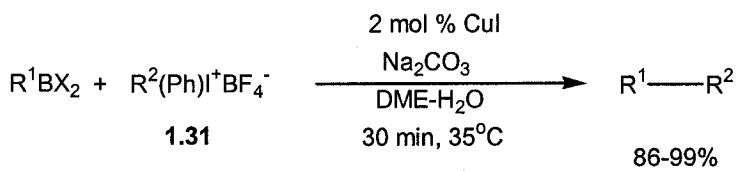
One recent use of copper-catalyzed cross-coupling with organosilanes is in the trifluoromethylation of heteroaromatics with trimethylsilyl-trifluoromethane, or TMS-CF_3.[34] This methodology has been used to introduce the CF_3 group to a number of biologically relevant molecules for drug development. An example of this is in the trifluoromethylation of 2-iodopyridine **1.29** (Scheme 1.19).[34b]



Scheme 1.19 Trifluoromethylation of organic halides by Me_3SiCF_3.

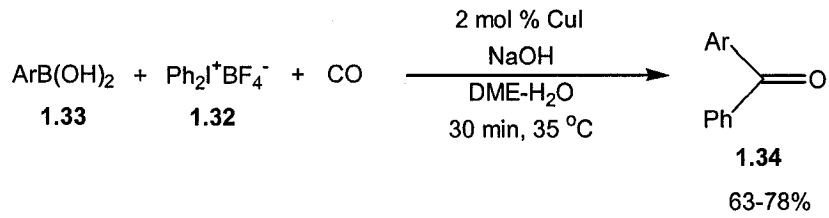
1.1.4 Coupling With Organoboron Compounds

The coupling between organic electrophiles and organoboron compounds in the presence of a Pd(0) catalyst, known as the Suzuki reaction, remains one of the most versatile, efficient, and functional group compatible methods of performing carbon-carbon bond formation.[35] However, there are very few examples of the coupling of organoboron compounds with R-X electrophiles catalyzed by copper complexes. The first example of this coupling involved aryliodonium salts **1.31**. These species will react with boronic acids, boronates, and BBN-derived alkylboranes (BBN = 9-borabicyclo[3.3.1]nonane) under very mild conditions (Scheme 1.20).[36]



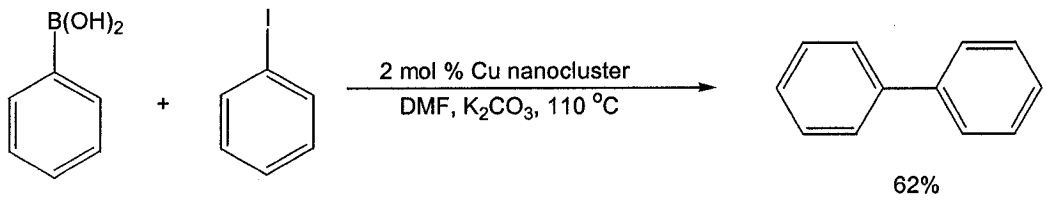
Scheme 1.20 Cross-coupling of iodonium salts with organoboron compounds.

An advantage of this methodology is that under an atmosphere of CO, diphenyliodonium salts **1.32** are able to cross-couple with aromatic boronic acids **1.33** and esters to generate benzophenone derivatives **1.34** (Scheme 1.21).



Scheme 1.21 Carbonylative coupling of iodonium salts with boronic acids.

In addition to copper (I) halide salts, it has been reported that successful coupling of aryl halides and boronic acids in the presence of copper nanoparticles is possible.[37] These copper nanoclusters have been found to catalyze the reaction between phenylboronic acid and iodobenzene in the presence of K_2CO_3 in DMF at 110°C (Scheme 1.22).

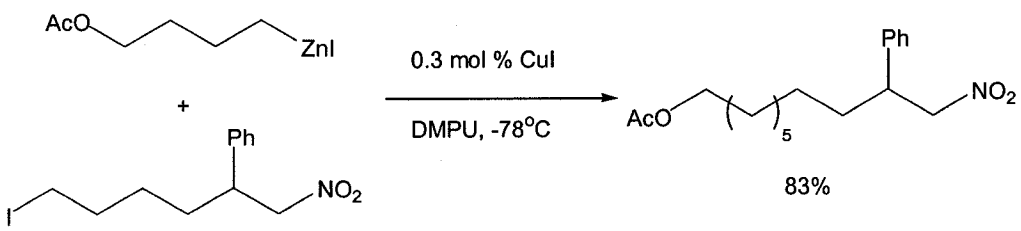


Scheme 1.22 Cross-coupling of aryl iodides with boronic acids catalyzed by copper nanoparticles.

1.1.5 Organozinc Reagents

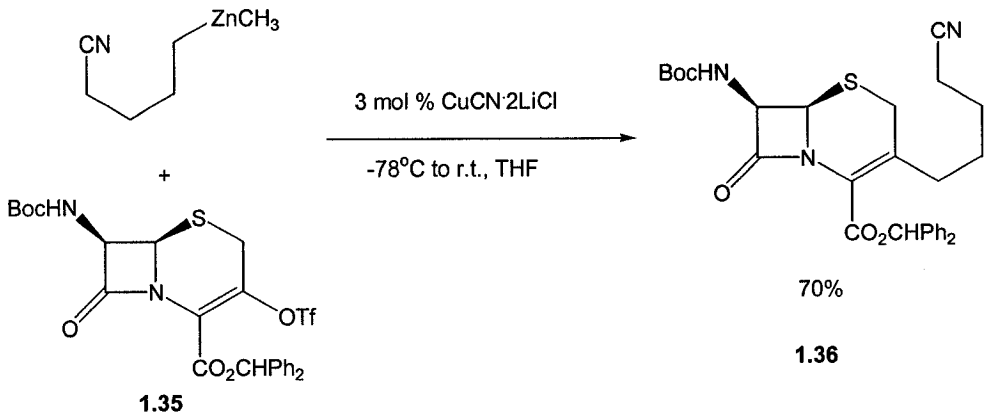
Organozinc reagents, like organolithium and Grignard reagents, are commonly employed in reactions with π-bonded electrophiles, both in 1,2- and 1,4-additions.[38] These species, however, are generally too unreactive to undergo

uncatalyzed coupling reactions with aromatic- and vinylic halides. In addition to palladium catalysts (the Negishi reaction),[39] copper catalysts have shown that cross-coupling between organozinc reagents and organic halides is possible under mild conditions with good selectivity and efficiency.[40] An early example of this showed that coupling of primary, secondary, and benzylic alkyl groups is possible (Scheme 1.23).[41]



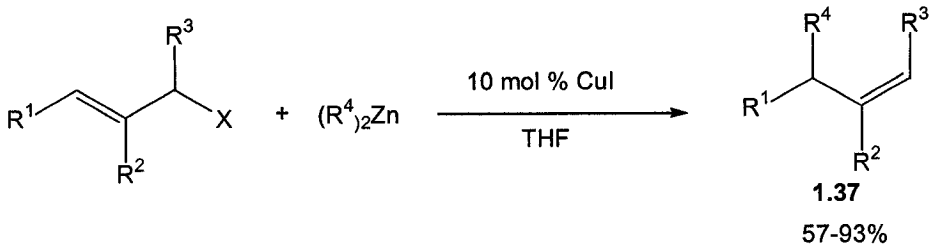
Scheme 1.23 Coupling of organozinc reagents with alkyl halides.

Organozinc reagents also provide a milder and more functional group-tolerant alternative to strong organolithium and Grignard reagents. For example, Lipshutz has performed highly selective alkyl-zinc additions on functionalized penicillin derivatives **1.35** (Scheme 1.24).[42]



Scheme 1.24 Organozinc addition with penicillin derivatives.

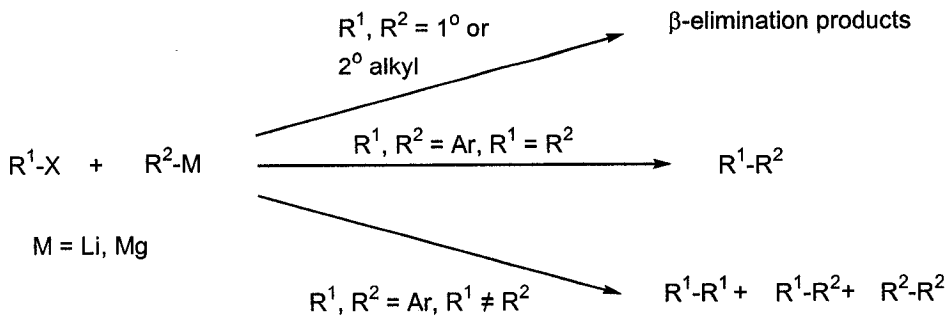
Additionally, when allylic halides are employed, copper catalysts can play a significant role. Organozinc reagents react with allylic substrates without catalysis, but this frequently provides mixtures of direct addition and 1,3-addition products. Selectivity can be achieved by the use of transition metal catalysts. Thus, palladium catalysts typically provide highly S_N2-selective reactions, while copper (I) salts tend to generate the allylic rearrangement (S_N2') product **1.37** (Scheme 1.25). A number of different C-X electrophiles are compatible in this copper-catalyzed organozinc reaction, including allylic-halides, -acetates, -perfluorobenzoates, -sulfonates, and -phosphates.[43] By analogy to the palladium versions of this type of reaction (e.g. the Tsuji-Trost reaction), copper π-allyl complexes represent a likely intermediate in this synthesis.



Scheme 1.25 Allylic substitution of organozinc reagents.

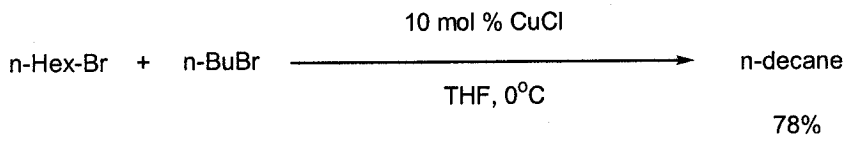
1.1.6 Organolithiums and Grignard Reagents in Cross-Coupling

The ability to generate organolithiums and Grignard reagents from aromatic- and vinylic halides has been known for almost a century.[44] The coupling of these species directly with C=X π-bonded electrophiles is extensively used in synthesis.[45] However, the corresponding reaction with organic halides suffers from significant limitations.[46] For example, unless one employs substrates that do not contain β-hydrogens, the predominant products of the reactions are those of β-elimination. Additionally, when two different organic groups are used, i.e. different groups on the organic halide and the organometallic reagent, mixtures of homocoupled and cross-coupled products can be obtained (Scheme 1.26). Many of the problems associated with the uncatalyzed reaction can be solved by simply using metal catalysis.



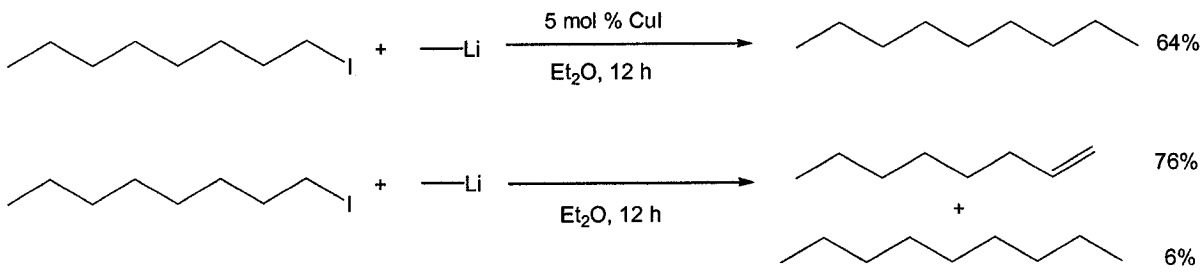
Scheme 1.26 Uncatalyzed coupling of strong organometallic reagents with organic halides.

Since the 1970s, copper, nickel, palladium, and iron catalysts have enabled the development of many methods for the selective coupling of these reactive organometallic reagents and organic halides.[47] The first example of copper salts in coupling of Grignards and organic halides was demonstrated by Kochi and Tamura. Their work showed that when a copper (I) catalyst is used, unsymmetrical coupling can be achieved with little or no homocoupling. An example of this reaction is shown in Scheme 1.27.[48] This catalytic reaction can also be performed with primary alkyl halides, providing good to excellent yields of the coupled products and only minor quantities of the alkene elimination products.



Scheme 1.27 Copper-catalyzed coupling of Grignards with organic halides.

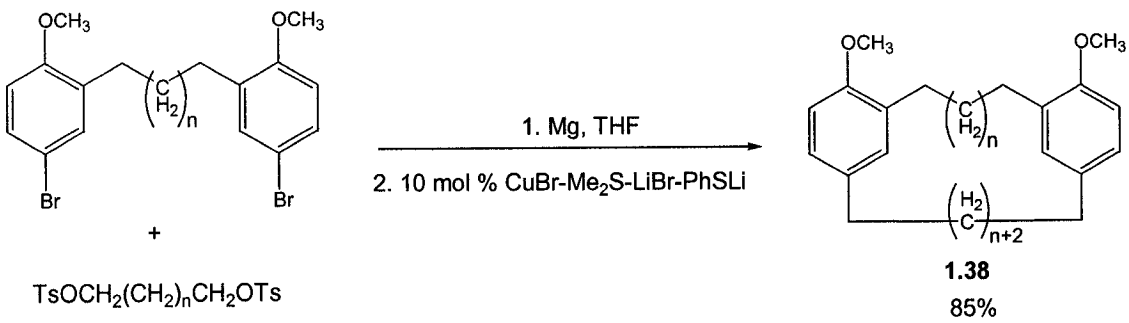
This selective copper-catalyzed coupling between organic halides and these reactive organometallic agents is not only applicable to Grignard reagents. Organolithium species are also compatible in cross-coupling reactions with alkyl halides in the presence of a copper catalyst. An example of this is shown below, in a reaction between n-octyl iodide and methyl lithium. It was discovered that by simply adding 5 mol % CuI to the reaction mixture, the yield increased from 6% (uncatalyzed) to 64% (Scheme 1.28).[49]



Scheme 1.28 Addition of copper (I) iodide to reaction between n-octyl iodide and methyl lithium.

A number of copper catalysts have been found to mediate these reactions. One effective version of these is $CuLi_2Cl_4$, which can catalyze the coupling of many organic halides, -tosylates, -phosphates, and -triflates with organolithiums and Grignard reagents.[47-50] Unfortunately, the $CuLi_2Cl_4$ catalyst tends to be insoluble in many organic solvents. However, a new soluble catalyst system comprising CuBr-Me_2S-LiBr-PhSLi has recently been developed.[51] This collection of reagents shows high performance in the coupling of primary alkyl tosylates and mesylates with a

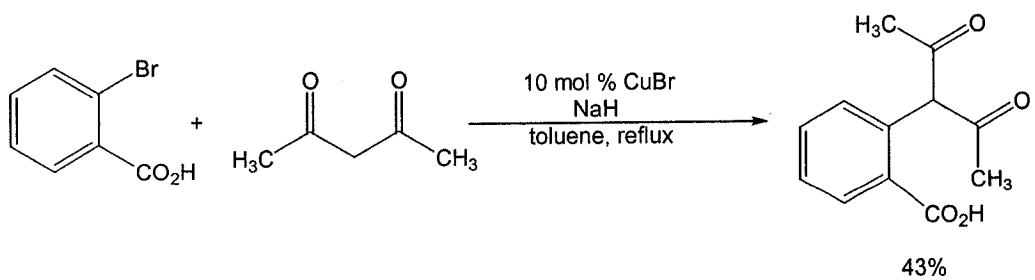
wide scope of Grignard reagents, including aliphatic, aromatic, and vinylic substrates. For example, it has been used in the synthesis of cyclophanes **1.38** (Scheme 1.29).[51b]



Scheme 1.29 Grignard reagents in aryl-alkyl cross-coupling to form cyclophanes.

1.1.7 Arylation of Acidic Methylene Compounds

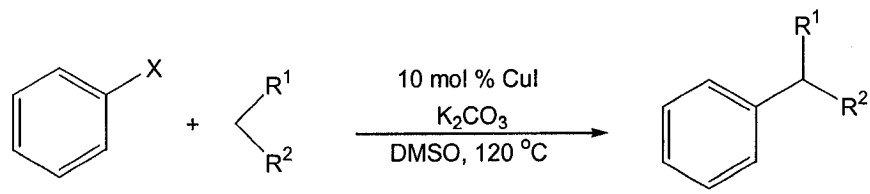
The arylation of acidic methylene compounds through the use of copper complexes or salts, known as the Hurtley reaction, was first reported in 1929 (Scheme 1.30).[52] The initial reaction was limited in scope and could only employ highly activated systems such as o-bromobenzoic acid.



Scheme 1.30 The Hurtley Reaction.

This reaction has since been shown to be applicable to a wider range of substrates, including halogenated derivatives of pyridine, thiophene, and benzofuran.[53] However, many reports involving the copper-catalyzed coupling of aromatic halides with acidic methylene compounds have suffered from the need for high reaction temperatures, polar solvents, and high catalyst loadings. Low yields are also obtained with substrates lacking electron-withdrawing groups on the aromatic halide. Additionally, the functional group compatibility of this reaction is poor, due to the use of NaH as the base.

A far more general approach has been reported in the recent literature for the arylation of a variety of active methylene compounds. Miura has shown that using dimethylsulfoxide (DMSO) as solvent allows for milder reaction conditions, incorporating a wider range of acidic methylene compounds such as ethyl cyanoacetate, malonodinitrile, and acetylacetone (Scheme 1.31).[54]



R^1,R^2 = CN,CN ; CN,CO_2Et ; Ac,Ac

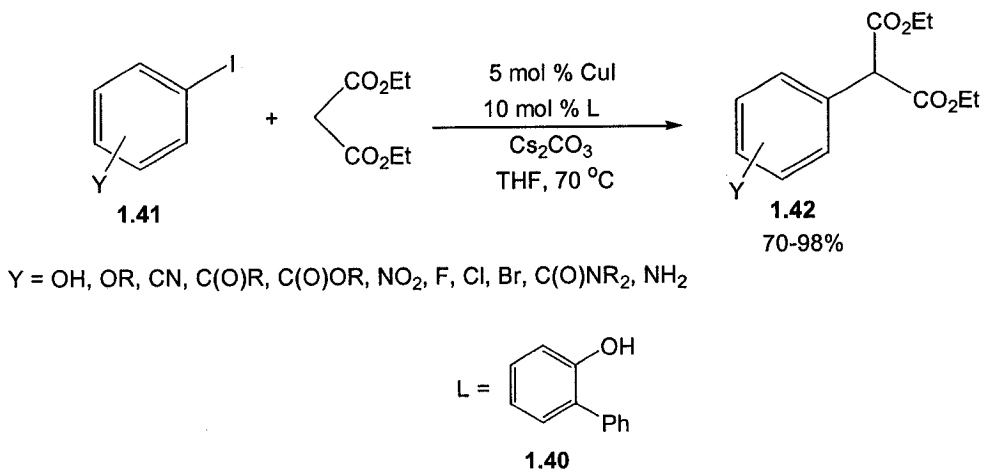
1.39

70-81%

Scheme 1.31 Miura's improved Hurtley reaction.

Although the Hurtley reaction does not involve the use of ligands, under the basic conditions required it is likely that the anionic methylene compound (in enolate form) could bind and chelate to the metal to act as a ligand for catalysis. The addition

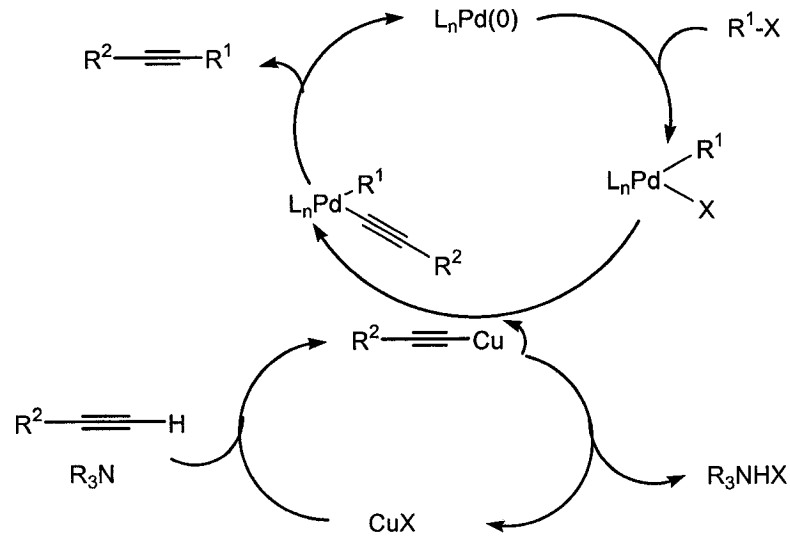
of a ligand to these reactions often proves to be detrimental to the yield, presumably by saturating the coordination sphere of the copper center. In spite of this, it has been shown that the weakly coordinating ligand o-phenyl phenol **1.40** with CuI and Cs_2CO_3 in tetrahydrofuran (THF) allows for efficient coupling of diethyl malonate with a wide range of aromatic halides **1.41** (Scheme 1.32).[55]



Scheme 1.32 Buchwald's improved Hurtley reaction.

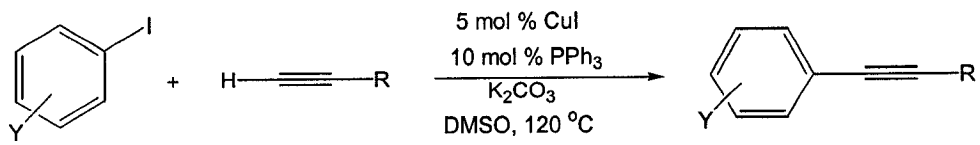
1.1.8 Coupling With Terminal Alkynes

The coupling of aryl- or alkenyl-halides with terminal alkynes is a fundamental palladium-catalyzed carbon-carbon bond forming reaction, known as the Sonogashira-Hagihara reaction.[56] Catalytic quantities of copper salts are generally a required component of this reaction. This catalyst allows for the *in situ* formation of copper acetylides, which transmetalate to palladium, and reductively eliminate the cross-coupled product (Scheme 1.33).



Scheme 1.33 Mechanism of the Sonogashira-Hagihara Reaction.

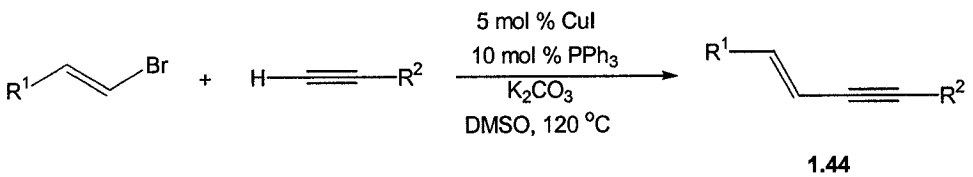
While few examples exist of Sonogashira couplings that are copper-free, there are many palladium-free versions of this reaction.[57] The copper-catalyzed coupling of aryl iodides with terminal acetylenes have been known for some time (Scheme 1.34).[58] Interestingly, while Pd/Cu-catalyzed Sonogashira reactions require amine bases, palladium-free versions of this chemistry are inhibited by amine bases. As such, most of the bases employed in copper-catalyzed alkynylations of organic halides are inorganic, e.g., K_2CO_3.



1.43

Scheme 1.34 Aryl iodide and terminal acetylene cross coupling.

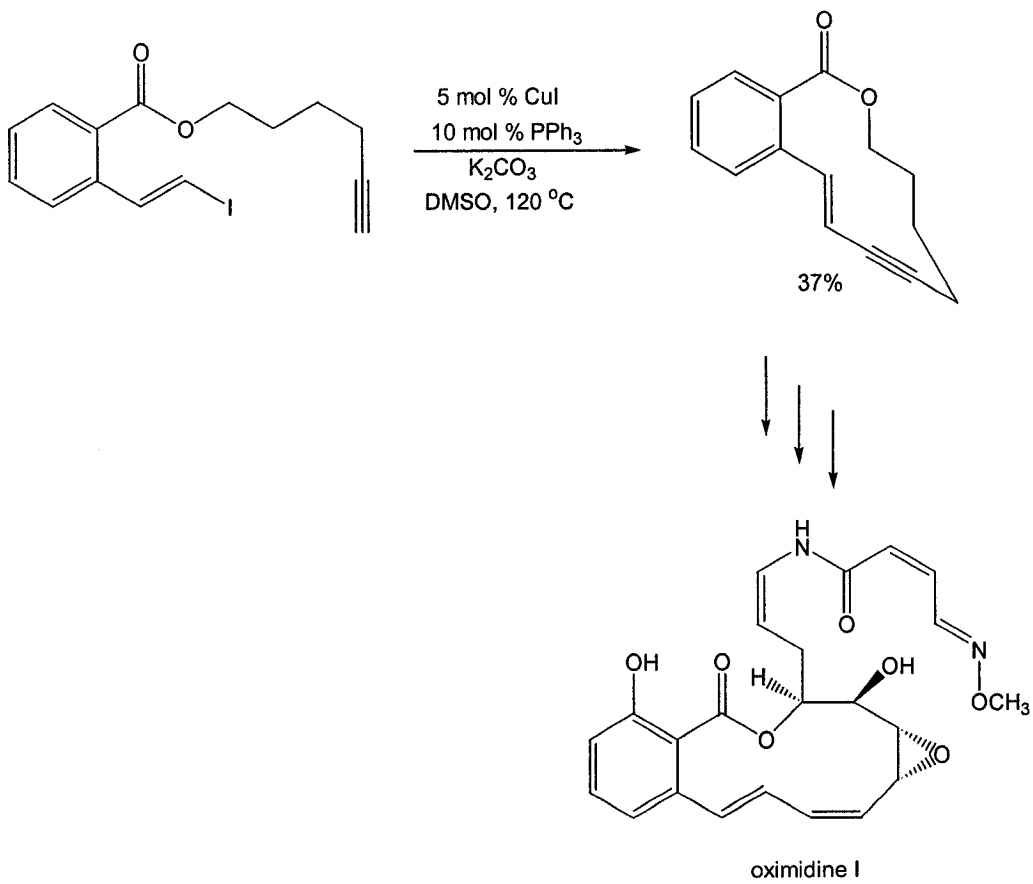
This methodology also works with alkenyl halides under the same reaction conditions (Scheme 1.35).[58] Aryl triflates, -tosylates, and -mesylates are also compatible under the reaction conditions shown above.[56c]



1.44

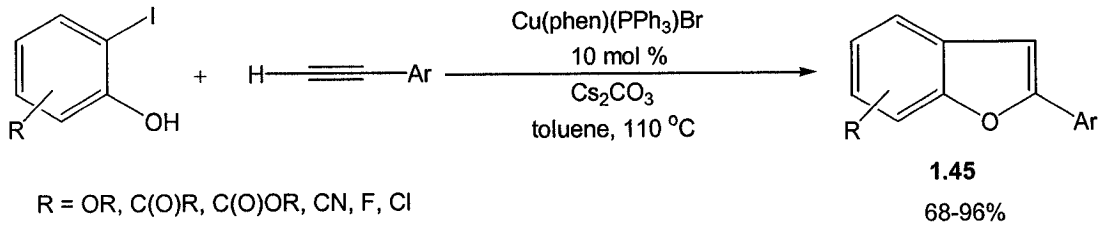
Scheme 1.35 Alkenyl bromide and terminal acetylene cross coupling.

This cross-coupling has also found significant utility in total synthesis. For example, copper-catalyzed alkynylation of organic halides was applied to the total synthesis of oximidine I, through an intramolecular macrocyclization (Scheme 1.36).[59]



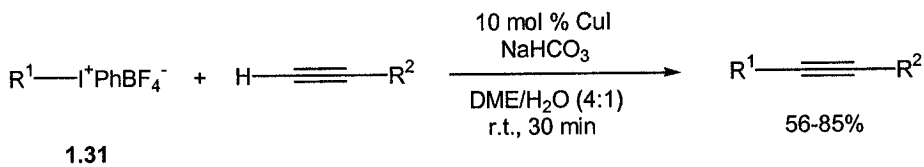
Scheme 1.36 Synthesis of the macrolactone subunit of oximidine I.

As well as simple copper salts, ligated copper complexes can catalyze cross-coupling between aromatic iodides and terminal acetylenes. An example of this involves the use of Cu(phen)(PPh_3)Br (phen = 1,10-phenanthroline). An advantage of using this complex is that it allows the use of toluene as a solvent, in which most CuX salts are insoluble.[60] Under these conditions, a wide range of substituted aryl alkynes, as well as a variety of aromatic iodides with various functional groups (including ethers, ketones, esters, nitriles, and halogens) are compatible. This includes o-iodophenols, which have been employed in the synthesis of benzofurans **1.45** through an *in situ* 5-*endo-dig* cyclization (Scheme 1.37).[60b]



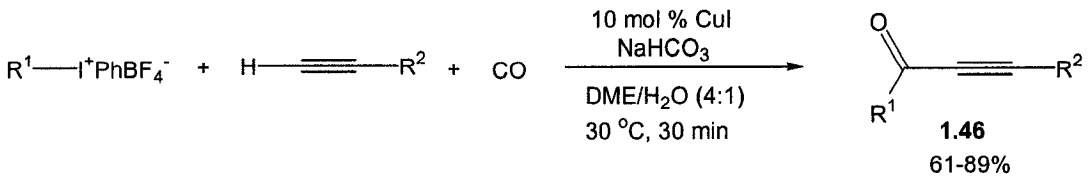
Scheme 1.37 Synthesis of benzofurans using $Cu(phen)(PPh_3)Br$.

While the copper-catalyzed cross-coupling of alkynes with organic halides has been extensively explored, no protocol has emerged that provides the coupling products under mild conditions. Disubstituted alkyne products, however, can be obtained under mild conditions using aryl-, heteroaryl-, alkenyl-phenyliodonium salts as the electrophilic coupling partner.[61] These substrates perform copper-catalyzed cross-coupling with alkynes in the absence of ligands at room temperature (Scheme 1.38).



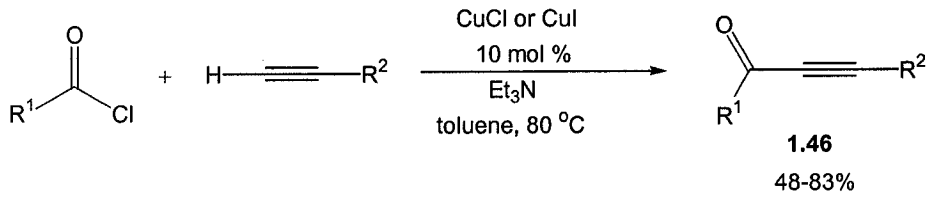
Scheme 1.38 Room temperature cross coupling with iodonium salts.

This reaction can be performed in the presence of one atmosphere of CO, which allows for the carbonylative coupling of aryl, heteroaryl, and alkenyl fragments from the iodonium salt with alkynes (Scheme 1.39).[62] It proceeds with a mild base ($NaHCO_3$) at near ambient conditions (30°C).

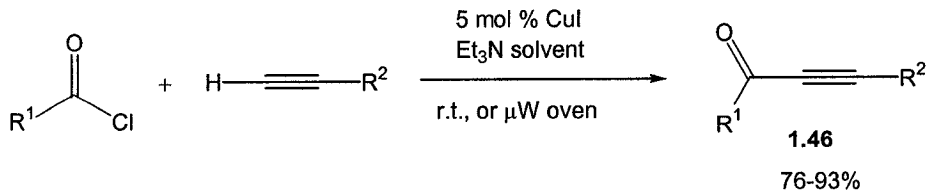


Scheme 1.39 Carbonylative cross coupling of iodonium salts with terminal alkynes.

Acetylenic ketones **1.46** can be generated via the reaction of acyl chlorides and terminal alkynes. It has been shown that copper (I) halide salts catalyze this reaction at high temperatures in toluene (Scheme 1.40).[63] Using triethylamine as a solvent permits this reaction to take place at room temperature, though longer reaction times are required for the coupling to go to completion. It has also been reported that microwave irradiation allows for much shorter reaction times (Scheme 1.41).[63c]



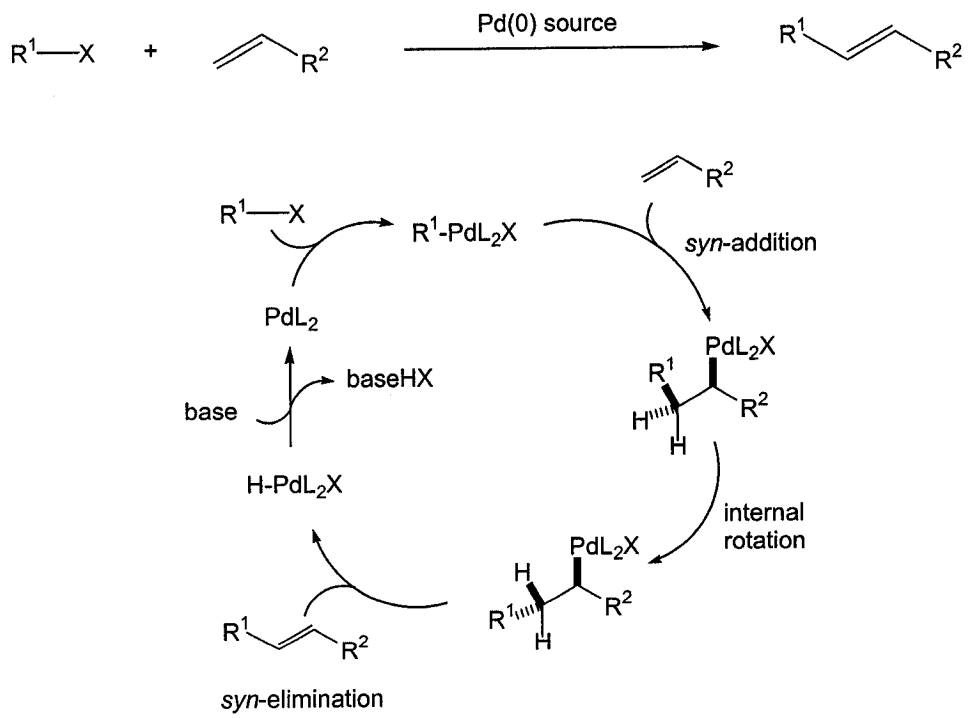
Scheme 1.40 Acid chloride and acetylene coupling in toluene.



Scheme 1.41 Acid chloride and acetylene coupling using Et_3N as solvent.

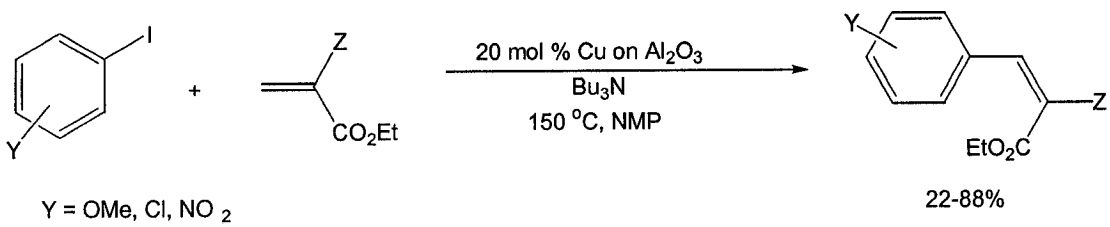
1.1.9 The Copper-Catalyzed Heck Reaction

The Heck reaction involves the palladium-catalyzed coupling of an aryl- or alkenyl halide with alkenes to form more highly substituted alkenes.[64] This process shows mechanistic similarities to cross-coupling reactions, and is believed to involve an initial oxidative addition of the organic fragment to palladium, followed by insertion of the alkene into the metal-carbon bond. A subsequent β-hydride elimination provides the product and elimination of HX regenerates Pd(0) (Scheme 1.42).



Scheme 1.42 Mechanism of the Heck coupling.

The Heck reaction with a copper catalyst has not been extensively explored. In fact, there have been only two examples of this process with copper catalysis; both involve copper (II) salts or copper metal on solid support (Scheme 1.43).[65] For example, copper metal on alumina provides Heck coupled products in moderate to good yields.



Y = OMe, Cl, NO 2

22-88%

Scheme 1.43 The copper-catalyzed Heck-type reaction.

1.2 Copper-Catalyzed Carbon-Carbon Bond Forming Nucleophilic Addition to Imines

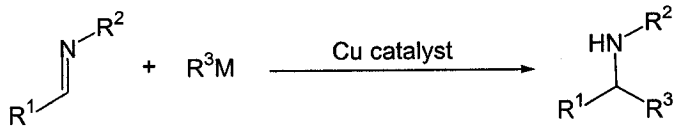
The addition of nucleophilic reagents to imines represents one of the most useful and versatile methodologies for the construction of α-substituted amines. These products are commonly found in many biologically-active molecules, such as amino acids, peptides, antibiotics, pharmaceutical agents, and many more. Nucleophilic carbon-carbon bond forming reactions with imines have been extensively reviewed, in particular those involving the addition of organometallic reagents and enantioselective additions.[66,67] While the direct addition of strongly nucleophilic organometallic reagents to imines provides a useful route to α-substituted amines, these harsh reagents often limit the scope of this reaction. For example, imines derived from enolizable aldehydes, or those possessing reactive functionality (e.g., carbonyl groups, alcohols, primary amines, etc.) are incompatible in most reactions with strong electrophiles.[66a,68] As such, milder, more functional group compatible methods of functionalizing these C=X electrophiles are of significant interest.

The use of metal complexes to catalyze the addition of nucleophiles to imines has received significant attention. These catalysts include, but are not limited to, complexes and salts of zinc, copper, boron, aluminum, scandium, and indium.[68,69] They can allow the use of less reactive nucleophilic reagents, leading to better functional group compatibility. Also, chiral metal complexes provide a handle for asymmetric control when employed in enantioselective additions with organometallic

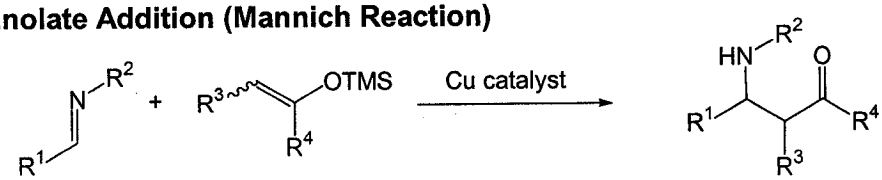
reagents and other nucleophilic substrates. Copper complexes and salts constitute a large part of the breadth of catalysts employed in imine addition reactions, and possess the features listed above as well as being widely available and inexpensive.[70] For these reasons, and due to their relevance to this thesis, copper catalysts in nucleophilic addition to imines will be discussed in this section of the introduction.

A wide range of nucleophilic agents have been used in copper-catalyzed additions to imines. In particular, those involving organometallic reagents, enolates (Mannich reaction), nitroalkanes (Henry reaction), alkenes (imino-ene reaction), aromatics (Friedel-Crafts), and terminal alkynes are some of the most common (Scheme 1.44). In the cases where there has been a significant body of research in the particular area, general trends will be discussed, as well as relevant examples to the given topic. Also, a general discussion of nucleophilic addition of organometallic reagents to imines, involving direct addition and Lewis acid-catalyzed processes, will be included. This will serve to give perspective on how copper catalysts fit in the general field of nucleophilic additions to imines. Additionally, some of the copper-catalyzed additions to imines discussed in this section of the introduction involve processes which provide racemic products without catalysis. Use of chiral copper complexes has been shown to provide enantioenriched products. These reactions will also be discussed.

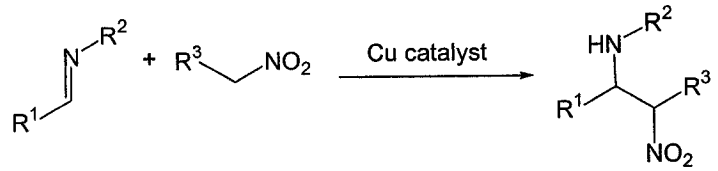
Organometallic Addition



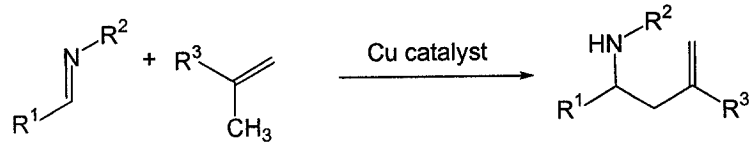
Enolate Addition (Mannich Reaction)



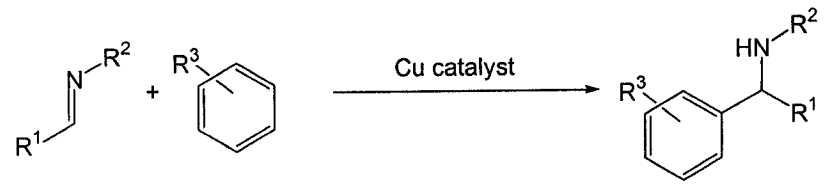
Addition of Nitroalkanes (Aza-Henry Reaction)



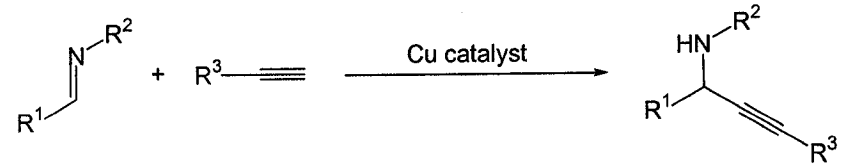
Addition of Alkenes (Imino-Ene Reaction)



Addition of Aromatics (Aza-Friedel Crafts Reaction)



Addition of Terminal Alkynes

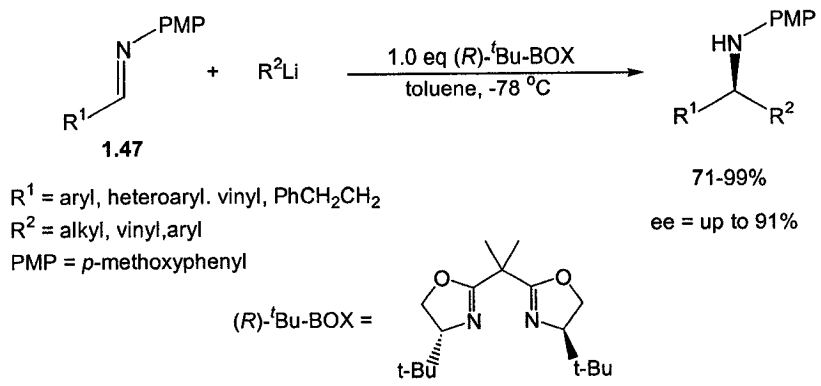


Scheme 1.44 Copper-catalyzed nucleophilic additions to imines.

1.2.1 Addition of Organometallic Reagents to Imines

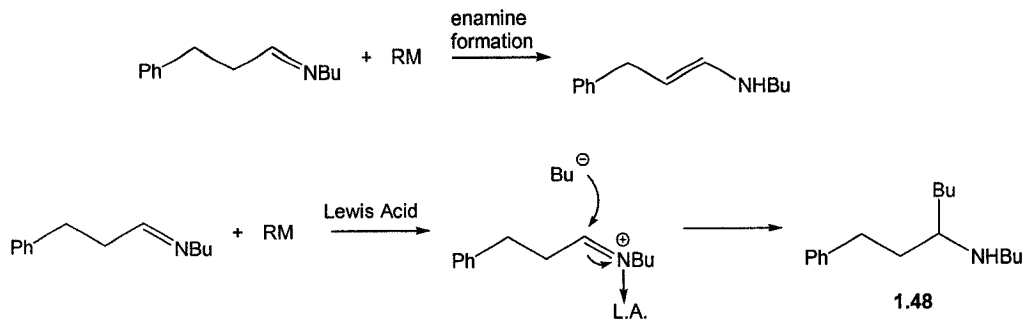
Strong organometallic nucleophiles such as organolithiums and Grignard reagents have been well established to react with imines under the appropriate conditions, to generate the corresponding α-substituted amines in good yields.[66] While effective, reactive functionality on the organometallic reagent or the imine (e.g., carbonyls, hydroxyls, amines, etc.) or acidic substrates (e.g., enolizable imines) can impede these reactions. There has been significant research effort expended to resolve these issues. One of the solutions involves the use of ligands to moderate the nucleophilicity of the organometallic reagent.[69] Also, Lewis acids can increase imine electrophilicity, such that weaker organometallic reagents become compatible in the addition reaction.[68,69] Furthermore, the imine electrophilicity can be increased through the use of *N*-electron-withdrawing groups, or through *N*-alkylation, -acylation, -sulfonylation, or -silylation.[66a,71] These strategies will be briefly discussed.

When organolithium reagents are complexed to stoichiometric quantities of ligands, their strong nucleophilicity and basicity can be moderated, making these reagents more compatible with reactive functionalities.[72] As an illustrative example, Denmark has shown that ^{t}Bu-BOX (bis-oxazoline) ligands with alkyllithiums will perform nucleophilic addition to aromatic and enolizable aliphatic imines **1.47** with good levels of selectivity (Scheme 1.45).[73]



Scheme 1.45 Organolithium / ^{t}Bu-BOX complex in organometallic addition to imines.

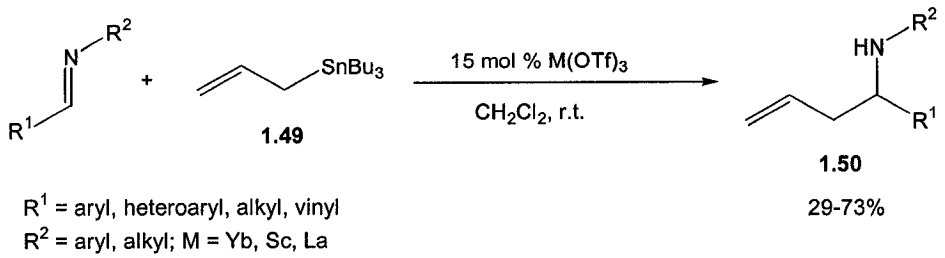
Another effective manner of performing nucleophilic addition to enolizable imines with organometallic reagents is to use Lewis acids to activate the imine.[68,69] This can both favour the addition reaction to the now more electrophilic imine carbon (as opposed to other sites), as well as enable less harsh organometallic reagents to perform nucleophilic attack at the activated imine carbon. Some of the most common Lewis acids used in activation of C=X π-bonds are those of boron, such as $BF_3{\cdot}Et_2O$. Akiba has shown that addition to aliphatic imines is possible through simultaneous activation of imine by the Lewis acid and nucleophilic attack by the organometallic reagent (Scheme 1.46).[74]



RM	Yield (%)
BuMgX	0
BuCu	0
BuLi	54
$BuCuBF_3$	78

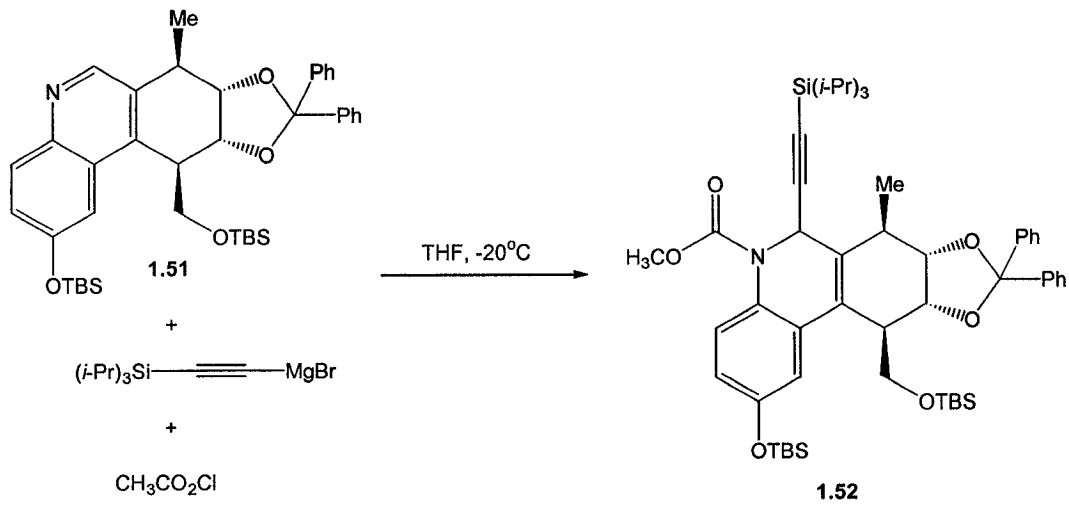
Scheme 1.46 Addition of organometallic reagents to alkyl aldimines.

Many Lewis acids other than boron-based reagents are compatible in such processes. The use of copper complexes as Lewis acids in such couplings will be discussed later, in Section 1.2.3 of this thesis. Other metal salts that are compatible include those of scandium, indium, titanium, tin, the lanthanides, and many more.[68,69] For example, Cozzi and co-workers has shown that lanthanum (III), scandium (III), and ytterbium (III) triflates will catalyze addition of allylstannanes **1.49** to imines. Aromatic-, aliphatic-, α,β-unsaturated-, and heteroaromatic imines are all compatible in this process (Scheme 1.47).[75]



Scheme 1.47 Allylation of imines catalyzed by Lewis acids.

In addition to Lewis acid-catalyzed activation of the imine, alkylation, acylation, and oxidation strategies have been employed to give iminium salts or nitrones, which are more electrophilic than the parent imines.[66a,71] It is well established that such activated imines will undergo addition reactions with organometallic reagents. Of particular relevance to this thesis is the addition of organometallics to *N*-acyl imines and *N*-acyl iminium salts.[68a] These species can react with a range of organolithiums, Grignard reagents, cuprates and organozinc species to generate α-subtituted amides instead of the corresponding α-subtituted amines.[71] One example is shown in Scheme 1.48, where the addition of an alkynyl Grignard reagent to an *N*-acyl quinolinium salt **1.51** leads to the formation of an intermediate in the synthesis of dynemicin.[76]

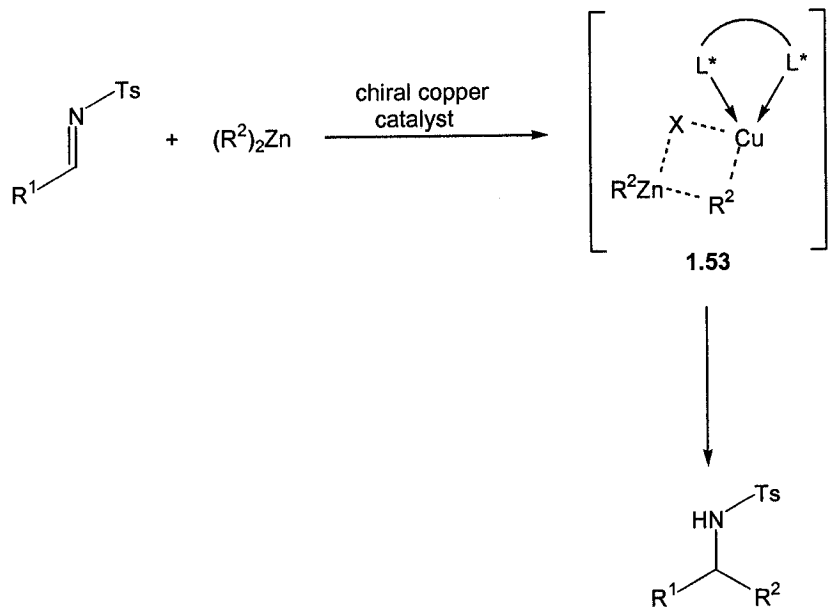


Scheme 1.48 Addition of alkynyl Grignard to *N*-acyl quinolinium salt, toward an intermediate in the synthesis of dynemicin.

1.2.2 Copper-Catalyzed Imine Addition with Organozinc Nucleophiles

Among the many examples of copper-catalyzed nucleophilic additions to imines, the use of organozinc reagents plays one of the most significant roles.[77] While certain organozinc reagents (e.g., allylzincs) will add to a range of imines, many of these compounds tend to react only with imines possessing electron-withdrawing groups as the *N*-substituent.[78] These imines are significantly more electrophilic at the imine carbon, allowing for more facile addition to form amine-based products. Electron-poor imines have been shown to react with chiral organozinc complexes to provide enantioenriched amine products.[78] However, these processes employ stoichiometric quantities of chiral ligand.

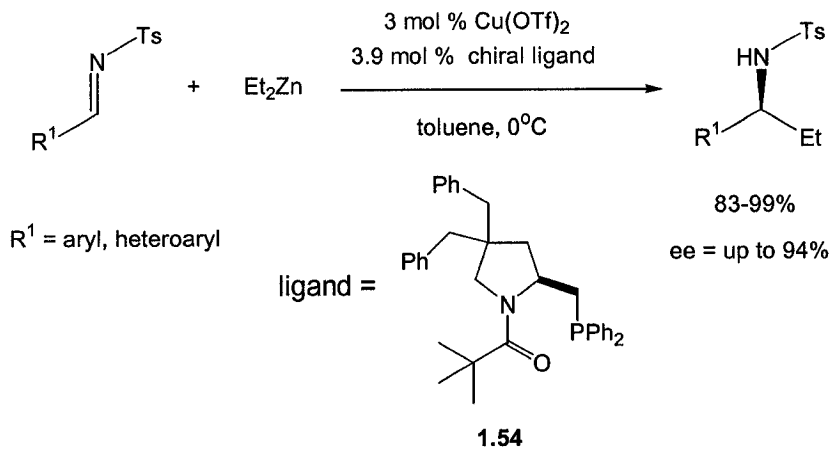
The discovery that copper complexes can catalyze organozinc addition to imines has brought to light the potential to perform catalytic, asymmetric additions to imines through the use of chiral copper catalysts. These processes are hypothesized to involve an initial transmetalation of the organic group from zinc to the copper metal center, and concomitant formation of a zinc-copper-chiral ligand complex **1.53**.[79] The same type of structure has been proposed as the reactive intermediate in copper-catalyzed 1,4-addition to α,β-unsaturated carbonyl-containing compounds.[80] Upon generation of this chiral complex, nucleophilic addition to the imine follows, providing the α-substituted amine product (Scheme 1.49).



Scheme 1.49 Proposed mechanism of copper-catalyzed addition of organozinc reagents to imines.

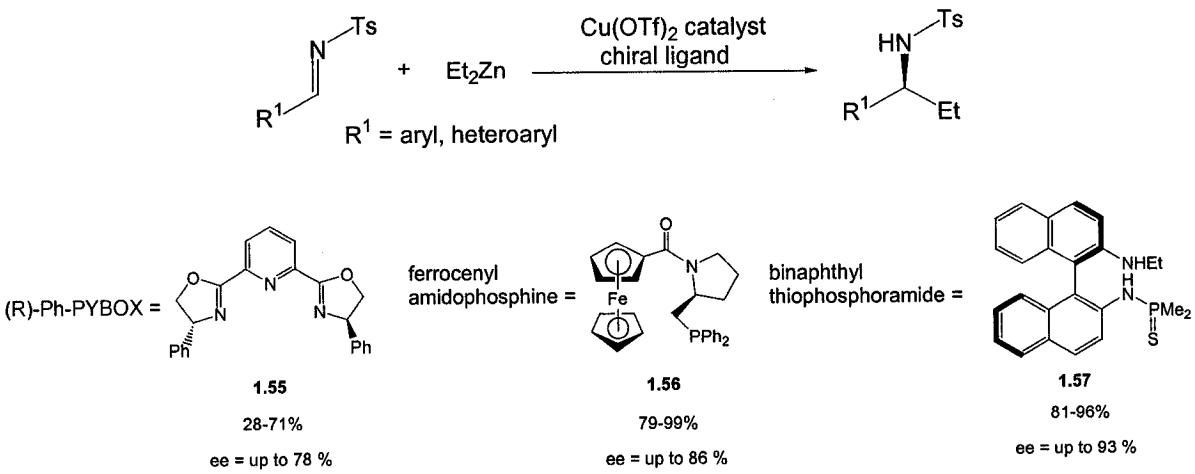
The first example of a copper-catalyzed enantioselective organozinc addition to imines came from the Tomioka laboratories, where *N*-tosyl imines were shown to

undergo asymmetric ethylation with Et_2Zn in the presence of 1 mol % of CuOTf and chiral amidophosphine **1.54**. (Scheme 1.50).[79]



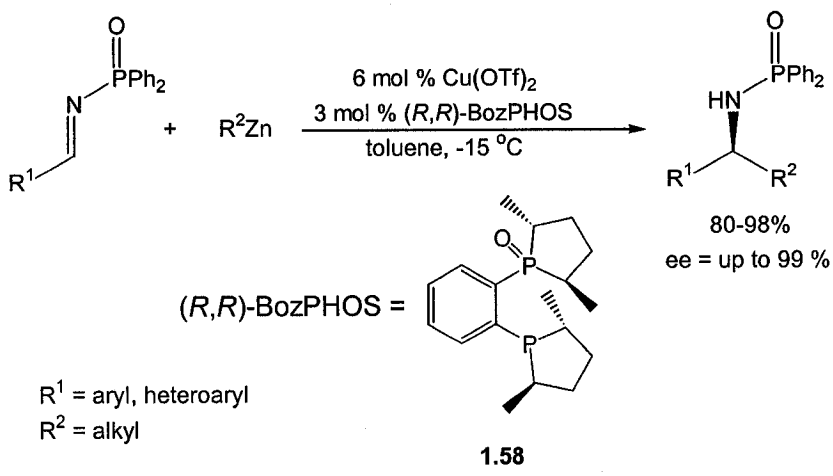
Scheme 1.50 First highly enantioselective diethylzinc addition to *N*-tosyl imines.

Subsequent investigations by a number of research groups showed that various chiral copper complexes were capable of performing this reaction.[81] A few of the more recent examples of these are shown below. For example, Ph-PYBOX **1.55**, ferrocenyl amidophosphines **1.56**, and binaphthyl thiophosphoramides **1.57** have been shown to perform asymmetric addition of zinc reagents to *N*-tosyl imines with high degrees of enantioselectivity (Scheme 1.51).



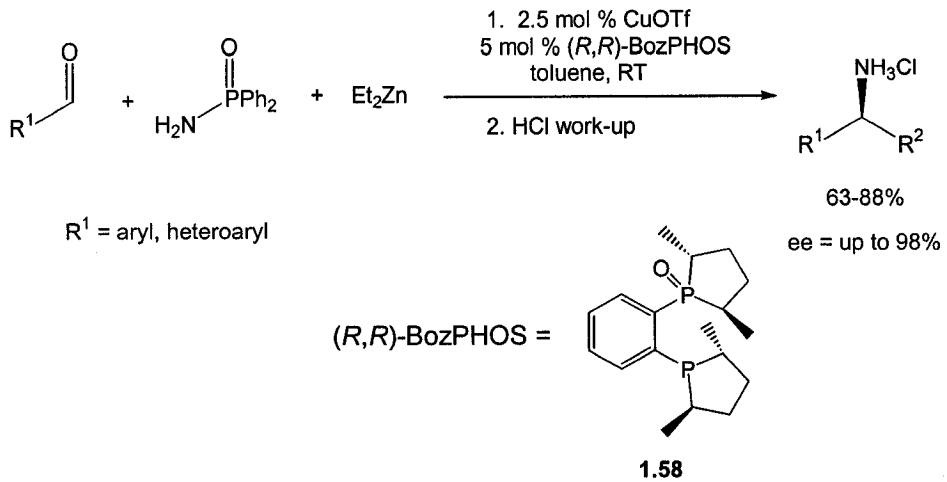
Scheme 1.51 Cu-ferrocenyl amidophosphine catalyzed Et_2Zn addition to *N*-tosyl imines.

In addition to *N*-tosyl imines, *N*-Diphenylphosphinoyl imines have also been employed in copper-catalyzed asymmetric organozinc additions. Charette and co-workers have shown that (*R*,*R*)-Me-DUPHOS, and its mono-oxidized form (BozPHOS, **1.58**), can be employed in organozinc addition to aromatic and heteroaromatic phosphinoyl imines (Scheme 1.52).[82]



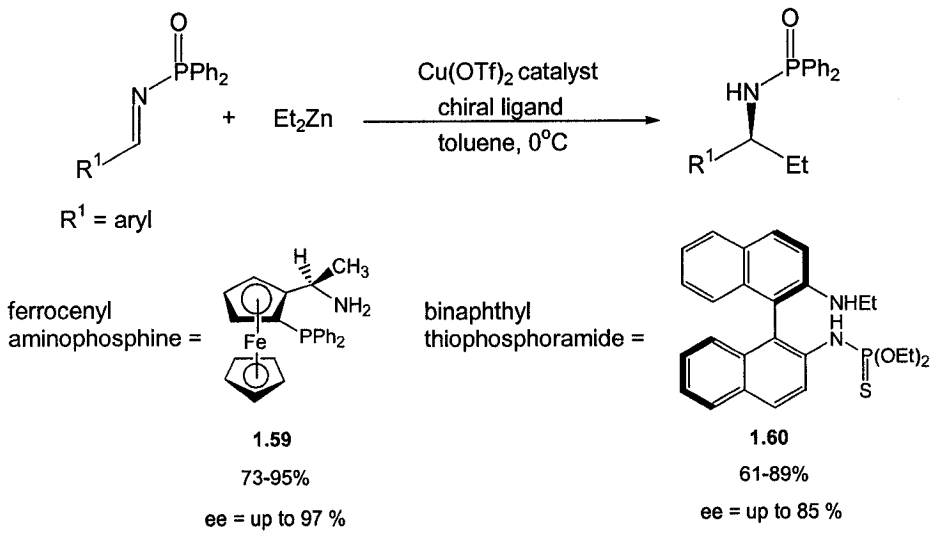
Scheme 1.52 BozPHOS-Cu(OTf)$_2$ catalyzed addition of diethyl zinc to *N*-phosphinoyl imines.

A useful feature of these imines is the ease of deprotection of the phosphinoyl group. In addition, this reaction can be performed via a multicomponent coupling procedure, where the *N*-phosphinoyl imine is generated *in situ* from aryl or heteroaryl aldehydes and diphenylphosphinoylamide, and is subsequently trapped by the dialkylzinc reagent. Following acidic work-up, the free α-chiral amine is formed (Scheme 1.53).[83]



Scheme 1.53 Charette's enantioselective multicomponent coupling forming primary ammonium salts.

The addition of organozinc reagents to *N*-diphenylphosphinoyl imines has also been pursued by other research groups. For example, aminophosphine (**1.59**) and thiophosphoramide (**1.60**) ligands have been shown to be viable in the alkylation of *N*-phosphinoyl imines (Scheme 1.54).[84] However, these ligands are not as simple to synthesize, nor are they commercially available like the BozPHOS precursor, (*R*,*R*)-Me-DUPHOS.



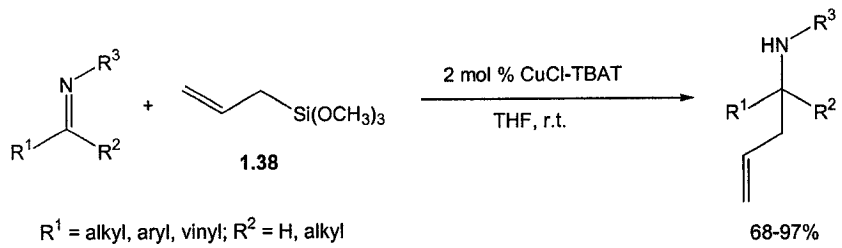
Scheme 1.54 Ferrocenyl aminophosphines and binaphthyl thiophosphoramides in asymmetric diethylzinc addition to imines.

1.2.3 Copper-Catalyzed Imine Addition with Other Organometallic Reagents

While the majority of the reported copper-catalyzed organometallic additions to imines involve organozinc substrates, there are other reagents that have been shown to undergo this process. Representative examples of these are shown below. The majority of these reactions involve allyl-substituted reagents, which tend to be more reactive than the related alkyl- and aryl-substituted organometallics. For example, allyl-substituted silanes, -stannanes, -zirconates, and others are useful coupling partners with imines in the generation of homo-allylic amines.[66] The high reactivity of these allylic substrates is postulated to arise, in part, from the

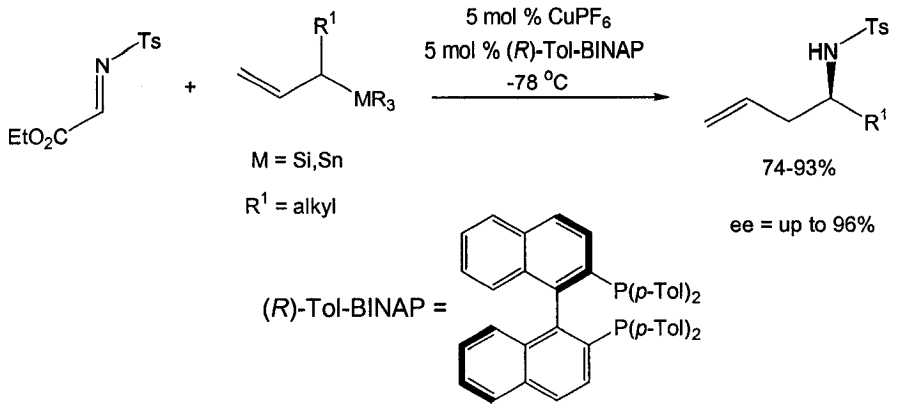
coordination of the allyl π-bond to the copper center, facilitating transmetalation from the organometallic reagent to the copper catalyst.[85] Also, the resonance stabilization of the allyl anion makes the carbon-metal bond more polarized, thus more reactive.

In the case of allylsilanes, Shibasaki has shown that allyltrimethoxysilane can be employed in allylation of imines using a CuCl-TBAT (tetrabutylammonium triphenyldifluorosilicate) catalyst (Scheme 1.55).[86] This reaction allows use of aromatic and aliphatic imines derived from both aldehydes and ketones.



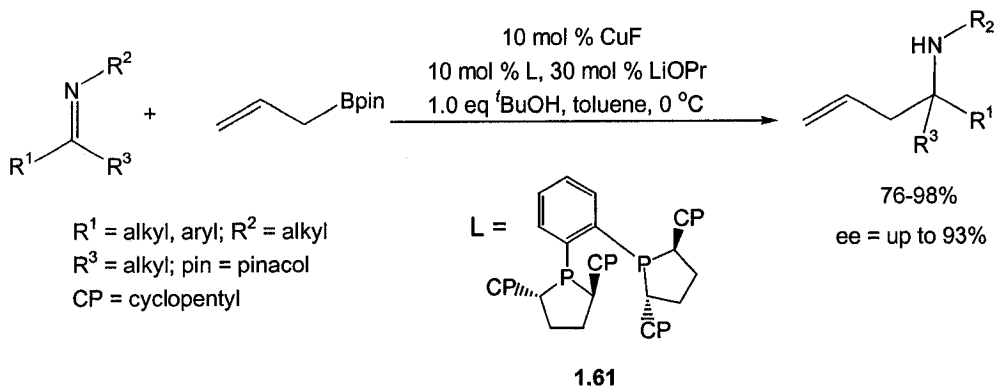
Scheme 1.55 CuCl catalyzed allylation of aldimines and ketimines.

An enantioselective version of this chemistry is possible using chiral ligands. Jørgensen has demonstrated that catalytic, enantioselective allylation of α-imino esters with allylsilanes or allylstannanes is possible using a $CuPF_6$ / Tol-BINAP complex (Scheme 1.56).[87]



Scheme 1.56 Chiral allylation of α-imino esters using silanes and stannanes.

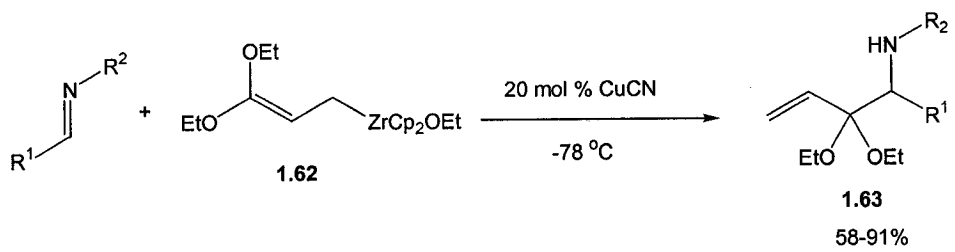
Recently, Shibasaki has shown that ketimines are also viable substrates in enantioselective copper-catalyzed allylation. Through the use of a copper (I) fluoride catalyst, a number of α-tertiary amines can be synthesized under mild reaction conditions with high levels of enantioselectivity (Scheme 1.57).[88]



Scheme 1.57 Catalytic, enantioselective allylation of ketimines.

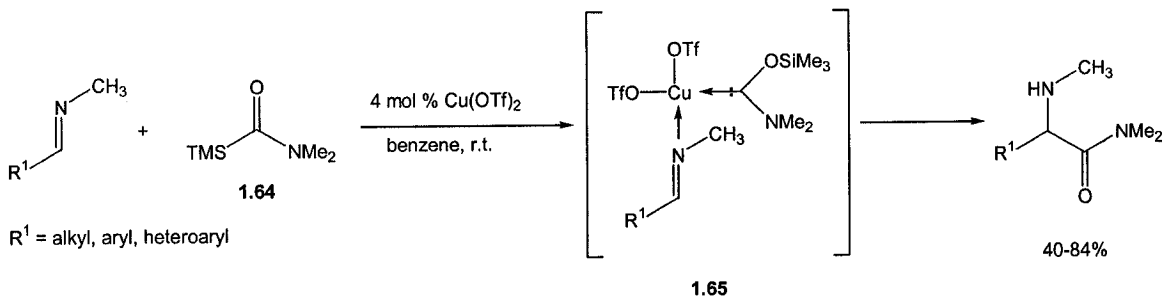
Another type of allyl-organometallic reagent capable of copper-catalyzed addition to imines is an allylic zirconate (**1.62**).[89] Taguchi has shown that CuCN can

catalyze the transfer of the allyl ligand from the zirconium center to form homoallylic amines (Scheme 1.58)



Scheme 1.58 Copper-catalyzed allyl zirconium addition to imines.

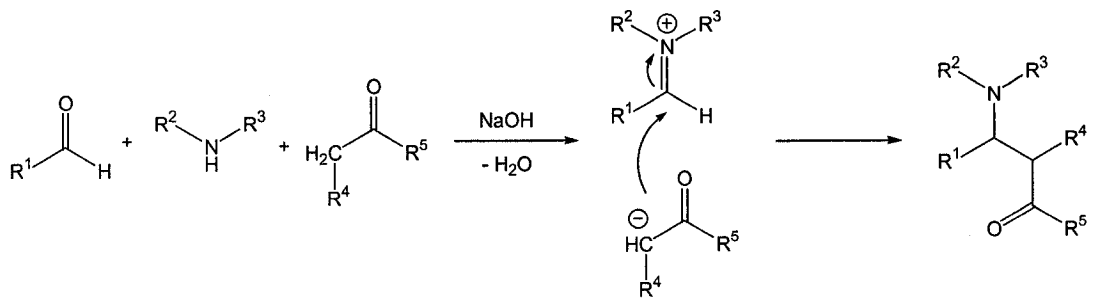
In addition to allylsilanes, copper complexes can catalyze the transfer of other reactive units from silanes to imines. One interesting example of this involves carbamoylsilane **1.64**. The product is thought to form through the *in situ* generation of metallocarbene **1.65**, which performs nucleophilic attack onto the imine to generate an α-amino amide (Scheme 1.59).[90] However, this reaction is very sensitive to electronic and steric factors, and is not very general.



Scheme 1.59 Copper-catalyzed carbamoylsilane addition to imines.

1.2.4 The Copper-Catalyzed Mannich Reaction

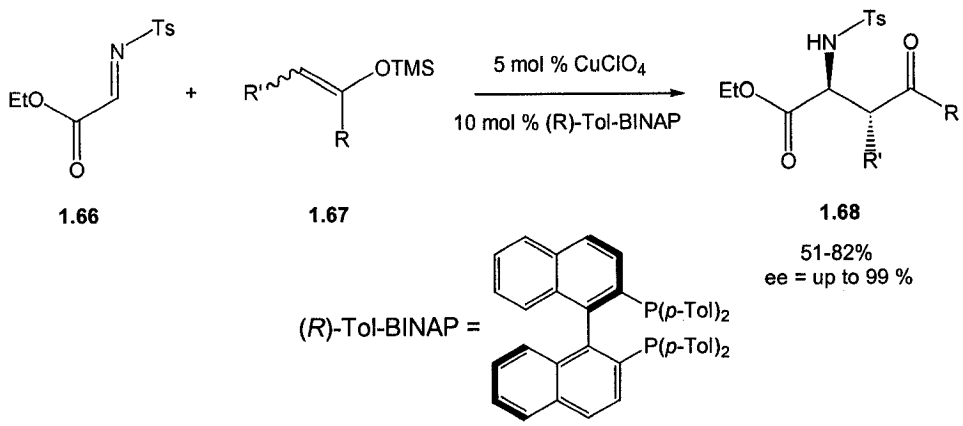
The Mannich reaction was initially reported in 1912 and involved the coupling of aldehydes, amines, and carbonyl-containing compounds.[93] This reaction is particularly useful for the synthesis of carbonyl-containing amines, and all three components in the reaction can be readily diversified. The Mannich reaction proceeds via generation of imine or iminium ion from the aldehyde and amine reagents. The enolate anion that reacts with the iminium ion can be formed *in situ* by α-deprotonation of a carbonyl-containing compound, or from other sources, such as silyl-enol ethers (Scheme 1.60).



Scheme 1.60 Mechanism of a Mannich reaction.

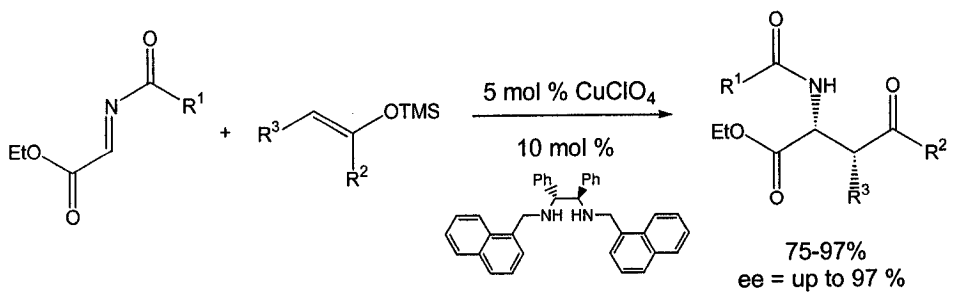
As Lewis acidic metal complexes can coordinate to imines, catalytic, enantioselective versions of this reaction have recently been explored. Kobayashi introduced the first metal-catalyzed enantioselective Mannich condensation involving lanthanide catalysts,[92] but copper catalysts have also been used by the research groups of Lectka, Kobayashi, and Jørgensen.[93] The first copper-catalyzed enantioselective Mannich condensation was reported by Lectka in 1998 using $CuClO_4$ with Tol-

BINAP, in the reaction of α-imino esters **1.66** with silyl enol ethers **1.67** (Scheme 1.61).[93a]



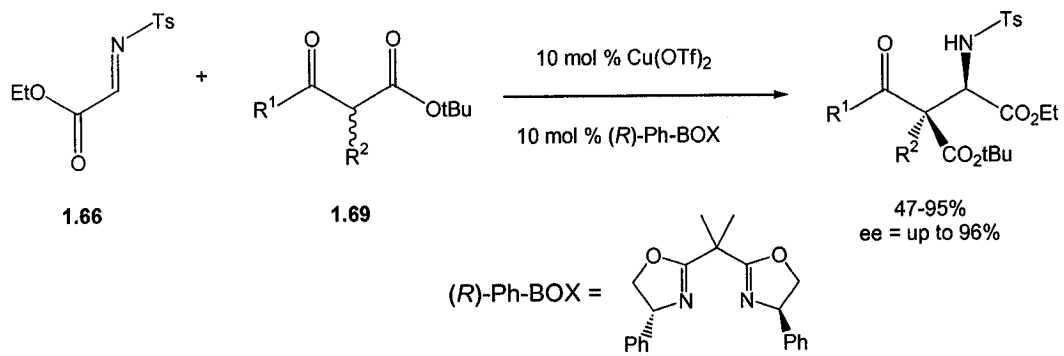
Scheme 1.61 Lectka's copper (I) catalyzed Mannich reaction.

Other copper complexes have proven to be effective catalysts in enantioselective Mannich reactions with α-imino esters. For example, Kobayashi has developed a chiral bis-amine copper (II) catalyst for the asymmetric Mannich reaction of *N*-acyl imino esters with silyl enol ethers (Scheme 1.62).[94] This methodology is readily diversifiable, and allows for the use of easily deprotectable groups on the imine nitrogen as well as silyl enol ethers derived from ketones, esters, and thioesters.



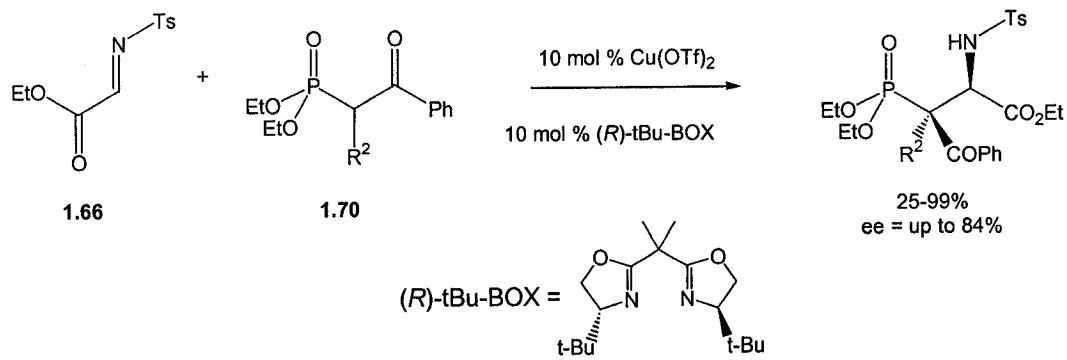
Scheme 1.62 Enantioselective Mannich reaction of *N*-acyl imino esters.

Also, Jørgensen *et. al.* have described the use of copper complexes of Ph-BOX (bis-oxazoline) catalyzed coupling of silyl enol ethers and *N*-tosyl α-imino esters with high enantiomeric excesses.[95] They have also shown that copper complexes of Ph-BOX and ^{t}Bu-BOX can perform this reaction with β-ketoesters and β-ketophosphonates (Schemes 1.63 and 1.64), thus expanding the scope of acidic methylene compounds that are compatible in asymmetric Mannich reactions.



1.66 **1.69** 47-95%, ee = up to 96%

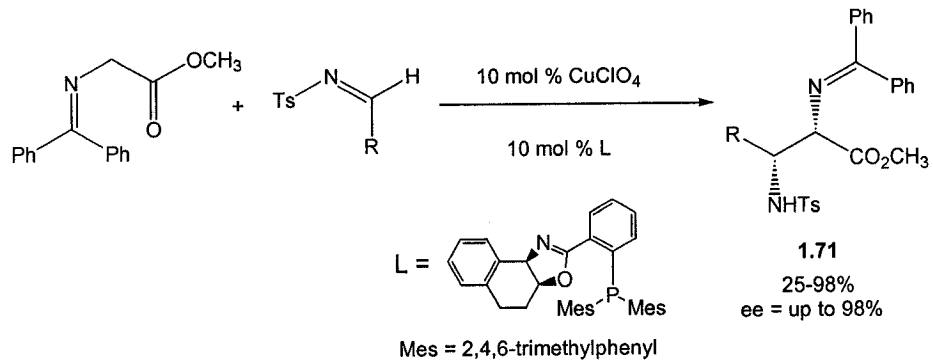
Scheme 1.63 Cu-Ph-BOX-catalyzed addition of malonates to *N*-tosylimines.



1.66 **1.70** 25-99%, ee = up to 84%

Scheme 1.64 Cu-^{t}Bu-BOX-catalyzed addition of β-ketophosphonates to *N*-tosylimines.

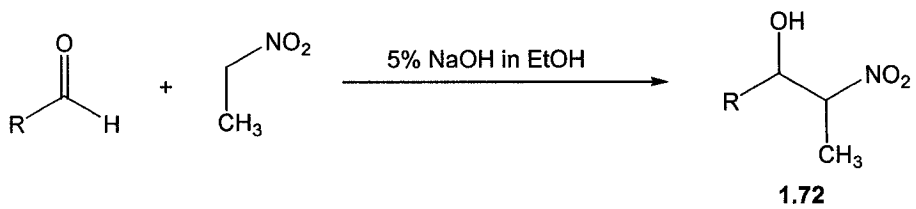
The same research group has shown that enantioselective addition of enolates derived from glycine methyl ester imines to *N*-tosyl imines is viable through copper catalysis (Scheme 1.65).[96] This provides a useful method of preparing orthogonally diprotected α,β-diamino acid derivatives **1.71** with good to excellent degrees of enantioselectivity. These diamines are useful building blocks for the synthesis of unnatural oligopeptides and nitrogen-containing heterocycles.[97]



Scheme 1.65 Enantioselective addition of azomethine ylides to *N*-tosylimines.

1.2.5 The Aza-Henry Reaction

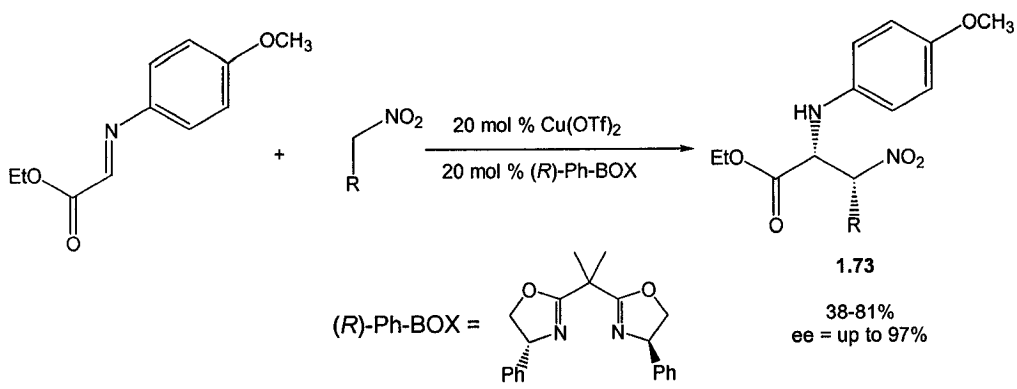
The Henry reaction, otherwise known as the nitro aldol reaction, involves the base-catalyzed addition of a nitroalkane to a carbonyl-containing compound.[98] The original work describes NaOH-catalyzed addition of nitromethane to aromatic and aliphatic aldehydes (Scheme 1.66). The Henry reaction has been extensively used in the synthesis of α-amino alcohols. [98b]



Scheme 1.66 The Henry reaction.

The aza-Henry reaction, where an imine is used instead of a carbonyl compound, is also noteworthy due to the ability to reduce the nitro functionality, allowing the generation of diamines.[99] Although this reaction in its racemic form has no need of a catalyst, Jørgensen has shown that it proceeds in the presence of chiral copper (I) complexes, thereby generating chiral products with moderate to high ee's.[100] There have also been reports of enantioselective aza-Henry reactions with organocatalysts and zinc complexes.[101]

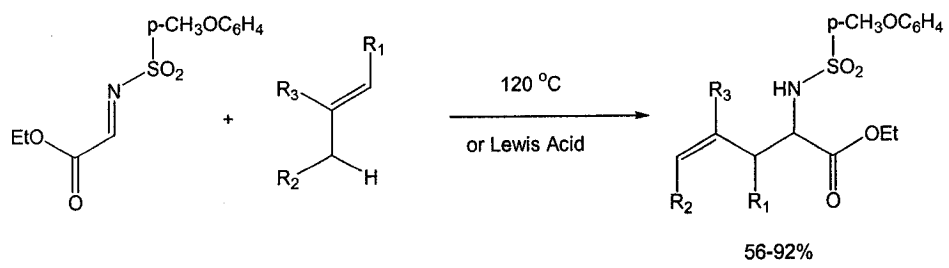
Copper (I) complexes of a variety of bis-oxazoline-based (BOX) ligands have been shown to provide β-nitro-α-amino esters in high enantioselectivities,[100] from both alkyl nitro compounds and nitronates (Scheme 1.67). This same reaction can be performed using the BOX-ligand grafted onto mesoporous silica, which allows for catalyst recycling.[100c]



Scheme 1.67 Jørgensen's asymmetric Aza-Henry reaction.

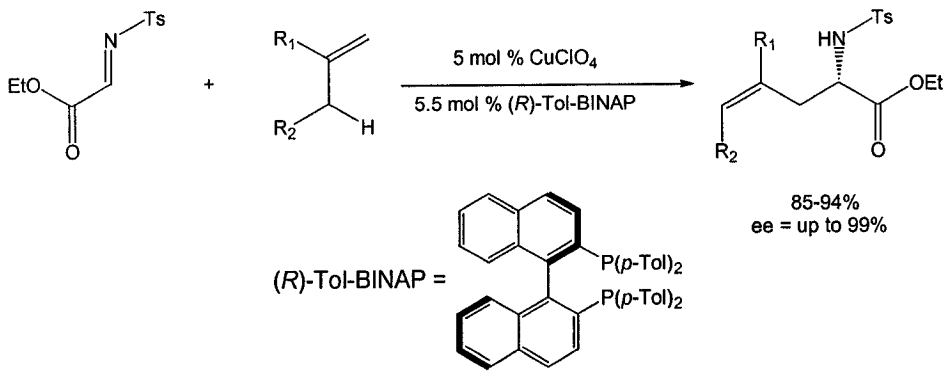
1.2.6 The Imino-Ene Reaction

The ene reaction typically involves the addition of an alkene possessing an allylic hydrogen atom to a multiply-bonded electrophile.[102] The imino-ene reaction, known since the 1980s, was first reported by Achmatowicz and co-workers (Scheme 1.68).[103,104] Although this reaction was shown to be most successful when performed at high temperatures, Lewis acid catalysts also generate the desired products in reasonable yields at milder reaction temperatures.



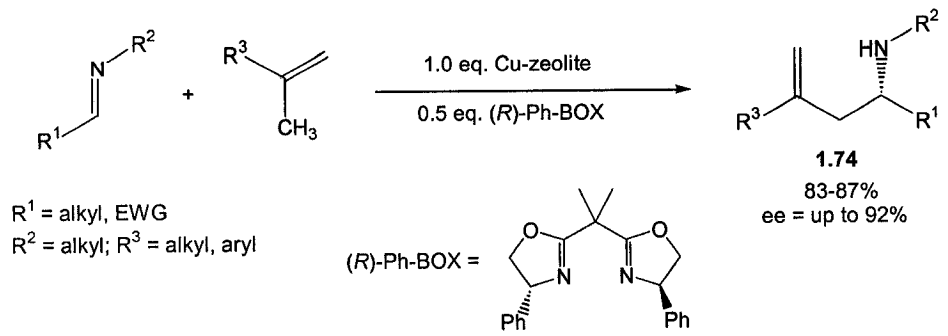
Scheme 1.68 First reported ene reaction involving imine substrates.

As the ene reaction with imines is accelerated by Lewis acids, use of a chiral metal complex would make an enantioselective variant possible. There have, however, been only three reports of copper-catalyzed enantioselective imino-ene reactions. It has recently been shown though in two concurrent publications that this reaction can be performed using $CuClO_4$ with Tol-BINAP as chiral ligand (Scheme 1.69).[105]



Scheme 1.69 Lectka's and Jørgensen's asymmetric imino-ene reaction.

Alternatively, a heterogeneous catalyst has also been reported for this reaction, where bis-oxazoline ligands bound to a Cu(II)-zeolite system have proven to be effective at inducing asymmetry into the imino-ene products **1.74** (Scheme 1.70).[106] This catalyst has been reused in the reaction up to four times without significant loss of yield or enantioselectivity.



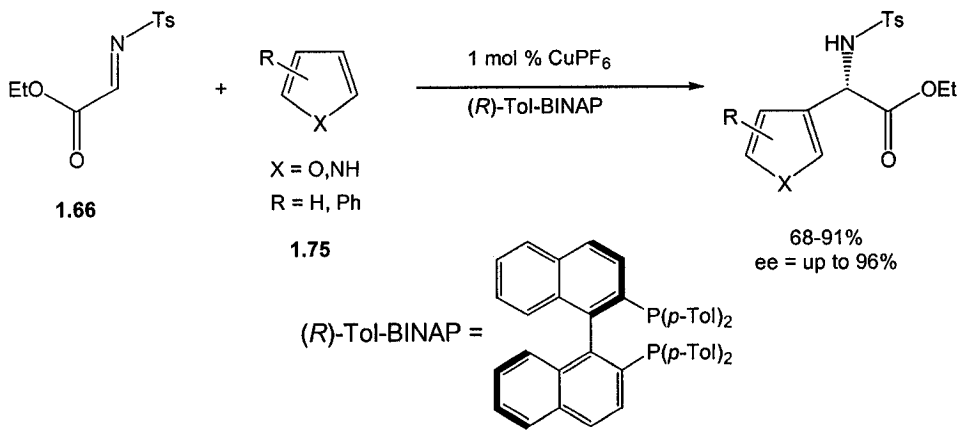
Scheme 1.70 Copper (II)-zeolite-BOX catalyst for the asymmetric imino-ene reaction.

1.2.7 The Friedel Crafts Reaction Involving Imine Substrates

The Friedel Crafts reaction typically involves Lewis acid-catalyzed addition of alkyl and acyl substituents to aromatic compounds.[107] This reaction has been used for many years and has been extensively reviewed.[108] Conversely, the similar addition of imines to arenes has been the subject of few reports. Since Friedel Crafts reactions with imines leads to the formation of chiral, albeit racemic α-substituted amines, there exists the potential for introducing asymmetry into this reaction by using chiral Lewis acid catalysts.

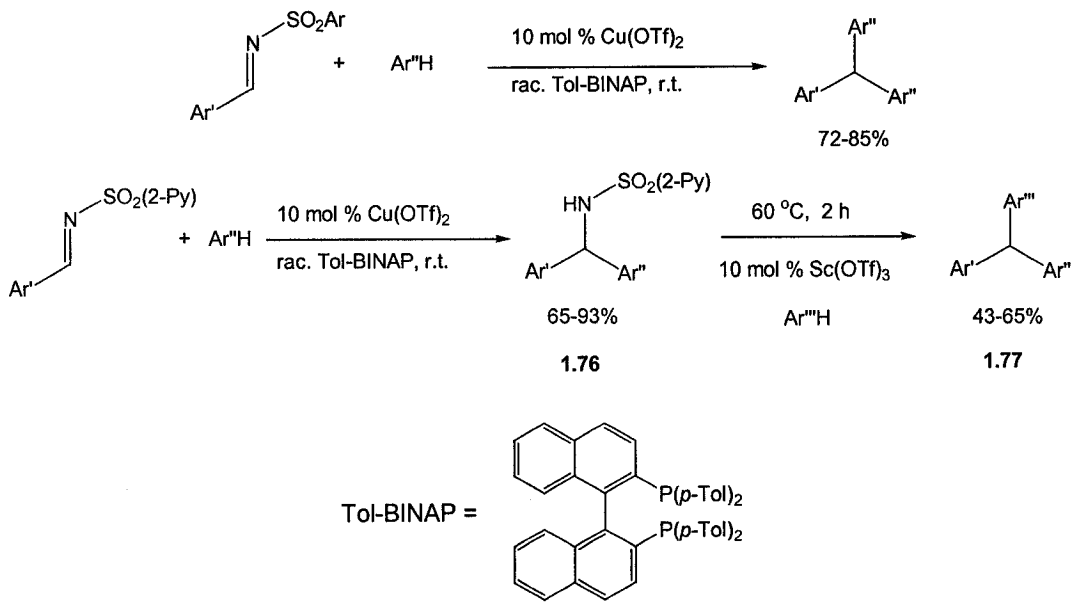
Reports of metal-catalyzed aza-Friedel Crafts reactions demonstrate that copper complexes can provide efficient routes to arylated amine products. For example, α-imino esters **1.66** have been shown to react with indoles, pyrroles, and furans (**1.75**) in the presence of $CuPF_6$ and Tol-BINAP, to provide enantiomerically

enriched α-heteroaryl amino esters in excellent yields (Scheme 1.71).[109] Electron-rich arenes are also viable reagents in this process.[110]



Scheme 1.71 Aza-Friedel Crafts reaction of heteroaromatics.

Carretero has shown that Cu(II) complexes with racemic BINAP can catalyze the addition of consecutive aromatic groups to imines (Scheme 1.72).[111] The nature of the sulfonyl group on the imine nitrogen allows for control of the number of aryl additions to the imine. For example, when a *p*-toluenesulfonyl group is employed, two aromatic moieties will add to the imine, providing triarylmethane products. Alternatively, through the use of a 2-pyridyl-sulfonyl group, the process is halted after addition of one arene, resulting in the generation of diaryl-substituted amines **1.76**. These products can be heated with 10 mol % $Sc(OTf)_3$ in the presence of another arene, to furnish unsymmetrical triarylmethanes **1.77**.

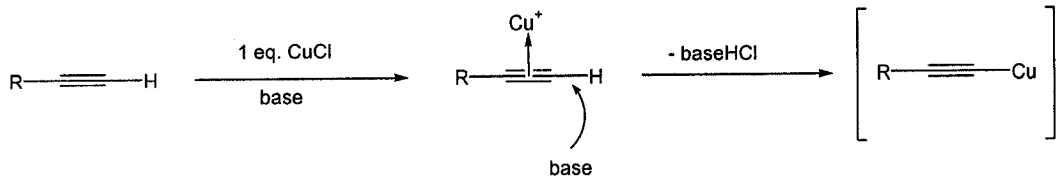


Scheme 1.72 Aza-Friedel Crafts reaction toward triarylmethanes.

1.2.8 Addition Of Terminal Alkynes To Imines

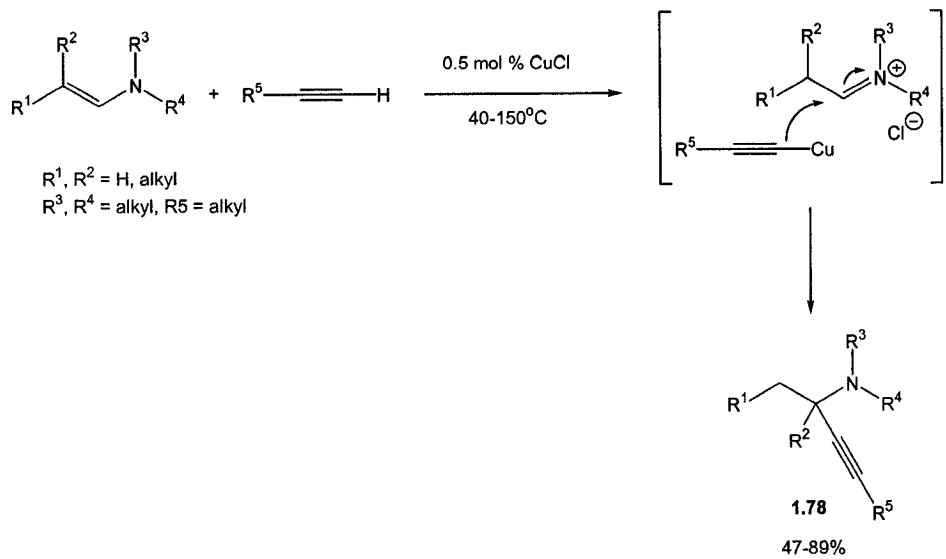
The addition of metal-acetylides to imines has been employed for decades to form propargylic amine derivatives.[112] Strong organometallic nucleophiles such as lithium- and magnesium-acetylides can add directly to imines to generate the corresponding propargylamine products.[113] These routes, however, are somewhat limited in the scope of imines and functional groups that can be incorporated into the resulting materials. More recently, the direct, metal-catalyzed addition of terminal alkynes to imines has been shown to be a mild and efficient method for the generation of propargylamines. Besides zinc,[114] iridium,[115] gold,[116] and silver[117] catalysts, copper complexes have shown significant promise in catalyzing these transformations.

Copper catalysts are thought to promote deprotonation of the terminal alkyne by coordination to its π-bond, thereby increasing the acidity of the carbon-hydrogen bond. This proton can be removed by mild bases in the presence of copper (I) salts and complexes, generating a transient copper-acetylide. This species can then perform nucleophilic attack on imines and imine derivatives (Scheme 1.73).[113]



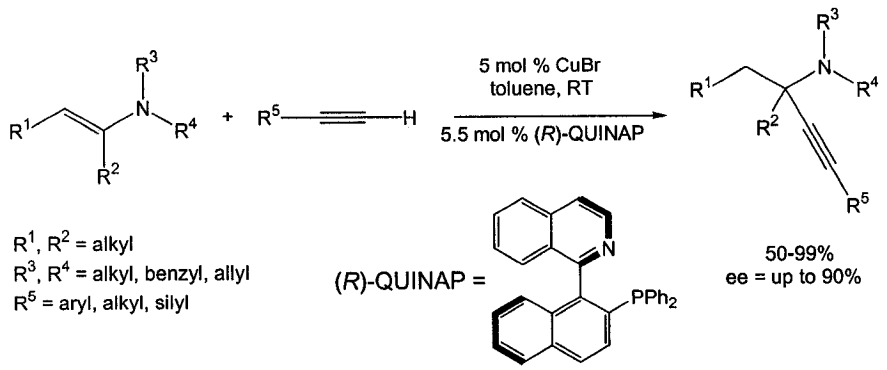
Scheme 1.73 Copper (I)-promoted deprotonation of terminal alkynes.

The copper-catalyzed addition of alkynes to enamines was first successfully employed in the generation of propargylamines by Brannock, Burpitt, and Thweatt in 1963.[118] This process presumably occurs via the *in situ* generation of an *N,N*-dialkyl iminium salt through protonation of the enamine, followed by alkyne attack to form the propargylamine product **1.78** (Scheme 1.74).



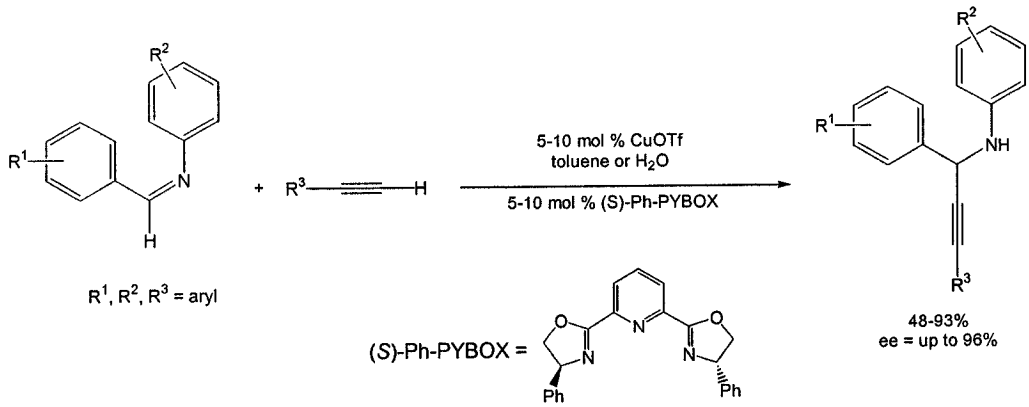
Scheme 1.74 First copper-catalyzed addition of alkynes to enamines.

This reaction has recently been developed by Knochel *et al.* into an asymmetric process using the chiral ligand QUINAP (Scheme 1.75).[119] The chiral tertiary propargylamine products are useful as synthetic intermediates toward many related structures. Some examples of these include primary and secondary amines, bicyclic pyrrolidines, and α-alkyl amines (through reduction of the alkyne). Many of these molecules have found utility in natural product synthesis and in pharmaceuticals.



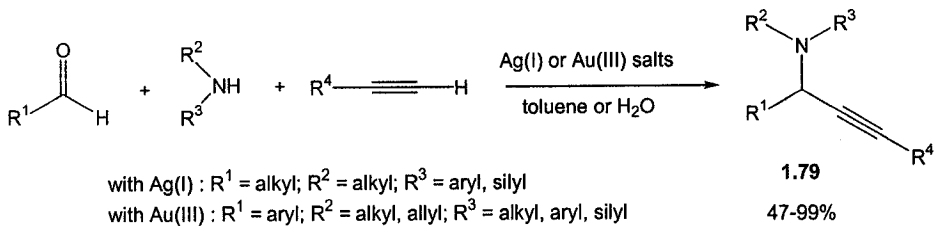
Scheme 1.75 Enantioselective addition of alkynes to enamines.

Regarding the addition to imines themselves, Li has demonstrated the ability of CuOTf complexes of Ph-PYBOX to catalyze enantioselective alkynyl addition to *N*-aryl imines both in toluene and water under mild reaction conditions (Scheme 1.76).[120] This work has been followed by Benaglia, who has also shown that enantioselective alkynylation of *N*-aryl imines is possible through the use of chiral bis-amine and bis-imine ligands, though with lower enantioselectivities than Li's system.[121]

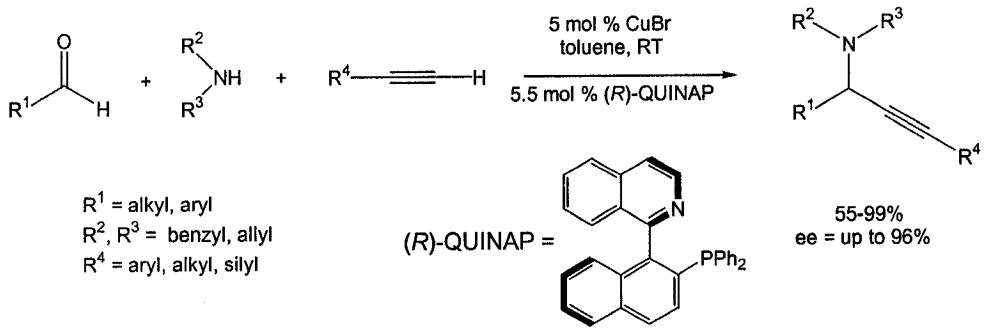


Scheme 1.76 Enantioselective alkynylation of *N*-aryl imines.

The Li and Knochel laboratories have also shown that copper, silver, and gold catalysts are competent in the three component coupling of aldehydes, amines, and alkynes. The silver and gold catalysts are complementary, where the coupling with aromatic aldehydes is more successful with the gold catalyst, while aliphatic aldehydes couple more efficiently in the presence of silver salts (Figure 1.77).[116,117] This three component coupling can also be performed enantioselectively with copper salts and chiral ligands (Scheme 1.83).[122]

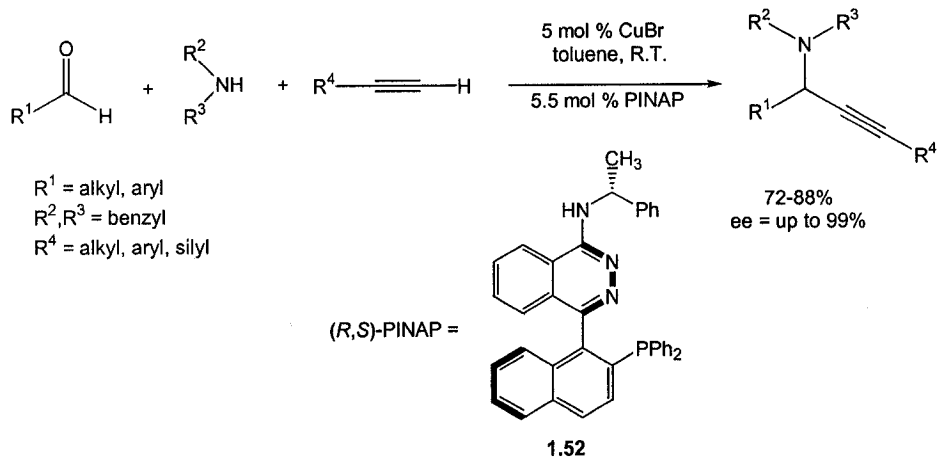


Scheme 1.77 Three component coupling of aldehydes, amines, and alkynes with silver or gold salts.



Scheme 1.78 Enantioselective three component coupling of aldehydes, amines, and alkynes with copper / QUINAP catalyst.

This three component coupling of aldehydes, amines, and alkynes has been further elaborated by many laboratories. It has been found that the coupling is compatible with a number of different conditions, including microwave heating, ultrasound, and the use of ionic liquids as solvent or neat conditions.[123] Carreira *et. al.* have provided asymmetric versions of this chemistry, employing the PINAP (**1.52**) series of ligands (Scheme 1.79).[124]

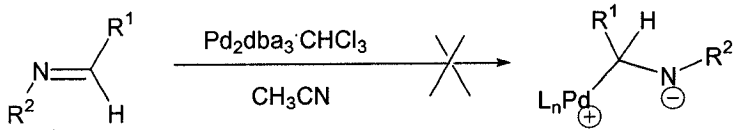


Scheme 1.79 Enantioselective three component coupling of aldehydes, amines, and alkynes.

1.3 The Use of Imines in Cross-Coupling Reactions

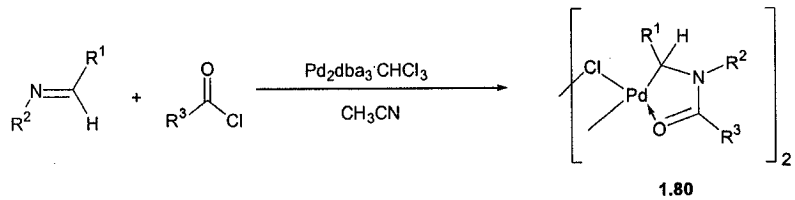
The palladium-catalyzed cross-coupling of organic electrophiles and organostannanes, known as the Stille reaction, is a mild and selective method for performing carbon-carbon bond formation.[125] It is part of a family of palladium-catalyzed processes known as cross-coupling reactions. The Stille reaction can

incorporate many functionalized groups on the organotin reagent, and is compatible with a wide range of R-X electrophiles. These electrophiles include organic halides and sulfonates, as well as a number of recently reported substrates, such as organic-ammonium salts, -diazonium salts, -iodonium salts, carboxylic acid derivatives, and many more.[126] However, multiply-bonded $R_2C{=}X$ electrophiles are not known to perform cross-coupling. This results from the inability of these electrophiles to undergo the first step of a cross-coupling reaction: oxidative addition (Scheme 1.80).[127] This limitation is of significance, since the products of carbon-carbon bond formation with imines are α-substituted amines and amides. The latter can be found in many biologically-relevant molecules, including amino acids, β-lactams, peptide-mimics, and biopolymers. α-Substituted amides can be constructed through nucleophilic additions to imines, however many of these methods are neither as mild nor as functional group-compatible as cross-coupling reactions.



Scheme 1.80 Proposed intermediate formed from oxidative addition of imines to palladium (0) sources.

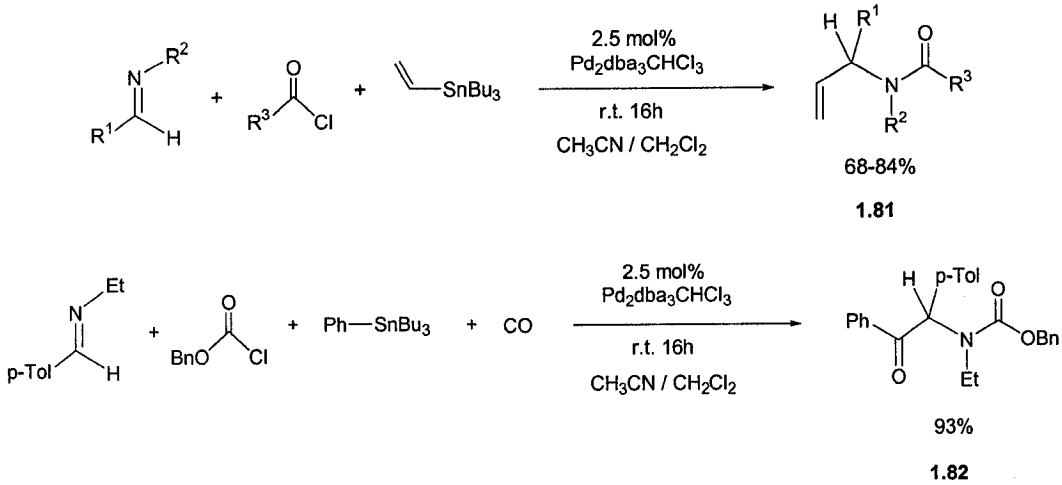
Research in the Arndtsen laboratories has recently shown that imines, in the presence of acid chlorides or chloroformates, can be induced to undergo oxidative addition to palladium (0) sources such as $Pd_2(dba)_3$ to form amido-substituted palladacycles **1.80** (Scheme 1.81).[128]



1.80

Scheme 1.81 Oxidative addition of imines and acid chlorides to generate amido-substituted palladacycles.

When comparing the structures of the proposed products resulting from oxidative addition of imines vs. imines and acid chlorides (Schemes 1.80 and 1.81), it is evident that the more stable structure would be the latter. This dimeric palladacycle is stabilized by the chelating effect of the acyl group, as well as the charge-balancing effect of the chloride ligand, resulting in a new palladium-carbon bond (Scheme 1.81). This discovery led to the development of a palladium-catalyzed cross-coupling of imines, acid chlorides, and organostannanes to form α-substituted amides (Scheme 1.82). This coupling occurs under mild reaction conditions, and is compatible with a wide range of imines and acid chlorides / chloroformates. In addition, under an atmosphere of carbon monoxide, α-amido ketones can be prepared. Overall, this represents the first use of multiply-bonded electrophiles in cross-coupling reactions, and provides a useful route to α-substituted amides and *N*-protected amines.[129]



Scheme 1.82 Oxidative addition of imines and acid chlorides to generate amido-substituted palladacycles.

1.4 Overview of Thesis

Copper-catalyzed cross-coupling reactions continue to be an important area of research in the formation of new carbon-carbon bonds. These reactions often possess high levels of functional group compatibility as well as the ability to incorporate starting materials that are typically not considered viable under traditional nucleophile-electrophile approaches. In addition, the use of catalysis provides a handle with which to control the regioselectivity and enantioselectivity of these reactions.

Similarly, carbon-carbon bond forming nucleophilic addition to imines is one of the most simple methods of generating α-substituted amines. These structures are among the most prevalent in biologically relevant molecules, and are useful building

blocks in the synthesis of nitrogen-containing heterocycles. While metal catalysts such as those of copper can mediate the addition of classic nucleophilic reagents to imines (e.g., organolithiums, Grignard reagents), the more mild and functional group compatible traditional cross-coupling reagents (e.g., organostannanes, boronic acids) are unreactive toward cross-coupling reactions with imines. Combining these features would provide a mild, selective, and facile route for generating α-substituted amines and amides.

However, recent work in this laboratory showed that imines can be induced to undergo a palladium-catalyzed Stille-type cross-coupling reaction with organostannanes in the presence of acid chlorides.[129] In addition to providing a unique method to use π-bonded electrophiles in cross-coupling reactions, this transformation provides a mild alternative to the use of more reactive nucleophilic agents in carbon-carbon bond formation with imines. While this reaction provides an important precedent, the initial report was only shown to proceed with vinyl- or aroyl-substituted stannanes. This issue significantly limits the range of α-substituted amides and *N*-protected amines that can be generated via this cross-coupling route. Thus, we have investigated the potential generalization of this reaction, by the design of more reactive metal catalysts. The initial research described in this thesis (Chapter 2) involves the development of a copper, rather than palladium, -catalyzed route to achieve the coupling of imines, acid chlorides, and organotin reagents.[130] This methodology provides a more general synthesis of α-substituted amides, through its ability to incorporate a far wider range of organostannanes in the cross-coupling. It also provides a catalyst that can provide control over regioselectivity of addition. This

is possible through simple changes to the catalyst structure, by addition of halide salts or nitrogen-containing ligands. When employing α,β-unsaturated imines, the former leads to a favouring of the 1,4-addition products, while the latter favours 1,2-addition.

The Stille-type reactions with organostannanes are only one type of a family of cross-coupling reactions as described in Section 1.1. Since each of these cross-coupling reactions proceeds via a similar mechanism, they are, in principle, each potentially applicable to this carbon-carbon bond formation with imines. For example, the similarities between the copper-catalyzed cross-coupling of organostannanes (Stille-type) and that of terminal alkynes (Sonogashira-type) indicate that alkynes could prove to be viable cross-coupling partners with imines. This was found to be the case; the copper-catalyzed three component coupling of imines, acid chlorides, and terminal alkynes provides propargylamides under mild reaction conditions in minutes (Chapter 3).[131] Many imines, acid chlorides / chloroformates, and terminal alkynes are compatible under the reaction conditions. Of note is the fact that pyridine will also undergo cross-coupling with alkynes in the presence of an acid chloride, producing the partially reduced 1,2-dihydropyridine product in good yield.

This process provided us with an efficient route to tertiary propargylamides and *N*-protected secondary amines from imines, acid chlorides, and terminal alkynes. However, we also sought a route to generate secondary propargylamides. These species are found in a range of biologically active molecules, e.g., oxotremorine, and in herbicides and fungicides. They are also useful in the synthesis of nitrogen-containing heterocycles: secondary propargylamides are known to undergo cyclization to form trisubstituted oxazoles. Chapter 4 will detail our investigation of

this process ultimately leading to a copper-catalyzed four component coupling reaction to form secondary propargylamides from aldehydes, lithium hexamethyldisilazide (LiHMDS), acid chlorides, and alkynes.[132] By exploiting the reactivity of these products, this methodology also led to a copper-catalyzed multicomponent synthesis of trisubstituted oxazoles.

In Chapter 5, a more atom economical and less toxic alternative to the cross-coupling of imines with organostannanes is presented. Organoindium reagents have recently been shown to undergo palladium-catalyzed cross-coupling reactions with aryl triflates, bromides and iodides. The most notable feature of such couplings is that all the organic fragments from the organoindium reagent are transferred to the electrophilic substrate. Here the copper-catalyzed coupling of imines, acid chlorides / chloroformates, and tri- / tetra-substituted organoindium reagents is presented.[133] A useful observation pertaining to this reaction is that addition of organo-indium reagents to α,β-unsaturated imines under CuCl catalysis provides exclusively the 1,4-addition product.

The products of the couplings described in Chapters 2-5 all contain racemic chiral centers. In Chapter 6, we describe studies directed toward the design of enantioselective, catalytic routes to these products, through the use of chiral-ligated copper catalysts. In the case of the catalytic alkynylation of nitrogen-containing heterocycles such as quinoline and isoquinoline, the synthesis and use of chiral PINAP-based ligands led to the discovery of a catalyst which provides alkynyl-substituted-1,2-dihydro-quinolines and alkynyl-substituted-1,2-dihydro-isoquinolines

in up to 84% ee. This process is also viable for the enantioselective alkynylation of pyridine with good enantioselectivity.

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CHAPTER TWO

The Copper-Catalyzed Cross-Coupling of Imines, Acid Chlorides, and Organostannanes: A Multicomponent Synthesis of α-Substituted Amides

2.0 Preface

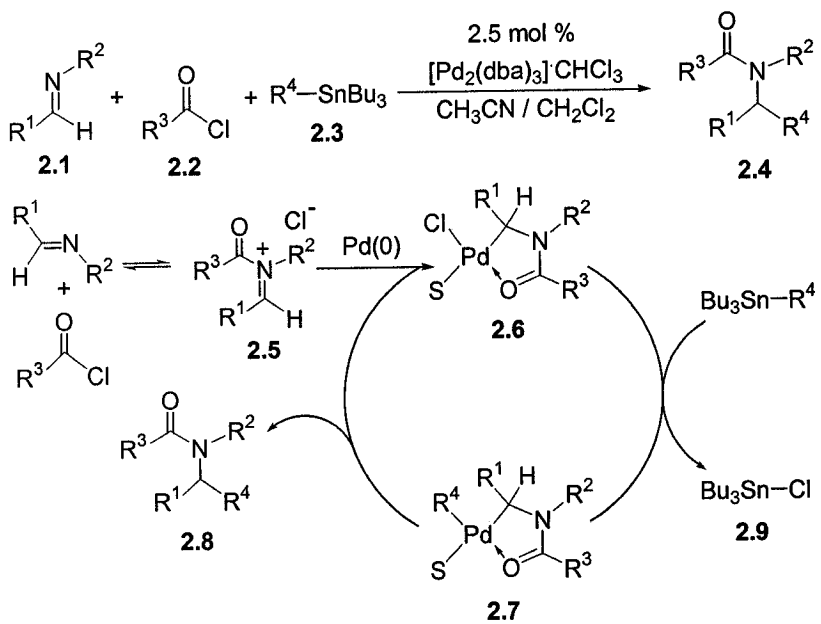
As mentioned in the introduction, previous work in this laboratory has shown that the cross-coupling of imines, acid chlorides and organostannanes is possible through the use of a palladium (0) catalyst. While providing a mild method of generating the amide products, a more general procedure able to incorporate a wider range of organostannanes was sought. This chapter details the development of a copper-catalyzed protocol, which, as well as performing the cross-coupling under mild reaction conditions, proceeds with a diverse range of aryl-, heteroaryl-, and vinyl-substituted organostannanes and employs an inexpensive and readily available catalyst.

2.1 Introduction

The palladium-catalyzed cross-coupling of organic electrophiles with organostannanes, known as the Stille coupling, has received growing attention as a mild and selective method for carbon-carbon bond formation.[1] A useful feature of the Stille reaction is the diverse array of organotin reagents compatible with coupling, as well as their low intrinsic reactivity. This often allows the reaction of functionalized electrophiles and organotin reagents in late stages of complex molecule synthesis without prior functional group protection.[1a,2] In addition, Stille and related cross-couplings have been demonstrated to proceed efficiently with a range of R-X electrophiles. These include classic examples, such as organic-halides or -sulfonates,[1] as well as a wide range of more recently developed coupling partners (e.g. diazonium salts,[3] iodonium salts,[4] esters or carboxylic acid derivatives,[5,6] aryl-imidazoles,[7] ammonium salts,[8] etc.).

While Stille couplings have proven to be a straightforward approach to carbon-carbon bond formation with R-X substrates, a typical limitation of this reaction is its inability to mediate a similar coupling with multiply-bonded electrophiles, such as imines. This results, in part, from the inability of these substrates to undergo what is presumably the first mechanistic step of cross-coupling reactions: the direct addition to Pd(0) to form a Pd-C bond.[9] This limitation is of significance, since imines are readily modified building blocks for synthesis, and carbon-carbon bond formation with imines provides a route to prepare α-substituted amines or amides. The latter represent one of the most

common core structures in biologically relevant molecules. The nucleophilic addition of organolithium, organozinc, or Grignard reagents to imines has been elegantly exploited as a route to prepare achiral and chiral α-substituted amines,[10] however, these reactions are often less mild and functional group compatible than typical Stille couplings. Alternatively, non-imine based palladium-catalyzed cross-coupling routes to α-substituted amines and amides have also been developed, such as the α-arylation or allylation of glycine derivatives.[11] In addition, the rhodium-catalyzed reaction of organoboranes or organostannanes with imines allows for the formation of α-substituted amines through an alternative mechanism.[12]



Scheme 2.1 Palladium-catalyzed coupling of imines, acid chlorides, and organostannanes.

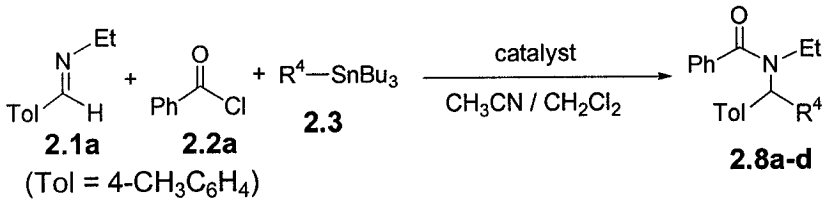
We have recently demonstrated that while imines themselves are incompatible with palladium-catalyzed Stille couplings with organotin reagents, they can be induced to undergo cross-coupling by the simple addition of acid chlorides (Scheme 2.1).[13] This presumably occurs via the acid chloride stabilization of imine oxidative addition, through *N*-acyliminium salt intermediate **2.5** addition to palladium as palladacycle **2.6**,[14] followed by transmetalation of the organotin reagent **2.3** and reductive elimination of product **2.8**. This provides a relatively mild cross-coupling method to employ imines **2.1** for the synthesis of α-substituted amides **2.8**. Nevertheless, our previous report was limited primarily to the use of vinyl-tin reagents as a coupling partner.[13] As such, we have undertaken a study of the potential use of more diverse organostannanes in this three component coupling. This has led to the design of an efficient copper(I) catalyzed multicomponent synthesis of a broad range of α-substituted amides and *N*-protected α-substituted amines, as is described below.

2.2 Results and Discussion

Our initial attempts to employ non-vinyl substituted organotin reagents in the palladium-catalyzed coupling with imine and acid chloride are outlined in Table 2.1. As can be seen, many of the other stannanes typically employed in Stille coupling (e.g. aryl-, heteroaryl-, and benzyl-stannanes) were unable to undergo this reaction. Although the reason for this is not clear, our working

postulate is that steric interactions at the palladium center between the metal-chelated amide (intermediate **2.7**) and the organotin reagent may prevent the transmetalation of these less reactive substrates from occurring at an appreciable rate. One potential approach that has been previously reported to accelerate transmetallation in Stille reactions involves the use of co-catalytic copper(I) salts.[1,15] The latter have been postulated to mediate the coupling through a reaction between the copper (I) center and the organostannane to form a transient organocuprate,[16] which can undergo a more rapid transmetalation to palladium than the organotin reagent itself. Indeed, the addition of 10 mol % CuCl to the palladium catalyzed coupling led to complete disappearance of the starting materials over 26 hours at 45°C, and formation of the α-aryl substituted amide in 88% yield. Interestingly, however, when this same catalytic reaction with 10 mol% CuCl is performed in the absence of Pd(0), the α-substituted amide product **2.8b** is also observed in 84% yield.

Table 2.1 Copper-Catalyzed Cross-Coupling with Imines.

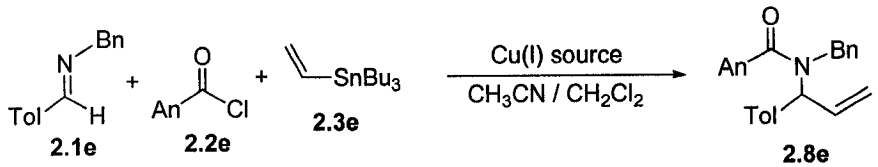


Cmpd #	R^4	Catalyst	Temp.	Time	Yield[a]
2.8a[b]		2.5 % $Pd_2(dba)_3CHCl_3$	25°C	16 h	82%
2.8b	Ph	2.5 % $Pd_2(dba)_3CHCl_3$	110°C	48 h	0%
2.8c	Bn	2.5 % $Pd_2(dba)_3CHCl_3$	110°C	48 h	0%
2.8d		2.5 % $Pd_2(dba)_3CHCl_3$	110°C	48 h	0%
2.8b	Ph	2.5 % $Pd_2(dba)_3CHCl_3$ 10 % CuCl	45°C	26 h	88%
2.8b	Ph	10 % CuCl	45°C	26 h	84%
2.8b	Ph	10 % CuCl	65°C	26 h	10%[c]

[a]0.48 mmol imine, 0.63 mmol acid chloride, 0.48 mmol organotin reagent, and with the given catalysts in CH_3CN (4 mL) and CH_2Cl_2 (3 mL). [b]See reference 13. [c]80 % benzophenone isolated, due to coupling of the organostannane and the acid chloride.

A variety of Cu(I) sources represent viable catalysts in this reaction, and these catalysts do provide the desired products in good to excellent yields (Table 2.2). However, the catalyst of choice remains CuCl due to its cost and its slightly higher efficiency.

Table 2.2 Copper (I) Sources in Cross-Coupling with Imines.



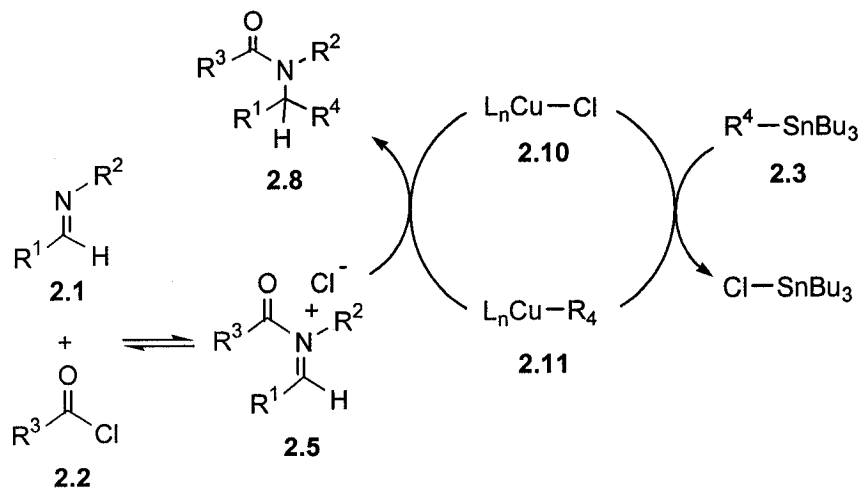
(Tol = 4-$CH_3C_6H_4$)
(An = 4-$CH_3OC_6H_4$)

Entry #	Copper (I) Source	NMR Yield[a]
1	10 % CuCl	91%
2	10 % CuBr	86%
3	10 % CuI	83%
4	10 % CuOTf	78%
5	10 % $CuPF_6$	79%
6	10 % CuCN	70%

[a]0.07 mmol imine, 0.09 mmol acid chloride, 0.08 mmol organotin reagent, and with the given catalysts in CD_3CN (0.4 ml) and CD_2Cl_2 (0.2 mL) at 45°C for 3 hours.

The use of copper (I) complexes as a replacement for palladium as the catalyst in intermolecular and intramolecular cross-coupling reactions involving organostannanes has been well-established through the research of Piers, Liebeskind, Falck, and others.[17] Mechanistically, these reactions have been postulated to proceed via the initial transmetalation of the organotin reagent to copper, followed by the formation of a transient Cu(III) species by oxidative addition. While a similar mechanism is possible here, it seems more plausible that the direct nucleophilic attack of the organocuprate intermediate **2.11** on the electrophilic *N*-acyl iminium salt **2.5** leads to product formation and regenerates the copper catalyst **2.10** (Scheme 2.2).[18] Most of the previously developed copper-

mediated cross coupling reactions require superstoichiometric quantities of Cu(I) salts to drive the reactions to completion, likely due to the reversibility of the Sn-Cu transmetallation, where build-up of Bu_3SnCl causes a decrease in the reaction rate.[17a] In our case, we believe that the high electrophilicity of the substrate *N*-acyl iminium salt, which rapidly traps any *in situ* generated organocuprate, allows the reaction to proceed with only 10 mol % CuCl catalyst.

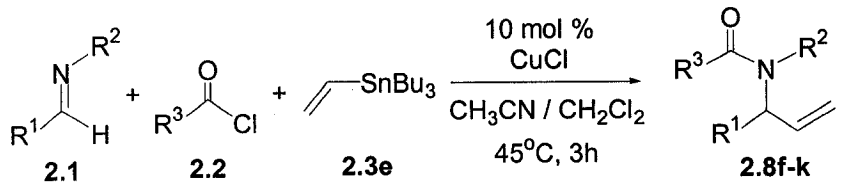


Scheme 2.2 Postulated mechanism of the copper-catalyzed coupling.

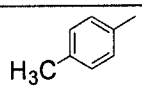
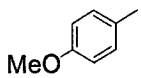
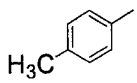
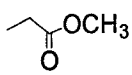
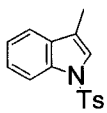
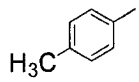
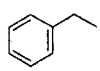
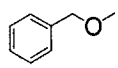
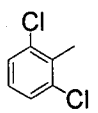
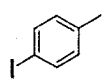
In addition to the practical utility of using copper (I) salts rather than palladium, this multicomponent coupling is also relatively general. As can be seen in Table 2.3, a range of R^1 and R^2 fragments can be incorporated via the imine substrate. For example, imines derived from aryl, heteroaryl, non-enolizable alkyl, and α,β-unsaturated aldehydes represent viable substrates. In contrast to our previously reported palladium catalyzed reaction, steric hindrance at the α-carbon of the imine does not seem to impede the reaction (**2.8h**, **2.8k**). Substitution at the

imine nitrogen allows for the incorporation of alkyl, aryl, and allyl groups, as well as α-amino acid derived imine (**2.8g**). A variety of different functional groups are well tolerated, including ethers, esters, tosylates, and halides. However, the use of enolizable imines leads to the formation of enamides upon addition of acid chloride, due to isomerization of the iminium salt substrate.[21] A wide array of small and bulky alkyl-, aryl- and heteroaryl-substituted acid chlorides generate α-substituted amides in good yield. *N*-protected α-substituted amines can also be formed by replacing the acid chloride with a chloroformate, allowing the generation of both TROC and CBz (using 2,2,2-trichloroethyl chloroformate and benzyloxychloroformate, respectively) protected products (**2.8i**, **2.8j**).

Table 2.3 Imines and acid chlorides in the copper-catalyzed coupling.



2.1 **2.2** **2.3e** **2.8f-k**

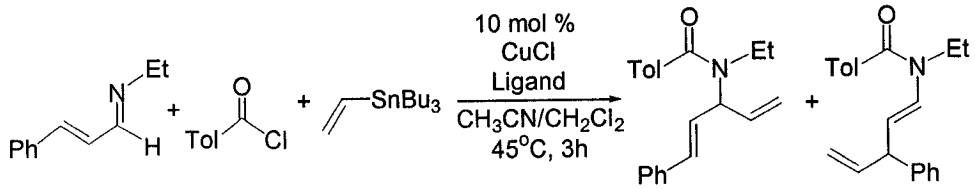
Product	R^1	R^2	R^3	Yield[b]
2.8f				76%
2.8g				82%
2.8h				85%
2.8i				81%
2.8j				88%
2.8k				72%

[a]0.48 mmol imine, 0.63 mmol acid chloride, 0.48 mmol organotin reagent, and 0.048 mmol CuCl in CH_3CN (4 mL) and CH_2Cl_2 (3 mL) for 3 hours. [b]Isolated yield.

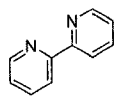
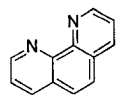
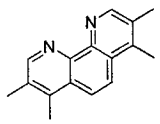
In the previously reported palladium-catalyzed version of this reaction, ligands were found to generally inhibit catalysis, likely due to their slowing transmetalation to palladium.[13] In contrast, this copper-catalyzed reaction can tolerate the presence of various donor ligands, providing a useful handle to control features such as reaction selectivity. For example, under standard conditions using CuCl, the catalytic coupling with a cinnamaldehyde-based imine (Table 2.4) leads to the formation of both 1,2- and 1,4-addition products (**2.8l** and

2.8m, respectively) in a 1 : 2 ratio. Upon addition of one equivalent of Bu_4NI, this selectivity can be enhanced to 1 : 3.8. Also, simply changing the catalyst from CuCl to CuBr or CuI changes the selectivity of attack on the α,β-unsaturated sytem. The use of 10% CuI as catalyst enhances the selectivity for the Michael addition product to 1 : 5. Alternatively, the addition of nitrogen donor ligands to the CuCl system diverts selectivity to favor the formation of the 1,2-addition product, with up to 9.5 : 1 ratio using 3,4,7,8-tetramethyl-1,10-phenanthroline. Although the reasons for this selectivity difference are not fully understood, it seems likely that their influence is through modulating the reactivity of an in situ generated organocuprate complex. For example, the addition of halide salts to cuprates is known to favor the formation of the softer nucleophiles, such as $[RCuI]^-$, which undergo 1,4-addition more than their CuR counterparts.[22] These softer nucleophiles could be generated from direct transmetalation of the $[CuX_2]^-$ with the organocuprate, allowing for the *in situ* formation of softer anionic organocuprates. It has also been shown that the addition of bulky ligands to cuprates favours 1,2-addition.[23] The highest level of 1,2-addition with the most sterically encumbered tetramethyl-1,10-phenanthroline ligand is consistent with this observation.

Table 2.4 1,2- versus 1,4-addition with α,β-unsaturated imines.[a]



2.1 **2.2** **2.3** **2.8l** **2.8m**

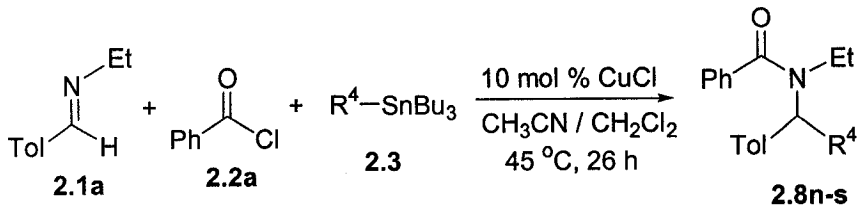
Ligand[b] (additive)	Ratio of **2.8l : 2.8m** (yield of major isomer)[c]
None	1 : 2.0 (50%)
LiCl	1 : 2.1 (53%)
Bu_4NBr	1 : 2.8 (62%)
Bu_4NI	1 : 3.8 (68%)
CuBr[d]	1 : 3.9 (56%)
CuI[e]	1 : 5.0 (55%)
	1.4 : 1 (51%)
	3 : 1 (64%)
	9.5 : 1 (76%)

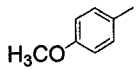
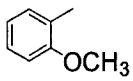
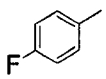
[a]Reaction performed with 0.48 mmol imine, 0.63 mmol acid chloride, 0.48 mmol organotin reagent, and 0.048 mmol CuCl in CH_3CN (4 mL) and CH_2Cl_2 (3 mL) for 3 hours. [b]Halide salt additives used in stoichiometric quantity (0.48 mmol). Nitrogen donor ligands in 12 mol % (0.053 mmol). [c]Isolated yield of major isomer of reaction. [d]Change of catalyst from 10% CuCl to 10% CuBr. [e]Change of catalyst from 10% CuCl to 10% CuI.

Perhaps most notable about this copper catalyzed coupling is the diversity of organotin reagents that can be employed (Table 2.5). While longer reaction

times are required for reactions of non-vinylstannanes, the product yields remain good. Thus, the transfer of phenyl as well as substituted aromatic groups can all be achieved with this reaction. Interestingly, the coupling with 2-(tributylstannyl)thiophene, occurs far more readily (ambient temperature) than in the case of the aryl substituents. This is likely due to initial coordination of the thiophene fragment to the copper metal center, leading to a chelation-assisted transmetalation to copper.[17] Consistent with this postulate, the ortho-methoxyphenyl organostannane also reacted more rapidly than the other arylorganostannanes. Benzylation is also viable in this three component coupling, and provides products in good yield.

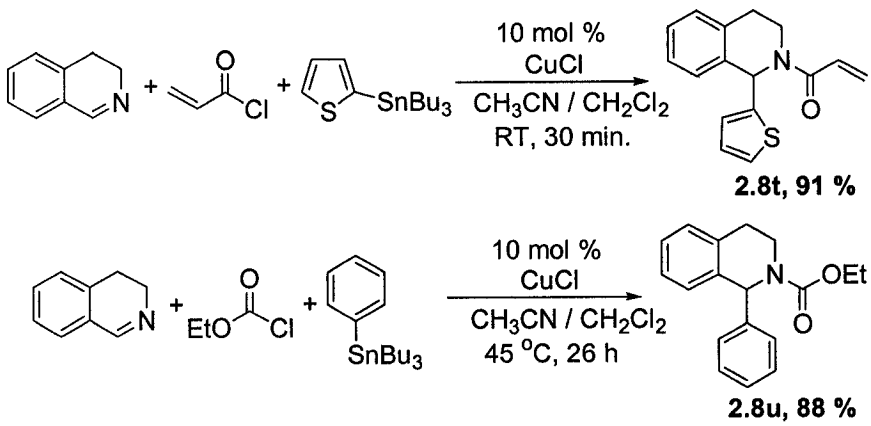
Table 2.5 Organostannanes in the copper-catalyzed coupling.



Product	R^4	Yield[b]
2.8n		84%
2.8o		91%[c]
2.8p		84%
2.8q		90%[d]
2.8r		93%
2.8s		69%[e]

[a]0.48 mmol imine and tin reagent, 0.63 mmol acid chloride, and 0.048 mmol CuCl in 4 ml CH_3CN / 3ml CH_2Cl_2. [b]Isolated yield. [c]30 min. at RT. [d]15 h at 45°C. [e]48 h at 95°C.

As a preliminary illustration of the utility of this reaction, we have probed its application to the construction of the antibacterially active molecule **2.8t**,[24] as well as the PCP analogue **2.8u**.[25] Both of these products can be formed in a single step and in high yield from readily available and air stable reagents (Scheme 2.3). In light of the functional group compatibility of this reaction, a range of other structurally analogous isoquinoline alkaloids could also be easily formed using this process.



Scheme 2.3 Synthesis of **2.8t** and **2.8u**.

2.3 Conclusions

In summary, we have developed a copper-catalyzed multicomponent synthesis of α-substituted amides from imines, organotin reagents, and acid chlorides. Considering the simplicity of the catalyst, the generality of the reaction, and the stability of each of these reagents, this provides a straightforward method to construct a diverse array of α-substituted amides and *N*-protected amines. Studies directed towards the use of other transmetalating agents, as well as the control of stereoselectivity in the reaction, are currently underway.

2.4 Experimental Section

General Procedures

Unless otherwise noted, all manipulations were performed under an inert atmosphere in a dry box or by using standard Schlenk or vacuum line techniques. All reagents were purchased unless otherwise stated below, and used as received. Acetonitrile and dichloromethane were distilled from CaH_2 under nitrogen. Deuterated acetonitrile was dried as its protonated analogue, but was transferred under vacuum from the drying agent, and stored over 3Å molecular sieves. Deuterated DMSO and chloroform were dried over 4Å molecular sieves. Imines were prepared as per standard literature procedures.[26] Organostannanes were prepared by the preparation of the appropriate Grignard reagent, and subsequent reaction with 0.67 equivalents of Bu_3SnCl in refluxing THF/toluene (1:2) for 12 hours. Subsequent distillation in vacuo gave the appropriate organotin reagent.[27] CuCl used was purchased as 99.999+% purity and used directly without further purification. ^1H and ^{13}C NMR spectra were recorded on 270 MHz, 300 MHz, and 400 MHz spectrometers. Mass spectra (all run using EI) were obtained from the McGill University mass spectral facilities.

General Procedure for Catalytic Synthesis of α-Substituted Amides

The imine (0.48 mmol) and the acid chloride / chloroformate (0.62 mmol) were mixed in 3 mL of acetonitrile. This was added to a solution of CuCl (4.2 mg, 0.048 mmol) in 1 mL of dry acetonitrile. The reaction mixture was transferred to a

25 mL reaction bomb. The organostannane (0.48 mmol) in 3 mL of methylene chloride was added into the reaction mixture, which was then heated (if necessary) in a temperature regulated oil bath for 30 minutes to 48 hours. The reaction mixture was cooled, then concentrated in vacuo and redissolved in 50 mL of ethyl acetate. Saturated KF solution (15 mL) was added and this mixture was stirred for 2 hours. The white solid that formed was then filtered off through Celite, and the organic layer was separated, and washed with 2 x 50 mL of distilled H_2O. The KF solution was extracted with 2 x 50 mL of ethyl acetate, and the organic layers were combined and dried over anhydrous $MgSO_4$. The drying agent was then filtered off and the solvent removed in vacuo. The residual crude product was purified with column chromatography using ethyl acetate / hexanes as eluent to afford the corresponding α-substituted amide.

Furan-2-carboxylic acid (4-methoxy-phenyl)-(1-p-tolyl-allyl)-amide (2.8f)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, with heating to 45°C for 3 hours. Chromatography solvent 80/20 hexanes / ethyl acetate. Isolated Yield: 76%. ^{1}H NMR (300 MHz, 60 °C, $CDCl_3$):δ 7.40 (s, 1H), 7.21-7.09 (m, 4H), 6.93-6.80 (m, 4H), 6.40 (d, 1H, J = 5.6Hz), 6.27-6.14 (m, 2H), 5.73 (s, 1H), 5.42-5.31 (m, 2H), 3.79 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (75.5 MHz, 60 °C, $CDCl_3$): δ 159.7, 158.9, 147.6, 144.7, 137.4, 136.7, 135.8, 132.8, 131.8, 129.0, 128.5, 118.4, 116.0, 114.2, 111.2, 63.0, 55.5,

20.5. IR (neat): 1709 (C=O). HRMS for $C_{22}H_{21}NO_3$ $(M)^+$, calculated: 347.1521, found: 347.1526.

[Isobutyryl-(1-p-tolyl-allyl)-amino]-acetic acid methyl ester (2.8g)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, with heating to 45°C for 3 hours. Chromatography solvent 75/25 hexanes / ethyl acetate. Isolated Yield: 82%. ^1H NMR (270 MHz, 20 °C, $CDCl_3$):δ 7.20-7.09 (m, 4H), 6.45 (d, 0.3H, J = 7.2Hz, minor rotamer), 6.20-5.95 (m, 1H), 5.69 (d, 0.7H, J = 7.2Hz, major rotamer), 5.44-5.23 (m, 2H), 4.03-3.79 (m, 2H), 3.60 (s, 2.1H, major rotamer), 3.50 (s, 0.9H, minor rotamer), 2.99-2.86 (m, 0.7H, major rotamer), 2.67-2.54 (m, 0.3H, minor rotamer), 2.32-2.22 (m, 3H), 1.21 (m, 6H). ^{13}C NMR (68.0 MHz, 20 °C, $CDCl_3$): for major and minor rotamers, δ 178.0, 177.8, 170.0, 169.6, 137.8, 137.4, 135.7, 135.1, 134.8, 134.6, 129.3, 129.0, 128.6, 127.8, 118.6, 117.6, 62.4, 58.2, 52.0, 51.8, 45.9, 45.3, 31.2, 30.4, 21.0, 21.0, 19.8, 19.7, 19.5, 19.4. IR (neat): 1648 (C=O). HRMS for $C_{17}H_{23}NO_3$ $(M)^+$, calculated: 289.1678, found: 289.1675.

N-Benzyl-N-(1-tert-butyl-allyl)-acetamide (2.8h)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, with heating to 45°C for 3 hours. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 85%. ^1H NMR (270 MHz, 130 °C,

d^6-DMSO):δ 7.35-7.12 (m, 5H), 6.13-5.98 (m, 1H), 5.17-4.94 (m, 2H), 4.57 (s, 2H), 1.94 (s, 3H), 0.96 (s, 9H). ^{13}C NMR (68.0 MHz, 130 °C, d^6-DMSO): δ 170.2, 138.5, 133.8, 127.3, 125.7, 125.6, 118.2, 48.9, 35.0, 26.9, 24.8, 21.5. IR (neat): 1636 (C=O). HRMS for $C_{16}H_{23}NO$ $(M)^+$, calculated: 245.1780, found: 245.1777.

Ethyl-{1-[1-(toluene-4-sulfonyl)-1H-indol-3-yl]-allyl}-carbamic acid 2,2,2-trichloro-ethyl ester (2.8i)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, with heating to 45°C for 3 hours. Chromatography solvent 85/15 hexanes / ethyl acetate. Isolated Yield: 81%. ^{1}H NMR (270 MHz, 80 °C, CD_3CN):δ 7.97 (d, 1H, J = 7.9Hz), 7.78 (d, 2H, J = 7.9 Hz), 7.55 (d, 2H, J = 6.2 Hz), 7.40-7.19 (m, 4H), 6.38-6.22 (m, 1H), 6.04 (d, 1H, J = 6.2 Hz), 5.40-5.31 (m, 2H), 4.86 (q, 2H, J = 6.5Hz), 3.40-3.13 (m, 2H), 2.33 (s, 3H), 0.69 (t, 3H, J = 6.5Hz). ^{13}C NMR (68.0 MHz, 80 °C, CD_3CN): δ 154.5, 146.1, 135.8, 135.3, 134.8, 130.3, 130.3, 137.0, 125.8, 125.5, 124.0, 122.1, 120.4, 117.8, 114.1, 96.3, 75.2, 55.4, 39.8, 20.8, 14.2. IR (neat): 1649 (C=O). HRMS for $C_{23}H_{23}N_2O_4S^{35}Cl_3$ $(M)^+$, calculated: 528.0444, found: 528.0449.

Benzyl-(1-p-tolyl-allyl)-carbamic acid benzyl ester (2.8j)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, with heating to 45°C for 3 hours. Chromatography solvent

92/8 hexanes / ethyl acetate.Isolated Yield: 88%. ^{1}H NMR (270 MHz, 90 °C, d^{6}-DMSO):δ 7.40-7.04 (m, 14H), 6.22-6.07 (m, 1H), 5.82-5.71 (br, 1H), 5.23-5.05 (m, 4H), 4.59 (d, 1H, J = 9.2Hz), 4.40 (d, 1H, J = 9.2Hz), 2.27 (s, 3H). ^{13}C NMR (68.0 MHz, 90 °C, d^{6}-DMSO): δ 155.2, 138.3, 136.2, 136.0, 135.9, 135.5, 128.3, 127.6, 127.4, 127.1, 126.9, 126.8, 126.6, 126.0, 117.3, 66.0, 62.2, 48.3, 19.9. IR (neat): 1693 (C=O). HRMS for $C_{25}H_{25}NO_2$ $(M)^+$, calculated: 371.1885, found: 371.1879.

N-Allyl-N-[1-(2,6-dichloro-phenyl)-allyl]-4-iodo-benzamide (2.8k)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, with heating to 45°C for 3 hours. Chromatography solvent 85/15 hexanes / ethyl acetate. Isolated Yield: 72%. ^{1}H NMR (270 MHz, 80 °C, CD_3CN):δ 7.63 (d, 2H, J = 6.4Hz), 7.30 (t, 4H, J = 6.4Hz), 7.20-7.05 (m, 4H), 6.50-6.34 (m, 1H), 6.20 (d, 1H, J = 9.2Hz), 5.26-4.98 (m, 4H). ^{13}C NMR (68.0 MHz, 80 °C, CD_3CN): δ 171.0, 137.7, 137.0, 135.8, 134.6, 133.6, 132.2, 129.8, 129.6, 129.2, 128.9, 119.7, 95.1, 63.0, 48.4. HRMS for $C_{19}H_{16}NO^{35}Cl_2I$, calculated: 470.9654, found: 470.9647. IR (neat): 1642 (C=O). HMRS for $C_{19}H_{16}NO^{35}Cl^{37}Cl$ $(M)^+$, calculated: 472.9624, found: 472.9631.

N-Ethyl-4-methyl-N-(3-phenyl-1-vinyl-allyl)-benzamide (2.8l)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, with heating to 45°C for 3 hours. Chromatography solvent 85/15 hexanes / ethyl acetate. Isolated Yield: 76%. ^{1}H NMR (270 MHz, 75 °C, CD_3CN):δ 7.43-7.08 (m, 9H), 6.42 (d, 1H, J = 6.9Hz), 6.29 (dd, 1H, J = 0.7, 6.9 Hz), 6.11-5.96 (m, 1H), 5.22-5.00 (m, 3H), 3.58-3.21 (m, 2H), 2.27 (s, 3H), 1.07 (t, 3H, J = 6.9Hz). ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ 171.7, 139.6, 137.3, 137.0, 135.4, 132.7, 129.2, 128.9, 128.1, 126.7, 126.6, 115.5, 115.3, 61.8, 39.8, 20.6, 14.8. IR (neat): 1635 (C=O). HRMS calculated for $C_{21}H_{23}NO$ $(M)^+$, calculated: 305.1780, found: 305.1775.

N-Ethyl-4-methyl-N-(3-phenyl-penta-1,4-dienyl)-benzamide (2.8m)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, with heating to 45°C for 3 hours. Chromatography solvent 85/15 hexanes / ethyl acetate. Isolated Yield: 68%. ^{1}H NMR (270 MHz, 75 °C, CD_3CN):δ 7.42-7.23 (m, 9H), 6.54-6.49 (m, 1H), 6.18-6.02 (m, 1H), 5.97-5.84 (m, 1H), 5.04-4.89 (m, 2H), 3.91 (t, 1H, J = 6.9Hz), 3.70 (q, 2H, J = 6.7Hz), 2.47 (s, 3H), 1.26 (t, 3H, J = 4.9Hz). ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ 170.0, 143.8, 141.3, 141.3, 140.5, 133.8, 129.7, 129.1, 128.8, 128.1, 127.8, 126.6, 114.5, 114.0, 103.6, 50.3, 39.2, 20.6, 12.0. IR (neat): 1641 (C=O). HRMS calculated for $C_{21}H_{23}NO$ $(M)^+$, calculated: 305.1780, found: 305.1776.

N-Ethyl-N-(phenyl-p-tolyl-methyl)-benzamide (2.8n)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, with heating to 45°C for 26 hours. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 84%. ^{1}H NMR (270 MHz, 80 °C, d^6-DMSO):δ 7.49-7.04 (m, 14H), 6.34 (s, 1H), 3.38 (q, 2H, J = 6.7Hz), 2.31 (s, 3H), 0.63 (t, 3H, J = 7.2Hz). ^{13}C NMR (68.0 MHz, 80 °C, d^6-DMSO): δ 170.5, 140.1, 137.9, 136.9, 136.9, 129.2, 129.1, 128.6, 128.5, 128.5, 128.5, 127.5, 126.2, 64.3, 40.2, 20.6, 14.1. IR (neat): 1628 (C=O). HRMS for $C_{23}H_{23}NO$ $(M)^+$, calculated: 329.1780, found: 329.1777.

N-Ethyl-N-(thiophen-2-yl-p-tolyl-methyl)-benzamide (2.8o)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, reaction complete in 30 minutes at room temperature. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 91%. ^{1}H NMR (270 MHz, 55 °C, $CDCl_3$):δ 7.47-7.10 (m, 10H), 6.98 (t, 1H, J = 5.2Hz), 6.89 (d, 1H, J = 5.2Hz), 6.57 (s,1H), 3.51 (q, 2H, J = 6.9Hz), 2.35 (s, 3H), 0.79 (t, 3H, J = 6.9Hz). ^{13}C NMR (68.0 MHz, 80 °C, d^6-DMSO): δ 171.8, 143.8, 137.8, 137.3, 136.3, 129.3, 129.2, 128.5, 128.3, 127.0, 126.8, 126.4, 125.3, 59.4, 40.2, 21.0, 14.0. IR (neat): 1622 (C=O). HRMS for $C_{21}H_{21}NOS$ $(M)^+$, calculated: 335.1344, found: 335.1347.

N-Ethyl-N-[(4-methoxy-phenyl)-p-tolyl-methyl]-benzamide (2.8p)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, with heating to 45°C for 26 hours. Chromatography solvent 80/20 hexanes / ethyl acetate. Isolated Yield: 84%. ^{1}H NMR (270 MHz, 75 °C, d^{6}-DMSO):δ 7.98-7.86 (m, 5H), 7.75-7.60 (m, 6H), 7.45 (d, 2H, J = 9.8Hz), 6.86 (s, 1H), 4.34 (s, 3H), 4.08-3.88 (m, 2H), 2.88 (s, 3H), 1.20 (t, 3H, J = 6.9Hz). ^{13}C NMR (68.0 MHz, 75 °C, d^{6}-DMSO): δ 170.9, 158.7, 137.5, 136.7, 136.6, 131.5, 129.4, 128.4, 128.3, 127.9, 127.7, 125.5, 113.4, 63.4, 54.5, 39.4, 19.4, 12.8. IR (neat): 1657 (C=O). HRMS for $C_{24}H_{25}NO_2$ $(M)^+$, calculated: 359.1885, found: 359.1891.

N-Ethyl-N-[(2-methoxy-phenyl)-p-tolyl-methyl]-benzamide (2.8q)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, with heating to 45°C for 26 hours. Chromatography solvent 80/20 hexanes / ethyl acetate. Isolated Yield: 90%. ^{1}H NMR (270 MHz, 60 °C, $CDCl_3$):δ 7.37-7.24 (m, 6H), 7.16 (d, 2H, J = 5.2Hz), 7.04 (d, 2H, J = 5.2Hz), 6.98-6.81 (m, 3H), 6.52-6.33 (s, 1H), 3.88-3.65 (m, 4H), 3.32-3.19(m, 1H), 2.39 (s, 3H), 0.73 (t, 3H, J = 6.9Hz). ^{13}C NMR (68.0 MHz, 100 °C, d^{6}-DMSO): δ 170.6, 157.0, 137.3, 136.6, 135.6, 128.9, 128.5, 128.4, 128.2, 127.9, 127.3, 126.9, 125.4, 119.7, 110.8, 58.7, 54.9, 39.3, 19.9, 12.8. IR (neat): 1625 (C=O). HRMS for $C_{24}H_{25}NO_2$ $(M)^+$, calculated: 359.1885, found: 359.1880.

N-Ethyl-N-[(4-fluoro-phenyl)-p-tolyl-methyl]-benzamide (2.8r)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, with heating to 45°C for 26 hours. Chromatography solvent 85/15 hexanes / ethyl acetate. Isolated Yield: 93%. ^{1}H NMR (270 MHz, 75 °C, CD_3CN):δ 7.37-7.25 (m, 5H), 7.21-7.10 (m, 4H), 7.07-6.96 (m, 4H), 6.31 (s, 1H), 3.38 (q, 2H, J = 6.9Hz), 2.27 (s, 3H), 0.61 (t, 3H, J = 6.9Hz). ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ 171.9, 138.2, 137.8, 137.1, 136.7, 130.9, 130.8, 129.4, 128.9, 128.7, 126.4, 115.5, 115.2, 64.1, 40.6, 20.3, 13.8. IR (neat): 1631 (C=O). HRMS for $C_{23}H_{22}NOF$ $(M)^+$, calculated: 347.1685, found: 347.1682.

N-Ethyl-N-(2-phenyl-1-p-tolyl-ethyl)-benzamide (2.8s)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, with heating to 45°C for 26 hours. Chromatography solvent 80/20 hexanes / ethyl acetate. Isolated Yield: 69%. ^{1}H NMR (270 MHz, 110 °C, d^6-DMSO):δ 7.42-6.94 (m, 14H), 5.35 (t, 1H, J = 6.9Hz), 3.34 (d, 2H, J = 5.2Hz), 3.19 (m, 2H), 2.23 (s, 3H), 0.68 (t, 3H, J = 6.9Hz). ^{13}C NMR (68.0 MHz, 110 °C, d^6-DMSO): δ 170.2, 137.9, 137.3, 136.2, 136.0, 128.5, 128.3, 128.0, 127.5, 127.4, 127.1, 125.5, 125.4, 59.7, 38.2, 36.5, 19.8, 13.6. IR (neat): 1634 (C=O). HRMS calculated for $C_{24}H_{25}NO$ $(M)^+$, calculated: 343.1936, found: 343.1932.

1-(1-Thiophen-2-yl-3,4-dihydro-1H-isoquinolin-2-yl)-propenone (2.8t)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, reaction complete after 30 minutes at room temperature. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 91%. ^{1}H NMR (270 MHz, 90 °C, d^{6}-DMSO):δ 7.36 (d, 1H, J = 4.9Hz), 7.30-7.15 (m, 4H), 6.96-6.66 (m, 4H), 6.18 (dd, 1H, J = 2.2, 16.8 Hz), 5.72 (d, 1H, J = 2.2, 16.8 Hz), 4.10 (br, 1H), 3.42 (br, 1H), 3.01-2.76 (m, 2H). ^{13}C NMR (68.0 MHz, 90 °C, d^{6}-DMSO): δ 164.3, 145.8, 134.7, 133.8, 128.2, 128.2, 127.5, 126.8, 126.8, 126.8, 125.9, 125.5, 125.0, 51.9, 38.3, 27.6. IR (neat): 1644 (C=O). HRMS calculated for $C_{16}H_{15}NOS$ $(M)^{+}$, calculated: 269.0874, found: 269.0868.

N-Ethyl-N-(2-phenyl-1-p-tolyl-ethyl)-benzamide (2.8u)

Prepared according to the general procedure for catalytic synthesis of α-substituted amides, with heating to 45°C for 3 hours. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 88%. ^{1}H NMR (270 MHz, 55 °C, $CDCl_3$):δ 7.34-7.03 (m, 9H), 6.42 (s, 1H), 4.32-4.04 (m, 3H), 3.37-3.23 (m, 1H), 3.06-2.92 (m, 1H), 2.83-2.70 (m, 1H), 1.31 (t, 3H, J = 7.2Hz). ^{13}C NMR (68.0 MHz, 55 °C, $CDCl_3$): δ 155.5, 142.7, 135.5, 135.0, 128.7, 128.4, 128.2, 128.1, 127.2, 126.9, 126.0, 61.3, 57.7, 38.1, 28.3, 14.6. IR (neat): 1687 (C=O). HRMS calculated for $C_{18}H_{19}NO_2$ $(M)^{+}$, calculated: 281.1416, found: 281.1407.

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CHAPTER THREE

The Copper Catalyzed Coupling of Imines, Acid Chlorides and Alkynes: A Multicomponent Route to Propargylamides

3.0 Preface

In Chapter 2, we discussed the reaction of imines, acid chlorides, and organostannanes in a copper-catalyzed multicomponent coupling reaction. Considering the mechanistic similarities of the Stille reaction to the Sonogashira reaction, we hypothesized that alkynes could be competent coupling partners with imines and acid chlorides in a manner similar to organostannanes. In this chapter, we will describe our efforts to accomplish this coupling, with both acid chlorides and chloroformates, as well as initial attempts to alkynylate nitrogen-containing heterocycles using a copper (I) iodide catalyst.

3.1 Introduction

Multicomponent coupling reactions have become of growing relevance in the development of efficient new syntheses.[1,2] When coupled with the reactivity of metal catalysts, this approach can be particularly effective in the conversion of

simple building blocks directly into important functional subunits.[3] One useful family of products toward which this approach has yet to be applied are propargylamides. These compounds represent the core of a range of biologically relevant molecules (*e.g.* oxotremorine,[4] dynemicin precursors,[5] and various herbicides and fungicides[6]), and are useful substrates in the synthesis of heterocycles[7] and biomimetic polymers.[8]

Traditional routes to prepare propargylamides include the Ritter reaction of olefins with nitriles,[9] or the addition of nucleophilic acetylides to imines,[10] followed by acylation. The stringent conditions, lack of functional group compatibility, and limited reagent diversity do provide limitations to these processes. More recently, a number of excellent transition metal-catalyzed strategies have been developed by Li, Carreira, Knochel, and Hoveyda for the synthesis of enantioenriched propargylamines, some of which can be converted to propargylamides.[10-14] Important examples of these include the copper or iridium-catalyzed coupling of alkynes with imines,[11] the addition of alkynes to enamines,[12] the condensation of aldehydes, amines and alkynes to generate tertiary propargylamines,[13] and the zirconium-catalyzed couplings generating secondary propargylamines.[14b,c] Such routes provide efficient access to the propargylamine core, in most cases, with high levels of enantioselectivity. To our knowledge, however, only one metal-mediated synthesis of propargylamides has been described, this involving the conversion of alkynes with pre-synthesized α-sulfonylcarbamates into propargylcarbamates in water.[15]

One of the more common methods for the synthesis of alkynyl-containing products is the Sonogashira coupling of alkynes with R-X substrates.[16] While this process has been found to be general with σ-bonded electrophiles (*e.g.* aryl- or vinyl-halides), it is typically incompatible with multiply bonded electrophiles such as imines. This is due to the inability of imines to undergo oxidative addition to Pd(0); a critical mechanistic step in cross-coupling reactions.[17] However, we have recently demonstrated that imines can be activated towards oxidative addition and multicomponent coupling with organotin reagents by the addition of acid chlorides.[18,19] In light of the mechanistic similarity of Stille couplings (transmetallation from organotin reagents) to Sonogashira couplings (transmetallation from an *in situ* formed copper-acetylide), we considered the possibility that a similar reaction of alkynes with imines and acid chlorides could provide a direct route to construct propargylamides.

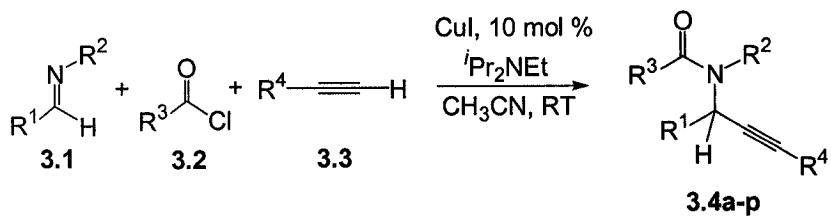
3.2 Results and Discussion

Our initial efforts towards this coupling examined the reaction of benzoyl chloride, phenylacetylene and *N*-benzyltolylaldimine in the presence of $Pd_2(dba)_3 \cdot CHCl_3$ (5 mol%), CuI (10 mol %), and the base $^{i}Pr_2NEt$. Monitoring the reaction by ^1H NMR reveals the rapid consumption of the reactants at ambient temperature. More importantly, examination of the reaction mixture reveals the clean formation of propargylamide **3.4a** (Table 3.1, entry 1). This coupling is

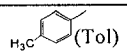
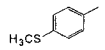
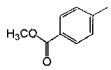
essentially quantitative, with **3.4a** representing the only observable reaction product (>95% NMR yield).

In an effort to further simplify this methodology, the importance of both catalysts (Pd(0) and Cu(I)) was examined. Performing a similar transformation with Pd(0) catalyst but without CuI leads to no reaction, consistent with the need for CuX to activate the alkyne towards coupling (*vide infra*). However, copper complexes themselves are known to mediate certain cross-coupling reactions in a fashion similar to palladium.[16a,20] Indeed, this three component coupling proceeds quite efficiently with 10 mol % CuI as the sole catalyst (**3.4a**, second entry in Table 3.1). The rates of the coupling are similarly rapid (< 15 minutes) both with and without palladium present, suggesting that in both instances the copper salt is the active catalyst. Other copper sources have also been found to be competent catalysts ($CuPF_6$, CuCN, CuCl), and the presence of bidentate phosphine (dppe) or nitrogen (2,2'-bipyridyl) ligands does not significantly inhibit the reaction. In addition to nitrogen bases ($^{i}Pr_2NEt$ or NEt_3), inorganic bases such as K_3PO_4 can also be employed, though the latter does lead to a more sluggish reaction (18 hrs).

Table 3.1 Copper-Catalyzed Three Component Coupling of Imines, Acid Chlorides, and Terminal Alkynes.[a]



3.1 3.2 3.3 3.4a-p

#	R^1	R^2	R^3	R^4	%[b]
3.4a[c]		Bn	Ph	Ph	(95)
3.4a	Tol	Bn	Ph	Ph	(98) 82
3.4b		Et	Ph	Ph	87
3.4c[d]		Bn	Ph	TMS	77
3.4d[d]		Bn	Ph	TMS	86
3.4e		Bn	Ph	Ph	92
3.4f	Tol	$CH_2CO_2CH_3$	Ph	Ph	87
3.4g	Tol	Bn	CH_3	Ph	76
3.4h		Et		Ph	81
3.4i	Tol	Bn		Ph	84
3.4j		Bn		Ph	93
3.4k	Tol	Ph	Ph	Ph	99
3.4l	Tol	Et	Ph	CH_2Cl	84
3.4m[e]	Tol	Bn	Ph	CH_2OTMS	90
3.4n	Tol	Bn	Ph	CH_2OAc	89
3.4o	Tol	Bn	Ph	n-C_4H_9	93
3.4p[d]	Tol	Bn	Ph	TMS	99

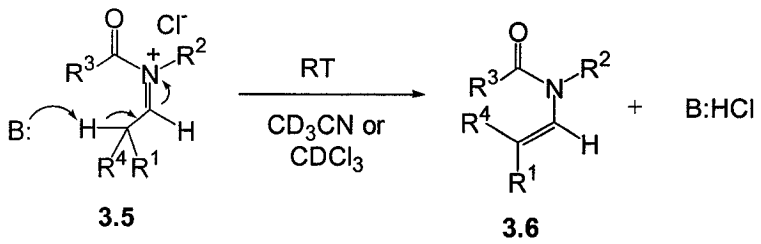
[a]All reactions run with 0.48 mmol imine, 0.63 mmol acid chloride, 0.48 mmol alkyne, 0.72 mmol $^iPr_2NEt$, and 0.048 mmol CuI in CH_3CN (7 mL) for 15-60 min. [b](NMR yield) Isolated yield. [c]5 mol% $Pd_2dba_3{\cdot}CHCl_3$ present. [d]2 h reaction. [e]Product isolated as hydroxy-propargylamide.

A particularly useful feature of this three-component coupling is the nature of the building blocks employed, each of which can be easily varied (Tables 3.1 and 3.2). In addition to electron rich and electron poor C-aryl substituted imines

(**3.4a-d**), imines derived from heteroaryl aldehydes (**3.4d**), α,β-unsaturated imines (**3.4j**), and even the less electrophilic C-alkyl imines (**3.4e**) all react to form propargylamides in high yields. The reaction is tolerant of various functional groups, including thioether, ester, furanyl, halide and indolyl units (**3.4b-d**, **3.4h**; **3.8c**). Alkyl and aryl diversity can be incorporated onto the imine nitrogen (**3.4f-h**, **3.4k**), as well as functionality derived from α-amino acids (**3.4f**). Alkyl, aryl, and vinylic fragments are all viable substituents as part on the acid chloride (**3.4f-j**), though the order of addition, with base being the final constituent added, is important to minimize competitive β-lactam formation.[21] The alkyne unit is also readily generalized, with electron rich (**3.4o,p**), electron poor (**3.8d**) and functionalized (**3.4l-n**) alkynes all forming propargylamides in good yields. In general, this level of diversity is high compared to the metal catalyzed alkynylation of imines themselves,[11] and even standard Sonogashira couplings (which are typically sluggish with electron poor alkynes),[16a] and can be attributed to the ability of acid chlorides to activate imines towards a facile coupling (*vide infra*).

The use of enolizable imines in this process has been investigated, and continues to be an ongoing project in our laboratories. Under the current conditions, due to competitive isomerization of the *N*-acyl iminium intermediate to the appropriate enamide, these are not viable substrates (Scheme 3.1). Work is in progress to alleviate this problem (this will be the subject of Appendix B). However, in considering the mild reaction conditions (ambient temperature), the building blocks employed (alkynes, imines, acid chlorides), and the commercial

availability of the catalyst (CuI), this multicomponent methodology still represents a very straightforward route to construct propargylamides.

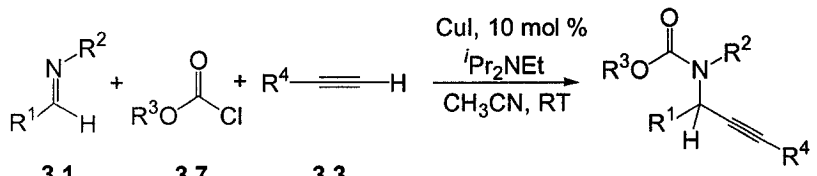


3.5 **3.6**

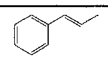
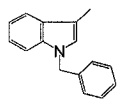
Scheme 3.1 Conversion of enolizable *N*-acyl iminium chlorides into enamides.

This methodology can also be extended to the use of chloroformates. This provides a facile one-pot route to convert imines into *N*-carbamate protected secondary propargylamines (Table 3.2). Similar yields and diversity can be attained in this process as observed with acid chlorides. Both CBz (**3.8a-d**) and FMOC (**3.8e**) protected propargylamines can be generated from the appropriate chloroformate.

Table 3.2 Copper-Catalyzed Synthesis of *N*-Carbamate Protected Propargylamines.[a]



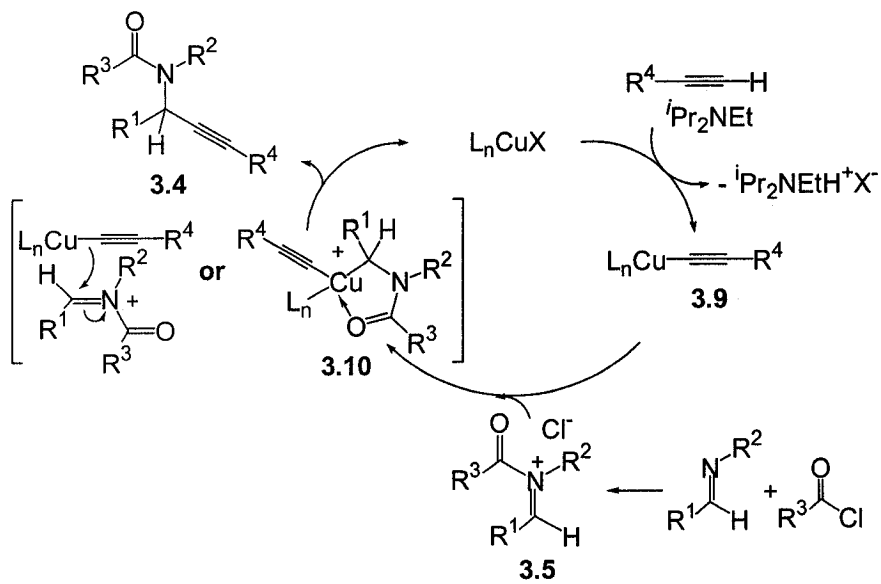
3.1 **3.7** **3.3** **3.8a-e**

#	R^1	R^2	R^3	R^4	%[b]
3.8a		Et	Bn	Ph	70
3.8b	Tol	Et	Bn	Ph	74
3.8c		Et	Bn	Ph	82
3.8d	Tol	Et	Bn	CO_2Me	68
3.8e	Tol	Et	FM[c]	Ph	88

[a]All reactions run with 0.48 mmol imine, 0.63 mmol chloroformate, 0.48 mmol alkyne, 0.72 mmol $^iPr_2NEt$, and 0.048 mmol CuI in CH_3CN (7 ml) for 15-60 min. [b]Isolated yield. [c] FM = 9-fluorenylmethyl.

The exact mechanism of the copper-catalyzed process is still under investigation. Control experiments demonstrate that, in contrast to the palladium-catalyzed cross-coupling reactions, the addition of imine and acid chloride to CuI does not lead to any appreciable oxidative addition. Conversely, monitoring the reaction by ^1H NMR reveals that CuI is immediately converted to the copper-acetylide **3.9**, and the imine **3.1** quickly reacts with acid chloride **3.2** to form *N*-acyliminium salt **3.5** (Scheme 3.2). While the mechanism for coupling of these two intermediates is unclear, one possibility is the oxidative addition of **3.5** to the copper center to generate a transient **3.10**, which subsequently reductively eliminates the product, in analogy to other cross-coupling reactions.[17] However, the fact that the addition of ligands (e.g., bidentate nitrogen-containing and

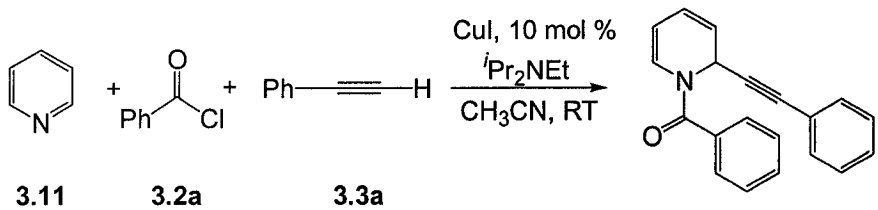
phosphine ligands) does not affect the rate of this reaction indicates that the intermediate **3.10** is not necessarily viable. Alternatively, nucleophilic attack of the copper-acetylide **3.9** on the *N*-acyliminium salt **3.5** is also possible. The latter is similar to that suggested for the coupling of copper acetylides to imines or iminium salts.[11-15] In either mechanism, the presence of acid chloride is undoubtedly an important feature in activating the imine towards coupling, by generating a more reactive **3.5** for either nucleophilic attack or stabilizing oxidative addition.[19] This is likely a factor in both the high catalytic activity, as well as the broad scope of the reaction.



Scheme 3.2 Postulated mechanism for the copper-catalyzed synthesis of propargylamides.

As suggested by this mechanism, this activation of the C=N bond by acid chlorides may not be limited to imine substrates. It should also be possible to activate other C=N species for coupling by acid chlorides, and perform

subsequent catalytic alkynylation. We have preliminarily examined this possibility in the reaction of pyridines. It is well established that the addition of acid chlorides to pyridines **3.11** generates a pyridinium salt, similar to the *N*-acyl iminium salts formed in our process. As shown in Scheme 3.3, the addition of phenylacetylene, the base $^{i}Pr_2NEt$ and catalytic CuI leads to the clean coupling of the three reagents at ambient temperature, and the partially reduced propargylamide product **3.12** was obtained in 73% yield. This provides a mild and selective route to ortho-functionalizing the pyridine core without strongly basic or nucleophilic reagents.



3.11 **3.2a** **3.3a** **3.12**

73%

Scheme 3.3 Three component coupling of pyridine, acid chloride, and alkyne catalyzed by CuI.

3.3 Conclusions

In conclusion, we have developed a copper catalyzed Sonogashira-type multicomponent coupling of imines, alkynes, and either acid chlorides or chloroformates. This provides an efficient method to construct propargylamides and *N*-protected propargylamines, as well as one that can be readily diversified.

Studies directed towards the control of enantioselectivity in this process, as well as the use of other transmetalating agents or C=N substrates, are currently underway.

3.4 Experimental Section

General Procedures

Unless otherwise noted, all manipulations were performed under an inert atmosphere in a Vacuum Atmospheres 553-2 dry box or by using standard Schlenk or vacuum line techniques. Acetonitrile was distilled from CaH_2 under nitrogen. Deuterated acetonitrile was dried as its protonated analogue, but was transferred under vacuum from the drying agent, and stored over 4Å molecular sieves. Deuterated DMSO and chloroform were dried over 3Å molecular sieves. Imines were prepared as per standard literature procedures.[22] Propargyl acetate was prepared in analogy to a standard literature procedure.[23] All other reagents were purchased from Aldrich® and used as received.

^{1}H, and ^{13}C were recorded on JEOL 270, Varian Mercury 300 MHz, and Mercury 400 MHz spectrometers. Mass spectra (all by EI) were obtained from the McGill University mass spectral facilities.

General Procedure for Catalytic Synthesis of Propargylamides

(4-$CH_3C_6H_4$)HC=N(CH_2Ph) (100.0 mg, 0.48 mmol) and benzoyl chloride (87.4 mg, 0.62 mmol) were mixed neat. After 10 minutes, this mixture was dissolved in 3 mL of acetonitrile and added to a solution of CuI in 2 mL of acetonitrile. EtN^iPr_2 (92.8 mg, 0.72 mmol) in 2 mL of acetonitrile was added to this mixture, then phenylacetylene (48.9 mg, 0.48 mmol) in 2 mL of acetonitrile was slowly added over 2 minutes. The reaction was allowed to stir at ambient temperature for 15 minutes. The mixture was concentrated in vacuo, and the product isolated by column chromatography using ethyl acetate / hexanes as eluent.

***N*-benzyl-N-(3-phenyl-1-*p*-tolyl-prop-2-ynyl)-benzamide (3.4a)**

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 82%. ^{1}H NMR (270 MHz, 130°C, d^6-DMSO):δ 7.55-7.28 (m, 13H), 7.26-7.10 (m, 6H), 6.49 (s, 1H), 4.73 (d, 1H), 4.39 (d, 1H), 2.32 (s, 3H). ^{13}C NMR (68.0 MHz, 130°C, d^6-DMSO): δ 171.8, 138.8, 138.3, 137.0, 134.8, 132.0, 130.2, 129.8, 129.3, 129.1, 129.0, 128.4, 127.9, 127.9, 127.1, 127.1, 122.6, 87.9, 86.8, 53.6, 48.6, 21.0. HRMS calculated for $C_{30}H_{25}NO$ $(M)^+$: 415.1936; found: 415.1932.

_N_-ethyl-_N_-[1-(4-methylsulfanyl-phenyl)-3-phenyl-prop-2-ynyl]-benzamide (3.4b)

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 87%. ^{1}H NMR (270 MHz, 100 °C, d^{6}-DMSO):δ 7.53-7.25 (m, 14H), 6.45 (s, 1H), 3.43 (m, 1H), 3.20 (m, 1H), 2.42 (s, 3H), 0.97 (t, 3H). ^{13}C NMR (68.0 MHz, 100°C, d^{6}-DMSO): δ 169.9, 137.9, 136.0, 133.6, 130.8, 128.8, 128.3, 128.0, 127.9, 127.2, 126.2, 125.7, 121.3, 86.0, 85.5, 50.6, 40.4, 14.5, 13.9. HRMS calculated for $C_{25}H_{23}NOS$ $(M)^{+}$ 385.1500; found: 385.1497.

4-[1-(benzoyl-benzyl-amino)-3-trimethylsilanyl-prop-2-ynyl]-benzoic acid methyl ester (3.4c)

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 85/15 hexanes / ethyl acetate. Isolated Yield: 77%. ^{1}H NMR (270 MHz, 125°C, d^{6}-DMSO):δ 7.87-7.84 (d, 2H), 7.50-7.47 (d, 2H), 7.36-7.30 (s, 5H), 7.12-7.02 (m, 5H), 6.34 (s, 1H), 4.58 (d, 1H), 4.28 (d, 1H), 3.79 (s, 3H), 0.03 (s, 9H). ^{13}C NMR (68.0 MHz, 125°C, d^{6}-DMSO): δ 170.5, 165.1, 141.2, 137.0, 135.4, 129.2, 128.9, 128.6, 127.7, 127.0, 126.8, 126.6,

125.9, 125.7, 100.8, 92.9, 52.1, 51.1, 47.9, -1.2. HRMS calculated for $C_{28}H_{29}NO_3Si$ $(M)^+$: 455.1917; found: 455.1922.

<u>*N*-benzyl-*N*-(1-furan-2-yl-3-trimethylsilanyl-prop-2-ynyl)-benzamide (3.4d)</u>

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 86%. ^{1}H NMR (270 MHz, 100°C, d^6-DMSO):δ 7.50 (s, 1H), 7.40-7.34 (m, 5H), 7.18-7.03 (m, 5H), 6.33 (d, 2H), 6.15 (s, 1H), 4.57 (d, 1H), 4.37 (d, 1H), 0.06 (s, 9H). ^{13}C NMR (68.0 MHz, 100°C, d^6-DMSO): δ 170.3, 148.9, 143.1, 137.3, 135.2, 129.1, 127.9, 127.2, 126.4, 125.9, 125.8, 109.9, 109.1, 99.4, 90.9, 47.4, 46.9, -1.1. HRMS calculated for $C_{24}H_{25}NO_2Si$ $(M)^+$: 387.1655; found: 387.1650.

<u>*N*-benzyl-*N*-(1-*tert*-butyl-3-phenyl-prop-2-ynyl)-benzamide (3.4e)</u>

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 80/20 hexanes / ethyl acetate. Yield: 92%. ^{1}H NMR (270 MHz, 130°C, d^6-DMSO):δ 7.40-7.06 (m, 15H), 5.47 (s, 1H), 4.81 (s, 2H), 1.14 (s, 9H). ^{13}C NMR (68.0 MHz, 130°C, d^6-DMSO): δ 171.2, 138.5, 136.4, 130.4, 128.4, 127.6, 127.6, 127.3, 127.0, 125.9, 125.8, 125.5, 121.5, 86.1, 85.8, 57.4, 49.4, 37.4, 26.4. HRMS calculated for $C_{27}H_{27}NO$ $(M)^+$: 381.2093; found: 381.2095.

[Benzoyl-(3-phenyl-1-*p*-tolyl-prop-2-ynyl)-amino]-acetic acid methyl ester (3.4f)

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 80/20 hexanes / ethyl acetate. Isolated Yield: 87%. ^{1}H NMR (270 MHz, 125 °C, d^{6}-DMSO):δ 7.58-7.31 (m, 12H), 7.27-7.18 (d, 2H), 6.46 (s, 1H), 4.17 (d, 1H), 3.96 (d, 1H), 3.50 (s, 3H), 2.33 (s, 3H). ^{13}C NMR (68.0 MHz, 125°C, d^{6}-DMSO): δ 171.4, 169.3, 138.3, 136.1, 134.2, 132.0, 130.3, 129.7, 129.4, 129.0, 127.8, 127.7, 127.1, 122.4, 87.8, 85.8, 52.9, 52.0, 46.6, 20.9. HRMS calculated for $C_{26}H_{23}NO_3$ $(M)^+$: 397.1678; found: 397.1681.

N-Benzyl-N-(3-phenyl-1-p-tolyl-prop-2-ynyl)-acetamide (3.4g)

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 76%. ^{1}H NMR (270 MHz, 75 °C, CD_3CN):δ 7.65-7.08 (m, 15H), 4.70-4.50 (q, 2H), 2.39 (s, 3H), 2.07 (s, 3H). ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ 170.2, 139.0, 138.3, 135.4, 131.7, 129.5, 128.9, 128.6, 128.5, 127.8, 127.0, 126.9, 122.7,

86.8, 86.7, 50.6, 48.8, 21.8, 20.3. HRMS for $C_{25}H_{23}NO$ $(M)^+$, calculated: 353.1780, found: 353.1775.

3-Methyl-but-2-enoic acid [1-(4-bromo-phenyl)-3-phenyl-prop-2-ynyl]-ethyl-amide (3.4h)

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 81%. ^1H NMR (270 MHz, 60 °C, $CDCl_3$):δ 7.56-7.26 (m, 9H), 7.09 (s, 1H), 5.93 (s, 1H), 3.57-3.21 (m, 2H), 2.08 (s, 3H), 1.93 (s, 3H), 1.22-1.07 (t, 3H). ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ 167.8, 138.4, 131.9, 131.8, 131.6, 129.8, 129.1, 128.9, 122.7, 121.7, 118.0, 86.6, 86.3, 55.8, 39.7, 25.6, 19.7, 14.9. HRMS for $C_{22}H_{22}{}^{79}BrNO$ $(M)^+$, calculated: 395.0885, found: 395.0878. HRMS for $C_{22}H_{22}{}^{81}BrNO$ $(M)^+$, calculated: 397.0864, found: 397.0862.

***N*-benzyl-*N*-(3-phenyl-1-*p*-tolyl-prop-2-ynyl)-isobutyramide (3.4i)**

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 84%. ^1H NMR (270 MHz, 130°C, d^6-DMSO):δ 7.44-7.10 (m, 14H), 6.79 (s, 1H), 4.67 (d, 1H), 4.51 (d, 1H), 2.82 (m, 1H), 2.31 (s, 3H), 1.11-0.95 (m, 6H). ^{13}C NMR (68.0 MHz, 130°C, d^6-DMSO): δ 176.6, 138.0, 136.6, 134.3, 130.5, 128.4, 127.8, 127.6, 127.2, 126.4, 125.9, 125.8, 121.3, 86.1, 85.7, 49.8, 47.2, 30.0,

19.7, 18.8, 18.4. HRMS calculated for $C_{27}H_{27}NO$ $(M)^+$: 381.2093; found: 381.2096.

N-Ethyl-3-methyl-N-(3-phenyl-1-phenylethynyl-allyl)-butyramide (3.4j)

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 93%. ^{1}H NMR (270 MHz, 75 °C, CD_3CN):δ 7.53-7.14 (m, 10H), 6.92-6.86 (d, 1H), 6.25-6.19 (q, 1H), 5.29-5.16 (m, 1H), 4.71-4.67 (d, 1H), 3.63-3.34 (m, 2H), 2.36-2.02 (m, 3H), 1.31-0.95 (dt, 3H), 0.94-0.84 (dd, 6H). ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ (two rotamers) 171.8, 170.8, 141.8, 136.8, 132.7, 131.8, 131.6, 129.3, 128.9, 128.9, 128.9, 128.8, 128.7, 128.6, 128.4, 128.2, 127.7, 127.2, 126.9, 126.2 122.9, 111.0, 90.1, 86.4, 86.1, 85.2, 42.7, 42.6, 42.2, 39.4, 38.9, 36.4, 26.0, 25.7, 22.2, 22.1, 15.6, 12.1. HRMS for $C_{24}H_{28}NO$ $(M)^+$, calculated: 345.2093, found: 345.2096.

***N*-phenyl-*N*-(3-phenyl-1-*p*-tolyl-prop-2-ynyl)-benzamide (3.4k)**

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 99%. ^{1}H NMR (270 MHz, 130°C, d^6-DMSO):δ 7.43-7.34 (m, 6H), 7.34-7.28 (m, 3H), 7.27-7.07 (m, 9H), 6.97-6.89 (m, 2H), 2.31 (s, 3H). ^{13}C NMR (68.0 MHz, 130 °C, d^6-DMSO): δ 168.8, 139.0, 136.7, 135.5, 133.9, 130.5, 129.4,

128.5, 128.2, 127.9, 127.8, 127.4, 127.2, 127.2, 126.8, 126.6, 121.4, 86.6, 85.9, 51.1, 19.7. HRMS calculated for $C_{29}H_{23}NO$ $(M)^+$: 401.1780; found: 401.1774.

_N_-(4-chloro-1-_p_-tolyl-but-2-ynyl)-_N_-ethyl-benzamide (3.4l)

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 84%. ^1H NMR (270 MHz, 80 °C, d^6-DMSO):δ 7.50-7.41 (s, 5H), 7.38-7.31 (d, 2H), 7.25-7.18 (d, 2H), 6.31 (s,1H), 4.56 (s, 2H), 3.37 (m, 1H), 3.12 (m, 1H), 2.30 (s, 3H), 0.92 (t, 3H). ^{13}C NMR (68.0 MHz, 80 °C, d^6-DMSO): δ 170.0, 137.2, 136.0, 133.3, 129.0, 128.8, 128.1, 126.5, 125.7, 82.7, 81.8, 50.3, 39.1, 30.3, 20.1, 14.0. HRMS calculated for $C_{20}H_{20}NO^{35}Cl$: 325.1233; found: 325.1235. HRMS calculated for $C_{20}H_{20}NO^{37}Cl$ $(M)^+$: 327.1204; found: 327.1210.

_N_-benzyl-_N_-(4-hydroxy-1-_p_-tolyl-but-2-ynyl)-benzamide (3.4m)

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 85/15 hexanes / ethyl acetate. Isolated Yield: 90%. ^1H NMR (270 MHz, 130 °C, d^6-DMSO):δ 7.48-7.37 (s, 5H), 7.35-7.30 (d, 2H), 7.21-7.05 (m, 7H), 6.26 (s, 1H), 4.67 (s, 1H), 4.59 (d, 1H), 4.38 (d, 1H), 4.13 (s, 2H), 2.29 (s, 3H). ^{13}C NMR (68.0 MHz, 130 °C, d^6-DMSO): δ 170.4, 137.4, 136.7, 135.7, 133.4, 128.7, 128.3, 127.6, 126.9, 126.6, 126.6, 125.7, 125.6,

87.2, 79.6, 51.9, 48.5, 47.2, 19.7. HRMS calculated for $C_{25}H_{23}NO_2$ $(M)^+$: 369.1729; found: 369.1724.

5-(benzoyl-benzyl-amino)-5-*p*-tolyl-pent-3-ynoic acid methyl ester (3.4n)

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 80/20 hexanes / ethyl acetate. Isolated Yield: 89%. ^{1}H NMR (270 MHz, 130°C, d^6-DMSO):δ 7.46-7.37 (s, 5H), 7.34-7.25 (d, 2H), 7.22-7.05 (m, 7H), 6.29 (s, 1H), 4.68 (s, 1H), 4.62 (d, 1H), 4.32 (d, 1H), 2.31 (s, 3H), 2.03 (s, 3H). ^{13}C NMR (68.0 MHz, 130°C, d^6-DMSO): δ 171.5, 169.8, 138.3, 138.1, 136.5, 133.9, 130.1, 129.6, 128.9, 128.2, 128.1, 127.6, 126.9, 126.8, 83.1, 82.8, 60.0, 52.0, 48.3, 20.9, 20.7. HRMS calculated for $C_{27}H_{25}NO_3$ $(M)^+$: 411.1834; found: 411.1826.

***N*-benzyl-*N*-(1-*p*-tolyl-hept-2-ynyl)-benzamide (3.4o)**

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 93%. ^{1}H NMR (270 MHz, 85°C, d^6-DMSO):δ 7.52-7.36 (s, 5H), 7.33-7.27 (d, 2H), 7.26-7.06 (m, 7H), 6.17 (s, 1H), 4.60 (d, 1H), 4.23 (d, 1H), 2.29 (s, 3H), 2.17 (t, 2H), 1.45-1.25 (m, 4H), 0.86 (t, 3H). ^{13}C NMR (68.0 MHz, 85°C, d^6-DMSO): δ 170.5, 137.8, 136.9, 135.8, 134.0, 129.1, 128.6, 128.0, 127.2, 127.1,

126.7, 126.6, 125.9, 87.9, 76.0, 52.3, 46.9, 29.5, 20.8, 20.0, 17.2, 12.7. HRMS calculated for $C_{28}H_{29}NO$ $(M)^+$: 395.2249; found: 395.2246.

<u>*N*-benzyl-*N*-(1-*p*-tolyl-3-trimethylsilanyl-prop-2-ynyl)-benzamide (3.4p)</u>

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 93/7 hexanes / ethyl acetate. Isolated Yield: 99%. ^{1}H NMR (270 MHz, 125°C, d^6-DMSO):δ 7.38-7.31 (s, 5H), 7.26-7.20 (d, 2H), 7.16-7.04 (m, 7H), 6.19 (s, 1H), 4.55 (d, 1H), 4.22 (d, 1H), 2.24 (s, 3H), 0.06 (s, 9H). ^{13}C NMR (68.0 MHz, 125°C, d^6-DMSO): δ 170.4, 137.4, 136.9, 135.6, 133.1, 128.8, 128.4, 127.7, 127.0, 126.5, 126.5, 125.7, 125.6, 101.6, 91.8, 52.3, 47.2, 19.7, -1.2. HRMS calculated for $C_{27}H_{29}NOSi$ $(M)^+$: 411.2018; found: 411.2025.

<u>Ethyl-(3-phenyl-1-phenylethynyl-allyl)-carbamic acid benzyl ester (3.8a)</u>

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 92/8 hexanes / ethyl acetate. Isolated Yield: 70%. ^{1}H NMR (270 MHz, 75°C, CD_3CN):δ 7.55-7.14 (m, 15H), 6.94-6.88 (d, 1H), 6.30 (m ,1H), 5.92 (d, 1H), 5.19 (s, 2H), 3.64-3.36 (m, 2H), 1.15 (m, 3H). ^{13}C NMR (68.0 MHz, 75°C, CD_3CN): δ 155.7, 137.6, 136.8, 132.9, 131.8, 129.0, 128.9, 128.8, 128.7, 128.3, 128.2, 128.0, 127.0, 126.5, 122.8, 86.3, 86.0, 67.3,

50.7, 39.6, 14.8. HRMS calculated for $C_{27}H_{25}NO_2$ $(M)^+$: 395.1885; found: 395.1889.

Ethyl-(3-phenyl-1-*p*-tolyl-prop-2-ynyl)-carbamic acid benzyl ester (3.8b)

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 74%. ^{1}H NMR (270 MHz, 125°C, d^6-DMSO):δ 7.53-7.26 (m, 12H), 7.20 (d, 2H), 6.39 (s, 1H), 5.21 (s, 2H), 3.45-3.19 (m, 2H), 2.31 (s, 3H), 1.06 (t, 3H). ^{13}C NMR (68.0 MHz, 125°C, d^6-DMSO): δ 154.4, 136.5, 136.0, 134.1, 130.5, 128.2, 127.8, 127.7, 127.4, 126.9, 126.6, 126.2, 121.3, 85.7, 85.2, 66.0, 50.8, 38.4, 19.6, 13.4. HRMS calculated for $C_{26}H_{25}NO_2$ $(M)^+$: 383.1885; found: 383.1880.

[1-(1-benzyl-1*H*-indol-3-yl)-3-phenyl-prop-2-ynyl]-ethyl-carbamic acid benzyl ester (3.8c)

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 80/20 hexanes / ethyl acetate. Isolated Yield: 82%. ^{1}H NMR (270 MHz, 125°C, d^6-DMSO):δ 7.61-6.96 (m, 20H), 6.68 (s, 1H), 5.42 (s, 2H), 5.26 (s, 2H), 3.42-3.22 (m, 2H), 0.97 (t, 3H). ^{13}C NMR (68.0 MHz, 125°C, d^6-DMSO): δ 154.4, 137.2, 136.3, 130.7, 128.1, 127.8, 127.8, 127.7, 127.6, 127.0, 126.9, 126.6, 126.3, 125.6, 124.5, 121.6, 121.2, 118.8, 118.2, 111.2,

109.7, 86.8, 83.3, 66.1, 48.8, 44.6, 37.6, 13.6. HRMS calculated for $C_{34}H_{30}N_2O_2$ $(M)^+$: 498.2307; found: 498.2312.

4-(Benzyloxycarbonyl-ethyl-amino)-4-*p*-tolyl-but-2-ynoic acid methyl ester (3.8d)

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 75/25 hexanes / ethyl acetate. Isolated Yield: 68%. ^{1}H NMR (270 MHz, 45°C, $CDCl_3$):δ 7.45-7.27 (m, 7H), 7.24-7.17 (d, 2H), 6.35 (s, 1H), 5.19 (s, 2H), 3.79 (s, 3H), 3.40-3.13 (m, 2H), 2.34 (s, 3H), 1.06-1.00 (t, 3H). ^{13}C NMR (68.0 MHz, 45°C, $CDCl_3$): δ 153.6, 150.5, 138.4, 136.5, 132.9, 129.4, 128.5, 128.1, 127.9, 127.4, 84.5, 77.6, 67.7, 52.7, 51.1, 39.7, 21.0, 14.5. HRMS calculated for $C_{22}H_{23}NO_4$ $(M)^+$: 365.1627; found: 365.1630.

Ethyl-(1-*p*-tolyl-3-phenyl-prop-2-ynyl)-carbamic acid 9*H*-fluoren-9-ylmethyl ester (3.8e)

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 95/5 hexanes / ethyl acetate. Isolated Yield: 88%. ^{1}H NMR (270 MHz, 100 °C, d^6-DMSO):δ 7.88-7.79 (d, 2H), 7.67-7.60 (d, 2H), 7.53-7.11 (m, 13H), 6.18 (s, 1H), 4.62 (m, 2H), 4.32 (t, 1H), 3.16-2.88 (m, 2H), 2.30 (s, 3H), 0.79 (t, 3H). ^{13}C NMR (68.0 MHz, 100 °C, d^6-DMSO): δ 155.5, 144.5, 144.4, 141.5, 137.9, 135.1, 131.9, 129.6, 129.1, 127.5,

127.4, 125.2, 125.2, 122.4, 120.4, 86.7, 86.3, 67.1, 51.6, 47.6, 39.3, 21.0, 14.5. HRMS calculated for $C_{33}H_{29}NO_2$ $(M)^+$: 471.2198; found: 471.2195.

Phenyl-(2-phenylethynyl-2*H*-pyridin-1-yl)-methanone (3.12)

Prepared according to the general procedure for catalytic synthesis of propargylamides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 73%. ^1H NMR (300 MHz, 60 °C, $CDCl_3$):δ 7.68-7.54 (d, 3H), 7.52-7.37 (m, 7H), 6.42 (br, 1H), 6.13 (m, 2H), 5.82 (br, 1H), 5.40 (br, 1H).). ^{13}C NMR (68.0 MHz, 60 °C, $CDCl_3$): δ 169.4, 133.9, 131.9, 130.9, 128.7, 128.4, 128.3, 128.1, 126.7, 122.6, 122.3, 120.0, 106.7, 86.1, 83.0, 43.0. HRMS for $C_{20}H_{15}NO$ $(M)^+$, calculated: 285.1154, found: 285.1149.

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CHAPTER FOUR

Metal-Catalyzed Multicomponent Syntheses of Secondary Propargylamides and Oxazoles from Silylimines, Acid Chlorides, and Alkynes

4.0 Preface

In Chapter 3 we presented a rapid copper-catalyzed three component coupling of imines, acid chlorides, and alkynes to generate tertiary propargylamides. Chapter 4 demonstrates the utility of these products, which are directly converted into oxazole heterocycles. Copper-catalyzed- and zinc-catalyzed protocols have been developed herein for the synthesis of secondary propargylamides from silyl-imines, acid chlorides, and terminal alkynes. The secondary propargylamide products are then, in a one pot sequence, transformed into trisubstituted oxazoles.

4.1 Introduction

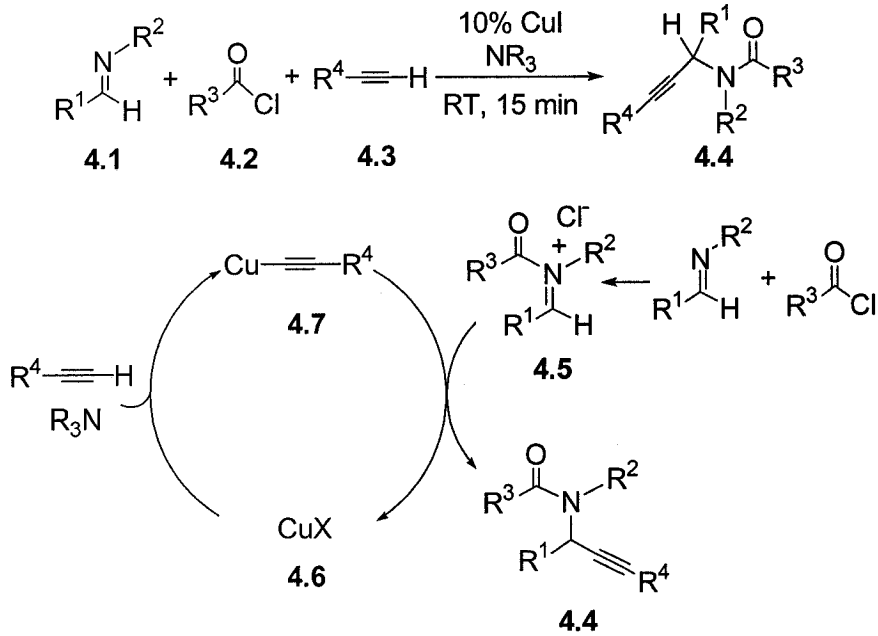
Multicomponent coupling reactions (MCRs) represent efficient methods of rapidly increasing molecular complexity in a modular fashion.[1] From early examples, such as the Strecker,[2] Hantsch,[3] and Mannich[4] reactions, to more recent reports,[5] this

approach has been used to prepare a wide range of important chemical structures. In principle, transition metal catalysis can provide a useful tool in the design of new MCRs, through the ability to both induce and control reactivity. Overall, this can allow the use of more readily available, easily diversified, and less complex building blocks, coupled together all at once via a metal-based mechanism.[6]

One class of molecules toward which metal-catalyzed multicomponent coupling has recently been applied are propargylamides. We[7] and others[8,9] have shown that these compounds, and their amine derivatives, can be assembled from available building blocks, such as imines, aldehydes, amines, acid chlorides, and alkynes, using a range of metal catalysts. Of the many propargylamides used in synthesis, secondary amides have found particular utility. These core structures are present in a variety of biologically active molecules (e.g. oxotremorine[10] and a range of fungicides and herbicides).[11] In addition, they are useful synthons in the formation of heterocycles[12-14] and biomimetic polymers.[15] Despite this utility, the current metal-catalyzed multicomponent routes to propargylamides all generate tertiary amides, and do not provide direct access to the secondary propargylamide core.[16] We describe herein our studies toward the development of a route to construct secondary propargylamides, via the copper or zinc-catalyzed coupling of imines, acid chlorides and terminal alkynes. This process has been subsequently employed to provide a novel route to construct trisubstituted oxazoles from four readily available building blocks in a single pot reaction.

4.2 Results and Discussion

We have previously reported that tertiary propargylamides **4.4** can be prepared through the copper-catalyzed three component coupling of imines **4.1**, acid chlorides **4.2**, and alkynes **4.3** (Scheme 4.1).[7]



Scheme 4.1 Three component synthesis of tertiary propargylamides.

This reaction is considered to proceed through the attack of a copper-acetylide **4.7** on an *in situ* generated *N*-acyl iminium salt **4.5**. In order to extend this approach to secondary propargylamides, N-H substituted imines would be required as substrates, which are typically unstable.[17] However, trimethylsilyl-substituted imines **4.8** have been used as N-H imine equivalents for nucleophilic addition chemistry,[18] suggesting their potential utility in this system. Not surprisingly, however, our initial attempt to employ these imines in the copper-catalyzed multicomponent coupling

with benzoyl chloride and phenylacetylene led instead to the formation of *N*-acyl imines **4.9**,[19] eliminating TMSCl in the process (Figure 4.1).

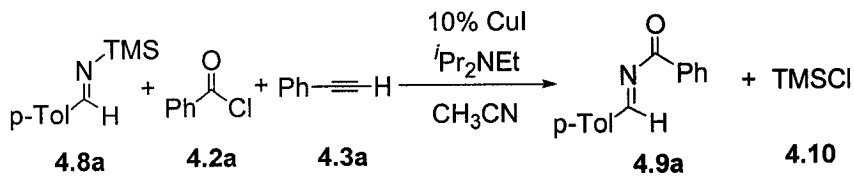


Figure 4.1 Reaction of trimethylsilyl-substituted imine **2a** with acid chloride and alkyne.

While in principle **4.9a** could react with an *in situ* generated copper-acetylide to form a propargylamide, even upon prolonged heating at 105°C, no reaction was observed. The lack of alkyne addition to the *N*-acyl imine is likely the result of its lower electrophilicity relative to *N*-acyl iminium salts **4.5** (*e.g.* in Scheme 4.1). Considering that Lewis acids have been shown to catalyze addition reactions to aldehydes and imines,[20] Lewis acid co-catalysts were examined in concert with copper salts. As was hoped, the reaction of **4.9a** and phenylacetylene in the presence of 10% CuI and 20% $BF_3{\cdot}Et_2O$ leads to the formation of the desired propargylamide **4.11a** in 83% yield. This reaction can also be performed in a multicomponent fashion, allowing the genertion of **4.11a** in similar yield directly from N-trimethylsilyl imine **4.8a**, acid chloride, and alkyne (Figure 4.2).

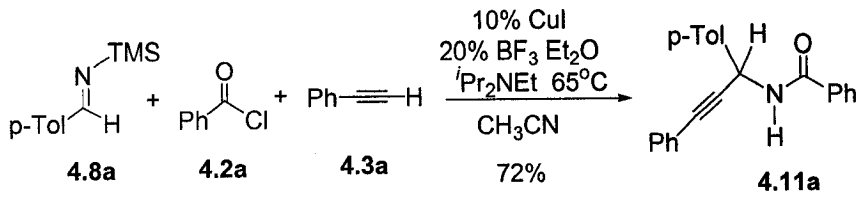


Figure 4.2 CuI / BF_3 catalyzed synthesis of **4a**.

Alternatively, the construction of the TMS-substituted imine **4.8** can be performed in the same reaction pot, eliminating the need to isolate these sensitive substrates (Figure 4.3; Table 4.1, **4.11a**), where the hexane solvent and other volatile byproducts were removed *in vacuo* prior to the addition of the alkyne, catalyst, and base in acetonitrile. The latter provides a modular method to construct secondary propargylamides directly from aldehydes **4.12**, silylamide **4.13**, acid chlorides **4.2**, and alkynes **4.3**.

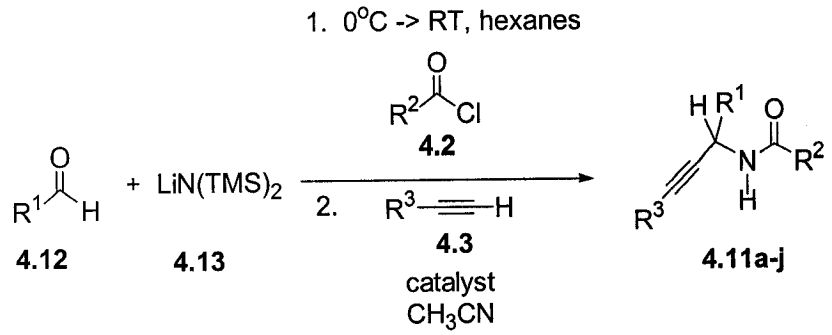
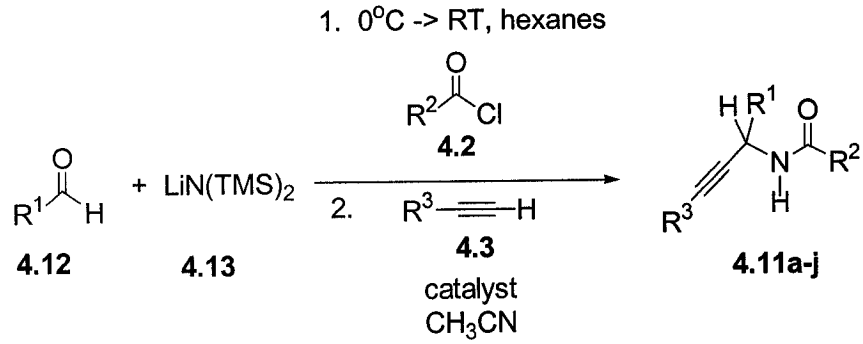


Figure 4.3 A one pot synthesis of propargylamides from aldehydes, acid chlorides, silylamide, and alkynes.

In addition to the use of Lewis acids to increase the electrophilicity of **4.9**, an alternative approach to this reaction involves increasing the nucleophilicity of the

metal-acetylide. In particular, zinc (II) salts have been shown by Carreira to form zinc-acetylides in a similar manner to copper acetylides, and have a higher propensity for addition to such substrates as aldehydes,[21a] imines,[21b,c] and enones.[21d] Indeed, 10% $Zn(OTf)_2$ can be employed as a catalyst for this same multicomponent reaction, in this case under more mild conditions than that with copper, leading to the formation of secondary propargylamide products after only 10 hours at ambient temperature (Table 4.1, **4.11f-j**).

Table 4.1 Copper (I) and zinc (II)-catalyzed multicomponent syntheses of secondary propargylamides.[a]

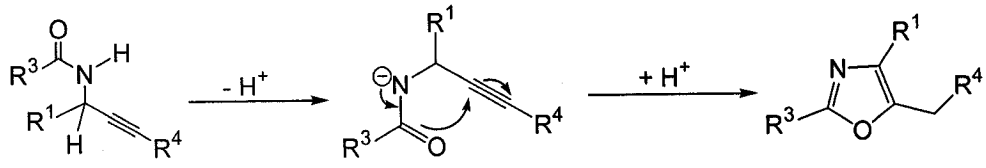


Product	R^1	R^2	R^3	Catalyst[b]	Yield
4.11a	p-Tol	Ph	Ph	CuI/ BF_3	80%
4.11b	^{t}Bu	Ph	^{n}Bu	CuI/ BF_3	88%
4.11c	p-Tol	vinyl	Ph	CuI/ BF_3	57%
4.11d	p-An	^{i}Pr	Ph	CuI/ BF_3	92%
4.11e	^{t}Bu	p-An	^{n}Bu	CuI/ BF_3	87%
4.11f	p-An	^{t}Bu	Ph	$Zn(OTf)_2$	73%
4.11g	^{t}Bu	p-I-C_6H_4	Ph	$Zn(OTf)_2$	67%
4.11h	p-Tol	Ph	CH_2OTMS	$Zn(OTf)_2$	62%[c]
4.11i	Ph	^{i}Bu	Ph	$Zn(OTf)_2$	91%
4.11j	Ph	Ph	Ph	$Zn(OTf)_2$	89%

[a]0.63 mmol aldehyde, 0.63 mmol LHMDS, and 0.83 mmol acid chloride in hexanes, followed by 0.83 mmol alkyne 0.63 mmol $EtiPr_2N$ and catalyst in CH_3CN (7 ml). [b]With 10% CuI with 20% BF_3 diethyletherate at 65 °C for 14 h, or 10% $Zn(OTf)_2$ at ambient temperature for 10 h. [c]Product isolated as the deprotected hydroxy-propargylamide.

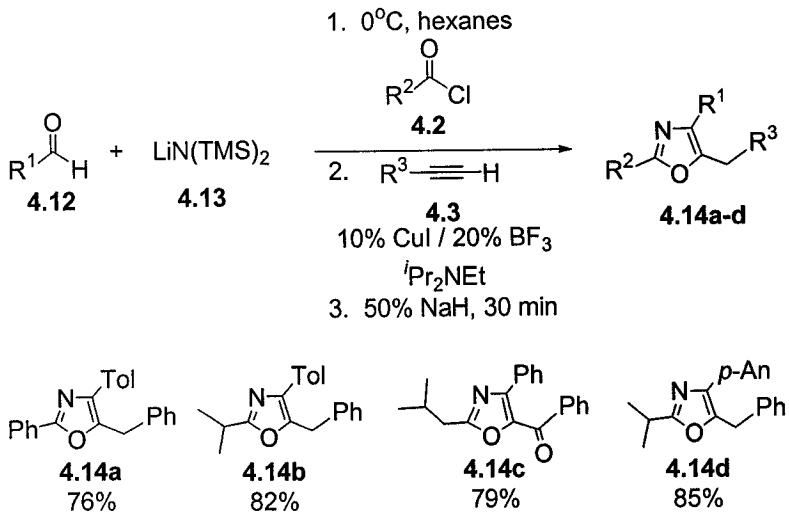
As shown in Table 4.1, these reactions can be readily diversified, allowing the formation of secondary amides with a range of aldehyde, acid chloride and alkyne substrates. This includes aryl and non-enolizable alkyl aldehydes,[22] as well as aryl, alkyl, α,β-unsaturated, and functionalized acid chlorides. Aryl, alkyl, and functionalized alkynes can also be successfully incorporated into the propargylamide

product. In general, both catalyst systems provide the products in similarly high yields.



Scheme 4.2: Mechanism of oxazole formation from secondary propargylamides.

Considering the utility of secondary propargylamides as synthetic building blocks, their generation by this multicomponent reaction provides the opportunity to consider the synthesis of other products in a similar modular fashion. As an illustration of this feature, we have probed the coupling of this reaction with the synthesis of oxazoles.[23] It has been reported that secondary propargylamides undergo cyclization to form oxazoles in the presence of base,[12] palladium,[13] or silica gel catalysts.[14] Thus, performing the catalytic synthesis of **4.11a** followed by the addition of catalytic NaH to the same reaction pot leads to the overall construction of oxazole **4.14a** in 76% yield (Scheme 4.3). This cycloisomerization can be coupled with several of the propargylamide syntheses (**4.14a-d**), providing a one pot method to assemble oxazoles from four separate units.



Scheme 4.3: Four component synthesis of oxazoles.

4.3 Conclusions

In conclusion, we have developed a metal catalyzed multicomponent synthesis of secondary propargylamides from trimethylsilyl-substituted imines, alkynes, and acid chlorides. These processes rely upon the *in situ* generation of *N*-acylimines and metal-acetylides, which in the presence of either BF_3 (with copper-acetylides), or with the use of nucleophilic zinc (II) acetylides, couple in a catalytic fashion. By combining this process with the cycloisomerization of the secondary propargylamide product, a modular method to assemble oxazoles in a single pot can be generated. The application of this chemistry to other secondary propargylamide targets is currently underway.

4.4 Experimental

General

Unless otherwise noted, all manipulations were performed under an inert atmosphere in a Vacuum Atmospheres 553-2 dry box or by using standard Schlenk or vacuum line techniques. All reagents were purchased from Aldrich® and used as received. Acetonitrile was distilled from CaH_2 under nitrogen. Deuterated acetonitrile was dried as its protonated analogue, but was transferred under vacuum from the drying agent, and stored over 4Å molecular sieves. ^{1}H and ^{13}C NMR spectra were recorded on JEOL 270, Varian Mercury 300 MHz, and Mercury 400 MHz spectrometers. Mass spectra (all by EI method) were obtained from the McGill University mass spectral facilities.

Typical procedure for preparation of 4.11a-e

To 1,1,1,3,3,3-hexamethyldisilazane (0.14 mL, 0.66 mmol) in a 25 mL reaction bomb equipped with a stir bar in a 0°C ice bath, was added a 2.5 M solution of BuLi in hexanes (0.25 mL, 0.66 mmol) over 10 minutes, under nitrogen. Tolualdehyde (77 mg, 0.63 mmol) was then added over 1 hour. The reaction was allowed to warm to ambient temperature, acryloyl chloride (75 mg, 0.83 mmol) in acetonitrile (3 mL) was added, and the mixture stirred for 30 minutes. The solvents and $(TMS)_2O$ were removed in vacuo, the residue dissolved in acetonitrile (2 mL), and phenylacetylene (65 mg, 0.63 mmol) in acetonitrile (1 mL), copper (I) iodide (12

mg, 0.063mmol) in acetonitrile (2 mL), boron trifluoride diethyl etherate (18 mg, 0.126 mmol), and diisopropylethylamine (110 μL, 0.63 mmol) in acetonitrile (2 mL) were added. The mixture was stirred at 65°C for 14 hours, the solvent was removed in vacuo, and the crude product was purified with column chromatography using ethyl acetate / hexanes as eluent.

N-(3-Phenyl-1-p-tolyl-prop-2-ynyl)-benzamide (4.11a)

Prepared according to the general procedure for copper-catalyzed synthesis of secondary propargylamides. Chromatography solvent 85/15 hexanes / ethyl acetate. Isolated Yield: 80 %. ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.80 (d, 2H, J = 7.8 Hz), 7.58-7.37 (m, 7H), 7.30 (d, 3H, J = 8.7 Hz), 7.23-7.17 (d, 2H, J = 11.7Hz), 6.84 (d, 1H, J = 8.4 Hz), 6.45 (d, 1H, J = 8.4 Hz), 2.40 (s, 3H). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 166.3, 138.2, 136.4, 134.1, 132.1, 132.0, 129.7, 128.8, 128.7, 128.5, 127.4, 127.3, 122.8, 87.5, 85.1, 45.8, 21.6. ν_{max} (KBr): 3236 (N-H), 1631 (C=O). HRMS for $C_{23}H_{19}NO$ $(M)^+$, calculated: 325.1467, found: 325.1458.

N-(1-tert-Butyl-hept-2-ynyl)-benzamide (4.11b)

Prepared according to the general procedure for copper-catalyzed synthesis of secondary propargylamides. Chromatography solvent 80/20 hexanes / ethyl acetate. Isolated Yield: 88 %. ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.80-7.72 (m, 2H), 7.49-7.36 (m, 3H), 6.20 (d, 1H, J = 8.7 Hz), 4.80 (dd, 1H, J = 1.5, 8.7 Hz), 2.18 (t, 2H, J =

6.6 Hz), 1.55-1.37 (m, 4H), 1.06 (s, 9H), 0.92 (t, 3H, J = 6.6 Hz). ^{13}C NMR (75.5 MHz, 60 °C, $CDCl_3$): δ 166.7, 134.8, 131.7, 128.8, 127.2, 84.5, 78.3, 51.4, 36.4, 31.2, 26.4, 22.3, 18.7, 14.0. ν_{max} (KBr): 3267 (N-H), 1634 (C=O). HRMS for $C_{18}H_{25}NO$ $(M)^+$, calculated: 271.1936, found: 271.1932.

N-(3-Phenyl-1-p-tolyl-prop-2-ynyl)-acrylamide (4.11c)

Prepared according to the general procedure for copper-catalyzed synthesis of secondary propargylamides. Chromatography solvent 85/15 hexanes / ethyl acetate. Isolated Yield: 57 %. ^1H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.48-7.43 (m, 4H), 7.39-7.28 (m, 3H), 7.18 (d, 2H, J = 7.8 Hz), 6.43-6.29 (m, 2H), 6.21-6.07 (m, 2H), 5.69 (dd, 1H, J = 1.5, 8.7 Hz), 2.39 (s, 3H). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 164.1, 138.0, 136.0, 131.8, 130.3, 129.4, 128.5, 128.3, 127.4, 127.1, 122.5, 87.0, 84.8, 44.9, 21.1. ν_{max} (KBr): 3274 (N-H), 1656 (C=O). HRMS for $C_{19}H_{17}NO$ $(M)^+$, calculated: 275.1310, found: 275.1304.

N-[1-(4-Methoxy-phenyl)-3-phenyl-prop-2-ynyl]-isobutyramide (4.11d)

Prepared according to the general procedure for copper-catalyzed synthesis of secondary propargylamides. Chromatography solvent 85/15 hexanes / ethyl acetate. Isolated Yield: 92 %. ^1H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.53-7.41 (m, 4H), 7.36-7.29 (m, 3H), 6.90 (d, 2H, J = 8.4 Hz), 6.22 (d, 1H, J = 8.4 Hz), 6.07 (d, 1H, J = 8.4 Hz), 3.82 (s, 3H), 2.49-2.35 (m, 1H), 1.24-1.17 (m, 6H). ^{13}C NMR (75.5 MHz, 25 °C,

$CDCl_3$): δ 175.6, 159.5, 132.0, 131.7, 128.7, 128.5, 128.5, 122.8, 114.3, 87.7, 84.8, 55.6, 44.7, 35.9, 19.9, 19.7. ν_{max} (KBr): 3304 (N-H), 1640 (C=O). HRMS for $C_{20}H_{21}NO_2$ $(M)^+$, calculated: 307.1572, found: 307.1581.

N-(1-tert-Butyl-hept-2-ynyl)-4-methoxy-benzamide (4.11e)

Prepared according to the general procedure for copper-catalyzed synthesis of secondary propargylamides. Chromatography solvent 80/20 hexanes / ethyl acetate. Isolated Yield: 87 %. ^1H NMR (270 MHz, 25 °C, $CDCl_3$): δ 7.70 (d, 2H, J = 8.7 Hz), 6.86 (d, 2H, J = 8.7 Hz), 6.19 (d, 1H, J = 9.6 Hz), 4.78 (d, 1H, J = 9.6 Hz), 3.82 (s, 3H), 2.18 (t, 3H, J = 6.6 Hz), 1.56-1.30 (m, 4H), 1.05 (s, 9H), 0.92 (t, 3H, J = 6.6 Hz). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 170.9, 158.7, 137.5, 136.7, 136.6, 131.5, 129.4, 128.4, 128.3, 127.9, 127.7, 125.5, 113.4, 63.4, 54.5, 39.4, 19.4, 12.8. ν_{max} (KBr): 3318 (N-H), 1629 (C=O). HRMS for $C_{19}H_{27}NO_2$ $(M)^+$, calculated: 301.2042, found: 301.2031.

General Procedure for the preparation of 4.11f-j

An analogous procedure to the formation of 4a-e was followed, except instead of adding CuI and boron trifluoride, zinc (II) triflate (24 mg, 0.063mmol) was added as catalyst, and the mixture was stirred at ambient temperature for 10 hours. The solvent was removed in vacuo, and the crude product purified by column chromatography using ethyl acetate / hexanes as eluent.

N-[1-(4-Methoxy-phenyl)-3-phenyl-prop-2-ynyl]-2,2-dimethyl-propionamide (4.11f)

Prepared according to the general procedure for zinc-catalyzed synthesis of secondary propargylamides. Chromatography solvent 85/15 hexanes / ethyl acetate. Isolated Yield: 73 %. ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.47 (d, 4H, J = 6.9 Hz), 7.36-7.31 (m, 3H), 6.89 (d, 2H, J = 8.7 Hz), 6.22 (s, 2H), 3.80 (s, 3H), 1.26 (s, 9H). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 177.2, 159.5, 132.0, 131.7, 128.7, 128.5, 128.4, 122.8, 114.2, 87.9, 84.8, 55.6, 44.9, 39.1, 27.8. ν_{max} (KBr): 3409 (N-H), 1648 (C=O). HRMS for $C_{21}H_{23}NO_2$ $(M)^+$, calculated: 321.1729, found: 321.1739.

N-(1-tert-Butyl-3-phenyl-prop-2-ynyl)-4-iodo-benzamide (4.11g)

Prepared according to the general procedure for zinc-catalyzed synthesis of secondary propargylamides. Chromatography solvent 85/15 hexanes / ethyl acetate. Isolated Yield: 67 %. ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.80 (d, 2H, J = 8.4 Hz), 7.51 (d, 2H, J = 8.4 Hz), 7.45-7.38 (m, 2H), 7.33-7.25 (m, 3H), 6.23 (d, 1H, J = 9.6 Hz), 5.06 (dd, 1H, J = 3.6, 6.0 Hz), 1.17 (s, 9H). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 165.9, 137.8, 133.8, 131.7, 128.6, 128.4, 128.3, 122.6, 98.6, 87.2, 84.0, 51.4, 36.3, 26.1. ν_{max} (KBr): 3296 (N-H), 1645 (C=O). HRMS for $C_{20}H_{20}NOI$ $(M)^+$, calculated: 417.0590, found: 417.0580.

N-(4-Hydroxy-1-p-tolyl-but-2-ynyl)-benzamide (4.11h)

Prepared according to the general procedure for zinc-catalyzed synthesis of secondary propargylamides. Chromatography solvent 75/25 hexanes / ethyl acetate. Isolated Yield: 62 %. ^{1}H NMR (270 MHz, 20 °C, $CDCl_3$): δ 7.71 (d, 2H, J = 6.3 Hz), 7.50-7.29 (m, 5H), 7.11 (d, 2H, J = 6.3 Hz), 6.62 (d, 1H, J = 9.4 Hz), 6.51 (d, 1H, J = 9.4 Hz), 4.33 (dd, 2H, J = 3.2, 13.4 Hz), 2.37-2.22 (m, 4H). ^{13}C NMR (68.0 MHz, 20 °C, $CDCl_3$): δ 167.2, 138.5, 135.8, 133.6, 132.0, 129.3, 128.6, 127.1, 125.9, 80.0, 79.7, 74.4, 56.2, 21.1. ν_{max} (KBr): 3272 (N-H), 1648 (C=O). HRMS for $C_{18}H_{17}NO_2$ $(M)^+$, calculated: 279.1259, found: 279.1265.

N-(1,3-Diphenyl-prop-2-ynyl)-3-methyl-butyramide (4.11i)

Prepared according to the general procedure for zinc-catalyzed synthesis of secondary propargylamides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 91 %. ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.57 (d, 2H, J = 6.3 Hz), 7.50-7.39 (m, 2H), 7.38-7.23 (m, 6H), 6.51 (d, 1H, J = 8.4 Hz), 6.29 (d, 1H, J = 8.4 Hz), 2.30-2.08 (m, 3H), 1.00 (m, 6H). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 171.6, 139.4, 132.0, 128.9, 128.7, 128.5, 128.2, 127.3, 122.8, 87.6, 84.9, 46.1, 45.3, 26.7, 22.9. ν_{max} (KBr): 3308 (N-H), 1641 (C=O). HRMS for $C_{20}H_{21}NO$ $(M)^+$, calculated: 291.1623, found: 291.1621.

N-(1,3-Diphenyl-prop-2-ynyl)-benzamide (4.11j)

Prepared according to the general procedure for zinc-catalyzed synthesis of secondary propargylamides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 89 %. ^{1}H NMR (300 MHz, 80 °C, CD_3CN): δ 7.83 (d, 2H, J = 8.4 Hz), 7.66 (d, 2H, J = 8.4 Hz), 7.52-7.30 (m, 11H), 6.76 (d, 1H, J = 8.4 Hz), 6.50 (d, 1H, J = 8.4 Hz). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 166.3, 139.4, 134.2, 132.0, 131.9, 129.0, 128.8, 128.7, 128.5, 128.3, 127.4, 127.3, 122.8, 87.4, 85.4, 46.1. ν_{max} (KBr): 3290 (N-H), 1633 (C=O). HRMS for $C_{22}H_{17}NO$ $(M)^+$, calculated: 311.1310, found: 311.1302.

General Procedure for the preparation of oxazoles 4.14a-d

Upon completion of either the copper or zinc catalyzed synthesis of the propargylamides, before removal of solvent, NaH (7.2 mg, 0.31 mmol) in 2 mL of acetonitrile was added and the reaction mixture was stirred for 30 minutes. The mixture was then quenched with 5 mL of methanol, the solvent removed in vacuo, and the product purified by column chromatography using ethyl acetate / hexanes as eluent.

5-Benzyl-2-phenyl-4-p-tolyl-oxazole (4.14a)

Prepared according to the general procedure for metal-catalyzed synthesis of oxazoles. Chromatography solvent 95/5 hexanes / ethyl acetate. Isolated Yield: 76 %. ^{1}H NMR (300 MHz, 25 °C, $CDCl_3$): δ 8.11 (d, 2H, J = 6.6 Hz), 7.68 (d, 2H, J = 8.4

Hz), 7.52-7.21 (m, 10H), 4.36 (s, 2H), 2.42(s, 3H). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 160.2, 145.4, 137.7, 137.6, 137.5, 130.3, 129.6, 129.4, 129.0, 128.9, 128.5, 127.9, 127.1, 127.0, 126.5, 32.4, 21.7. ν_{max} (KBr): 2964, 1604, 1555, 1495, 1262, 1100. HRMS calculated for $C_{23}H_{19}NO$ $(M)^+$, calculated: 325.1467, found: 325.1457.

5-Benzyl-2-isopropyl-4-p-tolyl-oxazole (4.14b)

Prepared according to the general procedure for metal-catalyzed synthesis of oxazoles. Chromatography solvent 95/5 hexanes / ethyl acetate. Isolated Yield: 82 %. ^1H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.57 (d, 2H, J = 8.4 Hz), 7.36-7.17 (m, 7H), 4.21 (s, 2H), 3.20-3.04 (m, 1H), 2.39 (s, 3H), 1.40 (d, 6H, J = 6.9 Hz). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 167.6, 144.4, 137.8, 137.3, 135.6, 129.7, 129.5, 128.9, 128.4, 127.0, 126.8, 32.2, 28.9, 21.7, 21.0. ν_{max} (KBr): 2972, 1659, 1611, 1413, 1286, 1178. HRMS for $C_{20}H_{21}NO$ $(M)^+$, calculated: 291.1623, found: 291.1627.

(2-Isobutyl-4-phenyl-oxazol-5-yl)-phenyl-methanone (4.14c)

Prepared according to the general procedure for metal-catalyzed synthesis of oxazoles. Chromatography solvent 80/20 hexanes / ethyl acetate. Isolated Yield: 79%. ^1H NMR (300 MHz, 25 °C, $CDCl_3$): δ 8.00-7.92 (m, 2H), 7.85 (d, 2H, J = 8.4 Hz), 7.56-7.48 (m, 1H), 7.44-7.34 (m, 5H), 2.80 (d, 2H, J = 7.2 Hz), 2.38-2.23 (m, 1H), 1.08 (d, 6H, J = 4.2 Hz). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 183.4, 165.9, 147.7, 143.7, 137.6, 133.0, 130.9, 129.8, 129.7, 129.4, 128.5, 128.4, 37.6, 28.0, 22.8. ν_{max}

(KBr): 2959, 1651, 1557, 1486, 1447, 1232, 1145. HRMS calculated for $C_{20}H_{19}NO_2$ $(M)^+$, calculated: 305.1416, found: 305.1408.

5-Benzyl-2-isopropyl-4-(4-methoxy-phenyl)-oxazole (4.14d)

Prepared according to the general procedure for metal-catalyzed synthesis of oxazoles. Chromatography solvent 95/5 hexanes / ethyl acetate. Isolated Yield: 85%. ^1H NMR (300 MHz, 25 °C, $CDCl_3$): δ 7.56 (d, 2H, J = 8.4 Hz), 7.36-7.18 (m, 5H), 6.91 (d, 2H, J = 8.4 Hz), 4.20 (s, 2H), 3.81 (s, 3H), 3.18-3.03 (m, 1H), 1.40 (d, 6H, J = 6.9 Hz). ^{13}C NMR (75.5 MHz, 25 °C, $CDCl_3$): δ 167.5, 159.1, 143.9, 137.9, 135.4, 128.9, 128.4, 126.8, 125.2, 114.3, 55.6, 32.1, 28.9, 21.0. ν_{max} (KBr): 2971, 1605, 1583, 1512, 1495, 1454, 1303, 1251, 1174. HRMS calculated for$C_{20}H_{21}NO_2$ $(M)^+$, calculated: 307.1572, found: 307.1570.

4.5 References

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CHAPTER FIVE

A General Approach to the Coupling of Organoindium Reagents with Imines via Copper Catalysis

5.0 Preface

In Chapter 2, we described the copper-catalyzed coupling of imines, acid chlorides, and organostannanes to generate α-substituted amides. A disadvantage of this procedure is that organostannanes are neurotoxic, and can only transfer one organic group from the metal center. In this chapter, we present the use of organoindium reagents as an alternative to organostannanes, and employ them in a three component coupling to form α-substituted amides and *N*-protected amines. Interestingly, triorganoindium reagents will transfer all three organic fragments under the catalytic conditions.

5.1 Introduction

Metal-catalyzed cross-coupling reactions between organic electrophiles and organometallic compounds represent one of the more important current methods to construct carbon-carbon bonds.[1] The performance of these reactions with a diverse variety of substrates, as well as with high conversion, selectivity, and atom economy, remains the focus of intense research efforts.[1a] One class of reagents that have recently been shown to be beneficial in these reactions are tri- and tetraorganoindiums.[2] These compounds have overcome several of the limitations associated with the organometallic reagents commonly employed in cross-coupling (e.g., organostannanes, organoboranes), including the facile coupling with sp^3-hybridized alkyl-indium groups, the low toxicity indium byproducts, and the important ability to transfer more than one of the organic substituents from the indium reagent.[2]

While organoindiums have been successfully employed in reactions with a range of traditional cross-coupling partners (e.g., organohalides),[2,3] and a number of other metal-catalyzed processes,[4-8] their application to carbon-carbon bond formation with C=N electrophiles such as imines is much more limited.[9] Barbier and Reformatsky-type reactions have been applied to imines,[10-14] however these processes are typically limited to the addition of allylic- or α-ester-indium functionalities. To our knowledge, there is no general method available to couple organoindium reagents with imines, as a mild route to important α-substituted amine building blocks.

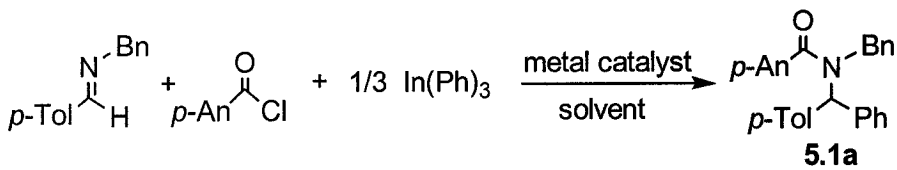
We have recently reported that multiply bonded electrophiles such as imines can be activated towards a Stille-like cross-coupling reaction with organostannanes by the simple addition of acid chlorides, to form α-substituted amides.[15] This presumably occurs via the *in situ* conversion of imine into *N*-acyl iminium salt for reaction with the metal catalyst. Nevertheless, we were unable to transfer many sp^3-hybridized groups from organostannanes, and the reaction leads to the formation of stoichiometric amounts of toxic tin by-products. We report herein that this approach can be used to generate what is to our knowledge a novel, general method to couple organoindium reagents with imines. This reaction occurs with a broad range of organoindium, imine and acid chloride substrates, and provides overall a mild multicomponent method to construct α-substituted amides and *N*-protected amines.

5.2 Results and Discussion

Our initial studies toward this coupling are outlined in Table 5.1. The model system involved the coupling of *N*-benzyltolylaldimine, *p*-anisoyl chloride (*p*-An = 4-$C_6H_4OCH_3$, *p*-Tol = 4-$C_6H_4CH_3$), and triphenylindium.[16] As can be seen, no coupling is observed when the triorganoindium reagent is used without any catalyst (entry 1), nor does a palladium catalyst lead to a reaction. The latter is in contrast to our results with organostannanes and imines, and is potentially the result of a slower transmetalation between indium and the palladium center.[15b] It

has previously been reported that unreactive tin reagents can be induced to undergo cross-coupling through the addition of copper salts.[17] Similarly, the addition of 10 mol % CuCl to this reaction provided the desired α-substituted amide product in 29% yield. Under optimized conditions, this coupling is nearly quantitative (Table 5.1, entry 4). While a number of copper salts proved to be competent catalysts, simple, commercially available CuCl is the most efficient.

Table 5.1 Catalytic Coupling of *N*-Benzyltolylaldimine, *p*-Anisoyl Chloride, and Triphenylindium.[a]



5.1a

Entry #	catalyst	solvent	yield **5.1a** (%)[b]
1	-	CH_3CN	0
2	5% $Pd_2(dba)_3$	CH_3CN	0
3	10% CuCl	CH_3CN	29
4	10% CuCl	CH_3CN/THF	98
5	10% CuCl	THF	45
6	10% CuCl	Toluene/THF	69
7	10% $CuCl_2$	CH_3CN/THF	55
8	10% CuI	CH_3CN/THF	95
9	10% Cu(OTf)[c]	CH_3CN/THF	84

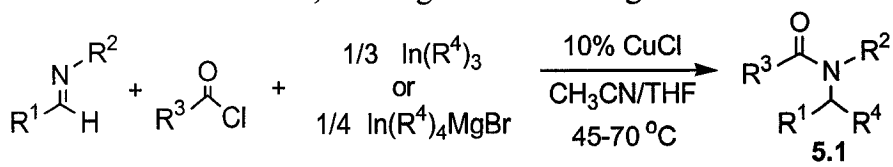
[a]0.50 mmol imine, 0.60 mmol acid chloride, 0.167 mmol triorganoindium and 0.05 mmol CuCl in 1:1 CH_3CN/THF (6 mL) for 14 h at 45 °C. [b]NMR yields using Ph-TMS as internal standard. [c]Cu(OTf) benzene complex used.

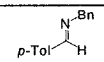
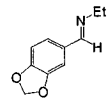
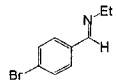
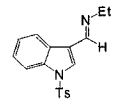
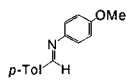
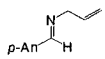
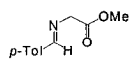
A notable feature of this chemistry is the ability of the organoindium reagent to transfer all of its organic groups to the imine carbon. Thus, the use of only one-third an equivalent of Ph_3In is required to generate **5.1a** in near quantitative yield, with the sole byproduct being $InCl_3$. As shown in Table 2, this reaction is not limited to phenyl group transfer, and efficient coupling can also be achieved with vinyl units (**5.1c, 5.1f, 5.1k**), functionalized arenes (**5.1d, 5.1j**), and even sterically encumbered aryllindium reagents (**5.1e, 5.1i**). The latter includes a 2,6-dimethylphenyl substrate in 84% yield. Even primary and secondary alkyl groups undergo reaction in good yields at slightly elevated temperatures. This level of diversity far surpasses that which we previously observed in Stille-type couplings with imines. A variety of imines and acid chlorides can also be employed in this coupling, including *N*-aryl and *N*-alkyl substituents, as well as imines derived from aryl, heteroaryl, and non-enolizable alkyl aldehydes. Both alkyl and aryl acid chlorides, as well as a range of chloroformates provide the α-substituted amides and *N*-protected α-substituted amines, respectively, in high yield. This chemistry also demonstrates good functional group compatibility, with even acidic substrates (e.g., enolizable acid chlorides, glycine derivatives), compatible with coupling.

It has been previously demonstrated that tetraorganoindium reagents can also behave as cross-coupling partners in a fashion similar to triorganoindium, and provide an atom economical method to transfer all four organic groups on the indium.[2d,3c] These reagents can also be employed in this reaction with imines (Table 5.2), and require only ¼ of an equivalent of indium for the reaction to

proceed in generally even higher yields than those observed with triorganoindium compounds.

Table 5.2 Copper-Catalyzed Three Component Coupling of Imines, Acid Chlorides, and Organoindium Reagents.[a]

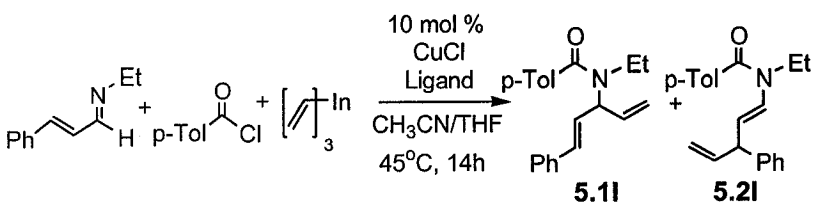


#	Imine	R^3	R^4	yield (%)[b]
5.1a		*p*-An	Ph	95 (96)
5.1b		BnO	Et	92 (94)[c]
5.1c		BnO		89 (91)
5.1d				81 (87)
5.1e			*o*-Tol	79 (84)
5.1f		CH_3		89 (95)
5.1g		EtO	*s*-Bu	77 (75)[e]
5.1h		PhO	Et	84 (84)[d]
5.1i		*p*-An		84 (94)
5.1j		*p*-An	*o*-An	86 (90)
5.1k		*i*-Pr		74

[a]Reactions performed with 0.50 mmol imine, 0.60 mmol acid chloride or chloroformate, 0.167 mmol triorganoindium or 0.133 mmol tetraorganoindate, and 0.05 mmol CuCl in 1:1 CH_3CN/THF (6 mL) for 14 h at 45 °C. [b]Yields in parentheses for reactions with tetraorganoindates. [c]65 °C for 36 h. [d]55 °C for 24 h. [e]70 °C for 72 h.

The use of an α,β-unsaturated imine in this coupling leads to the clean formation of the 1,4-addition product **5.2l** (Table 5.3). Interestingly, this Michael addition product contrasts with the previously reported mixture of 1,2- and 1,4-addition products in reactions with vinylstannanes under identical conditions.[15a]

Table 5.3 1,2- versus 1,4-Addition with α,β-Unsaturated Imines.[a]



ligand	% **5.1l**	% **5.2l**	ratio **5.1l : 5.2l**
-	-	81%	1 : >20
bipy	41%	16%	2.5 : 1
dppe	21%	25%	1 : 1.2
phen	24%	12%	2 : 1
3,4,7,8-tetramethyl-phenanthroline	49%	20%	2.4 : 1
CuBr[b]	61%	16%	3.8 : 1
CuI[b]	73%	11%	7 : 1
Bu_4NBr[c]	31%	23%	1.3 : 1
Bu_4NI[c]	13%	32%	1 : 2.5

[a]0.13 mmol imine, 0.16 mmol acid chloride, 0.042 mmol triorganoindium, and 0.013 mmol CuCl in 1:1 CH_3CN/THF (6 mL) for 14 h at 45 °C. [b]Used as catalyst instead of CuCl. [c]1 equivalent.

While the mechanism of this process is still under investigation, this data suggests a distinct carbon-carbon bond forming step with organoindium reagents, potentially with an interaction between the indium compound and copper catalyst **5.4** (Figure 5.1), or coordination of the Lewis acidic indium with an *in situ*

generated *N*-acyl iminium salt (**5.3**) prior to nucleophilic attack.[18] At present these possibilities cannot be distinguished, although it is notable that the addition of ligands to catalysis, which could presumably coordinate to copper and displace any indium association, leads to the favored formation of the 1,2-addition product **5.11**. This selectivity is similar to that observed with organostannanes.[19] Importantly, this also provides a useful catalyst-based method to influence 1,2- (CuI) versus 1,4-addition (CuCl), by simply modifying the copper salt employed.

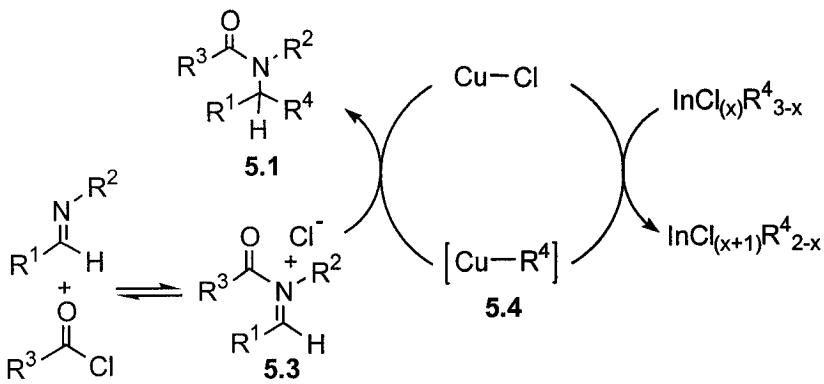


Figure 5.1 Proposed Mechanism of the Copper-Catalyzed Multicomponent Coupling.

5.3 Conclusions

In conclusion, we have developed a general, copper catalyzed method for coupling organoindium reagents with imines and acid chlorides. This provides an efficient method to construct α-substituted amides and *N*-protected α-substituted amines, as well as one that can be readily diversified. The method is highly

regiospecific and is atom efficient. Studies directed toward control of enantioselectivity in this process, as well as the use of other transmetalating agents, are currently underway.

5.4 Experimental Section

General Procedures

Unless otherwise noted, all manipulations were performed under an inert atmosphere in a Vacuum Atmospheres 553-2 dry box or by using standard Schlenk or vacuum line techniques. All reagents were purchased from Aldrich® and used as received. Acetonitrile was distilled from CaH_2 under nitrogen. THF was distilled over sodium benzophenone ketyl. Deuterated acetonitrile was dried as its protonated analogue, but was transferred under vacuum from the drying agent, and stored over 4Å molecular sieves. Deuterated DMSO and chloroform were dried over 3Å molecular sieves. Imines were prepared as per standard literature procedures.[20] Tetraorganoindium reagents were prepared by the slow addition (10 minutes) of the appropriate Grignard reagent to a solution of $InCl_3$ (0.25 equiv) in 1 mL of THF at –78°C, allowed to stir for 30 min. at –78°C, followed by warming to room temperature.[16] ^1H and ^{13}C NMR were recorded on JEOL 270, Varian Mercury 300 MHz, and Mercury 400 MHz spectrometers. Mass spectra (all by ESI method) were obtained from the McGill University mass spectral facilities.

Typical Procedure for Catalytic Synthesis of α-Substituted Amides

$(4\text{-}CH_3C_6H_4)HC{=}N(CH_2C_6H_5)$ (105 mg, 0.50 mmol) and p-anisoyl chloride (111 mg, 0.65 mmol) were mixed in 3 mL of acetonitrile. This was added to a solution of CuCl (4.4 mg, 0.05 mmol) in 2 mL of dry acetonitrile. The reaction mixture was transferred to a 25 mL reaction bomb. The in situ generated organoindium reagent $(Ph)_4InMgBr$ (0.0166 mmol) in 1 mL of THF was added into the reaction mixture, which was then heated at 45 °C for 16 hours. The reaction mixture was cooled then concentrated in vacuo and redissolved in 50 mL of diethyl ether. The organic layer was washed with 50 mL of sat. $NaHCO_3$ (aq), and this was extracted with 2 x 50 mL of diethyl ether. The organic layers were combined and dried over anhydrous $MgSO_4$. The drying agent was then filtered away, the solvent removed in vacuo, and the residual crude product was purified by column chromatography using ethyl acetate / hexanes as eluent. All compounds characterized by ^1H and ^{13}C NMR, and HRMS. Compounds 1c, 1f, 1k, and 1l, and 2l are previously reported compounds.[15a]

Spectroscopic Data

N-Benzyl-4-methoxy-N-(phenyl-p-tolyl-methyl)-benzamide (5.1a)

Prepared according to the typical procedure for copper-catalyzed synthesis of α-substituted amides. Chromatography solvent 80/20 hexanes / ethyl acetate.

Isolated Yield: 95 % with triorganoindium, 96 % with tetraorganoindate. ^{1}H NMR (300 MHz, 55 °C, $CDCl_3$): δ 7.40 (m, 2H), 7.33-7.14 (m, 6H), 7.14-6.98 (m, 6H), 6.94-6.76 (m, 4H), 6.53 (s, 1H), 4.75 (s, 2H), 3.80 (s, 3H), 2.32 (s, 3H). ^{13}C NMR (75.5 MHz, 55 °C, $CDCl_3$): δ 173.2, 160.8, 139.9, 138.5, 137.5, 136.6, 129.5, 129.3, 129.1, 128.6, 128.6, 127.9, 127.8, 127.7, 127.3, 126.4, 114.0, 66.2, 55.6, 49.0, 21.3. HRMS for $C_{29}H_{27}NO_2$ $(M+H)^+$, calculated: 421.2042, found: 421.2029.

(1-Benzo[1,3]dioxol-5-yl-propyl)-ethyl-carbamic acid benzyl ester (5.1b)

Prepared according to the typical procedure for copper-catalyzed synthesis of α-substituted amides, except with heating to 65°C for 36h. Chromatography solvent 75/25 hexanes / ethyl acetate. Isolated Yield: 92 % with triorganoindium, 94 % with tetraorganoindate. ^{1}H NMR (300 MHz, 55 °C, $CDCl_3$): δ 7.42-7.23 (m, 5H), 6.84-6.71 (m, 3H), 5.93 (s, 2H), 5.26-5.09 (m, 3H), 3.10 (q, J = 6.9 Hz, 2H), 1.90 (m, 2H), 1.02-0.85 (m, 6H). ^{13}C NMR (68.0 MHz, 55 °C, $CDCl_3$): δ 156.5, 147.8, 146.8, 137.2, 134.7, 128.4, 127.8, 127.8, 121.0, 108.5, 107.9, 100.9, 67.0, 60.2, 38.0, 24.3, 14.8, 11.1. HRMS for $C_{20}H_{23}NO_4Na^+$ $(M+Na)^+$, calculated: 364.1525, found: 364.1519.

Benzyl-(1-p-tolyl-allyl)-carbamic acid benzyl ester (5.1c)

Prepared according to the typical procedure for copper-catalyzed synthesis of α-substituted amides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 89 % with triorganoindium, 91 % with tetraorganoindate. ^{1}H NMR (270 MHz, 90 °C, d^{6}-DMSO): δ 7.40-7.04 (m, 14H), 6.15 (m, 1H), 5.76 (br, 1H), 5.23-5.05 (m, 4H), 4.59 (d, J = 9.2 Hz, 1H), 4.40 (d, J = 9.2 Hz, 1H), 2.27 (s, 3H). ^{13}C NMR (68.0 MHz, 90 °C, d^{6}-DMSO): δ 155.2, 138.3, 136.2, 136.0, 135.9, 135.5, 128.3, 127.6, 127.4, 127.1, 126.9, 126.8, 126.6, 126.0, 117.3, 66.0, 62.2, 48.3, 19.9. HRMS for $C_{25}H_{25}NO_2$ $(M+H)^+$, calculated: 371.1885, found: 371.1879.

N-[(4-Bromo-phenyl)-(4-fluoro-phenyl)-methyl]-N-ethyl-4-iodo-benzamide (5.1d)

Prepared according to the typical procedure for copper-catalyzed synthesis of α-substituted amides. Chromatography solvent 85/15 hexanes / ethyl acetate. Isolated Yield: 81 % with triorganoindium, 87 % with tetraorganoindate. ^{1}H NMR (300 MHz, 55 °C, $CDCl_3$): δ 7.80 (m, 2H), 7.57 (m, 2H), 7.24 (m, 2H), 7.16 (m, 6H), 6.38 (s, 1H), 3.46 (m, 2H), 0.73 (t, J = 6.9 Hz, 3H). ^{13}C NMR (75.5 MHz, 55 °C, $CDCl_3$): δ 171.0, 164.2, 160.6, 138.4, 137.7, 136.4, 134.7, 134.7, 131.9, 130.5, 130.4, 130.1, 127.9, 122.0, 115.9, 115.5, 95.5, 63.9, 40.4, 14.0. HRMS for

$C_{22}H_{18}{}^{79}BrFINO$, calculated: 536.9601, found: 536.9617. HRMS for $C_{22}H_{18}{}^{81}BrFINO$ $(M+H)^+$, calculated: 538.9580, found: 538.9598.

Furan-2-carboxylic acid ethyl-{[1-(toluene-4-sulfonyl)-1H-indol-2-yl]-o-tolyl-methyl}-amide (5.1e)

Prepared according to the typical procedure for copper-catalyzed synthesis of α-substituted amides. Chromatography solvent 75/25 hexanes / ethyl acetate. Isolated Yield: 79 % with triorganoindium, 84 % with tetraorganoindate. ^1H NMR (270 MHz, 75 °C, CD_3CN): δ 8.02 (d, J = 8.4 Hz, 1H), 7.72 (m, 2H), 7.51 (s, 1H), 7.40-7.20 (m, 6H), 7.19-6.92 (m, 5H), 6.84 (s, 1H), 6.47 (s, 1H), 3.66 (m, 2H), 2.34 (s, 3H), 2.19 (s, 3H), 0.60 (t, J = 3.9 Hz, 3H). ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ 160.6, 148.6, 146.1, 144.5, 137.7, 136.8, 136.2, 135.2, 131.0, 130.3, 130.2, 128.4, 128.4, 127.0, 126.3, 126.1, 125.6, 124.0, 123.6, 120.5, 115.5, 114.4, 111.4, 54.6, 41.0, 20.8, 18.5, 14.4. HRMS for $C_{30}H_{28}N_2O_4S$ $(M+H)^+$, calculated: 512.1770, found: 512.1783.

N-Benzyl-N-(1-tert-butyl-allyl)-acetamide (5.1f)

Prepared according to the typical procedure for copper-catalyzed synthesis of α-substituted amides. Chromatography solvent 80/20 hexanes / ethyl acetate. Isolated Yield: 89 % with triorganoindium, 95 % with tetraorganoindate. ^1H NMR (270 MHz, 130 °C, d^6-DMSO): δ 7.35-7.12 (m, 5H), 6.06 (m, 1H), 5.06 (m,

2H), 4.57 (s, 2H), 1.94 (s, 3H), 0.96 (s, 9H). ^{13}C NMR (68.0 MHz, 130 °C, d^6-DMSO): δ 170.2, 138.5, 133.8, 127.3, 125.7, 125.6, 118.2, 48.9, 35.0, 26.9, 24.8, 21.5. HRMS for $C_{16}H_{23}NO$ $(M+H)^+$, calculated: 245.1780, found: 245.1777.

(4-Methoxy-phenyl)-(2-methyl-1-p-tolyl-butyl)-carbamic acid ethyl ester (5.1g)

Prepared according to the typical procedure for copper-catalyzed synthesis of α-substituted amides, except with heating to 70°C for 72h. Chromatography solvent 75/25 hexanes / ethyl acetate. Isolated Yield: 77 % with triorganoindium, 75 % with tetraorganoindate. ^1H NMR (270 MHz, 75 °C, CD_3CN): δ 7.00 (m, 2H), 6.88 (m, 2H), 6.73 (m, 2H), 6.60 (m, 2H), 5.07 (br, 1H), 4.09 (m, 2H), 3.78 (s, 3H), 2.34 (s, 3H), 2.10 (m, 2H), 1.29 (m, 3H), 1.12 (m, 4H), 0.82 (t, J = 5.4 Hz, 1H), 0.73 (d, J = 6.9 Hz, 2H) . ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ 158.5, 158.5, 156.6, 156.6, 136.9, 136.8, 136.5, 136.4, 132.5, 132.2, 131.0, 130.9, 129.5, 129.4, 128.6, 128.5, 113.6, 113.5, 67.5, 67.2, 61.3, 61.3, 55.3, 35.3, 35.3, 26.5, 26.3, 21.0, 16.5, 16.5, 14.6, 11.3, 10.8. HRMS calculated for $C_{22}H_{29}NO_3$ $(M+H)^+$, calculated: 355.2147, found: 355.2151.

Allyl-[1-(4-methoxy-phenyl)-propyl]-carbamic acid phenyl ester (5.1h)

Prepared according to the typical procedure for copper-catalyzed synthesis of α-substituted amides, except with heating to 55°C for 24h. Chromatography solvent

85/15 hexanes / ethyl acetate. Yield: 84% with triorganoindium, 84% with tetraorganoindate. ^{1}H NMR (270 MHz, 75 °C, CD_3CN): δ 7.44-7.29 (m, 4H), 7.22-7.11 (m, 3H), 6.90 (d, J = 6.9 Hz, 2H), 6.71 (m, 1H), 5.27 (m, 1H), 5.04 (m, 2H), 3.83 (s, 3H), 3.70 (br, 1H), 2.06 (t, J = 6.7 Hz, 2H), 1.09 (br, 3H). ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ 159.2, 155.1, 151.8, 135.1, 132.1, 131.9, 129.2, 125.0, 121.7, 116.5, 114.0, 60.9, 55.3, 46.5, 24.4, 11.3. HRMS calculated for $C_{20}H_{23}NO_3$ $(M+H)^+$, calculated: 325.1678, found: 325.1677.

N-Benzyl-N-[(2,6-dimethyl-phenyl)-p-tolyl-methyl]-4-methoxy-benzamide (5.1i)

Prepared according to the typical procedure for copper-catalyzed synthesis of α-substituted amides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 84 % with triorganoindium, 94% with tetraorganoindate. ^{1}H NMR (270 MHz, 55 °C, $CDCl_3$): δ 7.36 (m, 2H), 7.13-6.90 (m, 8H), 6.88-6.62 (m, 7H), 5.00 (d, J = 10.9 Hz, 1H), 4.51 (d, J = 10.9 Hz, 1H), 3.75 (s. 3H), 2.33 (s, 3H), 2.01 (s, 6H). ^{13}C NMR (68.0 MHz, 55 °C, $CDCl_3$): δ 177.0, 164.4, 142.5, 142.4, 142.2, 140.2, 140.1, 133.5, 133.4, 133.1, 132.4, 131.6, 131.5, 131.0, 130.9, 130.2, 117.4, 65.9, 59.1, 53.8, 25.7, 24.7. HRMS for $C_{31}H_{31}NO_2$ $(M+H)^+$, calculated: 449.2355, found: 449.2366.

N-Benzyl-4-methoxy-N-[(2-methoxy-phenyl)-p-tolyl-methyl]-benzamide (5.1j)

Prepared according to the typical procedure for copper-catalyzed synthesis of α-substituted amides. Chromatography solvent 75/25 hexanes / ethyl acetate. Isolated Yield: 86 % with triorganoindium, 90% with tetraorganoindate. ^{1}H NMR (270 MHz, 55 °C, $CDCl_3$) :δ 7.36 (m, 2H), 7.10 (m, 2H), 7.07-6.99 (m, 5H), 6.92-6.70 (m, 6H), 6.62 (s, 1H), 6.50 (m, 1H), 5.18 (d, J = 15.1 Hz, 1H), 4.30 (d, J = 15.1 Hz, 1H), 3.76 (s, 3H), 3.55 (s, 3H), 2.35 (s, 3H). ^{13}C NMR (68.0 MHz, 55 °C, $CDCl_3$): δ 173.5, 160.5, 157.9, 138.6, 137.5, 136.6, 131.0, 130.6, 129.9, 129.2, 129.1, 128.3, 128.2, 127.7, 127.5, 125.9, 120.0, 113.4, 110.1, 60.9, 55.3, 54.8, 48.3, 21.0. HRMS for $C_{30}H_{29}NO_3$ $(M+H)^+$, calculated: 451.2147, found: 451.2152.

[Isobutyryl-(1-p-tolyl-allyl)-amino]-acetic acid methyl ester (5.1k)

Prepared according to the typical procedure for copper-catalyzed synthesis of α-substituted amides. Chromatography solvent 75/25 hexanes / ethyl acetate. Isolated Yield: 74 %. ^{1}H NMR (270 MHz, 20 °C, $CDCl_3$): δ 7.20-7.09 (m, 4H), 6.45 (d, J = 7.2 Hz, 0.3H, minor rotamer), 6.08 (m, 1H), 5.69 (d, J = 7.2 Hz, 0.7H, major rotamer), 5.44-5.23 (m, 2H), 4.03-3.79 (m, 2H), 3.60 (s, 2.1H, major rotamer), 3.50 (s, 0.9H, minor rotamer), 2.92 (q, 0.7H, major rotamer), 2.60 (q, 0.3H, minor rotamer), 2.34-2.30 (m, 3H), 1.21 (m, 6H). ^{13}C NMR (68.0 MHz, 20

°C, $CDCl_3$): for major and minor rotamers, δ 178.0, 177.8, 170.0, 169.6, 137.8, 137.4, 135.7, 135.1, 134.8, 134.6, 129.3, 129.0, 128.6, 127.8, 118.6, 117.6, 62.4, 58.2, 52.0, 51.8, 45.9, 45.3, 31.2, 30.4, 21.0, 21.0, 19.8, 19.7, 19.5, 19.4. HRMS for $C_{17}H_{23}NO_3$ $(M+H)^+$, calculated: 289.1678, found: 289.1675.

N-Ethyl-4-methyl-N-(3-phenyl-1-vinyl-allyl)-benzamide (5.1l)

Prepared according to the typical procedure for copper-catalyzed synthesis of α-substituted amides. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 73 % (optimal). ^1H NMR (270 MHz, 75 °C, CD_3CN): δ 7.43-7.08 (m, 9H), 6.42 (d, J = 6.9 Hz, 1H), 6.29 (dd, J = 0.7, 6.9 Hz, 1H), 6.04 (m, 1H), 5.22-5.00 (m, 3H), 3.58-3.21 (m, 2H), 2.27 (s, 3H), 1.07 (t, J = 6.9 Hz, 3H). ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ 171.7, 139.6, 137.3, 137.0, 135.4, 132.7, 129.2, 128.9, 128.1, 126.7, 126.6, 115.5, 115.3, 61.8, 39.8, 20.6, 14.8. HRMS calculated for $C_{21}H_{23}NO$ $(M+H)^+$, calculated: 305.1780, found: 305.1775.

N-Ethyl-4-methyl-N-(3-phenyl-penta-1,4-dienyl)-benzamide (5.2l)

Prepared according to the typical procedure for copper-catalyzed synthesis of α-substituted amides. Chromatography solvent 80/20 hexanes / ethyl acetate. Isolated Yield: 81 % with triorganoindium, 88% with tetraorganoindate. ^1H NMR (270 MHz, 75 °C, CD_3CN):δ 7.42-7.23 (m, 9H), 6.52 (m, 1H), 6.10 (m, 1H), 5.90

(m, 1H), 5.04-4.89 (m, 2H), 3.91 (t, J = 6.9 Hz, 1H), 3.70 (q, J = 6.7 Hz, 2H), 2.47 (s, 3H), 1.26 (t, J = 4.9 Hz, 3H). ^{13}C NMR (68.0 MHz, 75 °C, CD_3CN): δ 170.0, 143.8, 141.3, 141.3, 140.5, 133.8, 129.7, 129.1, 128.8, 128.1, 127.8, 126.6, 114.5, 114.0, 103.6, 50.3, 39.2, 20.6, 12.0. HRMS calculated for $C_{21}H_{23}NO$ $(M+H)^+$, calculated: 305.1780, found: 305.1776.

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(18) While a radical pathway is also possible, the addition of radical traps 9,10-dihydroanthracene and TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) to the reaction does not perturb the reaction rate or product yield.

(19) The selectivity observed with ligands present is similar to that noted with vinylstannanes (e.g., phenanthroline/CuI with vinyl$(Bu)_3$Sn: 3:1 ratio favoring the 1,2-addition product **5.11**).[15a]

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CHAPTER SIX

The Enantioselective Copper-Catalyzed Addition of Alkynes to Heterocycles: Synthesis of Chiral Alkynyl-Substituted Quinolines and Isoquinolines

6.0 Preface

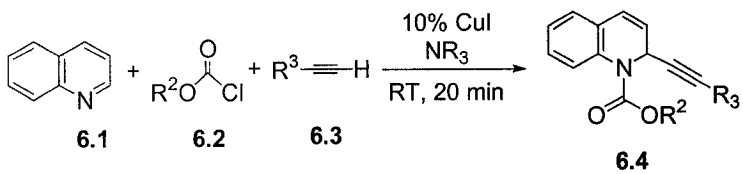
The results reported in Chapter 3 demonstrate that imines can be activated by acid chlorides toward a copper-catalyzed coupling with alkynes to form tertiary propargylamides and *N*-protected propargylamines. As part of this work, we preliminarily disclosed that nitrogen-containing heterocycles such as pyridine can undergo an analogous reaction, allowing the regioselective construction of 2-alkynyl-1,2-dihydropyridines. In this chapter, we describe a copper-catalyzed method for enantioselective alkynylation of nitrogen-containing heterocycles (e.g., quinolines and isoquinolines) through the use of axially chiral ligands. We will also describe initial attempts at the enantioselective alkynylation of imines.

6.1 Introduction

The direct functionalization of aza-aromatic heterocycles is an attractive route for generating cyclic amines.[1] In addition to the widespread availability of aromatic heterocycles as building blocks, the products of these addition reactions are found in a wide variety of biologically relevant compounds. For example, *ortho*-substituted quinoline and isoquinoline derivatives can be found in many natural products (e.g., alkaloids),[2-3] antibiotics (e.g., mycins),[4] pharmaceutical agents,[5] chiral ligands,[6] and polymers.[7] Many methodologies exist for the construction of these heterocyclic molecules.[8-13] Of these routes, the addition of organometallic reagents to activated forms of the parent heterocycle (e.g., *N*-acyl quinolinium salts) is one of the most simple and effective.[1a] As *ortho*-substituted quinoline and isoquinoline derivatives products are chiral, the design of enantioselective methods for their preparation has recently attracted attention. Most current research in enantioselective addition to activated pyridines, quinolines, and isoquinolines employs stoichiometric chiral auxiliaries.[14,15] More recently, efforts have focused on developing catalytic routes to these products. These include the addition of organolithium reagents,[16] nitriles,[17] and silyl-ketene acetals[18] to the activated heterocycles, as well as a copper-catalyzed alkynylation of preformed *N*-alkyl isoquinolinium bromides.[19]

We have recently reported that nitrogen-containing heterocycles such as pyridine can undergo a direct, copper-catalyzed coupling with terminal alkynes in the presence of chloroformates to generate 2-alkynyl-1,2-dihydropyridines (Scheme 6.1).[20] In contrast to most nucleophilic approaches, this process employs simple

terminal alkynes, leading to high functional group compatibility. It also selectively generates propargylamide products within minutes at ambient temperature. These products are highly versatile building blocks in synthesis.[21-23] Considering the ease with which this reaction can be performed, an asymmetric variant employing a copper complex instead of a simple salt would provide a straightforward method to assemble, in one step, chiral cyclic propargylamides from the parent heterocycles and alkynes. We have therefore undertaken the development of a catalytic, enantioselective alkynylation of aromatic nitrogen-containing heterocycles, which is presented herein.



6.1 6.2 6.3 6.4

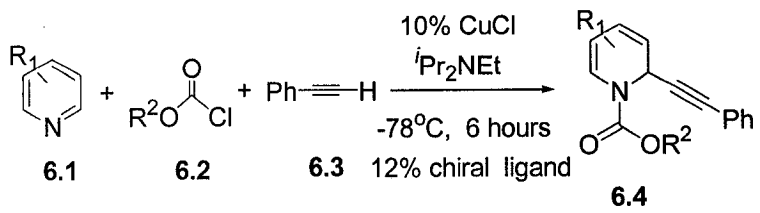
Scheme 6.1 Copper-catalyzed three component coupling of nitrogen-containing heterocycles, chloroformates, and alkynes.

6.2 Results and Discussion

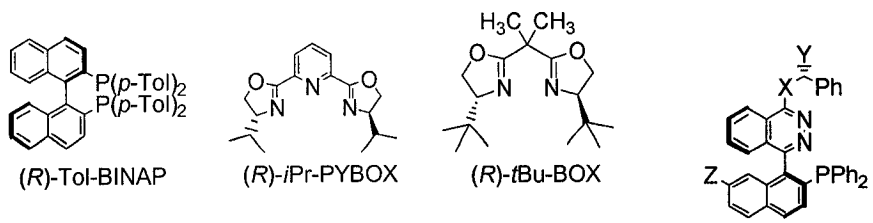
Our initial efforts examined the reaction of ethyl chloroformate, phenylacetylene, and pyridine in the presence of CuCl (10 mol %) and a chiral ligand (12 mol %). The use of several commercially available chiral phosphorus- and nitrogen-donor ligands in this reaction resulted in low enantioselectivity (Table 6.1, entries 1-5). However, we were encouraged by the results with (*R*)-QUINAP, which

provided the functionalized pyridine derivative in moderate enantioselectivity (49%, entry 6). A similar enantioselectivity was observed in the alkynylation of quinoline (entry 7). Due to the low yields obtained when using pyridine, we focused on quinoline derivatization.

Table 6.1 Copper-Catalyzed Enantioselective Alkynylation of Nitrogen-Containing Heterocycles.



6.1 **6.2** **6.3** **6.4**



(*R*)-Tol-BINAP (*R*)-*i*Pr-PYBOX (*R*)-*t*Bu-BOX

(*R*)-MOP (*R*)-MONOPHOS (*R*)-QUINAP

6.5a X = NH; Y = CH_3; Z = H
6.5b X = O; Y = CH_3; Z = H
6.5c X = NH; Y = $C(Et)_2OH$; Z = OCH_3
6.5d X = NH; Y = $C(Bn)_2OH$; Z = OCH_3
6.5e X = NH; Y = CH_3; Z = OCH_3

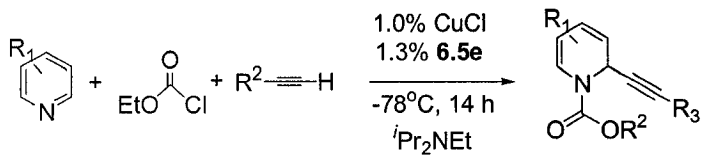
Entry	Heterocycle	R^2	Ligand	Yield (%)	ee (%)
1	Pyridine	Et	(*R*)-Tol-BINAP	ND[b]	2
2	Pyridine	Et	(*R*)-^{i}Pr-PYBOX	ND[b]	0
3	Pyridine	Et	(*R*)-^{t}Bu-BOX	ND[b]	1
4	Pyridine	Et	(*R*)-MONOPHOS	NR[c]	-
5	Pyridine	Et	(*R*)-MOP	72	0
6	Pyridine	Et	(*R*)-QUINAP	17	49
7	Quinoline	Et	(*R*)-QUINAP	86	43
8	Quinoline	Et	**6.5a**	91	53
9	Quinoline	Et	**6.5b**	84	53
10	Quinoline	Et	**6.5c**	86	75
11	Quinoline	Et	**6.5d**	75	66
12	Quinoline	Et	**6.5e**	92	81

[a] 0.10 mmol heterocycle, 0.12 mmol chloroformate, 0.11 mmol alkyne, and with 12 mol % of the given ligands, 10 mol % CuCl, and 1.5 equiv. $^i Pr_2NEt$ in CH_2Cl_2 / CH_3CN (5:1, 6 mL). [b] ND = not determined. [c] NR = no reaction.

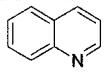
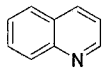
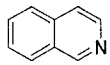
In order to further improve the enantioselectivity, we examined the PINAP series of ligands (**6.5a-c**) as tunable QUINAP analogues, whose copper complexes have been recently reported by Carreira and co-workers to be effective in the enantioselective three component coupling of aldehydes, amines, and alkynes.[24] As shown in Table 6.1, these ligands resulted in a further increase in the ee's observed (entries 8-10), with the methoxy-substituted ligand **6.5c** providing an enantioselectivity of 75%. Useful features of the PINAP series of ligands include their modularity and their ease of resolution, as the ligands can be separated as diastereomers. As such, two new variants of this ligand (**6.5d** and **6.5e**) were prepared, in analogy to literature procedures.[24] Gratifyingly, in the case of ligand **6.5e**, the enantioselective addition of phenylacetylene to quinoline provided an ee of 81% (entry 12).

As well as its simplicity, this method of functionalizing nitrogen-containing heterocycles can be readily generalized (Table 6.2). Phenylacetylene and trimethylsilyl acetylene provide the desired products in similarly good yields and enantioselectivities. As well as quinoline, isoquinoline and pyridine can undergo alkynylation with high enantioselectivity, albeit in low yield with pyridine. Work to further generalize this process is ongoing.

Table 6.2 Copper-Catalyzed Enantioselective Alkynylation of Quinolines and Isoquinolines.



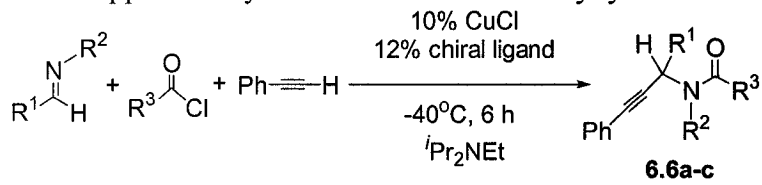
6.4a-d

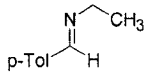
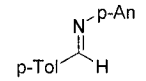
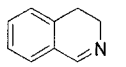
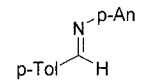
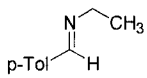
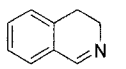
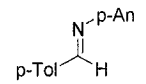
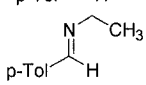
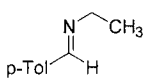
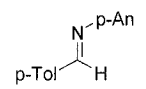
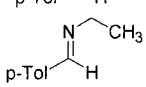
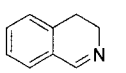
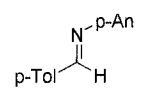
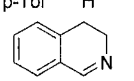
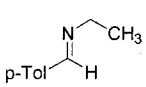
Prod. #[a]	Heterocycle	Alkyne	Yield (%)	ee (%)
6.4a		Ph—≡	86	81
6.4b		TMS—≡	72	84
6.4c		Ph—≡	88	72
6.4d		Ph—≡	8	77

[a]0.10 mmol heterocycle, 0.12 mmol chloroformate, 0.11 mmol alkyne, and with the given ligands, CuCl, and $^{i}Pr_2NEt$ in CH_2Cl_2 (5 mL) and CH_3CN (1 mL), at –78°C for 14 hours.

In addition to the alkynylation of heterocycles, we have examined the catalytic, enantioselective alkynylation of imines using copper complexes. As with quinoline and pyridine, the use of many commercially available ligands resulted in low enantioselectivities. Interestingly, even the PINAP ligand **6.5a,** which worked well with nitrogen-containing heterocycles, yields racemic products. While this chemistry has not met with the same success as that reported with the heterocycles, moderate levels of enantioselectivity can be obtained using (R)-QUINAP (21-43% ee).[25] The results are presented in Table 6.3.

Table 6.3 Copper-Catalyzed Enantioselective Alkynylation of Imines.



Entry #[a]	Imine	R^3	Ligand	ee (%)
1 (6.6a)		p-Tol	(*R*)-Tol-BINAP	6
2 (6.6b)		Ph	(*R*)-Tol-BINAP	0
3 (6.6c)		p-Tol	(*R*)-^{i}Pr-PYBOX	4
4		Ph	(*R*)-^{i}Pr-PYBOX	5
5		p-Tol	(*R*)-^{i}Pr-PYBOX	9
6		p-Tol	(*R*)-^{t}Bu-BOX	3
7		Ph	(*R*)-^{t}Bu-BOX	0
8		p-Tol	(*R*)-^{t}Bu-BOX	11
9		p-Tol	(*R*)-MONOPHOS	7
10		Ph	(*R*)-QUINAP	21
11		p-Tol	(*R*)-QUINAP	43
12		p-Tol	(*R*)-QUINAP	27
13		Ph	**6.8a**	0
14		p-Tol	**6.8a**	0
15		p-Tol	**6.8a**	0

[a]0.1 mmol imine, 0.12 mmol chloroformate, 0.12 mmol alkyne, and with the given ligands, CuCl, and ^{i}Pr$_2$NEt in CH_3CN (6 mL), at –40°C for 6 hours.

6.3 Conclusions

In conclusion, we have developed a copper-catalyzed enantioselective method to couple alkynes with nitrogen-containing heterocycles. To our knowledge, this represents the first copper-catalyzed enantioselective synthesis of cyclic propargylamides, directly from the parent aromatic heterocycles. Mechanistic studies, as well as efforts to use of this approach in the coupling of heterocycles with other reagents, are currently underway.

6.4 Experimental Section

General Procedures

Manipulations were performed by using standard Schlenk or vacuum line techniques. Acetonitrile and methylene chloride were distilled from CaH_2 under nitrogen. Deuterated acetonitrile was dried as its protonated analogue, but was transferred under vacuum from the drying agent, and stored over 3Å molecular sieves. Deuterated chloroform was dried over 4Å molecular sieves. 1,4-dichlorophthalazine was synthesized via a literature procedure,[26] as were the amino alcohols used for the synthesis of **6.8c** and **6.8d**.[27] Ligands **6.8a, 6.8b** and **6.8c** were prepared via literature procedures.[24] Imines were prepared via a literature procedure.[28] All other reagents were purchased from Aldrich® or Strem Chemical® and used as

received. Enantiomeric excesses were measured using ChiralCel-OD-H and ChiralPak-AD-H columns from Daicel, with a Waters HPLC system.

^{1}H and ^{13}C were recorded on JEOL 270, Varian Mercury 300 MHz, 400 MHz, and 500 MHz spectrometers. Mass spectra (ESI method used for all) were obtained from the McGill University Mass Spectrometry Unit.

Typical Procedure for Catalytic Synthesis of Alkynylated Heterocycles

Quinoline (12.0 mg, 0.093 mmol) and ethyl chloroformate (12.1 mg, 0.111 mmol) were mixed in 2 mL of CH_2Cl_2. Copper (I) chloride (0.09 mg, 0.93 μmol) and chiral ligand **6.5e** (0.71 mg, 1.21 μmol) were mixed in 2 mL of 1:1 CH_3CN:CH_2Cl_2. These solutions were mixed together, and phenylacetylene (10.5 mg, 0.102 mmol) in 1 mL of CH_2Cl_2 was slowly added. The entire mixture was transferred into a 25 mL Schlenk flask and placed under a flow of N_2. After 5 minutes, the flask was cooled to -78 °C , and $EtN^{i}Pr_2$ (24.3 μL, 0.140 mmol) in 1 mL of CH_2Cl_2 was added over 30 minutes in 0.1 mL increments. The reaction was stirred at -78 °C for 14 hours, then warmed to ambient temperature. The mixture was concentrated in vacuo, and the product isolated by column chromatography using ethyl acetate / hexanes as eluent (ratio from 1:4 to 3:97).

Typical Procedure for Catalytic Alkynylation of Imines

Imine (p-Tol)C(H)=NEt (10.0 mg, 0.068 mmol) and toluoyl chloride (12.6 mg, 0.082 mmol) were mixed in 2 mL of CH_3CN. Copper (I) chloride (0.7 mg, 6.8 μmol) and (R)-QUINAP (3.3 mg, 7.5 μmol) were thoroughly mixed in 2 mL of

CH_3CN. These solutions were mixed together, and phenylacetylene (8.3 mg, 0.082 mmol) in 1 mL of CH_2Cl_2 was slowly added. The entire mixture was transferred to a 25 mL Schlenk flask and placed under a flow of N_2. Over 10 minutes the flask was cooled to -40 °C, and $^iPr_2NEt$ (17.8 μL, 0.103 mmol) in 1 mL of CH_3CN was added over 30 minutes in 0.1 mL increments. The reaction was stirred at -40 °C for 6 hours, then allowed to warm overnight. The mixture was concentrated in vacuo, and the product isolated by column chromatography using ethyl acetate / hexanes as eluent.

Procedure for the Synthesis of Ligand 6.5d

A procedure analogous to that reported for ligands **6.5a-c** was followed.[24] Trifluoromethanesulfonic acid 1-(4-chlorophthalazin-1-yl)-7-methoxynaphthalen-2-yl ester (1.30 g, 2.77 mmol) and (R)-1-amino-2-benzyl-1,3-diphenylpropan-2-ol (4.40 g, 13.9 mmol) were mixed neat in a screw-capped vial. The suspension was stirred for 24h at 120°C. After cooling to ambient temperature, 30 mL of methylene chloride was added and the suspension was filtered. The filtrate was concentrated under reduced pressure. The product was isolated by column chromatography using toluene/EtOAc (10:1 to 5:1) as eluent, as a mixture of diastereomers. This product, 1-(4-((R)-2-benzyl-2-hydroxy-1,3-diphenylpropylamino)phthalazin-1-yl)-7-methoxy-naphthalen-2-yl trifluoromethanesulfonate (1.28 g, 1.62 mmol, 59% yield), was dried on a vacuum line for 24 hours and then used in the next step.

A solution of $Ni(dppe)Cl_2$ (0.082 g, 0.16 mmol) in 3 mL of DMF was mixed with a solution of diphenylphosphine (0.620 g, 3.32 mmol) in 2 mL of DMF, under a nitrogen atmosphere. This red solution was heated at 120°C for one hour. After

cooling, under nitrogen, a solution of 1-(4-((R)-2-benzyl-2-hydroxy-1,3-diphenylpropylamino)phthalazin-1-yl)-7-methoxynaphthalen-2-yl trifluoromethanesulfonate (1.28 g, 1.62 mmol) in 1.5 mL of DMF was added, followed by addition of DABCO (0.73 g, 6.50 mmol) in 3 mL of DMF. The solution was then heated at 120°C for 36 hours. The mixture was then concentrated under reduced pressure. The green/black residue was then purified by column chromatography in toluene/EtOAc (pure toluene to 4:1) as eluent, as a mixture of diastereomers. Separation of the diastereomers was performed subsequently by column chromatography in toluene/EtOAc (12:1). From this, 290 mg (23%) of ligand **6.5d** was isolated.

Procedure for the Synthesis of Ligand 6.5e

A procedure analogous to that reported for ligands **6.5a-c** was followed.[24] Trifluoromethanesulfonic acid 1-(4-chlorophthalazin-1-yl)-7-methoxynaphthalen-2-yl ester (1.30 g, 2.77 mmol) and (R)-α-methyl-benzylamine (1.70 g, 14.0 mmol) were mixed neat in a screw-capped vial. The suspension was stirred for 14h at 120°C. After cooling to ambient temperature, the product was isolated by column chromatography using hexanes/ethyl acetate (65:35) as eluent, as a mixture of diastereomers. This product, 7-methoxy-1-(4-((R)-1-phenylethylamino)phthalazin-1-yl)naphthalen-2-yl trifluoromethanesulfonate (1.10 g, 1.99 mmol, 72%), was dried on a vacuum line for 24 hours and then used in the next step.

A solution of $Ni(dppe)Cl_2$ (0.105 g, 0.020 mmol) in 3 mL of DMF was mixed with a solution of diphenylphosphine (0.745 g, 4.0 mmol) in 2 mL of DMF, under a nitrogen

atmosphere. This red solution was heated at 120°C for one hour. After cooling, under nitrogen, a solution of 7-methoxy-1-(4-((R)-1-phenylethylamino)phthalazin-1-yl)naphthalen-2-yl trifluoromethanesulfonate (1.10 g, 1.99 mmol) in 1.5 mL of DMF was added, followed by addition of DABCO (0.90 g, 8.0 mmol) in 3 mL of DMF. The solution was then heated at 120°C for 48 hours. The mixture was then concentrated under reduced pressure. The green/black residue was then purified by column chromatography in toluene/EtOAc (pure toluene to 4:1) as eluent, as a mixture of diastereomers. Separation of the diastereomers was performed subsequently by column chromatography in toluene/EtOAc (10:1). From this, 415 mg (35%) of ligand **6.5e** was isolated.

Ethyl-2-(phenylethynyl)quinoline-1(2*H*)-carboxylate (6.4a)

Prepared according to the typical procedure for catalytic synthesis of alkynylated heterocycles. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 86%. Enantiomeric Excess: 81%. ^{1}H NMR (300 MHz, $CDCl_3$):δ 7.63 (d, 1H, J = 6.8 Hz), 7.33-7.07 (m, 9H), 6.60-6.52 (m, 1H), 6.15-6.06 (m, 2H), 4.42-4.22 (m, 2H), 1.37 (t, 3H, J = 9.2 Hz). ^{13}C NMR (75.0 MHz, $CDCl_3$): δ 154.1, 134.6, 132.0, 128.5, 128.3, 128.0, 126.8, 126.2, 125.4, 124.6, 124.6, 122.8, 85.9, 83.7, 62.8, 44.9, 14.7. HRMS calculated for $C_{20}H_{18}NO_2$ $(M+H)^+$: 304.1332; found: 304.1330.

Ethyl-2-((trimethylsilyl)ethynyl)quinoline-1(2*H*)-carboxylate (6.4b)

Prepared according to the typical procedure for catalytic synthesis of alkynylated heterocycles. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 72%. Enantiomeric Excess: 84%. ^{1}H NMR (500 MHz, $CDCl_3$):δ 7.62 (br, 1H), 7.28-7.20 (m, 1H), 7.13-7.05 (m, 2H), 6.51 (d, 1H, J = 6.4 Hz), 6.04-5.97 (m, 1H), 5.88 (d, 1H, J = 5.3 Hz), 4.37-4.21 (m, 2H), 1.35 (t, 3H, J = 5.6 Hz), 0.05 (s, 9H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 154.0, 134.6, 127.9, 126.8, 126.7, 126.0, 125.5, 124.5, 102.0, 88.5, 62.7, 44.9, 14.7, 0.0. HRMS calculated for $C_{17}H_{22}NO_2Si$ $(M+H)^+$: 300.1414; found: 300.1409.

Ethyl-2-(phenylethynyl)-1,2-dihydroisoquinoline-1-carboxylate (6.4c)

Prepared according to the typical procedure for catalytic synthesis of alkynylated heterocycles. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 88%. Enantiomeric Excess: 72%. ^{1}H NMR (300 MHz, $CDCl_3$):δ 7.36-7.29 (m, 2H), 7.28-7.14 (m, 7H), 7.09 (d, 1H, J = 7.2 Hz), 6.92 (br, 1H), 6.38 (s, 1H), 5.95 (d, 1H, J = 8.4 Hz), 4.38 (m, 2H), 1.38 (t, 3H, J = 7.6 Hz). ^{13}C NMR (68.0 MHz, $CDCl_3$): δ 153.0, 131.9, 130.2, 129.9, 128.4, 128.2, 128.1, 127.3, 126.3, 125.2, 124.8, 122.9, 108.5, 87.5, 83.7, 62.7, 47.6, 14.6. HRMS calculated for $C_{20}H_{17}NO_2Na$ $(M+Na)^+$: 326.1152; found: 326.1147.

Ethyl 2-(phenylethynyl)pyridine-1(2*H*)-carboxylate (6.4d)

Prepared according to the typical procedure for catalytic synthesis of alkynylated heterocycles. Chromatography solvent 90/10 hexanes / ethyl acetate. Isolated Yield: 8%. Enantiomeric Excess: 77%. ^{1}H NMR (300 MHz, 60°C, $CDCl_3$):δ 7.41-7.32 (m, 2H), 7.28-7.21 (m, 3H), 6.80 (d, 1H, J = 6.8 Hz), 6.00 (m, 1H), 5.79 (d, 1H, J = 6.8 Hz), 5.65 (t, 1H, J = 5.6 Hz), 5.36 (t, 1H, J = 5.6 Hz), 4.32 (m, 2H), 1.37 (t, 3H, J = 8.2 Hz). ^{13}C NMR (68.0 MHz, 60°C, $CDCl_3$): δ 153.4, 131.9, 128.1, 125.2, 122.9, 122.5, 122.3, 118.6, 105.1, 86.8, 82.2, 62.5, 44.2, 14.4. HRMS calculated for $C_{16}H_{16}NO_2$ $(M+H)^+$: 254.1183; found: 254.1176.

(R,M)-4-(2-(diphenylphosphino)-7-methoxynaphthalen-1-yl)-*N*-(1-phenylethyl)phthalazin-amine (6.5d)

Prepared according to the procedure listed above. ^{1}H NMR (300 MHz, $CDCl_3$):δ 7.90 (m, 3H), 7.63 (t, 1H, J = 6.9 Hz), 7.57-7.09 (m, 19H), 6.48 (s, 1H), 5.82 (quint, 1H, J = 6.9 Hz), 5.47 (br, 1H), 3.42 (s, 3H), 1.73 (d, 3H, J = 6.8 Hz). ^{13}C NMR (68.0 MHz, $CDCl_3$): δ 158.2, 152.4, 144.9, 134.7, 134.6, 134.2, 133.9, 133.6, 133.3, 131.0, 129.6, 129.4, 128.9, 128.7, 128.6, 128.5, 128.4, 128.3, 128.2, 128.2, 127.3, 126.9, 126.9, 126.8, 120.7, 119.5, 118.0, 105.6, 55.3, 50.7, 22.5. ^{31}P NMR (81.0 MHz, $CDCl_3$): δ –12.07. HRMS calculated for $C_{39}H_{33}N_3OP$ $(M+H)^+$: 590.2356; found: 590.2350. $[\alpha]_D^{24}$ = 180.0 (c = 1.0, $CHCl_3$).

(1*S*,P)-2-benzyl-1-(4-(2-(diphenylphosphino)-7-methoxynaphthalen-1-yl)phthalazin-1-yloxy)-1,3-diphenylpropan-2-ol (6.5e)

Prepared according to the procedure listed above. ^{1}H NMR (300 MHz, $CDCl_3$):δ 7.84 (d, 1H, J = 7.6 Hz), 7.80 (d, 1H, J = 8.4 Hz), 7.69 (d, 2H, J = 7.6 Hz), 7.60-7.03 (m, 29H), 6.40 (d, 1H, J = 7.8 Hz), 5.93 (d, 1H, J = 7.8 Hz), 3.38 (s, 3H), 3.25-2.99 (m, 3H), 2.83 (br, 2H). ^{13}C NMR (68.0 MHz, $CDCl_3$): δ 158.3, 152.8, 152.8, 152.5, 141.0, 140.9, 140.6, 138.4, 138.2, 138.0, 137.8, 137.5, 137.5, 136.9, 136.7, 134.9, 134.8, 134.2, 134.0,133.7, 133.4, 131.2, 131.1, 131.0, 129.8, 129.7, 129.5, 128.9, 128.7, 128.6, 128.4, 128.3, 128.0, 127.5, 126.9, 126.8, 126.5, 120.9, 119.7, 118.3, 105.7, 77.5, 62.0, 55.3, 44.9, 43.7. ^{31}P NMR (81.0 MHz, $CDCl_3$): δ –12.38. HRMS calculated for $C_{53}H_{45}N_3O_2P$ $(M+H)^+$: 786.3244; found: 786.3241. $[\alpha]_D^{24}$ = 182.0 (c = 1.0, $CHCl_3$).

N-Ethyl-4-methyl-N-(3-phenyl-1-p-tolylprop-2-ynyl)benzamide (6.6a)

Prepared according to the typical procedure for catalytic synthesis of alkynylated imines. Chromatography solvent 85/15 hexanes / ethyl acetate. ^{1}H NMR (300 MHz, 60°C, $CDCl_3$):δ 7.60-7.43 (m, 6H), 7.40-7.31 (m, 3H), 7.28-6.16 (m, 4H), 6.15 (br, 1H), 3.61 (br, 1H), 3.33 (m, 1H), 2.40 (s, 3H), 2.38 (s, 3H), 1.18 (br, 3H). ^{13}C NMR (75.0 MHz, 60°C, $CDCl_3$): δ 171.5, 139.6, 137.9, 134.7, 133.9, 131.7, 129.3, 129.2, 128.6, 128.4, 127.4, 126.7, 122.7, 86.8, 86.2, 39.8, 21.3, 21.0, 14.7. HRMS calculated for $C_{26}H_{25}NONa$ $(M+Na)^+$: 390.1828; found: 390.1830.

N-(4-Methoxyphenyl)-N-(3-phenyl-1-p-tolylprop-2-ynyl)benzamide (6.6b)

Prepared according to the typical procedure for catalytic synthesis of alkynylated imines. Chromatography solvent 80/20 hexanes / ethyl acetate. ^{1}H NMR (300 MHz, 60°C, $CDCl_3$):δ 7.51-7.38 (m, 5H), 7.37-7.27 (m, 4H), 7.19-7.06 (m, 5H), 6.78 (m, 2H), 6.60 (d, 2H, J = 9.4 Hz), 3.64 (s, 3H), 2.37 (s, 3H). ^{13}C NMR (75.0 MHz, 60°C, $CDCl_3$): δ 170.6, 159.1, 138.0, 136.7, 135.3, 132.8, 131.9, 131.8, 129.4, 129.2, 128.8, 128.7, 128.5, 128.5, 127.8, 123.2, 113.7, 87.7, 86.9, 55.4, 52.1, 21.2. HRMS calculated for $C_{30}H_{25}NO_2Na$ $(M+Na)^+$: 454.1778; found: 454.1779.

(1-(Phenylethynyl)-3,4-dihydroisoquinolin-2(1H)-yl)(p-tolyl)methanone (6.6c)

Prepared according to the typical procedure for catalytic synthesis of alkynylated imines. Chromatography solvent 85/15 hexanes / ethyl acetate. ^{1}H NMR (300 MHz, 60°C, $CDCl_3$):δ 7.56-7.47 (m, 2H), 7.45-7.39 (m, 2H), 7.35-7.16 (m, 9H), 6.35 (br, 1H), 4.43 (br, 1H), 3.71 (br, 1H), 3.08 (br, 1H), 2.84 (br, 1H), 2.42 (s, 3H). ^{13}C NMR (75.0 MHz, 60°C, $CDCl_3$): δ 170.4, 140.2, 134.3, 133.6, 132.9, 131.8, 129.2, 129.1,128.4, 128.2, 127.5, 127.2, 126.7, 122.7, 88.4, 84.1, 47.8, 39.8, 28.5, 21.3. HRMS calculated for $C_{25}H_{21}NONa$ $(M+Na)^+$: 374.1515; found: 374.1517.

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CHAPTER SEVEN

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

This chapter gives a brief description of the results and conclusions presented in this thesis, and discloses contributions to original knowledge. Suggestions for future work are also provided.

7.0 Conclusions and Contributions to Knowledge

This thesis has demonstrated that copper complexes are viable catalysts for mediating the cross-coupling of imines with a range of transmetalating agents, as well as with terminal alkynes. These processes provide a mild, simple, and functional group compatible alternative to the use of strong organometallic nucleophiles in carbon-carbon bond formation with imines, as a route to construct α-substituted amine and amide derivatives. Previous research in this laboratory has shown that palladium (0) catalysts can be used in a Stille-type cross-coupling reaction between imines, acid chlorides, and organotin reagents. The initial studies described in this thesis demonstrate that the same reaction is possible using inexpensive copper (I) salts (Chapter 2). Through the use of these catalysts,

a wider range of organostannanes are compatible in this process than in the palladium-catalyzed chemistry.

Copper (I) salts have also allowed other reagents to be incorporated in three component reactions with imines. These include terminal alkynes (Chapter 3) and organo-indium reagents (Chapter 5). The copper-catalyzed coupling of imines, acid chlorides, and terminal alkynes provides a rapid and mild route to assemble propargylamides. This transformation can be performed with pyridines as imine analogues, as a route to prepare cyclic propargylamide derivatives. Alternatively, the use of organo-indium reagents provides an atom-economical alternative route to the organostannane chemistry for the generation of α-substituted amides. In addition to providing a milder, more functional group compatible method to access such products, these mild organometallic reagents have also been shown to add with 1,4-selectivity to α,β-unsaturated imines, resulting in an efficient synthesis of enamides.

As well as amide-based molecules, copper-catalyzed addition to imines has been shown to be applicable toward the synthesis of substituted heterocycles. As shown in Chapter 4, secondary propargylamides can be formed using *N*-silyl substituted imines, acid chlorides, and terminal alkynes under copper catalysis. By exploiting the reactivity of these products, this strategy can be used to design a one pot route to tri-substituted oxazoles. Overall, this provides a straightforward multicomponent route to construct these heterocycles directly from three readily available building blocks. An alternative route to convert propargylamides into heterocycles is described in Appendix A, where the multicomponent synthesis of

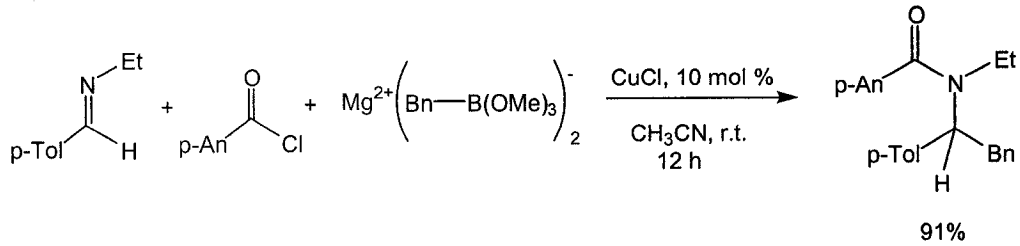
tertiary propargylamides is followed by a Pauson-Khand reaction, toward the generation of bicyclic pyrrolidines.

Finally, an important addition to the field of metal-catalyzed asymmetric synthesis is presented in Chapter 6, involving the alkynylation of nitrogen-containing heterocycles. The reactions described in the earlier chapters of this thesis all provide catalyic routes to generate chiral α-substituted amides. This suggests the potential of introducing asymmetry into these processes with chiral ligands. Over the course of our experiments we discovered that the use of new versions of chiral PINAP ligands can allow the alkynylation of quinoline, isoquinoline, and pyridine in up to 84% enantioselectivity. This work provides the first catalytic, enantioselective synthesis of cyclic propargylamides, and does so directly from the parent aromatic heterocycle.

7.1 Suggestions for Future Work

These studies have demonstrated that imines can be employed in copper-catalyzed cross-coupling reactions with a range of transmetalating agents. As such, future work could focus on the use of other organometallic reagents in this coupling to form α-substituted amides. For example, organoboranes are among the most common organometallic compounds employed in standard palladium-catalyzed cross-coupling reactions. This is due primarily to their ready availability, air- and moisture-stability, and low cost. This suggests that the

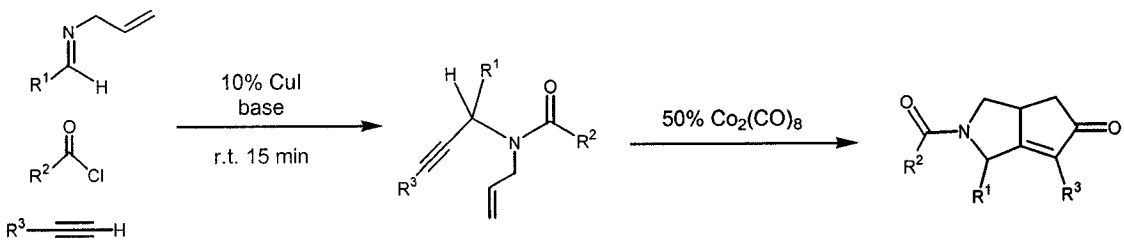
incorporation of organoboron derivatives into cross-coupling with imines would be a useful process. In fact, preliminary studies have shown that trimethylboronates will react with imines and acid chlorides in the presence of a copper catalyst, providing another route to α-substituted amides and *N*-protected amines (Scheme 7.1).



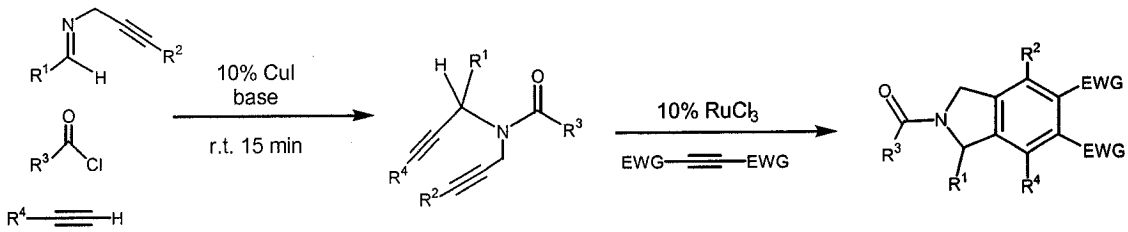
Scheme 7.1 Copper-catalyzed cross-coupling of imines, acid chlorides, and trimethylboronates.

Also, further transformations to increase the molecular complexity of the products formed could be carried out in these reactions. In particular, the tertiary propargylamides generated in Chapter 3 can be used to form heterocyclic products. One such transformation (Scheme 7.2) will be the focus of Appendix A, however there exist other possibilities for the subsequent reactions of these propargylamide products. For example, combining the copper-catalyzed coupling of imines, acid chlorides, and terminal alkynes with alkyne trimerization (Scheme 7.3) would provide a simple method of generating polysubstituted isoindolines. Also, combining the imine alkynylation reaction with a palladium-catalyzed cross-coupling could generate substituted indoles (Scheme 7.4). Each of these

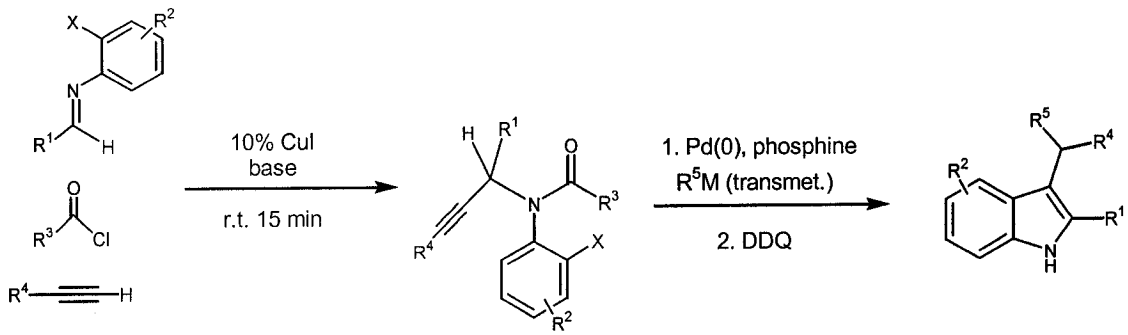
approaches could provide a route to prepare useful multicyclic heterocycles in two steps, directly from readily available starting materials, e.g., imines, acid chlorides, alkynes, alkenes, carbon monoxide, etc.



Scheme 7.2 Imine alkynylation / Pauson-Khand reaction.

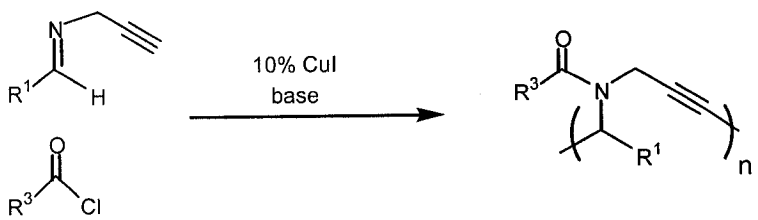


Scheme 7.3 Potential imine alkynylation / cyclotrimerization reaction.



Scheme 7.4 Potential imine alkynylation / cross-coupling reaction.

Alternatively, this chemistry could be applied to polymer synthesis, as a route to construct new polyamide-based materials. For example, the use of alkyne-substituted imines such as those shown in Scheme 7.5 would provide a one step route to construct alkyne-containing polyamides. This class of products could serve as interesting chiral materials, which could be easily functionalized at various positions of each monomer.



Scheme 7.5 Potential *N*-acyl iminium salt polymerization.

A final important area of study with this chemistry would be to further the initial efforts made to introduce enantioselectivity into these processes. Considering the ease with which these reactions can be performed, their coupling with chiral control could provide a useful route to form enantiopure α-substituted amides and *N*-protected amines. If the enantioselective alkynylation described in Chapter 6 gives any indication of the viability of these processes, it should be possible to perform many of these new catalytic reactions with enantioselectivity.

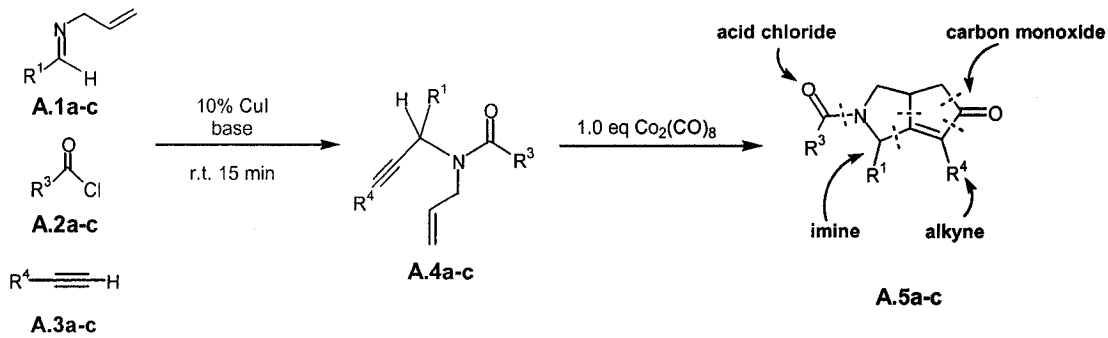
APPENDIX A

Further Studies on the Copper-Catalyzed Synthesis of Propargylamides: Application to the Synthesis of Bicyclic Heterocycles

A.0 Introduction

We have shown in Chapter 3 of this thesis that the copper-catalyzed coupling of imines, acid chlorides and alkynes can generate tertiary propargylamides.[1] Considering the reactivity of these alkyne-containing products, it could be possible to combine this synthesis with subsequent reactions as a route to access bicyclic heterocycles directly from basic building blocks, as theorized in Chapter 7. For example, employing an *N*-allyl-substituted imine in this copper-catalyzed coupling would result in the generation of an *N*-allyl-propargylamide. This class of alkene/alkyne-containing products is well suited to undergo a Pauson-Khand reaction, to form bicyclic pyrrolidines directly from imines, acid chlorides, alkynes, and carbon monoxide (CO) (Scheme A.1). Indeed, a similar approach has recently been demonstrated by Knochel *et. al.*, where the copper-catalyzed coupling of aldehydes, amines, and alkynes, followed by a subsequent Pauson-Khand reaction, forms a bicyclic pyrrolidine. Unlike this protocol, where the coupling of aldehyde, amine, and alkyne requires 1-6 days, our copper-

catalyzed synthesis of propargylamides can be done in minutes at room temperature. Therefore, the combination of this coupling with a Pauson-Khand reaction could provide a rapid, one-pot route to directly generate a new class of bicyclic *N*-protected pyrrolidines, that can be easily varied at multiple positions around the ring system.



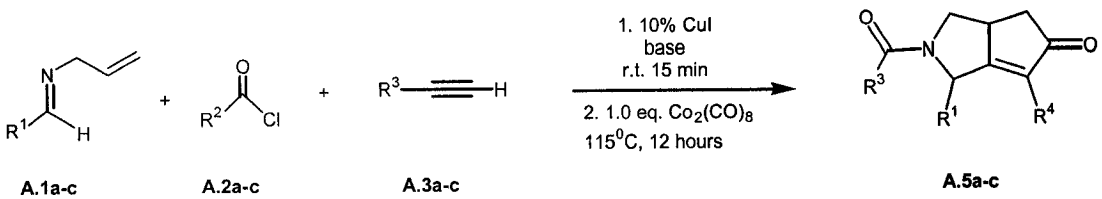
Scheme A.1 Multicomponent synthesis of pyrrolidines using imines, acid chlorides, alkynes, and carbon monoxide.

A.1 Results and Discussion

Our preliminary examination of this reaction involved the use of several *N*-allyl imines **A.1a-c** in our three component coupling with acid chlorides and alkynes. Subjecting the *in situ*-generated *N*-allyl-propargylamides to a subsequent Pauson-Khand reaction with one equivalent of $Co_2(CO)_8$ (after a change of solvent and decanting of the Et_3NHCl) resulted in the generation of the bicyclic pyrrolidines **A.5a-c** in high yield. As can be seen in Table A.1, both alkyl and aryl

acid chlorides are compatible with this reaction, as well as aromatic, aliphatic, and silylated alkynes.

Table A.1 Copper-Catalyzed Cross-Coupling with Imines.



A.1a-c A.2a-c A.3a-c A.5a-c

Cmpd. #	R^1	R^2	R^3	Yield (%)[a]
A.5a	Ph	Ph	Ph	**82**
A.5b	*p*-$CH_3C_6H_4$	*p*-$CH_3OC_6H_4$	^{n}Bu	**75**
A.5c	*p*-$CH_3OC_6H_4$	^{i}Pr	TMS	**73**

[a]0.30 mmol imine, 0.36 mmol acid chloride, 0.33 mmol alkyne, with the given catalysts in CH_3CN for step 1, then toluene for step 2.

A.2 Conclusions

In conclusion, we have developed a convenient method to convert imines, acid chlorides, alkynes, and carbon monoxide into bicyclic heterocycles. Considering the ease of diversification of many of these reagents, this protocol could prove of utility in generating diverse families of bicyclic pyrrolidines.

A.3 Experimental

Unless otherwise noted, all manipulations were performed under an inert atmosphere in a Vacuum Atmospheres 553-2 dry box or by using standard Schlenk or vacuum line techniques. Unless otherwise noted, all reagents were purchased from Aldrich® or Strem Chemical® and used as received. Toluene and acetonitrile 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 molecular sieves. Imines were prepared via a literature procedure.[4]

^{1}H and ^{13}C were recorded on Varian Mercury 300 MHz and Unity 500 MHz spectrometers. Mass spectra (all by ESI method) were obtained from the McGill University Mass Spectral Facility.

General Procedure for Catalytic Synthesis of Bicyclic Pyrrolidin-enones A.5a-c

Imine (0.30 mmol) and acid chloride (0.36 mmol) were dissolved in 2 mL of CH_3CN. Copper (I) iodide (5.7 mg, 0.03 mmol) in 2 mL of CH_3CN was added to this solution. Alkyne (0.33 mmol) in 1 mL of CH_3CN was slowly added. Et_3N (45.6 mg, 0.45 mmol) in 1 mL of CH_3CN was then added over the course of 3 minutes. After 15 minutes, the solvent was removed under reduced pressure, 10 mL of diethyl ether was added, and Et_3NHCl was removed by decanting this solution into a gas tight vessel. The diethyl ether was removed under reduced

pressure, the product was dissolved in 5 mL of toluene, and $Co_2(CO)_8$ (103.2 mg, 0.31 mmol) was added with stirring. This reaction vessel was then immersed in a 115°C oil bath and refluxed overnight. The mixture was concentrated in vacuo, and the product isolated by column chromatography using ethyl acetate / hexanes as eluent (ratio typically 1:1).

2-benzoyl-1,6-diphenyl-2,3,3a,4-tetrahydrocyclopenta[c]pyrrol-5(1H)-one (A.5a)

Prepared as per the general method for the catalytic synthesis of bicyclic pyrrolidin-enones. Chromatography conditions of 50/50 hexanes / ethyl acetate. Yield: 82%. ^{1}H-NMR (300 MHz, $CDCl_3$, 55°C): δ 7.70-6.98 (m, 15H), 6.17 (br, 1H), 4.39 (br, 1H), 3.72 (br quad, 1H), 3.20 (br, 1H), 2.87 (dd, 1H, J = 11.2 Hz, 6.6 Hz), 2.39 (d, 1H, 18.6 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$, 55°C): δ 205.8, 173.4, 171.2, 139.7, 136.9, 136.6, 130.6, 130.1, 129.1, 129.1, 129.0, 128.6, 128.5, 128.3, 127.3, 126.9, 61.7, 53.1, 41.5, 40.1. HRMS for $C_{26}H_{21}NO_2Na$ $(M+Na)^+$, calculated: 402.1465, found: 402.1462.

6-butyl-2-(4-methoxybenzoyl)-1-p-tolyl-2,3,3a,4-tetrahydrocyclopenta [c]pyrrol-5(1H)-one (A.5b)

Prepared as per the general method for the catalytic synthesis of bicyclic pyrrolidin-enones. Chromatography conditions of 50/50 hexanes / ethyl acetate.

Yield: 75%. ^{1}H-NMR (300 MHz, $CDCl_3$, 55°C): δ 7.36 (br, 2H), 7.22-7.05 (m, 4H), 6.80 (d, 2H, J = 11.2 Hz), 5.84 (br, 1H), 4.29 (t, 1H, J = 9.2 Hz), 3.78 (s, 3H), 3.41 (br, 1H), 3.22 (br, 1H), 2.63 (dd, 1H, J = 11.2 Hz, 6.6 Hz), 2.36-2.09 (m, 6H), 1.51-1.21 (m, 4H), 0.84 (t, 3H, J = 6.6 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$, 55°C): δ 207.8, 173.1, 171.0, 161.3, 137.9, 136.9, 136.6, 129.8, 129.2, 129.0, 126.1, 113.9, 61.1, 55.5, 53.4, 40.4, 39.0, 30.0, 24.1, 22.9, 21.1, 13.8. HRMS for $C_{26}H_{29}NO_3Na$ $(M+Na)^+$, calculated: 426.2040, found: 426.2040.

2-isobutyryl-1-(4-methoxyphenyl)-6-(trimethylsilyl)-2,3,3a,4-tetrahydrocyclopenta[c]pyrrol-5(1H)-one (A.5c)

Prepared as per the general method for the catalytic synthesis of bicyclic pyrrolidin-enones. Chromatography conditions of 50/50 hexanes / ethyl acetate. Yield: 73%. ^{1}H-NMR (300 MHz, $CDCl_3$, 55°C): two rotamers δ 7.22 (br, 2H), 6.94-6.73 (m, 2H), 5.93 (s, 0.6H), 5.72 (s, 0.4H), 4.18 (br, 1H), 3.76 (s, 3H), 3.56 (br, 0.6H), 3.34 (br, 0.4H), 3.24-3.07 (m, 1H), 2.73-2.36 (m, 2H), 2.22-2.08 (brd, 1H), 1.12 (br, 4.7H), 0.85 (br, 1.3H), 0.36-0.14 (brd, 9H). ^{13}C-NMR (75 MHz, $CDCl_3$, 55°C): two rotomers δ 211.9, 186.6, 176.9, 159.5, 137.3, 135.9, 131.4, 128.3, 127.2, 114.4, 60.1, 55.4, 51.5, 50.5, 44.0, 41.7, 40.4, 32.9, 32.4, 19.7, 18.6, -0.9. HRMS for $C_{21}H_{29}NO_3SiNa$ $(M+Na)^+$, calculated: 394.1809, found: 394.1809.

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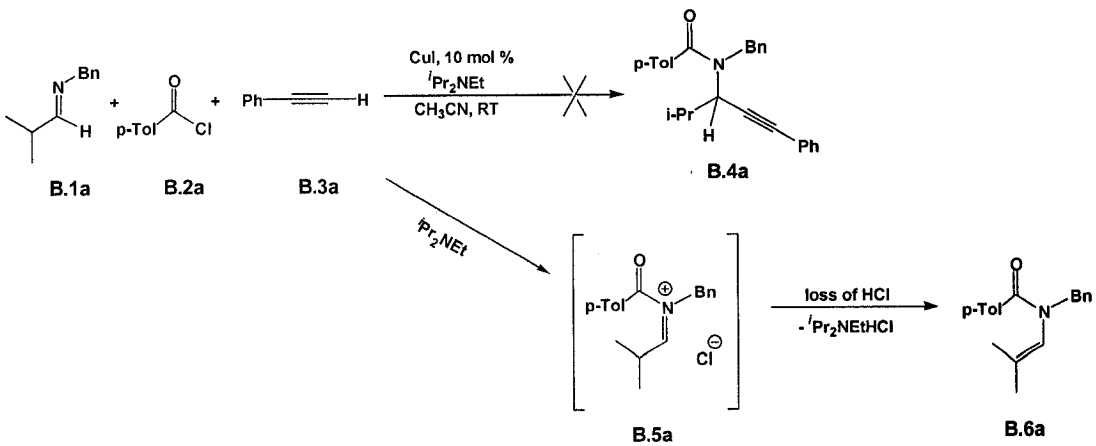
APPENDIX B

Enolizable N-Acyl Iminiums In Catalysis: Stability and Reactivity

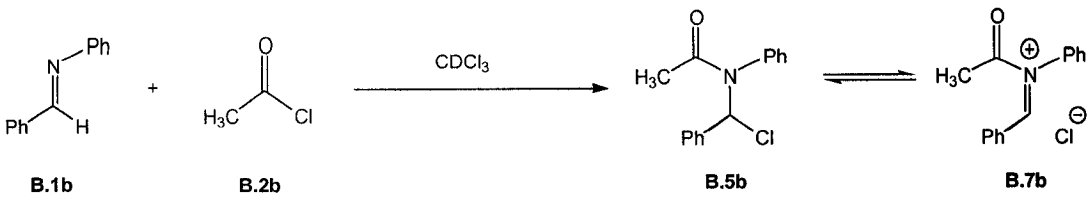
B.0 Introduction

In Chapter 3 of this thesis, the copper-catalyzed coupling of imines, acid chlorides and alkynes was shown to form tertiary propargylamides.[1] However, under these reaction conditions, imines derived from enolizable aldehydes were not viable substrates due to a competitive HCl elimination from the *N*-acyl iminium intermediate to generate enamides (Scheme B.1).[2] In order to alleviate this problem, we sought a better understanding of the stability of these enolizable *N*-acyl iminium salt intermediates, and conditions under which alkynylation would be possible.



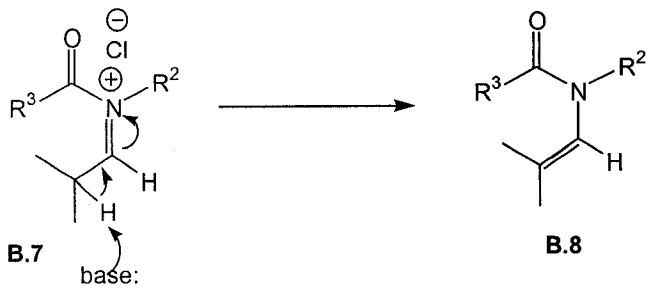
Scheme B.1 Reaction of enolizable imine with acid chloride to generate enamide.

It has been established that the reaction of non-enolizable imines with acid chlorides leads to the formation of α-chloroamides, in equilibrium with an *N*-acyl iminium chloride salt.[3] For example, the addition of acetyl chloride to benzalaniline has been reported to generate α-chloroamide **B.5b** in $CDCl_3$, as evidenced by an upfield shift in the ^1H NMR resonance of the imine CH proton (Scheme B.2).[3a] In general, the proportion of the ionic form (e.g., *N*-acyl iminium chloride) and the covalent form (e.g., α-chloroamide) may vary significantly depending on the counterion.[4] This has been shown by Yamamoto, where generation of similar iminium ions with trifluoromethanesulfonate counterions results in ^1H NMR signals of the imine CH protons downfield relative to their imine precursors. This observation is consistent with the formation of ionized *N*-acyl iminium intermediates.



Scheme B.2 Generation of α-chloroamide from acetyl chloride and benzalaniline.

In contrast to these studies, the structure and stability of α-chloroamides derived from an enolizable imine and an acid chloride has, to our knowledge, not been reported. This is likely due to the aforementioned instability of these substrates, which will undergo rapid deprotonation to form enamides at ambient temperature (Scheme B.3). Alternately, enolizable α-alkoxy amides can be formed and are stable even upon heating.[2b] Their decomposition can, however, be accelerated in the presence of acidic proton sources. For example, Speckamp has shown that rate of ROH elimination from cyclic α-alkoxy amides in the presence of *p*-toluenesulfonic acid, to form the corresponding enamides, is dependent on solvent polarity (i.e., shown to be more rapid in higher concentrations of *p*-toluenesulfonic acid).[2a] This demonstrates that generation of the ionized form of the iminium salt may be rate-determining in terms of its decomposition.

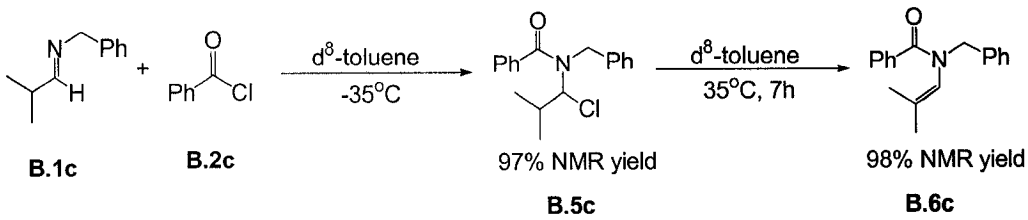


Scheme B.3 Enamide formation from enolizable *N*-acyl iminium salts.

We describe below the generation and characterization of intermediates of the form **B.5** upon reaction of an enolizable imine **B.1** and an acid chloride **B.2**. By operating at low temperature in non-polar solvents, these compounds are formed almost quantitatively and do not readily decompose, consistent with the need to form intermediate **B.7** for deprotonation.

B.1 Results and Discussion

Our initial experiments examined the generation of the α-chloroamide **B.5c** from benzoyl chloride and the imine (*i*-Pr)C(H)=NBn (Scheme B.4). Mixing these reagents at -80°C in d^8-toluene and monitoring the reaction by ^{1}H NMR spectroscopy shows that the acid chloride and imine do not interact at this temperature. However, upon warming to -35°C, α-chloroamide **B.5c** is generated in 97% NMR yield (Figures B.1 and B.2).



B.1c B.2c 97% NMR yield B.5c 98% NMR yield B.6c

Scheme B.4 Generation of α-chloroamide in d^8-toluene.

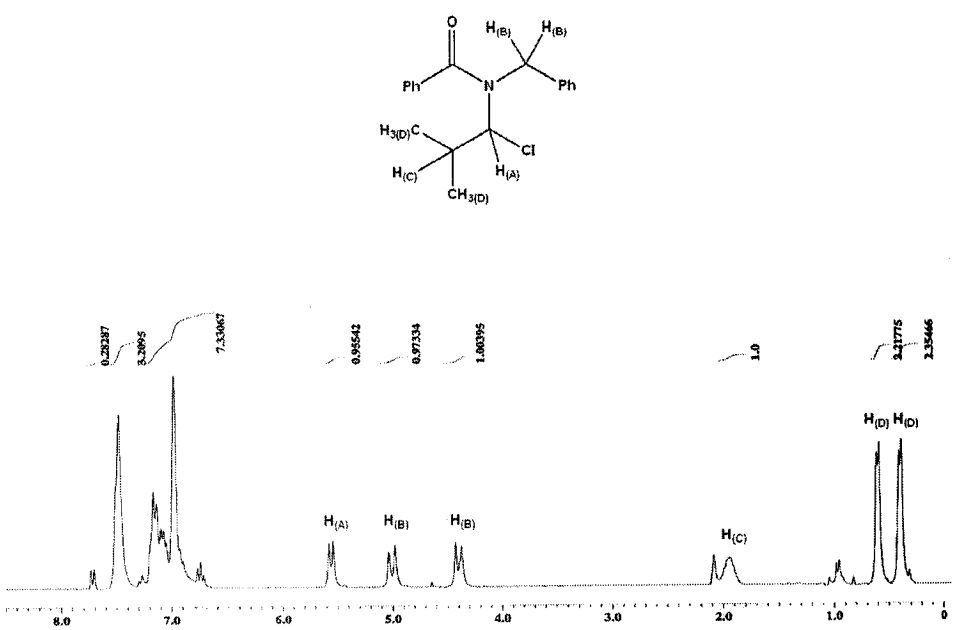


Figure B.1 ^{1}H NMR of enolizable α-chloroamide in d^8-toluene.

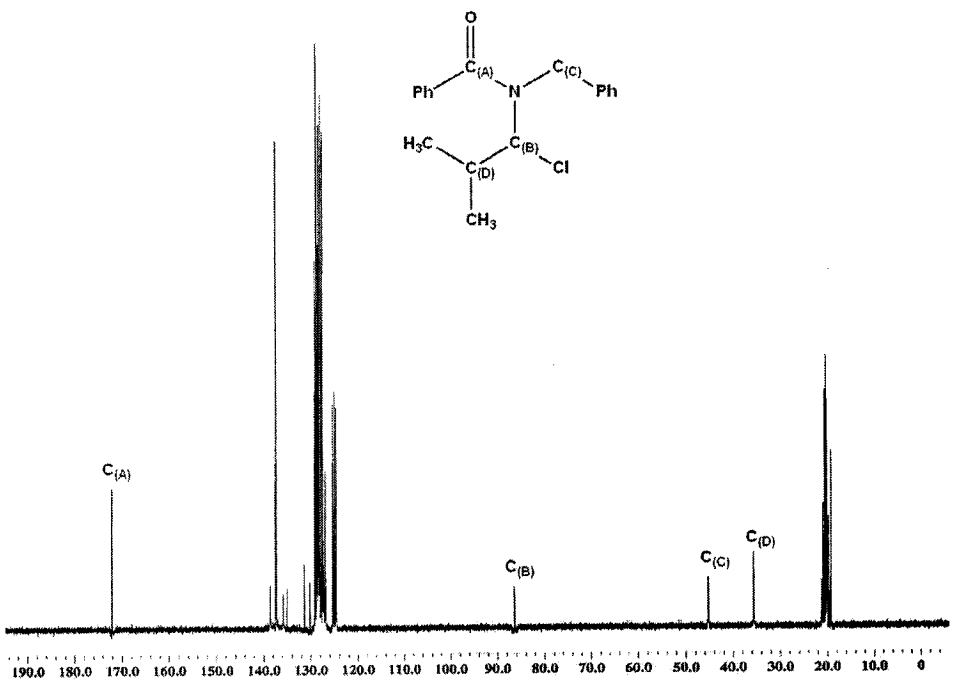


Figure B.2 ^{13}C NMR of enolizable α-chloroamide in d^8-toluene.

α-Chloroamide **B.5c** has been characterized *in situ* by ^{1}H and ^{13}C NMR spectroscopy. Perhaps most notably, the former imine α-hydrogen in **B.1c** has shifted upfield from 7.42 ppm to 5.56 (H_A) ppm in **B.5c**, suggesting reduction of this α-carbon to an α-chloroamide structure. Similarly, the benzylic CH_2 hydrogens (H_B) are now diastereotopic (doublet of doublets at 5.02 and 4.41 ppm), demonstrating the formation of a chiral center in the molecule. ^{13}C NMR spectroscopy is consistent with this structural assignment, and exhibits a significant upfield shift in the former imine α-carbon (C_B), to 86.4 ppm. Together, this data strongly suggests that **B.5c** exists as the covalent α-chloroamide structure, rather than the achiral, ionic *N*-acyl iminium salt.

In d^8-toluene, **B.5c** is quite stable, and does not decompose, even at room temperature for several hours. Upon warming to 35°C, **B.5c** does undergo a slow deprotonation to form the enamide **B.6c** in 98% NMR yield. The rate of conversion of **B.5c** to enamide **B.6c** has been monitored at 35°C, and found to follow 1st order kinetics, with a $t_{½}$ = 40.7 min (k_{obs} = 0.017035 min^{-1}) (Figure B.3).

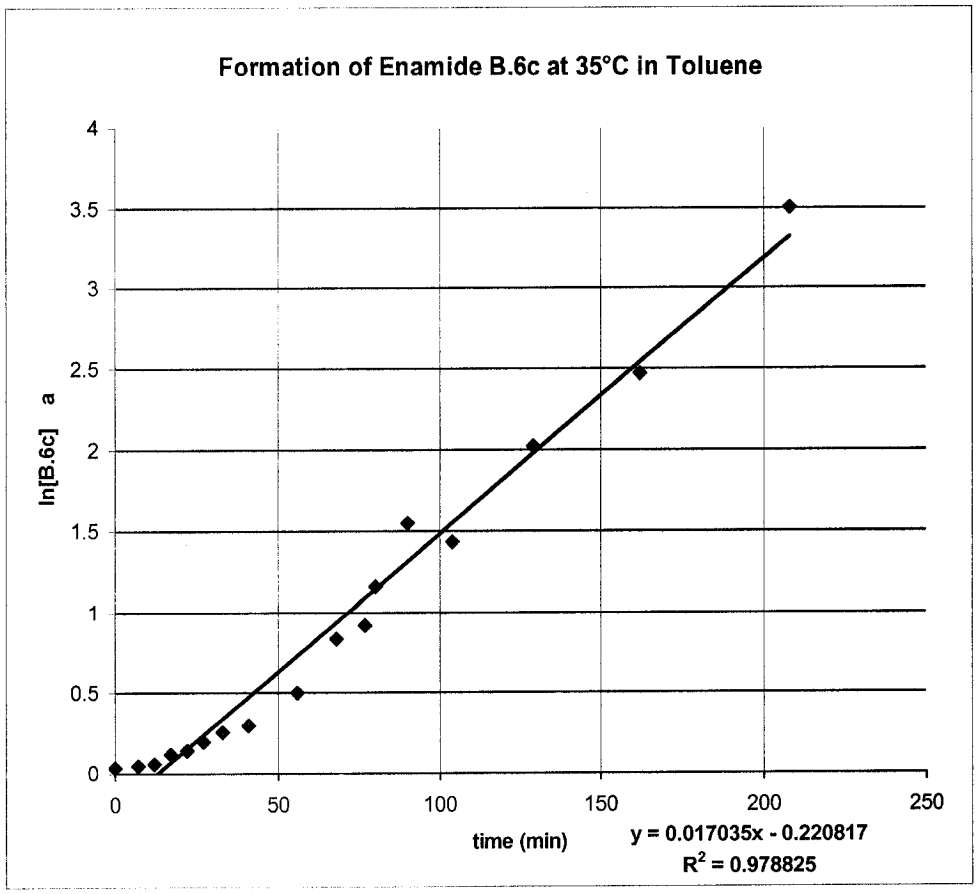


Figure B.3 Rate of enamide **B.6c** formation from α-chloroamide decomposition.

In contrast to the results in toluene, mixing the enolizable imine (*i*-Pr)C(H)=NBn with benzoyl chloride in the more polar d^3-acetonitrile solvent at -40°C results in the generation of the α-chloroamide **B.5c** in approximately 70%

NMR yield along with significant other side products (Figure B.4). This species shows similar ^{1}H NMR signals to those observed for **B.5c** in toluene; a doublet at 5.53 ppm presumably from the imine α-hydrogen (H_A), and a pair of doublets at 4.82 ppm and 4.63 ppm likely due to the diastereotopic benzyl CH_2 (H_B); suggesting a similar α-chloroamide structure.

As implied by the less clean formation of **B.5c**, this product is much less stable in CD_3CN, and undergoes decomposition to enamide **B.6c** with $t_{½}$ = 90 min at -40°C.

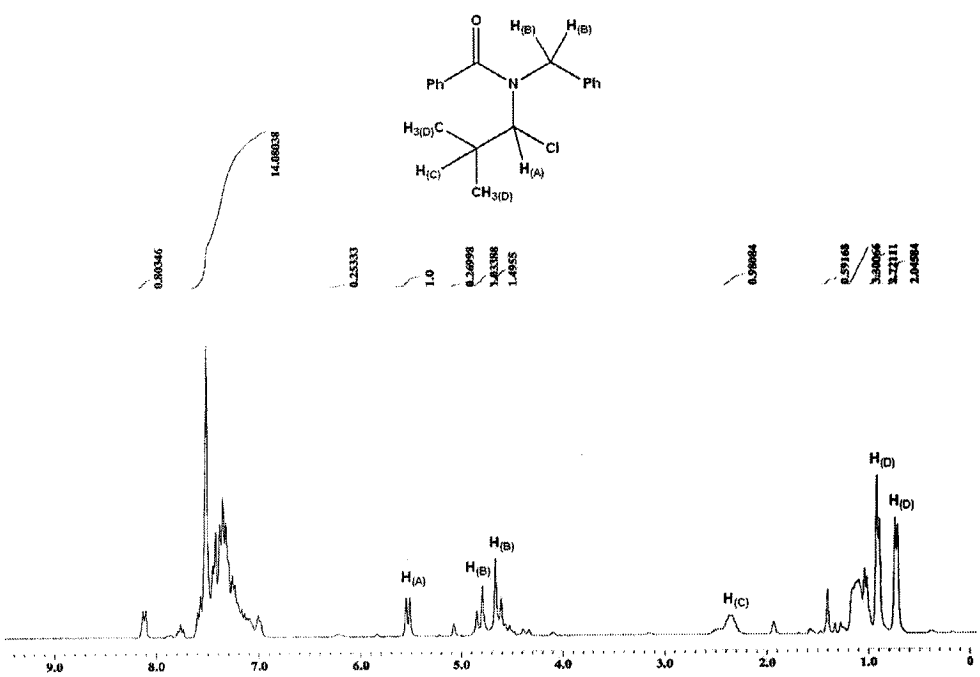
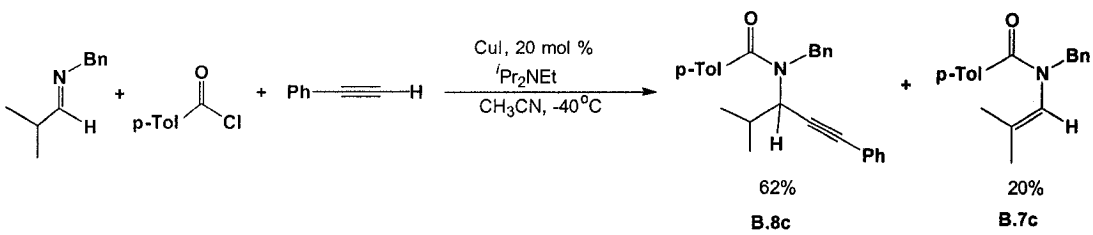


Figure B.4 ^{1}H NMR of enolizable α-chloroamide **B.5c** in CD_3CN.

The above studies demonstrate that, under the correct conditions, the α-chloroamide **B.5c** can be generated in high (toluene) to moderate (acetonitrile)

yield. The more rapid formation of the enamide **B.6c** in CD_3CN suggests that the proportion of the ionized form of **B.5c,** an *N*-acyl iminium salt, is directly related to its rate of decomposition. Despite this fact, the generation of **B.5c** in acetonitrile at -40°C is significant for catalysis. The copper-catalyzed coupling of imines, acid chlorides, and alkynes does not proceed in toluene, likely as a result of the insolubility of the catalyst CuI.

With this result in hand, we have further examined the copper-catalyzed coupling of the enolizable imine (*i*-Pr)C(H)=NBn at -40°C with toluoyl chloride and phenylacetylene. In contrast to the results at ambient temperature, this reaction proceeds smoothly to form the alkynylated product **B.4d** in 62 % yield, along with the enamide **B.6d** in 20 % yield (Scheme B.5).



Scheme B.5 Synthesis of propargylamide derived from enolizable imine.

B.2 Conclusions

In conclusion, through a better understanding of the stability, structure, and decomposition of enolizable *N*-acyl iminium salts, and their isomeric α-

chloroamides, we have been able to perform catalytic alkynylation of enolizable imines. The approximate rates of enamide formation from α-chloroamide decomposition have been measured, to provide a useful measure of their reactivity and stability.

B.3 Experimental

Unless otherwise noted, all manipulations were performed under an inert atmosphere in a Vacuum Atmospheres 553-2 dry box or by using standard Schlenk or vacuum line techniques. Unless otherwise noted, all reagents were purchased from Aldrich® and used as received. Toluene and acetonitrile 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 molecular sieves. Imines were prepared via a literature procedure.[5]

^{1}H and ^{13}C were recorded on Varian Mercury 300 MHz and JEOL 270 MHz spectrometers. Mass spectra (all ESI method) were obtained from the McGill University Mass Spectral Facility.

Generation of α-Chloroamide B.5c and Formation of Enamide B.6c

Benzoyl chloride (28.1 mg, 0.20 mmol) was dissolved in 0.6 mL of deuterated solvent and transferred into a screw cap NMR tube equipped with a

septum. This solution was cooled to -40°C (CD_3CN) or -80°C (d^8-toluene) and the imine (*i*-Pr)C(H)=NBn (31.9 mg, 0.20 mmol) was added through the septum. The tube was inverted for mixing of the reagents, and placed into the NMR probe at -40°C (CD_3CN) or -80°C (d^8-toluene). The solution was then monitored by ^1H and ^{13}C NMR spectroscopy.

Procedure for Catalytic Synthesis of Propargylamide B.4d

Toluoyl chloride (77.3 mg, 0.50 mmol) was dissolved in CH_3CN (3 mL). This was added to a solution of CuI (19.1 mg, 0.10 mmol) and phenylacetylene (51.1 mg, 0.50 mmol) in 2 mL of acetonitrile. This solution was cooled to -40°C in a Schlenk flask under nitrogen, with stirring. *N*-(2-methylpropylidene)(phenyl)methanamine (80.7 mg, 0.50 mmol) in 1 ml of CH_3CN was then added via syringe. EtN^iPr_2 (87.3 μL, 0.50 mmol) in 1 mL of acetonitrile was added to this mixture via syringe over 2 minutes. The reaction was stirred at -40°C for 2 hours, then allowed to warm to room temperature. The solvent was removed in vacuo, and the products were isolated by column chromatography using ethyl acetate / hexanes as eluent.

***N*-benzyl-4-methyl-*N*-(4-methyl-1-phenylpent-1-yn-3-yl)benzamide (B.4d)**

Procedure followed as above. Chromatography conditions of 85/15 hexanes / ethylacetate. Yield: 62%. ^1H-NMR (300 MHz, $CDCl_3$, 55°C): δ 7.54-6.83 (m, 14H), 4.86 (br, 1H), 4.71 (d, 1H, J = 19.2 Hz), 2.42 (s, 3H), 2.17 (m, 1H), 1.08

(br, 3H), 0.90 (br, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$, 55°C): δ 172.7, 139.7, 139.1, 134.2, 131.7, 129.2, 128.4, 128.3, 128.3, 128.0, 127.2, 127.0, 123.1, 87.3, 86.6, 57.8, 48.3, 33.2, 21.4, 20.0, 19.5. HRMS for $C_{27}H_{27}NONa$ $(M+Na)^+$, calculated: 404.1985, found: 404.1983.

<u>*N*-Benzyl-*N*-(1-chloro-2-methylpropyl)benzamide (B.5c) in d^8-toluene</u>

Procedure followed as above. Chromatography conditions none. Yield: 97% (by NMR). ^{1}H-NMR (270 MHz, d^8-toluene, -35°C): δ 7.49 (br, 3H), 7.39-6.69 (m, 7H), 5.56 (d, 1H, J = 10.4 Hz), 5.02 (d, 1H, J = 14.8 Hz), 4.41 (d, 1H, J = 14.6 Hz), 1.93 (br, 1H), 0.61 (d, 3H, J = 5.4 Hz), 0.40 (d, 3H, J = 5.7 Hz). ^{13}C-NMR (68.0 MHz, d^8-toluene, -35°C): δ 172.2, 138.5, 135.8, 134.9, 131.4, 130.2, 128.5, 127.3, 129.9, 86.4, 45.3, 35.7, 20.2, 19.3.

<u>*N*-Benzyl-*N*-(1-chloro-2-methylpropyl)benzamide (B.5c) in CD_3CN</u>

Procedure followed as above. Chromatography conditions none. Yield: 70% (by NMR). ^{1}H-NMR (270 MHz, CD_3CN, -40°C): δ 7.64-6.93 (m, 10H), 5.53 (d, 1H, J = 10.1 Hz), 4.82 (d, 1H, J = 15.6 Hz), 4.63 (d, 1H, J = 15.6 Hz), 2.34 (br, 1H), 0.90 (d, 3H, J = 6.4 Hz), 0.72 (d, 3H, J = 6.2 Hz).

***N*-benzyl-4-methyl-*N*-(2-methylprop-1-enyl)benzamide (B.6d)**

Procedure followed as above. Chromatography conditions 80/20 hexanes / ethyl acetate. Yield: 20%. ^{1}H-NMR (300 MHz, $CDCl_3$, 55°C): δ 7.45-7.23 (m, 7H), 7.08 (d, 2H, J = 7.8 Hz), 5.79 (s, 1H), 4.76 (s, 2H), 2.34 (s, 3H), 1.44 (s, 3H), 1.15 (s, 3H). ^{13}C-NMR (75 MHz, $CDCl_3$, 55°C): δ 170.9, 140.0, 137.6, 134.0, 133.9, 129.0, 128.6, 128.4, 128.4, 127.5, 124.8, 51.7, 21.9, 21.6, 17.8. HRMS for $C_{19}H_{21}NONa$ $(M+Na)^+$, calculated: 302.1515 found: 302.1517.

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1) Black, D. A.; Arndtsen, B. A. *Org. Lett.* **2004**, *6*, 1107.

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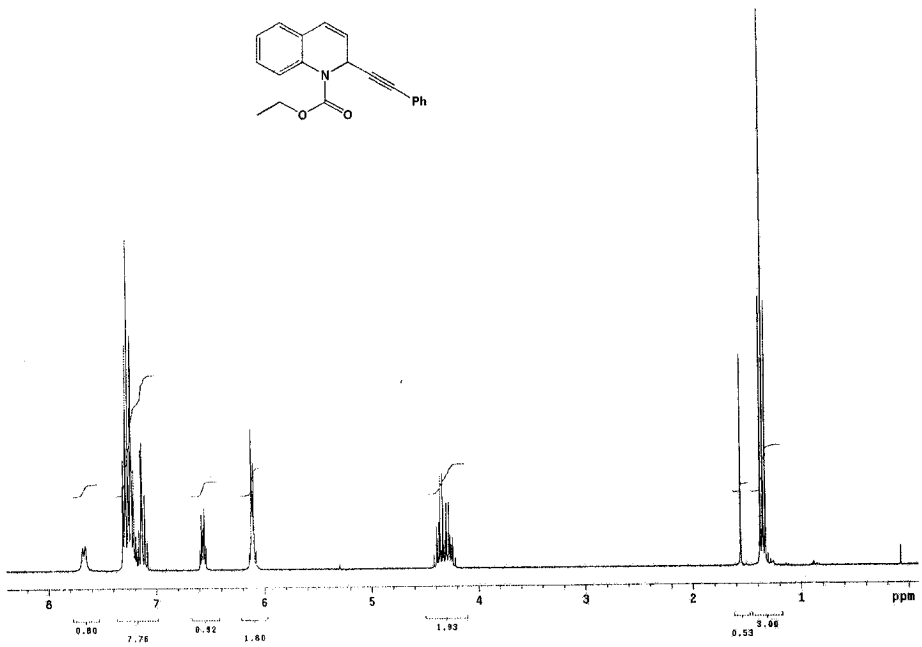
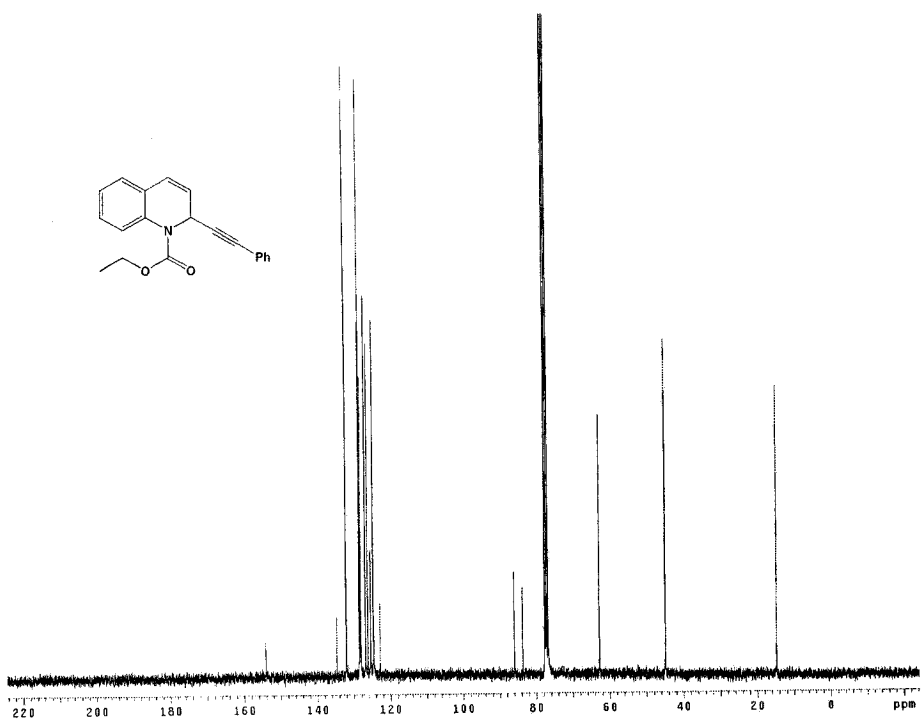
APPENDIX C

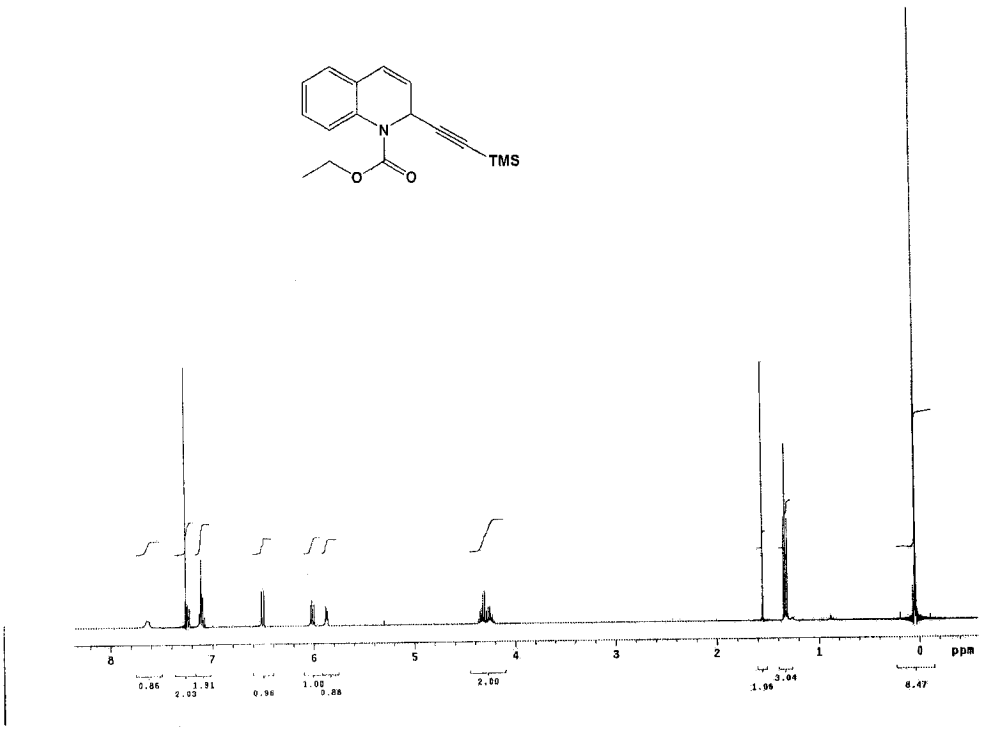
^{1}H and ^{13}C NMR data for Chapter 6

Compounds 6.4a-d, 6.5d, 6.5e, 6.6a-c



^{1}H and ^{13}C NMR; Compound **6.4a**





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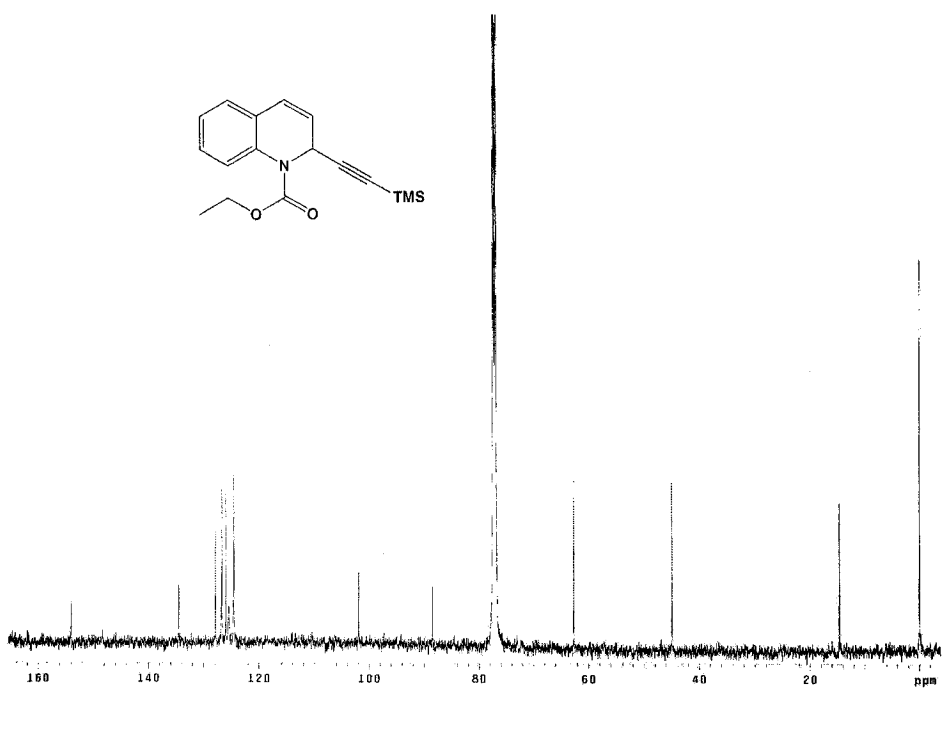
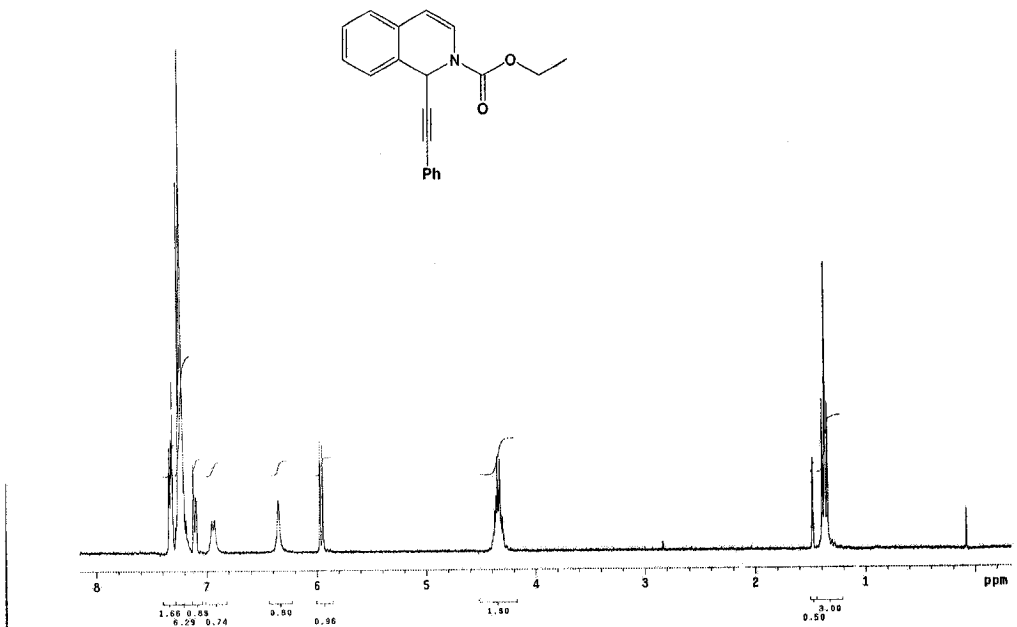
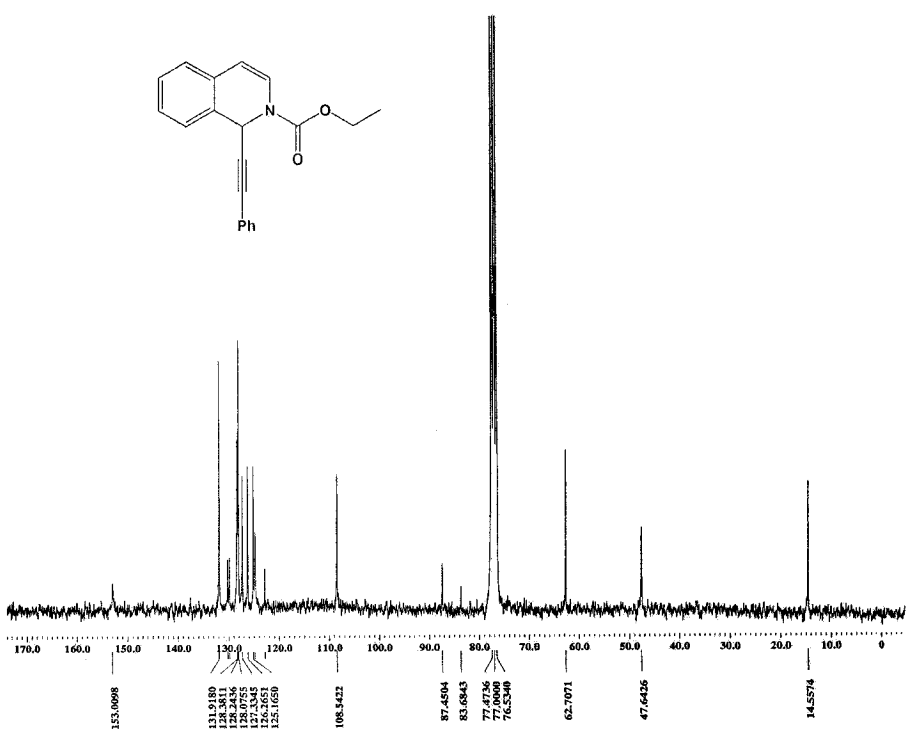
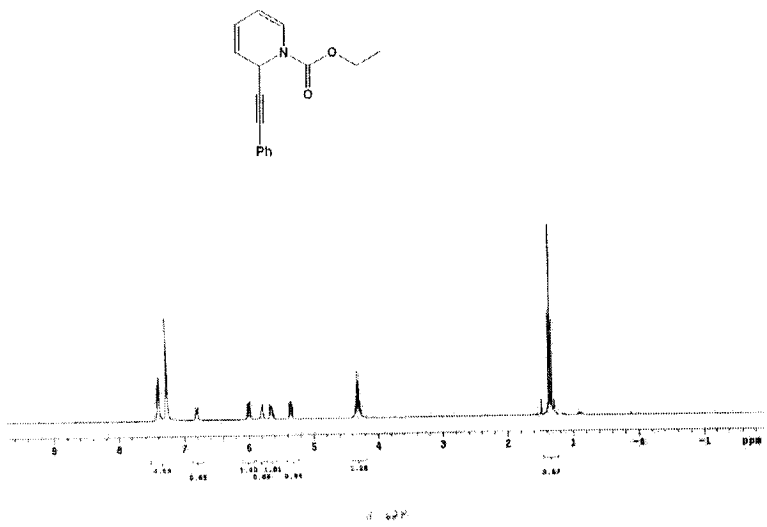


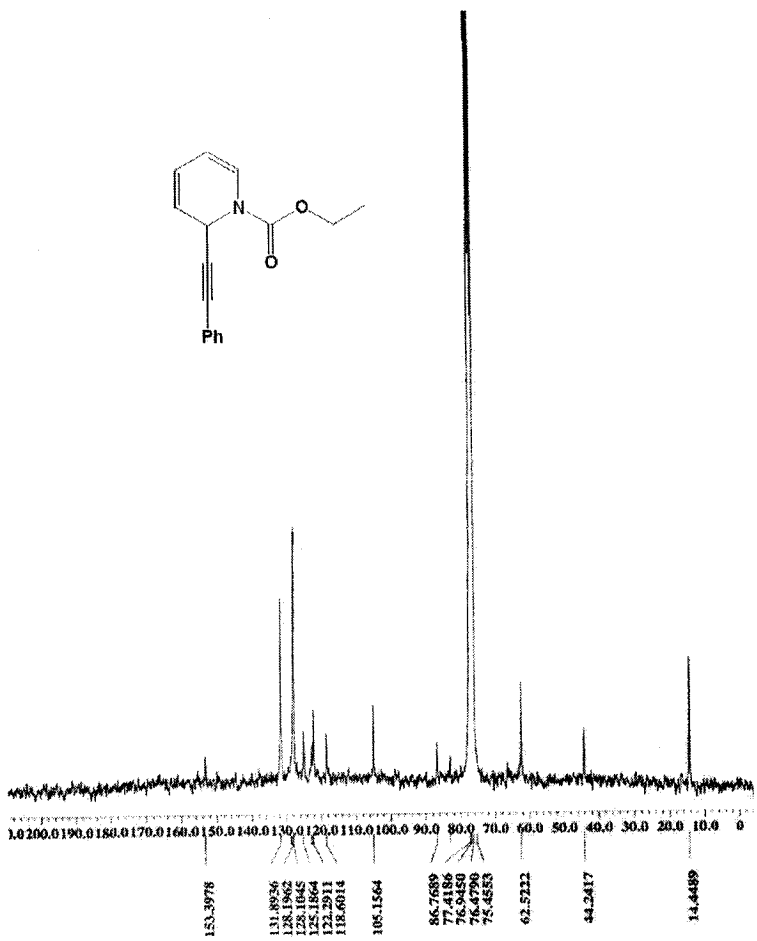


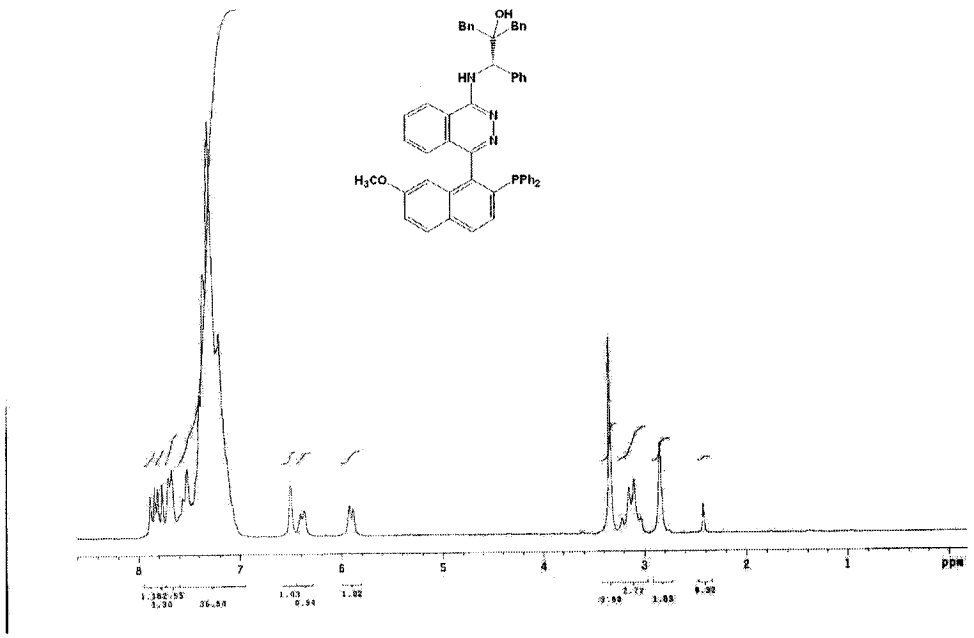
^{1}H and ^{13}C NMR; Compound **6.4c**



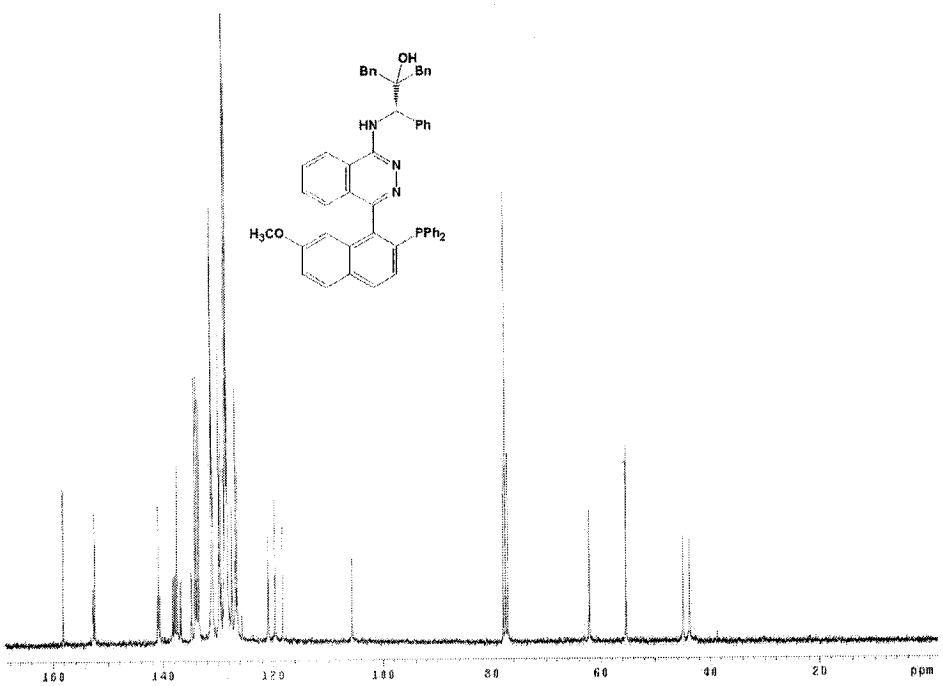


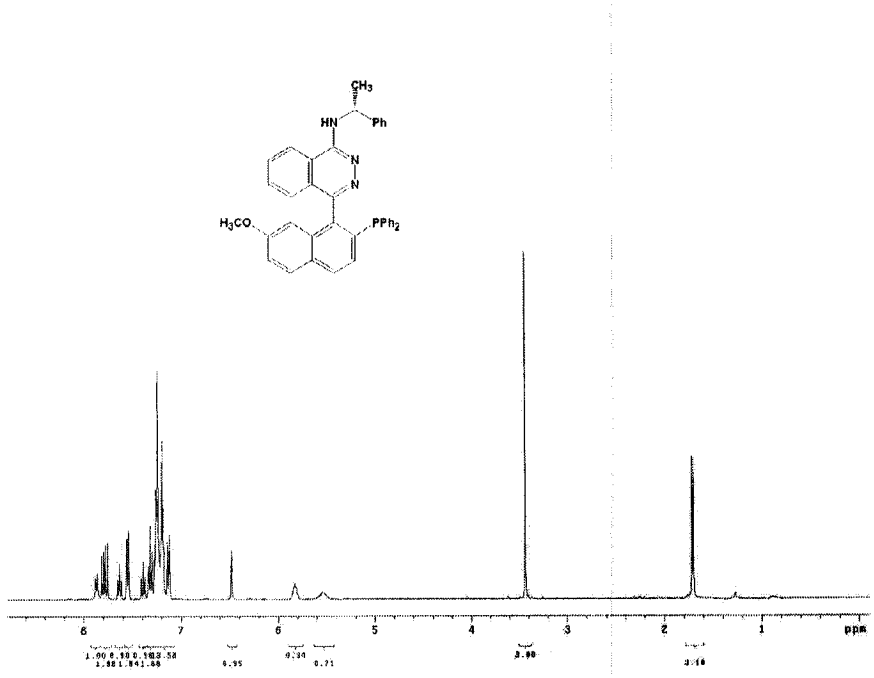
^{1}H and ^{13}C NMR; Compound **6.4d**



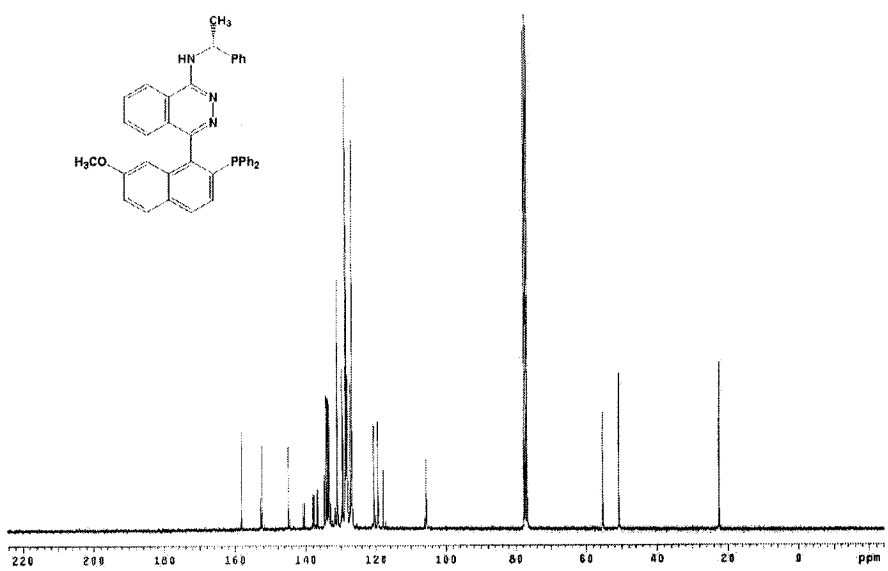


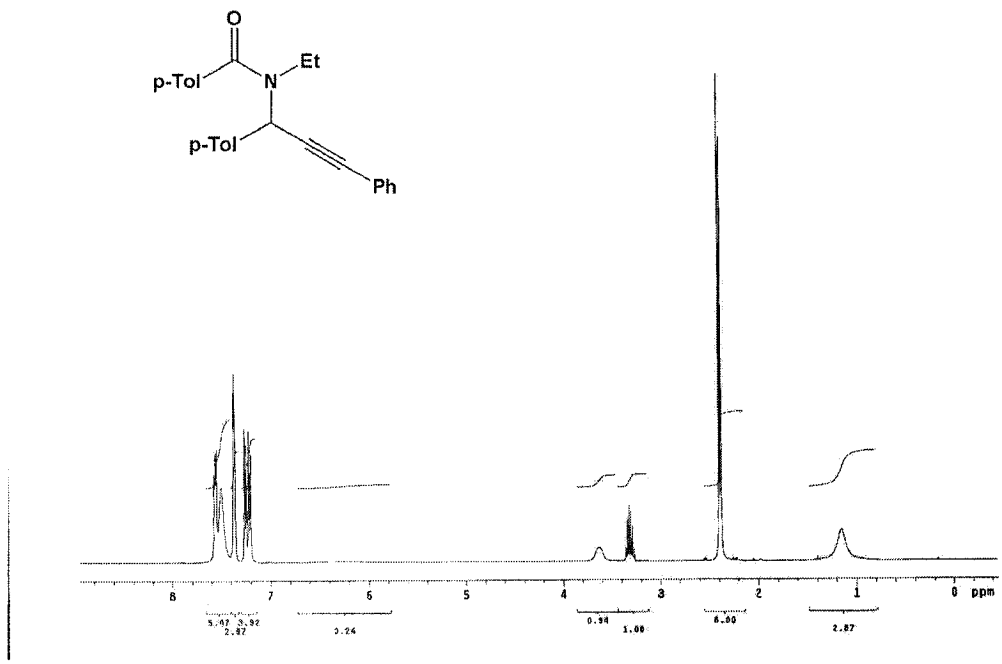
^{1}H and ^{13}C NMR; Compound **6.5c**



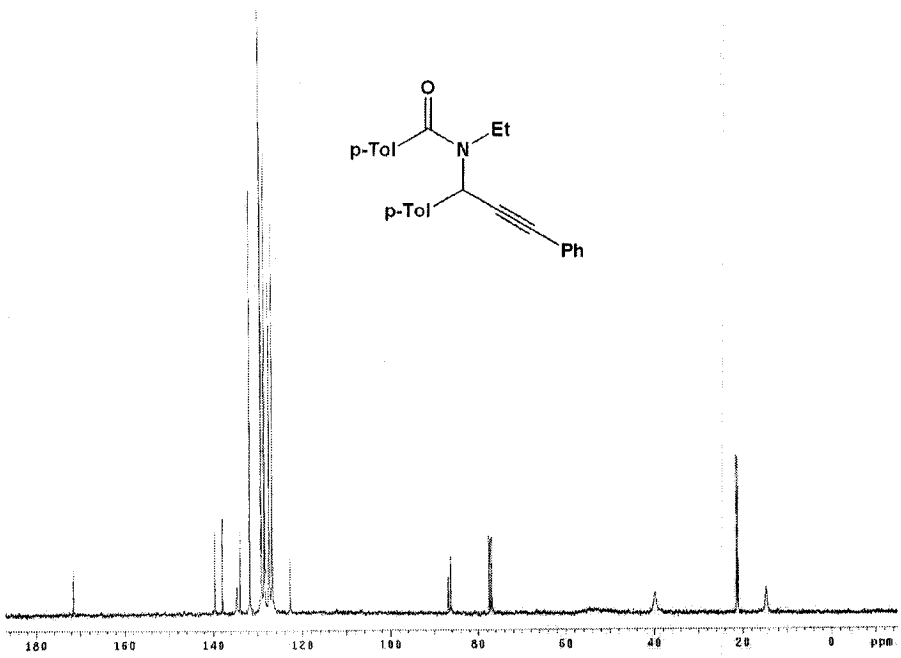


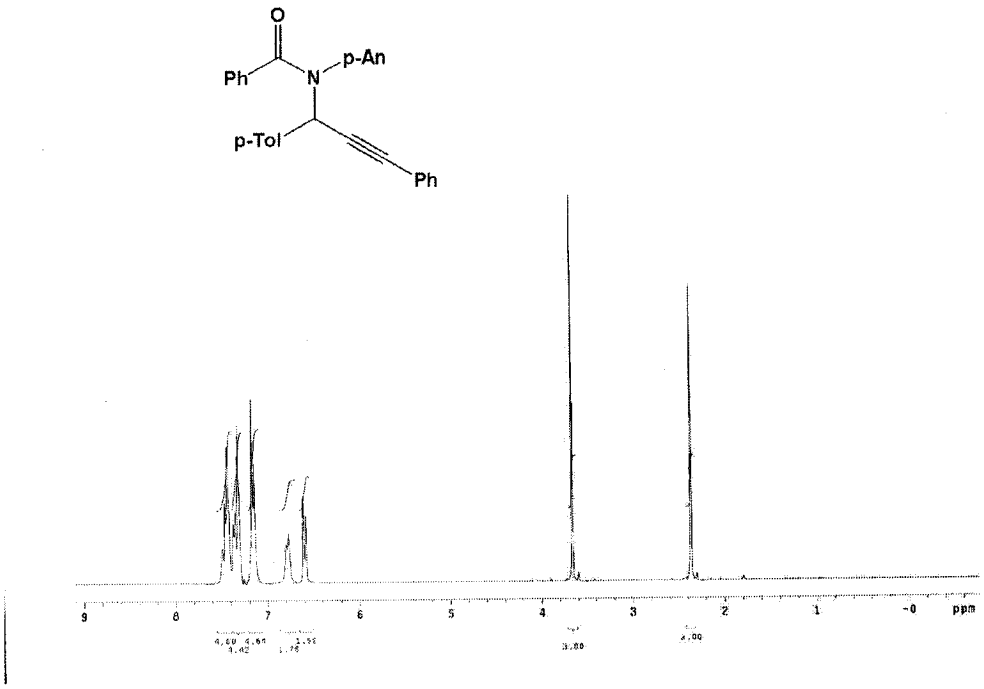
^{1}H and ^{13}C NMR; Compound **6.5e**



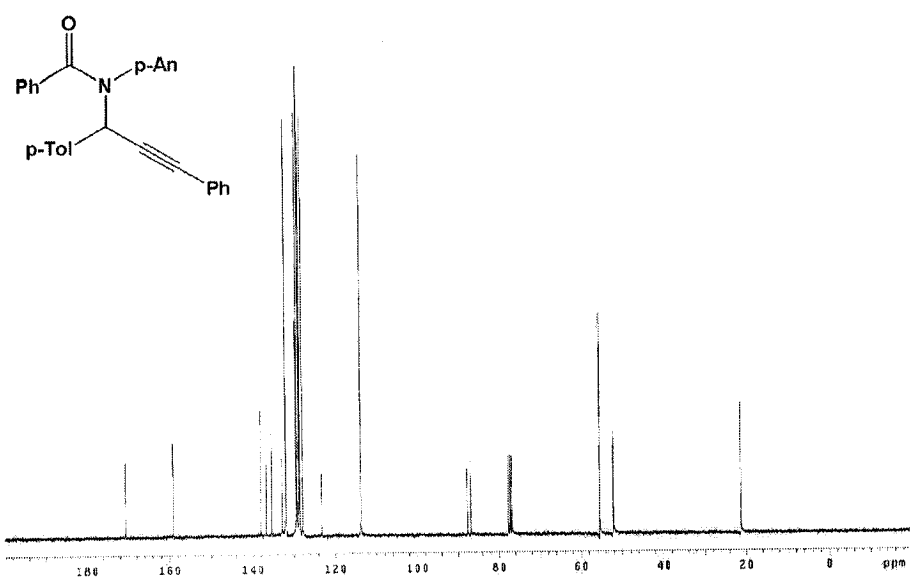


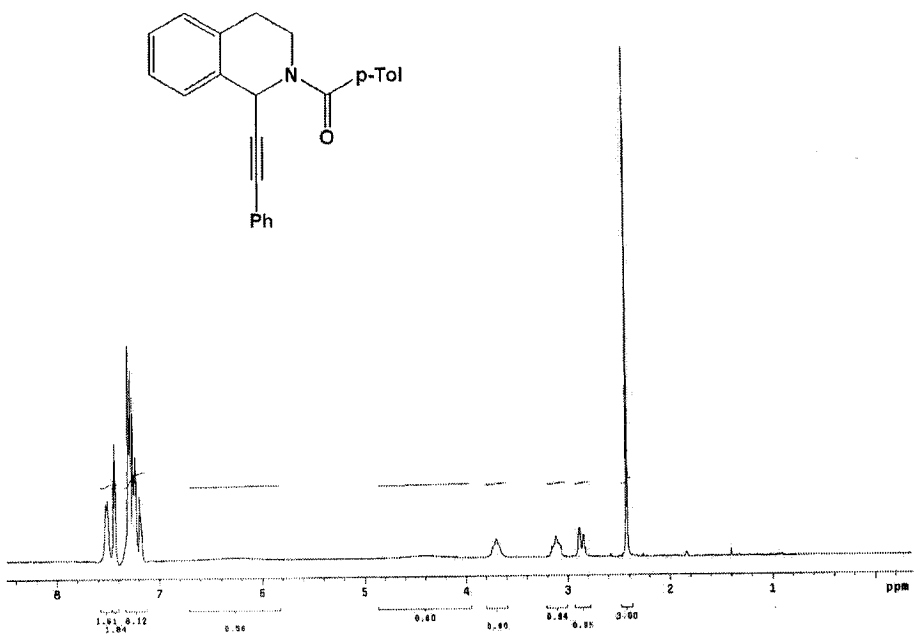
^{1}H and ^{13}C NMR; Compound **6.6a**



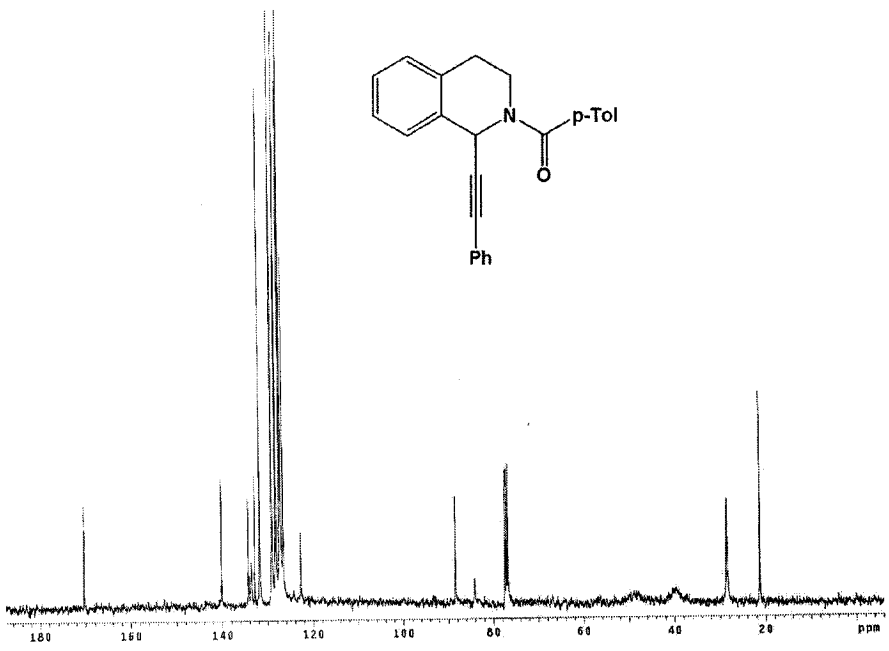


^{1}H and ^{13}C NMR; Compound **6.6b**





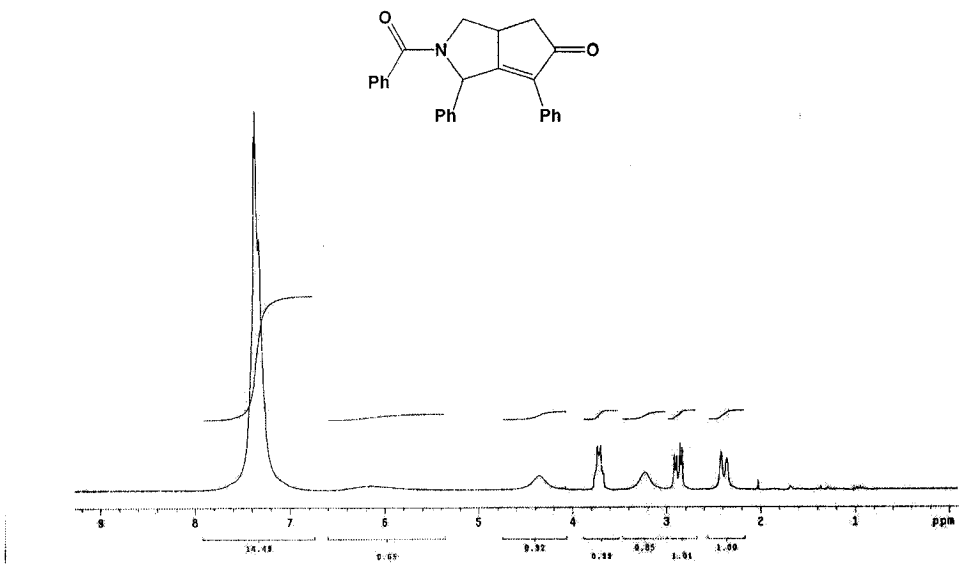
^{1}H and ^{13}C NMR; Compound **6.6c**



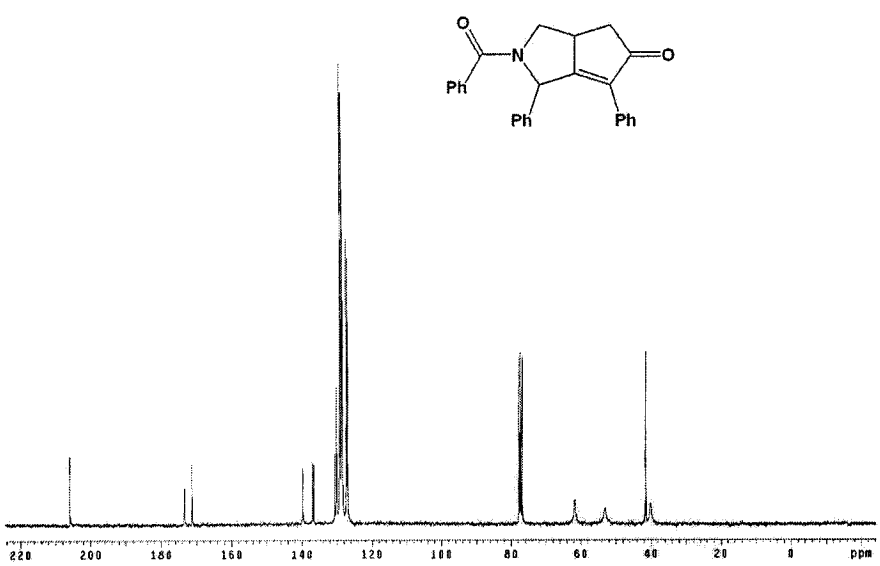
APPENDIX D

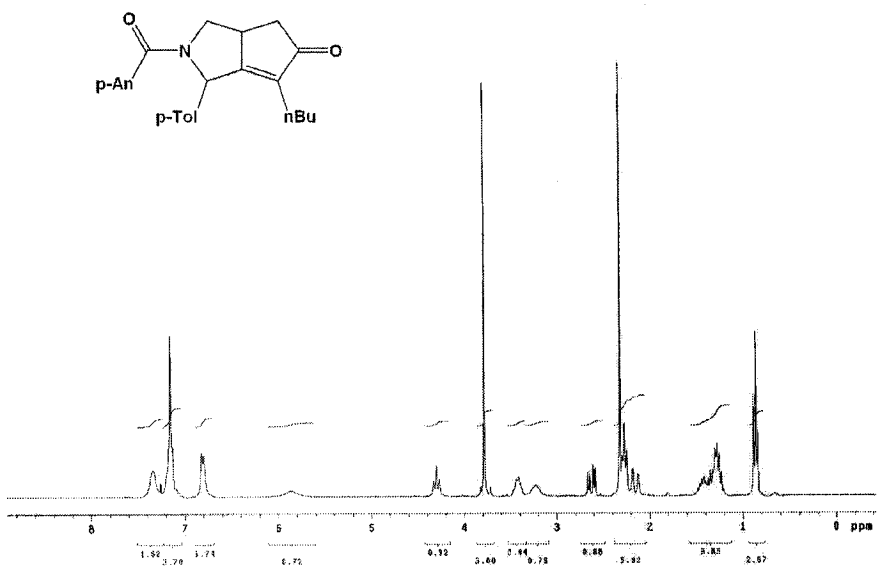
^{1}H and ^{13}C NMR data for Appendix A

Compounds A.5a-c

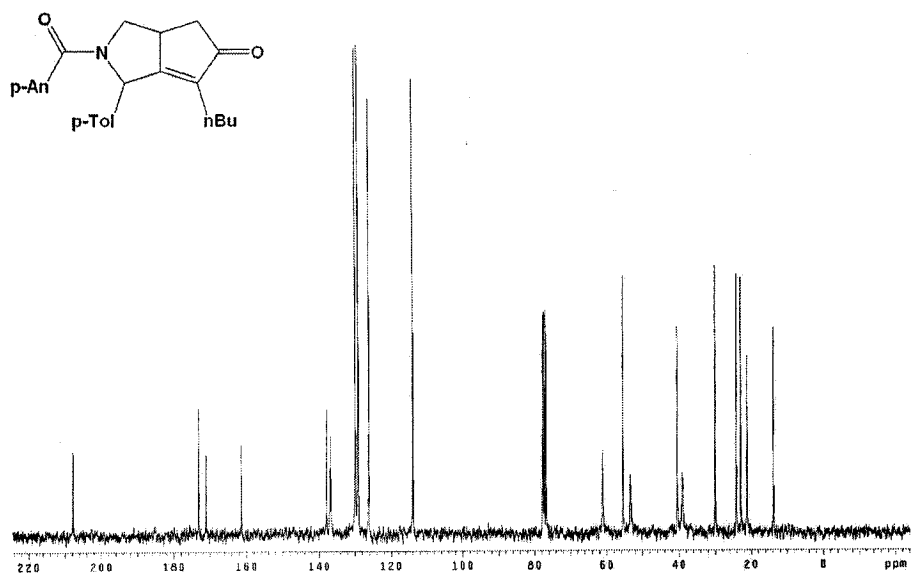


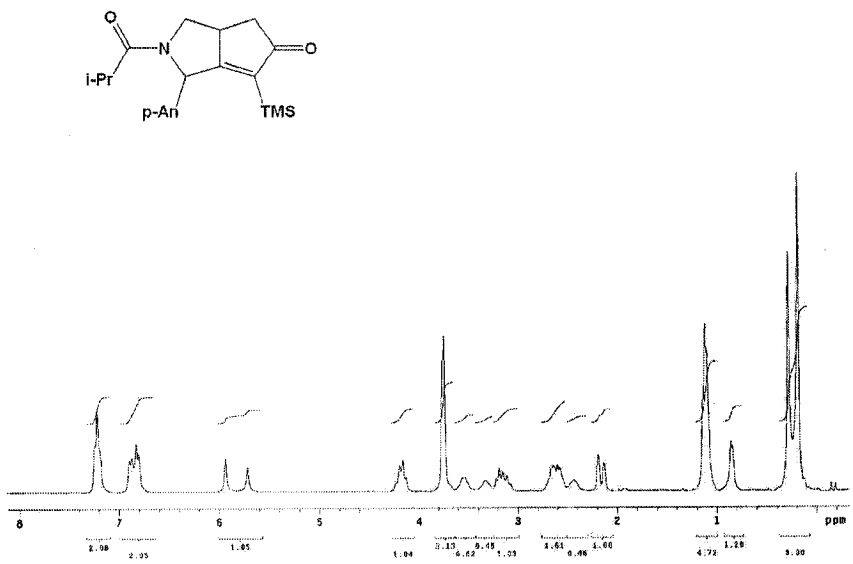
^{1}H and ^{13}C NMR; Compound **A.5a**



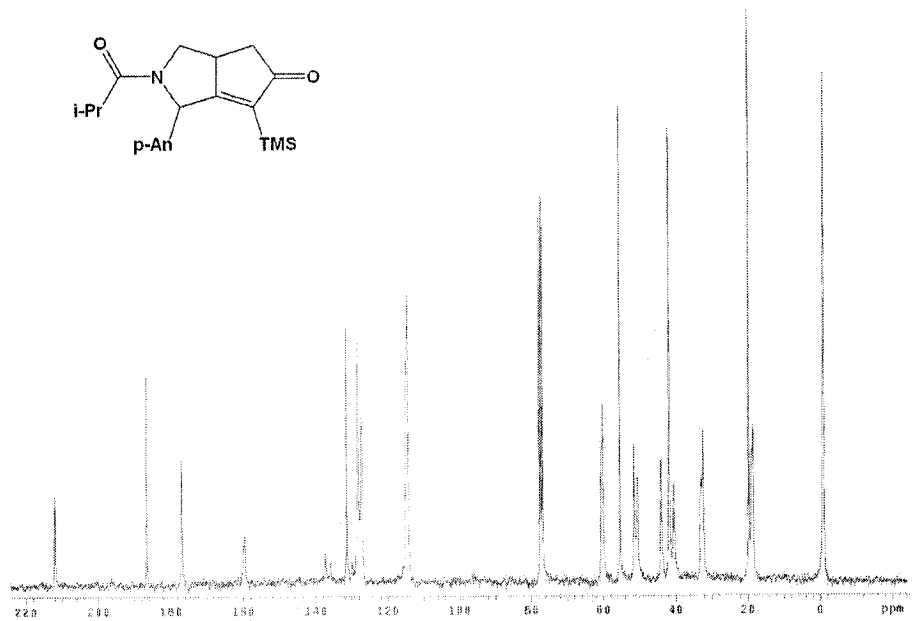


^{1}H and ^{13}C NMR; Compound **A.5b**





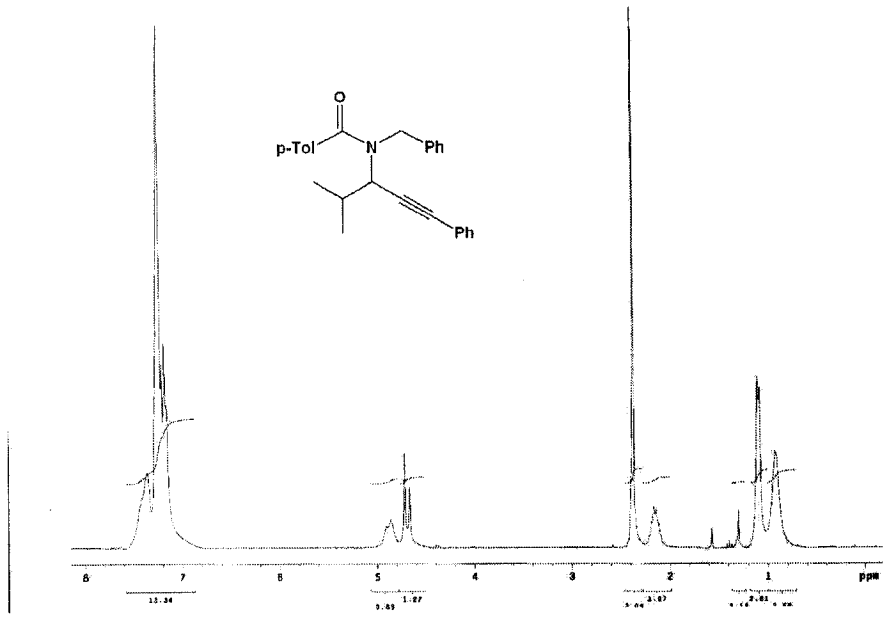
^{1}H and ^{13}C NMR; Compound **A.5c**



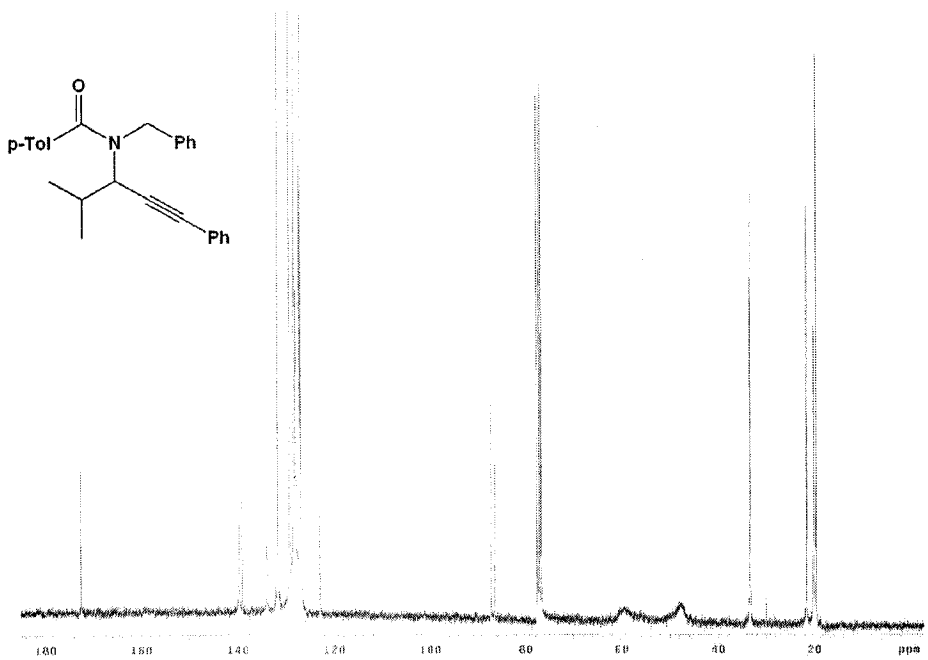
APPENDIX E

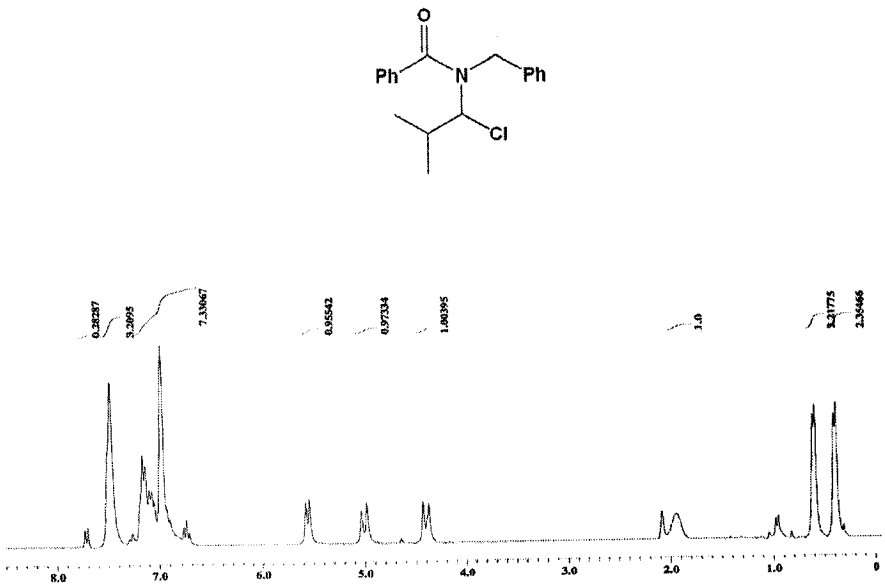
^{1}H and ^{13}C NMR data for Appendix B

Compounds B.4d, B.5c, B.6d

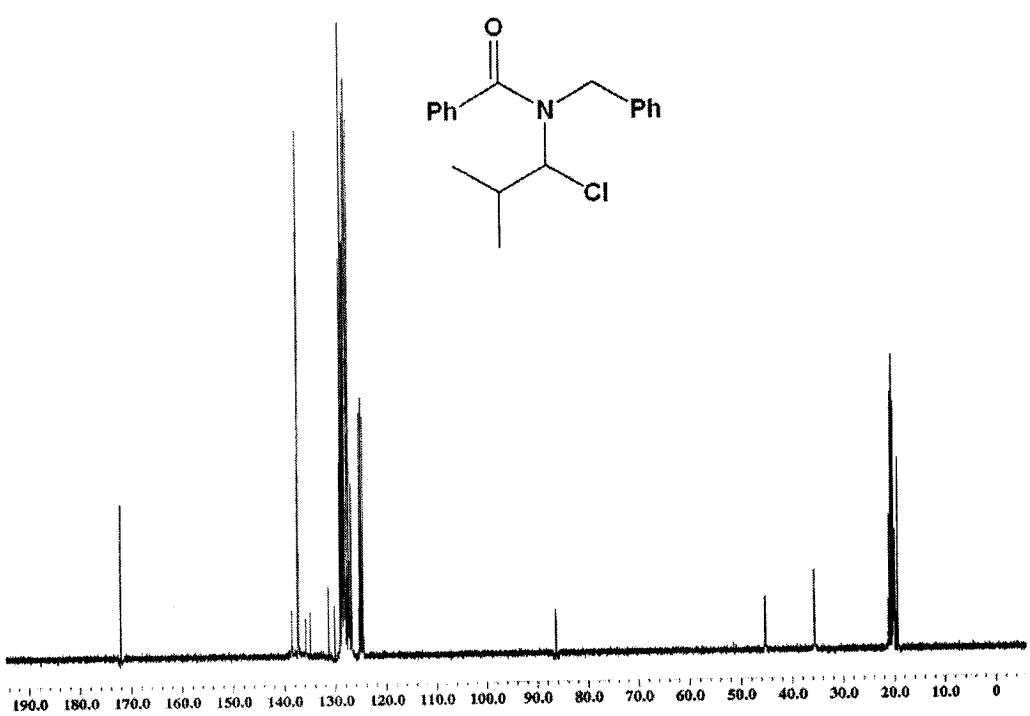


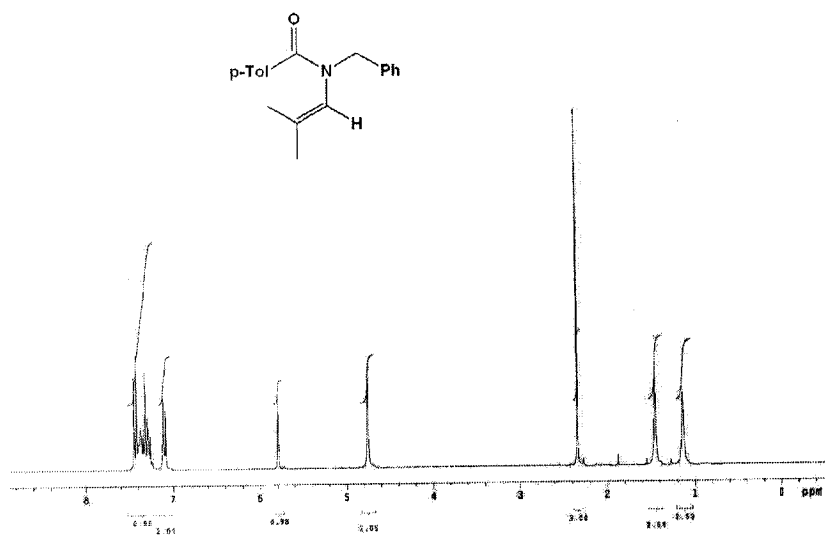
^{1}H and ^{13}C NMR; Compound **B.4d**





^{1}H and ^{13}C NMR; Compound **B.5c**





^{1}H and ^{13}C NMR; Compound **B.6d**