One Step Copper-Catalyzed Functionalization of Pyridines with Alkynes and Organooindium Reagents

A thesis submitted to McGill University in partial fulfillment of the requirements of the degree of M.Sc.

By

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This thesis is dedicated to all of the wonderful teachers that I’ve had who provided inspiration for the study of chemistry: Prof. B.A. ArndtSEN, Mr. Charles “Chuck” Eisner, Prof. J. Roscoe, Prof. J.T. Banks, Prof. J. Clyburne, Prof. R.A. Gossage, and in particular to my high school chemistry teacher Ms. McDonald.
ABSTRACT

The copper-catalyzed synthesis of functionalized pyridines and partially reduced pyridine derivatives has been developed and the results are presented herein. These studies have shown that pyridines (and related aromatic heterocycles) in the presence of chloroformates will undergo effective coupling with terminal alkynes and organoindium reagents using simple copper (I) salt catalysts to give good yields of dihydropyridine products. In addition, performing these reactions in tandem with base or oxidative additives has led to the copper-catalyzed one-pot preparation of substituted aromatic pyridines.

RÉSUMÉ

Une méthode catalytique médiée par le cuivre pour la synthèse des dérivés de pyridines ainsi que celles partiellement réduites est décrite dans le texte qui suit. Cette étude démontre que les pyridines (et autres hétérocycles aromatiques reliés), lorsque quaternisées in-situ par des réactifs tel que les chloroformates, celles-ci peuvent être couplées avec des alcynes terminaux ou des réactifs organo-indium au moyen de simple sels de cuivre (I) pour générer, bon rendement, des dihydropyridines. De plus, lorsque cette réaction est effectuée en tandem, soit avec l’ajout d’une base ou d’un agent oxydant, ce processus nous offre une méthodologie en un pot envers la synthèse de pyridines substituées.
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<th>Description</th>
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<tbody>
<tr>
<td>OTf</td>
<td>trifluoromethane sulfonate</td>
</tr>
<tr>
<td>THF</td>
<td>tetrahydrofuran</td>
</tr>
<tr>
<td>EtOAc</td>
<td>ethyl acetate</td>
</tr>
<tr>
<td>Et₂O</td>
<td>diethyl ether</td>
</tr>
<tr>
<td>DABCO</td>
<td>1,4-diazabicyclo[2.2.2]octane</td>
</tr>
<tr>
<td>DBU</td>
<td>1,8-diazabicyclo(5.4.0)undec-7-ene</td>
</tr>
<tr>
<td>TBAF</td>
<td>tetrabutylammonium fluoride</td>
</tr>
<tr>
<td>Fmoc</td>
<td>9-flourenylmethyloxycarbonyl</td>
</tr>
<tr>
<td>Troc</td>
<td>2,2,2-trichloro-ethyl-chloroformate</td>
</tr>
<tr>
<td>DMF</td>
<td>Dimethylformamide</td>
</tr>
<tr>
<td>mGluR5</td>
<td>Human metabotropic glutamate receptor</td>
</tr>
<tr>
<td>NADH</td>
<td>Nicotinamide adenine dinucleotide (reduced form)</td>
</tr>
<tr>
<td>NADP</td>
<td>Nicotinamide adenine dinucleotide phosphate</td>
</tr>
<tr>
<td>DDQ</td>
<td>2,3-dichloro-5,6-dicyano-1,4-quinone</td>
</tr>
<tr>
<td>o-chloranil</td>
<td>3,4,5,6-tetrachloro-1,2-quinone</td>
</tr>
<tr>
<td>mCPBA</td>
<td><em>meta</em>-Chloro-perbenzoic acid</td>
</tr>
<tr>
<td>MPEP</td>
<td>2-methyl-6-(phenylethynyl)pyridine</td>
</tr>
<tr>
<td>TMS</td>
<td>Trimethyls ilane</td>
</tr>
<tr>
<td>MeOH</td>
<td>Methanol</td>
</tr>
<tr>
<td>EWG</td>
<td>Electron-withdrawing group</td>
</tr>
<tr>
<td>eq.</td>
<td>Equivalents</td>
</tr>
<tr>
<td>[O]</td>
<td>Oxidative conditions</td>
</tr>
<tr>
<td>[H]</td>
<td>Reductive (hydrogenation) conditions</td>
</tr>
<tr>
<td>HMQC</td>
<td>Heteronuclear Multiple Quantum Coupling</td>
</tr>
<tr>
<td>HMBC</td>
<td>Heteronuclear Multiple-bond Coupling</td>
</tr>
<tr>
<td>NOESY</td>
<td>Nuclear Overhauser Effect Spectroscopy</td>
</tr>
<tr>
<td>NMR</td>
<td>Nuclear Magnetic Resonance</td>
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</table>
HRMS
High Resolution Mass Spectrometry

MO
Molecular Orbital

Ar
Aryl

LA
Lewis Acid

Nu
Nucleophile

E
Electrophile

TFA
Trifluoro-acetic acid

Alloc
Allyl Chloroformate

TCC
Trans-α-cumyl-cyclohexanol

de
Diastereomeric excess

dr
Diastereomeric ratio

DMSO
Dimethyl-sulfoxide

REACAP
Resin Activation/Capture Approach
CHAPTER 1

Synthetic Utility of Nucleophilic Additions to N-activated Pyridines

1.0 Perspective

Heterocycles make-up over half of all known organic compounds\(^1\) and pyridine bases represent one of the most prevalent nitrogen heterocycle sub-groups. The first pyridine bases were isolated from bone pyrolysis and coal tar residues in the mid-19th century. The pyridine structure was correctly proposed some 20 years later as a mono-aza-analogue of benzene, where one carbon atom of the benzene ring has been replaced with a nitrogen\(^2\).

The first commercialization of a pyridine derivative came in the 1930’s when it was found that niacin was useful in the prevention of dermatitis and dementia\(^2\). Since then countless pyridines have found industrial applications, including constituents of latex and other polymers, herbicides, insecticides, pharmaceuticals, adhesives and as a reaction medium\(^3\). In the pharmaceutical industry alone, it has been estimated that the pyridine core is in over 7000 existing therapeutic agents\(^2,4\), which is no surprise since pyridines also play important roles in nature. For example, the pyridine nucleotide NADP is involved in various oxidation-reduction processes crucial to metabolism, and pyridine is also found in the important vitamins niacin and vitamin B\(_6\) as well as in potent alkaloids like nicotine (Figure 1.1).\(^2\)
Figure 1.1 Representative important commercial and natural pyridines

This high bio-activity and commercial importance of pyridines has increased demand for these molecules beyond what can be extracted from coal tars, and synthetic methods for the construction of this important core have been developed. Pyridine itself can be produced commercially in ~ 60-70% yield by the vapour phase condensation of crotonaldehyde, formaldehyde, steam, air and ammonia at high temperature over a silica-alumina catalyst. Alkyl substituted pyridines are typically produced by the cyclizations of alkynes and nitriles catalyzed by cobalt complexes (Scheme 1.1). While many other substituted pyridines can be synthesized using related condensation methods (e.g. Hantzsh pyridine synthesis, Guareschi synthesis, Chichibabin Synthesis) or other metal catalyzed cyclizations, problems in regioselectivity, harsh reaction conditions, and restricted availability of starting materials can at times limit the diversity and scope of these syntheses. This can restrict the ability to develop specific pyridine structures crucial for natural product synthesis or product development where specific characteristics are necessary.
If a desired pyridine is not commercially available, it must be synthesized. The direct ring functionalization of commercially available pyridines is perhaps the most straight-forward route to highly substituted pyridines. Electrophilic and nucleophilic aromatic substitution reactions provide routes to simple substituted pyridines, but are limited by the incompatibility of many functional groups to the harsh conditions required. Metallation strategies have proven to be powerful methods for the regioselective addition of many functionalities, but too often require the presence of a
directing group, which must be installed and removed in separate steps.\textsuperscript{7} Transition metal catalyzed cross-couplings (e.g. Suzuki, Negishi, Stille, Sonogoshira, or Heck couplings)\textsuperscript{8} are mild and general methods for incorporation of various organic groups onto the pyridine ring. These methods require the initial generation of the correctly positioned halogenated (or more recently $N$-oxide)\textsuperscript{9} pyridine precursor, which can be cumbersome for the synthesis of complex pyridines.

The ability of pyridine bases to form quaternary salts with a number of electrophilic reagents is a well studied area of chemistry.\textsuperscript{10} These azaaromatic salts are extremely useful for a number of transformations including oxidations, reductions and cycloadditions. In particular, the addition of nucleophilic reagents to $N$-alkyl or $N$-acyl pyridinium salts has seen great success in the last 25 years in the synthesis of many useful pyridine derivatives, especially alkaloids.\textsuperscript{11} This chapter will provide a general overview of pyridinium salt formation, the synthetic utility of nucleophilic additions to these interesting electrophiles, and the impact this area has had in organic synthesis.

### 1.1 Formation of Pyridinium Salts

Although pyridine is a six-membered aromatic compound like benzene, the fact that it contains a nitrogen atom changes its reactivity drastically from other purely carbon-containing aromatic compounds. For example, pyridines do not undergo electrophilic aromatic substitutions as easily as benzene, but will undergo nucleophilic aromatic substitutions more readily.\textsuperscript{5} This observed difference is a direct result of the presence of the electronegative nitrogen atom, which influences the p-electron density on the ring carbon atoms. The increased susceptibility of pyridine towards nucleophilic aromatic substitution becomes clear when resonance structures are drawn, which clearly show the C-2 (or a) and C-4 (or ?) positions as more electron deficient than the other ring atoms (Scheme 1.2). This analysis is also supported by MO \textit{ab initio} calculations.\textsuperscript{5b}
Scheme 1.2  Resonance structures of pyridine showing difference in p-electron densities

These resonance structures also illustrate why it is so difficult to perform traditional electrophilic aromatic substitution reactions on pyridines. While the carbon atoms of the pyridine ring are more electrophilic, the nitrogen atom of pyridine is relatively electron rich and therefore nucleophilic. The nucleophilicity/basicity of the pyridine nitrogen is evidenced by the observed formation of pyridinium salts when it is exposed to electrophilic substrates, shown below in Scheme 1.3.

Scheme 1.3  Formation of pyridinium salts by reaction with various electrophilic agents\textsuperscript{5a}
The above scheme shows that a diverse set of quaternary pyridine salts can be synthesized by the direct addition of pyridines to an electrophile. In contrast with other aromatic N-heterocycles (i.e. pyrrole), the donation of the nitrogen lone pair in these reactions does not destroy the aromaticity of pyridine, and it remains isoelectronic with benzene. These salts are, however, much more polarized than benzene or simple pyridine, and further exaggerate the electrophilicity of the ortho- and para-carbon atoms.

The quaternization of pyridines in this manner are equilibrium processes and the amount of salt produced is dependant on both the nature and concentration of the electrophile and the pyridine. Obviously, higher concentrations and electrophilicities of the electrophile will result in more pyridinium salt formation compared to the reaction of the same amount of pyridine with a more dilute or less reactive electrophile. The rate of pyridinium salt formation is also dependant on these factors. For example, quaternization of pyridine with an acyl halide is typically instant at room temperature with complete salt formation within minutes to an hour, whereas quaternization with an alkyl halide requires longer reaction times.

In addition, steric and electronic effects are major contributing factors towards the efficiency and rates of these quaternization reactions. Substitution of pyridine with a simple methyl group at the a-position reduces the rate of N-alkylation by approximately a factor of three, and when there is extreme steric hindrance, as in the case of 2,6-di-t-butylpyridine, no reaction is observed with methyl-iodide. If, however, these electron-rich alkyl groups are well removed from the reaction site, they can increase the rate of quaternization by donating electron density into the ring. For example, 3-methyl pyridine will react 1.5 times faster with methyl-iodide than pyridine. Conversely, withdrawing electron density from the pyridine ring will slow reaction rates: substitution of pyridine at C-3 with simple chlorine slows the N-methylation reaction by a factor of 7.

While simple quaternization of pyridine with electrophiles is the most common route to pyridinium salts, there exist a number of alternative routes for their formation (Scheme
1.4). The reaction of primary amines with the extremely electrophilic \( N-2,4 \)-dinitrophenyl pyridinium salt releases 2,4-dinitro aniline and results in a new \( N \)-alkyl activated pyridinium species. This reaction was first reported by Zincke\(^ {14} \) in 1903 and is now known as the Zincke reaction. This reaction has a deceptively complex mechanism which was the subject of many studies,\(^ {15} \) but today is frequently used as a useful method to prepare chiral pyridinium salts\(^ {16} \) via the addition of chiral amines. Another common non-quaternization route to pyridinium salts is by treatment of pyrylium salts or ions with primary (or in rare cases secondary) alkyl amines. This results in nucleophilic addition to the \( a \)-position of the pyrylium ion to give a dihydropyran, which ring opens then self condenses producing the \( N \)-alkyl pyridinium salt.\(^ {17} \) Condensation of \( a,\beta \)-unsaturated ketones with primary amines and carbonyl-containing compounds with acidic hydrogens will also yield pyridinium salts via a related mechanism.\(^ {10b} \) Lastly, the oxidation or rearrangement of dihydropyridines\(^ {17b,18} \) can also yield pyridinium salts, although this route is seldom used due to lack of scope.
Access to an \( N \)-alkyl chiral pyridinium salt via the Zincke reaction:\(^{16a}\)

Pyridinium ion synthesis by primary amine addition to a pyrylium ion:\(^{17a}\)

Representative condensation procedure for pyridinium salt synthesis:\(^{10b}\)

Oxidation of \( N \)-dodecylacridan to the \( N \)-dodecylacridium chloride NAD\(^+\) model:\(^{18a}\)

Scheme 1.4 Alternative, non-quaternization preparations of pyridinium salts

1.2 Nucleophilic Additions to Pyridinium Salts

The pronounced susceptibility of pyridinium salts to nucleophilic addition at the \( \alpha \)- and \( \beta \)-positions has been exploited in the synthesis of many useful structures.\(^{5,10,11,19,20}\) These additions have been used to synthesize a range of biologically relevant structures, including NADH mimics and alkaloids,\(^{11}\) as well as providing easy access to synthetically useful dihydropyridines\(^{19}\) and pyridines.\(^{20}\)
The addition of a nucleophile to a pyridinium salt can result in either 1,2 or 1,4 addition, depending on the nature of the nucleophile, pyridine ring substitution, nature of the pyridinium salt, and conditions or additives used in the reaction (Scheme 1.5). The exact reasons for the difference in the position of attack by nucleophiles is not entirely understood, however, some studies on this issue have postulated that an intermediate charge-transfer complex\textsuperscript{21} could be involved, or that the hard or soft nature of the nucleophile is the determining factor.\textsuperscript{22}

**Scheme 1.5** Regioisomers resulting from nucleophilic addition to pyridinium salts

The rest of this chapter will provide a concise review of nucleophilic additions to pyridinium salts. Additions to pyridine $N$-oxides, and salts of benzo-fused pyridines (e.g. quinoline and isoquinoline) and related aza-aromatics will be largely ignored, but a few selected important examples will be included. A variety of nucleophiles will be considered and reviewed, however, particular emphasis will be to show the synthetic utility of nucleophilic additions to pyridinium salts and using this reactivity towards the synthesis of bio-active targets.

In a general sense, nucleophiles in additions to pyridinium salts can be divided into either organic or organometallic compounds. Organic nucleophiles can be considered as simple substituted amines and alcohols (including ammonia and the hydroxide ion), as well as carbanions such as enolates,\textsuperscript{*} malonates,\textsuperscript{*} isocyanides and the cyanide ion. Organometallic nucleophiles, however, are typically considered to be anionic carbon sources which can be either covalently or ionicly bonded to a metal.

\textsuperscript{*} Although these often also contain a metal, they will be considered organic nucleophiles here since the nucleophilic carbon is not bonded to the metal.
These include but are not limited to: organo-magnesium, -lithium, -cuprate, -titanium, -boronic acid or -borate, -zinc, -indium, and -tin reagents. While a number of organic nucleophiles have been added to pyridinium salts, organometallic species are far more common coupling partners, due in large part to the diversity of organometallic agents available.

1.3 Organic Nucleophile Additions

The hydroxide ion is believed to be the earliest reported nucleophile to be added to a pyridinium salt. The products of these reactions were originally proposed to be 1-substituted-2-hydroxy-1,2-dihydropyridines, but were later found to transform into 2-pyridones (Scheme 1.6). When related alkoxide nucleophiles are added to N-methyl salts of 3-substituted pyridines, more stable products can be isolated. In these cases, reversible addition occurs, and longer reaction times leads to the formation of the more stable 1,4-adduct.

Scheme 1.6 Alkoxy additions to pyridinium salts

Simple benzo-fused pyridine derivatives such as quinoline and isoquinoline, easily undergo cyanide ion addition to their N-acyl salts in what is known as the Reissert reaction. While these “Reissert compounds” are useful heterocyclic products, this reaction does not work well for most simple pyridines, often giving very low yields of the pyridine “Reissert” analogues (N-acyl-2-cyano-1,2-dihydropyridines). Efficient addition of cyanide ion to pyridinium salts occurs only when the pyridine ring is substituted with electron-withdrawing groups (e.g. ketones, amides, or cyano-substituents), or activated with more electron deficient chloroformates. These give
predominantly 1,4-cyano addition (non-“Reissert” addition) under thermodynamic control (Scheme 1.7).\textsuperscript{29}

![Scheme 1.7 Pyridines in “Reissert”-type reactions](image)

A recent advance in this chemistry has been the development of a catalytic enantioselective addition of cyanide ions to \( N \)-acyl quinoline and isoquinoline salts using chiral lewis acids (Scheme 1.8).\textsuperscript{30}

![Scheme 1.8 A catalytic enantioselective Reissert-type reaction](image)

Most importantly, these conditions were improved in a later report to include the catalytic asymmetric addition of cyanide ions to \( N \)-acyl pyridinium salts, in the first ever reported catalytic enantioselective addition to a pyridinium salt.\textsuperscript{31} This provides regio- and enantio-selective access to very useful Reissert-addition (\( \alpha \)-addition of cyanide) pyridine products, which are difficult to access even in a racemic fashion by other
methods. This reaction was also applied to the synthesis of the highly selective dopamine D₄ antagonist CP-293,019 (Scheme 1.9).

Scheme 1.9 Catalytic enantioselective cyanide addition to pyridinium salts and application to the synthesis of dopamine D₄ antagonist CP-293,019

Until recently, the addition of related isocyanides to activated quaternary pyridines was unknown, although successful examples of isocyanide reaction with salts of quinoline and isoquinoline had been reported. One possible reason for this difference in reactivity was proposed by the Lavilla group, who postulated that a reversible addition may occur with isocyanides and pyridinium salts. They proposed that stabilization of the nitrilium ion formed after addition could allow effective trapping of the isocyanide addition products. It was found that by using pyridines substituted in the 3-position with carboxyamido groups, they could isolate 4-amido substituted 1,4-
dihydropyridines in good yield (Scheme 1.10).\textsuperscript{33} This reaction represents the only known addition of isocyanides to pyridinium salts giving dihydropyridine products,\textsuperscript{34} and was also applied to the synthesis of other interesting pyridine derivatives, including amido-substituted aromatic pyridines, isoquinolines, and \textit{cis}-indoloquinolizidines.

\textbf{Scheme 1.10} Effective addition of iso-cyanides to nicotinamides as an efficient entry to substituted nicotinonitrile compounds

A variety of other carbanion sources (e.g. enolates, malonates, and nitro-alkanes) have been employed in addition reactions with quaternary pyridinium salts. This chemistry has been reviewed up to 1982.\textsuperscript{19b,c} Interestingly, these reactions were not commonly used for the synthesis of target structures until the late 1980’s. It has since become a general route to many bio-active molecules.\textsuperscript{19a,35} Some examples of these are shown below.
Wenkert and co-workers introduced an efficient protocol for the addition of carbon nucleophiles to pyridinium salts for the synthesis of a variety of indolo-alkaloids in the 1980’s (i.e. the “Wenkert Procedure”). The procedure typically involves the addition of an indolo-type enolate to an \(N\)-alkyl pyridinium salt, followed by an intramolecular cyclization on the resulting dihydropyridine. A representative example is shown in Scheme 1.11 for the synthesis of geissoschizine.

**Scheme 1.11** Synthesis of the indolo-alkaloid geissoschizine using the “Wenkert procedure”

Simple variation of the indole enolate and the pyridinium salt led to the discovery that a number of other indole-type alkaloid skeletons can be constructed (Scheme 1.12), where the first step is always the regioselective 1,4-addition of the indole enolate to the \(N\)-alkyl pyridinium salt. The convergent nature of these approaches, as well as the relative ease of diversification of the starting materials, make these attractive synthetic strategies to these heterocycle cores. This protocol was used to synthesize a number of
complex bio-active molecules, including akagerine, camptothecin, ervitsine, and vinoxine.

Scheme 1.12 Strategies to access highly complex indolo-alkaloid skeletons using pyridinium salts

In addition to these examples, use of a chiral enolate resulted in the synthesis of the enantio-enriched indole alkaloid products (−)-isovallesiachotamine and (+)-vallesiachotamine. Conversely, enantioselective products can also be obtained when the pyridinium salt employed contains a chiral auxiliary, as in the case of the synthesis of (−)-N-methylervitsine. These examples are summarized in Scheme 1.13.
Chiral enolate route to (-)-isovallesiachotamine:

\[
\begin{align*}
\text{Br}^- & \quad \text{O} \quad \text{O}^+ \\
\text{CO}_2\text{Bu} & \quad \text{O} \\
\text{CO}_2\text{Me} & \quad \text{O} \quad \text{O} \\
\text{CO}_2\text{Ph} & \quad \text{O} \quad \text{O} \\
\end{align*}
\]

Chiral pyridinium salt route to (-)-N-methylervitsine:

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\text{O} & \quad \text{Me} \\
\end{align*}
\]

Scheme 1.13 Examples of chiral indolo-alkaloid synthesis via pyridinium salt additions

The addition of simple enolates to pyridinium salts can also lead to interesting products outside of the indole alkaloids set. When titanium enolates are added to a mixture of pyridine and phenyl chloroformate, a mixture of 1,2- and 1,4-isomers is obtained.\textsuperscript{43} Treatment of these purified product(s) with elemental sulfur and catalytic Pd/C leads to decomposition of the 1,2-isomer, and exclusive isolation of the aromatic 4-(2-oxo-alkyl)-pyridines from the mixture (Scheme 1.14).

Scheme 1.14 Synthesis of 4-(2-oxo-alkyl)-pyridines by enolate addition to \(N\)-acyl pyridinium salts
In addition, the Comins group has shown that zinc enolates add with excellent regio- and diastereo-selectivity to pyridinium salts quaternized with the chiral chloroformate (+)-TCC\textsuperscript{44} (TCC= \textit{trans}-2-(\textalpha-cumyl)-cyclohexyl). These additions are analogous to the related reactions of organometallic reagents developed by the Comins group to chiral pyridinium salts, and are often referred to as the “Comins Protocol” (see Schemes 1.23, 1.27 and 1.28). The utility of this selective enolate addition was applied to the first asymmetric synthesis of (+)-cannabisativine\textsuperscript{45}, a natural product isolated from the common marijuana plant (Scheme 1.15).

\textbf{Scheme 1.15} Application of an asymmetric enolate addition to a pyridinium salt: Total synthesis of (+)-cannibativine\textsuperscript{45}
There are a few examples in the literature where π-basic nucleophiles (i.e. indoles, pyrroles, imidazoles) can be added to pyridinium salts, although the regioselectivity is poor unless the heterocyclic nucleophile is tethered to the pyridine. In a related procedure, the intramolecular attack of an enamide on a pyridinium salt was found to provide a diversifiable method to various indolo-alkaloids.

Very recently there was an interesting report from the Corey group, on the highly regioselective addition of nucleophilic aromatics to N-triflic pyridinium salts. This procedure, outlined in Scheme 1.16, is interesting for a number of reasons. The novel use of triflic anhydride as a pyridine activating agent resulted in a highly electron-poor (electrophilic) pyridinium intermediate in a simple and rapid procedure. The increased reactivity of this compound allowed for a variety of π-basic nucleophiles to be used in this reaction including pyrroles and electron rich aromatics. In addition, this reaction is tolerant of ortho-electron withdrawing groups on the pyridine ring (i.e. 2-bromo- and 2-cyano-pyridines). These are typically unreactive as pyridinium salt precursors, presumably due to the increased steric bulk and lower nucleophilicity of the pyridine. To illustrate the potential advantage of this procedure, a base-mediated aromatization protocol was also developed to allow access to 4-substituted aromatic pyridines.
Scheme 1.16 Addition of π-basic aromatics to pyridines activated with triflic anhydride and its application to the synthesis of 4-aryl-substituted pyridines

1.4 Organometallic Nucleophile Addition

Electrophilic pyridinium salts undergo addition with a variety of nucleophiles, however, the most common route to their functionalization probably involves reaction with organometallic reagents. Of the many organometallic reagents that can effectively add to pyridinium salts, the use of Grignard reagents are perhaps the most common. This is likely due to their ease of preparation, commercial availability, and the range of transferable organic groups available.
Prior to their reaction with pyridinium salts, it was found that phenyl-Grignard reagents underwent a direct, regioselective nucleophilic aromatic substitution with pyridine at low temperature. This coupling is presumed to go through an intermediate nitrogen bound Mg dihydropyridine adduct, which oxidizes upon isolation (Scheme 1.17). The same results can also be obtained when phenyl-lithium is added directly to pyridine. However, this reaction works poorly for other organo-lithium and –magnesium reagents, and is not functional group tolerant.5

Scheme 1.17 Direct addition of phenyl-magnesium bromide or phenyl-lithium to pyridine

In early attempts to increase the efficiency and utility of this reaction, it was found that addition of an acyl halide (i.e. chloroformate or acid chloride) to pyridines, forming an N-acyl pyridinium salt, followed by Grignard addition led to the formation of 1,2-dihydropyridine derivatives (Scheme 1.18).49,50 These early addition reports were regioselective because the 4-position was blocked by using a 4-substituted pyridine. Treating these dihydropyridines with elemental sulfur provided access to 2,4-di-substituted pyridines.49d

Scheme 1.18 Aryl Grignard addition to N-acyl salts of 3,4-lutidine for the regioselective synthesis of substituted pyridines
In contrast to the above studies, the regioselective 1,4-addition of Grignard reagents can be obtained with pyridines quaternized as $N$-(2,6-dimethyl-4-oxopyridin-1-yl) salts. This bulky $N$-substituent blocks the ortho positions of the pyridine ring, allowing the exclusive addition of the organo-magnesium to the 4-position. The resulting 1,4-dihydropyridines were too unstable to characterize, but the corresponding aromatic 4-substituted pyridines could be obtained and characterized by heating the crude intermediate in air (Scheme 1.19).

A more detailed investigation on the interaction of Grignard reagents and $N$-acyl pyridinium salts shortly after the above example showed that these compounds did favour addition to the 2-position, even when the 4-position isn’t blocked, but that a mixture of 1,2- and 1,4-regioisomers was common. Specifically, very poor regio-specificity was observed when alkyl Grignards were used. This study did find, however, that adding a catalytic amount of copper (I) iodide to the reaction mixture resulted in almost exclusive 1,4-addition of alkyl and aryl Grignards (Scheme 1.20). This procedure is a significant improvement over the Sammes protocol (Scheme 1.19) in its efficiency and simplicity, and was also amenable to the isolation of 4-substituted pyridines when the addition products were refluxed with sulfur. In addition to the aromatic pyridines, this study also
showed that catalytic reduction of the dihydropyridine mixtures could yield the substituted piperidines.

Scheme 1.20 Addition of Grignards to \( N \)-acyl pyridinium salts and the effect of catalytic copper (I) iodide towards the isolation of piperidines and pyridines\(^{52}\)

Although 4-substituted pyridines can be effectively prepared using this copper catalyzed Grignard addition to pyridinium salts and tandem oxidation protocol (Scheme 1.20), the preparation of the 2-substituted regioisomer pyridines was restricted to the harsh direct addition of organometallic reagents to pyridine (Scheme 1.17), or by using blocking groups (Scheme 1.18).

An exception to these examples involves the use of pyridine \( N \)-oxides in an interesting one-pot procedure.\(^{53}\) Pyridine \( N \)-oxides can react with chloroformates to give \( N \)-alkoxycarboxy pyridinium salts which rearrange spontaneously after addition of
Grignard reagents to yield 2-substituted pyridines (Scheme 1.21). The driving force for these reactions is proposed to be the formation of an alkylcarbonic acid. While some 4-addition most likely occurs in these reactions, the resulting 1,4-dihydropyridine is not arranged properly to allow for this favourable rearrangement. A few other examples of this reaction with other organometallic agents (e.g. organo-zincs and silver-acetylides) have also been reported. At a time when palladium catalyzed cross-coupling reactions were not fully developed as mild and versatile methods to construct substituted pyridines, these syntheses represented simple and relatively general routes to these important compounds.

The first application of the addition of organometallic reagents to pyridinium salts for natural product synthesis came from Yamaguchi and co-workers, in the total synthesis of piperidine alkaloids (+/−)-solenopsin A and (+/−)-monomorine. Both syntheses were

**Scheme 1.21** Grignard additions to N-alkoxycarboxy pyridinium chlorides as a method for the synthesis of 2-substituted pyridines
extremely short, and were based on the group’s findings that alkynyl Grignards add almost exclusively to the 2-position of an $N$-acyl pyridinium salt in the absence of catalytic copper salts. Simple metal catalyzed hydrogenation then gave the piperidine core skeleton. In the case of monomorine, just two more short steps resulted in the isolation of the natural product in 32% overall yield (Scheme 1.22).\textsuperscript{55b}

\[ \text{Scheme 1.22} \] Regioselective $\alpha$-addition of an alkynyl-Grignard to an $N$-acyl pyridinium salt and application to the synthesis of the piperidine alkaloid (+/-)-monomorine

A useful development for the synthesis of natural products via addition of organometallic reagents to pyridinium salts was developed in the late 1980’s and early 1990’s by Comins and co-workers. They discovered that the addition of Grignard reagents to 4-methoxy-$N$-acyl pyridinium salts, followed by treatment with acid, provided a straightforward route to substituted 4-pyridones (Scheme 1.23).\textsuperscript{11a} These structures could then be easily manipulated into highly substituted products with good stereo- and regio-control. This method was then applied to the racemic synthesis of some indolizidine, quinolizidine, and piperidine alkaloids.\textsuperscript{56}
These reports by Comins and Yamaguchi represented new synthetic strategies for the construction of biologically active piperidines and related alkaloids using organometallic reagents in additions to activated pyridiniums. A number of examples of using Grignard reagents in additions to pyridinium salts to make bio-active or structurally interesting compounds have since been reported.\textsuperscript{57,58} Other organometallic species have been similarly used to prepare dihydropyridine intermediates including organo-zincs,\textsuperscript{59} organo-cuprates,\textsuperscript{60} and others.\textsuperscript{61}
employed in Grignard addition to pyridinium salts. In contrast, organotin compounds are more functional group compatible, and have been found to react with \(N\)-acyl pyridinium salts. However, these reactions are limited to benzyl, allyl, or alkynyl group transfer. Benzyl-tin addition is 4-selective, and in some cases, 4,4-di-substituted dihydropyridines can be prepared when 4-substituted pyridinium salts are used. The addition of allyl- or alkynyl-tin reagents are \(\alpha\)-selective, while preferential 4-addition occurred in the case of crotyl- or prenyl-tin reagents. A short synthesis of the piperidine alkaloid (+/-)-coniine was also accomplished via allyl-tin addition to an \(N\)-acyl pyridinium salt (Scheme 1.24).

![Scheme 1.24](image)

Scheme 1.24 Application of allyl-tin additions to pyridinium salts towards the synthesis of (+/-)-coniine

1.5 Organometallic Additions to Pyridinium Salts Towards Library Development

Combinatorial chemistry and Diversity Oriented Synthesis (DOS) are two examples of methodologies developed in response to pharmaceutical companies growing need for techniques that increase the speed and efficiency of compound synthesis. Crucial to the effectiveness of combinatorial chemistry are reactions that couple more than two reagents together in one-pot, better known as “multicomponent coupling reactions,” from which compound libraries can be constructed. Nucleophilic additions to pyridinium salts involve the one-pot formation of a substituted dihydropyridine from three separate materials, and are therefore multicomponent. Due to the importance of the structures that can be obtained from such additions, there has been some research in using pyridinium additions in solid or solution phase parallel synthesis.
As one example, a number of 4-substituted piperidines have been prepared by a solution-phase parallel synthesis method involving the copper-catalyzed regioselective addition of organo-zinc reagents to N-acyl pyridinium salts. The dihydropyridine intermediates were first transformed into their N-Boc-protected derivatives, then reduced to the piperidines by an in situ palladium catalyzed transfer hydrogenation (Scheme 1.25).

![Scheme 1.25 Solution-phase parallel synthesis of some N-tBoc-protected piperidines](image)

**Scheme 1.25** Solution-phase parallel synthesis of some N-tBoc-protected piperidines

Similar studies have also been performed on solid-supports. For example, using a solid-supported chloroformate resin, a method termed Resin Activation/Capture Approach (REACAP) Technology was developed to prepare various dihydropyridines, pyridines, and interesting bicyclic products. This involves the addition of Grignard reagents to polystyrene supported pyridinium salts (Scheme 1.26).
Scheme 1.26 Solid-phase pyridinium salt REACAP approaches to heterocycle synthesis

1.6 Asymmetric Additions to Pyridinium Salts

Section 1.4 showed that the addition of organometallic reagents to pyridinium salts can provide access to interesting complex heterocyclic cores, though in a racemic fashion. Asymmetric organometallic additions to $N$-quaternized pyridines could therefore provide routes to enantio-pure biologically relevant molecules. One approach could involve the use of stoichiometric chiral chloroformate quaternization agents. For example, Comins has shown that excellent diastereo-selective additions occur using simple chiral cyclohexyl chloroformates in Grignard additions to 4-methoxy-pyridines (Scheme 1.27). Optimized conditions showed that a TIPS ($\text{Si}(\text{iPr})_3$) blocking group at position C-3, and $\text{trans-}$-$\alpha$-cumyl-cyclohexanols as the chiral auxiliaries are necessary for good selectivities with a variety of Grignard reagents (e.g. alkyl-, aryl-, vinyl-, and
alkynyl-magnesiums). While the original reaction used only Grignard reagents as the nucleophile, other organometallic compounds were also found to be selective, efficient coupling partners (i.e. organo-cuprates or organo-zincs).

Scheme 1.27 Diastereoselective Grignard addition to 3-TIPS-4-methoxy-pyridine using chiral cyclohexyl chloroformates

A detailed investigation of this system revealed that the face-selective addition was most likely due to a π-stack complex between the charged pyridinium and the phenyl of the cumyl group on the auxiliary. This effectively blocks one face of the pyridinium salt, allowing for selective addition on the opposite face. It was also found that the chloroformate derived from trans-α-cumyl-cyclohexanol (TCC) was the simplest to prepare and resolve, and has since been the auxiliary of choice for this reaction. The combined asymmetric control of the addition, and straightforward manipulations of the products (Scheme 1.23), has since allowed for the enantio-pure synthesis of a variety of alkaloids and bio-active products (Scheme 1.28). This convergent strategy is now commonly referred to as the “Comins Protocol”, and remains an important route to heterocyclic structures.
Recently, the Charette group has reported that amides in the presence of trifluoromethane-sulfonic acid, can activate pyridine towards an α-selective reaction with a variety of organometallic reagents. This reaction proceeds via the stereoselective formation of \( (E) \)-imidate pyridinium salts (Scheme 1.29). Grignard additions to this interesting new pyridinium species gave almost exclusive 1,2-addition even when mixed cuprates were used. This unprecedented highly α-selective organometallic addition is presumed to arise from a chelation assisted attack of the nucleophile due to the strong interaction of the metal with the imidate nitrogen lone pair. Aromatic 2-substituted
Pyridines were also prepared via this site-selective method after treating the purified products with either DDQ or a mixture of Mn(OAc) and H2IO6.

Scheme 1.29 Regioselective organometallic 1,2-addition to unsubstituted N-imidate pyridinium salts

Considering the large chiral pool of amides available, this site-selective addition can also be performed with asymmetric induction. In particular, the use of a chiral (E)-imidate derived from (S)-Valinol leads to excellent regio- and diastereo-control. This method has since been used by Charette to prepare synthetic drug candidates and other interesting heterocyclic cores using organometallic additions (Scheme 1.30). The straightforward preparation of the chiral activator auxiliary, and the high selectivities observed even when ring-unsubstituted pyridinium salts are used, makes this a very attractive approach.
Scheme 1.30 Asymmetric organometallic reagent addition to N-imidate pyridinium salts and application to the chiral synthesis of interesting heterocycles

A number of other related chiral auxiliary approaches have been reported for asymmetric additions to pyridinium salts. These include the use of N-pyridinium ylides, a bicyclic chiral acid chloride, or chiral primary amines in the Zincke reaction (Scheme 1.31). Other examples of asymmetric control in these types of reactions employ pyridines containing a chiral auxiliary at C-3 of the ring. Common chiral inducing groups include oxazolines, thiocarbonyls, nicotinic amides, and aminals (Scheme 1.31).
Other chiral N-quaternization examples:

- N-pyridinium ylides
- Chiral Zincke salts
- Wanner's chiral acid chloride

Pyridine ring C-3 chiral auxiliary examples:

- Thiocarbonyls
- Oxazolines
- Aminals

Nicotinic amides

Scheme 1.31  Examples of other chiral pyridines and quaternized pyridines for asymmetric additions to pyridinium salts

These chiral auxiliary approaches are effective, although they do show certain scope limitations, and of course require the use of a stoichiometric amount of the auxiliary, which is subsequently removed. While a catalytic enantioselective approach to pyridinium salt addition would be more efficient, only recently have these been reported. Examples most commonly involve additions to related quinoline and isoquinolinium salts, including the catalytic asymmetric addition of organolithium reagents,\textsuperscript{78} nitriles\textsuperscript{30,79} (Scheme 1.8), silyl-ketene acetics,\textsuperscript{80} and a copper-catalyzed alkynylation\textsuperscript{81} (Scheme 1.32). Thus far, however, there is only the one known catalytic enantioselective addition
to a pyridinium salt involving the lewis-acid and lewis-base bi-functional catalyzed cyanide addition previously mentioned in this chapter (Scheme 1.9).31

**Asymmetric Organo-lithium addition to quinolinium salts catalyzed by (-)-sparteine:**

![Chemical structure](image)

**Enantioselective thiourea-catalyzed acyl manich reaction of isoquinoline:**

![Chemical structure](image)

**Copper-catalyzed enantioselective alkyne addition to an isoquinolinium salt:**

![Chemical structure](image)

**Scheme 1.32** Examples of catalytic enantioselective additions to salts of quinoline and isoquinoline
1.7 Conclusion and Overview of Thesis

This chapter has illustrated that the addition of nucleophiles to pyridinium salts can be a powerful synthetic strategy for heterocycle synthesis. The robust nature of this chemistry in terms of the quaternization agent (or method), pyridines employed, broad nucleophile choice, and subsequent transformations possible, have all made this an important method to prepare complex natural products and bio-active compounds. However, while stoichiometric organometallic reagents are perhaps the most common nucleophiles employed in these types of reactions, they are not always compatible with common functional groups. For example, Grignard reagents are capable of transferring a number of organic units but are not compatible with alcohol or aldehyde containing pyridinium salts.\textsuperscript{11a}

One alternative to the use of strong stoichiometric organometallic reagents would be to use mild, metal catalyzed addition routes. While catalytic addition of copper salts with organometallic reagents, such as Grignards and organo-zincs, in pyridinium salt additions allows for preferential 1,4-regio-control, these still rely on using a stoichiometric amount of reactive organometallic compound limiting compatibility. The Arndtsen lab has previously developed mild, and general, copper-catalyzed addition routes to highly functionalized $\alpha$-substituted amides. These reactions involve the coupling of simple organic (e.g. terminal alkynes\textsuperscript{82}), or mild organometallic (e.g. organostannane\textsuperscript{83} or organoindium\textsuperscript{84}) nucleophiles with reactive $N$-acyl iminium salts in the presence of a simple copper(I) salt catalyst (Scheme 1.33).

\begin{center}
\includegraphics[width=\textwidth]{Scheme1.33.png}
\end{center}

**Scheme 1.33** Arndtsen lab copper-catalyzed one-pot multicomponent routes to highly functionalized $\alpha$-substituted amides
These reactions possess good functional group compatibility and give high yields of product under mild conditions without the need to use strong stoichiometric organometallic reagents. Considering that aromatic azine heterocycles such as pyridine contain an unsaturated imine C=N unit, this thesis will attempt to develop similar mild, and simple, copper-catalyzed methods of pyridine functionalization via easily prepared $N$-acyl pyridinium salts.

1.8 References

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CHAPTER 2
Development of a Copper-Catalyzed Coupling of Pyridines, Alkynes, and Chloroformates

2.0 Preface

A copper-catalyzed method to couple terminal alkynes with pyridines in the presence of an acid chloride (or chloroformate) is described. The reaction is extremely efficient and regioselective, generating the partially reduced $N$-acyl-2-ethynyl-1,2-dihydropyridine products in ~20 minutes at room temperature. This work is the foundation for the future development for the synthesis of aromatic pyridine derivatives in Chapter 3, as well as successful application to the asymmetric preparation of enantio-enriched dihydropyridine (and dihydroquinoline) products.

2.1 Introduction

Partially reduced dihydropyridine derivatives are useful intermediate structures for a variety of transformations, including the formation of piperidines, pyridines, and complex natural products. Perhaps the most common route to prepare these compounds is by nucleophilic addition to $N$-activated pyridinium salts. While a range of stoichiometric organic and organometallic nucleophiles can be employed in these reactions, problems in functional group compatibility and regioselectivity of the addition can occur. Metal-catalyzed addition reactions can provide attractive alternatives to the use of stoichiometric nucleophiles in coupling reactions with electrophiles, especially in terms of reaction scope and the potential for enantio-control. Currently, however, there exist only a few examples of metal catalyzed additions to quaternary pyridinium salts. These include the lewis-acid/lewis-base bi-functional catalyzed enantioselective cyanide addition, and the iridium or copper-catalyzed addition of alkynes.

Recently, we have reported that the addition of acid chlorides (or chloroformates) to imines can activate these substrates towards metal catalyzed coupling
reactions with a range of substrates (e.g. organostannanes, organoindium reagents, or terminal alkynes) as a versatile route to synthesize functionalized α-substituted amides. In light of the resonance structure similarity between imines and nitrogen-containing heterocycles such as pyridine, we became intrigued with the potential that pyridine itself might participate in similar coupling reactions (Figure 2.1). Described below are our studies towards the design of a copper-catalyzed method to couple pyridine derivatives with chloroformates and alkynes as a mild, and general route to cyclic propargylcarbamates and other functionalized heterocycles.

![Figure 2.1 Imines and pyridine in catalytic carbon-carbon bond formation](image)

### 2.2 Results and Discussion

Preliminary screening from our initial communication showed that pyridine undergoes a clean copper catalyzed coupling with phenylacetylene and benzoyl chloride to generate 2.1 in good yield (Table 2.1). While effective, attempts to couple other terminal alkynes with pyridine in the presence of benzoyl chloride resulted in very poor yields (entry 1b). Low yields were also observed with other metal salts as catalysts (entries 1c, 1d). Considering the electrophilicity of chloroformates, we examined the possibility that they might both interact strongly with pyridine, as well as similarly activate the heterocycle towards reaction. As shown in entries 1g-h, a number of common nitrogen protecting group reagents (Troc-Cl, Fmoc-Cl) can also participate in the coupling, providing access in this case to N-protected cyclic amines. Notably, this reaction is extremely rapid (20 minutes at ambient temperature), forms exclusively the 1,2-addition product, and employs only simple alkynes as the carbon-carbon bond
forming partner with pyridine. In addition, these chloroformates are compatible with coupling a number of functionalized alkynes (entries 1i–l).

Table 2.1. Copper-catalyzed coupling of pyridines, chloroformates and alkynes

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cat.</th>
<th>R₁</th>
<th>R₂</th>
<th>Yield 2.1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>CuI</td>
<td>Ph</td>
<td>Ph</td>
<td>73%</td>
</tr>
<tr>
<td>1b</td>
<td>CuI</td>
<td>Ph</td>
<td>n-C₄H₉</td>
<td>33% b</td>
</tr>
<tr>
<td>1c</td>
<td>CuOTf</td>
<td>Ph</td>
<td>Ph</td>
<td>31%</td>
</tr>
<tr>
<td>1d</td>
<td>Zn(OTf)₂</td>
<td>Ph</td>
<td>Ph</td>
<td>-</td>
</tr>
<tr>
<td>1e</td>
<td>CuI</td>
<td>OEt</td>
<td>Ph</td>
<td>82%</td>
</tr>
<tr>
<td>1f</td>
<td>CuI</td>
<td>OCH₂CHCl₂</td>
<td>Ph</td>
<td>88% b</td>
</tr>
<tr>
<td>1g</td>
<td>CuI</td>
<td>OPh</td>
<td>Ph</td>
<td>84%</td>
</tr>
<tr>
<td>1h</td>
<td>CuI</td>
<td>(9-fluorenyl)CH₂O</td>
<td>Ph</td>
<td>62%</td>
</tr>
<tr>
<td>1i</td>
<td>CuI</td>
<td>OEt</td>
<td>n-C₄H₉</td>
<td>83%</td>
</tr>
<tr>
<td>1j</td>
<td>CuI</td>
<td>OEt</td>
<td>TMS</td>
<td>72%</td>
</tr>
<tr>
<td>1k</td>
<td>CuI</td>
<td>OPh</td>
<td>CH₂Cl</td>
<td>64%</td>
</tr>
<tr>
<td>1l</td>
<td>CuI</td>
<td>OPh</td>
<td>CO₂Et</td>
<td>78%</td>
</tr>
</tbody>
</table>

a) Typical experimental procedure: 0.5 mmole pyridine, 0.6 mmole acid chloride, 0.5 mmole alkyne, combined with ~2 mL CH₃CN in the glove box, added to a mixture of 0.05 mmole catalyst and 0.7 mmole iPr₂NEt in ~1 mL CH₃CN and the solution stirred at rm. temp. for 20 mins. b) NMR yields. c) Cu(OTf) benzene complex used.

A potential mechanism of this multicomponent reaction involves the reaction between in situ generated copper-acetylide and pyridinium salt (Scheme 2.1). The observed regioselectivity of this reaction is in contrast with copper mediated Grignard additions to pyridinium salts, which instead favor the opposite 1,4 addition product,⁶ and is selective relative to many related additions to pyridinium salts, which often lead to 1,2- and 1,4-product mixtures.¹ Considering the formation of a coordinatively unsaturated and sterically unencumbered copper-acetylide, coordination to the amide (or carbamate) carbonyl of the pyridinium salt may direct the ortho-addition, in a similar manner to what has been observed by the Charrette group in mixed cuprate Grignard additions to N-imidate pyridinium salts.⁷ It’s interesting to note that the stoichiometric addition of other
metal acetylides (e.g. magnesium-\(^8\), silver-\(^9\), and tin-acetylides\(^{10}\)) to N-acyl pyridinium salts also result in preferential (or exclusive) 1,2-addition products.

**Scheme 2.1** Proposed mechanism for the copper catalyzed addition of terminal alkynes to pyridine

A number of functionalized pyridines were tested in this reaction. As shown in Table 2.2, the coupling is relatively general, and is compatible with halogen, alkyl, aryl\(^{11}\) and even sensitive aldehyde functionalized pyridines. The latter typically need to be protected in related organometallic additions to prevent carbonyl addition\(^{10,12}\). The reactions remained highly ortho-selective, although regio-isomeric mixtures of the two possible ortho-addition products were obtained for entries 2a and 2b. In the case of entry 2b, it’s likely that the presence of the aldehyde in the 3-position helps direct the addition to the more sterically encumbered 2-position, resulting in a 1:1 mixture of the 1,2- and 1,6- addition products.\(^{13}\) More curious is the preferential addition to the more sterically hindered 2-position of 3-picoline (entry 2a). The literature does show that this interesting regioselectivity is typical for this substrate in related additions.\(^{14}\)
Table 2.2 Copper-catalyzed multicomponent coupling of pyridines, chloroformates and alkynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Pyridine</th>
<th>R₁</th>
<th>Product</th>
<th>Yield 2.1 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2a</td>
<td></td>
<td>OPh</td>
<td><img src="image1.png" alt="Image" /></td>
<td>78ᵇ (3:1)</td>
</tr>
<tr>
<td>2b</td>
<td></td>
<td>OPh</td>
<td><img src="image2.png" alt="Image" /></td>
<td>78ᵇ (55:45)</td>
</tr>
<tr>
<td>2c</td>
<td></td>
<td>OPh</td>
<td><img src="image3.png" alt="Image" /></td>
<td>84</td>
</tr>
<tr>
<td>2d</td>
<td></td>
<td>OCHCICH₃</td>
<td><img src="image4.png" alt="Image" /></td>
<td>62</td>
</tr>
<tr>
<td>2e</td>
<td></td>
<td>OPh</td>
<td><img src="image5.png" alt="Image" /></td>
<td>70</td>
</tr>
<tr>
<td>2f</td>
<td></td>
<td>OPh</td>
<td><img src="image6.png" alt="Image" /></td>
<td>67ᶜ</td>
</tr>
<tr>
<td>2g</td>
<td></td>
<td>OPh</td>
<td><img src="image7.png" alt="Image" /></td>
<td>54ᶜ</td>
</tr>
</tbody>
</table>

a) Typical experimental procedure: 0.5 mmole pyridine, 0.6 mmole chloroformate, 0.5 mmole alkyne, combined in ~2 mL CH₃CN in the glove box then added to a stirring vial of 0.05 mmole CuI and 0.7 mmole iPr₂NEt in ~1 mL CH₃CN and the solution stirred at rm. temp. for 20 mins. b) combined yield of both regioisomers (ratio of 2,3 : 2,5 products from ¹H NMR of the crude rxn mixture). c) reaction heated for 1 hr at 45°C.
It can be seen in Table 2.2 that attempts to couple 2-substituted pyridines failed (entries 2f, g). This trend is typical of these substrates, since the increased steric hindrance of these substituents inhibits pyridinium salt formation. Instead, these reactions led to the formation of a Hoffmann elimination product, resulting from the interaction of Hunigs base (iPr$_2$NEt) with phenyl chloroformate (Scheme 2.2).

\[
\begin{align*}
\text{Scheme 2.2} & \quad \text{Hoffman elimination of Hunig's base with phenyl chloroformate} \\
\end{align*}
\]

Importantly, this catalytic approach to heterocycle alkynylation is not limited to pyridines, and other nitrogen containing heterocycles can be similarly functionalized (Table 2.3). For example, quinoline reacts smoothly under these conditions (entries 3a and 3b), as do the biologically relevant pyrimidine and pyrazine di-nitrogen heterocycles. In these latter cases, two equivalents of chloroformate, alkyne, and base are needed for efficient coupling (entries 3c-d). Functionalization of these substrates is typically difficult using related N-acyl quaternization procedures, and represents interesting new products.
Table 2.3. Copper-catalyzed multicomponent coupling of $N$-Heterocycles, acid chlorides and alkynes$^a$

![Chemical reaction diagram](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Heterocycle</th>
<th>$R_1$</th>
<th>$R_2$</th>
<th>Product</th>
<th>%Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>![image]</td>
<td>Et</td>
<td>CO$_2$Et</td>
<td>![image]</td>
<td>75</td>
</tr>
<tr>
<td>3b</td>
<td>![image]</td>
<td>Ph</td>
<td>Ph</td>
<td>![image]</td>
<td>75</td>
</tr>
<tr>
<td>3c</td>
<td>![image]</td>
<td>OPh</td>
<td>Ph</td>
<td>![image]</td>
<td>79$^b$</td>
</tr>
<tr>
<td>3d</td>
<td>![image]</td>
<td>OPh</td>
<td>Ph</td>
<td>![image]</td>
<td>54$^{b,c}$</td>
</tr>
</tbody>
</table>

a) Typical experimental procedure: 0.5 mmole heterocycle, 0.6 mmole acyl chloride, 0.5 mmole alkyne, combined with ~2 mL CH$_3$CN in the glove box, added to a mixture of 0.05 mmole catalyst and 0.7 mmole $i$Pr$_2$NEt in ~1 mL CH$_3$CN and the solution stirred at rm. temp. for 20 min. b) 2eq. chloroformate, alkyne, and 2.8 eq. $i$Pr$_2$NEt used. c) combined yield of addition products.

2.3 Conclusion

In summary, a mild and regioselective copper (I) catalyzed method of coupling alkynes with pyridines in the presence of chloroformates (or acid chlorides) has been developed. This methodology can be extended to the alpha functionalization of other $N$-containing heterocycles. The products of this coupling, $N$-acyl-2-ethynyl-1,2-dihydropyridines, can be useful intermediates, and an enantioselective variant of this reaction was subsequently developed in our laboratory.$^{18}$
2.4 Experimental

**General Procedures:**

All manipulations were performed under an inert atmosphere in a Vacuum Atmospheres 553-2 dry box. 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. Deuterated DMSO and chloroform were dried over 3 Å molecular sieves.

$^1$H and $^{13}$C NMR spectra were recorded on Varian Mercury 300 MHz, Mercury 400 MHz, Unity 500MHz, and JEOL 270 MHz spectrometers. 2D COSY spectra were recorded on a Varian Mercury 300MHz spectrometer, 2D HMQC, HMBC and 1D NOESY experiments were recorded on a Varian Mercury 400 MHz spectrometer. Mass spectra were obtained from the McGill University mass spectral facilities.

**Typical Procedure for the Synthesis of Cyclic-Propargylcarbamates:**

Pyridine (40 mg, 0.5 mmol), ethyl chloroformate (61 mg, 0.62 mmol) and phenylacetylene (50 mg, 0.5 mmol) were mixed in ~2 mL of acetonitrile and added to a vial of stirring CuI (9 mg, 0.05 mmol) and $i$Pr$_2$NEt (105 μL, 0.7 mmol) in ~1 mL of acetonitrile in the glove box. The reaction mixture was stirred at ambient temperature for 20 minutes then removed from the box and solvent removed by rotary evaporation. The crude residue was dissolved in CH$_2$Cl$_2$ and the product isolated by column chromatography using ethyl acetate/hexanes as eluent (5, 10, or 20% EtOAc:Hexanes; R$_f$’s ~ 0.5-0.8 in 20% EtOAc:Hex). All compounds were characterized by $^1$H and $^{13}$C NMR and HRMS. Compound 1a has been previously reported.$^{3c}$ Regioselectivities for compounds 2a and 2b were determined by 1D NOESY and 2D $^1$H-$^{13}$C HMQC.$^{19}$
Spectroscopic Data:

*N-phenacyl-2-phenylethynyl-1,2-dihydropyridine (Table 2.1, entry 1a)* Isolated
Yield: 73 %. $^1$H NMR (300 MHz, 60 °C, CDCl$_3$): $\delta$ 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$_3$): $\delta$ 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 (M+H) for C$_{20}$H$_{15}$NO, calculated: 285.1154, found: 285.1149.

**ethyl 2-(phenylethynyl)pyridine-1(2H)-carboxylate (Table 2.1, entry 1e)** Isolated
Yield: 82 %. $^1$H NMR (300 MHz, 60 °C, CDCl$_3$): d 7.32-7.41 (m, 2H), 7.21-7.28 (m, 3H), 6.8 (d, 1H), 6.0 (m, 1H), 5.79 (d, 1H), 5.65 (t, 1H), 5.36 (t, 1H), 4.32 (q, 2H), 1.37 (t, 3H). $^{13}$C NMR (67.9 MHz, 60 °C, CDCl$_3$): d 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 (M+H) for C$_{16}$H$_{15}$NO$_2$, calculated: 254.1183, found: 254.1176.

**phenyl 2-(phenylethynyl)pyridine-1(2H)-carboxylate (Table 2.1, entry 1g)** Isolated
Yield: 84 %. $^1$H NMR (500 MHz, 60 °C, CDCl$_3$): d 7.38-7.44 (m, 4H), 7.21-7.3 (m, 6H), 6.94 (s, 1H), 6.09 (q, 1H), 5.96 (s, 1H), 5.76 (s, 1H), 5.45 (t, 1H). $^{13}$C NMR (500 MHz, 60 °C, CDCl$_3$): d 151.3, 132.1, 129.5, 128.4, 125.9, 125.0, 122.9, 122.4, 121.7, 121.0, 119.4, 106.5, 86.5, 83.7, 44.8. HRMS (M+Na) for C$_{20}$H$_{15}$NO$_2$, calculated: 324.1003, found: 324.0994.

**(9H-fluoren-9-yl)methyl 2-(phenylethynyl)pyridine-1(2H)-carboxylate (Table 2.1, entry 1h)** Isolated
Yield: 62 %. $^1$H NMR (300 MHz, 60 °C, CDCl$_3$): d 7.61-7.79 (m, 4H), 7.22-7.43 (m, 9H), 6.79-6.83 (br, 1H), 6.0-6.08 (q, 1H), 5.78-5.83 (br, 1H), 5.63-5.72 (t, 1H), 5.39-5.45 (t, 1H), 4.43-4.62 (br, 2H), 4.27-4.38 (t, 1H). $^{13}$C NMR (68.0 MHz, 60 °C, CDCl$_3$): d 155.2, 143.8, 141.4, 132.0, 128.1, 127.8, 127.2, 122.7, 120.0, 105.8, 86.6, 83.5, 70.0, 68.7, 47.3, 44.4. HRMS (M+H) for C$_{28}$H$_{21}$NO$_2$, calculated: 404.1652, found: 404.1646.
ethyl 2-(hex-1-ynyl)pyridine-1(2H)-carboxylate (Table 2.1, entry 1i) Isolated Yield: 83 %. $^1$H NMR (300 MHz, 60 °C, CDCl$_3$): $d$ 6.72-6.77 (d, 1H), 5.87-5.95 (q, 1H), 5.49-5.58 (br, m, 2H), 5.25-5.33 (t, 1H), 4.21-4.34 (q, 2H), 2.12-2.19 (t, 2H), 1.27-1.48 (m, 5H), 0.82-0.94 (t, 3H). $^{13}$C NMR (75.5 MHz, 60 °C, CDCl$_3$): $d$ 125.3, 121.7, 119.7, 105.1, 83.9, 77.9, 62.5, 44.0, 30.8, 21.9, 18.6, 14.5, 13.5. HRMS (M+Na) for C$_{14}$H$_{19}$NO$_2$, calculated: 256.1316, found: 256.1306.

2-Trimethylsilanylethynyl-2H-pyridine-1-carboxylic acid ethyl ester (Table 2.1, entry 1j) Isolated Yield: 72 %. $^1$H NMR (400 MHz, 60 °C, CDCl$_3$): $d$ 6.71-6.78 (d, 1H), 5.87-5.96 (q, 1H), 5.52-5.59 (br, 2H), 5.27-5.34 (t, 1H), 4.21-4.36 (m, 2H), 1.31-1.38 (t, 3H), 0.18 (s, 9H). $^{13}$C NMR (68.0 MHz, 60 °C, CDCl$_3$): $d$ 153.8, 125.3, 122.3, 118.9, 105.1, 103.0, 87.8, 62.6, 44.5, 14.6, -0.003. HRMS (M+H) for C$_{13}$H$_{19}$NO$_2$Si, calculated: 250.1265, found: 250.1258.

2-(3-Chloro-prop-1-ynyl)-2H-pyridine-1-carboxylic acid phenyl ester (Table 2.1, entry 1k) Isolated Yield: 64 %. $^1$H NMR (500 MHz, 60 °C, CDCl$_3$): $d$ 7.35-7.41 (m, 2H), 7.16-7.25 (m, 3H), 6.83-6.89 (br, 1H), 6.01-6.09 (q, 1H), 5.72-5.78 (br, 1H), 5.61-5.68 (br, 1H), 5.41-5.45 (t,1H), 4.15-4.18 (s, 2H). $^{13}$C NMR (68.0 MHz, 60 °C, CDCl$_3$): $d$ 151.2, 129.5, 129.0, 125.0, 122.7, 121.6, 118.6, 106.3, 83.7, 78.5, 44.4, 30.3. HRMS (M+Na) for C$_{15}$H$_{12}$ClNO$_2$, calculated: 296.0450, found: 296.0449.

phenyl 2-(3-ethoxy-3-oxoprop-1-ynyl)pyridine-1(2H)-carboxylate (Table 2.1, entry 1l) Isolated Yield: 78 %. $^1$H NMR (300 MHz, 60 °C, CDCl$_3$): $d$ 7.33-7.42 (m, 2H), 7.19-7.29 (m, 3H), 6.86-6.93 (d, 1H), 6.06-6.13 (q, 1H), 5.81-5.87 (d, 1H), 5.59-5.67 (m, 1H), 5.41-5.48 (t, 1H), 4.20-4.25 (q, 2H), 1.22-1.35 (t, 3H). $^{13}$C NMR (68.0 MHz, 60 °C, CDCl$_3$): $d$ 153.3, 151.0, 129.6, 126.1, 121.6, 117.0, 106.4, 83.7, 75.5, 62.2, 44.0, 14.1. HRMS (M+H) for C$_{17}$H$_{15}$NO$_4$, calculated: 298.1081, found: 298.1074.

phenyl 3-methyl-2-(phenylethynyl)pyridine-1(2H)-carboxylate (Table 2.2, entry 2a) Isolated Yield: 78 % of a 3:1 mixture of 2,3:2,5 regioisomers. $^1$H NMR (300 MHz, 60 °C, CDCl$_3$): $d$ 7.7.34-7.47 (m, 5H), 7.19-7.33 (m, 10H), 6.80-6.84 (d, 1H, major 2,3 isomer),
6.69-6.73 (br, 0.3H, minor 2,5 isomer), 5.96-6.01 (br, d, 0.6H, minor 2,5 isomer), 5.77-5.83 (br, d, 1H, major 2,3 isomer), 5.67-5.73 (s, 1H, major 2,3 isomer), 5.42-5.48 (t, 1H, major 2,3 isomer), 2.00 (s, 3H, major 2,3 isomer), 1.86 (s, 1H, minor 2,5 isomer). 13C NMR (67.9 MHz, 60 °C, CDCl₃): δ 151.9 (minor), 151.2 (major), 132.0, 129.3, 128.3, 128.2, 126.2, 125.7, 121.6, 120.8, 117.8, 115.7, 106.9, 85.9, 83.6, 49.3 (major), 49.1 (minor), 20.2 (major), 17.7 (minor). HRMS (M+Na) for C₂₁H₁₇NO₂, calculated: 338.1159, found: 338.1154.

phenyl 3-formyl-2-(phenylethynyl)pyridine-1(2H)-carboxylate (Table 2.2, entry 2b)
Isolated Yield: 40%. ¹H NMR (400MHz, CDCl₃): δ 9.56 (s, 1H), 7.45-7.18 (m, 10H), 6.95-6.98 (d, 1H), 6.44 (s, 1H), 5.78-5.73 (t, 1H). ¹³C NMR (67.9 MHz, 60 °C, CDCl₃): δ 188.1, 150.8, 139.2, 132.8, 132.0, 130.0, 129.7, 129.5, 128.9, 128.6, 128.2, 126.2, 121.3, 105.1, 85.2, 83.9, 42.6. HRMS (M+Na) for C₂₀H₁₄NO₃, calculated: 352.0952, found: 352.0939.

phenyl 5-formyl-2-(phenylethynyl)pyridine-1(2H)-carboxylate (Table 2.2, entry 2b)
Isolated Yield: 38%. ¹H NMR (300MHz, CDCl₃): δ 9.39 (s, 1H), 7.45-7.20 (m, 10H), 6.63-6.58 (d, 1H), 6.01-5.97 (d, 1H), 5.87-5.79 (q, 1H). ¹³C NMR (67.9 MHz, 60 °C, CDCl₃): δ 187.0, 150.7, 141.1, 132.0, 131.8, 129.7, 128.9, 128.3, 128.1, 126.5, 122.3, 121.2, 119.8, 117.6, 85.4, 71.9, 47.1. HRMS (M+Na) for C₂₀H₁₄NO₃, calculated: 352.0952, found: 352.0939.

phenyl 5-bromo-2-(phenylethynyl)pyridine-1(2H)-carboxylate) (Table 2.2, entry 2c)
Isolated Yield: 84%. ¹H NMR (500 MHz, 60 °C, CDCl₃): δ 7.19-7.49 (m, 10H), 6.98-7.02 (d, 1H), 6.38-6.41 (d, 1H), 6.03 (s, 1H), 5.39-5.43 (t, 1H). ¹³C NMR (67.9 MHz, 60 °C, CDCl₃): δ 150.9, 132.1, 129.4, 128.7, 128.2, 126.2, 126.0, 124.7, 122.3, 121.4, 120.9, 111.7, 106.2, 84.8, 84.1, 52.2. HRMS (M+Na) for C₂₀H₁₄BrNO₂, calculated: 402.0108, found: 402.0102.

N-1-chloro-ethyl-4-t-butyl-2(phenylethynyl)pyridine-1(2H)-carboxylate (Table 2.2, entry 2d) Isolated Yield: 62%. ¹H NMR (300 MHz, CDCl₃): δ 7.43-7.25 (m, 5H), 6.80-
6.64 (br, 2H), 5.77-5.72 (br, d, 1H), 5.58-5.49 (br, t, 1H), 5.46-5.42 (br, 1H), 1.89-1.84 (d, 3H), 1.13 (s, 9H). $^{13}$C NMR (67.9 MHz, 60 °C, CDCl$_3$): d 154.9, 142.7, 131.9, 131.7, 128.6, 127.8, 123.0, 111.1, 107.5, 86.6, 83.3, 83.1, 44.9, 33.9, 28.6, 25.8. HRMS (M+Na) for C$_{20}$H$_{22}$NO$_2$Cl, calculated: 366.1239, found: 366.1231.

**phenyl 3,5-dimethyl-2-(phenylethynyl)pyridine-1(2H)-carboxylate (Table 2.2, entry 2e)** Isolated Yield: 70%. $^1$H NMR (500 MHz, 60 °C, CDCl$_3$): d 7.33-7.44 (m, 4H), 7.17-7.31 (m, 6H), 6.53-6.62 (br, 1H), 1.99 (s, 3H), 1.81 (s, 3H). $^{13}$C NMR (68.0 MHz, 60 °C, CDCl$_3$): d 151.3, 132.0, 129.5, 128.3, 126.2, 125.6, 122.9, 121.6, 120.8, 117.1, 115.6, 86.1, 83.2, 48.6, 20.0, 17.8. HRMS (M+H) for C$_{22}$H$_{19}$NO$_2$, calculated: 330.1496, found: 330.1490.

**phenyl ethyl(isopropyl)carbamate (Table 2.2, entry 2f)** Isolated Yield: 67%. $^1$H NMR (300 MHz, 60 °C, CD$_3$CN): d 7.42-7.39 (t, 2H), 7.25-7.21 (t, 1H), 7.16-7.12 (d, 2H), 4.37-4.25 (br, 1H), 3.39-3.26 (br, 2H), 1.34-1.18 (br, 9H). $^{13}$C NMR (68.0 MHz, 60 °C, CD$_3$CN): d 154.0, 152.1, 129.2, 129.1, 124.9, 121.9, 117.0, 116.8, 48.5, 38.0, 20.1, 14.9. HRMS (M+H) for C$_{12}$H$_{17}$NO$_2$, calculated: 208.1332, found: 208.1328.

**phenyl(2-(phenylethynyl)quinolin-1(2H)-yl)methanone (Table 2.3, entry 3a)** Isolated Yield: 75%. $^1$H NMR (300 MHz, 60 °C, CDCl$_3$): d 7.44-7.18 (m, 12H), 7.12-7.05 (t, 1H), 6.96-6.89 (t, 1H), 6.70-6.66 (d, 1H), 6.24-6.16 (m, 2H). $^{13}$C NMR (68.0 MHz, 60 °C, CDCl$_3$): d 169.7, 135.5, 135.3, 132.1, 130.9, 129.3, 128.6, 128.4, 128.3, 127.4, 127.2, 126.8, 126.5, 126.0, 125.9, 125.4, 122.7, 85.4, 84.0, 44.7. HRMS (M+H) for C$_{24}$H$_{17}$NO, calculated: 336.1320, found: 336.1380.

**Ethyl 2-(3-ethoxy-3-oxoprop-1-ynyl)quinoline-1(2H)-carboxylate (Table 2.3, entry 3b)** Isolated Yield: 75%. $^1$H NMR (200 MHz, CDCl$_3$): d 7.64 (d, 1H, J = 8.1 Hz), 7.24 (m, 1H), 7.13 (m, 2H), 6.58 (d, 1H, J = 9.0 Hz), 6.02 (d, 1H, J = 6.0 Hz), 5.98 (dd, 1H, J = 6.0 Hz, 3.0 Hz), 4.37-4.17 (m, 2H), 4.13 (dd, 2H, J = 7.2 Hz, 7.2 Hz), 1.32 (t, 3H, J = 7.2 Hz), 1.22 (t, 3H, J = 7.2 Hz), 1.32 (t, 3H, J = 7.2 Hz). $^{13}$C NMR (75.0 MHz, CDCl$_3$): d 153.9, 153.3, 134.2,
diphenyl 2-(phenylethynyl)pyrazine-1,4-dicarboxylate (Table 2.3, entry 3c) Isolated Yield: 79%. $^1$H NMR (300 MHz, 60 °C, CDCl$_3$): d 7.16-7.48 (m, 16H), 6.44-6.75 (br, m, 2H), 5.74 (s, 1H). $^{13}$C NMR (68.0 MHz, 60 °C, CDCl$_3$): d 150.9, 150.0, 132.1, 131.8, 129.5, 129.4, 129.2, 128.4, 126.3, 126.0, 121.4, 121.3, 108.8, 105.9, 106.1, 86.2, 81.8, 66.5, 51.1, 49.9. HRMS (M+H) for C$_{26}$H$_{18}$N$_2$O$_4$, calculated: 423.1347, found: 423.1333.

diphenyl 2,4-bis(phenylethynyl)pyrimidine-1,3(2H,4H)-dicarboxylate (Table 2.3, entry 3d) Isolated Yield: 54% of a 2:1 mixture of the bis-addition product (C$_{34}$H$_{24}$N$_2$O$_4$): mono-addition product (C$_{26}$H$_{20}$N$_2$O$_4$). $^1$H NMR (300 MHz, 60 °C, CDCl$_3$): d 7.60-7.03 (m, 33H), 5.79-5.72 (s, 1H, bis-add), 5.52-5.22 (m, br, 1H, bis-add), 4.72-4.51 (t, 0.5H, mono-add), 4.39-4.19 (br, 0.5H, mono-add). $^{13}$C NMR (67.9 MHz, 60 °C, CDCl$_3$): d 153.5 (mono), 152.7 (mono), 150.5 (bis), 150.1 (bis), 132.4, 132.2, 129.9, 129.8, 129.7, 129.6, 129.4, 128.9, 128.7, 128.5, 128.0, 126.4, 126.2, 123.2, 122.9, 122.6, 122.4, 122.1, 108.3 (bis), 105.2 (bis), 106.3 (mono), 85.9 (bis), 85.7 (mono), 84.1 (bis), 82.9 (mono), 54.4 (bis), 44.0 (mono), 43.1 (bis), 39.9 (mono). HRMS (M+Na) for C$_{34}$H$_{24}$N$_2$O$_4$, calculated: 547.1636, found: 547.1622. HRMS (M+Na) for C$_{26}$H$_{20}$N$_2$O$_4$, calculated: 447.1323, found: 447.1312.
$^1$H and $^{13}$C NMR Spectra:
X : parts per Million : 13C
HRMS supporting mixture of both structures:
2.4 References


11 The dihydropyridine resulting from addition of phenylacetylene to 4-phenyl-pyridine in the presence of a number of chloroformates was too unstable to fully characterize but is supported by the clean isolation of the corresponding aromatic 2-phenylethynyl-4-phenyl-pyridine in Chapter 3 of this thesis.


13 Ring carbonyl assisted attacks have been reported in some organometallic additions to pyridinium salts: Yamaguchi, R., Hata, E.-I., Utimoto, K.; *Tetrahedron Lett.* **1988**, *29*, 1785.


15 a) For an interesting recent report on the selective 4-addition of π-basic aromatic compounds to triflic anhydride activated salts of 2-cyano- and 2-bromo-pyridines see: Corey, E.J., Tian, Y.; *Org. Lett.* **2005**, *7*, 5535. b) For an example of an organoindium addition to an N-acyl salt of 2-cyano-pyridine see Chapter 4 of this thesis.

16 Attempts to circumvent this problem using other chloroformates or acid chlorides and a variety of other bases including K₃PO₄, Cs₂CO₃, DBU and DABCO failed.

17 The bis- addition products are also solely observed when only 1eq. of chloroformate and alkyne are used but in much lower yield.


19 Regioselectivities were also confirmed by the isolation and characterization of the corresponding aromatic alkynyl-pyridines in Chapter 3 of this thesis.
CHAPTER 3

A One-Pot Copper-Catalyzed Synthesis of Alkynyl Pyridines

3.0 Preface

A mild, efficient and regioselective copper-catalyzed method to couple terminal alkynes with pyridines in the presence of a chloroformate (or acid chloride) was developed in Chapter 2. By applying our reaction methodology from Chapter 2 in a tandem oxidation protocol, a one-pot copper-catalyzed method to access 2-alkynyl-pyridines has been developed, and is presented here in Chapter 3. This reaction has been used to synthesize a number of aromatic alkynyl pyridines directly from the parent heterocycles. In addition, alkenyl-pyridines were prepared via a related procedure.

3.1 Introduction

The pyridine core is found in a variety of natural products, ligands, dendrimers, polymers, and synthetic biologically-active compounds. For example, pyridine containing alkaloids have been found to exhibit potent cytotoxic, antimicrobial, and antiviral activities, while simple substituted pyridines can behave as antagonists of human metabotropic glutamate receptors (mGluR5), and cytotoxic agents to human cancer cells. Due to the broad utility of substituted pyridines, their construction remains a constantly active area of research. Currently, the most common approach to functionalize pyridines under mild conditions involves transition-metal catalyzed cross-coupling reactions with halogenated (or metallated) pyridines (e.g. Suzuki, Heck, Sonogashira, or Stille couplings), or more recently with pyridine N-oxides. The initial generation of the correctly positioned halogenated pyridine precursor (or N-oxide) prior to functionalization is required for this chemistry.

We have recently reported a regio-selective copper catalyzed alkynylation of pyridine in the presence of an acid chloride or chloroformate activator. This mild coupling was highly efficient, yielding the partially reduced pyridine derivatives in only ~ 20 minutes with a variety of terminal alkynes at ambient temperature (Scheme
Since dihydropyridines can serve as precursors to aromatic substituted pyridines, we considered the potential of applying this catalytic coupling to the development of a one-pot route to regioselectively access substituted aromatic pyridines. This would provide a straightforward method to directly derivatize the parent pyridine with simple alkynes. Our progress towards this goal is described below.

**Scheme 3.1** Copper-catalyzed multicomponent coupling of pyridines, acyl Chlorides and alkynes

### 3.2 Results and Discussion

Our initial efforts towards the synthesis of 3.2 (Table 3.1) probed the effect of treating the *in situ* generated 3.1 with various oxidants. As shown in entries 1a-e, no oxidized products were formed with oxygen or peroxide sources, or even with the known dihydropyridine oxidant, elemental sulfur. While these early attempts resulted in almost complete dihydropyridine recovery or decomposition, a moderate yield of 2-phenylalkynyl-pyridine 3.2 was obtained when the crude reaction mixture was treated with a stoichiometric amount of Cu(II)OTf (entry 1e).

In contrast to these results, treatment of the *in situ* generated 3.1 with DDQ (2,3-dichloro-5,6-dicyano-1,4-quinone), or the related quinone o-chloranil (3,4,5,6-tetrachloro-1,2-quinone), resulted in the high yield formation of 2-alkynyl pyridine 3.2 (Table 3.1, entries 1f, 1g). Interestingly, this copper mediated coupling/oxidation can also be performed in a single step, provided a stoichiometric amount of CuI is employed and the oxidant is added last to the reaction mixture (entry 1h). While this procedure is not as efficient as the copper-catalyzed route, it does provide a direct route to the substituted pyridine 3.2.
Towards a direct copper-catalyzed synthesis of 2-ethynyl-pyridines

(a) Typical experimental procedure: 0.5 mmole pyridine, 0.6 mmole chloroformate, 0.5 mmole alkyne in ~2 mL CH₃CN in the glove box added to 0.05 mmole CuI and 0.7 mmole iPr₂NEt in ~1 mL CH₃CN and the solution stirred for 20 mins, followed by oxidant. b) 1eq. CuI used, DDQ added last to the reaction pot after only brief (~30 secs) stirring.

A number of pyridines were found to undergo successful conversion to the 2-alkynyl-pyridines under these tandem copper-catalyzed alkyne coupling and DDQ oxidation conditions (Table 3.2). Aryl, alkyl, halogen, and even sensitive aldehyde functionalities are tolerated, leading to the formation of new alkynyl-pyridines not easily accessible through other routes (e.g. Sonagoshira coupling). A range of acid chlorides or chloroformates can be used in this reaction, though ethyl chloroformate generally gave the highest yields.

While exclusive α-alkyne substitution is observed for all aromatic products, regio-isomeric mixtures of the dihydropyridine intermediates were observed in entries 2f and 2g. However, in each case only one of the regioisomers was found to be reactive towards oxidation. In the case of entry 2f, the 2-alkynyl-3-picoline product isolated is an interesting regio-isomer of the highly selective human mGlu5 receptor antagonist MPEP.

Table 3.1  Towards a direct copper-catalyzed synthesis of 2-ethynyl-pyridines

<table>
<thead>
<tr>
<th>Entry</th>
<th>O</th>
<th>Time (hrs)</th>
<th>Temp. (°C)</th>
<th>Yield 3.2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>la</td>
<td>air</td>
<td>48</td>
<td>45</td>
<td>-</td>
</tr>
<tr>
<td>lb</td>
<td>O₂</td>
<td>46</td>
<td>rm. temp.</td>
<td>-</td>
</tr>
<tr>
<td>lc</td>
<td>H₂O₂</td>
<td>16</td>
<td>65</td>
<td>-</td>
</tr>
<tr>
<td>ld</td>
<td>S₈</td>
<td>40</td>
<td>45</td>
<td>-</td>
</tr>
<tr>
<td>le</td>
<td>Cu(OTf)₂</td>
<td>16</td>
<td>65</td>
<td>33</td>
</tr>
<tr>
<td>lf</td>
<td>DDQ</td>
<td>1</td>
<td>45</td>
<td>81</td>
</tr>
<tr>
<td>lg</td>
<td>o-chloranil</td>
<td>1</td>
<td>45</td>
<td>83</td>
</tr>
<tr>
<td>lh</td>
<td>DDQ</td>
<td>16</td>
<td>45</td>
<td>81&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

1) 1.4eq. iPr₂NEt; 10% CuI CH₃CN 20 min RT
2) [O] conditions

N O ClEtO Ph

1) 4.4e, iPr₂N; 10% CuI CH₃CN 20 min RT
2) [O] conditions

Entry [O] Time (hrs) Temp. (°C) Yield 3.2 (%)
Table 3.2 One pot tandem alkyne coupling and oxidation route to 2-ethynyl pyridines

\[
\text{Pyridine} + \text{Acid Chloride} + \text{Alkyne} \rightarrow \text{2-ethynyl Pyridine}
\]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Heterocycle</th>
<th>R₁</th>
<th>R₂</th>
<th>Product</th>
<th>% Yield</th>
</tr>
</thead>
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<tr>
<td>2a</td>
<td>N</td>
<td>Ph</td>
<td>Ph</td>
<td>![Image]</td>
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</tr>
<tr>
<td>2b</td>
<td>N</td>
<td>Troc</td>
<td>Ph</td>
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<tr>
<td>2c</td>
<td>N</td>
<td>OPh</td>
<td>Ph</td>
<td>![Image]</td>
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<td>OPh</td>
<td>CO₂Et</td>
<td>![Image]</td>
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<tr>
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<td>Ph</td>
<td>![Image]</td>
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<td>2f</td>
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<td>OEt</td>
<td>Ph</td>
<td>![Image]</td>
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</tr>
<tr>
<td>2g</td>
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</tr>
<tr>
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<td>O</td>
<td>OEt</td>
<td>Ph</td>
<td>![Image]</td>
<td>39</td>
</tr>
<tr>
<td>2i</td>
<td>Ph</td>
<td>OEt</td>
<td>Ph</td>
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</tr>
<tr>
<td>2j</td>
<td>O</td>
<td>OEt</td>
<td>Ph</td>
<td>![Image]</td>
<td>40</td>
</tr>
</tbody>
</table>

(a) Typical experimental procedure: 0.5 mmole pyridine, 0.6 mmole acid chloride, 0.5 mmole alkyne in ~2 mL CH₃CN in the glove box added to 0.05 mmole CuI and 0.7 mmole iPr₂NEt in ~1 mL CH₃CN and the solution stirred for 20 min, exposed to air and 1 eq. DDQ added and the reaction flask placed in a 45°C bath for 1 hr.
In addition to alkynylated pyridines, this approach can also provide access to 2-alkenyl pyridine derivatives. While probing the potential use of bases to deprotect the propargylcarbamate intermediates and facilitate oxidation, it was found that treatment of crude in situ generated 3.1 with base and overnight heating yielded the alkenyl pyridine products 3.3. Our preliminary results show this rearrangement to be base dependant (Table 3.3, entries 3a-f). Use of K$_2$CO$_3$ in methanol provided the highest overall conversion, though in a 1:1 E/Z mixture (entry 3f). Use of KO$_t$Bu did give exclusive formation of the trans-isomer in very poor yield (entry 3d), however, when the more hindered base DABCO is used the more hindered cis-isomer is the only product isolated in moderate yield (entry 3e).

**Table 3.3** A base mediated synthesis of 2-phenyl-alkenyl-pyridines$^a$

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>R$_1$</th>
<th>BASE</th>
<th>%Yield$^b$ (E:Z)$^c$</th>
</tr>
</thead>
<tbody>
<tr>
<td>3a</td>
<td>H</td>
<td>Ph</td>
<td>Pyridine (5eq.)</td>
<td>-</td>
</tr>
<tr>
<td>3b</td>
<td>H</td>
<td>Ph</td>
<td>iPr$_2$NEt (10eq.)</td>
<td>-</td>
</tr>
<tr>
<td>3c</td>
<td>H</td>
<td>Ph</td>
<td>K$_3$PO$_4$ (5eq.)$^d$</td>
<td>-</td>
</tr>
<tr>
<td>3d</td>
<td>H</td>
<td>Ph</td>
<td>KOtBu (2.2eq)</td>
<td>5 (100:0)</td>
</tr>
<tr>
<td>3e</td>
<td>H</td>
<td>Ph</td>
<td>DABCO (5eq.)</td>
<td>49 (0:100)</td>
</tr>
<tr>
<td>3f</td>
<td>H</td>
<td>Ph</td>
<td>K$_2$CO$_3$/MeOH</td>
<td>80 (1:1)</td>
</tr>
<tr>
<td>3g</td>
<td>H</td>
<td>CO$_2$Et</td>
<td>DABCO (5eq.)</td>
<td>30 (1:2.5)</td>
</tr>
<tr>
<td>3h</td>
<td>H</td>
<td>CO$_2$Et</td>
<td>K$_2$CO$_3$/MeOH</td>
<td>trace</td>
</tr>
<tr>
<td>3i</td>
<td>4-Ph</td>
<td>Ph</td>
<td>DABCO (5eq.)</td>
<td>29 (0:100)</td>
</tr>
<tr>
<td>3j</td>
<td>4-Ph</td>
<td>Ph</td>
<td>K$_2$CO$_3$/MeOH</td>
<td>36 (1.2:1)</td>
</tr>
<tr>
<td>3k</td>
<td>3-Br</td>
<td>Ph</td>
<td>DABCO (5eq.)</td>
<td>61 (1:3)</td>
</tr>
<tr>
<td>3l</td>
<td>3-Br</td>
<td>Ph</td>
<td>K$_2$CO$_3$/MeOH</td>
<td>18 (1:1)</td>
</tr>
</tbody>
</table>

$^a$ Typical experimental procedure: 0.5 mmole pyridine, 0.6 mmole ethyl chloroformate, 0.5 mmole alkyne in ~2 mL CH$_3$CN in the glove box added to 0.05 mmole CuI and 0.7 mmole iPr$_2$NEt in ~1 mL CH$_3$CN and the solution stirred for 20 mins, exposed to air and base added and the reaction flask placed in a 65°C bath for 16 hrs. b) Combined yield of both isomers. c) Ratio of isolated amounts of stereoisomers. d) 1eq. of 18-crown-6-ether was added to solubilize the K$_3$PO$_4$.

Cyclic propargylcarbamates, N-acyl-2-ethynyl-1,2-dihydropyridines, have been previously reported to undergo base mediated isomerization to alkenyl-pyridines, though
in low yield and stereoselectivity.\textsuperscript{21} This rearrangement is proposed to proceed via base mediated allene formation, and carbamate de-protection.\textsuperscript{21a} The observed Z-selectivity when an excess of DABCO is used (entries 3e, g, i, k) could be explained by the re-protonation of the central carbon of the allene from the less hindered face by protonated DABCO.\textsuperscript{22} We have preliminarily probed the use of this reaction to synthesize other alkenyl-pyridines and a similar stereochemical outcome was observed for these substrates (entries 3g-l), though in low overall yield.

3.3 Conclusion

A one-pot tandem copper-catalyzed coupling and oxidation protocol has been developed to regioselectively synthesize alkynyl pyridines directly from the parent heterocycles and terminal alkynes. In addition, a number of 2-alkenyl pyridines can be prepared in a related procedure by coupling the copper-catalyzed reaction with a base mediated rearrangement. Both these reactions provide efficient, one-pot access to 2-functionalized pyridines.

3.4 Experimental

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\textsuperscript{®} and used as received. Acetonitrile was distilled from CaH\textsubscript{2} under nitrogen. Deuterated acetonitrile was dried as its protonated analogue, but were transferred under vacuum from the drying agent, and stored over 4Å molecular sieves. Deuterated DMSO and chloroform were dried over 3 Å molecular sieves.

\textsuperscript{1}H and \textsuperscript{13}C NMR’s were recorded on Varian Mercury 200 MHz, 300 MHz, Mercury 400 MHz, Unity 500 MHz, and JEOL 270 MHz spectrometers, and 1D NOESY
spectra were recorded on a Varian Mercury 400 MHz spectrometer. Regioselectivities for all compounds were determined by $^1$H NMR and 1D NOESY and by comparison to literature data.$^{23}$ Stereoselectivities for the alkenyl-pyridines were determined by comparison to literature data$^{24}$ and by the size of the coupling constant ($J$ in Hz).$^{25}$ Mass spectra were obtained from the McGill University mass spectral facilities.

**Typical Procedure for the Copper-Catalyzed DDQ Oxidation Synthesis of 2-alkynyl-pyridines:**

Pyridine (40 mg, 0.5 mmol), ethyl chloroformate (61 mg, 0.62 mmol) and phenylacetylene (50 mg, 0.5 mmol) were mixed in ~2 mL of acetonitrile and added to a vial of stirring CuI (9 mg, 0.05 mmol) and $i$Pr$_2$NEt (105 μL, 0.7 mmol) in ~1 mL of acetonitrile in the glove box. The reaction mixture was stirred at ambient temperature for 20 minutes. The vial was removed from the glove box, exposed to air and DDQ (114 mg, 0.5 mmol) was added. The resulting black solution was placed in a 45°C bath for 1 hr then columned directly through silica gel using ethyl acetate/hexanes as eluent. All compounds were characterized by $^1$H and $^{13}$C NMR and HRMS.

**One-pot Copper-Mediated Synthesis of 2-phenylalkynyl-pyridine (Table 3.1, entry 1h):**

Pyridine (16 mg, 0.2 mmol), ethyl chloroformate (24 mg, 0.24 mmol) and phenylacetylene (20 mg, 0.2 mmol) were mixed in ~1 mL of acetonitrile and added to a vial of stirring CuI (38 mg, 0.2 mmol) and $i$Pr$_2$NEt (40 μL, 0.28 mmol) in ~1 mL of acetonitrile in the glove box. The reaction mixture was stirred briefly (< 30 seconds), then 4 equal portions of a CH$_3$CN solution (~1 mL) of DDQ (45 mg, 0.2 mmol) was added in only ~10-20 second intervals at ambient temperature. After 20 minutes, the vial was removed from the glove box, exposed to air and the black solution was placed in a 45°C bath for 16 hrs then columned directly through silica gel using ethyl acetate/hexanes as eluent.
**Copper-Catalyzed Synthesis of 2-alkenyl-pyridines using sat’d K$_2$CO$_3$ and MeOH (Table 3.3, entries 3f, h, j, l):**

Pyridine (40 mg, 0.5 mmol), ethyl chloroformate (61 mg, 0.62 mmol) and phenylacetylene (50 mg, 0.5 mmol) were mixed in ~2 mL of acetonitrile and added to a vial of stirring CuI (9 mg, 0.05 mmol) and iPr$_2$NEt (105 μL, 0.7 mmol) in ~1 mL of acetonitrile in the glove box. The reaction mixture was stirred at ambient temperature for 20 minutes then brought out of the box and ~2 mL of sat’d K$_2$CO$_3$ and ~2 mL of MeOH were added and the slurried solution was stirred and heated at 65°C for 16 hrs. When complete, 5 mL H$_2$O was added and the organics were extracted 3x with 5 mL portions of CH$_2$Cl$_2$, dried (MgSO$_4$), concentrated, then chromatographed on silica gel with EtOAc/Hexanes as eluent to yield purified product. All compounds were characterized by $^1$H and $^{13}$C NMR and HRMS.

**Copper-Catalyzed Z-selective Synthesis of 2-alkenyl-pyridines using DABCO (Table 3.3, entries 3e, g, i, k):**

Pyridine (40 mg, 0.5 mmol), ethyl chloroformate (61 mg, 0.62 mmol) and phenylacetylene (50 mg, 0.5 mmol) were mixed in ~2 mL of acetonitrile and added to a vial of stirring CuI (9 mg, 0.05 mmol) and iPr$_2$NEt (105 μL, 0.7 mmol) in ~1 mL of acetonitrile in the glove box. The reaction mixture was stirred at ambient temperature for 20 minutes then DABCO (280 mg, 2.5 mmole) was added and the reaction was stirred and heated at 65°C for 16 hrs. The crude reaction mixture was cooled to room temperature then columned directly through silica gel using EtOAc/Heaxanes as eluent.

**Spectroscopic Data:**

2-(phenylethynyl)pyridine (Table 3.1, entry 1f)$^{23a}$ Isolated yield: 81%. $^1$H NMR (300MHz, CDCl$_3$): δ 8.61-8.59 (d, 1H), 7.72-7.61 (t, 1H), 7.60-7.51 (br, 3H), 7.22-7.38 (br, 4H). $^{13}$C NMR (68.0MHz, CDCl$_3$): δ 149.9, 143.4, 136.7, 132.2, 129.3, 128.6, 127.5,
123.0, 122.3, 90.0, 88.4. HRMS (M+H) for C_{13}H_{9}N, calculated: 180.0815, found: 180.0807.

**Pyridin-2-yl-propynoic acid ethyl ester (Table 3.2, entry 2d)**\(^{23d}\) Isolated yield: 54%. 
\(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 8.62-8.60 (d, 1H), 7.72-7.69 (t, 1H), 7.59-7.57 (d, 1H), 7.35-7.31 (m, 1H), 4.31-4.25 (q, 2H), 1.37-1.31 (t, 3H). \(^{13}\)C NMR (68.0MHz, CDCl\(_3\)): \(\delta\) 153.9, 150.8, 140.6, 136.6, 128.7, 125.0, 84.0, 79.6, 62.7, 14.4. HRMS (M+H) for C\(_{10}\)H\(_9\)NO\(_2\), calculated: 176.0713, found: 176.0704.

**5-Bromo-2-phenylethynyl-pyridine (Table 3.2, entry 2e)**\(^{23c}\) Isolated yield: 73%. \(^1\)H NMR (500MHz, CDCl\(_3\)): \(\delta\) 8.58-8.56 (d, 1H), 7.92-7.90 (d, 1H), 7.64-7.61 (d, 2H), 7.39-7.36 (m, 3H), 7.12-7.09 (m, 1H). \(^{13}\)C NMR (68.0MHz, CDCl\(_3\)): \(\delta\) 148.5, 144.0, 140.1, 132.4, 129.6, 128.7, 124.1, 123.8, 122.2, 94.3, 87.7. HRMS (M+H) for C\(_{13}\)H\(_8\)BrN, calculated: 257.9920, found: 257.9911.

**3-Methyl-2-phenylethynyl-pyridine (Table 3.2, entry 2f)**\(^{23b}\) Isolated yield: 69%. \(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 8.46-8.42 (d, 1H), 7.56-7.62 (m, 3H), 7.39-7.36 (m, 3H), 7.19-7.15 (m, 1H), 2.54 (s, 3H), 2.37 (s, 0.15H, minor regioisomer). \(^{13}\)C NMR (68.0MHz, CDCl\(_3\)): \(\delta\) 150.8, 147.6, 143.4, 137.2, 136.2, 132.2, 129.1, 128.6, 126.8, 122.8, 93.3, 87.7, 19.7. HRMS (M+H) for C\(_{14}\)H\(_{11}\)N, calculated: 194.0871, found: 194.0962.

**6-Phenylethynyl-pyridine-3-carbaldehyde (Table 3.2, entry 2g)**\(^{23e}\) Isolated yield: 33%. \(^1\)H NMR (500MHz, CDCl\(_3\)): \(\delta\) 10.14 (s, 1H), 9.07 (s, 1H), 8.20-8.14 (d, 1H), 7.68-7.61 (m, 3H), 7.43-7.35 (m, 3H). \(^{13}\)C NMR (68.0MHz, CDCl\(_3\)): \(\delta\) 190.1, 152.6, 148.6, 136.1, 132.6, 130.0, 128.7, 128.8, 127.6, 121.7, 93.8, 88.6. HRMS (M+H+MeOH) for C\(_{14}\)H\(_9\)NO, calculated: 240.1026, found: 240.1017.

**3,5-Dimethyl-2-phenylethynyl-pyridine (Table 3.2, entry 2h)** Isolated Yield: 39%. 
\(^1\)H NMR (300MHz, CDCl\(_3\)): \(\delta\) 8.29 (s, 1H), 7.64-7.56 (m, 2H), 7.38-7.33 (m, 4H), 2.48 (s, 3H), 2.34 (s, 3H). \(^{13}\)C NMR (67.9 MHz, CDCl\(_3\)): \(\delta\) 148.0, 140.3, 137.7, 132.7, 131.9,
128.8, 128.6, 128.4, 122.8, 92.4, 87.6, 19.4, 18.4. HRMS (M+H) for C$_{15}$H$_{13}$N, calculated: 208.1058, found: 208.1118.

**4-phenyl-2-(phenylethynyl)pyridine (Table 3.2, entry 2i)** Isolated yield: 43%. $^1$H NMR (500MHz, CDCl$_3$): $\delta$ 8.62-8.66 (d, 1H), 7.79 (s, 1H), 7.60-7.67 (m, 4H), 7.44-7.53 (m, 4H), 7.36-7.39 (m, 3H). $^{13}$C NMR (68.0MHz, CDCl$_3$): $\delta$ 150.7, 149.0, 144.2, 137.7, 132.3, 129.6, 129.4, 129.2, 128.6, 127.2, 125.4, 122.5, 121.0, 89.5, 89.0. HRMS (M+H) for C$_{19}$H$_{13}$N, calculated: 256.1128, found: 256.1118.

**4-tert-butyl-2-(phenylethynyl)pyridine (Table 3.2, entry 2j)** Isolated yield: 40%. $^1$H NMR (500MHz, CDCl$_3$): $\delta$ 8.50-8.52 (d, 1H), 7.58-7.62 (m, 1H), 7.55 (s, 1H), 7.36-7.39 (m, 3H), 7.21-7.28 (m, 2H). $^{13}$C NMR (68.0MHz, CDCl$_3$): $\delta$ 160.6, 150.2, 143.5, 132.3, 129.1, 128.6, 124.6, 122.6, 120.3, 89.3, 88.8, 35.0, 30.7. HRMS (M+H) for C$_{17}$H$_{17}$N, calculated: 236.1441, found: 236.1432.

**2-[(E)-2-phenylethenyl]-pyridine (Table 3.3, entry 3f)$^{24a}$** Isolated yield: 40%. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 8.62-8.61 (d, 1H), 7.68-7.57 (m, 4H), 7.40-7.25 (m, 4H), 7.20-7.12 (m, 2H). $^{13}$C NMR (67.9MHz, CDCl$_3$): $\delta$ 155.7, 149.7, 136.7, 136.6, 132.8, 128.8, 128.4, 128.0, 127.2, 122.2, 122.1. HRMS (M+H) for C$_{13}$H$_{11}$N, calculated: 182.0967, found: 182.0964.

**2-[(Z)-2-phenylethenyl]-pyridine (Table 3.3, entry 3f)$^{24a}$** Isolated yield: 40%. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 8.59-8.58 (d, 1H), 7.45-7.40 (t, 1H), 7.27-7.22 (m, 5H), 7.17-7.14 (d, 1H), 7.10-7.06 (t, 1H), 6.85-6.81 (d, 1H, $J$=12Hz), 6.70-6.66 (d, 1H, $J$=12Hz). $^{13}$C NMR (67.9MHz, CDCl$_3$): $\delta$ 156.4, 149.6, 136.8, 135.7, 133.3, 130.6, 128.9, 128.3, 127.6, 123.9, 121.8. HRMS (M+H) for C$_{13}$H$_{11}$N, calculated: 182.0967, found: 182.0964.

**Z-Ethyl-3-(pyridin-2-yl)acrylate (Table 3.3, entry 3g)$^{24b}$** Isolated yield: 22%. $^1$H NMR (400MHz, CDCl$_3$): $\delta$ 8.60-8.59 (d, 1H), 7.67-7.65 (m, 2H), 7.26-7.19 (t, 1H), 6.96-6.93 (d, 1H, $J$=12Hz, CH=CHCO$_2$Et), 6.15-6.12 (d, 1H, $J$=12Hz, CH=CHCO$_2$Et), 4.24-
4.19 (q, 2H), 1.28-1.24 (t, 3H). $^{13}$C NMR (67.9MHz, CDCl$_3$): δ 166.9, 153.8, 149.4, 139.9, 136.2, 124.6, 123.3, 123.2, 60.8, 14.3. HRMS (M+H) for C$_{10}$H$_{11}$NO$_2$, calculated: 178.0880, found: 178.0862.

**E-Ethyl-3-(pyridin-2-yl)acrylate (Table 3.3, entry 3g)**$^{24b}$ Isolated yield: 9%. $^1$H NMR (500MHz, CDCl$_3$): δ 8.65-8.64 (d, 1H), 7.73-7.67 (m, 2H [7.70-7.67 d, J=15Hz, CH=CHCO$_2$Et]), 7.44-7.42 (d, 1H, J=10Hz Ar-H), 7.27-7.25 (t, 1H), 6.96-6.93 (d, 1H, J=15Hz CH=CHCO$_2$Et), 4.30-4.26 (q, 2H), 1.36-1.32 (t, 3H). $^{13}$C NMR (68.0MHz, CDCl$_3$): δ 167.0, 153.3, 150.4, 143.5, 136.9, 124.4, 122.7, 60.9, 14.5. HRMS (M+H) for C$_{10}$H$_{11}$NO$_2$, calculated: 178.0880, found: 178.0862.

**4-Ph-2-[(Z)-2-phenylethenyl]pyridine (Table 3.3, entry 3i)**$^{24c}$ Isolated yield: 29% $^1$H NMR (300MHz, CDCl$_3$): δ 8.64-8.62 (d, 1H), 7.39-7.26 (m, 12H), 6.93-6.89 (d, 1H, J=12Hz), 6.78-6.74 (d, 1H, J=12Hz). $^{13}$C NMR (125.7MHz, CDCl$_3$): δ 157.0, 150.2, 148.0, 138.4, 137.1, 133.8, 130.9, 129.2, 129.1, 129.0, 128.6, 127.9, 127.1, 122.3, 120.0. HRMS (M+H) for C$_{19}$H$_{15}$N, calculated: 258.1275, found: 258.1277.

**4-Ph-2-[(E)-2-phenylethenyl]pyridine (Table 3.3, entry 3j)**$^{24c}$ Isolated yield: 20% $^1$H NMR (500MHz, CDCl$_3$): δ 8.66-8.65 (d, 1H), 7.73 (s, 1H), 7.70-7.67 (m, 2H [7.70-7.67, d, 1H, J=15Hz]), 7.62-7.60 (m, 3H), 7.52-7.29 (m, 6H), 7.27-7.24 (m, 2H [7.27-7.24, d, 1H, J=15Hz]). $^{13}$C NMR (125.7MHz, CDCl$_3$): δ 156.4, 150.3, 149.3, 138.6, 137.0, 133.2, 129.3, 129.2, 129.0, 128.6, 128.2, 127.4, 127.2, 120.5, 120.4. HRMS (M+H) for C$_{19}$H$_{15}$N, calculated: 258.1275, found: 258.1277.

**3-Br-6-[(Z)-6-phenylethenyl]pyridine (Table 3.3, entry 3k)** Isolated yield: 46%. $^1$H NMR (300MHz, CDCl$_3$): δ 8.46-8.45 (d, 1H), 7.90-7.87 (d, 1H, J=9Hz), 7.19-7.05 (m, 6H), 6.85-6.81 (d, 1H, J=12Hz), 6.76-6.72 (d, 1H, J=12Hz). $^{13}$C NMR (68.0MHz, CDCl$_3$): δ 155.9, 148.2, 140.5, 136.2, 134.8, 129.4, 128.2, 128.0, 127.9, 123.6, 121.3. HRMS (M+H) for C$_{13}$H$_{10}$BrN, calculated: 260.0069, found: 260.0068.
$^1$H and $^{13}$C NMR Spectra:
3.5 References


Xinning Yang, Qi Wang, Robert A. Coburn, and Marilyn E. Morris; Drug Metabolism and Disposition (2005), 33(8), 1220-1228.


11 a) Recently an interesting reaction was developed employing pyridine N-oxides in palladium catalyzed type cross-couplings: Campeau, L.-C., Rousseaux, S., Fagnou, K.; J. Am. Chem. Soc. 2005, 127, 18020-18021. b) This methodology was also applied to aromatic diazine N-oxides: Leclerc, J.-P., Fagnou, K., Angew. Chem Int. Ed. 2006, 45, 7781-7786.

12 Black, D.A., Beveridge, R.E., Arndtsen, B.A.; Manuscript in Preparation


16 DDQ is a more cost effective quinone oxidant: Aldrich Chem. Co. lists 10g of DDQ at $39 whereas 5g of the same purity grade of o-chloranil is listed at $43.

17 These results suggest that the dihydropyridine intermediate must be formed prior to the addition of the oxidant.

18 The initial alkyne addition to the N-acyl salt of 3-picoline yields a 3:1 mixture of regioisomers selective for the 2-phenylethynyl-3-methyl-1,2-dihydropyridine. After oxidation a small amount of the minor 6-phenylethynyl-3-methyl-pyridine is present in a 9:1 ratio in favour of the major isomer shown.

19 The unreacted 2-phenylethynyl-3-carboxaldehyde-1,2-dihydropyridine regioisomer of compound 2f was almost completely recovered after oxidation.


The coupling constant $J$ for trans isomers is always larger ($>10$ Hz) than cis isomers and is typically $\sim 15$Hz for $E$-alkenyl-pyridines (see ref 24).
CHAPTER 4
Towards a General Method of Pyridine Functionalization by Copper-Catalyzed Organoindium Addition

4.0 Preface

The previous chapters of this thesis have described mild and regioselective methods to couple pyridines with terminal alkynes in the presence of chloroformates (or acid chlorides) and a copper (I) catalyst. While these provide access to both 2-alkynylpyridines, and the partially reduced 2-ethynyl-1,2-dihydropyridines, these reactions are limited to the functionalization of pyridines with terminal alkynes. This chapter will outline our attempt to develop a more general method of pyridine ring substitution by a copper-catalyzed addition of organoindium reagents to activated N-acyl pyridinium salts. The reaction was found to be tolerant of various pyridine ring functionalities, but regioselectivities were low. However, this reaction is amenable to the mild functionalization of aromatic azine heterocycles (e.g. benzoxazole, benzothiazole, pthalazine).

4.1 Introduction

The addition of stoichiometric organometallic nucleophiles to N-acyl pyridinium salts is an attractive route to access functionalized pyridine derivatives.1,2 A variety of nucleophiles have been used in this chemistry including Grignards,3 organo-zincs,4 organo-tins,5 and others.6,7 The products of these reactions, 1,2- or 1,4-dihydropyridine derivatives, are interesting products which display some biological activity as NADH mimics,8 and are also useful synthetic intermediates in the synthesis of pyridines2 and natural products.9,10,11 There are, however, some limitations for the synthesis of these compounds in terms of regioselectivity, functional group compatibility, and the use of organometallic reagents that can be employed.

With regards to the latter, many of the common organometallic reagents used in these reactions can be incompatible with common functional groups. For example,
regio-control in Grignard additions can be achieved using blocking groups on the pyridine ring,\textsuperscript{12} chelation-assisted directed addition,\textsuperscript{13} or catalytic copper salt influences,\textsuperscript{3a} but these reagents are still not compatible with carbonyl or alcohol containing pyridinium salts.\textsuperscript{9a} The use of other milder organometallic reagents such as organostannanes have been reported to demonstrate better functional group tolerance, but these are restricted to the transfer of allyl-, benzyl- or alkynyl-units.\textsuperscript{5} For these reasons, it would be advantageous to develop a mild, general, and regioselective method to synthesize these important partially reduced pyridine derivatives.

We have recently reported that pyridines can be functionalized with terminal alkynes in the presence of a copper (I) catalyst to give \( N \)-acyl-2-ethynyl-1,2-dihydropyridines in only 20 minutes at ambient temperature.\textsuperscript{14} While this represents a mild, regioselective, and catalytic method to derivatize pyridine, it is limited to the use of alkynes. Organoindium reagents have been found to be very useful reagents in cross-coupling chemistry.\textsuperscript{15} These substrates can transfer all of their organic groups to the electrophile coupling partner (providing high atom economy), and generate low toxicity \( \text{InCl}_3 \) as by-product. In addition, organoindium reagents are not highly nucleophilic and therefore display good functional group compatibility. We have recently reported that imines can be coupled with organoindium reagents in the presence of acid chlorides and copper catalysts, providing a mild and general route to \( \alpha \)-substituted amides.\textsuperscript{16} Considering the resonance similarity of imines and pyridine, we have investigated the potential of developing a mild and general site-selective method of pyridine functionalization using easily prepared tri-organoindium reagents in a similar procedure.\textsuperscript{17}

### 4.2 Results and Discussion

As shown in Table 4.1, triphenylindium reacts very slowly with pyridine and ethyl chloroformate, resulting in a poor yield of \textbf{4.1} (entry 1a). We have previously demonstrated, however, that copper (I) salts can catalyze the reaction of \textit{in situ} generated \( N \)-acyl iminium salts with these reagents, presumably by transmetallation of the organic
units from indium to copper to form a more reactive organo-cuprate intermediate.\textsuperscript{16} Similarly, we have found that copper(I) salts can significantly improve the efficiency of this reaction (Table 4.1, entries b-e). In the case of CuCl, the addition is both regioselective and high yielding, providing 4.1 in 85\% yield (entry 1e).

**Table 4.1** Addition of (Ph)\textsubscript{3}In reagent to pyridine and ethyl chloroformate\textsuperscript{a}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Yield 4.1 (%)</th>
</tr>
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<tbody>
<tr>
<td>1a</td>
<td>None</td>
<td>8</td>
</tr>
<tr>
<td>1b</td>
<td>CuI</td>
<td>46</td>
</tr>
<tr>
<td>1c</td>
<td>CuBr</td>
<td>48</td>
</tr>
<tr>
<td>1d</td>
<td>Cu(II)(OTf)\textsubscript{2}</td>
<td>57</td>
</tr>
<tr>
<td>1e</td>
<td>CuCl</td>
<td>85</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Typical reaction procedure: pyridine (40 mg, 0.5 mmole), and ethyl chloroformate (61 mg, 0.6 mmole) are combined in the glove box in \~2 mL of CH\textsubscript{3}CN then added to a vial of CuCl (5 mg, 0.05 mmole) in \~1 mL CH\textsubscript{3}CN. To this solution is added (Ph)\textsubscript{3}In (0.18 mmole) in \~3 mL of THF, the vial is then capped and placed in a 45°C bath for 16 hrs.

The mechanism of this reaction is presumed to occur by transmetallation of an organic fragment from an organoindium reagent to copper, generating a more reactive organo-cuprate in situ (Scheme 4.1). The organo-cuprate could then trap any electrophilic pyridinium salt formed generating product, allowing the copper to re-enter the catalytic cycle. The exact structure of the reactive organometallic species is unknown, and could be a “free” un-coordinated organo-cuprate, or a mixed organoindium/organocuprate.
Scheme 4.1 Proposed mechanism of copper-catalyzed coupling of pyridines with organoindium reagents

As shown in Table 4.2, a variety of functionalized pyridines were compatible with organoindium coupling. This includes a number of halogen, alkyl, nitrile, and even sensitive ring-carbonyl substituted pyridines. The latter can be sensitive to the use of more potent nucleophiles in additions, and often require protection.9a In addition, a range of aryl-indiums can be employed, as well as vinyl substrates. While most reactions were found to give preferential 1,4-addition, regioisomeric mixtures were observed in most cases. For example, in the case of 3-acyl pyridine (Table 4.2, entry 2a) all three regioisomers were isolated in equal amounts. Interestingly, the corresponding substituted aromatic pyridine is isolated in entry 2f, presumably formed by the rapid oxidation of the in situ generated N-acyl-1,4-dihydropyridine 4.1.18 This chemistry was also shown to be capable of derivatizing 2-cyano-pyridine (entry 2d), a typically unreactive substrate in related additions.19 However, other similarly 2-substituted pyridines did not yield substituted dihydropyridine addition products (Table 2, entries 2h-k). In the case of entry 2l, effective allyl ketone addition was observed.
Table 4.2. Copper-catalyzed coupling of pyridines and organoindium reagents

![Chemical structures and yields](image)

<table>
<thead>
<tr>
<th>Entry</th>
<th>Heterocycle</th>
<th>R(_2)</th>
<th>R(_3)</th>
<th>Product(s)(c)</th>
<th>%Yield(b)</th>
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<td></td>
<td>OPh</td>
<td>Vinyl</td>
<td><img src="image" alt="Structure" /></td>
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<tr>
<td>2b</td>
<td><img src="image" alt="Structure" /></td>
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<td><img src="image" alt="Structure" /></td>
<td>35(d)</td>
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<tr>
<td>2c</td>
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<td>OPh</td>
<td>Ph</td>
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<tr>
<td>2d</td>
<td><img src="image" alt="Structure" /></td>
<td>OPh</td>
<td>Ph</td>
<td><img src="image" alt="Structure" /></td>
<td>37 (71)(f)</td>
</tr>
<tr>
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<td><img src="image" alt="Structure" /></td>
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<td>15 (31)(f)</td>
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<td>2h</td>
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</tr>
<tr>
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<td><img src="image" alt="Structure" /></td>
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<td></td>
<td><img src="image" alt="Structure" /></td>
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<tr>
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<td><img src="image" alt="Structure" /></td>
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</tr>
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<td>2k</td>
<td><img src="image" alt="Structure" /></td>
<td>OPh</td>
<td>Allyl</td>
<td><img src="image" alt="Structure" /></td>
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</table>
a) Typical reaction procedure: pyridine (0.5 mmole), and chloroformate (0.6 mmole) are combined in the glove box in ~2 mL of CH$_3$CN then added to a vial of CuCl (5 mg, 0.05 mmole) in ~1 mL CH$_3$CN. To this solution is added (R$_3$)$_3$In (0.18 mmole) in ~3 mL of THF, the vial is then capped and placed in a 45°C bath for 16 hrs. b) Combined yield of all regioisomers. c) Isolated amounts of regioisomers. d) 45°C for 24 hrs. e) 45°C for 72 hrs. f) 55°C for 48 hrs.

While low regioselectivities were observed with pyridines, a number of benzo-fused heterocycles have been found to undergo regioselective functionalization using this protocol. As shown in Table 4.3, this copper-catalyzed derivatization methodology was effective in transferring aryl, alkyl, and vinyl groups to a range of heterocycles (phthalazine, benzoxazole, benzothiazole) in good yield. This chemistry is particularly applicable to these heterocycles containing more than one heteroatom in the ring (Table 4.3, entries 3a-e), since functionalization of these substrates under related addition conditions with nucleophiles can lead to ring-opened products.$^{20,21}$
Table 4.3 Copper-catalyzed coupling of organoindium reagents to aromatic N-heterocycles

![Chemical Structure Diagram]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Heterocycle</th>
<th>R₁</th>
<th>R₂</th>
<th>Product(s)</th>
<th>% Yield</th>
</tr>
</thead>
<tbody>
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<td></td>
<td>CHCCH₃</td>
<td>vinyl</td>
<td>![Image of Product 3a]</td>
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</tr>
<tr>
<td>3b</td>
<td></td>
<td>Et</td>
<td>Ph</td>
<td>![Image of Product 3b]</td>
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<tr>
<td>3c</td>
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<td>CHCICH₃</td>
<td>iPr</td>
<td>![Image of Product 3c]</td>
<td>39</td>
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<tr>
<td>3d</td>
<td></td>
<td>CHCICH₃</td>
<td>Ph</td>
<td>![Image of Product 3d]</td>
<td>38</td>
</tr>
<tr>
<td>3e</td>
<td></td>
<td>Et</td>
<td>Et</td>
<td>![Image of Product 3e]</td>
<td>65</td>
</tr>
</tbody>
</table>

a) Typical reaction procedure: heterocycle (0.5 mmole), and chloroformate (0.6 mmole) are combined in the glove box in ~2 mL of CH₃CN then added to a vial of CuCl (5 mg, 0.05 mmole) in ~1 mL CH₃CN. To this solution is added (R₂)₃In (0.18 mmole) in ~3 mL of THF, the vial is then capped and placed in a 45°C bath for 16 hrs.

4.3 Conclusion

This study has shown that the copper-catalyzed coupling of organoindium reagents with nitrogen containing heterocycles, in the presence of a chloroformate activator, can provide a mild approach to generate partially reduced heterocycle derivatives. Investigations on the application of this coupling towards the synthesis of substituted aromatic pyridines, as well as a catalytic enantioselective variant with chiral ligands are underway.
4.4 Experimental

**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\textsuperscript{®} and used as received. Acetonitrile was distilled from CaH\textsubscript{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 was dried over 3 Å molecular sieves. All organo-indium reagents were prepared from commercially available Grignard reagents and InCl\textsubscript{3} by standard literature procedures\textsuperscript{15a} and used fresh.

All compounds were characterized by \textsuperscript{1}H and \textsuperscript{13}C NMR and HRMS. Regioselectivities for all compounds were determined by \textsuperscript{1}H NMR, 1D NOESY and 2D \textsuperscript{1}H-\textsuperscript{13}C HMQC and HMBC experiments, and by comparison to literature data. \textsuperscript{1}H and \textsuperscript{13}C were recorded on Varian Mercury 200MHz, 300 MHz, 400 MHz, Unity 500MHz, and JEOL 270 MHz spectrometers. 1D NOESY spectra were recorded on a Varian Mercury 400MHz spectrometer, 2D \textsuperscript{1}H-\textsuperscript{13}C HMQC and HMBC were recorded on a Varian Mercury 400 or Unity 500MHz spectrometer. Mass spectra were obtained from the McGill University mass spectral facilities.

**Typical Procedure for the Synthesis of tri-Organoindium Reagents:**

The appropriate Grignard reagent in a solution of THF (0.5 mmole Grignard) was added to a schlenk flask under N\textsubscript{2} containing InCl\textsubscript{3} (0.18 mmole, 39 mg) in THF at -78\textdegree C over a period of 30 minutes (total volume ~ 3 mL THF). The solution was then allowed to warm to room temperature and stirred an additional 30-60 minutes until the solution became relatively clear. The schlenk was then purged into the glove box and the solution used fresh as is.
Typical Procedure for the Copper-Catalyzed Coupling of Pyridines, Chloroformates and Organoinidium Reagents:

Pyridine (0.5 mmole, 40 mg) and ethyl chloroformate (0.6 mmole, 62 mg) and Copper (I) chloride (0.05 mmole, 5 mg) were combined in the glove box in ~3 mL CH₃CN in a large screw cap vial. To this solution was added Ph₃In reagent solution (0.18 mmole Ph₃In) in ~3 mL THF. The vial was capped, brought out of the box and the reaction mixture was stirred and heated at 45°C for 16 hrs. After completion, the solution was concentrated in vacuo, and dissolved in ~30 mL Et₂O. Et₂O layer washed with sat’d NaHCO₃ (~15 mL), then back-extracted with ~15 mL Et₂O. Organic layers combined, dried (MgSO₄), filtered, and concentrated. The crude residue was then taken up in ~2-3 mL CH₂Cl₂ and purified by flash column chromatography through silica gel using 10% EtOAc:Hexanes as eluent.

Spectroscopic Data:

Ethyl-4-phenylpyridine-1(4H)-carboxylate (Table 4.1, entry 1e) Isolated Yield: 85%.

1H NMR (200MHz, CDCl₃): δ 7.39-7.22 (m, 5H), 7.03-6.80 (dd, 2H), 5.07-4.85 (br, 2H), 4.36-4.22 (q, 2H), 4.21-4.16 (t, 1H), 1.38-1.31 (t, 3H). 13C NMR (67.9 MHz, CDCl₃): δ 151.5, 145.9, 128.7, 127.8, 127.2, 126.7, 109.5, 62.6, 39.2, 14.4. HRMS (M+Na) for C₁₄H₁₅NO₂; calculated: 252.1003, found: 252.0998.

Phenyl 5-acetyl-2-vinylpyridine-1(2H)-carboxylate (Table 4.2, entry 2a) Isolated Yield: 11%. 1H NMR (300MHz, CDCl₃): δ 7.92 (s, 1H), 7.45-7.12 (m, 5H), 6.66-6.60 (d, 1H), 5.99-5.80 (m, 1H), 5.70-5.61 (m, 1H), 5.43-5.37 (t, 1H), 5.31-5.18 (m, 2H), 2.33 (s, 3H). 13C NMR (67.9 MHz, CDCl₃): δ 193.6, 150.7, 134.5, 129.6, 129.4, 129.3, 126.3, 121.3, 120.5, 119.4, 119.0, 116.9, 55.6, 24.8. HRMS (M+Na) for C₁₆H₁₅NO₃; calculated: 292.0952, found: 292.0940.

Phenyl 3-acetyl-4-vinylpyridine-1(4H)-carboxylate (Table 4.2, entry 2a) Isolated Yield: 11%. 1H NMR (300MHz, CDCl₃): δ 8.00-7.98 (s, 1H), 7.45-7.18 (m, 5H), 7.05-
6.99 (br, d, 1H), 6.00-5.87 (m, 1H), 5.31-5.20 (br, 1H), 5.15-5.04 (m, 2H), 4.10-4.03 (t, 1H), 2.38 (s, 3H). $^{13}$C NMR (67.9 MHz, CDCl$_3$): $\delta$ 195.8, 150.6, 149.7, 139.7, 132.8, 132.7, 129.6, 126.4, 121.5, 121.2, 115.4, 111.9, 35.0, 25.2. HRMS (M+Na) for C$_{16}$H$_{15}$NO$_3$; calculated: 292.0952, found: 292.0940.

**Phenyl 3-acetyl-2-vinylpyridine-1(2H)-carboxylate (Table 4.2, entry 2a)** Isolated Yield: 11%. $^1$H NMR (200MHz, CDCl$_3$): $\delta$ 7.43-7.22 (m, 4H), 7.18-7.09 (d, 2H), 7.06-6.99 (d, 1H), 6.17-6.00 (br, 1H), 5.89-5.69 (m, 1H), 5.60-5.52 (t, 1H), 5.21-5.09 (m, 2H), 2.38 (s, 3H). $^{13}$C NMR (67.9 MHz, CDCl$_3$): $\delta$ 194.7, 150.9, 133.2, 133.1, 132.6, 132.1, 130.2, 129.4, 126.0, 121.4, 115.4, 105.0, 52.4, 24.9. HRMS (M+Na) for C$_{16}$H$_{15}$NO$_3$; calculated: 292.0952, found: 292.0940.

**Ethyl 3-bromo-4-(2-methoxyphenyl)pyridine-1(4H)-carboxylate (Table 4.2, entry 2b)** Isolated Yield: 35%. $^1$H NMR (200MHz, CDCl$_3$): $\delta$ 7.38-7.17 (m, 3H), 7.01-6.84 (br, m, 3H), 4.98-4.88 (m, 1H), 4.33-4.26 (q, 2H), 3.85 (s, 3H), 3.82-3.77 (d, 1H), 1.37-1.31 (t, 3H). $^{13}$C NMR (67.9 MHz, CDCl$_3$): $\delta$ 156.9, 150.9, 131.5, 129.4, 126.8, 124.9, 120.8, 120.6, 111.6, 109.1, 106.9, 63.1, 55.8, 40.5, 14.5. HRMS (M+Na) for C$_{15}$H$_{16}$BrNO$_3$; calculated: 360.0214, found: 360.0205.

**Phenyl 3-formyl-4-phenylpyridine-1(4H)-carboxylate (Table 4.2, entry 2c)** Isolated Yield: 38%. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 9.41 (s, 1H), 7.91 (s, 1H), 7.48-7.20 (m, 10H), 7.12-7.08 (d, 1H), 5.40-5.35 (m, 1H), 4.59-4.57 (t, 1H). $^{13}$C NMR (67.9 MHz, CDCl$_3$): $\delta$ 189.8, 150.5, 149.4, 143.5, 139.4, 129.7, 128.6, 128.1, 127.0, 126.6, 123.8, 121.2, 121.0, 113.8, 37.0. HRMS (M+Na) for C$_{19}$H$_{15}$NO$_3$; calculated: 328.0952, found: 328.0942.

**Phenyl 3-formyl-6-phenylpyridine-1(6H)-carboxylate (Table 4.2, entry 2c)** Isolated Yield: 17%. $^1$H NMR (200MHz, CDCl$_3$): $\delta$ 9.39 (s, 1H), 7.82 (s, 1H), 7.43-7.20 (m, 8H), 7.12-6.89 (br, 2H), 6.62-6.56 (d, 1H), 6.02-5.98 (d, 1H), 5.82-5.75 (m, 1H). $^{13}$C NMR (67.9 MHz, CDCl$_3$): $\delta$ 187.1, 150.5, 142.0, 129.7, 129.5, 128.9, 128.6, 128.1,
127.0, 126.4, 123.8, 121.1, 119.5, 115.7, 59.6. HRMS (M+Na) for C_{19}H_{15}NO_{3}; calculated: 328.0952, found: 328.0942.

**Phenyl 2-cyano-4-phenylpyridine-1(4H)-carboxylate (Table 4.2, entry 2d)** Isolated Yield: 53%. $^1$H NMR (200MHz, CDCl$_3$): δ 7.48-7.24 (m, 10H), 7.14-7.09 (dd, 1H), 6.07-6.03 (m, 1H), 5.20-5.13 (m, 1H), 4.36-4.31 (t, 1H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 150.6, 148.9, 142.6, 129.7, 129.4, 129.3, 127.9, 127.8, 126.5, 123.6, 121.4, 114.0, 111.5, 110.1, 40.4. HRMS (M+Na) for C$_{19}$H$_{14}$N$_2$O$_2$; calculated: 325.0955, found: 325.0947.

**Phenyl 6-cyano-2-phenylpyridine-1(2H)-carboxylate (Table 4.2, entry 2d)** Isolated Yield: 18%. $^1$H NMR (300MHz, CDCl$_3$): δ 7.42-7.25 (m, 10H), 6.44-6.42 (d, 1H, J=6Hz), 6.32-6.28 (m, 2H), 6.15-6.13 (d, 1H, J=6Hz). $^{13}$C NMR (75.5 MHz, CDCl$_3$): δ 151.8, 150.9, 137.7, 130.8, 129.6, 129.0, 127.3, 127.1, 126.3, 125.8, 121.5, 121.3, 115.0, 110.6, 55.6. HRMS (M+Na) for C$_{19}$H$_{14}$N$_2$O$_2$; calculated: 325.0955, found: 325.0947.

**Phenyl 5-bromo-3-formyl-2-phenylpyridine-1(2H)-carboxylate (Table 4.2, entry 2e)** Isolated Yield: 31%. $^1$H NMR (300MHz, CDCl$_3$): δ 9.40 (s, 1H), 7.91 (s, 1H), 7.50-7.21 (m, 10H), 7.09-6.98 (br, 1H), 4.69 (s, 1H). $^{13}$C NMR (67.9 MHz, CDCl$_3$): δ 188.6, 150.4, 140.9, 137.4, 129.8, 128.6, 128.5, 127.7, 126.8, 123.5, 122.1, 121.0, 119.3, 11.7, 45.6. HRMS (M+Na) for C$_{19}$H$_{14}$BrNO$_3$; calculated: 406.0057, found: 406.0048.

**4-(4-flourophenyl)-3-methylpyridine (Table 4.2, entry 2f)** Isolated Yield: 48%. $^1$H NMR (500MHz, CDCl$_3$): δ 8.49-8.45 (d, 1H), 7.30-7.11 (m, 5H), 2.25 (s, 1H). $^{13}$C NMR (125 MHz, CDCl$_3$): δ 163.8, 161.8, 151.5, 148.5, 147.5, 135.2, 130.5, 124.3, 115.8-115.6 (d, $J_{C-F} = 20$Hz), 17.4. HRMS (M+H) for C$_{12}$H$_{10}$FN; calculated: 188.0896, found: 188.0869.
Ethyl 4-(2,6-dimethylphenyl)quinoline-1(4H)-carboxylate (Table 4.2, entry 2g)
Isolated Yield: 40%. $^1$H NMR (500MHz, CDCl$_3$): $\delta$ 8.04-8.01 (d, 1H), 7.22-7.19 (t, 1H), 7.10-6.92 (m, 5H), 6.62-6.59 (d, 1H), 5.21-5.18 (m, 2H), 4.38-4.32 (q, 2H), 2.52-1.90 (br, 6H), 1.41-1.38 (t, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 153.0, 139.4, 136.0, 130.8, 129.5, 127.2, 127.1, 126.6, 125.1, 125.0, 121.6, 121.5, 113.7, 62.5, 38.1, 20.9, 14.6. HRMS (M+H) for C$_{20}$H$_{21}$NO$_2$; calculated: 308.1662, found: 308.1643.

Ethyl 2-(2,6-dimethylphenyl)quinoline-1(2H)-carboxylate (Table 4.2, entry 2g)
Isolated Yield: 19%. $^1$H NMR (500MHz, CDCl$_3$): $\delta$ 7.99-7.96 (d, 1H), 7.21-7.18 (t, 1H), 7.02-6.95 (m, 5H), 6.53-6.50 (t, 1H), 6.39-6.36 (d, 1H), 5.66-5.61 (m, 1H), 4.19-4.05 (dq, 2H), 2.23 (s, 6H), 1.17-1.12 (t, 3H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 155.6, 139.5, 137.2, 136.5, 129.5, 128.6, 127.1, 127.0, 124.8, 123.8, 123.7, 123.3, 122.1, 62.2, 57.1, 20.7, 14.2. HRMS (M+H) for C$_{20}$H$_{21}$NO$_2$; calculated: 308.1662, found: 308.1643.

2-pyridin-2-ylpent-4-en-2-ol (Table 4.2, entry 2k) Isolated Yield: 62%. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 8.53-8.51 (d, 1H), 7.71-7.65 (t, 1H), 7.38-7.33 (d, 1H), 7.20-7.18 (m, 1H), 5.67-5.60 (m, 1H), 5.02-4.98 (m, 3H), 2.60-2.56 (d, 2H), 1.55 (s, 3H). $^{13}$C NMR (67.9 MHz, CDCl$_3$): $\delta$ 164.7, 147.6, 136.8, 133.9, 121.9, 119.4, 118.2, 74.0, 48.0, 28.5. HRMS (M+H) for C$_{10}$H$_{13}$NO; calculated: 164.10709, found: 164.10699.

2,2,2-trichloroethyl 2-vinyl-1,3-benzoxazole-3(2H)-carboxylate (Table 4.3, entry 3 a)
Isolated Yield: 61%. $^1$H NMR (200MHz, CDCl$_3$): $\delta$ 7.63-7.47 (br, 1H), 7.02-6.81 (m, 3H), 6.55-6.51 (d, 1H), 6.11-5.92 (m, 1H), 5.66-5.59 (d, 1H), 5.46-5.40 (d, 1H), 4.88-4.82 (s, 2H). $^{13}$C NMR (67.9 MHz, CDCl$_3$): $\delta$ 150.3, 149.8, 132.0, 128.2, 124.5, 121.6, 120.1, 114.8, 109.2, 94.9, 93.3, 75.4. HRMS (M+H) for C$_{12}$H$_{10}$Cl$_3$NO$_3$; calculated: 321.9825, found: 321.9799.

Ethyl 2-phenyl-1,3-benzothiazole-3(2H)-carboxylate (Table 4.3, entry 3b) Isolated Yield: 91%. $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 7.86-7.81 (d, 1H), 7.35-7.22 (br, m, 5H),
1-chloroethyl 2-isopropyl-1,3-benzothiazole-3(2H)-carboxylate (Table 4.3, entry 3c)  
Isolated Yield: 39%. $^1$H NMR (200MHz, CDCl$_3$): $\delta$ 7.84-7.45 (br, 1H), 7.17-6.97 (m, 3H), 6.74-6.63 (q, 1H), 5.67-5.66 (d, 1H), 2.27-2.12 (m, 1H), 1.92-1.84 (m, 3H), 0.98-0.86 (m, 6H). $^{13}$C NMR (125 MHz, CDCl$_3$): $\delta$ 150.3, 138.4, 129.9, 125.2, 122.2, 118.0, 83.2, 72.9, 35.2, 25.6, 18.4, 16.2. HRMS (M+H) for C$_{13}$H$_{16}$ClNO$_2$S; calculated: 286.0689, found: 286.0660.

1-chloroethyl 1-phenylphthalazine-2(1H)-carboxylate (Table 4.3, entry 3d)  
Isolated Yield: 38%. $^1$H NMR (200MHz, CDCl$_3$): $\delta$ 7.79-7.86 (d, 1H), 7.48-7.41 (t, 1H), 7.40-7.31 (m, 2H), 7.28-7.20 (m, 6H), 6.70-6.64 (q, 1H), 6.60 (s, 1H), 1.92-1.85 (m, 3H). $^{13}$C NMR (67.9 MHz, CDCl$_3$): $\delta$ 152.0, 143.6, 143.4, 142.8, 133.1, 132.1, 128.7, 128.6, 128.0, 127.0, 126.6, 126.3, 83.6, 57.1, 25.4. HRMS (M+Na) for C$_{17}$H$_{15}$ClN$_2$O$_2$; calculated: 337.0722, found: 337.0712.

Ethyl 1-ethylphthalazine-2(1H)-carboxylate (Table 4.3, entry 3e)  
Isolated Yield: 65%. $^1$H NMR (200MHz, CDCl$_3$): $\delta$ 7.67-6.61 (s, 1H), 7.44-7.21 (m, 3H), 7.14-7.07 (d, 1H), 5.43-5.32 (t, 1H), 4.40-4.29 (q, 2H), 1.75-1.60 (m, 2H), 1.40-1.31 (t, 3H), 0.85-0.76 (t, 3H). $^{13}$C NMR (67.9 MHz, CDCl$_3$): $\delta$ 154.3, 142.9, 133.7, 131.3, 128.1, 126.4, 125.7, 124.0, 62.8, 54.9, 27.9, 14.7, 9.6. HRMS (M+H) for C$_{13}$H$_{16}$N$_2$O$_2$; calculated: 233.1311, found: 233.1281.
$^1$H and $^{13}$C NMR Spectra:
4.5 References


7 a) An organo-titanium example: Gundersen, L-L., Rise, F., Undheim, K.; *Tetrahedron* **1992**, *48*, 5647. b) for an organo-cadmium example see ref. 3a.


18 1,4-dihydropyridines are more susceptible to oxidation than the 1,2-regioisomer: Comins, D.L., Brown, J.; Tetrahedron Lett. 1984, 25, 3297. see also refs 2a-d.

19 This is presumably due to these substrates inhibition of pyridinium salt formation, see ref. 1. For a recent example of effective 2-cyano- and 2-bromo-pyridinium salt nucleophilic addition see: Corey, E.J., Tian, Y.; Org. Lett. 2005, 7, 5535.


CHAPTER 5

Conclusions and Future Work

5.1 Summary of Thesis

Nucleophilic addition to $N$-acyl pyridinium salts is an attractive route to construct substituted pyridine derivatives.\(^1\) While effective, the high reactivity of many common organometallic reagent nucleophiles can limit the scope of this chemistry. This thesis has demonstrated how copper catalysis can be used to couple pyridines, and related aromatic heterocycles, with simple substrates, such as terminal alkynes and organoindium reagents, via reactive $N$-acyl aromatic azine salts. Overall, this provides a mild method to directly functionalize pyridines, and has been used to access a range of pyridine derived products (Scheme 5.1), all in one pot reactions.

\[
\begin{array}{c}
\text{Pyridine derivatives obtained through copper-catalyzed couplings with activated } N\text{-acyl pyridinium salts}
\end{array}
\]

The copper-catalyzed alkynylation of pyridines in the presence of acyl halide activators has been found to allow the regioselective preparation of a variety of $N$-acyl-2-ethynyl-1,2-dihydropyridines and other partially reduced alkynylated heterocycles (Chapter 2). This mild, efficient, 20 minute coupling protocol was then used in tandem with oxidants or base to prepare 2-alkynyl- and 2-alkenyl-pyridines directly from the parent heterocycles in one-pot (Chapter 3). In addition, mild organoindium reagents were found to be effective coupling partners with $N$-acyl aromatic azine salts in the presence of...
a copper (I) salt catalyst (Chapter 4). This has provided both an atom economical, and relatively general route to construct a range of functionalized heterocycles.

5.2 Future Work

The reactions developed in this thesis are all well designed for application to solid-phase library development. Using a method similar to the REACAP technology outlined in Chapter 1, polystyrene supported chloroformate resins could be used in conjunction with the chemistries developed in this thesis for the solid-phase synthesis of substituted pyridines (Scheme 5.2). This method could also potentially be used for the synthesis of piperidines, and other reduced heterocycles if these copper-catalyzed reactions were performed in tandem with hydrogenation sources. Solution-phase hydrogenations with these couplings are also possible. Overall, this could provide a mild and straightforward route to pyridine derivative library development for high-throughput screening.

Scheme 5.2 Potential solid-phase product synthesis using polystyrene supported chloroformates
Considering that the reactions in this thesis are all catalytic in copper, and generate chiral products, there is the potential to achieve enantio-control in these transformations using chiral ligands. In the case of the copper-catalyzed alkyne addition chemistry, this has already been extensively investigated in this laboratory as a route to prepare chiral cyclic-propargylcarbamates, using axially chiral PINAP ligands (Scheme 5.3). The use of organoindium reagents in a related protocol with pyridines is inhibited by the need to separate regioisomers. Catalytic enantioselective organoindium addition would most likely be successful with benzo-fused heterocycles (phthalazine, benzoazole, benzothiazole, isoquinoline), which contain only one addition site.

![Scheme 5.3](image)

**Scheme 5.3** Catalytic enantioselective cyclic propargylcarbamate synthesis

Finally, there is an analogy to be made with these \( N \)-acyl pyridinium salts and other metal-catalyzed reactions developed in our laboratory involving related \( N \)-acyl iminium salts. Research in our lab has shown that imines in the presence of acid chlorides will oxidatively add to palladium or nickel (0) sources to give amido-metallo-cycles, which have interesting carbon monoxide insertion chemistry. These results have led to the mild, general preparation of a number of bio-active compounds from readily-available starting materials. By exploring the use of pyridines in these routes interesting new chemistries could be invented (Scheme 5.4).
Scheme 5.4 Potential oxidative addition of N-acyl pyridinium salts towards new chemistry development

5.3 References


APPENDIX A

Studies Directed Towards Using a Copper-Catalyzed Organoindium Addition to Prepare Substituted Pyridines

A.1 Introduction

The research described in Chapter 4 of this thesis demonstrated that organoindium reagents could undergo a copper catalyzed coupling with pyridines and chloroformates, as a mild route to prepare partially reduced pyridine derivatives (Scheme A.1). While useful, a direct pyridine ring substitution is a more desirable synthetic goal because of the widespread application of functionalized aromatic pyridine structures. Considering that dihydropyridines can be oxidized to substituted pyridines, we envisioned incorporating oxidative conditions with the copper-catalyzed organoindium coupling from Chapter 4 as a potential one pot route to generate substituted pyridines. Our preliminary studies towards this goal are described herein.

Scheme A.1 Copper-catalyzed coupling of substituted pyridines and organoindium reagents

A.2 Results and Discussion

Our initial attempts at this reaction examined the copper-catalyzed reaction of pyridine, ethyl chloroformate, and triphenylindium reagent in the presence of air or under an atmosphere of oxygen, neither of which were successful (Table A.1, entries 1a, 1b). As shown, treatment of the crude reaction pot containing impure intermediate product A.1 with DDQ or o-chloranil quinone oxidants, also failed to yield any 4-phenyl-pyridine
product (entries 1c, 1d). It was found, however, that addition of base and mild heating produced A.2 in low yield (entries 1e,f).  

**Table A.1** Oxidation attempts to prepare 4-phenylpyridine using a copper-catalyzed organoindium route

<table>
<thead>
<tr>
<th>Entry</th>
<th>[O]</th>
<th>Temp. (°C)</th>
<th>Time (hrs)</th>
<th>Yield A.2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1a</td>
<td>Air</td>
<td>45</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>1b</td>
<td>O₂</td>
<td>45</td>
<td>16</td>
<td>-</td>
</tr>
<tr>
<td>1c</td>
<td>DDQ</td>
<td>45</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>1d</td>
<td>O-chloranil</td>
<td>rm. temp.</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>1e</td>
<td>Sat’d K₂CO₃</td>
<td>65</td>
<td>6</td>
<td>12</td>
</tr>
<tr>
<td>1f</td>
<td>0.5M KOH</td>
<td>65</td>
<td>6</td>
<td>20</td>
</tr>
</tbody>
</table>

a) Typical reaction procedure: pyridine (40 mg, 0.5 mmole), and ethyl chloroformate (61 mg, 0.6 mmole) are combined in the glove box in ~2 mL’s of CH₃CN then added to a vial of CuCl (5 mg, 0.05 mmole) in ~1 mL CH₃CN. To this solution is added InPh₃ (0.18 mmole) in ~3 mL’s of THF, the vial is then capped and placed in a 45°C bath for 16 hrs then exposed to the conditions described above. b) Modification of initial organoindium coupling conditions (i.e. pyridine, ethyl chloroformate, triphenylindium, CuCl in solvent heated in the presence of air or O₂ instead of under N₂).

A more convergent approach to 4-phenyl-pyridine was then considered by performing the copper-catalyzed reaction in the presence of base. Direct addition of base to the reaction pot was investigated (Table A.2), and the results showed that addition of ~2 equivalents of DABCO to the reaction pot produced the desired transformation in a low but promising 34% yield (Table A.2, entry 2g). Unfortunately, further attempts to optimize the oxidation conditions using DABCO were unsuccessful (entries 2h-k).
Table A.2  Base mediated one-pot one-step synthesis of 4-phenylpyridine

\[
\begin{align*}
\text{Pyridine (40 mg, 0.5 mmole), and ethyl chloroformate (61 mg, 0.6 mmole)} & \text{ are combined in the glove box in ~2 mL’s of CH}_3\text{CN then added to a vial of CuCl (5 mg, 0.05 mmole) in ~1 mL CH}_3\text{CN. To this solution is added InPh}_3 \text{ (0.18 mmole) in ~3 mL’s of THF then base as shown above. The vial is then capped and placed in a 45° C bath for 16 hrs.} \\
\text{b) 45° C for 82 hrs.} \\
\text{c) 80° C for 16 hrs.} \\
\text{d) 65° C for 24 hrs.}
\end{align*}
\]

It was then considered that using a more labile chloroformate may result in a more efficient reaction. Drawing an analogy of this procedure with popular amine protecting group strategies, use of Fmoc-Cl as the chloroformate pyridine activator did result in a moderate yield of 4-phenyl-pyridine after a TBAF (tetrabutylammonium flouride) carbamate deprotection (Scheme A.2).
Scheme A.2  Two-step Fmoc and TBAF mediated synthesis of 4-phenylpyridine

Similar aromatization studies were performed with other heterocycles obtained from organoindium coupling. It was found that treatment of purified A.3 with DDQ or o-chloranil provided good to excellent conversion to the corresponding aromatic 2-phenylbenzothiazole A.4 (Scheme A.4). When the partially reduced benzoxazole product A.5 was exposed to similar conditions, however, no reaction occurred and complete recovery of the starting material was obtained.

Scheme A.3  Oxidation of partially reduced substituted benzoxazole and benzothiazole

A.3 Conclusion

In conclusion, a base mediated procedure for the synthesis of 4-phenyl-pyridine via copper-catalyzed organoindium addition has been developed. It is believed that these methods could also be applied in other organoindium couplings to give substituted
aromatic pyridine products. In addition, 2-phenyl-benzothiazole was prepared using the known dihydropyridine oxidants DDQ and o-chloranil.

**A.4 Experimental**

**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 CaH₂ 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. Organo-indium reagents were prepared as in Chapter 4 of this thesis.

¹H and ¹³C spectra were recorded on Varian Mercury 300 MHz and JEOL 270 MHz spectrometers. Mass spectra were obtained from the McGill University mass spectral facilities. Characterization data for compounds A.2 and A.4 agree with previously reported data.

**TBAF and Fmoc Mediated Synthesis of 4-phenylpyridine (Compound A.2, Scheme A.2):**

Pyridine (0.5 mmole, 40 mg) and Fmoc (9-flourenylmethyloxycarbonyl) -Cl (0.6 mmole, 156 mg) and copper (I) chloride (0.05 mmole, 5 mg) were combined in the glove box in ~3 mL CH₃CN in a large screw cap vial. To this solution was added Ph₃In reagent solution (0.18 mmole) in ~3 mL THF. The vial was capped, brought out of the box and the reaction mixture was stirred and heated at 45°C for 16 hrs. The solvent was reduced *in vacuo* then 4.5 mL of DMF and 0.5 mL of a 1.0 M TBAF (tetrabutylammonium
fluoride) solution in THF were added and the mixture heated at 55°C for 4 hrs. When complete, 25 mL Et₂O added and the organics washed with 10 mL 0.5 M KOH and 6x with H₂O; aqueous extracts were then washed with 25 mL Et₂O which was then washed 4x with 10 mL H₂O to completely remove the DMF. Organic extracts were combined, dried (MgSO₄), and the Et₂O removed to give 125 mg of crude material which was dissolved in CH₂Cl₂ and columned through silica gel using 10% EtOAc:Hexanes to give 41 mg (53%) of 4-phenylpyridine (Rf ~ 0.15 in 20% EtOAc:Hex). ¹H NMR (300MHz, CDCl₃): δ 8.67-8.62 (d, 2H), 7.67-7.61 (m, 2H), 7.53-7.42 (m, 5H). ¹³C NMR (67.9 MHz, CDCl₃): δ 150.3, 148.4, 138.2, 129.2, 129.1, 127.1, 121.7. HRMS (M+H) for C₁₁H₉N; calculated: 156.0834, found: 156.0808.

**DABCO Mediated Synthesis of 4-phenylpyridine (Compound A.2, Table A.2 entry 2g):**

Pyridine (0.5 mmole, 40 mg) and ethyl chloroformate (0.6 mmole, 124 mg) and copper (I) chloride (0.05 mmole, 5 mg) were combined in the glove box in ~3 mL CH₃CN in a large screw cap vial. To this solution was added Ph₃In reagent solution (0.18 mmole Ph₃In) in ~3 mL THF and DABCO (1.1 mmol, 123 mg). The vial was capped, brought out of the box and the reaction mixture was stirred and heated at 45°C for 16 hrs. The solvent was reduced *in vacuo*, then 5 mL Et₂O and 5 mL H₂O added and the vial was stirred for 30 minutes at room temperature then the layers separated and the aqueous layer washed 2x with 5 mL of Et₂O. The organics were combined, dried (MgSO₄), filtered and Et₂O rotovaped off and the crude product dissolved in CH₂Cl₂ and columned through silica gel using 10% EtOAc: Hexanes as eluent to give 26 mg (34%) of 4-phenylpyridine.

**Synthesis of 2-phenyl-benzothiazole (Compound A.4, Scheme A.3):**

Compound A.3 (0.15 mmol, 42 mg) and o-chloranil (0.15 mmol, 37 mg) were mixed in 5 mL CH₃CN and heated at 45°C for 4 hrs. The solution was then columned directly through silica gel using 5% EtOAc:Hex as eluent to give 28 mg (87%) of 2-
phenyl-benzothiazole (Rf ~ 0.6 in 20% EtOAc:Hex, CAUTION: the Rf of the starting material compound A.3 is very similar). $^1$H NMR (300MHz, CDCl$_3$): $\delta$ 8.13-8.07 (m, 3H), 7.93-7.90 (d, 1H, $J = 9$Hz), 7.54-7.45 (m, 4H), 7.40-7.36 (t, 1H). $^{13}$C NMR (75.5 MHz, CDCl$_3$): $\delta$ 168.3, 154.4, 135.3, 133.9, 131.2, 129.2, 127.8, 126.5, 125.4, 123.5, 121.8. HRMS (M+H) for C$_{13}$H$_9$NS; calculated: 212.0529, found: 212.0528.

$^1$H and $^{13}$C NMR Spectra for Compounds A.2 and A.4:
A.5 References


