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Multi-Component Copper Catalyzed Methods to Access Highly-Substituted Amine-Bearing Carbon Centers from Simple Starting Materials

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Multi-Component Copper Catalyzed Methods to Access Highly-Substituted Amine-Bearing Carbon Centers from Simple Starting Materials

A Dissertation submitted in partial satisfaction of the requirements for the degree of

Doctor of Philosophy

in

Chemistry

by

Conor John Pierce

August 2013

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University of California, Riverside
ABSTRACT OF THE DISSERTATION

Multi-Component Copper Catalyzed Methods to Access Highly-Substituted Amine-Bearing Carbon Centers from Simple Starting Materials

by

Conor John Pierce

Doctor of Philosophy, Graduate Program in Chemistry
University of California, Riverside, August 2013
Dr. Catharine Larsen, Chairperson

The Larsen group specializes in maximizing the potential of simple organic substrates through single-step, multicomponent reactions to yield complex compounds with potential therapeutic and synthetic applications. Combining a carbonyl, an amine, and a terminal alkyne under a variety of novel conditions provides a range of propargylamines.

Attempts towards the incorporation of labile protecting groups on propargylamines led to the discovery of the first catalytic three-component method able to incorporate electron-poor amines, specifically p-toluenesulfonamide. Mechanistic studies showed copper(II) triflate to be unique in its ability to catalyze both the condensation of p-toluenesulfonamide onto an aldehyde and sequential coupling with a terminal alkyne. This method also provided a rare example of a three-component coupling between cyclohexanone, benzylamine, and 1-octyne. Investigations into the synthesis of this cyclohexanone-derived propargylamine led to an efficient copper(II) chloride catalyzed reaction yielding fully-substituted
centers on cyclohexane rings. Equimolar amounts of starting reagents, low-catalyst loading, and water as the sole byproduct of this reaction leant to its efficacy. Inclusion of Lewis acidic titanium tetraethoxide provided a Cu/Ti catalyzed method of novel scope, allowing for the first coupling of acyclic ketones with amines and alkynes to give fully-substituted amine-bearing carbon centers in a single step.

An alternate route to these densely-functionalized substrates was discovered to be a unique tandem hydroamination/alkynylation reaction. Markovnikov addition of an amine across a terminal alkyne yields enamine which, upon tautomerization to ketimine, is coupled with a second equivalent of the same alkyne to form propargylamine.
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Chapter 1

A Single Cu(II) Catalyst for the Three-Component Coupling of Diverse Nitrogen Sources With Aldehydes and Alkynes

I. Introduction

The demand for easily accessible therapeutic targets has kept small-molecule methodology at the forefront of academic and industrial research for decades. Of the immense scope of substrates now synthetically available, the inherent bioactivity of propargylamines has set them apart as an attractive target. Methods achieving these substrates have become more efficient over the last few years, moving from stoichiometric use of additives towards one-pot catalytic pathways.

A central focus of the Larsen group has become the development of novel routes to realize these propargylamine substrates from simple starting materials. This thesis describes investigations into the incorporation of electron-deficient amines into the three-component coupling of an aldehyde, a primary or secondary amine, and a terminal alkyne. Explorations into a novel catalytic system capable of alkynylating para-toluenesulfonyl-protected imines began with the development of a low-yielding, but first of its kind, copper acetylide addition to an electron-poor imine. It was discovered that copper(II) triflate is uniquely capable of producing propargylamines from both electron-rich and -poor imines generated in situ, efficiently expanding the scope of this reaction allowed under catalytic conditions.
II. Background

The value of propargylamines is derived from both their inherent bioactivity as well as their use as synthetic building blocks in the construction of more complex therapeutics.\textsuperscript{1} Both chiral and achiral propargylamines display a range of activities, including but not limited to: antiviral, antibiotic, anticancer, herbicidal, and antihypertensive.

**Figure 1.** Propargylamines show range of therapeutic activities

![Propargylamines](image)

Figure 1 displays select examples of propargylamine moieties in blue as part of simple small molecule therapeutics (Selegiline, Rasagiline, Ladostigyl, and Pargyline). Also shown are two examples of accessing propargylamines as a valuable intermediate step in the synthesis of larger, more complex molecules. The first is Dynemicin A, a natural product originally isolated from the bacteria
Micromonospora chemis found in the soils of India.\(^2\) This isolate contains a tertiary propargylamine and displays both antibiotic and cytotoxic activities, with the latter providing the most promise. The second of these more complex therapeutics is an HIV reverse transcriptase inhibitor synthesized, along with several active derivatives, by Yu et al. in 1995.\(^3\) These are only a few examples of the vast therapeutic potential provided by propargylamines.\(^3-6\) Due to this significant bioactive potential, research into routes providing access to these substrates, both as intermediates and end products, has gained increasing attention over the last decade.

**Scheme 1.** Two-step route via imine alkynylation provide propargylamines

Numerous synthetic routes have been developed with the purpose of accessing propargylamines from a wide-range of starting materials. Initial reports utilized a two-step method detailed in Scheme 1 that begins with the isolation of an imine intermediate formed from the condensation of a primary or secondary amine onto an aldehyde. This imine provides an excellent electrophile at the
electron-poor azomethine carbon adjacent to the nitrogen. A nucleophilic terminal alkyne, activated either by catalyst or stoichiometric additive, readily attacks this electrophilic center to from a new carbon-carbon bond and the desired propargylamine product.

The first catalytic addition of an alkyne to an imine was published by Carriera in 2001 and is summarized in Scheme 2 (1). An iridium catalyst was utilized to efficiently couple trimethylsilylacetylene to a range of imines derived from benzylamine and aniline. Using tetrahydrofuran (THF) as a solvent and stirring the reactants at room temperature provided a range of propargylamines in 54-85% isolate yields. Despite the limited scope, this reaction was sufficiently impressive given the low catalyst loading of only 4-5 mol%.

**Scheme 2.** First catalytic couplings of alkyne to aldehyde-derived imines

\[
\begin{align*}
1 & \quad N^\text{R}^2 + \text{SiMe}_3^\text{SiMe}_3 \quad \xrightarrow{\text{4-5 mol\% [IrCl(COD)]}_2, \text{THF, RT, 24 h}} \quad \text{R}^1\text{HN}^\text{R}^2 \quad 54-85% \\
\end{align*}
\]

- First example of catalytic addition of alkyne to imine

\[
\begin{align*}
2 & \quad \text{Pr}^\text{N} + \text{Ph} \quad \xrightarrow{\text{5 mol\% CuBr, 5.5 mol\% (+)-Quinap, Toluene, RT, 3-24 h}} \quad \text{Pr}^\text{N}^\text{Ph} \quad 99\% \text{ yield, 77\% ee} \\
\end{align*}
\]

- First enantioselective addition of alkynes to imines
Only one year later, Knochel was able to achieve the first asymmetric variant of this reaction (2).\(^8\) Utilizing copper(II) bromide as a catalyst and (+)-Quinap as ligand, this method allows asymmetric access to propargylamines from enamine and phenylacetylene starting materials. In as little as three hours, in toluene at room temperature, desired product is isolated in up to 99% yield and 77% ee. These same conditions, without need of (+)-Quinap, provide one of the first examples of a tetrasubstituted propargylamine synthesized from a cyclohexanone-derived enamine and phenylacetylene in 75% yield.

Both of these methods, while remarkable in their novelty, suffer from some of the same limitations that still plague this specific branch of organic synthesis even twelve years later. Like the initial report by Carreira, most published routes are limited to the use of anilines as an amine source.\(^9\)-\(^{14}\) Even those methods capable of expanding the scope of accessible nitrogen sources past aniline to incorporate secondary amine sources are usually limited to cyclic piperidines.\(^15\)-\(^{18}\) The scope of these reactions is further limited by the predominance of benzaldehyde-derived imines attacked by phenylacetylenes.\(^9\)-\(^{18}\) The example provided by Knochel and coworkers, highlighted earlier in Scheme 2, utilized the broadest scope of alkynes and alkyl-aldehyde-derived starting materials, but only secondary amines are tolerated.

As research into these areas progressed, methods evolved the ability to synthesize propargylamines via a three-component route.\(^19\)-\(^{25}\) Through application of a range of metal catalysts, predominantly copper but also zinc and iron, methods
were developed capable of achieving both the *in situ* generation of imine (or iminium) intermediate and sequential alkynylation to give propargylamine. The development of these three-component routes not only made the synthesis of propargylamines a more efficient process, but also allowed for a significant expansion of scope. Methods were now capable of incorporating both primary and secondary amines as well as alkyl, aryl, and silyl acetylenes. Despite these advancements however, one predominant limitation remained: the catalytic alkynylation of imines derived from an electron-poor amine source.

Of all of the research published in this area, there were no examples of a three-component coupling (3CC) incorporating an aldehyde, electron-poor amine, and terminal alkyne. Even the two-step method involving the alkynylation of an imine derived from an electron-deficient amine source lacks a catalytic variant. To the best of my knowledge, the best route to access electron-poor propargylamines involves the alkynylation of isolated $\textbf{p}$-toluenesulfonyl (Ts) imines with six equivalents (equiv) of dimethyl zinc ($\text{ZnMe}_2$) and 20 mol\% of binol ligand.\textsuperscript{26} The required use of an excess of toxic $\text{ZnMe}_2$ is not the only difficulty presented in the search for a catalytic 3CC method to incorporate electron-poor amine sources. Even synthesis and purification of the imine intermediate is difficult. Imines derived from electron-rich amine sources involve a significantly simpler synthesis than their electron-poor counterparts. As shown in Scheme 3, the formation of imine from equimolar amounts of aldehyde and benzylamine is spontaneous, requiring only the use of a drying agent to remove water evolved in the condensation and
dichloromethane (DCM) as a solvent. Desired substrate is isolated in quantitative yield in only 30 minutes. Comparing the facility of this synthesis with the three day, 2-step process described in Scheme 4 puts the difficulty of accessing these electron-poor products into perspective. First, the condensation of \( t \)-butyl carbamate (Boc-NH\(_2\)) onto an aldehyde involves exposure to formic acid in methanol:water over 48 hours. This condensation product requires stabilization to prevent deprotection of nitrogen by the acidic, so includes 2.0 equiv of benzenesulfonic acid sodium salt. This intermediate is then heated at reflux in THF for 15 hours in the presence of potassium carbonate (K\(_2\)CO\(_3\)) and sodium sulfate (Na\(_2\)SO\(_4\)) to elicit desired Boc-protected imine.\(^{28,29}\)

**Scheme 3.** Spontaneous synthesis of benzyl-protected imines

![Scheme 3](image)

**Scheme 4.** 3-day, 2-step synthesis of Boc-protected imines

![Scheme 4](image)
The current limitations imposed on the catalytic incorporation of electron-deficient nitrogen sources via 3CC methodology needed to be addressed sequentially. First, a catalyst capable of alkynylationing an imine derived from an electron-poor amine and aldehyde would need to be found. Next, conditions must be found which are able to integrate that same catalyst in the *in situ* formation of imine. From these investigations it was hoped that a novel route could be developed that could tolerate a wide variety of functional groups on amine, aldehyde, and alkyne.

**III. Studies into Catalyst Role Reveal Copper(II) Triflate as Uniquely Capable**

Explorations into operable catalyst sources began by screening available literature for potential candidates. As discussed previously, many published methods utilize copper, often copper(I) bromide, to efficiently couple alkynes to a range of imines either pre-formed or generated *in situ*. Coupling this knowledge with the report that ZnMe$_2$ allows for the alkynylation of Ts-protected imines when present in stoichiometric amounts and we can outline the likely attributes of a successful catalyst. First, that copper is an excellent choice of metal catalyst given that its low relative cost and previous success in generating propargylamines. Second, the utility of ZnMe$_2$ indicates a need for route that involves lewis acidic conditions. From there it is simply a matter of optimizing the reaction via use of ligand or base, two additives of general import in previous publications. The starting point for this research is summarized in Scheme 5.
Scheme 5. Can Cu catalyze the coupling of alkynes to Ts-protected imines?

Initial screening involved the use of 10 mol% of several different copper (I) and (II) sources. In order to test for catalytic efficacy, copper sources were added to reaction vials containing a magnetic stir bar (MSB), pre-formed Ts-protected imine derived from cyclohexanecarboxaldehyde, and 1-octyne in excess. Toluene was used as solvent. The results of this catalyst screen are summarized in Table 1, below. Surprisingly, Cu(II) triflate proved to be uniquely capable of providing alkynylation of this $N$-Ts imine. None of the other copper sources tested (Cu(I) iodide, Cu(I) bromide, Cu(I) bromide dimethylsulfide, Cu(I) triflate tetrakisacetonitrile, Cu(II) sulfate, and Cu(II) perchlorate) showed any catalytic activity. Even Cu(I) triflate, both pure and acetonitrile salt, provided no conversion to desired product. More interesting was the role of base in this reaction: addition of 20 mol% base (cesium carbonate, potassium carbonate, and potassium tert-butoxide) halts the reaction completely, causing Cu(II) triflate to give results identical to sources deemed ineffectual. However, use of only 10 mol% base simply slows the rate of reaction. It is this information that provides us our first real insight into the reasoning behind the unique ability of Cu(II) triflate to catalyze the alkynylation of Ts-protected imines.
Table 1. Alkynylation of N-Tosyl imines requires Copper(II) triflate

![Reaction Scheme](image-url)

<table>
<thead>
<tr>
<th>entry</th>
<th>Cu source</th>
<th>base</th>
<th>conversion (%)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cul</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>2</td>
<td>CuBr</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>CuBr•Me₂S</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Cu(NCCH₃)₄•CF₃SO₃</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>CuSO₄</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Cu(ClO₄)₂•5H₂O</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OTf)</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OTf)₂</td>
<td>--</td>
<td>85</td>
</tr>
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<td>9</td>
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</tr>
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<td>Cu(OTf)₂</td>
<td>K₂CO₃</td>
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</tr>
<tr>
<td>11</td>
<td>Cu(OTf)₂</td>
<td>KOtf-Bu</td>
<td>0</td>
</tr>
</tbody>
</table>

*Conversions calculated via GC

In an effort to study the mechanistic role of Cu(II) triflate in this reaction, a series of reactions was set up to determine if Cu(II) was dissociating into a Cu(I) species. Figure 2 summarizes the findings of this investigation. The setup involved the observation of four reactions running simultaneously. 20 mol% Cu(II) triflate (blue) was compared against only 10 mol% Cu(II) triflate (purple), 10 mol% Cu(I) iodide plus 10 mol% Cu(II) triflate (green), and 10 mol% Cu(I) bromide plus 10 mol% Cu(II) triflate (red). By monitoring the rate of each individual reaction we hoped to determine whether Cu(I) played any role. Cu(I) bromide and Cu(I) iodide
were chosen due to their prevalent use as catalysts in previously reported methods accessing propargylamines. The findings were conclusive: Cu(I) played no role in the alkynylation of Ts-protected imines with 1-octyne. Additionally, the reaction was determined to be first order in Cu(II) triflate due to the doubling of reaction rate when catalyst loading is also double. This study confirmed Cu(II) triflates inimitable ability to form N-Ts propargylamines. It was postulated that this ability is derived from the increased Lewis acidity on Cu due to the triflate ligands, providing superior activation of Ts-imine toward the addition of 1-octyne via its copper acetylide. Thus, the key to the first catalytic alkynylation forming sulfonylated propargylamines was the specific combination of Cu(II) with triflate counteranion.

**Figure 2.** Reaction rate of Ts-protected imine alkynylation dependent on Cu(II)
Still concerning was the mechanistic relationship between copper catalyst and basic additive. As Cu(II) triflate is present in only 10 mol%, we were initially perplexed why use of 20 mol% vs. 10 mol% base affected the rate of reaction. If the rate reduction was related to an interaction between the copper metal and basic additive, than addition of equivalent amounts of both should have been sufficient to halt reaction progress. This leads to the discussion of the triflate anions playing a role in the reaction mechanism. Specifically, that those triflate anions may be forming triflic acid in situ. This assumption is backed up by the literature, as Tschan et al. published in 2009 showing that copper(II) triflate serves as a solid source of trifluoromethane sulfonic (triflic) acid. Furthermore, Bowring, Bergman, and Tilley used a hydroarylation reaction to prove that another metal catalyst, specifically (COD)Pt(OTf)₂, can provide triflic acid in sufficiently catalytic amounts. Their findings explained that not only could a triflate counteranion on a metal form triflic acid in situ, but that the same amount of triflic acid added independently was actually a more efficient catalyst as it nullified side-products present due to stabilization of the reaction intermediate by the platinum metal. My own studies showed that while triflic acid added in tandem with Cu(II) triflate did indeed increase the reaction rate, triflic acid on its own could not catalyze the alkynylation of Ts-protected imines. As the accepted copper-catalyzed route to propargylamines involves the imine binding to a copper acetylde, with no mention of triflic acid, these investigations into the catalytic efficacy of Cu(II) triflate ended up yielding more questions than answers.
IV. N-Ts 3CC Proceeds More Efficiently Than from Preformed Imine

Having established the catalytic superiority of Cu(II) triflate in the alkynylation of Ts-protected imines, p-toluenesulfonamide (Ts-NH₂) was condensed upon a range of aldehydes to provide a variety of imines for testing the efficacy of these new conditions. Imines were prepared separately from both aryl and alkyl aldehydes, dissolved in dichloroethane, and successively exposed to 10 mol% Cu(II) triflate at 100 °C in the presence of 1.5 equiv. of terminal alkyne. Table 2 displays the results of these reactions.

**Table 2.** Cu catalyzed alkynylation of Ts-protected imines is incomplete
These conditions were shown to best couple alkyl terminal alkynes with Ts-protected imines derived from alkyl alkynes. As seen in Table 2, propargylamines were successfully synthesized from imines bearing branched (1b and 1d), cyclic (1c), long-chain (1e), and bulky side chains (1a). It was these groups alpha to the nitrogen in the final product that appeared to play the most important role in determining reaction efficiency. The highest yield, a modest 63%, was isolated in two days from the coupling of Ts-protected cyclohexyl imine and 1-octyne (1c). Structurally similar isopropyl imine provided a 55% isolated yield (1b) in the same amount of time. Sterically bulky pivaldehyde-derived imine gave propargylamine containing a t-butyl group in decent 49% yield after only one day when coupled with 1-octyne (1a). Achieving propargylamines bearing longer alkyl chains at the α-position proved more difficult. Inclusion of an isobutyl group reduces isolated yield down to 40% even after reaction time is doubled to four days (1d). Attempts to couple 1-octyne to n-butyl derived imine also led to lower conversion and slower rate, cutting the isolated yield to the lowest value in the table at only 21% (1e).

It is important to note that even though the isolated yields of these compounds are generally low, these conditions are the first to provide a catalytic alkynylation forming sulfonylated propargylamines. It was for this reason that investigations into the optimization of this novel, but currently low-yielding, method continued. First, we needed to understand why conversions of our starting reagents to propargylamine were so low. Listed beneath each isolated yield in Table 2 are corrected GC yield values in red. These numbers represent the amount
of product present in the reaction once it is deemed complete, corrected using dodecane as an internal standard and a previously obtained internal response factor (IRF) for each compound of interest. The disparity between these two listed values was believed to be the result of hydrolysis of imine in the reaction back to aldehyde and \( p \)-toluenesulfonamide. The low reactivity of our amine was believed to have prevented spontaneous reformation of imine \textit{in situ}, meaning this hydrolysis would be competitively inhibiting the desired alkynylation reaction by removing applicable starting materials.

To test this hypothesis, Ts-NH\(_2\) and cyclohexanecarboxaldehyde were added directly to reaction mixture containing 1-octyne and Cu(II) triflate in toluene. It was assumed that without the stabilizing intermediate provided by the necessary 2-step synthesis of Ts-protected imines detailed in Scheme 4 above, no imine would form and thus no conversion to product from starting reagents observed. Surprisingly, this assumption was proven false. In fact, not only did this 3CC approach produce sulfonylated propargylamine, it did so faster and gave higher yields than the previous 2-step approach. The direct comparison is detailed in Scheme 6 below. Imine preformed from Ts-NH\(_2\) and cyclohexanecarboxaldehyde then exposed to 1-octyne in the presence of 10 mol\% Cu(II) triflate resulted in a 63\% isolated yield after four days of stirring in toluene at 100 °C (1c). Forgoing the isolation of imine in lieu of direct addition of aldehyde and amine, the same conditions gave a 79\% isolated yield in only two hours (2a). This is an incredible 20-fold increase in rate, achieved through a simple alteration of reaction setup.
Scheme 6. Rate of imine alkynylation is 20-fold slower than 3CC reaction

- Imine is most basic species and readily binds to copper towards activation

- A smaller amount of a more highly activated imine intermediate is formed

- Copper acetylide attack on iminium could account for these rate effects

In addition to gains made to isolated yields, the success of this new 3CC route gave valuable insight into our reaction mechanism. The catalytic route most cited involves the formation of copper acetylide, activating the alkyne nucleophile, and sequential coordination of this copper acetylide to the basic nitrogen on the imine, activating it as the electrophile (Figure 3). The fact that our 3CC conditions work so much more efficiently than the 2-step method suggests that this new method progresses through an alternate, more reactive intermediate. Specifically, that the condensation of amine onto aldehyde in situ produces a charged, highly reactive, iminium intermediate (Scheme 6).
Figure 3. Literature cites catalytic cycle that proceeds via Cu activation of imine

![Catalytic Cycle Diagram](image)

Figure 4. Proposed alternate catalytic cycle proceeds via iminium intermediate

![Alternate Catalytic Cycle Diagram](image)
Copper acetylide is proposed to form in both catalytic pathways as activated nucleophile, so is treated as a constant and should not affect the rate at which our synthesis proceeds. Instead, this alternate catalytic cycle (Figure 4) utilizes the inherent electrophilicity of an iminium ion as justification for the drastic 20-fold rate increase discussed previously. Formation of an iminium intermediate also shed light on our earlier assumption involving the competitive inhibition of imine hydrolysis. Rather than impeding reaction progress, the hydrolysis we observed of imine back to aldehyde and amine by GC may have been the only reason the reaction with pre-formed imine worked at all. The assumption that Cu will readily coordinate to a Ts-protected nitrogen as readily as it would a benzyl-protected one may have been incorrect. It is possible that the strongly electron-withdrawing character of p-toluenesulfonate can effectively inhibit the coordination of copper to nitrogen, thus preventing activation and eventual alkynylation. This reasoning also helps explain why many copper catalyzed routes to propargylamines efficiently incorporate electron-rich protecting groups on imines such as aniline, but are unable to extend their scope to electron-poor imines.

Recognition of the opportunities presented by utilization of this novel 3CC method, and understanding of the limitations that were presented by the original 2-step route, meant that the scope of this reaction had to be reevaluated. Our initial findings so far indicated that this 3-component coupling of aldehydes, amines, and alkynes (A³ coupling) would be the first protocol to tolerate a wide variety of functional starting reagents.
V. Substrate Scope Provided by Cu(OTf)$_2$ Achieves Propargylamines From Range of Amines, Alkyl Aldehydes, and Terminal Alkynes

Our novel 3CC route was first used to reexamine the utility of Cu(II) triflate in synthesizing propargylamines from *para*-toluenesulfonamide. Previous optimization showed that though toluene and dichloroethane (DCE) yielded equally superior conversions, DCE’s carcinogenic attributes and toluene’s relative inexpense led to the primary use of the latter as solvent. Standard conditions involved Ts-NH$_2$ as limiting reagent, aldehyde present in a slight excess of 1.1 equiv., and alkyne added in 1.5 equiv., all stirred at 100 °C until conversion to propargylamine was determined complete by GC analysis.

Table 3 shows the variety of functional groups made available on the terminal alkyne when reacted with Ts-NH$_2$ and cyclohexanecarboxaldehyde. Both straight chain and branched alkyl alkynes reacted efficiently, with 1-octyne and 1-hexyne giving good yields of 79% (2a) and 70% (2b), respectively. The reaction involving 1-hexyne was run at a relatively lower temperature (60 °C) for longer (42 hours) due to its lower boiling point. Another alkyl alkyne, tert-butyl acetylene, provided sterically bulky 3c in 88% yield (2c). This method also proved to tolerate chloro-alkynes, as 5-chloro-1-pentyne provided an isolated 81% yield after only two hours at 100 °C (2g). Propargylsulfonamides 2d and 2f from sensitive alkynes bearing phenyl groups required an equivalent of sodium sulfate (Na$_2$SO$_4$), lower temperatures, and longer reaction times to proceed cleanly to 80% and 76% yield, respectively. Similarly, higher yields of acid-sensitive silyl alkynes 3h and 3i (78%
and 80%) were produced with 10 mol% of Cs$_2$CO$_3$ added. Presence of base slowed the reaction, but allowed for clean isolation and prevented acetyl deprotection. Reactions with alternate alkyl aldehydes under these conditions also proved effective, yielding propargylamines with iso-propyl and tert-butyl side chains from Ts-NH$_2$ and 1-octyne in respective 82% (2j) and 88% (2k) yields.

Table 3. Alkyne variation in forming $N$-Tosyl-propargylamines

<table>
<thead>
<tr>
<th>Alkyne Variation</th>
<th>Yields</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0 equiv.</td>
<td>79%</td>
</tr>
<tr>
<td>1.1 equiv.</td>
<td>70%</td>
</tr>
<tr>
<td>1.5 equiv.</td>
<td>88%</td>
</tr>
</tbody>
</table>

*1.0 equiv. Na$_2$SO$_4$**

**10 mol% Cs$_2$CO$_3$**
While 10 mol% of Cu(II) triflate was routinely employed at elevated temperatures in these investigations, couplings with sulfonamides did proceed at room temperature, but reaction time increased from hours to weeks. Also, catalyst loadings could be lowered to 2 mol% in some cases if the temperatures were decreased accordingly to avoid decomposition of remaining starting materials while awaiting reaction completion. For those coupling partners above that required the use of drying agent, it was found that addition of sodium sulfate to reactions involving any reagent whose label states “air sensitive” or recommends desiccator or cold storage improved conversion to product. Neither magnesium sulfate (MgSO₄) nor pulverized molecular sieves resulted in a similar effect, neither preventing the decomposition of starting materials prevented by Na₂SO₄.

One limitation to the scope of these conditions is obvious from the results displayed in Table 3: only alkyl aldehydes yield sulfonylpropargylamines. As an example, treatment of Ts-NH₂ with benzaldehyde and Cu(II) triflate efficiently forms imine that subsequently does not react. As all other nitrogen sources that form imine Cu(II) triflate catalysis underwent alkynylation, and all reaction conditions were kept constant, we can attribute this lack of reactivity to expanded conjugation: The stability provided by conjugation extending from the aryl imine up through the p-toluenesulfonyl group prevented alkynylation. This stabilizing factor was seen in every aryl and heteroaryl aldehyde partner tested. As expected, exposure of preformed imine from benzaldehyde to 1-octyne gave no conversion to product.
Table 4. Scope of first catalytic route to tolerate electron-poor amine sources

<table>
<thead>
<tr>
<th>R^1_N-R^2</th>
<th>R^3</th>
<th>10 mol% Cu(OTf)_2</th>
<th>toluene</th>
<th>80 °C</th>
<th>R^1_N-R^2</th>
<th>R^3</th>
<th>n-Hex</th>
</tr>
</thead>
<tbody>
<tr>
<td>H</td>
<td>O</td>
<td>n-Hex</td>
<td>3a</td>
<td>88%</td>
<td>72 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>n-Hex</td>
<td>3d</td>
<td>90%</td>
<td>1 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>n-Hex</td>
<td>3e</td>
<td>72%</td>
<td>24 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>Ph</td>
<td>n-Hex</td>
<td>74%</td>
<td>16 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>n-Hex</td>
<td>3h</td>
<td>78%</td>
<td>18 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>F</td>
<td>n-Hex</td>
<td>3g</td>
<td>97%</td>
<td>4 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>n-Hex</td>
<td>3i</td>
<td>89%</td>
<td>24 h</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>n-Hex</td>
<td>3k</td>
<td>71%</td>
<td>24 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CF_3</td>
<td>n-Hex</td>
<td>3j</td>
<td>77%</td>
<td>22 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>n-Hex</td>
<td>3l</td>
<td>92%</td>
<td>6 h</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>OMe</td>
<td>n-Hex</td>
<td>72%</td>
<td>48 h</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Me</td>
<td>N-Ts</td>
<td>n-Hex</td>
<td>88%</td>
<td>4 h</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Isolated yield (%) with variations noted: a) 1.0 or 2.0 equiv. Na_2SO_4; b) 100 °C
When \( p \)-toluenesulfonamide is substituted for any other of the tested nitrogen sources displayed in table 4, aryl aldehydes react efficiently. The top row of table 4 displays three different aldehydes that couple with benzylamines and 1-octyne under our Cu(II) triflate catalyzed conditions to give propargylamines. Incorporation of electron-poor 2-fluorophenyl (3a), isopropyl (3b), and electron-rich furanyl (3c) groups display this reactions impressive toleration of functionality. Cyclic piperidine reacts with 3-fluorobenzaldehyde to afford 7d in high 90% yield. While one of the highlights of this protocol is that it applies to non-aniline nitrogen sources, even hindered \( N \)-methylaniline reacts efficiently (3e). Morpholine capably condenses onto electron-rich aldehydes bearing benzothiophene (3f) and pyridyl (3g) groups to give excellent 74% and 97% isolated yields. Morpholine, along with greasy \( N \)-cyclopropylpropanemethylamine, also forms propargylamine from trifluorobenzaldehydes to give products 3i and 3j in 89% and 77% yields. As seen with substrates 3h and 3k, alkyl aldehydes react as efficiently with each new tested amine source as they do with Ts-NH\(_2\). 3-phenylpropylamine and pyrrolidine afford propargylamine from bulky trimethylacetaldehyde and \( iso \)-butyraldehyde in 78% and 71% isolated yields, respectively. Lastly, deprotectable \( p \)-methoxybenzyl (PMB) protected amine is reacted with 4-fluorobenzaldehyde and 1-octyne to give 3m in high 72% yield. In all, table 4 showcases how this single catalyst can couple alkynes to a variety of imines formed \textit{in situ} from aldehydes bearing both aryl or alkyl groups and a wide range of amino sources: anilines, alkylamines, benzylamines, \( N \)-heterocycles (piperidine, morpholine, and pyrrolidine), \( p \)-
methoxybenzylamine, and sulfonamide. From numerous commercially available starting materials we can access an extensive level of molecular complexity. Potential derivatization at multiple positions, the free position on the nitrogen or one of many alkyne substituents for example, further increase the value of this protocol.

VI. Same Method Provides Rare Three-Component Alkynylation with Ketone

The importance of this Cu(II) catalyzed route to the synthesis of highly-functionalized propargylamines is further stressed when the carbonyl source is switched from an aldehyde to a ketone. The incredible value of a synthetic method that can incorporate both of these types of compounds is discussed in Chapter 2 of this dissertation. Benzylamine and 1-octyne were stirred with cyclohexanone under our standard conditions to provide propargylamine 4 (Scheme 7) in 80% yield. This compound represents a rare, catalytic, three-component condensation-alkynylation involving a ketone. Surprisingly, despite the lower general reactivity of ketones compared to aldehydes, no additional reagents are required to instigate conversion of cyclohexanone to product. Also, the lower reactivity does not seem to affect the time required to achieve full conversion. In comparison to our other isolated benzyl-protected substrates, a reaction time of 22 hours is relatively quick. This three-component alkynylation incorporating a ketone attains fully substituted nitrogen centers in a single step.
Scheme 7. Rare 3-component alkynylation with a ketone

In summary of these findings, we have shown that Cu(II) triflate is uniquely capable of catalytically alkynyling sulfonamide-derived imines via a 3CC route. Additionally, this catalyst forms imine/iminium from electron-poor and -rich amines, powerfully coupling them with a range of alkynes to give propargylamines and water as sole byproduct. The dense functionality of these propargylic products, all from commercially available starting materials, marks them as both malleable synthetic building blocks and valuable potential therapeutic targets.
VII. Literature Citations

(1) Yamada, K.-i.; Tomioka, K. *Chemical Reviews* **2008**, *108*, 2874.


VIII. Supporting Information

General Reagent Information

All reactions were set up on the benchtop in oven-dried screw-cap test tubes with Teflon seal inserts and carried out under an atmosphere of argon. Flash column chromatography was performed using florisil purchased from Alfa Aesar. Toluene was purchased from Aldrich in Sure-Seal bottles and used as received. Copper(II) trifluoromethanesulfonate, Cu(OTf)$_2$, was purchased from Alfa Aesar and used as supplied. Amines were purchased from Acros Organics, Alfa Aesar, or Aldrich and flushed through alumina before use. All aldehydes and alkynes were purchased from Acros Organics, Alfa Aesar, or TCI America and were purified by distillation before use as in Amerengo, W. L. F.; Perrin, D. D. *Purification of Laboratory Chemicals*. 4th ed.; Butterworth-Heinemann: Oxford, U.K. 1996.

General Analytical Information

$^1$H and $^{13}$C NMR spectra were measured on a Varian Inova 400 (400 MHz) spectrometer using CDCl$_3$, acetone-d6, or CD$_3$CN as a solvent at room temperature. Some spectra include tetramethylsilane as an internal standard. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet and br - broad. NMR spectra were acquired at 300 K. Gas chromatography spectra were obtained on an Agilent Technologies 6850 GC System using dodecane as an internal standard. IR spectra of solids were recorded on Perkin Elmer Spectrum One FT-IR Spectrometer. Attenuated total reflection infrared (ATR-IR) was used
for analysis with selected absorption maxima reported in wavenumbers (cm\(^{-1}\)). No sample preparation was necessary for ATR analysis. ATR-IR is based on the propagation of the infrared radiation through an internal reflection element (crystal) with a high refractive index, and its reflection at the interface between the crystal and the solid material. Mass spectrometric data was collected on a HP 5989A GC/MS quadrupole instrument. Exact masses were recorded on a Waters GCT Premier ToF instrument using direct injection of samples in acetonitrile into the electrospray source (ESI) and either positive or negative ionization.

General Procedure

A. To an oven-dried test tube and magnetic stir bar was added amine (1.0 equiv.) and 10 mol% Cu(OTf)$_2$. The flask was purged with argon for 15 minutes. Aldehyde (1.1 equiv.), alkyne (1.5 equiv.), and toluene (1 mL) were added, and the reaction was stirred at the designated temperature for the indicated time. Upon completion (as judged by GC), the mixture was cooled to room temperature and diluted with 5 mL diethyl ether (Et$_2$O). Combined organics were washed with 1M aqueous HCl and sat. aq. NaHCO$_3$, dried over Na$_2$SO$_4$ for 30 minutes, and reduced in vacuo. Next, 20 mL chloroform and 1.0 g florisil were added and concentrated under vacuum for dry loading atop a florisil gel column. Chromatography with ethyl acetate (EtOAc) or Et$_2$O in hexanes as eluent afforded the desired product.
B. To an oven-dried test tube and magnetic stir bar was added amine (1.0 equiv.), Na$_2$SO$_4$ if specified, and 10 mol% Cu(OTf)$_2$. The flask was purged with argon for 15 minutes. Aldehyde (1.1 equiv.), alkyne (1.5 equiv.), and toluene (1 mL) were added, and the reaction was stirred at the designated temperature for the indicated time. Upon completion (as judged by GC), the mixture was cooled to room temperature and diluted with 20 mL chloroform and reduced in vacuo. Resulting oil was loaded directly onto column for chromatography with EtOAc or Et$_2$O in hexanes as eluent afforded the desired product.

C. To an oven-dried test tube and magnetic stir bar was added amine (1.0 equiv.), Na$_2$SO$_4$ (1.0 equiv.), and 10 mol% Cu(OTf)$_2$. The flask was purged with argon for 15 minutes. Aldehyde (1.1 equiv.), alkyne (1.5 equiv.), and toluene (1 mL) were added, and the reaction was stirred at the designated temperature for the indicated time. Upon completion (as judged by GC), the mixture was cooled to room temperature and diluted with 5 mL diethyl ether (Et$_2$O). Combined organics were washed with 1M aqueous HCl and sat. aq. NaHCO$_3$, dried over Na$_2$SO$_4$ for 30 minutes, and reduced in vacuo. Then 20 mL chloroform and 1.0 g florisil were added and concentrated under vacuum for dry loading atop a florisil gel column. Chromatography with EtOAc or Et$_2$O in hexanes as eluent afforded the desired product.

D. To an oven-dried test tube and magnetic stir bar was added amine (1.0 equiv.), Na$_2$SO$_4$ (1.0 equiv.), 10 mol% Cs$_2$CO$_3$, and 10 mol% Cu(OTf)$_2$. The flask was purged with argon for 15 minutes. Aldehyde (1.1 equiv.), alkyne (1.5 equiv.),
and toluene (1 mL) were added, and the reaction was stirred at the designated temperature for the indicated time. Upon completion (as judged by GC), the mixture was cooled to room temperature and diluted with 5 mL diethyl ether (Et₂O). Combined organics were washed with sat. aq. NaHCO₃, dried over Na₂SO₄ for 30 minutes, and reduced in vacuo. Then 20 mL chloroform and 1.0 g florisil were added and concentrated under vacuum for dry loading atop a florisil gel column. Chromatography with EtOAc or Et₂O in hexanes as eluent afforded the desired product.

(2a) N-(1-cyclohexylnon-2-yn-1-yl)-4-methylbenzene-1-sulfonamide

Prepared according to general procedure A: p-toluene sulfonamide (172 mg, 1.0 mmol), cyclohexanecarboxaldehyde (134 μL, 1.1 mmol), 1-octyne (222 μL, 1.5 mmol), Cu(OTf)₂ (36 mg, 10 mol%) were stirred at 100 °C for 2h to afford the title compound as a white crystalline powder in 79% yield (0.285 g, 0.79 mmol) after column chromatography on florisil gel (2-4-6-8-10-12-15% Et₂O in hexanes). IR (film) 3285, 2928, 2854, 1599, 1427, 1332, 1299, 1158, 1094, 1049, 1020, 929, 812, 742, 679 cm⁻¹. ¹H NMR (400 MHz, acetone, 25°C) δ 7.74 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.0 Hz, 2H), 6.53 (d, J = 9.3 Hz, 1H), 3.81 (ddt, J = 8.5, 6.3, 2.1 Hz, 1H), 2.40 (s, 3H), 2.03 (dt, J = 4.4, 2.2 Hz, 1H), 1.92 – 1.76 (m, 4H), 1.69 (s, J = 21.2 Hz, 2H), 1.62 (d, J = 10.9 Hz, 1H), 1.53 – 1.40 (m, 1H), 1.32 – 0.97 (m, 12H), 0.86 (t, J = 7.0 Hz, 3H).¹³C NMR (100 MHz, CDCl₃, 25°C) δ 143.26, 137.84,

(2b) N-(1-cyclohexylhept-2-yn-1-yl)-4-methylbenzene-1-sulfonamide

Prepared according to general procedure A: p-toluene sulfonamide (172 mg, 1.0 mmol), cyclohexanecarboxaldehyde (134 μL, 1.1 mmol), 1-hexyne (174 μL, 1.5 mmol), Cu(OTf)₂ (36 mg, 10 mol%) were stirred at 60 °C for 42 hours to afford the title compound as a white crystalline powder in 70% yield (0.242 g, 0.70 mmol) after column chromatography on florisil gel (5-10-15-20% EtOAc in hexanes). IR (film) 3282, 2927, 2855, 1680, 1598, 1496, 1433, 1332, 1302, 1289, 1211, 1157, 1093, 1054, 1024, 941, 910 cm⁻¹. ¹H NMR (400 MHz, CD₃CN, 25°C) δ 7.73 (dd, J = 17.6, 8.0 Hz, 2H), 7.38 (d, J = 7.9 Hz, 2H), 5.76 (d, J = 9.3 Hz, 1H), 3.88 – 3.71 (m, 1H), 2.43 (s, 3H), 1.88 (t, J = 5.8 Hz, 2H), 1.77 (dd, J = 21.9, 12.6 Hz, 3H), 1.65 (d, J = 11.9 Hz, 2H), 1.45 (s, 2H), 1.30 – 0.95 (m, 8H), 0.86 (t, J = 6.7 Hz, 2H). ¹³C NMR (100 MHz, CD₃CN, 25°C) δ 143.45, 138.50, 129.58, 127.36, 85.44, 77.16, 51.14, 43.41, 30.57, 29.22, 28.52, 26.25, 25.85, 25.77, 21.74, 20.78, 17.79, 13.10. HRMS calculated requires [M+Na]⁺: 370.1817. Found m/z: 370.1811.
(2c) N-(1-cyclohexyl-4,4-dimethylpent-2-yn-1-yl)-4-methylbenzene-1-sulfonamide

Prepared according to general procedure A: p-toluene sulfonamide (172 mg, 1.0 mmol), cyclohexanecarboxaldehyde (134 μL, 1.1 mmol), 3,3-dimethylbutyne (185 μL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol%) were stirred at 100 °C for 4 hours to afford the title compound as a yellow crystalline powder in 88% yield (0.305 g, 0.88 mmol) after column chromatography on florisil gel (5-10-15-20-30% EtOAc in hexanes). IR (film) 3289, 2925, 2853, 1703, 1599, 1495, 1449, 1333, 1302, 1289, 1158, 1093, 1053, 1020, 930, 909, 880, 813, 718, 666 cm$^{-1}$. $^1$H NMR (400 MHz, CD$_3$CN, 25°C) δ 7.73 (d, J = 8.3 Hz, 2H), 7.37 (d, J = 8.3 Hz, 2H), 5.74 (d, J = 9.5 Hz, 1H), 3.73 (dd, J = 9.5, 6.0 Hz, 1H), 2.41 (s, 3H), 1.95 (dt, J = 4.9, 2.5 Hz, 1H), 1.82 – 1.70 (m, 4H), 1.64 (d, J = 10.9 Hz, 1H), 1.41 (tdd, J = 12.1, 6.2, 3.1 Hz, 1H), 1.23 – 1.03 (m, 4H), 0.95 (s, J = 2.2 Hz, 9H). $^{13}$C NMR (100 MHz, CD$_3$CN, 25°C) δ 143.50, 138.51, 129.71, 127.35, 93.52, 75.69, 50.95, 43.60, 30.17, 29.22, 28.40, 26.95, 26.26, 25.87, 25.79, 20.71. HRMS calculated requires [M+Na]$^+$: 370.1817. Found m/z: 370.1822.

(2d) N-(1-cyclohexyl-6-phenylhex-2-yn-1-yl)-4-methylbenzene-1-sulfonamide

Prepared according to general procedure C: p-toluene sulfonamide (172 mg, 1.0 mmol), cyclohexanecarboxaldehyde (134 μL, 1.1 mmol), 5-phenyl-1-pentyne (228
μL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol%), Na$_2$SO$_4$ (142 mg, 1.0 mmol) were stirred at 60 °C for 28 hours to afford the title compound as a white crystalline powder in 80% yield (0.327 g, 0.80 mmol) after column chromatography on florisil gel (10-20-30-40-50% Et$_2$O in hexanes). IR (film) 3282, 2925, 2853, 1599, 1496, 1451, 1331, 1301, 1289, 1158, 1093, 1038, 1021, 935, 909, 881, 816 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.73 (dd, J = 18.7, 8.2 Hz, 2H), 7.46 – 7.12 (m, 5H), 7.09 (d, J = 7.2 Hz, 2H), 4.59 (d, J = 9.5 Hz, 1H), 3.93 – 3.80 (m, 1H), 2.50 (t, J = 7.6 Hz, 2H), 2.31 (s, J = 9.2 Hz, 3H), 1.89 (td, J = 7.0, 1.8 Hz, 2H), 1.84 – 1.68 (m, 4H), 1.63 (d, J = 11.1 Hz, 1H), 1.54 (td, J = 14.7, 7.3 Hz, 2H), 1.27 – 0.98 (m, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 143.38, 141.61, 137.83, 129.59, 128.62, 128.56, 127.60, 126.15, 85.36, 77.74, 51.40, 43.52, 34.96, 30.24, 29.36, 28.45, 26.40, 26.04, 25.94, 21.63, 18.10. HRMS calculated requires [M+Na]$^+$: 432.1973. Found m/z: 432.1985.

(2e) N-(1-cyclohexyl-6-methylhept-2-yn-1-yl)-4-methylbenzene-1-sulfonamide

Prepared according to general procedure A: p-toluene sulfonamide (172 mg, 1.0 mmol), cyclohexanecarboxaldehyde (134 μL, 1.1 mmol), 5-methyl-1-hexyne (198 μL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol%) were stirred at 100 °C for 3 hours to afford the title compound as a white crystalline powder in 79% yield (0.285 g, 0.79 mmol) after
column chromatography on florisil gel (10-20-30-40-50% Et₂O in hexanes). IR (film) 3265, 2923, 2852, 1738, 1598, 1331, 1211, 1156, 1092, 1054, 1020, 933, 882, 815, 670 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ, J = 8.4 Hz, 2H), 7.29 (d, J = 8.4 Hz, 2H), 4.65 (d, J = 9.2 Hz, 1H), 3.86 (m, J = 7.6 Hz, 1H), 2.42 (s, 3H), 1.88 (m, 2H), 1.80-1.58 (m, 5H), 1.52-1.42 (m, 2H), 1.25-1.01 (m, 6H), .80 (d, 6H). ¹³C NMR (100 MHz, acetone, 25°C) 142.71, 139.37, 129.35, 127.43, 85.07, 77.32, 51.12, 43.47, 37.54, 27.06, 26.35, 25.87, 21.75, 21.67, 20.78, 16.23. HRMS calculated requires [M+Na]⁺: 384.1968. Found m/z: 384.1973.

(2f) **N-(1-cyclohexyl-3-phenylprop-2-yn-1-yl)-4-methylbenzene-1-sulfonamide**

Prepared according to general procedure C: p-toluene sulfonamide (172 mg, 1.0 mmol), Na₂SO₄ (142 mg, 1.0 mmol), cyclohexanecarboxaldehyde (134 μL, 1.1 mmol), phenylacetylene (165 μL, 1.5 mmol), Cu(OTf)₂ (36 mg, 10 mol%) were stirred at 60 °C for 72 hours to afford the title compound as a light yellow powder in 76% yield (0.279 g, 0.76 mmol) after column chromatography on florisil gel (2-4-6-8-10-15-20% Et₂O in hexanes). IR (film) 3278, 2923, 2852, 1597, 1490, 1432, 1330, 1153, 1090, 1039, 921, 816, 762, 738, 692, 670 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.73 (d, J = 8.3 Hz, 2H), 7.28 – 7.08 (m, 5H), 6.97 (dd, J = 8.1, 1.5 Hz, 2H), 4.51 (d, J = 9.9 Hz, 1H), 4.04 (dd, J = 9.9, 5.9 Hz, 1H), 2.31 – 2.17 (m, 3H), 1.83 (d, J = 11.6 Hz, 1H), 1.76 – 1.68 (m, 2H), 1.63 – 1.53 (m, 2H), 1.21 – 1.02 (m, 5H). ¹³C NMR (100 MHz, CDCl₃, 25°C)

(2g) N-(6-chloro-1-cyclohexylhept-2-yn-1-yl)-4-methylbenzene-1-sulfonamide

Prepared according to general procedure A: p-toluene sulfonamide (172 mg, 1.0 mmol), cyclohexanecarboxaldehyde (134 μL, 1.1 mmol), 5-chloro-1-pentyne (161 μL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol%) were stirred at 100 °C for 2 hours to afford the title compound as an off-white crystalline powder in 81% yield (0.307 g, 0.81 mmol) after column chromatography on florisil gel (10-20-30% Et$_2$O in hexanes). IR (film) 3275, 2926, 2855, 1692, 1599, 1495, 1435, 1333, 1305, 1289, 1273, 1160, 1094, 1055, 1032, 938, 912, 880 cm$^{-1}$. $^1$H NMR (400 MHz, CD$_3$CN, 25°C) δ 7.77 – 7.69 (m, 2H), 7.41 – 7.32 (m, 2H), 5.75 (d, $J$ = 9.5 Hz, 1H), 3.83 – 3.74 (m, 1H), 3.50 – 3.41 (m, 2H), 2.42 (s, 3H), 2.07 – 2.00 (m, 2H), 1.81 – 1.70 (m, 4H), 1.64 – 1.60 (m, 2H), 1.25 – 0.97 (m, 6H). $^{13}$C NMR (100 MHz, CD$_3$CN, 25°C) δ 143.59, 138.43, 129.64, 127.37, 83.53, 78.16, 51.02, 43.98, 43.36, 31.20, 29.16, 28.55, 26.21, 25.83, 25.75, 20.78, 15.52. HRMS calculated requires [M+H]$^+$: 368.1451. Found m/z: 368.1446.
(2h) N-{1-cyclohexyl-3-[tris(propan-2-yl)silyl]prop-2-yn-1-yl}-4-methylbenzene-1-sulfonamide

Prepared according to general procedure D: p-toluene sulfonamide (172 mg, 1.0 mmol), cyclohexanecarboxaldehyde (134 μL, 1.1 mmol), triisopropyl silyl acetylene (337 μL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol%), Na$_2$SO$_4$ (142 mg, 1.0 mmol), Cs$_2$CO$_3$ (33 mg, 10 mol%) were stirred at 80 °C for 18 hours to afford the title compound as a white crystalline powder in 78% yield (0.349 g, 0.78 mmol) after column chromatography on florisil gel (5-10-20-30-40-50% EtOAc in hexanes, each with 1% triethylamine added). IR (film) 3263, 2929, 2862, 2170, 1598, 1447, 1428, 1326, 1160, 1083, 1036, 1001, 932, 883, 815, 707 cm$^{-1}$. $^1$H NMR (400 MHz, CD$_3$CN, 25°C) δ 7.72 (dd, J = 8.4, 1.8 Hz, 2H), 7.31 (t, J = 10.2 Hz, 2H), 5.96 (d, J = 9.2 Hz, 1H), 3.89 (dd, J = 9.1, 5.7 Hz, 1H), 2.39 (d, J = 7.4 Hz, 3H), 1.83 – 1.69 (m, 4H), 1.64 (d, J = 11.4 Hz, 1H), 1.50 (dtd, J = 9.0, 6.5, 3.3 Hz, 2H), 1.23 (dt, J = 23.5, 9.2 Hz, 4H), 1.15 – 1.05 (m, 2H), 0.94 (s, 18H), 0.90 – 0.82 (m, 2H). $^{13}$C NMR (100 MHz, CD$_3$CN, 25°C) δ 143.49, 138.49, 129.86, 127.11, 104.90, 85.13, 51.37, 43.83, 29.23, 28.24, 26.28, 25.87, 25.75, 20.79, 18.11, 11.11. HRMS calculated requires [M+Na]$^+$: 470.2525. Found $m/z$: 470.2519.
(2i) N-{5-[(tert-butyldimethylsilyl)oxy]-1-cyclohexylpent-2-yn-1-yl}-4-methylbenzene-1-sulfonamide

Prepared according to general procedure D: p-toluene sulfonamide (172 mg, 1.0 mmol), cyclohexanecarboxaldehyde (134 μL, 1.1 mmol), 4-(tert-butyldimethylsiloxy)-1-butyne (310 μL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol%), Na$_2$SO$_4$ (142 mg, 1.0 mmol), Cs$_2$CO$_3$ (32 mg, 10 mol%) were stirred at 80 °C for 18 hours to afford the title compound as an orange crystalline powder in 80% yield (0.359 g, 0.80 mmol) after column chromatography on florisil gel (2-5-10-15-20-25-30-35% EtOAc in hexanes, each a 1% solution of triethylamine). IR (film) 3264, 2926, 2852, 1710, 1599, 1494, 1449, 1335, 1303, 1290, 1258, 1165, 1093, 1052, 1032, 927, 918, 877 cm$^{-1}$. $^1$H NMR (400 MHz, CD$_3$CN, 25°C) δ 7.73 (d, J = 8.3 Hz, 2H), 7.35 (d, J = 8.1 Hz, 2H), 5.72 (d, J = 6.9 Hz, 1H), 3.76 (s, 1H), 3.50 – 3.36 (m, 2H), 2.41 (s, J = 5.9 Hz, 3H), 2.23 (s, J = 32.0 Hz, 2H), 2.03 (td, J = 6.8, 2.1 Hz, 2H), 1.75 (dd, J = 24.8, 12.2 Hz, 4H), 1.67 – 1.48 (m, 2H), 1.46 – 1.31 (m, 2H), 1.26 – 0.92 (m, 6H), 0.87 (s, J = 2.5 Hz, 9H). $^{13}$C NMR (100 MHz, CD$_3$CN, 25°C) δ 143.46, 143.43, 138.48, 129.55, 127.44, 82.76, 78.11, 61.68, 51.16, 43.20, 29.23, 28.56, 26.20, 25.85, 25.78, 25.48, 22.71, 20.84, 18.10, -5.84. HRMS calculated requires [M+H]$^+$: 450.2498. Found m/z: 450.2493.
(2k) N-(2,2-dimethylundec-4-yn-3-yl)-4-methylbenzene-1-sulfonamide

Prepared according to general procedure A: p-toluene sulfonamide (172 mg, 1.0 mmol), trimethylacetaldehyde (120 μL, 1.1 mmol), 1-octyne (222 μL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol%) were stirred at 100 °C for 4 hours to afford the title compound as a yellow powder in 72% yield (0.256 g, 0.72 mmol) after column chromatography on florisil gel (0-20% EtOAc in hexanes). IR (film) 3285, 2928, 2854, 1599, 1427, 1332, 1299, 1158, 1094, 1049, 1020, 929, 812, 742, 679 cm$^{-1}$.

$^1$H NMR (400 MHz, acetone, 25°C) δ 7.74 (d, J = 8.2 Hz, 2H), 7.35 (d, J = 8.3 Hz, 2H), 6.44 (d, J = 10.0 Hz, 1H), 3.69 (dt, J = 10.1, 2.1 Hz, 1H), 2.40 (s, 3H), 2.03 (dt, J = 4.3, 2.2 Hz, 1H), 1.94 – 1.71 (m, 2H), 1.34 – 1.10 (m, 7H), 0.96 (s, 9H), 0.86 (t, J = 7.0 Hz, 3H). $^{13}$C NMR (100 MHz, acetone, 25°C) δ 142.72, 139.14, 129.29, 127.54, 85.17, 77.24, 55.81, 35.39, 31.33, 25.77, 25.72, 22.51, 20.75, 18.13, 13.60. HRMS calculated requires [M+H]$^+$: 348.1992. Found m/z: 348.1995.

(3a) Benzyl[1-(2-fluorophenyl)non-2-yn-1-yl]amine

Prepared according to general procedure B: benzylamine (110 μL, 1.0 mmol), 2-fluorobenzaldehyde (128 μL, 1.2 mmol), 1-octyne (222 μL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol%), Na$_2$SO$_4$ (285 mg, 2.0 mmol) were stirred at 80 °C for 72 hours to afford the title compound as a dark yellow oil in 88%
yield (0.284 g, 0.88 mmol) after column chromatography on florisil gel (50% Et₂O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 3029, 2955, 2928, 2857, 1716, 1490, 1455, 1231, 1095, 1029, 754, 731, 697 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.64-7.60 (td, J=1.6 Hz, 7.6 Hz, 1H), 7.36-7.26 (m, 4H), 7.25-7.22 (m, 2H), 7.16-7.12 (td, J=1.2 Hz, 7.2 Hz, 1H), 7.05-7.00 (td, J=1.2 Hz, 8.4 Hz, 1H), 4.87-4.86 (t, J=2.4 Hz, 1H), 3.94-3.91 (d, J=12.8 Hz, 1H), 3.88-3.85 (d, J=12.8, 1H), 2.28-2.24 (td, J=2 Hz, 6.8 Hz, 2H), 1.72 (bs, 1H), 1.58-1.51 (quin, J=7.2 Hz, 2H), 1.45-1.38 (m, 2H), 1.35-1.26 (m, 4H), 0.91-0.87 (t, J=6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 161.7, 159.2, 139.7, 129.3, 128.4, 127.0, 124.1, 115.6-115.4 (J=23.5 Hz), 85.7, 78.9, 51.3, 47.4, 31.3, 28.8, 26.6, 22.6, 18.8, 14.1. HRMS calculated requires [M]+: 323.1998. Found m/z: 323.2000.

(3b) Benzyl(2-methylundec-4-yn-3-yl)amine

Prepared according to general procedure B: benzylamine (55 μL, 0.50 mmol), isobutyraldehyde (55 μL, 0.60 mmol), 1-octyne (110 μL, 0.75 mmol), Cu(OTf)₂ (18 mg, 10 mol%), Na₂SO₄ (142 mg, 1.0 mmol) were stirred at 80 °C for 72 hours to afford the title compound as a yellow oil in 94% yield (0.127 g, 0.47 mmol) after column chromatography on florisil gel (50% Et₂O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 3063, 3029, 2957, 2928, 2858, 1740, 1605, 1495, 1455, 1366, 1098, 1029, 842, 731, 697 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.37-7.29 (m, 4H), 7.25-7.22 (m, 1H), 4.04-4.01 (d,
J=12.8 Hz, 1H), 3.81-3.78 (d, J=13.2, 1H), 3.18-3.15 (dt, J=2.4 Hz, 5.6 Hz, 1H), 2.25-2.22 (td, J=2 Hz, 6.8 Hz, 2H), 1.86-1.78 (m, 1H), 1.57-1.39 (m, 4H), 1.33-1.27 (m, 4H), 1.26 (bs, 1H), 0.99-0.97 (d, J=6.8, 6H), 0.91-0.88 (t, J=7.2 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 140.4, 128.4, 128.3, 126.8, 84.7, 79.8, 55.8, 51.7, 32.8, 31.4, 29.1, 28.5, 19.8, 18.7, 17.8, 14.1. HRMS calculated requires [M+H]$^+$: 272.2378. Found m/z: 272.2386.

(3c) Dibenzyl[1-(furan-2-yl)non-2-yn-1-yl]amine

Prepared according to general procedure B: dibenzylamine (194 μL, 1.0 mmol), 2-furaldehyde (100 μL, 1.2 mmol), 1-octyne (222 μL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol%), Na$_2$SO$_4$ (285 mg, 2.0 mmol) were stirred at 80 °C for 24 hours to afford the title compound as a yellow oil in 76% yield (0.229 g, 0.76 mmol) after column chromatography on florisil gel (0-2% Et$_2$O in hexanes). IR (film) 3063, 3028, 2955, 2929, 2857, 2808, 1741, 1603, 1495, 1454, 1371, 1300, 1147, 1128, 1072, 1029, 1008, 967, 815, 789, 730, 696 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.43-7.41 (d, J=7.2 Hz, 4H), 7.39 (s, 1H), 7.31-7.27 (t, J=6.8 Hz, 4H), 7.22-7.19 (t, J=7.2 Hz, 2H), 6.42-6.41 (d, J=3.2 Hz, 1H), 6.29-6.28 (dd, J=2 Hz, 1H), 4.70 (s, 1H), 3.74-3.70 (d, J=14 Hz, 2H), 3.54-3.50 (d, J=14 Hz, 2H), 2.36-2.32 (td, J=2 Hz, 6.4 Hz, 2H), 1.65-1.58 (quin, J=6.4 Hz, 2H), 1.54-1.47 (m, 2H), 1.38-1.33 (m, 4H), 0.94-0.91 (t, J=6.8 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 153.2, 142.3, 139.6, 128.7, 128.2, 126.8, 109.9,
108.8, 86.5, 73.9, 54.5, 50.5, 31.4, 29.0, 28.6, 22.6, 18.8, 14.1. HRMS calculated requires [M+Na]+: 408.2298. Found m/z: 408.2299.

(3d) 1-{{3-[[3-(trifluoromethyl)phenyl]non-2-yn-1-yl]piperidine

Prepared according to general procedure B: piperidine (50 μL, 0.50 mmol), 3-fluorobenzaldehyde (59 μL, 0.55 mmol), 1-octyne (111 μL, 0.75 mmol), Cu(OTf)2 (18 mg, 10 mol%), Na2SO4 (142 mg, 1.0 mmol) were stirred at 100 °C for 1 hour to afford the title compound as a pale yellow oil in 90% yield (0.316 g, 0.45 mmol) after column chromatography on florisil gel (0-10% EtOAc in hexanes). IR (film) 2930, 2856, 2907, 1695, 1589, 1484, 1442, 1318, 1266, 1239, 1155, 1141, 1113, 992, 947, 912, 881, 865, 795, 771, 686 cm−1. 1H NMR (400 MHz, acetone, 25°C) δ 7.50 – 7.29 (m, 3H), 7.05 – 6.92 (m, 1H), 4.59 (s, 1H), 2.51 – 2.38 (m, 4H), 2.34 (td, J = 6.8, 2.1 Hz, 2H), 1.63 – 1.27 (m, 14H), 0.90 (t, J = 7.0 Hz, 3H). 13C NMR (100 MHz, acetone, 25°C) δ 164.14, 161.72, 143.11, 129.71, 124.12, 115.07, 114.11, 88.59, 75.31, 61.28, 50.49, 31.43, 29.14, 28.64, 26.30, 24.60, 22.67, 18.51, 13.73. HRMS calculated requires [M-H]−: 300.2122. Found m/z: 300.2127.

(3e) Benzyl(methyl)(2-methyldodec-5-yn-4-yl)amine

Prepared according to general procedure B: N-methylaniline (110 μL, 1.0 mmol), isovaleraldehyde (130 μL, 1.2 mmol), 1-octyne (222 μL, 1.5 mmol), Cu(OTf)2 (36 mg, 10 mol%), Na2SO4 (285 mg, 2.0 mmol) were stirred at 80 °C for 24 hours to
 afford the title compound as a pale yellow oil in 72% yield (0.204 g, 0.72 mmol) after column chromatography on florisil gel (0-5% Et₂O in hexanes). IR (film) 2955, 2929, 2869, 1739, 1650, 1598, 1500, 1466, 1366, 1315, 1288, 1229, 1217, 1146, 1116, 1095, 1034, 924, 870, 946, 690 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.25-7.21 (m, 2H), 7.09-7.04 (td, J=1.6 Hz, 7.6 Hz, 1H), 6.94-6.92 (dd, J=1.2, 7.2, 1H), 6.86-6.84 (d, J=8.4 Hz, 2H), 6.77-6.73 (t, J=7.6 Hz, 1H), 6.65-6.61 (t, J=7.6 Hz, 1H), 6.49-6.47 (d, J=8 Hz, 1H), 6.16 (s, 1H), 4.53-4.48 (m, 1H), 3.82-3.79 (dd, J=4.4 Hz, 6.4 Hz, 1H), 2.99 (s, 3H), 2.83 (s, 3H), 2.32-2.25 (m, 1H), 2.18-2.15 (td, J=2 Hz, 6.4 Hz, 2H), 1.80-1.72 (m, 1H), 1.69-1.43 (m, 6H), 1.39-1.24 (m, 6H), 1.20-1.18 (d, J=6.8 Hz, 3H), 1.15-1.13 (d, J=6.8 Hz, 3H), 0.95-0.83 (m, 12H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 150.3, 144.9, 143.5, 129.0, 127.8, 126.2, 123.4, 117.7, 117.2, 116.6, 114.7, 110.9, 84.5, 7.6, 60.6, 50.5, 42.6, 41.2, 38.2, 32.9, 31.7, 31.3, 28.9, 28.5, 25.2, 25.0, 23.6, 23.0, 22.9, 22.7, 22.6, 22.2, 20.6, 18.7, 14.0. HRMS calculated requires [M+Na]⁺: 286.2529. Found m/z: 286.2533.

(3f) 4-[1-(1-benzothiophen-3-yl)non-2-yn-1-yl]morpholine

Prepared according to general procedure C: morpholine (88 μL, 1.0 mmol), 1-benzothiophene-3-carbaldehyde (179 mg, 1.1 mmol), 1-octyne (222 μL, 1.5 mmol), Cu(OTf)₂ (36 mg, 10 mol%), Na₂SO₄ (142 mg, 1.0 mmol) were stirred at 80 °C for 16 hours to afford the title compound as a
white crystalline powder in 74% yield (0.253 g, 0.74 mmol) after column chromatography on florisil gel (1-2-3-4-5-7-10-15-20% EtOAc in hexanes). IR (film) 2954, 2927, 2853, 1455, 1427, 1319, 1252, 1115, 1072, 997, 870, 772, 753, 730, 666 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CD\(_3\)CN, 25°C) \(\delta\) 8.15 (dd, \(J = 7.1, 2.2\) Hz, 1H), 7.88 (dd, \(J = 6.8, 1.8\) Hz, 1H), 7.63 (s, \(J = 0.9\) Hz, 1H), 7.42 – 7.31 (m, 2H), 4.90 (s, 1H), 3.69 – 3.43 (m, 4H), 2.63 – 2.40 (m, 4H), 2.34 (td, \(J = 6.9, 2.1\) Hz, 2H), 1.95 (dq, \(J = 4.9, 2.3\) Hz, 2H), 1.62 – 1.52 (m, 2H), 1.52 – 1.42 (m, 2H), 1.36 – 1.30 (m, 3H), 0.95 – 0.84 (m, 3H). \(^{13}\)C NMR (100 MHz, CD\(_3\)CN, 25°C) \(\delta\) 141.03, 137.95, 134.25, 125.95, 124.76, 124.05, 123.80, 122.86, 88.26, 74.90, 66.90, 56.76, 49.64, 31.29, 28.94, 28.54, 22.57, 18.37, 13.63. HRMS calculated requires [M-H]: 340.1741. Found m/z: 340.1743.

(3g) 4-{1-[4-(trifluoromethyl)phenyl]non-2-yn-1-yl}morpholine

Prepared according to general procedure B: morpholine (88 μL, 1.0 mmol), 4-trifluoromethanebenzaldehyde (164 μL, 1.2 mmol), 1-octyne (222μL, 1.5 mmol), Cu(OTf)\(_2\) (36 mg, 10 mol%), Na\(_2\)SO\(_4\) (285 mg, 2.0 mmol) were stirred at 80 °C for 24 hours to afford the title compound as a pale yellow oil in 97% yield (0.343 g, 0.97 mmol) after column chromatography on florisil gel (0-10% Et\(_2\)O in hexanes). IR (film) 2959, 2931, 2857, 1619, 1455, 1412, 1323, 1288, 1272, 1247, 1162, 1116, 1103, 1066, 1019, 1002, 933, 862, 784, 758, 731, 667 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\), 25°C) \(\delta\) 7.72-7.70 (d, \(J=8.4\) Hz, 2H), 7.60-7.58 (t, \(J=8.4\) Hz, 2H), 4.57 (s, 1H), 3.72-3.69 (m, 2H), 2.52 (bs, 4H), 2.34-2.30 (td,
J=2 Hz, 7.2 Hz, 2H), 1.64 (s, 1H), 1.62-1.55 (quin, J=7.2, 2H), 1.48-1.41 (quin, J=7.2 Hz, 2H), 1.36-1.30 (m, 4H), 0.92-0.89 (t, J=7.2, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\), 25°C) δ 142.7, 128.8, 125.0, 89.7, 74.4, 67.1, 61.3, 49.7, 31.3, 28.9, 28.6, 22.6, 18.8, 14.0. HRMS calculated requires [M-H]: 352.1883. Found \(m/z\): 352.1890.

(3h) (2,2-dimethylundec-4-yn-3-yl)(3-phenylpropyl)amine

Prepared according to general procedure C: 3-phenyl-1-propylamine (143 μL, 1.0 mmol), trimethylacetaldehyde (120 μL, 1.1 mmol), 1-octyne (222 μL, 1.5 mmol), Cu(OTf)\(_2\) (36 mg, 10 mol%), Na\(_2\)SO\(_4\) (142 mg, 1.0 mmol) were stirred at 80 °C for 18 hours to afford the title compound as a white crystalline powder in 78% yield (0.244 g, 0.78 mmol) after column chromatography on florisil gel (1-2-3-4-5-6-7-8-10% EtOAc in hexanes). IR (film) 3277, 2926, 2853, 1731, 1597, 1491, 1445, 1329, 1154, 816, 762, 740, 695, 671 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CD\(_3\)CN, 25°C) δ 7.45 – 7.04 (m, 5H), 2.89 (t, J = 2.1 Hz, 2H), 2.67 (t, J = 7.9 Hz, 2H), 2.48 (ddd, J = 11.4, 7.5, 6.3 Hz, 1H), 2.18 (td, J = 6.7, 2.0 Hz, 2H), 1.95 (dt, J = 5.0, 2.5 Hz, 2H), 1.82 – 1.63 (m, 2H), 1.47 – 1.40 (m, 4H), 1.30 (m, J = 6.6, 2.9 Hz, 3H), 0.96 (s, 9H), 0.92 – 0.86 (m, 3H). \(^{13}\)C NMR (100 MHz, CD\(_3\)CN, 25°C) δ 142.94, 128.63, 128.46, 125.81, 83.94, 81.12, 60.52, 47.93, 34.69, 33.47, 31.83, 31.30, 29.06, 28.43, 26.05, 22.59, 18.37, 13.62. HRMS calculated requires [M+Na]\(^+\): 336.2667. Found \(m/z\): 336.2650.
(3i) 4-[1-(pyridin-2-yl)non-2-yn-1-yl]morpholine

Prepared according to general procedure C: morpholine (88 μL, 1.0 mmol), 2-pyridinecarboxaldehyde (105 μL, 1.1 mmol), 1-octyne (222 μL, 1.5 mmol), Cu(OTf)₂ (36 mg, 10 mol%), Na₂SO₄ (142 mg, 1.0 mmol) were stirred at 100 °C for 4 hours to afford the title compound as a brown oil in 88% yield (0.252 g, 0.88 mmol) after column chromatography on florisil gel (5-10-15-20-30-40-50% EtOAc in hexanes). IR (film) 3290, 2924, 2853, 1703, 1599, 1495, 1449, 1430, 1333, 1303, 1289, 1158, 1093, 1053, 1020, 929, 909, 880, 813 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.57 (s, 1H), 7.36 (d, J = 9.0 Hz, 1H), 6.43 (d, J = 19.2 Hz, 3H), 3.96 – 3.79 (m, 4H), 3.00 (s, 4H), 2.73 (s, 2H), 1.78 – 1.63 (m, 2H), 1.47 – 1.17 (m, 6H), 1.00 – 0.79 (m, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 128.14, 123.56, 122.18, 121.26, 117.58, 113.21, 110.18, 103.54, 67.68, 54.48, 31.87, 29.49, 27.41, 26.20, 22.82, 14.29. HRMS calculated requires [M]⁺: 286.2045. Found m/z: 286.2037.

(3j) (cyclopropylmethyl)(propyl){1-[2-(trifluoromethyl)phenyl]non-2-yn-1-yl}amine

Prepared according to general procedure A: N-cyclopropylpropanemethylamine (86 μL, 1.0 mmol), 2-trifluoromethylbenzaldehyde (146 μL, 1.1 mmol), 1-octyne (222 μL, 1.5 mmol), Cu(OTf)₂ (36 mg, 10
mol%) were stirred at 80°C for 22 hours to afford a clear orange oil in 77% yield (0.292 g, 0.77 mmol) after column chromatography on florisil gel (0-1% ethyl acetate in hexanes). IR (film) 3028, 2949, 2931, 2852, 1721 1493, 1461, 1236, 1090, 1027, 755, 734, 696 cm\(^{-1}\). \(^1\)H NMR (400 MHz, acetone) δ 8.05 (d, J = 7.8 Hz, 1H), 7.71 (d, J = 7.8 Hz, 1H), 7.62 (t, J = 7.6 Hz, 1H), 7.48 (t, J = 7.6 Hz, 1H), 5.35 (t, J = 2.1 Hz, 1H), 2.82 (s, J = 13.4 Hz, 1H), 2.64 (dd, J = 13.1, 5.5 Hz, 1H), 2.54 (ddt, J = 12.5, 9.1, 6.2 Hz, 1H), 2.39 – 2.25 (m, 3H), 2.21 (dd, J = 13.1, 7.6 Hz, 1H), 1.51 – 1.26 (m, 9H), 0.91 – 0.85 (m, 3H), 0.72 – 0.59 (m, 3H), 0.53 – 0.34 (m, 2H), 0.24 – 0.03 (m, 2H), -0.04 (dt, J = 9.4, 5.2 Hz, 1H). \(^{13}\)C NMR (100 MHz, acetone) δ 139.56, 131.70, 131.57, 128.60, 128.30, 128.05, 126.71, 126.65, 126.28, 123.56, 88.42, 76.38, 56.44, 54.71, 52.34, 31.36, 22.61, 20.68, 18.42, 13.63, 11.29, 9.07, 4.47, 2.61. HRMS calculated requires [M]+: 378.2400. Found m/z: 378.2403.

**3k 1-(3-ethyldec-5-yn-4-yl)pyrrolidine**

Prepared according to general procedure B: pyrrolidine (84 μL, 1.0 mmol), 2-ethylbutyaldehyde (150 μL, 1.2 mmol), 1-octyne (222 μL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol%) were stirred at 80 °C for 24 hours to afford the title compound as a pale yellow oil in 71% yield (0.187 g, 0.71 mmol) after column chromatography on florisil gel (0-5% Et$_2$O in hexanes). IR (film) 3456, 2959, 2929, 2874, 2859, 2809, 1739, 1457, 1366, 1217, 1116, 1033, 908, 882, 795, 725 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl$_3$, 25°C) δ 3.21-3.20 (m, 1H), 2.63-2.59
(m, 2H), 2.56-2.53 (m, 2H), 2.22-2.18 (td, J=2 Hz, 7.2 Hz, 2H), 1.76-1.66 (m, 5H), 1.53-1.26 (m, 12H), 0.91-0.84 (m, 9H). 13C NMR (100 MHz, CDCl3, 25°C) δ 85.2, 77.9, 58.2, 50.4, 43.9, 31.4, 29.1, 28.5, 23.5, 22.6, 22.2, 22.0, 18.7, 14.1, 11.0. HRMS calculated requires [M+H]+: 264.2686. Found m/z: 264.2688.

(3l) 1-[1-(4-methylphenyl)non-2-yn-1-yl]pyrrolidine

Prepared according to general procedure A:

pyrrolidine (84 µL, 1.0 mmol), p-tolualdehyde (131 µL, 1.1 mmol), 1-octyne (222 µL, 1.5 mmol), Cu(OTf)2 (36 mg, 10 mol%) were stirred at 100 °C for 6 hours to afford the title compound as a white crystalline powder in 89% yield (0.252 g, 0.89 mmol) after column chromatography on florisil gel (1-3-5-10-15-20-25-30-40-50% ethyl acetate in hexanes). IR (film) 2956, 2928, 2858, 2809, 1686, 1608, 1511, 1458, 1326, 1177, 1135, 1109, 1032, 1022, 966, 878, 815, 766, 724, 673 cm⁻¹. 1H NMR (400 MHz, CD3CN, 25°C) δ 7.37 (d, J = 7.9 Hz, 2H), 7.15 (d, J = 7.8 Hz, 2H), 4.57 (s, J = 19.9 Hz, 1H), 2.52 (d, J = 5.0 Hz, 5H), 2.32 (s, 3H), 2.27 (td, J = 6.7, 1.4 Hz, 2H), 1.75 – 1.66 (m, 3H), 1.63 – 1.17 (m, 8H), 0.90 (t, J = 6.9 Hz, 3H). 13C NMR (100 MHz, CD3CN, 25°C) δ 137.80, 137.18, 128.86, 128.12, 87.01, 77.37, 58.09, 49.88, 31.25, 28.90, 28.43, 23.39, 22.54, 20.32, 18.33, 13.56. HRMS calculated requires [M+H]+: 284.2378. Found m/z: 284.2373.
(3m) 1-(4-fluorophenyl)-N-[(4-methoxyphenyl)methyl]non-2-yn-1-amine

Prepared according to general procedure B: 4-methoxybenzylamine (131 μL, 1.0 mmol), 4-fluorobenzaldehyde (130 μL, 1.2 mmol), 1-octyne (222 μL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol%), Na$_2$SO$_4$ (285 mg, 2.0 mmol) were stirred at 80 °C for 48 hours to afford the title compound as a yellow oil in 72% yield (0.256 g, 0.72 mmol) after column chromatography on florisil gel (0-20% Et$_2$O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2929, 2857, 1603, 1507, 1245, 1221, 1036, 825, 738 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) $\delta$ 7.513-7.478 (m, J=6.3 Hz, 2H), 7.286-7.264 (d, J=8.8 Hz, 2H), 7.028-6.984 (m, J=6.3 Hz, 2H), 6.870-6.849 (d, J=8.4 Hz, 2H), 4.505 (s, 1H), 3.823-3.816 (d, J=2.8, 2H), 3.792 (s, 3H), 2.307-2.266 (td, J=2.4 Hz, 2H), 1.598-1.525 (q, 2H), 1.469-1.396 (q, 2H), 1.349-1.271 (m, 4H), 0.914-0.880 (t, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) $\delta$ 163.6, 161.2, 158.9, 137.1, 132.2, 129.9, 129.8, 129.5, 129.4, 115.4, 115.2, 114.0, 86.5, 7.9, 55.5, 52.6, 50.6, 31.6, 29.1, 28.8, 22.8, 19.0, 14.3. HRMS calculated requires [M-H]: 352.2071. Found m/z: 352.2082.

(4) N-benzyl-1-(oct-1-yn-1-yl)cyclohexan-1-amine

Prepared according to general procedure A: Cu(OTf)$_2$ (36 mg, 10 mol%), benzylamine (110 μL, 1.0 mmol),
cyclohexanone (114 μL, 1.1 mmol), 1-octyne (222 μL, 1.5 mmol) were stirred at 110°C for 22 hours to afford a clear yellow oil in 80% yield (0.238 g, 0.80 mmol) after column chromatography on florisil gel (0-1-2-3% EtOAc in hexanes). IR (film) 2928, 2854, 1495, 1452, 1343, 1282, 1173, 1116, 1028, 905, 731, 690 cm⁻¹. ¹H NMR (400 MHz, acetone) δ 7.35 (d, J = 7.3 Hz, 2H), 7.27 (t, J = 7.5 Hz, 2H), 7.18 (t, J = 7.3 Hz, 1H), 3.86 (s, J = 10.4 Hz, 2H), 2.26 (t, J = 6.6 Hz, 2H), 1.85 – 1.75 (m, 2H), 1.67 – 1.37 (m, 11H), 1.36 – 1.25 (m, 5H), 0.91 – 0.85 (m, 3H). ¹³C NMR (100 MHz, acetone) δ 142.14, 128.36, 128.23, 126.59, 84.33, 84.03, 54.51, 47.72, 38.51, 31.42, 26.10, 22.88, 22.63, 18.46, 13.64. HRMS calculated requires [M-H]⁻ : 296.2373. Found m/z: 296.2369.
Chapter 2

Green Catalysis Provides Cyclohexanone-Derived Propargylamines Free of Solvent or Excess Starting Materials: Sole By-Product is Water

I. Introduction

Propargylamines are valuable intermediates in organic synthesis, providing access to nitrogen-containing biologically active compounds and natural products. The most direct approach to accessing these substrates is via a three-component coupling (3CC) of an aldehyde, terminal alkyne, and primary or secondary amine. Referred to as A$^3$ coupling, this method has been widely investigated as it circumvents synthesis and isolation of imine or enamine intermediate.

As discussed in the previous chapter, one of the concentrations of the Larsen group is the development of novel routes achieving propargylamines efficiently in high yields from simple starting materials. To this end, our investigations have focused on the development of multicomponent reactions like A$^3$ couplings to provide propargylamines. While valuable, the utility of these reactions suffers from one major drawback: the vast majority of published methods are optimized solely towards the reaction of aldehydes as the carbonyl source with alkynes and amines. This chapter discusses our research into the development of a novel, green catalytic route that allows for the incorporation of less-reactive cyclohexanone into the production of a propargylamines.
II. Background

The inherent bioactivity and synthetic value of propargylamines\textsuperscript{1} discussed in Chapter 1 continued to serve as justification of our investigations into novel routes achieving more complex propargylic targets. The isolation of a propargylamine from cyclohexanone, benzylamine, and 1-octyne in the presence of a copper(II) triflate catalyst\textsuperscript{2} acted as a starting point for research into new methodology capable of achieving a broad scope of fully-substituted carbon centers from cyclohexanone. The results of these studies, and the efforts made to tailor them in green chemistry fashion, are discussed in this second chapter.

The most direct approach available for accessing propargylamines is the three-component coupling of an aldehyde, alkyne, and amine. This process, referred to as $A^3$ coupling, has been widely investigated.\textsuperscript{3-15} As cited in a number of multicomponent\textsuperscript{16-20} and $A^3$-coupling specific\textsuperscript{1,21-23} reviews, much of the efficiency of these routes is derived from their circumvention of intermediate isolation, specifically that of imine or enamine.\textsuperscript{8,24-29} These couplings are also greener processes as they eliminate materials that would have been used in the course of generating or purifying imine or enamine. The specific reasoning behind why our goal was to generate a green synthesis, and how it was done, will be covered later in this section.

The vast majority of $A^3$ methods are optimized towards the reaction of aldehydes with electron-rich primary anilines or secondary amines.\textsuperscript{3-15} To overcome this, our group published an alternative method catalyzed by copper(II)
triflate that provides propargylamines from both electron-rich and electron-poor primary and secondary amines.\textsuperscript{2} As discussed previously, these same reaction conditions allow for the incorporation of less-reactive cyclohexanone to produce a single propargylamine bearing a fully-substituted center. While the mechanism is proposed to be identical, formation of this cyclohexanone-derived substrate proceeds through a ketimine-type intermediate. Just as with aldehyde/amine-derived aldimines, the ketimine is formed \textit{in situ} via the condensation of an amine onto a ketone to provide a more substituted intermediate, and thus more substituted alkynylation product. The \textit{in situ} condensation of benzylamine onto cyclohexanone under unaltered conditions was surprising given that they are an order of magnitude less reactive as electrophiles than aldehydes.\textsuperscript{30} Even then, successful alkynylation was not expected as ketimines are known to be less reactive than their aldimine counterparts towards nucleophilic addition.\textsuperscript{31,32} This specific molecular transformation involving cyclohexanone-derived ketimines\textsuperscript{33-35} was allowed by the release of torsional strain at the electrophilic $sp^2$-center.\textsuperscript{36,37}

\textbf{Scheme 8}. Ketone-derived propargylamines take 7 days at high temperature.
Schemes 8, 9, and 10 highlight the difficulty of incorporating ketones versus aldehydes in the three-component synthesis of propargylamines. Yus et al. report propargylamine formation from aldehydes, piperidine, and phenylacetylene in greater than 92% yield in only three hours at 120 °C with only an impressive 0.1 mol% of a Cu(OH)$_x$Fe$_3$O$_4$ catalyst (Scheme 8).$^{38,39}$ In contrast, their best of two ketone-derived substrates requires seven days for a maximum 38% yield under identical conditions, and only secondary amines react.

**Scheme 9.** Cyclohexanone-derived propargylamines from $p$-methoxybenzylamine

Van der Eycken and co-workers describe what they term a KA$^2$ reaction of benzylamines and phenylacetylene with cyclohexanones using 20 mol% copper(I) iodide, microwave conditions, and varying excesses of alkyne and ketone for yields up to 82%.$^{40}$ These conditions allow for good isolated yields in the presence of a benign copper catalyst, but are limited in scope to primary amines with phenylacetylene. When aryl alkynes are substituted for 1-octyne, the isolated yield drops to only 31% (Scheme 9). Advantages to this reaction methodology include short reaction times and products protected with a labile $p$-methoxybenzyl group.
Scheme 10. 4 mol % gold catalyst effects fully-substituted propargylamines

Lastly, Chan et al. efficiently couple secondary amines, ketones, and phenylacetylene with only 4 mol% gold(III) bromide. Managing to lower the catalyst loading of the previous method considerably, this report still suffers from limitations in scope. Only cyclic amines react efficiently, use of dibenzylamine lowers yield to below 30%, and substitution of phenylacetylene with an alkyl alkyne again lowers conversion dramatically. Additionally, an excess of 0.5 equivalent each of ketone and alkyne is required, and the gold catalyst is expensive (Scheme 10). Accordingly, these KA$^2$ couplings remain a green synthetic challenge for a variety of reasons: waste in the form of excess substrate, high loading or expensive catalyst, long reaction times, and low yielding alkynes and amines.

To achieve the primary goal of an eco-friendly KA$^2$ reaction of cyclohexanones, one of the central tenants of organic chemistry had to be met: method efficiency. The value of any synthetic route is roughly determined by the weighing of product import against efficacy of the method used to achieve it. Desire to improve upon the latter was one of the founding principles of green chemistry.
The term "green" applies broadly across the generation and use of chemical products. Taking shape back in the early 1990s through concepts like atom economy and E factors, green chemistry is now defined more specifically: “Green chemistry efficiently utilizes (preferably renewable) raw materials, eliminates waste, and avoids the use of toxic and/or hazardous reagents and solvents in the manufacture and application of chemical products.” This broadly inclusive definition stems from development of the twelve principles of green chemistry published by J. C. Warner and P. T. Anastas nearly a decade earlier. These principles provide a framework for the better understanding and application of green chemical processes. By compartmentalizing the relatively wide-ranging ideas behind green chemistry, the twelve principles effectively serve as both detailed explanations and useful guidelines.

As broadly applicable as the practices they define, not all of these principles are relevant to the development of a method for the alkynylation of cyclohexanone-derived imines discussed in this chapter. The four that do apply are: (1) [Waste] Prevention, (2) Atom Economy, (3) Catalysis, and (4) Safer Solvents and Auxiliaries. When utilized in tandem during method development, these guidelines can provide maximum efficiency to an already powerful synthesis.

The first principle, prevention, relates specifically to waste: that it is better to prevent waste than to deal with it after it has already been created. An excellent example of the problem presented by an excess of waste is provided by the fine chemicals industry in the synthesis of phloroglucinol, seen in Scheme 8. Involving
dichromate oxidation of 2,4,6-trinitrotoluene in sulfuric acid and sequential Béchamp reduction with iron and hydrochloric acid while heating.

**Scheme 11.** Inefficient synthesis of phloroglucinol

Given the multiple steps of this synthesis however, phloroglucinol is not the only product. For every one mole of product produced via this reaction pathway, 1 mole Cr$_2$(SO$_4$)$_3$, 3 moles NH$_4$Cl, 9 moles FeCl$_2$, 2 moles KHSO$_4$, 1 mol of CO$_2$, and 8 moles of H$_2$O are generated. In terms of mass, this means that every one kilogram of phloroglucinol created would yield a calculated twenty kilograms of waste. However, given the excess of oxidant and sulfuric acid in the first step, reductant in the second step, materials used in basic workup, and an isolated yield of phloroglucinol lower than 100%, actual observed waste breached forty kilograms per one kilogram of product. When the plant responsible for this synthesis was closed in the 1980’s, it was revealed that phloroglucinol production at this location alone was yielding approximately 100 tons of waste per year.

This example provides an important lesson on the development of scalable procedures for organic chemists operating on an academic scale. By keeping the first principle of green chemistry in mind, investigations involving method development that prevents waste production on a small scale will have a
proportionally greater impact as these discoveries are incorporated into industry on a much larger scale. The alkynylation of cyclohexanone-derived imines discussed in this chapter views this first principle as the central tenant of the green chemistry philosophy, treating the rest as guidelines on how to achieve the minimization of waste. Scheme 9 details the general conditions that were developed as a result of this mindset. Specifically, that given the catalytic nature of the copper(II) salt used and the lack of solvent, conditions that will be addressed later in this chapter, the only waste produced in this reaction is the H$_2$O generated via *in situ* condensation of amine onto carbonyl. By developing a method yielding water as the only byproduct, this synthesis adheres successfully to the first principle of green chemistry.

**Scheme 12.** H$_2$O is sole byproduct of cyclohexyl-propargylamine synthesis

![Scheme 12](attachment:image.png)

The second principle of green chemistry applicable to our process is Atom Economy, the idea that synthetic methods should maximize incorporation of all reagents used into the final product. This ties in logically with the first principle we previously discussed concerning waste reduction, and was originally developed by Barry Trost. Atom economy builds on the traditional measurement of reaction efficiency, percent yield, by addressing factors independent of isolated product
mass such as non-catalytic additives consumed during conversion of starting materials. Percent atom economy is determined by dividing the molecular weight of the desired products by the combined molecular weights of all reactants. R. A. Sheldon provides an excellent example of this, comparing the atom economy of two routes achieving propylene oxide, detailed in Scheme 10.

**Scheme 13.** Atom economy of alternate routes achieving propylene oxide

The first set of conditions (1) utilizes a chlorohydrin intermediate obtained through chlorination of propene in water that is then exposed to calcium hydroxide (Ca(OH)$_2$) to give product, calcium chloride (CaCl$_2$) and H$_2$O. As these latter two byproducts are not incorporated into the propylene oxide, the atom economy of this reaction is a low 25%. Alternatively, oxidation with hydrogen peroxide (2) gives only water as a byproduct, providing an atom economy of 76%. This comparison allows us to make the valuable qualitative assessment that even if the chlorohydrin route gives a higher yield of product, it is a less efficient method of achieving propylene oxide than hydrogen peroxide oxidation.
Referring back to Scheme 9 in order to use atom economy as another means of analyzing the efficiency of our alkynylation of cyclohexanone-derived imines, we see the continued value of a single byproduct. The combination of three starting materials (cyclohexanone, amine, and alkyne) that are all catalytically incorporated into the final product, forming only H₂O as a byproduct, means this process is highly atom economical. The calculation of percent atom economy will differ for each specific substrate isolated, but as the total mass of reactants is only 18.015 g/mol more than that of the desired product, these values will be consistently high.

Further increasing the percent atom economy of this method, and serving as an excellent example of the third applicable principle of green chemistry, Catalysis, is the use of a benign copper catalyst. Systems like these are desirable as they allow for the regeneration of materials involved in a synthesis, meaning these materials are not considered waste so do not factor in to the calculation of percent atom economy. Thus, copper-catalyzed synthesis involving the in situ formation of a copper acetylide nucleophile provides us with a reliably atom economical route capable of efficiently generating novel propargylamine structures, the specifics of with will be discussed later in this chapter. However, despite its obvious value as a tool to quickly compare the efficacy of different chemical processes, the simplicity of the calculations is one of the downsides to percent atom economy. Especially given that this percentage is a purely theoretical value, applicable only to the substances that appear in a stoichiometric equation.
R. A. Sheldon provides an excellent solution, detailed in his 2008 *Chemical Communications* article, to the problem presented by this simplicity. Sheldon’s solution is the appropriately named E factor, a term representative of the actual amount of waste that a process produces. This definition provides for a much more detailed analysis of a chemical reaction than that from the percent atom economy calculation. The actual equation appears to be only slightly more complicated than Trost’s: dividing the total mass of materials used in the reaction, minus the mass of isolated product, by the mass of isolated product. Simply put, large E factors represent wasteful processes that require substantial molecular investment but yield little return in the form of desired product. Determining the actual sum of materials involved increases the complexity of the calculation, but allows for an analysis that incorporates every step of the synthesis. Solvents used, aqueous workups, and unrecoverable homogenous catalysts are only a few examples of the expanded metrics utilized by the E factor calculation.

A discussion concerning E factors also serves as an effective transition into the fourth and final green chemistry principle pertinent to our process achieving propargylamines from cyclohexanone: Safer Solvents and Auxiliaries. This principle relates to the use of materials not directly involved in the molecular transformation of a reaction such as solvents and separation agents like the silica used in column chromatography. So solvent-free conditions requiring no purification are ideal, but most synthetic routes require both. To compensate, this principle goes beyond values that can be plugged into the calculation of an E
factor: it considers the heating, distilling, pumping, filtering, etc. involved in the preparation and removal of any solvent needed in a chemical process. So while an E factor may view hexanes and 1,4-dioxane as essentially equivalent, this fourth principle allows for differentiation based on flammability versus carcinogenic activity, for example. Referring back to Scheme 9 again, our development of a solvent-free system allowed for a process with a low E factor that also adhered to the more complex guidelines laid out by the relevant fourth principle of green chemistry concerning safer solvents.

III. Catalyst Optimization and Insight into Advantage/Necessity of Solvent-Free System

From the initial reaction achieving cyclohexanone-derived propargylamine from benzaldehyde and 1-octyne in the presence of copper(II) triflate in toluene, highlighted in Scheme 7, a more atom economical method was sought. We wished to reduce catalyst loading, eliminate solvent, and avoid substrates in excess while maintaining yields at or above the 80% already isolated. The first two of these modes of rendering synthetic methods greener are a major focus, but reducing waste from excess starting materials, a serious detractor from the advantages of multicomponent reactions, receives less attention. In solution, the high reactivity of copper(II) triflate results in excellent conversion to product, but side-products appear with this catalyst in the absence of solvent. Therefore, the development of a greener method began by testing a wide array of copper
catalysts at half the catalyst loading under solvent-free conditions, with optimistically equimolar amounts of ketone, amine, and alkyne were used.

Table 5. Wide range of Cu(I) and Cu(II) sources operable at 5 mol% loading

Table 5 summarizes the copper(I) and copper(II) catalysts tested at 5 mol% loading. While every copper source tested exhibited reasonable activity, no product is detected over three days in the absence of a copper catalyst. No apparent correlation exists between metal oxidation state and catalytic activity:
copper(I) and copper(II) bromide produce identical GC yields (entry 12 vs. 3), and copper(I) acetate is superior to copper(II) acetate (entry 11 vs. 2), but copper(II) chloride outperforms copper(I) chloride (entry 4 vs. 13). The presence of halide ligands consistently provides >70% GC yield under solvent-free conditions (entries 3, 4, 12, 13, 14, and 16). CuCl₂ and CuBr·Me₂S afford the highest overall GC yields, 99% and 94%, respectively, but CuCl₂ is more reliable across the range of substrates. Entries 1 and 4 in Table 1 clearly show that copper(II) chloride is superior to the original copper(II) triflate catalyst; CuCl₂ provides near quantitative GC yield and faster reaction rate than Cu(OTf)₂.

**Table 6.** Optimal copper(II) chloride catalyst shows no activity in solution

<table>
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<th>Entry</th>
<th>Solvent</th>
<th>GC yield (%)</th>
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<tr>
<td>2</td>
<td>acetonitrile</td>
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<td>3</td>
<td>1,4-dioxane</td>
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<tr>
<td>7</td>
<td>toluene</td>
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As detailed in Table 6, if not for the goal of an eco-friendly solvent free synthesis, copper(II) chloride may not have been identified as the superior catalyst for our desired transformation as it is nearly inactive in solution. Cyclohexanone, benzylamine, and 1-octyne were stirred with catalyst at 110 °C for 18 hours. No conversion was observed in acetone, acetonitrile, 1,4-dioxane, tetrahydrofuran, hexanes, chloroform, toluene, ethyl acetate, dimethylformamide, dimethyl sulfoxide, methanol, dichloroethane, or water. Even present in microliter amounts, solvent significantly impeded reaction rate. CuCl$_2$, though the optimal catalyst under solvent-free conditions, is rendered almost inactive in the presence of small amounts of solvent, and completely inert as that presence increases. No difference in reactivity is observed under an atmosphere of nitrogen versus argon. In air, the reaction proceeds cleanly but conversion is 18% less.

IV. Cyclohexanone is Efficiently Coupled with a Range of Amines and Alkynes

As previous cyclohexanone KA$^2$ reactions were limited to either primary$^{40}$ or secondary$^{39}$ amines coupled mostly with phenylacetylene, investigations began by surveying the amine substrates operable with 1-octyne in the solvent-free catalytic system. The resultant scope of accessible propargylamine substrates is listed below in Table 7. The first entry (4a) shows that this greener process, using 5 mol% CuCl$_2$ in a neat 1:1:1 ratio of starting materials results in a higher 91% yield of product derived from benzylamine and 1-octyne (80% in Scheme 7).
Table 7. Fully-substituted propargylamines from primary and secondary amines

As the goal of this research was to expand on current allowable scope, a range of different types of nitrogen sources were tested. In addition to benzylamine, other primary amines that provided good yields include \( \text{N-propylphenylamine} \) (4c) and \( \text{p-methoxybenzylamine} \) (4b). The 87% isolated yield of the latter substrate (4c) nearly tripled the previous report's value of 31%, a method utilizing a four times higher catalyst loading.\(^{40}\)
Table 8. Wide range of alkynes successfully coupled by CuCl$_2$

Heterocyclic secondary amines piperidine, morpholine, and pyrrolidine convert in 2-3 hours to cyclohexanone derived propargylamines in 90% (4e), 92% (4f), and 88% (4g) yields, respectively.
Table 8 showcases the broad scope of the alkyne coupling partner made possible by this greener method. Note that in contrast to previous reports where application of 1-octyne instead of phenylacetylene cause a 45% drop in yield,40 under the green conditions reported herein, nearly identical yields are obtained when utilizing 1-octyne (4e, 90%) and phenylacetylene (4i, 89%). Alkyl alkynes bearing propylphenyl, 3-methylbutyl, and tert-butyl substituents also react efficiently with piperidine and cyclohexanone to provide 78% (4j), 92% (4k), and 81% (4l) isolated yields, respectively. As a testament to the mildness of these neat copper(II) chloride conditions compared to copper(II) triflate in toluene,2 no base is needed to buffer couplings of morpholine with acid sensitive alkynes. Both tert-butyldimethylsilyl and triisopropylsilyl acetylenes react efficiently to give yields above 70% (entries 4m and 4n). Finally, morpholine propargylamine bearing a silyl-protected alcohol is produced in 84% yield (4o). To the best of our knowledge, these represent the first silyl and siloxy alkynes incorporated under conditions sufficiently activating for the KA2 reaction of cyclohexanone.

In the development of the green method reported herein, solvent is removed, catalyst loading is halved, and the largest reduction in waste arises from the elimination of the excess starting materials generally utilized. It is important to note that if solvent-free green chemistry had not been targeted, the high reactivity of this inexpensive copper(II) chloride catalyst may have escaped discovery as it is nearly inactive in solution. Primary and secondary amines rapidly react with cyclohexanone and aryl, alkyl, silyl, and silyloxy alkynes to produce secondary and
tertiary \textit{N}-propargylamines on fully-substituted carbon centers. This efficient three-component coupling proceeds by adding copper(II) chloride catalyst to a 1:1:1 ratio of amines, cyclohexanone, and alkynes and producing water as the sole byproduct. These conditions effectively manage to utilize the guidelines provided by the green chemistry principles to provide a powerful synthesis with an eco-friendly framework.
V. Literature Citations

(5) Li, C.-J.; Wei, C. Chemical Communications 2002, 268.
(13) Wei, C.; Li, C.-J. Journal of the American Chemical Society 2003, 125, 9584.
(39) Aliaga, M. J.; Ramon, D. J.; Yus, M. Organic & Biomolecular Chemistry 2010, 8, 43.
(48) Sheldon, R. A. Green Chem. 2007, 9, 1273.
(49) Trost, B. M. Science 1991, 254, 1471.
VII. Supporting Information

General Reagent Information

All reactions were set up on the benchtop and carried out in oven-dried Teflon seal screw-cap test-tubes stirring by magnetic stir bars under an atmosphere of nitrogen. Flash column chromatography was performed using silica gel purchased from Silicycle. CuCl$_2$ (99%) was purchased from Acros and used as supplied. Amines were purchased from Acros Organics, Alfa Aesar, or Aldrich and purified by distillation before use. All ketones and alkynes were purchased from Acros Organics, Alfa Aesar or TCI America and purified by distillation before use.

General Analytical Information

$^1$H and $^{13}$C NMR spectra were measured on a Varian Inova 400 (400 MHz) spectrometer using CDCl$_3$ as a solvent and tetramethylsilane as an internal standard. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet and br - broad. NMR spectra were acquired at 300 K. Gas chromatograph spectra were obtained on an Agilent Technologies 6850 Network GC System using dodecane as an internal standard. IR spectra were recorded on Perkin Elmer Spectrum One FT-IR Spectrometer. Attenuated total reflection infrared (ATR-IR) was used for analysis with selected absorption maxima reported in wavenumbers (cm$^{-1}$). No sample preparation was necessary for ATR analysis. ATR-IR is based on the propagation of the infrared radiation through an internal reflection element (crystal) with a high refractive index, and its reflection at the interface between the
crystal and the solid material. Mass spectrometric data was collected on a HP 5989A GC/MS quadrupole instrument. Exact masses were recorded on a Waters GCT Premier ToF instrument using direct injection of samples in acetonitrile into the electrospray source (ESI) and either positive or negative ionization.

**General Procedure**

To an oven-dried test tube equipped with magnetic stir bar and Teflon-seal screw cap was added 5 mol % CuCl₂. The flask was purged with nitrogen for 5 minutes. Ketone (1.0 equiv), alkyne (1.0 equiv), and amine (1.0 equiv) were added, and the reaction was stirred at the designated temperature for the indicated time. Upon completion, as judged by GC, the mixture was cooled to room temperature and directly loaded atop a silica gel column. Chromatography with ethyl acetate (EtOAc) in hexanes as eluent afforded the desired product. The products were further identified by FT-IR, ¹H NMR, ¹³C NMR and HRMS, which were all in good agreement with the assigned structures. References are provided for compounds matching those previously reported in the literature.

**4a: Synthesis of N-benzyl-1-(oct-1-yn-1-yl)cyclohexan-1-amine**

Benzylamine (110 μL, 1.0 mmol), cyclohexanone (104 μL, 1.0 mmol), 1-octyne (148 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol) was stirred at 110 °C for 6 hours to afford the title compound as a clear light yellow oil in 91% yield (0.271 g, 0.91 mmol) after column chromatography on
silica gel (20% EtOAc/hexanes). IR (film) 2928, 2854, 1740, 1605, 1495, 1452, 1115, 1028, 905, 732, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.36 (d, $J = 7.2$ Hz, 2H), 7.30 (t, $J = 7.5$ Hz, 2H), 7.22 (t, $J = 7.2$ Hz, 1H), 3.96 – 3.80 (m, 2H), 2.25 (t, $J = 6.9$ Hz, 2H), 1.83 (d, $J = 12.5$ Hz, 2H), 1.71 – 1.17 (m, 17H), 0.90 (t, $J = 6.7$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 141.5, 128.7, 128.6, 127.0, 84.8, 84.1, 55.1, 48.2, 38.7, 31.6, 29.5, 28.6, 26.2, 23.3, 22.9, 18.0, 14.3. HRMS calculated requires [M-H]: 296.2373. Found m/z: 296.2376.

4b: Synthesis of N-[(4-methoxyphenyl)methyl]-1-(oct-1-yn-1-yl)cyclohexan-1-amine

4-methoxybenzylamine (131 $\mu$L, 1.0 mmol), cyclohexanone (104 $\mu$L, 1.0 mmol), 1-octyne (148 $\mu$L, 1.0 mmol), CuCl$_2$ (6.8 mg, 0.05 mmol) was stirred at 110 $^\circ$C for 5 hours to afford the title compound as a clear light yellow oil in 87% yield (0.285 g, 0.87 mmol) after column chromatography on silica gel (20% EtOAc/hexanes). IR (film) 2928, 2854, 1715, 1612, 1511, 1455, 1244, 1171, 1106, 1037, 822, 732 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.26 (d, $J = 8.6$ Hz, 2H), 6.84 (d, $J = 8.6$ Hz, 2H), 3.89 – 3.71 (m, 5H), 2.26 (t, $J = 6.9$ Hz, 2H), 1.81 (d, $J = 12.4$ Hz, 2H), 1.68 – 1.17 (m, 16H), 0.88 (t, $J = 7.0$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) $\delta$ 158.7, 133.7, 129.8, 114.0, 84.7, 84.1, 55.5, 55.0, 47.5, 38.6, 31.6, 29.4, 28.8, 26.2, 23.2, 22.8, 18.9, 14.3. HRMS calculated requires [M-H]: 326.2478. Found m/z: 326.2488.
4c: Synthesis of 1-(oct-1-yn-1-yl)-N-(3-phenylpropyl)cyclohexan-1-amine

3-phenylpropylamine (μL, 1.0 mmol), cyclohexanone (104 μL, 1.0 mmol), 1-octyne (148 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol) was stirred at 110 °C for 6 hours to afford the title compound as a brown oil in 82% yield (0.267 g, 0.82 mmol) after column chromatography on silica gel (15% EtOAc/hexanes). IR (film) 2927, 2854, 1715, 1603, 1496, 1453, 1121, 907, 733, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.21 (m, 5H), 2.69 (m, 4H), 2.18 (t, J = 6.8 Hz, 2H), 1.79 (dd, J = 16.4, 9.5 Hz, 4H), 1.69 – 1.08 (m, 16H), 0.89 (t, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 142.5, 128.6, 128.5, 125.9, 84.5, 84.0, 54.7, 43.0, 38.7, 34.1, 32.6, 31.5, 29.3, 28.7, 26.2, 23.3, 22.8, 18.9, 14.3. HRMS calculated requires [M-H]⁻: 324.2686. Found m/z: 324.2679.

4d: Synthesis of N-benzyl-N-methyl-1-(oct-1-yn-1-yl)cyclohexan-1-amine

N-methylbenzylamine (129 μL, 1.0 mmol), cyclohexanone (104 μL, 1.0 mmol), 1-octyne (148 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol) was stirred at 110 °C for 4 hours to afford the title compound as a light yellow oil in 88% yield (0.274 g, 0.88 mmol) after column chromatography on silica gel (15% EtOAc/hexanes). IR (film) 2927, 2854, 2790, 1604, 1494, 1452, 1237, 959, 733, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.38 – 7.25 (m, 4H), 7.21 (t, J = 7.1 Hz, 1H), 3.58 (s, 2H), 2.27 (t, J = 6.8 Hz, 2H), 2.12 (s, 3H), 2.02 – 1.85 (m, 2H), 1.70 (t, J = 10.3 Hz, 2H), 1.60 – 1.42 (m, 8H), 1.37 – 1.21 (m, 6H), 0.92 (t, J = 6.9 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 141.6, 129.0, 128.3, 126.6, 85.5,
80.9, 58.9, 55.8, 37.1, 35.4, 31.6, 29.6, 28.7, 26.1, 23.0, 22.9, 18.9, 14.3. HRMS calculated requires [M-H]: 310.2529. Found m/z: 310.2543.

4e: Synthesis of 1-[1-(oct-1-yn-1-yl)cyclohexyl]piperidine

Piperidine (99 μL, 1.0 mmol), cyclohexanone (104 μL, 1.0 mmol), 1-octyne (148 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol) was stirred at 110 °C for 3 hours to afford the title compound as a light yellow oil in 91% yield (0.251 g, 0.91 mmol) after column chromatography on silica gel (10% EtOAc/hexanes). IR (film) 2928, 2853, 2819, 1720, 1453, 1269, 1119, 1034, 973, 921, 882, 791 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.86 – 3.53 (m, 4H), 2.73 – 2.43 (m, 4H), 2.19 (t, J = 7.0 Hz, 2H), 1.86 (d, J = 12.5 Hz, 2H), 1.74 – 1.00 (m, 18H), 0.86 (t, J = 6.9 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 86.5, 80.0, 67.7, 58.7, 46.6, 35.8, 31.5, 29.4, 28.7, 25.9, 23.0, 22.8, 18.8, 14.2. HRMS calculated requires [M-H]: 274.2529. Found m/z: 274.2530.

4f: Synthesis of 4-[1-(oct-1-yn-1-yl)cyclohexyl]morpholine

Morpholine (88 μL, 1.0 mmol), cyclohexanone (104 μL, 1.0 mmol), 1-octyne (148 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol) was stirred at 110 °C for 3 hours to afford the title compound as a clear light brown oil in 92% yield (0.255 g, 0.92 mmol) after column chromatography on silica gel (15% EtOAc/hexanes). IR (film) 2927, 2853, 1716, 1453, 1269, 1119, 973, 882, 791 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.81 – 3.62 (m, 4H), 2.70 – 2.49 (m, 4H), 2.19 (t, J = 7.0 Hz, 2H), 1.86 (d, J = 12.5 Hz, 2H),
1.69 – 1.15 (m, 16H), 0.86 (t, \( J = 6.9 \, \text{Hz}, \, 3\text{H}\)). \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 86.5, 80.0, 67.7, 58.7, 46.6, 35.8, 31.5, 29.4, 28.7, 25.9, 23.0, 22.8, 18.8, 14.2. HRMS calculated requires \([\text{M-H}]^-\): 276.2322. Found \(m/z\): 276.2322.

**4g: Synthesis of 1-[1-(oct-1-yn-1-yl)cyclohexyl]pyrrolidine**

Pyrrolidine (84 \( \mu \text{L}, \, 1.0 \, \text{mmol}\)), cyclohexanone (104 \( \mu \text{L}, \, 1.0 \, \text{mmol}\)), 1-octyne (148 \( \mu \text{L}, \, 1.0 \, \text{mmol}\)), CuCl\(_2\) (6.8 mg, 0.05 mmol) was stirred at 110 °C for 2 hours to afford the title compound as a yellow oil in 88% yield (0.229 g, 0.88 mmol) after column chromatography on silica gel (30% EtOAc/hexanes). IR (film) 2927, 2855, 1716, 1678, 1446, 1125, 881, 808, 725 cm\(^{-1}\); \(^1\text{H}\) NMR (400 MHz, CDCl\(_3\)) \( \delta \) 2.71 (t, \( J = 6.1 \, \text{Hz}, \, 4\text{H}\)), 2.22 (t, \( J = 6.8 \, \text{Hz}, \, 2\text{H}\)), 1.89 (d, \( J = 12.5 \, \text{Hz}, \, 2\text{H}\)), 1.82 – 1.68 (m, 4H), 1.68 – 1.02 (m, 16H), 0.90 (t, \( J = 6.8 \, \text{Hz}, \, 3\text{H}\)). \(^{13}\text{C}\) NMR (100 MHz, CDCl\(_3\)) \( \delta \) 86.0, 80.2, 59.0, 47.0, 38.3, 31.5, 29.5, 28.6, 25.9, 23.6, 22.8, 18.8, 14.2. HRMS calculated requires \([\text{M-H}]^-\): 260.2373. Found \(m/z\): 260.2384.

**4h: Synthesis of 1,4-bis[1-(oct-1-yn-1-yl)cyclohexyl]piperazine**

Piperazine (86.2 mg, 1.0 mmol), cyclohexanone (208 \( \mu \text{L}, \, 2.0 \, \text{mmol}\)), 1-octyne (296 \( \mu \text{L}, \, 2.0 \, \text{mmol}\)), CuCl\(_2\) (6.8 mg, 0.05 mmol) was stirred at 110 °C for 16 hours to afford the title compound as a clear light brown oil in 68% yield (0.316 g, 0.68 mmol) after column chromatography on silica gel (20% EtOAc/hexanes). IR (film) 2927, 2855, 2186, 1720, 1455, 1284, 1128, 979, 907, 797, 731 cm\(^{-1}\); \(^1\text{H}\) NMR
(400 MHz, CDCl₃) δ 2.69 (s, 8H), 2.20 (t, J = 6.8 Hz, 4H), 1.93 (d, J = 12.1 Hz, 4H),
1.76 – 1.08 (m, 32H), 0.89 (t, J = 6.7 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 86.4, 80.3, 58.3, 46.5, 35.8, 31.4, 29.2, 28.6, 25.8, 23.0, 22.6, 18.8, 14.1. HRMS calculated requires [M-H]⁻: 465.4203. Found m/z: 465.4217.

4i: Synthesis of 1-[1-(2-phenylethynyl)cyclohexyl]piperidine

Piperidine (99 μL, 1.0 mmol), cyclohexanone (104 μL, 1.0 mmol), phenylacetylene (110 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol) was stirred at 110 °C for 2 hours to afford the title compound as a light yellow oil in 89% yield (0.238 g, 0.89 mmol) after column chromatography on silica gel (8% EtOAc/hexanes). IR (film) 2964, 2928, 2854, 2805, 2219, 1466, 1450, 1441, 1361, 1285, 1263, 1149, 1093, 962, 875, 800, 749, 668 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.49 – 7.38 (m, 2H), 7.32 – 7.23 (m, 3H), 2.66 (s, 4H), 2.08 (d, J = 12.3 Hz, 2H), 1.74 – 1.57 (m, 8H), 1.54 – 1.41 (m, 4H), 1.25 (s, 2H). ¹³C NMR (100 MHz, CDCl₃) δ 131.7, 128.2, 127.6, 123.8, 90.8, 86.1, 59.3, 47.2, 35.8, 26.6, 25.8, 24.8, 23.1. HRMS calculated requires [M+H]⁺: 268.2060. Found m/z: 268.2071.

4j: Synthesis of 1-[1-(5-phenylpent-1-yn-1-yl)cyclohexyl]piperidine

Piperidine (99 μL, 1.0 mmol), cyclohexanone (104 μL, 1.0 mmol), 5-phenyl-1-pentyne (152 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol) was stirred at 110 °C for 4 hours to afford the title compound as a yellow oil in 78% yield (0.241 g, 0.78 mmol) after column
chromatography on silica gel (15% EtOAc/hexanes). IR (film) 2928, 2854, 2800, 1717, 1603, 1495, 1453, 1443, 1244, 1151, 1098, 1077, 964, 908, 731, 697 cm\(^{-1}\);

\(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.31 – 7.15 (m, 5H), 2.84 – 2.69 (m, 2H), 2.69 – 2.46 (m, 4H), 2.32 – 2.13 (m, 2H), 1.94 (t, \(J = 15.7\) Hz, 2H), 1.89 – 1.74 (m, 2H), 1.71 – 1.34 (m, 12H), 1.31 – 1.10 (m, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 142.2, 128.7, 128.5, 126.0, 85.5, 81.5, 59.1, 47.2, 36.2, 35.2, 31.4, 26.8, 26.0, 25.0, 23.4, 18.5. HRMS calculated requires [M+Na]\(^+\): 332.2349. Found m/z: 332.2361.

4k: Synthesis of 1-[1-(5-methylhex-1-yn-1-yl)cyclohexyl]piperidine

Piperidine (99 \(\mu\)L, 1.0 mmol), cyclohexanone (104 \(\mu\)L, 1.0 mmol), 5-methyl-1-hexyne (112 \(\mu\)L, 1.0 mmol), CuCl\(_2\) (6.8 mg, 0.05 mmol) was stirred at 110 °C for 3 hours to afford the title compound as an orange crystalline solid in 92% yield (0.240 g, 0.92 mmol) after column chromatography on silica gel (5% EtOAc/hexanes). IR (film) 2927, 2853, 2795, 1722, 1467, 1453, 1442, 1259, 1244, 1152, 1109, 965, 859, 782 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.54 (s, 4H), 2.18 (dt, \(J = 9.4, 7.4\) Hz, 2H), 1.91 (d, \(J = 12.3\) Hz, 2H), 1.75 – 1.45 (m, 10H), 1.44 – 1.29 (m, 6H), 1.20 – 1.11 (m, 1H), 0.92 – 0.84 (m, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 85.9, 80.6, 59.0, 47.1, 38.6, 36.1, 27.4, 26.8, 26.0, 25.0, 23.3, 22.4, 16.9. HRMS calculated requires [M-H]: 260.2373. Found m/z: 260.2371.
4l: Synthesis of 1-[1-(3,3-dimethylbut-1-yn-1-yl)cyclohexyl]piperidine

Piperidine (99 μL, 1.0 mmol), cyclohexanone (104 μL, 1.0 mmol), 3,3-dimethyl-1-butyn (124 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol) was stirred at 110 °C for 2 hours to afford the title compound as a yellow solid in 81% yield (0.200 g, 0.81 mmol) after column chromatography on silica gel (10% EtOAc/hexanes). IR (film) 2964, 2854, 2806, 2748, 2218, 1466, 1451, 1441, 1361, 1285, 1263, 1150, 1093, 1019, 962, 876, 800, 749, 668 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.51 (s, 4H), 1.88 (d, ²J = 12.3 Hz, 2H), 1.73 – 1.42 (m, 10H), 1.42 – 1.23 (m, 4H), 1.18 (s, 9H). ¹³C NMR (100 MHz, CDCl₃) δ 95.1, 78.7, 58.8, 47.0, 36.1, 31.8, 27.6, 26.8, 26.0, 25.0, 23.4. HRMS calculated requires [M-H]⁻: 246.2216. Found m/z: 246.2226.

4m: Synthesis of 4-{1-[2-(tert-butyldimethylsilyl)ethynyl]cyclohexyl}morpholine

Piperidine (99 μL, 1.0 mmol), cyclohexanone (104 μL, 1.0 mmol), (tert-butyldimethylsilyl)acetylene (187 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol) was stirred at 110 °C for 5 hours to afford the title compound as a white crystalline solid in 91% yield (0.279 g, 0.91 mmol) after column chromatography on silica gel (4% EtOAc/hexanes). IR (film) 2947, 2927, 2890, 2850, 2153, 1467, 1447, 1270, 1255, 1247, 1168, 1118, 961, 882, 852, 836, 823, 806, 771, 683 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.75 – 3.64 (m, 4H), 2.68 – 2.52 (m, 4H), 1.91 (d, ²J = 12.5 Hz, 2H), 1.66 (dd, ²J = 8.4, 4.0 Hz,
2H), 1.54 (dd, J = 13.7, 5.4 Hz, 2H), 1.39 – 1.30 (m, 2H), 1.27 – 1.11 (m, 2H), 0.92 (s, 9H), 0.08 (s, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 106.9, 88.3, 67.7, 59.1, 46.7, 35.7, 26.3, 25.9, 22.9, 16.7, -4.1. HRMS calculated requires [M-H]: 306.2248. Found m/z: 306.2259.

4n: Synthesis of 4-(1-{2-[tris(propan-2-yl)silyl]ethynyl}cyclohexyl)morpholine

Piperidine (99 μL, 1.0 mmol), cyclohexanone (104 μL, 1.0 mmol), triisopropylsilylacetylene (225 μL, 1.0 mmol), CuCl$_2$ (6.8 mg, 0.05 mmol) was stirred at 110 °C for 6 hours to afford the title compound as a clear oil in 73% yield (0.253 g, 0.73 mmol) after column chromatography on silica gel (3% EtOAc/hexanes). IR (film) 2931, 2861, 2819, 2156, 1454, 1383, 1269, 1119, 973, 920, 881, 846, 734, 674 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.77 – 3.61 (m, 4H), 2.67 – 2.52 (m, 4H), 1.94 (d, J = 12.5 Hz, 2H), 1.74 – 1.40 (m, 6H), 1.32 (td, J = 12.2, 3.6 Hz, 2H), 1.17 – 0.98 (m, 21H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 108.1, 86.0, 67.7, 59.2, 46.8, 35.9, 25.9, 23.0, 18.9, 11.4. HRMS calculated requires [M-H]: 348.2717. Found m/z: 348.2710.

4o: Synthesis of 4-(1-{4-[(tert-butyldimethylsilyl)oxy]but-1-yn-1-yl}cyclohexyl)morpholine

Piperidine (99 μL, 1.0 mmol), cyclohexanone (104 μL, 1.0 mmol), 4-(tert-butyldimethylsiloxy)-1-butyne (207 μL, 1.0 mmol), CuCl$_2$ (6.8 mg, 0.05 mmol) was stirred at 110 °C
for 6 hours to afford the title compound as a light brown oil in 84% yield (0.295 g, 0.84 mmol) after column chromatography on silica gel (15% EtOAc/hexanes). IR (film) 2928, 2854, 2820, 1716, 1453, 1269, 1256, 1118, 1104, 974, 920, 882, 834, 774, 732, 664 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.69 (m, 6H), 2.67 – 2.47 (m, 4H), 2.41 (t, J = 7.1 Hz, 2H), 1.84 (d, J = 12.6 Hz, 2H), 1.63 (d, J = 4.8 Hz, 2H), 1.54 – 1.47 (m, 2H), 1.40 – 1.30 (m, 2H), 1.28 – 1.07 (m, 2H), 0.86 (s, 9H), 0.04 (s, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 83.1, 81.0, 67.7, 62.6, 58.6, 46.6, 35.7, 26.1, 26.0, 25.9, 23.3, 22.8, 18.5, -5.1. HRMS calculated requires [M+H]⁺: 352.2672. Found m/z: 352.3046.
Chapter 3

Copper/Titanium Catalysis Forms Fully-Substituted Carbon Centers from the Direct Coupling of Acyclic Ketones, Amines, and Alkynes

I. Introduction

Given the realization of the propargylamine syntheses discussed in previous chapters of this work, these production of these valuable organic targets continued to serve as a central focus of research within the Larsen group. The successful transition from aldehyde-amine-alkyne (A$^3$) to ketone-amine-alkyne (KA$^2$) coupling through substitution of aldehydes for cyclohexanone to give fully-substituted propargylamines initiated the next phase of our investigations: expanding the scope of these novel KA$^2$ routes to include much less reactive unactivated, acyclic ketones.

In contrast to the wide array of three-component couplings (3CC) with aldehydes, and now cyclohexanones, via the \textit{in situ} formation of imines, reactions of acyclic ketones as electrophiles require an extra step that costs time, energy, and materials to produce and purify ketimine starting material. The dozens of methods already published that allow for enantioselective addition to pre-formed ketimines without corresponding racemic 3CC alternatives suggests that a direct 3CC of ketones is more difficult to achieve than asymmetric variants involving ketimines. This chapter discusses our discovery and report of a copper/titanium dual-catalyzed racemic 3CC of unactivated ketones with amines and alkynes.
II. Background

A wide range of natural products and bioactive compounds contain fully-substituted carbon centers, a few examples of which are given in Figure 5.\textsuperscript{1-15} To circumvent the difficulty of creating these hindered C-N bonds in a single step, compounds are commonly synthesized and rearrangement induced.\textsuperscript{16} The Curtius rearrangement\textsuperscript{17} (Scheme 14) is given as an excellent example of a method to produce amine bearing fully-substituted carbon centers by Lebel and coworkers.\textsuperscript{18} Scheme 15 details their report of a one-pot method for the synthesis of Boc-protected amines from carboxylic acids. Here, a carbamate is formed via the treatment of a carboxylic acid on a fully-substituted center with a mixture of Boc\textsubscript{2}O and sodium azide in the presence of a phase transfer catalyst and heat.

**Scheme 14.** Curtius rearrangement gives amines from azides

\[
\text{Ph-N}_3 \xrightarrow{\text{H}_2\text{O, }\Delta} \text{Ph-NCO} \xrightarrow{-\text{N}_2} \text{Ph-NH}_2
\]

**Scheme 15.** Boc-protected amines on fully-substituted centers via Curtius

\[
\text{OH} \xrightarrow{\text{Boc}_2\text{O, }\text{NaN}_3, \text{Bu}_4\text{NBr, THF, }80\ ^\circ\text{C}} \text{NH}_{\text{Boc}}
\]
The need for rearrangement to form hindered C-N bonds could be bypassed if a catalytic system was developed that is capable of overcoming the barrier to in situ condensation of a ketone onto an amine to give ketimine intermediate, while leaving a nucleophile capable of attack. This route would provide direct single-step access to tetrasubstituted carbon atoms bearing amines.\textsuperscript{19} The difficulty of developing three-component routes with ketimine intermediates is shown in the comparison to its analogous aldehyde counterpart. Numerous 3CC involve the in situ generation of aldimines, whereas reactions utilizing ketones as electrophiles generally require preformation and isolation of the ketimine intermediate, a step
that requires additional time and reagents during production and purification.\textsuperscript{20} Additionally, many of these methods utilizing preformation of ketimine involve enantioselective additions, but even these have no corresponding 3CC in either asymmetric or enantioselective form.\textsuperscript{1-15} This contrast suggests that the direct 3CC of ketones is more difficult to achieve than the asymmetric addition of nucleophiles to preformed ketimines.

The addition of cyanide to ketimines is known as the Strecker reaction and serves as an excellent example of the difficulty presented by 3CC's with ketones. The first catalytic enantioselective Strecker variant, shown in Scheme 16, was reported by Jacobsen \textit{et al.} in 2000 and uses 2 mol\% loading of thiourea to add cyanide to pre-formed benzyl-protected ketimines.\textsuperscript{1} The reaction is run in toluene at -75 °C for up to 90 hours to give high yields and good ee.

**Scheme 16.** Thiourea-catalyzed HCN addition forms “quaternary amino acids”\textsuperscript{1}

\[
\begin{align*}
\text{RC} &= \text{Me} \\
\text{N} &\text{Me} \\
\text{HN} &\text{Me} \\
\text{CN} &\text{R}
\end{align*}
\]

\text{Scheme 16.} Thiourea-catalyzed HCN addition forms “quaternary amino acids”\textsuperscript{1}

\begin{itemize}
\item R = \text{o-BrPh:} 45\%, 42\% ee
\item R = \text{t-Bu:} 98\%, 70\% ee
\end{itemize}
Only a year later, Chavarot and coworkers published on a scandium-catalyzed trimethylsilyl cyanide (TMS-CN) addition, again to pre-formed benzyl-protected ketimines.\textsuperscript{2} Detailed in Scheme 17, this reaction utilized a heterobimetallic Sc(BINOL)\textsubscript{2}Li catalyst present in 10 mol% to couple TMS-CN to an acetophenone-derived ketimine in toluene at only -20 °C. This route achieves similar yields and higher ee’s, up to 95%, in a shorter amount of time than Vachal’s earlier thiourea catalysis.

**Scheme 17.** Scandium(III)-catalysis yields cyanide-bearing carbon centers\textsuperscript{2}

\[
\begin{align*}
\text{Me} & \quad \text{10 mol\% catalyst} \\
\text{1.0 equiv. TMS-CN} & \quad \text{toluene, -20 °C, 15-90h}
\end{align*}
\]

3h: 80% conversion, 91% ee
9h: >95% conversion, 88% ee

Despite these highly-efficient asymmetric Strecker protocols, it took seven years before Prakash \textit{et al.} reported the first racemic 3CC Strecker reaction of ketones.\textsuperscript{19} Figure 6 displays the substrate scope accessible via this gallium(III) triflate catalyzed synthesis of amine bearing fully-substituted centers. Lewis acidic Ga(OTf)\textsubscript{3} allows for the \textit{in situ} condensation of anilines onto a range of acyclic ketones. Activated mono-, di-, and trifluoromethyl ketones as well as unactivated
aryl ketones like acetophenone react efficiently, providing a broad array of substituted Strecker products in high yields.

**Figure 6.** Gallium(III) triflate catalyzes 1\textsuperscript{st} 3CC Strecker reaction of ketones\textsuperscript{19}

It wasn’t until a full decade after the first asymmetric Strecker from ketimines was reported that a 3CC enantioselective protocol was developed.\textsuperscript{21} Application of a chiral phosphoric acid catalyst to a mixture of acetophenones, anilines, and TMS-CN allows for an asymmetric transformation giving a range of cyano- and amine-bearing carbon centers in good yields. The maximum achieved ee stands at a low 40%, the other two chiral substrates sit at only 20% ee. As this is the first 3CC
method with a ketone the relatively low values are both unsurprising and forgivable. The ten year gap between the first asymmetric Strecker and this report, coupled with the still low ee values, serve to highlight how much more difficult accessing a ketimine \textit{in situ} for a 3CC is than any of the corresponding two-step counterparts.

\textbf{Scheme 18.} Chiral phosphoric acid-catalyzed Strecker proceeds in 20-40\% ee\textsuperscript{21}

An alternate nucleophile that has been successfully added into pre-formed ketimines is an allyl group via boronates. Like the Strecker, these allylations have
been reported on numerous times in both racemic and enantioselective manners. The first of each variant was reported in a single publication in 2006,\textsuperscript{9} with each prep involving dual-catalysis with copper. Scheme 19 gives an example of the catalytic racemic addition of allyl pinacol boronate to ketimine reported by Shibasaki.\textsuperscript{9} Utilizing CuF·3PPh\textsubscript{3} and La(Oi-Pr)\textsubscript{3} as co-catalysts, benzyl-protected ketimine converts to an amine and allyl functionalized fully-substituted center in a high 96\% yield. \textit{t}-Butanol additive is required for complete conversion to product as it allows protonolysis of allylated copper amide intermediate.

\textbf{Scheme 19.} Lanthanide as copper co-catalyst provides racemic allylation\textsuperscript{9}

\textbf{Scheme 20.} DuPHOS ligand allows first asymmetric allylation of ketimines\textsuperscript{9}
This racemic reaction acted as a template for Shibasaki and co-workers in their development of an asymmetric allylation. By exposing an acetophenone-derived benzyl-protected imine to a DuPHOS ligand in the presence of copper(II) and lithium(III) co-catalysts the group was able to isolate a 92% yield of substrate with an impressive 89% ee. To achieve this novel transformation, catalyst loading was increased 10-20 fold above what was required of the racemic variant, and t-butanol maintained its role in the protonolysis of the reaction intermediate. Despite the synthetic successes of this report, seven years later there is still no example of a 3CC of a ketone, amine, and allylboronate. Just as with the Strecker reaction, the difficulties of accessing an electrophilic ketimine intermediate in situ for allylation prove more problematic than the introduction of a ligand to induce enantioselective product formation. If the barrier to in situ ketimine formation could be overcome then each of the several reports disclosing nucleophilic addition to pre-formed ketimines,\textsuperscript{20} including allylations, would gain access to a potentially inclusive and potent new route.

Moving past additions of cyanide and allylboronates, coupling the prospect of a 3CC route involving ketones with the inherent bioactivity and synthetic importance of propargylamines\textsuperscript{22} would provide a powerful method of accessing potentially high-value therapeutic and synthetic targets. The nucleophilic attack on imines by terminal alkynes has been widely studied due to the utility of the resulting propargylamines.\textsuperscript{23-30} 3CC aldehyde-amine-alkyne (A\textsuperscript{3}) couplings abound,\textsuperscript{31-39} but as ketones are 750-times less-active than aldehydes as electrophiles,\textsuperscript{40} a
The corresponding ketone-amine-alkyne (KA\textsuperscript{2}) procedure for unactivated ketones has not been reported. The three catalytic methods developed for cyclohexanones,\textsuperscript{41-43} each of which is discussed in detail in the previous chapter, rely on the fact that they undergo nucleophilic attack 300-times faster than acyclic ketones.\textsuperscript{44} Cyclohexanone is a special case of near aldehyde-like reactivity,\textsuperscript{45,46} and its corresponding ketimines\textsuperscript{47,48} readily react to release torsional strain.\textsuperscript{49,50} For these reasons, the development of a 3CC route accessing full-substituted propargylamines from unactivated ketones requires a way to overcome the barrier to \textit{in situ} condensation and achieve reactive ketimine intermediate.

\section*{III. Inclusion of Lewis Acid Allows for \textit{in situ} Formation of Ketimine Intermediate}

In the previous chapter, a green\textsuperscript{51} copper(II) chloride catalyzed KA\textsuperscript{2} of cyclohexanone that uses 1:1:1 stoichiometry of three coupling partners was discussed.\textsuperscript{52} Heating cyclohexanone, benzylamine, and 1-octyne under these conditions produces an \textit{N}-benzyl propargylamine in 91\% yield (Scheme 21). However, when cyclohexanone is replaced with 2-butanone, an unactivated ketone, neither ketimine intermediate nor the desired propargylamine product is observed under identical conditions. Elevated temperatures, microwave conditions, and standard drying agents do not improve the reaction. The conditions reported by Van der Eycken\textsuperscript{41} and Ji\textsuperscript{42} also fail.
This failure was the first sign of the serious synthetic challenge posed by
the KA$^2$ of acyclic ketones. The general catalytic cycle proposed for these types of
reactions involves the condensation of amine and carbonyl with subsequent attack
of the resultant imine by the metal acetylide from the terminal alkyne.$^{36,37}$ We
hyposthesized that a more-active Lewis acid additive could overcome both the
barrier to in situ ketimine formation and activate these less-reactive ketimines for
subsequent attack. Ellman and co-workers and Davis et al. have demonstrated
that the formation of aldmines can be facilitated by a range of Lewis acidic
dehydrating agents.$^{53,54}$ However, their results showed that titanium(IV) ethoxide
was unique in its ability to form ketimines without competitive aldol reactions.
Ti(OEt)$_4$ is inexpensive and filtration removes the benign TiO$_2$ by-products. One
downside of these reactions conditions is the excess of titanium required to
generate ketimines in high yield. 5 equivalents of Lewis acid are needed to form
and isolate ketimine.
Our own exploration of Lewis acid additives began with the combination of 2-butanone, benzylamine, and 1-octyne. These reactants have proven completely unreactive under all tested known conditions (Scheme 21). Table 9 shows a range of Lewis acids tested in conjunction with 5 mol% CuCl$_2$. When added in a fraction of the 5 equivalents previously reported$^{53,54}$, 50 mol% Ti(OEt)$_4$ or Ti(O-i-Pr)$_4$ provide propargylamine in 92% or 34% GC yield, respectively. Lewis acid aluminum, iron, and gold sources tested induce no conversion from starting materials despite their documented utility in imine alkynylation.$^{36,37,42}$

**Table 9.** Only titanium capable of co-catalytic activity to give propargylamine

<table>
<thead>
<tr>
<th>Entry</th>
<th>Lewis acid</th>
<th>GC yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Ti(OEt)$_4$</td>
<td>92</td>
</tr>
<tr>
<td>2</td>
<td>Ti(O-i-Pr)$_4$</td>
<td>34</td>
</tr>
<tr>
<td>3</td>
<td>AlCl$_3$</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>FeCl$_3$</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>AuCl$_3$</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>AuBr$_3$</td>
<td>0</td>
</tr>
</tbody>
</table>

Under an atmosphere of either air or industrial grade Nitrogen, propargylamine forms cleanly but reaction progress is halted at two-thirds conversion compared to reaction run under industrial grade Argon. Thus, heating 2-butanone, benzylamine, and 1-octyne with 5 mol% CuCl$_2$ and 50 mol% Ti(OEt)$_4$
produces N-benzyl propargylamine in 74% isolated yield. The cooperative effect of both metals is required. In the absence of titanium, the starting materials do not react. If copper is not used, ketimine forms in the presence of titanium but is not alkynylated.

IV. Investigations into Catalyst/Solvent Efficiency and Role

Despite the success of the originally tested copper source, copper(II) chloride, we needed to test a number of other copper catalysts to see which provided superior conversion. To do this we added a range of copper(I) and copper(II) sources to a heated solution of 2-butanone, piperidine, 1-octyne, and 25 mol% Ti(OEt)$_4$. The results of this experiment are listed in Table 10, below.

**Table 10.** Copper halides catalyze synthesis of fully-substituted propargylamines

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu Source</th>
<th>GC yield (%) at 2d</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(II) trflate</td>
<td>61</td>
</tr>
<tr>
<td>2</td>
<td>Cu(II) acetate</td>
<td>28</td>
</tr>
<tr>
<td>3</td>
<td>Cu(II) bromide</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td><strong>Cu(II) chloride</strong></td>
<td><strong>91</strong></td>
</tr>
<tr>
<td>5</td>
<td>Cu(I) trflate tetrakisacetonitrile</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>Cu(I) acetate</td>
<td>37</td>
</tr>
<tr>
<td>7</td>
<td>Cu(I) bromide</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td><strong>Cu(I) chloride</strong></td>
<td><strong>89</strong></td>
</tr>
<tr>
<td>9</td>
<td>Cu(I) bromide dimethylsulfoxide</td>
<td>69</td>
</tr>
<tr>
<td>10</td>
<td><strong>Cu(I) iodide</strong></td>
<td><strong>88</strong></td>
</tr>
</tbody>
</table>
At 5 mol% loading with 25 mol% Ti(OEt)$_4$, every copper source examined exhibited activity in the absence of solvent: CuOTf$_2$, CuOAc$_2$, CuBr$_2$, CuCl$_2$, CuOTf•(CH$_3$CN)$_4$, CuOAc, CuBr, CuCl, CuBr•SMe$_2$, and Cul. The presence of halide ligands on copper consistently provides good conversion, but there appears to be no correlation between metal oxidation state and catalytic activity. GC yields with Cu(I) chloride and iodide (89% and 88%) are similar to Cu(II) chloride (91%).

Additional unanswered questions were raised by these catalyst studies. The role of titanium appears to extend beyond in situ imine formation: the rate of alkynylation from isolated ketimine in the presence of copper but without titanium proceeds at half the rate. The rate of production of propargylamine product does not differ significantly between conditions A and B but C drops reaction rate by 50%: A) standard simultaneous addition of copper, titanium, ketone, amine, and alkyne; B) in situ pre-formation of ketimine upon heating in the presence of 50 mol% Ti(OEt)$_4$ for 1h followed by the addition of 5 mol% CuCl$_2$ and alkyne; and C) purified ketimine heated in the presence of 5 mol% CuCl$_2$ and alkyne.

Additional optimization involved the use of drying agents and solvents in attempts push conversion all the way to completion. Unfortunately, higher temperatures, microwave conditions, and the addition of standard drying agents (pulverized 4Å molecular sieves, Na$_2$SO$_4$, Mg$_2$SO$_4$, and CuSO$_4$) did not furnish $N$-benzyl quaternary propargylamine. When solvents were re-examined, no conversion to piperidinyl propargylamine is observed in acetone, acetonitrile, chloroform, dichloroethane, 1,4-dioxane, DMF, DMSO, ethyl acetate, methanol, or
water. THF and toluene allow for condensation of piperidine and 2-butane to 25% and 40% iminium respectively, but subsequent alknylation does not occur. Acids intended to increase iminium formation (5 mol% acetic acid, HCl, or triflic acid) halted the reaction at 10% GC yield while producing many side products. Basic additives (CsCO₃ or NaHCO₃) resulted in similar conversion but no side products.

V. Cu/Ti Dual Catalysis Provides Expansive Range of Products from Acyclic Ketones

The simple method of heating equimolar amounts of ketone, amine, and alkyne with Cuᴵᴵ/Ti⁴ is successful for a variety of nonsymmetric ketones (Table 11). With 5 mol% CuCl₂ and 25 mol% Ti(OEt)₄, 2-butane combines with morpholine and 1-octyne to give product in 54% yield (5a, entry 1). For most substrates 25 mol% is sufficient for conversion to product but 50 mol % provides higher yields. These conditions form propargylamines bearing cyclopropyl and isopropyl sidechains in 71% (5b) and 75% (5c) yields (entries 2 and 3). 4-methyl-2-pentanone gives propargylamine bearing a branched functional group in 82% yield after 3 days (5f) entry 6). Hindered pinacolone (5d, entry 4) forms propargylamine where the new C-N bond bridges the tertiary amine and tetrasubstituted carbon with a vicinal quaternary center. However, despite the conversions allowed via this protocol, aromatic ketones remain unreactive.
Table 11. Acyclic ketones form fully-substituted C-N bonds

As nonsymmetric ketones are utilized throughout this protocol, all of the products described herein are chiral. However, each isolated substrate is assumed to be a racemic mixture of enantiomers. The first catalytic diastereoselective KA was achieved by reacting 1R-(+)-camphor, benzylamine, and 1-octyne (Scheme 22) to produce propargylamine in 61% yield (5g). Diastereoselectivity of >95:5 was determined by $^1$H NMR spectroscopy.
Scheme 22. Highly diastereoselective KA\(^2\) reaction with camphor

As shown in Table 12, terminal alkynes bearing aryl (6b, 6c), alkyl (6a, 6f), chlorinated (6e), and cyano (6d) groups couple efficiently (71%-91% yields). This contrasts with the previous cyclohexanone KA\(^2\) conditions in which utilization of alkyl alkynes reduces the product yield by half.\(^{41,42}\) In addition to the synthetic utility of propargylamines discussed previously, the nitrile (6d) and chloro (6e) groups can be readily converted into a variety of other functional groups.

Table 12. Alkynes with a range of functionality react efficiently

<table>
<thead>
<tr>
<th>Entry</th>
<th>Propargylamine 6</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6a: R = n-Hex</td>
<td>48</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>6b: R = Ph</td>
<td>22</td>
<td>70</td>
</tr>
<tr>
<td>3</td>
<td>6c: R = (CH(_2))(_3)Ph</td>
<td>72</td>
<td>71</td>
</tr>
<tr>
<td>4</td>
<td>6d: R = (CH(_2))(_3)CN</td>
<td>48</td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>6e: R = (CH(_2))(_3)Cl</td>
<td>21</td>
<td>91</td>
</tr>
<tr>
<td>6</td>
<td>6f: R = t-Bu</td>
<td>23</td>
<td>90</td>
</tr>
</tbody>
</table>
Table 13. Variation in amine coupling partners for KA² with 2-butanone

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>H₂NCH(Ph)</td>
<td>Et(\text{Me}^\text{n-Hex} )</td>
<td>22</td>
<td>74%</td>
</tr>
<tr>
<td>2</td>
<td>H₂NCH(9-anth)</td>
<td>Et(\text{Me}^\text{t-Bu} )</td>
<td>22</td>
<td>73%</td>
</tr>
<tr>
<td>3</td>
<td>MeNCH(Ph)</td>
<td>Et(\text{Me}^\text{t-Bu} )</td>
<td>23</td>
<td>81%</td>
</tr>
<tr>
<td>4</td>
<td>CH₂NH</td>
<td>Et(\text{Me}^\text{t-Bu} )</td>
<td>23</td>
<td>90%</td>
</tr>
<tr>
<td>5</td>
<td>CH₂OCH₂</td>
<td>Et(\text{Me}^\text{t-Bu} )</td>
<td>23</td>
<td>91%</td>
</tr>
<tr>
<td>6</td>
<td>NCH(Ph)Me</td>
<td>Et(\text{Me}^\text{t-Bu} )</td>
<td>48</td>
<td>73%</td>
</tr>
</tbody>
</table>
Table 13 displays the scope of the amine component of these KA$_2$ reactions. Propargylamines from piperidine and morpholine (entries 4 and 5) provide 90% (6f) and 91% (6g) yields of tertiary amines attached to a fully-substituted carbon center. While primary amines are considered to be difficult substrates compared to secondary amines,$^{41}$ aminomethyl naphthalene provides product with a free N-H moiety for derivatization in 73% yield (6h, entry 2). Deprotectable primary N-benzyl propargylamine is also synthesized under these conditions to give a 74% yield (5). Bearing additional pharmacophores, N-methyl benzyl amine and N-propyl cyclopropylmethyl amine are accessed in 81% (6j) and 73% (6i) yield, respectively.

To my knowledge, this was the first method developed for the catalytic KA$_2$ of acyclic ketones. This method overcomes barriers to reactivity for a broad range of unactivated ketones under solvent-free conditions and without the waste in terms of excess substrate$^{55,56}$ that often detracts from the advantages of multicomponent reactions.$^{57-59}$ Primary and secondary, cyclic and acyclic amines couple rapidly with nonsymmetric ketones and terminal alkynes to give secondary and tertiary N-propargylamines at tetrasubstituted carbon centers. Compared to current synthesis reliant on stoichiometric metal acetylide addition to ketimines,$^{26}$ our approach provides a faster route to compounds with both therapeutic activity and utility in natural product synthesis.$^{23-30}$ A highly diastereoselective example with camphor inspires the current efforts to make this KA$_2$ enantioselective.
The cooperative effects of inexpensive titanium(IV) ethoxide and copper(II) chloride catalyze \textit{in situ} ketimine formation and activate the ketimine for alkynylation. Nucleophiles successful in 3CC with aldehydes and amines lack the corresponding 3CC with ketones.\textsuperscript{19,20,23-30} This unique Cu\textsuperscript{II}/Ti\textsuperscript{IV} system for the activation of ketone electrophiles may enable expansion to nucleophiles other than alkynes for direct access to a wide range of fully-substituted carbon centers bearing amines.
VI. Literature Citations

(32) Li, C.-J.; Wei, C. Chemical Communications 2002, 268.
(35) Wei, C.; Li, C.-J. Journal of the American Chemical Society 2003, 125, 9584.
VII. Supporting Information

General Reagent Information

All reactions were set up on the benchtop and carried out in oven-dried Teflon seal screw-cap test-tubes stirring by magnetic stir bars under an atmosphere of argon. Flash column chromatography was performed using silica gel (230-400 mesh) purchased from Silicycle. CuCl$_2$ (99%) was purchased from Acros and used as supplied. Ti(OEt)$_4$, 85%, tech, contains 5-15% isopropanol, was purchased from Acros and used as supplied. Amines were purchased from Acros Organics, Alfa Aesar, or Aldrich and purified by distillation before use. All ketones and alkynes were purchased from Acros Organics, Alfa Aesar or TCI America and purified by distillation before use.

General Analytical Information

$^1$H and $^{13}$C NMR spectra were measured on a Varian Inova 400 (400 MHz) spectrometer using CDCl$_3$ as a solvent and tetramethylsilane as an internal standard. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet and br - broad. NMR spectra were acquired at 300 K. Gas chromatograph spectra were obtained on an Agilent Technologies 6850 Network GC System using dodecane as an internal standard. IR spectra were recorded on Perkin Elmer Spectrum One FT-IR Spectrometer. Attenuated total reflection infrared (ATR-IR) was used for analysis with selected absorption maxima reported in wavenumbers (cm$^{-1}$). No sample preparation was necessary for ATR
analysis. ATR-IR is based on the propagation of the infrared radiation through an internal reflection element (crystal) with a high refractive index, and its reflection at the interface between the crystal and the solid material. Mass spectrometric data was collected on a ThermoScientific TSQ triple quadrupole LCMS instrument. Exact masses were recorded on an Agilent LCTOF instrument using direct injection of samples in acetonitrile into the electrospray source (ESI) and either positive or negative ionization.

General Procedure

To an oven-dried test tube equipped with magnetic stir bar and Teflon-seal screw cap was added 5 mol % CuCl₂ and 50 mol% Ti(OEt)₄. The flask was purged with argon for 5 minutes. Ketone (1.0 equiv), alkyne (1.0 equiv), and amine (1.0 equiv) were added, and the reaction was stirred at 110 °C for the indicated time. Upon completion, as judged by GC, the mixture was cooled to room temperature and directly loaded atop a silica gel column. Chromatography with ethyl acetate (EtOAc) in hexanes as eluent afforded the desired product. The products were further identified by FT-IR, ¹H NMR, ¹³C NMR and HRMS, which were all in good agreement with the assigned structures.

5: Synthesis of benzyl(3-methylundec-4-yn-3-yl)amine

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\text{Benzyllamine(110 \, \mu\text{L}, 1.0 \, \text{mmol}), 2-butanone (90 \, \mu\text{L}, 1.0 \, \text{mmol}), 1-octyne (148 \, \mu\text{L}, 1.0 \, \text{mmol}, \text{CuCl}_2 (6.8 \, \text{mg}, 0.05 \, \text{mmol}), Ti(OEt)_4 (114.1 \, \text{mg}, 0.50 \, \text{mmol}) was stirred at 110 °C for 22 hours to}
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afford the title compound as a clear orange oil in 74% yield (0.201 g, 0.74 mmol) after column chromatography on silica gel (30% EtOAc/hexanes). IR (film) 2960, 2929, 2857, 1672, 1605, 1495, 1454, 1369, 1177, 1153, 1028, 729, 697 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.40 – 7.27 (m, 4H), 7.27 – 7.20 (m, 1H), 3.85 (q, \(J = 11.9\) Hz, 2H), 2.23 (t, \(J = 6.9\) Hz, 2H), 1.66 – 1.40 (m, 7H), 1.34 – 1.29 (m, 6H), 1.00 (t, \(J = 7.4\) Hz, 3H), 0.89 (t, \(J = 7.4\) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 141.3, 128.6, 128.6, 127.0, 84.3, 83.6, 54.4, 48.8, 35.1, 31.6, 29.4, 28.7, 27.0, 22.8, 18.9, 14.3, 9.1. HRMS calculated requires [M-H]\(^-\): 270.2216. Found m/z: 270.2226.

5a: Synthesis of 4-(3-methylundec-4-yn-3-yl)morpholine

Morpholine (88 μL, 1.0 mmol), 2-butanone (90 μL, 1.0 mmol), 1-octyne (148 μL, 1.0 mmol), CuCl\(_2\) (6.8 mg, 0.05 mmol), Ti(OEt)\(_4\) (114.1 mg, 0.50 mmol) was stirred at 110 °C for 2 days to afford the title compound as a clear yellow oil in 81% yield (0.211 g, 0.81 mmol) after column chromatography on silica gel (10% EtOAc/hexanes). IR (film) 2956, 2929, 2853, 2818, 1729, 1454, 1267, 1168, 1119, 956, 924, 865 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 3.72 (t, \(J = 4.7\) Hz, 4H), 2.69 – 2.51 (m, 4H), 2.24 – 2.12 (m, 2H), 1.72 – 1.55 (m, 2H), 1.53 – 1.45 (m, 2H), 1.42 – 1.18 (m, 9H), 0.99 – 0.83 (m, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 84.6, 81.4, 67.5, 57.8, 47.0, 31.9, 31.3, 29.1, 28.5, 23.2, 22.6, 18.6, 14.0, 8.5. HRMS calculated requires [(M+H)-H]: 251.2244. Found m/z: 251.2243.
5b: Synthesis of 1-(2-cyclopropyldec-3-yn-2-yl)piperidine

Piperidine (99 μL, 1.0 mmol), cyclopropyl methyl ketone (94 μL, 1.0 mmol), 1-octyne (148 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol), Ti(OEt)₄ (114.1 mg, 0.50 mmol) was stirred at 110 °C for 3 days to afford the title compound as a clear yellow oil in 71% yield (0.186 g, 0.71 mmol) after column chromatography on silica gel (10% EtOAc/hexanes). IR (film) 2927, 2855, 2796, 1736, 1455, 1442, 1368, 1248, 1155, 1137, 1116, 1023, 958, 864, 824, 770, 724 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.77 (s, 4H), 2.16 (t, J = 6.8 Hz, 2H), 1.67 – 1.55 (m, 4H), 1.51 – 1.20 (m, 13H), 0.95 – 0.79 (m, 4H), 0.69 – 0.59 (m, 1H), 0.56 – 0.47 (m, 1H), 0.39 – 0.30 (m, 1H), 0.27 - 0.17 (m, 1H). ¹³C NMR (100 MHz, CDCl₃) δ 85.6, 60.9, 48.5, 31.3, 29.7, 29.2, 28.5, 28.0, 26.5, 24.7, 22.6, 19.4, 18.5, 14.0, 5.8, 0.7. HRMS calculated requires [M-H]⁻: 260.2373. Found m/z: 260.2380.

5c: Synthesis of 1-(2,3-dimethylundec-4-yn-3-yl)piperidine

Piperidine (99 μL, 1.0 mmol), 3-methyl-2-butanone (107 μL, 1.0 mmol), 1-octyne (148 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol), Ti(OEt)₄ (114.1 mg, 0.50 mmol) was stirred at 110 °C for 2 days to afford the title compound as a clear yellow oil in 75% yield (0.198 g, 0.75 mmol) after column chromatography on silica gel (8% EtOAc/hexanes). IR (film) 2959, 2928, 2856, 2797, 1719, 1467, 1454, 1442, 1382, 1365, 1161, 1127, 1094, 942, 804 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.68 – 2.33 (m, 4H), 2.20 (t, J
= 6.9 Hz, 2H), 2.07 – 1.94 (m, 1H), 1.69 – 1.19 (m, 15H), 1.09 (s, 3H), 1.00 (d, J = 6.7 Hz, 3H), 0.92 – 0.86 (m, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 84.2, 81.9, 61.5, 47.5, 33.5, 31.4, 29.3, 28.5, 26.9, 25.2, 22.6, 18.7, 18.1, 16.7, 14.1. HRMS calculated requires [(M+Na)-H]$: 285.2427. Found m/z: 285.2429.

5d: Synthesis of 4-(2,2,3-trimethylundec-4-yn-3-yl)morpholine

Morpholine (88 μL, 1.0 mmol), pinacolone (125 μL, 1.0 mmol), 1-octyne (148 μL, 1.0 mmol), CuCl$_2$ (6.8 mg, 0.05 mmol), Ti(OEt)$_4$ (114.1 mg, 0.50 mmol) was stirred at 110 °C for 2 days to afford the title compound as a clear orange oil in 82% yield (0.229 g, 0.82 mmol) after column chromatography on silica gel (10% EtOAc/hexanes). IR (film) 2955, 2928, 2853, 2819, 1730, 1455, 1271, 1119, 960, 926, 863, 725 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.65 (t, J = 4.7 Hz, 4H), 2.63 – 2.43 (m, 4H), 2.12 (t, J = 7.0 Hz, 2H), 1.54 – 1.15 (m, 18H), 0.88 – 0.75 (m, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 84.7, 81.7, 67.6, 57.7, 47.2, 39.5, 31.9, 31.5, 29.9, 29.3, 28.7, 24.1, 23.9, 22.8, 22.7, 18.8, 14.2, 14.2. HRMS calculated requires [M+H]$^+$: 280.2635. Found m/z: 280.2630.

5e: Synthesis of 1-(3-cyclohexylundec-4-yn-3-yl)piperidine

Piperidine (99 μL, 1.0 mmol), 1-cyclohexyl propan-1-one (155 μL, 1.0 mmol), 1-octyne (148 μL, 1.0 mmol), CuCl$_2$ (6.8 mg, 0.05 mmol), Ti(OEt)$_4$ (114.1 mg, 0.50 mmol) was stirred at 110 °C for 3 days to afford the title compound as a clear yellow oil in
64% yield (0.203 g, 0.64 mmol) after column chromatography on silica gel (5% 
EtOAc/hexanes). IR (film) 2957, 2929, 2853, 2818, 1735, 1454, 1267, 1119, 955, 
866 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.54 (d, \(J = 6.5\) Hz, 4H), 2.19 (t, \(J = 6.9\) 
Hz, 2H), 1.63 – 1.21 (m, 27H), 0.92 – 0.84 (m, 6H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 
83.7, 82.7, 57.8, 47.6, 39.7, 31.8, 31.4, 29.8, 29.1, 28.5, 26.6, 24.8, 24.3, 24.0, 
22.7, 22.6, 18.7, 14.1. HRMS calculated requires \([M+H]^+\): 318.3155. Found \(m/z\): 
318.3164.

5f: Synthesis of 1-(2,4-dimethyl)dodec-5-yn-4-yl)piperidine

Piperidine (99 µL, 1.0 mmol), 4-methyl-2-pentanone 
(125 µL, 1.0 mmol), 1-octyne (148 µL, 1.0 mmol), CuCl\(_2\) 
(6.8 mg, 0.05 mmol), Ti(OEt)\(_4\) (114.1 mg, 0.50 mmol) 
was stirred at 110 °C for 3 days to afford the title compound as a clear yellow oil 
in 82% yield (0.212 g, 0.82 mmol) after column chromatography on silica gel (5% 
EtOAc/hexanes). IR (film) 2954, 2928, 2856, 2801, 1717, 1686, 1618, 1466, 
1455, 1442, 1368, 1274, 1166, 1081, 948, 861, 805, 724 cm\(^{-1}\); \(^1\)H NMR (400 
MHz, CDCl\(_3\)) \(\delta\) 2.52 (s, 4H), 2.15 (t, \(J = 6.9\) Hz, 2H), 1.86-1.77 (m, 1H), 1.57 – 
1.22 (m, 20H), 0.94 (t, \(J = 7.1\) Hz, 3H), 0.89 – 0.79 (m, 5H). \(^{13}\)C NMR (100 MHz, 
CDCl\(_3\)) \(\delta\) 83.9, 82.8, 57.8, 47.8, 47.7, 31.9, 31.4, 29.8, 29.1, 28.5, 26.6, 24.9, 
24.6, 22.6, 18.7, 14.1. HRMS calculated requires [(M+Na)-H]\(^+\): 299.2583. Found 
\(m/z\): 299.2587.
5g: Synthesis of N-benzyl-1,7,7-trimethyl-2-(oct-1-yn-1-yl)bicyclo[2.2.1]heptan-2-amine

Benzylamine (110 μL, 1.0 mmol), (1R)-(+)camphor (152 mg, 1.0 mmol), 1-octyne (148 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol) was stirred at 110 °C for 1 day to afford the title compound as a clear light yellow oil in 61% yield (0.214 g, 0.61 mmol) after column chromatography on silica gel (15% EtOAc/hexanes). IR (film) 2955, 2927, 2856, 1745, 1671, 1604, 1454, 1370, 727, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.30 (dd, J = 10.0, 4.8 Hz, 4H), 7.20 – 7.13 (m, 1H), 3.78 (q, J = 11.9 Hz, 2H), 2.16 (t, J = 6.9 Hz, 2H), 1.58 – 1.31 (m, 9H), 1.31 – 1.13 (m, 13H), 0.90 – 0.72 (m, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 140.0, 127.4, 127.4, 125.8, 83.3, 82.3, 52.7, 47.6, 41.4, 30.8, 30.4, 28.6, 28.1, 27.5, 26.3, 23.4, 21.6, 17.7, 13.0. HRMS calculated requires [M+H]⁺: 352.2999. Found m/z: 352.2997.

6a: Synthesis of 1-(3-methylundec-4-yn-3-yl)piperidine

Piperidine (99 μL, 1.0 mmol), 2-butanone (90 μL, 1.0 mmol), 1-octyne (148 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol), Ti(OEt)₄ (114.1 mg, 0.50 mmol) was stirred at 110 °C for 48 hours to afford the title compound as a clear yellow oil in 85% yield (0.212 g, 0.85 mmol) after column chromatography on silica gel (5% EtOAc/hexanes). IR (film) 2957, 2928, 2856, 2797, 1454, 1442, 1376, 1327, 1274, 1241, 1171, 944, 860, 724 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.67 – 2.42 (m, 4H), 2.19 (t, J = 6.9 Hz,
2H), 1.74 – 1.53 (m, 6H), 1.52 – 1.37 (m, 6H), 1.36 – 1.18 (m, 8H), 0.98 – 0.84 (m, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 83.8, 82.5, 58.1, 47.5, 32.1, 31.3, 29.1, 28.5, 26.6, 24.8, 23.5, 22.6, 18.7, 14.1, 8.9. HRMS calculated requires [M-H]: 248.2373. Found m/z: 248.2382.

6b: Synthesis of 1-(3-methyl-1-phenylpent-1-yn-3-yl)piperidine

Piperidine (99 μL, 1.0 mmol), 2-butanone (90 μL, 1.0 mmol), phenylacetylene (110 μL, 1.0 mmol), CuCl$_2$ (6.8 mg, 0.05 mmol), Ti(OEt)$_4$ (114.1 mg, 0.50 mmol) was stirred at 110 °C for 22 hours to afford the title compound as a clear orange oil in 70% yield (0.168 g, 0.70 mmol) after column chromatography on silica gel (15% EtOAc/hexanes). IR (film) 2974, 2930, 2852, 2798, 1670, 1598, 1489, 1442, 1240, 1172, 1070, 1004, 945, 911, 860, 753, 689 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.48 – 7.37 (m, 2H), 7.27 (dd, J = 5.3, 1.9 Hz, 3H), 2.74 – 2.49 (m, 4H), 1.87 – 1.67 (m, 2H), 1.65 - 1.56 (m, 4H), 1.50 – 1.39 (m, 2H), 1.37 (s, 3H), 1.02 (t, J = 7.4 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 131.7, 128.1, 127.6, 123.8, 92.4, 84.1, 58.6, 47.7, 32.1, 26.6, 24.8, 23.4, 8.8. HRMS calculated requires [M-H]: 240.1747. Found m/z: 240.1753.

6c: Synthesis of 1-(3-methyl-8-phenyloct-4-yn-3-yl)piperidine

Piperidine (99 μL, 1.0 mmol), 2-butanone (90 μL, 1.0 mmol), 5-phenyl-1-pentyne (152 μL, 1.0 mmol), CuCl$_2$ (6.8 mg, 0.05 mmol), Ti(OEt)$_4$ (114.1 mg, 0.50 mmol) was
stirred at 110 °C for 72 hours to afford the title compound as a clear orange oil in 71% yield (0.201 g, 0.71 mmol) after column chromatography on silica gel (12% EtOAc/hexanes). IR (film) 2973, 2930, 2854, 2794, 1717, 1603, 1495, 1453, 1442, 1241, 1171, 1153, 1109, 1077, 1030, 944, 744, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.26 (dt, J = 9.8, 7.7 Hz, 2H), 7.22 – 7.11 (m, 3H), 2.76 – 2.70 (m, 2H), 2.66 – 2.44 (m, 4H), 2.21 (q, J = 6.8 Hz, 2H), 1.86 – 1.75 (m, 2H), 1.68 – 1.51 (m, 6H), 1.46 – 1.38 (m, 2H), 1.27 (s, 3H), 0.97 (t, J = 7.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 142.1, 128.7, 128.5, 126.0, 83.5, 83.3, 47.8, 35.1, 32.4, 31.2, 26.8, 25.1, 23.7, 18.4, 9.1. HRMS calculated requires [M-H]⁺: 282.2216. Found m/z: 282.2226.

6d: Synthesis of 7-methyl-7-(piperidin-1-yl)non-5-ynenitrile

Piperidine (99 μL, 1.0 mmol), 2-butanone (90 μL, 1.0 mmol), 5-cyano-1-pentyne (106 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol), Ti(OEt)₄ (114.1 mg, 0.50 mmol) was stirred at 110 °C for 48 hours to afford the title compound as a brown oil in 76% yield (0.177 g, 0.76 mmol) after column chromatography on silica gel (25% EtOAc/hexanes). IR (film) 2972, 2932, 2853, 2799, 2257, 1665, 1453, 1442, 1241, 1172, 1109, 943, 860, 755, 734 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.57 – 2.47 (m, 5H), 2.40 (t, J = 6.6 Hz, 2H), 1.91 – 1.83 (m, 3H), 1.68 – 1.54 (m, 6H), 1.43 (d, J = 4.4 Hz, 2H), 1.26 (s, 3H), 0.94 (t, J = 7.3 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 119.5, 84.7, 81.0, 47.8, 32.2, 26.6, 25.2, 24.9, 23.5, 18.0, 16.3, 8.9. HRMS calculated requires [M-H]⁺: 231.1856. Found m/z: 231.1865.
6e: Synthesis of 1-(8-chloro-3-methyloct-4-yn-3-yl)piperidine

Piperidine (99 μL, 1.0 mmol), 2-butanone (90 μL, 1.0 mmol), 5-chloro-1-pentyne (106 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol), Ti(OEt)₄ (114.1 mg, 0.50 mmol) was stirred at 110 °C for 48 hours to afford the title compound as a dark orange oil in 91% yield (0.220 g, 0.91 mmol) after column chromatography on silica gel (15% EtOAc/hexanes). IR (film) 2974, 2930, 2852, 2796, 1669, 1453, 1441, 1305, 1281, 1241, 1172, 1070, 943, 859, 760, 726, 654 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.66 (t, J = 6.5 Hz, 2H), 2.52 (s, 4H), 2.40 (t, J = 6.8 Hz, 2H), 1.99 - 1.91 (m, 2H), 1.70 - 1.54 (m, 6H), 1.42 (d, J = 5.6 Hz, 2H), 1.25 (s, 3H), 0.94 (t, J = 7.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 83.7, 81.7, 58.2, 47.6, 43.8, 32.1, 31.9, 26.6, 24.8, 23.4, 16.2, 8.8. HRMS calculated requires [M+H]^+: 242.1670. Found m/z: 242.1678.

6f: Synthesis of 1-(3,6,6-trimethylhept-4-yn-3-yl)piperidine

Piperidine (99 μL, 1.0 mmol), 2-butanone (90 μL, 1.0 mmol), 3,3-dimethyl-1-butyne (124 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol), Ti(OEt)₄ (114.1 mg, 0.50 mmol) was stirred at 110 °C for 23 hours to afford the title compound as a clear orange oil in 90% yield (0.199 g, 0.90 mmol) after column chromatography on silica gel (30% EtOAc/hexanes). IR (film) 2968, 2929, 2856, 2797, 1721, 1454, 1442, 1361, 1262, 1240, 1171, 1072, 941, 860, 810, 740 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 2.60 – 2.44 (m, 4H), 1.63 – 1.50 (m, 6H), 1.44 – 1.35 (m, 2H), 1.22 (s, 3H), 1.21 (s, 9H), 0.93 (t, J = 7.4 Hz,
6g: Synthesis of 4-(3,6,6-trimethylhept-4-yn-3-yl)morpholine

Morpholine (88 μL, 1.0 mmol), 2-butanone (90 μL, 1.0 mmol), 3,3-dimethyl-1-butyne (124 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol), Ti(OEt)₄ (114.1 mg, 0.50 mmol) was stirred at 110 °C for 23 hours to afford the title compound as a clear orange oil in 91% yield (0.203 g, 0.91 mmol) after column chromatography on silica gel (30% EtOAc/hexanes). IR (film) 2966, 2852, 2818, 1454, 1361, 1264, 1119, 965, 924, 870, 860, 749 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 3.67 (t, J = 4.7 Hz, 4H), 2.60 – 2.45 (m, 4H), 1.63 – 1.45 (m, 2H), 1.26 – 1.06 (m, 12H), 0.88 (t, J = 7.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃) δ 93.6, 79.5, 67.6, 57.7, 47.2, 31.9, 31.7, 27.5, 23.5, 8.7. HRMS calculated requires [M+H]+: 280.2635. Found m/z: 280.2630.

6h: Synthesis of (naphthalen-2-ylmethyl)(3,6,6-trimethylhept-4-yn-3-yl)amine

1-naphthenemethylamine (147 μL, 1.0 mmol), 2-butanone (90 μL, 1.0 mmol), 3,3-dimethyl-1-butyne (124 μL, 1.0 mmol), CuCl₂ (6.8 mg, 0.05 mmol), Ti(OEt)₄ (114.1 mg, 0.50 mmol) was stirred at 110 °C for 22 hours to afford the title compound as a clear orange oil in 73% yield (0.214 g, 0.73 mmol) after column chromatography on silica gel (30% EtOAc/hexanes).
IR (film) 2928, 2854, 1740, 1495, 1452, 1115, 1028, 905, 732, 697 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 8.23 (d, \(J = 8.2\) Hz, 1H), 7.79 (d, \(J = 7.8\) Hz, 1H), 7.70 (d, \(J = 8.1\) Hz, 1H), 7.51 – 7.29 (m, 4H), 4.29 - 4.17 (m, 2H), 1.66 – 1.53 (m, 2H), 1.37 – 1.11 (m, 12H), 1.03 – 0.88 (m, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 136.7, 134.1, 132.2, 128.9, 128.0, 127.2, 126.2, 125.8, 125.7, 124.2, 92.6, 82.3, 54.5, 46.7, 35.3, 31.7, 26.9, 9.1. HRMS calculated requires \([M-H]^-\): 294.2216. Found \(m/z\): 294.2214.

6i: Synthesis of (cyclopropylmethyl)(propyl)(3,6,6-trimethylhept-4-yn-3-yl)amine

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\text{N-propylcyclopropanemethylamine (86 \mu L, 1.0 mmol), 2-butane (90 \mu L, 1.0 mmol), 3,3-dimethyl-1-butyne (124 \mu L, 1.0 mmol), CuCl}_2 (6.8 mg, 0.05 mmol), Ti(OEt\(_4\)) (114.1 mg, 0.50 mmol) was stirred at 110 °C for 48 hours to afford the title compound as a clear orange oil in 73% yield (0.182 g, 0.73 mmol) after column chromatography on silica gel (15% EtOAc/hexanes). IR (film) 2927, 2855, 2796, 1736, 1455, 1442, 1368, 1248, 1155, 1137, 1116, 1023, 958, 824, 770, 724 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 2.60 (dd, \(J = 9.2, 6.4\) Hz, 2H), 2.45 (dd, \(J = 6.4, 2.4\) Hz, 2H), 1.58 – 1.47 (m, 3H), 1.23 (s, 3H), 1.18 (s, 9H), 0.94 (t, \(J = 7.4\) Hz, 3H), 0.85 (t, \(J = 7.4\) Hz, 3H), 0.50 – 0.43 (m, 2H), 0.16 – 0.09 (m, 2H), 0.09 – 0.04 (m, 2H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 91.5, 82.1, 58.2, 54.7, 52.4, 33.1, 31.4, 27.3, 24.7, 22.9, 11.9, 11.2, 9.3, 4.5, 4.2. HRMS calculated requires \([M-H]^-\): 248.2373. Found \(m/z\): 248.2381.
6j: Synthesis of benzyl(methyl)(3,6,6-trimethylhept-4-yn-3-yl)amine

\[ \text{N-methyl benzylamine (130 \mu L, 1.0 mmol), 2-butanone (90 \mu L, 1.0 mmol), 3,3-dimethyl-1-butyn (124 \mu L, 1.0 mmol), CuCl}_2 (6.8 mg, 0.05 mmol), Ti(OEt)}_4 (114.1 mg, 0.50 mmol) was stirred at 110 °C for 23 hours to afford the title compound as a clear orange oil in 81% yield (0.209 g, 0.81 mmol) after column chromatography on silica gel (25% EtOAc/hexanes). IR (film) 2967, 2866, 2791, 1713, 1495, 1454, 1361, 1261, 1017, 946, 833, 754, 731, 696 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.35 (dd, \(J = 10.8, 3.8\) Hz, 2H), 7.32 – 7.26 (m, 2H), 7.24 – 7.18 (m, 1H), 2.08 (s, 3H), 1.70 (q, \(J = 7.4\) Hz, 2H), 1.31 (s, 3H), 1.24 (s, 9H), 1.01 (t, \(J = 7.4\) Hz, 3H), 0.92 (s, 2H).

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 141.56, 128.9, 128.3, 126.6, 92.7, 80.6, 58.2, 56.4, 35.5, 33.1, 31.8, 27.6, 24.3, 8.9. HRMS calculated requires [(M+Na)-H]: 279.1957. Found \(m/z\): 279.1967.
Chapter 4

Copper Catalyzed Tandem Markovnikov Hydroamination/Alkynylation

I. Introduction

Fully-substituted amine bearing carbon centers are a seemingly ubiquitous part of natural products and bioactive compounds. Circumvention of the difficulty presented by creating these hindered C-N bonds often involves synthesis and then induced rearrangement. The previous chapter of this work discussed formation of these centers in a single step via CuII/TiIV dual catalysis to couple unactivated ketones, amines, and alkynes. Here, the propitious discovery that removal of the carbonyl source under these same conditions resulted in a similarly highly-substituted propargylamine product is examined. It appeared our desired ketimine intermediates were forming despite lacking a ketone starting material.

Utilizing this knowledge to help overcome the difficulty of accessing tetrasubstituted carbons bearing amines, a transformation was envisioned in which the first equivalent of an alkyne acts as an electrophile, undergoing attack by an amine, and the second equivalent acts as a nucleophile, attacking the resultant ketimine. Despite the fact that copper is rarely utilized as a catalyst in alkyne hydroamination, and homogenous copper catalysts produce aldimines from aldehyde and amine, the ligand- and solvent-free copper(II) catalyzed system discussed in this chapter achieves the desired tandem alkynylation via ketimine.
II. Background

Primary or secondary amines can undergo addition reactions with alkynes to give enamines or imines. This atom-economical\textsuperscript{1,2} splitting of an N-H bond across the two sp-carbons of the alkyne is known as hydroamination.\textsuperscript{3-5} The obvious utility of this reaction as a mode of incorporating amines into organic compounds\textsuperscript{6-10} is hindered only for electronic reasons: both amines and alkynes are generally regarded as electron-rich species, so are not expected to react spontaneously. For this reason, numerous catalysts have been developed towards activation of the alkynyl π-bonds for nucleophilic attack.\textsuperscript{5}

Scheme 23. Tautomerization of reactive intermediates for subsequent reaction

As shown in Scheme 23, the conversion of alkynes via hydroamination yields reactive species such as imines that serve as excellent intermediates for subsequent transformations. As this desired species is one of two possible isomeric products, significant effort has been expended to develop organometallic catalysts (L\textsubscript{n}M) to induce regioselective formation of the Markovnikov product: di-substitution (in blue, Scheme 24) at the azomethine imine carbon. Anti-Markovnikov addition of the amine to alkyne would yield the alternate isomeric product (Scheme 24).
The first catalytic intermolecular hydroamination of alkynes was first accomplished with a cadmium/zinc system reported by Kruse and coworkers back in 1961. Through application of cadmium and zinc acetates, primary aliphatic amines were added into acetylene to give the anti-Markovnikov imine product. The first intermolecular hydroamination with zirconium wasn’t reported until 31 years later by Bergman et al. in 1992. They found that $\text{Cp}_2\text{Zr(NHR)}_2$ catalyzes the addition of 2,6-dimethylaniline to diphenylacetylene at 95 °C (Scheme 25). Only 3 mol% catalyst loading was required to provide enamine from 2,6-dimethylaniline and 2-butyne or diphenylacetylene. The authors make the interesting note that while the enamine formed from 2-butyne was observed by $^1\text{H}$ NMR, upon isolation it tautomerized to the isomeric imine. Product isolated from diphenylacetylene did not rearrange and was confirmed to be cis substitution of the phenyl groups on the enamine by $^1\text{H}$ NMR. The authors do not explain the lack of tautomerization, but I postulate it is due to the stability provided by the extended conjugation of dual aromatic groups on the enamine isomer. In THF, these conditions allow for the isolation of product in yields greater than 95%, but which isomer is actually isolated is substrate dependent and cannot be controlled.
Doye et al. reported on the first intermolecular hydroamination of alkynes catalyzed by titanium in 1999. 1.0 mol% of dimethyltitanocene (Cp₂TiMe₂) in dueterated benzene catalyzes the hydroamination of diphenylacetylene by aniline and allows for an isolation of 52% yield by crystallization from methanol (Scheme 26). This was the only imine structure isolated however, as subsequent hydroamination products were detected indirectly due to their susceptibility to hydrolysis. Imines were either hydrolyzed with SiO₂ to the stable ketones or reduced with LiAlH₄ to the stable imines. These reactions yielded products in 92% and 62% respective yields (Scheme 27).
Among the methods that followed those highlighted above, disparate metals\textsuperscript{14} developed for the activation of alkyne as electrophile are paired with bridging or bulky ligands to tune regioselectivity towards ketimine isomer during hydroamination.\textsuperscript{4,5} An excellent example of this isomeric steering involves the \textit{in situ} generation of catalyst from Ti(NE\textsubscript{2})\textsubscript{4} and two equivalents of bulky phenols (Scheme 28).\textsuperscript{15}

**Scheme 28.** Titanium catalyst formed \textit{in situ} controls regioisomer formed

\[
\begin{align*}
\text{Me} & \quad \text{Me} \\
\text{NH}_2 & \quad \text{NH}_2 \\
\equiv & \quad \equiv \\
n\text{Hex} \quad n\text{Hex}
\end{align*}
\]
In this study, Bellar et al. revealed that regioselectivity towards Markovnikov and anti-Markovnikov addition products can be controlled. Specifically, they found that increasing or decreasing steric bulk on aryloxo ligands will respectively favor or disfavor formation of Markovnikov ketimine (Scheme 28). Ligand A, bearing \( t \)-butyl groups adjacent to the coordination oxygen, provides 90:10 selectivity for ketimine. Less bulky ligand B, with \( iso \)-propyl groups, provides the opposite control and yields 94:6 regioselectivity for the anti-Markovnikov product.

The influx of methods utilizing these ligands as a form of control implied that development of any new routes would like similar coordinated bulk to achieve desired addition products. Even after the selective production of Markovnikov ketimine, many techniques require subsequent hydrogenation or addition of hydride nucleophiles to reduce these reactive substrates to more stable \( \alpha \)-secondary amines (Scheme 29). If carbon-based nucleophiles could be substituted for hydride sources and added during reaction, tetrasubstituted aminocarbons could be produced in a single step.

**Scheme 29.** Reduction of imine via hydride source

![Scheme 29](image)

As ketimine intermediates are harder to access and less reactive than the analogous aldimines,\(^\text{16}\) three-component couplings (3CC) from the condensation
of an amine and ketone electrophile terminating in attack by a carbon based nucleophile are extremely rare.\textsuperscript{17,18} These hindered \(\alpha\)-tertiary products are found in numerous medicinal compounds and natural isolates but are notoriously difficult to access in one catalytic step.\textsuperscript{19-21} Hydroamination presents an attractive alternative approach to these fully-substituted centers, circumventing the large barrier to \textit{in situ} condensation of amine onto ketone to form ketimine. A tandem catalytic Markovnikov hydroamination and subsequent alkynylation of ketimine would provide tetrasubstituted propargylamines in a single step.

\section*{III. Copper(II) Triflate in Dual-Catalytic Role is Superior Catalyst for Tandem Markovnikov Hydroamination/Alkynylation Reaction}

During a chemical reaction, each substrate plays the role of electrophile or nucleophile. The utility of carbonyl derivatives includes acting as both an electrophile and (in deprotonated form as an enolate) a nucleophile to form single homo-aldol products.\textsuperscript{22} Achieving similar reactivity with alkynes via a tandem hydroamination/alkynylation reaction is complicated because the best catalyst to activate the alkyne for hydroamination is unlikely to be ideal for subsequent acetylide addition. For example, although gold is well-precendented in imine alkynylation,\textsuperscript{23-26} the ketimine resulting from gold-catalyzed hydroamination is not attacked by a second equivalent of alkyne.\textsuperscript{27-31} Leyva and corma describe the intermolecular hydroamination of terminal alkynes with (SPhos)AuNTf\(_2\), a catalyst capable of converting less reactive internal alkynes.\textsuperscript{31}
Scheme 30. Au-catalyzed hydroamination yields divinylamines not alkynylation\textsuperscript{31}

This gold catalyzed method\textsuperscript{31} forms ketimine at room temperature, but even at 100 °C in the presence of an excess of phenylacetylene this method produces only the product of two sequential hydroaminations: an \textit{N,N}-divinyl derivative of \textit{p}-toluidine (Scheme 30). No formation of acetylide, and thus no propargylamine product, is observed. Thus, tandem reactions that begin with hydroamination do not provide \textalpha-tertiary propargylamines.\textsuperscript{32-36}

Copper displays a different reactivity pattern than gold. Whereas copper acetylides are ubiquitous nucleophiles,\textsuperscript{25} Markovnikov hydroamination via copper catalysis is restricted to a few solid-supported examples.\textsuperscript{37-40} Figure 7a shows the anti-Markovnikov hydroamination of electron-poor ethyl propiolate (blue). This alkyne was chosen to react solely as the electrophile, and only the electron-rich alkyne chosen to act as the nucleophile attacks (red).\textsuperscript{41-43} This subsequent attack
by phenylacetylene (red) produces the less-substituted α-secondary amine, substrates already easily accessed via 3CC with aldehydes. In comparison, figure 7b exhibits the proposed reaction in which a single alkyne acts as both electrophile and nucleophile (purple) to furnish the more highly-substituted α-tertiaryamine.

**Figure 7.** Development of hydroamination to access more-substituted centers

Due to an interest in green reactions, discussed in Chapters 2 and 3 of this work, for catalytic access to ketimine intermediates that do not form in the presence of solvent, we began by testing a variety of copper(I) and copper(II) salts under solvent-free conditions (Table 14). Surprisingly, many of the copper sources examined produce α-tertiary propargylamine from morpholine and 1-octyne. The presence of triflate (trifluoromethanesulfonate, OTf) counteranions appears to outweigh metal oxidation state in conferring catalytic activity as Cu(OTf)₂ and
Cu(OTf) give identical 94% corrected GC yields (Table 14, entries 1 and 5). Copper(I) bromide and copper(I) chloride also provide equivalent GC yields, but are a smaller 53% after 20 minutes. It is important to note that while the conversions provided by copper(I) chloride were never optimized, they allow for clean progression of starting materials to product, albeit slower than the overall superior copper(II) triflate catalyst.

**Table 14.** Copper triflate is best salt for tandem hydroamination reaction

<table>
<thead>
<tr>
<th>Entry</th>
<th>Cu Source</th>
<th>GC yield (%) at 20min</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(II) triflate</td>
<td>94</td>
</tr>
<tr>
<td>2</td>
<td>Cu(II) acetate</td>
<td>0</td>
</tr>
<tr>
<td>3</td>
<td>Cu(II) bromide</td>
<td>12</td>
</tr>
<tr>
<td>4</td>
<td>Cu(II) chloride</td>
<td>15</td>
</tr>
<tr>
<td>5</td>
<td>Cu(I) triflate tetrakisacetonitrile</td>
<td>94</td>
</tr>
<tr>
<td>6</td>
<td>Cu(I) acetate</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>Cu(I) bromide</td>
<td>53</td>
</tr>
<tr>
<td>8</td>
<td>Cu(I) chloride</td>
<td>53</td>
</tr>
<tr>
<td>9</td>
<td>Cu(I) bromide dimethylsulfoxide</td>
<td>43</td>
</tr>
<tr>
<td>10</td>
<td>Cu(I) iodide</td>
<td>0</td>
</tr>
</tbody>
</table>

Given that previous 3CC examples react via anti-Markovnikov aldimines to give α-secondary propargylamines (Figure 7a), it is an unexpected bonus that bulky ligands are not required with Cu(OTf)$_2$ to enforce Markovnikov formation of the more-hindered ketimine intermediate. It is postulated that the nitrogen of the
substrates act as ligands for the copper catalyst in this hydroamination\textsuperscript{46} in this hydroamination-alkynylation of an amine and an alkyne. If solvent is added, a maximum of 53\% corrected GC yield is observed while heating morpholine and 1-octyne in DMSO or acetonitrile under our now standard conditions.

**Figure 8.** Proposed catalytic cycle for hydroamination-alkynylation of one alkyne

This process represents the first catalytic method developed to synthesize propargylamines bearing tetrasubstituted carbon centers from an amine and terminal alkyne. Figure 8 displays a possible sequence for how a single copper source can activate one alkyne to react as either electrophile or nucleophile. On the left, Cu(OTf)$_2$ activates the alkyne (blue) as an electrophile for amine attack.\textsuperscript{4,5}
Markovnikov hydroamination liberates the catalyst and the more-substituted enamine, which tautomerizes to ketiminium. Along the right-hand path, copper activates another molecule of the same starting alkyne (red), and deprotonation by enamine forms the copper acetylide. This nucleophile attacks the alkyne-derived ketimine electrophile to produce tetrasubstituted propargylamine, regenerating copper catalyst. Matching the labeling experiments of others, Markovnikov hydroamination of terminally-dueterated cyano-substituted alkyne lead to deuterium incorporation at the methyl group of resulting propargylamine.

IV. Fully-Substituted Propargylamines with Range of Substituents Accessible Without Need for Carbonyl Source

Table 15 displays the range of amines that can be incorporated into tetrasubstituted organic compounds on a 1.0 mmol scale. Pyrrolidine (1b) consumes 2.2 equivalents of 1-hexyne in 20 minutes to provide \( \alpha \)-tertiary propargylamine 3b in 85% yield (Table 15, entry 1). Piperidine (1c) provides a nearly identical yield to \( N \)-Me benzylamine (1d) and \( N \)-Me aniline (1e) in 30 minutes or less. This is an advantage as various groups comment on the paucity of secondary alkyl amines (1a-1d) compared to the success of aryl amines (1e) in hydroamination. Benzylamine and \( p \)-methoxy benzylamine provide good yields of \( N \)-protected 3f and 3g. As these primary amines react and order of magnitude more slowly than secondary amines, this suggests that these reactions proceed through a neutral ketimine rather than activated ketiminium intermediate.
Table 15. Scope of amines in tandem hydroamination/ketimine alkynylation

<table>
<thead>
<tr>
<th>Entry</th>
<th>Amine</th>
<th>Time (h)</th>
<th>Product</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1b</td>
<td>0.3</td>
<td>3b</td>
<td>85</td>
</tr>
<tr>
<td>2</td>
<td>1c</td>
<td>0.3</td>
<td>3c</td>
<td>76</td>
</tr>
<tr>
<td>3</td>
<td>1d</td>
<td>0.5</td>
<td>3d</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>1e</td>
<td>0.5</td>
<td>3e</td>
<td>73</td>
</tr>
<tr>
<td>5</td>
<td>1f</td>
<td>12</td>
<td>3f</td>
<td>68</td>
</tr>
<tr>
<td>6</td>
<td>1g</td>
<td>10</td>
<td>3g</td>
<td>72</td>
</tr>
</tbody>
</table>

R^1, R^2, n-Bu → 10 mol % Cu(OTf)_2 → R^1, R^2, Me, n-Bu

1, 1 equiv. 2b, 2.2 equiv. 110 °C
Cu(OTf)$_2$ catalyzes hydroamination/alkynylation with range of alkynes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product 3</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a: $R = \text{ }^{n-\text{Hex}}$</td>
<td>45</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>3h: $R = \text{ }^{n-\text{Bu}}$</td>
<td>45</td>
<td>75</td>
</tr>
<tr>
<td>3</td>
<td>3i: $R = \text{Me}_{2}$</td>
<td>25</td>
<td>76</td>
</tr>
<tr>
<td>4</td>
<td>3j: $R = \text{Ph}_{2}$</td>
<td>40</td>
<td>83</td>
</tr>
<tr>
<td>5</td>
<td>3k: $R = \text{CN}_{2}$</td>
<td>60</td>
<td>80</td>
</tr>
<tr>
<td>6</td>
<td>3l: $R = \text{CN}$</td>
<td>20</td>
<td>71*</td>
</tr>
</tbody>
</table>

*20 mol% pyridine added

A variety of alkynes bearing alkyl, aryl, and nitrile groups react efficiently with morpholine (Table 16). Tetrasubstituted propargylamine 3a is synthesized in 88% yield from 1-octyne (entry 1). In 25-45 minutes, this method synthesizes products where the alkyl alkyne substituent is straight (3h), branched (3i), and aryl containing (3j). Nitrile 3k forms selectively in 1 hour in 80% yield. Cu(OTf)$_2$ is less selective when catalyzing alkynes bearing bulky substituents such as the $t$-butyl group of 3,3-dimethyl-1-butyne, forming both hydroamination isomeric products.
V. Pyridine-Buffered Conditions Allow for Synthesis of Uncommon 1,3-Aminodiene

Despite the variety of steps and divergent pathways possible with alkynes upon activation,\textsuperscript{4,5,28,29} a single hindered aminocarbon is produced in a matter of minutes. Aryl alkynes in particular can be converted into a wide range of products due to their propensity for hydroarylation and other arene-based mechanisms.\textsuperscript{33-36,47} Phenylacetylene requires the addition of 20 mol\% pyridine to provide 71\% yield of propargylamine 3l (Table 16). Schemes 31 and 32 contrasts this expected product with the 1,3-aminodiene (4) observed under standard conditions. In contrast with enamine tautomerization to the ketiminium electrophile to form propargylamine 3l, attack of the nucleophilic enamine\textsuperscript{48,49} on activated phenylacetylene as the electrophile could form product 4. It is postulated that inclusion of base favors deprotonation to form copper acetylide, allowing formation of 3l (Table 16.)

\textbf{Scheme 31.} Phenylacetylene selectively provides propargylamine or 1,3-diene
Scheme 32. Lack of pyridine may encourage nucleophilic enamine attack

1-amino-1,3-butadienes are difficult to synthesize in high yield.\textsuperscript{50-52} This is the first example of 1-aminodiene synthesis by hydroamination. Although simple dienes are common substrates for amine addition,\textsuperscript{53-57} this unique hydroamination-vinylination sequence cleanly provides a 1-amino-1,3-butadiene in one step from simple commercially available starting materials.

The presence of copper(II) triflate in catalytic amounts is sufficient to induce Markovnikov hydroamination and alkynylation of the resultant ketimine electrophile for the first synthesis of α-tertiary amines directly from an amine and terminal alkyne. New carbon-carbon and carbon-nitrogen bonds are created in one step with a single catalyst. This highly selective and rapid reaction minimizes waste and provides regioselectivity without added ligands or solvent. Due to the difficulty of \textit{in situ} condensation of an amine and a ketone, hydroamination provides an alternative route to ketimine intermediates for nucleophilic attack. With the same catalyst, phenylacetylene produces either a tetrasubstituted propargylamine or an equally rare 1-aminodiene. This hydroamination-alkynylation protocol provides a novel mechanistic route capable of accessing fully-substituted amine bearing carbon centers in a single step.
VI. Literature Citations

(14) Li, Y.; Marks, T. J. Organometallics 1996, 15, 3770.
(24) Wei, C.; Li, C.-J. Journal of the American Chemical Society 2003, 125, 9584.


VII. Supporting Information

General Reagent Information

All reactions were set up on the benchtop in oven-dried Teflon seal screw-cap test-tubes stirring by magnetic stir bars under an atmosphere of argon. Flash column chromatography was performed using silica gel (230-400 mesh) purchased from Silicycle. Cu(OTf)₂ (98%) was purchased from Acros and used as supplied. Amines were purchased from Acros Organics, Alfa Aesar, or Aldrich and purified by distillation before use. Alkynes were purchased from Acros Organics, Alfa Aesar or TCI America and purified by distillation before use.

General Analytical Information

¹H and ¹³C NMR spectra were measured on a Varian Inova 400 (400 MHz) spectrometer using CDCl₃ as a solvent and tetramethylsilane as an internal standard. The following abbreviations are used singularly or in combination to indicate the multiplicity of signals: s - singlet, d - doublet, t - triplet, q - quartet, m - multiplet and br - broad. NMR spectra were acquired at 300 K. Gas chromatograph spectra were obtained on an Agilent Technologies 6850 Network GC System using dodecane as an internal standard. IR spectra were recorded on Perkin Elmer Spectrum One FT-IR Spectrometer. Attenuated total reflection infrared (ATR-IR) was used for analysis with selected absorption maxima reported in wavenumbers (cm⁻¹). No sample preparation was necessary for ATR analysis. ATR-IR is based on the propagation of the infrared radiation through an internal reflection element (crystal) with a high refractive index, and its reflection at the interface between the
crystal and the solid material. Mass spectrometric data was collected on a ThermoScientific TSQ triple quadrupole LCMS instrument. Exact masses were recorded on an Agilent LCTOF instrument using direct injection of samples in acetonitrile into the electrospray source (ESI) and either positive or negative ionization.

General Procedure

To an oven-dried test tube equipped with magnetic stir bar and Teflon-seal screw cap was added 10 mol % Cu(OTf)$_2$. The flask was purged with argon for 5 minutes. Alkyne (2.2 equiv), and amine (1.0 equiv) were added, and the reaction was stirred at 110 °C for the indicated time. Upon completion, as judged by GC analysis, the mixture was cooled to room temperature and directly loaded atop a silica gel column. Chromatography with ethyl acetate (EtOAc) in hexanes as eluent afforded the desired product. The products were further identified by FT-IR, $^1$H NMR, $^{13}$C NMR and HRMS, which all agree with the assigned structures.

3a: Synthesis of 4-(7-methylpentadec-8-yn-7-yl)morpholine

Morpholine (88 μL, 1.0 mmol), 1-octyne (367 μL, 2.2 mmol), Cu(OTf)$_2$ (36.2 mg, 0.1 mmol), was stirred at 110 °C for 45 minutes to afford the title compound as an orange liquid in 88% yield (0.271 g, 0.88 mmol) after column chromatography on silica gel (10% EtOAc/hexanes). IR (film) 2955, 2928, 2853, 2819, 1455, 1271, 1120, 960, 925, 863, 732 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.65 (t, $J$ = 4.6 Hz, 4H), 2.60 – 2.46 (m, 4H), 2.12 (t, $J$ = 6.9 Hz, 2H), 1.54 – 1.14 (m, 21H), 0.86 – 0.76 (m, 6H). $^{13}$C
NMR (100 MHz, CDCl₃) δ 84.6, 81.7, 67.6, 57.6, 47.2, 39.5, 31.9, 31.5, 29.9, 29.2, 28.6, 24.1, 23.9, 22.8, 22.7, 18.7, 14.2, 14.2. HRMS calculated requires [M-H]⁻: 308.2800. Found m/z: 308.2791.

3b: Synthesis of 1-(5-methylundec-6-yn-5-yl)pyrrolidine-

\[
\text{Pyrrolidine (83 μL, 1.0 mmol), 1-hexyne (253 μL, 2.2 mmol), Cu(OTf)₂ (36.2 mg, 0.1 mmol), was stirred at 110 °C for 20 minutes to afford the title compound as a clear brown oil in 85% yield (0.200 g, 0.85 mmol) after column chromatography on silica gel (30% EtOAc/hexanes). IR (film) 2954, 2930, 2870, 2809, 1692, 1467, 1384, 1367, 1320, 1169, 1111, 1004, 916, 867 cm}^{-1}; \text{¹H NMR (400 MHz, CDCl₃) δ 2.63 (s, 4H), 2.11 (t, J = 7.3 Hz, 2H), 1.68 (s, 4H), 1.55 – 1.45 (m, 2H), 1.34 – 1.11 (m, 7H), 0.88 – 0.73 (m, 10H). ¹³C NMR (100 MHz, CDCl₃) δ 141.3, 128.6, 128.6, 127.0, 84.3, 83.6, 54.4, 48.8, 35.1, 31.6, 29.4, 28.7, 27.0, 22.8, 18.9, 14.3, 9.1. HRMS calculated requires [M+H]⁺: 236.2378. Found m/z: 236.2384.}

3c: Synthesis of 1-(5-methylundec-6-yn-5-yl)piperidine

\[
\text{Piperidine (99 μL, 1.0 mmol), 1-hexyne (253 μL, 2.2 mmol), Cu(OTf)₂ (36.2 mg, 0.1 mmol), was stirred at 110 °C for 20 minutes to afford the title compound as a clear orange oil in 76% yield (0.190 g, 0.76 mmol) after column chromatography on silica gel (10% EtOAc/hexanes). IR (film) 2956, 2930, 2859, 2799, 1466, 1455, 1442, 1378, 1326, 1262, 1221, 1167, 1109, 1079, 956, 861, 770, 742 cm}^{-1}; \text{¹H NMR (400 MHz, CDCl₃) δ 2.45 (m, 4H), 2.10 (t, J = 6.8 Hz, 2H), 1.52 – 1.14 (m, 19H), 0.82 (t, J = 7.1 Hz, 6H). ¹³C NMR}
\]
(100 MHz, CDCl₃) δ 83.6, 82.7, 57.8, 47.6, 39.6, 31.4, 26.7, 26.6, 25.0, 24.1, 23.3, 22.0, 18.5, 14.2, 13.7. HRMS calculated requires [M+H]⁺: 250.2535. Found m/z: 250.2586.

3d: Synthesis of benzyl(methyl)(5-methylundec-6-yn-5-yl)amine

\[ \text{N-methyl benzylamine (129 \mu L, 1.0 mmol), 1-hexyne (253 \mu L, 2.2 mmol), Cu(OTf)₂ (36.2 mg, 0.1 mmol), was stirred at 110 °C for 30 minutes to afford the title compound as a clear brown oil in 76\% yield (0.217 g, 0.76 mmol) after column chromatography on silica gel (12\% EtOAc/hexanes). IR (film) 2956, 2931, 2861, 2791, 1687, 1604, 1494, 1454, 1369, 1326, 1240, 1218, 1177, 1108, 956, 733, 697 cm}^{-1}; \text{ ¹H NMR (400 MHz, CDCl₃) δ 7.45 – 7.12 (m, 5H), 3.60 (dd, } J = 62.5, 13.7 \text{ Hz, 2H}, 2.25 (t, } J = 6.8 \text{ Hz, 2H}, 2.11 (s, 3H), 1.79 – 1.65 (m, 2H), 1.57 – 1.29 (m, 11H), 0.95 (dt, } J = 7.4, 3.8 \text{ Hz, 6H). ¹³C NMR (100 MHz, CDCl₃) δ 141.5, 128.9, 128.3, 126.7, 83.8, 82.7, 58.0, 56.3, 40.5, 35.7, 31.6, 26.5, 25.0, 23.4, 22.2, 18.6, 14.4, 13.8. HRMS calculated requires [M+H]⁺: 286.2535. Found m/z: 286.2555. \]

3e: Synthesis of N-methyl-N-(5-methylundec-6-yn-5-yl)aniline

\[ \text{N-methyl aniline (109 \mu L, 1.0 mmol), 1-hexyne (253 \mu L, 2.2 mmol), Cu(OTf)₂ (36.2 mg, 0.1 mmol), was stirred at 110 °C for 45 minutes to afford the title compound as a clear yellow oil in 73\% yield (0.194 g, 0.73 mmol) after column chromatography on silica gel (15\% EtOAc/hexanes). IR (film) 2956, 2931, 2861, 1596, 1490, 1371, 1275, 1174, 1136, 1073, 1026, 919, 776, 700 cm}^{-1}; \text{ ¹H NMR (400 MHz, CDCl₃) δ 7.49 – 6.92 (m, 5H), 2.78 (s, 3H), 2.22 (t, } J = 6.9 \text{ Hz, 2H).} \]
Hz, 2H), 1.67 – 1.34 (m, 8H), 1.36 – 1.18 (m, 5H), 0.90 (dt, J = 14.3, 7.2 Hz, 6H).

$^{13}$C NMR (100 MHz, CDCl$_3$) δ 151.7, 128.2, 127.8, 124.7, 84.8, 83.0, 58.1, 41.0, 39.2, 31.4, 26.8, 26.6, 23.3, 22.2, 18.6, 14.3, 13.8. HRMS calculated requires [M+H]$^+$: 273.2457. Found m/z: 273.2451.

3f: Synthesis of [(4-methoxyphenyl)methyl](5-methylundec-6-yn-5-yl)amine

4-methoxybenzylamine (131 μL, 1.0 mmol), 1-hexyne (253 μL, 2.2 mmol), Cu(OTf)$_2$ (36.2 mg, 0.1 mmol), was stirred at 110 °C for 12 hours to afford the title compound as a clear orange oil in 68% yield (0.205 g, 0.68 mmol) after column chromatography on silica gel (25% EtOAc/hexanes). IR (film) 2956, 2931, 2860, 1700, 1611, 1585, 1511, 1464, 1245, 1171, 1036, 823, 744 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.24 (d, J = 8.4 Hz, 2H), 6.83 (d, J = 8.6 Hz, 2H), 3.77 (s, 3H), 2.21 (t, J = 6.8 Hz, 2H), 1.70 – 1.18 (m, 15H), 1.00 – 0.80 (m, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 158.7, 133.5, 129.8, 114.0, 84.6, 83.3, 60.6, 55.5, 53.8, 48.2, 42.3, 31.5, 27.6, 26.9, 23.3, 22.1, 18.6, 14.3. HRMS calculated requires [M+H]$^+$: 302.2484. Found m/z: 302.2481.

3g: Synthesis of benzyl(5-methylundec-6-yn-5-yl)amine

Benzyllamine (110 μL, 1.0 mmol), 1-hexyne (253 μL, 2.2 mmol), Cu(OTf)$_2$ (36.2 mg, 0.1 mmol), was stirred at 110 °C for 10 hours to afford the title compound as a clear yellow oil in 72% yield (0.195 g, 0.72 mmol) after column chromatography on silica gel (25% EtOAc/hexanes). IR (film) 2956, 2931, 2860, 1668, 1604, 1495, 1454, 1370, 1327, 1172, 1091, 1028, 729, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.54 – 7.09 (m, 5H), 3.83 (dd, J =
22.6, 11.9 Hz, 2H), 2.22 (t, J = 6.8 Hz, 2H), 1.61 – 1.25 (m, 13H), 0.91 (dt, J = 12.7, 6.4 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 141.3, 128.7, 128.6, 127.0, 84.6, 83.3, 53.9, 48.8, 42.3, 31.5, 27.6, 26.9, 23.3, 22.1, 18.6, 14.3, 13.8. HRMS calculated requires [M+H]$^+$: 272.2378. Found m/z: 272.2386.

**3h: Synthesis of 4-(5-methylundec-6-yn-5-yl)morpholine**

Morpholine (88 μL, 1.0 mmol), 1-hexyne (256 μL, 2.2 mmol), Cu(OTf)$_2$ (36.2 mg, 0.1 mmol), was stirred at 110 °C for 45 minutes to afford the title compound as an orange liquid in 75% yield (0.189 g, 0.75 mmol) after column chromatography on silica gel (10% EtOAc/hexanes).

IR (film) 2956, 2856, 2818, 1455, 1271, 1119, 966, 865, 743 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.65 (t, J = 4.7 Hz, 4H), 2.59 – 2.44 (m, 4H), 2.12 (t, J = 6.9 Hz, 2H), 1.54 – 1.14 (m, 14H), 0.84 (t, J = 7.2 Hz, 5H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 84.5, 81.8, 67.6, 57.5, 47.2, 39.3, 31.4, 26.3, 24.0, 23.2, 22.1, 18.4, 14.2, 13.7. HRMS calculated requires [M+H]$^+$: 252.2321. Found m/z: 252.2324.

**3i: Synthesis of 4-(2,5,10-trimethylundec-6-yn-5-yl)morpholine**

Morpholine (88 μL, 1.0 mmol), 5-methyl-1-hexyne (290 μL, 2.2 mmol), Cu(OTf)$_2$ (36.2 mg, 0.1 mmol), was stirred at 110 °C for 60 minutes to afford the title compound as an orange liquid in 80% yield (0.223 g, 0.80 mmol) after column chromatography on silica gel (10% EtOAc/hexanes). IR (film) 2954, 2929, 2869, 2852, 1468, 1454, 1367, 1271, 1119, 969, 865 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.64 (t, J = 4.6 Hz, 4H), 2.57 – 2.43 (m, 4H), 2.12 (t, J = 7.4 Hz, 2H), 1.66 – 1.10 (m, 11H), 0.82 – 0.77
(m, 12H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 84.6, 81.5, 67.6, 57.5, 47.2, 38.3, 37.4, 33.0, 28.6, 27.4, 23.9, 22.9, 22.8, 22.3, 16.8. HRMS calculated requires [M+H]$^+$: 280.2634. Found m/z: 280.2645.

3j: Synthesis of 4-(4-methyl-1,9-diphenylnon-5-yn-4-yl)morpholine

Morpholine (88 μL, 1.0 mmol), 5-phenyl-1-pentyne (334 μL, 2.2 mmol), Cu(OTf)$_2$ (36.2 mg, 0.1 mmol), was stirred at 110 °C for 40 minutes to afford the title compound as an orange liquid in 83% yield (0.311 g, 0.83 mmol) after column chromatography on silica gel (20% EtOAc/hexanes). IR (film) 3025, 2946, 2852, 1739, 1603, 1495, 1453, 1270, 1117, 738 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.36 – 7.21 (m, 10H), 3.76 (t, $J = 4.4$ Hz 4H), 2.80 – 2.61 (m, 8H), 2.27 (t, $J = 7.0$ Hz, 2H), 1.91 – 1.82 (m, 4H), 1.76 – 1.68 (m, 2H), 1.33 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$) δ 142.6, 142.0, 126.2, 126.0, 84.4, 82.3, 67.7, 57.6, 47.3, 39.1, 36.4, 35.2, 31.1, 26.0, 24.2, 18.4. HRMS calculated requires [M-H]$^-$: 376.2635. Found m/z: 376.2644.

3k: Synthesis of 7-methyl-7-(morpholin-4-yl)undec-5-ynedinitrile

Morpholine (88 μL, 1.0 mmol), 5-hexynenitrile (230 μL, 2.2 mmol), Cu(OTf)$_2$ (36.2 mg, 0.1 mmol), was stirred at 110 °C for 25 minutes to afford the title compound as an orange liquid in 76% yield (0.199 g, 0.76 mmol) after column chromatography on silica gel (50% EtOAc/hexanes). IR (film) 2959, 2853, 2820, 2245, 1735, 1455, 1372, 1270, 1242, 1116 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 3.66 (t, $J = 4.6$ Hz, 4H),
2.54 – 2.49 (m, 4H), 2.43 (t, J = 7.1 Hz, 2H), 2.34 (dt, J = 7.9, 6.6 Hz, 4H), 1.85 – 1.66 (m, 6H), 1.23 (s, 3H). 13C NMR (100 MHz, CDCl3) δ 119.9, 119.3, 83.4, 82.4, 67.5, 57.2, 47.2, 38.2, 24.9, 223.9, 20.4, 17.9, 17.5, 16.4. HRMS calculated requires [M+H]+: 274.1919. Found m/z: 274.1925.

3l: Synthesis of 4-(2,4-diphenylbut-3-yn-2-yl)morpholine

Morpholine (88 μL, 1.0 mmol), phenylacetylene (242 μL, 2.2 mmol), Cu(OTf)2 (36.2 mg, 0.1 mmol), pyridine (16 μL, 0.2 mmol) was stirred at 110 °C for 20 minutes to afford the title compound as an orange solid in 71% yield (0.206 g, 0.71 mmol) after column chromatography on silica gel (20% EtOAc/hexanes). IR (film) 2965, 2860, 1961, 1735, 1681, 1597, 1488, 1444, 1270, 1219, 1112, 1068, 1022, 956, 860, 759, 702, 694 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 7.79 – 7.70 (m, 2H), 7.56 – 7.46 (m, 2H), 7.39 – 7.28 (m, 4H), 7.27 – 7.18 (m, 2H), 3.79 – 3.65 (m, 4H), 2.72 (s, 2H), 2.48 (s, 2H), 1.66 (s, 3H). 13C NMR (100 MHz, CDCl3) δ 145.0, 132.0, 130.4, 128.5, 128.4, 128.3, 127.4, 126.8, 88.4, 88.3, 67.7, 63.6, 48.2, 30.7. HRMS calculated requires [M-H]⁻: 290.1539. Found m/z: 290.1548.

4: Synthesis of 4-[(1Z,3E)-1,4-diphenylbuta-1,3-dien-1-yl]morpholine

Morpholine (88 μL, 1.0 mmol), phenylacetylene (242 μL, 2.2 mmol), Cu(OTf)2 (36.2 mg, 0.1 mmol) was stirred at 110 °C for 30 minutes to afford the title compound as an orange oil in 79% yield (0.230 g, 0.79 mmol) after column chromatography on silica gel (10% EtOAc/hexanes). IR (film) 3080, 2964, 2860, 1961, 1735, 1681, 1644, 1597, 1488,
1444, 1270, 1219, 1112, 1068, 1022, 998, 956, 920, 860, 759, 702, 694 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.50 – 7.32 (m, 5H), 7.26 – 7.16 (m, 4H), 7.15 – 7.03 (m, 1H), 6.70 (dd, J = 15.5, 10.8 Hz, 1H), 6.42 (d, J = 15.5 Hz, 1H), 5.64 (d, J = 10.7 Hz, 1H), 3.85 – 3.63 (m, 4H), 3.00 – 2.84 (m, 4H). ¹³C NMR (100 MHz, CDCl₃) δ 152.7, 143.4, 138.9, 137.0, 130.5, 128.7, 128.6, 128.0, 126.6, 126.2, 125.8, 106.8, 67.2, 49.7. HRMS calculated requires [M-H]: 290.1539. Found m/z: 290.1547.