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Copper Catalyzed Three-Component Couplings Form Propargylamines and Quinolines

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Copper Catalyzed Three-Component Couplings Form Propargylamines and Quinolines

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

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in

Chemistry

by

Courtney Elizabeth Meyet

August 2013

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Dedication

To my husband Brian W. Newberry, who kept the fort going, bussed the boys to their events and listened to my endless chemistry chatter every day I returned home from the lab.

To my boys Kiehl M. Smith and Shane C. Smith for giving up precious time with their Mom. It is my hope that they will always know the sacrifices we all made these last five years have been for the better times that lie ahead. I hope they will always understand the value of an education and seek it for themselves.

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ABSTRACT OF THE DISSERTATION

Copper Catalyzed Three-Component Couplings Form Propargylamines and Quinolines

by

Courtney Elizabeth Meyet

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

Copper-catalyzed three-component couplings have led to the development of one step routes to access propargylamines, 1,3-disubstituted allenes, α,β-unsaturated ketones, and 2,4-disubstituted aryl and alkyl quinolines. Electron-rich and electron-poor N-propargylamines were synthesized from pre-formed aldimines and terminal alkynes utilizing copper(II) triflate. Electron-poor alkyl aldimines were found to tolerate alkynylation, while electron-rich imines resulting from both aryl and alkyl derived aldehydes were alkynylated in moderate yields. Expansion of this work resulted in a copper-catalyzed three-component reaction of an amine, aldehyde, and alkyne to produce propargylamines in significantly higher yields. A wide range of amines, substituted aldehydes, and alkynes couple without the addition of ligand or base. In addition to these nitrogen-containing propargylamines, secondary amines pyrrolidine and N-methylaniline were found to act as promoters for the formation of 1,3-disubstituted allenes and α,β-unsaturated ketones, respectively.
While three-component syntheses of 2,4-diaryl quinolines have been catalyzed by various metal sources, herein is described the first method for the direct synthesis of alkyl-substituted quinolines by aniline-aldehyde-alkyne coupling. This robust process proceeded under solvent-free conditions in air and gave rapid access to quinolines with therapeutic potential. A collaboration with UC Riverside Biomedical Sciences demonstrated the Larsen Group’s 2-alkyl quinoline activity against lung cancer line A549, and glioma line GL26.

Work in nitrogen-containing compounds resulted in the organocatalytic double conjugate addition to a dipyrromethane followed by in situ reduction, representing the first known method for the synthesis of bis-alpha chiral dipyrromethanes. Immediate protection and mild oxidation resulted in a chiral dipyrren, establishing a route to asymmetric variants with potential as complexing agents and/or ligands.
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Chapter 1: Alkynylation of Imines

Abstract

Electron-rich and electron-poor $N$-propargylamines were synthesized from pre-formed aldimines and terminal alkynes utilizing copper(II) triflate. Electron-poor alkyl aldimines were found to tolerate alkynylation, while electron-rich imines resulting from both aryl and alkyl derived aldehydes were alkynylated in moderate yields.

Introduction

Organic synthetic chemists seek efficient means of constructing components of molecules, especially those with biological application and importance. A common route to access molecules containing nitrogen centers are through imines.\(^1\) Carbon-carbon bond-forming reactions can be accomplished through nucleophilic addition to the azomethine carbon of the imine. The reaction works similarly to that using an aldehyde or ketone, however the reduced reactivity of the azomethine carbon requires the addition of an electron-withdrawing substituent on the imine nitrogen to make the imine more electrophilic (Figure 1.1).\(^2\)
Figure 1.1. Substitution on imine nitrogen enhances reactivity of azomethine carbon

Propargylamines have been formed by addition of alkynes to imines in the presence of a copper catalyst which was reported by Li and Wei in 2002 (Scheme 1.1). Highly enantioselective alkyne additions to imines formed in situ from aldehyde and amine was accomplished in water or toluene using either CuBr or CuOTf with bis(oxazolinyl)pyridines (pybox), with yields ranging from 56% to 93%.
Scheme 1.1. Copper-catalyzed synthesis of propargylamines from imines by Li and Wei in 2002

During this time, Knochel also developed a synthesis for the copper-catalyzed addition of terminal alkynes to enamines. Two years later, Knochel's group reported a three component propargylamine synthesis involving an aldehyde, amine, and alkyne with 5 mol% CuBr eliminating the need for pre-formed enamine (Scheme 1.2). The amine source utilized was 2-phenylallyl which can be deprotected after alkynylation through a palladium(0)-catalyzed allylic substitution with 1,3-dimethylbarbituric acid.

Scheme 1.2. Knochel's enantioselective synthesis of propargylamines

Various research groups have proposed similar reaction mechanisms for propargylamine formation that either involve coordination of the copper (I) -ligand complex to the imine first, followed by the addition of alkyne or the alternate
copper-ligand complex coordinate to the alkyne prior to the introduction of imine or enamine. Depending upon whether the propargylamine is the result of an imine or enamine precursor, or a three-component reaction involving an aldehyde, amine, and alkyne, the reaction mechanism seems to differ between paths. Regardless of which mechanistic route is approached, the stereocenter is set when the imine, enamine, or activated iminium ion coordinates with the acetylide (Figure 1.2).

**Figure 1.2.** Stereocenter of propargylamine is set during nucleophilic addition to the imine.

Facile access to propargylamines is driven not only by their utility to precursors of larger molecules but also by their bioactive properties and therapeutic potential (Figure 1.3). Terminal propargylic amines such as Selegiline, Rasagiline, and Ladostigyl act as monoamine oxidase (MAO)
inhibitors. The propargylamine plays an important role as a HIV reverse transcriptase inhibitor and the moiety can also be found in Dynemycin A, an antibiotic and cytotoxic agent.

**Figure 1.3.** Medicinally significant propargylamines

![Figure 1.3: Medicinally significant propargylamines](image)

Dynemicin A
antibiotic and cytotoxic agent

HIV Reverse Transcriptase Inhibitor

**MAO Inhibitors**

Selegiline

Rasagiline

Ladostigyl

The synthesis of aldimines can be accomplished through the simple condensation reaction of an aldehyde and a primary amine source or can be achieved through an alternate route if the N-substituent is electron poor (Scheme 1.3).
A variety of imines with electron-withdrawing substituents on nitrogen were synthesized. Benzyl, Boc, and tosyl imines were prepared according to previous preparations.\textsuperscript{12,13} These substituents not only contribute to the reactivity of the azomethine carbon but also serve as protecting groups that can be removed to reveal a derivatized primary amine.

\subsection*{1.1 Alkynylation of Benzyl-Protected Imines}

The alkynylation of the stable mono benzyl-protected imines proved to be difficult. Where known preparations for alkynylation of dibenzyl substrates were found in literature, monobenzyl- or Boc-protected imines were not. Many proposed mechanisms for other alkynylation of imines suggested metal-alkynyl complexes were formed first, followed by coordination to the imine.\textsuperscript{3,4} However, specifically for benzyl-protected imines, it appeared that yield was more
dependent upon activation time between addition of imine and alkyne rather than order of addition (Table 1.1).

**Table 1.1.** Activation time is more critical than order of addition in the alkynylation of benzyl imines

<table>
<thead>
<tr>
<th>entry</th>
<th>added first</th>
<th>activation time (min.)</th>
<th>%yield by GC</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>control</td>
<td>0</td>
<td>63</td>
</tr>
<tr>
<td>2</td>
<td>imine</td>
<td>15</td>
<td>77</td>
</tr>
<tr>
<td>3</td>
<td>alkyne</td>
<td>15</td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>imine</td>
<td>30</td>
<td>62</td>
</tr>
<tr>
<td>5</td>
<td>alkyne</td>
<td>30</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>imine</td>
<td>60</td>
<td>87</td>
</tr>
<tr>
<td>7</td>
<td>alkyne</td>
<td>60</td>
<td>80</td>
</tr>
</tbody>
</table>

When a non-nucleophilic base such as cesium carbonate or potassium carbonate and/or ligand was added, the reaction failed to proceed. Adding the imine to copper in toluene and allowing the solution to stir for more than 1 hour before addition of the alkyne, resulted in the highest yields of alkynylated product. Alkynylation of benzyl imines with aryl or aliphatic side chains was successful, however, better yields were obtained when the benzyl imine had aliphatic side chains such as isobutyl or cyclohexyl. The alkynylated products are stable and do not exhibit degradation even after being left on the bench top open to air for several days. When *n*-octyne replaced the more volatile *n*-hexyne used
previously, the temperature could be increased from 60 °C to 80 °C without significant loss of alkyne. The reactions proceeded in half the time, some with better yields. Reactions carried out in toluene were the most successful, but some product was also observed in methylene chloride or tetrahydrofuran (THF). Copper(II) triflate was found to be the superior choice for activation of these imine substrates, however, results could also be obtained using the copper (I) source, copper bromide dimethylsulfide.

One of the Larsen group’s first successful alkynylations resulted in 46% yield of propargylamine 1 (Scheme 1.4). The reaction was run with Cu(OTf)₂ and 1.4 equivalents of n-hexyne. The volatility of the lower boiling hexyne prompted the use of n-octyne, which in conjunction with a doubling of the Cu(OTf)₂ catalyst resulted in 83% yield of 2. Attempts to use aryl alkynes proved to be unsuccessful. Propargylamines were formed using a range of aryl aldehyde derived imines including trifluoromethyl substituted 3 in 86% yield. The fluoro-substituted 4 was obtained in 65% yield synthesized using the copper(I) catalyst, copper bromide dimethylsulfide. This copper(I) catalyst was also successful in propargylating imines derived from alkyl aldehydes 5 and 6 in yields of 54% and 60% respectively. However, the most significant breakthrough of this synthetic methodology, was the first successful copper catalyzed tosyl protected propargylamine 7 isolated in 51% yield, acquired using Cu(OTf)₂, interestingly the only copper catalyst capable of producing this substrate.
**Scheme 1.4.** Synthesis of benzyl-propargylamines from imines catalyzed by either Cu(OTf)$_2$ or CuBr•Me$_2$S. Synthesis of tosyl-propargylamine by Cu(OTf)$_2$.

1.2 Alkynylation of Boc-Protected Imines

The alkynylation of imines with the nitrogen bearing an electron-poor substituent proved to be challenging. Multiple attempts in alkynylation of a Boc-protected imine were made with variation in copper sources, solvents, bases,
and ligands. Where benzyl protected imines could be alkynylationed using either a copper (I) source such as copper (II) triflate or with the copper (I) source, copper bromide dimethylsulfide, the Boc, and tosyl protected imines only alkynylationed with Cu(OTf)$_2$. It was unfortunate that the same reaction conditions that successfully alkynylationed the benzyl-protected imines could not be transferred directly to the Boc-protected imines (Scheme 1.5). The purification and isolation of alkynylationed Boc-protected product proved to be problematic as the product appeared to degrade quickly on a silica gel column. Attempts were made to remedy this problem by buffering the silica gel with triethylamine, and trying other solid phases such as florosil, alumina, and basic alumina, however no improvements in recovery were achieved.

**Scheme 1.5.** Initial reaction conditions to form Boc-protected propargylamines

![Scheme 1.5](image-url)
To increase yields in light of the severe sensitivity of the Boc-protected propargylamine to acid prompted the careful addition of 10 mol% catalytic base such as cesium carbonate, equal in equivalents to the potential amount of triflic acid that might be formed in situ from the copper triflate, enough to buffer the reaction in an attempt to increase yields. Although difficulties with solubility were encountered, extensive solvent screens revealed hexanes to have a higher than average percent conversion by GC analysis, followed closely by chloroform. To aid in solubility of the starting reagents, hexanes and chloroform were mixed in a 1:1 ratio. Results were found to be highly dependent upon the order of addition of imine and alkyne, favoring the addition of imine first with an activation time of twenty minutes before addition of alkyne suggesting that copper activation of the Boc imine occurs prior to addition of the alkyne (Scheme 1.6). Unfortunately, only alkyl aldehyde derived Boc-protected imines exhibited reactivity, while aryl-derived substrates proved unreactive under the current conditions.

**Scheme 1.6.** Improved reaction conditions for the Boc-protected propargylamine
Further investigation of this reaction and improved methods of isolation are needed to achieve the desired alkynylated product. When tosyl-protected imines were alkynylated using the same method as with benzyl- and Boc imines, complete conversion was obtained.

The research described herein has solved many problems and overcome many hurdles associated with the alkynylation of imines. Chapter 2 will describe an improved synthesis of propargylamines achieved simply by combining aldehyde, amine, and alkyne with copper catalyst.

**Literature Cited**


4) Gommerman, N.; Knochel, P. *Chem. Commun.* 2004, 2324. See also:


Chapter 2: Three-Component Synthesis of Propargylamines

Abstract

In contrast to the history of three-component couplings with only electron-rich amines, both electron rich and electron poor amines were incorporated through the three-component reaction with an aldehyde, and alkyne to produce propargylamines in high yields. A sole copper(II) catalyst facilitated a wide range of amine sources in a process that tolerated aryl and alkyl substituted aldehydes without the addition of ligand or base.

Introduction

The therapeutic value of propargylamines ranges from antihypertensives, MAO inhibitors and HIV reverse transcriptase inhibitors.\textsuperscript{1,2} The synthesis of propargylamines from preformed imines and enamines was explored in Chapter 1, and even methods to access propargylamines in this fashion is limited. Most syntheses have been successful using metal acetylides in stoichiometric ratios.\textsuperscript{3} Up until the work reported by the Larsen Group, previous methods to access propargylamines were limited to nitrogen sources such as anilines\textsuperscript{4} and piperidines.\textsuperscript{5} As discussed in Chapter 1, the work of Knochel was limited primarily to alkyl aldehydes, dibenzylamines, and phenylacetylenes.\textsuperscript{6}
2.1 Alkynylation of Tosyl-Protected Imines to Three-Component Coupling

As noted in Chapter 1, imine preparation was a simple condensation reaction if the amine was electron rich, however an electron poor amine source required a two-step process over 2-3 days to prepare imines for copper catalyzed alkynylation. In an attempt to save time as well as starting materials, it was proposed that the process of pre-forming imine be eliminated. Conor Pierce, of the Larsen Group combined $p$-toluene sulfonamide, alkyl aldehyde, and $n$-octyne with 10 mol% Cu(OTf)$_2$ in toluene at 100 °C, which resulted in tosyl-protected propargyamine in 79% yield after 2 hours, a rate 20 times faster than the original propargyamine preparation from tosyl-protected imine as shown by Conor Pierce (Scheme 2.1).

Scheme 2.1. Three-component coupling forms propargyamine 20 times faster than from pre-formed imine (Conor Pierce)
Interestingly, Cu(OTf)$_2$ was the sole copper source responsible for the outcome of this three-component coupling to form propargylamines. Addition of 10 mol% base did not significantly slow the reaction, but 20 mol% base inhibited it completely (Table 2.1).

**Table 2.1.** Cu(OTf)$_2$ was the sole copper source responsible for success of the three-component reaction to form propargylamines (Conor Pierce)

<table>
<thead>
<tr>
<th>entry</th>
<th>Cu source</th>
<th>base</th>
<th>conversion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>CuI</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•Me$_2$S</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>4</td>
<td>Cu(NCCH$_3$)$_4$•CF$_3$SO$_3$</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>5</td>
<td>CuSO$_4$</td>
<td>--</td>
<td>0</td>
</tr>
<tr>
<td>6</td>
<td>Cu(ClO$_4$)$_2$•5H$_2$O</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>
<tr>
<td>9</td>
<td>Cu(OTf)$_2$</td>
<td>Cs$_2$CO$_3$</td>
<td>0</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OTf)$_2$</td>
<td>K$_2$CO$_3$</td>
<td>0</td>
</tr>
<tr>
<td>11</td>
<td>Cu(OTf)$_2$</td>
<td>KOt-Bu</td>
<td>0</td>
</tr>
</tbody>
</table>

**2.2 Three-Component Coupling with Other Nitrogen Sources**

The three-component, copper-catalyzed methodology was not only applicable to the tosyl-protected propargylamine but could be extended to many
other nitrogen sources (Scheme 2.2). Although the three-component process with tosyl amines was only tolerant of alkyl aldehydes, a wide range of both aryl and alkyl aldehydes could be used with other primary and secondary amines with terminal alkynes and acetylenes. The sole byproduct of this reaction was water and an additional 1-5 equivalents of water had a negligible effect. A drying agent was added to the reaction mixture if a particular starting material was labeled as water sensitive.

Scheme 2.2. Cu(OTf)$_2$ catalyzed the three component reaction of aldehyde, amine, and alkyne to form propargylamines

Mono-$N$-benzylpropargylamines 8-14 were readily formed by the Cu(OTf)$_2$ catalyzed reaction with benzylamine, aldehyde, and $n$-octyne in toluene at 80 °C for 72 hours (Figure 1). Benzaldehyde derived 8 and isobutyraldehyde derived 9 exhibit the tolerance benzylamine had towards both aryl and alkyl aldehydes. The moisture sensitive fluoro- and (trifluoromethyl)benzaldehyde derived propargylamines 10-14, required the addition of Na$_2$SO$_4$, and were isolated in moderate to high yields.
Figure 2.1. Mono-N-benzylpropargylamines

N,N-Dibenzylpropargylamines 15-19, obtained in high yields, also exhibited a tolerance for incorporation of both alkyl and aryl aldehydes and alkynes. The interesting dibenzyl propargylamine 18, possessed a furan (Figure 2.2).
Figure 2.2. *N,N*-Dibenzyl propargylamines

Morpholine propargylamines 20-24, some obtained in nearly quantitative yields, were tolerant of aryl and alkyl aldehydes with *n*-octyne (Figure 2.3).
Figure 2.3. Morpholine-derived propargylamines

\[ \text{Morpholine-derived propargylamines} \]

\[ \begin{align*}
\text{20} & \quad \text{94\% yield} \\
\text{21} & \quad \text{83\% yield} \\
\text{22} & \quad \text{91\% yield} \\
\text{23} & \quad \text{97\% yield} \\
\text{24} & \quad \text{96\% yield}
\end{align*} \]

\[ \text{p-Methoxybenzyl (PMB)-derived propargylamines 25-35 with terminal alkyl alkynes were obtained in moderate yields of 54-73\% (Figure 2.4). When phenylacetylene was used, yields decreased to 20\% and 24\% when both aryl or alkyl aldehydes were used, respectively. PMB derived propargylamines 33-35 were an interesting case where consistent yields were obtained for ortho, meta, and para-fluoro substituted aryl aldehydes lending themselves to possible substrates for structure activity relationship studies (Scheme 2.3).} \]
Figure 2.4. *Para*-Methoxybenzyl (PMB)-derived propargylamines
Scheme 2.3. PMB derived propargylamines for structure activity relationships

\[
\text{H}_2\text{N} = \text{CH} \quad \text{H}_2\text{N} = \text{CH} \quad \text{H}_2\text{N} = \text{CH} \\
\text{F} \quad \text{F} \quad \text{F} \\
\text{OMe} \quad \text{OMe} \quad \text{OMe} \\
\text{Cl} \quad \text{Cl} \quad \text{Cl} \\
\text{Cu(O} \text{OTf)}_2 \rightarrow \text{toluene} 80 \degree \text{C} \\
\text{ortho-F: 73%} \quad \text{meta-F: 71%} \quad \text{para-F: 72%}
\]

o-Methoxybenzyl derived propargylamines 36-39 could also be synthesized but in significantly lower yields compared to propargylamines from other nitrogen sources (Figure 2.5).

Figure 2.5. Ortho-Methoxybenzyl-derived propargylamines

\[
\text{H}_2\text{N} \quad \text{H}_2\text{N} \quad \text{H}_2\text{N} \quad \text{H}_2\text{N} \\
\text{OMe} \quad \text{OMe} \quad \text{OMe} \quad \text{OMe} \\
\text{Me} \quad \text{Me} \quad \text{Me} \quad \text{F} \\
\text{H}_2\text{N} \quad \text{H}_2\text{N} \quad \text{H}_2\text{N} \quad \text{H}_2\text{N} \\
n-\text{Bu} \quad \text{Me} \quad n-\text{Hex} \quad n-\text{Hex}
\]

\[
\text{36: 61% yield} \\
\text{37: 55% yield} \\
\text{38: 45% yield} \\
\text{39: 58% yield}
\]
2.3 Three Nitrogen Sources Lead to Three New Classes of Substrates

Pyrrolidine derived propargylamine 40 and N-methylaniline derived 41, isolated in 71% and 72% yields respectively (Figure 2.6), were interesting cases in that when the pyrrolidine was combined under the same conditions with an aryl rather than an alkyl aldehyde, a 1,3-disubstituted allene was seen to form as a side product in approximately 40% yield (Scheme 2.4A), explored in detail in Chapter 3.

Figure 2.6. Other propargylamines lead to new chemistry

The N-methylaniline, when subjected to the same reaction conditions as its alkyl counterpart 41, resulted in no propargylamine formation, but instead the amine promoted appearance of an α,β-unsaturated ketone (Scheme 2.4B), explored in further detail in Chapter 3. A primary aniline resulted in the valuable A³ coupling to form 2,4-disubstituted quinolines (Scheme 2.4B), discussed in Chapter 4. These new substrates formed from the Larsen Group methodology for three component propargylamines, opened a new realm of intriguing small molecules to explore. The copper catalyzed three component synthesis had
proved not only its versatility in propargylamine synthesis, but its potential utility in opening doors to whole new groups of substrates for exploration.

**Scheme 2.4.** Three-component synthesis unlocked avenues to new substrate exploration

![Scheme 2.4](image)

**Literature Cited**


Chapter 3: One-Step Synthesis of 1,3-Disubstituted Allenes and Enones

Abstract

Secondary amine sources have been reported as promoters for the formation of allenes or enones. 1,3-Disubstituted allenes were discovered as a side product of pyrrolidine derived propargylamines in a ratio of approximately 2:3. The reaction was catalyzed by CuI in the presence of a pyrrolidine promoter with n-octyne and p-tolualdehyde in toluene. If the amine promoter was N-methylaniline, enones were seen to form as a Meyer-Schuster rearrangement product catalyzed by 10 mol% Cu(OTf)$_2$ in the presence of aryl aldehydes and terminal alkyl alkynes. After a significant body of research on these two phenomena, reports by other groups on similar syntheses were published, rendering the Larsen group’s work not significant enough for higher impact publication.

3.1 Introduction: Allenes

Allenes are present in biologically active natural products,$^1$ and are versatile synthons due to their orthogonal $\pi$-bonds.$^2$ They have been formed through $S_N2'$ displacement reactions with enones or propargyl alcohols and organometallics,$^3$ with propargyl alcohol derivatives that undergo 3,3-sigmatropic rearrangements,$^4$ asymmetric catalysis with chiral metal complexes,$^5$ two component couplings using Grubbs catalyst,$^6$ catalytic gold,$^8$ ZnI$_2$ and morpholine,$^9$ a lithium aluminum
hydride mediated retro-ene reaction,\textsuperscript{10} or use of copper(I) and a ligand or amine promoter.\textsuperscript{11}

The first one-pot synthesis of allenes was reported by Crabbé et al. in 1979 (Scheme 3.1).\textsuperscript{12} Homologous allenes were produced from the CuBr catalyzed, diisopropylamine promoted coupling of an acetylene to a formaldehyde in tetrahydrofuran or dioxane. The highest yielding substrates were derived from acetylenes with vicinal hydroxy groups that are most likely responsible or aid in the hydrogen transfer necessary for allene formation.

**Scheme 3.1.** CuBr catalyzed formation of allenes from acetylenes and formaldehyde promoted by diisopropylamine\textsuperscript{12}
The interesting use of an amine promoter for the formation of allenes was again reported in 2008 and 2010 by Lo et al.\textsuperscript{8a,b} Originally, a gold catalyst was used to synthesize axial chiral allenes from chiral propargylamines in acetonitrile at 40 °C, but the use of a silver-mediated process (Scheme 3.2), led to much higher enantiomeric excess. The Lo group found that when using a gold catalyst, their substrate scope was limited to electron-poor propargylamines, as the electron-rich propargylamines resulted in lower enatioselectivities.\textsuperscript{8a,b}

**Scheme 3.2.** AgNO\textsubscript{3}-mediated synthesis of axially chiral allenes from propargylamines\textsuperscript{8b}

\[ \text{R}^1\text{C}≡\text{C}H\text{N} \longrightarrow \text{R}^1\text{C}≡\text{C}H \text{R}^2 \quad \text{AgNO}_3 \text{ (50 mol%) } \text{CH}_3\text{CN, 40 °C} \quad 24 \text{ h} \]

99% ee

64-95% yield
96-99% ee

The Lo group found that a silver-mediated process preserved the enantioselectivities.\textsuperscript{8b} They also found that reaction time could be shortened from 24 hours to 20 minutes by incorporating microwave irradiation. Lo proposed a mechanism where the alkyne moiety of the propargylamine coordinated to the metal. This activation prompted an intramolecular hydride transfer from the cyclic amine portion of the molecule followed by its β-elimination to afford the allene product (Figure 3.1). Deuterium labeling experiments gave evidence that proton
transfer is indeed intramolecular as no deuterium crossover was seen (Scheme 3.3).

**Figure 3.1.** Proposed mechanism for silver-mediated synthesis of allenes from optically active propargylamines$^{8b}$
Scheme 3.3. Deuterium-labeling experiment\cite{6b}

\[
\begin{align*}
\text{Ph} & \quad \text{AgNO}_3 (50 \text{ mol} \%) \\
\text{Ph} & \quad \text{CH}_3\text{CN}, \text{N}_2, 40 \degree \text{C} \\
79\% \text{ D-incorporation} & \\
\text{Ph} & \quad \text{Ph} & \text{D} \quad \text{55\% conv.} \\
\text{Ph} & \quad \text{Ph} & \text{79\% yield} \\
\text{Ph} & \quad \text{Ph} & \text{79\% D-incorporation}
\end{align*}
\]

Kuang and Ma were also making great advances in allene chemistry using an amine promoter during this time.\cite{9a,b} Building upon the method published by Crabbé, terminal allenes were synthesized from 1-alkynes and 2.5 equivalents paraformaldehyde using 50 mol\% CuI as a mediator and 1.8 equivalents of dicyclohexylamine as a promoter (Scheme 3.4).\cite{9a}

Scheme 3.4. Modified Crabbé method for the synthesis of terminal allenes\cite{9a}

\[
\begin{align*}
\text{R}^1 & \quad (\text{CH}_2\text{O})_n & \quad \text{Cy}_2\text{NH} & \quad \text{Cul} (0.5 \text{ equiv}) \\
\text{2.5 equiv} & \quad 1.8 \text{ equiv} & \quad \text{dioxane, reflux} & \quad \text{R}^1 \equiv \text{R}
\end{align*}
\]
Kuang and Ma improved upon the methods to access allenes as published in their report of ZnI₂-promoted reaction of 1-alkynes with 1.8 equivalents of aldehyde in the presence of 1.4 equivalents of morpholine. No longer was their method limited to the formation of terminal allenes, but it was now expanded to form 1,3-disubstituted allenes from aromatic or aliphatic aldehydes (Scheme 3.5).

**Scheme 3.5.** ZnI₂-Promoted reaction of 1-alkynes with aldehydes in the presence of morpholine

\[
\begin{align*}
\text{ZnI}_2 \text{ (0.8 equiv)} & \quad \text{toluene 130 °C} \\
\text{R}_1 & \quad \text{R}_2
\end{align*}
\]

Reaction conditions were tolerant of terminal alkyl alkynes or propargylic alcohols, however aliphatic aldehydes required longer reaction time and higher reaction temperature. Kuang and Ma illustrated the importance of water generated *in situ* to the success of the reaction by subjecting potential reaction intermediate, morpholine derived propargylamine, to their reaction conditions (Scheme 3.6), with and without water.
Scheme 3.6. Importance of water for in situ allene formation

The mechanism proposed by Kuang and Ma, similar to that proposed by Lo et al. involves the formation of an alkynyl zinc species which adds into the iminium formed from condensation of the aldehyde and morpholine resulting in a propargylamine. The intramolecular proton transfer is followed by a β-elimination revealing the 1,3-disubstituted allene product (Figure 3.2).۹ب
The Larsen group interest in allenes stems from their synthetic value as intermediates as well as their biological impact. As an example, cytotoxic apo-9'-fucoxanthinone, an oxidative degradation product of fucoxanthin, was isolated and tested in 1995 (Figure 3.3). Allenes have been shown to confer anti-cancer inactivity where a simple inactive phenol becomes cytotoxic through the addition of an allene handle. Other bioactivities of allenes include their use as anti-angiogenics, antineoplastics, and suicide enzyme inhibitors.¹³
Figure 3.3. Important biological compounds containing allenic moieties

![Molecular structures and annotations]

induces apoptosis, anti-mutagenic, antiproliferative, anti-obesity, anti-inflammatory

3.2 Allenes Formed Through Pyrrolidine Promoter

The synthesis of an allene from a propargylamine or using an amine as a promoter is of significant interest as this phenomena was stumbled upon in our groups search for a variety of amine sources to use in the synthesis of propargylamines. In an attempt to broaden the scope of amines to use in our three-component coupling to form propargylamines, three of the amines sources resulted in completely different products. Anilines resulted in the formation of 2,4-disubstituted quinolines (refer to Chapter 4). N-Methylaniline resulted in the formation of α,β-unsaturated ketones (explained in the following section). Pyrrolidine resulted in the formation of 1,3-disubstituted allenes.
Scheme 3.7. 1,3-Disubstituted allenes were seen as a side product in the synthesis of Pyrrolidine derived propargylamine with p-tolualdehyde and n-octyne.

Allenes were discovered when pyrrolidine was used as an amine source for the formation of propargylamines (Scheme 3.7). The pyrrolidine-derived propargylamine was isolated along with another unknown compound. A $^1$H NMR on the isolated unknown revealed the absence of the $\alpha$-hydrogen normally present in the propargylamine, as well as key protons that would have been seen in the pyrrolidine moiety of the molecule. The $^{13}$C NMR was absent of the two alkyne carbons but revealed a carbon indicative of an allene. The spectral values were cross-referenced to a known allene compound and the product was confirmed as a 1,3-disubstituted allene. Because the pyrrolidine did not end up contributing its atoms to any portion of the molecule, it was postulated that perhaps the amine source was acting as an organic catalyst. However, when the pyrrolidine was decreased to catalytic quantities, the allene yields went down. Only in stoichiometric quantities did the allene yields stay at their optimum point (Table 3.1). Because both propargylamine and allene are formed from these reaction conditions, efforts to explore the conditions favoring the formation of the
allene were made, as no known direct route from commercially available materials to this structure was known at the time of discovery in the Larsen laboratory.

**Table 3.1.** Pyrrolidine in stoichiometric quantities results in best allene conversion

\[
\begin{align*}
\text{entry} & \quad \text{pyrrolidine (equiv.)} & \quad 48\text{ h} & \quad \text{allene} \\
1 & 0 & 0 \\
2 & 0.10 & \text{trace} \\
3 & 0.25 & \text{trace} \\
4 & 0.50 & 3 \\
5 & 1.00 & 33 \\
6 & 1.20 & 26 \\
7 & 1.50 & 15 \\
8 & 2.00 & 16 \\
\end{align*}
\]

An excess of pyrrolidine favored the propargylamine product, further decreasing allene formation. The optimum quantity of pyrrolidine required for optimum allene formation was one equivalent. Unfortunately yields of allene
could not be increased under these conditions requiring stoichiometric pyrrolidine promoter.

When reaction temperature was varied from room temperature, 50 °C, 80 °C, and 110 °C, best conversion to allene was seen at 110 °C with 57% of the starting materials converting to allene, and 11% to propargylamine. Yields of both allene and propargylamine were observed to decrease at temperatures higher than 110 °C.

To determine whether *in situ* water had a detrimental effect on allene formation, drying agents were examined. Sodium sulfate, magnesium sulfate, and mol sieves (pulverized), all produced slightly more allene than the control reaction which did not contain a drying reagent, however not enough of a significance to warrant excessive prevention of *in situ* water formation (Table 3.2).
Table 3.2: 2.0 Equivalents drying agent have negligible effect on formation of allene

<table>
<thead>
<tr>
<th>entry</th>
<th>drying agent (equiv.)</th>
<th>Na$_2$SO$_4$</th>
<th>MgSO$_4$</th>
<th>4A mol sieves</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0</td>
<td>18</td>
<td>18</td>
<td>18</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>18</td>
<td>16</td>
<td>22</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>20</td>
<td>22</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>1.5</td>
<td>22</td>
<td>12</td>
<td>19</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>20</td>
<td>23</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>2.5</td>
<td>18</td>
<td>22</td>
<td>23</td>
</tr>
<tr>
<td>7</td>
<td>3.0</td>
<td>18</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>8</td>
<td>4.0</td>
<td>20</td>
<td>20</td>
<td>23</td>
</tr>
<tr>
<td>9</td>
<td>5.0</td>
<td>20</td>
<td>22</td>
<td>22</td>
</tr>
</tbody>
</table>

Other cyclic secondary amine sources were substituted for pyrrolidine to determine if these amines would also facilitate the formation of allene. Although piperidine and morpholine showed small amounts of allene, pyrrolidine still promoted formation of significantly greater amounts of allene. Optimum yields of allene were recovered before 48 hours reaction time, after which, degradation appears to occur and less allene is formed. Concentration of reactants in toluene was found to have no effect. Optimal amount of aldehyde was 1.8 equivalents.
which increased the ratio of allene: propargylamine from 46:40 to 56:32. If 2.8 equivalents of aldehyde were used, a similar 51:26 ratio of allene to propargylamine was observed after only one hour (Table 3.3).

Table 3.3. Excess aldehyde favors formation of allene

<table>
<thead>
<tr>
<th>entry</th>
<th>aldehyde (equiv.)</th>
<th>1 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>allene</td>
<td>propargylamine</td>
<td>allene</td>
</tr>
<tr>
<td>1</td>
<td>1.0</td>
<td>31</td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>1.2</td>
<td>37</td>
<td>47</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
<td>38</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>1.8</td>
<td>38</td>
<td>49</td>
</tr>
<tr>
<td>5</td>
<td>2.0</td>
<td>49</td>
<td>39</td>
</tr>
<tr>
<td>6</td>
<td>2.2</td>
<td>52</td>
<td>28</td>
</tr>
<tr>
<td>7</td>
<td>2.5</td>
<td>48</td>
<td>25</td>
</tr>
<tr>
<td>8</td>
<td>2.8</td>
<td>51</td>
<td>26</td>
</tr>
<tr>
<td>9</td>
<td>3.0</td>
<td>53</td>
<td>21</td>
</tr>
</tbody>
</table>

Optimal loading of Cu(OTf)$_2$ was 10 mol%, yet interestingly, when more than 20 mol% of copper was loaded, exclusive allene formation was seen. Because of this observation, it had been suggested that perhaps trace amounts
of triflic acid formed in situ from the Cu(OTf)$_2$ was at least partially responsible for the formation of the allene. To determine whether the reaction to form allene was dependent upon acid as well as copper, the acid scavenger 2,6-ditertbutylpyridine was added. The acid scavenger did not inhibit the reaction, but slowed it greatly, suggesting that although the reaction can proceed without triflic acid, the acid might assist in the formation of both allene and propargylamine.

Additional amounts of catalytic acid slightly increased the amount of allene produced in relation to propargylamine (Table 3.4) – formic acid, methane sulfonic acid, trifluoroacetic acid, hexafluorophosphoric acid solution, and sulfuric acid. Addition of acid without a copper source did not result in either allene nor propargylamine formation.
Table 3.4. Ratio of allene to propargylamine with additional catalytic acid

Addition of protic solvent did not have an affect on allene formation. Addition of base, even in catalytic amounts greatly slowed the progress of the reaction.

When other copper sources were examined, CuI was seen to form more allene at 58% conversion after 24 hours compared to 43% for Cu(OTf)₂ (Table

![Chemical structure](image)
3.5). It was also found that only 2.5 mol% of Cul was needed as compared to the 10 mol% of Cu(OTf)$_2$ that was needed (Table 3.6).

**Table 3.5.** Optimum copper source is Cul to favor allene formation

<table>
<thead>
<tr>
<th>entry</th>
<th>Copper source</th>
<th>allene 2 h propargylamine</th>
<th>24 h propargylamine</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Cu(OTf)$_2$</td>
<td>50</td>
<td>43</td>
</tr>
<tr>
<td>2</td>
<td>CuCl$_2$</td>
<td>49</td>
<td>44</td>
</tr>
<tr>
<td>3</td>
<td>Cu(ClO$_4$)$_2$</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>4</td>
<td>Cu(OAc)$_2$</td>
<td>37</td>
<td>40</td>
</tr>
<tr>
<td>5</td>
<td>CuBr$_2$</td>
<td>49</td>
<td>48</td>
</tr>
<tr>
<td>6</td>
<td>CuOTf</td>
<td>45</td>
<td>50</td>
</tr>
<tr>
<td>7</td>
<td>Cul</td>
<td>53</td>
<td>58</td>
</tr>
<tr>
<td>8</td>
<td>CuBr</td>
<td>47</td>
<td>38</td>
</tr>
<tr>
<td>9</td>
<td>CuBr-Me$_2$S</td>
<td>trace</td>
<td>trace</td>
</tr>
<tr>
<td>10</td>
<td>Cu(OAc)</td>
<td>41</td>
<td>36</td>
</tr>
<tr>
<td>11</td>
<td>no metal</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Table 3.6. Less Cul is needed to get higher yields of allene than Cu(OTf)$_2$

<table>
<thead>
<tr>
<th>entry</th>
<th>mol % Cul</th>
<th>1 h</th>
<th>5 h</th>
<th>24 h</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>allene</td>
<td>propargylamine</td>
<td>allene</td>
</tr>
<tr>
<td>1</td>
<td>1.0</td>
<td>27</td>
<td>68</td>
<td>44</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>33</td>
<td>67</td>
<td>49</td>
</tr>
<tr>
<td>3</td>
<td>5.0</td>
<td>36</td>
<td>64</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>7.5</td>
<td>36</td>
<td>64</td>
<td>44</td>
</tr>
<tr>
<td>5</td>
<td>10.0</td>
<td>36</td>
<td>64</td>
<td>47</td>
</tr>
<tr>
<td>6</td>
<td>15.0</td>
<td>37</td>
<td>63</td>
<td>51</td>
</tr>
<tr>
<td>7</td>
<td>20.0</td>
<td>34</td>
<td>66</td>
<td>55</td>
</tr>
</tbody>
</table>

Unfortunately, allene was only formed with aryl derived aldehydes. Alkyl derived aldehydes favored propargylamine formation. Conversely, only alkyl derived terminal alkynes formed allene, possible due to MO delocalization/stabilization in aryl alkynes.

3.3 Introduction: Enones

$\alpha,\beta$-Unsaturated carbonyl compounds are commonly found in bioactive natural products and have served as building blocks for larger molecules, active components of pharmaceuticals, and use in cosmetics.$^{14}$ The most common route to access these enone compounds has been through the Meyer-Schuster rearrangement, first reported in 1922.$^{15}$ The Meyer-Schuster reaction is most
commonly achieved through exposure to an acidic environment and high heat, progressing by way of a 1,3-transfer of a hydroxy group forming an allenic intermediate from a propargyl alcohol (Scheme 3.8).\textsuperscript{16,17}

**Scheme 3.8.** Meyer-Schuster rearrangement\textsuperscript{16,17}

\[
\text{Ph} = \text{Ph} = \text{Ph} \overset{\text{Propargyl Alcohol}}{\rightleftharpoons} \left[\text{Ph}\right] \overset{\text{Allene Intermediate}}{\rightleftharpoons} \left[\text{Ph}\right] \overset{\text{Ph} = \text{Ph} = \text{O}}{\text{\alpha,\beta-Unsaturated Ketone}}
\]

The use of harsh acids has been overcome in recent years by adoption of the late-transition metal Lewis-acid catalyst, which has been reported to have a higher affinity to the acetylinic $\pi$-bonds rather than the harder acid affinity toward the oxygen atom.\textsuperscript{18}

A Gold(III) catalyzed (AuCl$_3$) olefination strategy for ketones was reported where propargyl alcohols were synthesized by addition of an ethoxyacetylide to a ketone, followed by a gold catalyzed Meyer-Schuster rearrangement (Scheme 3.9).\textsuperscript{19} This reaction resulted in the formation of $\alpha,\beta$-unsaturated esters in 95% conversion using only 5 mol% gold catalyst, and enones using 20 mol% gold catalyst. A later report from another group stated their use of molybdenum and cationic gold afforded the same transformation.\textsuperscript{20}
Scheme 3.9. AuCl₃ catalyzed Meyer-Schuster rearrangement²¹

Gold and silver catalyzed Meyer-Schuster rearrangements have been used to access enone moieties in natural products such as Daphenone, and E-isoegomaketone (Figure 3.4).²¹ and as a step in the synthesis of prostaglandins (Scheme 3.10).²²

Figure 3.4. Daphenone and E-isoegomaketone were made using a gold-catalyzed Meyer-Schuster rearrangement²¹
Scheme 3.10. Gold catalyzed Meyer-Schuster rearrangement had application to synthesis of prostaglandins\textsuperscript{22}

The Meyer-Schuster rearrangement has resulted in a mixture of $E$- and $Z$-isomers, with primarily the $E$-isomer being formed. The interesting recent report by Egi, et al. reported on a class of heteropoly compounds in 1 mol\% that can selectively produce only the $Z$-isomer or only the $E$-isomer in very high yields (Scheme 3.11).\textsuperscript{23}
**Scheme 3.11.** Heteropoly compounds catalyze both $E$- and $Z$-isomers$^{23}$

![Scheme 3.11](image)

3.4 Cu(OTf)$_2$-Catalyzed, N-Methylaniline Promoted Enone Synthesis

The Larsen group discovered an N-methylaniline promoted, copper catalyzed Meyer-Schuster type of reaction from aldehydes and alkynes (Scheme 3.12).

**Scheme 3.12.** Cu(OTf)$_2$ catalyzed, N-methylaniline promoted synthesis of an $\alpha,\beta$-unsaturated ketone

![Scheme 3.12](image)

The use of N-methylaniline resulted in the formation of an $\alpha,\beta$-unsaturated ketone. Like in the copper-catalyzed, pyrrolidine promoted 1,3-disubstituted
allene, the amine source, N-methylaniline in the formation of enone also acted as a consumable promoter. The amine had to be supplied in stoichiometric quantities for highest yields of enones to form. Interestingly, an excess beyond stoichiometric quantities of amine decreased the overall enone yield. Cu(OTf)_2 was the superior copper source yielding 68% conversion after 15 hours at 80 °C. The addition of an additional 10 mol% copper triflate (for 20 mol% total), increased the percent conversion, adding an additional 10 mol% catalytic triflic acid, decreased the percent conversion to 48%, ruling out additional trace amounts of triflic acid formed in situ as the reason for the yield increase. Only aryl aldehydes resulted in the formation of enones. Alkyl aldehydes resulted in exclusive propargylamine formation (Figure 3.5).

**Figure 3.5.** Alkyl aldehydes result in propargylamine formation while aryl aldehydes result in enone formation

Two of the starting materials, aldehyde and alkyne, have been common in the synthesis of propargyl alcohols, yet the final product obtained from the reaction of these with stoichiometric N-methylaniline and catalytic copper, resulted in a Meyer-Schuster type product. Suspecting this rearrangement, due to the 1,3 hydroxy group shift in the characterized enone, a propargyl alcohol
was synthesized. The propargyl alcohol was subjected to the reaction conditions that brought about the Larsen group discovery of the amine-promoted enone synthesis (Scheme 3.13).

**Scheme 3.13.** Enone forms from suspected propargyl alcohol intermediate under the Larsen Group conditions

\[
\begin{align*}
\text{F} & \quad \text{OH} & \quad \text{n-Hex} \\
\text{F} & \quad \text{=CHCH=CH} & \quad \text{n-Hex} \\
& \quad \text{10 mol\% Cu(OTf)}_2 \\
& \quad \text{toluene, 80 °C} \\
& \quad \text{48\% yield}
\end{align*}
\]

**Literature Cited**


14) T. Takeda in *Modern Carbonyl Olefination*, Wiley-VCH, Weinheim, **2004**.


Chapter 4: Three-Component Synthesis of Alkyl-Substituted Quinolines

Abstract

A copper-catalyzed three-component reaction to form 2,4-substituted quinolines from both aryl and alkyl aldehydes and alkynes with a variety of aniline sources has been developed. The one pot reaction from commercially available starting materials works under solvent-free conditions in air and gives rapid access to a wide variety of quinolines with therapeutic potential. An in vitro collaboration with UC Riverside Biomedical Sciences has discovered simple 2-alkyl quinolines selectively kill glioma cells.

Introduction

Quinolines have long been known for their medicinal properties, especially in the realm of anti-malarial compounds. Quinine, having been the first widely known malaria treatment isolated form the bark of cinchona trees in South America, has been basis for other quinoline-based anti-malarial compounds including linked quinolines.\(^1\) In addition to being potent anti-malarials, quinolines also have activity as anti-inflamatories,\(^2\) and as cytotoxic drugs\(^3\) (Figure 4.1).
Figure 4.1. Quinolines serve as potent antimalarial compounds

Figure 4.2. Identity and length of bisquinolines linkage effects antimalarial activity
Figure 4.3. Quinolines and polyquinolines have luminescent properties due to their extended π-conjugation.

The synthesis of quinoline derivatives is not new chemistry, as several named reactions exist in literature, and these methods have been built upon and improved over more than 100 years time. The earliest of these reactions to form quinolines include the Skraup synthesis from ferrous sulfate, glycerol, aniline, nitrobenzene, and sulfuric acid. The Doebner reaction appeared shortly after and incorporated anilines with aldehydes and pyruvic acid to form quinoline-4-carboxylic acids. Friedländer fabricated quinolines from 2-aminobezaldehyde and acetaldehyde, the Combes synthesis used anilines and diketones, and the Povarov method used an aniline, benzaldehyde, and an activated alkene.

The first A3 coupling of 2,4-disubstituted quinolines was achieved by Huma et al. in 2002 (Scheme 4.1). Under their conditions, aldehyde, alkyne, and aniline were combined with 30 mol% CuCl in tetrahydrofuran at reflux to afford 2,4-disubstituted quinolines. They also observed the formation of propargylamine and benzylamine side products. The substrate scope was limited to aniline or p-
anisidine, and alkyl alkynes. Aryl aldehydes worked best as they encountered difficulty with the use of alkyl aldehydes. Due to the appearance of the benzylamine side product, a reaction mechanism was proposed which first involved the condensation of the aldehyde and aniline to form a Schiff base that could be propargylated through an activated copper acetylide. They proposed that the propargylamine oxidizes to an allene intermediate before undergoing cyclization and oxidation by the Schiff base to afford the quinoline and reduced benzylamine product. Isolated quinoline yields ranged from 34-48%.
Six years after the report from Huma, a proposed $A^3$ mechanism highlighted the uncertainty between organometallic, Lewis, and Brønsted acid mechanisms (Scheme 4.2). Their reaction utilized the aniline, aldehyde, and alkyne with 5 mol% $\text{AuCl}_3$ catalyst and 30 mol% CuBr co-catalyst in methanol. Dihydroquinoline was seen as the initial product, but rapidly oxidized in air to afford the 2,4-disubstituted quinoline. They also examined Brønsted acid versus...
Lewis acid catalysis of quinoline formation. Protic solvents TsOH, TfOH, and HCl, were tested against the propargylamine intermediate, but no quinoline was seen to form. It was explained that the Brønsted acid preferentially interacts with imine nitrogen, while the softer Lewis acid preferentially coordinated with the triple bond of the propargylamine. Interestingly they noted that from the A³ starting materials, triflic acid alone resulted in 26% yield of quinoline indicating multiple mechanistic pathways to quinoline formation – either through a propargylamine intermediate as proposed by Huma et al.¹⁰ or through the mechanism outlined in Scheme 4.2.¹¹

Scheme 4.2. Proposed A³ mechanism highlights uncertainty between organometallic, Lewis, and Brønsted acid mechanisms
4.1 Quinoline Synthesis Requires an Aniline

The Larsen group recently published on an A\(^3\) reaction for propargylamine formation in the presence of a Cu(OTf)\(_2\) catalyst, which happened to be the only catalyst found capable of forming propargylamine derivatives with electron poor \(p\)-toluenesulfonamides. Efforts to broaden the amine scope for the three-component copper-catalyzed formation of propargylamines (Scheme 4.3),\(^{12}\) resulted in quinoline formation with anilines – obvious from the bright blue UV spot seen by thin-layer chromatography (TLC).

**Scheme 4.3.** The Larsen Group recently reported on a method for the A\(^3\) coupling to form propargylamines

Copper(II) triflate, the ideal copper catalyst for the formation of propargylamines, was key for the formation of quinolines. When \(p\)-anisidine, 4-fluorobenzaldehyde, \(n\)-octyne, and 10 mol% Cu(OTf)\(^2\) in toluene were allowed to stir at 80 °C for three hours, 4-alkylquinoline was obtained in 78% yield.
Interestingly, however, was when an alkyl aldehyde was used, the main product after 3 hours under the same conditions was a propargylamine (Scheme 4.4).

**Scheme 4.4.** Aryl and alkyl aldehydes produce different substrates under the same conditions

The conditions for forming 2-arylquinolines were optimized to find that they could be prepared readily from a wide variety of anilines, aryl aldehydes, and terminal alkynes. It was discovered that the reaction process was robust, not requiring the preparation of dry glassware, drying agents, or inert atmosphere (Table 4.1). In fact, up to 10.0 additional equivalents of water could be added to the 1.0 equivalent formed *in situ* without decreasing the yield. This mix-and-heat method required no advance preparation for setup except for the distillation and purification of starting materials.
Table 4.1. A³ quinoline preparation unaffected by air or moisture

<table>
<thead>
<tr>
<th>Atmosphere</th>
<th>GC Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Argon</td>
<td>73</td>
</tr>
<tr>
<td>Nitrogen</td>
<td>73</td>
</tr>
<tr>
<td>Air</td>
<td>72</td>
</tr>
</tbody>
</table>

The A³ synthesis of quinolines could also be performed under a wide range of solvents including toluene, chloroform, 1,4-dioxane, methanol, ethyl acetate, ethanol, hexanes, and even some conversion in water, lending much versatility for further reaction optimization. The reaction was also found to proceed without solvent at all (Table 4.2), which resulted in success in forming alkyl substituted quinolines. Chloroform was found to be the best solvent overall as it was more compatible with a large variety of starting materials resulting in higher overall yields for aryl aldehyde derived quinolines. Also important to note, increased temperature and half the copper loading (10 to 5 mol%), generated greater conversion of starting materials to quinoline.
A variety of copper catalysts were examined and interestingly only those whose counterion formed strong acid in the presence of water, were seen to be capable of forming quinoline (Table 4.3). These included Cu(OTf)$_2$, CuOTf, and
Cu(ClO$_4$)$_2$. CuBr and CuBr•Me$_2$S only formed small percentages of quinoline. The remaining copper sources did not progress past the initial imine formation resulting from the condensation of aldehyde with $p$-anisidine.

**Table 4.3.** Copper sources with a counterion capable of forming strong acid were capable of catalyzing formation of A$^3$ quinoline

<table>
<thead>
<tr>
<th>Copper source</th>
<th>GC yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu(OTf)$_2$</td>
<td>72</td>
</tr>
<tr>
<td>CuOTf</td>
<td>69</td>
</tr>
<tr>
<td>Cu(OAc)$_2$</td>
<td>imine</td>
</tr>
<tr>
<td>CuOAc</td>
<td>imine</td>
</tr>
<tr>
<td>Cu(ClO$_4$)$_2$</td>
<td>72</td>
</tr>
<tr>
<td>CuBr$_2$</td>
<td>imine</td>
</tr>
<tr>
<td>CuBr•Me$_2$S</td>
<td>7</td>
</tr>
<tr>
<td>CuBr</td>
<td>5</td>
</tr>
<tr>
<td>CuCl$_2$</td>
<td>imine</td>
</tr>
<tr>
<td>Cul</td>
<td>imine</td>
</tr>
</tbody>
</table>

Due to the greater success of running the A$^3$ quinoline reaction in chloroform with Cu(OTf)$_2$ at 100 °C, the question of whether trace amounts of HCl that may be present in the chloroform could be helping to activate an imine intermediate and may be responsible for the higher, cleaner yields. Because a
few copper sources that included a counterion capable of becoming a strong acid if exposed to the one equivalent of water formed from this reaction *in situ*, we began to ask the question of whether it was the copper or the strong acid formed *in situ* that was responsible for the quinoline formation (Table 4.4). The A$^3$ quinoline reaction was run in toluene spiked with concentrated HCl in amounts ranging from zero, being the control, all the way up to 30 mol% and compared to the yield of quinoline formation in chloroform. It was seen that the addition of acid to toluene did not result in an increase in quinoline formation over chloroform.
Table 4.4. Toluene doped with concentrated HCl does not result in increased quinoline formation

<table>
<thead>
<tr>
<th>HCl (mol %)</th>
<th>3h GC yield (%)</th>
<th>17h GC yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>40</td>
<td>74</td>
</tr>
<tr>
<td>1.0</td>
<td>15</td>
<td>65</td>
</tr>
<tr>
<td>2.5</td>
<td>13</td>
<td>66</td>
</tr>
<tr>
<td>5.0</td>
<td>4</td>
<td>25</td>
</tr>
<tr>
<td>10.0</td>
<td>5</td>
<td>23</td>
</tr>
<tr>
<td>20.0</td>
<td>8</td>
<td>28</td>
</tr>
<tr>
<td>30.0</td>
<td>9</td>
<td>29</td>
</tr>
<tr>
<td>0 (in CHCl₃)</td>
<td>80</td>
<td>90</td>
</tr>
</tbody>
</table>

To test the effect of trace triflic acid (TfOH) formed in situ from the Cu(OTf)₂ catalyst, the A³ reaction of aniline, benzaldehyde and phenylacetylene in CHCl₃ was carried out under 3 different catalyst combinations at 100 °C in CHCl₃: 1) 5 mol% Cu(OTf)₂, 85% GC yield, 2) 5 mol% TfOH, 28% GC yield, and 3) 5 mol% Cu(OTf)₂ and 5 mol% TfOH, 88% GC yield. The Cu(OTf)₂ catalyst appears unaffected by the additional 5 mol% TfOH.
4.2 Synthesis of Alkyl-Substituted Quinolines

Because alkyl-substituted quinolines and their hydrogenated tetrahydroquinolines derivatives (Figure 4.4)\textsuperscript{13} displayed activity against malaria, inflammation, cancer, and tuberculosis, the real incentive to readily access the potentially bioactive alkyl-substituted quinolines remained a priority. To confirm possible intermediates encountered in the formation of quinolines (Scheme 4.5), phenyl-sustituted quinoline was compared to cyclohexyl-substituted quinoline (scheme (a) of Scheme 4.5), where completion differs by 3 days depending on the nature of substitution. First, imine was synthesized from $p$-anisidine and cyclohexanecarboxaldehyde, then subjected conditions of the Larsen $A^3$ quinoline synthesis, resulting in formation of quinoline after 3 days (b), confirming imine as a possible mechanistic intermediate. Cyclohexyl-derived propargylamine in (c) was then synthesized and isolated, and subjected to the same conditions, and again, quinoline was seen, confirming that propargylamine must be an intermediate.

Figure 4.4 Bioactive alkyl-substituted quinoline derivatives\textsuperscript{13}
Upon re-examination of the original finding illustrated in Scheme 4.4, it became clear that mechanistic intermediates may not hold common between the alkyl and aryl-substituted quinolines. Seeing that in the presence of an alkyl aldehyde, the reaction stalls upon the formation of the propargylamine, even after a day, where the aryl substituted quinoline has gone to completion within just a few hours. A re-examination of the A³ literature commonly suggests the reaction goes through a dihydroquinoline intermediate before oxidation in air (Scheme 4.1 and 4.2) implies that a higher energy barrier to arrive at the final quinoline exists. As depicted in Scheme 4.6, after formation of the propargylamine intermediate,
cyclizations must occur for dihydroquinoline formation. The positive charge on this intermediate is better stabilized if substituents $R^1$ and $R^2$ are conjugated. Additionally, if the substituent at $R^1$ lacks the rigidity possessed by an aryl ring, the floppiness results in a greater level of entropy resulting in a higher energy barrier towards quinoline formation.

**Scheme 4.6.** One of the possible mechanisms demonstrates how 2- and 4-aryl substituents could better stabilize positively-charged intermediates.

Reoptimization of the A$^3$ quinoline synthesis for the alkyl aldehydes soon revealed that solvent-free conditions were the key to rapid formation of both aryl and alkyl substituted quinolines. By eliminating solvent, a higher concentration of copper catalyst was available for substrate formation and the molecular collisions and contact are increased, overcoming the energy barrier required for 2-alkylquinoline formation. In light of this observation, choice of copper catalyst and catalyst studies were reexamined under these new solvent-free conditions. As seen in Table 4.5, a large number of different copper catalysts are effective. Although Cu(ClO$_4$)$_2$ was comparable, its explosive potential made Cu(OTf)$_2$ a clear choice for this quinoline methodology. 90% GC yield was observed when 5
mol% Cu(OTf)$_2$ was applied under solvent-free conditions (neat). Copper catalyst loading remained optimum at 5 mol%, the same as previously determined for the A$^3$ quinoline synthesis method in solvent.

Table 4.5. Cu(OTf)$_2$ remains the ideal copper catalyst for Larsen A$^3$ quinoline synthesis

<table>
<thead>
<tr>
<th>Copper source</th>
<th>GC yield (%)</th>
<th>Copper source</th>
<th>GC yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu(OTf)$_2$</td>
<td>90</td>
<td>CuCl$_2$</td>
<td>41</td>
</tr>
<tr>
<td>CuOTf</td>
<td>83</td>
<td>CuSO$_4$</td>
<td>41</td>
</tr>
<tr>
<td>Cu(ClO$_4$)$_2$</td>
<td>94</td>
<td>CuCl</td>
<td>18</td>
</tr>
<tr>
<td>CuBr•Me$_2$S</td>
<td>12</td>
<td>CuOAc</td>
<td>2</td>
</tr>
<tr>
<td>CuBr$_2$</td>
<td>44</td>
<td>Cu(OAc)$_2$</td>
<td>2</td>
</tr>
<tr>
<td>CuBr</td>
<td>18</td>
<td>CuI</td>
<td>5</td>
</tr>
</tbody>
</table>

A variety of commercially available substituted anilines, aryl aldehydes, alkynes and acetylenes were incorporated into quinolines as shown in substrates 47-62 (Figure 4.5). Substrate 52, derived from o-anisaldehyde may have use as a bidentate ligand. Quinolines 59 and 60 with hindered nitrogens were isolated.
in 65% and 67% yield respectively. Quinolines 63-67 exhibit the variety of substituents tolerated under same conditions.
Figure 4.5. 2,4-Disubstituted quinolines can be formed from a wide variety of commercially available starting materials.
Impressively, the water tolerant reaction allowed quinoline 68 to be synthesized in 35% yield from aqueous formaldehyde, \( p \)-anisaldehyde, and phenylacetylene with position 2 left open for further derivatization (Figure 4.6). The bidentate bisquinoline 69 was synthesized from an aryl dialdehyde with \( p \)-anisidine and phenylacetylene in 43% yield (Figure 4.7).

**Figure 4.6.** The versatile quinoline synthesis can lead to formation of interesting substrates including quinoline with position 2 open and a bidentate pincer ligand

![Chemical structures](image)

Although the formation of quinolines using aryl aldehydes was known science at the time of the Larsen discovery, there were no methods developed for the formation of 2- or 4-alkyl quinolines. 2-Alkylquinolines 70-78 were synthesized in 63% to 85% yield (Figure 4.7).
Figure 4.7. 2-Alkyl quinoline synthesized from alkyl aldehydes, phenylacetylene, and a variety of aniline sources

Through collaborations of the Larsen Group with the research groups of Prof. Emma Wilson, and Dr. Jack Eichler at UCR, two of the alkyl substituted quinolines exhibited activity towards two cancer cell lines. The quinoline 76 showed activity against lung cancer cell line, A549. Quinoline 78 showed activity towards glioma line GL26. Further investigation of the alkyl quinolines activities are under way, handled by Eddie Laguna of the Larsen Group.

Not all alkyl aldehydes formed 2,4-disubstituted quinolines. If the α-carbon was unbranched, as in valeraldehyde or isovaleraldehyde, a mixture of products was observed. In the presence of a terminal alkyne or phenylacetylene, a mixture of both 2,4-disubstituted quinoline and 2,3-diaryl substituted quinoline was observed. If phenylacetylene was omitted from the reaction mixture, only 2,3-dialkyl quinoline was observed. This alternate reaction pathway arises from a Povarov-like reaction where the enolate of the second aldehyde out-competes...
phenylacetylene as the nucleophilic. By providing 2.1 equivalents of valeraldehyde or isovaleraldehyde, 2,3-disubstituted quinolines were formed in 70% and 67% yield respectively (Scheme 4.7).

**Scheme 4.7.** 2,3-Dialkylquinolines formed from 1.0 equivalents p-anisidine and 2.1 equivalents alkyl aldehyde unbranched at the α-carbon

![Scheme 4.7 diagram]

**Literature Cited**


Chapter 5: Bis-Alpha Chiral Dipyros and Dipyrrins

Abstract

The first bis-α-chiral dipyrrromethane from para-methoxyphenyl-substituted dipyrrromethane and cinnamaldehyde was obtained using MacMillan’s imidazolidinone organocatalyst. The efficient asymmetric conjugate addition with dipyrrromethane as the nucleophile, to cinnamaldehyde, resulted in a chiral dipyrrromethane diol that when protected with tert-butyldimethylsilyl chloride and oxidized using p-chloranil resulted in the formation of the first bis-α-chiral dipyrrin.

Introduction

1930 Nobel Prize winner in chemistry, Hans Fischer, has been synonymous with dipyrrin chemistry.¹ Famous for his synthesis of hemes and bilirubins, his interest in pyrrole chemistry stemmed from a fascination of pigments derived from pyrrole based molecules (Figure 5.1).
The most recent dipyrrin research focuses on the synthesis of charge-neutral complexes capable of chelating a multitude of metal cations. Dipyrrins are composed of two pyrrole rings connected at the α-position to nitrogen—essentially a dipyrromethane with more than one degree of unsaturation.\textsuperscript{2}

Meso-dipyrromethanes have been formed from two pyrrole rings and one aldehyde with connectivity happening at the α-positions to nitrogen of the pyrrole ring. The acid-catalyzed synthesis has incorporated aryl or alkyl derived aldehydes.\textsuperscript{3}

The disadvantage of dipyrromethane synthesis has been the unavoidable formation of oligomers, therefore a large excess of pyrrole to carbonyl must be used (Scheme 5.1).\textsuperscript{4} Oftentimes, pyrrole has been used as the solvent, the excess being distilled off after addition of the aldehyde to obtain a higher yield of dipyrromethane as opposed to the various oligomers.\textsuperscript{3} The resulting aldehyde
derived dipyrromethanes have been successfully oxidized to dipyrrins. Both
dipyrromethanes and dipyrrins, due to their soft nitrogen centers, have value in
coordination complexes.

**Scheme 5.1:** Dipyrrromethane and oligomers with their approximate
percentages

5.0 equiv.\[\begin{align*}
\text{H} & \quad \text{O} \\
\text{F} & \quad \text{R} \quad \text{H} \\
\text{H} & \quad \text{N} \\
\end{align*}\] + 10 mol% TFA
\[\begin{align*}
\text{r.t.} & \quad 5 \text{ min.} \\
\text{R} & \quad \text{H} \\
\text{N} & \quad \text{R} \\
\end{align*}\]

\[\begin{align*}
\text{H} & \quad \text{R} \quad \text{H} \\
\text{H} & \quad \text{R} \quad \text{H} \\
\text{N} & \quad \text{R} \quad \text{H} \\
\text{N} & \quad \text{R} \quad \text{H} \\
\end{align*}\] 35% 15%

\[\begin{align*}
\text{H} & \quad \text{R} \quad \text{H} \\
\text{H} & \quad \text{R} \quad \text{H} \\
\text{N} & \quad \text{R} \quad \text{H} \\
\text{N} & \quad \text{R} \quad \text{H} \\
\text{N} & \quad \text{R} \quad \text{H} \\
\text{N} & \quad \text{R} \quad \text{H} \\
\end{align*}\] 7%

\[\begin{align*}
\text{H} & \quad \text{R} \quad \text{H} \\
\text{H} & \quad \text{R} \quad \text{H} \\
\text{N} & \quad \text{R} \quad \text{H} \\
\text{N} & \quad \text{R} \quad \text{H} \\
\text{N} & \quad \text{R} \quad \text{H} \\
\text{N} & \quad \text{R} \quad \text{H} \\
\end{align*}\] 3%


**5.1 MacMillan Catalyst for Metal-Free Conjugate Addition**

Once a dipyrrromethane has been formed, the outer two reactive positions
of the pyrrole rings are available for carbon-carbon bond formation. From these
two positions, a conjugate addition of an $\alpha,\beta$-unsaturated aldehyde to these
carbon centers was proposed to be possible by a reaction based on an
organocatalytic reaction reported by the MacMillan group in 2000 (Scheme 5.2).
Scheme 5.2. Synthesis of 1st generation MacMillan catalyst

An organocatalyst has been defined as an organic molecule used as a reaction catalyst. MacMillan imidazolidinone catalysts act by forming an iminium intermediate in a LUMO-lowering activation. The first generation MacMillan catalyst was used to facilitate the first highly enantioselective Diels-Alder reaction (Figure 5.2).
Figure 5.2. Diels-Alder reaction between cinnamaldehyde and cyclopentadiene was catalyzed by the organic MacMillan catalyst.

The development of the second generation MacMillan catalyst was in response to the need for an organocatalyst capable of improving the enantioselective yields of indole alkylations. The difference can be illustrated in figure Scheme 5.3, where the first generation catalyst catalyzed 91-99% ee for a pyrrole alkylation, yet the indole alkylation gave only 55% ee. The first generation catalyst exhibited effective si-face coverage, re-face methyl substrate interaction, and diminished substrate addition rate. The second generation catalyst improved indole alkylation yields to 89-98% ee with increased si-face coverage, re-face addition unhindered, and an increased substrate addition rate.
5.2 Oxidation of Dipyrrromethanes to Dipyrrins

Synthesis of dipyrrins can be done either one of two possible routes: 1) condensation of pyrroles, commonly known as the MacDonald Coupling, or 2) oxidation of dipyrrromethanes using an agent such as 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) or tetrachloro-1,4-benzoquinone (p-chloranil). Often, p-
chloranil is preferred to the harsher DDQ. If the dipyrrole is not substituted at the 5 position, DDQ may consume the resulting dipyrrin product.\textsuperscript{7} Dipyrrinato complexes have been obtained as a side product of porphyrins from the Rothemund condensation,\textsuperscript{8a-e} especially with the use of \textit{ortho} substituted aldehydes in the bridge formation.\textsuperscript{8a-d} The resulting complex with an aldehyde derived R group at position 5, makes porphyrin cyclizations less likely.

\section*{5.3 Value of Dipyrrins as Coordination Complexes}

Metal ions such as zinc (II) were incorporated in organometallic dipyrrinato complexes.\textsuperscript{8c} Dipyrrins were first reported to coordinate a number of transition metals in 1938.\textsuperscript{9} Dipyrrins have been shown to form complexes with a wide variety of metal ions including magnesium, calcium, chromium, manganese, iron, cobalt, nickel, copper, zinc, gallium, rhodium, palladium, cadmium, indium, mercury, thalium.\textsuperscript{9-18} Complexes are commonly made by first forming the dipyrrin, then adding the metal salt in situ.\textsuperscript{15} The dipyrrinato metal complex chelates in a $\kappa^2$ coordination geometry, but in 2000 was reported to also bind in an $\eta^5$ manner as an azaferrocene ligand.\textsuperscript{19} Ruthenium has also been shown to bind in a $\eta^5$ manner.\textsuperscript{20} When 5-aryl-dipyrrins are coordinated to either copper (II) or nickel (II), a distorted tetrahedral geometry is adopted. Nickel has been advantageous over copper due to its diamagnetism, making structure determination possible through use of $^1$H NMR spectroscopy. In the case of cobalt (II), 5-phenyl-dipyrrins have been reported to be difficult to isolate due to the preferred octahedral tris-dipyrrin
coordination around cobalt (III).\textsuperscript{21} Iron (III) octahedral geometries have also been observed. Dipyrrinato complexes of boron are well known for their photochemical properties as they exhibit fluorescence which is useful for the purposes of biological staining and dye laser applications as the compound most commonly referred to as its commercial name, BODIPY.\textsuperscript{22} Dipyrrinato complexes of boron have shown applications in energy-transfer cassettes, light-harvesting arrays, and fluorescent molecular sensors. Dipyrrins have been shown to not only bind boron through nitrogen atoms of the dipyrrin moiety, but also to oxygen atoms of two phenolate substituents of the complex. Racemic mixtures of this complex form as a helically chiral moiety. The resulting fluorescence emission exhibited more intense, narrow, and more highly shifted wavelengths when compared to the well known borondifluoride derivatives.\textsuperscript{23} Metal coordinated compounds that exhibit only one type of ligand were referred to as homoleptic, while a metal complex with more than one type of ligand coordinated, were known as heteroleptic. In a heteroleptic dipyrrinato complex, a square geometry will be observed. In the case of copper(II), homoleptic complexes can be formed in the presence of 0.4 equivalents of a metal salt. If stoichiometric quantities are used, heteroleptic complexes form.\textsuperscript{24} Acetylacetonato (acac) and hexafluoroacetylacetonato (hfacac) metal salts made excellent heteroleptic dipyrrinato complexes due to the minimal interference with 1,9-substituents. Examples of these have been shown using copper(II) and palladium(II).\textsuperscript{9} Substituents at the 1,9-positions of dipyrrinato complexes have been found to
distort the coordination geometry of the metals. Even those metals whose normal coordination geometry is square planar, will adopt a pseudo-tetrahedral arrangement.\textsuperscript{25,26} A homoleptic dipyrrinato complex can arise from an initial formation of a heteroleptic complex. This equilibrium can be shifted to the right towards formation of the homoleptic complex by control of specific factors such as pH and the type of metal salt used.\textsuperscript{27} Metal acetylacetonates form heteroleptic complexes much more readily than metal chlorides.\textsuperscript{27}

5.4 Larsen Group Synthesis of a Chiral Dipyrrin

Dipyrrromethanes were synthesized according to literature procedure (Figure 5.3).\textsuperscript{3} One equivalent of aryl derived aldehyde to 40 equivalents of pyrrole were used. The reaction was either catalyzed by 10 mol\% trifluoroacetic acid (TFA) or boron trifluoride diethyl etherate.
Figure 5.3. Dipyrrromethanes with substituted aryl bridge

All dipyrrromethanes are light sensitive and were best to use immediately after isolation. However, if thoroughly dried and stored in the freezer in sealed vials, compounds could be maintained for several months.

Conjugate addition of cinnamaldehyde to the free positions alpha to the nitrogen atoms was accomplished using MacMillan’s 2nd generation catalyst in a solution of tetrahydrofuran and water at -50 °C for five days to afford the extended backbone. Double conjugate additions were successful with aryl-bridged dipyrrromethanes 81, 82, and 84. Difficulty in isolation of the bis-α-chiral dipyrrromethane of 83, made this substrate an unreliable starting point for further syntheses. Ortho-substituted dipyrrromethanes 86, and 87 resulted in only a single conjugate addition to α,β-unsaturated aldehyde (Figure 5.4).
Further work was not done with bis-α-chiral dipyrrromethanes 96a and 96b, as it was not possible to cleanly isolate them. The one-sided conjugate addition products 97 and 98 also were not isolated cleanly. In order to selectively oxidize the conjugate addition products, the alcohols of 94, 95, and 99 were protected. Many protecting groups were examined, with the best results in the shortest amount of time obtained by using tert-butyl dimethylsilyl chloride. Best results and cleanest isolation was obtained with bis-α-chiral dipyrrromethane 99.

Oxidizing agents examined included DDQ and p-chloranil. DDQ was found to be too harsh of an oxidizing reagent, oxidizing the desired methane center, as well as the tertiary positions adjacent to the phenyl rings. The action of DDQ was
fast, less than three hours, where the \( p \)-chloranil process took several days to achieve the desired dyprrin product (Scheme 5.4). This chiral dipyrrin has future potential as a complexing agent.

**Scheme 5.4.** Overall scheme from dipyrromethane to chiral dipyrrin

\[
\begin{align*}
\text{84} & \quad \text{2.5 equiv.} \quad \text{1st Gen MacMillan catalyst} \\
\text{99 and 100} & \quad \text{THF:H}_2\text{O (95:5)} \\
& \quad \text{-50 °C, 5 days} \\
& \quad \text{NaBH}_4 \text{ reduction} \\
\text{99 and 100} & \quad 89\% \text{ yield} \\
\text{99 and 100} & \quad \text{TBSCI} \\
& \quad \text{imidazole, CH}_2\text{Cl}_2 \\
& \quad \text{r.t. overnight} \\
\text{101 and 102} & \quad 80\% \text{ yield} \\
\text{101 and 102} & \quad \text{\( p \)-chloranil} \\
& \quad \text{THF, r.t.} \\
& \quad \text{5 days} \\
\text{103} & \quad 33\% \text{ yield}
\end{align*}
\]
Although not reported in this work, attempts at complexing these chiral dipyrrins to metal is underway.

**Literature Cited**


(c) Marchon, J. C.; Ramasseul, R.; Ulrich, J. *J. Heterocycl. Chem.* 1987, 5847


Commun. 1999, 1889.


Chapter 6: Supporting Information

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 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.
6.1 General Procedural and Reagent Information Chapter 1

All reactions were set up on the benchtop in test tubes, closed with Teflon seal insert screw caps, and carried out under an atmosphere of argon ("test tube" in general procedures A-C). 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 used. 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 Procedures**

A. To an oven-dried test tube and magnetic stir bar was added imine (1.0 equiv.), prepared according to Moonen, K.; Stevens, C. V. *Synthesis* **2005**, 3603, 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 Et2O in hexanes as eluent afforded the desired product.

**B.** To an oven-dried test tube and magnetic stir bar was added imine (1.0 equiv.), prepared according to Moonen, K.; Stevens, C. V. *Synthesis* **2005**, 3603, 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 Et2O in hexanes as eluent afforded the desired product.

**C.** To an oven-dried test tube and magnetic stir bar was added imine (1.0 equiv), prepared according to Chemla, F.; Hebbe, V.; Normant, J.-F. *Synthesis*, **2000**, 1, 75, 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. 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 ethyl acetate (EtOAc) or Et$_2$O in hexanes as eluent afforded the desired product.
(1) Benzyl(1-phenylhept-2-yn-1-yl)amine

Prepared according to general procedure A: benzoaldehyde derived benzylamine (387 mg, 2.0 mmol) was stirred with Cu(OTf)$_2$ (36 mg, 5 mol %) and toluene (1.0 mL) under argon at 80 °C for 1 hour before the addition of n-hexyne (260 µL, 1.4 mmol). Reaction mixture was stirred an additional 3 days to afford the title compound as a yellow oil in 46% yield (0.255 g, 0.92 mmol) after column chromatography on silica gel (0-2.5% Et$_2$O in hexanes and 1% Et$_3$N). IR (film) 3313, 3062, 3029, 2956, 2930, 2871, 1649, 1493, 1453, 1295, 1073, 1028, 730, 696 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.51 (d, J=7.4 Hz, 2ArH), 7.37-7.23 (m, 8ArH), 4.55 (s, 1H), 3.88 (d, J = 4.0 Hz, 2H), 2.78 (bs, 1H), 2.28 (td, J = 2.0 Hz, 6.8 Hz, 2H), 1.58-1.40 (m, 4H), 0.92 (t, J = 7.3 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 141.2, 140.2, 128.6, 127.8, 127.2, 86.3, 80.0, 53.5, 51.2, 31.2, 22.2, 18.8, 13.8. HRMS calculated requires [M]$^+$: 278.1903. Found m/z: 278.1892.

(2) Benzyl(1-phenylnon-2-yn-1-yl)amine

Prepared according to general procedure A: benzoaldehyde derived benzylamine (193 mg, 1.0 mmol) was stirred with Cu(OTf)$_2$ (36 mg, 10 mol %) and toluene (1.0 mL) under argon at 80 °C for 1 hour before the addition of n-octyne (220 µL, 1.5 mmol). Reaction mixture was stirred an additional 5 days to
afford the title compound as a yellow oil in 83% yield (0.252 g, 0.83 mmol) after column chromatography on florisil gel (0-2.5% EtOAc in hexanes). IR (film) 2955, 2928, 2857, 1663, 1602, 1493, 1453, 1072, 1028, 730, 696 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.53 (d, J = 7.3 Hz, 2ArH), 7.38-7.24 (m, 8ArH), 4.56 (s, 1H), 3.90 (dd, J = 13.0 Hz, 4.2 Hz, 2H), 2.29 (td, J = 7.0 Hz, 2.0 Hz, 2H), 1.64 (bs, 1H), 1.56 (quint, J = 6.8 Hz, 2H), 1.47-1.40 (m, 2H), 1.38-1.26 (m, 6H), 0.90 (t, J = 6.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 141.1, 140.0, 128.4, 127.6, 127.5, 127.0, 86.1, 79.8, 53.3, 51.1, 31.4, 28.9, 28.6, 22.6, 18.9, 14.1. HRMS calculated requires [M+H]+: 306.2223. Found m/z: 306.2197.

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

Prepared according to general procedure B: 2-fluorobenzaldehyde derived benzylimine (214 mg 1.0 mmol) was stirred with copper bromide dimethylsulfide (21 mg, 10 mol %) and toluene (1.0 mL) under argon at 80 °C for 1 hour before the addition of n-octyne (220 µL, 1.5 mmol). Reaction mixture was stirred an additional 5 days to afford the title compound as a yellow oil in 65% yield (0.209 g, 0.65 mmol) after column chromatography on florisil gel (0-7.5% EtOAc in hexanes). 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 7.62 (td, J=1.6 Hz, 7.6 Hz, 1H), 7.36-7.26 (m, 4H), 7.25-7.22 (m, 2H), 7.14 (td, J = 1.2 Hz, 7.2 Hz, 1H),
(4) Benzyl({1-[3-(trifluoromethyl)phenyl]non-2-yn-1-yl})amine

Prepared according to general procedure A: 3-(trifluoromethyl)benzaldehyde derived benzylimine (264 mg 1.0 mmol) was stirred with Cu(OTf)$_2$ (36 mg, 10 mol %) and toluene (1.0 mL) under argon at 80 °C for 1 hour before the addition of n-octyne (220 µL, 1.5 mmol). Reaction mixture was stirred an additional 5 days to afford the title compound as a dark yellow oil in 86% yield (0.321 g, 0.86 mmol) after column chromatography on florisil gel (0-7.5% EtOAc in hexanes). IR (film) 2930, 2858, 1604, 1454, 1329, 1163, 1123, 1072, 911, 802, 732, 698 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.849 (s, 1ArH), 7.74 (d, J = 7.7 Hz, 1ArH), 7.53 (d, J = 7.8 Hz, 1ArH), 7.46-7.42 (m, 1ArH), 7.38-7.31 (m, 4ArH), 7.27-7.23 (m, 1ArH), 4.60 (s, 1H), 3.91 (d, J = 1.7, 2H), 2.31 (td, J = 7.0 Hz, 2.1 Hz, 2H), 1.65 (s, 1H), 1.57 (quint, J = 6.7 Hz, 2H), 1.48-1.41 (m, 2H), 1.38-1.26 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 142.1, 139.7, 131.1, 128.7,
128.4, 127.1, 124.5, 124.4, 87.0, 79.0, 52.9, 51.1, 31.4, 28.8, 28.6, 22.6, 18.8, 14.1. HRMS calculated requires [M+H]+: 274.2090. Found m/z: 374.2107

(5) Benzyl(2,2-dimethylundec-4-yn-3-yl)amine

Prepared according to general procedure B: pivaldehyde derived benzylimine (176 mg 1.0 mmol) was stirred with copper bromide dimethylsulfide (21 mg, 10 mol %), and toluene (1.0 mL) under argon at 80 °C for 1 hour before the addition of n-octyne (220 µL, 1.5 mmol). Reaction mixture was stirred an additional 6 days to afford the title compound as a yellow oil in 54% yield (0.153 g, 0.54 mmol) after column chromatography on florisil gel (0-5% EtOAc in hexanes). IR (film) 3064, 3029, 2954, 2929, 2859, 1736, 1605, 1496, 1454, 1362, 1098, 1028, 909, 837, 732, 696 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\), 25°C) \(\delta\) 7.39 (d, \(J = 7.4\) Hz, 2ArH), 7.32 (t, \(J = 7.2\) Hz, 2ArH), 7.24 (t, \(J = 7.2\) Hz, 1ArH), 4.09 (d, \(J = 13.2\) Hz, 1H), 3.79 (d, \(J = 13.2\) Hz, 1H), 2.92 (s, 1H), 2.25 (td, \(J = 1.8\) Hz, 6.8 Hz, 2H), 1.58-1.51 (m, 2H), 1.49-1.41 (m, 2H), 1.37-1.28 (m, 4H), 1.00 (s, 9H), 0.92 (t, \(J = 6.6\) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\), 25°C) \(\delta\) 141.0, 128.5, 128.4, 127.0, 84.6, 80.7, 59.9, 52.4, 35.0, 31.6, 29.4, 28.8, 26.7, 22.9, 19.0, 14.3. HRMS calculated requires [M+H]+: 286.3808. Found m/z: 286.3729.
(6) Benzyl(2-methyl)dodec-5-yn-4-yl)amine

Prepared according to general procedure B:

Isovaleraldehyde derived benzyllimine (176 mg 1.0 mmol) was stirred with copper bromide dimethylsulfide (21 mg, 10 mol %) and toluene (1.0 mL) under argon at 80 °C for 1 hour before the addition of n-octyne (220 µL, 1.5 mmol). Reaction mixture was stirred an additional 3 days to afford the title compound as a yellow oil in 60% yield (0.172 g, 0.60 mmol) after column chromatography on florisil gel (0-10% EtOAc in hexanes). IR (film) 3064, 3029, 2955, 2928, 2858, 1714, 1605, 1496, 1455, 1366, 1101, 1028, 909, 731, 697 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.36 (d, J = 7.1 Hz, 2ArH), 7.31 (t, J = 7.2 Hz, 2ArH), 7.23 (t, J = 7.2 Hz, 1ArH), 4.03 (d, J = 12.8 Hz, 1H), 3.81 (d, J = 12.8 Hz, 1H), 3.41 (t, J = 7.5 Hz, 2H), 2.23 (td, J = 1.8 Hz, 6.8 Hz, 2H), 1.95-1.85 (m, 1H), 1.57-1.39 (m, 4H), 1.36-1.27 (m, 4H), 0.92-0.88 (m, 9H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 140.3, 128.6, 128.5, 127.1, 84.3, 81.6, 51.5, 48.3, 45.7, 31.6, 29.2, 28.8, 25.5, 23.2, 22.8, 22.3, 19.0, 14.3. HRMS calculated requires (M+H)+: 286.2529. Found m/z: 286.2519.

(7) N-(1-Cyclohexynon-2-yn-1-yl)-4-methylbenzene-1-sulfonamide

Prepared according to general procedure C:

Cyclohexylcarboxaldehyde derived tosylimine (265 mg 1.0 mmol) was stirred with Cu(OTf)₂ (36 mg, 10 mol %) and toluene (1.0 mL) under argon at 80 °C for 1
hour before the addition of \( n \)-octyne (148 µL, 1.0 mmol). Reaction mixture was stirred an additional 3 days to afford the title compound as a pale yellow solid in 51% yield (0.191 g, 0.51 mmol) after column chromatography on silica gel (0-10% EtOAc in hexanes with 1% Et\(_3\)N). IR (film) 3288, 2927, 2854, 1599, 1451, 1428, 1333, 1300, 1290, 1159, 1094, 1050, 1020, 930, 910, 881, 813, 743, 680 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\), 25°C) \( \delta \) 7.74 (d, \( J = 8.0 \) Hz, 2ArH), 7.25 (d, \( J = 8.3 \) Hz, 2ArH), 4.55 (d, \( J = 8.5 \) Hz, 1H), 3.84-3.81 (m, 1H), 2.39 (s, 3H), 1.85-1.83 (m, 2H), 1.78-1.69 (m, 4H), 1.63-1.60 (m, 2H), 1.50-1.43 (m, 2H), 1.27-0.99 (m, 8H), 0.85 (t, \( J = 6.7 \) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\), 25°C) \( \delta \) 143.3, 137.9, 129.6, 127.6, 85.9, 77.1, 51.4, 51.3, 43.5, 31.5, 29.3, 28.6, 28.6, 28.4, 26.4, 26.0, 22.7, 21.7, 18.6, 14.2. HRMS calculated requires (M+NH\(_4\))\(^+\): 393.2570. Found \( m/z \): 393.2578.
6.2 General Procedural and Reagent Information Chapter 2

All reactions were set up on the benchtop in test tubes, closed with Teflon seal insert screw caps, and carried out under an atmosphere of argon ("test tube" in general procedure A). 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) trifluoromethanesulphonate, 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 used. 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 Procedure**

A. To an oven-dried test tube and magnetic stir bar was added 10 mol % Cu(OTf)$_2$. The flask was purged with argon for 15 minutes. Amine (1.0 equiv.), 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.
(8) Benzyl(1-phenylnon-2-yn-1-yl)amine

Prepared according to general procedure A: benzylamine (110 µL, 1.00 mmol), benzaldehyde (122 µL, 1.20 mmol), 1-octyne (222 µL, 1.50 mmol), Cu(OTf)$_2$ (36 mg, 10 mol %), Na$_2$SO$_4$ (284 mg, 2.0 mmol) were stirred at 80 °C for 72 hours to afford the title compound as a yellow oil in 72% yield (0.219 g, 0.72 mmol) after column chromatography on florisil gel (0-10% Et2O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2955, 2928, 2857, 1663, 1602, 1493, 1453, 1072, 1028, 730, 696 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.53 (d, J = 7.3 Hz, 2ArH), 7.38-7.24 (m, 8ArH), 4.56 (s, 1H), 3.90 (dd, J = 13.0 Hz, 4.2 Hz, 2H), 2.29 (td, J = 7.0 Hz, 2.0 Hz, 2H), 1.64 (bs, 1H), 1.56 (quint, J = 6.8 Hz, 2H), 1.47-1.40 (m, 2H), 1.38-1.26 (m, 6H), 0.90 (t, J = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 141.1, 140.0, 128.4, 127.6, 127.5, 127.0, 86.1, 79.8, 53.3, 51.1, 31.4, 28.9, 28.6, 22.6, 18.9, 14.1. HRMS calculated requires [M+H]$^+$: 306.2223. Found m/z: 306.2197.
(9) Benzyl(2-methylundec-4-yn-3-yl)amine

Prepared according to general procedure A:

\[
\text{benzylamine (55 µL, 0.50 mmol), isobutyaldehyde (55 µL, 0.60 mmol), 1-octyne (110 µL, 0.75 mmol), Cu(OTf)}_2
\]

(18 mg, 10 mol %), Na$_2$SO$_4$ (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$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) $\delta$ 7.37-7.29 (m, 4H), 7.25-7.22 (m, 1H), 4.03 (d, J = 12.8 Hz, 1H), 3.80 (d, J = 13.2, 1H), 3.17 (dt, J = 2.4 Hz, 5.6 Hz, 1H), 2.24 (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), 0.98 (d, J = 6.8, 6H), 0.89 (t, J = 7.2 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) $\delta$ 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.
(10) Benzyl[1-(2-fluorophenyl)non-2-yn-1-yl]amine

Prepared according to general procedure A:

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$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.62 (td, J=1.6 Hz, 7.6 Hz, 1H), 7.36-7.26 (m, 4H), 7.25-7.22 (m, 2H), 7.14 (td, J = 1.2 Hz, 7.2 Hz, 1H), 7.03 (td, J = 1.2 Hz, 8.4 Hz, 1H), 4.87 (t, J = 2.4 Hz, 1H), 3.93 (d, J = 12.8 Hz, 1H), 3.87 (d, J = 12.8, 1H), 2.26 (td, J = 2 Hz, 6.8 Hz, 2H), 1.72 (bs, 1H), 1.55 (quin, J = 7.2 Hz, 2H), 1.45-1.38 (m, 2H), 1.35-1.26 (m, 4H), 0.89 (t, J = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 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, 28.6, 22.6, 18.8, 14.1. HRMS calculated requires [M]+: 323.1998. Found m/z: 323.2000.
(11) Benzyl[1-(3-fluorophenyl)non-2-yn-1-yl]amine

Prepared according to general procedure A: benzylamine (110 µL, 1.00 mmol), 3-fluorobenzaldehyde (128 µL, 1.20 mmol), 1-octyne (222 µL, 1.50 mmol), Cu(OTf)$_2$ (36 mg, 10 mol %), Na$_2$SO$_4$ (284 mg, 2.0 mmol) were stirred at 80 °C for 72 hours to afford the title compound as a yellow oil in 68% yield (0.220 g, 0.68 mmol) after column chromatography on florisil gel (0-10% Et$_2$O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2955, 2928, 2857, 1667, 1614, 1589, 1485, 1445, 1265, 877, 786, 729, 696 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.38-7.24 (m, 8ArH), 6.98-6.93 (m, 1ArH), 4.55 (s, 1H), 3.89 (d, J = 2.6 Hz, 2H), 2.29 (td, J = 7.0 Hz, 2.1 Hz, 2H), 1.60-1.53 (m, 4H), 1.48-1.40 (m, 2H), 1.35-1.27 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 139.8, 129.7, 129.7, 128.4, 127.1, 123.2, 114.7, 114.5, 114.3, 86.5, 79.3, 52.8, 51.0, 31.3, 28.9, 28.6, 22.6, 18.8, 14.1. HRMS calculated requires [M+H]+: 324.2128. Found m/z: 324.2200.

(12) Benzyl[1-(4-fluorophenyl)non-2-yn-1-yl]amine

Prepared according to general procedure A: benzylamine (110 µL, 1.00 mmol), 4-fluorobenzaldehyde (129 µL, 1.20 mmol), 1-octyne (222 µL, 1.50 mmol), Cu(OTf)$_2$ (36 mg, 10 mol %), Na$_2$SO$_4$ (284 mg, 2.0 mmol) were stirred at 80 °C for 72 hours to afford the title compound as a yellow oil in 84%
yield (0.271 g, 0.84 mmol) after column chromatography on florisil gel (0-20% Et₂O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2955, 2929, 2857, 1603, 1506, 1455, 1222, 1156, 1093, 831, 731, 697 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.53-7.48 (m, 2ArH), 7.37-7.29 (m, 4ArH), 7.26-7.22 (m, 1ArH), 7.05-6.98 (m, 2ArH), 4.53 (s, 1H), 3.88 (d, J = 3.3, 2H), 2.29 (td, J = 7.0 Hz, 2.1 Hz, 2H), 1.66 (bs, 1H), 1.56 (quint, J = 7.1 Hz, 2H), 1.47-1.40 (m, 2H), 1.37-1.23 (m, 6H), 0.90 (t, J = 6.9 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 163.4, 161.0, 139.9, 136.8, 129.3, 129.2, 128.4, 127.0, 115.2, 114.96, 83.4, 79.6, 52.5, 51.0, 31.3, 28.9, 28.6, 22.6, 18.8, 14.1. HRMS calculated requires [M+H]+: 324.2077. Found m/z: 324.2152.

(13) Benzyl(1-[2-(trifluoromethyl)phenyl]non-2-yn-1-yl)amine

Prepared according to general procedure A: benzylamine (110 µL, 1.00 mmol), 2-(trifluoromethyl)benzaldehyde (160 µL, 1.20 mmol), 1-octyne (222 µL, 1.50 mmol), Cu(OTf)₂ (36 mg, 10 mol %), Na₂SO₄ (284 mg, 2.0 mmol) were stirred at 80 °C for 72 hours to afford the title compound as a yellow oil in 80% yield (0.299 g, 0.80 mmol) after column chromatography on florisil gel (0-50% Et₂O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2930, 2858, 1607, 1455, 1311, 1158, 1121, 1058, 1035, 767, 697 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.92 (d, J = XX Hz, 1ArH), 7.62-7.54 (m, 2ArH), 7.37-7.28 (m, 5ArH), 7.25-7.21 (m, 1ArH), 4.95 (s, 1H), 3.96 (d, J = 12.7 Hz, 2H), 3.79
(d, J = 12.7 Hz, 2H), 2.23 (td, J = 7.0 Hz, 2.0 Hz, 2H), 1.74 (bs, 1H), 1.52 (quint, J = 6.9 Hz, 2H), 1.43-1.38 (m, 2H), 1.36-1.25 (m, 4H), 0.88 (t, J = 6.8 Hz, 3H).

$^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) $\delta$ 140.3, 139.6, 132.2, 129.7, 128.5, 128.3, 127.6, 127.1, 125.8, 125.7, 85.8, 79.7, 51.9, 49.7, 31.3, 28.7, 28.6, 22.6, 18.8, 14.0. HRMS calculated requires [M+H]$^+$: 374.2097. Found $m/z$: 374.2110.

**(14) Benzyl([1-[3-(trifluoromethyl)phenyl]non-2-yn-1-yl])amine**

Prepared according to general procedure A: benzyllamine (110 µL, 1.00 mmol), 3-(trifluoromethyl)benzaldehyde (161 µL, 1.20 mmol), 1-octyne (222 µL, 1.50 mmol), Cu(OTf)$_2$ (36 mg, 10 mol %), Na$_2$SO$_4$ (284 mg, 2.0 mmol) were stirred at 80 °C for 72 hours to afford the title compound as a yellow oil in 46% yield (0.170 g, 0.46 mmol) after column chromatography on florisil gel (0-50% Et$_2$O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2930, 2858, 1604, 1454, 1329, 1163, 1123, 1072, 911, 802, 732, 698 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) $\delta$ 7.849 (s, 1ArH), 7.74 (d, J = 7.7 Hz, 1ArH), 7.53 (d, J = 7.8 Hz, 1ArH), 7.46-7.42 (m, 1ArH), 7.38-7.31 (m, 4ArH), 7.27-7.23 (m, 1ArH), 4.60 (s, 1H), 3.91 (d, J = 1.7, 2H), 2.31 (td, J = 7.0 Hz, 2.1 Hz, 2H), 1.65 (s, 1H), 1.57 (quint, J = 6.7 Hz, 2H), 1.48-1.41 (m, 2H), 1.38-1.26 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) $\delta$ 142.1, 139.7, 131.1, 128.7, 128.4, 127.1, 124.5, 124.4, 87.0, 79.0, 52.9, 51.1, 31.4, 28.8, 28.6, 22.6, 18.8, 14.1. HRMS calculated requires [M+H]$^+$: 274.2090. Found $m/z$: 374.2107.
15) Dibenzyl(4-methyl-1-phenylpent-1-yn-3-yl)amine

Prepared according to general procedure A: dibenzylamine (194 µL, 1.0 mmol), isobutyaldehyde (110 µL, 1.2 mmol), phenylacetylene (165 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 80% yield (0.280 g, 0.80 mmol) after column chromatography on florisil gel (0-10% Et$_2$O in hexanes). IR (film) 3029, 2958, 1599, 1489, 1453, 1069, 1028, 974, 753, 742, 734, 690 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) $\delta$ 7.52-7.49 (m, 2ArH), 7.43 (d, J = 7.5 Hz, 4ArH), 7.34-7.26 (m, 7ArH), 7.22-7.19 (m, 2ArH), 3.89 (d, J = 13.8 Hz, 2H), 3.48 (d, J = 13.8 Hz, 2H), 3.12 (d, J = 10.4 Hz, 1H), 2.03-1.95 (m, 1H), 1.23 (td, J = 4.8 Hz, 1.2 Hz, 2H), 1.06-1.03 (m, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) $\delta$ 139.8, 131.8, 128.9, 128.2, 127.8, 126.8, 87.4, 86.1, 59.7, 55.1, 30.8, 21.0, 20.0. HRMS calculated requires M+[-H]: 352.2060. Found m/z: 352.2072.

(16) Dibenzyl(2-methylnon-4-yn-3-yl)amine

Prepared according to general procedure A: dibenzylamine (194 µL, 1.0 mmol), isobutyraldehyde (110 µL, 1.2 mmol), $n$-hexyne (174 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 colorless oil in 72% yield (0.240 g, 0.72
mmol) after column chromatography on florisil gel (0-10% Et₂O in hexanes). IR (film) 2957, 2932, 1494, 1454, 1363, 1069, 1028, 975, 743, 733, 696 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.40 (d, J = 7.4 Hz, 4ArH), 7.28 (t, J = 7.2 Hz, 4ArH), 7.21-7.18 (m, 2ArH), 3.79 (d, J = 13.8 Hz, 2H), 3.36 (d, J = 13.8 Hz, 2H), 2.86 (dt, J = 10.4 Hz, 2.0 Hz, 1H), 2.29 (td, J = 6.8 Hz, 2.0 Hz, 2H), 1.90-1.81 (m, 1H), 1.60-1.46 (m, 4H), 0.99-0.93 (m, 9H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 140.1, 128.8, 128.1, 126.7, 85.7, 76.7, 59.3, 55.0, 31.4, 22.0, 21.0, 19.9, 18.4, 13.7. HRMS calculated requires [M+H]+: 334.2529. Found m/z: 334.2538.

(17) Dibenzyl(5-methyl-1-phenylhex-1-yn-3-yl)amine

Prepared according to general procedure A: dibenzylamine (194 µL, 1.0 mmol), isovaleraldehyde (130 µL, 1.2 mmol), phenylacetylene (165 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 yellow oil in 85% yield (0.310 g, 0.85 mmol) after column chromatography on florisil gel (0-10% Et₂O in hexanes). IR (film) 3029, 2954, 1599, 1490, 1453, 1367, 1070, 1028, 969, 912, 746, 690 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.51-7.48 (m, 2ArH), 7.41 (d, J = 7.3 Hz, 4ArH), 7.33-7.26 (m, 7ArH), 7.22-7.19 (m, 2ArH), 3.88 (d, J = 13.6 Hz, 2H), 3.69 (t, J = 7.2Hz, 2H), 3.48 (d, J = 13.7 Hz, 1H), 1.97-1.85 (m, 1H), 1.75-1.70 (m, 1H), 1.58-1.50 (m, 1H), 1.28-1.17 (m, 2H), 0.81 (d, J = 6.7 Hz, 3H), 0.69 (d, J = 6.6 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 139.8,
131.8, 128.9, 128.2, 128.2, 127.8, 126.9, 88.2, 85.1, 55.0, 50.1, 42.9, 24.6, 22.8, 21.9. HRMS calculated requires \([M+H]^+\): 367.2295. Found \(m/z\): 367.2305.

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

Prepared according to general procedure A: dibenzylamine (194 µL, 1.0 mmol), 2-furaldehyde (100 µL, 1.2 mmol), 1-octyne (222 µL, 1.5 mmol), \(\text{Cu(OTf)}_2\) (36 mg, 10 mol %), \(\text{Na}_2\text{SO}_4\) (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% \(\text{Et}_2\text{O}\) 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) \(\delta\) 7.42 (d, \(J = 7.2\) Hz, 4H), 7.39 (s, 1H), 7.29 (t, \(J = 6.8\) Hz, 4H), 7.21 (t, \(J = 7.2\) Hz, 2H), 6.42 (d, \(J = 3.2\) Hz, 1H), 6.29 (dd, \(J = 2\) Hz, 1H), 4.70 (s, 1H), 3.72 (d, \(J = 14\) Hz, 2H), 3.52 (d, \(J = 14\) Hz, 2H), 2.34 (td, \(J = 2\) Hz, 6.4 Hz, 2H), 1.61 (quin, \(J = 6.4\) Hz, 2H), 1.54-1.47 (m, 2H), 1.38-1.33 (m, 4H), 0.93 (t, \(J = 6.8\) Hz, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\), 25°C) \(\delta\) 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.
(19) Dibenzyl[1-(4-fluorophenyl)non-2-yn-1-yl]amine

Prepared according to general procedure A: dibenzylamine (194 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 24 hours to afford the title compound as a colorless oil in 71% yield (0.238 g, 0.71 mmol) after column chromatography on florisil gel (0-10% Et$_2$O in hexanes). IR (film) 2929, 1603, 1506, 1454, 1222, 827, 784, 745, 696 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.63-7.59 (m, 2ArH), 7.38-7.37 (m, 4ArH), 7.31-7.27 (m, 4ArH), 7.23-7.19 (m, 2ArH), 7.01-6.97 (m, 2ArH), 4.63 (s, 1H), 3.67 (d, J = 13.5 Hz, 2H), 3.41 (d, J = 13.5 Hz, 2H), 2.42 (td, J = 2.1 Hz, 6.9 Hz, 2H), 1.71-1.63 (m, 2H), 1.59-1.53 (m, 2H), 1.40-1.35 (m, 4H), 0.94 (t, J = 7.0 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 163.3, 160.9, 139.7, 135.6, 129.9, 129.8, 128.8, 128.3, 128.1, 127.0, 114.8, 114.6, 89.1, 74.5, 55.0, 54.5, 31.4, 29.2, 28.7, 22.7, 18.9, 14.1. HRMS calculated requires [M+] 413.2513. Found m/z: 413.2508.

(20) 4-(1-phenylnon-2-yn-1-yl)morpholine

Prepared according to general procedure A: morpholine (44 µL, 0.50 mmol), benzaldehyde (61 µL, 0.60 mmol), 1-octyne (110µL, 0.75 mmol), Cu(OTf)$_2$ (18 mg, 10 mol %), Na$_2$SO$_4$ (142 mg, 1.0 mmol) were stirred at 80 °C for 12 hours to afford the title
compound as a pale yellow oil in 94% yield (0.134 g, 0.47 mmol) after column chromatography on florisil gel (0-20% Et$_2$O in hexanes). IR (film) 2955, 2929, 2855, 1451, 1116, 1001, 866, 724, 697 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) $\delta$ 7.55 (d, $J = 7.3$ Hz, 2ArH), 7.35-7.31 (m, 2ArH), 7.28-7.25 (m, 1ArH), 4.52 (s, 1H), 3.74-3.65 (m, 4H), 2.57-2.48 (m, 4H), 2.31 (td, $J = 7.0$ Hz, 2.0 Hz, 2H), 1.58 (quint, $J = 7.2$ Hz, 2H), 1.45 (quint, $J = 6.9$ Hz, 2H), 1.36-1.27 (m, 4H), 0.90 (t, $J=7.2$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) $\delta$ 138.5, 128.6, 128.1, 127.6, 88.7, 75.4, 67.2, 61.7, 49.8, 31.33, 29.0, 28.6, 22.6, 18.8, 14.1. HRMS calculated requires [M+H]$^+$: 285.2087. Found $m/z$: 285.2086.

(21) 4-(2-methylundec-4-yn-3-yl)morpholine

Prepared according to general procedure A: morpholine (88 µL, 1.00 mmol), isobutyraldehyde (110 µL, 1.20 mmol), $n$-octyne (222µL, 1.50 mmol), Cu(OTf)$_2$ (36 mg, 10 mol %), Na$_2$SO$_4$ (285 mg, 2.0 mmol) were stirred at 80 °C for 12 hours to afford the title compound as a yellow oil in 83% yield (0.207 g, 0.83 mmol) after column chromatography on florisil gel (0-10% Et$_2$O in hexanes). IR (film) 2929, 2856, 1735, 1653, 1454, 1325, 1253, 1117, 1012, 868 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) $\delta$ 3.76-3.66 (m, 4H), 2.75 (dt, $J = 9.4$Hz, 1.9 Hz, 1H), 2.62-2.57 (m, 2H), 2.44-2.38 (m, 2H), 2.22 (td, $J = 2.0$ Hz, 6.9 Hz, 2H), 1.82-1.73 (m, 1H), 1.51 (quint, $J = 6.8$ Hz, 2H), 1.44-1.35 (m, 2H), 1.34-1.26 (m, 4H), 1.02 (d, $J = 6.6$ Hz, 3H), 0.96 (d, $J = 6.6$ Hz, 3H), 0.89 (t, $J = 6.7$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) $\delta$ 158.5, 128.9, 128.3, 127.6, 88.7, 74.4, 67.2, 61.3, 39.8, 31.2, 29.0, 28.6, 22.5, 18.8, 14.0.
25°C) δ 86.5, 76.6, 67.2, 64.9, 50.0, 31.3, 29.9, 29.2, 28.6, 22.6, 20.1, 19.8, 18.7, 14.1. HRMS calculated requires [M+H]+: 251.2244. Found m/z: 251.2234.

(22) 4-[1-(4-fluorophenyl)non-2-yn-1-yl]morpholine

Prepared according to general procedure A: morpholine (88 µL, 1.00 mmol), 4-fluorobenzaldehyde (130 µL, 1.20 mmol), n-octyne (222µL, 1.50 mmol), Cu(OTf)₂ (36 mg, 10 mol %), Na₂SO₄ (285 mg, 2.0 mmol) were stirred at 80 °C for 12 hours to afford the title compound as a pale yellow oil in 91% yield (0.275 g, 0.91 mmol) after column chromatography on florisil gel (0-20% Et₂O in hexanes). IR (film) 2929, 2855, 1602, 1506, 1454, 1222, 1116, 1001, 858, 841, 779 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.55-7.51 (m, 2ArH), 7.03-6.99 (m, 2ArH), 4.50 (s, 1H), 3.74-3.65 (m, 4H), 2.51-2.49 (m, 4H), 2.31 (td, J = 2.1 Hz, 7.0 Hz, 2H), 1.58 (quint, J = 7.2 Hz, 2H), 1.45-1.42 (m, 2H), 1.35-1.29 (m, 4H), 0.90 (t, J = 6.9 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 163.6, 161.2, 141.1, 134.5, 130.3, 130.2, 116.4, 166.2, 115.1, 114.9, 89.3, 75.3, 67.3, 49.8, 31.5, 29.2, 28.8, 22.8, 19.0, 14.2. HRMS calculated requires [M+H]: 303.1993. Found m/z: 303.2002.
(23) 4-\{1-[4-(trifluoromethyl)phenyl]non-2-yn-1-yl\}morpholine

Prepared according to general procedure A: morpholine (88 µL, 1.0 mmol), 4-trifluoromethanebenzaldehyde (164 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 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) δ 7.71 (d, J = 8.4 Hz, 2H), 7.59 (t, J = 8.4 Hz, 2H), 4.57 (s, 1H), 3.72-3.69 (m, 4H), 2.52 (bs, 4H), 2.32 (td, J = 2 Hz, 7.2 Hz, 2H), 1.64-1.55 (m, J = 7.2, 2H), 1.45 (quin, J = 7.2 Hz, 2H), 1.36-1.30 (m, 4H), 0.91 (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.

(24) 4-\{1-[3-(trifluoromethyl)phenyl]non-2-yn-1-yl\}morpholine

Prepared according to general procedure A: morpholine (88 µL, 1.0 mmol), 3-trifluoromethanebenzaldehyde (161 µL, 1.2 mmol), $n$-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 20 hours to afford the title compound as a pale yellow oil in 96% yield (0.340 g, 0.96 mmol) after column chromatography on florisil gel (0-20% Et₂O in hexanes). IR (film) 2957, 2931, 2857, 1453, 1329, 1163, 1115, 1072, 1003, 909, 863, 811, 702, 671 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.87 (s, 1ArH), 7.78 (d, J = 7.6 Hz, 1ArH), 7.53 (d, J = 7.2 Hz, 1ArH), 7.45 (t, J = 7.6 Hz, 1ArH), 4.59 (s, 1H), 3.75-3.66 (m, 4H), 2.57-2.51 (m, 4H), 2.33 (td, J = 6.8 Hz, 1.6 Hz, 2H), 1.59 (quint, J = 7.2 Hz, 2H), 1.49-1.42 (m, 2H), 1.36-1.29 (m, 4H), 0.90 (t, J=7.2 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 139.8, 131.9, 131.0, 130.7, 130.4, 130.0, 128.5, 125.3, 124.4, 125.6, 122.9, 89.9, 74.4, 67.1, 61.2, 49.7, 31.4, 29.0, 28.6, 22.6, 18.8, 14.0. HRMS calculated requires [M+H]+: 353.1961. Found m/z: 353.1960.

(25) [(4-Methoxyphenyl)methyl][1-phenylhept-2-yn-1-yl]amine

Prepared according to general procedure A: 4-methoxybenzylamine (131 µL, 1.0 mmol), benzaldehyde (100 µL, 1.0 mmol),  n-hexyne (170 µL, 1.5 mmol), Cu(OTf)₂ (36 mg, 10 mol %), Na₂SO₄ (285 mg, 2.0 mmol) were stirred at 60 °C for 120 hours to afford the title compound as a yellow oil in 61% yield (0.187 g, 0.61 mmol) after column chromatography on florisil gel (0-50% Et₂O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2956, 2931, 1611, 1511, 1453, 1301, 1244, 1173, 1033, 827, 752, 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.55 (d, J =
7.4 Hz, 2ArH), 7.38-7.24 (m, 5ArH), 6.88 (d, J = 8.6 Hz, 2ArH), 4.57 (s, 1H), 3.87 (d, J = 3.1 Hz, 2H), 3.79 (s, 3H), 2.32 (td, J = 1.9 Hz, 6.9 Hz, 2H), 2.23 (bs, 1H), 1.62-1.45 (m, 4H), 0.97 (t, J = 7.3 Hz, 3H); \( ^{13} \)C NMR (100 MHz, CDCl\(_3\), 25°C) \( \delta \)

158.9, 141.3, 132.3, 129.8, 128.7, 128.6, 127.8, 127.7, 114.0, 86.2, 80.1, 31.3, 22.3, 18.8, 13.9. HRMS calculated requires [M+H]-: 307.1931. Found \( m/z: \)

307.1930.

(26) \([(4\text{-methoxyphenyl})\text{methyl}]\text{(1-phenyl}n\text{on-2-yn-1-yl)}\text{amine}

Prepared according to general procedure A: 4-methoxybenzylamine (131 µL, 1.0 mmol), benzaldehyde (100 µL, 1.0 mmol), \( n \)-octyne (220 µL, 1.5 mmol), Cu(OTf)\(_2\) (36 mg, 10 mol %), \( \text{Na}_2\text{SO}_4\) (285 mg, 2.0 mmol) were stirred at 60 °C for 120 hours to afford the title compound as a yellow oil in 59% yield (0.198 g, 0.59 mmol) after column chromatography on florisil gel (0-50% Et\(_2\)O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2954, 2929, 2857, 1611, 1511, 1453, 1245, 1173, 1035, 827, 752, 697 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\), 25°C) \( \delta \)

7.56 (d, J = 7.3 Hz, 2ArH), 7.41-7.24 (m, 5ArH), 6.88 (d, J = 8.6 Hz, 2ArH), 4.58 (s, 1H), 3.87 (d, J = 2.9 Hz, 2H), 3.80 (s, 3H), 2.32 (td, J = 3.0 Hz, 7.0 Hz, 2H), 2.14 (bs, 1H), 1.60 (quint, J = 6.6 Hz, 2H), 1.51-1.46 (m, 2H), 1.40-1.30 (m, 4H), 0.94 (t, J = 6.8 Hz, 3H); \(^{13} \)C NMR (100 MHz, CDCl\(_3\), 25°C) \( \delta \)

158.9, 141.4, 132.3, 129.8, 128.6, 127.8, 127.7, 114.0, 86.3, 80.2, 55.5, 53.4, 50.7, 31.6, 29.2, 28.9,
22.9, 19.1, 14.3. HRMS calculated requires [M*+H]: 335.2244. Found m/z: 335.2249.

(27) [(4-Methoxyphenyl)methyl](6-methyl-1-phenylhept-2-yn-1-yl)amine

Prepared according to general procedure A: 4-methoxybenzylamine (131 µL, 1.0 mmol), benzaldehyde (100 µL, 1.0 mmol), 5-methyl-1-hexyne (220 µL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol %), Na$_2$SO$_4$ (285 mg, 2.0 mmol) were stirred at 60 °C for 120 hours to afford the title compound as a yellow oil in 54% yield (0.173 g, 0.54 mmol) after column chromatography on florisil gel (0-50% Et$_2$O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2954, 2931, 2869, 1611, 1511, 1453, 1245, 1173, 1034, 829, 809, 753, 698 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, 25°C) $\delta$ 7.53 (d, $J = 7.3$ Hz, 2ArH), 7.37-7.26 (m, 5ArH), 6.87 (d, $J = 8.6$ Hz, 2ArH), 4.56 (s, 1H), 3.85 (d, $J = 3.3$ Hz, 2H), 3.79 (s, 3H), 2.31 (td, $J = 2.0$ Hz, 7.4 Hz, 2H), 1.80-1.71 (m, 1H), 1.48 (q, $J = 7.3$ Hz, 2H), 0.94 (d, $J = 6.6$ Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) $\delta$ 158.9, 141.3, 132.3, 129.8, 128.6, 127.8, 127.7, 114.0, 88.3, 80.0, 55.5, 53.3, 50.6, 38.1, 27.5, 22.5, 17.1. HRMS calculated requires [M*-H]: 321.2098. Found m/z: 321.2085.
(28) (1,3-Diphenylprop-2-ynyl-1-yl)[(4-methoxyphenyl)methyl]amine

Prepared according to general procedure B: 4-methoxybenzylamine (131 µL, 1.0 mmol), benzaldehyde (100 µL, 1.0 mmol), phenylacetylene (165 µL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol%), Na$_2$SO$_4$ (285 mg, 2.0 mmol) were stirred at 60 °C for 120 hours to afford the title compound as a yellow oil in 20% yield (0.066 g, 0.20 mmol) after column chromatography on florisil gel (0-50% Et$_2$O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 3029, 2932, 2834, 1610, 1510, 1451, 1442, 1244, 1173, 1031, 828, 813, 755, 691 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.79-7.76 (m, 1ArH), 7.61 (d, J = 7.2 Hz, 2ArH), 7.50-7.41 (m, 2ArH), 7.42-7.24 (m, 7ArH), 6.90-6.87 (m, 2ArH), 4.78 (d, J = 12.5 Hz, 2H), 3.94 (d, J = 1.2 Hz, 1H), 3.80 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 161.8, 159.0, 140.9, 132.1, 132.0, 130.9, 129.9, 129.4, 128.8, 128.7, 128.5, 128.4, 128.0, 127.9, 114.2, 114.1, 89.5, 85.9, 55.5, 53.7, 50.8. HRMS calculated requires [M$^+$$]$: 327.1618. Found m/z: 327.1622.
(29) [(4-Methoxyphenyl)methyl](2-methylundec-4-yn-3-yl)amine

Prepared according to general procedure A: 4-methoxybenzylamine (131 µL, 1.0 mmol), isobutyraldehyde (92 µL, 1.0 mmol), n-octyne (220 µL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol %), Na$_2$SO$_4$ (285 mg, 2.0 mmol) were stirred at 60 °C for 120 hours to afford the title compound as a yellow oil in 67% yield (0.202 g, 0.67 mmol) after column chromatography on florisil gel (0-50% Et$_2$O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2956, 2929, 2858, 1611, 1511, 1464, 1245, 1172, 1097, 1037, 827, 807 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.26 (d, J = 8.5 Hz, 2ArH), 6.83 (d, J = 8.5 Hz, 2ArH), 3.94 (d, J = 12.7 Hz, 1H), 3.77 (s, 3H), 3.73 (d, J = 12.7 Hz, 1H), 3.15-3.13 (m, 1H), 2.23 (td, J = 1.8 Hz, 6.8 Hz, 2H), 1.84-1.76 (m, 1H), 1.56-1.49 (m, 2H), 1.46-1.39 (m, 2H), 1.34-1.26 (m, 4H), 0.97 (d, J = 6.8 Hz, 6H), 0.89 (t, J = 6.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 158.8, 132.7, 129.7, 113.9, 84.8, 80.1, 55.8, 55.4, 51.2, 33.0, 31.9, 29.3, 28.8, 22.8, 20.0, 19.0, 18.0, 14.3. HRMS calculated requires [M+Na]$^+$: 324.2298. Found m/z: 324.2297.
(30) (2,8-Dimethylnon-4-yn-3-yl)[4-methoxyphenyl)methyl]amine

Prepared according to general procedure A: 4-methoxybenzylamine (131 µL, 1.0 mmol), isobutyaldehyde (92 µL, 1.0 mmol), 5-methyl-1-hexyne (200 µL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol %), Na$_2$SO$_4$ (285 mg, 2.0 mmol) were stirred at 60 °C for 120 hours to afford the title compound as a yellow oil in 57% yield (0.163 g, 0.57 mmol) after column chromatography on florisil gel (0-50% Et$_2$O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2956, 2930, 2870, 1611, 1511, 1465, 1244, 1171, 1096, 1037, 827, 808, 700 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.26 (d, J = 8.5 Hz, 2ArH), 6.84 (d, J = 8.5 Hz, 2ArH), 3.94 (d, J = 12.4 Hz, 1H), 3.77 (s, 3H), 3.72 (d, J = 12.7 Hz, 1H), 3.14-3.13 (m, 1H), 2.23 (td, J = 1.8 Hz, 7.4 Hz, 2H), 1.82-1.68 (m, 2H), 1.45-1.40 (m, 2H), 0.96 (d, J = 6.7 Hz, 6H), 0.91 (d, J = 6.6 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 158.8, 132.7, 129.7, 113.9, 84.8, 79.9, 55.8, 55.4, 51.2, 38.3, 33.0, 27.4, 22.4, 20.0, 18.0, 17.0. HRMS calculated requires [M$^+$]: 287.2244. Found m/z: 287.2240.
(31) [(4-Methoxyphenyl)methyl](4-methyl-1-phenylpent-1-yn-3-yl)amine

Prepared according to general procedure A: 4-methoxybenzylamine (131 µL, 1.0 mmol), isobutyaldehyde (92 µL, 1.0 mmol), phenylacetylene (165 µL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol %), Na$_2$SO$_4$ (285 mg, 2.0 mmol) were stirred at 60 °C for 120 hours to afford the title compound as a yellow oil in 24% yield (0.069 g, 0.24 mmol) after column chromatography on florisil gel (0-50% Et$_2$O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2958, 2931, 2871, 2835, 1610, 1511, 1463, 1442, 1244, 1172, 1034, 827, 755, 691 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.46-7.44 (m, 2ArH), 7.32-7.29 (m, 5ArH), 6.86 (d, J = 8.6 Hz, 2H), 4.04 (d, J = 12.8 Hz, 1H), 3.84 (d, J = 12.6 Hz, 1H), 3.79 (s, 3H), 3.40 (d, J = 5.4 Hz, 1H), 1.99-1.91 (m, 1H), 1.06 (d, J = 2.6 Hz, 3H), 1.04 (d, J = 2.6 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 158.9, 131.9, 129.9, 128.5, 128.1, 114.0, 89.7, 85.0, 56.2, 55.5, 51.3, 33.1, 20.1, 18.2. HRMS calculated requires [M$^+*$]: 293.1774. Found m/z: 293.1772.
(32) 1-(4-fluorophenyl)-N-[(4-methoxyphenyl)methyl]non-2-yn-1-amine

Prepared according to general procedure A: 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 %), Na₂SO₄ (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% Et₂O 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, CDCl₃, 25°C) \(\delta\) 7.51-7.48 (m, \(J = 6.3\) Hz, 2H), 7.28 (d, \(J = 8.8\) Hz, 2H), 7.03-6.99 (m, \(J = 6.3\) Hz, 2H), 6.86 (d, \(J = 8.4\) Hz, 2H), 4.51 (s, 1H), 3.82 (d, \(J = 2.8\) Hz, 2H), 3.79 (s, 3H), 2.28 (td, \(J = 2.4\) Hz, 2H), 1.56 (q, 2H), 1.43 (q, 2H), 1.35-1.27 (m, 4H), 0.90 (t, 3H). \(^{13}C\) NMR (100 MHz, CDCl₃, 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.
(33) [6-Chloro-1-(2-fluorophenyl)hex-2-yn-1-yl][(4-methoxyphenyl)methyl]amine

Prepared according to general procedure A: 4-methoxybenzylamine (131 µL, 1.0 mmol), 2-fluorobenzaldehyde (128 µL, 1.2 mmol), 5-chloro-1-pentyne (160 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 73% yield (0.252 g, 0.73 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) 3003, 2970, 2836, 1738, 1611, 1586, 1511, 1489, 1455, 1365, 1231, 1173, 1093, 1033, 825, 803, 755 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) $\delta$ 7.57 (td, $J = 2$ Hz, 8 Hz, 1H), 7.30-7.24 (m, 3H), 7.16-7.13 (t, $J = 7.6$ Hz, 1H), 7.04 (t, $J = 10$ Hz, 1H), 6.86 (d, $J = 8.4$ Hz, 2H), 4.83 (t, $J = 2$ Hz, 1H), 3.82 (dd, $J = 12.8$ Hz, 23.6 Hz, 2H), 3.80 (s, 3H), 3.67 (t, $J = 6.8$ Hz, 2H), 2.47 (td, $J = 2.4$ Hz, 6.8 Hz, 2H), 1.99 (quint, $J = 6.8$ Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) $\delta$ 161.6, 158.7, 131.6, 129.5, 129.4, 129.3, 129.1, 124.2, 115.7, 115.5, 113.8, 83.3, 80.1, 55.3, 50.7, 47.3, 31.4, 16.3. HRMS calculated requires [M+Na$^+$]: 368.1188. Found $m/z$: 368.1191.
(34) [6-Chloro-1-(3-fluorophenyl)hex-2-yn-1-yl][(4-methoxyphenyl)methyl]-amine

Prepared according to general procedure A: 4-methoxybenzylamine (131 µL, 1.0 mmol), 3-fluorobenzaldehyde (128 µL, 1.2 mmol), 5-chloro-1-pentyne (160 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 71% yield (0.249 g, 0.71 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) 2999, 2933, 2836, 1612, 1587, 1511, 1484, 1441, 1355, 1301, 1244, 1173, 1034, 824, 773, 691 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.31-7.24 (m, 6H), 6.87 (d, J = 8.4 Hz, 2H), 4.53 (t, J = 1.6 Hz, 1H), 3.82 (d, J = 3.6 Hz, 2H), 3.80 (s, 3H), 2.50 (td, J = 2.4 Hz, 6.8 Hz, 2H), 2.02 (quint, J = 6.4 Hz, 2H), 1.62 (s, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 164.1, 161.7, 158.8, 143.5, 143.4, 131.7, 129.9, 129.8, 129.5, 123.1, 114.6, 114.4, 113.8, 84.1, 80.6, 55.3, 52.5, 50.4, 43.7, 31.5, 16.3. HRMS calculated requires [M-H]-: 344.1221. Found m/z: 344.1225.
(35)  [6-Chloro-1-(4-fluorophenyl)hex-2-yn-1-yl][(4-methoxyphenyl)methyl]-amine

Prepared according to general procedure A: 4-methoxybenzylamine (131 µL, 1.0 mmol), 4-fluorobenzaldehyde (130 µL, 1.2 mmol), 5-chloro-1-pentyne (160 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 (0.248 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) 3000, 2957, 2836, 1610, 1506, 1441, 1355, 1301, 1244, 1220, 1173, 1155, 1091, 1034, 825, 725 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.50-7.46 (m, 2H), 7.29-7.25 (m, 2H), 7.02 (tt, J = 3.2 Hz, 8.4 Hz, 2H), 6.87 (dt, J = 2.8 Hz, 9.2 Hz, 2H), 4.51 (s, 1H), 3.81 (dd, J = 13.2 Hz, 18.4 Hz, 2H), 3.80 (s, 3H), 3.68 (t, J = 6.4 Hz, 2H), 2.49 (td, J = 1.6 Hz, 6.4 Hz, 2H), 2.01 (quint, J = 6.4 Hz, 2H); $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 163.5, 161.0, 158.8, 136.8, 136.6, 131.8, 129.5, 129.2, 129.1, 84.0, 80.9, 55.3, 52.3, 50.5, 43.7, 31.5, 16.3. HRMS calculated requires [M-H]-: 344.1221. Found m/z: 344.1212.
(36) [(2-Methoxyphenyl)methyl](1-phenylhept-2-yn-1-yl)amine

Prepared according to general procedure A: 2-methoxybenzylamine (131 µL, 1.0 mmol), benzaldehyde (100 µL, 1.0 mmol), n-hexyne (170 µL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol %), Na$_2$SO$_4$ (285 mg, 2.0 mmol) were stirred at 60 °C for 120 hours to afford the title compound as a yellow oil in 61% yield (0.186 g, 0.61 mmol) after column chromatography on florisil gel (0-50% Et$_2$O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2956, 2931, 2871, 1601, 1492, 1455, 1241, 1029, 751, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.54 (d, J = 7.3 Hz, 2ArH), 7.37-7.23 (m, 5ArH), 6.93 (t, J = 7.4 Hz, 1ArH), 6.86 (d, J = 8.2 Hz, 1ArH), 4.58 (s, 1H), 3.92 (dd, J = 13.3 Hz, 31.4 Hz, 2H), 3.82 (s, 3H), 2.71 (bs, 1H), 2.29 (td, J = 1.8 Hz, 6.8 Hz, 2H), 1.60-1.45 (m, 4H), 0.95 (t, J = 7.3 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 158.0, 141.5, 130.3, 128.9, 128.6, 128.5, 128.3, 127.9, 127.7, 120.6, 110.5, 85.9, 80.3, 55.5, 53.7, 47.0, 31.2, 22.2, 18.8, 13.9. HRMS calculated requires [M$^*$-H]$: 306.1852$. Found m/z: 306.1862.
(37) [(2-Methoxyphenyl)methyl](6-methyl-1-phenylhept-2-yn-1-yl)amine

Prepared according to general procedure A: 2-methoxybenzylamine (131 µL, 1.0 mmol), benzaldehyde (100 µL, 1.0 mmol), 5-methyl-1-hexyne (200 µL, 1.5 mmol), Cu(OTf)$_2$ (36 mg, 10 mol %), Na$_2$SO$_4$ (285 mg, 2.0 mmol) were stirred at 60 °C for 120 hours to afford the title compound as a yellow oil in 55% yield (0.176 g, 0.55 mmol) after column chromatography on florisil gel (0-50% Et$_2$O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2954, 2931, 2868, 1602, 1492, 1464, 1241, 1029, 751, 697 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.54 (d, J = 7.3 Hz, 2ArH), 7.37-7.23 (m, 5ArH), 6.93 (t, J = 7.4 Hz, 1ArH), 6.86 (d, J = 8.2 Hz, 1ArH), 4.58 (s, 1H), 3.92 (dd, J = 13.3 Hz, 31.5 Hz, 2H), 3.82 (s, 3H), 2.61 (bs, 1H), 2.30 (td, J = 2.0 Hz, 7.4 Hz, 2H), 1.82-1.72 (m, 1H), 1.51-1.45 (m, 2H), 0.93 (d, J = 6.6 Hz, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 158.0, 141.5, 130.3, 128.9, 128.6, 128.5, 128.3, 127.9, 127.7, 120.6, 110.5, 85.9, 80.2, 55.5, 53.7, 47.0, 38.1, 27.5, 22.5, 17.2, . HRMS calculated requires [M$^+$+H]: 321.2087. Found m/z: 321.2072.
(38) (2,2-Dimethylundec-4-yn-3-yl)[(2-methoxyphenyl)methyl]amine

Prepared according to general procedure A: 2-methoxybenzylamine (66 µL, 0.5 mmol), pivaldehyde (66 µL, 0.6 mmol), n-octyne (110 µL, 0.75 mmol), Cu(OTf)$_2$ (18 mg, 10 mol %), Na$_2$SO$_4$ (142 mg, 1.0 mmol) were stirred at 80 °C for 72 hours to afford the title compound as a yellow oil in 45% yield (0.071 g, 0.035 mmol) after column chromatography on florisil gel (50% Et$_2$O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2953, 2928, 2858, 1602, 1492, 1463, 1240, 1092, 1031, 751 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.33 (dd, J = 1.6 Hz, 7.4 Hz, 1ArH), 7.22 (td, J = 7.8 Hz, 2.0 Hz, 1ArH), 6.91 (td, J = 7.4 Hz, 0.9 Hz, 2ArH), 6.85 (d, J = 8.0 Hz, 1H), 4.11 (d, J = 13.8 Hz, 1H), 3.83 (s, 3H), 3.75 (d, J = 13.8 Hz, 1H), 2.91 (t, J = 2.4 Hz, 1H), 2.22 (td, J = 6.8 Hz, 2.0 Hz, 2H), 1.6 (bs, 1H), 1.52 (quin, J = 7.2 Hz, 2H), 1.46-1.39 (m, 2H), 1.35-1.24 (m, 6H), 0.96 (s, 9H), 0.89 (t, J = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 157.7, 129.8, 128.7, 127.9, 120.3, 110.2, 84.3, 80.3, 59.9, 55.3, 47.9, 34.8, 31.4, 29.1, 28.6, 26.5, 22.6, 18.8, 14.1. HRMS calculated requires [M+H]: 315.2557. Found m/z: 315.2546.
(39) [1-(3-fluorophenyl)non-2-yn-1-yl][2-methoxyphenyl)methyl]amine

Prepared according to general procedure A: 2-methoxybenzylamine (131 µL, 1.0 mmol), 3-fluorobenzaldehyde (128 µL, 1.2 mmol), n-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 redish oil in 58% yield (0.203 g, 0.58 mmol) after column chromatography on florisil gel (0-50% Et$_2$O in hexanes). Methylene chloride (1 mL) was added before loading onto florisil column. IR (film) 2955, 2928, 2857, 1713, 1613, 1588, 1489, 1464, 1439, 1242, 1029, 874, 783, 751, 694 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.29-7.22 (m, 4ArH), 6.98-6.85 (m, 4ArH), 4.54 (t, J = 1.8 Hz, 1H), 3.83 (s, 3H), 2.26 (td, J = 7.0 Hz, 2.0 Hz, 2H), 1.56 (quint, J = 6.9 Hz, 2H), 1.46-1.38 (m, 2H), 1.37-1.26 (m, 4H), 0.89 (t, J = 6.9 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 130.0, 129.8, 129.7, 128.3, 127.9, 123.3, 120.5, 114.8, 114.5, 114.4, 114.2, 110.3, 86.1, 79.6, 55.3, 53.0, 46.7, 31.4, 28.8, 28.6, 22.6, 18.9, 14.1. HRMS calculated requires [M+H]+: 269.3134. Found m/z: 269.3129.
(40) 1-(3-ethyldec-5-yn-4-yl)pyrrolidine

Prepared according to general procedure A: pyrrolidine (84 µL, 1.0 mmol), 2-ethylbutyraldehyde (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% Et₂O in hexanes). IR (film) 3456, 2959, 2874, 2859, 2809, 1739, 1457, 1366, 1217, 1116, 1033, 908, 882, 795, 725 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 3.21-3.20 (m, 1H), 2.63-2.59 (m, 2H), 2.56-2.53 (m, 2H), 2.20 (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.

(41) Benzyl(methyl)(2-methyldec-5-yn-4-yl)amine

Prepared according to general procedure A: 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$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 7.25-7.21 (m, 2H), 7.07 (td, J = 1.6 Hz, 7.6 Hz, 1H), 6.93 (dd, J = 1.2, 7.2, 1H), 6.85 (d, J = 8.4 Hz, 2H), 6.75 (t, J = 7.6 Hz, 1H), 6.63 (t, J = 7.6 Hz, 1H), 6.48 (d, J = 8 Hz, 1H), 6.16 (s, 1H), 4.51 (m, 1H), 3.81 (dd, J = 4.4 Hz, 6.4 Hz, 1H), 2.99 (s, 3H), 2.83 (s, 3H), 2.32-2.25 (m, 1H), 2.17 (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), 1.19 (d, J = 6.8 Hz, 3H), 1.14 (d, J = 6.8 Hz, 3H), 0.95-0.83 (m, 12H). $^{13}$C NMR (100 MHz, CDCl$_3$, 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.

(42) tert-butyl N-(1,3-diphenylprop-2-yn-1-yl)carbamate

Tert-butyl carbamate (71 mg, 0.5 mmol), benzaldehyde (51 µL, 0.6 mmol), phenylacetylene (166 µL, 0.75 mmol), Cu(OTf)$_2$ (18 mg, 10 mol %), cesium carbonate (16 mg, 10 mol%), chloroform and hexanes (1:1, 1 mL) were stirred at 100 °C for 18 hours. HRMS calculated requires [M+H]+: 308.1450. Found m/z: 308.1456. Compare commercially available, stable unsubstituted N-Boc propargylamine versus sole report of 16% yield of an α-substituted N-Boc propargylamine: Hatano, M.; Asai, T.; Ishihara, K. Tetrahedron Lett. 2008, 49, 379.
tert-butyl N-(1-cyclohexylhept-2-yn-1-yl)carbamate

Prepared from preformed imine as described in Wenzel, A.; Jacobsen, E. N. J. Am. Chem. Soc. 2002, 124, 12964., (211 mg, 1.0 mmol), Cu(OTf)₂ (36 mg, 10 mol %), Cs₂CO₃ (33 mg, 10 mol %) in 2 mL 1:1 CHCl₃:hexanes stirred at 60 °C for 15 minutes, followed by addition of 1-hexyne (138 µL, 1.2 mmol) and stirred for 6 days at 60 °C. Best attempt to isolate product by column chromatography on basic alumina (0-50% EtOAc in hexanes) resulted in deprotection, decomposition, and some fractions of clean product with diagnostic peaks Ha and Hb in 1H NMR (400 MHz, CDCl₃) δ 3.76 (m, 1Ha), 1.86 (m, 1Hb).
6.3 Supporting information Chapter 3

See general procedure A of Chapter 2.

(43) 1-Methyl-4-(nona-1,2-dien-1-yl)benzene

Under an atmosphere of argon, p-tolualdehyde (180 µL, 1.5 mmol), pyrrolidine (92 µL, 1.1 mmol), n-octyne (148 µL, 1.0 mmol), CuI (38 mg, 20 mol %), Na₂SO₄ (285 mg, 2.0 mmol) were stirred at 110 °C for 12 hours to afford the title compound as a pale yellow oil in 31% yield (0.036 g, 0.31 mmol) after column chromatography on silica gel (100% hexanes). IR (film) 2955, 2925, 2856, 1705, 1610, 1457, 1378, 1272, 1178, 1105, 1036, 1020, 810, 754, 725 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.16 (d, J=8.1 Hz, 2ArH), 7.08 (d, J = 8.1 Hz, 2ArH), 6.09-6.06 (m, 1H), 5.55-5.50 (m, 1H), 2.31 (s, 3H), 2.10 (qd, J = 2.8 Hz, 7.0 Hz, 2H), 1.50-1.42 (m, 2H), 1.36-1.24 (m, 6H), 0.86 (t, J = 6.7 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 205.0, 136.5, 132.4, 129.4, 126.7, 95.2, 94.5, 31.9, 29.9, 29.3, 29.1, 22.8, 21.4, 14.3. HRMS calculated requires (M+H)+: 215.1794. Found m/z: 215.1785.

(44) 1-[1-(4-Methylphenyl)non-2-yn-1-yl]pyrrolidine

Under an atmosphere of argon, p-tolualdehyde (180 µL, 1.5 mmol), pyrrolidine (92 µL, 1.1 mmol), n-octyne (148 µL, 1.0 mmol), CuI (38 mg, 20 mol %), Na₂SO₄ (285 mg, 2.0 mmol) were stirred at 110 °C for 12 hours to afford the title compound as a dark yellow oil in 54% yield (0.153 g, 0.54 mmol) after column
chromatography on silica gel (20% ether in hexanes). IR (film) 2957, 2928, 2872, 2858, 2808, 1511, 1458, 1345, 1300, 1267, 1135, 1108, 1022, 822, 766, 724, 676 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) $\delta$ 7.41 (d, $J$=8.0 Hz, 2ArH), 7.13 (d, $J$ = 8.0 Hz, 2ArH), 4.56 (s, 1H), 2.59 (bs, 4H), 2.34 (s, 3H), 2.27 (td, $J$ = 1.9 Hz, 6.9 Hz, 2H), 1.76 (bs, 4H), 1.59-1.51 (m, 2H), 1.47-1.40 (m, 2H), 1.36-1.25 (m, 4H), 0.90 (t, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) $\delta$ 137.5, 137.1, 129.0, 128.3, 87.0, 58.8, 50.4, 31.6, 29.2, 28.8, 23.7, 22.8, 21.3, 19.0, 14.3. HRMS calculated requires M$^+$:[-H]: 282.2216. Found m/z: 282.2202.

(45) (IE)-1-(4-Fluorophenyl)non-1-en-3-one

Under an atmosphere of argon, 4-fluorobenzaldehyde (130 µL, 1.2 mmol), N-methylaniline (120 µL, 1.1 mmol), n-octyne (148 µL, 1.0 mmol), Cu(OTf)$_2$ (38 mg, 20 mol %), Na$_2$SO$_4$ (285 mg, 2.0 mmol) were stirred at 80 °C for 12 hours to afford the title compound as a yellow oil in 59% yield (0.138 g, 0.59 mmol) after column chromatography on silica gel (20% ether in hexanes). IR (film) 2956, 2928, 2857, 1688, 1654, 1614, 1599, 1508, 1467, 1414, 1368, 1326, 1231, 1175, 1158, 1072, 979, 909, 824, 782, 730, 694 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) $\delta$ 7.54-7.49 (m, 2ArH), 7.49 (d, $J$ = 19.3 Hz, 1H), 7.09-7.03 (m, 2ArH), 6.65 (d, $J$ = 16.1 Hz, 1H), 2.62 (t, $J$ = 7.4 Hz, 2H), 1.69-1.61 (m, 2H), 1.35-1.24 (m, 6H), 0.87 (t, $J$ = 6.8 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) $\delta$ 200.6, 165.4, 162.9, 141.1,

HRMS calculated requires (M+H)+: 235.1493. Found m/z: 235.1496.
6.4 General Procedural and Reagent Information Chapter 4

All reactions were set up on the benchtop in test tubes equipped with magnetic stir bars and closed with screw caps. Column chromatography was performed using SiO$_2$ purchased from Silicycle. Copper(II) trifluoromethanesulfonate, Cu(OTf)$_2$, was purchased from Alfa Aesar and used as supplied. Anilines were purchased from: Acros Organics, Alfa Aesar, or Aldrich and used as supplied. 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 Procedure**

**A:** To a test tube equipped with a magnetic stir bar was added 5 mol % Cu(OTf)$_2$, aniline (1.0 equiv.), aldehyde (1.2 equiv.), and alkyne (1.2 equiv.), and the reaction was stirred at 100 °C for the indicated time. Upon completion (as judged by GC), the mixture was cooled to room temperature and loaded directly atop a wet-packed silica gel column. Chromatography with diethyl ether (Et$_2$O) or ethyl acetate (EtOAc) in hexanes as eluent afforded the desired product.

**B:** To a test tube equipped with a magnetic stir bar was added 5 mol % Cu(OTf)$_2$, CHCl$_3$ or toluene (1 mL or 1.0 M solution), aniline (1.0 equiv.), aldehyde (1.2 equiv.), and alkyne (1.2 equiv.), and the reaction was stirred at 80 °C for the
indicated time. Upon completion (as judged by GC), the mixture was cooled to room temperature and loaded directly atop a wet-packed silica gel column. Chromatography with diethyl ether (Et$_2$O) or ethyl acetate (EtOAc) in hexanes as eluent afforded the desired product.

46) 6-Methoxy, 2-(4-Fluorophenyl)-4-n-hexylquinoline

Prepared according to general procedure B: $p$-Anisidine (124 mg, 1.0 mmol), 4-fluorobenzaldehyde (127 µL, 1.2 mmol), $n$-octyne (177 µL, 1.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %), CHCl$_3$ (1.0 mL) were stirred at 80 °C for 12h to afford the title compound as a yellow oil in 78% yield (0.232 g, 0.78 mmol) after column chromatography on silica gel (0-2-4% Et$_2$O in hexanes). IR (film) 3075, 2959, 2928, 2872, 2864, 1599, 1495, 1453, 1353, 1210, 1076, 879, 807, 752, 740, 730 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 8.12-8.05 (m, 3ArH), 7.59 (s, 1ArH), 7.36 (dd, $J = 4.0$, 8.0 Hz, 1ArH), 7.24-7.22 (m, 1ArH), 7.20-7.14 (m, 2ArH), 3.93 (s, 3H), 3.02 (t, $J = 8.0$ Hz, 2H), 1.83-1.75 (m, 2H), 1.50-1.43 (m, 2H), 1.40-1.29 (m, 4H), 0.90 (t, $J = 4.0$ Hz). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 164.9, 162.5, 157.7, 153.8, 148.2, 144.5, 136.3, 132.0, 129.3, 127.5, 121.6, 118.6, 115.9, 115.7, 102.1, 55.7, 32.9, 31.9, 29.8, 29.6, 22.8, 14.3. HRMS calculated requires M$^{+}$-[H]: 336.1758. Found m/z: 336.1756.
47) 2,4-Diphenylquinoline

Prepared according to general procedure B: Aniline (92 µL, 1.0 mmol), benzaldehyde (122 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %), CHCl$_3$ (1.0 mL) were stirred at 80 °C for 12h to afford the title compound as a pale yellow solid in 87% yield (0.245 g, 0.87 mmol) after column chromatography on silica gel (0-2-4% Et$_2$O in hexanes). IR (film) 3055, 3028, 2920, 1589, 1488, 1444, 1405, 1356, 1072, 1027, 891, 767, 759, 693 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) $\delta$ 8.24 (d, J=8.0 Hz, 1ArH), 8.18 (d, J=8.0 Hz, 2ArH), 7.88 (d, J=12.0 Hz, 1ArH), 7.79 (s, 1ArH), 7.71-7.67 (m, 1ArH), 7.53-7.46 (m, 7ArH), 7.44-7.41 (m, 2ArH). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) $\delta$ 156.7, 149.1, 148.8, 139.6, 138.3, 130.1, 129.5, 129.4, 129.3, 128.8, 128.3, 127.5, 126.3, 125.7, 125.6, 119.3. HRMS calculated requires [M]$^+$: 282.1277. Found m/z: 282.1287.

48) 6-Methoxy-2,4-diphenylquinoline

Prepared according to general procedure B: $p$-anisidine (124 mg, 1.0 mmol), benzaldehyde (122 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %), CHCl$_3$ (1.0 mL) were stirred at 80 °C for 12h to afford the title compound as a yellow oil in 78% yield (0.290 g, 0.93 mmol) after column chromatography on silica gel (0-1% Et$_2$O in hexanes). IR (film) 3059, 2927, 2852,
49) 6-methoxy-2-(4-methylphenyl)-4-phenylquinoline

Prepared according to general procedure B: \( p \)-anisidine (124 mg, 1.0 mmol), \( p \)-tolualdehyde (130 \( \mu \)L, 1.1 mmol), phenylacetylene (165 \( \mu \)L, 1.5 mmol), Cu(OTf)\(_2\) (18 mg, 5 mol %), CHCl\(_3\) (1.0 mL) were stirred at 80 °C for 6h to afford the title compound as a yellow solid in 89% yield (0.289 g, 0.89 mmol) after column chromatography on silica gel (2-5-10% Et\(_2\)O in hexanes). IR (film) 3053, 3029, 2963, 2921, 2835, 1619, 1590, 1545, 1512, 1489, 1471, 1357, 1267, 1225, 1183, 1113, 1029, 845, 833, 824, 780, 768, 701, 658 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\), 25°C) \( \delta \) 8.12 (d, J = 9.2 Hz, 1ArH), 8.05 (d, J = 8.2 Hz, 2ArH), 7.74 (s, 1ArH), 7.57-7.45 (m, 5ArH), 7.37 (dd, J = 2.8 Hz, 9.2 Hz, 1ArH), 7.29 (d, J = 8.0 Hz, 2ArH), 7.15 (d, J = 2.8 Hz, 1ArH), 3.76 (s, 3H), 2.40 (s, 3H). \(^{13}\)C NMR (100 MHz, CDCl\(_3\), 25°C) \( \delta \) 157.6, 154.6, 147.6, 144.9, 138.9, 138.8, 136.9, 131.5, 129.7, 129.5, 129.3, 129.2, 128.7, 128.3, 127.5, 127.1, 126.5, 121.7,
119.5, 103.7, 55.4, 21.3. HRMS calculated requires [M+Na⁺]: 348.1359. Found m/z: 348.1365.

50) 2-(4-fluorophenyl)-6-methoxy-4-phenylquinoline

Prepared according to general procedure B: p-anisidine (124 mg, 1.0 mmol), 4-fluorobenzaldehyde (118 µL, 1.1 mmol), phenylacetylene (165 µL, 1.5 mmol), Cu(OTf)₂ (18 mg, 5 mol %), CHCl₃ (1.0 mL) were stirred at 100 °C for 4h to afford the title compound as a yellow solid in 93% yield (0.305 g, 0.93 mmol) after column chromatography on silica gel (5-25% Et₂O in hexanes). IR (film) 3058, 2932, 2833, 1621, 1600, 1590, 1549, 1507, 1490, 1356, 1266, 1219, 1155, 1030, 1014, 831, 786, 764, 700 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.15-8.11 (m, 2ArH), 8.10 (s, 1ArH), 7.70 (s, 1ArH), 7.56-7.52 (m, 5ArH), 7.38 (d, J = 2.8 Hz, 9.2 Hz, 1ArH), 7.23-7.14 (m, 3ArH), 3.77 (s, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 165.0, 162.6, 158.0, 153.7, 148.2, 145.0, 143.7, 138.9, 136.1, 133.1, 131.7, 130.6, 130.5, 129.6, 129.3, 128.9, 128.9, 128.8, 128.6, 126.8, 122.2, 119.5, 116.0, 115.8, 103.9, 55.7. HRMS calculated requires (M+NH₄)+[-H]: 346.1476. Found m/z: 346.1468.
51) 6-Methoxy-4-phenyl-2-[4-(trifluoromethyl)phenyl]quinoline

Prepared according to general procedure B: p-anisidine (124 mg, 1.0 mmol), 4-(trifluoromethyl)benzaldehyde (151 µL, 1.1 mmol), phenylacetylene (165 µL, 1.5 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %), CHCl$_3$ (1.0 mL) were stirred at 100 °C for 4h to afford the title compound as a yellow solid in 97% yield (0.367 g, 0.97 mmol) after column chromatography on silica gel (0-1-3-5% Et$_2$O in hexanes). IR (film) 3059, 3009, 2935, 2839, 1615, 1492, 1473, 1421, 1321, 1267, 1225, 1156, 1108, 1067, 1029, 1016, 843, 831, 825, 777, 708, 687, 658 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 8.26 (d, J = 8.2 Hz, 2ArH), 8.13 (d, J = 9.2 Hz, 1ArH), 7.75-7.72 (m, 3ArH), 7.56-7.55 (m, 4ArH), 7.40 (dd, J = 2.7 Hz, 9.2 Hz, 2ArH), 7.19 (d, J = 2.7 Hz, 1ArH), 3.78 (s, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 158.2, 154.8, 148.1, 144.9, 143.0, 138.5, 131.8, 129.3, 128.8, 128.5, 127.5, 127.1, 125.7, 122.3, 119.4, 55.0. HRMS calculated requires [M]+: 380.3823. Found m/z: 380.3819.

52) 2-(2-methoxyphenyl)-4-phenylquinoline

Prepared according to general procedure B: p-Anisidine (124 mg, 1.0 mmol), o-anisaldehyde (150 mg, 1.1 mmol), phenylacetylene (165 µL, 1.5 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %), and CHCl$_3$ (1 mL) were stirred at 100 °C for 4h to afford the title compound as a yellow solid in 59% yield.
(0.202 g, 0.59 mmol) after column chromatography on silica gel (20% Et₂O in hexanes). IR (film) 3060, 2930, 2833, 1621, 1590, 1509, 1489, 1462, 1432, 1357, 1266, 1226, 1023, 822, 755, 706 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.15 (d, J=9.3 Hz, 1ArH), 7.85 (dd, J = 1.7 Hz, 7.6 Hz, 1ArH), 7.79 (s, 1ArH), 7.59-7.35 (m, 7ArH), 7.22 (d, J = 2.7 Hz, 1ArH), 7.12 (t, J = 7.8 Hz, 1ArH), 7.01 (d, J = 8.3 Hz, 1ArH), 3.83 (s, 3H), 3.79(s, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 157.7, 157.1, 154.3, 146.1, 144.9, 138.9, 131.5, 131.4, 130.1, 129.7, 129.5, 128.6, 128.1, 126.4, 123.9, 121.3, 121.2, 111.4, 103.7, 55.7, 55.4. HRMS calculated requires [M+H]+: 342.4104. Found m/z: 342.1936.

53) 6-Methyl-2,4-diphenylquinoline

Prepared according to general procedure A:  p-toluidine (108 mg, 1.0 mmol), benzaldehyde (122 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)₂ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a yellow solid in 86% yield (0.254 g, 0.86 mmol) after column chromatography on silica gel (0-2-4% Et₂O in hexanes). IR (film) 3054, 2915, 2852, 1588, 1544, 1488, 1449, 1358, 1079, 1028, 877, 826, 787, 756, 699 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.23-8.17 (m, 3ArH), 7.77 (s, 1ArH), 7.64 (bs, 1ArH), 7.59-7.43 (m, 9ArH), 2.47 (s, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 156.1, 138.7, 136.7, 132.3, 129.7,
129.6, 129.1, 128.8, 128.6, 127.9, 126.0, 124.6, 119.7, 22.1. HRMS calculated requires [M]+: 296.1434. Found m/z: 296.1429.

54) 6-Fluoro-2,4-diphenylquinoline

Prepared according to general procedure A: 4-
Fluoroaniline (95 µL, 1.0 mmol), benzaldehyde (112 µL, 1.1 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %) were stirred at 90 °C for 4h to afford the title compound as a yellow solid in 52% yield (0.156 g, 0.52 mmol) after column chromatography on silica gel (0-2-4% Et$_2$O in hexanes). IR (film) 3053, 2998, 2923, 2852, 1619, 1591, 1549, 1489, 1462, 1356, 1229, 1188, 1178, 1029, 918, 891, 871, 824, 775, 752, 709, 695 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 8.30-8.26 (m, 1 ArH), 8.17 (d, J = 7.6 Hz, 2ArH), 7.83 (s, 1ArH), 7.58-7.44 (m, 10ArH). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 162.1, 159.6, 156.4, 149.2, 145.8, 139.3, 138.1, 132.6, 132.5, 129.8, 129.6, 129.1, 129.0, 128.9, 127.8, 126.8, 126.7, 120.2, 119.9, 109.4, 109.2. HRMS calculated requires [M]+: 298.1027. Found m/z: 298.1012.

55) 7-(Methylsulfanyl)-2,4-diphenylquinoline

Prepared according to general procedure A: 3-
(methylthio)aniline (124 µL, 1.0 mmol), benzaldehyde (122 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %) were stirred at 100
°C for 4h to afford the title compound as a yellow solid in 64% yield (0.209 g, 0.64 mmol) after column chromatography on silica gel (0-2-4-6% Et₂O in hexanes). IR (film) 3056, 3030, 2918, 1733, 1603, 1584, 1571, 1484, 1420, 1356, 1072, 820, 763, 691 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.17-8.15 (m, 2ArH), 7.98 (bs, 1ArH), 7.76 (d, J=8.0 Hz, 1ArH), 7.72 (s, 1ArH), 7.54-7.44 (m, 8ArH), 7.32 (dd, J=4.0 Hz, 8.0 Hz, 1ArH), 2.64 (s, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 157.5, 149.6, 149.4, 141.9, 139.6, 138.4, 129.7, 129.1, 128.9, 128.7, 126.0, 125.8, 123.5, 118.8, 15.3. HRMS calculated requires [M]+: 327.1076. Found m/z: 327.1084.

56) 6-(Methylsulfanyl)-2,4-diphenylquinoline

Prepared according to general procedure A: 4-((Methylthio)aniline (125 µL, 1.0 mmol), benzaldehyde (112 µL, 1.1 mmol), phenylacetylene (165 µL, 1.5 mmol), Cu(OTf)₂ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a yellow solid in 54% yield (0.175 g, 0.54 mmol) after column chromatography on silica gel (0-2% Et₂O in hexanes). IR (film) 3056, 3030, 2918, 2851, 1601, 1582, 1541, 1479, 1446, 1386, 1356, 1156, 1074, 1074, 1055, 1026, 888, 829, 786, 774, 761, 704, 693, 680, 658 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.18-8.11 (m, 3ArH), 7.78 (s, 1ArH), 7.66 (s, 1ArH), 7.60 (d, J=9.2 Hz, 1ArH), 7.55-7.48 (m, 7ArH), 7.47-7.42 (m, 1ArH), 2.45 (s, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 156.0, 147.8, 147.1, 139.5, 138.2, 137.1, 130.4, 129.5,
129.3, 128.9, 128.8, 128.7, 128.5, 127.4, 126.1, 121.0, 119.8, 15.8. HRMS calculated requires [M]+: 328.1154. Found \( m/z \): 328.1167.

57) 2,4-Diphenyl-6-(trifluoromethyl)quinoline

Prepared according to general procedure A: 4-(Trifluoromethyl)aniline (126 µL, 1.0 mmol), benzaldehyde (112 µL, 1.1 mmol), phenylacetylene (165 µL, 1.5 mmol), Cu(OTf)\(_2\) (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a pale yellow solid in 52% yield (0.181 g, 0.52 mmol) after column chromatography on silica gel (0-2% Et\(_2\)O in hexanes). IR (film) 3062, 3031, 2922, 2852, 1627, 1591, 1549, 1467, 1309, 1164, 1153, 1112, 1060, 907, 892, 833, 788, 761, 702, 695, 676, 666 cm\(^{-1}\). \(^1\)H NMR (400 MHz, CDCl\(_3\), 25°C) \( \delta \) 8.32 (d, \( J = 8.8 \) Hz, 1ArH), 8.21-8.20 (m, 3ArH), 7.95-7.87 (m, 1ArH), 7.90 (s, 1ArH), 7.60-7.40 (m, 8ArH). \(^13\)C NMR (100 MHz, CDCl\(_3\), 25°C) \( \delta \) 158.8, 150.1, 149.9, 138.9, 137.4, 131.3, 130.0, 129.5, 129.0, 128.5, 128.4, 128.2, 128.0, 127.8, 127.7, 125.2, 124.9, 123.7, 122.8, 120.3. HRMS calculated requires [M]+: 350.1151. Found \( m/z \): 350.1165.
58) 2,4,6-Triphenylquinoline

Prepared according to general procedure B: 4-aminobiphenyl (170 mg, 1.0 mmol), benzaldehyde (122 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %), CHCl$_3$ (1.0 mL) were stirred at 80 °C for 12h to afford the title compound as a pale yellow solid in 70% yield (0.250 g, 0.70 mmol) after column chromatography on silica gel (0-2% Et$_2$O in hexanes). IR (film) 3029, 1738, 1716, 1589, 1543, 1484, 1444, 1356, 848, 772, 759, 692, 664 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 8.36 (d, J = 8.8 Hz, 1ArH), 8.25-8.22 (m, 2ArH), 8.12 (d, J = 2.0 Hz, 1ArH), 8.02 (dd, J = 2.1, 8.8 Hz, 1ArH), 7.86 (s, 1ArH), 7.65-7.43 (m, 12ArH), 7.38-7.34 (m, 1ArH). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 157.0, 149.7, 148.3, 140.9, 139.6, 139.4, 138.6, 130.7, 129.8, 129.7, 129.6, 129.1, 129.0, 128.8, 127.8, 127.7, 126.2, 123.6, 120.0. HRMS calculated requires M$^+$-[H]: 356.1434. Found m/z: 356.1433.

59) 2,4,8-Triphenylquinoline

Prepared according to general procedure A: 2-aminobiphenyl (170 mg, 1.0 mmol), benzaldehyde (122 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a pale yellow solid in 65% yield (0.232 g, 0.65 mmol) after column chromatography on silica gel (0-1% Et$_2$O in hexanes). IR (film) 3059,
3024, 1554, 1485, 1443, 1356, 789, 759, 704, 697, 687, 657 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.18-8.15 (m, 2ArH), 7.90-7.85 (m, 4ArH), 7.78 (dd, J = 1.4, 7.1 Hz, 1ArH), 7.60-7.50 (m, 8ArH), 7.47-7.38 (m, 4ArH). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 155.5, 149.8, 146.1, 141.2, 140.0, 139.4, 139.0, 131.4, 129.8, 129.6, 128.9, 128.8, 127.9, 127.7, 118.8. HRMS calculated requires [M]+: 358.1590. Found m/z: 358.1605.

60) 2-(4-Fluorophenyl)-4,8-diphenylquinoline

Prepared according to general procedure B: 2-Aminobiphenyl (170 mg, 1.0 mmol), 4-fluorobenzaldehyde (118 µL, 1.1 mmol), phenylacetylene (165 µL, 1.5 mmol), Cu(OTf)₂ (18 mg, 5 mol %), and CHCl₃ (1 mL) were stirred at 100 °C for 24h to afford the title compound as a yellow solid in 67% yield (0.250 g, 0.67 mmol) after column chromatography on silica gel (1-3-5% Et₂O in hexanes). IR (film) 3432, 3055, 1740, 1600, 1591, 1553, 1506, 1487, 1440, 1407, 1355, 1220, 1155, 836, 769, 759, 696 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.15-8.10 (m, 2ArH), 7.86-7.81 (m, 3ArH), 7.78 (s, 1ArH), 7.74 (dd, J = 7.2 Hz, 1ArH), 7.54-7.38 (m, 10ArH), 7.32-7.29 (m, 1ArH), 7.23-7.20 (m, 1ArH), 7.17-7.13 (m, 1ArH), 7.10-7.05 (m, 1ArH), 6.76 (td, J = 7.6 Hz, 1ArH), 6.59 (d, J = 8.0 Hz, 1ArH). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 165.0, 163.1, 162.5, 160.7, 154.2, 149.5, 146.0, 144.6, 141.0, 139.8, 139.3, 138.7, 135.5, 135.1, 31.1, 130.4, 130.2, 129.5, 129.3, 129.2, 128.7, 128.6, 128.5, 128.4, 127.6, 127.3, 127.1,
126.1, 126.0, 125.3, 118.0, 117.3, 115.7, 115.5, 115.2, 110.7. HRMS calculated requires (M+Na)+: 398.1315. Found m/z: 398.1327.

61) 6,8-Diphenyl-2H-[1,3]dioxolo[4,5-g]quinoline

Prepared according to general procedure B: 5-aminobenzodioxole (138 mg, 1.0 mmol), benzaldehyde (122 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)₂ (18 mg, 5 mol %), CHCl₃ (1.0 mL) were stirred at 80 °C for 12h to afford the title compound as a pale yellow solid in 67% yield (0.220 g, 0.67 mmol) after column chromatography on silica gel (0-2-4% Et₂O in hexanes). IR (film) 2893, 1616, 1558, 1487, 1457, 1241, 1209, 1037, 937, 842, 763, 710, 688 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.15-8.13 (m, 2ArH), 7.66 (s, 1ArH), 7.55-7.41 (m, 9ArH), 7.14 (s, 1ArH), 6.08 (s, 2H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 154.8, 148.4, 138.8, 129.5, 129.0, 128.9, 128.7, 127.7, 123.0, 118.2, 106.1, 102.1, 101.3. HRMS calculated requires [M]+: 325.1097. Found m/z: 325.1102.

62) 8-Butyl-6-(4-fluorophenyl)-2H-[1,3]dioxolo[4,5-g]quinoline

Prepared according to general procedure B: 3,4-Methylenedioxyaniline(69 mg, 0.50 mmol), 4-fluorobenzaldehyde (65 µL, 0.60 mmol), n-hexyne (87 µL, 0.75 mmol), Cu(OTf)₂ (9 mg, 5 mol %), toluene
(250 µL) were stirred at 80 °C for 3h to afford the title compound as a pinkish-brown solid in 68% yield (0.110 g, 0.34 mmol) after column chromatography on silica gel (50-100% Et₂O in hexanes). IR (film) 2956, 2929, 2903, 2874, 2859, 1619, 1601, 1571, 1499, 1459, 1441, 1424, 1398, 1359, 1359, 1261, 1241, 1224, 1215, 1190, 1156, 1122, 1102, 1038, 1013, 946, 902, 857, 838, 811, 772, 653 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.10-8.06 (m, 2ArH), 7.50 (s, 1ArH), 7.43 (s, 1ArH), 7.27 (s, 1ArH), 7.19-7.15 (m, 2ArH), 6.10 (s, 2H), 2.98 (t, J = 10.0 Hz, 2H), 1.75 (m, J = , 2H), 1.48 (quint, J = 9.2 Hz, 2H), 0.99 (t, J = 10.0 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 164.7, 162.2, 154.0, 150.3, 148.1, 147.7, 146.8, 136.1, 129.0, 123.1, 117.0, 115.7, 115.5, 106.7, 101.6, 99.1, 32.8, 32.2, 22.9, 14.0. HRMS calculated requires [M+H]+: 324.1379. Found m/z: 324.1432.

63) 4-n-Butyl-2-(2-fluorophenyl)quinoline

Prepared according to general procedure A: Aniline (92 µL, 1.0 mmol), 2-fluorobenzaldehyde (127 µL, 1.2 mmol), n-hexyne (173 µL, 1.2 mmol), Cu(OTf)₂ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a yellowish-green solid in 89% yield (0.248 g, 0.89 mmol) after column chromatography on silica gel (0-2-4% Et₂O in hexanes). IR (film) 3075, 2959, 2928, 2872, 2864, 1599, 1495, 1453, 1353, 1210, 1076, 879, 807, 752, 740, 730 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.20 (d, J=8.3 Hz, 1 ArH), 8.09-8.03 (m, 2ArH), 7.72-7.69 (m, 2ArH), 7.57-7.53 (m, 1ArH), 7.43-7.38 (m,
1ArH), 7.32-7.28 (m, 1ArH), 7.21-7.16 (m, 1ArH), 3.11 (t, J=8.0 Hz, 2H), 1.77 (quintet, J=7.5 Hz, 2H), 1.48 (sextet, J=7.4 Hz, 2H), 0.98 (t, J=7.3 Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 162.2, 159.7, 153.9, 149.1, 148.6, 131.8, 130.9, 130.9, 130.6, 129.4, 128.3, 126.8, 126.5, 124.9, 123.7, 122.4, 122.3, 116.5, 116.3, 32.5, 32.3, 23.0, 14.2. HRMS calculated requires M$^+$-[H]: 278.1340. Found $m/z$: 278.1343.

64) 4-(3-Methylbutyl)-2-(4-methylphenyl)quinoline

Prepared according to general procedure A: Aniline (92 µL, 1.0 mmol), $p$-tolualdehyde (142 µL, 1.2 mmol), 5-methyl-1-hexyne (160 µL, 1.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a yellow oil in 72% yield (0.208 g, 0.72 mmol) after column chromatography on silica gel (2.5% Et$_2$O in hexanes). IR (film) 2931, 2866, 1738, 1598, 1551, 1505, 1430, 1365, 1348, 818, 740, 715, 676 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ  8.21 (d, J = 8.0 Hz, 1 ArH), 8.08 (d, J = 8.0 Hz, 2ArH), 8.01 (d, J = 8.0 Hz, 1ArH), 7.71-7.67 (m, 2ArH), 7.53-7.49 (m, 1ArH), 7.33 (d, J = 7.6 Hz, 2ArH), 3.09 (t, J = 16 Hz, 2H), 2.43 (s, 3H), 1.79-1.66 (m, 3H), 1.04 (d, J = 6.0 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 157.2, 149.7, 148.7, 139.5, 137.3, 130.6, 129.8, 129.4, 128.5, 127.7, 126.7, 126.0, 123.6, 118.7, 39.7, 30.7, 28.6, 22.8, 21.6. HRMS calculated requires M$^+$-[H]: 288.1747. Found $m/z$: 288.1756.
65) 4-[2-(4-Methylphenyl)-4-quinolinyl]butanenitrile

Prepared according to general procedure A: Aniline (92 µL, 1.0 mmol), p-tolualdehyde (142 µL, 1.2 mmol), 5-cyano-1-pentyne (126 µL, 1.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %) were stirred at 100 °C for 24h to afford the title compound as a pale yellow solid in 69% yield (0.196 g, 0.69 mmol) after column chromatography on silica gel (0-10-20% Et$_2$O in hexanes). IR (film) 3028, 2923, 2246, 1715, 1661, 1598, 1549, 1506, 1423, 1351, 1182, 1102, 980, 821, 761, 722 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 8.26 (d, J = 8.0 Hz, 1 ArH), 8.06 (d, J = 8.4 Hz, 2ArH), 7.98 (d, J = 8.8 Hz, 1ArH), 7.75-7.71 (m, 1ArH), 7.71 (s, 1ArH), 7.57-7.53 (m, 1ArH), 7.33 (d, J = 8.0 Hz, 2ArH), 3.30 (t, J = 8.0 Hz, 2H), 2.48-2.42 (m, 5H), 2.17 (quintet, J = 7.2 Hz, 2H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 157.1, 140.1, 130.5, 130.0, 129.9, 128.6, 127.8, 126.7, 126.1, 123.1, 119.3, 119.2, 31.3, 25.9, 21.6, 17.2. HRMS calculated requires [M+Na]$^+$: 309.1362. Found m/z: 309.1373.

66) 4-Benzyl-2-(2-naphthalenyl)quinoline

Prepared according to general procedure A: Aniline (92 µL, 1.0 mmol), 2-naphthaldehyde (188 µL, 1.2 mmol), 3-phenyl-1-propyne (150 µL, 1.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %) were stirred at 100 °C for 24h to afford the title compound as a pale yellow solid in 67% yield (0.231 g, 0.67 mmol) after column
chromatography on silica gel (0-2% Et₂O in hexanes). IR (film) 3055, 3022, 1595, 1553, 1492, 939, 863, 834, 815, 749, 741, 719, 696, 663 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.61 (s, 1ArH), 8.43-8.41 (m, 1ArH), 8.29 (dd, J = 1.6, 8.6 Hz, 1ArH), 8.04 (d, J = 8.3, 1ArH), 7.99-7.96 (m, 2ArH), 7.88-7.86 (m, 1ArH), 7.81 (s, 1ArH), 7.75 (t, J = 5.8, 1ArH), 7.54-7.49 (m, 3ArH), 7.34-7.31 (m, 2ArH), 7.26-7.24 (m, 3ArH), 4.54 (s, 2H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 156.8, 138.7, 134.2, 133.6, 130.2, 129.8, 129.2, 129.1, 128.9, 127.9, 127.2, 127.0, 126.9, 126.6, 125.2, 124.1, 120.5, 38.9. HRMS calculated requires [M]+: 345.1512. Found m/z: 345.1501.

67) 2,4-Bis(2-fluorophenyl)quinoline

Prepared according to general procedure A: Aniline (92 µL, 1.0 mmol), 2-fluorobenzaldehyde (127 µL, 1.2 mmol), 2-fluorophenylacetylene (136 µL, 1.2 mmol), Cu(OTf)₂ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a greenish crystalline solid in 71% yield (0.225 g, 0.71 mmol) after column chromatography on silica gel (2-4-6-8-10% Et₂O in hexanes). IR (film) 3341, 3218, 3056, 2926, 1615, 1594, 1582, 1486, 1453, 1408, 1359, 1214, 1104, 805, 798, 753, 682 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.27 (d, J=8.4 Hz, 1 ArH), 8.15 (td, J=1.7,7.8 Hz, 1ArH), 7.87 (d, J=2.5 Hz, 1ArH), 7.77-7.70 (m, 2ArH), 7.53-7.39 (m, 4ArH), 7.34-7.16 (m, 4ArH). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 162.2, 161.2, 159.7, 158.7, 153.7, 148.7, 143.1,
132.0, 131.8, 131.2, 130.7, 130.3, 129.9, 127.1, 125.8, 125.0, 124.6, 124.6, 116.6, 116.4, 116.1. HRMS calculated requires M*: 317.1011. Found m/z: 317.1017.

68) 6-Methoxy-4-phenylquinoline

Prepared according to general procedure A: p-Anisidine (124 mg, 1.0 mmol), 37% formaldehyde solution in water (150 µL), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)₂ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a dark yellow oil in 35% yield (0.083 g, 0.35 mmol) after column chromatography on silica gel (0-20% Et₂O in hexanes). IR (film) 3058, 3028, 2932, 2831, 1617, 1507, 1492, 1256, 1227, 1029, 852, 828, 761, 728, 700 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.77 (d, J = 4.4 Hz, 1 ArH), 8.09 (d, J = 9.2 Hz, 1ArH), 7.54-7.45 (m, 5ArH), 7.37 (dd, J = 2.8, 9.2 Hz, 1ArH), 7.28 (d, J = 4.5 Hz, 1ArH), 7.18 (d, J = 2.8 Hz, 1ArH), 3.76 (s, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 158.2, 147.7, 147.3, 144.6, 138.4, 131.2, 129.5, 128.9, 128.6, 128.0, 122.2, 122.9, 103.9, 55.6. HRMS calculated requires [M]+: 236.1070. Found m/z: 236.1077.
69) 6-Methoxy-2-[3-(6-methoxy-4-phenylquinolin-2-yl)phenyl]-4-phenylquinoline

Prepared according to general procedure B:  
- Anisidine (271 mg, 2.2 mmol), isophthalaldehyde (135 mg, 1.0 mmol), phenylacetylene (242 µL, 2.2 mmol), Cu(OTf)₂ (36 mg, 10 mol %), CHCl₃ (1.0 mL) were stirred at 80 °C for 12h to afford the title compound as a white solid in 43% yield (0.217 g, 0.43 mmol) after column chromatography on silica gel (0-10-25-50% Et₂O in hexanes). IR (film) 3045, 1619, 1588, 1551, 1491, 1474, 1404, 1349, 1224, 1109, 1068, 1026, 833, 794, 775, 766, 714, 707, 696 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.90 (s, 1ArH), 8.28 (dd, J = 1.5, 7.5 Hz, 2ArH), 8.19 (d, J = 9.6 Hz, 2ArH), 7.91 (s, 2ArH), 7.70-7.50 (m, 10ArH), 7.41 (dd, J = 3.0, 8.7 Hz, 2ArH), 7.20 (d, J = 2.7 Hz, 2ArH), 3.81 (s, 6H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 157.8, 154.5, 147.9, 144.9, 140.3, 138.7, 131.7, 129.4, 128.7, 128.3, 126.8, 126.1, 121.8, 119.7, 55.4. HRMS calculated requires [M+Na]+: 567.2043. Found m/z: 567.2053.

70) 2-Cyclohexyl-6-methoxy-4-n-hexylquinoline

Prepared according to general procedure A:  
- Anisidine (124 mg, 1.0 mmol), cyclohexancarboxaldehyde (146 µL, 1.2 mmol), n-octyne (178 µL, 1.2 mmol), Cu(OTf)₂ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the
title compound as a clear oil in 69% yield (0.225 g, 0.69 mmol) after column chromatography on silica gel (0-2-4% Et₂O in hexanes). IR (film) 2924, 2851, 1620, 1593, 1491, 1450, 1445, 1263, 1222, 1034, 907, 878, 832, 750, 731 cm⁻¹. 

¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.01 (d, J = 9.2 Hz, 1 ArH), 7.31 (dd, J = 2.8 Hz, 9.2 Hz, 1 ArH), 7.20 (d, J = 2.7 Hz, 1 ArH), 7.11 (s, 1 ArH), 3.91 (s, 3H), 2.96 (t, J = 7.7 Hz, 2H), 2.90-2.84 (m, 1H), 2.00-1.97 (m, 2H), 1.78-1.70 (m, 4H), 1.64-1.54 (m, 2H), 1.50-1.39 (m, 4H), 1.33-1.29 (m, 4H), 0.88 (t, J = 6.9 Hz, 3H). 

¹³C NMR (100 MHz, CDCl₃, 25°C) δ 164.0, 157.3, 130.9, 127.3, 121.1, 119.4, 102.3, 55.7, 47.2, 33.1, 32.7, 31.8, 29.7, 29.6, 26.8, 26.3, 22.8, 14.3. HRMS calculated requires M⁺+[H]: 324.2337. Found m/z: 324.2322.

71) 2-Cyclohexyl-6-methoxy-4-phenylquinoline

Prepared according to general procedure A: p-Anisidine (124 mg, 1.0 mmol), cyclohexane-carboxaldehyde (146 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)₂ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a yellow oil in 79% yield (0.250 g, 0.79 mmol) after column chromatography on silica gel (0-2-4-6-8-10% Et₂O in hexanes). IR (film) 2924, 2851, 1620, 1593, 1491, 1473, 1445, 1263, 1222, 1034, 907, 878, 832, 765, 730, 700 cm⁻¹. 

¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.02 (d, J = 9.2 Hz, 1 ArH), 7.51-7.44 (m, 5 ArH), 7.33 (dd, J = 2.8, 9.2 Hz, 1 ArH), 7.21 (s, 1 ArH), 7.15 (d, J = 2.7 Hz, 1 ArH), 3.75 (s, 3H), 2.91 (tt, J = 3.1,
11.8 Hz, 1H), 2.06-2.03 (m, 2H), 1.89-1.86 (m, 2H), 1.78-1.75 (m, 1H), 1.68-1.58 (m, 2H), 1.51-1.41 (m, 2H), 1.36-1.25 (m, 1H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 164.1, 157.5, 147.7, 144.4, 139.1, 131.0, 129.6, 128.8, 128.4, 126.5, 121.5, 120.3, 104.0, 55.6, 47.6, 33.2, 26.8, 26.4. HRMS calculated requires M$^*$+[H]: 316.1696. Found m/z: 316.1708.

72) 6-Methoxy-2-(pentan-3-yl)-4-phenylquinoline

Prepared according to general procedure A: p-Anisidine (124 mg, 1.0 mmol), 2-diethylbutyraldehyde (148 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a yellow oil in 77% yield (0.235 g, 0.77 mmol) after column chromatography on silica gel (0-2-4-6% Et$_2$O in hexanes). IR (film) 2960, 2930, 2873, 1621, 1491, 1263, 1224, 1033, 832, 731, 700 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 8.07 (d, J = 9.2 Hz, 1 ArH), 7.54-7.44 (m, 5ArH), 7.35 (dd, J = 2.8, 9.2 Hz, 1ArH), 7.18 (d, J = 2.6 Hz, 1ArH), 7.16 (s, 1ArH), 3.75 (s, 3H), 2.79 (qn, J = 7.2 Hz, 1H), 1.81 (qn, J = 7.4 Hz, 4H), 0.87 (t, J = 7.4 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 163.2, 157.5, 147.4, 144.6, 139.1, 129.6, 128.8, 128.4, 126.5, 121.3, 121.0, 104.1, 55.6, 52.2, 28.5, 12.5. HRMS calculated requires [M]+: 306.1852. Found m/z: 306.1853.
73) 2-(Butan-2-yl)-6-methoxy-4-phenylquinoline

Prepared according to general procedure A: p-Anisidine (124 mg, 1.0 mmol), 2-secbutyaldehyde (129 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)₂ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a yellow oil in 77% yield (0.224 g, 0.77 mmol) after column chromatography on silica gel (0-2-4-6% Et₂O in hexanes). IR (film) 2961, 2931, 2873, 1621, 1492, 1265, 1224, 1033, 907, 832, 729, 700 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.06 (d, J = 12.2 Hz, 1 ArH), 7.54-7.45 (m, 5ArH), 7.36 (dd, J = 3.8, 12.2 Hz, 1ArH), 7.20 (s, 1ArH), 7.18 (d, J = 3.7 Hz, 1ArH), 3.77 (s, 3H), 3.02 (sextet, J = 9.4 Hz, 1H), 1.88 (septet, J = 10.0 Hz, 1H), 1.73 (septet, J = 9.8 Hz, 1H), 1.39 (d, J = 9.3 Hz, 3H), 0.93 (t, J = 9.8 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 164.3, 157.5, 147.4, 144.4, 139.0, 131.0, 129.6, 128.8, 128.4, 126.5, 121.5, 120.4, 104.1, 55.6, 44.6, 30.3, 20.7, 12.5. HRMS calculated requires [M]+: 292.1696. Found m/z: 292.1703.

74) 2-Tert-butyl-6-methoxy-4-phenylquinoline

Prepared according to general procedure A: p-Anisidine (124 mg, 1.0 mmol), pivaldehyde (131 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)₂ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a yellow oil in 85% yield (0.246 g, 0.85 mmol) after column chromatography on
75) 2-Cyclohexyl-6-fluoro-4-phenylquinoline

Prepared according to general procedure A: 4-Fluoroaniline (95 µL, 1.0 mmol), cyclohexane-carboxaldehyde (146 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)₂ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a pale yellow solid in 81% yield (0.247 g, 0.81 mmol) after column chromatography on silica gel (0-2% Et₂O in hexanes). IR (film) 3066, 3027, 2949, 1623, 1596, 1557, 1513, 1489, 1467, 1445, 1383, 1296, 128.9, 128.7, 125.9, 121.2, 119.0, 103.8, 55.6, 38.1, 30.5, 30.4. HRMS calculated requires [M]+: 292.1696. Found m/z: 292.1709.

76) 6-Methyl-2-(3-pentanyl)-4-phenylquinoline

Prepared according to general procedure A: p-Toluidine (108 mg, 1.0 mmol), 2-ethylbutyraldehyde (148 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a yellow solid in 67% yield (0.194 g, 0.67 mmol) after column chromatography on silica gel (0-1.5% Et$_2$O in hexanes). IR (film) 3055, 2959, 2928, 2872, 1592,1557, 1489, 1449, 1030, 879, 832, 764, 703, cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 8.06 (d, J = 8.6 Hz, 1 ArH), 7.62 (m, 1ArH), 7.55-7.46 (m, 6ArH), 7.16 (s, 1ArH), 2.82 (quintet, J = 7.2 Hz, 1H), 2.44 (s, 3H), 1.81 (quintet, J = 7.4 Hz, 4H), 0.86 (t, J = 7.4 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 164.6, 148.1, 146.9, 138.9, 135.8, 131.5, 129.8, 129.3, 128.7, 128.4, 125.7, 124.6, 120.6, 52.3, 28.5, 29.9, 12.5. HRMS calculated requires M$^+$+[H]: 288.1747. Found m/z: 288.1760.
77) **6-Methylthio-2-(3-pentanyl)-4-phenylquinoline**

Prepared according to general procedure A: 4-Methylthio aniline (125 µL, 1.0 mmol), 2-diethylbutyraldehyde (148 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a yellow solid in 63% yield (0.201 g, 0.63 mmol) after column chromatography on silica gel (0-2% Et$_2$O in hexanes).

IR (film) 3057, 2959, 2922, 2872, 1737, 1587, 1552, 1481, 1455, 1376, 1240, 1074, 85, 826, 700 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) δ 8.06 (d, J = 8.8 Hz, 1 ArH), 7.67 (d, J = 2.0 Hz, 1ArH), 7.58 (dd, J = 2.1, 8.8 Hz, 1ArH), 7.54-7.44 (m, 5ArH), 7.18 (s, 1ArH), 2.81 (quintet, J = 7.2 Hz, 1H), 2.43 (s, 3H), 1.80 (quintet, J = 7.4 Hz, 4H), 0.85 (t, J = 7.4 Hz, 6H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) δ 164.9, 147.6, 146.6, 138.5, 136.4, 129.9, 129.7, 129.0, 128.8, 128.6, 121.8, 121.2, 52.2, 28.4, 16.2, 12.5. HRMS calculated requires M$^+$$-$$\text{H}$: 320.1467. Found m/z: 320.1465.

78) **N-[2-(3-Pentanyl)-4-phenyl-6-quinolinyl]acetamide**

Prepared according to general procedure A: 4-Aminoacetanilide (151 mg, 1.0 mmol), diethylbutyraldehyde (148 µL, 1.2 mmol), phenylacetylene (132 µL, 1.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a white
solid in 82% yield (0.271 g, 0.82 mmol) after column chromatography on silica gel (10-20-30-40-50% Et₂OAc in hexanes). IR (film) 3283, 3062, 2960, 2929, 2873, 1737,1695, 1655, 1621, 1604, 1552, 1516, 1459, 1403, 1369, 1310, 1290, 1276, 888, 821, 699 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 8.13-8.11 (m, 2ArH), 7.98 (bs, 1NH), 7.86 (dd, J = 1.8, 9.1 Hz, 1ArH), 7.49-7.42 (m, 5ArH), 7.18 (s, 1ArH), 2.82 (quintet, J = 7.6 Hz, 1H), 2.14 (s, 3H), 1.84-1.73 (m, 4H), 0.83 (t, J = 7.4 Hz, 6H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 168.9, 164.5, 138.3, 136.0, 129.7, 128.8, 128.7, 126.1, 123.6, 120.9, 114.7, 52.0, 28.4, 24.7, 12.4. HRMS calculated requires M⁺-[H]: 331.1805. Found m/z: 331.1809.

79) 6-Methoxy-2-(2-methylpropyl)-3-(2-propanyl)quinoline

Prepared according to general procedure A: p-Anisidine (124 mg, 1.0 mmol), valeraldehyde (234 µL, 2.2 mmol), Cu(OTf)₂ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a yellow oil in 67% yield (0.173 g, 0.67 mmol) after column chromatography on silica gel (0-4-6-10% Et₂O in hexanes). IR (film) 2956, 2930, 2871, 1625, 1492, 1465, 1456, 1379, 1233, 1217, 1164, 1031, 913, 829, 731 cm⁻¹. ¹H NMR (400 MHz, CDCl₃, 25°C) δ 7.92 (d, J = 9.2 Hz, 1 ArH), 7.74 (s, 1ArH), 7.25 (dd, J = 2.8, 9.2 Hz, 1ArH), 6.98 (d, J = 2.8 Hz, 1ArH), 2.93 (t, J = 8.0 Hz, 2H), 2.73 (t, J = 7.5 Hz, 2H), 1.78-1.65 (m, 5H), 1.47 (sextet, J = 7.4 Hz, 2H), 1.02 (t, J = 7.3 Hz, 3H), 0.96 (t, J = 7.4 Hz, 3H). ¹³C NMR (100 MHz, CDCl₃, 25°C) δ 159.8, 157.4, 142.5, 134.3, 129.9,
128.2, 121.2, 105.0, 104.8, 55.7, 35.5, 34.6, 32.2, 23.8, 23.3, 14.3, 14.3. HRMS calculated requires $M^+ +$: 257.1774. Found $m/z$: 257.1764.

80) 2-Isobutyl-6-methoxy-3-isopropylquinoline

Prepared according to general procedure A: $p$-Anisidine (124 mg, 1.0 mmol), isovaleraldehyde (236 µL, 2.2 mmol), Cu(OTf)$_2$ (18 mg, 5 mol %) were stirred at 100 °C for 4h to afford the title compound as a yellow oil in 70% yield (0.180 g, 0.70 mmol) after column chromatography on silica gel (0-2-5% Et$_2$O in hexanes). IR (film) 2957, 2834, 1624, 1599, 1512, 1491, 1464, 1383, 1224, 1165, 1031, 829 cm$^{-1}$. $^1$H NMR (400 MHz, CDCl$_3$, 25°C) $\delta$ 7.94 (d, $J = 9.2$ Hz, 1 ArH), 7.86 (s, 1 ArH), 7.26 (dd, $J = 2.8$, 9.2 Hz, 1 ArH), 7.01 (d, $J = 2.8$ Hz, 1 ArH), 3.28 (septet, $J = 6.8$ Hz, 1H), 2.88 (d, $J = 7.4$ Hz, 2H), 2.26-2.16 (m, 1H), 1.30 (d, $J = 6.8$ Hz, 6H), 0.97 (d, $J = 6.6$ Hz, 6H), 0.96 (t, $J = 7.4$ Hz, 3H). $^{13}$C NMR (100 MHz, CDCl$_3$, 25°C) $\delta$ 158.1, 157.4, 141.3, 131.2, 129.8, 128.3, 121.4, 105.0, 104.9, 55.7, 43.9, 29.7, 29.0, 24.1, 22.8. HRMS calculated requires $M^+ +$: 257.1774. Found $m/z$: 257.1762.
6.5 General Procedural and Reagent Information Chapter 5

All solvents were obtained from a glass contour solvent system built by Pure Process Technology, LLC. p-Chloranil was purchased from Alfa Aesar, tert-butylidimethylsilyl chloride from Oakwood Chemical. Column chromatography was performed using SiO\textsubscript{2} purchased from Silicycle. Pyrrole, imidazole, and aldehydes were purchased from Acros Organics 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. Dipyrrromethane backbones were synthesized as in Lee, C. –H.; Lindsey, J. S. *Tetrahedron* 1994, 50, 11427-11440. First generation MacMillan catalyst was synthesized as in Ahrendt, K. A.; Borths, C. J.; MacMillan, D. W. C. *Journal of the American Chemical Society* 2000, 122, 4243-4244.

(3S)-3-[5-[(5-((1S)-3-Hydroxy-1-phenylpropyl)-1H-pyrrol-2-yl]-(4-methoxyphenylmethyl)-1H-pyrrol-2-yl]-3-phenylpropan-1-ol

First generation MacMillan catalyst (R)(67 mg, 0.2 mmols), *trans*-cinnamaldehyde (315 µL, 2.5 mmols), tetrahydrofuran (3.8 mL), and water(0.2 mL) were stirred at -50 °C for 5 minutes before adding 2-[(4-Methoxyphenyl)(1H-pyrrol-2-yl)methyl]-1-H-pyrrole in one portion. Reaction mixture was allowed to stir at -50 °C for five days while monitoring by TLC for
completion. Reaction mixture was warmed to room temperature and diluted with additional tetrahydrofuran (10 mL), and reduced with sodium borohydride (152 mg, 4.0 mmols), allowing to stir at room temperature for 30 minutes. Reaction mixture was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. Organic layers were washed with water and brine and dried over sodium sulfate. After filtering off sodium sulfate, organic layers were concentrated in vacuo to afford the title compound as a sticky golden solid in 89% yield (463 mg, 0.89 mmols) after column chromatography on silica gel (20-30-40-50% EtOAc in hexanes). IR (film) 3565, 3298, 2944, 1695, 1608, 1509, 1243, 1175, 1022, 765, 701 cm⁻¹. ¹H NMR (400 MHz, CD₃COCD₃, 25°C) δ 9.39 (s, 2H), 7.26-7.24 (m, 8ArH), 7.17-7.13 (m, 2ArH), 7.05 (d, J = 8.7 Hz, 2ArH), 6.77 (d, J = 8.4 Hz, 2ArH), 5.86-5.83 (m, 2H), 5.60 (t, J = 2.8 Hz, 2H), 5.23 (s, 1H), 4.14 (td, J = 3.0 Hz, 7.7 Hz, 2H), 3.70 (s, 3H), 3.57-3.47 (m, 4H), 2.33-2.24 (m, 2H), 2.12-2.04 (m, 2H). ¹³C NMR (100 MHz, CD₃COCD₃, 25°C) δ 158.4, 145.4, 136.0, 134.4, 134.4, 133.2, 133.2, 129.6, 128.4, 128.1, 126.2, 113.5, 106.7, 104.5, 104.4, 60.0, 54.9, 43.5, 41.1, 39.1. HRMS calculated requires (M+H)+[-H]: 520.2720. Found m/z: 520.2712.
100) (3R)-3-[5-[(5-[(1R)-3-Hydroxy-1-phenylpropyl]-1H-pyrrol-2-yl]-4-methoxyphenylmethyl]-1H-pyrrol-2-yl]-3-phenylpropan-1-ol

First generation MacMillan catalyst (S)(67 mg, 0.2 mmols), trans-cinnamaldehyde (315 µL, 2.5 mmols), tetrahydrofuran (3.8 mL), and water (0.2 mL) were stirred at -50 °C for 5 minutes before adding 2-[(4-Methoxyphenyl)(1H-pyrrol-2-yl)methyl]-1H-pyrrole in one portion. Reaction mixture was allowed to stir at -50 °C for five days while monitoring by TLC for completion. Reaction mixture was warmed to room temperature and diluted with additional tetrahydrofuran (10 mL), and reduced with sodium borohydride (152 mg, 4.0 mmols), allowing to stir at room temperature for 30 minutes. Reaction mixture was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. Organic layers were washed with water and brine and dried over sodium sulfate. After filtering off sodium sulfate, organic layers were concentrated in vacuo to afford the title compound as a sticky golden solid in 81% yield (420 mg, 0.81 mmols) after column chromatography on silica gel (20-30-40-50% EtOAc in hexanes). IR (film) 3565, 3276, 2944, 1709, 1608, 1509, 1242, 1175, 1022, 766, 707 cm⁻¹. ¹H NMR (400 MHz, CD₃COCD₃, 25°C) δ 9.39 (s, 2H), 7.26-7.25 (m, 8ArH), 7.18-7.13 (m, 2ArH), 7.06 (d, J = 8.4 Hz, 2ArH), 6.78 (d, J = 8.7 Hz, 2ArH), 5.87-5.84 (m, 2H), 5.60 (t, J = 2.8 Hz, 2H), 5.23 (s, 1H), 4.14 (td, J = 2.9 Hz, 7.6 Hz, 2H), 3.71 (s, 3H), 3.57-3.47 (m, 4H), 2.33-2.25
(m, 2H), 2.13-2.04 (m, 2H). $^{13}$C NMR (100 MHz, CD$_3$COCD$_3$, 25°C) $\delta$ 158.4, 145.4, 136.1, 134.5, 134.4, 133.2, 129.6, 128.4, 128.1, 126.2, 113.5, 106.7, 104.6, 104.5, 60.0, 54.9, 43.5, 41.1, 39.2. HRMS calculated requires M$^*$+-[H]: 519.2642. Found m/z: 519.2656.

101) 2-[(1S)-3-[(tert-butyldimethylsilyl)oxy]-1-phenylpropyl]-5-[(5-[(1S)-3-
[(tert-butyldimethylsilyl)oxy]-1-phenylpropyl]-1H-pyrrol-2-yl](4-
methoxyphenylmethyl)-1H-pyrrole

Compound 7a (420 mg, 0.81 mmols) dissolved in dichloromethane (4 mL) with imidazole (330 mg, 4.84 mmols) and stirred at room temperature for 30 minutes. Tert-butyldimethylsilyl chloride added and reaction mixture allowed to stir at room temperature for 16 hours while monitoring by TLC for completion. Reaction mixture was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. Organic layers were washed with water and brine and dried over sodium sulfate. After filtering off sodium sulfate, organic layers were concentrated in vacuo to afford the title compound as a bright orange liquid in 80% yield (487 mg, 0.65 mmols) after column chromatography on silica gel (0-2.5% EtOAc in hexanes). IR (film) 2955, 2929, 2857, 1690, 1605, 1579, 1510, 1250, 1100, 949, 832, 775, 699 cm$^{-1}$. $^1$H NMR (400 MHz, CD$_3$COCD$_3$, 25°C) $\delta$ 9.29 (s, 2H), 7.24-7.22 (m, 8ArH), 7.16-7.11 (m,
2ArH), 7.01 (d, J = 8.6 Hz, 2ArH), 6.75 (d, J = 8.6 Hz, 2ArH), 5.85-5.82 (m, 2H), 5.55 (q, J = 3.0 Hz, 2H), 5.19 (s, 1H), 4.14 (td, J = 2.9 Hz, 7.7 Hz, 2H), 3.71 (s, 3H), 3.64-3.62 (m, 2H), 3.57-3.51 (m, 2H), 2.31-2.23 (m, 2H), 2.09-2.01 (m, 2H), 0.95 (s, 18H), 0.07 (s, 12H). $^{13}$C NMR (100 MHz, CD$_3$COCD$_3$, 25°C) δ 158.4, 145.2, 133.2, 129.6, 128.3, 128.1, 126.1, 113.4, 106.7, 106.7, 104.6, 104.4, 60.9, 54.8, 43.4, 40.8, 39.0, 25.9, 25.8, 18.2, 18.1, -3.6, -5.6. HRMS calculated requires M*+: 750.4482. Found m/z: 750.4483.

102) 2-[(1R)-3-[(tert-butyldimethylsilyl)oxy]-1-phenylpropyl]-5-[(5-[(1R)-3-[(tert-butyldimethylsilyl)oxy]-1-phenylpropyl]-1H-pyrrol-2-yl](4-methoxyphenylmethyl)-1H-pyrrole

Compound 7b (460 mg, 0.88 mmols) dissolved in dichloromethane (4 mL) with imidazole (361 mg, 5.30 mmols) and stirred at room temperature for 30 minutes. Tert-butyldimethylsilyl chloride (1.60 g, 10.6 mmols) added and reaction mixture allowed to stir at room temperature for 16 hours while monitoring by TLC for completion. Reaction mixture was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. Organic layers were washed with water and brine and dried over sodium sulfate. After filtering off sodium sulfate, organic layers were concentrated in vacuo to afford the title compound as a bright orange liquid in 65% yield (423 mg, 0.57 mmols)
after column chromatography on silica gel (0-2.5% EtOAc in hexanes). IR (film) 2953, 2928, 2856, 1700, 1579, 1510, 1249, 1100, 939, 831, 773, 698 cm⁻¹.

1H NMR (400 MHz, CD3COCD3, 25°C) δ 9.33 (s, 2H), 7.25-7.23 (m, 8ArH), 7.17-7.13 (m, 2ArH), 7.01 (d, J = 8.7 Hz, 2ArH), 6.75 (d, J = 8.7 Hz, 2ArH), 5.84-5.82 (m, 2H), 5.54 (q, J = 2.9 Hz, 2H), 5.19 (s, 1H), 4.14 (td, J = 3.0 Hz, 7.8 Hz, 2H), 3.71 (s, 3H), 3.66-3.60 (m, 2H), 3.57-3.51 (m, 2H), 2.31-2.22 (m, 2H), 2.09-2.01 (m, 2H), 0.94 (s, 18H), 0.06 (s, 12H). 13C NMR (100 MHz, CD3COCD3, 25°C) δ 158.4, 145.2, 145.2, 133.2, 129.5, 128.3, 128.1, 126.1, 113.4, 106.7, 106.7, 104.5, 104.4, 60.9, 54.8, 43.5, 40.8, 39.0, 25.8, 25.7, 18.2, -3.7, -5.7. HRMS calculated requires M⁺: 750.4482. Found m/z: 750.4438.

103) 2-[(1S)-3-[(tert-butyldimethylsilyl)oxy]-1-phenylpropyl]-5-{{[(2Z)-5-[(1S)-3-[(tert-butyldimethylsilyl)oxy]-1-phenylpropyl]-2H-pyrrol-2-ylidene}[4-methoxyphenylmethyl]-1H-pyrrole

Under a stream of argon, compound 7c (480 mg, 0.64 mmols) dissolved in dry tetrahydrofuran (9 mL), p-chloranil (174 mg, 0.71 mmols) dissolved in dry tetrahydrofuran (3 mL) added dropwise while stirring at room temperature. Allowed to stir at room temperature for 4 days while monitoring by TLC for completion. Reaction mixture was quenched with saturated aqueous sodium bicarbonate and extracted with ethyl acetate. Organic layers were
washed with water and brine and dried over sodium sulfate. After filtering off
sodium sulfate, organic layers were concentrated in vacuo to afford the title
compound as a dark red sticky solid in 33% yield (159 mg, 0.21 mmols) after
column chromatography on silica gel (0-5-10-25% EtOAc in hexanes). IR (film)
3278, 3061, 2953, 2928, 2898, 2855, 1675, 1602, 1510, 1471, 1463, 1447, 1388,
1361, 1249, 1174, 1094, 1067, 1032, 1005, 939, 884, 832, 809, 774, 699, 667
\text{cm}^{-1}. \textsuperscript{1}H NMR (400 MHz, CD\textsubscript{3}COCD\textsubscript{3}, 25°C) \(\delta\) 7.38-7.33 (m, 8ArH), 7.26-7.22
(m, 2ArH), 7.01-6.97 (m, 2ArH), 6.46-6.44 (m, 2ArH), 6.26 (dd, J = 1.6 Hz, 4.1
Hz, 1H), 4.33-4.26 (m, 2H), 3.82 (s, 3H), 3.75-3.68 (m, 2H), 3.63-3.58 (m, 2H),
2.52-2.42 (m, 2H), 2.26-2.16 (m, 2H), 1.38-1.29 (m, 2H), 0.94-0.84 (m, 18H),
0.05-0.03 (m, 12H). \textsuperscript{13}C NMR (100 MHz, CD\textsubscript{3}COCD\textsubscript{3}, 25°C) \(\delta\) 160.6, 159.7,
143.1, 143.0, 140.3, 132.2, 129.5, 128.8, 128.4, 128.2, 126.8, 116.5, 113.3, 60.7,
60.7, 55.0, 43.2, 37.8, 25.8, 25.6, 18.2, -5.7. HRMS calculated requires (M+H)+:
747.4372. Found \textit{m/z}: 747.4374.
Appendix A:

$^1$H and $^{13}$C NMR Spectra of Select Compounds
Benzyl(1-phenyl-2-yn-1-yl)amine

2
83% yield
Benzyl[1-(2-fluorophenyl)nnon-2-yn-1-yl]amine

65% yield
Benzyl(1-((3-(trifluoromethyl)phenyl)non-2-yn-1-yl)amine

86% yield
Benzyl(2,2-dimethylundec-4-yn-3-yl)amine

5
54% yield
Benzy(2-methyldec-5-yn-4-yl)amine

6
60% yield
N-(1-Cyclohexylbenz-2-yn-1-yl)-4-methylbenzene-1-sulfonamide

51% yield
Benzyl(1-phenylvinyl-2-yn-1-yl)amine

8

72% yield
Benzyl(2-methylundec-4-yn-3y)amine

9
94% yield
Benzyl[1-(2-fluorophenyl)n-prop-2-yn-1-yl]amine

10
88% yield

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

![NMR spectrum of 11, 68% yield]

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

![NMR spectrum of benzyl[1-(3-fluorophenyl)non-2-yn-1-yl]amine]
Benzyl(1-[2-(2-fluoromethyl)phenyl]-2-yn-1-yl)amine

80% yield

Benzyl(1-[2-(2-fluoromethyl)phenyl]-2-yn-1-yl)amine
Benzyl(1-[3-(trifluoromethyl)phenyl][non-2-yn-1-yl])amine

14
46% yield
dibenzyl(4-methyl-1-phenylpent-1-yn-3-yl)amine

15
80% yield

dibenzyl(4-methyl-1-phenylpent-1-yn-3-yl)amine
dibenzyl(5-methyl-1-phenylhex-1-yn-3-yl)amine

17
85% yield
dibenzyl-(1-{furan-2-yl}non-2-yn-1-yl)amine

18
n-Hex
76% yield
190
4-[(1-phenylnon-2-yn-1-yl)morpholine

20

94% yield
4-(2-methylundec-4-yn-3-yl)morpholine

Me
Me
n-Hex

21
83% yield
4-[[1-(4-fluorophenyl)non-2-yn-1-yl]methyl]morpholine

91% yield
4-[[1-(4-(trifluoromethyl)phenyl)-2-yn-1-yl]methyl]-1,4-diazepane

97% yield

4-[[1-(4-(trifluoromethyl)phenyl)-2-yn-1-yl]methyl]-1,4-diazepane

194
4-[1-[3-(trifluoromethyl)phenyl]non-2-yn-1-yl]morpholine

4-Hex

CF₃

24

96% yield

4-[1-[3-(trifluoromethyl)phenyl]non-2-yn-1-yl]morpholine
(4-Methoxyphenyl)methyl]-1-phenylhept-2-yn-1-ylamine

25
61% yield
[4-Methoxyphenyl]methyl][1-phenylvinyl-2-yn-1-yl]amine

26
59% yield
[(4-Methoxyphenyl)methyl][(6-methyl-1-phenylhept-2-yn-1-yl)amine

OMe

HN

Me

Me

27

54% yield
(1,3-Diphenylprop-2-yn-1-yl)(4-methoxyphenyl)methylamine

28

20% yield
[(4-Methoxyphenyl)methyl][2-methylundec-4-yn-3-yl]amine

29

67% yield
(2,8-Dimethylnon-4-yn-3-yl)(4-methoxyphenyl)methyl]amine

57% yield
[(4-Methoxyphenyl)methyl][4-methyl-1-phenylpent-1-yn-3-yl]amine

24% yield
[1-[(4-fluorophenyl)non-2-yn-1-yl][(4-methoxyphenyl)methyl]amine

![Diagram of the molecule 32 with a 72% yield](image)

[1-[(4-fluorophenyl)non-2-yn-1-yl][(4-methoxyphenyl)methyl]amine

![Another diagram of the same molecule](image)
[6-chloro-1-(2-fluorophenyl)hex-2-yn-1-yl][4-methoxyphenyl)methyl]amine

OMe

HN

\( \text{F} \)
\( \text{Cl} \)

33

73% yield

[6-chloro-1-(2-fluorophenyl)hex-2-yn-1-yl][4-methoxyphenyl)methyl]amine

\( \text{F} \)
\( \text{H} \)
\( \text{N} \)

\( \text{Cl} \)
[6-chloro-1-(3-fluorophenyl)hex-2-yn-1-yl][4-methoxyphenyl]methyl]amine

71% yield
[6-chloro-1-(4-fluorophenyl)hex-2-yn-1-yl][4-methoxyphenyl]methyl]amine

[6-chloro-1-(4-fluorophenyl)hex-2-yn-1-yl][4-methoxyphenyl]methyl]amine

72% yield
[2-Methoxyphenyl]methyl\[1-phenylhept-2-yn-1-yl\]amine

HN
OMe

36
61% yield

[2-Methoxyphenyl]methyl\[1-phenylhept-2-yn-1-yl\]amine
(2-Methoxyphenyl)methyl(6-methyl-1-phenylhept-2-yn-1-yl)amine

55% yield
(2,2-dimethylundec-4-yn-3-yl)(2-methoxyphenyl)methylamine

38
45% yield
[1-][3-fluorophenyl]n-propyn-1-yl][2-methoxyphenyl]methyl]amine

![NMR spectrum of the compound](image)

58% yield
1-(3-ethyldec-5-yn-4-yl)pymolidine

Me
N
Me

\( n\)-Hex

40

71% yield
N-Methyl-N-(2-methyldec-5-yn-4-yl)amine

41
72% yield
1-Methyl-4-(nona-1,2-dien-1-yl)benzene

Me

\( \text{n-Hex} \)

43
2-((4-fluorophenyl)-4-hexyl-6-methoxyquinoline

![Chemical structure of 2-((4-fluorophenyl)-4-hexyl-6-methoxyquinoline)](image-url)
6-Methoxy-2,4-diphenylquinoline

[Chemical structure image]

6-Methoxy-2,4-diphenylquinoline
2-(2-methoxyphenyl)-4-phenylquinoline

MeO

52

MeO

2-(2-methoxyphenyl)-4-phenylquinoline
6-Methyl-2,4-diphenylquinoline

Me

6-Methyl-2,4-diphenylquinoline
7-(Methylsulfonyl)-2,4-diphenyquinoline

\[
\begin{array}{c}
\text{MeS} \\
55
\end{array}
\]
6-(Methylsulfanyl)-2,4-diphenylquinoline

6-(Methylsulfanyl)-2,4-diphenylquinoline
2,4-Diphenyl-6-(trifluoromethyl)quinoline

\[ \text{F}_3\text{C} \]

57

2,4-Diphenyl-6-(trifluoromethyl)quinoline

\[ \text{C} \]

\[ \text{H} \]

\[ \text{N} \]

\[ \text{C} \]

\[ \text{C} \]
2,4,6-Triphenylquinoline
2-(4-Fluorophenyl)-4,8-diphenylquinoline

2-(4-Fluorophenyl)-4,8-diphenylquinoline
6,8-Diphenyl-2-H-[1,3]dioxolo[4,5-g]quinoline

6,8-Diphenyl-2-H-[1,3]dioxolo[4,5-g]quinoline
6-(4-Fluorophenyl)-8-phenyl-2H-[1,3]dioxolo[4,5-g]quinoline

6-(4-Fluorophenyl)-8-phenyl-2H-[1,3]dioxolo[4,5-g]quinoline
4-[2-(4-Methylphenyl)quinolin-4-yl]butanenitrile

![Chemical Structure](image)

4-[2-(4-Methylphenyl)quinolin-4-yl]butanenitrile

![NMR Spectrum](image)
6-Methoxy-4-phenylquinoline

35% yield
6-Methoxy-2-[3-(6-methoxy-4-phenylquinolin-2-yl)phenyl]-4-phenylquinoline

MeO

69

43% yield
2-Cyclohexyl-4-hexyl-6-methoxyquinoline

69% yield
2-Cyclohexyl-6-methoxy-4-phenylquinoline

[Chemical structure image]

71

79% yield
6-Methoxy-2-(pentan-3-yl)-4-phenylquinoline

77% yield
2-(Butan-2-yl)-6-methoxy-4-phenylquinoline

73

77% yield
6-Methoxy-2-(2-methylpropyl)-3-(propan-2-yl)quinoline

85% yield

2-tert-butyl-6-methoxy-4-phenylquinoline
2-Cyclohexyl-6-fluoro-4-phenylquinoline

75
81% yield
6-Methyl-2-(pentan-3-yl)-4-phenylquinoline

76
67% yield
6-(Methylsulfonyl)-2-(pentan-3-yl)-4-phenylquinoline

77
63% yield

6-(Methylsulfonyl)-2-(pentan-3-yl)-4-phenylquinoline
N-[2-(pentan-3-yl)-4-phenylquinolin-6-yl]acetamide

78
82% yield
2-Butyl-6-methoxy-3-propylquinoline

79
67% yield
6-Methoxy-2-(2-methylpropyl)-3-(propan-2-yl)quinoline

80
70% yield

6-Methoxy-2-(2-methylpropyl)-3-(propan-2-yl)quinoline
(3S)-3-[(5S)-[(5S)-3-Hydroxy-1-phenylpropyl]-1H-pyrrol-2-yl][(4-methoxyphosphanyl)-1H-pyrrol-2-yl]-3-phenylpropan-1-ol

\[
\begin{align*}
&\text{OMe} \\
&\text{NHNN} \\
&\text{OH} \quad \text{HO}
\end{align*}
\]

99

(3S)-3-[(5S)-[(5S)-3-Hydroxy-1-phenylpropyl]-1H-pyrrol-2-yl][(4-methoxyphosphanyl)-1H-pyrrol-2-yl]-3-phenylpropan-1-ol
(3R)-3-[5-[[5-[(1R)-3-hydroxy-1-phenylpropyl]-1H-pyrol-2-yl][4-methoxyphethyl]-1H-pyrol-2-yl]-3-phenylpropan-1-ol
2-[[1S]-3-[(tert-butyldimethylsilyl)oxy]-1-phenylpropyl]-5-[[1S]-3-[(tert-butyldimethylsilyl)oxy]-1-phenylpropyl]-1H-pyrol-2-yl](4-methoxyphenyl)methyl)-1H-pyrole

2-[[1S]-3-[(tert-butyldimethylsilyl)oxy]-1-phenylpropyl]-5-[[1S]-3-[(tert-butyldimethylsilyl)oxy]-1-phenylpropyl]-1H-pyrol-2-yl](4-methoxyphenyl)methyl)-1H-pyrole
2-[(1R)-3-[(tert-butyldimethylsilyl)oxy]-1-phenylpropyl]-5-[(1R)-3-[(tert-butyldimethylsilyl)oxy]-1-phenylpropyl]-1H-pyrrole