Ligand Effect on Copper-Promoted Coupling Reactions: Analysis of Allenes as Pi-Bond Ligands; Synthesis and Applications of Substituted 1,3-Dienes and [n]Dendralenes

A dissertation submitted in partial satisfaction of the requirements for the degree of Doctor of Philosophy in Chemistry

by

Brett Hart Cory

2019
ABSTRACT OF THE DISSERTATION

Ligand Effect on Copper-Promoted Coupling Reactions: Analysis of Allenes as Pi-Bond Ligands; Synthesis and Applications of Substituted 1,3-Dienes and [n]Dendralenes

By

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Doctor of Philosophy in Chemistry

University of California, Los Angeles, 2019

Professor Craig A. Merlic, Chair

Chapters one and two focus on the effect of allenes as π-ligands on copper-promoted coupling reactions. While there are many examples showcasing alkenes and alkynes as π-bond additives in transition-metal reactions, allenes have no precedent as π-bond ligands, despite the similarities to alkenes and alkynes. The added benefit provided by allenes was observed in several different copper-mediated cross-coupling reactions. Chapter two will discuss the π-ligands role in these reactions through mechanistic studies.

Chapter three described a method for preparing substituted 1,3-dienes and [n]dendralenes. These privileged products are accessed through palladium(II)-catalyzed oxidative homocoupling of alkynes and internal vinyl boronate esters. The method is extremely mind and offers a wide range of functional group tolerance. A minor modification to the oxidative protocol conditions
allows the synthesis of [3]dendralenes through palladium(0)-catalyzed cross-coupling of alkynes and vinyl triflates. The utility of the diene products in synthesis will also be highlighted.

Chapter four will highlight the synthesis of cyclic triynes for use in the transannular hexadehydro-Diels–Alder reaction. The hexadehydro-Diels–Alder reaction has recently reemerged as a powerful way of accessing benzyne intermediates through an intramolecular [4+2] cycloaddition of an alkyne and a diyne. While there exists numerous examples for the intramolecular hexadehydro-Diels–Alder reaction, the transannular case has yet to be explored. Efforts towards understanding how ring strain effects the hexadehydro-Diels–Alder reaction will be discussed.
The dissertation of Brett Hart Cory is approved.

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2019
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ABBREVIATIONS

~ Approximately
° Degree
* Star
α Alpha
β Beta
δ Delta
γ Gamma
η Eta
µ Micro
π Pi
σ Sigma
ω Omega
Ac Acetyl
ATR Attenuated total reflection
aq Aqueous
Ar Any aryl
atm Atmosphere
b Broadened
Bn Benzyl
Boc tert-Butyloxycarbonyl
Bu Butyl
C Celsius
cal  Calorie
cm$^{-1}$  Inverse centimeters
COD  cycloocta-1,5-diene
d  Doublet
DA  Diels-Alder
DCM  Dichloromethane
DEG  Diethylene glycol
DFT  Density functional theory
DMAP  4-Dimethylamino pyridine
DMF  $N,N$-Dimethylformamide
DMSO  Dimethyl sulfoxide
DoM  Directed-ortho metallation
dppb  1,3-Bis(diphenylphosphino)butane
dppe  1,3-Bis(diphenylphosphino)ethane
dppp  1,3-Bis(diphenylphosphino)propane
dr  Diastereomeric ratio
dtbpy  4,4’-di-tert-butyl-2,2’-bipyridine
$E$  Entgegen
$E_2$  Bimolecular elimination
$ee$  Enantiomeric excess
eg  Ethylene glycol
equiv  Equivalents
Et  Ethyl
Et$_2$O  Diethyl Ether
EtOAc  Ethyl Acetate
EtOH  Ethanol
FG  Functional group
g  Gram
gem  Geminal
h  Hour
HDDA  Hexadehydro-Diels–Alder
HMPA  Hexamethylphosphoramide
HRMS  High resolution mass spectroscopy
HO  Heme oxygenase
hv  Light
Hz  Hertz
i  Iso
IR  Infrared
J  joule
kcal  Kilocalorie
L  Ligand
LAH  Lithium aluminum hydride
m  meta
m  Milli
M  Molar
Me  Methyl
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ACKNOWLEDGEMENTS

I am extremely grateful for everything my research advisor, Craig Merlic, has done for me during my time at UCLA. You taught me valuable lessons and taught me the art of holding yourself accountable. I cannot thank you enough for taking the extra time to sit down and help me with mechanisms during the first year. Without that, passing those cumulative exams would have been a lot harder. Thank you so much Craig for all you have done and I wish you the best of luck moving forward.

I would also like to thank Michael Jung for being that second mentor I needed. I am truly thankful for all the time you let me teach for you. You always found a way to us laugh rather that was in the classroom or at the weekly seminars. I am extremely grateful for you giving me the opportunity to collaborate with David Vosburg at Harvey Mudd College and publish my first paper. Thank you very much for everything you have done for me.

I am also appreciative of Caius Radu for taking the time out of his schedule to attend my oral examination. Thank you for the kind words you said to me after my oral examination, that was really nice of you.

I also wish to acknowledge the all the help I received from my coworkers in the Merlic group. I personally want to thank Byron Boon, Sedef Karabiyikoglu, and Robert Tobolowsky for not only being helpful but also for being a friend.

Lastly, I would like to thank my family: Sharri Cory, Patrick Cory, and Patrick Jr. Cory. You three have made me who I am today and I would not change that for anything. I love you three very much. I would like to also thank the Robinson family for always keeping your door open.
open and being so accommodating. Daisy Robinson, you are beautiful and a wonderful woman. I am really excited to see what the next chapter of our lives brings. I love you very much and cannot wait to spend the rest of our lives together.
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Honors and Awards:

- Hanson-Dow Excellence in Teaching Award, University of California, Los Angeles, CA, 2015
- Research Showcase Fellowship Award for the ACS National Meeting, San Francisco, CA, 2017

Publications


• Cory, B. H.; Teuthorn, A.; Williams, C.; Merlic, C. A. Direct Access to Substituted 1,3-Dienes and [n]Dendralenes Through Pd(II)–Catalyzed Oxidative Coupling of Alkynes and Internal Vinyl Boronate Esters. *Org. Lett.* **2019 In preparation**

**Presentations:**


CHAPTER ONE

Allenes as Advantageous $\pi$-Ligands in Cu-Mediated Cross-Coupling Reactions

1.1 Background

Since the discovery of Zeise’s salt in 1827,\(^1\) there has been an explosion of interest in transition-metal-olefin complexes.\(^2\) Unsaturated hydrocarbons are often used as $\pi$-ligands to stabilize oxygen-sensitive low-valent transition metals, such as commercially available Ni(cod)\(_2\), Pd(dba)\(_2\), [Rh(cod)Cl]\(_2\), and (hfacac)Cu(I)-bis(trimethylsilyl)acetylene (Figure 1.1). The utility of these complexes lies in the $\pi$-bond donors’ ability to easily undergo a ligand exchange with other ligands, typically consisting a heteroatom.\(^3\) For this reason, transition-metal-olefin complexes are typically employed as precursors to access active catalysts in situ. However, utilizing olefins as ligands/additives in transition-metal reactions has received less attention due to their well-known ability to participate in such reactions.\(^4\)

*Figure 1.1* A variety of $\pi$-bond and heteroatom transition-metal ligands.

Fine-tuning a transition-metal catalyzed reaction has relied mostly on the properties of the ligand as well as its interactions with the transition metal. For example, Kambe *et al.* in 2007 demonstrated 1-phenylpropyne was a superior additive for improving the Cu-catalyzed cross-
coupling of alkyl chlorides with alkyl Grignard reagents (Scheme 1.1). In the absence of 1-phenylpropyne, only a 3% GC yield was obtained compared to 98% when catalytic amounts of the alkyne additive were used. The authors state that the alkyne’s role could be to stabilize alkyl-Cu(I) intermediates from thermal decomposition. It is known that coinage metals, such as Cu, Ag, Au, and Pt, all have strong alkene and alkyne binding affinities as C–C π-electrophilic Lewis acids.

**Scheme 1.1** Beneficial effect of an olefin additive in a Cu-catalyzed cross-coupling reaction.

![Scheme 1.1](image)

In 2014, Kambe et al. reported the beneficial effect of unsaturated hydrocarbon additives in a Cu-catalyzed cross-coupling reaction of alkyl halides with alkyl Grignard reagents (Scheme 1.2).

**Scheme 1.2** Effect of alkyne additives on product selectivity for a Cu-catalyzed cross-coupling reaction.

![Scheme 1.2](image)

They obtained only 26% of the desired cross-coupled product in the absence of 1-phenylpropyne. However, using 1-phenylpropyne additive gave an 89% yield of the cross-coupling product with only a minor amount of homocoupled product. The authors state the alkyne additive suppresses β-
hydride elimination, a process that leads to degradation of the Cu-catalysts. The alkyne additive may also have a role in accelerating the Grignard addition to the alkyl-Cu(I) complex, which is essential for product formation.

π-Bond ligands have been shown to affect the rate of reductive elimination for dialkyl-eNi(II) complexes (Scheme 1.3). The authors show that in the absence of an external olefin, the major pathway is β-hydride elimination. However, in the presence of an olefin, reductive elimination becomes favored. The rate of reductive elimination relies on both the electronic and steric factors of the olefin additive as determined by screening substituted alkenes.

**Scheme 1.3** Effect of π-ligands on the rate of reductive elimination for a Ni(II) complex.

- In the absence of an external olefin additive

- In the presence of an external olefin additive

Zhang and Rovis reported an interesting example highlighting the benefit of an olefin additive in a transition metal reaction (Scheme 1.4). The yields for cross-coupling organozinc reagents with carboxylic acid fluorides vastly improved for reactions that were conducted with 4-fluorostyrene. Not only did this simple alkene provide a boost in yield, but it also accelerated the
reaction rate affording a 97% yield of the product in only three minutes. The same reaction conducted without 4-fluorostryne provided only an 18% yield after 16 hours.

**Scheme 1.4** Example of an improved Ni-catalyzed cross-coupling reaction of acid fluorides with organozinc reagents using 4-fluorostyrene as an additive.

A similar olefin effect was reported by Kurosawa et al. in 1992 while studying a Pd-catalyzed cross-coupling of allylic chlorides with tributylphenylstannane (Scheme 1.5).\(^\text{10}\) The authors found that reactions conducted in the presence of a π-bond ligand gave different diastereoselectivities depending on the electronic nature of the olefin.

**Scheme 1.5** Change in product selectivity using olefin additives in a Pd-catalyzed cross-coupling reaction.

Electron-withdrawing olefins, such as maleic anhydride (MA) or dimethyl fumarate, gave a high preference for the *trans* product. In contrast, the same reaction conducted with 1,5-cyclooctadiene or styrene, gave the *cis* product. The reaction conducted without a π-bond additive gave only the *cis* product. The authors proposed the change in selectivity arises during the oxidative addition
step, where the Pd(MA) complex is syn-selective vs anti-selective as is the case when the olefin is absent.

Shirakawa et al. reported a π-ligand effect while studying Ni-catalyzed conjugate addition of arylboron reagents to α,β-unsaturated ketones (Scheme 1.6).\textsuperscript{11} The reaction conducted without an external ligand gave the product in only 1% yield, however when they added diphenylacetylene or 1,3-diphenyllallene as π-bond ligands, the yield improved to 65% and 32%, respectively.

\textbf{Scheme 1.6} Example of an intramolecular π-ligand effect improving a Ni-catalyzed reaction.

More interestingly, they showed that substrates with pendant π-bonds have a large influence on the reaction. For example, an enone with a pendant alkyne group gave the addition product in 27% yield, whereas only a 1% yield was obtained when the alkyne was removed.

While there are numerous examples showcasing alkenes and alkynes as π-bond additives in transition-metal C–C bond forming reactions, allenes essentially have no precedent as π-bond ligands, despite the similarities to alkenes and alkynes.\textsuperscript{12} Soai et al. demonstrated one of the first examples of using an allene in a transition metal reaction (Scheme 1.7).\textsuperscript{13} Several chiral allenes were used to induce asymmetry in the addition of an organozinc reagent to pyrimidine-5-
carboxaldehyde. The authors demonstrated that exceptionally high ee’s were achievable employing super-catalytic amounts of the chiral allene.

**Scheme 1.7** Example of asymmetric autocatalysis using chiral allenes.

The Ready group demonstrated the use of chiral allenes in a Rh(I)-catalyzed reaction. They successfully demonstrated that chiral allene-containing phosphine ligands (AllenePhos) provide excellent control for asymmetric addition of arylboronic acids to β-ketoesters. Currently, olefins, and especially allenes, remain underutilized as ligands/additives in transition-metal based reactions perhaps due to their ability to participate in many reactions.

Many publications on transition-metal cross-coupling reactions routinely do a ligand screen in order to obtain optimal results. This transition-metal ligand engineering has made the field of cross coupling much less general and more geared towards a single case. Often times these exotic ligands are expensive and carry a high risk of being oxidized, as in the case of precious phosphine-containing ligands. In contrast, olefins are much more stable, abundant, easy to prepare, can be chiral, and are inexpensive. With the numerous advantages olefins have to offer, we believe that exploring olefins as π-ligands in transition-metal reactions is necessary.

1.2 Introduction

During the course of an otherwise unrelated project, an interesting side product was obtained while studying the Pd(II)-catalyzed oxidative homocoupling of vinyl boronate esters.
The group members at the time were able to identity this side product to be a vinyl ether. I would like to thank those group members for dedicating the time and effort it took to identify the vinyl ether product. Without this small discovery, the vinyl ether synthesis probably would not have existed today and I am extremely grateful that did not happen.\textsuperscript{16} Studying the vinyl ether synthesis eventually lead us to publishing on the remarkably broad utility of alkynes as \(\pi\)-ligands that promote vinyl ether formation.\textsuperscript{17} The generality and power alkynes (and allenes) have to offer as \(\pi\)-ligands for Cu-mediated coupling reactions was initially revealed by serendipity (Figure 1.2).

\textbf{Figure 1.2} Serendipitous discovery that made the Cu-mediated vinyl ether synthesis and \(\pi\)-ligand project possible.

\begin{itemize}
  \item A. Discovery of the vinyl ether synthesis
  \item B. Improved vinyl ether synthesis using \(\pi\)-ligands as additives
\end{itemize}

This is perhaps due to the assumption that they will react in transition metal reactions and therefore are not even considered as potential ligands. This chapter will highlight recent progress towards expanding the scope of utilizing allenes as \(\pi\)-bond ligands in Cu-mediated coupling reactions. With
the number of Cu-promoted processes known today, we believe that such coupling reactions can benefit from using olefins and allenes as π-ligands.\textsuperscript{18,19} I will also elaborate on how the π-ligands are influencing the coupling reaction.

1.3 Alkynes and Allenes as π-Ligands for Cu-Mediated Vinyl Ether Synthesis

Intended In our previous study, we identified 3-hexyne as an impactful ligand for increasing yields in Cu-mediated cross-coupling of boronate esters with alcohol coupling partners. Major attractive features of using 3-hexyne are that it is very inexpensive and easily removed from the reaction. Interested in other potential alkyne π-bond ligands, Robert Tobolowsky prepared a family of cyclic alkynes to test in a standard coupling reaction (Table 1.1). Our initial intuition was that alkynes possessing ring strain would increase the π-coordination ability of the π-bond to Cu\textsuperscript{20} and should result in higher coupling yields. However, when we screened strained alkynes as potential π-bond ligands, the coupling yields were much lower than those that used acyclic alkynes. It is known that strained cyclic alkynes can react and isomerize to allenes under basic conditions.\textsuperscript{21}

Table 1.1 Results from screening cyclic and acyclic alkynes as ligands.

| Reaction conditions: 0.35 mmol of 1-1 at 0.17 M. Yields are given for chromatographically purified compounds. |
|---|---|---|---|---|---|---|---|
| BnO\[\text{HO}\] \rightarrow \text{solvent} \rightarrow 2 \text{equiv } Cu(OAc)\textsubscript{2} \rightarrow 2 \text{equiv Et\textsubscript{3}N} \rightarrow 4 \text{equiv ligand} \rightarrow \text{rt, 12 h} | BnO\[\text{HO}\] \rightarrow \text{solvent} \rightarrow 2 \text{equiv } Cu(OAc)\textsubscript{2} \rightarrow 2 \text{equiv Et\textsubscript{3}N} \rightarrow 4 \text{equiv ligand} \rightarrow \text{rt, 12 h} |
| 1-1 (1 equiv) | 1-2 no ligand – 87% |
| 1-3 | 1-4 | 1-5 | 1-6 | 1-7 | 1-8 |
| Me | Me | Me | OMe | Me | OMe |
| 91% | 83% | 72% | 69% | 56% | 41% |

Recognizing that copper has a strong affinity for various π-bonds,\textsuperscript{22} we decided to investigate allenes as ligands for Cu-mediated couplings. Thus, despite a scarcity of known Cu-allene complexes,\textsuperscript{23} a series of allenes were prepared by Tioga Martin and Robert Tobolowsky and
tested as \( \pi \)-ligands in a standard coupling reaction (Table 1.2). In contrast to cyclic alkynes, cyclic allenes were shown to be extremely advantageous in the reaction, resulting in nearly quantitative coupling yields. A meaningful comparison is ligand 1-9 vs undeca-5,6-diene (1-12) wherein the electronic nature of the ligands should be identical, yet ligand 1-9 provides an increase in yield. Ring strain-enhanced \( \pi \)-coordinating ability\(^{20}\) was initially presumed the primary cause for this effect, but calculations predict a ring strain of only 2.0 kcal/mol, so steric differences may contribute as well.\(^{24}\)

**Table 1.2** Results from screening cyclic and acyclic allenes as ligands.

<table>
<thead>
<tr>
<th>1-1 (1 equiv)</th>
<th>[\text{BnO} \rightarrow \text{B(pin)} + \text{HO} \rightarrow \text{solvent} \rightarrow 2 \text{equiv Cu(OAc)}_2 \rightarrow 2 \text{equiv Et}_3 \text{N} \rightarrow 4 \text{equiv ligand} \rightarrow \text{rt, 12 h} \rightarrow 1-2 \text{no ligand – 87%} ]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-9</td>
<td>94%</td>
</tr>
<tr>
<td>1-10</td>
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</tr>
<tr>
<td>1-11</td>
<td>89%</td>
</tr>
<tr>
<td>1-12</td>
<td>86%</td>
</tr>
<tr>
<td>1-13</td>
<td>62%</td>
</tr>
<tr>
<td>1-14</td>
<td>57%</td>
</tr>
<tr>
<td>1-15</td>
<td>42%</td>
</tr>
<tr>
<td>1-16</td>
<td>34%</td>
</tr>
<tr>
<td>1-17</td>
<td>33%</td>
</tr>
<tr>
<td>1-18</td>
<td>28%</td>
</tr>
</tbody>
</table>

**Reaction conditions:** 0.35 mmol of 1-1 at 0.17 M. Yields are given for chromatographically purified compounds.

### 1.4 Synthesis and Evaluation of Strained Allenes as \( \pi \)-Ligands for Cu-Mediated Vinyl Ether Synthesis

The nine-membered cyclic allene 1-9 is the smallest allene that can be isolated and stored without decomposing. Six-, seven-, and eight-membered cyclic allenes are usually prepared in situ and used as reactive intermediates.\(^{25}\) To further explore ring strain-enhanced \( \pi \)-coordinating ability, we prepared a family of strained allenes to determine the effect of ring-strain on coupling yields. Decreasing the allene ring size was ruled out as they are difficult to handle (vide supra). As
an alternative, we envisioned introducing strain by constructing different rings on the terminal ends of the allene. Thankfully, an established five-step synthesis to access these types of allenes was already reported by Bailey and Aspris in 1995 (Scheme 1.8). This synthesis, however, had many unforeseen problems which caused laborious purification processes for each step. Along with the time-consuming purifications, the yields were low, forcing us to perform the reactions multiple times to obtain sufficient quantities of material for testing. Clearly, this route is non-strategic to say the least, so we decided to create our own route, which solved the problems we had encountered.

Scheme 1.8 Initial synthetic route to alkenyldenecycloalkanes.

We solved the problems by using an O-silyl protected alkyne for the 1,2-addition step. This minor adjustment greatly improved the synthesis as each step needed little-to-no purification (Scheme 1.9). The reactions were also much easier to monitor as each compound differs substantially in polarity. This new route allowed rapid access to allenes 1-19–1-24 with some of them being able to be prepared in as little as one day.
With the desired allenes in hand, we used them as additives in a standard Cu-mediated vinyl ether synthesis (Table 1.3, A). The standard coupling reaction in the absence of allene ligands gave vinyl ether 1-26 in only 34% yield. As the data shows, addition of unstrained allenes dramatically improves the yield, but the coupling yields diminished as the allene becomes more strained (ligands 1-19–1-24). Similar to the results from testing cyclic alkynes, thin-layer chromatography suggested that the strained allenes were reacting under the standard coupling conditions as numerous new spots were observed. Ligand 1-27 (prepared from 1,5-cyclooctadiene by a Skattebøl rearrangement), which possesses more ring-strain than ligand 1-9 due to the added C=C bond, gave vinyl ether 1-26 in 86% yield. Tetrasubstituted allene 1-28 gave a nearly identical coupling yield for vinyl ether 1-26 compared to ligand 1-9. The screening results show allene ligands perform best when the internal Csp² bond angle approaches the ideal 120°. The same trend was observed coupling 1-1 with 2-chloroethanol (Table 1.3, B), where each allene ligand tested boosted the coupling yields compared to the reaction conducted without any π-ligand. It is well-
known that allenes can react under Cu(I) and Cu(II) conditions,\(^4\) however in our study we found that most beneficial allene ligands remain intact and can even be recovered from the reactions in good yields.

*Table 1.3* Influence of strained allenes on coupling yields.

A. Coupling results using boronate ester 1-25

\[
\text{BnO} - \text{B(pin)}_1 - 25 \text{ (1 equiv)} + \text{HO} - \text{Cl} \xrightarrow{2 \text{ equiv } \text{Cu(OAc)}_2} \text{BnO} - \text{O} - \text{Cl}_1 - 26 \text{ no ligand – 34\%}
\]

<table>
<thead>
<tr>
<th>Results</th>
<th>1-9</th>
<th>1-19</th>
<th>1-20</th>
<th>1-21</th>
<th>1-22</th>
</tr>
</thead>
<tbody>
<tr>
<td>89%</td>
<td>82%</td>
<td>86%</td>
<td>74%</td>
<td>59%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
<th>1-23</th>
<th>1-24</th>
<th>1-27</th>
<th>1-28</th>
</tr>
</thead>
<tbody>
<tr>
<td>47%</td>
<td>57%</td>
<td>86%</td>
<td>86%</td>
<td></td>
</tr>
</tbody>
</table>

B. Coupling results using boronate ester 1-1

\[
\text{BnO} - \text{B(pin)}_1 - 1 \text{ (1 equiv)} + \text{HO} - \text{Cl} \xrightarrow{2 \text{ equiv } \text{Cu(OAc)}_2} \text{BnO} - \text{O} - \text{Cl}_1 - 29 \text{ no ligand – 43\%}
\]

<table>
<thead>
<tr>
<th>Results</th>
<th>1-9</th>
<th>1-19</th>
<th>1-20</th>
<th>1-28</th>
</tr>
</thead>
<tbody>
<tr>
<td>80%</td>
<td>76%</td>
<td>81%</td>
<td>82%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Results</th>
<th>1-27</th>
</tr>
</thead>
<tbody>
<tr>
<td>86%</td>
<td></td>
</tr>
</tbody>
</table>

Reaction conditions: 0.35 mmol of 1-1 or 1-25 at 0.17 M. Yields are given for chromatographically purified compounds.

To demonstrate the generality of ligand 1-9, we screened it with a variety of alcohols in the Cu-promoted reaction. As shown in Table 1.4, addition of ligand 1-9 generally led to increased
yields compared to the control reaction without ligand.\textsuperscript{27} Isopropanol proved to be challenging, however using ligand 1-9 provided a nearly 200\% increase in yield compared to the reaction conducted without ligand. Tertiary alcohol tert-butanol did not couple under these conditions, even in the presence of ligand 1-9. Finally, demonstration of an autoligation effect was observed for alkene-containing alcohols in two reactions performed without added ligand: the coupling yield for allyl alcohol is higher than \textit{n}-propanol. A serious limitation for the Cu-promoted coupling arises when chelating diols such as ethylene glycol or 1,3-propanediol are used. The only product isolated was the alkene 1-36, which is derived from protodeboronation (PdB) of boronate ester 1-1. This result parallels recent reports that diols can bind and alter the reactivity of Cu(II).\textsuperscript{28}

\textit{Table 1.4} Screening results of coupling alcohols with and without ligand 1-9.

\begin{center}
\begin{tabular}{|c|c|c|c|}
\hline
R & product & yield (\%)\textsuperscript{a} without 1-9 & yield (\%)\textsuperscript{a} with 1-9 \\
\hline
Me & 1-30 & 89 & 97 \\
n-Pr & 1-31 & 60 & 88 \\
n-Pr\textsuperscript{b} & 1-32 & 18 & 52 \\
t-Bu & 1-33 & 0 & 0 \\
  & 1-2 & 87 & 94 \\
HO & 1-34 & 0 (67) & 0 (5) \\
HO & 1-35 & 0 (51) & 0 (57) \\
\hline
\end{tabular}
\end{center}

\textsuperscript{a}Reaction conditions: 0.35 mmol of 1-1 at 0.17 M. \textsuperscript{b}56 h. Yields in parentheses refer to 1-36. Yields are given for chromatographically purified compounds.

Next, we investigated the ligands’ effect on the coupling reaction at elevated temperature (Table 1.5). The cross coupling of isopropanol and boronate 1-1 at 50 °C gave vinyl ether 1-32 in 50\% after 12 hours. The same yield was obtained with ligand 1-9, suggesting this ligand is less
effective in the vinyl ether synthesis at elevated temperatures possibly due to reacting. Ligands 1-22 and 1-24 proved detrimental and were clearly observed to react under the reaction conditions by thin-layer chromatography.

Table 1.5 Effect of π-ligands on vinyl ether synthesis at elevated temperatures.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>no ligand</td>
<td>50%</td>
</tr>
<tr>
<td>1-9</td>
<td>50%</td>
</tr>
<tr>
<td>1-22</td>
<td>37%</td>
</tr>
<tr>
<td>1-24</td>
<td>36%</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.35 mmol of 1-1 at 0.17 M. Yields are given for chromatographically purified compounds.

1.5 Effect of Cyclonona-1,2-diene (1-9) on Cu-Mediated Cross-Coupling of Boronate Esters and Alcohols

Next, we investigated the scope of how the π-ligands perform under conditions our group developed using only four equivalents of the alcohol coupling partner (Table 1.6). Sterically bulky tert-butanol did not participate in the reaction and likely due to steric factors. Ligand 1-9 dramatically improved the coupling of n-octanol compared to 3-hexyne or no ligand. The same effect was observed coupling benzyl alcohol; nearly a 100% increase in yield for vinyl ether 1-38 was obtained with ligand 1-9 compared to the control reaction without ligand.
Table 1.6 Coupling results using 4 equivalents of the alcohol coupling partner.

The ability to use only four equivalents of alcohol as opposed to alcohol solvent, allows for a more practical approach to complex, biologically relevant targets. For example, coupling boronate ester 1-40 with (S)-(−)-perillyl alcohol (1-41) gave vinyl ether 1-42 in 61% yield using ligand 1-9, which is 12% higher than the control reaction (Scheme 1.10). Perillyl alcohol was demonstrated to have chemopreventative activity in animals, thus vinyl ether derivatives of the naturally occurring compound may have applications in medicinal chemistry.

Scheme 1.10 Improved coupling of boronate ester 1-40 with (S)-(−)-perillyl alcohol using ligand 1-9.
In the same vein, we also observed a $\pi$-ligand effect in the cross-coupling of boronate ester 1-43 with (1R)-(−)-myrtenol (Scheme 1.11). In each case, the reaction performed with ligand 1-9 provided a higher yield for vinyl ether 1-45 than the control reaction conducted without ligand. However, aiming to improve the coupling yields further using three equivalents of Cu(OAc)$_2$ proved ineffective.

**Scheme 1.11** Improved coupling of boronate ester 1-43 with (1R)-(−)-myrtenol using ligand 1-9.

![Scheme 1.11 Improved coupling of boronate ester 1-43 with (1R)-(−)-myrtenol using ligand 1-9.](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>additive</th>
<th>time (h)</th>
<th>yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>none</td>
<td>12</td>
<td>35%</td>
</tr>
<tr>
<td>2</td>
<td>4 equiv 1-9</td>
<td>12</td>
<td>44%</td>
</tr>
<tr>
<td>3</td>
<td>none</td>
<td>24</td>
<td>37%</td>
</tr>
<tr>
<td>4</td>
<td>4 equiv 1-9</td>
<td>24</td>
<td>51%</td>
</tr>
<tr>
<td>5$^b$</td>
<td>4 equiv 1-9</td>
<td>38</td>
<td>48%</td>
</tr>
</tbody>
</table>

$^a$Reaction conditions: 0.35 mmol 1-43, 4 equiv of (1R)-(−)-myrtenol, 2 equiv Cu(OAc)$_2$, 4 equiv of Et$_3$N, 2.0 ml PhMe. $^b$3 equiv of Cu(OAc)$_2$.

While not shown, the reactions conducted with ligand 1-9 also provided less side product 1-36 than the control reaction did. This is perhaps due to ligand 1-9 inhibiting the pathway leading to PdB, thus allowing more of the boronate ester to participate in the vinyl ether synthesis. It has been proposed that the pathway leading to PdB involves Cu(I) species and not Cu(II) species.$^{30}$ Kuivila et al. published in 1964 a series of articles detailing the effect of certain metals on the rate of PdB of arylboronic acids.$^{31}$ They showed that Cu(II) salts gave the highest rates of PdB compared to the other metal salts tested (Pb(II), Cd(II), Zn(II), Co(II), Mg(II), and Ni(II)). They proved that Cu(I) is the responsible ion for PdB of arylboronic acids by reacting a catalytic amount of CuCl$_2$
with the arylboronic acid. It is known that CuCl$_2$ and CuBr$_2$ react with arylboronic acids to afford the corresponding aryl halide.$^{32}$ The authors only expected a 1% yield of the aryl halide due to low catalysts loading of CuCl$_2$, however they obtained nearly a quantitative yield of PdB, thus strongly suggesting the Cu(I) byproduct is responsible for facilitating PdB. To further support an interaction between ligand 1-9 and Cu(I), we turned to calculations performed by Yamamoto.$^{33}$ He showed that Cu(I) salts have a much stronger binding affinity for C–C π-bonds than Cu(II) salts. Therefore, combining Yamamoto and Kuivila’s work suggests there is an interaction between ligand 1-9 and Cu(I) during the course of the vinyl ether synthesis and that ligand 1-9 is altering/inhibiting the regular activity of Cu(I) promoting PdB.

Former group member Tioga Martin showed that the vinyl ether synthesis is amenable for coupling testosterone although in low yield (Table 1.7).

**Table 1.7** Results of coupling boronate ester 1-40 with testosterone.

<table>
<thead>
<tr>
<th>entry</th>
<th>equiv of test</th>
<th>base</th>
<th>time</th>
<th>conc. of 1-40</th>
<th>yield (%)$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1</td>
<td>Et$_3$N</td>
<td>12 h</td>
<td>0.17 M</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>Et$_3$N</td>
<td>24 h</td>
<td>0.35 M</td>
<td>6</td>
</tr>
<tr>
<td>3</td>
<td>1</td>
<td>Et$_3$N</td>
<td>24 h</td>
<td>0.70 M</td>
<td>8</td>
</tr>
<tr>
<td>4</td>
<td>1</td>
<td>Et$_3$N</td>
<td>72 h</td>
<td>0.35 M</td>
<td>8</td>
</tr>
<tr>
<td>5</td>
<td>1</td>
<td>Et$_3$N</td>
<td>72 h</td>
<td>0.70 M</td>
<td>10</td>
</tr>
<tr>
<td>6</td>
<td>1</td>
<td>Et$_3$N</td>
<td>7 d</td>
<td>0.35 M</td>
<td>6</td>
</tr>
<tr>
<td>7</td>
<td>1</td>
<td>Et$_3$N</td>
<td>7 d</td>
<td>0.70 M</td>
<td>8</td>
</tr>
<tr>
<td>8</td>
<td>4</td>
<td>i-Pr$_2$NEt</td>
<td>72 h</td>
<td>0.17 M</td>
<td>12$^b$</td>
</tr>
</tbody>
</table>

$^a$Isolated yields are reported. $^b$3 equiv of Cu(OAc)$_2$ were used.
Following up on this result, however, consistently gave poor coupling yields. Steric factors around the alcohol moiety are likely the root cause for the low yields observed and parallels the results obtained for other sterically bulky alcohol coupling partners. Another cause may come from the fact that testosterone possess an enone moiety in the A-ring, which has been previously been shown to be a poor $\pi$-ligand.\textsuperscript{17}

While looking at different steroids to use, we found $\beta$-estradiol to be an attractive coupling partner to test for two reasons: it does not possess any detrimental $\pi$-bonds like testosterone and it has two potential coupling sites (Table 1.8, A).

*Table 1.8* Results of coupling boronate ester 1-1 with $\beta$-estradiol in PhMe and isopropanol solvent.

**A. Coupling $\beta$-estradiol (1-48) with boronate ester 1-1**

<table>
<thead>
<tr>
<th>entry</th>
<th>solvent</th>
<th>temperature</th>
<th>time (hr)</th>
<th>additive [equiv]</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe</td>
<td>50 °C</td>
<td>12</td>
<td>1-9 [4]</td>
<td>5</td>
</tr>
<tr>
<td>2</td>
<td>i-PrOH</td>
<td>rt</td>
<td>24</td>
<td>none</td>
<td>42</td>
</tr>
<tr>
<td>3</td>
<td>i-PrOH</td>
<td>rt</td>
<td>72</td>
<td>none</td>
<td>49</td>
</tr>
<tr>
<td>4</td>
<td>i-PrOH</td>
<td>rt</td>
<td>72</td>
<td>1-9 [4]</td>
<td>47</td>
</tr>
</tbody>
</table>

**B. Improved coupling of isopropanol using 1-9**

no ligand - 18%  with 4 equiv of 1-9 - 56%
Under the same conditions described in Table 1.7, coupling boronate ester 1-1 with β-estradiol provided only a 5% yield of 1-49. We noticed that β-estradiol was not very soluble in toluene even at the elevated temperature, so we decided to switch solvents to something that β-estradiol will be soluble in. After considering our options, we decided to use isopropanol as it couples relatively poorly due to steric factors. Switching the solvent from PhMe to isopropanol proved beneficial as vinyl ether 1-49 was obtained in a 42% yield. What is more impressive is that the reaction required no heating. However, the yields could not be improved using ligand 1-9 even with elongated reaction times. At first glance, it may seem that ligand 1-9 is ineffective in this case, but it is crucial to realize that the coupling yields improved in the presence of ligand 1-9 using isopropanol (Table 1.8, B). In other words, ligand 1-9 may be providing a higher total yield of vinyl ether products other than 1-49 than the control reaction.

In order to see if this was the case, we thought a triple competition experiment would be the best approach for answering this question. We started by screening different alcohol coupling partners that we could use in the reaction (Table 1.9). Methanol and allyl alcohol were chosen as control couplings as both alcohols couple well even in the absence of π-ligands. As predicted, both alcohols coupled in a competition reaction in nearly equal amounts (entry 1). Employing both phenol and n-butanol in a competition resulted in a 93:7 ratio of products with the phenol-coupled product being major. In the presence of ligand 1-9, the outcome was identical to the control reaction. In the last entry, coupling vinyl boronate ester 1-25 in the presence of both phenol and isopropanol gave a 69:31 product ratio, favoring coupling of the phenol. The last entry is rather remarkable as the major product is obtained using only two equivalents of phenol in isopropanol. We decided that entry 4 would be the best conditions to gauge if ligand 1-9 does indeed increase the total coupling yields compared to the reaction without it.
Table 1.9 Screening results of competitive alcohol substrate pairs.

<table>
<thead>
<tr>
<th>entry</th>
<th>R^1OH</th>
<th>R^2OH</th>
<th>time</th>
<th>additive [equiv]</th>
<th>% composition (1-1:A:B)^a</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeOH</td>
<td>MeOH</td>
<td>45 min</td>
<td>none</td>
<td>0:45:55</td>
</tr>
<tr>
<td>2</td>
<td>MeOH</td>
<td>MeOH</td>
<td>17 h</td>
<td>none</td>
<td>0:93:7</td>
</tr>
<tr>
<td>3</td>
<td>MeOH</td>
<td>MeOH</td>
<td>17 h</td>
<td>1-9 [4]</td>
<td>0:96:4</td>
</tr>
</tbody>
</table>

By using conditions outlined in Table 1.9 entry 4, we designed a triple competition experiment consisting of a phenol and a primary alcohol, in an excess of a secondary alcohol (Scheme 1.12). The results of the triple competition experiments indicate that the reaction is selective for coupling phenolic alcohols over primary aliphatic alcohols, with limited coupling to secondary alcohols despite being in significant excess. Reactions conducted with ligand 1-9 gave a higher total yield than reactions without ligand 1-9. These two experiments strongly support that in the presence of ligand 1-9, more of the vinyl boronate ester converts to the vinyl ether(s)
rather than PdB and helps explain the result obtained from coupling β-estradiol with boronate ester 1-1 in the presence of ligand 1-9 (See Table 1.8, entry 4).

Scheme 1.12 Triple competition results.

We prepared authentic samples for both vinyl ether 1-52 and 1-55 in order to compare and correctly identify them as both proved difficult to obtain in pure form from the triple competition experiments. (Scheme 1.13)
Having observed a self-ligating π-ligand effect using allyl alcohol vs n-propanol (*vide supra*), we were curious if we would observe the same trend with homoallylic alcohols (Scheme 1.14, A). Using n-hexanol as a control substrate, it coupled with boronate ester 1-1 to give vinyl ether 1-59 in 42% yield. The same reaction conducted with ligand 1-9 provided the vinyl ether in 77% yield. With these base values complete, we now evaluated how homoallylic alcohols behave in the vinyl ether synthesis (Scheme 1.14, B). Coupling of leaf alcohol (cis-3-hexen-1-ol) with boronate ester 1-1 gave vinyl ether 1-60 in 60% yield. When π-ligands 1-3 and 1-9 were added, the yields were nearly identical to the control reaction. We also observed the same trend when boronate ester 1-25 was used, thus supporting what we are observing is real. We speculate that the π-bond of the alcohol is somehow influencing the outcome of reaction. Unlike allyl alcohol, leaf alcohol has the potential to π-bond coordinate to Cu in an intramolecular fashion. Given that leaf alcohol is in gross abundance compared to the external π-ligand suggests a significant π-ligand effect is occurring through leaf alcohol. Next, we switched to conditions that employed only four equivalents of alcohol to better understand if this π-ligand effect is occurring through an intramolecular coordination.
Scheme 1.14 Intramolecular vs intermolecular π-ligand effect.

A. Control reaction

\[
\begin{align*}
\text{BnO} = \text{B(pin)} + n-\text{HexOH} & \xrightarrow{2 \text{ equiv Cu(OAc)}_2} \text{BnO} = \text{B(pin)} - n-\text{Hex} \\
\text{entry} & \quad \text{additive} & \quad \text{yield (\%)} \\
1 & \quad \text{none} & \quad 42 \\
2 & \quad 4 \text{ equiv 1-9} & \quad 77
\end{align*}
\]

B. Intramolecular π-ligand effect

\[
\begin{align*}
\text{BnO} = \text{B(pin)} + \text{MeOH} \text{ solvent} & \xrightarrow{2 \text{ equiv Cu(OAc)}_2} \text{Me} \text{Me} \\
\text{Boronate ester} & \quad \text{additive} & \quad \text{product} & \quad \text{yield (\%)} \\
1-1 & \quad \text{none} & \quad 60 \\
1-1 & \quad 3\text{-hexyne} & \quad 1-60 & \quad 56 \\
1-1 & \quad 1-9 & \quad 57 \\
1-25 & \quad \text{none} & \quad 67 \\
1-25 & \quad 3\text{-hexyne} & \quad 1-61 & \quad 62 \\
1-25 & \quad 1-9 & \quad 60
\end{align*}
\]

\textit{n-Hexanol was again used as the control alcohol, which coupled with boronate ester 1-1 to give vinyl ether 1-59 in 44\% yield, and 48\% yield with ligand 1-9 (Scheme 1.15, A). Next, coupling leaf alcohol gave a lower yield compared to \textit{n}-hexanol after 12 hours. Increasing the reaction time to 48 hours gave nearly identical results compared to the results using \textit{n}-hexanol. Having identified that allenes are excellent π-bond ligands, we tested how homoallenic alcohols behave in the coupling reaction. Again, the reaction with and without ligand 1-9 provided nearly identical yields for vinyl ether 1-62. In the last entry, coupling an alcohol with a pendant \textit{α,β}-unsaturated ester with boronate 1-63 afforded vinyl ether 1-64 in low yields, which was also contaminated with inseparable and unidentifiable side products (Scheme 1.15, B). These results}
suggest the π-bond of the alcohol is interacting with the Cu-catalysts in an intramolecular fashion and the intermolecular mode is unlikely given the alcohol and π-ligand are in a 1:1 ratio. The intramolecular ligation occurs when the Cu(II) species undergo substitution with leaf alcohol, which allows the pendant π-bond to occupy an empty coordination site on the Cu(II) species.

Scheme 1.15 Competitive π-ligand effect using alcohol coupling partners with pendent π-bonds.

That, in turn, does not allow the external π-ligand to coordinate to the Cu(II) species, rendering it ineffective. Therefore, using ligand 1-9 or 3-hexyne in cases where one or both of the coupling partners possess a π-bond (alkene, alkyne, or an allene) that can interact with the Cu species will
result in no change and instead, the outcome is solely dependent on the π-bond characteristic for the coupling partner.

1.6 Effect of Cyclonona-1,2-diene (1-9) on Cu-Mediated Cross-Coupling of Arylboronic Acids and Benzimidazole

Moving forward, we tested the effect of both 3-hexyne and ligand 1-9 on the Chan–Evans–Lam cross-coupling reaction. The standard reaction involves coupling a nitrogen nucleophile with an arylboronic acid to form a new C–N bond. We have shown that ligand 1-9 and 3-hexyne promote the cross-coupling reaction by providing products in higher yields. However, only a small substrate scope existed at the time consisting of electron-neutral and electron-rich arylboronic acids (Table 1.10).

Table 1.10 Effect of ligand 1-9 on the Cu-mediated oxidative cross-couplings of arylboronic acids with benzimidazole.

<table>
<thead>
<tr>
<th>Ligand</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-65</td>
<td>65% A, 95% B</td>
</tr>
<tr>
<td>1-66</td>
<td>60% A, 95% B</td>
</tr>
<tr>
<td>1-67</td>
<td>58% A, 99% B</td>
</tr>
<tr>
<td>1-68</td>
<td>79% A, 96% B</td>
</tr>
<tr>
<td>1-69</td>
<td>78% A, 98% B</td>
</tr>
<tr>
<td>1-70</td>
<td>67% A, 64% B</td>
</tr>
<tr>
<td>1-71</td>
<td>51% A, 39% B</td>
</tr>
<tr>
<td>1-72</td>
<td>45% A, 40% B</td>
</tr>
<tr>
<td>1-73</td>
<td>37% A, 42% B</td>
</tr>
<tr>
<td>1-74</td>
<td>5% A, 12% B</td>
</tr>
</tbody>
</table>

N N COOME N N Cl

1-65 (1 equiv)  B(OH)₂  2 equiv Cu(OAc)₂  2 equiv Cu(OAc)₂
4 equiv pyridine 4 Å mol. sieves DCM, rt, 24 h conditions [A] = no ligand [B] = 4 equiv 1-9
In the first four examples, ligand 1-9 provided a significant boost in yields compared to the reactions conducted without ligand. However, in cases where electron-withdrawing arylboronic acids were used, ligand 1-9 could not improve the coupling yields.

Hoping to improve the coupling yields in the latter cases, we conducted the cross-coupling reactions with extended reaction times (Scheme 1.16). Cross-coupling benzimidazole (1-65) with (4-(methoxycarbonyl)phenyl)boronic acid for 60 hours gave ester 1-72 in 80% yield. In the presence of ligand 1-9, however, only a 61% yield was obtained. The same trend was observed using (4-benzoylphenyl)boronic acid, but with a more dramatic effect. The reactions that used ligand 1-9 gave a red solid that was observed after filtering the reaction through Celite® that was potentially Cu₂O. In contrast, the control reactions gave a green solid indicating that the reaction environments are not the same.

Scheme 1.16 Results of cross-coupling electron-poor arylboronic acids and benzimidazole with extended reaction times.

We then directed our attention to using a preformed boroxine rather than the boronic acid. Boroxines are typically unavoidable and exist in equilibrium with the boronic acids. The equilibrium depends on the electronic nature of the boronic acid, where boronic acids with electron
withdrawing groups are slower to dehydrate and form the boroxine than those with electron donating groups.\textsuperscript{37} Unfortunately, in both cases, there was no substantial difference in yield of the product by using the preformed boroxine (Scheme 1.17).

\textit{Scheme 1.17} Efforts to couple an \textit{in situ} generated boroxine with benzimidazole.

Up to this point, each reaction has used two equivalents of ligand 1-9 with respect to Cu(OAc)\textsubscript{2}. We were curious how the coupling yields are affected when the ratios of Cu(OAc)\textsubscript{2} to ligand 1-9 are different (Scheme 1.18). The results without added ligand 1-9 show an optimal yield for the product when one equivalent of Cu(OAc)\textsubscript{2} was used (blue line). When using two equivalents of ligand 1-9 with respect to Cu(OAc)\textsubscript{2}, we observed that both 1.5 and two equivalents are optimal and outperformed the control reaction (gray line). As stated earlier, ligand 1-9 has a stronger binding affinity for Cu(I) vs Cu(II) and this binding may slow oxidation of Cu(I) to Cu(II) which is a crucial process for avoiding side reactions.\textsuperscript{28b} The reoxidation process is essential when using less than two equivalents of Cu(OAc)\textsubscript{2} as it takes two Cu(II) species to produce one product. The two Cu(II) species are reduced to Cu(I) and in the presence of an oxidant are oxidized back to Cu(II). Ligand 1-9 is likely slowing down the Cu(I) to Cu(II) oxidation process, which explains the lower yields observed when using one equivalent of Cu(OAc)\textsubscript{2} with ligand 1-9 (gray line and orange line using one equivalent of Cu(OAc)\textsubscript{2}).
Scheme 1.18 Evaluating the ratio of ligand 1-9 to Cu(OAc)$_2$ on the cross-coupling yield for coupled product 1-72.

1.7 Effect of Cyclonona-1,2-diene (1-9) on Cu-Mediated Cross-Coupling and Homocoupling of Heterocycles

Having identified ligand 1-9 as an impactful π-ligand for vinyl ether synthesis and the Chan–Evans–Lam coupling, we were curious if this π-ligand effect impacted other Cu-promoted reactions. Of the many Cu-mediated cross-coupling reactions, we set out to test those that involve a disproportionation process as that is the common thread between the vinyl ether synthesis and the Chan–Evans–Lam reaction. Calculations by our group suggest the π-ligands decrease the
transition state energy for the disproportionation step, which is the rate-limiting step. We decided to test for a π-ligand effect in the Cu-mediated dehydrogenative cross coupling of various heterocycles, as the authors propose the mechanism proceeds through a convergent disproportionation process.\textsuperscript{38,39} Coupling of benzothiazole with 5-phenyloxazole was chosen as a starting point, which afforded a 51\% yield for 1-77 and a 40\% yield for 1-78, respectively. In the presence of ligand 1-9 the coupling yields decreased affording 1-77 in a 19\% yield and 1-78 in a 24\% yield (Scheme 1.19, A).

**Scheme 1.19** Initial screening results for cross-coupling and homocoupling various heterocycles via Cu-mediated oxidative coupling protocol.

**A – Results for cross-coupling 1-75 with 1-76 (GC-yields)**

\[
\begin{align*}
1-75 \quad \text{(1 equiv)} &+ 1-76 \quad \text{(1 equiv)} \quad \xrightarrow{1.2 \text{ equiv Cu(OAc)}_2, \text{DMSO}, \text{N}_2, 100 \, ^\circ \text{C}, 24 \text{ hr}} \quad 1-77 \quad \text{(51\% yield)}; \quad 1-78 \quad \text{(40\% yield)} \\
\text{no additive} &\quad \text{51\%} \quad \text{40\%} \\
\text{with 4 equiv 1-9} &\quad \text{19\%} \quad \text{24\%}
\end{align*}
\]

Yields were determined by GC analysis using 1-chlorohexadecane as an internal standard.

**B – Results for cross-coupling 1-76 with 1-79 (isolated yields)**

\[
\begin{align*}
1-76 \quad \text{(1 equiv)} &+ 1-79 \quad \text{(1 equiv)} \quad \xrightarrow{1.2 \text{ equiv Cu(OAc)}_2, \text{DMSO}, \text{N}_2, 12 \text{ h}} \quad 1-80 \quad \text{(8\% yield)}; \quad 1-81 \quad \text{(36\% yield)} \\
130 \, ^\circ \text{C} &\quad \text{8\%} \quad \text{36\%} \\
100 \, ^\circ \text{C} &\quad \text{10\%} \quad \text{34\%}
\end{align*}
\]

**C – Results for homocoupling 1-76 at various temperatures (isolated yields)**

\[
\begin{align*}
1-76 \quad \text{(1 equiv)} \quad \xrightarrow{1.2 \text{ equiv Cu(OAc)}_2, \text{DMSO}, \text{N}_2, 14 \text{ h}} \quad 1-81 \quad \text{(isolated yields)} \\
\text{no additive} &\quad \text{130 \, ^\circ \text{C}: 30\%} \quad \text{33\%} \\
\text{with 4 equiv 1-9} &\quad \text{110 \, ^\circ \text{C}: 36\%} \quad \text{24\%} \\
&\quad \text{100 \, ^\circ \text{C}: 25\%} \quad \text{25\%}
\end{align*}
\]

29
To mitigate this problem, we switched to benzoxazole, which gave a much cleaner result with high selectivity for homocoupled product 1-81 (Scheme 1.19, B). To make the process even simpler to study, we decided to delete benzoxazole and test for a π-ligand effect for the homocoupling of 1-76 to 1-81 (Scheme 1.19, C). Unfortunately, no π-ligand effect was observed screening the reaction at 100 °C, 110 °C, or 130 °C. The reaction itself seemed incapable of achieving high yields and is perhaps due to the electronegativity of the heterocycle.

While screening other potential heterocycles to study, N-benzylbenzimidazole (1-82) proved best as it provided the highest yield of the homocoupled product. Similar to heterocycle 1-76, we investigated the effect of ligand 1-9 on the homocoupling of heterocycle 1-82 under different reaction conditions (Table 1.11). The information gained from this set of experiments proved beneficial in answering several important questions we had. A very clear trend is observed regardless of the reaction conditions: the homocoupling yields are severely impacted and diminish as the loading of ligand 1-9 increases. From the data, it appears that ligand 1-9 is inhibiting the forward reaction, which is not something we would have predicted. As suggested earlier, ligand 1-9 appears to play a pivotal role in the vinyl ether synthesis by sequestering Cu(I) species and preventing the boronate esters form undergoing PdB. However, in this case, it appears to be impacting the Cu(II) species.
Table 1.11 Effect of ligand 1-9 on the Cu-mediated oxidative homocoupling of N-benzylbenzimidazole (1-82).

![Chemical structure](image)

The proposed mechanism for the Cu-mediated oxidative coupling of heterocycles is shown below (Scheme 1.20). Our rationale for describing the low yields for reactions that used ligand 1-9 may be attributed to the high energy needed for disproportionation of CuOAc → Cu(0) and Cu(OAc)₂. As mentioned earlier, π-bonds coordinate more strongly to Cu(I) than Cu(II) and in the case of the disproportionation step above, this favorable interaction is lost.
**Scheme 1.20** Proposed mechanism for Cu-mediated oxidative cross-coupling of heterocycles.

A survey of the literature for other Cu-mediated cross-coupling reactions revealed that many do not employ a ligand for Cu. To evaluate if ligand 1-9 is unique or if any ligand is detrimental in the cross-coupling reaction, we screened various known Cu ligands in homocoupling reaction (Scheme 1.21).

**Scheme 1.21** Ligand screen in the Cu-mediated oxidative homocoupling of heterocycle 1-82.

Indeed, the reaction is less effective when any external ligand is present. Miura and co-workers found that the homocoupling pathway is suppressed in the presence of a cross-coupling partner containing a coordinating pyrimidyl nitrogen. The authors state that the interaction between the pyrimidyl nitrogen and the Cu(II) center is key for the cross-coupling pathway. In our cases, the homocoupling yields are always lower in the presence of ligand 1-9, thus strongly suggesting
ligand 1-9 is stabilizing the electron-deficient heterocycleCu(II) species by lowering its reactivity towards a second concerted metalation-deprotonation (CMD) process.

During the above studies, several unexpected side products were isolated from the reactions, which also help to explain the decreased yields observed when using ligand 1-9 (Scheme 1.22). One side product is the dimerization of ligand 1-9, which is known to occur under thermal conditions and proceeds through a diradical mechanism.\textsuperscript{41}

\textit{Scheme 1.22} Common byproducts isolated from the Cu-mediated dehydrogenative cross-coupling reaction.

For example, cyclohepta-1,2-diene, cycloocta-1,2-diene, and cyclonona-1,2-diene (1-9) are known to dimerize at -30, 0, and 100 °C, respectively. In most cases, reactions that were conducted with ligand 1-9, especially at higher temperatures contained 1-88 and 1-89 which results from ligand 1-9 dimerizing with itself.\textsuperscript{42} Another interesting side product isolated from the reaction was
cyclonon-2-en-1-one (**1-90**) via the oxidation of ligand **1-9**. Give that both Cu(OAc)$_2$ and DMSO are known oxidizing agents, oxidation of ligand **1-9** to cyclonon-2-en-1-one is likely to occur given the reaction conditions. As mentioned earlier, enones are detrimental $\pi$-ligands in the vinyl ether synthesis and may exhibit the same impact on the homocoupling process. The last side product commonly isolated is the methyl thioether **1-91**. This product is likely occurring from coupling of disulfide or methanethiol with 1-N-benzylbenzimidazole in the presence of Cu(OAc)$_2$. Knowing that Cu(II) species are involved in these unproductive side-pathways better explains the increased yields obtained when using greater than 1.2 equivalents of Cu(OAc)$_2$.

Based on mechanistic suggestions for the Chan–Evans–Lam cross-coupling reaction, a proposed mechanism for the vinyl ether synthesis is shown below (Scheme 1.23). The reaction initiates with transmetalation between Cu(OAc)$_2$ (**A**) and boronate ester to give **B**. Following ligand exchange, the resulting electron rich Cu(II) intermediate **C** undergoes disproportionation with **A** to give Cu(III) intermediate **D**. Reductive elimination from **D** releases product and an equivalent of CuOAc (**E**), which could be oxidized to Cu(OAc)$_2$ (**A**) in the presence of O$_2$. It is known that Cu(I) complexes coordinate more strongly to alkenes and alkynes than Cu(II) complexes. Thus either product-forming reductive elimination from the Cu(III) complex or disproportionation of the two Cu(II) complexes could be beneficially impacted by a $\pi$-bond ligand coordinating to the incipient Cu(I) byproduct. Alternatively, the ligand could sequester Cu(I) complexes and prevent undesired pathways. It should be noted that little is known of Cu(I)-allene complexes. Similarly, nothing is known of Cu(III) $\pi$-bond complexes despite known Au(III) $\pi$-bond complexes. So in a fourth rationale, the $\pi$-bond ligand could potentially facilitate formation of the Cu(III) intermediate **D** necessary for product-forming reductive
elimination. However, calculations performed by our group disfavor this possibility as Cu(III) was found to coordinate π-bonds much more weakly than Cu(I).

**Scheme 1.23** Proposed mechanism of the Cu-mediated vinyl ether synthesis.

---

1.8 Conclusion

In conclusion, we identified allenes as π-bond ligands to promote copper-based oxidative couplings of alcohols with boronate esters. The role of the π-ligands are to alter or inhibit Cu(I) activity towards facilitating undesired side pathways such as protodeboronation. The data suggests allenes possessing too much strain (ring- or allene-strain) tend to participate in the reaction and cyclonona-1,2-diene (1-9) possess just enough strain to be an effective additive, but not enough to participate in the reaction. However, using π-ligands as additives in other Cu-mediated reactions is not general and depends on the compatibility of the π-ligand and the reactions conditions. While not a panacea, we believe that oft-neglected allenes deserve further exploration as ligands in transition-metal reactions, and work is ongoing to ascertain the benefits of allenes in other Cu-
mediated transformations. The next chapter will describe mechanistic details on the role of $\pi$-ligands role in the vinyl ether synthesis and provide detailed mechanisms of how these undesired side products arise.
1.9 Experimental Section

General Information

Unless otherwise specified, all reactions were performed open to air using dry solvents. Toluene (PhMe) was distilled from Na/benzophenone. Triethylamine (Et$_3$N), Hünig’s base (i-Pr$_2$NEt), $i$-propanol, and tert-butanol were distilled from CaH$_2$. Methanol, ethanol, $n$-propanol, $n$-butanol, $n$-hexanol, $n$-octanol, and 2-propanol were all distilled from magnesium turnings. 2-Chloroethanol was dried over CaSO$_4$ first and then distilled over K$_2$CO$_3$ prior to use. All other alcohols were either synthesized and used immediately or used as received from commercial sources. NMR data was obtained with Bruker Avance-500, ARX-500, or ARX-400 instruments and calibrated to the solvent signal (CDCl$_3$ : $\delta = 7.26$ ppm for $^1$H NMR, $\delta = 77.2$ ppm for $^{13}$C NMR; C$_6$D$_6$ : $\delta = 7.16$ for $^1$H NMR, 128.1 for $^{13}$C NMR; DMSO-d$_6$ : $\delta = 2.50$ for $^1$H NMR and 39.5 for $^{13}$C NMR. Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), followed by integration. Data for $^{13}$C NMR spectra are reported in terms of chemical shift. The following abbreviations are used for the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; m = multiplet; br = broad; and app. = apparent. IR spectra were recorded on a JASCO FTIR-4100 spectrophotometer. High-resolution mass spectra (HRMS) were recorded on a LCT premier mass spectrometer by electrospray ionization time-of-flight (ESI-TOF) or on a Thermo Fisher Scientific Exactive Plus with IonSense ID-CUBE Direct Analysis in Real Time (DART) ion source experiments. Reactions were monitored using thin layer chromatography performed on Macherey-Nagel POLYGRAM® SIL G/UV254 silica gel TLC plates and visualized with either of the following: UV light, ceric ammonium molybdate (CAM) stain and heat, or potassium permanganate (KMnO$_4$) stain and heat. Flash column chromatography was performed using 40-63 mesh micron silica gel.
Safety:

Experiments contained in this experimental section were conducted with proper personal protective equipment (gloves, lab coat, safety glasses) and engineering controls (fume hood). Hazardous substances used in this experimental include water reactive reagents such as: Pinacolborane (HBpin), Schwartz’s reagent (Cp2ZrHCl), sodium borohydride, sodium hydride, as well as health hazardous chemicals such as: methyl iodide (acute toxin), benzene (carcinogen), bromoform (carcinogen), and toluene (reproductive toxin).

Experimental Procedures

Vinyl Ether Synthesis using Alcohol as Reaction Solvent

To an oven-dried round bottom flask was added vinyl boronic acid pinacol ester (0.35 mmol, 1.0 equivalent), 2.0 mL of alcohol, triethylamine or Hünig’s base (0.70 mmol, 2.0 equivalents), ligand (1.4 mmol, 4.0 equivalents), followed by Cu(OAc)₂ (0.70 mmol, 2.0 equivalents). The reaction was stirred open to air at rt over 12 h (in the case of n-propanol 40-56 h). The progress of the reaction was monitored by TLC using hexanes:EtOAc (typically 19:1) with staining with ceric ammonium molybdate (CAM). Upon completion, the reaction mixture was added directly to and purified by flash chromatography on silica gel (19:1 hexanes:EtOAc).

Vinyl Ether Synthesis using only Four Equivalents of Alcohol

To an oven-dried round bottom flask was added vinyl boronic acid pinacol ester (0.35 mmol, 1.0 equivalent), alcohol (1.4 mmol, 4.0 equivalents), triethylamine or Hünig’s base (1.4 mmol, 4.0 equivalents), ligand (1.4 mmol, 4.0 equivalents), 2.0 mL of PhMe, followed by Cu(OAc)₂ (0.70 mmol, 2.0 equivalents). The reaction was stirred open to air at 50 °C over 12 h. In the case of (S)-(−)-perillyl alcohol and (1R)-(−)-myrtenol, the reaction was stirred for 72 and 24 h at 75°C, respectively. 3 Å molecular sieves were added to the coupling reaction that used (1R)-(−)-myrtenol.
(250 mg/1.4 mmol of alcohol). The progress of the reaction was monitored by TLC using hexanes/EtOAc (typically a 19:1) with staining with ceric ammonium molybdate (CAM). Upon completion, the reaction mixture was added directly to and purified by flash chromatography on silica gel (19:1 hexanes/EtOAc).

**Triple competition experiment**

To an oven-dried round bottom flask was added vinyl boronic acid pinacol ester (0.35 mmol, 1.0 equivalent), alcohol (1.4 mmol, 4.0 equivalents), triethylamine (0.7 mmol, 2.0 equivalents), ligand (1.4 mmol, 4.0 equivalents), 0.75 mL of dry i-PrOH (28 equivalents), followed by Cu(OAc)$_2$ (0.70 mmol, 2.0 equivalents). The reaction was stirred open to air at rt over 40 h. The progress of the reaction was monitored by TLC using hexanes/EtOAc (9:1 up to a 6:4, ceric ammonium molybdate (CAM)). Upon completion, the reaction mixture was added directly to and purified by flash chromatography on silica gel (19:1 to 6:4 gradient with hexanes/EtOAc).

**NMR solvent side-note:**

Deuterated benzene (C$_6$D$_6$) was a more appropriate NMR solvent than CDCl$_3$ for sensitive vinyl ethers. In cases where spectral data is reported in CDCl$_3$, the deuterated solvent was neutralized prior to use in most cases by passing it through a small pipet containing basic alumina.
General Procedure 1 (GP1)—1,2-Addition of O-Silyl Alkynes to Cyclic Ketone (1-19a–1-24a)

To a round bottom flask was added the silyl protected alkyne (1.2 equiv) and the headspace was sparged with N₂ for 5 min, followed by addition of dry THF (0.4 M w.r.t alkyne). The flask was cooled to -78 °C and n-BuLi (1.2 equiv, 2.5 M in hexanes) was added dropwise and stirred at -78 °C for 2 h. The cyclic ketone (1.0 equiv) was added dropwise at -78 °C and the reaction was slowly warmed to rt over 12 h. The yellow solution was cooled to 0 °C, quenched with sat. NH₄Cl and diluted Et₂O. The layers were separated and the aqueous layer was further extracted three additional times with Et₂O. The combined organic extracts were washed with brine, dried over Na₂SO₄, filtered and concentrated in vacuo. The crude residue was purified by column chromatography (silica gel, typically 9:1 hexanes/EtOAc) to give the desired silyl ether. In the case of 1-24a, the product could be purified by distillation under reduced pressure.

Silyl Ether 1-19a: Following GP1, cyclohexanone (1.96 g, 20.0 mmol) and tert-butyl(hept-6-yn-1-yl oxy)dimethylsilane⁴⁶ (5.43 g, 24.0 mmol) were used to prepare 1-19a. Purification by column chromatography gave silyl ether 1-19a (6.23 g, 96% yield) as a colorless oil.

Physical State: Clear colorless oil

¹H NMR (400MHz, CDCl₃): δ 3.60 (t, J = 6.5 Hz, 2 H), 2.21 (t, J = 6.9 Hz, 2 H), 1.92–1.78 (m, 3 H), 1.71–1.62 (m, 2 H), 1.58–1.41 (m, 11 H), 1.29–1.18 (m, 1 H), 0.89 (s, 9 H), 0.04 (s, 6 H)
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 84.7, 84.1, 68.9, 63.3, 40.4, 32.5, 28.7, 26.1, 25.4, 25.3, 23.6, 18.8, 18.5, -5.1

IR (ATR): 3373, 2931, 2857, 1462, 1254, 1099, 963 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{19}$H$_{35}$O$_2$Si [M−OH]$^+$: 307.24516, found 307.24471

Silyl Ether 1-20a: Following GP1, cyclopentanone (1.68 g, 20.0 mmol) and tert-butyl(hept-6-yn-1-yloxy)dimethylsilane$^{46}$ (5.43 g, 24.0 mmol) were used to prepare 1-20a. Purification by column chromatography gave silyl ether 1-20a (5.77 g, 93% yield) as a colorless oil.

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.60 (t, $J = 6.4$ Hz, 2 H), 2.20 (t, $J = 7.1$ Hz, 2 H), 1.94–1.85 (m, 4 H), 1.82–1.76 (m, 2 H), 1.74–1.67 (m, 2 H), 1.62–1.46 (m, 5 H), 1.45–1.38 (m, 2 H), 0.88 (s, 9 H), 0.04 (s, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 84.3, 83.6, 74.8, 63.2, 42.7, 32.5, 28.7, 26.1, 25.3, 23.5, 18.8, 18.5, -5.0

IR (ATR): 3409, 2933, 2858, 1465, 1253, 1097, 832 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{18}$H$_{33}$O$_2$Si [M−OH]$^+$: 293.22951, found 293.22916

Silyl Ether 1-21a: Following GP1, cyclohexanone (4.90 g, 50.0 mmol) and tert-butyldimethyl(pent-4-yn-1-yloxy)silane$^{47}$ (11.90 g, 60.0 mmol) were used to prepare 1-21a.
Purification by column chromatography gave silyl ether 1-21a (13.20 g, 89% yield) as a colorless oil.

**Physical State:** Clear colorless oil

^1H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) (br s, 1 H), 3.66 (t, \(J = 6.1\) Hz, 2 H), 2.22 (t, \(J = 6.8\) Hz, 2 H), 1.71–1.65 (m, 2 H), 1.63–1.53 (m, 4 H), 1.47–1.36 (m, 5 H), 1.21–1.11 (m, 1 H), 0.86 (s, 9 H), 0.03 (s, 6 H)

^13C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 85.5, 82.0, 66.5, 61.0, 39.9, 31.4, 25.7, 24.9, 22.8, 17.9, 14.3, -5.4

IR (ATR): 3395, 2931, 2857, 2240, 1471, 1254, 1104, 835, 775 cm\(^{-1}\)

HRMS (DART-TOF) \(m/z\): Calculated for C\(_{17}\)H\(_{33}\)O\(_2\)Si [M+H]\(^+\) : 297.22443, found 297.22415

![Silyl Ether 1-23a](image)

Silyl Ether 1-23a: Following GP1, cyclopentanone (4.20 g, 50 mmol) and tert-butyldimethyl(pent-4-yn-1-ynoxy)silane\(^47\) (11.90 g, 60.0 mmol) were used to prepare 1-23a. Purification by column chromatography gave silyl ether 1-23a (13.26 g, 94% yield) as a colorless oil.

**Physical State:** Clear colorless oil

^1H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 4.96 (s, 1 H), 3.64 (t, \(J = 6.2\) Hz, 2 H), 2.20 (t, \(J = 6.9\) Hz, 2 H), 1.80–1.54 (m, 10 H), 0.86 (s, 9 H), 0.03 (S, 6 H)

^13C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 85.9, 80.8, 72.4, 60.9, 42.0, 31.3, 25.7, 22.8, 17.9, 14.3, -5.3

IR (ATR): 3417, 2957, 2932, 2859, 2239, 1465, 1259, 1103, 832 cm\(^{-1}\)

HRMS (DART-TOF) \(m/z\): Calculated for C\(_{16}\)H\(_{30}\)O\(_2\)Si [M+H]\(^+\) : 283.20878, found 283.20871
Silyl Ether 1-24a: Following GP1, cyclobutanone (3.29 g, 47.0 mmol) and tert-butyldimethyl(pent-4-yn-1-yloxy)silane\(^\text{47}\) (11.15 g, 56.2 mmol) were used to prepare 1-24a. Purification by distillation (observed b.p. 120 °C @ 1.0 mmHg) gave silyl ether 1-24a (9.87 g, 79% yield) as a colorless oil.

**Physical State:** Clear colorless oil

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 3.69 (t, J = 6.1\ \text{Hz}, 2\ \text{H}), 2.41–2.33\ (m, 2\ \text{H}), 2.30\ (t, J = 6.9\ \text{Hz}, 2\ \text{H}), 2.15\ (\text{br s, 1 H}), 1.82–1.73\ (m, 2\ \text{H}), 1.70\ (tt, J = 6.5, 6.5\ \text{Hz}, 2\ \text{H}), 0.89\ (s, 9\ \text{H}), 0.05\ (s, 6\ \text{H})\)

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta 84.1, 83.7, 68.2, 61.7, 38.9, 31.8, 26.1, 18.5, 15.3, 12.9, \) -5.1

IR (ATR): 3349, 2951, 2929, 2856, 2236, 1471, 1250, 1102, 833 cm\(^{-1}\)

HRMS (DART-TOF) \(m/z\): Calculated for C\(_{15}\)H\(_{27}\)OSi [M–OH]\(^+\) : 251.18256, found 251.18159

**General Procedure 2 (GP2)–Etherification (1-19b–1-24b)**

To a solution containing silyl ether (1.0 equiv) in dry DMF (0.5 M) was added NaH (1.3 equiv, 60% dispensed in mineral oil) portionwise at 0 °C and then stirred for an additional 20 min under N\(_2\). Methyl iodide (1.2 equiv) was added dropwise at 0 °C and the reaction was slowly warmed to rt over 12 h. The flask was cooled to 0 °C and quenched with sat. NH\(_4\)Cl. The contents were transferred to separatory funnel and diluted with Et\(_2\)O (10 x the amount of DMF used), washed
with H₂O (5 x (2 x the amount of DMF used)) then finally brine. The organic layer was over Na₂SO₄, filtered, and concentrated in vacuo. The crude residue was purified by column chromatography (typically 95:5 hexanes/EtOAc) to afford the desired methyl ether.

Methyl Ether 1-19b: Following GP2, 1-19a (3.24 g, 10.0 mmol) was used to prepare 1-19b. Purification by column chromatography gave methyl ether 1-19b (3.22 g, 95% yield) as a clear oil.

Physical State: Clear colorless oil

¹H NMR (400 MHz, CDCl₃): δ 3.60 (t, J = 6.5 Hz, 2 H), 3.30 (s, 3 H), 2.25 (t, J = 6.9 Hz, 2 H), 1.87–1.81 (m, 2 H), 1.68–1.41 (m, 13 H), 1.29–1.11 (m, 1 H), 0.88 (s, 9 H), 0.03 (s, 6 H)

¹³C NMR (100 MHz, CDCl₃): δ 86.4, 81.2, 74.2, 63.3, 50.6, 37.2, 32.5, 28.9, 26.1, 25.7, 25.3, 23.0, 18.8, 18.5, -5.1

IR (ATR): 2931, 2856, 1471, 1461, 1254, 1093, 833 cm⁻¹

HRMS (DART-TOF) m/z: Calculated for C₁₉H₃₅OSi [M−OMe]⁺: 307.24516, found 07.24478

Methyl Ether 1-20b: Following GP2, 1-20a (3.10 g, 10.0 mmol) was used to prepare 1-20b. Purification by column chromatography gave methyl ether 1-20b (3.12 g, 96% yield) as a clear oil.

Physical State: Clear colorless oil
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.60 (t, $J$ = 6.3 Hz, 2 H), 3.30 (s, 3 H), 2.20 (t, $J$ = 6.9 Hz, 2 H), 1.99–1.90 (m, 2 H), 1.86–1.76 (m, 2 H), 1.74–1.64 (m, 4 H), 1.55–1.49 (m, 4 H), 1.47–1.40 (m, 2 H), 0.89 (s, 9 H), 0.04 (s, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 85.3, 81.4, 81.0, 63.3, 51.9, 39.3, 32.5, 28.8, 26.1, 25.3, 23.4, 18.9, 18.5, -5.1

IR (ATR): 2949, 2931, 2857, 1471, 1254, 1100, 835 cm$^{-1}$

HRMS (DART-TOF) $m/z$: Calculated for C$_{19}$H$_{37}$O$_2$Si [M+H]$^+$: 325.25573, found 325.25546

Methyl Ether 1-21b: Following GP2, 1-21a (2.96 g, 10.0 mmol) was used to prepare 1-21b. Purification by column chromatography gave methyl ether 1-21b (2.79 g, 90% yield) as a clear oil.

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.70 (t, $J$ = 6.1 Hz, 2 H), 3.33 (s, 3 H), 2.31 (t, $J$ = 6.9 Hz, 2 H), 1.87–1.78 (m, 2 H), 1.71 (tt, $J$ = 6.5, 6.5 Hz, 2 H), 1.65–1.58 (m, 2 H), 1.55–1.46 (m, 5 H), 1.29–1.21 (m, 1 H), 0.89 (s, 9 H), 0.05 (s, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 86.0, 81.3, 74.1, 61.8, 50.6, 37.2, 32.1, 26.1, 25.7, 23.0, 18.5, 15.2, -5.1

IR (ATR): 2933, 2857, 2250, 1448, 1255, 1096, 776 cm$^{-1}$

HRMS (DART-TOF) $m/z$: Calculated for C$_{18}$H$_{34}$O$_2$Si [M−OMe]$^+$: 279.21386, found 279.2137
Methyl Ether 1-23b: Following GP2, 1-23a (2.82 g, 10.0 mmol) was used to prepare 1-23b. Purification by column chromatography gave methyl ether 1-23b (2.74 g, 93% yield) as a clear oil.

**Physical State:** Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.69 (t, $J = 6.2$ Hz, 2 H), 3.30 (s, 3 H), 2.30 (t, $J = 7.2$ Hz, 2 H), 1.99–1.91 (m, 2 H), 1.85–1.76 (m, 2 H), 1.75–1.63 (m, 6 H), 0.89 (s, 9 H), 0.05 (s, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 85.0, 81.4, 80.9, 61.8, 51.9, 39.3, 32.0, 26.1, 23.4, 18.5, 15.2, -5.1

IR (ATR): 2957, 2862, 1465, 1255, 1103, 774 cm$^{-1}$

HRMS (DART-TOF) $m/z$: Calculated for C$_{17}$H$_{32}$O$_2$Si [M–OMe]$^+$: 265.19821, found 265.19797

Methyl Ether 1-24b: Following GP2, 1-24a (13.42 g, 50.0 mmol) was used to prepare 1-24b. Purification by column chromatography gave methyl ether 1-24b (9.12 g, 68% yield) as a clear oil.

**Physical State:** Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.70 (t, $J = 6.2$ Hz, 2 H), 3.25 (s, 3 H), 2.33 (t, $J = 7.0$ Hz, 2 H), 2.30–2.22 (m, 2 H), 2.22–2.13 (m, 2 H), 1.87–1.76 (m, 2 H), 1.72 (app. p, $J = 6.6$ Hz, 2 H), 0.89 (s, 9 H), 0.06 (s, 6 H)
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 85.0, 81.1, 73.5, 61.8, 51.5, 35.7, 32.0, 26.1, 18.5, 15.3, 13.2, -5.1

IR (ATR): 2929, 2857, 2232, 1471, 1248, 1103, 833, 774 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{16}$H$_{30}$O$_2$Si [M–OMe]$^+$: 251.18256, found 251.18224

General Procedure 3 (GP3) – Deprotection of Silyl Ethers to Alcohols (1-19c – 1-24c)

To a solution containing methyl ether (1.0 equiv) in dry THF (0.2 M) at 0 °C under N$_2$ was added TBAF (1.4 equiv, 1 M in THF) dropwise. The reaction was warmed to rt and stirred until all of the methyl ether was consumed (monitored by thin-layer chromatography, hexanes/EtOAc). The reaction was quenched with H$_2$O and extracted with EtOAc. The organic extracts were washed with sat. NH$_4$Cl and brine then dried over Na$_2$SO$_4$ and filtered. The solvent was removed under reduced pressure and the resulting residue was purified by column chromatography (silica gel, 7:3 hexanes/EtOAc) to afford the desired alcohol.

Alcohol 1-19c: Following GP3, 1-19b (1.69 g, 5.0 mmol) was used to prepare 1-19c. Purification by column chromatography gave alcohol 1-19c (904 mg, 81% yield) as a clear oil.

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.65 (t, $J = 6.4$ Hz, 2 H), 3.34 (s, 3 H), 2.25 (t, $J = 6.8$ Hz, 2 H), 1.89–1.79 (m, 2 H), 1.65–1.45 (m, 13 H), 1.36 (br s, 1 H), 1.31–1.21 (m, 1 H)
$^{13}$C NMR (100 MHz, CDCl$_3$): δ 86.2, 81.4, 74.2, 63.0, 50.6, 37.2, 32.4, 28.8, 25.7, 25.1, 23.0, 18.8

IR (ATR): 3395, 2933, 2857, 1443, 1292, 1079, 762 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{14}$H$_{25}$O$_2$ [M+H]$^+$: 225.18490, found 225.18475

Alcohol 1-20c: Following GP3, 1-20b (1.62 g, 5.0 mmol) was used to prepare 1-20c. Purification by column chromatography gave alcohol 1-20c (1.02 g, 97% yield) as a clear oil.

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): δ 3.64 (t, $J = 6.5$ Hz, 2 H), 3.30 (s, 3 H), 2.23 (t, $J = 6.8$ Hz, 2 H), 2.00–1.90 (m, 2 H), 1.85–1.76 (m, 2 H), 1.73–1.65 (m, 4 H), 1.60–1.40 (m, 7 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 85.2, 81.5, 81.0, 63.0, 51.9, 39.3, 32.4, 28.7, 25.1, 23.4, 18.8

IR (ATR): 3435, 2939, 2862, 1454, 1327, 1071, 752 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{13}$H$_{22}$O$_2$ [M+H]$^+$: 211.16925, found 211.16893

Alcohol 1-21c: Following GP3, 1-21b (1.55 g, 5.0 mmol) was used to prepare 1-21c. Purification by column chromatography gave alcohol 1-21c (726 mg, 74% yield) as a clear oil.

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): δ 3.66 (t, $J = 6.4$ Hz, 2 H), 3.27 (s, 3 H), 2.54 (s, 1 H), 2.29 (t, $J = 6.9$ Hz, 2 H), 1.81–1.74 (m, 2 H), 1.70 (tt, $J = 6.4$, 6.4 Hz, 2 H), 1.61–1.53 (m, 2 H), 1.50–1.39 (m, 5 H), 1.25–1.16 (m, 1 H)
**Alcohol 1-22c, with a modified one-pot procedure:** Following GP1, cyclopentanone (1.68 g, 20.0 mmol) and tert-butyl(hex-5-yn-1-yloxy)dimethylsilane (5.09 g, 24.0 mmol) were reacted until all the cyclopentanone was consumed (ca 4 h, monitored by thin-layer chromatography). The flask was then cooled to 0 °C and diluted with dry DMF (40 mL) and methyl iodide (2.17 mL, 35 mmol, 1.75 equiv) was added dropwise. The reaction was allowed to warm to rt over 2 h. The reaction was then cooled to 0 °C and TBAF (40 mL, 40 equiv, 1.0 M in THF) was added dropwise. The reaction was slowly warmed to rt over 24 h, and then worked up as described in GP3. The crude residue was purified by column chromatography to give alcohol **1-22c** (2.82 g, 72% yield) as a clear oil.

**Physical State:** Clear colorless oil

**1H NMR (400 MHz, CDCl3):** δ 3.67 (t, J = 6.5 Hz, 2 H), 3.30 (s, 3 H), 2.27 (t, J = 6.8 Hz, 2 H), 1.99–1.92 (m, 2 H), 1.85–1.78 (m, 2 H), 1.72–1.57 (m, 8 H), 1.37 (br. s, 1 H)

**13C NMR (100 MHz, CDCl3):** δ 85.0, 81.7, 80.9, 62.5, 51.9, 39.3, 32.0, 25.2, 23.3, 18.6

**IR (ATR):** 3392, 2938, 2870, 2233, 1447, 1335, 1070 cm⁻¹

**HRMS (DART-TOF) m/z:** Calculated for C₁₂H₂₀O₂ [M+H]⁺: 197.15360, found 197.15340
Alcohol 1-23c: Following GP3, 1-23b (1.48 g, 5.0 mmol) was used to prepare 1-23c. Purification by column chromatography gave alcohol 1-23c (682 mg, 75% yield) as a clear oil.

**Physical State:** Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.69 (t, $J = 6.3$ Hz, 2 H), 3.26 (s, 3 H), 2.31 (t, $J = 6.9$ Hz, 2 H), 2.17 (br s, 1 H), 1.95–1.88 (m, 2 H), 1.82–1.62 (m, 8 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 84.6, 81.8, 80.9, 61.7, 51.8, 39.2, 32.6, 23.3, 15.4

IR (ATR): 3398, 2946, 2823, 2233, 1432, 1331, 1070 cm$^{-1}$

HRMS (DART-TOF) $m/z$: Calculated for C$_{11}$H$_{18}$O$_2$ [M–OMe]$^+$: 151.11174, found 151.11150

Alcohol 1-24c: Following GP3, 1-24b (2.82 g, 10.0 mmol) was used to prepare 1-24c. Purification by column chromatography gave alcohol 1-24c (1.49 g, 89% yield) as a clear oil.

**Physical State:** Clear colorless oil

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 4.47 (t, $J = 5.1$ Hz, 1 H), 3.46 (td, $J = 6.2$, 5.3 Hz, 2 H), 3.13 (s, 3 H), 2.27 (t, $J = 7.0$ Hz, 2 H), 2.19–2.06 (m, 4 H), 1.79–1.69 (m, 2 H), 1.59 (app. p, $J = 6.7$ Hz, 2 H)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 84.9, 81.1, 72.6, 59.3, 50.6, 34.9, 31.6, 14.5, 12.7

IR (ATR): 3363, 2939, 2232, 1433, 1272, 1129, 1051, 933, 810 cm$^{-1}$

HRMS (DART-TOF) $m/z$: Calculated for C$_{10}$H$_{16}$O$_2$ [M–OMe]$^+$: 137.09609, found 137.09600
General Procedure 4 (GP4)–Conversion of Alcohols to Iodides (1-19d–1-24d)

To a solution of PPh₃ (1.5 equiv) in CH₂Cl₂ (0.15 M w.r.t PPh₃) was added I₂ (1.5 equiv) in one portion (note: reaction slowly becomes dark purple) at rt and stirred for 10 min under N₂. Imidazole (2.5 equiv) was added in one portion at rt (note: addition of imidazole produces an orange/brown mixture) and stirred for 10 min under N₂. The primary alcohol (1.0 equiv) was added dropwise and stirred at rt until all of the alcohol was consumed (monitored by thin-layer chromatography, 9:1 hexanes/EtOAc). The reaction was quenched with H₂O (equal volume to CH₂Cl₂ used), then sat. Na₂S₂O₃ was added and stirred until two distinct clear colorless layers appeared. The CH₂Cl₂ layer was separated and the aqueous layer was further extracted with CH₂Cl₂. The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated in vacuo. The resulting white solid was dissolved in CH₂Cl₂ followed by addition of silica gel and concentrated again to give a free flowing white solid. Purification by column chromatography (dry-loading process) using 9:1 hexanes/EtOAc afforded the desired alkyl iodide.

Alkyl Iodide 1-19d: Following GP4, 1-19c (224 mg, 1.0 mmol) was used to prepare 1-19d. Purification by column chromatography gave alkyl iodide 1-19d (271 mg, 81% yield) as a clear oil.

Physical State: Clear colorless oil
**1H NMR (400 MHz, CDCl3):** δ 3.34 (s, 3 H), 3.19 (t, J = 6.8 Hz, 2 H), 2.25 (t, J = 6.5 Hz, 2 H), 1.89–1.79 (m, 4 H), 1.66–1.45 (m, 12 H), 1.31–1.22 (m, 1 H)

**13C NMR (100 MHz, CDCl3):** δ 85.9, 81.6, 74.1, 50.6, 37.2, 33.1, 29.8, 27.9, 25.7, 23.1, 18.7, 6.9

**IR (ATR):** 2932, 2855, 2820, 1447, 1292, 1089, 924 cm\(^{-1}\)

**HRMS (DART-TOF) m/z:** Calculated for C\(_{14}\)H\(_{24}\)IO [M+H]\(^+\) : 335.08663, found 335.08624

Alkyl Iodide 1-20d: Following GP4, 1-20c (210 mg, 1.0 mmol) was used to prepare 1-20d. Purification by column chromatography gave alkyl iodide 1-20d (244 mg, 76% yield) as a clear oil.

**Physical State:** Clear colorless oil

**1H NMR (400 MHz, CDCl3):** δ 3.30 (s, 3 H), 3.19 (t, J = 7.0 Hz, 2 H), 2.24 (t, J = 6.5 Hz, 2 H), 2.00–1.91 (m, 2 H), 1.87–1.77 (m, 4 H), 1.73–1.65 (m, 4 H), 1.55–1.46 (m, 4 H)

**13C NMR (100 MHz, CDCl3):** δ 84.8, 81.8, 80.9, 52.0, 39.3, 33.1, 29.8, 27.8, 23.4, 18.7, 6.9

**IR (ATR):** 2936, 2869, 1456, 1330, 1203, 1074, 970, 630 cm\(^{-1}\)

**HRMS (DART-TOF) m/z:** Calculated for C\(_{13}\)H\(_{21}\)IO [M+H]\(^+\) : 321.07098, found 321.07074

Alkyl Iodide 1-21d: Following GP4, 1-21c (392 mg, 2.0 mmol) was used to prepare 1-21d. Purification by column chromatography gave alkyl iodide 1-21d (581 mg, 95% yield) as a clear oil.

**Physical State:** Clear colorless oil
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.33 (s, 3 H), 3.30 (t, $J = 6.7$ Hz, 2 H), 2.39 (t, $J = 6.7$ Hz, 2 H), 1.99 (tt, $J = 6.7$, 6.7 Hz, 2 H), 1.88–1.79 (m, 2 H), 1.67–1.59 (m, 2 H), 1.56–1.44 (m, 5 H), 1.32–1.22 (m, 1 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 84.0, 82.6, 74.1, 50.6, 37.1, 32.3, 25.6, 23.0, 19.9, 5.5

IR (ATR): 2932, 2855, 2237, 1446, 1220, 1089, 924 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{12}$H$_{19}$IO [M−OMe]$^+$: 275.02912, found 275.02875

Alkyl Iodide 1-22d: Following GP4, 1-22c (981 mg, 5.0 mmol) was used to prepare 1-22d. Purification by column chromatography gave alkyl iodide 1-22d (1.53 g, 95% yield) as a clear oil.

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.30 (s, 3 H), 3.21 (t, $J = 6.8$ Hz, 2 H), 2.26 (t, $J = 6.9$ Hz, 2 H), 1.98–1.89 (m, 4 H), 1.85–1.77 (m, 2 H), 1.74–1.58 (m, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 84.3, 82.1, 80.9, 52.0, 39.3, 32.6, 29.5, 17.8, 6.3

IR (ATR): 2938, 2837, 2233, 1436, 1329, 1074, 971 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{12}$H$_{19}$IO [M+H]$^+$: 307.05533, found 307.05508

Alkyl Iodide 1-23d: Following GP4, 1-23c (364 mg, 2.0 mmol) was used to prepare 1-23d. Purification by column chromatography gave alkyl iodide 1-23d (554 mg, 95% yield) as a clear oil.

Physical State: Clear colorless oil
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 3.30 (s, 3 H), 3.29 (t, \(J = 6.8\) Hz, 2 H), 2.37 (t, \(J = 6.7\) Hz, 2 H), 1.98 (tt, \(J = 6.7, 6.7\) Hz, 2 H), 1.98–1.91 (m, 2 H), 1.85–1.77 (m, 2 H), 1.73 (m, 4 H)

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 83.0, 82.7, 80.9, 52.0, 39.3, 32.3, 23.4, 19.9, 5.4

IR (ATR): 2960, 2871, 2820, 2233, 1428, 1220, 1074, 969 cm\(^{-1}\)

HRMS (DART-TOF) \(m/z\): Calculated for C\(_{11}\)H\(_{17}\)IO [M–OMe]\(^+\) : 261.01347, found 261.01318

**Alkyl Iodide 1-24d:** Following GP4, 1-24c (1.00 g, 6.0 mmol) was used to prepare 1-24d. Purification by column chromatography gave alkyl iodide 1-24d (1.60 g, 96% yield) as a clear oil.

**Physical State:** Clear colorless oil

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 3.31 (t, \(J = 6.7\) Hz, 2 H), 3.25 (s, 3 H), 2.40 (t, \(J = 6.7\) Hz, 2 H), 2.29–2.14 (m, 4 H), 2.00 (p, \(J = 6.6\) Hz, 2 H), 1.87–1.76 (m, 2 H)

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 88.0, 82.6, 73.4, 51.6, 35.6, 32.2, 20.0, 13.2, 5.4

IR (ATR): 2986, 2937, 2817, 2232, 1426, 1220, 1170, 1048, 746 cm\(^{-1}\)

HRMS (DART-TOF) \(m/z\): Calculated for C\(_{10}\)H\(_{15}\)IO [M–OMe]\(^+\) : 246.99782, found 246.99693

**General Procedure 5 (GP5) – Preparation of Alkenyldiene Cycloalkanes (1-19–1-24)**

To a flame-dried round bottom flask containing a solution of the alkyl iodide (1.0 equiv) in \(n\)-pentane/Et\(_2\)O (3/2, 0.1 M total) at \(-78\) °C was added \(t\)-BuLi (2.2 equiv, 1.7 M in pentane). The reaction was stirred for 5 min at \(-78\) °C, then slowly warmed to rt over 1 h. The flask was then placed in an ice bath (0 °C) and quenched with dropwise addition of MeOH then diluted with H\(_2\)O.
The organic layer was separated and the aqueous layer was further extracted with Et₂O. The combined organic extracts were washed with H₂O and then dried over MgSO₄, filtered, and concentration in vacuo. The crude residue was purified by column chromatography on silica gel with 100% pentane to afford the desired allene.

![Allene 1-19](image)

**Allene 1-19:** Following GP5, alkyl iodide 1-19d (2.20 g, 6.6 mmol) was used to prepare 1-19. Purification by column chromatography gave allene 1-19 (462 mg, 40% yield) as a clear oil.

**Physical State:** Clear colorless oil

_1H NMR (400 MHz, C₆D₆):_ δ 2.24–2.14 (m, 8 H), 1.59–1.48 (m, 8 H), 1.44–1.33 (m, 4 H)

_13C NMR (100 MHz, C₆D₆):_ δ 193.2, 100.5, 32.9, 28.2, 26.7

IR (ATR): 2920, 2850, 2832, 1966, 1444, 1231, 990, 539 cm⁻¹

HRMS (DART-TOF) m/z: Calculated for C₁₃H₂₁ [M+H]⁺: 177.16377, found 177.16376

![Allene 1-20](image)

**Allene 1-20:** Following GP5, alkyl iodide 1-20d (1.87 g, 5.8 mmol) was used to prepare 1-20. Purification by column chromatography gave allene 1-20 (857 mg, 91% yield) as a clear oil.

**Physical State:** Clear colorless oil

_1H NMR (400 MHz, C₆D₆):_ δ 2.43–2.36 (m, 4 H), 2.26–2.20 (m, 4 H), 1.60–1.47 (m, 8 H), 1.42–1.34 (m, 2 H)

_13C NMR (100 MHz, C₆D₆):_ δ 192.1, 103.2m 1015, 32.7, 31.9, 28.1, 27.4, 26.6

IR (ATR): 2922, 2850, 1981, 1443, 1213, 979, 893, 854 cm⁻¹

HRMS (DART-TOF) m/z: Calculated for C₁₂H₁₉ [M+H]⁺: 163.14812, found 163.14732
Allene 1-21: Following GP5, alkyl iodide 1-21d (2.63 g, 8.6 mmol) was used to prepare 1-21. Purification by column chromatography gave allene 1-21 (778 mg, 61% yield) as a clear oil.

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 2.88–2.80 (m, 4 H), 2.24–2.18 (m, 4 H), 1.79–1.68 (m, 2 H), 1.55–1.48 (m, 4 H), 1.38–1.31 (m, 2 H)

$^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 190.8, 105.5, 98.8, 32.8, 31.0, 28.0, 26.5, 17.8

IR (ATR): 2923, 2851, 2831, 1991, 1445, 1205, 987, 893 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{11}$H$_{17}$ [M+H]$^+$: 149.13247, found 149.13231

Allene 1-22: Following GP5, alkyl iodide 1-22d (1.49 g, 4.8 mmol) was used to prepare 1-22. Purification by column chromatography gave allene 1-22 (585 mg, 82% yield) as a clear oil.

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 2.47–2.35 (m, 8 H), 1.56–1.45 (m, 8 H)

$^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 191.3, 104.4, 31.6, 27.3

IR (ATR): 2949, 2864, 1975, 1435, 1290, 1131, 944, 789 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{11}$H$_{16}$ [M+H]$^+$: 149.13247, found 149.13240

Allene 1-23: Following GP5, alkyl iodide 1-23d (2.89 g, 9.9 mmol) was used to prepare 1-23. Purification by column chromatography gave allene 1-23 (944 mg, 71% yield) as a clear oil.
**Physical State:** Clear colorless oil

$^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 2.90–2.83 (m, 4 H), 2.42–2.35 (m, 4 H), 1.79–1.68 (m, 2 H), 1.51–1.42 (m, 4 H)

$^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 189.9, 106.9, 101.7, 31.9, 30.9, 27.3, 17.8

**IR (ATR):** 2949, 2865, 1979, 1433, 1282, 1$^{11}$32, 1043, 944, 783 cm$^{-1}$

**HRMS (DART-TOF) m/z:** Calculated for C$_{10}$H$_{15}$ [M+H]$^+$: 135.11682, found 135.11658

![Allene 1-24](image)

**Allene 1-24:** Following GP5, alkyl iodide 1-24d (2.34 g, 8.4 mmol) was used to prepare 1-24. Purification by column chromatography gave allene 1-24 (805 mg, 79% yield) as a clear oil.

**Physical State:** Clear orange oil

$^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 2.82 (t, $J = 7.8$ Hz, 8 H), 1.70 (app. p, $J = 7.8$ Hz, 4 H)

$^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 188.6, 104.3, 31.1, 17.7

**IR (ATR):** 2978, 2949, 2918, 2029, 1416, 1225, 1044, 972 cm$^{-1}$

**HRMS (DART-TOF) m/z:** Calculated for C$_9$H$_{12}$ [M+H]$^+$: 121.10117, found 121.10002

![1-36](image)

**Physical State:** clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.38–7.25 (m, 5 H), 5.85 (ddt, $J = 17.0$, 10.2, 6.7 Hz, 1 H), 5.10 (ddt, $J = 17.2$, 1.6, 1.6 Hz, 1 H), 5.05 (ddt, $J = 10.2$, 1.2, 1.2 Hz, 1 H), 4.52 (s, 2 H), 3.53 (t, $J = 6.8$ Hz, 2 H), 2.38 (app. qt, $J = 6.8$, 1.4 Hz, 2 H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 138.6, 135.4, 128.5, 127.8, 127.7, 116.5, 73.0, 69.8, 34.4.

Matches previously reported spectral data.\(^{49}\)
Physical State: Clear yellow oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.20 (d, $J = 8.9$ Hz, 2 H), 7.50 (d, $J = 8.9$ Hz, 2 H), 7.36–7.26 (m, 5 H), 6.40 (dt, $J = 12.7$, 1.2 Hz, 1 H), 4.91 (dt, $J = 12.6$, 7.4 Hz, 1 H), 4.82 (s, 2 H), 4.51 (s, 2 H), 3.46 (t, $J = 6.7$ Hz, 2 H), 2.25 (app. qd, $J = 6.9$, 1.2 Hz, 2 H).

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 147.6, 146.9, 144.8, 138.6, 128.5, 127.8, 127.76, 127.72, 123.8, 102.2, 73.1, 70.9, 69.7, 28.5.

IR (ATR): 3062, 3028, 2923, 2854, 1653, 1604, 1519, 1343, 1158, 1097, 929, 845, 738, 698 cm$^{-1}$

HRMS (DART-TOF) $m/z$: Calculated for C$_{18}$H$_{23}$N$_2$O$_4$ [M+NH$_4$]$^+$ : 331.16523, found 331.16473.

Physical State: Clear colorless oil

$^1$H NMR (500 MHz, C$_6$D$_6$): $\delta$ 6.32 (dt, $J = 12.5$, 1.2 Hz, 1 H), 5.45–5.43 (m, 1 H), 4.87 (dt, $J = 12.5$, 7.4 Hz, 1 H), 3.95–3.93 (m, 2 H), 3.55 (t, $J = 6.3$ Hz, 2 H), 2.33 (dt, $J = 8.6$, 5.6 Hz, 1 H), 2.22–2.10 (m, 3 H), 2.02 (app. qd, $J = 7.2$, 1.1 Hz, 2 H), 1.98–1.94 (m, 1 H), 1.57 (app. p, $J = 6.3$ Hz, 2 H), 1.24 (d, $J = 8.5$ Hz, 1 H), 1.21 (s, 3 H), 0.93 (s, 9 H), 0.83 (s, 3 H), 0.00 (s, 6 H)

$^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 147.0, 145.1, 120.2, 103.9, 72.2, 62.5, 43.7, 41.3, 38.2, 34.3, 31.9, 31.5, 26.3, 26.2, 24.6, 21.3, 18.5, -5.0

IR (ATR): 3057, 2988, 2928, 2856, 1671, 1651, 1472, 1462, 1253, 1155, 1097, 834, 774 cm$^{-1}$

HRMS (DART-TOF) $m/z$: Calculated for C$_{21}$H$_{39}$O$_2$Si [M+H]$^+$ : 351.27138, found 351.27097
**Physical State:** Clear colorless oil

**$^1$H NMR (400 MHz, C$_6$D$_6$):** $\delta$ 7.30 (dd, $J = 7.2$, 1.2 Hz, 2 H), 7.19–7.09 (m, 4 H), 6.90 (dd, $J = 8.4$, 2.6 Hz, 1 H), 6.83 (d, $J = 2.6$ Hz, 1 H), 6.50 (dt, $J = 12.2$, 1.2 Hz, 1 H), 5.48 (dt, $J = 12.1$, 7.1 Hz, 1 H), 4.31 (s, 2 H), 3.44 (dd, $J = 8.6$, 8.6 Hz, 1 H), 3.28 (t, $J = 6.6$ Hz, 2 H), 2.64 (ddd, $J = 16.7$, 10.8, 6.0 Hz, 1 H), 2.60 (ddd, $J = 17.0$, 7.0, 2.6 Hz, 1 H), 2.21 (qd, $J = 6.9$, 1.3 Hz, 2 H), 2.10 (ddddd, $J = 13.2$, 4.3, 4.0, 2.3 Hz, 1 H), 2.00 (ddd, $J = 11.3$, 11.3, 4.3 Hz, 1 H), 1.93–1.81 (m, 2 H), 1.63 (ddddd, $J = 12.3$, 6.0, 3.0, 2.5 Hz, 1 H), 1.46–1.20 (m, 4 H), 1.17–0.84 (m, 4 H), 0.81 (ddd, $J = 12.1$, 10.9, 7.3 Hz, 1 H), 0.68 (s, 3 H).

**$^{13}$C NMR (100 MHz, C$_6$D$_6$):** $\delta$ 155.9, 144.1, 139.3, 138.4, 135.0, 128.6, 127.8, 127.6, 117.1, 114.5, 109.1, 126.9, 81.7, 73.0, 70.6, 50.2, 44.4, 43.5, 39.0, 37.2, 31.0, 30.0, 28.5, 27.5, 26.7, 23.4, 11.3.

**IR (ATR):** 3385, 2926, 2918, 1672, 1606, 1495, 1250, 1235, 1107 cm$^{-1}$

**HRMS (DART-TOF) m/z:** Calculated for C$_{29}$H$_{35}$O$_2$ [M–OH]$^+$: 415.26315, found 415.26196.

**Physical State:** Clear colorless oil

**$^1$H NMR (400 MHz, CDCl$_3$):** $\delta$ 7.39–7.22 (m, 6 H), 6.91 (d, $J = 7.5$ Hz, 1 H), 6.88–6.80 (m, 2 H), 6.49 (dt, $J = 12.1$, 1.2 Hz, 1 H), 5.38 (dt, $J = 12.1$, 7.4 Hz, 1 H), 4.54 (s, 2 H), 3.84 (t, $J = 6.4$ Hz, 2 H) 3.53 (t, $J = 6.7$ Hz, 2 H), 2.83 (t, $J = 6.5$ Hz, 2 H), 2.35 (app. qd, $J = 7.1$, 1.2 Hz, 2 H), 1.48 (br s, 1 H).
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.6, 143.1, 140.5, 138.5, 129.8, 128.5, 127.8, 127.7, 123.4, 117.2, 114.6, 109.8, 73.1, 70.4, 63.6, 39.2, 28.1

$^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.37–7.25 (m, 5 H), 7.21 (t, $J = 7.8$ Hz, 1 H), 6.90 (d, $J = 6.8$ Hz, 1 H), 6.87–6.84 (m, 1 H), 6.83–6.79 (m, 1 H), 6.68 (dt, $J = 12.1$, 1.2 Hz, 1 H), 5.29 (dt, $J = 12.1$, 7.5 Hz, 1 H), 4.61 (t, $J = 5.2$ Hz, 1 H), 4.48 (s, 2 H), 3.58 (td, $J = 7.0$, 5.2 Hz, 2 H), 3.48 (t, $J = 6.6$ Hz, 2 H), 2.69 (t, $J = 7.0$ Hz, 2 H), 2.29 (app. qd, $J = 7.0$, 1.2 Hz, 2 H)

$^{13}$C NMR (100 MHz, DMSO-d$_6$): $\delta$ 156.6, 142.8, 141.5, 138.5, 129.3, 128.2, 127.4, 127.3, 123.1, 116.4, 113.4, 109.1, 71.7, 69.7, 61.9, 38.8, 27.2

IR (ATR): 3420, 3061, 2926, 2857, 2167, 1667, 1585, 1486, 1448, 1249, 1161, 1094, 932, 736, 698 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{19}$H$_{23}$O$_3$ [M+H]$^+$ : 299.16417, found 299.16353

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.34–7.26 (m, 5 H), 7.15 (td, $J = 7.5$, 1.0 Hz, 1 H), 6.79–6.75 (m, 1 H), 6.69–6.66 (m, 2 H), 6.29 (dt, $J = 12.7$, 1.2 Hz, 1 H), 5.14 (bs, 1 H), 4.78 (dt, $J = 12.7$, 7.4 Hz, 1 H), 4.51 (s, 2 H), 3.84 (t, $J = 7.0$ Hz, 2 H), 3.44 (t, $J = 6.8$ Hz, 2 H), 2.88 (t, $J = 7.0$ Hz, 2 H), 2.22 (app. qd, $J = 6.7$, 1.2 Hz, 2 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 155.8, 147.5, 140.4, 138.5, 129.7, 128.5, 127.9, 127.7, 121.4, 116.0, 113.5, 100.5, 73.0, 71.1, 69.6, 35.7, 28.5

$^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 9.24 (s, 1 H), 7.36–7.23 (m, 5 H), 7.05 (t, $J = 7.4$ Hz, 1 H), 6.67–6.56 (m, 3 H), 6.34 (d, $J = 12.7$ Hz, 1 H), 4.71 (td, $J = 12.7$, 7.3 Hz, 1 H), 4.44 (s, 2 H), 3.78 (t, $J = 6.8$, 2 H), 3.37 (t, $J = 6.8$ Hz, 2 H), 2.77 (t, $J = 6.8$ Hz, 2 H), 2.13 (app. q, $J = 6.8$ Hz, 2 H)
$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 157.2, 147.2, 139.7, 138.6, 129.1, 128.1, 127.4, 127.2, 119.4, 115.7, 113.0, 99.8, 71.6, 70.4, 69.1, 34.9, 27.8

IR (ATR): 3327, 3061, 3027, 2935, 2861, 1653, 1594, 1455, 1158, 927, 739, 696 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{19}$H$_{23}$O$_3$ [M+H]$^+$ : 299.16417, found 299.16346.

Physical State: Clear yellow oil

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.68–7.62 (m, 1 H), 7.43–7.37 (m, 1 H), 7.27–7.21 (m, 2 H), 7.17 (d, $J = 3.1$ Hz, 1 H), 7.13 (ddd, $J = 7.9$, 6.9, 0.9 Hz, 1 H), 6.94 (d, $J = 7.7$ Hz, 1 H), 6.84–6.79 (m, 2 H), 6.60 (dt, $J = 12.2$, 1.3 Hz, 1 H), 6.56 (dd, $J = 3.1$, 0.8 Hz, 1 H), 5.55 (dt, $J = 12.2$, 6.7 Hz, 1 H), 4.74 (dd, $J = 6.7$, 1.3 Hz, 2 H), 3.83 (t, $J = 6.5$ Hz, 2 H), 2.83 (t, $J = 6.5$ Hz, 2 H)

$^{13}$C NMR (400 MHz, CDCl$_3$): δ 157.1, 145.5, 140.8, 136.1, 129.9, 128.9, 127.4, 124.1, 121.7, 121.3, 119.6, 117.6, 115.0, 109.6, 107.7, 101.7, 63.5, 44.1, 39.1

$^1$H NMR (400 MHz, DMSO-$d_6$): δ 7.59–7.56 (m, 1 H), 7.56–7.53 (m, 1 H), 7.40 (d, $J = 3.1$ Hz, 1 H), 7.24 (t, $J = 7.8$ Hz, 1 H), 7.14 (ddd, $J = 8.2$, 7.0, 1.1 Hz, 1 H), 7.08 (dt, $J = 12.0$, 1.0 Hz, 1 H), 7.02 (ddd, $J = 7.8$, 7.0, 1.0 Hz, 1 H), 6.94 (d, $J = 8.0$ Hz, 1 H), 6.90–6.88 (m, 1 H), 6.81 (ddd, $J = 8.1$, 2.5, 0.8 Hz, 1 H), 6.44 (dd, $J = 3.1$, 0.8 Hz, 1 H), 5.47 (dt, $J = 12.0$, 7.3 Hz, 1 H), 4.82 (dd, $J = 7.2$, 1.0 Hz, 2 H), 4.63 (t, $J = 5.2$ Hz, 1 H), 3.59 (dd, $J = 6.9$, 5.2 Hz, 2 H), 2.70 (t, $J = 6.9$ Hz, 2 H)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): δ 156.2, 145.5, 141.7, 135.4, 129.4, 128.2, 128.0, 123.6, 120.9, 120.4, 118.9, 116.7, 113.7, 110.0, 107.6, 100.7, 61.8, 43.1, 38.8
IR (ATR): 3464, 3098, 3053, 2924, 2867, 1671, 1582, 1483, 1441, 1242, 1156, 1044, 930, 738, 969 cm\(^{-1}\)

HRMS (DART-TOF) \(m/z\): Calculated for C\(_{19}\)H\(_{20}\)NO\(_2\) [M+H]\(^+\): 294.14885, found 294.14831

Physical State: Clear yellow oil

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.65–7.60 (m, 1 H), 7.38–7.34 (m, 1 H), 7.20 (ddd, \(J = 8.2, 7.0, 1.2\) Hz, 1 H), 7.17–7.08 (m, 3 H), 6.76 (d, \(J = 7.6\) Hz, 1 H), 6.69–6.65 (m, 1 H), 6.65–6.63 (m, 1 H), 6.54 (d, \(J = 12.6\) Hz, 1 H), 6.49 (dd, \(J = 3.1, 0.8\) Hz, 1 H), 4.98 (dt, \(J = 12.6, 7.1\) Hz, 1 H), 4.84 (bs, 1 H), 4.61 (dd, \(J = 7.0, 1.0\) Hz, 2 H), 3.87 (t, \(J = 6.8\) Hz, 2 H), 2.89 (t, \(J = 6.8\) Hz, 2 H)

\(^1^3\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 155.8, 149.7, 140.0, 136.0, 129.8, 128.9, 127.3, 121.5, 121.4, 121.1, 119.5, 116.0, 113.6, 109.6, 101.3, 99.5, 69.8, 44.9, 35.6

\(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 9.24 (s, 1 H), 7.54–7.51 (m, 1 H), 7.50–7.47 (m, 1 H), 7.32 (d, \(J = 3.1\) Hz, 1 H), 7.10 (ddd, \(J = 9.1, 7.0, 1.1\) Hz, 1 H), 7.04 (t, \(J = 8.0\) Hz, 1 H), 7.02–6.97 (m, 1 H), 6.76 (d, \(J = 12.5\) Hz, 1 H), 6.64–6.57 (m, 3 H), 6.40 (dd, \(J = 3.1, 0.7\) Hz, 1 H), 4.90 (dt, \(J = 12.5, 7.3\) Hz, 1 H), 4.66 (d, \(J = 7.2\) Hz, 2 H), 3.83 (t, \(J = 6.8\) Hz, 2 H), 2.78 (t, \(J = 6.7\) Hz, 2 H)

\(^1^3\)C NMR (100 MHz, DMSO-\(d_6\)): \(\delta\) 157.2, 149.7, 139.5, 135.4, 129.1, 128.2, 127.8, 120.8, 120.3, 119.4, 118.8, 115.7, 113.1, 109.9, 100.4, 99.4, 69.3, 43.8, 34.8

IR (ATR): 3411, 3048, 2928, 2872, 1655, 1583, 1457, 1152, 926, 740, 697 cm\(^{-1}\)

HRMS (DART-TOF) \(m/z\): Calculated for C\(_{19}\)H\(_{20}\)NO\(_2\) [M+H]\(^+\): 294.14885, found 294.14808
Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.35–7.26 (m, 5 H), 6.30 (dt, $J = 12.6$, 1.1 Hz, 1 H), 5.49 (dtt, $J = 10.9$, 7.2, 1.4 Hz, 1 H), 5.33 (dtt, $J = 10.9$, 7.2, 1.4 Hz, 1 H), 4.77 (dt, $J = 12.9$, 7.4 Hz, 1 H), 4.51 (s, 2 H), 3.64 (t, $J = 6.7$ Hz, 2 H), 3.44 (t, $J = 6.7$ Hz, 2 H), 2.38 (qd, $J = 7.7$, 0.8 Hz, 2 H), 2.23 (qd, $J = 6.9$, 1.1 Hz, 2 H), 2.05 (app. pd, $J = 7.4$, 1.4 Hz, 2 H), 0.96 (t, $J = 7.7$ Hz, 3 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 147.6, 138.7, 134.3, 128.5, 127.8, 127.7, 124.3, 100.2, 73.0, 71.2, 68.8, 28.6, 27.5, 20.8, 14.4

IR (ATR): 3004, 2964, 2857, 1674, 1654, 1455, 1169, 1097, 734 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{17}$H$_{25}$O$_2$ [M+H]$^+$: 261.18490, found 261.18393

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.64 (ddd, $J = 7.8$, 0.9, 0.9 Hz, 1 H), 7.39 (ddd, $J = 8.2$, 1.5, 0.8 Hz, 1 H), 7.22 (ddd, $J = 8.2$, 7.0, 1.1 Hz, 1 H), 7.15 (d, $J = 3.1$ Hz, 1 H), 7.12 (ddd, $J = 7.9$, 7.1, 1.0 Hz, 1 H), 6.58 (dt, $J = 12.7$, 1.1 Hz, 1 H), 6.51 (dd, $J = 3.1$, 0.8 Hz, 1 H), 5.51 (dtt, $J = 10.7$, 7.2, 1.5 Hz, 1 H), 5.33 (dtt, $J = 10.7$, 7.2, 1.5 Hz, 1 H), 5.00 (dt, $J = 12.7$, 7.1 Hz, 1 H), 4.64 (dd, $J = 7.1$, 1.1 Hz, 2 H), 3.68 (t, $J = 6.8$ Hz, 2 H), 2.40 (qd, $J = 6.8$, 1.0 Hz, 2 H), 2.06 (app. pd, $J = 7.1$, 1.2 Hz, 2 H), 0.98 (t, $J = 7.6$ Hz, 3 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 149.9, 136.0, 134.6, 128.9, 127.2, 124.0, 121.5, 121.1, 119.4, 109.6, 101.2, 99.2, 69.0, 44.9, 27.3, 20.8, 14.3
**IR (ATR):** 3052, 2956, 2881, 1673, 1654, 1462, 1167, 738 cm\(^{-1}\)

**HRMS (DART-TOF) m/z:** Calculated for C\(_{17}H_{22}NO\) [M+H]\(^+\) : 256.16959, found 256.16867

![Chemical Structure 1-62]

**Physical State:** Clear colorless oil

**\(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)):** \(\delta\) 7.31 (d, \(J = 7.7\) Hz, 2 H), 7.20–7.16 (m, 2 H), 7.09 (tt, \(J = 7.3, 1.3\) Hz, 1 H), 6.27 (dt, \(J = 12.7, 1.2\) Hz, 1 H), 5.01 (tqq, \(J = 6.6, 3.6, 3.0\) Hz, 1 H), 4.83 (dt, \(J = 12.6, 7.4\) Hz, 1 H), 4.33 (s, 2 H), 3.54 (t, \(J = 6.9\) Hz, 2 H), 2.24 (app. q, \(J = 6.7\) Hz, 2 H), 2.19 (qd, \(J = 7.4, 1.1\) Hz, 2 H), 1.60 (s, 3 H), 1.56 (s, 3 H)

**\(^13\)C NMR (100 MHz, C\(_6\)D\(_6\)):** \(\delta\) 203.0, 148.1, 139.5, 128.5, 127.8, 127.6, 100.1, 95.5, 85.6, 73.0, 71.5, 68.7, 29.8, 29.0, 20.6 (2 C’s)

**IR (ATR):** 2980, 2907, 2853, 1972, 1670, 1655, 1454, 1235, 1096, 739 cm\(^{-1}\)

**HRMS (DART-TOF) m/z:** Calculated for C\(_{18}H_{25}O_2\) [M+H]\(^+\) : 273.18490, found 273.18365

![Chemical Structure 1-69]

**\(^1\)H NMR (400 MHz, CDCl\(_3\)):** \(\delta\) 8.17 (s, 1 H), 7.93–7.91 (m, 1 H), 7.78 (d, \(J = 8.5\) Hz, 2 H), 7.67–7.63 (m, 2 H), 7.61–7.55 (m, 3 H), 7.50 (dd, \(J = 7.8, 7.8\) Hz, 2 H), 7.41 (ddd, \(J = 7.3, 1.1, 1.1\) Hz, 1 H), 7.38–7.34 (m, 2 H)

Matches previously reported spectral data.\(^{50}\)
1H NMR (400 MHz, CDCl3): δ 8.09 (br s, 1 H), 7.92–7.86 (m, 2 H), 7.56 (d, J = 8.7 Hz, 2 H), 7.52–7.49 (m, 1 H), 7.47 (d, J = 8.7 Hz, 2 H), 7.38–7.32 (m, 2 H)

Matches previously reported spectral data.51

1H NMR (400 MHz, CDCl3): δ 8.05 (br s, 1 H), 7.90–7.87 (m, 1 H), 7.60–7.61 (m, 1 H), 7.50–7.43 (m, 3 H), 7.32 (ddd, J = 7.2, 7.2, 1.4 Hz, 1 H), 7.32 (ddd, J = 7.2, 7.2, 1.4 Hz, 1 H), 7.23–7.20 (m, 1 H)

13C NMR (100 MHz, CDCl3): δ 143.3, 143.1, 134.4, 133.7, 131.6, 131.2, 130.4, 128.9, 128.9, 123.8, 122.9, 120.6, 110.7

Matches previously reported spectral data.50

**Physical State:** White solid

1H NMR (400 MHz, CDCl3): δ 8.25 (d, J = 8.1 Hz, 2 H), 8.16 (br s, 1 H), 7.91–7.85 (m, 1 H), 7.64–7.55 (m, 3 H), 7.39–7.33 (m, 2 H), 3.97 (s, 3 H)
\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \( \delta \) 66.1, 144.6, 142.0, 140.3, 133.3, 131.7, 129.6, 124.2 (2 C’s), 123.3, 121.0, 110.6, 52.6

IR (ATR): 3079, 2953, 1716, 1605, 1517, 1281, 1113 cm\textsuperscript{-1}

HRMS (DART-TOF) \( m/z \): Calculated for C\textsubscript{15}H\textsubscript{13}N\textsubscript{2}O\textsubscript{2} [M+H]\textsuperscript{+}: 253.09715, found 253.09612.

\begin{center}
\includegraphics[width=0.2\textwidth]{1-73.png}
\end{center}

\textbf{Physical State:} White solid

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 8.21 (br s, 1 H), 8.03 (d, \( J = 8.3 \) Hz, 2 H), 7.91 (br s, 1 H), 7.85 (d, \( J = 8.3 \) Hz, 2 H), 7.80–7.60 (m, 4 H), 7.53 (dd, \( J = 7.4, 7.4 \) Hz, 2 H), 7.40–7.35 (m, 2 H)

\textsuperscript{13}C NMR (100 MHz, DMSO-\textit{d}\textsubscript{6}): \( \delta \) 194.7, 138.4, 136.6, 132.9, 131.5, 129.6, 128.6, 124.8, 124.1, 123.7, 118.6, 111.6 (3 overlapping C signals)

IR (ATR): 3063, 1653, 1600, 1455, 1279, 905, 727 cm\textsuperscript{-1}

HRMS (DART-TOF) \( m/z \): Calculated for C\textsubscript{20}H\textsubscript{15}N\textsubscript{2}O [M+H]\textsuperscript{+}: 299.11788, found 299.11731.

\begin{center}
\includegraphics[width=0.2\textwidth]{1-74.png}
\end{center}

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \( \delta \) 8.48 (d, \( J = 9.1 \) Hz, 2 H), 8.21 (br s, 1 H), 7.96–7.89 (m, 1 H), 7.74 (d, \( J = 9.1 \) Hz, 2 H), 7.63 (app. br s, 1 H), 7.44–7.34 (m, 2 H)

Matches previously reported spectral data.\textsuperscript{52}
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.92 (d, $J = 7.3$ Hz, 2 H), 7.79 (d, $J = 7.8$ Hz, 2 H), 7.52 (ddd, $J = 8.3$, 7.5, 1.1 Hz, 2 H), 7.46 (ddd, $J = 8.3$, 7.6, 1.1 Hz, 2 H)

Matches previously reported spectral data.$^{53}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.82–7.78 (m, 4 H), 7.56 (s, 2 H), 7.47 (dd, $J = 7.6$, 7.6 Hz, 4 H), 7.39 (tt, $J = 7.4$, 1.2 Hz, 2 H)

Matches previously reported spectral data.$^{54}$

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.90–7.80 (m, 2 H), 7.40–7.26 (m, 6 H), 7.19–6.97 (m, 6 H), 6.24 (s, 4 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 143.1, 142.9, 137.1, 135.7, 128.8, 127.6, 127.0, 124.3, 123.1, 120.7, 111.0, 48.7

Matches previously reported spectral data.$^{55}$
\( ^1\text{H} \text{ NMR (400 MHz, CDCl}_3\):} \ \delta 6.30 \ (\text{dt, } J = 12.2, 9.1 \text{ Hz, 1 H}), \ 6.05 \ (\text{dt, } J = 12.5, 0.9 \text{ Hz, 1 H}), \ 2.73–2.68 \ (\text{m, 2 H}), \ 2.59–2.52 \ (\text{m, 2 H}), \ 1.85–1.77 \ (\text{m, 2 H}), \ 1.63–1.51 \ (\text{4 H}), \ 1.46–1.41 \ (\text{m, 2 H})

\( ^{13}\text{C NMR (100 MHz, CDCl}_3\):} \ \delta 206.3, \ 142.8, \ 134.1, \ 41.9, \ 28.89, \ 28.81, \ 26.6, \ 26.4, \ 24.2

Matches previously reported spectral data.\(^56\)

\( ^1\text{H} \text{ NMR (400 MHz, CDCl}_3\):} \ \delta 7.71 \ (\text{ddd, } J = 7.9, 0.9, 0.9 \text{ Hz, 1 H}), \ 7.33–7.26 \ (\text{m, 3 H}), \ 7.24–7.12 \ (\text{m, 5 H}), \ 5.28 \ (\text{s, 2 H}), \ 2.81 \ (\text{s, 3 H})

\( ^{13}\text{C NMR (100 MHz, CDCl}_3\):} \ \delta 153.3, \ 143.8, \ 136.6, \ 135.7, \ 129.0, \ 128.1, \ 127.0, \ 122.1, \ 122.0, \ 118.4, \ 109.1, \ 47.7, \ 14.9

Matches previously reported spectral data.\(^57\)

**Compound 1-56:** To a 100 mL oven-dried round bottom flask under an atmosphere of nitrogen was added 58\(^58\) (25.05 mmol, 1 equiv), 30 mL of dry CH\(_2\)Cl\(_2\), followed by Et\(_3\)N (6.98 mL, 50.1 mmol, 2 equiv) and cooled to 0 °C. Pivaloyl chloride (PivCl, 3.08 mL, 25.05 mmol, 1 equiv) in 10 mL of dry CH\(_2\)Cl\(_2\) was added dropwise at 0 °C and the mixture was allowed to warm to rt and stir for an additional 2 h. The reaction was monitored by TLC (1:1 hexanes/EtOAc, CAM stain) and
once all of 58 had been consumed the reaction was poured into ice water and extracted with CH2Cl2 (4 x 40 mL) and dried over MgSO4 and concentrated in vacuo. The crude oil was purified by column chromatography (6:4 hexanes/EtOAc) to give (4.6215 g, 83% yield) of 64 as colorless oil.

**Physical State:** Clear colorless oil

**1H NMR (400 MHz, DMSO-d6):** δ 7.30 (t, J = 7.7 Hz, 1 H), 7.10 (ddd, J = 7.6 Hz, 1.5, 1.0 Hz, 1 H), 6.93 (t, J = 1.8 Hz, 1 H), 6.90 (ddd, J = 8.0, 2.4, 1.0 Hz, 1 H), 4.63 (t, J = 5.2 Hz, 1 H), 3.60 (td, J = 6.9, 5.2 Hz, 2 H), 2.72 (t, J = 6.9 Hz, 2 H), 1.29 (s, 9 H)

**13C NMR (100 MHz, DMSO-d6):** δ 176.3, 150.6, 141.4, 128.9, 126.2, 121.8, 119.0, 61.7, 38.5, 38.4, 26.7

**IR (ATR):** 3398, 2965, 2977, 2874, 1750, 1612, 1589, 1482, 1281, 1236, 1147, 1110, 1043, 692 cm⁻¹

**HRMS (ESI-TOF) m/z:** Calculated for C13H18O3Na [M+Na]⁺: 245.1154, found 245.1150

![Vinyl Ether 1-52](image)

**Vinyl Ether 1-52:** Following **Vinyl Ether Synthesis using only Four Equivalents of Alcohol** Procedure, compound 1-56 (4 mmol, 4 equiv) was coupled with vinyl boronate ester 1-1 (1 mmol, 1 equiv) with the exception that the reaction was stirred at rt, rather than at 50 °C. The reaction mixture was passed through a small pad of silica gel, and washed with hexane/EtOAc (8:2) and concentrated in vacuo. The crude residue was dissolved in MeOH (5.8 mL), followed by addition of K₂CO₃ (5.0 equiv). The reaction was stirred at rt for 1. The reaction was then quenched with water (10 mL) and the aqueous layer was extracted with CH₂Cl₂ (3 x 20 mL). The organic exacts were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was
purified by column chromatography on silica gel (hexanes/EtOAc, 8:2) to afford vinyl ether **1-52** (81.2 mg, 27% yield) as a clear colorless oil.

![Vinyl Ether 1-55](image)

**Vinyl Ether 1-55:** Following the same procedure described for vinyl ether **1-52** with the exception that the reaction was stirred for 24 h in step 1. The crude residue was dissolved in MeOH (6.0 mL), followed by addition of K$_2$CO$_3$ (6.0 equiv). The reaction was stirred at rt for 16. The reaction was then quenched with water (10 mL) and the aqueous layer was extracted with CH$_2$Cl$_2$ (3 x 20 mL). The organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (hexanes/EtOAc, 9:1) to afford vinyl ether **1-55** (67.8 mg, 20% yield) as a clear yellow oil.

**Preparation of Starting Materials**

5-Methylhexa-3,4-dien-1-ol,$^{59}$ 4-biphenylboronic acid,$^{60}$ **1-1,$^{16}$ 1-9,$^{61}$ 1-15,$^{62}$ 1-25,$^{16}$ 1-27,$^{63}$ 1-28,$^{64}$ 1-40,$^{65}$ 1-43,$^{66}$ (1R)-(−)-myrtenol (1-44),$^{67}$ 1-63,$^{16}$ 1-76,$^{68}$ 1-88,$^{61}$ and 1-89,$^{61}$ were all prepared from known literature procedures.
1.10 $^1$H and $^{13}$C NMR Spectra
$^{13}$C NMR (100 MHz, CDCl$_3$)
\[^1\text{H NMR (400 MHz, CDCl}_3\)]

\[
\text{OTBS}
\]

\[
\text{1-20a}
\]

\[
\text{HCO}
\]
MeO

1-20d

$^1$H NMR (400 MHz, CDCl$_3$)
\[ ^{13}\text{C NMR (100 MHz, CDCl}_3) \]
$^1$H NMR (400 MHz, C$_6$D$_6$)
$^{1}$H NMR (400 MHz, CDCl$_3$)
$\text{13C NMR (100 MHz, CDCl}_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, C$_6$D$_6$)
$^{13}$C NMR (100 MHz, $C_6D_6$)
$^{13}$C NMR (100 MHz, DMSO-$d_6$)

Chemical shifts in ppm:
1H NMR (400 MHz, CDCl₃)
1H NMR (400 MHz, DMSO-d6)
$^{13}$C NMR (100 MHz, DMSC-d$_6$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
1H NMR (400 MHz, CDCl₃)
$^1$H NMR (400 MHz, C$_6$D$_6$)
$^{13}$C NMR (100 MHz, C$_6$D$_6$)
$^{1}$H NMR (400 MHz, CDCl$_3$)

N N

COOMe

1-72
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, DMSO-$_d$$_6$)
1.11 References


27. Martin, T. J. Phosphine Catalysis using Allenoates with pro-Nucleophiles or Aryldienes; Development of an Asymmetric Phosphine Catalyst; and Allenes as π-Ligands in Copper-Mediated Cross-Coupling. Ph.D. Dissertation University of California Los Angeles, 2014.


30. (a) See ref. 28b (b) Chu, L.; Qing, F-L. Org. Lett. 2010, 12, 5060.


CHAPTER TWO
Mechanistic Studies Towards Elucidating the Beneficial Effect of π-Ligands on Cu-Mediated Cross-Coupling Reactions

2.1 Background and Introduction

Pd–catalyzed cross-coupling reactions are robust methods for C–C and C–heteroatom bond formation.\(^1\) One of the most widely used is the Suzuki–Miyaura coupling and it stands alone as one of the most potent ways for forming C–C bonds.\(^2\) The Buchwald-Hartwig amination, discovered in 1995, is an extremely robust method for forming C–N bonds and is used extensively in the pharmaceutical and agrochemical industries.\(^3\) Complementing these Pd–catalyzed reactions are the Cu–catalyzed versions and are known as the Ullmann\(^4\) and the Goldberg\(^5\) condensations, which date back to the early 1900s. While revolutionary for their time, the Ullmann and Goldberg condensations are used much less in today’s era due to harsh reaction conditions such as elevated temperature, which severely limits the substrate scope and functional group compatibility.\(^6\)

The use of copper cross-couplings remained underutilized until the breakthrough work of Chan,\(^7\) Evans,\(^8\) and Lam\(^9\) in 1998 who demonstrated a cross-coupling reaction that proceeds at room temperature with excellent functional group compatibility. The reaction today is known as the Chan–Evans–Lam (CEL) reaction. The reaction utilizes arylboronic acids as arylating agents with a nitrogen or oxygen nucleophile to form a C–N or C–O bond through a Cu–mediated oxidative cross-coupling protocol. The ability to perform the reaction at room temperature is attributed to the low energy boron to copper transmetallation.\(^6b,10\) Another advantage of the CEL reaction is it can be conducted open to the air using simple copper catalysts without stabilizing ligands, which is not the case for the Buchwald–Hartwig amination as it requires an inert atmosphere and uses expensive palladium catalysts and ligands.\(^2b\)
However, one downside of using boronic acids in the CEL reaction or any cross-coupling reactions is that they often participate in undesired side reactions thus requiring an excess of the boronic acid (1.5 to 3 equivalents) to be used in order to achieve high cross-coupling yields.\textsuperscript{11} The fate of the boronic acids in these side pathways follows a general pattern such as protodeboronation (PdB),\textsuperscript{12} hydroxylation/oxidation,\textsuperscript{13} homocoupling,\textsuperscript{14} along with several other side products (Scheme 2.1).

**Scheme 2.1** Ullmann, Goldberg and the CEL cross-coupling reactions.

These undesired side products are suppressed using boronic acid derivatives such as the pinacol ester (B(pin)), the MIDA boronate, the potassium trifluoroborate salt, and others. However, the
increased stability of the boronic acid derivative requires harsher reaction conditions in order to achieve high cross-coupling yields.

The proposed mechanism of the CEL reaction consists of four main steps and has mostly remained the same since its discovery (Scheme 2.2). Coordination and dissolution of Cu(OAc)\(_2\) by the OH nucleophile gives Cu(II) species A. Next, complex A undergoes transmetalation with the arylboronic acid to give Cu(II) species B. Oxidation of complex B through disproportionation of Cu(OAc)\(_2\) to CuOAc gives a high energy Cu(III) species C. Product forming reductive elimination from complex C gives product and CuOAc, which oxidizes back to Cu(II) in the presence of \(O_2\).

**Scheme 2.2** Proposed mechanism of the CEL cross-coupling reaction.

While informative, this mechanism fails to provide information about the off-cycle inhibitory pathways leading to PdB, hydroxylation, and homocoupling. Detailed mechanistic insights have only recently been disclosed, focusing on these side pathways and how they arise. The detailed mechanistic work by Stahl and Watson on how to suppress these off-cycle pathways significantly improved the CEL reaction by providing general and straightforward reaction conditions that make the CEL reaction more atom-economic.

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2.2 A Unique Result that Initiated the Mechanistic Project

The inspiration to study the mechanism of the vinyl ether synthesis and how π-ligands impact the reaction blossomed from an intriguing result of an unrelated project focused on acid-catalyzed cyclization of vinyl ethers (Scheme 2.3). Vinyl ether 2-2 was chosen for screening process since it is readily obtained using our vinyl ether synthesis. During the preparation of vinyl ether 2-2, however, a unique and unexpected result occurred.

Scheme 2.3 Acid-catalyzed cyclization of vinyl ethers.

The general vinyl ether procedure calls for the addition of Cu(OAc)$_2$ to a solution of boronate 2-1 in methanol/Et$_3$N and stirring open to the air.$^{17}$ The reaction afforded vinyl ether 2-2 in only 19% yield along with alkene 2-3 derived from protodeboronation (PdB) of 2-1 and homocoupled product 2-4 each in 39% yield (Scheme 2.4, a). To our dismay, performing the reaction a second time resulted in the same outcome. A crucial observation made during the second attempt was that the initial blue color of the reaction turned brown to green all within 15 minutes, indicating different copper species were present. Luckily, this problem was quickly solved by stirring Cu(OAc)$_2$ in methanol/Et$_3$N for 10 minutes, then adding boronate 2-1. This simple change in the order of addition gave an 89% yield of vinyl ether 2-2 with no detection of 2-3 or 2-4 (Scheme 2.4, b). The reaction also did not change colors and remained a persistent baby blue throughout.
**Scheme 2.4** An interesting change in product distribution depending on the order of addition of reagents.

(a) Order of addition: vinyl B(pin), MeOH, Et₃N, stir 10 min, then Cu(OAc)₂

(b) Order of addition: Cu(OAc)₂, MeOH, Et₃N, stir 10 min, then vinyl B(pin)

2.3 Investigation of the Fate of Boronate Esters in the Cu-Mediated Vinyl Ether Synthesis

These results alone inspired us to investigate the underlying cause leading to the formation of these undesired side products (PdB and homocoupling). By understanding how PdB and homocoupling arise will help us better explain how the π-ligands affect the cross-coupling reaction. Our initial findings found that cyclonona-1,2-diene (cy9) suppresses PdB (See Chapter One), however, only had a handful of experimental results support this claim. The attention was more focused on how the π-ligand affects the coupling yields, which led to a poor understanding of their impact on the reaction details. Since boronate ester 2-5 has been used extensively in previous studies, it was chosen as a model substrate for understanding the fate of boronate esters in the vinyl ether synthesis. In each experiment, the percent composition of the crude mixture was determined using ¹H NMR. The results from the control reaction using Cu(OAc)₂ led to three distinct products, analogous to those obtained in Scheme 2.4 (Scheme 2.5). However, in the presence of cy9 only vinyl ether 2-6 was detected! Comparing cy9 to a known poor π-ligand,
diethyl fumarate (DEF), led to vinyl ether 2-6 along with dimer 2-7 and PdB 2-8. Consumption of boronate ester 2-5 was slower in the reactions were a π-ligand is present.

**Scheme 2.5** Effect of π-ligands on the product distribution for the coupling of boronate ester 2-5 with methanol using Cu(OAc)$_2$.

Next, we tested the effect of cy9 on conditions representative of a half complete reaction (Scheme 2.6). The results using a 1:1 Cu(OAc)$_2$/CuOAc mixture led to the formation of dimer 2-7 as the major product. Surprisingly, the same reaction conducted in the presence of cy9 afforded vinyl ether 2-6 in 89% yield. Another interesting finding is the pathway leading to dimer 2-7 is completely shut off in the presence of cy9, suggesting cy9 is inhibiting the homocoupling pathway. The essential piece of data extracted from these first two experiments is that Cu(I) is involved in the homocoupling pathway.
Scheme 2.6 Effect of cy9 on the product distribution for the coupling of boronate ester 2-5 with methanol using Cu(OAc)$_2$/CuOAc.

The final conditions tested are representative of using less than a 2:1 ratio of Cu(OAc)$_2$/boronate ester 2-5, where the boronate ester is in the presence of only CuOAc (Scheme 2.7). The results without added cy9 led to PdB 2-8 as the primary product with only minor amounts of vinyl ether 2-6 and dimer 2-7. In the presence of cy9, PdB is still the major product, which is an unexpected result given our original hypothesis that cy9 suppresses PdB. The control reaction using only CuOAc strongly indicates Cu(I) facilitates the PdB pathway, while the homocoupling pathway involves both Cu(I) and Cu(II). The ratio of Cu(I) to cy9 is also an essential factor governing PdB production. In the case where the Cu(I)/cy9 ratio is less than 1:4, cy9 inhibits the
PdB/homocoupling pathways. On the other hand, a ratio greater than 1:4 suggests cy9 promotes the PdB pathway.

**Scheme 2.7** Effect of cy9 on the product distribution for the coupling of boronate ester 2-5 with methanol using CuOAc.

In order to validate the above statements and prove methanol is not unique the same sets of experiments were performed using ethanol. The results using ethanol showed a similar product distribution as methanol did with the only difference being an incomplete conversion of boronate ester 2-5 in the presence of cy9 (Scheme 2.8, Scheme 2.9, and Scheme 2.10).
Scheme 2.8 Effect of π-ligands on the product distribution for the coupling of boronate ester 2-5 with ethanol using Cu(OAc)$_2$.

![Scheme 2.8 Diagram](image-url)

*66% vinyl ether 2-9 with 34% unreactive boronate ester 2-5*
**Scheme 2.9** Effect of cy9 on the product distribution for the coupling of boronate ester 2-5 with ethanol using Cu(OAc)$_2$/CuOAc.

- **Cu source**: Et$_3$N [2 equiv] EtOH [0.17 M] capped under air rt, 18 h
- **Products**:
  - 2-9 vinyl ether
  - 2-7 dimer
  - 2-8 PdB

### no ligand

- 40% 2-9 vinyl ether
- 49% 2-7 dimer
- 11% 2-8 PdB

### 4 equiv cy9$^a$

- 100% 2-9 vinyl ether

$^a$89% vinyl ether 2-9 with 11% unreactive boronate ester 2-5
Scheme 2.10 Effect of cy9 on the product distribution for the coupling of boronate ester 2-5 with ethanol using CuOAc.

Having confirmed that methanol is not unique we moved forward and tested the fate of boronate esters in the absence of the alcohol coupling partner (Scheme 2.11). By removing the alcohol coupling partner, we could study the role of the base in the reaction. Using boronate ester 2-5 with conditions mimicking a half complete reaction in the absence of Et₃N afforded a 6% yield of PdB 2-8 and 94% unreacted boronate ester 2-5. Introduction of Et₃N gave a 6% yield of PdB 2-8 along with the formation of vinyl acetate 2-10 in 18% yield. The acetate product is believed to arise from the fact that CuOAc is stable in the absence of the alcohol coupling partner, thus allowing the acetate ligand to participate in the cross-coupling reaction. In the absence of a proton source, PdB in unlikely to be detected, and the PdB observed in these experiments arises from
unavoidable contamination of water in the reactions. Overall, these two experiments demonstrated that the boronate is stable to both Cu(I) and Cu(II) in the absence of alcohol.

**Scheme 2.11** The fate of boronate ester 2-5 in the absence of the alcohol coupling partner using Cu(OAc)$_2$/CuOAc.

<table>
<thead>
<tr>
<th>% composition</th>
<th>2-5</th>
<th>dimer</th>
<th>PdB</th>
<th>acetate</th>
</tr>
</thead>
<tbody>
<tr>
<td>no Et$_3$N</td>
<td>94</td>
<td>0</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Et$_3$N [2 equiv]</td>
<td>76</td>
<td>0</td>
<td>6</td>
<td>18</td>
</tr>
</tbody>
</table>

Next, we studied how protic solvents affect these off-cycle pathways. By knowing the fact that tert-butanol does not participate in a vinyl ether synthesis, we chose it as the protic solvent for the reaction (Scheme 2.12).

**Scheme 2.12** The fate of boronate ester 2-5 in the presence of a non-participating alcohol coupling partner.

<table>
<thead>
<tr>
<th>Cu source</th>
<th>2-5 % composition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cu(OAc)$_2$ [2 equiv]</td>
<td>100 vinyl ether 0 dimer 0 PdB 0 acetate</td>
</tr>
<tr>
<td>Cu(OAc)$_2$ [1 equiv] CuOAc [1 equiv]</td>
<td>74 vinyl ether 0 11 dimer 15 PdB 0 acetate</td>
</tr>
<tr>
<td>CuOAc [2 equiv]</td>
<td>did not perform</td>
</tr>
</tbody>
</table>
The reaction conducted using Cu(OAc)$_2$ led to full recovery of boronate ester 2-5. Using a 1:1 ratio of Cu(OAc)$_2$/CuOAc converted boronate ester 2-5 to dimer 2-7 and PdB 2-8 in 11% and 15% yields, respectively. Considering that no reaction takes place using Cu(OAc)$_2$ alone indicates PdB and homocoupling occur from Cu(I) and not Cu(II). However, Cu(II) is likely involved in the homocoupling pathway, which is initiated by Cu(I) in the presence of a protic solvent (vide supra). Similarly, formation of vinyl acetate 2-10 is believed to arise from Cu(I) in the absence of a protic solvent.

### 2.4 Mechanistic Insight into Cu-Mediated Vinyl Ether Synthesis Through $^1$H NMR Analysis

With a solid understanding of how the reaction conditions affect the side product distribution, we sought to determine what triggers these off-cycle pathways. A series of NMR tubes were charged with a unique set of reaction combinations related to our vinyl ether synthesis and were analyzed frequently.

**Scheme 2.13** $^1$H NMR study results using Cu(OAc)$_2$.
The data collected from the NMR experiments led to the discovery of how these off-cycle pathways are arising (Scheme 2.13). In each case, Cu(OAc)$_2$ led to the formation of vinyl ether and PdB with no detection of either dimer or acetate product (Scheme 2.13, b and c). The unique case using cy9 in the absence of Et$_3$N gave only vinyl ether, whereas DEF gave a similar outcome as the control reaction did.

Plotting the percent composition for the experiments shown in Scheme 2.13, b (control vs cy9) ultimately answered the critical question of what triggers these off-cycle pathways (Figure 2.1). In the case where cy9 is absent, a rapid increase of PdB occurred from day two to four. Since each vinyl ether molecule produced yields two equivalents Cu(I), and since PdB occurs only after vinyl ether formation this suggests Cu(I) is solely responsible for PdB. The sudden spike in PdB also insinuates the pathway is more energetically favorable than the competing vinyl ether pathway. In the presence of cy9, however, the PdB pathway is suppressed entirely, and only conversion of boronate 2-5 to vinyl ether 2-6 is observed. The fact that there is no PdB detected in the presence of cy9 supports the earlier claim that cy9 binds to Cu(I) and inhibits it from participating in the PdB pathway. In this case, the ratio of Cu(I) to cy9 is much less than 1:4; therefore, the mode predicted is inhibition (vide supra). Analysis of the NMR tube containing cy9 after day-11 proved difficult due to the substantial accumulation of white solids and efforts to isolate and characterize the white solids were not successful as they quickly turned dark brown when exposed to the air. We believe that the white solids were a Cu(I) allene complex.
Figure 2.1 Effect of cy9 on the reaction progress for the coupling of boronate ester 2-5 with methanol.

The ease of monitoring the reaction progress using $^1$H NMR allowed us to investigate Cu(I) and Cu(II) salts other than Cu(OAc)$_2$ (Scheme 2.14). The result using CuBr$_2$ without Et$_3$N was
quite remarkable, as the cis-vinyl bromide 2-13 was the only product detected. Switching oxidation states and using CuBr without Et$_3$N gave nearly identical results as CuBr$_2$ did, albeit in lower amounts (percent composition not shown).

Scheme 2.14 $^1$H NMR study results using CuBr and CuBr$_2$.

This result is likely due to CuBr oxidizing to Cu(II), which is responsible for converting boronate 2-5 to cis-vinyl bromide. The same experiment conducted in the presence of cy9 showed only boronate ester 2-5, supporting that cy9 binds to Cu(I) and inhibits the oxidation of Cu(I) to Cu(II) by forming a stable Cu(I) cy9 complex. The results using CuBr in the presence of Et$_3$N with and without a π-ligand were all similar with the only difference being the amount of vinyl ether detected. The last three cases support that Cu(I)-X, where X = OAc or Br, participate in the cross-coupling reaction when a base is present (vide supra).$^{18}$ Authentic samples were prepared for both the trans- and cis-vinyl bromides confirming their identity (Scheme 2.15).$^{19}$

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Scheme 2.15 Synthesis of vinyl bromides 2-12 and 2-13.

Not related to this project, but synthetically useful, is how boronate ester 2-5 is transformed to the trans- or the cis-vinyl bromide under similar reaction conditions. A proposed mechanism accounting for the conversion of boronate 2-5 to cis-vinyl bromide 2-13 is shown in Scheme 2.16. CuBr₂ dissociates to give Br₂ and CuBr in the presence of methanol.²⁰ Next, bromination of the boronate ester gives intermediate Int. I. Methanol adds to boron to form a boronate Int. II and liberates H⁺. A 1,2-elimination of Int. II gives cis-vinyl bromide 2-13. It is equally likely that Int. I could be the result of a halo-etherification, where the bromide β to the B(pin) is a methoxy group.

Scheme 2.16 Proposed mechanism for the formation of cis-vinyl bromide 2-13 from boronate ester 2-5.
2.5 Synthesis of Cu(I)-Olefin Complexes

The next item explored was obtaining a Cu(I) allene crystal structure to support that allenes interact and bond to Cu(I) species. After surveying the literature, we only found a handful of protocols related to the preparation of Cu(I) allene complexes. Even more disheartening was the fact that all those protocols lacked crystal structures. Given the dearth of information on Cu(I) allene complexes, we still decided to move forward and devote our efforts to obtaining a Cu(I) allene complex. We choose to use a protocol for the generation of CuCl in situ by reducing CuCl$_2$·2H$_2$O with triphenylphosphite (P(OPh)$_3$) in methanol (Scheme 2.17). This procedure is straightforward and operationally simple, which allowed us to screen a variety of allenes rapidly. The purification of the CuCl complexes is simple as the complexes are sparingly soluble in methanol and obtained in high purity after a single decanting.

Control reactions using norbornadiene and 1,5-cyclooctadiene worked well and gave the corresponding CuCl olefin complexes in 49% and 53% yields, respectively. Of the alkynes tested, only bis(trimethylsilyl)acetylene afforded a Cu(I) alkyne complex in 78% yield. The Cu(I) alkene and alkyne complexes formed rather quickly upon olefin addition to the CuCl solution; however, it took roughly seven days for a substantial amount of crystals to grow using cy9. Other allenes tested were not successful as both produced crystals, but were not of sufficient quality to be identified using X-ray crystallography. The crystal structure obtained from the experiment using cy9 shows a dimer with a 1:1 ratio of CuCl to cy9 with each CuCl binding to one alkene of cy9 in a $\eta^2$ fashion and bridging chlorides (Figure 2.2). The CuCl cy9 crystal structure is arguably the most substantial piece of direct supporting the proposal that cy9 is interacting and binding to Cu(I) species. It is also to the best of our knowledge, the first reported Cu(I) allene crystal structure. Other techniques to extract information on the complex such as $^1$H and $^{13}$C NMR proved
problematic, as CuCl complexes are sparingly soluble in organic solvents, and only the free ligand was observed.

**Scheme 2.17** Synthesis of CuCl·olefin complexes.

\[
\text{CuCl}_2\cdot2\text{H}_2\text{O} \xrightarrow{i. (\text{PhO})_3\text{P, MeOH}} \xrightarrow{\text{ii. olefin (greater than 2 equiv)}} \text{CuCl} \cdot \text{olefin}_x
\]

CuCl·olefin complex results
(Cu : olefin ratio)

<table>
<thead>
<tr>
<th>alkenes</th>
<th>alkynes</th>
<th>allenes</th>
</tr>
</thead>
<tbody>
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</tr>
<tr>
<td>49% (2 : 1)</td>
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<td>72% (1 : 1)</td>
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<tr>
<td>light yellow solid</td>
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<td>white solid</td>
</tr>
<tr>
<td>53% (1 : 1)</td>
<td></td>
<td>78% (1 : 1)</td>
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**Figure 2.2** Crystal structure of CuCl·cy9 complex obtained by X-ray diffraction analysis.
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<table>
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<td>C(1)</td>
<td>C(2)</td>
<td>C(3)</td>
<td>126</td>
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2.6 Investigation into the Fate of Boronic Acids and Derivatives in Cu-Mediated Oxidative Coupling Reactions

Switching directions, we next studied the effect π-ligands display in the CEL reaction. As mentioned previously, both cy9 and 3-hexyne were shown to be beneficial additives in the CEL reaction resulting in improved coupling yields.\textsuperscript{23} One hypothesis is that the π-ligands are impacting the rate of the reaction, as shown earlier in Scheme 2-5–2-9 (Scheme 2.18, A). Curious to see if this translated to the CEL reaction, we monitored the rate of the Cu-mediated cross-coupling of isatin (2-14) with phenylboronic acid (2-15) (Scheme 2.18, B).\textsuperscript{7} Choosing this coupling pair (2-14 and 2-15) is appropriate as both reactions conducted with and without cy9 gave nearly quantitative yields for 2-16 within the same time frame.
**Scheme 2.18** Cross-coupling of isatin with phenylboronic acid as a control reaction for studying the effect of cy9 on the rate of the cross-coupling reaction.

The experiment consisted of eight individual reactions with and without cy9, and at a specific time point the reaction was purified by column chromatography. We were able to rapidly obtain data as product **2-16** is highly colored and is observed visually as it moves down the column making column chromatography extremely simple. The results without added cy9 steady product formation over 15 hours eventually affording **2-16** in 95% yield (Scheme 2.19, blue line). However, in the presence of cy9, the reaction was rather slow in the beginning but eventually achieved the same yield as the control reaction. The slope of the curve for the experiment conducted with cy9 is indicative of an induction period (Scheme 2.19, red line). The kinetic experiment is in agreement with earlier results where reactions performed with cy9 were slower than the control reactions.
Scheme 2.19 Effect of cy9 on the rate of the cross-coupling of isatin with phenylboronic acid.

With an understanding of how cy9 affects the reaction rate, we next directed our attention to results the Watson group published while studying the fate of boronic acids in copper-mediated cross-coupling reactions.\textsuperscript{16c} They showed that 4-biphenylboronic acid (2-17) converts to biphenyl (2-18) and 4-phenylphenol (2-19) in the presence of either Cu(OAc)$_2$ or CuOAc. The authors state that Cu(I), rather than Cu(II), is likely responsible for facilitating PdB and oxidation. Given the results from using vinyl boronates in the presence of cy9, we expected to observe a similar trend using boronic acids. The control reaction using Cu(OAc)$_2$ without cy9 gave three products: PdB 2-18, phenol 2-19 and ether 2-20 in 54%, 12%, and 15% yields, respectively (Scheme 2.20). In the presence of cy9 the amount of PdB 2-18 decreased while both phenol 2-19 and ether 2-20 products increased compared to the control reaction.
**Scheme 2.20** Effect of cy9 on the fate of 4-biphenylboronic acid in the absence of a coupling-partner under CEL reaction conditions using Cu(OAc)$_2$ and CuOAc.

This parallels earlier results when using boronate esters: when using only Cu(OAc)$_2$, cy9 suppresses the pathway leading to PdB. Switching from Cu(OAc)$_2$ and using CuOAc, the control reaction gave all three products with the major being PdB 2-18 as expected. However, the same reaction conducted in the presence of cy9 led to a 67% yield of PdB 2-18 with only minor amounts of phenol 2-19 and ether 2-20. The results using cy9 are consistent with the earlier explanation where the ratio of Cu(I) to cy9 heavily dictates the amount of PdB produced. In the case of Cu(OAc)$_2$ the ratio of Cu(I) to cy9 is small (less than 1:4) for early reaction times whereas in the case using CuOAc, the ratio is greater (initial ratio is 1:2) and PdB is expected.
The same trend was observed using 2-naphthylboronic acid (2-21), where the pathway leading to PdB is suppressed using Cu(OAc)$_2$ in the presence of cy9 (Scheme 2.21).

**Scheme 2.21** Effect of cy9 on the fate of 2-naphthylboronic acid in the absence of a coupling-partner under CEL reaction conditions using Cu(OAc)$_2$ and CuOAc.

Using electron deficient 4-benzoylphenylboronic acid (2-26) gave a similar product distribution as boronic acids 2-17 and 2-21 did (Scheme 2.22). The results using boronic acids 2-17, 2-21, and 2-26 suggest that the degradation of boronic acids in the CEL reaction is a general outcome and that the product distribution depends on the electronic properties of the boronic acid.
Scheme 2.22 Effect of cy9 on the fate of 4-benzoylphenylboronic acid in the absence of a coupling-partner under CEL reaction conditions using Cu(OAc)$_2$ and CuOAc.

To help validate the earlier claim that the ratio of Cu(I) to cy9 matters in terms of PdB production, the same reaction was conducted using a catalytic amount of CuOAc (Scheme 2.23). The reaction without added cy9 gave 34% PdB whereas, in the presence of cy9, the amount of PdB is lower, affording only a 24% yield (recovered starting material was not quantified). This result supports the claim that when the ratio of Cu(I) to cy9 is small, cy9 suppresses the PdB compared to the same reaction conducted without cy9.
**Scheme 2.23** Effect of cy9 on the fate of 2-naphthylboronic acid in the absence of a Coupling partner using catalytic amount of CuOAc.

Earlier, we demonstrated the effect of base in the copper–mediated vinyl ether synthesis where it was shown to promote reactivity. Given that the CEL reaction also uses a base, we studied the influence of base on the degradation of boronic acids in the reaction (Scheme 2.24). By deleting Et3N the reactions with and without Cu(OAc)2 resulted in no conversion of boronic acid 2-21. Addition of cy9 did not alter the reaction, which indicates that base plays a vital role in the transmetalation process of boron to copper or in dissociation of the inactive [Cu(OAc)]2 paddlewheel to the monomeric species.16c,25 Switching from Cu(OAc)2 to CuOAc gave only a 4% yield of PdB, whereas, the reaction conducted in the presence of cy9 afforded PdB in 37% yield. The increase in PdB using CuOAc with cy9 is explained by fact that CuOAc to cy9 ratio is 1:2 supporting cy9 alone can promote PdB even in the absence of a base.
**Scheme 2.24** Effect of cy9 on the fate of 2-naphthyboronic acid in the absence of Et₃N using Cu(OAc)₂ and CuOAc.

Boronic acids have a pKa of roughly 7–11 so one role of the base is to deprotonate the boronic acid, which enhances the boronic acids ability to transmetalate to a transition metal.²⁶ Using derivatives of boronic acids such as pinacol boronate esters (B(pin)), potassium trifluoroborate salts (BF₃K), or MIDA boronate esters is attractive due to their increased stability compared to boronic acids.¹ We choose to test the stability of pinacol boronate esters and the potassium trifluoroborate salts due to their frequent use in the CEL cross-coupling reaction (Scheme 2.25). Exposure to Cu(OAc)₂ or CuOAc with and without cy9, led to the full recovery of boronate ester 2-31. The potassium trifluoroborate derivative 2-32 displayed modest reactivity affording low yields of PdB and ether. Formation of the ether is not unexpected as the potassium trifluoroborate salts are known to slowly hydrolyze to the more reactive boronic acid.²⁷ Up to this point, the data suggest that PdB becomes problematic when both the boronic acid and Et₃N are present in the reaction.
**Scheme 2.25** Effect of cy9 on the fate of boronate esters and potassium trifluoroborate salts in the absence of a coupling-partner using Cu(OAc)$_2$ and CuOAc.

The classic CEL cross-coupling reaction typically employs an excess of the boronic acid (1.5–3 equivalents) to account for its participation in these off-cycle reaction pathways. With a good understanding of how these byproducts arise, we could now test how they affect an actual cross-coupling reaction. As a starting point, we used a 1:1 ratio of 2-naphthylboronic acid (2-21) to benzimidazole (2-33) (Scheme 2.26). In the presence of cy9 the reaction afforded a 41% yield of the cross-coupled product vs a 33% yield in the absence of cy9. In both cases, phenol, ether, and acetate were detected yet surprisingly no PdB. Using the same 1:1 ratio of 2-21/2-33 with added molecular sieves led to lower yields for the three side products along with a boost in yield for the cross-coupling product. Increasing the ratio of 2-21/2-33 to a 2:1 with added molecular sieves surprisingly did not substantially improve the reaction. Therefore, the optimal reaction conditions
in terms of economy employ a 1:1 ratio of 2-21/2-33 with added molecular sieves in the presence of cy9.

Scheme 2.26 CEL cross-coupling results.

The molecular sieves aid in sequestering water liberated from formation of the boroxine, thus decreasing the competitive coupling between water and benzimidazole. This also reduces the resulting coupling of naphthol with the boronic acid leading to ether 2-24. In all cases, the desired cross-coupling product is obtained in modestly higher yields using cy9 as an additive by decreasing the number of side products.
2.7 Mechanistic Proposal

Based on the experimental results above, along with previous mechanistic studies on Cu-based cross-coupling reactions, a mechanism for the vinyl ether synthesis can be proposed (Scheme 2.27). The reaction initiates by dissociation of the inactive \([\text{Cu(OAc)}_2]_2\) paddlewheel complex to the active Cu(II) complex I in the presence of alcohol and base.\(^\text{16}\) Transmetalation of organoboron species II to complex I gives Cu(II) complex III. Based on the experimental results, tert-butanol’s steric factors disfavor coordination of oxygen to boron, which explains why it does not participate in the vinyl ether cycle.\(^\text{28}\) On the same note, O → B coordination can explain the slow reaction rates observed when using isopropanol compared to \(n\)–propanol suggesting that a smooth transmetalation takes place when the R group on the alcohol is small or not sterically hindered. Oxidation of complex III through disproportionation involving Cu(II) complex I gives a high energy Cu(III) complex V and a Cu(I) complex IV.

*Scheme 2.27* Proposed mechanism for Cu-mediated vinyl ether synthesis.

Product forming reductive elimination from complex V affords the vinyl ether product and Cu(I)
complex IV. Oxidation of complex IV to Cu(II) complex I occurs in the presence of O₂ and is accelerated by Et₃N·HOAc. In this cycle, we believe beneficial π–ligands impact two specific key steps: facilitating the disproportionation of III to V by forming a stable complex with the incipient Cu(I) species²⁹ as well as inhibiting the oxidation of Cu(I) to Cu(II).

Based on the experimental results above, a mechanism for PdB and homocoupling can be proposed (Scheme 2.28). Accumulation of Cu(I) complex IV resulting from slow oxidation of IV to I leads to conversion to Cu(I) VI in the presence of a base. This essential Cu(I) complex VI is believed to be the common thread between the PdB and homocoupling cycles.

Scheme 2.28 Proposed mechanism for the PdB and homocoupling pathways.

Transmetalation of organoboron II to complex VI gives Cu(I) complex VII. In the presence of a base, Cu(I) VII is converted to cuprate species VIII, which undergoes rapid protodecupration to give the PdB product and regenerate complex VI.³⁰ In the same vein, the competing homocoupling
pathway initiates with a transmetalation of Cu(I) complex VII with Cu(II) species III (see vinyl ether cycle) to afford complex IX. Access to complex IX can also be envisioned to proceed through a transmetalation of VII to I, followed by a second transmetalation of VII to III. Oxidation of IX through disproportionation of I to IV gives complex X. C–C bond forming reductive elimination gives the homocoupled product and regenerates Cu(I) complex VI. This mechanism accounts for several experimental results described above. In the case where there is no protic solvent available, the PdB pathway is suppressed. When Et$_3$N is present however, PdB increases, suggesting base promotes or enhances the rate of the PdB pathway. The homocoupling pathway becomes operational only in the presence of Cu(I) species. Cu(OAc)$_2$ alone in the presence of tert-butanol did not afford any homocoupled product, whereas in the presence of both Cu(OAc)$_2$ and CuOAc the homocoupled product is observed. The alcohol coupling partner is involved in the homocoupling pathway, but the exact role at this time is unclear (vide infra).

Based on experimental results obtained from reactions conducted in the absence of an alcohol coupling partner, a mechanism can be proposed (Scheme 2.29). Dissociation of the paddlewheel complex by Et$_3$N gives Cu(II) complex XI. This species alone is not active and mainly exists in equilibrium favoring the paddlewheel complex. However, in the presence of CuOAc (XIV), a transmetalation of organoboron II to XIV gives Cu(I) complex XII (vinylCu(I) cycle). Transmetalation of Cu(I) XII to Cu(II) XI gives complex XIII and regenerates CuOAc (XIV). Oxidation of Cu(II) complex XIII through disproportionation of XI to XVI gives Cu(III) complex XV. Product forming reductive elimination gives the vinyl acetate product and Cu(I) complex XVI, which oxidizes to Cu(II) XI in the presence of O$_2$. It has been proposed that reductive elimination of the acetate ligand is 36.9 kcal mol$^{-1}$ higher in energy compared to the amine ligand thus suggesting this pathway is slow and unfavorable in the presence of a
participating alcohol coupling partner.\textsuperscript{16c} As mentioned above, in the absence of a proton source, the PdB pathway \textit{(i)} is suppressed and the other off-cycle pathways now become favored. The homocoupling pathway is also nonoperational in the absence of an alcohol coupling partner, which is likely facilitating one or both transmetalation process (\textbf{VII} $\rightarrow$ \textbf{IX}, Scheme 2.28, step d).

\textbf{Scheme 2.29} Proposed mechanism for reactions conducted in the absence of an alcohol coupling partner.

The influence of cy9 can now explained using both experimental results and the mechanisms proposed above. In the vinyl ether cycle, we believe that cy9 affects two critical steps, as mention previously. The first is lowering the transition-state energy for the disproportionation step by forming a stable and favorable complex with the incipient Cu(I) species. The second is that cy9 inhibits oxidation of Cu(I) to Cu(II) as a consequence of forming a stable complex to Cu(I).
The inhibition effect cy9 exerts on Cu(I) does not allow it to participate in these off-cycle pathways leading to PdB and homocoupling when there is a high concentration of cy9 to Cu(I) species. On the other hand, when the ratio of Cu(I) to cy9 increases (1:2), cy9 promotes rather than inhibits these off-cycle pathways.

### 2.8 Conclusion

In summary, we now have a better understanding on how π-ligands impact the copper-mediated vinyl ether synthesis as well as CEL reaction. The role of the π-ligands became possible by focusing on the mechanism and understanding how the boronate esters and boronic acids degrade under the reaction conditions. The experimental results support the beneficial effect of π-ligands, such as cy9, by suppressing the boronic acid/boronate ester from undergoing PdB, oxidation, and homocoupling thus allowing it to participate in the desired cross-coupling reaction. The main role of cy9 in this chemistry is to bind to Cu(I) and inhibit the normal reactivity of Cu(I), which is responsible for the PdB/homocoupling pathway and is supported by a CuCl cy9 crystal structure. More importantly, this work clearly demonstrates the utility of allenes as additives in Cu-promoted reactions and should be impetus for further investigating on using them as additives for other transition-metal reactions.
2.9 Experimental Section

General Information

Unless otherwise specified, all reactions were performed open to air using dry solvents. Triethylamine (Et$_3$N) and tert-butanol were distilled from CaH$_2$. Methanol, ethanol, were all distilled from magnesium turnings. Unless otherwise specified, all other reagents were used as received without further purification as is. NMR data was obtained with ARX-400 instrument and calibrated to the solvent signal (CDCl$_3$ : $\delta$ = 7.26 ppm for $^1$H NMR, $\delta$ = 77.2 ppm for $^{13}$C NMR; C$_6$D$_6$ : $\delta$ = 7.16 for $^1$H NMR, 128.1 for $^{13}$C NMR; DMSO-$d_6$ : $\delta$ = 2.50 for $^1$H NMR and 39.5 for $^{13}$C NMR; CD$_3$CN : $\delta$ = 1.94 for $^1$H NMR and 118.3 for $^{13}$C NMR. Data for $^1$H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), followed by integration. Data for $^{13}$C NMR spectra are reported in terms of chemical shift. The following abbreviations are used for the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; m = multiplet; br = broad; and app. = apparent. IR spectra were recorded on a JASCO FTIR-4100 spectrophotometer. High-resolution mass spectra (HRMS) were recorded on a LCT premier mass spectrometer by electrospray ionization time-of-flight (ESI-TOF) or on a Thermo Fisher Scientific Exactive Plus with IonSense ID-CUBE Direct Analysis in Real Time (DART) ion source experiments. Reactions were monitored using thin layer chromatography performed on Macherey-Nagel POLYGRAM® SIL G/UV254 silica gel TLC plates and visualized with either of the following: UV light, ceric ammonium molybdate (CAM) stain and heat, or potassium permanganate (KMnO$_4$) stain and heat. Flash column chromatography was performed using 40-63 mesh micron silica gel.
NMR Experiment: To an NMR tube was added vinyl boronate 2-5 (28 mg, 0.1 mmol), Cu(OAc)$_2$ (9.0 mg, 0.05 mmol), dry MeOH (0.05 mL), cy9 (48 mg, 0.4 mmol, when applicable), CD$_3$CN (0.45 mL). Next, the NMR tube was capped and gently shaken for 10 seconds to ensure the contents were thorough mixed. $^1$H NMR analysis was used to monitor the reaction progress and was stopped once all the vinyl boronate 2-5 was consumed.

Vinyl Boronate 2-1: Compound 2-1 was prepared following a known literature procedure.$^{17a}$

Physical State: White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.61 (ddd, $J = 7.7, 0.9, 0.9$ Hz, 1 H), 7.28–7.25 (m, 1 H), 7.18 (ddd, $J = 8.1, 7.0, 1.2$ Hz, 1 H), 7.09 (ddd, $J = 8.0, 7.0, 1.1$ Hz, 1 H), 7.05 (d, $J = 3.0$ Hz, 1 H), 6.70 (ddd, $J = 17.8, 4.7, 4.7$ Hz, 1 H), 6.50 (dd, $J = 3.2, 0.8$ Hz, 1 H), 5.35 (ddd, $J = 4.8, 1.8$ Hz, 2 H), 1.22 (s, 12 H)

Matches reported literature data.$^{17a}$

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.65 (ddd, $J = 7.8, 0.9, 0.9$ Hz, 1 H), 7.41–7.37 (m, 1 H), 7.22 (ddd, $J = 7.9, 7.0, 1.0$ Hz, 1 H), 7.15 (d, $J = 3.2$ Hz, 1 H), 7.12 (ddd, $J = 7.9, 7.1, 1.1$ Hz, 1 H), 6.64 (dt, $J = 12.6, 0.8$ Hz, 1 H), 6.51 (dd, $J = 3.1, 0.8$ Hz, 1 H), 4.97 (dt, $J = 12.6, 7.1$ Hz, 1 H), 4.63 (dd, $J = 7.1, 1.0$ Hz, 1 H), 3.54 (s, 3 H)
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 150.7, 136.0, 128.9, 127.2, 121.5, 121.1, 119.4, 109.6, 101.3, 98.4, 56.2, 44.8

IR (ATR): 3047, 2956, 2932, 2833, 1656, 1509, 1462, 1213, 741 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{12}$H$_{14}$NO [M+H]$^+$: 188.10699, found 188.10631.

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.64 (ddd, $J$ = 7.9, 0.9, 0.9 Hz, 1 H), 7.35–7.31 (m, 1 H), 7.21 (ddd, $J$ = 8.0, 7.0, 1.1 Hz, 1 H), 7.14–7.08 (m, 2 H), 6.53 (dd, $J$ = 3.1, 0.8 Hz, 1 H), 6.01 (dddd, $J$ = 17.0, 10.3, 5.3, 5.3 Hz, 1 H), 5.20 (app. dq, $J$ = 10.2, 1.4 Hz, 1 H), 5.10 (app. dq, $J$ = 17.1, 1.6 Hz, 1 H), 4.74 (ddd, $J$ = 5.4, 1.6, 1.6 Hz, 2 H).

Matches reported spectral data.$^{31}$

Physical State: White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.62 (ddd, $J$ = 7.7, 0.9, 0.9 Hz, 2 H), 7.30–7.26 (m, 2 H), 7.18 (ddd, $J$ = 8.0, 7.1, 1.0 Hz, 2 H), 7.10 (ddd, $J$ = 8.0, 7.2, 1.0 Hz, 2 H), 7.05 (d, $J$ = 3.0 Hz, 2 H), 6.50 (dd, $J$ = 3.1, 0.8 Hz, 2 H), 6.07–5.97 (m, 2 H), 5.84–5.72 (m, 2 H), 4.73 (d, $J$ = 5.4 Hz, 4 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 136.1, 131.2, 128.4, 128.3, 127.8, 121.7, 121.1, 119.6, 109.6, 101.7, 47.9

IR (ATR): 3047, 2913, 1611, 1509, 1483, 1462, 1313, 1185, 988 cm$^{-1}$
HRMS (DART-TOF) $m/z$: Calculated for C$_{22}$H$_{21}$N$_2$ [M+H]$^+$: 313.16992, found 313.16910

Vinyl Boronate 2-5: Compound 2-5 was prepared following a known literature procedure.$^{17a}$

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.36–7.27 (m, 5 H), 6.63 (dt, $J = 18.0$, 6.4 Hz, 1 H), 5.52 (dt, $J = 18.0$, 1.4 Hz, 1 H), 4.51 (s, 2 H), 3.55 (t, $J = 6.9$ Hz, 2 H), 2.48 (app. qd, $J = 7.0$, 1.7 Hz, 2 H), 1.26 (s, 12 H)

Matches reported spectral data.$^{17a}$

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 7.36–7.24 (m, 5 H), 6.36 (dt, $J = 12.4$, 1.1 Hz, 1 H), 4.74 (dt, $J = 12.5$, 7.4 Hz, 1 H), 4.52 (s, 2 H), 3.50 (s, 3 H), 3.45 (t, $J = 6.9$ Hz, 2 H), 2.24 (app. qd, $J = 7.2$, 1.1 Hz, 2 H)

Matches reported spectral data.$^{17a}$

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.40–7.25 (m, 10 H), 6.13–6.03 (m, 2 H), 5.66–5.57 (m, 2 H), 4.52 (s, 4 H), 3.51 (t, $J = 7.0$ Hz, 4 H), 2.39 (app. q, $J = 6.8$ Hz, 4 H)

Matches reported spectral data.$^{32}$
(E)-Vinyl Bromide 2-12: Compound 2-12 was prepared following the procedure described by Huffman and co-workers for the conversion of phenols to aryl halides. To a solution of boronate ester 2-5 (100 mg, 0.35 mmol) in MeOH/H₂O (1:1, 10 mL) was added CuBr₂ (312 mg, 1.4 mmol). The reaction was placed under N₂ and stirred at reflux for 1 h. The reaction was cooled to rt and diluted with 10 mL of sat. NH₄Cl, transferred to a separatory funnel and extracted Et₂O (4 x 10 mL). The organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel (95:5 hexanes/EtOAc) to give (E)-vinyl bromide 2-12 (80 mg, 95% yield) as a colorless oil.

Physical State: Clear colorless oil

¹H NMR (400 MHz, CD₃CN): δ 7.39–7.22 (m, 5 H), 6.27–6.15 (m, 2 H), 4.45 (s, 2 H), 3.49 (t, J = 6.2 Hz, 2 H), 2.30 (J = 6.4 Hz, 2 H)

¹³C NMR (100 MHz, CD₃CN): δ 139.7, 136.4, 129.2, 128.5, 128.3, 106.4, 73.1, 69.3, 33.7

HRMS (DART-TOF) m/z: Calculated for C₁₁H₁₃O [M–Br]⁺: 161.09609, found 161.09554

Matches reported spectral data.

(Z)-Vinyl Bromide 2-13: To a solution of boronate ester 2-5 (100 mg, 0.35 mmol) in dry MeCN (10 mL) was added dry MeOH (0.28 mL, 7.0 mmol, 20 equiv) followed by CuBr₂ (156 mg, 0.70 mmol). The reaction was placed under N₂ and stirred at rt for 5 d. The solvent was removed under reduced pressure and the resulting green solid was filtered through Celite® and the filtrate was
The crude residue was purified by column chromatography on silica gel (95:5 hexanes/EtOAc) to give (Z)-vinyl bromide 2-13 (51 mg, 60% yield) as a colorless oil.

**Physical State:** Clear colorless oil

1H NMR (400 MHz, CD3CN): δ 7.37–7.23 (m 5 H), 6.29 (dt, J = 6.8, 1.4 Hz, 1 H), 6.21 (app. q, J = 6.8 Hz, 1 H), 4.47 (s, 2 H), 3.52 (t, J = 6.4 Hz, 2 H), 2.44 (app. qd, J = 6.4, 1.4 Hz, 2 H)

13C NMR (100 MHz, CD3CN): δ 139.7, 133.2, 129.2, 128.5, 128.3, 109.6, 73.2, 68.9, 31.2

IR (ATR): 2955, 2924, 2853, 1624, 1578, 1419, 1266, 1209 cm⁻¹

HRMS (DART-TOF) m/z: Calculated for C11H13O [M–Br]⁺: 161.09609, found 161.09552

**Preparation of Cu(I)-Olefin Complexes**

The following Cu(I)-olefin complexes were prepared following the general procedure described by Todd and co-workers. To a 0.5 M solution of CuCl2·2H2O (1.0 equiv) in MeOH was added triphenylphosphite (1.0 equiv). The contents were stirred for 5 minutes followed by addition of the appropriate olefin (2.0 or more equiv). The reaction was left to sit at rt without stirring. The dark brown/green color eventually became pale orange with observable crystals. The solvent was carefully decanted and the crystals were washed with cold MeOH and decanted once more. The resulting crystals were allowed to air dry for approximately 5 min, then placed in a vial under an atmosphere of N₂.

![CuCl-norbornadiene complex](image)

**CuCl-norbornadiene complex**

**Physical State:** Yellow platelets

m.p.: 90 °C

IR (ATR): 3066, 3033, 2945, 1675, 1470, 1299, 1232, 908 cm⁻¹
Physical State: Pale yellow solid

IR (ATR): 3066, 2986, 2869, 1542, 1310, 875 cm\(^{-1}\)

\[
\text{CuCl}\cdot \text{cycloocta-1,4-diene complex}
\]

Physical State: Yellow solid

IR (ATR): 2949, 2919, 2878, 1473, 1427, 1239 cm\(^{-1}\)

Cycloocta-1,4-diene

Physical State: Clear colorless oil

IR (ATR): 3066, 2881, 2825, 1655, 1486, 1426, 1209, 1003 cm\(^{-1}\)

\[
\text{CuCl}\cdot \text{TMS}_{\text{bis(trimethylsilyl)acetylene complex}}
\]

Physical State: Off white solid

IR (ATR): 2954, 2901, 1950, 1243, 832 cm\(^{-1}\)

Matches reported spectral values.\(^{34}\)

Bis(trimethylsilyl)acetylene

Physical State: White solid
**IR (ATR):** 1960, 2900, 1410, 1244, 829 cm⁻¹

![CuCl-cyclonona-1,2-diene complex](image)

**CuCl-cyclonona-1,2-diene complex**

**Physical State:** White solid

**m.p.:** 159–161 °C

**IR (ATR):** 2927, 2863, 1827, 1461, 1323, 905 cm⁻¹

![Cyclonona-1,2-diene](image)

**Cyclonona-1,2-diene**

**Physical State:** Clear colorless oil

**IR (ATR):** 2987, 2923, 2855, 1961, 1451, 1321, 851 cm⁻¹

![Physical State: Orange solid](image)

**Physical State:** Orange solid

**¹H NMR (400 MHz, CDCl₃):** δ 7.69 (ddd, J = 7.5, 1.3, 0.5 Hz, 1 H), 7.61–7.50 (m, 3 H), 7.48–7.39 (m, 3 H), 7.17 (td, J = 7.5, 0.7 Hz, 1 H), 6.89 (d, J = 8.0 Hz, 1 H)

Matches reported literature spectra.³⁵
Boronic Acid 2-17: Compound 2-17 was prepared following a known literature procedure.\textsuperscript{36}

**Physical State:** White solid

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.25–7.96 (br. s, 2 H), 7.87 (d, $J = 8.0$ Hz, 2 H), 7.68 (d, $J = 7.9$ Hz, 2 H), 7.62 (d, $J = 7.8$ Hz, 2 H), 7.46 (t, $J = 7.7$ Hz, 2 H), 7.36 (t, $J = 7.4$ Hz, 1 H)

Spectra data matches literature values.\textsuperscript{36}

**Physical State:** White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.66–7.59 (m, 4 H), 7.50–7.44 (m, 4 H), 7.41–7.35 (m, 2 H)

Spectra data matches literature values.\textsuperscript{16c}

**Physical State:** White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.55–7.52 (m, 2 H), 7.48 (d, $J = 8.7$ Hz, 2 H), 7.41 (d, $J = 7.7$ Hz, 2 H), 7.30 (tt, $J = 7.4$, 1.8 Hz, 1 H), 6.90 (d, $J = 8.7$ Hz, 2 H), 4.72 (br. s, 1 H)

Spectral data matches literature values.\textsuperscript{37}

**Physical State:** White solid
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.61–7.55 (m, 8 H), 7.47–7.42 (m, 4 H), 7.38–7.32 (m, 2 H), 7.16–7.11 (m, 4 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.7, 140.5, 136.4, 128.7, 128.4, 127.0, 126.9, 119.1

Spectral data matches literature values.$^{16c}$

Physical State: White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.86–7.82 (m, 4 H), 7.50–7.45 (m, 4 H)

Spectral data matches literature values.$^{38}$

Physical State: White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.17 (s, 2 H), 7.98–7.92 (m, 4 H), 7.91–7.87 (m, 4 H), 7.55–7.48 (m, 4 H)

Spectral data matches literature values.$^{39}$

Physical State: White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.86 (t, $J = 7.4$ Hz, 4 H), 7.71 (d, $J = 7.8$ Hz, 2 H), 7.50–7.40 (m, 4 H), 7.39 (d, $J = 2.3$ Hz, 2 H), 7.33 (dd, $J = 8.7$, 2.3 Hz, 2 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 155.2, 134.5, 130.4, 130.1, 127.9, 127.3, 126.7, 124.9, 120.3, 114.6
IR (ATR): 3055, 2954, 2924, 1626, 1594, 1348, 1257, 1174, 969 cm⁻¹

HRMS (DART-TOF) m/z: Calculated for C₂₀H₁₄O [M⁺]: 270.10391, found 270.10349

Physical State: White solid

¹H NMR (400 MHz, CDCl₃): δ 7.87–7.78 (m, 3 H), 7.56 (d, J = 2.0 Hz, 1 H), 7.51–7.44 (m, 2 H), 7.23 (dd, J = 8.8, 2.3 Hz, 1 H), 2.36 (s, 3 H)

Spectra data matches literature values.⁴⁰

Physical State: White solid

¹H NMR (400 MHz, CDCl₃): δ 7.82–7.78 (m, 4 H), 7.58 (tt, J = 7.3, 2.0 Hz, 2 H), 7.48 (t, J = 7.3 Hz, 4 H)

Matches reported literature spectra.⁴¹

Physical State: Off white solid

¹H NMR (400 MHz, CDCl₃): δ 7.87 (d, J = 8.6 Hz, 4 H), 7.81–7.77 (m, 4 H), 7.59 (tt, J = 7.5, 2.1 Hz, 2 H), 7.52–7.45 (m, 4 H), 7.14 (d, J = 8.6 Hz, 4 H)

Matches reported literature spectra.⁴²
Physical State: Yellow solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.93–7.91 (m, 2 H), 7.87–7.83 (m, 2 H), 7.61–7.58 (m, 1 H), 7.53–7.50 (m, 2 H), 7.21 (d, $J = 8.7$ Hz, 2 H), 2.34 (s, 3 H)

Matches reported literature spectra.$^{43}$

Physical State: White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.80–7.73 (m, 4 H), 7.57 (tt, $J = 7.4$, 2.3 Hz, 1 H), 7.47 (t, $J = 7.3$ Hz, 2 H), 6.93 (d, $J = 8.9$ Hz, 2 H), 6.74 (br. s, 1 H)

Matches reported literature spectra.$^{41}$

**Boronate Ester 2-31:** To a solution containing 2-naphthyboronic acid (1.71 g, 10.0 mmol), Pinacol (1.29 g, 11.0 mmol) in dry Et$_2$O (25.0 mL) was added MgSO$_4$ (1.32 g, 11.0 mmol) and the reaction was placed under an atmosphere of N$_2$. After all of the starting material was consumed (ca 2 h), the reaction was filtered through a pad of Celite® and washed with Et$_2$O. The filtrate was concentrated and the crude residue was passed through a small pad of silica gel and washed with hexanes/EtOAc (9:1). The solvent was removed under reduced pressure to afford boronate ester 2-31 (2.41 g, 95% yield) as a clear oil.
Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.36 (s, 1 H), 7.88 (dd, $J = 7.3$, 1.0 Hz, 1 H), 7.85–7.80 (m, 3 H), 7.53–7.44 (m, 2 H), 1.39 (s, 12 H)

Spectral data matches reported values.$^{44}$

Potassium Trifluoroborate 2-32: To a solution containing 2-naphthyboronic acid (1.71 g, 10 mmol) in dry MeOH (35.0 mL) was added KHF$_2$ (2.43 g, 30.0 mmol) in one portion at 0 °C and placed under N$_2$. Water (~5.0 mL) was added dropwise at 0 °C and the reaction was warmed to rt over 12 h. The solvent was removed under reduced pressure until a dry solid was obtained. The crude solid was extracted with acetone (4 x 10 mL) and concentrated under reduce pressure to give a white solid. A minimal amount of hot acetone was added to dissolve the solid, and then Et$_2$O was added to precipitate the desired product. The solids were collected by filtration and air dried to give 3-32 (1.68 g, 72% yield) as a white solid.

Physical State: White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$7.78 (s, 1 H), 7.76–7.71 (m, 2 H), 7.61 (d, $J = 7.9$ Hz, 1 H), 7.52 (d, $J = 7.9$ Hz, 1 H), 7.37–7.29 (m, 2 H)

Spectral data matches literature values.$^{45}$

Physical State: White solid
\(^1\)H NMR (400 MHz, C\(_6\)D\(_6\)):  \(\delta\) 8.09 (d, \(J = 7.5\) Hz, 1 H), 7.77 (br. s, 1 H), 7.54–7.48 (m, 1 H), 7.45–7.39 (m, 2 H), 7.30 (d, \(J = 7.7\) Hz, 1 H), 7.24–7.15 (m, 3 H), 7.12–7.07 (m, 2 H), 6.93 (dd, \(J = 8.6, 2.0\) Hz, 1 H)

\(^13\)C NMR (100 MHz, CDCl\(_3\)):  \(\delta\) 143.6, 133.8, 133.7, 132.6, 130.3, 128.1, 128.0, 127.5, 127.0, 124.0, 123.1, 122.4, 122.3, 120.7, 110.7 (2 absent C signals)

IR (ATR): 3024, 1601, 1508, 1455, 1296 cm\(^{-1}\)

HRMS (ESI-TOF) m/z: Calculated for C\(_{17}\)H\(_{13}\)N\(_2\) [M+H]: 245.1079, found 245.1089
2.10 X-Ray Diffraction Analysis for CuCl-Cyclonona-1,2-diene Complex

*CuCl-cyclonona-1,2-diene complex*

**Graphical Data for CuCl·Cy9 Complex**

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<th>Complex Characteristics</th>
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2.11 $^1$H and $^{13}$C NMR Spectra
vinyl ether 2-2

$^1$H NMR (400 MHz, CDCl$_3$)
vinyl ether 2-2

$^{13}$C NMR (100 MHz, CDCl$_3$)
dimer 2-4

$^1$H NMR (400 MHz, CDCl$_3$)
$^1$C NMR (100 MHz, CDCl$_3$)
vinyl bromide 2-12

$^1$H NMR (400 MHz, MeCN-$d_3$)
vinyl bromide 2-12

$^{13}$C NMR (100 MHz, MeCN-$d_3$)
$^{1}H$ NMR (400 MHz, MeCN-$d_3$)

vinyl bromide 2-13
vinyl bromide 2-13

$^{13}$C NMR (100 MHz, MeCN-$d_3$)
$\text{C NMR (100 MHz, CDCl}_3$)
$^{1}\text{H NMR (400 MHz, C}_6\text{D}_6)$
$^{13}$C NMR (100 MHz, CDCl$_3$)
2.12 References


CHAPTER THREE

Direct Access to Substituted 1,3-Dienes and [n]Dendralenes Through Pd(II)–Catalyzed
Oxidative Coupling of Alkynes and Internal Vinyl Boronate Esters

3.1 Background and Introduction

Substituted 1,3-dienes and higher-order polyolefin motifs such as [n]dendralenes (n > 2) are of great interest as they find myriad applications in chemistry and materials science (Figure 3.1).1,2,3 There are also many complex biologically-active natural products that possess or are derived from these olefin units.4 The need for such privileged synthons has led synthetic chemists to devote considerable time and effort into their syntheses.5

**Figure 3.1** Representation of various unsaturated hydrocarbons.

Corey and Han reported an elegant synthesis of (–)-wodeshiol utilizing an interesting 1,3-diene compound as a key component (Scheme 3.1).6 In just four steps starting from the enone afforded the desired 1,3-diene compound in excellent ee. A hydroxyl-directed epoxidation followed by an acid-catalyzed rearrangement gave the desired natural product. While well-designed, this route required three steps in order to access the vinyl tin unit needed for the bimetallic homocoupling reaction and half of the total synthetic steps.
In the field of organic synthesis, the Diels–Alder reaction is prized for its ability to deliver high molecular complexity in a single step. [n]Dendralenes, however, have seen very little use in Diels–Alder reactions since it is difficult to control which diene reacts thus typical reactions employing [n]dendralenes result in multiple Diels–Alder products. The Sherburn group has devoted an enormous amount of time studying [n]dendralenes and how they participate in Diels–Alder reactions (Scheme 3.2). For example, the Diels–Alder cycloaddition of [4]dendralene with N-methylmaleimide gave two Diels–Alder adducts: the internal and terminal Diels–Alder adducts. The terminal Diels–Alder adduct further reacts with N-methylmaleimide via a diene-transmissive Diels–Alder cascade process to give the product shown below in 14% yield along with other diastereomers (not shown). In contrast, the internal adduct is quite stable at room temperature and does not further react with N-methylmaleimide. This example highlights that [n]dendralenes can rapidly build structurally rich and complex motifs with ease, which makes them synthetically valuable.

In another example, the Sherburn group utilized a [3]dendralene as a way to access branched aminosugars (Scheme 3.3). The unique reactivity of [3]dendralenes allowed the authors to rapidly construct the bicyclic compound through diene-transmissive double Diels–Alder sequence. Further manipulations of the bicyclic compound gave the enantioenriched diamino-tetrol in good yield. The hydrogenation step is rather remarkable as it accomplishes Cbz-deprotection, ring-opening, followed by N-methylation all in one pot.

Scheme 3.3 Synthesis of an enantioenriched diamino-tetrol starting from [3]dendralene.

In another example, the Shenvi group used an electron rich [3]dendralene to construct the tricyclic core found in the natural product shown below (Scheme 3.4). To essential unit was
accomplished through an initial intermolecular Diels–Alder reaction of the [3]dendralene and the enone. Exposure of the cyclic enone via elimination of methoxide by Yb(OTf)$_3$ triggered an intramolecular inverse electron demand Diels–Alder reaction to afford the desired tricyclic core. This example and the ones above really highlight the robust features [n]dendralenes have to offer, and should be considered when complexity is warranted in few steps.

**Scheme 3.4** Total synthesis of an antimalarial amphilectene natural product using an electron rich [3]dendralene.

While numerous strategies exist for preparing dienes and [n]dendralenes, a majority of them have limitations due to the reaction conditions employed.$^{10,11}$ In 2013, two groups reported the synthesis of highly substituted 1,3-dienes through a Pd-catalyzed homocoupling of N-tosylhydrazones.$^{12,13}$ Both protocols are similar and proceed through a Pd-carbene mechanism. While the protocols are attractive and use a more modern synthetic approach, some major drawbacks are apparent: the N-tosylhydrazone moiety needs to be pre-installed, mixtures of alkene isomers are produced when the methyl group on the ketone is replaced with longer alkyl chains, elevated temperatures are required, and a strong base is necessary. These drawbacks severely limit
the substrate scope and functional group compatibility. Recently, our group disclosed a strategy for stereospecifically preparing macrocyclic polynes using bis-vinyl boronate esters through a Pd(II)-catalyzed oxidative coupling protocol. Vinyl boronates were ideal substrates as they offer an excellent handle for controlling alkene stereochemistry in each macrocycle. This protocol offers exceptionally mild reaction conditions allowing for a wide range of functional group tolerance. Given the mildness of this protocol, we sought to extend it to the intermolecular version using similar reaction conditions to the intramolecular case.

Ultimately, our goal was to access dienes and [n]dendralenes while retaining structural/functional group compatibility, atom- and step-economy, and stereo- and regioselectivity (Figure 3.2).

**Figure 3.2** Methods for accessing substituted 1,3-dienes and [n]dendralenes.

- **Previous work**\(^{12,13}\)

- **Our approach:**

  - mild reaction conditions
  - rapid and scalable
  - highly regioselective
  - stereospecific
  - excellent functional group compatibility

Ideally, this all would be accomplished without needing to pre-functionalize the starting material. While challenging, if successful, this would represent a valuable strategy for accessing 1,3-dienes
and polyolefinic compounds. Herein, we demonstrate the use of two unique general protocols for accessing dienes and \([n]\)dendralene as well as illustrating their utilities in organic synthesis.

3.2 Pd(II)-Catalyzed Homocoupling of Vinyl Boronate Esters

Intermolecular homocoupling was initially investigated using vinyl boronate ester 3-2a and conditions our group previously reported for the synthesis of macrocyclic polyenes (Table 3.1). This initial conditions screened gave 3-3a in 38% and 37% yields along with several unidentified side products (entries 1 and 2). With those conditions as a starting point, we decided to optimize the reaction. Switching to a more organic-soluble inorganic base, Cs₂CO₃, over K₂CO₃, dramatically improved the reaction affording 3-3a in 82% yield (entry 3). Decreasing the Pd loading from 5% to 2.5% and 1% resulted in decreased yields (entries 4 and 5). Using less chloroacetone (3 vs 6 equiv) proved to have little effect on the coupling yield and gave 3-3a in 76% yield (entry 6). Decreasing the reaction concentration led to a 52% isolated yield suggesting that a higher concentration is optimal for the reaction (entry 7). By lowering the equivalents of Cs₂CO₃ and the temperature to 40 °C gave the best results affording 3-3a in 83% yield (entry 8). We also demonstrated that the reaction can be conducted at rt to afford 3-3a in 79% yield with the only difference being an extended reaction time of 22 h (entry 9). Screening other solvents, oxidants and bases proved not as successful as the results obtained in entry 8 (entries 10–15).
Table 3.1 Optimization of Pd(II)–catalyzed oxidative homocoupling of vinyl boronate esters.

With the optimization complete, the next step was to explore the scope of the coupling reaction. Vinyl boronate ester starting materials were obtained from alkynes through a hydroboration process (Table 3.2, A). The vinyl boronate esters were then subjected to the optimized coupling conditions and the results shown in Table 3.2, B.

<table>
<thead>
<tr>
<th>entry</th>
<th>PdCl₂(PPh₃)₂ (mol%)</th>
<th>base (equiv)</th>
<th>solvent [M]</th>
<th>oxidant (equiv)</th>
<th>temp. (°C)</th>
<th>time (h)</th>
<th>yielda</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>10% K₂CO₃ (5)</td>
<td>MeOH [0.1]</td>
<td>AcCH₂Cl (10)</td>
<td>rt</td>
<td>21</td>
<td>38%</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>5% K₂CO₃ (2.4)</td>
<td>MeOH [0.2]</td>
<td>AcCH₂Cl (3)</td>
<td>60</td>
<td>12.5</td>
<td>37%</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>5% Cs₂CO₃ (2.5)</td>
<td>MeOH [1]</td>
<td>AcCH₂Cl (6)</td>
<td>60</td>
<td>1</td>
<td>82%</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>2.5% Cs₂CO₃ (2.5)</td>
<td>MeOH [1]</td>
<td>AcCH₂Cl (6)</td>
<td>60</td>
<td>1</td>
<td>47%</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>1% Cs₂CO₃ (2.5)</td>
<td>MeOH [1]</td>
<td>AcCH₂Cl (6)</td>
<td>60</td>
<td>2.5</td>
<td>45%</td>
<td></td>
</tr>
<tr>
<td>6</td>
<td>5% Cs₂CO₃ (2.5)</td>
<td>MeOH [1]</td>
<td>AcCH₂Cl (3)</td>
<td>60</td>
<td>1</td>
<td>76%</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>5% Cs₂CO₃ (2.5)</td>
<td>MeOH [0.5]</td>
<td>AcCH₂Cl (3)</td>
<td>60</td>
<td>4</td>
<td>52%</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>5% Cs₂CO₃ (2)</td>
<td>MeOH [1]</td>
<td>AcCH₂Cl (3)</td>
<td>40</td>
<td>4</td>
<td>83%</td>
<td></td>
</tr>
<tr>
<td>9</td>
<td>5% Cs₂CO₃ (2)</td>
<td>MeOH [1]</td>
<td>AcCH₂Cl (3)</td>
<td>rt</td>
<td>22</td>
<td>79%</td>
<td></td>
</tr>
<tr>
<td>10</td>
<td>5% KF (1)</td>
<td>THF/H₂O (10:1) [0.2]</td>
<td>air</td>
<td>rt</td>
<td>24</td>
<td>0%</td>
<td></td>
</tr>
<tr>
<td>11</td>
<td>5% Cs₂CO₃ (2.5)</td>
<td>MeOH [1]</td>
<td>O₂ ballon</td>
<td>rt</td>
<td>24</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>5% Cs₂CO₃ (2.5)</td>
<td>DMF [1]</td>
<td>AcCH₂Cl (6)</td>
<td>60</td>
<td>1</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td>13</td>
<td>5% Cs₂CO₃ (2)</td>
<td>DMF [1]</td>
<td>Cu(OAc)₂ (3)</td>
<td>55</td>
<td>2</td>
<td>65%</td>
<td></td>
</tr>
<tr>
<td>14</td>
<td>5% Cs₂CO₃ (2)</td>
<td>dioxane [1]</td>
<td>AcCH₂Cl (3)</td>
<td>60</td>
<td>6</td>
<td>75%</td>
<td></td>
</tr>
<tr>
<td>15</td>
<td>5% Cs₂CO₃ (2)</td>
<td>THF/H₂O (85:15) [0.2]</td>
<td>AcCH₂Cl (2)</td>
<td>50</td>
<td>4</td>
<td>75%</td>
<td></td>
</tr>
</tbody>
</table>

Reactions were performed with 3-2a on a 1.0 mmol scale. aIsolated yields are reported.
Table 3.2 Preparation and substrate scope of vinyl boronate esters.

A. Preparation of vinyl boronate esters

<table>
<thead>
<tr>
<th></th>
<th>( \text{Ni(dppe)Cl}_2, \text{dibal-H} )</th>
<th>( \text{MeOB(pin)} )</th>
<th>( \text{terminal alkynes (3-1a–c, e–h, ref. 16a)} )</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-1</td>
<td>( R \equiv R ) alkyne</td>
<td>( \text{HB(pin), octane} )</td>
<td>( \text{internal alkynes (3-1d, ref. 16b)} )</td>
</tr>
</tbody>
</table>

\[
\begin{align*}
3-2 & \quad \text{alkyne} \\
\end{align*}
\]

B. Vinyl boronate ester substrate scope\(^\text{a}\)

\[
\begin{align*}
\text{PdCl}_2(\text{PPPh}_3)_2 (5 \text{ mol\%}) & \quad \text{Cs}_2\text{CO}_3 (2 \text{ equiv}) \\
\text{MeOH [1 M], AcCH}_2\text{Cl (3 equiv)} & \quad 40 ^\circ \text{C}, 4 \text{ h} \\
\end{align*}
\]

<table>
<thead>
<tr>
<th>Aromatic</th>
<th>3-3a</th>
<th>83%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-3b</td>
<td>91%</td>
<td></td>
</tr>
<tr>
<td>3-3c</td>
<td>73%</td>
<td></td>
</tr>
<tr>
<td>3-3d</td>
<td>62%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Alkyl</th>
<th>3-3e</th>
<th>33%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-3f</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>3-3g</td>
<td>50%</td>
<td></td>
</tr>
<tr>
<td>3-3h</td>
<td>68%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ester Substituted</th>
<th>3-3i</th>
<th>92%</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-3j</td>
<td>64%(^\text{b}) 77%(^\text{c})</td>
<td></td>
</tr>
<tr>
<td>3-3k</td>
<td>88%</td>
<td></td>
</tr>
<tr>
<td>3-3l</td>
<td>74%</td>
<td></td>
</tr>
</tbody>
</table>

\(^\text{a}\)Reactions were performed with 3-2 on a 1.0 mmol scale. \(^\text{b}\)Reaction time was 3 d. \(^\text{c}\)THF/H\(_2\)O (85:15) used in place of MeOH with a 24 h reaction time. Isolated yields are reported.
Aromatic vinyl boronates 3-2a–c coupled smoothly, producing homocoupled products 3-3a–c. Electronic factors enhancing transmetalation are most likely responsible for the increase in yield for 3-3b vs. 3-3c. Stilbene derived boronate ester 3-2d reacted well to give compound 3-3d in 62% yield. Alkyl vinyl boronates 3-2e–h coupled less efficiently affording compounds 3-3e–h in moderate to low yields. Employing vinyl boronate esters 3-2i–l that contain an ester functional group coupled to give compounds 3-3i–l in great yields. Diene 3-3j displayed no transesterification to the mono or bis-methyl ester under the standard reaction conditions. Compounds 3-3e and 3-3l, which both possess a [4]dendralene core, proved to be stable over time. For example, decomposition of structure 3-3e was minimal over a month when stored as a solution in hexanes in the freezer.1e,f,7,17 Compound 3-3l, however, showed no decay over 12 months at rt when stored neat, perhaps due to stabilization by the ester groups.

3.3 One-Pot Homocoupling Method Utilizing Alkyne Substrates

During the course of this project we faced several problems involving the synthesis of several vinyl boronate esters. One problem involved difficulties in controlling the regioselectivity for the hydroboration step as using regioisomeric borylated starting materials would give statistical mixtures of products. Another issue was that some vinyl boronate esters could not be obtained in acceptable yields. Furthermore, some vinyl boronate esters decomposed within 24–72 h suggesting they are quite unstable. We spent time trying to screen different conditions to address these issues, however, no clear improved method could be established. An example demonstrating the problems above is shown in Table 3.3. Following the procedure described by Hoveyda,16 conversion of 3-1e gave 3-2e-α in only 22% yield as a single regioisomer (entry 1). Next, we increased the time from 2 hours to 6 hours and obtained a mixture of 3-2e-α and 3-2e-β (5:1) in 48% yield (entry 2). Lowering the temperature from 80 °C to 60 °C gave 3-2e-α and 3-2e-β (10:1) in 63% yield (entry
3). These first three entries suggest temperature is an important factor for controlling the regioselectivity and increasing the yield. Decreasing the amount of dibal-H in step $i$ and lowering the temperature in step $ii$ afforded 3-2e-α only (entry 4). Increasing the reaction time for step $ii$ to 20 hours and 5 days eventually gave 3-2e-α in an appreciable yield (entries 5 and 6).

*Table 3.3* Screen of alternative Ni-catalyzed hydroalumination conditions.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>yield (3-2e-α:3-2e-β)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>$i.$ dibal-H (1.3 equiv), −5 °C, 16 h&lt;br&gt;$ii.$ MeOB(pin) (3 equiv), 80 °C, 2 h</td>
<td>22% (1:0)</td>
</tr>
<tr>
<td>2</td>
<td>$i.$ dibal-H (1.3 equiv), 0 °C → rt, 12 h&lt;br&gt;$ii.$ MeOB(pin) (3 equiv), 80 °C, 6 h</td>
<td>48% (5:1)</td>
</tr>
<tr>
<td>3</td>
<td>$i.$ dibal-H (1.3 equiv), 0 °C → rt, 12 h&lt;br&gt;$ii.$ MeOB(pin) (3 equiv), 60 °C, 2 h</td>
<td>63% (10:1)</td>
</tr>
<tr>
<td>4</td>
<td>$i.$ dibal-H (1.1 equiv), 0 °C → rt, 2 h&lt;br&gt;$ii.$ MeOB(pin) (3 equiv), 0 °C → rt, 2 h</td>
<td>N.D (3-2e-α only)$^a$</td>
</tr>
<tr>
<td>5</td>
<td>$i.$ dibal-H (1.1 equiv), 0 °C → rt, 2 h&lt;br&gt;$ii.$ MeOB(pin) (3 equiv), 0 °C → rt, 20 h</td>
<td>36% (1:0)$^b$</td>
</tr>
<tr>
<td>6</td>
<td>$i.$ dibal-H (1.1 equiv), 0 °C → rt, 2 h&lt;br&gt;$ii.$ MeOB(pin) (3 equiv), 0 °C → rt, 5 d</td>
<td>60% (1:0)</td>
</tr>
</tbody>
</table>

Reactions were performed with 3-1e on a 1.0 mmol scale. $^a$Crude $^1$H NMR analysis showed a 1:0.43 ratio of A to 3-2e-α. $^b$Crude $^1$H NMR analysis showed a 0.49:1 ratio of A to 3-2e-α. Isolated yields are reported.

The last three entries suggest that the Al → B transmetalation process is relatively slow and higher yields are achieved with longer reaction times. However, in step $i$ all of 3-1e was consumed within 2 hours implying the Ni-catalyzed hydroalumination step is fast. Knowing that all of 3-1e is consumed and no 3-2e-β is observed for entries 4–6 suggests that step $i$ is highly regioselective for internal hydroalumination of the terminal alkyne. While there are other known methods for
preparing 3-2e-α and similar compounds, we instead directed our attention to directly converting the alkyne to the coupled product in one step. This strategy is particularly attractive, as it completely obviates the need to isolate any potentially unstable vinyl boronate esters.

Show in Scheme 3.5 is our approach which utilizes alkynes and transforms them directly to homocoupled products in one step, thus circumventing the isolation of potentially problematic vinyl nucleophiles. We wished to keep step i (Ni-catalyzed hydroalumination step) the same as is highly regioselective. We instead focused our attention on conditions that would take intermediate B → E.

**Scheme 3.5** A general outline of the one-pot protocol.

Recognizing that intermediate B is a nucleophile, we wondered if addition of PdCl₂(PPh₃)₂ (5 mol %)/chloroacetone (3 equiv) in THF could directly convert intermediate B to E. Using 3-1a as our control alkyne, we obtained 3-3a in only 14% yield (Table 3.4, entry 1). Next we considered converting B to an alternative vinyl nucleophile via a transmetalation process. After screening different additives (ZnI₂, ZnCl₂, CuCl, CuCl₂/Cu(OAc)₂, and B(OMe)₃) we found that addition of ZnCl₂ (1.0 M in THF, 1.5 equiv) to B, followed by addition of a PdCl₂(PPh₃)₂ (5 mol %)/chloroacetone (3 equiv) suspension in THF gave 3-3a in 67% yield (entry 2). We also demonstrated that Pd is necessary for the homocoupling process and that Ni is not capable of doing so (entry 3). Varying the equivalents of chloroacetone did not improve the reaction yields (entries
Chloroacetone was shown to be superior to all other oxidants screened (entries 7–14). Appreciable yields were also obtained for reactions conducted at 0 °C in certain steps (entry 15 and 16). Increasing the amount of ZnCl₂ to three equivalents gave the best results affording 3-3a in 79% isolated yield (entry 17). Increasing the amount of ZnCl₂ further did not prove beneficial and afforded a lower yield of 3-3a (entry 18). The reaction is highly regioselective as no terminal-internal/terminal-terminal coupling was observed in any instance.

Table 3.4 Optimization of Pd–(II)–catalyzed oxidative homocoupling of alkynes.

<table>
<thead>
<tr>
<th>entry</th>
<th>oxidant [equiv]</th>
<th>deviation</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>entry</th>
<th>oxidant [equiv]</th>
<th>deviation</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>AcCH₂Cl [3]</td>
<td>no PdCl₂(PPh₃)₂</td>
<td>27</td>
<td>12</td>
<td>Ag₂CO₃ [1.5]</td>
<td>none</td>
<td>50</td>
</tr>
<tr>
<td>5</td>
<td>AcCH₂Cl [4]</td>
<td>none</td>
<td>53</td>
<td>14</td>
<td>O₂ (1 atm)</td>
<td>none</td>
<td>44</td>
</tr>
<tr>
<td>7</td>
<td>Cu(OAc)₂ [3]</td>
<td>no PdCl₂(PPh₃)₂</td>
<td>16</td>
<td>16</td>
<td>AcCH₂Cl [3]</td>
<td>steps ii and iii - 0 °C</td>
<td>56</td>
</tr>
<tr>
<td>8</td>
<td>Cu(OAc)₂ [3]</td>
<td>none</td>
<td>33</td>
<td>17</td>
<td>AcCH₂Cl [3]</td>
<td>ZnCl₂ [3 equiv]</td>
<td>78 (79)&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

Reactions were performed with 3-1a on a 1.0 mmol at a concentration of 0.11 M (final concentration). <sup>a</sup>Yields were determined by <sup>1</sup>H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard. <sup>b</sup>Isolated yield. yields were.

Next we conducted a concentration study using the conditions shown in Table 3.4 entry 17 (Table 3.5). Varying the concentration of ZnCl₂ in THF from 1 M to 0.5 M, 0.33M, and 0.2 M did not significantly affect the coupling reaction (entries 1–3). Increasing the concentration proved detrimental, as lower yields were obtained and this is potentially attributed to human error (too many manipulations which could introduce oxygen or water).

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Table 3.5 One-pot protocol concentration study results.

<table>
<thead>
<tr>
<th>Concentration Study</th>
<th>entry</th>
<th>deviation</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>i. Ni(dppe)Cl&lt;sub&gt;2&lt;/sub&gt; (3 mol%) dibal-H (1.1 equiv) THF, 0 °C → rt, 2 h</td>
<td>[1]</td>
<td>final concentration = 0.083 M (0.5 M ZnCl&lt;sub&gt;2&lt;/sub&gt; soln. in THF)</td>
<td>74</td>
</tr>
<tr>
<td>ii. ZnCl&lt;sub&gt;2&lt;/sub&gt; (3 equiv) THF, rt, 30 min</td>
<td>[2]</td>
<td>final concentration = 0.066 M (0.33 M ZnCl&lt;sub&gt;2&lt;/sub&gt; soln. in THF)</td>
<td>61</td>
</tr>
<tr>
<td>iii. PdCl&lt;sub&gt;2&lt;/sub&gt;(PPh&lt;sub&gt;3&lt;/sub&gt;)&lt;sub&gt;2&lt;/sub&gt; (5 mol%) AcCl&lt;sub&gt;2&lt;/sub&gt; (3 equiv), rt, 1 h</td>
<td>[3]</td>
<td>final concentration = 0.047 M (0.20 M ZnCl&lt;sub&gt;2&lt;/sub&gt; soln. in THF)</td>
<td>67</td>
</tr>
<tr>
<td>solvent was evaporated after step i</td>
<td>[4]</td>
<td>solvent was evaporated after steps i and ii</td>
<td>55</td>
</tr>
<tr>
<td>solvent was evaporated after step i</td>
<td>[5]</td>
<td></td>
<td>21</td>
</tr>
</tbody>
</table>

Reactions were performed with 3-1a on a 1.0 mmol scale. *Yields were determined by 1H NMR analysis using 1,3,5-trimethoxybenzene as an internal standard.

With the optimized reaction conditions for the one-pot protocol in hand, diverse arrays of alkynes were then transformed to the corresponding homocoupled products as shown in Table 3.6. Aromatic alkynes bearing F, Br, and OMe all coupled smoothly, giving homocoupled products 3-3a–c, and 3-3m–q in good to excellent yields (58%–92%). Naphthyl alkynes 3-1r and 3-1s were coupled to afford compounds 3-3r and 3-3s in 60% and 75% yield, respectively. Indole containing alkynes 3-1t and 3-1u coupled well under the reaction conditions giving 3-3t and 3-3u in 59% and 83% yields, respectively. Next, we aimed our focus on testing alkyl-containing alkynes to see if this one-pot protocol is an improvement over the two step protocol. The standard conditions smoothly transformed 3-1f–h to compounds 3-3f–h in good yields. A substantial yield increase was found using the one-pot protocol to prepare compounds 3-3f and 3-3g (68% and 82% yields, respectively) compared to 36% and 50% yields, respectively using the conditions in Table 3.2. Ether substituted alkynes 3-1v–3-1x coupled smoothly affording compounds 3-3v–3-3x. 3-Hexyne (3-1z), however, did not perform well affording 3-3z in only 33% yield. The low yield may be attributed to 3-hexyne not being as reactive as terminal alkynes in the Ni-catalyzed hydroalumination step.
Table 3.6 Alkyne substrate scope.

### Alkyne substrate scope

<table>
<thead>
<tr>
<th>R&lt;sup&gt;1&lt;/sup&gt;</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>( \text{Ni(dppe)}\text{Cl}_2 ) (3 mol%) dibal-H (1.1 equiv), THF, 0 °C → rt, 2 h</th>
<th>R&lt;sup&gt;2&lt;/sup&gt;</th>
<th>( \text{Ni(dppe)}\text{Cl}_2 ) (3 mol%) dibal-H (1.1 equiv), THF, 0 °C → rt, 2 h</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-1</td>
<td>3-2</td>
<td>i. ( \text{Ni(dppe)}\text{Cl}_2 ) (3 mol%) dibal-H (1.1 equiv), THF, 0 °C → rt, 2 h</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-3</td>
<td>3-4</td>
<td>ii. ( \text{ZnCl}_2 ) (3 equiv), THF, rt, 30 min</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3-5</td>
<td>3-6</td>
<td>iii. ( \text{PdCl}_2(\text{PPh}_3)_2 ) (5 mol%), AcCHCl (3 equiv)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### Alkyne substrate scope

<table>
<thead>
<tr>
<th>Product</th>
<th>X</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-3a</td>
<td>H</td>
<td>79%</td>
</tr>
<tr>
<td>3-3b</td>
<td>4-OMe</td>
<td>62%</td>
</tr>
<tr>
<td>3-3c</td>
<td>4-F</td>
<td>92%</td>
</tr>
<tr>
<td>3-3m</td>
<td>2-F</td>
<td>52%</td>
</tr>
<tr>
<td>3-3n</td>
<td>4-Br</td>
<td>58%</td>
</tr>
<tr>
<td>3-3o</td>
<td>2-OMe</td>
<td>87%</td>
</tr>
<tr>
<td>3-3p</td>
<td>3-OMe</td>
<td>65%</td>
</tr>
<tr>
<td>3-3q</td>
<td>3,4-OMe</td>
<td>77%</td>
</tr>
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</table>

#### Aromatic

<table>
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<tr>
<th>Product</th>
<th>Yield</th>
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<tbody>
<tr>
<td>3-3r</td>
<td>75%</td>
</tr>
<tr>
<td>3-3t</td>
<td>59%</td>
</tr>
<tr>
<td>3-3s</td>
<td>60%</td>
</tr>
<tr>
<td>3-3u</td>
<td>83%</td>
</tr>
</tbody>
</table>

#### Alkyl

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-3f</td>
<td>68%</td>
</tr>
<tr>
<td>3-3g</td>
<td>82%</td>
</tr>
<tr>
<td>3-3h</td>
<td>53%&lt;sup&gt;b&lt;/sup&gt;</td>
</tr>
<tr>
<td>3-3i</td>
<td>74%</td>
</tr>
<tr>
<td>3-3j</td>
<td>69%</td>
</tr>
</tbody>
</table>

#### Cross-Conjugated Tetraenes

<table>
<thead>
<tr>
<th>Product</th>
<th>Yield</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-3e</td>
<td>76%</td>
</tr>
<tr>
<td>3-3aa</td>
<td>53%</td>
</tr>
<tr>
<td>3-3ab</td>
<td>77%</td>
</tr>
<tr>
<td>3-3ac</td>
<td>78%</td>
</tr>
</tbody>
</table>

<sup>a</sup>Reactions were performed with 3-1 on a 1.0 mmol scale at a concentration of 0.11 M (final concentration).

<sup>b</sup>2.1 equiv of dibal-H was used in step i. Isolated yields are reported.

Employing diphenylacetylene in the one-pot protocol resulted in no coupled product with nearly quantitative recovery of the starting material (entry not shown). Intriguingly, compounds 3-3n and 3-3x, which both bear an aromatic bromide remained intact under the reaction conditions and no
Negishi-type coupling was observed. Next, a group of eneynes coupled smoothly to give substituted [4]dendralenes 3-3e, 3-3aa, 3-3ab, and 3-3ac in good yields. We were pleased to see that 1-ethynylcyclohex-1-ene (3-1e) converted to homocoupled product 3-3e in 76% yield, which is over a 100% increase compared to the 33% yield obtained previously (see Table 3.2). We also did not observe any regiochemistry issues for compound 3-1e using the one-pot protocol as was observed during the synthesis of 3-2e-α (vide supra). This observation further supports the hypothesis that the Ni-catalyzed hydroalumination step is highly selective and the issues involving the regioselectivity occur during the conversion of the vinylaluminum intermediate to vinyl boronate ester 3-2e-α. A benzo-fused eneyne 3-1aa was converted to compound 3-3aa in a modest 53% yield. Alkyne 3-1ab, which is derived from (1R)-(−)-myrtenal, coupled well to afford cross-conjugated compound 3-3ab in 77% yield. Coupling commercially available 2-methylbut-1-en-3-yne (3-1ac) gave 3-3ac in 78% yield. Compound 3-3ac, however, rapidly decomposed upon concentration, but was found to be stable when stored as a dilute solution of hexanes or THF. In all cases, no terminal-terminal or internal-terminal coupling was observed. An attractive feature of the one-pot protocol is that the reaction times are generally less than 4 hours allowing rapid access to these privileged polyene compounds. However, one limitation of this protocol is that functional groups have to be compatible with dibal-H. For example, an extra equivalent of dibal-H is needed to obtain diene 3-3h due to the acid-base reaction between the alcohol and dibal-H. Further, no aldehyde or ketone containing substrates were attempted.

Several substrates were found incompatible for this one-pot protocol (Figure 3.3). Substrates with chelating groups, such as nitrogen, do not participate in the full reaction. One explanation is that the heteroatom chelates to the aluminum and halts the reaction from proceeding.
forward. Alkynes bearing propargylic heteroatom groups gave negative results, as they most likely decomposed via a 1,2-elimination to an allene.\(^{20}\)

Figure 3.3 Limitations for the one-pot homocoupling protocol.
Typically all products from the one-pot protocol were able to be isolated without complications. However, some products, especially those without any polar functional groups, were problematic to isolate as the products co-eluted with the semi-hydrogenated side product.

To further expand the utility of the reaction, we demonstrated that the one-pot protocol conditions can be applied on large scale (Table 3.7). Using the standard coupling conditions outlined in Table 3.6, alkyne 3-1q coupled to give 3-3q in 88% yield on a 20 mmol scale. Excitingly, the yield obtained for 3-3q on a 20 mmol scale is better than the yield obtained on a 1 mmol scale (77% yield, Table 3.6). Next, alkyne 3-1ad coupled to give a 76% yield for 3-3ad. In the last example, indole-containing alkyne 3-1ae combined to give homocoupled product 3-3ae in 74% isolated yield. Even on a large scale, the conditions are highly regioselective for internal-internal coupling products.

Table 3.7 Gram scale synthesis of 2,3-disubstituted 1,3-butadienes from alkynes.
3.4 Proposed Series of Metalations for the One-Pot Homocoupling Strategy

Based on the above results, we propose a sequence of metalations for the mechanism of the one-pot protocol (Figure 3.4)

*Figure 3.4* Plausible sequence of metalations.

The reaction initiates with reduction of Ni(dppe)Cl₂ by dibal-H to afford Ni(0) species I.²¹ Oxidative addition of Ni(0) I into the Al–H bond of dibal-H gives intermediate II.²² Next, a regioselective hydronickelation of an alkyne by II provides III. Reductive elimination of intermediate III gives vinylaluminum intermediate IV and regeneration of Ni⁰ I. Once all the alkyne is consumed in the Ni-catalytic cycle (step a), a transmetalation of vinylaluminum intermediate IV with ZnCl₂ in step b gives vinylzinc intermediate V.²³ A double transmetalation
involving two vinylzinc species with Pd(II) VI furnishes bis-vinyl Pd(II) intermediate VII in step c. Subsequent C–C bond forming reductive elimination liberates the product and generates Pd(0) VIII. Oxidation of VIII mediated by chloroacetone regenerates VI and completes the Pd-catalytic cycle.14

3.5 Utilizing the One-Pot Protocol to Access Nonsymmetrical Polyenes

With the ability to quickly synthesize substituted 1,3-dienes and [4]dendralenes, we wondered if the one-pot protocol could be applied to the synthesis of substituted [3]- and [5]dendralenes (Table 3.8). In order for this transformation to occur it would need to proceed through a Pd(0) cross-coupling pathway not a Pd(II) homocoupling pathway. This is easily achieved by removing chloroacetone (the oxidant) from step iii (see Table 3.6), which turns the reaction into a Negishi type cross-coupling reaction. With these newly developed conditions, alkyne 3-1e coupled with vinyl triflate 3-4 to give [3]dendralene 3-5 in 94% yield. Next, we envisioned [5]dendralenes could be accessed from coupling eneynes with a linchpin reagent, such as 1,1-dichloroethylene (3-6). Unfortunately, we were unable to obtained 3-7 under the same conditions used for 3-5. However, we believe that with an appropriate linchpin the cross-coupling approach to access [5]dendralenes will work. Also, it would be advantageous if the linchpin has a chromophore which makes monitoring the reaction much easier. The fact that the one-pot approach was able to give 3-5 makes the process much more general considering only a minor adjustment was made to the Pd(II)-catalyzed oxidative homocoupling protocol.
Table 3.8 One-pot cross-coupling results.

![Reaction Scheme]

3.6 Synthetic Applications of Polyenes

Polycyclic aromatic hydrocarbons represent an important class of compounds as they are used for organic conductors, solar cells, and polymer chemistry. The ease of our coupling strategy now allows rapid construction of polycyclic aromatic hydrocarbons as can be seen in the following examples. In the first case, a Diels–Alder cycloaddition between diene 3-3a and maleic anhydride gave compound 3-8 in 95% yield (Scheme 3.6, A). Next, an oxidative photocyclization of 3-8 using I$_2$ gave polycyclic aromatic hydrocarbon 3-9 in 66% yield. In the next example, polycyclic aromatic hydrocarbon 3-11 was accessed in a similar way as described for 3-9. Diels–Alder cycloaddition of diene 3-3q with N-phenylmaleimide gave 3-10 in 81% yield (Scheme 3.6, B). A PIFA-mediated oxidative biaryl coupling protocol of 3-10 gave 3-11 in 76% yield as a single regioisomer. It should be noted that only three simple steps were necessary to construct polycycles 3-9 and 3-11 from commercially available alkynes.
Scheme 3.6 One-pot protocol enables rapid construction of polycyclic aromatic hydrocarbons.

With this Diels–Alder/oxidative biaryl cyclization strategy in hand, we wanted to apply it for the synthesis of phenanthroindolizine alkaloid tylophorine. Tylophorine possesses a phenanthrene motif similar to compound 3-11 and therefore a similar approach could potentially be used to rapidly construct the natural product.26 Our retrosynthetic analysis for the synthesis of (±)-tylophorine is shown in Scheme 3.7. We envisioned a hetero-Diels–Alder cycloaddition of diene 3-3q with heterocycle 3-12 would give compound (±)-3-13. Next, an oxidative biaryl coupling using conditions shown above on (±)-3-13 would afford the natural product in just three steps.

Scheme 3.7 Retrosynthetic analysis of (±)-tylophorine.
3,4-Dihydro-2H-pyrrole (3-12<sub>m</sub>) is achieved in one step starting from pyrrolidine (Scheme 3.8, A).<sup>28</sup> It is known that the monomer of 3-12 is unstable and converts to the more thermodynamically stable trimer 3-12<sub>t</sub>. However, the ratio of 3-12<sub>m</sub>:3-12<sub>t</sub> can change depending on if the mixture is stored neat, which favors 3-12<sub>t</sub> or in a solution of Et<sub>2</sub>O, which favors 3-12<sub>m</sub>.<sup>29</sup>

**Scheme 3.8** Hetero-Diels–Alder condition screening results.

(a) Preparation of 3,4-dihydro-2H-pyrrole

\[
\text{NH} \quad \xrightarrow{\text{Na}_{2}\text{S}_{2}\text{O}_{3}, \text{NaOH, AgNO}_3, \text{H}_2\text{O}} \quad \begin{array}{c}
\text{N} \\
3-12_m
\end{array} + \begin{array}{c}
\text{N} \\
3-12_t
\end{array}
\]

Stored neat – ~1:2 ratio of 3-12<sub>m</sub>:3-12<sub>t</sub>,

Stored as a ~0.12 M solution in Et<sub>2</sub>O – ~1:0 ratio of 3-12<sub>m</sub>:3-12<sub>t</sub>,

(b) Hetero-Diels–Alder results

![Hetero-Diels–Alder reaction](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;·OEt&lt;sub&gt;2&lt;/sub&gt;, Et&lt;sub&gt;2&lt;/sub&gt;O → rt, 1 h</td>
<td>N.R</td>
</tr>
<tr>
<td>2</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;·OEt&lt;sub&gt;2&lt;/sub&gt;, DCM → rt, 1 h</td>
<td>N.R</td>
</tr>
<tr>
<td>3</td>
<td>BF&lt;sub&gt;3&lt;/sub&gt;·OEt&lt;sub&gt;2&lt;/sub&gt;, DCM → rt, 16 h</td>
<td>N.R*</td>
</tr>
<tr>
<td>4</td>
<td>ZnI&lt;sub&gt;2&lt;/sub&gt;·3-12&lt;sub&gt;m&lt;/sub&gt;, MeCN rt, 16 h</td>
<td>N.R</td>
</tr>
</tbody>
</table>

*Compound 3-14 was isolated in 39% yield after flash column chromatography.*

With heterocycle 3-12<sub>m</sub> in hand, we attempted reactions of it with 3-3q in a hetero-Diels–Alder reaction in hopes of accessing (±)-3-13 (Scheme 3.8, B). We reasoned that thermal conditions would be disadvantageous for the hetero-Diels–Alder reaction due to 3-12<sub>m</sub> equilibrating to 3-12<sub>t</sub>. Instead, we envisioned using a Lewis acid to promote the reaction, such as BF<sub>3</sub>·OEt<sub>2</sub>, which has
shown to promote similar hetero-Diels–Alder reactions. Unfortunately, none of the desired Diels–Alder product was obtained under conditions that employed BF$_3$·OEt$_2$ (entries 1–3). The reaction conducted in the presence of excess BF$_3$·OEt$_2$ (5 equivalents) gave the indene product 3-14 in 39% yield. It is known that Brønsted and Lewis acids promote the cyclization of dienes to indene products in a Nazarov-type process. In the last attempt, a preformed ZnI$_2$·3-12$_m$ complex was used, but unfortunately no Diels–Alder product was observed. Compound 3-12$_m$ proved difficult to work with as other attempts reacting it with 2,3-dimethyl-1,3-butadiene (>500 equivalents) were unsuccessful.

In the last example of polycyclization, we wanted to control the site of the Diels–Alder reaction between 3-3ae and N-phenylmaleimide in hopes of achieving a high selectivity for compound 3-15 (Scheme 3.9).

**Scheme 3.9** Site-selective Diels–Alder cycloaddition of indole 3-3ae with N-phenylmaleimide.

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>3-15 (yield %)</th>
<th>3-16 (yield %)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>N-phenylmaleimide (1 equiv) PhMe, 80 °C, 24 h</td>
<td>47%</td>
<td>24%</td>
</tr>
<tr>
<td>2</td>
<td>N-phenylmaleimide (1 equiv) DMF, 80 °C, 24 h</td>
<td>38%</td>
<td>17%</td>
</tr>
<tr>
<td>3</td>
<td>N-phenylmaleimide (2 equiv) EtAlCl$_2$ (2 equiv) PhMe, DCM, –78 °C, 30 min; rt, 6 h</td>
<td>60%</td>
<td>27%</td>
</tr>
<tr>
<td>4</td>
<td>N-phenylmaleimide (2 equiv) EtAlCl$_2$ (2 equiv) PhMe, –78 °C, 15 h; rt, 33 h</td>
<td>66%</td>
<td>21%</td>
</tr>
</tbody>
</table>

Reactions were performed with 3-3ae on a 0.5 mmol scale. Isolated yields are reported.
However, the thermal cycloaddition gave 3-15 and 3-16 in 47% and 24% yields, respectively with the remaining mass being recovered starting material (entry 1). Switching the solvent to DMF had no beneficial impact on the outcome of the reaction (entry 2). Using conditions described by the Sherburn group,\textsuperscript{7} which use EtAlCl\textsubscript{2}, proved beneficial as compound 3-15 was obtained in a 60% yield (entry 3). Switching the solvent from DCM/toluene to only toluene proved best affording 3-15 in a 66% yield and 3-16 in a 21% yield (entry 4). The relative stereochemistry of compound 3-16 was determined using 2D NMR and arises from cycloaddition through the endo-transition state.

Next, a PIFA-mediated oxidative cyclization of 3-15 gave 3-17 in 56% yield, which proved best as other known conditions for the same cyclization were unsuccessful (Scheme 3.10).\textsuperscript{33}

*Scheme 3.10* PIFA-mediated oxidative cyclization of indole 3-15.

\textbf{Biologically active compounds}

\textit{Bisindolylmaleimides} \hspace{1cm} \textit{Indolocarbazoles}

- BMI-1
- Rydapt

\[
\begin{align*}
\text{PIFA (1 equiv)} & \hspace{1cm} \text{BF}_3\cdot\text{OEt}_2 (2 \text{ equiv}) \\
\text{DCM, \(-40 \rightarrow -10 ^\circ \text{C}\)} & \hspace{1cm} 5 \text{ h} \\
\text{56%} & \\
3-15 & \rightarrow & 3-17
\end{align*}
\]
No oxidation of the cyclohexene ring to an aromatic ring was observed. Interestingly, both compounds 3-15 and 3-17 are cyclohexeno-extended derivatives of bisindolylmaleimides and indolocarbazoles, respectively.\textsuperscript{34} Both classes of natural products exhibit biological activity, making 3-15 and 3-17 interesting candidates for bioassays. Derivatives of compound 3-15 can be viewed as potential photochromic molecules. Photochromic systems have attracted recent attention as these compounds are utilized in materials and electronics.\textsuperscript{35}

3.7 Conclusion

In summary, two mild and straightforward Pd–catalyzed strategies were developed allowing for an efficient conversion of vinyl boronate esters and alkynes to substituted 1,3-dienes, [3]-, and [4]dendralenes. Both protocols take place under mild reaction conditions and tolerate a wide range of functional groups. Several limitations are described where specific substrates are not tolerated under either of the conditions. The one-pot protocol offers the ability to quickly access dienes and [n]dendralenes in great yields with a high level of regioselectivity. starting from commercially available alkynes. The major advantage to the one-pot protocol is that the nucleophilic coupling compound is made \textit{in situ}, thus circumventing the need to isolate sensitive compounds. The strategy allowed the ability to quickly construct complex compounds, such as polycyclic aromatic hydrocarbons, which can be used in a variety of applications.
3.8 Experimental Section

General Information

**Solvents:** Toluene (PhMe), benzene (PhH), diethyl ether (Et\(_2\)O) and tetrahydrofuran (THF) were all distilled from Na/benzophenone. Triethylamine (Et\(_3\)N) and dichloromethane (DCM) were distilled from CaH\(_2\). Methanol was distilled from magnesium turnings. Anhydrous dimethylformamide (DMF) was purchased from ACROS. 1,2-Bis(diphenylphosphino)ethane (dppe), chloroacetone (AcCH\(_2\)Cl), and reagent grade diisobutylaluminum hydride (dibal-H) were purchased from Aldrich. Triphenylphosphine (PPh\(_3\)) and 2-methoxy-4,4,5,5-tetramethyl-1,3,2-dioxaborolane MeOB(pin) were purchased from Oakwood Chemicals. Cesium carbonate (Cs\(_2\)CO\(_3\)) and anhydrous zinc chloride (ZnCl\(_2\)) were stored in a dry box under an atmosphere of N\(_2\). All other reagents/compounds were either purchased and used without further purification or prepared by known literature procedures, unless otherwise specified.

**NMR data:** Spectra’s were obtained on Bruker Avance-500 or ARX-400 instruments and calibrated to the solvent signal (CDCl\(_3\) : \(\delta = 7.26\) ppm for \(^1\)H NMR, \(\delta = 77.2\) ppm for \(^{13}\)C NMR; C\(_6\)D\(_6\) : \(\delta = 7.16\) for \(^1\)H NMR, 128.1 for \(^{13}\)C NMR; DMSO-\(d_6\) : \(\delta = 2.50\) for \(^1\)H NMR and 39.5 for \(^{13}\)C NMR). Data for \(^1\)H NMR spectra are reported as follows: chemical shift (\(\delta\) ppm), multiplicity, coupling constant (Hz), followed by integration. Data for \(^{13}\)C NMR spectra are reported in terms of chemical shift. The following abbreviations are used for the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; m = multiplet, br. = broad, and app. = apparent.

**IR data:** Spectra’s were recorded on a JASCO FTIR-4100 spectrophotometer and significant peaks are reported in cm\(^{-1}\).

**High-resolution mass spectra:** Spectra’s were recorded on a LCT premier mass spectrometer by electrospray ionization time-of-flight (ESI-TOF) or on a Thermo Fisher Scientific Exactive Plus
with Ion Sense ID-CUBE Direct Analysis in Real Time (DART) ion source experiments.

**Thin-layer chromatography:** Reactions were monitored using thin layer chromatography performed on Macherey-Nagel POLYGRAM® SIL G/UV₂₅₄ silica gel TLC plates and visualized with either of the following: UV light, ceric ammonium molybdate (CAM) stain and heat, or potassium permanganate (KMnO₄) stain and heat. Flash column chromatography was performed using 40-63 micron silica gel.
Preparation of bis(triphenylphosphine)palladium(II) dichloride (PdCl$_2$(PPh$_3$)$_2$)

**Procedure:** To a suspension of palladium (II) chloride (2.20 g, 12.4 mmol, 1.0 equiv) in 80 mL of dry acetonitrile was added PPh$_3$ (6.50 g, 24.8 mmol, 2.0 equiv) portionwise at 80 °C. The resulting bright yellow mixture was stirred at 80 °C for 30 min, then rt for 1 h. The solids were collected by filtration, washed with small portions of Et$_2$O, and air-dried. The yellow solid was transferred to a vial to give PdCl$_2$(PPh$_3$)$_2$ (6.26 g, 72% yield) as a yellow solid.

**Physical State:** yellow solid

**$^1$H NMR (400 MHz, CDCl$_3$):** $\delta$ 7.76–7.65 (m, 12 H), 7.46–7.35 (m, 18 H)

**$^{13}$C NMR (100 MHz, CDCl$_3$):** $\delta$ 135.2 (app. t, $J_{CP}$ = 6.1 Hz), 130.7, 129.8 (app. t, $J_{CP}$ = 24.1 Hz), 128.2 (app. t, $J_{CP}$ = 5.2 Hz)

**$^{31}$P NMR (161 MHz, CDCl$_3$):** $\delta$ 23.2

**Graphical representation for preparation of PdCl$_2$(PPh$_3$)$_2$**
(Left) PdCl$_2$ in MeCN at 80 °C under N$_2$. (Middle) After addition of PPh$_3$ at 80 °C. (Right) PdCl$_2$(PPh$_3$)$_2$ after filtration and air drying.

Preparation of [1,2-bis(diphenylphosphino)ethane]nickel(II) chloride (Ni(dppe)Cl$_2$)

\[
\begin{align*}
\text{NiCl}_2 \cdot 6\text{H}_2\text{O}, & \quad \text{NiCl}_2 \cdot 6\text{H}_2\text{O} \text{ dissolved in absoluted EtOH} \\
\text{After addition of dppe}, & \quad \text{After addition of dppe} \\
\text{Final product prior to being transferred to a vial}, & \quad \text{Final product prior to being transferred to a vial}
\end{align*}
\]

**Procedure:** NiCl$_2$·6H$_2$O (2.99 g, 12.6 mmol, 1.0 equiv) was dissolved in 50 mL of absolute EtOH and placed under N$_2$. A solution of 1,2-bis(diphenylphosphino)ethane (dppe) (5.02 g, 12.6 mmol, 1.0 equiv) in 50 mL of absolute EtOH was added by syringe dropwise and the resulting suspension was stirred at rt for 2 h, then filtered. The orange solid was washed with hexanes/Et$_2$O (1:1), and allowed to air dry. The solid was transferred to a vial to give Ni(dppe)Cl$_2$ (6.10 g, 92% yield) as an orange solid.

**Graphical representation for preparation of Ni(dppe)Cl$_2$**

(Left) NiCl$_2$·6H$_2$O dissolved in absoluted EtOH. (Middle) After addition of dppe. (Right) Final product prior to being transferred to a vial.
General Procedure A: Palladium(II)-Catalyzed Oxidative Homocoupling of Vinylboronate Esters

To a round bottom flask was added Cs₂CO₃ (2.0 equiv), a methanol solution of vinyl boronate ester (1.0 equiv, 1 M solution), PdCl₂(PPh₃)₂ (5 mol %), and chloroacetone (3.0 equiv). The reaction was placed under N₂ and stirred at 40 °C for 4 h. The reaction was cooled to rt and the solvent was removed under reduced pressure. The resulting crude residue was purified by column chromatography (silica gel) to afford the desired homocoupled product.

Graphical representation for Oxidative Homocoupling of Vinylboronate Esters (preparation of 3-3j is shown as an example)

(Left) PdCl₂(PPh₃)₂, chloroacetone, Cs₂CO₃, and 3-2j in MeOH. (Middle) Reaction after heating at 40 °C for 1 h. (Right) TLC (hexanes/EtOAc (9:1)) where lane 1 is 3-2j, lane C is the co-spot and lane 2 is the reaction mixture. In lane 2 the UV active spot labeled (P) is 3-3j.
General Procedure B: Palladium(II)-Catalyzed Oxidative Homocoupling of Alkynes

To a solution of Ni(dppe)Cl₂ (0.03 equiv) in dry THF (3.0 mL/mmol of alkyne) was added dibal-H (1.3 equiv, reagent grade) dropwise. The resulting black solution was then placed in a 0 °C ice bath and the alkyne (1.0 equiv) was added to the solution over 5–10 min. After addition, the 0 °C ice bath was removed and the reaction was stirred at rt for 2 h (the reaction can be easily monitored by quenching a small aliquot with water and performing thin-layer chromatography or ¹H NMR analysis, which will indicate when the hydroalumination step is complete). A ZnCl₂ solution (3.0 equiv, 1 M solution in THF) was added and the mixture stirred for 30 min (In all cases, anhydrous ZnCl₂ was weighed out in the glove box followed by addition of dry THF to make a 1 M solution). A suspension containing PdCl₂(PPh₃)₂ (5 mol %), chloroacetone (3.0 equiv) in dry THF was added to the Ni/Al/Zn mixture by cannula or syringe needle and stirred at rt for 1 h (some substrates required a longer reaction time to achieve full conversion). The reaction was diluted with Et₂O and quenched with water (0.04 mL/mmol of dibal-H), then 15% aqueous NaOH (0.04 mL/mmol of dibal-H), and finally water (0.1 mL/mmol of dibal-H). The suspension was stirred for 30 min at rt then filtered through a pad of Celite®, washed with Et₂O, and concentrated under reduced pressure. The crude residue was purified by column chromatography on silica gel to afford the appropriate homocoupled product.
Graphical Representation for Oxidative Homocoupling of Alkynes (preparation of 3-3ad is shown as an example)

(Left) Purging the flask with N\textsubscript{2} containing Ni(dppe)Cl\textsubscript{2}. (Center) Addition of THF to Ni(dppe)Cl\textsubscript{2} prior to addition of dibal-H. After addition of dibal-H, the solution becomes black. (Right) Dropwise addition of 3-1ad in THF to the Ni\textsuperscript{0} solution at 0 °C.

(Left) TLC (hexanes/EtOAc (95:5), UV) of an aliquot quenched with H\textsubscript{2}O at 2 h to ensure complete consumption of 3-1ad. Lane 1 is the 3-1ad, lane C is the co-spot, and lane 2 is the alkene

\[
n\text{BuO} \quad \text{3-1ad} \quad \text{Ni(dppe)Cl}_2, \text{dibal-H} \quad \text{THF, 0 °C to rt} \quad \text{3-3ad} \quad \text{nBuO}
\]

ii. ZnCl\textsubscript{2}, THF, rt

iii. PdCl\textsubscript{2}(PPh\textsubscript{3})\textsubscript{2} \quad \text{AcCH}_2\text{Cl}, rt
derived from protodealumination. **(Center)** Anhydrous ZnCl₂ in a Schlenk flask. **(Right)** Freshly prepared 1 M ZnCl₂ in THF prior to addition to the Ni⁰ solution on the left.

**Left** Dram vial containing PdCl₂(PPh₃)₂, chloroacetone and THF under N₂. This suspension was transferred to in one portion at rt via a large gauge syringe needle. **(Middle)** TLC (hexanes/EtOAc (95:05), UV) of the reaction after 1 h. Lane 1 is the aliquot containing the alkene derived from protodealumination, lane C is the co-spot and lane 3 is from the reaction. The UV active spot from the top of the TLC plate in lane C is the product 3-3ad. **(Right)** Homocoupled product 3-3ad after purification by column chromatography on silica gel.
Characterization Data

Physical State: White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.41–7.38 (m, 4 H), 7.29–7.23 (m, 6 H), 5.54 (d, $J = 1.6$ Hz, 2 H), 5.31 (d, $J = 1.6$ Hz, 2 H)

Spectral data matched reported values.$^{13}$

Physical State: White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.31 (d, $J = 8.8$ Hz, 4 H), 6.78 (d, $J = 8.8$ Hz, 4 H), 5.47 (d, $J = 1.7$ Hz, 2 H), 5.23 (d, $J = 1.7$ Hz, 2 H), 3.76 (s, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 159.2, 149.5, 132.8, 128.6, 114.5, 113.7, 55.3

Spectral data matched reported values.$^{13}$

Physical State: Clear pale orange oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.32 (dd, $J = 8.8$, 5.4 Hz, 4 H), 6.49 (app. t, $J = 8.8$ Hz, 4 H), 5.48 (d, $J = 1.4$ Hz, 2 H), 5.29 (d, $J = 1.4$ Hz)
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 162.0 ($J_{CF} = 246.0$ Hz), 148.9, 136.1 ($J_{CF} = 3.3$ Hz), 129.2 ($J_{CF} = 8.1$ Hz), 116.5, 115.3 ($J_{CF} = 21.4$ Hz)

Spectral data matched reported values.$^{13}$

![diene 3-3d](image)

**Physical State:** White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.43–7.35 (m, 6 H), 7.33–7.29 (m, 4 H), 7.04–6.99 (m, 6 H), 6.76–6.72 (m, 4 H), 6.30 (s, 2 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 145.7, 139.9, 137.4, 131.8, 130.5, 129.6, 128.9, 127.9, 127.5, 126.7

Spectral data matched reported values.$^{13}$

![tetraene 3-3e](image)

**Physical State:** Clear colorless oil

$^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 6.05–5.97 (m, 2 H), 5.24 (d, $J = 2.6$ Hz, 2 H), 5.07 (d, $J = 2.3$ Hz, 2 H), 2.23–2.17 (m, 4 H), 2.01–1.95 (m, 4 H), 1.59–1.52 (m, 4 H), 1.44–1.38 (m, 4 H)

$^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 151.8, 136.4, 127.8, 110.9, 26.2, 25.9, 23.3, 22.6 (the signal at 127.8 overlaps with the C$_6$D$_6$ solvent signal and was confirmed using DEPT 135)

**IR (ATR):** 3089, 2926, 2832, 1633, 1597, 889, 854 cm$^{-1}$

**HRMS (DART-TOF):** Calculated for C$_{16}$H$_{23}$ [M+H]$^+$: 239.17942, found 239.17926
Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.05 (app. s, 2 H), 4.91 (app. s, 2 H), 2.23 (app. t, $J = 7.5$ Hz, 4 H), 1.47–1.39 (m, 4 H), 1.36–1.30 (m, 4 H), 0.91 (t, $J = 7.2$ Hz, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 148.2, 111.4, 34.1, 31.0, 22.7, 14.1

Spectral data matched reported values.$^{36}$

Physical State: Clear pale yellow oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.14 (s, 2 H), 5.01 (s, 2 H), 3.54 (t, $J = 6.5$ Hz, 4 H), 2.41 (t, $J = 7.5$ Hz, 4 H), 1.95–1.88 (m, 4 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 145.6, 113.3, 44.7, 31.5, 31.3

IR (ATR): 3091, 2988, 2957, 1594, 1442, 896 cm$^{-1}$

HRMS (DART-TOF): Calculated for C$_{10}$H$_{16}$Cl$_2$ [M]$^+$: 206.06235, found 206.06165

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.17 (s, 2 H), 5.07 (s, 2 H), 3.71 (t, $J = 6.3$ Hz, 4 H), 2.54 (t, $J = 6.3$ Hz, 4 H), 2.24 (br. s, 2 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 145.7, 114.8, 61.2, 37.7
**IR (ATR):** 3352, 2949, 1591, 893 cm\(^{-1}\)

**HRMS (DART-TOF):** Calculated for C\(_8\)H\(_{15}\)O\(_2\) [M+H]\(^+\): 143.10665, found 143.10602

![3-3i](image)

**Physical State:** White solid

**\(^1\)H NMR (400 MHz, CDCl\(_3\)):** δ 7.45–7.39 (m, 6 H), 7.24–7.21 (m, 4 H), 5.78 (s, 2 H), 3.48 (s, 6 H)

**\(^{13}\)C NMR (100 MHz, CDCl\(_3\)):** δ 166.2, 156.1, 136.9, 128.8, 128.4 (2 C signals), 125.5, 51.5

**IR (ATR):** 3061, 1725, 1596, 1494, 1429, 1265, 1197, 1073, 1000, 910, 847, 759, 696, 630, 604 cm\(^{-1}\)

**HRMS (DART-TOF):** Calculated for C\(_{20}\)H\(_{18}\)O\(_4\) [M+H]\(^+\): 323.12779, found 323.12665

![diene 3-3j](image)

**Physical State:** White solid

**\(^1\)H NMR (400 MHz, CDCl\(_3\)):** δ 7.44–7.37 (m, 6 H), 7.24–7.20 (m, 4 H), 5.76 (s, 2 H), 3.91 (q, J = 7.1 Hz, 4 H), 0.97 (t, J = 7.1 Hz, 6 H)

**\(^{13}\)C NMR (100 MHz, CDCl\(_3\)):** δ 165.9, 155.4, 137.1, 128.9, 128.3, 128.2, 126.0, 60.4, 13.9

**IR (ATR):** 3080, 3019, 2984, 2938, 2902, 1719, 1612, 1595, 1337, 1186, 1156, 1025, 878, 759, 700 cm\(^{-1}\)

**HRMS (DART-TOF):** Calculated for C\(_{22}\)H\(_{23}\)O\(_4\) [M+H]\(^+\): 351.15908, found 351.15820

247
**Physical State:** White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.03 (q, $J = 1.2$ Hz, 2 H), 3.73 (s, 6 H), 2.30 (d, $J = 1.2$ Hz, 6 H)

167.1, 155.8, 118.7, 51.5, 16.1

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 167.1, 155.8, 118.7, 51.5, 16.1

IR (ATR): 2953, 1714, 1605, 1375, 1269, 1169, 1016, 859, 703 cm$^{-1}$

HRMS (DART-TOF): Calculated for C$_{10}$H$_{15}$O$_4$ [M+H]$^+$: 199.09648, found 199.09634

**Physical State:** White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 5.98 (s, 2 H), 5.43–5.38 (m, 2 H), 3.67 (s, 6 H) 2.12–2.06 (m, 4 H), 2.06–2.00 (m, 4 H), 1.71–1.60 (m, 8 H) 166.8, 157.0, 134.8, 126.6, 121.1, 51.4, 28.7, 25.3, 22.8, 21.9

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.8, 157.0, 134.8, 126.6, 121.1, 51.4, 28.7, 25.3, 22.8, 21.9

IR (ATR): 3029, 2987, 2938, 2857, 1720, 1661, 1594, 1428, 1320, 1159, 1009, 872 cm$^{-1}$

HRMS (DART-TOF): Calculated for C$_{20}$H$_{27}$O$_4$ [M+H]$^+$: 331.19038, found 331.18893

**diene 3-3k**

**tetraene 3-3l**

**diene 3-3m**
**Physical State:** Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.34 (ddd, $J = 7.6$, 7.6, 1.8 Hz, 2 H), 7.30–7.26 (m, 2 H), 7.13 (ddd, $J = 7.6$, 7.6, 1.2 Hz, 2 H), 7.10–7.04 (m, 2 H), 5.33 (s, 2 H), 5.25 (s, 2 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 160.1 (d, $J_{CF} = 247.6$ Hz), 144.0, 131.5 (d, $J_{CF} = 3.6$ Hz), 129.4 (d, $J_{CF} = 8.3$ Hz), 128.6 (d, $J_{CF} = 15.0$ Hz), 124.0, 119.4, 115.7 (d, $J_{CF} = 22.7$ Hz)

Spectral data matched reported values.$^{13}$

![diene 3-3n]

**Physical State:** White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.41 (d, $J = 8.6$ Hz, 4 H), 7.24 (d, $J = 8.6$ Hz, 4 H), 5.56 (d, $J = 1.3$ Hz, 2 H), 5.36 (d, $J = 1.3$ Hz, 2 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 148.5, 138.8, 131.5, 129.2, 121.9, 117.2

Spectral data matched reported values.$^{13}$

![diene 3-3o]

**Physical State:** White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.29–7.24 (m, 4 h), 6.95 (ddd, $J = 7.5$, 7.5, 1.1 Hz, 2 H), 6.90–6.86 (m, 2 H), 5.13 (d, $J = 1.2$ Hz, 2 H), 5.08 (d, $J = 1.1$ Hz, 2 h), 3.81 (s, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.1, 147.3, 131.3, 131.0, 128.6, 120.5, 117.2, 111.1, 55.9

Spectral data matched reported values.$^{12}$
Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.20 (t, $J$ = 7.9 Hz, 2 H), 7.02 (ddd, $J$ = 7.7, 1.5, 1.0 Hz, 2 H), 6.95 (dd, $J$ = 2.4, 1.5 Hz, 2 H), 6.79 (ddd, $J$ = 8.2, 2.5, 1.0 Hz, 2 H), 5.56 (d, $J$ = 1.7 Hz, 2 H), 5.34 (d, $J$ = 1.7 Hz, 2 H), 3.77 (s, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 159.5, 149.7, 141.8, 129.3, 120.1, 116.6, 113.3, 113.1, 55.3

Spectral data matched reported values.$^{12}$

Physical State: Off white solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.94 (dd, $J$ = 8.3, 2.1 Hz, 2 H), 6.91 (d, $J$ = 2.1 Hz, 2 H), 6.76 (d, $J$ = 8.3 Hz, 2 H), 5.49 (d, $J$ = 1.7 Hz, 2 H), 5.28 (d, $J$ = 1.7 Hz, 2 H), 3.84 (s, 6 H), 3.82 (s, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 149.7, 148.7, 148.7, 133.2, 120.1, 114.8, 110.9, 110.7, 56.0, 55.9

IR (ATR): 3084, 2936, 2835, 1601, 1577, 1512, 1462, 1257, 1026 cm$^{-1}$

HRMS (DART-TOF): Calculated for C$_{20}$H$_{23}$O$_4$ [M+H]$^+$ : 327.15908, found 327.15747

Physical State: Orange solid
\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.86 (d, \(J = 1.5\) Hz, 2 H), 7.78–7.73 (m, 6 H), 7.62 (dd, \(J = 8.5, 1.8\) Hz, 2 H), 7.43–7.39 (m, 4 H), 5.74 (d, \(J = 1.6\) Hz, 2 H), 5.46 (d, \(J = 1.6\) Hz, 2 H)

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 149.9, 137.7, 133.4, 133.0, 128.3, 127.9, 127.6, 126.7, 126.1, 129.0, 125.7, 117.1

Spectral data matched reported values.\(^{12}\)

Physical State: Pale orange solid

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 8.20–8.14 (m, 2 H), 7.92–7.84 (m, 4 H), 7.57–7.50 (m, 8 H), 5.24 (d, \(J = 1.5\) Hz, 2 H), 5.09 (d, \(J = 1.5\) Hz, 2 H)

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 148.5, 139.3, 133.7, 132.5, 128.4, 127.8, 127.0, 126.3, 126.1, 125.9, 125.5, 121.0

Spectral data matched reported values.\(^{12}\)

Physical State: Off white solid

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.93 (dm, \(J = 8.3\) Hz, 2 H), 7.70 (dm, \(J = 7.8\) Hz, 2 H), 7.52 (s, 2 H), 7.48 (d, \(J = 8.3\) Hz, 4 H), 7.29 (ddd, \(J = 8.3, 7.3, 1.2\) Hz, 2 H), 7.21 (ddd, \(J = 8.0, 7.3, 1.1\) Hz, 2 H), 7.03 (d, \(J = 8.0\) Hz, 4 H), 5.59 (d, \(J = 1.5\) Hz, 2 H), 5.47 (d, \(J = 1.5\) Hz, 2 H), 2.27 (s, 6 H)
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 145.0, 141.4, 135.4, 134.9, 129.9, 129.6, 126.6, 125.1, 124.8, 123.6, 122.6, 121.1, 117.6, 113.8, 21.6

IR (ATR): 3144, 2922, 2854, 1596, 1557, 1446, 1361, 1174, 1132, 750 cm$^{-1}$

HRMS (DART-TOF): Calculated for C$_{32}$H$_{29}$N$_2$O$_4$S$_2$ [M+H]$^+$: 593.15632, found 593.15515

Physical State: White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 8.18 (d, $J = 7.8$ Hz, 2 H), 7.78 (d, $J = 7.8$ Hz, 2 H), 7.63 (s, 2 H), 7.33 (dd, $J = 7.5$, 7.2 Hz, 2 H), 7.25 (dd, $J = 7.5$, 7.2 Hz, 2 H), 5.62 (s, 2 H), 5.47 (s, 2 H), 1.67 (s, 18 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 149.8, 141.7, 135.8, 129.5, 124.6, 124.5, 122.9, 121.3, 120.8, 117.5, 115.4, 83.9, 28.3

IR (ATR): 3051, 2979, 1731, 1607, 1450, 1369, 1153 cm$^{-1}$

HRMS (DART-TOF): Calculated for C$_{30}$H$_{32}$N$_2$O$_4$ [M+H]$^+$: 485.24348, found 485.24338

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.70–7.67 (m, 8 H), 7.43–7.36 (m, 12 H), 4.96 (s, 2 H), 4.87 (s, 2 H), 3.75 (t, $J = 7.3$ Hz, 4 H), 2.50 (t, $J = 7.4$ Hz, 4 H), 1.06 (s, 18 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 143.8, 135.7, 134.1, 129.7, 127.7, 113.9, 63.6, 37.5, 27.0, 19.3
IR (ATR): 3071, 2931, 2857, 1591, 1472, 1428, 1109, 700 cm⁻¹

HRMS (DART-TOF): Calculated for C₄₀H₅₁Si₂O₂ [M+H]^+ : 619.34221, found 619.34222

Physical State: Clear colorless oil

¹H NMR (400 MHz, CDCl₃): δ 7.35–7.26 (m, 10 H), 5.16 (s, 2 H), 5.02 (s, 2 H), 4.50 (s, 4 H), 3.58 (t, J = 7.3 Hz, 4 H), 2.59 (t, J = 7.3 Hz, 4 H)

¹³C NMR (100 MHz, CDCl₃): δ 144.0, 138.6, 128.5, 127.8, 127.7, 113.6, 73.1, 69.6, 34.5

IR (ATR): 3033, 2862, 1596, 1454, 1361, 1101, 896 cm⁻¹

HRMS (DART-TOF): Calculated for C₂₂H₂₇O₂ [M+H]^+ : 323.20055, found 323.20004

Physical State: White solid

¹H NMR (400 MHz, CDCl₃): δ 7.52 (dd, J = 7.9, 1.1 Hz, 2 H), 7.47 (dm, J = 7.6 Hz, 2 H), 7.30 (ddd, J = 7.5, 7.5, 1.1 Hz, 2 H), 7.13 (ddd, J = 7.5, 7.5, 1.2 Hz, 2 H), 5.20 (s, 2 H), 5.06 (s, 2 H), 4.56 (s, 4 H), 3.67 (t, J = 7.1 Hz, 4 H), 2.64 (t, J = 7.1 Hz, 4 H)

¹³C NMR (100 MHz, CDCl₃): δ 143.9, 138.0, 132.6, 129.0, 128.9, 127.5, 122.7, 113.8, 72.3, 70.1, 34.5

IR (ATR): 3092, 2859, 1596, 1469, 1358, 1124, 1104 cm⁻¹

HRMS (DART-TOF): Calculated for C₂₂H₂₅Br₂O₂ [M+H]^+ : 479.02158, found 479.02133
Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$

Major product: 5.06 (d, $J = 1.3$ Hz, 2 H), 4.86 (s, 2 H), 3.29 (s, 6 H), 3.19–3.12 (m, 2 H), 2.29–2.14 (m, 4 H), 1.90–1.82 (m, 2 H), 1.79–1.74 (m, 2 H), 1.65–1.60 (m, 2 H), 1.27–1.11 (m, 6 H)

Minor product: 5.10 (s, 1.5 H), 4.92 (s, 1.5 H), 3.28 (s, 4.5 H), 3.19–3.12 (m, 1.5 H), 2.29–2.14 (m, 3 H), 1.90–1.82 (m, 1.5 H), 1.79–1.74 (m, 1.5 H), 1.65–1.60 (m, 1.5 H), 1.27–1.11 (m, 4.5 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$

Major product: 154.2, 109.7, 82.3, 56.6, 47.6, 33.5, 31.1, 26.2, 24.9

Minor product: 153.1, 109.6, 82.9, 56.4, 48.2, 33.5, 31.1, 26.2, 24.9

IR (ATR): 2929, 2856, 2819, 1601, 1448, 1191, 1098 cm$^{-1}$

HRMS (DART-TOF): Calculated for C$_{18}$H$_{31}$O$_2$ [M+H]$^+$: 279.23185, found 279.23184

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$

$\delta$ 5.34 (t, $J = 7.0$ Hz, 2 H), 2.19 (q, $J = 7.5$ Hz, 4 H), 2.09 (app. p, $J = 7.4$ Hz, 4 H), 0.99 (t, $J = 7.4$ Hz, 6 H), 0.93 (t, $J = 7.4$ Hz, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 141.6, 127.1, 21.5, 21.2, 14.8, 13.9

IR (ATR): 2949, 2822, 1601, 1119 cm$^{-1}$
HRMS (DART-TOF): Calculated for C_{12}H_{23} [M+H]^+ : 167.17942, found 167.17868

Physical State: Clear colorless oil

^1H NMR (400 MHz, CDCl$_3$): δ 7.28–7.23 (m, 2 H), 7.22–7.16 (m, 6 H), 6.03 (t, $J$ = 4.5 Hz, 2 H), 5.33 (dd, $J$ = 1.5, 1.0 Hz, 2 H), 5.15 (dd, $J$ = 1.5, 1.0 Hz, 2 H), 2.84 (t, $J$ = 7.9 Hz, 4 H), 2.36 (td, $J$ = 7.9, 4.6 Hz, 4 H)

^13C NMR (100 MHz, CDCl$_3$): δ 147.7, 139.1, 136.0, 135.2, 127.8, 127.5, 126.9, 126.4, 125.0, 118.3, 28.4, 23.3

IR (ATR): 3062, 2928, 2879, 2825, 1582, 1485, 909 cm$^{-1}$

HRMS (DART-TOF): Calculated for C$_{24}$H$_{23}$ [M+H]^+ : 311.17942, found 311.17810

Physical State: Clear colorless oil

^1H NMR (400 MHz, C$_6$D$_6$): δ 5.75–5.71 (m, 2 H), 5.21 (d, $J$ = 1.2 Hz, 2 H), 5.05 (d, $J$ = 1.2 Hz, 2 H), 2.68–2.63 (m, 2 H), 2.41–2.36 (m, 2 H), 2.28–2.25 (m, 2 H), 2.25–2.21 (m, 2 H), 2.01–1.97 (m, 2 H), 1.27 (s, 6 H), 1.25–1.22 (m, 2 H), 0.90 (s, 6 H)

^13C NMR (100 MHz, C$_6$D$_6$): δ 149.9, 147.0, 122.5, 111.1, 43.0, 41.1, 38.1, 32.1, 31.8, 26.7, 21.1

IR (ATR): 2985, 2913, 1616, 1584, 1365, 1069, 886 cm$^{-1}$

HRMS (DART-TOF): Calculated for C$_{22}$H$_{31}$ [M+H]^+ : 295.24202, found 295.24133
Caution: this compound proved to be unstable and decomposed when it was stored neat. It is recommended to store it as a solution in hexanes or THF.

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 5.19 (dt, $J$ = 1.7, 0.6 Hz, 2 H), 5.17 (ddd, $J$ = 2.0, 1.3, 0.6 Hz, 2 H), 5.07 (t, $J$ = 1.7 Hz, 2 H), 4.99–4.96 (m, 2 H), 1.81 (dd, $J$ = 1.3, 0.6 Hz, 6 H)

$^{13}$C NMR (100 MHz, C$_6$D$_6$): $\delta$ 150.9, 142.5, 116.2, 114.3, 20.4

IR (ATR): 3091, 2962, 1588, 1457, 1120 cm$^{-1}$

HRMS (DART-TOF): Calculated for C$_{10}$H$_{15}$ [M+H]$^+$: 135.11682, found 135.11627

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diene 3-3ad

Physical State: Yellow solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.78 (s, 2 H), 7.66–7.59 (m, 4 H), 7.57 (dd, $J$ = 8.5, 1.8 Hz, 2 H), 7.08 (dd, $J$ = 8.6, 2.4 Hz, 2 H), 7.05 (d, $J$ = 2.4 Hz, 2 H), 5.71 (d, $J$ = 1.6 Hz, 2 H), 5.41 (d, $J$ = 1.6 Hz, 2 H), 4.04 (t, $J$ = 6.5 Hz, 4 H), 1.81 (app. p, $J$ = 6.5 Hz, 4 H), 1.52 (app. sextet, $J$ = 7.3 Hz, 4 H), 0.99 (t, $J$ = 7.3 Hz, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 157.4, 150.0, 135.4, 134.2, 129.8, 128.8, 126.8, 126.7, 126.5, 126.0, 119.2, 116.0, 106.5, 67.8, 31.4, 19.4, 14.0

IR (ATR): 3059, 2956, 2872, 1627, 1389, 1185 cm$^{-1}$

HRMS (DART-TOF): Calculated for C$_{32}$H$_{35}$O$_2$ [M+H]$^+$: 451.26315, found 451.26300
**Physical State:** Off white solid

**$^1$H NMR (400 MHz, CDCl$_3$):** $\delta$ 7.89 (ddd, $J = 8.1, 0.8, 0.8$ Hz, 2 H), 7.78 (ddd, $J = 7.9, 1.1, 0.6$ Hz, 2 H), 7.45 (s, 2 H), 7.36 (ddd, $J = 8.3, 7.3, 1.2$ Hz, 2 H), 7.30 (ddd, $J = 8.3, 7.3, 1.2$ Hz, 2 H), 5.65 (d, $J = 1.4$ Hz, 2 H), 5.53 (d, $J = 1.5$ Hz, 2 H), 3.02 (s, 6 H)

**$^{13}$C NMR (100 MHz, CDCl$_3$):** $\delta$ 140.8, 135.4, 129.5, 125.2, 124.7, 123.8, 122.7, 121.4, 118.2, 113.3, 40.7

**IR (ATR):** 3130, 3020, 2930, 1604, 1447, 1361, 1165 cm$^{-1}$

**HRMS (DART-TOF):** Calculated for C$_{22}$H$_{21}$N$_2$O$_4$S$_2$ [M+H]$^+$: 441.09372, found 441.09348

**Preparation:** To a solution of 5-methoxy-2-tetralone (5.28 g, 30.0 mmol, 1.0 equiv), PhNTf$_2$ (11.78 g, 33.0 mmol, 1.1 equiv) in THF (0.1 M) at $-78$ °C was added NaHMDS (1.0 M in THF, 33.0 mL, 1.1 equiv) dropwise over 30 min. The reaction was allowed to warm to rt over 18 h. The reaction was quenched with sat. NaHCO$_3$ and the aqueous layer was extracted with Et$_2$O (4 x 50 mL). The organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude material was purified by column chromatography on silica gel (hexanes/EtOAc, 95:5) to give triflate **3-4** (8.40 g, 91% yield) as an orange oil.

**Physical State:** Orange oil
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.16 (t, $J = 7.8$ Hz, 1 H), 6.18 (d, $J = 8.2$ Hz, 1 H), 6.71 (d, $J = 7.5$ Hz, 1 H), 6.44 (t, $J = 1.3$ Hz, 1 H), 3.83 (s, 3 H), 3.05 (t, $J = 8.4$ Hz, 2 H), 2.66 (td, $J = 8.6$, 1.3 Hz 2 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 156.4, 150.4, 127.7, 120.8, 120.1, 118.4, 111.7, 55.6, 26.1, 21.4

IR (ATR): 3003, 2841, 1668, 1478, 1417, 1139, 845 cm$^{-1}$

HRMS (DART-TOF): Calculated for C$_{12}$H$_{11}$F$_3$O$_4$S [M$^+$]: 308.03246, found 308.03128

Procedure: Following General Procedure B for steps $i$ and $ii$ with alkyne 3-1e (530 mg, 5.0 mmol, 1.1 equiv) gives the in situ generated vinyl zinc reagent at the end of step $ii$. Next, a solution of triflate 3-4 (1.38 g, 4.5 mmol) and PdCl$_2$(PPh$_3$)$_2$ (63.1 mg, 0.09 mmol) in dry THF was added to the Ni/Al/Zn solution at rt. The reaction was stirred at rt and monitored by TLC for consumption of triflate 3-4. Upon completion, the reaction was quenched as described in General Procedure B and the resulting residue was purified by column chromatography on silica gel (hexanes/EtOAc, 99:1) to give 3-5 (1.12 g, 94% yield) as a clear colorless oil.

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 7.04 (t, $J = 7.8$ Hz, 1 H), 6.76 (d, $J = 7.2$ Hz, 1 H), 6.68 (t, $J = 1.2$ Hz, 1 H), 6.50 (d, $J =8.1$ Hz, 1 H), 5.88–5.84 (m, 1 H), 5.09 (d, $J = 1.6$ Hz, 1 H), 5.07 (d, $J = 1.6$ Hz, 1 H), 3.37 (s, 3 H), 3.02 (t, $J = 8.5$ Hz, 2 H), 2.40 (ddd, $J = 8.4$, 8.0, 1.3 Hz, 2 H), 2.21–2.16 (m, 2 H), 2.04–1.97 (m, 2 H), 1.61–1.54 (m, 2 H), 1.52–1.45 (m, 2 H)
\[ ^{13}\text{C NMR (100 MHz, C}_6\text{D}_6): \delta 156.7, 153.5, 140.1, 137.7, 136.4, 127.1, 126.9, 126.4, 123.2, 120.1, 109.8 (2 \text{ C signals}), 55.0, 28.3, 26.3, 25.9, 23.3, 22.6, 21.1 \]

\[ \text{IR (ATR): 2961, 2930, 2835, 1590, 1570, 1469, 1439, 1262, 1085 cm}^{-1} \]

\[ \text{HRMS (DART-TOF): Calculated for C}_{19}\text{H}_{23}\text{O} [\text{M+H}]^{+}: 267.17434, \text{found 267.17310} \]

**Procedure:** To a pressure tube was added 3-3a (206 mg, 1.0 mmol), maleic anhydride (108 mg, 1.1 mmol) and 1.5 mL of dry benzene. The solution was sparged with N\(_2\) for 1 min, then sealed with a Teflon cap and stirred at 80 °C for 48 h. The pressure tube was cooled to 0 °C and the solution was transferred to a round bottom flask and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes/EtOAc, 7:3) to give compound 3-8 (291 mg, 95% yield) as a white solid.

**Physical State:** White solid

\[ ^1\text{H NMR (400 MHz, CDCl}_3): \delta 7.16–7.09 (m, 6 H), 7.00–6.91 (m, 4 H), 3.61–3.54 (m, 2 H), 3.11 (d, \text{ } J = 15.5 \text{ Hz}, 2 \text{ H}), 2.79 (dd, \text{ } J = 15.0, 3.1 \text{ Hz}, 2 \text{ H}) \]

\[ ^{13}\text{C NMR (100 MHz, CDCl}_3): \delta 174.1, 140.5, 135.6, 128.8, 128.2, 127.0, 40.9, 31.9 \]

Spectral data matched reported values.\(^{12}\)

**Procedure:** To a solution of compound 3-8 (152 mg, 0.50 mmol) in dry benzene (160 mL) was
added I₂ (127 mg, 0.50 mmol) and the mixture was stirred for 5 min. Next, the 550 W Hanovia mercury lamp was turned on (caution: emits an extremely bright and intense light and produces a substantial amount of heat, so make sure there is a strong flow of water) and the reaction was stirred under N₂ for 2 h. The reaction was quenched with Na₂S₂O₃ and the organic layer was separated and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography (silica gel, hexanes/EtOAc, 8:2) to afford compound 3-9 (103 mg, 68% yield) as an off white solid.

**Graphical representation for oxidative cyclization of compound 3-8**

![Graphical representation](image)

**Physical State:** Off white solid

**¹H NMR (400 MHz, DMSO-d₆):** δ 8.89–8.79 (m, 2 H), 8.29–8.15 (m, 2 H), 7.71–7.59 (m, 4 H), 3.96–3.82 (m, 4 H), 3.11–2.97 (m, 2 H)

**¹³C NMR (100 MHz, DMSO-d₆):** δ 174.9, 130.1, 129.2, 129.0, 127.2, 126.5, 123.3 (2 C signals), 40.7, 23.9

**IR (ATR):** 3079, 1784, 1734, 1610, 1244, 932 cm⁻¹

**HRMS (DART-TOF):** Calculated for C₂₀H₁₄O₃ [M]⁺: 302.09374, found 302.09335
Procedure: To a pressure tube was added 3-3q (660 mg, 2.0 mmol), N-phenylmaleimide (524 mg, 3.0 mmol) and 3.0 mL of freshly distilled toluene. The solution was sparged with N₂ for 1 min then sealed with a Teflon cap. The reaction was stirred at 100 °C for 16 h, then cooled to rt and concentrated under reduced pressure. The crude material was purified by column chromatography (silica gel, hexanes/EtOAc, 6:4) to afford compound 3-10 (817 mg, 81% yield) as an orange solid.

Physical State: Orange solid

¹H NMR (400 MHz, CDCl₃): δ 7.44–7.34 (m, 3 H), 7.20–7.14 (m, 2 H), 6.67 (d, J = 8.3 Hz, 2 H), 6.60 (dd, J = 8.3, 1.9 Hz, 2 H), 6.48 (d, J = 1.9 Hz, 2 H), 6.48 (d, J = 1.9 Hz, 2 H), 3.80 (s, 6 H), 3.54 (s, 6 H), 3.46 (dd, J = 2.3, 1.6 Hz, 2 H), 3.22 (dd, J = 14.9, 1.5 Hz, 2 H), 2.77 (dd, J = 14.6, 2.3 Hz, 2 H)

¹³C NMR (100 MHz, CDCl₃): δ 179.0, 148.3, 147.7, 134.3, 133.9, 132.1, 129.1, 128.6, 126.4, 121.0, 112.3, 110.9, 77.3, 55.8, 55.5, 40.6, 32.4

IR (ATR): 3004, 2836, 1779, 1706, 1511, 1244 cm⁻¹

HRMS (DART-TOF): Calculated for C₃₀H₂₉NO₆ [M]⁺: 499.19893, found 499.19861
**Procedure:** A solution of PIFA (215 mg, 0.5 mmol) and BF$_3$·OEt$_2$ (0.12 mL, 1.0 mmol) in 10 mL of dry DCM was added at −40 °C to a solution of compound 3-10 (249.8 mg, 0.5 mmol) in 10 mL of dry DCM. The reaction was stirred at −40 °C for 1 h, then slowly warmed to 0 °C. Water (10 mL) was added followed by 10 mL of sat. aqueous NaHCO$_3$. The two layers were separated and the aqueous layer was further extracted with DCM (3 x 10 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:1) to afford compound 3-11 (190.2 mg, 76% yield) as a pale pink solid.

**Physical State:** Pale pink solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.83 (s, 2 H), 7.50 (s, 2 H), 7.27–7.20 (m, 3 H), 6.79–6.74 (m, 2 H), 4.11 (s, 6 H), 4.07 (s, 6 H), 3.90 (dd, $J$ = 15.1, 1.8 Hz, 2 H), 3.61 (app. t, $J$ = 2.7, 2.7 Hz, 2 H), 3.19 (dd, $J$ = 14.8, 2.5 Hz, 2 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 178.5, 148.9, 148.7, 131.5, 128.8, 128.3, 127.0, 126.1, 124.2, 123.7, 103.6, 103.2, 77.3, 55.9, 55.8, 40.2, 24.9

**IR (ATR):** 3089, 2832, 1707, 1618, 1471, 1149 cm$^{-1}$

**HRMS (DART-TOF):** Calculated for C$_{30}$H$_{27}$NO$_6$ [M]+: 497.18328, found 497.18329

![Chemical Structure](image)

1-Pyrroline (3-12): Following the procedure described by Tomoda,$^2$ eight pyrrolidine (12.3 mL, 150 mmol), Na$_2$S$_2$O$_8$ (35.7 g, 150 mmol), NaOH (12.0 g, 300 mmol), AgNO$_3$ (127 mg, 0.75 mmol), and water (260 mL) were used to prepare 1-pyrrolidine (3-12). Workup gave 2.80 g (27% yield), which was diluted with Et$_2$O and stored as a 0.12 M solution.
Spectral data matched reported values.  

Physical State: White solid  

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.06 (s, 1 H), 7.00 (dd, $J$ = 8.5, 1.7 Hz, 1 H), 6.98 (d, $J$ = 1.9 Hz, 1 H), 6.91 (d, $J$ = 8.3 Hz, 1 H), 6.89 (s, 1 H), 3.95 (s, 3 H), 3.92 (s, 3 H), 3.91 (s, 3 H), 3.91 (s, 3 H), 3.64 (q, $J$ = 1.9 Hz, 2 H), 2.28 (t, $J$ = 1.9 Hz, 3 H)  

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 148.7, 148.5, 147.8, 147.2, 140.5, 138.9, 134.6, 133.3, 130.7, 120.5, 111.5, 111.2, 107.8, 102.8, 56.3, 56.2, 55.9 (2 C signals), 40.8, 12.1  

Spectral data matched reported values.  

Procedure: To a solution of N-phenylmaleimide (346 mg, 2.0 mmol) in 10 mL of freshly distilled toluene was added EtAlCl$_2$ (0.21 mL, 2.0 mmol) dropwise at $-78^\circ$C and the contents were stirred for 30 min. Next, a solution of 3-3ae (440 mg, 1.0 mmol) in 10 mL of toluene was added dropwise at $-78^\circ$C and the reaction was allowed to warm to rt over 48 h. The reaction was quenched with water (20 mL) and extracted with EtOAc (3 x 30 mL). The combined organic extracts were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes/EtOAc gradient, 1:1 $\rightarrow$ 4:6 $\rightarrow$ 3:7) to give (405 mg, 66% yield) 3-15 and (129 mg, 21% yield) of 3-16.
Physical State: Orange solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.78 (ddd, $J$ = 8.3, 0.7, 0.7 Hz, 2 H), 7.44–7.35 (m, 4 H), 7.26–7.24 (m, 2 H), 7.21 (dd, $J$ = 8.3, 0.9 Hz, 2 H), 7.17–7.15 (m, 2 H), 7.12 (s, 2 H), 7.03 (ddd, $J$ = 8.1, 7.2, 0.85 Hz, 2 H), 3.58 (dd, $J$ = 3.3, 1.3 Hz, 2 H), 3.39 (dd, $J$ = 15.1, 1.3 Hz, 2 H), 2.98 (dd, $J$ = 15.0, 3.3 Hz, 2 H), 2.62 (s, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 178.7, 134.9, 131.9, 129.3, 129.0, 128.8, 128.3, 126.4, 125.3, 125.0, 123.6, 123.2, 120.9, 113.3, 77.4, 40.4, 40.1, 31.5

IR (ATR): 3128, 2928, 1707, 1364, 1169 cm$^{-1}$

HRMS (DART-TOF): Calculated for C$_{32}$H$_{27}$N$_3$O$_6$S$_2$ [M]$^+$: 613.13357, found 613.13318

Physical State: Off orange solid

$^1$H NMR (400 MHz, C$_6$D$_6$): $\delta$ 7.99 (ddd, $J$ = 8.2, 0.8, 0.8 Hz, 1 H), 7.72 (d, $J$ = 7.4 Hz, 1 H), 7.58 (ddd, $J$ = 7.8, 0.8, 0.8 Hz, 1 H), 7.42 (d, $J$ = 8.2 Hz, 1 H), 7.29 (s, 1 H), 7.14–7.10 (m, 2 H), 7.07–6.99 (m, 4 H), 6.95–6.90 (m, 2 H), 6.59 (ddd, $J$ = 7.8, 7.8, 0.9 Hz, 1 H), 5.46 (d, $J$ = 1.1 Hz, 1 H), 5.34 (d, $J$ = 1.1 Hz, 1 H), 4.65 (dd, $J$ = 6.8, 2.1 Hz, 1 H), 3.66 (dd, $J$ = 9.2, 6.8 Hz, 1 H), 2.95 (s, 3
H), 2.72 (dd, J = 15.2, 1.6 Hz, 1 H), 2.41 (ddd, J = 9.0, 7.1, 1.6 Hz, 1 H), 2.16 (s, 3 H), 1.66 (ddd, J = 15.2, 7.3, 2.1 Hz, 1 H)

\(^{13}\text{C NMR (100 MHz, C}\text{D}_6\): δ 176.8, 174.1, 146.0, 139.6, 136.2, 132.4, 132.2, 130.3, 129.4, 129.1, 128.6, 128.4, 126.5, 125.7, 125.5, 125.0, 124.3, 124.2, 122.8, 121.3, 120.2, 116.8, 113.9, 113.8, 62.9, 42.3, 39.9, 39.8, 37.6, 31.7

IR (ATR): 2983, 2907, 1733, 1711, 1372, 1241, 1045 cm\(^{-1}\)

HRMS (DART-TOF): Calculated for C\(_{32}\)H\(_{28}\)N\(_3\)O\(_6\)S\(_2\) [M+H]\(^{+}\): 614.14140, found 614.13916

**Procedure:** A solution of PIFA (215 mg, 0.5 mmol) and BF\(_3\).OEt\(_2\) (0.12 mL, 1 mmol) in 10 mL of dry DCM was added at \(-40^\circ\text{C}\) to a solution of compound 3-15 (307 mg, 0.5 mmol) in 10 mL of dry DCM, and the reaction was stirred at \(-40^\circ\text{C} \rightarrow -10^\circ\text{C}\) over 6 h. The reaction was then placed in an ice bath and water (10 mL) was added followed by 10 mL of sat. aqueous NaHCO\(_3\). The layers were separated and the aqueous layer was further extracted with DCM (3 x 10 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes/EtOAc, 1:1) to afford compound 3-17 (172 mg, 56% yield) as a white solid.

**Physical State:** White solid

\(^1\text{H NMR (400 MHz, CDCl}_3\): δ 8.45 (d, J = 7.7 Hz, 1 H), 8.37 (d, J = 7.3 Hz, 1 H), 8.17 (d, J = 7.8 Hz, 2 H), 7.60–7.46 (m, 4 H), 7.21–7.14 (m, 3 H), 6.71–6.65 (m, 2 H), 4.47 (dd, J = 15.0, 2.4
Hz, 1 H), 4.43 (dd, J = 15.0, 2.4 Hz, 1 H), 3.74 (d, J = 2.4 Hz, 1 H), 3.72 (d, J = 2.3 Hz, 1 H), 3.39 (dd, J = 14.8, 5.7 Hz, 1 H), 3.33 (dd, J = 14.7, 5.8 Hz, 1 H), 2.69 (s, 3 H), 2.22 (s, 3 H)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 179.1, 179.0, 141.0, 140.9, 132.2, 129.8, 129.3, 129.2 (2 C signals), 128.7, 128.5, 128.4, 128.1, 127.7, 126.8, 126.6 (3 C signals), 125.8, 125.7, 123.5, 123.4, 117.3, 117.1, 40.0, 38.1, 37.8, 25.8

IR (ATR): 3052, 2930, 1707, 1597, 1366, 1173, 957 cm$^{-1}$

HRMS (DART-TOF): Calculated for C$_{32}$H$_{26}$N$_3$O$_6$S$_2$ [M+H]$^+$: 612.12575, found 612.12427
Preparation of alkyne starting materials

Preparation of 1-ethynyl-4-methoxybenzene (3-1b)

1-(2,2-dibromovinyl)-4-methoxybenzene (3-SI-1)

Procedure: To a solution of PPh₃ (7.86 g, 30.0 mmol, 3.0 equiv) in 25 mL of dry DCM was added CBr₄ (4.97 g, 15.0 mmol, 1.5 equiv) portion wise at 0 °C. The reaction was placed under N₂ and stirred for 15 min followed by dropwise addition of 4-methoxybenzaldehyde (1.22 mL, 10.0 mmol, 1.0 equiv) at 0 °C. The resulting mixture was stirred at rt until there was no aldehyde present (thin-layer chromatography). A solution of hexanes/EtOAc (8:2, 100 mL) was added and stirred for an additional 1 h. The solid precipitates were removed by filtration and the filtrate was concentrated under reduced pressure to afford 3-SI-1 (2.73 g, 94% yield) as an orange solid.

Physical State: Orange solid

¹H NMR (400 MHz, CDCl₃): δ 7.51 (d, J = 8.9 Hz, 2 H), 7.40 (s, 1 H), 6.89 (d, J = 8.9 Hz, 2 H), 3.82 (s, 3 H)

¹³C NMR (100 MHz, CDCl₃): δ 159.8, 136.4, 130.0, 128.0, 113.9, 87.4, 55.4

Spectral data matched reported values.⁶⁷

1-ethynyl-4-methoxybenzene (3-1b)

Procedure: To a solution of 3-SI-1 (1.45 g, 5.0 mmol, 1.0 equiv) in 15 mL of dry THF was added n-BuLi (8.0 mL, 20.0 mmol, 2.5 M in hexanes, 4.0 equiv) dropwise at −78 °C. The solution was
stirred until all the starting material was consumed (ca 2 h, thin-layer chromatography, hexanes). The reaction was quenched with sat. NH₄Cl (15 mL), and the contents were transferred to a separatory funnel. The aqueous layer was extracted with Et₂O (4 x 10 mL) and the organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by column chromatography (silica gel, hexanes/EtOAc, 95:5) to give 3-1b (528 mg, 80% yield) as a pale yellow solid.

**Physical State:** Pale yellow solid

**1H NMR (400 MHz, CDCl₃):** δ 7.43 (d, J = 8.9 Hz, 2 H), 6.84 (d, J = 8.9 Hz, 2 H), 3.81 (s, 3 H), 2.99 (s, 1 H)

**13C NMR (100 MHz, CDCl₃):** δ 160.1, 133.7, 114.3, 114.1, 83.8, 75.9, 55.4

Spectral data matched reported values. ³⁸

Preparation of 1-ethynlcyclohex-1-ene (3-1e)

**Procedure:** To a 25 mL Schlenk flask equipped with a reflux condenser was added 1-ethynlcyclohexan-1-ol (7.31 g, 58.8 mmol) and 5 mL of freshly distilled pyridine. Next, a solution of POCl₃ (5.0 mL, 53.6 mmol) in 4 mL of pyridine was added dropwise over 50 min at rt under N₂. The reaction was stirred at rt for 3 h, and then 90 °C for 45 min. The flask was removed from the oil bath, cooled to rt and quenched by pouring the solution into beaker of ice and letting it sit for 1 h. The aqueous layer was extracted with petroleum ether/Et₂O (1:1, 3 x 25 mL). The combined organic extracts were washed with H₂O (2 x 20 mL), brine (1 x 25 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude oil was purified by distillation.
at reduced pressure (b.p. 45–47 °C @ 70 mmHg) to afford (3.63 g, 58% yield) 1-ethynylcyclohex-1-ene (1e) as a clear colorless oil.

**Physical State:** clear colorless oil

**b.p.:** 45–47 °C @ 70 mmHg

**1H NMR (400 MHz, C₆D₆):** δ 6.17–6.12 (m, 1 H), 2.59 (s, 1 H), 2.10–2.04 (m, 2 H), 1.75–1.69 (m, 2 H), 1.34–1.27 (m, 2 H), 1.26–1.20 (m, 2 H)

Spectral data matched reported values.³⁹

Preparation of methyl 3-phenylpropiolate (3-1i)

![Chemical structure of methyl 3-phenylpropiolate](image)

**Procedure:** To a solution of phenylacetylene (3-1a) (2.75 mL, 25.0 mmol, 1.0 equiv) in 60 mL of dry THF was added n-BuLi (11.0 mL, 27.5 mmol, 1.1.0 equiv) dropwise at −78 °C and stirred for 1 h. Next, methyl chloroformate (2.13 mL, 27.5 mmol, 1.1.0 equiv) was added dropwise at −78 °C and stirred for an additional 1 h. The −78 °C bath was removed and the solution was warmed to rt and stirred for 3 h. The reaction was quenched at with sat. NH₄Cl at 0 °C and the contents were transferred to a separatory funnel. The aqueous layer was extracted with Et₂O (4 x 40 mL) and the combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude oil was purified by distillation at reduced pressure (b.p. 84–87 °C @ 1.0 mmHg) gave (3.24 g, 81% yield) methyl 3-phenylpropiolate (3-1i) as a clear colorless oil.

**Physical State:** clear colorless oil

**b.p.:** 84–87 °C @ 1.0 mmHg

**1H NMR (400 MHz, CDCl₃):** δ 7.59–7.56 (m, 2 H), 7.47–7.42 (m, 1 H), 7.38–7.34 (m, 2 H), 3.85 (s, 3 H)
$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.6, 133.1, 130.8, 128.7, 119.7, 86.6, 80.5, 52.9

Spectral data matched reported values.$^{40}$

Preparation of methyl 3-(cyclohex-1-en-1-yl)propiolate (3-1l)

![Methyl 3-(cyclohex-1-en-1-yl)propiolate](image)

**Procedure:** To a 250 mL round bottom flask was added 1-ethynylcyclohex-1-ene (3-1e) (2.12 g, 20.0 mmol, 1.0 equiv), 60 mL of dry THF and the headspace was purged with N$_2$ then placed in a −78 °C bath. Next, $n$-BuLi (8.0 mL, 20 mmol, 2.5 M in hexanes, 1.0 equiv) was added dropwise at −78 °C and stirred for 1 h followed by dropwise addition of methyl chloroformate (1.85 mL, 24 mmol, 1.2 equiv). The solution was stirred at −78 °C to rt over 16 h. The reaction was quenched with sat. NH$_4$Cl (100 mL) and extracted with Et$_2$O (4 x 50 mL). The organic extracts were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by distillation at reduced pressure (b.p. 93–96 °C @ < 1.0 mmHg) to give 1.7453 g (53%) of methyl 3-(cyclohex-1-en-1-yl)propiolate (3-1l).

**Physical State:** clear colorless oil

**b.p.:** 93–96 °C @ < 1.0 mmHg

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.47–6.42 (m, 1 H), 3.77 (s, 3 H), 2.18–2.11 (m, 4 H), 1.66–1.56 (m, 4 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 154.9, 142.4, 118.5, 88.9, 78.4, 52.7, 28.2, 26.1, 22.0, 21.2

Spectral data matched reported values.$^{40}$

Preparation of 1-ethynyl-2-fluorobenzene (3-1m)

1-$(2,2$-dibromovinyl)$)$-2-fluorobenzene (3-SI-2)
**Procedure:** To a solution PPh$_3$ (7.87 g, 30 mmol, 3 equiv) in 25 mL of DCM at 0 °C was added CBr$_4$ (4.97 g, 15 mmol, 1.5 equiv) and stirred for 15 min under N$_2$. To the red-orange solution was added neat 2-fluorobenzaldehyde (1.05 mL, 10 mmol, 1.0 equiv) at 0 °C. After all the aldehyde was added the 0 °C ice bath was removed and stirred for 1.5 h at rt. A solution of hexanes/EtOAc (7:3, 150 mL) was added and stirred for 1 h. The suspension was filtered through a pad of silica gel and washed several times with hexanes/EtOAc (9:1). The solvent was removed under reduced pressure to afford 2.26 g (81%) of 1-(2,2-dibromovinyl)-2-fluorobenzene (3-SI-2)

**Physical State:** Pale yellow

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.75 (td, $J = 7.6, 1.4$ Hz, 1 H), 7.55 (s, 1 H), 7.37–7.30 (m, 1 H), 7.15 (td, $J = 7.6, 1.0$ Hz, 1 H), 7.06 (ddd, $J = 9.9, 8.3, 1.0$ Hz, 1 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 159.6 (d, $J_{CF} = 251.1$ Hz), 130.5 (d, $J_{CF} = 8.4$ Hz), 130.1 (d, $J_{CF} = 5.1$ Hz), 129.4 (d, $J_{CF} = 2.2$ Hz), 124.0 (d, $J_{CF} = 3.1$ Hz), 123.6 (d, $J_{CF} = 13.40$ Hz), 115.7 (d, $J_{CF} = 21.5$ Hz), 92.3 (d, $J_{CF} = 1.7$ Hz)

Spectral data matched reported values.$^{41}$

*1-ethynyl-2-fluorobenzene (3-1m)*

**Procedure:** To a 50 mL round bottom flask was added 1-(2,2-dibromovinyl)-2-fluorobenzene (3-SI-2) (850 mg, 3.02 mmol, 1.0 equiv), Cs$_2$CO$_3$ (2.47 g, 7.6 mmol, 2.5 equiv) and DMSO (10 mL). The reaction was placed under N$_2$ and stirred at 115 °C for 18 h. The flask was cooled to rt then
poured into 30 mL of brine and transferred to a separatory funnel and diluted with Et₂O (100 mL). The organic layer was washed with water (5 x 25 mL) and brine (1 x 25 mL). The organic layer was dried over MgSO₄, filtered and concentrated under reduced pressure. The crude oil was purified by column chromatography (silica gel, hexanes) to afford (130 mg, 36% yield) *1-ethynyl-2-fluorobenzene (3-1m)* as a clear colorless oil.

**Physical State:** Clear colorless oil

**¹H NMR (400 MHz, CDCl₃):** \( \delta \) 7.48 (td, \( J = 8.2, 1.8 \text{ Hz}, 1 \text{ H} \)), 7.34–7.30 (m, 1 H), 7.12–7.06 (m, 2 H), 3.30 (s, 1 H)

**¹³C NMR (100 MHz, CDCl₃):** \( \delta \) 163.5 (d, \( J_{CF} = 252.5 \text{ Hz} \)), 134.2, 130.7 (d, \( J_{CF} = 7.9 \text{ Hz} \)), 124.1 (d, \( J_{CF} = 3.5 \text{ Hz} \)), 115.7 (d, \( J_{CF} = 20.6 \text{ Hz} \)), 110.8 (d, \( J_{CF} = 15.7 \text{ Hz} \)), 82.5 (d, \( J_{CF} = 3.1 \text{ Hz} \)), 77.3

Spectral data matched reported values..

Preparation of *1-bromo-4-ethynylbenzene (3-1n)*

\(((4\text{-bromophenyl})\text{ethynyl})\text{trimethylsilane}\)

**Procedure:** To a Schlenk flask was added 1-bromo-4-iodobenzene (3.85 g, 30.0 mmol, 1.0 equiv), 60 mL of freshly distilled Et₃N and the solution was sparged with N₂ for 5 min. Next, ethynyltrimethylsilane (4.98 mL, 36.0 mmol, 1.2 equiv), PdCl₂(PPh₃)₂ (421.1 mg, 0.6 mmol, 0.02 equiv) and CuI (228.5 mg, 1.2 mmol, 0.04 equiv) were added and the solution was sparged again with N₂ for 2 min. The reaction was stirred at rt until all the starting material was consumed (ca 1.5 h, thin-layer chromatography, hexanes). The solution was filtered through a pad of Celite®, washed with hexanes and the filtrate was concentrated under reduced pressure to afford a brown solid, which was used in the next step without further purification.
1-bromo-4-ethynylbenzene (3-1n)

**Procedure:** The crude solid above was dissolved in 60 mL of dry MeOH and K$_2$CO$_3$ (1.24 g, 9.0 mmol) was added in one portion, placed under N$_2$ and stirred at rt. After 1.5 h, the mixture was filtered through a pad of Celite® and washed with hexanes. The filtrate was concentrated under reduced pressure and the resulting solid was passed through a small pad of silica gel, washed with hexanes, and concentrated under reduced pressure to afford (4.88 g, 90% yield) 1-bromo-4-ethynylbenzene (3-1n) as an off white solid.

**Physical State:** Off white solid

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.46 (d, $J = 8.7$ Hz, 2 H), 7.34 (d, $J = 8.6$ Hz, 2 H), 3.12 (s, 1 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 133.7, 131.7, 123.3, 121.2, 82.7, 78.5

Spectral data matched reported values.\(^{42}\)

Preparation of 1-ethynyl-2-methoxybenzene (3-1o)

1-(2,2-dibromovinyl)-2-methoxybenzene (3-SI-3)

**Procedure:** To a solution PPh$_3$ (7.86 g, 30 mmol, 3 equiv) in 20 mL of DCM at 0 °C was added CBr$_4$ (4.97 g, 15 mmol, 1.5 equiv) and stirred under N$_2$ for 15 min. To the red-orange solution was added neat 2-methoxybenzaldehyde (1.36 g, 10 mmol, 1.0 equiv) at 0 °C and stirred until all the aldehyde was consumed (ca 30 min, thin layer chromatography). A solution hexanes/EtOAc (7:3, 150 mL) was added and stirred for 1 h. The suspension was filtered through a pad of silica gel and
washed several times with hexanes/EtOAc (9:1). The solvent was removed under reduced pressure to afford (2.69 g, 92% yield) 1-(2,2-dibromovinyl)-2-methoxybenzene (3-SI-3) as a clear colorless oil

**Physical State:** Clear colorless oil

**1H NMR (400 MHz, CDCl3):** δ 7.70 (dd, J = 7.7, 1.2 Hz, 1 H), 7.60 (s, 1 H), 7.32 (ddd, J = 8.6, 7.9, 1.4 Hz, 1 H), 6.97 (dd, J = 7.7, 0.7 Hz, 1 H), 6.87 (dd, J = 8.4, 0.7 Hz, 1 H), 3.84 (s, 3 H)

**13C NMR (100 MHz, CDCl3):** δ 156.7, 133.0, 130.1, 129.3, 124.5, 120.3, 110.6, 89.8, 55.6

Spectral data matched reported values.37

1-ethynyl-4-methoxybenzene (3-1o)

![1-ethynyl-4-methoxybenzene](image)

**Procedure:** To a solution of 1-(2,2-dibromovinyl)-2-methoxybenzene (3-SI-3) (1.45 g, 5.0 mmol, 1.0 equiv) in 15 mL of dry THF was added n-BuLi (8.0 mL, 20.0 mmol, 2.5 M in hexanes, 4.0 equiv) dropwise at −78 °C. The reaction was stirred at −78 °C until all the starting material was consumed (ca 2 h, thin layer chromatograph). The reaction was quenched at −78 °C with 5 mL of sat. NH4Cl and brought to rt. Water (50 mL) and Et2O (25 mL) were added and transferred to a separatory funnel. The two layers were separated and the aqueous layer was further extracted with Et2O (2 x 25 mL). The combined organic extracts were washed with brine (1 x 50 mL), dried over MgSO4 filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes) to afford (602 mg, 91% yield) 1-ethynyl-2-methoxybenzene (3-10) as a clear colorless oil.

**Physical State:** Clear colorless oil
\( ^1\text{H NMR (400 MHz, CDCl}_3\): \delta 7.46 (d, \ J = 7.4 \text{ Hz}, 1 \text{ H}), \ 7.32 (t, \ J = 8.0, 1 \text{ H}), \ 6.94–6.87 (m, 2 \text{ H}), \ 3.90 (s, 3 \text{ H}), \ 3.30 (s, 1 \text{ H}) \)

\( ^{13}\text{C NMR (100 MHz, CDCl}_3\): \delta 160.7, 134.3, 130.4, 120.6, 111.3, 110.7, 81.2, 80.2, 55.9 \)

Spectral data matched reported values.\(^{43}\)

Preparation of \(1\text{-ethynyl-3-methoxybenzene (3-1p)}\)

\( 1\text{-}(2,2\text{-dibromovinyl)-3-methoxybenzene (3-SI-4)} \)

**Procedure:** To a solution PPh\(_3\) (7.86 g, 30.0 mmol, 3.0 equiv) in 20 mL of DCM at 0 °C was added CBr\(_4\) (4.97 g, 15.0 mmol, 1.5 equiv) and stirred under N\(_2\) for 15 min. To the red-orange solution was added neat 3-methoxybenzaldehyde (1.36 g, 10.0 mmol, 1.0 equiv) at 0 °C and stirred until all the aldehyde was consumed (ca 16 h, thin layer chromatography). A solution of hexanes/EtOAc (9:1, 200 mL) was added and stirred for 1 h. The suspension was filtered through a pad of silica gel and washed several times with hexanes/EtOAc (9:1). The solvent was removed under reduced pressure to afford (2.80 g, 96% yield) \(1\text{-}(2,2\text{-dibromovinyl)-3-methoxybenzene (3-SI-4)}\) as a clear pale yellow oil.

**Physical State:** Clear pale yellow oil

\( ^1\text{H NMR (400 MHz, CDCl}_3\): \delta 7.46 (s, 1 \text{ H}), \ 7.28 (t, \ J = 7.9 \text{ Hz}, 1 \text{ H}), \ 7.12 (dd, \ J = 2.2, 2.2 \text{ Hz}, 1 \text{ H}), \ 7.10–7.07 (m, 1 \text{ H}), \ 6.89 (ddd, \ J = 8.1, 2.5, 0.7 \text{ Hz}, 1 \text{ H}), \ 3.82 (s, 3 \text{ H}) \)

\( ^{13}\text{C NMR (100 MHz, CDCl}_3\): \delta 159.6, 136.9, 136.6, 129.5, 121.1, 114.4, 113.8, 89.9, 55.4 \)

Spectral data matched reported values.\(^{37}\)

\( 1\text{-ethynyl-3-methoxybenzene (3-1p)} \)
**Procedure:** To a solution of 1-(2,2-dibromovinyl)-3-methoxybenzene (2.91 g, 10.0 mmol, 1.0 equiv) in 20 mL of dry MeCN was added DBU (6.0 mL, 40.0 mmol, 4.0 equiv) and stirred at rt under N₂. The reaction was stirred for 24 h then quenched with 6 M HCl until the solution became slightly acidic (~10 mL, pH paper). The reaction was extracted with Et₂O (4 x 50 mL), dried over K₂CO₃, filtered and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, hexanes/EtOAc (9:1)) to afford (704 mg, 53% yield) 1-ethynyl-3-methoxybenzene (3-1p) as a clear pale yellow oil.

**Physical State:** Clear pale yellow oil

**¹H NMR (400 MHz, CDCl₃):** δ 7.23 (dd, J = 8.0, 7.3 Hz, 1 H), 7.09 (ddd, J = 7.5, 1.2, 1.2 Hz, 1 H), 7.02 (dd, J = 2.5, 1.37 Hz, 1 H), 6.09 (ddd, J = 8.1, 2.6, 1.2 Hz, 1 H), 3.08 (s, 3 H), 3.05 (s, 1 H)

**¹³C NMR (100 MHz, CDCl₃):** δ 159.4, 129.5, 124.8, 123.2, 117.1, 115.6, 83.7, 77.1, 55.4

Spectral data matched reported values.⁴⁴

Preparation of 4-ethynyl-1,2-dimethoxybenzene (3-1q)

4-(2,2-dibromovinyl)-1,2-dimethoxybenzene (3-SI-5)

**Procedure:** To a solution PPh₃ (23.6 g, 90.0 mmol, 3.0 equiv) in 60 mL of DCM at 0 °C was added CBr₄ (14.9 g, 15.0 mmol, 1.5 equiv) and stirred under N₂ for 15 min. To the red-orange
solution was added 3,4-dimethoxybenzaldehyde (5.0 g, 30.0 mmol, 1.0 equiv) portion wise at 0 °C and stirred until all the aldehyde was consumed (ca 1.5 h, thin-layer chromatography). Then, 300 mL of hexanes/EtOAc (8:2) was added and stirred for 1 h. The suspension was filtered through a pad of silica gel and washed several times with hexanes/EtOAc (8:2). The solvent was removed under reduced pressure to afford (9.17 g, 95% yield) 4-(2,2-dibromovinyl)-1,2-dimethoxybenzene (3-SI-5) as a pale yellow oil.

**Physical State:** Pale yellow oil

**1H NMR (400 MHz, CDCl₃):** δ 7.41 (s, 1 H), 7.18 (d, J = 2.0 Hz, 1 H), 7.09 (dd, J = 8.4, 2.0 Hz, 1 H), 6.85 (d, J = 8.4 Hz, 1 H), 3.89 (s, 3 H), 3.88 (s, 3 H)

Spectral data matched reported values.⁴⁵

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**Procedure:** To a solution of 4-(2,2-dibromovinyl)-1,2-dimethoxybenzene (9.65 g, 30.0 mmol, 1.0 equiv) in 150 mL of dry THF was added n-BuLi (39.4 mL, 63.0 mmol, 2.5 M in hexanes, 2.1.0 equiv) dropwise at −78 °C. The solution was stirred at −78 °C for 1 h and then for 2 h at rt. The reaction was quenched at −78 °C with sat. NH₄Cl (50 mL), brought to rt and transferred to a separatory funnel. Water (100 mL) was added and the aqueous layer was extracted with Et₂O (4 x 75 mL). The organic extracts were washed brine (1 x 100 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude solid was purified by flash column chromatography (silica gel, hexanes/EtOAc (9:1)) to afford (3.78 g, 78% yield) 4-ethynyl-1,2-dimethoxybenzene (3-1q) as a white solid.

**Physical State:** White solid
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.10 (dd, $J$ = 8.2, 1.8 Hz, 1 H), 6.98 (d, $J$ = 1.8 Hz, 1 H), 6.80 (d, $J$ = 8.2 Hz, 1 H), 3.88 (s, 3 H), 3.87 (s, 3 H), 3.00 (s, 1 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 149.8, 148.6, 125.4, 114.7, 114.2, 110.9, 83.7, 75.7, 55.84, 55.83

Spectral data matched reported values.$^{45}$

Preparation of 2-ethynlnaphthalene (1r)

*Trimethyl(naphthalen-2-ylethynyl)silane*

![Chemical structure](image)

**Procedure:** To a Schlenk flask was added 2-bromonaphthalene (6.21 g, 30 mmol, 1.0 equiv), 60 mL of freshly distilled Et$_3$N and the solution was sparged with N$_2$ for 5 min. Next, ethynyltrimethylsilane (6.23 mL, 45 mmol, 1.5 equiv), PdCl$_2$(PPh$_3$)$_2$ (421.1 mg, 0.6 mmol, 0.02 equiv) and CuI (228.5 mg, 1.2 mmol, 0.04 equiv) were added and the solution was sparged again with N$_2$ for 2 min. The flask was placed in a pre-heated 80 °C oil bath and stirred until all the starting material was consumed (ca 2 h, thin layer chromatography, hexanes). The flask was cooled to rt, filtered through a pad of Celite® and washed with hexanes/EtOAc (9:1). The filtrate was concentrated under reduced pressure to afford an orange solid, which was taken directly to the next step without further purification.

2-ethynlnaphthalene (3-1r)

![Chemical structure](image)

**Procedure:** To a solution of trimethyl(naphthalen-2-ylethynyl)silane (6.73 g, 30 mmol, 1.0 equiv) in 60 mL of dry MeOH was added K$_2$CO$_3$ (1.24 g, 9.0 mmol, 0.3 equiv) in one portion at rt. After consumption of all the starting material (ca 2 h, thin layer chromatography, hexanes) the mixture
was passed through a pad of Celite® and washed with Et₂O. The filtrate was concentrated under reduced pressure and the resulting crude residue was passed through a pad of silica gel and washed several times with hexanes/EtOAc (9:1). The solvent was removed under reduced pressure to afford 4.1021 g (90%) of 2-ethynlnaphthalene (3-1r)

**Physical State:** Brown solid

**1H NMR (400 MHz, CDCl₃):** δ 8.04 (s, 1 H), 7.84–7.78 (m, 3 H), 7.53 (dd, J = 8.6, 1.6 Hz, 1 H), 7.52–7.48 (m, 2 H), 3.16 (s, 1 H)

**13C NMR (100 MHz, CDCl₃):** δ 133.1, 132.9, 132.4, 128.6, 128.1, 127.91, 127.90, 127.0, 126.7, 119.5, 84.1, 77.6

Spectral data matched reported values.

**Preparation of 1-ethynlnaphthalene (3-1s)**

*trimethyl(naphthalen-1-ylethynyl)silane*

**Procedure:** To a Schlenk flask was added 1-iodonaphthalene (8.48 g, 33.4 mmol, 1.0 equiv), 150 mL of freshly distilled Et₃N and the solution was sparged with N₂ for 5 min. Next, ethynyltrimethylsilane (5.55 mL, 40.1 mmol, 1.2 equiv) was added followed by addition PdCl₂(PPh₃)₂ (468 mg, 0.66 mmol, 0.02 equiv) and Cul (254 mg, 1.33 mmol, 0.04 equiv) and the mixture was sparged again with N₂ for 2 min. The flask was placed in a 70 °C oil bath and stirred until all the starting material was consumed (ca 4 h, thin layer chromatography, hexanes/EtOAc (95:5)). The flask was cooled to rt, filtered through a pad of silica gel, washed with Et₂O and
concentrated under reduced pressure. The resulting brown solid was used in the next step without further purification.

1-ethynylnaphthalene (3-1s)

Procedure: To a solution of trimethyl(naphthalen-1-ylethynyl)silane (7.50 g, 33.46 mmol, 1.0 equiv) in 120 mL of dry MeOH was added K₂CO₃ (1.38 g, 10.0 mmol, 0.3 equiv) in one portion and stirred at rt. After consumption of all the starting material (ca 2 h, thin layer chromatography, hexanes) the mixture was passed through a pad of Celite® and washed with Et₂O. The filtrate was concentrated under reduced pressure then passed through a pad of silica gel and washed several times with hexanes. The solvent was removed under reduced pressure to afford 4.84 g (95%) of 1-ethynylnaphthalene.

Physical State: Clear pale green oil

¹H NMR (400 MHz, CDCl₃): δ 8.37 (d, J = 8.7 Hz, 1 H), 7.86 (dd, J = 8.2, 1.0 Hz, 1 H), 7.86 (dd, J = 7.1, 1.0 Hz, 1 H), 7.59 (ddd, J = 8.2, 6.9, 1.3 Hz, 1 H), 7.53 (ddd, J = 8.1, 6.8, 1.3 Hz, 1 H), 7.43 (dd, J = 8.2, 7.1 Hz, 1 H), 3.48 (s, 1 H)

¹³C NMR (100 MHz, CDCl₃): δ 133.6, 133.2, 131.3, 129.4, 128.4, 127.1, 126.6, 126.2, 125.2, 119.9, 82.1, 81.9

Spectral data matched reported values.⁴⁷

Preparation of 3-ethynyl-1-tosyl-1H-indole (3-1t)

3-iodo-1H-indole (3-SI-6)
Procedure: To a solution of indole (5.49 g, 46.9 mmol, 1.0 equiv) in 75 mL of anhydrous DMF was added KOH (6.57 g, 117.2 mmol, 2.5 equiv) and stirred for 10 min at rt under N₂. Next, a solution of I₂ (12.5 g, 49.2 mmol, 1.05 equiv) in 50 mL of anhydrous DMF was added dropwise and stirred for 16 h at rt. After the reaction was complete, the solution was poured into 250 mL of ice water and the precipitate was collected by filtration, washed with water and air-dried to afford roughly a quantitative yield of 3-iodo-1H-indole (3-SI-6). The crude ¹H NMR shows some EtOAc and DMF, but no starting material. Therefore, the residual solvent was not removed and carried forward in subsequent steps.

Physical State: Pale purple solid

¹H NMR (400 MHz, CDCl₃): δ 8.69 (br. s, 1 H), 7.48–7.43 (m, 1 H), 7.38–7.34 (m, 1 H), 7.28 (d, J = 2.5 Hz, 1 H), 7.24–7.17 (m, 2 H)

Spectral data matched reported values.⁴⁸

3-iodo-1-tosyl-1H-indole (3-SI-7)

Procedure: To a solution of 3-iodo-1H-indole (3-SI-6) (11.3 g, 46.9 mmol, 1.0 equiv) in 200 mL of freshly distilled benzene was added p-toluenesulfonyl chloride (8.9 g, 46.9 mmol, 1.0 equiv) in one portion at rt. Next, 50 mL of a 60% aqueous NaOH solution was added over 10 min and then stirred at rt for 16 h under N₂. The reaction was quenched with water (100 mL) and the organic layer was separated. The aqueous layer was further extracted with benzene (3 x 30 mL) and the
combined extracts were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure. The crude solid was purified by recrystallization from MeOH to afford 13.2562 g (71%) of 3-ido-1-tosyl-1H-indole (SI-7).

**Physical State:** White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.98–7.93 (m, 1 H), 7.77 (d, $J=8.3$ Hz, 2 H), 7.69 (s, 1 H), 7.39–7.34 (m, 2 H), 7.33–7.28 (m, 1 H), 7.24 (d, $J=8.2$ Hz, 2 H), 2.34 (s, 3 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 145.5, 135.0, 134.4, 132.5, 130.1, 129.9, 127.0, 125.8, 124.0, 122.1, 113.5, 67.0, 21.7

Spectral data matched reported values.$^{49}$

**1-tosyl-3-((trimethylsilyl)ethynyl)-1H-indole (3-SI-8)**

![Chemical structure](image)

**Procedure:** Compound 3-SI-8 was prepared following the procedure described by Yang and co-workers.$^{50}$ To a 250 mL pressure tube containing a solution of 3-ido-1-tosyl-1H-indole (3-SI-7) (13.25 g, 33.3 mmol, 1.0 equiv), ethynyltrimethylsilane (5.08 mL, 36.7 mmol, 1.2 equiv) in 100 mL of dry Et$_3$N was added Pd(OAc)$_2$ (38 mg, 0.16 mmol, 0.005 equiv), CuI (64 mg, 0.33 mmol, 0.01 equiv) and PPh$_3$ (131 mg, 0.50 mmol, 0.015 equiv). The mixture was sparged with N$_2$ for 5 min, then sealed with a Teflon cap and placed in an 80 °C oil bath. The reaction was stirred for 20 h, then cooled to 0 °C prior to opening the pressure tube. The contents were transferred to a round bottom flask and the solvent was removed under reduced pressure. The resulting black solid was passed through a pad of silica gel and washed with hexanes/EtOAc (7:3). The filtrate was
concentrated to afford a free-flowing orange solid, which was used in the next step without further purification.

3-ethynyl-1-tosyl-1H-indole (3-1t)

**Procedure:** To a solution of 1-tosyl-3-((trimethylsilyl)ethynyl)-1H-indole (3-SI-8) (12.26 g, 33.36 mmol, 1.0 equiv) in 200 mL of dry MeOH was added K₂CO₃ (23.06 g, 166.8 mmol, 5 equiv) in one portion at rt. The reaction was stirred until consumption of the starting material (ca 45 min, thin layer chromatography, hexanes/EtOAc (9:1)). The solvent was removed under reduced pressure and the crude residue was dissolved in water/DCM and transferred to a separatory funnel. The aqueous layer was extracted with DCM (4 x 70 mL) and the combined extracts were washed with brine (1 x 50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The crude brown solid was purified by recrystallization from MeOH to give 8.7252 g (89%) of 3-ethynyl-1-tosyl-1H-indole (3-1t).

**Physical State:** Light brown solid

**¹H NMR (400 MHz, CDCl₃):** δ 7.96 (ddd, J = 8.3, 0.9, 0.9 Hz, 1 H), 7.82–7.72 (m, 3 H), 7.63 (ddd, J = 7.8, 1.2, 0.9 Hz, 1 H), 7.35 (ddd, J = 8.4, 7.3, 1.2 Hz, 1 H), 7.32–7.27 (m, 1 H), 7.24 (d, J = 8.2 Hz, 2 H), 3.25 (s, 1 H), 2.35 (s, 3 H)

Spectral data matched reported values.⁵⁰

*Preparation of tert-butyl 3-ethynyl-1H-indole-1-carboxylate (3-1u)*

**tert-butyl 3-iodo-1H-indole-1-carboxylate (3-SI-9)**
**Procedure:** To a solution of 3-ido-1H-indole (3-SI-6) (8.28 g, 34.1 mmol, 1.0 equiv), freshly distilled Et$_3$N (14.3 mL, 102.6 mmol, 3 equiv), DMAP (418 mg, 3.42 mmol, 0.1.0 equiv) in 110 mL of dry DCM was added Boc$_2$O (8.21 g, 37.6 mmol, 1.10 equiv) in one portion at rt. The reaction was stirred open to air until the CO$_2$ evolution ceased (ca 5 min) then placed under N$_2$. The solution was stirred for an additional 10 min (monitored by thin layer chromatography, hexanes/EtOAc (9:1)). The reaction was quenched with 5% aqueous Na$_2$S$_2$O$_3$ (35 mL) and extracted with DCM (3 x 50 mL). The combined organic extracts were dried over MgSO$_4$, filtered and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, hexanes/EtOAc (9:1)) to afford 7.4190 g (63%) of tert-butyl 3-ido-1H-indole-1-carboxylate (3-SI-9)

**Physical State:** Clear pale purple oil

$^1$H NMR (400 MHz, CDCl$_3$): δ 8.13 (d, $J = 8.1$ Hz, 1 H), 7.73 (s, 1 H), 7.44–7.28 (m, 3 H), 1.67 (s, 9 H)

Spectral data matched reported values.$^{51}$

*tert-butyl 3-((trimethylsilyl)ethynyl)-1H-indole-1-carboxylate (3-SI-10)*

**Procedure:** To a Schlenk flask was added *tert-butyl 3-ido-1H-indole-1-carboxylate (3-SI-9)* (7.00 g, 20.3 mmol, 1.0 equiv), ethynyltrimethylsilane (3.39 mL, 29.4 mmol, 1.2 equiv) and 40
mL of freshly distilled Et₃N. The solution was sparged with N₂ for 5 min, followed by addition of PdCl₂(PPh₃)₂ (286 mg, 0.40 mmol, 0.02 equiv) and CuI (155 mg, 0.81 mmol, 0.04 equiv). The mixture was sparged with N₂ for 2 min then placed in a 60 °C oil bath and stirred under N₂ for 1 h. The flask was cooled to rt, filtered through Celite® and washed with Et₂O. The filtrate was concentrated under reduced pressure and used in the next step without further purification.

**tert-butyl 3-ethynyl-1H-indole-1-carboxylate (3-1u)**

![Chemical structure](image)

**Procedure:** To a solution of crude *tert-butyl 3-((trimethylsilyl)ethynyl)-1H-indole-1-carboxylate* (3-SI-10) (6.39 g, 20.3 mmol, 1.0 equiv) in 60 mL of dry THF was added TBAF (24.4 mL, 24.4 mmol, 1 M in THF, 1.2 equiv) dropwise at 0 °C. The reaction was stirred at 0 °C for 40 min, then quenched with sat. NH₄Cl (200 mL). The contents were transferred to a separatory funnel and the aqueous layer was extracted with EtOAc (3 x 75 mL). The combined organic extracts were dried over Na₂SO₄, filtered and concentrated under reduced pressure. The crude oil was purified by flash column chromatography (silica gel, hexanes/EtOAc (95:5)) to afford 4.0201 g (83%) of *tert-butyl 3-ethynyl-1H-indole-1-carboxylate (3-1u)*

**Physical State:** Pale pink oil

**¹H NMR (400 MHz, CDCl₃):** δ 8.14 (d, J = 8.2 Hz, 1 H), 7.81 (s, 1 H), 7.68 (ddd, J = 7.8, 1.3, 0.7 Hz, 1 H), 7.36 (ddd, J = 8.3, 7.3, 1.3, 1 H), 7.30 (ddd, J = 8.3, 7.3, 1.2 Hz, 1 H), 3.24 (s, 1 H), 1.67 (s, 9 H)

**¹³C NMR (100 MHz, CDCl₃):** δ 149.1, 134.7, 130.6, 130.0, 125.4, 123.4, 120.1, 115.4, 102.4, 84.5, 80.8, 75.9, 28.3
Spectral data matched reported values.\textsuperscript{51}

**Preparation of \textit{(but-3-yn-1-yloxy)(tert-butyl)diphenylsilane} (3-1v)**

\textbf{Procedure:} To a solution containing but-3-yn-1-ol (3.00 g, 42.8 mmol, 1.0 equiv), imidazole (8.14 g, 47.1 mmol, 1.1.0 equiv) in 240 mL of dry DCM was added \textit{tert}-butylchlorodiphenylsilane (12.1 mL, 47.1 mmol, 1.10 equiv) dropwise at 0 °C. After complete addition, the 0 °C ice bath was removed and the reaction was stirred at rt under N\textsubscript{2} until consumption of all the starting material (\textit{ca} 4 h, thin layer chromatography, hexanes/EtOAc (6:4)). Water (150 mL) was added and the DCM layer was separated. The aqueous layer was further extracted with DCM (3 x 75 mL) and the combined organic extracts were dried over MgSO\textsubscript{4}, filtered and concentrated under reduced pressure. The crude oil was purified by distillation under reduced pressure (b.p. 155 °C @ 1.0 mmHg) to afford 11.9633 g (91\%) of \textit{(but-3-yn-1-yloxy)(tert-butyl)diphenylsilane} (3-1v)

**Physical State:** Clear colorless oil

**b.p.:** 155 °C @ 1.0 mmHg

\textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}):} \(\delta 7.70–7.67 (m, 4 H), 7.46–7.36 (m, 6 H), 3.79 (t, \(J = 7.1 \text{ Hz}, 2 H), 2.45 (td, \(J = 7.1, 2.7 \text{ Hz}, 2 H), 1.95 (t, \(J = 2.6 \text{ Hz}, 1 H), 1.06 (s, 9 H)\)

\textbf{\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}):} \(\delta 135.7, 133.7, 129.8, 127.8, 81.6, 69.5, 62.4, 26.9, 22.7, 19.3\)

Spectral data matched reported values.\textsuperscript{52}

**Preparation of \textit{((but-3-yn-1-yloxy)methyl)benzene} (3-1w)**

\textbf{Procedure:} To a suspension of NaH (3.28 g, 136 mmol, 60\% in mineral oil, 2.03 equiv) in 70 mL of dry THF was added but-3-yn-1-ol (4.68 g, 66.9 mmol, 1.0 equiv) dropwise at 0 °C and stirred
for 30 min under N₂. Next, a solution of benzyl bromide (8.77 mL, 73.77 mmol, 1.10), TBAI (100 mg, 0.27 mmol, 0.004 equiv) in 25 mL of dry THF was added over 20 min at 0 °C. The solution was slowly warmed to rt and stirred for 60 h. The reaction was quenched with sat. NH₄Cl (100 mL) and extracted with EtOAc (4 x 50 mL). The combined organic extracts were dried over MgSO₄, filtered and concentrated under reduced pressure. The crude oil was purified by distillation under reduced pressure (b.p. 65 °C @ 1.0 mmHg) to give 9.5881 g (89%) of ((but-3-yn-1-yl)oxy)methyl)benzene (3-1w).

**Physical State:** Clear colorless oil

**b.p.:** 65 °C @ 1.0 mmHg

**¹H NMR (400 MHz, CDCl₃):** δ 7.37–7.27 (m, 5 H), 4.56 (s, 2 H), 3.61 (t, J = 6.9 Hz, 2 H), 2.51 (td, J = 6.9, 2.6 Hz, 2 H), 1.99 (t, J = 2.6 Hz, 1 H)

Spectral data matched reported values.⁵³

**Preparation of 1-bromo-2-((but-3-yn-1-yl)oxy)methyl)benzene (3-1x)**

**Procedure:** To a round bottom flask was added NaH (3.50 g, 39.6 mmol, 60% in mineral oil, 2 equiv) and 130 mL of dry THF then placed under N₂. The flask was placed in a 0 °C ice bath followed by dropwise addition of but-3-yn-1-ol (3.73 mL, 49.29 mmol, 1.1.0 equiv) and stirred for 40 min. Next, TBAI (827 mg, 2.24 mmol, 0.05 equiv) was added in one portion followed by dropwise addition of 1-bromo-2-(bromomethyl)benzene (11.20 g, 44.8 mmol, 1.0 equiv) in 20 mL of dry THF at 0 °C. The reaction was stirred at 0 °C to rt over 16 h, then quenched with sat. NH₄Cl (100 mL) and extracted with EtOAc (4 x 70 mL). The combined organic extracts were washed with brine (1 x 50 mL), dried over MgSO₄, filtered and concentrated under reduced pressure. The
crude residue was purified by flash column chromatography (silica gel, hexanes/EtOAc (95:5)) to afford 10.3221 g (96%) of 1-bromo-2-((but-3-yn-1-yloxy)methyl)benzene (3-1x)

**Physical State:** Clear pale yellow oil

**1H NMR (400 MHz, CDCl₃):** δ 7.54–7.49 (m, 2 H), 7.31 (ddd, J = 7.6, 7.6, 1.2, 1 H), 7.14 (ddd, J = 7.6, 7.6, 1.6 Hz, 1 H), 4.62 (s, 2 H), 3.69 (t, J = 6.9 Hz, 2 H), 2.55 (td, J = 6.9, 2.6 Hz, 2 H), 2.02 (t, J = 2.6 Hz, 1 H)

**13C NMR (100 MHz, CDCl₃):** δ 137.5, 132.6, 129.1, 129.0, 127.5, 122.7, 81.3, 72.2, 69.6, 68.9, 20.0

**IR (ATR):** 3302, 3072, 2921, 2121, 1568, 1439, 1103 cm⁻¹

**HRMS (DART-TOF):** Calculated for C₁₁H₁₁BrO [M+H]^+: 239.00660, found 239.00616

**Preparation of (±)-1-ethynyl-2-methoxycyclohexane (3-1y)

(±)-2-ethynylcyclohexan-1-ol (3-SI-11)

**Procedure:** To a solution of ethynyltrimethylsilane (10.39 mL, 75 mmol, 1.5 equiv) in 60 mL of dry THF at −78 °C under N₂ was added n-BuLi (30 mL, 75 mmol, 2.5 M in hexanes 1.5 equiv) dropwise over 15 min. The reaction was stirred for 30 min at −78 °C, followed by addition of BF₃·OEt₂ (9.74 mL, 79 mmol, 1.6 equiv) and stirred for an additional 15 min. Cyclohexene oxide (5.05 mL, 50 mmol, 1.0 equiv) was added dropwise at −78 °C and stirred for 1.5 h, then rt for 1 h. The reaction was quenched with the addition of sat. NH₄Cl (100 mL) at 0 °C and the aqueous layer was extracted with Et₂O (4 x 50 mL). The organic extracts were washed with sat. NaHCO₃ then dried over Na₂SO₄ and concentrated under reduced pressure to afford a yellow oil. The crude
residue was dissolved in 100 mL of dry MeOH and K$_2$CO$_3$ (8.0 g, 57.8 mmol) was added in one portion at rt and stirred for 24 h under N$_2$. The reaction was worked up by addition of 200 mL of H$_2$O and extracted with DCM (4 x 75 mL), washed with brine (1 x 75 mL), dried over Na$_2$SO$_4$ and concentrated under reduced pressure. The product was purified by distillation at reduced pressure (b.p. 59 °C @ 11 mmHg) to give 2.1506 g (35%) of (±)-2-ethynylcyclohexan-1-ol (3-SI-11)

**Physical State:** Clear colorless oil

**b.p.:** 59 °C @ 11 mmHg

$^1$H NMR (400 MHz, CDCl$_3$): δ 3.46 (dddd, J = 13.1, 9.7, 3.7, 2.7 Hz, 1 H), 2.29–2.17 (m, 2 H), 2.15 (d, J = 2.4 Hz, 1 H), 2.06–1.94 (m, 2 H), 1.81–1.72 (m, 1 H), 1.66 (td, J = 13.2, 3.7 Hz, 1 H), 1.39 (ddd, J = 25.2, 12.2, 3.7 Hz, 1 H), 1.33–1.11 (m, 3 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 85.9, 73.6, 70.4, 38.8, 33.3, 31.0, 24.9, 24.3

Spectral data matched reported values.$^{54}$

(±)-1-ethynyl-2-methoxycyclohexane (3-1y)

![OMe](OMe)

**Procedure:** To a suspension of NaH (484 mg, 12.1 mmol, 60% dispersed in mineral oil, 1.5 equiv) in 25 mL of dry THF at 0 °C was added (±)-2-ethynylcyclohexan-1-ol (3-SI-11) (8.1 mmol, 1.0 equiv) in 10 mL of dry THF over 10 min. The solution was stirred for 30 min at 0 °C before dropwise addition of MeI (1.37 g, 9.7 mmol, 1.2 equiv). The 0 °C ice bath was removed and stirred for 1 h at rt. The reaction was quenched with water and extracted with Et$_2$O (4 x 25 mL). The combined organic extracts were washed with brine (1 x 50 mL), dried over MgSO$_4$, and concentrated under reduced pressure. The product was purified by flash column chromatography
(silica gel, hexanes/EtOAc (8:2)) to give 874 mg (76%) of (±)-1-ethynyl-2-methoxycyclohexane (3-1y)

**Physical State:** Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 3.42 (s, 3 H), 3.16 (app. td, $J = 8.0, 4.0$ Hz, 1 H), 2.42 (dddd, $J = 11.7, 8.0, 4.0, 2.5$ Hz, 1 H), 2.09 (d, $J = 2.4$ Hz, 1 H), 2.07–2.00 (m, 1 H), 1.99–1.91 (m, 1 H), 1.72–1.61 (m, 2 H), 1.49–1.40 (m, 1 H), 1.32–1.21 (m, 3 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 86.7, 81.2, 69.2, 56.9, 34.6, 30.3, 29.4, 24.0, 23.1

Spectral data matched reported values.$^{55}$

**Preparation of 4-ethynyl-1,2-dihydronaphthalene (3-1aa)**

$I$-((trimethylsilyl)ethynyl)-1,2,3,4-tetrahydronaphthalen-1-ol (3-SI-12)

![Chemical Structure](image)

**Procedure:** To a solution of ethynyltrimethylsilane (8.31 mL, 60 mmol, 1.2 equiv) in 60 mL of dry THF at $-78^\circ$C was added $n$-BuLi (24 mL, 60 mmol, 2.5 M in hexanes, 1.2 equiv) dropwise and stirred for 1 h. $\alpha$-tetralone (6.65 mL, 50 mmol, 1.0 equiv) was added neat at $-78^\circ$C and the solution was slowly warmed to rt over 12 h. The flask was placed in a 0 $^\circ$C ice bath and quenched with sat. NH$_4$Cl (100 mL). The contents were transferred to a separatory funnel and the aqueous layer was extracted with Et$_2$O (4 x 75 mL). The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated under reduced pressure to give a clear orange oil. $^1$H NMR analysis showed a small amount of unreacted $\alpha$-tetralone, which has a similar R$_f$ to the product. For this reason, the crude mixture was taken forward to the next step without any further purification.
Procedure: The crude mixture above (3-SI-12) was dissolved in 60.0 mL dry DCM and freshly distilled Et₃N (56.0 mL, 400 mmol). The flask was cooled to 0 °C and POCl₃ (18.6 mL, 200 mmol) was added dropwise over 20 min. Once completely added, the 0 °C ice bath was removed and stirred at rt for 12 h. The reaction was poured into a large beaker of ice and was allowed to stand for 1 h to ensure all the POCl₃ was quenched. The aqueous layer was extracted with DCM (4 x 75 mL) and the combined organic extracts were filtered through a pad of silica gel and washed with hexanes. The filtrate was concentrated under reduced pressure to give a brown oil. The crude oil was purified by distillation at reduced pressure (b.p. 114–118 °C @ 1 mmHg) affording compound 3-SI-13 (6.28 g, 56% yield) as a clear colorless oil.

Physical State: Clear colorless oil

b.p.: 114–118 °C @ 1.0 mmHg

¹H NMR (400 MHz, CDCl₃): δ 7.56 (d, J = 7.5 Hz, 1 H), 7.23 (t, J = 7.5 Hz, 1 H), 7.17 (td, J = 7.5, 1.3 Hz, 1 H), 7.10 (d, J = 7.4 Hz, 1 H), 6.52 (t, J = 4.8 Hz, 1 H), 2.78 (t, J = 8.2 Hz, 2 H), 2.38 (td, J = 8.3, 4.9 Hz, 2 H), 0.26 (s, 9 H)

¹³C NMR (100 MHz, CDCl₃): δ 136.5, 135.1, 132.5, 127.8, 127.4, 126.8, 125.2, 122.0, 103.2, 95.3, 27.2, 23.7, 0.25
4-ethynyl-1,2-dihyronaphthalene (3-1aa)

**Procedure:** To a solution compound 3-SI-13 (6.28 g, 27.7 mmol, 1.0 equiv) in MeOH (140 mL) was added K$_2$CO$_3$ (10.36 g, 74.9 mmol, 2.7 equiv) at rt in one portion. The reaction was placed under N$_2$ and was stirred until all the starting material was consumed (*ca* 2 h, thin-layer chromatography). Water was added to the reaction and the contents were transferred to a separatory funnel. The aqueous layer was extracted with DCM (4 x 40 mL) and the combined organic extracts were dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude material was purified by distillation under reduced pressure (b.p. 91–93 °C @ 1 mmHg) to give 3-1aa (3.73 g, 87% yield) as a pale yellow oil.

**Physical State:** Pale yellow oil

**b.p.:** 91–93 °C @ 1.0 mmHg

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.59 (dd, $J = 7.6$, 1.0 Hz, 1 H), 7.23 (dd, $J = 7.4$, 1.4 Hz, 1 H), 7.18 (td, $J = 7.4$, 1.4 Hz, 1 H), 7.11 (app. d, $J = 7.2$ Hz, 1 H), 6.55 (t, $J = 4.8$ Hz, 1 H), 3.08 (s, 1 H), 2.81 (t, $J = 8.1$ Hz, 2 H), 2.39 (td, $J = 8.1$, 4.9 Hz, 2 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 137.1, 135.0, 132.4, 127.9, 127.5, 126.8, 125.1, 121.1, 81.7, 78.2, 27.2, 23.7

Spectral data matched reported values.$^{56}$

Preparation of (1R,5S)-2-ethynyl-6,6-dimethylbicyclo[3.1.1]hept-2-ene (3-1ab)

(1R,5S)-2-(2,2-dibromovinyl)-6,6-dimethylbicyclo[3.1.1]hept-2-ene (3-SI-14)
**Procedure:** To a solution of PPh₃ (14.86 g, 56.7 mmol, 3.0 equiv) in 40 mL of dry DCM was added CBr₄ (9.39 g, 28.3 mmol, 1.5 equiv) portionwise at 0 °C and the contents were stirred for 15 min. Next, (1R)-(--)-myrtenal (2.83 g, 18.9 mmol, 1.0 equiv) in 10 mL of dry DCM was added by syringe dropwise at 0 °C. After the addition was complete, the 0 °C ice bath was removed and the reaction was stirred at rt until full consumption of the starting material (ca 2 h, thin-layer chromatography). A solution of hexanes/EtOAc (8:2, 150 mL) was added and stirred for 1 h. The solid precipitates were removed by filtration and washed several times with hexanes/EtOAc (95:5). The filtrate was collected and concentrated under reduced pressure to give compound 3-SI-14 (4.77 g, 83% yield) as a clear orange oil which was taken forward to the next step without any further purification.

(1R,5S)-2-ethyl-6,6-dimethylbicyclo[3.1.1]hept-2-ene (3-1ab)

**Procedure:** To a solution of 3-SI-14 (4.50 g, 14.7 mmol, 1.0 equiv) in 50 mL of dry THF was added n-BuLi (23.5 mL, 58.8 mmol, 2.5 M in hexanes, 4.0 equiv) dropwise at −78 °C. The reaction was stirred at −78 °C for 30 min then at rt for 2 h. The reaction was quenched with sat. NH₄Cl (50 mL) at 0 °C and the contents were transferred to a separatory funnel. The aqueous layer was extracted with Et₂O (4 x 50 mL) and the combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by column
chromatography (silica gel, hexanes/EtOAc, 95:5) to afford compound 3-1ab (491 mg, 23% yield) as a clear colorless oil.

**Physical State:** Clear colorless oil

**1H NMR (400 MHz, C₆D₆):** δ 6.02–5.93 (m, 1 H), 2.76 (s, 1 H), 2.35 (td, J = 5.7, 1.2 Hz, 1 H), 2.20 (td, J = 9.0, 5.7 Hz, 1 H), 2.06–1.96 (m, 2 H), 1.83–1.77 (m, 1 H), 1.16 (d, J = 9.0 Hz, 1 H), 1.09 (s, 3 H), 0.83 (s, 3 H)

**13C NMR (100 MHz, C₆D₆):** δ 132.3, 129.9, 84.6, 77.7, 47.3, 40.5, 38.0, 32.1, 31.6, 26.0, 21.0

**IR (ATR):** 3311, 2950, 2094, 1467, 1367 cm⁻¹

**HRMS (DART-TOF):** Calculated for C₁₁H₁₅ [M+H]⁺: 147.11682, found 147.11626

Preparation of 2-butoxy-6-ethynlnaphthalene (3-1ad)

2-bromo-6-butoxynaphthalene (3-SI-15)

**Procedure:** Compound 3-SI-15 was prepared following the procedure described by Persoons and Bjørnholm.⁵⁷ To a Schlenk flask equipped with a reflux condenser was added 6-bromonaphthalen-2-ol (11.15 g, 50.0 mmol, 1.0 equiv), 150 mL of dry THF, and 5 mL of a 10.2 M aqueous NaOH solution. The mixture was stirred for 10 min at 60 °C followed by addition of 1-bromobutane (5.93 mL, 55.0 mmol, 1.1.0 equiv). The temperature was increased to 80 °C and stirred for 3 h prior to the addition of TBAI (923 mg, 2.5 mmol, 0.05 equiv). The reaction was stirred for 24 h at 80 °C then cooled to rt and the solvent was removed under reduced pressure. The crude residue was purified by recrystallization from absolute EtOH (~60 mL) to give 3-SI-15 (11.80 g, 85% yield) as an off white solid.

**Physical State:** Off white solid
**1H NMR (400 MHz, CDCl3):** δ 7.90 (d, J = 1.8 Hz, 1 H), 7.63 (d, J = 9.1 Hz, 1 H), 7.57 (d, J = 8.7 Hz, 1 H), 7.48 (dd, J = 8.7, 2.0 Hz, 1 H), 7.16 (dd, J = 9.0, 2.5 Hz, 1 H), 7.08 (d, J = 2.4 Hz, 1 H), 4.06 (t, J = 6.5 Hz, 2 H), 1.83 (app. p, J = 6.6 Hz, 2 H), 1.54 (app. sextet, J = 7.5 Hz, 2 H), 1.01 (t, J = 7.4 Hz, 3 H)

**13C NMR (100 MHz, CDCl3):** δ 157.5, 133.2, 130.0, 129.7, 129.6, 128.5, 128.4, 120.2, 117.0, 106.6, 67.9, 31.4, 19.4, 14.0

Spectral data matched reported values.57

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((6-butoxynaphthalen-2-yl)ethynyl)trimethylsilane (3-SI-16)
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**Procedure:** To a Schlenk flask was added 3-SI-15 (11.50 g, 41.2 mmol, 1.0 equiv) and 100 mL of freshly distilled Et3N and the solution was sparged with N2 for 5 min. Next, ethynyltrimethylsilane (6.84 mL, 49.4 mmol, 1.2 equiv), PdCl2(PPh3)2 (578 mg, 0.82 mmol, 0.02 equiv) and CuI (314 mg, 1.64 mmol, 0.04 equiv) were added and the resulting solution was stirred at 70 °C for 3 h. The reaction was cooled to rt, filtered through a pad of silica gel and washed with hexanes/EtOAc (9:1). The filtrate was concentrated under reduced pressure to afford a brown solid, which was taken to the next step without any further purification. (The 1H NMR of the crude material was extremely clean with only a few minor impurities. A small sample was taken and recrystallized from MeOH to give a brown crystalline solid, which was used for characterization. The rest of the mixture was taken forward without any further purification.)

Partial characterization data for 3-SI-16

**Physical State:** Clear pale yellow oil
\( ^1 \)H NMR (400 MHz, CDCl\(_3\)): \( \delta 7.91 \) (d, \( J = 0.8 \) Hz, 1 H), 7.66 (d, \( J = 9.0 \) Hz, 1 H), 7.62 (d, \( J = 8.5 \) Hz, 1 H), 7.45 (dd, \( J = 8.4, 1.6 \) Hz, 1 H), 7.14 (dd, \( J = 9.0, 2.5 \) Hz, 1 H), 7.07 (d, \( J = 2.5 \) Hz, 1 H), 4.07 (t, \( J = 6.6 \) Hz, 2 H), 1.83 (app. p, \( J = 6.5 \) Hz, 2 H), 1.53 (app. sextet, \( J = 7.3 \) Hz, 2 H), 1.00 (t, \( J = 7.5 \) Hz, 3 H)

\( ^{13} \)C NMR (100 MHz, CDCl\(_3\)): \( \delta 158.0, 134.4, 131.9, 129.4, 129.2, 128.4, 126.7, 119.8, 118.0, 106.6, 105.9, 93.7, 67.9, 31.4, 19.4, 14.0, 0.25 \)

IR (ATR): 2957, 2868, 2153, 1623, 1599, 1386, 1229 cm\(^{-1}\)

HRMS (DART-TOF): Calculated for C\(_{16}\)H\(_{16}\)O, \([\text{M+H-}\text{TMS}]^+\) 224.11956, found 224.11859

\( 2\)-butoxy-\( 6\)-ethynlnaphthalene (3-1ad)

Procedure: To a solution of 3-SI-16 (11.85 g, 40.0 mmol, 1.0 equiv) in 100 mL of dry MeOH was added K\(_2\)CO\(_3\) (1.65 g, 12.0 mmol, 0.3 equiv) in one portion and stirred at rt. After all the starting material was consumed (ca 2 h, thin-layer chromatography, hexanes/EtOAc, 95:5) the mixture was passed through a pad of Celite\(^\circledR\) and washed hexanes/EtOAc. The filtrate was concentrated under reduced pressure and the resulting crude residue was purified column chromatography (silica gel, hexanes/DCM, 10:1) to afford compound 3-1ad (5.50 g, 61% yield) as a yellow solid.

Physical State: Yellow solid

\( ^1 \)H NMR (400 MHz, CDCl\(_3\)): \( \delta 7.93 \) (app. s, 1 H), 7.68 (d, \( J = 9.1 \) Hz, 1 H), 7.65 (d, \( J = 8.6 \) Hz, 1 H), 7.47 (dd, \( J = 8.5, 1.6 \) Hz, 1 H), 7.15 (dd, \( J = 9.0, 2.5 \) Hz, 1 H), 7.09 (d, \( J = 2.5 \) Hz, 1 H), 4.08 (t, \( J = 6.5 \) Hz, 2 H), 3.10 (s, 1 H), 1.83 (app. p, \( J = 6.5 \) Hz, 2 H), 1.54 (app. sextet, \( J = 7.4 \) Hz, 2 H), 1.00 (t, \( J = 7.4 \) Hz, 3 H)
\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 158.2, 134.6, 132.2, 129.4, 129.2, 128.3, 126.9, 119.9, 116.9, 106.6, 84.4, 76.7, 67.9, 31.4, 19.4, 14.0

HRMS (DART-TOF): Calculated for C\(_{16}\)H\(_{17}\)O, [M+H]\(^+\) 225.12739, found 225.12682

Spectral data matched reported values.\(^{58}\)

Preparation of 3-ethynyl-1-(methylsulfonyl)-1H-indole (3-1ae)

3-ido-1-(methylsulfonyl)-1H-indole (3-SI-17)

Procedure: Compound 3-SI–17 was prepared following the general procedure described by Yamanaka and co-workers for cross-coupling of halogenated heterocycles with terminal alkynes.\(^{59}\)

To a solution of 3-ido-1H-indole (3-SI-6) (12.15 g, 50.0 mmol, 1.0 equiv), TBAB (1.61 g, 5.0 mmol, 0.1.0 equiv), 50 mL of a 50% aqueous NaOH) in 75 mL of freshly distilled benzene and 75 mL of water was added methanesulfonyl chloride (11.46 g, 100.0 mmol, 2.0 equiv) in 50 mL of benzene at rt. The reaction was stirred until all the starting material was consumed (ca 30 min, thin-layer chromatography, hexanes/EtOAc, 9:1). The organic layer was collected, washed with water (2 x 50 mL), dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The crude residue was passed through a pad of silica gel and washed several times with benzene. The filtrate was concentrated and purified by recrystallization from MeOH to give 3-SI-17 (9.79 g, 61% yield) as a pink solid.

Physical State: Pink solid

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.88 (dm, \(J = 8.0\) Hz, 1 H), 7.59 (s, 1 H), 7.47–7.37 (m, 2 H), 3.12 (s, 3 H)

\(^{13}\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 134.5, 132.5, 129.7, 126.1, 124.3, 122.4, 113.0, 66.9, 41.1
**IR (ATR):** 3135, 3011, 2928, 1566, 1443, 1156 cm\(^{-1}\)

**HRMS (DART-TOF):** Calculated for C\(_9\)H\(_8\)INO\(_2\)S [M]+: 320.93149, found 320.93088

\(1\)-(methylsulfonyl)-3-((trimethylsilyl)ethynyl)-1H-indole (3-SI-18)

![Chemical Structure]

**Procedure:** Compound 3-SI–18 was prepared following the general procedure described by Yamanaka and co-workers for cross-coupling of halogenated heterocycles with terminal alkynes.\(^{59}\) To a Schlenk flask was added 3-SI-17 (9.79 g, 30.5 mmol, 1.0 equiv) and 75 mL of freshly distilled Et\(_3\)N and the resulting solution was sparged with N\(_2\) for 5 min. Next, ethynyltrimethylsilane (5.20 mL, 36.6 mmol, 1.2 equiv), PdCl\(_2\)(PPh\(_3\))\(_2\) (427 mg, 0.61 mmol, 0.02 equiv) and CuI (232 mg, 1.22 mmol, 0.04 equiv). The mixture was sparged with again with N\(_2\) for 2 min, then placed in a 70 °C pre-heated oil bath and stirred for 1 h. The reaction was cooled to rt and filtered through a pad of silica gel and washed with hexanes/EtOAc (9:1). The filtrate was concentrated under reduced pressure to afford a brown/orange solid. The crude residue was purified by column chromatography (silica gel, hexanes/EtOAc, 9:1) to give 3-SI-18 (8.17 g, 92% yield) as a brown solid.

**Physical State:** Brown solid

**\(^1\)H NMR (400 MHz, CDCl\(_3\)):** \(\delta\) 7.89 (ddd, \(J = 8.2, 1.2, 0.9\) Hz, 1 H), 7.72 (ddd, \(J = 7.8, 1.4, 0.8\) Hz, 1 H), 7.63 (s, 1 H), 7.43–7.35 (m, 2 H), 3.11 (s, 3 H), 0.29 (s, 9 H)

**\(^{13}\)C NMR (100 MHz, CDCl\(_3\)):** \(\delta\) 134.3, 130.9, 129.4, 125.9, 124.2, 121.0, 113.1, 105.4, 99.6, 95.6, 41.1, 0.17

**IR (ATR):** 3124, 2959, 2158, 1448, 13691172 cm\(^{-1}\)
HRMS (DART-TOF): Calculated for C_{14}H_{17}NO_{2}SSi [M]^+ : 291.07437, found 291.07397

3-Ethynyl-1-(methylsulfonyl)-1H-indole (3-1ae)

\[
\begin{align*}
\text{Ms} \\
\text{\includegraphics[width=1cm]{molecule.png}}
\end{align*}
\]

**Procedure:** To a solution of 3-SI-18 (7.28 g, 25.0 mmol, 1.0 equiv) in 100 mL of dry MeOH was added K\textsubscript{2}CO\textsubscript{3} (1.03 g, 7.5 mmol, 0.3 equiv) and the reaction was stirred at rt for 30 min. The reaction solvent was removed under reduced pressure and the resulting solid residue was diluted with water and DCM. The two layers were separated, and the aqueous layer was further extracted with DCM (3 x 25 mL). The combined organic extracts were dried over MgSO\textsubscript{4}, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes/EtOAc, 9:1) to afford 3-1ae (5.21 g, 95% yield) as an off white solid.

**Physical State:** Off white solid

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.90 (ddd, \(J = 8.0, 1.3, 0.7\) Hz, 1 H), 7.74 (ddd, \(J = 8.0, 1.3, 0.8\) Hz, 1 H), 7.67 (s, 1 H), 7.43 (ddd, \(J = 8.5, 7.3, 1.3\) Hz, 1 H), 7.38 (ddd, \(J = 8.4, 7.3, 1.2\) Hz, 1 H), 3.28 (s, 1 H), 3.14 (s, 3 H)

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): \(\delta\) 134.2, 130.8, 129.8, 126.0, 124.2, 120.9, 113.1, 104.1, 81.8, 74.8, 41.2

IR (ATR): 3289, 3137, 2113, 1605, 1448, 1367, 1172 cm\textsuperscript{-1}

HRMS (DART-TOF): Calculated for C\textsubscript{11}H\textsubscript{9}NO\textsubscript{2}S [M]^+ : 219.03485, found 219.03461
Synthesis of α-Vinyl Boronate Esters

Representative procedure for Ni(dppe)Cl$_2$ catalyzed α-borylation of terminal alkynes:

Vinyl boronate esters **3-2a–c, e–h** were prepared following the general procedure described by Gao and Hoveyda for internal borylation of terminal alkynes.$^{16a}$ To a Schlenk flask was added Ni(dppe)Cl$_2$ (158 mg, 0.3 mmol, 0.03 equiv) and the flask was purged with N$_2$ for 10 min. Next, 30 mL of dry THF was added followed by dropwise addition of dibal-H (2.32 mL, 13.0 mmol, reagent grade, 1.3 equiv). The flask was then placed in a 0 °C ice bath and phenylacetylene (**3-1a**) (1.10 mL, 10.0 mmol, 1.0 equiv) was added over 5–10 min. After the addition was complete, the 0 °C ice bath was removed and stirred at rt for 2 h (*note: by quenching a small aliquot with water and performing thin-layer chromatography or $^1$H NMR analysis will indicate when the hydroalumination step is complete*). Next, MeOB(pin) (4.74 g, 30.0 mmol, 3.0 equiv) was added at 0 °C, then placed in an oil bath set to 80 °C and stirred for 16 h. The flask was brought to rt, diluted with Et$_2$O (75 mL) and quenched with water (0.52 mL), 15% aqueous NaOH solution (0.52 mL), followed by water (1.3 mL) and stirred for 30 min. The mixture was filtered through a pad of Celite®, washed with Et$_2$O, and the filtrate was concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes/EtOAc, 99:1) to afford **3-2a** (1.68 g, 73% yield) as an orange solid.
Graphical representation for Ni(dppe)Cl$_2$ catalyzed $\alpha$-borylation of terminal alkynes 3-2a–c, e–h (preparation of 3-2a is used as an example)

(Left) A Schlenk flask containing Ni(dppe)Cl$_2$ being purged with N$_2$. (Middle) Addition of THF to Ni(dppe)Cl$_2$. (Right) After addition of dibal-H to Ni(dppe)Cl$_2$.

(Left) Addition of 3-1a in THF to the Ni solution at 0 °C. (Middle) Reaction after being stirred at rt for 2 h. (Right) TLC (hexanes, UV, KMnO$_4$) of an aliquot to ensure all of the alkyne was consumed. Lane 1 is 3-1a, lane C is the co-spot, and lane 2 is the reaction mixture. Lane 2 represents the semi-hydrogenated compound derived from protodealumination.
(Left) Dropwise addition of MeOBpin at 0 °C. (Center) The reaction being refluxed under N2. (Right) TLC (hexanes/EtOAc (95:5), KMnO4) of the reaction after stirring at 80 °C for 24 h. Lane 2 is the alkene derived from protodealumination, lane C is the co-spot and lane 3 is the reaction. The yellow spot on lane 3 is vinyl boronate ester 3-2a.

Compound 3-2a

![B(pin)](phenyl)

Physical State: Pale orange solid

$^1$H NMR (400 MHz, CDCl3): $\delta$ 7.50–7.46 (m, 2 H), 7.34–7.29 (m, 2 H), 7.26–7.21 (m, 1 H), 6.08 (d, $J = 2.7$ Hz, 1 H), 6.05 (d, $J = 2.7$ Hz, 1 H), 1.32 (s, 12 H)

Spectral data matched reported values.$^{16a}$

Compound 3-2b

![B(pin)](phenyl)

MeO

Procedure: Compound 3-2b was prepared from 4-methoxyphenylacetylene (660 mg, 5.0 mmol) following the procedure described for compound 3-2a to give 522 mg (40% yield) of the desired product.
**Physical State:** Orange solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.48–7.41 (m, 2 H), 6.89–6.82 (m, 2 H), 6.03 (d, $J = 2.8$ Hz, 1 H), 5.96 (d, $J = 2.8$ Hz, 1 H), 3.80 (s, 3 H), 1.32 (s, 12 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 159.0, 134.1, 129.1, 128.4, 113.8, 83.9, 55.4, 24.9 (the boron-containing carbon was not observed)

Spectral data matched reported values.$^{60}$

**Compound 3-2c**

![Chemical Structure of Compound 3-2c]

**Procedure:** Compound 3-2c was prepared from 4-fluorophenylacetylene (240 mg, 2.0 mmol) following the procedure described for compound 3-2a to give 337 mg (68% yield) of the desired product.

**Physical State:** Light brown solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.45 (dd, $J = 8.9$, 5.5 Hz, 2 H), 6.99 (app. t, $J = 8.7$ Hz, 2 H), 6.06–6.00 (m, 2 H), 1.32 (s, 12 H)

Spectral data matched reported values.$^{60}$

**Compound 3-2d**

![Chemical Structure of Compound 3-2d]

**Procedure:** To a solution of diphenylacetylene (4.30 g, 24.1 mmol, 1.0 equiv), 4-(dimethylamino)benzoic acid (199 mg, 1.2 mmol, 0.05 equiv) in 24 mL of $n$-octane was added
HB(pin) (10.5 mL, 72.4 mmol, 3 equiv) at rt. The reaction was placed under N₂ and stirred at 100 °C for 12 h. The flask was cooled to rt and quenched with water (50 mL). The two layers were separated and the aqueous layer was further extracted with DCM (2 x 15 mL). The combined organic extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude solid was passed through a small pad of silica gel, washed with hexanes/EtOAc (99:1), and concentrated under reduced pressure to afford pure 3-2d (5.72 g, 77% yield) as a yellow solid.

**Physical State:** Yellow solid

**1H NMR (400 MHz, CDCl₃):** δ 7.36 (s, 1 H), 7.29–7.23 (m, 2 H), 7.22–7.19 (m, 1 H), 7.18–7.15 (m, 2 H), 7.13–7.09 (m, 3 H), 7.07–7.02 (m, 2 H), 1.31 (s, 12 H)

Spectral data matched reported values.\(^{16b}\)

**Compound 3-2e**

![B(pin)](attachment)

**Procedure:** Compound 3-2e was prepared from 1-ethynylcyclohexene (3-1e) (106 mg, 1.0 mmol) following the procedure described for compound 3-2a to give 140 mg (60% yield) of the desired product.

**Physical State:** Clear pale yellow oil

**1H NMR (400 MHz, C₆D₆):** δ 6.70–6.65 (m, 1 H), 6.14 (d, J = 2.9 Hz, 1 H), 5.83 (d, J = 2.3 Hz, 1 H), 2.25–2.19 (m, 2 H), 2.14–2.08 (m, 2 H), 1.61–1.55 (m, 2 H), 1.49–1.44 (m, 2 H), 1.06 (s, 12 H)

**13C NMR (100 MHz, C₆D₆):** δ 137.8, 128.6, 125.3, 83.2, 26.4, 26.3, 24.9, 23.3, 22.7 (the boron-containing carbon was not observed)

**11B NMR (128 MHz, C₆D₆):** δ 30.7
IR (ATR): 3036, 2976, 2925, 2857, 2833, 1632, 1607, 1575, 1296, 1143, 858 cm⁻¹

HRMS (DART-TOF): Calculated for C₁₄H₂₄BO₂ [M]⁺: 233.18219, found 233.18141

Compound 3-2g

\[
\begin{array}{c}
\text{Cl} \\
\text{B(pin)} \\
\end{array}
\]

**Procedure:** Compound 3-2g was prepared from 5-chloro-1-hexyne (510 mg, 5.0 mmol) following the procedure described for compound 3-2a to give 1.03 g (90% yield) of the desired product.

**Physical State:** Clear colorless oil

\[^1\text{H} \text{NMR (400 MHz, CDCl}_3\): δ 5.82 (d, \(J = 3.3 \) Hz, 1 H), 5.65 (app. s, 1 H), 3.52 (t, \(J = 6.8 \) Hz, 2 H), 2.28 (t, \(J = 7.4 \) Hz, 2 H), 1.90 (app. p, \(J = 7.3 \) Hz, 2 H), 1.26 (s, 12 H)

Spectral data matched reported values.\(^{61}\)

Compound 3-2h

\[
\begin{array}{c}
\text{HO} \\
\text{B(pin)} \\
\text{B(pin)} \\
\end{array}
\]

**Procedure:** Compound 3-2h was prepared from but-3-yn-1-ol (350 mg, 5.0 mmol) following the procedure described for compound 3-2a to give 208 mg (21% yield) of the desired product.

**Physical State:** Clear colorless oil

\[^1\text{H} \text{NMR (400 MHz, CDCl}_3\): δ 5.66 (d, \(J = 3.3 \) Hz, 1 H), 5.69 (app. s, 1 H), 3.66 (t, \(J = 6.0 \) Hz, 2 H), 2.41 (t, \(J = 6.0 \) Hz, 2 H), 2.12 (br. s, 1 H), 1.25 (s, 12 H)

Spectral data matched reported values.\(^{16a}\)

Compound 3-2i

\[
\begin{array}{c}
\text{B(pin)} \\
\text{COOMe} \\
\end{array}
\]
**Procedure:** Compound 3-2i was prepared following the general procedure described by Santos and co-workers for β-borylation of acetylenic esters, with minor modifications.\textsuperscript{16c} To a solution containing CuSO\textsubscript{4}·5H\textsubscript{2}O (19 mL, 1.3 mg/mL of H\textsubscript{2}O, 0.01 equiv of CuSO\textsubscript{4}·5H\textsubscript{2}O) and 4-picoline (0.048 mL, 0.5 mmol, 0.05 equiv) was added to methyl 3-phenylpropiolate (3-1i) (1.60 g, 10.0 mmol, 1.0 equiv), followed by B\textsubscript{2}(pin)\textsubscript{2} (1.39 g, 5.5 mmol). The reaction was stirred at rt and open to air for 10 min. Next, the remaining B\textsubscript{2}(pin)\textsubscript{2} (1.39 g, 5.5 mmol) was added in portions over 10 min at rt. The reaction was stirred open to the air at 50 °C for 24 h. The flask was cooled to rt and diluted with Et\textsubscript{2}O (10 mL) and transferred to a separatory funnel. The layers were separated and the aqueous layer was further extracted with Et\textsubscript{2}O (3 x 15 mL). The combined organic extracts were dried over MgSO\textsubscript{4}, filtered, and concentrated under reduced pressure. The crude residue was purified by column chromatography (silica gel, hexanes/EtOAc, 95:5) to afford 3-2i (1.05 g, 37% yield) as a white solid.

**Physical State:** White solid

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): δ 7.34–7.27 (m, 3 H), 7.23–7.20 (m, 2 H), 6.65 (s, 1 H), 3.58 (s, 3 H), 1.28 (s, 12 H)

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): δ 166.8, 138.6, 131.7, 128.0, 127.8, 127.5, 84.6, 54.4, 24.8 (the boron-containing carbon was not observed)

\textsuperscript{11}B NMR (128 MHz, CDCl\textsubscript{3}): δ 30.1

**IR (ATR):** 3055, 2981, 2954, 1729, 1688, 1657, 1617, 1602, 1322, 1141, 850, 697 cm\textsuperscript{-1}

**HRMS (DART-TOF):** Calculated for C\textsubscript{16}H\textsubscript{22}^{10}BO\textsubscript{4}, [M+H]\textsuperscript{+}: 288.16419, found 288.16315

Compound 3-2j

\begin{center}
\includegraphics[width=0.2\textwidth]{compound3-2j.png}
\end{center}
**Procedure:** Compound **3-2j** was prepared from ethyl 3-phenylpropiolate (2.61 g, 15.0 mmol, 1.0 equiv) following the procedure described for compound **3-2i**, except 1.3 equivalents of B$_2$(pin)$_2$ were used and the reaction was carried out at rt.

Column chromatography (silica gel, hexanes/EtOAc, 95:5) gave **3-2j** (3.98 g, 88% yield) as a clear yellow oil.

**Physical State:** Clear yellow oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.33–7.26 (m, 3 H), 7.23–7.20 (m, 2 H), 7.65 (s, 1 H), 4.03 (q, $J$ = 7.2 Hz, 2 H), 1.28 (s, 12 H), 1.07 (t, $J$ = 7.2 Hz, 3 H)

Spectral data matched reported values.$^{16c}$

Compound **3-2k**

**Procedure:** Compound **3-2k** was prepared from methyl but-2-ynoate (981 mg, 10.0 mmol, 1.0 equiv) following the procedure described for compound **3-2i**, except the reaction was carried out at rt. Column chromatography (silica gel, hexanes/EtOAc, 9:1) gave **3-2k** (1.77 g, 78% yield) as a clear colorless oil.

**Physical State:** Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.44 (q, $J$ = 1.8 Hz, 1 H), 3.71 (s, 3 H), 2.16 (d, $J$ = 1.8 Hz, 3 H), 1.27 (s, 12 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.8, 130.2, 84.3, 51.2, 24.9, 16.5 (the boron-containing carbon was not observed)

$^{11}$B NMR (128 MHz, CDCl$_3$): $\delta$ 30.2

**IR (ATR):** 2980, 2949, 1722, 1435, 1367, 1324, 1110, 1028, 858, 665 cm$^{-1}$
HRMS (DART-TOF): Calculated for C_{11}H_{20}BO_{4} [M+H]^+ : 226.14854, found 226.14799

Compound 3-2l

![Structure of 3-2l]

Procedure: Compound 3-2l was prepared to methyl 3-(cyclohex-1-en-1-yl)propiolate (3-1l) (1.64 g, 10 mmol, 1.0 equiv) following the procedure describe for compound 3-2i, except the reaction was carried out at rt. Column chromatography (silica gel, hexanes/EtOAc, 95:05) gave 3-2l (1.62 g, 56% yield) as a clear colorless oil.

Physical State: Clear colorless oil

$^1$H NMR (400 MHz, CDCl$_3$): δ 6.29 (br. s, 1 H), 5.45–5.42 (m, 1 H), 3.66 (s, 3 H), 2.10–2.03 (m, 4 H), 1.68–1.63 (m, 2 H), 1.61–1.56 (m, 2 H), 1.25 (s, 12 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 167.3, 137.5, 129.4, 123.8, 84.2, 51.4, 28.1, 25.5, 24.8, 22.8, 22.1

(the boron-containing carbon was not observed)

$^{11}$B NMR (128 MHz, CDCl$_3$): δ 29.9

IR (ATR): 2978, 2930, 2857, 2836, 1729, 1601, 1372, 1325, 1138, 854 cm$^{-1}$

HRMS (DART): Calculated for C$_{10}$H$_{25}$BO$_4$ [M+H]$^+$ : 292.19549, found 292.19516
3.9 $^1$H and $^{13}$C NMR Spectra
3-SI-17

Molar Mass: 41.179

66.946

76.875

77.193

77.511

113.029

122.401

124.370

126.146

129.729

132.565

134.521

136.029

138.029

140.029

142.029

144.029

146.029

148.029

150.029

152.029

154.029

156.029

158.029

160.029

162.029

164.029

166.029

168.029

170.029

172.029

174.029

176.029

178.029

180.029

182.029

184.029

186.029

188.029

190.029

ppm
- MeCOOMe
- B(pin)
- 3-2k
3-3q

343
353
dienes 3-3y

![Chemical structures with ppm values]
ppm

25.313
25.328
37.378
37.603
116.633
116.826
122.900
123.021
125.248
125.343
126.110
126.191
126.342
126.495
126.191
126.110
125.343
125.248
123.021
122.900
116.826
116.633

N
Ms
N
Ms
O
O
Ph
H
H
3-17

178.625
178.560
140.527
140.495
131.829
129.351
128.855
128.749
128.207
128.031
127.655
127.029
126.342
126.191
126.110
125.343
125.248
123.021
122.900
116.826
116.633

37.603
37.378
25.328
25.313
3.10 References


18. The authors note that the 5- and 7-membered ring derivatives of 3-2e-α were unstable and dimerized upon concentration. Renaud, J.; Graf, C-D.; Oberer, L. *Angew. Chem., Int. Ed. Engl.* 2000, 39, 3101. In our case, we observed that within 24 hours, the mixture containing 3-2e-α and 3-2e-β had decomposed as indicated by ¹H NMR.


21. It is known that dibal-H reduces Ni(acac)₂ to Ni(COD)₂ in the presence of 1,5-cyclooctadiene. Krysan, D. J.; Mackenzie, P. B. *J. Org. Chem.* 1990, 55, 4229.


CHAPTER FOUR

The Transannular Hexadehydro-Diels–Alder Reaction

4.1 Background and Introduction

Pericyclic reactions offer elegant and powerful strategies for the construction of complex molecules. Arguably, the most well-known is the Diels–Alder [4+2] cycloaddition as it provides up to four contiguous stereocenters. For that reason, numerous syntheses of natural products utilize Diels–Alder reactions to rapidly construct complex motifs in a single step.¹ For example, Nicolaou and co-workers utilized an impressive cascade of pericyclic reactions setting the tetracyclic core of endiandric acid B.² The cascade processes initiated with thermal 8π- then 6π-electrocyclizations, which set the stage for the final intramolecular [4+2] Diels–Alder reaction. The sequence of reactions is impressive as eight stereocenters were set in one step using the achiral starting material. (Scheme 4.1).

*Scheme 4.1* Nicolaou’s cascade approach in the synthesis of endiandric acids B and F.
Years later, a similar approach was used by the Sherburn group in the syntheses of endiandric acid A, kingianic acid E, and kingianins A, D, and F.³

Other than the Diels–Alder (DA) reaction, there are also similar [4+2] cycloadditions that use 4π- and 2π-components. For example, the didehydro-Diels–Alder reaction uses an alkyne in place of an alkene resulting in 1,4-cyclohexadiene products (Figure 4.1). In the next case, using an enyne in place of the diene results in construction of benzene products after a 1,5-H shift. In the last case, using a diyne with an alkyne generates benzyne intermediates, which are trapped with a variety of nucleophilic traps. This last case is known as the hexadehydro-Diels–Alder reaction (HDDA). In all these cases, the net [4+2] reaction yields a six-membered ring with an oxidation state dependent on the 4π- and 2π-components.⁴

Figure 4.1 A sample of common [4+2] cycloaddition reactions.

It is interesting that the utility of HDDA reactions has only recently emerged considering Diels–Alder, didehydro- and tetradehydro reactions have been known for decades.⁵ A key advantage of the HDDA reaction is the ability to further functionalize the aromatic ring via the highly reactive benzyne intermediates. Benzyne has shown to be a key intermediate in the synthesis of many natural products.⁶ However, only a few methods exist that generate benzyne in a mild and controlled fashion which severely limits its general utility.

Surprisingly, Johnson and co-workers reported one of the first examples of the HDDA reaction in 1997.⁷ By using a deuterium labeled 1,3,8-nonatriyne, the authors found the HDDA...
cyclization follows a [4+2] cycloaddition and ruled out the alternative vinylidene pathway (Scheme 4.2). In the same year and totally independently, Ueda and co-workers reported HDDA cyclizations of tetrynes with trapping agents for the benzyne intermediate.\textsuperscript{8} The authors proposed a stepwise mechanism through diradical intermediates rather than a concerted [4+2] cycloaddition. The Ueda lab would continue to study the HDDA reaction providing mechanistic details along the way supporting a stepwise diradical mechanism. The HDDA reaction essentially remained dormant for decades due to the harsh conditions required for the reaction and was viewed as impractical and essentially useless. However, it took a serendipitous discovery by the Hoye group at the University of Minnesota in 2012 while studying an unrelated project for the HDDA reaction to resurface.

*Scheme 4.2* Johnson and co-workers’ mechanistic work on the HDDA reaction using a deuterium labeled triyne.

Since their initial publication in 2012,\textsuperscript{4} the Hoye group has published on the HDDA reaction over 35 times! They have shown the generality and practicality of the HDDA reaction, which was previously viewed as impractical. In each publication, they introduce a new and creative way of trapping the benzyne intermediate in a controlled fashion. For example, when the triyne shown below is heated to 85 °C it undergoes the HDDA cyclization to generate the benzyne
intermediate and is hydrogenated with cyclooctane as the hydrogen transfer reagent (Scheme 4.3, eq. 1). In the next example, they utilize a bis-sulfide linker to facilitate the intramolecular HDDA cyclization of the tetrayne substrate. The benzyne intermediate is trapped with furan via a [4+2] cycloaddition. The next step is very clever, as they remove the bis-sulfide linker via hydrogenation, effectively achieving an intermolecular HDDA reaction, which is an unknown process (Scheme 4.3, eq. 2).

Scheme 4.3 Applications of HDDA reactions using substrates with three-atom linkers.

Since the Hoye work began, there has been an explosion of publications on the HDDA reaction. However, what is surprising is that almost all of them never mention the transannular HDDA (TAHDDA) reaction. The only example showcasing the TAHDDA reaction, to the best of our knowledge, was reported in 2014 by Tobe and co-workers (Scheme 4.4, eq. 1). They successfully synthesized the 14-membered cyclic triyne shown below in four straightforward steps. The sequence initiated with a double Suzuki coupling to give the dialdehyde substrate in 45% yield. Next, the aldehydes were converted to alkynes in 57% yield using a Corey–Fuchs homologation. Construction of the cyclic triyne core was accomplished with an Eglinton acetylenic
coupling forging the 14-membered ring in 51% yield. The authors note that the cyclic triyne compound is unstable at elevated temperatures (> 100 °C) in the absence of benzyne trapping reagents.

**Scheme 4.4** Synthesis and transannular HDDA (TAHDDA) cyclization of a highly strained biphenylophanetriyne.

**· Synthesis of triyne**

\[
\begin{align*}
&\text{Synthesis of triyne} \\
&\text{(HO)}_2\text{B} \\
&\text{Pd(PPh}_3\text{)}_4, \text{Cs}_2\text{CO}_3, \text{PhMe, EtOH} \\
&85^\circ\text{C} \\
&45\% \\
&\text{CHO} \\
&\text{Br} \\
&\text{Zn powder} \\
&\text{LDA, THF} \\
&-78^\circ\text{C} \\
&57\% \\
&\text{Cu(OAc)}_2\cdot\text{H}_2\text{O} \\
&\text{pyridine} \\
&51\% \\
\end{align*}
\]

**· TAHDDA reaction**

\[
\begin{align*}
&\text{Cl-Cl} \\
&\text{X = H or Cl} \\
&\text{Br}_2 \\
&\text{DCM} \\
&(1) \\
&(2)
\end{align*}
\]
The transannular cyclization to generate the benzyne intermediate was accomplished at 70 °C. Evidence of benzyne formation was observed by trapping it with 1,2-dichloroethane, bromine, or furan (Scheme 4.4, eq. 2). This abnormally low energy barrier required for the transannular cyclization is attributed to the large ring strain that is released upon benzyne formation. The thermodynamic stability of the product can be viewed as a driving force for transannular cyclization.

Given our captivation with transannular reactions, we were eager to study the TAHDDA reaction, despite the scarcity of information regarding the reaction. We saw this as an opportunity to study how ring strain affects the HDDA cyclization. Our idea was to prepare cyclic triynes of various ring sizes and measure the rates of cyclization via the TAHDDA reaction. Then, comparing the rates collected for cyclic and acyclic triynes would allow us to determine the influence ring strain imparts on the HDDA reaction. Given our idea, we hypothesized that smaller cyclic triynes would show an accelerated TAHDDA cyclization due to the ring strain that is released upon benzyne formation. In this chapter, I discuss efforts towards answering this question as well as overcoming the synthetic challenges of preparing acyclic and cyclic triyne substrates. At the end of this chapter, I provide future directions for the project based on experimental results and observations.

4.2 Results and Discussion

Prior to any experimental work, we first wanted to understand the dynamics of the TAHDDA reaction through computational studies. We quickly turned to Cyndi He in Professor Houk’s group for help due to her knowledge of transannular reactions as well as having collaborated with our group in the past. Her detailed calculations gave us a better understanding
of the mechanism for TAHDDA cyclizations of cyclic triynes as well as what structural features to aim for.

One substrate that she examined was an unsymmetrical triyne bis-ester shown in Figure 4.2. The mechanism for the TAHDDA reaction was found to occur through a stepwise pathway rather than a converted [4+2] cyclization due to lower transition state energies.

**Figure 4.2** Concerted and stepwise pathways for the TAHDDA cyclization of an asymmetric 13-membered triyne. Energies are calculated at the (U)B3LYP-D3BJ/6-311+G(d,p) level of theory and are reported in kcal/mol.

By using the asymmetric 13-membered triyne to model the TAHDDA mechanism, several important features were extracted. In the stepwise mechanism, the initial C–C bond forming event
preferentially occurs at the end containing a smaller atom linker (three vs four atoms). The most intriguing piece of information is that the second step is rate-determining, which is opposite for the intramolecular HDDA mechanism where it is suggested the first step is rate-determining.\(^{12}\)

With a better understanding of the TAHDDA reaction thanks to Cyndi, we next set out to prepare a family of cyclic triynes that we could evaluate in the TAHDDA reaction. The triynes would be symmetric 12- or 14-membered diethers or diesters for ease of synthesis (Scheme 4.5). Preparation of the cyclic triyne precursors was rapidly accomplished using either an \(\text{S}_2\text{N}^2\) protocol or a Fischer esterification.

**Scheme 4.5** Preparation of cyclic triyne precursors.

With desired cyclic triyne precursors in hand, the next task was to construct cyclic triynes \(4-2, 4-5,\) and \(4-6\) through an intramolecular acetylenic coupling strategy.\(^{13}\) Utilizing an acetylenic coupling strategy to cyclize and construct the cyclic triynes is attractive for several reasons. It is a reliable method due to the vast number of examples reported in the literature. It is also advantageous to use for the last step due to the high dilutions required for intramolecular coupling. Finally, many of the examples report using inexpensive Cu–catalysts and simple reaction conditions. We tested this coupling strategy on substrate \(4-1\) in hopes of preparing cyclic triyne \(4-2.\) Subjecting triyne \(4-\)
I to known Cu-based acetylenic coupling conditions was not fruitful as either 4-1 was recovered from the reaction, or a complex mixture was obtained (Table 4.1).\textsuperscript{11, 14} In order to validate conditions used for 4-1, we subjected alkyne 4-7 to CuCl conditions shown in Table 4.1, which gave diyne 4-8 in 81% yield. This control experiment suggests substrate 4-1 is not amenable to the conditions tested and this can be attributed to the ring size being too small. Taking this into consideration, we hypothesized other 12-membered triynes would follow this same trend. This is not immediately obvious as models of 12-membered triynes reveal only a slight bending of the diyne unit and other than that the triyne seems reasonable.\textsuperscript{15}

\textit{Table 4.1} Attempts at preparing cyclic triyne 4-2 via an acetylenic coupling of 4-1.

\begin{table}
\centering
\begin{tabular}{|c|c|p{10cm}|}
\hline
entry & 4-1 (mmol) & reaction conditions & yield 4-2 \\
\hline
1 & 0.25 & Cu(OAc)\textsubscript{2} [5.3 equiv] pyridine (100 mL) & N.A (sm) \\
2 & 5.0 & Cu(OAc)\textsubscript{2} [5.3 equiv] pyridine (35 mL) & N.A (sm) \\
3 & 0.5 & Pd(OAc)\textsubscript{2} [0.02 equiv] CuI [0.02 equiv] DABCO [3.0 equiv] MeCN (100 mL) & decomp. \\
4 & 0.5 & CuCl [0.1 equiv] TMEDA [0.3 equiv] DCM (20 mL) & complex mixture \\
\hline
\end{tabular}
\end{table}

\begin{table}
\centering
\begin{tabular}{c}
\textbullet Control reaction using a Glaser–Hay protocol \\
\end{tabular}
\end{table}

\begin{align*}
\text{TMS} & \quad \text{CuCl [0.1 equiv]} \\
4-7 & \quad \text{TMEDA [0.3 equiv]} \\
\text{DCM, rt} & \quad \text{81\%} \\
\text{TMS} & \quad \text{TMS} \\
4-8 & \quad \text{TMS}
\end{align*}
With the results from the 12-membered triyne, we moved forward and tested similar acetylenic conditions in hopes of making a 14-membered cyclic triyne. Triyne 4-4 was chosen to test if a 14-membered ring is possible using similar conditions described in Table 4.1. Despite the larger ring size, compound 4-4 failed to provide cyclic triyne 4-6 under any of the conditions tested (Table 4.2). Even using HRMS to analyze the reaction mixture, there was no evidence suggesting 4-6 was made. However, some useful data was extracted from this set of experiments related to substrate incompatibilities.

**Table 4.2** Attempts at preparing cyclic triyne 4-6 via an acetylenic coupling of 4-4.

<table>
<thead>
<tr>
<th>entry</th>
<th>4-4 (mmol)</th>
<th>reaction conditions</th>
<th>yield 4-6</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2.5</td>
<td>Cu(OAc)$_2$ [6.0 equiv] pyridine (35 mL)</td>
<td>side rxn</td>
</tr>
<tr>
<td>2</td>
<td>2.5</td>
<td>Cu(OAc)$_2$ [6.0 equiv] pyridine (35 mL) furan [481 equiv]</td>
<td>side rxn</td>
</tr>
<tr>
<td>3</td>
<td>1.0</td>
<td>Cu(OAc)$_2$ [6.0 equiv] Et$_3$N (35 mL) furan [481 equiv]</td>
<td>complex mixture</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
<td>CuCl [0.1 equiv] TMEDA [0.3 equiv] DCM (35 mL)</td>
<td>complex mixture</td>
</tr>
</tbody>
</table>

We found acyclic triyne 4-4 to be incompatible with conditions that employ pyridine (Table 4.2, entries 1 and 2). Unlike compound 4-1, addition of 4-4 to pyridine instantly produced a deep red solution. After 5 minutes, thin-layer chromatography of the solution revealed triyne 4-4 had been completely consumed and a new compound, which was more polar then 4-4 and UV active, was observed. $^1$H NMR analysis of the crude reaction showed five distinct protons in the alkene region suggesting a dearomatization of pyridine took place. The rest of the spectrum closely
resembled the spectrum for triyne 4-4, but more complex and with larger integration values. The substantial amount of information obtained from analyzing the $^{13}$C NMR and HRMS revealed this mysterious product to be compound 4-9 which incorporates two molecules of 4-4 per pyridine (Scheme 4.6). The spectral data for compound 4-9 also closely matches the data for similar structures that are reported in the literature.\textsuperscript{16} The proposed pathway leading to compound 4-9 shown in Scheme 4.6 is based on related transformations reported in the literature.\textsuperscript{17}

\textit{Scheme 4.6} Incompatibility of alkynyl diester substrates in acetylenic coupling protocols employing pyridine.

In addition to the substrate issue mentioned above, we also became aware of the fact that pyridine is known to react with benzyne to produce polymers.\textsuperscript{18} This would make it extremely difficult to isolate sensitive and unstable cyclic triynes. For example, if the acetylenic coupling produced a highly unstable cyclic triyne, which immediately cyclized to generate benzyne via the TAHDDA reaction, it would polymerize in the presence of pyridine. This would make it very difficult to evaluate if the acetylenic coupling was successful or not. It should be noted that there is little information regarding the stability and reactivity of cyclic triynes.\textsuperscript{15} The futile coupling results obtained from 4-1 and 4-4 prompted us to explore alternative strategies that assuage the issues above.
We envisioned installing a unit that would protect sensitive alkyne groups during the intramolecular acetylenic coupling. The unit would then be removed with hopes of triggering the TAHDDA reaction. The added benefit of a triggered TAHDDA reaction is the ability to control the reaction conditions. We also wanted a protecting unit that could provide structural features that would facilitate the acetylenic coupling. After careful consideration, we decided to use the two strategies shown below in Scheme 4.7.\textsuperscript{19,20}

**Scheme 4.7** Utilizing a protected alkyne strategy to access cyclic triynes.

![Scheme 4.7 Diagram](image)

We anticipated a smooth acetylenic coupling would take place in the synthesis of the retro-Diels–Alder (rDA) strategy substrate due to the close proximity of the terminal alkyne units resulting from the bicyclic structure, as a result of the DA reaction. Under thermal or Lewis acid conditions, the cyclic triyne could be obtained via a rDA process in the presence of a dienophile trap for cyclopentadiene. To save time, we wanted to ensure that the rDA reaction worked before spending time on the acetylenic coupling. Compound 4-10 was chosen as the test substrate for evaluating the rDA reaction with maleic anhydride as the cyclopentadiene trap.\textsuperscript{21} As shown in Table 4.3, compound 4-10 proved extremely stable under thermal and Lewis acid conditions.
Although this strategy offers several attractive features for preparing cyclic triynes, we decided the reaction conditions needed for the rDA to occur could possibly decompose the cyclic triynes.

**Table 4.3.** Reaction condition screen for the retro-Diels–Alder strategy.

![Diagram](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>PhMe, 120 °C</td>
<td>No conversion</td>
</tr>
<tr>
<td>2</td>
<td>Ph₂O, 210 °C</td>
<td>No conversion</td>
</tr>
<tr>
<td>3</td>
<td>Me₂AlCl [1.1 equiv] DCM, rt</td>
<td>No conversion</td>
</tr>
<tr>
<td>4</td>
<td>EtAlCl₂ [1.1 equiv] DCM, rt</td>
<td>No conversion</td>
</tr>
<tr>
<td>5</td>
<td>Me₂AlCl [3.0 equiv] DCM, 60 °C</td>
<td>No conversion</td>
</tr>
<tr>
<td>6</td>
<td>EtAlCl₂ [3.0 equiv] DCM, 60 °C</td>
<td>No conversion</td>
</tr>
<tr>
<td>7</td>
<td>BF₃·OEt₂ [1.1 equiv] DCM, rt</td>
<td>No conversion</td>
</tr>
</tbody>
</table>

Next, we directed our attention towards evaluating the dibromoalkene strategy as a way of preparing cyclic triynes. We envisioned obtaining the cyclic triynes through a Zn–mediated debromination of the cyclic enediyne substrate. To our surprise, a simple ball-and-stick model of compound 4-12 suggests it to be a reasonable structure despite the presence of a *trans* double bond. Compound 4-11 was chosen as the test substrate for evaluating the viability of the acetylenic coupling (Table 4.4). Even with the protected alkyne, the conditions screened proved ineffective for converting 4-11 to the desired cyclic enediyne 4-12. Interestingly, compound 4-11 was observed to be stable under conditions that employ pyridine, thus suggesting the dibromoalkene is truly a protecting group. However, this is not the case when low-valent transition metals are present.
due to removal of both Csp$^2$–Br bonds through an oxidative event (entries 4 and 5). These results determined that the Zn–mediated debromination strategy is no longer a viable option.

**Table 4.4.** Cyclization conditions screen for the dibromoalkene strategy.

<table>
<thead>
<tr>
<th>entry</th>
<th>4-11 (mmol)</th>
<th>reaction conditions</th>
<th>yield 4-12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>0.5</td>
<td>Cu(OAc)$_2$ [2.5 equiv] MeCN (150 mL)</td>
<td>sm</td>
</tr>
<tr>
<td>2</td>
<td>0.5</td>
<td>Cu(OAc)$_2$ [60 equiv] MeCN (150 mL)</td>
<td>sm</td>
</tr>
<tr>
<td>3</td>
<td>0.5</td>
<td>Cu(OAc)$_2$ [60 equiv] pyridine (150 mL)</td>
<td>sm$^a$</td>
</tr>
<tr>
<td>4</td>
<td>3.0</td>
<td>CuCl [3.0 equiv] TMEDA [6.0 equiv] acetone (150 mL)</td>
<td>sm$^b$</td>
</tr>
<tr>
<td>5</td>
<td>0.25</td>
<td>Pd$_2$(dba)$_3$ [0.02 equiv] CuI [0.02 equiv] 1:1 THF/Et$_3$N (150 mL)</td>
<td>decomp.</td>
</tr>
</tbody>
</table>

$^a$Crude mixture contained mainly starting material. $^b$The vinyl bromides of 4-11 were converted to chlorides during the reaction (determined by HRMS)

At this stage of the project, we realized that the acetylenic coupling strategy to close the macrocyclic ring was way more difficult than originally anticipated. While there are numerous examples in the literature that accomplish this feat, many offer minimal functional group variations. However, the acetylenic coupling protocol Myers and co-workers used for the synthesis of the kedarcidin chromophore stood out amongst the rest (Scheme 4.8). Not only was it tolerant of a variety of functional groups, but it also constructed a strained 12-membered enetriyne, which is really impressive.
Scheme 4.8 Myers approach to construction of the kedarcidin chromophore utilizing a modified Eglinton coupling protocol.

We tested this procedure using substrate 4-13, in hopes of constructing 17-membered diyne 4-14 (Scheme 4.9). On our first attempt we obtained cyclic diyne 4-14 in 69% yield! A comparable yield was obtained performing the reaction a second time proving that it is reliable. However, we were unable to convert compound 4-11 to cyclic triyne 4-12 under the same conditions.

Scheme 4.9 Construction of 17-membered diyne 4-14 using Myers modified Eglinton coupling Protocol.

We used the information gathered thus far to engineer a cyclic triyne precursor that would be compatible with the conditions described by Myers which employs pyridine (vide supra). We believed the acetylenic coupling would be amenable for preparing 16-membered triynes based on the experimental results shown above. The cyclic triyne would also need to possess a three-atom linker as this is shown to be the optimal atom linker for substrates in the HDDA reaction. With
these criteria in mind, we proposed compound 4-15 would be a perfect substrate to evaluate in the TAHDDA reaction (Scheme 4.10).

**Scheme 4.10 Synthesis of 16-membered triyne 4-15.**

The synthesis of 4-15 was achieved in just four steps starting from commercially available ethyl 2-hydroxybenzoate. The sequence was initiated by propargylation of ethyl 2-hydroxybenzoate with propargyl bromide followed by hydrolysis to give acid 4-16 in 71% yield over two steps. The acyclic triyne 4-18 was obtained in 88% yield by coupling alcohol 4-17 with acid 4-16 using a DCC protocol. Subjecting compound 4-18 to the acetylenic conditions described by Myers successfully gave the desired 16-membered triyne 4-15 in 44% yield.

With triyne 4-15 in hand, we next investigated its reactivity toward the TAHDDA cyclization with external benzyne trapping agents (Table 4.5). Unfortunately, evidence for a TAHDDA reaction proved difficult to find as triyne 4-15 was found to be unstable at elevated temperatures. Heating triyne 4-15 at 110 °C for 40 hours with cyclooctane as the benzyne trap
gave a 5% mass yield after purification, but contained several unidentifiable compounds. HRMS of the mixture showed evidence for the product expected for TAHDDA cyclization of triyne 4-15 with cyclooctane trapping benzyne via hydrogenation. The small amount of product observed means the process is indeed viable!

Table 4.5 Attempted TAHDDA reaction using cyclic triyne 4-15 with various trapping agents.

With the same design considerations made for 4-15, we envisioned using the substrate pairs shown in Figure 4.3 as a way of evaluating the effect of ring strain on the HDDA reaction. The cyclic triynes would be accessed utilizing a linchpin coupling approach. This approach is particularly attractive as it minimizes the synthetic steps required to access each cyclic triyne by utilizing common precursors.
Figure 4.3 Design strategy for comparing acyclic to cyclic triynes in HDDA reactions.

We decided to investigate the acyclic triyne first using compound 4-19 as a model substrate (Scheme 4.11). The synthesis of cyclic triyne 4-19 was accomplished in six steps starting from 2-bromobenzaldehyde.

Scheme 4.11 Synthesis of Acyclic Triyne 4-19.

The sequence initiated with a Sonogashira cross-coupling of trimethylsilylacetylene with 2-bromobenzaldehyde to give aldehyde 4-20 in greater than 90% yield. Desilylation using $K_2CO_3/MeOH$ gave compound 4-21 in excellent yield. Next, a 1,2-addition of lithiated 1-hexyne
to 4-21 gave alcohol 4-22 in 69% yield. Construction of the diyne unit was achieved by a Cadiot-Chodkiewicz coupling of 4-22 with 1-bromohex-1-yne\textsuperscript{27} to afford 4-23 in 96% yield. Finally, oxidation of 4-23 with MnO\textsubscript{2} gave the triyne 4-19 in 95% yield. This high yielding synthesis was thus amenable to preparing quantities of 4-19.

With triyne 4-19 in hand, its reactivity toward the HDDA reaction was studied (Table 4.6). By using \textsuperscript{1}H NMR analysis, we were able to quickly screen different reaction conditions as well as different benzyne traps. Of the benzyne trapping agents screened, the best result was observed with \textit{tert}-butanol. With this successful benzyne trap in hand, we could now measure the rates for the HDDA cyclization of triyne 4-19.

<table>
<thead>
<tr>
<th>Table 4.6 Screening results of trapping agents for HDDA-generated benzyne using triyne 4-19.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trap and trap’s role</td>
</tr>
<tr>
<td>· Anticipated product/conditions/results</td>
</tr>
<tr>
<td>65 °C, 20 h complex mixture</td>
</tr>
</tbody>
</table>

A solution containing ~4–5 mg of 4-19 with the appropriate trap in CDCl\textsubscript{3} was heated to the specified temperature for the allowed time and then analyzed by \textsuperscript{1}H NMR.
Prior to measuring the reaction rate, an authentic of 4-24 was prepared by heating 4-19 in tert-butanol at 100 °C for 17 hours affording the product in 40% yield (Scheme 4.12, A). However, while characterizing 4-24 the IR data suggested an alkyne was present. This puzzled us as the other spectral data collected (1H NMR, 13C NMR, and HRMS) supported the proposed structure of compound 4-24.

**Scheme 4.12** Initially proposed and revised structure for 4-24 via an unexpected Alder–ene pathway.

A. Initially proposed structure for compound 4-24

B. Revised structure for compound 4-24

C. Benzannulation of triynes reported by Lee and co-workers

The true identity of 4-24 was solved using 2D NMR techniques. Based on the data collected from the COSY and NOSEY experiments a revised structure of 4-24 is shown in Scheme 4.12, B. It is
known that structurally similar triynes engage in an intramolecular Alder–ene reaction affording an allenoate intermediate and, depending on the reaction conditions, is transformed to a number of unique and interesting compounds. For example, Lee and co-workers reported Alder–ene reactions of 1,3,8-triynes as a way to generate highly reactive allenoate intermediates, which were intercepted with a variety of nucleophiles, such as methanol, through Michael addition. Upon further heating, the Michael adduct undergoes a 1,3-H shift, thermal electrocyclization followed by a 1,3-H shift to generate a benzene ring (Scheme 4.12, C). In our case, we did not observe formation of a benzene ring for structure 4-24. This can be attributed to steric factors introduced by the tert-butyl group that hinders the molecule’s ability of adopting the correct configuration needed for electrocyclization to occur.

This issue involving the Alder–ene reaction was solved by replacing all propargylic Csp\(^3\)–H bonds of the ynone moiety with methyl groups. By modifying the original strategy shown in Figure 4.3, an updated design is shown below in Figure 4.4. After carefully analyzing the triyne for other potential problems we found no other structural flaws.

**Figure 4.4** An updated design strategy for comparing acyclic to cyclic triynes in the HDDA reaction.

Based on the reasoning described above, acyclic triyne 4-25 was chosen as a model substrate for testing in the HDDA reaction. The cyclic triyne was prepared using the same synthetic
steps described for 4-19 (Scheme 4.13). The sequence was initiated with a 1,2-addition of lithiated alkyne 4-26 to aldehyde 4-21 to give alcohol 4-27 in 74% yield. A Cadiot-Chodkiewicz coupling of 4-27 with 1-bromohex-1-yne gave compound 4-28 in 95% yield. Finally, oxidation of 4-28 using MnO2 gave triyne 4-25 in 91% yield. The triyne 4-25 was then tested in the HDDA reaction.

Scheme 4.13 Synthesis of acyclic triyne 4-25.

The same reaction screening process described for triyne 4-19 (Table 4.6) was applied on triyne 4-25. Of the various benzyne traps screened (cyclooctane, cyclohexanol, tert-butanol and bicyclo[2.2.1]hept-2-ene), cyclooctane performed best. Thus, an authentic sample of compound 4-29 was prepared by heating triyne 4-25 in cyclooctane at 100 °C for 17 hours affording the desired product in 64% yield (Scheme 4.14). Compound 4-29 was carefully characterized and the spectral data supports the structure shown for compound 4-29. The success of the HDDA cyclization for triyne 4-25 is attributed to the gem-dimethyl group which prevents Alder–ene reactions. We now could confidently measure the half-lives for the HDDA cyclization of triyne 4-25 at different temperatures given this clean and reasonable efficient reaction.
Scheme 4.14 Cyclooctane trap of HDDA-generated benzyne from cyclization of triyne 4-25.

The rates for the HDDA cyclization of triyne 4-25 at various temperatures were determined using $^1$H NMR analysis. For each temperature, eight NMR tubes were charged with 0.2 mL of a 0.05 M solution of triyne 4-25 in cyclooctane, tightly capped, and placed in an oil bath preheated to the desired temperature (100 °C, 80 °C, and 60 °C) (Figure 4.5). At a given time, an NMR tube was removed, cooled to 0 °C, diluted with 0.3 mL of CDCl$_3$, and analyzed by $^1$H NMR (400 MHz). The data collected for cyclization of compound 4-25 shows a $t_{1/2}$ of 1.6 hours at 100 °C, a $t_{1/2}$ of 11.7 hours at 80 °C, and a $t_{1/2}$ of 79.1 hours at 60 °C (Figures 4.6–4.8). Having completed the necessary data required for the acyclic triyne, we then moved to investigate the cyclic triyne substrates.

Figure 4.5 Rates for the HDDA cyclization of 4-25 with cyclooctane at various temperatures.
Figure 4.6 Plot of 4-25 : 4-29 ratios from the HDDA reaction using cyclooctane trap at 100 °C.

Control - 100 °C - Cyclooctane Trap

\[ y = 1.0374e^{0.442x} \]
\[ R^2 = 0.99658 \]
\[ t_{1/2} = 1.6 \text{ h} \]

Figure 4.7 Plot of 4-25 : 4-29 ratios from the HDDA reaction using cyclooctane trap at 80 °C.

Control - 80 °C - Cyclooctane Trap

\[ y = 1.0462e^{0.063x} \]
\[ R^2 = 0.99828 \]
\[ t_{1/2} = 11.7 \text{ h} \]
This next section describes efforts made towards preparing suitable TAHDDA substrates. The compounds shown in Figure 4.9 were studied as possible intermediates as each of them offers a different cyclization strategy for preparing cyclic triynes. The preparation and cyclization efforts are described below starting with triyne 4-30.

**Figure 4.9** Acyclic triyne precursors for construction of cyclic triyne compounds.
The preparation of acyclic triyne **4-30** is shown in Scheme 4.15. The sequence initiated by 1,2-addition of lithiated alkyne **4-34** to aldehyde **4-21** gave alcohol **4-35** in 50% yield. Next, a Cadiot-Chodkiewicz cross coupling of **4-35** with alkyne **4-36** gave triyne **4-37** in 88% yield. Desilylation of **4-37** using TBAF resulted in a complex mixture, whereas using a KF·2H2O/TMSCl protocol33 furnished triol **4-38** in 84% yield. Finally, oxidation of **4-38** using MnO2 gave triyne **4-30** in 70% yield. It should be noted that the MnO2 oxidation is particularly attractive as it is extremely mild, does not require heat, and the products can be isolated after a simple filtration. This procedure potentially makes it possible to isolate and study sensitive HDDA substrates.34

Scheme 4.15 Synthesis of triyne **4-30**.

<table>
<thead>
<tr>
<th>conditions</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TBAF, THF, 0 °C, mixture</td>
<td>mixture</td>
</tr>
<tr>
<td>KF·2H2O, TMSCl, MeCN, rt</td>
<td>84</td>
</tr>
</tbody>
</table>

The attempted cyclization results using triyne **4-30** are shown in Table 4.7. In the first case, triyne **4-30** was treated with silane **L1** at high dilution in hopes of making the dialkoxydimethylsilane closure to the cyclic triyne. However, no product was detected using this method. Due to the tertiary alcohol group in **4-30**, using derivatives of **L1** with alkyl groups bigger than methyl may deter Si–O bond formation. Next, we envisioned formation of the cyclic carbonate, which is more stable than the dialkoxydimethylsilane as they are known to easily
hydrolyze. We investigated forming the cyclic carbonate using phosgene (L2) as the linchpin reagent. Unfortunately, no cyclized product was observed as phosgene is difficult to handle, let alone extremely reactive. Switching to the more stable triphosgene (L3) also failed to provide the cyclic carbonate. The substrate itself possess potential problems as trying to engage the tertiary alcohol in bond formation is likely difficult due to severe steric hindrance around the nucleophilic oxygen. An alternative route that hasn’t been explored is to prefunctionalize the tertiary alcohol prior to the 1,2-addition to aldehyde 4-21.

**Table 4.7** Cyclic triyne results using triyne 4-30 with different linker reagents.

<table>
<thead>
<tr>
<th>linker</th>
<th>X</th>
<th>linker</th>
<th>X</th>
<th>linker</th>
<th>X</th>
</tr>
</thead>
<tbody>
<tr>
<td>MeMeSiCl L1 (1.5 equiv)</td>
<td>Cl Cl L2 (3 equiv) pyr. (30 equiv), DCM [0.002 M] 0 °C, N2 0%</td>
<td>MeMeSi L3 (1.1 equiv) ClCOOCOCl3 L3 (0.33 equiv) Et3N (2 equiv), THF [0.035 M] 0 °C, N2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>L1 (1.5 equiv) Et3N (30 equiv), DCM [0.002 M] rt, N2 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Preparation of triyne 4-31 is shown below in Scheme 4.16. The sequence initiated with an Sn2 reaction of compound 4-39 with 2-methylbut-3-yn-2-ol to give ether 4-40 in 80% yield. Next, addition of lithiated alkyne 4-40 to aldehyde 4-21 gave alcohol 4-41 in 86% yield. Construction of the diyne moiety was accomplished using a Cadiot-Chodkiewicz coupling of 4-41 with alkyne 4-42 to give 4-43 in 95% yield. MnO2 oxidation of 4-43 gave the desired triyne in 87% yield. Compound 4-31 is quite stable and can be stored in the freezer, neat, for months without any signs of decomposition.
Scheme 4.16 Synthesis of acyclic triyne 4-31.

Next, we examined strategies for preparation of cyclic triyne compounds using triyne 4-31. As opposed to the case using triyne 4-30, here we are beneficially utilizing the tertiary ether via *gem*-dialkyl effect from the methyl groups. With the two ends in proximity, the primary alcohol could possibly trap the benzylic cation intermediate resulting from a DDQ oxidation, which would form a ketal to give the cyclic triyne (Figure 4.10, A). When testing this approach however, it proved extremely difficult as only triyne 4-30 and 4-methoxybenzaldehyde were observed (Figure 4.10, B). Efforts to remove water that is responsible for hydrolyzing the PMB group to give 4-methoxybenzaldehyde using molecular sieves did not change the outcome. Due to competing intra- and intermolecular reaction arising from disadvantageous water, we moved forward to investigate other routes.
Figure 4.10 Inspiration and results of using a DDQ ring closing strategy on triyne 4-31.

A. Cyclic triyne strategy utilizing DDQ

B. Cyclization results using DDQ

<table>
<thead>
<tr>
<th>entry</th>
<th>conditions</th>
<th>result</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>DDQ (1.5 equiv), DCM [0.002 M] (no mol. sieves)</td>
<td>4-30 + 4-MBA</td>
</tr>
<tr>
<td>2</td>
<td>DDQ (1.5 equiv) DCM [0.002 M] (3 Å mol. sieves)</td>
<td>4-30 + 4-MBA</td>
</tr>
<tr>
<td>3</td>
<td>DDQ (1.5 equiv), PhH [0.002 M] (3 Å mol. sieves)</td>
<td>4-30 + 4-MBA</td>
</tr>
<tr>
<td>4</td>
<td>DDQ (1.5 equiv), MeCN [0.002 M] (3 Å mol. sieves)</td>
<td>4-30 + 4-MBA</td>
</tr>
</tbody>
</table>

Syntheses of triynes 4-32 and 4-33 are both shown in Scheme 4.17. The synthesis of triyne 4-32, like others, initiates with 1,2-addition of lithiated alkyne 4-44 to aldehyde 4-21 to give alcohol 4-45 in 90% yield. Deprotection of silyl protected 4-45 using TBAF gave diol 4-46 in 48% yield. Compound 4-46 coupled with acid 4-47 using an intermolecular Cadiot-Chodkiewicz
coupling protocol to give triyne 4-32 in 84% yield (Scheme 4.17, A). In the next synthesis, compound 4-33 was obtained by coupling compound 4-48, which was prepared in a similar way as described for 4-46, with acid 4-47 using a DCC coupling protocol (Scheme 4.17, B).

Well aware that these are not ideal TAHDDA substrates due to problems associated with the propargylic C sp³–H bonds of the ynone unit (vide supra), we instead used them as a way to evaluate different cyclization strategies. Cyclization of triyne 4-32 using a DCC or a Mitsunobu approach were unsuccessful in providing the desired cyclic lactone. As noted previously, both these conditions are sensitive to water, so strictly anhydrous conditions are needed to achieve a successful cyclization. Testing of an intramolecular Cadiot-Chodkiewicz coupling on triyne 4-33 was successful and triyne 4-33 was recovered along with a small amount of inseparable dialkyne resulting from debromination despite the aqueous reaction conditions. To our surprise, examples utilizing an intramolecular Cadiot-Chodkiewicz coupling approach to construct cyclic polyynes are scarce. This is perhaps due to the extra chemical steps needed for preparing the bromoalkyne unit, which in a lot of macrocyclizations of acyclic polyynes is necessary. However, due to the mild reaction conditions and broad functional group tolerance of the Cadiot-Chodkiewicz coupling, we see this as the best strategy for constructing sensitive cyclic triynes.
Scheme 4.17 Synthesis of triynes 4-32 and 4-33.

A. Synthesis of triyne 4-32

As a proof of concept for a ring expanded by two carbons, triyne 4-49 was prepared and subjected to the same intramolecular Cadiot-Chodkiewicz coupling conditions tested on triyne 4-33 (Scheme 4.18). Preparation of triyne 4-49 initiated by 1,2-addition of lithiated alkyne 4-50 to aldehyde 4-21, followed by desilylation using aqueous HCl gave alcohol 4-51 in 48% yield. Next, a series of steps gave compound 4-49 in 76% yield. The oxidation/reduction steps were introduced to give a cleaner result for the DCC coupling step. An intramolecular Cadiot-Chodkiewicz coupling of triyne 4-49 gave the cyclic triyne in 59% yield, proving this strategy is feasible! Finally, oxidation with MnO₂ gave the desired cyclic triyne 4-52 in 95% yield.
**Scheme 4.18** Synthesis of cyclic triyne 4-52 from 4-49 through an intramolecular Cadiot-Chodkiewicz coupling as a proof of concept.

With triyne 4-52 in hand, we next investigated its reactivity toward the TAHDDA cyclization (Table 4.8). Unfortunately, the TAHDDA results from testing cyclic triyne 4-52 were nearly identical to results from cyclic triyne 4-15 as for each case below compound 4-52 proved unstable under the reaction conditions.

**Table 4.8** TAHDDA cyclization results for cyclic triyne 4-52 with cyclooctane as the benzyne trap.
These results are in marked contrast with those employing acyclic triyne 4-25 and are more in line with the failed reactions using 4-19. This thus highlights the need to block propargylic C–H groups.

The computational studies mentioned earlier support a stepwise cyclization mechanism that proceeds through diradical intermediates. We wondered if we could observe any diradical intermediates by quenching them with a radical trap, such as 1,4-cyclohexadiene. However, despite several attempts, no detectable species were observed using triyne 4-52 with 1,4-cyclohexadiene as the radical trap.\textsuperscript{44}

At this stage, we thought a computational study could give a better understanding as to why the cyclic triynes tested failed (Figure 4.11).

*Figure 4.11* Stepwise free energy profile for TAHDDA cyclization of a 16-membered triyne

Energies are calculated at the (U)B3LYP-D3BJ/6-311+G(d,p) level of theory and are reported in kcal/mol.
The initial C–C distances for the 16-membered triyne and the 13-membered triyne are essentially the same. However, a much larger interatomic distance is predicted for the larger ring, suggesting larger ring sizes may be disadvantageous for TAHDDA cyclizations. In our original hypothesis, we proposed smaller ring sizes would show an accelerated TAHDDA cyclization rate (vide supra). Smaller ring sizes allow less flexibility thus placing the alkyne and diyne units close together.

4.3 Conclusion and Outlook

Shown in Figure 4.12 is a summary of the work described in this chapter as well as potential future directions for this project. With the information extracted from studying the 1st and 2nd generation cyclic triynes, we strongly believe the 3rd generation cyclic triyne prototype can be used successfully for this project. This design is particularly attractive as the same approach of constructing the 1st generation’s cyclic triyne motif can be used due to decreased steric factors around oxygen. Shown below the summaries is an example of an alkyne with a one carbon spacer that could potentially be used for preparing the 3rd generation substrate. Also shown in Figure 4.12 is a proposed route to access alkynes possessing a two carbon linker. However, as mentioned previously, the preparation of these moieties has one downside as many chemical steps are required.

In summary, a variety of cyclic and acyclic triynes were synthesized and tested as substrates for studying how ring size effects the HDDA reaction. An important structural motif was implemented for acyclic HDDA substrates in order to remove the possibility of an Alder–ene reaction. This was accomplished by removing all α-protons of the mono alkyne and replacing with methyl groups. With this added feature, we were able to measure the half-life of the HDDA reaction for triyne 4-25 using cyclooctane as a trap for the benzyne intermediate. The half-lives were calculated to be 1.6 hours at 100 °C, 11.7 hours at 80 °C, and 79.1 hours at 60 °C. Evaluation
of TAHDDA cyclizations for cyclic triynes substrates was not successful, however, the information gained helped elucidate which structural features are needed moving forward. Of the several ring-closing strategies examined for construction of cyclic triynes, we found that a modified Eglinton described by Myers or an intramolecular Cadiot-Chodkiewicz coupling were superior to all others tested. We strongly believe that utilizing these ring-closing strategies along with using 3rd generation prototype substrates will allow for a more facile approach for studying how ring size effects the HDDA reaction.

*Figure 4.12* Analysis of past and future directions for the TAHDDA project.

### Pros
- easily prepared
- stable at rt

### Cons
- decompose under TAHDDA cyclization conditions
- C1 possesses C–H bonds, which is disadvantageous for acyclic triynes due to the competing Alder–ene pathway

### Pros
- C1 possesses no C–H bonds
- utilize a *gem*-dimethyl effect with an appropriate cyclization strategy

### Cons
- difficult to prepare due to the steric factors centered around C1

### Pros
- C1 possesses no C–H bonds and can utilize a *gem*-dimethyl effect
- decreased steric factors by adding a carbon chain between C1 and oxygen
- added benefit of using 1st generation’s cyclization strategies

### Cons
- the C1 to oxygen carbon chain requires preparation
4.4 Experimental Section

General Methods: Unless otherwise specified, all reactions were performed open to air using dry solvents. Toluene (PhMe) was distilled from Na/benzophenone. Pyridine and tert-butanol were distilled from CaH₂ prior to use. All other reagents were used as received unless otherwise specified. NMR data was obtained with Bruker ARX-400 instrument and calibrated to the solvent signal (CDCl₃ : δ = 7.26 ppm for ¹H NMR, δ = 77.2 ppm for ¹³C NMR; C₆D₆ : δ = 7.16 for ¹H NMR, 128.1 for ¹³C NMR; DMSO-d₆ : δ = 2.50 for ¹H NMR and 39.5 for ¹³C NMR. Data for ¹H NMR spectra are reported as follows: chemical shift (δ ppm), multiplicity, coupling constant (Hz), followed by integration. Data for ¹³C NMR spectra are reported in terms of chemical shift. The following abbreviations are used for the multiplicities: s = singlet; d = doublet; t = triplet; q = quartet; p = pentet; m = multiplet; br. = broad; and app. = apparent. IR spectra were recorded on a JASCO FTIR-4100 spectrophotometer. High-resolution mass spectra (HRMS) were recorded on a LCT premier mass spectrometer by electrospray ionization time-of-flight (ESI-TOF) or on a Thermo Fisher Scientific Exactive Plus with IonSense ID-CUBE Direct Analysis in Real Time (DART) ion source experiments. Reactions were monitored using thin layer chromatography performed on Macherey-Nagel POLYGRAM® SIL G/UV254 silica gel TLC plates and visualized with either of the following: UV light, ceric ammonium molybdate (CAM) stain and heat, or potassium permanganate (KMnO₄) stain and heat. Flash column chromatography was performed using 40-63 mesh micron silica gel.
**Half-Life Experimental Set-Up:** To an individual NMR tube was added 0.20 mL of a 0.05 M solution of triyne 4-25 in cyclooctane (~ 4.0 mg of triyne 4-25), capped with an NMR cap, and heated to the indicated temperatures. At the indicated time points, each NMR tube was removed from the oil bath, cooled in a 0 °C ice bath, diluted with 0.30 mL of CDCl₃, and analyzed using ¹H NMR. The ratio of starting material to product (4-25 : 4-29) was determined by integrating the benzylic protons for both.

**Preparation:** Compound 4-1 was prepared following the procedure described by Merlic.⁴⁶

**Yield:** 62%

**Physical State:** Clear orange oil

**¹H NMR (400 MHz, CDCl₃):** δ 4.31 (s, 4 H), 4.25 (d, J = 2.4 Hz, 4 H), 2.45 (t, J = 2.4 Hz, 2 H)

Spectral data matched reported values.⁴⁶

**Preparation:** Compound 4-3 was prepared following the procedure described for compound 4-4

**Yield:** 82%

**Physical State:** Pale orange oil

**¹H NMR (400 MHz, CDCl₃):** δ 4.82 (d, J = 2.5 Hz, 4 H), 2.56 (t, J = 2.4 Hz, 2 H)

Spectral data matched reported values.¹⁷c
Preparation: To a solution of acetylenedicarboxylic acid monopotassium salt (7.60 g, 50.0 mmol) in H₂O (~15–20 mL) was added 4.5 mL of concentrated sulfuric acid and the contents were stirred for 15 min. The solution was extracted with Et₂O (4 x 30 mL) and the combined organic extracts were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The solid obtained above was added to a solution of but-3-yn-1-ol (7.70 g, 110 mmol) and TsOH·H₂O (951 mg, 5.0 mmol) in benzene (110 mL). The reaction flask was equipped with a Merlic trap and placed in an oil bath set to 100 °C and stirred under N₂ for 24 h. The reaction was cooled to rt, diluted with water and the aqueous layer was extracted with Et₂O (4 x 100 mL). The combined organic extracts were washed with 100 mL of sat. NaHCO₃, dried over MgSO₄, and concentrated under reduced pressure to give a thick brown oil. The crude residue was passed through a small pad of silica gel and washed with hexanes/EtOAc (7:3). The filtrate was concentrated to afford alkyne 4-4 (9.90 g, 90% yield) as a pale orange oil.

Physical State: Light orange oil

¹H NMR (400 MHz, CDCl₃): δ 4.33 (t, J = 6.7 Hz, 4 H), 2.59 (td, J = 6.7, 2.6 Hz, 4 H), 2.03 (t, J = 2.6 Hz, 2 H)

Spectral data matched reported values.⁴⁷

Preparation: Following the procedure described by Vilhelmsen and Nielsen for oxidative coupling of terminal alkynes,⁴ʰ ethynyltrimethylsilane (4-7) (294 mg, 3.0 mmol) was used to
prepare diyne 4-8. The product was purification by flash column chromatography to give 4-8 in 81% yield.

**Physical State:** White solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 0.18 (s, 18 H)

Characterization of crude 4-9 is reported as purification techniques failed to remove any of the inseparable/unidentifiable side products.

**Physical State:** Dark red solid

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 6.46 (d, $J = 7.4$ Hz, 1 H), 6.05 (ddd, $J = 8.0$, 5.3, 2.4 Hz, 1 H), 5.79 (ddd, $J = 7.0$, 7.0, 1.1 Hz, 1 H), 5.67–5.63 (m, 1 H), 4.43 (dd, $J = 2.7$, 2.7 Hz, 1 H), 4.46–4.17 (m, 12 H), 2.69–2.45 (m, 12 H), 2.05–1.96 (m, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 166.3, 163.0, 162.9, 162.2, 148.4, 135.5, 126.0, 121.0, 120.7, 113.6, 113.5, 97.1, 80.1, 79.7 (2 C signals), 79.5, 70.5, 70.3 (2 C signals), 69.9, 64.3, 63.4, 63.0, 62.9, 54.6, 18.8 (2 C signals), 18.6, 18.5

**HRMS (ESI-TOF) m/z:** Calculated for C$_{29}$H$_{25}$NO$_8$ [M]$^+$: 515.1580, found 515.1587
**Preparation:** Following a known literature procedure, DMAD (3.55 g, 25.0 mmol) and cyclopentadiene (3.30 g, 50.0 mmol) were used to prepare **4-10**. After workup, the product was obtained in 65% yield (3.38 g), which needed no further purification.

**Physical State:** Clear colorless oil

\(^1\text{H NMR (400 MHz, CDCl}_3\):} \(\delta 6.91 (\text{dd, } J = 1.9, 1.9 \text{ Hz, 2 H}), 3.94\text{--}3.92 (\text{m, 2 H}), 3.77 (\text{s, 6 H}), 2.27 (\text{ddd, } J = 6.8, 1.6, 1.6 \text{ Hz, 1 H}), 2.09 (\text{ddd, } J = 6.8, 1.4, 1.4 \text{ Hz, 1 H})\)

Spectral data matched reported values.

\[\text{HOOC} \quad \text{COOH}\]
\[\text{Br} \quad \text{Br}\]
\[\text{4-SI-1}\]

**Preparation:** Compound **4-SI-1** was prepared following a known literature procedure.

**Physical State:** White solid

\(^{13}\text{C NMR (100 MHz, D}_2\text{O):} \delta 167.4, 111.9\)

\[\text{O} \quad \text{O}\]
\[\text{Br} \quad \text{Br}\]
\[\text{4-11}\]

**Preparation:** Following a known literature procedure, compound **4-SI-1** (1.09 g, 4.0 mmol) was used to prepare **4-11**. The crude material was purified by flash column chromatography (silica gel, hexanes/EtOAc, 8:2) to give **4-11** in a 56% yield (846 mg).

**Physical State:** Clear colorless oil

\(^1\text{H NMR (400 MHz, CDCl}_3\):} \(\delta 4.38 (\text{t, } J = 6.7 \text{ Hz, 4 H}), 2.62 (\text{td, } J = 6.8, 2.6 \text{ Hz, 4 H}), 2.03 (\text{t, } J = 2.6 \text{ Hz, 2 H})\)

\(^{13}\text{C NMR (100 MHz, CDCl}_3\):} \(\delta 162.0, 112.9, 79.2, 70.7, 64.6, 18.8\)
IR (ATR): 3292, 2968, 1730, 1626, 1232, 1001 cm\(^{-1}\) (C–C triple bond is too low in intensity to report)

HRMS (DART-TOF) \(m/z\): Calculated for C\(_{12}\)H\(_{11}\)Br\(_2\)O\(_4\) [M+H]\(^+\): 376.90186, found 376.90182

\[
\begin{align*}
\text{Preparation:} & \text{ Following the procedure described by Myers and Goldberg,}^{24} \text{ compound 4-13}^{25} (75 mg, 0.20 mmol) \text{ was used to prepared compound 4-14. Purification by column chromatography gave 4-14 (50.1 mg, 69\% yield) as a colorless oil.} \\
\text{Physical State:} & \text{ Clear colorless oil} \\
\text{\(1^H\) NMR (400 MHz, CDCl}3\):} & \delta 7.71 (t, \(J = 7.6\) Hz, 1 H), 7.47 (d, \(J = 7.4\) Hz, 2 H), 7.34 (t, \(J = 7.8\) Hz, 2 H), 7.25 (t, \(J = 7.3\) Hz, 1 H), 7.18 (t, \(J = 7.4\) Hz, 1 H), 6.97 (t, \(J = 7.4\) Hz, 1 H), 6.85 (d, \(J = 7.8\) Hz, 1 H), 4.01 (t, \(J = 5.7\) Hz, 2 H), 3.91 (s, 2 H), 3.64 (s, 2 H), 2.67–2.60 (m, 2 H), 2.34–2.24 (m, 4 H), 2.09–2.01 (m, 2 H), 1.86–1.73 (m, 4 H), 1.44 (app. p, \(J = 6.5\) Hz, 2 H) \\
\text{\(13^C\) NMR (100 MHz, CDCl}3\):} & \delta 157.2, 140.5, 129.4, 128.5, 128.3, 227.9, 127.0, 126.7, 120.8, 111.9, 78.7, 78.4, 67.9, 67.6, 66.7, 57.9, 53.2, 51.6, 28.5, 25.5, 24.7, 22.9, 19.1, 18.9 \\
\text{IR (ATR):} & 2932, 1599, 1489, 1453, 1236, 1101 cm\(^{-1}\) \\
\text{HRMS (DART-TOF) \(m/z\):} & \text{Calculated for C}_{26}\text{H}_{30}\text{NO [M+H]}^{+}: 372.23219, \text{ found 372.23230}
\end{align*}
\]
Preparation of Triyne 4-15

Preparation: Following the procedure described by Queener and co-workers, ethyl 2-hydroxybenzoate (8.30 g, 50.0 mmol) was used to prepare 4-SI-2. After workup, 4-SI-2 was obtained in 86% yield (8.78 g), which was used in the next step without any further purification.

Preparation: Following the procedure described by Antes and Sieber, compound 4-SI-2 (10.0 mmol) was used to prepare 4-16. Purification of the crude material by flash column chromatography gave 4-16 in 83% yield.

Physical State: Off orange solid
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 10.57 (br. s, 1 H), 8.18 (dd, $J = 7.8$, 1.9 Hz, 1 H), 7.58 (ddd, $J = 8.4$, 7.4, 1.9 Hz, 1 H), 7.20–7.14 (m, 2 H), 4.94 (d, $J = 2.4$ Hz, 2 H), 2.64 (t, $J = 2.4$ Hz, 1 H)

Spectral data matched reported values.$^{51}$

![Image](image)

4-18

**Preparation:** To a solution containing 4-16 (1.0 mmol), 4-(prop-2-yn-1-yloxy)but-2-yn-1-ol$^{26}$ (4-17), (0.9 mmol), DMAP (0.04 mmol) in 2.0 mL of freshly distilled DCM at 0 °C under N$_2$ was added a solution of DCC (1.1 mmol) in 1.0 mL of DCM dropwise. The reaction was stirred and slowly warmed to rt over 16 h. The solvent was removed under reduced pressure and purified by flash column chromatography (silica gel, hexanes/EtOAc, 8:2) to give compound 4-18 in 88% yield.

**Physical State:** Pale clear yellow oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.86 (dd, $J = 7.7$, 1.7 Hz, 1 H), 7.49 (ddd, 8.4, 7.4, 1.8 Hz, 1 H), 7.13 (dd, 8.4, 0.9 Hz, 1 H), 7.05 (ddd, $J = 7.7$, 7.7, 0.9 Hz, 1 H), 4.94 (t, $J = 1.8$ Hz, 2 H), 4.79 (d, $J = 2.4$ Hz, 2 H), 4.31 (t, $J = 1.8$ Hz, 2 H), 4.25 (d, $J = 2.3$ Hz, 2 H), 2.53 (t, $J = 2.4$ Hz, 1 H), 2.44 (t, $J = 2.4$ Hz, 1 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 165.0, 157.5, 133.9, 132.1, 121.5, 120.3, 114.7, 82.0, 81.4, 78.9, 78.3, 76.2, 75.2, 57.1, 56.9, 56.7, 52.7

**IR (ATR):** 3287, 2932, 2855, 2121, 1725, 1601 cm$^{-1}$

**HRMS (DART-TOF) m/z:** Calculated for C$_{17}$H$_{15}$O$_4$ [M+H]$^+$: 283.09648, found 283.09769
**Preparation:** Following the procedure described by Myers and Goldberg,\textsuperscript{52} cyclization of 4-18 (0.35 mmol) gave cyclic triyne 4-15 in 44% yield, after purification by flash column chromatography (hexanes/EtOAc, 9:1).

**Physical State:** Yellow solid

\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): $\delta$ 7.80 (dd, $J = 7.7, 1.7$ Hz, 1 H), 7.50 (ddd, $J = 8.2, 7.4, 1.8$ Hz, 1 H), 7.19 (ddd, $J = 7.6, 7.6, 1.1$ Hz, 1 H), 7.10 (dd, $J = 8.1, 1.1$ Hz, 1 H), 5.05 (t, $J = 1.7$ Hz, 2 H), 4.79 (t, $J = 0.9$ Hz, 2 H), 4.28 (t, $J = 1.7$ Hz, 2 H), 4.23 (t, $J = 0.9$ Hz, 2 H)

\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}): $\delta$ 165.1, 157.3, 133.8, 131.1, 125.7, 124.3, 121.4, 83.5, 82.3, 76.8, 74.6, 72.6, 72.2, 62.8, 60.2, 59.9, 52.5

**IR (ATR):** 2920, 2852, 1732, 1600, 1485, 1244, 1079 cm\textsuperscript{-1}

**HRMS (DART-TOF) m/z:** Calculated for C\textsubscript{17}H\textsubscript{13}O\textsubscript{4} [M+H]\textsuperscript{+}: 281.08083, found 281.08151

**Preparation of Triyne 4-19**
Preparation: A round bottom flask containing 1-hexyne (4.10 g, 50.0 mmol) in 100 mL of dry THF at −78 °C under N₂ was added n-BuLi (18.6 mL, 46.5 mmol, 2.5 M in hexanes) dropwise over 15 min. The contents were stirred for an additional 30 min at −78 °C followed by dropwise addition of aldehyde 4-21 (5.46 g, 42.0 mmol) in 60 mL of dry THF. The −78 °C ice bath was removed and the reaction was slowly warmed to rt over 1 h. The reaction was quenched with sat. NH₄Cl at 0 °C and the mixture was transferred to a separatory funnel and the aqueous layer was extracted with Et₂O (4 x 75 mL). The combined organic extracts were washed with brine (1 x 50 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to give compound 4-22 (8.90 g, 69% yield) as an orange oil.

Physical State: Clear orange oil

¹H NMR (400 MHz, CDCl₃): δ 7.72 (d, J = 7.3 Hz, 1 H), 7.51 (dd, 7.6, 1.2 Hz, 1 H), 7.40 (ddd, J = 7.7, 7.7, 1.5 Hz, 1 H), 7.28 (ddd, J = 7.6, 7.6, 1.2 Hz, 1 H), 5.87 (dt, J = 5.1, 2.0 Hz, 1 H), 3.36 (s, 1 H), 2.49 (d, J = 5.4 Hz, 1 H), 2.27 (td, J = 7.1, 2.1 Hz, 2 H), 1.56–1.48 (m, 2 H), 1.46–1.37 (m, 2 H), 0.91 (t, J = 7.3 Hz, 3 H)

¹³C NMR (100 MHz, CDCl₃): δ 143.7, 133.2, 129.5, 128.2, 126.8, 120.4, 87.9, 82.6, 81.2, 79.2, 63.2, 30.7, 22.1, 18.6, 13.7

IR (ATR): 3292, 2932, 2225, 1443, 757 cm⁻¹

HRMS (DART-TOF) m/z: Calculated for C₁₅H₁₇O [M+H]⁺: 213.12739, found 213.12685
**Preparation:** Two separate round bottom flasks containing \(n\)-BuNH\(_2\) and H\(_2\)O were sparged with N\(_2\) for 45 min prior to use. A round bottom flask containing CuCl (147 mg, 1.5 mmol) and NH\(_2\)OH·HCl (10–15 mg, ~0.15 mmol) was purged with N\(_2\) for 5 min followed by addition of the sparged \(n\)-BuNH\(_2\) (13.5 mL) and H\(_2\)O (31.5 mL). The flask was cooled to 0 °C and compound 4-22 (3.18 g, 15.0 mmol) was added dropwise over 2 min and stirred for an additional 15 min. Next, 1-bromohex-1-yn\(_2\) (2.89 g, 18.0 mmol) was added dropwise over 1 h at 0 °C. If the reaction became green/blue, a few drops of a NH\(_2\)OH·HCl solution in \(n\)-BuNH\(_2\)/H\(_2\)O (~100 mg/mL) was added to maintain the characteristic bright yellow color of the reaction. After the bromoalkyne was added, the reaction was stirred for an additional 3 h at 0 °C. The contents were transferred to a separatory funnel, diluted with water, and extracted with Et\(_2\)O (4 x 50 mL). The organic extracts were washed with H\(_2\)O (3 x 25 mL), brine (1 x 50 mL), then dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 9:1) to give compound 4-23 (4.20 g, 96% yield) as a pale yellow oil.

**Physical State:** Pale yellow oil

\(^{1}\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 7.62 (d, \(J = 8.0\) Hz, 1 H), 7.50 (dd, \(J = 7.7, 1.0\) Hz, 1 H), 7.45 (ddd, \(J = 7.5, 7.5, 1.2\) Hz, 1 H), 7.30 (ddd, \(J = 7.5, 7.5, 1.2\) Hz, 1 H), 5.98 (d, \(J = 5.5\) Hz, 1 H), 5.54 (dt, \(J = 5.5, 2.0\) Hz, 1 H), 2.44 (t, \(J = 7.0\) Hz, 2 H), 2.18 (td, \(J = 6.7, 2.0\) Hz, 2 H), 1.54–1.46 (m, 2 H), 1.44–1.31 (m, 6 H), 0.89 (t, \(J = 7.3\) Hz, 3 H), 0.85 (t, \(J = 7.2\) Hz, 3 H)
**13C NMR (100 MHz, DMSO-d$_6$):** $\delta$ 145.8, 132.9, 129.5, 127.6, 126.1, 118.7, 86.7, 85.0, 81.2, 78.6, 72.1, 64.8, 60.7, 30.1, 29.6, 21.3, 21.2, 18.4, 17.6, 13.4, 13.3

**IR (ATR):** 3392, 2932, 2870, 2222, 1464, 755 cm$^{-1}$

**HRMS (DART-TOF) m/z:** Calculated for C$_{21}$H$_{23}$ [M–OH]$^+$ : 275.17942, found 275.17883

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**Preparation:** To a solution of compound 4-23 (1.0 mmol) in 20 mL of dry DCM at 0 °C was added MnO$_2$ (30.0 mmol) in one portion and the flask was capped with a rubber septum. After consumption of the starting material (ca 2 h), the reaction was filtered through a pad of Celite®, washed with DCM, and reduced pressure to give pure compound 4-19 in 95% yield, which required no further purification.

**Physical State:** Dark orange oil

**1H NMR (400 MHz, CDCl$_3$):** $\delta$ 8.06 (dd, $J = 7.7$, 1.3 Hz, 1 H), 7.59 (dd, $J = 7.6$, 1.3 Hz, 1 H), 7.46 (ddd, $J = 7.6$, 7.6, 1.3 Hz, 1 H), 7.41 (ddd, $J = 7.6$, 7.6, 1.3 Hz, 1 H), 2.49 (t, $J = 7.3$ Hz, 2 H), 2.37 (t, $J = 7.3$ Hz, 2 H), 1.69–1.40 (m, 8 H), 0.94 (t, $J = 7.3$ Hz, 3 H), 0.92 (t, $J = 7.2$ Hz, 3 H)

**13C NMR (100 MHz, CDCl$_3$):** $\delta$ 177.1, 139.6, 135.7, 132.3, 131.6, 128.4, 122.2, 98.0, 87.1, 80.7, 80.6, 73.0, 65.6, 30.3, 29.9, 22.2, 22.1, 19.5, 19.2, 13.6 (2 C signals)

**IR (ATR):** 2955, 2224, 2209, 1649, 1479 cm$^{-1}$

**HRMS (DART-TOF) m/z:** Calculated for C$_{21}$H$_{23}$O$_2$ [M+H]$^+$ : 291.17434, found 291.17493
**Preparation:** To a pressure tube was containing compound 4-19 (0.10 mmol) was added 10.0 mL of tert-butanol, sealed with a Teflon cap, then placed in an oil bath set to 85 °C and stirred for 19 h. After the allowed time, the solution was cooled to rt, and the solvent was removed under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/EtOAc (95:5)) to afford compound 4-24 in 40% yield.

**Physical State:** Clear pale yellow oil

**$^1$H NMR (400 MHz, CDCl$_3$):** δ 8.75 (d, $J = 8.0$ Hz, 1 H), 7.76 (ddd, $J = 7.4$, 7.4, 0.8 Hz, 1 H), 7.54 (ddd, $J = 7.6$, 7.6, 1.2 Hz, 1 H), 7.39 (ddd, $J = 7.5$, 7.5, 0.8 Hz, 1 H), 6.99 (t, $J = 2.6$ Hz, 1 H), 3.21–3.14 (m, 2 H), 2.55 (td, $J = 7.1$, 2.6 Hz, 2 H), 1.70–1.60 (m, 4 H), 1.57 (s, 9 H), 1.55–1.44 (m, 4 H), 0.97 (t, $J = 7.2$ Hz, 3 H), 0.97 (t, $J = 7.2$ Hz, 3 H)

**$^{13}$C NMR (100 MHz, CDCl$_3$):** δ 192.0, 175.0, 143.8, 140.5, 137.6, 133.3, 128.7, 124.3, 122.7, 117.3, 105.0, 101.1, 83.2, 80.8, 32.0, 31.9, 31.0, 30.5, 23.3, 22.3, 20.2, 14.0, 13.8

**IR (ATR):** 3068, 2932, 1685, 1585, 1466, 1370, 1148 cm$^{-1}$

**HRMS (DART-TOF) m/z:** Calculated for C$_{25}$H$_{33}$O$_2$ [M+H]+: 365.24750, found 365.24796
Preparation of Triyne 4-25

**Preparation:** A solution of alkyne **4-26** (12.6 mmol) in 30 mL of dry THF at −78 °C under N₂ was added n-BuLi (5.0 mL, 12.6 mmol, 2.5 M in hexanes) dropwise. The reaction was stirred for 30 min followed by dropwise addition of aldehyde **4-21** (11.5 mmol) in 10 mL of dry THF. The reaction was stirred at −78 °C for 2 h, then cooled to 0 °C and quenched with sat. NH₄Cl (50.0 mL). The contents were transferred to a separatory funnel and extracted with Et₂O (4 x 50 mL). The combined organic extracts were washed with brine (1 x 50 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to give compound **4-27** in 74% yield.

**Physical State:** Clear orange oil
**Preparation:** Two round bottom flasks, one containing \( n\)-BuNH\(_2\) and the other with H\(_2\)O were sparged with N\(_2\) for 45 min prior to use. A round bottom flask containing CuCl (0.32 mmol) and NH\(_2\)OH·HCl (1.64 mmol) was purged with N\(_2\) for 5 min followed by addition of the sparged \( n\)-BuNH\(_2\) (8.0 mL) and H\(_2\)O (12.0 mL). The flask was cooled to 0 °C and compound 4-27 (6.5 mmol) was added dropwise over 2 min and stirred for an additional 15 min. Next, 1-bromohex-1-yne\(^{27}\) (7.8 mmol) was added dropwise over 1 h at 0 °C. If the reaction became green/blue, a few drops of the NH\(_2\)OH·HCl solution were added to maintain a bright yellow color. After the addition of 1-bromohex-1-yne, the reaction was stirred for an additional 45 min at 0 °C. The contents were transferred to a separatory funnel and extracted with Et\(_2\)O (4 x 25 mL). The organic extracts were washed with H\(_2\)O (3 x 15 mL), brine (1 x 50 mL), dried over MgSO\(_4\), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to give compound 4-28 in 95% yield.

**Physical State:** Clear red oil
$^1$H NMR (400 MHz, CDCl$_3$): δ 7.63 (dd, $J = 7.6$, 1.2 Hz, 1 H), 7.50 (dd, $J = 7.6$, 1.2 Hz, 1 H), 7.37–7.23 (m, 7 H), 5.85 (d, $J = 5.8$ Hz, 1 H), 4.64 (d, $J = 11.4$ Hz, 1 H), 4.60 (d, $J = 11.3$ Hz, 1 H), 2.44 (d, $J = 5.9$ Hz, 1 H), 2.34 (t, $J = 7.1$ Hz, 2 H), 1.55–1.49 (m, 2 H), 1.49–1.38 (m, 2 H), 0.92 (t, $J = 7.0$ Hz, 3 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 143.8, 139.2, 133.8, 129.4, 128.4, 128.3, 127.9, 127.4, 126.7, 120.6, 89.1, 86.7, 83.6, 80.0, 71.8, 70.8, 66.8, 65.0, 63.2, 30.5, 22.1, 19.4, 13.6

IR (ATR): 3438, 3065, 2983, 2934, 2871, 2237, 1497, 1380, 1243 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{27}$H$_{27}$O [M–OH]$^+$ : 367.20564, found 367.20648

Preparation: As described for preparation of compound 4-19, 0.26 mmol of compound 4-28 reacted to give compound 4-25 in 91% yield.

Physical State: Bright yellow oil

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.98 (dd, $J = 7.8$, 1.2 Hz, 1 H), 7.60 (dd, $J = 7.8$, 1.2 Hz, 1 H), 7.48 (dddt, $J = 7.5$, 7.5, 1.3 Hz, 1 H), 7.41–7.30 (m, 5 H), 7.29–7.25 (m, 1 H), 4.70 (s, 2 H), 2.36 (t, $J = 7.0$ Hz, 2 H), 1.67 (s, 6 H), 1.55–1.51 (m, 2 H), 1.47–1.41 (m, 2 H), 0.91 (t, $J = 7.2$ Hz, 3 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): δ 176.8, 139.4, 138.6, 135.8, 132.6, 131.5, 128.5 (2 C signals), 127.8, 127.7, 122.2, 96.8, 87.6, 83.3, 80.9, 72.7, 71.0, 67.4, 65.6, 30.3, 28.4, 22.1, 19.5, 13.6

IR (ATR): 3063, 2958, 2209, 1651, 1592, 1480, 1448, 1160, 1050 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{27}$H$_{27}$O$_2$ [M+H]$^+$ : 383.20055, found 383.20148

440
Cyclization of Triyne 4-25: To a pressure tube was added compound 4-25 (0.10 mmol) and 4.20 mL of cyclooctane. The solution was sparged with N₂ for ~1 min then sealed with a Teflon cap and placed in an oil bath set to 100 °C. The reaction was stirred for 18 h then cooled to rt, and concentrated under reduced pressure to removed excess cyclooctane. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 9:1) to afford compound 4-29 in 64% yield.

Physical State: Golden oil

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.54 (ddd, \(J = 7.2, 0.8, 0.8\) Hz, 1 H), 7.43–7.41 (m, 2 H), 7.35–7.29 (m, 5 H), 7.27–7.20 (m, 3 H), 4.38 (s, 2 H), 3.04–2.97 (m, 2 H), 1.94 (s, 6 H), 1.46–1.40 (m, 2 H), 1.13 (app. sextet, \(J = 7.3\) Hz, 2 H), 0.77 (t, \(J = 7.3\) Hz, 3 H)

\(^13\)C NMR (100 MHz, CDCl\(_3\)): \(\delta\) 194.6, 148.6, 144.9, 144.0, 143.2, 139.5, 137.8, 134.4, 134.1, 133.2, 128.7, 128.3, 127.8, 127.2, 124.1, 119.1, 118.7, 80.2, 64.1, 35.4, 35.0, 27.1, 23.0, 14.2

IR (ATR): 3052, 2955, 1705, 1606, 1453, 1259, 965 cm\(^{-1}\)

HRMS (DART-TOF) \(m/z\): Calculated for C\(_{21}\)H\(_{21}\)O [M–OBn]\(^+\): 277.15869, found 277.15945
Preparation of Triyne 4-30

Preparation: Following the same procedure described for compound 4-27, aldehyde 4-21\(^{53}\) (30.7 mmol) and alkyne 4-34\(^{31}\) (36.8 mmol) were used to prepare compound 4-35. Purification by column chromatography (hexanes/EtOAc, 8:2) provided diyne 4-35 in 50% yield.

Physical State: Clear orange oil

\(^1\)H NMR (400 MHz, CDCl\(_3\)): δ 7.66 (d, \(J = 7.7\) Hz, 1 H), 7.51 (dd, \(J = 7.7, 1.3\) Hz, 1 H), 7.40 (ddd, \(J = 7.5, 7.5, 1.3\) Hz, 1 H), 7.29 (ddd, \(J = 7.6, 7.6, 1.3\) Hz, 1 H), 5.89 (d, \(J = 5.7\) Hz, 1 H), 3.37 (s, 1 H), 2.48 (d, \(J = 5.7\) Hz, 1 H), 1.51 (s, 3 H), 1.50 (s, 3 H)

\(^13\)C NMR (100 MHz, CDCl\(_3\)): δ 143.0, 133.3, 129.5, 128.3, 126.8, 120.4, 91.9, 82.8, 81.8, 81.2, 66.7, 63.1, 33.0, 1.9

IR (ATR): 3423, 3295, 2983, 2989, 1448, 1248, 1158, 1030 cm\(^{-1}\)

HRMS (DART-TOF) \(m/z\): Calculated for C\(_{17}\)H\(_{21}\)OSi [M-OH]\(^+\) : 269.13561, found 269.13583
**Preparation:** Two round bottom flasks containing $n$-BuNH$_2$ and H$_2$O were sparged with N$_2$ for 45 min prior to use. A round bottom flask containing CuCl (0.5 mmol) and NH$_2$OH·HCl (2.5 mmol) was purged with N$_2$ for 5 min prior to the addition of the sparged $n$-BuNH$_2$ (12.0 mL) and H$_2$O (18.0 mL). The flask was cooled to 0 °C and compound 4-35 (10.0 mmol) was added dropwise over 1–2 min and stirred for an additional 15 min. A 100 mg/mL solution of NH$_2$OH·HCl in sparged $n$-BuNH$_2$/H$_2$O (2:3, v/v) was prepared followed by dropwise addition of alkyne 4-36 (12.0 mmol) over 1 h at 0 °C. If the reaction became green/blue, a few drops of the NH$_2$OH·HCl solution were added to maintain a bright yellow color. The reaction was stirred for an additional 2 h at 0 °C. The contents were transferred to a separatory funnel and extracted with Et$_2$O (3 x 30 mL). The organic extracts were washed with H$_2$O (3 x 20 mL), brine (1 x 50 mL), then dried over MgSO$_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 95:5) to give compound 4-37 in 88% yield.

**Physical State:** Clear orange oil

$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.64 (d, $J = 7.7$ Hz, 1 H), 7.49 (dd, $J = 7.8$ Hz, 1 H), 7.38 (ddd, $J = 7.7$, 7.7, 1.2 Hz, 1 H), 7.27 (ddd, $J = 7.6$, 7.6, 1.2 Hz, 1 H), 5.83 (d, $J = 5.7$ Hz, 1 H), 3.79 (t, $J = 7.4$ Hz, 2 H), 2.59 (t, $J = 7.4$ Hz, 2 H), 2.39 (d, $J = 5.7$ Hz, 1 H), 1.51 (s, 3 H), 1.50 (s, 3 H), 0.91 (s, 9 H), 0.12 (s, 9 H), 0.09 (s, 6 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 143.8, 133.7, 129.4, 128.2, 126.7, 120.3, 91.7, 83.3, 81.9, 79.6, 72.2, 66.6, 66.2, 63.0, 61.5, 33.0, 26.0, 24.1, 18.4, 1.9, −5.1

**IR (ATR):** 3445, 2956, 2930, 2857, 2243, 1471, 1248, 1105 cm$^{-1}$
**HRMS (DART-TOF) m/z:** Calculated for C_{24}H_{31}O_{2}Si [M–OTMS]^+ : 379.20878, found 379.20801

[Diagram of compound 4-38]

**Preparation:** To a suspension of compound 4-37 (0.5 mmol), KF·2H_{2}O (1.0 mmol) in 2.0 mL of dry MeCN was added TMSCl (1.0 mmol) dropwise over 5 min. The reaction was stirred until all of the starting material was consumed (ca 10 min). The reaction was quenched with sat. NaHCO_{3}, and extracted with DCM (4 x 10 mL). The organic extracts were washed with H_{2}O (10 mL) and brine (10 mL), then dried over MgSO_{4}, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (DCM/MeOH, 9:1) to afford compound 4-38 in 84% yield.

**Physical State:** Pale yellow oil

**{^1}H NMR (400 MHz, CDCl_{3}):** \( \delta \) 7.63 (d, \( J = 7.8 \) Hz, 1 H), 7.50 (dd, \( J = 7.6, 1.1 \) Hz, 1 H), 7.39 (ddd, \( J = 7.6, 7.6, 1.2 \) Hz, 1 H), 7.28 (ddd, \( J = 7.6, 7.6, 1.2 \) Hz, 1 H), 5.79 (d, \( J = 5.6 \) Hz, 1 H), 3.80 (app. q, \( J = 6.0 \) Hz, 2 H), 2.65 (d, \( J = 5.5 \) Hz, 1 H), 2.65 (t, \( J = 6.0 \) Hz, 2 H), 2.21 (s, 1 H), 2.12 (t, \( J = 6.1 \) Hz, 1 H), 1.54 (s, 6 H)

**{^{13}}C NMR (100 MHz, CDCl_{3}):** \( \delta \) 143.8, 133.6, 129.6, 128.3, 126.9, 120.2, 91.3, 83.3, 81.4, 79.5, 72.7, 66.7, 65.3, 62.6, 60.5, 31.2 (2 C signals), 24.0

**IR (ATR):** 3353, 2981, 2935, 2890, 2246, 1482, 1414, 1376, 1233, 1162 cm\(^{-1}\)

**HRMS (DART-TOF) m/z:** Calculated for C_{18}H_{19}O_{3} [M+H]^+ : 283.13287, found 283.13242
Preparation: To a solution of compound 4-38 (2.0 mmol) in 100 mL of dry DCM was added MnO₂ (50 mmol) in one portion and the flask was placed under an atmosphere of N₂. The reaction was stirred at rt for 3 h, then filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure, and the crude residue was purified by flash column chromatography (silica gel, DCM/MeOH, 95:5) to afford compound 4-30 in 70% yield.

Physical State: Dark orange oil

¹H NMR (400 MHz, CDCl₃): δ 8.00 (dd, J = 7.8, 1.2 Hz, 1 H), 7.58 (dd, J = 7.8, 1.1 Hz, 1 H), 7.48 (ddd, J = 7.4, 7.4, 1.4 Hz, 1 H), 7.42 (ddd, J = 7.6, 7.6, 1.3 Hz, 1 H), 3.79 (app. q, J = 6.0 Hz, 2 H), 2.81 (br. s, 2 H), 2.64 (t, J = 6.1 Hz, 2 H), 1.64 (s, 6 H)

¹³C NMR (100 MHz, CDCl₃): δ 177.0, 139.2, 135.7, 132.8, 131.2, 128.9, 122.0, 99.2, 84.4, 81.2, 80.7, 73.4, 67.2, 65.5, 60.7, 30.7, 24.3

IR (ATR): 3357, 2983, 2885, 2210, 1640, 1480, 1248 cm⁻¹

HRMS (DART-TOF) m/z: Calculated for C₁₇H₁₃O₂ [M–CH₃O]⁻: 249.09100, found 249.08958
Preparation of Triyne 4-31

Preparation: To a solution of 2-methylbut-3-yn-2-ol (33 mmol) in hexanes/DCM (30 mL:11 mL) at 0 °C under N₂ was added acetimidate 4-39 (39.6 mmol) and stirred for 10 min. Next, PPTS (1.65 mmol) was added in one portion and the reaction was slowly warmed to rt over 19 h. The solids were removed by filtration through a pad of silica gel was washed with hexanes/EtOAc (9:1). The filtrate was washed with sat. NaHCO₃, brine (75 mL), then dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (hexanes/EtOAc, 95:5) to afford compound 4-40 in 80% yield.

Physical State: Clear pale yellow oil

¹H NMR (400 MHz, CDCl₃): δ 7.29 (d, J = 8.7 Hz, 2 H), 6.87 (d, J = 8.7 Hz, 2 H), 4.56 (s, 2 H), 3.79 (s, 3 H), 2.47 (s, 1 H), 1.54 (s, 6 H)

¹³C NMR (100 MHz, CDCl₃): δ 159.2, 131.2, 129.4, 113.9, 86.4, 72.3, 70.4, 66.3, 55.4, 29.0

IR (ATR): 3289, 2982, 1613, 1515, 1464, 1379 cm⁻¹
**HRMS (DART-TOF) m/z:** Calculated for C_{13}H_{17}O₂ [M+H]^+ : 203.10665, found 203.10640

**Preparation:** To a solution of compound **4-40** (24.0 mmol) in 50 mL of dry THF at −78 °C under N₂ was added n-BuLi (8.8 mL, 22 mmol, 2.5 M in hexanes) dropwise over 15 min. After addition of n-BuLi the contents were stirred for an additional 30 min at −78 °C. Next, a solution of aldehyde **4-21** (20.0 mmol) in 20 mL of dry THF was added over 30 min. The cold bath was removed and the reaction was slowly warmed to rt over 1.5 h. The reaction was quenched at 0 °C with sat. NH₄Cl and the contents were transferred to a separatory funnel and extracted with Et₂O (4 x 50 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 8:2)) to give compound **4-41** in 86% yield.

**Physical State:** Clear orange oil

**¹H NMR (400 MHz, CDCl₃):** δ 7.68 (d, J = 7.9 Hz, 1 H), 7.53 (dd, J = 7.6, 1.2 Hz, 1 H), 7.39 (ddd, J = 7.6, 7.6, 1.3 Hz, 1 H), 7.30 (ddd, J = 7.5, 7.5, 1.2 Hz, 1 H), 7.23 (d, J = 8.8 Hz, 2 H), 6.84 (d, J = 8.8 Hz, 2 H), 5.92 (d, J = 5.8 Hz, 1 H), 4.54 (s, 2 H), 3.79 (s, 3 H), 3.37 (s, 1 H), 2.53 (d, J = 5.9 Hz, 1 H), 1.51 (s, 6 H)

**¹³C NMR (100 MHz, CDCl₃):** δ 159.1, 143.1, 133.4, 131.2, 129.5, 129.4, 128.4, 128.4, 126.8, 120.5, 113.9, 89.2, 83.4, 82.9, 81.2, 70.7, 66.4, 63.1, 55.4, 29.0 (2 C signals)

**IR (ATR):** 3380, 2978, 2935, 2225, 1617, 1515, 1244, 1034 cm⁻¹

**HRMS (DART-TOF) m/z:** Calculated for C_{22}H_{21}O₂ [M–OH]^+ : 317.15360, found 317.15326
Preparation: Following the procedure described for compound 4-37, 4-41 (10 mmol) was coupled with 4-bromobut-3-yn-1-ol\textsuperscript{38} (4-42) (12.0 mmol) to give compound 4-43 in 95\% yield, after purification by flash column chromatography.

Physical State: Clear orange oil

\textbf{\textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3})}: δ 7.65 (d, \(J = 7.9\) Hz, 1 H), 7.51 (dd, \(J = 7.6, 1.1\) Hz, 1 H), 7.38 (ddd, \(J = 7.6, 7.6, 1.3\) Hz, 1 H), 7.29 (ddd, \(J = 7.6, 7.6, 1.3\) Hz, 1 H), 7.24 (d, \(J = 8.7\) Hz, 2 H), 6.84 (d, \(J = 8.7\) Hz, 2 H), 5.85 (d, \(J = 5.6\) Hz, 1 H), 4.56 (d, \(J = 11.4\) Hz, 1 H), 4.53 (d, \(J = 11.2\) Hz, 1 H), 3.78 (s, 3 H), 3.73 (q, \(J = 5.8\) Hz, 2 H), 2.60 (t, \(J = 6.1\) Hz, 2 H), 2.49 (d, \(J = 5.8\) Hz, 1 H), 1.83 (t, \(J = 5.5\) Hz, 1 H), 1.54 (s, 6 H)

\textbf{\textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3})}: δ 159.0, 144.0, 133.6, 131.0, 129.5 (2 C signals), 128.2, 126.6, 120.1, 113.8, 88.7, 83.7, 83.0, 79.4, 72.5, 70.7, 66.5, 66.4, 62.7, 60.5, 55.3, 28.9, 28.8, 23.8

\textbf{IR (ATR)}: 3382, 2984, 2935, 2233, 1612, 1513, 1449, 1379, 1245, 1033 cm\textsuperscript{-1}

\textbf{HRMS (DART-TOF) m/z}: Calculated for C\textsubscript{26}H\textsubscript{25}O\textsubscript{3} [M–OH]\textsuperscript{+} : 385.17982, found 385.17844
**Preparation:** To a solution of compound 4-43 (0.70 mmol) in 25 mL of dry DCM was added MnO₂ (14.1 mmol) in one portion and placed under N₂. The reaction was stirred until all of the starting material was consumed (ca 15 min, thin-layer chromatography) and then filtered through a pad of Celite®. The filtrate was concentrated under reduced pressure to afford compound 4-31 in 87% yield, which needed no further purification.

**Physical State:** Clear yellow/orange oil

**¹H NMR (400 MHz, CDCl₃):** δ 8.02 (dd, J = 7.8, 1.0 Hz, 1 H), 7.62 (dd, J = 7.7, 1.0 Hz, 1 H), 7.51 (ddd, J = 7.5, 7.5, 1.3 Hz, 1 H), 7.42 (ddd, J = 7.6, 7.6, 1.3 Hz, 1 H), 7.31 (d, J = 8.6, 2 H), 6.87 (d, J = 8.6 Hz, 2 H), 4.63 (s, 2 H), 3.79 (s, 3 H), 3.66 (q, J = 6.3 Hz, 2 H), 2.59 (t, J = 6.3 Hz, 2 H), 2.05 (t, J = 6.5 Hz, 1 H), 1.66 (s, 6 H)

**¹³C NMR (100 MHz, CDCl₃):** δ 176.7, 159.3, 139.3, 135.8, 132.7, 131.5, 130.4, 129.7, 128.7, 121.9, 113.9, 97.1, 84.0, 83.2, 80.6, 73.2, 70.9, 67.2, 67.1, 60.6, 55.4, 28.4, 24.3

**IR (ATR):** 3469, 2986, 2936, 2836, 2209, 1648, 1513, 1244 cm⁻¹

**HRMS (DART-TOF) m/z:** Calculated for C₂₆H₂₅O₄ [M+H]^+: 401.17473, found 401.17374

**Preparation of Triyne 4-32**
Preparation: To a solution of alkyne 4-44 (60 mmol) in 120 mL of dry THF at −78 °C under N₂ was added n-BuLi (22 mL, 55 mmol, 2.5 M in hexanes) dropwise over 15 min. After addition of n-BuLi, the contents were stirred for an additional 30 min at −78 °C. Next, a solution of aldehyde 4-21 (50 mmol) in 30 mL of dry THF was added over 30 min. The cold bath was removed and the reaction was slowly warmed to rt over 16 h. The flask was cooled to 0 °C and quenched with sat. NH₄Cl. The contents were transferred to a separatory funnel and extracted with Et₂O (4 x 75 mL). The combined organic extracts were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes/EtOAc (9:1)) to give 14.1970 g (90% yield) of 4-45.

Physical State: Clear orange oil

¹H NMR (400 MHz, CDCl₃): δ 7.72 (d, J = 7.8 Hz, 1 H), 7.50 (dd, J = 7.6, 1.2 Hz, 1 H), 7.39 (ddd, J = 7.6, 7.6, 1.2 Hz, 1 H), 7.28 (ddd, J = 7.5, 7.5, 1.2 Hz, 1 H), 5.87 (dt, J = 5.5, 1.9 Hz, 1 H), 3.74 (t, J = 7.0 Hz, 2 H), 3.36 (s, 1 H), 2.49 (td, J = 7.1, 2.0 Hz, 2 H), 2.48 (d, J = 5.6 Hz, 1 H), 0.88 (s, 9 H), 0.05 (s, 6 H)

¹³C NMR (100 MHz, CDCl₃): δ 143.4, 133.2, 129.5, 128.2, 126.9, 120.5, 84.7, 82.6, 81.2, 80.4, 63.2, 61.9, 26.0, 23.4, 18.4, -5.1

IR (ATR): 3402, 3294, 9254, 2857, 1729, 1471, 1253, 1098 cm⁻¹

HRMS (DART-TOF) m/z: Calculated for C₁₉H₂₇O₂Si [M+H]⁺: 315.17748, found 315.17593
Preparation: To a solution of 4-45 (17.5 mmol) in 60 mL of dry THF at 0 °C was added TBAF (35 mL, 35 mmol, 1 M in THF). The reaction was stirred at 0 °C for 15 min, then rt for 1 h. The reaction was diluted with sat. NH₄Cl, and the aqueous layer was extracted with Et₂O (4 x 50 mL). The combined extracts were dried over Na₂SO₄, filtered, and concentrated under reduced pressure. The resulting crude residue was purified by flash column chromatography (silica gel, hexanes/EtOAc, 6:4) to give 1.6751 g (48%) of 4-46.

Physical State: Orange solid

¹H NMR (400 MHz, CDCl₃): δ 7.69 (d, J = 7.8 Hz, 1 H), 7.51 (dd, J = 7.5, 1.2 Hz, 1 H), 7.40 (ddd, J = 7.5, 7.5, 1.2 Hz, 1 H), 7.28 (ddd, J = 7.5, 7.5, 1.3 Hz, 1 H), 5.86 (app. s, 1 H), 3.73 (t, J = 6.1 Hz, 2 H), 3.38 (s, 1 H), 2.94 (br. s, 1 H), 2.52 (td, J = 6.1, 2.0 Hz, 2 H), 2.23 (br. s, 1 H)

¹³C NMR (100 MHz, CDCl₃): δ 142.3, 133.2, 129.6, 128.2, 126.7, 120.2, 84.3, 82.8, 81.4, 81.2, 62.9, 60.9, 23.3

IR (ATR): 2389, 2939, 2888, 2231, 2103, 1480, 1477 cm⁻¹

HRMS (DART-TOF) m/z: Calculated for C₁₃H₁₃O₂ [M+H]⁺: 201.09100, found 201.09009

Preparation: Following the procedure described for compound 4-37, 4-46 (7.5 mmol), acid 4-47, CuCl (0.37 mmol), NH₂Cl·HCl (1.87 mmol), n-BuNH₂ (9.0 mL), and water (13.5 mL) were used to prepare 4-32. The reaction was made acidic using 6 N HCl, then extracted with Et₂O (4 x
60 mL). The combined organic extracts Na₂SO₄, filtered, and concentrated under reduced pressure. To the crude material was added water (20 mL), Et₂O (25 mL), and hexanes (150 mL) and allowed to stand for 16 at rt. The resulting orange solid was collected by filtration, washed with water, and allowed to air dry to give 1.85 g (84% yield) of 4-32.

**Physical State:** Orange solid

**¹H NMR (400 MHz, (CD₃)₂CO):** δ 7.72 (d, J= 7.6 Hz, 1 H), 7.46 (dd, J=7.5, 1.0 Hz, 1 H), 7.41 (ddd, J=7.6, 7.6, 1.1 Hz, 1 H), 7.28 (ddd, J=7.5, 7.5, 1.1 Hz, 1 H), 5.72 (t, J=1.8 Hz, 1 H), 4.96 (br. s, 1 H), 3.60 (t, J= 6.9 Hz, 2 H), 2.69–2.64 (m, 2 H), 2.38–2.54 (m, 2 H), 2.38 (td, J= 6.9, 1.9 Hz, 2 H)

**¹³C NMR (100 MHz, (CD₃)₂CO):** δ 172.6, 146.3, 133.7, 130.1, 128.4, 127.4, 120.3, 85.2, 83.6, 82.2, 79.2, 73.1, 65.6, 62.3, 61.1, 32.7, 23.5, 15.7

**IR (ATR):** 3397, 2954, 2239, 1712, 1418, 1248 cm⁻¹

**HRMS (DART-TOF) m/z:** Calculated for C₁₈H₁₅O₃ [M–OH]⁺: 279.10157, found 279.10098

**Preparation of Triyne 4-33**

4-21

\[ \text{phenylacetylene} \quad \text{OTBS} \quad \text{n-BuLi} \quad \text{THF, $-78 \, ^{\circ}\text{C}$.} \]

4-31

\[ \text{phenylacetylene} \quad \text{OTBS} \quad \text{TBAF, THF} \quad 0 \, ^{\circ}\text{C to rt}. \]

4-48

\[ \text{DCC, cat. DMAP, DCM} \]

4-33

\[ \text{Br} \quad \text{OH} \]

(4-47)
Preparation: To a solution of tert-butyldimethyl(2-propynoxy)silane\(^{54}\) (30 mmol) in 40 mL of dry THF at \(-78\) °C under N\(_2\) was added \(n\)-BuLi (12 mL, 30 mmol, 2.5 M in hexanes) dropwise over 15 min. After addition of \(n\)-BuLi, the contents were stirred for an additional 30 min at \(-78\) °C. Next, a solution of aldehyde 4-21\(^{53}\) (25 mmol) in 20 mL of dry THF was added over 30 min. The cold bath was removed and the reaction was slowly warmed to rt over 16 h, then quenched with sat. NH\(_4\)Cl at 0 °C. The contents were transferred to a separatory funnel and extracted with Et\(_2\)O (4 x 75 mL). The combined organic extracts were washed with brine (50 mL), dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes/EtOAc (9:1)) to give 5.7613 g (77% yield) of 4-SI-3.

Physical State: Orange oil

\(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta\) 7.69 (dd, J= 7.6, 1.1 Hz, 1 H), 7.50 (dd, J=7.6, 1.1 Hz, 1 H), 7.38 (ddd, J= 7.6, 7.6, 1.2 Hz, 1 H), 7.27 (ddd, J= 7.6, 7.6, 1.2 Hz, 1 H), 5.91 (td, J=5.5, 1.9 Hz, 1 H), 4.38 (d, J = 1.8 Hz, 2 H), 3.36 (s, 1 H), 2.70 (d, J = 5.6 Hz, 2 H), 0.88 (s, 9 H), 0.09 (s, 3 H), 0.09 (s, 3 H)

Spectral data matched reported values.\(^{44}\)

Preparation: To a solution of 4-SI-3 (16.6 mmol) in 80 mL of dry THF at 0 °C was added TBAF (19.9 mL, 19.9 mmol, 1 M in THF). The reaction was stirred at 0 °C for 15 min, then rt for 1 h.
The reaction was diluted with sat. NH$_4$Cl, and the aqueous layer was extracted with EtOAc (4 x 70 mL). The combined extracts were washed with water (2 x 50 mL), brine (50 mL), dried over Na$_2$SO$_4$, filtered, and concentrated under reduced pressure. The crude residue was purified by recrystallization from hexanes/EtOAc (9:1) to give 3.1334 g (95% yield) of 4-48.

**Physical State:** Off white solid

$^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.62 (dd, $J = 7.7$ Hz, 1 H), 7.44–7.36 (m, 2 H), 7.27 (ddd, $J = 7.7$, 7.7, 1.2 Hz, 1 H), 6.03 (d, $J = 5.4$ Hz, 1 H), 5.65 (td, $J = 5.5$, 1.8 Hz, 1 H), 5.11 (t, $J = 5.9$ Hz, 1 H), 4.40 (s, 1 H), 4.04 (dd, $J = 5.9$, 1.7 Hz, 2 H)

$^{13}$C NMR (100 MHz, DMSO-$d_6$): $\delta$ 144.2, 132.1, 129.2, 127.7, 126.4, 19.4, 85.3, 84.7, 84.4, 80.8, 60.4, 48.9

IR (ATR): 3278, 2912, 2865, 1481, 1447, 1128 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{12}$H$_{11}$O$_2$ [M+H]$^+$: 187.07535, found 187.07529

**Preparation:** To a solution of 4-48 (3.3 mmol), acid 4-47$^{41}$ (3.0 mmol), DMAP (0.75 mmol) in 60 mL of DCM at 0 °C was added a solution of DCC (3.3 mmol) in 5 mL of DCM over 10 min. The reaction was allowed to warm to rt and stirred for 22 h. The reaction was filtered through a small pad of silica gel, washed with Et$_2$O, and the filtrate was concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes/EtOAc (7:3)) to give 436 mg (42% yield) of 4-33.

**Physical State:** Pale yellow oil
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.68 (dd, $J = 7.8$, 1.3 Hz, 1 H), 7.52 (dd, $J = 7.6$, 1.2 Hz, 1 H), 7.41 (ddd, $J = 7.6$, 7.6, 1.3 Hz, 1 H), 7.31 (ddd, $J = 7.6$, 7.6, 1.3 Hz, 1 H), 5.92 (td, $J = 5.7$, 1.8 Hz, 1 H), 4.79 (d, $J = 1.8$ Hz, 2 H), 3.38 (s, 1 H), 2.61–2.50 (m, 5 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 171.0, 142.4, 133.2, 129.6, 128.5, 126.8, 120.4, 86.0, 83.0, 80.9, 80.4, 78.1, 62.8, 52.7, 29.5, 32.9, 15.5

IR (ATR): 3461, 3289, 2933, 2221, 2855, 1737, 1157 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{17}$H$_{12}$BrO$_2$ [M–OH]$^+$: 327.00151, found 327.00183

Preparation of Triyne 4-49 and Cyclic Triyne 4-52

4-21 $\xrightarrow{n$-BuLi, THF, $-78 \, ^\circ\text{C}$} 4-Si-4 $\xrightarrow{\text{HCl (aq), THF, rt}}$ 4-51

4-Si-6 $\xrightarrow{\text{DCC, cat. DMAP, DCM}}$ 4-Si-5 $\xrightarrow{\text{MnO$_2$, DCM, rt}}$

4-Si-7 $\xrightarrow{\text{CuCl (0.16 equiv), NH$_2$OH-HCl (0.80 equiv), n-BuNH$_2$/H$_2$O (40% v/v) [0.004 M], 0 \, ^\circ\text{C}, 2 h}}$ 4-49

4-49 $\xrightarrow{\text{MnO$_2$, DCM, 0 \, ^\circ\text{C}}}$ 4-52
To a solution of 5-(tert-butyl(dimethyl)silyloxy)-1-pentyne\(^{54}\) (4-50), (30 mmol) in 60 mL of dry THF at \(-78\, ^\circ\text{C}\) under N\(_2\) was added \(n\)-BuLi (11 mL, 27.5 mmol, 2.5 M in hexanes) dropwise over 15 min. After addition of \(n\)-BuLi, the contents were stirred for an additional 30 min at \(-78\, ^\circ\text{C}\). Next, a solution of aldehyde 4-21\(^{53}\) (25 mmol) in 20 mL of dry THF was added over 30 min. The cold bath was removed and the reaction was slowly warmed to rt over 16 h, then quenched with sat. NH\(_4\)Cl at 0 °C. The contents were transferred to a separatory funnel and extracted with Et\(_2\)O (4 x 60 mL). The combined organic extracts were washed with brine (50 mL), dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude residue was passed through a pad of silica gel, washed with hexanes/EtOAc (9:1) and the filtrate was concentrated under reduced pressure to afford crude 4-SI-4, which was used in the next step without further purification.

Compound 4-SI-4 was dissolved in 100 mL of dry THF and HCl (25 mL, 1 M) was added and stirred at rt for 1 h. The reaction was quenched with sat. NaHCO\(_3\) (50 mL) and the aqueous layer was extracted with Et\(_2\)O (3 x 75 mL). The combined organic extracts were washed with water (50 mL) and brine (50 mL), then dried over Na\(_2\)SO\(_4\), filtered, and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (silica gel, hexanes/EtOAc (6:4))
to give 2.5478 g (48% yield over two steps) of 4-51. The R$_f$ and $^1$H NMR data for 4-45 and 4-46 were used as a way to identify 4-SI-4 and 4-51, respectively, prior to moving forward.

Compound 4-45 – R$_f$: 0.25 (hexanes/EtOAc, 9:1)

Compound 4-SI-4 – R$_f$: 0.27 (hexanes/EtOAc, 9:1)

Compound 4-46 – R$_f$: 0.25 (hexanes/EtOAc, 6:4)

Compound 4-51 – R$_f$: 0.26 (hexanes/EtOAc, 6:4)

Compound 4-51 – $^1$H NMR (400 MHz, CDCl$_3$): δ 7.69 (d, 7.6 Hz, 1 H), 7.50 (dd, J = 7.6, 1.2 Hz, 1 H), 7.39 (ddd, J = 7.6, 7.6, 1.3 Hz, 1 H), 7.28 (ddd, J = 7.6, 7.6, 1.3 Hz, 1 H), 5.86 (td, J = 5.4, 2.0 Hz, 1 H), 3.74 (t, J = 5.3 Hz, 2 H), 3.37 (s, 1 H), 2.65 (d, J = 5.5 Hz, 1 H), 2.39 (td, J = 7.0, 2.0 Hz, 2 H), 1.78 (app. p, J = 6.1 Hz, 2 H)

To a solution of 4-51 (11.9 mmol) in 100 mL of DCM at rt was added MnO$_2$ (297 mmol) in one portion. The reaction was stirred for 1.5 h, then filtered through a small pad of silica gel and washed with DCM. The filtrate was concentrated under reduced pressure to afford a dark brown oil, which was purified by flash column chromatography (silica gel, Et$_2$O) to give 889 mg of 4-SI-5 as a brown oil. The $^1$H NMR data showed the desired compound along with minor impurities. Compound 4-SI-5 was taken forward to the next step without any further purification.

Compound 4-SI-5 – R$_f$: 0.23 (hexanes/EtOAc, 1:1)

Compound 4-SI-5 – $^1$H NMR (400 MHz, CDCl$_3$): δ 8.09 (dd, J = 7.6, 1.3 Hz, 1 H), 7.62 (dd, J = 7.6, 1.3 Hz, 1 H), 7.50 (ddd, J = 7.6, 7.6, 1.5 Hz, 1 H), 7.45 (ddd, J = 7.6, 7.6, 1.5 Hz, 1 H), 3.83–3.77 (m, 2 H), 3.40 (s, 1 H), 2.61 (t, J = 6.9 Hz, 2 H), 1.90 (app. p, J = 6.3 Hz, 2 H)

457
To a solution of 4-SI-5 (1.3 mmol), acid 4-47\textsuperscript{41} (1.3 mmol), DMAP (0.065 mmol) in 15 mL of DCM at 0 °C was added a solution of DCC (1.43 mmol) in 5 mL of DCM. The reaction was allowed to warm to rt over 1 h, then filtered through a small pad of silica gel and washed with hexanes/EtOAc (1:1). Compound 4-SI-6 was taken forward to the next step without any further purification.

To a solution of crude 4-SI-6 in 25 mL of dry methanol at 0 °C was added NaBH\textsubscript{4} (1.3 mmol) in one portion. The reaction was stirred until all of 4-SI-6 was consumed (ca 20 min). The reaction was quenched with sat. NH\textsubscript{4}Cl (10 mL) and extracted with Et\textsubscript{2}O (4 x 10 mL). The organic extracts were dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated under reduced pressure to afford a yellow oil. The crude material was purified by flash column chromatography (silica gel, hexanes/EtOAc (8:2)) to give 480 mg of 4-49. The spectral and R\textsubscript{f} data for 4-49 closely matched those reported for compound 4-33.

Compound 4-49 – R\textsubscript{f}: 0.26 (hexanes/EtOAc, 8:2)

Compound 4-49 – \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}): \(\delta\) 7.69 (d, \(J = 7.8\) Hz, 1 H), 7.51 (dd, \(J = 7.6, 1.2\) Hz, 1 H), 7.40 (ddd, \(J = 7.6, 7.6, 1.2\) Hz, 1 H), 7.28 (ddd, \(J = 7.6, 7.6, 1.3\) Hz, 1 H), 5.85 (td, \(J = 5.7, 2.2\) Hz, 1 H), 4.21 (t, \(J = 6.3\) Hz, 2 H), 3.38 (s, 1 H), 2.54 (d, \(J = 5.6\) Hz, 1 H), 2.53–2.50 (m, 4 H), 2.39 (td, \(J = 6.8, 2.1\) Hz, 2 H), 1.87 (app. p, \(J = 6.7\) Hz, 2 H)
Two round bottom flasks containing \( n \)-BuNH\(_2\) and H\(_2\)O were sparged with N\(_2\) for 45 min prior to use. To a round bottom flask containing CuCl (0.16 mmol) and NH\(_2\)OH·HCl (0.79 mmol) was added \( n \)-BuNH\(_2\) (100 mL) and H\(_2\)O (150 mL) and stirred until a clear colorless solution appeared. The flask was cooled to 0 °C followed by dropwise addition of 4-49 (0.98 mmol) in 20 mL of DCM over 2 h. A 100 mg/mL solution of NH\(_2\)OH·HCl in sparged \( n \)-BuNH\(_2\)/H\(_2\)O (2:3, v/v) was prepared and added dropwise to the reaction if it became green/blue. After addition of 4-49, the reaction was stirred for an additional 30 min, and then quenched with sat. NH\(_4\)Cl (100 mL). The contents were transferred to a separatory funnel and extracted with DCM (3 x 75 mL). The combined organic extracts were dried over Na\(_2\)SO\(_4\), filtered and concentrated under reduced pressure. The crude residue was purified by flash column chromatography (Et\(_2\)O) to give 171.2 mg (59% yield) of 4-SI-7, which was immediately taken forward.

To a solution of 4-SI-7 (0.26 mmol) in 10 mL of DCM at 0 °C was added MnO\(_2\) (5.32 mmol) in one portion. The reaction was stirred for 30 min, then filtered through a small pad of silica gel and washed with DCM. The filtrate was concentrated under reduced pressure at 0 °C to give 72.4 mg (93% yield) of 4-52. The compound was stored as a 3.33 mg/mL solution in DCM at 0 °C under N\(_2\).

**Physical State:** Orange solid
$^1$H NMR (400 MHz, CDCl$_3$): $\delta$ 7.95 (dd, $J = 7.9$, 1.2 Hz, 1 H), 7.57 (dd, $J = 7.7$, 1.3 Hz, 1 H), 7.48 (dd, $J = 7.6$, 7.6, 1.4 Hz, 1 H), 7.41 (ddd, $J = 7.7$, 7.7, 1.3 Hz, 1 H), 4.31–4.27 (m, 2 H), 2.77–2.71 (m, 4 H), 2.60–2.56 (m, 2 H), 2.09–2.02 (m, 2 H)

$^{13}$C NMR (100 MHz, CDCl$_3$): $\delta$ 177.0, 171.5, 139.6, 132.6, 129.5, 129.1, 122.6, 99.0, 84.1, 81.4, 81.4, 81.0, 73.3, 67.1, 63.1, 33.5, 28.0, 16.9 (2 C signals)

IR (ATR): 2959, 1729, 1722, 1631, 1601, 1463, 1257, 1152 cm$^{-1}$

HRMS (DART-TOF) m/z: Calculated for C$_{19}$H$_{15}$O$_3$ [M+H]$^+$: 291.10157, found 291.10095
4.5 $^1$H and $^{13}$C NMR Spectra
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, DMSO-$d_6$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, CDCl$_3$)

$\text{4-41}$

[Chemical structure diagram]
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl$_3$)
$^1$H NMR (400 MHz, (CD)$_2$CO)
$^1$H NMR (400 MHz, DMSO-$d_6$)
$^1$H NMR (400 MHz, CDCl$_3$)
$^{13}$C NMR (100 MHz, CDCl₃)
4.6 References


