I. TANDEM BENZANNULATION-RING CLOSING METATHESIS STRATEGY FOR THE SYNTHESIS OF BENZO-FUSED NITROGEN HETEROCYCLES

II. SYNTHESIS OF AMIDES AND LACTAMS IN SUPERCRITICAL CARBON DIOXIDE

By

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II. SYNTHESIS OF AMIDES AND LACTAMS IN SUPERCRITICAL CARBON DIOXIDE

By
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ABSTRACT

A tandem benzannulation-ring closing metathesis strategy for the efficient synthesis of benzo-fused nitrogen heterocycles such as dihydroquinolines, benzazepines, and benzazocines has been developed. This strategy is based on the benzannulation reaction of ynamides with cyclobutenones or α-diazo ketones to generate highly-substituted aniline derivatives, which then participate in ring-closing metathesis reactions to form nitrogen heterocycles. The synthetic utility of this strategy has been demonstrated by its successful application in a formal synthesis of the natural product (+)-FR900482.

In addition, an environmentally-friendly approach to the synthesis of amides and lactams has been developed using supercritical carbon dioxide as a ‘green’ replacement solvent. The amide products are generated from the addition of amines to ketenes, which are formed in situ from the retro-ene reaction of alkynyl ethers.

Thesis Supervisor: Rick L. Danheiser

Title: Professor of Chemistry
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Part I

Tandem Benzannulation-Ring Closing Metathesis Strategy for the Synthesis of Benzo-fused Nitrogen Heterocycles
Chapter 1 – Introduction and Background

The regioselective synthesis of highly-substituted and functionalized aromatic compounds is a challenging problem. Classical synthetic approaches to polysubstituted benzene derivatives typically involve multi-step processes based on the functionalization of an existing aromatic framework. Conventional methods used in this kind of strategy include electrophilic and nucleophilic aromatic substitutions, metatation-functionalization reactions, and cross-coupling reactions. In many cases, however, the synthetic utility of these approaches is limited, as achieving good chemoselectivity as well as regioselectivity becomes more and more difficult as the number of substituents present on the aromatic ring system increase.

Benzannulation strategies, on the other hand, provide a much more convergent and efficient route for the construction of polysubstituted aromatic frameworks, and these strategies often enable direct access to substitution patterns not easily available via more conventional methods. Benzannulation processes typically involve the combination of non-aromatic precursors in an event where two or more new carbon-carbon bonds are formed. The resulting aromatic ring is produced with a substitution pattern dictated by the functionality and structure of the starting materials used for the reaction.

Our laboratory has long been engaged in the development of methodology for the efficient synthesis of highly-substituted aromatic compounds. The aim of the research described in this thesis was the development of a general benzannulation strategy to synthesize amino-substituted aromatic compounds. A brief overview of some general annulation methods for the synthesis of highly-substituted benzene derivatives, with an emphasis on amino-substituted arenes, is presented in the next section.

---

2 This work was a continuation of research initiated by Aimee Crombie. See: Crombie, A. L. Annulation Strategies for the Synthesis of Azulenes and Polycyclic Nitrogen Heterocycles. Massachusetts Institute of Technology, Cambridge, MA, June 2004.
Annulation Strategies for the Synthesis of Polysubstituted Aromatic Systems

Many of the early methods developed for the regioselective synthesis of polysubstituted benzene derivatives were based on the condensation reactions of acyclic derivatives. One common approach involves a [3+3] annulation based on the combination of a dicarbanion equivalent with a dielectrophilic partner. An example of this strategy is shown in eq 1, in which the reaction of siloxyenone 1 with the Brassard diene 2 in the presence of TiCl₄ results in the formation of the salicylic acid derivative 3. Other condensation-based benzannulations include methods based on the Robinson annulation, as well as miscellaneous strategies often relying on Michael-type additions.

\[ \text{Me}_3\text{SiO} + \text{MeO} + \text{TiCl}_4 \rightarrow \text{MeO} + \text{OH} \]

The Diels-Alder cycloaddition is also a highly useful method for the assembly of substituted arenes, although in some cases the aromatic compound is not obtained directly and a subsequent aromatization step is required. Strategies involving cycloreversion as the final aromatization step include the Alder-Rickert reaction of alkynes with 1,3-cyclohexadienes and the [4+2] cycloaddition of α-pyrones with alkynes. Kočevar and co-workers have used the Diels-Alder reaction of 3-amino-substituted α-pyrones of type 4 with alkyne dienophiles to

---

prepare various highly-substituted aniline derivatives (eq 2). In this case, aromatization takes place by loss of CO₂ via the retro-Diels Alder reaction of the initial cycloaddition product, 6.

\[ \text{MeAcMeCo}_2 \text{MeaPh} + \ \text{Ph} \rightarrow \Delta \rightarrow \text{MeAcNHCOPh} \]  

Arenes can also be prepared using a [4+2] cycloaddition approach based on the reaction of furan derivatives with various dienophiles. In these Diels-Alder reactions, the aromatic ring system is formed via the ring-opening of the oxabicyclic cycloaddition product to form a cyclohexadiene adduct which can then be aromatized. For example, Padwa has introduced a [4+2] strategy involving the reaction of aminofurans with various dienophiles. Cycloaddition of aminofuran 8 with acrylonitrile is accomplished in refluxing benzene to form the oxabridged cycloadduct 9, which undergoes elimination under the reaction conditions to form the cyclohexadienol 10. Dehydration with BF₃·OEt₂ furnishes the aniline derivative 11 (eq 3).

\[ \text{CO}_2 \text{MeCN} \rightarrow \text{MeO₂C} \rightarrow \text{BF}_3 \cdot \text{OEt}_2 \]  

Our laboratory has developed a [4+2] strategy based on cycloadditions of alkynes with conjugated enynes. In the example shown in eq 4, the intramolecular cycloaddition of an enyne

---

[References]

with a benzyne leads to the direct formation of the polycyclic aromatic product \(14\).\(^{15,16}\) The reaction proceeds via the strained cyclic allene intermediate \(13\).

![Reaction diagram](image)

Numerous transition-metal catalyzed (or mediated) annulation processes have also been developed for the efficient and regioselective synthesis of highly substituted aromatic systems.\(^{17}\) The [2+2+2] cyclotrimerization of alkynes has proven to be a synthetically useful method and remains an area of interest for further developments.\(^{18}\) While the intermolecular version of this reaction suffers generally from poor regioselectivity, partially or fully intramolecular approaches have been shown by Vollhardt and others to be reliable and more widely applicable. For example, indoline \(17\) was synthesized by the Rh(I)-catalyzed [2+2+2] cycloaddition of alkynylamide \(15\) with acetylene \(16\) in 65% yield.\(^{19}\)

\[\text{Ph} \quad \text{Ph} \quad \text{cat. RhCl(PPh}_3)_3 \quad \text{to} \text{toluene, rt, 3 h} \quad \text{65\%} \quad \text{Ph} \quad \text{Ts} \quad \text{16} \quad \text{15} \quad \text{17}\]


\(^{16}\) For a recent review of this type of cycloaddition, see: Wessig, P.; Müller, G. Chem. Rev. 2008, 108, 2051.


Palladium-catalyzed [4+2] annulations of enynes with activated alkynes have also been investigated extensively for the regioselective synthesis of polysubstituted arenes.\textsuperscript{20} This reaction has been applied to the synthesis of anilines through the use of amino-substituted enynes such as 18 (eq 6).\textsuperscript{21} More recently, \(\pi\)-Lewis acidic metal-catalyzed [4+2] benzannulation reactions have also been developed.\textsuperscript{22}

\[
\begin{align*}
\text{Boc-} & \quad \text{NH} \\
& \quad \text{Me} \\
\text{18} & \quad + \\
& \quad \text{Me} \\
2 \text{ mol\% } \text{Pd}_2(\text{dba})_3\cdot\text{CH}_2\text{Cl}_2 & \quad \text{2 mol\% P(Ar)}_3, \text{ toluene, rt} \\
& \quad 60\% \\
& \quad \text{20} \\
\text{2 mol\% Pd}_2(\text{dba})_3\cdot\text{CH}_2\text{Cl}_2 & \quad \text{2 mol\% P(Ar)}_3, \text{ toluene, rt} \\
& \quad 60\% \\
\text{MeO} & \quad \text{MeO} \\
\text{Ar} & \quad \text{MeO} \\
\text{MeO} & \quad \text{MeO} \\
\end{align*}
\]

Despite these recent advances, the Dötz benzannulation reaction\textsuperscript{23} still stands out as the most general and highly regioselective transition-metal-catalyzed method for the synthesis of benzene derivatives, with numerous examples of applications in total syntheses.\textsuperscript{24} As shown in eq 7, a typical Dötz reaction involves the reaction of a chromium alkoxycarbene 21 with an alkyne 23 to form a chromium-complexed dienyketene intermediate, which undergoes electrocyclic ring-closure followed by decomplexation to give the annulation product 25. Aminocarbene complexes (22) have also been used but due to the strong donor effect of the nitrogen, these derivatives are generally less reactive and more prone to undergo a competitive cyclopentannulation reaction. The benzannulation reaction is more favorable when an \(N\)-
acylaminocarbene complex is used in which the donor properties of the nitrogen atom is reduced by the electron-withdrawing group.\textsuperscript{25}

\[
\begin{array}{c}
\text{R}^2 \text{C}^\varnothing \text{(CO)}_5 \\
\text{R}^1 \text{C}^\text{=CR}^3 \text{X} \\
\text{R}^2 \text{C}^\text{=CR}^4 \text{X} \\
\text{X} = \text{OR}, \text{NR}_2
\end{array}
\xrightarrow{23}
\begin{array}{c}
\text{R}^2 \text{C}^\text{(CO)}_4 \text{C}^\text{=CR}^3 \text{X} \\
\text{R}^1 \text{C}^\text{=CR}^4 \text{X} \\
\text{X} = \text{OR}, \text{NR}_2
\end{array}
\xrightarrow{24}
\begin{array}{c}
\text{R}^2 \text{C}^\text{(CO)}_4 \text{C}^\text{=CR}^3 \text{X} \\
\text{R}^1 \text{C}^\text{=CR}^4 \text{X} \\
\text{X} = \text{OR}, \text{NR}_2
\end{array}
\xrightarrow{25}
\end{array}
\]

Barluenga has recently found the alkenyl(amo)ncarbene chromium complex \textbf{26} with an electron-withdrawing group on the alkene to be a reliable partner in the Dötz benzannulation reaction. As shown in eq 8, reaction of \textbf{26} with excess 1-hexyne provided the aniline derivative \textbf{27} in excellent yield.\textsuperscript{26}

\[
\begin{array}{c}
\text{EtO}_2 \text{C} \\
\text{N}
\end{array}
\xrightarrow{4.0 \text{ equiv 1-hexyne}}
\begin{array}{c}
\text{Bu} \\
\text{CO}_2 \text{Et}
\end{array}
\xrightarrow{\text{THF, 60 °C}}
\begin{array}{c}
\text{OH}
\end{array}
\xrightarrow{\text{then SiO}_2}
\begin{array}{c}
\text{88%}
\end{array}
\]

Merlic and co-workers have developed a chromium carbene-mediated annulation method closely related to the Dötz reaction for the synthesis of substituted aminobenzene derivatives.\textsuperscript{27} As shown in eq 9, reaction of the Fischer carbene complex \textbf{28} with \textit{tert}-butyl isonitrile gives the dienylketenimine complex \textbf{29} which undergoes electrocyclization to the naphthalene adduct \textbf{30}.

\textsuperscript{25} Grotjahn, D. B.; Dötz, K. H. \textit{Synlett} 1991, 381.
In summary, the development of benzannulation reactions remains an area of intense interest. The next section will discuss in detail the benzannulation method developed in our laboratory.

**The Danheiser Benzannulation Strategy**

Our laboratory has developed an aromatic annulation strategy\(^\text{28,29}\) based on the reaction of cyclobutenones or \(\alpha\)-diazo ketones with activated alkynes. Our general strategy emerged from our laboratory at around the same time as the Dötz annulation and involves a pericyclic cascade culminating in the electrocyclization of a dienylketene intermediate to produce the aromatic compound. As depicted in Scheme 1, the annulation proceeds under the influence of heat or light through cascade process involving a sequence of 3 to 4 pericyclic reactions.


Vinylketene\textsuperscript{30} 35, generated either via the 4-electron electrocyclic cleavage of a cyclobutene\textsuperscript{28} (31) or from the photo-Wolff rearrangement of a diazo ketone\textsuperscript{29} (32), participates in a [2 + 2] cycloaddition\textsuperscript{31} with an activated alkyne 2\pi component 33 to form the vinylcyclobutene 36. Subsequent electrocyclic cleavage of 36 is followed by rapid six-electron electrocyclic ring closure and tautomerization to the polysubstituted aromatic compound 34.


'First Generation' Benzannulation Strategy

In the 'first generation' benzannulation reaction, the vinylketene intermediate is generated from a cyclobutenone either under thermal or photochemical conditions. The reactivity of the vinylketene in the initial [2 + 2] cycloaddition varies depending on the substitution pattern of the cyclobutenone. 3-Substituted cyclobutenones (e.g., 39) undergo electrocyclic opening at ca. 80 °C, as confirmed by trapping experiments with amines and vinylketenes of type 41 typically react with alkynes smoothly at this temperature. However, elevated temperatures are typically required for [2 + 2] cycloaddition involving 'ketoketenes' such as 42 that are generated from 2-substituted cyclobutenones (e.g., 40).

![Chemical structures](image)

The benzannulation with alkynyl ethers under thermal conditions is limited to alkynyl ethers that lack β-hydrogens, otherwise the alkynes undergo retro-ene reaction to form ketenes. Trialkylsiloxyalkynes are useful alternatives for the preparation of resorcinol derivatives, as the harsh conditions often required for methyl ether cleavage can be avoided. Also, other activated alkynes such as alkynyl thioethers participate readily in the benzannulation reaction and can serve as a surrogate for the unactivated alkynyl. For example, as shown in eq 11,

---

37 Unactivated alkynes can react with 4,4-dichlorocyclobutenones to give mixtures of monochloro- and dichlorophenols, see: Kowalczyk, J. J. Annulation Approaches to Highly Substituted Aromatic Compounds. Massachusetts Institute of Technology, Cambridge, MA, June 1988.
benzannulation with 45 results in the thiophenol 46, which can be desulfurized via treatment with excess Raney Ni to give phenol 47.

\[
\begin{align*}
\text{CH}_3 & + \text{H}_3\text{C} & \xrightarrow{120^\circ\text{C}, \, 73 \, h, \, \text{CHCl}_3} & \xrightarrow{73\%} \text{OH} \text{H}_2\text{O} & \xrightarrow{\text{xs Raney-Ni}} & \xrightarrow{99\%} \text{OH} \text{H}_3\text{C} \\
\text{SCH}_3 & & & \text{CH}_3 & & \text{CH}_3 \\
45 & & & 46 & & 47
\end{align*}
\]

Several total syntheses\(^{36, \, 38}\) have been accomplished using the first generation benzannulation strategy. For example, in 2000 our laboratory reported the completion of a total synthesis of ascochlorin.\(^{38d}\) The key benzannulation reaction involved an advanced intermediate, benzyloxy alkynyl ether 48, and cyclobutenone 49 (Scheme 2). Reaction under photochemical condition provided the substituted aromatic product 50 in 71% yield. From this intermediate only three subsequent steps were needed to complete the synthesis. In this case, photochemical conditions were best suited for the benzannulation as the benzyloxy alkyne moiety is thermally sensitive towards [3,3] sigmatropic rearrangement. The reaction mixture was heated at reflux briefly following irradiation with a Hanovia mercury lamp to complete conversion of remaining vinylcyclobutenone intermediate to the annulation product 50.

Scheme 2

Second Generation Benzannulation

In 1990, our laboratory reported a new variant of the benzannulation strategy, in which α-diazo ketones were utilized as the vinylketene precursor. This development extended the scope of the method to include the synthesis of polycyclic aromatic compounds as well as heterocyclic derivatives which were previously not readily accessible using the cyclobutenone-based strategy. For the benzannulation, the requisite vinyl- and (het)arylketenes were generated in situ via photo-Wolff rearrangement of the corresponding α-diazo ketones. For example, the marine natural product hyellazole (54) was synthesized from diazo ketone 52 in three steps (Scheme 3).

---

The carbazole framework of hyellazole was formed by irradiating a solution of 38 and 52 followed by heating at reflux. As in the ascochlorin synthesis described previously, this photochemical benzannulation also requires heating after the irradiation in order to convert some remaining vinylcyclobuteneone intermediate to the annulation product. Triflation of carbazole 53 followed by Stille cross coupling with concomitant BOC deprotection then furnished hyellazole (54).

Other natural product syntheses have since been completed using this variation of the benzannulation strategy. This method has been particularly effective in the construction of diterpene natural products.41

**Liebeskind and Moore Benzannulation Strategies**

Liebeskind42 and Moore43 have independently reported a general method for the synthesis of substituted quinone derivatives. The final steps in the mechanism of their reaction involves

---

the generation and electrocyclization of a dienylketene analogous to the final steps in our pericyclic cascade. The first step of their general strategy involves the addition of a vinyl or aryllithium reagent 56 to a squaric acid derivative 55 to form a 4-vinyl or 4-aryl substituted cyclobutenone 57. Thermolysis of 57 then produces the dienylketene intermediate 58 which cyclizes to give a hydroquinone adduct. Subsequent oxidation provides the substituted quinone 59.

Mechanism of the Benzannulation Reaction

As outlined earlier in this chapter, the benzannulation reaction mechanism proceeds through a vinylcyclobutenone intermediate, which under some conditions can be isolated. As shown in eq 13, the thermal four-electron electrocyclic ring opening of 36 can provide the desired dienylketene 37, which rapidly undergoes further reaction to the annulation product. However, the electrocyclic cleavage of 36 can alternatively also produce the stereoisomeric dienylketene 60, which would not be able to cyclize to form an aromatic compound.

---

Studies by Houk and coworkers have shown that the torquoselectivity of the 4-electron electrocyclic ring-opening of cyclobutenones is influenced by the nature of the substituent at the C-4 position. Calculations showed that electron withdrawing substituents at C-4 rotate outwards, while electron donor substituents at that position rotate inwards. Houk rationalizes this effect in terms of orbital interactions in the transition state. Specifically, the inward rotation of a donor group provides stabilization of the LUMO σ* antibonding orbital of the breaking bond, thus lowering the activation energy of this process. The outward rotation of an acceptor substituent possessing low-lying orbitals provides a stabilizing overlap with the HOMO of the breaking bond, which leads to the lowering the activation energy.

In general, experimental observations correlate well with these predictions. For example, Baldwin showed that the trapping of the vinylketene produced by the thermal and photochemical electrocyclic reactions of cyclobutenone 61 provided esters 62 and 63, respectively (Scheme 4). Under thermal conditions, the outward rotation of the electron-accepting chlorine atom results in the \( E \) geometry observed in 62.

Interestingly, for the vinylcyclobuteneone intermediates generated by our method, the distinction between the electronic contributions of the two substituents at C-4 is not as clear-cut. With regard to the key benzannulation reaction used in our laboratory’s total synthesis of salvilenone, Houk has suggested that torquoselectivity predicts the outward rotation of the

---

47 Baldwin, J. E.; McDaniel, B. L. J. Am. Chem. Soc. 1968, 90, 6118.
somewhat more strongly donating aryl group to form 64 as the major product (eq 13). In this case, however, the benzannulation adduct is obtained in 70% yield. 

\[
\begin{align*}
\text{(i-Pr)}_3\text{SiO} & \quad \text{Br} & \quad \text{OSi(i-Pr)}_3 \\
\text{Br} & \quad \text{OSi(i-Pr)}_3 & \quad \text{Br}
\end{align*}
\]

A possible explanation for the good yield obtained in this benzannulation reaction is that the electrocyclic ring opening process is reversible, so that any unproductive dienylketene isomer 64 that is formed can convert back to the vinylcyclobutenone 65, while any 66 that is formed is quickly consumed by electrocyclization to give the annulation product. Vinylketenes are known to undergo electrocyclic ring closure to cyclobutenones. For example, Snider has found that the \( \alpha \)-substituted vinylketene 68, generated by via dehydrohalogenation of the acid chloride 60, undergoes electrocyclic ring-closure to form the 2,3-cyclobutenone 69 in 56% yield (Scheme 5). 

\[\text{Me} \quad \text{Me} \quad \text{I} \quad \text{Et}_3\text{N} \rightarrow \text{Cl} \quad \text{Me} \quad \text{Me} \quad \text{O} \quad \text{Me} \quad \text{O} \]

\[\begin{align*}
\text{toluene} & \quad 110 \degree \text{C} & \quad 3 \text{h} \\
\text{67} & \quad \text{68} & \quad \text{69} \\
\text{125-130 \degree \text{C} toluene, 4 d} & \quad 76\%
\end{align*}\]

\[\text{Me} \quad \text{O} \quad \text{Me} \quad \text{O} \]

The electrocyclic ring-opening of 69 was found to be reversible at higher temperatures. Heating a solution of 69 in a sealed tube resulted in the eventual formation of the intramolecular [2 + 2] cycloaddition adduct 70. Moore and co-workers have also reported examples of a reversible electrocyclc ring-opening of 4-aryl-4-hydroxycyclobutene.\(^{49}\)

**The Use of Ynamines - Synthesis of Amino-Substituted Benzene Derivatives**

As discussed in the previous section, oxygen- as well sulfur-activated alkynes are useful participants in the benzannulation reaction, providing access to resorcinol and phenolic aromatic compounds. The use of nitrogen-activated alkynes in the benzannulation reaction would provide a method for preparing highly substituted aniline derivatives. Early work in our laboratory did in fact explore the use of ynamines. In general, ynamines are highly reactive, electron-rich compounds which are able to react with a number of electrophilic partners.\(^{50}\) Their high reactivity is exemplified in the example shown in eq 15, where under thermal conditions, dialkylynamine 72 reacts smoothly with trisubstituted cyclobutenone 71 to give the hexa-substituted aniline adduct 73. Similar attempts to use the cyclobutenone 71 in an annulation with 1-methoxyoctyne under the same conditions provided the corresponding benzannulated adduct in only 33% yield, despite prolonged reaction times.\(^{28}\)

![Reaction of ynamine 72 with 3-methylcyclobutenone (39) under similar conditions](image)

<table>
<thead>
<tr>
<th>Ynamine</th>
<th>Cyclobutenone</th>
<th>Adduct</th>
</tr>
</thead>
<tbody>
<tr>
<td>72</td>
<td>71</td>
<td>73</td>
</tr>
</tbody>
</table>

Reaction of ynamine 72 with 3-methylcyclobutenone (39) under similar conditions also provides the desired aniline 74 in good yield; however, in this case an allenamide byproduct 75 was also isolated (Scheme 6).\(^{44}\) Under milder thermal conditions, the intermediate

---


vinylcyclobutenone 76 can be obtained and converted at elevated temperatures directly to 74 in near quantitative yield.

Moore has also reported the thermal conversion of a 3-aminosubstituted cyclobutenone to an aniline derivative (77→78, eq 16).\textsuperscript{51}

Similarly, Liebeskind and co-workers have prepared 3-amino-4-hydroxycyclobutenones substrates and used them to synthesize amino-substituted aromatic compounds.\textsuperscript{52} For example, as shown in eq 17, the thermolysis of cyclobutenone 79 provided the tetrahydroquinolinequinone derivative 80 in 89% yield.


Eq 18 illustrates another example of an ynamine benzannulation from our laboratory. Under photochemical conditions, the aniline adduct 83 is formed in 41% yield, accompanied by ca. 5% of amide byproduct 84.\textsuperscript{33}

The formation of this unusual byproduct, as well as the allenamide 75 from the thermal ynamine benzannulation described previously (Scheme 6) was not surprising, as similar observations were made in prior studies of the reaction between ynamines and ketenes.\textsuperscript{53} For example, Ghosez and Delaunois reported that diphenylketene reacts with diethylaminopropyne to afford the allenamide 87 as the sole product in 74% yield (eq 19a).\textsuperscript{53b}

Battaglia has also observed the formation of an allenamide byproduct, in this case from the reaction of methylvinylketene with diethylaminopropylene (eq 19b).\textsuperscript{53k}

\[
\begin{align*}
\text{H}_3\text{C} & \quad \text{CHCl} \\
& \quad \text{Et}_3\text{N} \\
0 \, ^\circ \text{C}, \text{CCl}_4 & \quad \xrightarrow{\text{Me},\text{O}} \\
& \quad \text{Et}_2\text{N} \\
\end{align*}
\]

These interesting adducts are produced as a consequence of the strongly nucleophilic and electron-rich character of ynamines. The [2 + 2] cycloaddition of ynamines with ketenes occurs through a dipolar, rather than a concerted, mechanism, in which initial addition of the ynamine to the ketene proceeds in a stepwise manner.\textsuperscript{53} This is likely also the case in our the benzannulation reactions. As outlined in Scheme 7, the initial stepwise reaction between ynamine 82 and the vinylketene generated from cyclobutenone 81 produces the zwitterionic intermediate 88. This intermediate 88 can then proceed through three alternative reaction pathways: (a) collapsing to the strained oxete 89, (b) cyclizing to the cyclobutenone 90, or (c) cyclizing directly, in the case of this substrate, to the aniline 83. The allenamide 91 is formed via 4π-electrocyclic ring-opening of the oxete 89. Further reaction of allenamide 91 with another equivalent of ynamine 82 either via a direct Michael-type addition or a cycloaddition provides the amide 84.

In addition to the formation of allenamide byproducts, another concern if a stepwise mechanism is occurring, is that a different regioisomeric product would form (e.g., 88→83). As compared to the product obtained from the concerted pericyclic cascade sequence (Figure 1), this regiosomer would have the substituents at R\textsuperscript{2} and R\textsuperscript{4} reversed.
A further example of the interesting reactivity of ynamines was documented by Ficini in 1977. At low temperatures, the ynamine 94 reacted with cyclobutenone 93 to give the vinylcyclobutenone adduct 95, which upon thermolysis provided aniline 96. Deuterium labelling of the C-Me group of the ynamine provided the basis for the structure assignment as shown.

Scheme 8

\[
\begin{align*}
\text{Me} & \quad \text{NiEt}_2 \\
\text{Me} & \quad \text{Et}_2\text{O}, -50^\circ\text{C}, 30\text{ min} \\
\text{Me} & \quad 140^\circ\text{C} \\
\text{Me} & \quad \text{SMe} \text{D}_3 \text{O} \\
\text{Me} & \quad \text{CD} \text{t} 55\% \\
\end{align*}
\]

Ficini proposed that the initial addition of ynamine 94 to cyclobutenone 95 forms the strained bicyclic adduct 97, which then undergoes a concerted rearrangement to the vinylcyclobutenone 95. Interestingly, the aniline 96 obtained from the thermolysis of 95 possesses an alternative regiochemistry to what would be expected from a fully concerted pericyclic cascade process, as detailed for our benzannulation (vide infra) (Figure 2).

Figure 2

<table>
<thead>
<tr>
<th>&quot;Pericyclic Product&quot;</th>
<th>&quot;Ficini Product&quot;</th>
</tr>
</thead>
<tbody>
<tr>
<td><img src="image1" alt="Pericyclic Product" /></td>
<td><img src="image2" alt="Ficini Product" /></td>
</tr>
</tbody>
</table>

Thus, while ynamines participate as 2π components in our annulation strategy to give the desired substituted aniline derivatives, the formation of certain byproducts suggests that the annulation mechanism could be non-concerted. In conjunction with Ficini’s peculiar result, this places some concern as to the overall regiochemical integrity of our benzannulation, when ynamines are employed as the 2π component.

Furthermore, there are limitations with regard to yamine synthesis, handling, and storage. Due to the strong electron-donating effect of the nitrogen, reaction with electrophiles
is rapid. Ensuing nucleophilic attack on the reactive keteniminium is quite likely, leading to undesired decomposition and polymerization processes (eq 20).

\[
\begin{align*}
\text{R}^1 \quad \text{N} \quad \text{R}^3 \\
\text{R}^2 \\
\end{align*}
\xrightarrow{\text{Hydrolysis}}
\begin{align*}
\text{R}^1 \quad \text{O} \quad \text{N=CO} \quad \text{R}^3 \\
\text{R}^2 \\
\end{align*}
\text{Decomposition} (20)

However, recent advances have been made towards the preparation of a class of more stable ynamines – ynamides. Placement of an electron withdrawing group on the nitrogen of the ynamine serves the purpose of attenuating its overall strong donor effect, leading to improved stability, while maintaining an adequate degree of reactivity. The preparation of ynamides will be discussed in the next section.

The Synthesis of Ynamides

In recent years, several practical and general methods for the synthesis of ynamides have been developed. These approaches specifically involve the transition metal-mediated formation of the C(sp)-N bond of the ynamide.\(^{55,56}\)

In 2003, Hsung and Danheiser independently reported protocols for the copper-mediated N-alkynylation of amides. In their preliminary communication, Hsung and co-workers disclosed conditions employing the use of catalytic CuCN in the presence of a diamine ligand, at elevated temperatures (eq 21).\(^{57}\) Under these conditions, oxazolidinones coupled efficiently to alkynyl

---


\(^{56}\) Alkynyliodonium salts have also been used for the synthesis of ynamides via the C(sp)-N bond disconnection. However, a lack of generality and the overall expense and effort associated with the preparation of alkynyliodonium salts limits the use of this method. See: (a) Witulski, B.; Stengel, B. L. *Angew. Chem., Int. Ed.* **1998**, 37, 489. (b) Feldman, K. S.; Bründl, M. M.; Schildknegt, K.; Bohnstedt, A. C. *J. Org. Chem.* **1996**, 61, 5440. (c) Murch, P.; Williamson, B. L.; Stang, P. *J. Synthesis*, **1994**, 1255.

bromides. However, reaction with other amide derivatives such as acyclic carbamates, sulfonamides, lactams, and ureas generally resulted in lower yields due to poor conversion.

Concurrently, our laboratory reported an alternative milder N-alkynylation method using stoichiometric CuI, in which sulfonamides, cyclic and acyclic carbamates, and ureas all were able to couple efficiently with various alkynyl bromides and iodides at room temperature. For example, allyl carbamate 101 was coupled to the bromo dialkyne 102 to give diynamide 103 in 73-74% yield (eq 22).

In 2004, Hsung reported a ‘second generation’ protocol for the synthesis of ynamides utilizing catalytic CuSO₄·5H₂O and 1,10-phenanthroline. This new procedure addressed the limitations of the earlier method and expanded the scope of the reaction to allow a wider spectrum of amides, including some nitrogen heterocycles, to be effectively coupled to a variety of alkynyl bromides (eq 23).

---

10 mol% $\text{CuSO}_4 \cdot 5\text{H}_2\text{O}$

20 mol% 1,10-phenanthroline

2.0 equiv $\text{K}_2\text{CO}_3$, toluene, 60-65°C

18-36 h

92%

Subsequently, in 2005, Tam and co-workers reported an alternative, modified procedure for the preparation of ynamides,\textsuperscript{61} based on the combination of the protocols developed by Hsung and our laboratory. KHMDS was used as the base and was added slowly (over 3-4 h) to the reaction which was driven by catalytic CuI and 1,10-phenanthroline in toluene at 90 °C (eq 24).

Tam was motivated to introduce this variant following difficulties encountered in reproducing results previously reported by our laboratory and also that of Hsung. We have identified the experimental variable which might be responsible for some of Tam’s unsuccessful results. Specifically, the quality of pyridine used in our reactions greatly effects the outcome. The use of freshly distilled pyridine from CaH₂, as recommended in our original communication,\textsuperscript{58} is key. Use of pyridine that had been distilled but exposed to the atmosphere for several days resulted in no reaction.\textsuperscript{59}

Earlier this year, a new N-alkynylation approach to ynamides was reported by Stahl.\textsuperscript{62} The direct amidation of terminal alkynes was made possible using Cu(II)-catalyzed oxidative coupling conditions with atmospheric O₂ as the stoichiometric oxidant, providing a more efficient route to ynamides. This method thus avoids the need for haloalkynes as intermediates. However, the Stahl protocol requires the use of an excess amount of the nitrogen component, among which cyclic carbamates, amides, and ureas provided the desired ynamide in high yields. Sulfonamides were also amenable towards coupling, as were indoles with an electron


withdrawing substituent at the 2 or 3 position (eq 25). Unfortunately, acyclic carbamates and amides showed no reactivity in this amidation reaction.

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{5.0 equiv} & \quad 109
\end{align*}
\]

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{2.0 equiv pyridine} & \quad 2.0 \text{ equiv } \text{CuCl}_2 \\
\text{2.0 equiv Na}_2\text{CO}_3 & \quad \text{O}_2 \text{ (atm), toluene, 70 °C, 4 h} \\
\text{TBSO} & \quad 110
\end{align*}
\]

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{H} \\
\text{N} & \quad \text{H} \\
\text{20 mol%} & \quad 111
\end{align*}
\]

81%

With the development of these general and convenient methods for preparing ynamides, there have been an increasing number of reports on their applications in synthesis in recent years, showcasing the synthetic versatility of these compounds. For example, in recent work from our laboratory, indoline 113 was prepared from the corresponding enynamide 112, via a thermally driven intramolecular [4+2] cycloaddition process (eq 26).

\[
\begin{align*}
\text{MeO}_2\text{C} & \quad \text{Me} \\
\text{SiMe}_3 & \quad \text{Me} \\
\text{1.0 equiv BHT} & \quad 1.0 \text{ equiv BHT} \\
\text{tcl (0.05 M)} & \quad 110 \degree \text{C, 16 h} \\
\text{86%} & \quad 86%
\end{align*}
\]

A Tandem Ynamide Benzannulation-Cyclization Strategy for the Synthesis of Nitrogen Heterocycles

As discussed at the beginning of this chapter, our aim was to develop a general benzannulation method to synthesize amino-substituted aromatic compounds. Early work in our


laboratory established the use of ynamines as a means to deliver the nitrogen substituent to the aromatic ring; however, as discussed, several limitations are associated with the use of these compounds. Consequently, we sought to explore the use of more stable ynamide derivatives in the benzannulation reaction.

In particular, with the advent of practical methodology for the synthesis of diversely functionalized ynamides, we became interested in extending our benzannulation strategy beyond the synthesis of simple aniline derivatives. The development of methods for the synthesis of benzo-fused heterocycles is an area of particular importance, as these types of ‘privileged structures’ are prevalent in many bioactive natural products and pharmaceuticals. By integrating a tandem cyclization step in sequence with the benzannulation reaction, benzo-fused nitrogen heterocycles can be directly constructed (eq 27).

![Diagram](image)

The overall facility in which a diverse array of functionalized ynamides can be synthesized is a particularly attractive feature of this tandem-ring forming strategy, as a number of different cyclization methods can potentially be employed. The benzannulation reaction allows for the modular synthesis of aromatic derivatives and so the pairing of this reaction with an equally versatile and general cyclization method would create a practical platform for the synthesis of libraries of nitrogen heterocycles.

Preliminary studies on the use of ynamides in the benzannulation reaction was initiated by Aimee Crombie. Specifically, this work focused on the use of ynamides equipped for implementation of a tandem ring-closing metathesis cyclization strategy. Further advances in

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66 For a review on the synthesis of benzo-fused medium ring nitrogen heterocycles, see: Majhi, T. P.; Achari, B.; Chattopadhyay, *P. Heterocycles* 2007, 71, 1011.
the synthesis of nitrogen heterocycles using this strategy will be discussed in detail in the next chapter.
Chapter 2 – ‘First Generation’ Tandem Benzannulation-Ring Closing Metathesis Strategy

As discussed in the previous chapter, the convergent synthesis of highly-substituted aromatic systems can be accomplished using the benzannulation reaction developed in our laboratory. With the recent development of convenient methods to synthesize highly-functionalized ynamides, we recognized an opportunity to use the aromatic annulation in tandem with various cyclization reactions to construct libraries of different benzo-fused nitrogen heterocycles.

Ring-closing metathesis (RCM) is a powerful and reliable tool for constructing carbocyclic and heterocyclic ring systems, and has been used in an enormous number of different applications in organic synthesis. The use of RCM in tandem with our benzannulation strategy could potentially provide rapid access to a variety of nitrogen heterocycles. As shown in Scheme 9, dihydroquinoline, benzazepine, and benzazocine derivatives (117-119) would be readily accessible in only two steps starting from an appropriately functionalized ynamide 121.

Scheme 9

Benzannulation using a cyclobutenone of type 31 with an appropriately substituted ynamide 121 would provide anilines of type 120, and the desired benzo-fused heterocycles could then be formed directly via RCM. Although ring-closing metathesis has been used previously in a similar fashion to form benzo-fused nitrogen heterocycles, we believed that our benzannulation strategy would provide a uniquely powerful means to access RCM aniline substrates with a high level of substitution on the benzenoid ring.

The development of this tandem strategy will be discussed over the course of this chapter, beginning in the next section with the preparation of the ynamide substrates.

**Preparation of Ynamides**

As shown in Table 1, the series of ynamides (128-135) used in our benzannulation-RCM studies were synthesized using the N-alkynylation protocol previously developed in our laboratory. Carbamates 101 and 122 were prepared by treatment of allylamine and methylamine with methyl chloroformate. Homoallyl carbamate 123 was conveniently prepared via the Curtius rearrangement of 4-pentenoic acid using diphenylphosphorylazide (DPPA). The iodo- and bromoalkyne coupling partners 99 and 124-127 were synthesized from terminal alkynes under mild conditions with NBS or NIS in the presence of cat. AgNO₃ following the method of Hofmeister, and were purified either via distillation or column chromatography and stored in solution at -18 °C. In general, the bromoalkynes can be stored over several months with

---


69 Ynamides 129, and 131-133 were first synthesized by Aimee Crombie, see ref. 2.

70 Carbamate 101 was prepared according to Ref. 59.

71 Carbamate 123 was prepared following the general method of Capson, T. L.; Poulter, D. C. Tetrahedron Lett. 1984, 25, 3515.


73 For details on the preparation of haloalkynes 124-127 see the following: (a) 124: Prepared according to Amatore, C.; Blart, E.; Genêt, J. P.; Jutand, A.; Lemaire-Audoire, S.; Savignac, M. J. Org. Chem. 1995, 60, 6829. (b) 125: See the Experimental Section. (c) 126: Ref. 58. (d) 127: See the Experimental Section.

negligible decomposition, with the exception of allyl-substituted bromoalkyne 125 and conjugated bromoalkyne 126 which were less stable and were used within a few weeks of preparation.

The use of our milder N-alkynylation method was preferred, especially when performing the coupling reaction with the volatile and sensitive bromoalkynes 125 and 126. The use of Hsung's N-alkynylation method, which requires elevated temperatures, resulted in no or little product in the case of the allyl-substituted bromoalkyne 125. Also, iodoalkynes can be coupled using our method (Table 1, entry 2 and 7), which is convenient when the preparation and purification of the iodoalkyne (e.g., 124) is much easier compared to bromoalkyne analog.

75 For a comparison study of our method (Ref. 58 and 59) and Hsung's (Ref. 60) N-alkynylation method, see: Dunetz, J. R. "I. Synthesis of Indolines and Indoles via Intramolecular [4+2] Cycloaddition of Ynamides and Conjugated Enynes. II. Synthesis of Nitrogen Heterocycles in Supercritical Carbon Dioxide." Massachusetts Institute of Technology, Cambridge, MA, September 2005.

76 The bromoalkyne analog of 124 is fairly volatile and attempts to prepare it by treatment of (trimethylsilyl)acetylene with NBS/cat. AgNO₃ resulted in multiple unidentified products.
Table 1. Preparation of Ynamides

<table>
<thead>
<tr>
<th>entry</th>
<th>carbamate</th>
<th>halo alkyne</th>
<th>ynamide</th>
<th>yield (%)(^a)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>122</td>
<td>99, (R^1 = \text{Me})</td>
<td>(X = \text{Br}, R^2 = \text{Hex})</td>
<td>61(^b)</td>
</tr>
<tr>
<td>2</td>
<td>122</td>
<td>124, (R^1 = \text{Me})</td>
<td>(X = \text{I}, R^2 = \text{SiMe(_3)})</td>
<td>64(^b)</td>
</tr>
<tr>
<td>3</td>
<td>101</td>
<td>125, (R^1 = \text{CH}_2\text{CH=CH}_2)</td>
<td>(X = \text{Br}, R^2 = \text{CH}_2\text{CH=CH}_2)</td>
<td>44</td>
</tr>
<tr>
<td>4</td>
<td>101</td>
<td>126, (X = \text{Br}, R^2 = \text{C(CH}_3\text{)=CH}_2)</td>
<td>49</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>123</td>
<td>125, (R^1 = \text{(CH}_2\text{)}_2\text{CH=CH}_2)</td>
<td>(X = \text{Br}, R^2 = \text{CH}_2\text{CH=CH}_2)</td>
<td>52</td>
</tr>
<tr>
<td>6</td>
<td>123</td>
<td>126, (X = \text{Br}, R^2 = \text{C(CH}_3\text{)=CH}_2)</td>
<td>68(^b)</td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>101</td>
<td>124, (X = \text{I}, R^2 = \text{SiMe(_3)})</td>
<td>58</td>
<td></td>
</tr>
<tr>
<td>8</td>
<td>101</td>
<td>127, (X = \text{Br}, R^2 = \text{CH}_2\text{CH(OTBS)CH=CH}_2)</td>
<td>49</td>
<td></td>
</tr>
</tbody>
</table>

\(^a\) Isolated yield of products purified by column chromatography on silica gel. \(^b\) Kohnen, A. L.; Mak, X. Y.; Lam, T. Y.; Dunetz, J. R.; Danheiser, R. L. *Tetrahedron* 2006, 62, 3815.
Other ynamide derivatives can be prepared through elaboration of terminal ynamides via cross-coupling\textsuperscript{77} or alkylation reactions. The terminal ynamides themselves are available via the desilylation of silyl-substituted ynamides. For example, as shown in eq 28, ynamide 129 was desilylated using K\textsubscript{2}CO\textsubscript{3} in MeOH to give terminal ynamide 136 in 70\% yield.

\[
\text{Me}_3\text{Si} - \text{N} - \text{MeO}_2\text{C} \xrightarrow{1.5 \text{ equiv } K_2\text{CO}_3} \text{Me}_3\text{Si} - \text{N} - \text{H} \quad (28)
\]

Two reports in the literature have appeared previously describing the alkylation of ynamides. Hsung has reported conditions for the alkylation of an oxazolidinone-based ynamide with MeI, using LHMDS as the base.\textsuperscript{57} Witulski was also able to methylate a sulfonamide-based ynamide, using KHMDS as the base.\textsuperscript{78} We have also successfully alkylated several terminal ynamides. For example, ynamide 139 was obtained in good yield following the protocol of Hsung\textsuperscript{60} (Scheme 10), and desilylated with TBAF to afford the terminal ynamide, which was alkylated with MeI using Witulski’s method to give ynamide 140.

\textbf{Scheme 10}

\[
\begin{align*}
\text{Me}_3\text{Si} - \text{N} - \text{H} \xrightarrow{\text{cat. CuSO}_4\cdot 5\text{H}_2\text{O}} & \xrightarrow{\text{cat. 1,10-phenanthroline}} \text{Me}_3\text{Si} - \text{N} - \text{Si(i-Pr)}_3 \\
\text{Me}_3\text{Si} - \text{N} - \text{H} \xrightarrow{1.2 \text{ equiv } \text{Br} - \text{Si(i-Pr)}_3} & \text{Me}_3\text{Si} - \text{N} - \text{H} \\
\text{Me}_3\text{Si} - \text{N} - \text{H} \xrightarrow{1) \text{TBAF}, \text{THF}, -40 \degree\text{C} \rightarrow \text{rt}, 1 \text{ h} 86\%} & \text{Me}_3\text{Si} - \text{N} - \text{H} \\
\text{Me}_3\text{Si} - \text{N} - \text{H} \xrightarrow{2) \text{KHMDS, MeI, THF, -78} \rightarrow 0 \degree\text{C}, 3 \text{ h} 90\%} & \text{Me}_3\text{Si} - \text{N} - \text{H}
\end{align*}
\]


\textsuperscript{78} Witulski, B.; Lumtscher, J.; Bergsträsser, U. \textit{Synlett} \textbf{2003}, \textit{708}.
In an effort to develop an alternative route to ynamide 132, we attempted to alkylate the terminal ynamide 141 with allyl bromide. Unfortunately, decomposition of 141 was observed during deprotonation with LiHMDS or KHMDS. We were able to alkylate 141, however, by using the general conditions developed by Jeffery for the Cu-catalyzed allylation of terminal alkynes (eq 29).⁷⁹ Although this approach did produce the desired ynamide, it was contaminated with an inseparable impurity and this route was not pursued further since this ynamide was available via the N-alkynylation approach beginning with commercially available allylacetylene (see Table 1).

Scheme 11 shows the successful propargylation of an ynamide using conditions developed by Spinella and coworkers for the preparation of skipped diyynes from terminal alkynes.⁸⁰ Thus, treatment of terminal ynamide 142 with 3-(trimethylsilyl)propargyl bromide in the presence of NaI, Cs₂CO₃ and CuI provided the skipped diynamide 143 in 54-60% yield (Scheme 11).

---

[2 + 2] Cycloaddition of Ynamides with Ketenes

Based on our interest in using ynamides in the benzannulation strategy, we first decided to examine the reactivity of these compounds in [2 + 2] cycloadditions with several simple classes of ketenes. One initial objective in this study was to confirm our prediction that the use of ynamides would suppress the formation of the allene byproducts that were produced in the reaction with ynamines.

The reaction of ketene generated by the pyrolysis of acetone in a Hurd ketene generator was examined first. When ketene was bubbled into a solution of ynamide, 3-aminocyclobutenone was obtained in excellent yield, with no evidence of any significant byproducts (Scheme 12).

In a similar fashion, ynamide reacted with dichloroketene (generated via reductive dechlorination of trichloroacetyl chloride with zinc-copper couple) to afford 3-aminocyclobutenone in excellent yield. The reactions of other ketenes such as phenylthioketene and dimethylketene in [2 + 2] cycloadditions with 128 were also successful, and in all of these cases no allene byproducts were observed.

---

The scope of the reaction of ketene with a variety of ynamides was also examined. As shown in Scheme 13, terminal ynamide 136 reacts with ketene to give 3-aminocyclobutenone 146 in excellent yield. Of particular interest to us was the [2 + 2] cycloaddition of ketene with ynamide 133, which provided the cyclobutenone 147 in good yield. The addition of the ketene occurs chemoselectively at the nitrogen-activated triple bond, and not at the conjugated or terminal double bonds. Interestingly, the [2 + 2] cycloaddition of 133 with ketene was relatively sluggish compared to several other ynamides, requiring a longer reaction time and also the absence of solvent. We believe that the ketenophilicity of this ynamide is reduced by the inductive effect of the sp$^2$ alkenyl substituent.

During this study, we also compared the relative rate of the [2 + 2] cycloaddition of ketene with 1-ethoxyoctyne vs. ynamide 128. As discussed in the previous chapter, alkoxy- and siloxyacetylenes are excellent participants in the benzannulation reaction and in [2 + 2] cycloadditions with ketenes. Ynamide 128 was found to react at a similar, though slightly slower rate compared to 1-ethoxyoctyne.

Using the [2 + 2] cycloaddition of ketenes with ynamides, we were able to synthesize a family of 3-aminocyclobutenones. 3-Alkoxysubstituted cyclobutenones have previously been used in aromatic annihilations to synthesize phloroglucinol derivatives. We anticipated that

---

these 3-aminocyclobutenones can be used in our benzannulation reaction as a means to generate bis-aniline derivatives (vide infra).

**Benzannulation of Ynamides with Cyclobutenones**

*Feasibility of the Benzannulation with Ynamides*

The feasibility of employing ynamides in the benzannulation reaction with ynamides was initially investigated using 3-butylcyclobutenone (81) and 128 as test substrates. 2

As shown in Scheme 14, the benzannulation of ynamide 128 with a slight excess (1.2 equiv) of cyclobutenone 81 proceeds very efficiently under both thermal (including microwave) and photochemical conditions. In our prior work using cyclobutenone 81 and alkoxyacetylenes, reaction temperatures of 80°C were sufficient to drive the benzannulation reaction, which was also the case here. We observed that all of the cyclobutenone was consumed after reaction at 80 °C for 1.5 h, at which point a significant portion of the reaction mixture consisted of the vinylcyclobutenone intermediate 149. Key 1H NMR spectral characteristics of 149 (as well as that of related vinylcyclobutenones) include the two terminal olefin singlet peaks at δ 4.9 and 4.8 ppm and the C-4 proton singlet at δ 4.2 ppm. Strong IR stretches at 1738 cm⁻¹ and 1600 cm⁻¹ are also particularly indicative of the vinylcyclobutenone. The intermediate 149 is rapidly converted to the annulation product 148 at 110 °C (Scheme 15). By carrying out the reaction in refluxing toluene from the start, the benzannulation can be completed in 1 h.
Our ability to isolate samples of the vinylcyclobutenone 149 provided an opportunity to investigate stereochemical aspects of the key electrocyclic ring opening step involving these intermediates in the benzannulation cascade. As discussed previously (see Chapter 1), the electrocyclic cleavage of 4-vinylcyclobutenones is predicted by Houk to afford mixtures of stereoisomeric dienylketenes in which the major product results from outward rotation of the electron-donating alkenyl substituent. This would lead predominantly to a dienylketene unable to undergo electrocyclization. Significantly, we found that vinylcyclobutenone 149 is transformed in nearly quantitative yield to phenol 148 upon heating in toluene for 1 h at reflux (Scheme 15). This suggests that either (a) ring opening of 149 produces exclusively a (Z)-dienylketene in contradiction to the prediction of Houk, or (b) the electrocyclic ring opening is reversible, and any (E)-dienylketene generated undergoes electrocyclic closure to reform 149 more rapidly than it engages in alternative reactions.

Further experiments are planned in our laboratory to investigate this issue. In a preliminary study, vinylcyclobutenone 149 was heated in the presence of various nucleophilic trapping agents. When 149 was heated in toluene at reflux for 1 h in the presence of 7 equiv of benzylamine, a mixture of benzylamides (60%) and phenol 148 (40%) was obtained. The amides comprised a mixture of α,β- and β,γ isomers which also were each present in stereoisomeric forms. The formation of a complex mixture of isomeric amides is not surprising in view of the possibility of isomerization under these reaction conditions. In a similar fashion, heating vinylcyclobutenone 149 in n-butanol (as solvent) at reflux gave a mixture of esters (20%) and benzannulation product 148 (80%). In this case, it appears that the less nucleophilic alcohol is
not as effective as the amine in intercepting the intermediate dienylketene prior to electrocyclization.

We next turned our attention to the benzannulation reaction using sulfonamides such as 140. As shown in Scheme 16, reaction of 140 with 81 was also successful, and the sulfonyl-protected aniline derivative 150 was obtained in 81% yield. However, in this reaction, small amounts of phenolic ester derivatives 152a and 152b (mixture of α,β- and β,γ-unsaturated isomers) were also obtained. As shown below, these byproducts are believed to form from the reaction of the normal phenol annulation product with the vinylketene intermediate (i.e., 151).85

Scheme 16

![Scheme 16](image)

As in previous studies, these ester byproducts were easily converted to the desired annulation product by treatment of the crude reaction mixture in MeOH with 6M KOH solution at 65 °C for 2 h. These general conditions were found by Aimee Crombie to be optimal for the hydrolysis of esters of this type.2

We believe that the occurrence of ester byproducts depends on the rate of the vinylketene [2 + 2] cycloaddition step relative to the rate of the electrocyclic opening of the vinylcyclobutenone intermediate. These phenolic esters are generally formed when the [2 + 2] cycloaddition step in the cascade is relatively slow, leading to a buildup of the vinylketene intermediate which can then be trapped by the growing concentration of the phenolic final

85 Phenolic ester products were also observed in our previous work. See refs. 28 and 44.
annulation product. Alternatively, these esters may be formed if the electrocyclic cleavage of the vinylcyclobutenone intermediate is exceptionally fast, leading to a build up of the phenol product while a significant amount of the vinylketene is still present. In any case, this was not a significant problem in the reaction of sulfonamide 140 and the annulation product was obtained in excellent yield after treatment of the crude reaction mixture with aqueous base. In the benzannulation reactions using the carbamate 128 (Scheme 14), no ester products were observed, perhaps because the [2 + 2] cycloaddition of this more nucleophilic ynamide is faster than the cycloaddition of sulfonamide 140.

With these findings in hand, we moved on to investigate the scope of the benzannulation with respect to cyclobutenone and ynamides suitably functionalized for the subsequent tandem ring-closing metathesis strategy.

**Scope of the Benzannulation**

As delineated in Table 2, the reaction of 3-cyclobutenone (81) with ynamides 130-131 and 143 provided the desired aniline products 153-155 in good to excellent yields. In all of these cases, there was no evidence of addition of vinylketene to the pendant olefin moieties.
Due to the thermal sensitivity of these N-allyl ynamides (vide infra), under optimized conditions the benzannulation reaction was run initially at 80 °C for 1.5 h until no cyclobutenone was observed by TLC analysis and then the reaction mixture was heated at reflux for 1.5 h to convert the vinylcyclobutenone intermediate (the predominant species present at that point) to the desired phenol. In the benzannulation reaction with the conjugated enynamide 131, 2.0 equiv of cyclobutenone 81 was used to compensate for losses due to consumption of some vinylketene by formation of phenolic esters (entry 2). As noted earlier (see Scheme 13), enynamides show reduced ketenophilicity due to the electron-withdrawing effect of the alkenyl substituent. This leads to a buildup of vinylketene while phenol is being formed. Hydrolysis of the crude reaction mixture with 5M KOH in MeOH at 65 °C gave the desired isopropenyl-substituted phenol 154 in 69% yield.

We also attempted to carry out the benzannulation reaction of the diynamide 103\(^{86}\) with cyclobutenone 81 (eq 27). Over the course of 1.5 h, the gradual disappearance of the cyclobutenone was observed, while ynamide 103 remained unchanged.

\(^{86}\) Diynamide 103 was prepared according to ref. 59.
We next examined whether this diynamide would undergo [2 + 2] cycloaddition with more reactive ketenes. No reaction was observed upon exposure of 103 to excess ketene, although a reaction did occur when 103 was treated with dichloroketene. In this case, however, a mixture of products were obtained which we were unable to separate and characterize. We suspect that the strong electron-withdrawing nature of the conjugated alkynyl substituent this ynamide so that it no longer reactive enough to participate in [2 + 2] cycloadditions.

Successful results from our investigation of the benzannulation reaction with other substituted cyclobutenones and ynamides are listed in Table 3. We first investigated the reaction of ynamides with 2,3-disubstituted cyclobutenones 157\(^{87}\) and 158\(^{88}\) (Table 3, entries 1 and 2). As mentioned previously in Chapter 1, the ‘ketoketenes’ formed from 2-substituted cyclobutenones have lower reactivity in [2 + 2] cycloadditions; consequently benzannulations with these compounds require higher reaction temperatures. Aimee Crombie first explored the reaction of cyclobutenone 157 using the N-allyl ynamide 130, but discovered that significant decomposition of 130 occurred at temperatures above 125 °C, presumably via [3,3] sigmatropic rearrangement resulting in an unstable ketenimine.\(^{2,89}\) No reaction of 130 with 157 was observed under photochemical conditions,\(^{90}\) although photochemical benzannulations are often successful when thermally sensitive substrates are used. Unfortunately, this limitation prevents the use of N-allyl substituted ynamides for those benzannulation reactions that require higher than normal temperatures.

The homoallyl-substituted ynamide 132 was not expected to exhibit thermal instability as in the case of the allyl-substituted derivative, and indeed this ynamide does not decompose when heated at temperatures in the range 125-150 °C. When the benzannulation was carried out in

\(^{87}\) Prepared via the reaction of methoxy-1-propyne with ketene, see: ref. 44.
\(^{88}\) Prepared according to ref. 38b.
\(^{89}\) The analogous [3,3] sigmatropic rearrangement of allyl-substituted alkynyl thioethers is known, see ref. 34.
\(^{90}\) 2,3,4-trisubstituted cyclobutenones undergo photochemical benzannulations but 2,3-disubstituted cyclobutenones do not, see: ref. 33.
toluene or benzene at 150 °C, the reaction was sluggish and failed to go to completion even after 40 h. Improved results were obtained when the reaction was performed in chloroform (Table 3, entry 1). Under these conditions, the pentasubstituted annulation product 160 was obtained in 62% yield following hydrolysis. The assignment of regiochemistry in this benzannulation product is discussed in detail later in this chapter. Excess cyclobutenone 157 was used to compensate for losses due to ester formation, which in this case was significant. Prior to hydrolysis, the crude product consisted entirely of the phenolic esters of 160. This was also the case in the reaction of ynamide 132 with the 2,3-substituted cyclobutenone 158 (entry 2).

### Table 3 Scope of the Benzannulation with Ynamides

<table>
<thead>
<tr>
<th>entry</th>
<th>cyclobutenone</th>
<th>ynamide</th>
<th>conditions</th>
<th>benzannulation product</th>
<th>yield (%)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeC=O</td>
<td>MeO</td>
<td>CHCl₃</td>
<td>150 °C, 16.5 h&lt;sup&gt;p&lt;/sup&gt;</td>
<td>62</td>
</tr>
<tr>
<td>2</td>
<td>MeOCH₂O</td>
<td>MeO</td>
<td>CHCl₃</td>
<td>150 °C, 16.5 h&lt;sup&gt;p&lt;/sup&gt;</td>
<td>60</td>
</tr>
<tr>
<td>3</td>
<td>BuCl₂Cl</td>
<td>MeO</td>
<td>toluene</td>
<td>135 °C, 4 h&lt;sup&gt;c&lt;/sup&gt;</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>N≡N</td>
<td>CO₂Me</td>
<td>toluene</td>
<td>110 °C, 10 h&lt;sup&gt;p&lt;/sup&gt;</td>
<td>53</td>
</tr>
</tbody>
</table>

<sup>a</sup> Isolated yield of products purified by column chromatography on silica gel. Yields based on ynamide (using 1.2-2.0 equiv of cyclobutenone).<br> <sup>b</sup> Crude product was heated with 5M KOH in MeOH (65 °C, 2-3.5 h).<br> <sup>c</sup> Reaction performed in presence of 2.0 equiv of BHT using 1.0 equiv of cyclobutenone and 1.5 equiv of ynamide.

The reaction of 4,4-dichlorocyclobutenone 159 with ynamide 132 in the presence of 2.0 equiv of BHT provided a chloro-substituted aniline derivative 162 in good yield (Table 3, entry 3). The chlorine substituent can potentially serve as a useful synthetic handle for the
incorporation of other functionality on the aromatic ring. BHT was added as a chlorine radical scavenger, as the final aromatization in this reaction maybe occurring via homolytic cleavage of a carbon-chlorine bond (eq 31). Alternatively, heterolytic cleavage (to form Cl$^+$ and a phenolate anion) maybe involved in the aromatization. Excess (1.5 equiv) ynamide 132 was used in this reaction, as some destruction of the ynamide was observed during the reaction due to the HCl formed in the aromatization step.

\[
\begin{array}{c}
\text{Cl} \quad \text{Cl} \\
\text{Bu} \quad \text{N} \quad \text{Bu} \quad \text{N} \\
164 \quad \text{CO}_2\text{Me} \\
\end{array}
\quad \rightarrow \quad
\begin{array}{c}
\text{Cl} \quad \text{O} \\
\text{Bu} \quad \text{N} \quad \text{Bu} \quad \text{N} \\
165 \quad \text{CO}_2\text{Me} \\
\end{array}
\quad \rightarrow \quad 162 \quad (31)
\]

The use of 3-aminosubstituted cyclobutenones as the vinylketene precursor in our ynamide benzannulation reaction could provide access to various interesting diaminobenzene derivatives. In addition, nitrogen heterocycles with different substitution patterns could potentially be synthesized using these cyclobutenones as shown in eq 32.

\[
\begin{array}{c}
R^* \quad Z \\
166 \\
\end{array} + \quad \begin{array}{c}
R \\
167 \\
\end{array} \quad \rightarrow \quad
\begin{array}{c}
\text{OH} \quad R \\
\text{Z} \quad R^* \quad Z \\
168 \quad \text{OH} \\
\end{array}
\quad \rightarrow \quad
\begin{array}{c}
\text{OH} \quad R \\
\text{Z} \quad \text{N} \\
169 \\
\end{array} 
\quad (32)
\]

We began our study of benzannulations with aminocyclobutenones by examining the reaction of cyclobutenone 144 with ynamide 133. This cyclobutenone was found to undergo electrocyclic ring opening at 110 °C,\textsuperscript{91} which is in agreement with our observations with regard to the temperatures required to effect the ring opening transformation of the 3-aminovinylcyclobutenone intermediates. Unfortunately, no reaction of the resulting vinylketene with ynamide 133 was observed at 110 °C in toluene (eq 33). At more elevated temperatures

\textsuperscript{91} Trapping of the vinylketene derived from 3-aminocyclobutenone 144 with 4-methoxyphenol was observed at 110 °C in toluene, while no reaction was observed at 80 °C.
(125-150 °C), decomposition of both starting materials was observed. The reaction of cyclobuteneone 144 with 1-triisopropylsiloxo-1-octyne was also unsuccessful.

We believe that the poor reactivity of the 3-amino-substituted cyclobuteneone 144 is due to steric effects in the vinylketene produced by its electrocyclic cleavage which prevents the required antarafacial approach of the activated alkyne partner in the [2 + 2] cycloaddition step. Consistent with this hypothesis are the results obtained with cyclobuteneone 146 which lacks substitution at the 3-position and therefore should generate a more reactive ‘aldoketene’ intermediate. As shown in Table 3 (entry 4), cyclobuteneone 146 successfully participates in the benzannulation reaction with ynamide 133. Optimal conditions also required the use of 2.0 equiv of the cyclobuteneone, as the bis-anilino adduct 163 was initially obtained entirely in the form of its phenolic ester derivative.

We next turned our attention to the preparation of a fully-subsituted aniline via a benzannulation using a trisubstituted cyclobuteneone. The thermal reaction of trisubstituted cyclobuteneone 71\textsuperscript{92} with ynamide 132 was attempted first; however, annulation product 171 was isolated in less than 10% yield under a variety of conditions with decomposition of both starting materials predominantly observed. Slightly higher yields of 171 could be obtained under photochemical conditions, although this required long irradiation time (>40 h) and a significant portion of ynamide 132 remained unreacted (eq 34).

\textsuperscript{92} Tri-substituted cyclobuteneone 71 was prepared by addition of ethyllithium to 2,4-dimethyl-3-ethoxycyclobuteneone, followed by hydrolysis. See: ref. 44.
This lack of reactivity with the ynamide was not surprising, as in our previous work with trisubstituted cyclobutenone 71, the thermal benzannulation with an alkoxyacetylene derivative required a very long reaction time and only provided the desired annulation product in modest yield.28

The benzannulations with cyclobutenone 17293 were examined next based on the expectation that the chloroketene generated by electrocyclic opening of 172 would exhibit enhanced reactivity in [2 + 2] cycloadditions relative to ketoketenes. However, none of the desired phenol was observed upon reaction of this cyclobutenone with ynamide 128 under a variety of conditions (eq 32).

Electrocyclic ring opening of this cyclobutenone was found to occur readily at 85-90°C.94 However, no cycloaddition was observed when a solution of ynamide 128 and 172 was heated at reflux at toluene, and decomposition of both reaction partners became significant when the reaction was carried out at higher temperatures. We suspect that at higher temperatures the ynamide is decomposing due to the influence of decomposition products produced from 172.

Regiochemical Assignment of the Benzannulation Products

As discussed in Chapter 1, in our previous studies the use of ynamines in the benzannulation reaction provided the desired aniline derivatives in good yield. The isolation of allenamide byproducts, however, led us to believe that this annulation process might be

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94 Trapping of the vinylketene derived from cyclobutenone 172 with EtOH was observed at 85-90 °C in toluene.
operating via a non-concerted, stepwise mechanism raising questions concerning the regiochemistry of the annulation products (see Chapter 1, Scheme 7). Furthermore, Ficini's peculiar result from the reaction of ynamine with cyclobutenones\textsuperscript{54} demonstrated that another alternative pathway could conceivably be in operation, providing yet another regioisomeric annulation product. To confirm that the benzannulation with ynamides provided only the regioisomer predicted by the pericyclic cascade mechanism, the product of the reaction of cyclobutenone 157 and ynamide 132 was examined carefully for the presence of any of the regioisomers of type 174 and 175.

Only one phenolic product was observed to form in this reaction, and its regiochemistry was determined via spectroscopic analysis and chemical modifications as follows. Specifically, the phenolic hydroxyl group in the annulation product was removed, resulting in a product with strong ortho-proton coupling ($J = 8.5$ Hz), ruling out 174 as the structure of the original
benzannulation product. Removal of the hydroxyl group was accomplished as outlined in Scheme 18. The annulation product was first hydrogenated to remove the terminal olefins, as initial attempts to directly deoxygenate the triflate derivative of 160 resulted in an inseparable complex mixture of partially deoxygenated compounds in which some of the alkenes were also reduced. Treatment of the hydrogenated adduct 176 with triflic anhydride and DMAP provided triflate 177, which was then deoxygenated using transfer hydrogenation conditions\(^95\) to give 178 as the sole product.

**Scheme 18**

To rule out 175 (the “Ficini product”) as the structure of the benzannulation product, the product was subjected to iodoetherification conditions and then treated with base (eq 36). Benzofuran 179 was formed in 56% overall yield as the only product from this two-step sequence. This experiment indicated that the allyl and hydroxyl groups were adjacent on the aromatic ring, ruling out 175 as the product of the benzannulation.

As shown by these experiments, the benzannulation reaction using ynamides does proceed with good regiocontrol producing a single product as predicted by our pericyclic cascade mechanism. Also, as demonstrated by the example in eq 36, the implementation of a tandem cyclization strategy results in the direct synthesis of a highly-substituted heterocycle, in this case a benzofuran.

**Photochemical Benzannulation with Ynamides**

The benzannulation of ynamides with cyclobutenones can take place under photochemical as well as thermal conditions (see Scheme 14). We were interested in exploring the use of these conditions for the benzannulation with ynamides functionalized for tandem RCM reactions. Unfortunately, a few limitations arose during this study.

First, we discovered that ynamide 131 has poor photo-stability, probably due to the presence of the conjugated enyne moiety. Decomposition of ynamide 131 resulted in the rapid coating of the reaction tube walls with an insoluble colored polymer film, effectively preventing any further reaction and the desired annulation product 154 was obtained in low yield (eq 37).

In contrast to this enynamide, however, ynamide 130 was found to be stable to irradiation, but unfortunately the aromatic annulation product derived from it was not (eq 42). The annulation adduct 153 was isolated in 39% yield, along with a significant amount of its cyclization product 180 which was isolated in 26% yield.
Photo-induced ortho-cyclization of allylphenol is a known process. Upon irradiation, the phenol chromophore is activated and intramolecular excited-state proton transfer to the olefin of the adjacent o-allyl substituent results in a zwitterion which can cyclize to form a dihydrofuran. The annulation product derived from any ynamide possessing a C-allyl substituent would be susceptible to this reaction, although we speculate that this side-reaction could potentially be hindered by the addition of a quenching agent or by irradiation at other wavelengths. Future studies will explore these stratagems to suppress cyclization.

**Tandem Benzannulation-Ring Closing Metathesis**

Olefin metathesis has emerged to be a very important and versatile method for the formation of carbon-carbon bonds. Since the development of highly active, stable, and functional group-tolerant ruthenium catalysts, e.g (181-184), numerous synthetic applications of olefin metathesis have been reported.67,99
The use of ring-closing metathesis as a means to generate nitrogen heterocycles is well established.\textsuperscript{67a-c} Benzo-fused nitrogen heterocycles such as indoles, dihydroquinolines, quinolines, benzazepines, as well as benzazocines have been synthesized via ring-closing metathesis.\textsuperscript{68} For example, Nishida and coworkers used RCM as the key step in their synthesis of the quinoline alkaloid (+)-angustureine 187 (eq 39).\textsuperscript{100}

\[ \text{185} \xrightarrow{5 \text{ mol}\% \text{ 182}} \text{186} \xrightarrow{\text{steps}} \text{187} \]

Ring-closing enyne metathesis\textsuperscript{101} is also a synthetically useful transformation, providing ring systems incorporating a 1,3 diene moiety. In the example shown in eq 40, exposure of the 188 to 5 mol\% of Grubbs’ second generation catalyst 182 in refluxing dichloromethane resulted in the formation of benzazepine derivative 189 in 93% yield.\textsuperscript{68c}

\[ \text{188} \xrightarrow{5 \text{ mol}\% \text{ 182}} \text{189} \]


Exposure of our annulation products 153-146 and 160-163 to 5 mol% Grubbs’ second generation catalyst 182 in refluxing dichloromethane provided the desired benzo-fused heterocycles in generally excellent yields (Table 4). Initial reactions performed by Aimee Crombie were generally run for 12-14 h. Subsequently, we found that with the exception of 163 (entry 6), all RCM reactions were complete within 1 h. In fact, a prolonged reaction time was found to be detrimental for the synthesis of benzazocine 192. After 12 h of reaction, an inseparable 60:40 mixture of 192 and an isomer (identified as the benzazocine in which the double bond had isomerized into conjugation with the benzene ring) was obtained. Olefin isomerization is a well known side reaction in metathesis reactions and is attributed to the decomposition of the active ruthenium carbene catalysis to form a ruthenium hydride species. No isomerization products were detected when the reaction was stopped after completion at 1 h.

### Table 4. Tandem Ring-Closing Metathesis

<table>
<thead>
<tr>
<th>entry</th>
<th>benzannulation product</th>
<th>cyclization product</th>
<th>yield (%) (^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>153 (\text{Bu}_2\text{NCO}_2\text{Me})</td>
<td>190 (\text{Bu})</td>
<td>95</td>
</tr>
<tr>
<td>2</td>
<td>154 (\text{Bu}_2\text{NCO}_2\text{Me})</td>
<td>191 (\text{Bu})</td>
<td>98</td>
</tr>
<tr>
<td>3</td>
<td>160 (\text{MeO}_2\text{NMeCO}_2\text{Me})</td>
<td>192 (\text{MeO}_2\text{NMeCO}_2\text{Me})</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>161 (\text{MeOCH}_2\text{O}_2\text{NMeCO}_2\text{Me})</td>
<td>193 (\text{MeOCH}_2\text{O}_2\text{NMeCO}_2\text{Me})</td>
<td>94</td>
</tr>
<tr>
<td>5</td>
<td>162 (\text{ClBu}_2\text{NMeCO}_2\text{Me})</td>
<td>194 (\text{ClBu}_2\text{NMeCO}_2\text{Me})</td>
<td>87</td>
</tr>
<tr>
<td>6</td>
<td>163 (\text{MeNCO}_2\text{MeCO}_2\text{Me})</td>
<td>195 (\text{MeNCO}_2\text{MeCO}_2\text{Me})</td>
<td>78</td>
</tr>
</tbody>
</table>

\(^a\) Conditions: 5 mol% \(\text{182, CH}_2\text{Cl}_2\), reflux, 40 min (2.5 h for entry 6). \(^b\) Isolated yields of products purified by column chromatography.

Next, we examined the enyne ring-closing metathesis of the annulation product 155. Grimaud has reported the enyne-RCM of a similar benzo-fused 1,7-ene system 196, which
was carried out in tandem with a cross metathesis reaction with methacrylate to afford 197 (eq 41).  

Unfortunately, enyne-RCM failed to work on our original annulation product 155, as well as its derivatives 198-199 (Scheme 19). No reaction was observed for 198 under any conditions. In general poor reactivity was observed for the terminal alkyne derivative 199 as well. Heating at 199 at reflux in CH₂Cl₂ or at higher temperatures in toluene in the presence of Grubbs’ second generation catalyst 182 over a long period of time resulted in slow but gradual decomposition to uncharacterizable products. Decomposition of 199 was more rapid using the Hovyeda catalyst 184 and occurred at room temperature.

We did not observe any interference by chelation of the phenol moiety of our substrates in the previous examples using olefin-RCM, although we did not rule this possibility out for this enyne-RCM (Figure 4). To see if this was affecting the enyne-RCM reaction, the phenolic hydroxyl group in 198 was protected as the silyl ether 199. Heating a dilute solution of 199 in CH₂Cl₂ to Ru catalyst 182 at reflux resulted in the sluggish consumption of 199 to form an undesired compound, which we were unable to definitively characterize. No change was observed when the reaction was carried out under an ethylene atmosphere.

Alternatively, a six-membered chelate with the carbamate functional group (Figure 4) would be possible. Formation of this ruthenium carbene intermediate would occur from initial reaction of the catalyst with the alkene of the substrate. The chelate 208 would hinder the

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104 For example of chelation in enyne metathesis, see: Kinoshita, A.; Sakakibara, N.; Mori, M. Tetrahedron, 1999, 55, 8155.  
105 Ethylene gas has been found to be beneficial for some enyne-RCM reactions, see: Mori, M; Sakakibara, N.; Kinoshita, A. J. Org. Chem. 1998, 63, 6082.  
subsequent key metathesis step in the catalytic cycle, which involves the intramolecular reaction with the alkyne. To test this hypothesis, we prepared the N-tosyl-substituted annulation product 203 and its derivative 204. Unfortunately, similar results were obtained: no reaction was observed for 203 and decomposition of 204 occurred slowly.

Scheme 19

![Scheme 19](image)

Figure 4

![Figure 4](image)

It is not clear why enyne-RCM had failed with this particular substrate and its derivatives. We suspect that unfavorable conformational effects may play a role, or else that the metathesis product or an intermediate is unstable and decomposes under these reaction conditions.
Summary

The convergent synthesis of highly-substituted, benzo-fused nitrogen heterocycles such as dihydroquinolines, benzazepines, and benzazocines has been accomplished using our tandem benzannulation-ring closing metathesis strategy. Ynamides participate in the benzannulation reaction with cyclobutenones, forming substituted aniline derivatives with good regiocontrol. The appropriate alkenyl functional groups required for the tandem ring-closing metathesis are incorporated in the aromatic ring directly via the ynamide. No further modifications are then necessary for the subsequent transformation to the desired nitrogen heterocycle.

The next chapter details our work aimed at extending this tandem strategy to the ‘second generation’ benzannulation in which diazo ketones are used as the vinylketene precursor.
Chapter 3 – ‘Second Generation’ Benzannulation with Ynamides

Application of the ‘second generation’ version of the benzannulation to ynamides would significantly expand the scope of our tandem strategy. As discussed in Chapter 1, this variant of the annulation relies on the in situ generation of the vinyl-, aryl-, and hetarylketene intermediates by the photochemical-Wolff rearrangement of an α-diazo ketone and allows for the efficient construction of functionalized polycyclic and heteroaromatic compounds. As shown in Scheme 19, linking this version of the benzannulation with a second transformation in tandem would result in the formation of polycyclic nitrogen heterocycles. The use of the cyclobutenone-based benzannulation to generate these types of systems would have required the non-trivial synthesis of appropriately functionalized polycyclic cyclobutenones. On the other hand, a wide variety of α-diazo ketones can easily be readily prepared in one-step from carboxylic acid derivatives or via a diazo transfer process directly from the corresponding ketones.

Scheme 20

![Scheme 20](image)
Alkoxy- and siloxyacetylenes were used in previous examples of the α-diazo ketone-based benzannulation reaction. Since ynamides have similar reactivity to these derivatives in the thermal [2 + 2] cycloaddition with ketenes, we anticipated that ynamides would have equivalent behavior in these photochemical benzannulations. On the other hand, since this version of the benzannulation relies on photochemical activation, the compatibility of ynamides with the reaction conditions was unknown and required careful investigation.

Optimization of the ‘Second Generation’ Benzannulation with Ynamide 128

We initially examined the reaction of α-diazo ketone 214 with ynamide 128 for optimization of conditions for the benzannulation reaction (Table 5). The reactions were carried out in a quartz reaction tube placed either in a Rayonet photochemical reactor fitted with a circular array of 16 low-pressure mercury lamps (254 or 300 nm) or next to a water-cooled quartz immersion well containing a Hanovia 450W medium-pressure mercury lamp (wavelength range 250-600 nm). Each reaction mixture was thoroughly degassed via three cycles of freeze-pump-thaw (0.05 mmHg) prior to irradiation. Irradiation of the reaction mixture was continued until complete consumption of diazo ketone 214 was observed as indicated by TLC analysis. As seen in many previous photochemical aromatic annulations, at that point the reaction mixture consisted of a mixture of varying amounts of the intermediate vinylcyclobutenone together with the desired annulation product. Consequently, the crude reaction products were then heated to complete the conversion of vinylcyclobutenone to the phenol. The failure of all of the vinylcyclobutenone to transform to product upon continued irradiation is attributed to the build up of colored polymeric residues on the walls of the reaction tubes.

As shown in Table 5, the isolated yield of the annulation product 215 was improved when the reaction was performed in dichloromethane as compared to toluene. The use of a Hanovia 450W lamp, which has a larger range of wavelength output, gave similar results to irradiation using the Rayonet photoreactor fitted with 254 nm lamps. Addition of an excess (2.5 equiv) of diazo ketone 214 significantly improved the reaction yield and less unreacted ynamide was

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108 The reaction mixture generally occupied a significant (half to two-thirds of the total) volume of the reaction tube in order to maximize the surface area of exposure to the lamps.

65
observed in the crude reaction mixture. The best results were obtained when the same amount of diazo ketone was slowly added to the reaction mixture via a syringe pump (entry 5).\textsuperscript{109} However, good yields can also be obtained by the slow addition of only 1.5 equiv of diazo ketone \textit{214} (entry 6). These conditions are more practical in cases where the diazo ketone partner is a valuable intermediate.

### Table 5. Optimization of Conditions for Second Generation Benzannulation

<table>
<thead>
<tr>
<th>entry</th>
<th>diazoketone</th>
<th>solvent</th>
<th>hv source</th>
<th>$\lambda$ (nm)</th>
<th>time</th>
<th>yield$^a$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0 equiv</td>
<td>toluene</td>
<td>Rayonet</td>
<td>254 nm</td>
<td>1.5 h</td>
<td>25$^b$</td>
</tr>
<tr>
<td>2</td>
<td>1.0 equiv</td>
<td>CH$_2$Cl$_2$</td>
<td>Rayonet</td>
<td>254 nm</td>
<td>1.5 h</td>
<td>40$^b$</td>
</tr>
<tr>
<td>3</td>
<td>1.1 equiv</td>
<td>CH$_2$Cl$_2$</td>
<td>Hanovia</td>
<td>250-600 nm</td>
<td>8 h</td>
<td>48</td>
</tr>
<tr>
<td>4</td>
<td>2.5 equiv</td>
<td>CH$_2$Cl$_2$</td>
<td>Hanovia</td>
<td>250-600 nm</td>
<td>5.5 h</td>
<td>67</td>
</tr>
<tr>
<td>5</td>
<td>2.5 equiv</td>
<td>CH$_2$Cl$_2$</td>
<td>Hanovia</td>
<td>250-600 nm</td>
<td>10 h</td>
<td>85$^c$</td>
</tr>
<tr>
<td>6</td>
<td>1.5 equiv</td>
<td>CH$_2$Cl$_2$</td>
<td>Hanovia</td>
<td>250-600 nm</td>
<td>4.5 h</td>
<td>65$^c$</td>
</tr>
<tr>
<td>7</td>
<td>2.5 equiv</td>
<td>CICH$_2$CH$_2$Cl</td>
<td>Hanovia</td>
<td>250-600 nm</td>
<td>9 h</td>
<td>73$^{c,d}$</td>
</tr>
</tbody>
</table>

$^a$ Isolated yields of products purified by column chromatography. $^b$ Reaction was performed in the presence of 1,4-dimethoxybenzene (internal standard). $^c$ Diazo ketone \textit{214} was added as a 0.4 M solution to a 0.3 M solution of ynamide 128 via syringe pump at a rate of ca. 0.009 mL/min. $^d$ Heated at reflux in 1,2-dichloroethane for 24 h after irradiation.

Interestingly, we observed during the course of our optimization studies that the use of a uranium glass filter, which blocks wavelengths below 340 nm, resulted in production of only the vinylcyclobutenone \textit{216} (eq 42).

\textsuperscript{109} The use of the Hanovia lamp was preferable in this case for ease of setting up the syringe pump, as the reaction is carried out in a shielded fume hood. Use of this equipment would be more difficult with the Rayonet photoreactor, which is a stand-alone apparatus not easily accommodated in our fume hoods.
As observed previously, the rapid conversion of these vinylicyclobutenone intermediates to the annihilation product typically requires temperatures of 110 °C. 1,2-Dichloroethylene (boiling point = 83 °C) was also found to be suitable for the irradiation stage of the photo-Wolff-benzannulation process (Table 5, entry 7), but when the resulting reaction mixture was directly heated at reflux, complete conversion to the desired product 215 required 24 h (instead of 90 min). Consequently, it was more convenient to carry out the thermal conversion of 216→215 in toluene at reflux, which required only 1.5 h at the higher temperature.

**Benzannulation with Aryl- and Hetaryldiazo ketones**

Aryl- and hetaryldketenes\(^\text{110}\) are easily prepared via the photo-Wolff rearrangement of the corresponding diazo ketones, permitting the efficient synthesis of naphthalene derivatives and heteroaromatic compounds. Our next focus was to investigate the benzannulation of these types of ketenes with ynamides.

First, the reaction of ynamide 128 with α-diazoacetophenone (217) was examined (Scheme 21). With only 1.1 equiv of diazo ketone, the naphthalene adduct 218 was produced in good yield. We discovered that for this case, neither slow addition nor an excess of the diazo ketone partner was necessary. An explanation for this result is that the arylketene intermediate is more stable and longer-lived as compared to the vinylketene derived from 214, permitting the [2 + 2] cycloaddition with the ynamide to take place with greater efficiency.

---

Scheme 21 also shows the benzannulation of ynamide 128 with the pyrrole diazo ketone 219, which was prepared from the corresponding N-Boc-protected 2-acylpyrrole. Use of this diazo ketone resulted in the direct formation of the highly-substituted indole 220. Interestingly, no vinylcyclobutene intermediate was observed at any point in this reaction. We believe that the benzannulation reaction is efficient and that the rather modest yield is attributed to some decomposition of the indole product under the reaction conditions. Irradiation of a sample of pure 220 resulted in complete decomposition to uncharacterizable colored byproducts within 3 h. The use of various wavelength filters and other solvents did not prevent this decomposition. A uranium glass filter was used in the hope of isolating the vinylcyclobutenone, but after 23 h of irradiation with the Hanovia lamp only ca. 50% conversion was observed with the indole 220 as the sole product. Weedon has reported that N-acyl and N-Boc indoles are photoactive and can undergo photo-Fries type of rearrangements, as well as cycloadditions to alkenes. Unfortunately, no improvements in yield were obtained when the pyrrole protecting group was switched to N-tosyl or N-triisopropylsilyl (in the latter case, a 3-acetylpyrrole-derived diazo ketone was used) (Figure 5).

111 Pyrrole diazo ketone 219 was synthesized via detrifluoroacetylatative diazo transfer (see ref. 107) from N-Boc-protected 2-acylpyrrole, which was prepared as described by: Kaiser, H.-P.; Muchowski, J. M. J. Org. Chem. 1984, 49, 4203.

Reaction of \textbf{128} with pyrrole diazo ketone \textbf{221} resulted in the rapid formation of colored byproducts which coated the walls of the reaction tube, preventing further reaction. Only ca. 37\% yield of the indole product obtained; this product was also found to be photochemically unstable. Under the reaction conditions, \textit{N}-triisopropylsilyl protected diazoketone derivative \textbf{222} decomposed and no significant reaction with the ynamide \textbf{128} was observed.

\textbf{Application of the Tandem Benzannulation-Ring Closing Metathesis Strategy}

Having optimized conditions for three classes of ketenes in the 'second generation' benzannulation strategy, we next investigated the incorporation of this version of the reaction in our tandem strategy for the synthesis of benzo-fused nitrogen heterocycles. Due to limitations with regard to the photo-reactivity of enynamides and also that of the annulation products derived from ynamide \textbf{125} (see Chapter 1, pp 47-48), we did not attempt to use these ynamides in this variant of the benzannulation.

The synthesis of benzazocine derivatives was, however, within reach of our tandem benzannulation-RCM strategy. Indeed, as illustrated in Scheme 22, aromatic annulation of ynamide \textbf{135} with \textit{\textalpha{}}-diazooacetophenone (\textbf{217}) proceeded in 62-66\% yield which is consistent with the results obtained using the unfunctionalized ynamide \textbf{128}. The resulting naphthalene derivative \textbf{223} was subjected to the standard RCM conditions and naphthalenylazocine \textbf{224} was formed in 76\% yield.
Summary

We have found that ynamides can also be employed in the ‘second generation’ variant of the benzannulation reaction. By using this aromatic annulation strategy with ynamide 128, three different classes of amino-substituted heterocycles were synthesized. Unfortunately, the application of ring-closing metathesis in tandem with this benzannulation is limited, due to significant photoreactivity of either the ynamide and/or the annulation product. However, this strategy was successfully used for the synthesis of the polycyclic benzazocine derivative 224.

Nevertheless, other cyclization reactions can potentially be applied in tandem to the diazo ketone-based benzannulation reaction, using ynamides which are perhaps more amenable to the photochemical conditions. Several other tandem cyclization strategies, including electrophilic cyclizations, hydroarylation reactions, and various indole-forming strategies are currently under investigation in our laboratory.
Part II

Formal Synthesis of (+)-FR900482
Chapter 1 – Introduction and Background

As discussed in Part I of this thesis, our goal in developing a tandem benzannulation-heterocyclization strategy was to devise an efficient method for the rapid construction of benzo-fused nitrogen heterocycles. Part II describes the implementation of this strategy in an efficient and highly convergent synthesis of the benzazocine core of the antitumor natural product (+)-FR900482.

Introduction

The natural product (+)-FR900482 (225) and its congener (+)-FR66979 (226) were first isolated from a fermentation harvest of Streptomyces sandaensis No. 6897 in the late 1980s at the Fujisawa Pharmaceutical Co.¹¹³

![Figure 6.](image)

Potent activity of these compounds was demonstrated against a variety of tumor cell lines, including vincristine- and mitomycin C-resistant P388 leukemia cell lines.¹¹⁴ These compounds


bear close structural similarities to the clinically significant anti-cancer drug mitomycin C\textsuperscript{115} (229) (Figure 6) showing comparable levels of biological activity, but with decreased toxicity levels.\textsuperscript{114} Indeed, semi-synthetic derivatives FK973 (227)\textsuperscript{116} and in particular FK317 (228)\textsuperscript{117} reached advanced clinical trials in Japan.

\[
\begin{align*}
\text{FR900482 exists as a mixture of two diastereomers (230-\alpha and 230-\beta) that are in equilibrium via the intermediacy of N-hydroxybenzazocinone 231 (eq 43).} \textsuperscript{113b} Extensive studies on the mode of action of FR900482 and its derivatives have revealed that like other compounds in the mitomycin family, these compounds act as DNA-DNA\textsuperscript{118} and DNA-oncoprotein\textsuperscript{119} crosslinking agents. The generally accepted mechanism involves an initial two-electron reductive cleavage of the labile N-O bond resulting in the formation of the benzazocinone 232. Cyclization, followed by dehydration and subsequent tautomerization, leads to the formation of mitosene 234, an intermediate believed to be the active alkylating species. In analogy to the mitomycin activation cascade, alkylation of DNA occurs at the C-1 and C-10 positions of 234 (Scheme 23).\textsuperscript{120}
\end{align*}
\]
The novel and challenging structures of 225 and 226 have generated much interest in the synthetic community, resulting in seven total syntheses\textsuperscript{121, 122, 123, 124, 125, 126, 127} and two formal syntheses.\textsuperscript{128, 129} A number of synthetic approaches and methods for the synthesis of benzazocine derivatives relevant to these natural products have also been developed.\textsuperscript{130}

In recognition of the tautomeric nature of these natural products, most of the effort towards the construction of 225 and 226 have focused, with the exception of two of the syntheses, on the direct assembly of a benzazocinone intermediate. In all cases, an aniline precursor serves as the linchpin fragment for the preparation of a substrate suitable for cyclization to form the eight-membered ring. Several disconnections for the synthesis of the benzazocine ring are depicted in Scheme 24. Endgame strategies have subsequently relied on a few key oxidations to furnish the equilibrating hydroxylamine hemiacetal functionality. Highlights of the previous syntheses include:


total and formal syntheses of FR900482 and FR66979 are discussed in the remainder of this chapter.

Scheme 24

Previous Total and Formal Syntheses of FR900482/FR66979

*Fukuyama First Synthesis of (±)-FR900482*

The first total synthesis of racemic FR900482 (225) was accomplished by Fukuyama and co-workers in 1992. In a route involving 43 linear steps, the total synthesis of 225 focused on the construction of the benzazocine ring system. As depicted in Scheme 25, aniline 235 was elaborated via a multi-step sequence to lactone 236, setting the stage for a reductive amination to form the eight-membered ring. Subsequent oxidation with m-CPBA afforded a sulfoxide intermediate which upon heating furnished the benzazocine 237.

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131 Aniline 235 was prepared in one step from ethyl acetoacetate and benzylamine.
The C-8 acetoxy group was cleaved with NaOH in MeOH and the resulting allylic alcohol intermediate was subjected to a trans-selective epoxidation using m-CPBA. Swern oxidation of the resulting epoxy alcohol intermediate afforded ketone 238 which was treated with LiOH and paraformaldehyde to install the C-7 hydroxymethyl sidechain. The ketone moiety of the single diastereomer formed from this reaction was then immediately reduced and protected as a silyl ether to prevent decomposition. Cleavage of the acetamide was followed by N-oxidation and acetylation to give acetyl protected hydroxylamine 239, a derivative from which 15 more steps were required to complete the synthesis.

**Terashima Total Synthesis of (+)-FR900482**

In 1996, Terashima and co-workers reported the first enantioselective total synthesis of FR900482. Their synthesis relied on the union of an aromatic fragment 240 and enantiopure fragment 241 to form the benzazocine ring system. Completion of the synthesis was achieved in a total of 42 linear steps.

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132 Fragment 240 was prepared in 15 steps from commercially available 5-hydroxyisopthalic acid. See ref. 123(b).
133 Fragment 241 was prepared in 12 steps from commercially available L-diethyl tartrate. See ref. 123(b).
Coupling of the two fragments proceeded first through the nucleophilic displacement of the primary triflate 241 with aniline 240. The key step to form the benzazocine ring system involved the intramolecular aldol reaction of 242, which unfortunately provided only the wrong diastereomer at C-7 in a modest 42% yield. Epimerization of the C-7 substituent was accomplished by treatment of 243 with DBU, but gave a 2.1:1 mixture of isomers. Benzazocine 244 was carried on further in 14 steps to FR900482 (225).

**Danishefsky Total Synthesis of (±)-FR900482**

In 1995, Danishefsky reported the total synthesis122 of racemic FR900482 (225) in 33 linear steps. Danishefsky’s unique approach towards the construction of this natural product centered on a direct disconnection of the C-6/C-7 bond, resulting in the intermediate 246. This hydroxylamine hemiketal construct could then be derived from a hetero Diels-Alder reaction of an aryl nitroso compound 247 and activated diene 248.
The hetero Diels-Alder reaction of the nitroso arene 249 with diene 250 resulted in formation of the oxazine derivative 251, as shown in Scheme 28. Further elaboration in a 7-step reaction sequence furnished the aziridine 252, which after deacetylation, oxidation, and methylenation provided the key intermediate 253, setting the stage for assembly of the FR900482 framework.

Scheme 28

---

134 Nitroso compound 249 was prepared in 8 steps from commercially available methyl vanillate. See ref. 122.
Treatment of intermediate 253 under Heck reaction conditions was notably successful, particularly considering the complex functionality present in the substrate. In order to install the requisite side chain at C-7, dihydroxylation of the olefin moiety was followed by epoxide formation under Mitsunobu conditions to provide 254, with 10:1 diastereoselectivity observed at C-7. Taking advantage of the vinylogous glycidate system present in the framework of 254, treatment with SmI₂ resulted in reduction to 255. In 255, all of the key features of the natural product are present; somewhat unfortunate, however, was the fact that 10 further steps were required for deprotections and functional group interchanges in order to reach the final target.

Scheme 29

\[
\begin{align*}
\text{253} & \xrightarrow{1 \text{) } (\text{Ph}_3 \text{P})_4 \text{Pd, Et}_3 \text{N, CH}_3 \text{CN, 90 °C, 18 h}} \ 93\% \text{) } (\text{Ph}_3 \text{P}) \text{OMOM} \\
& \xrightarrow{2 \text{) } \text{OsO}_4, \text{NMO, acetone/H}_2\text{O}} \text{90}\% \\
& \xrightarrow{3 \text{) } \text{DIAD, PH}_3 \text{P, THF}} \text{86}\% \\
& \text{254} \xrightarrow{\text{2 equiv SmI}_2, \text{10 equiv K}_2\text{OH, THF, -78 °C}} \text{92}\% \\
& \xrightarrow{\text{10 steps}} \text{255}
\end{align*}
\]

\[
\begin{align*}
\text{253} & \xrightarrow{1 \text{) } (\text{Ph}_3 \text{P})_4 \text{Pd, Et}_3 \text{N, CH}_3 \text{CN, 90 °C, 18 h}} \ 93\% \text{) } (\text{Ph}_3 \text{P}) \text{OMOM} \\
& \xrightarrow{2 \text{) } \text{OsO}_4, \text{NMO, acetone/H}_2\text{O}} \text{90}\% \\
& \xrightarrow{3 \text{) } \text{DIAD, PH}_3 \text{P, THF}} \text{86}\% \\
& \xrightarrow{\text{2 equiv SmI}_2, \text{10 equiv K}_2\text{OH, THF, -78 °C}} \text{92}\% \\
& \xrightarrow{\text{10 steps}} \text{255}
\end{align*}
\]

Fukuyama Total Synthesis of (+)-FR900482

In 2002, Fukuyama published an enantioselective route\textsuperscript{125} to FR900482. As in his earlier synthesis\textsuperscript{121} of racemic compound, this new route proceeded via the construction of a key benzazocinone intermediate. As shown in Scheme 30, the eight-membered ring in 256 was derived from 257 via a cyclization, followed by stereoselective installation of the hydroxymethyl group at C-7. Intermediate 257 itself was envisioned to be constructed from cross coupling of an aryl sulfonate 258 with a tartaric acid-derived alkyne 259.
Alkyne 260\textsuperscript{136} was coupled under the conditions shown below with aryl triflate 261\textsuperscript{137} to give aryl alkyne 262. Regioselective addition of pyrrolidine to the alkyne conjugated with the nitro group followed by hydrolysis afforded a ketone, which was stereoselectively reduced with \( \text{Zn(BH}_4\text{)}_2 \) to the alcohol 263, with 9:1 selectivity at C-6 (Scheme 31). TIPS protection of the resulting alcohol was followed by acetonide cleavage (with simultaneous cleavage of the TBS ether) and reprotction of the primary alcohol, setting the stage for formation of epoxide 264.

Hydrolysis of the primary tert-butyldimethylsilyl ether in 264 under mild acidic conditions and treatment with Dess-Martin periodinane was followed by partial reduction of the nitro group over Pt/C in methanol, which in the event resulted in cyclization to form the N-

\textsuperscript{136} Intermediate 260 was prepared from commercially available l-tartaric acid in 5 steps, see ref. 125.

\textsuperscript{137} Intermediate 261 was prepared from commercially available methyl vanillate in 6 steps according to ref. 122.
hydroxybenzazocine 265. Further elaboration afforded benzazocinone 266, which was advanced towards the natural product with a key hydroxymethylation reaction at C-7. Addition of the lithium enolate of 266 to formalin occurred with high diastereoselectivity (94:6); the product of this reaction was directly treated in a one-pot fashion with 1M HCl to give an 87:13 mixture of hydroxylamine hemiketals which were protected as the acetonide to give 267.

Scheme 32

The remainder of the synthesis of the racemic natural product then proceeded using tactics similar to those employed in Fukuyama’s earlier synthesis. The major diastereomer from the hemiketalization step was carried on in 13 further steps to FR900482; overall the enantioselective total synthesis was achieved in a total of 35 linear steps.

Williams Total Synthesis of (+)-FR900482 and (+)-FR66979

As shown in Scheme 11, William’s retrosynthetic plan for the synthesis of 225 and 226 relied on the preparation of benzazocinone 269. Taking a novel approach to the assembly of the hydroxylamine hemiketal structure, it was envisioned that a tandem oxidative cleavage/N-oxidation of an appropriately labile p-methoxybenzyl protecting group on the azocine nitrogen.
would lead to the in situ formation of 268. Retrosynthetic analysis of the eight-membered ring intermediate led to two fragments: enantiopure aziridine 271\textsuperscript{138} and the nitrobenzene 270\textsuperscript{139}.

Scheme 33

As depicted in Scheme 34, condensation of 270 under basic conditions with the aldehyde 271 was followed by protection of the resulting alcohol with DEIPSCI. Reduction of the nitro group under transfer hydrogenation conditions, nosylation, and oxidative cleavage of the primary OPMB group afforded the intermediate 272. Under Mitsunobu conditions, the nosyl sulfonamide cyclized to form the key eight-membered ring. Sequential nosyl group removal with Cs\textsubscript{2}CO\textsubscript{3} and thiophenol, protection of the amine as the PMB ether, and finally TASF deprotection of the secondary silyl ether furnished the alcohol 273.


\textsuperscript{139} Prepared in 4 steps from commercially available 3,5-dinitro-p-toluic acid. See ref. 129 and ref. 130f.
Dess-Martin oxidation of the benzazocine set the stage for hydroxymethylation at the C-7 position, which despite extensive optimization gave at best a 1:1 mixture of C-7 diastereomers 274a and 274b in 50% yield, with 45% recovery of unreacted ketone. Fortunately, the undesired epimer 274a could be transformed by treatment with DBU in toluene to the desired epimer 274b in 70% yield. Following protection of the alcohol as the TBS silyl ether, treatment with dimethyldioxirane (DMDO) in a saturated K$_2$CO$_3$ solution resulted in formation of the advanced intermediate hydroxylamine hemiketal 275 in 30-50% yield (with 40-50% recovered benzazocinone).
From this point, only 4 and 5 steps were required to construct FR66979 and FR900482, respectively. Williams's enantioselective total synthesis of FR900482 (225) encompassed a total of 32 linear steps and proceeded in 0.32% overall yield.

**Ciufolini Total Synthesis of (±)-FR66979**

In 2002, Ducray and Ciufolini reported the total synthesis of racemic FR66979 (226). This synthesis featured a unique tandem homo-Brook rearrangement-fragmentation of silylated aziridine as a key step to create the benzazocine core. Construction of the aziridine would proceed via the stereoselective allylation of aldehyde 278. Overall, the synthesis provided racemic 225 in a total of 29 linear steps.

As outlined in Scheme 36, aldehyde 280 was synthesized from the known propanediol via a 4-step sequence commencing with Raney-Ni reduction of the nitro group of 279 and subsequent diazotization. Monobenzylation and IBX oxidation then furnished the aldehyde 280. Treatment of 280 with the allylating reagent 281 provided the desired allylic alcohol as a single diastereomer with the expected configuration as dictated by Felkin-Ahn selectivity.

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141 Propanediol 279 was prepared in 7 steps from commercially available 3-nitrovanillin, see ref. 128.
Intramolecular azide cycloaddition to the allyl moiety resulted in triazoline 282, which fragmented upon photolysis to form the aziridine 283 in 77% yield.

In the key step of this synthesis, diastereomERICALLY pure benzoazocine 284 was produced in 49% yield via treatment of 283 with $n$-Bu$_4$NOH. An initial homo-Brook rearrangement provided the trigger for the ring-fragmentation of the strained bicyclic aziridine 283 to form the eight-membered ring.

**Scheme 36**

Next at hand was the installation of the aziridine moiety, as well as various protective group manipulations. As depicted in Scheme 37, the amine in 284 was oxidized and acetylated to give 285, which was treated with m-CPBA to form the epoxide from the more exposed convex face of the azocine. Ley oxidation was followed by acetate cleavage, which in the event resulted in intramolecular condensation to form the hydroxylamine hemiketal framework of FR66979. Global debenzylation then revealed the tetraol 287, which was selectively protected as the acetonide. Subsequent regioselective epoxide ring opening with sodium azide and then acetylation of the remainder of the free alcohols provided 288.
As depicted in Scheme 38, mesylation of 288 was followed by substitution of the acetonide protecting group with the carbonate via cleavage with TFA and treatment with phosgene to provide 289, a reaction sequence that unfortunately proceeded in rather poor yield. Staudinger reduction of the azide 289 induced formation of the desired aziridine moiety, and ammonolysis furnished racemic FR66979 (226), in a total of 29 linear steps. As demonstrated by Williams, it is possible to transform 226 to FR900482 (225) via a Swern oxidation, albeit with modest (33%) conversion.124
Martin Formal Synthesis of (+)-FR900842

Martin’s enantioselective formal synthesis\textsuperscript{128} of FR900842 (225) relied on the construction of the benzazocinone core as in the previously discussed total syntheses. To this end, the key step in his formal synthesis employed the use of ring-closing metathesis as an efficient method for assembling the azocine ring (Scheme 39). The requisite diene 291 was envisioned to be derived from a 1,3-diol derivative 292 which would be obtained enantioselectively via an enzymatic resolution. Martin’s formal synthesis intersects with an intermediate from Fukuyama’s first total synthesis.\textsuperscript{121}
As shown in Scheme 40, Martin’s synthesis begins with the prochiral 1,3 propanediol\(^{142}\) 293 which is enzymatically acetylated with *Pseudomonas* sp. Lipase (PSL) in the presence of vinyl acetate and 4Å molecular sieves to give acetate 294 in 74% yield. The product is obtained with 94% ee and with the S configuration at the C-7 position, which is opposite to that of the natural product. This was remedied by a protecting group interchange to give the nitroarene 295. For practical reasons, the remainder of the synthesis was carried out with racemic 294 in order to avoid the need for the protection group interchange. Compound 295 was reduced with Raney-Ni in 99% yield and protected as the Troc carbamate 296. Desilylation with pyridine buffered HF then set the stage for a tandem Swern oxidation - vinyl Grignard addition, providing allylic alcohol 297 in 65% overall yield, as a single diastereomer with the stereochemical configuration as shown.

*Scheme 40*

In the key step of the formal synthesis, ring-closing metathesis of diene 297 with 10 mol% Grubbs 1st generation catalyst 181 afforded the desired benzazocine 298 in 78% yield. Zn/AcOH was then used to remove the Troc protecting group to provide the free amine, which was oxidized to the corresponding hydroxylamine and O-acetylated. Further treatment with *m*-CPBA at rt gave epoxide 299 in 61% yield together with 18% recovered starting material.

\(^{142}\) 1,3-Propanediol 293 was prepared in 7 steps from 3-nitrovanillin, see ref. 128.
Scheme 41

At this point, Martin elected to connect his RCM product to the key intermediate epoxide 239 in Fukuyama's synthesis as attempts to install an aziridine in 298 via a cyclization proved to be unsuccessful. Conversion of 298 to 239 required exchange of the O-PMB protecting group to a TBS silyl ether, followed by hydrogenolysis of the benzylic benzyl ether group, which was accomplished in 42% yield. Finally, Mitsunobu reaction with p-methoxyphenol provided 239, an intermediate that requires an additional 15 linear steps for conversion to FR900482. Overall, Martin's formal synthesis of Fukuyama's intermediate 239 required a total of 25 linear steps.

Rapoport Formal Synthesis of (+)-FR900482

Rapoport and co-workers developed an enantioselective route to FK973 (227) in 2003 which constitutes a formal synthesis of FR900482 (225) since 227 can be converted through deacetylation with NaHCO₃ to 225. The basis of their synthesis, as with many of the other syntheses discussed thus far, involves the assembly of a benzazocine derivative.
Combination of the epoxide 301 with aniline 300 led via a 5-step sequence to the ester 302. The ring-closing event to form the benzazocinone 303 was achieved by benzylic deprotonation of 302 and addition to the methyl ester to form the C-7 to C-8 bond. Installation of the C-7 hydroxymethyl chain proved to be problematic under various conditions due to elimination of water, and the most effective method was to use the following three step sequence where an enone is deliberately generated. Treatment of 303 with Triton B and paraformaldehyde yielded an enone intermediate in 97% yield, which was epoxidized with TBHP and Triton B to give the epoxide with the desired stereochemistry at C-7 as the major isomer in 77% yield. The minor diastereomer could be recycled back to the enone through treatment with SmI₂. Catalytic hydrogenation in the presence of pyridine resulted in the reduction of the α,β-epoxy ketone, providing the desired β-hydroxy ketone 304. From this intermediate, 9 further steps were required to reach FK973 (227).

143 Epoxide 301 was derived from commercially available L-methionine methyl ester hydrochloride in 4 steps as a mixture of 1:4 anti:syn isomers which were used directly without separation and then separated at a later stage in the synthesis.

144 Aniline 300 was prepared from commercially available 3,5-dinitro-p-toluic acid in 5 steps.
The most recent endeavor to synthesize (+)-FR900482 (225) was reported by Trost\(^\text{126}\) earlier this year. The synthesis of the C-7 epimer of FR900482 (305) was accomplished in 23 steps, which is the shortest route to date for this family of compounds. Biological testing of this C-7 epimer revealed levels of cytotoxicity towards several human cancer cell lines comparable to that of the natural compound.\(^\text{126}\) Trost proposed an approach to this target via intermediate 306, which can be disconnected to an iodoaniline derivative 307 and to an optically active aziridine 308.

Aziridine 308 was prepared in 9 steps from commercially available 1,5-hexadiene-3,4-diol; the requisite stereochemistry was established using a palladium-catalyzed DYKAT (dynamic catalytic asymmetric transformation) reaction.\(^\text{145}\) Coupling of the aniline 307 with 308 via reductive amination, followed by cyclization to pyrrolidine derivative 309, and then intramolecular Heck reaction provided the intermediate 310. No inversion of C-8 during the cyclization step was observed; neighboring group participation of the BOC group is suspected to be occurring under these reaction conditions.


\(^{146}\) Prepared from commercially available 5-nitrovanillin in 6 steps.
At this stage a series of oxidations, most notably a ring-expanding Polovonski reaction (311 → 312) were carried out, leading to the formation of precursor 311 in which the FR900482 skeleton is almost complete. Difficulties in removing the carbonate to form the C-7 hydroxymethyl substituent were encountered. However, treatment of 311 with NaBH₄ in the presence of ethanol did proceed to give 312 (with the wrong stereochemistry at C-7), presumably through the intermediacy of an o-quinone methide (eq 45). Four additional transformations led to the completion of the synthesis of epi C-7 FR900482 (305).

Summary

Over the span of two decades, quite a number of synthetic approaches to (+)-FR900482 and related compounds have been developed, a the consequence of a challenging structure in combination with potent bioactivity. The highly functionalized and novel framework of these natural products have provided ample opportunities for the development of new synthetic
methods and strategies. In the next chapter, the application of our tandem benzannulation-ring-closing metathesis strategy towards the synthesis of the benzazocine core of (+)-FR900482 will be discussed.
Chapter 2 - Formal Synthesis of (+)-FR900482

Retrosynthetic Analysis

The goal of this investigation was to incorporate our tandem benzannulation-RCM strategy in a synthesis of the core structure of (+)-FR900482. As discussed in the previous chapter, many of the previous total and formal syntheses of this compound have focused on the assembly of a benzo-fused azocine ring system. Fairly lengthy, linear routes involving multiple functional group interchanges were employed in some cases to prepare the requisite substituted aniline substrate for cyclization to the eight-membered ring. As outlined retrosynthetically in Scheme 43, we felt that the application of our tandem benzannulation-RCM strategy could provide a very efficient and convergent approach to a fully substituted benzazocine, avoiding major structural alterations to the aniline adduct prior to the key cyclization.

Scheme 43
Specifically, in analogy to Martin’s formal synthesis, we envisioned that our synthesis would employ a ring closing metathesis reaction as the pivotal cyclization step leading to 313. An extremely direct route to substrate 314 would involve the benzannulation reaction of ynamide 316 with the 3-substituted cyclobutenone derivative 315.

Ynamide 316 would be constructed using an N-alkynylation reaction between an allyl-substituted carbamate 318 and alkynyl halide derivative 317. The stereochemistry of alkyne 317 would be set via the use of a chiral auxiliary-controlled stereoselective aldol reaction involving acrolein. Consequently, the stereochemistry at C-7 and C-8 of the FR900482 core would be established early on in our synthesis, avoiding the potential loss of advanced intermediates later in the synthesis due to poor selectivities. It should also be mentioned, that while the C-8 hydroxyl moiety on benzazocines of type 313 eventually becomes trigonal in the natural product, it has been found to be important for the stereoselective installment of the aziridine moiety of the natural product. Thus, the preparation of a single C-7/C-8 stereoisomer would not only simplify purification and analysis, but would also be key for a completion of a total synthesis of FR900482.

Overall, this general approach would also provide an opportunity to prepare various analogs of the benzazocine core. However, in this initial study we elected to intersect with benzazocine 284 from Ciufolini’s total synthesis of (+)-FR66979 for completion of a formal synthesis (Figure 7). Our objective was to develop a more streamlined approach to 284, which had required a total of 15 steps to prepare in Ciufolini’s synthesis.

Figure 7

![Figure 7](image)

Preparation of the Ynamide – The Anti Aldol Strategy

Our initial objective in assembling the ynamide benzannulation partner was to develop a viable synthetic route to the alkynyl subtarget \( \text{317} \), with the main challenge being to find an effective method for installing the substituents with the correct stereochemical configuration as shown earlier in the retrosynthetic scheme. Initial work was focused on the preparation of an appropriate chiral auxiliary-based substrate of type \( \text{320} \) which would take part in a stereoselective anti-aldol reaction\(^\text{148}\) with acrolein (eq 46). The most direct approach would employ a derivative of 3-butynoic acid, but in the case of such compounds we were concerned that isomerization of the \( \pi \)-bond might occur to form a conjugated allenyl carbonyl compound. We therefore turned our attention to dibromo alkenes of type \( \text{320} \) for the aldol reaction. In this case we believed that isomerization would not be as facile and we expect that under suitable conditions the dibromo olefin could be conveniently transformed directly to the bromoalkyne \( \text{317} \) by elimination.

![Chemical structure](image)

Eq 47 outlines the two-step sequence to the acid required for the preparation of intermediates of type \( \text{320} \). DABCO-catalyzed addition of bromal with ketene\(^\text{149}\) led to the formation of \( \beta \)-lactone \( \text{321} \) in 82% yield. Reductive fragmentation\(^\text{150}\) of \( \text{321} \) via treatment with


Zn and acetic acid at 0 °C for 15 min produced the desired acid in 70% yield. Prolonged reaction times were found to lead to over-reduction, complicating the purification of acid 322.\textsuperscript{151}

\begin{center}
\begin{align*}
\text{Br}_3\text{C} & \quad \text{cat. DABCO} \\
0\text{ to } -30 \degree\text{C}, 2\text{ h} & \quad \text{Br}_3\text{C} \\
& \quad \text{AcOH, Et}_2\text{O} \\
\text{Br} & \quad 0\degree\text{C}, 15\text{ min} \\
& \quad \text{6 equiv Zn (dust)} \\
\text{O} & \quad \text{Br} \\
\text{O} & \quad \text{321} \\
\end{align*}
\end{center}

Our next goal was to explore anti-aldol methodology with this substrate, including conditions using Evans’ chiral oxazolidinone auxiliaries. Aldol substrates bearing the dibromo-vinyl functionality were not previously known. Interestingly, attempts to append acid 322 to an oxazolidinone chiral auxiliary proved to be problematic. Under conditions described by Dobarro and Velasco\textsuperscript{152} for the preparation of $\beta,\gamma$-unsaturated $N$-acyl-2-oxazolidinones, acylation of $N$-benzyloxazolidinone with the mixed anhydride of 322 (prepared by reaction with pivaloyl chloride in the presence of NMM) resulted in a modest yield of the isomerized product 323 (eq 48).

\begin{center}
\begin{align*}
\text{Br} & \quad \text{i) 1.0 equiv NMM} \\
\text{1.0 equiv PivCl} & \quad \text{THF, 0 \degree\text{C}, 1 h, then -78 \degree\text{C};} \\
\text{Br} & \quad \text{N} \\
\text{O} & \quad \text{Li} \\
\text{Br} & \quad \text{323} \\
\end{align*}
\end{center}

Alternative conditions for the preparation of the desired aldol substrate were tested in a model case employing the acid chloride 324, and in the absence of a tertiary amine. Under these conditions, the desired acylation product 325 was obtained, albeit in poor yield (eq 49). We surmised that the relative high acidity of the $\alpha$-position of the acid and its activated derivatives plays a significant role in the poor outcome of these reactions. Some concern arose with regard to potential reactivity and behavior of these substrates in the aldol reaction, particularly during

\textsuperscript{151} I would like to thank Shaun Fontaine for contributions towards the optimization of this step.

\textsuperscript{152} Dobarro, A.; Velasco, D. \textit{Tetrahedron} \textbf{1996}, \textit{52}, 12733.
the enolization step. At this point, further optimization of the acylation was not pursued, as studies focusing on the use of a syn-aldol route had proved to be more promising.

\[ \text{322} \xrightarrow{\text{1.8 equiv (COCl)}_2} \text{cat. DMF, CH}_2\text{Cl}_2, \text{rt 2h}} \]

\[ \begin{array}{c} \text{Br} \\ \text{324} \end{array} \xrightarrow{\text{1.1 equiv LiOTf, THF, -78 °C to rt, 2h}} \begin{array}{c} \text{O} \\ \text{325} \end{array} \]

\(~33\%~

Preparation of the Ynamide - The Syn Aldol Strategy

As shown in eq 50, an alternative strategy to access the key bromo alkyne 317 was available to us in the form of a syn-aldol addition of an enolate derivative of 327 to acrolein.

Transformation of the aldol product to aldehyde 326 would then allow direct access to bromo alkyne 317 via a homologation reaction.

Syn aldol additions involving chiral auxiliaries have been studied extensively over the years, and many uses have been found for this highly useful asymmetric process in natural product syntheses.\(^{153}\) However, few examples of the use of \(\beta\)-alkoxy-substituted compounds of type 327 known, presumably because \(\beta\)-elimination can be a competitive process during the enolization step. Nonetheless, Mukaiyama has demonstrated that under \(\text{Sn(OTf)}_2\)-mediated aldol

conditions,\textsuperscript{154} \(N\)-acylthiazolidinethione \(328^{154b}\) can successfully participate in the aldol reaction with no \(\beta\)-elimination observed (eq 51).

\[
\begin{align*}
\text{328} & \xrightarrow{1.2 \text{ equiv } \text{Sn(OTf)}_2, 1.5 \text{ equiv } N\text{-ethylpiperidine, CH}_2\text{Cl}_2, -78 ^\circ \text{C}} \text{329} \\
\text{O} & \text{S} \\
\text{Me} & \text{N} \\
\end{align*}
\]

73%

50:50 syn:anti

In later studies by Nagao and co-workers,\textsuperscript{155} high diastereoselectivity was obtained using chiral thiazolidinethione auxiliaries. As shown in eq 52, treatment of \(330\) with \(\text{Sn(OTf)}_2\) and \(N\)-ethylnlepididine generated a chiral Sn(II) enolate, which upon addition to acetaldehyde gave the 'anti-Evans' syn aldol adduct \(331\), which was used in the total synthesis of non-natural \(1\beta\)-methylcarbapenems.\textsuperscript{155d} No elimination of the \(\beta\)-benzyloxy group was observed to take place in this reaction.

\[
\begin{align*}
\text{330} & \xrightarrow{3.0 \text{ equiv } \text{Sn(OTf)}_2, 3.3 \text{ equiv } N\text{-ethylpiperidine, CH}_2\text{Cl}_2, -78 ^\circ \text{C}} \text{331} \\
\text{O} & \text{S} \\
\text{Me} & \text{OBn} \\
\end{align*}
\]

84%, 94% de

The diastereoselectivity in this reaction was proposed to be the result of a tightly chelated, six-membered transition state (Figure 8), in which the aldehyde approaches the tin(II) (\(Z\))-enolate from the less hindered side, away from the isopropyl group of the thiazolidinethione auxiliary.


Based on this precedent, we attempted to employ Nagao’s chiral tin(II) enolate addition for the construction of bromo alkynes of type 317. The use of a thiazolidinethione chiral auxiliary\textsuperscript{156} provided a further advantage to our overall synthesis, as compared to the more commonly used oxazolidinones, since these auxiliaries can be directly converted to the aldehyde using DIBAL-H.

Thiazolidinethione 332 was available by reaction of (S)-valinol with excess carbon disulfide in aq KOH according to the general method of Le Corre.\textsuperscript{157}

As depicted in Scheme 44, one-pot acylation of 332 with the mixed anhydride 333 afforded the N-acylthiazolidinethione 334\textsuperscript{158} in 74% yield. The requisite mixed anhydride was generated by

---


the reaction of 3-benzyloxypropanoic acid\textsuperscript{159} with pivaloyl chloride in the presence of Et\textsubscript{3}N and cat. DMAP. Alternatively, 334 can be obtained in 85\% yield from the acyl chloride 335 which was prepared by treatment of the corresponding acid with oxalyl chloride and cat. DMF in CH\textsubscript{2}Cl\textsubscript{2}.

With \textit{N}-acylthiazolidinethione 334 in hand, our next step was to examine the key stereoselective syn aldol addition with acrolein using Nagao’s conditions. To our delight, enolization of 334 with 1.7 equiv of Sn(OTf\textsubscript{2}) in the presence of 1.8 equiv of \textit{N}-ethytpiperidine at -78 °C in CH\textsubscript{2}Cl\textsubscript{2} for 3 h, followed by addition of acrolein, furnished the desired aldol adduct 336 in 73-76\% yield. The reaction proceeded with 95:5 syn/anti diastereoselectivity, as determined by \textsuperscript{1}H NMR analysis of the crude product.\textsuperscript{160} As discussed in detail later in this chapter, \textsuperscript{1}H NMR analysis and chemical correlation indicated that the syn product had the correct absolute stereochemistry. The reaction was found to be very sensitive to the quality of the reagents used. \textit{N}-Ethylpiperidine had to be freshly distilled prior to use, and in particular, Sn(OTf\textsubscript{2}) had to be dried and handled under an inert atmosphere. Reproducible, complete conversion was obtained only when the Sn(OTf\textsubscript{2}) was pre-washed with Et\textsubscript{2}O and dried under vacuum overnight to remove traces of triflic acid.\textsuperscript{161}

 Attempts were made to ascertain whether substrates like 334 would undergo TiCl\textsubscript{4}-promoted aldol reactions,\textsuperscript{162, 163} especially since TiCl\textsubscript{4} is much easier to handle and less

\begin{eqnarray*}
\text{334} & \xrightarrow{1.7 \text{ equiv Sn(OTf\textsubscript{2}), 1.8 equiv NEP, CH\textsubscript{2}Cl\textsubscript{2}, -78 °C, 3 h}} & \text{336} \\
\text{then 2.0 equiv acrolein, 1.5 h, -78 °C} & \text{73-76\%} & \text{(53)}
\end{eqnarray*}

\textsuperscript{158} I would like to thank Chung-Yang (Dennis) Huang for assistance in preparing significant quantities of 334 for this synthesis.


\textsuperscript{159} The assignment of the syn isomer as the major product was based on the analysis discussed later in this chapter. The diastereomeric ratio was determined by comparing integration of the methyl resonance at 0.94 ppm of the syn isomer to that of the methyl resonance at 0.92 ppm for the anti isomer.

\textsuperscript{160} See the Experimental Section for details.

expensive than Sn(OTf)₂. Of particular interest was Crimmins’ method for the preparation of titanium(IV) enolates of N-acyl thiazolidinethiones. High diastereoselectivities have been reported for the aldol additions of these titanium(IV) enolates, and depending on the stoichiometry with respect to TiCl₄ and amine, either the Evans syn or the non-Evans syn products can be obtained.¹⁶³ Unfortunately, when our N-acyl thiazolidinethione 337 was treated with 1.1 equiv of TiCl₄ and 1.0 equiv of sparteine at 0 °C in CH₂Cl₂ under Crimmins’ standard conditions for soft enolization of N-acylthiazolidinethiones, complete decomposition of the substrate was observed (eq 54). Further attempts to achieve enolization at lower temperatures were unsuccessful; substrate degradation was still observed, although in a few instances unreacted 337 was recovered. Similar attempts to use an Evans’ oxazolidinone chiral auxiliary-based substrate also failed and only trace amounts of elimination products were isolated.

![Reaction Diagram](54)

Our next focus was to determine both the relative as well as the absolute stereochemistry of the aldol adduct 336. To this end, the aldol reaction of the achiral substrate 339 with acrolein was performed for comparison purposes. Reaction under analogous enolization conditions afforded a 68:32 inseparable diastereomeric mixture of 340 in 61% yield (Scheme 45). Reduction of this mixture with NaBH₄ gave an inseparable mixture of 1,3-diol diastereomers 341. Comparison of ¹³C NMR data for these compounds to data disclosed by Breit¹⁶⁴ for the analogous anti and syn 1,3-diols 342 suggested that the major product of our aldol reaction was the syn diastereomer.

We next turned our attention to carrying out the analogous reduction of the major and minor aldol products formed in the reaction of the chiral thiazolidinonethione 334 with acrolein. As shown in Scheme 46, sodium borohydride reduction of the major product gave a 1,3-diol 343 with $^{13}$C NMR data consistent with the syn configuration. Similar treatment of the minor product 344 (isolated in 3% yield in ca. 90-95% purity from the aldol addition reaction) revealed 1,3-diol 345 with $^{13}$C NMR characteristics consistent with an anti configuration. Further confirmation of these assignments was obtained by conversion of 343 and 345 to their corresponding benzylidene acetonides (343b and 345b) (Scheme 46). For acetonide 345b, a vicinal coupling constant value of 10.2 Hz was observed for $J(H_3, H_4)$, which is in agreement with the predictions of the Karplus equation\textsuperscript{165} for typical $^3J$ axial-axial coupling constants. Unfortunately, an unresolved multiplet for $H_3$ of the acetonide 343b was observed. However, based on the peak line width, the maximum $J$ value of this multiplet would be 6.5 Hz, which falls into the smaller $^3J$ axial-equatorial vicinal coupling value ranges expected for this compound.

For determination of the absolute stereochemistry of the syn isomer we turned to Kakisawa’s modified Mosher ester analysis. Initial attempts to directly form the Mosher ester (2-methoxy-2-trifluoromethylphenylacetic acid (MPTA) ester) from N-acylthiazolidinethione 336 were met with failure, as cleavage of the auxiliary and ensuing decomposition was observed. Consequently, 336 was converted to the methyl ester 346 in 63% yield by cleavage with MeOH in the presence of imidazole. Methyl ester 346 was then successfully converted to the corresponding (R)-MPTA and (S)-MPTA esters, 347 and 348, by reaction with (R)-MPTA acid or (S)-MPTA acid in the presence of EDAC and DMAP (Scheme 47).

Scheme 47

Comparison of the chemical shift differences for the proton assignments between the Mosher ester derivatives 347 and 348 are summarized in Table 6. The application of Kakisawa’s model\textsuperscript{166} to our ester (protons to the right of the plane of the MPTA ester moiety show positive $\Delta \delta_{S,R}$, while protons to the left of this plane show negative $\Delta \delta_{S,R}$) is depicted in Figure 9. All of the assigned protons, based on their $\Delta \delta_{S,R}$ values, correlated with the model. Consequently, the absolute configuration of the C-3 carbinol could be determined from this model and was found to be the (S)-configuration, which was the expected outcome from the aldol addition reaction.
Table 6. $^1$H NMR (400 MHz, CDCl$_3$) for the (S)- and (R)-MTPA Mosher Esters 347 and 348.$^a$

<table>
<thead>
<tr>
<th>Proton $H_x$</th>
<th>$\delta$ (S)-ester (ppm)</th>
<th>$\delta$ (R)-ester (ppm)</th>
<th>$\Delta \delta_{S,R}$ (ppm)</th>
<th>Hz (400 MHz)</th>
</tr>
</thead>
<tbody>
<tr>
<td>$H_a$</td>
<td>5.81</td>
<td>5.92</td>
<td>-0.11</td>
<td>-44</td>
</tr>
<tr>
<td>$H_b$</td>
<td>5.32</td>
<td>5.44</td>
<td>-0.23</td>
<td>-48</td>
</tr>
<tr>
<td>$H_c$</td>
<td>5.28</td>
<td>5.35</td>
<td>-0.07</td>
<td>-28</td>
</tr>
<tr>
<td>$H_d$</td>
<td>5.78</td>
<td>5.76</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>$H_e$</td>
<td>3.08-3.13</td>
<td>3.08-3.13</td>
<td>0.00</td>
<td>0</td>
</tr>
<tr>
<td>$H_f$</td>
<td>3.76-3.80</td>
<td>3.64</td>
<td>+0.12 to +0.16</td>
<td>+48 to +64</td>
</tr>
<tr>
<td>$H_g$</td>
<td>3.62</td>
<td>3.49</td>
<td>+0.13</td>
<td>+52</td>
</tr>
<tr>
<td>$H_h$</td>
<td>4.48</td>
<td>3.63</td>
<td>+0.05</td>
<td>+28</td>
</tr>
<tr>
<td>$H_i$</td>
<td>3.68</td>
<td>3.63</td>
<td>+0.05</td>
<td>+20</td>
</tr>
</tbody>
</table>

$^a$ Chemical shifts are expressed in ppm relative to tetramethylsilane.

Figure 9. Application of Kakisawa's Model for Determining Absolute Configuration
With the absolute and relative stereochemistry of \( 336 \) confirmed to be that required for our synthesis, we next turned our attention to the transformation of \( 336 \) into the bromo alkyne subtarget. Protection of the secondary alcohol was accomplished via silylation with TBSOTf in the presence of 2,6-lutidine in \( \text{CH}_2\text{Cl}_2 \) at \(-78^\circ\text{C}\) to give silyl ether \( 349 \) in 96% yield. Cleavage of the thiazolidinethione with excess DIBAL-H furnished the aldehyde \( 350 \) in 83-89% yield (Scheme 48). The thiazolidinethione auxiliary was readily recovered in 75% yield by trituration with hexanes prior to purification of the aldehyde by column chromatography.

\[ \begin{align*}
\text{Scheme 48} \\
1.2 \text{ equiv TBSOTf} \\
2.2 \text{ equiv 2,6-lutidine} \\
\text{CH}_2\text{Cl}_2, 0 \text{ }^\circ\text{C} & \rightarrow 96\% \\
\text{1.8 equiv DIBAL-H} \\
\text{CH}_2\text{Cl}_2, -78 \text{ }^\circ\text{C}, 10 \text{ min} & \rightarrow 83-89\%
\end{align*} \]

At this point, we hoped to convert the aldehyde \( 350 \) to the bromo alkyne\(^{167}\) in a one-pot, single step transformation via a Corey-Fuchs type homologation\(^{168}\). In 1999, Rassat and co-workers reported a tandem olefination-elimination procedure using dibromomethyltriphenylphosphonium bromide (352)\(^{169}\) and potassium \( t \)-butoxide as the base. Aldehydes were transformed directly to the corresponding alkyne, and in some cases, the bromo alkyne (eq 55).\(^ {170,171}\) In the case of aliphatic aldehydes, bromo alkynes are obtained if the reaction is performed at \(-78^\circ\text{C}\); reduction to afford the terminal alkyne occurs on warming to rt. However, most aromatic aldehydes undergo reduction even at low temperature. In comparison to conventional Corey-Fuchs conditions, THF can be used for the initial olefination step, and the Rassat method avoids the generation of (\( \text{Ph}_3\text{P-Br} \))\(^+ \text{Br}^-\) which is a strong electrophilic and brominating reagent.


\(^{171}\) A similar procedure was developed for the one-pot synthesis of iodoalkynes, see: Michel, P.; Rassat, A. *Tetrahedron Lett.* 1999, 40, 8579.

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In our first attempt at this overall transformation, we elected to separately carry out the two steps. As shown in Scheme 49, the gem-dibroomoolefin 355 was obtained in excellent yield upon treatment of 350 with excess phosphonium bromide salt 352 and t-BuOK. Subsequent exposure of the dibromoalkene 355 to t-BuOK at -78 °C provided the desired bromo alkyne 356, also in very good yield, with an overall yield of 82% for the two steps. No terminal alkyne product was observed.

With these reactions successfully completed in sequence, we next attempted the reaction as a one-pot transformation. In this fashion, the desired bromo alkyne 356 could be obtained in 82-92% yield, which is fairly consistent with the overall yield obtained when the individual reactions were carried out separately. Little to no terminal alkyne product was observed (eq 56).
We observed that the use of solvent-free dibromomethylphosphonium bromide 352 was very important in avoiding generation of the terminal alkyne product, which was not easy to separate from bromo alkyne 356. We found that dibromomethylphosphonium bromide 352 was most conveniently prepared according to a procedure reported by Gais and co-workers,\textsuperscript{172} in which 352 was purified by recrystallization from MeOH/EtOAc. In particular, reactions using 352 contaminated with traces of MeOH or CH\textsubscript{3}CN\textsuperscript{173} usually resulted in inseparable mixtures of dibromoolefin 355, bromoalkyne 356, and the terminal alkyne derivative, with ratios varying depending on the extent of the solvent contamination. The mechanism by which the terminal alkyne is obtained under these conditions is unclear.

Occasionally the olefination step did not proceed to completion, requiring the addition of a larger excess of triphenylphosphonium dibromomethylide. In their synthesis of dihaloolefins, Speziale and Ratts observed that triphenylphosphonium dihalomethylides (prepared via the addition of triphenylphosphine to a dihalocarbene, generated from the corresponding haloform with t-BuOK) decomposed in the presence of excess t-BuOH, leading to low yields of the desired dihaloolefin (but high yields of triphenylphosphine oxide).\textsuperscript{174} They hypothesized that a competitive side reaction was occurring in which a dihalomethylphosphonium alkoxide 359 is formed. This subsequently fragments to triphenylphosphine oxide, isobutylene, and dihalomethane (Scheme 50).

\textsuperscript{172} Lerm, M.; Gais, H.-J.; Cheng, K.; Vermeeren, C. J. Am. Chem. Soc. 2003, 125, 9654
\textsuperscript{173} CH\textsubscript{3}CN can be used for the recrystallization of 352, as described by Wolkoff, P. Can. J. Chem. 1975, 53, 1333.
Our initial procedure to generate the ylide from 352 involved reaction at rt for 15-20 min. The reaction mixture prior to addition of the aldehyde would thus consist of the ylide, potassium bromide, and t-BuOH. Incomplete olefination could be due to the decomposition of the ylide by the pathway described above. When we reduced the time to generate the ylide to 5 min at rt, the reaction became reproducible and we no longer observed incomplete olefination. Although the reaction proceeds in comparable yield with a smaller excess (1.7 equiv) of phosphonium salt 352, more reliable results were obtained using 2.5 equiv.

Having completed the synthesis of bromo alkyne 356, our focus shifted to the coupling of 356 with tert-butyl N-allylcarbamate 360. Table 7 summarizes the results for the N-alkynylation of 356 with 360, utilizing the protocol previously developed in our laboratory.58,59 Under the standard conditions (entry 1), poor conversion was observed and ynamide 361 was obtained in a disappointing 5% yield, along with a significant amount of the unproductive diyne homodimer 362.
Table 7. N-Alkynylation of 356

\[
\begin{align*}
\text{NH} & \quad \text{KHMDS, Cul, 25 equiv pyr} \\
360 & \quad \text{THF, 0 °C to rt, 2 h;} \\
& \quad 1.0 \text{ equiv 356 16-24 h}
\end{align*}
\]

\[
\begin{array}{cccccc}
\text{entry} & \text{equiv 360} & \text{equiv KHMDS} & \text{equiv Cul} & \text{361}\text{a} & \text{362}\text{a} & \text{356}\text{a} \\
1 & 1.0 & 1.0 & 1.0 & 5 & 32 & 45 \\
2 & 3.0 & 3.0 & 3.0 & 42 & 40 & 0 \\
3b & 3.0 & 3.0 & 3.0 & 32 & 46 & 0 \\
\end{array}
\]

\text{a Isolated yield of products purified by column chromatography on silica gel. b A solution of 356 was added over 3.5 h.}

In previous syntheses of ynamides, an excess of the bromo alkyne was sometimes employed to compensate for losses due to competitive homodimerization, but this was not an attractive option in the case of bromo alkyne 356 which required some synthetic effort to prepare. Fortunately, complete consumption of 356 was observed when three equiv of the copper amide was utilized. The yield of ynamide 361 increased to 42%; however, homocoupling was not suppressed and 40% of the diyne 362 was obtained. In an attempt to decrease the extent of dimerization, slower addition of a solution of bromoalkyne 356 (over 3.5 h, via syringe pump) was explored, but no positive change in the outcome was observed. Tam’s conditions\textsuperscript{61} for the N-alkynylation of 356 with 360 were examined but quickly abandoned, as complete decomposition of 356 was immediately observed upon the addition of KHMDS.

Concurrently we also examined method of Hsung\textsuperscript{60} for this transformation (Table 8). When the reaction was carried out using higher than usual amounts of catalyst and ligand only 21% of ynamide 361 was obtained.\textsuperscript{175} An equivalent yield of homodimer 362, along with ca. 41% of the unreacted bromoalkyne 356 was recovered (entry 1).

\textsuperscript{175} This modification of Hsung’s conditions was recently found to be superior for alkynylation of tert-butyl carbamates, see: Istrate, F. M.; Buzas, A. K.; Jurberg, I. D.; Odabachian, Y.; Gago\'sz, F. Org. Lett. 2008, 10, 925
Table 8. N-Alkynylation of 347

<table>
<thead>
<tr>
<th>entry</th>
<th>equiv 360</th>
<th>equiv CuSO₄·5H₂O</th>
<th>equiv 1,10-phenanthroline</th>
<th>361ᵃ</th>
<th>362ᵇ</th>
<th>356ᵃ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>1.0</td>
<td>0.2</td>
<td>0.4</td>
<td>21</td>
<td>20</td>
<td>41</td>
</tr>
<tr>
<td>2</td>
<td>3.0</td>
<td>0.2</td>
<td>0.4</td>
<td>38</td>
<td>&lt;5</td>
<td>47</td>
</tr>
<tr>
<td>3ᵇ</td>
<td>3.0</td>
<td>0.4</td>
<td>0.8</td>
<td>68</td>
<td>&lt;5</td>
<td>15</td>
</tr>
</tbody>
</table>

ᵃ Isolated yield of products purified by column chromatography on silica gel. ᵇ CuSO₄·5H₂O and 1,10-phenanthroline was added in two portions over 46 h.

Homodimerization was minimized when 3.0 equiv of the carbamate was employed; however, conversion remained poor despite the long reaction times. The addition of 0.4 equiv of CuSO₄·5H₂O and 0.8 equiv of 1,10-phenanthroline (total) in two equal portions over 46 h resulted in a significant improvement and provided the ynamide 361 in 68% yield with essentially none of the homodimer formed as a byproduct.

Preparation of Cyclobutenones 364 and 365

With ynamide 361 at hand, the next objective was to synthesize the 3-substituted cyclobutene partner for the key benzannulation reaction. As shown in Scheme 51, 3-ethoxycyclobutene 363¹⁷⁶ was conveniently prepared in 50% yield by the reaction of ethoxyacetylene with excess ketene. The addition of the benzylxymethyl- and methoxymethyl organolithium compounds, generated in situ from the corresponding organostannanes, provided cyclobutenones 364 and 365 respectively in good yield. Initial attempts at hydrolysis of the intermediate tertiary alcohol with aqueous HCl resulted in poor yields of 365, and in the case of 364, none of the desired product. Mild hydrolysis via the addition of TFAA, followed by quenching with satd NaHCO₃, proved to be a superior procedure. These conditions were introduced by Liebeskind¹⁷⁷ and later applied in our synthesis of ascochlorin³⁸d for the

preparation of related 3,4-substituted cyclobutenones. MsCl was also explored as a trapping reagent, but cleaner reactions and higher yields were obtained in general with TFAA. Cyclobutenones 364 and 365 were purified by column chromatography on acetone-deactivated silica gel and stored at -18 °C under argon.

Scheme 51

Cyclobutenone 364 was the annulation partner required for the completion of the formal synthesis of FR900482. Cyclobutenone 365, on the other hand, was prepared as an alternative partner as its benzannulation would provide a benzazocine core in which all of the oxygen and nitrogen atoms would be differentially protected, providing maximum flexibility with regard to the elaboration of this intermediate.

Application of the Tandem Benzannulation-RCM Approach to the Benzazocine Core

With the preparation of both the ynamide 361 and cyclobutenones 364 and 365 completed, we next turned our attention to the key benzannulation reaction which would provide the substituted aromatic framework of FR900482.
As depicted in Scheme 52, the reaction between ynamide 361 and a slight excess of 365, using conditions previously employed for 3-substituted cyclobutenones, proceeded smoothly to give the desired benzannulation adduct in excellent yield. Similarly, annulation product 367 was obtained in good yield via the reaction of 361 with cyclobutenone 364. Treatment of the benzannulation products 366, 367, and benzyl ether derivative 368 with Grubbs’ second generation catalyst 182 afforded benzazocines 369-371 directly in good yields (Scheme 53).

Through the successful implementation of our tandem benzannulation-RCM strategy, we were able to rapidly assemble the fully functionalized benzazocine core of FR900482. As demonstrated by the preparation of benzazocine 369, use of this convergent approach provided

\[ \text{366 R}^1 = \text{CH}_2\text{OMe}, \text{R}^2 = \text{H}\]
\[ \text{367 R}^1 = \text{OBn}, \text{R}^2 = \text{H}\]
\[ \text{368 R}^1 = \text{OBn}, \text{R}^2 = \text{Bn}\]
\[ \text{369 R}^1 = \text{CH}_2\text{OMe}, \text{R}^2 = \text{H} \quad 80-89\%\]
\[ \text{370 R}^1 = \text{OBn}, \text{R}^2 = \text{H} \quad 84\%\]
\[ \text{371 R}^1 = \text{OBn}, \text{R}^2 = \text{Bn} \quad 83\%\]

\[ \text{178 Prepared in 95\% yield through the treatment of 367 with 2.5 equiv NaH and 2.0 equiv BnBr at DMF for 3 h.}\]
us with immediate access to an intermediate with completely differentiated protecting groups. This allows for further elaborations to the natural product, as well as other derivatives.

With benzazocine 370 and its benzyl ether derivative 371\textsuperscript{179} in hand, we moved on to complete the formal synthesis of FR900482.

**Double-Deprotection of Benzazocine 371**

We expected that the completion of a formal synthesis of FR900482 would require only one transformation from our benzazocine intermediate 371 (eq 57). Removal of the N-Boc and secondary tert-butyldimethylsilyl ether simultaneously in a one-pot transformation would give Ciufolini’s intermediate 284 directly.

![Chemical structure of 371 and 284](image)

Martin had reported a similar attempt to remove an N-Boc group in one of his early approaches to the synthesis of FR900482.\textsuperscript{128} Martin was unable to selectively deprotect the azocine nitrogen of 372 under various conditions to give 373 as concomitant cleavage of the primary PMB ether was always observed. This unexpected outcome was rationalized to result from the close proximity of the free hydroxyl group at C-8.

![Chemical structure of 372 and 373](image)

\textsuperscript{179} Benzazocine 370 can also be converted into 371 via treatment with NaH and BnBr in DMF at rt in 74% yield.
In the case of our related compound 371, we expected the benzyl ether to be more robust towards cleavage as compared to Martin’s PMB ether. We examined a number of Brønsted and Lewis acids to effect the tandem removal of the Boc and the silyl ether functionality.

In initial screening experiments, the treatment of 371 with anhydrous methanolic HCl under dilute (ca 0.15 M) conditions resulted in selective removal of the secondary silyl ether. Increasing the concentration to ca. 2.8 M in HCl resulted in cleavage of the Boc functionality as well, producing 284 together with a byproduct which was not identified at that time.

Scheme 54

Interestingly, reaction with 3.4 M TFA in CH₂Cl₂ led to only the same undesired byproduct. The unknown compound was isolated as a single stereoisomer in 69% yield, and identified by ¹H NMR and IR analysis, as well as comparison to similar compounds in the literature,¹⁸⁰ to be the dihydropyrroloindole adduct 375 (eq 59, stereochemistry tentative). Presumably, the close proximity of the aniline nitrogen atom permitted a transannular cyclization by displacement at the allylic C-8 position.¹⁸¹

---

¹⁸¹ A similar transannular cyclization of an N-Boc benzazocine intermediate was reported in ref. 147b.
At this point, other deprotection conditions were explored. Exposure of 371 to 10 equiv of BF₃·OEt₂ in the presence of 4A sieves¹⁸²,¹⁸³ in CH₂Cl₂ for several hours resulted in a mixture of the desired azocine 284 and dihydropyrroloindole 375. However, when the reaction was stopped at 1 h, neither of these products was observed. Instead, a much more polar product 376 was observed by TLC analysis (Scheme 55). Curiously, during attempts to isolate this compound, small amounts of 284 and 375 were also obtained, although these compounds were not observed to be present prior to column chromatography on silica gel. The ¹H NMR spectrum of 376 showed the absence of tert-butyl and silyl ether protons and IR spectrum with a C=O stretch at 1657 cm⁻¹. Upon exposure to weakly acidic conditions (silica gel or chloroform with traces of HCl), 376 decomposes to form both the desired azocine 284 and dihydropyrroloindole 375. Indeed, when 376 was stirred with silica gel in CH₂Cl₂ at rt for 30 min, complete conversion to a ca. 1:1 mixture of 284 and 375 was observed by TLC. Attempts to promote the conversion of 376 to desired azocine 284 only were not fruitful.

Speculative structures for 376 include a highly strained seven-membered bridged carbamate formed as a result of the close transannular proximity of the Boc moiety to C-8. It

should be noted though, that this carbamate is structurally constrained such that the nitrogen lone-pair is not in-plane for delocalization into the carbonyl moiety (i.e. ‘twisted amide-like’).\textsuperscript{184} Alternatively, \textbf{376} could be a five-membered carbamate which is formed from nucleophilic attack of the BOC group at C-10 (Scheme 55).\textsuperscript{185}

We next attempted to deprotect \textbf{371} using TMSOTf and 2,6-lutidine.\textsuperscript{186,187} Our hope was that under these conditions, cleavage of the \textit{tert}-butyl group would be accomplished under relatively nonpolar and non-acidic conditions and would result in an intermediate with a TMS-capped carbamate. Subsequent cleavage with TBAF would then provide \textbf{284}. Conversion of \textbf{371} to a new product was observed by TLC after 1 h under these reaction conditions. This compound was tentatively identified to be the \textit{tert}-butyldimethylsilyl carbamate \textbf{377} (Scheme 56). This compound could arise via a transannular silyl-transfer or via the reaction of \textbf{371} with TBDMSOTf which is generated in the reaction. Treatment of the presumed \textbf{377} with TBAF provided the desired product \textbf{284}.

\begin{scheme}
\centering
\includegraphics[width=\textwidth]{scheme56.png}
\caption{Scheme 56}
\end{scheme}

While these conditions appeared to be promising, no further optimization was pursued. Aware of the sensitive nature of \textbf{371} towards undesirable transannular reactions under both Brønsted and Lewis acidic conditions, we next examined the the use of an alternative nitrogen


\textsuperscript{185} For a review on the nucleophilic reactivity of Boc protecting groups, see: Agami, C.; Couty, F. \textit{Tetrahedron} 2002, 58, 2701.


protecting group which would allow for simultaneous cleavage of the C-8 silyl ether under basic conditions.

Completion of the Formal Synthesis of (+)-FR900482

Our new synthetic plan required that we replace the N-Boc allyl carbamate 360 used previously with the N-Teoc allyl carbamate 378\(^\text{188}\) in the preparation of the new ynamide for the key benzannulation step. Use of the Teoc group would allow for simultaneous cleavage of this group and the C-8 silyl ether under basic conditions in the final step of the formal synthesis.

As depicted in Scheme 57, application of the conditions which were found to be optimal for the Boc-carbamate in the N-alkynylation reaction provided ynamide 379 in 78% yield. In addition, 2.1 equiv of unreacted carbamate was recovered from this reaction. No homodimer or unreacted bromo alkyne 356 was observed. Reaction of 379 with cyclobutenone 364 under the conditions previously described furnished the benzannulation product 380 in 83-90% yield.

Next, 380 was subjected to the standard RCM conditions. However, exposure of 380 to 5 mol% of Grubbs second generation catalyst 182 in refluxing CH\(_2\)Cl\(_2\) over 8 h resulted in only ca. 50% conversion to the desired benzazocine. Addition of another 2.5 mol% of 182 to the reaction

---
\(^\text{188}\) Prepared in near quantitative yield by the reaction of 1.5 equiv of N-allyl isocyanate with 1.0 equiv of 2-trimethylsilylethanol in toluene at 65 °C in the presence of 2.0 equiv i-Pr\(_2\)NEt.
mixture and further heating for 4 h improved the conversion and provided 381 in 56% yield but some loss of the product to isomerization was observed as a consequence of catalyst degradation over the longer course of the reaction. Our hypothesis was that one of the diastereomeric rotational isomers of 380 persisted under the reaction conditions, as a result of an unfavorable conformation for the ring-closing metathesis reaction to take place. Use of toluene as the reaction solvent allowed for higher reaction temperature and indeed, reaction at 65 °C resulted in the faster formation of 381 and gave an improved yield. However, incomplete conversion was still a problem and some difficulties were encountered in separating unreacted 380 from the benzazocine 381.

At this point, we decided to protect the phenol of 380 prior to RCM, with the hope that the presence of the benzyl ether would have a positive impact on changing the conformational isomers of the compound. As shown in eq 61, benzannulation product 380 was converted to the benzyl ether 382 by deprotonation with NaH, followed by addition of excess BnBr in DMF at rt. We were delighted to find that RCM of 382 proceeded smoothly under the usual conditions to give benzazocine 383 in excellent yield.

Finally, deprotection of 383 with excess TBAF proceeded smoothly to furnish the target of our formal synthesis target, 284, in 71-74% yield as a pale yellow oil (eq 62). Initial deprotection, presumably of the silyl ether, occurred rapidly at rt within a few hours, but
complete removal of the Teoc group required longer reaction time. Spectral characteristics of 284 were found to be identical to that reported by Ciufolini, and are summarized in Tables 9 and 10.

![Chemical Structure](image)

**Table 9.** $^1$H NMR (CDCl$_3$) Spectral Data for Compound 284$^a$

<table>
<thead>
<tr>
<th></th>
<th>Ciufolini (300 MHz)$^{127}$</th>
<th>Compound 284 (400 MHz)</th>
</tr>
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<tr>
<td></td>
<td>$\delta$ (m)</td>
<td>$J$ (Hz)</td>
</tr>
<tr>
<td>H(Ph)</td>
<td>7.25-7.41 (m, 15H)</td>
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<tr>
<td>H(4)</td>
<td>6.78 (s, 1H)</td>
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<tr>
<td>H(2)</td>
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<td>H(10)</td>
<td>5.83-5.88 (m, 1H)</td>
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<td>H(9)</td>
<td>5.58-5.65 (m, 1H)</td>
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</tr>
<tr>
<td>H(8)</td>
<td>5.23-5.30 (m, 1H)</td>
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<td>H(17)</td>
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</tr>
<tr>
<td>H(13, 14, 15)</td>
<td>4.56 (s, 2H)</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>4.53 (s, 2H)</td>
<td>-</td>
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<td></td>
<td>4.48 (s, 2H)</td>
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<tr>
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<td></td>
<td>3.85 (app dt, 1H)</td>
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<td></td>
<td>3.69-3.76 (m, 2H)</td>
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</tr>
<tr>
<td>H(7)</td>
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</table>

$^a$ Chemical shifts are expressed in ppm relative to tetramethylsilane
Table 10. $^{13}$C NMR (CDCl$_3$) Spectral Data for 284

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<th>Ciufolini (75 MHz)</th>
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<td>156.8</td>
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<td>137.2</td>
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<td>135.2</td>
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<td>128.4</td>
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<td>128.3</td>
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<td>127.99, 127.97</td>
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<td>127.9</td>
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<tr>
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<td>127.8</td>
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<td>127.3</td>
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<td>51.2</td>
</tr>
<tr>
<td>46.0</td>
<td>46.2</td>
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</table>

*Chemical shifts are expressed in ppm relative to tetramethylsilane*

Summary

In conclusion, we have developed a novel and efficient route requiring 9 steps to the functionalized benzazocine cores of (+)-FR900482 and (+)-FR66979. A formal synthesis of these natural products was completed in a total of 11 steps: a stereoselective Sn(OTf)$_2$ mediated syn-aldol strategy was used to prepare the thiazolidinethione intermediate 336 in 3 steps.
Further transformation of the aldehyde derivative 350 using a one-pot Corey-Fuchs protocol gave the bromo alkyne 356. N-alkynylation of 356 provided the ynamide 379, which was transformed in the key benzannulation reaction with 3-cyclobutenone 355 to give the substituted aromatic product 380. Formation of the benzazocine 383 was carried out via ring-closing metathesis of the benzyl ether of 380, and subsequent deprotection afforded the formal synthesis target 284.

Scheme 58
Part III

Synthesis of Amides and Lactams in Supercritical Carbon Dioxide
Chapter 1 – Introduction and Background

Our laboratory has enjoyed a longstanding collaboration with the laboratory of Professor Jefferson Tester in the Department of Chemical Engineering at MIT, exploring various aspects of organic synthesis in supercritical carbon dioxide. Part III describes some of the latest results from the collaboration, specifically in the area of C-N bond formation.

Supercritical Carbon Dioxide as a Reaction Medium

Interest in the synthetic community on the use of supercritical carbon dioxide (scCO₂) as a reaction medium has grown over the years in conjunction with an increasing awareness of a need for developing sustainable and environmentally-friendly ‘green’ chemistry. Carbon dioxide is cheap, non-flammable, non-toxic, and readily available as a byproduct from various fermentation and industrial processes. Furthermore, the waste disposal of CO₂ has little environmental or economic impact. In view of these characteristics, CO₂ can be considered a good replacement for conventional solvents. Indeed, the use of scCO₂ in some industrial processes such as caffeine extraction and fluoropolymer synthesis are fairly well established.

The supercritical state of carbon dioxide can be achieved at a relatively low temperature ($T_c = 31.1 \degree C$) and pressure ($P_c = 73.8$ bar) (Figure 10). With characteristics intermediate to that of a liquid and a gas, scCO₂ has highly tunable solvent properties such as density, viscosity, and diffusivity, all of which are dependent on changes in temperature and pressure. For example, the bulk density of scCO₂ at a given temperature can vary significantly from low gas-like...
densities to more liquid-like densities with changes in pressure. In practice, this could provide a means for the selective solvation of compounds, which could be beneficial in terms of developing post-reaction purification protocols. In general, the solvating ability of scCO\textsubscript{2} extends only to relatively non-polar and highly fluorinated compounds; however, this does not by any means provide a severe constraint on its use as a solvent. The addition of a small amount of a co-solvent modifier such as MeOH or toluene to scCO\textsubscript{2} can be effective in adjusting polarity, and in the case of catalytic reactions in scCO\textsubscript{2}, modifications to catalyst and/or ligand structure can enhance their ‘CO\textsubscript{2}-philicity’.

Figure 10

<table>
<thead>
<tr>
<th>Fluid</th>
<th>T\textsubscript{c} (°C)</th>
<th>P\textsubscript{c} (bar)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHF\textsubscript{3}</td>
<td>26</td>
<td>49</td>
</tr>
<tr>
<td>CO\textsubscript{2}</td>
<td>31</td>
<td>74</td>
</tr>
<tr>
<td>NH\textsubscript{3}</td>
<td>133</td>
<td>112</td>
</tr>
<tr>
<td>hexane</td>
<td>234</td>
<td>30</td>
</tr>
<tr>
<td>H\textsubbox{2}O</td>
<td>374</td>
<td>220</td>
</tr>
</tbody>
</table>

A wide range of reactions have in fact been explored using scCO\textsubscript{2} as a replacement solvent, including catalytic hydrogenation, oxidation reactions, cycloadditions, cycloaditions.

enzyme-catalyzed reactions, olefin-metathesis, and palladium-catalyzed couplings. The advantages of using \( \text{scCO}_2 \) are not limited to improving the ‘green-ess’ of a given reaction; in some cases improvements in conversion, selectivity, and reaction rates over reaction in conventional media have also been reported. For example, the gas-like nature of \( \text{scCO}_2 \) permits complete miscibility with \( \text{H}_2 \) (as with other gases such as \( \text{O}_2 \) and \( \text{CO} \)). Thus, for reactions such as hydrogenation, reaction rates in \( \text{scCO}_2 \) have been found to surpass levels observed in conventional solvents, where the solubility of the gas in the liquid media is usually the rate-limiting factor. Also, with reactions operating at conditions near the critical point, unusual selectivities have been observed where differences in local density versus the bulk average density of the system may occur, resulting in clustering and solvent-cage phenomena.

**Carbon-Nitrogen Bond-Forming Reactions in \( \text{scCO}_2 \)**

In general, supercritical carbon dioxide behaves as a relatively inert reaction medium. However, carbon dioxide can react reversibly with primary and secondary amines to form carbamic acids and carbamates. This is a key concern in transferring carbon-nitrogen bond-forming reactions from conventional solvents to \( \text{scCO}_2 \), as the formation of these intermediates may compromise the reactivity of the amine and can lead to the formation of undesired byproducts and polymers. Consequently, one goal of our program has been to investigate the feasibility of carrying out synthetically significant carbon-nitrogen bond-forming reaction in \( \text{scCO}_2 \).

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203 For an example of outstanding improvement of diastereoselectivity in \( \text{scCO}_2 \) vs conventional solvents, see: Oakes, R. S.; Clifford, A. A.; Bartle, K. D.; Pett, M. T.; Rayner, C. M. *Chem. Commun.* 1999, 247.

A few examples of C-N bond formation in scCO$_2$ have been reported, some of which take advantage of the reactivity of CO$_2$ with amines and use it either as a building block or as an in situ protecting group. For example, Leitner has reported a dramatic change in product selectivity in the intramolecular hydroaminomethylation of 387 when the reaction is carried out in scCO$_2$.$^{204}$ In conventional solvents, the cyclic amide 391 is predominantly formed; however, in scCO$_2$ this reaction pathway is essentially shut down in favor of the hydroaminomethylation pathway to give pyrrolidine 392 (Scheme 59). This selectivity reversal was attributed to the in situ protection of the nitrogen by CO$_2$, reducing the nucleophilicity of the nitrogen atom and suppressing attack at the acyl rhodium intermediate 390. The formation of the carbamic acid derivative of 387 was verified spectroscopically using high-pressure $^1$H NMR and $^{15}$N NMR.$^{204}$

---

**Scheme 59**

$$\text{387} \xrightarrow{1 \text{ mol}\% 388, 3 \text{ mol}\% 389} \text{CO, H}_2, \text{scCO}_2, 80 \degree \text{C, 44 h}} \xrightarrow{\text{cyclization}} \text{390} \xrightarrow{+ \text{H}_2} \text{reductive amination} \xrightarrow{392 (59\%)} $$

---

Holmes has successfully developed conditions for the palladium-catalyzed amination of aryl halides in scCO$_2$ (eq 64).$^{201}$ The amine coupling partners for these arylation reaction were protected as silylamines to prevent the formation of carbamic acid derivatives. The reaction is believed to proceed via transmetallation of the nitrogen from silicon to the palladium catalyst. Whilst N-silyl aliphatic amines were found to react with carbon dioxide to form silyl carbamates, less nucleophilic N-silylaniline derivatives and N-silylsulfonamides participated readily in the amination reaction.

\[
\begin{align*}
\text{R}^1 & \text{Br} + \text{Me}_3\text{Si-NMe} \quad 1.2 \text{ equiv} \quad 100^\circ \text{C}, 17 \text{ h} \quad \text{scCO}_2 (124 \text{ bar}) \\
\text{393} & \quad \text{394} \quad \text{R}^1 = \text{t-Bu}, \text{R}^2 = \text{H} \quad 74\% \\
\text{395a} & \quad \text{R}^1 = \text{NO}_2, \text{R}^2 = \text{CO}_2\text{Me} \quad 80\% \\
\text{395b} & \quad \text{R}^1 = \text{OMe}, \text{R}^2 = \text{H} \quad 73\% \\
\text{395c} & \quad \text{R}^1 = \text{OMe, R}^2 = \text{OMe} \quad 61\%
\end{align*}
\]

Recently, our laboratory has reported a strategy for the synthesis of N-heterocycles using the Pictet-Spengler reaction in scCO$_2$/CO$_2$-expanded media, in which CO$_2$ serves a dual role as both the solvent and reagent.$^{205}$ Reaction of primary amines such as 396 with aldehydes under standard Pictet-Spengler conditions in scCO$_2$ leads to the formation of polymeric materials and none of the desired heterocycles. However, successful Pictet-Spengler reactions can be achieved via an efficient in situ protection strategy. Thus, β-arylethylamine 396, in equilibrium under the reaction conditions with its corresponding carbamic acid and carbamate salt derivatives, is converted in situ to the carbamate 397 by alkylation with a dialkyl carbonate. Condensation with an aldehyde then forms the reactive N-acyliminium species leading to the Pictet-Spengler cyclization to provide tetrahydroisoquinoline derivatives 398 (Scheme 60). Other heterocycles such as quinazolines$^{206}$ and oxazolidinone$^{207}$ derivatives have also been synthesized in scCO$_2$, using carbon dioxide as a building block as well as the solvent.

The study of carbon-nitrogen bond-forming reactions in scCO₂ remains an interesting area for further development. Expanding the range of C-N bond forming reactions that can be achieved in an environmentally friendly and benign solvent is of interest, particularly in context of pharmaceutical and fine-chemical synthesis, where the use of functional groups incorporating the nitrogen heteroatom is prevalent. The next chapter discusses our investigation of amide and lactam synthesis in scCO₂, work performed in collaboration with the Tester Laboratory.
Chapter 2 – Amide and Lactam Synthesis in scCO₂

Amide Bond-Forming Strategy

As discussed in the previous chapter, the primary objective of our program is to extend the scope of carbon-nitrogen bond forming reactions using supercritical carbon dioxide as the reaction medium. In particular, we became interested in studying the synthesis of amides and lactams, as these functional groups are essentially ubiquitous, not only in natural products but also in the pharmaceutical compounds. The amide bond is present in an estimated 25% of known drug molecules. Indeed, in a recent survey of 128 syntheses of drug candidate molecules, 8% of the reactions in the syntheses involved the acylation of amines.

Typically, amide bond formation is accomplished via the reaction of an amine with an activated carboxylic acid derivative which is generated either in situ or in a separate step from the corresponding carboxylic acid (eq 65).

Commonly used acylating agents include acid chlorides, mixed anhydrides, and activated carboxylic intermediates which are formed from the reaction of a carboxylic acid with coupling reagents such as carbonyl diimidazole or carbodiimides. A major drawback associated with the stoichiometric use of these often toxic reagents is the general lack of atom economy. An excess amount of chemical waste is generated which can lead to difficulties in separation from the desired amide product. Recently, some efforts have been made to simplify and improve the efficiency of amide synthesis.

---

In our investigation of amide bond forming processes in scCO$_2$, we decided to use an atom economical strategy. Specifically, we focused on the preparation of amides via the reaction of amines with ketenes, which are generated in situ from alkynyl ether precursors (eq 66).

\[ \text{EtO} \equiv \text{R} \xrightarrow{\Delta} \begin{array}{c}
\text{O} \\
\text{H} \\
\text{O} \\
\text{C} \\
\text{R}
\end{array} \xrightarrow{\text{retro-ene}} \begin{array}{c}
\text{O} \\
\text{C} \\
\text{R}
\end{array} \xrightarrow{R_1R_2NH} \begin{array}{c}
\text{N} \\
\text{R} \\
\text{R}^1
\end{array} \] (66)

Ficini, and later Arens were the first to demonstrate that alkynyl ethers undergo the retro-ene reaction upon thermolysis to form ketenes which can then be trapped by various nucleophiles. Ethoxy alkynyl ethers 402 undergo the retro-ene at ca. 120 °C, while branched ethers are thermally more labile and react at lower temperatures. For example, as shown by Pericàs in the synthesis of silylamide 406 (eq 67), tert-butoxyalkynyl ethers undergo the retro-ene reaction readily in refluxing chloroform.

\[ t\text{-BuO} \equiv \text{SiMe}_3 \xrightarrow{\text{PhNH}_2} \text{Me}_3\text{Si} \xrightarrow{\text{NPh}_2} \] (67)

With regard to other examples of the use of this strategy to synthesize amides, MaGee has applied this process to the synthesis of lactams. For example, under high dilution conditions, 408 was heated in refluxing xylenes at 150 °C for 3 h, providing the eight-membered lactam derivative 409 in 68% yield (eq 68).

---


132
xylenes, 150 °C N (68)

Overall, this approach to amide bond formation is both atom-economical and environmentally friendly, with ethylene (or isobutylene, in the case of t-butoxy alkynyl ether derivatives) as the only byproduct. Our initial objective was to examine the feasibility and scope of the intermolecular version of this reaction in scCO₂. The visual monitoring of reaction phase-behavior in scCO₂ is generally an important tool for reaction optimization. As only two substrates are present in this reaction system, visual monitoring is greatly simplified. With the use of scCO₂ as the reaction solvent, completely solvent-free amide products (assuming minimal side-reactions) can be obtained, by depressurizing the reaction cell.

**Preparation of the Alkynyl Ethers**

The general strategy used for preparing the various alkynyl ethers required for our studies involved the addition of a metalated alkynyl ether to an electrophilic partner. As depicted in Scheme 61, ethoxyacetylene²¹⁴ was converted to the corresponding lithium acetylide and alkylated directly with iodohexane in the presence of HMPA to give 411 following the method of Kocienski.²¹⁵ Alternatively, lithium ethoxyacetylide 413 can be conveniently generated in situ from chloroacetaldehyde diethyl acetal using the method of Raucher.²¹⁶ Addition of propionaldehyde then provided an ethoxyethynyl carbino²¹⁶ which was silylated with TBSCI to give alkynyl ether 414. The alkynyl ethers 411 and 414 were purified by silica gel chromatography and in the case of 411, stable to storage at -18 °C over several months. Alkynyl ether 414 is stable to several weeks storage under analogous conditions.

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²¹⁴ Commercially available as a ~50% w/wt solution in hexane from Alfa Aesar.
As illustrated in Scheme 62, alkynyl ether 416 was prepared in 39% yield following a protocol developed for the preparation of an analogous derivative used for the synthesis of mycophenolic acid. Geranyl mesylate 415, prepared in situ from treatment of geraniol with MeLi and MsCl, was treated with the Grignard derivative of ethoxyacetylene in the presence of Li₂CuCl₄. Alkynyl ether 416 was found to be relatively unstable towards prolonged storage and was used immediately subsequent to preparation.
A similar strategy was used for the preparation of tert-butoxyalkynyl ethers.\(^{217}\) Greene has developed a method in which alkynyl ethers can be synthesized directly from alcohols using a one-pot procedure.\(^{218}\) In this method, a potassium alkoxide is added to dichloroacetylene (generated in situ from trichloroethylene\(^ {219}\)) and treatment with \(n\)-BuLi then forms the alkoxyacetylide which can be trapped in situ with an electrophile (eq 69).

\[
\begin{align*}
ROH & \xrightarrow{KH, \text{THF, rt; } \text{Cl}_2\text{C=CCl}_2, -50 \degree C} \left[ \begin{array}{c}
\text{Cl} \\
\text{Cl} \\
\text{H}
\end{array} \right] \\
& \xrightarrow{n\text{-BuLi, } -78 \degree C} \text{E}^+ \\
& \xrightarrow{\text{E}^+} \text{(69)}
\end{align*}
\]

Our initial attempts to use this one-pot method to synthesize tert-butoxyoctyne \(^{420}\) gave the desired products in poor yield and as impure mixtures. Subsequently, we decided to isolate the product of the initial step of this reaction sequence, vinyl ether \(^{419}\). We discovered that this reaction\(^ {220}\) proceeded inconsistently, usually producing \(^{419}\) along with varying amounts of an inseparable and unidentified byproduct. Pre-treatment of the potassium hydride used to generated the tert-butoxide with I\(_2\) minimized the formation of this byproduct,\(^ {221}\) and pure \(^{419}\) was obtained in 67% yield (Scheme 63).

---


\(^{220}\) A previous, unsuccessful attempt to prepare \(^{419}\) was reported by Löffler, A.; Himbert. G. Synthesis 1992, 495. Himbert reports that in using 3.0 equiv of KOt-Bu, a bis(tert)-butoxy derivative was obtained in 85% yield. We used only 1.0 equiv of KOt-Bu and none of this byproduct was observed, except in one instance when the thick slurry which forms upon addition of trichloroethylene was not sufficiently stirred.

\(^{221}\) Treatment of KH with I\(_2\) was performed to remove traces of elemental potassium or potassium superoxide which often leads to improved yields, see: MacDonald, T. L.; Natalie, K. J.; Prasad, G.; Sawyer, J. S. J. Org. Chem. 1986, 51, 1124.
Treatment of 419 with n-BuLi, followed by iodohepane in the presence of HMPA, provided 420 in 57% yield. The same lithium acetylide can be trapped with propionaldehyde to afford tert-butoxyalkynyl ether 421 in 50% overall yield after silylation. These tert-butoxy alkynyl ethers were found to be thermally sensitive as well as acid sensitive and purification required the use of acetone-deactivated silica gel.

We were also interested in investigating macrolactamization processes in scCO₂. For this purpose, alkynyl ether 422 was prepared using a two-step sequence. Alkylation of 401 in the presence of HMPA with 1,10-dibromodecane furnished an alkyl bromide derivative which was subsequently treated with benzylamine and cat. NaI to provide 422, in 40% overall yield (eq 70).
Optimization of Conditions for Amide Synthesis in scCO₂.

All reactions in scCO₂ were performed in a Thar stainless steel view cell reactor fitted with two coaxial sapphire windows, allowing visual inspection. The exterior of the cell was wrapped tightly with insulated heating tape which was interfaced to a temperature controller. The cell temperature and pressure were monitored with an internal thermocouple probe and a pressure gauge. The cell reactor was placed on a magnetic stirrer and the reactor contents were mixed using a magnetic stir bar. The reactants were charged into the reactor via syringe, either as a solution in dichloromethane or neat. The minimal solvent used to dissolve the reactants, if any, was then removed by evacuation of the reactor cell which was purged with argon prior to introduction of CO₂. Further details on the reactor set-up are presented in the Experimental section.

Our preliminary optimization experiments were focused on the reaction of N-benzylbutylamine (423) with ethoxy-1-octyne (411) (Table 11). We were pleased to find that addition of the amine to the in situ generated ketene proceeded as cleanly and efficiently in scCO₂ as the reaction in toluene which was carried out in a sealed tube. In this case the acylation proceeded smoothly without interference from the equilibrium reaction of the amine with CO₂. The optimal temperature for the reaction in scCO₂ was 120 °C; at 110 °C unreacted alkynyl ether 411 (ca. 25%) was recovered even after 39 h. At 120 °C, the minimum pressure required to completely solubilize reactants 411 and 423 was observed to be ca. 215 bar (entry 2). The use of 1-t-butoxy-1-octyne 420 (entry 4) permitted the reaction to be carried out at 90 °C, and amide 424 was obtained in yields similar to those obtained using 411 at 120 °C.
TABLE 11. Optimization of Conditions for Amide Synthesis

![Reaction Scheme](image)

<table>
<thead>
<tr>
<th>entry</th>
<th>alkynyl ether</th>
<th>solvent</th>
<th>temperature (°C)</th>
<th>pressure (bar)</th>
<th>yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>411</td>
<td>toluene</td>
<td>120</td>
<td>1.3</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>411</td>
<td>CO₂</td>
<td>120</td>
<td>215</td>
<td>85</td>
</tr>
<tr>
<td>3</td>
<td>411</td>
<td>CO₂</td>
<td>120</td>
<td>394</td>
<td>86</td>
</tr>
<tr>
<td>4</td>
<td>420</td>
<td>CO₂</td>
<td>90</td>
<td>224</td>
<td>82</td>
</tr>
</tbody>
</table>

* Isolated yield of products purified by column chromatography on silica gel. \(^b\) Reaction carried out in a sealed tube. Pressure calculated based on the vapor pressure of toluene at 120 °C.

Under the conditions of these reactions, the phase behavior is originally monophasic and becomes biphasic after ca. 5 h, at which time a liquid phase begins to form. Eventually, the reaction mixture consists of an upper, lower-density CO₂-rich supercritical-like phase and a lower, higher-density amide-rich liquid phase, as depicted in Figure 10a.

![Figure 10a](image)

![Figure 10b](image)

**FIGURE 10.** Phase behavior observed for Table 11: (a) entry 2 and (b) entry 3. The solid object is a stir bar.

The appearance of a liquid phase initially led to some concern with regard to the potential detrimental effects of phase partitioning of the reactants. However, no difference in yield was observed when the reaction was performed at a higher pressure of 394 bar (entry 3), in which case monophasic phase behavior was observed for the entire duration of the reaction (Figure 222).

\(^{222}\) In control experiments, amide 424 was found to be insoluble at 215 bar in scCO₂ at 120 °C.
No ketene dimer or [2+2] cycloadducts were detected in the crude products during our optimization experiments.

Depressurization of the reaction mixture after 24 h provided the amide 424 with 95-98% purity as determined by $^1$H NMR analysis; however, some solid debris originating from abrasion of the O-rings and reactor wall was also present. Subsequently, the amide 424 was transferred out of the reactor and subjected to column chromatography to remove this material, during the process of which an estimated 5% of material was lost, as confirmed by control experiments to track the overall mass balance.

Scope of the Reaction with Respect to Amines

Next, we examined the reaction of various amines with alkynyl ether 411 in scCO$_2$ (Table 12). Reactions were run at 120-130 °C; in some cases at 120 °C after 24 h ca. 5% of 411 was still detected. All runs were performed within a 210-282 bar range, each at the minimum pressure required to solubilize both the amine and alkyne 411 in order to achieve initial homogeneity. During the course of the reaction, all amides eventually precipitated from the mixture upon formation (see Figure 12a).

Secondary amines 425 and 427 (entries 1 and 2) readily participate in the reaction, providing amides 426 and 428 in good yield. The use of $\alpha$-branched primary amines 429 and 433 (entries 3 and 5) also provided the corresponding amides in good yield; however, in these cases the formation of solids presumed to be carbamate salts was observed immediately upon the addition of CO$_2$ to the reactor at room temperature (Figure 11). As the reactor temperature reached ca. 100 °C, the solids disappeared, forming a liquid phase that was soluble in CO$_2$ upon reaching the final reaction temperature of 130 °C.²²⁴

²²³ Amide 434 was isolated and characterized by Julia M. Robinson.
²²⁴ For a discussion on the effect of temperature and solvation effects on carbamic acid and carbamate salt equilibrium, see ref. 203a.
FIGURE 11. Phase behavior observed for Table 12, entries 3, 5, and 6.

TABLE 12. Synthesis of Amides with 1-Ethoxy-1-octyne

<table>
<thead>
<tr>
<th>entry</th>
<th>amine</th>
<th>amide&lt;sup&gt;a&lt;/sup&gt;</th>
<th>yield (%)&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>NH&lt;sub&gt;4&lt;/sub&gt; 425</td>
<td>O</td>
<td>87</td>
</tr>
<tr>
<td>2</td>
<td>PhNH&lt;sub&gt;2&lt;/sub&gt; 427</td>
<td>N</td>
<td>87</td>
</tr>
<tr>
<td>3</td>
<td>PhNH&lt;sub&gt;2&lt;/sub&gt; 429</td>
<td>O</td>
<td>79&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
<tr>
<td>4</td>
<td>PhNH&lt;sub&gt;2&lt;/sub&gt; 431</td>
<td>N</td>
<td>61</td>
</tr>
<tr>
<td>5</td>
<td>NH&lt;sub&gt;2&lt;/sub&gt; 433</td>
<td>O</td>
<td>74</td>
</tr>
<tr>
<td>6</td>
<td>PhNH&lt;sub&gt;2&lt;/sub&gt; 435</td>
<td>N</td>
<td>37-43&lt;sup&gt;c&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> Reaction Conditions: 1:1 ratio of amine and 411, scCO₂ (210-282 bar), 130 °C (120 °C in the case of entry 2), 24 h.  
<sup>b</sup> Isolated yield of products purified by column chromatography on silica gel unless otherwise indicated.  
<sup>c</sup> Isolated yield of product purified by trituration with dichloromethane/hexanes.
In the case of the more electron-deficient primary amine 431, amide formation also proceeded in fairly good yield. The limit with regard to the use of primary amines was revealed by the reaction of benzylamine 435. As in the case of entries 3 and 5, the immediate precipitation of carbamate salt was observed upon introduction of CO2 to the mixture of amine and alkyne. However, in this case the desired amide 436 was obtained in only 37-43% yield. Presumably, in this case the equilibrium of benzylamine with CO2 is shifted more in favor of the carbamic acid, thereby inhibiting addition of the amine to the in situ generated ketene. In contrast, the reaction of benzylamine with the same alkylnyl ether in toluene at 130 °C produced the desired amide in 98% yield. These observations are in agreement with the findings of Albert and co-workers203c and previous experiments in our laboratory: the formation of carbamates is lower in the case of primary amines that are sterically shielded.

Scope of the Reaction with Respect to Alkynyl Ethers

Further work focused on the use of this method to prepare a wider range of amide products beginning with more functionalized alkylnyl ether derivatives. As summarized in Table 13, a number of alkylnyl ethers were found to participate in the reaction with amines in scCO2, providing access to a diverse series of amides.
TABLE 13. Synthesis of Amides: Scope with Regard to Alkynyl Ether

<table>
<thead>
<tr>
<th>entry</th>
<th>alkynyl ether</th>
<th>amine</th>
<th>amide(s)\textsuperscript{a}</th>
<th>yield (%)\textsuperscript{b}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>t-BuO≡Hex</td>
<td>420</td>
<td>PhO N C\textsubscript{7}H\textsubscript{5}</td>
<td>78\textsuperscript{c,d}</td>
</tr>
<tr>
<td>2</td>
<td>EtO≡OSi-BuMe\textsubscript{2}</td>
<td>414</td>
<td>PhO C\textsubscript{7}H\textsubscript{5}N Bu + PhO C\textsubscript{7}H\textsubscript{5}N Bu</td>
<td>437 56 438 31</td>
</tr>
<tr>
<td>3</td>
<td>t-BuO≡OSi-BuMe\textsubscript{2}</td>
<td>421</td>
<td>437 + 438</td>
<td>437 80\textsuperscript{c} 438 3</td>
</tr>
<tr>
<td>4</td>
<td>EtO≡2Et</td>
<td>416</td>
<td>N CO\textsubscript{2}Et</td>
<td>68</td>
</tr>
<tr>
<td>5</td>
<td>EtO≡NH-CO\textsubscript{2}Et</td>
<td>440</td>
<td>N CO\textsubscript{2}Et</td>
<td>66</td>
</tr>
<tr>
<td>6</td>
<td>EtO≡HN-CO\textsubscript{2}Et</td>
<td>442</td>
<td>N CO\textsubscript{2}Et</td>
<td>85</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Reaction conditions: 1:1 ratio of amine and alkynyl ether, scCO\textsubscript{2} (220-275 bar), 130 °C, 24 h. \textsuperscript{b} Isolated yield of products purified by column chromatography on silica gel unless otherwise indicated. \textsuperscript{c} Isolated yield of product purified by trituration with dichloromethane/hexanes. \textsuperscript{d} Reaction conditions: 1:1 ratio of amine and alkynyl ether, scCO\textsubscript{2} (220 bar), 90 °C, 24 h.

As shown previously in our optimization studies, the use of a tert-butoxy alkynyl ether derivative allows for lower reaction temperatures. Thus, reaction of alkynyl ether 420 with benzyhydrylamine (entry 1) afforded the amide 4230 at 90 °C in similar yield to the reaction with the corresponding ethoxyacetylene 411 at 130 °C (Table 12, entry 3). Interestingly, in this reaction carbamate salt is visually observed for nearly the entire duration of the reaction (Figure 11). In previous cases (entries 3 and 5 of Table 12), salts are also formed initially but disappear once the reaction temperature reaches 130 °C. The fact that the yield is similar to those cases suggests that that free amine 429 is liberated fast enough to permit amide formation over undesired ketene cycloaddition reactions.

Entries 2 and 3 present our attempts to synthesize β-siloxyamides. Reaction of ethoxy alkynyl ether 414 with amine 423 (entry 2) afforded amide 437 in 56% yield, accompanied with
31% of the undesired β-elimination product 438. In a model experiment at 130 °C using toluene as the reaction medium, the desired amide 437 was formed in only 10% yield; 80% of elimination product 438 was obtained. The reasons for the improved selectivity in scCO₂ are not clear. Gratifyingly, the use of the tert-butoxy alkynyl ether 421 enabled the reaction to proceed at lower temperature, resulting in an improved yield of 437 with negligible formation of the α,β-unsaturated amide 438. Alkynyl ether 416 (entry 4) was also used successfully in the synthesis of amide 439, with no competing side reactions from ketene addition to the olefinic groups observed.

Our focus moved next to the synthesis of β-amino amides. Reaction of both alkynyl ethers 440 (entry 5) and 442 (entry 6) with amine 425 afforded the amides 441 and 443, respectively, in good yield.²²⁵ None of the undesired β-elimination product was obtained in either case.

### Lactam Synthesis in scCO₂

After exploring the scope of the intermolecular reactions of amines with alkynyl ethers in scCO₂, we next turned our attention to the intramolecular version of this reaction, targeting specifically the synthesis of macrocyclic lactams.²²⁶ The efficient synthesis of medium- and large-ring structures typically require high-dilution conditions in order to minimize competitive intermolecular oligomerization.²²⁷ The necessity for the use of high-dilution for this type of reaction accordingly provides an excellent opportunity for the use of scCO₂ as a replacement solvent.

Unfortunately, preliminary screening reactions involving scCO₂ as a reaction medium indicated that lactam 444 was formed in lower yield compared to the same reaction performed in toluene in a sealed tube (Scheme 64). At the indicated reaction conditions in scCO₂, the phase behavior is originally monophasic but after ca. 5 h appears to become heterogenous in which a

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²²⁵ Alkynyl ethers 440 and 442 were prepared by addition of lithium ethoxyacetylide to an N-acyl imine equivalent, in analogy to a method reported by Mecozzi, T.; Petrini, M. J. Org. Chem. 1999, 64, 8970. The synthesis of 440 and 442, as well as the β-amino amides 441 and 443 was work carried out by Julia M. Robinson.

²²⁶ For an analogous study in xylenes, see ref. 212f and 212g.

film-like liquid phase develops, presumably containing the dilactam $^{445}_{228}$ and other higher-molecular weight oligomers. We were able to observe some improvement in lactam yield when 10% vol of toluene was added as a co-solvent. Under these conditions, the liquid phase is not visible until near the end of the reaction. This suggests that the poorer yield obtained in the absence of the co-solvent may be due to the preferential partitioning of substrate $^{422}$ from the CO$_2$-rich phase to the more-polar and smaller-volume liquid phase, resulting in an increase of the molar concentration of $^{422}$ in this liquid phase (compared to the 0.002 M concentration of the bulk CO$_2$-rich phase). As such, competitive oligomerization pathways would be favored.

**Scheme 64**

<table>
<thead>
<tr>
<th>Reaction Conditions</th>
<th>Product Yield</th>
<th>$^{422}$</th>
<th>$^{444}$</th>
<th>$^{445}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toluene (1.3 bar)</td>
<td>63%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>scCO$_2$ (322 bar)</td>
<td>31%</td>
<td>6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>10 vol % toluene in scCO$_2$ (322 bar)</td>
<td>58%</td>
<td>0%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Summary**

Carbon dioxide can be employed as an environmentally benign alternative to conventional solvents for the synthesis of a variety of amides. With the exception of primary, unbranched amines, most amines are not compromised by the competitive side reaction with CO$_2$ and participate readily in the addition to ketenes, which are generated in situ from the retro-ene reaction of alkynyl ethers, to generate the desired amide products. Preliminary work in extending the amide synthesis protocol to an intramolecular variant to afford lactams revealed a significant decrease in yield when compared to conventional solvents, however the use of a CO$_2$/co-solvent mixture suggests that these results can be augmented with further studies and optimization.

$^{228}$ Dilactam $^{445}$ was found to be insoluble at 322 bar and 120 °C in scCO$_2$. 
Part IV

Experimental Section
Experimental Section for Part I and Part II

**General Procedures.** All reactions were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg and then at ca. 0.1 mmHg (vacuum pump) unless otherwise indicated. Thin layer chromatography was performed on Merck precoated glass-backed silica gel 60 F-254 0.25 mm plates. Column chromatography was performed on EM Science silica gel 60 or Silicycle silica gel 60 (230-400 mesh).

**Materials.** Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane, diethyl ether, and tetrahydrofuran were purified by pressure filtration through activated alumina. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Chloroform, pivaloyl chloride, oxalyl chloride, and trifluoroacetic anhydride were distilled at atmospheric pressure under argon. Triethylamine, pyridine, N-ethylpiperidine, 2,6-lutidine, and benzene were distilled under argon from calcium hydride prior to use. Acrolein was distilled under vacuum at 150 mmHg immediately prior to use. Copper (I) iodide was extracted with THF for 24 h in a Soxhlet extractor and then dried under vacuum (0.1 mmHg). N-Bromosuccinimide was recrystallized from boiling water. Triflic anhydride was distilled under argon from P₂O₅. n-Butyllithium was titrated according to the Watson-Eastham method using BHT in THF with 1,10-phenanthroline as an indicator. Potassium tert-butoxide was titrated using p-toluenesulfonic acid in MeOH with phenolphthalein as an indicator.

**Instrumentation.** Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR

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spectrophotometer. $^1$H NMR spectra were recorded on Varian XL-300 (300 MHz), Varian Inova 500 (500 MHz) spectrometers and Bruker Avance-400 (400 MHz). $^1$H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the CHCl$_3$ peak at 7.27 ppm used as a standard). $^{13}$C NMR spectra were recorded on Varian XL-300 (75 MHz), Varian Inova 500 (125 MHz) spectrometers and Bruker Avance-400 (400 MHz). $^{13}$C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of CHCl$_3$ at 77.23 ppm used as a standard). High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEX II 3 tesla Fourier transform mass spectrometer.
Pent-4-en-1-ynyl bromide (125)

A 500-mL, one-necked, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with 1-penten-4-yne (4.03 g, 60.5 mmol, 1.0 equiv), N-bromosuccinimide (11.8 g, 66.6 mmol, 1.1 equiv), AgNO₃ (1.00 g, 6.05 mmol, 0.1 equiv), and 300 mL of acetone, and the resulting mixture was stirred in the dark at rt for 12.5 h. The cloudy yellow reaction mixture was then diluted with 300 mL of pentane and washed with three 125-mL portions of ice-cold water. The combined aqueous layers were extracted with 100 mL of pentane, and the combined organic layers were washed with three 80-mL portions of saturated aq Na₂S₂O₃ solution and two 80-mL portions of brine, dried over MgSO₄, filtered, and concentrated at atmospheric pressure through a 9-cm Vigreux column to give 10.27 g of a pale yellow liquid. Bulb to bulb distillation (100 mmHg, 80 °C oven temperature) afforded 6.55 g (75%, ca. 95% pure) of pent-4-en-1-ynyl bromide 125 as a colorless liquid: IR (thin film) 2254, 1077, 1006, and 895 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 5.74-5.86 (m, 1H), 5.53 (app dq, J = 1.7 Hz, 17.0 Hz, 1H), 5.15 (app dq, J = 1.6, 10.0 Hz, 1H), and 3.00 (app dt, J = 1.8, 5.3 Hz, 2H); ¹³C NMR (75 MHz, CDCl₃) δ 131.8, 116.8, 77.1, 40.6, and 24.2; HRMS-ESI (m/z) calcd for C₅H₄Br, 142.9491; found: 142.9493.
A 7-mL capacity resealable tube fitted with a rubber septum was charged with N-methyltoluenesulfonamide 137 (0.250 g, 1.35 mmol, 1.0 equiv), 1,10-phenanthroline (0.049 g, 0.27 mmol, 0.2 equiv), K₂CO₃ (0.373 g, 2.70 mmol, 2.0 equiv), CuSO₄.5H₂O (0.034 g, 0.135 mmol, 0.1 equiv), 1-bromo-2-(triisopropylsilyl)acetylene (0.423 g, 1.62 mmol, 1.2 equiv), and 1.1 mL of toluene. The reaction mixture was heated at 65 °C for 24 h. The resulting yellow-green reaction mixture was cooled to rt and filtered, and the filtrate was concentrated to afford 1.1 g of yellow oil which was purified by column chromatography on 15 g of silica gel (gradient elution with 0-10% EtOAc-hexanes) to afford 0.326 g (66%) of ynamide 139 as a white solid: m.p. 50-51 °C; IR (thin film) 2943, 2865, 2166, 1598, 1463, 1371, 1173, 987 and 883 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, J = 8.0 Hz, 2H), 7.33 (d, J = 7.9 Hz, 2H), 3.06 (s, 3H), 2.44 (s, 3H), and 1.04 (app br s, 21H); ¹³C NMR (100 MHz, CDCl₃) δ 144.9, 133.3, 129.8, 127.9, 98.2, 67.5, 39.4, 21.7, 18.7, and 11.4. Anal. Calcd for C₁₉H₃₁NO₂SSi: C, 62.42; H, 8.55; N, 3.83. Found: C, 62.13; H, 8.67; N, 3.82.
$\text{Me}_2\text{N}=\text{Si(i-Pr)}_3\text{Ts}$

39
N-(Methyl)-N-(p-toluenesulfonyl)ethynylamine.

A two-necked, 50-mL pear flask fitted with a rubber septum and an argon inlet adapter was charged with ynamide 139 (1.22 g, 3.34 mmol, 1.0 equiv) and 20 mL of THF. The solution was cooled to -40 °C and tetrabutylammonium fluoride (3.60 mL, 3.67 mmol, 1.0 M solution in THF, 1.1 equiv) was added dropwise over 2 min via syringe. The resulting cloudy yellow mixture was allowed to warm to rt over 1 h. The resulting reaction mixture was diluted with 25 mL of satd NH₄Cl solution and 20 mL of Et₂O and the aqueous phase was extracted with three 10-mL portions of Et₂O. The combined organic phases were washed with 30 mL of brine, dried over MgSO₄, filtered, and concentrated to give 1.41 g of pale yellow solid. This material was recrystallized from hot hexanes to afford 0.601 g of N-(methyl)-N-(p-toluenesulfonyl)ethynylamine (86%) as white crystals: mp 74-76 °C; IR (thin film) 3280, 2936, 2137, 1597, 1450, 1361, 1174, and 960 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.78 (d, J = 8.3 Hz, 2H), 7.36 (d, J = 8.1 Hz, 2H), 3.04 (s, 3H), 2.69 (s, 1H), and 2.44 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 145.1, 133.1, 130.0, 127.9, 77.6, 57.6, 39.0, and 21.8. Anal. Calcd for C₁₀H₁₁NO₂S: C, 57.39; H, 5.30; N, 6.69. Found: C, 57.31; H, 5.28; N, 6.56.
A 50-mL, two-necked, pear flask fitted with a rubber septum and argon inlet adapter was charged with \(N\)-(methyl)-\(N\)-(p-toluenesulfonyl)ethynylamine (0.300 g, 1.43 mmol, 1.0 equiv) and 14 mL of THF. The solution was cooled to -78 °C and KHMDS (2.00 mL, 1.86 mmol, 0.91 M solution in THF, 1.3 equiv) was added dropwise via syringe over 3 min. The reaction mixture was stirred at -78 °C for 1.5 h. MeI (0.160 mL, 2.58 mmol, 1.8 equiv) was then added to the cloudy yellow reaction mixture in one portion by syringe. The resulting mixture was allowed to warm to rt over 1.5 h and then diluted with 15 mL of satd NH\(_4\)Cl solution and 20 mL of Et\(_2\)O. The aqueous layer was extracted with two 10-mL portions of Et\(_2\)O and the combined organic layers were washed with 20-mL of brine, dried over MgSO\(_4\), filtered, and concentrated to afford 0.289 g of orange-yellow solid. Recrystallization from ca. 5 mL of hot hexanes resulted in 0.249 g of ynamide 140 (78%), as a pale yellow solid: mp 93-95 °C; IR (thin film) 2931, 2262, 1595, 1451, 1357, 1169, and 1038 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.76 (d, \(J = 8.3\) Hz, 2H), 7.35 (d, \(J = 8.1\) Hz, 2H), 3.00 (s, 3H), 2.45 (s, 3H), and 1.86 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 144.7, 133.2, 129.8, 127.9, 73.8, 64.2, 39.4, 21.8 and 3.3. Anal. Calcd for C\(_{11}\)H\(_{13}\)NO\(_2\)S: C, 59.17; H, 5.87; N, 6.27. Found, C, 58.97; H, 5.75; N, 6.27.
**N-Methoxycarbonyl-N-(trimethylsilylethynyl)methylamine (129)**

A 250-mL, three-necked, round-bottomed flask fitted with a rubber septum, argon inlet adapter, and glass stopper was charged with carbamate **122** (1.48 g, 16.6 mmol, 1.0 equiv) and 66 mL of THF. The solution was cooled to 0 °C, and a solution of KHMDS (18.0 mL, 16.6 mmol, 1.0 equiv) was then added rapidly dropwise. The resulting slurry was stirred at 0 °C for 15 min and 33 mL of pyridine was then added, followed by Cul (3.20 g, 16.6 mmol, 1.0 equiv) in one portion. The reaction mixture was allowed to warm to rt over 2 h, and a solution of the iodoalkyne **124** (5.20 g, 23.3 mmol, 1.4 equiv) in 20 mL of THF was then added dropwise via cannula over 40 min. The reaction mixture was stirred at rt for 21 h and then diluted with 120 mL of Et₂O and washed with three 100-mL portions of a 2:1 mixture of brine and concd NH₄OH solution. The combined aqueous layers were extracted with two 80-mL portions of Et₂O, and the combined organic phases were washed with 100 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 4.50 g of black oil. Column chromatography on 60 g of silica gel (gradient elution with 0-5% EtOAc-hexanes) afforded 1.96 g (64%) of ynamide **129** as a dark yellow oil: IR (thin film) 2959, 2179, 1733, 1447, and 1344 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 3.76 (s, 3H), 3.12 (s, 3H), and 0.14 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) 156.0, 96.8, 71.2, 54.2, 37.9, and 0.29; HRMS-ESI (m/z) [M+Na] calcd for C₈H₁₅NO₂Si, 208.0674, found 208.0674.
A 100-mL, one-necked, round-bottomed flask fitted with an argon inlet adapter was charged with ynamide 129 (1.08 g, 5.84 mmol) and 30 mL of methanol. K₂CO₃ (1.21 g, 8.76 mmol) was added in one portion and the reaction mixture was stirred at rt for 1 h. The resulting cloudy mixture was diluted with 30 mL of H₂O and 30 mL of Et₂O. The aqueous layer was separated and extracted with three 30-mL portions of Et₂O, and the combined organic phases were washed with 50 mL of brine, dried over MgSO₄, filtered, and concentrated to provide 0.456 g (69%) of 136 as a flaky yellow solid: mp 43-45 °C; IR (thin film) 2959, 2145, 1729, 1448, and 1341 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) 3.76 (s, 3H), 3.11 (s, 3H), and 2.78 (s, 2H); ¹³C NMR (100 MHz, CDCl₃) 156.3, 105.2, 58.0, 54.4, and 37.7; HRMS-ESI (m/z) [M+Na] calcd for C₅H₇NO₂, 136.0369, found 136.0372.
Me
\[\text{N} \equiv \text{H}\]
MeO\(_2\text{C}\)

136
N-(Methoxycarbonyl)-N-(2-propenyl)-2-(trimethylsilyl)ethynylamine (134).

A 50-mL, three-necked, round-bottomed flask fitted with a rubber septum, glass stopper, and argon inlet adapter was charged with allyl carbamate 101 (0.283 g, 2.45 mmol, 1.0 equiv) and 10 mL of pyridine. The solution was cooled at 0 °C while 2.70 mL of KHMDS (0.91 M in THF, 2.45 mmol, 1.0 equiv) was added dropwise via syringe over 5 min, and the resulting tan slurry was stirred at 0 °C for 15 min. A solution of CuI (0.520 g, 2.71 mmol, 1.0 equiv) in 4 mL of pyridine was added via cannula in one portion. The cooling bath was removed, and the green-brown reaction mixture was allowed to warm to rt over 2 h. A solution of the iodoalkyne 124 (6.1 mL, 0.6M in benzene, 3.67 mmol, 1.5 equiv) was then added via cannula over 25 min, and the resulting dark brown mixture was stirred at rt for 22 h. The reaction mixture was diluted with 100 mL of Et₂O and washed with three 30-mL portions of a 2:1 mixture of brine and conc NH₄OH solution. The combined aqueous layers were extracted with two 50-mL portions of Et₂O, and the combined organic layers were dried over MgSO₄, filtered, and concentrated to give 0.754 g of black oil, which was purified by column chromatography on 20 g of silica gel (gradient elution with 0-10% EtOAc-hexanes) to afford 0.300 g (58%) of ynamide 134 as a dark orange oil: IR (thin film) 2958, 2179, 1737, 1444, 1274, and 866 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.89 (ddt, J = 17.0, 10.3, 6.2 Hz, 1H), 5.25-5.32 (app t, J = 11.2, 17.0 Hz, 2H), 4.07 (d, J = 6.1 Hz, 2H), 3.83, (s, 3H), and 0.21 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 155.6, 131.4, 118.9, 95.5, 72.6, 54.2, 52.7, and 0.4; HRMS-ESI (m/z) [M+Na] calcd for C₁₀H₁₇NO₂Si; 234.0921, found 234.0925.
$$\text{N SiMe}_3$$

$$\text{CO}_2\text{Me}$$

134
\[ \text{SiMe}_3 H \quad \text{NN} \quad \text{CO}_2 \text{Me} \quad \text{CO}_2 \text{Me} \]

\[ \text{134} \quad \text{142} \]

\textit{N-(Methoxycarbonyl)-N-(2-propenyl)ethynylamine (142).}

A 100-mL recovery flask fitted with a rubber septum and argon inlet needle was charged with ynamide 134 (1.11 g, 5.25 mmol, 1.0 equiv) and 52 mL of THF. The yellow solution was cooled to \(-78^\circ\text{C}\), and TBAF (5.80 mL, 1.0 M in THF, 5.78 mmol, 1.1 equiv) was added dropwise via syringe over 8 min. The resulting dark green solution was stirred at \(-78^\circ\text{C}\) for 20 min and then allowed to warm to rt over 20 min. The reaction mixture was quenched by addition of 40 mL of satd NH\(_4\)Cl solution and the aqueous layer was separated and extracted with three 30-mL portions of Et\(_2\)O. The combined organic layers were washed with 50 mL of brine, dried over MgSO\(_4\), filtered, and concentrated to give 1.0 g of dark brown oil. Column chromatography on 30 g of silica gel (elution with 10% EtOAc-hexanes) provided 0.617 g (84%) of ynamide 142 as a yellow oil: IR (thin film) 3298, 2958, 2241 (weak), 2146, 1734, 1445, 1362, and 1277 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 5.88 (ddt, \(J = 6.0, 10.5, 16.9\) Hz, 1H), 5.26-5.32 (app t, \(J = 10.3, 17.2\) Hz, 2H), 4.08 (d, \(J = 6.0\) Hz, 2H), 3.84 (s, 3H), and 2.83 (s, 1H); \(^1^3\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 155.8, 131.4, 119.0, 77.5, 59.0, 54.4, and 52.5; HRMS-ESI (m/z) [M+Na] calcd for C\(_7\)H\(_9\)NO\(_2\), 162.0525; found, 162.0531.
\[HN \text{SiMe}_3\]
\[\text{CO}_2\text{Me}\]
\[142\]
\[\text{CO}_2\text{Me}\]
\[143\]

\[N-(\text{Methoxycarbonyl})-N-(2\text{-propenyl})-5-(\text{trimethylsilyl})\text{-penta-1,4-diynylamine (143).}\]

A 25-mL, pear flask fitted with a rubber septum and argon inlet needle was charged with ynamide 142 (0.127 g, 0.913 mmol, 1.0 equiv) and 2 mL of DMF. Sodium iodide (0.137 g, 0.913 mmol, 1.0 equiv), Cs\textsubscript{2}CO\textsubscript{3} (0.297 g, 0.913 mmol, 1.0 equiv), and CuI (0.174 g, 0.913 mmol, 1.0 equiv) were added and the resulting bright yellow heterogenous mixture was stirred at rt for 25 min. 3-Trimethylsilylpropargyl bromide (0.155 mL, 0.209 g, 1.10 mmol, 1.2 equiv) was then added dropwise over 4 min by syringe, and the reaction mixture was stirred at rt for 16 h. The resulting dark red-brown mixture was diluted with 20 mL of Et\textsubscript{2}O and 10 mL of satd NH\textsubscript{4}Cl solution. The organic layer was washed with two 10-mL portions of H\textsubscript{2}O, and the combined aqueous layers were extracted with two 15-mL portions of Et\textsubscript{2}O. The combined organic layers were washed with 20 mL of brine, dried over MgSO\textsubscript{4}, filtered, and concentrated to give 0.282 g of dark brown oil. Column chromatography on 20 g of silica gel (elution with 5% EtOAc-hexanes) afforded 0.142 g (62%) of diynamide 143 as a dark yellow oil: IR (thin film) 2959, 2269, 2182, 1732, 1446, 1251, and 845 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 5.87 (ddt, \(J = 6.0, 10.1, 15.8\) Hz, 1H), 5.23-5.31 (app t, \(J = 11.1, 19.4\) Hz, 2H), 4.06 (d, \(J = 5.8\) Hz, 2H), 3.81 (s, 3H), 3.34 (s, 2H), and 0.17 (s, 9H); \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}) \(\delta\) 156.1, 131.9, 118.9, 100.7, 85.2, 74.3, 64.4, 54.5, 54.3, 52.8, 11.1, and 0.2; HRMS-ESI (m/z) [M+Na] calcd for C\textsubscript{13}H\textsubscript{19}NO\textsubscript{2}Si, 272.1077; found 272.1080.
1-bromo-4-(tert-butyl(dimethyl)siloxy)-hex-5-yn-yne (127).

A 250-mL round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with 4-(tert-butyl(dimethyl)siloxy)-hex-5-en-1-yne<sup>230</sup> (2.40 g, 11.4 mmol, 1.0 equiv) and 50 mL of acetone. N-bromosuccinimide (2.23 g, 12.6 mmol, 1.1 equiv) was added and the mixture was stirred until all of the NBS dissolved. AgNO<sub>3</sub> (0.194 g, 1.14 mmol, 0.1 equiv) was added and then the reaction mixture was stirred at rt for 16 h. The resulting grey slurry was diluted with 50 mL of H<sub>2</sub>O and 80 mL of Et<sub>2</sub>O. The aqueous layer was extracted with two 50-mL portions of Et<sub>2</sub>O, and the combined organic layers were washed with two 50-mL portions of satd Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub> solution and 50 mL of brine, dried over MgSO<sub>4</sub>, filtered, and concentrated to afford ca. 3.9 g of green oil. Column chromatography on 20 g of silica (elution with hexanes) afforded 2.60 g (81%) of alkynyl bromide 127 as a colorless oil: IR (thin film) 2957, 2858, 2228, 1473, 1362, 1255, and 1090 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>) δ 5.88 (ddd, <i>J</i> = 5.6, 10.4, 17.1 Hz, 1 H), 5.25 (dt, <i>J</i> = 1.5, 17.1 Hz, 1 H), 5.11 (dt, <i>J</i> = 1.5, 10.4 Hz, 1 H), 4.24-4.29 (m, 1H), 2.38 (app qd, <i>J</i> = 6.8, 16.5 Hz, 2H), 0.91 (s, 9H), 0.10 (s, 3H), and 0.07 (s, 3H); <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>) δ 140.1, 115.0, 77.6, 72.3, 39.8, 29.7, 26.0, 18.5, -4.4, and -4.7; HRMS-ESI (m/z) [M+Na] calcd for C<sub>12</sub>H<sub>21</sub>BrOSi, 311.0443, found: 311.0438.

A 50-mL, three-necked, round-bottomed flask fitted with a rubber septum, argon inlet adapter and glass stopper was charged with allyl carbamate 101 (0.160 g, 1.39 mmol, 1.0 equiv) and 6 mL of THF. The solution was cooled to 0 °C, and a solution of KHMDS (1.5 mL, 0.91 M in THF, 1.0 equiv) was then added rapidly dropwise over ca. 4 min. The resulting pale yellow slurry was stirred at 0 °C for 15 min and 3.8 mL of pyridine was then added, followed by CuI (0.265 g, 1.39 mmol, 1.0 equiv) in one portion. The reaction mixture was allowed to warm to rt over 2 h, and a solution of the bromo alkyne 127 (0.528 g, 1.83 mmol, 1.3 equiv) in 5 mL of THF was then added dropwise via cannula over 25 min. The reaction mixture was stirred at rt for 18 h and then diluted with 25 mL of Et₂O and washed with three 20-mL portions of a 2:1 mixture of brine and concd NH₄OH solution. The combined aqueous layers were extracted with two 15-mL portions of Et₂O and the combined organic phases were washed with 30 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.871 g of red-brown oil. Purification by column chromatography on 35 g of silica gel (elution with 3% EtOAc-hexanes) provided 0.222 g (49%) of 135 as a pale yellow oil: IR (thin film) 3084, 2956, 2858, 2265, 1732, 1646, and 1388 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.81-5.94 (m, 2H), 5.2105.28 (m, 3H), 5.09 (app dt, J = 1.5, 10.4 Hz, 1H), 4.20-4.25 (m, 1H), 3.98-4.08 (m, 2H), 3.79 (s, 3H), 2.40-2.55 (app qd, J = 6.0, 16.3 Hz, 2 H), 0.90 (s, 9H), 0.08 (s, 3H), and 0.06 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.2, 140.4, 132.0, 118.4, 114.6, 77.4, 75.2, 72.8, 54.1, 52.8, 28.5, 26.0, 18.4, -4.4, and -4.7; HRMS-ESI (m/z) [M+] calcd for C₁₇H₂₉NO₃Si: 346.1809, found: 346.1807.
N-Methoxycarbonyl-N-(3-methyl-3-buten-1-ynyl)but-3-enylamine (133).

A 100-mL, three-necked, round-bottomed flask fitted with a rubber septum, argon inlet adapter, and glass stopper was charged with carbamate 123\(^{231}\) (0.994 g, 7.70 mmol, 1.0 equiv) and 30 mL of THF. The solution was cooled to 0 °C, and a solution of KHMDS (8.5 mL, 7.70 mmol, 0.91 M in THF, 1.0 equiv) was then added rapidly dropwise. The resulting pale yellow slurry was stirred at 0 °C for 15 min and 15 mL of pyridine was then added, followed by CuI (1.47 g, 7.70 mmol, 1.0 equiv) in one portion. The reaction mixture was allowed to warm to rt over 2 h, and a solution of the bromo alkyne 126 (1.84 g, 12.6 mmol, 1.6 equiv) in 12 mL of THF was then added dropwise via cannula over 40 min. The reaction mixture was stirred at rt for 15 h and then diluted with 100 mL of Et\(_2\)O and washed with three 70-mL portions of a 2:1 mixture of brine and concd NH\(_4\)OH solution. The combined aqueous layers were extracted with two 30-mL portions of Et\(_2\)O and the combined organic phases were washed with 60 mL of brine, dried over MgSO\(_4\), filtered, and concentrated to afford 4.20 g of red-brown oil. Column chromatography on 55 g of silica gel (gradient elution with hexane-5% EtOAc-hexane) to afford 1.02 g (68%) of ynamide 133 as a yellow oil: IR (thin film) 2955, 2235, 1732, 1615, 1445 and 1308 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) 5.76-5.83 (m, 1H), 5.07-5.20 (m, 4H), 3.81 (s, 3H), 3.57 (t, J = 7.0 Hz, 2H), 2.43 (app q, J = 7.1 Hz, 2H), and 1.92 (s, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) 155.8, 134.3, 126.5, 119.6, 117.6, 82.2, 72.4, 54.2, 49.4, 32.3, and 23.9; HRMS-ESI (m/z) [M+Na] calcd for C\(_{11}\)H\(_{13}\)NO\(_2\), 216.0995, found 216.0999.

\(^{231}\)Prepared in 66% yield via Curtius rearrangement of 4-pentenoic acid with subsequent trapping by methanol (1.0 equiv Et\(_3\)N, 1.0 equiv DPPA, toluene, 80 °C, 2 h then 10 equiv MeOH, 50 °C, 16 h).
3-((N-methyl-N-(methoxycarbonyl))-2-cyclobuten-1-one (146).

Ketene was generated by pyrolysis of acetone over an electrically heated metal filament using the apparatus described by Williams and Hurd.\textsuperscript{232} A two-necked, 25-mL pear flask fitted with a rubber septum and argon inlet adapter was charged with ynamide 136 (0.456 g, 4.03 mmol, 1.0 equiv) and 8 mL of acetonitrile. The argon inlet adapter was replaced with an adapter fitted with a glass pipette connected via Tygon tubing to the ketene generator. The septum was fitted with an outlet needle connected via tubing to a column of calcium sulfate leading into a trap of water. Ketene was bubbled into the solution at rt over a period of 10 h. The reaction mixture was then concentrated to afford 1.49 g of dark brown liquid. Column chromatography on 20 g of silica gel (elution with 50% EtOAc-hexanes) yielded 0.496 g (80%) of the cyclobutenone 146 as a reddish brown solid: mp 52-53 °C; IR (thin film) 2960, 1741, 1570, 1445, 1365, and 1226 cm\(^{-1}\); \(\text{H NMR (400 MHz, CDCl}_3\)} \(\delta\) 5.16 (s, 1H), 3.71 (s, 3H), 3.42 (s, 2H), and 3.25 (s, 3H); \(\text{C NMR (125 MHz, CDCl}_3\)} \(\delta\) 184.3, 166.4, 153.1, 112.2, 49.9, and 34.7; HRMS-ESI (m/z) [M+Na]\(^+\) calcd for C\(_7\)H\(_9\)Cl\(_2\)NO\(_3\), 178.0475, found 178.0472.

2-Hexyl-3-(N-methyl-N-(methoxycarbonyl))-2-cyclobuten-1-one (144).

Ketene was generated by pyrolysis of acetone over an electrically heated metal filament using the apparatus described by Williams and Hurd. A two-necked, 25-mL pear flask fitted with a rubber septum and argon inlet adapter was charged with ynamide 128 (0.152 g, 0.77 mmol, 1.0 equiv) and 1.5 mL of acetonitrile. The argon inlet adapter was replaced with an adapter fitted with a glass pipette connected via Tygon tubing to the ketene generator. The septum was fitted with an outlet needle connected via tubing to a column of calcium sulfate, and then into a trap of water. Ketene was bubbled into the solution at rt over a period of 5 h. The reaction mixture was then concentrated to afford 0.279 g of dark brown liquid. Purification by column chromatography on 16 g of silica gel (elution with 25% EtOAc-hexanes) gave 0.184 g (94%) of 144 as a yellow oil: IR (thin film) 2957, 2930, 2858, 1738, 1611, 1382, 1326, and 1202 cm⁻¹; \(^1\)H NMR (400 MHz, CDCl₃) 3.83 (s, 3H), 3.44 (s, 2H), 3.39 (s, 3H), 2.15 (t, J = 7.8 Hz, 2 H), 1.45-1.49 (m, 2H), 1.25 (app s, 6H), and 0.85 (t, J = 7.0 Hz, 3H); \(^1\)3C NMR (100 MHz, CDCl₃) 188.3, 160.4, 153.9, 127.3, 54.5, 51.0, 35.4, 32.0, 29.6, 29.4, 24.1, 23.0, and 14.5; HRMS-EI (m/z) [M⁺] calcd for C₁₃H₂₁NO₃, 239.1516, found 239.1524.
2-Hexyl-3-(N-methyl-N-(methoxycarbonyl))-4, 4-dichloro-2-cyclobuten-1-one (145).

A one-necked 10-mL pear flask fitted with a rubber septum and argon inlet needle was charged with ynamide 128 (0.100 g, 0.507 mmol, 1.0 equiv) and 1.7 mL of diethyl ether and cooled to 0 °C in an ice-water bath. Zinc-copper couple (0.149 g, 2.28 mmol, 4.5 equiv) was then added in one portion, followed by a solution of trichloroacetyl chloride (0.170 mL, 1.52 mmol, 3.0 equiv) in 0.5 mL of DME dropwise via syringe over 15 min. The reaction mixture was allowed to warm to rt over 3.5 h, then diluted with 10 mL of diethyl ether, and washed with 4 mL of ice-cold 0.5 M HCl solution followed by 4 mL of ice-cold 5% NaOH solution. The combined aqueous layers were extracted with two 5-mL portions of diethyl ether, and the combined organic phases were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to give 0.165 g of dark yellow oil. Column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.138 g (88%) of the cyclobutenone 145 as a yellow oil: IR (thin film) 2958, 2931, 1785, 1754, 1601, 1448, 1384, and 1295 cm⁻¹; $^1$H NMR (500 MHz, CDCl₃) δ 3.94 (s, 3H), 3.61 (s, 3H), 2.35 (t, $J$ = 6.7 Hz, 2H), 1.53-1.56 (m, 2H), 1.26-1.32 (m, 6H), 0.88 (t, $J$ = 6.7 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl₃) δ180.1, 163.0, 152.9, 133.1, 88.6, 54.7, 35.1, 31.5, 29.2, 29.7, 24.9, 22.6, and 14.1; HRMS-EI (m/z) [M+] calcd for C₁₃H₁₉Cl₂NO₃, 307.0737, found 307.0749.
N-(Methyl)-N-(\(\rho\)-toluenesulfonyl)-[5-butyl-3-hydroxy-2-methyl]amine (150).

A 25-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with ynamide 140 (0.100 g, 0.448 mmol, 1.0 equiv), cyclobutenone 81 (0.069 g, 0.556 mmol, 1.2 equiv) and 0.8 mL of toluene. The septum and needle were replaced with a cold finger condenser with an argon inlet and the pale yellow reaction mixture was heated at reflux for 1h. The reaction mixture was cooled to rt and concentrated to afford 0.179 g of light brown oil. This material was diluted with 2 mL of MeOH and ca. 1.5 mL of 5 M KOH solution and heated at 60-70 °C for 3h. The resulting mixture was cooled to rt, and then diluted with 2 mL of 10% HCl solution and 8 mL of Et\(_2\)O. The aqueous layer was separated and extracted with two 2-mL portions of Et\(_2\)O, and the combined organic layers were washed with 5 mL of satd NaHCO\(_3\) solution and 5 mL of brine, dried over MgSO\(_4\), filtered, and concentrated to 0.197 g of orange oil. Purification by column chromatography on 15 g of silica gel (elution with 15% EtOAc-hexanes) afforded 0.127 g of aniline 150 (81%) as an off-white solid: mp 96-98 °C; IR (thin film) 3447, 2929, 1586, 1428, 1342, 1160, 1035 and 917 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.60 (d, \(J = 8.3\) Hz, 2H), 7.30 (d, \(J = 8.1\) Hz, 2H), 6.59 (s, 1H), 5.97 (s, 1H), 5.27 (br s, 1H), 3.11 (s, 3H), 2.46 (s, 3H), 2.35 (t, \(J = 7.6\) Hz, 2H), 2.24 (s, 3H), 1.40 (tt, \(J = 7.2, 7.6\) Hz, 2H), 1.26 (m, 2H), and 0.89 (t, \(J = 7.3\) Hz, 3H); \(^1\)^C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 155.0, 143.6, 141.4, 141.1, 135.0, 129.6, 128.3, 122.4, 119.0, 115.4, 39.2, 35.1, 33.4, 22.4, 21.8, 14.2, and 11.2. Anal. Calcd for C\(_{19}\)H\(_{25}\)NO\(_3\)S: C, 65.38; H, 7.25; N, 4.03. Found: C, 65.38; H, 7.13; N, 3.92.
\(N\)-(Methoxycarbonyl)-\(N\)-allyl-[5-butyl-3-hydroxy-2-isopropenyl phenyl]amine (154).

A 10-mL pear flask equipped with a rubber septum and argon inlet needle was charged with ynamide 131 (0.058 g, 0.324 mmol, 1.0 equiv), cyclobutenone 81 (0.080 g, 0.647 mmol, 2.0 equiv), and 0.4 mL of benzene. The septum was replaced with a cold finger reflux condenser and the yellow reaction mixture was heated at reflux for 3 h. The resulting dark orange mixture was cooled to rt and concentrated to afford 0.163 g of orange oil. Column chromatography on 14 g of silica gel (elution with 15% EtOAc-hexanes) provided 0.066 g (67%) of aniline 154 as a yellow tinted solid: mp 74-76 °C; IR (thin film), 3340, 2957, 1679, 1614, 1575, 1457, 1389, 1315, 1269, 1195, and 1152 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 6.75 s, 1H), 6.52 (s, 1H), 5.87-5.95 (m, 1H), 5.50-5.54 (m, 2H), 5.06-5.14 (m, 3H), 4.54-4.58 (m, 1H), 3.80 (br s, minor rotamer), 3.63 (s, 3H), 2.54 (t, \(J = 7.4\) Hz, 2H), 1.97 (s, 3H), 1.55-1.61 (m, 2H), 1.26-1.40 (m, 2H), and 0.93 (t, \(J = 7.3\) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \(\delta\) 156.3, 152.6, 143.6, 140.1, 139.3, 133.7, 125.1, 121.5, 119.0, 117.9, 114.6, 53.6, 52.9, 35.4, 33.3, 23.4, 22.5, and 14.1; HRMS-ESI (\(m/z\)) [M+Na] calcld for C\(_{18}\)H\(_{25}\)NO\(_3\), 326.1727; found, 326.1734. Anal. Calcd for C\(_{18}\)H\(_{25}\)NO\(_3\): C, 71.26; H, 8.31; N, 4.62. Found: C, 71.17; H, 8.55; N, 4.34.
A 15-mL resealable tube fitted with a rubber septum and argon inlet needle was charged with ynamide 130 (0.093 g, 0.519 mmol, 1.0 equiv), cyclobutenone 81 (0.077 g, 0.623 mmol, 1.2 equiv), and 0.5 mL of toluene. The reaction mixture was stirred at 80-85 °C for 1.5 h, and then at 110 °C for 1.5 h. The reaction mixture was cooled to rt and concentrated to afford 0.213 g of orange-red oil. Column chromatography on 11 g of silica gel (gradient elution with 10-15% EtOAc-hexanes) afforded 0.132 g (84%) of aniline 153 as a pale yellow solid: mp 39-40 °C; IR (thin film), 3338, 2957, 2930, 1677, 1584, 1459, 1389, 1273, 1197, 1151, and 991 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.67 s, 1H), 6.55 (s, 1H), 5.86-5.94 (m, 2H), 5.50-5.54 (m, 2H), 5.41 (br s, 1H), 5.08-5.18 (m, 4H), 4.35 (dd, J = 6.1, 14.7 Hz, 1H), 3.88-3.93 (m, 1H), 3.30 (m, 2H), 2.43 (t, J = 7.6 Hz, 2H), 1.57 (quintet, J = 7.6 Hz, 2H), 1.34 (q, J = 7.4 Hz, 2H), and 0.92 (t, J = 7.3 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.5, 155.5, 143.1, 140.8, 135.8, 135.4, 121.4, 120.7, 116.9, 116.7, 115.8, 53.1, 50.1, 35.3, 33.3, 30.4, 22.5, and 14.1; HRMS-ESI (m/z) [M+Na] calcd for C₁₈H₂₅NO₃, 326.1727; found, 326.1741. Anal. Calcd for C₁₈H₂₅NO₃: C, 71.26; H, 8.31; N, 4.62. Found: C, 71.05; H, 8.55; N, 4.34.
A 50-mL pear flask fitted with a rubber septum and argon inlet needle was charged with the diynamide 143 (0.543 g, 2.18 mmol, 1.0 equiv), cyclobutenone 81 (0.351 g, 2.61 mmol, 1.2 equiv), and 2.1 mL of toluene. The septum and needle were replaced with a cold finger condenser with an argon inlet and the reaction mixture was heated at 80-85 °C for 1.5 h and then at reflux for 1 h. The resulting dark red reaction mixture was cooled to rt and concentrated to afford ca. 1.5 g of red liquid. Column chromatography on 45 g of silica gel (elution with 15% EtOAc-hexanes) provided 0.644 g (79%) of 155 as a yellow solid: mp 106-108 °C; IR (CH₂Cl₂) 3328, 2957, 2174, 1678, 1588, 1458, 1389, 1249, and 842 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.72 (s, 1H), 6.56 (s, 1H), 6.11 (s, 1H), 5.92 (ddt, J = 6.4, 10.4, 17.1 Hz, 1H), 5.10-5.14 (m, 2H), 4.52 (app dd, J = 5.8, 6.7, and 14.6, 15.6 Hz, 1H), 4.07-4.10 (m, 1H), 3.65 (s, 3H), 3.45 (s, 2H), 2.53 (t, J = 7.6 Hz, 2H), 1.57 (app quintet, J = 7.6 Hz, 2H), 1.35 (app sextet, J = 7.5 Hz, 2H), 0.93 (t, J = 7.3 Hz, 3H) and 0.16 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 156.6, 155.7, 143.7, 140.2, 133.4, 121.0, 118.9, 118.4, 116.6, 103.1, 87.6, 54.1, 53.5, 35.3, 33.5, 22.7, 17.2, 14.3, and 0.3; HRMS-ESI (m/z) [M+Na]⁺ calcd for C₂₁H₃₁NO₃Si: 396.1965, found: 396.1955.
N-(Methoxycarbonyl)-N-(but-3-enyl)-[2-allyl-3-hydroxy-5-methoxy-5-methylphenyl]amine (169).

A threaded Pyrex tube (ca. 5 mL capacity) fitted with a rubber septum and argon inlet needle was charged with ynamide 132 (0.180 g, 0.931 mmol, 1.0 equiv), cyclobutenone 157 (0.208 g, 1.85 mmol, 2.0 equiv), and 1 mL of CHCl₃. The resulting yellow solution was degassed via three cycles of freeze-pump-thaw (-196 °C, 0.05 mmHg), and sealed under argon with a threaded Teflon screw cap. The tube was submerged in an oil bath and heated at 150 °C for 16.5 h. After cooling to rt, the reaction mixture was transferred to a 25-mL, round-bottomed flask and concentrated to ca. 0.45 g of dark brown oil, which was diluted with 3 mL of MeOH and 2 mL of 5 M KOH solution. The flask was fitted with a reflux condenser and the reaction mixture was heated at 65 °C for 2 h and then cooled to rt and diluted with 2 mL of 10% HCl solution and 10 mL of Et₂O. The aqueous layer was extracted with three 4-mL portions of Et₂O, and the combined organic layers were washed with 8 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.355 g of red-brown oil. Column chromatography on 23 g of silica gel (gradient elution with 20-25% EtOAc-hexanes) afforded 0.176 g (62%) of aniline 160 as a yellow tinted solid: mp 167-170 °C; IR (thin film) 3331, 2954, 1677, 1605, 1461, 1393, 1327, 1309, 1196, 1172, 1124, 1020, and 917 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, 50 °C) δ 6.46 (s, 1H), 6.32 (s, minor rotamer), 5.88-5.96 (m, 1H), 5.68-5.76 (m, 1H), 5.48 (s, 1H), 5.12-5.17 (m, 2H), 4.99-5.11 (m, 2H), 3.81 (s, minor rotamer), 3.80 (s, 3H), 3.74 (s, minor rotamer), 3.61 (s, 3H), 3.53-3.57 (m, 2H), 3.48-3.51 (m, minor rotamer), 3.26-3.33 (m, 2H), 2.33 (m, 2H), 2.01 (s, minor rotamer) and 2.00 (s, 3H);¹³C NMR (125 MHz, CDCl₃, 50 °C) δ 157.7, 156.7, 154.1, 140.5, 136.4, 135.3, 117.5, 116.8, 116.4, 115.1, 99.5, 55.7, 53.0, 50.6, 32.3, 30.8, and 11.3, (Peaks corresponding to minor rotamer: 137.1, 116.1, 99.7, 33.0, and 31.0); HRMS-ESI (m/z) [M+H] calcd for C₁₇H₂₃NO₄, 306.1700; found 306.1704. Anal. Calcd for C₁₇H₂₃NO₄: C, 66.86; H, 7.59; N, 4.59. Found: C, 66.59; H, 7.55; N, 4.54.
\[N-(\text{Methoxycarbonyl})-N-(\text{butyl})-\{3\text{-hydroxy}-4\text{-methoxy}-5\text{-methyl}-2\text{-propylphenyl}\}amine \ (176)\].

A 25-mL round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with aniline 160 (0.088 g, 0.288 mmol, 1.0 equiv), 12 mL of EtOH, and 5% Pd/C (0.061 g, 0.029 mmol, 0.1 equiv). The rubber septum and needle were replaced with a Claisen adapter equipped with an argon stopcock adapter and an adapter fitted with a glass pipette. Argon was bubbled through the reaction mixture for 5 min and then a balloon of H₂ was fitted over the pipette. H₂ was bubbled into the solution at a steady rate at rt for 4 h (the balloon was refilled with H₂ at ca. 30-45 min intervals) after which the reaction mixture was purged with argon for 5 min. The resulting mixture was then carefully filtered through a pad of Celite (rinsed with four 10-mL portions of EtOH) and the filtrate was concentrated to provide 0.077 g (82%) of aniline 176 as a pale yellow oil which was used in the next step without further purification: IR (thin film); 3343, 2959, 1675, 1604, 1464, 1309, and 1125 cm⁻¹; \(^1\)H NMR (500 MHz, CDCl₃) \(\delta \) 6.39 (s, 1H), 6.21 (s, minor rotamer), 5.43 (s, minor rotamer), 4.91 (s, 1H), 3.82 (s, minor rotamer), 3.79 (s, 3H), 3.72 (s, minor rotamer), 3.62 (s, 3H), 3.57-3.61 (m, 1H), 3.32 (app ddd, \(J = 5.5, 11.3, 13.1 \) Hz), 2.37-2.48 (m, 2H), 1.99 (s, minor rotamer), 1.97 (s, 3H), 1.46-1.64 (m, 4H), 1.22-1.31 (m, 2H), 0.97 (t, \(J = 7.3 \) Hz, 3H), and 0.89 (t, \(J = 7.3 \) Hz, 3H).

\[N-(\text{Methoxycarbonyl})-N-(\text{butyl})-\{4\text{-methoxy}-5\text{-methyl}-2\text{-propyl}-3-(\text{trifluoromethane}\text{-sulfonyl})\text{phenyl}\}amine \ (177)\].

A 25-mL recovery flask fitted with a rubber septum and argon inlet needle was charged with aniline 176 (0.074 g, 0.239 mmol, 1.0 equiv), DMAP (0.066 g, 0.540 mmol, 2.3 equiv), and 1.2 mL of CH₂Cl₂. The resulting mixture was cooled to -20 °C and triflic anhydride (0.100 mL, 0.162 g, 0.574 mmol, 2.4 equiv) was added dropwise via syringe over ca. 1 min, resulting in a
white precipitate. The cooling bath was removed and the reaction mixture was allowed to warm to rt over 6 h. The resulting mixture was diluted with 6 mL of CH₂Cl₂ and washed with 3 mL of H₂O and 3 mL of 1 M HCl solution. The combined aqueous layers were extracted with three 3-mL portions of CH₂Cl₂ and the combined organic layers were washed with 6 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.150 g of light brown oil. Purification by column chromatography on 6 g of silica gel (elution with 10% EtOAc-hexanes) provided 0.077 g (73%) of aryl triflate 177 as a pale yellow oil: IR (thin film) 2963, 1777, 1715, 1445, 1422, 1214, and 1143 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.74 (s, 1H), 3.84 (s, 3H), 3.83 (s, minor rotamer), 3.65 (s, 3H), 3.58-3.66 (m, 1H), 3.28-3.33 (app ddd, J = 3.0, 10.9, 13.6 Hz), 2.41-2.59 (m, 2H), 2.07 (s, minor rotamer), 2.04 (s, 3H), 1.43-1.59 (m, 4H), 1.22-1.32 (m, 2H), 0.95 (t, J = 7.3 Hz, 3H), and 0.90 (t, J = 7.3 Hz, 3H).

\[N-(\text{Methoxycarbonyl})-N-(\text{butyl})-[4\text{-methoxy-5-methyl-2-propyl phenyl}]amine (178)\]

A 10-mL pear flask fitted with a rubber septum and argon inlet needle was charged sequentially with the aryl triflate 177 (0.072 g, 0.163 mmol, 1.0 equiv), 0.4 mL of DMF, Et₃N (0.070 mL, 0.489 mmol, 3.0 equiv), formic acid (0.012 mL, 0.326 mmol, 2.0 equiv), Pd(OAc)₂ (0.002 g, 0.0098 mmol, 0.06 equiv), and dppf (0.005 g, 0.0098 mmol, 0.06 equiv). The rubber septum was replaced with a cold finger condenser and the reaction mixture was heated at 85-90 °C for 12.5 h. The resulting mixture was cooled to rt, diluted with 6 mL of Et₂O, and washed with two 3-mL portions of 1M HCl and then 3 mL of H₂O. The combined aqueous layers were extracted with three 3-mL portions of Et₂O and the combined organic layers were washed with 6 mL of brine, dried over MgSO₄, filtered, and concentrated to provide 0.050 g of dark brown oil. Column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.033 g (69%) of aniline 178 as a colorless oil: IR (thin film) 2958, 1708, 1600, 1486, 1450, 1304, and 1261 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.08 (d, J = 8.5 Hz), 6.80 (d, J = 8.5 Hz), 3.84 (s, 3H), 3.82 (s, minor rotamer), 3.79 (s, minor rotamer), 3.61 (s, 3H), 3.54-3.60 (m, 1H), 3.38 (app ddd, J = 5.7, 8.8, 10.7 Hz, 1H), 2.35-2.43 (m, 2H), 2.09 (s, minor rotamer), 2.06 (s, 3H), 1.48-1.65 (m, 4H), 1.24-1.33 (app sextet, J = 7.3 Hz), 0.95 (t, J = 7.3 Hz, 3H), and 0.90 (t, J = 7.4 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.7, 156.3, 140.0, 132.0, 126.8, 125.1, 109.4, 55.7, 52.9, 51.1, 33.0,
30.2, 23.7, 20.6, 14.6, 14.0, and 11.7; HRMS-ESI (m/z) [M+Na] calcd for C_{17}H_{27}NO_{3}; 316.1883, found 316.1893.
4-{N-(3-butenyl)-N-(carbomethoxy)amino}-2, 5-dimethyl-6-methoxy-benzo[b]furan (179).

A 25-mL pear flask fitted with a rubber septum and argon inlet needle was charged with phenol 160 (0.048 g, 0.157 mmol, 1.0 equiv) and 1.6 mL of CH₂Cl₂. N-iodosuccinimide (0.042 g, 0.189 mmol, 1.2 equiv) was added in one portion, and the resulting red-orange mixture was stirred at rt for 2 h. The reaction mixture was diluted with 10 mL of CH₂Cl₂ and washed with two 5-mL portions of satd Na₂S₂O₃ solution and 5 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.092 g of pale yellow oil. This material was diluted with 3 mL of MeOH, NaOH (ca. 0.050 g, 1.25 mmol) was added, and the resulting mixture was heated at 65 °C for 2 h. The reaction mixture was cooled to rt and diluted with 2 mL of 1M HCl solution and 3 mL of CH₂Cl₂. The aqueous layer was extracted with three 2-mL portions of CH₂Cl₂, and the combined organic layers were washed with 5 mL of satd NaHCO₃ solution and 5 mL of brine, dried over MgSO₄, filtered, and concentrated to provide 0.062 g of dark yellow oil. Purification by column chromatography on 5 g of silica (gradient elution with 5%-15% EtOAc-hexanes) afforded 0.027 g (56%) of benzofuran 179 as a white solid: mp 79-81 °C; IR (thin film) 2952, 1709, 1592, 1452, 1317 and 1120 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.93 (s, 1H), 6.18 (s, 1H), 5.73 (ddt, J = 6.7, 10.4, 17.2 Hz, 1H), 5.04 (d, J = 17.3 Hz, 1H), 5.00 (d, J = 10.4 Hz, 1H), 3.87 (s, 3H), 3.83 (s, minor rotamer), 3.75-3.81 (m, 2H), 3.62 (s, 3H), 3.57-3.61 (m, minor rotamer), 2.42 (s, 3H), 2.28-2.34 (m, 2H), 2.13 (s, minor rotamer), and 2.10 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.6, 155.7, 154.4, 153.8, 135.3, 131.6, 120.5, 120.1, 116.9, 100.6, 93.5, 56.1, 53.2, 49.7, 32.8, 14.3, and 11.3. Anal. Calcd for C₁₇H₂₁N0₄: C, 67.31; H, 6.98; N, 4.62. Found: C, 67.24; H, 6.95, N, 4.59.
N-(Methoxycarbonyl)-N-(but-3-enyl)-[2-allyl-3-hydroxy-5-(methoxymethoxymethyl)-5-methylphenyl]amine (161).

A 5-mL threaded Pyrex tube fitted with a rubber septum and argon inlet needle was charged with ynamide 132 (0.098 g, 0.507 mmol, 1.0 equiv), cyclobutenone 158 (0.158 g, 1.01 mmol, 2.0 equiv) and 0.7 mL of CHCl₃. The pale yellow solution was degassed (three freeze-pump-thaw cycles at -196 °C, 0.05 mmHg), sealed under argon with a Teflon screw cap, and then heated at 150 °C for 16.5 h. The resulting mixture was cooled to rt, transferred to a 25-mL round-bottomed flask, and concentrated to give 0.410 g of dark brown oil. The flask was equipped with a reflux condenser fitted with an argon inlet adapter, 3 mL of MeOH and 2 mL of 5M KOH solution were added, and the resulting mixture was heated at 60-70 °C for 2.5 h. The reaction mixture was cooled to rt and diluted with 2 mL of 10% HCl solution and 4 mL of Et₂O. The aqueous layer was extracted with three 2-mL portions of Et₂O, and the combined organic layers were washed with 4 mL of satd NaHCO₃ solution and 4 mL of brine, dried over MgSO₄, filtered, and concentrated to yield 0.222 g of a dark orange oil. Column chromatography on 20 g of silica gel (elution with 30% EtOAc-hexanes) afforded 0.106 g (60%) of aniline 161 as an off-white solid: mp 81-83 °C; IR (thin film) 3336, 2952, 1706, 1676, 1453, 1390, 1326, 1150, 1042 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.93 (s, 1H), 6.83 (s, minor rotamer), 6.24 (s, minor rotamer), 6.21 (s, 1H), 5.85-5.97 (m, 1H), 5.64-5.75 (m, 1H), 4.98-5.09 (m, 4H), 4.74 (s, 2H), 4.70 (s, minor rotamer), 4.50-4.57 (m, 2H), 3.81 (s, minor rotamer), 3.59 (s, 3H), 3.55-3.68 (m, 2H), 3.43 (s, 3H), 3.41 (s, minor rotamer), 3.25-3.39 (m, 2H), 2.28-238 (br dt, 2H), and 2.08 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.7, 153.4, 140.2, 136.1, 136.0, 135.1, 126.3, 123.2, 116.9, 116.0, 115.8, 96.1, 67.7, 55.6, 53.1, 32.3, 31.3, and 13.6. (Peaks corresponding to minor rotamer: 156.4, 153.6, 140.5, 136.2, 126.4, 123.5, 95.9, 53.3, 32.9, and 31.2). Anal. Calcd for C₁₉H₂₇NO₅: C, 65.31; H, 7.79; N, 4.01. Found: C, 65.07; H 7.65; N, 3.98.
N-(Methoxycarbonyl)-N-(but-3-enyl)-[3-hydroxy-2-isopropenyl-5-(N-methoxycarbonyl-N-methylamino) phenyl]-amine (163).

A 10-mL, pear flask equipped with a rubber septum and argon inlet needle was charged with ynamide 133 (0.118 g, 0.611 mmol, 1.0 equiv), cyclobutenone 146 (0.168 g, 1.08 mmol, 1.8 equiv) and 0.8 mL of toluene. The septum was replaced with a cold finger reflux condenser and the mixture was stirred at 110 °C for 10 h. The reaction mixture was cooled to rt and concentrated to furnish ca. 0.450 g of a red-brown oil. Unreacted ynamide 133 was removed from this material via column chromatography on 13 g of silica gel (elution with 50% EtOAc-hexanes) to provide 0.222 g of a viscous yellow oil which was transferred into a 25-mL, round-bottomed flask and diluted with 3 mL of MeOH and 2 mL of 5M KOH. The flask was fitted with a reflux condenser and the mixture was stirred at 65 °C for 3.5 h. After cooling to rt, the reaction was quenched with 2 mL of 10% HCl solution and diluted with 10 mL of Et₂O. The aqueous layer was separated and the organic layer was washed with 5 mL of H₂O and 5 mL of brine, dried over MgSO₄, filtered, and concentrated to 0.169 g yellow oil. Column chromatography on 13 g of silica gel (gradient elution with 40-50% EtOAc-hexanes) afforded 0.112 g (53%) of aniline 163 as a pale yellow waxy solid: IR (thin film) 3311, 2956, 1709, 1680, 1609, 1452, 1359, 1264, and 1157 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.83 (s, 1H), 5.51 (s, 1H), 5.68-5.78 (m, 1H), 5.61 (s, minor rotamer), 5.44 (s, 1H), 5.00-5.06 (m, 3H), 3.90-4.04 (m, 1H), 3.74 (s, minor rotamer), 3.72 (s, 3H), 3.28 (s, 3H), 3.17 (s, minor rotamer), 3.03-3.08 (m, 1H), 2.77 (d, minor rotamer), 2.44 (s, minor rotamer), 2.29-2.4 (m, 2H), and 1.95 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 170.4, 159.4, 156.1, 153.4, 142.8, 139.4, 135.3, 125.7, 118.9, 117.0, 111.6, 109.8, 53.2, 49.7, 37.6, 36.9 (minor rotamer), 32.6, 23.0, and 19.0. Anal. Calcd for C₁₈H₂₄N₂O₅: C, 62.05; H, 6.94; N, 8.04; Found: C, 61.97; H, 6.73; N, 7.83.
OH

C +

NC

Bu Cl CO₂ Me Bu N

N-(Methoxycarbonyl)-N-(but-3-enyl)-[2-allyl-5-butyl-4-chloro-3-hydroxyphenyl]amine (162).

A 5-mL threaded Pyrex tube fitted with a rubber septum and argon inlet needle was charged with cyclobutenone 159 (0.100 g, 0.518 mmol, 1.0 equiv), ynamide 132 (0.150 g, 0.777 mmol, 1.5 equiv), BHT (0.342 g, 1.55 mmol, 3.0 equiv) and 0.7 mL of toluene. The orange-yellow solution was degassed via three freeze-pump-thaw cycles (-196 °C, 0.05 mmHg) and the tube was sealed under argon with a threaded Teflon screwcap. The tube was heated in an oil bath at 135 °C for 4 h. The resulting solution was cooled to rt, diluted with 10 mL of Et₂O, and washed with two 8-mL portions of H₂O and 8 mL of satd NaHCO₃ solution. The combined aqueous layers were extracted with two 8-mL portions of Et₂O and the combined organic layers were washed with 10 mL of brine, dried over MgSO₄, filtered, and concentrated to give ca. 0.5 g of dark red-orange oil. Purification by column chromatography on 24 g of silica gel (eluted with 10% EtOAc-hexanes) and then on 15 g of silica gel (elution with 7% EtOAc-hexanes) provided 0.082 g (45%) of aniline 162 as a viscous orange oil: IR (thin film) 3367, 3078, 2956, 2862, 1694, 1455, 1305, 1152, and 915 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.62, (s, 1H), 5.73-5.93 (m, 2H), 5.82 (s, 1H), 5.02-5.10 (m, 4H), 2.90-3.95 (m, 1H), 3.77 (br s, minor rotamer), 3.59, (s, 3H), 3.21-3.32 (m, 3H), 2.64-2.73 (m, 2H), 2.30-2.35 (m, 2H), 1.56-1.64 (app quintet, J = 7.5 Hz, 2H), 1.35-1.45 (app sextet, J = 7.5 Hz, 2H), and 0.96 (t, J = 7.3 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 156.3, 150.5, 139.2, 139.0, 135.3, 135.2, 123.1, 122.3, 119.7, 117.0, 115.7, 53.0, 50.1, 33.4, 31.7, 30.9, 22.6, and 14.1; HRMS-ESI (m/z) [M+Na] calcd for C₁₉H₂₆ClNO₃, 374.1493, found 374.1506.
7-Butyl-5-hydroxy-4-methyl-2H-quinoline-1-carboxylic acid methyl ester (191).

A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of the Grubbs catalyst 182 (0.015 g, 0.018 mmol, 0.05 equiv) in 28 mL of CH₂Cl₂. The aniline 154 (0.109 g, 0.359 mmol, 1.0 equiv) in 5 mL of CH₂Cl₂ was added to the reaction flask via cannula in one portion. The rubber septum was replaced with a reflux condenser fitted with an argon inlet adapter. The pale pink-colored reaction mixture was heated at reflux for 40 min, allowed to cool to rt, and then concentrated to afford ca. 0.131 g of green-brown foam. Column chromatography on 10 g of silica gel (elution with 15% EtOAc-hexanes) provided 0.097 g (98%) of dihydroquinoline 191 as a tan waxy solid: IR (thin film) 3360, 2957, 2923, 1680, 1616, 1502, 1440, 1351, 1297, 1248, 1220 and 1146 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.97 (br s, 1H), 6.39 (d, J = 1.5 Hz, 1H), 5.72, (dt, J = 1.5, 4.7 Hz, 1H), 5.64 (br s, 1H), 4.14-4.15 (m, 2H), 3.78 (s, 3H), 2.51 (q, J = 7.6 Hz, 2H), 2.24 (q, J = 1.5 Hz, 3H), 1.54-1.60 (m, 2H), 1.36 (app dt, J = 7.5, 15.0 Hz, 2H), and 0.93 (t, J = 7.3 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 154.9, 152.8, 142.8, 138.5, 132.6, 121.6, 117.0, 116.0, 113.2, 53.9, 53.3, 42.9, 35.5, 33.4, 22.5, 21.9 and 14.1; HRMS-ESI (m/z) [M+Na] calcd for C₁₆H₂₁NO₃, 298.1414; found, 298.1417.
8-Butyl-6-hydroxy-2,5-dihydro-benzo[\(b\)]azepine-1-carboxylic acid methyl ester (190).

A 100-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of the Grubbs catalyst 182 (0.018 g, 0.0217 mmol, 0.05) in 33 mL of CH\(_2\)Cl\(_2\). The aniline 153 (0.132 g, 0.435 mmol, 1.0 equiv) in 10 mL of CH\(_2\)Cl\(_2\) was added to the reaction flask via cannula in one portion. The rubber septum was replaced with a reflux condenser fitted with an argon inlet adapter. The pale pink-colored reaction mixture was heated at reflux for 40 min, allowed to cool to rt, and then concentrated to afford ca. 0.195 g of brown foam. Column chromatography on 10 g of silica gel (gradient elution with 15-20% EtOAc-hexanes) provided 0.114 g (95%) of dihydrobenzoazepine 190 as a tan wax: IR (thin film) 3348, 2956, 2930, 1682, 1620, 1587, 1443, 1364, 1267, 1231, and 1020 cm\(^{-1}\); \(^1\)H NMR (500 MHz, CDCl\(_3\)) \(\delta 6.60 (s, 1H), 6.40 (s, 1H), 6.26 (br s, minor rotamer), 5.76-5.83 (m, 2H), 5.49 (d, \(J = 11.0, 1H\)), 4.94 (br s, 3H), 4.23 (br s, 1H), 3.83 (s, minor rotamer), 3.68 (s, 3H), 3.38 (br s, 2H), 2.54-2.55 (m, 2H), 1.51-1.62 (m, 2H), 1.25-1.42 (m, 2H), and 0.93 (t, \(J = 7.3\) Hz, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta 156.5, 152.6, 142.4, 142.4, 142.3, 127.0, 125.3, 123.6, 120.0, 115.1, 53.4, 47.9, 35.3, 33.4, 22.6, 22.5, and 14.1; HRMS-ESI (m/z) [M+Na] calcd for C\(_{16}\)H\(_{21}\)NO\(_3\), 298.1414; found, 298.1424.
7-Hydroxy-9-methoxy-10-methyl-3,6-dihydro-2H-benzo[b]azocine-1-carboxylic acid methyl ester (192).

A 100-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a solution of the Grubbs catalyst 182 (0.014 g, 0.0169 mmol, 0.05 equiv) in 20 mL of CH₂Cl₂. The aniline 160 (0.103 g, 0.337 mmol, 1.0 equiv) in 13 mL of CH₂Cl₂ was added to the reaction flask via cannula in one portion. The rubber septum was replaced with a reflux condenser fitted with an argon inlet adapter. The pale pink-colored reaction mixture was heated at reflux for 40 min, allowed to cool to rt, and then concentrated to afford ca. 0.120 g of grey foam. Column chromatography on 9 g of silica gel (elution with 20% EtOAc-hexane) yielded 0.083 g (86%) of benzoazocine 192 as a grey-white solid: mp 165-168 °C; IR (thin film) 3325, 2936, 1704, 1674, 1606, 1464, 1390, 1322, 1192, 1165, 1129, and 1105 cm⁻¹; ¹H NMR (500 MHz, CDCl₃, 55 °C) δ 6.34 (s, 1H), 6.05 (s, minor rotamer), 5.92 (app q, J = 8.7 Hz, 1H), 5.66 (app q, J = 8.4 Hz, 1H), 5.59 (app q, minor rotamer), 4.86 (s, 1H), 4.38 (dd, J = 6.9, 13.0 Hz, 1 H), 4.21 (dd, minor rotamer), 3.88 (s, minor rotamer), 3.79 (s, 3H), 3.69 (s, minor rotamer), 3.67 (s, 3H) 3.26-3.34 (m, 1 H), 3.09-3.14 (m, 1H), 2.57-2.70 (m, 2H), 2.13-2.19 (m, 1H), 1.97 (s, minor rotamer), 1.95 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 157.2, 156.5, 156.4, 155.9, 152.3, 151.5, 140.8, 139.6, 133.5, 132.2, 128.3, 127.1, 120.7, 120.1, 116.9, 115.0, 98.9, 98.8, 55.7, 55.0, 53.6, 53.3, 49.4, 49.2, 27.5, 26.9, 25.1, 25.0, 10.2, and 10.0, (Peaks corresponding to minor rotamer): δ 156.4, 151.5, 140.8, 132.2, 128.3, 120.1, 116.9, 98.8, 55.7, 53.3, 49.2, 26.9, 25.0, and 10.2.). Anal. Calcd for C₁₅H₁₉NO₄: C, 64.97; H, 6.91; N, 5.05. Found: C, 64.88; H, 6.83; N, 4.91.

A 100-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a solution of the Grubbs catalyst 182 (0.013g, 0.015 mmol, 0.05 equiv) in 20 mL of CH₂Cl₂. The aniline 161 (0.111 g, 0.309 mmol, 1.0 equiv) in 10 mL of CH₂Cl₂ was added to the reaction flask via cannula in one portion. The rubber septum was replaced with a reflux condenser fitted with an argon inlet adapter. The pale pink-colored reaction mixture was heated at reflux for 40 min, allowed to cool to rt, and then concentrated to afford ca. 0.125 g of brown foam. Column chromatography on 10 g of silica gel (elution with 40% EtOAc-hexane) yielded 0.093 g (94%) of benzoazocine 193 as a grey-white solid: mp 110-112 °C; IR (thin film) 3338, 2939, 1704, 1676, 1607, 1454, 1389, 1322, 1037, and 919; ¹H NMR (500 MHz, CDCl₃) δ 6.82 (s, 1H), 6.74 (br s, minor rotamer), 5.95 (app q, ¹J = 8.5 Hz), 5.62-5.70 (m, 1H), 4.73 (s, 3H), 4.70 (s, minor rotamer), 4.52 (AB, ¹J = 12.2 Hz, each 1H), 4.37-4.51 (m, 1H), 3.85 (s, minor rotamer), 3.66 (s, 3H), 3.43 (s, 3H), 3.42 (s, minor rotamer), 3.37 (app dd, ¹J = 7.2, 13.3 Hz, 1H), 3.13 (app dd, ¹J = 8.9, 13.4 Hz, 1H), 2.61-2.76 (m, 1H), 2.54 (app dd, ¹J = 10.0, 13.7 Hz), 2.19 (app quintet, ¹J = 7.3 Hz, 1H), 2.06 (s, minor rotamer), and 2.03 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.5, 151.6, 140.7, 134.6, 132.1, 128.5, 128.2, 116.3, 115.5, 95.9, 67.8, 55.6, 53.3, 49.0, 27.0, 25.4, and 12.6, (Peaks corresponding to minor rotamer: δ 156.6, 151.8, 140.3, 132.8, 127.7, 116.3, 53.4, and 27.6). Anal. Calcd for C₁₇H₂₃NO₅: C, 63.54; H, 7.21; N, 4.36. Found: C, 63.23; H, 7.11; N, 4.25.
9-Butyl-8-chloro-7-hydroxy-3,6-dihydro-2H-benzo[b]azocine-1-carboxylic acid methyl ester (194).

A 100-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a solution of the Grubbs catalyst 182 (0.016 g, 0.019 mmol, 0.05 equiv) in 25 mL of CH₂Cl₂. The aniline 162 (0.134 g, 0.381 mmol, 1.0 equiv) in 15 mL of CH₂Cl₂ was added to the reaction flask via cannula in one portion. The rubber septum was replaced with a reflux condenser fitted with an argon inlet adapter. The pale pink-colored reaction mixture was heated at reflux for 30 min, allowed to cool to rt, and then concentrated to afford 0.203 g of dark brown foam. Column chromatography on 11 g of silica gel (elution with 10% EtOAc-hexanes) yielded 0.107 g (87%) of benzoazocine 194 as a brown-white solid: mp 112-114 °C, IR (thin film) 3367, 2956, 1693, 1571, 1456, 1323, and 1181 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 6.67 (s, minor rotamer), 6.60 (s, 1H), 5.93-6.00 (m, 1H), 5.84 (s, 1H), 5.65-5.70 (m, 1H), 4.36-4.40 (m, 1H), 3.82 (s, minor rotamer), 3.66 (s, 3H), 3.42-3.47 (app dd, J = 13.6, 7.1 Hz, 1H), 3.09-3.15 (m, 1H), 2.60-2.68 (m, 4H), 2.16-2.20 (m, 1H), 1.54-1.62 (tt, J = 7.1, 7.5 Hz, 2H), 1.34-1.43 (app sextet, J = 7.4 Hz, 2H), and 0.95 (t, J = 7.2 Hz); ¹³C NMR (100 MHz, CDCl₃) δ 156.2, 149.2, 140.4 (minor rotamer), 140.0, 139.1 (minor rotamer), 138.8, 131.7 (minor rotamer), 131.3, 128.9, 128.4 (minor rotamer), 126.9, 121.7, 119.5, 53.1, 49.9, 33.4, 31.7, 27.8 (minor rotamer), 27.1, 25.7, 22.5, and 14.0; HRMS-EI (m/z) [M⁺] calcd for C₁₇H₂₂ClNO₃; 323.1283, found 323.1286. Anal. Calcd for C₁₇H₂₂ClNO₃: C, 63.06; H, 6.85; N, 4.33. Found: C, 62.88; H, 6.80; N, 4.35.
8-(N-Methoxycarbonyl-N-methylamino)-5-methyl-2,3-dihydro-benzo[b]azepine-1-carboxylic acid methyl ester (195).

A 50-mL, round-bottomed flask equipped with a rubber septum and argon inlet needle was charged with a solution of the Grubbs catalyst 182 (0.013 g, 0.0153 mmol, 0.05 equiv) in 20 mL of CH₂Cl₂. The aniline 163 (0.113 g, 0.324 mmol, 1.0 equiv) in 6 mL of CH₂Cl₂ was added to the reaction flask via cannula in one portion. The rubber septum was replaced with a reflux condenser fitted with an argon inlet adapter. The pale pink-colored reaction mixture was heated at reflux for 2 h, allowed to cool to rt, and then concentrated to afford ca. 0.143 g of brown foam. Column chromatography on 15 g of silica gel (elution with 50% EtOAc-hexanes) provided 0.079 g (76%) of dihydrobenzoazepine 195 as an off-white solid: mp 200-202 °C; IR (thin film) 3297, 2954, 1706, 1676, 1609, 1580, 1450, and 1365 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.94 (bs, 1H), 6.82 (s, 1H), 6.72 (bs, minor rotamer), 6.61 (s, 1H), 5.90 (m, 1H), 4.35-4.42 (m, 1H), 4.19 (bs, minor rotamer), 3.78 (s, 3H), 3.75 (s, minor rotamer), 3.60 (s, 3H), 3.48-3.51 (m, 1H), 3.25 (s, 3H), 3.23 (s, minor rotamer), 2.00 (s, 3H), 1.98-2.01 (m, 2H), and 1.85 (bs, minor rotamer); ¹³C NMR (100 MHz, CDCl₃) δ 157.0, 156.6, 154.6, 142.4, 139.7, 135.9, 126.3, 124.8, 54.9, 53.4, 53.1, 37.7, 22.2, and 21.3. Anal. Calcd for C₁₆H₂₀N₂O₅: C, 59.95; H, 6.29; N, 8.74. Found: C, 59.85; H, 6.15; N, 8.64.
3-[N-(carbomethoxy)-N-(methyl)amino]-2-hexyl-5, 6, 7, 8-tetrahydro-naphthalen-1-ol (215).

A 20-cm long quartz tube (7 mm I. D.; 9 mm O. D.) equipped with a rubber septum and argon inlet needle was charged with ynamide 128 (0.106 g, 0.537 mmol, 1.0 equiv) and 1.7 mL of CH₂Cl₂. A 10-mL Pyrex tube fitted with a rubber septum and argon inlet needle was charged with diazo ketone 214 (0.202 g, 1.34 mmol, 2.5 equiv) and 3.3 mL of CH₂Cl₂. Both solutions were degassed (three freeze-pump-thaw cycles at -196 °C, 0.05 mmHg). The solution of diazo ketone was taken up in a 5-mL glass syringe wrapped in aluminium foil and fitted with an 20-gauge, 20-cm long steel needle. The upper portion (ca. 5-7 cm length) of the quartz tube was wrapped in aluminium foil. The quartz tube was positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, cooled by recirculating tap water). Irradiation was begun and the diazo ketone solution was added to the reaction tube via syringe pump at 28 °C over 6 h. The Pyrex tube was rinsed with 0.5 mL CH₂Cl₂ and added via the same syringe in one portion to the reaction mixture. Irradiation was continued for 4 h. The resulting mixture was concentrated to afford 0.320 g of orange oil, which was transferred to a 10-mL Pyrex tube with the aid of 3.5 mL of toluene. The solution was heated at reflux for 1.5 h, and then cooled to rt and concentrated to afford 0.347 g of dark orange oil. Purification by column chromatography on 13 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.146 g (85%) of the aniline 215 as a viscous yellow oil: IR (thin film) 3408, 2960, 2929, 1688, 1455, 1261, and 1101 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 6.53 (s, minor rotamer), 6.49 (s, 1H), 4.95 (s, 1H), 3.79 (s, minor rotamer), 3.64 (s, 3H), 3.19 (s, 3H), 2.73-2.67 (m, 2H), 2.60 (t, J = 6.3 Hz, 2H), 2.49-2.45 (m, 2H), 1.88-1.83 (m, 2H), 1.79-1.72 (m, 2H), 1.53-1.47 (m, 2H), 1.41-1.35 (m, 2H), 1.33-1.27 (m, 4H), and 0.89 (t, J = 6.8 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) 156.9, 152.4, 139.6, 136.6, 123.4, 122.4, 120.1, 53.1, 38.9, 31.9, 30.1, 29.4, 29.3, 25.9, 23.1, 22.8, 22.7, and 14.3; HRMS-ESI (m/z) [M+H] calcd for C₁₉H₂₉NO₃; 320.2220, found 320.2229.
3-\textit{[N-(carbomethoxy)-N-(methyl)amino]-2-hexyl-naphthalen-1-ol} (218).

A 25-cm long quartz tube (5 mm I. D.; 7 mm O. D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone 217 (0.081 g, 0.552 mmol, 1.1 equiv), ynamide 128 (0.099 g, 0.502 mmol, 1.0 equiv), and 1.7 mL of CH$_2$Cl$_2$. The yellow reaction mixture was degassed (three freeze-pump-thaw cycles at -196 °C, 0.05 mmHg). The quartz tube was positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 2.5 h. The reaction mixture was concentrated to afford 0.244 g of yellow oil, which was transferred with 2 mL of toluene to a 10-mL reaction tube. The solution was heated at reflux for 2.5 h and then cooled to rt and concentrated to give 0.262 g orange oil. This material was dissolved in 1 mL of CH$_2$Cl$_2$ and concentrated onto 0.5 g of silica gel. The free-flowing powder was deposited on a column of 12 g of silica gel and eluted with 20% EtOAc-hexanes to afford 0.102 g (64%) of 218 as a waxy orange solid: IR (thin film) 3385, 2955, 2928, 2857, 1684, 1573, 1461, 1374, 1194, and 1164 cm$^{-1}$; $^1$H NMR (500 MHz, CDCl$_3$) $\delta$ 8.12 (d, $J$ = 9 Hz, 1 H), 7.95 (bs, minor rotamer), 7.74 (d, $J$ = 9 Hz, 1H), 7.60 (bs, minor rotamer), 7.46 (app dt, $J$ = 3.8, 7.0 Hz, 2H), 7.34 (bs, minor rotamer), 7.26 (s, 1H), 7.24 (s, minor rotamer), 6.19 (s, minor rotamer), 5.85 (s, 1H), 3.88 (s, minor rotamer), 3.64 (s, 3H), 3.30 (s, 3H), 3.28 (s, minor rotamer), 2.67 (t, $J$ = 7.1 Hz, 2H), 1.61-1.55 (m, 2H), 1.43-1.39 (m, 2H), 1.33-1.27 (m, 4H), and 0.90 (t, $J$ = 6.3 Hz, 3H); $^{13}$C NMR (75 MHz, CDCl$_3$) $\delta$ 157.0, 150.1, 140.6, 132.8, 127.7, 126.3, 125.8, 124.1, 121.3, 121.0, 118.8, 53.1, 39.1, 31.9, 30.3, 29.5, 26.0, 22.8, and 14.3; HRMS-EI (m/z) [M$^+$] calcd for C$_{19}$H$_{25}$NO$_3$: 315.1829, found 315.1823.
1-(tert-Butoxycarbonyl)-5-hexyl-4-hydroxy-6-(N-methoxycarbonyl-N-methylamino)indole (220).

A 20-cm long quartz tube (7 mm I. D.; 9 mm O. D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone 219 (0.158 g, 0.672 mmol, 1.1 equiv), ynamide 128 (0.099 g, 0.502 mmol, 1.0 equiv), and 2.5 mL of CH₂Cl₂. The yellow reaction mixture was degassed (three freeze-pump-thaw cycles at -196 °C, 0.05 mmHg). The quartz tube was positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 7.5 h. The reaction mixture was concentrated to afford 0.250 g of dark orange oil. Purification by column chromatography on 16 g of silica gel (gradient elution with 12-15% EtOAc-hexanes) afforded 0.101 g of indole 220 as a yellow oil. IR (thin film) 3460, 2957, 2930, 1739, 1613, 1450, 1372, 1323, and 1163 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.21 (app dd, J = 1.8, 3.3 Hz, 1H), 6.08 (app t, J = 3.3 Hz, 1H), 5.93 (app dd, J = 1.7, 2.9 Hz, 1H), 5.75 (s, 1H), 3.70 (s, 3H), 3.37 (s, 3H), 2.18-2.33 (m, 2H), 1.62 (s, 9H), 1.50-1.55 (m, 2H), 1.26-1.36 (m, 6H), and 0.88 (t, J = 6.9 Hz, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 187.3, 160.7, 153.5, 149.6, 131.1, 128.9, 122.1, 111.0, 110.4, 84.3, 60.1, 54.1, 35.5, 31.8, 29.4, 28.9, 28.2, 24.2, 22.8, and 14.3; HRMS-ESI (m/z) [M+H]⁺ calcd for C₂₂H₂₂N₂O₅: 405.2384; found: 405.2429.
3-[N-(carbomethoxy)-N-(allyl)amino]-2-{but-3-en-2-((tert-butyl-dimethylsilanyloxy)yl)-naphthalen-1-ol (223).

A 25-cm long quartz tube (5 mm I. D.; 7 mm O. D.) equipped with a rubber septum and argon inlet needle was charged with diazo ketone 217 (0.075 g, 0.510 mmol, 1.1 equiv), ynamide 135 (0.150 g, 0.469 mmol, 1.0 equiv), and 1.8 mL of CH$_2$Cl$_2$. The yellow reaction mixture was degassed (three freeze-pump-thaw cycles at -196 °C, 0.05 mmHg). The quartz tube was positioned ca. 20 cm from a Hanovia 450W lamp (quartz immersion well, cooled by recirculating tap water) and irradiated under argon at 25 °C for 2.5 h. The reaction mixture was concentrated to afford 0.260 g of yellow oil, which was transferred with 2 mL of toluene to a 10-mL reaction tube. The solution was heated at reflux for 2.5 h, allowed to cool to rt, and then concentrated to give 0.291 g orange oil. Purification by column chromatography on 16 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.036 g (24%) of unreacted ynamide 135 and 0.129 g (62%) of 223 as a viscous yellow oil: IR (thin film) 3238, 2955, 2859, 1716, 1636, 1597, 1574, 1448, 1386, and 1256 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 9.16 (s, minor rotamer), 9.01 (s, 1H), 8.28-8.30 (m, 1H), 7.71-7.74 (m, 1H), 7.45-7.47 (m, 2H), 7.20-7.23 (m, 1H), 5.84-6.08 (m, 2H), 5.11-5.30 (m, 4H), 4.47-4.54 (m, 2H), 3.81-3.95 (m, 2H), 3.66 (s, 3H), 3.60 (s, minor rotamer), 3.03-3.11 (m, 1H), 2.82-2.89 (m, 1H), 0.92 (s, 9H), 0.08 (s, minor rotamer), 0.05 (s, 3H), -0.05 (s, minor rotamer), and -0.15 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 156.5, 152.9, 140.4, 139.8, 139.0, 133.5, 133.1, 127.4, 126.6, 124.6, 125.3, 122.8, 119.5, 118.7, 117.3, 115.7, 54.4, 53.0, 35.5, 35.0, 25.9, 18.2, -4.3, and -5.0, (Peaks corresponding to the minor rotamer: δ 153.2, 133.2, 127.3, 122.9, 119.2, 118.5, 117.0, 54.4, 53.1, 26.0, 18.3, -4.2, and -4.8); HRMS-ESI (m/z) [M+Na] calcd for C$_{28}$H$_{35}$NO$_4$Si: 464.2228, found: 464.2217.
5-(tert-butyldimethylsilanyloxy)-7-hydroxy-5,6-dihydro-2H-napthaleno[b]azocine-1-carboxylic acid methyl ester (224).

A 100-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a solution of the Grubbs catalyst 182 (0.012 g, 0.014 mmol, 0.05 equiv) in 20 mL of CH₂Cl₂. The naphthalenol 223 (0.124 g, 0.281 mmol, 1.0 equiv) in 8 mL of CH₂Cl₂ was added to the reaction flask via cannula in one portion. The rubber septum was replaced with a reflux condenser fitted with an argon inlet adapter. The pale pink-colored reaction mixture was heated at reflux for 6 h, allowed to cool to rt, and then concentrated to afford ca. 0.134 g of yellow brown foam. Column chromatography on 12 g of silica gel (elution with 15% EtOAc-hexane) yielded 0.088 g (76%) of azocine 224 as an off-white solid: mp 74-76°C; IR (thin film) 3351, 2955, 2857, 1709, 1684, 1572, 1450, 1388, 1250 and 1065 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 8.24-8.26 (m, 1H), 7.70 (s, 1H), 7.72-7.75 (m, 1H), 7.44 (app dd, J = 3.1, 6.2 Hz, 2H), 7.26 (bs, 1H), 5.57 (app d, J = 11.6 Hz, 1H), 5.34-5.41 (m, 1H), 5.14 (app s, 1H), 4.44 (bs, 1H), 4.20 (dd, J = 7.9, 14.4 Hz, 1H), 3.72 (bs, 3H), 3.24 (app d, J = 2.7 Hz, 2H), 1.01 (s, 9H), 0.26 (s, 3H), and 0.19 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 156.3, 150.6, 140.6, 137.7, 133.1, 127.5, 127.3, 126.3, 125.3, 124.7, 122.5, 118.9, 117.7, 72.6, 53.3, 48.0, 35.9, 26.0, 18.4, -4.5, and -4.8; HRMS-EI (m/z) [M+Na]⁺ calcd for C₂₃H₃₁NO₄Si, 436.1915; found: 436.1922.
(4S)-3-[3-Benzzyloxy]propanoyl]-4-isopropyl-1,3-thiazolidine-2-thione (334).

Procedure A. A 100-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with 3-(benzyloxy)propionic acid (3.66 g, 20.3 mmol, 1.0 equiv) and 40 mL of CH$_2$Cl$_2$. Oxalyl chloride (3.2 mL, 36.6 mmol, 1.8 equiv) was added dropwise over 3 min via syringe, followed by 1-2 drops of DMF, resulting in rapid effervescence. The reaction mixture was stirred at rt for 1.5 h, then concentrated to afford the 3-(benzyloxy)propionyl chloride 335 as pale yellow oil which was used immediately in the next step without further purification.

A 100-mL, two-necked pear flask fitted with a rubber septum and argon inlet adapter was charged with the thiazolidinethione 332 (2.69 g, 16.67 mmol, 1.0 equiv) and 30 mL of THF. The solution was cooled at -78 °C, while n-BuLi solution (6.5 mL, 2.57 M in hexanes, 1.0 equiv) was added dropwise via syringe over 3 min. The resulting mixture was stirred at -78 °C for 30 min. The solution of acyl chloride 335 prepared above (ca 1.2 equiv) in 20 mL of THF was rapidly added to the reaction mixture over 5 min via cannula, and the resulting mixture was stirred at -78 °C for 30 min. The cooling bath was then removed and the reaction mixture was allowed to warm to rt over 1.5 h. To the resulting bright orange mixture was then added 30 mL of H$_2$O and the aqueous layer was separated and extracted with three 20-mL portions of Et$_2$O. The combined organic phases were washed with 80 mL of brine, dried over MgSO$_4$, filtered, and concentrated to afford 6.16 g of a dark orange oil. Purification by column chromatography on 70 g of silica gel (gradient elution with 5-10% EtOAc-hexanes) provided 4.08 g (76%) of the thiazolidine-2-thione 334 as a bright yellow oil: $[\alpha]_{D}^{21} +292.0$ (c 1.0, CHCl$_3$); IR (thin film) 2963, 1694, 1365, 1260, 1169, and 1094 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.38 (app s, 2H), 7.35 (app s, 2H), 7.27-7.32 (m, 1H), 5.15 (app t, $J$ = 7.0 Hz, 1H), 4.59, 4.53 (AB, $J$ = 11.9 Hz, 1H each), 3.78-3.90 (m, 2H), 3.53-3.60 (m, 2H), 3.49 (dd, $J$ = 8.0, 11.4 Hz, 1H), 3.02 (app d, $J$ = 11.5 Hz), 2.32-2.44 (m, 1H).
1.05 (d, J = 7.2 Hz, 3H), and 0.97 (d, J = 6.8 Hz, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 203.0, 171.8, 138.3, 128.6, 128.0, 127.9, 73.4, 71.8, 65.6, 39.1, 31.0, 30.7, 19.3, and 17.9. Anal Calcd for C$_{16}$H$_{21}$NO$_2$S$_2$: C, 59.41; H, 6.54; N, 4.33. Found: C, 59.33; H, 6.68; N, 4.26.

Procedure B. A two-necked, 25-mL pear flask fitted with an argon inlet adapter and rubber septum was charged with a solution of 3-(benzyloxy)propionic acid (0.208 g, 1.15 mmol, 1.1 equiv) in 4 mL of THF. The solution was cooled to -78 °C and Et$_3$N (0.15 mL, 1.26 mmol, 1.2 equiv) was added in one portion via syringe, followed by pivaloyl chloride (0.16 mL, 1.32 mmol, 1.2 equiv) rapidly dropwise via syringe. The resulting thick white slurry was stirred at 0 °C for 1 h and then recooled to -78 °C. A solution of (4S)-isopropyl-1,3-thiazolidine-2-thione (332) (0.169 g, 1.05 mmol, 1.0 equiv), Et$_3$N (0.15 mL, 1.24 mmol, 1.0 equiv), and DMAP (0.012 g, 0.105 mmol, 0.1 equiv) in 3 mL of THF was added dropwise over 5 min via cannula and the resulting mixture was allowed to warm to rt over 20 h. The reaction mixture was then diluted with 25 mL of Et$_2$O and washed with 10 mL of H$_2$O, three 10-mL portions of 1M NaOH solution, and 10 mL of brine. The combined organic phases were dried over MgSO$_4$, filtered, and concentrated to give 0.423 g yellow oil. Purification by column chromatography on 10 g of silica gel (elution with 10% EtOAc-hexanes) provided 0.252 g (74%) of the N-acylthiazolidinethione 334.
A 200-mL recovery flask fitted with a rubber septum and argon inlet needle was charged with freshly purified tin (II) trifluoromethanesulfonate (7.77 g, 18.6 mmol, 1.7 equiv) and 54 mL of CH₂Cl₂ and cooled to -78 °C. Freshly distilled N-ethylpiperidine (2.70 mL, 20.6 mmol, 1.8 equiv) was then added in one portion via syringe. The resulting off-white suspension was stirred at -78 °C for 5 min, and then a solution of the N-acyl thiazolidinethione 334 (3.57 g, 11.0 mmol, 1.0 equiv) in 30 mL of CH₂Cl₂ was added dropwise via cannula over 20 min. The cloudy yellow reaction mixture was stirred at -78 °C for 3 h, after which freshly distilled acrolein (1.50 mL, 21.9 mmol, 2.0 equiv) was added rapidly dropwise via syringe. After stirring at -78 °C for 1.5 h, the cold reaction mixture was poured into 80 mL of pH 7 phosphate buffer, resulting in the formation of a thick white precipitate which was filtered through Celite with the aid of four 50-mL portions of CH₂Cl₂. The filtrate was washed with 250 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 6.79 g of a viscous orange oil. Purification by column chromatography on 120 g of silica gel (gradient elution with 15-20% EtOAc-hexanes) afforded 1.94 g (73%) of 336 as a viscous bright yellow oil: [α]²¹°₃ +354.8 (c 0.95, CHCl₃); IR (thin film) 3428, 2964, 1694, 1372, and 1160 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.24-7.34 (m, 5H), 5.90 (ddd, J = 5.7, 10.5, 16.2 Hz, 1H), 5.31 (app dt, J = 1.5, 17.2 Hz, 1H), 5.18-5.23 (m, 1H), 5.17

233 Tin (II) trifluoromethanesulfonate was prepared according to the procedure reported in Evans, D. A.; Weber, A. E. J. Am. Chem. Soc. 1986, 108, 6757. What was estimated to be the desired amount of Sn(OTf)₂ was transferred to the tared 200-mL recovery flask as a suspension in 50 mL of anhydrous Et₂O via cannula. Et₂O was removed from the flask via cannula by applying a positive pressure of argon, and the Sn(OTf)₂ was washed with three 40-mL portions of Et₂O while under argon. Following the addition of each portion of Et₂O, the resulting suspension was stirred vigorously for 1-2 min and then allowed to stand for 1-2 min before removing the Et₂O via cannula. After the final wash, the Sn(OTf)₂ was dried overnight at 0.3-0.5 mmHg at 100 °C for ca. 16 h.
(app dt, \( J = 1.5, 10.5 \) Hz), 5.00 (app t, \( J = 6.7 \) Hz, 1H), 4.62-4.67 (m, 1H), 4.41, 4.46 (AB, \( J = 11.8 \) Hz, each 1H), 3.86 (app t, \( J = 8.4 \) Hz, 1H), 3.71 (dd, \( J = 4.8, 9.3 \) Hz, 1H), 3.25 (dd, \( J = 7.8, 11.4 \) Hz, 1H), 3.20 (d, \( J = 3.1 \) Hz, 1H), 2.91 (dd, \( J = 0.9, 11.4 \) Hz, 1H), 2.27-2.39 (m, 1H), 1.01 (d, \( J = 6.8 \) Hz, 3H), and 0.94 (d, \( J = 6.9 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 204.2, 174.8, 138.1, 137.2, 128.5, 127.9, 127.7, 116.6, 73.6, 72.6, 72.3, 69.2, 48.3, 31.1, 30.9, 19.3, and 18.1. Anal. Calcd for C\(_{19}\)H\(_{25}\)NO\(_3\)S\(_2\): C, 60.13; H, 6.64; N, 3.69. Found: C, 59.95; H, 6.53; N, 3.72. Further elution with 50% EtOAc-hexanes afforded 0.148 g (3%, ca. 90-95% pure) of the anti diastereomer 344 as a yellow oil: IR (thin film) 3446, 2963, 1695, 1455, 1373, 1258, and 1164 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \( \delta \) 7.25-7.37 (m, 5H), 5.90 (ddd, \( J = 5.1, 10.5, 15.7 \) Hz, 1H), 5.32 (d, \( J = 17.2 \) Hz, 1H), 5.18 (d, \( J = 10.5 \) Hz, 1H), 5.08-5.14 (m, 2H), 4.55 (s, 1H), 4.54 (AB, \( J = 12.0 \) Hz, 1H each), 3.87 (d, \( J = 6.4 \) Hz, 2H), 4.45 (dd, \( J = 8.0, 11.4 \) Hz, 1H), 3.03-3.10 (m, 1H), 2.99 (d, \( J = 11.5 \) Hz, 1H), 2.26-2.36 (m, 1H), 0.99 (d, \( J = 6.83 \) Hz, 3H), and 0.92 (d, \( J = 6.9 \) Hz, 3H); \(^{13}\)C NMR (100 MHz, CDCl\(_3\)) \( \delta \) 203.4, 173.9, 138.5, 137.8, 128.5, 127.8, 116.0, 73.5, 71.9, 71.6, 68.5, 49.4, 33.3, 30.9, 19.5, and 17.8; HRMS-ESI (m/z) [M+Na]\(^+\) calcd for C\(_{19}\)H\(_{25}\)NO\(_3\)S\(_2\): 402.1168, found: 402.1177.
(2R, 3S)-2-(Benzylxoymethyl)-pent-4-en-1,3-diol (343).

A 25-mL recovery flask fitted with a rubber septum and argon inlet needle was charged with a solution of N-acylthiazolidinethione 336 (0.068 g, 0.179 mmol, 1.0 equiv) in 1 mL of EtOH and cooled to 0 °C. NaBH₄ (0.017 g, 0.448 mmol, 2.5 equiv) as added in a single portion and the reaction mixture was allowed to warm to rt over 30 min. The resulting colorless mixture was diluted with 5 mL of brine and 10 mL of CH₂Cl₂. The organic phase was washed with two 5-mL portions of 1 M NaOH solution followed by 5 mL of brine, then dried over MgSO₄, filtered, and concentrated. Methanol (5 mL) was added, and the resulting solution was concentrated. This was repeated to afford 0.052 g of oil. Purification by column chromatography on 10 g of silica gel (elution with 25% EtOAc-hexanes) afforded 0.037 g (92%) of 1,3-diol 343 as a pale yellow oil: IR (thin film) 3385, 2918, 1454, and 1096 cm⁻¹; ¹H NMR (400 MHz, CDC1₃) δ 7.29-7.41 (m, 5H), 5.92 (ddd, J = 5.7, 10.5 Hz, 16.4 Hz, 1H), 5.33 (d, J = 16.8 Hz, 1H), 5.20 (d, J = 10.5 Hz, 1H), 4.51 (s, 2H), 4.41 (app t, J = 5.3 Hz, 1H), 3.91 (dd, J = 5.6, 10.9 Hz, 1H), 3.80 (dd, J = 5.7, 10.9 Hz, 1H), 3.74 (dd, J = 5.6, 9.3 Hz, 1H), 3.67 (dd, J = 4.5, 9.3 Hz, 1H), 2.27 (bs, 2H), and 1.95-2.01 (m, 1H); ¹³C NMR (100 MHz, CDC1₃) δ 139.3, 137.9, 128.7, 128.1, 127.9, 115.9, 73.8, 73.4, 69.4, 63.2, and 45.7; HRMS-ESI (m/z) [M+Na]+ calcd for C₁₃H₁₈O₃: 245.1148, found: 245.1145.

Preparation of the Benzylidene Acetonide 343b.

A 15-mL pear flask fitted with a rubber septum and argon inlet needle was charged with a solution of 1,3-diol 343 (0.023 g, 0.103 mmol, 1.0 equiv) and 2-dimethoxymethylbenzene (0.019 mL, 0.124 mmol, 1.2 equiv) in 0.5 mL of CH₂Cl₂. A crystal of toluenesulfonic acid monohydrate and 4A sieves (ca. 10-15 beads) were added and the reaction mixture was stirred at rt for 63 h. The resulting mixture was then diluted with 5 mL of satd NaHCO₃ solution and 6 mL.
of CH$_2$Cl$_2$ and the aqueous phase was separated and extracted with two 2-mL portions of CH$_2$Cl$_2$. The combined organic phases were washed with 5 mL of brine, dried over MgSO$_4$, filtered, and concentrated to afford 0.035 g of white semi-solid. Purification by column chromatography on 5 g of silica gel (gradient elution with 5-10% EtOAc-hexanes) afforded 0.021 g of 343b as a white semi-solid: IR (thin film) 2920, 2858, 1455, 1394, and 1165 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.50-7.53 (m, 2H), 7.28-7.41 (m, 8H), 5.90 (ddd, $J = 4.5$, 10.8, 15.4 Hz, 1H), 5.63 (s, 1H), 5.38 (d, $J = 17.3$ Hz, 1H), 5.22 (d, $J = 10.8$ Hz, 1H), 4.62-4.64 (m, 1H), 4.55 (s, 2H), 4.52 (d, $J = 11.8$ Hz, 1H), 4.04 (dd, $J = 1.8$, 11.3 Hz, 1H), 3.93 (app t, $J = 11.8$ Hz, 1H), 3.93 (app t, $J = 9.9$ Hz, 1H), 3.74 (dd, $J = 4.4$, 9.2 Hz, 1H), and 1.90-1.94 (m, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 138.7, 138.6, 135.9, 129.1, 128.6, 128.4, 127.8, 127.7, 126.4, 115.5, 101.9, 78.9, 73.5, 68.7, 66.8, and 38.9.
(2S, 3S)-2-(Benzyloxymethyl)-pent-4-en-1,3-diol (45).

A 15-mL pear flask fitted with a rubber septum and argon inlet needle was charged with a solution of N-acetyltiazolidinethione 344 (0.044 g, ca. 0.12 mmol, 1.0 equiv) in 1 mL of EtOH and cooled to 0 °C. NaBH₄ (0.013 g, 0.35 mmol, 3.0 equiv) was added in a single portion and the reaction mixture was allowed to warm to rt over 30 min. The resulting colorless mixture was diluted with 1 mL of satd NH₄Cl solution and 10 mL of CH₂Cl₂. The organic phase was washed with two 5-mL portions of 1 M NaOH solution and 5 mL of brine, then dried over MgSO₄, filtered, and concentrated. Methanol (5 mL) was added, and the resulting solution was concentrated. This was repeated to afford 0.027 g of oil. Purification by column chromatography on 4 g of silica gel (gradient elution with 25-50% EtOAc-hexanes) afforded 0.015 g (ca. 58% ) of 1,3-diol 345 as a colorless oil: IR (thin film) 3376, 2869, 1454, and 1038 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.41 (m, 5H), 5.91 (ddd, J = 5.9, 10.4, 17.1 Hz, 1H), 5.31 (d, J = 17.2 Hz, 1H), 5.20 (d, J = 10.5 Hz, 1H), 4.52 (AB, J = 11.9 Hz, 1H each), 4.42 (app t, J = 5.6 Hz, 1H), 3.88 (ABX, JₐB = 11.1, JₐX = JₓB = 4.7 Hz, 1H each). 3.67 (ABX, JₐB = 9.3 Hz, JₐX = JₓB = 5.8 Hz, 1H each), 2.66 (bs, 2H), and 1.90-1.98 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 139.3, 138.1, 128.7, 128.0, 127.9, 115.9, 73.7, 70.4, 62.5, and 45.6.

Preparation of the Benzylidene Acetonide of 345.

A 15-mL pear flask fitted with a rubber septum and argon inlet needle was charged with a solution of 1,3-diol 345 (0.015 g, 0.068 mmol, 1.0 equiv) and 2-dimethoxymethylbenzene (0.015 mL, 0.10 mmol, 1.2 equiv) in 0.5 mL of CH₂Cl₂. A crystal of toluenesulfonic acid monohydrate and 4A sieves (ca. 10-15 beads) were added and the reaction mixture was stirred at rt for 16 h.
and then diluted with 5 mL of satd NaHCO₃ solution and 6 mL of CH₂Cl₂. The aqueous phase was separated and extracted with two 2-mL portions of CH₂Cl₂. The combined organic phases were washed with 5 mL of brine, dried over MgSO₄, filtered, and concentrated to 0.020 g of a white semi-solid. Purification by column chromatography on 3 g of silica gel (elution with 5% EtOAc-hexanes) afforded 0.016 g of 345b as a white semi-solid: IR (thin film) 2858, 1454, 1375, 1306, 1215, and 1115 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.52-7.56 (m, 2H), 7.30-7.40 (m, 8H), 5.92 (ddd, J = 7.2, 10.4, 17.4 Hz, 1H), 5.56 (s, 1H), 5.36 (d, J = 16.7 Hz, 1H), 5.26 (d, J = 9.8 Hz, 1H), 4.48 (AB, J = 12.0 Hz, 1H each), 4.36 (dd, J = 4.7, 11.4 Hz, 1H), 4.30 (dd, J = 7.3, 10.2 Hz, 1H), 3.96 (app t, J = 11.4 Hz, 1H), 3.38-3.48 (m, 2H), and 2.04-2.16 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 138.5, 138.2, 136.0, 129.0, 128.6, 128.4, 127.9, 127.7, 126.4, 118.5, 101.1, 80.4, 73.4, 69.9, 68.0, and 39.8.
3-Hydroxy-2-(benzyloxymethyl)-pent-4-en-oyl-1,3-thiazolidine-2-thione (340).

A 50-mL recovery flask fitted with a rubber septum and argon inlet needle was charged with freshly purified tin (II) trifluoromethanesulfonate (0.765 g, 1.84 mmol, 1.7 equiv) and 3 mL of CH₂Cl₂ and cooled to -78 °C. Freshly distilled N-ethylpiperidine (0.27 mL, 1.94 mmol, 1.8 equiv) was then added in one portion via syringe. The resulting off-white suspension was stirred at -78 °C for 5 min, and then a solution of the N-acyl thiazolidinethione 339 (0.304 g, 1.08 mmol, 1.0 equiv) in 3 mL of CH₂Cl₂ was added dropwise via cannula over 20 min. The cloudy yellow reaction mixture was stirred at -78 °C for 3 h, after which freshly distilled acrolein (0.15 mL, 2.16 mmol, 2.0 equiv) was added rapidly dropwise via syringe. After stirring at -78 °C for 1.5 h, the cold reaction mixture was poured into 8 mL of pH 7 phosphate buffer, resulting in the formation of a thick white precipitate which was filtered through Celite with the aid of four 15-mL portions of CH₂Cl₂. The filtrate was washed with 40 mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.698 g of a viscous orange oil. Purification by column chromatography on 25 g of silica gel (gradient elution with 20-25% EtOAc-hexanes) afforded 0.222 g (61%) of 340 as a 68:32 mixture of diastereomers: IR (thin film) 3421, 2918, 1699, 1496, 1454, 1365, 1278, 1223, and 1160 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.28-7.37 (m, 5H), 5.89-5.97 (m, 1H), 5.34 (d, J = 15.7 Hz, 1H), 5.33 (d, J = 17.1 Hz, minor isomer), 5.20 (d, J = 9.1 Hz, 1H), 5.14 (dd, J = 12.7 Hz, minor isomer), 5.07 (dd, J = 5.1, 10.4 Hz, 1H), 4.70-4.72 (m, minor isomer), 4.45-4.58 (m, 6H), 3.96 (dd, J = 6.6, 9.5 Hz, 1H), 3.83-3.88 (m, 1H), 3.77 (dd, J = 6.1, 9.3 Hz, minor isomer), and 3.15-3.28 (m, 4H); ¹³C NMR (100 MHz, CDCl₃) Major isomer δ 202.3, 175.3, 175.0, 137.5, 128.6, 128.0, 127.8, 116.5, 73.6, 73.0, 68.8, 56.7, 49.9, 28.73 and

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Substrate 339 was prepared from thiazolidinethione in 81% yield in analogy to 334, using procedure A.
peaks corresponding to the minor isomer: δ 175.3, 138.2, 137.8, 128.5, 127.9, 127.7, 73.4, 72.2, 69.2, 56.5, 50.3, and 28.69.
2-(Benzyloxymethyl)-pent-4-en-1,3-diol (341).

A 15-mL pear flask fitted with a rubber septum and argon inlet needle was charged with a solution of N-acylthiazolidinethione 340 (0.032 g, 0.095 mmol, 1.0 equiv) in 1 mL of EtOH and cooled to 0 °C. NaBH₄ (0.009 g, 0.24 mmol, 2.5 equiv) as added in a single portion and the reaction mixture was allowed to warm to rt over 30 min. The resulting colorless mixture was diluted with 1 mL of satd NH₄Cl solution and 10 mL of CH₂Cl₂. The organic phase was washed with two 5-mL portions of 1 M NaOH solution and 5 mL of brine, dried over MgSO₄, filtered, and concentrated. Methanol (5 mL) was added, and the resulting solution was concentrated. This was repeated to afford 0.027 g of oil. Purification by column chromatography on 3 g of silica gel (elution with 25% EtOAc-hexanes) afforded 0.013 g (ca. 62%) of 1,3-diol 341 as a 68:32 mixture of diastereomers: ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.38 (m, 5H), 5.87-5.96 (m, 1H), 5.33 (d, J = 17.1 Hz, 1H), 5.32 (d, J = 17.2 Hz, minor isomer), 5.20 (d, J = 10.5 Hz, 1H), 4.51 (s, 2H), 4.39-4.43 (m, 1H), 3.89-3.93 (m, 1H), 3.85 (dd, J = 4.8, 11.1 Hz, minor isomer), 3.80 (dd, J = 5.7, 11.0 Hz, 1H), 3.74 (dd, J = 5.6, 9.3 Hz, 1H), 3.63-3.71 (m, 1H), 2.44 (bs, 2H), and 1.92-2.01 (m, 1H); ¹³C NMR (100 MHz, CDCl₃) Major isomer: δ 139.3, 137.9, 128.7, 128.1, 127.9, 115.9, 73.8, 73.4, 69.4, 63.2, and 45.7; peaks corresponding to the minor isomer: 139.4, 138.1, 128.0, 116.0, 73.7, 70.5, 62.5, and 45.7.
(2R,3S)-methyl-2-(benzyloxy)methyl-3-hydroxy-pent-4-enoate (346).

A 25-mL pear flask equipped with a rubber septum and argon inlet needle was charged with N-acylthiazolidinethione 336 (0.261 g, 0.688 mmol, 1.0 equiv), 2.5 mL of CH$_2$Cl$_2$, methanol (0.280 mL, 6.88 mmol, 10.0 equiv), and imidazole (0.070 g, 1.03 mmol, 1.5 equiv). The resulting mixture was stirred at rt for 17 h and then diluted with 15 mL of CH$_2$Cl$_2$. The solution was washed with 5 mL of H$_2$O, two 5-mL portions of 1M NaOH solution, and 5-mL of brine, dried over MgSO$_4$, filtered, and concentrated to afford 0.167 g viscous yellow oil. Purification by column chromatography on 8 g of silica gel (elution with 20% EtOAc-hexanes) provided 0.109 g (63%) of the methyl ester 346 as a pale yellow oil: [α]$^2$$_D$ -3.9 (c 0.76, CHCl$_3$); IR (thin film) 3453, 2952, 2874, 1732, 1435, 1362, 1201, and 1099 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.28-7.37 (m, 5H), 5.87 (ddd, $J = 5.9, 10.5, 16.9$ Hz, 1H), 5.33 (dd, $J = 17.1$ Hz, 1H), 5.20 (dd, $J = 10.4$ Hz), 4.54 (app s, 3H), 3.83 (app dd, $J = 1.8, 6.0$ Hz, 2H), 3.73 (s, 3H), and 2.89 (app q, $J = 5.9$ Hz, 1H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 172.7, 137.7, 137.6, 128.6, 128.0, 127.9, 116.7, 73.6, 72.5, 68.3, 52.1, and 51.2; HRMS-ESI [M+Na]$^+$ calcd for C$_{14}$H$_{18}$O$_4$: 273.1097; found: 273.1100.
Preparation of the (S-) and (R)-MTPA Esters of 346.

A 15-mL pear flask fitted with a rubber septum and argon inlet needle was charged with a solution of (S)-MPTA (0.010 g, 0.043 mmol, 1.5 equiv) and alcohol 346 (0.007 g, 0.029 mmol, 1.0 equiv) in 0.5 mL of CH₂Cl₂. EDC (0.008 g, 0.043 mmol, 1.5 equiv) and DMAP (0.005 g, 0.043 mmol, 1.5 equiv) were added, and the reaction mixture was stirred at rt for 16 h. The resulting mixture was diluted with 10 mL of CH₂Cl₂ and 10 mL of H₂O, and the organic phase was washed with 5-mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.021 g of yellow oil. Purification by column chromatography on 6 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.005 g of (S)-MPTA ester 348 (38%) as a colorless oil: ¹H NMR (400 MHz, CDCl₃) δ 7.49 (app d, J = 7.0 Hz, 2H), 7.29-7.41 (m, 8H), 5.81 (ddd, J = 7.2, 10.2, 17.4 Hz, 1H), 5.77-5.79 (m, 1H), 5.32 (d, J = 17.0 Hz, 1H), 5.28 (d, J = 10.4 Hz, 1H), 4.48 (AB, J = 12.1 Hz, each 1H), 3.76-3.80 (m, 1H), 3.68 (s, 3H), 3.62 (dd, J = 5.2, 9.3 Hz, 1H), 3.48 (s, 3H), and 3.08-3.13 (m, 1H). The (R)-MPTA ester 347 was prepared analogously using (R)-MPTA on 0.054 mmol scale with respect to alcohol 348. 347: ¹H NMR (400 MHz, CDCl₃) δ 7.50 (app d, J = 7.5 Hz, 2H), 7.25-7.43 (m, 8H), 5.92 (ddd, J = 7.8, 10.4, 17.9 Hz, 1H), 5.76 (app t, J = 7.5 Hz, 1H), 5.44 (d, J = 17.1 Hz, 1H), 5.35 (d, J = 10.4 Hz, 1H), 4.41 (AB, J = 12.0 Hz, each 1H), 3.64 (app t, J = 9.0 Hz, 1H), 3.63 (s, 3H), 3.52 (s, 3H), 3.49 (dd, J = 5.2 Hz, 9.4 Hz, 1H), 3.08-3.13 (m, 1H).
(4S)-3-[(2R,3S-3-tert-Butyldimethylsilyloxy-2-[(benzyloxy)methyl]pent-4-en-oyl]-4-isopropyl-1,3-thiazolidine-2-thione (349).

A 100-mL recovery flask fitted with a rubber septum and argon inlet needle was charged with alcohol 336 (2.50 g, 6.59 mmol, 1.0 equiv) and 30 mL of CH₂Cl₂ and cooled to 0 °C. 2,6-Lutidine (1.7 mL, 1.56 g, 14.6 mmol, 2.2 equiv) and then TBSOTf (1.7 mL, 1.92 g, 7.25 mmol, 1.1 equiv) were added rapidly dropwise via syringe. The yellow reaction mixture was stirred at 0 °C for 50 min, and then 25 mL of H₂O was added. The aqueous layer was separated and extracted with two 10-mL portions of CH₂Cl₂, and the combined organic phases were washed with 35 mL of brine, dried over MgSO₄, filtered, and concentrated to give 4.40 g of a dark yellow oil. Purification by column chromatography on 50 g of silica gel (gradient elution with 0-5% EtOAc-hexanes) provided 3.11 g (96%) of 349 as a viscous bright yellow oil, which solidified to a yellow solid: mp 74-76 °C; [α]22°D +266.3 (c 0.62, CHCl₃); IR (thin film) 2929, 1694, 1471, 1363, 1168, 1091, 838 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.25-7.35 (m, 5H), 5.99 (ddd, J = 7.0, 10.3, 17.2 Hz, 1H), 5.18-5.25 (m, 2H), 5.10 (app d, J = 10.4 Hz, 1H), 4.99 (app t, J = 6.9 Hz, 1H), 4.58 (app t, J = 6.9 Hz, 1H), 4.43, 4.49 (AB, J = 11.9 Hz, each 1H), 3.91 (app t, J = 9.1 Hz, 1H), 3.81 (dd, J = 4.5, 9.1 Hz, 1H), 3.20 (dd, J = 7.8, 11.3 Hz, 1H), 2.88 (app d, J = 11.4 Hz, 1H), 2.30-2.38 (m, 1H), 1.03 (d, J = 6.8 Hz, 3H), 0.95 (d, J = 6.9 Hz, 3H), 0.89 (s, 9H), 0.03 (s, 3H) and 0.02 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 203.8, 173.7, 139.3, 138.5, 128.4, 127.7, 127.6, 116.3, 73.9, 73.3, 72.6, 70.7, 49.8, 30.9, 30.8, 26.0, 19.4, 18.3, 18.0, -3.9, and -4.8. Anal. Calcd for C₂₅H₃₉NO₅S₂Si: C, 60.81; H, 7.96; N, 2.84. Found: C, 60.69; H, 8.04; N, 2.87.
(2R,3S)-2-(Benzyloxy)methyl-3-(tert-butyldimethylsilyloxy)pent-4-en-al (350).

A 25-mL recovery flask equipped with a rubber septum and argon inlet needle was charged with the N-acylthiazolidinethione 349 (1.01 g, 2.06 mmol, 1.0 equiv) and 10 mL of CH₂Cl₂ and cooled to -78 °C. DIBAL-H (1.0 M in hexanes, 3.7 mL, 3.71 mmol, 1.8 equiv) was added dropwise via syringe over 3 min. The bright yellow solution was stirred for ca. 10 min (until the reaction mixture became colorless), and 5 mL of satd Na/K tartrate solution was added. The reaction mixture was allowed to warm to rt over 1.5 h and the aqueous layer was then extracted with two 5-mL portions of CH₂Cl₂. The combined organic layers were washed with 15 mL of brine, dried over MgSO₄, filtered, and concentrated to provide 1.05 g of an off-white semi-solid consisting of the aldehyde and white crystals of the thiazolidinethione auxiliary 332. This material was triturated with ca. 15 mL of hexanes, and the resulting solution was concentrated and purified by column chromatography on 6 g of silica gel (elution with 5% EtOAc-hexanes), to afford 0.586 g (85%) of the aldehyde 350 as a very pale yellow oil: [α]²²D -2.45 (c 1.35, CHCl₃); IR (thin film) 2858, 1727, 1472, 1362, and 1092 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 9.78 (d, J = 1.8 Hz, 1H), 7.27-7.40 (m, 5H), 5.82 (ddd, J = 6.3, 10.4, 16.9 Hz, 1H), 5.25 (app d, J = 17.1 Hz, 1H) 5.15 (app d, J = 10.4 Hz, 1H), 4.65 (app t, J = 6.1 Hz, 1H), 4.48, 4.55 (AB, J = 11.9 Hz, 1 H each), 3.91 (dd, J = 7.2, 9.6 Hz, 1H), 3.67 (dd, J = 5.9, 9.6 Hz, 1H), 2.72-2.77 (m, 1H), 0.88 (s, 9H), 0.08 (s, 3H), and 0.03 (s, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 203.7, 138.4, 138.1, 128.6, 127.9, 127.8, 116.4, 73.6, 71.9, 66.0, 58.2, 25.9, 18.3, -4.1, and -5.0. Anal. Calcd for C₁₉H₃₂O₃Si: C, 68.22; H, 9.04. Found: C, 68.09; H, 9.08.
(2R,3S)-2-(Benzyloxy)methyl-1-bromo-3-(tert-butyldimethylsilyloxy)hex-5-en-1-yne (356).

A two-necked, 25-mL pear flask equipped with a rubber septum and argon inlet adapter was charged with phosphonium bromide 352 (0.110 g, 0.329 mmol, 2.5 equiv) and 1.6 mL of THF. A solution of KOt-Bu (0.82 mL, 0.790 mmol, 0.96 M in THF, 2.4 equiv) was added rapidly dropwise via syringe over 2 min. The resulting dark brown reaction mixture was stirred for 3 min at rt and then cooled to 0 °C. A solution of the aldehyde 350 (0.110 g, 0.329 mmol, 1.0 equiv) in 1.6 mL of THF was added dropwise over 4 min via cannula. The reaction mixture was stirred at 0 °C for 10 min, and then cooled to -78 °C. A second portion of KOt-Bu solution (1.5 mL, 1.45 mmol) was added rapidly via syringe, resulting in a dark brown reaction mixture which was allowed to stir at -78 °C for 20 min. The reaction was diluted with 6 mL of brine and the aqueous layer was separated and extracted with three 6-mL portions of Et2O. The combined organic phases were washed with 10 mL of brine, dried over MgSO4, filtered, and concentrated to afford 0.562 g of a brown semi-solid which was dissolved with 2 mL of CH2Cl2 and concentrated onto ca. 0.8 g of silica. The resulting free-flowing powder was added to the top of a column of 10 g of silica gel and eluted with 2% EtOAc-hexanes to provide 0.127 g (92%) of bromo alkyne 356 as a yellow oil: [α]D22 -1.54 (c 0.32, CHCl3); IR (thin film) 2928, 1472, 1361, 1252, 1082, 927, and 836 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 7.36 (app s, 2H), 7.35 (app s, 2H), 7.28-7.34 (m, 1H), 5.92 (ddd, J = 6.6, 10.4, 17.0 Hz, 1H), 5.23 (app d, J = 17.2 Hz, 1H), 5.17 (app d, J = 10.4 Hz, 1H), 4.53, 4.62 (AB, J = 12.2 Hz, each 1H), 4.32 (app t, J = 6.4 Hz, 1H), 3.59 (d, J = 9.3 Hz, 2H), 2.78 (app q, J = 6.0 Hz, 1H), 0.90 (s, 9H), 0.08 (s, 3H), and 0.04 (s, 3H); 13C NMR (100 MHz, CDCl3) δ 139.0, 138.3, 128.5, 127.8, 127.7, 116.3, 79.3, 73.3, 73.2, 75.3, 72.5, 45.8, 45.6, 45.4, 45.2, 45.0, 44.8, 44.6, 44.4, 44.2, 44.0, 43.8, 43.6, 43.4, 43.2, 43.0, 42.8, 42.6, 42.4, 42.2, 42.0, 41.8, 41.6, 41.4, 41.2, 41.0, 40.8, 40.6, 40.4, 40.2, 40.0, 39.8, 39.6, 39.4, 39.2, 39.0, 38.8, 38.6, 38.4, 38.2, 38.0, 37.8, 37.6, 37.4, 37.2, 37.0, 36.8, 36.6, 36.4, 36.2, 36.0, 35.8, 35.6, 35.4, 35.2, 35.0, 34.8, 34.6, 34.4, 34.2, 34.0, 33.8, 33.6, 33.4, 33.2, 33.0, 32.8, 32.6, 32.4, 32.2, 32.0, 31.8, 31.6, 31.4, 31.2, 31.0, 30.8, 30.6, 30.4, 30.2, 30.0, 29.8, 29.6, 29.4, 29.2, 29.0, 28.8, 28.6, 28.4, 28.2, 28.0, 27.8, 27.6, 27.4, 27.2, 27.0, 26.8, 26.6, 26.4, 26.2, 26.0, 25.8, 25.6, 25.4, 25.2, 25.0, 24.8, 24.6, 24.4, 24.2, 24.0, 23.8, 23.6, 23.4, 23.2, 23.0, 22.8, 22.6, 22.4, 22.2, 22.0, 21.8, 21.6, 21.4, 21.2, 21.0, 20.8, 20.6, 20.4, 20.2, 20.0, 19.8, 19.6, 19.4, 19.2, 19.0, 18.8, 18.6, 18.4, 18.2, 18.0, 17.8, 17.6, 17.4, 17.2, 17.0, 16.8, 16.6, 16.4, 16.2, 16.0, 15.8, 15.6, 15.4, 15.2, 15.0, 14.8, 14.6, 14.4, 14.2, 14.0, 13.8, 13.6, 13.4, 13.2, 13.0, 12.8, 12.6, 12.4, 12.2, 12.0, 11.8, 11.6, 11.4, 11.2, 11.0, 10.8, 10.6, 10.4, 10.2, 10.0, 9.8, 9.6, 9.4, 9.2, 9.0, 8.8, 8.6, 8.4, 8.2, 8.0, 7.8, 7.6, 7.4, 7.2, 7.0, 6.8, 6.6, 6.4, 6.2, 6.0, 5.8, 5.6, 5.4, 5.2, 5.0, 4.8, 4.6, 4.4, 4.2, 4.0, 3.8, 3.6, 3.4, 3.2, 3.0, 2.8, 2.6, 2.4, 2.2, 2.0, 1.8, 1.6, 1.4, 1.2, 1.0, 0.8, 0.6, 0.4, 0.2, 0.0.

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253 The phosphonium bromide 352 was prepared according to the procedure reported by Lerm, M.; Gais, H.-J.; Cheng, K.; Vermeeren, C. J. Am. Chem. Soc. 2003, 125, 9653.
The diagram shows a chemical structure with various chemical shifts labeled on the x-axis from 7.5 to 0.5 ppm. The structure includes a bromine (Br) and two oxygen functionalities (OTBDMS and OBn) with a peak at 3.56 ppm.

A 15-mL resealable Pyrex tube fitted with a rubber septum and argon inlet adapter was charged with CuSO₄·5H₂O (0.032 g, 0.128 mmol, 0.2 equiv), 1,10-phenanthroline (0.046 g, 0.257 mmol, 0.4 equiv), K₃PO₄ (0.273 g, 1.28 mmol, 2.0 equiv), and by a solution of the bromo alkyne 356 (0.263 g, 0.642 mmol, 1.0 equiv) and tert-butylallyl carbamate 360 (0.303 g, 1.93 mmol, 3.0 equiv) in 2 mL of toluene. The resulting heterogenous reaction mixture was heated at 80-85 °C for 24 h, and then a second portion of CuSO₄·5H₂O (0.032 g, 0.128 mmol, 0.2 equiv) and 1,10-phenanthroline (0.036 g, 0.257 mmol, 0.4 equiv) was added. The resulting mixture was stirred at 80-85 °C for 22 h, cooled to rt, and then filtered through a plug of ca. 2 g of silica gel with the aid of ca. 15 mL of Et₂O and concentrated to give 0.532 g of orange oil. Purification by column chromatography on 30 g of silica gel (gradient elution with 2-5% EtOAc-hexanes) afforded 0.039 g (15%) of unreacted bromo alkyne 356 and 0.213 g (68%) of ynamide 361 as a pale yellow oil: [α]²²D -8.4 (c 0.75, CHCl₃); IR (thin film) 3087, 2928, 2263, 1717, 1646, 1473, 1392, 1153, and 924 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.28-7.35 (m, 5H), 5.96 (ddd, J = 6.6, 10.4, 17.1 Hz, 1H), 5.85 (ddt, J = 6.6, 10.3, 17.0 Hz, 1H), 5.11-5.25 (m, 4H), 4.55 (AB, J = 12.1 Hz, each 1H), 4.27 (app t, J = 6.3 Hz, 1H), 3.97 (app bd, J = 5.4 Hz, 2H), 3.57 (app bd, J = 5.5 Hz, 2H), 2.87 (app q, J = 6.1 Hz, 1H), 1.48 (s, 9H), 0.89 (s, 9H), 0.06 (s, 3H), and 0.03 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 154.4, 139.5, 138.6, 132.4, 128.5, 127.8, 127.6, 118.0, 115.7, 82.1, 73.6, 73.2, 70.1, 68.0, 51.9, 40.4, 28.2, 26.0, 18.3, -4.1, and -4.7. Anal Calcd for C₂₈H₄₃NO₃Si: C, 69.24; H, 8.92; N, 2.88. Found: C, 69.31; H, 8.88; N, 2.67.


A 25-mL pear flask fitted with a cold finger condenser with argon inlet was charged with the bromo alkyne 356 (0.161 g, 0.393 mmol, 1.0 equiv), carbamate 378\(^\text{237}\) (0.238 g, 0.1.18 mmol, 3.0 equiv), 1, 10-phenanthroline (0.028 g, 0.157 mmol, 0.4 equiv), K\(_2\)PO\(_4\) (0.167 g, 0.0.786 mmol, 2.0 equiv), CuSO\(_4\).5H\(_2\)O (0.020 g, 0.0786 mmol, 0.2 equiv), and 1 mL of toluene. The heterogenous reaction mixture was heated at 85-90 °C for 24 h and then a second portion of CuSO\(_4\).5H\(_2\)O (0.020 g, 0.0786 mmol, 0.2 equiv) and 1,10-phenanthroline (0.028 g, 0.157 mmol, 0.4 equiv) was added. The reaction mixture was heated at 85-95 °C for 24 h, cooled to rt, and then filtered through a plug of ca. 3 g of celite with the aid of ca. 15 mL of Et\(_2\)O. Concentration gave ca. 0.4 g of an orange-brown oil. Purification by column chromatography on 24 g of silica gel (gradient elution with 2-5% EtOAc-hexanes)\(^\text{238}\) afforded 0.162 g (78%) of the ynamide 379 as a pale yellow oil: [\(\alpha\)]\(_D\)\(^{21}\) -5.1 (c 0.28, CHCl\(_3\)); IR (thin film) 2955, 2857, 2265, 1724, 1402, 1251, 1075, 925, and 837 cm\(^{-1}\); \(^1\)H NMR (400 MHz, CDCl\(_3\)) \(\delta\) 7.27-7.36 (m, 5H), 5.81-5.99 (m, 2H), 5.11-5.27 (m, 4H), 4.56 (AB, \(J = 12.1\) Hz, 1H each); 4.23-4.30 (m, 3H), 4.02 (d, \(J = 5.7\) Hz, 2H), 3.50-3.61 (m, 2H), 2.87 (app q, \(J = 6.1\) Hz, 1H), 1.04 (t, \(J = 8.5\) Hz, 2H), 0.89 (s, 9H), 0.06 (s, 9H), 0.04 (s, 9H), and 0.03 (s, 3H); \(^{13}\)C NMR (125 MHz, CDCl\(_3\)) \(\delta\) 155.8, 139.4, 139.4, 138.6, 132.1, 128.5, 127.8, 127.7, 118.3, 115.9, 76.7, 73.6, 73.2, 70.0, 68.5, 65.5, 52.6, 40.4, 26.0, 18.3, 17.8, -1.3, -4.1, and -4.7; Anal Calcd for C\(_{29}\)H\(_{47}\)NO\(_4\)Si\(_2\): C, 65.74; H, 8.94; N, 2.64; found: C, 65.69; H, 8.96; N, 2.51.

\(^\text{237}\) a) Shu, L.; Schäfer, A.; Schlüter, A. D. Macromolecules 2000, 33, 4321. b) Carbamate 378 used in this reaction was prepared in near quantitative yield from the reaction of 2-trimethylsilylethanol with 1.2 equiv allyl isocyanate in the presence of 2.0 equiv of i-Pr\(_2\)NEt in toluene at 65 °C for 20 h.

\(^\text{238}\) Further elution with 10% EtOAc-hexanes resulted in the recovery of 2.1 equiv of unreacted carbamate 378.
3-(Methoxymethoxymethyl)cyclobut-1-enone (365).

A 25-mL, two-necked pear flask fitted with a rubber septum and argon inlet adapter was charged with a solution of tributyl[(methoxymethoxy)methyl]stannane\textsuperscript{239} (0.739 g, 2.03 mmol, 1.5 equiv) in 5 mL of THF. The solution was cooled to -78 °C and n-BuLi solution (0.69 mL, 2.36 M in hexane, 1.2 equiv) was added rapidly dropwise via syringe. The reaction mixture was allowed to stir at -78 °C for 2 h and then a solution of 3-ethoxy-cyclobutenone 363\textsuperscript{240} (0.151 g, 1.35 mmol, 1.0 equiv) in 2 mL of THF was added rapidly dropwise via cannula. The resulting orange reaction mixture was stirred at -78 °C for 2 h and then trifluoroacetic anhydride (0.250 mL, 1.76 mmol, 1.3 equiv) was added via syringe in a single portion. The reaction mixture was stirred at -78 °C for 75 min and diluted with 3 mL of satd NaHCO\textsubscript{3} solution and allowed to warmed to rt over 30 min. The resulting mixture was diluted with 15 mL of CH\textsubscript{2}Cl\textsubscript{2} and the aqueous phase was separated and extracted with two 5-mL portions of CH\textsubscript{2}Cl\textsubscript{2}. The combined organic phases were washed with 15 mL of brine, dried over MgSO\textsubscript{4}, filtered, and concentrated to give 0.901 g of a dark orange, biphasic oil. Purification by column chromatography on 19 g of silica gel (elution with 25% EtOAc-hexanes) afforded 0.125 g (65%) of 365 as an orange oil: FT-IR (neat) 2923, 1772, 1599, 1438, 1152, and 1048 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \delta 6.10 (s, 1H), 4.74 (s, 2H), 4.54 (s, 2H), 3.40 (s, 3H), and 3.23 (s, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \delta 186.7, 175.2, 135.0, 96.5, 65.6, 55.8, and 49.6; HRMS-ESI (m/z) [M+Na] calcd for C\textsubscript{7}H\textsubscript{10}O\textsubscript{3}: 165.0522, found: 165.0526.

3-(Methylbenzyloxy)cyclobut-1-enone (364).

A 50-mL, two-necked pear flask fitted with a rubber septum and argon inlet adapter was charged with a solution of tributyl(benzyloxyethyl)stannane\textsuperscript{241} (1.05 g, 2.59 mmol, 1.2 equiv) in 4 mL of THF. The solution was cooled to -78 °C and n-BuLi solution (0.92 mL, 2.59 M in hexanes, 1.1 equiv) was added rapidly dropwise via syringe. The resulting mixture was stirred at -78 °C for 5 min, then a solution of 3-ethoxycyclobutenone\textsuperscript{240} (363) in 3 mL of THF was added rapidly dropwise via cannula. The resulting orange reaction mixture was stirred at -78 °C for 2.5 h, then trifluoroacetic anhydride (0.544 g, 0.36 mL, 2.59 mmol, 1.2 equiv) was added via syringe in a single portion. The reaction mixture was stirred at -78 °C for 3 h and then diluted with 10 mL of satd NaHCO\textsubscript{3} solution and allowed to warm to rt over 30 min. The aqueous phase was extracted with three 10-mL portions of Et\textsubscript{2}O, and the combined organic phases were washed with 15 mL of brine, dried over Na\textsubscript{2}SO\textsubscript{4}, filtered, and concentrated to 1.43 g of a biphasic orange oil. Purification by column chromatography on 30 g of acetone-deactivated silica gel (elution with 20% EtOAc-hexanes) afforded 0.265 g (65%) of cyclobutenone 364 as a yellow oil: FT-IR (thin film) 2920, 1769, 1597, 1497, 1454, 1225, 1143, and 1095 cm\textsuperscript{-1}; \textsuperscript{1}H NMR (400 MHz, CDCl\textsubscript{3}) \(\delta\) 7.29-7.47 (m, 5H), 6.14 (s, 1H), 4.65 (s, 2H), 4.48 (s, 2H), and 3.22 (s, 2H); \textsuperscript{13}C NMR (100 MHz, CDCl\textsubscript{3}) \(\delta\) 186.8, 175.4, 137.7, 135.1, 128.8, 128.3, 128.0, 73.5, 68.3, and 49.7; HRMS-ESI (\(m/z\)) [M+Na] calcd for C\textsubscript{12}H\textsubscript{12}O\textsubscript{2}: 211.0730, found: 211.0735.

\textsuperscript{241} a) Still, C. W. J. Am. Chem. Soc. 1978, 100, 1481. b) Tributyl(benzyloxyethyl)stannane was prepared according to Kaufman, T. S. Synlett. 1997, 1377.
N-Allyl-N-(2-trimethylsilanyloxycarbonyl)-[2-(1R, 2S)-{1-(benzyloxy)methyl-2-(tert-butyldimethylsilanyloxy)-but-3-enyl}-3-hydroxy-5-(benzyloxy)methylphenyl]amine (380).

A 25-mL pear flask fitted with a rubber septum and argon inlet needle was charged with a solution of ynamide 379 (0.077 g, 0.145 mmol, 1.0 equiv) and cyclobutenone 364 (0.036 g, 0.189 mmol, 1.3 equiv) in 0.4 mL of toluene. The septum was replaced with a cold finger reflux condenser with an argon inlet and the reaction mixture was heated at 80 °C for 1.5 h and then at reflux for 1.5 h. After cooling to rt, the reaction mixture was concentrated to yield 0.121 g of viscous orange oil. Purification by column chromatography on 10 g of silica gel (gradient elution with 5-10% EtOAc-hexanes) provided 0.086 g (83%) of 380 as a viscous pale yellow oil: [α]D21 = -4.05 (c 0.35, CHCl3); IR (thin film) 3272, 2954, 2857, 1703, 1573, 1454, 1404, 1251, 1075, 924, and 837 cm⁻¹; ¹H NMR (400 MHz, 70 °C, d6-DMSO) δ 9.38 (s, 1H), 9.33 (s, minor rotamer), 7.23-7.41 (m, 9H), 7.17-7.19 (m, 1H), 6.81 (s, minor rotamer), 6.79 (s, 1H), 6.58 (s, minor rotamer), 6.51 (s, 1H), 5.98 (dddd, minor rotamer), 5.86 (dddd, J = 5.2, 7.1, 10.2, 17.3 Hz, 1H), 5.68-5.73 (m, minor rotamer), 5.63 (ddd, J = 6.8, 10.3, 17.2 Hz, 1H), 4.77-5.16 (m, 5H), 4.55 (s, minor rotamer), 4.54 (s, 2H), 4.46 (s, minor rotamer), 4.45 (s, 4H), 4.43 (m, 1H), 4.09-4.23 (m, 2H), 3.91-4.05 (m, 2H), 3.86 (dd, J = 7.2, 15.4 Hz, 1H), 3.66 (dd, minor rotamer), 3.11 (dt, J = 4.2, 14.6 Hz, 1H), 0.93 (s, minor rotamer), 0.91 (s, 11H), 0.08 (s, 3H), 0.06 (s, minor rotamer), 0.04 (s, 3H), 0.01 (s, 9H), and -0.07 (s, minor rotamer); ¹³C NMR (100 MHz, 70 °C, d6-DMSO) δ 156.1, 154.7, 140.1, 138.1, 138.0, 136.9, 133.8, 127.8, 127.7, 127.1, 127.0, 126.9, 126.8, 126.7, 123.6, 119.7, 116.4, 113.7, 113.3, 72.6, 72.2, 71.0, 70.6, 69.8, 62.3, 52.2, 46.8, 25.5, 17.5, 17.0, -1.94, -4.36, and -4.95, (Peaks corresponding to the minor rotamer: δ 133.9, 116.7, 72.4, 71.8, 71.1, 62.5, 16.9, -2.01, -4.48, and -5.07). Anal. Calcd for C₄₁H₉₉NO₅Si₂: C, 68.58; H, 8.28; N, 1.95. Found: C, 68.67; H, 8.19; N, 1.94.
$N$-Allyl-$N$-(2-trimethylsilanyloxycarbonyl)-[2-(1R, 2S)-{1-(benzyloxy)methyl-2-(tert-butyldimethylsilanyloxy)-but-3-enyl}-3-benzyloxy-5-(benzyloxy)methyl-phenyl]amine (382).

A 25-mL pear flask fitted with a rubber septum and argon inlet needle was charged with a solution of the phenol 380 (0.099 g, 0.138 mmol, 1.0 equiv) in 0.7 mL of DMF. NaH (0.011 g, 0.276 mmol, 2.0 equiv, 60% dispersion in mineral oil) was added to the solution in a single portion. The reaction mixture was stirred at rt for 2-3 min and benzyl bromide (0.025 mL, 0.207 mmol, 1.5 equiv) was added rapidly dropwise via microsyringe. The reaction mixture was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous phase was stirred at rt for 3 h and then diluted with 10 mL of H$_2$O and 10 mL of Et$_2$O. The aqueous...
127.03, 126.98, 126.9, 125.4, 121.4, 116.7, 113.7, 110.1, 72.7, 72.1, 71.1, 70.7, 69.8, 62.4, 52.3, 46.9, 25.4, 25.3, 17.3, 17.0, -1.9, -4.6, and -5.3. Anal. calcd for C₄₈H₆₅NO₆Si₂: C, 71.33; H, 8.11; N, 1.73. Found: C, 71.06; H, 8.19; N, 1.89.
(5S, 6R)-7-Benzylxoy-6, 9-benzyloxymethyl-5-(tert-butyldimethylsilanyloxy)-5, 6-dihydro-2H-benzo[b]azocine-1-carboxylic acid (2-trimethylsilyl)ethyl ester (383).

A 50-mL, recovery flask fitted with a rubber septum and argon inlet needle was charged with a solution of the Grubbs catalyst 182 (0.005 g, 0.0057 mmol, 0.05 equiv) in 9 mL of CH$_2$Cl$_2$. The aniline 382 (0.092 g, 0.114 mmol, 1.0 equiv) in 2.4 mL of CH$_2$Cl$_2$ was added via cannula in one portion and the septum was replaced with a reflux condenser fitted with an argon inlet adapter. The pale pink-colored reaction mixture was heated at reflux for 4.5 h and then allowed to cool to rt and concentrated to afford ca. 0.110 g of yellow brown oil. Column chromatography on 12 g of silica gel (elution with 10% EtOAc-hexane) yielded 0.082 g (92%) of benzoazocine 383 as a viscous pale yellow oil: [α]$^{22}_D$ -48.6 (c 0.38, CHCl$_3$); IR (thin film) 3031, 2954, 2856, 1699, 1613, 1577, 1453, 1403, 1311, 1250 and 1073 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 7.32-7.40 (m, 10H), 7.12-7.25 (m, 5H), 6.94 (s, 1H), 6.66 (s, 1H), 5.54 (ddd, $J$ = 3.0, 7.3, 10.5 Hz, 1H), 5.17-5.26 (m, 1H), 5.04 (app AB, $J$ = 11.9 Hz, 3H), 4.57 (s, 2H), 4.52 (s, 2H), 4.39-4.47 (m, 2H), 4.14-4.24 (m, 1H), 3.86-3.96 (m, 1H), 3.83-3.86 (m, 1H), 3.72-3.79 (m, 2H), 3.60 (dd, $J$ = 5.4, 16.6 Hz, 1H), 0.91 (s, 10 H), 0.09 (s, 3H), 0.06 (s, 3H), and -0.08 (s, 9H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 158.1, 138.3, 137.7, 137.3, 128.6, 128.2, 128.0, 127.9, 127.8, 127.5, 127.2, 127.1, 72.3, 72.0, 71.7, 70.9, 70.2, 64.1, 49.1, 45.9, 26.1, 18.4, 18.1, -1.44, -4.26, and -4.73. Anal. Calcd for C$_{46}$H$_{61}$NO$_6$Si$_2$: C, 70.82; H, 7.88; N, 1.80. Found: C, 70.71; H, 7.72; N, 1.62.

A 25-mL pear flask fitted with a rubber septum and argon inlet needle was charged with a solution of ynamide 361 (0.108 g, 0.222 mmol, 1.0 equiv) and cyclobutenone 365 (0.041 g, 0.289 mmol, 1.3 equiv) in 0.7 mL of toluene. The septum was replaced with a cold finger condenser with an argon inlet and the reaction mixture was heated at 80 °C for 1.5 h and then at reflux for 1.5 h. After cooling to rt, the reaction mixture was concentrated to yield 0.200 g of viscous orange oil. Purification by column chromatography on 14 g of silica gel (elution with 15% EtOAc-hexanes) provided 0.125 g (94%) of 366 as a viscous pale yellow oil: [α]_D^{21} -6.3 (c 0.125, CHCl_3); IR (thin film) 3281, 2927, 1699, 1667, 1624, 1574, 1437, 1254, 1049 and 922 cm⁻¹; ^1H NMR (500 MHz, 90 °C, d_6-DMSO) 8 9.20 (s, 1H), 9.13 (s, minor rotamer), 7.22-7.30 (m, 3H), 7.15-7.16 (m, 2H), 6.73 (s, minor rotamer), 6.70 (s, 1H), 6.52 (s, minor rotamer), 6.43 (s, 1H), 5.93-5.97 (m, minor rotamer), 5.79-5.83 (m, 1H), 5.62-5.68 (m, 1H), 5.03-5.13 (m, minor rotamer), 4.97-4.99 (m, 2H), 4.87 (app d, J = 18.1 Hz, 1H), 4.73-4.80 (m, 2H), 4.61 (s, 2H), 4.41 (s, 4H), 4.31-4.37 (m, 1H), 4.14 (t, J = 9.0 Hz, 1H), 3.90-3.97 (m, 2H), 3.80 (dd, J = 6.8, 15.3 Hz, 1H), 3.61-3.64 (m, minor rotamer), 3.30 (s, 3H), 3.12 (bs, 1H), 1.38 (s, 9H), 1.32 (s, minor rotamer), 0.88 (s, 9H), 0.05 (s, 3H), and 0.01 (s, 3H); ^13C NMR (125 MHz, 90 °C, d_6-DMSO) 8 155.9, 153.8, 142.5, 140.1, 138.2, 136.4, 134.0, 127.6, 126.9, 126.8, 126.7, 123.6, 119.9, 116.0, 113.6, 113.4, 94.9, 78.5, 73.0, 72.2, 70.0, 67.8, 54.4, 52.2, 46.7, 27.7, 25.4, 17.4, -4.4, and -4.9, (peaks corresponding to minor rotamer: 8 134.1, 116.4, 113.5, 95.0, 70.8, -4.5, and -5.1). Anal. Calcd for C_{35}H_{53}NO_7Si: C, 66.95; H, 8.51; N, 2.23. Found: C, 66.91; H, 8.46; N, 2.40.

A 50-mL recovery flask fitted with a rubber septum and argon inlet needle was charged with a solution of the Grubbs catalyst 182 (0.005 g, 0.00593 mmol, 0.05 equiv) in 9 mL of CH₂Cl₂. The aniline 366 (0.0745 g, 0.119 mmol, 1.0 equiv) in 3 mL of CH₂Cl₂ was added to the reaction flask via cannula in one portion and the rubber septum was replaced with a reflux condenser fitted with an argon inlet adapter. The pale pink-colored reaction mixture was heated at reflux for 5.5 h, allowed to cool to rt, and then concentrated to afford ca. 0.134 g of yellow-brown foam. Column chromatography on 11 g of silica gel (elution with 15% EtOAc-hexane) yielded 0.057 g (80%) of benzoazocine 369 as a viscous pale yellow oil: \([\alpha]^{21}_D -18.7\) (c 0.44, CHCl₃); IR (thin film) 3343, 2927, 1694, 1670, 1624, 1573, 1442, 1391, 1258, and 1075 cm⁻¹; ¹H NMR (500 MHz, 55 °C, d₆-DMSO) δ 9.21 (s, 1H), 7.22-7.28 (m, 5H), 6.77 (s, 1H), 6.49 (s, 1H), 5.38-5.41 (m, 1H), 5.19-5.21 (m, 1H), 5.04 (app t, J = 7.9 Hz, 1H), 4.78 (app d, J = 15.4 Hz, 1H), 4.63 (s, 2H), 4.42 (s, 2H), 4.39-4.46 (m, 2H), 3.76 (bs, 1H), 3.64 (app t, J = 8.4 Hz, 1H), 3.48-3.56 (m, 2H), 3.30 (s, 3H), 1.37 (bs, 9H), 0.87 (s, 9H), 0.04 (s, 3H), and 0.02 (s, 3H); ¹³C NMR (125 MHz, 55 °C, d₆-DMSO) δ 156.0, 139.7, 138.6 137.5, 136.2, 127.8, 127.0, 126.8, 122.7, 118.5, 113.3, 95.1, 79.2, 71.6, 70.4, 70.3, 67.8, 54.6, 48.3, 45.0, 27.9, 25.6, 25.5, 17.6, -4.71, and -5.13 (peaks corresponding to minor rotamer: 156.5, 139.3, 138.4, 130.3, and 72.4). Anal. Calcd for C₃₃H₄₉NO₇Si: C, 66.08; H, 8.23; N, 2.34. Found: C, 65.96; H, 8.23; N, 2.42.
(5S, 6R)-7-Benzyloxy-6, 9-benzyloxymethyl-5-hydroxyl-5, 6-dihydro-2H-benzo[b]azocine (284).

A 10-mL pear flask fitted with a rubber septum and argon inlet needle was charged with a solution of benzoazocine 383 (0.051 g, 0.0654 mmol, 1.0 equiv) and 0.9 mL of THF. TBAF (0.24 mL, 0.235 mmol, 3.6 equiv) was added rapidly dropwise via syringe and the reaction mixture was sealed with a glass stopper under argon and stirred at rt for 39 h. The resulting mixture was then diluted with 5 mL of Et₂O and 5 mL of H₂O, and the aqueous layer was extracted with two 5-mL portions of Et₂O. The combined organic phases were washed with 10-mL of brine, dried over MgSO₄, filtered, and concentrated to afford 0.040 g of orange oil. Purification by column chromatography on 4 g silica gel (elution with 30% EtOAc-hexanes) provided 0.025 g (74%) of benzazocine 284 as a viscous pale yellow oil: [α] D 21 -111.5 (c 0.41, CHCl₃); IR (thin film) 3390, 3029, 2860, 1608, 1580, 1496, 1453, 1360, 1311, 1205, 1112, 1074, 1027, 839, 736, and 697 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.25-7.42 (m, 15H), 6.77 (s, 1H), 6.66 (s, 1H), 5.85 (app t, J = 7.4 Hz, 1H), 5.60 (ddd, J = 2.8, 6.7, 9.6 Hz, 1H), 5.24-5.29 (m, 1H), 5.05 (AB, J = 7.3 Hz, 1H each), 4.55 (s, 2H), 4.52 (s, 2H), 4.47 (s, 2H), 3.91-3.94 (m, 1H), 3.69-3.76 (m, 2H), and 3.53 (dd, J = 5.6, 16.2 Hz, 1H); ¹³C NMR (100 MHz, CDCl₃) δ 156.8, 148.2, 138.6, 138.3, 138.0, 137.2, 135.2, 128.7, 128.58, 128.57, 127.99, 127.97, 127.9, 127.8, 127.7, 127.3, 126.3, 125.0, 119.2, 107.9, 74.6, 73.5, 73.3, 72.5, 72.0, 70.4, 51.2, and 46.2. Anal. Calcd for C₃₄H₃₅NO₄: C, 78.28; H, 6.76; N, 2.69. Found: C, 78.18; H, 6.87; N, 2.77.
Experimental Section for Part III

Equipment. All amide synthesis reactions using carbon dioxide (CO₂) were performed in the 25-mL (nominal) Thar stainless steel view cell reactor (model 05422-2) shown in Figure 1. A schematic flow diagram of the experimental apparatus is shown in Figure 2. With fittings, the actual vessel volume was 31.8 ± 0.3 mL. The reactor allowed visual access via two 1-in. coaxial sapphire window assemblies. Cell pressure was monitored by a Swagelok pressure gauge (model PGI-63C-PG6000-LAQX, 1 to 415 bar span, accurate to ± 6 bar) and a Newark pressure transducer (model MSP-300-05K-P-4-N-1, 1 to 346 bar range, accurate to ± 3.5 bar) interfaced with a Measurement Computing data acquisition (DAQ) module and a local computer. Cell temperature was measured by an Omega J-type dual-element thermocouple (model SIC316SS-125U-6-DUAL, accurate to ± 0.1 °C) connected to both a local Omega controller (model CN9121A) and the DAQ system. Temperature set-points were achieved within ± 0.5 °C by interfacing the controller with a Powerstat variable autotransformer (model 3PN116B) and Omega insulated heating tape (model STH051-080) wrapped tightly around the exterior cell wall. Inlet and outlet valves were needle-type and obtained from High Pressure Equipment (model 15-21AM1NMA). Agitation was provided by a Teflon-coated magnetic stir bar driven externally by a Corning stir plate (model PC-410). All lactam synthesis reactions using CO₂ were performed in an apparatus identical to the one described above, but with a 50-mL (nominal) Thar stainless steel view cell reactor (model 05422-3). With fittings, the actual vessel volume was 54.1 ± 0.4 mL.
Figure 1. Photograph of the stainless steel view cell reactor: (1) view cell with the front window assembly installed; (2) magnetic stir bar; (3) inlet valve; (4) pressure transducer; (5) pressure gauge; (6) outlet valve; (7) thermocouple; (8) back window assembly (from top to bottom: fluoropolymer-encapsulated viton o-ring, sapphire window, cap).

Figure 2. Simplified schematic flow diagram of the experimental apparatus (not to scale): (1) liquid carbon dioxide supply cylinder; (2) liquid regulator; (3) gaseous argon supply cylinder; (4) gas regulator; (5) shell-and-tube heat exchanger; (6) refrigerated circulating bath; (7) metering pump; (8) view cell (9) magnetic stir bar; (10) stir plate; (11) insulated heating tape; (12) thermocouple; (13) variable autotransformer; (14) temperature controller; (15) sparge chamber.
**General Procedures.** All reactions other than those conducted in scCO\textsubscript{2} were performed in flame-dried or oven-dried glassware under a positive pressure of argon. Reaction mixtures were stirred magnetically unless otherwise indicated. Air- and moisture-sensitive liquids and solutions were transferred by syringe or cannula and introduced into reaction vessels through rubber septa. Reaction product solutions and chromatography fractions were concentrated by rotary evaporation at ca. 20 mmHg. Column chromatography was performed on EM Science silica gel 60 or Silicycle silica gel 60 (230-400 mesh).

**Materials.** Commercial grade reagents and solvents were used without further purification except as indicated below. Dichloromethane, diethyl ether, and tetrahydrofuran were purified by pressure filtration through activated alumnia. Toluene was purified by pressure filtration through activated alumina and Cu(II) oxide. Ethoxyacetylene (~50% w/wt in hexanes, Alfa Aesar), trichloroethylene, and propionaldehyde were distilled at atmospheric pressure under argon. Piperidine and cyclohexylamine were distilled under argon from calcium hydride prior to use. HMPA, diphenylmethylamine, aniline, and benzylamine were distilled under vacuum from calcium hydride prior to use. \(N\)-butylbenzylamine and \(N\)-butyl(diphenylmethyl)amine\textsuperscript{242} were purified by column chromatography.

**Instrumentation.** Melting points were determined with a Fisher-Johns melting point apparatus and are uncorrected. Infrared spectra were obtained using a Perkin Elmer 2000 FT-IR spectrophotometer. \(^1\)H NMR spectra were recorded on Varian XL-300 (300 MHz), Varian Inova 500 (500 MHz) and Bruker Avance-400 (400 MHz) spectrometers. \(^1\)H NMR chemical shifts are expressed in parts per million (\(\delta\)) downfield from tetramethylsilane (with the CHCl\textsubscript{3} peak at 7.27 ppm used as a standard). \(^{13}\)C NMR spectra were recorded on Varian XL-300 (300 MHz), and Bruker Avance-400 (400 MHz) spectrometers. \(^{13}\)C NMR chemical shifts are expressed in parts per million (\(\delta\)) downfield from tetramethylsilane (with the central peak of CHCl\textsubscript{3} at 77.23 ppm used as a standard). High resolution mass spectra (HRMS) were measured on a Bruker Daltonics APEXII 3 telsa Fourier transform mass spectrometer.

**tert-Butyl(1,2-dichlorovinyl)ether (419).**

A 100-mL, three-necked, round-bottomed flask fitted with a rubber septum and argon inlet adapter and glass stopper was charged with potassium hydride (~30% w/wt suspension in mineral oil; the oil was removed by rinsing with three 10-mL portions of hexanes to give a grey powder: 0.570 g, 14.21 mmol, 1.5 equiv) and 15 mL of THF. A solution of I₂ (0.36 g, 1.42 mmol, 0.1 equiv) in 5 mL of THF was added dropwise via syringe over 5 min at rt, resulting in a dark purplish-orange suspension. The solution was then removed via cannula and the residue was washed with 10 mL of THF, which was also decanted. The potassium hydride was resuspended in 15 mL of THF and a solution of t-BuOH (0.90 mL, 9.47 mmol, 1.0 equiv) was added dropwise over 5 min via cannula. The suspension was stirred at rt for 1 h, then cooled to 0 °C. Trichloroethylene (0.85 mL, 9.47 mmol, 1.0 equiv) was added dropwise via syringe over 3 min, resulting in a dark brown reaction mixture, which was allowed to warm to rt over 2 h. The reaction mixture was recooled to 0 °C and carefully quenched with 50 mL of H₂O. The aqueous phase was extracted with two 25-mL portions of Et₂O, then the combined organic phases were washed with 50 mL of brine, dried over MgSO₄, filtered, and concentrated to give a dark brown liquid which was filtered through 8 g of silica gel (elution with pentane) to afford 1.04 g (67%) of vinyl ether 419 as a colorless liquid: IR (thin film) 2984, 1622, 1462, 1395, 1371, 1285, 1263, 1162, and 1080 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 5.72 (s, 1H), and 1.48 (s, 9H); ¹³C NMR (100 MHz, CDCl₃) δ 142.0, 102.3, 86.1, and 28.7. Anal. Calcd. for C₆H₁₀Cl₂O: C, 42.63; H, 5.96. Found: C, 42.49; H, 5.87.

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1-tert-Butoxy-1-octyne (420).

A 100-mL, three-necked, round-bottomed flask fitted with an argon inlet adapter and rubber septum was charged with a solution of the vinyl ether 419 (1.81 g, 11.0 mmol, 1.2 equiv) in 30 mL of THF and cooled to -78 °C. A solution of n-BuLi (8.2 mL, 22.1 mmol, 2.7 equiv, 2.68 M in hexane) was added dropwise over 5 min via syringe. The reaction mixture was allowed to warm to -40 °C over 1 h. HMPA (4.0 mL, 24.6 mmol, 2.2 equiv) was then added to the reaction mixture in a single portion via syringe. After stirring at -40 °C for 10 min, iodohexane (1.35 mL, 9.2 mmol, 1.0 equiv) was added in a single portion via syringe and the reaction mixture was allowed to warmed to rt over 20 h. The reaction was quenched with 40 mL of H2O and further washed with two 40-mL portions of H2O, followed by 40 mL of brine. The organic phase was dried over MgSO4, filtered, and concentrated to give 1.70 g of an orange oil. Purification by column chromatography on 50 g of acetone-deactivated silica gel (elution with hexanes), followed by concentration under vacuum at ~100 mmHg for ca. 40 min afforded 0.956 g (57%) of the alkynyl ether 420 as a yellow oil: IR (thin film) 2981, 2931, 2265, 1458, 1393, 1370, 1269, 1237, 1161, and 836 cm⁻¹; 1H NMR (400 MHz, CDCl3) δ 2.14 (t, J = 6.8 Hz, 2H), 1.37-1.50 (m, 4H), 1.37 (s, 9H), 1.25-1.33 (m, 4H), and 0.89 (t, J = 6.9 Hz, 3H); 13C NMR (75 MHz, CDCl3) δ 85.8, 84.3, 40.4, 31.6, 30.1, 28.7, 27.2, 22.8, 17.7, and 14.3; HRMS-EI (m/z): [M+] calcd for C6H9O: 97.0648; found: 97.0644.
t-BuO\text{---}\text{Hex}

420 ppm
I-tert-Butyl-3-(tert-butyldimethylsilyloxy)-1-pentyne (421).

A 100-mL, three-necked, round-bottomed flask fitted with rubber septa and argon inlet adapter was charged with a solution of 419 (1.85 g, 11.3 mmol, 1.0 equiv) in 40 mL of THF and cooled to -78 °C. A solution of n-BuLi (9.0 mL, 22.6 mmol, 2.0 equiv, 2.49 M in hexane) was added dropwise over 5 min via syringe, and the reaction mixture was allowed to warm to -40 °C over 1 h. Propionaldehyde (1.6 mL, 22.6 mmol, 2.0 equiv) was added as a single portion via syringe and the reaction was allowed to warm to 0 °C over 2 h, then quenched with 30 mL of H2O. The aqueous phase was extracted with two 20-mL portions of Et2O and the combined organic phases were washed with 30 mL of brine, dried over MgSO4, filtered, and concentrated to 3.03 g of oil. Purification by column chromatography on 25 g of acetone-deactivated silica gel (gradient elution with 15-20% EtOAc-hexanes) furnished 1.09 g of alcohol as a pale yellow oil. This material was diluted with 20 mL of CH2Cl2 and transferred to a 50-mL, two-necked pear flask, fitted with a rubber septum and argon inlet adapter. The solution was cooled to 0 °C and imidazole (0.57 g, 8.37 mmol, 0.74 equiv) and TBSCl (1.05 g, 6.98 mmol, 0.62 equiv) were added in single portions. The reaction mixture was warmed to rt over 3 h, then washed sequentially with two 15-mL portions of H2O and 15-mL of brine. The organic phase was dried over MgSO4, filtered and concentrated to give 1.78 g of pale yellow oil. Purification by column chromatography on 16 g of acetone-deactivated silica gel (elution with hexanes) afforded 1.54 g (50%) of the propargyl silyl ether 421 as a pale yellow oil: IR (thin film) 2960, 2858, 2256, 1473, 1464, 1371, 1251, 1161, 1098, 1061, and 1005 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ 4.36 (t, J = 6.3 Hz, 1H), 1.66 (app q, J = 7.5 Hz, 2H), 1.39 (s, 9H), 0.96 (t, J = 7.4 Hz, 3H), 0.91 (s, 9H), 0.13 (s, 3H), and 0.11 (s, 3H); ¹³C NMR (100 MHz, CDCl3) δ 89.7, 85.5, 64.7, 43.1, 33.0, 27.2, 26.1, 18.5, 10.1, -4.2, and -4.8; HRMS-ESI (m/z): [M+Na] calcd for C15H30O2Si: 293.1907; found: 293.1919.
$t$-Bu$\equiv$$\equiv$O$\backslash$Sit-BuMe$_2$

421
A 50-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle was charged with a solution of 1-ethoxypent-1-yn-3-ol (0.956 g, 7.46 mmol, 1.0 equiv) in 20 mL of CH₂Cl₂ and cooled to 0 °C. Imidazole (0.660 g, 9.70 mmol, 1.3 equiv) was added to the solution in a single portion followed by TBSCI (1.12 g, 7.46 mmol, 1.0 equiv) in a single portion. The reaction mixture was allowed to warm to rt over 16 h, then washed with two 20-mL portions of H₂O, followed by 20 mL of brine. The organic phase was dried over MgSO₄, filtered, and concentrated to 1.68 g of dark yellow oil. Purification by column chromatography on 15 g of acetone-deactivated silica gel (elution with 5% EtOAc-hexanes) afforded 1.38 g (72%) of 414 as a colorless oil: IR (neat) 2931, 2266, 1473, 1390, 1253, 1062, and 837 cm⁻¹; ¹H NMR (300 MHz, CDCl₃) δ 4.32 (t, J = 6.4 Hz, 1H), 4.07 (q, J = 7.0 Hz, 2H), 1.66 (m, 2H), 1.37 (t, J = 7.5 Hz, 2H), 0.95 (t, J = 6.3 Hz, 2H), 0.91 (s, 9H), 0.13 (s, 3H), and 0.11 (s, 3H); ¹³C NMR (75 MHz, CDCl₃) δ 93.1, 74.4, 64.4, 40.2, 32.8, 26.1, 18.5, 14.6, 10.1, -4.2, and -4.8; HRMS-ESI (m/z) [M+Na]⁺ calcd for C₁₃H₂₆O₂Si: 265.1594; found: 265.1595.

(E)-5,9-Dimethyl-1-ethoxy-deca-4,8-dien-1-yne (416).

A 100-mL, two-necked, pear flask fitted with a rubber septum and argon inlet adapter was charged with a solution of ethoxyacetylene (1.78 g, 12.5 mmol, 1.25 equiv, ~50% w/wt in hexanes) in 40 mL of THF and cooled to 0 °C. A solution of EtMgBr (12.0 mL, 12.0 mmol, 1.2 equiv, 1.0 M in THF) was added dropwise via syringe over 6 min. The resulting reaction mixture was stirred at 0 °C for 2.5 h.

A 200-mL, three-necked round-bottomed flask fitted with rubber septa and an argon inlet adapter was charged with a solution of geraniol (1.75 mL, 10.0 mmol, 1.0 equiv) in 25 mL of THF. The solution was cooled to -78 °C and MeLi (6.7 mL, 11.0 mmol, 1.1 equiv, 1.63 M in Et2O) was added via syringe over 5 min and the reaction mixture was stirred at -78 °C for 1 h. MsCl (0.85 mL, 11.0 mmol, 1.1 equiv) was added dropwise via syringe over 3 min and the reaction was stirred at -78 °C for an additional 1 h. To this solution was added the acetylide mixture prepared above, which was added dropwise via cannula over 15 min, followed by addition of a solution of Li2CuCl4 (10 mL, 1.0 mmol, 0.1 equiv, 0.1M in THF) via syringe over 5 min. The resulting reaction mixture was warmed to -20 °C over 2.5 h, then to rt over 1.5 h. The reaction was quenched with 80 mL of satd aq NH4Cl solution and the aqueous phase was extracted with three 40-mL portions of Et2O. The combined organic phases were washed with 120 mL of brine, dried over MgSO4, filtered, and concentrated to ca. 2.5 g red-brown oil. Purification by column chromatography on 60 g of acetone-deactivated silica gel (elution with hexanes) afforded 0.515 g (25%) of alkynyl ether 416 as a colorless oil. Ca. 0.5 g of impure alkynyl ether was also obtained and was repurified on a second column on 30 g of acetone-deactivated silica gel (elution with hexanes) to provide 0.285 g (14%) of 416 as a colorless oil; overall yield 0.800 g (39%), with spectral data consistent with that previously reported for this
compound: IR (thin film) 2979, 2271, 1731, 1446, 1379, and 1224 cm⁻¹; H NMR (400 MHz, CDCl₃) δ 5.17-5.21 (m, 1H), 5.08-5.12 (m, 1H), 4.04 (q, J = 7.1 Hz, 2H), 2.84 (dd, J = 0.8, 6.8 Hz, 2H), 1.98-2.11 (m, 4H), 1.69 (s, 3H), 1.62 (s, 3H), 1.61 (s, 3H), and 1.35 (t, J = 7.1 Hz, 3H); C NMR (75 MHz, CDCl₃) δ 136.3, 131.6, 124.3, 121.0, 89.0, 74.0, 39.6, 36.5, 26.7, 25.8, 17.8, 16.3, 16.1, and 14.5.


A 25-mL, stainless steel Thar view cell reactor was charged with *N*-butylbenzylamine (423) (0.556 g, 3.40 mmol, 1.0 equiv) and 1-ethoxy-1-octyne (411) (0.525 g, 3.40 mmol, 1.0 equiv). The reactor was pressurized to 50 bar with CO₂, heated to 130 °C, and then pressurized with additional CO₂ to 228 bar. The reaction mixture was stirred at 130 °C (228 bar) for 24 h and then allowed to cool to rt. The reactor outlet valve was opened and the CO₂ phase was vented through a bubbler containing 15 mL of CH₂Cl₂. The residual 424 in the reactor was purified by column chromatography on 12 g of silica gel (elution with 15% EtOAc-hexanes) to provide 0.871 g (88%) of amide 424 as a yellow oil: IR (neat) 2926, 1651, 1453, 1377, 1301, 1266, and 1218 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) major rotamer: δ 7.16-7.38 (m, 5H), 4.61 (s, 2H), 3.18 (t, J = 7.7 Hz, 2H), 2.38 (t, J = 7.6 Hz, 2H), 1.48-1.75 (m, 4H), 1.26-1.35 (m, 10H), and 0.85-0.94 (m, 6H) and for minor rotamer: δ 4.54 (s), 3.36 (t, J = 7.6 Hz), and 2.31 (t, J = 7.6 Hz); ¹³C NMR (100 MHz, CDCl₃) Major rotamer: δ 173.3, 138.3, 128.6, 128.1, 127.3, 48.2, 47.0, 33.3, 31.9, 29.7, 29.3, 25.8, 22.8, 20.2, 14.3, and 14.0, and for minor rotamer: 173.6, 137.5, 129.0, 127.6, 126.3, 51.2, 46.1, 33.5, 30.8, 29.9, 29.5, 29.3, 25.6, 22.8, 20.4, 14.3, and 14.0); HRMS-ESI (m/z): [M+Na]⁺ calcd for C₁₉H₃₁NO: 312.2298; found: 312.2292.
Reaction of N-butylbenzylamine (423) (0.506 g, 3.10 mmol, 1.0 equiv) with 1-tert-butoxy-1-octyne (420) (0.565 g, 3.10 mmol, 1.0 equiv) at 90 °C (224 bar) for 24 h according to the General Procedure provided ca. 1.0 g of yellow-orange oil. Purification by column chromatography on 15 g of silica gel (elution with 10% EtOAc-hexanes) afforded 0.738 g (82%) of amide 424 as a pale yellow oil.
1-Piperidyl octanamide (426).

Reaction of piperidine (425) (0.34 mL, 3.40 mmol, 1.0 equiv) and 1-ethoxy-1-octyne 411 (0.525 g, 3.40 mmol, 1.0 equiv) at 130 °C (210 bar) for 24 h according to the General Procedure provided 0.703 g of brown oil. Purification by column chromatography on 15 g of silica (gradient elution with 10-20% EtOAc-hexanes) afforded 0.623 g (87%) of amide 426 as a pale yellow oil with spectral data consistent with that previously reported.246

N-(Butyl)-N-(diphenylmethyl)octanamide (428).

Reaction of N-butyl(diphenylmethyl)amine (429) (0.551 g, 2.30 mmol, 1.0 equiv) with 1-ethoxy-1-octyne (411) (0.350 g, 2.27 mmol, 1.0 equiv) at 120 °C (282 bar) for 24 h according to the General Procedure provided 0.860 g of brown oil. Purification by column chromatography on 25 g of silica gel (elution with 15% EtOAc-hexanes) afforded 0.720 g of 428 as a pale yellow oil: IR (neat) 2920, 1644, 1454, 1378, 1193, and 1102 cm⁻¹; ¹H NMR (500 MHz, CDCl₃) δ 7.28-7.37 (m, 6H), 7.15-7.19 (m, 4H), 6.29 (s, 1H), 3.24-3.31 (m, 2H), 2.44 (t, J = 7.5 Hz, 2H), 2.39 (t, minor rotamer), 1.73-1.77 (m, 2H), 1.65-1.68 (m, minor rotamer), 1.25-1.36 (m, 9H), 0.81-0.99 (m, 6H), and 0.59-0.66 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) Major rotamer: δ 173.6, 140.1, 129.1, 128.4, 127.4, 60.8, 45.9, 33.7, 31.9, 31.8, 29.7, 29.5, 25.9, 22.8, 20.3, 14.2, and 13.5, and for minor rotamer: δ 139.7, 128.9, 128.6, 127.9, 64.9, 45.0, 33.9, 32.0, 31.7, 30.2, 29.6, 25.5, 20.4, and 13.6); HRMS-ESI (m/z) [M+H]⁺ calcd for C₂₅H₃₅NO” 366.2791; found: 366.2796.
N-(Diphenylmethyl)octanamide (430).

Reaction of benzhydrylamine (429) (0.585 g, 3.20 mmol, 1.0 equiv) with 1-ethoxy-1-octyne (411) (0.493 g, 3.20 mmol, 1.0 equiv) at 130 °C (208 bar) for 24 h according to the General Procedure provided ca 1.0 g of an orange solid. Purification by two trituration cycles with CH₂Cl₂-hexanes afforded 0.786 g (79%) of amide 430 as an off white solid: mp 104-105 °C; IR (thin film) 3245, 3051, 2922, 2852, 1637, 1544, 1495, 1453, and 1122 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.22-7.36 (m, 1OH), 6.27 (app d, J = 7.9 Hz, 1H), 5.98 (app d, J = 7.2 Hz, 1H), 2.27 (t, J = 7.6 Hz, 2H), 1.65-1.70 (m, 2H), 1.27-1.30 (m, 8H), and 0.87-0.89 (m, 3H); ¹³C NMR (100 MHz, CDCl₃) δ 172.4, 141.8, 128.8, 127.6, 56.9, 37.0, 31.9, 29.4, 29.2, 25.9, 22.8, and 14.3; HRMS-ESI (m/z): [M+Na]+ calcd for C₂₁H₂₇NO: 332.1985; found: 332.1976.

Reaction of benzhydrylamine (429) (0.623 g, 3.40 mmol, 1.0 equiv) with 1-tert-butoxy-1-octyne (420) (0.620 g, 3.40 mmol, 1.0 equiv) at 90 °C (228 bar) for 24 h according to the General procedure provided 1.08 g of a pale yellow solid. Purification by two trituration cycles with CH₂Cl₂-hexanes afforded 0.830 g of amide 430 as a white solid.
$N$-Phenyl-octanamide (432).

Reaction of aniline (431) (0.289 g, 3.10 mmol, 1.0 equiv) with 1-ethoxy-1-octyne (411) (0.478 g, 3.10 mmol, 1.0 equiv) at 130 °C (238 bar) for 24 h according to the General Procedure provided 0.833 g of a grey-yellow solid. Purification by column chromatography on 15 g of silica (elution with 10% EtOAc-hexanes) afforded 0.416 g (61%) of amide 432 as a pale yellow oil with spectral data consistent with that previously reported.247

Reaction of benzylamine (435) (0.332 g, 3.10 mmol, 1.0 equiv) with 1-ethoxy-1-octyne (411) (0.478 g, 3.10 mmol, 1.0 equiv) at 130 °C (238 bar) for 24 h according to the General Procedure provided 0.432 g of a yellow solid. Purification by two trituration cycles with CH$_2$Cl$_2$-hexanes afforded 0.270 g (37%) of amide 436 as a white solid with spectral data consistent with that previously reported.\(^{248}\)

$N$-Benzy1-$N$-butyl-3-($terr$-butyldimethylsilyloxy)pentanamide (437).

Reaction of $N$-butylbenzylamine (423) (0.556 g, 3.40 mmol, 1.0 equiv) with alkynyl ether 414 (0.824 g, 3.40 mmol, 1.0 equiv) at 130 °C (243 bar) for 24 h according to the General Procedure provided 1.32 g of a dark orange oil. Purification by column chromatography on 20 g of silica gel (gradient elution with 5-10% EtOAc-hexanes) afforded 0.727 g (56%) of the $\beta$-siloxy-amide 437 as a pale yellow oil and 0.261 g (31%) of the $\alpha,\beta$-unsaturated amide 438 as a yellow oil. Amide 437: IR (thin film) 2959, 2930, 1646, 1463, 1254, 1076, and 836 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.24-7.38 (m, 4H), 7.18 (d, $J$ = 7.0 Hz, 1H), 4.37-4.81 (m, 2H), 4.20-4.32 (m, 1H), 3.33-3.40 (m, 1H), 3.16-3.31 (m, 1H), 2.32-2.63 (m, 2H), 1.41-1.66 (m, 4H), 1.24-1.34 (m, 2H), 0.83-0.98 (m, 6H), 0.88 (s, 9H), 0.09 (s, 3H), 0.07 (s, minor rotamer), and 0.04 (s, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) major rotamer: $\delta$ 172.0, 138.2, 128.3, 127.6, 126.4, 71.4, 48.8, 46.4, 40.7, 31.1, 30.7, 26.1, 20.3, 18.3, 14.0, 9.6, -4.4, and -4.5, and for minor rotamer: $\delta$ 171.5, 137.5, 129.0, 128.6, 127.4, 51.5, 47.4, 40.4, 30.0, 20.5, 14.1, and 9.7; HRMS-ESI (m/z) [M+Na]$^+$ calcd for C$_{22}$H$_{39}$NO$_2$Si: 400.2642; found: 400.2626. Amide 438: IR (neat) 2962, 1660, 1615, 1425, 1371, 1282, 1210, and 1118 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) $\delta$ 7.25-7.42 (m, 4H), 7.19 (d, $J$ = 7.4 Hz, 1H), 7.03 (app ddd, $J$ = 6.4, 13.3, 21.6 Hz, 1H), 6.27 (d, $J$ = 15.0 Hz, 1H), 6.18 (d, minor rotamer), 4.66 (s, 2H), 4.60 (s, minor rotamer), 3.40 (t, minor rotamer), 3.24 (t, $J$ = 7.3 Hz, 2H), 2.27 (app quint, $J$ = 7.0 Hz, 2H), 2.19 (app quint, minor rotamer), 1.52-1.59 (m, 2H), 1.27-1.34 (m, 2H), 1.10 (t, $J$ = 7.4 Hz, 3H), 1.01 (t, minor rotamer), and 0.85-0.94 (m, 3H); $^{13}$C NMR (100 MHz, CDCl$_3$) Major rotamer: $\delta$ 167.0, 148.6, 138.2, 128.7, 128.2, 126.6, 119.4, 49.1, 47.1, 31.3, 25.8, 20.2, 14.0, and 12.8, and for minor rotamer: $\delta$ 167.4, 137.6, 129.0, 127.6, 127.4, 119.7, 51.2, 46.5, 29.9, 26.1, 20.5, and 14.1; HRMS-ESI (m/z): [M+Na]$^+$ calcd for C$_{16}$H$_{23}$NO: 268.1672; found: 268.1669.
Reaction of N-butylbenzylamine (423) (0.555 g, 3.40 mmol, 1.0 equiv) and 1-tert-butyl-3-(tert-butyldimethylsilanyloxy)-1-pentyne (421) (0.920 g, 3.40 mmol, 1.0 equiv) at 90 °C (217 bar) for 24 h according to the General Procedure provided 1.35 g of a yellow oil. Purification by column chromatography on 25 g of silica gel (gradient elution with 5-10% EtOAc-hexanes) afforded 1.03 g (80%) of the β-siloxyamide 437 as a pale yellow oil and 0.027 g (3%) of the α,β-unsaturated amide 438 as a yellow oil.
(E)-4,9-Dimethyl-1-(piperidin-1-yl)deca-4,8-dien-1-one (439).

Reaction of piperidine (425) (0.264 g, 3.10 mmol, 1.0 equiv) with alkynyl ether 416 (0.640 g, 3.10 mmol, 1.0 equiv) at 130 °C (274 bar) for 24 h according to the General Procedure provided 0.757 g of a brown oil. Purification by column chromatography on 18 g of silica gel (elution with 20% EtOAc-hexanes) afforded 0.552 g (68%) of amide 439 as a yellow oil: IR (thin film) 2933, 1646, 1436, 1376, 1267, 1220, 1137, and 1010 cm$^{-1}$; $^1$H NMR (400 MHz, CDCl$_3$) δ 5.14 (bs, 1H), 5.08 (t, $J$ = 6.0 Hz, 1H), 3.55 (t, $J$ = 5.5 Hz, 2H), 3.39 (t, $J$ = 5.4 Hz, 2H), 2.33 (app s, 4H), 2.03-2.08 (m, 2H), 1.95-1.99 (m, 2H), 1.67 (s, 3H), 1.62 (s, 3H), 1.59 (s, 3H), and 1.49 (m, 6H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 171.2, 136.3, 131.5, 124.4, 123.2, 46.8, 42.7, 39.9, 33.6, 26.8, 26.9, 25.9, 25.7, 24.7, 24.2, 17.8, and 16.2; HRMS-ESI (m/z): [M+Na]$^+$ calcd for C$_{17}$H$_{29}$NO: 286.2141; found: 286.2152.
12-(Benzylamino)-1-ethoxydodec-1-yne (422).

A 100-mL, three-necked, round-bottomed flask fitted with a glass stopper, argon inlet adapter and rubber septum was charged with ethoxyacetylene (1.00 g, 14.3 mmol, 1.0 equiv, ~50 w/wt in hexane) and 16 mL of THF. The solution was cooled to -78 °C and a solution of n-BuLi (5.6 mL, 14.3 mmol, 1.0 equiv, 2.54 M in hexane) was added dropwise via syringe over 5 min. The reaction mixture was stirred at -78 °C for 1 h, then HMPA (5.50 mL, 31.4 mmol, 2.2 equiv) was added in one portion. The reaction mixture was allowed to warm to 0 °C over 20 min, then cannulated over into a 100-mL round-bottomed flask containing a solution of 1,10-dibromodecane (8.56 g, 28.5 mmol, 2.0 equiv) in 14 mL of THF over a period of 35 min. The resulting reaction mixture was stirred at rt for 16 h, then diluted with 40 mL of H2O and 40 mL of Et2O. The organic phase was washed with three 30-mL portions of H2O and 40 mL of brine, dried over MgSO4, filtered, and concentrated to 8.8 g of dark red oil. Purification by column chromatography on 56 g of silica gel (gradient elution with hexanes-10% EtOAc-hexanes) provided 2.41 g of yellow oil, which was dissolved in 7 mL of DMSO and transferred to a 100-mL, round-bottomed flask fitted with a rubber septum and argon inlet needle. Benzylamine (1.8 mL, 16.6 mmol, 2.0 equiv) was added, followed by NaI (0.062 g, 0.42 mmol, 0.05 equiv). The reaction mixture was stirred at 55 °C for 3 h, then poured onto 20 mL of H2O. The aqueous phase was extracted with three 20-mL portions of Et2O and the combined organic phases were washed with 30 mL of brine, dried over MgSO4, filtered, and concentrated to ca. 3 g of viscous yellow oil. Purification by column chromatography on 50 g of silica gel (elution with 5% Et3N in 1:1 Et2O/hexanes) provided 1.73 g (40% over two steps) of alkynyl ether 422 as a pale yellow oil (xx is an off-white solid at ca. 0 °C): IR (thin film) 2926, 2271, 1454, 1223, 1119, and 1013 cm⁻¹; ¹H NMR (400 MHz, CDCl3) δ 7.23-7.33 (m, 5H), 4.01 (q, J = 7.1 Hz, 2H), 3.79 (s, 2H), 2.63 (t,
$J = 7.2$ Hz, 2H), 2.11 (t, $J = 6.9$ Hz, 2H), 1.41-1.53 (m, 4H), 1.35 (t, $J = 7.1$ Hz, 3H), and 1.27 (app bs, 12H); $^{13}$C NMR (100 MHz, CDCl$_3$) δ 140.8, 128.6, 128.3, 127.0, 89.5, 74.0, 54.3, 49.7, 37.6, 30.3, 29.2, 29.8, 29.7, 29.4, 29.0, 27.6, 17.4, and 14.6; HRMS-ESI (m/z): [M+H]$^+$ calcd for C$_{21}$H$_{33}$NO: 316.2635; found: 316.2631.
**N-benzylazacyclotridecan-2-one (444).**

(In scCO₂): A 50-mL, stainless steel Thar view cell reactor was charged with alkynyl ether 422 (0.035 g, 0.111 mmol, 1.0 equiv). The reactor was pressurized to 50 bar with CO₂, heated to 120 °C, and then pressurized with additional CO₂ to 322 bar. The reaction mixture was stirred at 120 °C (322 bar) for 24 h and then allowed to cool to rt. The reactor outlet valve was opened and the CO₂ phase was vented through a bubbler containing 15 mL of CH₂Cl₂. The residual material in the reactor was deposited onto 0.3 g of silica gel with the aid of 5 mL of CH₂Cl₂, resulting in a free-flowing powder which was loaded onto the top of a 5 g of silica gel column. Gradient elution with 20-50% EtOAc-hexanes provided 0.010 g (31%) of lactam 444 as an oil and 0.002 g (6%) of dilactam 445 as a white solid. 444: IR (thin film) 2929, 2860, 1642, 1451, 1419 and 1353 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.00-7.36 (m, 5H), 4.88 (app d, minor isomer), 4.59 (s, 2H), 4.40-4.46 (m, minor isomer), 4.30 (app d, minor isomer), 3.19 (t, J = 7.9 Hz, 2H), 2.52-2.66 (m, minor isomer), 2.41 (t, J = 8.0 Hz, 2H), 2.11 (ddd, minor isomer), and 1.31-1.86 (m, 18H); ¹³C NMR (100 MHz, CDCl₃) δ major isomer: 173.8, 138.2, 128.6, 128.0, 126.4, 48.4, 45.6, 32.3, 27.0, 26.0, 25.7, 25.5, 25.14, 24.65, 24.5, 24.1, and 23.9; and for minor isomer: δ 174.8, 137.4, 129.0, 127.6, 127.3, 51.4, 44.6, 33.7, 26.9, 26.6, 25.6, 25.3, 25.11, 25.06, 24.71, 24.2, and 23.7; HRMS-ESI (m/z): [M+H]⁺ calcd for C₁₉H₂₉NO: 288.2322; found: 288.2316. For 445: IR (thin film) 2925, 2853, 1643, 1451, 1421, 1356, and 1209 cm⁻¹; ¹H NMR (400 MHz, CDCl₃) δ 7.15-7.39 (m, 10 H), 4.60 (s, 4H), 4.53-4.56 (m, minor isomer), 3.34-3.45 (m, minor isomer), 3.18 (t, J = 7.6 Hz, 4H), 2.29-2.42 (m, 4H), 1.53-1.77 (m, 8H), and 1.28 (app bs, 28H); ¹³C NMR (100 MHz, CDCl₃) major isomer: δ 173.5, 138.2, 128.6, 128.1, 127.3, 51.1, 48.2, 47.0, 33.2, 29.7, 29.6, 29.5, 29.4, 29.3, 29.1, 28.4, 26.4, and 25.8; for minor isomer: δ 173.9, 137.4, 129.0, 127.6, 126.4, 51.1, 47.3, 45.4, 33.6, 33.2, 29.3, 28.6, 27.7, 26.9, 26.7, and 25.7; HRMS-ESI (m/z): [M+Na]⁺ calcd for C₃₈H₅₈N₂O₂: 597.4390; found: 597.4377.
(In scCO$_2$/10% vol toluene): A 50-mL, stainless steel Thar view cell reactor was charged with a solution of alkynyl ether 422 (0.035 g, 0.111 mmol) in 5.4 mL of toluene. The reactor was pressurized to 50 bar with CO$_2$, heated to 120 °C, and then pressurized with additional CO$_2$ to 322 bar. The reaction mixture was stirred at 120 °C (322 bar) for 24 h and then allowed to cool to rt. The reactor outlet valve was opened and the CO$_2$ phase was vented through a bubbler containing 15 mL of CH$_2$Cl$_2$. The residual material in the reactor was deposited onto 0.3 g of silica gel with the aid of 5 mL of CH$_2$Cl$_2$, resulting in a free-flowing powder which was loaded onto the top of a 5 g of silica gel column. Gradient elution with 20-50% EtOAc-hexanes provided 0.0185 g (58%) of lactam 444 as an oil.
Xiao Yin Mak

Education

Advisor: Professor Rick L. Danheiser

B.S. Biochemistry, B.A. Chemistry (High Distinction) and German (Minor)
*University of Rochester, cum laude* May 2003

Research Experience

Graduate Research, *Massachusetts Institute of Technology* Jan. 2004 - Present
Advisor: Professor Rick L. Danheiser
- Developed a tandem benzannulation-heterocyclization strategy for the synthesis of polycyclic benzofused nitrogen heterocycles
- Completed an efficient formal synthesis of (+)-FR900482
- Studies on C-N bond forming reactions in supercritical carbon dioxide
- Supervised and mentored research projects for an undergraduate student

Undergraduate Research, *University of Rochester* Sept. 2002- May 2003
Advisor: Professor Robert K. Boeckman
- Studies on a retro-Claisen methodology for the synthesis of eight-membered nitrogen heterocycles

Summer Internship, *Novartis, East Hanover, NJ* Summer 2002
Advisor: Dr. Mahavir Prashad
- Investigated the double Heck reaction of o,o'-dibromobiaryls with ethyl acrylate
- Explored the palladium-catalyzed synthesis of N-alkyl-substituted diarylamines

Teaching and Service

- Conducted interesting and exciting chemistry demonstrations for local high school students

- Led recitation sections and review sessions for Organic Chemistry I & II, and General Chemistry
- Composed, edited and graded problem sets and exams
- Head TA responsibilities for one semester of Organic Chemistry II

- Led workshop sessions to teach problem solving techniques to Organic Chemistry I & II students

Publications and Presentations


**Awards and Honors**

Masamune Summer Fellowship, 2006

Martin Family Society of Fellows for Sustainability, 2005-2006

Elected to Phi Beta Kappa, 2003

John McCreary Memorial Prize, 2003

Merck Junior Scholar Award, 2002