Synthesis of Indoles via
Zirconocene-Stabilized Benzyne Complexes

by
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Abstract

A method for the regiospecific synthesis of polysubstituted indoles and indolines has been developed. The method relies on the regiospecific generation of zirconocene-stabilized benzyne complexes from N-allyl-2-bromoaniline derivatives. The benzyne complexes undergo an intramolecular olefin insertion reaction to provide tricyclic indoline zirconacycles in high yield. The zirconacycles can be cleaved with two equivalents of an electrophile, usually iodine, to provide a regiochemically pure 3,4-substituted indoline. When iodine is used to cleave the metallacycle, a 4-iodo-3-iodomethylindoline is produced, which has been shown to be a versatile synthetic intermediate for the preparation of highly functionalized indolines and indoles.

Dehydrohalogenation of the diiodoindolines with DBU provides 3-methylene indolines in excellent yield. The 3-methyleneindolines so generated have been shown to be exceptionally reactive partners in the ene reaction with a variety of activated enophiles. In addition, the methyleneindolines undergo reactions with electrophiles such as iminium salts, to give tryptamine derivatives in excellent yield.

The synthesis of 3,4,n-trisubstituted (n= 5,6) indoles and indolines was also undertaken. A number of 3,4,5-trisubstituted indoline derivatives were prepared and converted to serotonin analogs. A 3,4,6-trisubstituted indoline was also prepared and was used as an intermediate for the preparation of the common pharmacophore of CC-1065 and duocarmycin A.

Lastly, a study of the preparation and reactions of 3-bromomethyl-1-carboethoxy-4-iodoindole was performed. It was discovered that this
compound could be prepared in high yield by reaction of a 3-methyleneindoline with N-bromosuccinimide in chloroform. A variety of 3,4-disubstituted indoles were prepared from this intermediate using a sequential nucleophilic displacement/Pd(0)-catalyzed substitution process.

Thesis Supervisor: Stephen L. Buchwald
Title: Professor of Chemistry
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I always thought that it sounded cliché to say that I couldn’t have completed my degree by myself, but it’s true. I have a lot of people to thank for their support and help during my stay at M.I.T. First, I would like to sincerely thank my thesis supervisor, Steve Buchwald. Steve has been responsible for my development as a scientist. Although it was sometimes painful, I have learned some valuable lessons under his supervision that will serve me well throughout my scientific career. Foremost among these lessons is that you will never be sorry if you are always honest and straightforward in everything that you do. I also want to thank him for his patience and his willingness to let me take my project in directions that were interesting to me, but were not always interesting to him. I think that his willingness to let me strike out on my own is, perhaps, how I learned the most chemistry during my years at M.I.T.

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Preface

Parts of this thesis have been adapted from articles co-written by the author:


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Introduction

Chemical synthesis is uniquely positioned at the heart of chemistry, the central science, and its impact on our lives and society is all pervasive. For instance, many of today's medicines are synthetic and many of tomorrow's will be conceived and produced by synthetic chemists. To the field of synthetic chemistry belongs an array of responsibilities which are crucial for the future of mankind, not only with regard to the health, material and economic needs of our society, but also for the attainment of an understanding of matter, chemical change and life at the highest level of which the human mind is capable.

-Elias James Corey
Nobel lecture, December 8, 1990

It can be argued that the practicing synthetic organic chemist has two goals. The first is to devise new methods to form carbon-carbon and carbon-heteroatom bonds. The second goal is to use these new and existing methods to manipulate molecules in a selective fashion in order to create new and useful molecules. Although the repertoire of available reagents and reactions from which the organic chemist can draw is already quite large, there still remains much work to be done so that the increasingly difficult synthetic challenges of the future can be easily overcome. One useful tool that organic chemists are just beginning to successfully exploit is organotransition metal chemistry. Organometallic chemistry, the study of compounds that contain carbon-metal bonds, is relatively young with most of the major advances having been made since the mid-1950's. Although it is a young science, it has enjoyed some enormous successes in those few short years. One example is the asymmetric synthesis of L-Dopa using a chiral rhodium catalyst. Today, organometallic
chemistry is finding increased use in all areas of chemistry including the manufacture of high value "fine" chemicals such as pharmaceuticals, perfumes, agrochemicals and food additives.

Among the many different types of organometallic complexes that have been prepared and studied, those that contain an unsaturated organic fragment bound to the metal center form the basis for many of the most important organometallic reactions. For instance, the processes of olefin hydrogenation, hydroformylation, hydrosilylation, and polymerization are used to make billions of pounds of important chemicals every year and they all involve the binding of an unsaturated fragment to a metal center as one of the key steps. In order to understand the chemistry of these types of complexes, one must first understand their structure and bonding. A model of the bonding in these types of complexes was put forth by Dewar, Chatt and Duncanson (Figure 1). In this model only the frontier orbitals of the metal and the organic fragment are

Figure 1
Group Orbitals

considered. There are two interactions that are involved in the bonding that are important for our discussion. The first is donation of electron density from the olefin $\pi$ bond into the metal $d_{z^2}$ orbital creating a $\sigma$ bond (ligand to metal donation). The second portion consists of donation of electron density from the metal $d_{xz}$ orbital into the vacant $\pi^*$ orbital of the olefin (metal to ligand donation), which is termed backbonding. This type of synergistic bonding between ligand and metal has important consequences for the properties of the
ligand, in this case an olefin. These consequences are manifested in the carbon-carbon bond length and the hybridization of the carbons. Upon binding to a metal, the C-C bond length in an olefin tends to increase for two reasons. First, since electron density in the π bond is donated into the orbitals of the metal, the π bond is weakened, causing an increase in the bond length. Secondly, electron density from the metal is donated into the π* orbital, which decreases the C-C bond order resulting in bond lengthening. Another important consequence of backbonding is that as the metal center becomes more electron rich, thus increasing the amount of backbonding that can occur, the substituents on the olefin bend out of planarity away from the metal, due to the change in hybridization of the carbons. Therefore, there are two extremes that can be considered for olefin complexes (Figure 2). The first is one in which the metal center is electron deficient so that backbonding is kept at a minimum (1). These types of complexes can be considered to be "true" olefin complexes since the C-C bond length will be close to that of the uncomplexed olefin. The other extreme is one in which the metal center is electron rich and is capable of donating a great deal of electron density into the olefinic π* orbital (2). These complexes will resemble metallacyclopropanes because the C-C bond length will be increased and the substituents on the olefin will be bent away from the metal. This type of backbonding can help to stabilize strained or high energy
olefins as shown by Buchwald in the preparation of a zirconocene-stabilized cyclobutene complex.\(^4\) In addition, the olefinic ligand in a complex like 2 will behave in its reaction chemistry as though it contains two metal-carbon \(\sigma\) bonds. As an example, the olefin in Zeise's salt,\(^5\) \(\text{K}[\text{PtCl}_3(\text{C}_2\text{H}_4)]\), demonstrates little lengthening of the C-C bond length (1.375 Å, which is very close to that of free ethylene 1.337 Å). However, in the more electron rich complex, \(\text{Pt(PPh}_3)_2(\text{C}_2\text{H}_4)\),\(^6\) increased backbonding lengthens the carbon-carbon bond to 1.43 Å. The true nature of most olefin complexes lies somewhere in the continuum between these two extremes. It is also worth noting that the metal center in these two extremes differs in formal oxidation state by two units.

The same type of bonding scheme can be drawn for metal complexes of alkynes. This type of bonding picture is at the heart of the complexes that are the subject of this thesis. Like olefin complexes, backbonding from an electron rich metal can help to stabilize a strained or high energy alkyne. Buchwald has demonstrated that this kind of stabilization is important in the preparation of zirconocene complexes of cyclopentyne,\(^7\) cyclohexyne\(^8\) and ortho-benzyn\(^9\) (vide supra). In the complexes that will be discussed in this thesis, backbonding from an electron rich bis(cyclopentadienyl)zirconium species helps to stabilize ortho-benzyn \(\text{fragments which would be highly strained in the absence of the metal. Stable benzyn complexes of tantalum}^{10} \text{and nickel}^{11} \text{have been isolated and structurally characterized by Schrock and Bennett. Although ortho-benzyn itself has been estimated to have 80 kcal/mol of strain energy,}^{12} \text{the backbonding provided by these metals makes them stable, isolable species. Benzyn complexes of group 4 metals had been postulated for many years to be intermediates in the thermolytic decomposition of bis(cyclopentadienyl)M(aryl)\(_2\), M= Ti, Zr, complexes based largely on labeling} \)
and trapping studies. In 1986, Buchwald and Watson discovered that when diphenylzirconocene (3) was thermolyzed in the presence of PMe$_3$, a strongly basic ligand, an isolable, 18-electron complex (4) was formed (Scheme I.1). X-ray analysis revealed that complex 4 contained an η$^2$-benzyne ligand. Interestingly, unlike the tantalum benzyne complex studied by Schrock, the C-C bond lengths of the benzyne fragment in complex 4 did not show long and short alternation, corresponding to "frozen out" single and double bonds. Instead, like the nickel complex isolated by Bennett, the bond lengths were, within experimental error, the same. In addition, the bond angles in the benzyne moiety vary only slightly from those observed in benzene indicating that it experiences little angle strain. This argues that a high degree of backbonding occurs in the complex from the zirconium to the π* orbital of the benzyne ligand. Therefore, the complex can be better represented as a metallacyclopentene containing two zirconium-carbon σ bonds such as resonance structure 4. In order to understand the bonding in this complex, we should examine the frontier molecular orbitals of the bent zirconocene fragment as they were described by Hoffmann and Lauher (Figure 3). Interaction of the metal-centered 2a$_1$ orbital with the benzyne π bond occurs to give a bond with σ symmetry. The backbonding occurs with interaction of the metal b$_2$ orbital with the π* orbital of the benzyne ligand.

Figure 3
There are two possible mechanisms for the formation of benzyne complex 4 as shown in Scheme 1.2. Pathway A consists of a $\beta$-hydride elimination to produce intermediate $d^0$ benzyne/hydride complex 6, which then

Scheme 1.2
Pathway A:

\[
\begin{align*}
\ce{Cp_2Zr} & \xrightleftharpoons{\beta-\text{H}} \ce{Cp_2Zr-H} & \xrightarrow{\text{red. elim.}} \ce{Cp_2Zr<=>C_6H_6} \\
\ce{Cp_2Zr} & \xrightleftharpoons{\beta-\text{H}} \ce{Cp_2Zr-H} & \xrightarrow{\text{red. elim.}} \ce{Cp_2Zr<=>C_6H_6} 
\end{align*}
\]

Pathway B:

\[
\begin{align*}
\ce{Cp_2Zr} & \xrightarrow{\text{cyclometallation}} \ce{Cp_2Zr<=>C_6H_6} \\
\ce{Cp_2Zr} & \xrightarrow{\text{cyclometallation}} \ce{Cp_2Zr<=>C_6H_6} 
\end{align*}
\]

undergoes a reductive elimination reaction giving benzyne complex 7 and benzene. Pathway B involves a 4-centered, concerted cyclometallation reaction in which no discrete zirconium hydride complex is ever produced as a long-lived intermediate. The mechanism of this reaction was first studied by O'Brien and co-workers using deuterium labeling experiments. They discounted a radical mechanism, but were unable to distinguish between the two pathways described above. Erker prepared a series of isomeric ditolylzirconocene complexes and thermolyzed them in benzene (Scheme 1.3). He showed that the benzyne complexes were capable of reversibly activating aromatic solvents to give diaryl zirconocene complexes. He also showed that photolysis of ditolylzirconocene complexes produced dimethylbiphenyl products that accurately reflected the substitution pattern of the zirconocene complex. For example, heating di-p-tolylzirconocene 8
followed by photolysis produced 4,4'-dimethylbiphenyl (9), 4-methylbiphenyl (10) and 3-methylbiphenyl (11). No 3,4'-dimethylbiphenyl (13) was produced. Based on this observation, pathway A was discounted because it predicts that a reversible hydrozirconation of the benzyne ligand would give p-tolyl-m-tolylzirconocene which was not observed. Other evidence for the concerted nature of this elimination reaction comes from the study by Buchwald and Nielsen on the mechanism of formation of zirconocene thioaldehyde complexes such as 15 from (alkylthio)-methylzirconocene intermediates (14) (Scheme 1.4).16 The mechanism of this reaction is postulated to be closely related to the formation of zirconocene benzyne and alkyne complexes. They determined the activation parameters for the reaction as well as determining the kinetic isotope

Scheme 1.3

![Scheme 1.3 Diagram]

Scheme 1.4

![Scheme 1.4 Diagram]
effect for this reaction. They found that the decomposition of 14 was first-order and was independent of the phosphine concentration. This data is consistent with the view that the reaction is unimolecular in nature. The large primary isotope effect of 5.2 at 80 °C implies that the rate-determining step involves breaking of the carbon-hydrogen bond. The large value is inconsistent with those reported by other groups for a β-hydride elimination or a reductive elimination step. In addition, the large, negative entropy of activation is more consistent with a rate-determining β-hydride elimination or a concerted elimination rather than a reductive elimination. They contend that while the data do not entirely rule out other mechanisms, the one that is most consistent with the data is a 4-centered, concerted cyclometallation process that does not proceed a zirconocene hydride intermediate. These results indicate that the lowest energy pathway for the formation of the thioaldehyde intermediate is via a concerted cyclometallation. Therefore, it seems likely that the lowest energy pathway for the formation of a benzyne complex would involve the same type of concerted cyclometallation since backbonding to a benzyne moiety would be more important to due its significant strain energy.

The reaction chemistry of benzyne complexes like 7 is consistent with the view that they are better represented as metallacyclopropenes containing two carbon-zirconium σ bonds. Watson and Buchwald found that benzyne complexes of zirconocene insert olefins, alkynes, nitriles and ketones to produce the expected metallacycles in good yields. The selective coupling reactions that are possible with this type of complex make it a useful vehicle for the synthesis of compounds that would be difficult to prepare using other methods. For instance, complex 16 undergoes an insertion reaction with acetonitrile to give azametallacycle 17 (Scheme I.5). Iodination, followed by workup, gives iodoketone 18 in 61% overall yield from 2-bromoanisole. It is
noteworthy that iodoketone 18 is the anti Friedel-Crafts isomer in which the acyl group is positioned \textit{meta} to the electron donating methoxy group. Prior to this work, there were no efficient methods available to prepare compounds of this type. However, in order to make this methodology more attractive to the synthetic chemist, and also more efficient, a procedure was developed that

\textbf{Scheme 1.5}

\[
\begin{align*}
\text{Cp}_2\text{Zr} & \quad \text{CH}_2\text{CN} \\
16 & \quad \rightarrow \\
\text{OCH}_3 & \quad \text{CH}_3 \quad \text{CN} \\
\text{CH}_3 & \quad \text{I} \\
17 & \quad \text{OCH}_3 \\
18 & \quad \text{61\% overall yield from 2-bromoanisole}
\end{align*}
\]

required the use of only one equivalent of the aryl starting material. In this modification, an aryl(methyl) zirconocene complex is first produced by the reaction of an aryl lithium species with zirconocene (methyl)chloride.\textsuperscript{19} Upon warming, these complexes undergo a concerted loss of methane to give the desired benzyne complex.

Until recently, most of the work in our laboratories has dealt with the intermolecular insertion reactions of substituted benzyne complexes. We reasoned, however, that the intramolecular insertion of an N-allyl group into a suitably disposed benzyne complex 19 would produce tricyclic zirconacycle 20 as shown in Scheme 1.6. Cleavage of the metallacycle with various electrophiles would then yield a regiochemically pure 3,4-disubstituted

\textbf{Scheme 1.6}
indoline such as 21. This sequence of reactions would represent a fundamentally new approach to the synthesis of 3,4-disubstituted indolines and indoles. Further, since highly substituted aniline precursors are either commercially available or are readily prepared, polysubstituted indolines and indoles could be prepared in relatively few steps.

The indole ring system can be found in a large number of natural products, many of which have important medicinal properties.20 Among the many naturally occurring indole alkaloids, those that have substituents at the 3 and 4 positions such as the ergot alkaloids (22),21 indolactam V (23),22 chuangxinmycin (24)23 and CC-1065 (25)24 have received much recent attention from synthetic chemists due to their potent biological activity (Figure 4). Although a large number of methods exist for the preparation of substituted

Figure 4
indoles, the synthesis of these natural products and other 4-substituted indoles still remains a formidable task. The main difficulty is that the 4-position is less electron rich than many of the other positions, rendering "traditional" synthetic strategies, such as electrophilic aromatic substitution, less effective.\textsuperscript{25} The strategies that have been developed for the synthesis of these important compounds can be divided into two categories. The first approach is to construct the pyrrole ring onto an appropriately substituted aromatic precursor using an annelation method. Among the most widely used methods in this category are the Fischer,\textsuperscript{26} Madelung,\textsuperscript{27} Reissert\textsuperscript{28} and Batcho-Leimgruber\textsuperscript{29} indole syntheses. Recently, organometallic methods have played an increasingly important role in this approach. The most useful methods are those based on cyclizations catalyzed by Pd and Ni as developed by Ban,\textsuperscript{30} Larock,\textsuperscript{31} Hegedus\textsuperscript{32} and Stille.\textsuperscript{32} Although these methods have been used
for the construction of a number of indolic products, the main disadvantage is that in order to prepare a 4-substituted indole, the required starting material is a trisubstituted aromatic compound. Depending upon the substitution pattern and the substituents themselves, trisubstituted aromatic compounds can be either expensive or difficult to prepare.

The second approach is to introduce a substituent into the 4 position of an existing indole ring system. Among the most successful methods in this category are the use of chromium tricarbonyl complexes of indole studied first by Kozikowski\textsuperscript{33} and then developed more extensively by Widdowson\textsuperscript{33b} and Semmelhack,\textsuperscript{22} the thallation/palladation method of Somei,\textsuperscript{34} and the recently developed lithiation of gramine by Iwao.\textsuperscript{35} The drawback of some of these methods is that they are non-regioselective. In addition, two of them use a stoichiometric amount of toxic metals, thallium and chromium, which present waste disposal problems if used on an industrial scale.

Our approach, briefly outlined earlier, was to utilize the intramolecular insertion reaction of an N-allyl group into a benzyne complex to produce a regiochemically pure 3,4-disubstituted indoline skeleton. The metallacycle is then cleaved with various electrophiles to provide a disubstituted indoline product which could be further manipulated to yield a variety of indolic products. The advantages of our method over those methods discussed above include the use of readily available 1,2-disubstituted aniline precursors to prepare compounds which are regiochemically pure and the use of a non-toxic, inexpensive, and readily available zirconocene reagent.
Chapter 1:
The Synthesis of 3,4-Disubstituted Indoles
via a Sequential Olefin Insertion/
Ene Route
from 26. The LAH reduction proved to be difficult to perform on a large scale, so we sought a more direct route to our starting material. Barr and Buchwald found that if 2-bromoaniline was treated with n-butyllithium (n-BuLi) at -78 °C in tetrahydrofuran (THF), only deprotonation of the amino group took place and no halogen-metal exchange was observed. Treatment of the lithioamide with allyl bromide followed by a second deprotonation with n-BuLi and addition of benzyl bromide gave 29 in 73% overall yield. Later in our studies we discovered that the use of a second allyl group as a protecting group did not affect the yield of metallacycle formation. In addition, the allyl group could be cleaved from the indoline in the same fashion and in similar yield as the benzyl group. Since the diallyl material 30 was more convenient to prepare on a large scale by simply refluxing a mixture of 2-bromoaniline and allyl bromide in DMF (Scheme 1.2), this group was used exclusively in later studies.

**Scheme 1.2**

After trying many conditions to affect the zirconocene-mediated cyclization, we found that the best procedure was to treat a mixture of aniline derivative 29 or 30 and zirconocene (methyl) chloride in THF at -78 °C with 2 equivalents of tert-butyl lithium (t-BuLi) (Scheme 1.3). The mixture was allowed
to stir at -78 °C for 15 minutes and was then allowed to warm to room temperature. Upon warming to room temperature, methane elimination occurred to produce the zirconocene-stabilized benzyne complex which underwent an intramolecular olefin insertion reaction to yield tricyclic zirconacycle 33 or 34. It is interesting that benzyne formation occurs at or near room temperature since Buchwald and Cox have observed that the analogous allyl phenyl ethers require heating at 70-80 °C overnight to effect methane elimination.

Scheme 1.3

The reason for this difference is that the diallylamino group is bulkier than the allylphenol, causing the hydrogen that is going to be abstracted to be moved closer to the Zr-centered LUMO. This effect was observed again later in our study when the two aryl (methyl) zirconocene complexes 35 and 37 were prepared (Scheme 1.4). Complex 35 in which the zirconocene fragment occupies a position ortho to the bulky diallylamino group underwent the desired cyclometallation reaction at 45 °C. In contrast, complex 37 in which the
zirconocene moiety is *meta* to the amino group required heating at 70 °C for 16 hours in order to form the same metallacycle. A similar effect was observed by Buchwald and Lum when they were attempting to prepare cyclopentyne

**Scheme 1.4**

![Scheme 1.4](image)

complex 39 (Scheme 1.5). They observed that complex 38 would not eliminate methane even upon prolonged heating at 120 °C. In order to test their postulate that it was necessary to increase the overlap of the vinylic hydrogen with the Zr-centered LUMO, 5,5-dimethylcyclopentenyl analog 40 was prepared. Thermolysis of 40 at 90 °C ($\tau_{1/2}$ = 4 h) was sufficient to induce cyclometallation. Presumably this is a manifestation of the interaction of the cyclopentadienyl (Cp) ligands with the two methyl groups. Steric interaction of the methyl groups with the Cp ligands causes them to move away from the metal center. Consequently, the vinylic hydrogen that is abstracted is moved closer to the metal-centered LUMO.

**Scheme 1.5**
In the formation of the indoline metallacycle intermediates, \( 31 \) and \( 32 \) have never been observed. However, metallacycles \( 33 \) and \( 34 \) have been isolated in pure form and spectroscopically characterized by Barr and Buchwald. The yield of \( 33 \) or \( 34 \) as estimated by \( ^1 \)H NMR is greater than 90%, while the yield of isolated material is typically 63%.

We found that addition of a methylene chloride (\( \text{CH}_2\text{Cl}_2 \)) solution of \( \text{I}_2 \) to \( 33 \) or \( 34 \) at 0 \( ^\circ \)C gives diiodoindoline \( 42 \) and \( 43 \), respectively, in 98% yield. In our studies we have found that the transformation of \( 29 \) to \( 42 \) and \( 30 \) to \( 43 \) can be achieved in a "one-flask" procedure in an overall yield of 65-70%.

**Scheme 1.6**
We were interested in using diiodides 42 and 43 as an intermediate in the synthesis of more highly substituted indolines and indoles. One approach we studied was the displacement of the alkyl iodide by a variety of nucleophiles. In general, we found that when 43 was treated with nucleophiles, two competing reactions occurred. In the first, the alkyl iodide was displaced to give the desired substitution product and in the second an elimination reaction took place to give olefin 45 (Scheme 1.7). For most nucleophilic reagents such as sodium acetate, sodium methoxide, and Grignard reagents, olefin 45 was the sole product. However, if 43 was treated with soft carbon nucleophiles such as malonate anion, both the olefin and substitution product were formed in a ratio that depended on the reaction conditions employed. For example, if the sodio malonate anion was generated before the addition of 43, by reaction of dimethyl malonate with NaH, olefin 45 was the only observed product. However, if the reaction of dimethyl malonate with sodium or potassium carbonate was conducted in the presence of 43 and in benzene then both products 45 and 46 were formed. Under these conditions, 46 constituted 50-
60% of the material produced (estimated by $^1$H NMR); the remainder of the material was 45. The addition of a phase-transfer catalyst, such as tetra-$n$-butylammonium bromide, improved the yield of 46 only slightly, even when a stoichiometric amount was used. However, the addition of a stoichiometric amount of 18-crown-6 with $\text{K}_2\text{CO}_3$ as base, significantly improved the yield of 46. Of the solvents investigated, benzene proved to be the best. Under these conditions, 46 was obtained in 80% isolated yield. Olefin 45 was produced in 10-15% yield as estimated by $^1$H NMR. We found that olefins 44 and 45 were efficiently produced if 42 or 43 were allowed to react with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) at 45-60 °C in benzene (Scheme 1.8).

Attempts to isolate either 44 or 45 in pure form by extractive workup with water or by chromatography on silica, alumina or florisil gave significant amounts of the isomeric 3-methylindole derivative. This is easily understood since the isomerization should be either acid or base catalyzed. However, we found that 44 and 45 were stable under the reaction conditions in which they were
formed, and that they could be isolated in reasonably pure form simply by filtration of the DBU salts and removal of the solvent via rotary evaporation. Benzene was found to be the best solvent for the elimination reaction because the DBU-HI was insoluble and could be easily removed by filtration of the reaction mixture. If a solvent was used in which the DBU salts were soluble, such as acetonitrile, then the only observed product was the rearranged indole derivatives.

**Scheme 1.8**

\[
\begin{align*}
\text{DBU, } C_6H_6 & \quad 45-60 ^\circ C \\
42, R= \text{Bn} & \quad 44, R= \text{Bn} \\
43, R= \text{allyl} & \quad 45, R= \text{allyl}
\end{align*}
\]

Due to the relationship of 44 and 45 to their aromatic isomers, we were intrigued by the possibility they could undergo Alder-ene reactions with activated enophiles. The ene reaction is a 6π-electron electrocyclic reaction that is closely related to the better-known Diels-Alder reaction. In the ene reaction, an alkene bearing an allylic hydrogen (the ene) reacts with an enophile with formation of a new σ bond to the terminal carbon of the allyl group, 1,5 migration of the allylic hydrogen and transposition of the double bond (Scheme 1.9). Although this reaction has been known for over a century, it has not been as widely used in organic synthesis as the Diels-Alder reaction.

**Scheme 1.9**
because it involves breaking a carbon-hydrogen bond and normally requires higher temperatures. Like the Diels-Alder reaction, the ene reaction works best when the two reaction partners are electronically dissimilar, one being electron rich and the other electron poor. Typical conditions for a thermal (not catalyzed by a Lewis acid) ene reaction are high temperatures (200 °C) and long reaction times. However, due to the ease of isomerization of either 44 or 45 to their aromatic isomers, we expected that the ene reactions of them would proceed under more mild conditions. After we had begun our studies, we found that Achmatowicz and co-workers had observed that structurally similar, electron-rich styrene derivatives shown in Figure 5 underwent ene reactions at low temperatures (50-100 °C). In contrast, the corresponding 4-nitrostyrene derivatives failed to undergo ene reactions with activated enophiles. We were pleased to find that the reaction of 44 with a variety of activated enophiles proceeded as expected under mild conditions (85 °C in toluene, 2-12 hours), to provide 4-iodoindole derivatives in good yield (Table 1). For example, treatment of 44 with diethylacetylene dicarboxylate gave olefin 47 in 53% yield. Reactions with activated carbonyl compounds such as diethylketomalonate and n-butylglyoxalate gave exclusive formation of the α-hydroxymalonate and propionate derivatives in 76% and 72% yields, respectively.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Eneophile</th>
<th>Product</th>
<th>Yield&lt;sup&gt;a&lt;/sup&gt;(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>EtO&lt;sub&gt;2&lt;/sub&gt;C≡CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td><img src="image1" alt="Image" /></td>
<td>53</td>
</tr>
<tr>
<td>2</td>
<td>EtO&lt;sub&gt;2&lt;/sub&gt;C=CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td><img src="image2" alt="Image" /></td>
<td>56</td>
</tr>
<tr>
<td>3</td>
<td>NC≡CN</td>
<td><img src="image3" alt="Image" /></td>
<td>60</td>
</tr>
<tr>
<td>4</td>
<td>EtO&lt;sub&gt;2&lt;/sub&gt;C=CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td><img src="image4" alt="Image" /></td>
<td>76</td>
</tr>
<tr>
<td>5</td>
<td>HCO&lt;sub&gt;2&lt;/sub&gt;nBu</td>
<td><img src="image5" alt="Image" /></td>
<td>72</td>
</tr>
<tr>
<td>6</td>
<td>EtO&lt;sub&gt;2&lt;/sub&gt;C=N=CO&lt;sub&gt;2&lt;/sub&gt;Et</td>
<td><img src="image6" alt="Image" /></td>
<td>83</td>
</tr>
</tbody>
</table>

<sup>a</sup>Yields refer to isolated yields of purified products based on diiodide precursor, 42.
We were interested in using this methodology for the synthesis of the skeleton of the Chinese antibiotic chuangxinmycin 24 (Scheme 1.10).23 A majority of the past syntheses of this compound have relied upon closure of the C ring by a Knoevenagel condensation to form the C\textsubscript{3}-C\textsubscript{4} bond. The problem with this approach is that the vinyl sulfide must be selectively reduced. In most cases, the result of the reduction is extrusion of the sulfur or fragmentation of the ring. We envisioned that the tricyclic skeleton could be assembled by first performing an ene reaction with the thio analog of a glyoxalate ester. We had already shown glyoxalate esters to be excellent substrates for the ene reaction with 44. The thiol produced would then be converted into an alkylthiotrialkylstannane by reaction with tributyltin chloride. Ring closure would be accomplished using a palladium mediated thiation of the aromatic ring based on chemistry developed by Widdowson.41 Although thioaldehydes are known to be unstable, several research groups have been successful

Scheme 1.10
Past Syntheses:

Our Approach:

in generating them *in situ* and using them as dienophiles in the Diels-Alder reaction. However, not much work has been done using thioaldehydes as enophiles. We thought that a potential problem would be the regiochemistry of addition of the thioaldehyde to olefin 44 or 45. Would the thioaldehyde favor addition to form a carbon-carbon bond giving the thiol as we had observed with the glyoxolate esters, or would it favor carbon-sulfur bond formation to yield the
undesired sulfide product? Reports in the literature indicate that this question is not straightforward, and that both the thiol and sulfide can be formed depending on the electronic structure of the thioaldehyde and the ene component of the reaction.\(^4\) For instance, when thioaldehyde 53 was allowed to react with \(\beta\)-pinene (Scheme 1.11), products 54 and 55 were formed in 19% and 37% yields, so that in this case the thiol was the major product.\(^4\) Conversely, when dithioester 56 was allowed to react with the same olefin, exclusive formation of sulfide 57 was observed.\(^4\) In comparison, the thioaldehyde in our study would be less electron rich than 53. However, olefins 44 and 45 are more electron rich than \(\beta\)-pinene. Since there did not seem to be any clear-cut answer to our question about the regiochemistry of addition, we decided to try the reaction. The thioaldehyde was generated by allowing ethyl-2-mercaptoacetate (58) to react with N-chlorosuccinimide (NCS) in benzene to produce S-chloromercaptoacetate 59 (Scheme 1.12).\(^{42e}\) The succinimide was filtered away from 59 and it was added to olefin 45, which had been prepared.
beforehand. Triethylamine (Et₃N) was then added to the reaction mixture in order to generate the thioaldehyde. After workup of the reaction mixture, we observed starting olefin and sulfide 61 as the only product, none of the desired thiol had been produced. We reason that this may be due to the electron deficiency of the thioaldehyde 60. The two examples in Scheme 1.11 clearly indicate that as the thioaldehyde is made more electron poor, the major reaction pathway is the one that yields sulfide products and not thiols.

**Scheme 1.12**

We were also interested in using imines as the enophiles, since this would provide us with a method for preparing 4-iodotryptophan derivatives. The development of methods for the preparation of nonproteinaceous α-amino acids is an active area of research. In particular, several reports have recently appeared in the literature dealing with the preparation of substituted tryptophan derivatives. The most common methods that are used to synthesize tryptophan derivatives are electrophilic aromatic substitution reactions on tryptophan, Fischer indolization of a suitably substituted arylhydrazone, the enzymatic modification of indolic starting materials and annulation strategies employing ortho-haloanilines and γ,δ-acetylenic amino acid derivatives. The first report of an ene reaction with an imine enophile
was in 1981 by Achmatowicz and Pietraszkiewicz. They found that the reaction of an electron poor N-tosylimine with alkenes gave γ,δ-unsaturated α-amino acids in good yields. Since that initial report appeared, several others, most notably Weinreb and co-workers, have reported on the use of the imino ene reaction for the synthesis of natural products. We tried several times to prepare the N-sulfinyl imines, used by Achmatowicz, from glyoxalate esters and N-sulfinyl-p-toluenesulfonamide according to the procedure of Weinreb, but we were unsuccessful. These types of imines are known to be particularly water and temperature sensitive and once prepared they must be used immediately. We decided to examine other electron deficient imines to use as enophiles, even though the N-sulfinyl imines were the only ones that had been reported to undergo intermolecular ene reactions. The imines that we chose to examine were N-(t-butoxycarbonyl)imino acetates such as 64 (Scheme 1.13). Compounds of this type have been used as glycine cation equivalents by Munster and Steglich. The methyl ester was prepared by allowing glycine methyl ester hydrochloride (62) to react with (BOC)2O in water/chloroform to give the BOC carbamate. The carbamate was then photolyzed in carbon tetrachloride in the presence of NBS to give bromoacetate 63, which was used immediately without purification. Imine 64 was generated at -78 °C in THF by the addition of Et3N and the mixture was allowed to stir for 15 minutes. Olefin 45, which had been prepared beforehand, was added at -78 °C and the resulting mixture was allowed to slowly warm to room temperature overnight. Workup and flash chromatography provided 4-iodotryptophan derivative 65 in 70% isolated yield. This reaction is one of the few known intermolecular ene reactions with an imino enophile. In addition, to our knowledge, this is the first imino ene reaction that proceeds at or below room temperature in the absence of a Lewis acid catalyst.
Although the reactions of olefins 44 and 45 presented thus far can be called ene reactions, no experiments have been performed in order to elucidate the mechanisms by which they proceed. It can be argued that some of these reactions could proceed via a concerted mechanism, while others may proceed via stepwise, polar mechanisms. However, according to Hoffmann, an ene reaction does not have to proceed by a concerted mechanism to be termed an ene reaction. Instead, "a broad spectrum of transition states" exists, including biradical and zwitterionic transition states. For example, Snider has studied the Lewis acid catalyzed ene reactions of aldehydes with alkenes. Most of these reactions are postulated to go through a zwitterionic mechanism, yet these reactions are still termed ene reactions. The reaction of imino acetate 64 with olefin 45 is particularly intriguing, since compounds of this type have been used as glycine cation equivalents with nucleophiles as weak as enamines and silyl enol ethers. This particular reaction may very well proceed via a stepwise, polar mechanism in which the electron rich olefin acts as a nucleophile. This would not be unexpected since the carbocation that
would be formed would be benzylic and ortho to an amino group which could help to stabilize it.

We became interested in studying how well olefins 44 and 45 would react with electrophiles such as iminium salts. We chose to study iminium salts because it would give us entry into the synthesis of a wide range of tryptamine derivatives. Tryptamines, or [2-(3-indolyl)ethylamine derivatives have intense, sometimes hallucinogenic, physiological effects. Therefore, there has been great interest, particularly in the pharmaceutical industry, in developing improved and general methods for the synthesis of these compounds in order to "fine tune" psychotomimetic tryptamines. In general, tryptamine derivatives are synthesized in multi-step sequences, the yields of which can vary widely depending on the substituents on the indole ring. For instance, Macor at Pfizer has reported the synthesis of two serotonin analogs using the same method for the introduction of the 2-ethylamino side chain (Scheme 1.14). In one case, reaction of electron rich 5-allyloxyindole 66 with

Scheme 1.14
glyoxylyl chloride followed by addition of dimethyl amine gave the glyoxylyl amide 67 in 63% yield. However, when the same reaction conditions were applied to electron poor 5-nitroindole 68, the desired amide 69 was produced in only 36% yield. We did not anticipate that the substituents on the indoline ring would have much effect on the yield of the reaction of olefins 44 and 45 with iminium salts. We anticipated that a wide range of polysubstituted tryptamine derivatives could be easily synthesized simply by starting with a substituted aniline precursor. In addition, since a wide range of iminium salts can be readily prepared according to literature procedures, we reasoned that it would be experimentally simple to change the substituents on the amino group in order to make a number of analogs. We found that the reaction of olefins 44 and 45 with iminium salts could be effected in CH$_3$CN under mild conditions (45 °C, 2 h) to give the desired tryptamine derivatives in excellent yield (Table 2). For example, reaction of 44 with N$_2$N-diethylmethylene ammonium chloride gave diethyltryptamine 70 in 85% overall yield from diiodide 42.

The iminium salts that were used were prepared according to literature procedures from the corresponding secondary amines. Since many structurally different secondary amines are commercially available, this method should be general enough to allow for the synthesis of a wide variety of tryptamine analogs in a straightforward fashion.
<table>
<thead>
<tr>
<th>Entry</th>
<th>Iminium Salt</th>
<th>Product&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>$\text{H}_2\text{C} \equiv \text{N}(\text{Et})_2^+$</td>
<td><img src="image" alt="Product 70" /></td>
<td>85%</td>
</tr>
<tr>
<td>2</td>
<td>$\text{H}_2\text{C} \equiv \text{N}(\text{Me})_2$</td>
<td><img src="image" alt="Product 71" /></td>
<td>70%</td>
</tr>
<tr>
<td>3</td>
<td>$\text{H}_2\text{C} \equiv \text{N}(\text{Me})_2^+$</td>
<td><img src="image" alt="Product 72" /></td>
<td>85%</td>
</tr>
<tr>
<td>4</td>
<td>$\text{H}_2\text{C} \equiv \text{N}(\text{O})$</td>
<td><img src="image" alt="Product 73" /></td>
<td>84%</td>
</tr>
<tr>
<td>5</td>
<td>$\text{H}_2\text{C} \equiv \text{N}(\text{Ph})$</td>
<td><img src="image" alt="Product 74" /></td>
<td>79%</td>
</tr>
</tbody>
</table>

<sup>a</sup>R<sub>1</sub> = Bn, R<sub>2</sub> = allyl.  
<sup>b</sup>Yield refers to isolated yields based on diiodide precursors 42 or 43.
With the goal in mind of applying this methodology to the total synthesis of a natural product, we thought it desirable to use a protecting group on aniline precursor 29 or 30 that could be easily removed from either an indoline such as 42 or an indole such as 70. After much experimentation, we found that alkyl groups such as benzyl and allyl functioned best in the zirconocene-mediated coupling reaction. Attempted hydrogenolysis of the benzyl group from 42 proved to be troublesome. We found that when 42 was allowed to react with Pd/C in the presence of hydrogen or ammonium formate as the hydrogen source, only unchanged starting material was recovered. We next attempted to remove the allyl protecting group from 43 by an isomerization/hydrolysis sequence (Scheme 1.15). The catalyst that is used most often for this type of reaction is Wilkinson's catalyst, (PPh₃)₃RhCl. The reaction is conducted in an alcoholic solvent and the active catalyst is proposed to be a rhodium hydride. Using literature procedures for this reaction proved fruitless, since only unchanged starting material was recovered. Another rhodium catalyst that has been used to deprotect 1-allylindolines is (PPh₃)₄RhH. Reaction of this catalyst with 43 in ethanol and in the presence of trifluoroacetic acid was successful, giving indoline 75 in good yield. Unfortunately, in order for the reaction to proceed to completion, we had to add up to 25 mol% of the rhodium catalyst. This same problem was reported by Sundberg in a similar system, although no explanation was provided. In our system, poisoning of the catalyst could be occurring by a competitive oxidative addition reaction of the rhodium(I) species to the aryl iodide. This would, perhaps, give a rhodium(III) complex that is no longer active in the isomerization reaction. Another possibility could be poisoning of the catalyst by the product amine. However, no evidence for either of these hypotheses was obtained.
The next deprotection method that we studied was dealkylation by chloroformates. Olofson has demonstrated that tertiary amines can be selectively dealkylated by chloroformates to produce intermediate carbamates which can then be cleaved under mild conditions. The proposed mechanism for the dealkylation is shown in Scheme 1.16. Initial attack of the amine on the chloroformate produces an ammonium salt, from which either the alkyl group is cleaved by nucleophilic attack of chloride ion or the chloroformate is fragmented, producing CO₂ and an alkyl chloride. The most useful chloroformate for this type of reaction is 1-chloroethyl chloroformate (ACE-CI). Although there are literature reports detailing the dealkylation of aromatic amines using ACE-CI, the conditions required are quite harsh, requiring a large excess of the chloroformate, high temperatures (>150 °C) and long reaction
Using ACE-CI according to the original conditions reported by Olofson with either 42 or 43 no dealkylation occurred and only unchanged starting material was recovered (Scheme 1.17). Upon increasing the number of equivalents of the chloroformate and heating the reaction mixture to higher temperatures, only decomposition of the starting material was observed. We reasoned that the problem was due to the low nucleophilicity of the aromatic amine. Our solution was to make the chloroformate more reactive by converting it in situ to an iodoformate. This was accomplished by conducting the reaction in acetone with two equivalents of ACE-CI and 3 equivalents of sodium iodide. Under these conditions, the dealkylation reaction took place readily at room temperature with either 42 or 43 to give the desired carbamate 78 (Scheme 1.18). We propose that the first step is acyl halide exchange to produce an iodoformate which is attacked by the amine giving an ammonium iodide salt. Not only does the iodoformate add more quickly to the amine than
the chloroformate, but since iodide is more nucleophilic than chloride,\textsuperscript{63} the cleavage reaction also takes place more readily. Unfortunately, experiments using mass spectroscopy were inconclusive as to whether the second halide in the chloroformate is also undergoing exchange in the reaction. Carbamate \textsuperscript{78} was then cleaved using methanol and 1,2-dichloroethane (DCE) as cosolvent to give the secondary amine \textsuperscript{75} in 65-70\% overall yield from either \textsuperscript{42} or \textsuperscript{43}. This modification of Olofson's method was used with a number of different chloroformates. For instance, the reaction of \textsuperscript{43} with ethyl chloroformate and sodium iodide in acetone gave ethyl carbamate \textsuperscript{79} in 91\% yield (Scheme 1.19). However, one limitation of the method is that R' must be less prone to nucleophilic attack by iodide than R, otherwise fragmentation of the chloroformate becomes the dominant reaction pathway (see Scheme 1.16). It is worth noting that the carbamate protected indolines gave the same yield in their ene reactions and in their reactions with iminium salts as those that were protected with either an allyl or benzyl group. For example, reaction of \textsuperscript{79} with DBU and Eschenmoser's salt gave tryptamine derivative \textsuperscript{80} in 83\% yield, which is comparable to that observed for the allyl or benzyl protected indolines (Scheme 1.20).

\textbf{Scheme 1.19}

\chemfig{I-\begin{tangle}C\end{tangle}-I\textbf{43} |-\textbf{N}|-\begin{tangle}C\end{tangle}\textbf{79} @I} \begin{align*}
\text{I} & \quad \text{Cl} \quad \text{OE} \\
\text{NaI} & \quad \text{acetone} \\
\text{91\%} & 
\end{align*}

\textbf{Scheme 1.20}
In conclusion, we have demonstrated that the intramolecular coupling of an N-allyl group with a zirconocene-stabilized benzyne complex gives regiochemically pure 3,4-disubstituted indoline metallacycles in good yield. The two carbon-zirconium bonds of the metallacycle can be cleaved with iodine to give 3,4-diiodoindolines. These diiodoindolines undergo dehydrohalogenation reactions to give 3-methyleneindolines which proved to be excellent ene partners in the ene reaction with activated enophiles. The ene reaction of the 3-methyleneindolines was used to synthesize novel indole products, including a 4-iodotryptophan derivative. In addition, the 3-methyleneindolines were shown to react as nucleophiles with iminium salts to give tryptamine derivatives in excellent yield.
Chapter 2:
Preparation of 3,4,n-Trisubstituted \((n= 5,6)\)
Indoles and Indolines:
Synthesis of Serotonin Analogs and the
CC-1065/Duocarmycin A Pharmacophore
Synthesis of Serotonin Derivatives

We became interested in using substituted aniline precursors to prepare more highly functionalized indoline and indole derivatives. One potentially useful application is the synthesis of serotonin analogs. Serotonin, or 5-hydroxytryptamine (Figure 6), is an important neurotransmitter that has been implicated in playing a primary or modulatory role in important physiological processes. Among these processes are appetite, memory, thermoregulation, sleep, sexual behavior, anxiety, and depression. Serotonin, produced from the amino acid tryptophan, is found in bacteria, plants, and many animals. In humans, it is found in the intestinal mucosa, blood platelets and the central nervous system. Thousands of research papers have been published on serotonin showing that it has important effects on the heart and vascular system, the central nervous system, respiration, muscle tissue, and the gastrointestinal tract. Dysfunction of serotonin receptors has been implicated in playing a role in many diseases of the central nervous system.

Figure 6

5-Hydroxytryptamine
Serotonin

The family of serotonin receptors in mammals has been classified into four groups: 5-HT1, 5-HT2, 5-HT3 and 5-HT4 with each group having many subtypes. The structure, binding requirements and function of many of these receptor sites remain unknown. The tools that are used most often to probe the structure and function of these receptors are site specific binding agents. These agents are most often the product of a structure/activity study by medicinal
chemists. Glennon has stated that "one of the most significant problems facing serotonin research today is a lack of site selective agonists and antagonists; a continued lack of such tools will surely retard further advances in this field." There are several different types of compounds that exhibit strong binding to serotonin receptors and are currently being studied as site specific binding agents (Figure 7). Among these ligands are aminotetrals 81,

**Figure 7**

N(CH₂CH₂CH₃)₂

HO

N

NH₂

3

81

aminotetrals

82

arylpirizines

83

phenalkylamines

Et₂NO₂C

CH₃

84

ergolines

H₃CO

85

indolylalkylamines

arylpirizines 82, phenalkylamines 83, ergolines 84, and indolylalkylamines 85. Even though 5-HT is an indolylalkylamine, this structural class of ligands has not been well-studied with respect to its binding characteristics. We reasoned that using a trisubstituted aniline precursor containing a substituent para to the amino group would allow for the synthesis of these important compounds. Only recently, have the binding properties of 4-substituted serotonin
derivatives at 5-HT receptors been studied, most notably by Macor and co-workers at Pfizer.\textsuperscript{54, 55} Some of the compounds that Macor has prepared manifest interesting binding activity as shown in Figure 8. Among these compounds, CP-132,484 \textbf{86} proved to be a highly selective agonist for the 5-HT\textsubscript{1} family of receptors. The 5-HT\textsubscript{1} group of receptors have received much recent attention because they are believed to be involved in the vasoconstriction of cranial blood vessels. Glaxo recently began marketing a drug, called Sumatriptan, for the treatment of migraine headaches that is a selective binding agent for 5-HT\textsubscript{1} receptors. It is speculated that this drug will generate millions of dollars in sales per year. This is further evidence that finding other ligands that are specific for one group of receptors is a very active area of research.

The targets we were interested in preparing (\textbf{89}) are shown below (Figure 9), in which \(R^2\) represents functional groups capable of acting as hydrogen-bond acceptors. This design is based on the work of Street at Merck.
who demonstrated that the critical pharmacophoric element for binding to a 5-HT1 receptor is a hydrogen-bond acceptor at the 5-position of the indole ring.65 We were successful in preparing compounds in which \( R^2 \) is methoxy, fluoro, and diallylamino. We also synthesized the compound in which \( R^2 \) is methyl as we envisioned that the methyl group could be converted to a functional group capable of hydrogen-bonding if desired.

**Figure 9**

![Chemical structures](image)

5-hydroxytryptamine

\[ R^1 = \text{allyl or carboethoxy} \]

\[ R^2 = \text{hydrogen-bond acceptors} \]

\[ R^3 = \text{iodide} \]

The first compound prepared was 99 (\( R^2 = \text{OCH}_3 \)). We began with commercially available 2-bromo-4-nitroanisole 90 (Scheme 2.1). The nitro group was reduced using iron (Fe\( ^0 \))/(AcOH) and the resulting amine was diallylated to give N,N-diallyl-3-bromo-4-methoxyaniline 91 in 75% overall yield from 90.Treating 91 with 2 equivalents of t-BuLi in THF at -78 °C in the presence of zirconocene (methyl) chloride, followed by warming to room temperature gave aryl (methyl) zirconocene complex 92. However, we also observed the production of N,N-diallyl-4-methoxyaniline 93 as a side product. Aniline derivative 93 constituted 15-20% of the material as judged by \(^1\)H NMR. At first we believed that the source of 93 was the hydrolysis of zirconocene complex 92. Consequently, we took extra precautions to exclude water and air from the reaction mixture and to make certain that all of our reagents were dry. However, we still observed 93 as a significant by-product. One puzzling fact
was that the percentage of 93 was consistent from reaction to reaction, making us believe that it was not an experimental artifact. In addition, we also tried using n-BuLi in place of t-BuLi and Cp₂Ti(CH₃)Cl in place of Cp₂Zr(CH₃)Cl. In every case we observed that 93 constituted 15-20% of the material produced. Since the indoline metallacycles that we had previously prepared were derived from aryl (methyl) zirconocene complexes in which the zirconocene fragment was ortho to the amino group, we prepared N,N-diallyl-2-bromo-4-methoxyaniline 97 and tested it as a substrate. The synthesis of 97 began with the preparation of 2-bromo-4-methoxyaniline 95. The highest yielding and most convenient method that we found for preparing 95 was to brominate 4-methoxyaniline 94 using tetra-n-butylammonium tribromide in a
mixture of CH₃OH and CH₂Cl₂ to give 95 in 42% isolated yield (Scheme 2.2). We found that it was necessary to use a 1:1 mixture of CH₃OH and CH₂Cl₂ for this reaction. If either CH₃OH or CH₂Cl₂ were used alone, a

**Scheme 2.2**

\[
\begin{array}{c}
\text{NH}_2 \\
\text{OCH}_3 \\
94
\end{array}
\xrightarrow{\text{Bu}_4\text{NBr}_3, \text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH} (1:1)}
\begin{array}{ccc}
\text{Br} & \text{NH}_2 & \text{Br} \\
\text{OCH}_3 & 95 & \text{OCH}_3 \\
50\% \\
\end{array} +
\begin{array}{ccc}
\text{Br} & \text{NH}_2 & \text{Br} \\
\text{OCH}_3 & 96 & \text{OCH}_3 \\
25\% & 25\%
\end{array}
\]

(crude yields as estimated by gas chromatography)

mixture of all possible regioisomeric products was the result. Interestingly, using these conditions, bromination took place only ortho to the amino group. Attempts to use other brominating agents such as Br₂ or N-bromosuccinimide (NBS) to prepare 95 gave inseparable mixtures of products including bromination meta and ortho to the amino group. Although the yield of this reaction was rather low, it was better and more convenient to perform on a large scale than existing literature procedures. Amine 95 was converted to the desired N,N-diallyl-2-bromo-4-methoxyaniline 97 by reaction with allyl bromide and Na₂CO₃ in DMF in 88% yield (Scheme 2.3). Treatment of 97 with 2 equivalents of t-BuLi in THF at -78 °C in the presence of zirconocene methyl (chloride) followed by warming to room temperature and then briefly warming to 45 °C, cleanly gave metallacycle 36, as evidenced by ¹H NMR. Unlike, the reaction of 91, none of the reduction by-product 93 was observed. Cleavage of the metallacycle with I₂ in CH₂Cl₂ gave diiodide 98 in 63% overall yield from 97. The indoline was converted to serotonin analog 99 in 93% yield as
previously described by reaction with DBU and treatment with Eschenmoser's salt.

Scheme 2.3

Alternatively, the allyl protecting group in 98 was cleaved with NaI and ethyl chloroformate in acetone to give carbamate 100 in 89% yield (Scheme 2.4). Carbamate 100 was then converted to dimethyltryptamine derivative 101 in 79% yield. Converting 98 to the corresponding carbamate before performing the ene reaction should allow the nitrogen in indole 101 to be deprotected.

Kozikowski and co-workers have demonstrated that 1-carboethoxy indoles can be deprotected to give the secondary amine by reaction with sodium hydroxide. However, we have not attempted this transformation with any of our substrates.

Scheme 2.4
The 5-fluoro analog was constructed beginning with commercially available 2-bromo-4-fluoroaniline 102, which was dialylated to give 103 in 94% yield (Scheme 2.5). Metallacyle formation under standard conditions proceeded cleanly as evidenced by $^1$H NMR. However, we found that electrophilic cleavage of the metallacyle with I$_2$ was quite sensitive to the solvent employed. When THF was used, a complex mixture of products resulted, of which the desired product 104 was only a minor component. Unfortunately, we were never able to separate the products in order to determine their identity. However, this problem could be circumvented by using CH$_2$Cl$_2$ to give 104 in approximately 70% yield (estimated by $^1$H NMR) from 103. Another problem that we encountered was that we were unable to isolate 104 in pure form. All attempts at chromatographic separation of 104 from other products failed, giving the product in 80-90% purity ($^1$H NMR). Kugelrohr distillation of 104 also failed, giving only decomposed material. However, we
reasoned that 104 could be converted directly to the corresponding tryptamine derivative 105, which we felt could be isolated in pure form by chromatography. The crude indoline 104 was heated with DBU and the resulting olefin was allowed to react with Eschenmoser’s salt to give 105 which was obtained in pure form in 54% overall yield from 103.

**Scheme 2.5**

\[
\begin{align*}
\text{F} & \quad \text{Br} \\
\text{NH}_2 & \quad \text{Na}_2\text{CO}_3, \text{DMF} \\
\text{102} & \quad \text{94\%} \\
\end{align*}
\]

\[
\text{1. Cp}_2\text{Zr(CH}_3\text{)}\text{Cl} \\
\text{2 t-BuLi/THF} \\
\text{-78 }\text{°C to 45 }\text{°C} \\
\]

\[
\text{1. DBU, C}_6\text{H}_6 \\
\text{2. H}_2\text{C}=\text{N(\text{CH}_3)}_2 \text{I}^- \\
\text{CH}_3\text{CN} \\
\]

54\% from 103

We next turned our attention to the preparation of a 5-amino substituted analog (Scheme 2.6). 4-Nitroaniline 106 was brominated using Bu4NBr3 in CH2Cl2 and CH3OH to give 2-bromo-4-nitroaniline in 96\% yield. Like the bromination of 4-methoxyaniline, we found that bromination of 4-nitroaniline with NBS or Br2 gave overbrominated products that were difficult to separate by chromatography. The nitro group was reduced using Fe0/HCl to give diamine 107 which was immediately alkylated with allyl bromide to give tetraallyl-1,4-diamine 108 in 70\% yield. The zirconacyle formed cleanly under the usual
conditions but the iodination again proved to be troublesome. Although the iodination proved to be cleaner in CH$_2$Cl$_2$ than THF, it was not as clean as we had observed for some other metallacycles. Like the fluoro analog 104, we were unable to obtain 109 in pure form. Crude 109 was converted to serotonin analog 110 which was isolated in 26% overall yield from 108.

**Scheme 2.6**

\[
\begin{align*}
\text{1. Bu}_4\text{NBr} & \quad \text{CH}_2\text{Cl}_2, \text{CH}_3\text{OH} \\
\text{2. Fe}^0/\text{HCl} & \quad \text{EtOH}
\end{align*}
\]

\[
\begin{align*}
\text{NH}_2 & \quad \text{Br} \\
\text{NH}_2 & \quad \text{Br}
\end{align*}
\]

\[
\begin{align*}
\text{1. } & \text{Cp}_2\text{Zr(CH}_3\text{)Cl} \\
\text{2. } & \text{t-BuLi/THF} \\
\text{2. CH}_2\text{Cl}_2/I_2
\end{align*}
\]

\[
\begin{align*}
\text{R} & = \text{allyl}
\end{align*}
\]

\[
\begin{align*}
\text{1. DBU, C}_6\text{H}_6 \\
\text{2. } & \text{H}_2\text{C}=\text{N(CH}_3\text{)}_2\text{I} \\
\text{CH}_3\text{CN}
\end{align*}
\]

26% overall from 108
Attempted intramolecular Heck cyclization of 110, using conditions reported by Larock and Hegedus, failed to give the desired [3,2-e]pyrroloindole product 111 (Scheme 2.6). The failure of the cyclization could be due to the reluctance of the PdO species to undergo oxidative addition to the electron rich aryl iodide. A similar result was observed by Hegedus in his study of the synthesis of pyrroloquinones (Scheme 2.7). Cyclization of compound 112 using similar conditions to those used with 110 gave only monocyclized product 113. Hegedus and co-workers were never able to find conditions that would affect the second cyclization to give a pyrroloindole. The reasoning for the failure of the second cyclization was that the first cyclization replaced the electron-withdrawing bromide with an electron rich indole ring, retarding the oxidative addition of the PdO species to the aryl bromide. Amatore and Pfluger studied the kinetics and mechanism of the oxidative addition of Pd(0) species to aryl iodides. They performed a Hammett study and found that for a series of substituted aryl iodides, $\rho = +2$ in THF and $\rho = +2.3$ in toluene. The positive values for the Hammett coefficient indicate that electron-donating substituents on the aromatic ring slow the oxidative addition reaction. Therefore, it seems likely that in the reaction of indole 110 with a Pd(0) species that the initial oxidative addition reaction would be expected to be slow.

Scheme 2.7

We were also interested in preparing an analog of 108 in which the two amino groups were differentially protected. To this end, we synthesized 115
using the three-step sequence shown in Scheme 2.8. First, 114 was diallylated using NaH and allyl bromide in DMF. The nitro group was reduced using Fe$^0$/HCl and the amine was protected as a 2,5-dimethylpyrrole derivative using 2,5-hexandione and catalytic acetic acid. While formation of metallacycle 116 occurred cleanly ($^1$H NMR), we were unable to find conditions in which iodination of the metallacycle gave reasonable yields of the diiodoindoline.

**Scheme 2.8**

The last serotonin analog that we prepared contained a methyl group in the 5-position. Commerically available 2-bromo-4-methylaniline 117 was diallylated to give N,N-diallyl-2-bromo-4-methylaniline 118 (Scheme 2.9). Metallacycle formation and cleavage with I$_2$ proceeded as expected to give diiodoindoline 119 in 64% yield from 118. Reaction of 119 with DBU and Eschenmoser's salt gave tryptamine derivative 120 in 87% yield. Alternatively, the allyl protecting group was cleaved using ethyl chloroformate and NaI in acetone (85%) followed by dehydrohalogenation with DBU and reaction with Eschenmoser's salt to give 123 in 91% yield. We envision that the methyl group in 120 or 123 could be further manipulated in order to convert it to a functional group capable of acting as a hydrogen-bond acceptor.

**Scheme 2.9**

60
\[
\begin{align*}
\text{117} & \quad \text{Na}_2\text{CO}_3, \text{DMF} \quad \rightarrow \quad \text{118} \\
\text{118} & \quad \text{1. } \text{Cp}_2\text{Zr(CH}_3\text{)Cl} \quad \text{2. } t\text{-BuLi, THF} \\
& \quad -78^\circ\text{C} \text{ to } 45^\circ\text{C} \\
\text{119} & \quad \text{1. DBU, } \text{C}_6\text{H}_6 \quad \text{2. } \text{H}_2\text{C}\equiv\text{N(CH}_3\text{)}_2 \quad \text{I}^- \\
& \quad \text{CH}_3\text{CN} \quad 93\% \\
\text{119} & \quad \text{ClO}_2\text{Et} \quad \text{Nal, acetone} \quad 85\% \\
\text{120} & \quad \text{1. DBU, } \text{C}_6\text{H}_6 \\
\text{121} & \quad \text{1. DBU, } \text{C}_6\text{H}_6 \\
& \quad \text{2. } \text{H}_2\text{C}\equiv\text{N(CH}_3\text{)}_2 \quad \text{I}^- \\
& \quad \text{CH}_3\text{CN} \quad 91\% \\
\text{123} & \quad \text{H}_3\text{C} \quad \text{N(CH}_3\text{)}_2 \quad \text{NCO}_2\text{Et}
\end{align*}
\]
Synthesis of the CC-1065/Duocarmycin A Pharmacophore

The natural products CC-1065 25 and duocarmycin A 124 (Figure 10) are two antitumor antibiotics that possess potent in vitro cytotoxic activity, broad spectrum antimicrobial activity and in vivo antitumor activity. They belong to a growing class of agents that manifest their biological activity through a selective minor groove alkylation of B-DNA. The mode of action of CC-1065, isolated from cultures of *Streptomyces zelensis*, was established by Chidester and coworkers. They showed that CC-1065 binds in the minor groove of duplex DNA, in a non-intercalative fashion, and forms an irreversible covalent adduct. The alkylation itself has been shown to proceed by an acid catalyzed 3'-
adenine N-3 alkylation of the electrophilic spiro[2.5]octa-4,7-dien-6-one subunit present in the left-hand segment of the molecule. Boger has shown that duocarmycin A alkylates DNA in the same manner as CC-1065. Synthetic studies by Boger have shown that the parent spirocyclic cyclopropylcyclohexadienone ring system, the Cl subunit 125, is the "minimum potent pharmacophore" and is the common pharmacophore of both CC-1065 and duocarmycin A. Although both 25 and 124 display potent antitumor and antibiotic activity, they also display delayed toxic effects in the liver of mice. Consequently, there has been much recent interest in preparing analogs of these compounds in which the left-hand, middle and right-hand segments are modified with the hope that the antibacterial and antitumor activity remains but the toxic effects are reduced. In a 1981 communication, Wierenga reported the first synthesis of the left-hand segment of CC-1065. One of the critical features of the strategy for the synthesis was the efficient preparation of a regiochemically pure 6-hydroxy-3-methylindoline such as 128 (Scheme 2.10).

**Scheme 2.10**
Since that initial report, there have been a multitude of synthetic studies directed toward the development of a general method for the preparation of analogs of the left-hand segment of CC-1065.\textsuperscript{24} However, very few papers have appeared that deal with a method for the synthesis of the parent CI subunit \textsuperscript{125}. Most of the work in this area has been performed by Boger with contributions from Cava, Sundberg, and Sakamoto.\textsuperscript{24} Two of the most efficient syntheses are shown below. Boger's synthesis (Scheme 2.11)\textsuperscript{24e} began with 5-benzyloxyaniline \textsuperscript{129} which was converted to the BOC protected aniline derivative \textsuperscript{130} in three steps. The key step of the synthesis is a 5-exo-trig aryl radical-alkene cyclization effected by treatment of aniline \textsuperscript{130} with tributyltin hydride using AIBN as an initiator. The cyclization afforded N-BOC-6-benzyloxy-3-vinylindoline \textsuperscript{131} in 91% yield. Oxidative cleavage of the olefin with ozone followed by reduction of the ozonide with sodium borohydride provided 3-hydroxymethyl indoline derivative \textsuperscript{132}. Conversion of the hydroxy group to mesylate \textsuperscript{133}, deprotection of the benzyl aryl ether and reaction of the resulting phenol with sodium hydride in THF gave the desired spirocycle \textsuperscript{134}.

**Scheme 2.11**
The synthesis of the Cl subunit by Sakamoto and co-workers, reported in 1993, is also quite efficient (Scheme 2.12).\textsuperscript{24u} The synthesis began with 4-methoxy-2-nitroaniline 135 which is converted to 2-iodo-5-methoxyaniline 136 by a Sandmeyer reaction followed by reduction of the nitro group. Reaction of amine 136 with phenylsulphonyl chloride followed by alkylation of the sulphonamide with allyl bromide gave sulfonamide 137. The key step of this synthesis is the Pd(0) catalyzed closure of the o-iodoaniline using an intramolecular Heck reaction.\textsuperscript{32} Interestingly, they found that when silver carbonate (Ag\textsubscript{2}CO\textsubscript{3}) is used as the base, the reaction could be stopped to provide \textit{exo}-methylene indoline 138 as the major product (73%). Normally, in this reaction, the intermediate 3-methyleneindoline is isomerized to the corresponding indole by reinsertion of the HPdX species. Similar results have been observed by Hallberg and Overman in unrelated systems.\textsuperscript{7,8} Hydroboration of the olefin followed by oxidative work-up under basic conditions gave the 3-hydroxymethyl indoline derivative 139, which is similar to
the intermediate prepared by Boger. Conversion of the alcohol to an alkyl iodide, deprotection of the methyl phenyl ether and treatment of the resulting phenol with NaH in THF gave the desired spirocycle 140.

Scheme 2.12

Since the products of the zirconocene-mediated cyclization that we had developed were very similar in structure to 6-hydroxy-3-methylindole 128, where X is iodide, we reasoned that a synthesis of the common pharmacophore of CC-1065 and duocarmycin A would be a useful application of the method. We began with commercially available 4-methoxy-2-nitroaniline 135 which was converted to aryl bromide 141 in 88% yield using copper (II) bromide and tert-
butyl nitrite (Scheme 2.13). The nitro group was reduced with Fe\(^0\)/HCl to give the primary amine which was diallylated with allyl bromide and Na\(_2\)CO\(_3\) in DMF to give diallyl amine 142 in 76% yield from 141. Treatment of 142 with 2 equivalents of t-BuLi in THF at -78 °C in the presence of zirconocene (methyl) chloride, followed by warming to room temperature cleanly gave the desired metallacycle 145. Cleavage of metallacycle 145 with I\(_2\) in CH\(_2\)Cl\(_2\)

**Scheme 2.13**
gave diiodide 146 in 65% yield. The methyl phenyl ether was selectively cleaved with boron tribromide (BBr₃) in CH₂Cl₂ followed by a methanolic workup to give phenol 147. The phenol was unstable for long periods of time, so it was used immediately after purification. Closure to the spirocycle by an
Ar3-1 type Winstein cyclization\textsuperscript{81} was accomplished by adding 147 to a suspension of NaH in THF\textsuperscript{24e} until bubbling ceased (10-15 min). In this way, tetrahydrocycloprop[1,2-c]indol-4-one analog 148 was obtained in 89\% yield. Spirocycle 148 proved to be too unstable to purify by chromatography. It was isolated by filtering the reaction mixture to remove any excess NaH and the NaI by-product and evaporating the solvent under vacuum. The purity of 148 isolated in this fashion was estimated by $^1$H NMR to be greater than 95\%. Like the phenol, spirocycle 148 was unstable for long periods of time. As a THF solution, it began to afford insoluble, possibly polymeric, material after 30 min at room temperature. Similar behavior was observed by Boger for compounds 140 and 134 (Scheme 2.14).\textsuperscript{24e} They first attempted to prepare 140 by an intramolecular Mitsunobu reaction. Although the spirocycle formed, they were unable to separate it from the reaction byproducts due to its instability. They further report that the attempted purification of 134 or 140 by flash chromatography on silica gel typically gave a 10\% recovery of material. The instability of these compounds is presumably due to their extremely electrophilic nature and their ability to react with weak nucleophiles like water. For example, the measured half-lives of 140 and 134 in 1:1 water:THF are 15 and 30 seconds, respectively.

\textbf{Scheme 2.14}
Boger has also shown that the coupling of compounds like indoline 150 with CDPI [151, 3-carbamoyl-1,2-dihydro-3H-pyrrolo[3,2-e]indol-7-carboxylic acid] and CDPI dimer (Scheme 2.15)\textsuperscript{24e} give functional CC-1065 analogs that show some binding selectivity with B-DNA. In order to allow for the synthesis of functional analogs from our material, it is necessary to deprotect the nitrogen in 146. This was accomplished using the method described in Chapter 1.
(Scheme 2.16). Reaction of 146 with ACE-Cl in acetone and in the presence of NaI gave the intermediate carbamate which was cleaved with CH$_3$OH and DCE as co-solvent to provide secondary amine 153 in 67% overall yield from 146.

**Scheme 2.16**

![Scheme 2.16](image)

The use of this methodology in the formal synthesis of entire left-hand segment of CC-1065 was recently reported by Tietze and Grote (Scheme 2.17). They began with 2-bromo-5-benzyloxyaniline, 154, which was prepared according to literature procedures. Amine 154 was allowed to react with phenylsulfonyl chloride to furnish the corresponding sulfonamide which was alkylated with allyl bromide to give allyl amide 155. The first key step of the synthesis was the zirconocene-mediated cyclization method that we had developed. Reaction of 155 with 2 equivalents of t-BuLi at -78 °C in THF and in the presence of Cp$_2$Zr(CH$_3$)Cl, followed by warming to room temperature, gave the desired metallacycle. Cleavage of the metallacycle with I$_2$ in CH$_2$Cl$_2$ at 0 °C, gave diiodoindoline 156 in 45% overall yield from sulfonamide 155. Regioselective nitration of diiodide 156 with nitric acid in nitromethane gave nitro aniline derivative 157 in 95% yield. Due to the predicted instability of the alkyl iodide under the conditions required for reduction of the nitro group, the alkyl iodide was converted to the corresponding alcohol by a two-step process that involved elimination with DBU, followed by hydroboration of the resulting olefin and oxidation of the borane to give alcohol 158 in 79% yield. Interestingly, they reported that all attempts to convert diiodide 157 to either the alcohol or the acetate by nucleophilic substitution of the iodide failed due to a
facile dehydrohalogenation reaction to give the exo-cyclic olefin. Reduction of the nitro group with hydrazine and Fe (III), followed by acylation of the resulting amine and the alcohol gave the diacetate. The acetamide was alkylated with allyl bromide and NaH in DMF to give allyl acetamide 159 in 94% yield. The second key step of the synthesis was an intramolecular Heck reaction to form the pyrrole ring using the N-allyl group and the iodide at the 4-position of indoline 159. The Heck cyclization was accomplished in 70% yield by reaction of 159 with tetrakis(triphenylphosphine)palladium and Et₃N in CH₃CN. Saponification of both the acetate and the acetamide with potassium hydroxide in MeOH gave alcohol 161 in quantative yield. The conversion of 161 to the spirocyclic left-hand segment of CC-1065 has been previously described by Boger and co-workers.²⁴

**Scheme 2.17**
In summary, we have demonstrated that readily available disubstituted aniline precursors can be effectively used to synthesize regiochemically pure 3,4,n-trisubstituted (n= 5,6) indoline and indole derivatives. Among the products that were prepared were a variety of 4-iodo substituted serotonin analogs in which the substituent at the 5-position equals a methoxy, dialkylamino, fluoro and methyl group. In addition, a new approach to the synthesis of the common pharmacophore of CC-1065 and duocarmycin A was developed. Recently, Tietze and Grote used this methodology for the formal synthesis of the entire left-hand segment of CC-1065.
Chapter 3:
Synthesis and Reactions of
1-Carboethoxy-3-bromomethyl-4-iodoindole:
Preparation of 3,4-Disubstituted Indoles
by Sequential Nucleophilic Displacement,
Pd(0)-Catalyzed Substitution
Our inability to perform selective nucleophilic substitution reactions on diiodide 43 (Scheme 3.1), caused us to seek an alternative solution for this problem. We reasoned that if diiodide 43 was oxidized to an indole, the elimination reaction which produces olefin 45 would not take place. Furthermore, 3-halomethylindoles such as 163 (Scheme 3.2) are known to be extremely good electrophiles because (1) the halomethyl group in the 3 position of the indole ring system can be viewed as being both allylic and benzylic, making it prone to nucleophilic attack and (2) the nitrogen in the pyrrole portion of the indole increases the electrophilicity of the 3-halomethyl group because it can be considered to be a vinylogous α-haloamine.

We envisioned two possible synthetic routes for the preparation of compounds like 163. The first involved the dehydrogenation of an indoline such as 43 to the desired indole product. The second employed the reaction of an olefin such as 45 with an electrophilic halogen source. Based on our success in reactions of olefins 44 and 45 with electrophiles such as iminium
salts and a glycine cation equivalent, we chose to focus on the second of these two routes. NBS was an obvious first choice as a source of electrophilic bromine, primarily because of its success in several electrophilic aromatic substitution reactions that we had studied. We reasoned that the reaction between NBS and olefins 44 and 45 could proceed by two mechanisms: radical and ionic (Scheme 3.3). Both of these mechanisms would yield the

**Scheme 3.3**

**Radical Mechanism:**

![Radical Mechanism Diagram]

**Ionic Mechanism:**

![Ionic Mechanism Diagram]

same product, due to preferential formation of 3\textsuperscript{0} radical 166 or 3\textsuperscript{0} cation 168. We further reasoned that it would be important to protect the indoline nitrogen in olefin 44 or 45 either as a carbamate or an amide in order to increase the stability of the corresponding 3-bromomethylindole. It has been demonstrated that 3-halomethylindoles are stable only if the lone pair electrons on nitrogen are "tied up" by resonance.\textsuperscript{83}
The initial substrate was olefin 169, which was prepared from diiodide 79 as previously described (Scheme 3.4). When solid NBS was added to a CH_2Cl_2 solution of 169 at 0 °C, the color of the reaction mixture immediately turned from yellow to orange. After 3 hours at 0 °C, ^1H NMR of the crude reaction mixture showed a significant amount of starting olefin 169 remaining, in addition to another product. Based on comparison of the ^1H NMR shifts of this other product to literature values, we assigned the other product to be the desired 3-bromomethyl-1-carboethoxy-4-iodoindole 170. The reaction mixture was allowed to warm to room temperature in an effort to force the reaction to completion. However, after 2 hours at room temperature, ^1H NMR indicated that approximately 20% of olefin 169 still remained. In addition, it appeared that a third product was growing in at the expense of bromide 170. We thought that perhaps the source of the third product was reaction of bromide 170 with the succinimide by-product to give imide 171. We reasoned that one
solution to this problem would be to use a solvent in which NBS and the olefin are soluble, but succinimide is not. It is well-known that succinimide exhibits limited solubility in carbon tetrachloride, while NBS is freely soluble in it. However, when CCl₄ was tested as a solvent for this reaction, it was discovered that olefin 169 was only sparingly soluble in it, making the reaction very sluggish. The last solvent that we tried for this reaction was chloroform since it was known that succinimide has limited solubility in it at low temperatures. We were pleased to find that treatment of a CHCl₃ solution of olefin 169 at 0 °C with NBS cleanely gave the desired bromide 170 (as evidenced by ¹H NMR) in only 2 hours (Scheme 3.5). When NBS was added to the CHCl₃ solution of olefin 169 at 0 °C, it dissolved and succinimide began to precipitate almost immediately. If however, the solution was allowed to warm to room temperature, the succinimide became soluble and the imide substitution product began to slowly form. In order to obtain pure bromide 170, we attempted to precipitate the succinimide by the addition of CCl₄ to the crude reaction mixture. However, this method proved to be unsuccessful since a small amount of succinimide always remained in the product. As an alternative, a simple aqueous extraction of the crude mixture followed by filtration through a small pad of silica gel, and evaporation of the solvent proved to be successful. In this way, bromide 170 was obtained in analytically pure form in 80% overall yield from diiodide 79. It was surprising that bromide 170 was stable to aqueous work-up and silica gel filtration since we had assumed that due its
electrophilicity, it would be hydrolyzed quickly in the presence of water. The filtration of 170 through silica must be performed quickly, otherwise a small amount of the hydrolysis product was observed. Bromide 170 was found to be stable: it has been stored on the benchtop for over one month with no signs of decomposition visible by $^1$H NMR.

We were interested in exploring whether the carbamate protecting group was necessary in bromide 170 (Scheme 3.6). To this end, allyl protected olefin 45 was allowed to react with NBS under the same conditions as carbamate 169. Although $^1$H NMR showed that all of the starting olefin 45 was consumed, we could no identifiable products were isolated. This was also the case when olefin 45 was treated with N-chlorosuccinimide (NCS). Several methods for the preparation of compounds like 170 have been reported in the literature. For the preparation of 3-bromomethyl indole derivatives, three methods currently exist, two of which use 3-hydroxymethylindoles as the starting material. These alcohols can be prepared by a two-step process; Vilsmeier-Haack reaction to introduce a carboxaldehyde group at the 3-position, followed by reduction of the aldehyde using sodium borohydride.
(NaBH₄). For example, Cook has shown that 3-hydroxymethyl-6-methoxy-1-phenylsulfonylindole 174 can be prepared as shown in Scheme 3.7. Initial reaction of phosphorous oxychloride and DMF with 5-methoxyindole 172,

**Scheme 3.7**

followed by base hydrolysis gave formylated indole 173 in 95% yield. Formation of the sulfonamide and reduction of the formyl group with NaBH₄ gave alcohol 174 in 97% yield. The Vilsmier-Haack reaction is proposed to proceed through alkylation of iminium salt 175 (Scheme 3.8), to give iminium salt 176 which is then hydrolyzed to give aldehyde 177. The success of this reaction depends upon the nucleophilicity of the 3-position of the indole precursor. As such, electron-withdrawing substituents would be expected to decrease the yield of the reaction.

**Scheme 3.8**
Two methods that have been reported for converting the 3-hydroxymethyl group into a 3-bromomethyl group both involve bromination in the presence of triphenylphosphine (PPh\textsubscript{3}) and either bromine (Br\textsubscript{2}) or NBS. The first of these methods was developed by Schöllkopf\textsuperscript{83a} and employs the reaction of an alcohol such as 1-(tert-butoxycarbonyl)-3-hydroxymethylindole \textit{178} with Br\textsubscript{2} and PPh\textsubscript{3} to give the desired 3-bromomethylindole derivative \textit{179} in an unspecified yield (Scheme 3.9). There are two drawbacks to using this method. First, adventitious HBr from the bromine can cause cleavage of the BOC protecting group, which leads to decomposition of the bromide. Second, the by-product, triphenylphosphine oxide, is difficult to separate from the bromide. Removal of the phosphine oxide usually involves several extractions and filtrations which can significantly decrease the yield of the reaction.

\textbf{Scheme 3.9}
Diksic and co-workers have reported that their attempts to repeat the results of Schöllkopf were unsuccessful. As an alternative, they developed a method for converting 3-hydroxymethylindoles to the corresponding bromides by reaction with NBS and PPh₃ (Scheme 3.10). This method avoids the use of Br₂ so that the inadvertent addition of HBr is not a problem. However, this protocol also suffers from the drawback that triphenylphosphine oxide is a by-product, and that it is difficult to obtain bromide 179 in pure form.

Scheme 3.10

The last method for the production of 3-bromomethylindoles such as 170 involves free-radical bromination of 3-methylindole derivatives using NBS (Scheme 3.11). For example, reaction of 3-methyl-1-phenylsulfonylindole 180 with NBS in CCl₄ and in the presence of benzoyl peroxide gave bromide 181 in 96% yield. One advantage of using this method is that the only by-product, succinimide, is easily removed from the reaction mixture by filtration.

Scheme 3.11
The preparation of a compound that is closely related to 3-bromomethylindoles, 3-iodo-1-phenylsulfonylindole 183 was recently reported by Sato and Kahn (Scheme 3.12). Treatment of 3-methoxymethyl-1-phenylsulfonylindole 182 with dichloroiodomethylsilane, generated in situ from trichloromethylsilane and NaI in acetonitrile, effected cleavage of the methoxy group to give iodide 183 in 98% yield.

Scheme 3.12

A compound that is closely related to the 3-halomethylindole derivatives discussed above is 3-(N,N-dimethylamino)methylindole, commonly known as gramine. This compound and its derivatives can be prepared by a Mannich-like reaction with an indole derivative. For example, reaction of 5-nitroindole 184 with dimethylamine and formaldehyde in the presence of acetic acid gives the desired gramine derivative 185 (Scheme 3.13). Gramine derivatives can be converted to electrophiles by alkylation of the amino group with methyl iodide to produce a trimethyl ammonium iodide salt such as 186. The ammonium group can be displaced with nucleophiles such as cyanide anion to give 3-substituted indoles 187.

Scheme 3.13
The method that we developed for the synthesis of bromide 170 is complementary to the procedures presented above. However, like the method that relies upon the free-radical bromination of 3-methylindoles, the only by-product in the reaction to prepare 170, succinimide, is easily removed to provide pure 170 in good yield. We thought that bromide 170 would be a valuable intermediate in the synthesis of a variety of 3,4-disubstituted indoles via a sequential nucleophilic displacement/Pd(0)-catalyzed substitution process (Figure 11).

**Figure 11**

We began our exploration of the chemistry of bromide 170 by studying its hydrolysis to produce 1-carboethoxy-3-hydroxymethyl-4-iodoindole 188
(Scheme 3.14). Initially, attempted hydrolysis of the bromide with either sodium or potassium hydroxide gave inseparable mixtures of products. The main difficulty was that under these conditions, the carbamate was being cleaved as well as the bromide being displaced. However, selective hydrolysis of bromide was achieved under neutral conditions with water in acetonitrile at 50 °C. In this way, the desired alcohol 188 was obtained in 79% yield after purification by chromatography.

**Scheme 3.14**

Peat, Broene and Buchwald have developed a synthesis of a compound very closely related to alcohol 188 (Scheme 3.15). The preparation of 1-allyl-3-hydroxymethyl-4-iodoindoline 191 takes advantage of the preferential reactivity of an sp³ carbon-zirconium bond versus an sp² carbon-zirconium bond in zirconacycle 34. The first step was reaction of zirconacycle 34 with 9-bromo-9-borabicyclo[3.3.1]nonane (B-Br-9-BBN) in hexane. This reaction affects the selective cleavage of the sp³ carbon-zirconium bond giving borane 189. The remaining carbon-zirconium bond can then be cleaved with I₂, and the resulting iodoborane 190 is oxidized with hydrogen peroxide under basic conditions to give iodo alcohol 191 in 51-63% yield from N,N-diallyl-2-bromoaniline 30.

**Scheme 3.15**
Oxidation of alcohol 188 to the corresponding 3-carboxaldehyde derivative 192 was accomplished in 90% yield using activated manganese (IV) oxide (MnO₂) in CH₂Cl₂ (Scheme 3.16). A large excess of MnO₂, typically 25-30 equivalents, was required in order to get the reaction to go to completion.

Scheme 3.16

Somei and co-workers have used similar 3-carboxy-4-iodoindoles in the synthesis of several naturally occurring indole alkaloids as shown in Scheme 3.17.
Peat and Buchwald have converted 1-allyl-3-hydroxymethyl-4-iodoindoline 191 to the corresponding indole 3-carboxaldehyde 198 using a "single-flask" double oxidation procedure (Scheme 3.13). They reasoned that initial oxidation of indoline 191 to indole 197 would give a compound that is similar to indole alcohol 188 and would be further oxidized to aldehyde 198. Oxidation of 191 with 100 equivalents of MnO2 under similar conditions used for indole 188 gave poor yields of aldehyde 198. However, treatment of indoline 191 with an excess of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in benzene accomplished both oxidations smoothly to give aldehyde 198 in 73% yield.

Scheme 3.13
It has been well established that aryl or vinyl halides can be converted to esters or amides by palladium-catalyzed carbonylation reactions in the presence of either alcohols or amines.\textsuperscript{89} We found that alcohol 188 could be carbonylated using bis(triphenylphosphine)palladium dichloride, (PPh\textsubscript{3})\textsubscript{2}PdCl\textsubscript{2}, Et\textsubscript{3}N and 600 psig carbon monoxide in DMF to give tricyclic lactone 199 in 78\% yield (Scheme 3.14). The proposed mechanism of the carbonylation reaction is shown in Scheme 3.15.\textsuperscript{1} Initial reduction of the Pd(II) species by Et\textsubscript{3}N takes place to give a Pd(0) complex. Oxidative addition of the
Pd(0) complex to aryl iodide 188 gives Pd(II) complex 200. Binding of CO, followed by a 1,1-insertion reaction gives acyl complex 201. The mechanism for the conversion of acyl complex 201 to the lactone product is not well-defined. It could involve either reductive-elimination of the acyl iodide to give acid iodide 202, which would undergo an intramolecular ring closure reaction yielding 199. Alternatively, the acyl iodide complex could be attacked by the hydroxy group to yield complex 203 which would undergo a reductive elimination reaction giving lactone 199. The last possibility would be attack of the hydroxy group on Pd-acyl species 201 to give lactone 199.

Scheme 3.15
Interestingly, Peat and Buchwald have found that the carbonylation of indoline 191 under the same conditions used for 188 gave none of the lactone 204, only unchanged starting material was recovered (Scheme 3.16). However, if 191 was treated with Cl2Pd(PPh3)2, K2CO3, CO (55 psig) and hydrazine (1 drop) at 70 °C for 72h, the desired lactone 204 was produced in good yield. We are unsure why this great difference in reactivity between alcohols 188 and 191 exists. However, we believe that when Et3N is used as a reducing agent for Cl2Pd(PPh3)2 in reactions with indoline 191, reduction of
the Pd(II) precatalyst to an active Pd(0) complex is not taking place. This conclusion is based on the fact that in the carbonylation reaction of indole derivative 188, the reaction mixture turns orange after addition of the dichloride pre-catalyst. However, under identical conditions with indoline 191, the reaction mixture remains light yellow. When 1 drop of hydrazine was added to this mixture, it turned orange and the lactone was produced in good yield.

Scheme 3.16

Based on our success in preparing alcohol 188, we became interested in synthesizing the corresponding 3-aminomethyl-1-carboethoxy-4-iodoindole 206 (Scheme 3.17). We reasoned that in order to prepare a primary amine from bromide 170, we required the use of an ammonia synthon. Many ammonia synthons have been developed for the synthesis of primary amines from alkyl halides. Among them are guanadine, phthalimide (Gabriel synthesis), diethyl phosphoramidate, diethyl N-(trimethylsilyl)phosphoramidate, and diethyl N-sodio-N-(tert-butoxycarbonyl)phosphoramidate. The major drawback to using these synthons is that N,N-dialkyl derivatives are often observed as by-products. However, 2,2,2-trifluoroacetamide has been reported...
to give good yields of monoalkylated products under phase-transfer conditions even when a very reactive alkylating agent such as benzyl bromide was used. However, several different sets of reaction conditions failed to give the desired monoalkylated product in satisfactory yield. In all cases, mixtures of the mono and dialkylated products were formed, indicating that bromide 170 was an extremely active electrophile. As an alternative, we sought a doubly protected ammonia equivalent. Our first choice was sodium N,N-bis(trimethylsilyl)amide (NaN(TMS)2). This amide and the corresponding lithium salt have been used extensively as hindered, non-nucleophilic bases for the generation of enolates in Claisen chemistry. However, they have been little used as a nucleophile, primarily because they are extremely hindered and tend to be more basic than nucleophilic. Murai and co-workers recently published a study of the reaction of LiN(TMS)2 with allylic chlorides. They found that in the absence of additives, the reaction of LiN(TMS)2 with allylic chlorides gave predominantly deprotonation products and very little of the desired allylic amine. However, the addition of silver iodide (AgI) in catalytic quantities greatly improved the yield of the allylic amines. Bestmann has demonstrated that primary alkyl bromides and tosylates give the corresponding N,N-bis(trimethylsilyl)amines in good yield if the reactions are performed in neat hexamethylphosphoramide (HMPA). We reasoned that if reaction of NaN(TMS)2 with bromide 170 gave little of the desired amine, that AgI or HMPA could be added to improve the yield. However, preliminary experiments have shown that the reaction of bromide 170 with NaN(TMS)2 in THF at room temperature proceeded cleanly to give the desired bis(trimethylsilyl)amine 205 (quantitative by 1H NMR) as shown in Scheme 3.17.

Scheme 3.17
The silyl groups on amine 205 proved to be stable to aqueous workup and filtration through a small pad of silica gel, thus allowing 205 to be easily purified. The silyl groups were cleaved from 205 in good yield to provide primary amine 206 by reaction with 2 N HCl in ethanol/CH$_2$Cl$_2$. Like alcohol 188, we found that the amine could be carbonylated to give lactam 207.

Barr and Buchwald found that a lactam similar in structure to 207 could be synthesized directly from zirconacycle 33 (Scheme 3.18).$^{96}$ Insertion of tritylazide into the metallacycle 33 provides azazirconacycle 208 in quantitative yield by $^1$H NMR. Carbonylation of 208 at 1400 psig of CO, followed by treatment of the trityl protected lactam with trimethyl ammonium hydrochloride gave lactam 207 in 45% overall yield from zirconacycle 33.

Scheme 3.18
The reactions of bromide 170 with malonate esters and related compounds were also explored (Scheme 3.1). Reaction of 170 with 1.26 equivalents of dimethylmalonate, potassium carbonate, and 18-crown-6 in benzene gave the desired substitution product 210 in 70-75% yield as estimated by $^1$H NMR. The remaining material consisted of the dialkylated ester 211. This result was unexpected for two reasons. First we had found that reaction of diiodide 43 with dimethylmalonate, under essentially identical conditions, yielded none of the dialkylated product. Secondly, one would expect that after the first alkylation took place, the remaining malonate proton would be much less acidic than any remaining unreacted malonate. This problem was circumvented by utilizing a large excess of the malonate ester (5
equivalents). Under these conditions, malonate product 210 was obtained in 82% isolated yield after work-up and purification.

**Scheme 3.19**

\[
\begin{align*}
\text{I} & \quad \text{Br} \\
\text{CO}_2\text{Et} & \quad \text{K}_2\text{CO}_3, \text{PhH} \\
18\text{-crown-6, RT} & \quad \text{CO}_2\text{Et}
\end{align*}
\]

1.26 eq H$_3$CO$_2$C$\equiv$CO$_2$CH$_3$ 

70-75% by $^1$H NMR

\[ + \]

\[
\begin{align*}
\text{I} & \quad \text{CO}_2\text{Et} \\
\text{CO}_2\text{Et} & \quad 211
\end{align*}
\]

25-30% by $^1$H NMR

Similar results were observed when ethyl cyanoacetate was used as the nucleophile (Scheme 3.20). When 1.27 equivalents of ethyl cyanoacetate were employed, the major product was the dialkylated ester 213. However, when 15 equivalents were used, the desired monoalkylated product 212 was isolated in 75% yield.

**Scheme 3.20**

\[
\begin{align*}
\text{I} & \quad \text{Br} \\
\text{CO}_2\text{Et} & \quad \text{K}_2\text{CO}_3, \text{PhH} \\
18\text{-crown-6, RT} & \quad \text{CO}_2\text{Et}
\end{align*}
\]

5 eq H$_3$CO$_2$C$\equiv$CO$_2$CH$_3$ 

82% isolated yield

\[ \text{CO}_2\text{Et} \]

\[ \text{CO}_2\text{Et} \]

\[ 210 \]
We found that malonate product 210 could be cyclized to give tricyclic ketone 214 using a tandem carboxylation/anion capture process developed by Negishi (Scheme 3.21). The reaction of acyl-metal species, generated via carboxylation reactions, are known to undergo reaction with heteroatoms to form carbon-heteroatom bonds (cf. Schemes 3.14 and 3.17). However, the reaction of metal-acyl complexes with carbon nucleophiles to generate carbon-carbon bonds is relatively rare. When 210 was treated with Cl2Pd(PPh3)2, CO (600 psig) and Et3N in CH3CN at 95 °C for 16 hours,
Ketone 214 was produced in 68% yield. The reaction temperature proved to be critical to the success of this transformation. If the temperature of the reaction fell below 80 °C, significant amounts of by-products were formed. Similarly, if the temperature of the reaction was too high (>110 °C), unwanted side products were also formed. Ketone 214 is an interesting intermediate because it is closely related to an important ergot alkaloid precursor tricyclic ketone 215, designated as Uhle's ketone.99

Scheme 3.21

Malonate ester 210 was also subjected to the Castro-Stevens reaction, which is used to couple a terminal acetylene to an aryl or vinyl halide (Scheme 3.22).100 Reaction of 210 with trimethylsilylacetylene in the presence of copper (I) iodide, Et₃N, PPh₃ and a catalytic amount of palladium acetate in DMF gave alkyne 216 in 65% yield.

Scheme 3.22
The displacement of the bromide in 170 with cyanide was also examined (Scheme 3.23). 3-indolylacetonitrile derivatives are interesting intermediates that have been used for the synthesis of primary tryptamines and recently by Martin and Liras for the total synthesis of Rugulovasines A and B. The reaction of bromide 170 with 1 equivalent of potassium cyanide (KCN) in DMF proceeded smoothly to provide the desired nitrile 217 in 76% isolated yield. However, when an excess of KCN was used, not only was the bromide displaced, but the carbamate also reacted to give a second, unidentified product 218.

**Scheme 3.23**
A nitrile very similar in structure to 217 was recently reported by Martin as an intermediate in the total synthesis of Rugulovasines A and B (Scheme 3.24). 4-Bromoindole 220 was prepared from 2-bromo-6-nitrotoluene 219 using the Batcho-Leimgruber indole synthesis. Indole 220 was then converted to the corresponding gramine derivative. The gramine derivative was allowed to react with KCN, followed by reaction with (BOC)₂O to give BOC protected nitrile 221. Rugulovasines A and B were synthesized in several steps from this intermediate.

Scheme 3.24

Some preliminary experiments have been performed in synthesizing enantiomerically enriched 4-iodotryptophan derivatives. The synthesis of substituted tryptophan derivatives using compounds similar to bromide 170
have been studied by Schöllkopf,\textsuperscript{83a} Cook\textsuperscript{83e} and Seebach\textsuperscript{83b} using chiral glycine synthons (Scheme 3.25). One interesting note is that in Schöllkopf's Scheme 3.25
$N_1, N_2, N_3, R_1 = H$

$R_2 = OCH_3$

$n$-BuLi, THF, $-70 \degree C$

$HCl$, THF

Seebach:

$R_1 = H$, Schöllkopf $88\%$ ee

$R_2 = OCH_3$

$H_3C \quad N_3 \quad O \quad H_3C$

$H_3C \quad N_3 \quad O \quad H_3C$

$229$

$230$

$90\%$ de

$69\%$ yield

$1. NaOCH_3$

$2. HCl$

$\text{CO}_2H$

$\text{NH}_2$

$231$
method, the use of naturally occurring L-valine results in the production of D-tryptophan, which is the unnatural enantiomer. We decided to use the Schöllkopf chiral auxiliary, (3S-isopropyl-2,5-diethoxypyrazine) 224, since it can be readily prepared in enantiopure form from L-valine and glycine. The synthesis of reagent 224 is shown in Scheme 3.26. L-Valine was allowed to react with triphosgene in THF to provide N-carboxyanhydride 233. 

**Scheme 3.26**

Glycine methyl ester hydrochloride was then added to anhydride 233 and Et₃N in CHCl₃ and THF at -78°C. The resulting mixture was then filtered to remove triethylammonium hydrochloride and the solvents were removed to leave a yellow oil. The oil was dissolved in toluene and heated to reflux overnight, causing diketopiperazine 234 to precipitate out of solution. A suspension of
in CH$_2$Cl$_2$ was then treated with triethyloxonium tetrafluoroborate to provide bis-lactim ether 224, which was isolated by Kugelrohr distillation. When 224 is treated with one equivalent of $n$-BuLi in THF at -78°C, it is selectively deprotonated to give anion 235 (Figure 12). When this anion is allowed to react with electrophiles such as bromide 170, the alkylation takes place with a high degree of diastereoselectivity in most cases. Schöllkopf has proposed that the high de's observed are a result of the anion 235 being planar.$^{102}$ One diastereotopic face is blocked by the bulky isopropyl group, forcing the incoming electrophile to approach from the opposite face, leading to an R configuration at that center (assuming that L-valine is used).

**Figure 12**

![Figure 12](image)

Some preliminary experiments in the reaction between bromide 170 and dihydropyrazine 224 indicate that the intermediate alkylation product 236 is obtained in 70-75% de, as estimated by $^1$H NMR (Scheme 3.27). The absolute configuration at the new chiral center was determined by comparison to literature values for the shifts in the $^1$H NMR. As Scheme 3.25 shows, Schöllkopf reported the de of the reaction of 1-($\text{ tert}$-butoxycarbonyl)-3-bromomethylindole 179 with the bis-lactim ether was 88%.$^{83a}$ Cook used a similar electrophile 3-bromomethyl-1-($\text{ tert}$-butoxycarbonyl)-6-methoxyindole 223 for this reaction.$^{83e}$ Unfortunately, the de of this reaction was never
reported. At this point in our study, more work needs to be done in order to understand why the de that we obtain is lower than that obtained by Schöllkopf and co-workers. The two diastereomeric alkylation products 236 can be separated by flash chromatography, giving diastereomerically pure 236. The pyrazine 236 can be cleaved with 2 N HCl in THF\(^{83e}\) to give optically pure 4-iodotryptophan ethyl ester derivative 237.

**Scheme 3.27**

In conclusion, we have demonstrated that 3-bromomethyl-1-carboethoxy-4-iodoindole 170 is a useful intermediate in the synthesis of structurally interesting 3,4-disubstituted indoles. Some of the studies presented in this chapter are preliminary and much work remains to be done in order to exploit the usefulness of 170.
**General Experimental:**

All reactions involving organometallic reagents were conducted under an atmosphere of purified argon using standard Schlenk techniques or under nitrogen in a Vacuum Atmospheres Co. drybox. The argon was purified was deoxygenated by passage through a column of activated R3-11 catalyst obtained from Schweizer-Hall, Plainfield, NJ. It was then dried by passage through a column of activated 3Å molecular sieves. All organic reactions were performed under an atmosphere of argon or nitrogen. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-300, VXR-500 or a Bruker AC250 FT spectrometer. Infrared (IR) spectra were recorded on either a Mattson Cygnus Starlab 100 or Perkin-Elmer Series 1600 FT spectrometer. Gas chromatography analyses were performed on a Hewlett Packard model 5890 GC with a 3392A integrator and FID detector using a 25 m capillary column with crosslinked SE-30 as a stationary phase. Liquid chromatography analyses were performed on a Hewlett Packard model 1050 HPLC equipped with a Hewlett Packard model 1040A diode array detector using an Alltech 250 mm x 4.6 mm silica 5 μ column. Electron impact mass spectra and high resolution mass determinations (HRMS) were recorded on a Finnegan MAT System 8200. Tetrahydrofuran, benzene and diethyl ether were dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation. Hexane was deolefinated by stirring over H₂SO₄, from which it was decanted and then stored over CaH₂. The deolefinated hexane thus obtained was dried and deoxygenated by refluxing over sodium/benzophenone ketyl followed by distillation. Alternatively, HPLC grade hexane was dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation.
Methylene chloride was dried by refluxing over CaH₂, followed by distillation. Acetonitrile was stored over activated 3 Å molecular sieves prior to use. Anhydrous N,N-dimethyl formamide (DMF) was purchased from Aldrich Chemical Co. and was used without further purification. Cp₂ZrCl₂ was purchased from Boulder Scientific Inc., Mead, Colorado. All other reagents were either prepared according to published procedures or were available from commercial sources and used without further purification. Unless otherwise stated, preparative flash chromatography was performed on E.M. Science Kieselgel 60 (230-400 mesh). Yields refer to isolated yields of compounds estimated to be ≥95% pure (unless otherwise noted) as determined by ¹H NMR, and either capillary GC or HPLC analysis. All reported yields are representative. Elemental analyses were performed by Onieda Research Services, Whitesboro, NY.

**N- Allyl-N-benzyl-2-bromoaniline (29).** A flame-dried Schlenk flask was charged with a stir bar, THF (150 mL) and 2-bromoaniline (8.56 g, 49.7 mmol). The solution was cooled to -78 °C and n-butyllithium (19.0 mL of a 2.68M solution in hexane, 50.9 mmol) was added dropwise. The solution was stirred for 15 min at -78 °C, at which time benzyl bromide (5.90 mL, 49.6 mmol) was added via syringe, and the solution was kept at -78 °C for 15 min and then allowed to warm to RT. After 2 h, the solution was again cooled to -78 °C and another portion of n-butyllithium (19.0 mL of a 2.68M solution in hexane, 50.9 mmol) was added. After 15 min at -78 °C, allyl bromide (4.32 mL, 50.0 mmol) was added, and the solution was kept at -78 °C for 15 min and then allowed to warm to RT. After stirring for 2 h, the THF was removed using a rotary
evaporator to leave a dark oil. Vacuum distillation (0.2 mm Hg, 140-145 °C), using a 15 cm vigreux column) gave 34 as a yellow oil (11.7 g, 78%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.56 (d, \(J= 7.86\) Hz, 1H), 7.4-7.1 (m, 6H), 7.0 (d, \(J = 7.85\) Hz, 1H), 6.85 (t, \(J = 7.50\) Hz, 1H), 5.83 (m, 1H), 5.17 (m, 2H), 4.23 (s, 2H), 3.62 (d, \(J= 5.93\) Hz, 2H). \(^{13}\)C (CDCl\(_3\)) \(\delta\) 148.9, 138.1, 134.5, 133.7, 128.5, 128.1, 127.5, 126.9, 124.5, 124.2, 121.3, 117.8, 56.3, 55.0. IR (film, cm\(^{-1}\)) 1028, 1474, 1494, 1584, 2837, 2926, 3027, 3062, 3083. HRMS (El) calcd for C\(_{16}\)H\(_{16}\)BrN: 301.0461, found: 301.0465 amu.

\[\text{N,N-diallyl-2-bromoaniline (30).}\]

Into a flask were placed 2-bromoaniline (15.22 g, 88.46 mmol), allyl bromide (19.0 mL, 26.56 g, 219.56 mmol), Na\(_2\)CO\(_3\) (104.0 g, 0.98 mol), and DMF (250 mL). The mixture was heated to reflux for 3 h, after which time it was allowed to cool and poured into a separatory funnel containing ether (500 mL) and water (300 mL). The organic layer was collected and washed with water (3 x 300 mL), brine (300 mL), dried over MgSO\(_4\), filtered and the solvents were removed to leave a brown oil. The product was isolated by Kugelrohr distillation (109-115 °C, 1 mm Hg) to give 17.35 g (78%) of a yellow oil. \(^1\)H NMR (CDCl\(_3\), 250 MHz) \(\delta\) 7.56 (d, \(J= 7.0\) Hz, 1H), 7.20 (t, \(J= 7.0\) Hz, 1H), 7.03 (d, \(J= 7.0\) Hz, 1H), 6.87 (t, \(J= 7.0\) Hz, 1H), 5.9-5.7 (m, 2H), 5.15 (m, 4H), 3.68 (d, \(J= 5.93\) Hz, 4H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 148.9, 134.7, 133.8, 127.4, 124.3, 124.0, 121.1, 117.6, 55.3. IR (neat, cm\(^{-1}\)) 3076, 2817, 1585, 1474, 1417, 1275, 1217, 1029, 921. HRMS (El) calcd for C\(_{12}\)H\(_{14}\)BrN: 251.0310, found: 251.0312 amu.
1-benzyl-4-iodo-3-iodomethylindoline (42). A flame-dried Schlenk flask was charged with a stir bar, THF (50 mL), zirconocene (methyl) chloride (4.06 g, 15 mmol), and 29 (4.53 g, 15 mmol). The solution was cooled to -78 °C and t-butyllithium (17.8 mL of a 1.69M solution in hexane, 30 mmol) was added. Stirring was continued at -78 °C for 15 min after which time the solution was allowed to warm to RT and was stirred for an additional 2 h. The THF was then removed in vacuo and the residue dissolved in CH2Cl2 (50 mL). The solution was filtered and the filtrate cooled to 0 °C. Into a separate Schlenk flask were placed a stir bar, I2 (9.75 g, 38.4 mmol) and CH2Cl2 (50 mL). The I2 solution was cooled to 0 °C and transferred into the solution of the metallacycle via cannula. Stirring was continued at 0 °C for 4 h, at which time the CH2Cl2 was removed using a rotary evaporator and the residue dissolved in ether (150 mL). The organic layer was washed with aqueous Na2SO3 (3 x 50 mL), water (3 x 50 mL) and brine, dried over MgSO4, filtered, and concentrated to leave a dark brown oil. Flash chromatography (99:1, hexane:ether) yielded 4.61 g (65%) of a yellow oil. 1H NMR (CDCl3, 300 MHz) δ 7.4-7.2 (m, 5H), 7.01 (d, J= 7.89 Hz, 1H), 6.79 (t, J= 7.67 Hz, 1H), 6.40 (d, J= 7.91 Hz, 1H), 4.34 (d, J= 15.4 Hz, 1H), 4.15 (d, J= 15.4 Hz, 1H), 3.58 (dd, J=9.13, 1.59 Hz, 1H), 3.47-3.41 (m, 3H), 3.17 (t, J= 9.91 Hz, 1H). 13C NMR (CDCl3, 75 MHz) δ 151.9, 137.2, 134.1, 130.6, 128.6, 127.5, 127.3, 126.7, 107.1, 93.2, 57.9, 52.3, 47.5, 9.0. IR (CHCl3, cm⁻¹) 3065, 3033, 3009, 2926, 1591, 1566, 1451. HRMS (El) calcd for C16H15NI2: 474.9288, found: 474.9292 amu.
1-allyl-4-iodo-3-iodomethylindoline (43). To a flame-dried Schlenk flask were added N,N-diallyl-2-bromoaniline 30 (2.52 g, 10.0 mmol), zirconocene (methyl) chloride (2.77 g, 10.19 mmol), and THF (50 mL). The mixture was cooled to -78°C and t-butyl lithium (11.22 mL of a 1.81 M solution in pentane, 20.31 mmol) was added dropwise from a syringe. Stirring was continued at -78°C for 15 min, after which time it was allowed to warm to RT and stir for an additional 1 h. The THF was removed in vacuo and CH$_2$Cl$_2$ (15 mL) was added to the remaining residue. Into a separate Schlenk flask were placed I$_2$ (6.42 g, 25.30 mmol) and CH$_2$Cl$_2$ (45 mL). Both solutions were cooled to 0°C and the I$_2$ was added to the metallacycle via cannula. The resulting solution was allowed to stir at 0°C for 4 h, after which time it was poured into a separatory funnel containing ether (150 mL) and Na$_2$SO$_3$ solution (150 mL). The organic layer was collected and washed with water (2 x 150 mL), brine (150 mL), dried over MgSO$_4$, filtered and the solvents removed by rotary evaporation. The product was isolated by flash chromatography (95:5 hexane: ethyl acetate) followed by heating to 100°C at 2 mm Hg for 10 min to remove any remaining volatile impurities to give 2.76 g (65%) of a yellow oil. $^1$H NMR (CDCl$_3$, 250 MHz) δ 6.97 (d, J= 8.0 Hz, 1H), 6.79 (t, J= 7.8 Hz, 1H), 6.39 (d, J= 7.8 Hz, 1H), 5.80 (m, 1H), 5.20 (m, 2H), 3.8-3-3.35 (m, 6H), 3.11 (t, J= 10.1 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 151.3, 134.0, 132.4, 130.1, 126.3, 117.4, 106.9, 92.6, 57.1, 50.5, 47.2, 8.34. IR (neat, cm$^{-1}$) 3073, 3007, 2976,
HRMS (EI) calcd for C$_{12}$H$_{13}$NI$_2$: 424.9141, found: 424.9140 amu.

1-benzyl-4-iodo-3-methyleneindoline (44). A flame-dried round-bottom flask, equipped with a stir bar, was charged with toluene (8 mL), 42 (0.481 g, 1.01 mmol), and DBU (0.173 mL, 176 mg, 1.16 mmol). The reaction mixture was heated to 60 °C for 2 h, after which it was filtered to remove the precipitated DBU salts. Removal of the solvents by rotary evaporation left a viscous, yellow oil. $^1$H NMR (C$_6$D$_6$, 250 MHz) $\delta$ 7.2-6.9 (m, 6H), 6.52 (t, $J$= 3.06 Hz, 1H), 6.42 (t, $J$= 7.93 Hz, 1H), 6.14 (d, $J$= 7.93 Hz, 1H), 4.66 (t, $J$= 2.75 Hz, 1H), 3.77 (s, 2H), 3.67 (t, $J$= 3.00 Hz, 2H).

46. Into a flask were placed 1-allyl-4-iodo-3-iodomethylindoline 43 (160 mg, 0.38 mmol), 18-crown-6 (125 mg, 0.473 mmol), K$_2$CO$_3$ (89 mg, 0.644 mmol), dimethylmalonate (0.08 mL, 102 mg, 0.722 mmol) and benzene (5.5 mL). The reaction mixture was heated to reflux overnight and then it was allowed to cool. It was filtered through a plug of silica which was washed with benzene (2 x 20 mL). The solvents were removed and the product was isolated by flash chromatography (9:1 hexane: ethyl acetate) to give 128 mg (80%) of a clear oil. $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 6.98 (d, $J$= 7.83 Hz, 1H), 6.74 (d, $J$= 7.83 Hz, 1H), 6.40 (d $J$= 7.80 Hz, 1H), 5.75 (m, 1H), 5.20 (m, 2H), 3.76 (s, 3H), 3.70
(m, 1H), 3.64 (s, 3H), 3.53 (m, 2H), 3.27 (m, 2H), 3.10 (m, 1H), 2.25 (m, 2H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 169.4, 151.9, 135.5, 133.1, 129.8, 127.0, 117.7, 107.0, 93.1, 56.1, 52.5, 51.3, 49.5, 42.1, 30.8. IR (neat, cm$^{-1}$) 3073, 3003, 2951, 1732, 1591, 1567, 1446, 1234, 1159, 916, 764, 732. HRMS (El) calcd for C$_{17}$H$_{20}$NO$_4$I: 429.0438, found: 429.0434 amu.

**Ene Reactions: General Procedure I.** A flame-dried round-bottom flask was charged with a stir bar, toluene or benzene (10mL/mmol 42) and 42. The solution was heated to 50-60 °C, at which time one eq of DBU was added dropwise via syringe. The reaction mixture was stirred at 50-60 °C for 2 h, after which time the solution was filtered to remove the precipitated DBU salts. The ene substrate was then added to the solution and the reaction mixture heated to 85 °C for 8 h. Isolation of the reaction product was accomplished by dilution of the mixture with ether, extracting the organic layer with water and brine, drying over MgSO$_4$, filtering and concentrating *in vacuo*. Flash chromatography was used when further purification was necessary.

**General Procedure II.** A flame-dried round-bottom flask was charged with a stir bar, toluene or benzene (10 mL/mmol 42 or 43) and 42 or 43. The solution was heated to 50-60 °C, at which time one eq of DBU was added dropwise via syringe. The reaction mixture was kept at 50-60 °C for 2 h, after which time the solution was filtered to remove the precipitated DBU salts. The solvent was removed *in vacuo* and the remaining residue was dissolved in CH$_3$CN (10 mL). The resulting solution was heated to 50-60 °C and the iminium salt was added in one portion. The reaction was generally complete after 2 h. Isolation of the reaction product was accomplished by dilution of the mixture with ether, extracting the organic layer with 2N NaOH, water (3x) and brine (1x), drying over MgSO$_4$, filtering and concentrating *in vacuo*. Flash chromatography was used when further purification was necessary.
(Table 1, Entry 1) 47. Indoline 42 (0.51 g, 1.06 mmol), DBU (0.16 mL, 163 mg, 1.07 mmol), and diethylacetylenedicarboxylate (0.375 mL, 2.3 mmol) were employed according to general procedure I. Flash chromatography (4:1 hexane:ethyl acetate) yielded 47 as a yellow oil (0.260 g, 53%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.55 (d, $J$ = 7.13 Hz, 1H), 7.30-7.26 (m, 4H), 7.06 (m, 3H), 6.85 (t, $J$ = 7.64 Hz, 1H), 5.58 (m, $J$ = 1.79 Hz, 1H), 5.23 (s, 2H), 4.23 (q, $J$ = 6.90 Hz, 2H), 4.13 (q, $J$ = 7.40 Hz, 2H), 4.09 (s, 2H), 1.2 (m, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 168.7, 165.3, 150.1, 136.9, 136.6, 131.4, 129.9, 128.9, 127.8, 126.7, 123.3, 121.6, 110.3, 110.1, 84.6, 61.3, 60.6, 50.1, 30.3, 29.9, 14.1, 13.9. IR (film, cm$^{-1}$) 1732, 1736, 2954, 3029. HRMS (EI) calcd for C$_{24}$H$_{24}$O$_4$NI: 517.0750, found: 517.0748 amu.

( Table 1, Entry 2) 48. Indoline 42 (0.541 g, 1.06 mmol), DBU (0.16 mL, 163 mg, 1.07 mmol), and diethylfumarate (0.26 mL, 273 mg, 1.59 mmol) were employed according to general procedure I. Flash chromatography (4:1, hexane:ethyl acetate, $R_f$ = 0.31) yielded 48 as a yellow oil (0.278 g, 56%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.56 (d, $J$ = 7.71 Hz, 1H), 7.25 (m, 3H), 7.21 (d, $J$ = 8.14 Hz, 1H), 7.04 (d, $J$ = 7.73 Hz, 2H), 7.00 (s, 1H), 6.80 (t, $J$ = 7.06 Hz, 1H), 5.21 (s, 2H), 4.04 (m, 4H), 3.45 (m, 2H), 3.15 (m, 1H), 2.71-2.50 (m, 2H), 1.20 (m, 6H). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 174.7, 171.8, 137.0, 136.8, 131.2, 129.3, 128.8, 128.4, 127.7, 126.6, 122.9, 112.9, 110.0, 85.1, 60.42, 60.41, 49.9, 43.5, 35.8,
IR (film, cm\(^{-1}\)) 1723, 2905, 2935, 2981. HRMS (El) calcd for C\(_{24}H_{26}O_4NI\): 519.0906, found: 519.0903 amu.

**(Table 1, Entry 3) 49.** Indoline 42 (0.265 g, 0.56 mmol), DBU (0.11 mL, 112 mg, 0.6 mmol) and fumaronitrile (0.052 g, 0.67 mmol) were used according to general procedure I. Flash chromatography (4:1, hexane: ethyl acetate) yielded 49 as a yellow oil (0.143 g, 60%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.59 (d, \(J = 7.64\) Hz, 1H), 7.40-7.25 (m, 5H), 7.10 (dd, \(J = 8.11, 2.40\) Hz, 2H), 6.88 (t, \(J = 7.67\) Hz, 1H), 5.28 (s, 2H), 3.50 (m, 2H), 3.35 (m, 1H), 2.80 (dd, \(J = 17.13, 4.83\) Hz, 1H), 2.70 (dd, \(J = 17.13, 6.12\) Hz, 1H). \(^1\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 137.2, 136.3, 131.4, 130.4, 128.0, 127.7, 126.7, 123.5, 118.9, 115.6, 110.6, 109.5, 84.4, 60.3, 50.3, 31.3, 27.4, 20.0. IR (CHCl\(_3\), cm\(^{-1}\)) 2249, 2959, 3050, 3054, 3068. HRMS (El) calcd for C\(_{20}H_{16}N_3I\): 425.0388, found: 425.0387 amu.

**(Table 1, Entry 4) 50.** Indoline 42 (0.456 g, 0.97 mmol), DBU (0.16 mL, 163 mg, 1.07 mmol), and diethyl ketomalonate (0.09 mL, 101 mg, 0.580 mmol) were used according to general procedure I. Flash chromatography (4:1, hexane: ethyl acetate, \(R_f = 0.26\)) yielded 50 as a light yellow oil (0.378 g, 76%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.56 (d, \(J = 7.73\) Hz, 1H), 7.27 (m, 4H), 7.18 (d, \(J = 8.21\) Hz, 1H), 7.0 (dd, \(J = 7.77, 1.72\) Hz, 2H), 6.77 (t, \(J = 7.77\) Hz, 1H), 5.23 (s, 2H), 4.15 (m, 4H), 4.04 (s, 2H), 3.97 (s, 1H), 1.25 (t, \(J = 7.15\) Hz, 3H), 1.17 (t, \(J = 7.15\) Hz, 3H).
7.16 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 171.0, 170.3, 136.8, 136.3, 131.8, 129.9, 128.7, 127.6, 126.5, 122.6, 110.0, 109.3, 85.1, 79.4, 62.3, 60.3, 49.9, 29.0, 21.0, 14.1, 13.9. IR (CHCl$_3$, cm$^{-1}$) 1430, 1546, 1736, 1741, 2984, 3032, 3509 (br). HRMS (El) calcd for C$_{23}$H$_{25}$O$_5$NI: 522.0777, found: 522.0774 amu.

(Table 1, Entry 5) 51. Indoline 42 (1.87 g, 3.93 mmol), DBU (0.6 mL, 611 mg, 4.01 mmol) and butyl glyoxalate (0.698 g, 3.9 mmol) were used according to general procedure I. Flash chromatography (4:1, hexane: ethyl acetate, R$_f$ = 0.27) yielded 51 as a yellow oil (1.34 g, 72%). $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.56 (d, $J$ = 7.70 Hz, 1H), 7.18 (d, $J$ = 8.22 Hz, 1H), 7.13 (s, 1H), 7.03 (dd, $J$ = 7.03, 1.76 Hz, 2H), 6.67 (t, $J$ = 7.67 Hz, 1H), 5.17 (s, 2H), 4.60 (m, 1H), 4.12 (t, $J$ = 6.54 Hz, 2H), 3.80 (dd, $J$ = 14.8, 4.29 Hz, 1H), 3.20 (dd, $J$ = 14.8, 8.41 Hz, 1H), 2.97 (d, $J$ = 5.74 Hz, 1H), 1.54 (m, 2H), 1.28 (m, 2H), 0.86 (t, $J$ = 7.50 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 174.7, 136.7, 131.1, 129.7, 129.6, 128.6, 128.3, 127.6, 126.5, 122.7, 111.0, 109.9, 84.8, 71.1, 65.7, 65.2, 49.8, 30.4, 18.9, 13.5. IR (CHCl$_3$, cm$^{-1}$) 1727, 2962, 3010, 3031, 3540 (br). HRMS (El) calcd for C$_{22}$H$_{24}$NO$_3$I: 477.0800, found: 477.0800 amu.

(Table 1, Entry 6) 52. Indoline 42 (0.480g, 1.0 mmol), DBU (0.15mL, 153 mg, 1.0 mmol), and diethyl azadicarboxylate (0.235 mL, 1.49 mmol) were used according to general procedure I. Flash chromatography (3:2, hexane:ethyl acetate, R$_f$ = 0.35) yielded 52 as a light yellow oil (0.432g, 83%).
1H NMR (CDCl₃, 300 MHz) δ 7.55 (d, J= 7.71 Hz, 1H), 7.3 (m, 5H), 7.05 (m, 2H), 6.80 (t, J= 7.94 Hz, 1H), 5.23 (s, 2H), 5.16 (br s, 2H), 4.20 (q, J= 6.93 Hz, 2H), 4.05 (q, J= 6.93 Hz, 2H), 1.25 (t, J= 6.93 Hz, 3H), 1.14 (t, J= 6.93 Hz, 3H). 13C NMR (acetone-d₆, 75 MHz) δ 158.2, 157.8, 138.4, 138.0, 131.9, 131.6, 129.7, 129.3, 128.9, 128.2, 127.6, 123.5, 111.6, 111.2, 84.7, 62.3, 61.5, 50.3, 14.9, 14.8. IR (CHCl₃, cm⁻¹) 1712, 1743, 3019, 3027, 3418 (br). HRMS (El) calcd for C₂₂H₂₄N₃O₄I: 521.0811, found: 521.0812 amu.

65. Into a flask were placed 1-allyl-4-iodo-3-iodomethylindoline 43 (412 mg, 0.970 mmol), DBU (0.16 mL, 163 mg, 1.07 mmol), and benzene (3 mL) and the solution was heated to 50 °C for 90 min, then allowed to cool to RT. The DBU salts were filtered away and the benzene was removed by rotary evaporation. Into a separate flask were placed bromoacetate 63 (669 mg, 2.5 mmol), and THF (4 mL). The solution was cooled to -78 °C and Et₃N (0.370 mL, 269 mg, 2.65 mmol) was added causing the immediate formation of a precipitate. The mixture was allowed to stir at -78 °C for 30 min, then the THF solution of olefin 45 was added. The resulting mixture was allowed to stir and slowly warm to RT overnight. It was then poured into a separatory funnel containing ether (50 mL) and water (50 mL). The organic layer was collected and washed with water (2 x 50 mL), brine (50 mL), dried over MgSO₄, filtered and the solvents were removed. The product was isolated by flash chromatography (85:15 hexane:ethyl acetate) to give 328 mg (70%) of a white solid, mp= 127-130 °C. An analytically pure sample was prepared by recrystallization from ethanol/hexane to give white needles, mp= 128-130 °C.
\(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.55 (d, \(J = 7.5\) Hz, 1H), 7.23 (d, \(J = 8.1\) Hz, 1H), 7.00 (br s, 1H), 6.82 (t, \(J = 7.8\) Hz, 1H), 5.92 (m, 1H), 5.17 (d, \(J = 10.2\) Hz, 1H), 5.03 (br m, 2H), 4.71 (m, 1H), 4.63 (d, \(J = 5.7\) Hz, 2H), 3.70 (br s + m, 4H), 3.40 (br m, 1H), 1.4-1.1 (br s, 9H). 13C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 28.2, 48.6, 52.1, 54.7, 54.9, 79.6, 85.0, 109.9, 110.9, 117.5, 122.9, 128.4, 128.7, 131.3, 132.7, 136.8, 155.2, 173.2. IR (neat, cm\(^{-1}\)) 3378 (br), 2976, 1739, 1709. Anal. calcd for C\(_{20}\)H\(_{25}\)N\(_2\)O\(_4\): C, 49.6; H, 5.2; N, 5.78. Found: C, 49.9; H, 4.95; N, 5.67.

(Table 2, Entry 1) 70. Indoline 42 (0.483 g, 1.10 mmol) DBU (0.170 mL, 173 mg, 1.14 mmol) and N,N-diethyl methylene ammonium chloride (0.153 g, 1.26 mmol) were used according to general procedure II. Flash chromatography (1:1, hexane:ether, 3% triethylamine, \(R_f = 0.23\)) yielded 70 as a yellow oil (0.372 g, 85%). \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 1.07 (t, \(J = 7.23\) Hz, 6H), 2.65 (q, \(J = 7.23\) Hz, 4H), 2.80 (t, \(J = 8.10\) Hz, 2H), 3.17 (t, \(J = 8.10\) Hz, 2H), 5.17 (s, 2H), 6.75 (t, \(J = 7.87\) Hz, 1H), 7.01 (m, 3H), 7.15 (d, \(J = 8.37\) Hz, 1H), 7.23 (m, 3H), 7.53 (d, \(J = 7.41\) Hz, 1H). 13C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 11.9, 23.1, 46.9, 49.8, 55.1, 85.3, 109.8, 115.3, 122.7, 126.5, 127.6, 128.1, 128.5, 128.7, 130.8, 136.8, 136.9. IR (film, cm\(^{-1}\)) 1355, 1429, 1446, 1490, 2805, 2930, 2968, 3030, 3063. HRMS (EI) calcd for C\(_{21}\)H\(_{25}\)N\(_2\)I: 432.1062, found: 432.1060 amu.

(Table 2, Entry 2) 71. Indoline 42 (0.481 g, 1.01 mmol), DBU (0.17 mL, 173 mg, 1.16 mL) and N-methylene piperidinium chloride (155 mg, 1.16
mmol) were used according to general procedure II. Spinning-plate chromatography (1:1, hexane: ether, with 3% Et₃N,) gave 71 as a yellow oil (0.312 g, 70%). ¹H NMR (CDCl₃, 300 MHz) δ 7.53 (d, J= 7.74 Hz, 1H), 7.35-7.2 (m, 3H), 7.17 (d, J= 8.18 Hz, 1H), 7.05 (m, 3H), 6.77 (t, J= 6.93 Hz, 1H), 5.20 (s, 2H), 3.23 (t, J= 8.20 Hz, 2H), 2.69 (t, J= 8.20 Hz, 2H), 2.54 (br s, 4H), 1.62 (m, 4H), 1.47 (m, 2H). ¹³C NMR (CDCl₃, 75 MHz) δ 137.0, 136.8, 130.9, 128.8, 128.6, 128.2, 127.6, 126.6, 122.7, 115.3, 109.8, 85.3, 61.5, 54.7, 49.9, 26.1, 24.5, 22.9. IR (film, cm⁻¹) 1116, 1323, 1429, 1453, 2799, 2932, 2970, 3063. HRMS (EI) calcd for C₂₂H₂₅N₂I: 444.1057, found: 444.1063.

(Table 2, Entry 3) 72. 1-allyl-4-iodo-3-iodomethylindoline 43 (318 mg, 0.748 mmol), DBU (0.12 mL, 122 mg, 0.802 mmol), and N,N-dimethylmethylene ammonium iodide (153 mg, 0.827 mmol) were employed according to general procedure II. The product was isolated by flash chromatography (3:2 hexane: ethyl acetate then 60:35:5 hexane: ethyl acetate:triethylamine) to yield 225 mg (85%) of a yellow oil. ¹H NMR (CDCl₃, 300 MHz) δ 7.55 (d, J=7.51 Hz, 1H), 7.22 (d, J= 8.1 Hz, 1H), 6.98 (s, 1H), 6.82 (t, J= 7.8 Hz, 1H), 5.90 (m, 1H), 5.16 (d, J= 10.5 Hz, 1H), 5.06 (d, J= 10.5 Hz, 1H), 4.61 (d, J= 5.70 Hz, 2H), 3.18 (t, J= 8.1 Hz, 2H), 2.64 (t, J= 8.1 Hz, 2H), 2.36 (s, 6H). ¹³C NMR (CDCl₃, 75 MHz) δ 136.7, 132.9, 130.8, 128.4, 127.7, 122.5, 117.3, 114.6, 109.7, 85.2, 61.8, 48.6, 45.6, 23.8. IR (neat, cm⁻¹) 2939, 2857, 2817, 1545, 1469, 1430, 1418, 1324, 925, 734. HRMS (EI) calcd for C₁₅H₁₉N₂I: 354.0595, found: 354.0592 amu.
(Table 2, entry 4) 73. 1-allyl-4-iodo-3-iodomethylindoline 43 (313 mg, 0.737 mmol), DBU (0.12 mL, 122 mg, 0.802 mmol), and N-methylenemorpholine ammonium chloride (117 mg, 0.863 mmol) were employed according to general procedure II. The product was isolated by flash chromatography (4:1 hexane: ethyl acetate then 80:15:5 hexane: ethyl acetate: triethylamine) to give 246 mg (84%) of a viscous, yellow oil. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.54 (d, $J$= 7.5 Hz, 1H), 7.22 (d, $J$= 8.1 Hz, 1H), 6.98 (s, 1H), 6.81 (t, $J$= 7.95 Hz, 1H), 5.92 (m, 1H), 5.18 (d, $J$= 10.0 Hz, 1H), 5.05 (d, $J$= 10.0 Hz, 1H), 4.60 (d, $J$= 5.10 Hz, 2H), 3.25 (t, $J$= 8.1 Hz, 2H), 2.81 (t, $J$= 8.1 Hz, 2H), 2.65 (m, 4H), 1.81 (m, 4H). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 136.6, 133.0, 130.7, 128.4, 127.6, 122.5, 117.4, 115.0, 109.6, 85.3, 58.6, 54.2, 48.6, 25.1, 23.5. IR (neat, cm$^{-1}$) 2960, 2926, 2789, 1544, 1469, 1429, 1325, 1178, 1123, 736. HRMS (EI) calcd for C$_{17}$H$_{21}$N$_2$O: 396.0700, found: 396.0700 amu.

(Table 2, Entry 5) 74. 1-allyl-4-iodo-3-iodomethylindoline 43 (323 mg, 0.760 mmol), DBU (0.12 mL, 122 mg, 0.802 mmol), and N-
methyleneprrolidine ammonium chloride (105 mg, 0.878 mmol) were employed according to general procedure II. The product was isolated by flash chromatography (4:1 hexane: ethyl acetate then 80:15:5 hexane: ethyl acetate: triethylamine) to yield 228 mg (79%) of a yellow oil. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.55 (d, $J =$ 7.8 Hz, 1H), 7.23 (d, $J =$ 8.1 Hz, 1H), 6.99 (s, 1H), 6.84 (t, $J =$ 7.95 Hz, 1H), 5.92 (m, 1H), 5.18 (d, $J =$ 10.5 Hz, 1H), 5.01 (d, $J =$ 10.5 Hz, 1H), 4.63 (d, $J =$ 5.10 Hz, 2H), 3.75 (t, $J =$ 4.65 Hz, 4H), 3.21 (t, $J =$ 8.1 Hz, 2H), 2.71 (t, $J =$ 8.1 Hz, 2H), 2.60 (t, $J =$ 4.65Hz, 4H). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 136.7, 133.0, 130.8, 128.4, 127.8, 122.6, 117.4, 114.4, 109.7, 85.2, 67.1, 61.0, 53.8, 48.6, 22.7. IR (neat, cm$^{-1}$) 2957, 2920, 2810, 1470, 1444, 1430, 1324, 1116, 909, 733. HRMS (El) calcd for C$_{17}$H$_{21}$N$_2$I: 380.0751, found: 380.0751 amu.

4-iodo-3-iodomethylindoline 75. To a flask were added 1-allyl-4-iodo-3-iodomethylindoline 43 (128 mg, 0.301 mmol), NaI (90 mg, 0.600 mmol), 1-chloroethyl chloroformate (0.06 mL, 80 mg, 0.556 mmol), and acetone (4 mL). The resulting mixture was stirred at RT for 3 h, after which time the solvent was removed leaving a brown oil and a white solid. The oil was dissolved in a minimum amount of ether and was eluted down a flash column using 9:1 hexane:ether as eluent. All of the UV active compounds were collected and the solvent removed to leave a clear oil, which was dissolved in 1,2-dichloroethane (3 mL) and placed in a flask to which methanol (3 mL) was added. The solution was heated to reflux for 90 min, cooled to RT and poured into a separatory funnel containing ether (25 mL) and NaHCO$_3$ solution (25 mL). The organic layer was collected and washed with water (25 mL), brine (25 mL), dried over MgSO$_4$, filtered and the solvents were removed by rotory evaporation. The
product was isolated by flash chromatography (95:5 hexane:ether) to give 78 mg (68%) of a yellow oil that turned green upon exposure to air. $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.02 (d, $J$= 7.2 Hz, 1H), 6.76 (t, $J$=7.7 Hz, 1H), 6.54 (d, $J$= 7.7 Hz, 1H), 3.8-3.5 (m, 5H), 3.17 (t, $J$= 9.22 Hz, 1H). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 151.2, 133.9, 130.4, 127.9, 109.5, 92.9, 52.1, 49.0, 8.7. IR (neat, cm$^{-1}$) 3385, 2934, 2863, 1594, 1569, 1474, 1443, 1286, 764, 735, 635. HRMS (El) calcd for C$_9$H$_9$N$_2$: 384.8828, found: 384.8830 amu.

1-carboethoxy-3-iodomethyl-4-iodoindoline (79). Into a flask were placed 1-allyl-4-iodo-3-iodomethylindoline 43 (1.00g, 2.35 mmol), NaI (1.10 g, 7.34 mmol), ethyl chloroformate (0.67 mL, 760 mg, 7.01 mmol) and acetone (15 mL). The mixture was heated to reflux for 6 h, after which time it was allowed to cool and was then poured into a separatory funnel containing ether (50 mL) and water (50 mL). The organic layer was collected and washed with water (2 x 50 mL), brine (50 mL), dried over MgSO$_4$, filtered and the solvents removed to leave a dark oil. The product was isolated by flash column (95:5 hexane: ethyl acetate) to give 972 mg (91%) of a yellow oil. $^1$H NMR (CDCl$_3$, 250 MHz) $\delta$ 7.8 (br, 1H), 7.31 (d, $J$= 8.4 Hz, 1H), 6.95 (t, $J$= 8.4 Hz, 1H), 4.26 (br q, $J$= 7.0 Hz, 2H), 4.10 (m, 2H), 3.6 (m, 2H), 3.12 (t, $J$= 9.8 Hz, 1H), 1.35 (t, $J$= 7.0 Hz, 3H). $^{13}$C NMR(C$_6$D$_6$, 125 MHz, 60 °C) $\delta$. 152.7, 143.6, 135.8, 132.2, 130.7, 115.4, 92.5, 61.7, 53.7, 46.2, 14.6, 9.0. IR (neat, cm$^{-1}$) 2979, 1713, 1472, 1448, 1380, 1327, 1307, 1191, 773. HRMS (El) calcd for C$_{12}$H$_{13}$NO$_2$I$_2$: 456.9039, found: 456.9035 amu.
80. 1-carboethoxy-4-iodo-3-iodomethylindoline 79 (720 mg, 1.58 mmol), DBU (0.240 mL, 244 mg, 1.60 mL), and N,N-dimethylmethylene ammonium iodide (370 mg, 2.0 mmol) were employed according to general procedure II. The product was purified by flash chromatography (7:3 hexane: ethyl acetate then 60:35:5 hexane: ethyl acetate: triethylamine) to yield 506 mg (83%) of a clear, viscous oil. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 8.21 (d, $J = 8.1$ Hz, 1H), 7.67 (d, $J = 8.1$ Hz, 1H), 7.47 (s, 1H), 6.94 (t, $J = 7.8$ Hz, 1H), 4.43 (q, $J = 6.9$ Hz, 2H), 3.11 (t, $J = 7.5$ Hz, 2H), 2.63 (t, $J = 7.5$ Hz, 2H), 2.34 (s, 6H), 1.43 (t, $J = 6.9$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 150.2, 136.4, 134.7, 131.1, 125.5, 124.6, 120.4, 115.2, 84.7, 63.3, 60.4, 45.6, 24.3, 14.4. IR (neat, cm$^{-1}$) 2975, 2939, 2816, 2765, 1740, 1462, 1419, 1377, 1350, 1290, 1249, 1093. HRMS (EI) calcd for C$_{15}$H$_{19}$N$_2$O$_2$I: 386.0491, found: 386.0488 amu.

2-bromo-4-methoxyaniline (95). Into a flask were placed p-aniside 94 (2.47 g, 20.05 mmol), methanol (40 mL), and CH$_2$Cl$_2$ (80 mL). To the colorless solution was added n-Bu$_4$NBr$_3$ (9.68 g, 20.07 mmol) in one portion, causing the reaction mixture to turn purple. The resulting mixture was allowed to stir at RT for 35 min and was then poured into a separatory funnel containing saturated aqueous Na$_2$SO$_3$ (100 mL) and ether (100 mL). The organic layer
was collected and washed with water (2 x 100 mL), brine (100 mL), dried over 
MgSO$_4$, filtered through a short plug of silica and the solvents were removed to 
leave a dark, red oil. The product was isolated by flash chromatography (4:1 
hexane:ethyl acetate) to yield 1.72 g (42%) of a brown oil. $^1$H NMR (CDCl$_3$, 
300 MHz) $\delta$ 6.98 (d, $J$= 2.4 Hz, 1H), 6.69 (m, 2H), 3.78 (br s, 2H), 3.69 (s, 3H). 
$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 152, 138, 117, 116, 115, 109, 56. IR (neat, cm$^{-1}$) 
3442, 3358, 3203, 2999, 2949, 2832, 1623, 1600, 1499, 1440, 1275, 1230, 
1212, 1037, 865.

Bu$_4$NBr$_3$

**Tetra-n-butylammonium tribromide.** Into a flask were placed tetra-
$n$-butylammonium bromide (15.15 g, 46.98 mmol) and CH$_2$Cl$_2$ (100 mL). 
Bromine (2.40 mL, 7.44 g, 46.58 mmol) was added last via syringe causing the 
solution to turn orange. The solution was allowed to stir at RT for 30 min, then it 
was poured into a flask containing ether (300 mL), causing the product to 
crystallize. The orange crystals were collected using a Büchner funnel and 
were dried *in vacuo* giving 22.45 g (99%) of an orange solid, mp= 72-74 °C 
(lit.$^{66}$ mp= 74-76 °C). This compound is also available from Aldrich Chemical 
Co. (catalog #30,159-0).

![Structure of Bu$_4$NBr$_3$](image)

**N,N-diallyl-2-bromo-4-methoxyaniline** (97). To a flask were 
added 2-bromo-4-methoxyaniline 95 (3.75 g, 18.56 mmol), allyl bromide (4.0 
ml, 5.59 g, 46.22 mmol), Na$_2$CO$_3$ (5.92 g, 55.85 mmol), and DMF (30 mL). The 
mixture was heated to reflux for 1h, allowed to cool to RT and poured into a 
separatory funnel containing ether (60 mL) and water (60 mL). The organic
layer was collected and washed with water (2 x 60 mL), brine (60 mL), dried over MgSO₄ and the solvents were removed to leave a dark, brown oil. The product was isolated by Kugelrohr distillation (T= 120-130 °C, P= 0.1 mm Hg) to give 4.58 g (88%) of a yellow oil. ¹H NMR (CDCl₃, 300 MHz) δ 7.13 (d, J= 3.3 Hz, 1H), 6.97 (d, J= 9.0 Hz, 1H), 6.77 (dd, J= 3.3, 9.0 Hz, 1H), 5.79 (m, 2H), 5.10 (m, 4H), 3.75 (s, 3H), 3.60 (d, J= 6.0 Hz, 4H). ¹³C NMR (CDCl₃, 75 MHz) δ 155.9, 141.9, 134.9, 124.8, 122.4, 118.5, 117.3, 113.2, 56.2, 55.6. IR (neat, cm⁻¹) 3076, 3005, 2977, 2938, 2834, 1601, 1563, 1495, 1463, 1440, 1418, 1286, 1209, 1040, 992, 921, 810, 740, 675. HRMS (El) calcd for C₁₃H₁₆BrNO: 281.0416, found: 281.0415 amu.

**1-allyl-4-iodo-3-iodomethyl-5-methoxyindoline (98).** Into a Schlenk flask were placed N,N-diallyl-2-bromo-4-methoxyaniline 97 (544 mg, 1.93 mmol), zirconocene(methyl) chloride (580 mg, 2.13 mmol), and THF (6 mL). The solution was cooled to -78 °C and t-BuLi (2.0 mL of a 1.96 M solution in pentane, 3.92 mmol) was added dropwise. The resulting solution was allowed to stir at -78 °C for 15 min and was then allowed to warm to RT and stir for an additional 1 h. The THF was removed *in vacuo* leaving an orange foam to which CH₂Cl₂ (3 mL) was added. Into a separate Schlenk flask were placed iodine (1.22 g, 4.81 mmol), and CH₂Cl₂ (3 mL). Both solutions were cooled to 0 °C and the iodine solution was added by cannula to the solution of the metallacycle. The resulting dark mixture was allowed to stir at 0 °C for 4 h and then at RT for an additional 10 h. The whole mixture was poured into a separatory funnel containing saturated aqueous Na₂SO₃ solution (50 mL) and
ether (50 mL). The organic layer was collected and washed with water (2 x 50 mL), brine (50 mL), dried over MgSO₄ and the solvents were removed to leave a dark oil. The product was isolated by flash chromatography (95:5 hexane:ethyl acetate) to yield 553 mg (63%) of a yellow oil. ¹H NMR (CDCl₃, 250 MHz) δ 6.62 (d, J= 8.5 Hz, 1H), 6.39 (d, J= 8.5 Hz, 1H), 5.85 (m, 1H), 5.24 (m, 2H), 3.79 (m, 2H), 3.75 (m, 1H), 3.7-3.5 (m, 4H), 3.32 (t, J= 8.25 Hz, 1H), 3.15 (t, J= 9.47 Hz, 1H). ¹³C NMR (CDCl₃, 75 MHz) δ 150.9, 146.2, 136.7, 133.2, 117.6, 111.7, 108.0, 86.2, 58.3, 57.4, 52.3, 48.5, 8.4. IR (neat, cm⁻¹) 2931, 2830, 1599, 1474, 1459, 1432, 1258, 1236, 1063, 796, 758. HMRS (El) calcd for C₁₃H₁₅I₂NO: 454.9246, found: 454.9245 amu.

99. 1-allyl-4-iodo-3-iodomethyl-5-methoxyindoline 98 (320 mg, 0.703 mmol), DBU (0.11 mL, 112 mg, 0.736 mmol), and N,N-dimethylmethylene ammonium iodide (156 mg, 0.843 mmol) were employed according to general procedure II. The product was isolated by flash chromatography (95:5 ethyl acetate:triethylamine) to yield 250 mg (93%) of a viscous, yellow oil. ¹H NMR (CDCl₃, 250 MHz) δ 7.15 (d, J= 8.8 Hz, 1H), 6.98 (s, 1H), 6.83 (d, J= 8.8 Hz, 1H), 5.9 (m, 1H), 5.15 (m, 2H), 4.62, (m, 2H), 3.88 (s, 3H), 3.21 (t, J= 8.1 Hz, 2H), 2.63 (t, J= 8.1 Hz, 2H), 2.36 (s, 6H). ¹³C NMR (CDCl₃, 75 MHz) δ 151.9, 132.9, 132.6, 129.2, 128.6, 117.1, 114.4, 109.9, 108.2, 77.3, 61.9, 58.3, 48.7, 45.6, 24.1. IR (neat, cm⁻¹) 2936, 2855, 2815, 2768, 1644, 1610, 1461, 1426, 1249, 1066, 784. HRMS (El) calcd for C₁₆H₂₁N₂OІ: 384.0700, found: 384.0696 amu.
1-carboethoxy-4-iodo-3-iodomethyl-5-methoxyindoline (100).

Into a flask were placed 1-allyl-4-iodo-3-iodomethyl-5-methoxyindoline 98 (1.29 g, 2.83 mmol), sodium iodide (1.49 g, 10 mmol), ethyl chloroformate (1.0 mL, 1.14 g, 10.46 mmol) and acetone (20 mL). The mixture was heated to reflux for 90 min, cooled to RT, and poured into a separatory funnel containing ether (50 mL) and water (50 mL). The organic layer was collected and washed with water (2 x 50 mL), brine (50 mL), dried over MgSO₄ and the solvents were removed to leave a dark oil. The product was isolated by flash chromatography (9:1 hexane:ethyl acetate) to yield 1.22 g (89%) of a yellow, viscous oil. ^1H NMR (CDCl₃, 300 MHz) δ 7.8 (br, 1H), 6.71 (d, J= 9.0 Hz, 1H), 4.29 (br, 2H), 4.05 (m, 2H), 3.86 (s, 3H), 3.61 (m, 2H), 3.15 (t, J= 10.2 Hz, 1H), 1.37 (t, J= 7.0 Hz, 3H). ^13C NMR (C₆D₆, 75 MHz, obtained at 65 °C) δ 154.5, 152.9, 137.9, 137.2, 115.8, 111.3, 85.4, 61.5, 56.5, 54.0, 46.9, 14.6, 8.9. IR (neat, cm⁻¹) 2977, 1699, 1595, 1463, 1398, 1327, 1309, 1261, 1220, 1173, 1152, 1060. HRMS (EI) calcd for C₁₃H₁₅NO₃I₂: 486. 9145, found: 486.9146 amu.

101. 1-carboethoxy-4-iodo-3-iodomethyl-5-methoxyindoline 100 (243 mg, 0.500 mmol), DBU (0.08 mL, 81 mg, 0.534 mmol), and N,N-dimethylmethylene ammonium iodide (120 mg, 0.649 mmol) were employed according to general procedure II. The product was isolated by flash
chromatography (7:2:1 hexane:ethyl acetate:triethylamine) to yield 165 mg (79%) of a viscous, yellow oil.  

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 8.13 (br d, $J=9.3$ Hz, 1H), 7.49 (s, 1H), 6.88 (d, $J=9.3$ Hz, 1H), 4.47 (q, $J=6.9$ Hz, 2H), 3.92 (s, 3H), 3.17 (t, $J=7.8$ Hz, 2H), 2.66 (t, $J=7.8$ Hz, 2H), 2.36 (s, 6H), 1.45 (t, $J=6.9$ Hz, 3H).  

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 154.3, 150.2, 132.5, 131.6, 125.5, 120.7, 115.6, 108.8, 77.2, 63.1, 60.4, 57.6, 45.6, 24.6, 14.4. IR (neat, cm$^{-1}$) 3120, 2975, 2938, 2857, 2817, 2767, 1732, 1603, 1583, 1557, 1455, 1417, 1379, 1252, 1105, 1058, 842, 795, 732. HRMS (EI) calcd for C$_{16}$H$_{20}$N$_2$O$_3$I (M-H$^+$): 415.0521, found: 415.0523 amu.

103. Into a flask were placed 2-bromo-4-fluorobenzene 102 (4.581 g, 24.11 mmol), allyl bromide (6.30 mL, 8.81 g, 72.80 mmol), Na$_2$CO$_3$ (6.97 g, 65.76 mmol) and DMF (50 mL). The mixture was heated to reflux for 3 h, after which time it was allowed to cool and then poured into a separatory funnel containing ether (200 mL) and water (200 mL). The organic layer was collected and washed with water (3 x 200 mL), brine (200 mL), dried over MgSO$_4$, filtered and solvents removed to leave a brown oil. The product was isolated by Kugelrohr distillation (100-110 °C, 0.1 mm Hg) to give 6.06 g (94%) of a yellow oil.  

$^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 7.29 (dd, $J=2.7$, 8.4 Hz, 1H), 6.95 (m, 2H), 5.78 (m, 2H), 5.12 (m, 4H), 3.61 (d, $J=6.0$ Hz, 4H).  

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 158.5 (d, $^1$J$_{C-F}=243$ Hz), 145.1, 134.6, 124.8 (d, $^3$J$_{C-F}=7.9$ Hz), 121.9 (d, $^3$J$_{C-F}=9.07$ Hz), 120.5 (d, $^2$J$_{C-F}=23.6$ Hz), 117.7, 114.2 (d, $^2$J$_{C-F}=20$ Hz), 55.8. IR (neat, cm$^{-1}$) 4332, 3417, 3077, 3009, 2979, 2926, 2815, 1643, 1596,
To a Schlenk flask were added N,N-diallyl-2-bromo-4-fluoroaniline 103 (270 mg, 1 mmol), zirconocene (methyl) chloride (285 mg, 1.05 mmol) and THF (4 mL). The solution was cooled to -78 °C and t-butyl lithium (1.10 mL of a 1.89 M solution in pentane, 2.08 mmol) was added dropwise from a syringe. The resulting orange solution was stirred at -78 °C for 15 min and was then allowed to warm to RT and stir for an additional 1 h. The THF was removed in vacuo leaving an orange foam to which CH₂Cl₂ (4 mL) was added. Into a separate Schlenk flask were placed I₂ (636 mg, 2.51 mmol) and CH₂Cl₂ (4 mL). Both solutions were cooled to 0 °C and the I₂ solution was added to the solution of the metallacycle via cannula. The resulting dark mixture was allowed to stir at 0 °C for 4 h, after which time it was poured into a separatory funnel containing ether (75 mL) and Na₂SO₃ solution (75 mL). The organic layer was collected and washed with water (2 x 75 mL), brine (75 mL), dried over MgSO₄, filtered and the solvents removed to leave a dark, brown oil. The oil was dissolved in benzene (5 mL) and was placed into a flask to which DBU (0.164 mL, 0.167 g, 1.10 mmol) was added and the mixture was heated to 50 °C for 1 h. The DBU salts were filtered away and the benzene evaporated to leave a brown oil which was dissolved in CH₃CN (4 mL). To this solution was added N,N-dimethylmethylene ammonium iodide (237 mg, 1.28 mmol) and the mixture was heated to 45 °C for 2 h. It was then allowed to cool and poured into a separatory funnel containing ether (25 mL) and 2N NaOH (25 mL). The
organic layer was collected and washed with water (25 mL), brine (25 mL),
dried over MgSO₄, filtered and the solvents removed. The product was isolated
by flash chromatography (65:35 hexane:ethyl acetate then 60:35:5 hexane:ethyl
acetate:triethylamine) to give 201 mg (54%) of a yellow oil. ¹H NMR (CDCl₃,
300 MHz) δ 7.08 (dd, J=4.2, 9.0 Hz, 1H), 7.01 (s, 1H), 6.87 (t, J= 8.4 Hz, 1H), 5.9
(m, 1H), 5.10 (m, 2H), 4.6 (d, J= 5.4 Hz, 2H), 3.16 (t, J= 8.1 Hz, 2H), 2.61 (t, J= 8.1 Hz, 2H), 2.34 (s, 6H). ¹³C NMR (CDCl₃, 75 MHz) δ 156.2 (d, ¹JC-F=230
MHz), 145.2, 133.1, 132.8, 129.1, 128.5, 117.5, 115.1, 110.4 (d, ³JC-F= 9.23
Hz), 109.2 (d, ²JC-F= 28 Hz), 71.3 (d, ²JC-F= 28 Hz), 61.7, 48.9, 45.6, 23.8. IR
(neat, cm⁻¹) 3084, 2940, 2858, 2819, 1466, 1429, 1235, 1040, 925, 909, 789.

N,N-diallyl-2-bromo-4-(N,N-diallylamino)aniline  (108). Into a
flask were placed 2-bromo-4-nitroaniline (2.35 g, 10.83 mmol), iron powder
(2.78 g, 49.78 mmol), concentrated HCl (8.5 mL of a 37% solution, 3.77 g, 103.5
mmol) and ethanol (35 mL). The mixture was heated to reflux for 1 h, then
allowed to cool and poured into a separatory funnel containing ether (100 mL)
and 2N NaOH (50 mL). The organic layer was collected and washed with water
(2 x 50 mL), brine (50 mL), dried over MgSO₄, filtered and the solvents were
removed to leave a brown oil which was used without further purification. The
oil was added to a flask containing allyl bromide (5.60 mL, 7.82 g, 64.70 mmol),
Na₂CO₃ (9.16 g, 86.40 mmol) and DMF (70 mL). The mixture was heated to
reflux for 3 h, allowed to cool and poured into a separatory funnel containing
ether (100 mL) and water (100 mL). The organic layer was collected and washed with water (2 x 100 mL), brine (100 mL), dried over MgSO4, filtered and the solvents were removed by rotary evaporation. The product was isolated by Kugelrohr distillation (135-140 °C, 0.1 mm Hg) to give 2.62 g (70%) of a yellow oil. ¹H NMR (CDCl₃, 300 MHz) δ 6.89 (m, 2H), 6.55 (dd, ³J= 3.15, 8.75 Hz, 1H), 5.82 (m, 4H), 5.13 (m, 8H), 3.85 (d, ³J= 4.8 Hz, 4H), 3.56 (d, ³J= 6.6 Hz, 4H). ¹³C NMR (CDCl₃, 75 MHz) δ 146.2, 138.0, 135.4, 133.7, 124.8, 123.2, 117.0, 116.8, 116.2, 111.6, 56.3, 52.9. IR (neat, cm⁻¹) 3076, 2978, 2814, 1642, 1603, 1501, 1417, 1227, 992, 919. HRMS (El) calcd for C₁₈H₂₃BrN₂: 346.1045, found: 346.1047 amu.

110. To a Schlenk flask were added N,N-diallyl-4-diallylamino-2-bromoaniline 108 (368 mg, 1.06 mmol), zirconocene (methyl) chloride (300 mg, 1.10 mmol), and THF (4 mL). The solution was cooled to -78 °C and t-butyl lithium (1.13 mL of a 1.89 M solution in pentane, 2.14 mmol) was added dropwise via syringe. The resulting mixture was stirred at -78 °C for 15 min, after which time it was heated to 60 °C for 30 min, then it was allowed to cool to RT and stir for an additional 1 h. The THF was removed in vacuo to leave an orange foam to which CH₂Cl₂ (4 mL) was added. Into a separate Schlenk flask were placed iodine (662 mg, 2.61 mmol) and CH₂Cl₂ (10 mL). Both solutions were cooled to 0 °C and the iodine solution was added to the solution of the metallacycle via cannula and the resulting dark solution was allowed to stir at 0 °C for 4 h and an additional 12 h at RT. The mixture was then poured into a
separatory funnel containing ether (25 mL) and Na₂SO₃ solution (25 mL). The organic layer was collected and washed with water (25 mL), brine (25 mL), dried over MgSO₄, filtered and the solvents removed to leave a dark oil. The oil was dissolved in benzene (5 mL) and was placed in a flask to which DBU (0.180 mL, 183 mg, 1.20 mmol) was added and the mixture was heated to 50 °C for 1 h. The DBU salts were filtered away and the benzene was removed via rotovap to leave a brown oil which was dissolved in CH₃CN (4 mL). To the CH₃CN solution was added N,N-dimethylmethylene ammonium iodide (240 mg, 1.30 mmol) and the mixture was heated to 45 °C for 2 h. The solution was allowed to cool and was poured into a separatory funnel containing ether (25 mL) and 2N NaOH (25 mL). The organic layer was collected and washed with water (25 mL), brine (25 mL), dried over MgSO₄, filtered and the solvents removed. The product was purified by flash column (7:3 hexane:ethyl acetate then 65:35:5 hexane: ethyl acetate: triethylamine) to give 124 mg (26%) of a yellow oil. ¹H NMR (CDCl₃, 300 MHz) δ 7.14 (d, J= 9.0 Hz, 1H), 6.96 (s, 1H), 6.92 (d, J= 9.0 Hz, 1H), 5.90 (m, 3H), 5.15 (m, 6H), 4.59 (d, J= 5.41 Hz, 2H), 3.56 (d, J= 6.0 Hz, 4H), 3.23 (t, J= 7.8 Hz, 2H), 2.63 (t, J= 7.8 Hz, 2H), 2.35 (s, 6H). ¹³C NMR (CDCl₃, 75 MHz) δ 143.7, 135.6, 134.4, 133.2, 129.5, 127.9, 117.9, 117.4, 117.0, 115.3, 109.4, 94.3, 62.0, 57.7, 48.9, 45.7, 24.5. IR (neat, cm⁻¹) 3075, 2975, 2937, 2814, 1457, 1417, 1040, 992, 919, 733. HRMS (EI) calcd for C₂₁H₂₈N₃I: 449.1330, found: 449.1331 amu.

2-bromo-4-nitroaniline (114). Into a flask were placed 4-nitroaniline (4.32 g, 31.28 mmol), CH₂Cl₂ (120 mL), and CH₃OH (70 mL). Bu₄NBr₃ (16.94 g, 35.13 mmol) was added as a solid and in one portion at RT causing the solution to turn orange. After 5 min at RT, the mixture was poured into a separatory funnel containing CH₂Cl₂ (50 mL) and aqueous Na₂SO₃ solution (100 mL). The organic layer was collected and washed with water (2 x 100 mL),
brine (100 mL), dried over MgSO₄, filtered through a short plug of silica gel and the solvents were removed to leave 6.51 g (96%) of a yellow solid, mp=102-104 °C. Lit. mp ←ref = 104 °C. The spectral data were consistent with literature values. 

\[ ^1H\text{ NMR (CDCl}_3, 250 MHz) \delta 8.37 (d, J= 2.5 Hz, 1H), 8.03 (dd, J= 2.5, 8.8 Hz, 1H), 6.75 (d, J= 8.8 Hz, 1H), 4.85 (br s, 2H). \]

\[
\text{N,N-diallyl-2-bromo-4-methylaniline (118).} \quad \text{Into a round-bottom flask were placed 2-bromo-4-methylaniline (3.76 g, 20.21 mmol), allyl bromide (4.0 mL, 5.59 g, 46.22 mmol), Na}_2\text{CO}_3 (6.53 g, 61.61 mmol) and DMF (50 mL). The mixture was heated to reflux for 90 min, allowed to cool to RT then poured into a separatory funnel containing ether (250 mL) and water (250 mL). The organic layer was collected and washed with water (2 x 250 mL), brine (250 mL), dried over MgSO₄, and the solvents were removed to leave a yellow oil. The product was purified by Kugelrohr distillation (T= 100-105 °C, P= 0.1 mm Hg) to give 5.88 g (95%) of a clear oil.} \]

\[ ^1H\text{ NMR (CDCl}_3, 300 MHz) \delta 7.24 (d, J= 1.8 Hz, 1H), 6.84 (dd, J= 1.8, 7.8 Hz, 1H), 6.75 (d, J= 7.8 Hz, 1H), 5.64 (m, 2H), 4.95 (m, 4H), 3.49 (d, J= 6.0 Hz, 4H), 2.10 (s, 3H). \]

\[ ^13C\text{ NMR (CDCl}_3, 75 MHz) \delta 146.3, 134.9, 134.1, 134.0, 128.1, 123.8, 121.2, 117.4, 55.6, 20.3. \]

IR (neat, cm⁻¹) 3416, 3076, 3008, 2978, 2921, 2814, 1642, 1603, 1518, 1491, 1417, 1221, 1160, 1048, 992, 920. HRMS (El) calcd for C₁₃H₁₆BrN: 265.0467, found: 265.0466 amu.
1-allyl-4-iodo-3-iodomethyl-5-methylindoline (119). Into a Schlenk flask were placed N,N-diallyl-2-bromo-4-methylaniline 118 (565 mg, 2.12 mmol), zirconocene(methyl) chloride (640 mg, 2.35 mmol), and THF (6 mL). The mixture was cooled to -78 °C and t-BuLi (2.20 mL of a 1.96 M solution in pentane, 4.31 mmol) was added dropwise causing the solution to turn orange. The resulting mixture was stirred at -78 °C for 15 min, allowed to warm to RT, and was then heated to 45 °C for 1 h. The THF was removed in vacuo leaving an orange foam to which CH2Cl2 (3 mL) was added. Into a separate Schlenk flask were placed iodine (1.35 g, 5.31 mmol), and CH2Cl2 (4 mL). Both solutions were cooled to 0 °C and the iodine solution was transferred via cannula into the solution of the metallacycle. The resulting dark solution was allowed to stir for 4 h at 0°C and an additional 2 h at rt. The mixture was poured into a separatory funnel containing ether (50 mL) and saturated Na2SO3 solution (50 mL). The organic layer was collected and washed with water (2 x 50 mL), brine (50 mL), dried over MgSO4 and solvents removed to leave a dark oil. The product was purified via flash chromatography (95:5 hexane:ethyl acetate) to give 600 mg (64%) of a yellow oil. 1H NMR (CDCl3, 300 MHz) δ 6.97 (d, J= 8.1 Hz, 1H), 6.36 (d, J= 8.1 Hz, 1H), 5.83 (m, 1H), 5.23 (m, 2H), 3.74 (dd, J= 6.1, 15 Hz, 1H), 3.65-3.5 (m, 4H), 3.35 (t, J= 9.9 Hz, 1H), 3.10 (dd, J= 9.4, 11 Hz, 1H), 2.32 (s, 3H). 13C NMR (CDCl3, 75 MHz) δ 149.5, 135.6, 133.1, 130.0, 129.6, 117.8, 107.8, 100.1, 57.9, 51.6, 49.1, 26.9, 8.7. IR (neat, cm⁻¹) 3074, 3008, 2917, 2830, 1643, 1595, 1570, 1477, 1455, 1417, 1308, 1271,
1247, 1174, 924, 801. HRMS (El) calcd for C_{13}H_{15}I_{2}: 438.9298, found: 438.9298 amu.

120. 1-allyl-4-iodo-3-iodomethyl-5-methylindoline 119 (231 mg, 0.526 mmol), DBU (0.09 mL, 92 mg, 0.602 mmol), and N,N-diethylmethylene ammonium iodide (122 mg, 0.659 mmol) were employed according to general procedure II. The product was isolated by flash chromatography (60:35:5 hexane:ethyl acetate:triethylamine) to yield 168 mg (87%) of a viscous, yellow oil. \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 7.11 (d, \(J=8.3\) Hz, 1H), 6.96 (s, 1H), 5.92 (m, 1H), 5.05 (m, 2H), 4.60 (d, \(J=5.4\) Hz, 2H), 3.22 (t, \(J=7.8\) Hz, 2H), 2.65 (t, \(J=7.8\) Hz, 2H), 2.54 (s, 3H), 2.36 (s, 6H). \(^{13}\)C NMR (CDCl\(_3\), 75 MHz) \(\delta\) 134.9, 133.0, 132.2, 129.2, 127.8, 122.9, 117.2, 114.6, 109.3, 92.1, 62.1, 48.7, 45.7, 28.9, 24.6. IR (neat, cm\(^{-1}\)) 2967, 2938, 2855, 2814, 2765, 1551, 1461, 1417, 1294, 1262, 1206, 1038, 789, 606. HRMS (El) calcd for C_{16}H_{21}N_{2}I: 368.0751, found: 368.0748 amu.

1-carboethoxy-4-iodo-3-iodomethyl-5-methylindoline (121).
To a flask were added 1-allyl-4-iodo-3-iodomethyl-5-methylindoline 119 (516 mg, 1.18 mmol), sodium iodide (531 mg, 3.54 mmol), ethyl chloroformate (0.28 mL, 0.32 g, 2.95 mmol) and acetone (13 mL). The mixture was heated to reflux for 3 h, cooled to RT and poured into a separatory funnel containing ether (30
mL) and water (30 mL). The organic layer was collected and washed with water (2 x 30 mL), brine (30 mL), dried over MgSO₄ and the solvents were removed to leave a dark oil. The product was isolated by flash chromatography (9:1 pentane:ether) to yield 472 mg (85%) of a clear, viscous oil. ¹H NMR (CDCl₃, 300 MHz) δ 7.70 (br, 1H), 7.11 (d, J= 8.4 Hz, 1H), 4.29 (br q, J= 7.2 Hz, 2H), 4.10-3.95 (m, 2H), 3.65 (dd, J= 1.95, 10.1 Hz, 1H), 3.54 (t, J= 8.2 Hz, 1H), 3.11 (t, J= 10.1 Hz, 1H), 2.39 (s, 3H), 1.37 (t, J= 7.2 Hz, 3H). ¹³C NMR (CDCl₃, 125 MHz, obtained at 65 °C) δ 152.9, 140.9, 136.6, 135.3, 130.0, 115.2, 99.5, 61.5, 53.8, 47.6, 27.2, 14.6, 8.9. IR (neat, cm⁻¹) 2977, 2251, 1710, 1591, 1475, 1460, 1324. HRMS (El) calcd for C₁₃H₁₅N₂O₂: 470.9190, found: 470.9190 amu.

123. 1-carboethoxy-4-iodo-3-iodomethyl-5-methylindoline 121 (300 mg, 0.637 mmol), DBU (0.1 mL, 102 mg, 0.669 mmol), and N,N-dimethylmethylene ammonium iodide (143 mg, 0.773 mmol) were employed according to general procedure II. The product was purified by flash chromatography (60:35:5 hexane:ethyl acetate:triethylamine) to give 230 mg (91%) of a yellow, viscous oil. ¹H NMR (CDCl₃, 300 MHz) δ 8.10 (d, J= 8.1 Hz, 1H), 7.46 (s, 1H), 7.16 (d, J= 8.1 Hz, 1Hz), 4.45 (q, J= 7.1 Hz, 2H), 3.17 (t, J= 8.1 Hz, 2H), 2.64 (t, J= 8.1 Hz, 2H), 2.53 (s, 3H), 2.36 (s, 6H), 1.45 (s, J= 7.1 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ 150.3, 136.5, 134.3, 132.7, 126.4, 125.3, 121.6, 115.7, 92.1, 63.8, 61.2, 46.5, 29.1, 25.8, 14.7. IR (neat, cm⁻¹) 2977, 2942, 2818, 2733, 1739, 1459, 1434, 1379, 1259, 1099, 909, 838, 801, 733. HRMS (El) calcd for C₁₆H₂₁N₂O₂I: 400.0650, found: 400.0647 amu.
4-bromo-3-nitroanisole (141). Into a flask under a nitrogen atmosphere were placed copper(II)bromide (1.70 g, 7.61 mmol), t-butyl nitrite (1.25 mL, 1.08 g, 10.51 mmol), and acetonitrile (15 mL). The solution was heated to 65 °C and 4-methoxy-2-nitroaniline 135 (1.03 g, 6.10 mmol) in 15 mL of CH₃CN was added dropwise to the copper(II)bromide solution over 10 min. After the addition was complete, the solution was left at 65 °C for 1 h, after which time it was allowed to cool to RT and was then poured into a flask containing 20% aqueous HCl (100 mL). The aqueous solution was extracted with ether (3 x 100 mL), the ether layers were combined and were washed with water (3 x 100 mL), brine (1 x 100 mL), dried over MgSO₄ and the solvents were removed to leave a dark red oil. The product was purified via Kugelrohr distillation (T= 120-125 °C, P= 0.01 mm Hg) to give 1.24 g (88%) of a bright yellow solid: mp= 32-34 °C (lit. mp³ = 32-34 °C). ¹H NMR (CDCl₃, 250 MHz) δ 7.59 (d, J= 8.9 Hz, 1H), 7.37 (d, J= 2.95 Hz, 1H), 6.98 (dd, J= 2.95, 8.9 Hz, 1H), 3.86 (s, 3H). IR (neat, cm⁻¹) 3099, 3012, 2969, 2939, 2896, 2840, 1526, 1481, 1354, 1306, 1274, 1236, 1021, 801.

2-bromo-5-methoxyaniline. To a flask were added 141 (3.45 g, 14.84 mmol), iron powder (2.48 g, 44.48 mmol), ethanol (50 mL) and concentrated HCl (6.15 mL of a 37% solution). The reaction was heated to reflux and was shown by TLC analysis to be complete after 3 h. The solution was allowed to cool to RT and solid Na₂CO₃ was added until no more bubbling occurred. The solution was then extracted with ether (200 mL). The ether layer was collected and was washed with water (3 x 100 mL), brine (1 x 100 mL),
N,N-diallyl-2-bromo-5-methoxyaniline(142). A 2-neck, round-bottom flask equipped with a reflux condenser and a stir bar was placed under a nitrogen atmosphere. To the flask were added 2-bromo-5-methoxyaniline (2.60 g, 12.8 mmol), Na2CO3 (5.42 g, 51.1 mmol), allyl bromide (4.00 mL, 5.59 g, 46.2 mmol) and DMF (55 mL). The reaction mixture was heated to reflux and was shown by TLC analysis to be complete after 4 h. The solution was allowed to cool to RT and was extracted with ether (200 mL). The ether layer was collected and was washed with water (3 x 100 mL), brine (1 x 100 mL), dried over MgSO4 and the solvents removed to leave a dark oil. Further purification of the product was accomplished by Kugelrohr distillation (T= 100 °C, P= 0.01 mm Hg) to give 2.97 g (82%) of a yellow oil. 1H NMR (CDCl3, 250 MHz) δ 7.30 (d, J= 8.8 Hz, 1H), 6.47 (d, J= 2.8 Hz, 1H), 6.33 (dd, J= 2.8, 8.8 Hz, 1H), 5.71 (m, 2H), 5.05 (m, 4H), 3.63 (s, 3H), 3.56 (d, J= 6.0 Hz, 4H). 13C NMR (CDCl3, 75 MHz) δ 159.2, 149.9, 134.7, 133.8, 117.6, 111.4, 110.7, 109.2, 55.4, 55.2. IR (neat, cm⁻¹) 3040, 2990, 2968, 2946, 1627, 1578, 1449, 1429, 1322, 1277,
1186, 1144, 1046, 1007, 947, 845. HRMS (EI) calcd for C\textsubscript{13}H\textsubscript{16}BrNO: 281.0416, found: 281.0415 amu.

1-allyl-4-iodo-3-iodomethyl-6-methoxyindoline(146). Into a Schlenk flask equipped with a stir bar and under an argon atmosphere were placed 142 (2.85 g, 10.08 mmol), zirconocene (methyl) chloride (3.08 g, 11.34 mmol) and THF (60 mL). The solution was cooled to -78 °C and t-BuLi (12.23 mL of a 1.74 M solution in pentane, 21.33 mmol) was added dropwise from a syringe. The resulting solution was left at -78 °C for 15 min and was then slowly warmed to 45 °C. When the solution reached 45 °C, it began to bubble and darken considerably. The resulting solution was left at 45 °C until the bubbling ceased (15 min) and was then allowed to cool to RT and stir for 2 h. The THF was removed \textit{in vacuo} to leave an orange foam to which CH\textsubscript{2}Cl\textsubscript{2} (30 mL) was added. Into a separate Schlenk flask were placed iodine (7.06 g, 27.81 mmol) and CH\textsubscript{2}Cl\textsubscript{2} (50 mL). Both solutions were cooled to 0 °C and the iodine solution was added via cannula to the solution of the metallacycle. The resulting dark solution was maintained at 0 °C for 4 h, after which time it was added to a separatory funnel containing ether (200 mL) and a saturated Na\textsubscript{2}SO\textsubscript{3} solution (100 mL). The ether layer was collected and washed with water (3 x 100 mL), brine (1 x 100 mL), dried over MgSO\textsubscript{4} and the solvents removed to leave a dark brown oil. Further purification was accomplished by flash chromatography (95:5 hexane:ethyl acetate) to give 2.96 g (65%) of a yellow, viscous oil. \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 300 MHz) δ 6.50 (d, \textit{J} = 1.6 Hz, 1H), 5.96 (d, \textit{J} = 1.6 Hz, 1H), 5.80 (m, 2H), 5.22 (m, 2H), 3.72 (m, 1H), 3.50 (m, 5H), 3.08 (t,
\( J = 9.5 \text{ Hz, } 1\text{H}. \) \(^{13}\text{C} \text{NMR (CDCl}_3, 75 \text{ MHz) } \delta 162, 152, 133, 128, 118, 111, 95, 93, 58, 56, 51, 47, 10. \) IR (neat, cm\(^{-1}\)) 3077, 3000, 2954, 2933, 2832, 1608, 1568, 1478, 1335, 1208, 1171, 1039, 629. HRMS (EI) calcd for C\(_{13}\)H\(_{15}\)I\(_2\)NO: 454.9246, found:454.9243 amu.

1-allyl-6-hydroxy-4-iodo-3-iodomethylindoline (147). Into a Schlenk flask equipped with a stir bar and under an argon atmosphere were placed 146 (256 mg, 0.563 mmol) and CH\(_2\)Cl\(_2\) (3 mL). The solution was cooled to -78 °C and BBr\(_3\) (1.5 mL of a 1.0 M solution in CH\(_2\)Cl\(_2\), 1.50 mmol) was added dropwise from a syringe. The resulting yellow solution was maintained at -78 °C for 30 min, after which time it was allowed to slowly warm to RT and stirring was continued overnight. The solution was then cooled to 0 °C and methyl alcohol (3 mL) was slowly added. The whole mixture was then poured into a separatory funnel containing ethyl acetate (60 mL) and water (50 mL). The ethyl acetate layer was collected and was washed with water (3 x 100 mL) and brine (1 x 100 mL), dried over MgSO\(_4\) and the solvents removed to leave a brown oil. Further purification was accomplished by flash chromatography (4:1 hexane: ethyl acetate) to give 214 mg (86%) of a yellow oil. The \(^1\text{H} \text{NMR indicated that the sample contained approximately 2% ethyl acetate that could not be removed in vacuo without considerable decomposition due to the short half-life of the compound. HPLC analysis of the sample showed that the sample was >95% pure with respect to UV active compounds. Based on this data, we estimated the sample to be 95% pure.} \(^1\text{H} \text{NMR (CDCl}_3, 250 \text{ MHz) } \delta 6.48 (d, J = 1.92 \text{ Hz, } 1\text{H}), 5.83 (d, J = 1.92 \text{ Hz, } 1\text{H}), 5.75 (m, 1\text{H}), 5.23
(m, 2H), 4.81 (br s, 1H), 3.80-3.40 (m, 5H), 3.08 (t, J= 9.47 Hz, 1H). $^{13}\text{C}$ NMR (d$_8$-THF, 75 MHz) $\delta$ 163.6, 156.3, 134.2, 126.7, 117.8, 114.6, 97.0, 92.9, 58.9, 51.7, 48.0, 9.8. IR (neat, cm$^{-1}$) 3250 (br), 3080, 2975, 2872, 2680, 2237, 1603, 1578, 1479, 1452, 1336, 1287, 1190, 1170, 991, 821. HRMS (EI) calcd for C$_{12}$H$_{13}$I$_2$NO: 440.9090, found: 440.9090 amu.

1-allyl-4-iodo-1,2,7,7a-tetrahydrocycloprop[1,2-c]indol-4-one (148). Into a Schlenk flask under an argon atmosphere were placed a stir bar and sodium hydride (22 mg of a 60% suspension in oil, 0.55 mmol), which was washed with hexane (1 x 5 mL) and suspended in THF (2 mL). A solution of 147 (65 mg, 0.147 mmol in 1.5 mL THF) was added dropwise to the sodium hydride suspension at room temperature. The resulting solution was maintained at room temperature for 15 min, after which time it was filtered and the solvent removed to leave an off-white foam (41 mg, 89%). Compound 148 was estimated to be reasonably pure by $^1$H NMR. Compound 148 was unstable to chromatography and was only sparingly soluble in most solvents, making an estimate of the purity difficult. $^1$H NMR (d$_8$-THF, 250 MHz) $\delta$ 6.76 (s, 1H), 5.76 (m, 1H), 5.32 (s, 1H), 5.15 (m, 2H), 3.75-3.48 (m, partially obscured by solvent, 4H), 2.50 (dt, J= 5.4, 7.9 Hz, 1H), 1.75 (dd, J= 4.6, 7.9 Hz, 1H), 1.03 (t, J= 4.6 Hz, 1H). $^{13}\text{C}$ NMR (d$_8$-THF, 75 MHz) $\delta$ 183.9, 167.5, 143.0, 132.8, 118.3, 96.2, 68.2, 55.1, 49.4, 41.9, 28.0, 27.0. IR (neat, cm$^{-1}$) 2922, 2360, 1611, 1535, 1455, 1394, 1349, 1240, 1022, 988, 918, 868, 807. HRMS (EI) calcd for C$_{12}$H$_{12}$NOI: 312.9965, found: 312.9962 amu.
4-iodo-3-iodomethyl-6-methoxyindoline (153). Into a flask under a nitrogen atmosphere were placed 146 (121 mg, 0.266 mmol), sodium iodide (120 mg, 0.8 mmol), and acetone (4.5 mL). 1-chloroethyl chloroformate (0.07 mL, 0.09 g, 0.649 mmol) was added via syringe to the reaction mixture at room temperature, immediately causing a precipitate to form. The mixture was then heated to reflux and the progress of the reaction was followed by TLC analysis. After conversion to the intermediate carbamate was complete, the reaction mixture was allowed to cool to room temperature, filtered and the solvents removed to leave a dark oil. The oil was dissolved in 9:1 hexane:ethyl acetate, filtered through a column of silica gel collecting all of the strongly UV active compounds and the solvents were removed to leave a yellow oil. The oil was dissolved in 1,2-dichloroethane (3 mL) and was added to a flask under a nitrogen atmosphere that contained an equal volume of methyl alcohol. The mixture was heated to reflux until conversion of the carbamate to the amine was approximately 80% complete as judged by TLC analysis. As the reaction proceeds past this point, significant amounts of side products begin to form. In order to obtain optimal yields for this reaction, it is best not to let it proceed until all of the intermediate carbamate has been consumed. The solution was cooled to room temperature and was extracted with ether (1 x 75 mL). The ether layer was collected and was washed with water (3 x 100 mL), brine (1 x 100 mL), dried over MgSO4 and the solvents removed. The product was purified via flash column (using 85:15 hexane:ethyl acetate) to give 74 mg (67%) of a yellow oil that later solidified upon standing at -10 °C. Like
compound 147, compound 153 is not stable for long periods of time. The purity of 153 was estimated to be approximately 95% by both $^1$H NMR and HPLC analysis. $^1$H NMR (CDCl₃, 300 MHz) δ 6.59 (d, $J= 2.10$ Hz, 1H), 6.12 (d, $J= 2.10$ Hz, 1H), 3.72 (s, 3H), 3.70-3.4 (m, 5H), 3.16 (t, $J= 9.30$ Hz, 1H). $^{13}$C NMR (CDCl₃, 75 MHz) δ 161.3, 152.0, 126.9, 113.0, 96.5, 92.5, 55.6, 52.7, 48.1, 9.3. IR (neat, cm⁻¹) 3388 (br), 2935, 2864, 1600, 1567, 1484, 1436, 1331, 1297, 1197, 1169, 1112, 1035, 908, 821, 731. HRMS (El) calcd for C₁₀H₁₁NO₂: 414.8934, found: 414.8931 amu.

3-bromomethyl-1-carboethoxy-4-idoindole (170). Into a flask were placed 1-carboethoxy-4-iodo-3-iodomethylindoline 79 (980 mg, 2.14 mmol), DBU (0.35 mL, 356 mg, 2.34 mmol), and benzene (5 mL). The mixture was heated to 50 °C for 1 h, then filtered and the benzene was removed via rotary evaporation leaving a brownish solid. The solid was dissolved in CHCl₃ (5 mL), the solution cooled to 0 °C and NBS (402 mg, 2.26 mmol) was added as a solid in one portion. The resulting mixture was allowed to stir at 0 °C for 2 h, then it was poured into a separatory funnel containing CHCl₃ (15 mL) and water (15 mL). The organic layer was collected and washed with water (2 x 15 mL), brine (15 mL), dried over MgSO₄, filtered through a plug of silica (15 cm) and the solvents were removed via rotovap to leave 700 mg (80%) of a white solid, mp= 109-110 °C. An analytical sample was prepared by recrystallization from CH₃CN. $^1$H NMR (CDCl₃, 300 MHz) δ 8.22 (d, $J= 8.40$ Hz, 1H), 7.79 (d, $J= 8.10$ Hz, 1H), 7.00 (t, $J= 8.10$ Hz, 1H), 4.90 (s, 2H), 4.46 (q, $J= 7.05$ Hz, 2H), 1.45 (t, $J= 7.05$ Hz, 3H). $^{13}$C NMR (CDCl₃, 75 MHz) δ 149.7, 136.3, 135.0, 129.1, 127.8, 126.2, 118.7, 115.3, 84.2, 63.8, 25.1, 14.5. IR (film, cm⁻¹) 1734, 1425.
Anal. Calcd for C$_{12}$H$_{11}$BrNO$_2$I: C, 35.32; H, 2.72; N, 3.43. Found: C, 35.41; H, 2.68; N, 3.64.

1-carboethoxy-3-hydroxymethyl-4-iodoindole (188). Into a flask were placed 3-bromomethyl-1-carboethoxy-4-iodoindole 170 (1.23 g, 3.01 mmol), water (5 mL, 5.00 g, 278 mmol), and CH$_3$CN (16 mL). The suspension was heated to 50 °C at which time it became a homogeneous, yellow solution. After 10 min at 50 °C, TLC analysis showed no remaining starting material. The reaction mixture was allowed to cool to RT, and was then poured into a separatory funnel containing ethyl acetate (20 mL) and water (20 mL). The organic layer was collected and washed with water (2 x 20 mL), brine (20 mL), dried over MgSO$_4$, filtered and the solvents were removed to leave 825 mg (79%) of a yellow solid, mp= 109-111 °C. An analytical sample was prepared by recrystallization from ethanol to give white solid. $^1$H NMR (CDCl$_3$, 300 MHz) δ 8.18 (d, J= 8.10 Hz, 1H), 7.62 (m, 2H), 6.96 (t, J= 7.95 Hz, 1H), 4.94 (d, J= 5.40 Hz, 2H), 4.43 (q, J= 7.20 Hz, 2H), 2.39 (t, J= 6.30 Hz, 1H), 1.42 (t J= 7.20 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 150.0, 136.5, 134.0, 130.8, 125.7, 125.6, 121.5, 115.2, 84.1, 63.5, 56.5, 14.4. IR (film, cm$^{-1}$) 3407 (br), 1735, 1422. Anal. Calcd for C$_{12}$H$_{12}$NO$_3$I: C, 41.76; H, 3.50; N, 4.06. Found: C, 41.70; H, 3.45; N, 4.22.
192. Into a flask were placed 1-carboethoxy-3-hydroxymethyl-4-iodoindole 188 (349 mg, 1.01 mmol), CH$_2$Cl$_2$ (3 mL) and MnO$_2$ (2.27 g, 26.11 mmol). After 45 min at RT, TLC analysis showed no remaining starting material. The reaction mixture was filtered through celite and the solvent was removed via rotovap to leave a white solid. The product was recrystallized from ethanol to yield 312 mg (90%) of a white solid, mp= 124-125 °C. $^1$H NMR (CDCl$_3$, 300 MHz) δ 11.19 (s, 1H), 8.40 (s, 1H), 8.31 (d, $J$= 8.40 Hz, 1H), 7.81 (d, $J$= 7.50 Hz, 1H), 7.08 (t, $J$= 7.95 Hz, 1H), 4.51 (q, $J$= 6.90 Hz, 2H), 1.47 (t, $J$= 6.90 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 185.6, 149.5, 136.8, 135.8, 131.9, 130.2, 126.4, 121.2, 115.3, 83.2, 64.6, 14.4. IR (film, cm$^{-1}$) 2985, 1758, 1664. Anal. Calcd for C$_{12}$H$_{10}$NO$_3$I: C, 42.01; H, 2.94; N, 4.08. Found: C, 42.24; H, 3.12; N, 4.15.

193. Into an autoclave were placed 1-carboethoxy-3-hydroxymethyl-4-iodoindole 188 (116 mg, 0.336 mmol), C$_2$Pd(PPh$_3$)$_2$ (23 mg, 0.03 mmol), Et$_3$N (0.20 mL, 145 mg, 1.43 mmol) and DMF (2 mL). The autoclave was flushed three times with CO and then pressurized to 600 psig. The mixture was heated to 35-45 °C for 16 h, then allowed to cool to rt and poured into a separatory funnel containing ether (30 mL) and water (30 mL). The organic layer was collected and washed with water (2 x 30 mL), brine (30 mL), dried over MgSO$_4$, filtered and the solvents removed via rotary evaporation to leave an orange solid. The product was recrystallized from ethanol to give 64 mg (78%) of a white solid, mp= 156-157 °C. $^1$H NMR (CDCl$_3$, 300 MHz) δ 8.10 (bs, 1H), 8.08 (d, $J$= 7.20 Hz, 1H), 7.43 (m, 2H), 5.78 (d, $J$= 1.50 Hz, 2H), 4.47 (q, $J$= 6.90 Hz, 2H), 1.47 (t, $J$= 6.90 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 162.3,
150.8, 132.7, 131.3, 126.3, 122.5, 120.2, 119.1, 117.0, 110.6, 68.4, 63.9, 14.4.
IR (film, cm\(^{-1}\)) 2980, 2935, 1737, 1709, 1634. Anal. Calcd for C\(_{13}\)H\(_{11}\)NO\(_4\): C, 63.67; H, 4.52; N, 5.71. Found: C, 63.45; H, 4.46; N, 5.71.

![Chemical Structure](image)

**205.** Into a flask were placed sodium hexamethyldisilylamide (413 mg, 2.25 mmol), and THF (3 mL). 3-bromomethyl-1-carboethoxy-4-iodoindole 170 (810 mg, 1.99 mmol, 0.884 eq) in THF (2 mL) was added dropwise at RT. After 1 h at RT, the mixture was poured into a separatory funnel containing ether (20 mL) and water (20 mL). The organic layer was collected and washed with water (2 x 20 mL), brine (20 mL), dried over MgSO\(_4\), filtered and the solvents were removed to leave a yellow oil which was used without further purification. \(^1\)H NMR (CDCl\(_3\), 300 MHz) \(\delta\) 8.21 (d, \(J = 8.40\) Hz, 1H), 7.65 (d, \(J = 7.80\) Hz, 1H), 7.57 (s, 1H), 6.93 (t, \(J = 8.10\) Hz, 1H), 4.52 (d, \(J = 1.50\) Hz, 2H), 4.46 (q, \(J = 7.20\) Hz, 2H), 1.45 (t, \(J = 7.20\) Hz, 3H), 0.14 (s, 18H).

![Chemical Structure](image)

**206.** The bis(silyl) amine 205 was placed into a flask with CH\(_2\)Cl\(_2\) (3 mL), ethanol (2.5 mL), and 2N HCl (2.5 mL) was added causing the solution to turn cloudy green. The solution was allowed to stir at RT for 1 h and was then poured into a separatory funnel containing ether (20 mL) and water (5 mL). 2N NaOH was added until the aqueous layer was basic to pH paper. The organic layer was collected and washed with water (2 x 20 mL), brine (20 mL), dried over MgSO\(_4\), filtered and the solvents removed to provide amine 206 as a
yellow oil that was used without further purification. $^{1}$H NMR (CDCl$_3$, 300 MHz) $\delta$ 8.22 (d, $J$= 8.40 Hz, 1H), 7.68 (d, $J$= 7.50 Hz, 1H), 7.61 (s, 1H), 6.97 (t, $J$= 8.10 Hz, 1H), 4.44 (q, $J$= 7.20 Hz, 2H), 4.16 (s, 2H), 1.60 (br, 2H), 1.43 (t, $J$= 7.20 Hz, 3H).

207. Into an autoclave were placed a stir bar, amine 206 (1.99 mmol), Cl$_2$Pd(PPh$_3$)$_2$ (67 mg, 0.10 mmol) Et$_3$N (1.17 mL, 849 mg, 8.39 mmol), and DMF (3 mL). The autoclave was flushed with CO (3 x 1000 psig) and was then pressurized to 600 psig. The mixture was heated to 40-45 °C and the pressure was readjusted to 600 psig. The reaction was allowed to stir at 40-45 °C for 18 h. The mixture was allowed to cool to RT, and was poured into a seperatory funnel containing ether (20 mL) and water (20 mL). The organic layer was collected and washed with water (2 x 20 mL), brine (20 mL), dried over MgSO$_4$, filtered through a small plug of silica and the solvents were removed to leave an orange oil. The product was purified by flash chromatography (100% ethyl acetate) to leave 50 mg of a white solid which was recrystallized from ethanol to yield white crystals, mp= 243-245 °C. $^{1}$H NMR (CDCl$_3$, 300 MHz) $\delta$ 8.05 (br, 1H), 7.77 (d, $J$= 7.50 Hz, 1H), 7.41 (m, 2H), 6.00 (br, 1H), 4.90 (s, 2H), 4.50 (q, $J$= 7.20 Hz, 2H), 1.47 (t, $J$= 7.20 Hz, 3H). These are preliminary results and are not optimized.
210. Into a flask were placed 3-bromomethyl-1-carboethoxy-4-iodoindole 170 (964 mg, 2.36 mmol), dimethylmalonate (1.30 mL, 1.50 g, 11.37 mmol), K$_2$CO$_3$ (1.66 g, 12.01 mmol), 18-crown-6 (47 mg, 0.18 mmol) and benzene (10 mL). The resulting mixture was allowed to stir at RT for 4 h, then poured into a separatory funnel containing ether (30 mL) and water (30 mL). The organic layer was collected and washed with water (2 x 30 mL), brine (30 mL), dried over MgSO$_4$, filtered and the solvents were removed via rotary evaporation to leave a brownish solid. The product was recrystallized from ethanol to yield 889 mg (82%) of a white solid, mp= 102-104 °C. $^1$H NMR (CDCl$_3$, 300 MHz) δ 8.21 (d, $J$= 8.40 Hz, 1H), 7.67 (d, $J$= 7.50 Hz, 1H), 7.47 (s, 1H), 6.96 (t, $J$= 8.40 Hz, 1H), 4.45 (q, $J$= 6.90 Hz, 2H), 4.01 (t, $J$= 7.80 Hz, 1H), 3.71 (s, 6H), 3.53 (d, $J$= 7.50 Hz, 2H), 1.43 (t, $J$=6.90 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz) δ 168.9, 149.9, 136.3, 134.6, 130.4, 125.9, 125.7, 117.5, 115.2, 84.3, 63.5, 52.9, 52.6, 24.8, 14.5. IR (film, cm$^{-1}$) 2952, 1737, 1420. Anal. Calcd for C$_{17}$H$_{18}$NO$_6$I: C, 44.46; H, 3.95; N, 3.05. Found: C, 44.60; H, 4.06; N, 3.19.

212. Into a flask were placed 3-bromomethyl-1-carboethoxy-4-iodoindole 170 (110 mg, 0.27 mmol), ethyl cyanoacetate (0.43 mL, 457 mg, 4.04 mmol) K$_2$CO$_3$ (43 mg, 0.311 mmol), 18-crown-6 (12 mg, 0.05 mmol) and benzene (3 mL). The resulting mixture was allowed to stir at RT for 15 h, then it wa poured into a separatory funnel containing ether (15 mL) and water (15 mL). The organic layer was collected and washed with water (2 x 15 mL), brine (15 mL), dried over MgSO$_4$, filtered and the solvents were removed via rotary
evaporation to leave a yellow oil. The product was isolated by flash chromatography (85:15 hexane: ethyl acetate) to give 88 mg (75%) of a yellow oil. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 8.27 (d, $J=8.10$ Hz, 1H), 7.68 (d, $J=6.90$ Hz, 1H), 7.67 (s, 1H), 7.01 (t, $J=8.10$ Hz, 1H), 4.46 (q, $J=7.40$ Hz, 2H), 4.27 (q, $J=7.40$ Hz, 2H), 4.10 (dd, $J=6.30$, 9.30 Hz, 1H), 3.83 (dd, $J=6.30$, 14.4 Hz, 1H), 3.27 (dd, $J=9.30$, 14.4 Hz, 1H), 1.45 (t, $J=7.40$ Hz, 3H), 1.30 (t, $J=7.40$ Hz, 3H). $^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 165.4, 149.9, 136.6, 134.8, 130.0, 127.1, 126.2, 116.1, 115.6, 115.5, 84.0, 63.7, 62.9, 39.4, 25.9, 14.3, 14.0. IR (film, cm$^{-1}$) 2983, 2250, 1747, 1465. HRMS (EI) calcd for C$_{17}$H$_{17}$N$_2$O$_4$I: 440.0235. Found: 440.0237 amu.

216. To a flask were added 210 (197 mg, 0.43 mmol), triphenylphosphine (21 mg, 0.08 mmol), trimethylsilylacetylene (65 $\mu$L, 0.47 mmol), copper (I) iodide (18 mg, 0.09 mmol), triethylamine (0.19 mL, 1.39 mmol), palladium acetate (7 mg, 0.03 mmol) and DMF (4 mL). The mixture was heated to 70 °C for 14 h, after which time it was allowed to cool and was poured into a separatory funnel containing ether (20 mL) and saturated CuSO$_4$ solution (20 mL). The organic layer was collected and washed with water (20 mL), brine (20 mL), dried over MgSO$_4$, filtered and the solvents were removed to leave a dark oil. The product was isolated by flash chromatography (4:1 hexane:ethyl acetate) to give 153 mg (84%) of a yellow oil. This material was estimated to be greater than 94% pure by $^1$H NMR. An analytical sample was prepared by recrystallization from hexane to give a white powder, mp= 60-61 °C. $^1$H NMR
(CDCl$_3$, 300 MHz) $\delta$ 8.16 (d, $J= 8.4$ Hz, 1H), 7.39 (s, 1H), 7.37 (dd, $J= 7.6$, 1.0 Hz, 1H), 7.22 (t, $J= 8.2$, 7.6 Hz, 1H), 4.44 (q, $J= 7.10$ Hz, 2H), 4.05 (t, $J= 8.20$ Hz, 1H), 3.68 (s, 6H), 3.57 (d, $J= 8.20$ Hz, 2H), 2.87 (t, $J= 7.10$ Hz, 3H), 0.23 (s, 9H).

$^{13}$C NMR (CDCl$_3$, 75 MHz) $\delta$ 169.1, 150.5, 136.0, 129.9, 128.8, 124.6, 124.3, 117.8, 115.9, 114.7, 103.4, 98.1, 63.3, 52.5, 52.4, 24.9, 14.3, 0.32. IR (KBr, cm$^{-1}$) 2962, 2144, 1733.

214. Into an autoclave were placed indole 210 (220 mg, 0.479 mmol), Cl$_2$Pd(PPh$_3$)$_2$ (26 mg, 0.04 mmol), Et$_3$N (0.28 mL, 203 mg, 2.0 mmol), and CH$_3$CN (2 mL). The autoclave was flushed three times with CO and then pressurized to 600 psig. The mixture was then heated to 95-100 °C, and the pressure was readjusted to 600 psig. The reaction was allowed to stir at 95-100 °C for 16 h, then allowed to cool to RT and poured into a separatory funnel containing ether (50 mL) and water (50 mL). The organic layer was collected and washed with water (2 x 50 mL), brine (50 mL), dried over MgSO$_4$, filtered and the solvents removed via rotovap to leave a brown oil. The product was isolated by flash chromatography (4:1 hexane: ethyl acetate) to yield 117 mg (68%) of a white solid, mp= 138-140 °C. An analytical sample was prepared by recrystallization from ethanol. $^1$H NMR (CDCl$_3$, 300 MHz) $\delta$ 8.18 (br, 1H), 7.74 (d, $J= 7.50$ Hz, 1H), 7.54 (bs s, 1H), 7.43 (t, $J= 7.95$ Hz, 1H), 4.48 (q, $J= 7.20$ Hz, 2H), 3.85 (d, $J= 1.20$ Hz, 2H), 1.46 (t, $J= 7.20$ Hz, 3H). $^{13}$C NMR (C$_6$D$_6$, 75 MHz) $\delta$ 188.9, 168.3, 150.4, 134.3, 133.3, 126.0, 125.9, 122.6, 120.6, 120.3, 112.6, 68.7, 63.3, 53.0, 29.5, 14.3. IR (film, cm$^{-1}$) 3125, 2956, 1732, 1694,

217. Into a flask were placed 3-bromomethyl-1-carboethoxy-4-iodoindole 170 (456 mg, 1.12 mmol), KCN (78 mg, 1.20 mmol) and DMF (3 mL). The mixture was heated to 50 °C and was allowed to stir overnight. The mixture was then poured into a separatory funnel containing ether (25 mL) and water (25 mL). The organic layer was collected and washed with water (2 x 25 mL), brine (25 mL), dried over MgSO₄, filtered and the solvents were removed to leave a yellow oil. The product was purified by flash chromatography (9:1 hexane: ethyl acetate) to give 302 mg (76%) of a white solid, mp= 122-124 °C. An analytical sample was prepared by recrystallization from ethanol to give a white solid. ¹H NMR (CDCl₃, 300 MHz) δ 8.25 (d, J= 8.40 Hz, 1H), 7.78 (s, 1H), 7.67 (d, J= 7.50 Hz, 1H), 7.01 (t, J= 7.80 Hz, 1H), 4.48 (q, J= 7.20 Hz, 2H), 4.16 (d, J= 1.50 Hz, 2H), 1.46 (t, J= 7.20 Hz, 3H). ¹³C NMR (CDCl₃, 75 MHz) δ 149.7, 136.4, 134.6, 129.3, 126.4, 125.9, 116.9, 115.5, 111.2, 83.8, 63.9, 16.6, 14.5. IR (film, cm⁻¹) 2987, 2249, 1743, 1422, 1377. Anal. Calcd for C₁₃H₁¹N₂O₂: C, 44.09; H, 3.13; N, 7.91. Found: C, 43.84; H, 2.81; N, 7.62.

236. Into a flask were placed bis-lactim ether 224 (107 mg, 0.504 mmol) and THF (2 mL). The solution was cooled to -78 °C and n-BuLi (0.2 mL of a
2.62 M solution in hexane, 0.524 mmol, 1.04 eq) was added. The resulting solution was allowed to stir at -78 °C for 20 min, then 170 (168 mg, 0.412 mmol, 0.817 eq) in 1 mL THF was added dropwise via syringe over 1 min. The mixture was allowed to stir at -78 °C for 16 h, then it was allowed to warm to RT and was poured into a separatory funnel containing ether (20 mL) and water (20 mL). The organic layer was collected and washed with water (2 x 20 mL), brine (20 mL), dried over MgSO4, filtered and the solvents were removed to leave a yellow oil. Analysis of the 1H NMR spectrum of the crude reaction mixture showed a 4.5:1 mixture of diastereomers. The diastereomers were separated by flash chromatography (9:1 hexane:ethyl acetate) to give a yellowish oil. 1H NMR (CDCl3, 300 MHz) δ 8.25 (d, J= 8.40 Hz, 1H), 7.70 (d, J= 7.50 Hz, 1H), 7.61 (s, 1H), 6.95 (t, J= 7.95 Hz, 1H), 4.45 (q, J= 7.50 Hz, 2H), 4.33 (m, 1H), 4.2-3.8 (m, 6H), 3.07 (dd, J= 9.0, 15.1 Hz, 1H), 2.25 (m, 1H), 1.44 (t, J= 7.20 Hz, 3H), 1.27 (t, J= 6.90 Hz, 3H), 1.21 (t, J= 6.90 Hz, 3H), 1.04 (d, J= 6.60 Hz, 3H), 0.72 (d, J= 6.60 Hz, 3H). 13C NMR (CDCl3, 75 MHz) δ 163.3, 163.1, 150.3, 136.1, 134.9, 131.4, 126.2, 125.2, 118.7, 115.1, 84.8, 77.2, 63.1, 60.9, 60.7, 60.5, 55.9, 31.9, 30.1, 19.1, 16.8, 14.3, 12.5. IR (film, cm⁻¹) 2973, 2869, 1742, 1690, 1596, 1463, 1420, 1248, 1183, 1093, 774. HRMS (El) Calcd for C23H30N3O4I: 539.1283, found: 539.1283.
References


84. While this work was in progress a similar transformation was reported with benzofurans: Aso, M.; Ojida, A.; Yang, G.; Cha, O.J.; Osawa, E.; Kanematsu, K. *J. Org. Chem.* **1993**, *58*, 3960.


