Novel Approaches to Functionalized Indoles and Polysubstituted Aromatic Compounds

By Andrew J. E. Peat

B. S. Chemistry, Miami University, 1992

Submitted to the Department of
Chemistry in Partial Fulfillment of the
Requirements for the Degree of

DOCTOR OF PHILOSOPHY IN
ORGANIC CHEMISTRY

at the

Massachusetts Institute of Technology

August 1997

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Abstract

A method developed by Buchwald and co-workers for the formation of polyfunctionalized heterocyclic and aromatic compounds has been investigated for its utility in organic synthesis. The procedure involves the insertion reactions of unsaturated molecules into the carbon-metal bonds of a metallocene-stabilized benzyne complex. The resulting metallacyclic intermediate reacts with a variety of electrophiles, providing access to synthetically valuable precursors which have been used to prepare a number of structurally interesting molecules, as well as several natural products.

Initially, we investigated the reactions of 3,4-diiodoindoline derivatives, which are readily prepared via intramolecular insertion of an olefin into a zirconocene-benzyne complex. These compounds served as useful intermediates for the construction of more complex 3- and 4-substituted indole compounds, which include an enantiomerically-enriched tryptophan, as well as an intermediate in the total synthesis of the claviciptic acids.

In addition, we have synthesized a variety of tricyclic indole derivatives which contain a common structural subunit, a tetrahydropyrroloquinoline. These compounds have received considerable attention since several exhibit potent cytotoxity against human tumor cell lines, presumably acting as DNA topoisomerase II inhibitors. The key steps involve intramolecular insertion of an olefin into the Zr–C bond of a benzyne-complex, as well as the Pd-catalyzed intramolecular aryl amination reaction which has been developed in our laboratories. This approach has resulted in the syntheses of dehydrobufotenine, makaluvamine A, B, and C, and also damirones A and B.

Lastly, we have developed a novel method for the construction of polysubstituted aromatic compounds. The procedure involves the combination of directed lithiation methodology with our previously developed zirconium-benzyne chemistry, which allows for the facile and efficient synthesis of di- and trisubstituted aromatic derivatives from monofunctionalized arene precursors.

Thesis Supervisor: Stephen L. Buchwald

Title: Camille & Henry Dreyfus Professor of Chemistry

Acknowledgments

First, I would like to thank my research supervisor Stephen Buchwald. It has been a pleasure working in his laboratories for the last five years, and if I had to do this all over again (thank God I don't), I would definitely come back to work for him. He has given me a great deal of advice and has been immensely patient when things were not working well. In addition, I would like to thank him for being a friend, as well as an advisor, which has made coming to work a great deal more fun.

During my stay at MIT, I have been fortunate to make some very good friends. In the current group, I would like to thank the following: Joseph Sadighi, Ross Widenhoefer, Mike (Shirt Boy) Frid, John Wolfe, Michael Palucki, and Natasha Kablaoui. They have provided a great deal of chemistry advice, and more importantly, they drink a lot of beer. I will dearly miss going to the Muddy Charles Pub for a medicinal/motivational/inspirational beer. I would like to especially thank Joseph Sadighi. In addition to being a perfect bay-mate, he saved my life by allowing me to stay at his house for my last month at MIT. I will never forget the day we left lab to ride in the local radio station (WAAF) rock-bus with a twelve-pack of beer. You have been a great friend, and I hope that we will stay in touch. I also would like to thank Jeff Marcoux. He has spent hours helping me format this thesis, as well as solving all of my computer problems.

From the old group members, I would like to thank Jeff (Turtle) Depinto, Roger Rennels, Nancy Lee, Jeff Tidwell, and Rick Broene. They helped make my early years in the Buchwald group fun, and taught me how to stay alive in graduate school.

There are three people in particular who deserve my deepest thanks, they are my mother and father, and my wife Jennifer. Throughout the years, my parents have been at my side through the good times and the bad. They have provided advice when needed, provided optimism when I was down, and listened when I needed a friend. But mostly I thank them for their greatest gift of all, their time. They were never too busy to drive me to practice, to help with my homework, or to just sit and talk. I hope I can be half as good a parent to my children as they have been to me. I would also like to thank my brother, David, who has been a great friend and makes me very proud. It makes me happy that we are growing closer as the years pass by.

Lastly, but most importantly, I want to thank my beautiful wife, Jennifer. Since the first time we dated, January 8, 1988, she has made my life truly special. You are a constant reminder that I am a very lucky person, and that life is good. Without your unconditional love, support, and patience I would not be in this position today. Although I can never repay you for what you have given me, I will spend my life trying to make you as happy as you have made me. You are wonderful Jennifer, and the thought of starting a new life with you makes the last five years worthwhile. I love you.

Preface

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

Tidwell, J. H; Peat, A. J.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 7164.

Peat, A. J.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 1028.

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Introduction

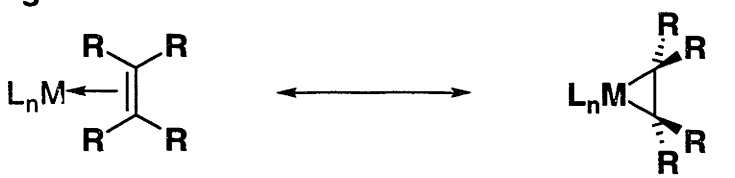
In the last ten years, much of the research conducted in the Buchwald laboratories has focused on the synthesis of zirconocene-complexes of unsaturated molecules; e.g., cyclobutene,[1] cyclopentyne,[2] and benzyne.[3] It should be noted that in the free state, these organic species are quite unstable. For example, "free" benzyne has been estimated to have 80 kcal/mol of strain energy;[4] however, this strain is greatly diminished upon coordination to various metals due to the unique bonding that exists in these complexes. Dewar, Chatt, and Duncanson have proposed a model to explain this bonding which involves the frontier molecular orbitals of the metal and the π-orbitals of the organic fragment (Figure 1).[5] In the case of an alkene complex, one interaction involves σ-donation from the filled π-orbital of the olefin into the empty d-orbital of the

Figure 1: Dewar, Chatt, Duncanson Model

metal. The second involves the backbonding of electron-density from the metal's filled d-orbital to the empty π*-orbital of the alkene, which results in an

increase in the strength of metal-olefin bond and a decrease in strength of the olefin π-bond. The actual bonding in metal-olefin complexes lies somewhere in between the two extremes depicted in Figure 2. If the alkene is bound to an electron-deficient metal-center, only a small amount of backbonding occurs and the olefin displays little, if any, structural changes as compared with the unbound structure (Extreme A). However, if the olefin is complexed to an electron-rich metal, a great deal of backbonding occurs, resulting in the lengthening of the C–C bond and a distortion in the hybridization of the olefinic carbons (Extreme B). These complexes are best described as metallacyclopropanes.

Figure 2



Extreme A Extreme B

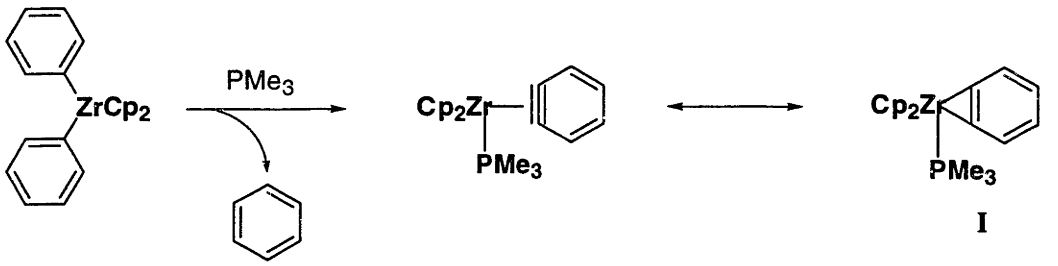
The interaction between metal-fragments and a benzyne unit can be described in an analogous fashion. Backbonding from electron-rich metals to the benzyne greatly reduces the strain energy, thereby increasing the stability of the complex as illustrated in the transition-metal benzyne complexes isolated and characterized by Schrock[6] and Bennett[7] (Figure 3). In addition,

Figure 3

Schrock Bennett

Buchwald and Watson were able to trap a zirconocene-stabilized benzyne complex with PMe_3, as the isolable 18-electron intermediate **I** (Scheme 1).[3] X-ray analysis revealed that the two Zr–C bond lengths were approximately the same distance, and the C–C bond angles were approximately the same as those observed in benzene. These results indicate

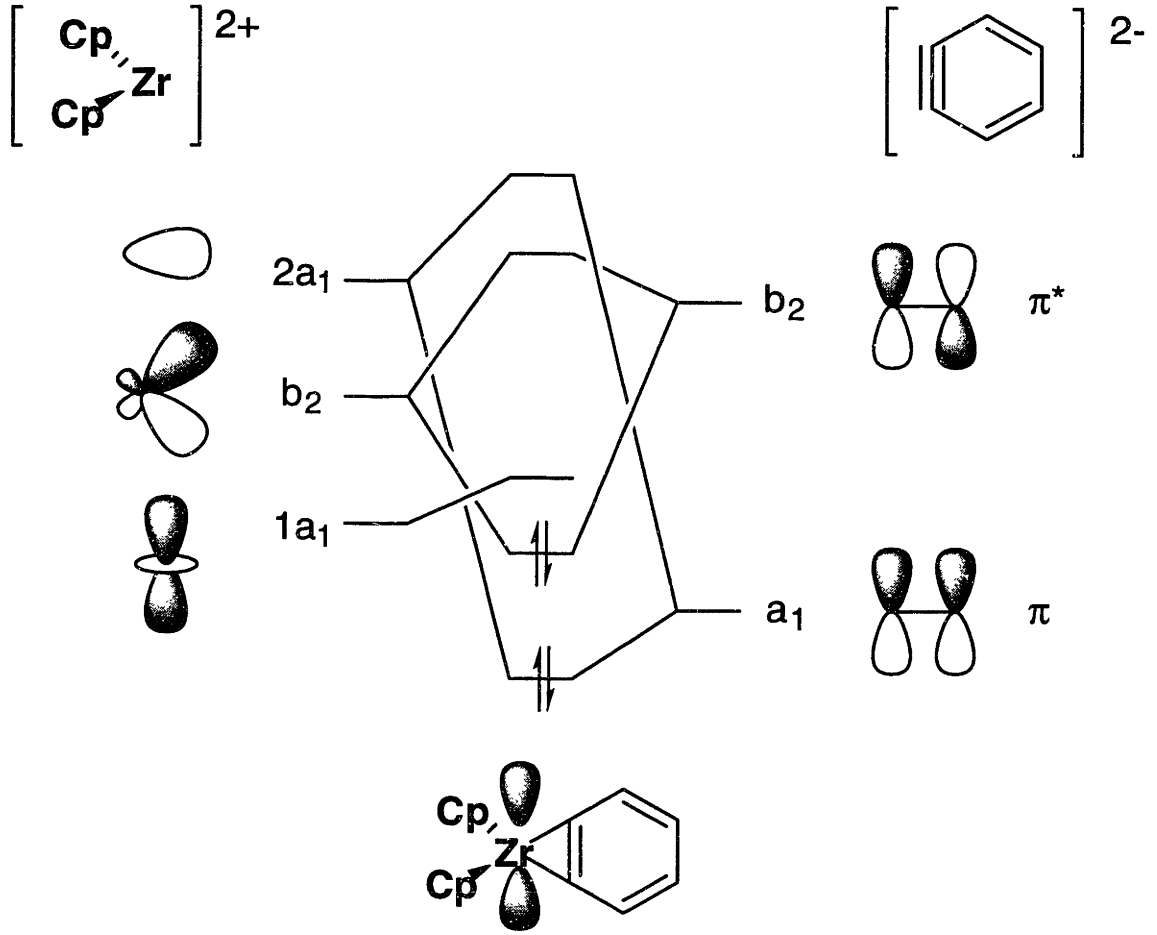
Scheme 1



I

that there is a high degree of backbonding taking place within the complex, and therefore the structure is best described as a metallacyclopropene. The molecular orbital diagram developed by Hoffmann and Lauher for bent metallocene complexes is shown in Figure 4.[8] Overlap of the metal $2a_1$ orbital with the a_1 symmetric π-orbital of the benzyne yields a bonding orbital with σ symmetry. Backbonding between the metal b_2 orbital and the benzyne π^*-orbital produces the second bonding orbital. The metal non-bonding $1a_1$ orbital is situated in the plane of the benzyne.

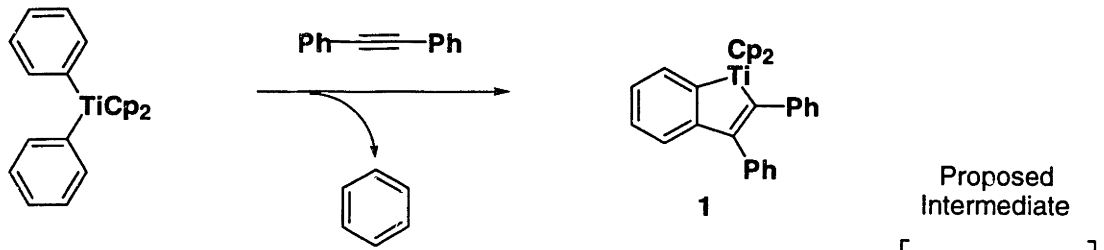
Figure 4



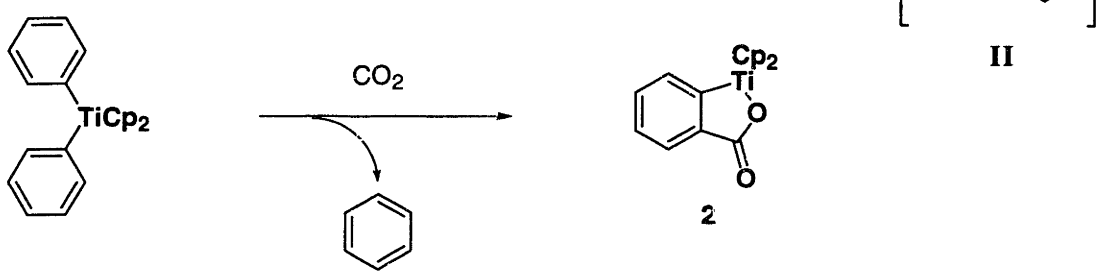
Initial work by Hagihara[9] and Vol'pin[10] showed that thermolysis of diphenyltitanocene in the presence of an unsaturated organic molecule led to the formation of titanacycles **1** and **2** (Scheme 2). Vol'pin proposed that the titanacycles were formed via the insertion of the unsaturated species into the Ti–C bond of a titanocene-benzyne complex **II**. Further evidence supporting the group 4 metallocene-benzyne intermediate was provided by Erker, who investigated the thermolysis of diarylzirconocenes.[11] The formation of the proposed intermediate was finally confirmed when Buchwald and Watson isolated the zirconocene-benzyne•PMe_3 complex **I**. The mechanism for the

Scheme 2

Hagihara:



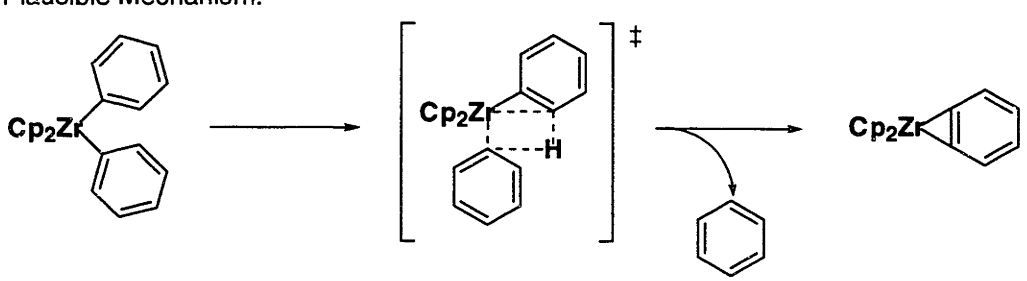
Vol'pin:



formation of the metallocene-benzyne complexes has been investigated by Erker[12] and Buchwald[13], and is believed to proceed via a four-centered, concerted cyclometallation (Scheme 3).

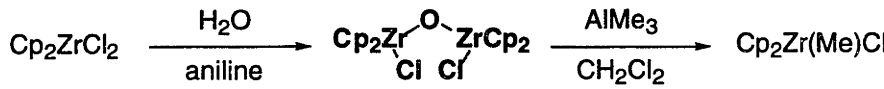
Scheme 3

Plausible Mechanism:



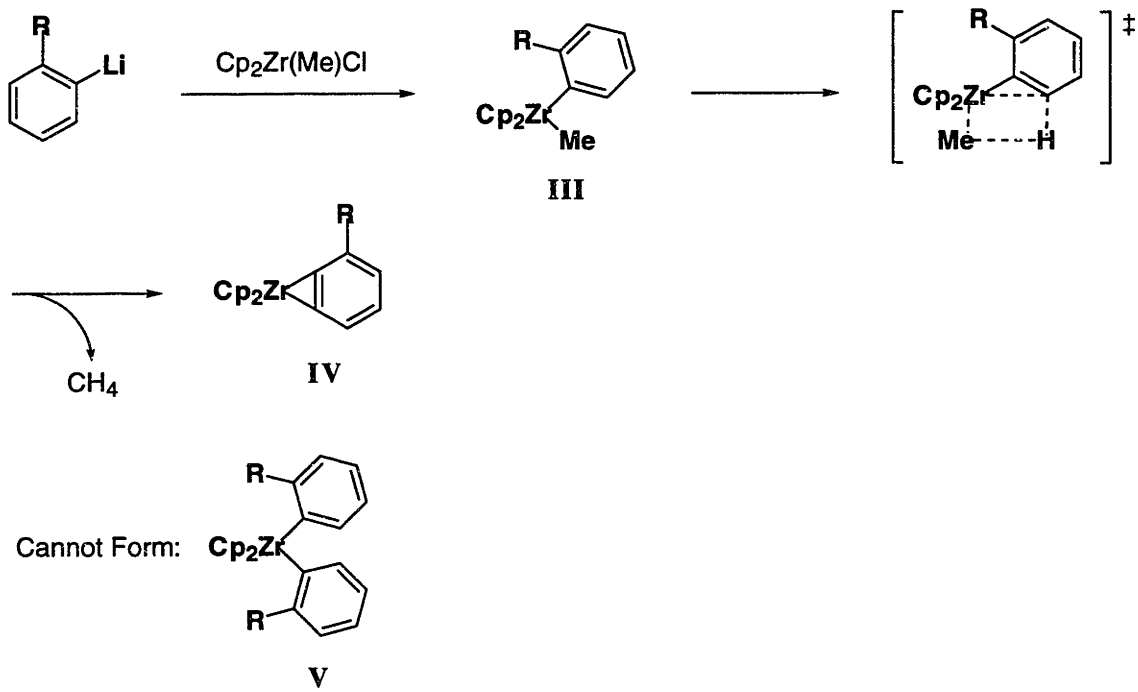
In addition to the thermolysis of diarylzirconocenes, Buchwald and co-workers have shown that the Zr–benzyne complex can be generated from an aryl(methyl)zirconocene **III** (Scheme 4).[14] This complex is readily prepared

Scheme 4



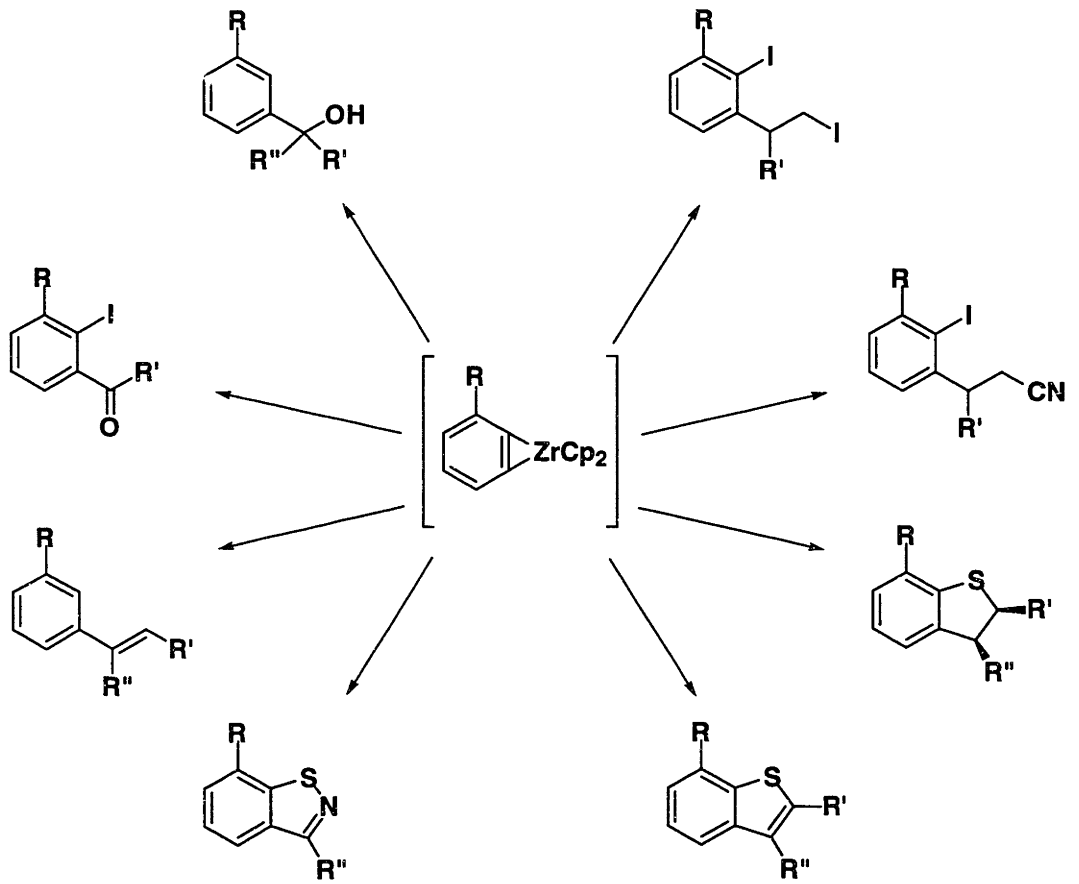
from an aryl lithium and zirconocene(methyl)chloride (Scheme 5). This is significant in that ortho-substituted benzyne complexes **IV** can be generated, which was previously not possible since the requisite *o*-substituted diarylzirconocene **V** cannot be formed due to steric factors. In addition, the use of diarylzirconocenes necessitates that one of the valuable aryl ligands be discarded upon benzyne formation. However, this problem is avoided using zirconocene(methyl)chloride since methane is the by-product formed.

Scheme 5



Since the metallocene-benzyne complexes undergo insertion reactions with a variety of unsaturated organic molecules, they show great synthetic potential for the construction of functionalized aromatic compounds (Scheme 6).[15] In addition, the insertion reactions exhibit a high-degree of regioselectivity, further increasing their utility. For example, insertion of a nitrile

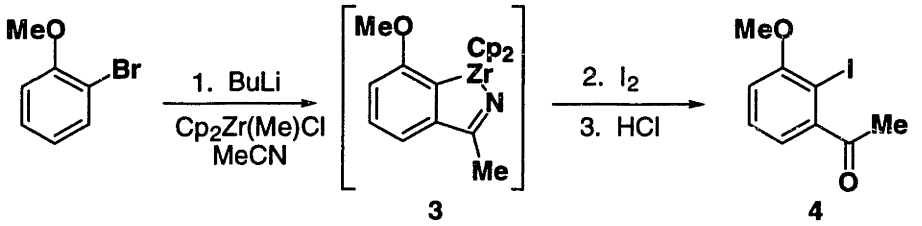
Scheme 6



into the Zr–C bond of the benzyne complex yields the appropriate azametallacycle **3** (Scheme 7). Upon iodination and subsequent hydrolysis, the contiguously trisubstituted aryl ketone **4** is produced in good yield. It is important to note that **4** is the anti Friedel-Crafts aryl ketone, which is difficult to

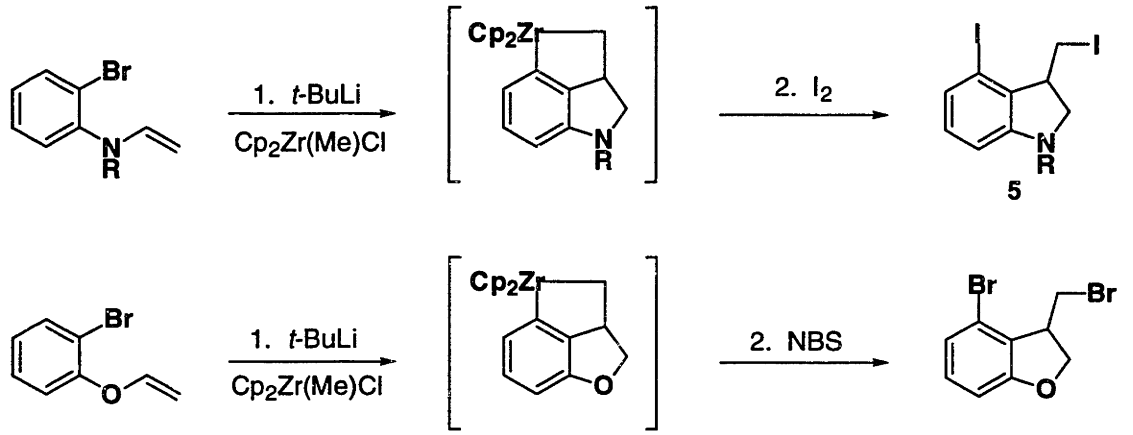
obtain by traditional methods. In addition, the metallacyclic intermediate can be cleaved with sulfur electrophiles to prepare heterocyclic derivatives.

Scheme 7



Recently, Tidwell and Buchwald have used an intramolecular variant of this methodology to produce 3,4-diiodoindolines **5** in a regiospecific fashion (Scheme 8).[16] In a similar manner, the oxygen-containing systems have also been investigated, providing access to benzofurans.[17]

Scheme 8



Due to the facile and efficient manner in which polysubstituted aromatic compounds can be constructed via the reactions of metallocene-benzyne complexes, we wished to further investigate the synthetic utility of this method.

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Part One:

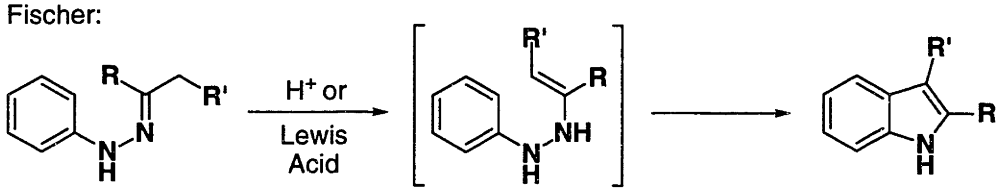
Novel Approaches to Fuctionalized Indoles

Introduction

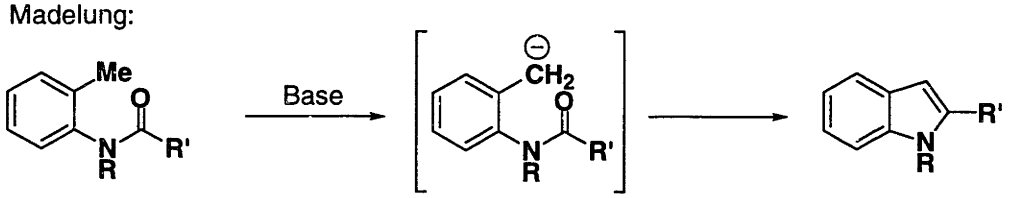
The synthesis of functionalized indoles has been of interest to organic chemists for many years due to the large number of natural products that contain this structural element.[1] More importantly, indole-containing compounds have pronounced effects in many biological processes, especially in the central nervous system.[2] For these reasons, numerous methods exist to synthesize the indole framework, such as the Fischer,[3] Madelung,[4] and Batcho-Leimgruber[5] syntheses (Scheme 1). In addition to these classical approaches,

Scheme 1

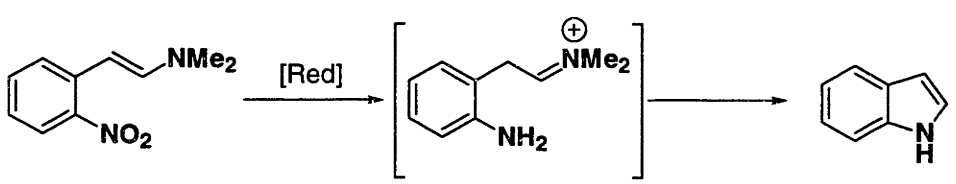
Fischer:



Madelung:



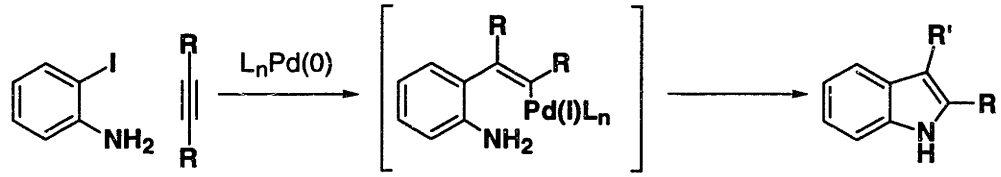
Batcho-Leimgruber:



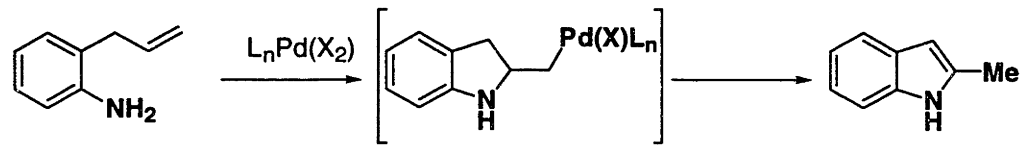
recent interest in organometallic chemistry has led to the development of several metal-mediated approaches (Scheme 2).[6]

Scheme 2

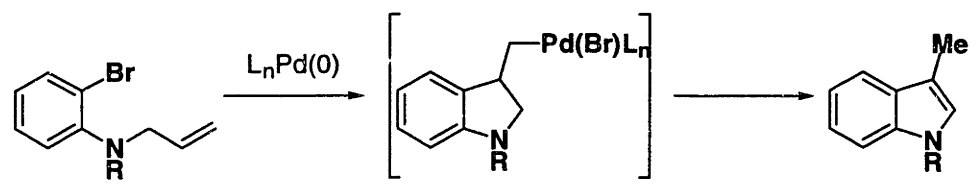
Larock Method:



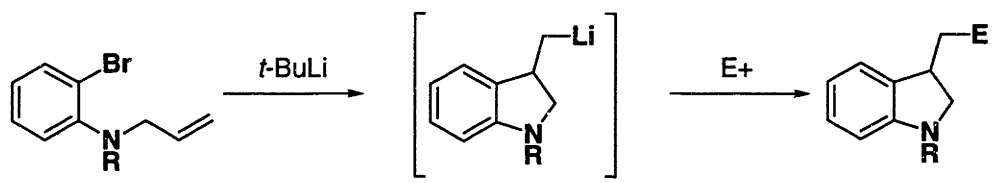
Hegedus Method:



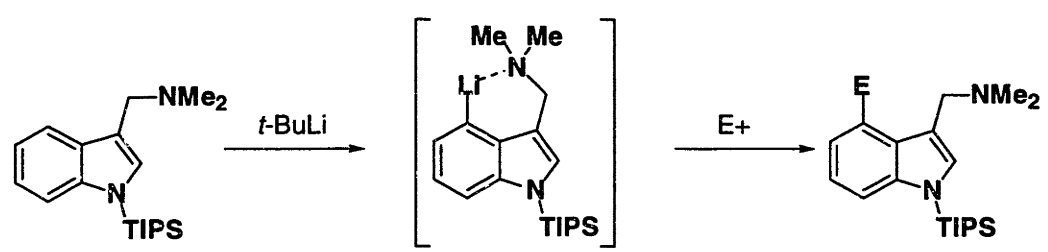
Mori-Ban Method:



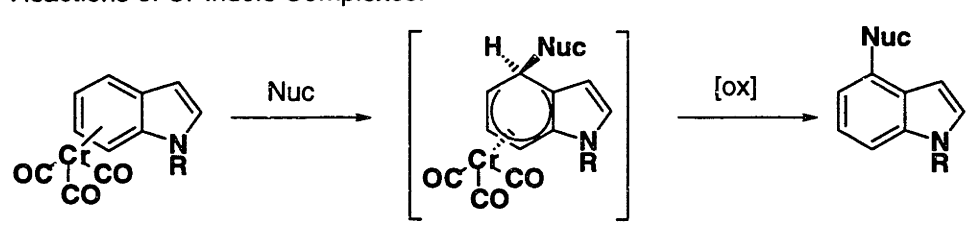
O-Lithiated N-Allyl Cyclization:



Directed-Lithiation of Gramine:

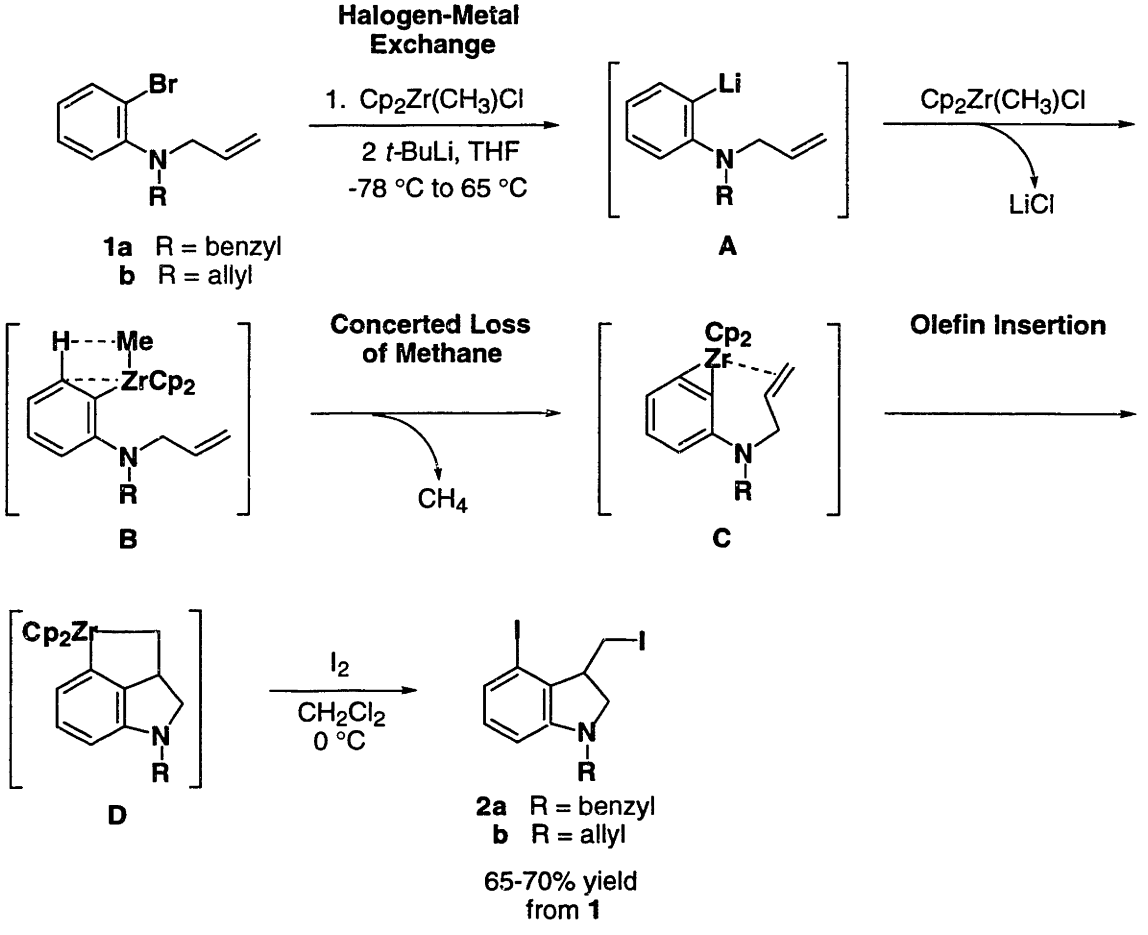


Reactions of Cr-Indole Complexes:



Recently, Tidwell, Senn, and Buchwald reported an approach to the indoline framework which is based upon the intramolecular olefin insertion reactions of zirconocene-stabilized benzyne complexes;[7] the general reaction is shown in Scheme 3. Halogen-metal exchange of an *N,N*-diallyl-*o*-bromoaniline (**1a,b**) with *t*-BuLi at –78 °C affords the aryl lithium **A**, which reacts with $Cp_2Zr(Me)Cl$ to produce the aryl(methyl)zirconocene **B**. Upon warming to 65 °C, the desired zirconocene-benzyne complex **C** is generated with the loss of methane. Coordination of the olefin to the metal, followed by insertion, yields the 5,5,6-tricyclic zirconacycle **D**. Iodination of **D** in CH_2Cl_2 at 0 °C gives 3,4-diiodoindoline **2a,b** in good yield.

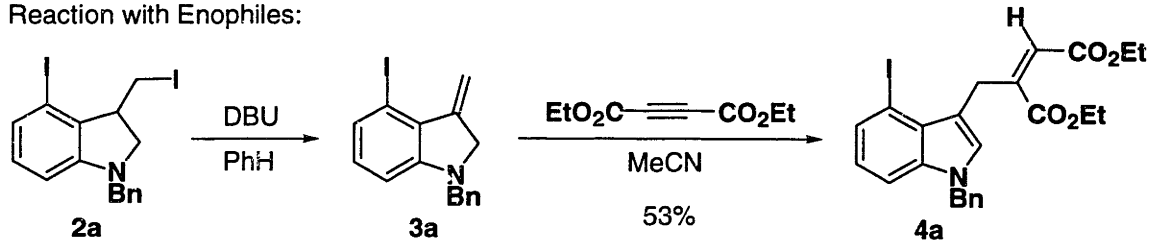
Scheme 3



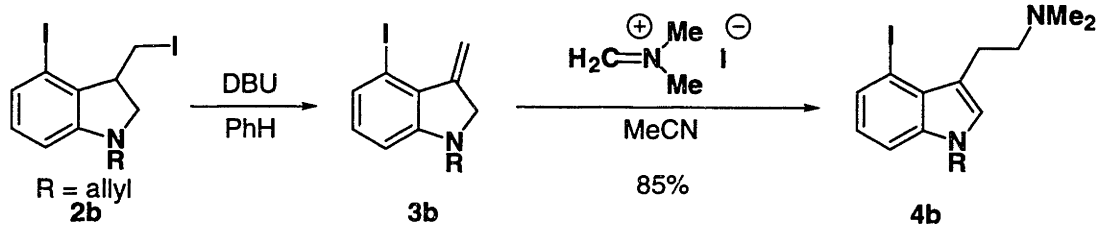
Initial investigations by Tidwell and Buchwald showed that the 3,4-diiodoindoline derivatives were useful precursors for the synthesis of more complex indoles. For example, treatment of the diiodide **2a** with 1 equiv of 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) in benzene affords the 3-methyleneindole **3a**, which readily undergoes ene-type reactions with activated enophiles such as diethylacetylenedicarboxylate to produce a variety of 3-substituted indoles **4a** (Scheme 4).[7a,c] Similarly, the reaction of **3b** with iminium ions such as Eschenmoser's salt provides access to tryptamine derivatives **4b**.

Scheme 4

Reaction with Enophiles:

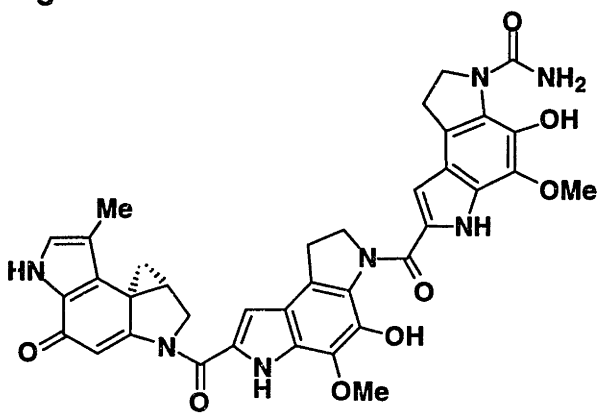


Reaction with Iminium Ions:

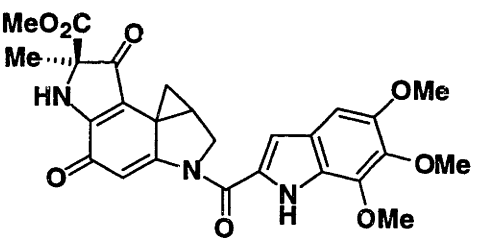


In addition, Tidwell and Buchwald employed a diiodoindoline derivative as a key intermediate in the synthesis of the pharmacophore of CC-1065 and duocarmycin A,[7b] which are potent antitumor antibiotics (Figure 1).[8] For example (Scheme 5), cleavage of the *O*–Me bond of **5** with BBr_3 affords the

Figure 1



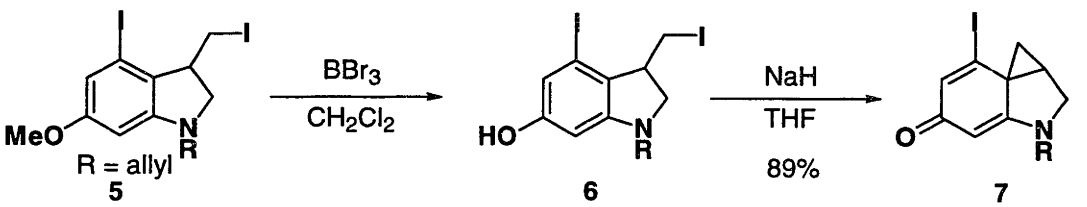
CC-1065



Duocarmycin A

phenol **6**, which upon treatment with NaH affords the pharmacophore **7** in 89% yield. A similar approach was employed by Tietze and co-workers in the formal synthesis of the entire left-hand segment of CC-1065.[9]

Scheme 5



R = allyl

5 **6** **7**

Based on the success of these initial investigations, we wished to exploit the use of the zirconocene-stabilized benzyne methodology for the construction of complex indole derivatives. In addition, we planned to apply the method towards the syntheses of small natural products.

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Chapter One:

The Synthesis of 3,4-Disubstituted Indoles

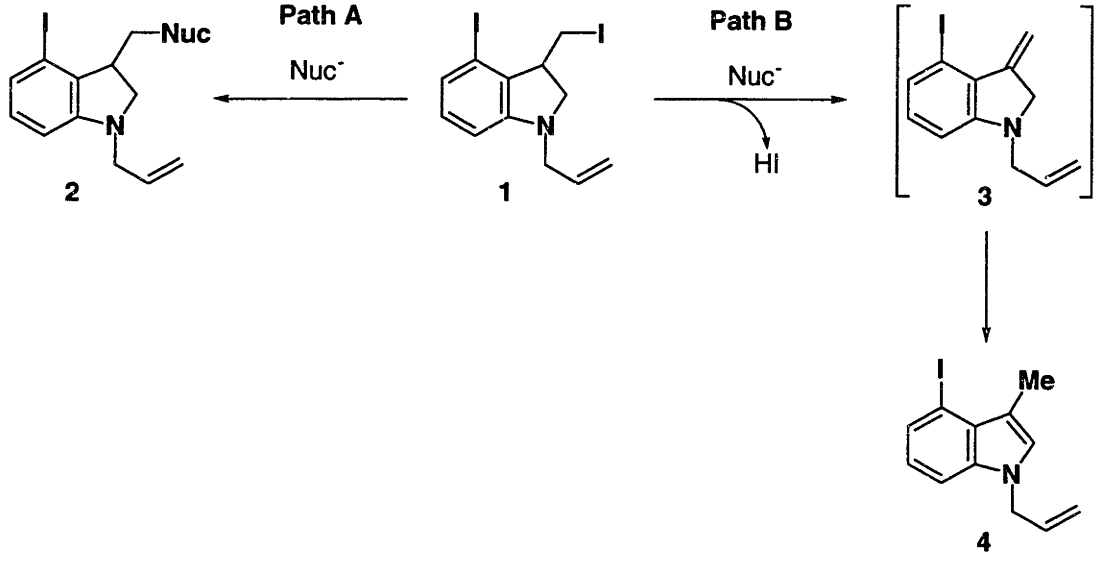
Note: This work was carried out in collaboration with Dr. Jeffrey H Tidwell. My contribution involved the synthesis of the following compounds:

Compounds **10**, **25**, **27**, **29**, **32**, **33**, **34**, **35**.

Results and Discussion

Initially, we wished to investigate the synthetic utility of the diiodoindoline derivative **1** for the construction of more complex indoles. In one approach, Tidwell and Buchwald attempted the displacement of the alkyl iodide with various nucleophiles (Scheme 1).[1] Unfortunately, nucleophiles such as alkoxides gave poor yields of the desired product **2**, and instead produced the unsubstituted 3-methylindole **4**. Compound **4** is formed via dehydrohalogenation of the diiodide yielding the exocyclic olefin **3**, which can tautomerize to the more stable 3-methylindole. This side reaction was anticipated since previous studies from our laboratories had shown that the exocyclic olefin was cleanly formed upon treatment of the diiodoindoline with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).[2]

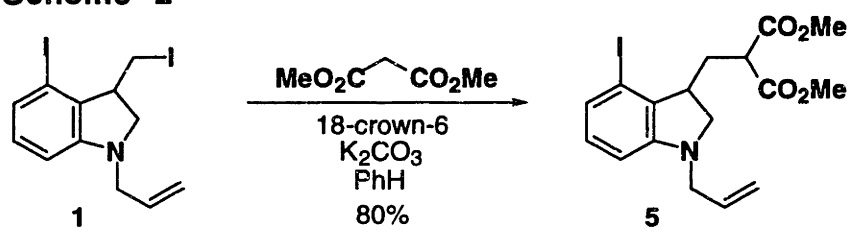
Scheme 1



Tidwell and Buchwald found that the alkyl iodide could be displaced by the use of a soft nucleophile such as dimethyl malonate and a stoichiometric

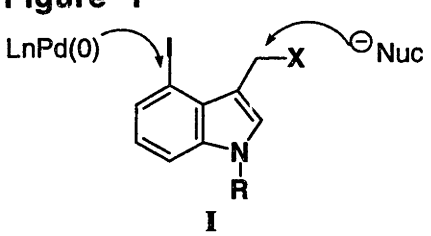
amount of 18-crown-6.[1,2a] For example, treatment of **1** with dimethyl malonate, 18-crown-6, and K_2CO_3 in benzene produced **5** in 80% yield (Scheme 2).

Scheme 2



Recognizing that the diiodoindoline derivatives were a poor choice as substrates in nucleophilic displacement reactions, we searched for an alternative approach to functionalize the 3-position. One solution to the problem of dehydrohalogenation involves oxidizing the indoline ring to the indole derivative. The resulting 4-iodo-3-halomethylindole **I** (Figure 1) should serve as an excellent electrophile.[3,4] In addition, the 4-iodo group could be subsequently elaborated by a variety of methods such as Pd-catalyzed cross-coupling reactions.

Figure 1

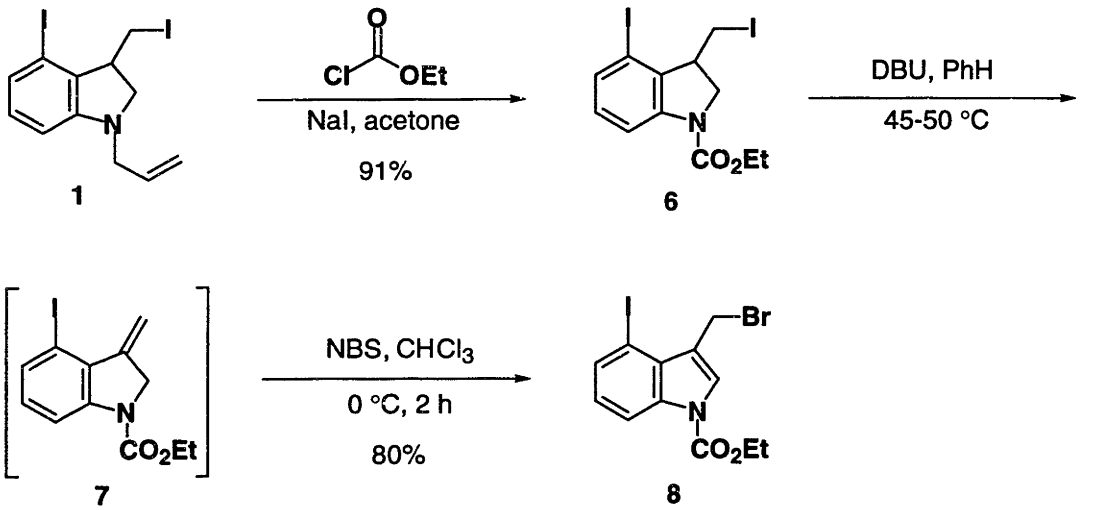


We envisioned two possible synthetic approaches to compounds such as **I**. The first would involve direct dehydrogenation of the indoline to the indole using reagents such as DDQ,[5] MnO_2,[6] palladium on carbon,[7] or chloranil.[8] Our second idea was based on the earlier work of Tidwell and Buchwald

involving the reaction of a 3-methyleneindole derivative with electrophilic iminium ions.[2] In an analogous fashion, reaction of the exocyclic olefin with an electrophilic halogen source should produce the necessary 3-haloindole.

We decided to investigate the second approach (Scheme 3). Starting with diiodide **1**, the allyl group was cleaved to yield the carbamate-protected diiodoindoline **6**.[2a,9] Compound **6** was treated with DBU in benzene to afford the exocyclic olefin **7**, which was filtered and concentrated. This compound was not isolated but immediately treated with *N*-bromosuccinimide in $CHCl_3$ at 0 °C to provide the bromomethylindole **8** in 80% yield.

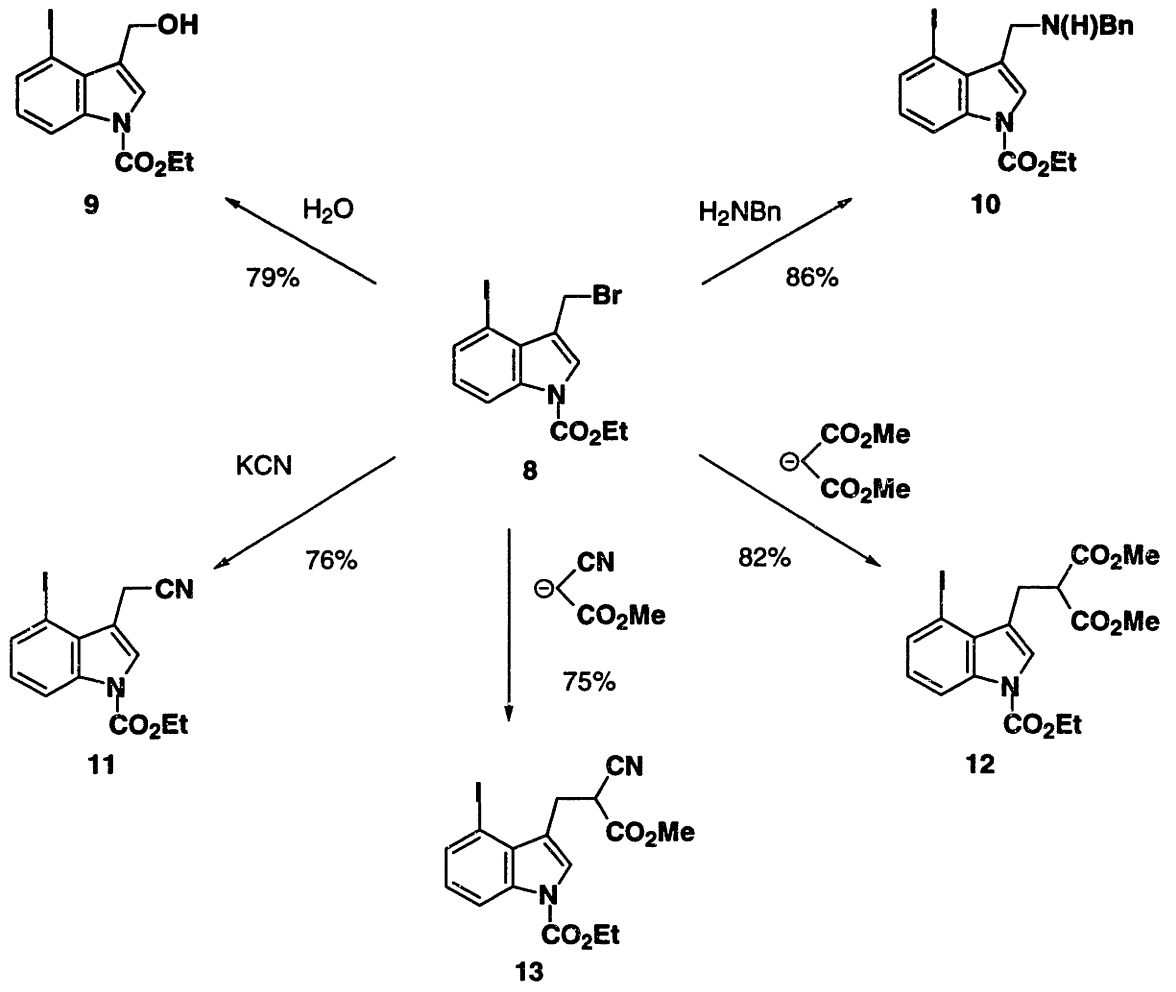
Scheme 3



1 **6** **7** **8**

The chemistry of **8** was first explored by examining its reactivity towards a variety of nucleophiles (Scheme 4). The first reaction involved the hydrolysis of **8** to produce 1-carboethoxy-3-hydroxymethyl-4-iodoindole **9**. Addition of water to **8** in acetonitrile at 50 °C afforded the desired alcohol **9** in 79% yield. In addition, **8** reacts readily with nitrogen-based nucleophiles. For example, addition of benzylamine and K_2CO_3 to a solution of **8** in refluxing THF gave 3-benzylaminomethyl-1-carboethoxy-4-iodoindole **10** in 86% yield.

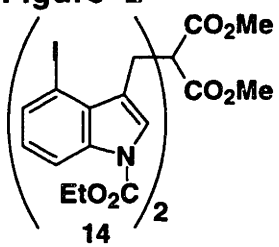
Scheme 4



The displacement reaction was also conducted with various carbon nucleophiles (Scheme 4). The reaction of **8** with one equivalent of KCN proceeded smoothly to afford the nitrile derivative **11** in 76% yield. The reaction of **8** with soft carbon nucleophiles, such as malonate esters, gave the desired compounds in good yield provided that a large excess of the malonate ester was used. For example, treatment of **8** with five equivalents of dimethyl malonate, K_2CO_3, and catalytic 18-crown-6 in benzene gave the malonate indole derivative **12** in 82% yield. Significant amounts of overalkylated product

14 were obtained if only one equivalent of dimethyl malonate was used (Figure 2).[1] In a similar example, excess ethyl cyanoacetate was added to **8** to produce the desired substituted derivative **13** in 75% yield.

Figure 2

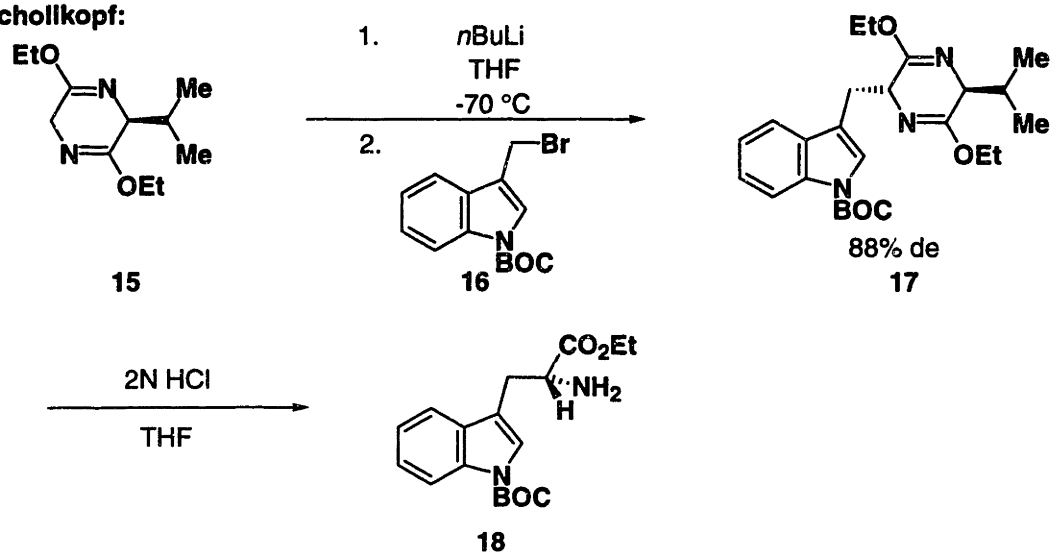


14

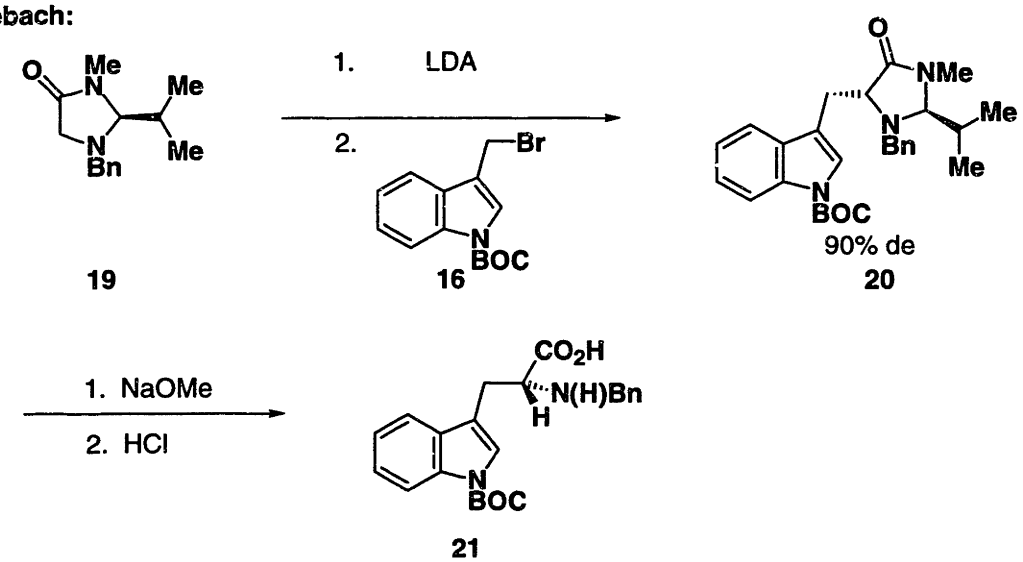
The displacement of the bromide group with an asymmetric glycine equivalent to afford 4-iodotryptophan derivatives was also investigated.[4,10] Substitution reactions of 3-bromomethylindole derivatives with chiral glycine synthons have been shown to proceed with good levels of diastereoselectivity (Scheme 5).[4] Schöllkopf and co-workers have shown that treatment of the bis-lactim ether **15** with one equivalent of *n*-BuLi at –78 °C generated the desired stabilized anion.[4a] Addition of the electrophile **16** to the anion occurred away from the bulky isopropyl group, producing the *trans*-diastereomer **17** in 88% de. The pyrazine ring was cleaved upon stirring in 2N HCl to afford the optically-enriched tryptophan **18** in high yield with little racemization. We decided to employ the bis-lactim ether **15** as the nucleophilic reagent since it is readily prepared from L-valine and glycine.[4a] L-Valine **22** was treated with

Scheme 5

Schollkopf:

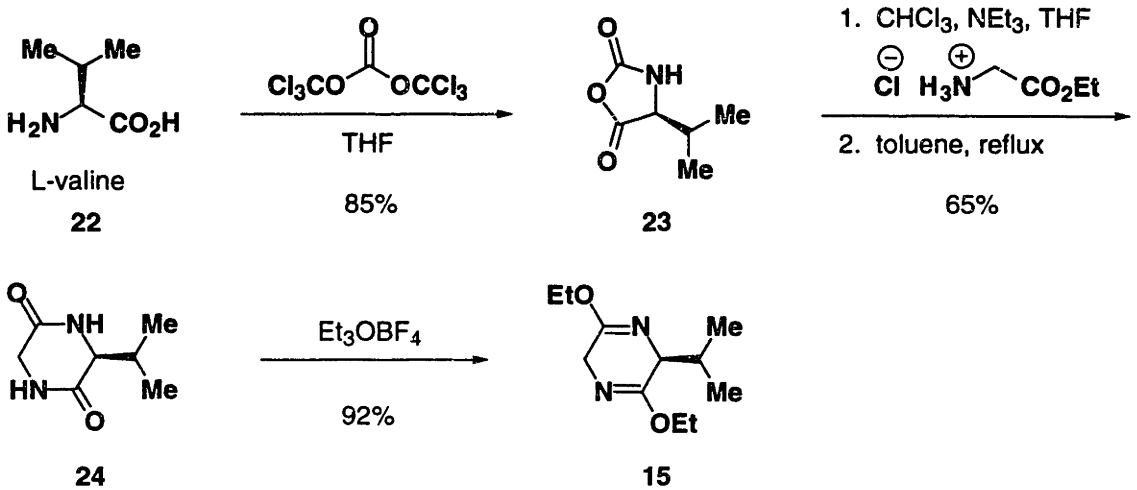


Seebach:



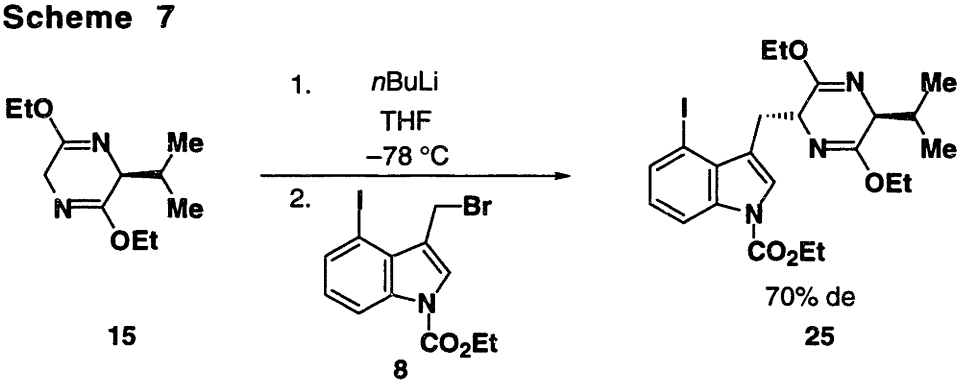
triphosgene in THF to provide the *N*-carboxyanhydride **23** (Scheme 6), which was treated with glycine methyl ester and triethylamine to afford the diketopiperazine **24**. *O*–alkylation of **24** with triethyloxonium tetrafluoroborate gave the desired bis-lactim ether **15**.

Scheme 6



Initial attempts by Tidwell and Buchwald resulted in the formation of the desired substituted product, however the diastereoselectivity was low.[1] Following Schöllkopf's protocol, the bis-lactim ether **15** was treated with *n*-BuLi at –78 °C in THF to generate the anion (Scheme 7). After 20 min, a solution of the bromomethylindole **8** in THF was added dropwise to the anion and the reaction was warmed slowly to RT. ^{1}H NMR of the crude mixture showed the desired product **25** but in only 70% de. This was disappointing compared to the

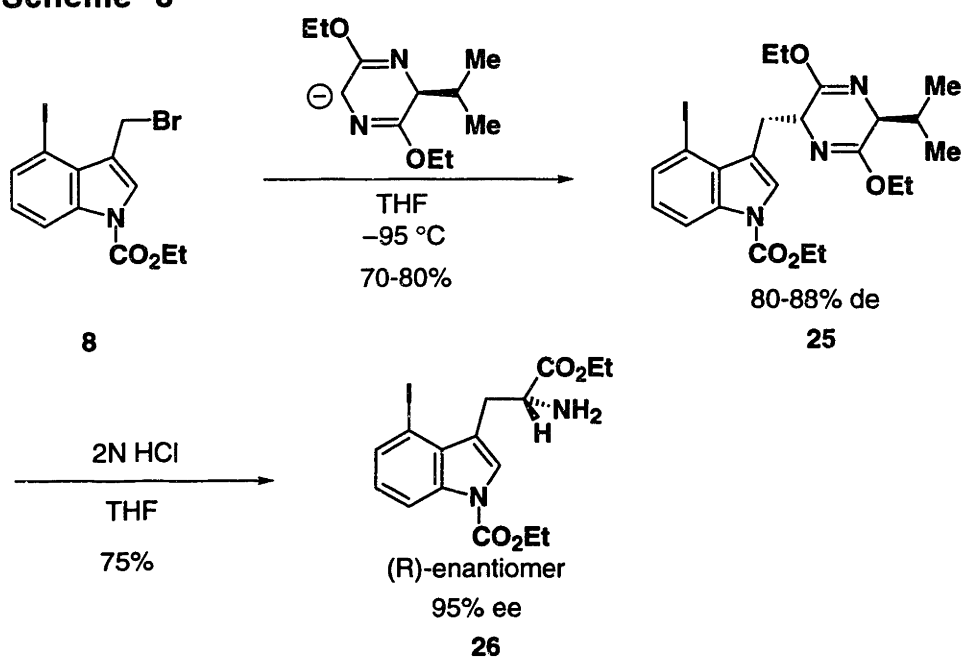
Scheme 7



88% de obtained by Schöllkopf for the *N*-*t*BOC-3-bromomethylindole **16** in Scheme 5. We speculated that the 4-iodo group may be responsible for the poor selectivity.

After extensive experimentation, we found that the *trans*-diastereomer could be formed with good diastereoselectivity by cooling the reaction to –95 °C (Scheme 8). A solution of the anion in THF at –95 °C was added dropwise via cannula to a solution of the 3-bromomethylindole **8** in THF also at –95 °C. After 24 h, the reaction was quenched with MeOH at –78 °C. Analysis of the crude reaction mixture shows the desired product **25** in 80-88% de. The two

Scheme 8

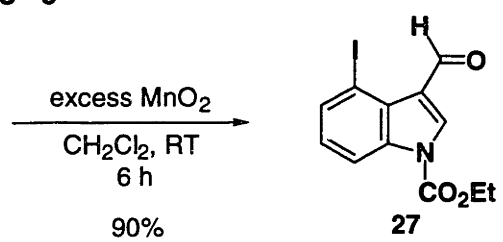


diastereomers were separated by column chromatography to yield the analytically pure compound. The pyrazine ring of the major diastereomer was cleaved by Limanto and Buchwald with 2N HCl, producing the 4-iodotryptophan **26** in 75% yield and 95% ee.[11] It should be noted that the use of the bis-lactim

ether derived from the naturally occurring amino acid L-valine results in the formation of the unnatural (*R*)-enantiomer of tryptophan.

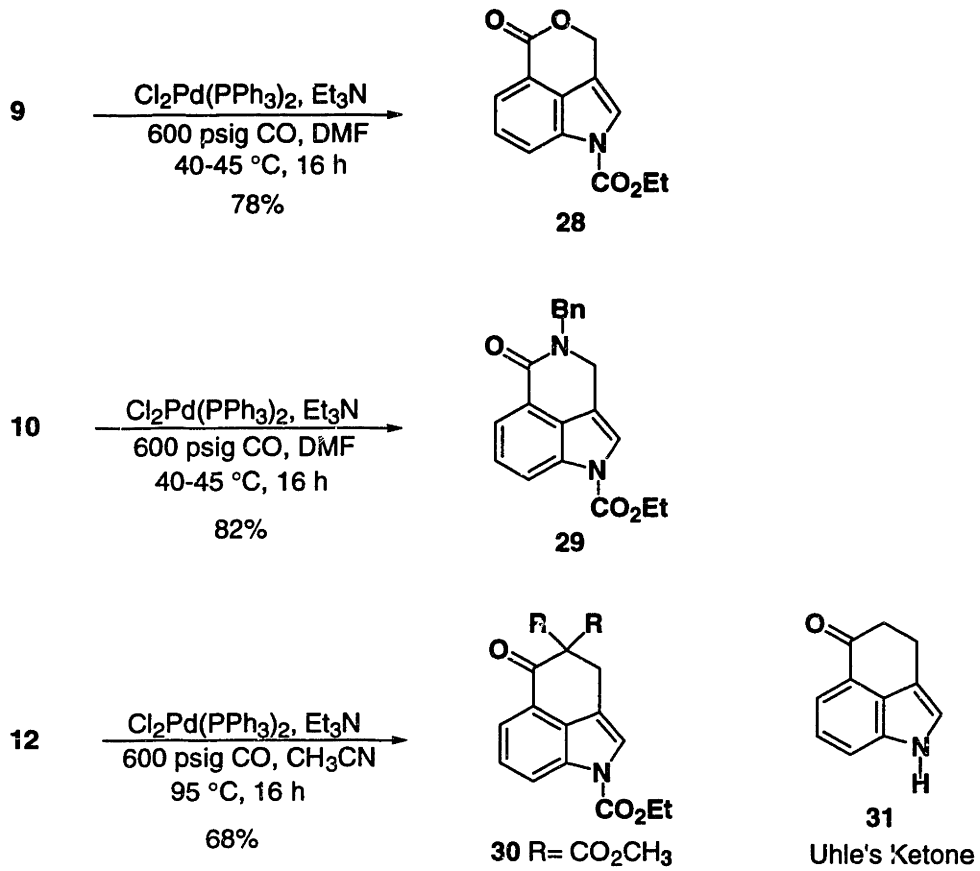
While products **9-13** are interesting in their own right, they also serve as convenient precursors to other novel indoles. For example, 4-iodo-3-hydroxymethylindole **9** could be oxidized to the corresponding carboxaldehyde derivative **27** using an excess of MnO_2 in CH_2Cl_2 (Scheme 9).[12] Somei and co-workers have used similar 3-carboxy-4-iodoindoles in the synthesis of several indole alkaloid natural products.[13]

Scheme 9



After investigating the elaboration of the 3-position, we turned our attention to the reactions of the aryl-iodide moiety. One avenue we explored was the palladium-catalyzed carbonylation reactions of compounds **9, 10,** and **12** (Scheme 10). It is well-known that treatment of an aryl halide with a Pd(0)-catalyst and carbon monoxide in the presence of an alcohol generates the ester product.[14] We found that the alcohol **9** could be carbonylated at 600 psig of carbon monoxide using a catalytic amount of $Cl_2Pd(PPh_3)_2$ to afford the tricyclic indole lactone **28** in 78% yield. Under similar conditions, the benzylamine adduct **10** wasconverted to the tricyclic lactam **29**. Finally, the malonate derivative **12** was carbonylated and cyclized using an anion capture process[15] to give the tricyclic ketone **30**. The reaction temperature is critical for

Scheme 10

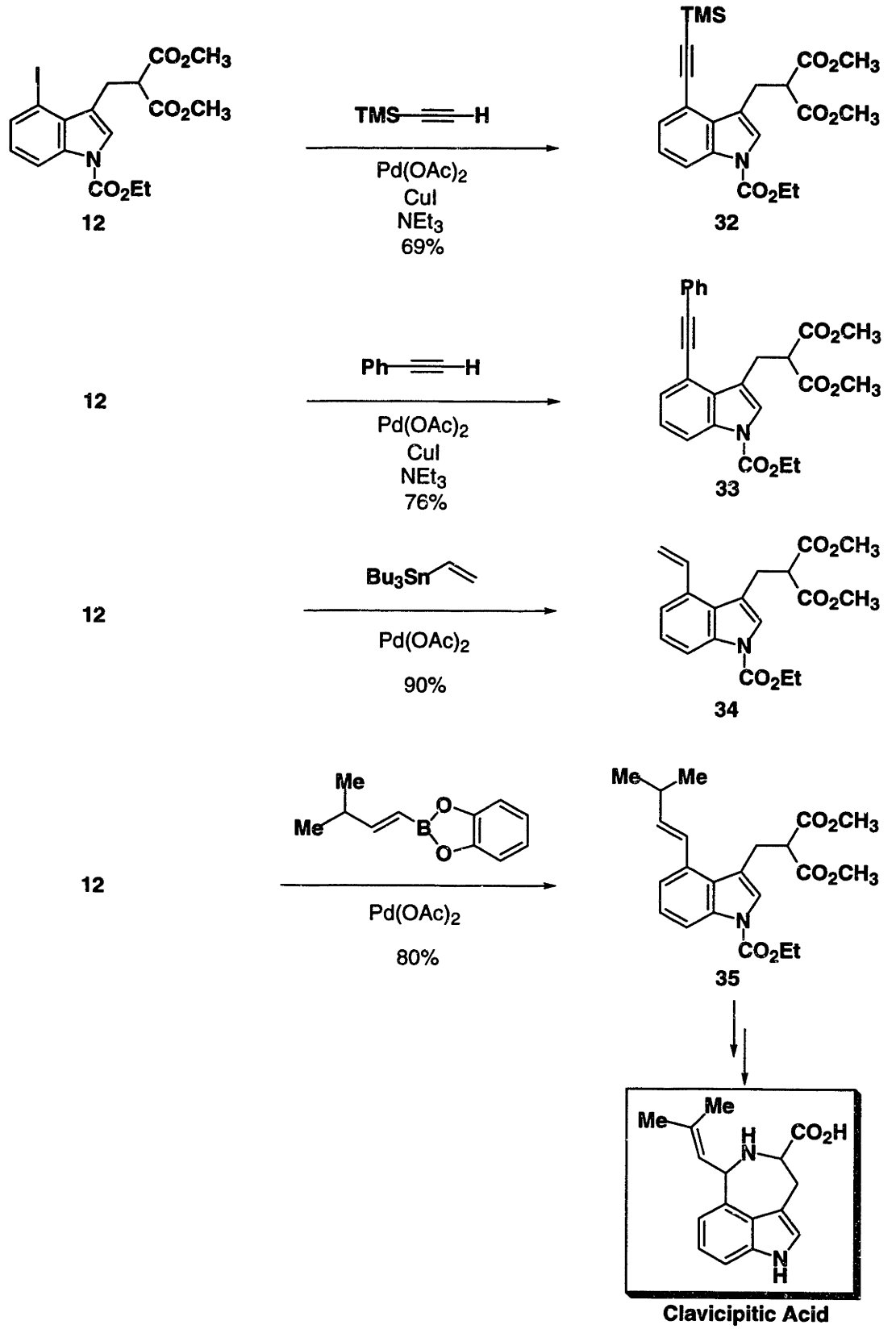


the success of this transformation. If the temperature was below 80 °C, significant amounts of unidentifiable side products were formed. This also proved to be the case if the temperature was too high (> 110 °C). This ketone is closely related to Uhle's ketone **31** which has been used as an intermediate in the synthesis of ergot alkaloids.[16]

In a final effort to explore the reactivity of these compounds, we further exploited the aryl-iodide moiety through a variety of palladium-catalyzed cross-coupling reactions (Scheme 11). First, the malonate derivative was subjected to a Castro-Stephens reaction, which involves the coupling of an aryl or vinyl halide to a terminal acetylene.[17] Treatment of **12** with trimethylsilylacetylene, triethylamine, and catalytic amounts of $Pd(OAc)_2$ and CuI gave the desired

alkyne **32** in 69% yield. Likewise, the alkynylindole **33** was obtained in 76% yield when phenylacetylene was employed. Not suprisingly, **12** readily undergoes a Stille cross-coupling reaction[18] with vinyltributyltin to give the corresponding styrene adduct **34** in 90% yield. Finally, treatment of **12** with the boronate ester prepared from the hydroboration of 3-methyl-1-butyne with catechol borane, under Suzuki cross-coupling reaction conditions,[19] gave the desired *trans*-olefin derivative **35** in 80% yield which has been converted to the clavicipitic acids by Kozikowski and co-workers.[20] Thus, the preparation of **35** represents the formal synthesis of the clavicipitic acids.

Scheme 11


CO2CH3
CO2CH3
N
CO2Et
12
TMS—≡—H
Pd(OAc)2
CuI
NEt3
69%
TMS
32
Ph—≡—H
76%
Ph
33
Bu3Sn
90%
34
Me
Me
B
O
O
80%
35
H
N
CO2H
Clavicipitic Acid

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 and 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 chromatographic analyses were performed on a Hewlett Packard model 5890 GC with a 3392A integrator and FID detector using a 25 m capillary column with cross linked 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. 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 CaH_2, 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. Cp_2ZrCl_2 was purchased from Boulder Scientific Inc., Mead, Colorado, and converted to $Cp_2Zr(Me)Cl$. 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, HPLC analysis, or combustion analysis. Elemental analyses were performed by Onieda Research Services, Whitesboro, NY.

3-Bromomethyl-1-carboethoxy-4-iodoindole (8). Into a flask were placed 1-carboethoxy-4-iodo-3-iodomethylindoline **6** (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 using a rotary evaporator leaving a brownish solid. The solid was dissolved in $CHCl_3$ (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 $CHCl_3$ (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 through a plug of silica (15 cm) and the solvents were removed using a rotary evaporator to leave 700 mg (80%) of a white solid, mp 109-110 °C. An analytical sample was prepared by recrystallization from CH_3CN. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, J= 8.4 Hz, 1H), 7.79 (d, J= 8.1 Hz, 1H), 7.00 (t, J= 8.1 Hz, 1H), 4.90 (s, 2H), 4.46 (q, J= 7.0 Hz, 2H), 1.45 (t, J= 7.0 Hz, 3H). ^{13}C NMR ($CDCl_3$, 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 $C_{12}H_{11}BrNO_2I$: 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 (9). Into a flask were placed 3-bromomethyl-1-carboethoxy-4-iodoindole **8** (1.23 g, 3.01 mmol), water (5 mL, 5.00g, 278 mmol), and CH_3CN (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 using a rotary evaporator 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. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.18 (d, *J*= 8.1 Hz, 1H), 7.62 (m, 2H), 6.96 (t, *J*=7.9 Hz, 1H), 4.94 (d, *J*= 5.4 Hz, 2H), 4.43 (q, *J*= 7.2 Hz, 2H), 2.39 (t, *J*= 6.3 Hz, 1H), 1.42 (t *J*= 7.2 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 $C_{12}H_{12}NO_3I$: C, 41.76; H, 3.50; N, 4.06. Found: C, 41.70; H, 3.45; N, 4.22.

3-Benzylaminomethyl-1-carboethoxy-4-iodoindole (10). Into a flask fitted with a reflux condenser were placed 3-bromomethyl-1-carboethoxy-4-iodoindole **8** (210 mg, 0.51 mmol), THF (10 mL), benzylamine (0.28 mL, 2.6 mmol), and K_2CO_3 (0.36 g, 2.6 mmol). The mixture was heated to reflux for 12 h, then poured into a separatory funnel containing ether (25 mL) and water (25 mL). The organic layer was collected and washed with brine (25 mL), dried over $MgSO_4$, filtered and concentrated. The product was purified by flash chromatography (66: 33: 1 hexane: ethyl acetate: triethylamine) to give 182 mg (82%) of a white solid, mp 83-85 °C. An analytical sample was prepared by recrystallization from acetonitrile. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.22 (d, *J*= 8.2

Hz, 1H), 7.66 (dd, *J*= 8.1, 1.6 Hz, 1H), 7.61 (s, 1H), 7.37-7.21 (m, 5H), 6.95 (dd, *J*= 8.3, 7.8 Hz, 1H), 4.43 (q, *J*= 6.9 Hz, 2H), 4.08 (s, 2H), 3.87 (s, 2H), 1.83 (s, 1H), 1.41 (t, *J*= 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) d 150.1, 140.0, 136.6, 134.4, 131.0, 128.3, 126.9, 125.7, 125.6, 120.1, 115.2, 84.4, 63.4, 53.3, 44.1, 14.5. IR (KBr, cm^{-1}) 3319, 2991, 1736, 1417. Anal. Calcd for $C_{19}H_{19}N_2O_2I$: C, 52.55; H, 4.41; N, 6.45. Found: C, 52.70; H, 4.40; N, 6.58.

11. Into a flask were placed 3-bromomethyl-1-carboethoxy-4-iodoindole **8** (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 $MgSO_4$, filtered and the solvents were removed using a rotary evaporator 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 ($CDCl_3$, 300 MHz) δ 8.25 (d, *J*= 8.4 Hz, 1H), 7.78 (s, 1H), 7.67 (d, *J*= 7.5 Hz, 1H), 7.01 (t, *J*= 7.8 Hz, 1H), 4.48 (q, *J*= 7.2 Hz, 2H), 4.16 (d, *J*= 1.5 Hz, 2H), 1.46 (t, *J*= 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 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 $C_{13}H_{11}N_2O_2I$: C, 44.09; H, 3.13; N, 7.91. Found: C, 43.84; H, 2.81; N, 7.62.

12. Into a flask were placed 3-bromomethyl-1-carboethoxy-4-iodoindole **8** (964 mg, 2.36 mmol), dimethylmalonate (1.30 mL, 1.50 g, 11.37 mmol), K_2CO_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 using a rotary evaporator to leave a brownish solid. The product was recrystallized from ethanol to yield 889 mg (82%) of a white solid, mp 102-104 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.21 (d, *J*= 8.4 Hz, 1H), 7.67 (d, *J*= 7.5 Hz, 1H), 7.47 (s, 1H), 6.96 (t, *J*= 8.4 Hz, 1H), 4.45 (q, *J*= 6.9 Hz, 2H), 4.01 (t, *J*= 7.8 Hz, 1H), 3.71 (s, 6H), 3.53 (d, *J*= 7.5 Hz, 2H), 1.43 (t, *J*=6.9 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 $C_{17}H_{18}NO_6I$: C, 44.46; H, 3.95; N, 3.05. Found: C, 44.60; H, 4.06; N, 3.19.

13. Into a flask were placed 3-bromomethyl-1-carboethoxy-4-iodoindole **8** (110 mg, 0.27 mmol), ethyl cyanoacetate (0.43 mL, 457 mg, 4.04 mmol), K_2CO_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 was 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 using a rotary evaporator 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. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.27 (d, *J*= 8.1 Hz, 1H), 7.68 (d, *J*= 6.9 Hz, 1H), 7.67 (s, 1H), 7.01 (t, *J*= 8.1 Hz, 1H), 4.46 (q, *J*= 7.4 Hz, 2H), 4.27 (q, *J*= 7.4 Hz, 2H), 4.10 (dd, *J*= 6.3, 9.3 Hz, 1H), 3.83 (dd, *J*= 6.3, 14.4 Hz, 1H), 3.27 (dd, *J*= 9.3, 14.4 Hz, 1H), 1.45 (t, *J*= 7.4 Hz, 3H), 1.30 (t, *J*= 7.4 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 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 $C_{17}H_{17}N_2O_4I$: 440.0235. Found: 440.0237 amu.

25.[1] A solution of *n*-BuLi (0.26 mL, 0.44 mmol) was added dropwise to a solution of the bis-lactim ether (78 mg, 0.37 mmol) in THF (3 mL) under argon at –78 °C. After 15 min, the solution was cooled to –95 °C and added dropwise via cannula to a solution of the bromoindole **8** (150 mg, 0.37 mmol) in THF (2 mL) at –95 °C under argon. The mixture was stirred between –95 °C and –78 °C for 24 h, then MeOH (3 mL) was added. Upon warming to 0 °C, the mixture was poured into a separatory funnel containing H_2O (5 mL) and Et_2O (5 mL). The organic layer was washed with brine (5 mL), dried over $MgSO_4$, filtered, and the solvent was removed using a rotary evaporator. 1H NMR analysis of the crude reaction mixture showed the desired product in 80% de. The diastereomers were separated by flash chromatography (10:1 hexane/ethyl acetate) to give 176 mg (88%) a white solid, mp 75.0-76.0 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.21 (d, *J*= 8.4 Hz, 1 H), 7.70 (d, *J*= 7.5 Hz, 1 H), 7.60 (s, 1 H), 6.95 (t, *J*= 8.0 Hz, 1 H), 4.45 (q, *J*= 7.5 Hz, 2 H), 4.38-3.80 (m, 7 H), 3.05 (dd, *J*= 9.0 Hz, 1 H), 2.25 (m, 1 H), 1.45 (t, *J*= 7.2 Hz, 3 H), 1.25 (t, *J*= 6.9 Hz, 3 H), 1.20 (t, *J*= 6.9 Hz, 3 H), 1.05 (d, *J*= 6.6 Hz, 3 H), 0.72 (d, *J*= 6.6 Hz, 3 H).

27. Into a flask were placed 1-carboethoxy-3-hydroxymethyl-4-iodoindole **9** (349 mg, 1.01 mmol), CH_2Cl_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 using a rotary evaporator 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*= 8.4 Hz, 1H), 7.81 (d, *J*= 7.5 Hz, 1H), 7.08 (t, *J*= 7.9 Hz, 1H), 4.51 (q, *J*= 6.9 Hz, 2H), 1.47 (t, *J*= 6.9 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 $C_{12}H_{10}NO_3I$: C, 42.01; H, 2.94; N, 4.08. Found: C, 42.24; H, 3.12; N, 4.15.

28. Into an autoclave were placed 1-carboethoxy-3-hydroxymethyl-4-iodoindole **9** (116 mg, 0.336 mmol), $Cl_2Pd(PPh_3)_2$ (23 mg, 0.03 mmol), Et_3N (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 ^oC for 16 h, then allowed to cool to RT and the CO pressure was released completely. The solution was 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 using a rotary evaporator to leave an orange solid. The product was recrystallized from ethanol to give 64 mg (78%) of a white solid, mp 156-157 ^oC. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.10 (br s, 1H), 8.08 (d, *J*= 7.2 Hz, 1H), 7.43 (m, 2H), 5.78 (d, *J*= 1.5 Hz, 2H), 4.47 (q, *J*= 6.9 Hz, 2H), 1.47 (t, *J*= 6.9 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.

29. Into an autoclave were placed 3-benzylaminomethyl-1-carboethoxy-4-iodoindole **10** (182 mg, 0.42 mmol), $Cl_2Pd(PPh_3)_2$ (29 mg, 0.04 mmol), Et_3N (0.25 mL, 1.81 mmol) and DMF (10 mL). The autoclave was flushed three times with CO and then pressurized to 600 psig. The mixture was heated to 45 ^oC for 12 h, then allowed to cool to RT and the CO pressure was released completely. The solution was poured into a separatory funnel containing ether (30 mL) and water (30 mL). The organic layer was collected and washed with water (30 mL), brine (30 mL), dried over $MgSO_4$, filtered and the solvents were removed using a rotary evaporator to leave a black solid. The product was purified by flash

chromatography (methylene chloride, then 20:1 methylene chloride: acetonitrile) to give 120 mg (85%) of a white solid, mp 131-132 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.00 (m, 1H), 7.87 (d, *J*= 7.6 Hz, 1H), 7.45-7.23 (m, 7H), 4.86 (s, 2H), 4.74 (d, *J*= 2.0 Hz, 2H), 4.48 (q, *J*= 7.1 Hz, 2H), 1.45 (t, *J*= 7.1Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.4, 150.91, 137.0, 132.3, 130.0, 128.6, 128.1, 127.5, 125.9, 121.0, 120.7, 119.0, 118.2, 111.0, 63.5, 50.6, 46.5, 14.3. IR (KBr, cm^{-1}) 3122, 1739, 1644, 1290. Anal. Calcd for $C_{20}H_{18}N_2O_3$: C, 71.84; H, 5.43; N, 8.38. Found: C, 71.47; H, 5.47; N, 8.22.

30. Into an autoclave were placed indole **12** (220 mg, 0.479 mmol), $Cl_2Pd(PPh_3)_2$ (26 mg, 0.04 mmol), Et_3N (0.28 mL, 203 mg, 2.0 mmol), and CH_3CN (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 the CO pressure was released completely. The solution was 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 using a rotary evaporator 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) δ 8.18 (br, 1H), 7.74 (d, *J*= 7.5 Hz, 1H), 7.54 (br s, 1H), 7.43 (t, *J*= 7.9 Hz, 1H), 4.48 (q, *J*= 7.2 Hz, 2H), 3.85 (d, *J*= 1.2 Hz, 2H), 3.71 (s, 6 H), 1.46 (t, *J*= 7.2 Hz, 3H). ^{13}C NMR (C_6D_6, 75 MHz) δ 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, 1613. Anal. Calcd for $C_{18}H_{17}NO_7$: C, 60.17; H, 4.77; N, 3.90. Found: C, 60.23; H, 4.62; N, 3.92.

32. To a flask were added **12** (197 mg, 0.43 mmol), triphenylphosphine (21 mg, 0.08 mmol), trimethylsilylacetylene (65 μL, 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 using a rotary evaporator 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 ^1H NMR. An analytical sample was prepared by recrystallization from hexanes at -78 °C to give 124 mg (67%) of a white powder, mp 60-61 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 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*= 7.1 Hz, 2H), 4.05 (t, *J*= 8.2 Hz, 1H), 3.68 (s, 6H), 3.57 (d, *J*= 8.2 Hz, 2H), 1.87 (t, *J*= 7.1 Hz, 3H), 0.23 (s, 9H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 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, 0.3. IR (KBr, cm^{-1}) 2962, 2144, 1733. Anal. Calcd for $C_{22}H_{27}NO_6Si$: C, 61.52; H, 6.34; N, 3.26. Found: C, 61.39; H, 6.27; N, 3.29.

33. To a flask were added **12** (126 mg, 0.27 mmol), PPh_3 (10 mg, 0.038 mmol), CuI (8 mg, 0.042 mmol), phenylacetylene (33 μL, 0.30 mmol), NEt_3 (0.12 mL, 0.87 mmol), $Pd(OAc)_2$ (3 mg, 0.013 mmol) and DMF (2.5 mL). The reaction mixture was heated to 70 °C for 15 h, after which time it was allowed to cool to RT and was poured into a separatory funnel containing ether (20 mL) and sat. aq. $CuSO_4$ (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 using a rotary evaporator to leave a yellow oil. The product was

purified by flash chromatography (85:15 hexane/ethyl acetate) to give 88 mg (75%) of a white solid, mp 103-105 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.16 (d, *J*= 8.2 Hz, 1H), 7.5-7.2 (m, 8H), 4.43 (q, *J*= 7.2 Hz, 2H), 4.07 (t, *J*= 7.9 Hz, 1H), 3.63 (d, *J*= 7.9 Hz, 2H), 3.52 (s, 6H), 1.42 (t, *J*= 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.1, 150.4, 135.9, 131.4, 129.2, 128.3, 128.2, 128.0, 124.7, 124.4, 123.0, 117.7, 115.7, 114.7, 92.6, 87.8, 63.4, 52.5, 25.3, 14.5. IR (KBr, cm^{-1}) 3460, 3121, 3005, 2958, 2204, 1731, 1426, 1325, 1231. Anal. Calcd for $C_{25}H_{23}NO_6$: C, 69.27; H, 5.35; N, 3.23. Found: C, 69.31; H, 5.31; N, 3.29.

34. To a flask were added **12** (85 mg, 0.18 mmol), PPh_3 (3 mg, 0.011 mmol), vinyltributyltin (59 μL, 0.20 mmol), $Pd(OAc)_2$ (2 mg, 0.009 mmol) and THF (2 mL). The reaction mixture was heated to 85 °C for 15 h, after which time it was allowed to cool 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 (20 mL), brine (20 mL), dried over $MgSO_4$, filtered and the solvents were removed using a rotary evaporator to leave a yellow oil. The product was purified by flash chromatography (85:15 hexane/ethyl acetate) to yield 58 mg (87%) of a white solid, mp 91-93 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.10 (d, *J*= 7.6 Hz, 1H), 7.4-7.2 (m, 4H), 5.66 (dd, *J*= 16.9, 1.0 Hz, 1H), 5.36 (dd, *J*= 11.1, 1.7 Hz, 1H), 4.41 (q, *J*= 6.9 Hz, 2H), 3.79 (t, *J*= 7.6 Hz, 1H), 3.69 (s, 6H), 3.40 (d, *J*= 7.7 Hz, 2H), 1.40 (t, *J*= 6.9 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.0, 150.5, 136.1, 134.5, 132.2, 126.7, 124.7, 124.2, 120.9, 117.6, 117.2, 114.6, 63.2, 52.7, 52.0, 26.9, 14.5. IR (KBr, cm^{-1}) 2990, 1740, 1432, 1254, 1099. Anal. Calcd for $C_{19}H_{21}NO_6$: C, 63.50; H, 5.89; N, 3.90. Found: C, 63.76; H, 5.83; N, 3.92.

35.[20] To a flask were added the boronate ester (61 mg, 0.32 mmol), prepared from the hydroboration reaction of 3-methyl-1-butyne with catechol borane, **12** (99 mg, 0.22 mmol), triphenylphosphine (6.0 mg, 0.02 mmol), $Pd(OAc)_2$ (2.5 mg, 0.01 mmol), K_2CO_3 (61 mg, 0.44 mmol) and THF (2 mL).

Finally, methanol (8.9 μL, 0.22 mmol) was added and the reaction was heated to 70 °C for 15 h. The mixture was poured into a separatory funnel containing ether (20 mL) and water (20 mL). The organic layer was washed with brine (20 mL), dried over $MgSO_4$, filtered and the solvents were removed using a rotary evaporator to give a brown oil. The product was purified by flash chromatography (4:1 hexane: ethyl acetate) to yield 70 mg (79%) of a pale yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.12-8.08 (m, 1H), 7.40 (s, 1H), 7.26-7.24 (m, 2H), 6.95 (dd, *J*= 15.4, 1.1 Hz, 1H), 6.12 (dd, *J*= 15.4, 7.2 Hz, 1H), 4.45 (q, *J*= 7.4 Hz, 2H), 3.84 (t, *J*= 7.5 Hz, 1H), 3.72 (s, 6H), 3.45 (d, *J*= 7.6 Hz, 2H), 2.58-2.46 (m, 1H), 1.44 (t, *J*= 7.4 Hz, 3H), 1.11 (d, *J*= 7.2 Hz, 6H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 151.0, 142.0, 136.6, 132.9, 127.1, 125.2, 124.8, 124.6, 121.6, 118.1, 114.3, 63.6, 53.1, 52.8, 32.3, 27.5, 22.8, 15.0. IR (neat, cm^{-1}) 2959, 1735, 1428, 1252.

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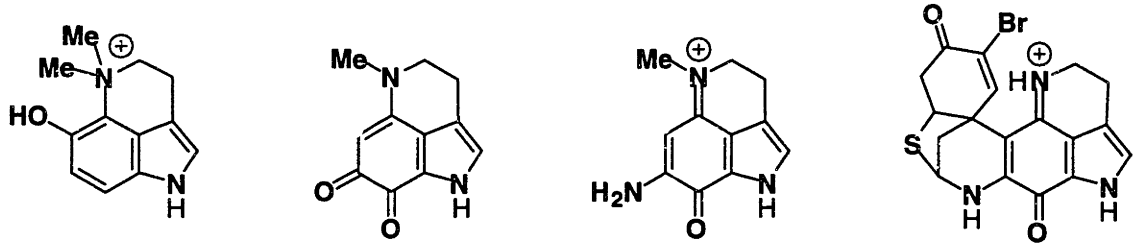
Chapter Two:

The Synthesis of Tetrahydropyrroloquinolines

Background

Recently, a number of indole alkaloids isolated from various marine sponges have been shown to contain a common structural subunit, a tetrahydropyrroloquinoline (Figure 1). Representative examples include the damirones,[1] makaluvamines,[2] discorhabdines,[3] batzellines,[4] isobatzellines,[5] prianosines,[6] and epinardines.[7] This framework was first recognized as an important feature of natural products when the structure of the toad poison, dehydrobufotenine, was determined.[8] These compounds have received considerable attention due to the fact that several exhibit potent *in vitro* cytotoxicity against human tumor cell lines, presumably acting as DNA topoisomerase II inhibitors.[9]

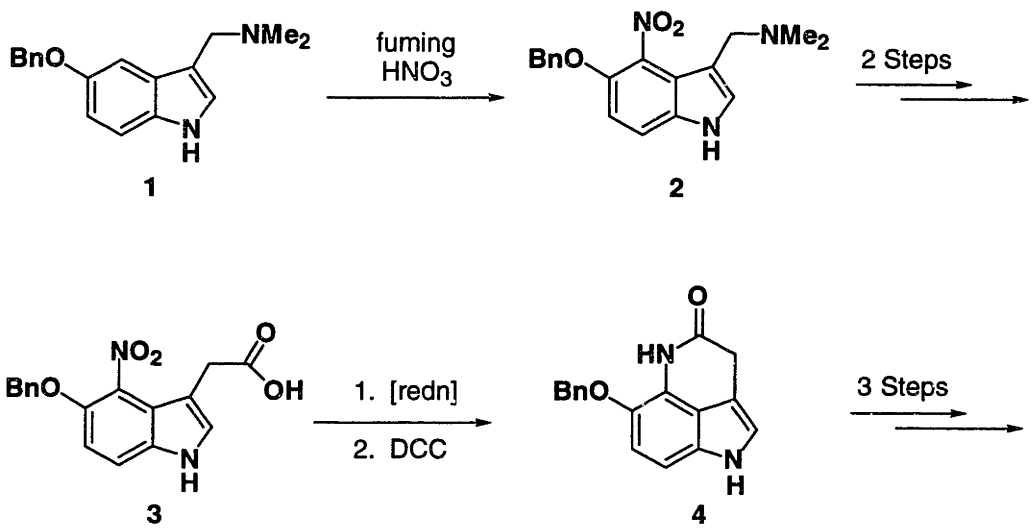
Figure 1



The majority of the synthetic work pertaining to these compounds can be divided into two categories based on the strategy employed. In the first approach, the tricyclic heterocycle is formed from a preexisting indole derivative and the six-membered nitrogen-containing ring is closed as a late step by one of two methods. The most common approach, which involves the cyclization of a 4-aminoindole bearing a two-carbon tether at the 3-position, has been employed in the syntheses of the *O*-methylnordehydrobufotenine,[10]

dehydrobufotenine,[11] makaluvamines,[12] batzelline C and isobatzelline C,[13] and discorbhadin C.[12a,b,14] For example, nitration of the gramine derivative **1** afforded the 4-nitroindole **2** as the sole regioisomer, which was then converted to the carboxylic acid **3** in two steps.[11] Reduction of the nitro-group, followed by lactam formation, afforded the tricyclic skeleton **4** in good yield, which was then converted to dehydrobufotenine (**5**) in three steps.

Scheme 1

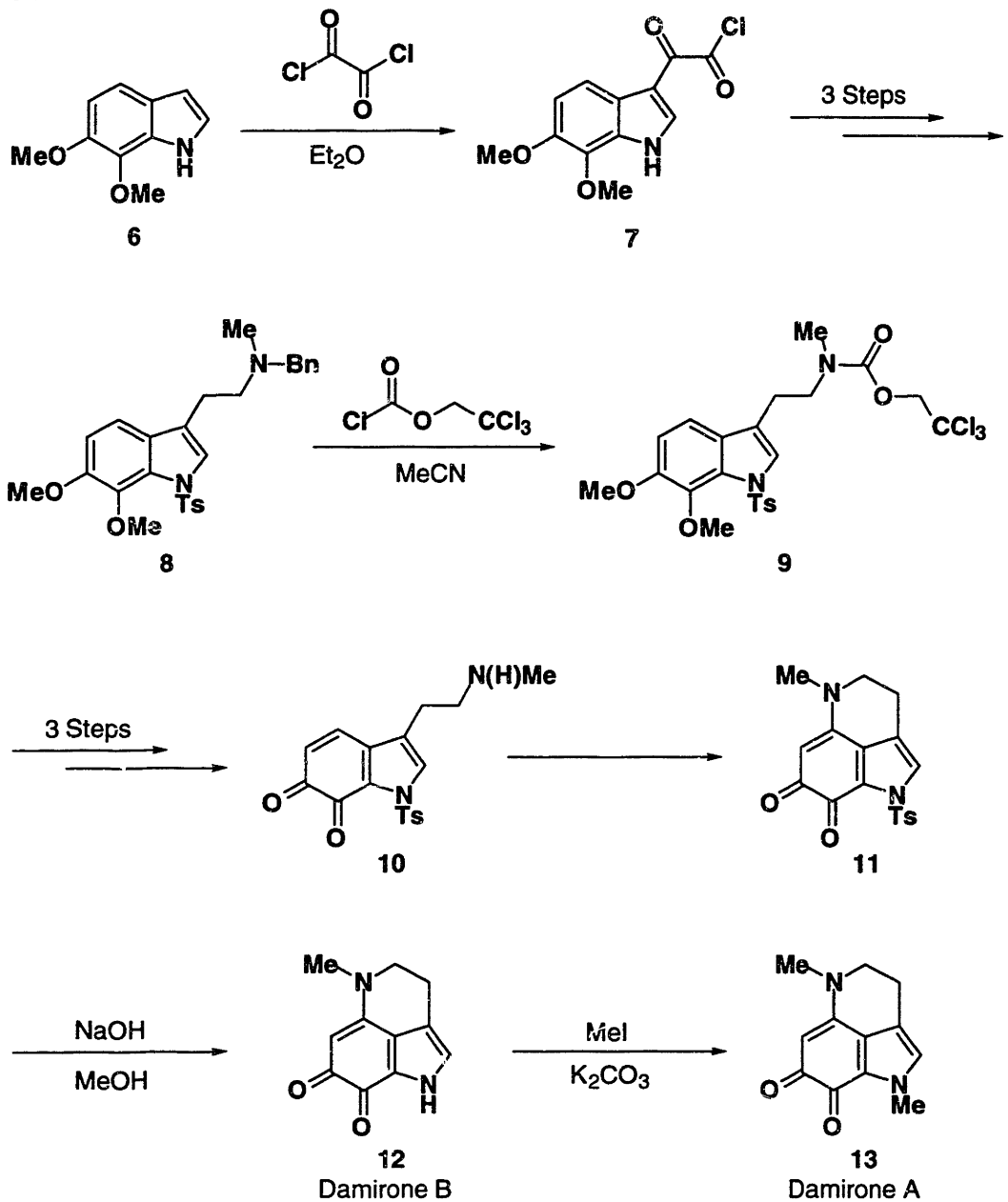


5
Dehydrobufotenine

Another approach to close the six-membered ring onto an indole precursor involves the cyclization of a tryptamine quinone. This strategy was employed by Cava and co-workers in the total syntheses of damirones A and B

(Scheme 2).[15] Treatment of the electron-rich indole **6** with oxalyl chloride afforded the 3-substituted acid chloride **7**, which was converted to the

Scheme 2

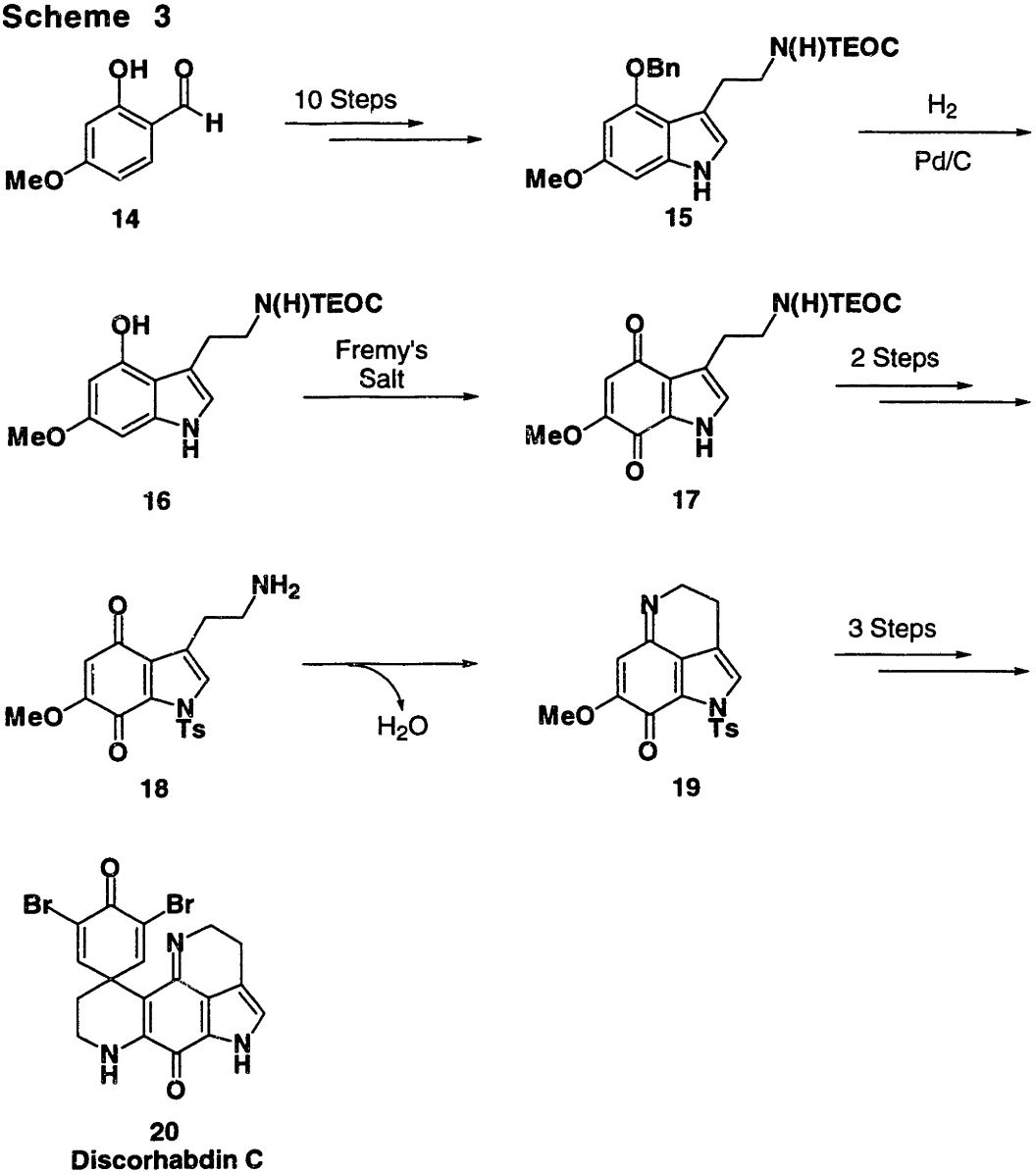


carbamate-protected tryptamine **9** in four steps. The *O*–Me groups were cleaved with BBr_3, and the hydroquinone was oxidized with ceric ammonium

nitrate (CAN). Deprotection of the nitrogen produced **10**, which subsequently cyclized via an intramolecular Michael addition followed by air-oxidation to give the tricyclic system **11**. Lastly, cleavage of the N–tosyl group gave damirone B (**12**), which was converted readily to damirone A (**13**) by treatment with MeI.

Similarly, Kita and co-workers have employed a tryptamine quinone intermediate in the total synthesis of discorhabdin C (Scheme 3).[16] First, the trisubstituted arene **14** was converted to the secondary tryptamine **15** in ten

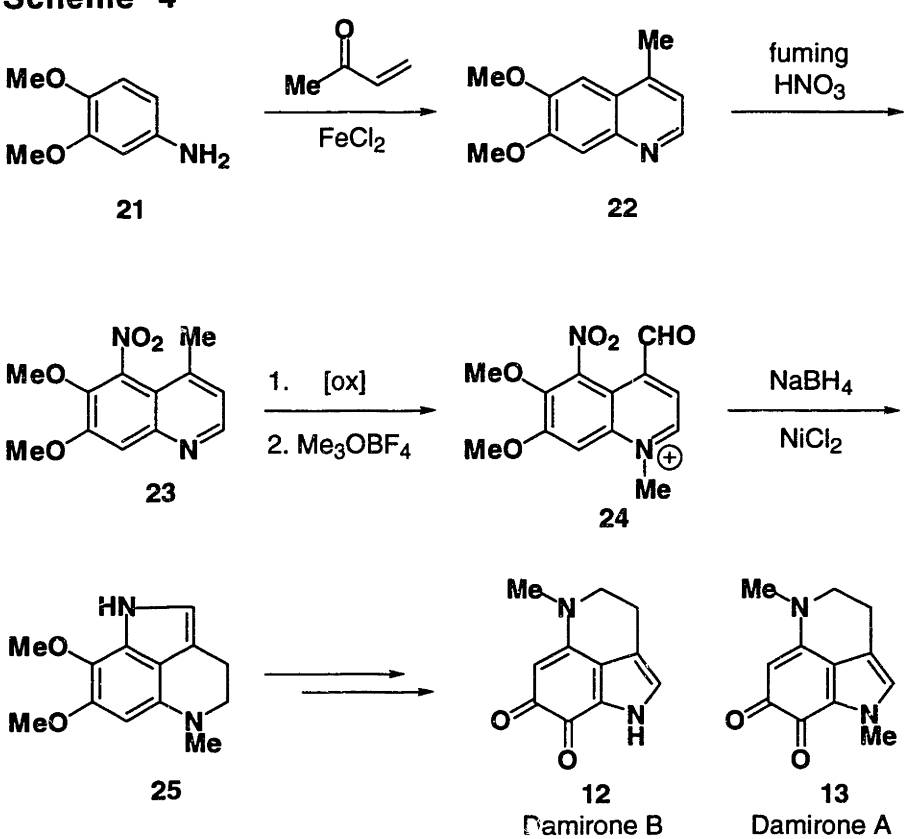
Scheme 3



steps. The *O*–Bn group was hydrogenated over Pd/C to give phenol **16**, which upon oxidization with Fremy's salt afforded the required quinone **17**. Cleavage of the *N*-protecting group with acid resulted in cyclization to yield the iminoquinone **19**, which was converted to discorhabdin C (**20**) in three steps.

The second strategy to construct the tetrahydropyrroloquinoline framework involves annulation of the pyrrole ring onto an appropriately substituted quinoline. Joule and co-workers have employed this approach in the syntheses of damirones A and B, batzelline C, isobatzelline C, discorhabdin C, and makaluvamines A-D.[17a-e] For example (Scheme 4), nitration of 6,7-

Scheme 4

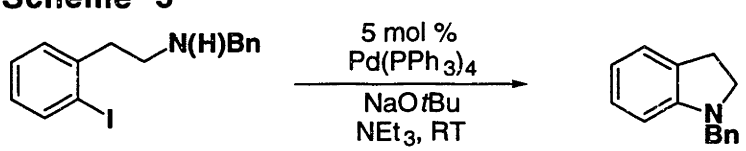


dimethoxy-4-methylquinoline **22**, which was prepared from 4-aminoveratrole (**21**), gave the nitrated quinoline **23** as the sole regioisomer.[17a,d] Oxidation of **23** gave the aldehyde, which upon treatment with Me_3OBF_4 afforded the *N*-quaternized quinoline **24**. Reduction of the nitro-group with $NaBH_4$ afforded the aniline, which readily cyclized to the tricyclic skeleton **25**. Compound **25** was then converted to damirones A (**12**) and B (**13**).

Results and Discussion

Recently, we became interested in developing novel approaches for the construction of tetrahydropyrroloquinoline natural products. We believed that the intramolecular olefin insertion reactions of zirconocene-stabilized benzyne complexes would allow for the facile formation of the highly functionalized, aromatic ring systems. In addition, we reasoned that the aryl-nitrogen bonds could be assembled using the palladium-catalyzed aryl amination reaction developed in our laboratories.[18] For example, treatment of the aryl iodide bearing a tethered amine **26** with sodium *t*-butoxide and catalytic $Pd(PPh_3)_4$ at RT yields the desired indoline adduct **27** in high yield.[18d,e]

Scheme 5

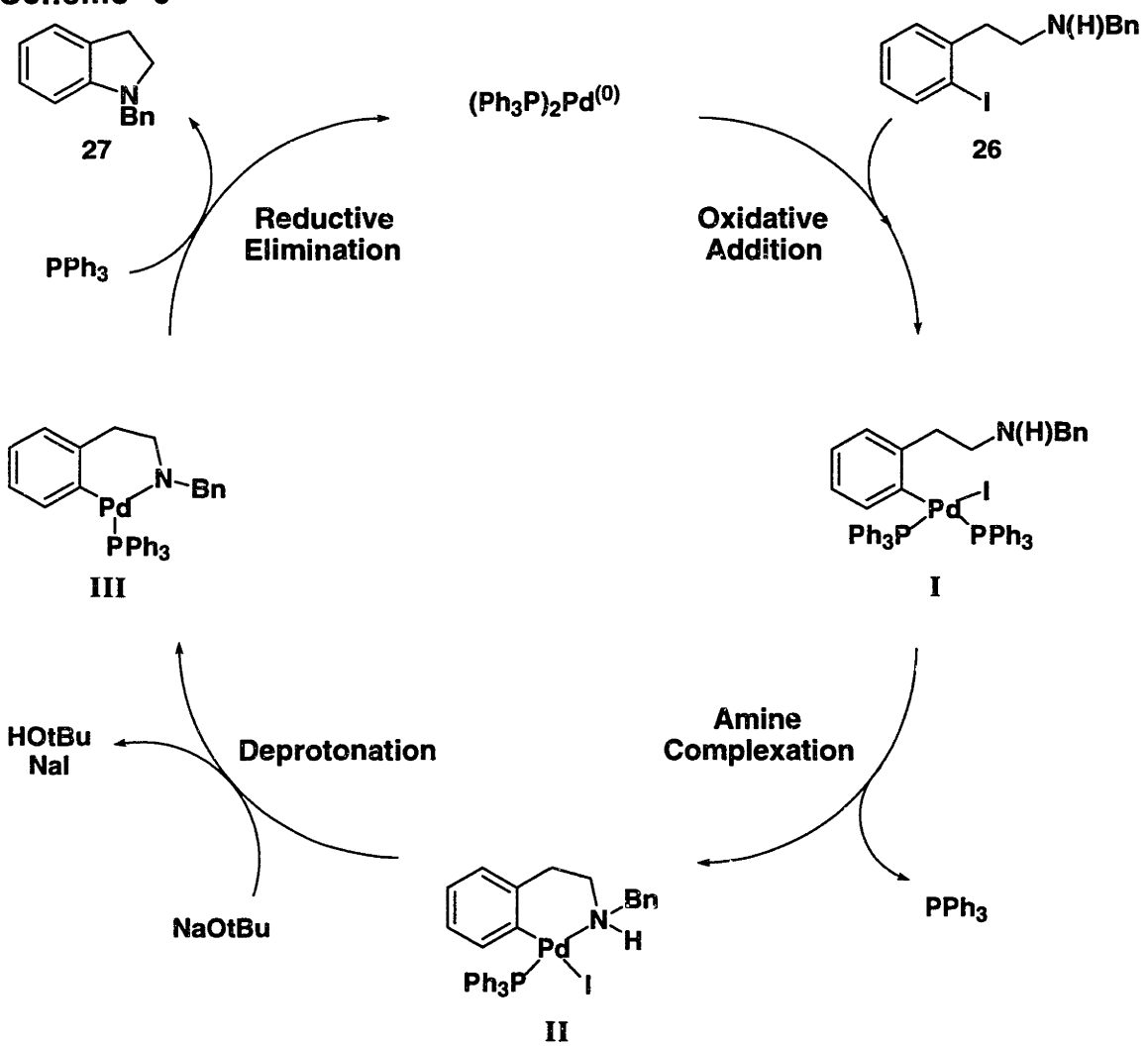


26 83-87% **27**

The proposed catalytic cycle for this reaction involves the dissociation of two triphenylphosphine ligands from $Pd(PPh_3)_4$ to generate the active $L_2Pd(0)$ catalyst (Scheme 6),[19] which oxidatively adds the aryl halide **26** to yield the

Pd(II) intermediate **I**. The amine complexes to the metal center with the loss of a phosphine ligand to give **II**. Deprotonation of the coordinated amine by sodium *t*-butoxide produces the Pd-amido complex **III**, which reductively eliminates the cyclized indoline **27** and regenerates the $L_2Pd(0)$ catalyst.

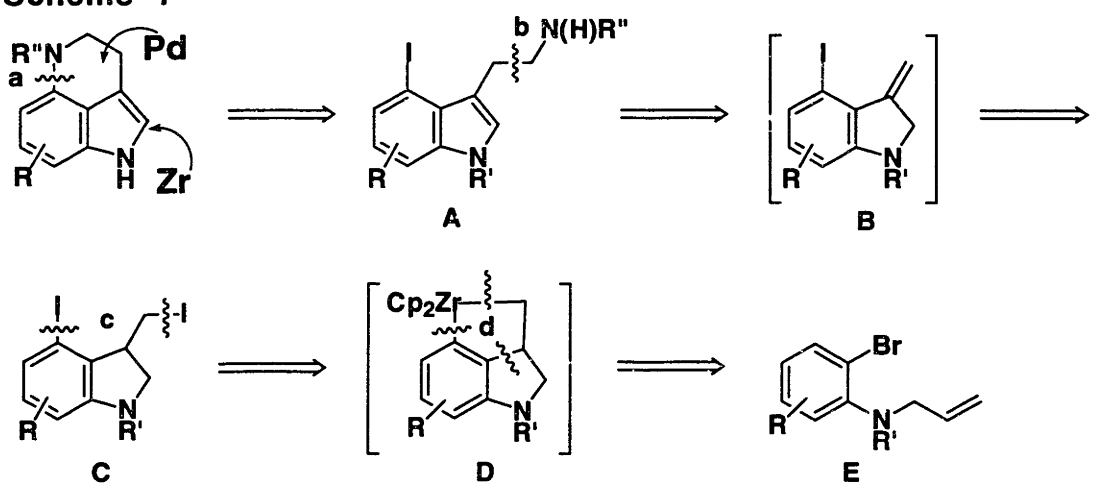
Scheme 6



From a retrosynthetic viewpoint, we envisioned two possible routes to the desired tricyclic systems. In the first approach (Scheme 7), disconnection of bond **a** (the aryl amine bond in the six-membered ring) yields a 4-iodo-

tryptamine **A**. We anticipated that this ring closure could be accomplished using the Pd-catalyzed intramolecular aryl amination reaction. Disconnection at bond **b** affords the exocyclic olefin **B**, which upon reaction with an electrophilic iminium ion as described by Tidwell and Buchwald[20] provides the necessary tryptamine. The olefin is prepared via dehydrohalogenation of the diiodoindoline **C**, which in turn is formed (bonds **c**) by the iodination of the metallacycle **D**. Disconnection of bonds **d** produces the appropriate starting material, an *N*-allyl-*o*-bromoaniline **E**. In this approach, the six-membered ring is closed as a late step by the Pd-catalyzed methodology, and the five-membered ring is formed by a zirconium-promoted reaction.

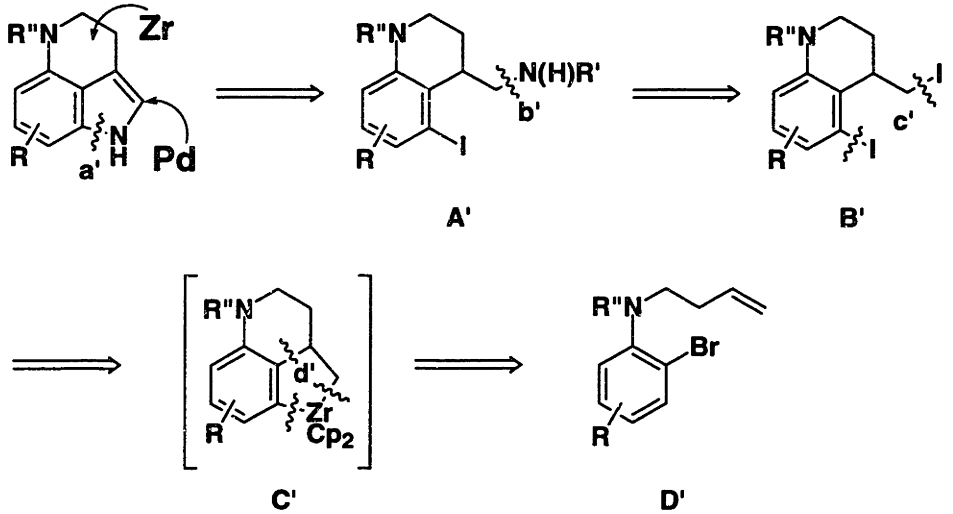
Scheme 7



The second approach to the tetrahydropyrroloquinolines is shown in Scheme 8. It is similar to the first approach, except that the five-membered ring is closed as a late step via the Pd-catalyzed reaction, and the six-membered ring is constructed via olefin insertion into the carbon-zirconium bond of the benzyne complex. Disconnection of bond **a'** yields a 4-aminomethyl-5-iodotetrahydroquinoline **A'**. The C–N bond **b'** is formed upon nucleophilic

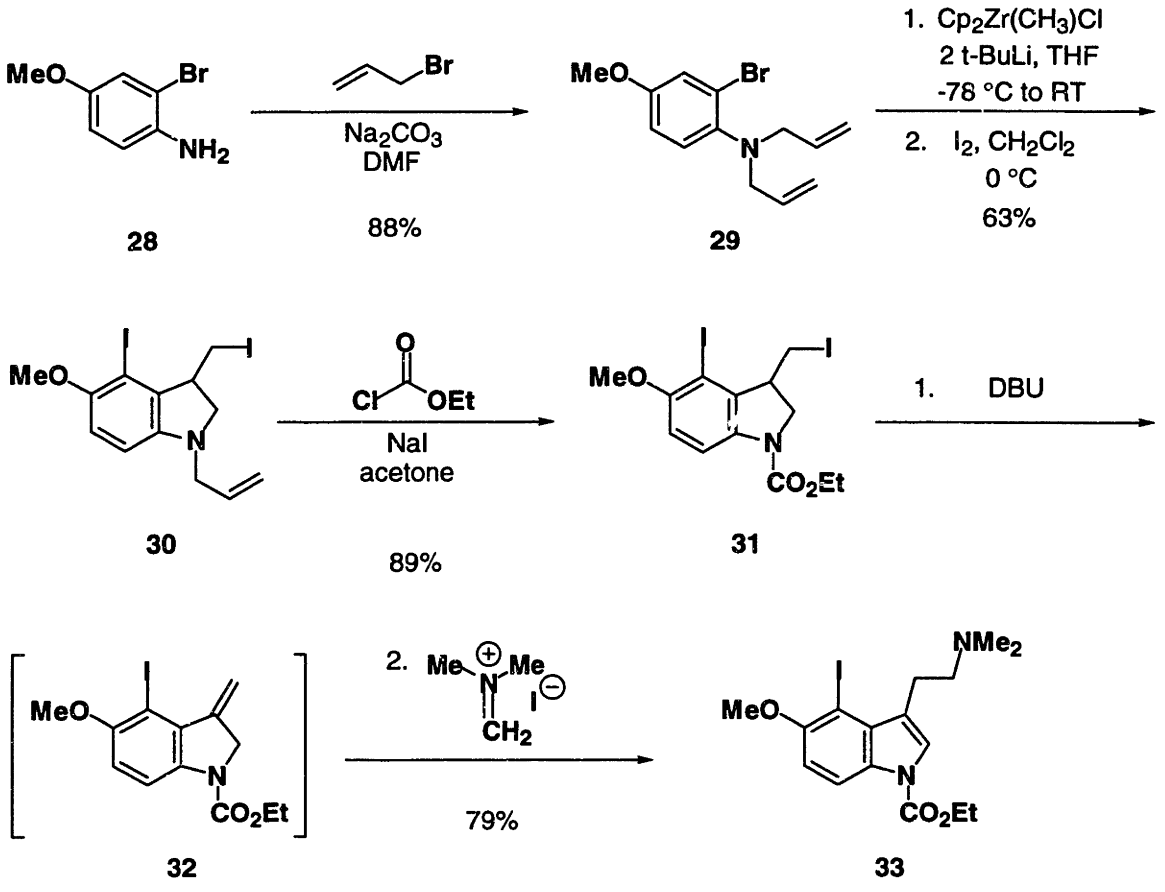
displacement of the alkyl iodide from **B'**. As in the above case, the carbon-iodide bonds **c'** are constructed via iodination of the metallacycle **C'**. Finally, disconnection at bonds **d'** affords the appropriate starting material, an *N*-homoallyl-*o*-bromoaniline **D'**.

Scheme 8



In an effort to demonstrate the utility of our first approach, we undertook the total synthesis of the South American toad poison, dehydrobufotenine **5**.[8,11] The synthesis of the required dimethyltryptamine **32** is shown in Scheme 9.[20] Treatment of *o*-bromo-*p*-anisidine[20] **28** with excess allyl bromide gave the diallylated aniline **29** in 88% yield. Slow addition of *t*-BuLi to a solution of **29** and $Cp_2Zr(Me)Cl$ in THF at –78 °C, followed by heating to 65 °C, gave the 5,5,6-tricyclic metallacycle. The solvent was removed *in vacuo* and CH_2Cl_2 was added. Addition of iodine in CH_2Cl_2 at 0 °C afforded the diiodoindoline

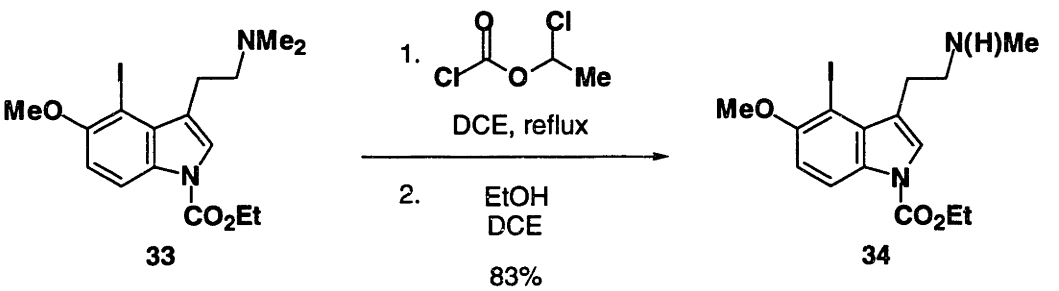
Scheme 9



30 in 63% yield. Based on previous work in our laboratories, we recognized that the *N*-allyl group must be converted to another protecting group at this stage, since it is quite difficult to remove once the indoline is oxidized to the indole derivative.[20] Using a modified Olofson dealkylation procedure developed by Tidwell and Buchwald,[20] **30** was treated with ethyl chloroformate and NaI in acetone to afford the ethyl carbamate-protected indoline **31** in 89% yield. This protecting group can be cleaved by a variety of methods at the conclusion of our synthesis.[21] Dehydrohalogenation of the diiodide produced the exocyclic olefin **32**, which underwent an ene-type reaction with Eschenmoser's salt to give the desired dimethyltryptamine **33** in 79% yield.

At this point, we needed to remove one of the *N*-methyl groups. Although there are several methods for the cleavage of alkyl groups from amines, many of the procedures suffer from harsh reaction conditions and/or expensive reagents.[21,22] A particularly attractive method reported by Olofson and co-workers employs α-chloroethyl chloroformate (ACE-Cl).[22] In addition to the fact that the reagents are inexpensive and the conditions are quite mild, the authors report that *N*-methyl groups are readily removed. Therefore, the dimethyltryptamine **33** was treated with excess ACE–Cl at 0 °C in dichloroethane (DCE), then heated to reflux for 12 h (Scheme 10). Upon removal of the solvent and excess ACE-Cl, the residue was heated to reflux in DCE and EtOH which afforded the secondary tryptamine **34** in 83% yield.

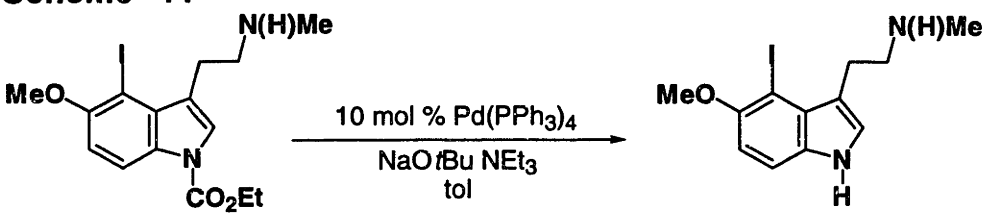
Scheme 10



With the requisite secondary tryptamine in hand, we were ready to attempt the palladium-catalyzed aryl amination reaction to close the six-membered ring. Following the protocol developed by Buchwald and co-workers for the intramolecular coupling of aryl iodides and amines,[18d,e] **34** was treated with triethylamine, sodium *t*-butoxide, and a catalytic amount of $Pd(PPh_3)_4$ in toluene (Scheme 11). Unfortunately, none of the desired cyclized product was detected. Instead, we obtained only the deprotected indole

derivative **35**. The sodium *t*-butoxide required to deprotonate the Pd-complexed amine is also capable of cleaving the ethyl carbamate.[21]

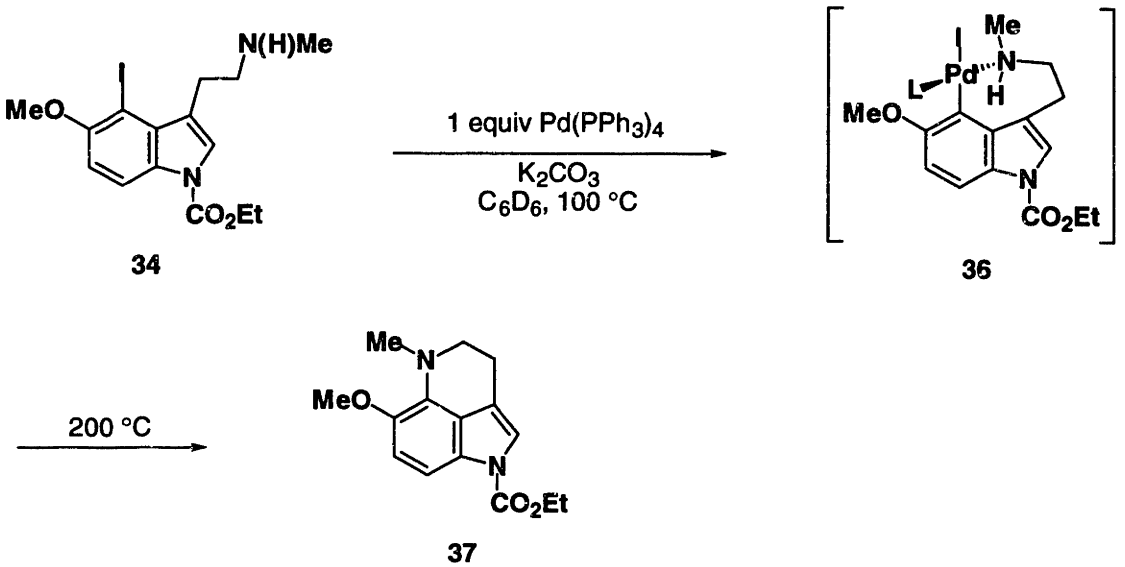
Scheme 11



34 **35**

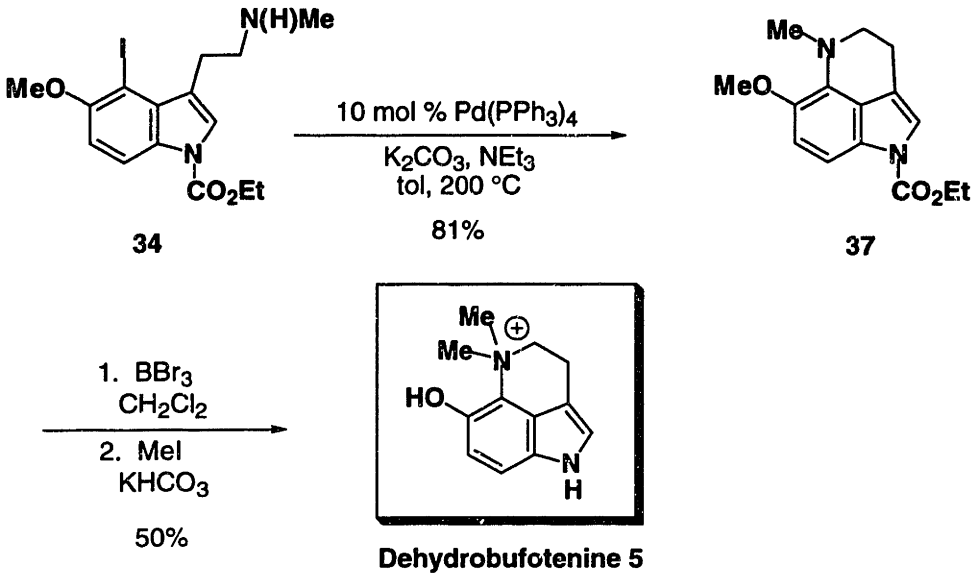
Next, we investigated the use of weaker bases such as carbonates, which could deprotonate the complexed amine while leaving the carbamate intact. Upon heating **34** with one equivalent of K_2CO_3 and a stoichiometric amount of $Pd(PPh_3)_4$ in C_6D_6 in a sealed NMR tube to 100 °C, we were pleased to find that the indole protecting group was left intact. More importantly, we observed the quantitative conversion of **34** to the oxidative-addition complex **37** (Scheme 12). An increase in the temperature of the oil bath to 200 °C gave the tricyclic indole **37** in good yield as estimated by ^1H NMR.

Scheme 12



Based on the success of the ^1H NMR experiment, our next goal was to make the transformation catalytic with respect to palladium. A mixture of **34**, K_2CO_3, NEt_3, toluene, and 10 mol % of $Pd(PPh_3)_4$ was heated in a sealed tube to 200 °C to afford the desired tricyclic compound **37** in 81% isolated yield (Scheme 13). Addition of excess BBr_3 in CH_2Cl_2 at 0 °C removed both the *O*-methyl group, as well as the ethyl carbamate.[23] The solvent and excess BBr_3 were removed and the residue was dissolved in MeOH. Methyl iodide and $KHCO_3$ were added to the solution resulting in the quaternization of the amine yielding dehydrobufotenine **5**.[24] This represents the second synthesis of dehydrobufotenine.[11]

Scheme 13

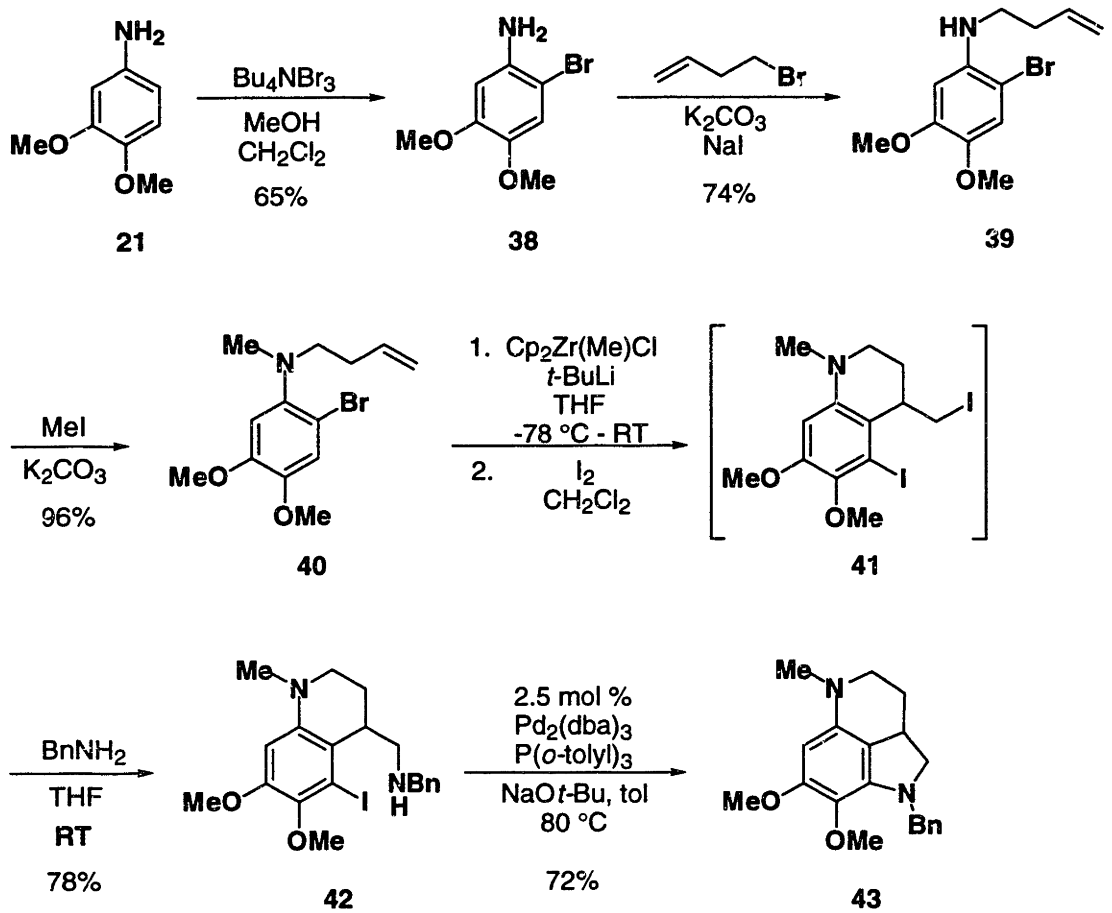


Although we were able to complete the total synthesis of dehydrobufotenine, we recognize that the above synthesis is not ideal due to the unusually high reaction temperature required for the Pd-catalyzed ring-closure. These harsh conditions are a result of the incompatibility of the optimal base for the Pd-catalyzed aryl amination reaction, NaO*t*-Bu, with the ethyl carbamate protecting group. An obvious solution to this problem would be to change the indole protecting group. Unfortunately, benzyl- or allyl-protecting groups are not an option since they are difficult to remove from an indole nitrogen.[20] One possibility would be the use of the bulky *t*-butyl carbamate. However, instead of exhaustively varying protecting groups, we decided to focus on our second approach.

In an effort to evaluate the synthetic utility of this strategy, we undertook the formal syntheses of makaluvamine C and damirones A & B. Commercially available 4-aminoveratrole **21** was brominated with tetrabutylammonium tribromide in 65% yield (Scheme 14).[25] The aniline **38** was alkylated first with 4-bromo-1-butene, then methyl iodide to generate the appropriate starting

material **40** in 71% overall yield. Slow addition of *t*-BuLi to a solution of **40** and $Cp_2Zr(Me)Cl$ in THF at –78 °C, followed by heating to 65 °C, produced the

Scheme 14

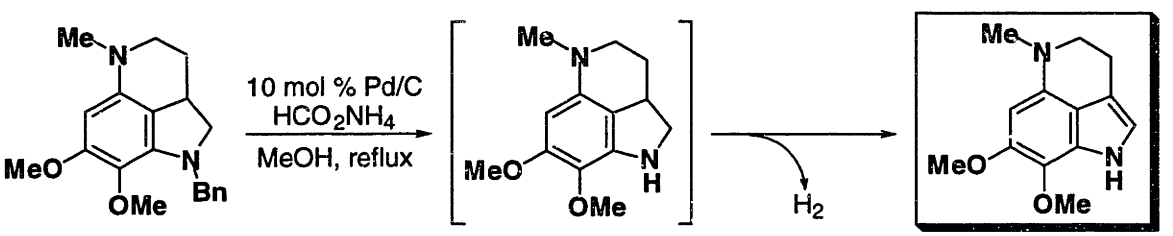


5,6,6-tricyclic metallacycle, which was treated with iodine. The diiodide **41** was not isolated but treated immediately with excess benzylamine at *room temperature* forming the 4-aminomethyl-tetrahydroquinoline **42** in good overall yield. It should be noted that upon heating, the diiodide undergoes facile rearrangement which will be discussed later in greater detail. Since there was no base-sensitive functionality present, we could employ NaO*t*-Bu as the base for the Pd-catalyzed ring-closing reaction. Reaction of **42** with $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, and NaO*t*-Bu gave the tricyclic systems **43** in good yields. This strategy

allows for the simple, efficient construction of the tricyclic *indoline* framework and is complementary to the first approach which forms the tricyclic *indole* skeleton.

The fact that this approach forms the indoline, as opposed to the indole, derivative is quite significant since the benzyl group can be readily removed at this stage by a variety of methods.[21] We decided to use a procedure reported by Naito and co-workers which removes the benzyl group from an indoline nitrogen with subsequent oxidation of the indoline ring.[26] Addition of 10 mol % Pd/C and excess ammonium formate to a solution of **43** in refluxing MeOH leads first to the reduction of the benzyl group affording the deprotected indoline **44**. Upon further heating, the indoline is dehydrogenated to produce the desired tricyclic indole **45** in 80% yield. The conversion of **45** to makaluvamine C and damirones A & B has been reported,[12c,17d] therefore this represents the formal syntheses of these natural products.

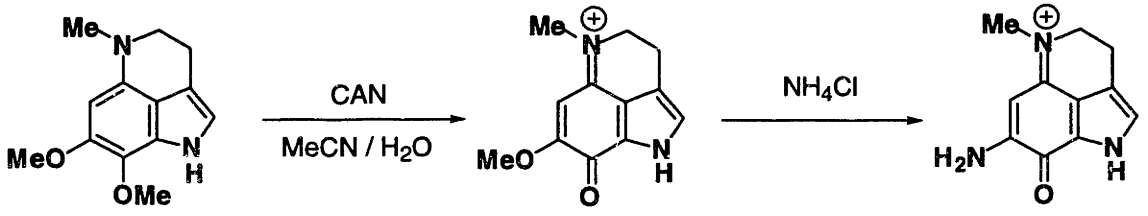
Scheme 15



43 **44** **45**

The conversion of the dimethoxyindole **45** into makaluvamine C (**47**), reported by Nishiyama and Yamamura, involved oxidation using cerium ammonium nitrate (CAN) to produce the iminoquinone **46** (Scheme 16).[12c] Addition of ammonium chloride afforded the natural product **47**.

Scheme 16

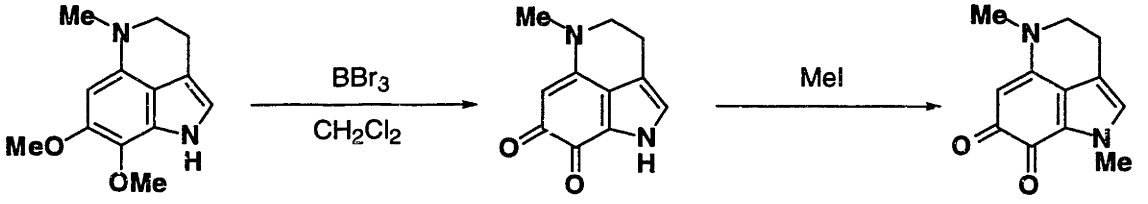


45 **46** **47**

Makaluvamine C

In addition, Joule and co-workers reported that treatment of **45** with BBr_3 affords the natural product damirone B (**12**) (Scheme 17).[17d] Subsequent alkylation of the indole nitrogen with MeI produced damirone A (**13**).

Scheme 17



45 **12** **13**

Damirone B **Damirone A**

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. 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 a 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 cross linked SE-30 as a stationary phase. Electron impact mass spectra and high resolution mass determinations (HRMS) were recorded on a Finnegan MAT System 8200. Tetrahydrofuran, benzene, diethyl ether, and hexane were dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation. Methylene chloride was dried by refluxing over CaH_2 under nitrogen 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. Cp_2ZrCl_2 was purchased from Boulder Scientific Inc., Mead, Colorado, which was converted to $Cp_2Zr(Me)Cl$. 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 combustion analysis. All reported yields

are representative. Elemental analyses were performed by E & R Microanalytical Laboratory, Inc., Corona, N.Y.

34. 1-Chloroethyl chloroformate (0.54 mL, 5 mmol) was added dropwise to a solution of **33** (0.35 g, 0.84 mmol) in dichloroethane (6 mL) at 0 °C. The solution was stirred at 0 °C for 10 min then heated to reflux. After 12 h, the solution was cooled to RT and the solvent was removed using a rotary evaporator to yield a red/white precipitate. The precipitate was dissolved in dichloroethane (6 mL), then EtOH (6 mL) was added dropwise. The red solution was heated to reflux for 12 h, cooled to RT, and the solvent was removed using a rotary evaporator. The residue was partitioned between Et_2O (15 mL) and 1N NaOH solution (15 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (2:6:2 hexane: ethyl acetate: NEt_3) to give 0.28 g (82%) of a white solid, mp 208-210.5 °C. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.18 (d, J = 8.5 Hz, 1 H), 7.49 (s, 1 H), 6.90 (d, J = 8.8 Hz, 1 H), 4.45 (q, J = 7.1 Hz, 2 H), 3.92 (s, 3 H), 3.17 (t, J = 7.1 Hz, 2 H), 2.96 (t, J = 7.1 Hz, 2 H), 2.49 (s, 3 H), 1.45 (t, J = 7.1 Hz, 3 H), 1.17 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.2, 150.1, 132.3, 131.7, 125.7, 120.2, 115.6, 108.8, 77.2, 63.1, 57.5, 52.4, 36.4, 26.4, 14.3. IR (KBr, cm^{-1}) 3239, 2934, 2784, 1733, 1411, 1252, 1128. Anal. Calcd for $C_{15}H_{19}N_2O_3I$: C, 44.79; H, 4.76. Found: C, 44.69; H, 4.91.

37. $Pd(PPh_3)_4$ (92 mg, 0.08 mmol) was added to a mixture of **34** (0.32 g, 0.80 mmol), NEt_3 (4 mL), and K_2CO_3 (0.33 g, 2.4 mmol) in toluene (10 mL). The yellow mixture was heated to 200 °C for 15 h, cooled to RT, and poured into a separatory funnel containing Et_2O (15 mL) and water (15 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was

purified by flash chromatography (4:1 hexane: ethyl acetate) to give 0.18 g (82%) of a white powder, mp 71.1-72.8 °C. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.42 (br s, 1 H), 7.16 (s, 1 H), 6.90 (d, J = 8.9 Hz, 1 H), 4.45 (q, J = 7.5 Hz, 2 H), 3.87 (s, 3 H), 3.27 (t, J = 6.6 Hz, 2 H), 3.09 (s, 3 H), 2.85 (t, J = 6.5 Hz, 2 H), 1.44 (t, J = 7.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.5, 144.0, 131.2, 129.4, 123.3, 117.4, 116.0, 113.0, 107.1, 62.7, 57.6, 52.7, 41.1, 20.0, 14.4. IR ($CDCl_3$, cm^{-1}) 3129, 2951, 1726, 1408, 1258, 1080. Anal. Calcd for $C_{15}H_{18}N_2O_3$: C, 65.68; H, 6.61. Found: C, 65.75; H, 6.56.

Dehydrobufotenine (5).[11] A solution of 1M BBr_3 in CH_2Cl_2 (1 mL, 1 mmol) was added dropwise to a flask containing **37** (46 mg, 0.17 mmol) in CH_2Cl_2 (10 mL) at -78 °C . The solution was warmed to RT overnight, then the solvent was removed *in vacuo*. CH_2Cl_2 (10 mL) and $KHCO_3$ (0.14 g, 1.0 mmol) were added, then the mixture was cooled to 0 °C and MeOH (5 mL) was added dropwise. After 0.5 h at 0 °C, the mixture was warmed to RT and stirred for 1 h. The solvent was removed *in vacuo*, and the residue was dissolved in MeOH (5 mL). Methyl iodide (16 μL, 0.26 mmol) was added and the mixture was stirred at RT until TLC (10% MeOH/MeCN) showed no remaining starting material. The solvent was removed using a rotary evaporator and the residue was extracted with CH_2Cl_2. The organic phase was concentrated to give a gray solid. Slow recrystallization from MeOH gave 28 mg (50%) of a gray/white solid, mp 241.0-243.8 °C. ^{1}H NMR (CD_3OD, 300 MHz) δ 7.09 (d, J = 8.3 Hz, 1 H), 6.90 (s, 1 H), 6.62 (d, J = 8.3 Hz, 1 H), 3.9 (t, J = 5.4 Hz, 2 H), 3.7 (s, 6 H), 3.24 (t, J = 5.4 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.4, 134.2, 130.4, 122.6, 120.0, 114.8, 104.1, 102.8, 69.5, 53.7, 20.2. Anal. Calcd for $C_{12}H_{15}N_2OI$: C, 43.65; H, 4.58. Found: C, 43.97; H, 4.46.

2-bromo-4,5-dimethoxyaniline (38).[27] Bu_4NBr_3 (36 g, 75 mmol) was added to a solution of 4-aminoveratrole (**21**) (10 g, 65 mmol) in CH_2Cl_2

(265 mL) and MeOH (130 mL). After 20 min at RT, the solution was poured into a separatory funnel containing Et_2O (300 mL) and sat. Na_2SO_3 solution (300 mL). The organic layer was washed with water (200 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (10:1 then 4:1 hexane: ethyl acetate) to give 10.7 g (67%) of a purple oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.92 (s, 3 H), 6.38 (s, 1 H), 3.83-3.76 (br s, 2 H), 3.81 (s, 3 H), 3.78 (s, 3 H).

39. A mixture of **38** (9.9 g, 42.7 mmol), sodium iodide (19.4 g, 129 mmol), K_2CO_3 (17.8 g, 129 mmol), and 4-bromo-1-butene (6.5 mL, 64 mmol) in DMF (150 mL) was heated to 100 °C for 10 h, cooled to RT, and poured into a separatory funnel containing Et_2O (200 mL) and water (200 mL). The organic layer was washed with water (2 x100 mL), brine (100 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (10:1 then 4:1 hexane: ethyl acetate) to give 9.0 g (74%) of a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.97 (s, 1 H), 6.28 (s, 1 H), 5.82 (m, 1 H), 5.17 (m, 2 H), 4.00 (br s, 1 H), 3.86 (s, 3 H), 3.79 (s, 3 H), 3.20 (q, J = 6.1 Hz, 2 H), 2.42 (q, J = 5.9 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.2, 140.6, 139.4, 134.9, 116.9, 116.4, 98.4, 96.9, 56.5, 55.6, 43.2, 33.1. IR (film, cm^{-1}) 3395, 2931, 1515, 1211. HRMS (EI) calcd for $C_{12}H_{16}N_1O_2Br$: 285.03644. Found: 285.03667 amu.

40. A mixture of **39** (2.5 g, 8.74 mmol), K_2CO_3 (3.62 g, 26.2 mmol), and methyl iodide (1.62 mL, 26.2 mmol) in DMF (30 mL) was heated to 100 °C for 2 h, cooled to RT, and poured into a separatory funnel containing Et_2O (75 mL) and water (75 mL). The organic layer was washed with water (2 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator to give 2.45 g (94%) of a pale yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.04 (s, 1 H), 6.70 (s, 1 H), 5.82 (m, 1 H), 5.02 (m, 2 H), 3.86 (s, 3 H),

3.84 (s, 3 H), 2.99 (t, J = 7.8 Hz, 2 H), 2.72 (s, 3 H), 2.27 (q, J = 7.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 148.7, 144.9, 144.2, 136.3, 116.4, 115.8, 110.9, 106.5, 56.4, 56.2, 42.1, 32.1. IR (film, cm^{-1}) 3075, 2935, 2839, 1504, 1213, 1034. HRMS (EI) calcd for $C_{13}H_{18}N_1O_2Br$: 299.05209. Found: 299.05272 amu.

42. A solution of 1.7M *t*-BuLi (1.56 mL, 2.66 mmol) was added dropwise to a Schlenk flask containing **40** (0.4 g, 1.33 mmol) and $Cp_2Zr(Me)Cl$ (0.36 g, 1.33 mmol) in THF (7 mL) at -78 °C. The solution was stirred at -78 °C for 3 h, then warmed to RT. After 10 h, the THF was removed *in vacuo* to give an orange foam, which was dissolved in CH_2Cl_2 (7 mL). The solution was cooled to 0 °C and a solution of iodine (1 g, 3.99 mmol) in THF (1 mL) and CH_2Cl_2 (7 mL) was added quickly. The purple solution was stirred at 0 °C for 3 h, then warmed to RT. After 3 h, the solution was poured into a separatory funnel containing Et_2O (25 mL) and sat. Na_2SO_3 solution (25 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator to give an orange oil. Note: the diiodide compound should not be heated since it undergoes facile rearrangement to the indoline isomer. The oil was dissolved in THF (1 mL), cooled to 0 °C, and benzylamine (15 mL) was added. The solution was allowed to warm to RT overnight, then the excess benzyl amine was removed via Kugelrohr distillation. Flash chromatography (2:1 hexane: ethyl acetate with 5% NEt_3) of the remaining residue gave 0.47 g (78%) of an orange oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33 - 7.19 (m, 5 H), 6.12 (s, 1 H), 3.87 (d, J = 13.8 Hz, 1 H), 3.79 (s, 3 H), 3.77 (d, J = 13.8 Hz, 1 H), 3.69 (s, 3 H), 3.20 (dt, J = 4.0, 11.7 Hz, 1 H), 3.10 - 3.00 (m, 2 H), 2.85 (s, 3 H), 2.82 (dd, J = 2.9, 9.3 Hz, 1 H), 2.44 (dd, J = 10.6, 13.2 Hz, 1 H), 2.19 (m, 1 H), 1.79 (m, 1 H), 1.39 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.3, 143.5, 140.8, 139.3, 128.3, 128.0, 126.8, 117.9, 101.7, 96.8, 60.4, 56.0, 53.8, 51.8, 46.4, 41.2,

39.1, 23.2. IR (film, cm^{-1}) 3332, 2926, 1592, 1494, 1262, 1018. HRMS (EI) calcd for $C_{20}H_{25}N_2O_2I$: 452.09608. Found: 452.09573 amu.

43. A mixture of **42** (0.4 g, 0.88 mmol), $Pd_2(dba)_3$ (20 mg, 0.022 mmol), P(*o*-tolyl)$_3$ (28 mg, 0.088 mmol), and NaO*t*-Bu (0.34 g, 3.52 mmol) in toluene (5 mL) was heated to 80 °C for 20 h, cooled to RT, and poured into a separatory funnel containing Et_2O (20 mL) and water (20 mL). The organic layer was washed with water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (10:1 hexane: ethyl acetate) to give 0.21 g (72%) of a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.44 - 7.26 (m, 5 H), 5.75 (s, 1 H), 5.14 (d, *J* = 14.5 Hz, 1 H), 4.01 (d, *J* = 14.4 Hz, 1 H), 3.87 (s, 3 H), 3.73 (s, 3 H), 3.43 (t, *J* = 8.1 Hz, 1 H), 3.22 - 3.14 (m, 3 H), 2.90 (s, 3 H), 2.68 (dd, *J* = 8.5, 11.9 Hz, 1 H), 2.07 (m, 1 H), 1.70 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.7, 142.9, 139.4, 139.3, 128.4, 128.2, 127.2, 126.8, 108.4, 87.3, 62.2, 61.1, 56.3, 54.5, 51.0, 37.8, 35.4, 27.0. IR (film, cm^{-1}) 2934, 2822, 1622, 1504, 1256, 1101. HRMS (EI) calcd for $C_{20}H_{24}N_2O_2$: 324.18378. Found: 324.18341.

45.[12c, 17d] A mixture of **43** (0.12 g, 0.37 mmol), 5 mol % Pd/C by weight (79 mg, 0.037 mmol) and ammonium formate (0.23 g, 3.7 mmol) in MeOH (6 mL) was heated to reflux for 17 h, cooled to RT, and filtered thru Celite. The MeOH was removed via rotary evaporation and the residue was dissolved in CH_2Cl_2 (10 mL). The organic phase was washed with water (5 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (4:1 hexane: ethyl acetate) to give 69 mg (80%) of an amorphous solid. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.97 (br s, 1 H), 6.64 (s, 1 H), 6.01 (s, 1 H), 3.94 (s, 3 H), 3.92 (s, 3 H), 3.26 (t, *J* = 5.7 Hz, 2 H), 3.04 (t, *J* = 5.7 Hz, 2 H), 2.94 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.2,

139.2, 127.8, 114.7, 114.4, 111.0, 89.3, 61.0, 58.2, 52.8, 38.2, 23.4. IR (film, cm^{-1}) 3345, 2932, 1621, 1520.

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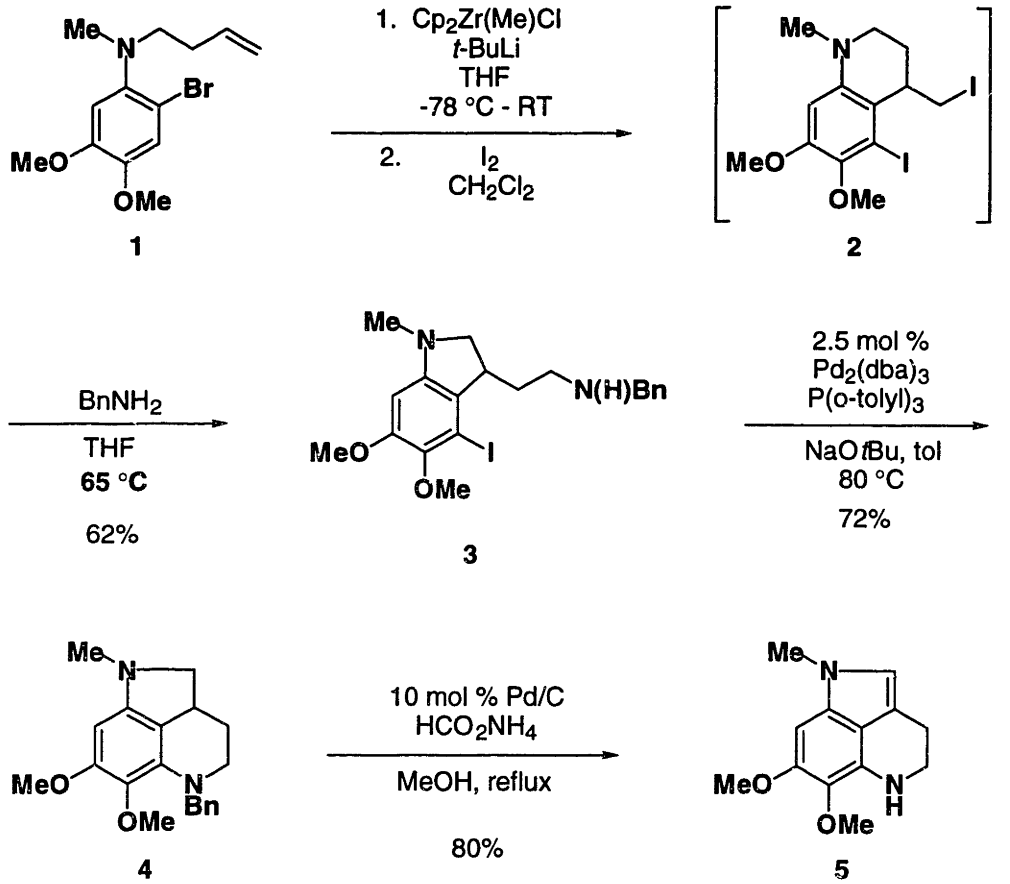
Chapter Three:

Preliminary Investigations of the Rearrangement of 5-Iodo-4-Iodomethyltetrahydropyrroloquinolines

Results and Discussion

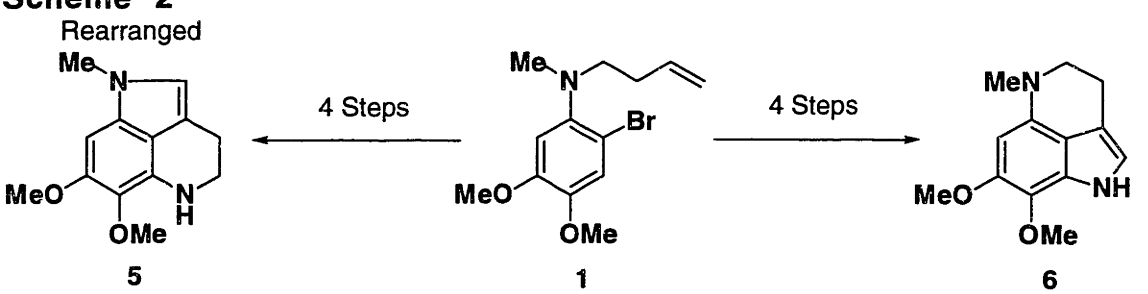
While exploring the synthesis of makaluvamine C and damirones A & B, we discovered an interesting side reaction. When the diiodide **2** was treated with benzylamine at RT, the alkyl iodide was displaced to give the 4-aminomethyl-tetrahydroquinoline as previously shown in Chapter 2 (Scheme 14).[1] However, if **2** was treated with benzylamine in THF and the solution was heated to reflux, we unexpectedly obtained the rearranged aminoindoline compound **3** in good yield (Scheme 1). This compound was treated with NaO*t*-Bu, P(*o*-tolyl)$_3$, and a catalytic amount of $Pd_2(dba)_3$ to close the six-membered ring and form the tricyclic system **4**.[2] The benzyl group was cleaved and the indoline ring was dehydrogenated using Pd/C and ammonium formate to

Scheme 1



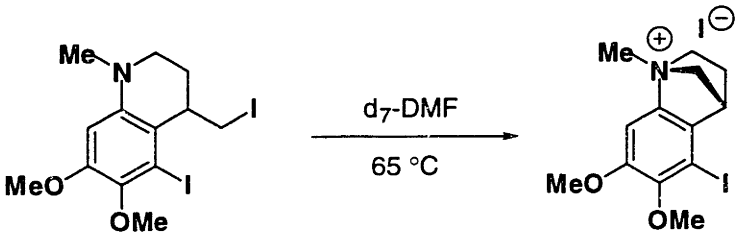
produce the tetrahydropyrroloquinoline **5** in good yield.[3] We believed that this rearrangement reaction could be synthetically useful since two tricyclic indole derivatives **5** and **6** can be efficiently constructed from a common starting material (Scheme 2).

Scheme 2



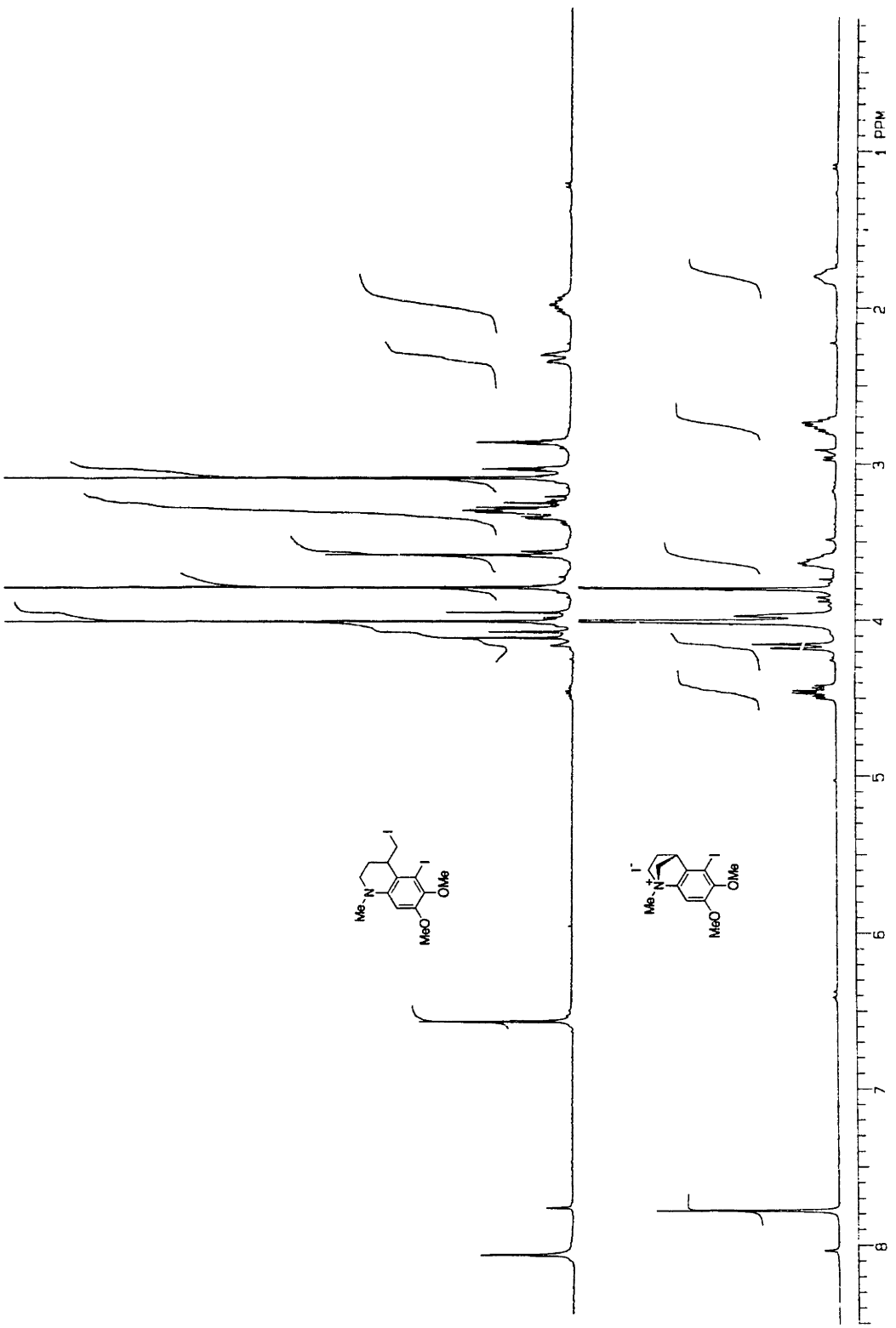
We decided to examine the chemistry of 6,7-dimethoxy-5-iodo-4-iodomethyl-*N*-methyltetrahydroquinoline (**2**) in greater detail. Upon heating a solution of **2** in d_7-DMF to 65 °C, we observed by ^1H NMR spectroscopy the quantitative conversion of **2** to the quaternized intermediate **7** (Scheme 3). We assigned the structure of **7** based on the large downfield shifts of the *N*-methyl group (from 2.97 ppm to 3.83 ppm) and of the aromatic proton (from 6.42 ppm to 7.75 ppm), which would be expected upon formation of the ammonium ion (Figure 1).

Scheme 3



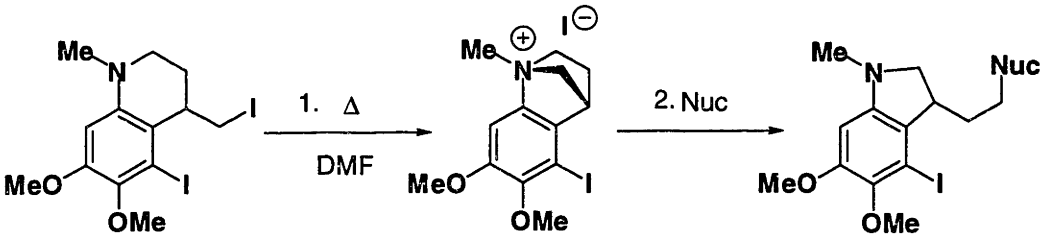
2 **7**

Figure 1 (NMR spectra in d7-DMF for Compounds 2 and 7)



Next, we investigated the reactions of **2** with several nucleophiles (Table 1). A solution of **2** was heated to 65 °C in DMF for 1 h, then KCN was added. After 2 h at 90 °C, we obtained a 97% yield of the desired indoline adduct (Table 1, entry 1). In a similar fashion, the use of dimethyl malonate and 18-crown-6 gave the malonate indoline derivative in 77% yield (Table 1, entry 2).

Table 1

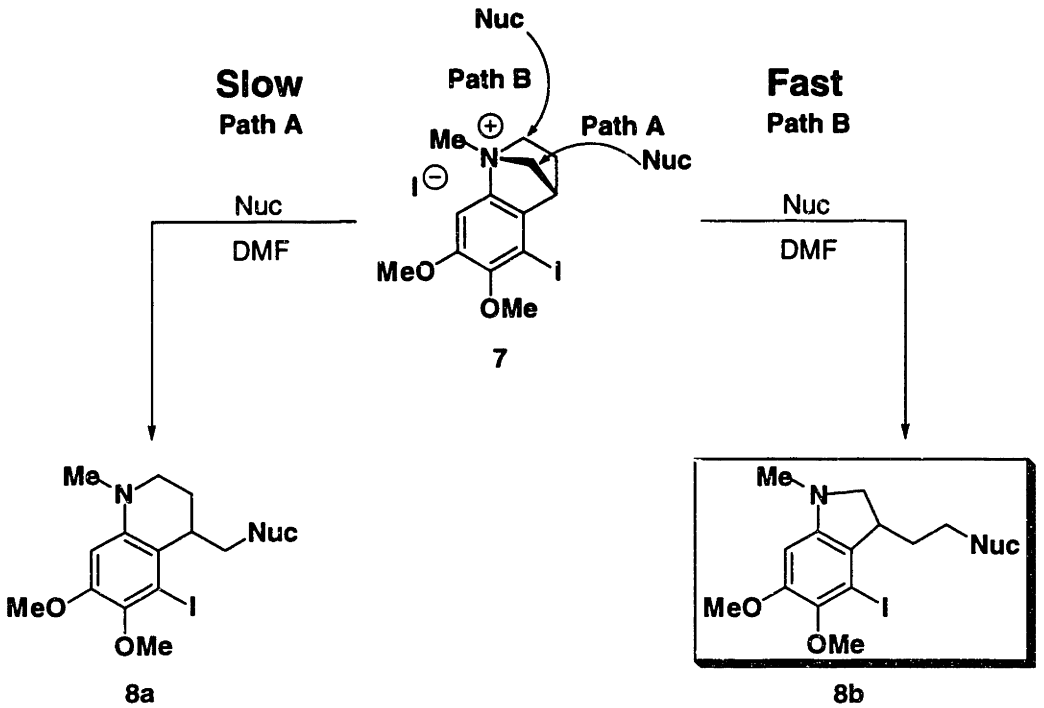


2 **7** **8**

Entry	Nucleophile	Yield from 2
1	-CN	97%
2	CO_2Me / CO_2Me	77%

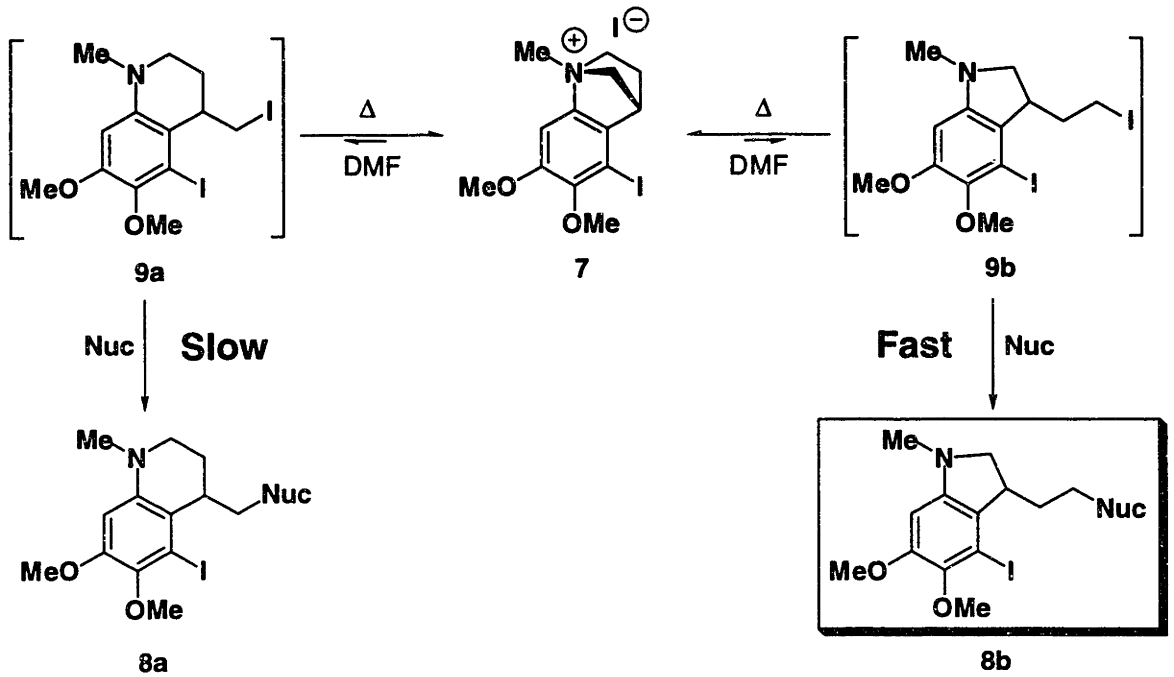
Two possible mechanisms for the reaction of **2** with nucleophiles are shown in Schemes 4 and 5. In the first (Scheme 4), the nucleophile attacks the carbon bonded to the ammonium ion (Path A or B), thereby displacing the neutral aniline and forming the substituted derivatives **8a** or **8b**. Evidently, Path B is favored since we did not observe the formation of compound **8a** when using the cyanide or malonate nucleophiles. In addition, we did not observe the displacement of the *N*-methyl group to produce the tricyclic aniline.

Scheme 4



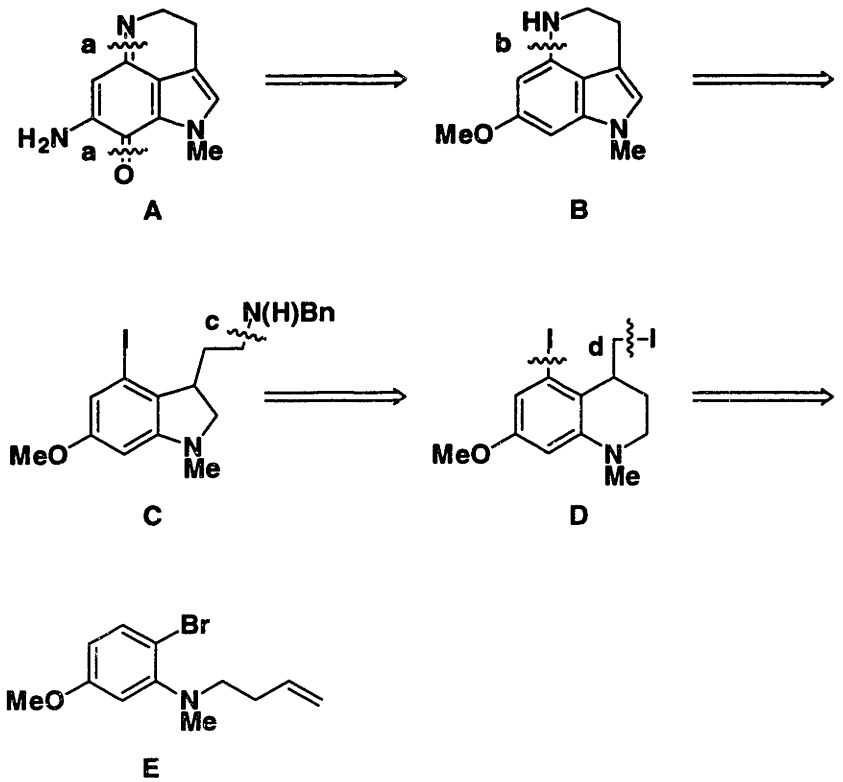
In the second plausible mechanism (Scheme 5), the nucleophile reacts with the diiodide intermediates **9a** or **9b** to give the substituted products. One would expect that the nucleophilic displacement of the alkyl iodide would occur faster from the indoline species **9b**, as compared to the more sterically-hindered tetrahydroquinoline intermediate **9a**. Unfortunately, we do not have enough information to support one mechanism over the other.

Scheme 5



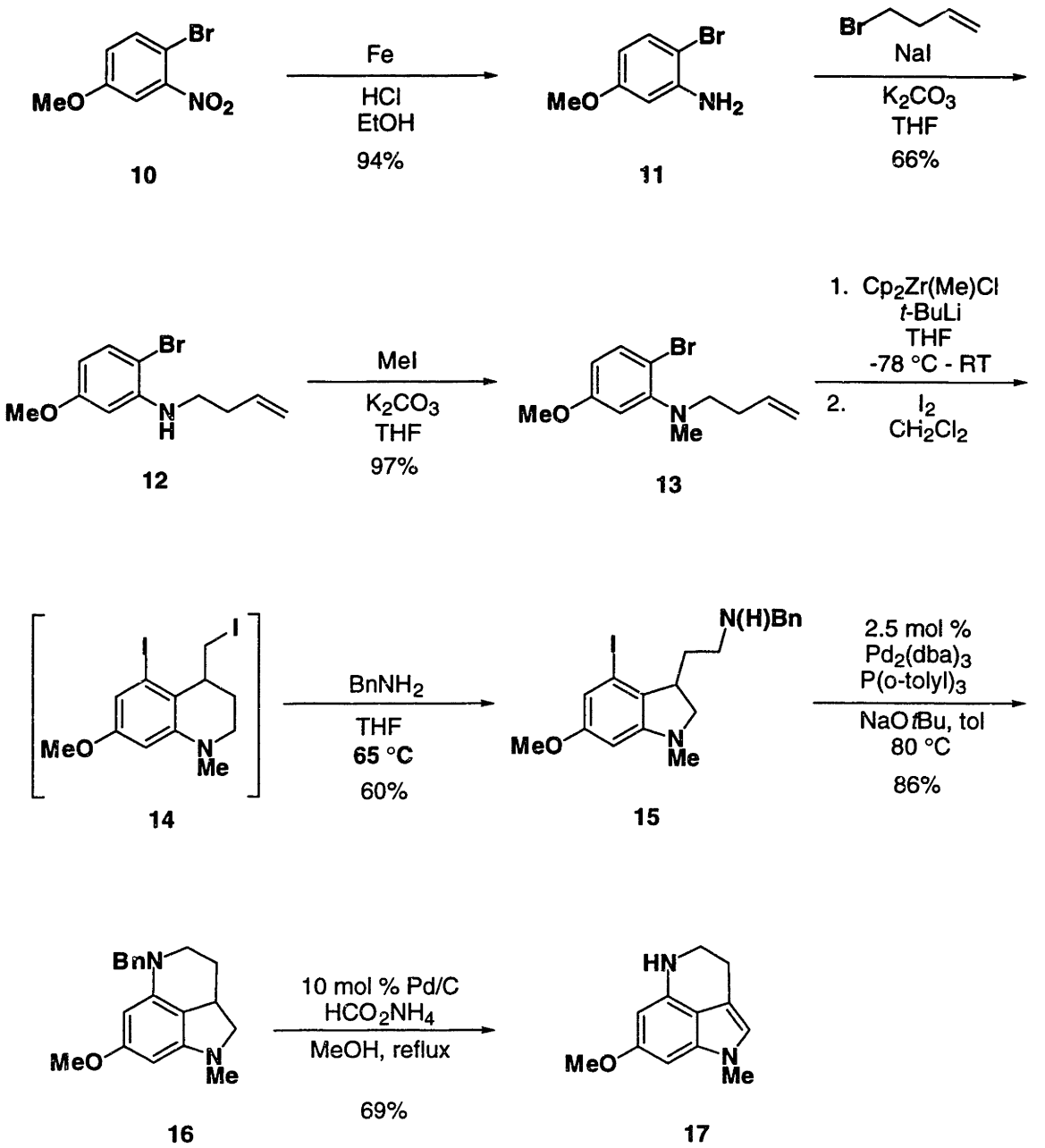
While investigating the rearrangement reaction, we became interested in employing this methodology in the formal synthesis of makaluvamine A and B, which is a topoisomerase II inhibitor that exhibits potent cytotoxicity against human tumor cell lines.[4] From a retrosynthetic viewpoint (Scheme 6), disconnection of the iminoquinone bonds **a** yields a tetrahydropyrroloquinoline **B**, which is prepared via the Pd-catalyzed ring closure (bond **b**) of the 4-iodo secondary tryptamine **C**. The C–N bond **c** is formed upon the nucleophilic displacement of the alkyl iodide from the rearranged diiodoindoline, which is prepared from **D**. The carbon-iodide bonds **d** are formed via iodination of the 5,6,6-tricyclic zirconacycle, which is constructed from **E**.

Scheme 6



Reduction of the nitro-group of 4-bromo-3-nitroanisole (**10**) with Fe(0) and HCl in EtOH afforded the aniline derivative **11**,[5] which was subsequently alkylated with 4-bromo-1-butene and then methyl iodide to produce the desired starting material **13** in good yield (Scheme 7). Addition of *t*-BuLi to **13** in the presence of $Cp_2Zr(Me)Cl$ afforded the zirconacycle, which was treated with iodine to produce the 5-iodo-4-iodomethyltetrahydroquinoline **14**. The diiodide was not isolated, but instead was heated to 65 °C in THF for 1 h, then benzylamine was added to give the aminoindoline **15** in good yield. The palladium-catalyzed aryl amination reaction was employed to close the six-membered ring, affording the tricyclic system **16** in 86% yield.[2] The benzyl group was removed and the indoline ring dehydrogenated using Pd/C and ammonium formate to produce the tetrahydropyrroloquinoline **17**.[3]

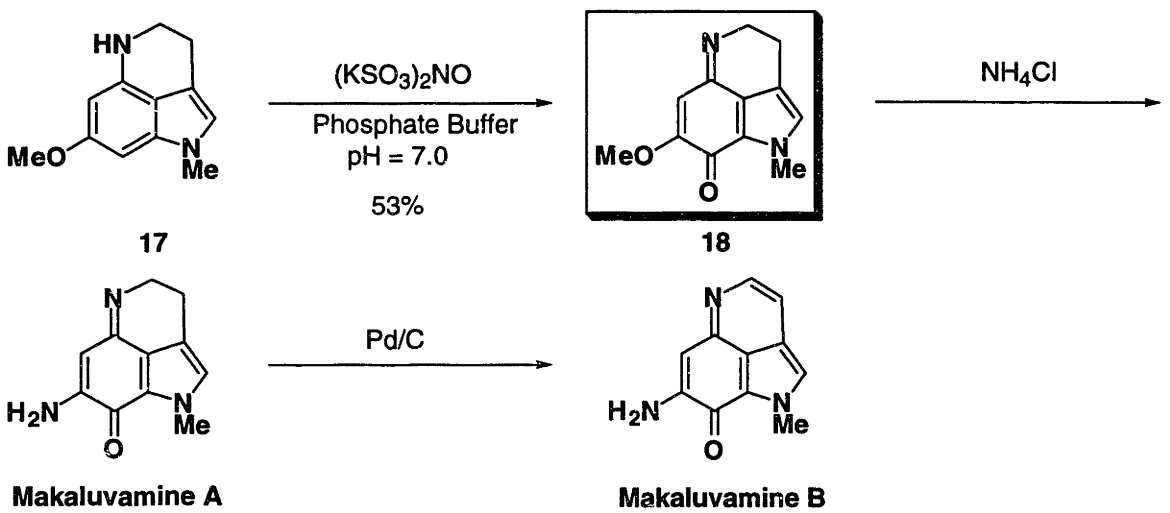
Scheme 7



The final step for our synthesis requires the oxidation of **17** to the iminoquinone **18**. Initial attempts using ceric ammonium nitrate (CAN) led to the formation of unidentifiable products.[6] Next, we investigated the use of potassium nitrosodisulfonate (Fremy's salt).[7] Addition of Fremy's salt to a mixture of **17** in THF and a phosphate buffer at pH = 7.0 afforded the desired

iminoquinone **18**. The conversion of **18** to makaluvamine A and B has been reported by Nishiyama and Yamamura,[6a] thus this represents the formal synthesis of these natural products.

Scheme 8



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. 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 a 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 cross linked SE-30 as a stationary phase. Electron impact mass spectra and high resolution mass determinations (HRMS) were recorded on a Finnegan MAT System 8200. Tetrahydrofuran, benzene, diethyl ether, and hexane were dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation. Methylene chloride was dried by refluxing over CaH_2 under nitrogen 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. Cp_2ZrCl_2 was purchased from Boulder Scientific Inc., Mead, Colorado, and converted to $Cp_2Zr(Me)Cl$. 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 $\geq$95% pure (unless otherwise noted) as determined by ^1H NMR and either capillary GC or combustion analysis. Elemental

analyses were performed by E & R Microanalytical Laboratory, Inc., Corona, N.Y.

2. A solution of 1.7M *t*-BuLi (14.7 mL, 25.0 mmol) was added dropwise to a Schlenk flask containing **1** (3.75 g, 12.5 mmol) and $Cp_2Zr(Me)Cl$ (3.57 g, 13.1 mmol) in THF (90 mL) at –78 °C. The solution was stirred at –78 °C for 3 h, then warmed to 65 °C. After 10 h, the solvent was removed *in vacuo* to give an orange foam, which was dissolved in CH_2Cl_2 (60 mL). The solution was cooled to 0 °C and a solution of iodine (9.49 g, 37.5 mmol) in CH_2Cl_2 (60 mL) was added quickly. The purple solution was stirred at 0 °C for 3 h, then warmed to RT. The solution was poured into a separatory funnel containing saturated Na_2SO_3 (90 mL) and Et_2O (90 mL). The organic layer was washed with brine (90 mL), dried over $MgSO_4$, filtered, and the solvent was removed using a rotary evaporator. The product was purified by flash chromatography (9:1 hexane/ethyl acetate) to give 3.49 g (59%) of the a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.27 (s, 1 H), 3.80 (s, 3 H), 3.65 (s, 3 H), 3.49-3.46 (m, 1 H), 3.27-3.10 (m, 3 H), 3.00 (d, J = 9.6 Hz, 1 H), 2.83 (s, 3 H), 2.29-2.24 (m, 1 H), 1.84 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.4, 144.4, 141.1, 117.5, 102.3, 98.2, 60.4, 56.4, 46.3, 44.6, 39.4, 25.9, 11.6.

3. A solution of 1.7M *t*-BuLi (9.40 mL, 15.92 mmol) was added dropwise to a Schlenk flask containing **1** (2.39 g, 7.96 mmol) and $Cp_2Zr(Me)Cl$ (2.20 g, 7.96 mmol) in THF (40 mL) at –78 °C. The solution was stirred at –78 °C for 3 h, then warmed to 65 °C. After 10 h, the solvent was removed *in vacuo* to give an orange foam, which was dissolved in CH_2Cl_2 (40 mL). The solution was cooled to 0 °C and a solution of iodine (6.00 g, 23.72 mmol) in THF (10 mL) and CH_2Cl_2 (40 mL) was added quickly. The purple solution was stirred at 0 °C for 3 h, then warmed to RT. The solvent was removed *in vacuo*, and THF (80 mL) was added. The solution was heated to 65 °C for 2 h, then benzylamine (4.35

mL, 39.8 mmol) was added and the solution was heated at 65 °C for 12 h. Upon cooling to RT, the solution was poured into a separatory funnel containing H_2O (80 mL) and Et_2O (80 mL). The organic layer was washed with brine (80 mL), dried over $MgSO_4$, filtered, and the solvent was removed using a rotary evaporator. The desired amine was purified by flash chromatography (4:1 hexane/ethyl acetate with 5% NEt_3) to give 2.23 g (62%) of a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.24 (m, 5 H), 6.05 (s, 1 H), 3.86 (d, J = 13.2 Hz, 1 H), 3.85 (s, 3 H), 3.79 (d, J = 13.2 Hz, 1 H), 3.74 (s, 3 H), 3.37 (d, J = 7.4 Hz, 1 H), 3.20- 3.12 (m, 2 H), 2.77-2.72 (m, 2 H), 2.70 (s, 3 H), 1.92 (m, 1 H), 1.77 (m, 1 H), 1.30 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.0, 149.3, 140.2, 139.9, 128.9, 128.0, 127.8, 126.5, 93.4, 91.1, 60.3, 60.0, 55.9, 53.6, 46.8, 42.0, 36.1, 31.7. IR (neat, cm^{-1}) 3312, 3024, 2928, 1599, 1454, 1238. HRMS (EI) calcd for $C_{20}H_{25}N_2O_2I$: 452.09680 amu. Found: 452.09635 amu.

4. A mixture of **3** (0.79 g, 1.75 mmol), $Pd_2(dba)_3$ (40 mg, 0.044 mmol), P(*o*-tolyl)$_3$ (53 mg, 0.175 mmol), and NaO*t*-Bu (0.67 g, 7.00 mmol) in toluene (7 mL) was heated to 80 °C for 20 h, cooled to RT, and poured into a separatory funnel containing Et_2O (20 mL) and water (20 mL). The organic layer was washed with water (15 mL), brine (15 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (4:1 hexane/ethyl acetate) to give 0.39 g (69%) of a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38-7.21 (m, 5 H), 5.77 (s, 1 H), 4.87 (d, J = 15.4 Hz, 1 H), 4.76 (d, J = 15.4 Hz, 1 H), 3.85 (s, 3 H), 3.65 (s, 3 H), 3.59 (t, J = 7.8 Hz, 1 H), 3.24-3.00 (m, 3 H), 2.69 (s, 3 H), 2.58 (dd, J = 8.1, 11.9 Hz, 1 H), 2.05 (m, 1 H). 1.60 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.4, 148.7, 140.2, 136.7, 130.9, 128.2, 127.7, 126.5, 111.2, 85.6, 64.9, 60.4, 56.4, 56.2, 50.0, 37.2, 36.3, 26.5. IR (neat, cm^{-1}) 2934, 1613, 1453, 1218. HRMS (EI) calcd for $C_{20}H_{24}N_2O_2$: 324.18378 amu. Found: 324.18341 amu.

5. A mixture of **4** (0.165 g, 0.51 mmol), 5 mol % Pd/C by weight (0.11 g, 0.051 mmol) and ammonium formate (0.32 g, 5.10 mmol) in MeOH (6 mL) was heated to reflux for 17 h, ccoled to RT, and filtered thru Celite. The MeOH was removed via rotary evaporation and the residue was dissolved in CH_2Cl_2 (10 mL). The organic phase was washed with water (5 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (4:1 hexane/ethyl acetate) to give 96 mg (81%) of a clear oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.49 (s, 1 H), 6.18 (s, 1 H), 4.35 (s, 1 H), 3.92 (s, 3 H), 3.82 (s, 3 H), 3.67 (s, 3 H), 3.47 (t, J = 5.8 Hz, 2 H), 2.99 (t, J = 5.7 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 152.0, 132.6, 131.2, 127.5, 119.0, 112.6, 109.0, 82.6, 60.8, 56.2, 43.2, 32.8, 22.8. IR (neat, cm^{-1}) 3366, 2929, 2836, 1616, 1510, 1257, 1116. HRMS (EI) calcd for $C_{13}H_{16}N_2O_2$: 232.12118 amu. Found: 232.12095 amu.

7. A solution of **2** was heated to 65 °C in d_7-DMF in an NMR tube for 2 h. ^1H NMR (d_7-DMF, 300 MHz) δ 7.75 (s, 1 H), 4.39 (m, 1 H), 4.10 (d, J = 7.7 Hz, 1 H), 4.02-3.98 (m, 2 H), 4.00 (s, 3 H), 3.98 (s, 3 H), 3.83 (s, 3 H), 3.67-3.56 (m, 1 H), 2.81-2.70 (m, 1 H), 1.87-1.78 (m, 1 H). ^{13}C NMR (d_7-DMF, 75 MHz) δ 153.5, 150.8, 142.8, 137.6, 102.8, 89.1, 79.2, 66.0, 61.1, 57.7, 46.2, 42.6, 28.9.

(Table 1, Entry 1). A solution of **2** (0.15 g, 0.31 mmol) in DMF (5 mL) was heated to 65 °C for 3 h under argon. Potassium cyanide (41 mg, 0.63 mmol) was added and the mixture was heated to 90 °C for 2 h. Upon cooling to RT, the solution was poured into a separatory funnel containing H_20 (10 mL) and Et_2O (10 mL). The organic phase was washed with H_2O (3 x 10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and the solvent was removed using a rotary evaporator. The product was purified by flash chromatography (4:1 hexane/ethyl acetate) to give 0.113 g (98%) of a clear oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.05 (s, 1 H), 3.84 (s, 3 H), 3.73 (s, 3 H), 3.35 (d, J = 8.0 Hz, 1 H), 3.25 (t,

J = 8.0, 1 H), 3.18-3.13 (m, 1 H), 2.69 (s, 3 H), 2.47-2.27 (m, 2 H), 2.05-1.98 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 153.1, 150.0, 140.8, 126.6, 120.0, 94.0, 91.6, 61.0, 60.1, 56.6, 43.5, 36.7, 28.2, 14.8. IR (neat, cm^{-1}) 2919, 2821, 2244, 1600, 1458, 1223. Anal. Calcd for $C_{14}H_{17}N_2O_2I$: C, 45.18; H, 4.60. Found: C, 45.37, H, 4.79.

(Table 1, Entry 2). A solution of **2** (0.13 g, 0.27 mmol) in DMF (5 mL) was heated to 65 °C for 3 h under argon. Dimethyl malonate (62 μL, 0.54 mmol), K_2CO_3 (75 mg, 0.54 mmol), and 18-crown-6 (0.143 g, 0.54 mmol) were added, and the mixture was heated at 65 °C for 12 h. Upon cooling to RT, the solution was poured into a separatory funnel containing H_20 (10 mL) and Et_2O (10 mL). The organic phase was washed with H_2O (3 x 10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and the solvent was removed using a rotary evaporator. The product was purified by flash chromatography (4:1 then 2:1 hexane/ethyl acetate) to give 0.98 g (77%) of a clear oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.026 (s, 1 H), 3.83 (s, 3 H), 3.74 (s, 3 H), 3.72 (s, 6 H), 3.40-3.36 (m, 2 H), 3.19 (t, J = 8.4 Hz, 1 H), 3.02-2.91 (m, 1 H), 2.69 (s, 3 H), 1.98 (q, J = 7.9 Hz, 2 H), 1.72-1.54 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.6, 152.3, 149.4, 140.2, 128.2, 124.4, 93.6, 60.7, 59.8, 56.3, 52.6, 51.7, 44.1, 36.4, 29.7, 26.5. IR (neat, cm^{-1}) 2948, 2844, 1733, 1453, 1236.

12. A mixture of **11** (6.30 g, 31.2 mmol), sodium iodide (14.0 g, 93.6 mmol), K_2CO_3 (12.9 g, 93.6 mmol), and 4-bromo-1-butene (6.30 mL, 62.4 mmol) in DMF (100 mL) was heated to 100 °C for 16 h, cooled to RT, and poured into a separatory funnel containing Et_2O (150 mL) and water (150 mL). The organic layer was washed with water (2 x100 mL), brine (100 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (20:1 hexane/ethyl acetate) to give 5.34 g (67%) of a clear oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.29 (d, J = 8.9

Hz, 1 H), 6.20 (t, J = 2.1 Hz, 1 H), 6.16 (dd, J = 2.0, 9.0 Hz, 1 H), 5.91-5.78 (m, 1 H), 5.22-5.13 (m, 2 H), 4.33 (br s, 1 H), 3.78 (s, 3 H), 3.20 (q, J = 5.4 Hz, 2 H), 2.44 (q, J = 5.3 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 145.6, 135.3, 132.4, 117.4, 102.4, 101.0, 98.1, 55.2, 42.6, 33.3. IR (neat, cm^{-1}) 3403, 3076, 2934, 1601, 1511, 1214. HRMS (EI) calcd for $C_{11}H_{14}N_1O_1Br$: 255.02588 amu. Found: 255.02607 amu.

13. A mixture of **12** (4.50 g, 17.6 mmol), K_2CO_3 (4.86 g, 35.2 mmol), and methyl iodide (1.60 mL, 26.3 mmol) in DMF (100 mL) was heated to 100 °C for 2 h, cooled to RT, and poured into a separatory funnel containing Et_2O (100 mL) and water (100 mL). The organic layer was washed with water (2 x 50 mL), brine (50 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (20:1 hexane/ethyl acetate) to give 4.56 g (96%) of a clear oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.43 (d, J = 8.5 Hz, 1 H), 6.64 (d, J = 2.7 Hz, 1 H), 6.48 (dd, J = 2.7, 8.6 Hz, 1 H), 5.90-5.77 (m, 1 H), 5.10-4.99 (m, 2 H), 3.78 (s, 3 H), 3.07 (t, J = 7.3 Hz, 2 H), 2.77 (s, 3 H), 2.34 (q, J = 7.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 159.5, 152.0, 136.0, 133.9, 115.8, 110.5, 108.7, 108.6, 55.5, 41.0, 31.8, 12.2. IR (neat, cm^{-1}) 3076, 2936, 1640, 1594, 1234. HRMS (EI) calcd for $C_{12}H_{16}N_1O_1Br$: 269.04153 amu. Found: 269.04163 amu.

15. A solution of 1.7M *t*-BuLi (17.2 mL, 29.2 mmol) was added dropwise to a Schlenk flask containing **13** (3.95 g, 14.6 mmol) and $Cp_2Zr(Me)Cl$ (3.97 g, 14.6 mmol) in THF (100 mL) at –78 °C. The solution was stirred at –78 °C for 3 h, then warmed to 65 °C. After 10 h, the solvent was removed *in vacuo* then CH_2Cl_2 (100 mL) was added. The solution was cooled to 0 °C and a solution of iodine (11.1 g, 43.9 mmol) in CH_2Cl_2 (100 mL) was added quickly. The purple solution was stirred at 0 °C for 3 h, then warmed to RT. The solvent was removed *in vacuo*, and THF (100 mL) was added. The solution was heated to

65 °C for 2 h, then benzylamine (8.0 mL, 73.0 mmol) and K_2CO_3 (10.0 g, 73.0 mmol) were added and the solution was heated at 65 °C for 12 h. Upon cooling to RT, the solution was poured into a separatory funnel containing H_2O (100 mL) and Et_2O (100 mL). The organic layer was washed with brine (100 mL), dried over $MgSO_4$, filtered, and the solvent was removed using a rotary evaporator. The product was purified by flash chromatography (4:1 hexane/ethyl acetate with 5% NEt_3) to give 3.70 g (60%) of a clear oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.30-7.19 (m, 5 H), 6.51 (d, J = 1.7 Hz, 1 H), 5.93 (d, J = 1.8 Hz, 1 H), 3.81 (d, J = 13.2 Hz, 1 H), 3.74 (d, J = 13.2 Hz, 1 H), 3.70 (s, 3 H), 3.30 (dd, J = 1.3, 8.7 Hz, 1 H), 3.20 (t, J = 8.4 Hz, 1 H), 3.10-3.04 (m, 1 H), 2.73-2.68 (m, 2 H), 2.64 (s, 3 H), 1.96-1.84 (m, 1 H), 1.80-1.68 (m, 1 H), 1.34 (br s, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 160.8, 153.6, 134.8, 129.2, 128.7, 128.6, 128.1, 111.2, 94.9, 92.0, 60.0, 55.5, 51.8, 44.9, 41.2, 35.4, 30.0. IR (neat, cm^{-1}) 3396, 2938, 1599, 1456, 732. HRMS (EI) calcd for $C_{19}H_{23}N_2O_1I$: 422.08552 amu. Found: 422.08550 amu.

16. A mixture of **15** (2.11 g, 4.99 mmol), $Pd_2(dba)_3$ (0.11 g, 0.12 mmol), P(*o*-tolyl)$_3$ (0.15 mg, 0.50 mmol), and NaO*t*-Bu (1.92 g, 19.96 mmol) in toluene (25 mL) was heated to 80 °C for 20 h, cooled to RT, and poured into a separatory funnel containing Et_2O (30 mL) and water (30 mL). The organic layer was washed with water (20 mL), brine (20 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (4:1 hexane/ethyl acetate) to give 1.31 g (89%) of a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.21 (m, 5 H), 5.69 (d, J = 1.3 Hz, 1 H), 5.61 (d, J = 2.2 Hz, 1 H), 4.47 (d, J = 16.7 Hz, 1 H), 4.39 (d, J = 16.7 Hz, 1 H), 3.70 (s, 3 H), 3.63 (t, J = 7.8 Hz, 1 H), 3.32-3.19 (m, 3 H), 2.69 (s, 3 H), 2.66 (dd, J = 8.4, 11.7 Hz, 1 H), 2.14-2.09 (m, 1 H), 1.74-1.60 (m, 1 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 162.3, 154.1, 142.9, 139.1, 128.5, 127.0, 126.8, 107.2,

87.3, 84.8, 65.2, 55.4, 53.6, 48.6, 36.8, 35.4, 27.0. IR (neat, cm^{-1}) 3026, 2940, 1622, 1503, 1202. HRMS (EI) calcd for $C_{19}H_{22}N_2O_1$: 294.17321 amu. Found: 294.17347 amu.

17. A mixture of **16** (1.13 g, 3.84 mmol), 5 mol % Pd/C by weight (0.38 g, 0.38 mmol) and ammonium formate (2.42 g, 38.4 mmol) in MeOH (38 mL) was heated to reflux for 25 h, cooled to RT, and filtered thru Celite. The MeOH was removed via rotary evaporation and the residue was dissolved in CH_2Cl_2 (30 mL). The organic phase was washed with water (30 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography (4:1 hexane/ethyl acetate) to give 0.54 g (69%) of a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.49 (s, 1 H), 6.20 (s, 1 H), 5.96 (d, J = 1.7 Hz, 1 H), 4.07 (br s, 1 H), 3.86 (s, 3 H), 3.68 (s, 3 H), 3.47 (t, J = 5.6 Hz, 2 H), 3.00 (t, J = 5.3 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 157.4, 141.3, 135.5, 118.5, 112.8, 109.2, 90.2, 83.2, 55.8, 43.6, 32.7, 23.0. IR (neat, cm^{-1}) 3366, 2933, 1614, 1504, 1148. HRMS (EI) calcd for $C_{12}H_{14}N_2O_1$: 202.11061 amu. Found: 202.11084 amu.

18.[6a] A solution of Fremy's salt (0.33 g, 1.24 mmol) in a pH=7.0 phosphate buffer (μ=1.0 KCl) (15 mL) was added to a suspension of **17** (41 mg, 0.20 mmol) in THF (1 mL) and pH=7.0 phosphate buffer (μ=1.0 KCl) (5 mL). The mixture was stirred at RT for 1 h, then poured into a separatory funnel containing CH_2Cl_2 (25 mL). The aqueous layer was extracted with CH_2Cl_2 (2 x 25 mL), and the combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed using a rotary evaporator. The product was purified by flash chromatography (8:1 $CHCl_3$/methanol) to give 0.23 g (53%) of an orange oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 6.86 (s, 1 H), 5.94 (s, 1 H), 3.98 (t, *J* = 8.0 Hz, 2 H), 3.86 (s, 3 H), 3.76 (s, 3 H), 2.68 (t, *J* = 8.0 Hz, 2 H).

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Chapter Four:

The Synthesis of Indoles Using the Air- and Moisture-Stable Precursor: Cp_2TiCl_2

Note: This work was carried out in collaboration with Dr. Kazu Aoki. My contribution involved the synthesis of the following compounds:

Table 1, Entry 6

Compound **7**

Table 2, Entry 1

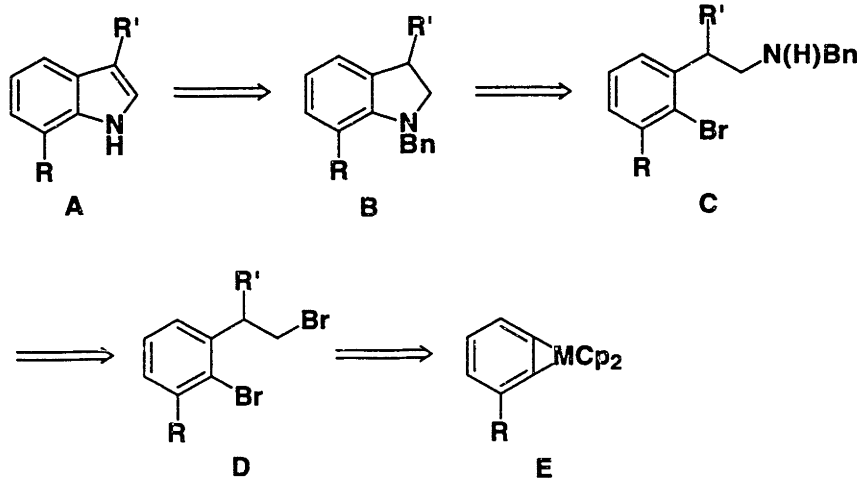
Table 2, Entry 2

Results and Discussion

While we have been pleased with our newly developed indole methodology,[1] we recognize that there are several drawbacks, such as the use of the air- and moisture-sensitive complex, $Cp_2Zr(Me)Cl$. In addition, the synthesis of the other starting material, an *N*-allyl-*o*-bromoaniline, can be difficult depending upon the substituents and the substitution-pattern of the aromatic ring. Lastly, the method is limited to the formation of indoles bearing substituents at both the 3- and 4-positions. In an effort to remove these problems, we decided to investigate another approach. Herein, we describe a novel approach to indole synthesis involving the intermolecular olefin insertion reactions of a titanocene-benzyne complex which employs the air-stable reagent, Cp_2TiCl_2. The required starting materials, an aryl Grignard reagent and an olefin, are commercially available or readily prepared. This allows for the efficient construction of indoles with diverse substituents and substitution patterns. In addition, the olefin insertion reaction procedes with a high-degree of regioselectivity, thereby producing indoles with high regiochemical purity.

The retrosynthetic analysis for our indole synthesis is shown in Scheme 1. The indole system **A** is constructed from the indoline adduct **B**, which is formed from an aryl bromide bearing a tethered amine **C** via the palladium-catalyzed ring-closure of the pyrrole ring.[2] The required amine **C** is formed from dibromide **D**, which in turn is prepared from the appropriate metallocene-benzyne complex **E**.[3]

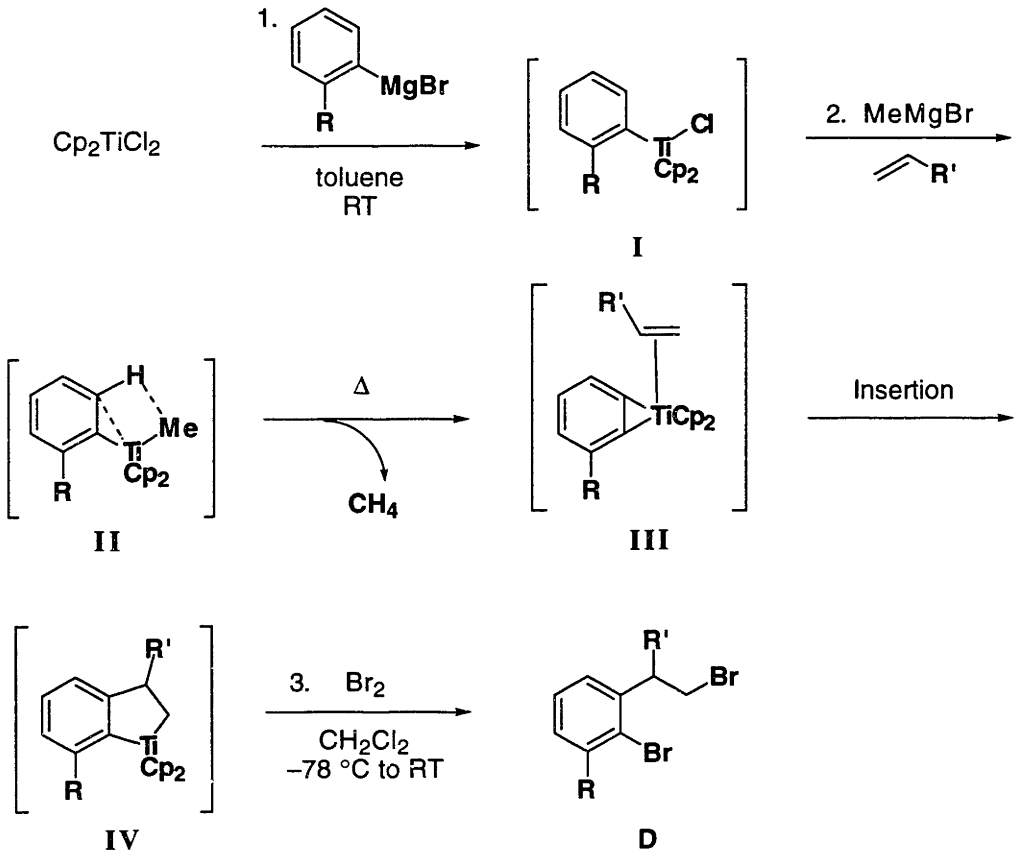
Scheme 1



Previous research conducted in our laboratories provides ready access to the requisite dihalide **D** via intermolecular olefin insertion into the Zr–C bond of the benzyne complex, followed by treatment with iodine.[3] In an effort to make this procedure more accessible, we modified the previous procedure to replace zirconocene(methyl)chloride with titanocene dichloride. The reasons for this are that: 1) titanocene dichloride is air- and moisture-stable, and 2) we hoped the titanium complex would exhibit greater functional group tolerance than the corresponding, highly oxophilic zirconium reagent.[4] A plausible mechanism for the formation of the dihalide is shown in Scheme 2. Treatment of titanocene dichloride with 1.1 equiv of an *o*-substituted aryl Grignard reagent in toluene at RT cleanly affords aryl(chloro)titanocene **I**. It should be noted that the analogous aryllithium reagents do not give **I**, but instead reduce the metal complex to a Ti(III) species.[5] An olefin (2.0 equiv) and 1.0 equiv of MeMgBr are added to the reaction mixture to produce aryl(methyl)titanocene **II**, which upon heating generates the titanocene-stabilized benzyne complex **III**. The olefin coordinates to the metal opposite from the *ortho*-aryl substituent,[3] with the olefin R'-substituent situated away from the cyclopentadienyl ligands as depicted in

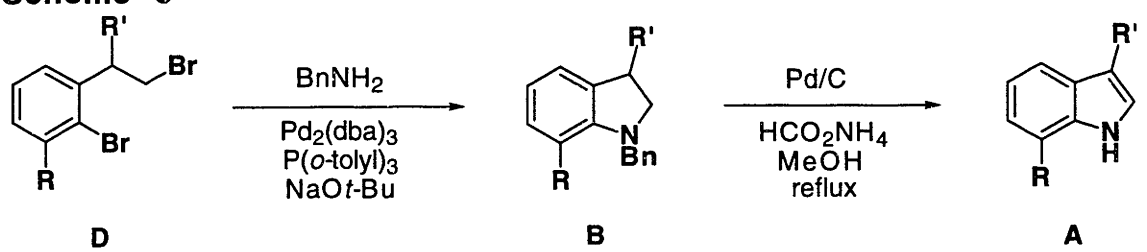
intermediate **III**.[3] Insertion of the olefin into the carbon-titanium bond of the benzyne complex yields metallacyclopentane **IV**. The toluene was removed in vacuo and CH_2Cl_2 was added. Addition of a solution of bromine in CH_2Cl_2 at –78 °C produces the desired dibromide **D** in moderate yield with excellent regiochemical purity. In addition, the overall level of ring-substitution for the aryl component has been increased by one, thereby producing a contiguously trisubstituted benzene derivative. However, it should be noted that the formation of the dibromide is the yield limiting step in all of the following procedures.

Scheme 2



With a method to prepare the requisite dibromides in hand, we turned our attention to their conversion to indolines. Our original idea was to convert **D** to the corresponding amine **C**, and then close the five-membered ring via the Pd-catalyzed intramolecular aryl amination reaction.[2] After much experimentation, we found that it was not necessary to isolate the amine. Instead, the dibromide could be converted directly to the indoline derivative (Scheme 3). Treatment of **D** with benzylamine, $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, and NaO*t*-Bu in toluene affords the indoline adduct **B** in good overall yield. It is necessary to remove the P(*o*-tolyl)$_3$ by flash chromatography since it hinders the subsequent reaction. Lastly, deprotection and oxidation of indoline **B** with Pd/C and ammonium formate gives the desired indole **A**.[6]

Scheme 3



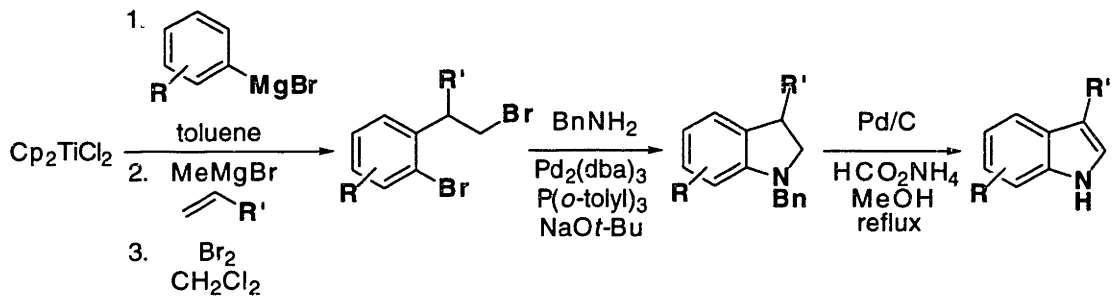
D **B** **A**

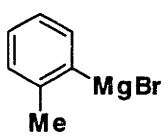
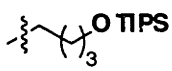
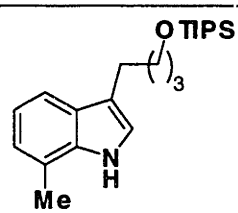
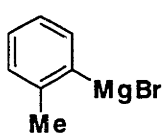
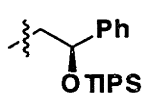
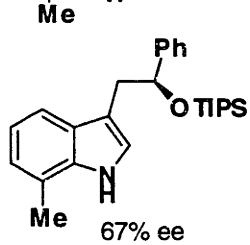
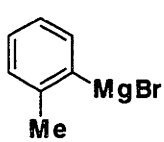
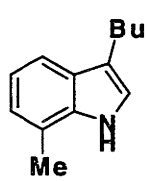
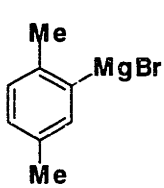
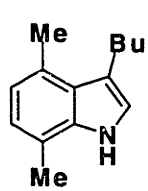
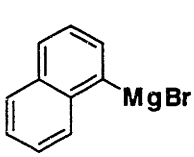
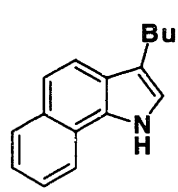
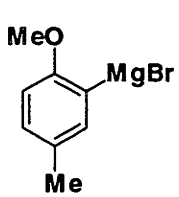
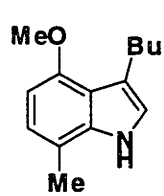
A variety of substituted indoles were prepared using the above three-step procedure (Table 1). Initially, we used the commercially available *o*-tolylmagnesium bromide to test the feasibility of our approach. Insertion of olefins containing TIPS-protected alcohols (entries 1 and 2) gave good overall yields of the indole derivatives. It should be noted that no racemization was detected when the enantiomerically-enriched TIPS-protected alcohol[7] was used (entry 2). Also, 1-hexene was inserted to give 3-butyl-7-methylindole in 54% yield (entry 3). In addition to *o*-tolylmagnesium bromide, the use of disubstituted aryl Grignard reagents allowed for the construction of trisubstituted

indole derivatives (entries 4-6). For example, 1-napthylmagnesium bromide and 1-hexene produced the 3-butyl-napthylindole in 34% yield.

Table 1

Procedure A:

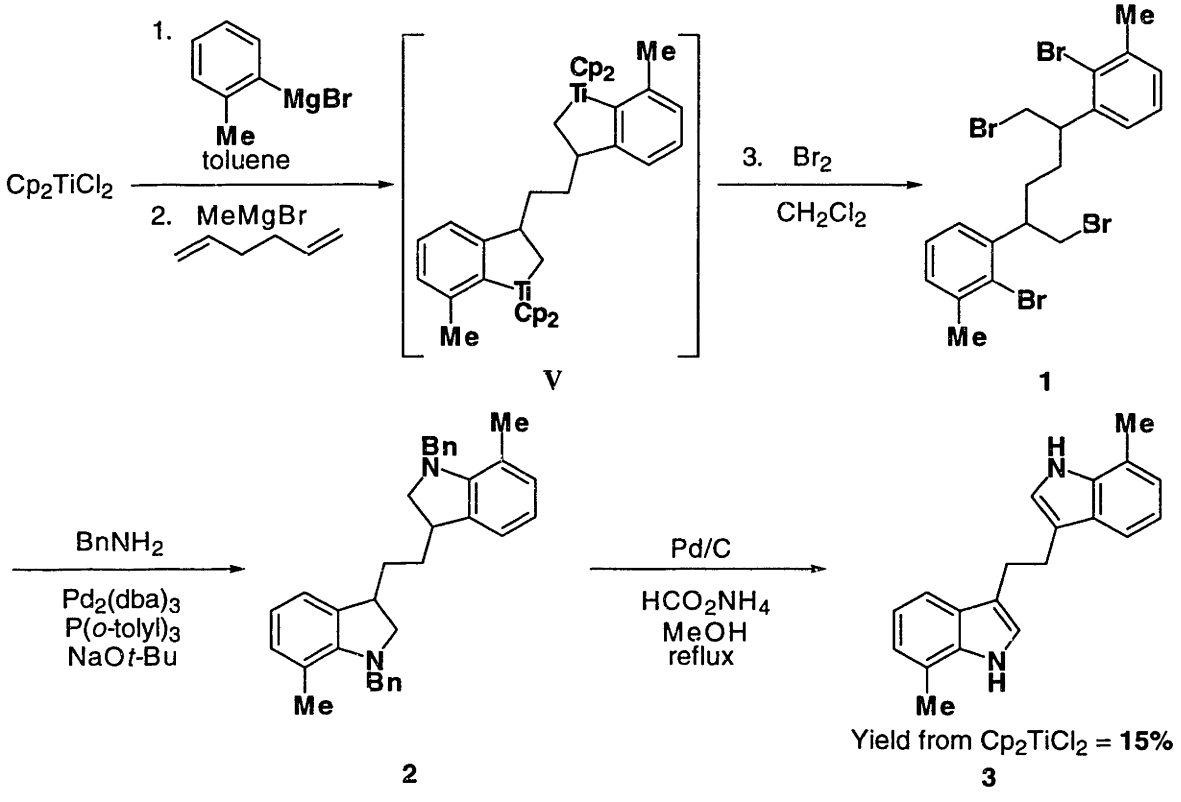


Entry	ArMgBr	R'	Indole Product	Yield of Indole (based upon Cp_2TiCl_2)
1				44%
2		 66% ee	 67% ee	45%
3				54%
4				37%
5				34%
6				18%

Entry 6 afforded the desired indoline adduct, however the yield was disappointingly low. This is due to only a modest level of regioselectivity (8:1 mixture of regioisomers) obtained for the insertion of 1-hexene into the Ti–benzyne, which will be discussed in greater detail in Scheme 6.

The use of 1,5-hexadiene produced the interesting bis-indole compound **3** (Scheme 4). Addition of *o*-tolylmagnesium bromide, MeMgBr, and 1,5-

Scheme 4



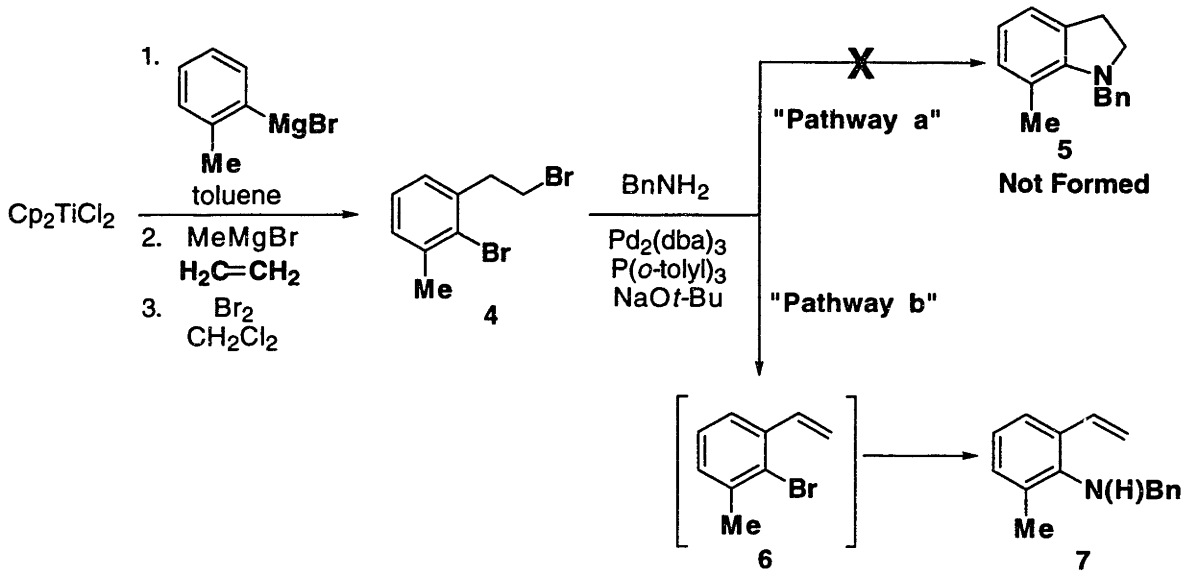
hexadiene to a solution of titanocene dichloride in toluene afforded the desired bis-metallacyclopentane **V**, which was treated with bromine to form **1** as a mixture of diastereomers. The Pd-catalyzed aryl amination reaction proceeded smoothly using excess benzylamine to produce the bis-indoline adduct **2**.

Lastly, the benzyl groups were cleaved and the indoline rings were oxidized to afford bis-indole **3** in 15% overall yield from Cp_2TiCl_2.

In an effort to make the procedure as general as possible, we wished to synthesize indoles that were not functionalized at the 3-position. Such compounds are important precursors in the syntheses of more elaborate indole compounds.[8] With this in mind, we became interested in using ethylene as the olefin component in our method (Scheme 5). A solution of titanocene dichloride in toluene in a Fischer-Porter bottle was treated with *o*-tolylmagnesium bromide at RT to generate the aryl(chloro)titanocene. The solution was cooled to 0 °C and MeMgBr was added. After stirring for 0.5 h, the Fischer-Porter bottle was charged with 30 psig of high-purity ethylene,[9] and the vessel was heated to 65 °C for 16 h. The solution was cooled to RT, completely vented, and the solvent was removed. Addition of CH_2Cl_2, followed by a solution of bromine in CH_2Cl_2 at –78 °C gave the dibromide **4**. It should be noted that the success of the reaction is highly dependent upon the purity of the ethylene.[10]

Next, we examined the conversion of the dibromide to the indoline system via the Pd-catalyzed aryl amination reaction. Following the protocol described above, dibromide **4** was treated with benzylamine, $Pd_2(dba)_3$, P(*o*-tolyl)$_3$, and NaO*t*-Bu in toluene. Unfortunately, we obtained only trace amounts of the desired indoline adduct **5**. Instead, the majority of the starting material had been converted to the styrene derivative **7**. It appears that formation of the indoline compound (pathway a) is slow compared to a competing side reaction (pathway b). Elimination of HBr by NaO*t*-Bu produces the *o*-bromo styrene adduct **6**, which then undergoes a cross-coupling reaction with benzylamine to give the aniline product **7**.

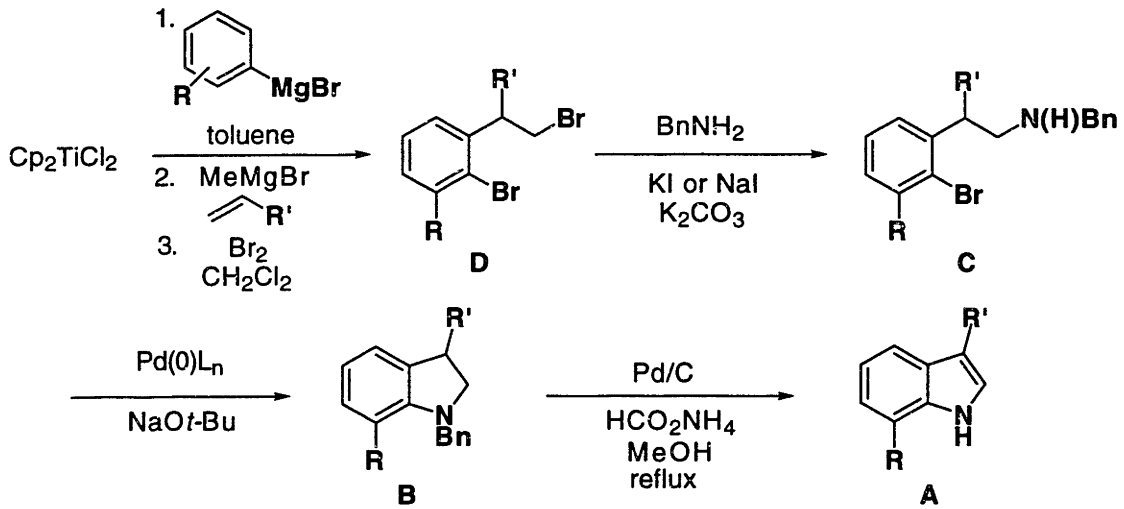
Scheme 5

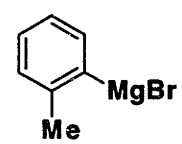
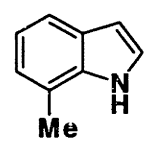
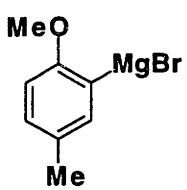
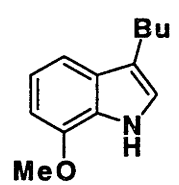
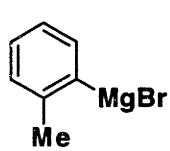
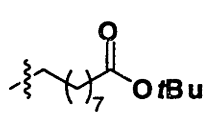
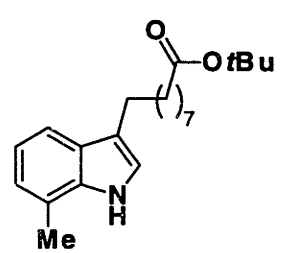


We reasoned that the elimination of HBr could be circumvented by first displacing the alkyl bromide with benzylamine and isolating intermediate **C** (Table 2: Procedure B, C). Treatment of dibromide **D** with excess benzylamine, NaI, and K_2CO_3 gave the desired amine **C** with little formation of the styrene by-product. Closure of the five-membered ring proceeded smoothly to form indoline **B**. Lastly, indole **A** was formed using Pd/C as described above. In addition to the ethylene case, several other systems gave only minor amounts of the desired indole products when the first procedure was used. However, we obtained much better yields of these compounds by switching to procedure B, C (Entries 3, 4).

Table 2

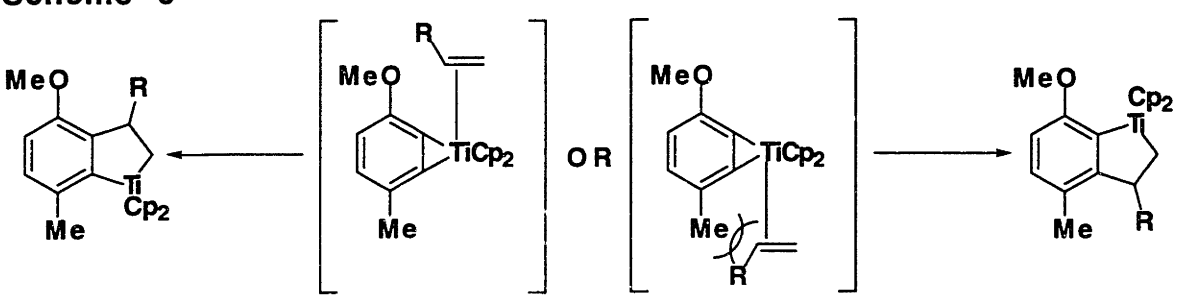
Procedure B, C:



Entry	ArMgBr	R'	Indole Product	Yield of Indole (based upon Cp_2TiCl_2)
1				41%
2				30%
3				38%
4				34%

The use of 2-methoxy-5-tolylmagnesium bromide allowed for the syntheses of 4,7-differentially disubstituted indole derivatives (Table 1, entry 6; Table 2, entry 2). We were pleased to find that the insertion of the olefin into the Ti–C bond of the unsymmetrical benzyne complex **8a,b** proceeded with a high degree of regioselectivity,[3] especially when ethylene was used (Scheme 6). We believe this selectivity is a result of the difference in size between the two substituents (Me versus OMe). The olefin preferentially coordinates to the metal opposite from the larger methyl substituent, thereby favoring the formation of metallacycle **9a**. Treatment of metallacycles **9a** and **9b** with bromine produces the two isomeric dihalides. We found that it was not necessary to separate these compounds. Instead, the crude mixture was used in the subsequent reactions and the major indole isomer was easily purified by flash chromatography.

Scheme 6



R	9a : 9b
-{-H	20 : 1
-{-Bu	8 : 1

In summary, a novel procedure for the regioselective synthesis of substituted indoles has been developed. The key steps in this methodology

involve the intermolecular olefin insertion reaction of a titanocene-stabilized benzyne complex, and also the Pd-catalyzed aryl amination reaction. We believe this approach will allow for the facile construction of a wide variety of highly substituted indoles since the required starting materials, an aryl Grignard reagent and an olefin, are commercially available or readily synthesized. In addition, the use of titanocene dichloride removes the need to prepare air- and moisture-sensitive organometallic intermediates. Further investigations of this methodology are currently underway in our laboratories.

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. Other 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 a 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 cross linked SE-30 as a stationary phase. Electron impact mass spectra and high resolution mass determinations (HRMS) were recorded on a Finnegan MAT System 8200. Tetrahydrofuran, benzene, diethyl ether, and hexane were dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation. Methylene chloride was dried by refluxing over CaH_2 under nitrogen followed by distillation. Anhydrous *N,N*-dimethyl formamide (DMF) was purchased from Aldrich Chemical Co. and was used without further purification. Cp_2TiCl_2 was a gift 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 $\geq$95% pure (unless otherwise noted) as determined by ^1H NMR and either capillary GC or combustion analysis. All reported yields are representative. Elemental

analyses were performed by E & R Microanalytical Laboratory, Inc., Corona, N.Y.

General Procedure A. A solution of arylmagnesium bromide (1.1 equiv) in THF was added dropwise to a solution of Cp_2TiCl_2 (1.0 mmol) in toluene at RT under argon in a sealable Schlenk flask. After 1 h, the olefin (2.0 equiv) and a solution of MeMgBr (1.0 equiv) in Et_2O was added, then the flask was sealed and heated to 50 °C for 4 h. The solution was cooled to RT, and the solvent was removed *in vacuo*. Upon the addition of CH_2Cl_2 (0.08 M), the solution was cooled to –78 °C and a solution of Br_2 (2.05 equiv) in CH_2Cl_2 (0.08 M) at –78 °C was added dropwise. The solution was warmed slowly to RT, then the solvent was removed *in vacuo*. Caution: care should be used to insure excess bromine has been destroyed. Hexane (0.03 M) was added, then the mixture was filtered through Celite, and the solvent was removed using a rotary evaporator. The dibromide product was purified by flash chromatography.

The dibromide (1.0 equiv) was treated with $Pd_2(dba)_3$ (4 mol %), P(*o*-tolyl)$_3$ (16 mol %), NaO*t*-Bu (4.0 equiv), and benzylamine (2.0 equiv) in toluene (0.1 M). The flask was sealed then heated to 80 °C for 16 h. Upon cooling to RT, the mixture was poured into a separatory funnel containing Et_2O and H_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered and the solvent was removed using a rotary evaporator. The indoline product was purified by flash chromatography.

The indoline derivative (1.0 equiv) was treated with 10 mol % (by weight) Pd/C (10 mol %) and ammonium formate (10.0 equiv) in MeOH (0.1 M). The solution was heated to reflux for 1.5 h, then allowed to cool to RT and filtered through Celite. The solvent was removed using a rotary evaporator, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with H_2O,

brine, dried over Na_2SO_4, filtered and the solvent was removed using a rotary evaporator. The product was purified by flash chromatography.

General Procedure B. A solution of arylmagnesium bromide (1.1 equiv) in THF was added dropwise to a solution of Cp_2TiCl_2 (1.0 mmol) in toluene at RT under argon in a Fischer-Porter bottle. After 1 h, the solution was cooled to 0 °C and a solution of MeMgBr (1.0 equiv) was added dropwise. After 0.5 h, the bottle was charged with 30 psig of ethylene, and the solution was heated to 50 °C for 8 h. Caution: reactions at elevated pressure should be run behind a safety shield. The solution was cooled to RT, the pressure was carefully vented, and the solvent was removed *in vacuo*. Upon the addition of CH_2Cl_2 (0.08 M), the solution was cooled to –78 °C. At this point, a solution of Br_2 (2.05 equiv) in CH_2Cl_2 (0.08 M) at –78 °C was added dropwise. The solution was warmed slowly to RT, then the solvent was removed *in vacuo*. Caution: care should be used to insure excess bromine has been destroyed. Hexane (0.03 M) was added, then the mixture was filtered through Celite, and the solvent was removed using a rotary evaporator. The dibromide product was purified by flash chromatography.

The dibromide (1.0 equiv) was treated with benzylamine (6.0 equiv), K_2CO_3 (6.0 equiv), NaI (6.0 equiv) in THF (0.17 M), then the mixture was heated to 65 °C for 12 h. Upon cooling to RT, the mixture was poured into a separatory funnel containing Et_2O and H_2O. The organic layer was washed with H_2O, brine, dried over $MgSO_4$, filtered, and the solvent was removed using a rotary evaporator. The excess benzylamine was removed by Kugelrohr distillation. The desired product was purified by flash chromatography.

A mixture of $Pd_2(dba)_3$ (2 mol %), P(*o*-tolyl)$_3$ (8 mol %), and NaO*t*-Bu (1.4 equiv) was added to a solution of the amine (1.0 equiv) in toluene (0.2 M), and the flask was heated to 80 °C for 16 h. Upon cooling to RT, the solution

was poured into a separatory funnel containing H_2O and Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo.* The indoline product was purified by flash chromatography.

The indoline derivative (1.0 equiv) was treated with 10 mol % (by weight) Pd/C (10 mol %) and ammonium formate (10.0 equiv) in MeOH (0.12 M). After heating to reflux for 24 h, the solution was cooled to RT and filtered through Celite. The solvent was removed using a rotary evaporator, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, filtered and the solvent was removed using a rotary evaporator. The product was purified by column chromatography.

General Procedure C. A solution of arylmagnesium bromide (1.1 equiv) in THF was added dropwise to a solution of Cp_2TiCl_2 (1.0 mmol) in toluene at RT under argon in a resealable Schlenk flask. After 1 h, the olefin (2.0 equiv) and a solution of MeMgBr (1.0 equiv) in Et_2O was added, then the flask was sealed and heated to 50 °C for 4 h. The solution was cooled to RT, and the solvent was removed *in vacuo.* To the flask was added CH_2Cl_2 (0.08 M), and the solution was cooled to –78 °C. At this point a solution of Br_2 (2.05 equiv) in CH_2Cl_2 (0.08 M) at –78 °C was added dropwise. The solution was warmed slowly to RT, then the solvent was removed *in vacuo.* Caution: care should be used to insure excess bromine has been destroyed. Hexane (38 mL) was added, then the mixture was filtered through Celite, and the solvent was removed using a rotary evaporator. The dibromide product was purified by flash chromatography.

The dibromide (1.0 equiv) was treated with benzylamine (4.0 equiv), K_2CO_3 (4.0 equiv), KI (2.0 equiv) in DMF (0.1 M), then the mixture was heated to 100 °C for 4 h. After cooling to RT, the mixture was poured into a separatory funnel containing Et_2O and H_2O. The organic layer was washed with H_2O,

brine, dried over $MgSO_4$, filtered, and the solvent was removed using a rotary evaporator. The amine product was purified by flash chromatography.

A mixture of $Pd(PPh_3)_4$ (4 mol %), K_2CO_3 (1.7 equiv), and NaO*t*-Bu (1.7 equiv) was added to a solution of the amine (1.0 equiv) in toluene (0.2 M), the flask was heated to 100 °C for 16 h. After cooling to RT, the solution was poured into a separatory funnel containing H_2O and Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. The indoline product was purified by flash chromatography.

The indoline derivative (1.0 equiv) was treated with 10 mol % (by weight) Pd/C (10 mol %) and ammonium formate (10.0 equiv) in MeOH (0.12 M). After heating to reflux for 2 h, the solution was cooled to RT and filtered through Celite. The solvent was removed using a rotary evaporator, and the residue was dissolved in CH_2Cl_2. The organic layer was washed with H_2O, brine, dried over Na_2SO_4, filtered and the solvent was removed using a rotary evaporator. The product was purified by column chromatography.

(Table 1, Entry 1) 7-Methyl-3-(4-triisopropylsilyloxy)butylindole. Cp_2TiCl_2 (0.50 g, 2.00 mmol) in toluene (25 mL) was employed according to general procedure A. The indole product was purified by flash chromatography (4:1 then 2:1 hexane/CH_2Cl_2) to yield 0.32 g of a colorless needles (45% from Cp_2TiCl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (br s, 1H), 7.46 (d, J = 7.5 Hz, 1 H), 7.07-6.95 (m, 3 H), 3.72 (t, J = 6.3 Hz, 2H), 2.77 (t, J = 7.5 Hz, 2 H), 2.47 (s, 3 H), 1.86-1.72 (m, 2 H), 1.71-1.59 (m, 2 H), 1.20-1.04 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.0, 127.2, 122.4, 120.7, 120.1, 119.3, 117.6, 116.8, 63.3, 33.0, 26.4, 25.1, 18.1, 16.5, 12.1; IR (neat) 3422, 2941, 2865, 1459, 1106, 882 cm^{-1}; Anal. Calcd for $C_{22}H_{37}NOSi$: C, 73.48; H, 10.37. Found: C, 73.74; H, 10.59.

(Table 1, Entry 2) 7-Methyl-3-(2-phenyl-2-triisopropylsilyloxy)ethylindole. Cp_2TiCl_2 (0.50 g, 2.00 mmol) in toluene (25 mL) was employed according to general procedure A. The indole product was purified by flash chromatography (2:1 hexane/Et_2O) to yield 0.33 g of a colorless needles (40% from Cp_2TiCl_2): $[\alpha]_D^{25}$ = +23.9 (*c* 1.09, $CHCl_3$); HPLC: Chiralcel OD 25 cm x 0.46 cm column (Daicel Chemical Ind., Ltd.), eluent: 99:1 hexane/isopropyl alcohol, flow rate: 0.5 mL/min, detection: UV 254 nm, retention time: (*S*)-enantiomer, 23.6 min ; (*R*)-enantiomer, 25.5 min, optical purity: 67 % ee. ^1H NMR (300 MHz, $CDCl_3$) δ 7.7 (br s, 1H), 7.35-6.90 (m, 8H), 6.56 (m, 1H), 5.01 (dd, *J* = 5.4, 8.0 Hz, 1 H), 3.31 (dd, *J* = 5.4, 14.0 Hz, 1 H), 3.05 (dd, *J* = 8.0, 14.0 Hz, 1 H), 2.43 (s, 3 H), 1.10-0.85 (m, 21 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.5, 135.6, 127.6, 126.8, 126.5, 122.8, 122.2, 119.9, 119.3, 116.6, 112.8, 75.7, 37.5, 18.0, 17.9, 16.5, 12.4; IR (neat) 3425, 2942, 2865, 1460, 1090, 1065, 882 cm^{-1}; Anal. Calcd for $C_{26}H_{37}NOSi$: C, 76.60; H, 9.15. Found: C, 76.79; H, 8.96.

(Table 1, Entry 3) 3-Butyl-7-methylindole. Cp_2TiCl_2 (1.00 g, 4.00 mmol) in toluene (50 mL) was employed according to general procedure A. The indole product was purified by flash chromatography (3:1 hexane/CH_2Cl_2) to yield 0.40 g of a colorless needles (54% from Cp_2TiCl_2): mp 39.5–40.0 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.80 (br s, 1 H), 7.47 (d, *J* = 7.5 Hz, 1 H), 7.10-6.95 (m, 3 H), 2.75 (t, *J* = 7.0 Hz, 2 H), 2.48 (s, 3 H), 1.75-1.60 (m, 2 H), 1.42 (sextet, *J* = 7.0 Hz, 2 H), 0.95 (t, *J* = 7.0 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 135.9, 127.2, 122.3, 120.7, 120.1, 119.3, 117.7, 116.8, 32.4, 25.0, 22.7, 16.6, 14.0; IR (KBr) 3433, 2960, 2920, 2855, 1464, 1430, 1100, 1066, 788, 745 cm^{-1}; Anal. Calcd for $C_{13}H_{17}N$: C, 83.37; H, 9.15. Found: C, 83.40; H, 9.33.

(Table 1, Entry 4) 3-Butyl-4,7-dimethylindole. Cp_2TiCl_2 (1.00 g, 4.00 mmol) in toluene (50 mL) was employed according to general procedure

A. The indole product was purified by flash chromatography (3:1 hexane/CH_2Cl_2) to yield 0.30 g of a colorless needles (37% from Cp_2TiCl_2): mp 73.5-74 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.77 (br s, 1 H), 6.94 (s, 1 H), 6.85 (d, J = 7.1 Hz, 1 H), 6.75 (d, J = 7.1 Hz, 1 H), 2.90 (t, J = 7.4 Hz, 2 H), 2.68 (s, 3 H), 2.42 (s, 3 H), 1.67 (m, 2 H), 1.47 (sextet, J = 7.3 Hz, 2 H), 0.97 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 136.3, 128.6, 125.5, 122.2, 120.9, 118.8, 117.7, 33.7, 26.9, 22.6, 20.0, 16.2, 14.0; IR (KBr) 3425, 2953, 2856, 1511, 803 cm^{-1}; Anal. Calcd for $C_{14}H_{19}N$: C, 83.53; H, 9.51. Found: C, 83.76; H, 9.79.

(Table 1, Entry 5) 3-Butyl-naphthoindole. Cp_2TiCl_2 (1.00 g, 4.00 mmol) in toluene (50 mL) was employed according to general procedure A. The indole product was purified by flash chromatography (4:1 hexane/CH_2Cl_2) to yield 0.31 g of a colorless needles (35% from Cp_2TiCl_2): mp 132–133 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 8.6 (br s, 1H), 7.98 (d, J = 8.4 Hz, 1 H), 7.92 (d, J = 8.4 Hz, 1 H), 7.71 (d, J = 9.3 Hz, 1 H), 7.38–7.55 (m, 3 H), 7.06 (m, 1H), 2.83 (t, J = 7 Hz, 2 H), 1.64–1.80 (m, 2 H), 1.45 (sextet, J = 7.2 Hz, 2 H), 0.97 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 130.8, 130.4, 128.8, 125.3, 123.7, 123.4, 121.8, 119.9, 119.3, 119.2, 119.0, 32.7, 24.9, 22.6, 14.0; IR (KBr) 3411, 2957, 2915, 2855, 1524, 1452, 1392, 811 cm^{-1}; Anal. Calcd for $C_{16}H_{17}N$: C, 86.05; H, 7.67. Found: C, 86.34; H, 7.83.

(Table 1, Entry 6) 3-Butyl-4-methoxy-7-methylindole. Cp_2TiCl_2 (0.75 g, 3.00 mmol) in toluene (40 mL) was employed according to general procedure A. The indole product was purified by flash chromatography (10:1 hexane/ethyl acetate) to yield 0.12 g of a colorless oil (18% from Cp_2TiCl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 7.76 (br s, 1 H), 6.86 (m, 2 H), 6.40 (d, J = 7.9 Hz, 1 H), 3.89 (s, 3 H), 2.87 (t, J = 7.4 Hz, 2 H), 2.39 (s, 3 H), 1.66 (m, 2 H), 1.42 (sextet, J = 7.3 Hz, 2 H), 0.95 (t, J = 7.3 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.8, 137.4, 122.4, 119.5, 118.5, 113.0, 99.3, 97.3, 55.2, 42.0, 33.4, 26.5, 22.6,

14.1; IR (neat) 3470, 2958, 2861, 1604, 1515, 1264 cm^{-1}; Anal. Calcd for $C_{14}H_{19}N_1O$: C, 77.38; H, 8.81. Found: C, 77.44; H, 9.04.

7-Methyl-3-{2-(7-methyl-3-indolyl)ethyl}indole (3). Cp_2TiCl_2 (2.00 g, 8.00 mmol) in toluene (100 mL) was employed according to general procedure A using 1,5-hexadiene (0.48 mL, 4.00 mmol). The indole product was purified by flash chromatography (2:1 hexane/acetone) to yield 0.37 g of a colorless needles (16% from Cp_2TiCl_2): mp 225–226 °C. ^1H NMR (250 MHz, acetone-d_6) δ 9.90 (br s, 2 H), 7.49 (d, J = 7.1 Hz, 2 H), 7.15 (m, 2 H), 7.05-6.85 (m, 4 H), 3.15 (s, 4 H), 2.49 (s, 6 H); ^{13}C NMR (75 MHz, acetone-d_6) δ 137.2, 128.5, 122.7, 122.6, 122.4, 121.3, 119.7, 117.3, 27.4, 17.0; IR (KBr) 3406, 2880, 2838, 2536, 1492, 1458, 1436, 1064 cm^{-1}; Anal. Calcd for $C_{20}H_{20}N_2$: C, 83.30; H, 6.99. Found: C, 83.55; H, 7.28.

2-Methyl-6-vinyl-N-benzylaniline (7). A mixture of $Pd_2(dba)_3$ (41 mg, 2 mol %), P(*o*-tolyl)$_3$ (84 mg, 6 mol %), and NaO*t*-Bu (0.30 g, 3.16 mmol) was added to a solution of the dibromide **4** (0.63 g, 2.26 mmol) in toluene, the flask was heated to 80 °C for 16 h. Upon cooling to RT, the solution was poured into a separatory funnel containing H_2O and Et_2O. The organic layer was washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo.* The product was purified by flash chromatography (20:1 hexane/ethyl acetate) to give 0.19 g (38%) of a yellow oil. ^1H NMR (250 MHz, $CDCl_3$) δ 7.62-7.56 (m, 6 H), 7.36-7.30 (m, 2 H), 7.19 (t, J = 7.5 Hz, 1 H), 5.93 (dd, J = 1.6, 19.2 Hz, 1 H), 5.54 (dd, J = 1.6, 10.8 Hz, 1 H), 4.43 (s, 2 H), 3.63 (br s, 1 H), 2.45 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 145.0, 140.4, 134.6, 130.8, 130.1, 129.4, 128.5, 127.8, 127.3, 125.2, 122.2, 114.4, 54.0, 13.0; IR (neat) 3367, 3028, 2928, 1591, 1464, 700 cm^{-1}.

(Table 2, Entry 1) 7-methylindole.[14] Cp_2TiCl_2 (2.61 g, 10.48 mmol) in toluene (70 mL) was employed according to general procedure B.

The indole product was purified by flash chromatography (10:1 hexane/ethyl acetate) to yield 0.56 g of a white solid (40% from Cp_2TiCl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.02 (br s, 1 H), 7.56 (d, J = 7.5 Hz, 1 H), 7.20 (m, 1 H), 7.10 (t, J = 7.3 Hz, 1 H), 7.04 (d, J = 7.3 Hz, 1 H), 6.60 (s, 1 H), 2.52 (s, 3 H).

(Table 2, Entry 2) 4-methoxy-7-methylindole. Cp_2TiCl_2 (0.93 g, 3.75 mmol) in toluene (25 mL) was employed according to general procedure B. The indole product was purified by flash chromatography (10:1 hexane/ethyl acetate) to yield 0.21 g of a white solid (34% from Cp_2TiCl_2). ^1H NMR (300 MHz, $CDCl_3$) δ 8.06 (br s, 1 H), 7.11 (s, 1 H), 6.94 (d, J = 7.7 Hz, 1 H), 6.72 (s, 1 H), 6.50 (d, J = 7.7 Hz, 1 H), 3.98 (s, 3 H), 2.45 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.8, 136.6, 122.6, 122.5, 118.0, 113.3, 100.3, 99.6, 55.4, 16.0; IR (KBr) 3394, 3105, 2962, 1524, 1500, 1262 cm^{-1}; Anal. Calcd for $C_{10}H_{11}NO$: C, 74.51; H, 6.88. Found: C, 74.59; H, 7.22.

(Table 2, Entry 3) 3-Butyl-7-methoxyindole. Cp_2TiCl_2 (1.00 g, 4.00 mmol) in toluene (50 mL) was employed according to general procedure C. The indole product was purified by flash chromatography (4:1 hexane/CH_2Cl_2) to yield 0.35 g of a colorless needles (43 % based on Cp_2TiCl_2). ^1H NMR (250 MHz, $CDCl_3$) δ 8.10 (br s, 1H), 7.22 (d, J = 7.8 Hz, 1 H), 7.02 (t, J = 7.8 Hz, 1 H), 6.9 (m, 1 H), 6.62 (d, J = 7.8 Hz, 1 H), 3.93 (s, 3 H), 2.73 (t, J = 7.3 Hz, 2 H), 1.75-1.55 (m, 2 H), 1.40 (sextet, J = 7.2 Hz, 2 H), 0.94 (t, J = 7.2 Hz, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.1, 129.0, 126.8, 120.6, 119.4, 117.5, 111.8, 101.7, 55.3, 32.4, 25.0, 22.6, 14.0; IR (neat) 3416, 2952, 2927, 2854, 1577, 1498, 1446, 1373, 1258, 1077, 1040 cm^{-1}; Anal. Calcd for $C_{13}H_{17}ON$: C, 76.81; H, 8.43. Found: C, 77.08; H, 8.56.

(Table 2, Entry 4) 3-{8-(*tert*-Butoxycarbonyl)octyl}-7-methylindole. Cp_2TiCl_2 (1.00 g, 4.00 mmol) in toluene (50 mL) was employed according to general procedure C. The indole product was purified

by flash chromatography (3:1 hexane/Et_2O) to yield 0.45 g of a colorless needles (33 % based on Cp_2TiCl_2): mp 57–58 °C. ^1H NMR (300 MHz, $CDCl_3$) δ 7.8 (br s, 1H), 7.46 (d, J = 7.8 Hz, 1 H), 7.08-6.95 (m, 3 H), 2.73 (t, J = 7.2 Hz, 2 H), 2.48 (s, 3 H), 2.19 (t, J = 6.9 Hz, 2 H), 1.76-1.50 (m, 4 H), 1.44 (s, 9 H), 1.42-1.20 (m, 8 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.4, 135.9, 127.1 122.3, 120.7, 120.1, 119.2, 117.6, 116.7, 79.9, 35.6, 30.2, 29.5, 29.3, 29.1, 28.1, 25.3, 25.1, 16.6; IR (KBr) 3356, 2917, 2849, 1718, 1466, 1160 cm^{-1}; Anal. Calcd for $C_{22}H_{33}O_2N$: C, 76.92; H, 9.68. Found: C, 77.15; H, 9.95.

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(9) The ethylene used was of Grade 5 quality (99.99% pure) and was purchased from Middlesex Gases & Technology Inc.

(10) We obtained only trace amounts of the desired product when using the 95% ethylene purchased from Aldrich Chemical Co.

(11) Commercially available from Aldrich Chemical Co.

Part Two:

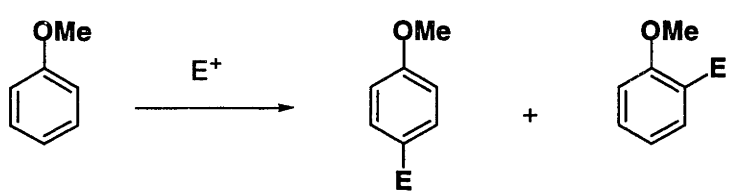
The Synthesis of Polysubstituted Aromatic Compounds

Introduction

Polysubstituted aromatic ring systems are a common feature of a variety of biologically active natural products, which make them of considerable interest to synthetic organic and medicinal chemists.[1] In addition, they are structural constituents in important materials such as polymers[2] and liquid crystals.[3] For these reasons, there has been intense effort directed towards the general and efficient construction of highly substituted aromatic compounds. The majority of the synthetic approaches rely on direct functionalization of a pre-existing benzene ring. Examples include electrophilic aromatic substitution,[4] vicarious nucleophilic substitution of hydrogen,[5] directed lithiation,[6] and the reactions of transition metal-arene complexes[7] (Scheme 1). The second approach involves

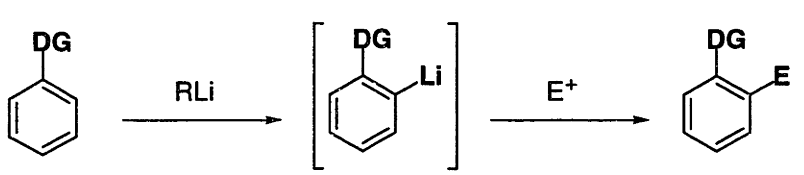
Scheme 1

Electrophilic Aromatic Substitution:

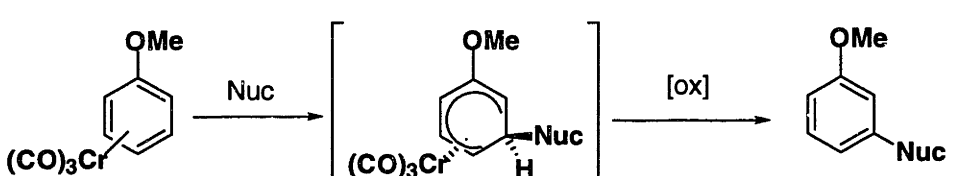


Major

Directed Lithiation:



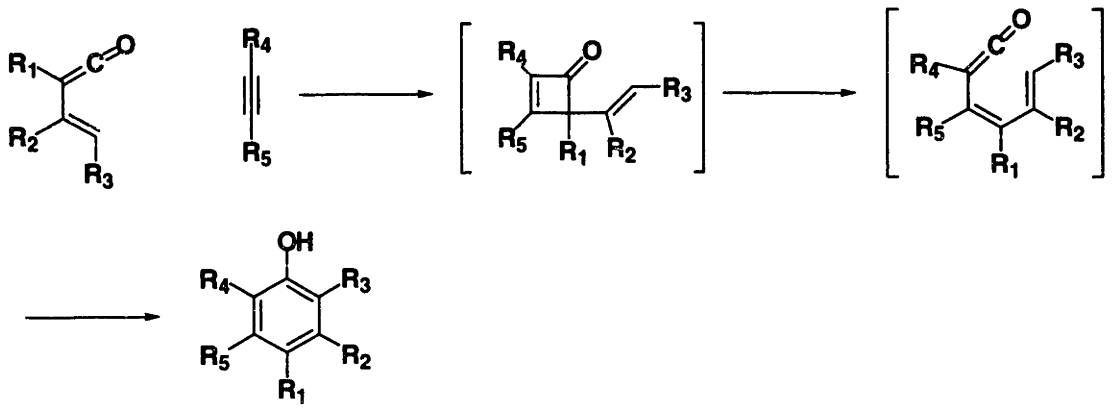
Reactions of Cr-Arene Complexes:



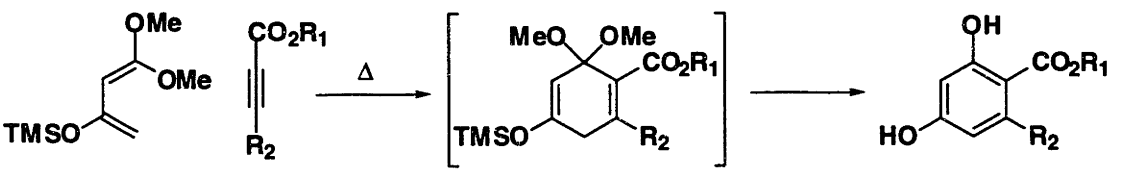
annulation reactions of acyclic precursors such as cycloaddition reactions of vinyl ketenes,[8] [4+2] cycloadditions,[9] cyclotrimerization,[10] and the cyclization of chromium aryl carbene complexes (Scheme 2).[11]

Scheme 2

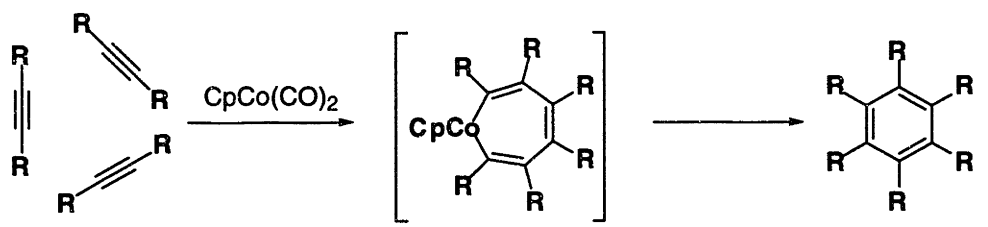
Cycloadditions of Vinyl Ketenes:



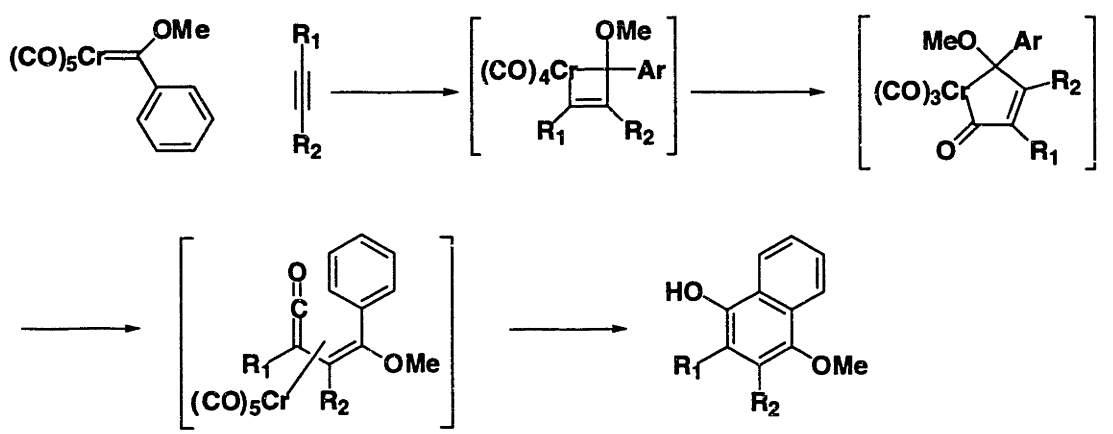
[4 + 2] Cycloaddition Approach:



Cyclotrimerization:



Fischer Carbene Complexes:



Of the methods to directly functionalize the aromatic ring, electrophilic aromatic substitution reactions are the most commonly employed. Examples include the Friedel-Crafts alkylation and acylation,[4a-d] the Vilsmeier-Haack reaction,[4e,f] and the Fries rearrangement.[4g] Although these methods have been studied extensively and applied to a variety of aromatic systems, regiochemical ambiguities often arise, resulting in mixtures of compounds that can be difficult to separate. Such problems can be circumvented by introducing blocking groups; however, this limits the efficiency of the method.

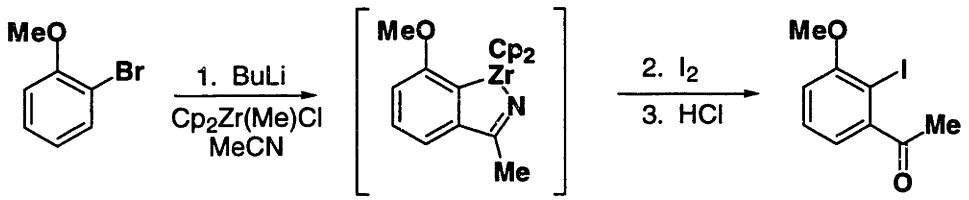
Recently, a strategy involving the directed lithiation of an aromatic ring has emerged as a powerful technique for the construction of 1,2-disubstituted aromatic compounds.[6] A variety of functional groups act as directing groups for the ortho-lithiation of the benzene ring, which can be treated with a wide range of electrophiles to give the disubstituted derivatives. It is worth noting that the lithiation conditions for many of these procedures have been optimized by Beak and Snieckus. Another important feature of this method is the hierarchy that exists for the directing groups, allowing one to predict *a priori* where lithiation will occur when multiple directing groups are present on the ring. A cooperative directing effect is often observed with meta-disubstituted aromatics, allowing for the construction of contiguously trisubstituted benzene derivatives. Finally, the directing groups themselves can be elaborated, further widening the synthetic potential of the methodology.

The functionalization of aromatic systems employing an intermediate zirconocene-benzyne complex, which is prepared readily via halogen-metal exchange of an aryl halide in the presence of $Cp_2Zr(Me)Cl$, has been reported from our laboratories (Scheme 3).[12] Insertion of an unsaturated compound (e.g., an. olefin, alkyne, nitrile, isonitrile) into the carbon-zirconium bond of the benzyne-complex produces a zirconacycle, which can be cleaved with various

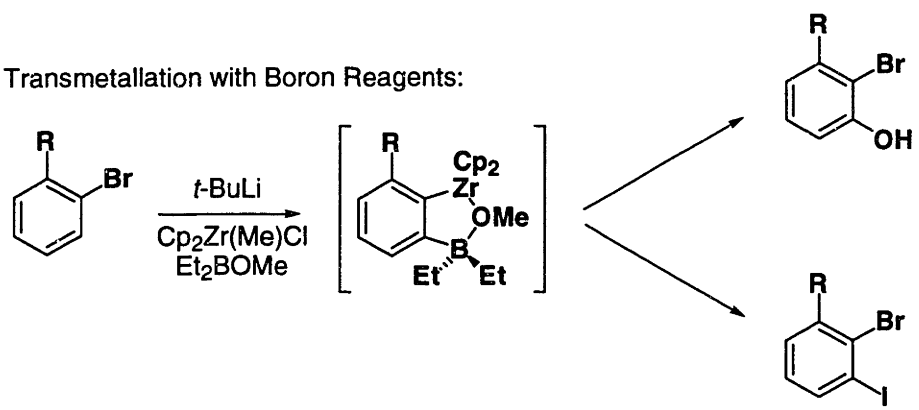
electrophilic reagents. Alternatively, transmetallation of the zirconium-benzyne complex with boron reagents has been used to prepare a variety of bromoiodobenzenes and iodophenols.[13] The overall process results in the formation of a 1,2-disubstituted aromatic derivative with a net increase in ring-functionality by one. Of importance is that the reactions exhibit good to excellent regioselectivity when ortho-substituted aryl halides are employed.

Scheme 3

Nitrile Insertion:



Transmetallation with Boron Reagents:



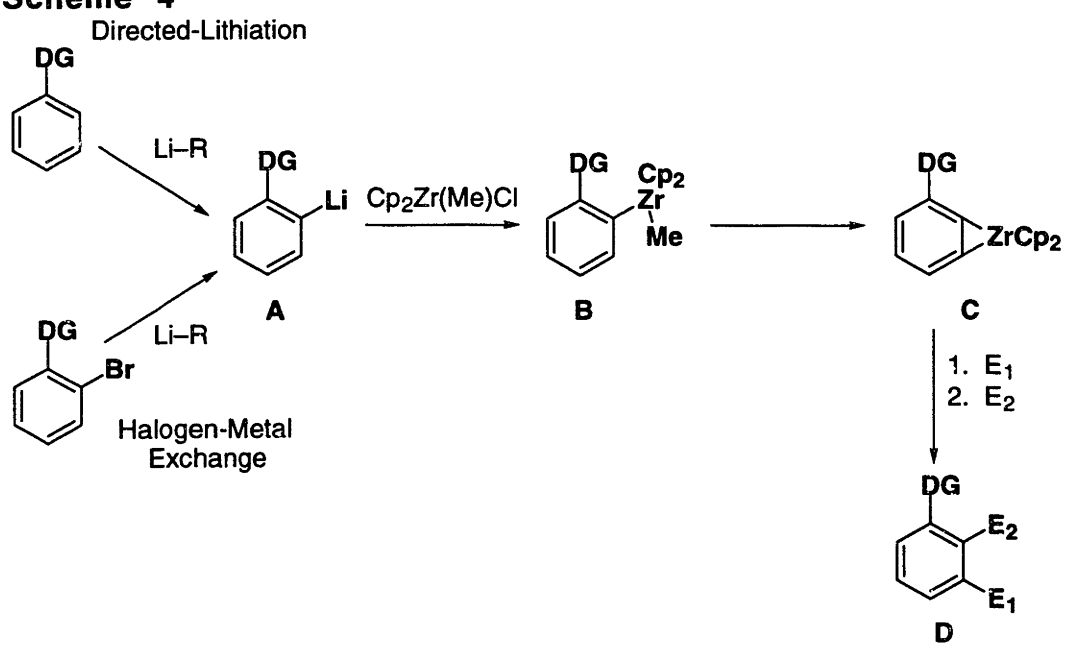
Herein, we describe a procedure for the synthesis of highly substituted benzenoid derivatives from readily available mono- and disubstituted aromatic starting materials. The method involves the combination of directed lithiation methodology with our zirconium-benzyne chemistry, thereby eliminating the need for an aryl halide starting material. The net result is the directed meta- **or** meta- and ortho-metalation of the aromatic ring, transformations not possible

using existing methods. In addition, there is an overall increase in ring-substitution by *at least* two, providing access to di- and tri-substituted aromatics from a monofunctionalized arene. The procedure benefits from the advantages enjoyed by both methodologies.

Results and Discussion

In an effort to increase the synthetic utility of our zirconium-benzyne chemistry, we were interested in eliminating the use of an aryl halide starting material. We reasoned that the aryllithium intermediate **A** could be generated via the directed lithiation methodology instead of *via* halogen-metal exchange (Scheme 4). Addition of $Cp_2Zr(Me)Cl$ to the aryllithium yields the

Scheme 4



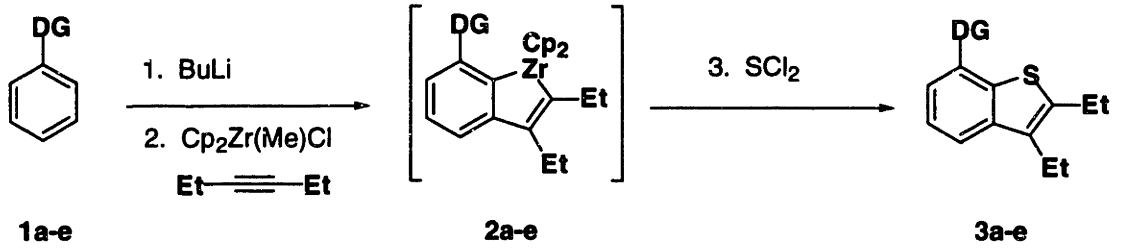
aryl(methyl)zirconocene **B**, which upon heating eliminates methane and generates the desired zirconocene-stabilized benzyne complex **C**. Previous

research conducted in our laboratories has shown that various electrophiles insert selectively into the carbon-zirconium bond, thereby affording a trisubstituted aromatic derivative **D** with a high level of regiochemical purity.[12]

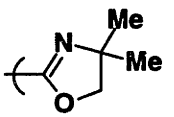
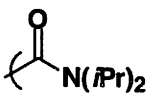
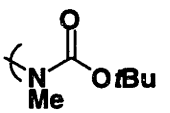
To test the feasibility of our proposed method, we investigated the construction of benzothiophenes from various monosubstituted aromatic starting materials (Table 1). For example, treatment of anisole (**1a**) in Et_2O with 1.05 equiv of *n*-BuLi at 0 °C, followed by heating the resulting solution to 37 °C for 24 h, afforded the ortho-lithiated anisole. The solution was cooled to –78 °C, then 3-hexyne and a suspension of $Cp_2Zr(Me)Cl$ in Et_2O at –78 °C were added, and mixture was warmed slowly to RT. The zirconium-benzyne complex was formed upon heating to 80 °C, which upon reaction with the alkyne produced zirconacycle **2a**. The reaction mixture was cooled to RT and the solvent was removed *in vacuo*. The residue was dissolved in THF, cooled to –78 °C, and SCl_2 was added. After 1 h, the solution was warmed to RT, and then poured into a separatory funnel containing Et_2O and water. Conventional workup, followed by flash chromatography on silica gel afforded the desired 7-methoxybenzothiophene **3a** in 68% yield.

In addition to anisole, several other directing groups were investigated to determine their suitability to this method. For example, oxazoline **1c** could be used as the precursor to the benzothiophene **3c** which was formed in 77% yield. In addition, carbonyl-containing directing groups (**1d** and **1e**) also gave the desired products (**3d** and **3e**) in moderate to good yields.

Table 1: Procedure A



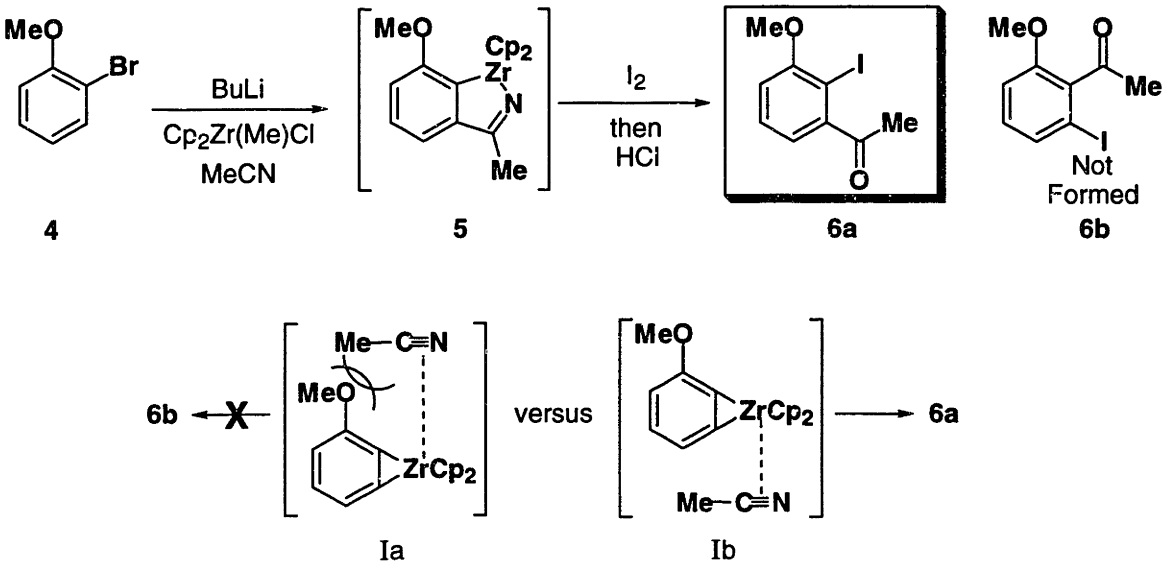
1a-e 2a-e 3a-e

Entry	DG	Yield of 3
a		67%
b		73%
c		75%
d		69%
e		59%

With these initial results in hand, we decided to investigate whether this method could be extended to the reactions of zirconocene-benzyne complexes with other unsaturated molecules. An important feature of the original zirconocene-benzyne methodology is that it can be used to produce anti Friedel-Crafts aryl ketones by reaction of the Zr–benzyne complex with nitriles, followed by hydrolysis of the intermediate azametallacycle (Scheme 5).[12] For example, treatment of o-bromotoluene with *n*-BuLi, followed by the addition of $Cp_2Zr(Me)Cl$ and acetonitrile affords the azametallacycle **5**. Addition of iodine and then aqueous HCl produced the aryl ketone **6a** in 61% yield. It is important to note that two regioisomeric ketones (**6a** and **6b**) could be formed, however

only **6a** is produced.[12a] The reason is that the nitrile regioselectively inserts into the Zr–C bond away from the bulky methoxy substituents (**Ia**), thereby forming the azametallacycle **5**. Insertion of the nitrile into the Zr–C on the same side as the methoxy group (**IIa**) is disfavored due to steric factors. We therefore examined

Scheme 5

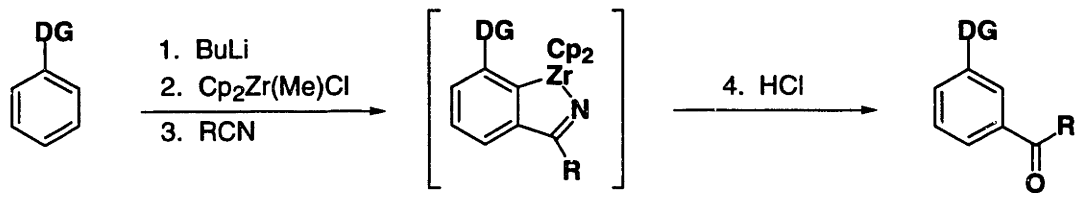


the use of various nitriles using our directed lithiation/zirconocene-benzyne approach (Table 2). For example, $Cp_2Zr(Me)Cl$ was added at –78 °C to ortho-lithiated anisole, as prepared above, to yield the aryl(methyl)zirconocene. After warming the solution to RT, 7-chloroheptanenitrile was added and the solution was heated to 80 °C for 16 h, resulting in the formation of the azazirconacycle **8a**. The mixture was cooled to RT and the solvent was removed *in vacuo*. The residue was dissolved in THF, then 1N HCl was added to protonate both the Zr–C and the Zr–N bonds, as well as hydrolyze the resulting imine to the aryl ketone **9a**. It is important to note that the overall process is synthetically

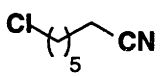
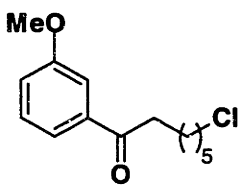
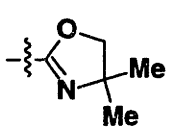
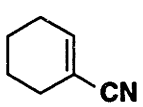
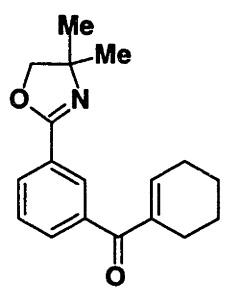
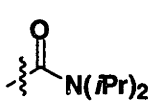
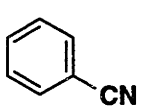
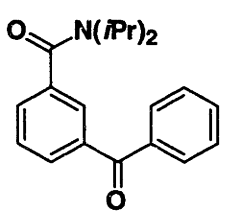
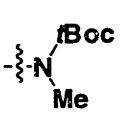
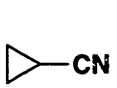
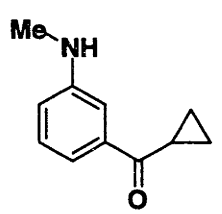
equivalent to the directed meta-metalation of anisole, followed by the selective reaction of an acid chloride.

We examined various directing groups, as well as several nitriles, to construct a number of anti Friedel-Crafts aryl ketones. Use of oxazoline **7b** and

Table 2: Procedure B



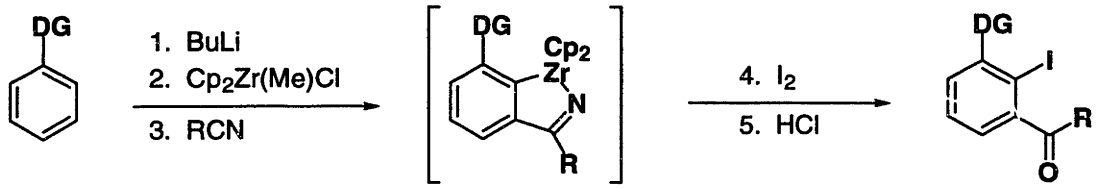
7a-d **8a-d** **9a-d**

Entry	DG	Nitrile	Product (9)	Yield
a				72%
b				66%
c				69%
d				57%

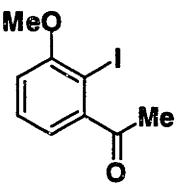
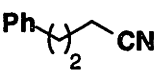
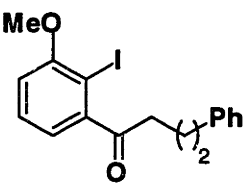
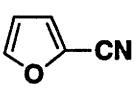
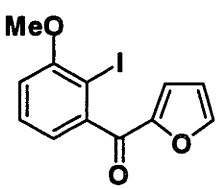
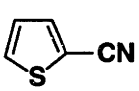
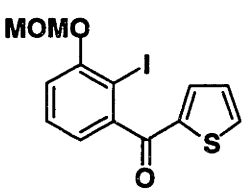
1-cyclohexenenitrile afforded the α,β-unsaturated aryl ketone **9b** in 67% yield. A particularly interesting example involves the addition of acid to the azazirconacycle **8d,** formed from *t*-BOC-protected *N*-methylaniline **7d** and cyclopropylnitrile, which resulted in the cleavage of the *t*-BOC group, affording the aniline aryl ketone **9d**. The overall transformation is synthetically equivalent to using a zirconocene-benzyne complex containing an ortho-amino group, which cannot be used directly due to the presence of an acidic proton.

In addition to forming 1,3-disubstituted aryl ketones, we were also interested in exploiting the aryl-zirconium bond of the azametallacycle, thereby introducing substituents at the ortho-position as well. Based on previous work conducted in our laboratories,[12] the azazirconacycle **11** was first treated with iodine, which cleaves the zirconium-carbon bond to afford the aryliodoimine (Table 3). Upon addition of acid the imine was hydrolyzed, producing a contiguously trisubstituted aryl ketone **12** from a monofunctionalized starting material **10**. For example, the coupling of the MOM–protected phenol **10d** with 2-thiophenecarbonitrile produced the thiophene containing aryl ketone **12d** in 60% yield.

Table 3: Procedure C



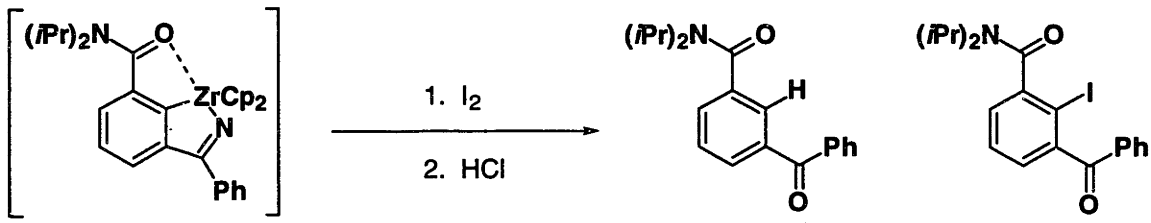
10a-d 11a-d 12a-d

Entry	DG	Nitrile	Product (12)	Yield
a	-OMe	MeCN		77%
b	-OMe			73%
c	-OMe			54%
d	-OMOM			60%

It is important to note that carbonyl-containing directing groups such as *N,N*-diisopropylamide did not produce the desired aryliodoketone, but instead gave only the protonated disubstituted derivative (Scheme 5). One explanation may be that iodine cannot coordinate to the empty $1a_1$-orbital of zirconium due to the steric bulk of these directing groups. The more likely possibility is that upon formation of the azazirconacycle **13**, the carbonyl group coordinates to the empty $1a_1$-orbital of zirconium creating an unreactive 18-electron complex

which is inert to iodine.[14] Other more reactive halogen sources such as Br_2 and ICl were also tried but to no avail.

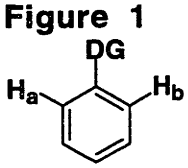
Scheme 5



13 14 15

We also investigated the construction of 1,2,4-trisubstituted aryl ketones by taking advantage of the fact that there are two possible sites (H_a and H_b) for ortho-lithiation on the monofunctionalized aromatic starting materials (Figure 1). It has previously been demonstrated that both ortho-positions can be functionalized in a one-pot procedure by sequential deprotonation followed by trapping of an electrophile to produce contiguously trisubstituted arenes.[6]

Figure 1

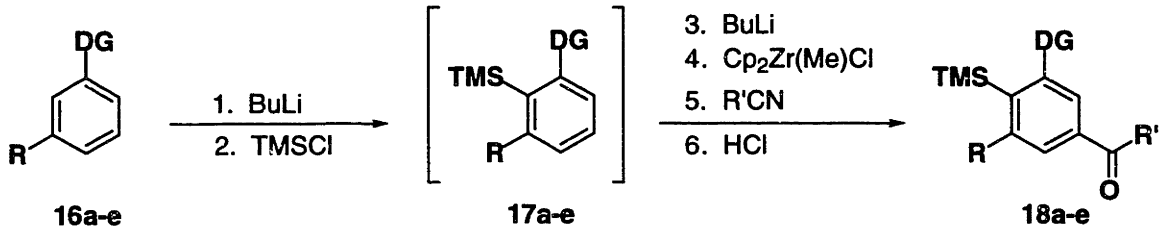


According to these procedures, addition of *t*-BuLi to a solution of the MOM-protected phenol **16a** in Et_2O at 0 °C followed by warming to RT afforded the desired aryllithium complex (Table 4). The solution was cooled to 0 °C and TMSCl was added, then the solvent was removed *in vacuo* yielding the aryltrimethylsilane **17a**. The residue was dissolved in Et_2O, then *t*-BuLi was added to generate a solution of a second aryllithium intermediate, which was

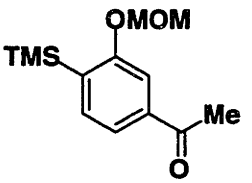
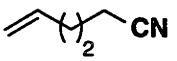
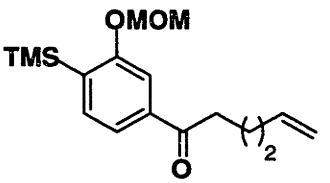
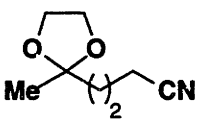
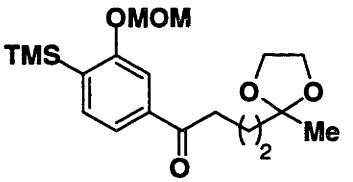
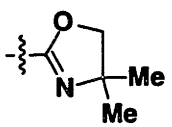
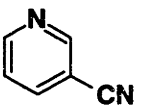
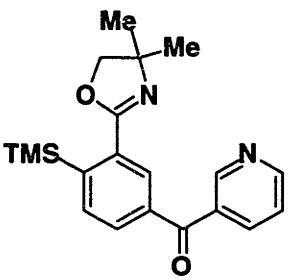
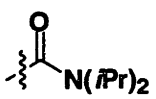
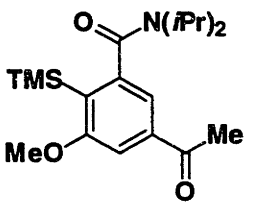
then cooled to –78 °C. A suspension of $Cp_2Zr(Me)Cl$ in Et_2O was added and the solution was warmed slowly to –50 °C. The aryl(methyl)zirconocene was treated with acetonitrile, then heated to 80 °C to produce the azazirconacycle. Upon cooling to RT, 1N HCl was added and the desired 1,2,4-trisubstituted aryl ketone **18a** could be isolated in good yield.

The use of the 3-methoxy-*N,N*-diisopropylbenzamide **16d** illustrates the cooperative effect that exists between meta-substituents. The first lithiation occurs at the carbon between the directing groups, and the anion was quenched with TMSCl.[6] The second lithiation occurs ortho to the *N,N*-diisopropylamide-group since this is a better director than the methoxy-substituent. Addition of $Cp_2Zr(Me)Cl$ and acetonitrile, followed by heating to 80 °C afforded the azametallacycle, which upon acid hydrolysis gave the tetrasubstituted aryl ketone **18e** in 51% yield.

Table 4: Procedure D



16a-e 17a-e 18a-e

Entry	DG	R	Nitrile	Product (18)	Yield
a	-OMOM	-H	MeCN		74%
b	-OMOM	-H			78%
c	—OMOM	-H			66%
d		-H			70%
e		-OMe	MeCN		52%

In summary, we have developed an efficient method for the construction of polysubstituted aromatic compounds which involves the combination of the

directed lithiation methodology with our previously developed zirconocene-benzyne chemistry. The required starting materials are an aromatic compound containing a directing group, an unsaturated organic molecule (e.g. an alkyne or nitrile), and $Cp_2Zr(Me)Cl$, all of which are commercially available or readily prepared. When nitriles are employed, the result is the formation of meta-substituted aryl ketones, several of which are the anti Friedel-Crafts isomers. The overall transformation can be described as the directed meta-metalation of the aromatic ring, followed by the selective reaction with an acid chloride; such a process is not possible using traditional methods. Finally, a number of functional groups are tolerated, providing access to aryl ketones with diverse substituents, as well as a variety of substitution patterns. Therefore, we believe this new approach complements the powerful technique of directed lithiation.

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. 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 spectrometer. Infrared (IR) spectra were recorded on a 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 cross linked SE-30 as a stationary phase. Electron impact mass spectra and high resolution mass determinations (HRMS) were recorded on a Finnegan MAT System 8200. Tetrahydrofuran, benzene, diethyl ether, and hexane were dried and deoxygenated by continuous refluxing over sodium/benzophenone ketyl under nitrogen or argon followed by distillation. Methylene chloride was dried by refluxing over CaH_2 under nitrogen 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. Cp_2ZrCl_2 was a gift 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 $\geq$95% pure (unless otherwise noted) as determined by ^1H NMR and either capillary GC or

combustion analysis. Elemental analyses were performed by E & R Microanalytical Laboratory, Inc., Corona, N.Y.

General Lithiation Conditions:

Lithiation of Anisole: A solution of 1.6M *n*-BuLi in hexanes (1.05 equiv) was added dropwise to a solution of anisole (1.00 equiv) in Et_2O (10 mL) at 0 °C under argon in a resealable Schlenk flask. After 1 h, the solution was heated to 37 °C for 24 h.

Lithiation of Methoxymethylphenol: A solution of 1.6M *n*-BuLi in hexanes (1.05 equiv) or 1.7M *t*-BuLi in pentane (1.05 equiv) was added dropwise to a solution of the MOM ether (1.00 equiv) in Et_2O (10 mL) at 0 °C under argon in a resealable Schlenk flask. After 1 h, the solution was warmed to RT and allowed to stir for an additional 8 h.

Lithiation of 4,4-dimethyl-2-phenyl-2-oxazoline: A solution of 1.7M *t*-BuLi in pentane (1.05 equiv) was added dropwise to a solution of the 4,4-dimethyl-2-phenyl-2-oxazoline (1.00 equiv) in Et_2O (10 mL) at –78 °C under argon in a resealable Schlenk flask and the remaining solution was stirred at –78 °C for 1 h.

Lithiation of *N,N*-dimethylbenzamide: A solution of 1.7M *t*-BuLi in pentane (1.05 equiv) was added dropwise to a solution of *N,N*-diisopropylbenzamide (1.00 equiv) in Et_2O/THF (9 mL/1 mL) at –78 °C under argon in a resealable Schlenk flask and the remaining solution was stirred at –78 °C for 1 h.

Lithiation of *N*-methyl-*N*-*t*BOC-aniline: A solution of 1.7M *t*-BuLi in pentane (1.05 equiv) was added dropwise to a solution of *N*-methyl-*N*-*t*BOC-aniline (1.00 equiv) in Et_2O/THF (9 mL/1 mL) at –78 °C under argon in a

resealable Schlenk flask and the remaining solution was stirred at –78 °C for 1 h.

General Procedure A: A solution of the appropriate aryllithium, prepared as described above, in a resealable Schlenk flask was cooled to –78 °C and 3-hexyne (3.00 equiv) and a suspension of $Cp_2Zr(Me)Cl$ (1.05 equiv) in Et_2O (10 mL) at –78 °C were added. The flask was warmed to RT, sealed, then placed in an oil bath at 80 °C (or 105 °C) for 15 h. The reaction mixture was cooled to RT and the solvent was removed *in vacuo*. THF (10 mL) was added, then the solution was cooled to –78 °C and SCl_2 (1.20 equiv) was added. After 1 h, the solution was warmed to RT and poured into a separatory funnel containing Et_2O (10 mL) and water (10 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography.

General Procedure B: A solution of the aryllithium, prepared as described above, in a resealable Schlenk flask was cooled to –78 °C and a suspension of $Cp_2Zr(Me)Cl$ (1.05 equiv) in Et_2O (10 mL) at –78 °C was added. Upon warming to RT, the nitrile (1.5 equiv) was added, then the flask was sealed and placed in an oil bath at 80 °C (or 105 °C) for 15 h. The solution was cooled to RT and the solvent was removed *in vacuo*. THF (10 mL) was added, followed by 1N HCl (10 mL), and after 4 h the mixture was poured into a separatory funnel containing Et_2O (10 mL) and water (10 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography.

General Procedure C: A solution of the aryllithium, prepared as described above, in a resealable Schlenk flask was cooled to –78 °C and a

suspension of $Cp_2Zr(Me)Cl$ (1.05 equiv) in Et_2O (10 mL) at –78 °C was added. Upon warming to RT, the nitrile (1.5 equiv) was added, then the flask was sealed and placed in an oil bath at 80 °C (or 105 °C) for 15 h. The solution was cooled to RT and the solvent was removed *in vacuo*. THF (10 mL) was added, followed by a solution of iodine (2.5 equiv) in THF (10 mL). After 5 h, 1N HCl (10 mL) was added and the mixture was stirred for 4 h, then was poured into a separatory funnel containing Et_2O (10 mL) and water (10 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography.

General Procedure D: A solution of the aryllithium, prepared as described above, in a resealable Schlenk flask was cooled to 0 °C and TMSCl (1.20 equiv) was added. After 1 h, the solution was warmed to RT, then the solvent was removed *in vacuo*. Solvent was added and the second aryllithium was generated as described above. The solution was cooled to –78 °C and a suspension of $Cp_2Zr(Me)Cl$ (1.05 equiv) in Et_2O (10 mL) at –78 °C was added. Upon warming to RT, the nitrile (1.5 equiv) was added, then the flask was sealed and placed in an oil bath at 80 °C (or 105 °C) for 15 h. The solution was cooled to RT and the solvent was removed *in vacuo*. THF (10 mL) was added, followed by 1N HCl (10 mL), and after 4 h the mixture was poured into a separatory funnel containing Et_2O (10 mL) and water (10 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and the solvents were removed using a rotary evaporator. The product was purified by flash chromatography.

3a.[12] Anisole (0.32 g; 3.00 mmol) in Et_2O (10 mL) was used following general procedure A. The product was purified by flash chromatography (10:1 hexane/ethyl acetate) to give 0.45 g (68%) of a

yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.21 (t, *J* = 7.6 Hz, 2 H), 6.66 (dd, *J*= 1.0, 6.0 Hz, 1 H), 3.92 (s, 3 H), 2.83 (q, *J* = 8.0 Hz, 2 H), 2.72 (q, *J* = 8.0 Hz, 2 H), 1.27 (t, *J* = 8.0 Hz, 3 H), 1.14 (t, *J* = 8.0 Hz, 3 H).

3b. Methoxymethylphenol (0.41 g; 3.00 mmol) in Et_2O (10 mL) was used following general procedure A. The product was purified by flash chromatography (40:1 then 20:1 hexane/ethyl acetate) to give 0.55 g (73%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.26 (m, 2 H), 6.98 (dd, *J*= 1.5, 7.2 Hz, 1 H), 5.36 (s, 2H), 3.54 (s, 3 H), 2.90 (q, *J*= 7.5 Hz, 2 H), 2.80 (q, *J*= 7.6 Hz, 2 H), 1.35 (t, *J* = 7.5 Hz, 3 H), 1.22 (t, *J* = 7.6 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 151.9, 142.2, 141.6, 133.1, 125.1, 115.1, 107.5, 94.7, 56.2, 21.7, 19.8, 16.2, 14.7. IR (film, cm^{-1}) 3062, 2965, 1551, 1472, 1251. Anal. Calcd for $C_{14}H_{18}O_2S$: C, 67.17; H, 7.25. Found: C, 67.35; H, 7.12.

3c. 4,4-dimethyl-2-phenyl-2-oxazoline (0.53 g; 3.00 mmol) in Et_2O (10 mL) was used following general procedure A. The product was purified by flash chromatography (10:1 hexane/ethyl acetate) to give 0.66 g (77%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (d, *J*= 7.6 Hz, 1 H), 7.74 (d, *J*= 7.6 Hz, 1 H), 7.39 (t, *J* = 7.6 Hz, 1 H), 4.15 (s, 2 H), 2.91 (q, *J*= 7.5 Hz, 2 H), 2.82 (q, *J*= 7.5 Hz, 2 H), 1.45 (s, 6 H), 1.36 (t, *J* = 7.5 Hz, 3 H), 1.21 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 161.2, 143.7, 141.1, 137.4, 131.9, 124.1, 123.8, 123.4, 122.2, 78.9, 68.1, 28.6, 21.6, 19.4, 16.2, 14.8. IR (film, cm^{-1}) 3066, 2965, 1645, 1408, 1301, 1086. Anal. Calcd for $C_{17}H_{21}N_1O_1S_1$: C, 71.04; H, 7.36. Found: C, 70.98; H, 7.37.

3d. *N,N*-diisopropylbenzamide (0.26 g; 1.30 mmol) in Et_2O (9 mL) and THF (1 mL) was used following general procedure A (heating to 105 °C). The product was purified by flash chromatography (10:1

hexane/ethyl acetate) to give 0.29 g (70%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.60 (d, *J*= 8.1 Hz, 1 H), 7.32 (t, *J*= 7.7 Hz, 1 H), 7.12 (d, *J* = 7.1 Hz, 1 H), 3.70 (brs, 2 H), 2.88 (q, *J*= 7.5 Hz, 2 H), 2.80 (q, *J*= 7.5 Hz, 2 H), 1.38 (brs, 12 H), 1.32 (t, *J* = 7.5 Hz, 3 H), 1.21 (t, *J* = 7.5 Hz, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 169.4, 142.2, 141.0, 135.4, 133.0, 132.4, 123.7, 121.1, 119.8, 48.9, 21.7, 20.9, 19.6, 16.1, 14.6. IR (film, cm^{-1}) 3051, 2967, 1632, 1438, 1334, 737. Anal. Calcd for $C_{19}H_{27}N_1O_1S_1$: C, 71.88; H, 8.57. Found: C, 71.64; H, 8.69.

3e. *N*-methyl-*N*-*t*BOC-aniline (0.47 g; 2.27 mmol) in Et_2O (9 mL) and THF (1 mL) was used following general procedure A (heating to 105 °C). The product was purified by flash chromatography (10:1 hexane/ethyl acetate) to give 0.43 g (59%) of a brown oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.52 (d, *J*= 7.8 Hz, 1H), 7.32 (t, *J*= 7.8 Hz, 1H), 7.11 (brs, 1H), 3.29 (s, 3H), 2.89 (q, *J*= 7.2 Hz, 2H), 2.79 (q, *J*= 7.2 Hz, 2H), 1.52-1.26 (m, 12H), 1.21 (t, *J* = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 154.6, 141.7, 141.3, 138.0, 136.1, 132.9, 124.5, 121.8, 119.6, 80.0, 36.4, 28.2, 21.6, 19.7, 16.0, 14.6. IR (film, cm^{-1}) 3065, 2963, 1700, 1360, 1157. Anal. Calcd for $C_{18}H_{25}N_1O_2S_1$: C, 67.68; H, 7.89. Found: C, 67.92; H, 7.97.

9a. Anisole (0.22 g; 2.00 mmol) in Et_2O (10 mL) was used following general procedure B. The aryl ketone was purified by flash chromatography (10:1 hexane/ethyl acetate) to give 0.39 g (76%) of a colorless oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.53 (d, *J*= 7.8 Hz, 1 H), 7.48 (m, 1 H), 7.36 (t, *J*= 8.0 Hz, 1 H), 7.10 (dd, *J*= 2.1, 8.0 Hz, 1 H), 3.86 (s, 3 H), 3.54 (t, *J*= 6.8 Hz, 2 H), 2.96 (t, *J*= 7.4 Hz, 2 H), 1.82-1.73 (m, 4 H), 1.52-1.41 (m, 4 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.1, 159.8, 138.4, 129.5, 120.6, 119.3, 112.3, 55.4, 45.0, 38.5, 32.4, 28.5, 26.7, 24.1. IR

(film, cm^{-1}) 3070, 2941, 1680, 1582, 1465, 1264. Anal. Calcd for $C_{14}H_{19}O_2Cl$: C, 66.01; H, 7.52. Found: C, 65.78; H, 7.87.

9b. 4,4-dimethyl-2-phenyl-2-oxazoline (0.53 g; 3.00 mmol) in Et_2O (10 mL) was used following general procedure B. The aryl ketone was purified by flash chromatography (4:1 hexane/ethyl acetate) to give 0.32 g (66%) of a yellow oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.12 (s, 1 H), 8.06 (d, *J*= 7.8 Hz, 1 H), 7.70 (d, *J*= 7.7 Hz, 1 H), 7.45 (t, *J*= 7.7 Hz, 1 H), 6.58 (br s, 1 H), 4.12 (s, 2 H), 2.41-2.38 (m, 2 H), 2.29-2.24 (m, 2 H), 1.75-1.65 (m, 4 H), 1.39 (s, 6 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 234.8, 197.5, 161.4, 144.9, 139.1, 138.7, 131.6, 130.7, 128.6, 128.2, 79.2, 67.8, 28.4, 26.2, 23.8, 21.9, 21.6. IR (film, cm^{-1}) 3037, 2931, 1650, 1250, 711. Anal. Calcd for $C_{18}H_{21}N_1O_2$: C, 76.30; H, 7.47. Found: C, 76.16; H, 7.31.

9c. *N,N*-diisopropylbenzamide (0.41 g; 2.00 mmol) in Et_2O (18 mL) and THF (2 mL) was used following general procedure B (heating to 105 °C). The aryl ketone was purified by flash chromatography (4:1 hexane/ethyl acetate) to give 0.40 g (65%) of an orange oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.81-7.72 (m, 4 H), 7.62-7.46 (m, 5 H), 3.85-3.52 (m, 2 H), 1.59-1.08 (m, 12 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 196.1, 169.9, 139.0, 137.9, 137.1, 132.7, 130.2, 130.1, 129.5, 128.6, 128.4, 127.0, 50.7, 45.8, 20.7. IR (film, cm^{-1}) 2964, 1667, 1634, 1342, 1264, 719. Anal. Calcd for $C_{20}H_{23}N_1O_2$: C, 77.64, H, 7.49. Found: C, 77.45; H, 7.20.

9d. *N*-methyl-*N*-*t*BOC-aniline (0.42 g; 2.03 mmol) in Et_2O (18 mL) and THF (1 mL) was used following general procedure B (heating to 105 °C). The aryl ketone was purified by flash chromatography (4:1 then 2:1 hexane/ethyl acetate) to give 0.21 g (60%) of a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.38 (d, *J*= 7.7 Hz, 1 H), 7.28 (t, *J*= 7.8 Hz, 1 H), 7.20

(s, 1 H), 6.80 (dd, *J*= 2.1, 7.8 Hz, 1 H), 3.87 (br s, 1 H), 2.88 (s, 3 H), 2.68-2.63 (m, 1 H), 1.24-1.19 (m, 2 H), 1.04-0.98 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 149.4, 139.0, 134.3, 129.2, 117.3, 116.8, 110.9, 30.7, 17.2, 11.6. IR (film, cm^{-1}) 3395, 1660, 1602, 1584, 1417, 1207. Anal. Calcd for $C_{11}H_{13}N_1O_1$: C, 75.40, H, 7.48. Found: C, 75.46; H, 7.53.

12a.[12a] Anisole (0.32 g; 3.00 mmol) in Et_2O (10 mL) was used following general procedure C. The aryl ketone was purified by flash chromatography (20:1 then 4:1 hexane/ethyl acetate) to give 0.67 g (81%) of an orange oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34 (t, *J*= 7.7 Hz, 1 H), 6.90 (dd, *J*= 1.3, 7.6 Hz, 1 H), 6.86 (dd, *J*= 1.2, 8.2 Hz, 1 H), 3.90 (s, 3 H), 2.59 (s, 3 H).

12b. Anisole (1.19 g; 11.00 mmol) in Et_2O (37 mL) was used following general procedure C. The aryl ketone was purified by flash chromatography (10:1 then 4:1 hexane/ethyl acetate) to give 3.06 g (73%) of a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.34-7.19 (m, 6 H), 6.84 (dd, *J*= 1.7, 8.4 Hz, 1 H), 6.79 (dd, *J*= 1.7, 7.2 Hz, 1 H), 3.90 (s, 3 H), 2.88 (t, *J*= 7.3 Hz, 2 H), 2.72 (t, *J*= 7.3 Hz, 2 H), 2.07 (m, 2 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 205.9, 158.1, 148.2, 141.4, 129.6, 128.4, 128.3, 125.9, 119.1, 111.7, 83.0, 56.6, 41.8, 35.0, 25.3. IR (film, cm^{-1}) 3024, 2937, 1698, 1562, 1463, 1455, 1001. Anal. Calcd for $C_{17}H_{17}O_2I_1$: C, 53.70; H, 4.51. Found: C, 53.91; H, 4.27.

12c. Anisole (0.22 g; 2.00 mmol) in Et_2O (10 mL) was used following general procedure C. The aryl ketone was purified by flash chromatography (10:1 then 4:1 hexane/ethyl acetate) to give 0.34 g (52%) of a red oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.60 (s, 1 H), 7.37 (t, *J* = 8.0 Hz, 1 H), 6.94 (d, *J* = 8.3 Hz, 1 H), 6.87 (d, *J* = 8.6 Hz, 1 H), 6.44 (m, 1 H), 6.37 (s, 1 H), 3.93 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ IR (film, cm^{-}

$^{-1}$) 3253, 2937, 1776, 1563, 1463, 1264. Anal. Calcd for $C_{12}H_9O_3I_1$: C, 43.93; H, 2.76. Found: C, 43.68; H, 3.04.

12d. Methoxymethylphenol (0.38 g; 2.73 mmol) in Et_2O (10 mL) was used following general procedure C. The aryl ketone was purified by flash chromatography (10:1 then 4:1 hexane/ethyl acetate) to give 0.62 g (61%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 9.21 (br s, 1 H), 7.51 (dd, *J*= 1.1, 4.9 Hz, 1 H), 7.35 (t, *J*= 8.3 Hz, 1 H), 7.11 (dd, *J*= 1.3, 8.3 Hz, 1 H), 7.02-6.95 (m, 2 H), 5.29 (s, 2 H), 3.54 (s, 3 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 172.7, 156.2, 147.0, 143.0, 132.1, 130.5, 129.4, 127.6, 121.3, 114.5, 94.9, 87.6, 56.4. IR (film, cm^{-1}) 2924, 1598, 1427, 1153, 1012. Anal. Calcd for $C_{13}H_{11}O_3S_1I_1$: C, 41.73; H, 2.96. Found: C, 42.03; H, 3.24.

18a. Methoxymethylphenol (0.28 g; 2.00 mmol) in Et_2O (10 mL) was used following general procedure D (using *t*-BuLi). The aryl ketone was purified by flash chromatography (9:1 hexane/ethyl acetate) to give 0.25 g (80%) of a yellow oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (d, *J*= 1.7 Hz, 1 H), 7.55 (dd, *J*= 1.6, 8.2 Hz, 1 H), 7.48 (d, *J*= 8.1 Hz, 1 H), 5.26 (s, 2 H), 3.48 (s, 3 H), 2.59 (s, 3 H), 0.31 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 198.0, 162.0, 139.4, 135.1, 134.9, 121.4, 110.8, 93.7, 56.1, 26.7, -1.2. IR (film, cm^{-1}) 3064, 2954, 1686, 1384, 1245, 1008. Anal. Calcd for $C_{13}H_{20}O_3Si_1$: C, 61.87; H, 7.99. Found: C, 62.15; H, 8.02.

18b. Methoxymethylphenol (0.14 g; 1.00 mmol) in Et_2O (10 mL) was used following general procedure D (using *t*-BuLi). The aryl ketone was purified by flash chromatography (9:1 hexane/ethyl acetate) to give 0.25 g (80%) of an orange oil. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.59 (s, 1 H), 7.55, (dd, *J*= 1.3, 7.3 Hz, 1 H), 7.47 (d, *J*= 7.4 Hz, 1 H), 5.82 (m, 1 H), 5.26 (s, 2 H), 5.06-5.02 (m, 2 H), 3.48 (s, 3H), 2.95 (t, *J*= 7.3 Hz, 2 H), 2.15

(q, *J*= 7.7 Hz, 2 H), 1.84 (quintet, *J*= 7.2 Hz, 2 H), 0.31 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.2, 162.1, 139.4, 138.1, 135.1, 134.7, 121.0, 115.2, 110.8, 93.8, 56.2, 37.9, 33.2, 23.4, -1.1. IR (film, cm^{-1}) 3069, 2955, 1686, 1386, 1156, 840. Anal. Calcd for $C_{17}H_{26}O_3Si$: C, 66.62, H, 8.55. Found: C, 66.70; H, 8.63.

18c. Methoxymethylphenol (0.10 g; 0.75 mmol) in Et_2O (8 mL) was used following general procedure D (using *t*-BuLi). The aryl ketone was purified by flash chromatography (10:1 hexane/ethyl acetate) to give 0.18 g (65%) of an orange oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 7.58 (s, 1 H), 7.55, (d, *J*= 7.3 Hz, 1 H), 7.4 (d, *J*= 7.3 Hz, 1 H), 5.25 (s, 2 H), 3.94 (s, 4 H), 3.48 (s, 3 H), 2.97 (t, *J*= 7.1 Hz, 2 H), 1.84-1.72 (m, 4 H), 1.34 (s, 3 H), 0.30 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 200.0, 162.1, 139.4, 135.1, 134.7, 121.0, 110.8, 109.9, 93.8, 64.6, 56.2, 38.6, 38.4, 23.8, 18.9, -1.1. IR (film, cm^{-1}) 2954, 1686, 1384, 1245, 843. Anal. Calcd for $C_{19}H_{30}O_5Si$: C, 62.26; H, 8.25. Found: C, 62.32; H, 8.15.

18d. 4,4-dimethyl-2-phenyl-2-oxazoline (0.35 g; 2.00 mmol) in Et_2O (10 mL) was used following general procedure D. The aryl ketone was purified by flash chromatography (4:1 then 2:1 hexane/ethyl acetate) to give 0.49 g (70%) of a colorless oil. ^1H NMR ($CDCl_3$, 300 MHz) δ 8.99 (d, *J*= 2.0 Hz, 1 H), 8.81 (dd, *J*= 1.8, 4.9 Hz, 1 H), 8.24 (s, 1 H), 8.11 (m, 1 H), 7.79 (s, 2 H), 7.61 (dd, *J*= 4.6, 7.4 Hz, 1 H), 4.10 (s, 2 H), 1.38 (s, 6 H), 0.36 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 194.4, 162.4, 153.0, 151.0, 146.8, 137.2, 136.9, 135.6, 134.5, 132.9, 130.4, 130.2, 123.4, 79.3, 68.2, 28.5, 0.6. IR (film, cm^{-1}) 2964, 1660, 1584, 1262, 842, 739. Anal. Calcd for $C_{20}H_{24}N_2O_2Si$: C, 68.15, H, 6.86. Found: C, 68.05; H, 7.01.

18e. 3-methoxy-*N,N*-diisopropylbenzamide (0.71 g; 3.00 mmol) in Et_2O (18 mL) and THF (2 mL) was used following general procedure D

(heating to 105 °C). The aryl ketone was purified by flash chromatography (4:1 hexane/ethyl acetate) to give 0.54 g (52%) of a white powder. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.34 (s, 1 H), 7.22 (s, 1 H), 3.87 (s, 3 H), 3.70 (m, 1 H), 3.50 (m, 1 H), 2.57 (s, 3 H), 1.55 (m, 6 H), 1.14 (m, 6 H), 0.31 (s, 9 H). ^{13}C NMR ($CDCl_3$, 75 MHz) δ 197.4, 170.9, 165.4, 146.3, 138.8, 131.4, 118.7, 107.6, 55.3, 50.9, 45.8, 26.6, 20.6, 20.4, 20.2, 20.1, 0.6. IR (film, cm^{-1}) 2968, 1686, 1630, 1457, 1342, 850. Anal. Calcd for $C_{19}H_{31}N_1O_3Si_1$: C, 65.29; H, 8.94. Found: C, 65.31; H, 9.23.

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