ABSTRACT

Title of Dissertation: DEVELOPMENT OF ARYL SILOXANE CROSS-
                                COUPLING TECHNOLOGY AND ITS
                                APPLICATION TO THE SYNTHESIS OF
                                COLCHICINE AND ALLOCOLCHICINE
                                DERIVATIVES

William Michael Seganish, Doctor of Philosophy, 2005

Dissertation directed by: Professor Philip DeShong
                                   Department of Chemistry and Biochemistry

One of the most versatile methods for the formation of aryl-aryl bonds is the palladium-catalyzed cross-coupling reaction. Previous work in the DeShong laboratory has demonstrated the utility of aryl siloxanes for the palladium-catalyzed cross-coupling of aryl iodides, bromides, and chlorides, as well as new synthetic methods for the formation of aryl siloxanes. The work reported herein details (1) the synthesis of aryl siloxanes using *ortho*-metallation techniques (2) the coupling of aryl bis(catechol) silicates with aryl triflates, and (3) the application of aryl siloxane coupling technology to the synthesis of colchicine and allocolchicine derivatives.

The synthesis of aryl siloxanes had previously been performed using either metal-halogen exchange, or transition metal-catalyzed silylation. These techniques

necessitate the use of an aryl halide as the starting material. The application of *ortho*-metallation conditions avoids this requirement and allows for the synthesis of siloxanes directly from the unfunctionalized arene. Using this approach, *ortho*-ether and carbamate siloxanes were prepared in good yields, however, *o*-benzamide siloxanes could not be prepared using this method.

The coupling of aryl triflates with aryl siloxanes had previously proven problematic due to competitive hydrolysis of the triflate. The use of aryl bis(catechol) silicates as siloxane surrogates facilitated the coupling of aryl triflates and iodides bearing a range of functional groups in excellent yield. Additionally, aryl bromides could be successfully coupled by switching from conventional heating to microwave irradiation.

The use of aryl siloxanes in the synthesis of the natural products colchicine and allocolchine was explored. It was found that the carbocyclic framework of colchicine could be constructed using an aryl siloxane coupling reaction; however, the reaction required the use of a stoichiometric amount of the palladium "catalyst." This amount of catalyst was required because of the competition between a slow oxidative addition step, and a fast protodesilylation pathway that lead to the decomposition of the siloxane. The synthesis of the allocolchicine carbocyclic framework was successful utilizing a siloxane coupling reaction, and a phenanthrol ring expansion protocol as the key steps.

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AND ITS APPLICATION TO THE SYTHESIS OF COLCHICINE AND
ALLOCOLCHICINE DERIVATIVES

By

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DEDICATION

To my parents, Mike and Nancy,

Sister Kate,

Wife Jenny,

And baby David

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My sincerest gratitude goes to Phil, my advisor and mentor. It was he who made me the chemist I am today. Thanks for prodding me in the right direction and keeping me focused, especially toward the end.

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Last, and certainly not least, I wish to thank my wife Jenny for putting up with me through these years of graduate school. Her constant support and encouragement made my difficult tasks and choices much easier to bear.

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LIST OF ABBREVIATIONS

Ac	acetyl
aq.	aqueous
ar	aryl
Bn	benzyl
BOC	*t*-butoxycarbonyl
Bu	butyl
calcd	calculated
conc	concentrated
cy	cyclohexyl
dba	dibenzylideneacetone
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
decomp	decomposition
DMF	*N,N*-dimethylformamide
DMSO	dimethyl sulfoxide
ee	enantiomeric excess
EI	electron ionization
equiv	equivalent(s)
Et	ethyl
Et$_2$O	diethyl ether
FAB	fast atom bombardment
h	hour(s)
Hz	Hertz

IPA	isopropyl alcohol
i-Pr	isopropyl
IR	infrared
J	coupling constant
L	ligand
m	meta
M^+	molecular ion
m/z	mass-to-charge ratio
Me	methyl
MeCN	acetonitrile
MEM	2-methoxyethoxymethyl
MHz	megahertz
min	minute
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
NMR	nuclear magnetic resonance
o	ortho
OAc	acetate
p	para
Ph	phenyl
Piv	pivaloyl
Pr	propyl

py	pyridine
R_f	retardation factor
rt	room temperature
t-Bu	tertiary butyl
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldifluorosilicate
Tf	trifluoromethanesulfonyl
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TLC	thin layer chromatography
TMEDA	*N,N,N′,N′*-tetramethylethylene diamine
TMS	trimethylsilyl
tol	tolyl

Chapter 1 – The Development and Use of Palladium(0)-Catalyzed Coupling Reactions in the Synthesis of Biaryl Natural Products

INTRODUCTION

The biaryl moiety is the central structural element of a wide range of structurally and biologically interesting, as well as pharmacologically promising natural products.[1] These biaryls range in complexity from the simple diterpenoid biaryl **I-1**, to the multifaceted vancomycin (**I-2**).
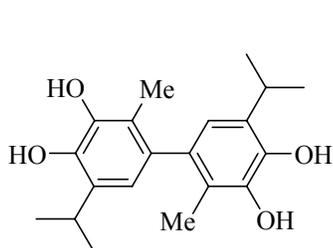
I-1
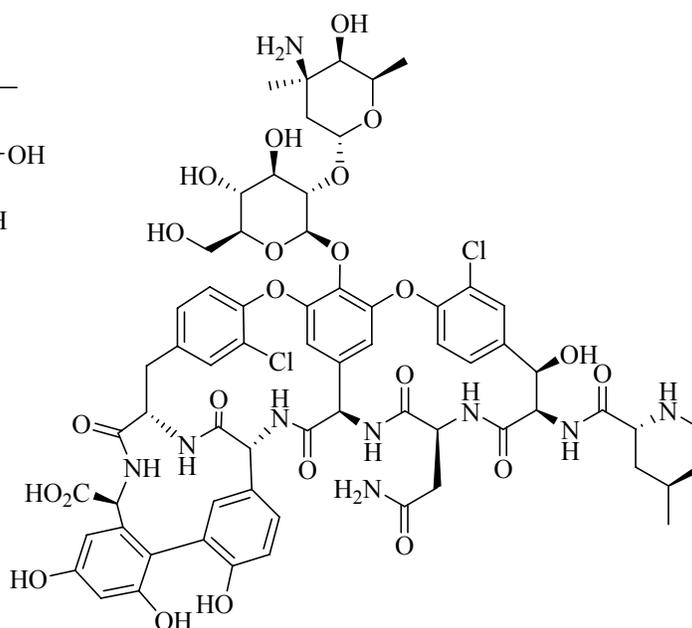
vancomycin (**I-2**)

The development of synthetic techniques and methodology for the formation of biaryls has seen many great advances and inventions since the discovery of copper-

promoted reductive coupling of aromatic halides by Ullmann in 1901,[2] and the subject

has been comprehensively reviewed.[3,4] The most useful and widely employed techniques

for the synthesis of biaryls involves the palladium-catalyzed coupling of an aryl halide or

triflate with an organometal compound (e. g. B, Sn, Zn, Mg, Si). These techniques have

facilitated the synthesis of a vast array of biaryl natural products, due in part to their

tolerance for functional groups, mild reaction conditions, and high yields.[5] Of these

techniques, the two most commonly used are the Suzuki (organoboron) and the Stille

(organotin) coupling reactions. Coupling reactions involving organosilanes has become

more popular in recent years due to the development of new and more versatile reagents

and milder reaction conditions.

Palladium-catalyzed cross-coupling reactions to form biaryls follow the general

catalytic cycle presented in Scheme 1. The active catalyst is Pd (0) **I-3**, which undergoes

oxidative addition into the bond of the aryl halide (bromide shown). The resulting aryl

Pd (II) complex **I-4** participates in transmetallation with an aryl metalloid compound (M

= B, Sn, Zn, Mg, Si, etc.) to form the biaryl Pd (II) adduct **I-5**. Reductive elimination

provides the biaryl, while at the same time regenerating the Pd (0) catalyst. **I-3**.

Scheme 1

Ar—Ar   Ar—Br

Reductive Elimination PdL_n **Oxidative Addition**

I-3

2L   2L

Ar   Ar
| |
Ar—Pd—L   L—Pd—Br
| |
L   L

I-5   **I-4**

MBr   Ar—M

Transmetallation
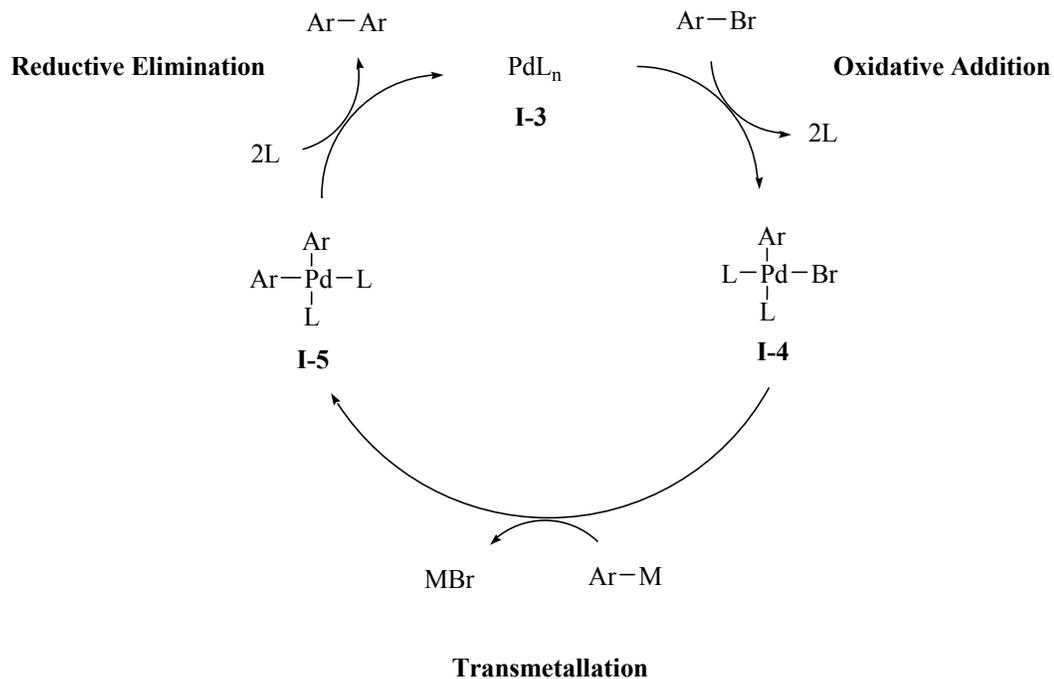
STILLE COUPLING

The coupling of an organostannane reagent **I-6** with aryl halides and triflates is known as the Stille reaction (Scheme 2).[6-10] Even though the reaction employs toxic trialkyltin reagents, the ability to conduct this reaction under mild conditions with very complicated substrates has led to its use in many biaryl natural product total syntheses. The mild reaction conditions for the Stille reaction are exemplified by Danishefsky's synthesis of himastatin (**I-7**).[11,12]

Scheme 2

I-6
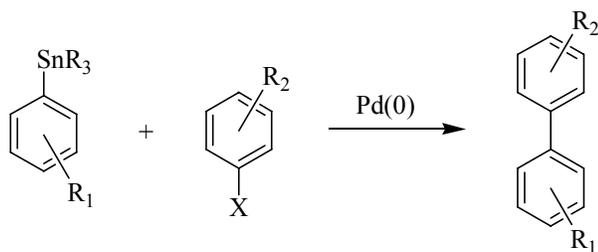
X = I, Br, Cl, OTf
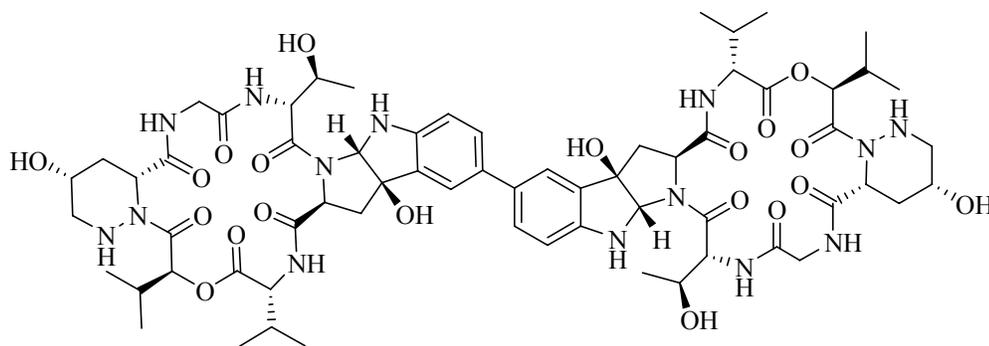
himastatin **I-7**

Himastatin (**I-7**) is an antitumor antibiotic that displays activity against leukemia and melanoma cells, in addition to antibiotic activity toward Gram-positive bacteria.[13,14] Himastatin is a structurally complex $(C_{72}H_{104}N_{14}O_{20})$ metabolite whose central core consists of a biaryl which was assembled by Danishefsky using a Stille coupling reaction (Scheme 3). Coupling of aryl stannane **I-8** with aryl iodide **I-9** provided the biaryl **I-10** in excellent yield. It is important to note that the reaction conditions were compatible with many functional groups present, and preserved the highly sensitive pyrroloindoline core present in both of the coupling partners. This allowed for a more convergent and ultimately shorter synthetic design for himastatin.[11]

4
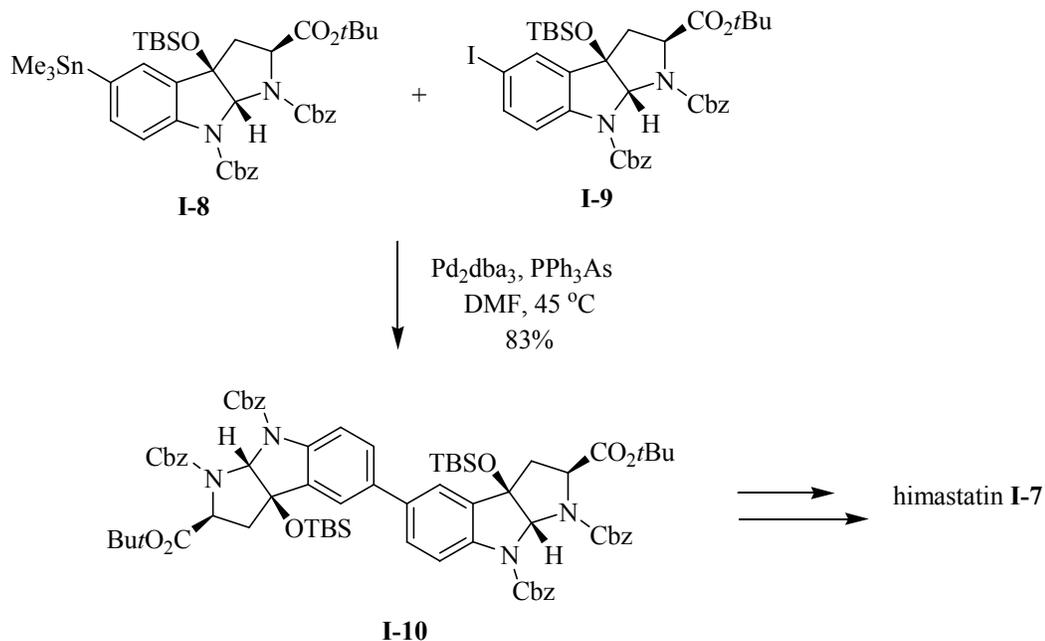
Scheme 3

SUZUKI COUPLING

The Suzuki reaction is by far the most popular and versatile coupling reaction for the formation of unsymmetrical biaryls (Scheme 4).[15-19] Boronic acids (**I-11**) are useful reagents because they are generally thermally stable and are inert to water and oxygen, and are relatively non-toxic. However, purification of these reagents can be problematical due to their incompatibility with silica gel chromatography, and decomposition upon recrystallization.[20] Despite this potential drawback, Suzuki couplings have been utilized in the synthesis of many complex natural products.

Scheme 4

B(OH)$_2$ ... R$_2$ ... Pd(0) ... R$_2$

I-11

X = I, Br, Cl, OTf
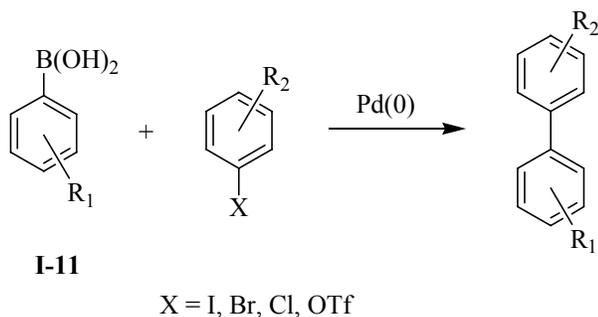
Boger and coworkers utilized a double Suzuki reaction as a key step in their synthesis of ningalin D (**I-12**).[21] This unique compound consists of a biphenylene quinone methide superimposed on an oxidized pentasubstituted pyrrole core. Ningalin displayed promising activity against multidrug resistant cancer cell lines when used in conjunction with an existing antitumor therapeutic (taxol, vinblastine).[21] This activity is due to the ability of nigalin to suppress the P-gy drug efflux pump, which is responsible for the majority of drug resistant tumors.[22,23]
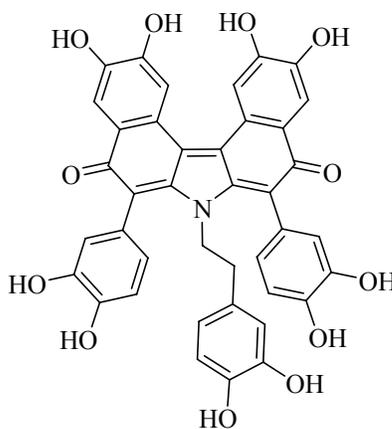
ningalin D (**I-12**)

In Boger's synthesis of ningalin D, reaction of symmetrical alkyne **I-13** with tetazine **I-14** in a [4+2] cycloaddition provided the symmetrical diazine **I-15** in excellent

yield (Scheme 5).[21] Conversion of diazine **I-15** proceeded uneventfully through a series

of steps to provide bistriflate **I-16**. This triflate was treated with a palladium(0) catalyst

in the presence of boronic acid **I-17** to carry out the key double Suzuki coupling reaction.

Scheme 5
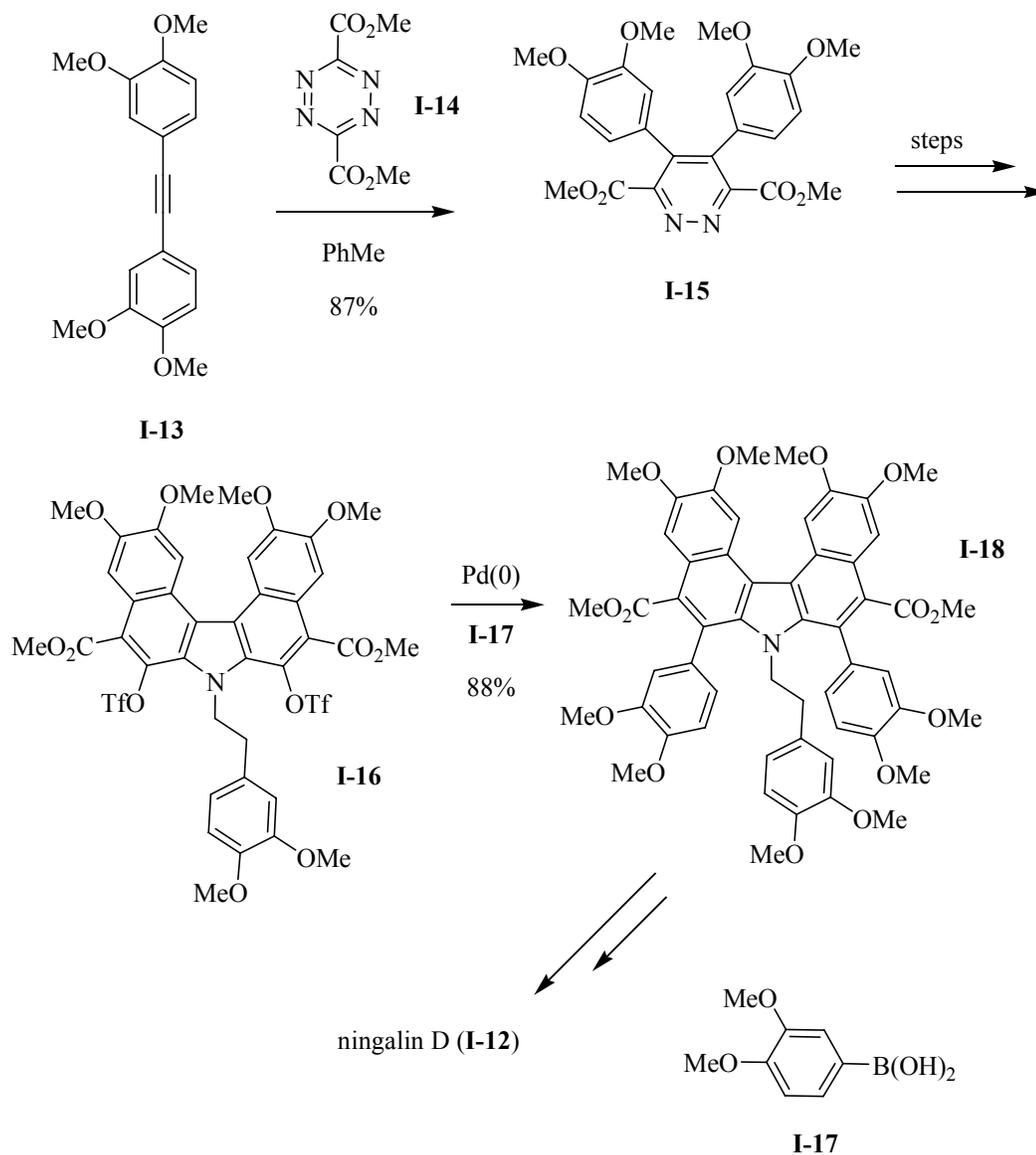
ningalin D (**I-12**)

The coupling reaction proceeded in excellent yield to give the coupled product **I-18**. Oxidation of the esters to the quinone methide moiety, followed by global demethylation provided synthetic ningalin D (**I-12**).

Another recent example of the Suzuki reaction in natural product synthesis involves the synthesis of dragmacidin F (**I-19**) by Stoltz and coworkers.[24-26] Instead of a phenyl biaryl bond, the synthesis of this compound involves the Suzuki coupling of heteroaryl substrates. These substrates have traditionally proven difficult to cross-couple by other methods.[27,28] Dragmacidin, a structurally complex indole alkaloid containing a pyrazinone core, possesses potent antiviral activity against herpes simplex virus, and HIV.[29]
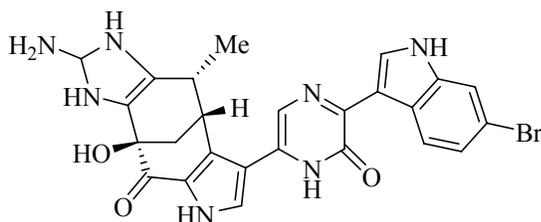
dragmacidin F (**I-19**)

Stolz's synthesis revolved around a series of halogen selective Suzuki reactions. The first coupling involved the coupling of pyrazine **I-20** with indole boronic acid **I-21** (Scheme 6).[26] This reaction entailed the selective coupling of an iodide in preference to a bromide. After considerable experimentation, conditions were developed to allow for the reaction to proceed selectively in good yield. At room temperature, the reaction of the bromide with the catalyst was significantly slower than the iodide. If the temperature is raised, however, the reaction became less selective, and a mixture of bromide and iodide coupled products was obtained.[26]

Scheme 6
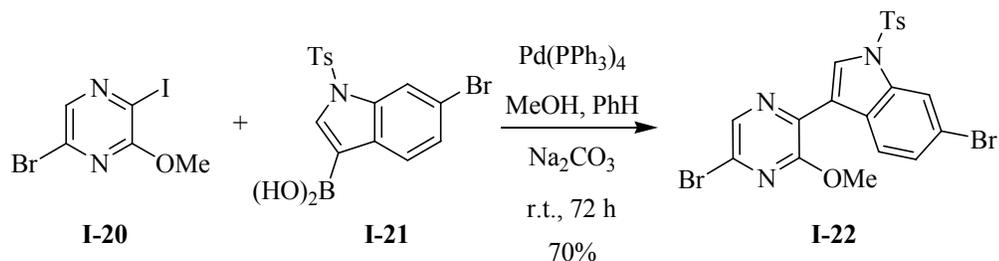
Having attained coupling product **I-22**, attention turned to the coupling of the bromide (Scheme 7). A pinacol boronate ester **I-23** was used in place of a boronic acid coupling partner. In this case, reaction using the corresponding boronic acid gave poor selectivity for the pyrazole bromide, versus the indole bromide.[24] The coupling reaction proceeded in good yield with excellent selectivity for the pyrazine bromide to produce the indolopyrazine **I-24**. This selectivity was obtained again through careful control of the reaction temperature. Heating at 50 ˚C for 65 h led to coupling of the pyrazine bromide. Attempts to shorten the reaction time by elevating the temperature led to competitive coupling of the indole bromide. The selective, sequential Suzuki couplings of bromo-iodo-pyrazole **I-20** and dibromo-pyrazoleindole **I-24** followed for the facile construction of the complex heteroaromatic skeleton of dragmacidin F, which eventually was converted to dragmacidin F.

Scheme 7

I-23

+

I-22

Pd(PPh$_3$)$_4$
MeOH, PhH
Na$_2$CO$_3$
50 °C., 65 h
77%

I-24

dragmacidin F (**I-19**)
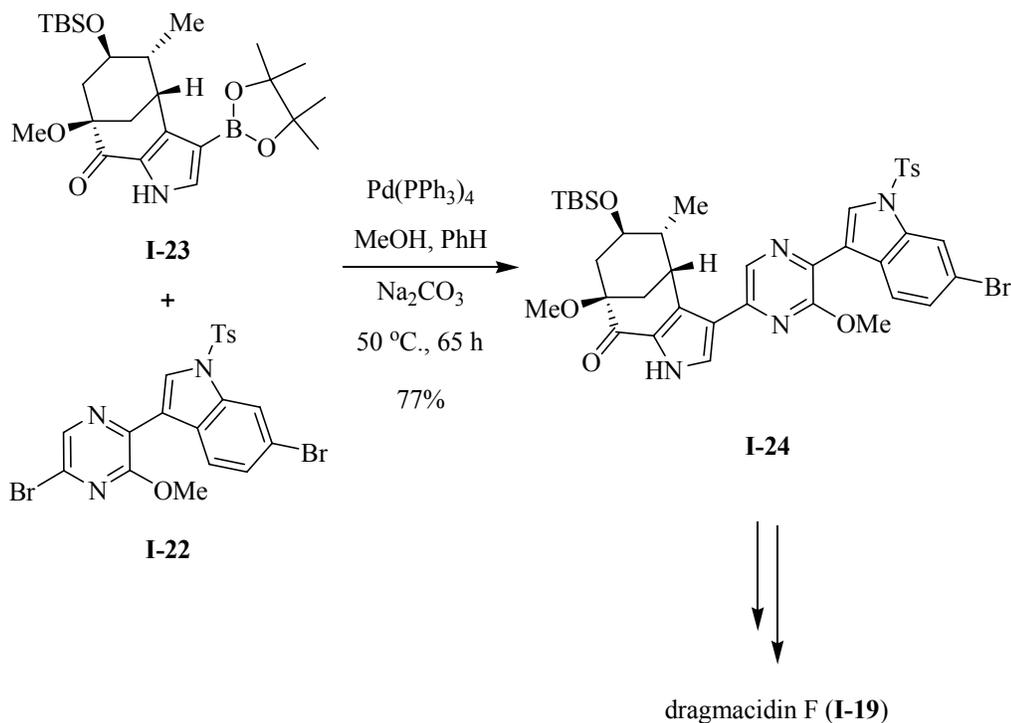
HIYAMA COUPLING

The silicon-based alternative to the Suzuki and Stille coupling reactions has been termed Hiyama coupling.[30-36] The use of silicon has several distinct advantages over other organometal reagents (boron, tin): silicon has a low molecular weight, silicon-based reagents are easily prepared and are stable toward many types of reaction conditions. The silicon reagents are readily activated for cross-coupling, and the by-products are harmless.[32] Hiyama demonstrated that aryl(fluoro)silanes **I-25** cross-couple with aryl iodides and bromides in moderate to good yields (Scheme 8).[35] These reactions required the use of a fluoride activator, such as KF. Fluoride is used because of the unusually strong bond that is formed between fluoride and silicon.[37-39] Several sources of fluoride ion can be employed in silane coupling reactions including, alkali fluoride salts,

tris(diethylamino)sulfonium trimethyldifluorosilcate (TASF), tetramethylammonium fluoride (TMAF), tetrabutyl ammonium fluoride (TBAF), and tetrabutylammonium(triphenylsilyl)difluorosilicate (TBAT).[40] TBAT itself has the ability to efficiently cross couple. This fact was uncovered when it was found that TBAT was able to phenylate allylic benzoates.[41]

Scheme 8
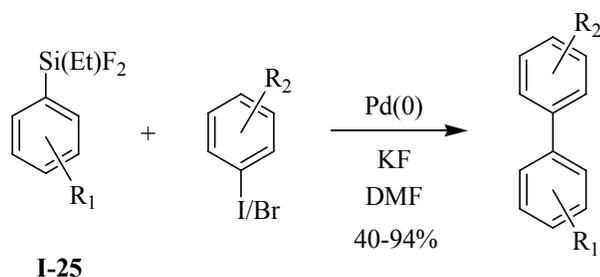
Denmark and Ober reported the coupling of organosilanols **I-26** with aryl iodides (Scheme 9).[42] This protocol necessitated the use of an expensive and toxic catalyst-ligand system ([allylPdCl]$_2$, Ph$_3$As). In addition, a controlled amount of water was required in order for the reaction to be reproducible. For example, the use of anhydrous Cs$_2$CO$_3$ failed to provide coupled product, and commercially available hydrated Cs$_2$CO$_3$ also failed to provide product. However, when 3 equiv of water was added to anhydrous Cs$_2$CO$_3$ the reaction reproducibly provided coupled product.[42]

Scheme 9
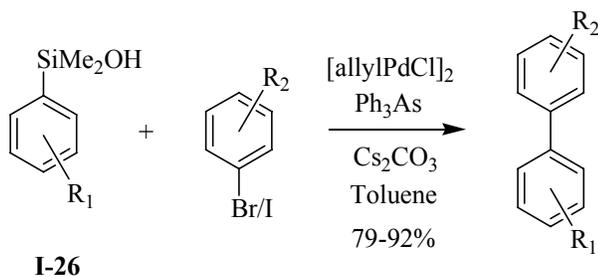
Tamao and Ito pioneered the use of a different type of silane.[43] Instead of using moisture sensitive chloro- or fluoro-silanes that were employed by Hiyama, siloxanes were developed (Scheme 10). The coupling of alkenylalkoxysilanes proceeded in good yields with mono- and dialkoxysilanes (**I-27**, and **I-28**, respectively), however, yields were moderate when trialkoysilanes (**I-29**) were employed.

Scheme 10

R = SiMe$_2$OEt **I-27**   95%

R = SiMe(OEt)$_2$ **I-28**   96%

R = Si(OEt)$_3$ **I-29**   54%
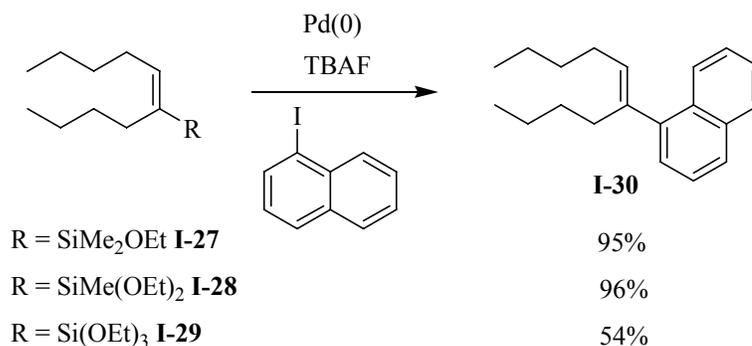
In 1997 Shibata reported the coupling of aryl siloxanes **I-31** with aryl bromides (Scheme 11).[44] In these reactions, tetrabutylammonium fluoride (TBAF) was used as the fluoride activator. The reaction gave high yields for electron-deficient aryl bromides, however, yields were moderate (60%) for electron-rich aryl bromides.[44]

Scheme 11

I-31
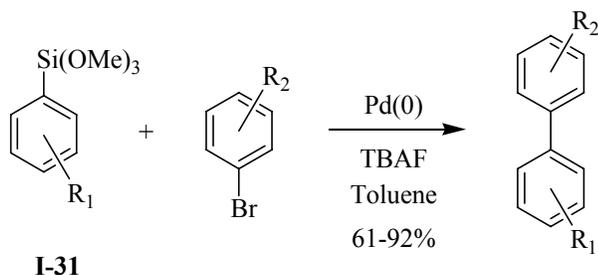
Work in the DeShong laboratory has focused on the development of a generalized set of reaction conditions for the efficient cross-coupling of aryl siloxanes with aryl iodides,[45] bromides,[45-49] chlorides,[46] and triflates.[50,51] Recently, Fu and coworkers developed conditions for the room temperature couplings of aryl siloxanes with alkyl bromides.[52,53]

Mowery and coworkers demonstrated that aryl siloxanes **I-31** readily couple in high yields with aryl iodides, bromides and chlorides (Scheme 12).[45-47] Later, this methodology was extended to include aryl triflates using silatranes **I-32** and bis(catechol) silicates **I-33** as siloxane surrogates.[50,51] The preparation and cross-coupling of silicates **I-33** is presented in Chapter 3. These methodologies allow for the coupling of virtually any aryl halide or triflate with an aryl siloxane to produce an unsymmetrical biaryl.

Scheme 12

I-31

X = I, Br, Cl
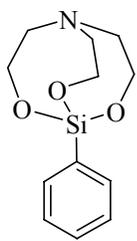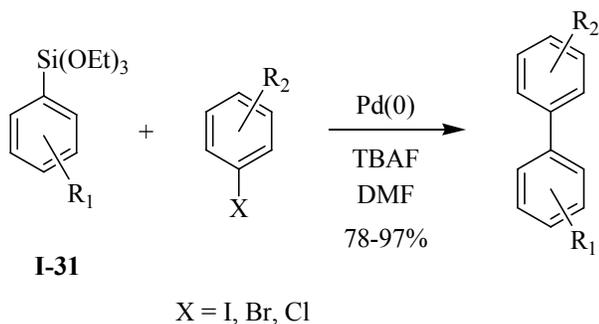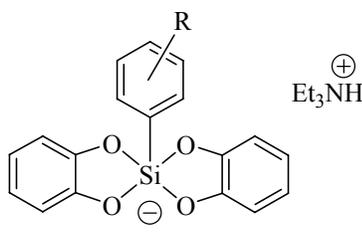
I-32   **I-33**

Nolan and Lee have modified the aryl siloxane coupling methodology to include the use of palladium-imidazolium catalyst systems.[54] Imidazolium ligands such as **I-34**, are phosphine ligand alternatives. Using ligand **I-34**, Nolan found that aryl bromides could be coupled in excellent yields with phenyl trimethoxysilane, but only electron-deficient aryl chlorides could be coupled using this catalyst system. The use of ligand **I-34** did, however, allow Nolan to reduce the catalyst loading from 5-10% reported by Mowery and DeShong,[45,46] to 3 mol%.[54]
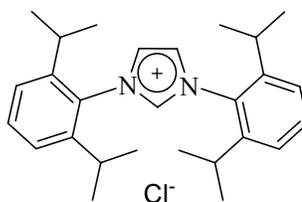
I-34

Recently, Wolf and Lerebours reported the coupling of aryl siloxanes under aqueous conditions using a palladium-phosphinous acid catalyst **I-35**.[55] Using this catalyst, efficient coupling of aryl and heteroaryl halides was achieved. More importantly, the authors found that the use of an expensive fluoride activating agent (such as TBAF) could be avoided, and NaOH could be used as a substitute. Unfortunately, the coupling reactions required heating to high temperatures (140 ˚C) in a sealed tube for 24 h, limiting the functional group tolerance of the reaction.[55]

$$L\overset{}{\underset{L}{>}}Pd-P\overset{O^{\ominus}}{\underset{tBu}{<}}tBu$$
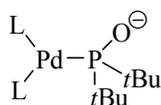
I-35

Several complementary methods are available for the synthesis of aryl siloxanes. The most common method utilizes aryl bromide precursors. Aryl bromides are metallated (Mg or Li) to form the corresponding organomagnesium (Grignard) or lithium reagent, and the aryl metal derivative is added to tetraethylorthosilicate (Scheme 13).[56] This protocol enjoys high yields, with the siloxane products readily purified *via* distillation or chromatography. A closely related synthesis of aryl siloxanes involves directed *ortho*-metallation and this topic is addressed in Chapter 2.[57] This technique allows for the synthesis of *ortho*-substituted aryl siloxanes, without the need for an aryl halide precursor.

Scheme 13

55-88%
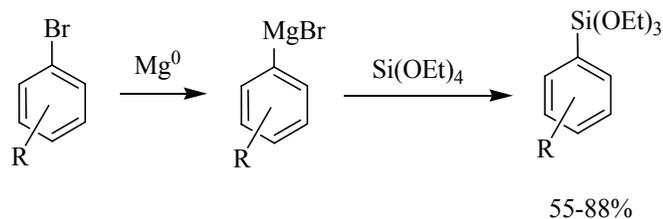
Another approach to aryl siloxanes involves the use of metal-catalyzed hydrosilylation (Scheme 14). Masuda and coworkers initially developed a Pd(0) catalyst system for this silylation reaction,[58] which was later improved by Manoso and DeShong.[59] Masuda then developed a more powerful Rh(I) catalyst.[60] These metal-catalyzed silylation reactions are tolerant of functional groups (e. g. esters) which would not be suitable for the Grignard or organolithium conditions.

Scheme 14
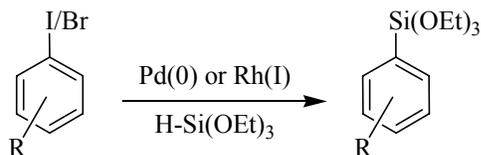
The use of aryl silanes in biaryl natural product synthesis has been limited. McElroy and DeShong have developed conditions for the coupling of bromopyridines **I-36** with aryl siloxanes to provide 4-arylpyridines **I-37** (Scheme 15).[48] It is expected that this coupling reaction can be used in the construction of the biaryl bonds present in streptonigrin (**I-38**) and lavendamycin (**I-39**).

Scheme 15

I-36 → I-37

Pd(0), Ar-Si(OEt)₃

streptonigrin (**I-38**)
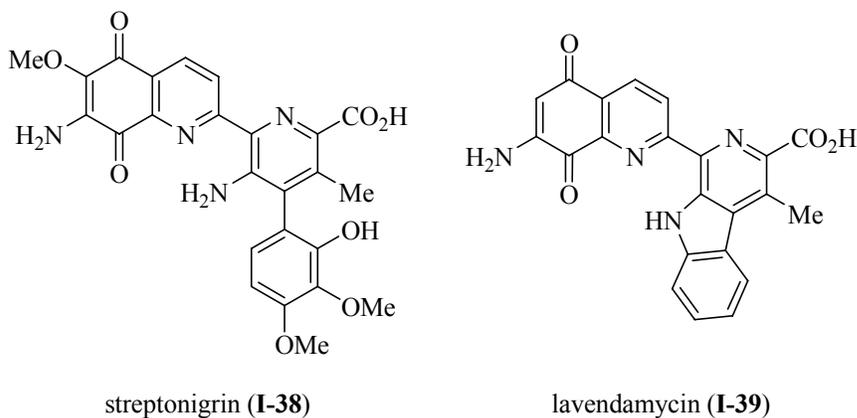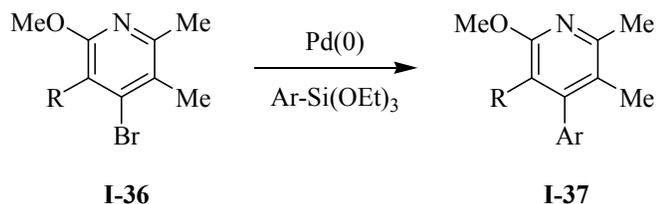
lavendamycin (**I-39**)

In addition to streptonigrin and lavendamycin, the use of aryl siloxanes is currently being studied for the synthesis of colchicine (**I-40**) and allocolchicine (**I-41**) and is discussed in Chapter 4. The synthesis of these two natural products, when combined with the synthesis of streptonigrin and lavendamycin, will provide a suitable testing ground for the application of aryl siloxanes technology to biaryl natural product synthesis.

(-)-(aR, 7S)-colchicine (**I-40**)   (-)-(aR, 7S)-allocolchicine (**I-41**)
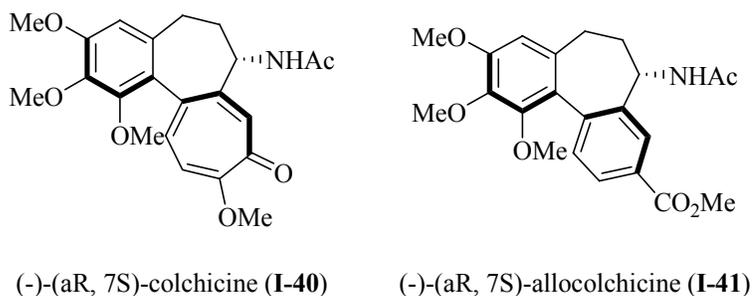
CONCLUSIONS

The formation of unsymmetrical biaryls using Stille and Suzuki cross-coupling reactions has received great attention. These methodologies have been applied to the synthesis of structurally diverse and highly functionalized natural products. The development of aryl siloxane coupling methodology is in its relative infancy. While aryl siloxanes have been proven to cross-couple efficiently with simple substrates, their application to complex natural product synthesis has yet to be completed.

Chapter 2 - Application of Directed *Ortho*-Metallation Toward the Synthesis of Aryl Siloxanes

INTRODUCTION

Many methods have been developed for the addition of functional groups onto the basic aromatic ring. These techniques include electrophilic and nucleophilic substitution, sigmatropic rearrangements, and metal-catalyzed substitutions. These methods often suffer from poor regioselectivity or harsh reaction conditions. The concomitant discovery of directed *ortho*-metallation by Gilman and Wittig in 1939 opened the door to a new range of regiospecific chemical transformations that would allow the selected addition of chemical groups onto aromatic rings.[61]

Directed *ortho*-metallation (DOM) (Scheme 1) involves the use of a directing group that is able to chelate and direct an organolithium reagent to a position that is *ortho* to the directing group. Deprotonation then occurs creating the aryl lithium salt which can be quenched with an electrophile to give the *ortho*-substituted product.

Scheme 1

ODG = *ortho*-directing group
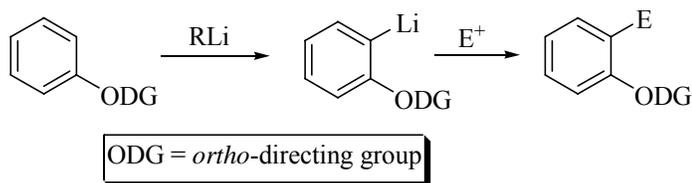
A technique that is closely related to *ortho*-metallation is lithium-halogen exchange.[62-65] This method involves the metallation of an aryl halide with lithium

creating an organolithium reagent. This lithiated species is then able to attack electrophiles in a manner identical to the lithium salts formed from *ortho*-metallation. Lithium-halogen exchange is limited by the obvious fact that a halogen must be present in order to carry out the reaction. The proper regiospecific placement of a halogen on an aromatic system is not always a trivial task, especially in the presence of other functionalities. It usually involves multiple steps with a mixture of regioisomers being obtained. In addition, if there are multiple halogens on the aryl system, then all will be lithiated, which would lead to a large combination of products upon the addition of the electrophile. Thus, the use of DOM groups, which are ideally a part of the desired product, would prove advantageous over the use of lithium-halogen exchange in complicated systems.

Along a similar vein as the lithium-halogen exchange is the use of magnesium in place of an organolithium. These reactions are known as either the Barbier or Grignard reactions.[66-69] The Barbier reaction differs from the more common Grignard reaction in the manner of addition of the reagents.[70] In the Barbier reaction, all the reagents are added simultaneously, while in the Grignard reaction, the reagents are added sequentially.[66,67] These reactions benefit from their simplicity and the facile manner in which they are conducted. However, they have the same drawback as the lithium-halogen exchange reaction; a halogen must be present to form the anionic reagent.[68,69,71] *Ortho*-metallation eliminates the need for a pre-existing aryl halide and allows for the generation of the aryl lithium reagent directly.

Mechanistic Studies

Ortho-metallation is influenced predominately by two factors: the nature of the directing group, and media effects. It is known that the reactivity of the organolithium compound can be enhanced by using polar, coordinating solvents which are able to break up lithium aggregates.[72-74] However, Slocum has recently shown that a solution of THF/hexanes is generally superior in DOM reactions than a solvent system of pure THF, which is currently considered the ideal solvent for DOM reactions.[75] It was suggested that the most active form of the lithium is that of the dimer, as the fastest rates of metallation are observed in a solvent mixture that favors dimer formation over the tetrameric or monomeric lithium complexes (e.g. THF/hexane). Other studies by Collum and coworkers have supported the hypothesis that the dimeric form of the lithium aggregate is the most active in DOM.[74] The key importance of the extent of lithium aggregation has been observed using di-substituted *ortho*-directing groups.[76] DOM reactions do not readily occur in non-coordinating hydrocarbon solvents. However, using 1,2 dimethoxybenzene (DMB) in hexane allows for efficient *ortho*-metallation to occur, presumably through a substrate promoted metallation pathway where the substrate (DMB) is capable of dispersing the lithium aggregates.[76]

In addition to the use of polar solvents, the addition of coordinating compounds to DOM reactions has been found to greatly enhance the extent of metalation.[72,77] One of the most commonly used coordination compounds is tetramethylethylenediamine (TMEDA). Hauser has demonstrated that not only is the rate of the reaction increased in the presence of TMEDA, but the yields of the metallation reactions are enhanced as well.[77] In their study, *N,N*-dimethyl-*o*-toluidine was *ortho*-lithiated (D$_2$O quench) in the

presence of TMEDA after only 4 hours (90% yield), compared to the reaction without TMEDA, which required 30 hours and only proceeded in 50% yield. Recent *ab initio* studies by Saa and coworkers have shown that the role of TMEDA is to prevent over-coordination of the lithium to the DOM group.[78]

Schleyer has indicated that the presence of the DOM group may in fact be more important in the transition state, rather than in the initial coordination and direction of the organolithium.[72,79-82] Without TMEDA present, lithium tends to form large aggregates around the directing group and thus slow or hinder the deprotonation. However, the coordination of TMEDA to the lithium frees it from these complexes and allows the brief coordination of the lithium to the DOM group only transiently during the deprotonation transition state.[72,78] Thus, Schleyer concluded that it is the transient coordination, and not the initial complexation of the organolithium reagent, that is responsible for the accelerating and *ortho*-directing effect of substituents.

In order for the DOM group to efficiently direct metallation, it must have a heteroatom available for chelation. Beak and coworkers discovered that relatively small changes in the directing group orientation have a dramatic effect on the rate of metallation.[83] They studied the effect of altering the position of an amide directing group (Scheme 2). By merely adjusting the distance by a very small amount (0.3Å) between the proton and the directing group, large changes in the rate of deprotonation were observed.[83] Beak was able to explore the effect of proximity in the synthesis of bicyclic carbamates where it was observed that an increase in the efficiency of metallation when the directing group was held in close proximity to the site of deprotonation.[84]

Scheme 2. Influence of Directing Group Orientation on the Rate of Metallation

Relative Rate of Metalation   1   2.8   24
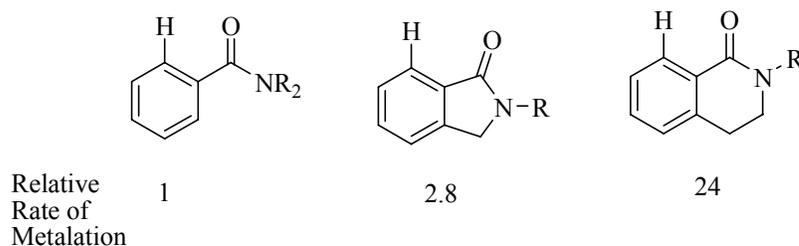
A recent study by Clayden and coworkers has provided the first crystallographic evidence for the structure of the *ortho*-lithiated benzamide species.[85] Benzamides are one of the best directors of *ortho*- metallation because they possess the two characteristics of a good directing group; electron rich heteroatoms to promote lithium chelation,[73] and electron withdrawing capabilities to withdraw electron density from the aromatic ring and facilitate deprotonation. Despite widespread use of the benzamide as DOM group, the exact coordination structure of the lithiated intermediate had not been elucidated. The X-ray structure of the lithiated benzamide DOM group exists as a dimer where the lithium is coordinated by a solvent molecule, a benzamide oxygen, and the carbanions (Scheme 3).[85] The crystal structure provide evidence that oxygen coordination of the lithium center is crucial to the stability of the metallated species.[85] Further studies are necessary to elucidate the solution properties of this complex, as it is evident that solvent plays a major role in the formation of the *ortho*-lithium complex.

Scheme 3. Proposed Structure of *ortho*-Lithiated Benzamides
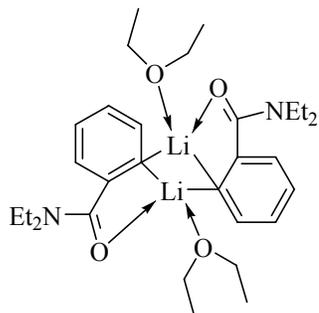
Many DOM groups have been discovered and extensively studied throughout the years since the discovery of the *ortho*-metallation of anisole in 1939. All of these directing groups have specific synthetic strengths and weaknesses. What follows is a brief overview of some of the most important directing groups.

O-Alkyl Directing Groups

Since the discovery of *ortho*-metallation using anisole, oxygen containing directing groups have received considerable attention. Parham in 1948 proposed the synthesis of certain phenolic acetals for their use in DOM.[86] He concluded that phenolic ethers (e. g. anisole) were too difficult to remove and would result in decomposition of the compound. However, more modern techniques of phenolic ether cleavage have been realized and the use of acetals[87] has largely been replaced by phenolic ethers.

Early studies used tetrahydropyranyl ethers **II-1** and anisole.[88-90] These studies demonstrated that these groups were able to direct *ortho*-metallation in high yields. Subsequent studies sought to ascertain the effect of other substituents on the DOM

abilities of these ethers. The presence of alkyl groups *ortho* to the DOM group would lead to a mixture of products; the desired *ortho*-metallated product, and the deprotonated alkyl group in an approximately 5:2 mixture (Scheme 4).[91,92] However, if the alkyl group was farther away in the ring, then it was not deprotonated. These results would seem to indicate that the DOM group is able to direct deprotonation of the alkyl substituent as well, making the presence of *ortho*-alkyl groups undesirable.
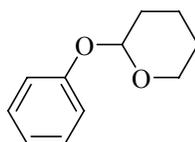
II-1

Scheme 4
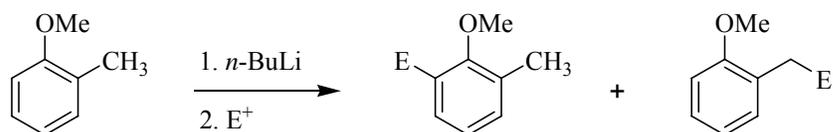
The directing capabilities of anisole have been compared to that of many other directing groups.[93,94] Slocum concluded that CH_2NMe_2, CONHMe, SO_2NHMe, and SO_2NMe_2 were more powerful *ortho*- directing groups. In addition, $CH_2CH_2NMe_2$, CF_3, NMe_2, and F were all weaker directing groups than anisole. In these cases, mixtures of metallated products were not obtained; metallation occurred exclusively *ortho* to the more powerful group.

The use of methoxymethyl (MOM) groups has also been reported.[95-99] These phenol protecting groups have the advantage over methoxy groups in ease of their

removal and have been utilized in the synthesis of coumarins[100] and polycoumarin[101] compounds.

Carbamate Directing Groups

Carbamates (-OCONR$_2$) as efficient directors of *ortho*-metallation were discovered in 1983 by Snieckus (Scheme 5).[102,103] They were found to be better directing groups than O-methyl or MOM, but show lower regioselectivity in the metallation of non-equivalent *ortho* sites.

Scheme 5. DOM of Carbamates
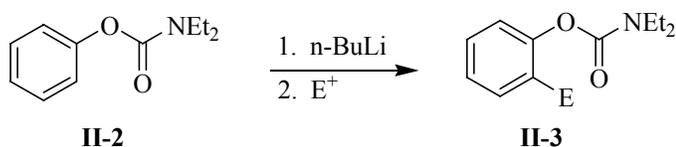
where E = DMF, CO$_2$, TMSCl, MeI

An additional and unexpected effect was noticed with carbamates. If, after lithiation, the reaction was allowed to warm (-78 °C to r. t.), without the addition of an electrophile, then it was observed that 1,3-acyl migration occurred, termed anionic *ortho*–Fries rearrangement (Scheme 6).[103] These rearranged compounds were obtained in good yields (65-78%) and allow for further DOM reactions because of the presence of the new benzamide DOM moiety.[102,104,105]

Scheme 6. 1,3-Acyl Migrations of Carbamates

II-4   **II-5**
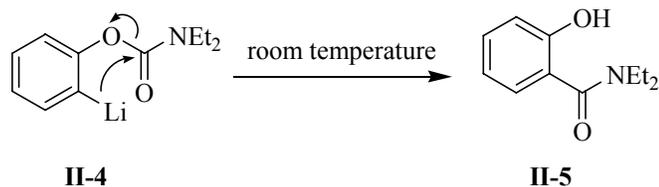
Snieckus utilized this DOM/rearrangement reaction in his synthesis of ochratoxin A and B (Scheme 7).[106] This use of carbamate *ortho*-metallation-rearrangement was the key step in the synthesis of these bacterial toxins in four steps with 14 and 6 % overall yields for ochratoxin A and B, respectively. The synthesis of other unusually substituted isocoumarins was accomplished also.[106] Accordingly, *ortho*-metallation of carbamate **II-6** allowed for the introduction of electrophile E_1 (pathway 1). This *ortho*-metallation was followed by an anionic *ortho*-Fries rearrangement (pathway 2). Another *ortho*-metallation of the resulting benzamide derivative positioned electrophile E_2 (pathway 3). This series of steps generated the highly functionalized arene **II-7**. Compound **II-7** was then converted through a series of steps to ochratoxin B (**II-8**) and ochratoxin A (**II-9**).

Scheme 7. Carbamate DOM Synthesis of Ochratoxin A and B

II-6   **II-7**

R= H Ochratoxin B (**II-8**)
R= Cl Ochratoxin A (**II-9**)
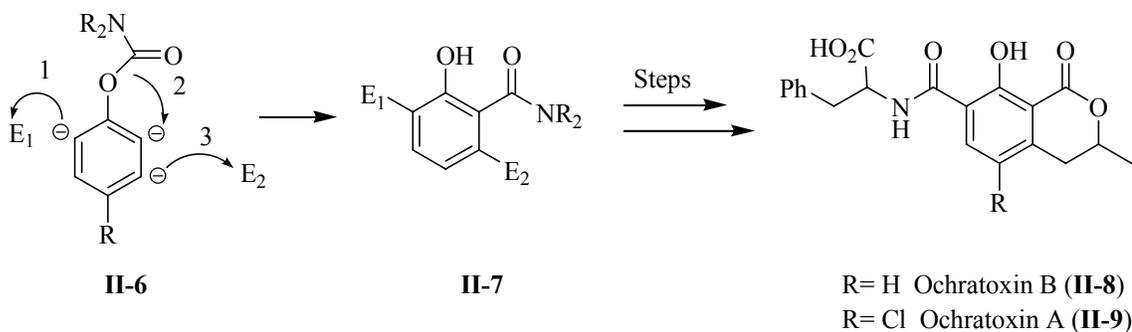
Chromenes are important heterocyclic components in several natural products and are difficult to construct by classical methods such as Friedel-Crafts alkylation. Recently, Snieckus and coworkers employed aryl carbamate DOM groups in the regiospecific synthesis of chromenes.[107] Snieckus first utilized the carbamate as an *ortho*-directing group, followed by rearrangement, to give the chromene products (Scheme 8). For example, *ortho*-metallation of carbamate **II-10** followed by quenching the anion with enone **II-11** to generate allylic alcohol **II-12** which underwent intramolecular carbamate migration to generate intermediate **II-13.** Compound **II-13** was cyclized subsequently to chromene **II-14**. If R is another *ortho*-directing group, then the molecule is poised for further directed metallation and functionalization.

Scheme 8. Carbamate DOM and Synthesis of Chromenes
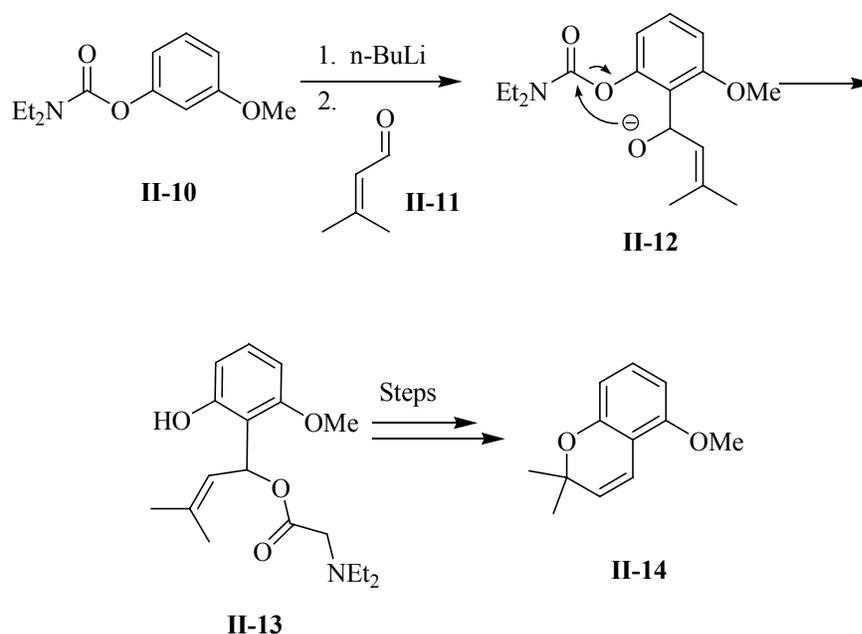
Hauser first observed that tertiary amines are effective directors of metallation.[108] Since then, there have been many aniline derivatives that have been developed to direct metallation. *N*-pivaloylanilines **II-15**,[109-113] and dimethylureas **II-16**[111] have both been widely employed in DOM chemistry. Deprotonation of the N-H proton of pivaloylaniline **II-15** occurred with the first equivalent of base to create the oxyanion **II-17** which directed the subsequent metallation (Scheme 9). This formed dianion **II-18** which was quenched with an electrophile to generate the *ortho*-substituted product **II-19**.

II-15   **II-16**
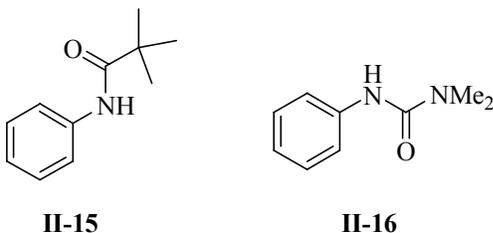
Scheme 9

II-15   **II-17**   **II-18**   **II-19**
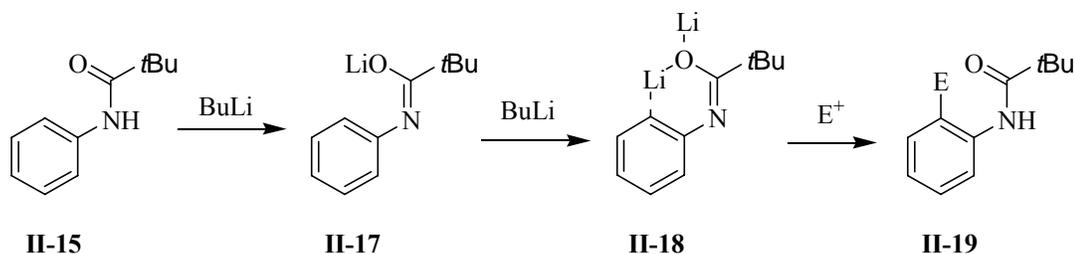
N –Pivaloylanilines have been employed as DOM groups for natural product synthesis. An example of which is the synthesis of β-carbolines (**II-20**) (Scheme 10).[114] In his synthesis, Queguiner utilized the *ortho*-directing abilities of *N* –pivaloylaniline (**II-21**) to form the boronic acid **II-22** which is able to then cross-couple *via* Suzuki coupling to form **II-23** which is then *ortho*-metallated again, but this time utilizing the fluorine in

preference to the *N*–pivaloylaniline to attach electrophiles to the ring system to produce, upon ring closure, substituted β-carboline **II-20**.

Scheme 10
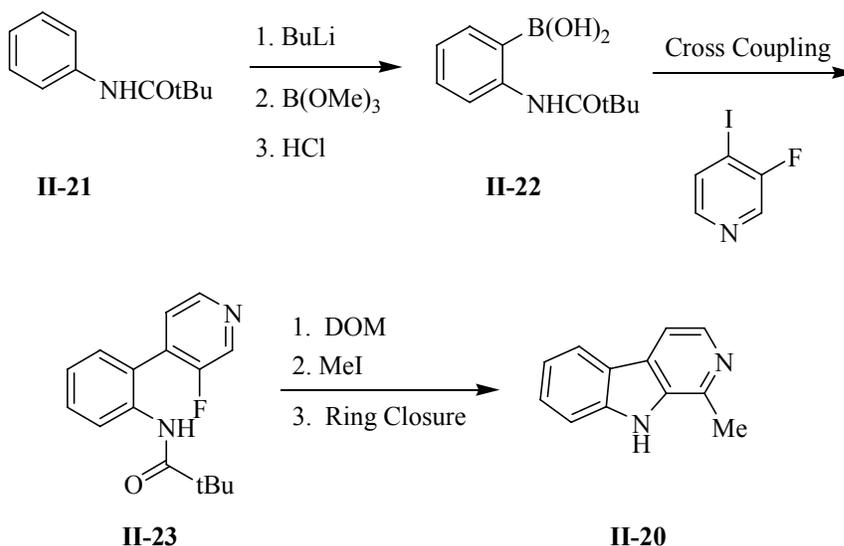
Benzamide Directing Groups

The most important and widely used carboxylic acid derivative in *ortho*-metallation chemistry is the benzamide functionality. This directing group yields the desired *ortho*-substituted products in very high yields (80-90%).[115,116] *o*-Metallation of benzamides has been applied to the synthesis of a multitude of natural products[117-129] including isocoumarins **II-24**,[130] phthalideisoquinoline alkaloids **II-25**,[131,132] and anthraquinones **II-26**.[133] In each of these syntheses, the use of benzamide DOM groups allowed for a more facile and shorter synthetic pathway than was available from classical reactions.

30
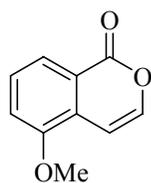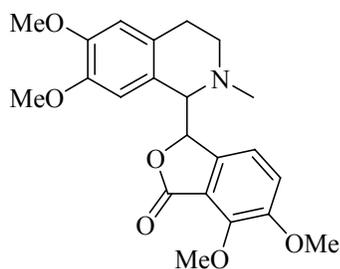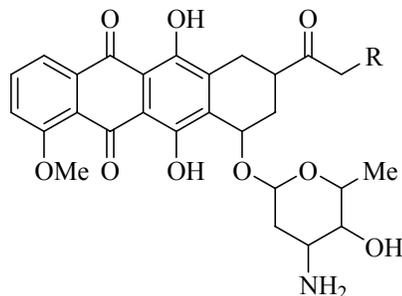
II-24   **II-25**   **II-26**

Despite their potential ability to direct *ortho*-metallation, the benzamides have several drawbacks. First, the possibility of intermolecular condensation with the *ortho*-carbanion can occur (Scheme 11). This is usually avoided by keeping the temperature of the reactions below -78°C.[134] Secondly, the amide can be resistant to hydrolysis. Secondary benzamides are easier to hydrolyze than tertiary amides; however, secondary amides require two equivalents of base and suffer from reduced reactivity toward DOM and, in some cases, pose solubility problems.[134,135] As a result, Phillion has developed a tertiary benzamide **II-30** which is easy to synthesize, is a good DOM, and is easily converted to the secondary amide via HCl in dioxane for hydrolysis.[134]

Scheme 11

II-27   **II-28**   **II-29**
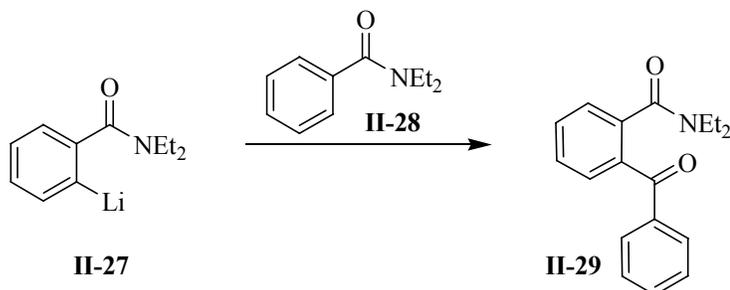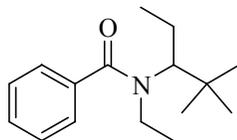
II-30

Application of Directed Ortho-Metallation to the Synthesis of Aryl Siloxanes

Research in the DeShong group has focused on the use of aryl silane reagents in palladium-catalyzed cross-coupling reactions. This methodology has proven to be excellent for aryl-aryl couplings,[45-51] and can also be used for the arylation of allylic esters.[136] The synthesis of aryl siloxanes is accomplished in one of several complementary methods. Classically, the synthesis of aryl siloxanes is achieved by treatment of aryl Grignard or aryllithium reagents with a silicon electrophile, typically tetraethylorthosilicate.[56] Additionally, Pd (0)[58,59] or Rh (I)[60] catalyzed silylation reactions of aryl halides has been developed. These transition metal-catalyzed silylation reactions are tolerant of functional groups (e.g. ester) that are not suitable for the Grignard approach. Eachof these methods, however, requires the use of a suitable aryl halide as the substrate.

As part of the development of the siloxane coupling methodology, we were interested in synthesizing highly functionalized aryl siloxane derivatives for application in natural product total synthesis. In several instances, the desired substitution pattern on the aromatic ring precluded the efficient synthesis of the requisite aryl halide. An *ortho*-metallation strategy, on the other hand, presened an attractive alternative route for the preparation these complex substrates (Scheme 12). Organoboranes and organostannanes have been synthesized by *ortho*-metallation; however, aryl siloxanes have not been

32

prepared using this method.[20] The results presented herein demonstrate the scope and limitations of directed *ortho*-metallation for the synthesis of aryl siloxanes and the subsequent coupling reactions of the resulting derivatives.

Scheme 12
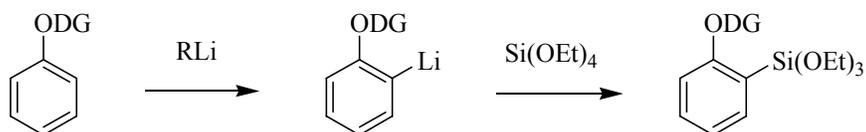
RESULTS AND DISCUSSION

Our studies have focused on surveying *ortho*-directing groups (ODG) that have previously proven to be most versitile (*vide supra*).[20] The synthesis of siloxanes using these groups is summarized in Table 1. Ethers (entries 1 and 2) and carbamates (entries 3 and 5, respectively) smoothly yielded the desired siloxanes in good yields. In addition, the *N*-pivaloylaniline (entry 4) served as a suitable substrate for the formation of the requisite siloxane. However, *N,N*-diethylbenzamide siloxane proved elusive (entry 6). The only product obtained from a multitude of reaction conditions was the benzophenone derivative, which arose from nucleophilic attack of the lithiated benzamide species with another benzamide molecule.

Table 1. Synthesis of Aryl Siloxanes via *Ortho*-Metallation

entry	substrate[a]	electrophile	product	yield[b] (%)
1	MeO-, Li, $Si(OEt)_4$ substrate	$Si(OEt)_4$	MeO-, $Si(OEt)_3$ product	62
2	MOMO-, Li	$Si(OEt)_4$	MOMO-, $Si(OEt)_3$	61
3	Et_2N-C(O)-O-, Li	$Si(OEt)_4$	Et_2N-C(O)-O-, $Si(OEt)_3$	57
4	pivaloyl HN-, Li	$Si(OEt)_4$	pivaloyl HN-, $Si(OEt)_3$	63
5	Boc HN-, Li	$Si(OEt)_4$	Boc HN-, $Si(OEt)_3$	61
6	Et_2N-C(O)-, Li	$Si(OEt)_4$	Et_2N-C(O)-, C(O)-Ph	94
7	Et_2N-C(O)-, Li	CH_3I	Et_2N-C(O)-, CH_3	85

[a] For detailed metalation procedures for each substate see experimental section. [b] Yield of purified product.

In order to show that the lithiated benzamide species was being generated and could be efficiently trapped with an electrophile, the reaction was quenched with CH$_3$I (entry 7). This led to the formation of the expected *ortho*-substituted product in 85% yield. It was thought that the inability to form the desired ortho-substituted benzamide siloxane was due to the poor electrophilicity of tetraethylorthosilicate. Accordingly, we hypothesized that a more electrophilic siloxane source would give the desired siloxane in preference to the benzophenone adduct.

To this end, several silicon electrophiles were surveyed and the results are presented in Table 2. The most promising proved to be triethoxysilyltriflate. This reagent is readily obtained *via* treatment of allyltriethoxysilane with triflic acid.[137] Yields of the *o*-methoxy, *o*-MOM, and *o*-O-carbamate siloxanes were markedly increased with this electrophile (entries 1-3, compare to Table 1 entries 1-3)). Unfortunately, there was no reaction with the benzamide substrate (entry 4). The use of another silane electrophile, SiCl$_4$ (entry 5), provided only a marginal increase in yield over Si(OEt)$_4$ (69% versus 62%). Like the silyl triflate, no benzamide siloxane product was obtained using SiCl$_4$.

Table 2. Use of Alternative Silicon Electrophiles
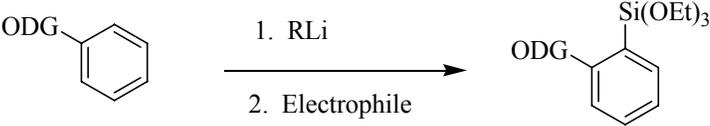
entry	substrate	electrophile	product	yield (%)
1	MeO— (phenyl)	TfO-Si(OEt)$_3$	MeO—, Si(OEt)$_3$ (o-substituted)	88
2	MOMO— (phenyl)	TfO-Si(OEt)$_3$	MOMO—, Si(OEt)$_3$ (o-substituted)	83
3	Et$_2$N-C(O)-O— (phenyl)	TfO-Si(OEt)$_3$	Et$_2$N-C(O)-O—, Si(OEt)$_3$ (o-substituted)	86
4	Et$_2$N-C(O)— (phenyl)	TfO-Si(OEt)$_3$	Et$_2$N-C(O)—, Si(OEt)$_3$ (o-substituted)	0
5	MeO— (phenyl)	SiCl$_4$[a]	MeO—, Si(OEt)$_3$ (o-substituted)	69
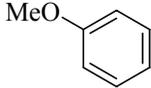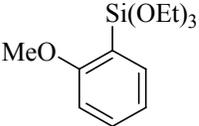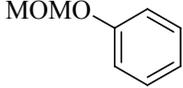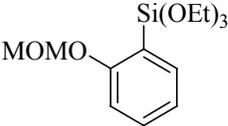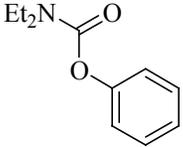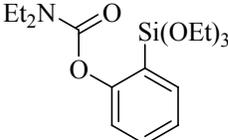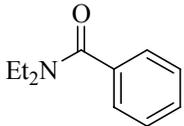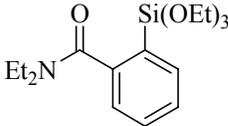
[a] Lithiated arene was quenched with SiCl$_4$ followed by the addition of anhydrous EtOH to obtain the desired siloxane. See Experimental section for full reaction details.

Having synthesized a variety of *o*-substituted aryl siloxanes, attention turned to assessing their ability to participate in palladium-catalyzed cross-coupling. The results of these cross-coupling studies are presented in Table 3, and data indicate that siloxanes possessing either *o*-ether (entries 1 and 3) or *o*-O-carbamate (entry 2) functionalities

couple poorly with aryl bromides using 10 mol % catalyst. Previous studies in our laboratory,[138] had shown that the presence of oxygen-base *ortho*-substituents on the aryl siloxane often led to poor yields of coupled product; however, the results can be significantly improved by increasing the catalyst loading to 50 mol %.[138]

The low yields of coupled product obtained using 10 mol % catalyst with *o*-phenolic derivatives (Table 3, entries 1-3) was due to competitive protodesilylation of the siloxane (Scheme 13). However, in the case of the aniline derivatives of the siloxane (entries 4 and 5, respectively), excellent yields of coupled products are observed with only 10 mol % catalyst, with no detectable protodesilylation.

Scheme 13
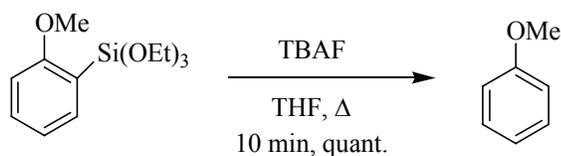
Table 3. Palladium-Catalyzed Cross-Coupling of Aryl Siloxane Derivatives

$$\text{aryl siloxane} \quad + \quad \text{Ar-Br} \quad \xrightarrow[\substack{\text{TBAF} \\ \text{DMF}}]{\substack{\text{Pd(OAc)}_2 \\ \text{PPh}_3}} \quad \text{biaryl product}$$

entry	aryl siloxane	Ar	Pd(OAc)$_2$[a] (mole %)	biaryl product	yield[b] (%)
1	Si(OEt)$_3$ / OMe	Ph	50(10)	OMe	39(75)
2	Si(OEt)$_3$ / OCONEt$_2$	p-OMePh	50(10)	OMe / OCONEt$_2$	12(49)
3	Si(OEt)$_3$ / OMOM	Ph	50(10)	OMOM	54(87)
4	Si(OEt)$_3$ / NH / O= / tBu	Ph	10	NH / O= / tBu	86
5	Si(OEt)$_3$ / NH / O= / O−tBu	Ph	10	NH / O= / O−tBu	88

[a] In all cases, ratio of Pd(OAc)$_2$ to PPh$_3$ was 1:2. Reactions performed with 50 mol % catalyst were complete in less than 15 min at 90 °C and reactions performed with 10 mol % catalyst were complete after 4 h at 90 °C. [b] Yield in parenthesis is the yield obtained with 50 mol % catalyst.

The cross-coupling reactions were found to be extremely sensitive to the presence of *o*-substituents in the aryl halide partners. For example, cross-coupling of *o*-methoxy

siloxane **II-31** to *p*-bromoanisole (**II-32**) proceeded in good yield to generate biaryl **II-33**; however, attempted coupling of siloxane **II-31** to *o*-bromoanisole (**II-34**) was not successful and the siloxane was protodesilylated (Scheme 14). The formation of the disubstituted biaryl is slow due to steric congestion, providing time for the protodesilylation pathway to consume the siloxane.

Scheme 14
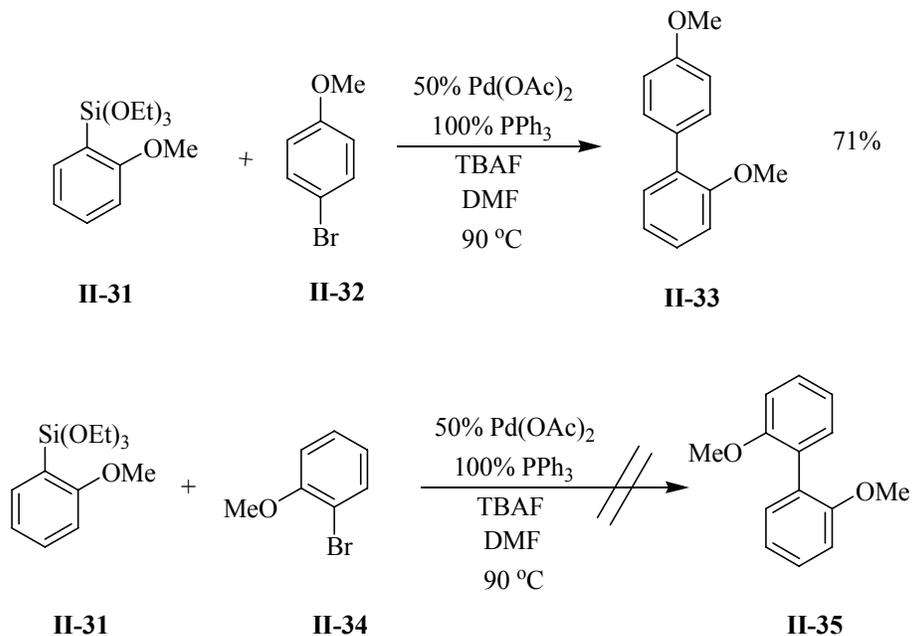
In an attempt to elucidate the source of the proton and the mechanism of protodesilylation of *o*-substituted derivatives, several control experiments were performed. Studies using deuterium-labeled DMF or THF showed that solvent was not the source of the proton. Commercially available (Aldrich) solutions of TBAF in THF contain approximately 5% water and it was initially thought that water in the TBAF may be serving as the proton source for protodesilation. Accordingly, alternative anhydrous fluoride sources were investigated and the results of these studies are presented in Table 4. In most cases (entries 1-4, 8-11) neither cross-coupling nor protodesilylation occurred

upon treatment with the fluoride reagent, and the siloxane was recovered unchanged. For

comparison, *p*-methoxy siloxane is stable for 24 h in the presence of TBAF•3H$_2$O.

Table 4. Use of Alternative Fluoride Sources[a]

entry	" F⁻ " source	yield of coupled product (%)
1	LiF	0[b]
2	NaF	15[c]
3	KF	20[c]
4	CsF	17[c]
5	TBAF (1.0 M in THF)[f]	40[d]
6	TBAF• 3H$_2$O	42[d]
7	TMAF• 4H$_2$O	41[d]
8	TMAF (anhydrous)[g]	0[e]
9	TASF	0[e]
10	NaBF$_4$	0[e]
11	Bu$_4$NBF$_4$	0[e]

[a] Reactions were perfomed at 90 °C for 4 h. [b] No reaction occurred. [c] Trace amounts
of protodesilylated siloxane were present, remainder of siloxane was unreacted.
[d] Remainder of siloxane was hydrolyzed. [e] Greater than 70% of the starting siloxane
was recovered from the reaction. [f] Contains 5% water. [g] Purchased from Aldrich.

It was discovered that if the siloxane was heated in the presence of tetrabutylammonium fluoride trihydrate (TBAF•3H$_2$O), rapid and efficient protodesilylation occurred with the generation of tributylamine (Table 5). This result clearly indicated that a proton was abstracted from the tetrabutylammonium cation in a Hoffman-like elimination to generate tributyl amine and butene (Scheme 15).[139,140] Further support for the hypothesis that this reaction was the source of the proton for protodesilylation was obtained from deuterium studies. TBAF•3H$_2$O was recrystallized from D$_2$O to give TBAF•3D$_2$O, the structure of which was confirmed by IR (loss of OH peak, appearance of OD peak at 2550 cm^{-1}). When TBAF•3D$_2$O was utilized in these experiments, no deuterium incorporation was observed in the product.

Table 5. Search for the Source of the Proton for Protodesilylation

aryl siloxane	"F⁻" source	products[a]

aryl siloxane $\xrightarrow[\text{30 min}]{\substack{\text{"F}^-\text{" Source} \\ \text{DMF} \\ 90\,°C}}$ products
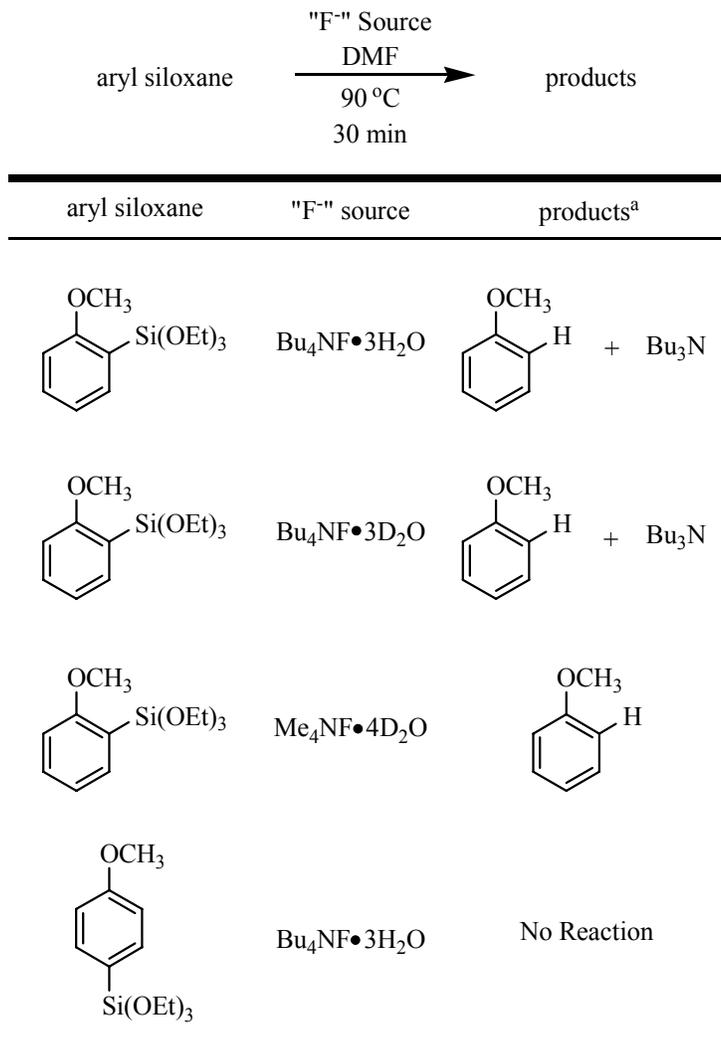
[a] Yields of products are greater than 90%.

Scheme 15
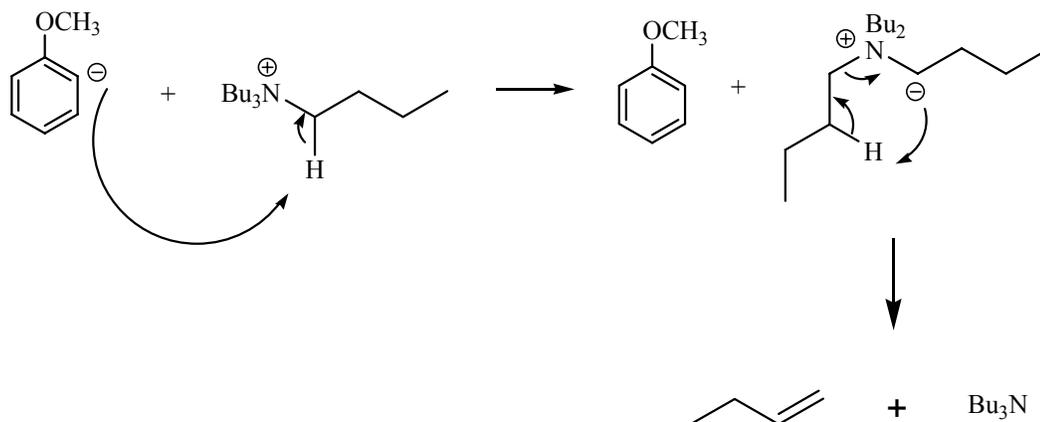
The protodesilylation mechanism was further probed using TMAF•4D$_2$O (prepared in an analogous manner to TBAF•3D$_2$O). This reagent does not possess β-hydrogens and thus would not be able to undergo Hoffman elimination. However, rapid protodesilylation still occurred, also with no deuterium incorporation. This result indicated that the α-proton was abstracted from the tetramethylammonium cation generating the yilde, which can then undergo Stevens rearrangement to generate dimethylethylamine;[141] however, attempts to isolate or identify dimethylethylamine from the reaction mixture were unsuccessful. The ideal test for this side reaction would be to use the perdeuterated alkylammonium fluoride. This experiment would provide direct evidence for the elimination pathway, as deuterium would be incorporated into the protodesilylated product.

CONCLUSIONS

In conclusion, directed *ortho*-metallation protocols have been developed for the synthesis of aryl siloxane derivatives. Subsequent cross-coupling of the resulting aryl

siloxanes has been achieved. For phenolic derivatives, high catalyst loading is required for good yields of product. On the other hand, aniline derivatives underwent cross-coupling under standard conditions.

Synthetic organic chemistry has witnessed the development of many different techniques that have allowed the formation of thousands of different molecules. The addition to this repertoire of *ortho*-metallation by Gilman and Wittig has simplified the synthesis of many different natural products, and has opened the door to synthesis of novel compounds that were unrealized before. The combination of this methodology with cross- coupling technology has become a powerful tool in the synthesis of countless unsymmetric biaryl systems. Specifically, *ortho*-metallation has value in palladium-catalyzed cross-coupling technology where it allows the facile preparation of aryl siloxanes which can be coupled to aryl halides in the synthesis of biologically active natural products.

EXPERIMENTAL SECTION

General Experimental

Thin-layer chromatography (TLC) was performed on 0.25 mm silica gel coated plates treated with a UV-active binder with compounds being identified by UV (254 nm). Flash chromatography was performed using thick walled columns and medium pressure silica gel (Whatman 200-425 mesh), with column length and diameter being determined by the method of Still.[142]

Melting points were taken in Kimax soft glass capillary tubes using a Thomas-Hoover Uni-Melt capillary melting point apparatus (Model 6406K) equipped with a calibrated thermometer.

IR band positions are reported in reciprocal centimeters (cm^{-1}) and relative intensities are listed as br (broad), s (strong), m (medium), or w (weak). Nuclear magnetic resonance (^1H, ^{13}C NMR) spectra were recorded on a 400 MHz spectrometer. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (TMS). Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet).

Low resolution mass spectrometry (LRMS) and high resolution mass spectrometry (HRMS) data are reported in the form of m/z (intensity relative to base peak = 100). The matrix used for fast atom bombardment (FAB) was ethylene glycol.

Tetrahydrofuran and diethyl ether were distilled from sodium/benzophenone ketyl. Methylene chloride and tetraethylorthosilicate were distilled from calcium hydride. Dimethylformamide and acetonitrile were distilled from calcium hydride. Ethanol was fractionally distilled from calcium chloride.

Palladium (II) acetate ($Pd(OAc)_2$) and tetrabutylammonium fluoride (1M solution in THF) were purchased from Acros and used as received. Triphenylphosphine was purchased from Aldrich and recrystallized from hexane prior to use. All glassware used in these reactions was either oven dried at 120 ºC for 12 hours or flame dried prior to use. All reactions were conducted under an atmosphere of argon.

All compounds were determined to be >95% pure by ^{1}H NMR or GC analysis. Previously reported compounds were characterized *via* ^{1}H and ^{13}C NMR and IR and compared to literature values. All new compounds were characterized using ^{1}H NMR, ^{13}C NMR, IR, low resolution and high resolution mass spectrometry.

Synthesis of Starting Materials

Methoxymethoxybenzene (Table 1, entry 2). Phenol (1.88 g, 20.0 mmol) was dissolved in 15 mL of DMF. The solution was transferred *via* cannula to a suspension of NaH (0.768 g, 20.0 mmol) in 35 mL of DMF at 0 °C with significant evolution of gas. The reaction was allowed to warm to room temperature and was stirred for 15 min, then cooled to 0 °C. Chloromethylmethyl ether (3.04 mL, 40.0 mmol) was added, and the reaction stirred for 5 min at 0 °C, then 15 min at room temperature. The cloudy white solution was diluted with 50 mL of ether and poured into 50 mL of water. The organic layer was washed with 1M KOH (50 mL), water (50 mL), dried (MgSO$_4$), and concentrated *in vacuo* to yield a pale yellow oil which was purified *via* column chromatography (19:1 hexanes/EtOAc, TLC R$_f$ = 0.32) to give 2.76 g of the title compound as a colorless oil (97%). The ^{1}H and ^{13}C NMR and IR match that reported by LeBel.[143]

O-Phenyl diethylcarbamate (Table 1, entry 3). Diethyl carbamoyl chloride (12.6 mL, 100 mmol) was added to a mixture of K$_2$CO$_3$ (13.8 g, 100 mmol) and phenol (6.31 g, 67.0 mmol) in 135 mL of MeCN. The reaction was refluxed for 3.5 h followed by the addition of 100 mL of water. The aqueous layer was extracted with ether (100 mL x3).

The combined organic layers were washed with 100 mL of a 1M KOH solution followed by 100 mL of water. The ethereal solution was then dried (MgSO$_4$) and concentrated *in vacuo* to produce a yellow oil. Kugelrohr distillation (95 °C, 0.3 mm Hg) yielded 17.8 g of a colorless oil (92%). ^{13}C NMR (CDCl$_3$) δ 13.4, 14.2, 41.9, 42.2, 121.7, 125.0, 129.2, 151.6, 154.2. The ^{1}H NMR and IR match that reported by Snieckus.[144]

Pivalanilide (Table 1, entry 4). Pivaloyl chloride (26.3 mL, 214 mmol) was added slowly to a vigorously stirred biphasic solution of Na$_2$CO$_3$ (22.7 g, 214 mmol) in 100 mL H$_2$O and aniline (9.78 mL, 107 mmol) in 100 mL of CH$_2$Cl$_2$. The reaction was refluxed for 1 h and diluted with 100 mL of CH$_2$Cl$_2$. The organic layer was extracted once with 100 mL of 1M NaOH, and twice with 100 mL of water, dried (MgSO$_4$) and concentrated to yield a slightly yellow crystalline solid. The solid was recrystallized from hexanes/EtOAc to produce 18.2 g of white needles (96%) mp 133.1-134.5 °C (lit. 133.8-135.0 °C)[145]. IR (CCl$_4$) 3458 (s), 3064 (w), 3026 (w), 2964 (m), 2902 (w), 2871 (w), 1697 (s), 1597 (s), 1521 (s), 1435 (s), 1435 (s), 1314 (s), 1241 (m), 1148 (s). The ^{1}H and ^{13}C NMR match that reported by Lappert.[145]

***tert*-Butyl *N*-phenylcarbamate (Table 1, entry 5).** Di-*tert*-butyl dicarbonate (5.14 g, 23.5 mmol) was added in one portion to a stirred solution of aniline (1.96 mL, 21.4 mmol) in 25 mL of THF. The reaction was heated to reflux for 3 h. The solvent was removed *in vacuo* and the residue dissolved in 50 mL of EtOAc. The organic layer was washed twice with 1M HCl (50 mL), once with water (50 mL), dried (MgSO$_4$) and concentrated to yield a slightly yellow solid. Recrystallization (CH$_2$Cl$_2$) yielded 4.07 g of

white flakes (97%) mp 137.1-137.4 °C (lit. 136-137 °C).[146] IR (CCl$_4$) 3451 (m), 3061 (w), 3029 (w), 3012 (w), 2978 (m), 2926 (w), 1735 (s), 1604 (m), 1521 (s), 1435 (s), 1366 (m), 1307 (m), 1162 (s). The ^{1}H and ^{13}C NMR match that reported by Smith.[146]

N,N-Diethylbenzamide (Table 1, entry 6). To a stirred solution of benzoyl chloride (2.48 mL, 21.3 mmol) in 25 mL of THF at 0 °C is added 6.62 mL (64.0 mmol) of diethylamine. The reaction is heated at reflux for 2 h, followed by evaporation of the solvent. The residue is dissolved in 50 mL of EtOAc and washed three times with 1M HCl (50 mL), twice with saturated NaHCO$_3$ (50 mL), and once with water (50 mL). The organic layer was then dried (MgSO$_4$) and concentrated to a yellow oil. Kugelrohr distillation (90 °C, 0.2 mm Hg) yielded 3.26 g of a colorless oil (96%). The ^{1}H and ^{13}C NMR and IR match that reported by Burke.[147]

Synthesis of Aryl Siloxanes

2-(Triethoxysilyl)anisole (Table 1, entry 1). To a colorless solution of anisole (0.523 mL, 5.00 mmol) in Et$_2$O (10 ml), was added 0.906 ml of TMEDA (6.00 mmol). The reaction was cooled to 0 °C and 3.75 ml of a 1.60 M solution n-BuLi in hexane was added. The resulting yellow solution was stirred at room temperature for 1 h. The dark yellow ethereal solution was added to 3.35 mL (15.0 mmol) of Si(OEt)$_4$ in 15 ml of Et$_2$O at −78 °C. The solution was stirred at −78 °C for 1 h then allowed to warm to room temperature for an additional hour. A saturated aqueous solution of NH$_4$Cl (50 mL) was added and the aqueous layer extracted with 50 mL of ether (x3), dried (MgSO$_4$), and concentrated *in vacuo* to give a yellow oil. Kugelrohr distillation (125 °C, 0.9 mmHg)

yielded 838 mg of pure siloxane as a colorless oil (62%). The ^{1}H and ^{13}C NMR and IR match that reported by DeShong.[59]

2-(Triethoxysilyl)-methoxymethoxybenzene (Table 1, entry 2). Title compound was synthesized using a modified metalation procedure of Barve.[15] Methoxymethoxybenzene (0.718 g, 5.00 mmol) and TMEDA (0.755 mL, 5.00 mmol) were dissolved in 10 mL of ether. The solution was cooled to 0 °C and 3.13 mL (5.00 mmol) of a 1.60 M *n*-BuLi solution in hexanes was added slowly inducing the formation of a yellow slurry. The mixture was stirred for a further 30 min at 0 °C. The lithiated arene was then transferred *via* cannulation to a solution of tetraethylorthosilicate (2.23 mL, 10.0 mmol) in 10 mL of ether at -78 °C. The reaction was stirred for 1 h at -78 °C and then allowed to warm to room temperature over the period of 1 h. The reaction was quenched with saturated aqueous NH$_4$Cl (50 mL). The aqueous layer was extracted with ether (50 mL x2), dried (MgSO$_4$), and the solvent removed *in vacuo* to give a pale yellow oil. Kugelrohr distillation (130 °C, 0.9 mm Hg) yielded 916 mg of pure siloxane as a colorless oil (61%). IR (CCl$_4$) 2974 (m), 2926 (m), 2895 (m), 1591 (m), 1474 (m), 1230 (m), 1156 (m), 1105 (s), 1080 (s), 1006 (s); ^{1}H NMR (CDCl$_3$) δ 1.22 (t, *J*=7.2, 9H), 3.49 (s, 3H), 3.83 (q, *J*=7.2, 6H), 5.23 (s, 2H), 6.98 (t, *J*=7.0, 1H), 7.13 (d, *J*=7.0, 1H), 7.42 (t, *J*=7.0, 1H), 7.60 (d, *J*=7.0, 1H); ^{13}C NMR (CDCl$_3$) δ 18.2, 56.0, 58.6, 94.2, 113.1, 120.0, 121.5, 132.1, 137.5, 162.2; LRMS (FAB$^+$) m/z 300 (M$^+$, 25), 255 (60), 210 (100), 163 (35), 139 (30), 107 (35), 79 (28), 45 (97); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{14}$H$_{24}$O$_5$Si 300.1393, found 300.1387.

2-(Triethoxysilyl)-*O*-*N,N*-diethylcarbamoylbenzene (Table 1, entry 3). Title compound was synthesized using a modified metalation procedure of Snieckus.[16] A solution of *O*-phenyl diethyl carbamate (0.966 g, 5.00 mmol) in 5 mL of THF was added dropwise to a stirred solution of *sec*-BuLi (4.01 mL, 5.50 mmol) and TMEDA (0.830 mL, 5.50 mmol) in 50 mL of THF at -78 °C. The reaction was stirred for 1 h at -78 °C and was then slowly added to a stirred solution of tetraethylorthosilicate (3.35 mL, 15.0 mmol) in 30 mL of THF at -78 °C. The reaction was stirred at -78 °C for 2 h followed by 2 h at room temperature. Saturated aqueous NH_4Cl (50 mL) was added to the reaction mixture. The aqueous layer was then extracted with ether (50 mL x2), dried ($MgSO_4$), and the solvent removed *in vacuo* to give a dark yellow oil. Kugelrohr distillation (135 °C, 0.9 mmHg) yielded 1.01 g of pure siloxane as a colorless oil (57%). IR (CCl_4) 2978 (w), 2929 (w), 2885 (w), 1718 (s), 1421 (m), 1200 (m), 1155 (s), 1103 (s), 1086 (s); ^{1}H NMR ($CDCl_3$) δ 1.19-1.28 (m, 15H), 3.38 (q, *J*=7.2, 2H), 3.53 (q, *J*=7.2, 2H), 3.82 (q, *J*=7.2, 6H), 7.17-7.26 (m, 2H), 7.43-7.45 (m, 1H), 7.71-7.30 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 13.3, 14.0, 18.0, 41.6, 42.0, 58.4, 122.4, 122.9, 124.6, 131.7, 137.0, 154.0, 156.5; LRMS (EI^+) m/z 355 (M^+, 5), 309 (30), 100 (100), 72 (25); HRMS (EI^+, M^+) m/z calcd for $C_{17}H_{29}O_5NSi$ 355.1815, found 355.1822.

2-(Triethoxysilyl)-pivalanilide (Table 1, entry 4). Pivalanilide (886 mg, 5.00 mmol) was dissolved in 30 mL of a 50:50 solution of THF:Et_2O. To this colorless solution at 0 °C was added 12.4 mL of a 1.21 M solution of *n*-BuLi in hexane (15.0 mmol). The pale yellow solution was stirred at 25 °C for 20 h. The resulting white slurry was cooled to 0 °C and diluted with 50 mL of THF. Tetraethylorthosilicate (3.35 mL, 15.0 mmol) was

then added *via* syringe. The reaction was stirred for a further 4 h at room temperature. The solvent was removed *in vacuo* and the residue dissolved in ether. The organic layer was washed with saturated aqueous NH_4Cl (50 mL) twice, dried ($MgSO_4$), and the solvent removed *in vacuo* to give a pale yellow oil. Column chromatography (9:1 hexanes/EtOAc, TLC R_f = 0.28) yielded 1.05 g of a pale yellow oil (62%). IR (CCl_4) 3368 (s), 3054 (w), 2971 (s), 2922 (s), 2895 (s), 1683 (s), 1576 (s), 1535 (s), 1431 (s), 1300 (s), 1159 (s), 1103 (s), 1076 (s), 962 (s); ^{1}H NMR ($CDCl_3$) δ 1.24 (t, *J*=8.0, 9H), 1.30 (s, 9H), 3.88 (q, *J*=8.0, 6H), 7.07 (t, *J*=8.0, 1H), 7.41 (m, 1H), 7.55 (m, 1H), 8.33 (d, *J*=8.4, 1H), 8.99 (s, 1H); ^{13}C NMR ($CDCl_3$) δ 18.1, 27.6, 39.8, 59.1, 119.1, 121.0, 123.2, 131.7, 135.6, 144.1, 177.0; LRMS (FAB$^+$) m/z 339 (M$^+$, 10), 294 (100); HRMS (FAB$^+$, M$^+$) m/z calcd for $C_{17}H_{29}O_4NSi$ 339.1866, found 339.1860.

2-(Triethoxysilyl)-*N*-(*tert*-butoxycarbonyl)aniline (Table 1, entry 5). A solution of *t*-BuLi (4.20 mL, 6.30 mmol) was added dropwise to a stirred, colorless solution of *N*-(*tert*-butoxycarbonyl)aniline (500 mg, 2.52 mmol) in 10 mL of THF. The yellow solution was stirred at –20 °C for 2 h. The solution was diluted with 20 mL of THF, cooled to –78 °C, and tetraethylorthosilicate (1.69 mL, 7.56 mmol) was added *via* syringe. The reaction was then allowed to warm to room temperature overnight and quenched with saturated aqueous NH_4Cl (50 mL). The aqueous layer was then extracted with ether (50 mL x2), decolorized with activated carbon, dried ($MgSO_4$), and the solvent removed *in vacuo* to give a dark yellow oil. Column chromatography (9:1 hexanes/EtOAc, TLC R_f = 0.33) yielded 546 mg of a colorless oil (61%). IR (CCl_4) 3337 (m), 3054 (w), 2978 (s), 2926 (m), 2888 (m), 1725 (s), 1580 (m), 1535 (m), 1438 (m), 1369 (m), 1300 (m), 1159 (s),

1079 (s), 958 (m); ^{1}H NMR (CDCl$_3$) δ 1.27 (t, J=6.8, 9H), 1.51 (s, 9H), 3.89 (q, J=6.8, 6H), 7.01 (t, J=7.6, 1H), 7.38-7.42 (m, 1H), 7.49-7.51 (m, 1H), 8.12 (d, J=8.4, 1H), 8.72 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 18.0, 28.4, 29.5, 59.0, 118.6, 122.0, 131.8, 135.5, 144.7, 153.1; LRMS (FAB$^+$) m/z 355 (M$^+$, 42), 310 (22), 299 (40), 254 (100), 210 (45), 57 (25); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{17}$H$_{29}$O$_5$NSi 355.1815, found 355.1826.

2-(Diethylcarbamoyl)benzophenone (Table 1, entry 6). *N, N*-Diethyl benzamide (500 mg, 2.82 mmol) in 20 mL of THF was added slowly to a solution of *sec*-BuLi (2.38 mL, 3.10 mmol) and TMEDA (0.468 mL, 3.10 mmol) in 40 mL of THF at -78 °C. The reaction was stirred at -78 °C for 1 h. The reaction mixture was then added to Si(OEt)$_4$ (1.89 mL, 8.46 mmol) in 100 mL of THF at -78 °C. The reaction was stirred for 1 h at -78 °C and quenched with saturated aqueous NH$_4$Cl (100 mL). The aqueous layer was then extracted with ether (50 mL x2), dried (MgSO$_4$), and the solvent removed *in vacuo* to give a dark yellow oil. Column chromatography (1:1 hexanes/EtOAc, TLC R$_f$ = 0.29) yielded 310 mg of a white solid (95%) mp 76.8-77.2 °C (lit. 76-77 °C).[17] IR (neat) 3059 (w), 2975 (w), 2935 (w), 2866 (w), 1660 (m), 1620 (s), 1591 (m), 1428 (m), 1268 (s), 1083 (m), 927 (m); ^{13}C NMR (CDCl$_3$) δ 12.2, 13.7, 38.8, 43.2, 126.8, 128.1, 128.3, 129.8, 130.3, 130.7, 133.0, 137.0, 137.2, 138.8, 169.9, 196.7; LRMS (FAB$^+$) m/z 282 (M$^+$, 95), 209 (100), 105 (32), 72 (32), 57 (19); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{18}$H$_{20}$O$_2$N 282.1499, found 282.1507. The ^{1}H NMR matches that reported by Snieckus.[102]

***N,N*-Diethyl-*o*-toluamide (Table 1, entry 7).** Title compound was synthesized using a modified metallation procedure of Beak.[18] *N, N*-Diethyl benzamide (570 mg, 3.22 mmol)

in 10 mL of THF was added slowly to a solution of *sec*-BuLi (2.58 mL, 3.53 mmol) and TMEDA (0.533 mL, 3.53 mmol) in 40 mL of THF at -78 °C. The reaction was stirred at -78 °C for 1 h. Methyl iodide (0.501 mL, 8.05 mmol) was then added *via* syringe. The solution was then allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl (50 mL). The aqueous layer was then extracted with ether (50 mL x2), dried ($MgSO_4$), and the solvent removed *in vacuo* to give a dark yellow oil. Kugelrohr distillation (85 °C, 0.3 mmHg) yielded 523 mg of the title compound as a colorless oil (85%). IR (CCl_4) 3061 (w), 3026 (w), 2974 (w), 2933 (w), 2871 (w), 1635 (s), 1552 (m), 1473 (m), 1455 (m), 1428 (m); ^{13}C NMR ($CDCl_3$) δ 12.9, 14.0, 18.8, 38.7, 42.6, 125.4, 125.8, 128.5, 130.3, 133.8, 137.1, 170.8. The ^1H NMR matches that reported by Beak.[148]

Palladium-catalyzed cross-coupling reactions of aryl siloxanes with aryl bromides, representative procedure: To a solution of siloxane (1.50 mmol), aryl bromide (1.00 mmol), $Pd(OAc)_2$ (0.100 mmol), PPh_3 (0.200 mmol), in DMF (10 mL) is added 1.50 mL of TBAF in THF (1.0 M solution, 1.50 mmol). The reaction is heated at 90 °C for 4 h after which time, the reaction is cooled to room temperature and poured into 25 mL of water, and the aqueous layer extracted with ether (25 mL x3). The combined organic layers are dried ($MgSO_4$) and concentrated *in vacuo*. The biaryl product is then purified *via* column chromatography.

2-Methoxybiphenyl (Table 3, entry 1). Column chromatography (19:1 hexanes/EtOAc, TLC R_f = 0.37) yielded 71.7 mg of a colorless oil (39%). The ^{1}H and ^{13}C NMR and IR match that reported by Buchwald.[149]

4′-Methoxy-2-(*N,N*-diethyl-*O*-carbamoyl)biphenyl (Table 3, entry 2). Column chromatography (4:1 hexanes/EtOAc, TLC R_f = 0.27) yielded 35.9 mg of a colorless oil contaminated with a small amount of hexanes (12%). IR (CCl$_4$) 3078 (w), 3036 (w), 2971 (w), 2926 (w), 2867 (w), 2829 (w), 1718 (s), 1555 (m), 1521 (m), 1417 (m), 1272 (m), 1248 (m), 1196 (m), 1155 (m); ^{1}H NMR (CDCl$_3$) δ 1.04 (t, *J*=6.5, 6H), 3.26 (q, *J*=6.5, 4H), 3.83 (s, 3H), 6.92 (d, *J*=8.0, 2H), 7.18-7.36 (m, 6H); ^{13}C NMR (CDCl$_3$) δ 13.9, 13.2, 41.6, 41.9, 55.3, 113.5, 123.2, 125.5, 127.9, 130.2, 130.5, 134.7, 148.5, 154.1, 158.8; LRMS (EI$^+$) m/z 299 (M$^+$, 78), 294 (23), 100 (100), 72 (21); HRMS (EI$^+$, M$^+$) m/z calcd for C$_{18}$H$_{21}$O$_3$NSi 299.1521, found 299.1518.

2-Methoxymethoxybiphenyl (Table 3, entry 3). Column chromatography (19:1 hexanes/EtOAc TLC R_f= 0.28) yielded 116 mg of a colorless oil (54%). IR (CCl$_4$) 3061 (w), 3026 (w), 2992 (w), 2954 (w), 2926 (m), 2895 (m), 2847 (m), 1480 (s), 1435 (m), 1228 (m), 1190 (m), 1148 (m), 1076 (s), 1017 (s). The ^{1}H and ^{13}C NMR match that reported by Reinhoudt.[150]

2-Pivalanilinebiphenyl (Table 3, entry 4). Column chromatography (9:1 hexanes/EtOAc TLC R_f = 0.27) yielded a yellow solid. Recrystallization from ethanol yielded 218 mg of a white solid (86%) mp 70.2-70.5 °C (lit. 69.7-70.1°C).[20] ^{1}H NMR

(CDCl$_3$) δ 1.09 (s, 9H), 7.14-7.16 (m. 1H), 7.24-7.2 (m, 1H), 7.36-7.48 (m, 7H), 8.36 (1H); ^{13}C NMR (CDCl$_3$) δ 27.4, 39.8, 120.9, 123.9, 128.1, 128.5, 129.1, 129.4, 129.7, 132.1, 135.2, 138.1, 176.3; LRMS (EI$^+$) m/z 254 (M$^+$, 20), 253 (100), 196 (15), 169 (67), 168 (25), 57 (45); HRMS (EI$^+$, M$^+$) m/z calcd for C$_{17}$H$_{20}$ON 254.1545, found 254.1543. The IR matches that reported by Ohashi.[151]

2-N-(*tert*-Butoxycarbonyl)biphenyl (Table 3, entry 5). Column chromatography (19:1 hexanes/EtOAc TLC R$_f$ = 0.25) yielded 237 mg of a white solid (88%) mp 72.3-73.1 °C. IR (CCl$_4$) 3426 (m), 3067 (w), 3009 (w), 2978 (w), 2926 (w), 2898 (w), 1738 (s), 1590 (m), 1514 (s), 1493 (m), 1445 (s), 1162 (s); ^{1}H NMR (CDCl$_3$) δ 1.46 (s, 9H), 6.49 (s, 1H), 7.07-7.12 (m, 1H), 7.18-7.21 (m, 1H), 7.32-7.42 (m, 4H), 7.48 (t, *J*=7.2, 2H), 8.10 (d, *J*=8.4, 1H); ^{13}C NMR (CDCl$_3$) δ 28.3, 30.0, 119.8, 123.1, 127.8, 128.4, 129.1, 129.3, 130.2, 130.9, 132.0, 135.3, 138.4; LRMS (FAB$^+$) m/z 269 (M$^+$, 65), 214 (100), 170 (78), 169 (52), 57 (45); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{17}$H$_{19}$O2N 269.1420, found 269.1429.

4-Methoxy-2′-methoxybiphenyl (3). Column chromatography (9:1 hexanes/EtOAc TLC R$_f$ = 0.30) yielded 152 mg of a white solid (71%) mp 69.7-70.4 °C (lit. 69-70 °C).[22] The ^{1}H and ^{13}C NMR and IR match that reported by Denmark.[42]

General procedure for the synthesis of aryl siloxanes using triethoxysilyltriflate: Triflic acid (3.50 mmol), is added dropwise to a stirred solution of allyltrimethoxysilane (3.50 mmol) in 50 mL of CH$_2$Cl$_2$ at -20 °C. After addition is complete, the solution is

stirred at -20 °C for 1 h, followed by a further hour at room temperature. The solvent is removed *in vacuo* and the residue dissolved in 50 mL of THF. After cooling to -78 °C, the silyltriflate is added dropwise to the aryl lithium (3.50 mmol) in 100 mL of THF at –78 °C.   The resulting solution is stirred at -78 °C for 1 h, room temperature for 1 h, and then quenched with 100 mL of saturated aqueous NH_4Cl.   The aqueous layer is extracted with ether (50 mL x2), dried ($MgSO_4$), and the solvent removed *in vacuo*. The siloxane is purified as stated above.

General procedure for the synthesis of aryl siloxanes using silicon tetrachloride: Lithiated arene (5.00 mmol) is prepared as described above and cooled to -78 °C. The lithiated arene is added *via* cannula to a stirred solution of $SiCl_4$ (10.0 mmol) in 100 mL of THF at -78 °C. The reaction is stirred at -78 °C for 1 h. Dry EtOH (100 mmol) is added *via* syringe and the resulting mixture stirred at room temperature for 15 min. The reaction is quenched with 100 mL of saturated aqueous NH_4Cl. The aqueous layer is extracted with ether (100 mL x2), dried ($MgSO_4$), and the solvent removed *in vacuo*. The siloxane is purified as stated above.

Chapter 3 - Preparation and Palladium-Catalyzed Cross-Coupling of Aryl Triethylammonium (Bis)catechol Silicates With Aryl Halides and Triflates

PART 1: Cross-Coupling of Aryl Bis(catechol) Silicates with Aryl Triflates.

INTRODUCTION

Synthesis and Structure of Bis(catechol) Silicates

Pentacoordinate bis(catechol) silicates (**III-1**) were first synthesized by Frye in 1962.[152] Since that time, studies have elucidated the structural properties and unique reactivity of these compounds and several comprehensive reviews have appeared.[153-157] Bis(catechol)silicates are readily prepared in excellent yields from alcoholic solutions of catechol, phenyl trimethoxysilane, and a variety of amine and tetralkylammonium hydroxide bases (Scheme 1).[152]

Scheme 1

Base: py, Et$_3$N, R$_4$NOH
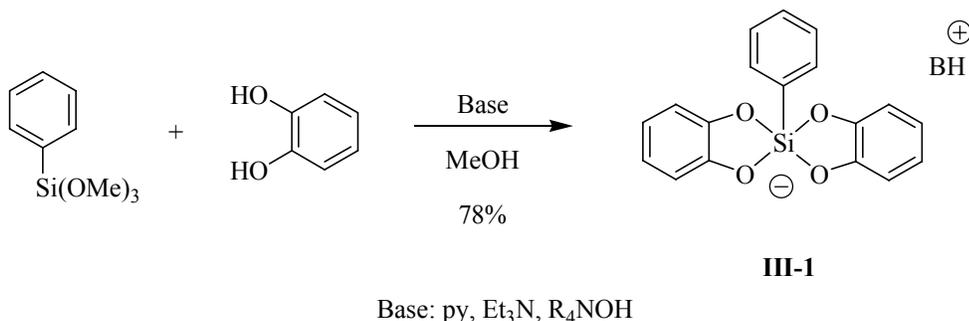
The stability of these compounds is exemplified by the fact that they are prepared in alcohol solvents, despite the opportunity for solvolysis and reversal of the reaction.[152] In fact, these compounds can even be formed in aqueous solutions. Although Frye was able to synthesize a variety of pentacoordinate silicates, the exact structure of these compounds was not known until 1968 when Boer and coworkers were able to obtain a crystal structure.[158] They were able to confirm the proposed distorted trigonal bipyramidal geometry.

Frye has also studied the silicate salts derived from aliphatic 1,2-diols such as bis(pinacol) silicate **III-2**.[159] These compounds proved to be significantly more hydrolytically unstable than the catechol analogues. The aliphatic 1,2-diol silicates could only be formed under anhydrous conditions, and were found to be unstable when exposed to atmospheric moisture.[159] For these reasons, the use of aliphatic 1,2-diol silicates in organic synthesis has been limited.
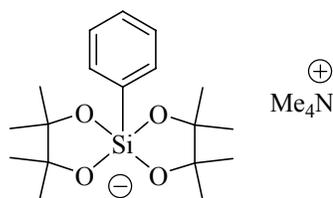
III-2

Tacke and coworkers studied an interesting zwitterionic form of the bis(catechol) silicate.[160,161] Instead of forming a tetraalkylammonium salt, the starting silane **III-3** contains an amino functionality which could be protonated upon formation of the silicate, creating an overall neutral molecule **III-4** (Scheme 2). Tacke has used these zwitterionic silicates **III-4** as traceless linkers in solid phase synthesis.[162]

Scheme 2

III-3   III-4
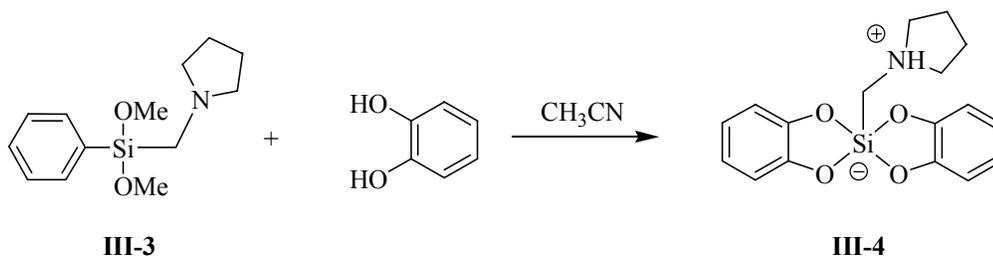
The formation of silicate **III-4** entails a carbon-silicon bond cleavage (phenyl) in order to form the silicate **III-4**. A similar carbon-silicon bond cleavage was observed by Frye when he attempted to synthesize dialkyl hexacoordinate silicates **III-6** from diphenylmethoxysilane (**III-5**) (Scheme 3). Instead, the observed product was pentacoordinate silicate **III-7**. The facile Si-C bond cleavage in these reactions is attributed to the relief of steric strain in the formation of the pentacoordinate species.[152]

Scheme 3

III-5   III-6
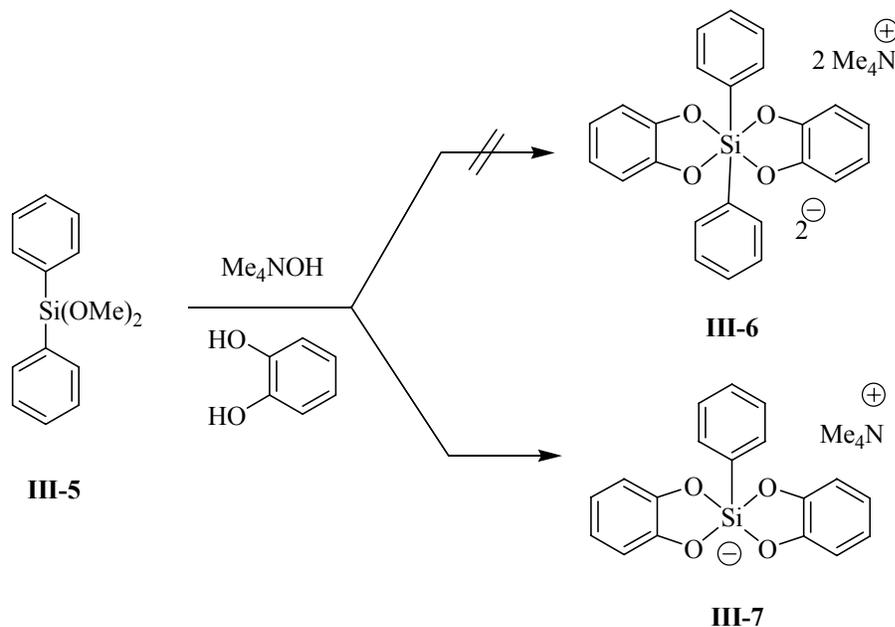
III-7

Reaction Of Bis(catechol) Silicates with Strong Nucleophiles

The reactivity of pentacoordinate silicates with strong nucleophiles has been studied extensively by Corriu.[163-166] When silicate **III-7** is treated with an excess of phenyl magnesium bromide, tetraphenyl silane is rapidly formed. If the number of equivalents of Grignard reagent are reduced, tri-organosilanes can be formed after reduction with a metal hydride (Scheme 4). Mechanistically, these reactions proceed via attack of an anionic nucleophile upon an anionic electrophile; however, the exact mechanistic details have yet to be elucidated.

Scheme 4

III-7
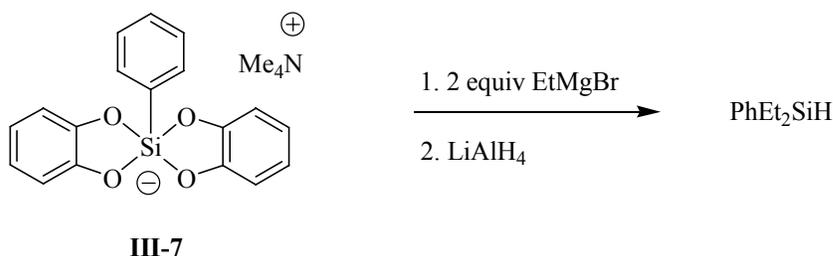
Use of Bis(catechol) Silicates for the Allylation of Aldehydes

Hosomi has reported that allyl bis(catechol) silicates **III-8** are effective aldehyde allylation reagents.[167-169] These allylation reactions allow for the generation of homoallylic alcohols **III-9** in high yield and without the use of a Lewis acid catalyst (Scheme 5). The addition of chiral additives allows the reaction to proceed with moderate enantiomeric excess (54%). Kira and Sakurai were able to effect a similar allylation using pentacoordinate allyl silicates generated *in situ* from allyl trichlorosilane and dilithiocatecholate.[170]

Scheme 5

III-8 → **III-9**

1. benzaldehyde
2. HCl
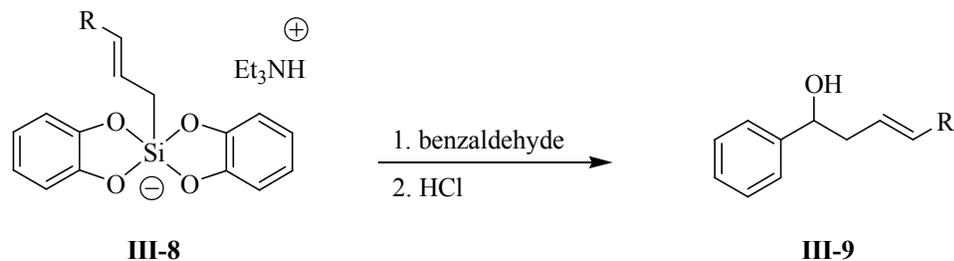
Use of Bis(catechol) Silicates in Palladium-Catalyzed Coupling Reactions

In an example of the use of bis(catechol) silicates in a palladium-catalyzed cross-coupling reaction, Hosomi[171,172] has shown that pentacoordinate alkenylsiliconates **III-8** will couple in good yields with electron deficient aryl iodides (60-84%) and in poor to moderate yields with aryl bromides, triflates, and electron-rich aryl iodides (21-57%) (Scheme 6). In addition to low yields and poor functional group tolerance, these reactions suffered from long reaction times (30-110 hours).

Scheme 6

III-8

+

X= I/Br/OTf

PdCl$_2$(PhCN)$_2$
P(OEt)$_3$
21-84%
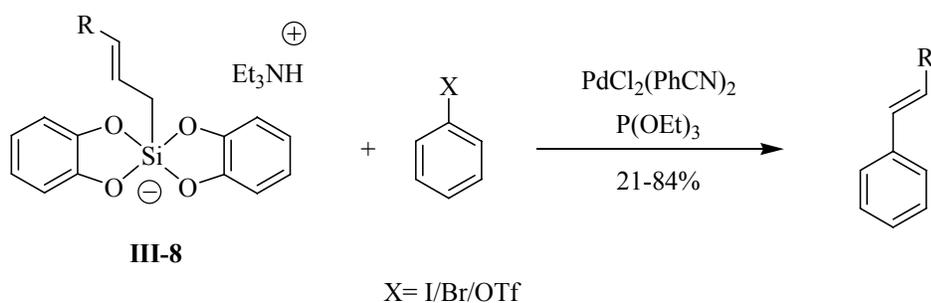
Palladium-Catalyzed Cross-Coupling Methodologies

Palladium-catalyzed cross-coupling reactions of aryl halides or triflates to form unsymmetrical biaryls are one of the most useful tools in synthetic organic chemistry.[3] Several of the most common methods for performing these transformations are the Stille (organostannane),[6-10] Suzuki-Miyaura (organoboron),[15-19] and the Hiyama (organosilicon)[30-36] reactions (Scheme 7). The more established Suzuki-Miyaura and Stille reactions have benefited from high yields and wide functional group tolerances. Despite these advantages, organosilicon reagents have emerged as a viable alternative for the synthesis of unsymmetrical biaryls, due in part to the inherent drawbacks in the Stille and Suzuki-Miyaura methodologies. For example, Stille couplings require the use of toxic organotin reagents; while the boronic acid derivatives utilized in Suzuki couplings can be difficult to synthesize and purify.

Scheme 7

$X = I$
$= Br$
$= Cl$
$= OTf$

$Y = SnBu_3$
$= B(OH)_2$
$= Si(OEt)_3$
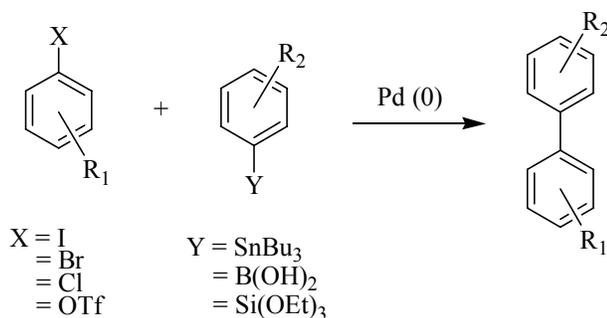
Work in the DeShong group has focused on the use of aryl trialkoxysilanes as alternatives to the organotin and organoboron compounds. These siloxanes can be readily synthesized *via* metalation (Li or Mg) of the corresponding aryl halide followed by nucleophilic attack upon readily available tetraalkylorthosilicates,[56] or through

palladium[58,59] or rhodium[60] catalyzed silylation (Scheme 8). In the presence of a fluoride activator, aryl siloxanes undergo Pd(0)-catalyzed cross-coupling with aryl iodides,[45] bromides,[45,46] and chlorides.[46] In addition, Fu has recently extended this methodology to include couplings with alkyl bromides and iodides.[52]

Scheme 8
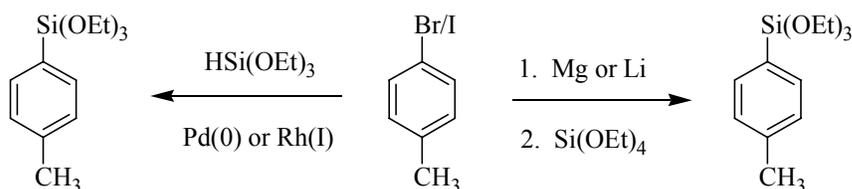
One limitation of the siloxane-based methodology is that aryl siloxanes do not couple efficiently to aryl triflates due to competing hydrolysis of the triflate under the basic reaction conditions. However, the use of aryl triflates is advantageous because they can easily be synthesized from the corresponding phenol and are often more accessible than the analogous aryl halide.[173] Recent studies in our laboratory have demonstrated that siloxane derivatives can be employed for the coupling of aryl triflates under strictly controlled conditions.[51] Nonetheless, we sought to develop new silicon-based reagents that would give better yields and show greater functional group tolerance and synthetic utility than the siloxane based approach. It is within this context we sought to develop a methodology for the efficient cross-coupling of (bis)catechol silicates with aryl triflates. Additionally, we sought to extend the scope of the coupling to electron-rich aryl iodides, substrates that had proven problematic in previous studies by Hosomi.[171]

RESULTS AND DISCUSSION

Aryl (bis)catechol silicates were readily prepared in excellent yields by the reaction of their siloxane counterparts with two equivalents of catechol in the presence of triethylamine (see Table 1). The silicates are white, air stable, crystalline solids that can be recrystallized from methanol-ether or acetonitrile. The salts are freely soluble in warm ethereal solvents (THF, dioxane) and DMF.

Table 1. Synthesis of Triethlyammonium Aryl Bis(catechol) Silicates from Aryl Siloxanes
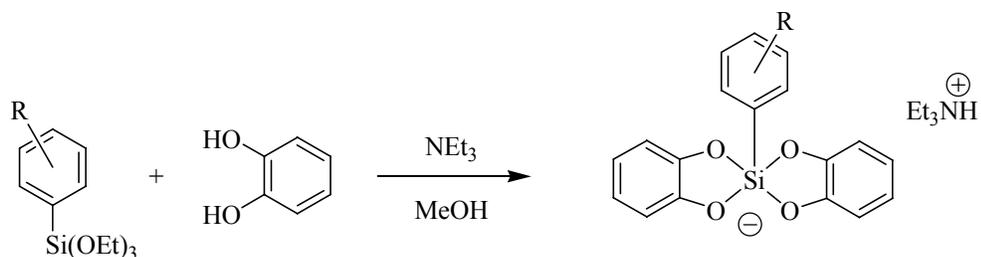
entry	R	yield (%)
1	H	88
2	2-OCH$_3$	82
3	3-OCH$_3$	94
4	4-OCH$_3$	86
5	2-CH$_3$	83
6	3-CH$_3$	90
7	4-CH$_3$	88
8	3,4-methylenedioxy	82
9	4-CO$_2$Et	89

Employing the protocol established in our lab for siloxane couplings, the (bis)catechol silicates did not cross-couple efficiently with aryl bromides (Table 2, entries

1-4) or chlorides (data not shown). With bromides, the yields of coupled product were generally less than 40% and chlorides provided no coupled product. For comparison, the analogous reaction with the aryl trialkoxysilane afforded 90% of the respective unsymmetrical biaryl.[45]

The (bis)catechol silicates coupled successfully with aryl iodides (Table 2, entries 5 and 6). However, the best coupling substrates for the (bis)catechol silicates were aryl triflates (Table 2, entries 7-16). As summarized in Table 2 (entries 9, 14-16), the best conditions for the cross- coupling with anisoyl triflate were 5 mol % palladium catalyst and 5 mol % dicyclohexylphosphinobiphenyl (**III-10**) in refluxing dioxane, although satisfactory yields can be obtained at lower temperatures in refluxing THF.

The success of the biphenyl phosphine **III-10** is attributed to a combination of two factors. The electron-rich nature of the phospine, due to the cyclohexyl substituents, facilitates rapid oxidative addition into the aryl triflate, while at the same time its steric bulk allows it to readily disassociate and facilitate transmetallation with the hypercoordinate silicate species. Employing a similar ligand to **III-10**, di-*tert*-butylphosphinobiphenyl **III-11**,[149] provided only a 23% yield of the cross-coupled product (Table 3, entry 12), providing further evidence that phosphine **III-10** combines the optimal combination of steric and electronic effects to promote the coupling reaction.
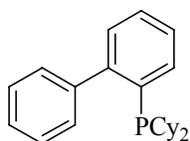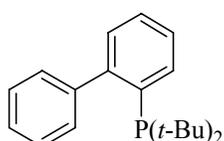
III-10   III-11

Table 2. **Optimization of the Palladium-Catalyzed Cross-Coupling Reaction of Triethylammonium Bis(catechol) Phenyl Silicate with Aryl Triflates.**
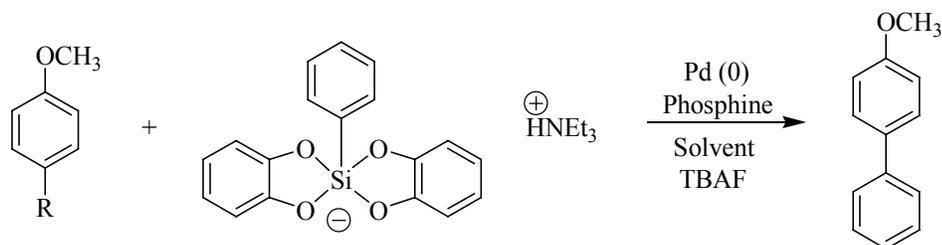
entry	R	silicate complex (equiv)[a]	PdL$_n$ (mol %)	phosphine (mol %)	solvent (temp., °C)	yield (%)
1	Br	2.0	Pd(OAc)$_2$ (10)	PPh$_3$ (20)	DMF (90)	40
2	Br	2.0	Pd(OAc)$_2$ (10)	PPh$_3$ (20)	DMF (150)	40
3	Br	2.0	Pd(dba)$_2$ (10)	**III-10** (10)	DMF (90)	38
4	Br	2.0	Pd(dba)$_2$ (10)	**III-10** (10)	THF (65)	7
5	I	2.0	Pd(OAc)$_2$ (10)	PPh$_3$ (20)	DMF (90)	87
6	I	2.0	Pd(dba)$_2$ (10)	**III-10** (10)	THF (65)	9
7	OTf	2.0	Pd(OAc)$_2$ (10)	PPh$_3$ (20)	DMF (90)	75
8	OTf	2.0	Pd(OAc)$_2$ (10)	PPh$_3$ (20)	THF (65)	0
9	OTf	2.0	Pd(dba)$_2$ (10)	**III-10** (10)	THF (65)	96
10	OTf	2.0	Pd(dba)$_2$ (10)	none	THF (65)	11
11	OTf	2.0	Pd(dba)$_2$ (10)	PPh$_3$ (10)	THF (65)	0
12	OTf	2.0	Pd(dba)$_2$ (10)	**III-11** (10)	THF (65)	23
13	OTf	1.0	Pd(dba)$_2$ (10)	**III-10** (10)	THF (65)	49
14	OTf	1.5	Pd(dba)$_2$ (10)	**III-10** (10)	THF (65)	95
15	OTf	1.5	Pd(dba)$_2$ (5)	**III-10** (5)	THF (65)	93
16	OTf	1.5	Pd(dba)$_2$ (5)	**III-10** (5)	Dioxane (101)	97

[a] For each equivalent of the catechol complex, 1.0 equivalent of TBAF was added.

The poor yields of coupled product obtained in DMF versus THF or dioxane indicate that increasing the polarity of the reaction solvent has an adverse effect upon the reaction. This result can be attributed to the ability of the solvent to coordinate to the palladium and occupy an otherwise vacant coordination site that would be utilized to catalyze the coupling reaction.

Two notable features of this reaction were discovered during the course of the optimization studies. It was found that catechol could be quantitatively recovered from the crude cross-coupling reaction mixture by extraction with aqueous base (1M NaOH), followed by acidification and re-extraction of the aqueous layer. Also, approximately 50% of the phosphine **III-10** could be recovered during chromatographic separation of the reaction products.

Having established that iodides and triflates are effective coupling substrates with aryl (bis)catechol silicates, a systematic investigation of the scope and limitations of the reaction was undertaken. The results summarized in Table 3 indicate that *ortho, meta,* and *para*-substituted electron-rich aryl iodides (entries 1-3) couple with phenyl (bis)catechol silicate with almost equal efficiency. In addition, *meta* and *para*-substituted (bis)catechol silicates were successfully coupled with iodobenzene (Table 3, entries 5 and 6). However, the *ortho* substituted silicate coupled in poor yield. (entry 4). This is most likely due to steric crowding around the silicon atom, which hinders transmetalation of the aryl ring to the palladium. This drastic reduction in yield that occurs with *ortho*-substituted bis(catechol) silicates is not observed with aryl siloxanes. For example, the coupling of *ortho*-methyl siloxane proceeds in 85% yield.[138]

Table 3.   **Palladium-Catalyzed Cross-Couplings of Aryl Triethylammonium Bis(catechol) Silicates with Aryl Iodides.**

entry	Ar-I	Ar	biaryl product	yield (%)
1		phenyl		74
2		phenyl		82
3		phenyl		86
4		2-methoxyphenyl		29
5		3-methoxyphenyl		84
6		4-methoxyphenyl		81

Efficient cross-coupling reactions with aryl triflates is gratifying because previously we had previously found that siloxanes failed to undergo cross-coupling with triflates due to facile hydrolysis of the triflate under the coupling conditions.[45,46] Subsequently, we had reported a revised protocol using silatrane analogues that allows

for cross coupling with electron-rich aryl triflates in fair to good overall yields.[51] The silicate methodology discussed above, however, is more general and consistently gives higher yields of product than the silatrane method.

The analogous study was performed with aryl triflates to evaluate the functional group and steric tolerances of the reaction. The results are summarized in Table 4. The data indicates that this new methodology is applicable to a wide range of aryl triflates. Attempted coupling of very strongly electron-deficient triflates (Table 4, entry 12) proceeded in only moderate yield, with the remainder of the mass balance being 4-nitrophenol (hydrolysis product). Coupling of unprotected 4-aniline triflate was not successful (Table 4, entry 9); however, when the amine was acylated, cross-coupling proceeded in excellent yield (Table 4, entry 7). The inability of the cross-coupling reaction to proceed in the presence of a free amino group is attributed to coordination of the amine to the palladium and poisoning of the catalyst.

Table 4. Coupling of Triethylammonium (Bis)catechol Phenyl Silicate with Aryl Triflates.[a]
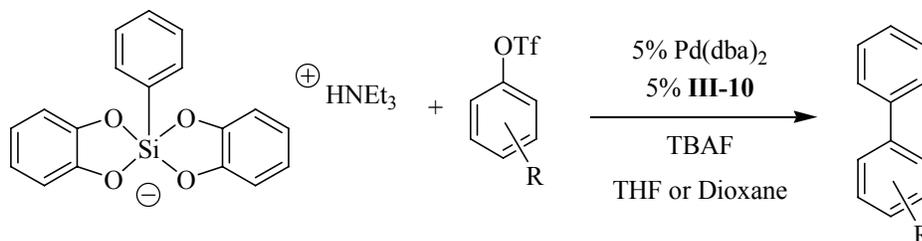
entry	R	yield (%)[b]	bromide[c]
1	4-OCH$_3$	96	88
2	2-OCH$_3$	95	
3	4-CHO	98	
4	4-COCH$_3$	96	86
5	2-COCH$_3$	93	
6	4-CO$_2$CH$_3$	94	93
7	4-NHAc	92	77
8	4-*tert*-butyl	95	
9	4-NH$_2$	0	90
10	4-CN	91	24
11	2-CN	89	
12	4-NO$_2$	46[d]	58
13	1-naphthyl	86	
14	2,6-dimethoxy	0[e] (0)[f]	
15	2-CH$_3$	92	
16	2,6-dimethyl	96[e] (0)[f]	
17	2-methoxy-6-formyl	86[e] (64)[f]	

[a] Reactions were perfomed for 6 hours. [b] Reaction was performed in refluxing THF as solvent unless otherwise noted. [c] Yields are obtained using the corresponding aryl bromide in place of the triflate, coupling to phenyltrimethoxysilane. [d] Remainder of mass balance was hydrolyzed triflate. [e] Yield in refluxing dioxane. [f] Yield in refluxing THF.

Entries 16 and 17 are of particular interest. These di-*ortho* substituted aryl triflates coupled in only moderate yield (Table 4, entry 17), or not at all (entry 16) when the reaction was performed in THF. However, when the reaction was run at a higher temperature (refluxing dioxane), these substrates coupled in excellent yields. This result indicates that it is possible to couple more stericly demanding substrates by switching the solvent to dioxane and performing the reaction at a higher temperature. It is thought that the higher reaction temperature achieved in refluxing dioxane facilitates oxidative addition of the palladium into these hindered systems. This assertion is supported by the fact that at lower temperatures (THF), the triflate is recovered quantitatively (Table 4, entries 14 and 16). However, 2,6-dimethoxyphenyl trifluoromethanesulfonate (Table 4, entry 14) would not couple with the silicate, even in refluxing dioxane. The triflate was recovered quantitatively.

The coupling of (bis)catechol silicates with heteroaryl triflates was also investigated. Palladium-catalyzed cross-coupling reactions of heteroaryl halides with aryl siloxanes proceed in only moderate yields and we were therefore interested to see if we could improve on the yield by employing a coupling between heteroaryl triflates and aryl (bis)catechol silicates.[47,138] The results are presented in Table 5.

The coupling of pyridyl triflates with triethylammonium (bis)catechol phenyl silicate in refluxing dioxane gave the desired cross-coupled products in yields that were comparable to the equivalent heteroaryl bromide/siloxane reactions (Table 5, entries 1 and 2).[46] However, the coupling of unprotected 5-indole trifluoromethanesulfonate (Table 5, entry 3) proceeded in a significantly higher yield than that observed in the

corresponding siloxane reaction.[47]   In addition, the coupling of 2-quinoline trifluoromethanesulfonate (Table 5, entry 4), proceeded in excellent yield.

The scope and limitations of triflate coupling was extended to the highly functionalized triflates shown in Table 6.   The first coupling was 2-tropolone trifluoromethanesulfonate (**III-12**) with (bis)catechol phenyl silicate (Table 6, entry 1). The tropolone ring system is present in the colchicine family of alkaloids and these compounds have shown promise as anti-cancer agents by binding to cellular tubulin.[174] Thus, there is interest in developing novel analogues. Tropolone **III-12** cross coupled in excellent yield with triethylammonium (bis)catechol phenyl silicate to produce the functionalized tropone **III-13**, thus demonstrating the ability to add aryl functionality to the tropolone system.

Table 5. Palladium-Catalyzed Cross-Couplings of Triethylammonium (Bis)catechol Phenyl Silicate with Heteroaryl Triflates.[a]

entry	Ar-OTf	biaryl product	yield[b]	bromide yield[c]
1			73 (51)	76
2			78 (53)	62
3			69 (51)	40
4			91[d]	75

[a] Reactions were run using 1.5 eq. of triethylammonium (bis)catechol phenyl silicate, 1.5 eq. of TBAF, 5 mol % Pd(dba)$_2$, 5 mol % **III-10** in refluxing dioxane for 6 h. [b] Value in parenthesis is the yield obtained in refluxing THF. [c] Bromide yield refers to the coupling of phenyl trimethoxysilane with the corresponding heteroaryl bromide. [d] Reaction run in refluxing THF.

Table 6. Palladium-Catalyzed Cross-Coupling of Triethylammonium (Bis)catechol Phenyl Silicate with Functionalized Triflates.

entry	Ar-OTf	Ar-Ph	yield (%)
1	**III-12**	**III-13**	89[a]
2	**III-14**	**III-15**	90[b]
3	**III-16**	**III-17**	0[c]

[a] Solvent was THF. [b] Solvent was dioxane. [c] Triflate was hydrolyzed under all conditions investigated.

Similarly, the triflate of α-tocopherol **III-14** (vitamin E) was chosen to evaluate the ability of the (bis)catechol silicates to cross couple with highly hindered systems (Table 6, entry 2). When triflate **III-14** was allowed to couple with (bis)catechol phenyl

silicate in refluxing dioxane, the desired cross coupled product **III-15** was obtained in excellent yield. Attempts to couple 5-coumarin trifluoromethanesulfonate (**III-16**) yielded none of the desired cross-coupled product **III-17** (Table 6, entry 3). Instead, the triflate was quantitatively hydrolyzed.

Having demonstrated the scope and limitations of the reaction with various triflate substrates, attention was turned to a systematic investigation of substituent effects on the aryl (bis)catechol silicates. These results are presented in Table 7. In summary, the presence of either electron-rich (Table 7, entries 5 and 6) or electron-deficient (entry 7) substituents on the silicate was well tolerated. The presence of functional groups in the *meta* and *para* positions of the aryl ring did not adversely affect the yields of cross-coupled product. However, when a substituent was present in the *ortho* position, the yield droped dramatically (Table 7, entries 1 and 4). The yield can be improved slightly by performing the reaction at a higher temperature (refluxing dioxane). This outcome is not entirely unexpected as a similar result was obtained in the coupling of the aryl iodides (Table 3, entry 4).

Table 7. **Palladium-Catalyzed Cross-Couplings of Aryl Triethylammonium (Bis)catechol Silicates with Aryl Triflates.**

entry	Ar-OTf	Ar	biaryl product	yield (%)
1	phenyl-OTf	*o*-toluene	biaryl product	40[a] (20)[b]
2	H$_3$CO-phenyl-OTf	*m*-toluene	biaryl product	97
3	H$_3$CO-phenyl-OTf	*p*-toluene	biaryl product	92
4	phenyl-OTf	*o*-anisole	biaryl product	41[a] (21)[b]
5	phenyl-OTf	*m*-anisole	biaryl product	87
6	phenyl-OTf	*p*-anisole	biaryl product	91
7	H$_3$CO-phenyl-OTf	*p*-ethyl benzoate	biaryl product	94
8	H$_3$CO-phenyl-OTf	3,4-methylenedioxybenzene	biaryl product	89

[a] Yield obtained in refluxing dioxane. [b] Yield obtained in refluxing THF.

Another interesting system that would further define the scope of the (bis)catechol silicate coupling technology was the coupling of a heteroaromatic triflate with a

heteroaromatic (bis)catechol silicate. Quinoline-pyridyl moieties are found in multiple natural products such as streptonigrin[175] and camptothecin.[176] We, therefore, designed a template that would probe the feasibility of applying the (bis)catechol silicate coupling technology to these systems. Pyridyl derivative **III-19** is readily available in excellent yield from the respective pyridyl siloxane **III-18** (Scheme 9).[59] Having obtained the desired heteroaromatic (bis)catechol silicate **III-19**, a simple triflate was chosen to probe the feasibility of the coupling reaction. Accordingly, heteroaromatic (bis)catechol silicate **III-19** was coupled with 4-methoxyphenyl trifluromethanesulfonate **III-20** to yield the heteroaromatic biaryl **III-21** in 96% yield (Scheme 5).

Encouraged by the high yield obtained in this reaction, the coupling of 2-quinoline trifluoromethanesulfonate **III-22** with heteroaromatic (bis)catechol silicate **III-19** was attempted (Scheme 5) and we were pleased to find that this coupling proceeded smoothly to produce the quinolopyridine **III-23** in 97% yield. It is anticipated that an analogous coupling reaction will be applicable to the total synthesis of streptonigrin and related substances.

Scheme 9
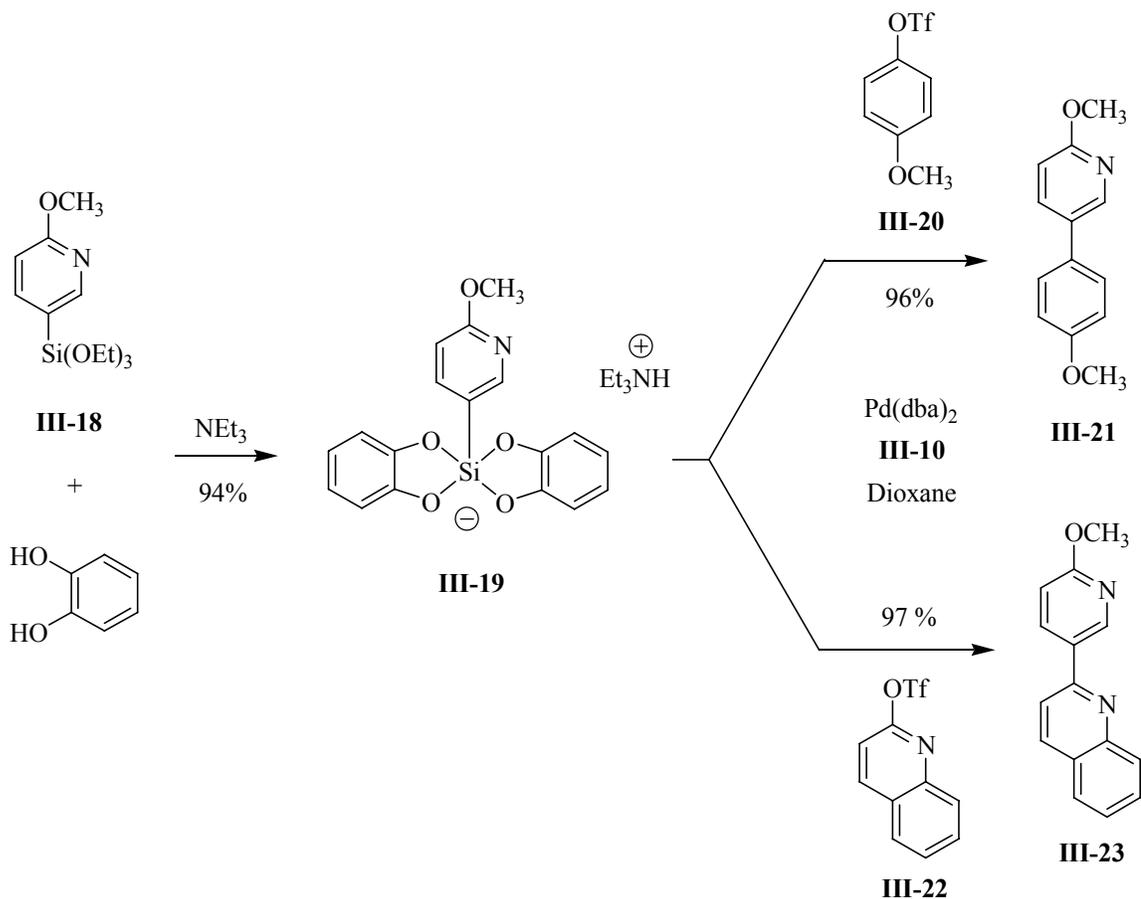
A final feature of the cross-coupling reaction that was investigated was the source of the fluoride activator. For aryl halide substrates, the typical fluoride source in siloxane couplings was tetrabutylammonium fluoride (TBAF) in THF solution (Acros) containing 5% water. However, this reagent induced extensive hydrolysis of triflates derived from phenols bearing strong electron-withdrawing groups (Table 4, entry 12). Accordingly, a variety of alternative fluoride sources was investigated and the results are summarized in Table 8.

Table 8. Effect of Varying the Fluoride Source on Cross-Coupling Efficiency
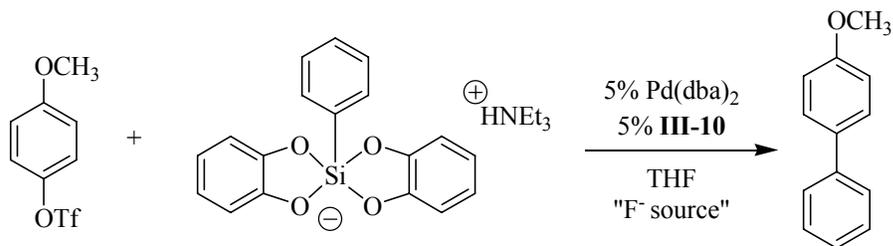
entry	"F⁻ Source"	yield (%)
1	none	0[a]
2	KF	29[a]
3	NaF	0[a]
4	CsF	3[a]
5	LiF	0[a]
6	NaBF$_4$	30[a]
7	TBAF · 3H$_2$O	94
8	TBAF (1.0M in THF)	95
9	TMAF · 3H$_2$O	96
10	TMAF (anhydrous)[b]	74[c]
11	NaOSiMe$_3$	33[a]

[a] Remainder of triflate was unreacted. [b] Commercially available "anhydrous" TMAF contains less than 3 % water. [c] Remainder of triflate was hydrolyzed.

In the absence of a fluoride source, the cross coupling reaction does not occur (entry 1). Alkali fluoride salts were ineffective as fluoride sources for the coupling reactions, most likely caused by their poor solubilities in THF (entries 2-6). TBAF trihydrate, available as a crystalline solid, was as effective as the 1.0 M solution of TBAF

in THF in promoting the cross-coupling reaction (entries 7 and 8). Tetramethylammonium fluoride trihydrate (TMAF) was also found to have similar activity (entry 9). It is interesting to note that the use of anhydrous TMAF actually lowered the yield of the cross-coupling reaction, with the remainder of the triflate undergoing hydrolysis (entry 10). It is plausible that the water present in the hydrated TMAF is serving to moderate the bacicity of the fluoride ion in solution and slow the rate of hydrolysis of the triflate. A similar effect was noticed in the coupling of aryl triflates and nonaflates with silanols,[177] and with phenyl silatrane.[51]

Denmark had previously reported that silanolates were effective promoters in the cross-coupling of organosilanols.[178] However, this reagent was not effective when extended to the coupling of (bis)catechol silicates with aryl triflates (Table 8, entry 11).

CONCLUSION

Aryl siloxanes efficiently couple to aryl iodides, bromides, and chlorides to provide unsymmetrical biaryl derivatives. However, the cross-coupling of aryl triflates to aryl siloxanes has been largely unsuccessful due to hydrolysis of the triflate under the reaction conditions. This study demonstrated that crystalline pentacoordinate aryl (bis)catechol silicates effectively serve as siloxane surrogates and couple to a wide range of aryl and heteroaryl triflates in excellent yields.

Part 2: Palladium-Catalyzed Cross-Coupling of Aryl Triethylammonium Bis(catechol) Silicates with Aryl Bromides Using Microwave Irradiation

INTRODUCTION

Since the first reported use of microwave irradiation to promote a chemical reaction by Gedye in 1986,[179] the use of microwave irradiation has emerged as a valuable method for inducing or accelerating chemical reactions.[180,181] The microwave reactor has evolved from a simple domestic microwave oven, which was prone to explosions and irreproducible results, to complex multimode microwave reactors replete with internal stirring and cooling capabilities. These new reactors allow for the processing of kilograms of material by microwave technology.[181]

Microwave Effects in Chemical Reactions

Microwave assisted reactions are known for their fast reaction times, suppression of side reactions, and higher yields. These effects have been attributed to two different features of microwave reactions: rapid and uniform heating, and specific "microwave effects." These "microwave effects" have been proposed to be due to changes in theromodynamic paramaters under microwave irradiation. For example, it has been proposed that there is a change in the activation energy of a reaction, possibly due to a change in the entropy of the system.[182] Today, the existence of specific microwave effects has been largely discounted. Strauss and coworkers have demonstrated that

reactions conducted under microwave and conventional heating have similar kinetics and the increase in yields and faster reaction times are due to rapid, uniform heating.[182-184]

Choice of solvent plays a key role in microwave reactions. Polar solvents (DMF, DMSO) absorb microwaves efficiently, which in turn leads to rapid heating of the solvent. This thermal energy is then transferred to the reactants. On the other hand, non-polar solvents are transparent to microwaves. When a reaction is carried out in a non-polar solvent (toluene, hydrocarbon), the majority of the microwave energy goes to the reactants. This allows for a more direct flow of energy to the reactants, and may be responsible for the decreased reaction times and higher chemical yields.[185]

Synthetic Applications

Microwave technology has been extended to many different types and classes of reactions. Two of the most popular research areas to employ microwave reactors are solid supported reactions,[186-188] and homogeneous catalysis. Solid supported reactions can suffer from long reaction times, which can be dramatically shortened by using microwave heating.[187] Homogenous catalysis can also suffer from long reaction times and side reactions that reduce overall product yield.[189]

Of the different areas of homogenous catalysis, by far the most well studied using microwave irradiation is the Suzuki cross-coupling reaction. This reaction is of wide scope and conditions have been developed to allow for the coupling of almost any boronic acid with any aryl halide or triflate.[19] The use of microwave irradiation has expanded the scope of the Suzuki reaction by permitting more cost-effective and environmentally friendly reaction conditions.

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Recently, Leadbeater and coworkers have developed conditions for the coupling of aryl bornic acids with aryl chlorides in water using microwave irradiation (Scheme 10).[190] Aryl chlorides are typically difficult substrates for palladium-catalyzed cross-coupling reactions due to their low reativity.[191] In addition, water is usually a poor solvent for these reactions because of the low solubility of the reactants. In this case, the solubility problem was overcome by addition of tetrabutylammonium bromide (TBAB) as a phase transfer reagent. Leadbeater was able to couple a variety of aryl chlorides in moderate to excellent yield using this reaction. For comparison, under thermal conditions, no reaction occurred.[190]

Scheme 10
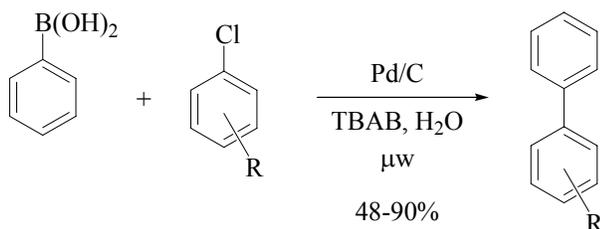
The use of a microwave promoted Suzuki coupling reaction in total synthesis has recently been reported. Zhu has recently completed the total synthesis of the cyclic tripeptide biphenomycin B (**III-24**) using a microwave promoted Suzuki-Miyaura coupling reaction as the key macrolactonization step (Scheme 11).[192] The key couping reaction was conducted intra-molecularly between an aryl iodide and an aryl pinacol boronate ester present in compound **III-25** to form the biaryl linkage of intermediate **III-26**. This approach allowed for the formation of the biaryl linkage with concomitant macrolactonization of the 15-membered macrocycle. In addition, the reaction conditions were tolerant of the protecting groups present in the molecule.
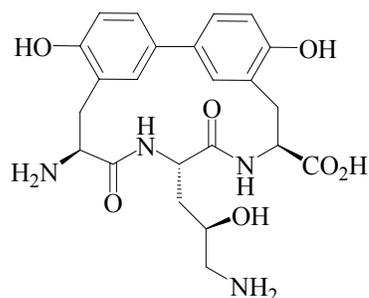
Biphenomycin B (**III-24**)

Scheme 11

III-25   **III-26**
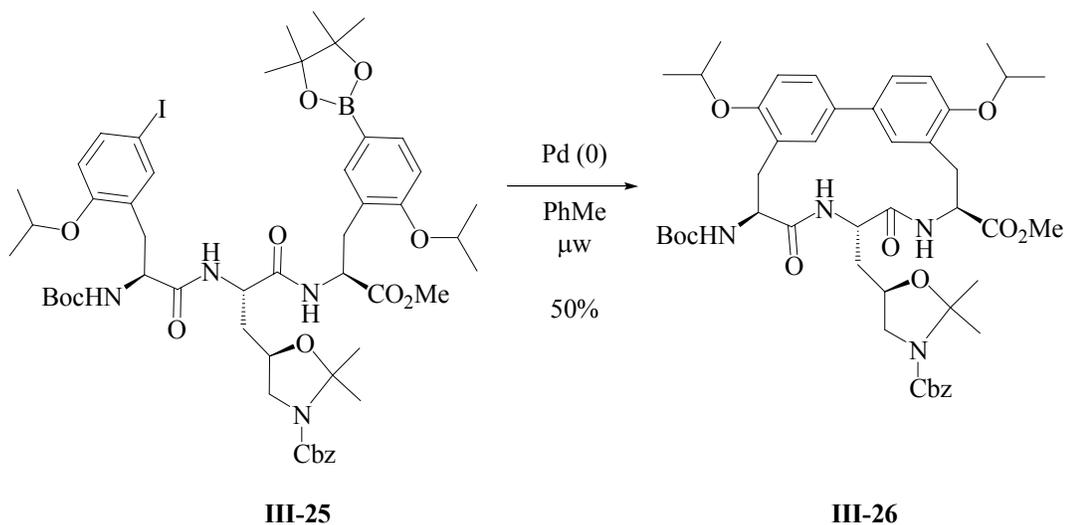
Cross-Coupling of Aryl Bromides with Aryl Bis(catechol) Silicates

Using conventional heating, aryl bis(catechol) silicates **III-27** undergo coupling

with aryl iodides and triflates to provide unsymmetrical biaryl derivatives (Scheme 12).

However, under these reaction conditions, it is not possible to couple aryl bromides in

greater than 40% yield.   In order to circumvent this limitation, we explored the

application of microwave irradiation to the coupling of aryl bromides and aryl

bis(catechol) silicates. It was hoped that microwave irradiation would provide the additional energy required to couple the silicates with the less reactive aryl bromides.

Scheme 12. Cross-Coupling of Aryl Iodides and Triflates

III-27   X=I or OTf
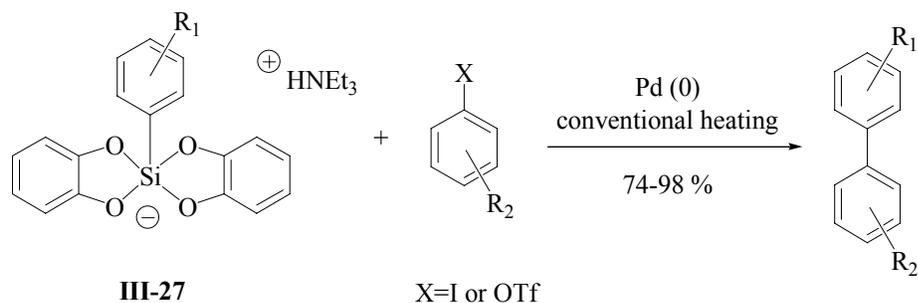
RESULTS AND DISCUSSION

The coupling of silicate **III-28** with bromobenzene under idealized thermal conditions had resulted in the formation of biphenyl in a yield of only 38%. However, under the influence of microwave irradiation, rapid and efficient cross-coupling of aryl bromides was realized (Scheme 13).

Scheme 13

III-28   89%
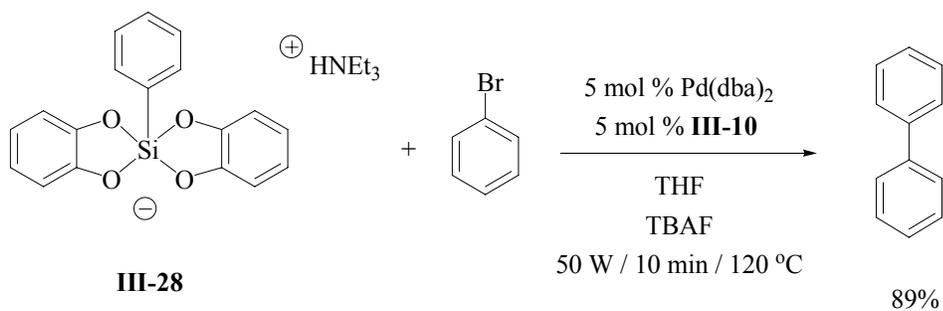
Reaction conditions for this coupling were found to be analogous to the thermal reaction and entailed 5 mol % Pd(dba)$_2$ as the Pd(0) source, 5 mol % dicyclohexyl phosphinobiphenyl (**III-10**) and 1.5 equiv of tetrabutylammonium fluoride (TBAF) in THF (Scheme 13). Exposure of the reaction mixture to microwave irradiation (50 W / 10 min / 120 °C) led to efficient cross-coupling of bromobenzene with triethylammonium phenyl bis(catechol) silicate (**III-28**). In the absence of irradiation, the yield of coupling product under identical conditions was <40%.

Having demonstrated the effectiveness of microwave irradiation for the coupling reaction, the functional group tolerance of substituted aryl bromides was investigated and the results are summarized in Table 9. The data indicates that the reaction is tolerant of both electron-donating (entries 1-5) and electron-withdrawing (entries 8 and 9) functional groups.

In addition, it was possible to couple di-*ortho* substituted aryl bromides demonstrating that even highly hindered biaryls could be realized under these conditions (entry 6). The only functional group that was found to fail in the coupling study was the amino group which gave starting materials back in high yield (entry 10). We attribute the failure of this coupling reaction to poisoning of the catalyst by the amino function. The analogous triflate coupling under thermal conditions had also failed in the presence of free amino groups.

Table 9. Probing the Functional Group Tolerance of the Microwave Assisted

Coupling Reaction
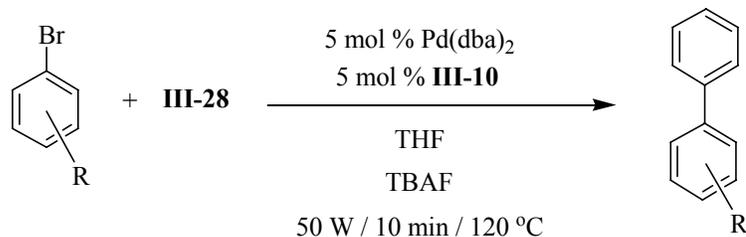
entry	R	yield (%)
1	H	89
2	4-OCH$_3$	81
3	2-OCH$_3$	84
4	4-t-Bu	88
5	2-CH$_3$	86
6	2,6-dimethyl	80
7	1-naphthyl	84
8	4-COCH$_3$	89
9	4-NO$_2$	93
10	4-NH$_2$	0

Once the feasibility of the coupling of simple aryl bromides had been demonstrated, attention turned to the cross-coupling of more complex substrates bearing multiple functional groups. In the less idealized world of natural product synthesis, one can only determine the full scope of the new coupling protocol by investigating these more complex substrates. The results of these investigations are shown in Table 10. As

was observed in the simpler substrates, electron-rich aryl bromides (entries 1-3) couple in good to excellent yields. Particularly noteworthy are the couplings shown in entries 2 and 3 which involved substrates with di-*ortho* substitution. Even though the silicate is bulky, coupling at highly hindered centers occurred.

Table 10. Coupling of Complex Aryl Bromides

$$\text{Aryl Bromide} \quad + \quad \textbf{III-28} \xrightarrow[\substack{\text{THF} \\ \text{TBAF} \\ 50\ \text{W} / 10\ \text{min} / 120\ ^{\circ}\text{C}}]{\substack{5\ \text{mol}\ \%\ \text{Pd(dba)}_2 \\ 5\ \text{mol}\ \%\ \textbf{III-10}}} \text{Biaryl Product}$$
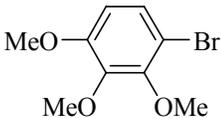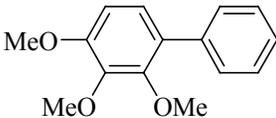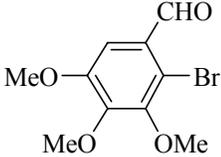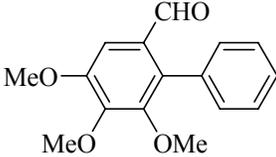
entry	aryl bromide	biaryl product	yield (%)
1			84
2			74
3			79
4			76

Another important achievement of the microwave methodology was the coupling of 5-bromo tropolone with silicate **III-28** (entry 4). Previous studies in our group had found that siloxane and silicate derivatives underwent coupling with this tropolone to provide low yields of biaryl product. The excellent yield of coupling with silicate **III-28**, on the other hand, bodes well for an approach to the natural products colchicine (**III-29**) and allocolchicine (**III-30**) based on this methodology.
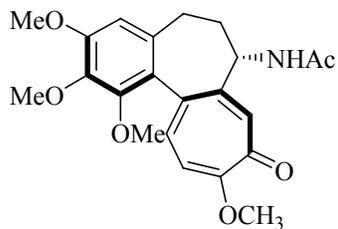
(-)-(aR, 7S)-colchicine (**III-29**)   (-)-(aR, 7S)-allocolchicine (**III-30**)
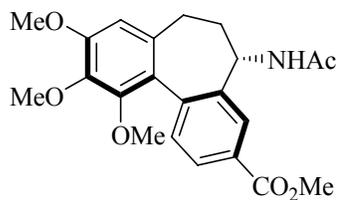
To fully explore the scope and limitations of the coupling reaction, the coupling of a select number of substituted aryl bis(catechol) silicates with aryl bromides was also studied (Table 11). Substituents in the *para-* and *meta-*positions were well tolerated and gave adducts in yields comparable to their unsubstituted counterpart (entries 1, 2, and 5). In addition, electronic effects associated with the substituent did not manifest themselves in either the yields of adduct obtained nor the conditions required to achieve the coupling. However, coupling efficiency was significantly altered when *ortho-*substituents were present on the bis(catechol) silicate (entries 3 and 4). This effect on the yield by *ortho-*substituents was also observed in the thermal coupling of aryl triflates with silicates.

Table 11. Coupling of Substituted Bis(catechol) Silicate Complexes

entry	R₁	R₂	coupled product	yield (%)
1	H	4-OMe		88
2	H	3-OMe		84
3	H	2-OMe		49
4	H	2-Me		47
5	4-OMe	4-CO₂Et		82

CONCLUSIONS AND OUTLOOK

Using microwave irradiation, we have extended the palladium-catalyzed cross-coupling methodology of aryl bis(catechol) silicates to aryl bromides to form unsymmetrical biaryls. Aryl bis(catechol) silicates are particularly attractive reagents for

coupling reactions due to their ease of formation, crystallinity, and stability. These results, combined with our previous coupling studies, provide a valuable resource for the cross-coupling of aryl bromides, iodides, and triflates with aryl bis(catechol) silicates.

Future work with aryl (bis)catechol silicates will entail the use of solid supported reagents such as silicate **III-31** (Scheme 14). This would allow for the possibility of recycling reagents thereby reducing waste. In addition, this technique could allow for the elimination of costly and time consuming chromatographic purification of the biaryl products.

Scheme 14
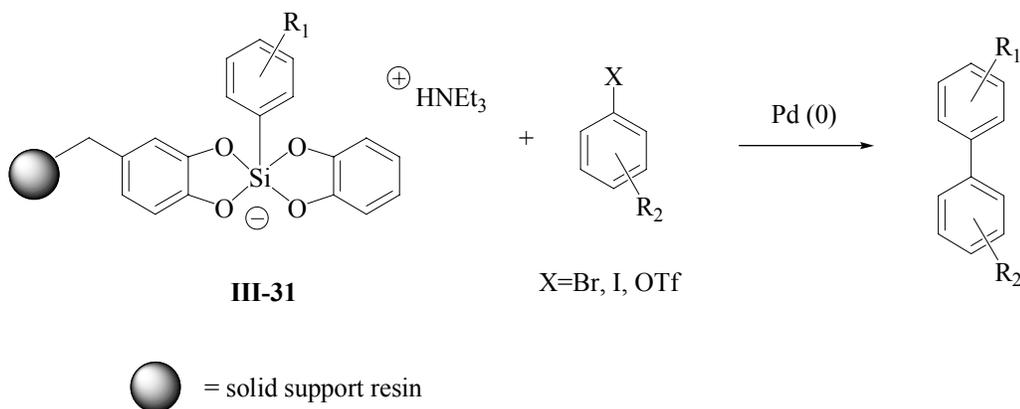
III-31

X=Br, I, OTf

= solid support resin

PART 3: Experimental Section

General Experimental

Thin-layer chromatography (TLC) was performed on 0.25 mm Merck silica gel coated plates treated with a UV-active binder with compounds being identified by UV (254 nm). Flash chromatography was performed using thick walled columns and

medium pressure silica gel (Whatman 200-425 mesh), with column length and diameter being determined by the method of Still.[142]

Melting points were taken in Kimax soft glass capillary tubes using a Thomas-Hoover Uni-Melt capillary melting point apparatus (Model 6406K) equipped with a calibrated thermometer. Melting points above 200 ºC were taken with a Mel-Temp apparatus using a calibrated thermometer. Melting points are corrected.

Samples used for obtaining infrared spectra were either dissolved in carbon tetrachloride or prepared as a potassium bromide pellet. Band positions are reported in reciprocal centimeters (cm^{-1}) and relative intensities are listed as br (broad), s (strong), m (medium), or w (weak).

Nuclear magnetic resonance (^1H, ^{13}C NMR) spectra were recorded at 400 and 200 MHz respectively. Chemical shifts are reported in parts per million (δ) relative to tetramethylsilane (TMS). Coupling constants (J values) are reported in hertz (Hz), and spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet).

Low resolution mass spectrometry (LRMS) and high resolution mass spectrometry (HRMS) data are reported in the form of m/z (intensity relative to base peak = 100). The matrix used for fast atom bombardment (FAB) was ethylene glycol.

Tetrahydrofuran, diethyl ether, and dioxane were distilled from sodium/benzophenone ketyl. Methylene chloride and pyridine were distilled from calcium hydride. Dimethylformamide and triethylamine were distilled from calcium sulfate. Methanol was fractionally distilled from calcium chloride.

2-(Dicyclohexylphosphino)biphenyl and 2-(di-*tert*-butylphosphino)biphenyl were recrystallized from ethanol prior to use Catechol and triphenylphosphine were each recrystallized from hexanes prior to use.

All glassware used in these reactions was either oven dried at 120 ºC for 12 hours or flame dried prior to use. All reactions were conducted under an atmosphere of argon.

Microwave reactions were conducted in a CEM Discover microwave reactor with a circular, single mode, self tuning, microwave applicator operating at 2450 MHz. The reaction vessel was purged with argon prior to use.

All compounds were determined to be >95% pure by ^{1}H NMR or GC analysis, unless otherwise noted. Previously reported compounds were characterized *via* ^{1}H and ^{13}C NMR and IR and compared to literature values. All new compounds were characterized using ^{1}H NMR, ^{13}C NMR, IR, low resolution and high resolution mass spectrometry.

Synthesis and Characterization of Aryl Bis(catechol) Silicates.

Triethylammonium bis(1,2-benzenediolato)phenylsilicate (Table 1 Entry 1). To a maroon colored solution of catechol (13.1 g, 120 mmol) in EtOH (30 mL) was added PhSi(OMe)$_3$ (11.2 mL, 60.0 mmol) and NEt$_3$ (8.36 mL, 60.0 mmol). The reddish-brown solution was stirred for 15 minutes during which time a white precipitate formed. The silicate complex was further precipitated by the addition of 10 mL of ether. The reaction mixture was then filtered and the filter cake was washed with ether to yield a white

powder which was dried under vacuum at 60 °C for two days to give 22.4 g (88 %) of the title compound as a white powder mp 218-220 °C (lit. 220-230 ºC).[152] IR (KBr) 3421 (m), 3064 (w), 3040 (m), 2943 (s), 2802 (m), 2722 (m), 2360 (s), 2329 (s), 1597 (s), 1493 (s), 1359 (s), 1241 (s), 1110 (s), 1014 (s); LRMS (FAB⁻) m/z 321 (M⁻ - HNEt₃, 56), 319 (12), 239 (30), 118 (16), 102 (100), 85 (9); HRMS (FAB⁻, M⁻ - NHEt₃) m/z calcd for $C_{18}H_{13}O_4Si$ 321.0564, found 321.0563. The spectral data (^{1}H, ^{13}C NMR) were identical to those previously reported by Woolins.[193]

General Procedure for the Synthesis and Characterization of

Triethylammonium (Bis)catechol Arylsilicates. To a maroon solution of catechol (1.71 g, 15.5 mmol) in MeOH (10 mL) was added the aryl siloxane (7.40 mmol) and NEt₃ (1.13 mL, 8.10 mmol). The reaction was stirred overnight at room temperature, during which time some precipitation of the arylsilicate occurred. The arylsilicate was further precipitated with 20 mL of ether. The solid was filtered and the filter cake washed with 50 mL of ether. The arylsilicate was dried under vacuum at 60 ºC overnight.

Triethylammonium bis(1,2-benzenediolato)-(2-methoxyphenyl)silicate (Table 1 Entry 2). White crystals 2.75 g (82%) mp 195-199 ºC; IR (KBr) 3426 (m), 3064 (m), 3036 (m), 1487 (s), 1242 (s), 1013 (m), 831 (s); ^{1}H NMR (DMSO-d₆) δ 1.15 (t, *J*=7.6, 9H), 3.07 (q, *J*= 7.6, 6H), 3.27 (s, 3H), 6.44-6.53 (m, 8H), 6.66-6.69 (m, 2H), 7.03-7.08 (m, 2H), 8.8 (br s, 1H); ^{13}C NMR (DMSO-d₆) δ 10.7, 47.6, 56.8, 111.2, 112.0, 118.9, 121.3, 130.2, 134.0, 134.6, 152.8, 163.4; LRMS (FAB⁻) m/z 351 (M⁻ - NHEt₃, 100), 339 (30),

325 (20), 323 (9); HRMS (FAB⁻, M⁻ - HNEt₃) m/z calcd for $C_{19}H_{15}O_5Si$ 351.0689, found 351.0688.

Triethylammonium   bis(1,2-benzenediolato)-(3-methoxyphenyl)silicate   (Table   1, Entry 3).   Precipitation from ether produced a white powder which was recrystallized from methanol to yield colorless needles 3.16 g (94%) mp 219-220 ºC; IR (KBr) 3423 (m), 3095 (s), 3057 (m), 3002 (m), 2936 (m), 2878 (m), 2836 (m), 2733 (w), 1566 (s), 1483 (s), 1407 (s), 1355 (s), 1252 (s), 1107 (m), 1048 (m), 1014 (s), 827 (s); ^{1}H NMR (DMSO-d₆) δ 1.15 (t, J=7.2, 9H), 3.06 (t, J=7.2, 6H), 3.62 (s, 3H), 6.48 (m, 4H), 6.59-6.62 (m, 4H), 6.71-6.74 (m, 1H), 7.06-7.08 (m, 3H), 8.70 (br s, 1H); ^{13}C NMR (DMSO-d₆) δ 9.0, 46.1, 54.9, 110.1, 113.0, 117.9, 121.0, 127.4, 128.2, 143.7, 150.7, 158.4; LRMS (FAB⁻) m/z 351 (M⁻ - NHEt₃, 100), 259 (9); HRMS (FAB⁻, M⁻ - HNEt₃) m/z calcd for $C_{19}H_{15}O_5Si$ 351.0689, found 351.0679.

Triethylammonium   bis(1,2-benzenediolato)-(4-methoxyphenyl)silicate   (Table   1, Entry 4).   White crystals 2.89 g (86%) mp 184-185 °C; IR (KBr) 3430 (m), 3040 (w), 2943 (s), 2831 (s), 2900 (s), 2831 (w), 2730 (s), 2077 (s), 2046 (s), 1910 (s), 1860 (s), 1751 (s), 1596 (s), 1487 (s), 1363 (s), 1246 (s), 1180 (s), 1114 (s), 1017 (s); ^{1}H NMR (DMSO-d₆) δ 1.24 (t, J=7.3, 9H), 3.22 (q, J=7.3, 6H), 3.69 (s, 3H), 6.66-6.74 (m, 10H), 7.54 (d, J=3.2, 2H), 9.51 (br s, 1H); ^{13}C NMR (DMSO-d₆) δ 8.4, 46.2, 54.8, 110.7, 112.8, 118.8, 130.8, 136.6, 149.6, 160.1; LRMS (FAB⁻) m/z 351 (M⁻ - NHEt₃, 40), 251 (100),

138 (30), 122 (26), 46 (22); HRMS (FAB$^+$) (M$^-$ - HNEt$_3$ + Li) m/z calcd for C$_{12}$H$_{15}$O$_5$SiLi 358.0849, found 358.0841.

Triethylammonium bis(1,2-benzenediolato)-(2-methylphenyl)silicate (Table 1, Entry 5). White crystals 2.69 g (83%) mp 194-196 ºC; IR (KBr) 3429 (m), 3029 (s), 3002 (s), 2702 (s), 2536 (m), 2494 (m), 1590 (m), 1486 (s), 1355 (m), 1241 (s), 834 (s); ^{1}H NMR (DMSO-d$_6$) δ 1.15 (t, *J*=8.0, 9H), 2.32 (s, 3H), 3.06 (q, *J*=8.0, 6H), 6.61-6.72 (m, 8H), 6.92-6.95 (m, 2H), 7.00-7.02 (m, 1H), 7.43-7.45 (m, 1H), 9.45 (br s, 1H); ^{13}C NMR (DMSO-d$_6$) δ 8.2, 22.9, 46.1, 110.8, 118.7, 124.0, 128.0, 129.3, 133.8, 140.1, 142.2, 149.5; LRMS (FAB$^-$) m/z 335 (M$^-$ - NHEt$_3$, 100) 153 (10); HRMS (FAB$^-$) (M$^-$ - NHEt$_3$) m/z calcd for C$_{19}$H$_{15}$O$_4$Si 335.0740, found 335.0750.

Triethylammonium bis(1,2-benzenediolato)-(3-methylphenyl)silicate (Table 1, Entry 6). White powder 2.91 g (90%) mp 177-179 ºC; IR (KBr) 3432 (m), 3064 (m), 1490 (s), 1355 (m), 1245 (s), 824 (s); ^{1}H NMR (DMSO-d$_6$) δ 1.14 (t, *J*=7.2, 9H), 2.17 (s, 3H), 3.05 (q, *J*=7.2, 6H), 6.24-6.25 (m, 1H), 6.45-6.50 (m, 4H), 6.58-6.62 (m, 4H), 6.95-7.03 (m, 2H), 7.30-7.33 (m, 2H), 8.95 (br s, 1H); ^{13}C NMR (DMSO-d$_6$) δ 8.7, 21.3, 45.8, 109.8, 117.5, 126.7, 128.4, 131.9, 135.1, 135.3, 141.7, 150.4; LRMS (FAB$^-$) m/z 335 (M$^-$ - NHEt$_3$, 100), 297 (23), 148 (69), 146 (10); HRMS (FAB$^-$, M$^-$ - NHEt$_3$) m/z calcd for C$_{19}$H$_{15}$O$_4$Si 335.0740, found 335.0742.

Triethylammonium bis(1,2-benzenediolato)-(4-methylphenyl)silicate (Table 1, Entry 7). The product was contaminated with a small amount of catechol which could not be separated despite repeated recrystallizations from THF. White crystals 2.85 g (88%) mp 190-194 ºC; IR (KBr) 3431 (m), 3040 (s), 2971 (s), 2809 (m), 2777 (m), 2746 (m), 1600 (m), 1493 (s), 1359 (s), 1238 (s), 1103 (s), 1017 (s), 831 (s); ^{1}H NMR (DMSO-d$_6$) δ 1.14 (t, J=7.2, 9H), 2.18 (s, 3H), 3.05 (q, J=7.2, 6H), 6.22-6.28 (m, 4H), 6.47-6.50 (m, 2H), 6.58-6.61 (m, 2H), 6.94 (d, J=7.6, 2H), 7.41 (d, J=7.6, 2H), 8.87 (br s, 1H); ^{13}C NMR (DMSO-d$_6$) δ 8.7, 21.0, 45.7, 109.0, 109.7, 115.4, 117.4, 127.4, 135.1, 150.5; LRMS (FAB$^-$) m/z 335 (M$^-$ - NHEt$_3$, 100), 243 (9); HRMS (FAB$^-$, M$^-$ - NHEt$_3$) m/z calcd for C$_{19}$H$_{15}$O$_4$Si 335.0740, found 335.0738.

Triethylammonium bis(1,2-benzenediolato)-(3,4-benzodioxole)silicate (Table 1, Entry 8). Precipitation from ether produced a light red solid which was recrystallized from methanol to yield light brown plates 2.84 g (82%) mp 219.0-219.5ºC; IR (KBr) 3430 (m), 3052 (m), 2994 (m), 2877 (m), 2772 (m), 2726 (w), 1479 (s), 1411 (m), 1352 (m), 1246 (s), 1034 (s), 1014 (m), 893 (s), 827 (s); ^{1}H NMR (DMSO-d$_6$) δ 1.14 (t, J=7.2, 9H), 3.05 (t, J=7.2, 6H), 5.85 (s, 2H), 6.48-6.52 (m, 4H), 6.60-6.62 (m, 4H), 6.72 (d, J=7.6, 1H), 6.99 (s, 1H), 7.07 (d, J=7.6, 2H), 8.70 (br s, 1H); ^{13}C NMR (DMSO-d$_6$) δ 9.1, 46.1, 100.2, 107.9, 110.1, 114.9, 117.9, 129.4, 135.3, 146.5, 147.4, 150.7; LRMS (FAB$^-$) m/z 365 (M$^-$ - NHEt$_3$, 100), 298 (9), 148 (45); HRMS (FAB$^-$, M$^-$ - NHEt$_3$) m/z calcd for C$_{19}$H$_{13}$O$_6$Si 365.0481, found 365.0480.

Triethylammonium bis(1,2-benzenediolato)-(4-carboethoxyphenyl)silicate (Table 1, Entry 9). White crystals 3.26 g (89%) mp 230-240 ºC (decomp.); IR (KBr) 3433 (m), 3043 (m), 2981 (m), 2736 (w), 1721 (s), 1486 (s), 1279 (s), 1245 (s), 1089 (m), 1020 (m), 824 (s); ^{1}H NMR (DMSO-d$_6$) δ 1.13 (t, *J*=7.2, 9H), 1.26 (t, *J*=6.8, 3H), 2.99-3.00 (m, 6), 4.24 (q, *J*=6.8, 2H), 6.47-6.50 (m, 4H), 6.59-6.62 (m, 4H), 7.68 (d, *J*=8.0, 2H), 7.71 (d, *J*=8.0, 2H), 8.70 (br, 1H); ^{13}C NMR (DMSO-d$_6$) δ 9.1, 14.2, 45.7, 60.4, 109.9, 115.7, 117.7, 127.3, 129.1, 134.5, 150.1; LRMS (FAB[-]) m/z 393 (M[-] - NHEt$_3$, 100), 320 (11); HRMS (FAB[-], M[-] - NHEt$_3$) m/z calcd for C$_{21}$H$_{17}$O$_6$Si 393.0794, found 393.0791.

Triethylammonium bis(1,2-benzenediolato)-3-(4-methoxy)pyridylsilicate (**III-19**). White powder, recrystallization from methanol yielded white flakes 3.16 g (94%); mp 173-174 ºC; IR (KBr) 3405 (w), 3056 (s), 3013 (s), 2932 (m), 2833 (m), 2730 (m), 1583 (s), 1491 (s), 1355 (s), 1234 (s), 1110 (s), 1020 (s), 819 (s); ^{1}H NMR (DMSO-d$_6$) δ 1.15 (t, *J*=7.1, 9H), 3.10 (q, *J*=7.1, 6H), 3.73 (s, 3H), 6.19-6.25 (m, 4H), 6.48-6.50 (m, 2H), 6.58-6.63 (m, 2H), 7.71-7.74 (m, 2H), 8.22 (s, 1H), 8.89 (br s, 1H); ^{13}C NMR (DMSO-d$_6$) δ 10.1, 47.2, 54.2, 111.4, 116.7, 119.2, 147.5, 151.7, 153.5, 155.1, 165.1; LRMS (FAB[-]) m/z 352 (M[-] - NHEt$_3$, 100), 169 (60); HRMS (FAB[-], M[-] - NHEt$_3$) m/z calcd for C$_{18}$H$_{14}$O$_5$NSi 352.0641, found 352.0648.

General Procedures for the Synthesis and Characterization of Aryl Triflates.

Method A. In a modified procedure of Ritter,[173] triflic anhydride (3.10 g, 11.0 mmol) was added dropwise to the corresponding phenol (10.0 mmol) in pyridine (10.0 mL) at 0 °C and stirred for 10 minutes at 0 °C. The reaction was then allowed to stir at room temperature for 12 h. The solution was diluted with 25 mL of ether and extracted with a 1M solution of $CuSO_4$ (25 mL x3). The organic layer was then washed with water (25 mL), dried ($MgSO_4$), and concentrated *in vacuo*. The aryl triflate was then purified *via* silica gel chromatography.

Method B. Triflate was prepared according to a modified procedure of Barf.[194] Phenyl trifluromethanesulfonamide (3.09 g, 11.0 mmol), triethylamine (1.57 mL, 11.0 mmol) and the corresponding phenol (10.0 mmol) were combined in 20 mL of CH_2Cl_2 and stirred at room temperature for 12 h. The solution was then poured into 50 mL of water and extracted twice with 50 mL of CH_2Cl_2. The organic layer was dried ($MgSO_4$), and concentrated *in vacuo*. The aryl triflate was then purified *via* silica gel chromatography.

Method C. The following is a modified procedure of Genet.[195] 4-aminophenol (545 mg, 5.00 mmol) and triethylamine (0.715 mL, 5.00 mmol) were added to CH_2Cl_2 (20 mL) and stirred at room temperature for 30 minutes. The solution was cooled to -40 °C and trifluoromethanesulfonyl chloride (840 mg, 5.00 mmol) in 3 mL of CH_2Cl_2 was added over 10 minutes. The resulting solution was stirred at -40 °C for 30 min, followed by 1 hour at room temperature. Diethyl ether was added (50 mL) and the mixture was

filtered. The filtrate was washed with brine (50 mL), dried (MgSO$_4$), and evaporated. The triflate was then purified *via* silica gel chromatography.

4-Methoxyphenyl trifluoromethanesulfonate (Table 4, Entry 1). Triflate was prepared according to method A. Column chromatography (4:1 hexane/EtOAc, TLC R$_f$ = 0.49) yielded 2.26 g of a pale yellow oil (94%); ^{13}C NMR (CDCl$_3$) δ 55.4, 114.0, 119.0 (q, J_{CF} = 322), 122.2, 143.0, 159.1. The spectral data (IR, ^{1}H NMR) were identical to those previously reported by Stille.[196]

2-Methoxyphenyl trifluoromethanesulfonate (Table 4, Entry 2). Triflate was prepared according to method A. Column chromatography (4:1 hexane/EtOAc, TLC R$_f$ = 0.46) yielded 1.99 g of a colorless oil (83%); ^{13}C NMR (CDCl$_3$) δ 56.2, 113.36, 119.0 (q, J_{CF} = 321), 121.0, 122.6, 129.5, 139.0, 151.6. The spectral data (IR, ^{1}H NMR) were identical to those previously reported by Cabri.[197]

4-Phenylcarbaldehyde trifluoromethanesulfonate (Table 4, Entry 3). Triflate was prepared according to method A. Column chromatography (4:1 hexane/EtOAc, TLC R$_f$ = 0.46) yielded 2.05 g of a white solid mp 140-142 °C (86%); IR (CCl$_4$) 2826 (m), 2791 (w), 2729 (m), 1714 (s), 1593 (s), 1500 (m), 1438 (s), 1210 (s), 1141 (s), 886 (s); ^{1}H NMR (CDCl$_3$) δ 7.51 (m, 2H), 8.01-8.04 (m, 2H), 10.06 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 118.7 (q, J_{CF} = 320), 123.3, 131.6, 135.8, 153.0, 190.1; LRMS (EI$^+$) m/z 254 (M$^+$, 80),

253 (12), 189 (100), 161 (10), 95 (18), 69 (10), 65 (25); HRMS (EI$^+$) m/z for C$_8$H$_4$O$_4$F$_3$S calcd 252.9782, found 252.9790.

4-Acetylphenyl trifluoromethanesulfonate (Table 4, Entry 4) is commercially available from Aldrich.

2-Acetylphenyl trifluoromethanesulfonate (Table 4, Entry 5). Triflate was prepared according to method A. Column chromatography (4:1 hexane/EtOAc, TLC R$_f$ = 0.33) yielded 2.30 g of a pale yellow oil (91%); ^{13}C NMR (CDCl$_3$) δ 29.3, 118.2 (q, J_{CF} = 319), 122.9, 128.9, 131.1, 132.0, 134.0, 146.9, 196.9; LRMS (EI$^+$) m/z 268 (M$^+$, 35), 253 (100), 189 (10), 120 (75), 107 (17), 92 (39), 77 (28), 69 (39), 63 (23), 43 (19); HRMS (EI$^+$) m/z calcd for C$_9$H$_7$O$_4$F$_3$S 268.0017, found 268.0027. The spectral data (IR, ^{1}H NMR) were identical to those previously reported by Cabri.[197]

4-Carbomethoxyphenyl trifluoromethanesulfonate (Table 4, Entry 6). Triflate was prepared according to method A. Column chromatography (4:1 hexane/EtOAc, TLC R$_f$ = 0.51) yielded 2.55 g of a colorless oil (95%); The spectral data (IR, ^{1}H and ^{13}C NMR) were identical to those previously reported by DeShong.[198]

4-Acetamidophenyl trifluoromethanesulfonate (Table 4, Entry 7).   Triflate was prepared according to method A.   Crude compound was isolated as a red solid.

Recrystallization from toluene yielded 2.46 g of colorless needles (92%) mp 125.5-126.0

ºC (lit. 120-124 ºC);[199] IR (KBr) 3306 (s), 3202 (w), 3130 (w), 3081 (w), 3040 (w), 2795

(w), 1673 (s), 1535 (s), 1428 (s), 1221 (s), 1138 (s) 896 (s); ^{1}H NMR (DMSO) δ 2.06 (s,

3H), 7.41 (d, J=8.1, 2H), 7.72 (d, J=8.1, 2H). 10.23 (s, 1H); ^{13}C NMR (DMSO) δ 24.0,

118.3 (q, J_{CF} = 322), 120.3, 121.8, 139.7, 144.0, 168.7; LRMS (EI$^+$) m/z 283 (M$^+$, 51),

150 (33), 108 (100), 43 (34); HRMS (EI$^+$) m/z for $C_9H_9O_4NF_3S$ calcd 284.0204, found

284.0202.

4-*tert*-Butyl phenyl trifluoromethanesulfonate (Table 4, Entry 8).   Triflate was

prepared according to method A.   Column chromatography (19:1 hexane/EtOAc, TLC R$_f$

= 0.52) yielded 2.32 g of a colorless oil (87%); IR (CCl$_4$) 3064 (w), 2967 (s), 2905 (m),

2867 (m), 1504 (s), 1424 (s), 1214 (s), 1145 (s), 889 (s); ^{13}C NMR (CDCl$_3$) δ 31.3, 34.8,

118.7 (q, J_{CF} = 319), 120.9, 123.8, 127.3, 147.7, 151.8; LRMS (EI$^+$) m/z 282 (M$^+$, 15),

267 (100), 175 (20), 134 (11), 91 (17); HRMS (EI$^+$) m/z for $C_{11}H_{13}O_3F_3S$ calcd

282.0538, found 282.0534. The spectral data (^{1}H NMR) was identical to that previously

reported by Zhu.[200]

4-Aminophenyl trifluoromethanesulfonate (Table 4, Entry 9).   Triflate was prepared

according to method C. Column chromatography (1:1 hexane/EtOAc, TLC R$_f$ = 0.52)

yielded 1.04 g of a light brown oil (92%); IR (CCl$_4$) 3496 (m), 3402 (m), 3054 (w), 3023

(w), 1618 (m), 1545 (m), 1504 (s), 1421 (s), 1252 (m), 1214 (s), 1145 (s), 889 (s); ^{1}H

NMR (CDCl$_3$) δ 3.58 (br s, 2H), 6.56 (d, J=8.8, 2H), 7.99 (d, J=8.8, 2H); ^{13}C NMR

(CDCl$_3$) δ 115.6, 118.6 (q, J_{CF} = 320), 122.3, 141.6, 147.2; LRMS (EI+) m/z 241 (M$^+$, 40), 108 (100), 80 (15); HRMS m/z calcd for C$_7$H$_6$O$_3$NF$_3$S 241.0020 found 241.0018.

4-Cyanophenyl trifluoromethanesulfonate (Table 4, Entry 10). Triflate was prepared according to method A. Column chromatography (4:1 hexane/EtOAc, TLC R$_f$ = 0.43) yielded 1.98 g of a colorless oil (84%); IR (CCl$_4$) 3105 (w), 3074 (w), 2236 (s), 1600 (s), 1504 (s), 1421 (s), 1245 (s), 1210 (s), 1155 (s), 882 (s); ^{13}C NMR (CDCl$_3$) δ 113.2, 117.3, 118.5 (q, J_{CF} = 320), 122.9, 134.9, 152.3. The spectral data (^{1}H NMR) was identical to that previously reported by Cabri.[197]

2-Cyanophenyl trifluoromethanesulfonate (Table 4, Entry 11). Triflate was prepared according to method A. Column chromatography (4:1 hexane/EtOAc, TLC R$_f$ = 0.40) yielded 2.35 g of a colorless oil (77%); ^{13}C NMR (CDCl$_3$) δ 107.4, 113.8, 118.7 (q, J_{CF} = 319), 122.8, 123.6, 129.2, 134.6, 135.2, 149.8; LRMS (EI$^+$) m/z 251 (M$^+$, 55), 187 (35), 159 (100), 139 (11), 90 (45), 69 (85), 63 (15); HRMS (EI$^+$) m/z for C$_8$H$_4$O$_3$NF$_3$S calcd 250.9864, found 250.9869. The spectral data (IR, ^{1}H NMR) were identical to those previously reported by Cabri.[197]

4-Nitrophenyl trifluoromethanesulfonate (Table 4, Entry 12). Triflate was prepared according to method A. Column chromatography (4:1 hexane/EtOAc, TLC R$_f$ = 0.56)

yielded 2.45 g of a white solid (96%) mp 51.0-51.9 °C (lit. 50.5-52 °C).[198] The spectral

data (IR, ^{1}H and ^{13}C NMR) were identical to those previously reported by DeShong.[198]

1-Naphthyl trifluoromethanesulfonate (Table 4, Entry 13). Triflate was prepared

according to method A. Column chromatography (19:1 hexane/EtOAc, TLC R_f = 0.36)

yielded 2.11 g of a colorless oil (81%). The spectral data (IR, ^{1}H and ^{13}C NMR) were

identical to those previously reported by DeShong.[198]

2,6-Dimethoxyphenyl trifluoromethanesulfonate (Table 4, Entry 14). Triflate was

prepared according to method A. Column chromatography (4:1 hexane/EtOAc, TLC R_f =

0.39) yielded 2.54 g of a colorless oil (94%). The spectral data (IR, ^{1}H and ^{13}C NMR)

were identical to those previously reported by Saa.[201]

2-Methylphenyl trifluoromethanesulfonate (Table 4, Entry 15). Triflate was prepared

according to method A. Column chromatography (19:1 hexane/EtOAc, TLC R_f = 0.49)

yielded 1.86 g of a colorless oil (83%); ^{13}C NMR (CDCl$_3$) δ 118.9 (q, J_{CF} = 318), 121.4,

123.7, 128.5, 131.1, 132.4, 148.8. The spectral data (IR, ^{1}H NMR) were identical to those

previously reported by Cabri.[197]

2,6-Dimethylphenyl trifluoromethanesulfonate (Table 4, Entry 16). Triflate was

prepared according to method A. Column chromatography (4:1 hexane/EtOAc, TLC R_f

= 0.66) yielded 2.07 g of a colorless oil (87%). The spectral data (IR, ^{1}H and ^{13}C NMR) were identical to those previously reported by Saa.[202]

2-Formyl-6-methoxyphenyl trifluoromethanesulfonate (Table 4, Entry 17).   Triflate was prepared according to method A. Column chromatography (4:1 hexane/EtOAc, TLC R_f = 0.26) yielded 2.36 g of white crystals (88%) mp 37.9-38.5 ºC (lit. 36-38 ºC);[202] IR (CCl_4) 3023 (w), 2964 (w), 2947 (m), 2888 (w), 2843 (m), 2757 (w), 1704 (s), 1583 (s), 1486 (s), 1431 (s), 1221 (s), 1148 (s), 1076 (s), 882 (s). The spectral data (^{1}H and ^{13}C NMR) were identical to those previously reported by Saa.[202]

2-Pyridyl trifluoromethanesulfonate (Table 5, Entry 1).   Triflate was prepared according to method A. Triflate was isolated in 96% yield (2.03 g) and 97% purity (GC) without purification as a colorless oil; ^{13}C NMR ($CDCl_3$) δ 118.9 (q, J_{CF} = 320), 115.4, 124.6, 141.4, 148.9, 156.2. The spectral data (IR, ^{1}H NMR) were identical to those previously reported by Umemoto.[203]

3-Pyridyl trifluoromethanesulfonate (Table 5, Entry 2).   Triflate was prepared according to method A. Column chromatography (4:1 hexane/EtOAc, TLC R_f = 0.30) yielded 1.88 g of a colorless oil (89%); IR (CCl_4) 3064 (w), 1593 (s), 1569 (s), 1466 (s), 1428 (s), 1228 (s), 1165 (s), 1141 (s), 893 (s); ^{1}H NMR ($CDCl_3$) δ 7.43-7.46 (m, 1H), 7.66-7.69 (m, 1H), 8.64-8.67 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 118.9 (q, J_{CF} = 319), 124.9,

129.2, 143.1, 147.1, 149.8; LRMS (EI$^+$) m/z 228 (M$^+$, 10), 227 (100), 163 (32), 94 (18), 66 (44), 39 (31); HRMS (EI$^+$) m/z for C$_6$H$_5$O$_3$NF$_3$S calcd 227.9942, found 227.9939.

5-Indole trifluoromethanesulfonate (Table 5, Entry 3). Triflate was prepared according to method B. Column chromatography (4:1 hexane/EtOAc, TLC R$_f$ = 0.24) yielded 1.89 g of a colorless oil (76%); IR (CCl$_4$) 3489 (s), 1428 (s), 1221 (s), 1145 (s), 1100 (s), 941 (s), 879 (s); ^{1}H NMR (CDCl$_3$) δ 6.49 (s, 1H), 6.98-7.01 (m, 1H), 7.15-7.21 (m, 2H), 7.49 (s, 1H), 8.26 (br s, 1H); ^{13}C NMR (CDCl$_3$) δ 103.1, 112.1, 112.8, 114.8, 118.6 (q, J_{CF} = 318), 126.9, 128.0, 129.5, 134.6, 143.6; LRMS (EI$^+$) m/z 265 (M$^+$, 67), 132 (100), 104 (64); HRMS (EI$^+$) m/z for C$_9$H$_6$O$_3$NF$_3$S calcd 265.0020, found 265.0019.

2-Quinolyl trifluoromethanesulfonate (**III-22**). Triflate was prepared according to method A. Triflate was isolated in 97% yield (2.53 g) and 98% purity (GC) without purification as a pale yellow oil; ^{13}C NMR (CDCl$_3$) δ 113.1, 118.8 (q, J_{CF} = 320), 127.8, 128.8, 131.3, 142.1, 145.9, 153.8 The spectral data (IR, ^{1}H NMR) were identical to those previously reported by Stille.[196]

Phenyl trifluoromethanesulfonate (Table 7 Entries 1,4-6). Triflate was prepared according to method A. Column chromatography (4:1 hexane/EtOAc, TLC R$_f$ = 0.63) yielded 1.79 g of a colorless oil (85%). The spectral data (IR, ^{1}H and ^{13}C NMR) were identical to those previously reported by DeShong.[198]

2-[(Trifluoromethyl)sulfonyl)oxy]-2,4,6-cycloheptatrienone (III-12). Triflate was prepared according to method A. Column chromatography (1:1 hexane/EtOAc, TLC R_f = 0.34) yielded 1.52 g of a yellow oil (64%). The spectral data (IR, ^{1}H and ^{13}C NMR) were identical to those previously reported by Stille.[204]

α-Tocopherol trifluoromethanesulfonate (III-14). Triflate was prepared according to method A. Column chromatography (pentane, TLC R_f = 0.44) yielded 4.78 g of a viscous colorless oil (85%); IR (CCl$_4$) 2957 (s), 2929 (s), 2867 (m), 1466 (m), 1421 (m), 1404 (s), 1380 (m), 1221 (s), 1145 (s), 1111 (w), 1035 (w), 879 (m); ^{1}H NMR (CDCl$_3$) δ 0.84-0.87 (m, 13H), 1.07-1.54 (m, 23H), 1.72-1.80 (m, 2H), 2.10 (s, 3H), 2.19 (s, 3H), 2.22 (s, 3H), 2.57-2.59 (m, 2H); ^{13}C NMR (CDCl$_3$) δ 12.0, 13.2, 14.0, 19.7, 19.8, 20.7, 21.0, 22.7, 22.8, 23.9, 24.5, 24.9, 28.0, 32.8, 32.9, 37.3, 37.4, 37.5, 39.4, 75.7, 77.4, 118.5, 119.0 (q, J_{CF} = 321), 124.4, 126.7, 128.1, 139.7, 151.0; LRMS (FAB$^+$) m/z 562 (M$^+$, 6), 429 (60), 428 (15), 337 (16), 297 (64), 203 (22), 165 (100), 149 (44), 55 (34), 43 (33); HRMS (FAB$^+$) m/z calcd for C$_{30}$H$_{49}$O$_4$F$_3$S 562.3304, found 562.3303.

4-Trifluoromethanesulfonyloxy coumarin (III-16). Triflate was prepared according to method A. Filtration through a short pad of silica gel yielded 2.59 g of pale yellow crystals (88%) mp 59.5-60.9 °C (lit. 59-60 °C);[205] ^{13}C NMR (CDCl$_3$) δ 105.9, 113.9, 117.4, 118.6 (q, J_{CF} = 320), 122.6, 125.3, 134.2, 153.5, 157.2, 159.6; LRMS (EI$^+$) m/z 294 (M$^+$, 76) 202 (100), 133 (98), 116 (11), 105 (70), 92 (31), 69 (92), 63 (24), 51 (18);

HRMS (EI$^+$) m/z calcd for $C_{10}H_5O_4F_3S$ 293.9807, found 293.9798. The spectral data (IR, ^{1}H NMR) were identical to those previously reported by Wattanasin.[205]

General Procedure for the Palladium-Catalyzed Cross-Coupling of

Pentacoordinate Aryl (Bis)catechol Silicates. Aryl triflate (1.00 mmol), catechol complex (1.50 mmol), Pd(dba)$_2$ (0.0500 mmol), and dicyclohexyl phosphinobiphenyl (0.0500 mmol) were combined in a 50 mL round bottom flask equipped with a magnetic stir bar and placed under argon. THF was added *via* syringe (10 mL), followed by 1.50 mmol of TBAF (1.0 M solution in THF). The deep red-brown solution was subjected to one freeze-pump-thaw cycle followed by heating at reflux for 6 h. The crude reaction mixture was diluted with ether (50 mL), and poured into 50 mL of an aqueous 1.0 M NaOH solution. The aqueous layer was then washed twice with 50 mL of ether. The combined ethereal extracts were dried (MgSO$_4$), and evaporated *in vacuo*. The coupled products were purified *via* column chromatography.

4-Methoxybiphenyl (Table 4, Entry 1). Column chromatography (19:1 hexanes/EtOAc, TLC R$_f$ = 0.32) yielded 175 mg of a white solid (95%) mp 87.0-87.5 °C (lit. 87.5 °C).[198] The spectral data (IR, ^{1}H and ^{13}C NMR) were identical to those previously reported by DeShong.[198]

2-Methoxybiphenyl (Table 4, Entry 2). Column chromatography (19:1 hexanes/EtOAc, TLC R_f = 0.37) yielded 175 mg of a colorless oil (95%). The spectral data (IR, [^1]H and [^13]C NMR) were identical to those previously reported by Buchwald.[149]

4-Phenylbenzaldehyde (Table 4, Entry 3).   Column chromatography (4:1 hexanes/EtOAc, TLC R_f = 0.49) yielded of a yellow solid.   Recrystallization from petroleum ether yielded 179 mg of a white powder (98%) mp 60.5-61.0 ºC (lit. 60-61°C);[206] IR (CCl$_4$) 3064 (w), 3029 (w), 2822 (w), 2726 (w), 1707 (s), 1604 (m), 1549 (m), 1210 (w), 1165 (w). The spectral data (IR, [^1]H and [^13]C NMR) were identical to those previously reported by Leadbeater.[206]

4-Acetylbiphenyl (Table 4, Entry 4).   Column chromatography (9:1 hexanes/EtOAc, TLC R_f = 0.31) yielded 188 mg of a white solid (96%) mp 119.0-119.4 °C (lit. 119.0-119.5 °C).[198] The spectral data (IR, [^1]H and [^13]C NMR) were identical to those previously reported by DeShong.[198]

2-Acetylbiphenyl (Table 4, Entry 5).   Column chromatography (9:1 hexanes/EtOAc, TLC R_f = 0.43) yielded 183 mg of a slight yellow oil (93%). The spectral data (IR, [^1]H and [^13]C NMR) were identical to those previously reported by Clive.[207]

4-Carbomethoxybiphenyl (Table 4, Entry 6). Column chromatography (19:1 hexanes/EtOAc, TLC R_f = 0.32) yielded 197 mg of a white solid (93%) mp 115-116 ºC (lit. 116-117 °C);[198] ^{13}C NMR (CDCl$_3$) δ 52.1, 127.1, 127.3, 128.1, 128.8, 128.9, 130.1, 140.0, 145.6, 167.0. The spectral data (IR, ^{1}H NMR) were identical to those previously reported by DeShong.[198]

N-**Acetyl-4-aminobiphenyl** (Table 4, Entry 7). Column chromatography (1:1 hexanes/EtOAc, TLC R_f = 0.27) yielded 195 mg of a white solid (92%) mp 152-153 ºC (lit. 150-153 °C).[149] The spectral data (IR, ^{1}H and ^{13}C NMR) were identical to those previously reported by Buchwald.[149]

4-*tert*-Butylbiphenyl (Table 4, Entry 8). Column chromatography (pentane, TLC R_f = 0.36) yielded 200 mg of a white solid (95%) mp 49-50 ºC (lit. 47-49 ºC).[149] The spectral data (IR, ^{1}H and ^{13}C NMR) were identical to those previously reported by Buchwald.[149]

4-Cyanobiphenyl (Table 4, Entry 10). Column chromatography (1:1 hexanes/EtOAc, TLC R_f = 0.40) yielded 163 mg of a white solid (91%) mp 85.6-86.2 ºC (lit. 86-87 ºC);[149] IR (CCl$_4$) 3064 (w), 3033 (w), 2232 (m), 1545 (m). The spectral data (^{1}H and ^{13}C NMR) were identical to those previously reported by Buchwald.[149]

2-Cyanobiphenyl (Table 4, Entry 11). Column chromatography (9:1 hexanes/EtOAc, TLC R_f = 0.32) yielded 160 mg of a pale yellow oil (89%); IR (CCl$_4$) 3067 (w), 3036 (w), 2933 (w), 2853 (w), 2229 (m), 1480 (m). The spectral data (^{1}H and ^{13}C NMR) were identical to those previously reported by Lemaire.[208]

4-Nitrobiphenyl (Table 4, Entry 12). Column chromatography (4:1 hexanes/EtOAc, TLC R_f = 0.20) yielded 97.6 mg of a white solid (49%) mp 114-115 ºC (lit. 113-115 °C);[209] IR (CCl$_4$) 3064 (w), 3036 (w), 1600 (m), 1552 (m), 1521 (s), 1476 (w), 1341 (s). The spectral data (^{1}H and ^{13}C NMR) were identical to those previously reported by Novak.[209]

1-Phenylnapthalene (Table 4, Entry 13). Column chromatography (pentane, TLC R_f = 0.42) yielded 176 mg of a colorless oil (86%); LRMS (EI$^+$) m/z 204 (M$^+$, 100), 203 (74), 188 (20), 29 (50), 18 (90); HRMS (EI$^+$) m/z calcd for C$_{16}$H$_{12}$ 204.0939, found 204.0948. The IR and ^{1}H NMR were identical to those reported by DeShong.[198] The ^{13}C NMR was identical to that reported by Bergbreiter.[210]

2-Methylbiphenyl (Table 4, Entry 15). Column chromatography (pentane, TLC R_f = 0.57) yielded 155 mg of a colorless oil (92%). The spectral data (IR, ^{1}H and ^{13}C NMR) were identical to those previously reported by DeShong.[198]

2,6-Dimethylbiphenyl (Table 4, Entry 16).   Reaction was run in refluxing dioxane. Column chromatography (pentane, TLC R_f = 0.47) yielded 175 mg of a colorless oil (96%); IR (CCl$_4$) 3029, (w), 2992 (w), 2950 (w), 2916 (w), 2829 (w), 1611 (m), 1500 (m), 1241 (m), 1176 (w), 1045 (w). The spectral data (^{1}H and ^{13}C NMR) were identical to those previously reported by Buchwald.[149]

2-Methoxy-6-formyl-biphenyl (Table 4, Entry 17).   Reaction was run in refluxing dioxane. Column chromatography (19:1 hexanes/EtOAc, TLC R_f= 0.23) yielded 183 mg of a pale yellow oil (86%); IR (CCl$_4$) 3064 (w), 3033 (w), 3005 (w), 2960 (w), 2933 (w), 2864 (w), 2833 (w), 2746 (w), 1694 (s), 1593 (m), 1576 (m), 1469 (m), 1259 (s), 1065 (m), 910 (m); ^{1}H NMR (CDCl$_3$) δ 3.77 (s, 3H), 7.18 (d, J=8.4, 1H), 7.31-7.33 (m, 2H), 7.42-7.46 (m, 4H), 7.62 (d, J=7.6, 1H), 9.73 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 56.0, 115.8, 119.0, 127.9, 128.0, 128.7, 131.0, 133.1, 134.9, 135.4, 157.0, 192.5; LRMS (EI$^+$) m/z 212 (M$^+$, 100), 211 (50), 197 (19), 180 (25), 169 (27), 152 (26), 139 (28), 115 (18); HRMS (EI$^+$) m/z calcd for C$_{14}$H$_{12}$O$_2$ 212.0837, found 212.0831.

2-Phenylpyridine (Table 5, Entry 1).   Column chromatography (4:1 hexanes/EtOAc, TLC R_f = 0.39) yielded 77.6 mg of a pale yellow oil (50%); IR (CCl$_4$) 3088 (w), 3067 (m), 3037 (w), 3009 (w), 1580 (s), 1566 (s), 1466 (s), 1445 (s), 1424 (m). The spectral data (^{1}H and ^{13}C NMR) were identical to those previously reported by Furukawa.[211]

3-Phenylpyridine (Table 5, Entry 2). Column chromatography (4:1 hexanes/EtOAc, TLC R_f = 0.24) yielded 82.2 mg of a yellow oil (53%); IR (CCl$_4$) 3095 (w), 3061 (w), 3029 (w), 2929 (w), 2853 (w), 1476 (m), 1455 (m), 1411 (s), 1007 (m); ^{13}C NMR (CDCl$_3$) δ 123.5, 127.1, 128.1, 129.1, 134.3, 136.6, 137.8, 148.3, 148.4; LRMS m/z (EI$^+$) 155 (M$^+$, 100), 154 (39), 127 (11), 76 (15), 63 (9), 43 (23); HRMS (EI$^+$) m/z for C$_{11}$H$_9$N calcd 155.0735, found 155.0725. The spectral data (^{1}H NMR) was identical to that previously reported by Sakamoto.[212]

5-Phenylindole (Table 5, Entry 3). Column chromatography (4:1 hexanes/EtOAc, TLC R_f = 0.24) yielded 147 mg of a light brown oil (76%); IR (CCl$_4$) 3485 (m), 3067 (w), 3029 (w), 907 (m); ^{1}H NMR (CDCl$_3$) δ 6.56 (s, 1H), 7.10-7.12 (m, 1H), 7.27-7.44 (m, 5H), 7.64 (d, J=7.6, 2H), 7.85 (s, 1H), 7.99 (br s, 1H); ^{13}C NMR (CDCl$_3$) δ 102.8, 111.3, 119.2, 121.8, 124.9, 126.3, 127.3, 128.3, 128.6, 133.3, 135.2, 142.5; LRMS (FAB$^+$) m/z 194 (M$^+$, 100), 193 (70), 165 (10); HRMS (FAB$^+$) m/z calcd for C$_{14}$H$_{11}$N 193.0891, found 193.0900.

2-Phenylquinoline (Table 5, Entry 4). Column chromatography (9:1 hexanes/EtOAc, TLC R_f = 0.36) yielded 187 mg of a white solid (91%) mp 82.0-83.0 °C (lit. 82.0-82.5 °C);[213] IR (CCl$_4$) 3061 (m), 3033 (m), 1604 (m), 1552 (s). The spectral data (^{1}H and ^{13}C NMR) were identical to those previously reported by Miyaura.[213]

2′-Methyl-4-methoxybiphenyl (Table 7, Entry 1). Column chromatography (4:1 hexanes/CH$_2$Cl$_2$, TLC R$_f$ = 0.27) yielded 39.7 mg of a colorless oil (20%); IR (CCl$_4$) 3064 (w), 3002 (w), 2954 (w), 2933 (w), 2909 (w), 2840 (w), 1614 (w), 1545 (s), 1248 (m); LRMS (FAB$^+$) m/z 198 (M$^+$, 24), 133 (22), 89 (35), 73 (35), 45 (35); HRMS (FAB$^+$) m/z calcd for C$_{14}$H$_{14}$O 198.1045, found 198.1052. The spectral data (^{1}H and ^{13}C NMR) were identical to those previously reported by Lipshutz.[214]

3′-Methyl-4-methoxybiphenyl (Table 7, Entry 2). Column chromatography (4:1 hexanes/EtOAc, TLC R$_f$ = 0.47) yielded 192 mg of a white solid (97%) mp 52.0-53.2 °C (lit. 54 °C);[215] IR (CCl$_4$) 3057 (w), 3033 (w), 2995 (w), 2957 (w), 2936 (w), 2840 (w), 1614 (s), 1514 (s), 1252 (s), 1170 (m), 1038 (m); ^{13}C NMR (CDCl$_3$) δ 21.6, 55.3, 114.1, 123.8, 127.4, 127.6, 128.2, 128.6, 133.9, 138.3, 140.8, 159.0; LRMS (FAB$^+$) m/z 198 (M$^+$, 100), 184 (5), 183 (5); HRMS (FAB$^+$) m/z calcd for C$_{14}$H$_{14}$O 198.1045, found 198.1036. The spectral data (^{1}H NMR) was identical to that previously reported by Rao.[215]

4′-Methyl-4-methoxybiphenyl (Table 7, Entry 3). Column chromatography (19:1 hexanes/EtOAc, TLC R$_f$ = 0.40) yielded 182 mg of a white solid (92%) mp 107.4-108.1 °C (lit. 105-107 °C);[216] IR (CCl$_4$) 3064 (w), 3019 (w), 2957 (w), 2919 (w), 2857 (w), 1462 (w), 1448 (w); ^{13}C NMR (CDCl$_3$) δ 21.1, 55.3, 114.1, 126.6, 128.0, 129.4, 133.7, 136.3, 138.0, 158.9. The spectral data (^{1}H NMR) was identical to that previously reported by Roth.[216]

3-Methoxybiphenyl (Table 7, Entry 5). Column chromatography (19:1 hexanes/EtOAc, TLC R_f = 0.21) yielded 160 mg of a colorless oil (87%); IR (CCl$_4$) 3064 (m), 3033 (m), 3005 (w), 2957 (m), 2940 (m), 2833 (m), 1604, (s), 1569 (s), 1480 (s), 1424 (m), 1293 (m), 1214 (s), 1176 (m), 1058 (m); ^{13}C NMR (CDCl$_3$) δ 55.1, 112.6, 112.6, 112.9, 119.6, 127.2, 127.4, 128.7, 129.7, 141.1, 142.7, 159.9; LRMS (EI$^+$) m/z 184 (M$^+$, 100), 154 (22), 141 (46), 139 (18), 115 (42); HRMS (EI$^+$) m/z calcd for C$_{13}$H$_{12}$O 184.0888, found 184.0884. The spectral data (^{1}H NMR) was identical to that previously reported by Nielson. [217]

2′-Methoxy-biphenyl-4-carboxylic acid ethyl ester (Table 7, Entry 7). Column chromatography (4:1 hexanes/EtOAc, TLC R_f = 0.53) yielded 241 mg of a white solid (94%) mp 104.5-105.0 °C (lit. 105 °C);[218] IR (CCl$_4$) 3040 (w), 2985 (w), 2957 (w), 2933 (w), 2874 (w), 2833 (w), 1718 (s), 1604 (m), 1500 (m), 1462 (w), 1276 (s), 1245 (m), 1183 (m), 1107 (m), 1045 (m). The spectral data (^{1}H and ^{13}C NMR) were identical to those previously reported by Gosmimi.[219]

5-(4-Methoxy-phenyl)-1,3-benzodioxole (Table 7, Entry 8). Column chromatography (19:1 hexanes/EtOAc, TLC R_f = 0.24) yielded a sticky white solid. The solid was recrystallized from Et$_2$O/hexanes to yield 176 mg of colorless plates (89%) mp 95.6-96.2 ºC (lit 95-96 ºC);[220] IR (CCl$_4$) 3071 (w), 3040 (w), 3006 (w), 2961 (m), 2930 (m), 2888 (w), 2833 (w), 2775 (w), 1611 (m), 1480 (s), 1256 (s), 1218 (s), 1183 (m), 1045 (s), 945

(m). The spectral data (^{1}H and ^{13}C NMR) were identical to those previously reported by Bannwarth.[220]

2-Phenylcyclohepta-2,4,6-triene-1-one (**III-13**).   Column chromatography (4:1 hexanes/EtOAc, TLC R_f = 0.27) yielded 162 mg of a slightly yellow solid (89%) mp 83.5-84.2 ºC (lit. 84.5-85.5 ºC);[221] IR (CCl$_4$) 3065 (w), 3030 (w), 2930 (w), 2850 (w), 1632 (m), 1595 (s); ^{13}C NMR (CDCl$_3$) δ 128.1, 128.4, 129.1, 133.3, 133.7, 135.3, 136.5, 139.9, 142.4, 152.6, 186.6; LRMS (EI$^+$) m/z 182 (M$^+$, 25), 181 (100), 154 (56), 153 (38), 76 (15); HRMS (EI$^+$) m/z calcd for C$_{13}$H$_{10}$O 183.0732, found 182.0727. The spectral data (^{1}H NMR) was identical to that previously reported by Mann.[222]

Phenyl-α-tocopherol (III-15).   Column chromatography (pentane, TLC R_f = 0.35) yielded 442 mg of a viscous, colorless oil (90%); IR (CCl$_4$) 3085 (w), 3057 (w), 3026 (w), 2957 (s), 2926 (s), 2864 (s), 1562 (m), 1459 (m) 1155 (m), 1103 (s); ^{1}H NMR (CDCl$_3$) δ 0.84-0.87 (m, 14H), 1.07-1.60 (m, 21H), 1.80 (m, 3H), 1.86 (s, 3H), 1.90 (s, 3H), 2.15 (m, 1H), 2.19 (s, 3H), 2.61-2.65 (m, 2H), 7.12 (m, 2H), 7.30 (t, J=8.0, 1H), 7.38 (t, J=8.0, 2H); ^{13}C NMR (CDCl$_3$) δ 11.9, 16.7, 17.7, 19.7, 20.8, 22.6, 22.7, 24.0, 24.5, 24.8, 27.9, 32.7, 37.4, 37.5, 39.4, 75.0, 116.6, 121.7, 126.1, 128.1, 130.1, 130.2, 131.6, 133.1, 133.4, 142.7, 150.7; LRMS (FAB$^+$) m/z 490 (M$^+$, 19), 265 (11), 225 (100), 223 (18), 55 (16); HRMS (FAB$^+$) m/z calcd for C$_{35}$H$_{54}$O 490.4175, found 490.4176.

5-(4-Methoxybenzene)-2-methoxypyridine (III-21).   Column chromatography (19:1 hexanes/EtOAc, TLC R_f = 0.26) yielded 207 mg of a white solid (96%) mp 75.0-75.9 ºC; IR (CCl$_4$) 3043 (m), 3016 (m), 2981 (m), 2847 (m), 2902 (m), 2840 (m), 1604 (s), 1486 (s), 1373 (m), 1290 (s), 1279 (s), 1245 (s), 1172 (m), 1055 (m), 1020 (m); ^{1}H NMR (CDCl$_3$) δ 3.85 (s, 3H), 3.97 (s, 3H), 6.79 (d, J=12.0, 1H), 6.98 (d, J=8.0, 2H), 7.45 (d, J=8.0, 2H), 7.73-7.76 (m, 1H), 8.34 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 53.5, 55.4, 110.7, 114.4, 127.7, 129.8, 130.4, 137.2, 144.5, 159.1, 163.2; LRMS (FAB$^+$) m/z 216 (M$^+$, 100), 215 (30); HRMS (FAB$^+$) m/z calcd for C$_{13}$H$_{14}$O$_2$N 216.1025, found 216.1033.

5-(2-Quinoyl)-2-methoxypyridine (III-23).   Column   chromatography   (9:1 hexanes/EtOAc, TLC R_f = 0.31) yielded 229 mg of a white solid (97%) mp 78.5-79.0 ºC; IR (CCl$_4$) 3067 (w), 3040 (w), 3016 (w), 2981 (w), 2947 (w), 2905 (w), 2850 (w), 1604 (s), 1490 (s), 1390 (m), 1286 (m), 1020 (m); ^{1}H NMR (CDCl$_3$) δ 4.03 (s, 3H), 6.90 (d, J=8.4, 1H), 7.53 (m, 1H), 7.73 (m, 1H), 7.82 (d, J=8.4, 2H), 8.13 (d, J=8.8, 1H), 8.21 (d, J=8.8, 1H), 8.47-8.50 (m, 1H), 8.91 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 54.3, 111.6, 118.7, 126.8, 127.6, 128.0, 129.4, 130.1, 130.4, 137.5, 138.5, 146.7, 148.8, 155.3, 165.4; LRMS (EI$^+$) m/z 236 (M$^+$, 100), 235 (79), 207 (33), 192 (22); HRMS (EI$^+$) m/z calcd for C$_{15}$H$_{12}$ON$_2$ 236.0950, found 236.0940.

General Procedure for the Palladium-Catalyzed Cross-Coupling Reaction of Aryl Bromides with Aryl (Bis)catechol Silicates Using Microwave Irradiation: Aryl bromide (1.00 mmol), aryl bis(catechol) silicate (1.50 mmol), Pd(dba)$_2$ (0.0500 mmol)

and dicyclohexylphosphinobiphenyl (0.0500 mmol) were combined in a microwave tube

with a magnetic stir bar. The microwave tube was sealed with a septum and 5 mL of

THF was added, followed by TBAF (1.0 M in THF, 1.50 mmol). The reaction was

stirred briefly to dissolve the reagents and placed into the microwave reactor. The

reaction was then heated to a set temperature of 120 °C (100 W) for 10 min. The tube

was removed from the reactor and the contents filtered through a short plug (2 cm) of

silica gel (CH$_2$Cl$_2$ elutant). The solvent was removed *in vacuo* and the biaryl product

purified via column chromatography.

Biphenyl (Table 9, Entry 1)**.** Column chromatography (TLC R$_f$ = 0.54, pentane) yielded

137 mg of a white solid (89%) mp 69-71 °C (lit. 69-70°C). The ^{1}H and ^{13}C NMR and IR

match that reported by Koza.[223]

4-Methoxybiphenyl (Table 9, Entry 2). Column chromatography (19:1 hexanes/EtOAc,

TLC R$_f$ = 0.32) yielded 149 mg of a white solid (81%) mp 87.0-87.5 °C (lit. 87.5 °C).[198]

The spectral data (IR, ^{1}H and ^{13}C NMR) were identical to those previously reported by

DeShong.[198]

2-Methoxybiphenyl (Table 9, Entry 3). Column chromatography (19:1 hexanes/EtOAc,

TLC R$_f$ = 0.37) yielded 154 mg of a colorless oil (84%). The spectral data (IR, ^{1}H and

^{13}C NMR) were identical to those previously reported by Buchwald.[149]

4-*tert*-Butylbiphenyl (Table 9, Entry 4). Column chromatography (pentane, TLC R_f = 0.36) yielded 185 mg of a white solid (88%) mp 49-50 ºC (lit. 47-49 ºC).[149] The spectral data (IR, ^{1}H and ^{13}C NMR) were identical to those previously reported by Buchwald.[149]

2-Methylbiphenyl (Table 9, Entry 5). Column chromatography (19:1 hexanes/EtOAc, TLC R_f = 0.32) yielded 145 mg of a white solid (86%) mp 87.0-87.5 °C (lit. 87.5 °C).[198] The spectral data (IR, ^{1}H and ^{13}C NMR) were identical to those previously reported by DeShong.[198]

2,6-Dimethylbiphenyl (Table 9, Entry 6). Column chromatography (pentane, TLC R_f = 0.47) yielded 146 mg of a colorless oil (80%); IR (CCl_4) 3029, (w), 2992 (w), 2950 (w), 2916 (w), 2829 (w), 1611 (m), 1500 (m), 1241 (m), 1176 (w), 1045 (w). The spectral data (^{1}H and ^{13}C NMR) were identical to those previously reported by Buchwald.[149]

1-Phenylnapthalene (Table 9, Entry 7). Column chromatography (pentane, TLC R_f = 0.42) yielded 172 mg of a colorless oil (84%); LRMS (EI[+]) m/z 204 (M[+], 100), 203 (74), 188 (20), 29 (50), 18 (90); HRMS (EI[+]) m/z calcd for $C_{16}H_{12}$ 204.0939, found 204.0948. The IR and ^{1}H NMR were identical to those reported by DeShong.[198] The ^{13}C NMR was identical to that reported by Bergbreiter.[210]

4-Acetylbiphenyl (Table 9, Entry 8). Column chromatography (9:1 hexanes/EtOAc, TLC R_f = 0.31) yielded 175 mg of a white solid (89%) mp 119.0-119.4 °C (lit. 119.0-119.5 °C).[198] The spectral data (IR, ^{1}H and ^{13}C NMR) were identical to those previously reported by DeShong.[198]

4-Nitrobiphenyl (Table 9, Entry 9). Column chromatography (4:1 hexanes/EtOAc, TLC R_f = 0.20) yielded 185 mg of a white solid (93%) mp 114-115 °C (lit. 113-115 °C);[209] IR (CCl$_4$) 3064 (w), 3036 (w), 1600 (m), 1552 (m), 1521 (s), 1476 (w), 1341 (s). The spectral data (^{1}H and ^{13}C NMR) were identical to those previously reported by Novak.[209]

3-Methoxybiphenyl (Table 11, Entry 2). Column chromatography (19:1 hexanes/EtOAc, TLC R_f = 0.21) yielded 155 mg of a colorless oil (84%); IR (CCl$_4$) 3064 (m), 3033 (m), 3005 (w), 2957 (m), 2940 (m), 2833 (m), 1604, (s), 1569 (s), 1480 (s), 1424 (m), 1293 (m), 1214 (s), 1176 (m), 1058 (m); ^{13}C NMR (CDCl$_3$) δ 55.1, 112.6, 112.6, 112.9, 119.6, 127.2, 127.4, 128.7, 129.7, 141.1, 142.7, 159.9; LRMS (EI$^+$) m/z 184 (M$^+$, 100), 154 (22), 141 (46), 139 (18), 115 (42); HRMS (EI$^+$) m/z calcd for C$_{13}$H$_{12}$O 184.0888, found 184.0884. The spectral data (^{1}H NMR) was identical to that previously reported by Nielson. [217]

4′-Methoxy-biphenyl-4-carboxylic acid ethyl ester (Table 11, Entry 5). Column chromatography (4:1 hexanes/EtOAc, TLC R_f = 0.53) yielded 210 mg of a white solid

(82%) mp 104.5-105.0 °C (lit. 105 °C);[218] IR (CCl$_4$) 3040 (w), 2985 (w), 2957 (w), 2933 (w), 2874 (w), 2833 (w), 1718 (s), 1604 (m), 1500 (m), 1462 (w), 1276 (s), 1245 (m), 1183 (m), 1107 (m), 1045 (m). The spectral data (^{1}H and ^{13}C NMR) were identical to those previously reported by Gosmimi.[219]

2,3,4-Trimethoxybiphenyl (Table 10, Entry 1). Column chromatography (TLC R$_f$ = 0.31, 9:1 Hexanes/EtOAc) yielded a yellow oil which was recrystallized (hexane) to give 205 mg of a white solid (84%) mp 47.2-47.9 °C (lit. 46-47 °C). The ^{1}H, and ^{13}C NMR, and IR match that reported by Banwell.[224]

2,3,4-Trimethoxy-6-carbaldehyde-biphenyl (Table 10, Entry 2). Column chromatography (TLC R$_f$ = 0.24, 9:1 hexanes/EtOAc) yielded 202 mg of a white solid (74%) mp 91.2-92.4 °C. IR (CCl$_4$) 3085 (w) 3067 (w), 3009 (w), 2960 (m), 2933 (m), 2857 (m), 1683 (s), 1587 (m), 1328 (s), 1193(m), 1141 (s), 1096 (s); ^{1}H NMR (CDCl$_3$) δ 3.59 (s, 3H), 3.94 (s, 3H), 3.99 (s, 3H), 7.30-7.35 (m, 3H), 7.42-7.43 (m, 2H), 9.63 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 56.6, 61.4, 61.5, 105.6, 110.2, 127.5, 128.1, 123.3, 128.4, 129.9, 130.1, 131.4, 133.2, 191.8; LRMS (FAB$^+$) m/z 273 (M$^+$ + H, 100), 272 (80), 255 (42), 230 (24), 214 (19), 151 (18), 135 (24), 119 (25), 85 (29), 55 (34), 43 (25); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{16}$H$_{16}$O$_4$ 272.1049, found 272.1045.

2,3,4-Trimethoxy-6-carbomethoxy-biphenyl (Table 10, Entry 3)**.** Column chromatography (TLC R_f = 0.31, 4:1 hexanes/EtOAc) yielded 239 mg of a white solid (79%) mp 67.2-67.8 °C. IR (CCl$_4$) 3065 (w), 3002 (w), 2940 (m), 2836 (w), 1718 (s), 1593 (m), 1486 (m), 1435 (m), 1397 (m), 1335 (s), 1224 (m), 1134 (m), 1100 (s), 1045 (m), 1007 (m); ^{1}H NMR (CDCl$_3$) δ 3.54 (s, 3H), 3.57 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 7.22-7.26 (m, 3H), 7.37-7.38 (m, 3H); ^{13}C NMR (CDCl$_3$) δ 51.9, 56.1, 59.9, 60.0, 108.9, 126.4, 126.9, 127.6, 129.3, 130.7, 136.7, 145.3, 151.5, 152.3, 168.1; LRMS (FAB$^+$) m/z 302 (M$^+$, 100), 271 (79), 256 (20); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{17}$H$_{20}$O$_5$ 302.1154, found 302.1148.

2-Methoxy-5-phenylcyclohepta-2,4,6-trien-1-one (Table 10, Entry 4). 5-Bromotropolone was prepared according to a literature procedure.[225] Column chromatography (TLC R_f = 0.38, EtOAc) yielded 161 mg of a light tan solid (76%) mp 139.2-140.4 °C (lit. 140-141 °C).[226] The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[226]

Chapter 4 - Application of Aryl Siloxane Cross-Coupling

Technology to the Synthesis of Colchicine and Allocolchicine

PART 1: Efforts Directed Toward the Synthesis of Colchicine

INTRODUCTION

Biological Activity of the Colchicinoids

Colchicine (**IV-1**) was first isolated from the meadow saffron *Colchicum autumnale* over one hundred years ago and is commonly used in the treatment of gout.[227] More recently, the activity of colchicine as a spindle poison has been reported.[228,229] Its mechanism of action involves binding to tubulin monomers and prevention of the formation of microtubules, which are essential to cellular mitosis.[230-234]
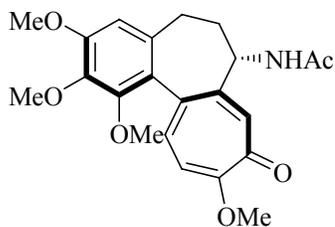
colchicine (**IV-1**)

Tubulin consists of α and β protein subunits which combine to form a heterodimer. These heterodimers polymerize in a helical fashion to form long tubes, called microtubules. Microtubules are responsible for a multitude of cellular functions including: formation of the cytoskeleton to maintain the cellular shape, transport systems

for moving material around inside the cell, and most importantly, microtubules are required for the formation of the mitotic spindle during cell division. Colchicine disrupts these activities by binding to the tubulin heterodimer and preventing polymerization to form microtubules.[234] This leads to a halt to cellular mitosis and subsequent cell death.

Despite this promising activity, attempts to develop colchicine as an antitumor compound have been ineffective due to its potent broad spectrum cytotoxicity. The mitigation of the cytotoxicity of colchicinoids has been extensively investigated in an effort to find new antitumor agents with improved therapeutic properties. [231-238] This has led to the development of colchicine derivatives that display lower toxicity, and these compounds have seen limited therapeutic activity.[235]

Due to the success of taxol in the treatment of certain types of cancer, there has been renewed interest in the development of the colchicinoids for therapeutic use.[239] Currently, the obstacle to accessing new and potentially useful derivatives of colchicine is the availability of synthetically useful pathways. The majority of the syntheses of colchicine are long, tedious, or suffer from very poor yields. In recent years there has been an effort to develop new and more efficient synthetic procedures for the production of colchicine, and more importantly, colchicine derivatives.[240]

Biosynthesis and Previous Total Syntheses of Colchicine

The biosynthesis of colchicine was unknown until the early 1970's when Battersby[241-245] and others[246] performed extensive isotope labeling and feeding studies to determine the biosynthetic pathway of colchicine. Preliminary studies demonstrated that colchicine was a modified isoquinoline alkaloid, derived from autumnaline (**IV-2**)

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(Scheme 1).[245] Autumnaline is ultimately derived from tyrosine and phenylalanine. Methylation of autumnaline, followed by oxidative coupling generates *O*-methylandrocymbine (**IV-3**).[241,246] At this point an interesting, and not completely understood fragmentation of the ethaneamine bridge occurs to give the ring expanded 7-membered tropolone ring of *N*-formyldemecolcine (**IV-4**), which is directly converted to colchicine. This ring expansion step is thought to occur *via* a P-450 radical mediated process, however, no intermediates have been isolated to conclusively prove this theory.[242,243]

Scheme 1
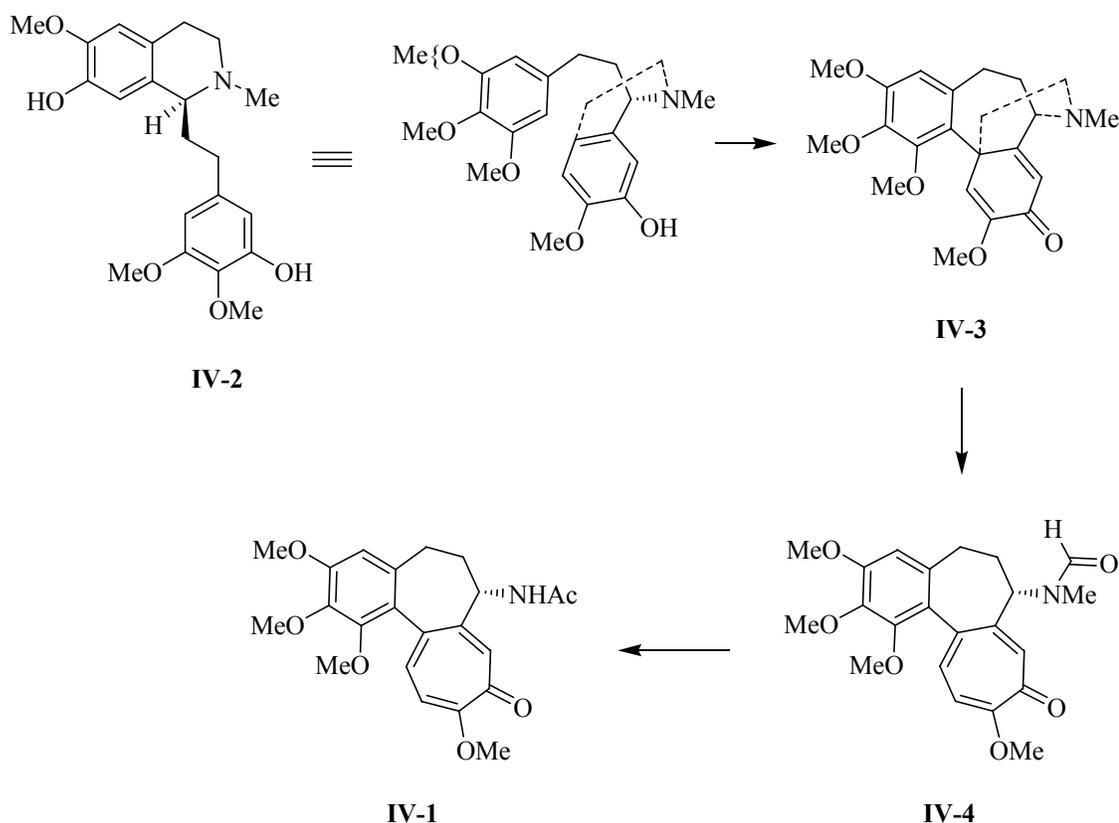
Colchicine has attracted the attention of the synthetic community over the years.[240,247,248] Its deceptively simple structure poses several significant challenges, most

notably the synthesis of the tropolone ring system,[249,250] and the construction of the 6-7-7 fused ring system.

The majority of the total syntheses of colchicine have been linear, and suffer from one or more steps that proceed in poor yields. Recently, several synthetic approaches have been developed facilitating a more efficient construction of the carbocyclic framework.[240]

Cha developed a novel approach to the tropolone ring based upon an oxyallyl cycloaddition as the key step (Scheme 2).[251] Accordingly, treatment of advanced intermediate **IV-5** with an *in situ* generated oxallyl cation **IV-7**, formed *in situ* from TMS enol ether **IV-6** (see Scheme 3), generated the cycloaddition product **IV-8** in good yield. Base-induced ring opening of ether **IV-8** led to the generation of the tropolone ring in colchicinoid **IV-9**. Deprotection and acylation provided to colchicine (**IV-1**).

Scheme 2
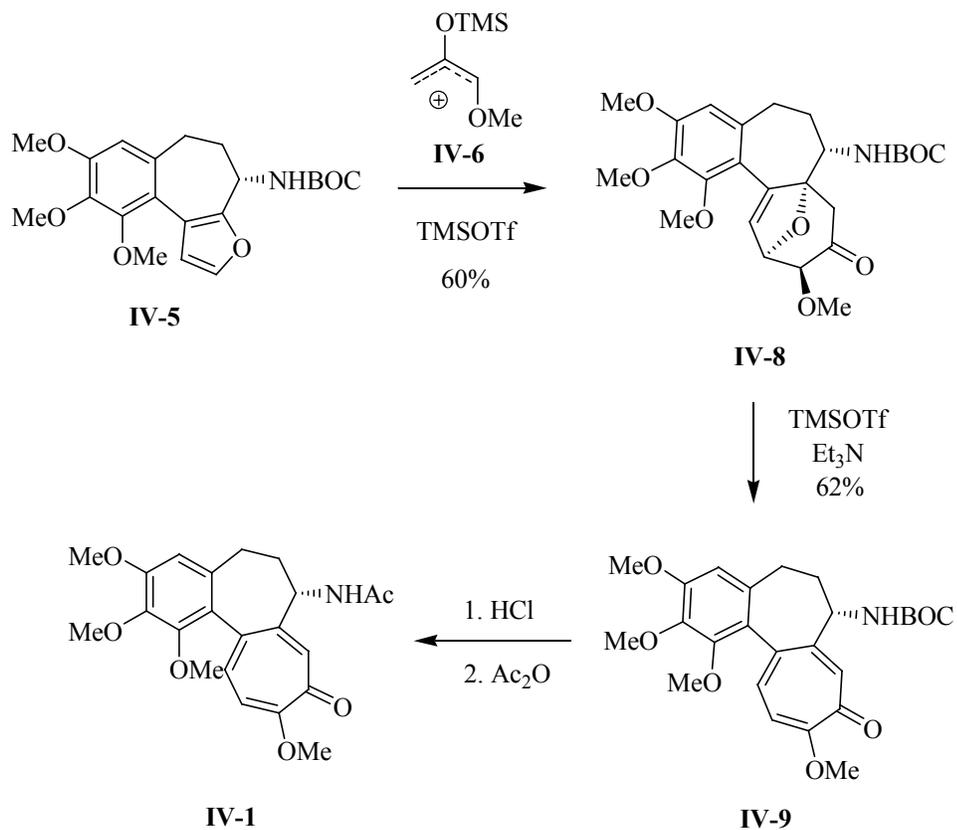
Scheme 3
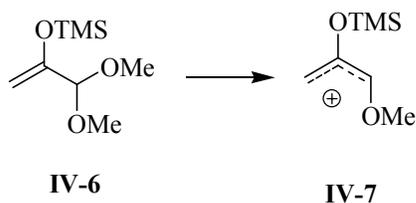
Another recent approach to the colchicine skeleton entailed a rhodium-catalyzed cyclization/cycloaddition cascade performed by Schmalz and coworkers (Scheme 4).[252] Cyclization precursor **IV-10** (readily obtained in 7 steps from commercially available starting materials) was treated with a rhodium catalyst to generate carbonyl ylide **IV-11** as an intermediate, which cyclized with the alkyne moiety to form advanced colchicinoid

intermediate **IV-12**.   Fragmentation and aromatization led to colchicinoid **IV-13**, which

was converted to colchicine in moderate overall yield.[253]

Scheme 4
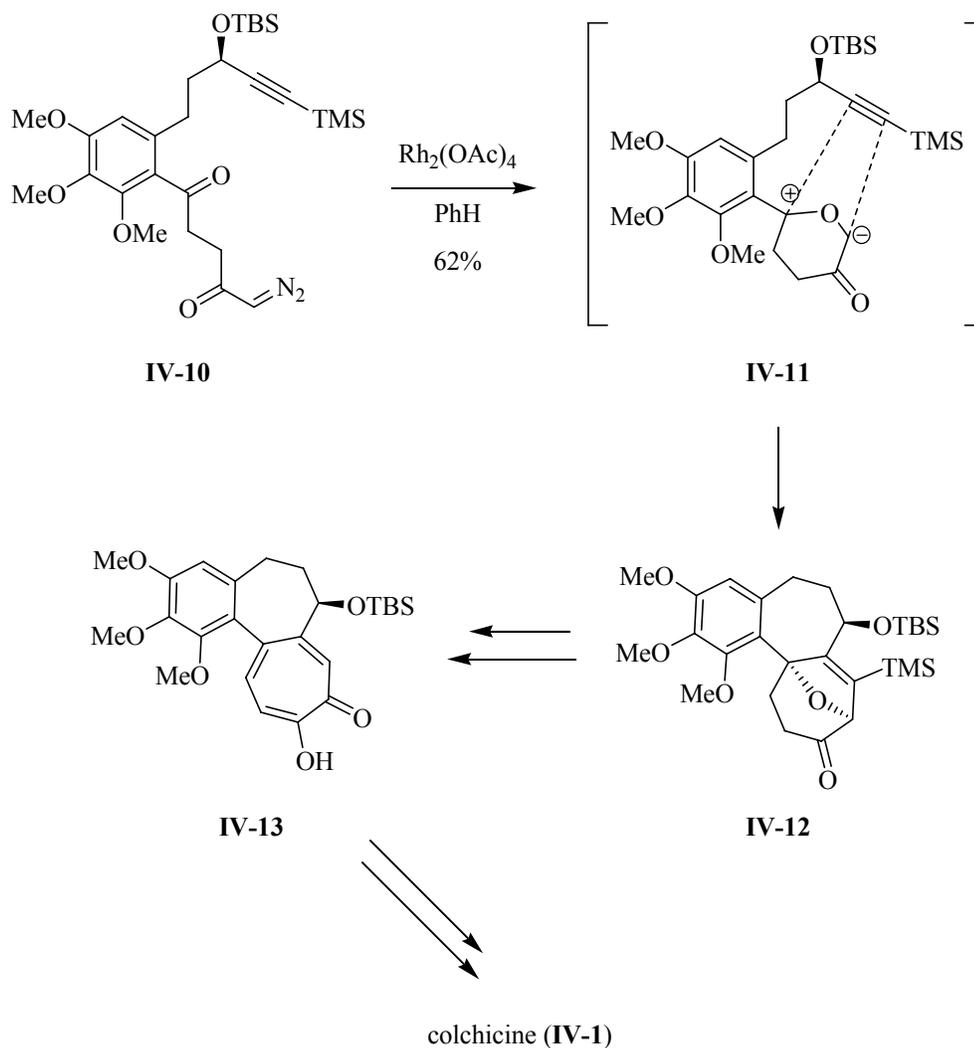
Aryl Siloxane Cross-Coupling Approach

Despite the recent advances in the synthesis of colchicine, no methods exist that

permit the facile production of analogues, which may prove to be therapeutically more

useful than colchicine itself.   Our approach to the synthesis of colchicine and its

derivatives employed a palladium-catalyzed siloxane cross-coupling reaction to form the carbon-carbon bond between the aryl ring siloxane **IV-15** and the tropolone ring **IV-16** (Scheme 5). This coupling would allow facile access to functionalized derivatives of Fitzgerald's compound (**IV-14**, R=H), which has been shown to possess the same biological activity as colchicine.[230]

Formation of the aryl-tropolone bond by a cross-coupling reaction has been investigated previously in model systems using Stille couplings[254] and Fitzgerald's compound (**IV-14**) has been prepared using a Suzuki coupling.[255,256] We chose to investigate a siloxane coupling reaction for the synthesis of the colchicine carbocyclic framework. This study would yield a direct comparison of the siloxane reaction to other cross-coupling strategies.

Scheme 5
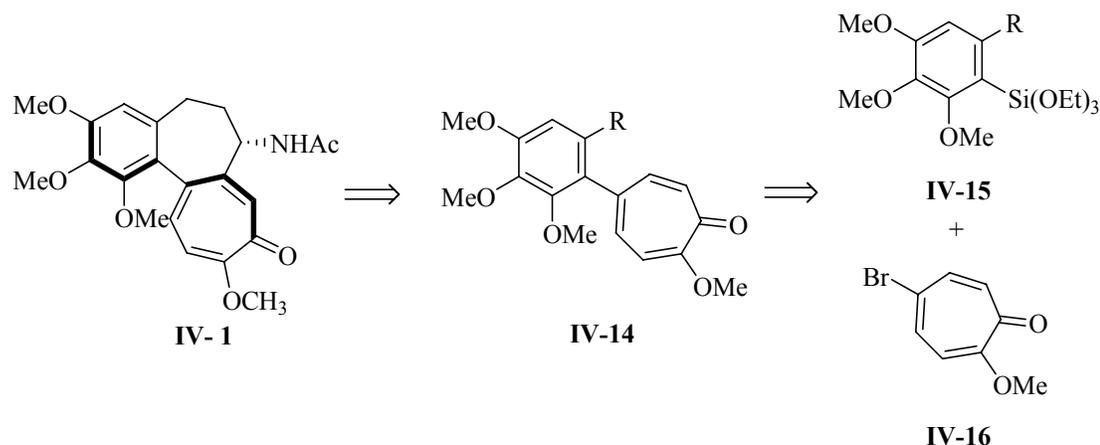
Palladium-catalyzed coupling reactions play an ever increasing role in organic synthesis since the ability to efficiently form carbon-carbon bonds in molecules with complex chemical architecture remains a challenging task.[5] Work in our laboratory has

focused on the formation of aryl-aryl bonds using hypercoordinate siloxane derivatives,[45-51,56,57,59] a variant of the Hiyama cross-coupling reaction.[30-36] This reaction has advantages over traditional cross-coupling protocols[3] such as the Suzuki-Miyaura[15-19] (organoboron) or Stille[6-10] (organostannane) coupling reactions (Scheme 6) because the siloxane methodology eliminates the purification difficulties associated with organoboron reagents,[20] and the toxic by-products associated with the use of organotin compounds.[10] The goal of this study was to demonstrate that siloxane-based couplings could be employed effectively in complex natural product synthesis. In addition, the use of colchicine (**IV-1**) as a target would also allow for the direct comparison of the siloxane and boronic acid based strategies.

Scheme 6

X = I, Br, Cl, OTf

Y = SnBu$_3$, B(OH)$_2$, Si(OEt)$_3$
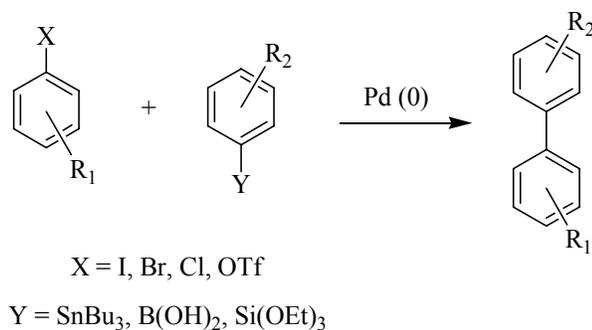
RESULTS AND DISCUSSION

The aryl bromide coupling partner for the key siloxane coupling reaction is 5-bromotropolone (**IV-16**). Banwell and coworkers have developed an efficient synthesis of this compound and we adopted a modified sequence of the Banwell procedure for this

study (Scheme 7).[225] Treatment of 1,4 cyclohexadiene (**IV-17**) with *in situ* generated

dibromocarbene provided dibromide **IV-18**. Formation of dibromo ester **IV-19**

proceeded uneventfully. Oxidation of the hydroxyl moiety of **IV-19** using PCC led to

ketone **IV-20** that underwent base-induced ring expansion to give unprotected

bromotropolone **IV-21** in excellent yield. Methylation with dimethyl sulfate provided the

desired methoxybromotropolone **IV-16.**

Scheme 7
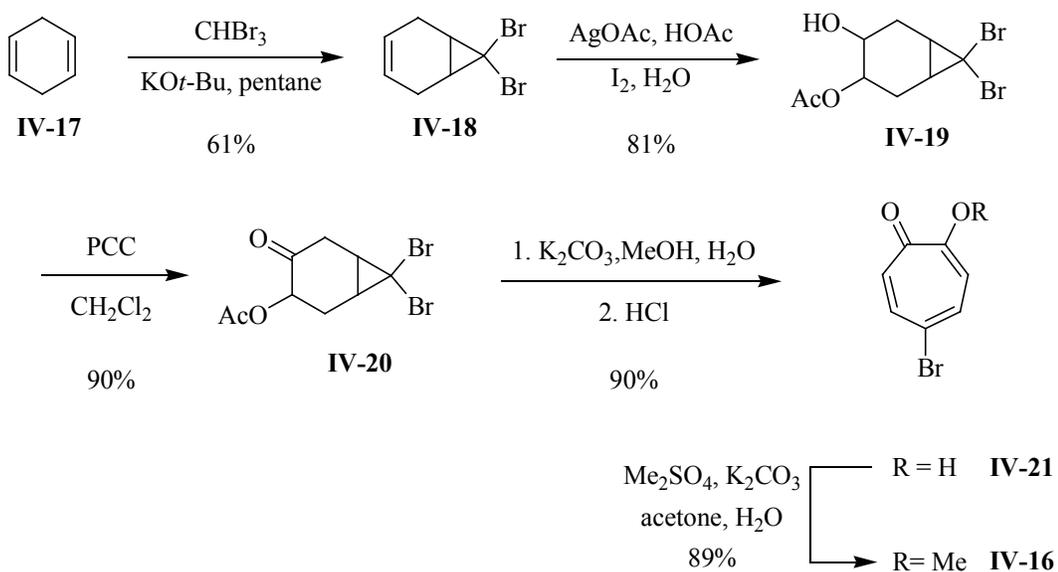
With bromotropolone (**IV-16**) in hand, an investigation of the cross-coupling with

phenyltrimethoxysilane was undertaken. The results are summarized in Table 1. A

variety of catalyst and phosphine combinations were tested and palladium acetate and

triphenyl phosphine in a 1:5 ratio was found to be the optimum catalyst for the cross-

coupling reaction (entries 4 and 5).

Table 1. Optimization of 5-Bromotropolone Coupling with Phenyl Trimethoxysilane
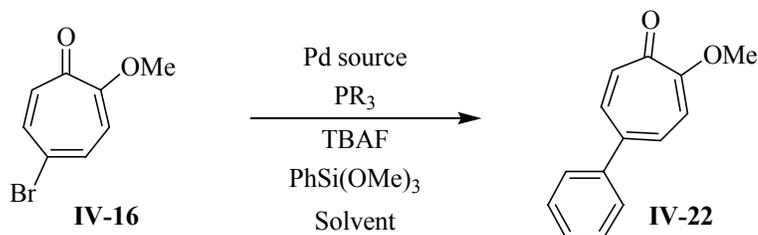
entry	Pd source (mol %)	PR$_3$ (mol %)	solvent[b]	yield (%)[c]
1	Pd(OAc)$_2$ (10)	P(o-tol)$_3$ (20)	DMF	0
2	Pd(OAc)$_2$ (10)	PPh$_3$ (20)	DMF	15
3	Pd(OAc)$_2$ (10)	PPh$_3$ (40)	THF	51
4	Pd(OAc)$_2$ (10)	PPh$_3$ (50)	THF	86
5	Pd(OAc)$_2$ (5)	PPh$_3$ (25)	THF	84
6	Pd(OAc)$_2$ (1)	PPh$_3$ (5)	THF	52
7	Pd(PPh$_3$)$_4$ (10)	-	DMF	0
8	Pd(PPh$_3$)$_4$ (10)	-	THF	24
9	Pd(PPh$_3$)$_4$ (10)	PPh$_3$ (10)	THF	84
10	Pd(PPh$_3$)$_4$ (10)	PPh$_3$ (20)	THF	88
11	Pd(PPh$_3$)$_4$ (5)	PPh$_3$ (10)	THF	23
12	Pd(PPh$_3$)$_4$ (10)	-	dioxane	0
13	Pd(dba)$_2$ (10)	-	DMF	0
14	Pd(dba)$_2$ (10)	-	THF	0
15	Pd(dba)$_2$ (10)	PPh$_3$ (50)	THF	46
16	Pd(dba)$_2$ (10)	PPh$_3$ (100)	THF	54
17	Pd(dba)$_2$ (10)	P(cy)$_2$(o-biphenyl) (10)	DMF	0
18	Pd(dba)$_2$ (10)	P(t-Bu)$_2$(o-biphenyl) (10)	DMF	0
19	[Pd(allyl)Cl]$_2$ (10)	PPh$_3$ (20)	THF	0
20	[Pd(allyl)Cl]$_2$ (10)	PPh$_3$ (20)	DMF	0
21	[Pd(allyl)Cl]$_2$ (10)	P(cy)$_2$(o-biphenyl) (10)	DMF	0

[a] Reactions were stirred for 10 h unless otherwise noted. [b] Reactions conducted in THF or dioxane were performed at the reflux temperature of the solvent. Reactions in DMF were heated to 90 °C. [c] Isolated yields.

The reaction could be conducted with no appreciable loss in yield with as little as 5 mol % catalyst (entry 5). Similar results could be obtained using tetrakis(triphenylphosphine) palladium(0) with the addition of 10 to 20 mol % of excess phosphine (entries 9 and 10). However, it was interesting to note that without the additional phosphine, $Pd(PPh_3)_4$ was a poor catalyst for the reaction (entry 8).

Clearly, the optimum catalyst for the reaction requires a high degree of triphenylphosphine ligation to palladium. This observation is particularly evident when the palladium source is changed to $Pd(dba)_2$. No cross-coupling occurred (entries 13 and 14) unless a large excess (5 equiv) of triphenylphosphine was added (entry 15). The addition of further equivalents of phosphine did not improve the yield (entry 16). More importantly, the yield of coupled product was poor compared to the palladium acetate and $Pd(PPh_3)_4$ systems.

These results indicate that even though the active catalyst in each case is a palladium(0) triphenylphosphine complex, the original ligands on the palladium source (OAc, PPh_3, dba) play important roles in determining the activity of the catalyst. Particularly in the case of $Pd(dba)_2$, the original ligand (dba) may be effectively competing with triphenylphosphine for ligation to the metal, thus decreasing the activity of the catalyst. The detrimental effect of dba on palladium(0) catalyst efficiency was observed by Amatore and Jutand, and is attributed to the strong binding affinity of the dba ligand to the palladium metal.[257] In addition, other studies have shown that dba slows the oxidative addition of Pd(0) and aryl halides.[258]

After optimizing the conditions for the palladium-catalyzed coupling of 5-bromotropolone with phenyltrimethoxysilane, attention turned to the preparation of functionalized aryl siloxanes that would be more typical tropolone coupling partners for colchicine analogue synthesis. The preparation of functionalized siloxanes is presented in Table 2. All of the selected siloxanes contain highly electron-rich aryl rings, which can prove to be difficult substrates for palladium-catalyzed coupling reactions.

Using (triethoxysilyl)-2,3,4-trimethoxybenzene (Table 2, entry 1) as the coupling partner with 5-bromotropolone (**IV-16**) would give Fitzgerald's compound (**IV-14**). Entries 2 through 7 would define the scope and limitations of the siloxane coupling technology by demonstrating the ability to couple highly substituted electron-rich aryl rings. The siloxanes shown in Table 2 were readily prepared in high yields using either *ortho*-metallation (entries 1,2),[57] Grignard (entries 3-6),[56] or hydrosilylation (entry 7)[58-60] reactions. These three methods are complementary, and taken together allow for the synthesis of virtually any aryl siloxane (Scheme 8).

Table 2. Synthesis of Siloxanes as Substrates for the Palladium-Catalyzed Coupling with Bromotropolone.[a]

entry	starting material	siloxane	method[a]	yield (%)[b]
1	MeO, MeO, OMe benzene	MeO—Si(OEt)$_3$, MeO, OMe benzene	ortho-metallation	77
2	OMe benzene	—Si(OEt)$_3$, OMe benzene	ortho-metallation	62
3	MeO—, MeO—Br benzene	MeO—, MeO—Si(OEt)$_3$ benzene	Grignard	61
4	—Br, Me benzene	—Si(OEt)$_3$, Me benzene	Grignard	81
5	O, O Br benzodioxole	O, O Si(OEt)$_3$ benzodioxole	Grignard	59
6	MeO—benzene—Br	MeO—benzene—Si(OEt)$_3$	Grignard	82
7	MeO, MeO—Br, MeO benzene	MeO, MeO—Si(OEt)$_3$, MeO benzene	hydrosilylation	66
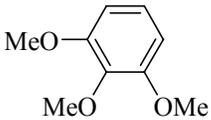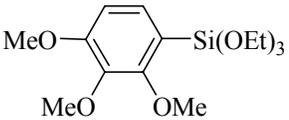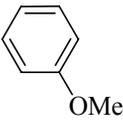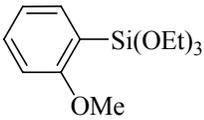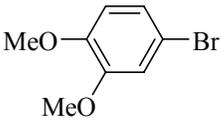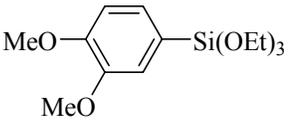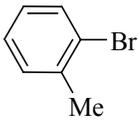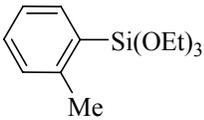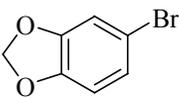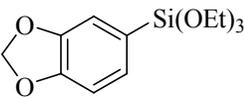
[a] See Experimental Section for details. [b] Isolated yields of purified product.

Scheme 8
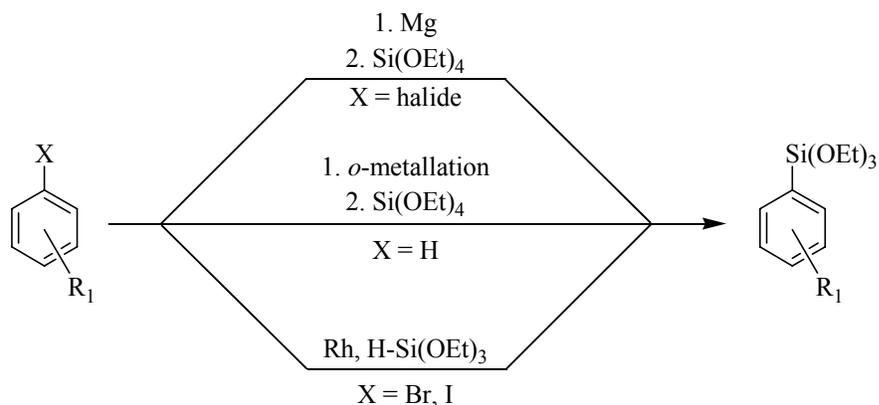
The next aspect of the study was to investigate the cross-coupling reaction between functionalized siloxane substrates and 5-bromotropolone (**IV-16**). In addition to coupling reactions using aryl siloxanes, we were presented with an opportunity to directly compare the coupling efficiency of aryl stannanes and boronic acids with aryl siloxanes. Banwell has reported the coupling of a variety of aryl stannanes with bromotropolone,[254] and Nair[256] has reported the synthesis of Fitzgerald's compound (**IV-14**) using a boronic acid coupling. Using the aryl stannane coupling results of Banwell, and the aryl boronic acid and siloxane couplings from our laboratory, a side-by-side comparison of the coupling methodologies could be made. The results of this comparison study are presented in Table 3. In the case of aryl siloxanes, the coupling reaction is tolerant of both *meta*- and *para*-substituents (entries 1, 2, 4-7). The coupling of *o*-methoxy-substituted siloxanes (entries 3 and 8) failed, however, and no coupling product was observed under standard coupling conditions (*vide infra*). On the other hand, the coupling of *o*-methyl siloxane (entry 4) proceeded smoothly under standard conditions.

In general, when the three methodologies are compared, the aryl siloxanes provide similar yields to the corresponding boronic acids, while both the siloxanes and boronic acids provide superior yields to organostannane reagents. All three methodologies efficiently coupled a simple phenyl group (entry 1), however, the coupling of electron-rich substrates proved more problematic for the Stille couplings (entries 2,3, 5-8). Notable is the fact that only the boronic acid was able to efficiently provide coupled product for the 2,3,4-trimethoxy moiety (Table 3, entry 8), while the Stille reaction failed to provide any product,[254] and the siloxane coupling required a stoichiometric amount of palladium to yield the desired biaryl.

Table 3. Coupling of Aryl Siloxanes with 5-Bromotropolone[a]

entry	Ar-M	M =	SnBu₃[c]	B(OH)₂	Si(OEt)₃
				yield (%)[b]	
1	phenyl-M		98	89	84
2	MeO-C₆H₄-M		53	87	81
3	o-OMe-C₆H₄-M		31	80	0
4	o-CH₃-C₆H₄-M		-	96	81
5	benzodioxole-M		60	92	87
6	3,4-(MeO)₂-C₆H₃-M		57	89	88
7	3,4,5-(MeO)₃-C₆H₂-M		59	87	89
8	2,3,4-(MeO)₃-C₆H₂-M		0	94[d]	92[e](0)[f]

[a] All coupling reactions performed with 5 mol % catalyst unless otherwise noted. See Experimental Section (boronic acid, siloxane) or ref xx (organostannane) for details. [b] Isolated yield of purified product. [c] Data from ref 254. [d] ref 255. [e] Bromotropolone premixed with a stoichiometric amount of palladium before addition of the siloxane. See experimental section for details. [f] Reaction performed with 5 mol % catalyst.

The failure of the *o*-methoxy siloxane to undergo coupling was not unexpected as it had been previously observed that siloxanes containing an *ortho*-methoxy substituent were rapidly protodesilylated under the cross-coupling conditions, yielding poor yields of coupled product.[57] This propensity for protodesilylation could be overcome, to a degree, by increasing the catalyst loading to 50 mol % (Scheme 9).[57] However, in the case of the tropolone ring system, increasing the catalyst loading to 50 mol % failed to provide any coupled product and the siloxane underwent quantitative protodesilylation. In contrast to the tropolone coupling, when siloxane **IV-23** was coupled with bromobenzene to generate biaryl **IV-24**, good yields of coupled product could be isolated with high catalyst loading (see Scheme 9).

Scheme 9

IV-23

10 % Pd(OAc)$_2$
20 % PPh$_3$
Bromobenzene

TBAF, THF

35%

IV-24

50 % Pd(OAc)$_2$
100 % PPh$_3$
Bromobenzene

TBAF, THF

70%

IV-24

50 % Pd(OAc)$_2$
100 % PPh$_3$
IV-18

TBAF, THF

0%

IV-14
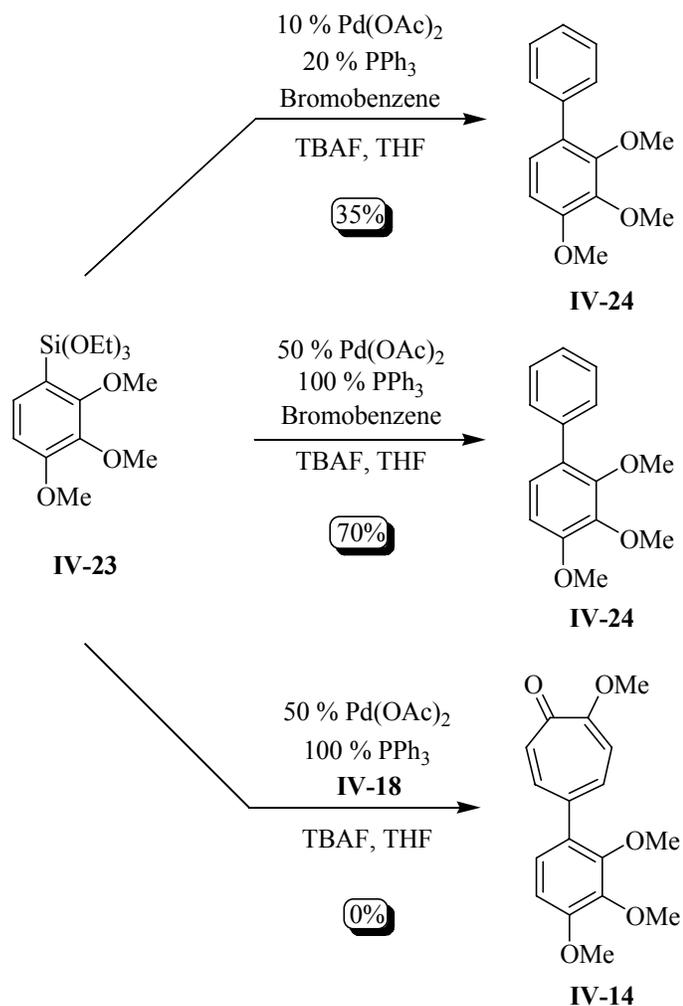
The failure of the bromotropolone ring system to couple with *o*-methoxy containing siloxanes is attributed to a slower oxidative addition step for the tropolone coupling, thus permitting protodesilylation to consume the siloxane before coupling can occur. In support of this hypothesis, treatment of 5-bromotropolone *with a stoichiometric amount of the palladium catalyst*, followed by the addition of siloxane **IV-23** and TBAF, gave a 92% yield of the coupled product (Scheme 10). There are several notable features of the coupling reaction under these conditions: the oxidative addition product **IV-25** was

formed, and upon addition of the siloxane and TBAF, transmetallation occured faster than protodesilylation to give Fitzgerald's compound **IV-14**. The isolation and characterization of a palladium(0)-aryl halide oxidative addition product has been accomplished previously.[259-261] In their study, however, Hartwig and coworkers used haloarenes as substrates and were able to isolate and fully characterize the product. No studies exist that report the synthesis and characterization of a bromotropolone oxidative insertion product such as **IV-25**. Thus, we were disappointed when all attempts at isolation and characterization of **IV-25** were unsuccessful.[262]

Scheme 10
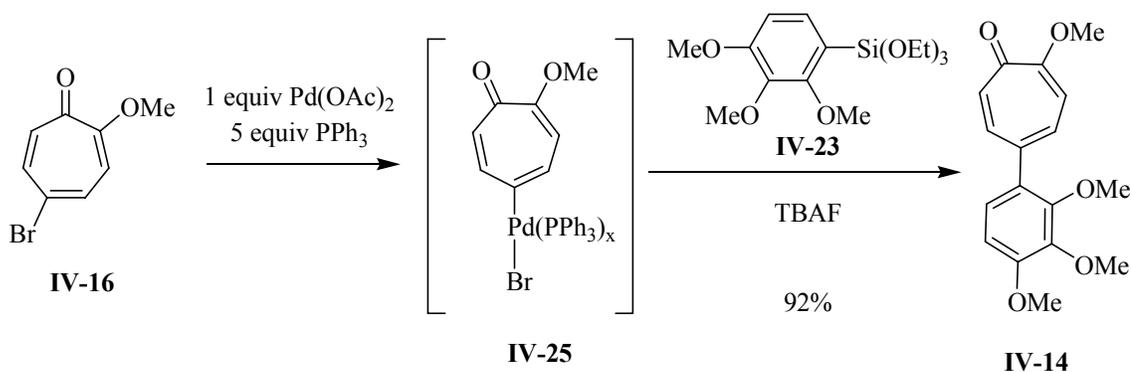
It is plausible that the pre-mixing of the palladium, phosphine, and 5-bromotropolone is actually allowing time for the formation of Pd(0), and not necessarily the formation of the oxidative addition product. In their study of the rates and mechanism of formation of zerovalent palladium from Pd(OAc)$_2$ and PPh$_3$, Amatore and Jutand have indicated that the reduction of Pd(II) to Pd(0) requires approximately 10-15 min at 60 ˚C in THF.[263,264] Consequently, if protodesilylation is complete after 10 minutes, then it would be expected that no coupled product would be observed.

In view of the Amatore results, pre-mixing palladium acetate and triphenylphosphine, followed by the simultaneous addition of 5-bromotropolone, aryl siloxane **IV-22**, and TBAF should yield coupled product. When this experiment was conducted, however, the yield of coupled product was low (43%). This result indicated that the slow formation of Pd(0) is indeed allowing significant protodesilylation to occur; however, since the yield of coupled product is still low after allowing the formation of Pd(0), a slow oxidative addition is also hindering the coupling reaction.

Based on our initial observations, we can propose relative rates of reaction for several key steps in the catalytic cycle for the coupling of siloxane **IV-22** with bromotropolone **IV-15** (Scheme 11). The oxidative addition reaction for the catalytic cycle (K_{oa}) is the slowest step. The high yield of coupled product obtained (92%) after allowing the Pd catalyst and bromotropolone **IV-15** to be pre-mixed (Scheme 10) demonstrated that the rate of transmetalation (K_{trans}) is much faster than the rate of protodesilylation (K_{demet}). Without the pre-mixing of the Pd(0) catalyst and bromotropolone **IV-15**, no coupled product was observed, with the only product being protodesilylated siloxane. Because $K_{trans} > K_{demet}$, the lack of coupled product is the result of a slow oxidative addition that permits time for all of the siloxane to be protodesilylated before any oxidative insertion product is generated. Therefore, the relative rates for the reaction are: $K_{trans} > K_{demet} \gg K_{oa}$.

Scheme 11
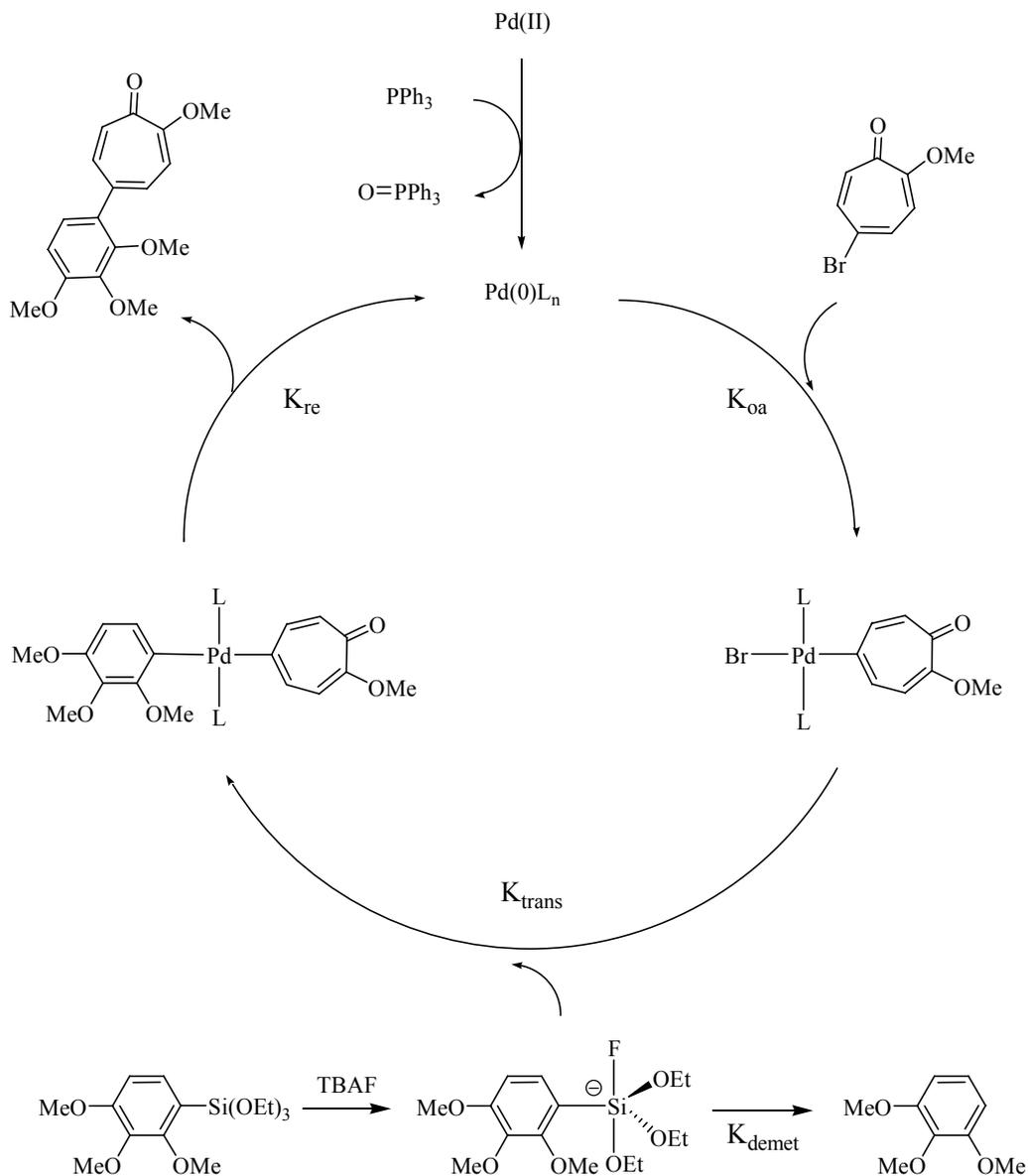
An alternative approach to the coupling reaction would be to employ a siloxane derived from 5-bromotropolone and 2,3,4-trimethoxybromobenzene as the coupling partners (Scheme 12). However, attempts to prepare the tropolone siloxane **IV-26** via metallation,[56] rhodium-,[58,60] or palladium-catalyzed[59] silylation were unsuccessful.

Additionally, attempts to form the corresponding boronate ester **IV-27** using established

protocols were unsuccessful.[265-270]

Scheme 12

| IV-27 | IV-16 | IV-26 |
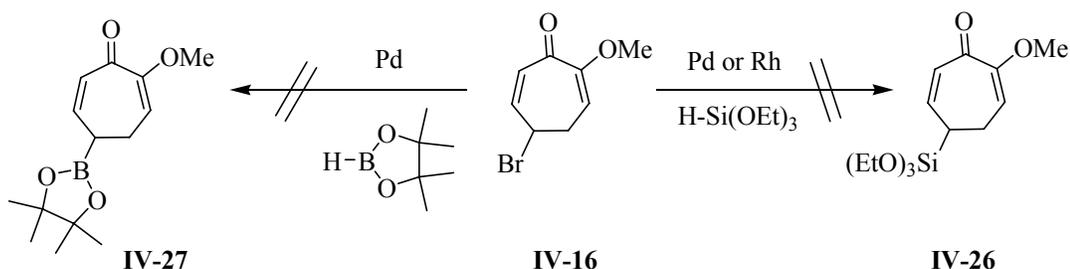
CONCLUSION

In conclusion, these studies of the synthesis of aryl tropolone derivatives have

allowed for a side-by-side comparison between tin, boron, and silicon cross-coupling

reagents. The organoboron and organosilicon reagents were found to couple in

comparable yields, with the exception of *ortho*-methoxy containing siloxanes. Both

methods produced higher yields of coupled product than the organotin reagents. Using a

stoichiometric amount of palladium to overcome a slow oxidative addition step, the

siloxane coupling to form Fitzgerald's compound (**IV-13**) could be realized.

PART 2: Synthesis of the Carbocyclic Framework of Allocolchicine

INTRODUCTION

Allocolchicine (**IV-28**) and *N*-acetyl colchinol-*O*-methyl ether (NCME) (**IV-29**)

possess a 6-7-6 carbocyclic framework, related to the 6-7-7 tricylic system present in

colchicine (**IV-1**). Like colchicine, allocolchicine (**IV-28**) displays potent antitumor activity.[271-278] Importantly, allocolchicine displays diminished cytotoxicity compared to colchicine. This reduced toxicity of the allocolchicinoids has led to an interest in the development of synthetic protocols to provide allocolchicine and its derivatives for biological evaluation.[271]

allocolchicine (**IV-28**)   *N*-acetyl colchinol-*O*-methyl ether (**IV-29**)
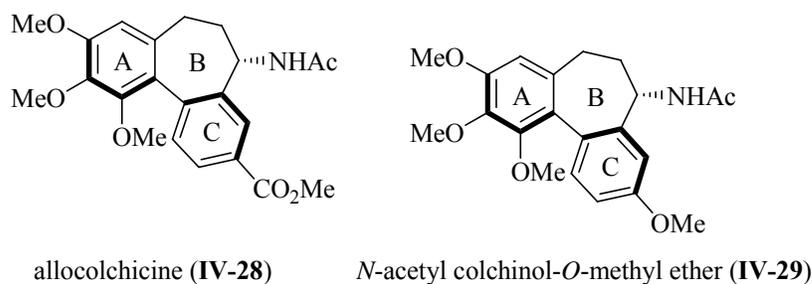
Previous Synthetic Work

The majority of the synthetic work on allocolchicine has relied on chemical degradation of colchicine to provide allocolchicine and its analogues. This has therefore severely limited access to novel derivatives. Several approaches have been reported for the partial synthesis of allocolchicine, or for derivatives.[279-283] Additionally, a racemic total synthesis has been achieved by Sawyer and Macdonald.[284] All of these approaches do not facilitate the production of B ring analogues. It has been demonstrated that the A and B rings are required to maintain full biological activity.[285-287] However, the B ring can be manipulated to generate different analogues that may still retain the antitumor activity, while at the same time moderate the toxicity of these compounds. Accordingly, a synthetic approach that would allow for the facile construction of the A, B and C rings, while also permitting functionalization of all of the rings, would have great synthetic value.

Recently, Seitz and coworkers have developed a synthetic approach to seven-membered heterocylic B ring allocolchicine analogues (Scheme 13).[287] The key biaryl formation reaction was conducting using a Ziegler-Ullmann reaction between the aryl-copper reagent **IV-30** and aryl iodide **IV-31** to generate biaryl **IV-32**. This biaryl was transformed to a variety of allocolchicinoids **IV-33** bearing B ring heteroatom substitutions.   These compounds displayed similar biological activity to natural allocolchicine.[287]

Scheme 13
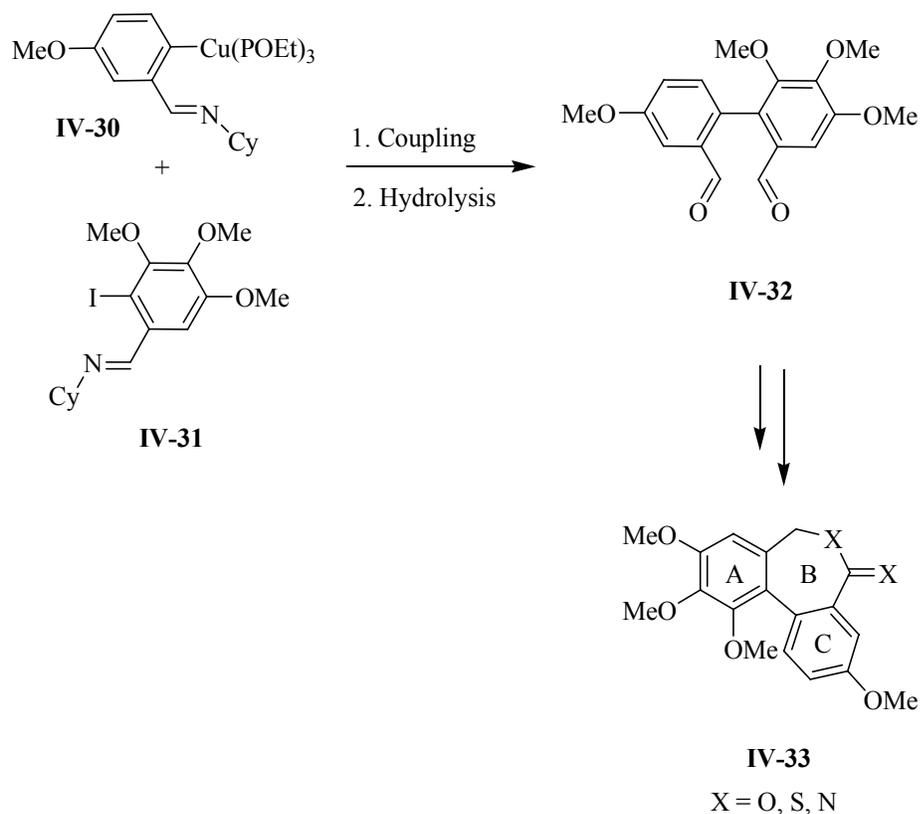
Another synthetic approach to allocolchicinoids was developed by Wulff and coworkers.[288]   The key step of this synthesis involved a Diels-Alder/aromatization reaction (Scheme 14) in which reaction of diene **IV-34** with methyl propiolate (**IV-35**)

followed by aromatization with DDQ provided the allocolchicinoid carbocyclic

framework in tricycle **IV-36**. The protected alcohol is converted asymmetrically through

a series of steps to the *N*-acetyl moiety, generating the natural product.

Scheme 14
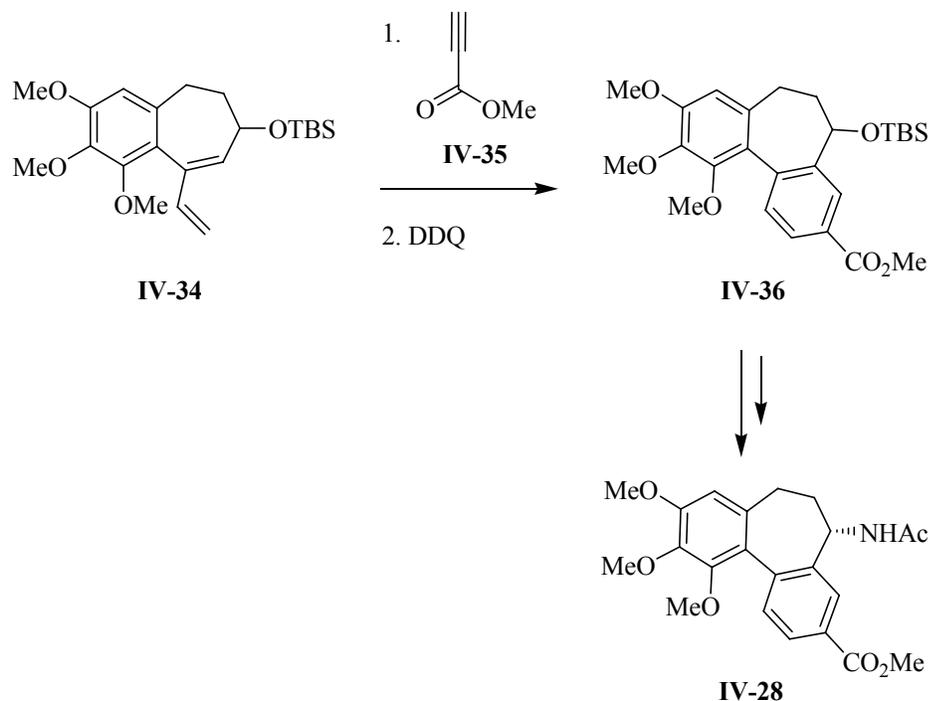
Fagnou and coworkers have developed a formal total synthesis of allocolchicine

based upon a direct arylation reaction to form the A-C biaryl linkage (Scheme 15).[289-291]

The synthesis began with a Sonagashira coupling of alkyne **IV-37** with aryl chloride **IV-**

38 to provide ketone **IV-39** in 92% yield. Ketone **IV-39** was subsequently converted

through a series of steps to MOM-protected alcohol **IV-40**. Direct arylation of this

compound using Pd(OAc)$_2$ and biphenyl phosphine **IV-41** gave allocolchicinoid **IV-42**.

Deprotection of the TBS ether completed the formal total synthesis of the natural product.

Scheme 15
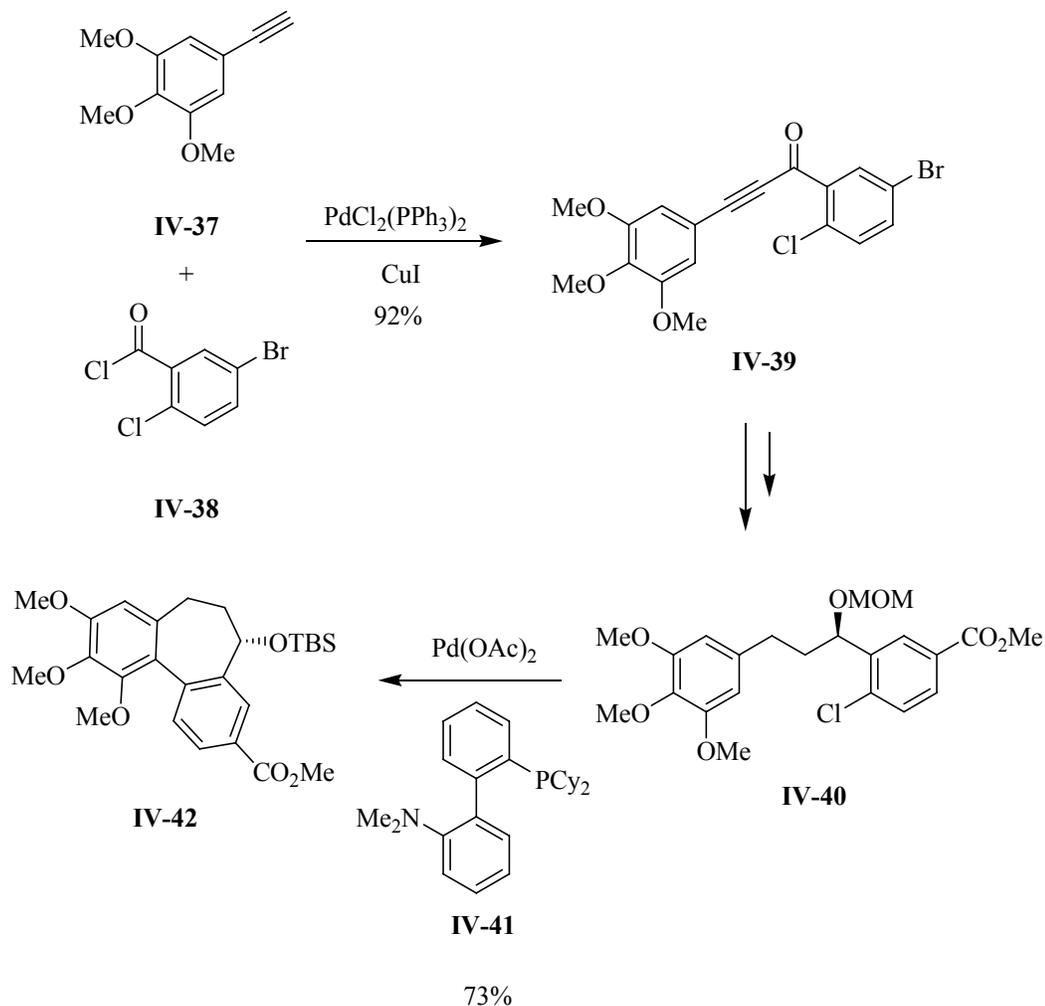
Aryl Siloxane Approach to Allocolchicine

We envisioned an approach to allocolchicine that would entail the connection of ring A and ring C using an aryl siloxane coupling reaction, followed by either a ring expansion of a fluoreneone (**IV-43**) or phenanthrene (**IV-44**) intermediate to give the 7-membered B ring (Scheme 16). Alternatively, the B ring could be formed *via* an intramolecular nitrile coupling using substrate **IV-45**. In all three approaches, the key A-C ring coupling would be achieved using bromide **IV-46** and siloxane **IV-47**. These

approaches are advantageous because altering the substitution of either the aryl bromide or the aryl siloxane coupling partner would generate a wide range of colchicinoid derivatives. Additionally, using the phenanthrene (**IV-44**) or nitrile (**IV-45**) pathways would allow for the generation of B ring analogues (*vide infra*).

Scheme 16

IV-28

IV-43

IV-44

IV-45

IV-46

+

IV-47
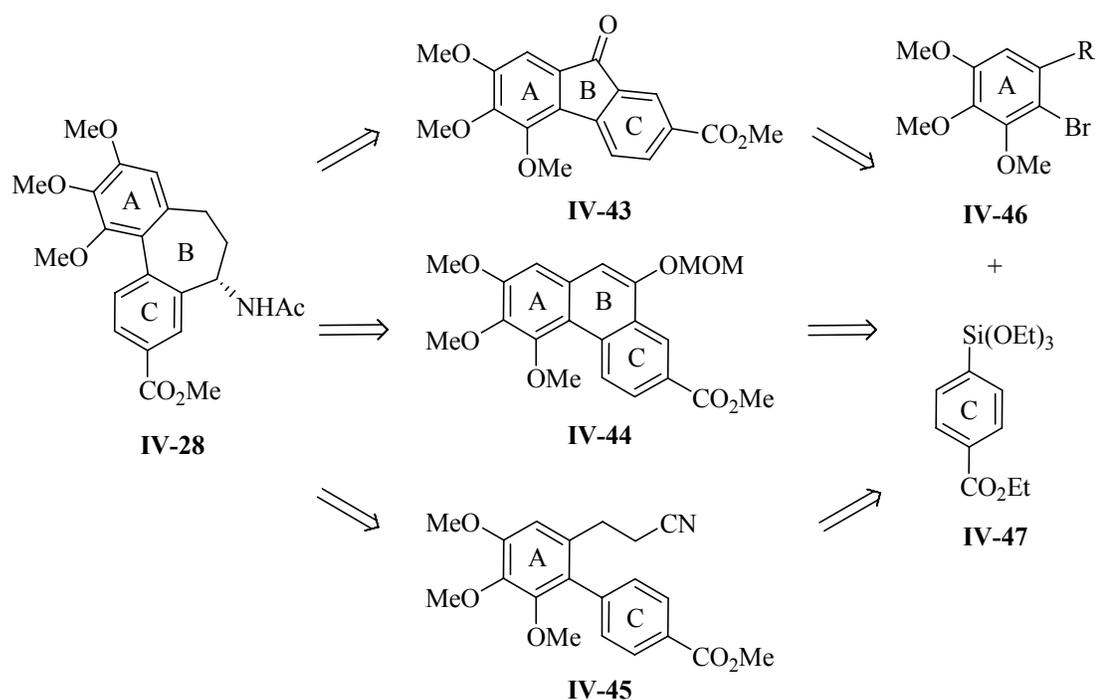
RESULTS AND DISCUSSION

Fluorenone Ring Expansion Pathway

The first synthetic route that was explored was the two-carbon homologation of fluorenone. The impetus for this study was the report of a two-carbon ring expansion by Liao and coworkers.[292-294] Tertiary allylic alcohol **IV-48** was deprotonated and the resulting anion heated, inducing an anionic [1,3] rearrangement to ketone **IV-49** (Scheme

17). This reaction involved the incorporation of the two ethylene carbons into the macrocycle, resulting in a two-carbon ring expansion.

Scheme 17

IV-48   **IV-49**
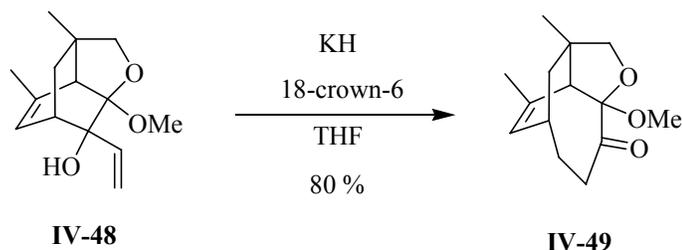
In an attempt to employ a similar ring expansion in our synthesis of allocolchicine, the first task was the synthesis of the fluorenone substrate (Scheme 18). Accordingly, bromination of ester **IV-50** smoothly generated aryl bromide **IV-51**. Under palladium (0) cross-coupling conditions, aryl bromide **IV-51** was coupled in excellent yield with phenyl trimethoxysilane to generate the biaryl **IV-52**. Hydrolysis of the ester to the acid, followed by conversion to the acid chloride with SOCl$_2$, provided a substrate for intramolecular Friedal-Crafts ring closure to generate fluorenone **IV-53** in 92% yield. Treatment of fluorenone **IV-53** with vinylmagnesium bromide led to the formation of allylic alcohol **IV-54**. When this alcohol was treated under the anionic fragmentation conditions developed by Liao,[294] only unreacted starting material was recovered. A wide range of solvents, bases, and temperatures were employed to induce fragmentation/rearrangement with no success. It may be that the substrate used by Liao possessed sufficient ring strain to promote the fragmentation whereas the alcohol **IV-54** was unstrained.

Scheme 18
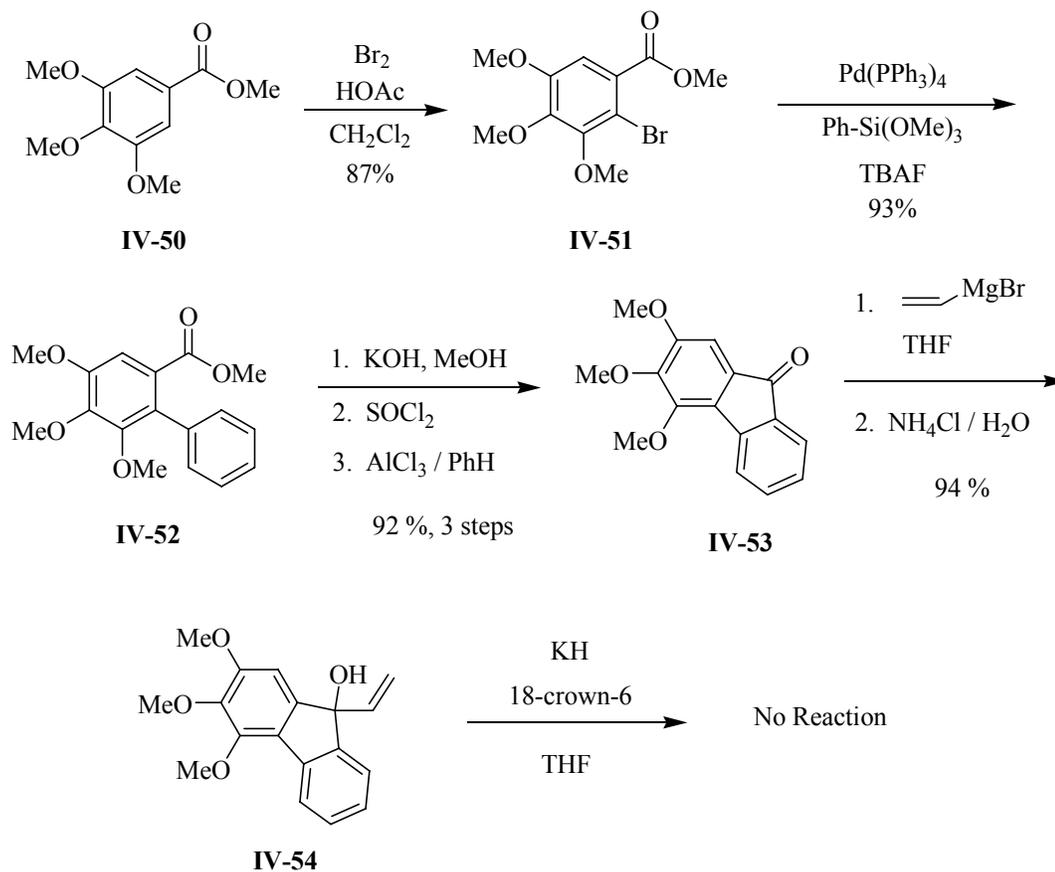
At this time, we sought other conditions that would facilitate a two-carbon ring expansion of the allylic alcohol substrate **IV-54**. However, instead of an anionic fragmentation, a radical fragmentation was investigated.[295-297] Pattenden and Ellwood had reported the allylic radical fragmentation of tertiary alcohol **IV-55** using diacetoxyiodosylbenzene (DIB) to give β-iodoketone **IV-56** (Scheme 19).[295] DIB generated the oxygen radical **IV-57**, which then fragmented to form carbon radical **IV-58** with concomitant formation of the enone. The carbon radical attacked the alkene to generate the primary radical **IV-59**. This radical was captured using iodine to generate the β-iodoketone **IV-58**.

Scheme 19

IV-55   IV-57   IV-58

cyclization

IV-56   IV-59
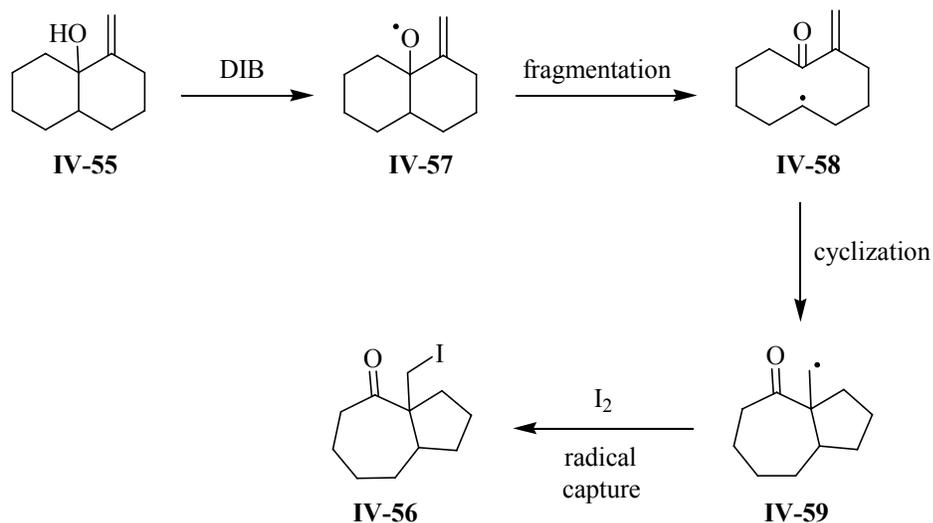
In the fluorenone system, DIB would generate oxygen radical **IV-60** (Scheme 20). It was then envisioned that fragmentation could occur to generate enone **IV-61**. The carbon radical could then added *via* conjugate addition to the enone to provide the seven-membered ring product **IV-62**, which would be quenched with iodine to give the α-iodoketone **IV-63**. Treatment of allylic alcohol **IV-54** with DIB in refluxing cyclohexane provided none of the desired α-iodoketone **IV-63**. Instead, an excellent yield of fluorenone **IV-53** was obtained (Scheme 21). This product was unexpected as it would necessitate the loss of an ethylene radical to generate the ketone.

Scheme 20

IV-60

IV-61

IV-63

I₂

IV-62

Scheme 21

IV-54

IV-63
none detected

IV-53
86%
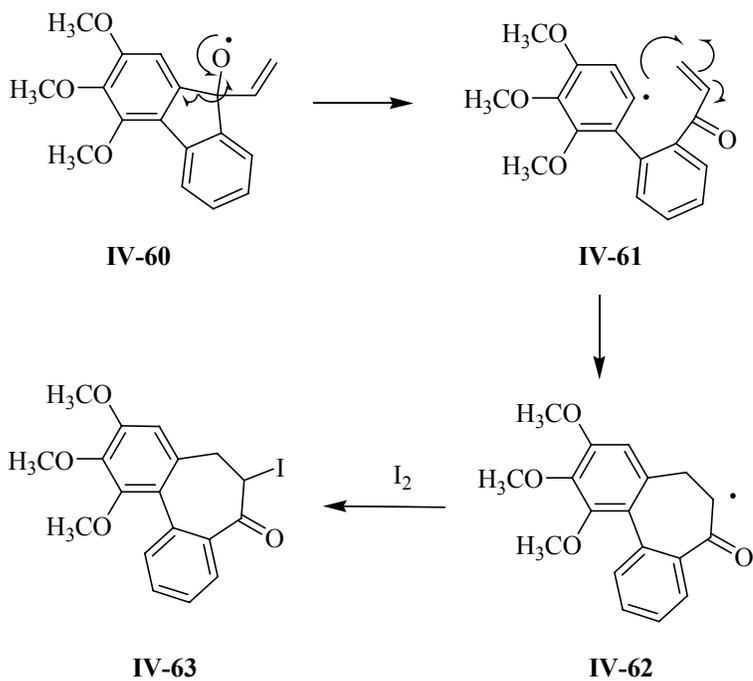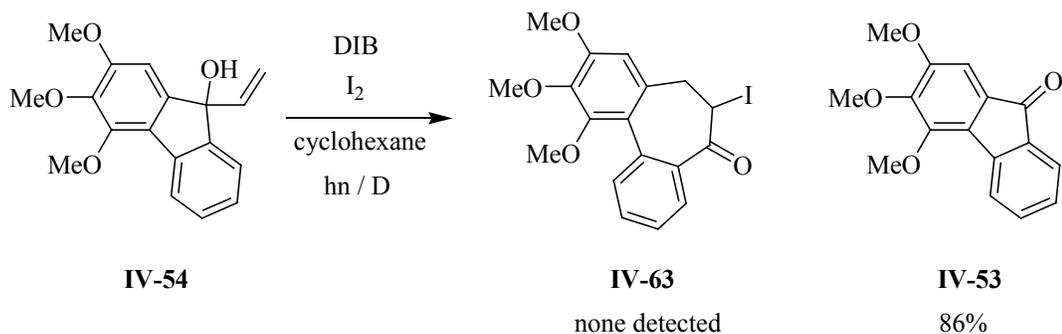
In an attempt to circumvent the ethylene loss, it was thought that if the alkene was changed to an alkyne, the loss of the alkynyl radical should be more disfavored, thus favoring the desired reaction pathway. The preparation of the required alkyne is shown in Scheme 22. Treatment of fluorenone **IV-53** with alkynyl magnesium bromide led to the formation of propargylic alcohol **IV-64** in excellent yield. Exposure of propargylic

alcohol to the radical fragmentation conditions led to the recovery of equimolar amounts of starting material **IV-64** and fluorenone **IV-53**, with decomposition of the remainder of the starting material. Like the allylic alcohol, the propargyl alcohol fragmented to provide fluorenone **IV-53**. In the case of the propargyl alcohol, the reaction did not go to completion, and it is likely that the generation of a reactive alkynyl radical led to the decomposition of the remainder of the starting material, which would explain the poor mass balance.

Scheme 22

IV-53   IV-64

IV-54   IV-53   IV-65

32 %   31 %   no product detected
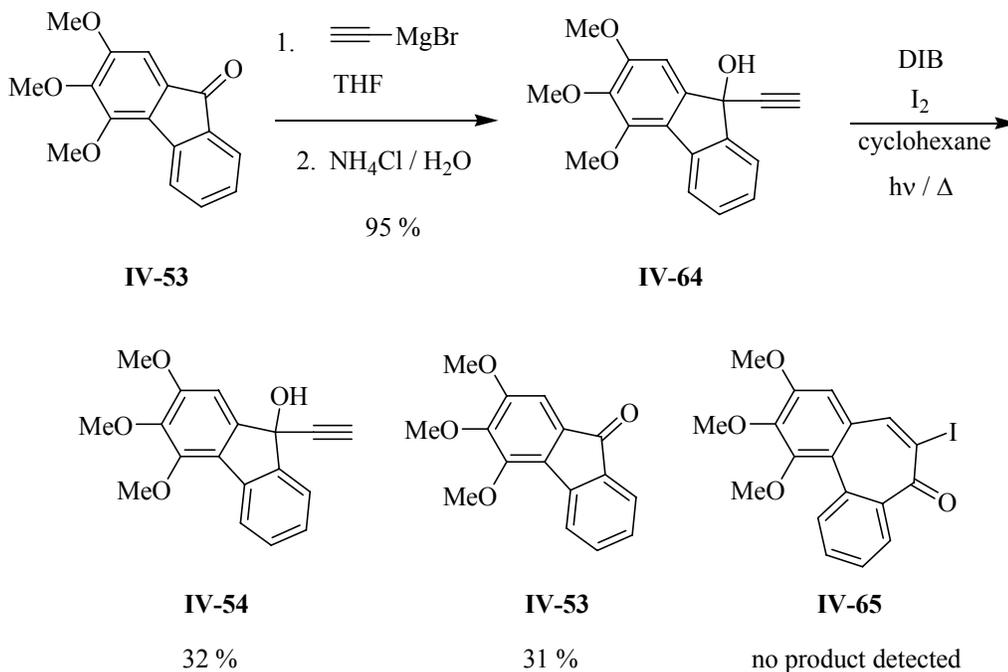
Having been unsuccessful in performing a two-carbon ring expansion of fluorenone, attention turned to an alternative pathway that would allow for the formation of the allocolchicine B ring in a single step. In order to carry out this transformation, we studied the C-H activation/nitrile coupling reaction developed by Larock and coworkers.[298]

Nitrile Coupling

The activation of C-H bonds for chemical functionalization is an active area of ongoing research.[299-301] The ability to directly install chemical groups onto hydrocarbon substrates has the potential to provide economical and clean pathways for the synthesis of complex molecules. This transformation is difficult due to the high strength of the C-H bond (105-110 kcal/mol). The use of highly electron-deficient palladium(II) catalysts have permitted the functionalization of a wide range of substrates.[299] The electron-poor palladium, under specific condition, is able to oxidatively insert into the C-H bond and thus permit the installation of various functional groups.

Recently, Larock and Zhou reported a methodology for the synthesis of aryl ketones by a palladium-catalyzed C-H activation followed by carbopalladation of a nitrile (Scheme 23).[298] This reaction was utilized to generate a range of aryl ketones, both intramolecularly (as in Scheme 23) and intermolecularly. The proposed mechanism for this reaction is presented in Scheme 24. The active catalyst is the palladium(II) trifluoroacetate adduct **IV-67** that undergoes C-H insertion with the arene to form the aryl palladium adduct **IV-68**. Following ligand exchange, **IV-69** undergoes aryl group transfer to the nitrile, forming an imine, which is then lost from the catalyst to regenerate **IV-67**. The imine can then be hydrolyzed to form the ketone.

Scheme 23

IV-65   IV-66
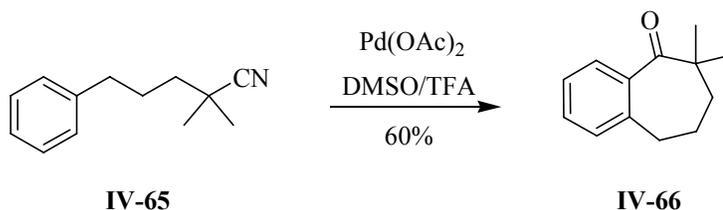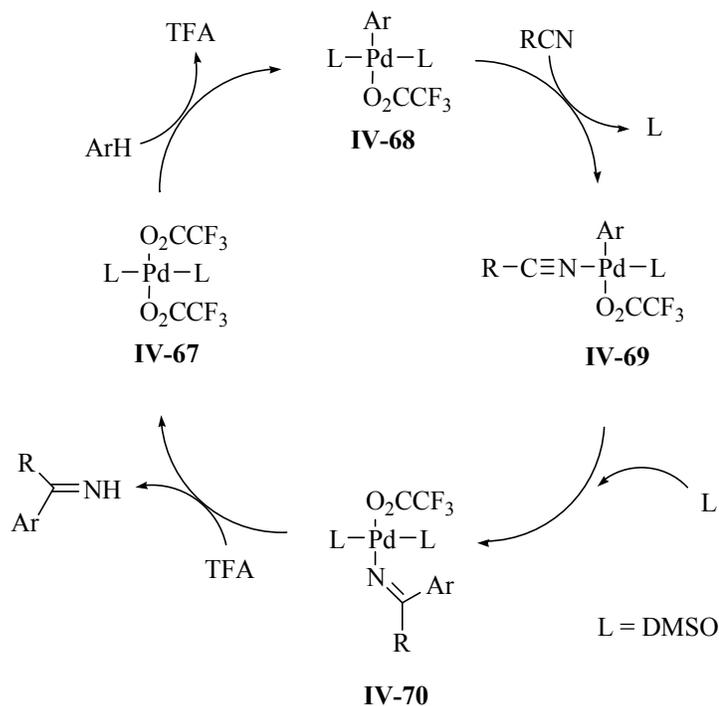
Scheme 24

Our initial task was to develop of a model system to probe whether intramolecular reaction in a biaryl system could be achieved. Synthesis of the model system is presented in Scheme 25. Alkylation of 2-phenylbenzyl bromide (**IV-71**) with the lithium salt of 2-propylnitrile provided *gem*-dimethyl nitrile **IV-72**. Treatment of this nitrile with a palladium (II) catalyst in refluxing TFA cleanly provided the intramolecular ring closure product **IV-73**. During the course of optimization studies, it was discovered that the presence of molecular oxygen was vital for the reaction to occur. If the reaction was performed under Ar, or using degassed solvents, no product was obtained. It is hypothesized that oxygen is serving to maintain palladium (II) during the course of the reaction.

Scheme 25

IV-71　　99%　　**IV-72**

IV-73
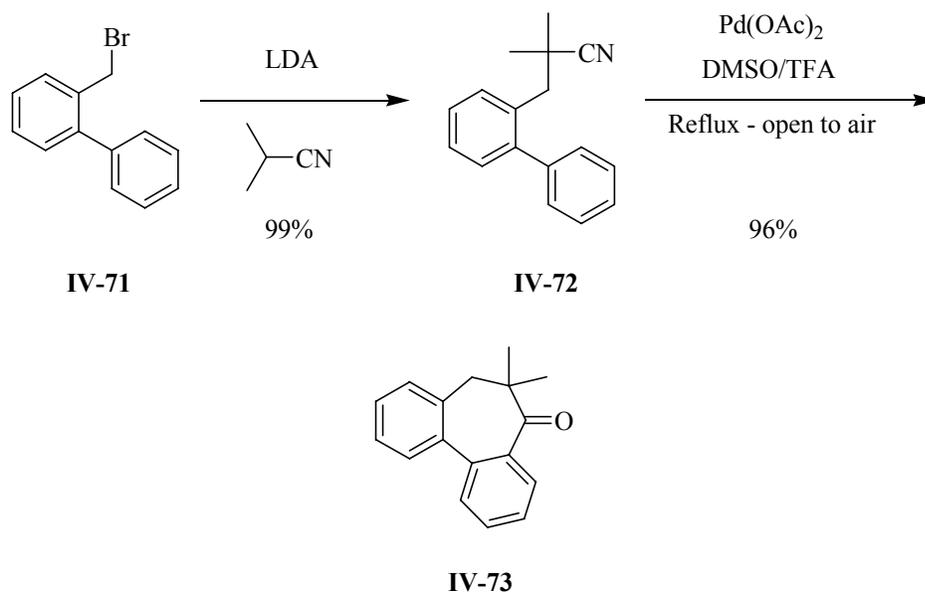
Having shown that the ring closure was successful in the model, the next task was to apply this reaction to the synthesis of the allocolchicine carbocyclic skeleton. The synthesis began with bromination of benzaldehyde **IV-74** to provide aryl bromide **IV-75**. Palladium-catalyzed siloxane cross-coupling gave biaryls **IV-76** (R = H), and **IV-77** (R = OMe) in excellent yields. Reduction of the aldehyde, followed by conversion of the resulting alcohol to the bromide and subsequent alkylation generated the cyclization precursors **IV-82** and **IV-83**. Gratifyingly, these compounds cyclized in good yields to generate *gem*-dimethyl allocolchicinoids **IV-84** and **IV-85** (Scheme 26).

Scheme 26

IV-74

Br$_2$

HOAc, CH$_2$Cl$_2$

94%

IV-75

5 % Pd(OAc)$_2$

25 % PPh$_3$

R—⟨benzene⟩—Si(OEt)$_3$

TBAF / THF

IV-76: R = H, 94%

IV-77: R = OMe, 89%

NaBH$_4$

MeOH

IV-78: R = H, 99%

IV-79: R = OMe, 86%

PBr$_3$

CH$_2$Cl$_2$

IV-80: R = H, 97%

IV-81: R = OMe, 89%

LDA /THF

IV-82: R = H, 92%

IV-83: R = OMe, 76%

Pd(OAc)$_2$

DMSO, TFA

IV-84: R = H, 89%

IV-85: R = OMe, 76%
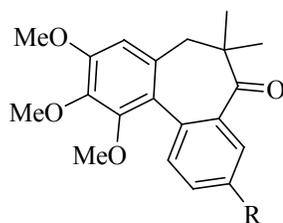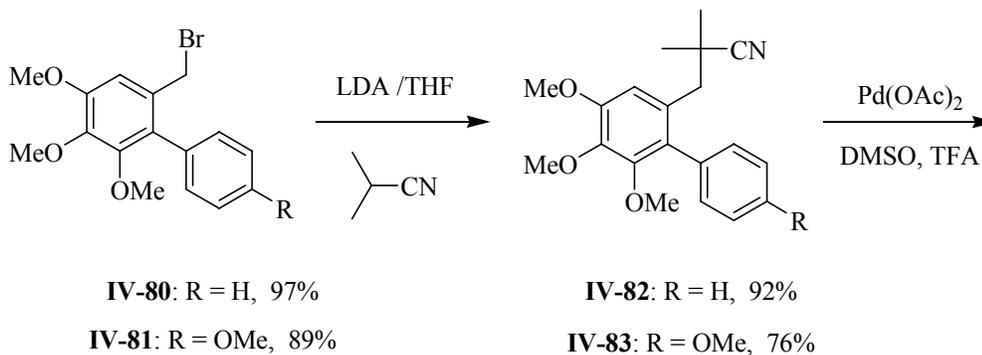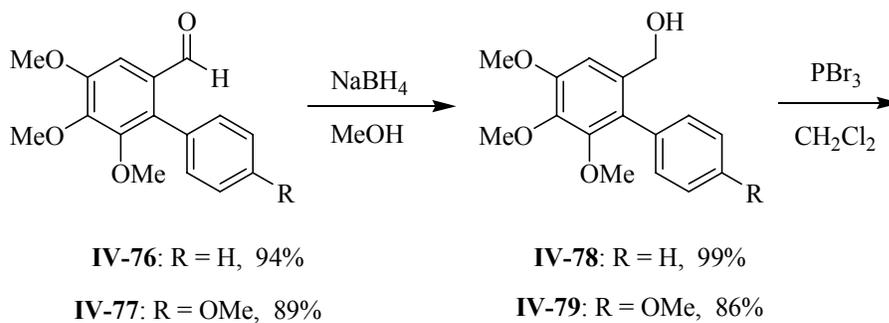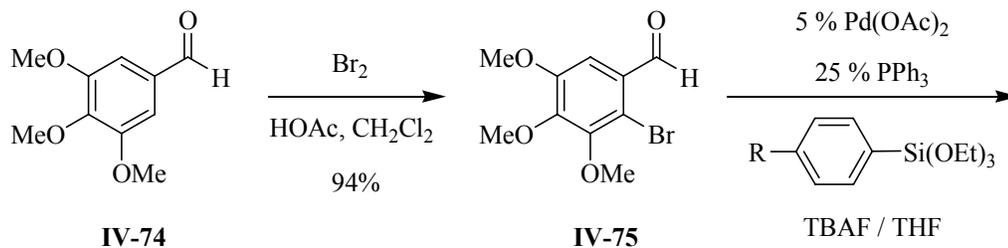
While this approach allowed facile access to *gem*-dimethyl allocolchicinoids, our goal was to establish the parent allocolchicine framework, which is devoid of *gem-*

dimethyl substituents. We, therefore, sought to perform the nitrile coupling in the absence of these groups. In his studies, Larock was unable to successfully react nitriles that did not possess *gem*-dimethyl groups (*vide infra*). However, because our substrate was different from those previously studied, it was deemed important to perform the cyclization without the *gem*-dimethyls present. Starting with biaryl **IV-76**, Wittig olefination gave α-β unsaturated nitile **IV-86** in 86% yield. Selective reduction of the alkene with sodium borohydride in methanolic pyridine provided the saturated nitrile **IV-87** in excellent yield. Disappointingly, all attempts to cyclize nitrile **IV-87** led to decomposition.

Scheme 27
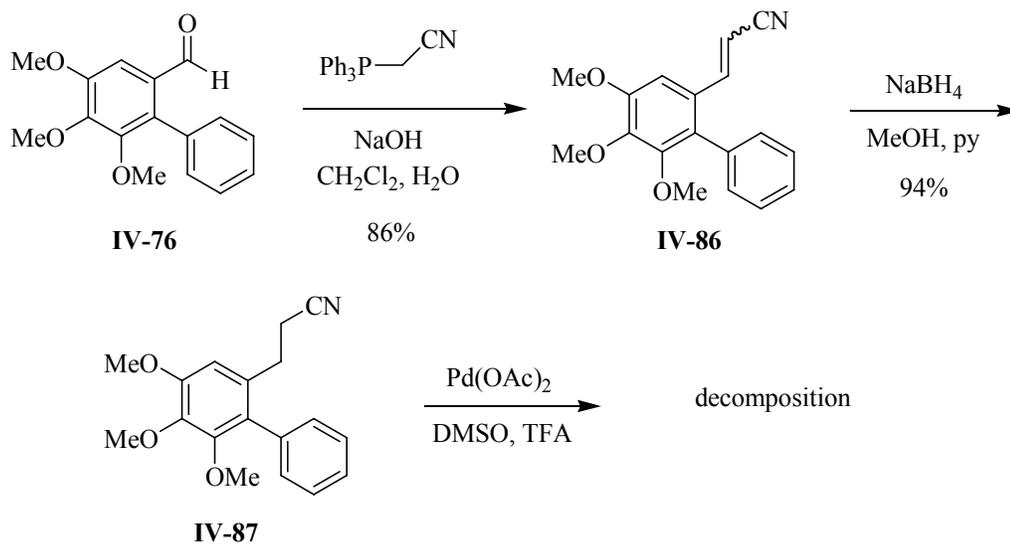
The role of the *gem*-dimethyl groups had been studied by Larock and Pletnev.[302] It was proposed that the *gem*-dimethyl groups control the orientation of the nitrile (Scheme 28). Without the presence of these groups, the nitrile is not oriented toward the palladium, and no productive reaction occurs. However, when these groups are present,

the nitrile, as it is the smallest of the substituents, is oriented directly toward the palladium, allowing for the cyclization to proceed. An alternative reason for the presence of the methyl groups is that they prevent the enolization of the nitrile. Coordination of the nitrile (see **IV-88** below) would make the α-protons more acidic, potentially leading to enolization and competitive side reactions. However, using deuterium-labeled substrates,[302] Larock demonstrated that these protons are not abstracted under the reaction conditions, and the most likely role for the methyl groups is to control conformation.

Scheme 28
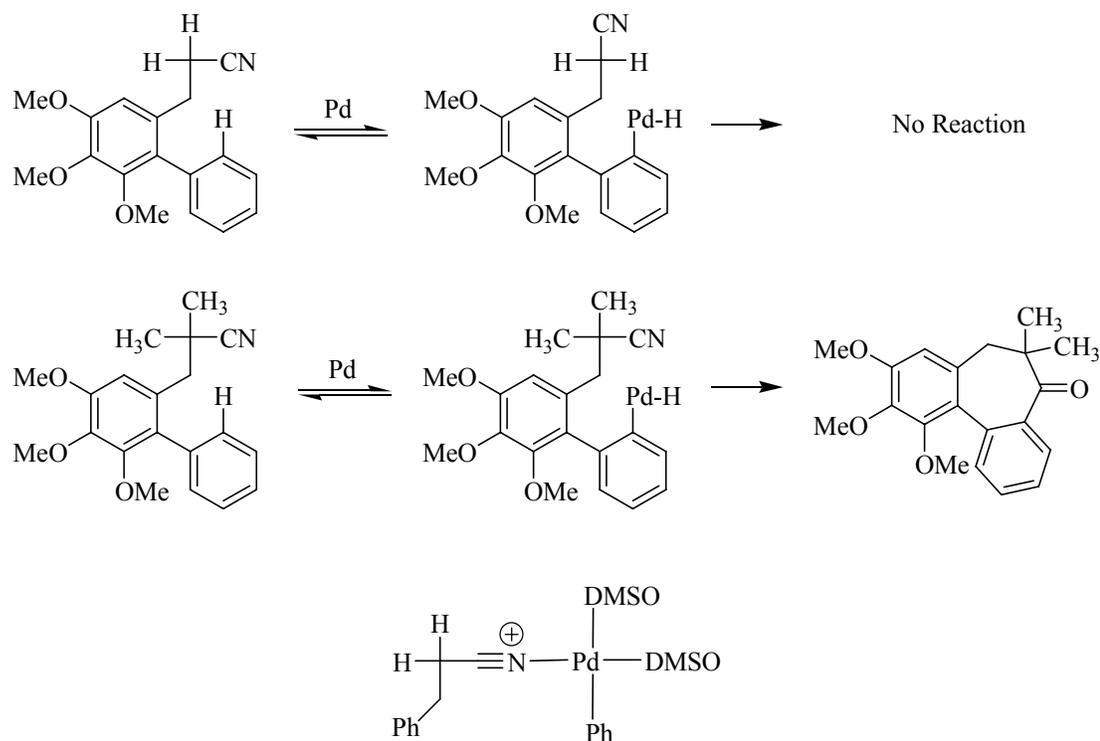
IV-88

Carbene Annulation

Our final approach to the synthesis of the carbocyclic skeleton of allocolchicine was centered upon a one-carbon ring expansion of a functionalized phenanthrene ring system. Joshi and coworkers developed a procedure whereby the 9-10 double bond of phenanthrene **IV-89** can be selectively reacted with dichlorocarbene to generate dichlorocyclopropyl adduct **IV-90** (Scheme 29).[303] If compound **IV-90** is heated neat, followed by an aqueous quench, the ring expanded allyic alcohol **IV-91** is obtained quantitatively.[304-306] Oxidation provides the α-chloroenone **IV-92**. This compound possesses the 6-7-6 ring system of allocolchicine. We, therefore, sought to develop this methodology beyond the simple phenanthrene system, and use it to synthesize the unsymmetrical allocolchicine skeleton.

Scheme 29
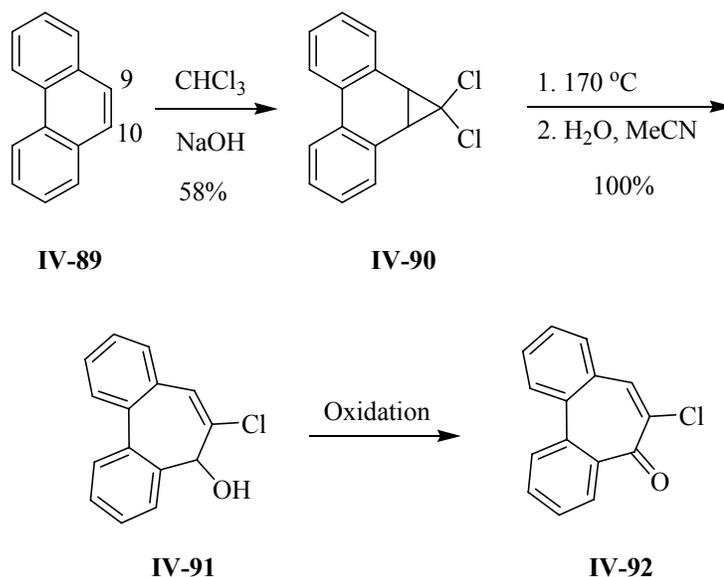
The initial target was allocolchicinoid **IV-93**. This compound, lacking the C ring ester of natural allocolchicine, has been shown to possess potent antitumor activity.[283]

Retrosynthetically, this compound would be obtained from a ring expansion of phenanthrol **IV-94**, which in turn would be obtained from a siloxane coupling of functionalized aryl bromide **IV-75** and phenyl trimethoxysilane (Scheme 30). However, as the ring expansion of phenanthrols has received little attention, a model system utilizing 9-phenanthrol (**IV-95**) as substrate was examined.

Scheme 30
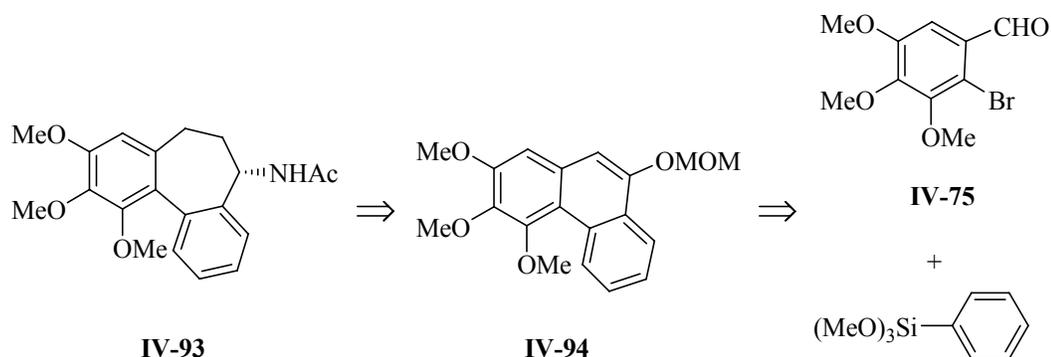
Protection of the hydroxyl of 9-phenanthrol (**IV-95**) as a MOM group proceeded smoothly to provide ether **IV-96** (Scheme 31). Reaction of this compound under optimized conditions (CHCl$_3$, 50% NaOH, BnEt$_3$NCl, r. t., 5h), led to the formation of the dichlorocyclopropyl adduct **IV-97** in excellent yield. Treatment of compound **IV-97** with dilute acid removed the MOM ether and induced cyclopropane ring cleavage providing the ring expanded α-chloroenone **IV-92**. Hydrogenation of the chloroenone, using conditions developed by Jones and Coburn,[304] smoothly generated aryl ketone **IV-98**.

Scheme 31
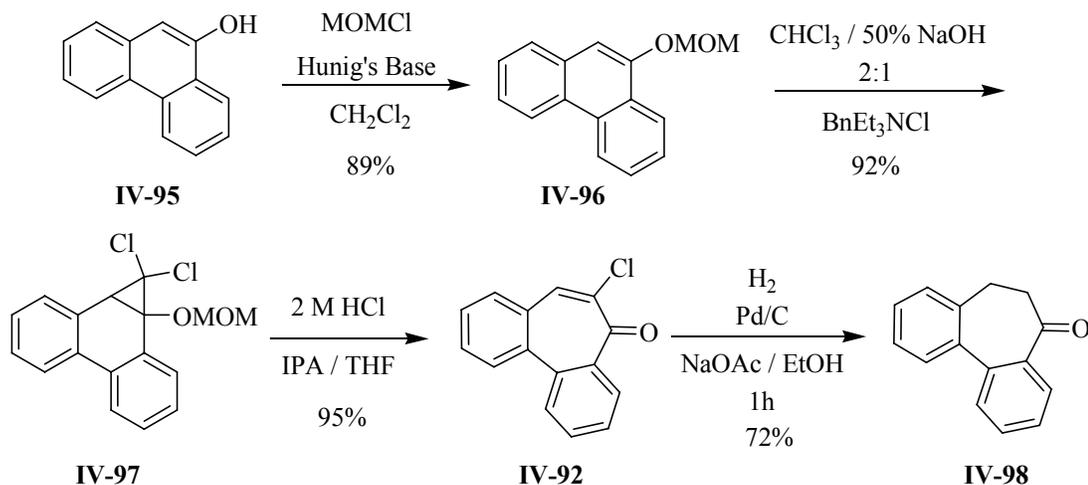
The final task remaining was to construct the unsymmetrical allocolchicine framework. Up to now, the ring expansion had been conducted on a simple phenanthrol derivative and a synthesis of the full A-B-C ring system of allocolchicine was necessary. Accordingly, biaryl **IV-76** (obtained *via* siloxane coupling, see Scheme 26 above), was homologated by Wittig reaction, followed by oxidation to acid **IV-99** (Scheme 32). Friedal-Crafts ring closure generated air sensitive phenanthrol **IV-100**. Phenanthrol **IV-100** was oxidized by atmospheric oxygen to generate the 9,10-diketone.[307] This oxidation was circumvented by immediately protecting the free hydroxyl to provide MOM ether **IV-94**.

Scheme 32
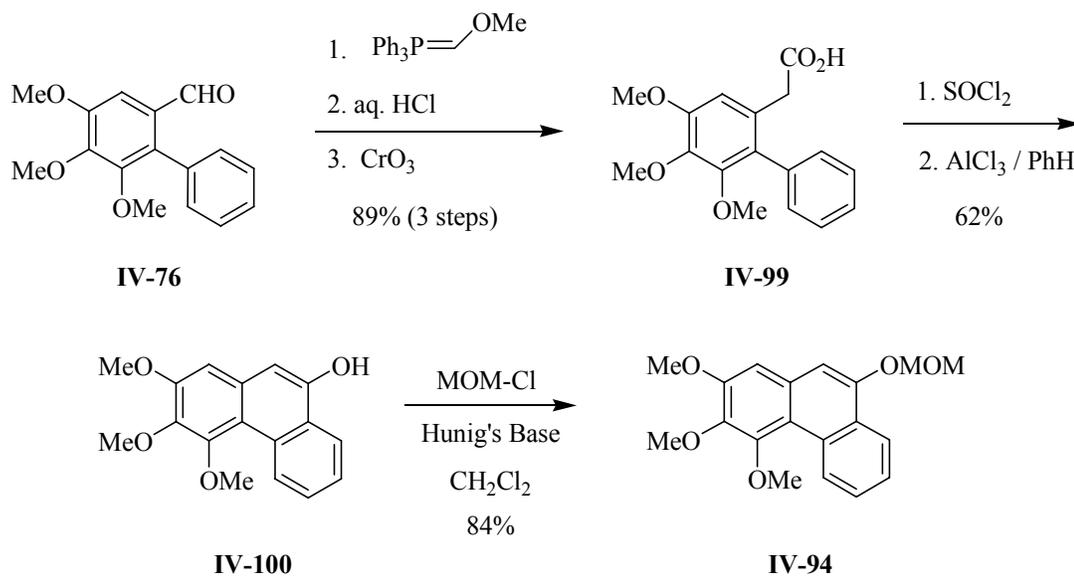
Cyclopropanation of MOM ether **IV-94** provided dichlorocyclopropyl adduct **IV-101** (Scheme 33). Ring expansion, presumably occurring *via* deprotected alcohol **IV-102**, proceeded uneventfully to provide α-chloroenone **IV-103**. Hydrogenation of enone **IV-103** gave saturated ketone **IV-104**. Reductive amination followed by acylation provided the known[291] allocolchicinoid **IV-93**.

Scheme 33

Having successfully generated the allocolchicine carbocyclic framework, attention focused onto functionalization of α-chloroenone **IV-92** (Scheme 34). This compound possesses a high degree of functionalization, which could be utilized to generate allocolchicine B ring analogues, which have proven difficult to obtain.[273,277] Analogues of allocolchicine are desirable for medicinal studies; however, the generation of analogues derived from the natural product are difficult to obtain. Accordingly, enone **IV-92** can be hydrogenated to the benzyl alcohol **IV-105**. Alternatively, by switching the hydrogenation solvent from EtOH to EtOAc,[304] hydrogenation can be stopped at the α-chloroketone, which can be eliminated to generate the Michael acceptor **IV-106**.

Scheme 34

The palladium-catalyzed cross-coupling of the chloride moiety of α-chloroenone

IV-92 was also investigated. Gratifyingly, when α-chloroenone **IV-92** was subjected to

basic Suzuki coupling conditions,[19] a good yield of the coupled product **IV-107** was

obtained. This result is particularly noteworthy because it constitutes the first example of

the coupling of an α-chloroenone. The coupling of iodides and bromides has been

reported previously,[308-316] but there are no examples of the coupling of chlorides. The

corresponding aryl siloxane coupling reaction proceeded in a moderate (35%) yield;

therefore, in this instance the use of an aryl boronic acid is advantageous.

The phenanthrene-carbene ring expansion pathway has facilitated the synthesis of

the full carbocyclic skeleton of allocolchine and its derivatives. This pathway is based

upon two key steps. First, the siloxane coupling reaction to generate the A-C ring biaryl

bond. Using a variety of aryl siloxanes as shown in Table 4, allows for the generation of

a variety of allocolchicine derivatives in excellent yields, including allocolchicine itself

(Table 4, entry 4). Additionally, the generation of an α-chloroenone upon ring expansion of the phenanthrol intermediate allowed for extensive modification of the B ring, including a novel Suzuki cross-coupling.

Table 4. Coupling of Substituted Siloxanes[a]
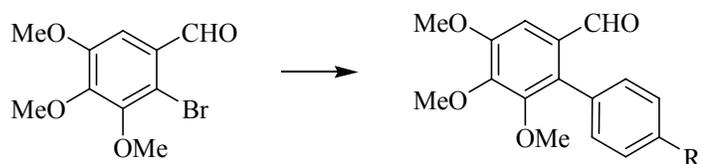
entry	R	yield[b]
1	H	94
2	OMe	93
3	Me	87
4	CO_2Et	94

[a] Conditions: 5 % Pd(OAc)$_2$, 25 % PPh$_3$, 1.5 equiv aryl siloxane, 1.5 equiv TBAF, THF. [b] Isolated yield of purified product.

CONCLUSION

Several pathways were explored for the synthesis of allocolchicine and its analogues. Attempts to develop a novel two-carbon ring expansion of a fluorenone derivative were unsuccessful. However, the application of Larock's nitrile coupling reaction has allowed for the synthesis of *gem*-dimethyl allocolchicinoids. This methodology has the potential to be modified to allow for the synthesis of

allocolchicinoids without the *gem*-dimethyl groups present by utilizing a removable alkyl protecting group. The phenanthrene-carbene ring expansion pathway holds the most promise as a useful synthetic route to allocolchicinoids. When the synthetic utility of the α-chloroenone is combined with the flexibility of the aryl siloxane coupling reaction, it is possible to selectively functionalize and modify every carbon present in allocolchine; thus making it possible to access derivatives that may prove therapeutically useful.

PART 3: Experimental Section

COLCHICINE EXPERIMENTAL SECTION

Synthesis of 5-Bromotroplone (IV-16)

7,7-Dibromo-bicyclo[4.1.0]hept-3-ene (IV-18). The dibromide was prepared using a modified procedure of Hofmann.[317] To 300 mL of *tert*-butyl alcohol was added 10.0 g of potassium. Upon dissolution of all of the potassium, excess alcohol was removed *in vacuo*. The resulting white potassium *tert*-butoxide was dried *in vacuo* for 12 h. The dry potassium *tert*-butoxide (14.6 g, 130 mmol) was added to 250 mL of pentane. The suspension was cooled to 0 °C and 25.0 mL (260 mmol) of 1,4-cyclohexadiene was added. With stirring, 11.0 mL (130 mmol) of bromoform was added over 30 min at a rate to maintain an internal temperature between 0 °C and 5 °C. The reaction was stirred for an additional 30 min at 0 °C followed by the addition of 200 mL of water. The organic layer was separated, and the aqueous fraction extracted with pentane (100 mL x2). The

combined organic extracts were dried (MgSO$_4$) and concentrated *in vacuo* to give a pale yellow oil. Column chromatography (pentane, TLC R$_f$ = 0.59) yielded colorless crystals (60%) mp 36-37 °C (lit. 36.8-37 °C).[318] The IR matched that reported by Coates.[318] The ^{1}H NMR and ^{13}C NMR match that reported by Rigby.[319]

(1α, 3β, 4β, 6α)-4-Acetoxy-7,7-dibromobicyclo[4.1.0]heptan-3-ol (IV-19). The hydroxyacetate was prepared using a modified procedure of Banwell.[320] Iodine (4.47 g, 17.6 mmol) was added over a 30 min period to a stirred mixture of 7,7-Dibromo-bicyclo[4.1.0]hept-3-ene (4.00 g, 16.0 mmol), and silver acetate (5.34 g, 32.0 mmol) in acetic acid (70 mL). Upon completion of the addition of the iodine, water was added (0.288 mL, 16.0 mmol). The reaction was stirred in the dark for 3 days. The mixture was then filtered through celite and diluted with 100 mL of CH$_2$Cl$_2$. Water (100 mL) was added, followed by solid Na$_2$CO$_3$ until all of the acetic acid had been consumed. The layers were separated and the aqueous layer was washed with 75 mL of CH$_2$Cl$_2$ twice. The combined organic layers were washed with successively with saturated NaHCO$_3$ (100 mL), 20% NaHSO$_3$ (100 mL), water (100 mL), and brine (100 mL), dried with MgSO$_4$, and concentrated *in vacuo*. Column chromatography (1:1 hexanes/EtOAc, TLC R$_f$ = 0.39) yielded a white solid (81%) mp 82.6-83.8 °C (lit. 82-83 °C).[320] The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[320]

(1α, 4β, 6α)-4-Acetoxy-7,7-dibromobicyclo[4.1.0]heptan-3-one (IV-20). The α-acetoxy ketone was prepared according to a modified procedure of Banwell.[320] (1α, 3β, 4β, 6α)-4-Acetoxy-7,7-dibromobicyclo[4.1.0]heptan-3-ol (3.91 g, 9.50 mmol) was added

to 100 mL of CH_2Cl_2. Pyridinium chlorochromate (5.11 g, 24.0 mmol) was then added in one portion. The reaction was stirred at room temperature until TLC indicated the all of the starting alcohol had been consumed (2 h). The reaction was concentrated to 1/5 of the original volume and 100 mL of ether was added. The mixture was then filtered through a short pad of silica gel using 500 mL of 1:1 ether/CH_2Cl_2. The solvents were removed *in vacuo* to produce a light brown solid. Column chromatography (3:1 hexanes/EtOAc, TLC R_f = 0.39) yielded a white solid (90%) mp 119.6-120.3 °C (lit. 118-120 °C).[320] The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[320]

5-Bromo-2-hydroxycyclohepta-2,4,6-triene-1-one (IV-21).   5-Bromotropolone was prepared according to a literature procedure.[320]

5-Bromo-2-methoxy-cyclohepat-2,4,6-trien-1-one (IV-16).   Dimethyl sulfate (0.283 mL, 2.99 mmol) was added to a stirred solution of K_2CO_3 (1.03 g, 7.47 mmol) and 5-Bromo-2-hydroxycyclohepta-2,4,6-triene-1-one (500 mg, 2.49 mmol) in 10 mL of 90:10 acetone/water. The bright yellow suspension was refluxed for 4 h to produce a cloudy white mixture. The acetone was then removed *in vacuo* and the remaining mixture extracted with CH_2Cl_2 (30 mL x3). The combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to produce pale yellow needles (89%) mp 136.2-137.0 °C (lit. 135-137 °C).[320] The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[320]

Synthesis of Aryl Siloxanes for Bromotropolone Couplings

4-(Triethoxysilyl)-1,2,3-trimethoxybenzene (Table 2, entry 1). Siloxane was prepared according to the ortho-lithiation procedure of DeShong[57] and purified by column chromatography (TLC R_f = 0.41 4:1 hexanes/EtOAc) to yield a colorless oil (77%). IR (CCl$_4$) 3071 (w), 2978 (s), 2940 (s), 2895 (s), 2836 (m), 1587 (s), 1493 (s), 1455 (s), 1400 (s), 1293 (s), 1234 (s), 1089 (vs), 958 (s); ^{1}H NMR (CDCl$_3$) δ 1.23 (t, J=7.0, 9H), 3.87 (q, J=7.0, 6H), 3.83 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 6.65 (d, J=8.4, 1H), 7.27 (d, J=8.4, 1H); ^{13}C NMR (CDCl$_3$) δ 18.3, 55.9, 58.6, 60.6, 60.8, 107.4, 116.7, 131.7, 141.5, 156.2, 158.7; LRMS (FAB$^+$) m/z 331 (M$^+$ +H, 95), 330 (92), 285 (100), 241 (40), 163 (40); HRMS (EI$^+$) m/z calcd for C$_{18}$H$_{26}$O$_6$Si 330.1499, found 330.1513.

2-(Triethoxysilyl)anisole (Table 2, entry 2). The title compound was synthesized according to a published procedure.[57] The spectral data match those reported previously.[57]

4-(Triethoxysilyl)-1,2-dimethoxybenzene (Table 2, entry 3). Siloxane was prepared according to the metallation procedure of DeShong.[56] Kugelrohr distillation (130 °C, 0.1 mm Hg) yielded a colorless oil (61%). IR (CCl$_4$) 3054 (w), 2971 (s), 2936 (s), 2898 (s), 2833 (m), 1590 (s), 1507 (s), 1466 (m), 1390 (m), 1259 (s), 1114 (vs), 962 (s); ^{1}H NMR (CDCl$_3$) δ 1.25 (t, J=7.0, 9H), 3.86 (q, J=7.0, 6H), 3.90 (s, 3H), 3.91 (s, 3H), 6.90 (d, J=8.4, 1H), 7.15 (m, 1H), 7.26 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 18.3, 55.7, 55.8, 58.7,

110.9, 116.8, 122.2, 128.4, 148.6, 150.9; LRMS (FAB$^+$) m/z 300 (M$^+$, 100), 299 (15), 255 (48), 163 (38); HRMS (EI$^+$) m/z calcd for $C_{14}H_{24}O_5Si$ 300.1393, found 300.1385.

2-(Triethoxysilyl)toluene (Table 2, entry 4). The title compound was synthesized according to a published procedure.[56] The spectral data match those reported previously.[56]

1-(Triethoxysilyl)-3,4-methylenedioxybenzene (Table 2, entry 5). The title compound was synthesized according to a published procedure.[56] The spectral data match those reported previously.[50]

4-(Triethoxysilyl)anisole (Table 2, entry 6). The title compound was synthesized according to a published procedure.[56] The spectral data match those reported previously.[56]

5-(Triethoxysilyl)-1,2,3-trimethoxybenzene (Table 2, entry 7). Siloxane was prepared according to the hydrosilylation procedure of Masuda[60] using 1-bromo-2,3,4-trimethoxybenzene, which was prepared according to a literature procedure.[254] Title compound was isolated as a colorless oil (66%) using column chromatography (TLC R_f = 0.21, 9:1 hexane/EtOAc). IR (CCl$_4$) 3078 (w), 2974 (s), 2926 (s), 2881 (m), 2836 (w), 1576 (s), 1500 (m), 1459 (m), 1400 (s), 1307 (s), 1110 (vs), 969 (m); ^{1}H NMR (CDCl$_3$) δ

1.27(t, J=7.0, 9H), 3.86 (q, J=7.0, 6H), 3.87s, 3H), 3.89 (s, 6H), 6.88 (s, 2H); ^{13}C NMR (CDCl$_3$) δ 18.3, 56.1, 58.8, 60.8, 111.3, 125.8, 140.1, 153.1; LRMS (FAB$^+$) m/z 330 (M$^+$, 100), 329 (15), 285 (23), 162 (37); HRMS (EI$^+$) m/z calcd for C$_{15}$H$_{26}$O$_6$Si 330.1499, found 330.1493.

Representative procedure for the palladium-catalyzed cross-coupling of 5-bromotropolone (IV-16) with aryl siloxanes: **2-Methoxy-5-phenylcyclohepta-2,4,6-trien-1-one (Table 3, entry 1)**. To a 25 mL round bottom flask was added 5-bromo-2-methoxy-cyclohepat-2,4,6-trien-1-one (104 mg, 0.480 mmol), 10.8 mg Pd(OAc)$_2$ (0.0480 mmol), 63.0 mg PPh$_3$ (0.240 mmol) and phenyl trimethoxysilane (180 μL, 0.970 mmol). The flask was placed under argon and 5 mL of THF was added, followed by 0.970 mL of a 1.0 M solution of TBAF in THF (0.970 mmol). The reaction was refluxed for 12 h. Following this time, the reaction mixture was poured into 20 mL of water and extracted three times with CH$_2$Cl$_2$ (50 mL). The organic extracts were combined and dried (Na$_2$SO$_4$) and evaporated to produce a dark brown oil. Column chromatography (TLC R$_f$ = 0.38, EtOAc) yielded 86.0 mg of a light tan solid (84%) mp 139.2-140.4 °C (lit. 140-141 °C).[226] The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[226]

2-Methoxy-5-(4′-methoxyphenyl)cyclohepta-2,4,6-trien-1-one (Table 3, entry 2). Title compound was prepared in a similar manner as described above and was purified via column chromatography (TLC R$_f$ = 0.30, EtOAc) to provide 94.0 mg of a light tan

solid (81%) mp 148.5-148.9 °C (lit. 151.5-152.0 °C).[254] The IR, ^{1}H NMR, and ^{13}C NMR

matched that reported by Banwell.[254]

2-Methoxy-5-(2′-methylphenyl)cyclohepta-2,4,6-trien-1-one (Table 3, entry 4). Title

compound was prepared in a similar manner as described above and was purified via

column chromatography (TLC R_f = 0.30, EtOAc) to provide 88.3 mg of a light tan solid

(81%) mp 110.0-110.5 °C. IR (CCl$_4$) 3080 (w), 3057 (w), 3020 (w), 2957 (w), 2933 (w),

2863 (w), 2840 (w), 1632 (m), 1596 (s), 1483 (m), 1248 (s), 1204 (m), 1117(s); ^{1}H NMR

(CDCl$_3$) δ 2.26 (s, 3H), 3.99 (s, 3H), 6.80 (d, J=10.4, 1H), 7.03 (d, J=10.4, 1H); 7.18 (m,

1H), 7.26-7.29 (m, 2H), 7.46-7.55 (m, 2H), 7.65-7.70 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 20.2,

56.3, 112.4, 128.4, 129.1, 130.6, 130.8, 131.9, 132.6, 133.6, 139.3, 142.0, 142.3, 164.5,

180.1; LRMS (FAB$^+$) m/z 227 (M$^+$, 100), 226 (10), 164 (10); HRMS (EI$^+$) m/z calcd for

C$_{15}$H$_{15}$O$_2$ 227.1072, found 227.1081.

2-Methoxy-5-(3′,4′-methylenedioxyphenyl)cyclohepta-2,4,6-trien-1-one (Table 3,

entry 5). Title compound was prepared in a similar manner as described above and was

purified via column chromatography (TLC R_f = 0.30, 4:1 EtOAc/hexanes) to provide 107

mg of a light tan solid (87%) mp 150-151°C. IR (CCl$_4$) 3081 (w), 3061 (w), 3009 (w),

2964 (w), 2926 (w), 2850 (w), 1635 (m), 1587 (m), 1507 (m), 1486 (m), 1245 (s), 1121

(m); ^{1}H NMR (CDCl$_3$) δ 3.98 (s, 3H), 6.02 (s, 2H), 6.81-6.94 (m, 1H), 6.95-6.96 (m, 1H),

7.19-7.22 (m, 1H), 7.29-7.32 (m, 1H), 7.47-7.50 (m, 2H), 7.68-7.69 (m, 1H); ^{13}C NMR

(CDCl$_3$) δ 56.3, 101.5, 107.7, 108.7, 112.8, 121.2, 128.4, 128.6, 130.6, 137.0, 137.9, 141.4, 148.3, 164.1, 179.8; LRMS (FAB$^+$) m/z 257 (M$^+$, 20), 245 (100), 243 (30), 239 (20); HRMS (EI$^+$) m/z calcd for C$_{15}$H$_{13}$O$_4$ 257.0814, found 257.0822.

2-Methoxy-5-(3′,4′-dimethoxyphenyl)cyclohepta-2,4,6-trien-1-one (Table 3, entry 6). Title compound was prepared in a similar manner as described above and was purified via column chromatography (TLC R$_f$ = 0.30, EtOAc) to provide 115 mg of a light tan solid (88%) mp 168.1-168.3 °C (lit. 168-168.5 °C).[254] The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[254]

2-Methoxy-5-(3′,4′,5′-trimethoxyphenyl)cyclohepta-2,4,6-trien-1-one (Table 3, entry 7). Title compound was prepared in a similar manner as described above and was purified via column chromatography (TLC R$_f$ = 0.40, EtOAc) to provide 129 mg of a light tan solid (89%) mp 137-138 °C (lit. 138-139 °C).[254] The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[254]

2-Methoxy-5-(2′,3′,4′-trimethoxyphenyl)cyclohepta-2,4,6-trien-1-one (IV-14). To a 25 mL roundbottom flask was added 50.0 mg (0.233 mmol) of 5-bromotropolone, 225 mg (0.253 mmol) Pd(OAc)$_2$, and 336 mg (1.28 mmol) PPh$_3$. The contents of the flask were placed under argon and THF (5 mL) was added. The reaction was refluxed for 15 min, and 154 mg (0.466 mmol) of 4-(triethoxysilyl)-1,2,3-trimethoxybenzene (**IV-23**) in

2.0 mL of THF was added via syringe, followed by 0.466 mL of TBAF (1.0 M in THF, 0.466 mmol). The reaction was maintained at reflux for a further 30 min, poured into water (50 mL) and extracted three times with 50 mL of CH_2Cl_2. The organic extracts were dried ($MgSO_4$) and evaporated. Column chromatography (TLC R_f = 0.21 EtOAc) yielded 70.4 mg of a light tan powder (92%) mp 116-117 °C (lit. 112-117°C).[254] The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[254]

2,3,4-Trimethoxybiphenyl (IV-24). 4-(Triethoxysilyl)-1,2,3-trimethoxybenzene (**IV-23**) (496 mg, 1.50 mmole), bromobenzene (157 mg, 1.00 mmol), Pd(OAc)$_2$ (112 mg, 0.500 mmol), and PPh$_3$ (262 mg, 1.00 mmol) were combined in a 25 mL round bottom flask and placed under argon. THF (10 mL) was added, followed by 1.50 mL (1.50 mmol) of TBAF (1.0 M in THF). The reaction was heated to reflux for 1 h. The reaction mixture was cooled to room temperature and diluted with ether (20 mL). The organic layer was washed with water (20 x2), dried ($MgSO_4$), and evaporated to yield a brown oil. Column chromatography (TLC R_f = 0.31, 9:1 Hexanes/EtOAc) yielded a yellow oil which was recrystallized (hexane) to give 171 mg of a white solid (70%) mp 47.2-47.9 °C (lit. 46-47 °C).[224] The ^{1}H, and ^{13}C NMR, and IR match that reported by Banwell.[224]

Representative procedure for the palladium-catalyzed cross-coupling of 5-bromotropolone (IV-16) with aryl boronic acids: **2-Methoxy-5-(2'-methoxyphenyl)cyclohepta-2,4,6-trien-1-one (Table 3, entry 3)**. 2-Bromoanisole (748 mg, 4.00 mmol) was added to a suspension of Mg (107 mg, 4.40 mmol) in 10 mL of

THF. The reaction mixture was heated to reflux until all of the aryl bromide had been consumed (3 h). After cooling to -78 °C, the aryl Grignard reagent was transferred via cannula to a -78 °C solution of trimethyl borate (538 μL, 4.80 mmol) in 15 mL of THF. The reaction mixture was allowed to warm to room temperature overnight, at which time the yellow solution was poured into 50 mL of 1M HCl. The aqueous layer was extracted three times with 40 mL of ether. The combined ether extracts were washed with three 50 mL portions of 1M NaOH. The combined basic extracts were acidified with 2 M HCl. The boronic acid was then extracted into CH_2Cl_2, dried ($MgSO_4$) and the solvent evaporated to provide the boronic acid as a white solid which was used without further purification in the coupling reaction

The palladium-catalyzed cross-coupling reaction is a modified procedure of Nair.[256] To a 50 mL round bottom flask was added 5-bromo-2-methoxy-cyclohepat-2,4,6-trien-1-one (**IV-16**) (215 mg, 1.00 mmol) and 57.8 mg Pd(PPh$_3$)$_4$ (0.05 mmol). The flask was placed under an Ar atmosphere and 10 mL of toluene was added. The boronic acid (228 mg, 1.50 mmol), dissolved in 1.5 mL of EtOH, was added by syringe, followed by 1.50 mL of a 2.0 M Na$_2$CO$_3$ solution. The reaction mixture was refluxed for 5 h to consume all of the aryl bromide. The reaction was cooled to room temperature and 5 drops of 20 % H$_2$O$_2$ was added and the mixture was stirred for a further hour. Following this time, the reaction mixture was poured into 20 mL of water and extracted three times with CH$_2$Cl$_2$ (50 mL). The organic extracts were combined, dried (Mg$_2$SO$_4$), and evaporated to produce a dark brown oil. Purification via column chromatography (TLC $R_f = 0.27$, EtOAc) provided 194 mg (80%) of the title compound as a pale yellow oil. The IR, ^{1}H NMR, and ^{13}C NMR matched that reported by Banwell.[254]

ALLOCOLCHICINE EXPERIMENTAL SECTION

CROSS COUPLING REACTIONS

2-Bromo-3,4,5-trimethoxy-benzaldehyde (IV-75). Title compound was prepared according to the procedure of Fukuyama.[321] The ^{1}H, and ^{13}C NMR, and IR match that reported by Fukuyama.[321]

Methyl 2-bromo-3,4,5-trimethoxybenzoate (IV-51). Title compound was prepared according to the procedure for compound (**IV-75**) above. Column chromatography (TLC R_f = 0.44, 1:1 hexanes/EtOAc) yielded a light yellow solid, which was recrystallized (ether/pentane) to provide 2.34 g of white needles (87%) mp 34.0-35.0 °C. IR (CCl$_4$) 3009 (s), 2936 (s), 2909 (s), 2847 (m), 1742 (s), 1486 (s), 1341 (s), 1224 (s), 1114 (s); ^{1}H NMR (CDCl$_3$) δ 3.89 (s, 6H), 3.93 (s, 3H), 3.94 (s, 3H), 7.16 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 52.5, 56.2, 61.0, 61.2, 109.6, 110.0, 127.4, 146.0, 151.5, 152.3, 166.5; LRMS (FAB$^+$) m/z 305 (M$^+$ + H, 100), 304 (M$^+$, 60), 273 (30), 226 (55); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{11}$H$_{13}$O$_5$Br 303.9946, found 303.9949.

6-Carbomethoxy-2,3,4-trimethoxy-biphenyl (IV-52). Tetrakis(triphenylphosphine) palladium (116 mg, 0.100 mmol) was added to 305 mg (1.00 mmol) of methyl-2-bromo-3,4,5-trimethoxybenzoate in a 50 mL round bottom flask. The flask was placed under argon and 10 mL of THF was added. Phenyltrimethoxysilane (373 μL, 2.00 mmol) was

added to the solution, followed by 2.00 mL of a 1.0 M solution of TBAF in THF (2.00 mmol). The pale yellow solution was heated to reflux for 12 h. The reaction was cooled to room temperature, poured through a short pad of silica gel, and diluted with ether (20 mL). The organic layer was washed with water (20 mL x2), dried, and evaporated to yield a brown oil. Column chromatography (TLC R_f = 0.31, 4:1 hexanes/EtOAc) yielded 281 mg of a white solid (93%) mp 67.2-67.8 °C. IR (CCl$_4$) 3065 (w), 3002 (w), 2940 (m), 2836 (w), 1718 (s), 1593 (m), 1486 (m), 1435 (m), 1397 (m), 1335 (s), 1224 (m), 1134 (m), 1100 (s), 1045 (m), 1007 (m); ^{1}H NMR (CDCl$_3$) δ 3.54 (s, 3H), 3.57 (s, 3H), 3.94 (s, 3H), 3.96 (s, 3H), 7.22-7.26 (m, 3H), 7.37-7.38 (m, 3H); ^{13}C NMR (CDCl$_3$) δ 51.9, 56.1, 59.9, 60.0, 108.9, 126.4, 126.9, 127.6, 129.3, 130.7, 136.7, 145.3, 151.5, 152.3, 168.1; LRMS (FAB$^+$) m/z 302 (M$^+$, 100), 271 (79), 256 (20); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{17}$H$_{20}$O$_5$ 302.1154, found 302.1148.

6-Carbaldehyde-2,3,4-trimethoxy-biphenyl (IV-76). To a 250 mL round bottom flask was added 2-bromo-3,4,5-trimethoxybenzaldehyde (5.00 g, 18.2 mmol), Pd(OAc)$_2$ (204 mg, 0.910 mmol), and PPh$_3$ (1.19 g, 4.55 mmol). The flask was placed under argon and 100 mL of THF was added *via* syringe. Phenyltrimethoxysilane (6.75 mL, 36.4 mmol) was added to the yellow solution, followed by 36.4 mL of a 1.0 M solution of TBAF in THF (36.4 mmol). The reaction was heated to reflux for 18 h, at which time, the reaction was cooled to room temperature, poured through a short pad of silica gel, and diluted with ether (100 mL). The organic layer was washed with water (100 mL x2), dried (MgSO$_4$), and evaporated to yield a yellow oil. Column chromatography (TLC R_f = 0.24, 9:1 hexanes/EtOAc) yielded 4.66 g of a white solid (94%) mp 91.2-92.4 °C. IR (CCl$_4$)

3085 (w) 3067 (w), 3009 (w), 2960 (m), 2933 (m), 2857 (m), 1683 (s), 1587 (m), 1328 (s), 1193(m), 1141 (s), 1096 (s); ^{1}H NMR (CDCl$_3$) δ 3.59 (s, 3H), 3.94 (s, 3H), 3.99 (s, 3H), 7.30-7.35 (m, 3H), 7.42-7.43 (m, 2H), 9.63 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 56.6, 61.4, 61.5, 105.6, 110.2, 127.5, 128.1, 123.3, 128.4, 129.9, 130.1, 131.4, 133.2, 191.8; LRMS (FAB$^+$) m/z 273 (M$^+$ + H, 100), 272 (80), 255 (42), 230 (24), 214 (19), 151 (18), 135 (24), 119 (25), 85 (29), 55 (34), 43 (25); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{16}$H$_{16}$O$_4$ 272.1049, found 272.1045.

6-Carbaldehyde-2,3,4,4′-tetramethoxy-biphenyl (IV-77). Title compound was prepared according to the cross-coupling procedure for biaryl **IV-76**. Column chromatography (TLC R$_f$ = 0.25, 4:1 hexanes/EtOAc) yielded a pale yellow oil. Recrystallization (hexane/EtOAc) provided 5.12 g of a white solid (93%) mp 68.0-69.0 °C. IR (CCl$_4$) 3002 (m), 2954 (s), 2933 (s), 2874 (s), 2853 (m), 2836 (m), 1745 (s), 1690 (s), 1587 (s), 1480 (s), 1462 (s), 1331 (s), 1252 (s), 1152 (s), 1100 (s); ^{1}H NMR (CDCl$_3$) δ 3.60 (s, 3H), 3.87 (s, 3H), 3.96 (s, 3H), 4.00 (s, 3H), 6.98 (d, J=8.8, 2H), 7.25 (d, J=8.8, 2H), 7.35 (s, 1H), 9.68 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 55.3, 56.1, 61.0, 61.1, 105.2, 113.5, 124.8, 129.9, 132.2, 134.3, 147.7, 151.3, 152.9, 159.4, 191.5; LRMS (FAB$^+$) m/z 303 (M$^+$ + H, 100), 302 (65), 285 (20); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{17}$H$_{18}$O$_5$ 302.1154, found 302.1154.

6-Carbaldehyde-4′-methyl-2,3,4-trimethoxy-biphenyl (Table 4, entry 3). Title compound was prepared according to the cross-coupling procedure for biaryl **IV-76**.

Column chromatography (TLC R_f = 0.23, 9:1 hexanes/EtOAc) yielded 4.53 g of a white solid (87%) mp 58.0-59.0 °C. IR (CCl$_4$) 3087 (w), 3054 (w), 3007 (m), 2967 (m), 2937 (s), 2856 (m), 1689 (s), 1586 (s), 1482 (s), 1331 (s), 1137 (s), 1097 (s), 1004 (s); ^{1}H NMR (CDCl$_3$) δ 2.43 (s, 3H), 3.61 (s, 3H), 3.96 (s, 3H), 4.00 (s, 3H), 7.21 (d, J=8.0, 2H), 7.25 (d, J=8.0, 2H), 7.36 (s, 1H), 9.66 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 21.3, 56.0, 56.1, 61.1, 105.1, 128.7, 129.7, 129.8, 130.9, 134.6, 137.7, 147.6, 151.2, 153.0, 191.5; LRMS (EI$^+$) m/z 286 (M$^+$, 100), 271 (20), 129 (20); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{17}$H$_{18}$O$_4$ 286.1205, found 286.1205.

6-Carbaldehyde-4′-carboethoxy-2,3,4-trimethoxy-biphenyl (Table 4, entry 4). Title compound was prepared according to the cross-coupling procedure for biaryl **IV-76**. Column chromatography (TLC R_f = 0.28, 4:1 hexanes/EtOAc) yielded 5.89 g of a colorless oil (94%). IR (CCl$_4$) 3004 (w), 2979 (m), 2939 (m), 2841 (m), 1711 (s), 1679 (s), 1588 (s), 1319 (s), 1268 (s), 1145 (s), 1086 (s), 1000 (s); ^{1}H NMR (CDCl$_3$) δ 1.41 (t, J=7.2, 3H), 3.58 (s, 3H), 3.95 (s, 3H), 3.99 (s, 3H). 4.40 (q, J=7.2, 2H), 7.24 (s, 1H), 7.40 (d, J=8.0, 2H), 8.11 (d, J=8.0, 2H), 9.61 (s, 3H); ^{13}C NMR (CDCl$_3$) δ 14.4, 29.0, 56.2, 61.1, 61.2, 105.5, 129.2, 129.5, 130.1, 131.1, 133.3, 137.8, 147.7, 151.0, 153.5, 166.3, 190.6; LRMS (FAB$^+$) m/z 345 (M$^+$ + H, 100), 327 (55), 299 (30), 55 (30); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{19}$H$_{20}$O$_6$ 344.1260, found 344.1275.

3,4,5-Trimethoxy-2-phenyl-benzoic acid. 6-Carbomethoxy-2,3,4-trimethoxy-biphenyl (500 mg, 1.65 mmol) and NaOH (330 mg, 8.27 mmol) were heated in a 1:1 mixture of THF and water (40 mL) to 90 °C for 24 h. At the conclusion of this time, the THF was evaporated, and the aqueous mixture was washed with Et_2O (20 mL x2). The aqueous layer was acidified, inducing the formation of a white precipitate. The precipitate was collected *via* filtration and washed thoroughly with water. The resulting white powder was dried *in vacuo* to provide 399 mg of the title compound (84%) mp 198.2-199.1 °C. IR (neat) 3082 (w), 2978 (w) 2932 (w) 2900 (s), 1671 (s), 1583 (m), 1552 (m), 1319 (s), 1085 (s); ^1H NMR ($CDCl_3$) δ 3.52 (s, 3H), 3.91 (s, 3H), 3.94 (s, 3H), 7.21-7.24 (m, 2H), 7.31-7.36 (m, 4H); ^{13}C NMR ($CDCl_3$) δ 56.6, 61.4, 61.5, 110.2, 124.9, 127.5, 128.1, 129.9, 132.1, 136.7, 146.6, 152.0, 152.7, 171.5; LRMS (FAB^+) m/z 289 (M^+ + H, 100), 288 (M^+, 95), 271 (95), 256 (40), 154 (50), 119 (70); HRMS (FAB^+, M^+) m/z calcd for $C_{16}H_{16}O_5$ 288.0998, found 288.0992.

2,3,4-Trimethoxy-9H-fluoren-9-one (IV-53). 3,4,5-Trimethoxy-2-phenyl-benzoic acid (200 mg, 0.700 mmol) was brought to a gentle reflux in 3 mL of $SOCl_2$ for 1 h. The re-orange solution was evaporated to dryness, and dried for a further hour *in vacuo*. The acid chloride was dissolved in 6 mL of benzene and the solution was added to 467 mg (3.50 mmol) of $AlCl_3$ in 3 mL of benzene at 5 °C. The reaction immediately turned dark green. The reaction mixture was stirred for a further 10 min, then quenched with ice and extracted with Et_2O (50 mL x3). The organic extracts were combined and washed with

sat. aq. NaHCO$_3$ and water, dried (MgSO$_4$), and evaporated to yield 179 mg of an orange

solid (95%) mp 108.2-108.7 °C. IR (CCl$_4$) 3071 (w), 3005 (m), 2960 (m), 2940 (m), 2867

(w), 2840 (w), 1718 (s), 1597 (m), 1455 (s), 1314 (s), 1134 (s); ^{1}H NMR (CDCl$_3$) δ 3.89,

(s, 3H), 3.94 (s, 3H), 3.99 (s, 3H), 7.05 (s, 1H), 7.17 (t, J=7.6, 1H), 7.41 (t, J=7.6, 1H),

7.55 (d, J=7.2, 1H), 7.66 (d, J=7.2, 1H); ^{13}C NMR (CDCl$_3$) δ 56.4, 60.7, 61.1, 104.3,

122.9, 123.9, 127.7, 129.8, 130.0, 134.2, 134.9, 143.4, 148.0, 149.4, 154.5, 193.2; LRMS

(FAB$^+$) m/z 271 (M$^+$ + H, 100), 270 (M$^+$, 60), 219 (25), 147 (15), 73 (30); HRMS (FAB$^+$,

M$^+$) m/z calcd for C$_{16}$H$_{14}$O$_4$ 270.0892, found 270.0882.

2,3,4-Trimethoxy-9-vinyl-9H-fluoren-9-ol (IV-54).   2,3,4-Trimethoxy-9H-fluoren-9-

one (135 mg, 0.500 mmol) was dissolved in 10 mL of THF. Vinylmagnesium bromide

(0.750 mL, 0.75 mmol, 1.0 M in THF) was added dropwise. The reaction was brought to

reflux for 1 h. The solution was cooled to room temperature and diluted with 60 mL of

ether and poured into 50 mL of sat. aq. NH$_4$Cl. The organic layer was separated and the

aqueous solution was extracted twice with 50 mL of ether. The combined organic

extracts were dried (MgSO$_4$), and evaporated to yield a yellow oil. Column

chromatography (TLC R$_f$ = 0.21, 4:1 hexanes/EtOAc) yielded 135 mg of a white solid

(91%) mp 104.0-105.0 °C. IR (CCl$_4$) 3305 (s), 3040 (w), 2967 (w), 2921 (m), 2827 (w),

1593 (m), 1453 (m), 1354 (s), 1313 (s), 1137 (s), 1090 (s), 997 (s); ^{1}H NMR (CDCl$_3$) δ

2.13 (s, 1H), 3.89 (s, 3H), 3.90 (s, 3H), 4.01 (s, 3H), 5.20-5.23 (m, 1H), 5.54-5.59 (m,

1H), 5.88-5.95 (m, 1H), 6.80 (s, 1H), 7.21-7.24 (m, 1H), 7.31-7.37 (m, 2H), 7.83 (d,

J=7.2, 1H); ^{13}C NMR (CDCl$_3$) δ 56.3, 60.7, 61.1, 82.6, 103.7, 113.5, 122.6, 123.9,

124.8, 126.7, 129.4, 138.6, 139.1, 142.9, 143.9, 147.4, 149.3, 154.2; LRMS (EI$^+$) m/z 298 (M$^+$, 100), 271 (25), 267 (18); HRMS (EI$^+$, M$^+$) m/z calcd for C$_{18}$H$_{18}$O$_4$ 298.1205, found 298.1216.

9-Ethynyl-2,3,4-trimethoxy-9H-fluoren-9-ol (IV-64). 2,3,4-Trimethoxy-9H-fluoren-9-one (150 mg, 0.550 mmol) was dissolved in 5 mL of THF. The orange solution was cooled to 0 °C and 1.65 mL (0.825 mmol, 0.5 M solution in THF) of ethynylmagnessium bromide was added dropwise. The reaction was stirred at room temperature for 2 h, then reflux for 1 h. The solution was cooled to room temperature and diluted with 40 mL of ether and poured into 20 mL of sat. aq. NH$_4$Cl. The organic layer was separated and the aqueous solution was extracted twice with 25 mL of ether. The combined organic extracts were dried (MgSO$_4$), and evaporated to yield a yellow oil. Column chromatography (TLC R$_f$ = 0.13, 4:1 hexanes/EtOAc) yielded 155 mg of a white solid (95%) mp 134.2-134.9 °C. IR (CCl$_4$) 3605 (m), 3309 (s), 3074 (w), 3002 (w), 2964 (m), 2933 (s), 2857 (w), 2836 (w), 1459 (m), 1355 (s), 1317 (m), 1134 (s), 1003 (s); ^{1}H NMR (CDCl$_3$) δ 2.50 (s, 1H), 2.56 (s, 1H), 3.90 (s, 3H), 3.94 (s, 3H), 4.02 (s, 3H), 7.07 (s, 1H), 7.25-7.29 (m, 1H), 7.36-7.37 (m, 1H), 7.64 (d, *J*=7.6, 1H), 7.82 (d, *J*=7.6, 1H); ^{13}C NMR (CDCl$_3$) δ 56.3, 60.7, 61.0, 71.5, 74.7, 83.9, 103.6, 122.7, 123.7, 124.6, 127.2, 130.1, 138.2, 142.2, 143.4, 146.1, 149.3, 154.5; LRMS (FAB$^+$) m/z 296 (M$^+$, 70), 279 (100), 271 (20); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{18}$H$_{16}$O$_4$ 296.1049, found 296.1055.

NITRILE COUPLING REACTIONS

Model System

2-(2,2-Dimethyl-propanenitrile)-biphenyl (IV-72). To a cooled (-78 °C) colorless

solution of 272 μL (1.94 mmol) of diisoproyl amine in 10 mL of THF was added 2.27

mL of a 0.90 M solution of *n*-BuLi in hexanes (2.04 mmol). After 5 min, 2-

propanenitrile (164 μL, 1.69 mmol) was added *via* syringe to the pale yellow solution.

The yellow solution was stirred at -78 °C for 1 h, at which time 370 μL (2.02 mmol) of 2-

phenylbenzylbromide in 4 mL of THF was added dropwise. The stirred solution changed

color from yellow, to red, to brown during the addition. The reaction was allowed to

warm to room temperature and stirred for 12 h, at which time the reaction was poured

into a saturated solution of NH_4Cl and extracted with ether (30 mL x3). The combined

organic phases were dried ($MgSO_4$), and evaporated to yield a yellow oil. Column

chromatography (TLC R_f = 0.17, 19:1 hexanes/EtOAc) yielded 395 mg of a white solid

(99%) mp 65.0-66.0 °C. IR (CCl_4) 3064 (w), 3026 (w), 2978 (m), 2929 (w), 2232 (w),

1483 (m), 1466 (m); ^{1}H NMR ($CDCl_3$) δ 1.07 (s, 6H), 2.98 (s, 2H), 7.26-7.28 (m, 3H),

7.33-7.41 (m, 5H), 7.56-7.57 (m, 1H); ^{13}C NMR ($CDCl_3$) δ 26.6, 34.0, 41.7, 125.1, 127.0,

127.2, 127.5, 128.2, 129.9, 130.5, 130.8, 133.2, 141.6, 143.1; LRMS (EI$^+$) m/z 235 (M$^+$,

30), 167 (100), 165 (34); HRMS (EI$^+$, M$^+$) m/z calcd for $C_{17}H_{17}N$ 235.1361, found

235.1355.

6,6-Dimethyl-5H-dibenzo[a,c]cycloheptan-5-one (IV-73). A 50 mL round bottom

flask was charged with 47.0 mg (0.200 mmol) of 2-(2,2-dimethyl-propanenitrile)-

biphenyl and 6.70 mg (30.0 μmol) of Pd(OAc)$_2$. Trifluoracetic acid (5 mL) was added, followed by 0.200 mL of DMSO. The reaction was heated to reflux for 12 h open to the atmosphere. Water (15 mL) was added and the reaction heated to 70 °C for 2 h, cooled to room temperature, and extracted with ether (20 mL x3). The combined organic extracts were dried (MgSO$_4$), and evaporated to yield a yellow oil. Column chromatography (TLC R_f = 0.39, 9:1 hexanes/EtOAc) yielded 46.8 mg of a pale yellow oil (99%). IR (CCl$_4$) 3071 (w), 3023 (w), 2964 (m), 2926 (m), 2857 (m), 1687 (s), 1476 (m), 1200 (m); ^{1}H NMR (CDCl$_3$) δ 1.21 (s, 6H), 2.83 (s, 2H), 7.20-7.45 (m, 7H), 7.52-7.56 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 25.1, 44.1, 53.9, 127.6, 127.7, 127.9, 128.0, 128.5, 129.2, 129.9, 131.2, 136.9, 138.2, 138.7, 139.8, 212.2; LRMS (FAB$^+$) m/z 236 (M$^+$, 50), 179 (55), 154 (100), 136 (80), 89 (40); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{17}$H$_{16}$O 236.2140, found 236.2129.

Phenyl System

2,3,4-Trimethoxy-6-(methanol)-biphenyl (IV-78). Sodium borohydride (45.4 mg, 1.2 mmol) was added in small portions at 0 °C to a stirred solution of 6-carbaldehyde-2,3,4-trimethoxy-biphenyl (272 mg, 1.00 mmol) in 4 mL of MeOH. The reaction was stirred at room temperature overnight to consume all of the aldehyde, at which time, the reaction was poured into 20 mL of cold 1M HCl and extracted with ether (30 mL x3). The combined organic extracts were dried (MgSO$_4$), and evaporated to yield a yellow oil. Column chromatography (TLC R_f = 0.39, 1:1 hexanes/EtOAc) yielded 273 mg of a white solid (99%) mp 82.0-83.0 °C. IR (CCl$_4$) 3613 (m), 3065 (w), 2999 (m), 2964 (m), 2933 (s), 2840 (m), 1604 (m), 1490 (s), 1404 (s), 1335 (s), 1145 (s), 1107 (s); ^{1}H NMR

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(CDCl$_3$) δ 3.60 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 4.39 (s, 2H), 6.91 (s, 1H), 7.25-7.27 (m, 2H), 7.36-7.43 (m, 3H); ^{13}C NMR (CDCl$_3$) δ 56.0, 60.9, 61.0, 63.1, 106.9, 127.2, 128.1, 129.9, 134.5, 135.9, 141.5, 151.3, 152.9; LRMS (EI$^+$) m/z 274 (M$^+$, 100), 241 (40), 199 (25), 115 (25); HRMS (EI$^+$, M$^+$) m/z calcd for C$_{16}$H$_{18}$O$_4$ 274.1205, found 274.1213.

2,3,4-Trimethoxy-6-(bromomethyl)-biphenyl (IV-80). Phosphorous tribromide (38.0 μL, 0.410 mmol) in 1 mL of CH$_2$Cl$_2$ was added dropwise to a cold (0 °C), stirred solution of 2,3,4-trimethoxyl-6-(methanol)-biphenyl (150 mg, 0.550 mmol) in 3 mL of CH$_2$Cl$_2$. The reaction was stirred for 45 min at 0 °C, at which time the solution was poured into ice water and extracted with CH$_2$Cl$_2$ (20 mL x2). The combined organic extracts were dried (MgSO$_4$), and evaporated to yield a yellow oil. Column chromatography (TLC R$_f$ = 0.40, 4:1 hexanes/EtOAc) yielded 180 mg of a white solid (97%) mp 96.0-97.0 °C. IR (CCl$_4$) 3058, (w), 3002 (m), 2957 (m), 2937 (m), 2837 (m), 1608 (m), 1480 (s), 1401 (s), 1352 (s); ^{1}H NMR (CDCl$_3$) δ 3.59, (s, 3H), 3.92 (s, 3H), 3.93 (s, 3H), 4.27 (s, 2H), 6.83 (s, 1H), 7.26-7.44 (m, 5H); ^{13}C NMR (CDCl$_3$) δ 32.6, 56.1, 60.9, 61.0, 109.1, 127.4, 128.1, 129.8, 129.9, 131.2, 135.5, 142.6, 151.4, 152.9; LRMS (FAB$^+$) m/z 337 (M$^+$ + H, 15), 257 (100), 242 (50), 226 (45); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{16}$H$_{17}$O$_3$Br 336.0361, found 336.0351.

2,3,4-Trimethoxy-6-(2,2-dimethyl-propanenitrile)-biphenyl (IV-82). Title compound was prepared from 2,3,4-trimethoxyl-6-(bromomethyl)-biphenyl using the procedure for

IV-72. Column chromatography (TLC R_f = 0.34, 4:1 hexanes/EtOAc) yielded 543 mg of a white solid (99%) mp 79.0-80.0 °C. IR (CCl$_4$) 3064 (w), 3030 (w), 2980 (s), 2933 (s), 2870 (w), 2843 (w), 2238 (m), 1602 (m), 1492 (s), 1405 (s), 1097 (s); ^{1}H NMR (CDCl$_3$) δ 1.10 (s, 6H), 2.72 (s, 2H), 3.56 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 7.02 (s, 1H), 7.17-7.19 (m, 2H), 7.38-7.40 (m, 3H); ^{13}C NMR (CDCl$_3$) δ 26.7, 33.9, 41.9, 56.0, 60.8, 60.9, 109.2, 125.5, 126.9, 127.9, 129.7130.2, 130.9, 136.6, 141.3, 151.3, 152.5; LRMS (EI$^+$) m/z 325 (M$^+$, 85), 257 (100), 242 (90), 226 (90); HRMS (EI$^+$, M$^+$) m/z calcd for C$_{20}$H$_{23}$O$_3$N 325.1678, found 325.1685.

1,2,3-Trimethoxy-6,6-dimethyl-5H-dibenzo[a,c]cycloheptan-5-one (IV-84).   Title compound was obtained *via* palladium-catalyzed cyclization of 2,3,4-trimethoxy-6-(2,2-dimethyl-propanenitrile)-biphenyl using an identical procedure to compound **IV-73**, except the reaction was refluxed for 36 h to consume all of the nitrile.   Column chromatography (TLC R_f = 0.31, 4:1 hexanes/EtOAc) yielded 58.0 mg of a white solid (89%) mp 111.0-112.0 °C. IR (CCl$_4$) 3064 (w), 2960 (m), 2933 (s), 2860 (w), 2833 (w), 1689 (s), 1596 (s), 1338 (s), 1111 (s); ^{1}H NMR (CDCl$_3$) δ 1.14 (s, 3H), 1.22 (s, 3H), 2.34 (d, J_{AB}=13.6), 3.05 (d, J_{AB}=13.6), 3.51 (s, 3H), 3.90 (s, 6H), 6.55 (s, 1H), 7.35-7.39 (m, 2H), 7.47-7.51 (m, 1H), 7.58-7.60 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 21.6, 28.0, 44.6, 54.1, 56.1, 61.0, 61.2, 108.9, 124.3, 127.1, 127.2, 129.9, 130.4, 133.3, 133.5, 140.2, 141.6, 151.9, 152.7, 212.6; LRMS (FAB$^+$) m/z 326 (M$^+$, 100), 269 (40), 135 (25), 85 (20); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{20}$H$_{22}$O$_4$ 326.1518, found 326.1510.

2,3,4,4′-Tetramethoxy-6-(methanol)-biphenyl (IV-79). Title compound was prepared in an identical manner as alcohol **IV-78**. Column chromatography (TLC R_f = 0.32, 1:1 hexanes/EtOAc) yielded 261 mg of a white solid (86%) mp 81.0-82.0 °C. IR (CCl$_4$) 3613 (m), 3002 (w), 2957 (m), 2937 (m), 2902 (w), 2833 (m), 1597 (m), 1494 (s), 1245 (s); ^{1}H NMR (CDCl$_3$) δ 3.60 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 4.42 (s, 2H), 6.90 (s, 1H), 6.96 (d, *J*=8.4, 2H), 7.18 (d, *J*=8.4, 2H); ^{13}C NMR (CDCl$_3$) δ 55.2, 56.0, 60.9, 61.0, 63.2, 106.9, 113.6, 127.8, 128.0, 131.0, 134.7, 141.2, 151.3, 153.4, 158.7; LRMS (EI$^+$) m/z 304 (M$^+$, 100), 287 (80), 256 (50); HRMS (EI$^+$, M$^+$) m/z calcd for C$_{17}$H$_{20}$O$_5$ 304.1311, found 304.1324.

2,3,4,4′-Tetramethoxy-6-(bromomethyl)-biphenyl (IV-81). Title compound was prepared in an identical manner as bromide **IV-80**. Column chromatography (TLC R_f = 0.31, 4:1 hexanes/EtOAc) yielded 201 mg of a white solid (89%) mp 73.0-74.0 °C. IR (CCl$_4$) 3037 (w), 2997 (m), 2957 (s), 2940 (s), 2903 (m), 2836 (s), 1599 (s), 1489 (s), 1335 (s), 1238 (s); ^{1}H NMR (CDCl$_3$) δ 3.58 (s, 3H), 3.87 (s, 3H), 3.91 (s, 3H), 3.92 (s, 3H), 4.29 (s, 2H), 6.82 (s, 1H), 6.97 (d, *J*=8.4, 2H), 7.25 (d, *J*=8.4, 2H); ^{13}C NMR (CDCl$_3$) δ 32.8, 55.2, 56.1, 60.9, 109.1, 113.6, 127.6, 129.4, 131.0, 131.5, 142.6, 151.7, 152.8, 158.8; LRMS (EI$^+$) m/z 366 (M$^+$, 70), 287 (90), 256 (100), 241 (60); HRMS (EI$^+$, M$^+$) m/z calcd for C$_{17}$H$_{19}$O$_4$Br 366.0467, found 366.0484.

2,3,4,4′-Tetramethoxy-6-(2,2-dimethyl-propanenitrile)-biphenyl (IV-83). Title compound was prepared in an identical manner as nitrile **IV-72** (model system). Column chromatography (TLC R_f = 0.24, 4:1 hexanes/EtOAc) yielded 456 mg of a white powder (76%) mp 85.0-86.0 °C. IR (CCl$_4$) 3030 (w), 2980 (m), 2953 (m), 2936 (m), 2228 (m), 1596 (m), 1486 (s), 1248 (s), 1101 (s); ^{1}H NMR (CDCl$_3$) δ 1.11 (s, 6H), 2.73, (s, 2H), 3.55 (s, 3H), 3.86 (s, 3H), 3.91 (s, 3H), 3.93 (s, 3H), 6.93 (d, J=8.4, 2H), 7.00 (s, 1H), 7.08 (d, J=8.4, 2H); ^{13}C NMR (CDCl$_3$) δ 26.7, 34.0, 42.0, 55.2, 56.0, 60.8, 60.9, 109.1, 113.4, 125.5, 128.7, 129.8, 130.1, 131.9, 141.2, 151.5, 152.3, 158.4; LRMS (FAB$^+$) m/z 356 (M$^+$ + H, 100), 355 (M$^+$, 61), 287 (25), 256 (42); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{21}$H$_{26}$O$_4$N 355.1757, found 355.1753.

1,2,3,4′-Tetramethoxy-6,6-dimethyl-5H-dibenzo[a,c]cycloheptan-5-one (IV-85). Title compound was obtained *via* palladium-catalyzed cyclization of 2,3,4,4′-tetramethoxy-6-(2,2-dimethyl-propanenitrile)-biphenyl using an identical procedure to compound **IV-73**, except the reaction was refluxed for 4 days to consume all of the nitrile. Column chromatography (TLC R_f = 0.24, 4:1 hexanes/EtOAc) yielded a sticky white solid which was recrystallized from hexane to provide 63.0 mg of the title compound as white plates (89%) mp 115.5-116.0 °C. IR (CCl$_4$) 3050 (w), 3003 (m), 2963 (m), 2933 (s), 2832 (m), 1686 (s), 1602 (s), 1485 (s), 1234 (s); ^{1}H NMR (CDCl$_3$) δ 1.15 (s, 3H), 1.25 (s, 3H), 2.35 (d, J_{AB}=13.2), 3.07 (d, J_{AB}=13.2), 3.52 (s, 3H), 3.89 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 6.55 (s, 1H), 6.92 (s, 1H), 7.05 (d, J=8.8, 1H), 7.53 (d, J=8.8, 1H); ^{13}C NMR (CDCl$_3$) δ 22.2, 28.8, 45.2, 54.6, 56.0, 56.7, 61.5, 61.7, 109.5,

112.1, 116.9, 124.7, 126.6, 132.4, 133.7, 141.8, 142.2, 152.3, 152.9, 158.9, 212.9; LRMS (EI$^+$) m/z 356 (M$^+$, 100), 300 (60); HRMS (EI$^+$, M$^+$) m/z calcd for C$_{21}$H$_{24}$O$_5$ 356.1624, found 356.1629.

Attempted Cylization of Unprotected Nitrile

1,2,3-Trimethoxy-6-(*E/Z*-acrylonitile)-biphenyl (IV-86).   6-Carbaldehyde-2,3,4-trimethoxy-biphenyl (3.72 g, 13.7 mmol), (cyanomethyl)triphenylphosphonium chloride (5.07 g, 15.0 mmol), and NaOH (1.10 g, 27.4 mmol) were placed into a 100 mL round bottom flask.   Water (20 mL) and CH$_2$Cl$_2$ were added and the reaction mixture was vigorously stirred at room temperature for 12 h.   The organic layer was separated and the aqueous layer was extracted with CH$_2$Cl$_2$ (30 mL x2).   The combined organic extracts were dried (MgSO$_4$), and evaporated to yield a yellow solid.   Column chromatography (TLC R$_f$ = 0.22, 9:1 hexanes/EtOAc) yielded 3.48 g of a white solid (86%) mp 87-91 °C. The *E* and *Z* isomers could be separated, but were usually not due to the hydrogenation of the double bond in the next synthetic step. For the *Z* isomer: IR (CCl$_4$) 3068 (w), 3006 (w), 2961 (w), 2940 (m), 2836 (w), 2219 (m), 1587 (m), 1487 (m), 1335 (s), 1156 (s), 1100 (s); ^{1}H NMR (CDCl$_3$) δ 3.59 (s, 3H), 3.97 (s, 3H), 3.99 (s, 3H), 5.26 (d, *J*=12, 1H), 6.84 (d, *J*=12, 1H), 7.20-7.22 (m, 2H), 7.39-7.42 (m, 3H), 7.64 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 56.2, 61.0, 61.1, 94.5, 106.6, 117.9, 127.6, 127.7, 128.1, 130.7, 130.9, 135.0, 144.4, 147.9, 151.3, 152.7. For the *E* isomer: IR (CCl$_4$) 3061 (w), 3006 (m), 2964 (m), 2937 (m), 2830 (w), 2222 (m), 1591 (m), 1483 (s), 1342 (s), 1152 (s), 1104 (s); ^{1}H NMR (CDCl$_3$) δ 3.56 (s, 3H), 3.92 (s, 3H), 3.94 (s, 3H), 5.24 (d, *J*=16.8, 1H), 6.85 (s, 1H), 7.10

(d, J=16.8, 1H), 7.16-7.18 (m, 2H), 7.39-7.42 (m, 3H); ^{13}C NMR (CDCl$_3$) δ 56.2, 61.0, 61.1, 95.6, 104.0, 118.4, 127.7, 127.8, 128.3, 130.5, 131.1, 134.6, 144.9, 149.2, 151.6, 153.1; LRMS (EI$^+$) m/z 295 (M$^+$, 100), 265 (15), 248 (23), 220 (25), 166 (25); HRMS (EI$^+$, M$^+$) m/z calcd for C$_{18}$H$_{17}$O$_3$N 295.1208, found 295.1202.

1,2,3-Trimethoxy-6-(propanenitrile)-biphenyl (IV-87).   The following is a modified procedure of Boykin.[322]   1,2,3-Trimethoxy-6-(*E/Z*-acrylonitrile)-biphenyl (2.47 g. 8.40 mmol) was placed into a round bottom flask followed by pyridine (15 mL) and methanol (5 mL). Sodium borohydride (3.82 g, 10.1 mmol) was added in three portions. The reaction was stirred in a 120 °C oil bath for 2 h. At the conclusion of this time period, the reaction was poured into 75 mL of 1 M HCl. The aqueous layer was extracted with ether (50 mL x3). The combined organic extracts were dried (MgSO$_4$), and evaporated to yield a yellow solid. Column chromatography (TLC R$_f$ = 0.29, 4:1 hexanes/EtOAc) yielded 2.35 g of colorless plates (94%) mp 91.2-91.9 °C. IR (CCl$_4$) 3057 (w), 3029 (w), 2998 (m), 2960 (s), 2936 (s), 2864 (w), 2840 (w), 2249 (m), 1486 (s), 1404 (s), 1103 (s); ^{1}H NMR (CDCl$_3$) δ 2.30 (t, J=7.6, 2H), 2.74 (t, J=7.6, 2H), 3.59 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 6.66 (s, 1H), 7.20-7.23 (m, 2H), 7.37-7.43 (m, 3H); ^{13}C NMR (CDCl$_3$) δ 18.6, 29.3, 56.1, 60.9, 61.0, 108.4, 119.2, 127.4, 128.4, 129.1, 129.9, 131.7, 136.3, 141.4, 151.7, 152.9; LRMS (FAB$^+$) m/z 297 (M$^+$, 100), 160 (40); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{18}$H$_{19}$O$_3$N 297.1365, found 297.1378.

Model System

9-(Methoxymethoxy)-phenanthrene (IV-96). 9-Phenanthrol (1.00 g, 3.09 mmol) was dissolved in 25 mL of CH_2Cl_2. Chloromethylmethyl ether (1.26 mL, 10.3 mmol) was added *via* syringe, followed by 1.12 mL (10.3 mmol) of Hunig's base. The brown solution was stirred at room temperature for 12 h to consume all of the starting material. After 12 h, the reaction was diluted with 25 mL of CH_2Cl_2. The organic phase was washed with water (50 mL), 1M HCl (50 mL) and brine (50 mL), dried ($MgSO_4$), and evaporated to yield a brown oil. Column chromatography (TLC R_f = 0.41, 9:1 hexanes/EtOAc) yielded 0.894 g of a white solid (89%) mp 55.0-56.0 °C. IR (CCl_4) 3077 (m), 3060 (s), 3010 (m), 2960 (s), 2983 (s), 2850 (w), 2823 (m), 1632 (s), 1606 (s), 1452 (s), 1315 (s), 1147 (s); ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 3H), 5.48 (s, 2H), 7.49-7.79 (m, 6H), 8.37 (d, *J*=8.0, 1H), 8.58, (d, *J*=8.4, 1H), 8.65 (d, *J*=8.4, 1H); ^{13}C NMR ($CDCl_3$) δ 56.3, 94.6, 105.9, 122.4, 122.5, 122.6, 124.6, 126.4, 126.6, 126.9, 127.0, 127.1, 127.7, 131.3, 132.7, 150.9; LRMS (FAB^+) m/z 238 (M^+, 100), 207 (45), 165 (22), 45 (65); HRMS (FAB^+, M^+) m/z calcd for $C_{16}H_{14}O_2$ 238.0994, found 238.0999.

7,7-Dichlorodibenzo[a,c]bicyclo(4.1.0)-6-(methoxymethoxy)-heptane (IV-97). To a solution of 9-(methoxymethoxy)-phenanthrene (238 mg, 1.00 mmol) in 10 mL of $CHCl_3$ was added 22.7 mg (0.100 mmol) of benzyltriethylammonium chloride and 2.00 mL of a 50% solution of NaOH. The colorless biphasic mixture was stirred for 5 h at room temperature, during which time the reaction changed from colorless, to orange, to brown.

The brown suspension was diluted with 50 mL of CH_2Cl_2 and poured into 50 mL of water. The layers were separated and the aqueous phase extracted with CH_2Cl_2 (3 x 50 mL). The organic extracts were combined, washed with brine (50 mL), dried ($MgSO_4$), and evaporated to yield a brown oil. Column chromatography (TLC R_f = 0.32, 9:1 hexanes/EtOAc) yielded 296 mg of an off white solid (92%) mp 91-92 °C. IR (CCl_4) 3077 (w), 3037 (w), 2997 (w), 2963 (m) 2927 (m), 2896 (m), 2843 (m), 2826 (w), 1492 (m), 1455 (m), 1157 (s), 1030 (s); ^1H NMR ($CDCl_3$) δ 3.44 (s, 3H), 3.64 (s, 1H), 4.79 (dd, J=6.8, 3.8, 2H), 7.35-7.49 (m, 4H), 7.86-7.88 (m, 1H), 8.04-8.07 (m, 3H); ^{13}C NMR ($CDCl_3$) δ 41.6, 56.7, 62.3, 66.4, 96.3, 122.6, 122.9, 123.1, 127.4, 128.1, 128.2, 128.3, 128.8, 128.9, 130.4, 130.9, 132.5; LRMS (FAB$^+$) m/z 320 (M$^+$, 10), 285 (15), 259 (100), 241 (35), 194 (40), 154 (38), 45 (90); HRMS (FAB$^+$, M$^+$) m/z calcd for $C_{17}H_{14}O_2Cl_2$ 320.0371, found 320.0367.

6-Chloro-5H-dibenzo[a,c]cyclohepten-5-one **(IV-92)**. 7,7-Dichlorodibenzo[a,c]bicyclo(4.1.0)-6-(methoxymethoxy)-heptane (813 mg, 2.53 mmol) in 30 mL of IPA, 30 mL of THF and 30 mL of 2.0 M HCl was heated to 100 °C for 5 h. The solution was cooled to room temperature and the organic solvents were removed *in vacuo*. The remaining mixture was partitioned between 75 mL of ether and water. The aqueous phase was extracted three times with ether (50 mL) and the combined organic extracts were dried ($MgSO_4$), and evaporated to yield a yellow oil. Column chromatography (TLC R_f = 0.41, 4:1 hexanes/EtOAc) yielded 579 mg of a white solid (95%) mp 100.0-100.8 °C (lit. 98.0-98.8 °C).[304] IR (CCl_4) 3100 (w), 3070 (m), 3030 (m),

1672 (s), 1592 (m); ^{1}H NMR (CDCl$_3$) δ 7.52-7.63 (m, 4H), 7.72-7.89 (m, 2H), 7.90-7.96 (m, 3H); ^{13}C NMR (CDCl$_3$) δ 128.6, 128.8, 129.6, 129.7, 130.0, 130.9, 131.0, 131.4, 131.9, 134.1, 136.6, 137.2, 137.7, 139.1, 187.3; LRMS (FAB$^+$) m/z 241 (M$^+$, 100), 154 (60), 136 (55); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{15}$H$_{10}$OCl 241.0420, found 241.0419.

6,7-Dihydro-5H-dibenzo[a,c]cyclohepten-5-one **(IV-98)**. 6-Chloro-5H-dibenzo[a,c]cyclohepten-5-one (75.0 mg, 0.312 mmol), sodium acetate (79.3 mg, 0.967 mmol), and palladium on carbon (5%, 65.8 mg, 16.8 μmol) were stirred in 10 mL of EtOH under 1 ATM of hydrogen for 1 h. The reaction mixture was filtered, and poured into 50 mL of ether. The organic layer was washed with water (50 mL x2) and brine (50 mL). The ethereal phase was dried (MgSO$_4$), and evaporated to yield a yellow oil. Column chromatography (TLC R$_f$ = 0.21, 4:1 hexanes/EtOAc) yielded 46.8 mg of a white solid (72%) mp 84.5-85.6 °C (lit. 85-86 °C).[304] IR (CCl$_4$) 3074 (m), 3027 (m), 2957 (m), 2927 (w), 2863 (w), 1689 (s), 1596 (m), 1448 (m), 1271 (s); ^{1}H NMR (CDCl$_3$) δ 2.99 (s, 4H), 7.27-7.46 (m, 6H), 7.58-7.67 (m, 2H); ^{1}H NMR (benzene d$_6$) δ 2.45 (t, J=6.8, 2H), 2.63 (t, J=6.8, 2H), 6.85-6.87 (m, 1H), 7.05-7.16 (m, 6H), 7.80-7.82 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 29.5, 47.6, 127.6, 127.9, 128.0, 128.4, 128.6, 129.6, 130.0, 132.2, 138.8, 138.9, 139.0, 139.5, 206.2; LRMS (EI$^+$) m/z 208 (M$^+$, 100), 180 (90), 179 (70), 165 (39), 152 (25); HRMS (EI$^+$, M$^+$) m/z calcd for C$_{15}$H$_{12}$O 208.0888, found 208.0895.

6,7-Dihydro-5H-dibenzo[a,c]cyclohepten-5-ol **(IV-105)**. 6-Chloro-5H-dibenzo[a,c]cyclohepten-5-one (75.0 mg, 0.312 mmol), sodium acetate (79.3 mg, 0.967

mmol), and palladium on carbon (5%, 65.8 mg, 0.0168 mmol) were stirred in 10 mL of EtOH under 1 ATM of hydrogen for 24 h. The reaction mixture was filtered, and poured into 50 mL of ether. The organic layer was washed with water (50 mL x2) and brine (50 mL). The ethereal phase was dried (MgSO$_4$), and evaporated to yield a yellow oil. Column chromatography (TLC R$_f$ = 0.25, 4:1 hexanes/EtOAc) yielded 43.0 mg of a white solid (66%) mp 114.5-115.0 °C. IR (CCl$_4$) 3619 (s), 3070 (m), 3020 (m), 2940 (s), 2860 (m), 1482 (m), 1455 (m), 1047 (s); ^{1}H NMR (CDCl$_3$) δ 2.08-2.10 (m, 1H), 2.46-2.67 (m, 4H), 4.65-4.67 (m, 1H), 7.25-7.64 (m, 7H), 7.64-7.65 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 30.1, 41.9, 70.6, 123.1, 123.2, 126.9, 127.3, 127.6, 127.8, 128.2, 128.3, 137.9, 139.4, 139.8, 141.5; LRMS (EI$^+$) m/z 210 (M$^+$, 100), 192 (90), 191 (40), 165 (30), 152 (20); HRMS (EI$^+$, M$^+$) m/z calcd for C$_{15}$H$_{14}$O 210.1045, found 210.1035.

5H-dibenzo[a,c]cyclohepten-5-one (IV-106). Title compound was prepared according to a procedure by Jones and coworkers[304] starting with 150 mg (0.623 mmg) of 6-chloro-5H-dibenzo[a,c]cyclohepten-5-one and yielding 102 mg of the title compound as a white solid (79%) mp 82.3-83.7 °C (lit. 83-84.5 °C).[304] IR (CCl$_4$) 3060 (w), 3031 (m), 2953 (s), 2921 (m), 2847 (w), 1658 (s); ^{1}H NMR (CDCl$_3$) δ 6.66 (d, J=12, 1H), 7.35 (d, J=12, 1H), 7.47-7.59 (m, 4H), 7.65-7.69 (m, 1H), 7.88-7.96 (m, 3H); ^{13}C NMR (CDCl$_3$) δ 110.8, 128.2, 128.5, 129.0, 129.4, 130.3, 131.1, 131.5, 131.6, 133.1, 137.0, 138.2, 139.9, 141.2, 192.6; LRMS (EI$^+$) m/z 206 (M$^+$, 40), 178 (100), 176 (30), 88 (30); HRMS (EI$^+$, M$^+$) m/z calcd for C$_{15}$H$_{10}$O 206.732, found 206.0728.

6-Phenyl-5H-dibenzo[a,c]cyclohepten-5-one **(IV-107)**. 6-Chloro-5H-dibenzo[a,c]cyclohepten-5-one (240 mg, 1.00 mmol) was weighed into a 25 mL round bottom flask and placed under argon. Tetrakis(triphenylphosphine)palladium(0) (116 mg, 0.100 mmol) was added, followed by 10 mL of benzene, and 1.50 mL (3.00 mmol) of a 2M aqueous solution of Na_2CO_3. Phenyl boronic acid (377 mg, 3.00 mmol) in 3 mL of EtOH was added *via* syringe. The reaction mixture was brought to reflux for 72 h to consume all of the α-chloro enone. The reaction was cooled to room temperature and diluted with water (30 mL), and ether (30 mL). The layers were separated and the aqueous phase extracted twice with 30 mL of ether. The organic phases were combined and dried ($MgSO_4$) and evaporated to yield a yellow solid. Column chromatography (TLC R_f = 0.31, 9:1 hexanes/EtOAc) yielded 200 mg of a white solid (71%) mp 136.8-138.2 °C. IR (CCl_4) 3030 (m), 3023 (w), 2921 (s), 2843 (m), 1670 (s), 1368 (m), 1290 (s); ^{1}H NMR ($CDCl_3$) δ 7.36-7.68 (m, 10H), 7.77-7.90 (m, 1H), 7.85-7.89 (m, 2H); ^{13}C NMR ($CDCl_3$) δ 127.6, 127.9, 128.1, 128.4, 128.5, 128.7, 129.2, 130.4, 131.0, 133.3, 135.2, 136.2, 137.1, 138.4, 143.4, 144.4, 196.2; LRMS (EI$^+$) m/z 282 (M$^+$, 30), 254 (100), 252 (60); HRMS (EI$^+$, M$^+$) m/z calcd for $C_{21}H_{14}O$ 282.1045, found 282.1036.

Phenyl System

2,3,4-Trimethoxy-6-((*E/Z*)-2-methoxyvinyl)biphenyl. Sodium hydride (60% dispersion in mineral oil, 2.15 g, 53.6 mmol) was added to a 250 mL round bottom flask and placed under argon. The sodium hydride was washed three times with dry pentane to remove the mineral oil. Ether was added (130 mL), followed by

methoxymethyltriphenylphosphonium chloride (20.2 g, 57.6 mmol), which was added in three portions over 10 min. The reaction mixture was brought to reflux for 30 min and cooled to room temperature. 2,3,4-Trimethoxy-6-carbaldehyde-biphenyl (3.64 g, 13.4 mmol) was added in one portion. The reaction was heated to reflux for 12 h to consume all of the aldehyde, after which time the reaction was filtered, and diluted with 100 mL of ether. The organic layer was washed with water (100 mL x2), 1 M HCl (100 mL), brine (100 mL), dried (MgSO$_4$), and evaporated to yield a white solid. Column chromatography (TLC R$_f$ = 0.34, 4:1 hexanes/EtOAc) yielded 3.90 g of a white solid (97%) mp 105-108 °C as a 60:40 mixture of E/Z isomers which were not separated. IR (CCl$_4$) 3060 (m), 3003 (m), 2957 (s), 2930 (s), 2903 (m), 2830 (m), 1639 (s), 1489 (s), 1398 (s), 1328 (s), 1147 (s), 1101 (s); LRMS (FAB$^+$) m/z 300 (M$^+$, 100), 269 (60), 238 (29), 89 (22), 45 (35); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{18}$H$_{20}$O$_4$ 300.1362, found 300.1367.

6-Acetylaldehyde-2,3,4-trimethoxybiphenyl. 2,3,4-Trimethoxy-6-((*E/Z*)-2-methoxyvinyl)biphenyl (5.25 g, 17.5 mmol) was dissolved in 50 mL of THF. A 2.0 M HCl (0.600 mL, 13.1 mmol) solution was added and the reaction was refluxed for 1.5 h. The pale yellow solution was diluted with 75 mL of ethyl acetate, washed twice with 50 mL of a sat. solution of NaHCO$_3$, water (50 mL), brine (50 mL), dried (MgSO$_4$), and evaporated to yield a yellow solid. Column chromatography (TLC R$_f$ = 0.28, 4:1 hexanes/EtOAc) yielded a viscous oil which crystallized upon cooling to provide 3.58 g of the title compound as white needles (97%) mp 56.0-56.5 °C. IR (CCl$_4$) 3064 (w), 2993 (m), 2963 (m), 2940 (s), 2833 (m), 2719 (w), 1733 (s), 1489 (s), 1147 (s), 1101 (s);

^{1}H NMR (CDCl$_3$) δ 3.47 (s, 2H), 3.61 (s, 3H), 3.89 (s, 3H), 3.92 (s, 3H), 6.55 (s, 1H), 7.17-7.19 (m, 2H), 7.34-7.43 (m, 3H), 9.55 (s, 1H); ^{13}C NMR (CDCl$_3$) δ 48.4, 56.1, 60.9, 61.0, 109.2, 126.1, 127.4, 128.3, 130.0, 130.2, 136.5, 141.6, 151.9, 152.9, 199.4; LRMS (FAB$^+$) m/z 286 (M$^+$, 40), 269 (100), 258 (60), 242 (43), 226 (40); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{17}$H$_{18}$O$_4$ 286.1205, found 286.1217.

6-(Acetic acid)-2,3,4-trimethoxybiphenyl (IV-99). A stock solution of Jones reagent was prepared by dissolving 5.0 g of CrO$_3$ in 7 mL of water. The red solution was cooled to 0 °C and sulfuric acid (4.21 mL) was added dropwise, followed by an additional 18 mL of water. 6-Acetylaldehyde-2,3,4-trimethoxybiphenyl (3.76 g, 13.1 mmol) was dissolved in 130 mL of acetone and the colorless solution was cooled to 0 °C. Jones reagent was added dropwise until the persistence of a deep red color. Isopropanol was added dropwise to quench the excess Jones reagent, forming a dark green reaction mixture. The solvents were removed *in vacuo* and the residue was dissolved in 100 mL of 1 M NaOH. The aqueous layer was washed with ether (50 mL x2) and acidified with concentrated HCl. The aqueous suspension was extracted with CH$_2$Cl$_2$ (75 mL x3). The combined organic extracts were dried (MgSO$_4$), and evaporated to yield 3.76 g of a white solid (95%) mp 108.0-108.5 °C. IR (CCl$_4$) 3528 (m), 3060 (m), 3007 (m), 2960 (m), 2933 (m), 2840 (m), 1709 (s), 1489 (m), 1395 (m), 1147 (s), 1104 (s); ^{1}H NMR (CDCl$_3$) δ 3.43 (s, 2H), 3.60 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 6.68 (s, 1H), 7.22-7.24 (m, 2H), 7.35-7.42 (m, 3H), 9.20 (br, 1H); ^{13}C NMR (CDCl$_3$) δ 38.1, 56.0, 60.9, 61.0, 108.9, 127.2, 127.8, 128.2, 129.9, 130.1, 136.4, 136.7, 151.6, 152.7, 175.0; LRMS (FAB$^+$) m/z

302 (M$^+$, 100), 257 (25), 226 (20); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{17}$H$_{18}$O$_5$ 302.1154, found 302.1144.

2,3,4-Trimethoxy-9-phenanthrol (IV-100). 6-(Acetic acid)-2,3,4-trimethoxybiphenyl (3.76 g, 12.4 mmol) was dissolved in 36.0 mL SOCl$_2$ and brought to a gentle reflux for 2 h. Excess thionyl chloride was removed *in vacuo*. The residue was dissolved in 50 mL of benzene and added dropwise to a stirred, cooled (5 °C) mixture of AlCl$_3$ (3.31 g, 24.8 mmol) in benzene (80 mL). The reaction mixture was allowed to warm to room temperature, at which time 100 mL of a 1.0 M HCl solution was added in one portion. The phases were separated and the aqueous layer extracted with EtOAc (75 mL x3). The combined organic extracts were dried (MgSO$_4$), and evaporated to yield a brown oil. Column chromatography (TLC R$_f$ = 0.31, 1:1 hexanes/EtOAc) yielded 2.19 g of an air sensitive off-white solid which was immediately stored under argon (62%) mp 130-132 °C (decomp). IR (CCl$_4$) 3609 (m), 3064 (w), 2997 (m), 2960 (m), 2933 (s), 2876 (m), 2856 (m), 1746 (m), 1609 (m), 1469 (s), 1221 (s), 1101 (s); ^{1}H NMR (CDCl$_3$) δ 3.99 (s, 3H), 4.01 (s, 3H), 4.02 (s, 3H), 5.22 (s, 1H), 6.91 (s, 1H), 6.92 (s, 1H), 7.59-7.66 (m, 2H), 8.29 (d, *J*=8.0, 1H), 9.52 (d, *J*=8.0, 1H); ^{13}C NMR (CDCl$_3$) δ 56.4, 60.9, 61.9, 104.1, 106.8, 115.7, 122.3, 125.5, 125.9, 127.3, 128.0, 131.2, 131.9, 141.6, 149.9, 153.2, 153.4; LRMS (FAB$^+$) m/z 284 (M$^+$, 100), 154 (30), 136 (40); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{16}$H$_{16}$O$_4$ 284.1049, found 284.1050.

2,3,4-Trimethoxy-9-(methoxymethoxy)-phenanthrene (IV-94). 3,4,5-Trimethoxy-9-phenanthrol (2.19 g, 7.71 mmol) was dissolved in 40 mL of CH_2Cl_2. To this dark brown solution was added 1.88 mL (15.4 mmol) of chloromethylmethyl ether, followed by 1.67 mL of Hunig's base (15.4 mmol). The light brown solution was stirred at room temperature for 12 h to consume all of the starting material (TLC). The reaction was diluted with ether (150 mL), washed with water (100 mL), 1M HCl (100 mL), brine (100 mL), dried ($MgSO_4$), and evaporated to yield a brown oil. Column chromatography (TLC R_f = 0.27, 4:1 hexanes/EtOAc) yielded 2.13 g of a white solid (84%) mp 91.1-92.5 °C. IR (CCl_4) 3074 (w), 3000 (m), 2963 (m), 2933 (s), 2903 (m), 2826 (m), 1632 (s), 1612 (s), 1502 (s), 1462 (s), 1351 (s), 1144 (s), 1064 (s); ^{1}H NMR ($CDCl_3$) δ 3.58 (s, 3H), 4.00 (s, 3H), 4.01 (s, 3H), 4.02 (s, 3H), 5.47 (s, 2H), 7.02 (s, 1H), 7.20 (s, 1H), 7.55-7.67 (m, 2H), 8.36 (d, *J*=8.0, 1H), 9.50 (d, *J*=8.0, 1H); ^{13}C NMR ($CDCl_3$) δ 55.8, 56.2, 60.3, 61.3, 94.6, 104.5, 106.0, 115.2, 121.9, 125.3, 125.9, 126.6, 127.2, 130.6, 131.0, 141.3, 150.7, 152.4, 152.7; LRMS (FAB$^+$) m/z 328 (M$^+$, 100), 297 (20), 283 (25); HRMS (FAB$^+$, M$^+$) m/z calcd for $C_{19}H_{20}O_5$ 328.1311, found 328.1318.

1,1-Dichloro-1a,9b-dihydro-6,7,8-trimethoxy-1a-(methoxymethoxy)-1H-cyclopropa[*l*]phenanthrene (IV-101). 2,3,4-Trimethoxy-9-(methoxymethoxy)-phenanthrene (2.13 g, 6.49 mmol) and 148 mg (0.649 mmol) of benzyltriethylammonium chloride were dissolved in 65 mL of $CHCl_3$. To this colorless solution was added 13 mL of 50% NaOH in one portion. The vigorously stirred, reaction mixture was stirred at room temperature for **x** h during which time the reaction changed from pale yellow to orange to brown. The reaction mixture was diluted with CH_2Cl_2 (100 mL) and water

(100 mL). The layers were separated and the aqueous phase was extracted with CH_2Cl_2

(75 mL x3). The combined organic extracts were dried ($MgSO_4$), and evaporated to yield

a brown oil. Column chromatography (TLC R_f = 0.26, 4:1 hexanes/EtOAc) yielded 1.95

g of a yellow oil (73%) which was used without further purification. IR (CCl_4) 3137 (w),

3064 (w), 2997 (m), 2957 (s), 2937 (s), 2846 (m), 1596 (s), 1492 (s), 1328 (s), 1161 (s);

^{1}H NMR ($CDCl_3$) δ 3.45 (s, 3H), 3.56 (s, 1H), 3.85 (s, 3H), 3.93 (s, 3H), 3.96 (s, 3H),

4.78 (q_{AB}, J=6.8, 7.2, 2H), 6.80 (s, 1H), 7.26-7.42 (m, 2H), 7.84-7.85 (m, 1H), 8.94-8.96

(m, 1H); ^{13}C NMR ($CDCl_3$) δ 42.1, 55.9, 56.7, 60.4, 61.0, 62.4, 66.6, 96.2, 109.8, 117.7,

125.1, 126.9, 127.0, 128.5, 129.0, 132.5, 143.2, 152.9, 153.8; LRMS (FAB^+) m/z 410

(M^+, 10), 349 (100), 331 (70), 283 (90), 154 (65), 136 (50), 45 (85); HRMS (FAB^+, M^+)

m/z calcd for $C_{20}H_{20}O_5Cl_2$ 410.0688, found 410.0687.

6-Chloro-1,2,3-trimethoxy-5H-dibenzo[a,c]cyclohepten-7-one   **(IV-103)**.   1,1-

Dichloro-1a,9b-dihydro-6,7,8-trimethoxy-1a-(methoxymethoxy)-1H-

cyclopropa[l]phenanthrene (757 mg, 1.84 mmol) was dissolved in 12 mL of THF, 12 mL

of iPrOH, and 12 mL of 2 M HCl. The reaction mixture was heated to 100 °C for 5 h.

The solution was cooled to room temperature and the organic solvents were removed *in*

vacuo. The remaining mixture was partitioned between 50 mL of ether and 50 mL of

water.   The aqueous phase was extracted three times with ether (30 mL) and the

combined organic extracts were dried, ($MgSO_4$), and evaporated to yield a yellow oil.

Column chromatography (TLC R_f = 0.26, 4:1 hexanes/EtOAc) yielded a light yellow

solid. Recrystallization (benzene/pentane) provided 407 mg of colorless crystals (67%)

mp 141.1-141.8 °C. IR (CCl_4) 3064 (w), 3007 (m), 2963 (s), 2927 (s), 2850 (s), 1733

(m), 1672 (s), 1592 (s), 1492 (s), 1338 (s), 1151 (s), 1121 (s); ^{1}H NMR (CDCl$_3$) δ 3.44 (s, 3H), 3.96 (s, 3H), 4.00 (s, 3H), 6.75 (s, 1H), 7.50-7.59 (m, 2H), 7.57 (s, 1H), 7.78-7.80 (m, 1H), 8.02-8.04 (m, 1H); ^{13}C NMR (CDCl$_3$) δ 56.1, 61.2, 61.4, 108.6, 124.7, 127.8, 128.2, 128.4, 130.0, 131.7, 132.1, 133.1, 137.0, 139.6, 144.1, 152.9, 153.0, 188.3; LRMS (FAB$^+$) m/z 331 (M$^+$, 30), 307 (22), 154 (35), 137 (100); HRMS (FAB$^+$, M$^+$) m/z calcd for C$_{18}$H$_{16}$O$_4$Cl 331.0737, found 331.0733.

5,6-Dihydro-1,2,3-trimethoxy-5H-dibenzo[a,c]cyclohepten-7-one (IV-104). 6-Chloro-1,2,3-trimethoxy-5H-dibenzo[a,c]cyclohepten-7-one (36.5 mg, 0.110 mmol), sodium acetate (22.6 mg, 0.275 mmol), and palladium on carbon (5%, 11.7 mg, 5.52 μmol) were stirred in 5 mL of EtOH under 1 ATM of hydrogen for 1 h. The reaction mixture was filtered, and poured into 25 mL of ether. The organic layer was washed with water (25 mL x2) and brine (25 mL). The ethereal phase was dried (MgSO$_4$), and evaporated to yield a yellow oil. Column chromatography (TLC R$_f$ = 0.21, 4:1 hexanes/EtOAc) yielded a colorless oil, which was recrystallized from hexane to provide 26.0 mg of white crystals (72%) mp 79.0-80.0 °C. IR (CCl$_4$) 3067, (w), 3000 (m), 2957 (m), 2933 (s), 2863 (m), 2836 (m), 1689 (s), 1599 (s), 1405 (s), 1348 (s), 1114 (s); ^{1}H NMR (CDCl$_3$) δ 2.64-2.67 (m, 1H), 2.88-3.09 (m, 3H), 3.50 (s, 3H), 3.90 (s, 3H), 3.91 (s, 3H), 6.61 (s, 1H), 7.37-7.41 (m, 1H), 7.51-7.79 (m, 3H); ^{13}C NMR (CDCl$_3$) δ 31.3, 48.4, 56.5, 61.4, 61.6, 107.4, 124.7, 127.8, 128.0, 131.2, 131.7, 134.4, 136.2, 139.9, 142.0, 152.7, 153.5, 207.5; LRMS (EI$^+$) m/z 298 (M$^+$, 100), 283 (10), 241 (10); HRMS (EI$^+$, M$^+$) m/z calcd for C$_{18}$H$_{18}$O$_4$ 298.1205, found 298.1203.

5-Acetamido-5,6-dihydro-1,2,3-trimethoxy-5*H*-dibenzo[a,c]cycloheptene **(IV-93)**.

Title compound was prepared from 114 mg (0.380 mmol) of 5,6-dihydro-1,2,3-trimethoxy-5*H*-dibenzo[a,c]cyclohepten-7-one according to the reductive amination/acylation protocol of Wulff and coworkers[288] to yield 73.9 mg (57%) of product (mixture of stereo and atropisomers) as a white solid mp 184.3-187.1 (lit. 185.2-187.6).[291] The ^{1}H and ^{13}C NMR, and IR spectral data match those reported by Fagnou and coworkers.[291]

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