ABSTRACT

Title of Document: ADVANCES IN SILOXANE-BASED COUPLING TECHNOLOGIES: APPROACHES TOWARD PANCRATISTATIN AND STREPTONIGRIN

Frederick Emil Nytko, III, Doctor of Philosophy, 2015

Directed By: Professor Philip DeShong, Department of Chemistry and Biochemistry

The ability to form carbon-carbon bonds, arguably the most important transformation in synthetic chemistry, has been critically facilitated *via* the implementation of transition metal catalysts with main group element-associated carbon moieties. Specifically, organosilane coupling technology previously reported in the DeShong group provides ease of access to a wide variety of structurally important carbon-carbon bond motifs. The stability, tolerance of numerous implicit functional groups, simplicity of use, and ease of synthetic access to a multitude of organosilane coupling partners, makes the coupling technology developed in the DeShong lab markedly attractive for implementation in syntheses of complex natural product targets. Two targets of specific interest are pancratistatin and streptonigrin.

Synthetic approaches toward pancratistatin *via* complex organosilane coupling precursors proved promising, however mechanistic studies performed in the DeShong

group determined that standard 18-electron palladium(0) catalysts fail in transmetallation. Therefore, a new class of 16-electron Pd(0) catalysts have been developed and surveyed for applications in siloxane based allyl-aryl coupling protocols. The ability to "tune" these catalysts' activity by varying either the cone angle or the electronic characteristics of the alkene ligands attached to palladium has also been demonstrated. Unfortunately, attempts to prepare chiral adducts in the coupling reaction utilizing chiral bicyclooctadiene derivatives as a ligand for palladium provided no significant enantioenrichment in the coupled product.

Similarly, previous work in the DeShong lab toward the synthesis of streptonigrin has been reported. Particularly, the synthesis of the structurally congested pyridyl C-ring proved difficult, requiring numerous steps at low yields. Development of new synthetic pathways toward the pyridyl C-ring was undertaken, exploiting the electronically withdrawn nature of the pyridone intermediate in order to brominate and alcohol, as well as change a methyl group to an aldehyde, *via* an enamine intermediate.

The specific goals of this work were (1) to investigate new palladium(0) catalysts for the coupling of analogues of pancratistatin precursors, and (2) to improve upon problematic portions of our previous synthesis of streptonigrin’s pyridyl C-ring.

ADVANCES IN SILOXANE-BASED COUPLING TECHNOLOGIES: APPROACHES TOWARD PANCRATISTATIN AND STREPTONIGRIN

By

Frederick Emil Nytko, III

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Advisory Committee:
Professor Philip DeShong, Chair
Professor Jeffery Davis
Professor Herman Sintim
Professor Neil Blough
Professor Volker Briken

Dedication

To my loving family, friends, and Callie.

Acknowledgements

There are numerous people to whom I owe my sincerest thanks for their support, guidance, and friendship throughout my graduate career.

Foremost, I must thank my advisor, Dr. Philip DeShong, for his guidance, support, insight, and patience throughout my time as his student. While incredibly knowledgeable in seemingly every aspect of the field, Dr. DeShong exemplifies the definition of being an educator and mentor, by knowing exactly how to convey foreign topics to any audience. Dr. DeShong has always emphasized an atmosphere of collegiality between himself and his group, fostering an environment in which I felt as though I was sharing my ideas and concerns with a coworker, rather than asking my boss a question. Beyond being a model for the type of scientist I hope I am on my way to becoming, Dr. DeShong is genuine in his compassion for the members of his group, always knowing that some things have to take precedent over science. I have undoubtedly learned more about chemistry from my time spent in the DeShong group then I ever could have imagined, but I have also learned a tremendous amount about myself and what I am capable of accomplishing. For all of this, I am indebted to Dr. DeShong.

The sense of collegiality, friendship, and openness for the constructive sharing of ideas that has been fostered by the members of the DeShong research group has made my time at Maryland as pleasant as anyone could have possibly hoped for. I must first thank those who have helped to lay the foundations for the work I describe herein, particularly Dr. William McElroy, Dr. Matthew Sandelier, and Dr. Krupa Shukla. My experience with these individuals has always been supportive and

encouraging, while also commiserative to the struggles my projects entailed. The examples they have set in their research and mentorship of me have been a model of the type of scientist and mentor I hope I am on my way to becoming. I am also especially grateful for the friendship and support of Dr. Juhee Park, Dr. Matthew Hurley, Dr. Lenea Stocker, Dr. Neeraja Dashaputre, Mr. Reyniak Richards, and Dr. Dennis Mayo. Despite working on disparate topics, everyone was always willing to let me bounce ideas off of them and to provide their unique insight into any problem I might have been experiencing. I hope that I was able to live up to, and reciprocate, the great examples of friendship and support these people have shown me during my graduate career.

I must also acknowledge Dr. Phong Truong and Dr. Xichen Xu for their time and assistance with chiral HPLC and chiral gas chromatography.

One of my greatest experiences in graduate school was working in our department's Analytical NMR facility. I must extend my warmest thanks to Dr. Yiu-fai Lam, Dr. Yinde Wang, Dr. Eugene Mazzola, and Mr. Scott Taylor, for their friendship, expert guidance, and patience over the years. While being one of the most experienced and knowledgeable individuals I have had the pleasure of working with during my graduate career, Dr. Yiu-fai Lam has proven time-and-again to be an amazingly kindhearted person, making me feel like part of his family rather than just an employee. Through his mentorship and compassion, he has made me strive to be a better scientist and a better person, and for that I will always be thankful.

I would be remiss to not thank those who helped to nurture my interest in chemistry and mentored me along the way, especially: Dr. Keith Schray, who, despite

the number of students regularly waiting at his door, always made time to field my questions and make sure I understood the material, Dr. James Roberts, who fostered my love of NMR, Dr. Robert Flowers, Dr. Daniel Zeroka, Dr. Jeanne Berk, Dr. Natalie Foster, all from the Chemistry Department at Lehigh University, and Dr. Jane Klassen at Montana State University, for helping me find my way in my early graduate career. The time and patience each has shown me during my formative years has helped me get to the point I am today, for which I will be ever grateful.

Finally, and most importantly, I must extend my greatest thanks to my family, friends, loved ones, and God. You have believed in me, even when, at times, I did not believe in myself, and for that I extend the sincerest gratitude and love from the bottom of my heart. Without your love, encouragement, and support over the years, none of this would have ever been possible.

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List of Abbreviations

*	chiral center
Ac	acetyl
aq.	aqueous
Ar	aryl
Bn	benzyl
BOC	*tert*-butoxycarbonyl
BQ	1,4-benzoquinone
Bu	butyl
Bz	benzoyl
calcd	calculated
COD	1,5-cyclooctadiene
conc.	concentrated
Cy	cyclohexyl
CBz	carboxybenzyl
d	day(s)
d	deuterated
dba	dibenzylideneacetone
DQ	duroquinone
DMAP	4-dimethylaminopyridine
DMF	*N,N*-dimethylformamide
DMFDA	*N,N*-dimethylformamide dimethyl acetal
DMSO	dimethyl sulfoxide
R,R-DPBCO	(1*R*,4*R*) 2,5-diphenylbicyclo[2.2.2]octa-2,5-diene
EDG	electron-donating group
ee	enantiomeric excess
EI	electron ionization
equiv.	molar equivalent(s)
Et	ethyl
Et_2O	diethyl ether

EtOH	ethanol
ESI	electrospray ionization
EWG	electron-withdrawing group
FT	Fourier transform
GC	gas chromatography
h	hour(s)
HPLC	high performance liquid chromatography
HRMS	high resolution mass spectrometry
Hz	Hertz
i-Pr	isopropyl
IR	infrared
J	coupling constant
L	ligand
LRMS	low resolution mass spectrometry
m	*meta*
M^+	molecular ion
m/z	mass-to-charge ratio
MAH	maleic anhydride
Me	methyl
MeCN	acetonitrile
MHz	megahertz
min	minute(s)
MOM	methoxymethyl
mp	melting point
MS	mass spectrometry
NBD	norbornadiene
NBE	norbornene
NMM	*N*-methyl maleimide
NMO	*N*-methylmorpholine-*N*-oxide
NMP	*N*-methyl-2-pyrrolidone
NMR	nuclear magnetic resonance

NOESY	nuclear Overhauser effect spectroscopy
NPM	N-phenyl maleimide
NQ	1,4-naphthoquinone
Nuc	nucleophile
o	*ortho*
OAc	acetate
OBz	benzoate
p	*para*
PE	petroleum ether
Ph	phenyl
PMB	*p*-methoxybenzyl
R_f	retention factor
satd	saturated
rt	room temperature
t-Bu	tertiary butyl
TBAF	tetrabutylammonium fluoride
TCNE	tetracyanoethylene
TEA	triethylamine
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TIPS	triisopropylsilyl
TMS	trimethylsilyl
Ts	tosyl
UV	ultraviolet

Chapter 1

Development of Novel 16-electron Palladium(0) Complexes for Allyl-Aryl Coupling

Parts of this chapter are taken from the published manuscript:
Nytko, F. E.; Shukla, K. H.; DeShong, P., Advances in Siloxane-Based Coupling Reactions: Novel 16-Electron Palladium(0) Tri-alkene Catalysts for Allyl-Aryl Coupling in Precursors to *Amaryllidaceae* Alkaloids. *Heterocycles* **2014**, *88*, 1465-1476.

Introduction

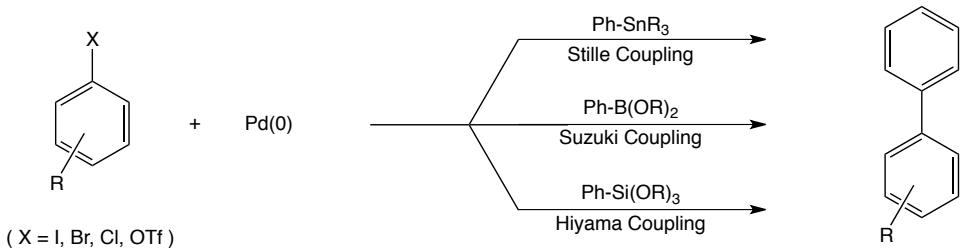
Metal-Catalyzed Cross-Couplings

Transition-metal complexes have found a wide variety of uses in organic synthesis, due in part to their versatility and ease of access to transformations that would otherwise prove difficult or inaccessible. The ability to form carbon-carbon bonds, arguably the most important transformation in synthetic chemistry, has been critically facilitated *via* the implementation of transition metal catalysts with main group element-associated carbon moieties.[1-3] The difficulty in carbon-carbon bond formation arises from the fact that, in most cases, the targeted coupling carbon centers possess identical electronegativities, and thus no affinity for binding. Through covalent association with any number of varying main group metals, the relative nucleophilicity of the metal-bound carbon atom can be modified, thus increasing its reactivity toward an electrophilic species.

The most widely used transition metal for the electrophilic activation of carbon centers for coupling is palladium,[3] while a vast number of different

organometallic electrophilic species have been developed, each with their own benefits and drawbacks (Scheme 1).

Scheme 1



The most commonly used organometallic reagents for cross-coupling include organostannanes (Stille coupling),[4] organoboron compounds (Suzuki coupling),[5] and organosilanes (Hiyama coupling).[6]

While Stille couplings generally provide good-to-excellent yields of the desired coupled product, while simultaneously tolerating a wide array of functional groups present in the coupling partners, issues arise in the difficulty of removal of the tin reagents from the reaction products. Given the toxicity of the organostannane byproducts remaining in the final product, Stille coupling is not suitable in the synthesis of compounds that may be used *in vivo*, thus limiting its scope.

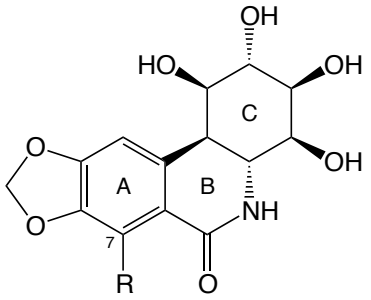
Suzuki coupling technology improved upon several of the shortcomings of Stille coupling chemistry. While still high yielding in coupled product and tolerant of numerous functional groups, Suzuki coupling employs organoboron compounds (boronic acids and esters), which are both less toxic and easier to remove from the reaction products than its Stille coupling, organostannane counterpart. These attributes make organoboron coupling technology applicable for the synthesis of

biologically active target molecules, thus leading Suzuki coupling to be embraced and widely implemented by the pharmaceutical industry. However, Suzuki coupling has its limitations, namely the synthesis, purification, and instability of boronic acids, which are more reactive toward coupling than their boronic ester counterparts. Also, organoboron compounds will not tolerate Lewis basic functionalities.

Provided these successes and shortcomings, further advancement in main group element-bound nucleophiles came with the development of Hiyama's organosilane technology. These silicon-coupling precursors are tolerant of various functional groups, less toxic than organostannanes, inexpensive and easily accessible, able to be chromatographically purified, and are tremendously robust until activated.[7] The scope, mechanistics, and applicability of palladium-catalyzed organosilane cross-couplings has been thoroughly investigated in the DeShong group, as well in the Denmark group and others.[8-14]

Amaryllidaceae Natural Products

The *Amaryllidaceae* family of plants is home to several subfamilies of alkaloid producing organisms, including *Agapanthoideae* (lily of the Nile), *Allioideae* (onion, garlic, leek), and *Amaryllidoideae* (Amaryllis). It was determined by the National Cancer Institute that some species of the *Amaryllidaceae* family contain alkaloids that had varying degrees of anticancer character. The large number of biologically relevant natural products isolated from this family of plants led Pettit and coworkers to investigate *Pancratium littorale* (Hawaiian daffodil), ultimately leading to the isolation of the natural product (+)-pancratistatin (**1**) in 1984 (Figure 1).[15]



1, (+)-pancratistatin, R = OH
2, (+)-7-deoxypancratistatin, R = H

Figure 1. Structure of *Amaryllidaceae* alkaloids

Studies conducted in the late 1980s - early 1990s by the National Cancer Institute provided a greater insight into the scope of action of (+)-pancratistatin (**1**) toward various cancer cell lines, including notable inhibition of growth in ovarian sarcoma.[16,17] Similar studies have gone on to show that (+)-pancratistatin (**1**) is *selectively* apoptotic toward colon,[18] prostate,[19] leukemia,[20] lymphoma,[21] neuroblastoma,[22] and melanoma[23] cancer cell lines in micromolar dosages. The structurally similar, though significantly less biologically active,[24,25] (+)-7-deoxypancratistatin (**2**) was isolated from *Scadoxus multiflorus* (blood lily, formerly *Haemanthus kalbreyeri*) by Ghosal and coworkers in 1989.[26]

Beyond marked anticancer capabilities, both (+)-pancratistatin (**1**) and (+)-7-deoxypancratistatin (**2**) have been shown to have significant antiviral activity against certain RNA flaviviruses (Japanese encephalitis, yellow fever, and dengue fever) and bunyaviruses (Punta Toro and Rift Valley fever).[24] Attempts at intensifying the biological activity through synthetic derivation of key structural and functional features of (+)-pancratistatin (**1**) and (+)-7-deoxypancratistatin (**2**) proved to be in

vain; both natural products displayed higher bioactivity than any unnatural analogues.[27-30]

The promising biological activity of (+)-pancratistatin (**1**) was tempered, however, by the low natural abundance of the compound in the dry plant bulb biomass (45 kg of bulb sections provided just 6.5 g of racemic pancratistatin, 0.028%).[15] Without a consistent natural supply available, the future of clinical studies and potential implementation as a therapy would rely upon the discovery of a practical synthetic means of access.

Synthetic Approaches Toward Pancratistatin and Analogues

The synthetic community has shown great interest in (+)-pancratistatin (**1**) and its analogues, not only for their potential as desirable therapies for various diseases, but also for their synthetic complexity. The structures of (+)-pancratistatin (**1**) and (+)-7-deoxypancratistatin (**2**) are stereochemically complex, with the cyclohexyl C-ring containing six contiguous stereocenters, one of which is the attachment point to the aryl A-ring. The A- and C-rings are fused futher *via* a trans lactam B-ring (Figure 1).

The majority of syntheses of pancratistatin and its analogues rely predominantly on the enantioselective formation of the bond between the aryl A-ring and the cyclohexyl C-ring, though approaches toward forming this connection span a diverse array of reaction types (Figure 2).

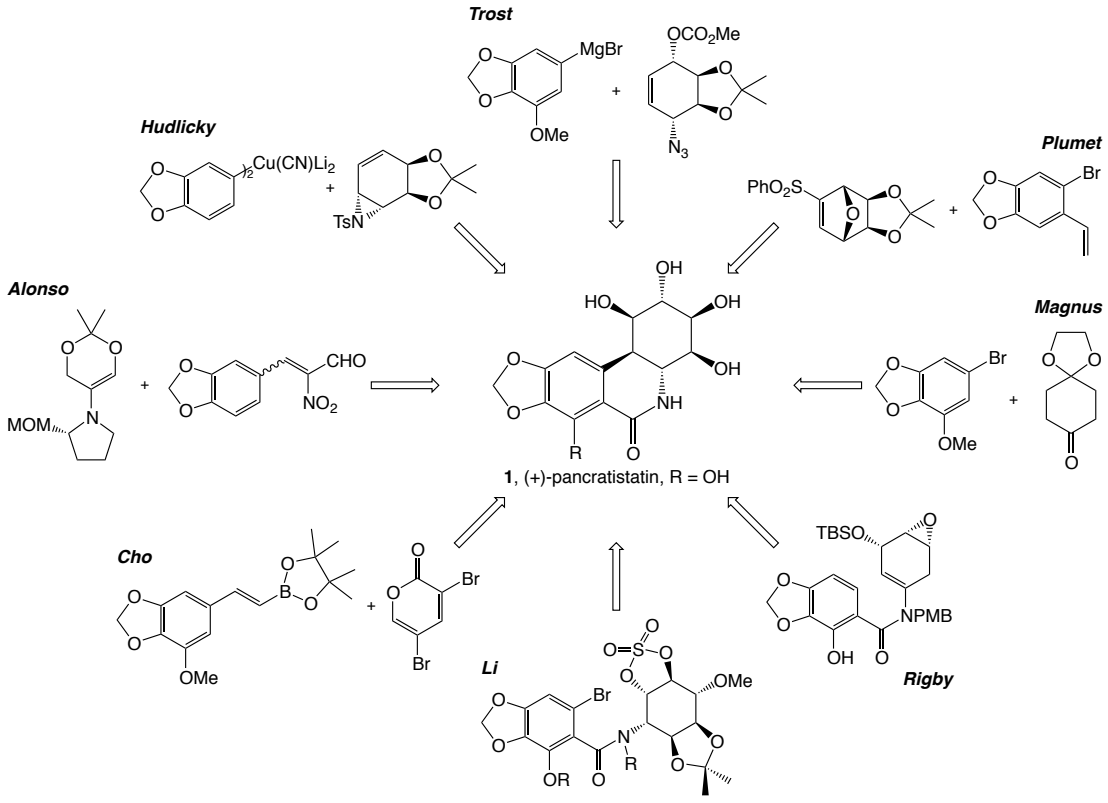
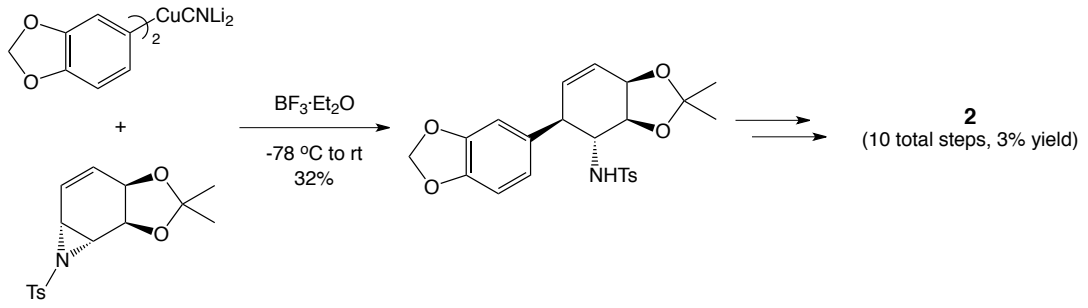


Figure 2. Survey of synthetic strategies for (+)-pancratistatin and analogues. Modified from reference 55

One of the earliest total syntheses of (+)-7-deoxypancratistatin (**2**), focusing on the formation of the A-C ring bond, was reported by Hudlicky in 1995.[31,32] By employing an aryl cuprate precursor of the A-ring as the nucleophile in the S_N2 ring opening of an aziridine appended to a C-ring precursor, the trans stereochemistry of the A-C ring bond and the B-ring lactam fusion site were established in a single step (Scheme 2).

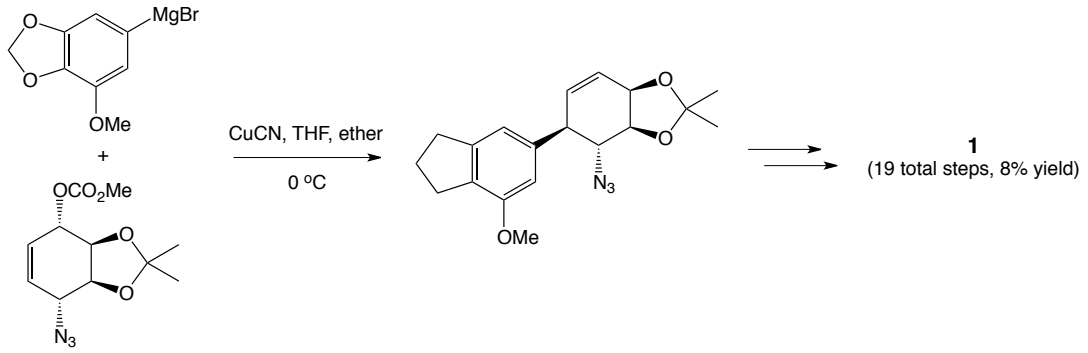
Scheme 2



The steric bulk of the acetonide-protected diol present in the C-ring precursor also imparted regioselectivity upon the nucleophilic addition of the aryl substrate, providing the desired ring-attachment position. While elegant and concise in its approach to establishing both the regio- and stereochemical aspects of the ring fusion points in the natural product, Hudlicky's synthesis of (+)-7-deoxypancratistatin (**2**) was hindered by the relatively low yields reported in these steps, as displayed in Scheme 2, as well as the difficulty in preparation and instability of the A- and C-ring precursors. That being said, Hudlicky's synthetic intermediate proved an attractive target for our formal total synthesis, due to advancements in access to analogues of his C-ring precursor, and their tolerance toward our developed coupling methodology (*vide infra*).

Also published in 1995, the next notable synthesis of (+)-pancratistatin (**1**) was completed by Trost.[33] The formation of the A-C ring system was approached via the nucleophilic S_N2' addition of an aryl Grignard A-ring precursor to an allyl carbonate C-ring precursor (Scheme 3).

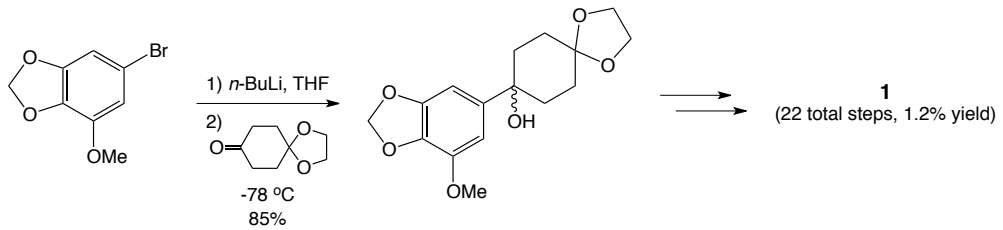
Scheme 3



The reported instability of Trost's azido A-C ring intermediate precluded isolation and characterization, requiring immediate cis-dihydroxylation of the C-ring olefin in order to properly distinguish the regio- and stereochemical outcome the S_N2' reaction. Length ultimately encumbered Trost's synthesis, as well as observed instability in the prepared precursors. Also, several important procedures from this synthesis have gone unreported.

Magnus next completed a total synthesis of (+)-pancratistatin (**1**) in 1998.[34,35] Treating an aryl bromide A-ring precursor with *n*-butyl lithium provided an aryl anion, which was subsequently introduced to a protected cyclohexanone C-ring precursor (Scheme 4).

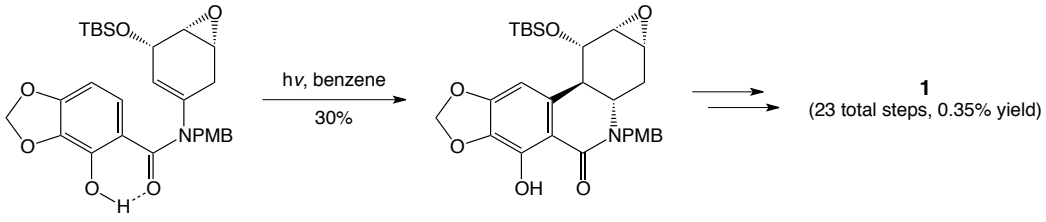
Scheme 4



While Magnus's nucleophilic acyl addition provided an A-C ring intermediate in high yield, it lacked stereocontrol, thus providing racemic product. In order to attain the targeted product stereochemistry, dehydration, hydrogenation, deprotection, and subsequent treatment with a chiral amide base were required, all adding to the length and low overall yield of this synthetic approach.

In 2000, Rigby and coworkers proposed a photocyclic means of approach to (+)-pancratistatin.[36] By exploiting the hydrogen-bonding interaction present between the phenolic hydrogen and the aryl enamide carbonyl oxygen, Rigby set the conformation of the starting material such that in would readily undergo photocyclization to provide the desired ring-fusion product in the proper conformation (Scheme 5).

Scheme 5

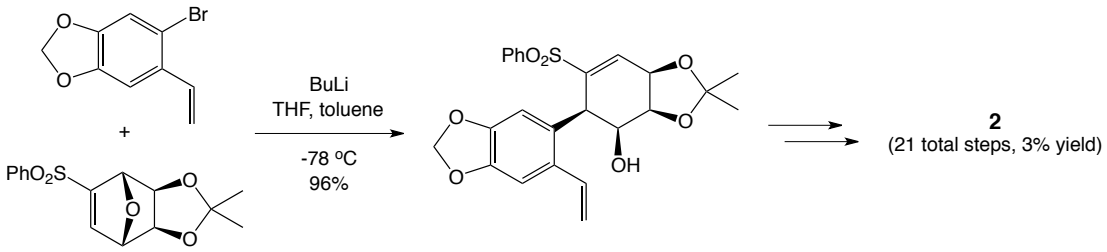


While cleverly planned, the low overall yield and significant number of steps required make this synthesis unattractive in practice.

Also in 2000, Plumet approached the synthesis of (+)-7-deoxypancratistatin (**2**) by way of ring opening a bicyclic ether bridge.[37] Through the treatment of a bromostyrene A-ring with butyl lithium, Plumet created a nucleophile *in situ* for

addition to the bicyclic C-ring precursor, which then proceeded through and allylic rearrangement to open the ring-fusion bridge (Scheme 6).

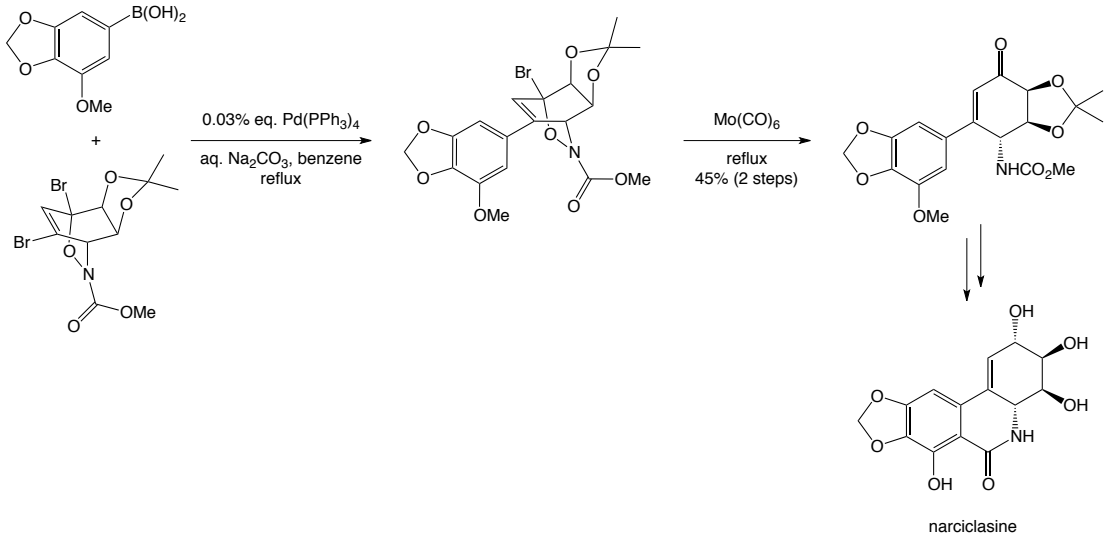
Scheme 6



While the conformation of the bicyclic system directed the stereoselectivity of A-ring addition, providing the desired A-C ring fusion stereochemistry in excellent yield, synthetically rigorous starting materials, overall length, and low total yield hurt Plumet's synthesis.

Hudlicky continued work on this topic, publishing a seminal article in 2002 describing various syntheses of pancratistatin and its analogues, including one of the first reported uses of palladium-catalyzed Suzuki cross-coupling in the synthesis of the analogue narciclasine.[38] Coupling of an aryl boronic acid A-ring with a dibromo oxazine tricycle using a catalytic amount of $Pd(PPh_3)_4$ proceeded in good yield, providing a coupled, tricycle-containing product which was subsequently ring opened (Scheme 7).

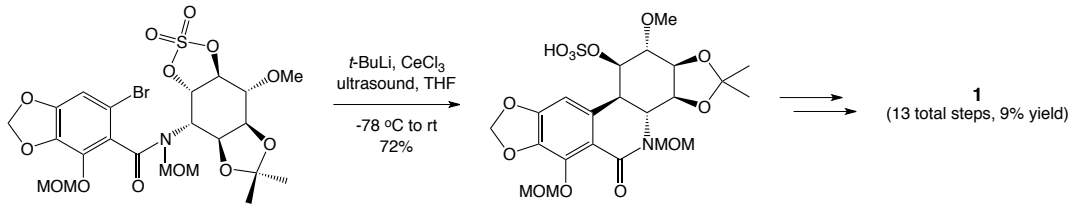
Scheme 7



Ring opening of the oxazine tricycle was noteworthy, in that it provided easy access to the desired stereochemistry in the subsequent carbamate, which was then used for the formation of the B-ring lactam. Both the implementation of palladium coupling technology, and the usage of stereochemically-dense tricycles would prove useful in future synthetic pathways developed in the DeShong group (*vide infra*).

In 2006, Li reported one of the highest yielding and shortest routes toward the synthesis of (+)-pancratistatin to date.[39] By employing pinitol as a starting material, a near stereochemical duplicate of pancratistatin's C-ring, much of the length reported in previous syntheses could be avoided. Through the creation of an aryl cerium nucleophile, Li was able to affect an intramolecular ring closure through the opening of a cyclic sulfate, affording the complete skeleton of the natural product with desired substituent configuration (Scheme 8).

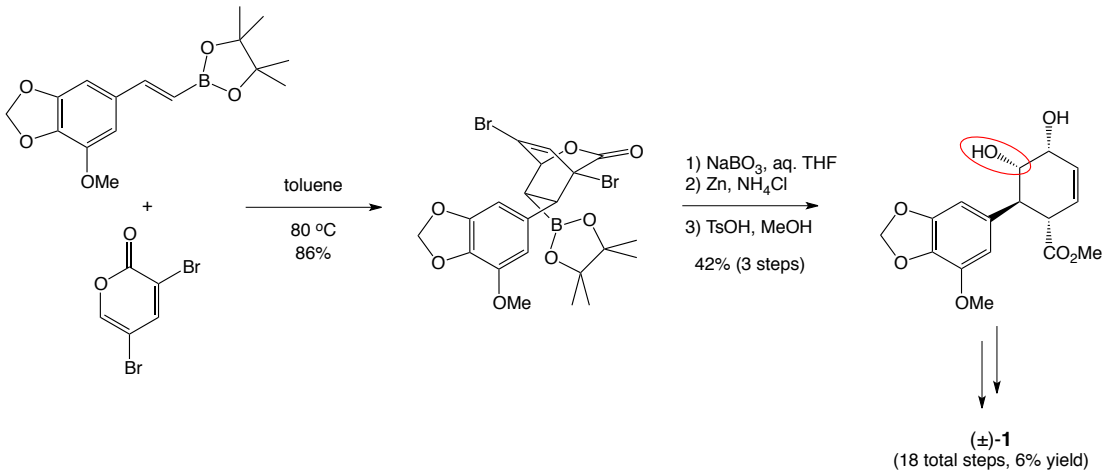
Scheme 8



While high yielding and expedient, the prohibitive cost of pinitol dramatically effects the viability Li's synthesis.

More recently, Cho has described the synthesis of racemic pancratistatin by way of an inverse electron-demand Diels-Alder cycloaddition between a borylstyrene A-ring analogue and dibromo pyrone.[40,41] The endo selectivity exhibited in the Diels-Alder cycloaddition reaction provided the desired stereochemistry at the A-C ring junction. Upon formation of the cycloaddition adduct, subsequent boronate cleavage, debromination, and methanolysis of the bicycle produced the distinguishable A-C ring skeleton intermediate of pancratistatin (Scheme 9).

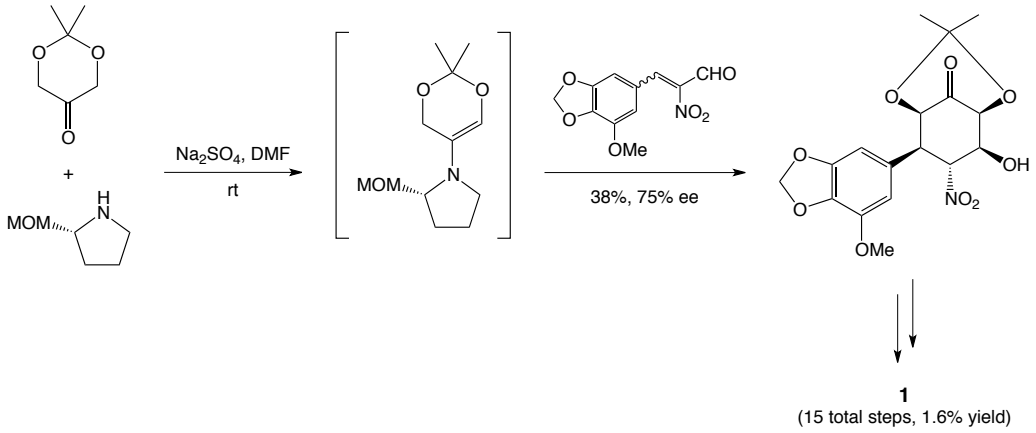
Scheme 9



While seemingly innocuous, the formation of the dibromo pyrone starting material proved synthetically challenging, and the resulting C-ring substituent stereochemistry in Cho's A-C intermediate required an inversion at the highlighted position, adding to the overall synthetic length.

The most recent synthesis of (+)-pancratistatin was reported by Alonso in 2012.[42] By treating dioxanone with a chiral pyrrolidine, a chiral enamine intermediate was generated, which upon introduction to an A-ring precursor aryl nitro enal, underwent annulation (Scheme 10).

Scheme 10



While an interesting application of a chiral pyrrolidine auxiliary, the subsequent annulation was low yielding, while providing only good enantioenrichment. Required recrystallizations to provide enantiopure products throughout Alonso's synthesis ultimately encumbered overall target yields.

Synthetic Approaches Toward 7-Deoxypancratistatin in the DeShong Group

Advances in palladium-catalyzed organosilane allyl-aryl cross-coupling methodologies have been made in the DeShong group, with the goal of being able to achieve a coupled, late-stage intermediate of the 7-deoxypancratistatin A-C ring system (Figure 3).

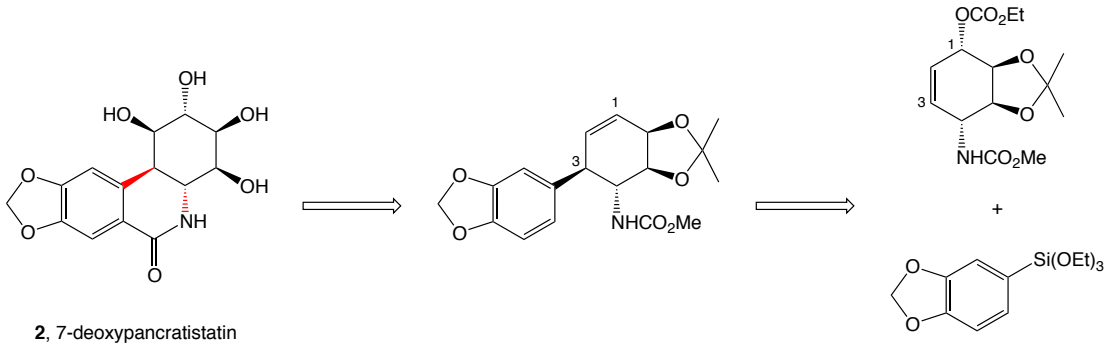


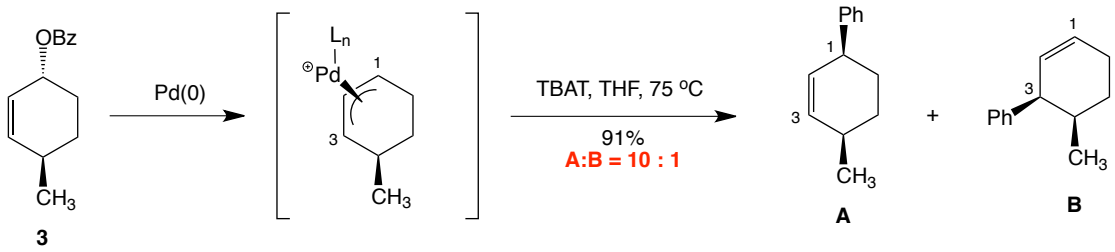
Figure 3. Proposed retrosynthesis of 7-deoxypancratistatin

Through the use of previously installed stereocenters in the readily accessible starting materials, the direction of the regio- and stereochemical outcomes of the palladium-catalyzed coupling to create the desired late-stage A-C ring intermediate should be attainable. For the reasons mentioned previously, we determined the use of our organosilane coupling technology is advantageous to the formation of this complex coupled product.

Initially, proof-of-concept studies into the regioselectivity of organosilane palladium-catalyzed allyl-aryl coupling of simplified analogues were undertaken. Investigation into the palladium-catalyzed coupling of trans-4-methylcyclohex-2-en-1-yl benzoate (**3**) and TBAT, tetrabutylammonium triphenyldifluorosilicate, a

silicate-based phenyl source that has been extensively studied in the DeShong group,[9,43,44] provided results that followed conventional understanding (Scheme 11).[45]

Scheme 11



After associating with the π-system, the palladium complex can displace the benzyl-protected alcohol from the anti- face in an S_N2 fashion with inversion of configuration, providing the π-allyl intermediate shown. Upon transmetallation of the phenyl group from the activated TBAT silicate, there remains a regiochemical question for the subsequent reductive elimination. The strength of the phenyl nucleophile predicates its addition to the palladium center in the π-allyl intermediate, providing the relative stereochemistry of the nucleophilic addition. Reductive elimination would be predicted to provide a cis coupled product, an overall inversion of stereochemistry from the starting material, which was observed.

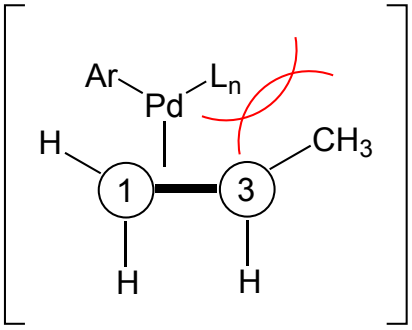
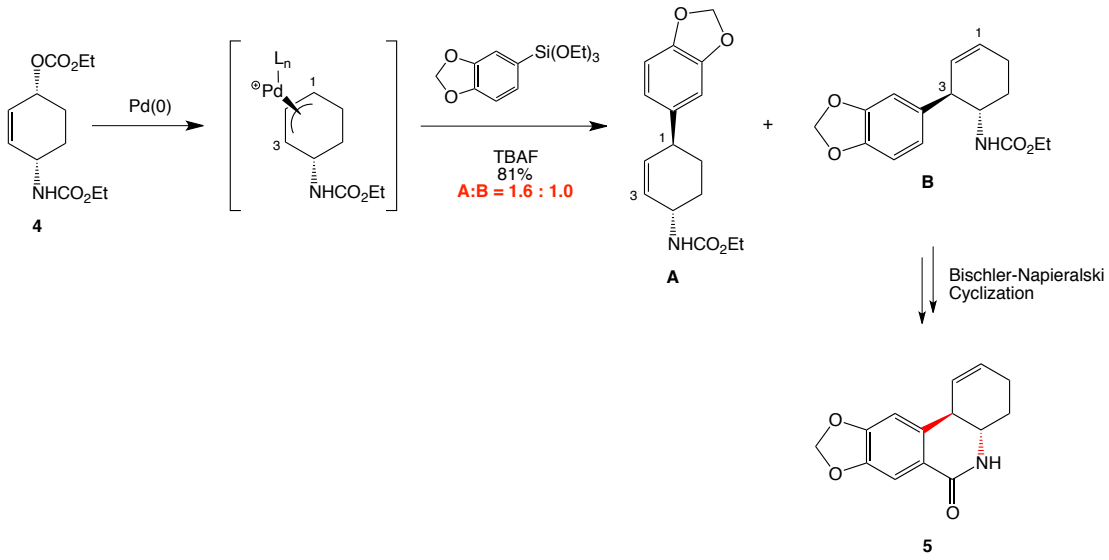


Figure 4. Unsymmetrical transmetallated π-allyl palladium intermediate

Ultimately, support for the regiochemical outcome can be gathered by observing the asymmetry in the π-allyl intermediate (Figure 4). The steric bulk of the methyl group at the 4-position would encumber the palladium species from residing predominantly over the 3-position as a π-allyl, or similarly as a σ-complex bound at the 3-position. Upon reductive elimination, one would expect notable product to derive from the more stable intermediate geometry of a σ-complex bound at the 1-position, which was experimentally observed in the regioisomeric product ratios.

With the result of this investigation being in agreement with the accepted mechanistic model, further extrapolation in complexity with regard to the coupling partners employed was studied. By installing a carbamate functionality into the π-allyl precursor moiety, cis-4-ethyl carbamate cyclohex-2-en-1-yl ethyl carbonate (**4**), the opportunity for the formation of the B-ring lactam which would complete the carbon skeleton of the target molecule with proper stereochemistry (**5**) *via* a Bischler-Napieralski cyclization would be available, provided the coupling reaction gave the desired 1,2- substituted cyclohexenyl product (Scheme 12).[46]

Scheme 12



Similarly to the initial proof-of-concept studies, displacement by the palladium complex of the carbonate leaving group occurs from the face anti to the leaving group, providing the intermediate show above. Once again, given the highly nucleophilic nature of the activated fluorosilicate intermediate of the aryl alkoxysilane transfer reagent used, the relative stereochemistry observed at the position of coupling can be reasoned to arise *via* transmetallation with the π-allyl palladium intermediate (Figure 5).

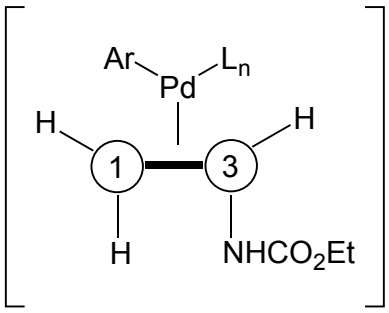


Figure 5. Symmetrical transmetallated π-allyl palladium intermediate

In this instance, however, the regioselectivity displayed in the coupling reaction was low, due to the lack of a sterically directing group occupying a position on the same face as the palladium complex. By this absence of a capable steric occupant in the π-allyl intermediate, residence of the transmetallated palladium complex in any of the σ^1-π-σ^3 isomers should be statistically equivalent, therefore providing only modest regioselectivity in products observed upon reductive elimination (Figure 6).

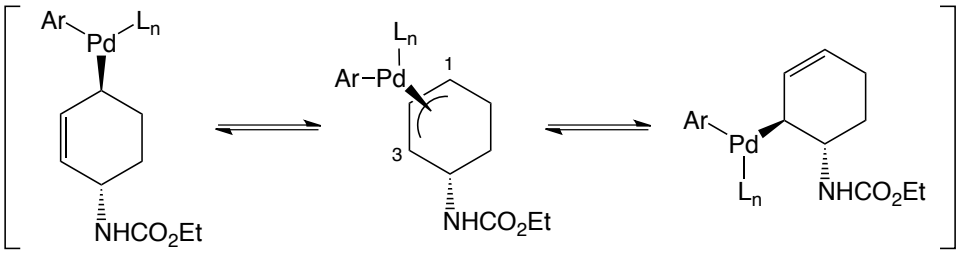


Figure 6. σ^1-π-σ^3 isomerization in the symmetrical transmetallated π-allyl palladium intermediate

Work by Szabó and coworkers further elucidates a conformational bias experienced in the trans π-allyl palladium intermediates derived from 1,4 disubstituted cyclohexenes of this type, leading to favorable reductive elimination from the 1-position, thereby explaining the slight variance from statistical distribution in regioisomeric coupled product ratio observed.[47]

By further derivatization of the coupling precursor to include an acetonide-protected diol (**6**), it was envisioned that a steric bias could be imparted on the π-allyl intermediate, thereby imparting potentially high regioselectivity for coupling at the

desired C-3 position of the π-allyl system in the subsequent reductive elimination to provide the desired product (Figure 7).

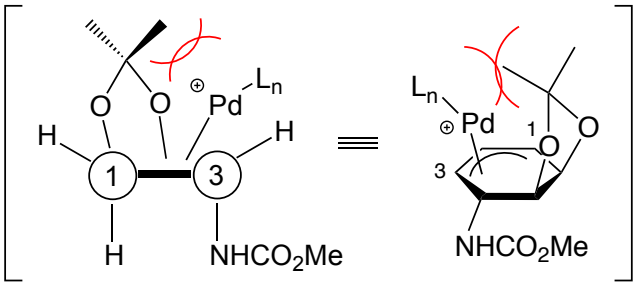
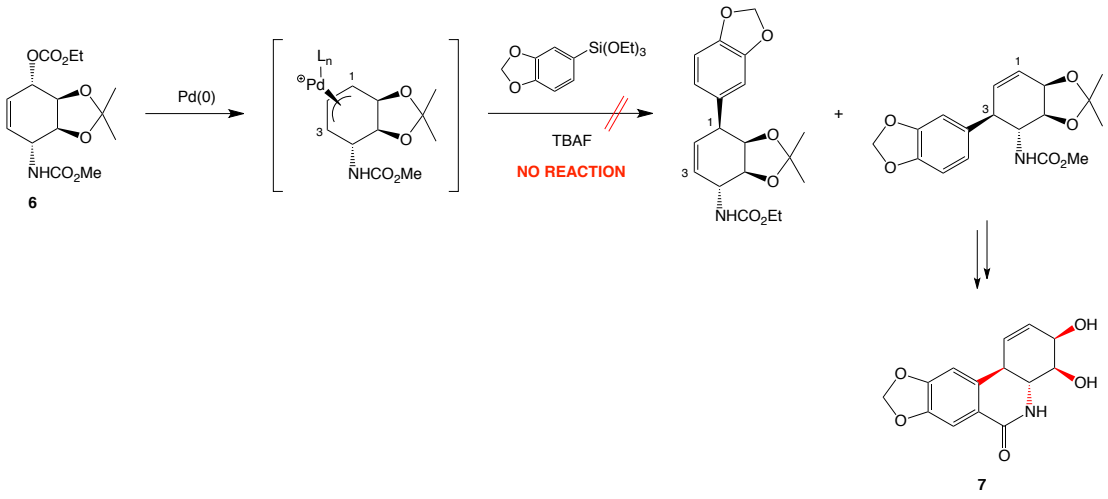


Figure 7. Complex asymmetric π-allyl palladium intermediate

While allowing for the previously absent coupling-site direction, the inclusion of the bulky protected diol would also set two stereocenters that are present in the natural product targets backbone (**7**) (Scheme 13).

Scheme 13



Unfortunately, the coupling reaction did not proceed as expected, failing to provide the desired coupled product.[48] It was initially reasoned that the steric bulk of the acetonide protecting group was too substantial for the palladium(0) substrate to either complex with the π-system then displace the leaving group in the coupling precursor, or, if that were successful, to allow the activated aryl fluorosilicate nucleophile subsequent access to the π-allyl palladium intermediate to undergo transmetallation. In order to better identify the cause of our coupling process shortcomings, it was determined that the Tsuji-Trost coupling methodology would provide valuable insight into where in the coupling cycle the reaction failed.

It was envisioned that, by implementing Tsuji-Trost technology, it could be determined if the steric bulk from the acetonide protection of the diol was too great for the initial palladium(0) complexation or leaving group displacement to occur. In Tsuji-Trost coupling, oxidatively-inserted palladium(II) species are displaced by the addition of weak nucleophiles, via an anti- addition to the allyl moiety with respect to the palladium center.[49] Provided the anti- face of approach for the nucleophile is much less sterically congested, the outcome of the Tsuji-Trost coupling will be solely dependent on formation of the palladium(II) intermediate (Figure 8).

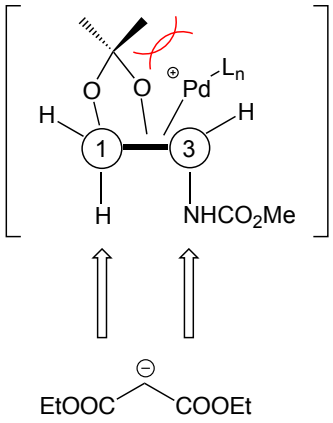
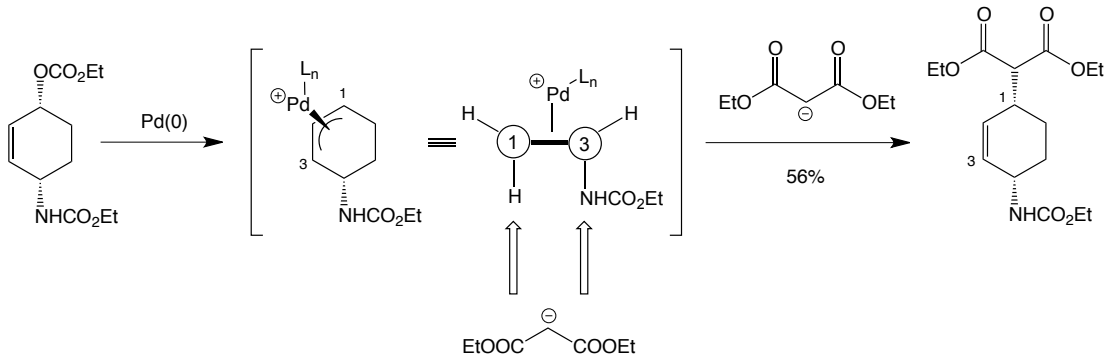


Figure 8. Proposed Tsuji-Trost coupling intermediate

If Tsuji-Trost coupling product were to be observed, it would follow that the palladium π-allyl intermediate shown in Scheme 13 and Figure 8 was indeed being formed, despite the steric encumbrance presented by the acetonide group, and that our previously attempted coupling to form the late-stage natural product intermediate (Scheme 13) was impeded at the transmetallation stage of the coupling cycle.

With this in mind, a proof-of-concept investigation with basic coupling partners, analogous to our desired complex systems, was undertaken in order to examine the general efficacy of the Tsuji-Trost coupling technology with our model π-allyl coupling systems (Scheme 14).[45]

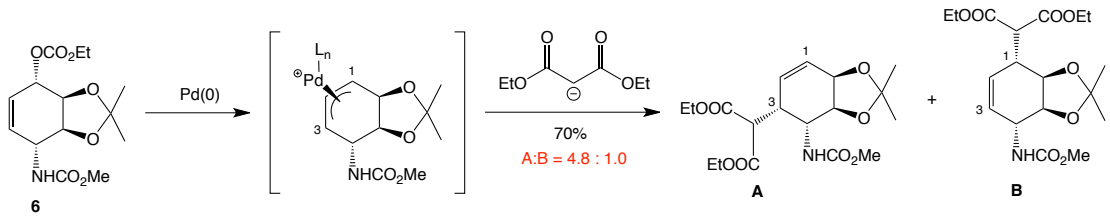
Scheme 14



The stereoselectivity of this basic Tsuji-Trost coupling follows the expected approach of the nucleophile from the anti- face in relation to the π-allyl palladium intermediate, providing an overall retention of stereochemistry from the starting material (arising from an inversion-inversion). Similarly, the regiospecificity displayed in the coupled product arises from a favorable nucleophilic attack at the less hindered 1-position, compared to a 3-position approach which is effectively blocked by the 4-position carbamate residing on the face of addition.

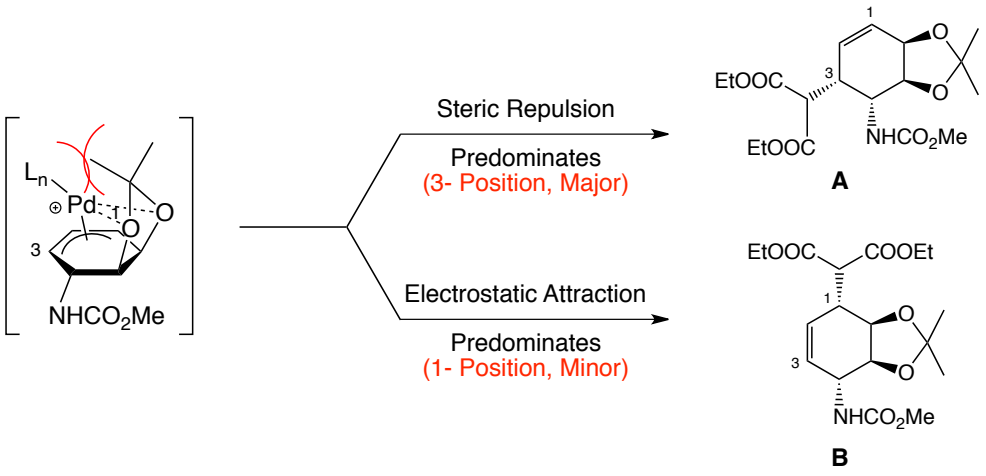
With the Tsuji-Trost technology proving efficacious with our basic coupling system analogue, extrapolation to our desired coupling precursor (**6**), to test if the palladium(0) complex was capable of achieving leaving group displacement, could now be observed (Scheme 15).

Scheme 15



Interestingly, and to the benefit of our projected couplings for the formation of the carbon skeleton of *Amaryllidaceae* natural product targets, the observed regioselectivity of addition of the malonate nucleophile goes against the predicted steric effects in the proof-of-concept studies (Scheme 14). From said studies, product arising from malonate addition at the 1- position (**B**) was expected to predominate, provided the steric encumbrance that was projected to occur during a 3- position addition (**A**) due to the bulk of the carbamate in the 4- position residing on the same face of addition. It was rationalized that the regioselectivity of addition was predicated upon the relative overall balance between the steric interaction of the palladium(II) complex with the acetonide protected diol, forcing the complex to reside more toward the 3- position and thus yielding product **A**, versus the electrostatic interaction of the positively-charged palladium(II) complex and the lone pairs of oxygen in the acetonide protected diol, pulling the complex toward the 1-position and providing product **B** upon nucleophilic addition (Scheme 16).[50]

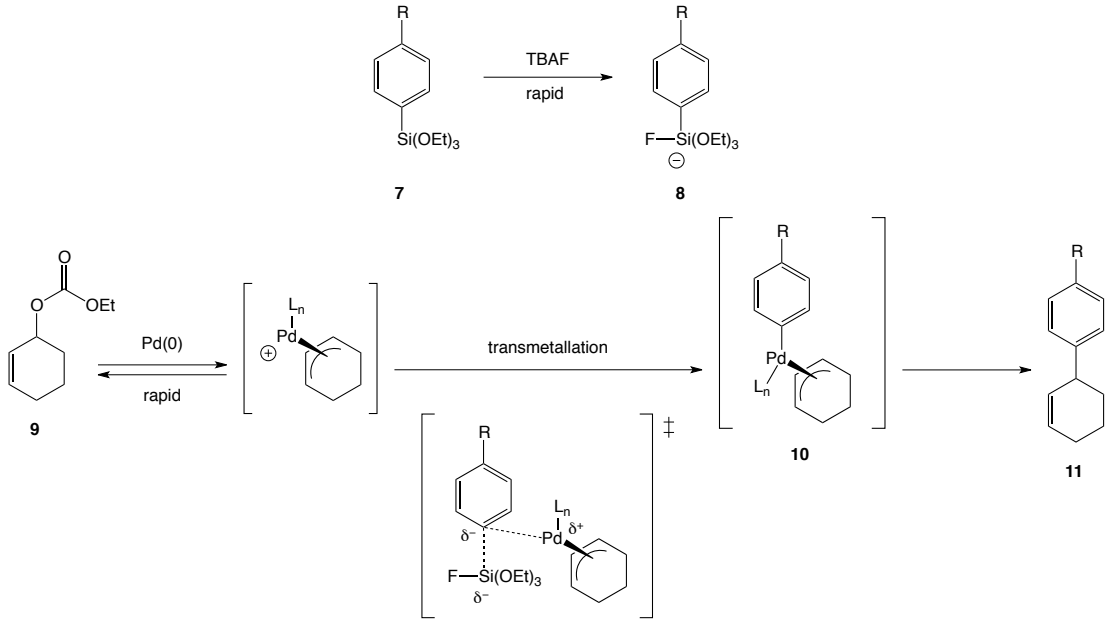
Scheme 16



With the observation of Tsuji-Trost coupled products arising from our complex coupling intermediate, it can be established that the π-allyl palladium intermediate must be forming despite the congested sterics. This also suggests that the underlying issue with our original complex allyl-aryl coupling process must be the inability of the π-allyl palladium complex to undergo transmetallation. In order to better understand the mechanistic aspects of our allyl-aryl coupling, with a specific focus on the transfer of the aryl group during transmetallation, a Hammett Analysis of the coupling of various aryl silicate derivatives with a standard allyl carbonate was undertaken.[51]

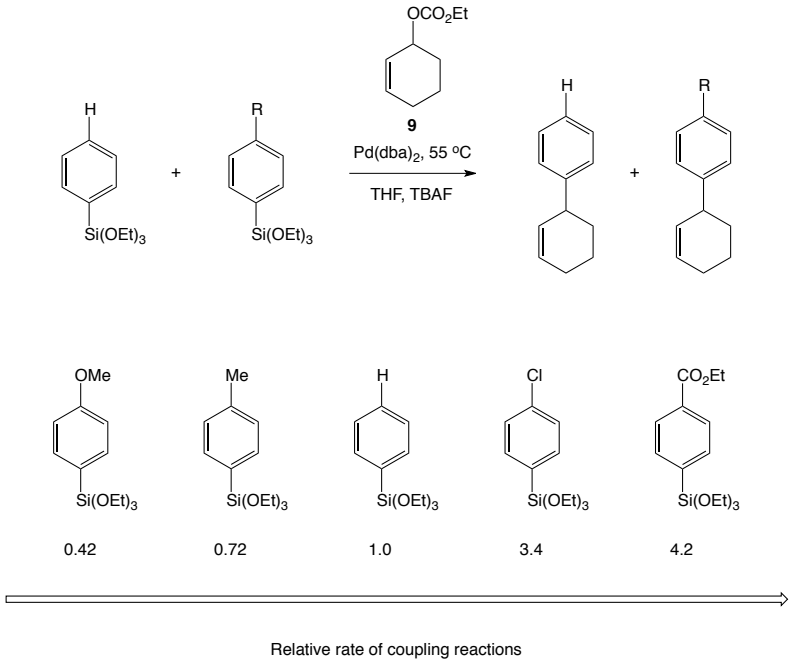
The proposed mechanism for our allyl-aryl coupling follows the expected route: rapid activation of aryl siloxane **7** with the TBAF fluoride source to produce a pentacoordinate silicate (**8**), while palladium(0) catalyst displaces the carbonate leaving group in the allyl carbonate moiety of **9**. Transmetallation of the activated silicate with the π-allyl palladium complex provides intermediate **10**, which, upon reductive elimination, yields our desired allyl-aryl coupled product **11** (Scheme 17, modified from reference 51).

Scheme 17



By examining the effects incorporating a variety of electron-donating and electron-withdrawing substituents into the aryl silicate moiety had on the relative rates of coupling compared to an unsubstituted aryl silicate, information was gathered regarding the electronic character of the predicted transition state (Scheme 18, redrawn from reference 51).

Scheme 18



The information provided by the Hammett correlation was twofold: (1) the relative rates for the coupling reactions were enhanced through the presence of an electron-withdrawing group, leading to the belief that our proposed coupling mechanism and transition state were accurate, as the development of negative charge on the aryl ring during the transition state would be better stabilized by the presence of an EWG via inductive effects, and (2) the observation in correlation between aryl silicate modification and the relative rate of the coupling reaction corroborates that transmetallation is the rate-determining step in our mechanism.[51]

To this point, the 18-electron $Pd(dba)_2$ catalyst had been our chosen source of Pd(0), given its relative stability, ease of use, and ubiquity of employment throughout the literature.[52-54] Provided the success of the Hammett analysis on our allyl-aryl coupling methodology however, investigation into the qualitative effects of varying

catalyst parameters on transmetallation was begun.[51] Without a more exhaustive investigation into the specifics of conformation of the metal center and ligand environment during transmetallation, the scope of this study could only provide insight into the product yield outcomes relative to the variability in ligand characteristics. It was hypothesized, however, that certain ligands might enhance the rate of transmetallation by electronically or sterically stabilizing the transition state (Scheme 17).

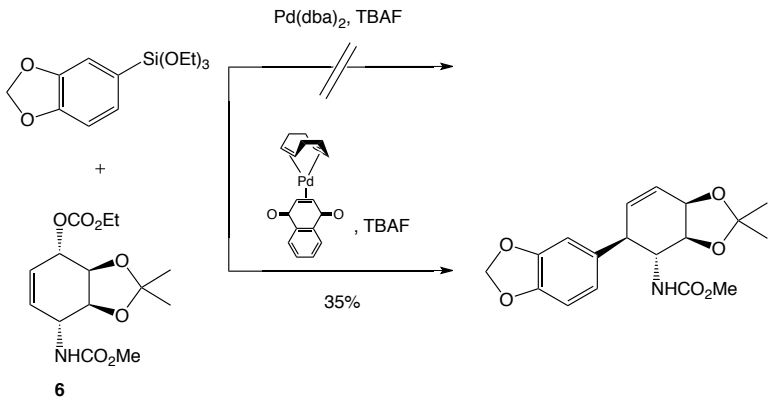
It was experimentally determined that ligands with a larger cone angle provided higher yields of allyl-aryl coupled products ($P(o\text{-tolyl})_3 > PPh_3$), most likely due to the steric bulk of the ligand creating a π-allyl palladium complex with a low coordination number, thus expediting transmetallation of the aryl group from the activated silicate. While the ability to tune the coupled product yield through ligand modification was displayed, $Pd(dba)_2$ still proved to be the most effective catalyst for our model coupling reaction. With this in mind, modification of the $Pd(dba)_2$ alkene-liganded catalyst model, to investigate their ability to be tuned and optimized, was envisaged. As was previously mentioned, $Pd(dba)_2$ has a full compliment of 18 electrons and no open coordination sites; its rate of catalytic action is based on the ability for ligand dissociation to occur to free up a coordination site. As such, it was posited that a certain class of triolefin palladium(0) catalysts, possessing only 16 electrons and a free coordination site might improve the rate of transmetallation, and thus increase coupled product yield.

It was believed that the ideal alkene ligands for our coupling methodology would be sterically daunting (*vide supra*), while also lacking electron-withdrawing

character that might slow ligand dissociation, and thus impede transmetallation. However, a balance must be found between the extremes of these characteristics, in order to provide a species that is reactive enough to expedite transmetallation, but also stable enough to not degrade before catalyzing the desired coupling.

From a preliminary investigation into modified alkene-based palladium(0) catalysts, we have recently reported that the coupling of A-C ring analogues that had previously failed (Scheme 13), could now be achieved by employing Pd(COD)(NQ) as a catalyst (Scheme 19),[55] producing a late-stage intermediate in the Hudlicky synthesis of (+)-7-deoxypancratistatin.[32]

Scheme 19



While successful in achieving the original goal of completing our formal total synthesis of (+)-7-deoxypancratistatin, the application of a new class of alkene catalysts now necessitated a more thorough, systematic evaluation to better understand the subtle effects modifying alkene ligands has on coupling yields (*vide infra*).

While a variety of tridentate, 16-electron Pd(0) complexes of this general structure have been reported in the literature (Figure 9),[56-68] few studies of their catalytic capabilities have been reported.[58,59]

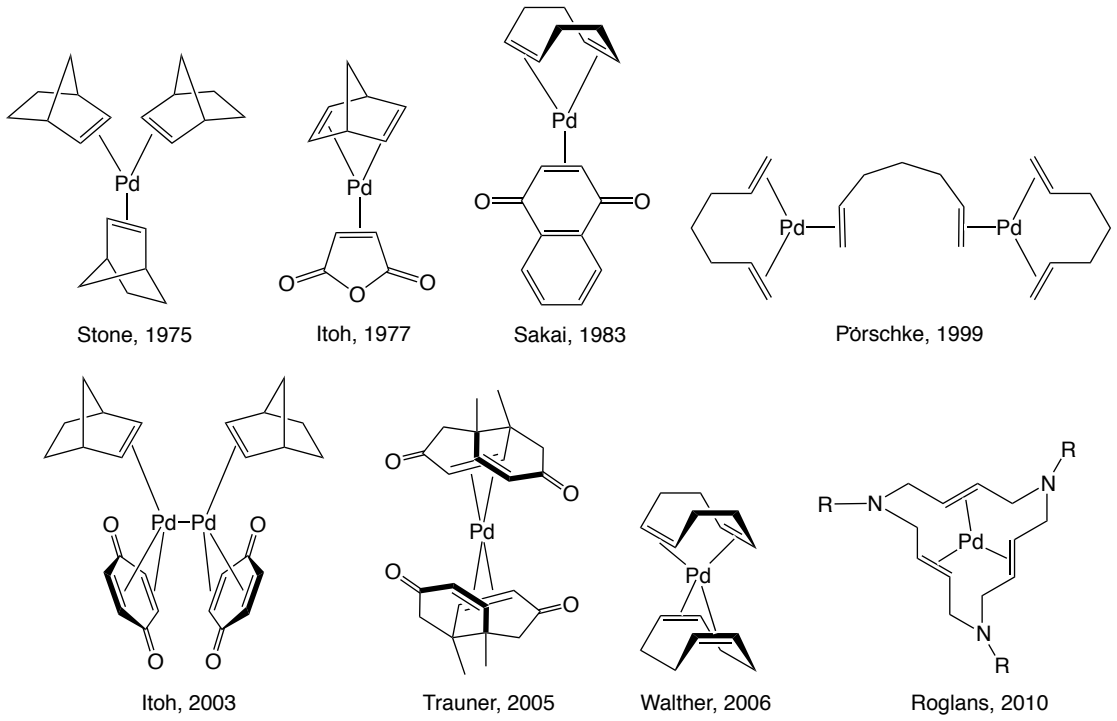


Figure 9. Alkene-based palladium(0) complexes

In certain fused bicycles containing alkenes, the geometric configurations for optimal orbital overlap in the sp^2-hybridized centers are unattainable, leading to marked energetic strain present in these ring structures. The relief of this ring strain is affected via rehybridization of the sp^2 centers. The process of rehybridization is twofold.[69] The electron density residing in the π orbital of the olefin ligand is donated into the vacant metal dσ orbital, further delocalizing the π electrons onto the metal center and weakening the π bond. Similarly, the occupied dπ orbital of the metal can

donate electron density to the LUMO π* orbitals of both carbon centers in the olefin ligand, effectively weakening the π bond via "back bonding" (Figure 10).

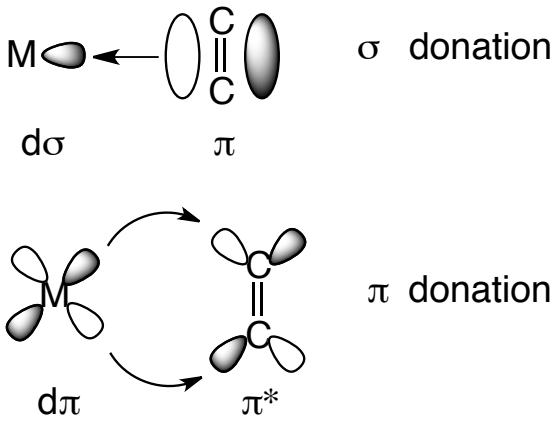


Figure 10. π-back bonding, as it effects rehybridization of olefin ligands

The binding of the ring-strained olefin ligands with the metal center of our catalysts should have an overall stabilizing effect, with their association effectively reducing the sp^2 character of the geometrically constrained olefin to produce a more sp^3-like carbon center, providing greater freedom in orbital overlap and relieving torsional strain. This relief in strain could be a major contributing force for the strong association we believe is present between our diene ligands and the metal center; the ligand-bound catalyst should be more energetically favorable than the free, ring-strained ligand.

The degree to which either of these modes of ligand binding occurs depends heavily on the nature of both the olefin and the metal. Electron rich, lower oxidation state metals allow for greater π back bonding, while higher oxidation state metals tend to provide weaker π back bonding.[69] Similarly, electronically withdrawn olefins have

less π localized energy density present, so donation to the metal dσ is decreased. The precise degree to which electronics, ring-strain relief, ligand cone angle, and other factors affects the overall success of our catalysts remains to be seen.

The purpose of this work was to systematically study the siloxane-based allyl-aryl coupling technology previously developed in the DeShong group[8,44,70] while employing a new class of tri-olefin liganded Pd(0) catalysts.

Results and Discussion

Based on the experience we have gained from our studies with pancratistatin analogues, the initial studies comparing the effectiveness of the 16-electron Pd(0) catalysts in the allyl-aryl coupling reaction were performed via the coupling of allyl carbonate **9** and aryl siloxane **7**. It had previously been reported in the DeShong group that this coupling could be accomplished in good yield using the typical 18-electron Pd(0) catalyst $Pd(dba)_2$.[8,44,51,70] The initial study was a comparison of $Pd(dba)_2$ (**I**) and a series of maleic anhydride 16-electron Pd(0) catalysts based on the complexes reported by Itoh in 1977, as well as derivatives thereof (Figure 11).

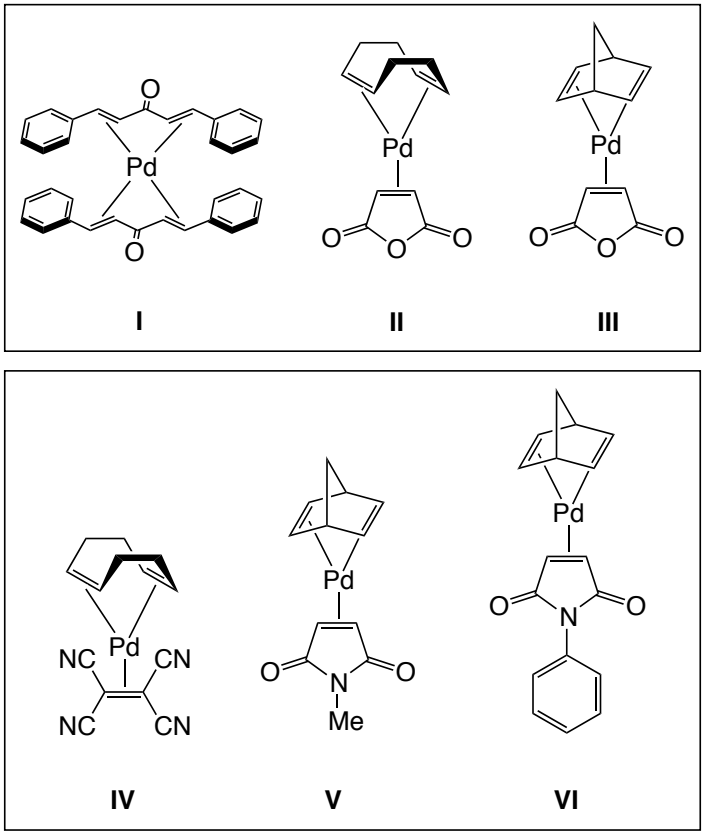
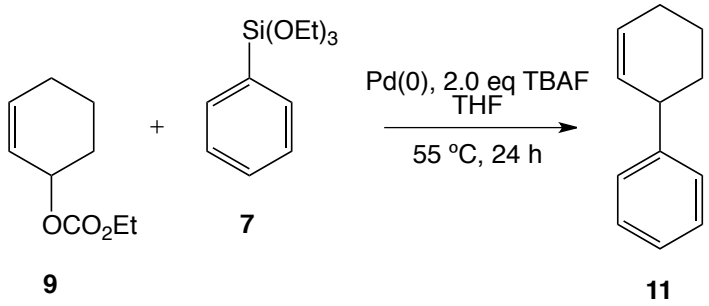


Figure 11. Unsaturated cyclic anhydride and imide-based Pd(0) 16-electron complexes

These complexes were chosen for investigation into their catalytic abilities in our allyl-aryl coupling reaction for numerous reasons. Several of these complexes had been previously reported by Itoh and Sakai, so their syntheses and characteristics were well known.[56-58] Also reported, several catalysts selected possessed reasonable air and moisture stability for transition-metal complexes, circumventing the need for use of glovebox techniques, and allowing their creation *in situ*. Also, provided the variety of 16-electron palladium(0) complexes reported with similar structural motifs, the formation of new derivatives appeared attainable, thus allowing for a systematic investigation into the effects of modification of ligands on catalytic ability to be undertaken, and the general premise of "catalytic tunability" to be explored. Finally,

very little investigation into these species' ability to catalyze coupling reactions had been reported to date, so this class of complexes was primed for deeper examination.

Under a variety of reaction conditions, neither bis-alkene maleic anhydride complex **II** nor **III** was as effective as $Pd(dba)_2$ (**I**) in catalyzing the allyl-aryl coupling reaction (Table 1). However, it is noteworthy that the norbornadiene complex **III** gave a higher yield of the coupled product than its cyclooctadiene (COD) analogue **II** (38% vs. 54%, respectively). Since the only difference between these two complexes was the cone angle associated with the diene ligands (norbornadiene and cyclooctadiene, respectively), it was concluded that the cone angle must have a significant effect on the stability or reactivity of the intermediate π-allyl complex in the coupling process. Complex **III** is also more thermally stable than complex **II**.



Pd(0) (25 mol%)	Yield (%)*
I	70
II	38
III	54

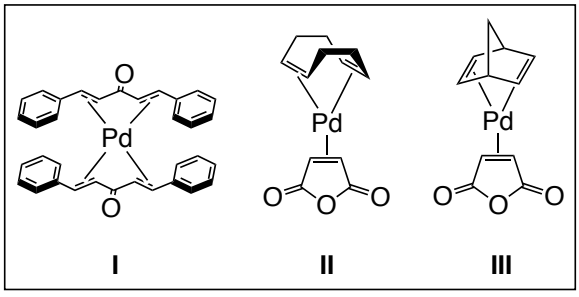
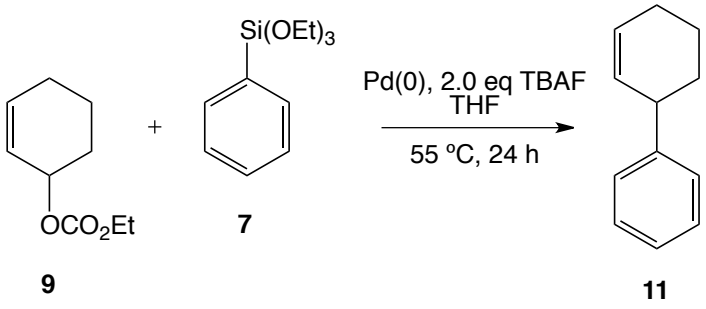


Table 1. Synthesis of 3-phenylcyclohex-1-ene using unsaturated cyclic anhydride-based Pd(0) 16-electron complexes.
All reactions were performed at 55 °C for 24 h, using 2 equiv of TBAF.
*Yields represent isolated yields.

Itoh has also reported complex **IV**, in which maleic anhydride has been replace with tetracyanoethylene in the COD complex. However, Pd-complex **IV** was an ineffective coupling catalyst (Table 2), as we attribute the low yields in this case with the instability of the complex under the typical coupling conditions, with palladium black rapidly precipitating during the reaction. Analogous complexes **V** and **VI** were also prepared using the Itoh method, in which maleimide derivatives were substituted for maleic anhydride. The N-methyl maleimide complex **V** gave the best yield of the coupled product and demonstrated excellent stability under the coupling conditions. From these results, two major conclusions can be drawn: (1) norbornadiene (NBD) complexes give higher yields of the allyl-aryl coupling product than the complementary cyclooctadiene (COD) analogues (comparing the yields when using complex **II** vs. **III**, and the improved yields of the coupled product with complex **V**), and (2) the catalytic activity of the complexes can be "tuned" by modifying the electron-deficient alkene ligand (comparing the coupling yields for norbornadiene complexes **III**, **V**, and **VI**).



Pd(0) (25 mol%)	Yield (%)*
III	54
IV	17
V	77
VI	41

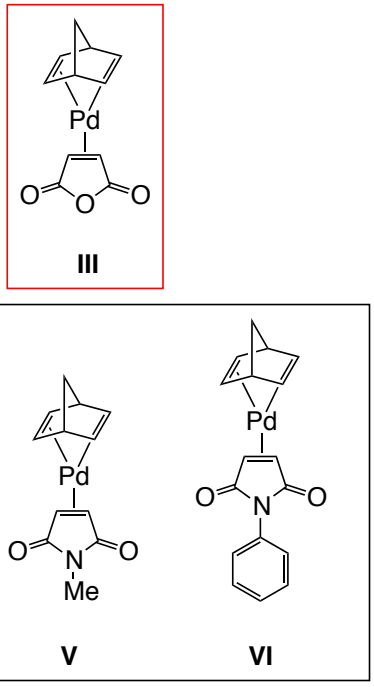


Table 2. Synthesis of 3-phenylcyclohex-1-ene using unsaturated cyclic imide-based Pd(0) 16-electron complexes.
All reactions were performed at 55 °C for 24 h, using 2 equiv of TBAF.
*Yields represent isolated yields.

As summarized above, it was concluded from the results in Tables 1 and 2 that cone angle and/or the sterics of the bis-alkene ligands, norbornadiene or cyclooctadiene, play an important role in determining the catalytic activity of the Pd(0) complex. Alkenes, such as norbornene and norbornadiene, possess a high binding affinity to the metal center, because of the relief of ring strain upon carbon

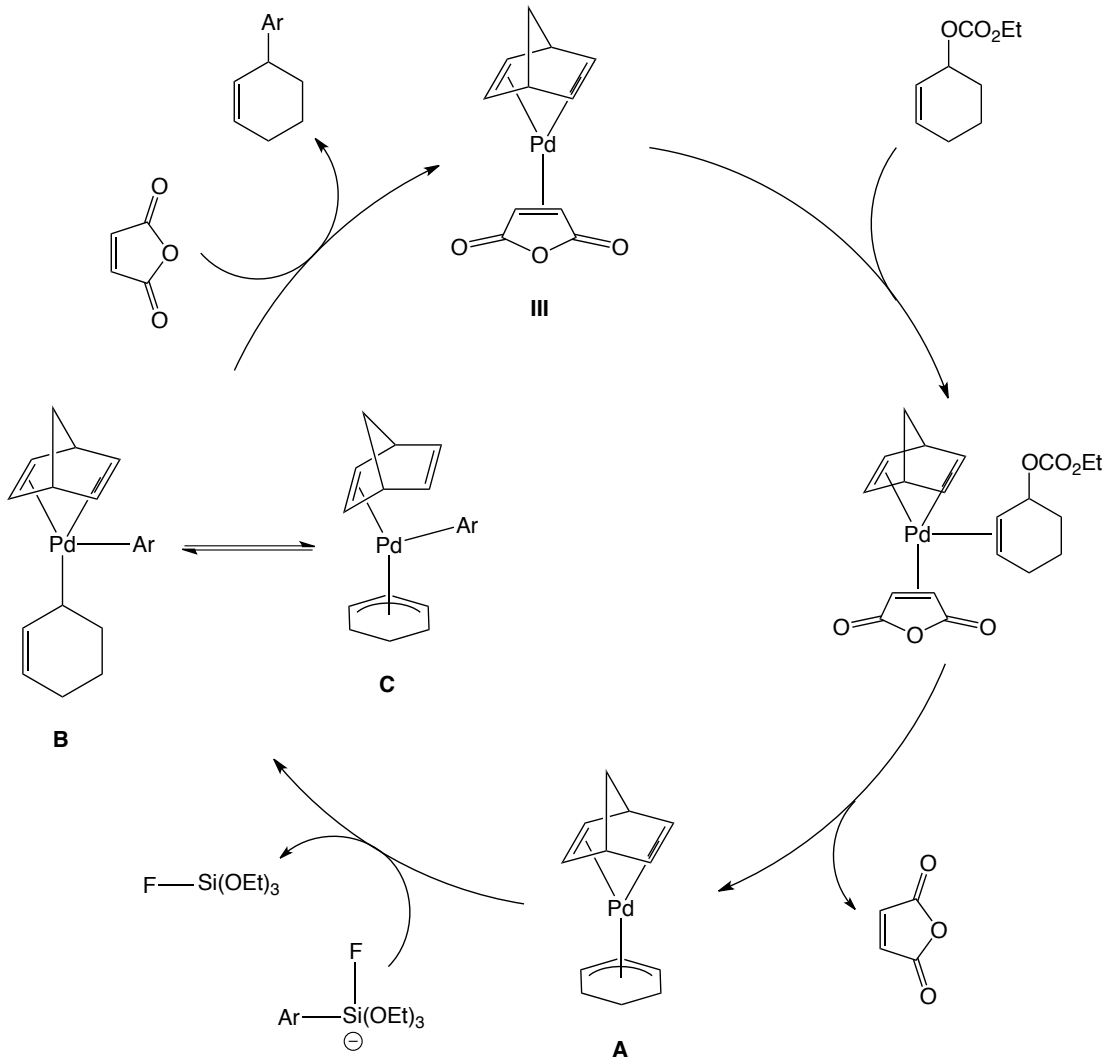
rehybridization, as well as a reduction of steric hindrance. Thus, the effective cone angle of the diene ligand can greatly affect the rate of coupling.[71] The metal-alkene bond is described as a combination of σ-donation from a from a filled alkene π-orbital to an empty metal orbital, and π-back donation, from a filled metal orbital to an empty alkene π* orbital.[53,71] For an electron rich d^{10}-configuration metal such as Pd(0), π-back donation from the palladium center to the alkene is extremely important for stabilization. Stronger π-back donation results in a stronger palladium-alkene bond, thereby increasing the stability of the palladium complex, but reducing the lability of the alkene ligand and slowing transmetallation.

While the reactions reported thus far were performed at 55 ^{o}C, it is important to note that both Pd(COD)(MAH) (**II**) and Pd(NBD)(MAH) (**III**) catalyzed the allyl-aryl coupling reaction even at ambient temperature, which is not the case with $Pd(dba)_2$, even though they provide lower yields of the coupling product. The decrease in yield can be attributed to instability of the 16-electron complexes in solution, compared to $Pd(dba)_2$. As noted above, complex **II** rapidly decomposes to palladium black under the coupling conditions, while complex **III** is more stable. While the preparation of Pd(NBD)(MAH) (**III**) was trivial, the preparation of Pd(COD)(MAH) (**II**) and Pd(COD)(TCNE) (**IV**) (TCNE = tetracyanoethylene) was tedious and required careful handling due to their instability (precipitation of palladium black) when exposed to air at ambient temperature. Similarly, the incorporation of maleimides into the Pd(0) catalysts to give complexes **V** and **VI**, while providing good yields of the coupled product, we highly unstable at ambient temperature.

A comparison of the results in Tables 1 and 2 also demonstrates that the catalytic activity, as well as stability, of the metal-alkene complex can be "tuned" by adjusting the electronic properties of the electron-deficient ligand on the metal center. There are two possible explanations for the excellent yields of the NBD complexes **III** and **V**, respectively: (1) the NBD complexes have faster turnover rates than the other catalysts, or (2) the NBD complexes were more stable than the other catalysts. In the first scenario, if the rates of the catalytic cycle are faster for the NBD complexes, then more cycles can occur before the catalysts decompose, providing higher coupling yields. In the second case, if the catalysts are more stable, then more substrate could be processed before the catalysts decomposed, and higher yields of coupled product could be achieved. Without a complete mechanistic study of this coupling process, it is not possible to decipher the exact mode of increase in coupling product yield for this reaction.

At this point, there are several mechanistic factors that require additional consideration: as shown in Scheme 20, NBD complex **III** presumably undergoes π-allyl formation with concomitant loss of maleic anhydride to give complex **A**. Transmetallation of the aryl group from the silicate to palladium provides either complex **B** or **C**. Reductive elimination from **B** / **C** releases the coupled product and regenerates the catalyst. It is believed that the monodentate, electron deficient alkene is the ligand that initially departs to open a coordination site, as doping the coupling reaction with excess equivalents of this ligand increases the competition for binding at this site, and significantly decreases the coupled product yield (4 equiv. MAH added, 22% coupled yield observed).

Scheme 20



The short catalytic lifetime of the Itoh complexes **II-VI** limited their application in the allyl-aryl coupling reaction. Accordingly, the examination of 16-electron Pd(0) complexes containing quinones was undertaken, as prepared from $Pd_2dba_3 \cdot CHCl_3$ by both the Sakai and Itoh groups (Figure 12).[57,58]

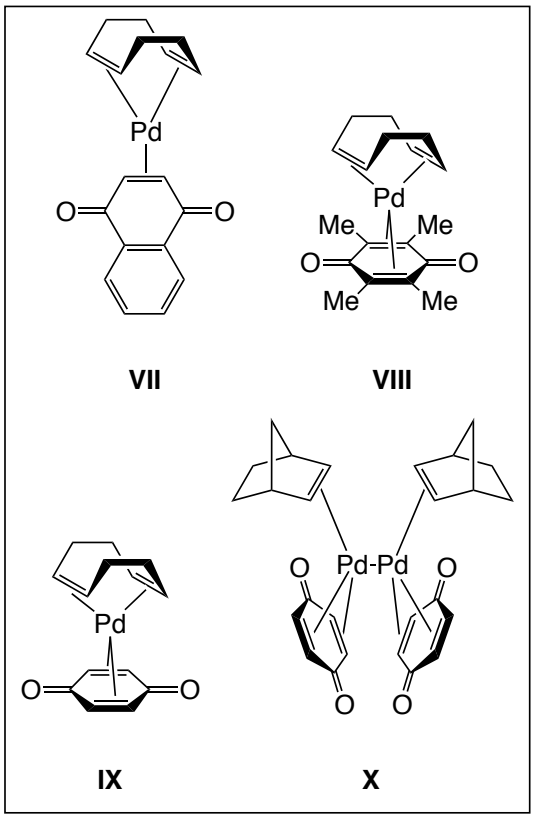
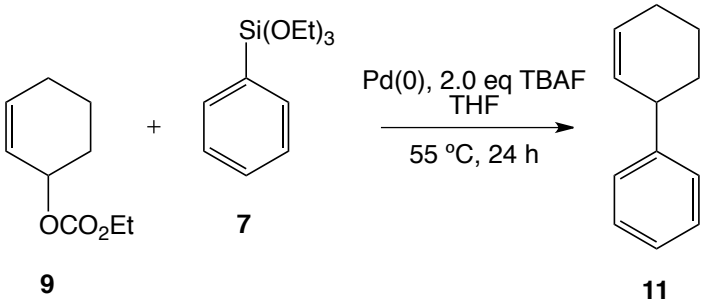


Figure 12. Quinone-based Pd(0) 16-electron complexes

These complexes are significantly more stable at ambient temperature, and therefore more readily prepared without resorting to glove box protocols. When employed in the allyl-aryl coupling reaction, Pd(COD)(NQ) (**VII**) gave superior yields in comparison to Pd(COD)(DQ) (**VIII**) and Pd(COD)(BQ) (**IX**), indicating a strong electronic influence in the catalysts' performance. It is interesting to note that a subtle change, such as the inclusion of an aromatic ring from naphthoquinone (NQ) in the catalyst, dramatically improves the coupling yield compared to benzoquinone (BQ) and duroquinone (DQ). With duroquinone and benzoquinone acting as bidentate ligands, the palladium center has a full compliment of 18 electrons and no open coordination sites, theoretically leading to slower transmetallation and lower yields. A

dinuclear Pd(0) complex possessing BQ as a bidentate ligand and NBE (norbornene) as a monodentate ligand was also prepared,[58] however this catalyst (**X**) provided a poor coupling yield (Table 3). Strangely, analogous complexes containing norbornadiene rather than cyclooctadiene proved too unstable to use for these coupling reactions, precipitating palladium black immediately upon formation.



Pd(0) (25 mol%)	Yield (%)*
VII	48
VIII	23
IX	20
X	21

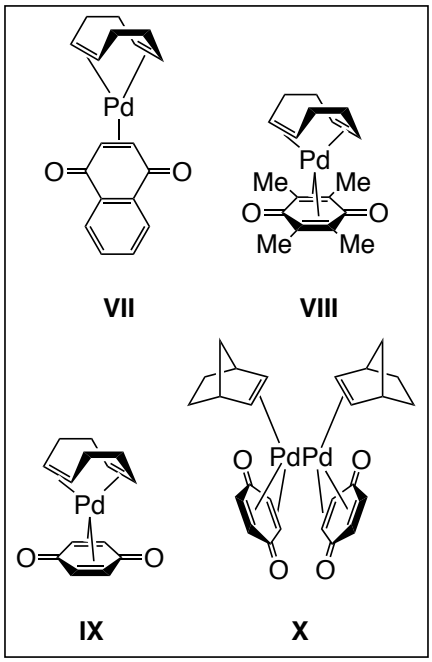
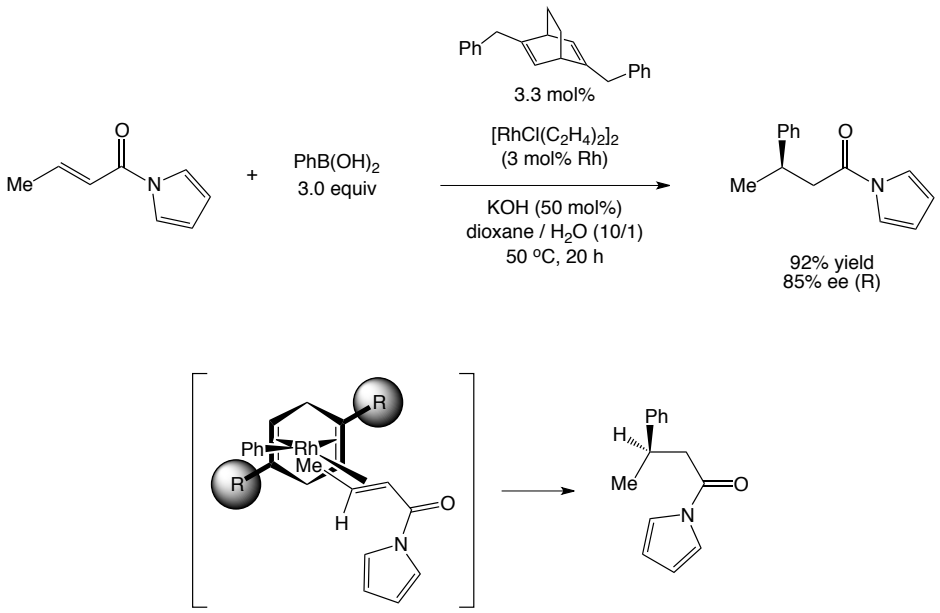


Table 3. Synthesis of 3-phenylcyclohex-1-ene using quinone-based Pd(0) 16-electron complexes.
All reactions were performed at 55 °C for 24 h, using 2 equiv of TBAF.
*Yields represent isolated yields.

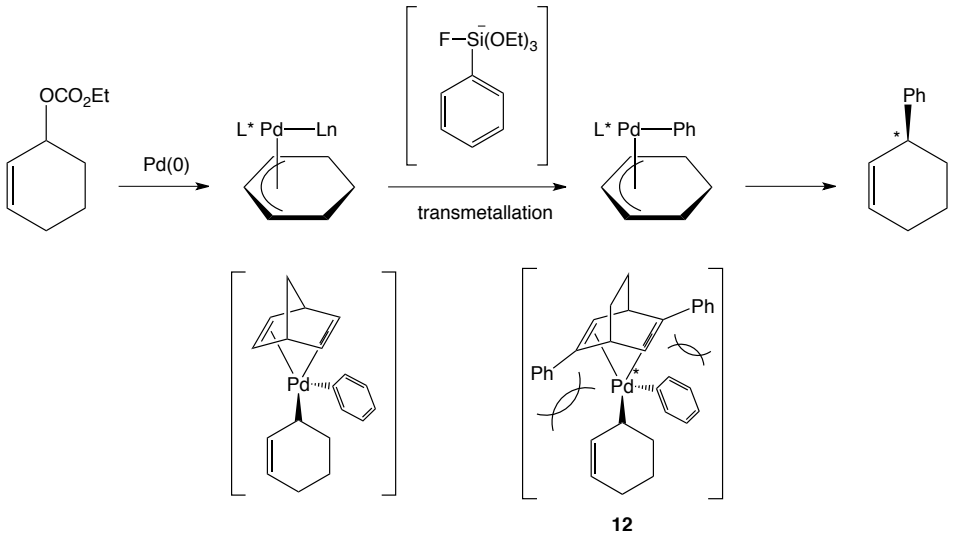
While the use of chiral dienes as ligands in transition-metal mediated reactions is well established with other metals, specifically rhodium (Scheme 21),[72] their implementation as ligands on palladium is less widely reported.[73]

Scheme 21



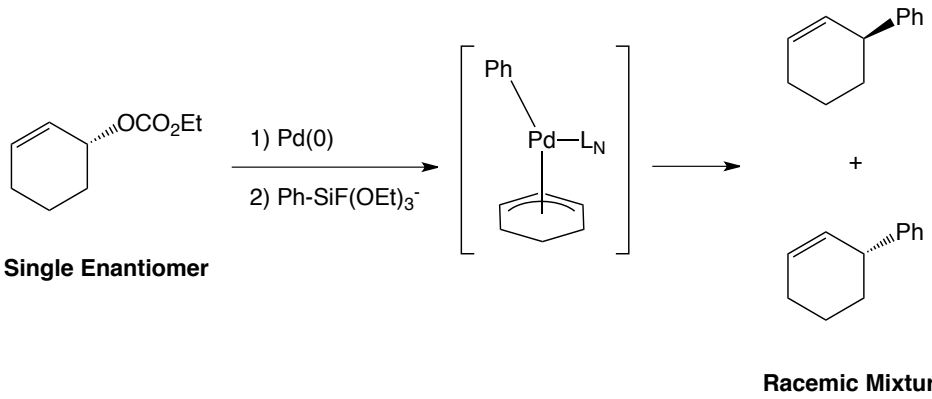
Given that the intermediate π-allyl complex derived from cyclohexenyl carbonate is a *meso*-compound (Scheme 22; when L* is achiral), the coupling reaction provided a racemic product. On the other hand, enantioenrichment of the coupled product should be possible if chirality can be imparted upon the intermediate (Scheme 22) by the incorporation of a chiral diene ligand into the catalyst.

Scheme 22



By using (1*R*,4*R*)2,5-diphenylbicyclo[2.2.2]octa-2,5-diene (*R*,*R*-DPBCO), possessing C_2 rotational symmetry, as a ligand in the preparation of the Itoh catalysts, the intermediate (**12**) prior to reductive elimination to provide the coupled product is chiral, and should favor formation of one enantiomer based on the sterics of the chiral ligand (Scheme 22). The enantiopurity of the starting cyclohexenyl carbonate should be immaterial, as upon leaving group displacement, the π-allyl complex is symmetric, and the stereochemistry of the final product is determined by the position from which reductive elimination occurs (Scheme 23).

Scheme 23



While the yield of coupled product using Pd(*R*,*R*-DPBCO)(MAH) as a catalyst was notable at 78%, no appreciable enantioenrichment (upper limit: >2% ee) was observed via chiral GC.

The lack of enantioselectivity observed in the coupling reaction could stem from several sources. It was predicted that the chiral ligand statically associated with the palladium center in a bidentate fashion. If, however, the ligand rapidly interchanged between a bidentate and monodentate metal-binding motif, then the ability for chiral induction to be observed in the coupled product would be compromised, as the chiral environment ceases to exist when the ligand is associated to the metal center at only one position. Similarly, if the length of the coordinative bonds between the palladium center and the chiral diene present in intermediate **12** are substantial, the ability for chiral induction to be observed in the coupling product may be limited, due to a decrease in the predicted steric interaction between the chiral ligand and the aryl moiety being added. Attempts at coupling more thoroughly functionalized allyl carbonate and phenyl siloxane derivatives may provide a greater

degree of observed enantioenrichment, given the higher predicted incidence of steric interaction.

Conclusion

In conclusion, a novel set of 16-electron palladium(0) complexes have been demonstrated to be catalytically active in the coupling of allyl carbonates and aryl siloxanes. In several instances, these complexes behaved comparable to the widely employed catalyst $Pd(dba)_2$. While not requiring glovebox techniques, *in situ* generation of these catalysts was employed due to air and moisture stability issues. These complexes have also been demonstrated to possess "tunable" reactivity by two parameters: (1) the choice of diene ligand, which controls the cone angle of the alkene coordination, and (2) by adjusting the electronic characteristics of the electron-deficient alkene attached to the metal center. The use of norbornadiene as the bidentate ligand in our complexes was shown to provide higher yields of coupled product, when compared to the implementation of cyclooctadiene. Similarly, N-methylmaleimide was demonstrated to be superior to the other electron-deficient, monodentate alkene ligands surveyed. Finally, while providing good yields of racemic coupled product, attempts to employ a chiral class of these complexes for enantioselective couplings proved unsuccessful.

Experimental Procedures

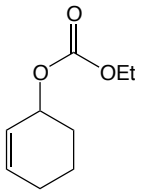
General Methods

All reactions were performed under an atmosphere of argon unless otherwise noted. Glassware used in the reactions was dried for a minimum of 12 h in an oven at 120 ºC and cooled in a dessicator prior to assembly. Tetrahydrofuran and diethyl ether were distilled from sodium / benzophenone ketyl, while methylene chloride, pyridine, and dimethylformamide were distilled from calcium hydride.

Infrared spectra were recorded on a Nicolet 560 FT-IR spectrophotometer. Samples used for obtaining infrared spectra were either dissolved in carbon tetrachloride, taken neat, or obtained using the total attenuated reflectance adapter for solids. 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).

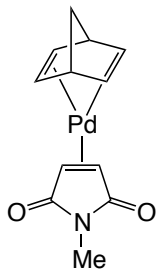
Nuclear magnetic resonance (^{1}H, ^{13}C, DEPT-135 NMR) spectra were recorded on a 400 or 500 MHz spectrometer. Chemical shifts are reported in parts per million (δ) and coupling (*J* values) are reported in hertz (Hz). Spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet), and br d (broad doublet). Low-resolution mass spectrometry (LRMS) and high-resolution mass spectrometry (HRMS) were obtained on a JEOL SX-02A instrument.

2-Cyclohexenyl Carbonate (9)



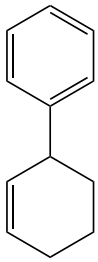
To 2.09 g (21.3 mmol) of 2-cyclohexen-1-ol, in 20 mL anhydrous CH_2Cl_2 and 2.6 mL (31.9 mmol) anhydrous pyridine, was added 3.2 mL (31.9 mmol) of ethyl chloroformate dropwise *via* syringe under argon. The reaction was allowed to stir at room temperature for 7 days. The completed reaction mixture was then extracted with CH_2Cl_2 (3 × 50 mL), and the combined organic layers were washed with H_2O (50 mL), dried over $MgSO_4$ and concentrated *in vacuo* to give a slightly yellow, translucent oil. Flash chromatography on silica gel (5% EtOAc/95% hexane, R*f* = 0.51) afforded 2.32 g (64%) of 2-cyclohexenyl carbonate (**9**) as a colorless oil; IR (CCl_4) 3042 (w), 2981 (w), 2947 (m), 2875 (w), 2838 (w), 1737 (s), 1373 (s), 1265 (s), 1017 (s) cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$) δ 5.97-5.93 (m, 1H), 5.76- 5.73 (m, 1H), 5.10-5.08 (m, 1H), 4.16 (q, *J* = 7 Hz, 2H), 2.09-2.04 (m, 1H), 1.99-1.84 (m, 1H), 1.83-1.72 (m, 3H), 1.63-1.60 (m, 1H), 1.28 (t, *J* = 7 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.9, 133.2, 125.1, 71.6, 63.7, 28.3, 24.9, 18.6, 14.3.

General Pd(0) Catalyst Preparation



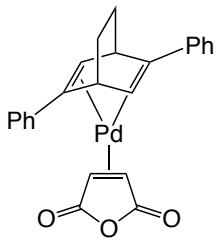
To 50 mg (0.048 mmol) of $Pd_2dba_3 \cdot CHCl_3$ in 1.5 mL of anhydrous acetone was added 134 mg (1.45 mmol) of norbornadiene (bidentate ligand) and 27 mg (0.24 mmol) of N-methylmaleimide (monodentate ligand) under an atmosphere of argon. The reaction mixture was stirred for 30 minutes at room temperature, upon which noticeable palladium black had accumulated in the reaction vessel. The reaction mixture was transferred via cannula and filtered under argon to provide a translucent yellow-green solution. The solution was briefly concentrated *in vacuo* to provide a slightly more viscous, yellow-green oil, to which 5.0 mL of anhydrous diethyl ether was added. This provided an opaque, yellow-green suspension of Pd(NBD)(NMM) catalyst as a fine yellow powder, which was used immediately in the coupling reactions to avoid degradation.

3-Phenylcyclohex-1-ene (11)



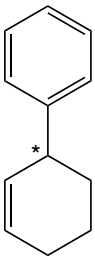
To 30 mg (0.097 mmol) of Pd(NBD)(NMM) catalyst from the previous reaction, under an atmosphere of argon, was added 66 mg (0.39 mmol) of cyclohexenyl carbonate **9** and 186 mg (0.78 mmol) of phenyl triethoxysilane **7** in 5.0 mL of anhydrous THF. Immediately following the addition of the aryl siloxane, 0.78 mL (0.78 mmol) of 1 M TBAF solution in THF was introduced via syringe, and the reaction mixture was allowed to stir at 55 ºC for 24 h. Upon completion, the reaction mixture was cooled to room temperature, quenched with 10 mL of water, then extracted with Et_2O (5 × 25 mL) and washed with 25 mL H_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to provide crude 3-phenylcyclohex-1-ene (**11**) as a translucent, yellow oil. Purification by column chromatography (pentane; R*f* = 0.65) provided 47 mg (77%) of racemic 3-phenylcyclohex-1-ene (**11**), a known compound, as a colorless oil; IR (CCl_4) 3025 (s), 2934 (s), 2858 (m), 2838 (m), 1601 (w), 1492 (m), 1452 (m) cm^{-1}; ^1H NMR (400 MHz, d_6-benzene) δ 7.20-7.17 (m, 4H), 7.11-7.07 (m, 1H), 5.82-5.73 (m, 2H), 3.32-3.27 (m, 1H), 1.92-1.89 (m, 3H), 1.56-1.47 (m, 3H); ^{13}C NMR (125 MHz, d_6-benzene) δ 147.2, 131.0, 129.0, 128.8, 128.7, 128.5, 128.3, 126.7, 42.6, 33.4, 25.7, 21.8. It is important to note that NMR characterizations were obtained in d_6-benzene, to avoid potential double bond isomerization catalyzed by acid impurities in $CDCl_3$.

Palladium((1*R*,4*R*)2,5-Diphenylbicyclo[2.2.2]octa-2,5-diene)(Maleic Anhydride)



Similarly to the specified general Pd(0) catalyst formation reported above, to 50 mg (0.048 mmol) of $Pd_2dba_3 \cdot CHCl_3$ in 2.0 mL of anhydrous acetone was added 50 mg (0.19 mmol) of (1*R*,4*R*)2,5-diphenylbicyclo[2.2.2]octa-2,5-diene (bidentate ligand) and 19 mg (0.19 mmol) of maleic anhydride (monodentate ligand) under an atmosphere of argon. The burnt orange reaction mixture was stirred for 30 minutes at room temperature, upon which a small amount of palladium black had accumulated in the reaction vessel and the solution changed color to yellow-green. The reaction mixture was then transferred via cannula and filtered under argon to provide a translucent yellow-green solution. The solution was briefly concentrated *in vacuo* to provide a slightly more viscous, yellow-green oil, to which 5.0 mL of anhydrous diethyl ether was added. This provided an opaque, yellow-green suspension of Pd(*R*,*R*-DPBCO)(MAH) catalyst, which was used immediately in the chiral coupling reactions to avoid degradation.

Chiral 3-Phenylcyclohex-1-ene (11*)



The known chiral compound **11*** was formed using the same procedure reported above for the synthesis of racemic 3-phenylcyclohex-1-ene (**11**), with only scaling modifications being made. To 20 mg (0.043 mmol) of Pd(*R*,*R*-DPBCO)(MAH) catalyst from the previous reaction, under an atmosphere of argon, was added 29 mg (0.17 mmol) of cyclohexenyl carbonate **9** and 83 mg (0.35 mmol) of phenyl triethoxysilane **7** in 4.0 mL of anhydrous THF. Immediately following the addition of the aryl siloxane, 0.35 mL (0.35 mmol) of 1 M TBAF solution in THF was introduced via syringe, and the purple reaction mixture was allowed to stir at 55 ºC for 24 h. Upon completion, the reaction mixture was cooled to room temperature, quenched with 10 mL of water, then extracted with Et_2O (5 × 25 mL) and washed with 25 mL H_2O. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo* to provide crude chiral 3-phenylcyclohex-1-ene (**11***) as a translucent, yellow oil. Purification by column chromatography (pentane; R*f* = 0.65) gave 21 mg (78%) of chiral 3-phenylcyclohex-1-ene (**11***) as a colorless oil; IR, ^{1}H and ^{13}C NMR matched the spectra obtained for racemic 3-phenylcyclohex-1-ene (**11**) *vide supra*. It is important to note that NMR characterizations were obtained in d_6-benzene, to avoid potential double bond isomerization catalyzed by acid impurities in $CDCl_3$. Indication of enantioenrichment in the known compound **11*** was obtained through the use of

chiral gas chromatography. Using the following chiral gas chromatography parameters as employed by Andersson and coworkers,[51] the (+)-R enantiomer is reported as having a retention time of 53.80 minutes, while the (-)-S enantiomer has a retention time of 54.40 minutes. Chiral gas chromatography of our chiral coupling product **11*** was accomplished using an Astec CHIRALDEX B-DM GC column (30m long x 0.25mm diameter). The helium carrier gas flow rate was set to 1 mL/min, with the injector temperature set to 200 ^{o}C. The initial column temperature was 70 ^{o}C (held for 10 minutes), with a temperature ramp of 1 ^{o}C/min until a final temperature of 160 ^{o}C was reached (held for 150 minutes). Poor resolution of enantiomers prevented the precise indication of degree of enantioenrichment in our final coupling product (Figure 13), but visual inspection of the chromatogram indicated a minimal amount of chiral induction (upper limit: >2% ee).

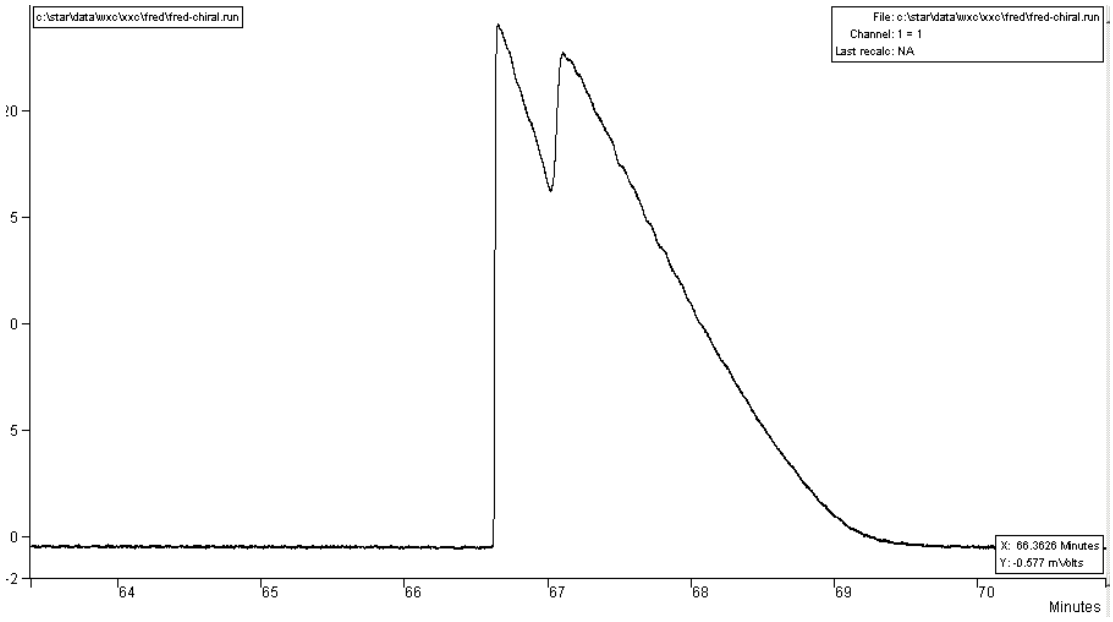


Figure 13. Chiral gas chromatogram of allyl-aryl cross-coupling product 3-phenylcyclohex-1-ene (**11***) using Pd(*R*,*R*-DPBCO)(MAH) chiral catalyst

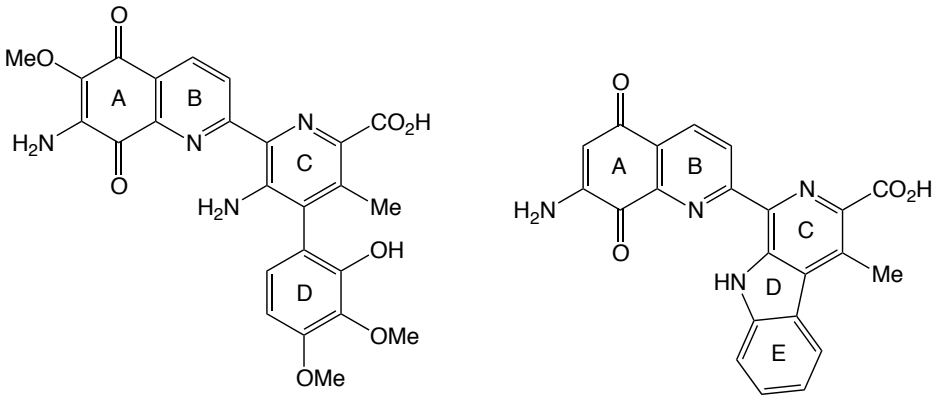
Chapter 2

Synthetic Approaches Toward the Pyridyl C-Ring of the Aminoquinone Natural Product Streptonigrin

Introduction

Streptonigrin and Analogues

Several metabolites of soil-dwelling bacteria of the genus *Streptomyces*, particularly the aminoquinone containing natural products streptonigrin (**13**) and lavendamycin (**14**), possess marked antitumor, antiviral, and antimicrobial characteristics (Figure 14). Isolated by Rao and colleagues from the bacterium *Streptomyces flocculus* in 1959,[74] streptonigrin displays remarkable chemotherapeutic abilities against various types of cancer, including lymphoma, melanoma, breast, lung, head, and neck.[75] Similarly, lavendamycin, isolated from the bacterium *Streptomyces lavendulae* in 1981 by Doyle and coworkers,[76] possesses antibacterial (strep and staph), antifungal (athlete's foot, yeast, and ringworm),[77] antitumor (leukemia, colon, and gastric carcinomas,[78,79] and, most intriguingly, anti-HIV reverse transcriptase characteristics.[80]



13, streptonigrin **14**, lavendamycin

Figure 14. Structure of *Streptomyces* alkaloids

The main structural discrepancy between these two metabolites is the presence of the D-ring pyrrole fusion in lavendamycin (**14**), creating a CDE-carbazole moiety, which falls coplanar with the AB-quinolinequinone fused-ring system. The absence of CDE-ring system fusion in streptonigrin (**13**) allows for the C- and D- rings to offset from each other. X-ray studies of the natural product have determined the C- and D- rings are nearly orthogonally oriented.[81] While this deflection from coplanarity allows for the circumvention of steric interactions between the C-ring 5-position methyl group and the D-ring 2-position hydroxyl functionality, free rotation about the CD- ring junction bond is impeded by the same interactions, leading to atropisomerism (Figure 15).

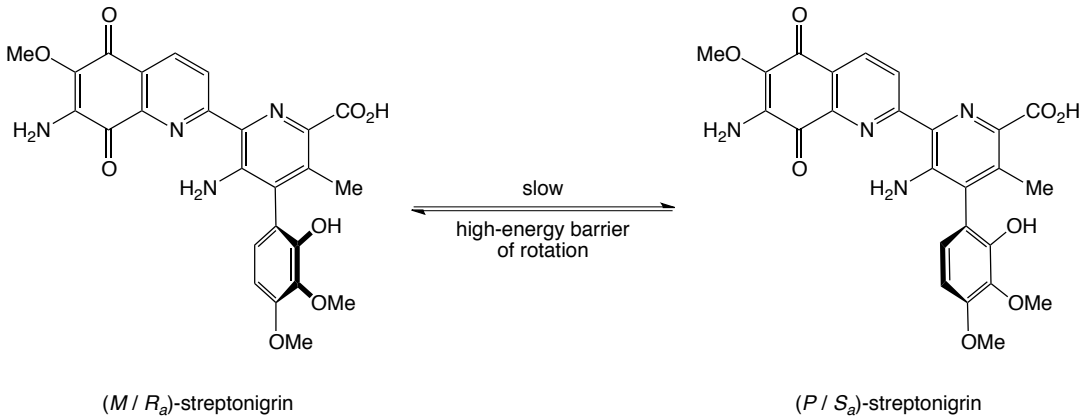


Figure 15. Atropisomerism in streptonigrin arising from CD- ring system deflection

Despite the absence of classic tetracoordinated, sp^3 stereocenters in the natural product, streptonigrin (**13**) is optically active, possessing axial chirality.[82] Naturally isolated streptonigrin has been determined to occur in the *M* / R_a orientation, via exciton coupled circular dichroism spectroscopy.[83] The non-coplanarity of the CD-ring system hinders synthetic access via coupling methodologies, given the steric encumbrance experienced by the transmetallated intermediate in attempting to orient properly for reductive elimination.

Derivative studies have shown that the pharmacophoric region leading to the cytotoxic and antimicrobial characteristics of streptonigrin and lavendamycin is their substituted quinoline-5,8-quinone AB-ring systems.[84,85] Derivatives of the AB-ring system of lavendamycin, including an isopropylaza functional group substituted at the 7- and 8-positions,[86] as well as hydroxyl and methoxy groups replacing the amine group at the 7-postion,[87] have displayed limited activity as anticancer agents.

The precise mechanism of streptonigrin and lavendamycin's biological activity is still uncertain, however several models have been proposed. Despite the

structural differences between the CD- and CDE- ring systems of these natural products, the proposed route of action in biological systems should be consistent, as their AB-ring system active sites are remarkably similar.

The mode of the cellular toxicity of streptonigrin and lavendamycin has been linked to various processes: the depletion of the biological reducing agents NADH and NADPH, the inhibition of enzymes which promote the transfer of electrons in the inner mitochondrial membrane, the bypassing of oxidative phosphorylation, the depletion of cellular ATP, an irreversible binding to the minor groove of DNA and the direct insertion of the ring systems in between the base-pair hydrogen bonds, and the quinone moiety's propensity for the formation of radicals, which lead to single-strand breaks in DNA, have all be proposed.[84]

The structure of the AB-ring systems of streptonigrin and lavendamycin, as well as the free rotation of the bond between the AB- and C-ring systems, also make these compounds functional chelating agents for polyvalent metal cations. The presence of an M^{2+} cation, which can be chelated by both natural products (Figure 16), makes the quinone moiety more reactive toward reduction by NADPH and NADH, thereby depleting overall cellular levels of these cofactors.[88]

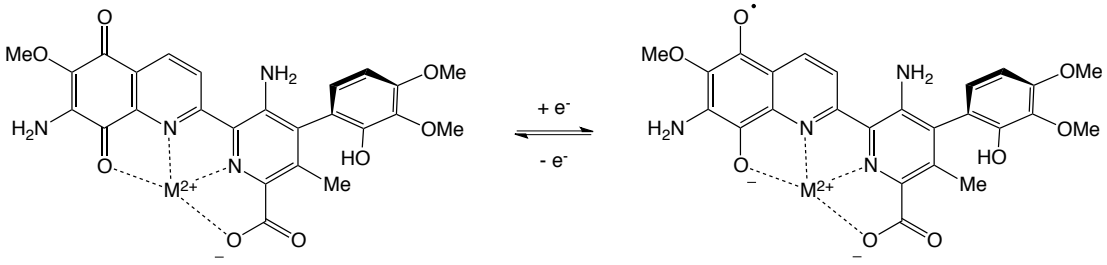


Figure 16. Metal chelation and reduction of streptonigrin

The enzymatic reduction of streptonigrin by one electron, to form a semiquinone radical (Figure 16), or two electrons, to form hydroquinone, often leads to the production of free hydroxyl and superoxide radicals via auto-oxidation with oxygen gas, which can in turn cause significant damage to DNA.[89] This auto-oxidation occurs outside the pathway of oxidative phosphorylation, thereby obliquely decreasing cellular ATP counts as well.[84]

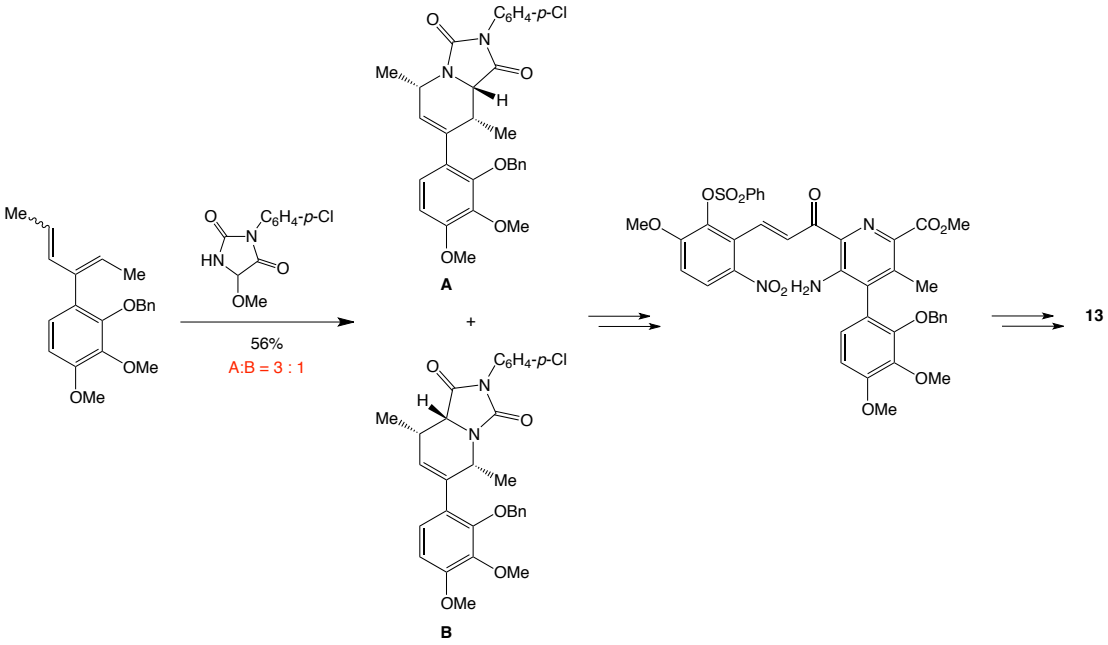
Further preclinical studies of streptonigrin have proven its toxicity to be rather indiscriminant, in that it kills both cancerous and healthy cells.[75,79,84] Due to poor solubility in aqueous systems and most organic solvents, streptonigrin has also proven difficult to administer. These, along with other problems, have prevented the drug from proceeding past phase II clinical trials, which were ended in 1977.[90] However, streptonigrin's marked antibiotic and antitumor capabilities supported further research into its pharmaceutical potential. With a general knowledge of the active pharmacophoric region of the molecule, rational modifications to the compound could be designed in order to attempt to temper the deleterious side effects while maintaining desired ones. Due to low-occurring natural yields of streptonigrin,[91] synthetic approaches were undertaken to produce the natural product in a concise fashion, in high yields, so that the formation of new analogs for clinical testing could be completed with greater ease and economy.

Synthetic Approaches Toward Streptonigrin

While several syntheses of lavendamycin have been reported,[92-98] the remainder of this discussion will focus on work relating to streptonigrin. To date, the fully functionalized tetracyclic structure of streptonigrin (**13**) has only been synthesized four times in the literature: by Weinreb's group,[99] Kende's group,[100] Boger's group,[101] and Donohoe's group.[102] We will focus the majority of our discussion on the creation of the C-ring in these syntheses.

The first total synthesis of streptonigrin, completed by Weinreb in 1980, is highlighted by the use of a hetero Diels-Alder reaction to form the C-ring system (Scheme 24).[99]

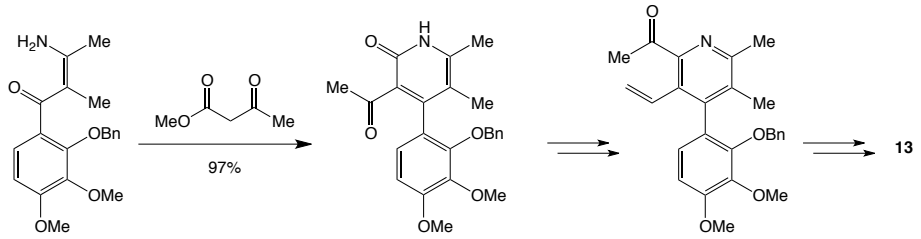
Scheme 24



The poor regioselectivity and yield of this reaction, provided the nearly identical molecular-orbital energy coefficients in the diene, and the overall length of Weinreb's total synthesis (34 steps) hinders the practicality of its application in access to streptonigrin.

Kende's synthesis, completed in 1981, was notable for the relative economy of steps taken to attain the core structure of streptonigrin (27 steps). Final yields, while also a slight improvement over Weinreb's route, still fell well below 1% (Scheme 25).[100]

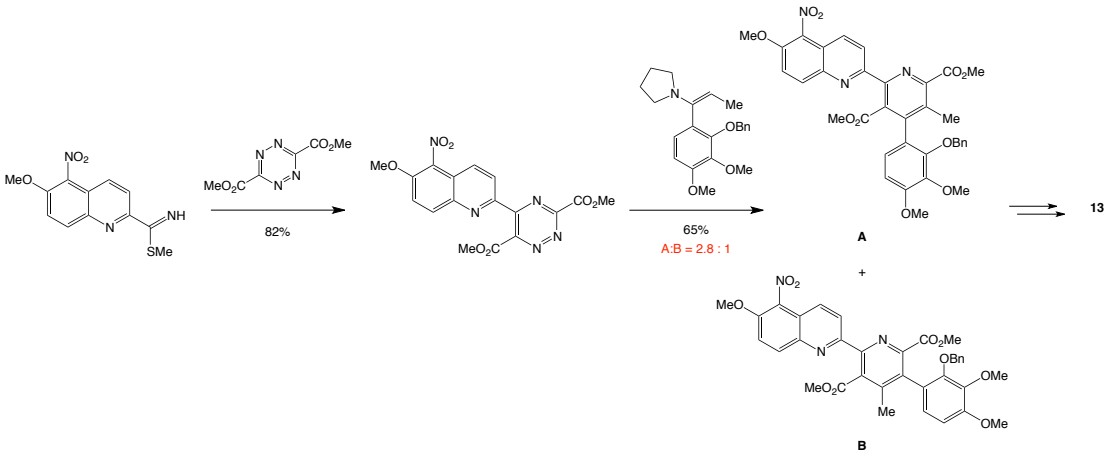
Scheme 25



While quickly accessing the CD-ring backbone in excellent yield *via* condensation, problems arise with Kende's approach to streptonigrin upon completion of the total skeleton of the natural product, when 11 subsequent steps must be undertaken to get to the desired advanced intermediate. Kende's synthetic approach of forming the carbon backbone first and then functionalizing largely precluded subsequent opportunities for the formation of functional analogues without major modifications and planning, limiting its applicability toward future pharmaceutical derivation. The formation of the pyridone C-ring precursor *via* condensation proved intriguing, however, and was later exploited for synthesis in the DeShong group (*vide infra*).

Two years later, in 1983, Boger reported his total synthesis of streptonigrin. Similar to Weinreb's synthesis, Boger approached the tetracyclic system through a set of Diels-Alder cycloadditions. By employing a symmetric tetrazine as the diene in the first cycloaddition, Boger ensured only one possible regioisomeric product would be provided (Scheme 26).[101]

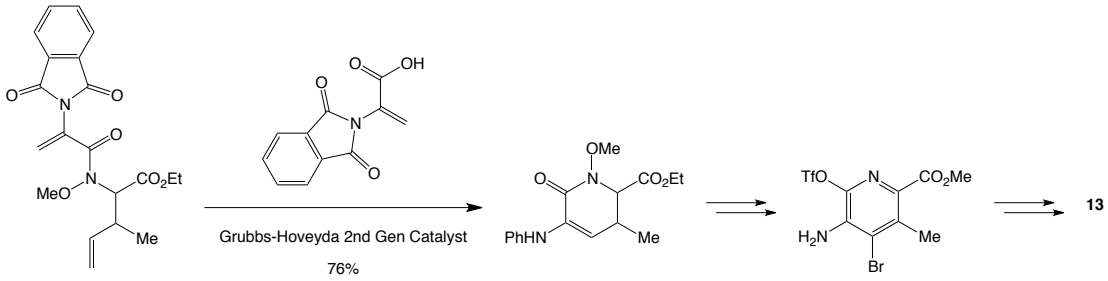
Scheme 26



However, the regioselectivity of the second cycloaddition could not be guaranteed, and a 2.8 : 1 mixture of desired product **A** to side product **B** was obtained. Once again, the issue of regioselectivity in forming late-stage intermediates limits the applicability of Boger's synthesis. However, Boger's synthesis is notable, given the fact that the AB-ring system of streptonigrin is initially constructed in near entirety, with a dieneophilic moiety attached for subsequent cycloadditions. This affords the opportunity to make AB-ring modifications prior to the formation of the CD-ring system, creating an avenue for the formation of streptonigrin analogues.

The most recent synthesis of streptonigrin was completed by Donohoe in 2011, and implements many of the concepts of modularity for derivatization we aim to highlight herein.[102] Through the employment of Grubbs-Hoveyda second-generation metathesis catalyst, Donohoe was able to affect the ring closure of a C-ring intermediate from a branched, functionalized amide and an α,β-unsaturated carboxylic acid (Scheme 27).

Scheme 27



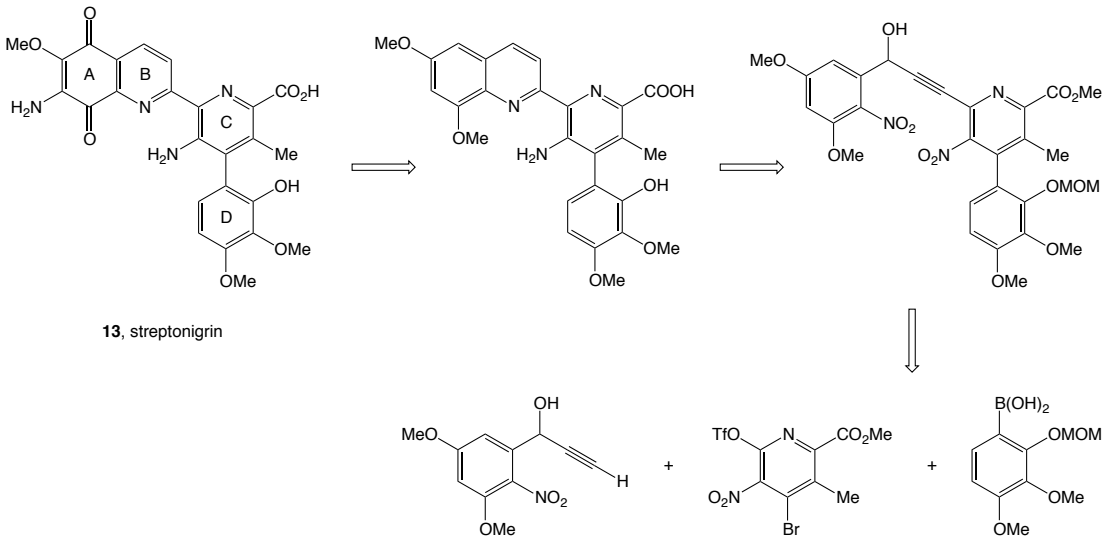
By installing two varied coupling points in his C-ring intermediate, a triflate and a bromide group, Donohoe was able to selectively couple his AB- and D-ring systems to complete the skeleton of streptonigrin. Unfortunately, for reasons mentioned earlier in this manuscript, Donohoe's selection of Stille's tin-based coupling for the attachment of his AB- and C-ring precursors will prove problematic if biological studies of his synthetic products are to be undertaken.

Ideally, the synthesis of streptonigrin would be completed modularly, with the different ring segments being functionalized separately and then brought together at the end to yield the desired product. This route would offer greater freedom of variety in terms of analogue formation and would also limit the occurrence of undesired

chemical transformations of substituents in larger systems, as was a concern in many of the previous syntheses. With great strides made in the field of cross-coupling technology since Boger's synthesis in 1983, the application of such technology to the synthesis of streptonigrin seemed a promising area of research. Therefore, studies on the modular total synthesis of streptonigrin were begun in the DeShong group.

Synthetic Approaches Toward Streptonigrin in the DeShong Group

The implementation of siloxane-based coupling technology developed in the DeShong group was envisioned for the modular total synthesis of streptonigrin and subsequent analogues.[103-106] Unfortunately, the ring precursors of streptonigrin developed by McElroy and Sandelier were not amenable to siloxane coupling, so other modes of ring attachment needed to be designed.[107] It was ultimately settled that Sonogashira and Suzuki couplings would be used in our proposed total synthesis of the natural product (Figure 17).



13, streptonigrin

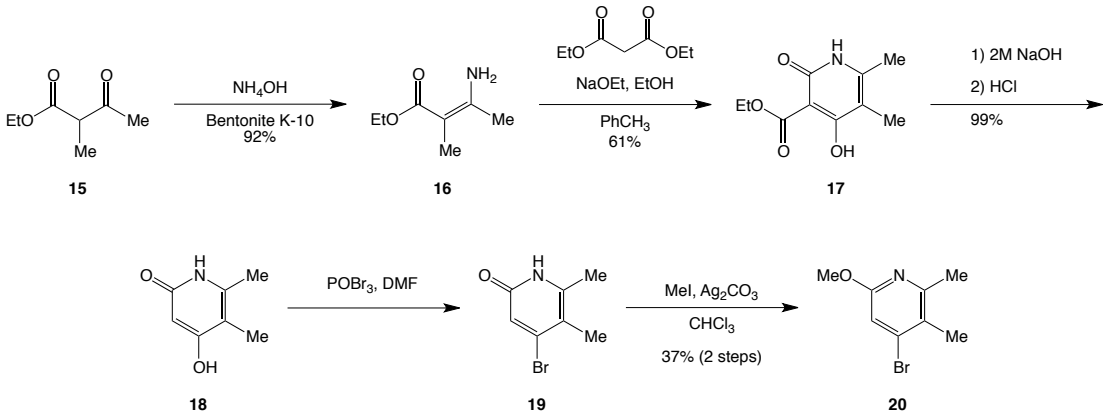
Figure 17. Proposed retrosynthesis of streptonigrin

While the development of CD-ring Suzuki coupling[103] and AB-ring reductive cyclization[105] were undertaken separately, efforts at coupling analogues of the AB-ring system to McElroy's biaryl CD-ring intermediate,[104] and C-ring analogues of to Sandelier's bicyclic AB-ring precursor,[106] proved problematic.

In order to better examine the shortcomings in Sandelier's Sonogashira coupling and subsequent reductive cyclization to provide substituted quinolines for our proposed synthesis, I was tasked with producing sufficient quantities of pyridyl C-ring precursors and analogues, while also addressing some of the deficiencies observed in McElroy's reported synthesis.

Upon examination of the first section of McElroy's C-ring synthesis (Scheme 28), one can see that the functionalization, rather than ring assembly, posed the most difficulty, leading to notable loss of total yield in only a few localized steps.

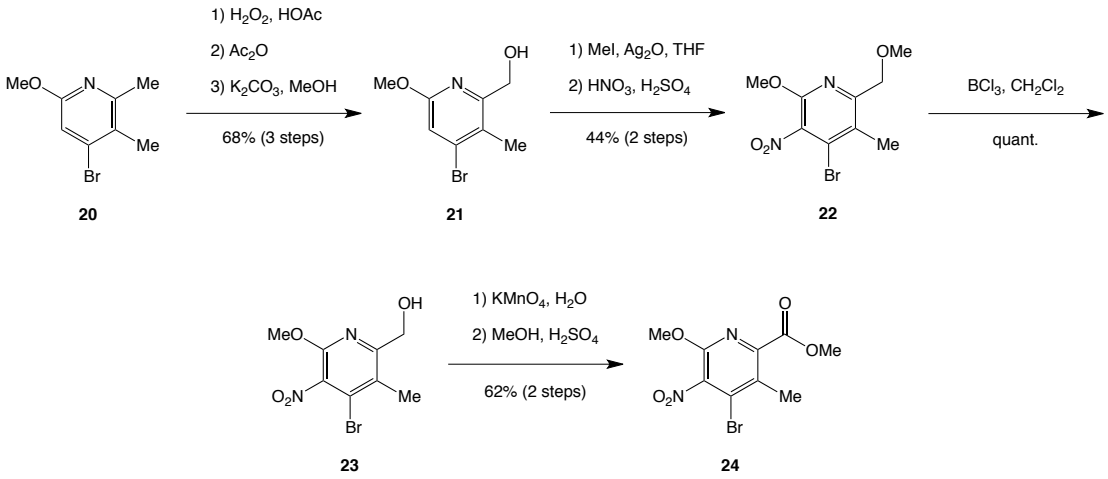
Scheme 28



Amination of ethyl-2-methylacetoacetate (**15**) on a clay substrate, followed by diethyl malonate condensation to provide hydroxypyridone ethyl ester (**17**) proceeded unremarkably and in good yields. Subsequent decarboxylation occurred nearly quantitatively to provide hydroxypyridone **18**. Issues began to arise, however, upon attempted bromination using phosphorus oxytribromide. In order to improve the CD-ring synthesis, I began work toward the optimization of the bromination of hydroxypyridone intermediate **18**.

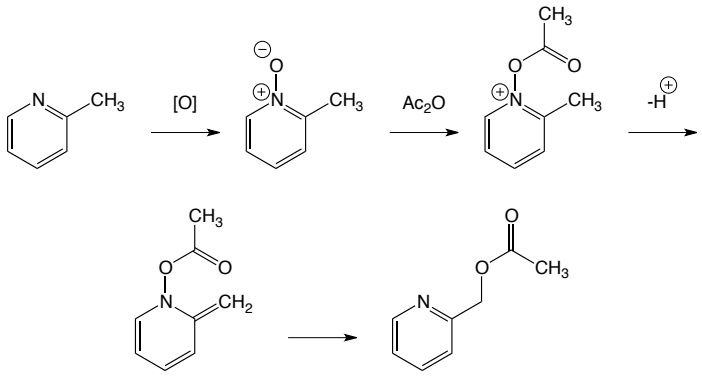
Similarly, the later portion of the McElroy pyridyl C-ring synthesis proceeded relatively expeditiously, containing transformations that predominantly proceed in good yield, with a few notable exceptions (Scheme 29).

Scheme 29



Interestingly, bromomethoxypyridine **20** was oxidized to the N-oxide, which was subsequently captured by acetate, rearranged, and hydrolyzed to provide pyridyl alcohol **21** (Scheme 30, redrawn from reference 104). This pyridyl alcohol was then methylated to protect during mixed acid nitration, then demethylated, oxidized, and esterified to provide the completed C-ring intermediate **24**.

Scheme 30



While conceptually reasonable, the number of steps undertaken in order to functionalize the 6-position methyl group, including protection and deprotection, added to the overall length of the synthesis and diminished total product yield. To further improve on McElroy's CD-ring synthesis, I also focused on streamlining some of the late stage modifications, to minimize the number of steps and avoid loss in total product yield.

With the moderate length of this synthesis, numbering 14 linear steps, 3.8% product yield is a reasonable figure. By undertaking the modifications previously mentioned, it was hoped that further improvement could be made.

The purpose of this work was to improve upon problematic portions of our previously reported synthesis of streptonigrin's pyridyl C-ring,[103] particularly regarding the 4-position bromination and 6-position oxidation, to provide higher yields of key intermediates and to improve overall economy of steps.

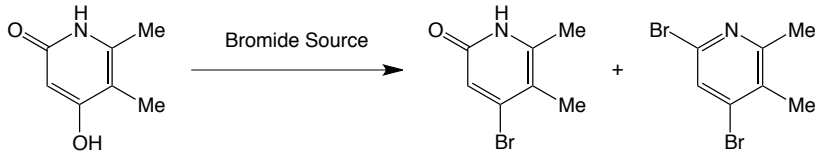
Results and Discussion

Selective bromination at the 4-position of hydroxypyridone **18** is vital for the subsequent Suzuki coupling with the D-ring aryl boronic acid intermediate in latter steps of the synthesis. Solubility and polarity issues precluded the chromatographic purification of many synthetic intermediates from impurities, particularly the brominated products. This being the case, crude products from several steps were carried through. Preliminary steps toward the formation of adequate hydroxypyridone

intermediate **18** for study proceeded without note, all providing within 15% of McElroy's reported yields.

The brominating agent chosen by McElroy, phosphorus oxytribromide, is a markedly air sensitive solid at room temperature, which readily degrades to provide phosphoric acid in the presence of water, so the utmost care must be taken during its delivery to the reaction. Furthermore, each equivalent of brominating agent had the ability to donate 3 equivalents of bromide, so care must be taken to avoid overbromination. While monobrominated product **19** normally predominated, the formation dibromopyridine **25** also was observed via NMR (Scheme 31). All yields reported account for both mono- and dibrominated product.

Scheme 31



It appears that solubility was a key issue in the low yields of this reaction. The bromination method chosen by McElroy utilized 0.67 equivalents of phosphorus oxytribromide in N,N-dimethylformamide to selectively provide 62% yield of the monobromopyridone **19** intermediate. Attempts to duplicate the reaction under the described conditions, however, only resulted in 35% yield of **19**. Given that the product's high solubility in the extremely polar DMF solvent may have led to an overall reduction in isolatable yields, using the minimum amount of solvent necessary

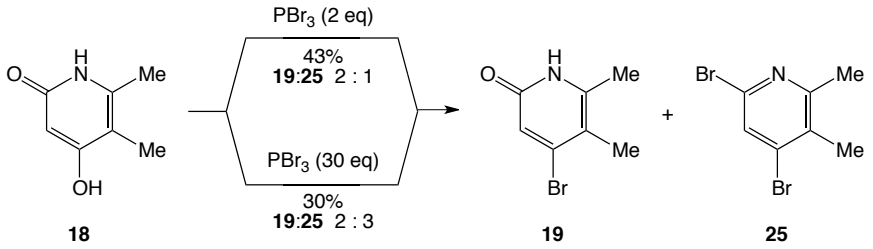
to solubilize the starting material was attempted as well. Unfortunately, similarly low yields were observed when under these minimal solvent conditions.

Following our planned reduction in solvent usage, alternative reagents for bromination were also examined, particularly phosphorous tribromide (a liquid at room temperature), for their efficacy in affecting bromination under solvent-free conditions. Results from bromination *via* PBr_3 were mixed.

The neat bromination of hydroxypyridone **18** with phosphorus tribromide proceeded relatively unremarkably. Similarly to the McElroy bromination, upon completion of the reaction, quenching with water, and basifying the solution with sodium carbonate, the yellow product precipitated from solution giving approximately 43% yield. Given that the reaction was being run neat in PBr_3, a greater number of equivalents of brominating reagent were employed (~2 eq) to ensure adequate solvation, compared to McElroy's bromination with $POBr_3$ in DMF. However, the initial neat reaction only yielded a 2 : 1 monobrominated (**19**) to dibrominated (**25**) product ratio.

Testing the limits of the reaction selectivity, the number of equivalents of PBr_3 was increased by an order of magnitude, to see the effect it would have on product distribution. Interestingly, the significant increase in amount of brominating reagent used had a twofold effect: (1) the ratio of monobrominated (**19**) to dibrominated (**25**) product flipped to 2 : 3, now favoring multiple brominations, and (2) the total product yield was markedly decreased, to approximately 30% (Scheme 32).

Scheme 32



One of the major hypothesized avenues that we believe is affecting our yields is the formation of highly water-soluble phosphate esters—intermediate species in the bromination process that ultimately fail to react further to provide the desired products (Figure 18). This follows logically with both observations previously stated: that the more equivalents of brominating reagent present in the reaction mixture, the lower the observed yields tend to be, and for the products that do form, multiple brominations are favored. With more equivalents of reactive PBr_3 present in solution, the opportunity to phosphorylate all oxygen species increases as well. Whether these remain as phosphate esters or are displaced by bromide to provide the desired products, depends on the intransience of bromide in the reactive environment.

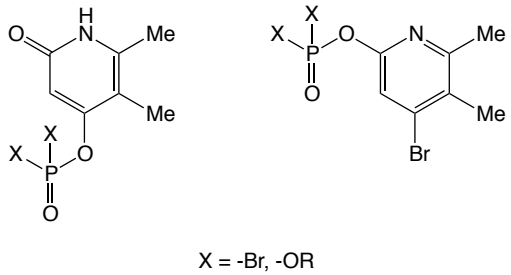
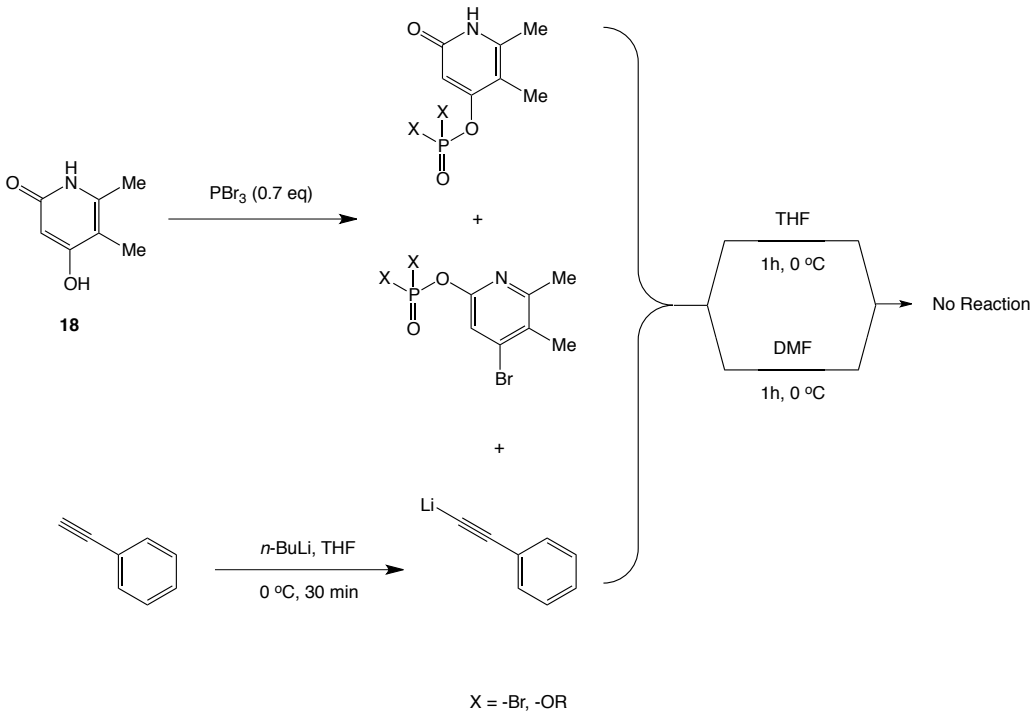


Figure 18. Proposed pyridone and pyridine phosphate esters

With this in mind, we attempted to examine the phosphate's ability to promote coupling to the 2- or 4-position using nothing more than an *in situ* formed phenylacetylide anion, which acts as a model A-ring system (Scheme 33).

Scheme 33



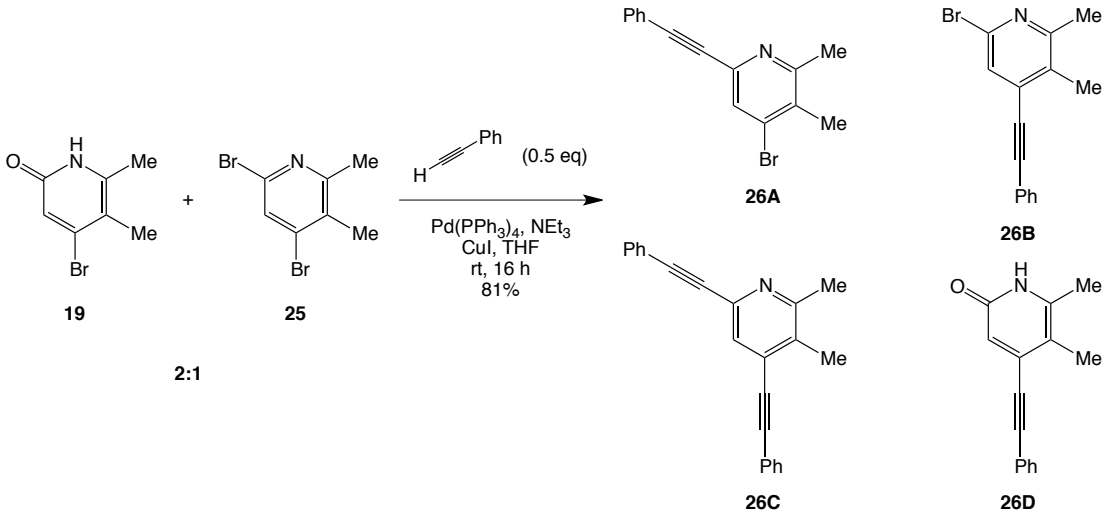
Great care was required in order to avoid quenching from the introduction of moisture to either the acetylide or the pyridine phosphate ester reaction vessels. Unfortunately, even by employing cannula transfer techniques and various solvents, only quenched starting materials were observed upon the completion of the reaction. The phenyl acetylide most likely acted more as a strong base than as a nucleophile, with various, relatively acidic protons present.

Provided the shortcomings of the direct phosphate coupling of the model A-ring, examination of the Sonogashira coupling with our brominated products was begun next. In our proposed retrosynthesis of streptonigrin (Figure 17), we envisioned the completed C-ring intermediate undergoing Sonogashira coupling with an *o*-nitro propargyl alcohol A-ring precursor at the C-ring's 2-position triflate moiety. It has been previously reported that electron-poor halogen-carbon bonds facilitate Sonogashira coupling reactions. Iodides, triflates, and bromides, for example, react markedly better than chlorides, and vinyl halides provide greater coupling than aryl halides.[108] These tendencies have been exploited by various groups to provide selectivity in the coupling of non-symmetric dihalogenated systems, namely employing both iodide and bromide in the same system while limiting the number of equivalents of alkyne, so that only the iodide center will couple.[109] Similarly, electronic manipulations to different coupling centers baring the same halogen have been examined for several different dihaloheterocycles, including 2,4-dibromoquinoline,[110] pyrimidine,[111] and 2,5-dibromopyridine.[112]

Most relevant to our synthesis, however, is the work published on the stereoselective synthesis of the visual pigment A2E, in which 2,4-dibromopyridine underwent a selective Suzuki coupling at the 2-position, followed by subsequent Sonogashira coupling at the 4-position.[113] All things being equal, the electronically deficient nature of the carbon-halogen bond adjacent to the heteroatom in the ring usually directs the coupling reaction to the 2-position over others, when coupling partner equivalents are duly limited. With this information supporting the proposed

formation of the desired 2-alkynyl-4-bromopyridine (**26A**), the Sonogashira coupling of phenylacetylene with mixed bromination products was attempted (Scheme 34).

Scheme 34



The use of preferential coupling would be the ideal arrangement for our desired total synthesis, however the issue of mixtures of bromination products prevents this from being realized. As mentioned above, the direct separation of monobromopyridone **19** from dibromopyridine **25** has proven problematic, so a 2:1 mixture of starting materials was used in these studies. With three possible coupling locations available, and the potential for four different coupling products, it was apparent that the varying electronic characteristics of the different coupling partners and coupling centers would determine what, if any, regioselectivity was to be achieved.

By adding only 0.5 equivalents of phenylacetylene, we attempted to prevent the statistical formation of coupling products, thus elucidating the regioselective

inclinations of the Sonogashira coupling for our intermediate. One of the major difficulties in our method, however, was the sheer complexity of the potential final coupled products that it yielded. With four potential products and three starting materials mixed in our final yield, chromatographic separation of the mixture would be of paramount importance in determining what reactivity, if any, had predominated.

While trace unreacted phenylacetylene and various other uncoupled side-products were flushed from the product mixture, what appeared to be our coupled targets remained at baseline. Another issue that arose during the investigation of the coupled system mix was the proper selection of analysis method. Given the lack of proton-carbon correlation across the 4-carbon bridge formed during the coupling reaction, direct ^{1}H, ^{13}C, or correlated spectroscopy provide no regio- information, only that it did occur. We decided to investigate through-space, proximity magnetic relaxation via NOESY experiments. Given the probable orthogonal configuration of the coupled ring to the pyridine / pyridone C-ring, and the relatively long-range from the A / A' position protons on the coupled ring to the 5-position methyl of the pyridine / pyridone C-ring, we were concerned that we may not be able to detect NOE signal (Figure 19).

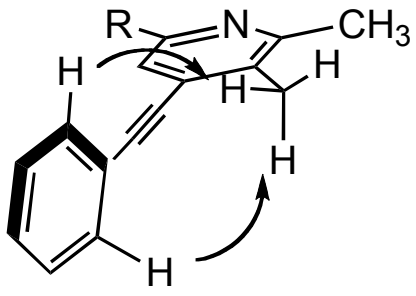


Figure 19. Long-range NOE interactions between phenyl and methyl protons

Similarly, our spectroscopic results would most likely only indicate if coupling had occurred at the 4-position, as the 2-position doesn't offer suitably large neighboring groups for long distance relaxation to be observe.

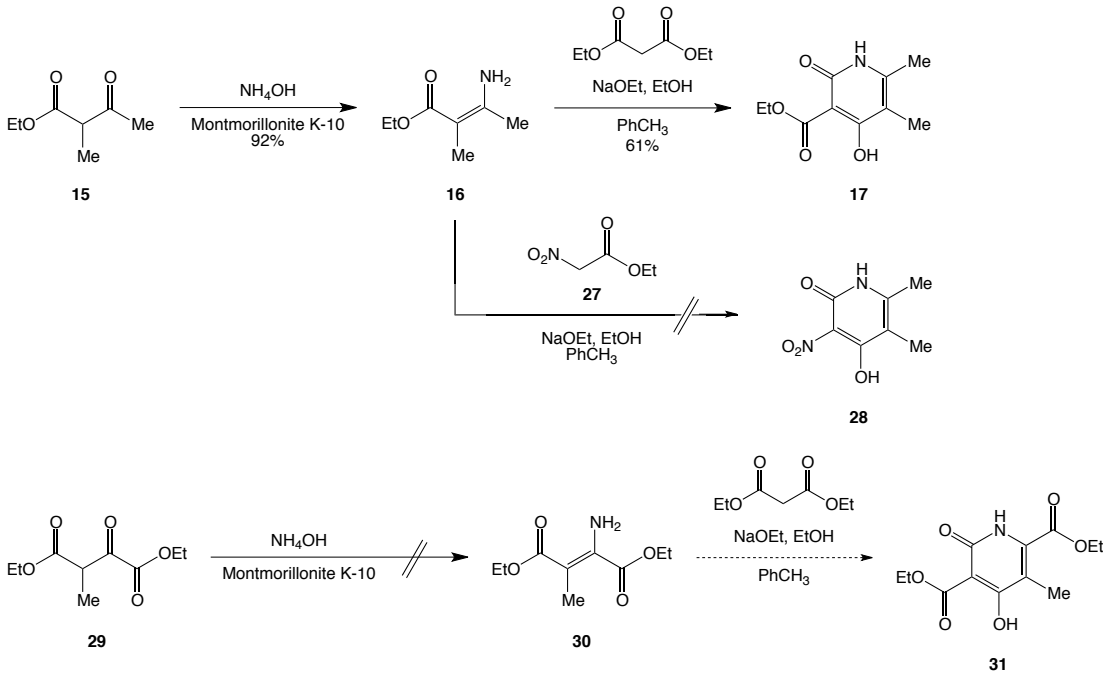
A selective NOE experiment was chosen over 2D-NOESY, given the high complexity displayed in the aromatic region of the ^{1}H NMR. In each experiment, what was deemed the A/A' proton on the aromatic coupling partner was selectively pulsed to search for the presence of spatially neighboring groups on the pyridine / pyridone. While most of the NMR experiments provided no NOE signals, two of the peaks pulsed did show correlation to peaks in the methyl group range of our pyridine / pyridone, signifying coupling to the 4-position of our C-ring intermediate.

While the direct ratio of coupled products **26A-D** is still indeterminate, these results are promising, given that the coupling product at the 4-position was expected to be minor. However, until a direct measurement of the 2-ethynyl-4-bromopyridine coupling product (**26a)** can be made, no specific claims regarding the regioselectivity of the coupling reaction can be made. In order to improve this experiment, pure starting materials should be used. We could then determine the degree of conversion of starting material to some form of product, directly measure those coupling products at the 4-position via NOESY, and then infer the remaining percentage of other coupling partners based on the side product and 4-position coupling partner yields. Similarly, a better choice of coupling partner for our pyridine / pyridone system could be made while remaining true to the A-ring precursor after which it would be modeled. By increasing the bulk of the A / A' substituents on the coupling

phenyl ring, a greater NOE might be observed, potentially allowing for direct identification and measurement of coupling occurring at the 2-position of the C-ring. This would make the analysis of the regioselectivity of the Sonogashira coupling with our C-ring intermediate significantly easier.

Similar work was also undertaken for the study of modifications to other parts of our C-ring precursor, as well. Provided the relative success of our early-stage amination and condensation reactions for the standard C-ring precursor system (Scheme 28), attempts were made to modify the starting materials being aminated or condensed, in order to impart desired functionality onto our ring system immediately upon annulation (Scheme 35).

Scheme 35



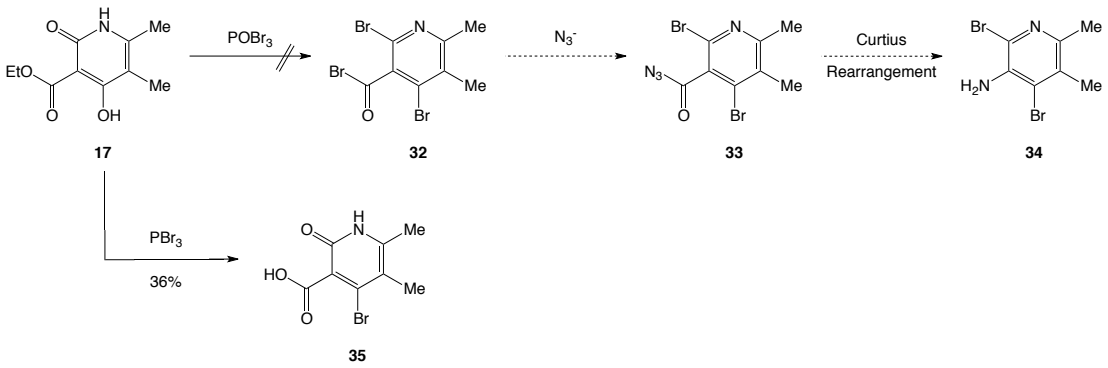
Initially, attempts to annulate a C-ring precursor analogue by replacing the standard diethylmalonate substrate with ethyl nitroacetate (**27**) were begun. The proposed product (**28**) this modification would generate would possess the desired 3-position nitration, saving us subsequent steps. Possessing highly acidic protons alpha to both the nitro and ethyl acetate groups when compared with those in diethylmalonate, ethyl nitroacetate should readily provide a nitronate substrate under the conditions employed, which we believed would undergo ring annulation expeditiously in the presence of aminated substrate **16**. A disappointing lack of desired product **28** was observed however, causing us to ultimately abandon this route.

Similarly, the implementation of diethyl oxalpropionate (**29**) as an amination substrate was investigated. Amination should proceed selectively at the ketone position of oxalpropionate **29**, providing us with enamine product **30**. This can be envisaged to undergo ring annulation with diethyl malonate to provide C-ring precursor analogue **31**, possessing an ethyl ester in the 6-position which otherwise would require several subsequent steps to install in our originally proposed synthesis. Unfortunately however, aminated product **30** was never realized.

Modifications to later stages of our C-ring precursor were also attempted, to interesting result. The use of diethyl malonate to produce hydroxypyridone ethyl ester **17**, with concomitant decarboxylation at the 3-position appeared atom-uneconomical. By removing functionality at a position that would eventually require refunctionalization, it appeared we were adding more steps to our overall synthesis. With this in mind, and with information provided in McElroy's thesis work,[104]

attempts were made at utilizing the ethyl ester intermediate functionality at the 3-position (Scheme 36).

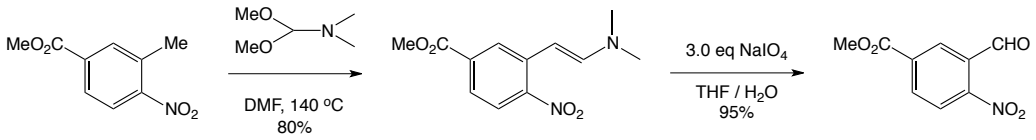
Scheme 36



McElroy reported that, upon treatment of hydroxypyridone ethyl ester **17** with $POBr_3$, dibromopyridine acid bromide **32** was produced in 58% yield. It was planned that, upon addition of an azide source to the activated acid bromide, acyl azide **33** would be produced, which, under Curtius conditions, would rearrange to yield dibromoaminopyridine **34**. Unfortunately, attempts to affect the formation of dibromopyridine acid bromide **32** via treatment of hydroxypyridone ethyl ester **17** with PBr_3 proved unfruitful. Rather, the isolated product of this transformation was bromopyridone carboxylic acid **35**, potentially arising from the hydrolysis of and acyl bromide intermediate upon bromination quenching and workup with water. While an interesting and unexpected product, subsequent transformations of the bromopyridone carboxylic acid **35** proved unremarkable, and this course of study was deserted.

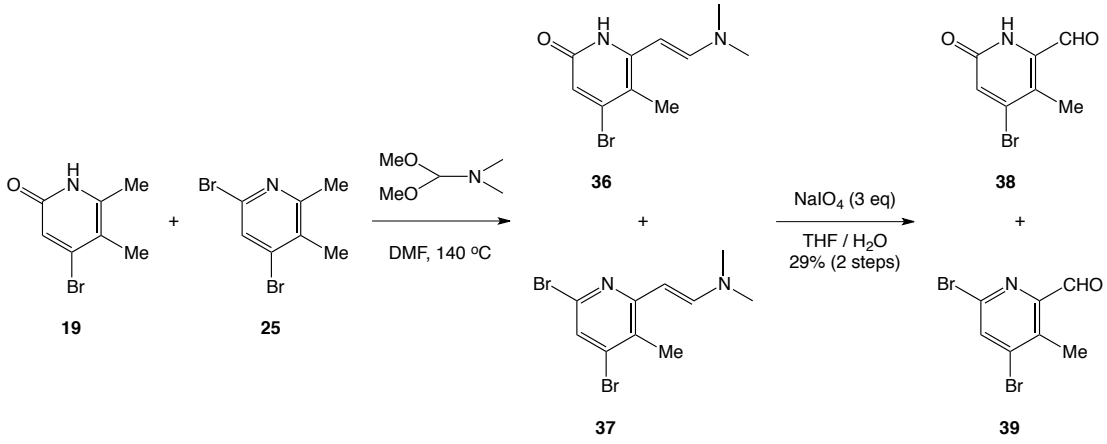
The final major C-ring synthetic modification of interest examined was the attempted application of the Coe methodology for the formation of aldehydes from activated methyl groups on electron deficient ring systems (Scheme 37).[114]

Scheme 37



The Coe methodology offers a facile route to the desired aldehyde moiety present in the C-ring intermediate, which can undergo subsequent oxidation and esterification to provide the desired functionality at the 6-position. This reaction was undertaken with the 2:1 monobromopyridone **19** to dibromopyridine **25** intermediate mixture (Scheme 38).

Scheme 38



Provided the strongly electron-deficient character of both of these starting materials, they are perfect candidates for the Coe reaction, which proceeded without issue. With the inductive withdrawing effects of the bromine atoms at the 4-, or 2- and 4-positions, along with the resonance stabilizing effects also provided from the pyridone carbonyl, we expect that the 6-position methyl group on the rings will be more electron deficient than the 5-position, making the 6-position methyl more likely to undergo the formation of desired enamines **36** and **37.** Sodium periodate cleavage yielded monobromopyridone carboxyaldehyde **38** and dibromopyridine carboxyaldehyde **39** in 29% yield for the two steps, in a 10:1 ratio, respectively, based on ^{1}H NMR. The purification process via flash chromatography is once again an issue with this system, so a viable mode of separation must be determined or pure starting materials should be used. While these findings are notable, as they help to streamline the conclusion of the C-ring synthesis, yield improvements must be made in order for this to supplant our current synthetic methodology.

Introducing an electron-withdrawing aldehyde group would further activate the C-ring intermediate toward nucleophilic additions, so attempts were made at introducing the Coe methodology earlier in our C-ring synthesis. Unfortunately, it appears that the presence of any particularly acidic protons quenches the methoxide base formed *in situ*, potentially leading to the formation of amine mixed acetals (Figure 20).

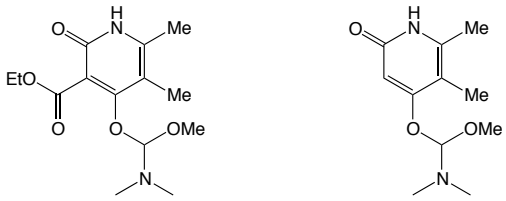
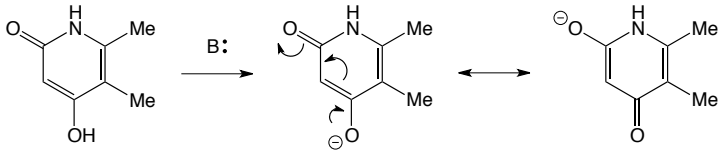


Figure 20. Proposed structure of amine mixed acetal byproducts of **17** and **18**

Desired aldehyde product from the Coe methodology was only observed when the 4-position hydroxyl group had been brominated. This follows logically, as the 4-position hydroxyl group is vinylogous to the pyridone carbonyl, thereby stabilizing the conjugate base *via* resonance and lowering the expected pK_a of the hydroxyl proton (Scheme 39).

Scheme 39



Conclusion

In conclusion, investigation into modifications of McElroy's C-ring synthesis has been completed. While resulting product yields fall below expectations due to solubility and impurity issues, interesting findings regarding bromination, intermediate couplings, and the application of Coe methodology have been reported. Development of new purification techniques would be paramount to the future success of further studies of pyridone moieties and their analogues.

Experimental Procedures

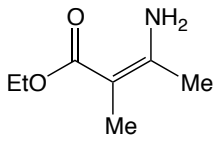
General Methods

All reactions were performed under an atmosphere of argon unless otherwise noted. Glassware used in the reactions was dried for a minimum of 12 h in an oven at 120 ºC and cooled in a dessicator prior to assembly. Tetrahydrofuran and diethyl ether were distilled from sodium / benzophenone ketyl, while methylene chloride, pyridine, and dimethylformamide were distilled from calcium hydride.

Infrared spectra were recorded on a Nicolet 560 FT-IR spectrophotometer. Samples used for obtaining infrared spectra were either dissolved in carbon tetrachloride, taken neat, or obtained using the total attenuated reflectance adapter for solids. 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).

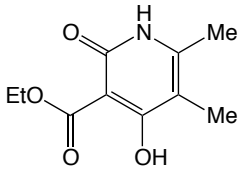
Nuclear magnetic resonance (^{1}H, ^{13}C, DEPT-135 NMR) spectra were recorded on a 400 or 500 MHz spectrometer. Chemical shifts are reported in parts per million (δ) and coupling (*J* values) are reported in hertz (Hz). Spin multiplicities are indicated by the following symbols: s (singlet), d (doublet), t (triplet), q (quartet), m (multiplet), br s (broad singlet), and br d (broad doublet). Low-resolution mass spectrometry (LRMS) and high-resolution mass spectrometry (HRMS) were obtained on a JEOL SX-02A instrument.

α,β-Unsaturated Amino Ester (16)



This reaction was not performed under inert atmosphere. Ethyl 2-methylacetoacetate (50 g, 0.35 mol) was absorbed onto 75 g of montmorillonite K-10 clay. To the viscous clay suspension, 43 mL (0.65 mol) of 14.9 M ammonium hydroxide were added, and the resulting mixture was stirred for 24 h at room temperature. Upon completion, the clay was washed 4x with 300 mL aliquots of methylene chloride, and the combined organic washings were dried over $MgSO_4$. The dried washings were then concentrated *in vacuo* to yield 39.8 g (80%) of α, β-unsaturated amino ester product **16** as slightly yellow, crystalline plates. No purification of the product was necessary. Spectral data correspond to that reported by McElroy.[104]

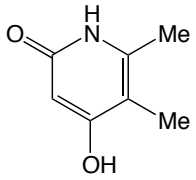
Hydroxypyridone Ethyl Ester (17)



Sodium ethoxide solution was prepared by adding 1.7 g (74 mmol) of sodium metal to 29.0 mL of anhydrous ethanol. To this solution was added a mixture of 10.5 mL (69 mmol) of diethyl malonate in 4.0 mL of toluene. The resulting solution was stirred at room temperature for 1 h. A solution of 5.0 g (35 mmol) of α, β-unsaturated amino ester **16** in 11.0 mL of toluene was then added, and the resulting mixture was refluxed for 4 d. After cooling, the mixture was diluted with water and stirred for 30

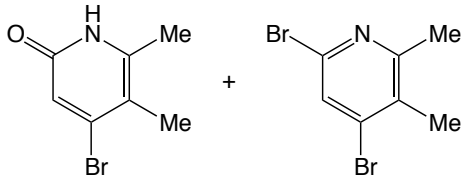
min. The phases were separated and the aqueous layer was washed with toluene. The aqueous layer was then concentrated *in vacuo* to remove ethanol, then acidified with concentrated HCl to yield precipitate. The precipitate thus obtained was filtered, washed with water, and dried to yield 4.3 g (59%) of hydroxypyridone ethyl ester **17** as an off-white powder. No further purification of the product was necessary. Spectral data coincides with that reported by McElroy.[104]

Hydroxypyridone (18)



A solution of 3.0 g (14 mmol) of hydroxypyridone ethyl ester **17** and 5.4 g (0.13 moles) of NaOH in 65.0 mL of water was heated at reflux for 2 h. The solution was then cooled to 0 ^{o}C, brought to pH = 7 with concentrated HCl, and stirred at room temperature for 12 h. The precipitate thus obtained was filtered and washed with water to yield 1.7 g (87%) of the white solid hydroxypyridone **18**. No further purification of the product was necessary. Spectral data matched that reported by McElroy.[104]

Monobromopyridone (19) and **Dibromopyridine (25)**[115]



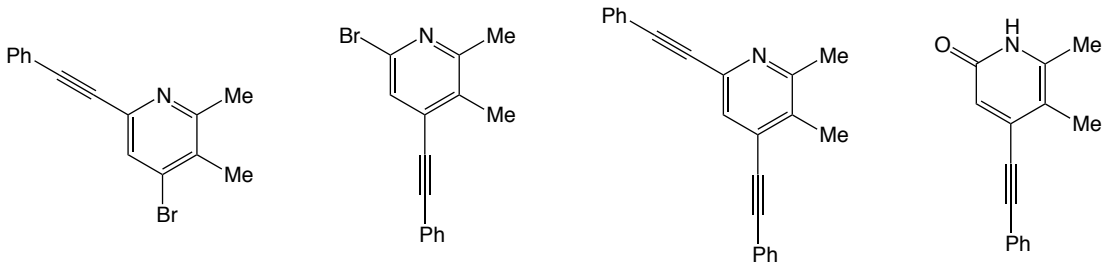
A mixture of 50 mg (0.36 mmol) of hydroxypyridone **18** and 1.0 mL (2.87 g, 10.6 mmol) of PBr_3 was heated at 140 ^oC for 4 h. During the course of the reaction, any solid that was deposited on the sides of the vessel was scraped back in to the mixture. Upon completion, the solution was allowed to cool to room temperature, and then ice water was added dropwise. The quenched solution was then allowed to stand overnight, upon which time a yellow-orange powder had precipitated. The suspension was then brought to pH = 7 with $NaHCO_3$, which provided an opaque, tan solution. This mixture was transferred to a centrifuge tube and spun down to provide a tan-orange pellet. The supernatant was decanted off, and the pellet was resuspended with distilled water. This mixture was then spun down again, to remove any remaining $NaHCO_3$, and the supernatant was again removed. The pellet was left exposed to the atmosphere to allow for moisture to evaporate overnight. The pellet yielded 18 mg (19%) of mostly dibromopyridine **25** as an orange-brown powder. To attempt an acid-base extraction, the combined aqueous supernatants were then reacidified with hydrochloric acid and extracted with methylene chloride. The organic phase was then removed and discarded, and the aqueous phase was neutralized with sodium hydroxide. Upon neutralization, the aqueous phase was extracted 3x with 15 mL of methylene chloride, and the combined organic layers were dried over $MgSO_4$. The dried organic phase was then concentrated *in vacuo* to provide 9 mg (10%) of a

mixture of monobromopyridone **19** and dibromopyridine **25** as a tan powder. Spectral data for these products coincide with that reported by McElroy.[104]

Phosphate Coupling Procedure

A mixture of 0.41 g (2.96 mmol) of hydroxypyridone **18** and 1.76 g (6.51 mmol) of PBr_3 was heated at 110 ^oC for 1 h under inert atmosphere and stirring. Upon completion and cooling, 10 mL of anhydrous THF was added to increase the slurry volume. At the same time, a solution of 0.92 g (9.62 mmol) of phenylacetylene in 15 mL of anhydrous THF was cooled to 0 ^oC under inert atmosphere. To this solution, 0.47 g (7.40 mmol) of 2.5 M *n*-butyllithium was added dropwise *via* syringe, and the resulting mixture was stirred for 30 min at 0 ^oC. The bromination slurry was then added to the phenylacetylide solution *via* cannula. The mixture was stirred at 0 ^oC for 1h, then quenched with water. THF was removed *in vacuo*, and then the aqueous layer was extract 3x with 30 mL of diethyl ether. The combined organic layers were dried over $MgSO_4$, and then concentrated *in vacuo* to yield 0.75 g of crude product mixture as an orange oil. Column chromatography (7:3 hexanes:ethyl acetate) eluted 0.493 g of pure phenylacetylene (^1H NMR ($CDCl_3$) δ 3.09 (s, 1H), 7.36 (m, J = 2, 6 Hz, 3H), 7.57 (d, J = 4 Hz, 2 H)) and 0.072 g of an unidentified side product (^1H NMR ($CDCl_3$) δ 1.74 (m, J = 4 Hz, 2H), 1.97 (m, J = 4 Hz, 2H), 3.46 (t, J = 8 Hz, 2H), 3.71 (t, J = 8 Hz, 2H)). A methanol flush of the column provided 0.171 g of monobromopyridone **19** (spectral data coincides with that reported by McElroy).[104]

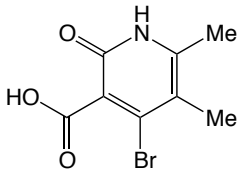
Sonogashira Coupling Products (26)



A solution of 100 mg (0.45 mmol) of a 2:1 mixture of monobromopyridone **19** and dibromopyridine **25**, 23 mg (0.23 mmol) of phenylacetylene, 10 mg (0.009 mmol) of tetrakistriphenylphosphine palladium(0), 2 mg (0.009 mmol) of copper(I) iodide, and 0.2 mL of dry triethylamine in 4 mL of anhydrous THF was stirred at room temperature for 16h under inert atmosphere. The crude mixture was filtered through Celite, concentrated *in vacuo*, dissolved in diethyl ether, washed with water and brine, dried over $MgSO_4$, and then concentrated *in vacuo* to provide the crude Sonogashira Coupling products **26** as a brown oil. Column chromatography (7:3 hexanes:ethyl acetate) was useful in removing unreacted phenylacetylene. A methanol flush of the column yielded 50 mg (81%) of the Sonogashira coupling products mixture **26** as a viscous, brown oil. Further specific characterization provided limited information, due to the complex product mixture and unworkable concentration of similar peaks in important areas of the ^{1}H NMR spectrum. Selective NOE experiments were run on each set of aromatic peaks displayed in the ^{1}H NMR. While most yielded no visible NOE signals, pulsing a doublet at δ 6.99 ppm provide NOE signal to protons at δ 2.28 and 2.82 ppm, which are believed to correspond to the 5-position methyl group on either our pyridone **19** or pyridine **25** ring systems. This signifies the successful coupling of our model A-ring precursor to the 4-position of said ring(s). Direct

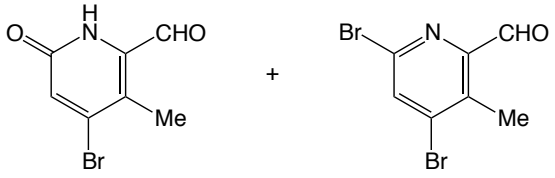
measurements of NOE signals originating from any coupling products to the 2-position of **19** or **25** were unable to be observed.

Bromopyridone Carboxylic Acid (35)



A mixture of 1.0 g (4.74 mmol) of hydroxypyridone ethyl ester **17** and 1.6 mL (4.5 g, 16.6 mmol) of PBr_3 was heated at 140 ^oC for 4 h. Once cool, water was added to the system and the resulting solution was brought to pH = 7 with $NaHCO_3$. The precipitate thus obtained was filtered, washed with water and diethyl ether to yield 415 mg (36%) of bromopyridone carboxylic acid **35** as an orange powder; IR (solid) 3133 (br), 3000 (br), 2924 (br), 2812 (br), 1693 (m), 1637 (s), 1609 (s), 931 (s) cm^{-1}; ^1H NMR (400 MHz, *d*-DMSO) δ 13.66 (br s, 1H), 12.65 (br s, 1H), 2.31 (s, 3H), 1.93 (s, 3H); ^{13}C NMR (100 MHz, *d*-DMSO) δ 172.9, 172.0, 164.6, 149.5, 107.7, 94.2, 17.2, 8.9; MS (ESI+) *m/z* for $C_8H_8BrNO_3$ $(M)^+$ calcd 244.9688, found 245.9542.

Monobromopyridone Carboxyaldehyde (38) and **Dibromopyridine Carboxyaldehyde (39)**



To a solution of 100 mg (0.45 mmol) of a 2 : 1 mixture of monobromopyridone **19** and dibromopyridine **25** in 5 mL of DMF was added 70 mg (0.58 mmoles) of N,N-

dimethylformamide dimethyl acetal. The solution was stirred for 24 h at 140 ^{o}C under inert atmosphere. The resulting brown liquid was concentrated *in vacuo* to yield a crude mixture of enamine products **36** and **37** as a waxy, brown oil. An inability to separate the product mixture led to it being directly dissolved in 5 mL of 50% aqueous THF, then 0.29 g (1.35 mmol) of sodium periodate was added. The mixture was stirred vigorously for 16 h at room temperature under inert atmosphere. The resulting brown solution was filtered to remove insoluble $NaIO_3$, and the solids were washed with ethyl acetate. The organic layer was separated and washed with 50 mL of saturated sodium bicarbonate solution three times, then dried over $MgSO_4$. Concentration *in vacuo* of the organic layer provided 35 mg (29%) of a 10:1 mixture of monobromopyridone carboxyaldehyde **38** and dibromopyridine carboxyaldehyde **39** as a brown powder. Purification by column chromatography (1:1 dichloromethane:hexanes) removed some of the impurities. IR (CCl_4, thin film) 2966 (br), 2928 (br), 2850 (m), 1669 (s), 1650 (s) cm^{-1}. The relative amounts of products present in the complex mixture was determined by the ratio of aldehydic proton signals (^{1}H NMR ($CDCl_3$) δ 10.02 (s, 0.12H), 10.21 (s, 1H)). Further spectral assignment proved difficult due to the overall level of impurity and spectral congestion in important areas. The reported yields represent crude material.

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