ABSTRACT

Title of Dissertation: SYNTHETIC APPROACHES TO THE ANTICANCER AGENT STREPTONIGRIN

William Thomas McElroy, Doctor of Philosophy, 2005

Dissertation directed by: Professor Philip DeShong
Department of Chemistry

Pd-catalyzed coupling reactions have a central place in synthetic chemistry. In particular, studies from the DeShong laboratory have demonstrated that aryltrialkoxysilanes, in the presence of Pd(0) and fluoride, are capable of aryl group transfer to a range of aryl halides and triflates and allylic benzoates. The cross-coupling reaction represents an ideal opportunity to construct the tetracyclic core of the anticancer agent streptonigrin. This strategy is highly convergent and readily amenable to the synthesis of analogues, and as such would constitute an improvement over previous total syntheses of this natural product.

A series of 4-bromopyridines (streptonigrin C ring precursors) were prepared, and their couplings with various arylsiloxanes (streptonigrin D ring precursors) examined. The coupling reaction generally tolerated the preparation of sterically demanding biaryls.

The coupling of the 3-nitro-4-bromopyridine derivative was problematic, as dehalogenation was found to compete with arylation. The use of nitro group surrogates and a variety of catalyst systems offered no improvement. These results indicated the coupling reaction is highly sensitive to the electronic environment of bromopyridine.

The analogous biaryl coupling reaction employing an organoboron species was more effective and allowed for additional streptonigrin CD analogues to be prepared. This reaction was found to be highly sensitive to the reaction conditions. A fully functionalized C ring precursor (prepared in 10 synthetic operations) underwent Suzuki coupling with a fully functionalized D ring precursor (prepared in 3 steps) to give an adduct possessing the streptonigrin CD skeleton. This species was elaborated to a precursor suitable for appendage to the AB ring component.

A streptonigrin A ring derivative has been prepared in 6 steps from resorcinol. The functionalities present in this species are compatible with several possible strategies to prepare the ABCD framework of the natural product. Results of a model study indicate that the coupling of an A ring aryl siloxane with the CD fragment (possessing a three-carbon fragment in the form of an allylic benzoate) is viable approach to the natural product. Further studies are warranted to evaluate the requisite annulation to prepare the B ring.

Synthetic Approaches to the Anticancer Agent Streptonigrin

by

William Thomas McElroy

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Ac	acetyl
Ar	aryl
Bn	benzyl
BOC	*tert*-butoxycarbonyl
Bz	benzoyl
calcd	calculated
cod	1,5-cyclooctadiene
conc	concentrated
Cy	cyclohexyl
d	day (s)
dba	dibenzylideneacetone
decomp	decomposition
DIBAL	diisobutylaluminum hydride
DIPEA	diisopropylethylamine
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
EDG	electron donating group
EI	electron ionization
EMG	electropositive main group atom

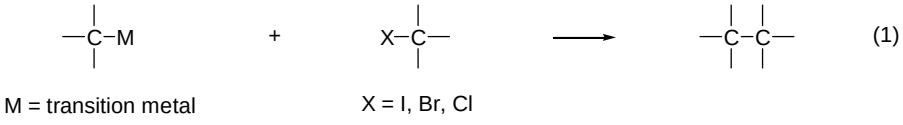
Eq.	equation
equiv	equivalent (s)
Et	ethyl
EWG	electron withdrawing group
FAB	fast-atom bombardment
h	hour (s)
Hz	Hertz
J	coupling constant
L	ligand
m	*meta*
m-CPBA	*meta*-chloroperoxybenzoic acid
m/z	mass to charge ratio
Me	methyl
min	minute (s)
mp	melting point
MOM	methoxymethyl
MS	mass spectrometry
NADH	nicotinamide adenine dinucleotide
NADPH	nicotinamide adenine dinucleotide phosphate
NBS	*N*-bromosuccinamide
NMR	nuclear magnetic resonance
nOe	nuclear overhauser enhancement
Nuc	nucleophile

o	*ortho*
p	*para*
Ph	phenyl
Piv	pivaloyl
PMB	*para*-methoxybenzyl
py	pyridine
TASF	tris(diethylamino)sulfonium difluoro(trimethyl)silicate
TBAF	tetrabutylammonium fluoride
TBAT	tetrabutylammonium triphenyldiflurosilicate
t-Bu	*tert*-butyl
TEA	triethylamine
Tf	triflate
THF	tetrahydrofuran
TLC	thin layer chromatography
TMAF	tetramethylammonium fluoride
TMEDA	*N*,*N*,*N'*,*N'*-tetramethylenediamine
Ts	tosyl

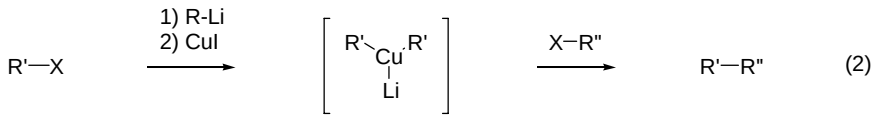
Introduction

The formation of carbon-carbon bonds continues to be the most crucial transformation in synthetic chemistry. The development of new protocols for carbon-carbon bond construction, however, remains an area of active investigation.[1] From an intellectual perspective, carbon-carbon bond formation poses the challenge of attaching two atoms with identical electronegativities. Perhaps more significantly, the development of new methodologies in this arena often allows for the preparation of target molecules that are inaccessible by other means.

During the first half of the twentieth century, numerous strategies were developed for the attachment of two saturated, sp^3 hybridized carbon atoms to one another. There were few methods for the creation of carbon-carbon bonds in which one or both of the atoms were sp^2 or sp hybridized. The last fifty years have witnessed the invention of a number of new reactions that address this void. A particularly significant finding has been that carbon atoms covalently bonded to transition metals behave as nucleophiles, and as such react with organic electrophiles (Eq. 1). Although formally a substitution reaction, the mechanism and substrate restrictions of this reaction are different from those observed in an S_N1 or S_N2 process. Importantly, the reaction allows for the coupling of sp^2 and sp hybridized carbon atoms, which may be present in either partner.



One of the older, although still widely used, examples of this process involves the addition of a dialkyl or diaryl organocuprate to an alkyl halide, with concomitant loss of copper (Eq. 2).[2] The organocuprate, or Gilman reagent, is in turn usually prepared upon treatment of an organohalide with an alkyl lithium, followed by CuI (or CuCN). The reaction is of wide scope, and generally allows for sp, sp^2, and sp^3 hybridized carbons to be coupled.



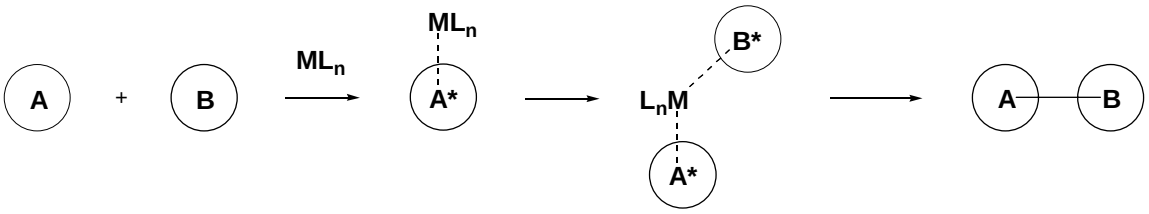
(2)

There are nevertheless several limitations of this reaction. The strongly basic conditions required to generate the organocuprate make this operation incompatible with several functional groups. Although the coupling step is tolerant of most functionalities, aldehydes notably may not be present, since they react faster than the alkyl halide. The instability of the dialkylcuprate usually necessitates that a large excess of this reagent be employed. Additionally, as presented in Eq. 2 only half of the starting R' group is transferred from the Gilman reagent to the alkyl halide, although the development of higher order cuprates has addressed this issue.[3]

In response to these limitations, other methods for the cross-coupling of unsaturated centers have been explored.[1] Of critical importance has been the discovery that ligand stabilized transition metals can be added *in situ* to a reaction mixture, and are capable of mediating the cross-coupling reaction between two organic partners. This finding has led to an explosion in the number of methods available for carbon-carbon bond formation. Although each of these reactions possesses its own mechanistic nuances, many are fundamentally similar, and operate as outlined in Scheme 1.

In the absence of the transition metal complex, organic species A and B are unreactive to each other. However, upon the addition of a suitable metal complex (M, L = ligand), one of the two species interacts with the metal to generate a reactive intermediate, denoted A*. This intermediate frequently possesses some type of bonding interaction between the metal and organic molecule, illustrated as the dashed line. Association with the second organic reactant B converts it to its reactive state, denoted B*. Finally, the metal mediates covalent bond formation between the two reactive species A* and B* to generate the A-B bond.

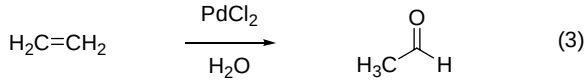
Scheme 1



In addition to requiring less reactive nucleophilic partners (than, for example, lithium dialkylcuprates) the use of transition metal complexes to control carbon-carbon bond formation offers several other advantages. The metal complex frequently can be used catalytically, and in many instances can be recovered following the reaction. Additionally, the rational modification of the metal's ligands can alter the chemo-, regio-, and stereochemical course of the reaction.

No other metal has been as widely studied for these and other synthetic purposes as palladium.[4] The origin of applications involving this metal can be traced to the catalytic hydrogenation of olefins,[5] and although numerous other metals have since been shown to catalyze the reaction, Pd continues to find widespread use in catalytic hydrogenations.

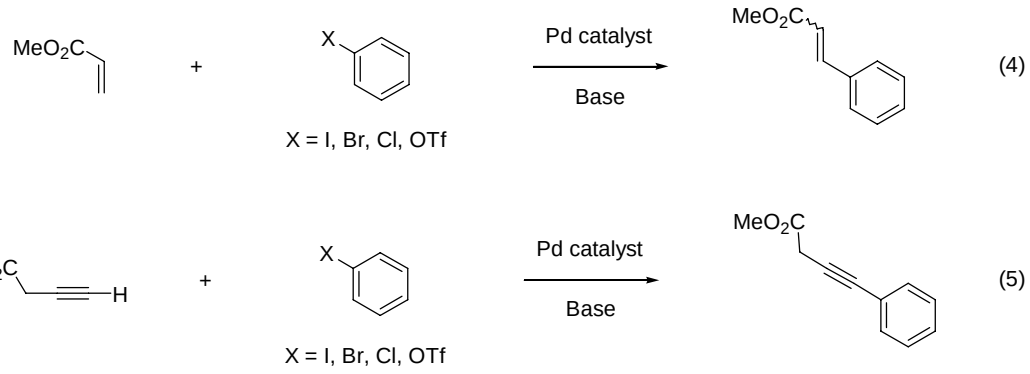
Similarly, the Wacker process[6] (Eq. 3), first reported in 1959 as a method for the conversion of ethylene to acetaldehyde, remains a valuable method for the oxidation of olefins and is frequently used in the synthesis of complex targets.[7]



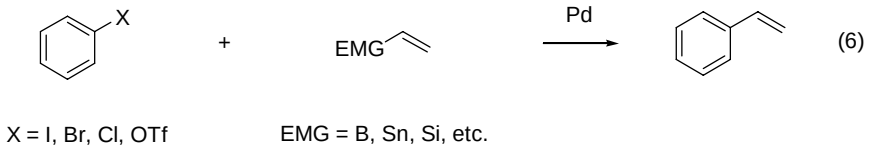
(3)

The above reactions serve as a testament to Pd's versatility: the metal is capable of catalyzing both the oxidation and reduction of carbon atoms. More remarkable, however, is the ability of Pd complexes to mediate carbon-carbon bond formation. Cross-coupling reactions involving Pd have proven to be highly valuable in the construction of biologically active targets.[8] Several of these reactions deserve further comment.

One of the earliest cross-coupling strategies to be developed is the Heck reaction (Eq. 4).[9] This transformation involves the Pd-catalyzed addition of an olefin to an aryl or vinyl halide or triflate. The alkene functionality is retained in the product, allowing for subsequent modification, and the reaction tolerates a wide variety of functional groups. Although the Heck coupling has been performed with a variety of olefins, it has been shown that the best alkene substrates for the reaction are those that possess an electron-withdrawing group (EWG). Presumably this group increases the electrophilicity of the β carbon of the α,β-unsaturated olefin and improves it susceptibility to nucleophilic attack by a transient organopalladium species. The EWG also provides a regiochemical bias. The analogous Sonogashira reaction, in which a terminal alkyne rather than an alkene is employed, has also been reported (Eq. 5).[10]



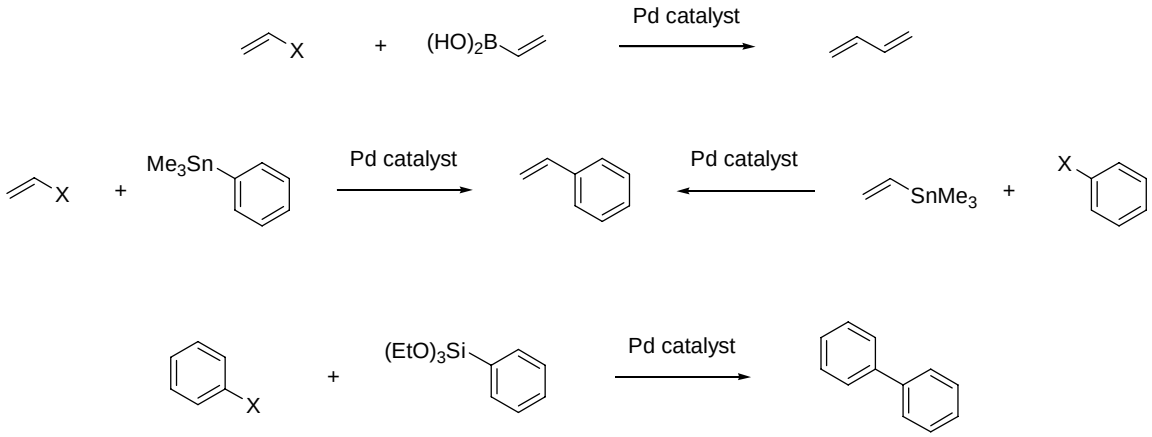
Perhaps the most significant development in the field has been the Pd-catalyzed cross-coupling of aryl and vinyl halides and triflates with carbon atoms possessing an electropositive main group atom (EMG) (Eq. 6). Some examples of these species include, but are not limited to, organoboranes, organostannanes, and organosilanes (*vide infra*). These compounds can be viewed as weakly nucleophilic by virtue of the higher electronegativities of carbon relative to the EMG. This reaction is frequently applied to systems in which the two carbon atoms to be coupled to each other are sp^2 hybridized.



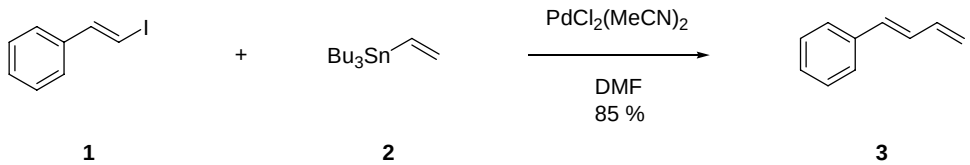
The cross-coupling of alkenyl and aryl partners makes possible the synthesis of 1,3-butadiene, styrene, and biaryl derivatives, as depicted in Scheme 2 (X = I, Br, Cl, OTf). In terms of reactants and reaction products, this method resembles the organocuprate coupling previously discussed. An important difference, however, is the attenuated reactivity of the species bearing the EMG atom relative to its organocuprate cousin. This

limited reactivity allows for a myriad of functional groups to be present. The two most well-studied reactions are the Stille[11] and Suzuki-Miyaura[12] couplings.

Scheme 2

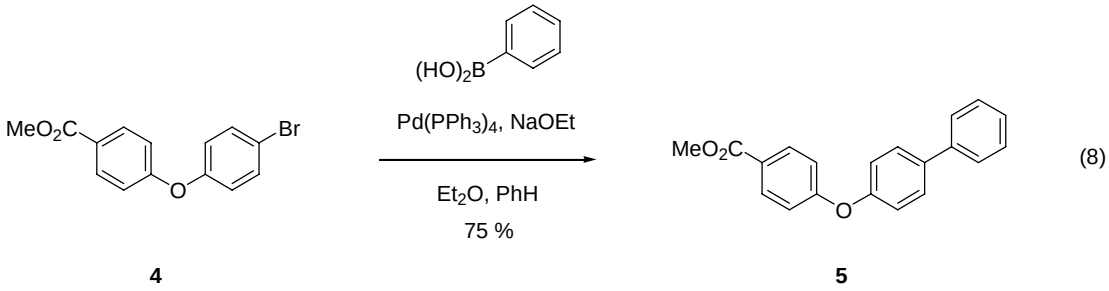


An example of the Stille coupling[13] is presented in Eq. 7. Reaction of an organohalide (**1**) with an organostannane (**2**), in the presence of a catalytic amount of Pd(0) gives cross-coupled adduct **3**. The Sn atom usually possesses an aryl or alkenyl substituent that is to be transferred, and three alkyl groups, which are essentially non-transferable. The reaction is of wide scope, as virtually all functional groups are tolerated, and has been performed with heteroaromatic coupling partners. The generality of the method has allowed for its widespread use in natural products synthesis.[14] However, a major limitation of the Stille coupling is the use and generation of toxic tin reagents. Additionally, the tin by-products formed during the reaction are often difficult to separate from the desired product.



1 **2** **3** (7)

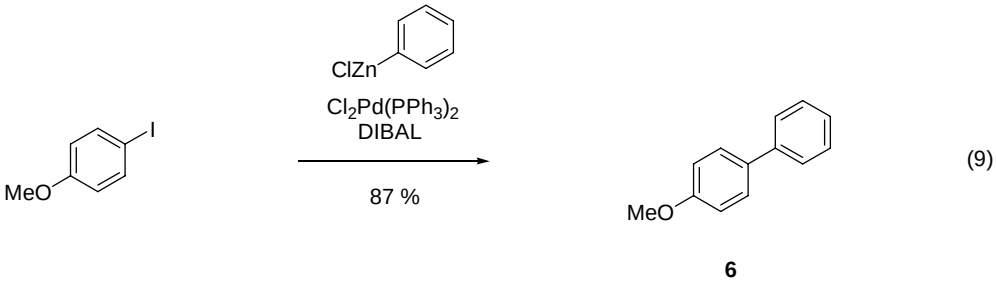
The Suzuki-Miyaura coupling is analogous to the Stille reaction but deploys a boronic acid (or boronic ester) in place of the organostannane. An example[15] is shown in Eq. 8. The Pd-catalyzed reaction of aryl halide **4** and phenylboronic acid gave adduct **5** in good yield. The Suzuki-Miyaura reaction, like the Stille coupling, is generally tolerant to other functional groups and has also found widespread use in natural products chemistry.[16] An advantage of the Suzuki-Miyaura coupling over the Stille reaction is that organoboranes are much less toxic than their organostannane counterparts, and the boron byproducts generated during the course of the reaction are easily removed after an aqueous wash. However, boronic acids are somewhat unstable, and can be difficult to purify. This usually requires that this functionality be installed immediately prior to the coupling reaction. The use of boronic esters addresses this issue since these compounds are easier to handle; however, they are in some instances less reactive than the parent boronic acids.[17]



4 **5** (8)

More recently, the use of atoms other than tin or boron in the cross-coupling process has been described. In particular aluminum, zirconium, and especially zinc have been shown to be viable alternatives to their tin and boron counterparts. The use of such metals in cross-coupling reactions is generally referred to as the Negishi coupling,[18] and an example is presented in Eq. 9.[19] *p*-Iodoanisole and phenylzinc chloride, when treated with a catalyst prepared from $Cl_2Pd(PPh_3)_2$ and DIBAL, reacted to afford cross-coupled

adduct **6** in high yield. In general, the organometallic species present in Negishi couplings possess the advantage of being more reactive than organostannanes or organoboranes, and their use usually requires milder reaction conditions. However, they are at times tedious to prepare, and lack the chemoselectivity possessed by tin and boron reagents.



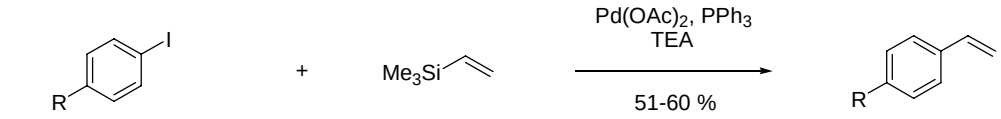
(9)

6

The limitations associated with the above protocols, particularly the Stille and Suzuki couplings, have prompted the development of alternatives to these reactions. Importantly, organosilanes have been shown to undergo Pd-catalyzed coupling with organic halides and triflates. The cross-coupling of organosilanes, like those of organoboranes and organostannanes, is tolerant of most functional groups. The silicon-based couplings offer added benefits: organosilanes are less toxic than organostannanes, and a major advantage relative to their organoboron counterparts is that the silanes can typically be purified by chromatography, and in some cases distillation. Several research groups have been active in this area, and the development of silicon-based coupling strategies has recently been reviewed.[20] The following discussion provides a brief overview.

Several structural motifs are accessible through the cross-coupling of organosilanes (Scheme 2), and the formation of styrene derivatives has been thoroughly examined.

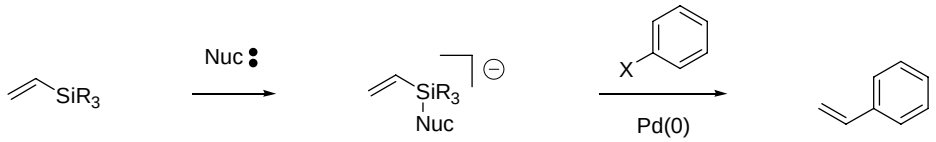
There are few examples of neutral alkenylsilanes undergoing coupling with aryl halides. For example, Westerlund[21] has shown that aryl iodides possessing various substituents in the *para* position react with vinyltrimethylsilane, in the presence of a Pd catalyst, to give styrene derivatives (Eq. 10).



(10)

R = H, Me, OMe, NO_2

Most Pd-catalyzed couplings of organosilanes, however, require prior conversion of the neutral silane to its "ate" complex (Eq. 11).[22] This is typically accomplished *in situ* upon treatment of the silane (**7**) with an appropriate nucleophile, which generates a pentacoordinate silicate species such as **8** (Eq. 11). This complex is then capable or vinyl (or aryl) group transfer to Pd. The natures of the R groups have a dramatic impact on the process, as these groups must be capable of withdrawing electron density from the silicon atom in **7**, increasing its electrophilicity and favoring formation of **8**.

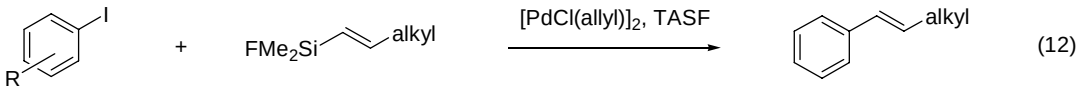


(11)

7 **8**

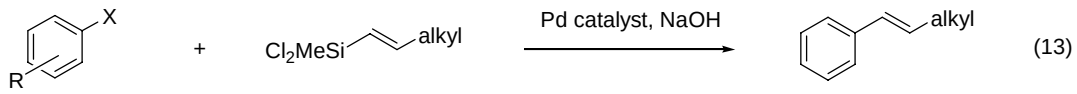
Hiyama[23] has shown that alkenylfluorosilanes, when activated with tris(diethylamino)sulfonium difluoro(trimethyl)silicate (TASF), undergo Pd-catalyzed coupling with a variety of aryl iodides (Eq. 12). In most cases the fluorosilane may be prepared from treatment of its corresponding chlorosilane with copper fluoride. This strategy is therefore limited by the availability of the precursor chlorosilanes, as well as

the necessity of the expensive, moisture sensitive TASF. Additionally, in this case only aryl iodides, and not the more readily available bromides and chlorides, have been demonstrated to undergo the reaction.



(12)

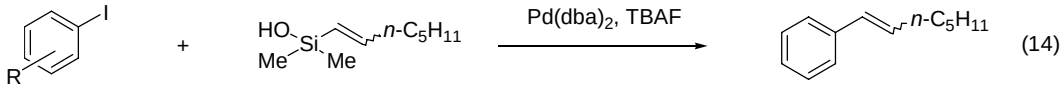
A more general process makes use of alkenyldichlorosilanes as olefin transfer reagents (Eq. 13),[24] with activation of the silane being accomplished through the addition of NaOH. This reagent combination has been shown to undergo alkenyl group transfer to aryl bromides and chlorides, as well as iodides. Again, the strategy is limited by the availability of the alkenylchlorosilane. Additionally, the use of the highly nucleophilic and basic hydroxide ion makes this process incompatible with several functional groups.



(13)

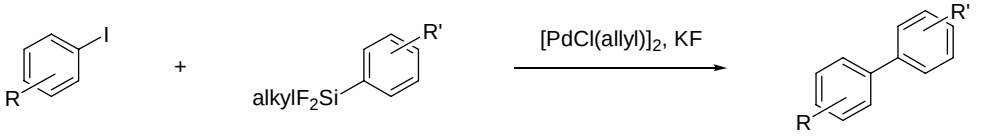
X = Br, Cl

Denmark has addressed some of these concerns through the coupling of alkenylsilanols with aryl iodides (Eq. 14).[25-27] Either TBAF or Ag_2O[28] can be employed as the activator, and the silanol may be prepared from the corresponding alkenyl bromide or iodide. Importantly, the reaction proceeds with retention of alkene geometry, and both *E* and *Z* alkenyl groups have been transferred. The reaction has recently been expanded to allow for the use of fluorosulfonate esters in place of iodides.[29] In a related process, alkenylsilacyclobutanes[30] have been shown to be competent in the Pd-catalyzed transfer of olefinic groups (*vide infra*).



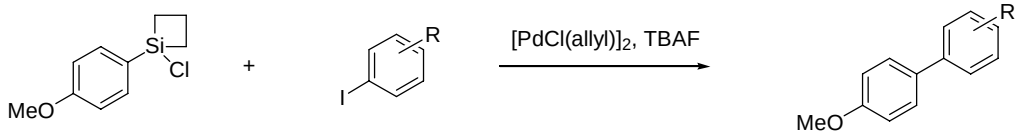
(14)

The Pd-catalyzed coupling of aryl silanes with aryl halides also represents a well-examined area since the biaryl motif accessible through this strategy is found in numerous natural products.[31] Many of the developments in biaryl formation parallel those described for the synthesis of styrene derivatives. For instance, Hiyama[32] has used arylfluorosilanes in couplings with aryl iodides (Eq. 15). The reaction was found to be tolerant of both electron donating and electron withdrawing groups present on either partner. A more useful variation of this reaction utilizes aryldichlorosilanes as the coupling partners,[33] as this allows for reaction with more readily available aryl bromides.



(15)

Denmark has demonstrated that arylsilacyclobutanes[34] (Eq. 16), as well as silanols[35, 36] (Eq. 17), are suitable partners for Pd-catalyzed coupling with aryl iodides. A few examples of aryl bromides undergoing the reaction have also been reported.[35, 36]



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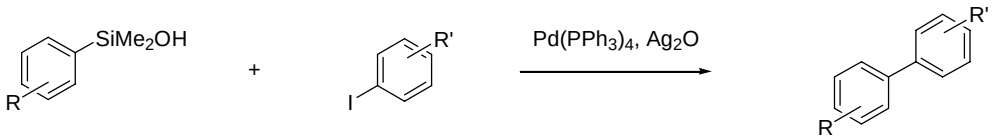
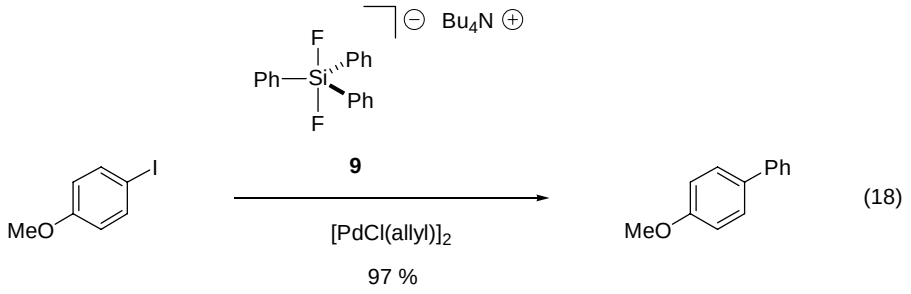


(17)

As an alternative to the Stille and Suzuki-Miyaura couplings, each of the reactions described above has merit. Nevertheless, there a number of limitations associated with these and other silicon-based strategies. Many of the requisite organosilanes require several synthetic operations to prepare. Furthermore, several of the described processes are compatible with only aryl iodides, and not bromides or chlorides. From a practical standpoint, the ideal coupling technology would be address both of these issues.

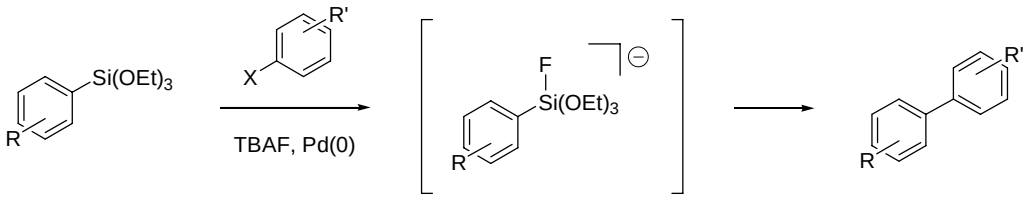
The DeShong group has for some time been pursuing silicon-based cross-coupling strategies. Initial studies focused on the use of tetrabutylammonium triphenyldifluorosilicate (TBAT, **9**) as a phenylating agent.[37, 38] TBAT is an air- and moisture-stable crystalline salt which is readily prepared from triphenylsilanol.[39] It has been shown that TBAT undergoes Pd-catalyzed cross-coupling with a variety of aryl iodides and electron-deficient aryl bromides and triflates. An example is presented in Eq. 18. The use of TBAT is limited, however, by the fact that only unsubstituted phenyl groups may be transferred.



(18)

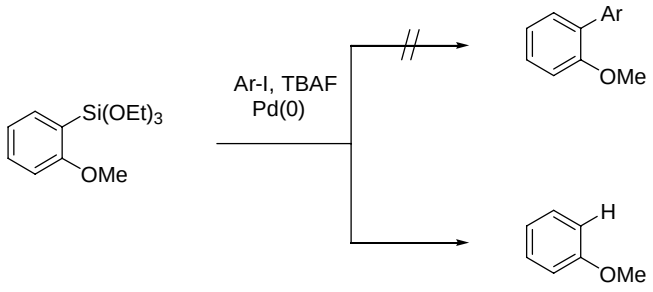
Recent findings have addressed this issue. It has been shown that aryltrialkoxysilanes, upon exposure to TBAF, are presumably converted to their corresponding fluorosilicate complexes (Scheme 3, X = I, Br). These species, in the presence of a catalytic amount of Pd(0), undergo aryl group transfer to a range of aryl iodides and bromides.[40-42]

Scheme 3



Much effort has been devoted to determine the scope and limitations of the above process. It has been found that the reaction is generally tolerant of both electron donating and electron withdrawing groups, which may be present in either partner. An exception, however, regards the coupling of arylsiloxanes that bear a heteroatom in the position *ortho* to silicon on the aromatic ring. These species have been found to undergo rapid protodesilylation under the reaction conditions (Scheme 4).[43, 44]

Scheme 4



The proposed catalytic cycle[38] for the cross-coupling reaction is presented in Figure 1. Oxidative addition of a Pd(0) species into the carbon-halogen bond of the aryl halide generates **10**, which then undergoes transmetallation with the silicate to form **11**. Reductive elimination yields the cross-coupled product and regenerates the Pd(0) catalyst. A similar catalytic cycle has been proposed for the Stille[11] and Suzuki[12] couplings.

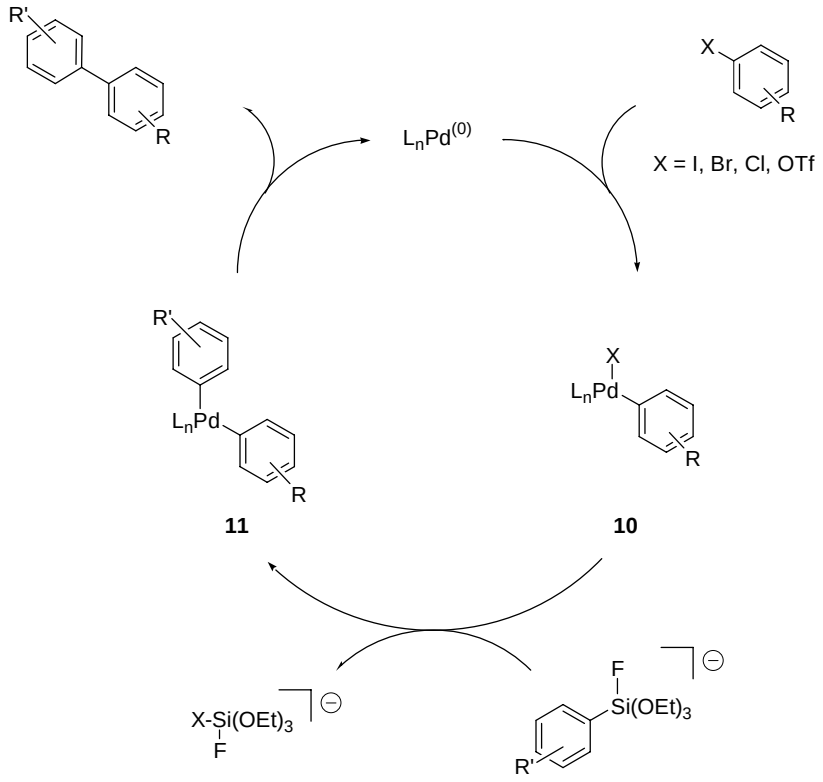
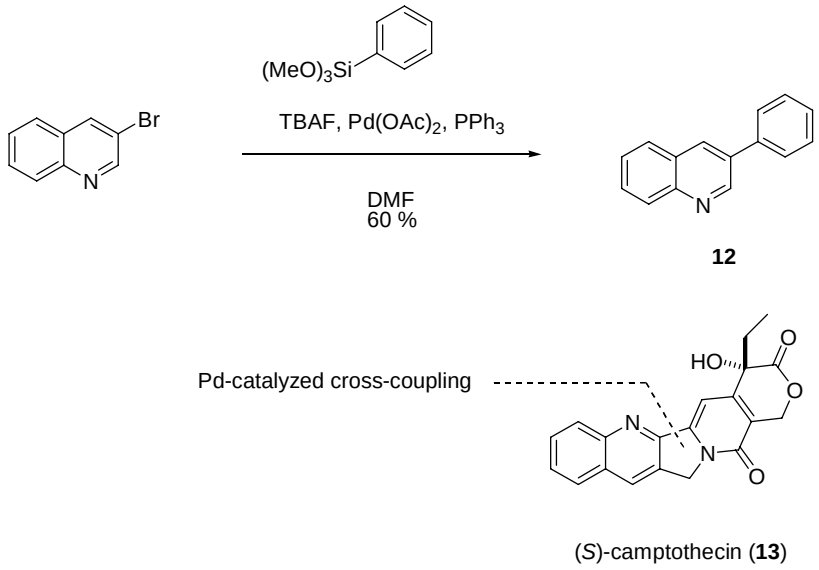


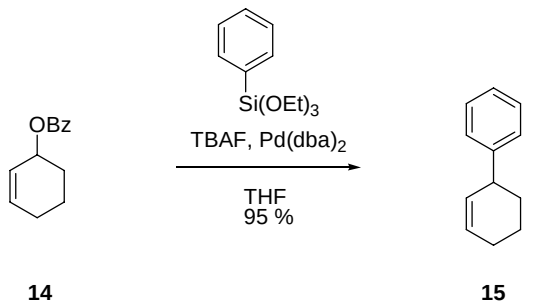
Figure 1. Proposed catalytic cycle for the Pd-catalyzed cross-coupling of aryl halides with aryltrialkoxyfluorosilicates.

Very recently the siloxane coupling technology has been extended to allow for the preparation of biaryls in which one or both of the rings are heteroaromatic.[44] These explorations have obvious importance since many pharmaceutical agents possess heteroaromatic ring systems. For example, 3-bromoquinoline underwent cross-coupling with $PhSi(OMe)_3$ to deliver adduct **12** in 60% yield (Eq. 19). The framework present in **12** resembles that found in the anticancer agent camptothecin (**13**),[45] and it is anticipated that this approach to camptothecin and its analogues would be successful.



(19)

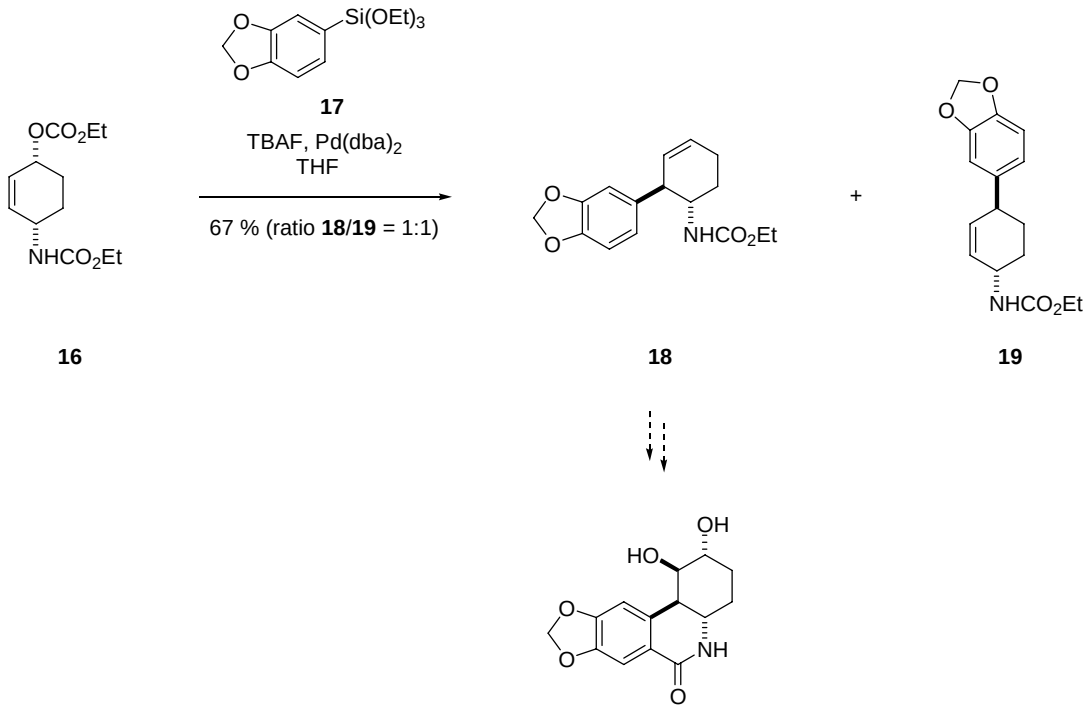
The Pd-catalyzed cross-coupling of aryltrialkoxysilanes and aryl halides to form unsymmetrical biaryls has been a fruitful area of research. No less significant, though, has been the development of the coupling strategy as a method for allylic arylation.[37, 46, 47] While the Pd-catalyzed addition of stabilized nucleophiles (i.e., malonates, azides) to allylic alcohol derivatives has been known for some time,[48] the addition of aryl groups to these systems has remained less explored. The DeShong lab has shown that aryltrialkoxysilanes, upon treatment with fluoride and catalytic Pd(0), are capable of aryl group transfer to allylic carbonates and benzoates (Eq. 20). For example, the reaction of allylic benzoate **14** with $PhSi(OEt)_3$ gave a 95% yield of adduct **15**.[46]



14 **15**

(20)

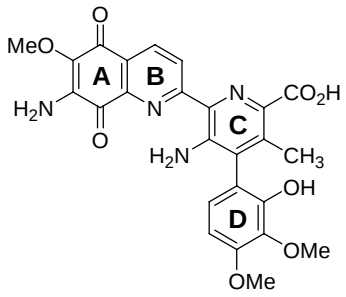
Scheme 5



This methodology is currently being developed for the synthesis of more complex systems. For example, arylation of allylic carbonate **16** with siloxane **17** afforded a 67% yield of regioisomers **18** and **19** in a 1:1 ratio (Scheme 5).[47] The regio- and stereochemical aspects of this and related transformations have been discussed.[37, 46, 47] Efforts are currently underway to apply this technology in a regio- and stereoselective manner to the synthesis of biological targets.[49]

As described above, Pd-catalyzed cross-coupling reactions represent an enormously powerful synthetic method for complex natural product synthesis. Our interest in these reactions stems from the fact that they may be used in the formation of highly functionalized molecules. We were particularly interested in further exploring the Pd-catalyzed coupling of aryltrialkoxysilanes with aryl halides to form heteroaromatic

systems. Since it incorporates a dense array of functionality on three aromatic rings, the anticancer agent streptonigrin (**20**) represents an attractive target. Our synthetic strategy is to first form the CD biaryl using a Pd-catalyzed coupling of a suitably functionalized 4-bromopyridine and appropriately substituted D ring siloxane. Appendage of the quinoline moiety would likewise be accomplished through a second coupling with an suitably functionalized quinoline siloxane. The approach is described in detail in Scheme 10 (Results and Discussion). What follows is a description of streptonigrin's biological activity and relevant synthetic studies. Several reviews regarding the isolation, structure determination, biological activity, and synthetic endeavors toward streptonigrin have appeared.[50-55]

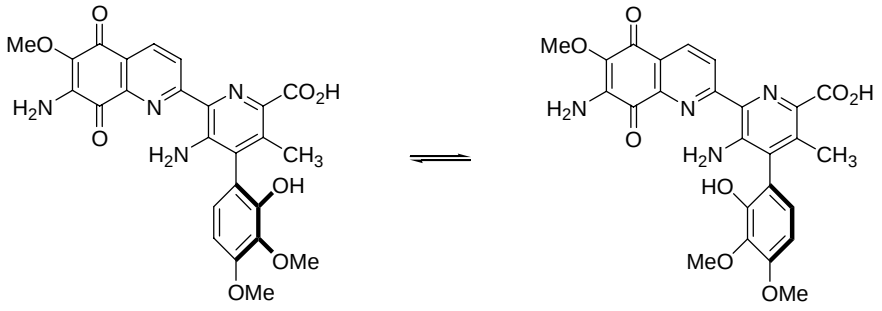


Streptonigrin (**20**)

The ability of *Streptomyces* bacteria to produce metabolites that possess a range of biological activities is well known.[56] It was armed with this knowledge that in 1959 Rao and Cullen described the isolation of a dark brown, crystalline solid from *Streptomyces flocculus*.[57] The same compound was later isolated from *S. rufochromycin* and *S. echinatus*[58] and *Actinomyces albus var bruneomycini*.[59] Interest in the newly isolated metabolite was heightened by reports of potent anticancer activity. Thus, following a series of spectroscopic and degradative studies,[60] the structure of streptonigrin was

determined (**20**), and assignment was subsequently confirmed through X-ray crystallography.[61] Recently the proton, carbon, and nitrogen resonances in the respective NMR spectra have been assigned.[62, 63]

It has been shown that the AB and C ring systems of **20** are oriented coplanar to one another (at least in the solid state), while the C and D rings are orthogonal.[61] This latter observation is to be expected, given the sterically congested nature of the CD ring juncture. Thus, streptonigrin may be found as either of two atrope isomers, with hindered rotation about the CD bond expected (Figure 2). Indeed, naturally occurring streptonigrin is optically active,[64] and an *M* configuration has recently been assigned.[65] The barrier to interconversion is at present unknown.



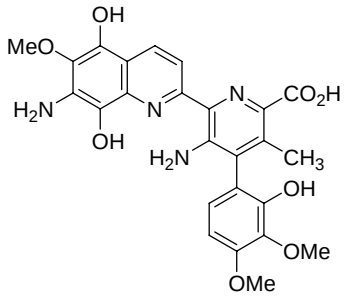
(*M*)-**20** (*P*)-**20**

Figure 2. Atrope isomers of streptonigrin.

Streptonigrin exhibits potent antiviral, antibiotic and anticancer activities (*vide infra*). It is the last property that has made this natural product the subject of numerous biological and medicinal studies. The compound was ultimately advanced to clinical trials; however, toxic side effects resulted in the termination of these studies.[66] Nevertheless, the use of streptonigrin in combination chemotherapy suggests that this compound (or analogues) may be of future clinical use.[67-69]

Several studies have explored streptonigrin's mode of action, and the ability of **20** to induce apoptosis has been recently been reported.[70, 71] Additionally, the cytotoxic properties of streptonigrin have been attributed to depletion of NADH/NADPH,[72, 73] the disruption of oxidative phosphorylation,[74, 75] and single-strand DNA cleavage.[76-79] The last property has been the most thoroughly studied.

The quinoline-5,8-dione is a recurring structural feature in several agents known to possess antitumor properties.[80] It has been demonstrated that the quinone functionality of streptonigrin is capable of accepting hydrogen atoms from NADH to form a reduced (**21**) or semireduced species.[81] Subsequent production of radicals (hydroxide or superoxide), in a process that involves oxygen and metal ions, is postulated to be the direct cause of DNA damage.[77, 79, 81-85] Little is known about this event, but what is established is that streptonigrin itself interacts only weakly with DNA, but when in its reduced form or in presence of metal ions this interaction is magnified significantly.[86-92]



21

Several structure-activity-relation (SAR) studies have been reported.[55] The minimum functionalities required for biological activity are the A ring quinone, quinoline and pyridine nitrogen atoms, and C-ring carboxylic acid. The modification of peripheral functional groups on the A ring affects the biological activity, as these groups presumably

influence the reduction potential of the quinone. These findings, in conjunction with the observation that metal ions are required for biological activity, have led to the hypothesis that the ring nitrogen atoms and carboxylate group of **21** exhibit coordination with metal ions, with the resulting species responsible for free radical production (Figure 3).

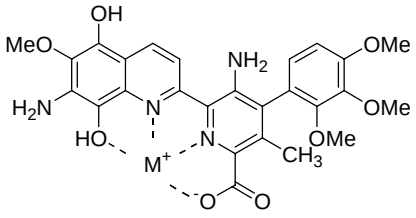


Figure 3. Possible coordination event of **21** with a metal ion.

The roles of the C ring methyl and amino groups, as well as the entire D ring, are unclear. Analogues lacking each of each of these functionalities show somewhat diminished activity relative to the parent compound. The fact that these analogues devoid of the D ring exhibit attenuated activity relative to the parent compound is significant since this structural feature confers optical activity upon the molecule.

The biogenesis of streptonigrin has been established.[93] Gould has elegantly determined through feeding experiments that streptonigrin is formulated in *S. flocculus* through a convergent pathway involving condensation of quinoline acid **22** with tryptophan derivative **23**. These pieces are in turn derived from anthranilic acid **24** and amino anthranilic acid **25**. Each of the anthranilic acids is obtained through condensation of phosphoenolpyruvate **26** with erythrose-4-phosphate **27**. Interestingly, **26** and **27** both originate from glucose metabolism.

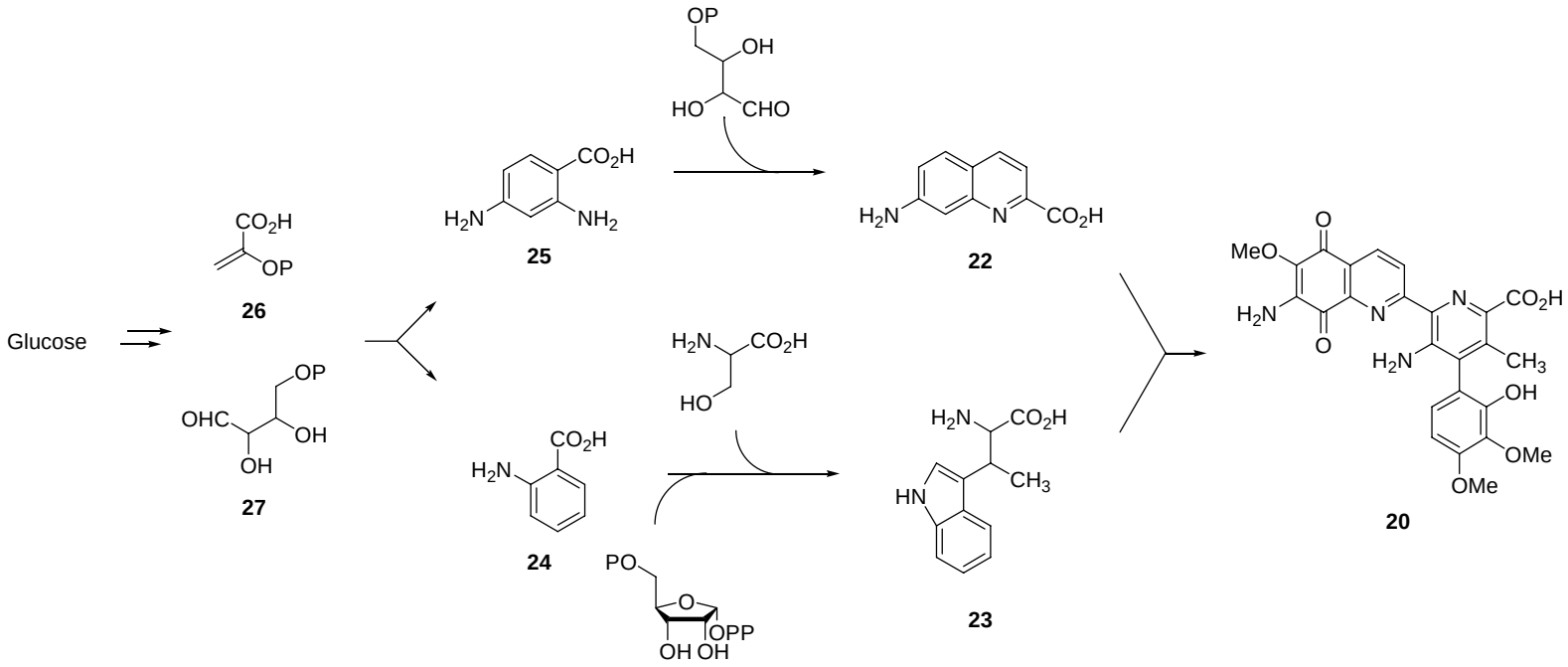
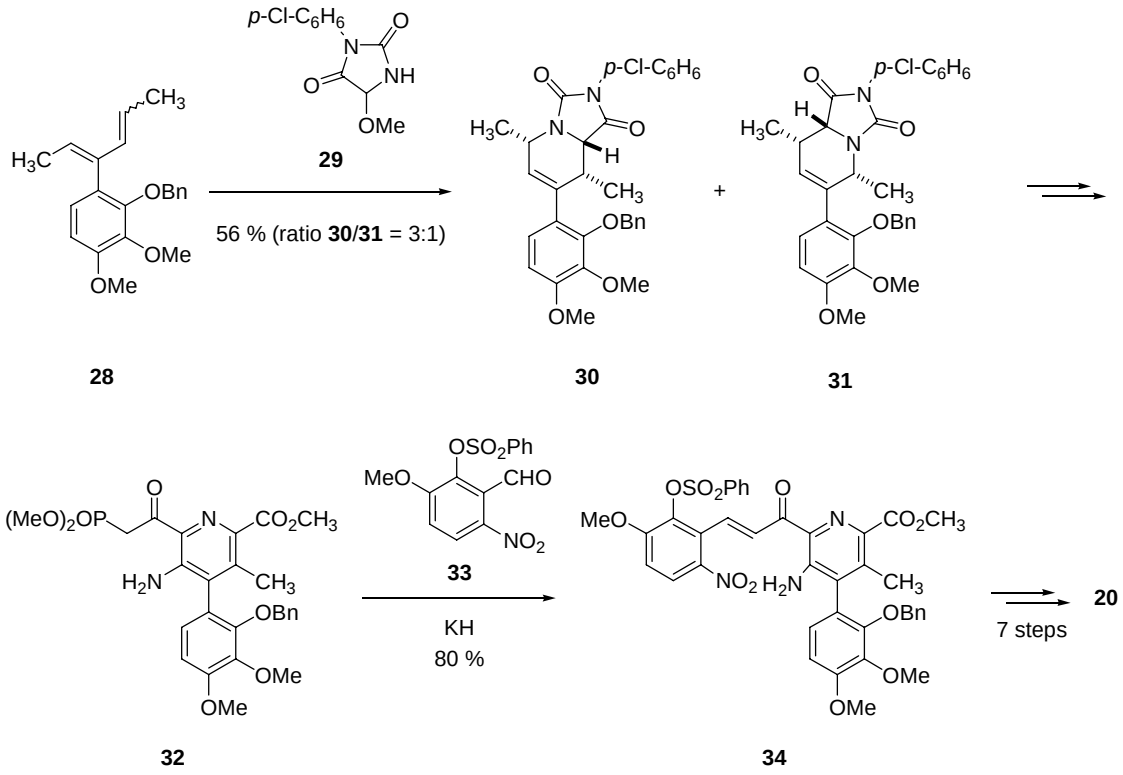


Figure 4. Proposed biosynthesis of streptonigrin.

In addition to displaying potent biological activity, streptonigrin represents a formidable synthetic challenge, as both acid and base sensitive functional groups are present. The pyridine ring is highly functionalized, and the CD ring juncture is extremely congested. Nevertheless, three total syntheses have been reported.

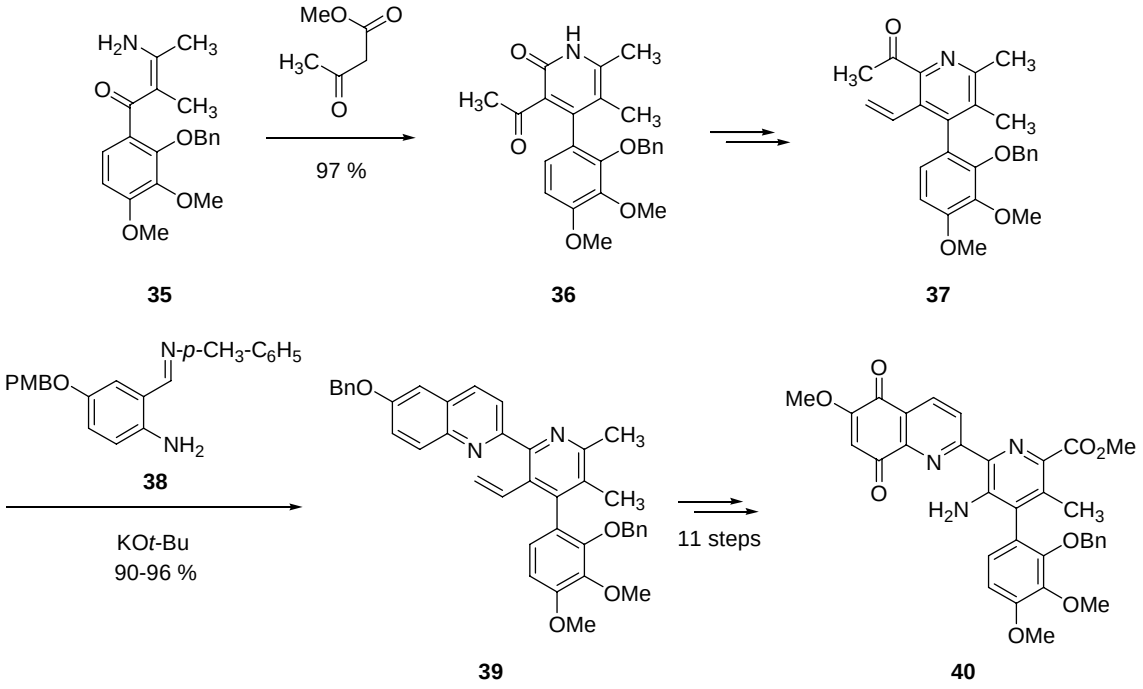
Weinreb[94] reported the first total synthesis, with the key element of the approach being construction of the C ring through a hetero Diels-Alder reaction of diene **28** with dienophile precursor **29** (Scheme 6). This resulted in the formation of a 3:1 ratio of the desired (**30**) to undesired (**31**) regioisomeric products. The cycloaddition was plagued by incomplete conversion, and the 56% yield reported was obtained after one recycle of unreacted starting material. Elaboration of **30** to phosphonate ester **32** was achieved after several steps. This compound underwent Horner-Wadsworth-Emmons condensation with aldehyde **33** to afford enone **34** in good yield. Reduction of the nitro group resulted in spontaneous conversion to the corresponding quinoline, thus establishing the tetracyclic core of the target. This compound was converted to the natural product in 6 steps. Although imaginative, the synthesis is hampered by the number of steps and low overall yield. Additionally, the key imino Diels-Alder reaction proceeds in only modest yield and regioselectivity.

Scheme 6



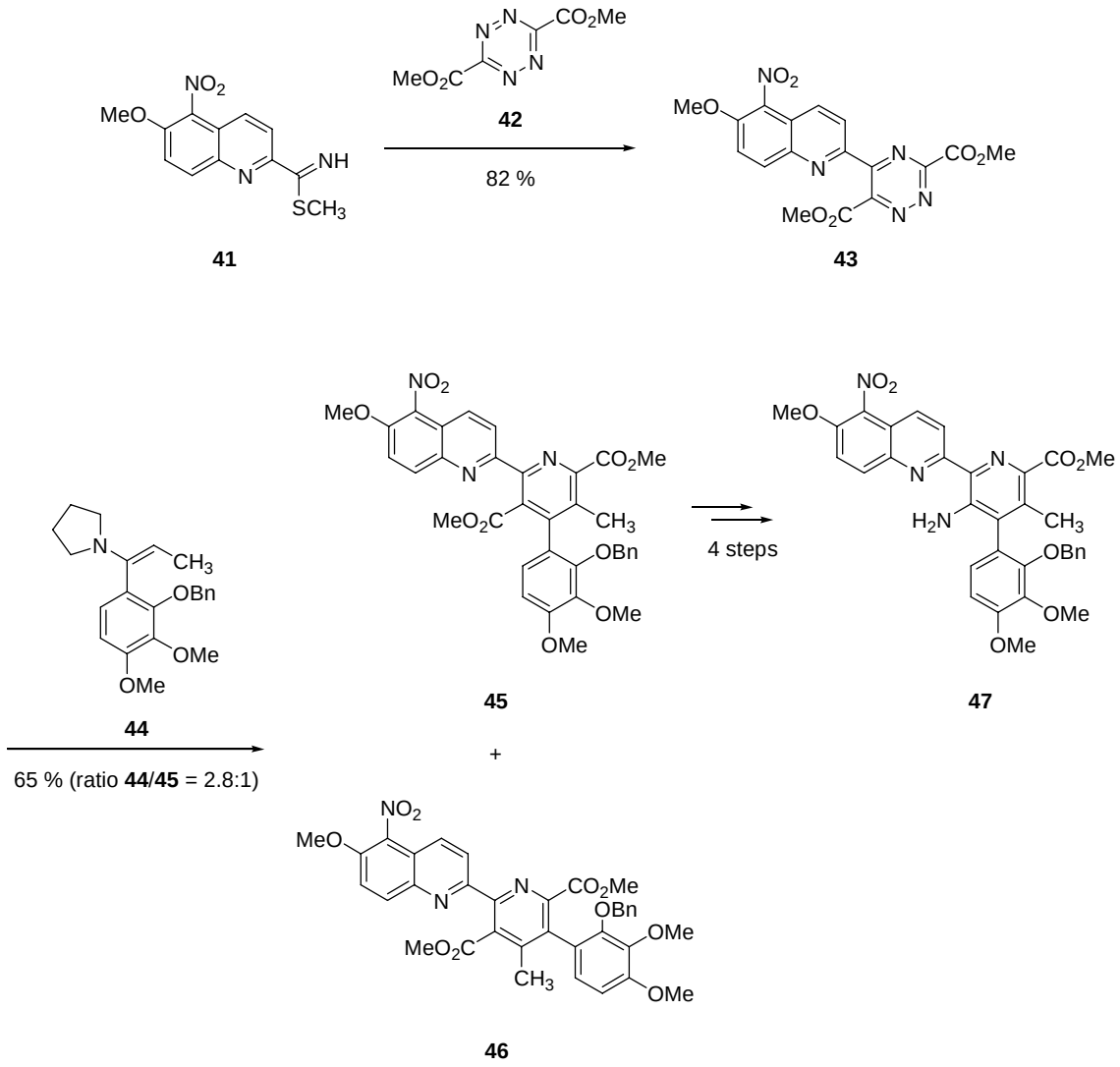
The Kende[95] synthesis allows for a much higher overall yield (1.3% to 0.013%) and fewer steps (Scheme 7). In this case, the CD ring system was efficiently prepared through condensation of amino ketone **35** with methyl acetoactetate to afford pyridone **36**. After some manipulations, pyridone **36** was converted to methyl ketone **37**, which underwent cyclization with amino imine **38** to deliver quinoline **39** in high yield. Although the core of streptonigrin may be rapidly accessed using this pathway, **39** requires 11 more steps to be converted to advanced intermediate **40**, constituting a formal total synthesis of the natural product. Most of these steps involve A ring functional group manipulations. The synthesis is almost entirely linear and provided little opportunity to construct streptonigrin analogues that possess variable AB ring substituents.

Scheme 7



The most recent formal synthesis has been reported by Boger (Scheme 8).[96] The described route relies on two successive imino Diels-Alder reactions to prepare the C ring of the natural product. Thus, thioimidate **41** (prepared in four steps from 6-methoxyquinoline) underwent Diels-Alder cycloaddition with tetrazine **42** to afford adduct **43** as a single regioisomer. The second cycloaddition took place between **43** and enamine **44** to yield a 2.8:1 mixture of regioisomeric Diels-Alder adducts in a combined yield of 65%. The regioselectivity in this process is comparable to that reported by Weinreb in his construction of the C ring. Ultimately, the desired adduct **45** was elaborated to advanced intermediate **46**, which had been previously prepared by Weinreb.

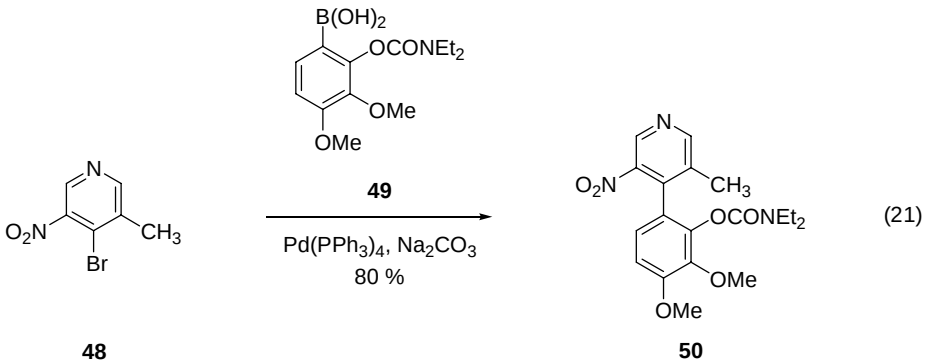
Scheme 8



The Boger strategy is attractive since the entire AB ring is constructed prior to attachment to the C ring. Thus, the approach readily lends itself to the formation of nonnatural analogues. One limitation, however, in the late stage conversion of the pyridine ring C-5 methyl ester in **45** to an amino group, as this requires the two methyl esters of intermediate **45** to be differentiated.

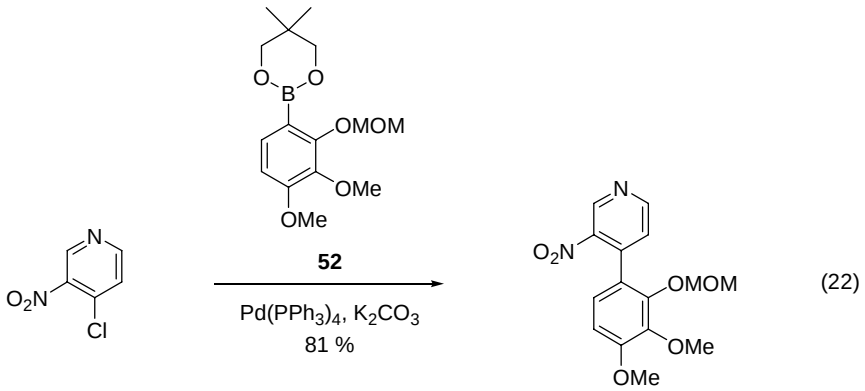
The ideal synthetic approach to streptonigrin would allow for the efficient construction of the parent compound as well as a variety of analogues. Several research

groups have been actively pursuing a synthetic route to **20** that addresses the concerns present in the three total syntheses. In this regard, Pd-catalyzed cross-coupling reactions are uniquely suited to the synthesis of streptonigrin for several reasons. First, the AB, C, and D rings may be independently prepared and variably functionalized prior to being coupled to each other, allowing for maximum convergence. Second, many of the coupling reactions are tolerant to a variety of functional groups, thus minimizing protecting group strategies. Finally, a wide variety of Pd catalysts, possessing varying reactivities, have been developed. Several groups have engaged in the use of Pd-catalyzed reactions in the total synthesis of streptonigrin and analogues.[54] A major concern to be addressed in formation of the CD ring system is the sterically congested nature of the biaryl bond. Formation of this bond requires the use of sterically hindered, and thus presumably less reactive, coupling partners. The most significant results to date have been reported by Queguiner,[97] who showed that 4-bromopyridine **48** underwent Pd-catalyzed coupling with boronic acid **49** to afford biaryl **50** in 80% yield (Eq. 21). The nitro group was found to be essential in this process, as analogs of **48** that possessed a free amine or carbamate in place of the nitro functionality were shown to be unreactive. A similar approach which utilizes an Ullmann coupling has also been reported.[98]



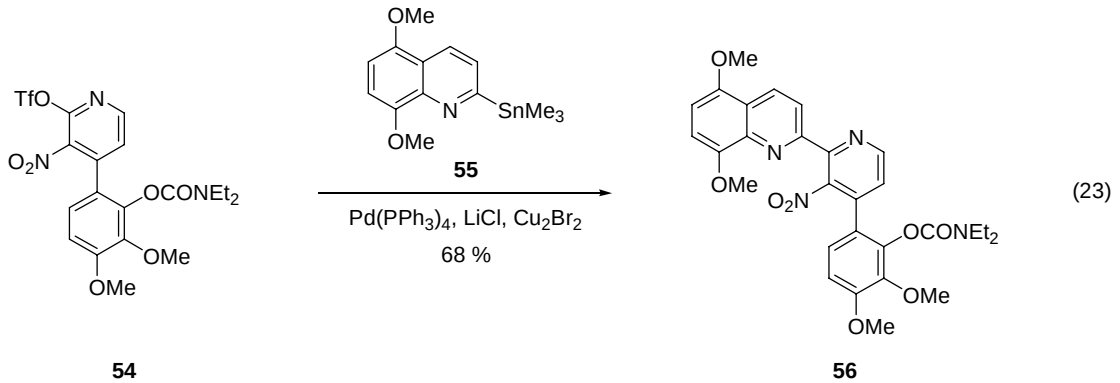
48 **50** (21)

Similarly, Hozapfel[99] reported that the reaction of 4-chloropyridine **51** with boronic ester **52** afforded the cross-coupled product **53** in 80% yield (Eq. 22). It is significant that the pyridyl chloride was sufficiently reactive in this process, as most Suzuki couplings require the use of the more reactive bromides or iodides. The ability to prepare more hindered derivatives of **51** has yet to be reported by these authors.



(22)

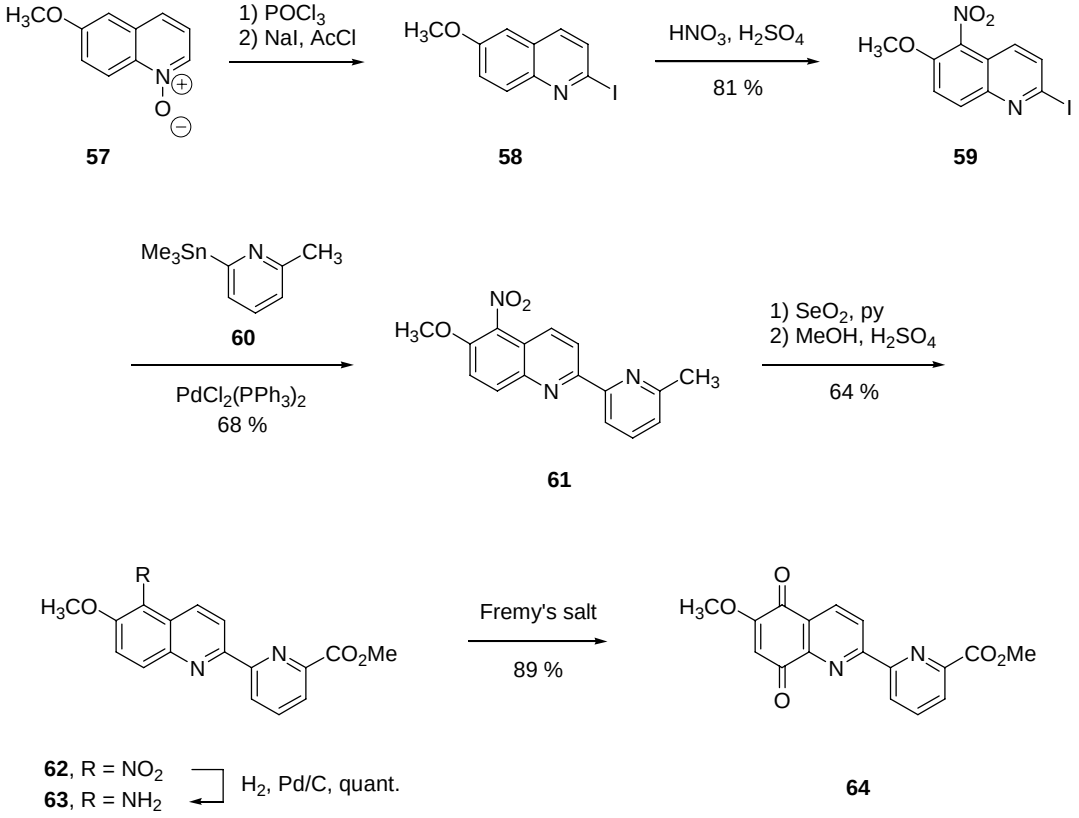
Several groups have also explored the use of Pd-catalyzed methods to prepare ABC analogues of streptonigrin. Queguiner[100] has demonstrated that the Stille coupling of quinoline stannane **55** with pyridyl triflate **54** gave the expected product in 68% yield (Eq. 23). Dimethoxy arene **56** could then be oxidized to its corresponding quinone.



(23)

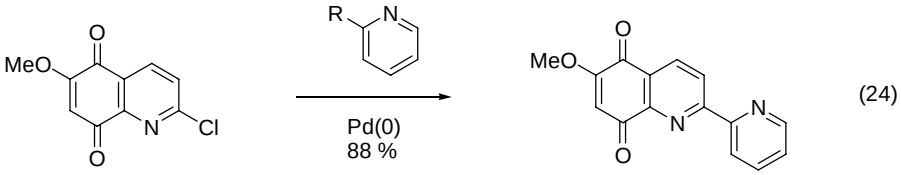
Harding[101] has developed an elegant approach to ABC analogues of streptonigrin (Scheme 9). Quinoline N-oxide **57** was converted to 2-iodoquinoline **58** via the intermediate chloroquinoline. Nitration, followed by Stille coupling with pyridyl stannane **60** gave biaryl **61** in good yield. Oxidation of the pyridine methyl group to its acid was accomplished upon treatment with SeO_2; the acid was subsequently converted to its methyl ester. After reduction of nitroquinoline **62**, the quinoline-5,8-dione functionality was obtained upon reaction with Fremy's salt.

Scheme 9



Finally, it has recently been reported that 2-chloroquinoline **65** underwent couplings with a variety of organoboranes and organostannanes.[102] Most significantly, adduct **66** could be prepared in high yield using this protocol (Eq. 24), although the use of a 5-

methyl pyridine derivative led to a marked decrease in yield. It is interesting to note that the quinone functionality did not adversely affect the coupling reaction.



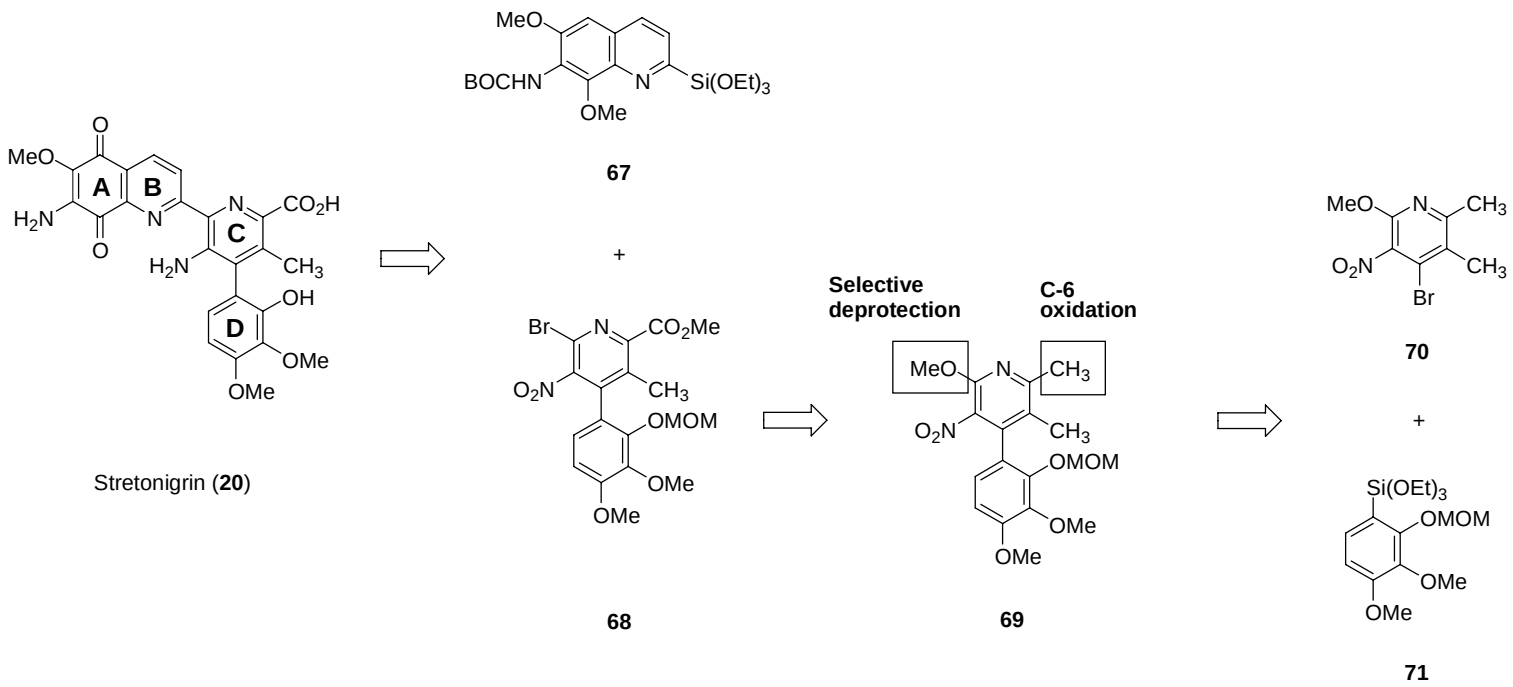
65 R = $B(OH)_2$, $SnMe_3$ **66** (24)

Results and Discussion

Synthesis of the Streptonigrin CD Biaryl

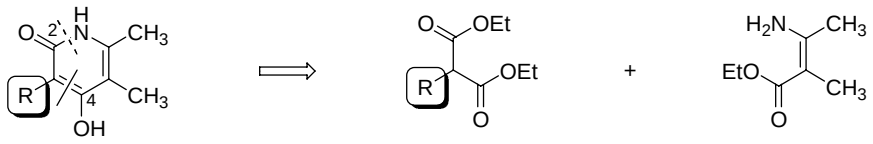
Our retrosynthetic analysis for streptonigrin (**20**) is depicted in Scheme 10. The tetracyclic core was to be established through the Pd-catalyzed coupling of quinoline siloxane **67** with 2-bromopyridine **68**. Conversion to the natural product would then be accomplished upon oxidation of the A ring to its *p*-quinone and global deprotection. 2-Bromopyridine **68** would in turn to be prepared from biaryl **69**. This strategy would require the development of methods for the selective deprotection of the C-2 methyl ether of the pyridine ring, while the C-6 methyl group of pyridine **69** could be converted to a benzylic alcohol through application of the well-known pyridine N-oxide rearrangement.[103] Further oxidation to the carboxylic acid would establish the functional group found in the natural product. Biaryl **69** was envisaged as the product of a Pd-catalyzed coupling of 4-bromopyridine **70** and aryl siloxane **71**. Successful implementation of this strategy would require the development of coupling conditions amenable to the synthesis of highly functionalized (and hindered) biaryls, as well as tolerant of the MOM ether *ortho* to a silicon-based functional group as in **71** (see Scheme 4).

Scheme 10


MeO
BOCHN
N
Si(OEt)3
OMe
67
+
Br
N
CO2Me
O2N
CH3
OMOM
OMe
OMe
68
Selective deprotection
C-6 oxidation
MeO
N
CH3
O2N
CH3
OMOM
OMe
OMe
69
MeO
N
CH3
O2N
CH3
Br
70
+
Si(OEt)3
OMOM
OMe
OMe
71
O
MeO
A
B
N
N
CO2H
C
H2N
CH3
H2N
OH
D
OMe
OMe
O
Stretonigrin (20)

The aforementioned coupling reaction to form the CD biaryl presents a major synthetic challenge. We decided to develop an approach to C ring coupling precursors that was amenable to the preparation of analogues, in order that the steric and electronic factors that influence the coupling reaction be investigated in a systematic manner (Scheme 11). The synthetic precursors for the study were to be 4-hydroxypyridones (**72**), as it was believed that the C-4 hydroxyl group and C-2 carbonyl of **72** could be independently manipulated. The pyridone would be prepared from condensation of amino ester **74** and diethyl malonate, or a derivative thereof (**73**).[104, 105] An attractive element of this strategy is that the C-3 substituent of pyridone **72** presents the opportunity for diversification, since the identity of this group may be easily controlled at the malonate stage (**73**).

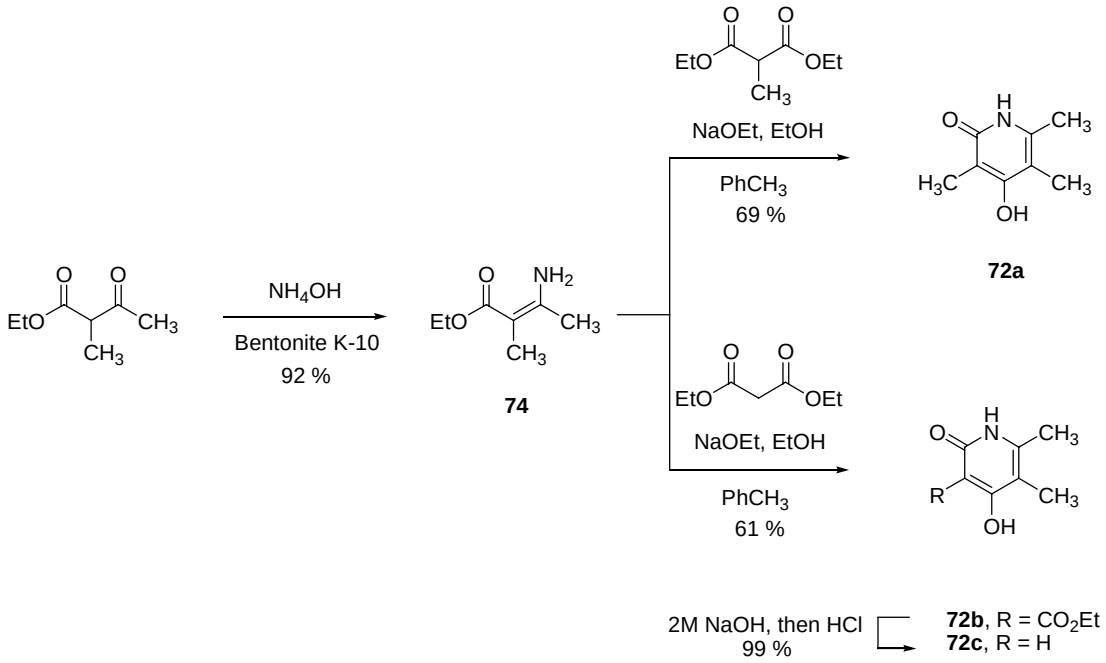
Scheme 11



72 **73** **74**

The preparation of a series of pyridones in which the C-3 substituent was varied was accomplished as shown in Scheme 12. Condensation of ethyl 2-methylacetoacetate and ammonium hydroxide gave enamine **74**. The use bentonite K-10 clay as a solid support allowed this reaction to be performed under mild conditions.[106] Base-promoted reaction of **74** with diethyl methylmalonate afforded methyl pyridone **72a**[104] in 69% yield.

Scheme 12

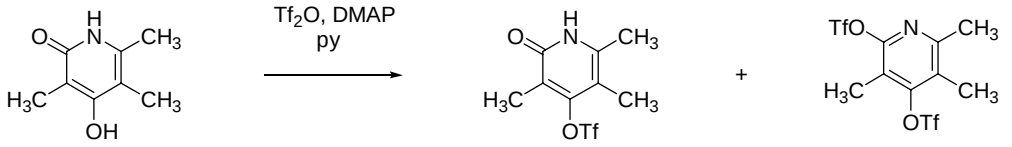


Ester pyridone **72b** was obtained in 61% yield upon condensation of enamine **74** with diethyl malonate. The ethyl ester was easily removed upon hydrolysis of **72b** followed by acid-promoted decarboxylation to give pyridone **72c**, which possesses a hydrogen at C-3.

Although not part of our retrosynthetic plan, the coupling reactions of pyridyl triflates derived from **72a** were briefly investigated (Scheme 13). Thus, reaction of **72a** under standard triflating conditions gave a mixture of mono-triflate **75** and bis-triflate **76**, obtained in 38 and 41% yield, respectively. Attempted couplings of **75** and **76** failed to give the desired adducts, due to facile hydrolyses of the fluorosulfonate ester

functionalities. Accordingly, no attempt was made to improve the selectivity of triflate formation, and triflates were excluded from further studies.

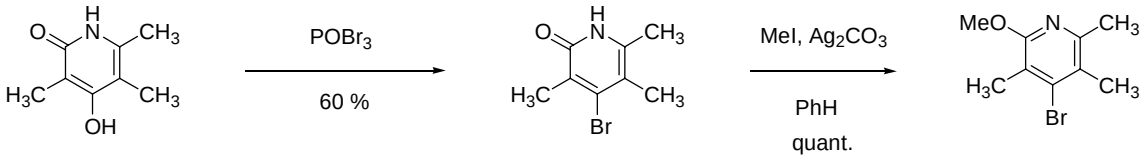
Scheme 13



72a **75**, 38 % **76**, 41 %

Hydroxypyridone **72a** was converted to bromopyridone **77** upon treatment with neat $POBr_3$, as previously reported (Scheme 14).[104] The cross-coupling of **77** with TBAT, as well as $PhSi(OMe)_3$, was investigated. Under all conditions the starting bromopyridone was recovered unchanged. The failure of this compound to undergo coupling is not surprising in consideration of the fact that previously reported couplings of 4-halopyridones have required prior protection of the N-H proton.[107] Accordingly, pyridones were excluded from further coupling studies.

Scheme 14

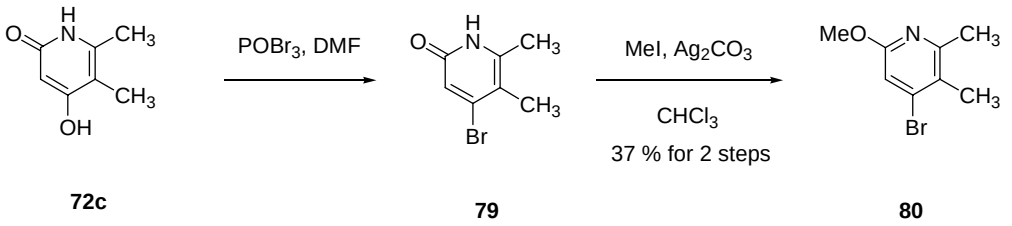


72a **77** **78**

The reaction of pyridone **77** with MeI using Ag_2CO_3 as the base gave pyridine **78** in quantitative yield, providing a species with which to investigate the coupling reaction (*vide infra*). Notably, the attempted protection of the pyridine as a benzyl ether or methoxymethyl ether proved unsuccessful.

The analogous replacement of the C-4 hydroxyl group of **72c** with a bromine substituent proved to be problematic, due in part to competitive bromination at C-2 (Scheme 15). After significant experimentation, it was found that reaction of **72c** with 0.70 equiv $POBr_3$ using DMF as the solvent led reproducibly to bromopyridone **79**. Although the bromopyridone could be purified, it was found more convenient to carry the crude material through the next step. Thus, methylation of the crude mixture gave pyridine **80** in 37% isolated yield over two steps.

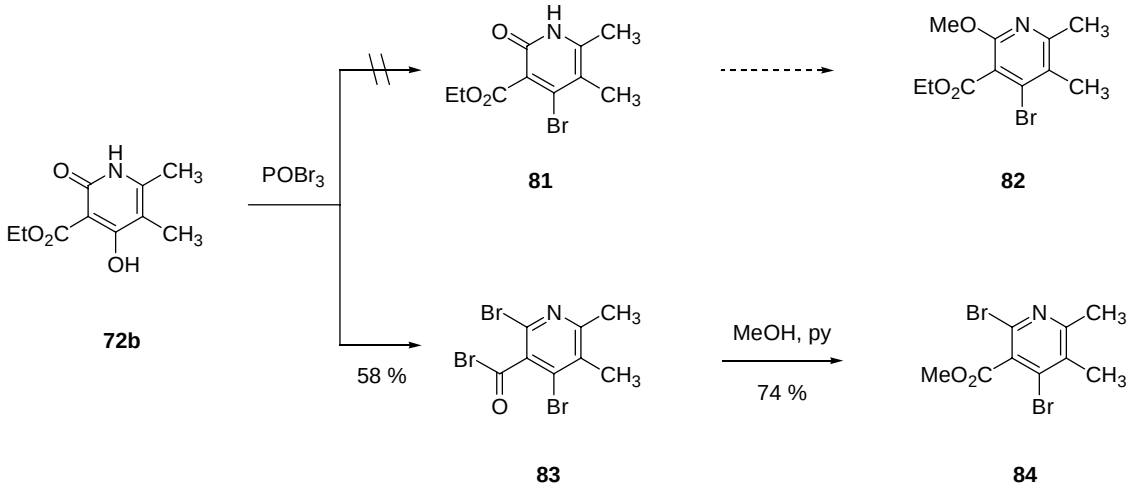
Scheme 15



The cross-coupling reactions of bromopyridines **78** and **80** were expected to provide information regarding steric effects in the coupling process. The cross-coupling of **82**, though, would present an opportunity examine the influence of electronic factors. More significantly, the ester functionality of **82** could in the future be converted to the amino group required for streptonigrin through a Curtius rearrangement. Thus, the synthesis of **82** emerged as the next challenge.

Much to our surprise, treatment of **72b** with $POBr_3$ gave not the expected bromopyridone **81**, but rather acid bromide **83** (Scheme 16). A variety of brominating reagents and reaction conditions were examined in an effort to prepare **81** to no avail. The regioselectivity issues of the bromination reaction were compounded by the (presumed) poor solubility of the desired product.

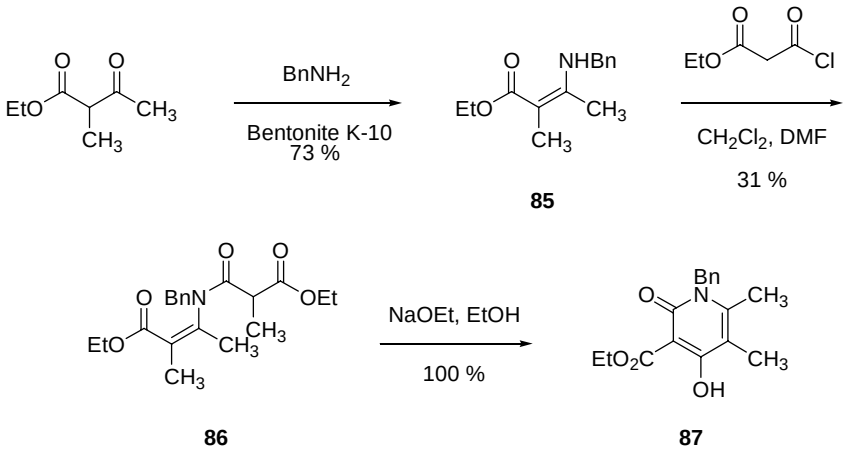
Scheme 16



Tribromide **83** did, however, prove useful. Conversion of **83** to its methyl ester **84** proceeded smoothly, allowing for an investigation into whether 2,4-dibromopyridine **84** would undergo regioselective Pd-catalyzed cross-coupling. Under a variety of coupling conditions, however, complex mixtures of products were obtained, and this strategy was not pursued further.[108]

It was hoped that the protection of the N-H proton of **72b** prior to bromination would improve the regioselectivity of the reaction, as well as the solubility of the desired product. Accordingly, N-benzyl pyridone **87** was prepared as described in Scheme 17. Condensation of ethyl 2-methylacetoacetate with benzylamine gave enamine **85** in 73% yield. Acylation with ethyl chloromalonate,[109] followed by base induced ring closure delivered the desired N-benzyl pyridone **87**. Numerous attempts to replace the hydroxyl group of **87** with a bromine substituent were unsuccessful. The ethyl ester was found to be labile under the reaction conditions, and the hydroxyl group proved to be unreactive.

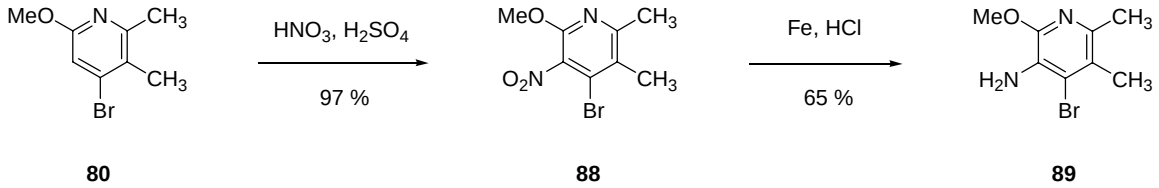
Scheme 17



The synthesis of bromopyridine **82** was clearly problematic, and the preparation of a more accessible species was explored. Our initial interest in **82** had rested on two factors: first, the compound contains an electron-withdrawing group at the C-3 position, which would allow for information regarding electronic effects in the coupling process to be obtained; second, the ester substituent could be ultimately be converted to an amino group required for the synthesis of streptonigrin. Since nitropyridine **88** possesses both of these attributes, it represented a suitable alternative to **82** and became the next synthetic target.

Gratifyingly, pyridine **88** was obtained in near quantitative yield upon nitration of pyridine **80** (Scheme 18). As stated above, the nitro group would allow for an immediate investigation into the electronic factors that influence the coupling reaction. Additionally, this substituent was to serve as a gateway to several other nitrogen containing functional groups, as **88** was readily reduced to the corresponding amine **89**, which could then be protected in a variety of manners.

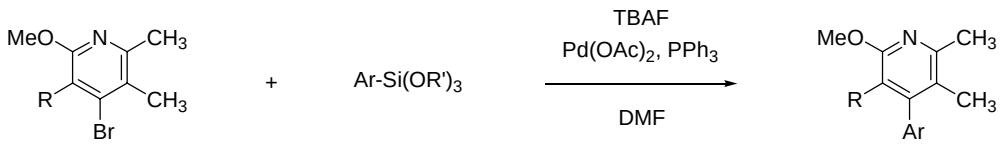
Scheme 18

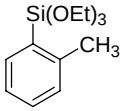
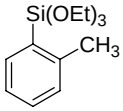
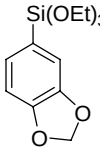


80 **88** **89**

With several 4-bromopyridine derivatives in hand, an investigation into their reactivities in the cross-coupling process was undertaken (Table 1). Coupling reactions were performed under identical conditions employing 20 mole % $Pd(OAc)_2$ and 40 mole % PPh_3. Two equivalents of aryl siloxane and TBAF were used, and all reactions were conducted at 80 °C with DMF as the solvent. The coupling of pyridine **80** was investigated first, since this is the least sterically hindered of the bromopyridine series. The Pd-catalyzed reaction of **80** and $PhSi(OMe)_3$ gave an excellent yield of the expected adduct (Table 1, entry 1). However, the reaction of **80** with *o*-methyl siloxane **90**[110] gave only a 10% yield of the desired product (entry 2); the remainder of the mass balance was reduced (hydrodebrominated) pyridine. This result was somewhat surprising since it had previously been shown that siloxane **90** underwent coupling with bromobenzene in good yield.[111]

In order to further assess the steric tolerances of the coupling reaction, the coupling of trimethylbromopyridine **78** was examined. The Pd-catalyzed reaction of **78** and $PhSi(OMe)_3$ gave an 89% yield of the coupled adduct **91**, while reaction of **78** and *o*-methyl siloxane **90** provided only 10% of the desired biaryl product (**92**) (entries 3 and 4, respectively). These results are similar to those obtained with bromopyridine **80**, and demonstrate that *ortho*-disubstituted bromopyridines are suitable coupling partners.



Entry	R	Ar-Si(OR')$_3$	yield (%)
1	H, **80**	PhSi(OMe)$_3$	97
2	H, **80**	 **90**	10[a]
3	Me, **78**	PhSi(OMe)$_3$	89
4	Me, **78**	 **90**	10[a]
5	Me, **78**	 **93**	61
6	NH_2, **89**	PhSi(OMe)$_3$	0[b]
7	N_3, **94**	PhSi(OMe)$_3$	0[c]
8	NHAc, **95**	PhSi(OMe)$_3$	0[a]
9	NHBOC, **96**	PhSi(OMe)$_3$	0[d]
10	NO_2, **88**	PhSi(OMe)$_3$	36[a]

[a]the remainder of the mass balance was reduced bromopyridine. [b]the starting pyridyl bromide was recovered unchanged. [c]the reaction gave only residual tar. [d]the BOC group was cleaved

Table 1. Cross-coupling reactions of 4-bromopyridine derivatives with various siloxanes.

The reaction of bromopyridine **78** with methylenedioxy siloxane **93**[112] gave a 61% yield of coupled product (entry 5), indicating that the coupling additionally allows for electron-rich arylsiloxanes to be employed. This was a significant finding since the substitution pattern found in siloxane **93** resembles the D ring of streptonigrin.

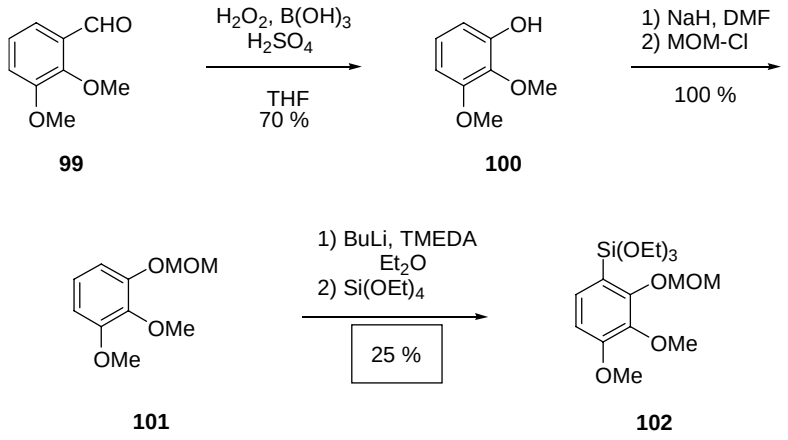
The couplings of 4-bromopyridines possessing various nitrogen containing substituents in the C-3 position allowed for an investigation into the electronic factors that govern the reaction. Analogues containing the amino (entry 6), azido (entry 7), and protected amino (entries 8 and 9) functionalities at C-3 failed to yield coupled adduct upon reaction with $PhSi(OMe)_3$. However, reaction of nitropyridine **88** and $PhSi(OMe)_3$ gave a 36% yield of the desired product (**97**, entry 10), as well as 36% of reduced pyridine **98** (*vide infra*).

The fact that nitropyridine **88** underwent successful coupling (albeit with a simple arylsiloxane) was a pivotal result as it validated our overall synthetic strategy for the preparation of streptonigrin. The low yield observed in the reaction was disappointing, but it was hoped that the coupling with more functionalized arylsiloxanes would provide more satisfactory results. Thus, the coupling of nitropyridine **88** with siloxane derivatives was investigated.

Siloxane **102** was prepared as outlined in Scheme 19. Dakin oxidation of benzaldehyde **99** gave phenol **100** in good yield,[113] which was then converted to its MOM ether **101**. In addition to protecting the phenol, the MOM group was to be employed in a directed metallation to prepare siloxane **102**.[43] In the event, treatment of **101** with BuLi followed by trapping of the organolithium with $Si(OEt)_4$ provided

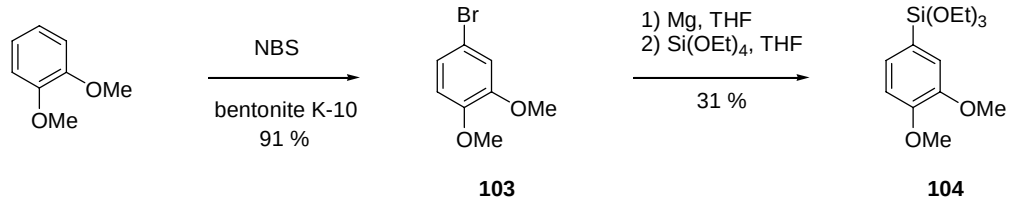
siloxane **102** in 25% yield. The yield for this reaction was somewhat less than expected based on previous results.

Scheme 19



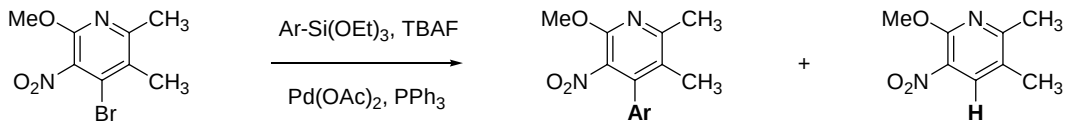
Veritrole siloxane **104** was obtained as described in Scheme 20. Selective of veritrol was accomplished using NBS and bentonite K-10 clay as a solid support.[114] Conversion of bromide **103** to its organomagnesium derivative, followed by reaction with $Si(OEt)_4$ gave siloxane **104** in 31% yield.

Scheme 20

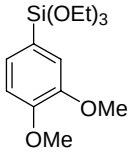
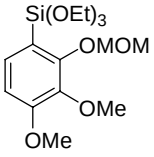
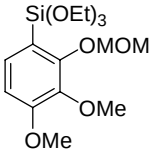


Results of siloxane-based coupling reactions between bromopyridine **88** and streptonigrin D ring analogues are presented in Table 2. The reaction of **88** with $PhSi(OMe)_3$ gave a 36% yield of the coupled product and 36% of reduced pyridine **96** (Table 2, entry 1), as previously stated. The reaction of **88** with veritrole siloxane **104** (entry 2) resulted in the formation of 21% coupled adduct, along with 17% of reduced

pyridine **98**. Although the yields obtained using this siloxane are slightly lower than with $PhSi(OMe)_3$, the ratios of coupled to reduced product are comparable. Reaction of bromopyridine **88** with siloxane **102**, using 20 mole % catalyst, resulted in the exclusive formation of the reduced pyridine **98** (entry 3). This was not unexpected given the previous observation that aryl siloxanes that possess an oxygen atom *ortho* to silicon undergo rapid protodesilylation under the reaction conditions. In the absence of a competent coupling partner, **88** would then be expected to undergo reduction. It was surprising that the even when a stoichiometric amount of Pd reagent[111] was employed for the coupling of bromopyridine **88** and siloxane **102** reduced pyridine **98** was the sole reaction product (entry 4). This result underscores the reluctance of aryl siloxanes possessing heteroatoms in the *ortho* position to undergo Pd-catalyzed couplings.



88 **98**

entry	Ar-Si(OEt)$_3$	Yield of coupled product (%)	Yield **98** (%)
1[a]	PhSi(OEt)$_3$	36	36
2[a]	 **104**	21	17
3[a]	 **102**	-	only product observed[c]
4[b]	 **102**	-	only product observed[c]

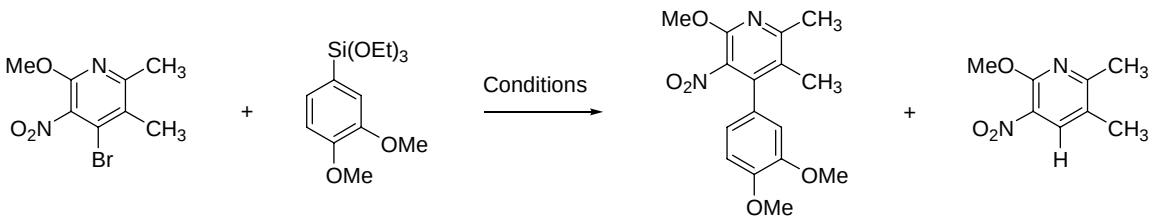
[a]the coupling was performed using 20 mole % $Pd(OAc)_2$. [b]the coupling was performed using 100 mole % Pd $(OAc)_2$. [c]the product composition was estimated by crude NMR.

Table 2. Cross-coupling reactions of bromopyridine **88** with various siloxanes.

It is well known that the nature of the Pd catalyst and its ligands have a dramatic effect on cross-coupling reactions, and alternative catalyst systems were examined in an effort to improve the ratio of coupled to reduced products with regard to coupling reactions of bromopyridine **88** (Table 3). Veritrole siloxane **104** was selected as the coupling partner

for this catalyst study, as the substitution pattern found on the aryl ring resembles that of streptonigrin's D ring. Additionally, this reaction under previously developed conditions had been shown to give only modest yields (*vide supra*), and presented the opportunity for improvement.

As previously stated, when catalyzed by $Pd(OAc)_2$ and PPh_3, the reaction of bromopyridine **88** with siloxane **104** gave a 1:1 ratio of the biaryl adduct **105** and reduced pyridine **98** (Table 3, entry 1). The isolated yields of the two reaction products for this and subsequent entries were not measured; rather their ratios were determined by GC analysis. Substitution of the more sterically hindered phosphines $Pd(t\text{-}Bu)_2(o\text{-biphenyl})$ or $PdCy_2t\text{-}Bu$ for PPh_3 was examined (entries 2 and 3), as these phosphines had previously been shown to be effective catalyst activators in recalcitrant cross-couplings.[115, 116] Unfortunately, no changes in the product compositions were observed. The use of imidizolium salt **106** was also explored (entry 4), as this ligand had been shown to be exceptionally active in Pd-catalyzed cross-couplings.[117] However, this alteration similarly afforded no improvement in the coupling reaction.



88 **104** **105** **98**

Entry	Conditions	Ratio **105** : **98**[a]
1	TBAF, Pd(OAc) PPh_3, DMF	1:1
2	TBAF, $Pd(OAc)_2$ P(*t-Bu)*$_2$(*o*-biphenyl), DMF	1:1
3	TBAF, $Pd(OAc)_2$ PCy_2*t*-Bu, DMF	1:1
4	TBAF, $Pd(OAc)_2$  **106** 1,4-dioxane	1:2
5	TBAF, $Pd(dba)_2$ PPh_3, THF	only reduced
6	TBAF, $Pd(PPh_3)_2Cl_2$ MeCN	only reduced
7	TBAF, $Pd(PPh_3)_4$ THF	3:1
8	TMAF $3H_2O$, $Pd(OAc)_2$ PPh_3, DMF	only reduced

[a]product composition was determined by GC analysis.

Table 3. Effect of catalyst system on the cross-coupling of bromopyridine **88** with siloxane **104**.

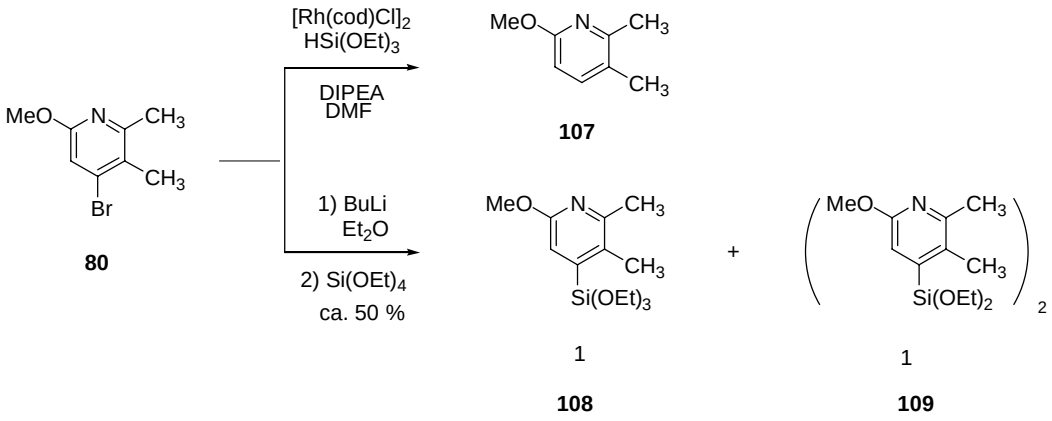
The use of alternative Pd catalysts in the siloxane couplings was investigated also. Switching from $Pd(OAc)_2$ to $Pd(dba)_2$ (entry 5) or $Pd(PPh_3)_2Cl_2$ (entry 6) gave reduced pyridine **98** as the sole product. Encouraging results were, however, obtained using of $Pd(PPh_3)_4$ as the catalyst (entry 7). These conditions provided a 3:1 ratio of coupled product to reduced pyridine, as determined by GC, although the isolated yield of coupled product was only 26%. Several other products derived from bromopyridine **88** were observed in the ^1H NMR spectrum of the crude reaction mixture. The use of tetramethylammonium fluoride as the activator[118] (entry 8) gave only reduced product **98**.

The couplings of 4-bromopyridines and appropriately functionalized D-ring siloxanes had thus far not provided satisfactory results. It was thought the alternative coupling combination of a pyridyl siloxane and D-ring halide might offer an improvement. This approach was probed using pyridyl siloxane **108**, which was chosen since it possesses only a single (non-hydrogen) *ortho* substituent to silicon.

Treatment of bromopyridine **80** under Masuda's previously defined hydrosilylation conditions[119] gave none of the desired siloxane; instead only reduced pyridine **107** was obtained (Scheme 21). Lithium-halogen exchange, however, proved fruitful. Reaction of **79** with *n*-BuLi and trapping of the resultant aryllithium with $Si(OEt)_4$ gave siloxanes **108** and **109** in approximately a 1:1 ratio and combined 50% yield.[120] Diaryl siloxane **109** is the result of multiple additions of the organolithium to $Si(OEt)_4$, and its presence as a reaction product underscores the heightened reactivity of the organolithiums derived from halopyridines. These findings are consistent with previous observations regarding 3-bromopyridine derivatives.[110] The mixture of **108** and **109** proved difficult to separate,

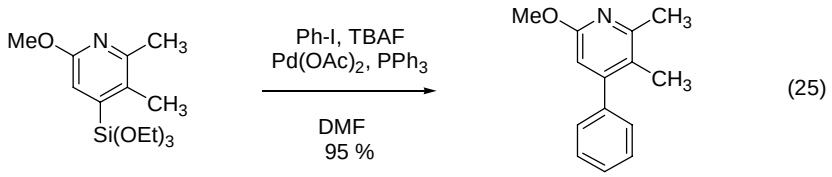
and inasmuch as both were expected to be capable of aryl group transfer,[111] the mixture was taken to the next step.

Scheme 21



80 **107** **108** **109**

The competency of the mixture of siloxanes **108** and **109** to undergo the coupling reaction was first verified upon Pd-catalyzed reaction with iodobenzene, which afforded biaryl product **110** in excellent yield (Eq. 25).

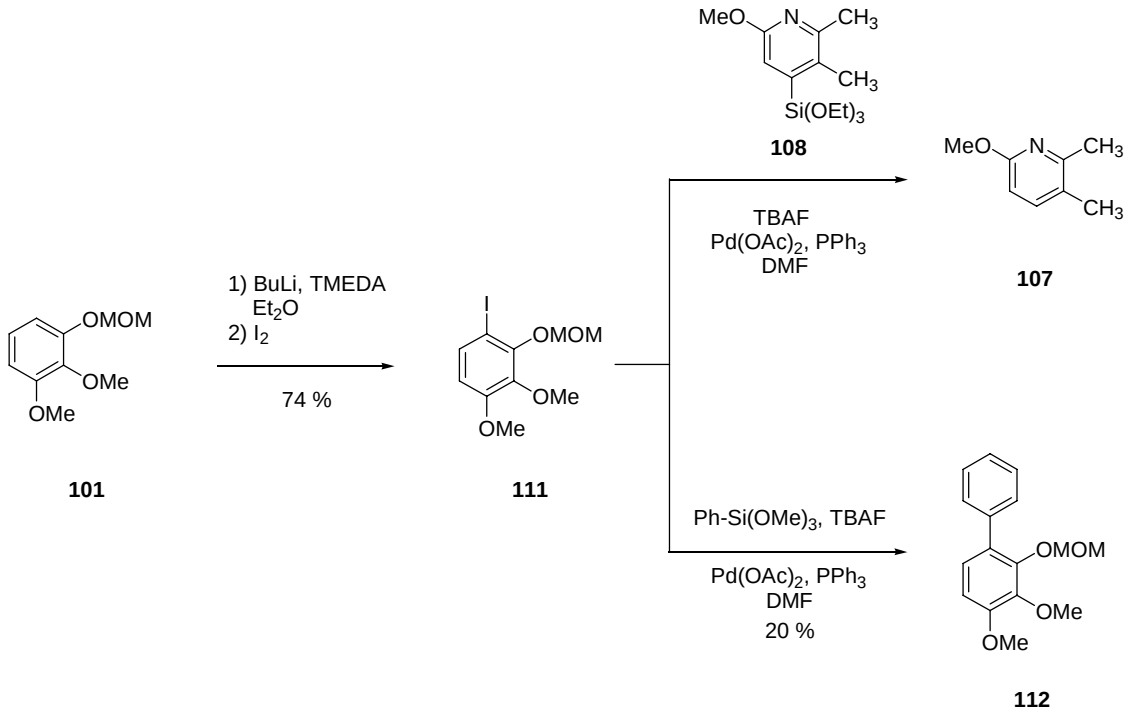


108 **110** (25)

The reaction of siloxanes **108** and **109** with streptonigrin D ring precursor **111**, prepared as previously reported,[99] gave none of the cross-coupled product; rather reduced pyridine **107** was obtained (Scheme 22). In contrast, iodobenzene **111** was found to undergo successful coupling with the less hindered $PhSi(OMe)_3$. The isolated yield for the reaction was only 20%; however, the remainder of the mass balance was a mixture of coupled adduct **112** and reduced D ring analogue **101**, indicating this reaction was

effective to some extent. The fact that pyridyl siloxane **108** and iodide **111** each underwent cross-coupling with unsubstituted partners, but not with each other, further demonstrates the sensitivity of the cross-coupling reaction to the steric environment possessed by both reacting partners.

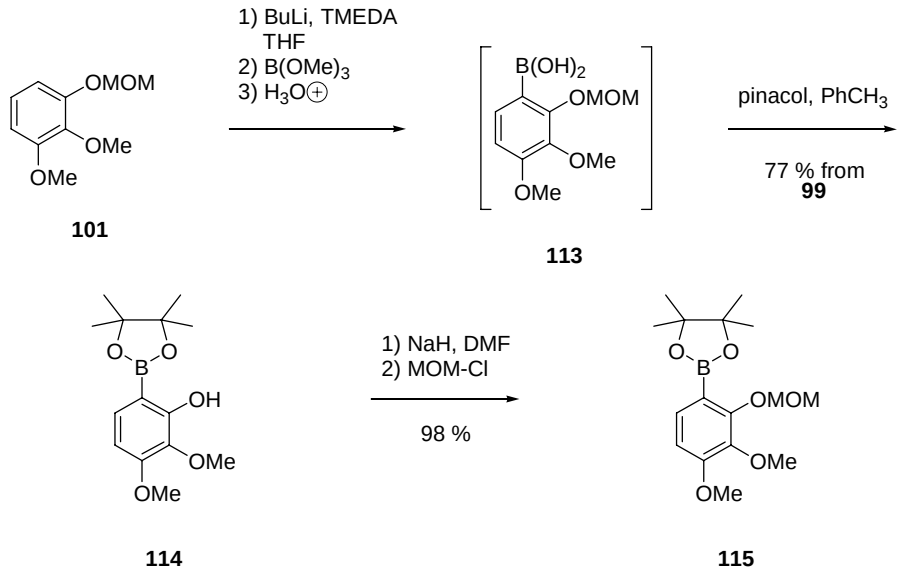
Scheme 22



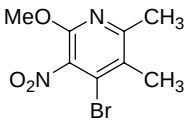
The difficulty experienced in preparing the streptonigrin CD skeleton using the siloxane technology led us to wonder if this unit may better be synthesized using another coupling method. In particular, the use of organoboron reagents was explored. Boronic acid **113** and boronic ester **115** were prepared as shown in Scheme 23. Directed *ortho*-metallation of arene **101**, followed by reaction with $B(OMe)_3$ and then aqueous acid gave boronic acid **113**.[99] Due to its expected instability, this species was not isolated but rather the crude reaction mixture used directly in subsequent studies. Transformation of **113** to

the corresponding pinacol boronic ester unexpectedly occurred with concomitant hydrolysis of the MOM ether, thus requiring a reprotection step to generate **115**.

Scheme 23

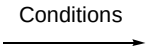


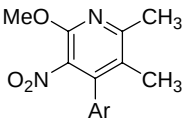
The Pd-catalyzed cross-coupling of bromopyridine **88** with a variety of arylating agents was investigated (Table 4). For reference, the coupling of **88** with $PhSi(OMe)_3$ afforded 36% yield of the cross-coupled product and 36% of the reduced pyridine (Table 4, entry 1). Reaction of **88** with TBAT, however, gave a 67% yield of the biaryl product (entry 2). No evidence of reduced pyridine **98** was observed in this reaction.



88

+ Arylating Agent





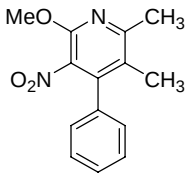
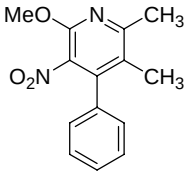
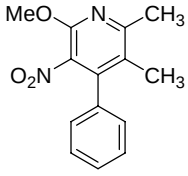
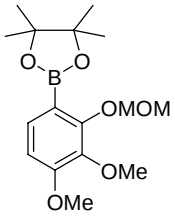
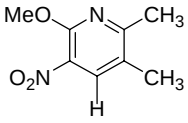
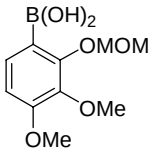
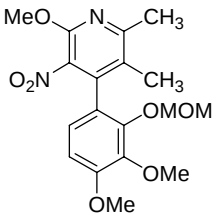
entry	Arylating Agent	Conditions	Product	Yield (%)
1	Ph-Si(OMe)$_3$	TBAF Pd(OAc)$_2$, PPh$_3$ DMF		36
2	TBAT	Pd(OAc)$_2$, PPh$_3$		67
3	Ph-B(OH)$_2$	Pd(PPh$_3$)$_4$, Na$_2$CO$_3$ PhCH$_3$, EtOH, H$_2$O		80
4	 **115**	Pd(PPh$_3$)$_4$, Na$_2$CO$_3$ PhCH$_3$, EtOH, H$_2$O		-
5	 **113**	Pd(PPh$_3$)$_4$, Na$_2$CO$_3$ PhCH$_3$, EtOH, H$_2$O	 **69**	78

Table 4. Cross-coupling reactions of bromopyridine **88** with various arylating agents.

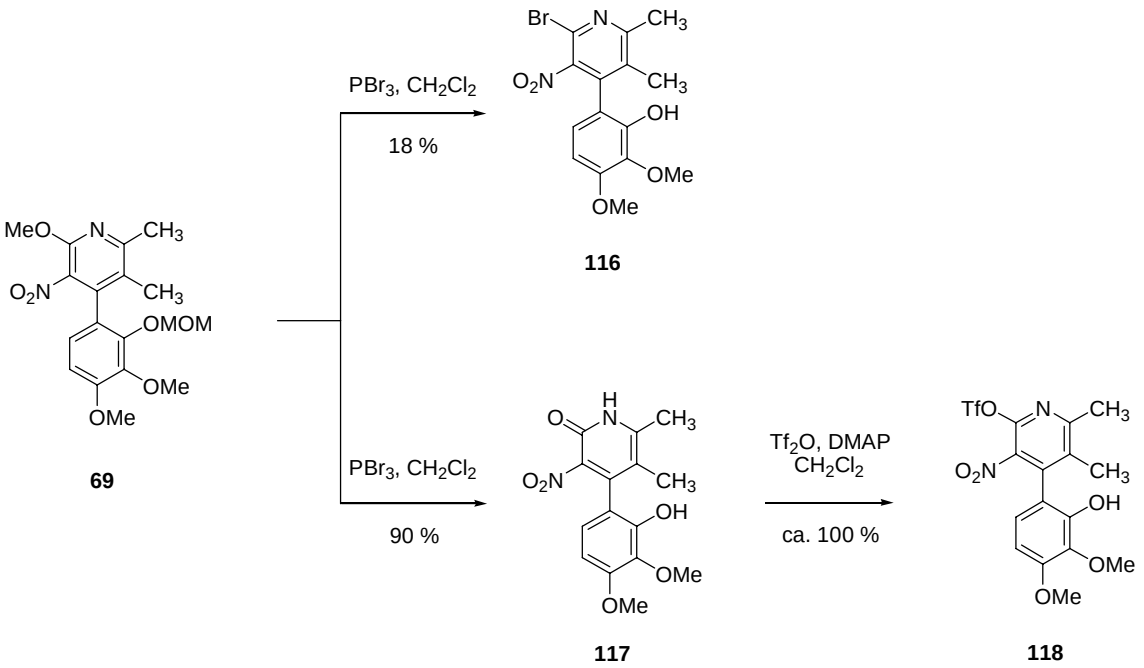
The results in entries 1 and 2 were significant in light of the fact that cross-coupling reactions of aryl siloxanes such as $PhSi(OMe)_3$ require the addition of TBAF as an external activator, whereas couplings of TBAT do not. Since TBAF is available commercially as a 1 M solution in THF and contains ca. 5% water, it seems likely that the water in the TBAF provides the hydrogen atom necessary for the reduction pathway. Notably, other anhydrous fluoride sources such as CsF and KF have proven ineffective as activators in the coupling process.[111]

The coupling of bromopyridine **88** with $PhB(OH)_2$ under typical Suzuki conditions [$Pd(PPh_3)_4$, Na_2CO_3, $PhCH_3$, EtOH, H_2O] afforded an 80% yield of the biaryl product (entry 3). Again, no evidence of reduced pyridine **98** was observed, and the yield obtained is comparable to that observed when TBAT is employed the phenylating agent. The use of more substituted organoboranes was examined: reaction of **88** with pinacol borate **115** gave reduced pyridine as the sole reaction product; no cross-coupled adduct was detected (entry 4). This was surprising given that the unsubstituted boronic acid had undergone coupling with **88** in high yield. We wished to explore whether the discrepancy in the two reactions was the result of varying functionalities at boron (boronic acid vs. boronic ester), or the different substitution patterns of the aromatic rings. Reaction of bromopyridine **88** with boronic acid **113** resulted in the exclusive formation of the cross-coupled product, which was isolated in 78% yield. Of note is the fact that the crude boronic acid, obtained as described in Scheme 23, was used directly in the latter reaction; no further purification of this reagent was necessary.

Two issues remained to be addressed prior to the union of the CD and AB ring systems. First, the C-6 methyl group of the pyridine ring of **69** required oxidation to its acid; second, the C-2 methoxy of the pyridine ring needed to be converted to a halogen (or triflate), thus setting the stage for the second cross-coupling. This latter transformation was examined initially.

The original strategy was to convert the C-2 methoxy group of pyridine **69** into a bromide in a single chemical operation (Scheme 24). However, reaction of **69** with PBr_3 in refluxing CH_2Cl_2 gave only an 18% yield of the desired bromide **116**, with the remainder of the mass balance attributed to pyridone **117**. Longer reaction times and larger excesses of PBr_3 afforded no improvement in yield. Similarly, change of solvent or substitution of the more reactive $POBr_3$ as the brominating agent proved unsuccessful in preparation of bromopyridine **116**.

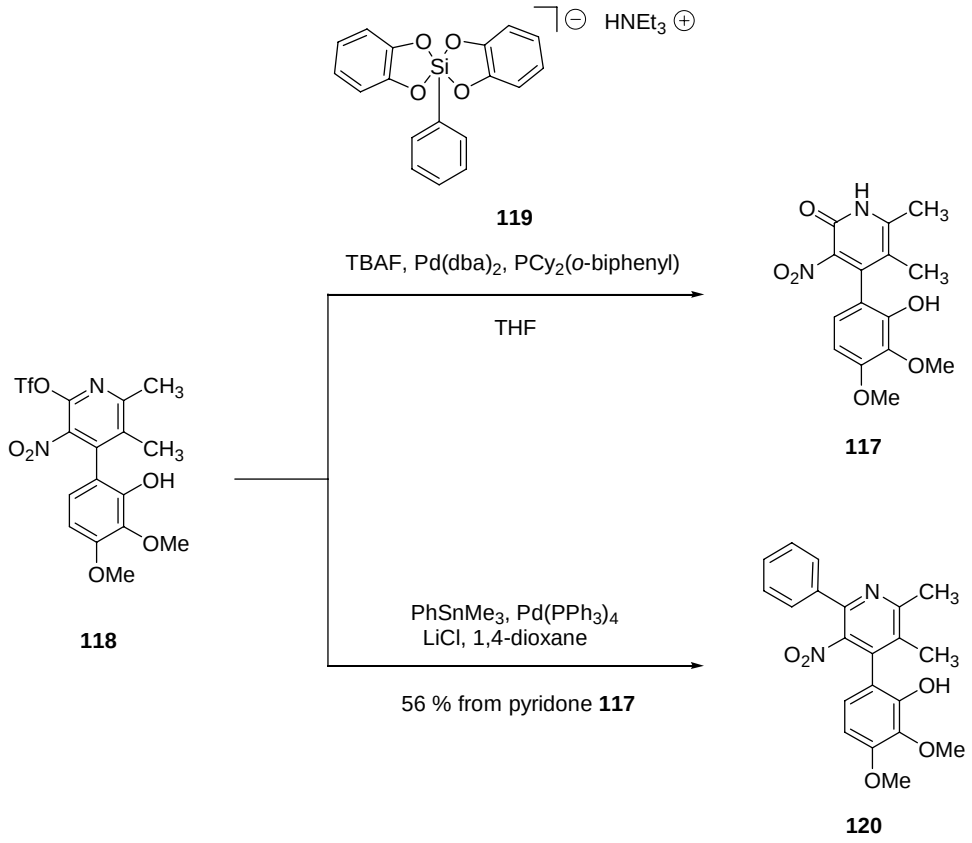
Scheme 24



Pyridone **117**, however, proved valuable inasmuch as this compound could readily be converted to triflate **118**. In the event, careful monitoring of the reaction of **69** with PBr_3 allowed for the isolation of pyridone **117** in 90% yield. This compound underwent facile reaction with Tf_2O under standard conditions to deliver pyridyl triflate **118**. Due to its expected sensitivity, triflate **118** was not purified, although analysis of the reaction by TLC indicated the conversion to be quantitative.

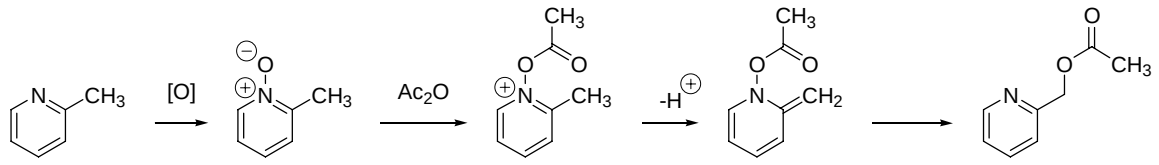
The Pd-catalyzed cross-coupling of triflate **118** was investigated next. Previous studies had demonstrated that triflates are poor coupling partners for use in the siloxane-based strategy, since this functional group undergoes rapid hydrolysis under the basic reaction conditions. Seganish and DeShong,[121] have shown, however, that aryl biscatechol silicates are capable of undergoing Pd-catalyzed group transfer to aryl triflates, with a minimal amount of accompanying triflate hydrolysis. Treatment of triflate **118** with silicate **119**,[121] under previously defined conditions, unfortunately gave pyridone **117** as the sole reaction product (Scheme 25). The high electrophilicity possessed by the sulfur atom of triflate **118**, imposed by the alkoxy pyridine ligand, presumably renders this triflate more susceptible to hydrolysis than those previously examined. Triflate **118** did, however, undergo Stille coupling with $PhSnMe_3$ to provide triaryl **120** in 56% yield from pyridone **117**. This finding demonstrated, in principle, the viability of our synthetic strategy.

Scheme 25



Since the cross-coupling strategy to join the AB and CD ring systems appeared feasible, oxidation of the pyridine C-6 methyl group of **69** to its carboxylic acid (the functional group present at this position in streptonigrin) was explored. This transformation would represent the last major hurdle to be overcome prior to formation of the tetracyclic core, and our intention was to convert **69** to its N-oxide, followed by application of the pyridine N-oxide rearrangement.[103] This strategy has been executed during the course of numerous natural products syntheses, including streptonigrin,[94] and an overview is presented in Scheme 26.

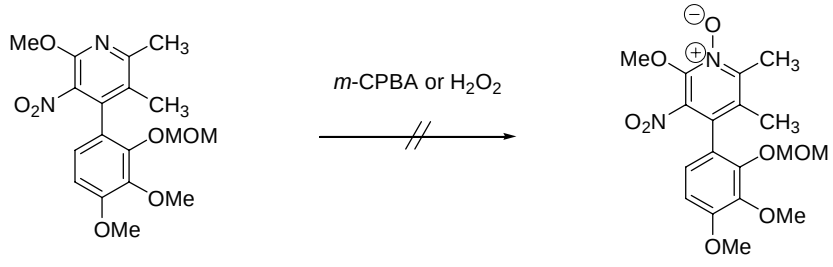
Scheme 26



121 **122** **123** **124** **125**

The conversion of 2-methylpyridine (**121**) to its N-oxide **122**, followed by treatment with Ac_2O, is known to give acetate **125**. The latter reaction is thought to proceed via initial O-acylation of **122** to give pyridium ion **123**. Loss of a proton to form **124**, followed by acetate transfer from oxygen to carbon restores aromaticity and yields acetate **125**. The acetate transfer may be intra- or intermolecular.[122]

Conversion of pyridine **69** to its N-oxide **126** was investigated (Eq. 26). Attempted oxidation with *m*-CPBA and H_2O_2/HOAc proved ineffective, as the starting pyridine was recovered unchanged from the reaction mixture. It was believed that the electron-withdrawing effect of the nitro group of **69** was limiting the nucleophilicity of the pyridine.

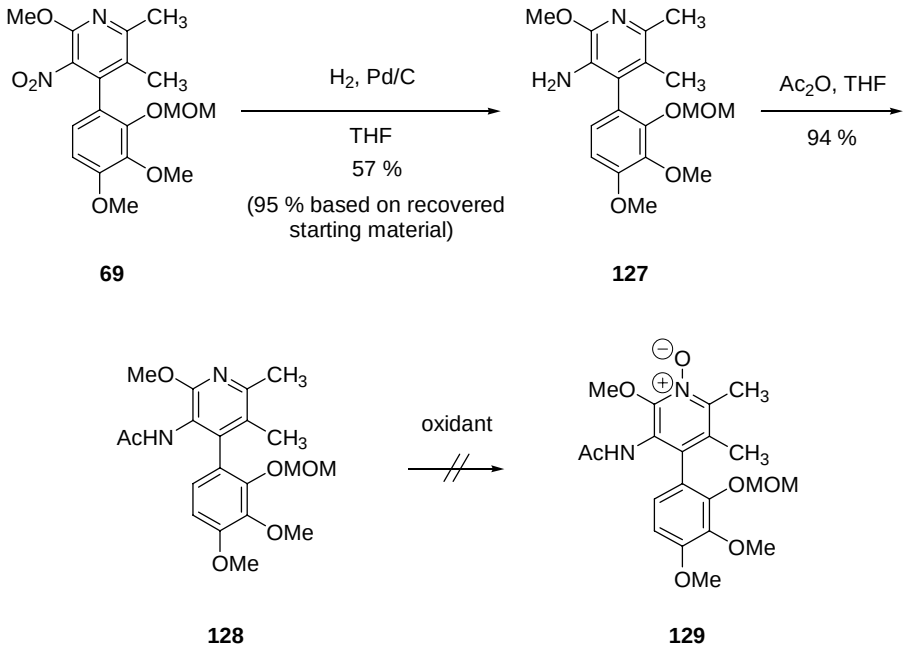


69 **126** (26)

A series of nitro analogues of **69** were prepared and examined for their abilities to undergo the oxidation (Scheme 27). Reduction of nitropyridine **69** with H_2 and Pd/C provided aminopyridine **127** in 57% yield (95% based upon recovered starting material). Attempted oxidation of **127** with *m*-CPBA led only to decomposition products, which

was not surprising given the known reactivity of the free amino group towards oxidants.[123, 124] Protection of the amino group of **127** proceeded uneventfully to afford acetamide **128**, which similarly proved unreactive at room temperature to *m*-CPBA or H_2O_2. If more forcing conditions were applied using these reagents decomposition of **128** was observed. Other oxidants surveyed for use with pyridine **128** included oxone[125] and trifluoroperoxyacetic acid;[94] in both cases the starting pyridine was recovered unchanged.

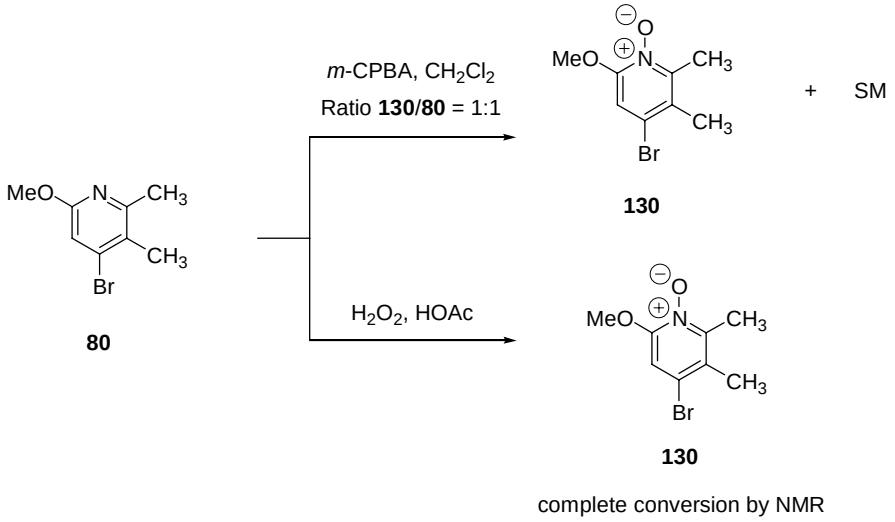
Scheme 27



It was unclear whether the lack of reactivity of pyridines **69** and **128** to oxidation was the result of the electron-withdrawing nature of the pyridine C-3 substituent (whether it be nitro or acetamido), or another unconsidered structural feature. To address this, the oxidation was attempted with pyridine **80**, which possesses a hydrogen substituent at C-3 (Scheme 28). Treatment of **80** with *m*-CPBA gave a mixture of N-oxide **130** and

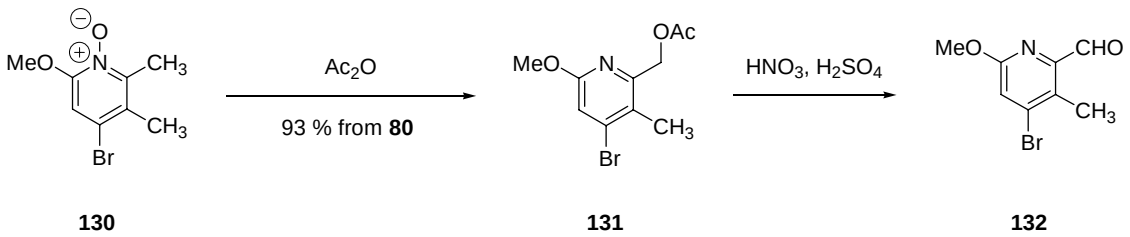
unreacted starting material, which were obtained in a 1:1 ratio. This reaction will not go to completion. Larger excesses of *m*-CPBA, higher temperatures, or longer reaction times led to no improvement in the ratio of **130** to **80**.

Scheme 28



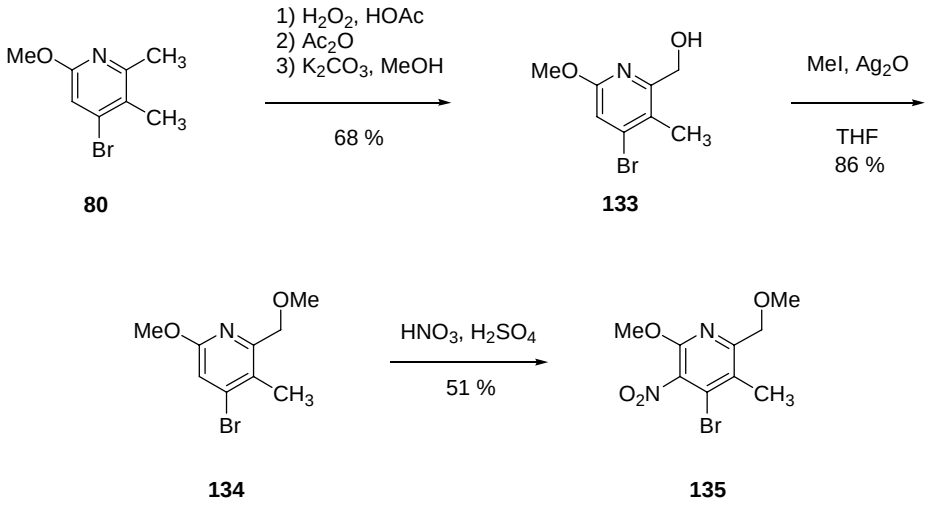
Gratifyingly, when performed with 1.5 Eq. of H_2O_2 and HOAc as the solvent, the oxidation of **80** led reproducibly to N-oxide **130**. Analysis of the crude reaction mixture by ^{1}H NMR indicated complete conversion to the N-oxide. This species was not isolated, but was treated immediately with Ac_2O to give rearranged product **131** in 93% yield over two steps (Scheme 29).

Scheme 29



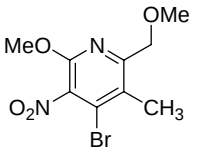
With acetate **131** in hand the sequence of transformations that would deliver the fully functionalized CD biaryl required for our synthesis could be explored. One possible route would first incorporate the nitrogen functionality at the C-3 position of **131**, and then commence with coupling studies and manipulations involving the acetate. Much to our surprise, however, treatment of **131** under previously developed nitrating conditions gave aldehyde **132** as the major product. This species presumably results from hydrolysis of the acetate functional group, followed by nitric acid-promoted oxidation of the resulting primary alcohol.[126] Given the electron-withdrawing nature of the aldehyde substituent of **132**, it is understandable why this compound is reluctant to undergo electrophilic nitration at C-3. Similarly, attempted nitration of alcohol **133**, prepared from methanolysis of acetate **131** (Scheme 30), produced aldehyde **132** as the major product. Attempted nitration of N-oxide **130** also proved fruitless. It was clear that an acid-stable protecting group for the 1° alcohol of **133** would be required to effect nitration.

Scheme 30



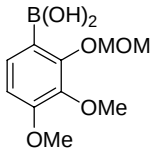
Several derivatives of alcohol **133**, possessing various protecting groups for the hydroxyl functionality, were prepared and their relative abilities to undergo the nitration examined. The best results were obtained using methyl ether **134**, synthesized upon reaction of alcohol **133** with MeI and Ag_2O. Notably, installation of the methyl ether from **133** employing NaH as the base gave less satisfactory results. Nitration of **134** under previously defined conditions gave nitropyridine **135** in modest 51% yield. It is unclear why the yield of this nitration reaction is not as high as that observed with pyridine **80**. Nevertheless, with **135** in hand, the stage was set to explore coupling reactions to prepare the CD biaryl.

The Pd-catalyzed reaction of bromopyridine **135** and crude boronic acid **113** was examined under a variety of conditions (Table 5). Regretfully, the Suzuki coupling of **135** and boronic acid **113**, using the same conditions that had proven successful for the coupling of bromopyridine **88**, gave reduced pyridine **98** as the major reaction product (Table 5, entry 1, yield not determined). This was surprising since bromopyridines **88** and **135** present the steric similarity of possessing identical substituents *ortho* to bromine, and the pyridyl rings are electronically almost identical.



135

\+



113

Conditions → Product

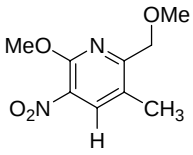
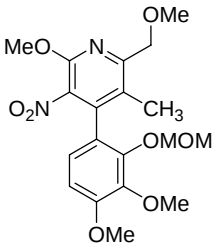
Entry	Conditions	Major Product, yield (%)
1	$Pd(PPh_3)_4$, Na_2CO_3 $PhCH_3$, EtOH, H_2O	 **98**
2	$Pd(PPh_3)_4$, Na_2CO_3 DMF	NR
3	$Pd(PPh_3)_4$, Na_2CO_3 DME	NR
4	$Pd(PPh_3)_4$, CsF DME	 **136** 87 %

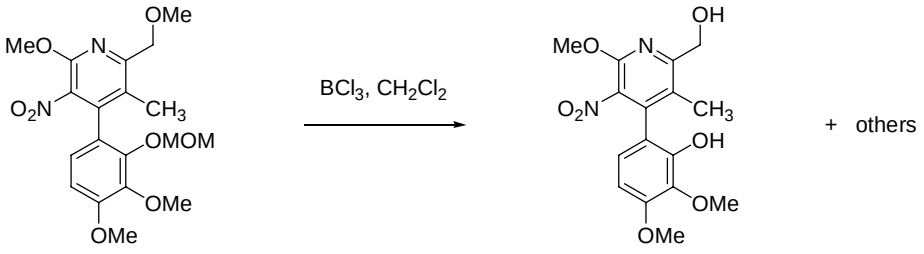
Table 5. Cross-coupling reactions of bromopyridine **135** with boronic acid **113**

Although the source of the hydrogen atom on this reduction pathway is unknown, it was assumed that either the ethanol or water (co-solvents in the reaction) was furnishing the hydrogen. Accordingly, the use anhydrous conditions for the reaction was investigated. Substitution of DMF or DME as reaction solvent (entries 2 and 3, respectively), gave no evidence of reduced pyridine **98** as a reaction product; however,

the starting aryl bromide was recovered unchanged following the reaction. A survey of the literature revealed that boronic acids could be effectively activated by CsF using DME as the solvent.[127] In the event, coupling of bromopyridine **135** and boronic acid **113** using $Pd(PPh_3)_4$ as the catalyst and CsF as the activator gave an 87% yield of biaryl **136** (entry 4), without any trace of contamination by reduced pyridine **98**.

Conversion of the methylene methoxy group of **136** to its carboxylic acid became the next subgoal. This strategy would require cleavage of the methyl ether, followed by oxidation of the resulting primary alcohol. Deprotection of **136** with BCl_3 gave only a 13% yield of the desired product **137** (Scheme 31). Analysis of the crude ^1H NMR spectrum indicated that several other reaction products, in which one or more of the D ring methyl ethers had underwent cleavage, were present in the reaction mixture; these species were not isolated. The use of alternative Lewis acids to promote the deprotection was not examined, nor was systematic optimization of the reaction conditions undertaken. Rather, the synthetic strategy was revised such that the key coupling reaction to prepare the CD biaryl of streptonigrin would occur between bromoester **139** and boronic acid **113**. In addition to circumventing the problem of selective deprotection (*vide supra*), this approach would allow for maximum convergence.

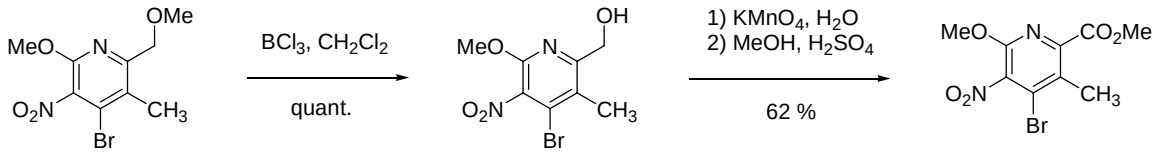
Scheme 31



136 **137**, 13 %

Methyl ester **139** was thus prepared as shown in Scheme 32. Deprotection of the methyl group of **135** with BCl_3 proceeded in quantitative yield to afford alcohol **138**. Subsequent oxidation with $KMnO_4$, followed by acid-catalyzed esterification, gave ester **139** in 62% yield over two steps.

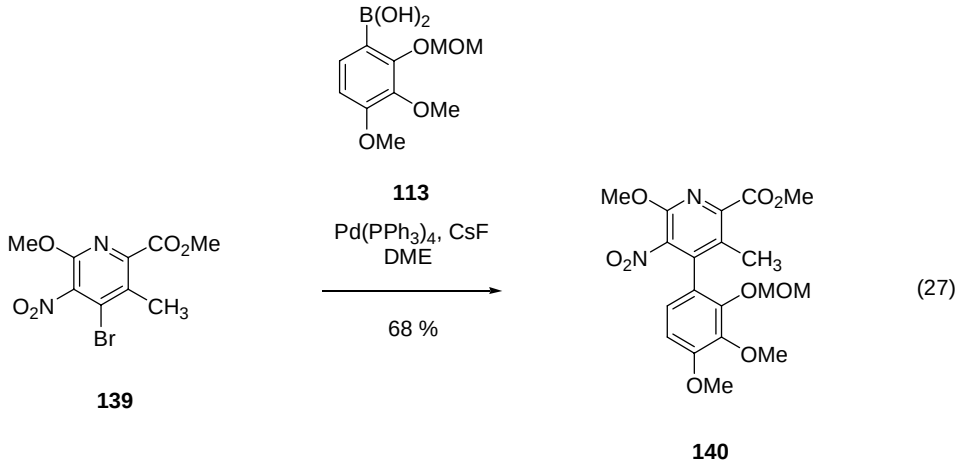
Scheme 32



135 **138** **139**

The cross-coupling of bromopyridine **139** with crude boronic acid **113**, using CsF as the activator and $Pd(PPh_3)_4$ as catalyst, gave a 38% yield of coupled adduct **140** (Eq. 27), although analysis by crude ^1H NMR indicated that no products derived from the starting bromopyridine **139** other than **140** were present. The low isolated yield of **140** is attributed to tedious purification (column chromatography and recrystallization), required to remove impurities originating from crude boronic acid **113**, present in the coupling mixture. Purification of the crude boronic acid mixture prior to the coupling was expected to simplify isolation and improve the yield of coupled product **140**.

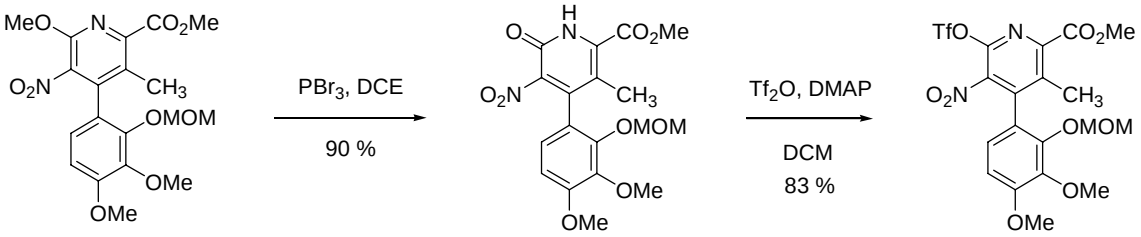
The crude boronic acid mixture containing **113** could be recrystallized, which delivered the boronic acid completely free of impurities. However, rapid decomposition of this species was observed. It was found more convenient and equally effective to purify the crude boronic acid through a series of extractions,[128] which delivered **113** almost entirely free from contamination. Following this protocol and subsequent coupling with bromopyridine **139**, the biaryl product **140** could be purified through routine column chromatography and obtained 68% yield, a marked improvement to that observed above.



(27)

Biaryl **140** was elaborated into a suitable coupling partner using our previously established protocol (Scheme 33). Thus, treatment of **140** with PBr_3 gave pyridone **141**, which was subsequently converted to triflate **142**.

Scheme 33



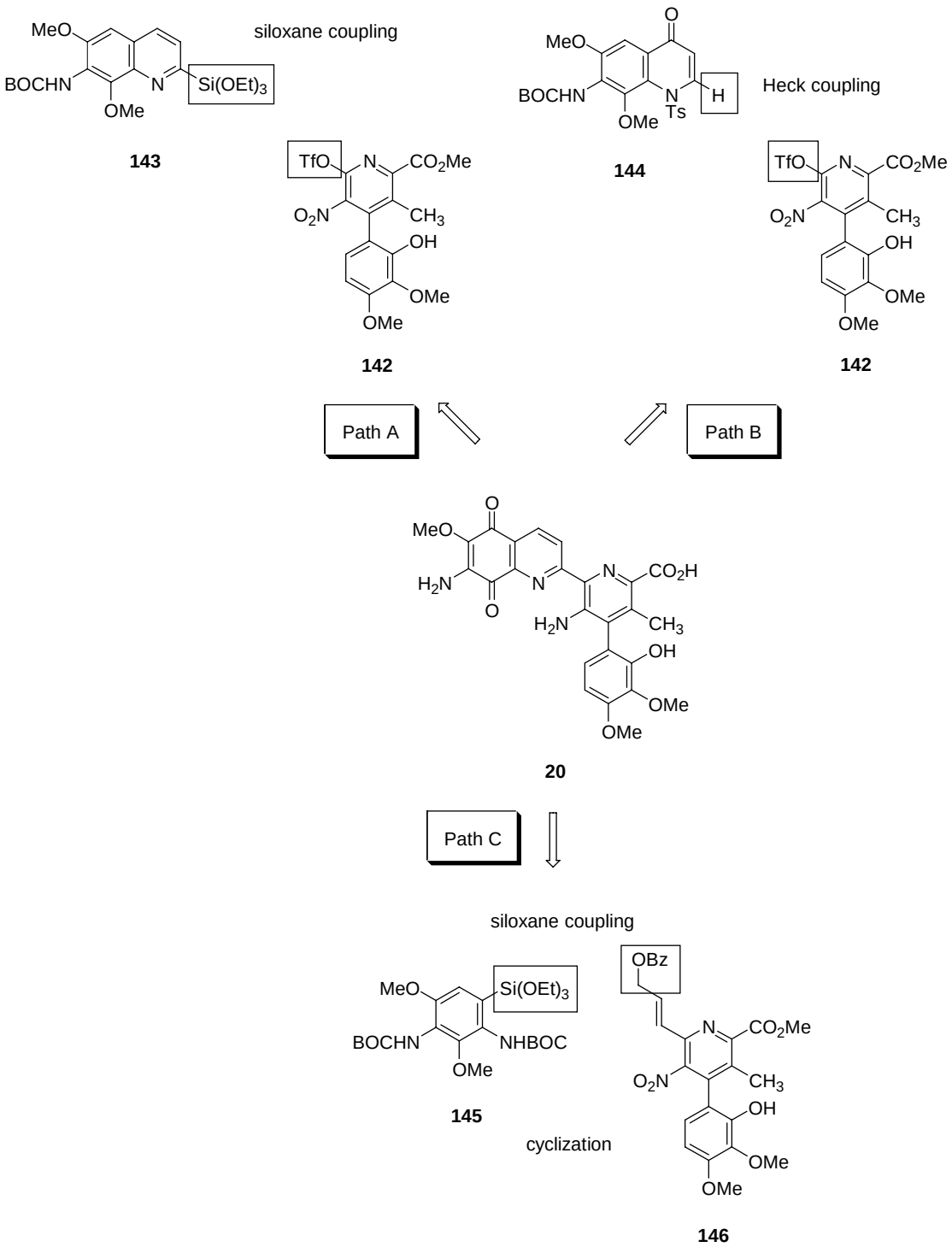
140 **141** **142**

Synthesis of a Streptonigrin AB Coupling Precursor

Biaryl **142** represents the fully functionalized CD ring system of streptonigrin, with the triflate functional group at the pyridine C-2 position enabling an investigation into the second coupling event. In anticipation of this, attention was focused on the preparation of a suitable AB ring coupling precursor. Our initial premise was that quinoline siloxane **143** would fulfill this role (Scheme 34, Path A), as the coupling of **143** and triflate **142** represents the most convergent route to streptonigrin's skeleton. However, given the difficulties experienced in the coupling reaction to prepare the CD biaryl, other strategies were conceived also.

One alternative approach to the natural product framework would deploy a Heck coupling of quinolinone **144** and pyridyl triflate **142**. This route is also highly convergent, but not without risk, since Heck couplings of α,β-unsaturated carbonyls that possess a β-amino substituent (as found in **144**) are as of yet unreported. Nevertheless, the successful implementation of this strategy would constitute a novel method for the preparation of 2-arylquinolines and may pave the way for the syntheses of other natural product targets possessing quinoline rings.

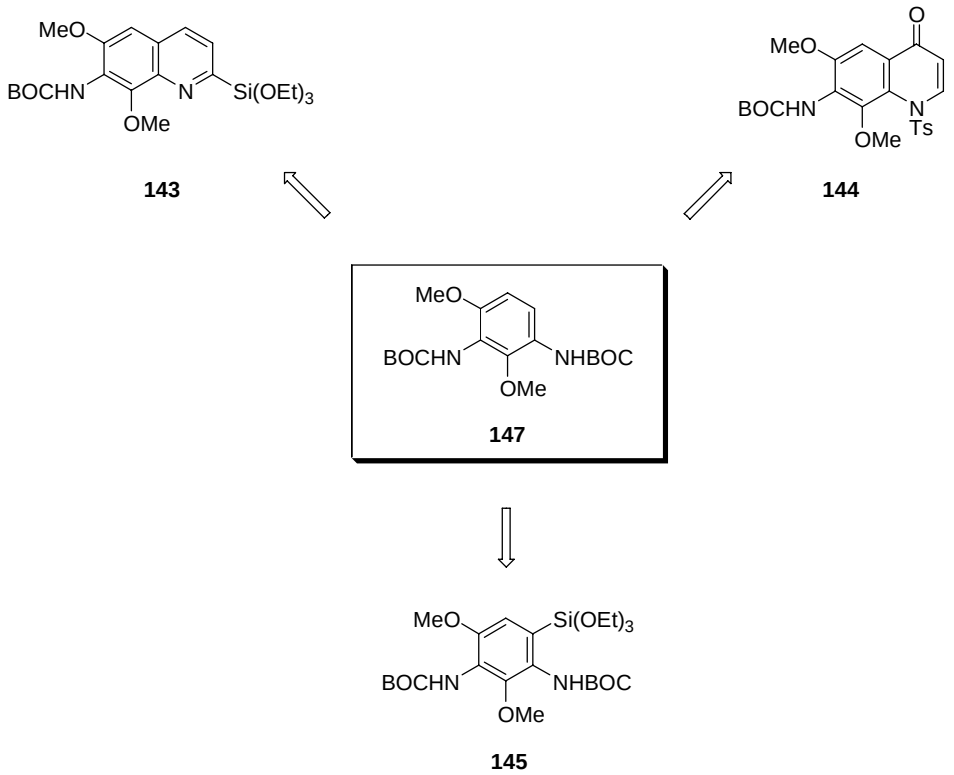
Scheme 34


MeO
BOCHN
N
Si(OEt)3
OMe
siloxane coupling
143
O
MeO
BOCHN
N
Ts
H
OMe
Heck coupling
144
TfO
N
CO2Me
O2N
CH3
OH
OMe
OMe
142
142
Path A
Path B
O
MeO
H2N
N
O
N
CO2H
H2N
CH3
OH
OMe
OMe
20
Path C
siloxane coupling
MeO
Si(OEt)3
BOCHN
NHBOC
OMe
145
OBz
N
CO2Me
O2N
CH3
OH
OMe
OMe
cyclization
146

Yet a third pathway would capitalize on the Pd-catalyzed coupling of an aryl siloxane with an allylic benzoate (Path C, see Scheme 5). The required components for this process would be siloxane **145** and allylic benzoate **146**, itself the product of a Pd-catalyzed coupling of pyridyl triflate **142** and an appropriately functionalized three-carbon fragment. Subsequent cyclization would then deliver the tetracyclic core of streptonigrin. If successful, this arylation-cyclization approach would also represent a novel route to the 2-arylquinoline motif.

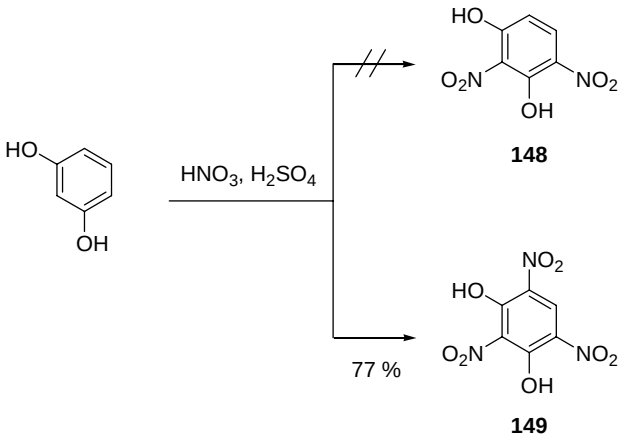
Whichever of these strategies was ultimately adopted, the immediate goal became the design and implementation of the synthesis an AB ring precursor that could be elaborated into quinoline siloxane **143**, quinolinone **144**, or siloxane **145**. Streptonigrin A-ring analogue **147** was selected for this purpose (Scheme 35), since the C-6 position of **147** may be readily functionalized, either by directed *ortho*-metallation or Friedel-Crafts reaction of **147** (or one of its precursors). In this way, coupling precursors **143**, **144**, and **145** may each originate from **147**.

Scheme 35



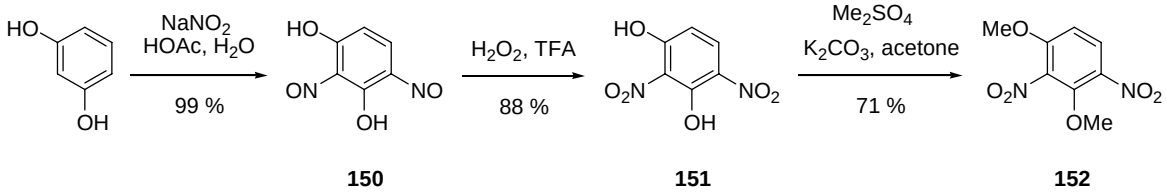
Thus, synthetic studies towards the preparation of **147** were begun (Scheme 36), and the initial surmise was that this compound would be available from resorcinol. Indeed, the preparation of dinitro arene **148** from resorcinol, upon treatment with a mixture of nitric and sulfuric acids, had been described.[129] In our hands, however, trinitroresorcinol **149** was obtained as the sole product of this reaction (Scheme 36). Analysis of the crude reaction mixture by ^{1}H NMR showed no evidence of dinitroresorcinol **148**.

Scheme 36



We were, however, able to reproduce the results of Kametani and Ogasawara[130] regarding the preparation of dinitrosoresorcinol **150** (Scheme 37). Thus, reaction of resorcinol with $NaNO_2$, under strictly defined conditions, afforded dinitroso arene **150** in nearly quantitative yield. Subsequent oxidation to the dinitro species **151** proceeded smoothly, and methylation of the two hydroxyl groups of **151** with dimethyl sulfate gave dimethoxy arene **152**. Interestingly, the order in which the latter two reactions are performed is critical: attempted methylation of dinitroso species **150** resulted in decomposition of the starting material.

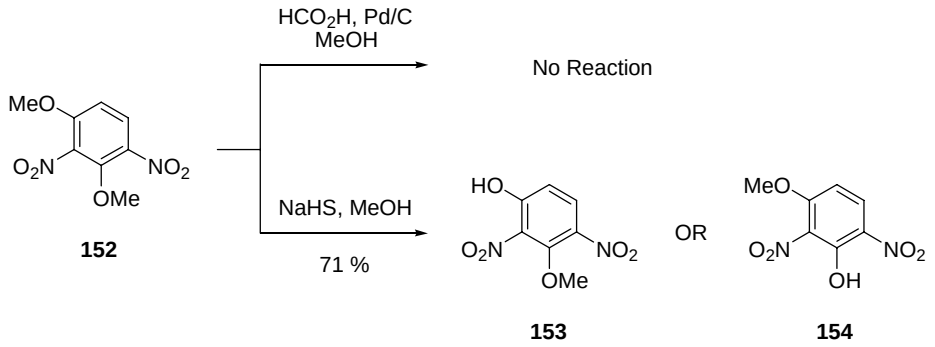
Scheme 37



While not part of the initial strategy, the selective reduction of one of the nitro groups of **152** was examined (Scheme 38). This would allow for the orthogonal protection of the two nitrogen atoms of **152**, and ensure that if necessary the nitrogen functionalities could

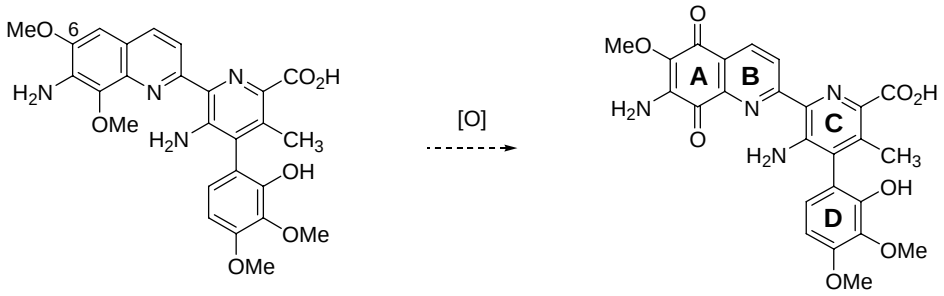
be independently manipulated to affect quinoline formation. The use of formic acid and Pd/C has previously been shown to be selective for the monoreduction of aromatic diamino derivatives.[131] However, the reaction of **152** under these conditions proved fruitless as only starting material was recovered (Scheme 38).

Scheme 38



Treatment of **152** with NaSH and MeOH,[132] resulted in complete consumption of the starting material, as determined by TLC. Following reaction work-up, analysis of the crude reaction mixture by ^{1}H NMR indicated the presence of a single species of which one of the methoxy groups was removed (either phenol **153** or **154**). Which of the two regioisomers had been obtained was not established, and although neither compound was of immediate synthetic use, this reaction is noteworthy. Our synthetic strategy for streptonigrin requires late stage oxidation of A ring precursor **155** to its *p*-quinone (Scheme 39). This oxidation is expected to occur selectively to give streptonigrin (**20**), leaving the methoxy group at C-6 of the A ring (streptonigrin numbering) unchanged.[133] Oxidation to give the *o*-quinone would be undesirable. The ability to differentiate the two methoxy groups of **155** (or a precursor thereof) allows for protecting group strategies to be employed if necessary to ensure regioselective formation of the *p*-quinone.

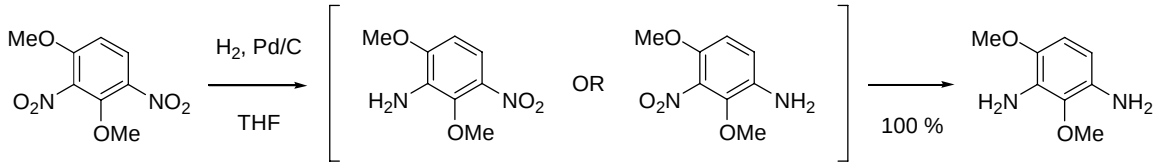
Scheme 39



155 Stretonigrin (**20**)

In the effort to selectively reduce one of the nitro groups of **154**, the reduction of **152** with H_2 and Pd/C was investigated (Scheme 40). It was observed that one of the nitro groups of **152** is reduced at a faster rate than the other one. Indeed, this product (**155a** or **155b**) was isolated in excellent yield from the reaction mixture without any contamination of the other regioisomeric nitroamine. No attempt was made at this point to determine which regioisomeric nitroamine was obtained. Rather, further exposure of the reaction mixture to H_2 and Pd/C gave diamine **156**.

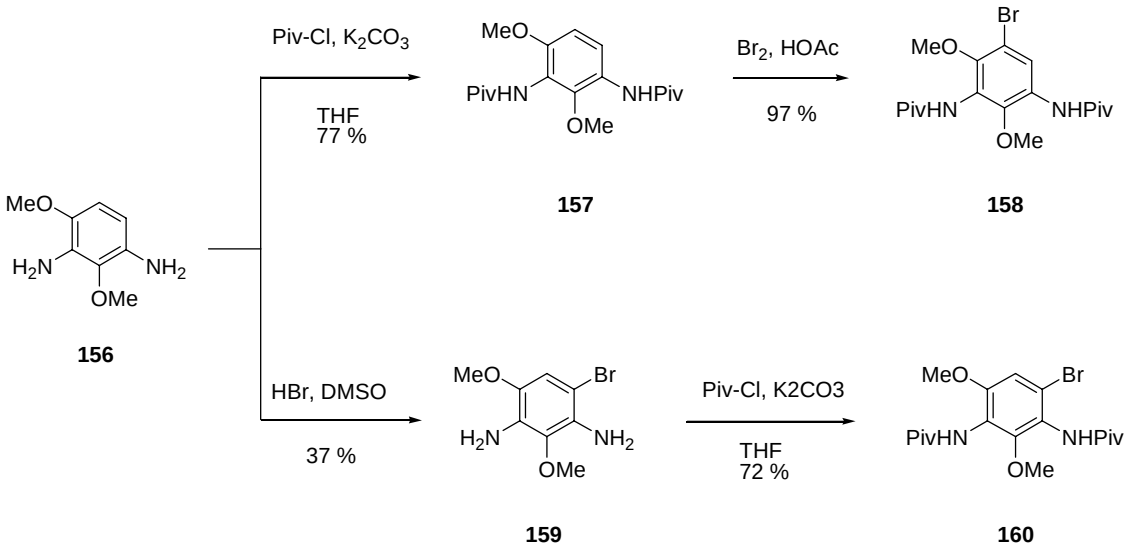
Scheme 40



152 **155a** **155b** **156**

After protection of diamine **156** as its bis-pivanilide (Scheme 41), the bromination of arene **157** was investigated. It was hoped that this reaction would be selective for the C-6 position, and treatment of arene **157** under standard bromination conditions delivered a single monobrominated species in 97% yield. The structure of this species was tentatively assigned to be **158**, and later confirmed by nOe analysis (*vide infra*).

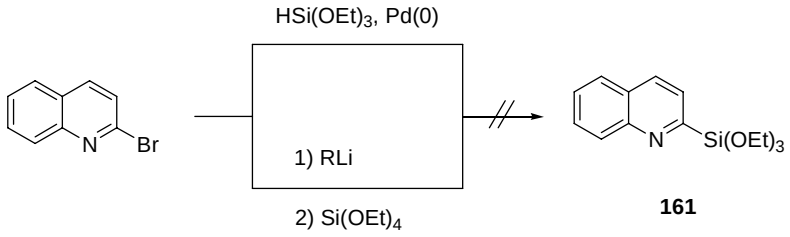
Scheme 41



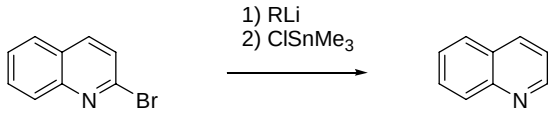
The stronger directing abilities of the methoxy groups (relative to the amides) of arene **157** were responsible for the regiochemical outcome of bromination, and it was hypothesized that bromination of diamine **156** would give the alternate regioisomer **159** (Scheme 42). Attempted bromination of diamine **156** under a variety of reaction conditions employing Br_2 as the electrophile gave only decomposition. The use of PyHBr•Br_2 also proved unsuccessful, but reaction of **156** with HBr and DMSO[134] gave the desired product. Ultimately this reaction was optimized to give diamine **159** in 37% yield. Protection of diamine **159** as its bis-pivalanilide gave **160** in good yield. The TLC and ^{1}H NMR properties of the two bromobis-pivalanilides **158** and **160** were clearly different, and their tentative structural assignments were confirmed through selective nOe experiments:[135] the aromatic proton of **160** showed an nOe with one of the methoxy groups, whereas the aromatic proton of **158** did not. At this point the synthetic route to AB precursor **159** had been secured, and what remained was elaboration of this compound to a suitable coupling partner for CD triflate **142**.

One proposed approach to streptonigrin involves coupling of pyridyl triflate **142** with quinoline siloxane **143**. The feasibility of this was explored through the attempted preparation of model siloxane **161** (Scheme 42). Attempted conversion of 2-bromoquinoline[136] to quinoline siloxane **161,** under previously developed hydrosilylation conditions, failed to give any siloxane product.[137] Likewise, lithium halogen exchange, followed by quenching with $Si(OEt)_4$ did not afford any of the desired siloxane.[138]

Scheme 42



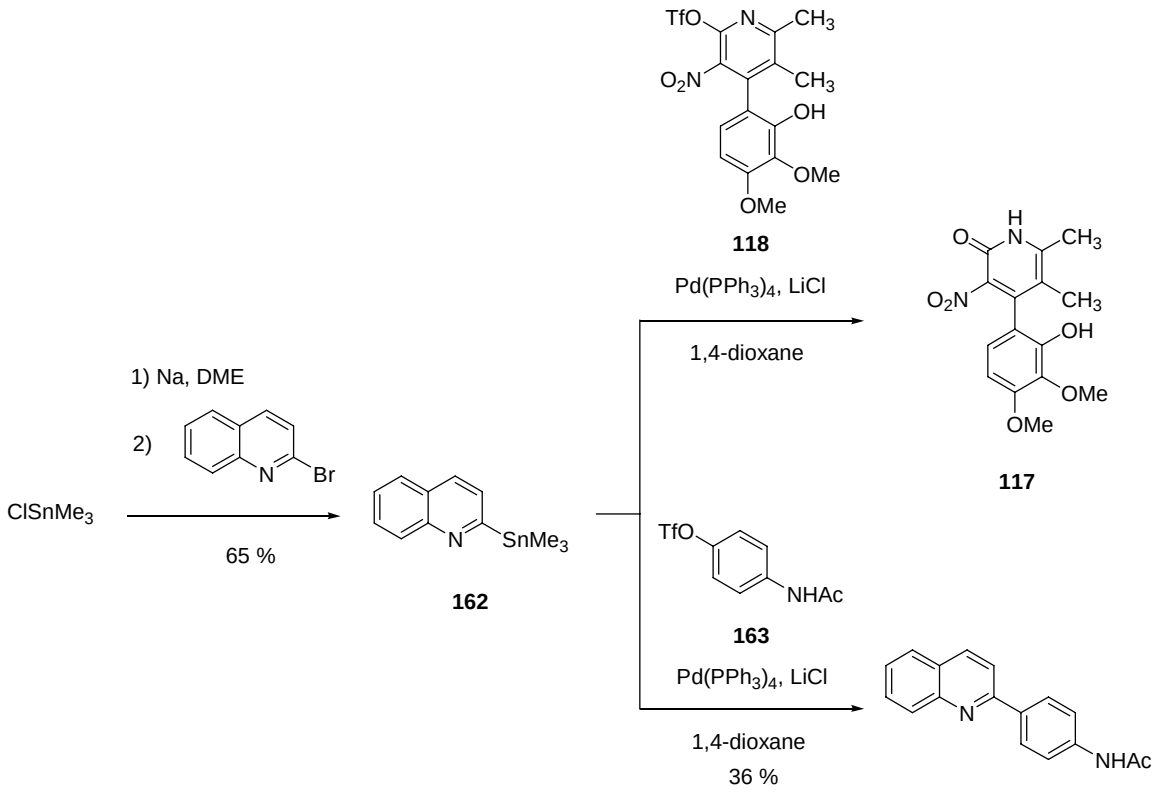
The preparation of the related quinoline stannane was investigated (Eq. 28). Metallation of 2-bromoquinoline, followed by reaction with $ClSnMe_3$ gave quinoline as the sole product.



(28)

Reversing the nucleophilic and electrophilic components in this process was however greeted with some success (Scheme 43).[139] Conversion of $ClSnMe_3$ to its sodium salt, followed by reaction with 2-bromoquiniline, afforded quinoline stannane **162** in 65% yield.

Scheme 43

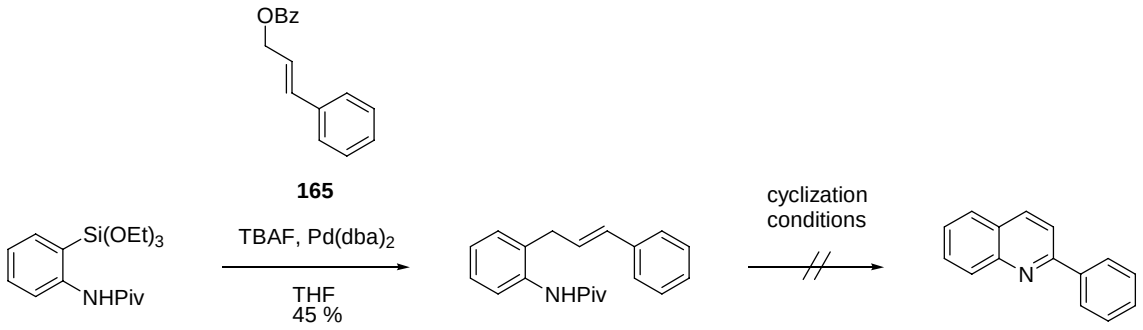


The Stille coupling of stannane **162** and triflate **118** was found to be problematic, as the major product of the reaction was pyridone **117**. This finding is consistent with previous observations in which fluorosulfonate esters derived from 2-pyridones are especially prone to hydrolysis (see Scheme 25). The ability of stannane **162** to undergo Pd-catalyzed cross-coupling was confirmed, however, upon successful reaction with aryl triflate **163**.[121] The conclusion drawn from these results was that the coupling of a quinoline siloxane or quinoline stannane (Scheme 34, Path A) to prepare the ABCD system of streptonigrin was not feasible.

A second approach to the streptonigrin framework would involve the cross-coupling of siloxane **145** and allylic benzoate **146**, followed by ring closure to form the AB

quinoline (Scheme 34, Path C). The viability of this strategy was explored using the model system shown in Scheme 44.

Scheme 44

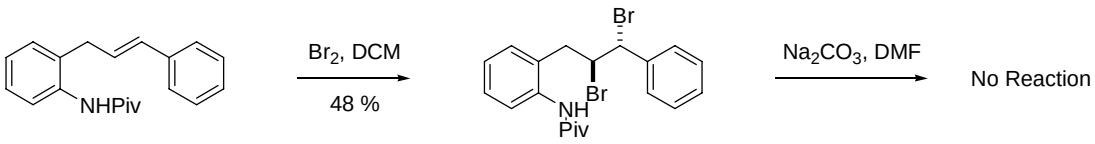


Siloxane **164**, prepared as previously described by Seganish,[43] underwent Pd-catalyzed coupling with allylic benzoate **165**[46] in 45% yield. Although the yield obtained for this reaction was lower than expected, the reaction was unoptimized and it was assumed that a systematic catalyst and solvent study would allow for an improvement. The ring closure to form the desired quinoline framework was investigated using a variety of electrophiles that have previously shown affinity for the alkene functionality. The reaction of amido olefin **166** with I_2 or $Hg(OAc)_2$, when conducted both with and without the addition of base, failed to provide any cyclized product. In all instances, the starting amido olefin was recovered unchanged. The use of stoichiometric amounts of $PdCl_2(PhCN)_2$, $PdCl_2$, and $PdBr_2$, which had previously been shown to affect intramolecular amination[140] also proved unsuccessful. Only in the reaction employing $PdBr_2$ was any quinoline product obtained, and the yield in this process did not exceed 10%. Again, these reactions were evaluated both with and without the addition of bases.

There are two possible explanations for the lack of reactivity of amido olefin **166**: either the alkene is unreactive to the electrophile, or the nucleophilicity of the nitrogen

has been too severely diminished by the protecting group to undergo cyclization. To question this, olefin **166** was allowed to react with Br_2 under standard alkene brominating conditions (Scheme 45), resulting in the formation of dibromide **168** in 48% yield. This result clearly demonstrated that the alkene functionality of **166** was sufficiently nucleophilic, and the failures observed in the cyclization reaction were due to a lack of nucleophilicity of the protected nitrogen. Interestingly, treatment of dibromide **168** with base failed to affect ring closure. Attempts to remove the pivalanilide protecting group of **168** at room temperature under acidic conditions were unsuccessful, as only unreacted starting material was recovered. If elevated temperatures were used, decomposition products were observed.

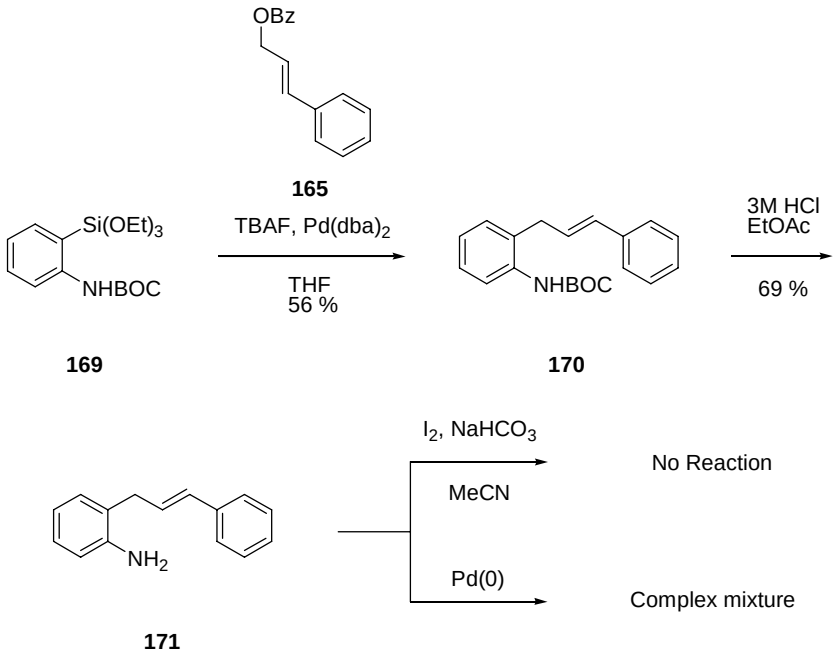
Scheme 45



166 **168**

Thus a similar reaction sequence using the more labile BOC group as a protection strategy for the nitrogen atom (Scheme 46) was performed. The cross-coupling of N-BOC protected aryl siloxane **169**[43] with allylic benzoate **165** gave adduct **170** in 55% yield. Removal of BOC group proceeded uneventfully upon treatment with 3M HCl to give aniline **171**. Reaction of **171** with I_2 and $NaHCO_3$ failed to induce cyclization, as the starting amine was recovered unchanged. Attempted ring closure using Pd reagents gave a complex mixture of inseparable products and this pathway was not pursued further.

Scheme 46



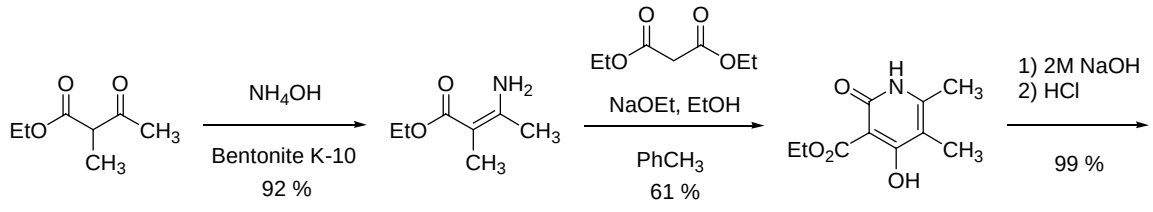
The conclusion drawn from these studies was that the cross-coupling of a protected (*o*-amino)-arylsiloxane with an allylic benzoate serves as a useful tactic in linking the major subunits of streptonigrin. However, further investigations into the annulation reaction of **171** are warranted if this strategy is to be adopted for the preparation of the natural product.

In summary, a series of 4-bromopyridines have been synthesized and their abilities to undergo Pd-catalyzed coupling with streptonigrin D ring siloxane analogues evaluated. This method proved generally amenable to the preparation of sterically demanding biaryls. However, it was shown that the coupling process is highly sensitive to the electronic properties of both coupling partners.

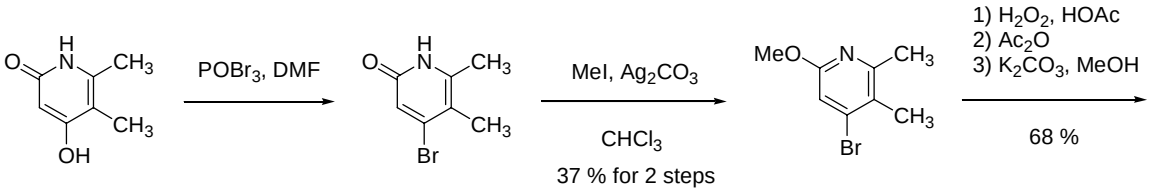
The current status of the total synthesis is summarized in Schemes 47 and 48. Streptonigrin C ring precursor **139**, prepared in 10 steps from ethyl 2-methylacetoacetate,

was shown to undergo Suzuki coupling with boronic acid **133** (prepared in three steps from 2,3-dimethoxybenzaldehyde) in good yield. This reaction was found to be highly dependent on the conditions employed (activator and solvent). Triflate **142**, representing the fully functionalized CD ring system, has thus been prepared in a highly convergent manner in 13 steps at the longest linear sequence.

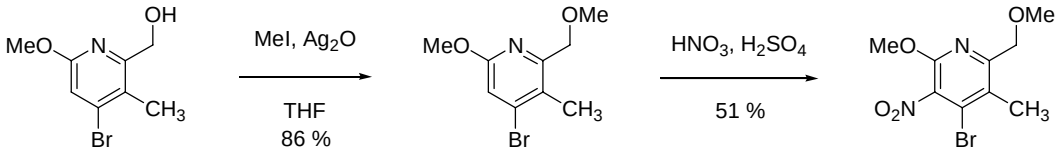
Scheme 47



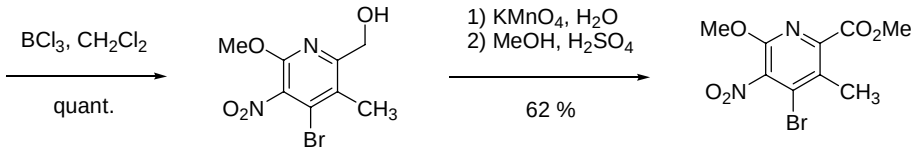
74 **72b**



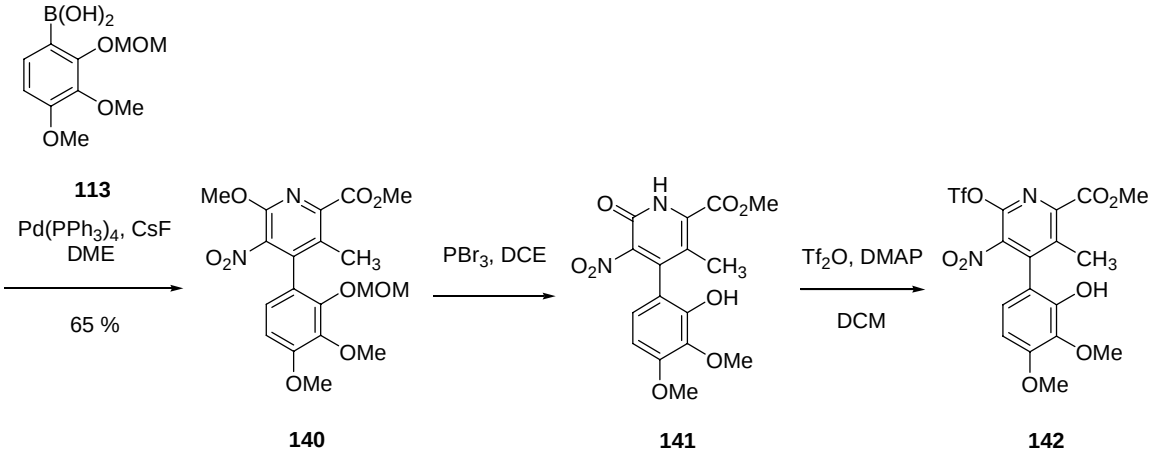
72c **79** **80**



133 **134** **135**



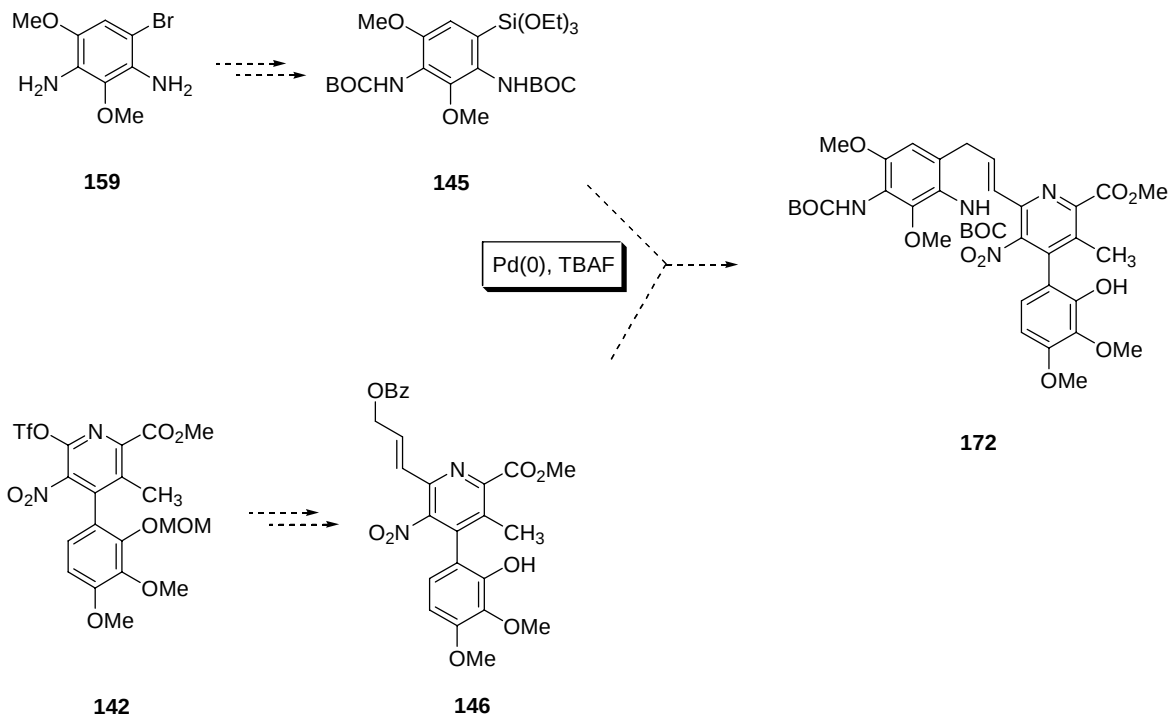
138 **139**



113 **140** **141** **142**

Streptonigrin AB ring analogue **159** has been prepared in 6 steps from resorcinol. The results of model studies indicate that, following transformation to siloxane **145**, the coupling of this piece with allylic benzoate **146** (derived from triflate **142**) represents a viable strategy for the union of the molecule's two major subunits (Scheme 49). Further studies are needed to evaluate the viability of the ring closure of **172**, which will be required for completion of the synthesis.

Scheme 48



Experimental

General Methods. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker DRX-400 spectrometer. Chemical shifts are reported in parts per million (ppm). Coupling constants (*J*) are given in Hertz (Hz). Spin multiplicities are indicated by standard notation.

Infrared spectra were recorded on a Nicolet 560 FT-IR spectrophotometer. Band positions are given in reciprocal centimeters (cm^{-1}) and relative intensities are listed as br (broad), s (strong), m (medium), or w (weak).

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

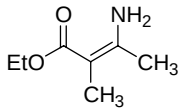
Low resolution (LRMS) and high resolution (HRMS) were obtained on a JEOL SX-102A instrument.

Thin layer chromatography (TLC) was performed on 0.25 mm Analtech silica-coated glass plates, with compounds being identified in one or both of the following manners: UV (254 nm) and vanillin/sulfuric acid/ethanol charring. Flash chromatography was performed using glass columns and "medium pressure" silica gel (Sorbent Technologies, 45-70 μ).

Tetrahydrofuran (THF), diethyl ether, toluene, and 1,4-dioxane were distilled from sodium/benzophenone ketyl. *N*,*N*-Dimethylformamide (DMF) was distilled from calcium hydride and dried over 4Å molecular sieves. Pyridine, methylene chloride, and 1,2-dichloroethane (DCE) were distilled from calcium hydride. *N*,*N*,*N*,*N*-tetramethylethylenediamine (TMEDA) and 1,2-dimethoxyethane (DME) were distilled

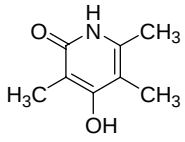
from sodium metal. PBr_3, oxalyl chloride, and $B(OMe)_3$ were distilled prior to use. Triphenylphosphine was recrystallized from hexanes. All other reagents were purchased and used as received. Glassware used in the reactions was dried overnight in an oven at 120 °C. All reactions were performed under an atmosphere of argon unless otherwise noted.

Amino ester 74



This reaction was not performed under inert atmosphere. Ethyl 2-methylacetoacetate (100 g, 0.693 mol) was absorbed onto 135 g of bentonite K-10 clay. To the mixture was added 85 mL (1.3 mol) of 14.9 M ammonium hydroxide and this mixture stirred at room temperature for 24 h. The clay was washed 4x with 500 mL of CH_2Cl_2 and the combined washings dried over $MgSO_4$ and concentrated *in vacuo* to yield 90.9 g (92%) of amino ester **74** as a white, crystalline solid, mp 46-49 °C (literature[104] mp 52 °C), which was used without further purification. The ^{1}H NMR spectrum matched that of the reported compound.[104] IR (CCl_4) 3506 (m), 3309 (m), 2975 (m), 2905 (m), 2866 (w), 1666 (s), 1616 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.24 (t, J = 7 Hz, 3H), 1.72 (s, 3H), 1.91 (s, 3H), 4.10 (q, J = 7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 12.8, 15.0, 21.6, 59.3, 89.4, 156.6, 171.2. EI-MS *m/z* 143 (100), 114 (26), 98 (93), 69 (62), 42 (23). HRMS for $C_7H_{13}NO_2$ calcd 143.0946, found 143.0951.

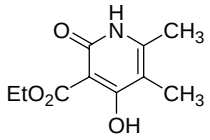
Pyridone 72a



Sodium ethoxide was generated by adding 3.65 g (0.158 mol) of sodium metal to 55 mL of ethanol. To this solution was added a solution of 27.2 mL (0.158 mol) of diethyl methylmalonate in 8 mL of toluene. The resulting solution was stirred at room temperature for 1 h. A solution of 22.6 g (0.158 mol) of amino ester **74** in 22 mL of

toluene was added over a period of 20 min. The reaction was heated at reflux for 24 h, during which time a white precipitate formed. After cooling, the mixture was diluted with water and stirred for 30 min. The phases were separated and the aqueous layer washed with toluene. The aqueous layer was acidified with conc HCl to pH 7.0, and the precipitate thus obtained filtered and dried to yield 16.8 g (69%) of pyridone **72a** as a white, crystalline solid, mp 270-275 °C (decomp, literature[104] mp 260 °C), which was used without further purification. The ^{1}H NMR spectrum matched that of the reported compound.[104] IR (KBr) 3429 (br), 3262 (br), 2955 (m), 2928 (m), 1631 (s) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.80 (s, 3H), 1.83 (s, 3H), 2.06 (s, 3H), 9.12 (br s, 1H), 10.85 (br s, 1H). ^{13}C NMR (DMSO-d_6) δ 6.9, 8.2, 14.0, 101.5, 101.8, 135.8, 160.0, 161.3. EI-MS *m/z* 153 (100), 124 (32), 98 (41), 78 (37), 63 (33). HRMS for $C_8H_{10}NO_2$ calcd 153.0790, found 153.0783.

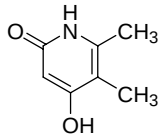
Pyridone 72b



Sodium ethoxide was generated by adding 23.0 g (1.00 mol) of sodium metal to 400 mL of ethanol. To this solution was added a solution of 145 mL (0.959 mol) of diethyl malonate in 55 mL of toluene. The resulting yellow solution was stirred at room temperature for 1 h. A solution of 68.9 g (0.481 mol) of amino ester **74** in 150 mL of toluene was added, and the resulting solution refluxed for 4 d during which time a white precipitate formed. After cooling, the mixture was diluted with water and stirred for 30 min. The phases were separated and the aqueous layer washed with toluene. The

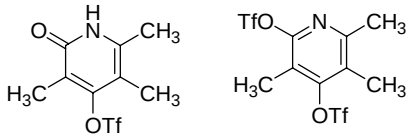
aqueous layer was concentrated *in vacuo* to remove the ethanol and acidified with conc HCl. The precipitate thus obtained was filtered, washed with water, and dried to yield 61.78 g (61%) of pyridone **72b** as a white, crystalline solid. mp 215-220 °C (decomp literature[105] mp 216-221 °C), which was used without further purification. The ^{1}H NMR spectrum matched that of the reported compound.[105] IR (CCl_4) 3317 (w), 3165 (w), 2986 (m), 2932 (m), 2866 (m), 2803 (m), 1654 (s) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 1.42 (t, *J* = 8 Hz, 3H), 1.65 (s, 3H), 1.95 (s, 3H), 4.41 (q, *J* = 8 Hz, 2H), 12.33 (s, 1 H). ^{13}C NMR ($CDCl_3$) δ 9.9, 14.5, 17.9, 62.1, 96.8, 106.5, 149.2, 163.0, 172.9, 175.2. EI-MS *m/z* 211 (93), 165 (100), 139 (48), 137 (47), 109 (64). HRMS for $C_{10}H_{13}NO_4$ calcd 211.0845, found 211.0844.

Pyridone 72c



A solution of 61.78 g (0.2925 mol of pyridone **72b** and 111 g of NaOH (2.78 mol) in 1.3 L of water was heated at reflux for 2 h. The solution was cooled to 0 °C, brought to pH = 7 with conc HCl, and stirred at room temperature for 12 h. The precipitate thus obtained was filtered and washed with water to yield 40.29 g (99%) of pyridone **72c** as a white solid, mp > 320 °C. IR (KBr) 3421 (w), 3266 (w), 3087 (m), 3002 (m), 2928 (m), 2882 (m), 1662 (s), 1616 (s) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 1.79 (s, 3H), 2.09 (s, 3H), 5.49 (s, 1H), 10.53 (br s, 1H), 10.91 (br s, 1H). ^{13}C NMR (DMSO-d_6) δ 9.8, 16.7, 96.1, 104.2, 142.3, 163.7, 167.3. EI-MS *m/z* 139 (100), 111 (76), 110 (80), 69 (72), 44 (84). HRMS for $C_7H_9NO_2$ calcd 139.0633, found 139.0638.

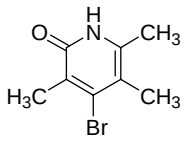
Triflate 75 and bis-triflate 76



A solution of 115 mg (0.751 mmol) of hydroxypyridone **72a** and a catalytic amount of DMAP in 10 mL pyridine was cooled to 0 °C. To this solution was added dropwise 140 μL (0.826 mmol) of Tf_2O, causing the immediate evolution of gas. The solution was stirred at 0 °C for 1 h, quenched with water, and neutralized with 1 M HCl. The solution was extracted 3x with Et_2O and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:1 hexanes:EtOAc, R_f = 0.67) yielded 127 mg (41%) of bis-triflate **76** as a colorless oil. IR (CCl_4) 3006 (w), 2959 (w), 2924 (w), 2874 (w), 2858 (w), 1615 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.24 (s, 3H), 2.26 (s, 3H), 2.44 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 9.6, 12.1, 21.4, 115.4, 117.4 (q, J = 320 Hz), 117.6 (q, J = 320 Hz), 125.3, 151.6, 153.7, 155.7.

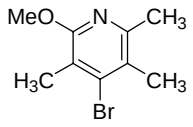
82 mg (38%) of triflate **75**, was also obtained by column chromatography (R_f = 0.39) as a white, crystalline solid, mp 91-93 °C. IR (CCl_4) 3596 (s), 3002 (w), 2936 (w), 2925 (w), 2870 (w), 1623 (m). ^1H NMR ($CDCl_3$) δ 2.12 (s, 3H), 2.15 (s, 3H), 2.38 (s, 3H), 5.64 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 6.7, 9.0, 20.0, 105.5, 115.8, 116.4 (q, J = 320 Hz), 150.4, 151.7, 159.5.

Bromopyridone 77



A mixture of 5.0 g (0.033 mol) of pyridone **72a** and 14 g (0.049 mol) of $POBr_3$ was heated at 110° C for 1 h. The solution was allowed to cool to room temperature and quenched with water. The precipitate thus obtained was filtered and washed with water. Recrystallization from ethanol afforded 4.3 g (60%) of bromopyridone **77** as a white, crystalline solid, mp 226-228 °C (literature[104] mp 227° C). The ^{1}H NMR spectrum matched that of the reported compound.[104] IR (CCl_4) 3289 (w), 3134 (w), 2979 (m), 2928 (m), 2870 (m), 2769 (m), 1647 (s), 1616 (m) cm^{-1}. ^{1}H NMR (DMSO-d_6) δ 2.01 (s, 3H), 2.05 (s, 3H), 2.27 (s, 3H). ^{13}C NMR (DMSO-d_6) δ 17.3, 17.5, 17.7, 111.2, 125.6, 139.1, 140.7, 161.0. EI-MS *m/z* 217 (100), 215 (94) 188 (45), 186 (40). HRMS for $C_8H_{10}BrNO_2$ calcd 216.9925, found 216.9917.

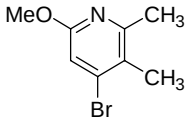
Bromopyridine 78



To a suspension of 3.45 g (0.0125 mol) of Ag_2CO_3 and 3.58 g (0.0177 mol) of pyridone **77** in 30 mL of benzene was added 1.25 mL (0.0200 mol) of MeI. The resulting solution was heated in the dark at 45 °C for 12 h. The mixture was cooled to 0 °C, filtered, and the filtrate washed with 50 mL of 2% $NaHCO_3$, followed by 50 mL water. The benzene was evaporated under reduced pressure and the remaining aqueous solution extracted 3x with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated *in*

vacuo to give 3.84 g (100%) of pyridine **78** as a white, crystalline solid, mp 44-45° C, which was used without further purification. IR (CCl_4) 3006 (w), 2953 (w), 2951 (m), 2920 (w), 2893 (w), 2866 (w) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.19 (s, 3H), 2.22 (s, 3H), 2.37 (s, 3H), 3.83 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 14.5, 19.1, 23.8, 53.9, 118.4, 124.0, 139.4, 151.1, 159.9. EI-MS *m/z* 231 (100), 229 (87), 216 (29). HRMS for $C_9BrH_{12}NO_2$ calcd 229.0102, found 229.0104.

Pyridine 80

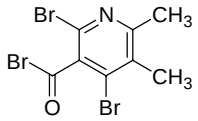


This compound was obtained directly from pyridone **72c**. A mixture of 22.06 g (0.1585 mol) of hydroxypyridone **72c** and 30.54 g (0.1068 mol) of $POBr_3$ in 30 mL DMF were heated at 110 °C for 45 min. After cooling, water was added and the resulting solution brought to pH = 7 with Na_2CO_3. The precipitate thus obtained was filtered, washed with water and then Et_2O to yield 19.80 g of a yellow solid. Although the intermediate bromopyridone could be purified, it was more convenient to use the crude material in the next step.

To a solution of the crude bromopyridone and 32.2 g (0.117 mol) of Ag_2CO_3 in 110 mL $CHCl_3$ was added 20.0 mL (0.314 mmol) MeI and the mixture heated at 50 °C for 24 h in the dark. After cooling, the mixture was filtered and the filtrate concentrated *in vacuo*. Purification by column chromatography (19:1 hexanes:EtOAc, R_f = 0.38) afforded 12.70 g (37% from **72c**) of pyridine **80** as a white, crystalline solid, mp = 38-41 °C. IR (CCl_4) 3014 (w), 2971 (w), 2944 (w), 2897 (w) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.27 (s, 3H), 2.44 (s,

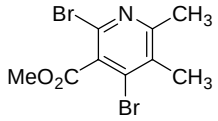
3H), 3.85 (s, 3H), 6.80 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 18.0, 24.1, 54.0, 111.6, 124.0, 137.3, 155.4, 161.9. EI-MS *m/z* 216 (98), 214 (100), 187 (37), 185 (32).

Acid bromide 83



A mixture of 2.00 g (9.51 mmol) of pyridone **72b** and 8.20 g (28.6 mmol) of $POBr_3$ was heated at 110 °C for 4 h. The solution was allowed to cool to room temperature and water was added. The precipitate thus obtained was filtered and washed with water to yield 2.05 g (58%) of acid bromide **83** as a white solid, mp 105-108 °C, which was used immediately without further purification. IR (CCl_4) 2959 (w), 2925 (w), 2862 (w), 1790 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.37 (s, 3H), 2.60 (s, 3H) cm^{-1}. ^{13}C NMR ($CDCl_3$) δ 18.7, 24.4, 130.0, 130.6, 132.5, 138.4, 160.7, 161.1. FAB-MS *m/z* 376 (19), 374 (67), 372 (70), 370 (25), 294 (29), 292 (54), 290 (27), 155 (60), 119 (100), 85 (93). HRMS for $C_8H_6Br_3NO$ calcd 369.8088, found 369.8095.

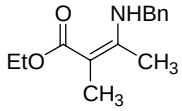
Methyl ester 84



Freshly prepared acid bromide **83** (1.10 g, 3.41 mmol) was dissolved in 20 mL of CH_2Cl_2 and 20 mL MeOH. To this solution was added 2.0 mL of pyridine and the resulting solution stirred for 3 h at room temperature. The solution was concentrated under reduced pressure and the residue dissolved in 20 mL of CH_2Cl_2 and washed with 20 mL

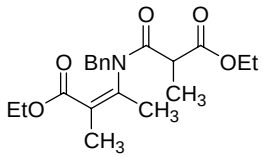
of water, followed by 20 mL of brine. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. Recrystallization from MeOH afforded 720 mg (74%) of methyl ester **84** as a white, crystalline solid, mp 133-136 °C. IR (CCl_4) 2955 (w), 2920 (w), 2950 (w), 1748 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H), 2.56 (s, 3H), 3.96 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 18.5, 23.8, 53.3, 131.6, 132.7, 133.2, 133.7, 159.4, 165.8. FAB-MS *m/z* 326 (42), 324 (100), 322 (53), 292 (22). HRMS for $C_9H_9Br_2NO_2$ calcd 321.9078, found 321.9081.

Amino ester 85



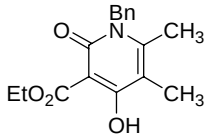
Ethyl 2-methylacetoacetate (10.0 mL, 0.0707 mol) was absorbed onto 17 g of bentonite K-10 clay. To this mixture was added 9.2 mL (0.084 mol) of benzylamine and the resulting mixture stirred at room temperature for 7 h. The clay was washed 4x with 200 mL CH_2Cl_2 and the combined washings dried over $MgSO_4$ and concentrated *in vacuo* to yield 11.9 g (73%) of amino ester **85** as a pale yellow oil, which was used without further purification. IR (CCl_4) 3250 (br), 3173 (w), 3087 (w), 3064 (w), 3025 (w), 2975 (m), 2932 (m), 2862 (w), 1720 (w), 1647 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.26 (t, J = 7 Hz, 3H), 1.78 (s, 3H), 1.97 (s, 3H), 4.10 (q, J = 7 Hz, 2H), 4.41 (d, J = 6 Hz, 2H), 7.25 (m, 5 H), 9.63 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 12.8, 14.7, 15.3, 47.1, 58.8, 87.6, 126.7, 127.1, 128.7, 139.5, 159.4, 171.1. FAB-MS *m/z* (234 (70), 233 (100), 232 (48), 188 (40), 91 (63). HRMS for $C_{14}H_{19}NO_2$ calcd 233.1416, found 233.141.

Amide 86



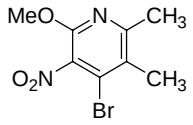
A solution of 1.11 g (8.4 mmol) of ethyl malonic acid and 1 drop DMF in 20 mL CH_2Cl_2 was cooled to 0 °C. Oxalyl chloride was added dropwise, causing the evolution of gas. The resulting solution was stirred 1.5 h at 0 °C, and then allowed to warm to room temperature and stirred an additional 2 h. A solution of 3.91 g (16.8 mmol) of amine **85** in 20 mL CH_2Cl_2 was added and the resulting solution stirred 20 h at room temperature. To the solution was added 40 mL brine and the layers separated. The aqueous layer was further extracted 2x with CH_2Cl_2 and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:1 hexanes:EtOAc, R_f = 0.19 afforded 900 mg (31%) of the title compound as a yellow oil. IR (CCl_4) 3091 (w), 3068 (w), 3029 (w), 2979 (m), 2936 (m), 2874 (w), 1741 (s), 1718 (s), 1670 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.17 (t, *J* = 7 Hz, 3H), 1.26 (t, *J* = 7 Hz, 3H), 1.75 (s, 3H), 1.86 (s, 3H), 3.37 (d, *J* = 15 Hz, 1H), 3.43 (d, *J* = 15 Hz, 1H), 3.93 (m, 2H), 4.18 (q, *J* = 7 Hz, 2H), 4.37 (d, *J* = 14 Hz, 1H), 4.84 (d, *J* = 14 Hz, 1H), 7.25 (m, 5H). ^{13}C NMR ($CDCl_3$) δ 14.3, 14.5, 16.3, 20.2, 41.9, 51.0, 61.6, 61.7, 96.0, 128.0, 128.8, 129.5, 129.6, 137.4, 140.9, 165.9, 167.6, 168.3. FAB-MS *m/z* 348 (100), 91 (63). HRMS for $C_{19}H_{25}NO_5$ calcd 348.1824, found, 348.1822.

Pyridone 87



Sodium ethoxide was generated upon the addition of 100 mg (4.35 mmol) of sodium metal to 50 mL of EtOH. A solution of 850 mg (2.35 mmol) of amido ester **86** in 50 mL EtOH was added and the resulting solution stirred at room temperature for 30 min. The solution was concentrated *in vacuo* and the residue extracted 2x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford 715 mg (100%) of pyridone **87** as a white solid, which was used without further purification. IR (CCl_4) 3091 (w), 3068 (w), 3033 (w), 2943 (w), 2905 (w), 2866 (w), 1666 (s), 1638 (m), 1608 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.42 (t, *J* = 7 Hz, 3H), 2.01 (s, 3H), 2.24 (s, 3H), 4.43 (q, *J* = 7 Hz, 2H), 5.30 (br s, 2H), 7.09 (d, *J* = 8 Hz, 2H), 7.21 (m 3H), 13.87 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 11.0, 14.7, 17.9, 47.7, 62.4, 97.0, 107.0, 111.3, 126.6, 127.6, 129.2, 137.2, 150.5, 161.0, 173.5, 173.7. FAB-MS *m/z* 302 (100). HRMS for $C_{17}H_{19}NO_4$ calcd 302.1392, found 302.1399.

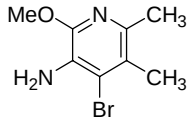
Nitropyridine 88



A solution of 1.32 g (6.11 mmol) of pyridine **80**, 0.60 mL (8.6 mmol) of HNO_3 and 15 mL of H_2SO_4 was stirred at room temperature for 14 h. The solution was diluted with 100 mL of water and neutralized with Na_2CO_3. The solution was extracted 2x with 100 mL Et_2O and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*

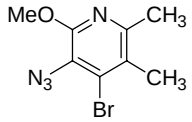
to yield 1.55 g (97%) of nitropyridine **88** as a yellow solid, mp 86-89 °C, which was used without further purification. IR (CCl_4) 3025 (w), 2998 (w), 2951 (w), 2924 (w), 2905 (w), 1581 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.33 (s, 3H), 2.51 (s, 3H), 3.97 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 18.5, 24.4, 55.0, 125.2, 127.5, 152.5, 156.9. FAB-MS *m/z* 263 (66), 261 (61), 155 (57), 152 (59), 119 (68), 103 (48), 85 (100). HRMS for $C_8H_9BrN_2O_3$ calcd 260.9875, found 260.9872.

Aminopyridine 89



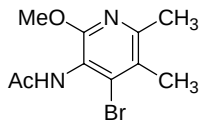
To a solution of 1.39 g (5.32 mmol) of nitropyridine **88**, 28 mL of EtOH, and 7 mL of water was added 3.5 g (63 mmol) of Fe and 2 drops of conc HCl. The resulting solution was heated at reflux for 2 h. After cooling, the solution was filtered and the filtrate concentrated *in vacuo*. Purification by column chromatography (9:1 hexanes:EtOAc, R_f = 0.40) gave 0.800 g (65%) of aminopyridine **89** as a yellow crystalline solid, mp 52-54 °C. IR (CCl_4) 3487 (s), 3394 (s), 3014 (w), 2983 (w), 2948 (m), 2920 (w), 2858 (w), 1654 (m), 1612 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.29 (s, 3H), 2.41 (s 3H), 3.98 (s, 3H), 4.05 (br s, 2H). ^{13}C NMR ($CDCl_3$) δ 18.2, 22.3, 53.3, 119.8, 122.7, 127.1, 140.7, 149.6. EI-MS m/z 232 (98), 230 (100), 189 (68), 187 (68). HRMS for $C_8H_{11}BrN_2O$ calcd 232.0034, found 232.0049.

Azide 94



A solution of 41 mg (0.62 mmol) of $NaNO_2$ in 2 mL water was cooled to 0 °C. To this solution was added dropwise a solution of 121 mg (0.524 mmol) of aminopyridine **89** in 5 mL 10% HCl. The resulting solution was allowed to warm to room temperature and stirred 15 min. The solution was then cooled to 0 °C and a solution of 35 mg (0.55 mmol) NaN_3 in 2 mL water added dropwise. The resulting solution was allowed to warm to room temperature and stirred 45 min. The solution was basicified with Na_2CO_3 and extracted 3x with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (19:1 hexanes:EtOAc, R_f = 0.40) afforded 109 mg (80%) of the title compound as a yellow oil. IR (CCl_4) 3018 (w), 2990 (w), 2948 (m), 2925 (m), 2870 (w), 2851 (w), 2175 (m), 2132 (s), 2101 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.40 (s, 3H), 3.96 (s, 3H). ^{13}C ($CDCl_3$) δ 18.7, 23.5, 54.3, 120.8, 125.3, 127.6, 149.8, 155.0.

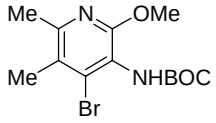
Acetamide 95



To a suspension of 244 mg (1.06 mmol) of aminopyridine **89** and 1.05 g (7.60 mmol) of K_2CO_3 in 15 mL THF was added 0.45 mL (6.3 mmol) of AcCl. The reaction was stirred for 45 min at room temperature and quenched with water. The solution was extracted 3x with Et_2O and the combined organic extracts dried over $MgSO_4$ and concentrated *in*

vacuo. Purification by column chromatography (1:1 hexanes:EtOAc, R_f = 0.19) afforded 198 mg (69%) of the title compound as a white, crystalline solid, mp 175-176 °C. IR (CCl_4) 3433 (m), 3386 (w), 3014 (w), 2983 (w), 2948 (m), 2924 (m), 2854 (w), 1701 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.19 (s, 3H), 2.25 (s, 3H), 2.45 (s, 3H), 3.90 (s, 3H), 6.65 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 16.9, 21.7, 21.8, 52.2, 115.5, 122.7, 135.0, 151.4, 155.4, 167.1. FAB-MS *m/z* 275 (100), 273 (97), 233 (34), 231 (39). HRMS for $C_{10}H_{13}BrN_2O_2$ calcd 273.0239, found 273.0245.

Carbamate 96

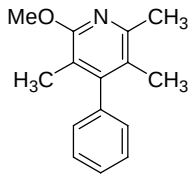


The title compound was obtained directly from nitropyridine **88**. The reduction of 940 mg (3.60 mmol) of nitropyridine **88** was performed as described above (to give amine **89**). The crude product thus obtained was dissolved in 40 mL THF. To this solution was added 5.6 g (26 mmol) of BOC_2O and a catalytic amount of DMAP, and the resulting solution heated at reflux for 5 h. After cooling, 3.0 g (22 mmol) of K_2CO_3 and 40 mL MeOH were added and the resulting solution heated at reflux for 24 h. After cooling, 100 mL of 0.5 M HCl was added and the solution was extracted 3x with 100 mL EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:1 hexanes:EtOAc R_f = 0.43) afforded 751 mg (63%) of the title compound as a white crystalline solid, mp = 101-104 °C. IR (CCl_4) 3429 (m), 3010 (w), 2979 (m), 2951 (w), 2928 (w), 1740 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.47 (s, 9H), 2.02 (s, 3H), 2.43 (s, 3H), 3.91 (s, 3H), 5.88 (br s, 1H). ^{13}C NMR (CDCl3)

δ 16.9, 21.7, 26.5, 52.1, 78.9, 116.0, 122.5, 134.8, 150.5, 151.7, 155.4. EI-MS *m/z* 332 (12), 330 (13), 232 (90), 230 (88), 57 (100). HRMS for $C_{13}H_9BrN_2O_3$ calcd 330.0579, found 330.0579.

General procedure for the siloxane-based synthesis of biaryls. Coupling reactions were performed under identical conditions using 20 mole % $Pd(OAc)_2$ and 40 mole % PPh_3, 2 equiv of siloxane and 2 equiv of TBAF. The following example is illustrative.

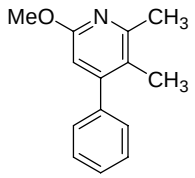
Table 1, entry 3, (biaryl 90)



To a solution of 261 mg (1.15 mmol) of bromopyridine **78**, 440 mg (2.22 mmol) of phenyltrimethoxysilane, 52 mg (0.21 mmol) of $Pd(OAc)_2$, and 110 mg (0.419 mmol) of PPh_3 in 10 mL DMF was added 2.2 mL (2.2 mmol) of a 1M solution of TBAF in THF. The solution was degassed *via* a single freeze-pump-thaw cycle and heated at 80 °C for 12 h. The reaction was quenched with water and the solution extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (hexanes, R_f = 0.14) afforded 230 mg (89%) of the title compound as a colorless oil. IR (CCl_4) 3084 (w), 3056 (w), 2967 (s), 2944 (s), 2924 (m), 2858 (w) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.82 (s, 3H), 1.83 (s, 3H), 2.42 (s, 3H), 3.94 (s, 3H), 7.05 (d, *J* = 7 Hz, 2 H), 7.33 (d, *J* = 7 Hz, 1H), 7.40 (t, *J* = 7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 13.5, 16.3, 23.1, 53.6, 115.6, 121.9, 127.5, 128.8, 128.9, 140.9, 120.7,

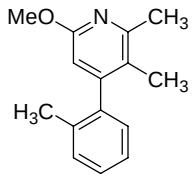
152.0, 160.0. EI-MS *m/z* 227 (70), 226 (100). HRMS for $C_{15}H_{17}NO$ calcd 226.1232, found 226.1228

Table 1, entry 1 (biaryl 110)



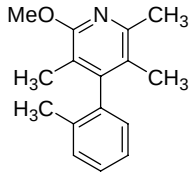
Following column chromatography (19:1 hexanes:EtOAc, R_f = 0.29), the title compound was obtained in 97% yield as a white, crystalline solid, mp 52-54 °C, IR (CCl_4) 3087 (w), 3060 (w), 2948 (m), 2920 (m), 2850 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.06 (s, 3H), 2.46 (s, 3H), 3.90 (s, 3H), 6.45 (s, 1H), 7.25 (d, *J* = 8 Hz, 2H), 7.37 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 14.4, 22.1, 52.3, 106.6, 120.2, 126.5, 127.2, 127.6, 139.2, 151.7, 135.8, 160.3. EI-MS *m/z* 213 (94), 212 (100), 184 (49), 183 (56), 128 (51), 127 (38). HRMS for $C_{14}H_{15}NO$ calcd 213.1154, found 213.1149.

Table 1, entry 2



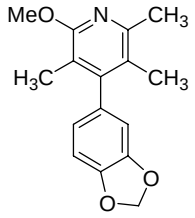
Following column chromatography (19:1 hexanes:EtOAc, R_f = 0.32), the title compound was obtained in 10% yield as a colorless oil. ^1H NMR ($CDCl_3$) δ 1.86 (s, 3H), 2.04 (s, 3H), 2.46 (s, 3H), 3.90 (s, 3H), 6.36 (s, 1H), 7.02 (d, *J* = 8 Hz, 1H), 7.23 (m, 3H).

Table 1, entry 4 (biaryl 92)



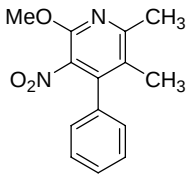
Following column chromatography (19:1 hexanes:EtOAc, R_f = 0.23), the title compound was obtained in 10% yield as a pale yellow oil. IR (CCl_4) 3072 (w), 3002 (m), 2921 (m), 1581 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.70 (s, 3H), 1.71 (s, 3H), 1.87 (s, 3H), 2.36 (s, 3H), 3.89 (s, 3H), 6.84 (d, *J* = 7 Hz, 1H), 7.24 (m, 3H); ^{13}C ($CDCl_3$) δ 13.1, 15.8, 19.8, 23.0, 53.5, 115.5, 121.9, 126.4, 127.9, 128.6, 130.4, 135.6, 139.6, 150.8, 151.5, 160.1. EI-MS *m/z* 241 (100), 240 (84), 226 (94), 216 (65).

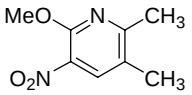
Table 1, entry 5



Following column chromatography (19:1 hexanes:EtOAc, R_f = 0.30), the title compound was obtained in 61% yield as a colorless oil. IR (CCl_4) 3072 (w), 3002 (m), 2948 (s), 2920 (s), 2829 (s), 1581 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.79 (s, 3H), 1.81 (s, 3H), 2.35 (s, 3H), 3.87 (s, 3H), 5.93 (s, 2H), 6.43 (d, *J* = 7 Hz, 1H), 6.44 (s, 1H), 6.79 (d, *J* = 7 Hz, 1H) ^{13}C NMR ($CDCl_3$) δ 13.5, 16.4, 23.1, 53.6, 101.5, 108.8, 109.5, 116.0, 122.1, 122.2, 133.7, 147.0, 148.1, 150.1, 151.6, 160.0. EI-MS *m/z* 271 (74), 270 (100). HRMS for $C_{16}H_{17}NO_3$ calcd 270.1130, found 270.1125.

Biaryl 97 and pyridine 98





Via Siloxane Coupling (Table 1)

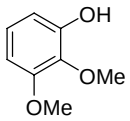
These compounds were prepared according to the general siloxane coupling procedure outlined previously. Following column chromatography (hexanes, R_f = 0.19), biaryl **97** isolated in 36% yield as a white, crystalline solid, mp 79-82 °C. IR (CCl_4) 3087 (w), 3064 (w), 3025 (w), 2990 (w), 2955 (w), 2920 (w), 2901 (w), 2874 (w) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.95 (s, 3H), 2.50 (s, 3H), 4.00 (s, 3H), 7.16 (m, 2 H), 7.40 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 16.0, 23.8, 54.6, 123.2, 128.6, 129.1, 129.3, 133.9, 134.4, 144.3, 152.1, 157.1. EI-MS *m/z* 250 (100), 211 (57). HRMS for $C_{14}H_{14}N_2O_3$ calcd 258.1004, found 258.0997. Reduced pyridine **98** was obtained in 36% yield as a white, crystalline solid, mp 69-72 °C, R_f = 0.15 (hexanes). IR (CCl_4) 3025 (m), 2994 (m), 2955 (m), 2928 (m), 2866 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.25 (s, 3H), 2.45 (s, 3H), 4.05 (s, 3H), 8.03 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 18.2, 23.1, 54.9, 124.8, 131.5, 136.4, 154.4, 161.8.

Via Suzuki Coupling (Table 4)

A solution of 278 mg (1.06 mmol) of 4-bromopyridine **88**, 202 mg (1.66 mmol) phenylboronic acid, 270 mg (2.55 mmol) Na_2CO_3, and 206 mg (0.178 mmol) $Pd(PPh_3)_4$, 2 mL EtOH, 2 mL water, and 25 mL toluene was heated at reflux for 12 h. After cooling, 30 mL of water was added and the solution extracted 3x with Et_2O. The combined

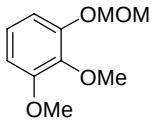
organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography afforded 220 mg (80%) of the title biaryl.

Phenol 100



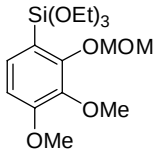
To a mixture of 9.3 mL (0.066 mol) of 30% H_2O_2 and 9.3 g of boric acid (0.15 mol) in 90 mL of THF was added 3 mL of sulfuric acid. The mixture was stirred at room temperature for 30 min and a solution of 5.0 g (0.030 mol) of 2,3-dimethoxybenaldehyde in 30 mL of THF was added. The mixture was heated at 50° C for 24 h, quenched with saturated $NaHCO_3$, and filtered. The filtrate was extracted 3x with Et_2O and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:1 hexanes:EtOAc R_f = 0.29) afforded 3.22 g (70%) of the title compound as a pale yellow oil. Spectral data matched that of the reported compound.[113] IR (CCl_4) 3530 (m), 3002 (m), 2979 (m), 2936 (m), 2893 (m), 2866 (m), 2835 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.84 (s, 3H), 3.88 (s, 3H), 6.74 (br s, 1 H), 6.45 (dd, *J* = 8 Hz, 1 Hz, 1H), 6.58 (dd, *J* = 8 Hz, 1 Hz, 1H), 6.90 (t, *J* = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 56.3, 61.4, 104.5, 108.5, 124.5, 136.0, 149.9, 153.0.

MOM ether 101



NaH (60% dispersion in mineral oil, 1.2 g, 30 mmol) was washed 2x with 3 mL of hexanes. To the solid was added 20 mL of DMF and the resulting suspension cooled to 0° C. A solution of 3.42 g (22.2 mmol) of phenol **100** in 15 mL of DMF was added and the resulting solution stirred at 0° C for 30 min. To the solution was added 2.3 mL (30 mmol) of MOM-Cl, causing the immediate evolution of gas. The solution was allowed to warm to room temperature and quenched with 50 mL of water. The solution was extracted 3x with ether and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo* to afford 4.40 g (100%) of the title compound as a pale yellow oil, which was used without further purification. IR (CCl_4) 2998 (m), 2955 (s), 2932 (s), 2834 (m), 1596 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.47 (s, 3H), 3.82 (s, 3H), 3.83 (s, 3H), 5.18 (s, 2H), 6.58 (d, J = 8 Hz, 1H), 6.74 (d, J = 8 Hz, 1H), 6.92 (t, J = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 56.4, 56.6, 61.3, 95.7, 106.7, 109.9, 124.1, 139.6, 151.4, 154.1.

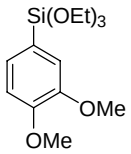
Siloxane 102



A solution of 1.88 g (9.49 mmol) of arene **101** and 2.2 mL (1.4 mmol) of TMEDA in 40 mL of THF was cooled to -78 °C. To this solution was added dropwise BuLi (15.3 mL of a 0.80 M solution, 0.014 mol) and the resulting solution stirred at -78 °C for 10 min and then allowed to warm to 0 °C and stirred an additional 2 h. This solution was added

over 30 min to 4.3 mL (1.9 mmol) of $Si(OEt)_4$ dissolved in 40 mL of THF at –78 °C. The resulting solution was allowed to warm to room temperature, quenched with water, and extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (15% EtOAc:hexanes, R_f = 0.24) afforded 850 mg (25%) of siloxane **102** as a pale yellow oil. IR (CCl_4) 2971 (s), 2924 (s), 2889 (s), 2835 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.22 (t, *J* = 7 Hz, 9 H), 3.62 (s, 3H), 3.81 (s, 3 H), 3.85 (s, 3 H), 3.86 (q, *J* = 7 Hz, 6H), 5.17 (s, 2 H), 6.67 (d, *J* = 8 Hz, 1 H), 7.32 (d, *J* = 8 Hz, 1 H). ^{13}C NMR $CDCl_3$ δ 18.6, 56.3, 57.9, 59.0, 61.1, 99.6, 108.0, 117.2, 123.6, 141.9, 155.5, 156.6. EI-MS *m/z* 360 (87), 271 (95), 270 (100), 255 (53), 166 (56), 45 (53). HRMS for $C_{15}H_{28}O_7Si$ calcd 360.1590, found 360.1604.

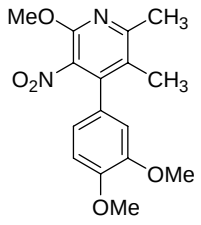
Siloxane 104



Mg turnings were washed 3x with 1M HCl, 3x with water, once with EtOH, and finally with Et_2O. A mixture of 430 mg (17.7 mmol) of the turnings and 15 mL of THF was heated to reflux and a solution of 3.49 g (16.1 mmol) of 4-bromoveritrole[114] in 10 mL THF added dropwise over 30 min. The mixture was refluxed an additional 1.5 h and the solution transferred via cannula to a solution of 10.0 mL (44.6 mmol) of $Si(OEt)_4$ in 50 mL THF. The resulting solution was stirred at room tmeperature for 20 h and concentrated *in vacuo*. The residue was dissolved in 150 mL pentane and washed 2x with water and once with brine. The organic phase was dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (9:1 hexanes:EtOAc, R_f

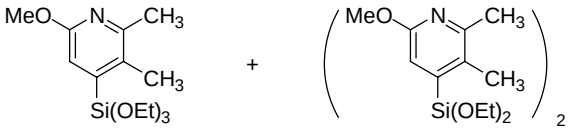
= 0.15) afforded 1.50 g (31%) of the title compound as a colorless oil. IR (CCl_4) 3064 (w), 3014 (w), 2951 (m), 2920 (m), 2858 (w), 1612 (s), 1604 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.23 (t, *J* = 7 Hz, 9H), 3.84 (q, *J* = 7 Hz, 6H), 3.87 (s, 3H), 3.88 (s, 3H), 6.89 (d, *J* = 8 Hz, 1H), 7.13 (s, 1H), 7.23 (d, *J* = 8Hz, 1H). ^{13}C NMR δ 18.7, 56.1, 56.2, 59.1, 111.3, 117.2, 122.6, 128.8, 149.0, 151.3. FAB-MS *m/z* 300 (100), 255 (52). HRMS for $C_{14}H_{19}O_5Si$ calcd 300.1393, found 300.1385.

Biaryl 105



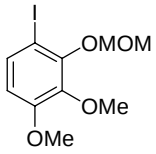
This compound was prepared according to the general siloxane coupling procedure outlined above. Purification by column chromatography (3:1 hexanes:EtOAc, R_f = 0.31) afforded the title compound in 21% yield as a yellow, crystalline solid, mp 129-132 °C. IR (CCl_4) 3006 (m), 2959 (m), 2932 (m), 2913 (m), 2839 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.99 (s, 3H), 2.49 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 3.99 (s, 3H), 6.66 (s, 1H), 6.72 (d, *J* = 8 Hz, 1H), 6.88 (d, *J* = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 14.5, 22.2, 53.0, 54.7, 54.8, 109.9, 110.3, 119.7, 121.8, 124.5, 133.5, 142.5, 147.7, 148.2, 150.5, 155.4. FAB-MS *m/z* 319 (H^+, 100) 318 (41). HRMS for $C_{16}H_{18}N_2O_5$ calcd 318.1216, found 318.1209.

Siloxanes 108 and 109



A solution of 583 mg (2.70 mmol) of pyridyl bromide **80** in 100 mL Et_2O was cooled to –78 °C. To the solution was added dropwise 3.5 mL (3.0 mmol) of a 0.85 M solution of BuLi in hexanes, and the resulting solution stirred at this temperature for 75 min. A solution of 1.2 mL (5.4 mmol) $Si(OEt)_4$ in 100 mL Et_2O was added dropwise at this temperature and the solution stirred a further 1 h at –78 °C. The solution was warmed to room temperature, quenched with water, and the phases separated. The aqueous layer was extracted with Et_2O and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (19:1 hexanes:EtOAc, R_f = 0.40) gave 475 mg (ca. 50%) of a 1:1 ratio of siloxanes **108** and **109**, as determined by ^{1}H NMR. ^{1}H NMR ($CDCl_3$) δ 1.22 (t, *J* = 7 Hz, 15 H), 2.05 (s, 3H), 2.30 (s, 3H), 2.35 (s, 3H), 2.39 (s, 3H), 3.73 (q, *J* = 7 Hz, 2H), 3.82 (q, *J* = 7 Hz, 6H), 3.87 (s, 3H), 3.89 (s, 3H), 6.92 (s, 1H), 7.04 (s, 1H).

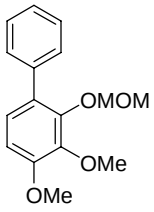
Iodobenzene 111



This compound was prepared according to the procedure of Holzapfel.[99] A solution of 1.01 g (5.10 mmol) of arene **101** and 0.85 mL (5.6 mmol) TMEDA in 75 mL Et_2O was cooled to –78 °C. To the solution was added dropwise 7.0 mL (5.6 mmol) of a 0.80 M

solution of BuLi in hexanes. The resultant solution was allowed to warm to room temperature and stirred 30 min. The solution was cooled to –78 °C and a solution of 2.64 g (10.4 mmol) I_2 in 25 mL Et_2O was added dropwise over 20 min. The resulting solution was warmed to room temperature and quenched upon the addition of aqueous $Na_2S_2O_3$. The phases were separated and the aqueous layer extracted with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to a pale yellow oil, which used without further purification. The ^{1}H NMR spectra matched that of the reported compound.[99] ^{1}H NMR ($CDCl_3$) 3.65 (s, 3H), 3.81 (s, 3H), 3.83 (s, 3H), 5.18 (s, 2H), 6.48 (d, J = 9 Hz, 1H), 7.42 (d, J = 9 Hz, 1H).

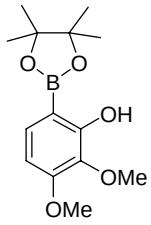
Biaryl 112



This compound was prepared from iodide **107** and $PhSi(OMe)_3$, according to the general method outlined above for couplings of siloxanes. Following column column chromatography (15% EtOAc:hexanes, R_f = 0.29) biaryl **112** was isolated in 20% yield as a colorless oil. IR (CCl_4) 3056 (w), 2994 (m), 2959 (m), 2932 (m), 2901 (m), 2831 (m), 1681 (w), 1608 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.05 (s, 3 H), 3.84 (s, 3 H), 3.91 (s, 3H), 4.87 (s, 2 H), 6.75 (d, J = 7 Hz, 1 H), 7.02 (d, J = 7 Hz, 1 H), 7.28 (t, J = 7 Hz, 1 H), 7.36 (t, J = 7 Hz, 2 H), 7.49 (d, J = 7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 56.5, 57.3, 61.3, 99.5, 108.3, 125.3, 127.1, 128.5, 129.9, 130.0, 138.9, 142.8, 148.5, 153.5. FAB-MS *m/z* 274

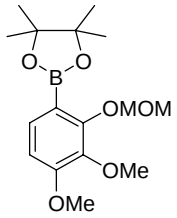
(76), 243 (100), 242 (47), 45 (47). The remainder of the mass balance was an inseperable mixture of the desired product and a small amount of reduced iodide **101**.

Boronic Ester 114



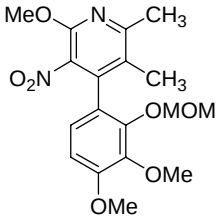
This compound was prepared directly from crude boronic acid **113**. A solution of 0.477 mg (1.97 mmol) of the crude boronic acid (obtained as described below for the preparation of biaryl **69**) and 361 mg (3.05 mmol) pinacol in 20 mL toluene was heated at reflux and water azeotropically removed. After 5 h the reaction was concentrated and the residue purified by column chromatography (3:1 hexanes:EtOAc, R_f = 0.23) to yield 390 mg (77%) of the title compound as a white, crystalline solid, mp 109-111 °C. IR (CCl_4) 3441 (br), 3002 (m), 2979 (m), 2932 (m), 2835 (m), 1623 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.33 (s, 12 H), 3.85 (s, 3H), 3.85 (s, 3H), 6.48 (d, 1 H, *J* = 8 Hz), 7.30 (d, 1 H, *J* = 8 Hz), 7.74 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 25.2, 56.4, 61.0, 84.7, 104.5, 131.4, 136.4, 157.2, 157.5. FAB-MS *m/z* 281 (74), 280 (100), 223 (48). HRMS for $C_{14}H_{21}BO_5$ calcd 280.1482, found 280.1488.

Boronic Ester 115



To 10 mg (0.25 mmol) of a 60% dispersion of NaH in mineral oil suspended in 5 mL DMF was added 48 mg (0.17 mmol) of phenol **114**. The mixture was stirred 15 min and 0.050 mL (0.66 mmol) MOM-Cl was added. The resulting solution was stirred at room temperature for 1 h and quenched with water. The solution was extracted 3x with Et_2O and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo* to give 55 mg (98%) of the title compound as colorless oil, which was used without further purification. ^{1}H NMR ($CDCl_3$) δ 1.31 (s, 12H), 3.60 (s, 3H), 3.82 (s, 3H), 3.88 (s, 3H), 5.13 (s, 2H), 6.68 (d, J = 8 Hz, 1H), 7.45 (d, J = 8 Hz, 1H).

Biaryl 69

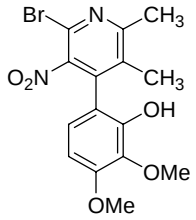


A solution of 1.08 g (5.45 mmol) MOM-protected phenol **101** and 0.90 mL (5.4 mmol) TMEDA in 30 mL THF was cooled to –78 °C. To the solution was added dropwise 7.0 mL (5.6 mmol) of a 0.8 M solution of *n*-BuLi in hexanes and the resulting solution allowed to warm to 0 °C. After 1.5 h at 0 °C the solution was cooled to –78 °C and 1.2 mL (11 mmol) of $B(OMe)_3$ in 30 mL THF was added over 10 min. The resulting

solution was allowed over 1 h to warm to room temperature and stirred an additional 16 h. 30 mL of 5% HCl was added and the solution extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to yield crude boronic acid **113** a white, crystalline solid, which was used immediately in the next step without further purification.

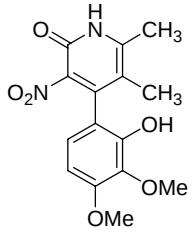
A mixture of the crude boronic acid, 645 mg (2.47 mmol) 4-bromopyridine **88**, 615 mg (5.32 mmol) $Pd(PPh_3)_4$, and 579 mg (5.46 mmol) Na_2CO_3, 60 mL toluene, 6 mL H_2O, and 6 mL EtOH was heated at reflux for 40 h. After cooling, 60 mL of water was added and the solution extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:1 hexanes:EtOAc, R_f = 0.25) afforded a yellow solid, which was recrystallized from hexanes/Et_2O to yield 737 mg (78%) of the title compound as a white, crystalline solid, mp 128-129 °C. IR (CCl_4) 2990 (m), 2955 (m), 2924 (m), 2874 (m), 2831 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.97 (s, 3H), 2.49 (s, 3H), 3.11 (s, 3H), 3.85 (s, 3H), 3.86 (s, 3H), 3.99 (s, 3H), 4.80 (d, *J* = 6 Hz, 1 H), 5.08 (d, *J* = 6 Hz, 1H), 6.69 (d, *J* = 8 Hz, 1H), 6.76 (d, *J* = 8 Hz, 1 H). ^{13}C NMR ($CDCl_3$) δ 15.9, 23.7, 54.5, 56.4, 57.1, 61.4, 99.4, 108.3, 121.1, 124.2, 124.9, 134.8, 141.4, 142.8, 148.5, 152.2, 155.0, 156.5. EI-MS *m/z* 378 (100), 332 (37). HRMS for $C_{18}H_{22}N_2O_7$ calcd 378.1427, found 378.1443.

2-Bromopyridine 108



To a solution of 101 mg (0.267 mmol) of 2-methoxypyridine **69** in 3 mL CH_2Cl_2 was added 0.50 mL (5.3 mmol) of PBr_3. The resulting solution was heated at 90 °C for 20 h. After cooling, the solution was diluted with water, neutralized with $NaHCO_3$, and extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1:1 hexanes:EtOAc, R_f = 0.45) gave 20 mg (18%) of the title compound as a white, crystalline solid, mp 139-144 °C. IR (CCl_4) 3526 (br), 3010 (w), 2959 (m), 2928 (m), 2854 (w) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.03 (s, 3H), 2.59 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), 5.96 (s, 1H), 6.50 (d, *J* = 9 Hz, 1H), 6.70 (d, *J* = 9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 16.4, 23.7, 56.3, 61.6, 104.8, 112.4, 124.2, 127.8, 133.1, 135.9, 140.5, 147.1, 153.7, 160.1. FAB-MS *m/z* 385 (100), 383 (98), 309 (87). HRMS for $C_{15}H_{15}BrN_2O_5$ calcd 385.0222, found 385.0218.

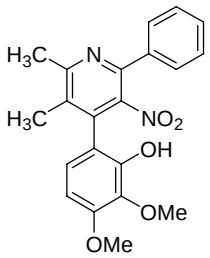
Pyridone 117



To a solution of 324 mg (0.856 mmol) of 2-methoxypyridine **69** in 25 mL CH_2Cl_2 was added 0.40 mL (4.2 mmol) PBr_3 and the resulting solution heated at reflux for 2.5 h.

After cooling water was added and the mixture neutralized with Na_2CO_3. The phases were separated and the aqueous layer extracted 2x with CH_2Cl_2. The combined organic extracts were concentrated *in vacuo* and the residue triturated with EtOAc to give 247 mg (90%) of the title compound as a white crystalline solid, mp > 330 °C. IR (KBr) 3313 (br), 3002 (m), 2936 (m), 2878 (m), 2831 (m), 1662 (s) cm^{-1}. ^1H NMR (DMSO – d_6) δ 1.65 (s, 3H), 2.24 (s, 3H), 3.65 (s, 3H), 3.76 (s, 3H), 6.52 (d, J = 10 Hz, 1H), 6.59 (d, J = 10 Hz, 1H), 9.23 (s, 1H), 12.52 (br s, 1H). EI-MS *m/z* 320 (100). HRMS for $C_{15}H_{15}N_2O_6$ calcd 320.1008, found 320.1003.

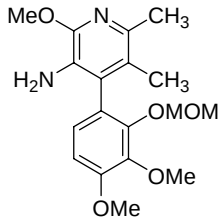
Triaryl 120



This compound was prepared directly from pyridone **117**. A suspension of 42 mg (0.13 mmol) of pyridone **117** and 19 mg (0.16 mmol) DMAP in 1 mL CH_2Cl_2 was cooled to 0 °C. Tf_2O (0.050 mL, 0.30 mmol) was added dropwise and the resulting solution stirred at 0 °C for 12 h. The reaction was quenched with water and extracted 3x with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in 7 mL of 1,4-dioxane and 29 mg (0.68 mmol) of LiCl and 0.025 mL (0.14 mmol) of $PhSnMe_3$ were added. The resulting solution was stirred for room temperature for 30 min and 13 mg (0.011 mmol) $Pd(PPh_3)_4$ was added and the solution heated at reflux for 18 h. After cooling, 10% ammonium chloride was added and the

solution extracted 3x with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:1 hexanes:EtOAc, R_f = 0.14) and subsequent recrystallization from hexanes/Et_2O afforded 28 mg (56%) of the title compound as a white, crystalline solid, mp 165-168 °C. IR (CCl_4) 3518 (m), 3068 (w), 3010 (w), 2959 (m), 2924 (s), 2850 (m), 2835 (m), 1623 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.11 (s, 3H), 2.66 (s, 3H), 3.88 (s, 3H), 3.93 (s, 3H), 5.97 (s, 1H), 6.51 (d, *J* = 9 Hz, 1H), 6.74 (d, *J* = 9 Hz, 1H), 7.39 (m, 3H), 7.58 (m, 2H). FAB-MS *m/z* 381 (100). HRMS for $C_{21}H_{20}N_2O_5$ calcd 381.1450, found 381.1450.

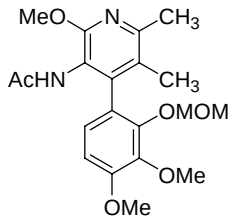
Aminopyridine 127



H_2 was bubbled through a suspension of 937 mg (2.48 mmol) of nitropyridine **69** and 680 mg 10% Pd/C in 100 mL THF for 3 d. The mixture was filtered through a pad of celite and the filtrate concentrated *in vacuo*. Purification by column chromatography (3:1 hexanes:EtOAc, R_f = 0.10) gave 494 mg (57%) of the title compound as a white, crystalline solid, mp 97-100 °C. IR (CCl_4) 3487 (w), 3386 (w), 2998 (m), 2948 (s), 2928 (s), 2854 (m), 2835 (m), 1608 (s) cm^{-1}. ^1H NMR (C_6D_6) δ 1.96 (s, 3H), 2.44 (s, 3H), 2.88 (s, 3H), 3.27 (s, 3H), 3.41 (br s, 2H), 3.71 (s, 3H), 3.89 (s, 3H), 4.86 (s, 2H), 6.32 (d, *J* = 9 Hz, 1H), 6.66 (d, *J* = 9 Hz, 1H). ^{13}C NMR (C_6D_6) δ 16.2, 22.4, 53.2, 55.7, 56.4, 60.7, 99.3, 109.2, 123.4, 124.8, 127.7, 131.9, 140.7, 144.0, 149.5, 150.8, 154.3, 204.0 EI-MS *m/z* 348 (100), 315 (33), 299 (42). HRMS for $C_{18}H_{24}N_2O_5$ calcd 348.1685, found

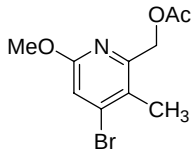
348.1688. An additional 356 mg (38%) of unreacted starting material (R_f = 0.25) was collected as well.

Acetamide 128



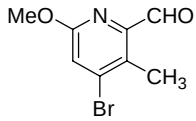
To a solution of 134 mg (0.385 mmol) of aminopyridine **127** in 7 mL THF was added 0.150 mL (1.59 mmol) of Ac_2O and the resulting solution heated at 70 °C for 16 h. After cooling, the solution was diluted with water and extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to yield 140 mg (94%) of the title compound, which was used without further purification. IR (CCl_4) 3394 (br), 3006 (m), 2948 (m), 2928 (m), 2835 (m), 1693 (s) cm^{-1}. ^1H NMR (CD_3OD) δ 1.83 (s, 3H), 1.94 (s, 3H), 2.43 (s, 3H), 2.92 (s, 3H), 3.81 (s, 3H), 3.86 (s, 3H), 3.89 (s, 3H), 4.78 (d, *J* = 6 Hz, 1H), 4.87 (d, *J* = 6 Hz, 1H), 6.76 (d, *J* = 8 Hz, 1H), 6.84 (d, *J* = 8 Hz, 1H). ^{13}C NMR (CD_3OD) δ 15.1, 21.3, 21.9, 52.9, 55.6, 55.7, 60.3, 99.1, 108.3, 116.8, 123.7, 124.1, 124.8, 142.5, 147.7, 148.3, 152.9, 154.2, 157.7, 171.7. EI-MS *m/z* 390 (74), 299 (100). HRMS for $C_{20}H_{26}N_2O_6$ calcd 390.1791, found 390.1790.

Acetate 131



This compound was prepared directly from pyridine **80**. A solution of 520 mg (2.41 mmol) pyridine **80** and 1.0 mL (7.2 mmol) of 30% H_2O_2 in 15 mL HOAc were heated at 60 °C for 3 d. After cooling, the solution was concentrated *in vacuo* and the residue dissolved in 10 mL Ac_2O. This solution was heated at 120 °C for 24 h and concentrated *in vacuo* to give 628 mg (93%) of the title compound as a pale brown oil, which was used without further purification. IR (CCl_4) 3017 (m), 2983 (m), 2948 (m), 2924 (m), 2905 (m), 2854 (m), 1748 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.11 (s, 3H), 2.28 (s, 3H), 3.85 (s, 3H), 5.14 (s, 2H), 6.93 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 16.9, 21.2, 54.0, 66.3, 114.4, 124.9, 138.1, 151.1, 162.2, 171.1.

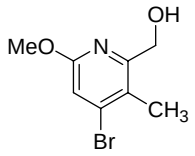
Aldehyde 132



A solution of 322 mg (1.17 mmol) acetate **131**, 0.50 mL HNO_3, and 2.5 mL H_2SO_4 was heated at 50 °C for 48 h. After cooling, the solution was diluted with water, neutralized with $NaHCO_3$, and extracted 3x with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to yield 173 mg (64%) of the title compound as a white, crystalline solid, mp 65-69 °C. IR (CCl_4) 2959 (m), 2920 (m), 2862 (m), 2819 (m), 1717 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.62 (s, 3H), 3.96 (s, 3H), 7.16 (s, 1H), 9.97 (s,

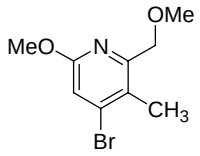
1H). ^{13}C NMR ($CDCl_3$) δ 16.3, 54.3, 199.0, 129.1, 139.9, 147.3, 162.5, 194.5.

Alcohol 133



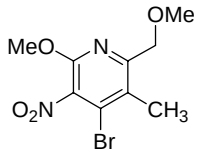
This compound was obtained directly from pyridine **80**. A solution of 701 mg (3.24 mmol) of pyridine **80**, 0.50 mL (4.4 mmol) 30% H_2O_2, and 22 mL acetic acid was heated at 60 °C for 3 d. After cooling, the solution was concentrated *in vacuo* and the residue dissolved in 7 mL of acetic anhydride. This solution was heated at 120 °C for 2 h. After cooling, the solution was concentrated *in vacuo*. To the residue was added 2.28 g (16.5 mmol) K_2CO_3 and 25 mL methanol. The resulting solution was stirred at room temperature for 18 h and concentrated *in vacuo*. The residue was suspended in water and extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to yield 509 mg (68%) of the title compound as a white, crystalline solid, mp 49-52 °C, which was used without further purification. IR (CCl_4) 3456 (br), 3021 (m), 2983 (m), 2951 (m), 2928 (m), 2866 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H), 3.82 (br s, 1H), 3.92 (s, 3H), 4.62 (s, 2H), 6.90 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 15.3, 54.2, 62.3, 112.7, 122.0, 138.2, 154.4, 161.9.

Methyl ether 134



To a solution of 2.16 g (9.31 mmol) of alcohol **133** and 3.31 g (14.3 mmol) of Ag_2O in 40 mL THF was added 2.0 mL (32 mmol) of iodomethane. The resulting solution was heated in the dark at 65 °C for 4 d. The suspension was filtered through a pad of celite and the filtrate concentrated *in vacuo* to yield 1.97 g (86%) of the title compound as a white, crystalline solid, mp = 48-50 °C, which was used without further purification. IR (CCl_4) 3014 (w), 2986 (w), 2951 (m), 2928 (m), 2893 (w), 2918 (w) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.34 (s, 3H), 3.39 (s, 3H), 3.88 (s, 3H), 4.50 (s, 2H), 6.93 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 17.0, 54.1, 58.9, 75.6, 114.0, 125.9, 138.3, 153.6, 162.0.

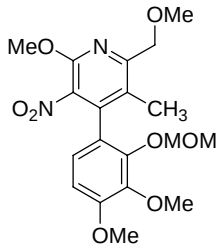
Nitropyridine 135



A solution of 914 mg (3.71 mmol) of pyridine **134** in 1.5 mL of HNO_3 and 8.5 mL of H_2SO_4 was stirred at room temperature for 2 d. The solution was diluted with water, neutralized with Na_2CO_3, and extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (9:1 hexanes:EtOAc, R_f = 0.11) afforded 550 mg (51%) of the title compound as a white, crystalline solid, mp 47-50 °C. IR (CCl_4) 3025 (m), 2990 (m), 2959 (m), 2928 (m), 2921 (m), 2819 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.40 (s, 3H), 3.40 (s,

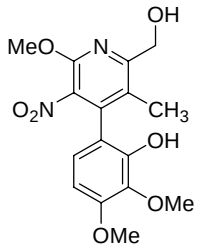
3H), 4.00 (s, 3H), 4.53 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 17.5, 55.1, 59.1, 75.1, 111.3, 127.2, 128.7, 152.9, 154.8. EI-MS *m/z* 292 (6), 290 (8), 262 (91), 260 (100), 247 (30), 245 (28). HRMS for $C_9H_{11}BrN_2O_4$ calcd 291.9882, found 291.9893.

Biaryl 136



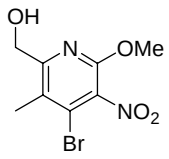
Boronic acid **113** was prepared as described above. A solution of 287 mg (1.19 mmol) of the crude boronic acid, 190 mg (0.653 mmol) of bromopyridine **135**, 350 mg (2.30 mmol) CsF, and 138 mg (0.119 mmol) $Pd(PPh_3)_4$ in 6 mL DME was heated at reflux for 20 h. After cooling, the solution was diluted with water and the solution extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:1 hexanes:EtOAc, R_f = 0.09) yielded 233 mg (87%) of the title compound as a white, crystalline solid, mp 71-73 °C. IR (CCl_4) 2994 (m), 2963 (m), 2932 (m), 2893 (m), 2835 (m), 1600 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H), 3.09 (s, 3H), 3.43 (s, 3H), 3.84 (s, 3H), 3.86 (s, 3H), 4.02 (s, 3H), 4.52 (d, *J* = 12 Hz, 1H), 4.56 (d, *J* = 12 Hz, 1H), 4.80 (d, *J* = 6 Hz, 1H), 5.08 (d, *J* = 6 Hz, 1H), 6.69 (d, *J* = 9 Hz, 1H), 6.76 (d, *J* = 9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 14.8, 54.7, 56.4, 57.1, 59.1, 61.4, 74.9, 99.4, 108.3, 120.5, 124.3, 126.8, 136.0, 142.5, 142.8, 148.5, 152.3, 154.3, 155.1. EI-MS *m/z* 408 (46), 286 (100). HRMS for $C_{19}H_{24}N_2O_8$ calcd 408.2498, found 408.2484.

Alcohol 137



A solution of 101 mg (0.247 mmol) of biaryl **136** in 7 mL CH_2Cl_2 was cooled to 0 °C, and 0.30 mL (0.30 mmol) of a 1M solution of BCl_3 in CH_2Cl_2 was added dropwise, causing the evolution of gas. After stirring at room temperature for 4 h, the reaction was quenched with water and extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:1 hexanes:EtOAc, R_f = 0.06) and subsequent recrystallization from hexanes/Et_2O gave 11 mg (13%) of the title compound as a white, crystalline solid. IR (CCl_4) 3515 (br), 3006 (m), 2979 (m), 2955 (m), 2936 (m), 2866 (m), 2835 (m), 1623 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.90 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), 4.08 (s, 3H), 4.70 (d, *J* = 4 Hz, 2H), 5.92 (s, 1H), 6.50 (d, *J* = 9Hz, 1H), 6.71 (d, *J* = 9Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 13.2, 54.9, 56.3, 61.6, 62.4, 104.7, 112.5, 122.9, 124.2, 135.9, 142.1, 147.1, 152.8, 153.5, 155.4.

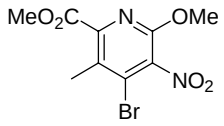
Alcohol 138



A solution of 403 mg (1.38 mmol) of methyl ether **135** in 20 mL CH_2Cl_2 was cooled to 0 °C and 3.0 mL (3.0 mmol) of a 1.0 M solution of BCl_3 in CH_2Cl_2 was added dropwise. The resulting solution was stirred 16 h at room temperature and quenched with water.

The phases were separated and the aqueous layer extracted 2x with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give 383 mg (100 %) of the title compound as a white, crystalline solid, mp 96-99 °C, which was used without further purification. IR (CCl_4) 3483 (br), 3026 (m), 2991 (m), 2949 (m), 2925 (m), 2898 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.26 (s, 3H), 3.83 (t, J = 5 Hz, 1H), 4.05 (s, 3H), 4.70 (d, 2H, J = 5 Hz). ^{13}C NMR ($CDCl_3$) δ 16.0, 55.4, 62.8, 123.5, 128.9, 153.3, 155.9.

Ester 139



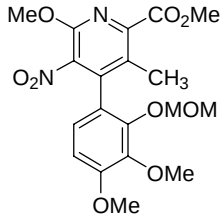
To a suspension of 397 mg (1.43 mmol) of alcohol **138** and 64 mg (1.6 mmol) NaOH in 30 mL water was added 710 mg (4.49 mmol) $KMnO_4$ and the resulting mixture stirred at room temperature for 24 h. MeOH was added and the suspension stirred 30 min and filtered. The filtrate was acidified with 1M HCl and concentrated *in vacuo*. The residue was dissolved in 20 mL MeOH and 4 mL H_2SO_4, and the solution heated at reflux for 16 h. The solution was diluted with water and basicified with K_2CO_3. The MeOH was removed *in vacuo* and the remaining aqueous solution extracted 3x with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give 269 mg (62%) of the title compound as a yellow, crystalline solid, mp 90-93 °C, which was used without further purification. IR (CCl_4) 3029 (w), 3002 (w), 2951 (m), 2924 (m), 2850 (w), 1740 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.48 (s, 3H), 3.96 (s, 3H), 4.02 (s, 3H). ^{13}C NMR ($CDCl_3$) δ 18.5, 53.5, 55.6, 127.6, 129.6, 147.0, 153.3, 165.7. EI-MS *m/z* 306 (65),

304 (59), 274 (89), 272 (100), 246 (58), 244 (59). HRMS for $C_9H_9BrN_2O_5$ calcd 303.9695, found 303.9683.

Purification of boronic acid 113

The crude boronic acid was obtained using the same reaction conditions as described above. After extracting with Et_2O, the combined organic layers were extracted with 2 M KOH. The aqueous layer was neutralized with conc HCl and extracted 3x with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. An analytical sample was obtained following recrystallization from hexanes/Et_2O as a white, crystalline solid, mp 125-129 °C. IR (CCl_4) 3526 (br), 3468 (br), 2998 (m), 2955 (m), 2928 (m), 2854 (m), 2835 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.49 (s, 3H), 3.79 (s, 3H), 3.87 (s, 3H), 5.25 (s, 2H), 6.29 (br s, 2H), 6.72 (d, J = 8 Hz, 1H), 7.52 (d, J = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 56.4, 58.6, 61.1, 100.7, 108.5, 131.8, 140.8, 156.5, 156.8.

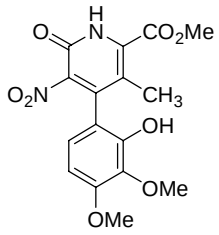
Biaryl 140



A solution of 682 mg (2.24 mmol) of ester **139**, 1.20 g (4.96 mmol) boronic acid **113**, 387 mg (0.335 mmol) $Pd(PPh_3)_4$, and 673 mg (4.43 mmol) CsF in 35 mL DME was heated at 75 °C for 24 h. After cooling, the solution was diluted with water and extracted 3x with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated *in*

vacuo. Purification by column chromatography (4:1 hexanes:EtOAc, R_f = 0.20) gave 646 mg (68%) of the title compound as a white, crystalline solid, mp 90-93 °C. IR (CCl_4) 3002 (m), 2948 (m), 2932 (m), 2897 (m), 2839 (m), 1740 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.16 (s, 3H), 3.11 (s, 3H), 3.84 (s, 3H), 3.87 (s, 3H), 3.96 (s, 3H), 4.04 (s, 3H), 4.84 (d, *J* = 6 Hz, 1H), 5.10 (d, *J* = 6 Hz, 1H), 6.71 (d, *J* = 8 Hz, 1H), 6.76 (d, *J* = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 15.9, 53.2, 55.2, 56.5, 57.2, 61.4, 99.5, 108.4, 119.6, 124.2, 127.7, 137.6, 142.8, 143.6, 146.7, 148.5, 152.6, 155.5, 166.7. EI-MS *m/z* 422 (100), 300 (32), 272 (36). HRMS for $C_{19}H_{22}N_2O_9$ calcd 422.1325, found, 422.1332.

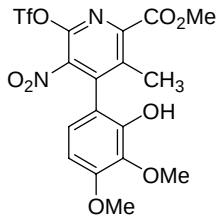
Pyridone 141



A solution of 81 mg (0.192 mmol) pyridine **140** and 0.12 mL (1.27 mmol) PBr_3 in 4 mL of DCE was heated at reflux for 12 h. After cooling, the reaction was quenched with water and the mixture extracted 3x with CH_2Cl_2. The combined organic extracts were concentrated *in vacuo* the residue washed with Et_2O to obtain 63 mg (90%) of the title compound as a white solid, mp 225-235 (decomp), which was used without further purification. IR ($CHCl_3$) 3515 (br), 3344 (br), 2843 (w), 1750 (w) 1685 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.18 (s, 3H), 3.87 (s, 3H), 3.92 (s, 3H), 3.98 (s, 3H), 6.02 (br s, 1H), 6.51 (d, *J* = 9 Hz, 1H), 6.72 (d, *J* = 9 Hz, 1H), 10.35 (br s). ^{13}C NMR ($CDCl_3$) δ 15.44, 54.1, 56.3, 61.6, 105.0, 111.6, 122.8, 123.6, 130.6, 135.9, 146.1, 146.4, 146.9, 153.7,

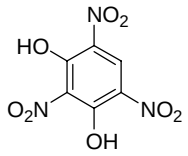
154.0, 161.5. FAB-MS 365 (100). HRMS for $C_{16}H_{16}N_2O_8$ calcd 365.0985, found 365.0979.

Triflate 142



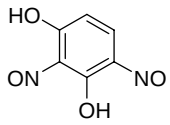
A suspension of 63 mg (0.172 mmol) of pyridone **141** and 23 mg (0.188 mmol) DMAP in 4 mL CH_2Cl_2 was cooled to 0 °C and 35 μL (0.21 mmol) Tf_2O added. The resulting solution was allowed to warm to room temperature and stirred 12 h. The reaction was quenched with water and the mixture extracted 3x with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Recrystallization from hexanes/Et_2O gave 71 mg (83%) of the title compound as a white, crystalline solid, mp 163-165. IR (CCl_4) 3515 (br), 3010, (w), 2955 (w), 2936 (w), 2839 (w), 1740 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.32 (s, 3H), 3.89 (s, 3H), 3.93 (s, 3H), 3.98 (s, 3H), 6.01 (br s, 1H), 6.55 (d, J = 8 Hz, 1H), 6.72 (d, J = 8Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 16.6, 53.7, 56.4, 61.7, 105.1, 110.9, 123.9, 136.1, 137.8, 139.5, 143.4, 146.1, 147.1, 147.5, 154.3, 164.8. EI-MS *m/z* 496 (98), 418 (52), 317 (100). HRMS for $C_{17}H_{15}F_3N_2O_{10}S$ calcd 496.0400, found 496.0385.

Trinitroresorcinol 149



A solution of 1.16 g (10.5 mmol) of resorcinol in 5.0 mL H_2SO_4 was heated to 95 °C. To this solution was added 4.5 mL HNO_3 over 15 min, and after 75 min at 95 °C, 2 mL water was added and the resulting mixture filtered. The filtrate was heated to reflux for 30 min, causing the evolution of gas. After cooling, the solution was neutralized with saturated $NaHCO_3$ and concentrated to 100 mL. Conc HCl was added, causing the formation of white precipitate, which was collected by filtration and recrystallized from $CHCl_3$ to give 1.98 g (77%) of the title compound as a white, red solid, mp 173-177 °C (decomp). IR (CCl_4) 3181 (br), 3078 (m) cm^{-1}. ^1H NMR (DMSO-d_6) δ 8.57 (s, 1 H), 8.75 (br s, 2 H). ^{13}C NMR (DMSO-d_6) 126.3, 126.6, 135.9, 156.4.

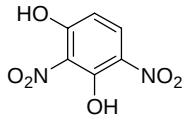
Diol 150



To a solution of 6.21 g (0.00564 mol) of resorcinol in 1.2 L water and 18 mL HOAc was added 38.2 g (0.554 mol) of $NaNO_2$ in one portion. The resulting solution was allowed to stir for 1 h during which time a precipitate formed. The product was collected by filtration to yield 9.37 g (99%) of a brown solid, mp 148-149 °C (decomp), which was used without further purification. Spectral data matched that of the reported compound.[130] IR (CCl_4) 3503 (br), 3383 (br), 2920 (m), 2847 (m) cm^{-1}. ^1H NMR

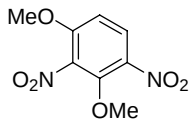
(DMSO-d_6) δ 6.33 (d, J = 10 Hz, 1 H), 6.44 (d, J = 10 Hz, 1 H), 7.77 (m, 2H), 13.78 (br s, 2 H). ^{13}C NMR (DMSO-d_6) δ 129.3, 130.0, 130.2, 131.4, 131.8, 147.6, 147.9, 173.9, 178.5, 179.5, 183.3. FAB-MS *m/z* 169 (21), 154 (100), 136.0 (88), 107 (32), 89.0 (38), 77 (33). HRMS for $C_6H_4N_2O_4$ calcd 169.0249, found 169.0249.

Dinitroresorcinol 151



To a solution of 3.67 g (21.8 mol) of dinitroso diol **150** in 50 mL TFA was added 5.0 mL (44 mmol) of 30% H_2O_2. The solution was stirred at room temperature for 24 h and concentrated *in vacuo*. The residue was recrystallized from $CHCl_3$ to yield 3.85 g (88%) of the title compound as a white, crystalline solid, mp 145-146 °C. IR (KBr) 3433 (br) 3216 (br), 3099 (w), 2920 (w), 2850 (w) cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 6.76 (d, J = 8 Hz, 1 H), 8.31 (d, J = 8 Hz, 1 H), 11.31 (br s, 1 H), 12.61 (s, 1 H). ^{13}C NMR (DMSO-d_6) δ 109.5, 128.7, 129.1, 132.2, 148.5, 157.4. EI-MS *m/z* 200 (94), 96 (100), 80 (47). HR-MS for $C_6H_4N_2O_6$ calcd 200.0069, found 200.0064.

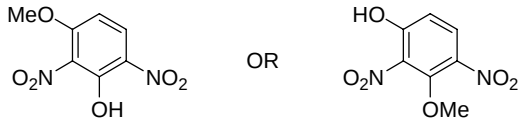
Dimethoxy arene 152



To a solution of 2.92 g (14.6 mmol) of diol **151** in 125 mL acetone was added 7.38 g (53.4 mmol) of K_2CO_3. To this mixture was added 4.5 mL (45 mmol) of dimethyl sulfate, and the resulting mixture heated at reflux for 16 h. After cooling, the mixture

was concentrated *in vacuo* and the residue dissolved in Et_2O. The organic phase was washed 2x with 2M KOH, dried over $MgSO_4$, and concentrated *in vacuo*. Recrystallization from hexanes/Et_2O afforded 2.35 g (71%) of the title compound as a white, crystalline solid, mp 72-73 °C. IR (CCl_4) 3107 (w), 3021 (w), 2983 (m), 2940 (m), 2639 (m), 1616 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.99 (s, 3H), 4.00 (s, 3H), 6.86 (d, J = 10 Hz, 1H), 8.16 (d, J = 10 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 57.7, 65.1, 107.6, 129.1, 136.5, 138.0, 148.8, 155.9. EI-MS *m/z* 228 (100), 198 (32). HRMS for $C_8H_8N_2O_6$ calcd 228.0382, found 228.0394.

Phenol 153 or 154

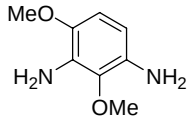


A solution of 67 mg (0.29 mmol) of dinitroarene **152** in 1.5 mL MeOH was heated to 60 °C. To the solution was added 165 mg (2.94 mmol) of NaHS in 6 mL MeOH and the resulting solution heated at 80 °C for 2.5 h. After cooling, the solution was neutralized with conc HCl and concentrated *in vacuo*. Water was added to the residue and precipitate obtained by filtration to yield 45 mg (71%) as orange solid, mp 102-106 °C. IR (CCl_4) 3161 (br), 2979 (w), 2944 (w), 2847 (w) cm^{-1}. ^1H NMR ($CDCl_3$) δ 4.02 (s, 3H), 6.68 (d, J = 8 Hz, 1H), 8.25 (d, J = 8 Hz, 1H), 11.05 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 57.8, 104.3, 128.5, 128.6, 131.5, 149.4, 158.2.

Nitroamine 155a or 155b

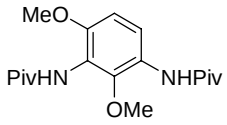
H_2 was bubbled through a suspension of 2.21 g (10.0 mmol) of dinitroarene **154** and 117 mg of 10% Pd/C in 100 mL THF. After 24 h, analysis by TLC indicated the starting material was consumed. The mixture was filtered through celite and the filtrate concentrated *in vacuo* to give 1.80 g (95%) of a single compound as an orange oil. IR (CCl_4) 3383 (br), 2924 (m), 2850 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.65 (br s, 2H), 3.79 (s, 3H), 3.84 (s, 3H), 6.62 (d, J = 9 Hz, 1H), 6.76 (d, J = 9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 57.4, 61.9, 109.3, 117.6, 134.7, 139.8, 144.2,

Diamine 156



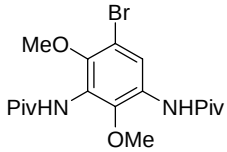
H_2 was bubbled through a mixture of 800 mg of 10% Pd/C, 2.76 g (12.1 mmol) of dinitro arene **154**, and 100 mL THF. The reaction was minotored by TLC until only a single compound remained and the mixture filtered through celite. The filtrate concentrated *in vacuo* to yield 2.03 g (100%) of diamine **156** as an orange oil, which was used without further purification. IR (CCl_4) 3460 (m), 3375 (m), 3041 (w), 2998 (m), 2936 (m), 2905 (m), 2827 (m), 1612 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.58 (br s, 4H), 3.76 (s, 6 H), 6.09 (d, J = 9 Hz, 1H), 6.43 (d, J = 9 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 56.7, 58.9, 104.0, 107.8, 130.7, 134.3, 135.9, 141.6. EI-MS *m/z* 168 (58), 153 (100), 138 (56). HRMS for $C_8H_{12}N_2O_2$ calcd 168.0899, found 168.0902.

Bis-pivalanilide 157



To a suspension of 598 mg (3.56 mmol) of diamine **156** and 6.6 g (48 mmol) K_2CO_3 in 40 mL THF was added 5.5 mL (45 mmol) of pivaloyl chloride, causing the immediate formation of a white precipitate. The resulting suspension was heated a reflux for 90 min. After cooling, the reaction was quenched with water and the solution extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1:1 hexanes:EtOAc, R_f = 0.15) yielded 925 mg (77%) of the title compound as a white, crystalline solid, mp 123-126 °C. IR (CCl_4) 3449 (m), 2963 (m), 2905 (m), 2866 (m), 2835 (m), 1693 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.28 (s, 9H), 1.36 (s, 9H), 3.72 (s, 3H), 3.77 (s, 3H), 6.63 (d, *J* = 8 Hz, 1H), 6.95 (br s, 1H), 7.94 (br s, 1 H), 8.15 (d, *J* = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 15.7, 28.0, 28.1, 39.9, 40.2, 56.6, 60.7, 66.3, 106.8, 119.0, 119.1, 126.0, 146.2, 151.0, 176.9, 177.4. FAB-MS *m/z* 337 (100), 336 (64),, 253 (62), 57 (67). HRMS for $C_{18}H_{28}N_2O_4$ calcd 337.2127, found 337.2137.

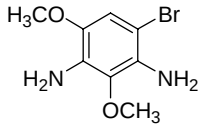
Bromide 158



To a solution of 105 mg (0.312 mmol) of bis-pivalanilide **157** in 4 mL HOAc was added a solution of 0.020 mL (0.39 mmol) Br_2 in 5 mL HOAc. The resulting solution was stirred 24 h at room temperature, quenched with aqueous $Na_2S_2O_3$, and extracted 2x with

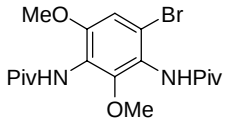
Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo* to afford 124 mg (95%) of the title compound as a white, crystalline solid, mp 140-143 °C. IR (CCl_4) 3441 (m), 3309 (br), 2963 (m), 2924 (m), 2850 (m), 1697 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.33 (s, 9H), 3.65 (s, 3H), 3.78 (s, 3H), 6.87 (br s, 1H), 6.91 (s, 1H), 6.97 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 28.0, 28.1, 39.7, 39.8, 56.8, 61.2, 111.3, 120.0, 121.6, 123.7, 153.9, 154.8, 177.5, 177.6.

Diaminobromide 159



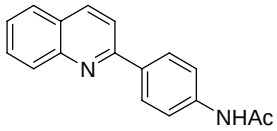
To a solution of 0.10 mL (0.59 mmol) of a 48% solution of HBr in water and 0.10 mL DMSO in 3 mL CH_2Cl_2 was added a solution of 0.046 mg (0.27 mmol) of amine **159** in 3 mL CH_2Cl_2. The resultant solution was stirred for 3 d, diluted with water, and basicified with K_2CO_3. The solution was extracted 3x with CH_2Cl_2, and the combined organic extracts dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (3:1 hexanes:EtOAc, R_f = 0.22) gave 25 mg (37%) of the title compound as yellow, crystalline solid, mp 144-148 °C (decomp). IR (CCl_4) 3476 (m), 3379 (m), 3002 (m), 2967 (m), 2944 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.68 (br s, 4H), 3.75 (s, 6 H), 6.66 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 56.7, 58.8, 96.3, 110.9, 130.1, 133.0, 135.6, 141.5.

Bromobis-pivalanilide 158



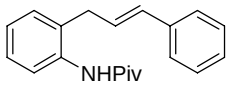
This compound was obtained in 72% yield according to the same procedure as bis-pivalanilide **158**, as a white, crystalline solid. IR (CCl_4) 3441 (w), 3309 (br), 2963 (m), 2924 (m), 2850 (m), 1697 (m) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.31 (s, 9H), 1.33 (s, 9H), 3.65 (s, 3H), 3.78 (s, 3H), 6.87 (br s, 1H), 6.91 (s, 1H), 6.97 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 28.0, 28.1, 39.7, 39.8, 56.8, 61.2, 111.3, 120.0, 121.6, 123.7, 153.9, 154.8, 177.5, 177.6.

Biaryl 163



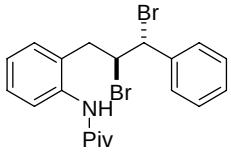
A solution of 39 mg (0.14 mmol) triflate **118**, 140 mg (0.473 mmol) stannane **161**,[139] and 41 mg (0.97 mmol) LiCl was stirred at room temperature for 30 min. To the solution was added 29 mg (0.025 mmol) of $Pd(PPh_3)_4$ and the resulting solution heated at reflux for 20 h. After cooling, saturated NH_4Cl was added and the product extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (1:1 EtOAc:hexanes, R_f = 0.40) yielded 13 mg (36%) of the title compound as a white, crystalline solid, mp 155-160 °C. IR (CCl_4) 3445 (w), 2967 (m), 2920 (s), 2854 (m), 1709 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.19 (s, 3H), 7.44 (br s, 1H), 7.50 (t, *J* = 8 Hz, 1H), 7.65-7.72 (m, 3H), 7.79-7.84 (m, 2H), 8.12-8.20 (m, 4 H). FAB-MS *m/z* 263 (H^+, 62), 262 (14), 154 (70), 136 (70). HRMS for $C_{18}H_{14}N_2O$ calcd 262.1106, found 262.1103.

Amidoolefin 166



A solution of 240 mg (1.00 mmol) allyic benzoate **165**,[46] 353 mg (1.08 mmol) siloxane **164**,[43] and 87 mg (0.16 mmol) $Pd(dba)_2$ in 15 mL THF was degassed via a single freeze-pump-thaw cycle. TBAF (1.15 mL of a 1M solution in THF, 1.15 mmol) was added and the resulting solution degassed via a second freeze-pump-thaw cycle. The solution was heated at 60 °C for 24 h, diluted with water, and extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (9:1 hexanes:EtOAc, R_f = 0.14) gave 134 mg (45%) of the title compound as a white, crystalline solid, mp 96-99 °C. IR (CCl_4) 3425 (br), 3091 (w), 3060 (w), 3021 (w), 2959 (m), 2924 (m), 2870 (w), 1693 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.24 (s, 9H), 3.53 (d, 2H, *J* = 5 Hz), 6.31 (dt, *J* = 16 Hz, 5 Hz, 1H), 6.42 (d, *J* = 16 Hz, 1H), 7.10 (dt, *J* = 8 Hz, 1 Hz, 1H), 7.21-7.32 (m, 7H), 7.48 (br s, 1H), 7.95 (d, *J* = 8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 28.1, 36.5, 40.1, 123.8, 125.4, 126.6, 127.8, 128.1, 129.1, 130.3, 130.6, 132.3, 136.8, 137.0, 177.0.

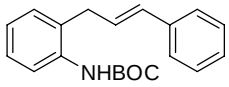
Dibromide 168



A solution of 0.050 mg (0.17 mmol) of alkene **166** in 3 mL CH_2Cl_2 was cooled to 0 °C. To this solution was added a dropwise a solution of 7 drops of Br_2 in 3 mL CH_2Cl_2 and the resulting solution allowed to warm to room temperature and stirred 16 h. Water was

added and the solution extracted 2x with CH_2Cl_2. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (9:1 hexanes:EtOAc, R_f = 0.10) afforded 37 mg (48%) of the title compound as a white, crystalline solid, mp 159-160 °C (decomp). IR (CCl_4) 3433 (br), 2955 (m), 2920 (m), 2854 (m), 1685 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.32 (s, 9H), 3.16 (dd, *J* = 15 Hz, 10 Hz, 1H), 3.85 (dd, *J* = 15 Hz, 2 Hz, 1H), 4.67 (dt, *J* = 10 Hz, 2 Hz, 1H), 5.18 (d, *J* = 10 Hz, 1H), 7.18 (dt, *J* = 8 Hz, 1Hz, 1H), 7.27-7.40 (m, 7H), 7.62 (d, *J* = 8 Hz, 1H), 7.67 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 28.2, 38.8, 40.0, 57.8, 60.1, 126.4, 128.3, 128.4, 129.2, 129.5, 131.0, 131.3, 136.2, 139.9, 177.6. FAB-MS *m/z* 456 (78), 454 (94), 452 (52), 294 (100), 292 (86). HRMS for $C_{20}H_{23}Br_2NO$ calcd 454.0204, found 454.0220.

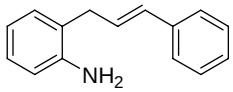
Carbamate 170



To a solution of 114 mg (0.478 mmol) of allylic benzoate **165**, 202 mg (0.595 mmol) siloxane **169**, and 109 mg (0.199 mmol) $Pd(dba)_2$ in 10 mL THF was added 0.60 mL (0.60 mmol) of a 1M solution of TBAF in THF. The solution was degassed via a single freeze-pump-thaw cycle and heated at 60 °C for 24 h. After cooling, the solution was diluted with water and extracted 3x with Et_2O. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. Purification by column chromatography (9:1 hexanes:EtOAc, R_f = 0.34) afforded 79 mg (56%) of title compound as a white, crystalline solid, mp 104-107 °C. IR (CCl_4) 3441 (br), 3021 (w), 2979 (w), 1740 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.46 (s, 9H), 3.50 (d, *J* = 6 Hz, 2H), 6.30 (dt, *J* = 16 Hz, 6 Hz,

1H), 6.42 (d, *J* = 16 Hz, 1H), 6.45 (br s, 1H), 7.05 (t, *J* = 8 Hz, 1H), 7.17-7.34 (m, 7H), 7.77 (d, *J* = 8 Hz, 1H). EI-MS *m/z* 310 (5), 253 (100), 118 (58). HRMS for $C_{20}H_{21}NO_2$ calcd 309.1729, found 309.1728.

Amino olefin 171



A solution of 79 mg (0.27 mmol) of carbamate **170** dissolved in 4 mL of 3M HCl and 10 mL EtOAc was stirred at room temperature for 18 h. The reaction was neutralized with saturated Na_2CO_3 and the product extracted 3x with EtOAc. The combined organic extracts were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was purified after passing through a plug of silica gel using pentane as the eluent to yield 38 mg (69%) of the title compound as a colorless oil. IR (CCl_4) 3460 (br), 3390 (br), 3087 (m), 3060 (m), 3029 (m), 1619 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 3.46 (d, *J* = 6 Hz, 2H), 3.68 (br s, 2H), 6.34 (dt, *J* = 16 Hz, 6 Hz, 1H), 6.46 (d, *J* = 16 Hz, 1H), 6.69 (d, *J* = 8 Hz, 1H), 6.76 (t, *J* = 7 Hz, 1H), 7.09 (t, *J* = 8 Hz, 2H), 7.20 (t, *J* = 7 Hz, 1H), 7.28 (t, *J* = 8 Hz, 2H), 7.34 (d, *J* = 7 Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 36.1, 116.3, 119.3, 124.6, 126.6, 127.7, 128.1, 128.2, 129.0, 130.7, 131.6, 137.6, 145.3. EI-MS *m/z* 209 (99), 118 (100). HRMS for $C_{15}H_{15}N$ calcd 209.1204, found 209.1201.

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