Formal Total Synthesis of Diazonamide A

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Mai, Cheng-Kang (Ph.D., Chemistry)

Formal Total Synthesis of Diazonamide A

Thesis directed by Professor Tarek Sammakia

This dissertation describes efforts toward the total synthesis of diazonamide A, a complex marine natural product. First, efficient methods to prepare 3,3-diaryloxindoles from 3-aryloxindoles were developed via either Pd-catalyzed α-arylations or nucleophilic aromatic substitutions using the oxindole enolate as the nucleophile. Second, this method has been successfully applied to a formal synthesis of diazonamide A via the highly diastereoselective construction of the C10 quaternary center. Third, a cyclization precursor for a cascade α-arylation/direct arylation approach to the total synthesis was synthesized and tested, and this substrate was found to be failed to cyclize. Finally, two approaches to the synthesis of the aromatic core of diazonamide A, via our Pd-catalyzed α-arylation method and Au-catalyzed oxazole formation developed by Liming Zhang and coworkers, were attempted. Unfortunately, neither of these two methods was able to provide the desired product.

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1 Diazonamide A: Isolation, Biological Activity, and Synthesis

1.1 Isolation and Structural Determination of Diazonamides

The diazonamides (Figure 1.1) are a family of cytotoxic macrocylic peptide derivative isolated from colonial ascidians of the genus *Diazona*. Diazonamide A (**1**) and B were first isolated by Fenical and Clardy in 1991 from the secondary metabolites of the ascidian *Diazona Angulata* (originally misidentified as *Diazona Chinensis*) collected in Siquijor Island, Phillipines.[1] Three other members, Diazonamides C-E, were later isolated by a group at PharmaMar in 2008 from extracts of a tunicate of the genus *Diazona* collected in Indonesia.[2]

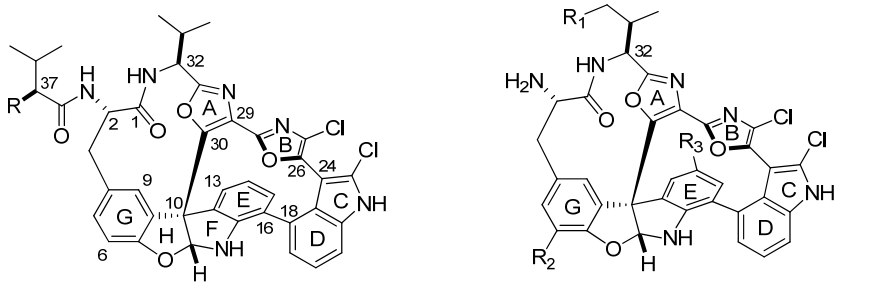

Figure 1.1 Structures of the Diazonamides

The diazonamides represent a new class of halogenated, unsaturated cyclic peptides, and they share a common highly rigid heterocyclic scaffold with essentially no conformational freedom, and two peripheral chlorine atoms, but they differ in the C2 and C32 side chains and in the halogenation on the *G* and *E* carbocyclic rings.

In the original isolation paper, Fenical and Clardy proposed the structure **2** (Figure 1.2), for diazonamide A, with a valine residue at C2 and a hemiacetal moiety, based on the analogy of diazonamide B.[1] The hemiacetal moiety of diazonamide B can explain the vicinal coupling between the C11 and the D_2O exchangeable proton, and the dehydrated cyclic acetal moiety, which was obtained from the single crystal X-ray structure of the *p*-bromobenzamide derivative of diazonamide B. Similar spectral data prompted them to propose the same heterocyclic core of diazonamide B for diazonamide A with unidentified stereochemistry on the terminal valine.

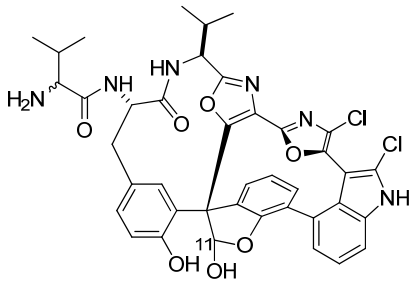

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Figure 1.2 Fenical and Clardy's Proposed Structure

The novelty of the proposed structure by Clardy and Fenical, along with impressive antitumor activity rendered this molecule a popular target for synthesis by the groups of Feldman,[3] Harran,[4-8] Konopelski,[9,10] Liebscher,[11,12] Magnus,[13-18] Moody,[19-23] Nicolaou,[24-27] Pattenden,[28] Vedejs,[29-31] Wipf,[32-33] and Wood[34]. In 2001, the Harran group reported a total synthesis of the proposed structure **2**, and found that it had different spectral properties, was unstable, and lacked the potent biological activity of the natural product.[6] These results prompted the Harran group to re-evaluate the original data obtained by Fenical and Clardy.

It had been known that acid digests of diazonamide A do not provide valine.[35] Reevaluation of the NMR data reported by Fenical and Clardy suggested that C37 substituent in natural diazonamide A should be an alcohol instead of an amine. This NH_2 to OH change requires a compensatory permutation at other position to match the mass, and Harran proposed that the original X-ray data for the *p*-bromobenzamide derivative of diazonamide B (from which the structure of diazonamide A had been inferred) had been misinterpreted. The closed hemiaminal moiety of diazonamide A and B explain the observed mass spectral data without invoking a dehydrative cyclization, and also accounted for the vicinal coupling of C11 and an exchangeable proton.[8] Furthermore, the total syntheses of this revised structure by Nicolaou[36-39] and Harran[40] have confirmed that **1** is the correct structure of diazonamide A.

1.2 Biological Activity of Diazonamide A and its Derivatives

Although all the diazonamides are cytotoxic, diazonamide A is by far most potent, with *in vitro* IC_{50} values less than 15 ng/mL against human HCT-116 colon carcinoma and B-16 murine melanoma cell lines.[1] A re-isolation of diazonamide A from natural sources was funded by the Development Therapeutics Program of the Natural Products Branch of the National Cancer Institute, and the compound was subjected to NCI60 human tumor cell line anticancer drug screen.[41] Analysis by the COMPARE algorithm of differential cytotoxicity patterns indicated that the activity of diazonamide A correlated most closely with the known tubulin binding agents, such as the vinca alkaloids and paclitaxel, and suggested a tubulin-active mechanism of action.[42] Cells treated with diazonamide A arrest at the G2/M boundary, and fail to form organized bipolar mitotic

spindles, similar to cells treated with paclitaxel and vinblastine.[8,43] However, neither diazonamide A nor its close analog **3** significantly inhibits vinblastine, colchicine and dolastatin 10 binding to tubulin, or nucleotide exchange on β-tubulin. And neither of them can stabilize the colchicine binding activity of tubulin.[44] All these results suggest that diazonamide A either binds to tubulin at a unique and unidentified binding site, or does not bind to tubulin at all.

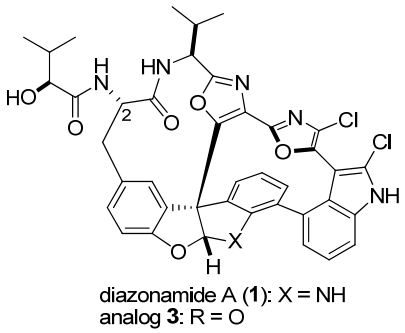
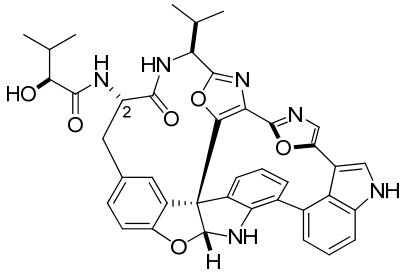


Figure 1.3 Structures of Diazonamide A and its Analog **3**

In 2007, in collaboration with the Wang and McKnight groups, Harran reported studies of the mechanism of action of diazonamide A and its analogs,[45] and the efficacy of these compounds as anticancer agents in mouse models.[43] They identified a known mitochondrial matrix enzyme, ornithine δ-amino transferase (OAT), as a diazonamide binding protein, and suggested that diazonamide A disrupts the interaction of OAT with mitotic-spindle-promoting proteins. However, diazonamide A does not inhibit the amino transferase activity of OAT, and the known inhibitors of OAT are not cytotoxic. In addition, a role for OAT in cancer cell mitosis is redundant in healthy cells. This finding renders OAT a new target for anticancer drug research.

In the mouse model study, they found that a close analog (AB5, **4**) of diazonamide A lacking two peripheral chlorine atoms, retained the cytotoxicity of diazonamide A, did

not display overt toxicity nor did it cause weight loss, a change in overall physical appearance, or showed any evidence of causing neutropenia in mice. Although paclitaxel and vinblastine show indistinguishable efficacy, mice treated with these two drugs display significant weight loss and neutropenia. These results render diazonamide A and its analogs as more attracting synthetic targets.



AB5 (**4**)

Figure 1.4 Structure of Diazonamide Derivative AB5 (**4**)

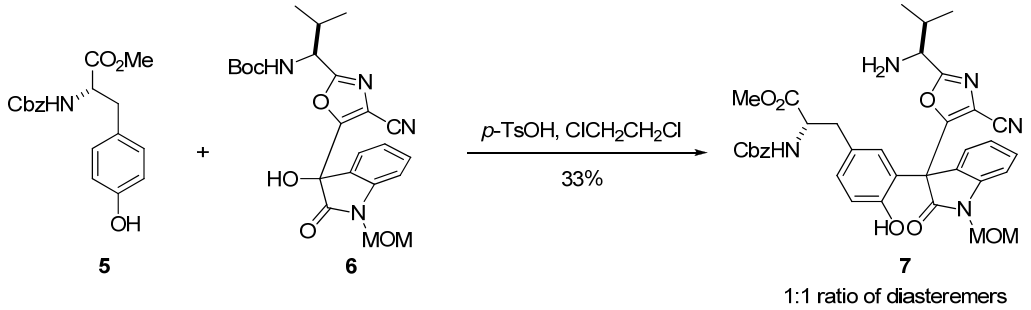
1.3 Synthesis of Diazonamide A

Diazonamide A is a challenging synthetic target, due to its highly rigid heterocyclic core with a deeply buried central C10 quaternary stereocenter.[46] Synthetic efforts toward the synthesis of the original Fenical and Clardy's structure (**2**) provide some useful insights for the synthesis of Harran's revised correct structure. For example, Wipf,[32] Magus,[14] and Harran[6] have shown that selective introduction of the two peripheral chlorine atoms at late stage is possible. And Harran also demonstrated that atropselective cyclization of the right hand macrocycle could be furnished by a Witkop-type photocyclization.[40] Taking advantage of these known transformations, the synthetic challenge of diazonamide A, in great part, lies in the stereoselective construction of the highly hindered quaternary C10.

A lot of groups have contributed their synthetic efforts towards diazonamide A, since Harran published its correct structure. Numerous papers of methods developments and progress towards the total synthesis of diazonamide A have been reported (Ciufolini,[47] Konopelski,[48] Magnus,[49] Moody,[50-54] Pattenden,[55] Vedejs,[56] and Wood[57]). Because Moody has written a comprehensive review[46] about syntheses of diazonamide A recently, only the four successful total syntheses and one formal synthesis are discussed as follows.

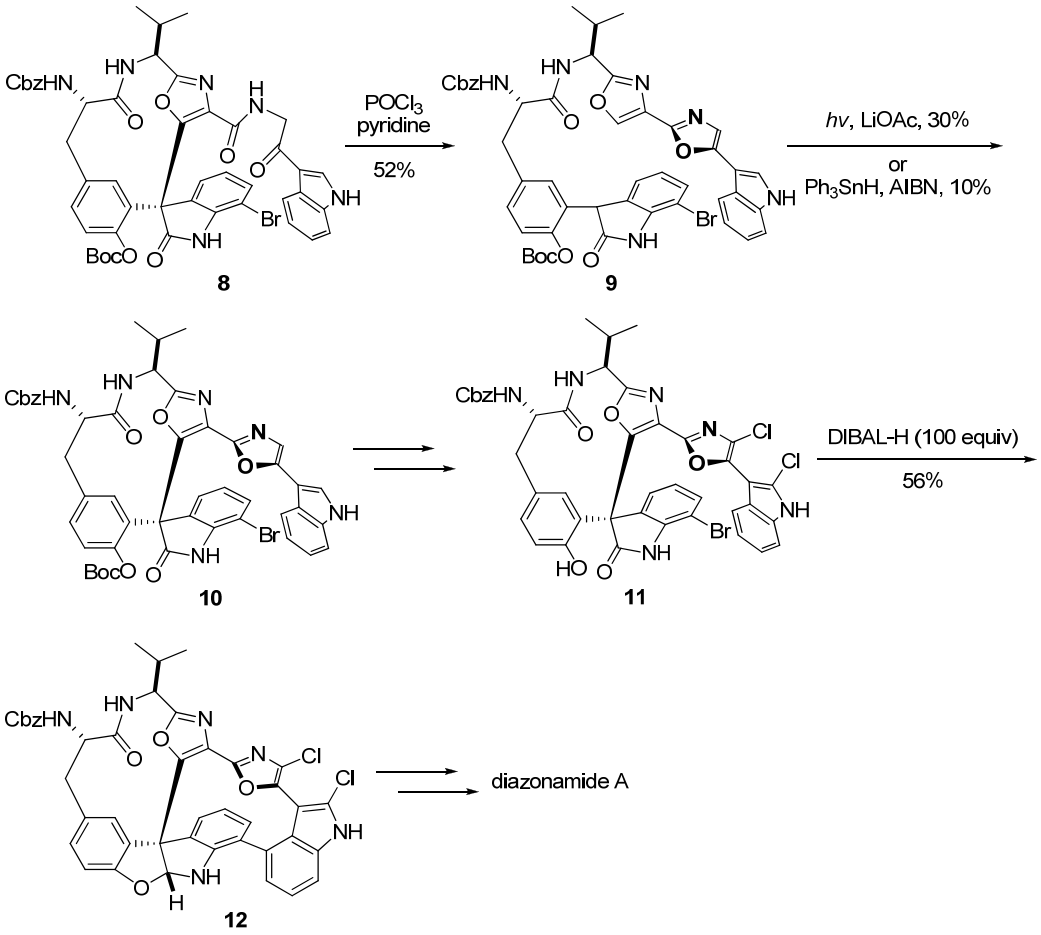
1.3.1 Nicolaou's First Total Syntheses of Diazonamide A

In 2002, the Nicolaou group published the first total synthesis of diazonamide A.[36,37] They utilized a Friedel-Crafts type alkylation (electrophilic aromatic substitution, S_EAr) of a tyrosine phenol **5** and a tertiary alcohol **6** to construct the quaternary C10. Although both the coupling partners, **5** and **6**, bear stereocenters, the reaction proceeds with no diastereselectivity to provide compound **7** as a mixture of 1:1 ratio of diastereomers (Scheme 1.1), because both the stereocenters are too far away from the reaction center to induce the diastereoselectivity. And the diastereomeric mixture can be separated by flash chromatography after protection of the free amine as the *tert*-butyl carbamates.



Scheme 1.1 Construction of Quaternary C10 in Nicolaou's First Synthesis

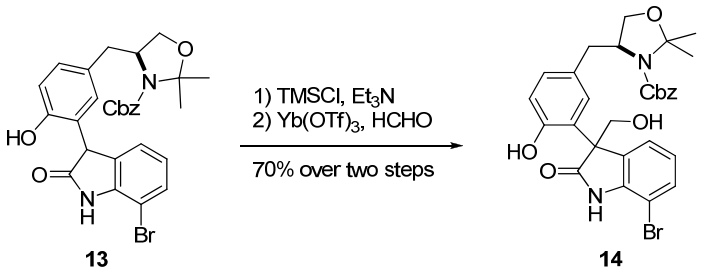
During the study of the first total synthesis, Nicolaou developed an efficient Robinson-Gabriel oxazole formation using $POCl_3$ in pyridine to convert keto amide **8** to oxazole **9**. This method works in hindered substrates better than other oxazole syntheses. The right hand macrocycle was constructed via a direct arylation similar to that used in Harran's total synthesis of the original incorrect structure of diazonamide A.[8] Both photochemical and radical cyclization conditions were examined, and Witkop-type photocyclization was found to provide a better yield. After elaboration to intermediate **11**, the hemiaminal moiety was formed via a reductive cyclization induced by 100 equivalents of DIBAL-H to provide **12**. They reported that portionwise addition of DIBAL-H was critical for the success. Synthesis of diazonamide A was then accomplished by removing the Cbz protecting group and installing the isovaleric acid side chain. This synthesis confirmed Harran's revised structure to be the correct structure of diazonamide A with all the stereochemistry set up, including the isovaleric acid side chain (Scheme 1.2).



Scheme 1.2 Completion of Nicolaou's First Total Synthesis

1.3.2 Nicolaou's Second Total Synthesis of Diazonamide A

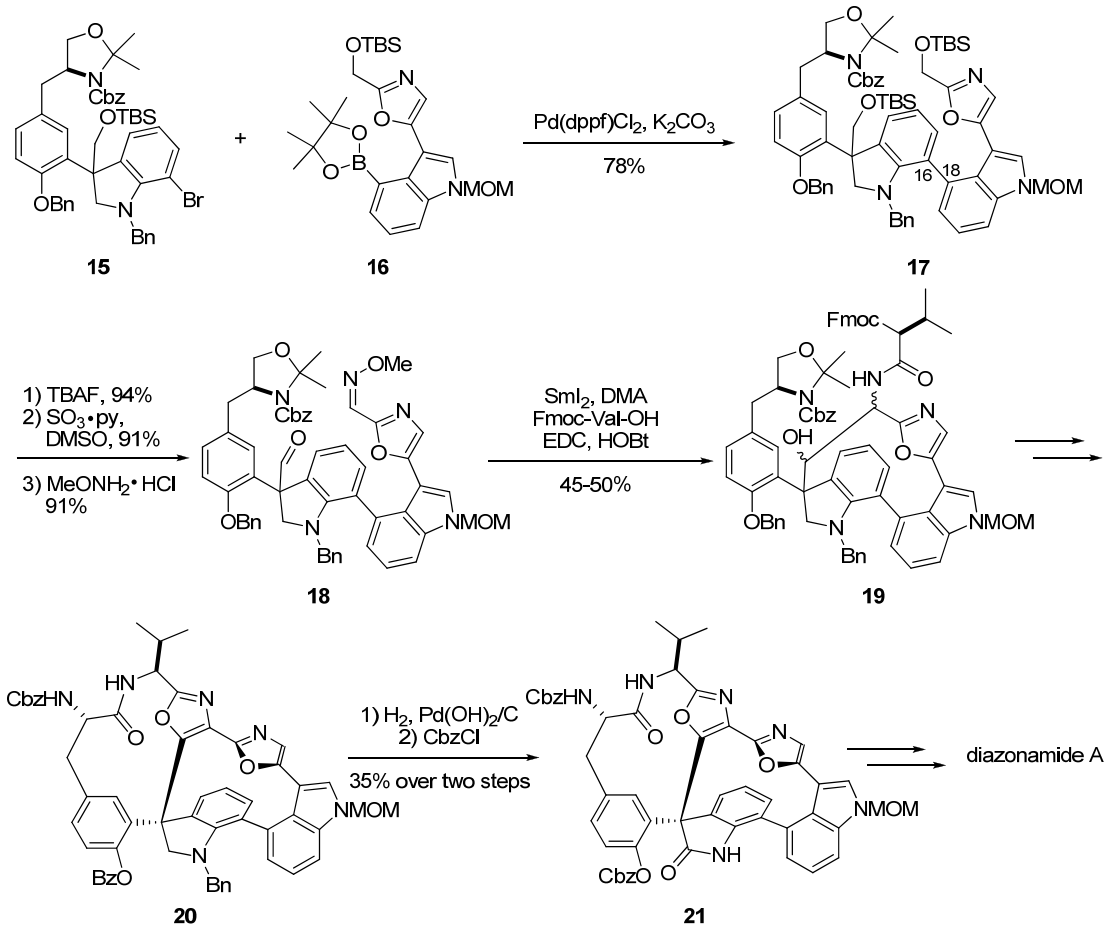
Nicolaou's second total synthesis[38,39] applied a Lewis acid catalyzed Mukaiyama aldol reaction of oxindole **13**, which was converted to a TMS enol ether, and formaldehyde to provide alcohol **14** as a mixture of 1:1 ratio of diastereomers (Scheme 1.3). This reaction is non-stereoselective because the stereocenter on oxindole **13** is too far to induce the diastereoselectivity.



13 14

Scheme 1.3 Construction of Quaternary C10 in Nicolaou's Second Synthesis

The C16-C18 bond of biaryl **17** was formed by Suzuki coupling of bromide **15** and boronic ester **16** (Scheme 1.4), which provided much higher yield than Witkop-type photocyclization. Both TBS protecting groups were removed by TBAF, and oxidized by Parikh-Doering oxidation using SO_3-pyridine activated DMSO.[58] The aromatic aldehyde was then converted to oxime **18** with $MeONH_2$. A one-pot reaction sequence consisting of macrocyclization, N-O bond cleavage, and peptide coupling induced by SmI_2 with DMA as an activating ligand and Fmoc-Val-OH, provided hydroxyl amide **19**. After oxazole formation and amide formation to cyclize the left hand macrocycle, compound **20** was subjected to hydrogenation with Pearlman's catalyst ($Pd(OH)_2$). Interestingly, hydrogenation not only removed both the benzyl and Cbz protecting groups, but also oxidized the amine to an oxindole to provide compound **21** after reprotection of the phenol with a Cbz protecting group. This set the stage for the reductive cyclization to furnish the hemiaminal moiety and completion of the total synthesis via a similar route as in their first total synthesis.

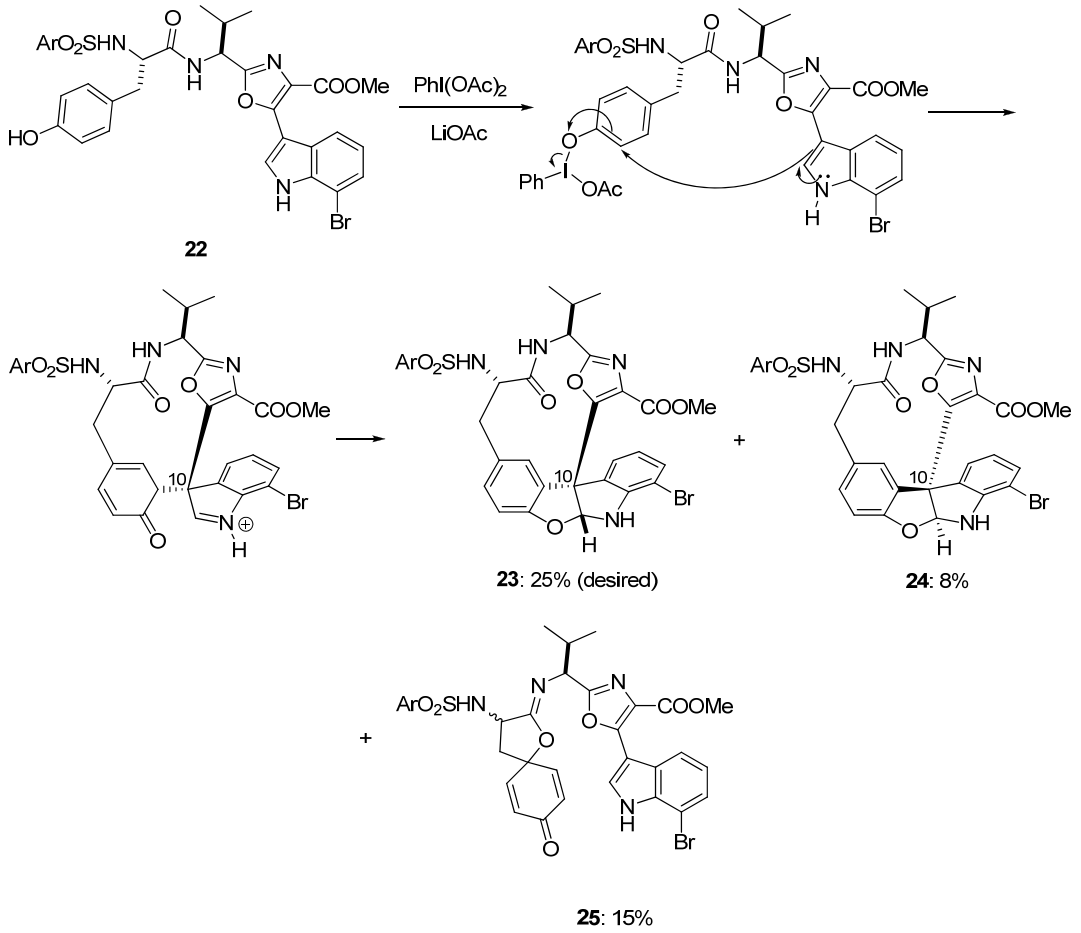


Scheme 1.4 Completion of the Heterocyclic Core in Nicolaou's Second Synthesis

1.3.3 Harran's Total Synthesis of Diazonamide A

Harran's total synthesis of diazonamide A applied a cascade oxidative [3+2] cyclization reaction initiated by a hypervalent iodine reagent,[59] $PhI(OAc)_2$, to construct the quaternary C10 along with the complete hemiaminal moiety (Scheme 1.5).[40] The phenol of compound **22** reacts with $PhI(OAc)_2$ to form an active hypervalent iodine intermediate which is attacked by the nucleophilic indole to form a C-C bond and dearomatize the phenol. After tautomerization, the regenerated phenol attacks the

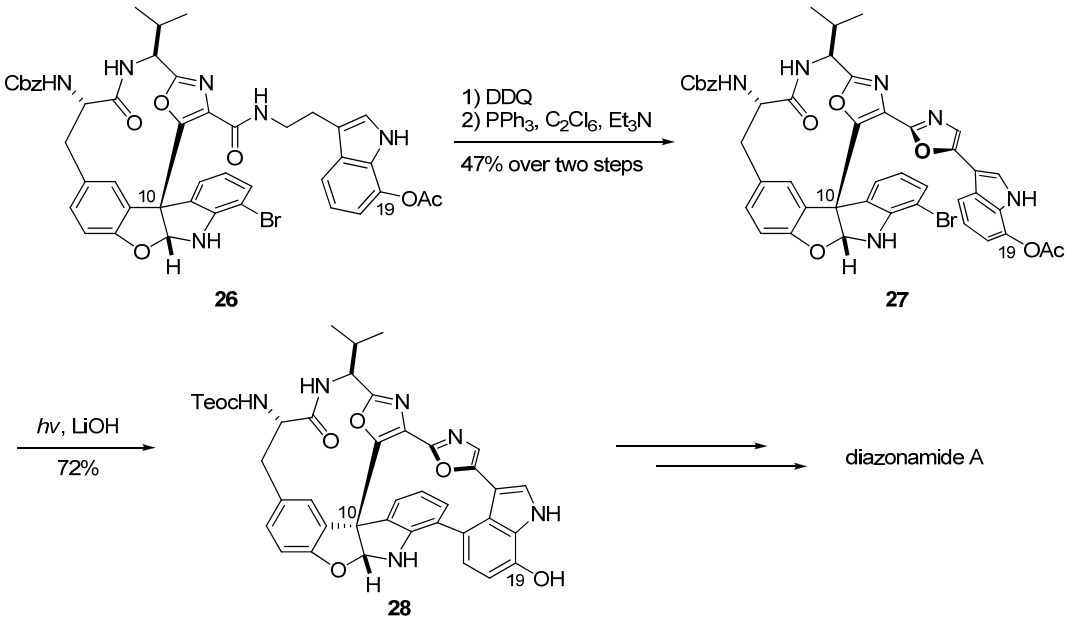
indoline to furnish the hemiaminal. The desired C10 macrocycle **23** with the correct stereochemistry on C10 can be obtained in 25% yield, along with 8% yield of the undesired C10 epimer (**24**, structure confirmed by single crystal X-ray crystallography), and 15% yield of compound **25** generated via the attack of the active hypervalent iodine intermediate by the amide. Although the yield for the desired product (**23**) was low, this reaction indicated that the two stereocenters on the backbone could induce some diastereoselectivity for the macrocyclization.



Scheme 1.5 Harran's Synthesis of Quaternary C10

For the cyclization of the right hand macrocycle, the Harran group used a modified Witkop-type photocyclization, different from the strategy used in their synthesis of

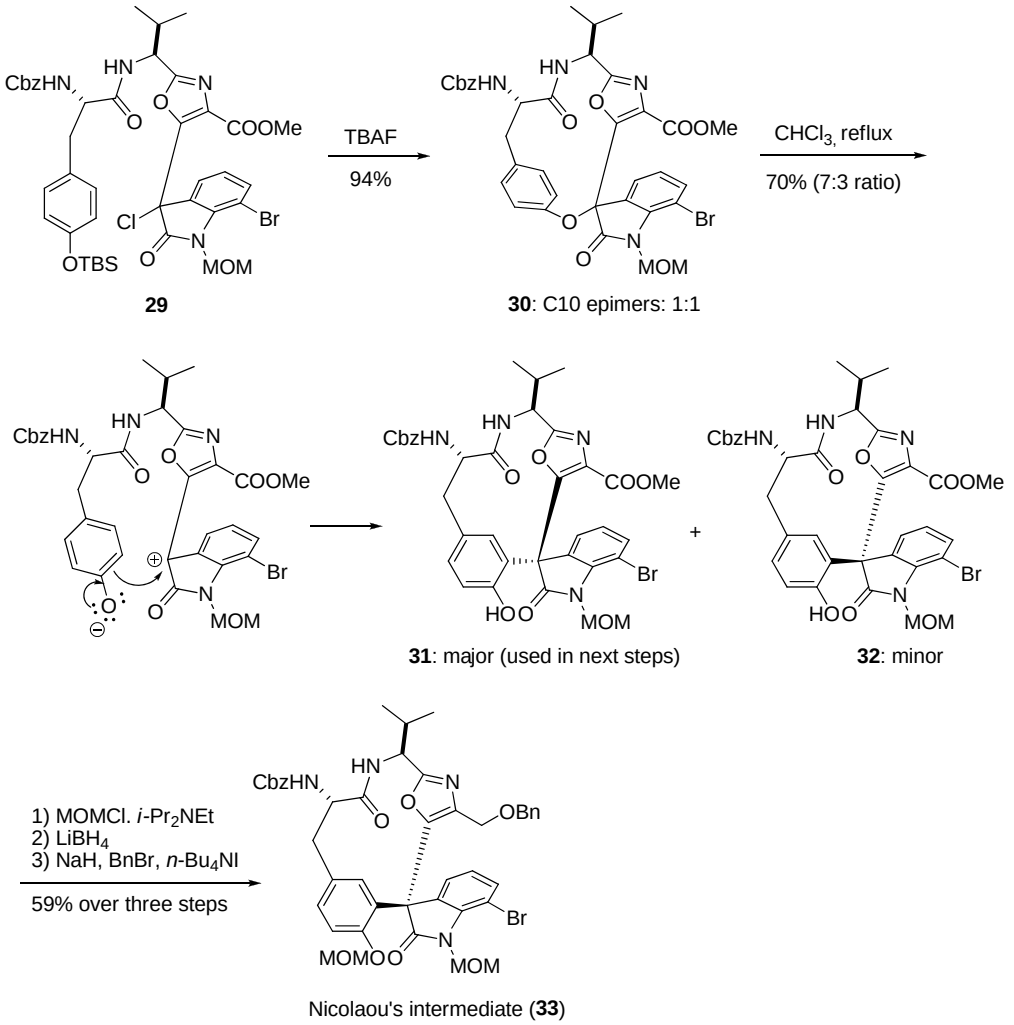
Fenical and Clardy's structure (Scheme 1.6).7 After elaboration to amide **26** from ester **23** with the correct stereochemistry at C10, DDQ oxidation of the benzylic position of indole **26** provided a keto amide, which was cyclized under Wipf's conditions[32, 60] (PPh_3, C_2Cl_6, Et_3N) to furnish oxazole **27**. Photocyclization of the phenol acetate under basic condition provided the direct arylation product **28** in very good yield (72%). An acetoxy group was introduced at C19 of the indole in order to render the indole more electron rich and facilitate electron transfer to the bromoaniline via the phenolate, which is produced by saponification of the acetate under the reaction conditions. The hydroxyl group at C19 was removed via conversion to its triflate followed by hydrogenation. Diazonamide A was obtained after several steps of protecting and functional groups manipulations.



Scheme 1.6 Completion of the Heterocyclic Core in Harran's Total Synthesis

1.3.4 Magnus's Formal Synthesis of Diazonamide A

In 2007, the Magnus group reported a formal synthesis of diazonamide A, intersecting intermediate **33** in Nicolaou's first total synthesis (Scheme 1.7).[61] TBS-protected phenol **29** was subjected to TBAF to provide ether **30** as a 1:1 mixturer of diastereomers. Upon heating, ether **30** underwent a C-O bond cleavage to form an acyclic zwitterion, which closed via a C-C bond formation to provide macrocycles **31** and **32** bearing the quaternary C10. This rearrangement was moderately diastereoselective, and provided a mixture of diastereomers (7:3 ratio) in 70% overall yield, favoring the desired C10 epimer (**31)** over the undesired epimer (**32**, structure confirmed by single crystal X-ray crystallography). Compound **31** was protected as the MOM ether and reduced with $LiBH_4$ to generate a primary alcohol, which was then protected as the benzyl ether to provide the same intermediate **33** in Nicolaou's first total synthesis of diazonamide A. Magus's formal synthesis also demonstrated that the two stereocenters on the left hand backbone can be used to induce a moderate diastereoselective macrocyclization. This was the state of the art when we were conducting our research, and subsequent to the publication of our results, the MacMillan group described a stereoselctive total synthesis of diazonamide A as described below.

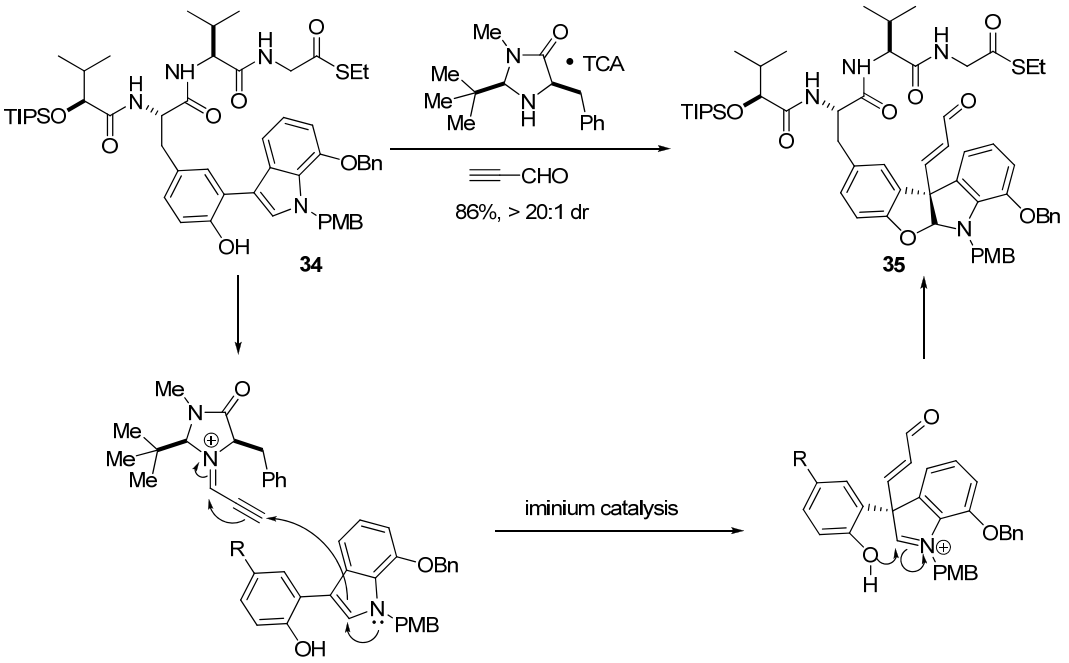


Scheme 1.7 Magnus's Formal Synthesis

1.3.5 MacMillan's Total Synthesis of Diazonamide A

In 2011, MacMillan reported a total synthesis of diazonamide A using a highly enantioselective iminium catalyzed cascade addition / cyclization reaction to install the quaternary C10 as well as the complete hemiaminal core (Scheme 1.8).[62] This synthetic strategy had been successfully used in his total synthesis of (-)-flustramine B in 2004.[63] When compound **34** and propynal were treated with MacMillan's second generation

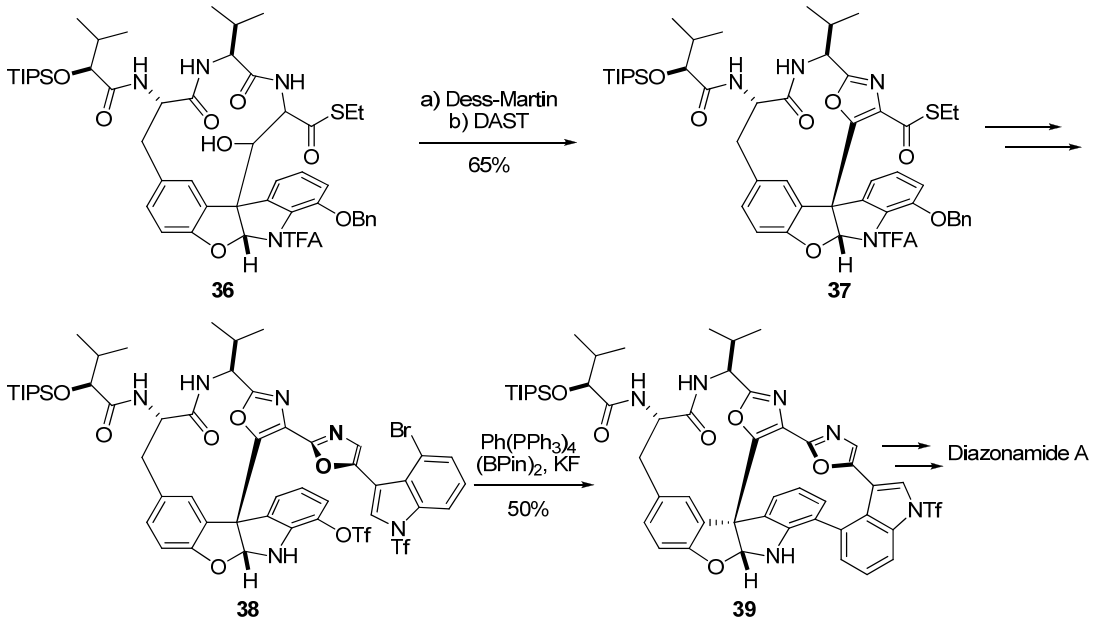
imidazolidinone catalyst,[64,65] conjugate addition of the indole to the generated iminium occurred to provide an intermediate indoline that was trapped by the adjacent phenol to provide compound **35** in good yield with excellent enantioselectivity (>20:1 dr). This reaction is an example of application of organocatalysis to a challenging and complex synthetic substrate.



Scheme 1.8 MacMillan' Synthesis of Quaternary C10

In MacMillan's total synthesis (Scheme 1.9), they were the first to report that DAST (diethylaminosulfur trifluoride) can be used to convert a keto-amide to an oxazole. In their synthesis, Dess-Martin oxidation of compound **36** produced a keto amide that was subjected to DAST to provide oxazole **37**. The right hand macrocycle was produced via a Pd-catalyzed tandem borylation-annulation reaction on compound **38** to form the biaryl bond of **39**. This possesses the complete heterocyclic core of diazonamide A, and the

natural product was obtained after removing the protecting groups and installing the two peripheral chlorine atoms.



Scheme 1.9 Completion of the Heterocyclic Core in MacMillan's Total Synthesis

1.4 Abbreviations

AIBN	Azobisisobutyronitrile
Bz	Benzyl
Cbz	Carboxybenzyl
S_EAr	Electrophilic Aromatic Substitution
DAST	Diethylaminosulfur Trifluoride
DMA	Dimethylacetamide
DMSO	Dimethyl Sulfoxide
MOM	Methoxymethyl
OAT	Ornithine δ-Amino Transferase
TBAF	Tetra-*n*-butylammonium fluoride
TBS	*tert*-Butyldimethylsilyl
TCA	Trichloroacetic acid
TIPS	Triisopropylsilyl

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2 α-Arylation of 3-Aryloxindoles

2.1 Introduction

Developing new efficient methods to construct quaternary carbon centers remains a challenging goal for synthetic organic chemists.[1] 3,3-Disubstituted oxindoles represent an important structural motif found in many natural products (Figure 2.1),[2-6] and some biological small molecules.[7,8] Recently, several synthetic methods, some of which are catalytic and asymmetric, have been reported for the synthesis of 3,3-disubstituted oxindoles. However, reports on synthesis of 3,3-diaryloxindoles are rare. This chapter describes the development of our methods for the α-arylation of 3-aryloxindoles and studies related to the synthesis of diazonamide A.

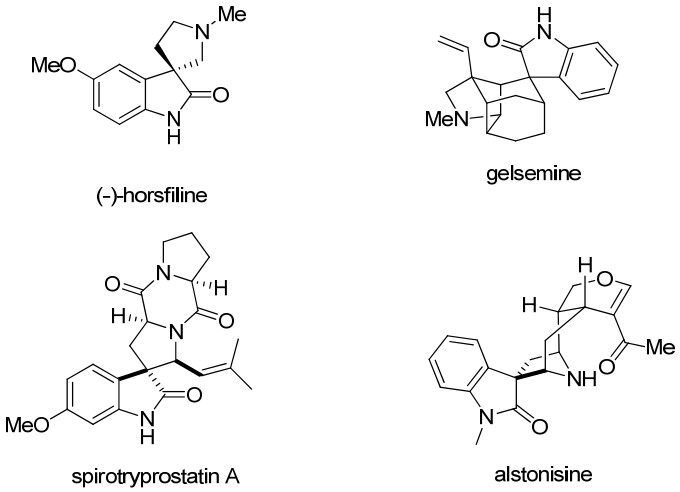


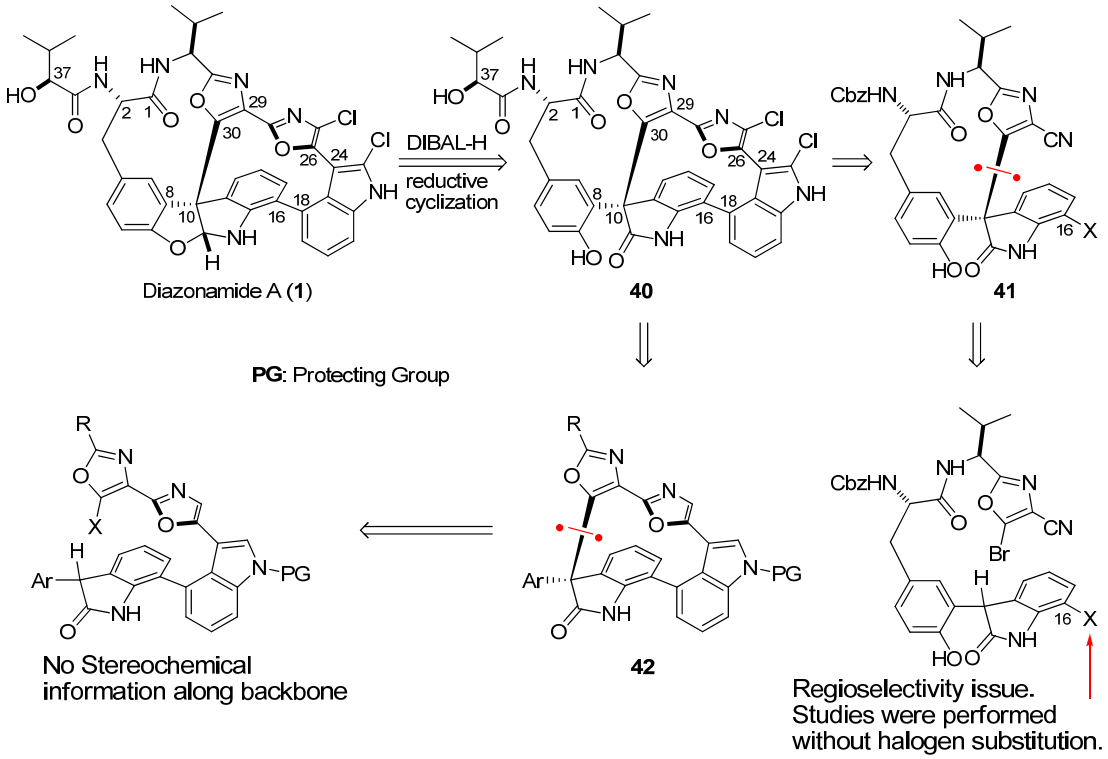
Figure 2.1 Examples of Natural Products with 3,3-Disubstituted Oxindoles

2.2 Retrosynthetic Analysis of Diazonamide A

The total synthesis of diazonamide A is of interest, due to its limited natural supply, unique biological activity, and highly rigid complex molecular structure. One of the challenges in the synthesis of this compound is the efficient construction of the congested quaternary C10, and in response, we devised a retrosynthetic plan that installed this carbon center in a stereoselective fashion.

In our retrosynthetic analysis (Scheme 2.1), we anticipated that the hemiaminal moiety can be prepared via a reductive cyclization,[9,10] and the peripheral chlorine atoms can be introduced at late stage using NCS. As such, our target could be simplified to compound **40**. We were interested in studying the formation of C10-C30 bond via α-arylation of 3-aryloxindole, and we considered two options, studying the macrocyclization to form a compound either corresponding to the left hand half (**41**) of diazonamide A or the right hand half (**42**). Because the right hand scaffold **42** does not have any stereocenters along the backbone, we thought that it would be unlikely that the cyclization to form this ring would be stereoselective. We instead chose to study cyclization to form the left hand macrocycle (**41**), and we envisioned taking advantage of the two stereocenters along the backbone, both of which are derived from natural amino acids (L-tyrosine and L-valine), to influence the stereochemical outcome of the cyclization and provide a diastereoselective reaction. Therefore, we required a reliable synthetic method of the α-arylation of 3-aryloxindoles. Our initial thought was to employ a transition metal catalyzed α-arylation reaction, and we chose to prepare a model system to study this reaction. We decided that our intial target should lack a halogen substituent at C16, as this halogen may interfere with the transition metal catalyzed reaction, rendering the reaction not regioselective. With a successful model cyclization, we would

study the cyclization of the substrate with a halogen atom at C16, which is required as a handle to install the right hand half of diazonamide A.



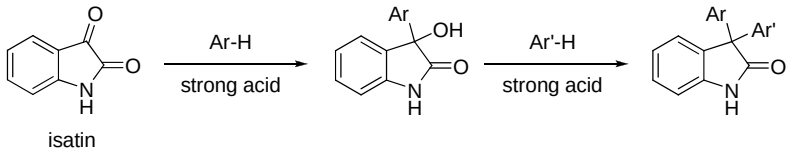
Scheme 2.1 Our Retrosynthetic Analysis of Synthesis of Diazonamide A

2.3 Synthesis of 3,3-Diaryloxindole via Electrophilic Aromatic Substitution (S_EAr)

3,3-Diaryloxindoles have been prepared and studied as mineralocortocoid receptor antagonists[7] and potential anticancer agents.[8] However, the synthesis of these compounds and studies on structure-activity relationship (SAR) were limited by the available synthetic methods.

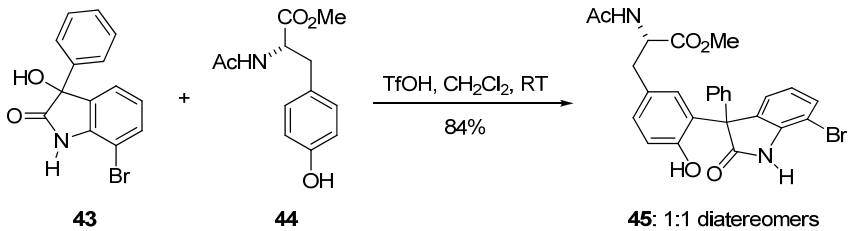
The most common method to prepare 3,3-diaryloxindoles is electrophilic aromatic substitutions (S_EAr) of electron rich aromatics with isatin and its derivatives (Scheme 2.2). In 1885, Baeyer and Lazarus reported that symmetrical 3,3-diaryloxindoles could

be prepared via double electrophilic aromatic substitution of isatin by using electron-rich arenes under strong acidic conditions (concentrated sulfuric acid).[11] In 1998, Klumpp, Olah and coworkers modified the conditions by using a superacid, triflic acid (TfOH), to synthesize symmetrical 3,3-diaryloxindoles.[12] They also reported that unsymmetrical 3,3-diaryloxindoles could be prepared by using a mixture of different electron-rich arenes and isatin derivatives, although this method is not synthetically useful as it produces mixtures of products.



Scheme 2.2 Synthesis of 3,3-Diaryloxindoles via S_EAr

When tertiary alcohols, such as compound **43**, are used, unsymmetrical 3,3-diaryloxindoles can be prepared. Upon treating tertiary alcohols with strong acids, the resulting tertiary carboncation can be trapped with electron rich arenes to form the 3,3-diaryloxindoles. This method was successfully applied by Nicolaou in his model study (Scheme 2.3), and in the first total synthesis of diazonamide A (see Scheme 1.1).[10] Reaction of tertiary alcohol **43** and phenol **44** mediated by super acid, TfOH, furnished 3,3-diaryloxindole **45** as a 1:1 mixture of diastereomers in good yield.



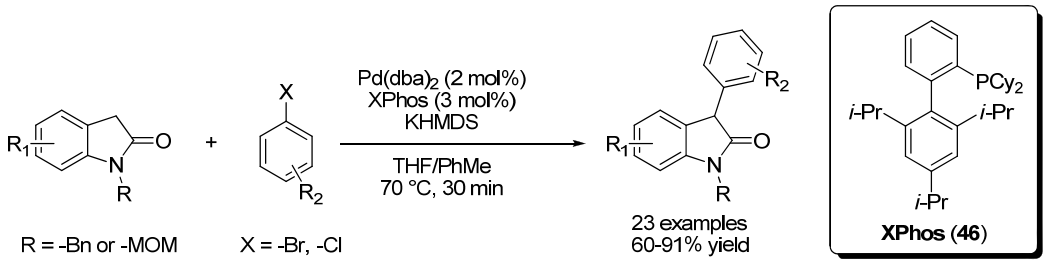
Scheme 2.3 Nicolaou's Model Study of Diazonamide A

These S_EAr reactions suffer from some severe drawbacks, which narrow their scope. First, strongly acidic conditions are required, and many functional groups cannot survive in such harsh conditions. Second, electron-rich arenes have to be used, which limits the functionality that can be on the arenes. Third, the regiochemical outcome of such Friedel-Crafts type reactions is dictated by the intrinsic substitution preference of the substrates, again, limiting the scope of products that can be produced. These limitations as well as our interest in the preparation of 3,3-diarlyoxindole substrates as model studies for the synthesis of diazonamide A prompted us to pursue a more versatile method under milder conditions.

2.4 Transition Metal Catalyzed α-Arylation of Oxindoles

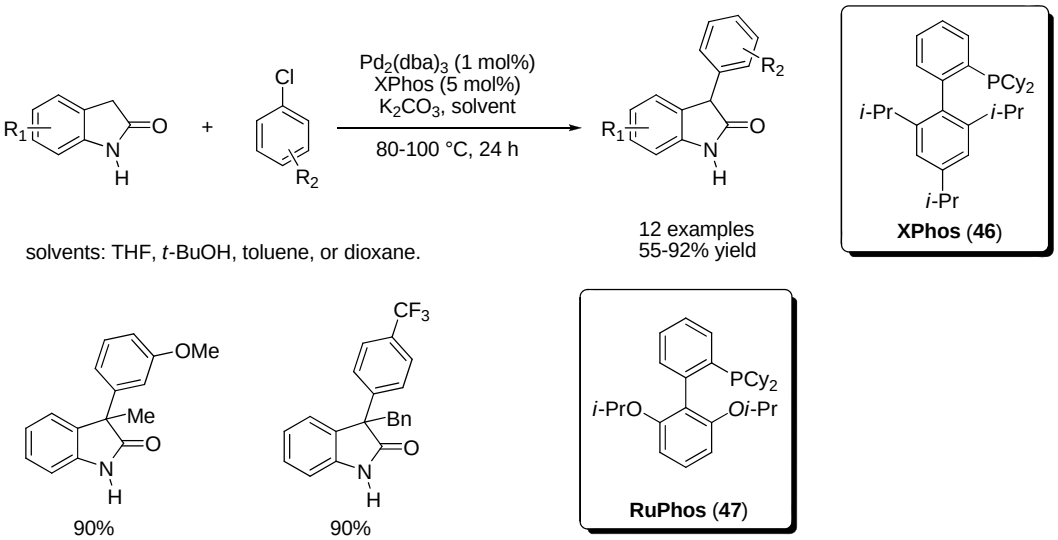
The transition-metal-catalyzed α-arylation of carbonyl compounds has been widely studied due to the importance of α-aryl carbonyl moieties in some biologically active molecules and the mild conditions used in these reactions.[13-15]

In 2008, the Willis group published the first Pd-catalyzed α-arylations of oxindoles to prepare 3-aryloxindoles (Scheme 2.4).[16] The oxindoles were protected as either benzyl or MOM (methoxymethyl) ethers. Either aryl bromide or chlorides could be used, and the best conditions described utilized 2 mol% $Pd(dba)_2$, 3 mol% XPhos (**46**, 2-dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl)[17] as ligand, and KHMDS as base. The bulky electron-rich phosphine ligand, XPhos, was found to be the most effective ligand among all the phosphine ligands screened. These reactions represent a general method to prepare mono-substituted 3-aryloxindoles in mild conditions and high yields.



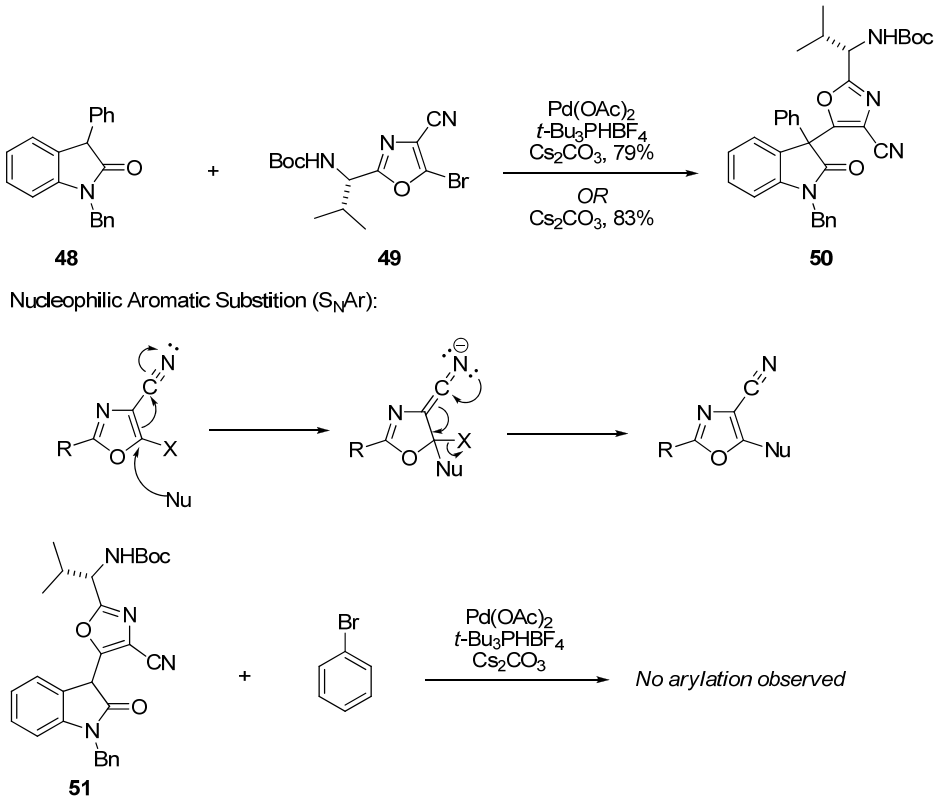
Scheme 2.4 Willis' Pd-Catalyzed α-Arylations of Oxindoles

Several months later, the Buchwald group reported similar α-arylations of oxindoles under even milder conditions by using K_2CO_3 as base, and unproteced oxindoles as substrates (Scheme 2.5).[18] Interestingly, they also showed that by using 3-benzyl or 3-methyl oxindoles with RuPhos (**47**, 2-dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl) as ligand and *t*-BuONa as base, they were able to construct quaternary carbons of 3,3-disubstituted oxindoles. Although there were no reports on transition metal catalyzed reactions to prepare 3,3-diaryloxindoles, the intriguing results of Willis and Buchwald inspired us to consider Pd-catalyzed α-arylations of 3-aryloxindoles for the preparation of 3,3-diaryloxindoles with appropriate combinations of catalysts and ligands.



Scheme 2.5 Buckwald's Pd-Catalyzed α-Arylations of Oxindoles and 3-Alkyloxindoles

Dr. Matthew F. Sammons, a former graduate student in our group, found that *N*-benzyl-3-phenyloxindole (**48**) could be successfully arylated with bromooxazole **49** using $Pd(OAc)_2$ (5 mol%), *t*-Bu_3PHBF_4 (10 mol%) and Cs_2CO_3 (3.0 equiv) in toluene at reflux to provide 3,3-diaryloxindole **50** in good yield (Scheme 2.6). Later, he found that no Pd-catalysis was required, and the reaction can proceed via an S_NAr mechanism. Interestingly, switching the order of bond formation, such that the synthesis of compound **50** is attempted via the Pd-catalyzed arylation of **51**, was not successful under the same conditions studied. This suggests that, the enolate of **51**, which is conjugated to both the oxindole and the electron-deficient oxazole, is too stable to react with the Pd-activated bromobenzene.



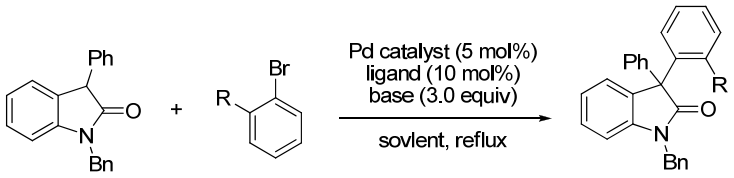
Scheme 2.6 Dr. Sammons' α-Arylations of 3-Aryloxindoles

2.5 Optimizations of Pd-Catalyzed α-Arylations of 3-Aryloxindoles

I began my research by optimizing the conditions for the Pd-catalyzed α-arylations of 3-aryloxindoles, and I studied the α-arylation of *N*-benzyl-3-phenyoxindole (**48**) with bromobenzene and *ortho*-bromotoluene as simple models of varying steric demand (Table 2.1). We found using bromobenzene that the best conditions were $Pd(OAc)_2$ (5 mol%), *t*-Bu_3PHBF_4 (10 mol%),[19] and Cs_2CO_3 (3.0 equiv) in toluene at reflux (entry 1). These were related to the conditions of Hartwig, who prepared quaternary centers via the α-arylation of dialkyl esters.[20] Under these conditions, *ortho*-bromotoluene also reacts to provide the product in 80% yield (entry 7). $Pd(dba)_2$ can also be used as a palladium

source and provides comparable yield (entry 2); however, in later studies, we found that the dibenzylideneacetone (dba) by-product at times co-elutes with our desired products in flash chromatography, thereby complicating purification. Other ligands were less satisfactory; for example, XPhos (**46**), which was used in successful α-arylations of oxindoles by both Willis and Buchwald, provides only recovered starting material (entry 3), while RuPhos (**47**) provides good yields, but is significantly slower than *t*-Bu_3P (entry 4). Other carbonate bases, such as K_2CO_3, provide high yields, but the reactions are slower (entry 5). A solvent survey was also conducted, and toluene was found to be superior to polar, ethereal, or protic solvents, such as DMF (no arylation, entry 6), 1,4-dioxane (slow, entry 8), or *tert*-butanol (no arylation, entry 9). The use of chlorobenzene instead of bromobenzene did not provide any arylated product using our optimized conditions.

Table 2.1 Optimization of Pd-Catalyzed α-Arylations

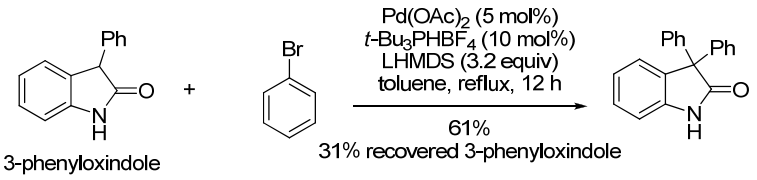


48

entry	conditions	R	yield (%)[a]
1	**$Pd(OAc)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, toluene, 30 min**	**H**	**95**
2	$Pd(dba)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, toluene, 30 min	H	93
3	$Pd(dba)_2$, XPhos, Cs_2CO_3, toluene, 3 h	H	0
4	$Pd(dba)_2$, RuPhos, Cs_2CO_3, toluene, 3 h	H	93
5	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, K_2CO_3, toluene, 5 h	H	92
6	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, DMF, 120 °C, 3 h	H	0
7	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, toluene, 3.5 h	Me	80
8	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, dioxane, 18 h	Me	10
9	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, *t*-BuOH, 12 h	Me	0

[a] Isolated yields after flash chromatography.

The oxindole nitrogen had to be protected in these reactions. Otherwise, strong base, such as, LiHMDS, had to be used to provide the product in reasonable yield. Under our optimized reaction conditions, the reaction of 3-phenyloxindole with bromobenzene did not proceed, but using LiHMDS instead of Cs_2CO_3 provided the desired product in 61% yield along with 31% recovered 3-phenyloxindole (Scheme 2.7).

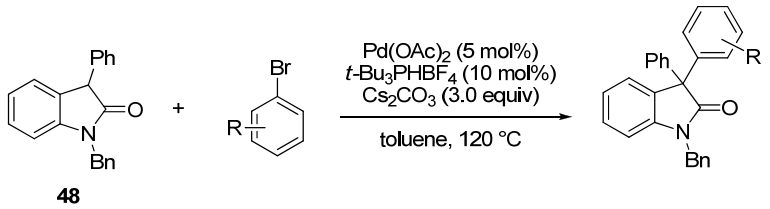


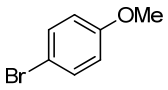
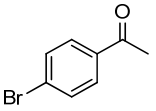
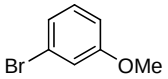
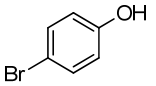
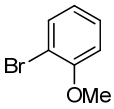
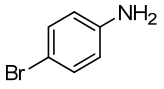
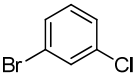
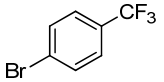
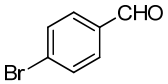
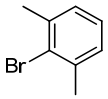
Scheme 2.7 Pd-Catalyzed α-Arylation of Unprotected 3-Phenyloxindole

With optimized conditions in hand, I continued exploring the substrate scope using *N*-benzyl-3-phenyoxindole (**48**, Table 2.2). I found that the reaction conditions are compatible with a variety of substitution patterns and functional groups on the aryl bromide, including electron donating (methoxy, hydroxy, and amino groups) and electron withdrawing substituents (chloro, formyl, keto, and trifluromethyl groups). All are good partners in these reactions, and provide the products in excellent yields (entries 1-9). In addition, due to the enhanced acidity of the 3-aryloxindole (the pKa of unsubstituted oxindole in DMSO is 18.5, and that of the 3-aryloxindole is likely lower than 15.),[21] no ketone arylation was observed (entry 6). Further, the use of a mild, reversible carbonate base renders the reaction compatible with protic substituents, such as phenol (entry 7) and aniline (entry 8) groups. The reaction is also remarkably tolerant of steric hinderance in the aryl bromide component. In addition to *ortho*-bromotoluene (Table 1, entry 7) and *ortho*-bromoanisole (entry 3), the highly hindered di-*ortho*-substituted aryl bromide shown in entry 10 also reacted cleanly to provide the product in 64% yield, although

longer reaction time was required. This is in contrast to other Pd-catalyzed enolate arylations, wherein low yields were reported with *ortho*-substituted aryl halides.[22-24]

Table 2.2 Arylations of *N*-Benzyl-3-Phenyloxindole

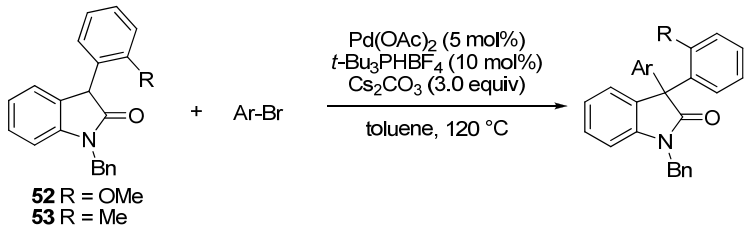


entry	Ar-Br	yield (%)[a]	entry	Ar-Br	yield (%)[a]
1		91	6		88
2		94	7		81[c]
3		75[b]	8		85
4		78	9		85
5		79	10		64[d]

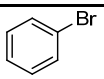
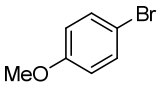
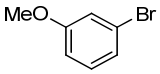
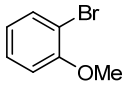
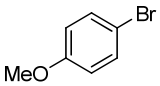
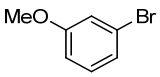
[a] Isolated yield after flash chromatography. [b] After 2 h. [c] $Pd(dba)_2$ was used instead of $Pd(OAc)_2$, which provided lower yield (53%). [d] After 20 h.

I continued studying the effects of sterics in the enolate component using the 3-*ortho*-substitued-phenyloxindole substrates **52** and **53** (Table 2.3). Both substrates were competent with *para*- and *meta*-substituted aryl bromides, providing the products in good yields (entries 1-3, 5-6), although long reaction times were required. No arylation products were observed in the case of *ortho*-bromoanisole, possibly due to the extreme steric hindrance at the transition state (entry 4).

Table 2.3 Arylation of 3-*ortho*-Substitued-Pheyloxindoles



52 R = OMe
53 R = Me

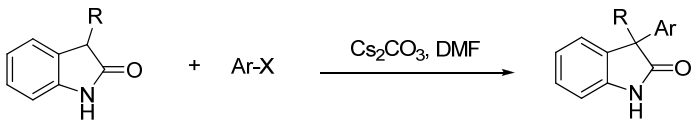
entry	oxindole	Ar-Br	time (d)	yield (%)[a]
1	**52**		1	92
2	**52**		2	90
3	**52**		2	81
4	**52**		1	0
5	**53**		2	82[b,c]
6	**53**		2	86[b,d]

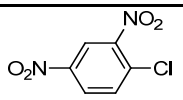
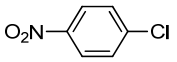
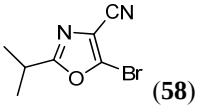
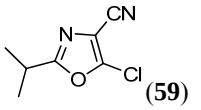
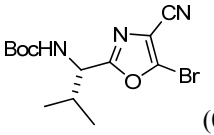
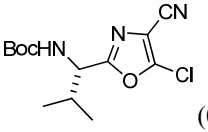
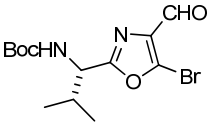
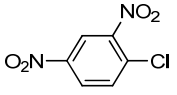
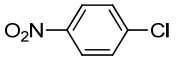
[a] Isolated yield after flash chromatography. [b] $Pd(dba)_2$ (10 mol%), *t*-Bu_3PHBF_4 (20 mol%), Cs_2CO_3 (3.0 equiv), toluene, sealed tube, 120 °C, 2 d. [c] 52% yield after 3 days when the title condition was used. [d] 50% yield after 3 days when the title condition was used.

For highly electron-deficient aryl halides, arylations can proceed without Pd catalysts via an S_NAr mechanism (Table 2.4). Common S_NAr substrates, such as 2,4-dinitrochlorobenzene (entry 1) and *p*-nitrochlorobenzene (entry 2) react with 3-phenyloxindole (**54**) to cleanly provide the α-arylation products in excellent yields. The protection on the oxindole nitrogen is not required for this reaction, and no *N*-arylation was observed. More relevant to the synthesis of natural products, such as diazonamide A, electron deficient 5-halooxazoles (**58**-**62**) all provided the desired products in good yields under these conditions (entries 3-7). Other 3-aryl substituted oxindoles, **55** and **56**, also provided good yields in these S_NAr reactions with bromooxazole **60** (entries 8 and 9).

Our conditions are also compatible with 3-alkylloxindole **57** (entries 10-12), although higher temperature, stronger base, and longer reaction time are required than in the cases of 3-aryloxindoles.

Table 2.4 Arylations via Nucleophilic Aromatic Substitution (S_NAr)

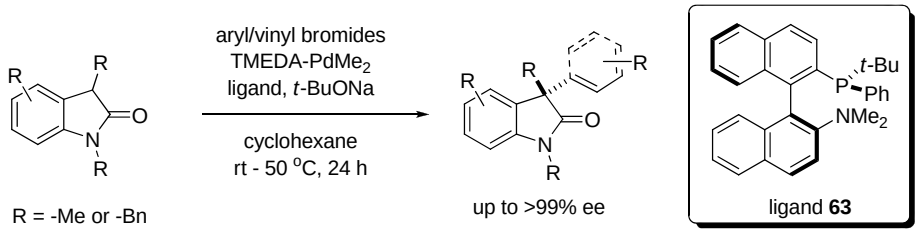


entry	oxindole	Ar-X	temp (°C)	time (h)	yield (%)[a]
1	R = Ph (**54**)		RT	1	96
2	**54**		120	3	93
3	**54**	 (**58**)	65	7	75
4	**54**	 (**59**)	65	5	58
5	**54**	 (**60**)	65	5	76[b]
6	**54**	 (**61**)	65	5	68[b]
7	**54**	 (**62**)	65	5	70[b]
8	R = 4-MePh (**55**)	**60**	65	5	78[b]
9	R = 4-MeOPh (**56**)	**60**	65	5	61[b]
10[c]	R = Me (**57**)		RT	1	89
11[c]	**57**		120	3	92
12[d]	**57**	**60**	75	0.5	74[b]

[a] Isolated yield after flash chromatography. [b] 1:1 mixture of diastereomers. [c] 2.0 equiv Cs_2CO_3 was used. [d] 2.0 equiv NaH was used instead of Cs_2CO_3.

2.6 Attempted Asymmetric α-Arylations of 3-Aryloxindoles

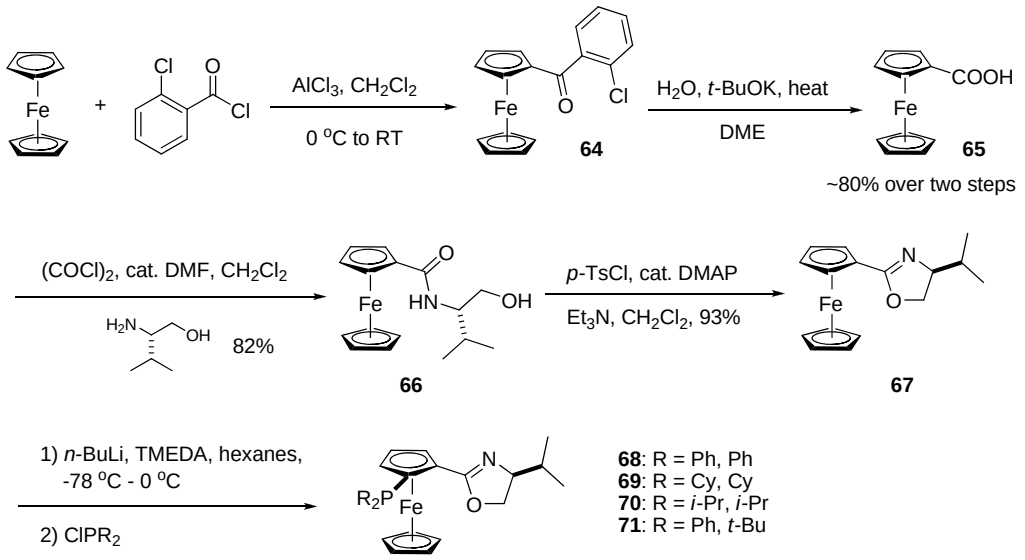
In 2009, the Buchwald group reported asymmetric Pd-catalyzed α-arylations and vinylations of 3-alkyloxindole (Scheme 2.8). They used an air-stable precatalyst, dimethyl palladium TMEDA complex,[25] which was known to be easily activated and facilitated low temperature oxidative additions of aryl chlorides, an axially chiral P-stereogenic ligand **63**, sodium *tert*-butoxide as a base, and a nonpolar solvent, cyclohexane. Based on the optimization studies of our Pd-catalyzed α-arylations (Table 2.1), nonpolar solvents were better than polar solvents for the formations of 3,3-disubstituted oxindoles. All these reactions were reported in good yields with excellent *ee* values. The two chiral elements, the axially chiral biaryl backbone and the stereogenic phosphine atom, accounted for the high *ee* values.



Scheme 2.8 Buchwald's Asymmetric α-Arylations and Vinylations of 3-Alkyloxindoles

Our successful Pd-catalyzed α-arylations of 3-aryloxindoles intrigued us to pursue an asymmetric version of such reactions. Our group had developed a series of ferrocenyloxazolines ligands, and had applied them to other catalytic asymmetric reactions, such as, Ru-catalyzed transfer hydrogenations,[26] and Cu-catalyzed conjugative additions of Grignard reagents to enones.[27] Herein, we were interested in applying these ligands to our Pd-catalyzed α-arylations of 3-aryloxindoles.

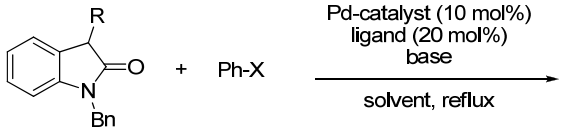
Synthesis of these chiral P-N-ligands relied on methods previously developed in our group (Scheme 2.9). $AlCl_3$-mediated Friedel-Crafts reaction of ferrocene with 2-chlorobenzoyl chloride provided ketone **64**, which was then hydrolyzed to afford carboxylic acid **65** under strong basic conditions (*t*-BuOK).[28] A chiral valine side chain was introduced onto carboxylic acid **65**, which was first activated as an acid chloride via a Vilsmeier-Haack reaction, to provide amide **66**. Amide **66** was subjected to cyclization to form oxazoline **67** via a tandem tosylation (*p*-TsCl with catalytic amount of DMAP), and substitution of the *in situ* generated tosylate. Our group had found that we could install phosphines on the chiral ferrocene backbone with highly diastereoselective oxazoline directed lithiation and trapping with a variety of disubstituted chlorophosphoines to provide various chiral phosphine ligands.[29-31] I prepared ligands **68**–**71** wherein the phosphine bears two Ph, Cy, or *i*-Pr groups using this method. Unfortunately, trapping the lithiated ferrocenyloxazoline with the highly hindered *t*-Bu_2PCl did not provide the desired phosphine product; however, I was able to synthesize the *t*-Bu, Ph substituted phosphine **71**.



Scheme 2.9 Synthesis of Ferrocenyloxazolines Ligands

With all these chiral phosphine ligands in hand, I set out to study the asymmetric α-arylations of 3-phenyloxindole **48**. Unfortunately, I was not able to obtain any arylation products (Scheme 2.5), probably due to the hinderance of 3-phenyl substitution on the oxindole. I, therefore, went on studying the less hinder substrate, 3-methyloxindole (**72**), in order to conduct the same transformations as Buchwald reported. However, even this substrate was too bulky and no product was observed. During the course of these studies, I found that $Pd(dba)_2$ without any other ligand can provide the arylated product in 19% yield (entry 8). However, only trace or no arylated product was observed in the cases with our ligands (**68** – **71**). These observations indicated that our ligands (**68** – **71**) did bind to the Pd-catalysts. However, these complexes were not able to promote the desired α-arylations of 3-substituted oxindoles.

Table 2.5 Attempted Asymmetric α-Arylations of 3-Substituted Oxindoles



48: R = Ph
72: R = Me

entry	conditions[a]	results[b]
1	**48**, PhBr, $Pd(OAc)_2$, **68**, Cs_2CO_3, toluene, reflux	NR
2	**48**, PhBr, $Pd(OAc)_2$, **68**, Cs_2CO_3, toluene, reflux[c]	NR
3	**48**, PhBr, $Pd(dba)_2$, **69**, Cs_2CO_3, toluene, reflux	NR
4	**48**, PhBr, $Pd(dba)_2$, **69**, LiHMDS, toluene, reflux	NR
5	**48**, PhI, $Pd(dba)_2$, **69**, Cs_2CO_3, toluene, reflux	NR
6	**48**, PhI, $Pd(OAc)_2$, **69**, Cs_2CO_3, toluene, reflux	NR
7	**48**, PhI, $Pd(dba)_2$, **71**, Cs_2CO_3, toluene, reflux	NR
8	**48**, 3-MeOPhI, $Pd(dba)_2$, no ligand, LiHMDS, toluene, reflux	19%
9	**48**, 3-MeOPhI, $Pd(dba)_2$, **70**, LiHMDS, toluene, reflux	trace
10	**48**, 3-MeOPhI, $Pd(dba)_2$, **70**, *i*-Pr_2NEt, toluene, reflux[d]	trace
11	**72**, PhBr, $Pd(OAc)_2$, **68**, Cs_2CO_3, toluene, reflux	NR
12	**72**, PhI, $Pd(OAc)_2$, **68**, Cs_2CO_3, toluene, reflux	NR
13	**72**, PhI, CuI, **68**, Cs_2CO_3, toluene, reflux	mixture
14	**72**, PhI, $Pd(dba)_2$, **71**, Cs_2CO_3, toluene, reflux	NR
15	**72**, PhI, $Pd(dba)_2$, **71**, LiHMDS, toluene, reflux	NR

[a] Reactions were run using Pd-catalyst (10 mol%), ligand (20 mol%), base (3.0 equiv of Cs_2CO_3 of 2.2 equiv of LiHMDS), concentration (0.1 mol/L), reflux. [b] Results were determined by TLC and the crude NMR. [c] only 10 mol% ligand **68** was used. [d] 3.0 equiv of *i*-Pr_2NEt.

2.7 Conclusion

In summary, we have developed a versatile method for the preparation 3,3-diaryloxindoles via Pd-catalyzed α-arylations of 3-aryloxindoles or via a nucleophilic aromatic substitution (S_NAr) with electron deficient aryl halides. The reaction proceeds using mild base, is tolerant of a variety of functional groups, and is capable of preparing hindered all-carbon quaternary centers. The broad substrate scope and ability to form highly hindered carbon-carbon bonds should render this method applicable to the synthesis of complex natural products, such as, diazonamide A, and other biologically active compounds. In addition, asymmetric Pd-catalyzed α-arylations of 3-substituted

oxindoles with various chiral ferrocenyloxazoline monophosphine ligands were attempted; however, they did not provide any of the desired asymmetric α-arylation products.

2.8 Abbreviations

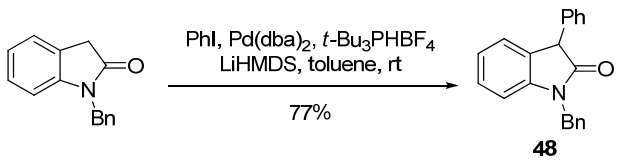
dba	Dibenzylideneacetone
KHMDS	Potassium bis(trimethylsilyl)amide
LiHMDS	Lithium bis(trimethylsilyl)amide
MOM	Methoxymethyl
RuPhos	2-Dicyclohexylphosphino-2′,6′-diisopropoxybiphenyl
TMEDA	Tetramethylethylenediamine
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

2.9 Experimental Details

All glassware was oven-dried or flame-dried. DMF was freshly distilled over CaH_2 under reduced pressure prior to use; THF and Et_2O were distilled from sodium benzophenone ketyl under N_2; CH_2Cl_2, hexanes, and toluene were distilled over CaH_2 under N_2; TMEDA was distilled from Na under reduced pressure. Unless specifically mentioned, all chemicals are commercially available and were used as received. For reactions of 3-monosubstituted oxindoles under basic conditions, solvents were degassed by sparging with N_2 or Ar, in order to prevent the oxidation of oxindole enolates.[32] Thin layer chromatography (TLC) was performed using EM Science Silica Gel 60 F254 glass plates. Flash chromatography was performed using 60 Å silica gel (37-75 μm). ^{1}H NMR spectra were recorded at either 400 MHz or 500 MHz, and ^{13}C NMR spectra were

recorded at either 75 MHz or 100 MHz in $CDCl_3$, [D6]acetone, or [D6]DMSO as indicated. Chemical shifts are reported in ppm referenced to residual solvent peaks as follows: $CDCl_3$, 7.24 ppm for ^1H NMR, 77.16 ppm for ^{13}C NMR; [D6]acetone, 2.05 ppm for ^1H NMR, 29.84 ppm for ^{13}C NMR; and [D6]DMSO, 2.50 ppm for ^1H NMR, 39.52 ppm for ^{13}C NMR. Infrared (FT-IR) spectra were obtained as thin films on NaCl plates. Exact mass was determined using electrospray ionization (M+H, M+Na, or M+K as indicated).

***N*-Benzyl-3-Phenyloxindole:**

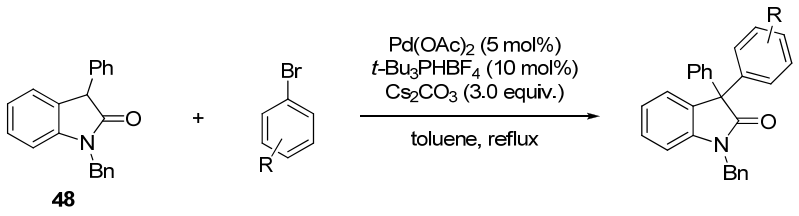


48

N-Benzyloxindole[2] (1.22 g, 5.46 mmol, 1.0 equiv), $Pd(dba)_2$ (157 mg, 0.273 mmol, 0.05 equiv), and *t*-Bu_3PHBF_4 (159 mg, 0.546 mmol, 0.10 equiv) were charged in a 100 mL round bottom flask, which was purged with Ar. Iodobenzene (0.82 mL, 6.01 mmol, 1.1 equiv) was dissolved in dry toluene (50 mL) in a 100 ml pear–shape flask. The solution was degassed by sparging with Ar for 15 min, and cannulated into the flask containing *N*-benzyloxindole and other reagents. LiHMDS (11.5 mL of a 1.0 M solution in toluene, 11.5 mmol, 2.1 equiv) was then added via syringe, and the dark brown solution was stirred at room temperature for 5 h. The reaction was quenched by the addition of 1M HCl (aq, 50 mL), and extracted with EtOAc (50 mL×3). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and

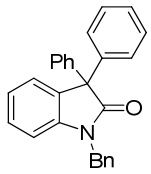
concentrated under reduced pressure. The crude product was purified by recrystallization from Et_2O/hexanes to provide *N*-benzyl-3-phenyloxindole (**48**, 1.26 g, 77%). Spectral data for compound **48** are consistent with that reported in the literature.[33]

Pd-Catalyzed Arylation of *N*-Benzyl-3-Phenyloxindole (Table 2.1 & Table 2.2):



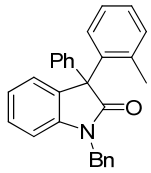
General procedure:

N-Benzyl-3-phenyloxindole (**48**, 0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5 mol%), *t*-Bu_3PHBF_4 (10 mol%), and Cs_2CO_3 (3.0 equiv) were charged in a 25 mL round bottom flask, which was then fitted with a condenser, and purged with N_2. The aryl bromide (1.1 equiv) was dissolved in dry toluene (5 mL), and the solution was degassed by sparging with N_2 for 15 min before cannulated into the flask containing compound **48** and the other reagents. The suspension was heated to reflux, until compound **48** was consumed as indicated by TLC. The reaction was then cooled to ambient temperature, quenched by the addition of 1 M HCl (10 mL), and extracted with EtOAc (25 mL×3). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography using a mixture of hexanes and EtOAc provided the desired 3,3-diaryloxindoles.



***N*-Benzyl-3,3-Diphenyl-2-Oxindole** (Table 2.1, entry 1):

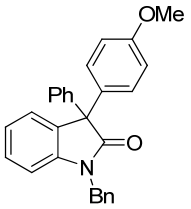
A white crystalline solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.23 – 7.30 (m, 16H), 7.16 (dd, *J* = 7.5, 2.0 Hz, 1H), 7.03 (t, *J* = 7.5 Hz, 1H), 6.77 (d, *J* = 8 Hz, 1H), 4.98 (s, 2H). **^{13}C NMR** (100 MHz, CDCl3) δ 177.8, 142.3, 142.2, 136.0, 133.1, 129.0, 128.7, 128.6, 128.4, 127.5, 127.40, 127.38, 126.3, 123.1, 109.8, 62.7, 44.2. **^{1}H NMR** (500 MHz, [D6]acetone) δ 7.40 – 7.20 (m, 17H), 7.07 (td, *J* = 7.6, 1.0 Hz, 1H), 7.01 (d, *J* = 7.9 Hz, 1H), 5.06 (s, 2H). **^{13}C NMR** (75 MHz, [D6]acetone) δ177.8, 143.2, 143.2, 137.4, 133.6, 129.5, 129.31, 129.27, 129.19, 129.15, 128.3, 128.1, 126.9, 123.5, 110.5, 63.1, 44.2. **m.p.**: 160 – 161 °C. **IR** (cm^{-1}) 1713, 1608, 1487, 1347, 1181. **HRMS** calcd for $C_{27}H_{21}NONa^{+}$: 398.1515; found: 398.1502.



***N*-Benzyl-3-(2-Methylphenyl)-3-Phenyl-2-Oxindole** (Table 2.1, entry 7):

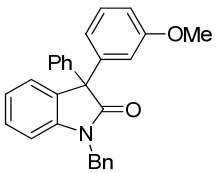
A white foam. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.69 (br s, 1H), 6.99 – 7.46 (m, 15H), 6.90 (d, *J* = 7.5 Hz, 1H), 6.80 (d, *J* = 7.5 Hz, 1H), 4.93 (AB, *J* = 15.6 Hz, ν_{ab} = 160.2 Hz, 2H), 1.88 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$, 55 °C) δ 178.2, 142.8, 141.1, 140.3, 138.0, 136.1, 132.8, 132.4, 130.3, 128.8, 128.6, 128.4, 127.7, 127.7, 127.6, 127.6, 126.4,

125.8, 122.8, 109.5, 63.2, 44.3, 21.2. **IR** (cm^{-1}) 1712, 1608, 1485, 1465, 1343. **HRMS** calcd for $C_{28}H_{23}NONa^{+}$: 412.1671; found: 412.1672.



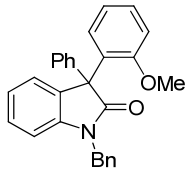
***N*-Benzyl-3-(4-Methoxyphenyl)-3-Phenyl-2-Oxindole** (Table 2.2, entry 1):

A white crystalline solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.20 – 7.31 (m, 11H), 7.18 (d, *J* = 9 Hz, 2H), 7.15 (dd, *J* = 8, 1 Hz, 1H), 7.02 (td, 7.5, 1 Hz, 1H), 6.81 (d, *J* = 9 Hz, 2H), 6.76 (d, *J* = 7.5 Hz, 1H), 4.97 (s, 2H), 3.76 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 178.1, 159.0, 142.5, 142.5, 136.0, 134.0, 133.4, 129.8, 129.0, 128.7, 128.5, 128.3, 127.8, 127.4, 127.4, 126.2, 123.0, 114.0, 109.8, 62.0, 55.4, 44.2. **^{1}H NMR** (500 MHz, [D6]acetone) δ 7.41 – 7.17 (m, 14H), 7.06 (td, *J* = 7.6, 1.0 Hz, 1H), 7.00 (d, *J* = 7.9 Hz, 1H), 6.93 – 6.84 (m, 2H), 5.04 (s, 2H), 3.75 (s, 3H). **^{13}C NMR** (75 MHz, [D6]acetone) δ 178.0, 159.8, 143.5, 143.13, 137.4, 134.8, 134.0, 130.4, 129.5, 129.2, 129.0, 128.3, 128.1, 128.0, 126.8, 123.4, 114.5, 110.4, 62.4, 55.5, 44.1. **m.p.**: 75 – 77 °C. **IR** (cm^{-1}) 1712, 1607, 1509, 1250, 1179. **HRMS** calcd for $C_{28}H_{23}NO_2Na^{+}$: 428.1621; found: 428.1622.



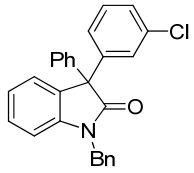
***N*-Benzyl-3-(3-Methoxyphenyl)-3-Phenyl-2-Oxindole** (Table 2.2, entry 2):

A white foam. **^{1}H** NMR (500 MHz, [D6]acetone) δ 7.43 – 7.19 (m, 13H), 7.07 (td, *J* = 7.6, 1.0 Hz, 1H), 7.02 (d, *J* = 7.9, 1H), 6.91 – 6.81 (m, 3H), 5.06 (AB, *J* = 15.8 Hz, ν_{ab} = 9.4 Hz 2H), 3.69 (s, 3H). **^{13}C NMR** (75 MHz, [D6]acetone) δ 177.6, 160.6, 144.6, 143.2, 142.9, 137.5, 133.6, 130.2, 129.5, 129.3, 129.2, 128.4, 128.1, 127.0, 123.5, 121.5, 115.7, 113.0, 110.5, 63.0, 55.4, 44.2. **IR** (cm^{-1}) 3056, 3031, 2925, 2835, 1708, 1605, 1487. **HRMS** calcd for $C_{28}H_{23}NO_2H^+$: 406.1802; found: 406.1814.



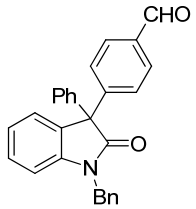
***N*-Benzyl-3-(2-Methoxyphenyl)-3-Phenyl-2-Oxindole** (Table 2.2, entry 3).

A white crystalline solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.45 (br s, 2H), 7.28 – 7.34 (m, 5H), 7.15 – 7.28 (m, 5H), 7.03 (dd, *J* = 7.5, 2.0 Hz, 1H), 6.97 (dt, *J* = 7.5, 1 Hz, 1H), 6.91 (dd, *J* = 7.5, 1.5 Hz, 1H), 6.85 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.77 – 6.80 (m, 2H), 4.92 (AB, *J* = 15.5 Hz, ν_{ab} = 20.0 Hz, 2H), 3.26 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 179.0, 157.6, 143.4, 139.3, 136.6, 132.5, 131.8, 130.8, 129.4, 128.9, 128.8, 128.4, 128.0, 127.8, 127.6, 125.8, 122.2, 120.8, 112.5, 109.0, 59.9, 55.9, 44.3. **m.p.**: 155 – 156 °C. **IR** (cm^{-1}) 1716, 1609, 1488, 1343, 1251. **HRMS** calcd for $C_{28}H_{23}NO_2Na^+$: 428.1621; found: 428.1620.



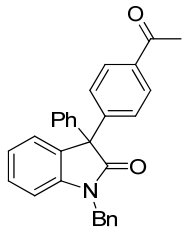
***N*-Benzyl-3-(3-Chlorophenyl)-3-Phenyl-2-Oxindole** (Table 2.2, entry 4):

A white foam. **^{1}H NMR** (500 MHz, [D6]acetone) δ 7.46 – 7.18 (m, 16H), 7.11 (td, *J* = 7.6, 1.0 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 5.07 (AB, *J* = 15.8 Hz, ν_{ab} = 12.1 Hz, 2H). **^{13}C NMR** (75 MHz, [D6]acetone) δ 177.3, 145.4, 143.2, 142.6, 137.4, 134.6, 132.9, 130.9, 129.6, 129.5, 129.4, 129.3, 129.2, 128.43, 128.37, 128.30, 128.1, 127.9, 127.0, 123.8, 110.8, 62.8, 44.3. **IR** (cm^{-1}) 3056, 3027, 2921, 1704, 1610, 1491, 1474. **HRMS** calcd for $C_{27}H_{20}ClNOH^{+}$: 410.1306; found: 410.1320.



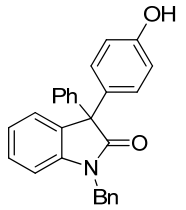
***N*-Benzyl-3-(4-Formylphenyl)-3-Phenyl-2-Oxindole** (Table 2.2, entry 5):

A white foam. **^{1}H NMR** (500 MHz, CDCl3) δ 9.98 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 2H), 7.43 (d, *J* = 8.5 Hz, 2H), 7.15 – 7.35 (m, 11H), 7.06 (td, *J* = 7.5 Hz, 1.0 Hz, 1H), 6.82 (d, *J* = 7.5 Hz, 1H) 4.98 (s, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 192.0, 177.0, 148.9, 142.3, 141.3, 135.7, 135.5, 132.1, 130.0, 129.4, 129.04, 128.90, 128.86, 128.5, 127.9, 127.9, 127.4, 126.2, 123.3, 110.1, 62.9, 44.3. **IR** (cm^{-1}) 1707, 1605, 1356. **HRMS** calcd for $C_{28}H_{21}NO_2Na^{+}$: 426.1464; found: 426.1468.



***N*-Benzyl-3-(4-Acetylphenyl)-3-Phenyl-2-Oxindole** (Table 2.2, entry 6):

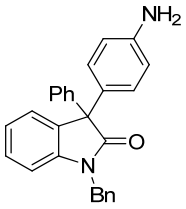
A white foam. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.87 (d, *J* = 8.5 Hz, 2H), 7.36 (d, *J* = 8.5 Hz, 2H), 7.21 – 7.33 (m, 11H), 7.20 (dt, *J* = 7.8, 1.0 Hz, 1H), 7.05 (dt, *J* = 7.5, 1.0 Hz, 1H), 6.81 (d, *J* = 8 Hz, 1H), 4.98 (AB, *J* = 15.8 Hz, ν_{ab} = 8.0 Hz, 2H), 2.55 (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 197.9, 177.2, 147.4, 142.3, 141.5, 136.2, 135.8, 132.3, 129.03, 128.90, 128.86, 128.76, 128.71, 128.5, 127.9, 127.8, 127.4, 126.2, 123.3, 110.0, 62.8, 44.3, 26.8. **IR** (cm^{-1}) 1713, 1683, 1606, 1487, 1357, 1267. **HRMS** cacld for $C_{29}H_{23}NO_2Na^+$: 440.1621; found: 440.1623.



***N*-Benzyl-3-(4-Hydroxyphenyl)-3-Pheny-2-Oxindole** (Table 2.2, entry 7,):

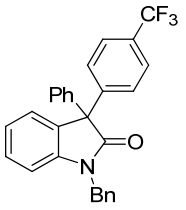
A white crystalline solid. **^{1}H NMR** (500 MHz, [D6]acetone) δ 8.42 (s, 1H), 7.42 – 7.18 (m, 12H), 7.16 – 7.10 (m, 2H), 7.07 (td, *J* = 7.6, 1.0 Hz, 1H), 6.99 (d, *J* = 7.9 Hz, 1H), 6.83 – 6.77 (m, 2H), 5.05 (s, 2H). **^{13}C NMR** (75 MHz, [D6]acetone) δ 178.2, 157.5, 143.7, 143.2, 137.5, 134.2, 133.7, 130.5, 129.5, 129.2, 129.1, 129.0, 128.3, 128.1, 127.9, 126.9, 123.4, 115.0, 110.4, 62.4, 44.1. **m.p.**: 170 – 171 °C. **IR** (cm^{-1}) 3362 (br s), 3060,

3023, 2925, 1679, 1609, 1511, 1458. **HRMS** cacld for $C_{27}H_{21}NO_2H^+$: 392.1645; found: 392.1628.



3-(4-Aminophenyl)-*N*-Benzyl-3-Phenyl-2-Oxindole (Table 2.2, entry 8):

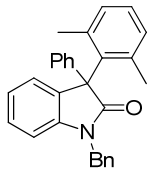
A colorless oil. **^{1}H NMR** (500 MHz, [D6]acetone) δ 7.38 – 7.15 (m, 12H), 7.05 (td, *J* = 7.6, 1.0 Hz, 1H), 6.97 (m, 3H), 6.64 – 6.55 (m, 2H), 5.03 (s, 2H), 4.68 (br s, 2H). **^{13}C NMR** (75 MHz, [D6]acetone) δ 178.4, 148.6, 144.0, 143.2, 137.6, 134.5, 130.5, 130.0, 129.5, 129.2, 129.0, 128.8, 128.3, 128.1, 127.8, 126.8, 123.3, 114.9, 110.3, 62.4, 44.1. **IR** (cm^{-1}) 3461, 3367, 3047, 3028, 1708, 1601, 1515, 1479. **HRMS** cacld for $C_{27}H_{22}N_2OH^+$: 391.1805; found: 391.1810.



***N*-Benzyl-3-Phenyl-3-(4-(Trifluoromethyl)phenyl)-2-Oxindole** (Table 2.2, entry 9):

A white foam. **^{1}H NMR** (500 MHz, [D6]acetone) δ 7.72 (d, *J* = 8.3 Hz, 2H), 7.52 (d, *J* = 8.2 Hz, 2H), 7.40 (dd, *J* = 7.5, 0.7 Hz, 1H), 7.39 – 7.23 (m, 11H), 7.11 (td, *J* = 7.6, 0.9 Hz, 1H), 7.06 (d, *J* = 7.9 Hz, 1H), 5.08 (AB, *J* = 15.9 Hz, ν_{ab} = 7.7 Hz, 2H). **^{13}C NMR** (75 MHz, [D6]acetone) δ 177.2, 147.6, 147.6, 143.3, 142.6, 137.3, 132.8, 130.1,

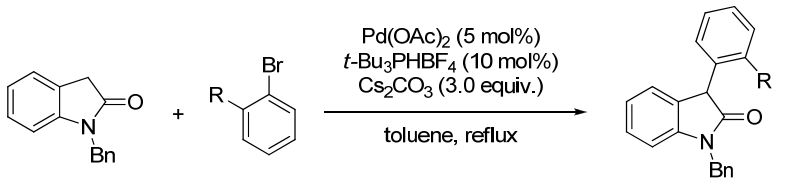
129.60, 129.58, 129.55, 129.47, 129.2, 128.43, 128.42, 128.12, 127.0, 126.16 (q, J = 3.8Hz), 123.8, 110.8, 63.0, 44.4. **^{19}F NMR** (100 MHz, [D6]acetone) δ -62.9. **IR** (cm^{-1}) 3081, 3052, 3023, 2925, 1712, 1601, 1483, 1327. **HRMS** calcd for $C_{28}H_{20}F_3NOH^+$: 444.1570; found: 444.1563.



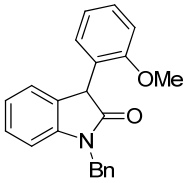
***N*-Benzyl-3-(2,6-Dimethylphenyl)-3-Phenyl-2-Oxindole** (Table 2.2, entry 10):

A white foam. **^{1}H NMR** (400 MHz, [D6]DMSO, 76 °C) δ 7.34 (dt, J = 7.6, 1.6 Hz, 1H) 6.98 – 7.30 (m, 16H), 4.90 (AB, J = 19.6 Hz, ν_{ab} = 163.7 Hz, 2H), 1.77 (s, 6H). **^{13}C NMR** (100 MHz, [D6]DMSO, 76 °C) δ 177.0, 142.8, 142.1, 138.4, 137.4, 135.7, 130.6, 129.9 (br), 128.2, 127.9, 127.9, 126.9, 126.8, 126.8, 126.3, 124.8, 122.5, 109.2, 62.2, 42.8, 22.2 (br). **IR** (cm^{-1}) 1715, 1609, 1486, 1466. **HRMS** calcd for $C_{29}H_{25}NONa^+$: 426.1828; found: 426.1820.

Preparations of *N*-Benzyl-3-*ortho*-Substituent Phenyloxindoles:



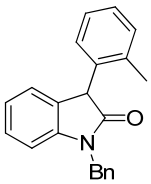
52 R = OMe, 92%
53 R = Me, 86%



***N*-Benzyl-3-(2-Methoxyphenyl)-2-Oxindole (52):**

Prepared by the same procedure as compound **53**. Purification by flash chromatography (5:1 hexanes:EtOAc) provided the title product (**52**, 2.73g, 92%) as a pink solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.35 – 7.43 (m, 2H), 7.29 – 7.35 (m, 2H), 7.24 – 7.29 (m, 2H), 7.08 – 7.19 (m, 2H), 7.02 (d, *J* = 7.5 Hz, 1H), 6.84 – 6.95 (m, 3H), 6.75 (d, *J* = 8 Hz, 1H), 4.86 and 5.09 (AB, *J* = 15.5 Hz, 2H), 4.90 (br s, 1H), 3.61, (s, 3H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ ppm 176.9, 157.6, 143.5, 136.5, 130.7, 129.9, 129.2, 128.9, 127.8, 127.8, 127.7, 126.0, 124.2, 122.5, 121.1, 111.6, 108.9, 55.8, 48.6, 44.1. **m.p.**: 113 – 114 °C. **IR** (cm^{-1}) 1714, 1611, 1491, 1464, 1351. **HRMS** calcd for $C_{22}H_{19}NO_2Na^+$: 352.1308; found: 352.1306.

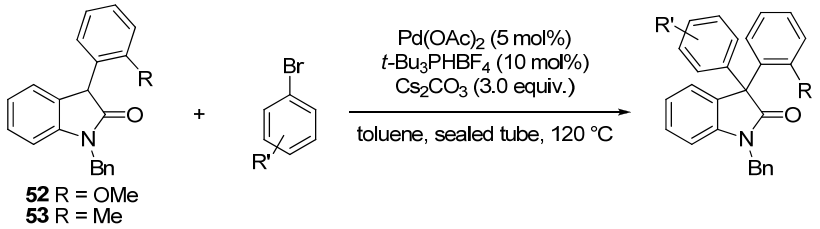


***N*-Benzyl-3-(2-Methylphenyl)-2-Oxindole (53):**

A suspension of *N*-benzyloxindole (205 mg, 0.92 mmol, 1.0 equiv), $Pd(OAc)_2$ (10.3 mg, 0.046 mmol, 0.05 equiv), *t*-Bu_3PHBF_4 (26.6 mg, 0.092mmol, 0.10 equiv), and Cs_2CO_3 (890 mg, 2.7 mmol, 3.0 equiv) in freshly distilled toluene (9 mL) was heated to reflux for 1 h. After cooling to room temperature, the reaction was quenched by the

addition of 1 M HCl (15 mL), and the biphasic mixture was extracted with EtOAc (20 mL×3). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (10:1 hexanes:EtOAc) provided the title product **53** as a colorless sticky oil (248 mg, 86%), which was crystallized by slow evaporation from Et_2O/hexanes to provide a white solid. Spectral data of **53** are consistent with that reported in the literature.[16]

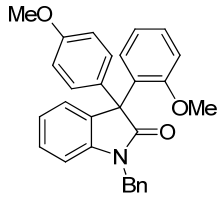
Arylation of *N*-Benzyl-3-*ortho*-Substituent Phenyloxindoles 52 & 53 (Table 2.3):



General procedure:

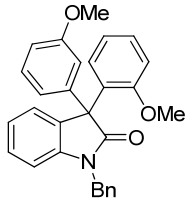
Compound **52** or **53** (0.25 mmol, 1.0 equiv), $Pd(OAc)_2$ (5 mol%), *t*-Bu_3PHBF_4 (10 mol%), and Cs_2CO_3 (3.0 equiv) were charged in a resealable tube, which was purged with Ar. The aryl bromide (1.2 equiv) was dissolved in dry toluene (5 mL), and the solution was degassed by sparging with Ar for 15 min before cannulating into the resealable tube. The resealable tube was sealed, and placed in a 120 °C sand bath for the length of time indicated in Table 2.3. After cooling to ambient temperature, the schlenk tube was open to air, and the reaction was stirred overnight in order to consume the unreacted compound **52** or **53** to the tertiary alcohol.[32] The reaction was then quenched by the addition of 1 M HCl (10 mL), and extracted with EtOAc (25 mL×3). The

combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography using a mixture of hexanes and EtOAc provided the desired 3,3-diaryloxindoles as white solids.



***N*-Benzyl-3-(2-Methoxyphenyl)-3-(4-Methoxyphenyl)-2-Oxindole** (Table 2.3, entry 2):

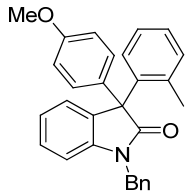
A white crystalline solid. **^{1}H NMR** (500 MHz, [D6]acetone) δ 7.39 (m, 4H), 7.33 – 7.18 (m, 5H), 7.04 – 6.85 (m, 8H), 4.96 (AB, J = 15.7 Hz, ν_{ab} = 70.0 Hz, 2H), 3.80 (s, 3H), 3.32 (s, 3H). **^{13}C NMR** (75 MHz, [D6]acetone) δ 179.1, 160.1, 158.4, 144.4, 138.0, 133.4, 133.2, 131.7, 131.2, 131.1, 129.5, 129.4, 128.63, 128.58, 128.2, 126.1, 122.5, 121.2, 114.3, 113.1, 109.6, 59.6, 56.0, 55.5, 44.3. **m.p.**: 170 – 171 °C. **IR** (cm^{-1}) 2950, 2921, 1703, 1605, 1503, 1491, 1450. **HRMS** calcd for $C_{29}H_{25}NO_3H^+$: 436.1907; found: 436.1909.



***N*-Benzyl-3-(2-Methoxyphenyl)-3-(3-Methoxyphenyl)-2-Oxindole** (Table 2.3, entry 3):

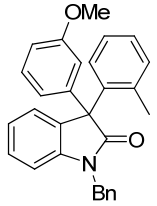
A white crystalline solid. **^{1}H NMR** (500 MHz, [D6]acetone) δ 7.43 – 7.36 (m, 2H), 7.33 – 7.18 (m, 6H), 7.10 (br s, 1H), 7.05 (dd, J = 7.4, 1.0 Hz, 2H), 7.00 (td, J = 7.5, 1.0

Hz, 1H), 6.97 (d, J = 7.8, 1H), 6.95 – 6.83 (m, 4H), 4.97 (AB, J = 15.6 Hz, ν_{ab} = 59.4 Hz, 2H), 3.72 (s, 3H), 3.32 (s, 3H). **^{13}C NMR** (75 MHz, [D6]acetone) δ 178.7, 160.4, 158.4, 144.4, 141.6, 138.0, 133.1, 132.7, 131.2, 129.8, 129.6, 129.4, 128.8, 128.6, 128.2, 126.2, 122.5, 122.2, 121.2, 116.5, 113.3, 113.2, 109.7, 60.3, 56.0, 55.4, 44.4. **m.p.**: 68 – 70 °C. **IR** (cm^{-1}) 2925, 2835, 1712, 1610, 1593, 1486. **HRMS** calcd for $C_{29}H_{25}NO_3Na^+$: 458.1727; found: 458.1729.



***N*-Benzyl-3-(4-Methoxyphenyl)-3-(2-Methylphenyl)-2-Oxindole** (Table 2.3, entry 5):

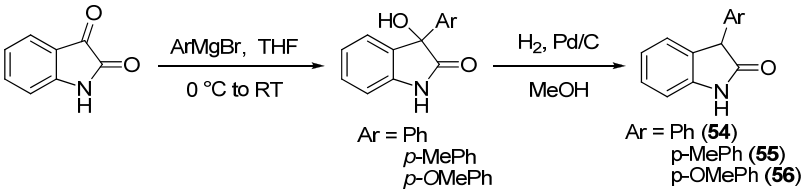
A white crystalline solid. **^{1}H NMR** (500 MHz, [D6]acetone) δ 7.65 (br s, 1H), 7.36 – 6.72 (m, 16H), 5.00 (AB, J = 15.6 Hz, ν_{ab} = 149.4 Hz, 2H), 3.80 (s, 3H), 1.85 (s, 3H). **^{13}C NMR** (75 MHz, [D6]acetone) δ 178.6, 160.1, 143.6, 141.6, 138.3, 137.4, 133.3, 133.1, 132.8, 130.9, 130.4 (br), 129.4, 129.1, 128.32, 128.30, 128.26, 126.7, 126.4, 123.3, 114.4 (br), 110.2, 62.6, 55.5, 44.2, 21.1. **m.p.**: 145 – 146 °C. **IR** (cm^{-1}) 3060, 3032, 2962, 2925, 2831, 1712, 1610, 1503, 1479, 1467. **HRMS** calcd for $C_{29}H_{25}NO_2Na^+$: 442.1778; found: 442.1772.

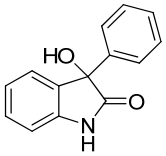


***N*-Benzyl-3-(3-Methoxyphenyl)-3-(2-Methylphenyl)-2-Oxindole** (Table 2.3, entry 6):

A white crystalline solid. **^{1}H NMR** (500 MHz, [D6]acetone) δ 7.53 – 7.01 (m, 14H), 6.91 (m, 2H), 6.73 (br s, 1H), 5.02 (AB, J = 15.6 Hz, ν_{ab} = 130.3 Hz, 2H), 3.71 (s, 3H), 1.90 (s, 3H). **^{13}C NMR** (75 MHz, [D6]acetone) δ 178.19, 160.69, 143.49, 143.20, 141.05, 138.56, 137.35, 133.14, 132.95, 130.81, 130.21, 129.43, 129.23, 128.37, 128.35, 126.88, 126.43, 123.39, 115.64, 110.32, 63.41, 55.45, 44.28, 21.31. **m.p.**: 67 – 68 °C. **IR** (cm^{-1}) 3052, 3027, 2954, 2921, 1712, 1601, 1487, 1462. **HRMS** calcd for $C_{29}H_{25}NO_2Na^+$: 442.1778; found: 442.1775.

Preparations of 3-Aryloxindoles:

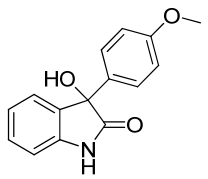




3-Hydroxy-3-Phenylindolin-2-One:

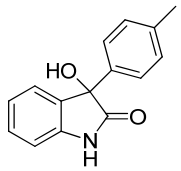
To a 250 ml three-neck flask were added magnesium turning (3.70 g, 150 mmol, 2.2 equiv), anhydrous THF (100 mL), and bromobenzene (22.48 g, 143 mmol, 2.1 equiv). The mixture was heated until almost all the magnesium turning was consumed. Then the brown solution was cannulated slowly to a THF (300 mL) solution of isatin (10.03 g, 68 mmol, 1.0 equiv), which was cooled in an ice bath. The solution was warmed to room temperature and stirred for an additional 3 h. The mixture was diluted with Et_2O (200

mL), cooled in an ice bath, and quenched with 1 M HCl (200 mL). The aqueous layer was extracted with Et_2O (200 ml×3), and the combined organic layer was washed with water (200 mL), brine (200 mL), dried over $MgSO_4$, and concentrated under reduced pressure. Recrystallization from hot EtOAc and hexane provide a crystalline yellow solid (12.33 g, 80 %). NMR data were consistent with literature values.[34]



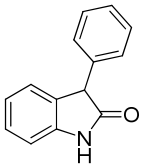
3-Hydroxy-3-*p*-Methoxylphenylindolin-2-One:

This compound was prepared from 4-bromoanisole by following the procedure for the preparation of 3-hydroxy-3-phenylindolin-2-one and was purified by crystallization from hot EtOAc and hexanes to provide a white cotton-like solid (3.19 g, 88 %). NMR data were consistent with literature values.[35]



3-Hydroxy-3-*p*-Tolylindolin-2-One:

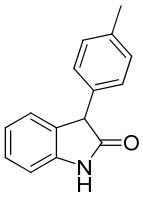
This compound was prepared from 4-bromotoluene by following the procedure for the preparation of 3-hydroxy-3-phenylindolin-2-one and was purified by crystallization from hot EtOAc and hexanes to provide a crystalline yellowish solid (2.92 g, 85 %). NMR data were consistent with literature values.[35]



3-Phenylindolin-2-One (54):

3-Hydroxy-3-phenylindolin-2-one (4.03 g, 17.9 mmol) was dissolved in a 250 mL round bottom flask with methanol (100 ml). After addition of 10 % Pd/C (1.9 g, 1.79 mmol), the mixture was reacted under H_2 atmosphere overnight (15 h), using balloon untill all the starting alcohol was consumed. The mixture was diluted with Et_2O (100 mL), filtrated over celite, and concentrated under reduced pressure to provide a yellowish solid. The crude product was recrystallized from hot EtOAc to provide compound **54** as a crystalline white solid (3.50 g, 93 %).

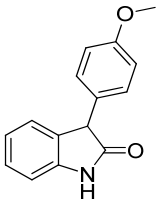
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.04 (s, 1H), 7.35 – 7.25 (m, 3H), 7.23 – 7.18 (m, 2H), 7.12 (d, *J* = 7.4 Hz, 1H), 7.02 (td, *J* = 7.5, 1.0 Hz, 1H), 6.92 (d, *J* = 7.8 Hz, 1H), 4.62 (s, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.29, 141.96, 136.69, 129.87, 129.20, 128.73, 128.62, 127.90, 125.43, 122.92, 110.35, 53.00.



3-*p*-Tolylindolin-2-One (55):

Compound **55** was prepared from 4-bromotoluene via the similar procedure for the preparation of **54** and was purified by recrystallization from hot EtOAc and hexanes to provide a yellowish crystalline solid (1.82 g, 95 %).

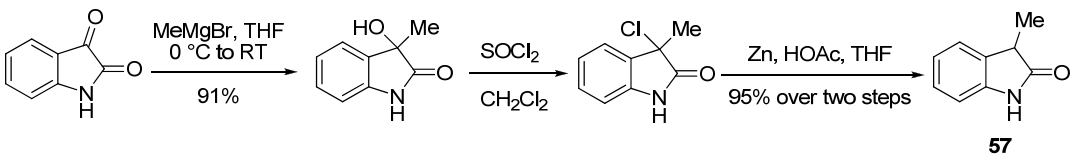
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.26 (s, 1H), 7.26 – 7.19 (m, 1H), 7.17 – 7.06 (m, 5H), 7.01 (td, *J* = 7.6, 0.8 Hz, 1H), 6.91 (d, *J* = 7.8 Hz, 1H), 4.58 (s, 1H), 2.31 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 179.67, 142.05, 137.61, 133.67, 130.08, 129.89, 128.57, 128.50, 125.33, 122.84, 110.37, 52.71, 21.36.

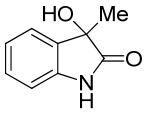


3-(4-Methoxyphenyl)indolin-2-One (56):

Compound **56** was prepared from 4-bromotoluene by following the procedure for the preparation of **54** and was purified by recrystallization from hot EtOAc and hexanes to provide a white crystalline solid (1.02 g, 86 %). NMR data were consistent with literature values.[18]

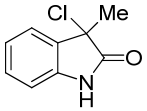
Preparation of 3-Methyloxindole:





3-Hydroxy-3-Methylindolin-2-One:

Isatin (5.04 g, 34.3 mmol) was dissolved in anhydrous THF (75 mL), and cooled in a dry ice / acetone bath, and MeMgBr in Et_2O (3.0 M, 28 ml, 84.0 mmol) was added dropwise via syringe. After stirring for 2 h in -78 °C, the reaction was quenched with saturated NH_4Cl (50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (100 ml×3), and the combined organic layers were washed with water (50 mL), brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude product as a yellow solid. Recrystallization from hot EtOAc and hexanes provided a crystalline yellow solid (5.08 g, 91 %). NMR data were consistent with literature values.[34]

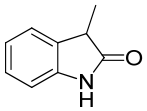


3-Chloro-3-Methylindolin-2-One:

3-Hydroxy-3-methylindolin-2-one (4.00 g, 24.5 mmol) was dissolved in dry CH_2Cl_2 (60 mL), cooled in the ice bath. $SOCl_2$ (4.5 ml, 61.8 mmol) was added dropwise via syringe. The resultant mixture was warmed to room temperature and stirred for additional 3 h, and the reaction was quenched with saturated $NaHCO_3$ (50 mL), diluted with EtOAc (50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (50 ml×3), and the combined organic layers were washed with water (50 mL), brine (50 mL),

dried over $MgSO_4$, filtrated, and concentrated under reduced pressure. The crude product was used directly in next step without purification.

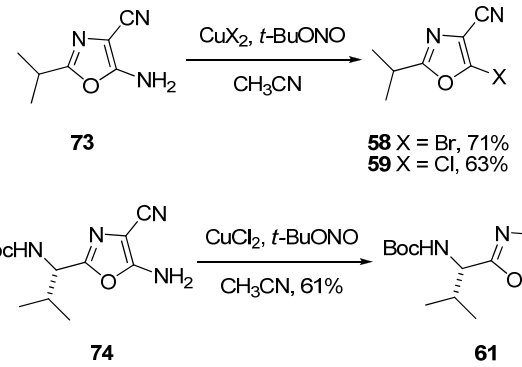
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.52 (s, 1H), 7.39 (dd, J = 7.5, 0.6 Hz, 1H), 7.27 (td, J = 7.7, 1.2 Hz, 1H), 7.08 (td, J = 7.6, 1.0 Hz, 1H), 6.98 (d, J = 7.8 Hz, 1H), 1.91 (s, 3H).

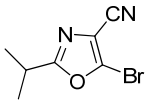


3-Methylindolin-2-one (57):

3-Chloro-3-methylindolin-2-one (4.36 g, 24.0 mmol) was dissolved in dry THF (120 mL), and activated zinc dust (4.98 g, 76 mmol) and glacial acetic acid (9.0 ml, 157 mmol) were added. After stirring at room temperature for 3 h, the mixture was filtrated over celite, and washed with EtOAc. The filtrate was evaporated on rotary evaporator (using toluene to azeotrope off acetic acid) to provide a brown oil. The crude product was purified by flash chromatography (2:1 hexanes:EtOA) to provcide compound **57** as a white solid (3.37 g, 95 %). NMR data of **57** were consistent with literature values.[36]

Preparations of 5-Halooxazoles:





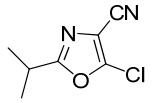
58

5-Bromo-2-*iso*-Propyloxazole-4-Carbonitrile (58):

Prepared according to a modification of the procedure of Harran.[37] Compound **73** (1.79 g, 11.9 mmol, 1.0 equiv), which was prepared by Freeman's method,[38] was added in small portions to a stirred suspension of $CuBr_2$ (5.30 g, 23.7 mmol, 2.0 equiv) and *t*-BuONO (90%, 2.72 mL, 23.7 mmol, 2.0 equiv) in anhydrous CH_3CN (100 mL). After stirring at room temperature for 1 h, the mixture was diluted with Et_2O (100 mL) and H_2O (100 mL), and washed with 1 M HCl (aq, 100 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (100 mL×3). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure to provide a yellow oil. Purification by flash chromatography (10:1 hexanes:EtOAc) provided compound **58** as a colorless oil (1.82 g, 71 %), which solidified upon cooling.

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.08 (hept, J = 7.0 Hz, 1H), 1.34 (d, J = 7.0 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 171.8, 130.6, 115.6, 111.3, 29.0, 20.0. **m.p.**: 70 – 71 °C.

IR (cm^{-1}): 2966, 2933, 2880, 2255, 1576, 1552, 1142, 1045. **HRMS** m/z calcd for $(C_7H_7ClN_2O)_2Na^+$: 450.9376; found: 450.9376.

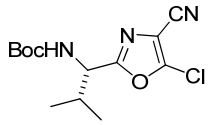


59

5-Chloro-2-*iso*-Propyloxazole-4-Carbonitrile (59):

Prepared according to a modification of the procedure of Harran.[37] Compound **73** (920 mg, 6.08 mmol, 1.0 equiv), which was prepared by Freeman's method,[38] was added in small portions to a stirred suspension of $CuCl_2$ (1.68 g, 12.5 mmol, 2.05 equiv) and *t*-BuONO (90%, 1.6 mL, 13.45 mmol, 2.2 equiv) in anhydrous CH_3CN (50 mL). After stirring at room temperature for 1 h, the mixture was diluted with Et_2O (100 mL) and H_2O (50 mL), and washed with 1 M HCl (aq, 50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (50 mL×3). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure to provide a yellow oil. Purification by flash chromatography (10:1 hexanes:EtOAc) provided compound **59** (651 mg, 63 %) as a colorless oil. (Note: Compound **59** is volatile, and can be pumped off under high vacuum.)

^{1}H NMR (400 MHz, $CDCl_3$) δ 3.06 (hept, J = 7.0 Hz, 1H), 1.33 (d, J = 7.0 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 169.5, 144.2, 110.9, 110.8, 29.0, 20.0. **IR** (cm^{-1}): 2978, 2929, 2880, 2242, 1564, 1184, 1127. **HRMS** m/z calcd for $(C_7H_7ClN_2O)_2Na^+$: 363.0386; found: 363.0383.



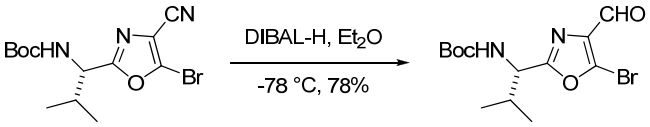
61

(S)-*tert*-Butyl-1-(5-Chloro-4-Cyanooxazol-2-yl)-2-Methylpropylcarbamate (61):

Prepared according to a modification of the procedure of Harran.[37] Compound **74** (1.02 g, 3.64 mmol, 1.0 equiv)[37,38] was added in small portions to a stirred suspension of $CuCl_2$ (1.24 g, 9.22 mmol, 2.5 equiv) and *t*-BuONO (90%, 1.1 mL, 9.16 mmol, 2.5 equiv) in anhydrous CH_3CN (50 mL). After stirring at room temperature for 1 h, the mixture was diluted with Et_2O (100 mL) and H_2O (50 mL), and washed with 1 M HCl (aq, 50 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (50 mL×3). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, concentrated under reduced pressure to provide a yellow oil. Purification by flash chromatography (10:1 hexanes:EtOAc) provided compound **61** as a colorless oil (502 mg, 46 %), which solidified upon cooling.

^{1}H NMR (500 MHz, $CDCl_3$) δ 5.00 (d, *J* = 8.9 Hz, 1H), 4.80 – 4.63 (m, 1H), 2.15 (dd, *J* = 13.3, 6.6 Hz, 1H), 1.43 (s, 9H), 0.94 (t, *J* = 7.3, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 164.7, 155.4, 144.7, 111.2, 110.5, 80.7, 54.7, 32.3, 28.4, 19.0, 18.0. **m.p.**: 69 – 70 °C. **IR** (cm^{-1}): 3332, 2245, 1714, 1513, 1367, 1167. **HRMS** m/z calcd for $C_{13}H_{18}ClN_3O_3Na^+$: 322.0928; found: 322.0922.

(S)-*tert*-Butyl-1-(5-Bromo-4-Formyloxazol-2-yl)-2-Methylpropylcarbamate (62):



60 **62**

DIBAL-H (10.5 mL of a 1.0 M solution in hexanes, 10.5 mmol, 2.4 equiv) was added dropwise via syringe to a -78 °C solution of nitrile **60** (1.5 g, 4.36 mmol, 1.0 equiv) in dry Et_2O (40 mL). After the addition was complete, the reaction was stirred at -78 °C for an additional 15 min. Dry acetone (200 μL) was added to quench the excess DIBAL-H, and the reaction was stirred at -78 °C for an additional 15 min. The cold bath was then removed, saturated citric acid (aq, 30 mL) was added, and the biphasic mixture stirred at room temperature for 1 h. The aqueous layer was extracted with Et_2O (20 mL×3), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a yellow oil. Purification by flash chromatography (5:1 hexanes:EtOAc) provided aldehyde **62** as a colorless oil (1.17 g, 78 %).

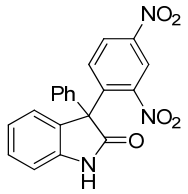
^{1}H NMR (500 MHz, $CDCl_3$, ~15% rotamer peaks were observed) δ 9.73 (d, J = 14.3 Hz, 1H), 5.30 (d, J = 9.3 Hz, 1H), 4.65 (dd, J = 9.1, 6.1 Hz, 1H), 2.07 (dq, J = 13.3, 6.7 Hz, 1H), 1.28 (s, 9H), 0.84 (t, J = 19.5 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 182.2, 166.4, 155.3, 136.3, 130.0, 80.1, 54.4, 32.3, 28.2, 18.8, 17.8. **IR** (cm^{-1}) 3334, 1703, 1515, 1167. **HRMS** m/z calcd for $C_{13}H_{19}BrN_2O_4K^+$: 385.0159; found: 385.0157.

Arylations of 3-Phenyloxindole (**54**, Table 2.4):

54

General procedure:

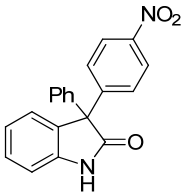
3-Phenyloxindole (**54**, 0.1 mmol, 1.0 equiv), aryl halide (1.0 equiv), and Cs_2CO_3 (1.0 equiv) were charged in a 10 mL round bottom flask, which was purged with N_2. Fresh distilled DMF (2 mL, degassed by sparing with N_2 for 15 min) was cannulated into the above flask, and the septum was then sealed with electrical tape. The reaction was stirred at room temperature, or in a preheated oil bath (65 °C or 120 °C) for the length of time indicated in Table 2.4. After cooling to ambient temperature, the reaction was quenched with saturated NH_4Cl (20 mL), extracted with 1:1 hexanes:EtOAc (20 mL×3), and the combined organic layers were washed by water (10 ml×3), brine (10 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography using a mixture of hexanes:EtOAc provided the desired 3,3-diaryloxindoles.



3-(2,4-Dinitrophenyl)-3-Phenylindolin-2-One (Table 2.4, entry 1):

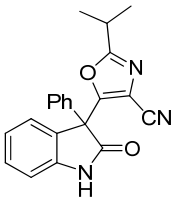
A yellowish crystalline solid. **^{1}H NMR** (500 MHz, [D6]acetone) δ 9.77 (s, 1H), 8.69 (d, *J* = 2.5 Hz, 1H), 8.49 (dd, *J* = 8.8, 2.5 Hz, 1H), 7.59 – 7.54 (d, *J* = 8.8 Hz, 1H), 7.40 – 7.30 (m, 5H), 7.26 (br, 2H), 7.13 – 7.08 (m, 2H). **^{13}C NMR** (101 MHz, [D6]acetone) δ 177.1, 177.0, 150.2, 147.8, 143.2, 143.0, 141.1, 136.4, 131.0, 130.1, 129.5, 129.4, 129.2, 127.3, 126.0, 122.9, 121.2, 111.3, 111.2, 61.9. **m.p.**: 237 – 238 °C. **IR** (cm^{-1}): 3276 (br),

3101, 1728, 1708, 1532, 1352. **HRMS** m/z calcd for $C_{20}H_{13}N_3O_5Na^+$: 398.0747; found: 398.0739.



3-(4-Nitrophenyl)-3-Phenylindolin-2-One (Table 2.4, entry 2):

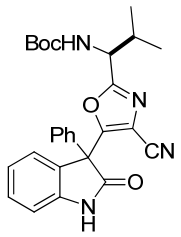
A yellowish crystalline solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.58 (s, 1H), 8.41 – 8.28 (m, 2H), 7.73 – 7.65 (m, 2H), 7.51 – 7.42 (m, 1H), 7.30 (ddt, *J* = 14.7, 7.4, 1.1 Hz, 2H), 7.20 (d, *J* = 7.8 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.4, 148.0, 147.3, 140.5, 134.3, 129.0, 128.1, 124.5, 124.0, 123.5, 111.0, 77.6, 77.2, 76.9, 53.1, 23.8. **m.p.**: 215 – 216 °C. **IR** (cm^{-1}): 3248 (br), 1716, 1593, 1348. **HRMS** m/z calcd for $C_{20}H_{14}N_2O_3Na^+$: 353.0897; found: 353.0894.



2-*iso*-Propyl-5-(2-Oxo-3-Phenylindolin-3-yl)Oxazole-4-Carbonitrile (Table 2.4, entries 3 & 4):

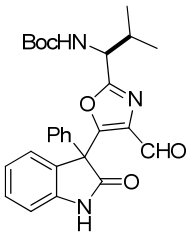
A white crystalline solid. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.71 (s, 1H), 7.40 – 7.28 (m, 7H), 7.12 (dd, *J* = 11.1, 4.1 Hz, 1H), 7.04 (d, *J* = 7.8 Hz, 1H), 3.03 (hept, *J* = 7.0 Hz, 1H), 1.28 (dd, *J* = 7.0, 1.3 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.2, 170.0, 157.5,

141.0, 135.8, 130.3, 129.2, 129.1, 128.6, 127.8, 126.4, 123.6, 112.5, 111.8, 111.6, 57.5, 28.6, 20.2, 20.0. **m.p.**: 179 – 180 °C. **IR** (cm^{-1}): 3280 (br), 2983, 2246, 1719, 1621, 1593, 1470. **HRMS** m/z calcd for $C_{21}H_{17}N_3O_2Na^+$: 366.1213; found: 366.1202.



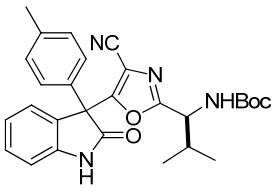
***tert*-Butyl-(1S)-1-(4-Cyano-5-(2-Oxo-3-Phenylindolin-3-yl)Oxazol-2-yl)-2-Methylpropylcarbamate** (Table 2.4, entries 5 & 6):

A white foam. **^{1}H NMR** (500 MHz, $CDCl_3$; ~14% rotamer peaks were observed; obtained as an approximately 1:1 mixture of diastereomers) δ 9.05 (s, 1H), 7.42 – 7.25 (m, 7H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 5.16 (t, *J* = 7.1Hz, 1H), 4.71 (dd, *J* = 14.0, 8.0 Hz, 1H), 2.15 – 1.98 (m, 1H), 1.46 – 1.18 (m, 9H), 0.91 – 0.71 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 174.7, 165.0, 158.2, 155.5, 140.9, 135.5, 130.4, 129.3, 129.3, 128.3, 127.9, 126.4, 123.7, 112.7, 111.6, 111.5, 80.5, 57.4, 54.4, 32.8, 28.5, 18.8, 18.7, 17.9. **IR** (cm^{-1}): 3288 (br), 2970, 2246, 1719, 1475, 1168. **HRMS** m/z calcd for $C_{27}H_{28}N_4O_4Na^+$: 495.2003; found: 495.1988.



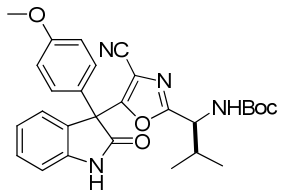
***tert*-Butyl-(1S)-1-(4-Formyl-5-(2-Oxo-3-Phenylindolin-3-yl)Oxazol-2-yl)-2-Methylpropylcarbamate** (Table 2.4, entry 7):

A white foam. **^{1}H NMR** (500 MHz, $CDCl_3$; ~13% rotamer peaks were observed; obtained as an approximately 1:1 mixture of diastereomers) δ 9.59 (d, *J* = 32.9 Hz, 1H), 9.40 (d, *J* = 13.9 Hz, 1H), 7.37 – 7.21 (m, 7H), 7.06 (dd, *J* = 13.8, 7.3 Hz, 2H), 5.65 (br, 1H), 4.77 – 4.65 (m, 1H), 2.13 – 1.95 (m, 1H), 1.30 (dd, *J* = 50.1, 12.7 Hz, 9H), 0.89 – 0.71 (m, 6H). **^{13}C NMR** (100 MHz, $CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 184.2, 184.2, 175.7, 175.6, 164.2, 158.0, 157.8, 155.6, 141.0, 137.2, 137.1, 136.4, 136.4, 130.0, 130.0, 129.2, 129.2, 129.0, 128.9, 128.7, 127.8, 127.7, 126.2, 126.1, 123.5, 111.6, 111.6, 80.1, 58.1, 54.2, 54.2, 33.1, 29.8, 28.4, 18.7, 18.6, 18.1, 17.9. **IR** (cm^{-1}): 3297 (br), 2978, 1715, 1503, 1176. **HRMS** m/z calcd for $C_{27}H_{29}N_3O_5Na^+$: 498.1999; found: 498.1993.



***tert*-Butyl-(1S)-1-(4-Cyano-5-(2-Oxo-3-*p*-Tolylindolin-3-yl)oxazol-2-yl)-2-Methylpropylcarbamate** (Table 2.4, entry 8):

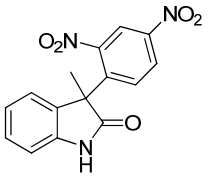
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (d, *J* = 10.9, 1H), 7.30 (dd, *J* = 18.0, 7.8 Hz, 2H), 7.15 (q, *J* = 8.7 Hz, 4H), 7.09 (t, *J* = 7.6 Hz, 1H), 7.03 (d, *J* = 7.8 Hz, 1H), 5.23 (t, *J* = 8.8 Hz, 1H), 4.78 – 4.61 (m, 1H), 2.31 (s, 3H), 2.15 – 1.95 (m, 1H), 1.49-1.16 (m, 9 H), 0.92 – 0.71 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$, obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 175.15, 164.94, 158.39, 155.49, 140.99, 139.12, 132.51, 130.28, 129.96, 129.93, 128.52, 127.68, 126.24, 123.53, 112.58, 111.59, 111.54, 80.43, 77.58, 77.26, 76.94, 57.15, 54.37, 32.75, 29.89, 28.44, 21.30, 18.69, 17.87. **IR** (cm^{-1}): 3289, 2974, 2235, 1736, 1515, 1164.



***tert*-Butyl-(1S)-1-(4-Cyano-5-(3-(4-Methoxyphenyl)-2-Oxoindolin-3-yl)oxazol-2-yl)-2-Methylpropylcarbamate** (Table 2.4, entry 9):

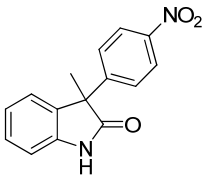
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.34 (s, 1H), 7.36 – 7.26 (m, 2H), 7.26 – 7.19 (d, *J* = 5.0 Hz, 2H), 7.10 (t, *J* = 7.5, 1H), 7.02 (d, *J* = 7.8, 1H), 6.90 – 6.82 (m, 2H), 5.21 (t, *J* = 10.1, 1H), 4.79 – 4.62 (m, 1H), 3.75 (s, 3H), 2.17 – 1.98 (m, 1H), 1.45 – 1.18 (m, 9H), 0.91 – 0.72 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$, obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals) δ 175.22, 164.89, 160.24, 158.71, 155.48, 140.92, 130.27, 129.13, 128.55, 127.15, 126.24, 123.52, 114.60, 114.57, 112.55, 111.56,

111.50, 80.43, 56.65, 55.50, 54.35, 32.77, 28.43, 18.70, 18.66, 17.87. **IR** (cm^{-1}): 3277 (br), 2966, 2239, 1720, 1507, 1249, 1172.



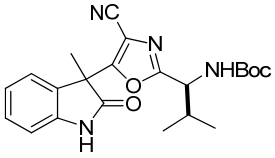
3-(2,4-Dinitrophenyl)-3-Methylindolin-2-One (Table 2.4, entry 10):

^{1}H NMR (500 MHz, [D6]acetone) δ 9.72 (s, 1H), 8.63 (dd, *J* = 8.8, 2.5 Hz, 1H), 8.57 (d, *J* = 2.5 Hz, 1H), 8.42 (d, *J* = 8.8 Hz, 1H), 7.25 (td, *J* = 7.7, 1.3 Hz, 1H), 7.04 – 6.96 (m, 2H), 6.93 (td, *J* = 7.5, 1.0 Hz, 1H), 1.87 (s, 3H). **^{13}C NMR** (101 MHz, [D6]acetone) δ 179.13, 150.42, 148.07, 142.76, 140.76, 134.01, 133.63, 129.51, 127.38, 123.27, 122.86, 120.93, 110.80, 52.38, 27.43. **IR** (cm^{-1}): 3244 (br), 1715, 1535, 1352.



3-Methyl-3-(4-Nitrophenyl)indolin-2-One (Table 2.4, entry 11):

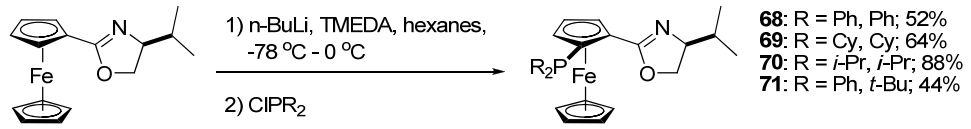
^{1}H NMR (500 MHz, $CDCl_3$) δ 9.37 (s, 1H), 8.19 – 8.08 (m, 2H), 7.54 – 7.44 (m, 2H), 7.26 (td, *J* = 7.5, 1.7 Hz, 1H), 7.09 (dtd, *J* = 14.7, 7.4, 1.1 Hz, 2H), 6.99 (d, *J* = 7.8 Hz, 1H), 1.84 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 181.35, 148.00, 147.30, 140.54, 134.30, 128.99, 128.06, 124.52, 123.95, 123.47, 110.97, 53.12, 23.79. **IR** (cm^{-1}): 3248 (br), 1728, 1622, 1524, 1348.



***tert*-Butyl-(1S)-1-(4-Cyano-5-(3-Methyl-2-Oxoindolin-3-yl)oxazol-2-yl)-2-Methylpropylcarbamate** (Table 2.4, entry 12):

^{1}H NMR (500 MHz, $CDCl_3$) δ 9.19 (d, *J* = 10.0 Hz, 1H), 7.29 (t, *J* = 7.7 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.99 (dd, *J* = 7.7, 3.8 Hz, 1H), 5.23 (d, *J* = 9.3 Hz, 1H), 4.73 (dd, *J* = 9.0, 5.6 Hz, 1H), 2.17 – 2.01 (m, 1H), 1.90 (s, 3H), 1.44 – 1.28 (m, 9H), 0.86 (dd, *J* = 11.8, 6.2 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$, obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 176.51, 164.89, 164.77, 158.23, 155.55, 140.39, 140.32, 130.34, 130.13, 124.31, 123.71, 111.96, 111.88, 111.38, 111.16, 80.56, 54.40, 48.86, 32.77, 29.92, 28.49, 21.47, 18.74, 18.02, 17.94. **IR** (cm^{-1}): 3276 (br), 2974, 2239, 1707, 1532, 1470, 1172.

Synthesis of Ferrocenyloxazoline Phosphine Ligands:[26]



67

General Procedure:

n-BuLi (740 µL, 1.179 mmol, 1.2 equiv) was added dropwise to a solution of compound **67** (292 mg, 0.083 mmol, 1.0 equiv) and TMEDA (176 µL, 1.179 mmol, 1.2

equiv) in dry hexanes (10 mL) in a dry ice / acetone bath. The reaction was allowed to stir at -78 °C for 1 h, and the cooling bath was switched to an ice bath. After stirring in the ice bath for 5 min, $ClPPh_2$ (242 μL, 1.179 mmol, 1.2 equiv) was added, and the reaction was slowly warmed up to room temperature stirring overnight (~ 15 h). The reaction was quenched with sat. $NaHCO_3$ (10 mL) and water (10 mL), and further diluted with hexanes (10 mL). The organic layer was separated, and the aqueous layer was extracted with hexanes (10 mL×2). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to provide an orange solid. Purification by flash chromatography with 5:1 hexanes:EtOAc provided compound **68** (248 mg, 52%) as an orange solid. Spectral data of compound **68** were consistent with literature values.[26]

Compound 69:

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.91 (s, 1H), 4.41 (dd, *J* = 9.7, 7.3 Hz, 2H), 4.18 (s, 1H), 4.11 (d, *J* = 8.9 Hz, 5H), 4.02 – 3.85 (m, 2H), 2.49 (d, *J* = 12.7 Hz, 1H), 1.96 – 1.63 (m, 7H), 1.63 – 1.13 (m, 11H), 1.12 – 0.77 (m, 9H), 0.67 (dd, *J* = 25.3, 12.6 Hz, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.66, 166.63, 78.73, 78.36, 72.03, 71.96, 71.84, 71.28, 71.26, 71.03, 70.86, 70.53, 69.62, 36.56, 36.34, 32.81, 32.66, 32.17, 31.84, 31.62, 30.20, 30.04, 29.45, 29.28, 29.03, 28.96, 27.85, 27.70, 27.61, 27.32, 27.20, 27.17, 27.08, 26.54, 26.31, 19.27, 17.82. **^{31}P NMR** (121 MHz, $CDCl_3$) δ -10.71.

Compoudn 70:

^{1}H NMR (500 MHz, $CDCl_3$) δ 4.94 (s, 1H), 4.50 – 4.40 (m, 2H), 4.25 (dd, *J* = 2.4, 1.5 Hz, 1H), 4.17 (s, 5H), 3.99 (t, *J* = 8.77 Hz, 1H), 3.91 (td, *J* = 9.2, 6.3 Hz, 1H), 2.04 (dq, *J* = 13.9, 7.0 Hz, 1H), 1.89 – 1.61 (m, 3H), 1.48 (dd, *J* = 14.7, 7.0 Hz, 3H), 1.13 (dd, *J* = 13.3, 6.9 Hz, 3H), 0.98 (d, *J* = 6.8 Hz, 3H), 0.89 – 0.81 (m, 6H), 0.77 (dd, *J* = 10.0, 7.1 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.50, 166.47, 78.98, 78.61, 74.29, 74.10, 72.23, 72.04, 71.98, 71.53, 71.51, 70.95, 70.57, 69.93, 32.54, 26.63, 26.41, 22.45, 22.30, 22.20, 21.95, 20.23, 20.00, 19.51, 19.35, 18.79, 18.70, 18.13. **^{31}P NMR** (122 MHz, $CDCl_3$) δ -2.45.

Compound 71:

^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 – 7.89 (m, 2H), 7.46 – 7.36 (m, 3H), 4.94 (dt, *J* = 2.8, 1.5 Hz, 1H), 4.48 (dd, *J* = 9.6, 8.4 Hz, 1H), 4.39 (td, *J* = 2.6, 0.7 Hz, 1H), 4.28 (dd, *J* = 2.5, 1.5 Hz, 1H), 4.04 (t, *J* = 8.7 Hz, 1H), 3.97 – 3.89 (m, 6H), 1.82 (dq, *J* = 13.4, 6.7 Hz, 1H), 1.04 – 0.93 (m, 12H), 0.88 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.43, 166.40, 136.68, 136.42, 136.09, 129.44, 129.43, 127.89, 127.78, 76.85, 76.18, 75.82, 74.35, 74.27, 72.73, 72.68, 72.00, 71.47, 71.47, 70.51, 70.06, 32.44, 32.28, 32.09, 28.87, 28.67, 19.35, 18.12. **^{31}P NMR** (122 MHz, $CDCl_3$) δ 2.65.

2.10 References and Notes

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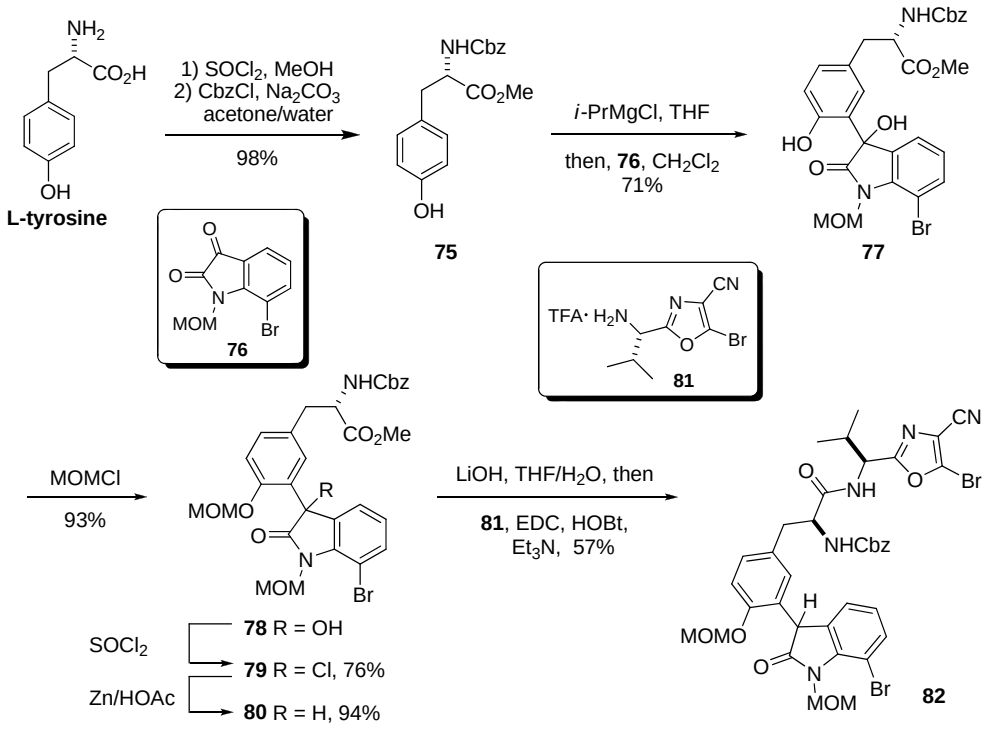
3 Formal Synthesis of Diazonamide A

3.1 Background and Previous Work by Dr. Matthew Sammons

The synthetic challenge of diazonamide A, for the most part, lies in the stereoselective construction of the highly congested C10 quaternary carbon. Although three total syntheses and one formal synthesis of diazonamide A were reported prior to our work, the reactions of constructing the C10 quaternary center preceded with either low or moderate diastereoselectivity. Our success in the development of methods for the α-arylation of 3-aryloxindoles encouraged us to apply these reactions to the total synthesis of diazonamide A.

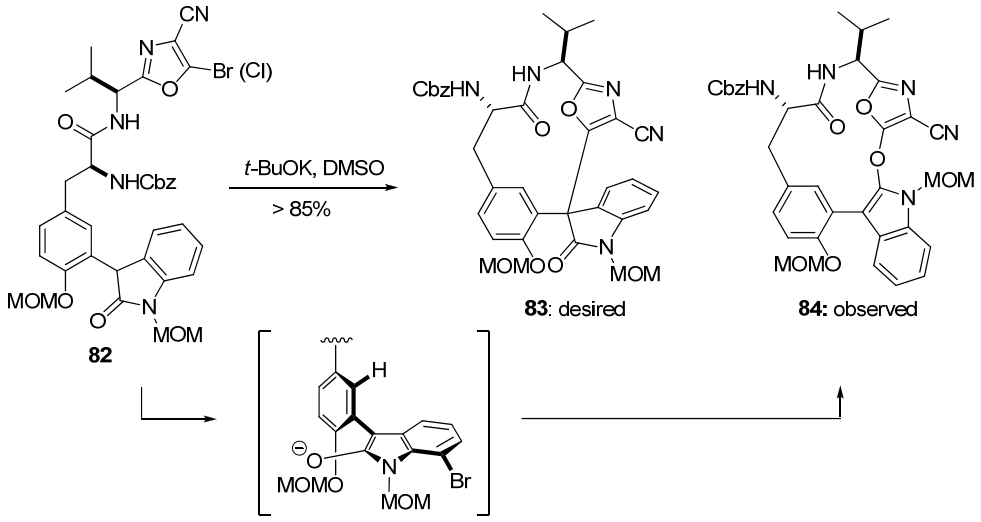
Dr. Matthew Sammons studied, among other things, the macrocyclization of compound **82** via an intramolecular nucleophilic aromatic substitution reaction. Synthesis of compound **82** (Scheme 3.1) started with the esterification and protection of L-tyrosine to provide compound **75**.[1] Treatment of **75** with *i*-PrMgCl provided the magnesium phenolate that added to the carbonyl group of *N*-MOM-7-bromoisatin (**76**) to provide tertiary alcohol **77**.[2,3] The phenol hydroxyl group of compound **77** was then protected as the MOM ether to provide **78**, and the tertiary alcohol of **78** was reduced via the two-step sequence of chlorination ($SOCl_2$) and reduction (Zn/HOAc) to provide compound **80**. Saponification of the methyl ester of **80** with degassed LiOH aqueous solution, followed by amide bond formation using amine TFA salt **81**, under the typical peptide coupling conditions (EDC/HOBt) furnished cyclization precursor **82**.



Scheme 3.1 Preparation of Cyclization Precursor **82**

However, treatment of compound **82** with a variety of bases in different solvents only provided the undesired *O*-arylation product **84** (Scheme 3.2), with none of the desired *C*-arylation product (**83**) being observed. The lack of *C*-arylation was in contrast to previous observations on the intramolecular S_NAr arylations of *N*-MOM-3-phenyloxindole (**48**, Scheme 2.6). We hypothesized that the enolate derived from compound **82** would not be able to adopt a planar conformation. Rather it would adopt a conformation such that the *ortho*-substituent on the phenol ring would like to avoid the alkoxide of the enolate and twist the phenol ring to become perpendicular to the enolate, thus rendering the carbon of the enolate at the junction of the two aromatic rings too hindered to approach the oxazole. As such, the less hindered oxygen of the enolate would attack the bromooxazole to form the macrocycle via an S_NAr mechanism. Changing the MOM protecting group on the phenol to a smaller protecting group, such as a methyl

group, was also studied, but did not provide the desired *C*-arylation product either.[4] At this point, we felt that varying the reaction conditions or making minor changes in the substrate would not be productive, and we sought to test our hypothesis that the conformation of the enolate was non-planar and was to blame for the lack of reactivity.

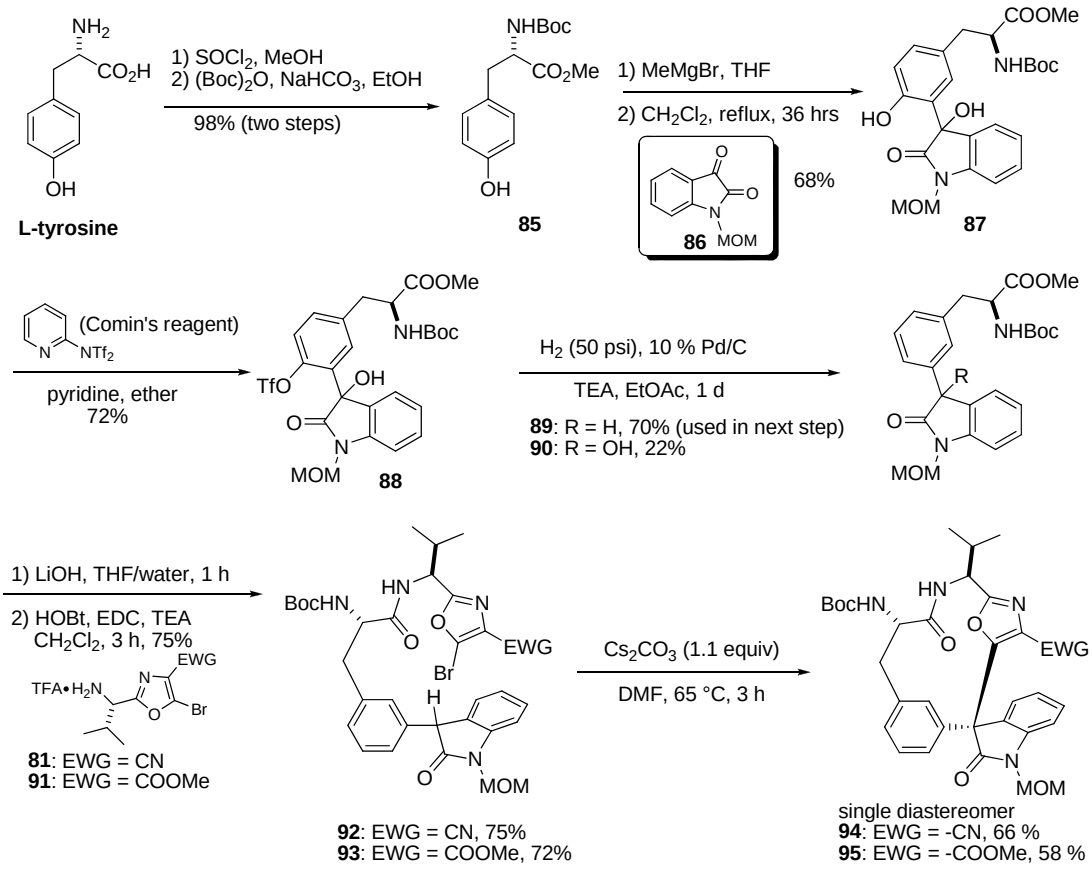


Scheme 3.2 Cyclization of **82** with *ortho*-substituent by Dr. Matthew Sammons

3.2 Cyclization of a Precursor Without *ortho*-Substituent

A straightforward test of the above hypothesis is to prepare a cyclization substrate analogous to **82** but lacking the *ortho*-MOM substituent. This compound should be capable of adopting a planar conformation and cyclizing on carbon. I, therefore, prepared cyclization precursors **92** and **93** without *ortho*-substitution on the tyrosine phenyl ring as described in Scheme 3.3. The methyl ester of L-tyrosine was prepared ($SOCl_2$ in MeOH), and the amino group was protected as the *tert*-butyl carbamate to provide **85**.[5] The magnesium phenolate, generated by deprotonation of the phenol of protected tyrosine **85** with MeMgBr, was added to the carbonyl group of *N*-MOM-isatin (**86**) to provide tertiary

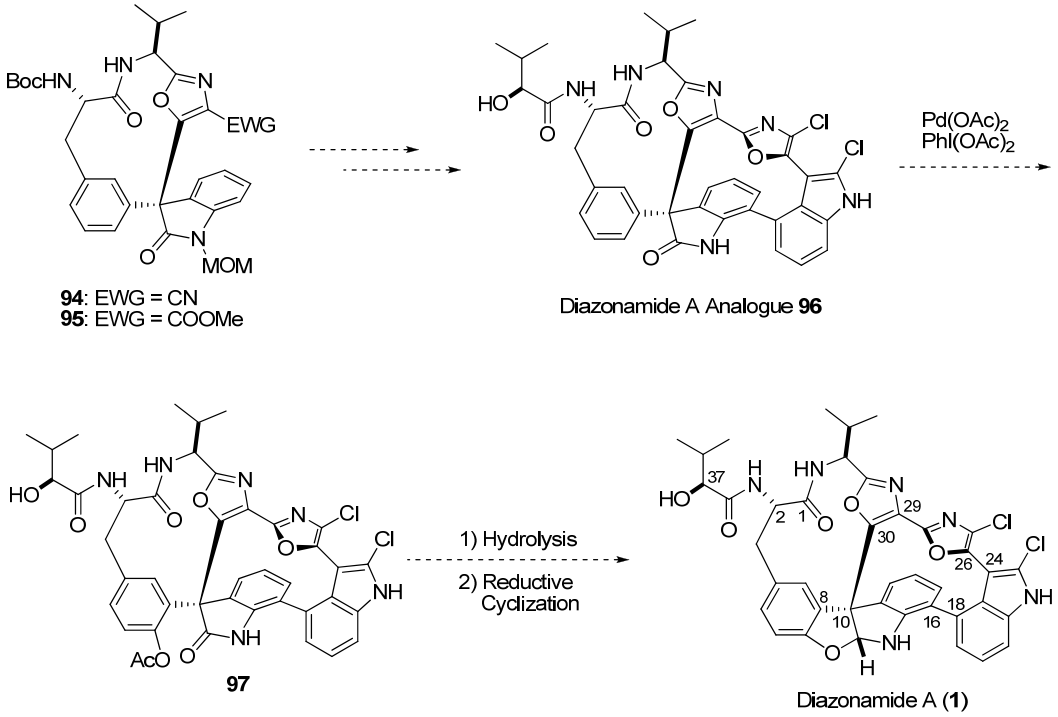
alcohol **87** after acidic work-up. Comin's reagent[6] was used to convert the phenol of **87** to triflate **88**, which was reduced by hydrogenation (H_2, Pd/C) along with the doubly-benzylic tertiary alcohol to provide the doubly reduced product (**89**) and some partially reduced product (**90**). Saponification of compound **89** provided a carboxylic acid, which was coupled with amine TFA salt, **81** and **91**, under typical amide bond formation conditions (EDC/HOBt) to provide cyclization precursors **92** and **93**, respectively. To our delight, upon treating with KHMDS (compound **94** was produced in 53% yield) or Cs_2CO_3 in DMF, both **92** and **93** were cyclized to provide the desired *C*-arylation products **94** and **95**, respectively, as single diastereomers. The stereochemistry of these products was assigned as showed in Scheme 3.3 in analogy to that of compound **111** (*vide infra*). No other stereoisomers were observed by NMR in the crude reaction mixture.



Scheme 3.3 Preparation and Cyclization of **92** and **93** without *ortho*-Substituent

With the success of the cyclizations of **92** and **93**, I anticipated that I could prepare a diazonamide A analogue **96** without the formation of the hemiaminal moiety, and test whether this analogue display biological activity comparable to that of diazonamide A (Scheme 3.4). Further conversion of compound **96** to diazonamide A might be accomplished by subjection of this compound to amide-directed C-H bond oxidation methods in order to introduce an acetate group,[7] which can be hydrolyzed to the phenol. Reduction of the oxindole and cyclization to the hemiaminal moiety would provide the desired natural product. However, this approach was deemed risky, due to the late stage functionalization of C-H bond in a very complex substrate and was not pursued. Instead,

ideas that would allow cyclization of a substrate bearing an *ortho*-substituted phenol and reaction on the carbon of the oxindole enolate were pursued.

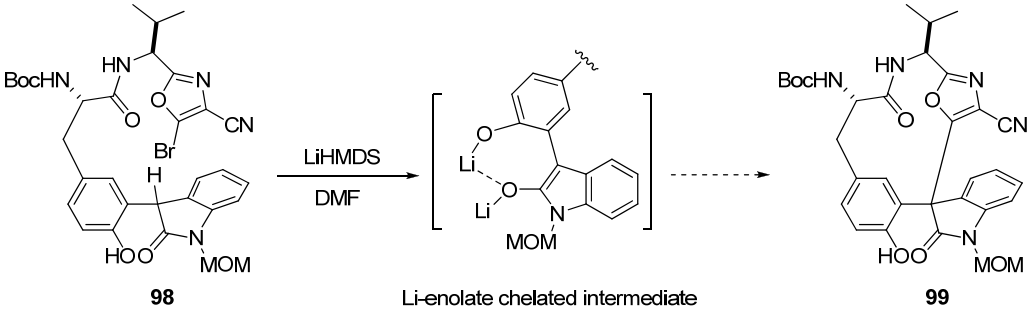


Scheme 3.4 Proposed Synthetic Strategies for Synthesis of Diazonamide A and its Analogue

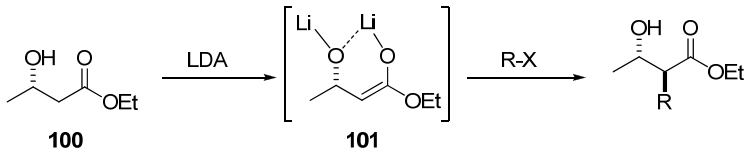
3.3 Cyclization of a Precursor with Unprotected Phenol

In order to synthesize diazonamide A, I wished to study the use of a cyclization precursor bearing a hydroxyl group on the tyrosine phenyl ring. I felt that the enolate had to adopt a planar conformation in order for the cyclization to occur on carbon, and wanted to devise a system that would allow an attractive interaction between the enolate and the phenol oxygen. Lithium is a well-known oxophillic metal, and this oxophilicity has been used in the past to form intermediates with constrained conformations in systems such as populations using Evans' oxazolidinone auxiliary[8] and in the Frater-

Seebach alkylations.[9,10] I anticipated that the pronation of cyclization precursor **98** with a lithium base would provide a di-anion wherein the lithium alkoxides can interact with each other in an attractive fashion as showed in Scheme 3.5. This bridged lithium-chelated structure would adopt a planar confirmation and might favor the *C*-arylation of the oxindole enolate over the undesired *O*-arylation to provide macrocycle **99**.



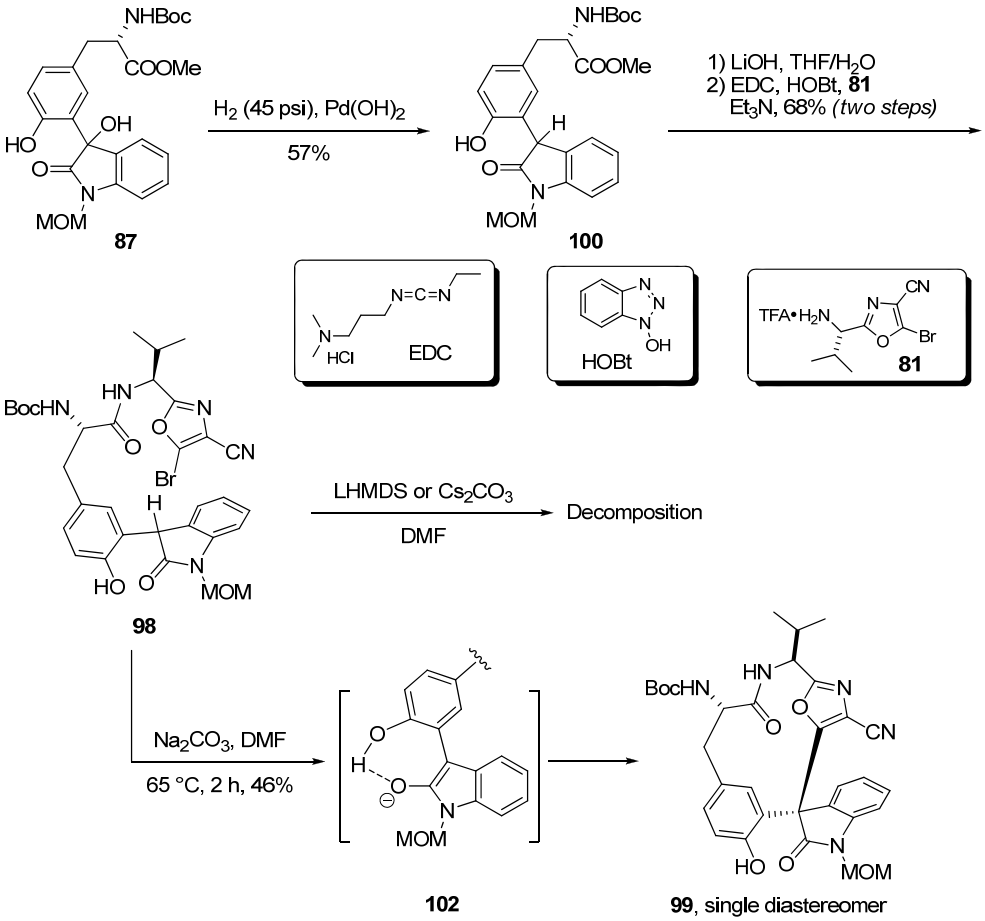
Frater-Seebach Alkylation



Scheme 3.5 Proposed Lithium-Chelated Intermediate

To investigate this idea, cyclization precursor **98** was prepared from tertiary alcohol **87** as shown in Scheme 3.6. Tertiary alcohol **87** was reduced via hydrogenation using H_2 and Pearlman's catalyst ($Pd(OH)_2$), to provide compound **100**. Saponification of **100** with degassed LiOH solution followed by acidification provided the corresponding carboxylic acid which was coupled with amine TFA salt **81** under typical amide bond formation conditions (EDC/HOBt) to provide cyclization precursor **98** with the pendant unprotected phenol hydroxyl group. While treating compound **98** with LiHMDS or Cs_2CO_3, did not provide any of the desired *C*-arylation product, and only lead to complex mixtures, treatment with a weaker base, Na_2CO_3, provided the desired *C*-arylation product **99** as a

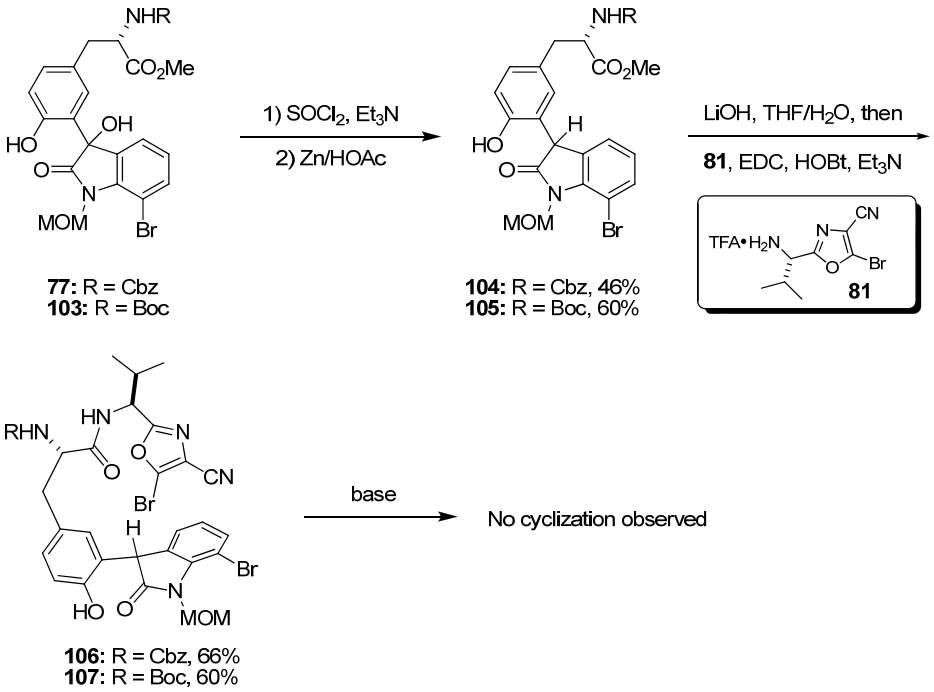
single diastereomers in 46% yield after flash chromatography. No other stereoisomers were observed in the NMR of the crude reaction mixture, and the stereochemistry of **99** was assigned by analogy to that of compound **111** (*vide infra*). Although Na_2CO_3 is not appreciably soluble in DMF, the very small amount of solvated Na_2CO_3 could partially deprotonate the C3-H of the oxindole. The resulting intermediate was anticipated to undergo hydrogen bonding to form a seven member ring bridged structure, which provides a planar structure and minimizes hindrance around the oxindole carbon, thus, facilitating the formation of *C*-arylation product **99**.



Scheme 3.6 Cyclization of Compound **101** with Free Phenol

3.4 Attempted Cyclizations of Substrates with C16-Bromine

Encouraged by the exciting results of the cyclization of compound **98** with the free phenol, I was very interested in applying this strategy to the total synthesis of diazonamide A. In order to render this cyclization viable for a synthesis of the natural product, it is necessary to install a handle at C16 for introducing the right hand ring (the bisoxazole-indole moiety) of the molecule. Typically, a bromine atom can be used for transition-metal-catalyzed cross-coupling reactions, and I targeted compounds **106** and **107** for synthesis (Scheme 3.7). I first synthesized cyclization precursor **106** bearing a Cbz protecting group on the tyrosine nitrogen. Because Magnus reported in his formal synthesis that protecting groups on the tyrosine nitrogen atom were crucial for his macrocyclizations,[11] I also prepared cyclization precursor **107** bearing a Boc protecting group. The synthesis of compound **103** proceeded via similar procedures as compound **77**, which was previously prepared by Dr. Sammons in his synthesis of compound **82** (Scheme 3.1). Thus, tertiary alcohols **77** and **103** were reduced by a two-step sequence consisting of chlorination with $SOCl_2$ and reduction of the resultant tertiary chloride with Zn/HOAc to provide **104** and **105**, respectively. Compounds **106** and **107** were then obtained after saponification of **104** and **105** with degassed LiOH solution and amide bond formation with amine TFA salt **81** under typical amide bond formation conditions (EDC/HOBt), respectively.

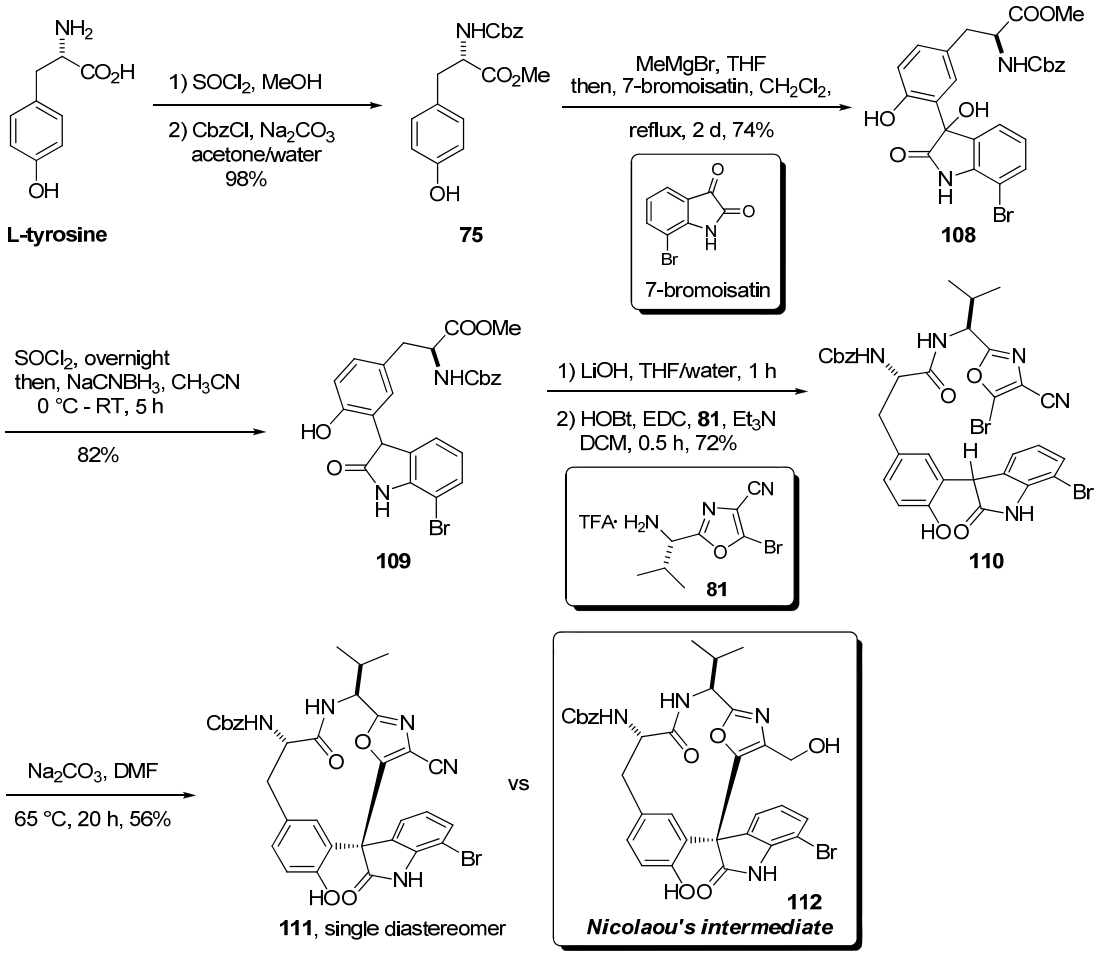


Scheme 3.7 Syntheses and Attempted Cyclizations of Cyclization Precursors **106** and **107**

Unfortunately, treatments of compound **106** or **107** with several different bases only lead to decomposition (Cs_2CO_3) or recovered staring materials (Na_2CO_3 or K_2CO_3). We hypothesized that the bulky bromine atom could influence the conformation of the adjacent MOM protecting group, which hindered the C3 position of the oxindole enolate, thus preventing the formation of the desired *C*-arylation product. Although it was still unclear that how the conformation of the MOM group changed upon introduction of the bromine atom, this hypothesis did give me some insights on how to solve this problem. If this hypothesis was true, cyclization precursor **110** without an MOM protecting group on the phenol should not encounter such a problem, and this substrate should then be able to cyclize via *C*-arylation. Therefore, compound **110** was synthesized and tested for macrocyclization.

3.5 Formal Synthesis of Diazonamide A

The synthesis of **110** proceeded by the addition of *N*-Cbz-L-tyrosine methyl ester (**75**) to 7-bromoisatin (**76**) to provide tertiary alcohol **108**, which was converted to compound **109** by Nicolaous' two-step procedure of chlorination ($SOCl_2$) and reduction of the resultant tertiary chloride ($NaCNBH_3$, Scheme 3.8).[13,14] Saponification of the methyl ester of **109** with degassed LiOH solution, followed by amide bond formation of the resulting carboxylic acid with amine TFA salt **81** provided cyclization precursor **110** in 72% yield over two steps. To our delight, subjecting **110** to Na_2CO_3 in DMF at 65 °C for 20 h provided the desired *C*-arylation product **111** in 56% yield as a single diastereomer. ^1H NMR of the crude reaction mixture reveals no other stereoisomers in this reaction, and the remainder of the material was determined by mass spectrometry to be a mixture of starting material and an unidentified non-isomeric side product bearing two bromine atoms. Under similar conditions, other carbonate bases either afford comparable yields (K_2CO_3, 40-50%), no reaction (Li_2CO_3), or a complex mixture of products (Cs_2CO_3). Other polar solvents, CH_3CN provided comparable yields to DMF, while DMA and DMSO provided slightly diminished yields (~40%).



Scheme 3.8 Cyclization of Unprotected Phenol/Oxindole **110**

The structure and stereochemistry of macrocycle **111** was determined by single crystal X-ray crystallography. This compound was a solid, and after screening numerous solvents for crystallization, I obtained crystals suitable for single crystal X-ray crystallography by slow evaporation of an acetone solution of this compound. The X-ray structure of **111** (Figure 3.1) provided direct evidence that the stereochemistry of C10 was consistent with that of the natural product. Two acetone molecules and hydrogen atoms are excluded for clarity from the ORTEP drawing (Figure 3.1) of macrocycle **111** shown below.

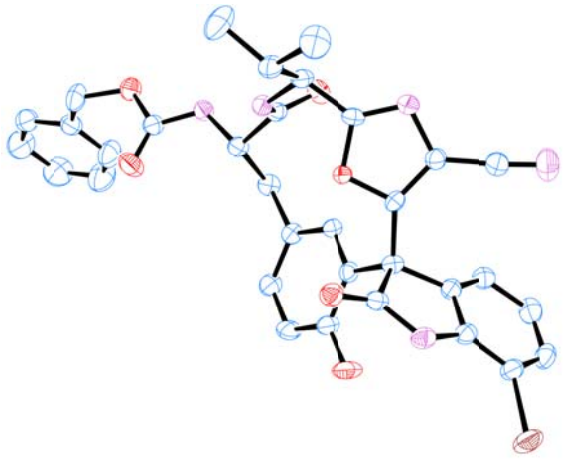
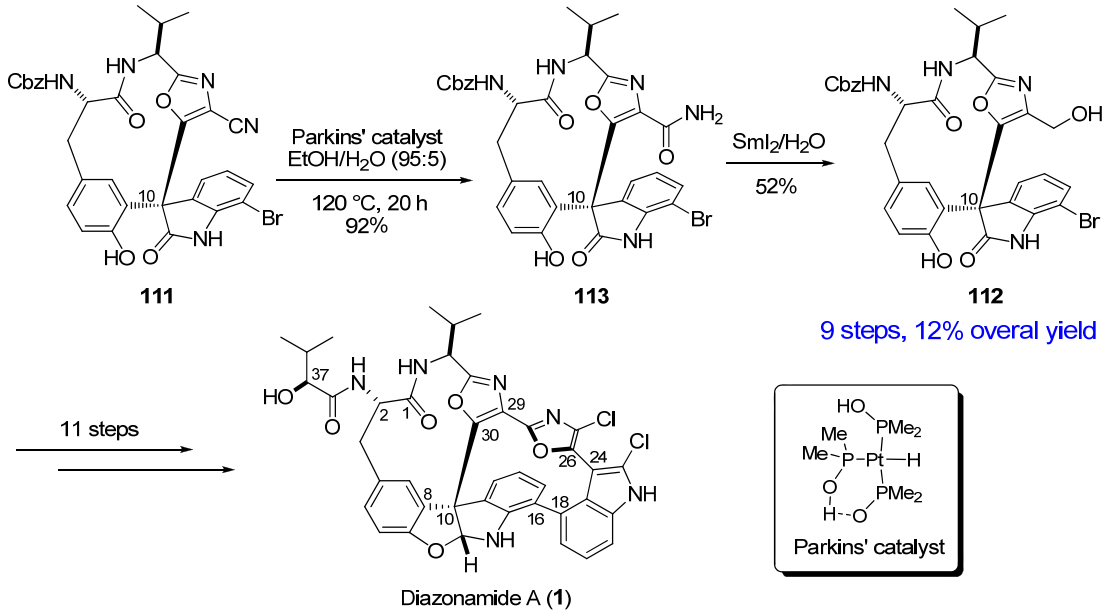


Figure 3.1 X-ray Structure of Macrocycle **111**

The structure of macrocycle **111** is very similar to compound **112**, an intermediate synthesized by Nicolaou in his first total synthesis of diazonamide A. Thses two structures only differ by the substitution on the oxazole ring, and the synthesis of compound **112** would serve as a formal synthesis of the natural product as well as an additional structure proof. I was able to convert nitrile **111** to primary alcohol **112** via a two-step sequence shown in Scheme 3.9. Thus, hydrolysis of nitrile **111** using typical acidic or basic reaction conditions was unsuccessful; however, the reaction was smoothly catalyzed by Parkins' catalyst[15,16] to provide primary amide **113** in 92% yield. Compound **113** bears a primary aromatic amide that can be selectively reduced using SmI_2 and H_2O as an activating ligand to primary alcohol **112** in 52% yield in the presence of the two other secondary amides in the molecule.[17] Spectra data of compound **112** were identical as that reported by Nicolaou. This synthesis provides Nicolaou's intermediate **112** starting from commercially available L-tyrosine in 9 steps and 12% overall yield. Because the Nicolaou group has reported the conversion of **112** into diazonamide A by an 11-step sequence[18,19] the synthesis of **112** constituted a highly diastereoselective formal total

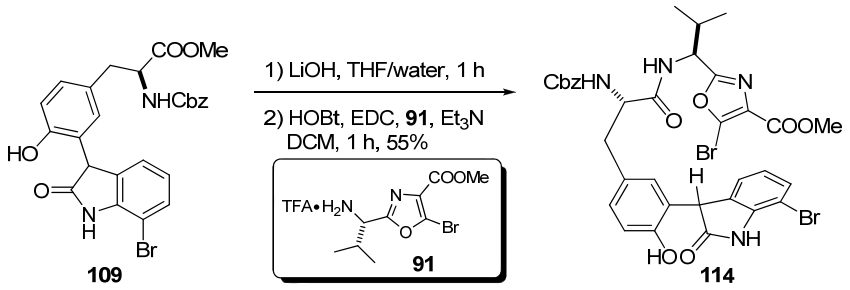
synthesis of diazonamide A. This was the most stereoselective synthesis of the C10 quaternary carbon center at that time of publication.



Scheme 3.9 Formal Synthesis of Diazonamide A

3.6 Attempted Cyclization of Oxazolyl Ester 114

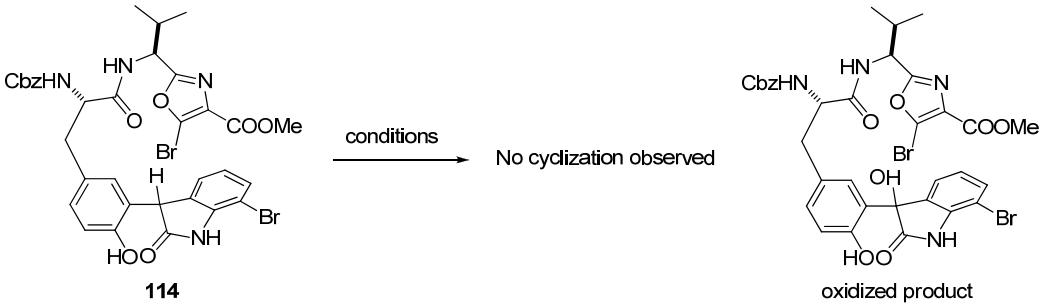
Although I could, in principle, synthesize diazonamide A from intermediate **112** via Nicolaou's procedures, I was more interested in developing a new synthetic route. Because nitriles are generally hard to functionalize, I wished to synthesize the corresponding ester as I felt that introduction of the right hand ring could be more readily accomplished from the ester. I, therefore, synthesized compound **111** with an ester group appended to the oxazole and anticipated introducing the indole moiety of diazonamide A via amide bond formation after saponification of the ester. Synthesis of ester **114** was similar to that of nitrile **110** by saponification (degassed LiOH solution) and amide bond formation (EDC/HOBt) with amine TFA salt **91**, as showed in Scheme 3.10.



Scheme 3.10 Synthesis of Ester **114**

Attempted cyclizations of compound **114** were studied using a variety of conditions (Table 3.1). Typical S_NAr cyclization conditions (Na_2CO_3 in DMF, entry 1) did not provide any cyclization product, and only starting material and some oxidation product were recovered. Higher temperature (entry 2), stronger base (Cs_2CO_3, entry 3 and Ag_3PO_4, entry 5), and an additive (AgOTf, entry 4) all provided complex mixtures. Our typical Pd-catalyzed conditions (entry 6) only provided recovered starting material and some of the oxidation product. All these results indicated that methyl ester was not sufficiently electron-withdrawing to induce the desired S_NAr reaction. As such, we abandoned this approach in reference to an approach, which utilizes the nitrile in a cyclization reaction as described above.

Table 3.1 Attempted Cyclizations of Ester **114**



entry	conditions	result
1	Na_2CO_3, DMF, 65 °C, 8 h	no cyclization[a]
2	Na_2CO_3, DMF, 90 °C, 5 h	complex mixtures

3	Cs_2CO_3, DMF, 65 °C, 15 h	complex mixtures
4	Na_2CO_3, AgOTf, DMF, 65 °C, 15 h	complex mixtures
5	Ag_3PO_4, DMF, 65 °C, 15 h	complex mixtures
6	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, Na_2CO_3, toluene, 120 °C, 15 h	no cyclization[a]

[a] recovered starting material and tertiary alcohol generated after oxidation of 3-substituted oxindole.

3.7 Conclusion

A formal synthesis of diazonamide A has been achieved in a highly diastereoselective fashion employing an intermolecular S_NAr cyclization of 3-aryloxindole **110**. Because this cyclization occurs under very mild conditions using Na_2CO_3 as the base, and no protecting groups on the phenol or the oxindole N-H are required, this strategy can be potentially integrated into a total synthesis of diazonamide A that requires either minimal or no protecting groups and proceeds under mild conditions.

3.8 Abbreviations

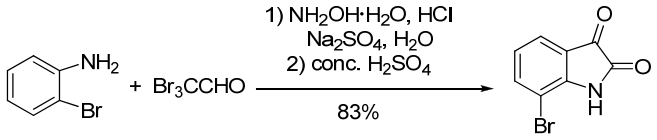
Cbz	Carboxybenzyl
EDC	1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide
EWG	Electron-Withdrawing Group
HOBt	Hydroxybenzotriazole
KHMDS	Potassium bis(trimethylsilyl)amide
LDA	Lithium diisopropylamide
LiHMDS	Lithium bis(trimethylsilyl)amide
MOM	Methoxymethyl
TFA	Trifluoroacetic acid

3.9 Experimental Details

General Information

All glassware was oven-dried or flame-dried. DMF was freshly distilled over CaH_2 under reduced pressure prior to use; CH_2Cl_2, MeOH, and toluene were distilled from CaH_2 under nitrogen; THF and Et_2O were distilled from sodium benzophenone ketyl under nitrogen. Unless specifically mentioned, all chemicals are commercially available and were used as received. For reactions of 3-monosubstituted oxindoles under basic conditions, solvents were degassed by either sparging with N_2 or three freeze-pump-thaw cycles, in order to prevent the oxidation of oxindole enolates.[3] Thin layer chromatography (TLC) was performed using EM Science Silica Gel 60 F254 glass plates. Flash chromatography was performed using 60 Å silica gel (37-75 μm). ^{1}H NMR spectra were recorded at either 400 MHz or 500 MHz, and ^{13}C NMR spectra were recorded at 75 MHz or 100 MHz in $CDCl_3$, CD_3CN, [D_6]acetone, [D_6]DMSO, or CD_3OD as indicated. Chemical shifts are reported in ppm referenced to residual solvent peaks as follows: $CDCl_3$ (7.24 ppm for ^{1}H NMR; 77.16 ppm for ^{13}C NMR.); CD_3CN (1.94 ppm for ^{1}H NMR; 1.32 ppm for ^{13}C NMR.); [D_6]acetone (2.05 ppm for ^{1}H NMR; 29.84 ppm for ^{13}C NMR.); [D_6]DMSO (2.50 ppm for ^{1}H NMR; 39.52 ppm for ^{13}C NMR.); and CD_3OD (49.00 ppm for ^{13}C NMR). Several compounds were obtained as an inseparable mixture of diastereomers. NMR data for these are provided with fractional integrals for non-overlapping peaks for each single diastereomer. Optical rotations were determined using a Jasco P-1030 digital polarimeter and concentrations are reported as g/100 mL. Infrared (IR) spectra were obtained as thin films on NaCl plates. Exact mass was determined using electrospray ionization (M+H or M+Na as indicated).

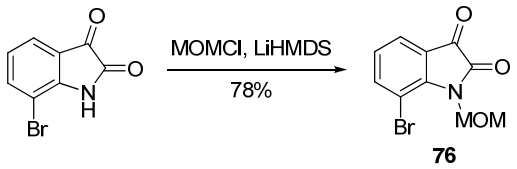
7-Bromoisatin:



Nicolaou reported the synthesis of 7-bromoisatin via condensation of 2-bromoaniline with chloral hydrate.[12,14] However, chloral hydrate was no longer commercially available. Magnus used 2,2,2-trichloro-1-ethoxyethanol as a replacement for chloral hydrate. Herein, I found another cheaper replacement, tribromoacetaldehyde.

A mixture of 2-bromoaniline (6.0 g, 34.2 mmol, 1.0 equiv) and 36% HCl (5 mL) in H_2O (20 mL) was added to a solution of tribromoacetaldehyde (14.84 g, 51.3 mmol, 1.5 equiv), sodium sulfate (33.0 g, 232.0 mmol, 6.8 equiv) and hydroxylamine hydrochloride (7.84 g, 113 mmol, 3.3 equiv) in H_2O (180 mL) with vigorous stirring. The reaction was slowly heated to 70 °C and kept at that temperature for 2 h, during which time a yellow precipitate formed (**Caution**: DO NOT overheat higher than 70 °C or stir longer than 2 h. Otherwise, the precipitate may decompose and redissolve into the solution.). After cooling to ambient temperature, the precipitate was collected by filtration, washed with H_2O (50 mL), isolated and allowed to stand in the fume hood overnight to dry. The crude solid was added portion-wise to concentrated sulfuric acid (40 mL) at 55 °C. The resulting brown solution was warmed to 70 °C, stirred for an additional 30 min, and then cooled to ambient temperature. The mixture was poured carefully onto crushed ice (150 g), and allowed to stir for 1 h. The resulting orange precipitate was collected by filtration, washed with H_2O (50 mL), and then dried under high vacuum overnight to provide 7-bromoisatin (6.45 g, 83%) as an orange solid, which was used without further purification. Spectral data for 7-bromoisatin were consistent with that reported in the literature.[12,14]

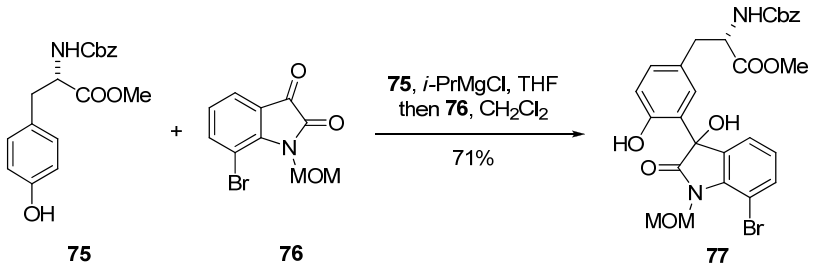
***N*-MOM-7-Bromoisatin (76):**



76

LiHMDS (7.0 mL of a 1.0 M in toluene, 7.0 mmol, 1.05 equiv) was added via syringe to a 0 °C solution of 7-bromoisatin (1.50 g, 6.64 mmol, 1.0 equiv) in dry THF (60 mL). Neat MOMCl (560 μL, 7.73 mmol, 1.1 equiv) was then added via syringe. The mixture was warmed to room temperature, stirred for 20 h, and concentrated under reduced pressure. The residue was dissolved in EtOAc (200 mL), washed with H_2O (50 mL), brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (5:1 hexanes:EtOAc) provided the *N*-MOM-7-bromoisatin (**76**) as an orange solid (1.37 g, 78%). Spectral data for **76** were consistent with that reported in the literature.[12,14]

Tertiary alcohol 77:



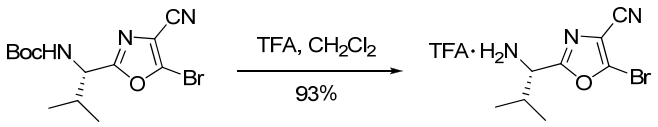
75 **76** **77**

To a cold (-78 °C) solution of *N*-Cbz-L-tyrosine methyl ester[1] (**75**, 7.0 g, 21.25 mmol, 1.05 equiv) in THF (150 mL) was added *i*-PrMgCl (11.2 mL of a 1.9 M solution

in THF, 21.28 mmol, 1.05 equiv). The solution was stirred at -78 °C for 20 min, and then warmed to room temperature. The solvent was removed under reduced pressure to provide a colorless foam. *N*-MOM-7-bromoisatin (**76**, 5.5 g, 20.3 mmol, 1.0 equiv) was added as a solid to the foam. Dry CH_2Cl_2 (300 mL) was then added, and the heterogeneous mixture was heated to reflux for 18 h. The reaction was cooled to room temperature, quenched with 1 M HCl (aq, 50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (100 mL×3), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (2:1 then 1:1 hexanes:EtOAc) to provide tertiary alcohol **77** (8.63 g, 71%) as a white foam as an approximately 1.2:1 ratio of diastereomers.

^{1}H NMR (500 MHz, $CDCl_3$; obtained as an approximately 1.2:1 mixture of diastereomers) δ 8.34 (br s, 1H), 7.44 (app t, *J* = 8.5 Hz, 1H), 7.14 – 7.40 (m, 6H), 6.80 – 6.98 (m, 2H), 6.74 (app t, *J* = 8.5 Hz, 1H), 6.56 (s, 1H), 5.32 – 5.44 (m, 2H), 5.26 (d, *J* = 8 Hz, 0.45H), 5.20 (d, *J* = 8 Hz, 0.55H) 4.95 – 5.07 (m, 2H), 4.86 (br s, 0.55H), 4.78 (br s, 0.45H), 4.40 – 4.50 (m, 1H), 3.58 (s, 1.3H), 3.57 (s, 1.7H), 3.27 (s, 3H), 2.80 – 2.95 (m, 2H). **^{13}C NMR** (100 MHz, $CDCl_3$; obtained as an approximately 1.2:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 179.6, 179.5, 172.1, 172.0, 155.9, 154.8, 139.6, 136.3, 136.1, 133.0, 132.9, 131.7, 131.6, 128.74, 128.73, 128.44, 128.42, 128.3, 128.2, 128.0, 127.9, 127.64, 127.58, 125.6, 125.0, 124.6, 124.5, 118.8, 103.9, 78.3, 71.7, 67.3, 56.5, 54.8, 52.6, 52.5, 37.6. **m.p.**: 78 – 90 °C. **IR** (cm^{-1}) 3341, 1723, 1509, 1460, 1242, 1217. **HRMS** calcd for $C_{28}H_{27}BrN_2O_8Na^+$: 621.0843; found: 621.0838.

TFA Salt 81:

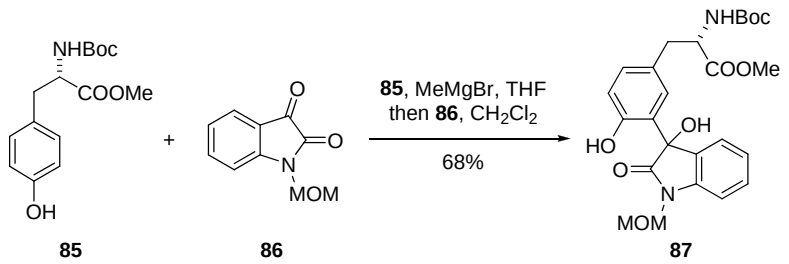


60 **81**

N-Boc-Bromooxazole **60** (2.28 g, 6.62 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (13 mL), and freshly distilled TFA (2.6 mL, 33.7 mmol, 5.0 equiv) was added via syringe. The solution was stirred at room temperature until all the starting material was consumed (~ 5 h). The solvent was removed under reduced pressure. After successive solvent exchanges with toluene, the resulting solid was triturated with hexanes, collected by vacuum filtration, and washed with cold Et_2O to provide a white solid. The solid was dried under high vacuum overnight to provide amine TFA salt **81** (2.10 g, 93%).

^{1}H NMR (500 MHz, [D_6]DMSO) δ 8.69 (s, 3H), 4.57 (d, *J* = 6.6 Hz, 1H), 2.34 – 2.14 (m, 1H), 1.00 (d, *J* = 6.8 Hz, 3H), 0.90 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, [D_6]DMSO) δ 162.4, 134.7, 114.7, 111.3, 53.0, 30.5, 18.2, 17.5. **m.p.**: 148 – 150 °C.

Tertiary alcohol 87:



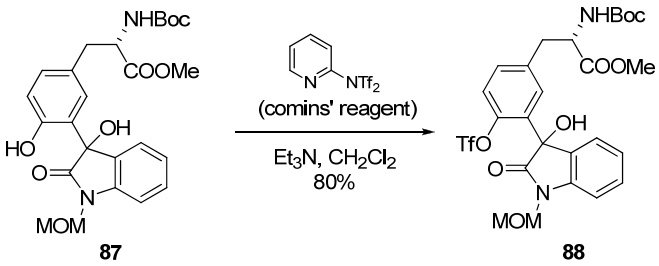
85 **86** **87**

To a 0 °C solution of *N*-Boc-L-tyrosine methyl ester[5] (**85**, 2.62 g, 8.85 mmol, 1.15 equiv) in THF (30 mL) was added MeMgBr (3.6 mL of a 3.0 M solution in Et_2O, 10.8 mmol, 1.4 equiv) dropwise. After addition was completed, the ice bath was removed. The mixture was warmed to ambient temperature, stirred for an additional 30 min, and concentrated to yield a white solid. Residual solvent was removed under high vacuum. *N*-MOM-isatin (**86**, 1.47 g, 7.70 mmol, 1.0 equiv) was added to the white solid followed by anhydrous CH_2Cl_2 (60 mL). The flask was fitted with a condenser and a drying tube, and the heterogeneous dark brown mixture was heated to reflux for 14 h. The reaction was quenched by addition of 1 M HCl (20 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (80 mL×3), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a yellow foam. Purification by flash chromatography (2:1 then 1:2 hexanes:EtOAc) provided tertiary alcohol **87** (2.54 g, 68%) as a yellowish foam as an approximately 1:1 mixture of diastereomers.

^{1}H NMR (500 MHz, CD_3CN; obtained as an approximately 1:1 mixture of diastereomers) δ 7.53 (s, 1H), 7.34 (td, *J* = 7.7, 1.4 Hz, 1H), 7.30 (s, 1H), 7.15 – 7.03 (m, 3H), 7.00 (t, *J* = 7.8 Hz, 1H), 6.69 (dd, *J* = 8.1, 3.3 Hz, 1H), 5.47 (d, *J* = 8.3 Hz, 1H), 5.19 – 4.94 (m, 2H), 4.61 (s, 1H), 4.32 (dt, *J* = 15.9, 6.8 Hz, 1H), 3.65 (s, 1.5H, 1/2 Me), 3.64 (s, 1.5H, 1/2 Me), 3.37 – 3.30 (m, 3H), 3.02 (td, *J* = 13.7, 5.5 Hz, 1H), 2.86 (m, 1H), 1.37 (d, *J* = 6.2 Hz, 9H). **^{13}C NMR** (75 MHz, CD_3CN; obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 178.3, 173.4, 156.8, 153.9, 143.9, 131.8, 131.7, 131.1, 130.7, 129.0, 128.93, 128.88, 126.9, 125.3, 125.2, 124.1, 116.68,

116.66, 110.5, 80.0, 77.7, 72.4, 56.7, 56.11, 56.07, 52.7, 37.6, 37.5, 28.5. **m.p.**: 90 – 98 °C. **IR** (cm^{-1}): 3342 (br), 3052, 2978, 1724, 1613, 1511, 1462, 1356, 1156. **HRMS** m/z calcd for $C_{25}H_{30}N_2O_8Na^+$: 509.1894; found: 509.1910.

Triflate 88:

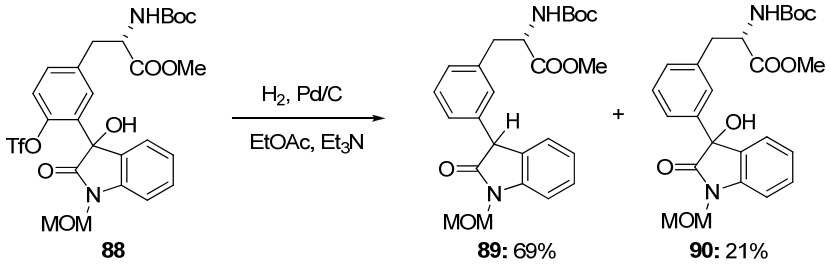


Tertiary alcohol **87** (814.5 mg, 1.67 mmol, 1.0 equiv) and Comins' reagent[6] (750 mg, 2.09 mmol, 1.25 equiv) were dissolved in anhydrous CH_2Cl_2 (35 mL) in a 100 mL round bottom flask. Et_3N (720 μL, 5.12 mmol, 3.0 equiv) was then added via syringe. The resulting yellow solution was stirred at room temperature for 1 h, and then concentrated under reduced pressure to give a yellow oil. Purification by flash chromatography (2:1 hexanes:EtOAc) provided triflate **88** as a colorless oil (826 mg, 80%).

^{1}H NMR (500 MHz, CD_3CN; obtained as an approximately 1:1 mixture of diastereomers) δ 7.97 (br s, 0.5 H), 7.96 (d, *J* = 2.2 Hz, 0.5 H), 7.43 – 7.28 (m, 2H), 7.21 (t, *J* = 7.4 Hz, 1H), 7.13 (d, *J* = 3.0 Hz, 0.5 H), 7.12 (d, *J* = 3.0 Hz, 0.5 H), 7.10 – 7.01 (m, 2H), 5.69 (d, *J* = 8.4 Hz, 0.5 H), 5.64 (d, *J* = 8.5 Hz, 0.5 H), 5.24 (s, 0.5 H), 5.22 (s, 0.5 H), 5.02 (s, *J* = 2.2 Hz, 0.5 H), 5.00 (d, *J* = 2.2 Hz, 0.5 H), 4.82 (s, 1H), 4.60 – 4.41 (m, 1 H), 3.72 (s, 1.5 H, 1/2 Me), 3.71 (s, 1.5 H, 1/2 Me), 3.37 (s, 3H), 3.35 – 3.18 (m, 1 H), 3.12 – 2.94 (m, 1H), 1.41 – 1.29 (two s, 9H). **^{13}C NMR** (75 MHz, CD_3CN; obtained as an

approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 176.8, 173.1, 173.0, 146.6, 143.8, 138.9, 138.8, 133.0, 132.1, 132.0, 131.5, 131.4, 131.0, 130.7, 130.6, 125.5, 125.4, 124.4, 121.2, 120.9, 120.8, 117.0, 111.4, 111.3, 80.2, 76.1, 72.6, 56.8, 55.8, 55.6, 52.9, 37.8, 37.6, 28.5. **IR** (cm^{-1}): 3362 (br), 3060, 2974, 2945, 2823, 1724, 1614, 1479, 1426, 1348, 1213, 1164. **HRMS** m/z calcd for $C_{26}H_{29}F_3N_2O_{10}SNa^+$: 641.1387; found: 641.1360.

3-Aryloxindole 89 and Tertiary Alcohol 90:

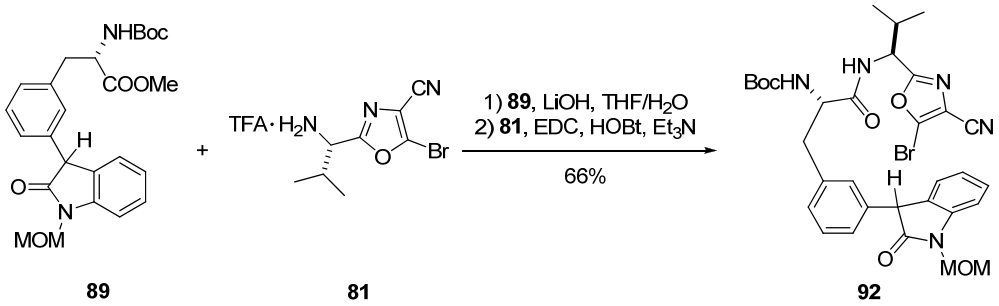


5% Pd/C (66 mg, 0.031 mmol, 0.1 equiv) was added to a solution of triflate **88** (190.2 mg, 0.307 mmol, 1.0 equiv) and Et_3N (150 μL, 1.067 mmol, 3.5 equiv) in EtOAc (6 mL). The suspension was degassed by sequentially evacuating the flask and then admitting H_2 three times. A hydrogen-filled balloon was attached to the flask, and the reaction was stirred vigorously for 48 h. The heterogeneous mixture was filtered through a short pad of celite and rinsed with EtOAc (50 mL). Evaporation of the solvent provided a colorless oil. Purification by flash chromatography (2:1 hexanes:EtOAc) provided **89** (96 mg, 69%) as a white foam and the partially reduced product **90** as a colorless oil (30 mg, 21%).

Compound **89**: **^{1}H NMR** (400 MHz, $CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers) δ 7.36 – 7.21 (m, 2H), 7.15 (d, *J* = 7.6 Hz, 1H), 7.08 (m, 4H), 6.90 (d, *J* = 5.9 Hz, 1H), 5.20 – 5.07 (m, 2H), 4.94 (d, *J* = 8.1 Hz, 1H), 4.64 (s, 1H), 4.59 – 4.43 (m, 1H), 3.59 (s, 1.5 H, 1/2 Me), 3.62 (s, 1.5 H, 1/2 Me), 3.38 – 3.23 (s, 3H), 3.14 – 2.88 (m, 2H), 1.40 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 176.5, 172.3, 172.2, 155.2, 142.8, 142.7, 136.9, 136.8, 129.34, 129.29, 129.24, 128.9, 128.8, 128.7, 128.3, 128.2, 127.4, 127.3, 125.4, 125.3, 123.5, 109.79, 109.77, 80.0, 71.6, 56.5, 54.4, 54.3, 52.24, 52.18, 38.3, 38.2, 28.4. **m.p.**: 85 – 90 °C. **IR** (cm^{-1}): 3428 (br), 3354 (br), 3048, 2970, 2823, 2251, 1712, 1605. **HRMS** m/z calcd for $C_{25}H_{30}N_2O_6H^+$: 455.2177; found: 455.2178.

Compound **90**: **^{1}H NMR** (500 MHz, CD_3CN; obtained as an approximately 1:1 mixture of diastereomers) δ 7.42 – 7.36 (m, 1H), 7.32 – 7.20 (m, 5H), 7.19 – 7.08 (m, 3H), 5.67 – 5.57 (m, 1H), 5.09 (AB, 2H), 4.87 (s, 1H), 4.44 – 4.14 (m, 1H), 3.56 (s, 3H), 3.29 (s, 3H), 3.06 (m, 1H), 3.00 – 2.83 (m, 1H), 1.39 (s, 9H). **^{13}C NMR** (75 MHz, CD_3CN; obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 178.41, 178.39, 173.3, 173.2, 156.3, 143.0, 141.9, 138.24, 138.19, 132.93, 132.91, 130.8, 129.94, 129.89, 129.5, 129.4, 127.2, 125.7, 124.9, 124.6, 118.3, 110.9, 80.1, 78.7, 72.3, 56.7, 55.9, 55.7, 52.72, 52.70, 38.2, 28.5. **IR** (cm^{-1}): 3367 (br), 3064, 2974, 1744, 1617, 1487, 1348, 1172. **HRMS** m/z calcd for $C_{25}H_{30}N_2O_7H^+$: 471.2126; found: 471.2135.

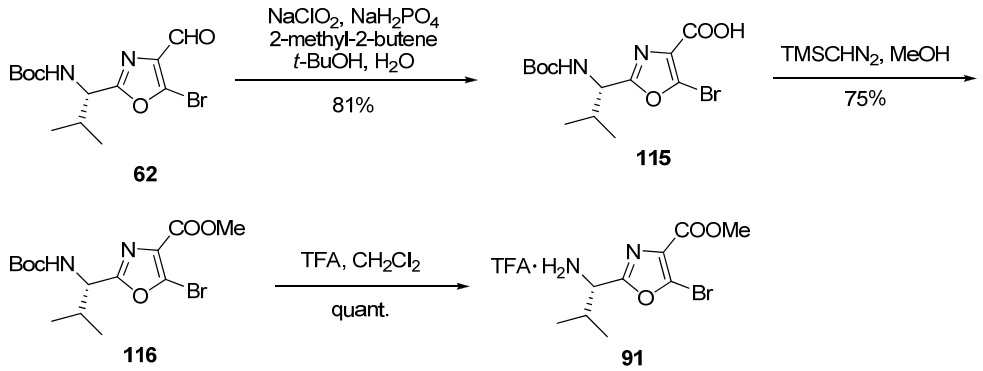
Amide 92:



3-Aryloxindole **89** (95 mg, 0.209 mmol, 1.0 equiv) was dissolved in anhydrous THF (4 mL), and the solution degassed by three freeze-pump-thaw cycles. Degassed LiOH solution (2.1 mL of a 1.0 M aqueous solution, 2.1 mmol. 10.0 equiv, sparged with N_2 for 1 h prior to use) was then cannulated into the THF solution. The resulting mixture was stirred at ambient temperature for 1 h, and then quenched by addition of 1 M HCl (10 mL). The mixture was extracted with CH_2Cl_2 (30 mL), the layers separated, and the aqueous layer extracted with CH_2Cl_2 (20 mL×2). The combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude acid as a white solid. The crude acid was dissolved in anhydrous CH_2Cl_2 (8 mL), and oxazole salt **81** (71 mg, 0.209 mmol, 1.0 equiv), Et_3N (35 μL, 0.249 mmol, 1.2 equiv), HOBt·H_2O (28.2 mg, 0.209 mmol, 1.0 equiv) and EDC (40.2 mg, 0.209 mmol, 1.0 equiv) were added sequentially. The resulting yellow solution was stirred at room temperature for 1 h, diluted with CH_2Cl_2 (100 mL), washed with 1 M HCl (aq, 20 mL), H_2O (20 mL), then brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (2:1 hexanes:EtOAc) to provide amide **92** as a white foam (95 mg, 66%) as an approximately 1:1 mixture of diastereomers.

^{1}H NMR (500 MHz, CD_3CN; obtained as an approximately 1:1 mixture of diastereomers) δ 7.36 – 7.29 (m, 1H), 7.26 – 7.04 (m, 7H), 7.00 (t, *J* = 8.7 Hz, 1H), 5.71 – 5.58 (m, 1H), 5.12 (AB, 2H), 4.91 (m, 1H), 4.72 (d, *J* = 6.4 Hz, 1H), 4.29 (m, 1H), 3.31 (two s, 3H), 3.09 – 2.97 (m, 1H), 2.88 – 2.75 (m, 1H), 2.24 – 2.13 (m, 1H), 1.34 (two s, 9H), 0.96 – 0.91 (m, 3H), 0.91 – 0.85 (m, 3H). **^{13}C NMR** (75 MHz, CD_3CN; obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 177.3, 172.6, 167.05, 167.02, 156.4, 143.8, 139.1, 139.0, 138.4, 138.3, 132.94, 132.91, 130.6, 130.5, 129.80, 129.77, 129.71, 129.4, 129.32, 129.31, 127.63, 127.57, 125.9, 125.8, 124.00, 123.98, 116.2, 112.2, 110.5, 80.1, 72.2, 56.6, 53.7, 52.92, 52.88, 38.1, 32.3, 28.5, 19.2, 18.3. **m.p.**: >95 °C (dec). **IR** (cm^{-1}): 3321, 3252, 3052, 2966, 2933, 2880, 2819, 2239, 1732, 1670, 1642, 1516. **HRMS** m/z calcd for $C_{32}H_{36}BrN_5O_6K^+$: 704.1481; found: 704.1470.

Amine TFA salt 91:



Pinnick-Lindgren oxidation:[20] To a solution of aldehyde **62** (1.38 g, 3.97 mmol, 1.0 equiv) and 2-methyl-2-butene (10 mL) in *t*-BuOH was added a solution of NaH_2PO_4 monohydrate (3.9 g, 28.3 mmol, 7.1 equiv) and $NaClO_2$ (3.2 g, 28.3 mmol, 7.1 equiv) in

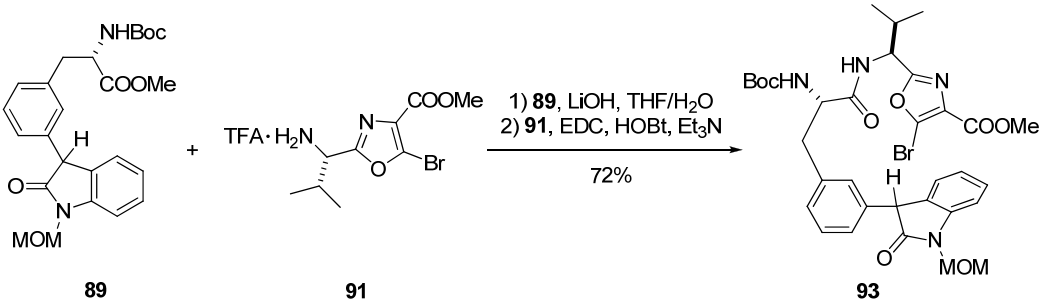
H_2O (20 mL). After stirring at room temperature for 2 h, H_2O (50 mL) and CH_2Cl_2 (50 mL) were added. The aqueous layer was extracted with CH_2Cl_2 (50 mL×3), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to provide a colorless foam. Purification by flash chromatography (5:1 hexanes:EtOAc with 5% HOAc), followed by successive solvent exchanges with cyclohexane to remove residual HOAc, provided carboxylic acid **115** (1.172 g, 81%) as a colorless foam. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 11.27 (br s, 1H), 6.43 (s, ~15% rotamer peaks), 6.05 (d, *J* = 9.1 Hz, 1H), 4.79 (dd, *J* = 9.6, 6.3 Hz, 1H), 4.62 (s, ~15% rotamer peaks), 2.36 – 2.00 (m, 1H), 1.37 (s, 9H), 0.93 (dd, *J* = 9.5, 7.0 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 166.65, 163.19, 155.86, 130.25, 129.54, 80.31, 54.70, 32.72, 28.38, 19.00, 18.16.

Carboxylic acid **115** (60 mg, 0.168 mmol, 1.0 equiv) was dissolved in anhydrous MeOH (3.5 mL), and $TMSCHN_2$ in toluene (2.0 mol/L, 450 μL, 5.2 equiv) was added via syringe. After stirring at room temperature for 2 h, the reaction was concentrated to provide a yellow oil. Purification by flash chromatography (5:1 hexanes:EtOAc) provided ester **116** (47 mg, 75%) as a colorless oil. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 5.17 (d, *J* = 9.3 Hz, 1H), 4.85 (s, 12% rotamer peaks), 4.73 (dd, *J* = 9.1, 6.2 Hz, 1H), 4.53 (s, 12% rotamer peaks), 3.89 (two s, major and rotamer, 3H), 2.26 – 1.95 (m, 1H), 1.39 (s, 9H), 0.89 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 165.49, 160.90, 155.35, 130.46, 128.45, 80.31, 54.45, 52.54, 32.78, 28.36, 18.90, 17.95.

Ester **116** (390 mg, 1.034 mmol, 1.0 equiv) was dissolved in anhydrous CH_2Cl_2 (10 mL), and freshly distilled TFA (2.0 mL, 25.8 mmol, 25 equiv) was added via syringe. The solution was stirred at room temperature until all the starting material was consumed (~ 3 h). The solvent was removed under reduced pressure. After successive solvent

exchanges with toluene, the resulting solid was triturated with hexanes, dried under vacuum to provide amine TFA salt **91** (387 mg, quantative) as a sticky oil, which solidified to provide a white solid upon seating in the freezer.

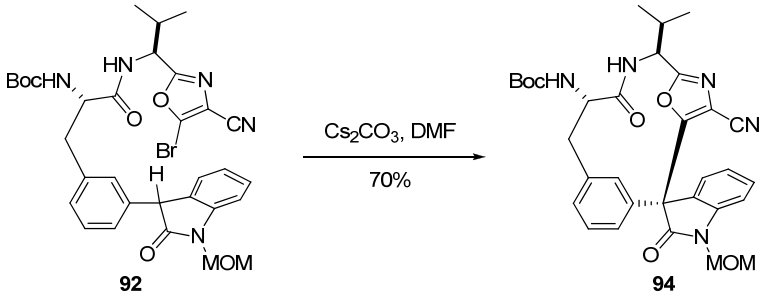
Amide 93:



Compound **93** was prepared in 72% yield via a similar procedure as the preparation of amide **92**. **^{1}H NMR** (500 MHz, $CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers) δ 7.31 (dd, *J* = 12.1, 7.7 Hz, 1H), 7.22 – 6.97 (m, 6H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.69 (br d, *J* = 7.9 Hz, one diastereomer, 0.5H), 6.59 (br d, *J* = 7.9 Hz, one diastereomer, 0.5H), 5.14 (s, 2H), 4.99 (m, 2H), 4.63 (d, *J* = 3.4 Hz, 1H), 4.34 (m, 1H), 3.89 (s, one diastereomer, 1/2Me), 3.86 (s, one diastereomer, 1/2Me), 3.32 (two s, 3H), 3.02 (m, 2H), 2.16 (m, 1H), 1.39 (s, 9H), 0.95 – 0.74 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 176.49, 171.16, 171.07, 164.53, 164.36, 160.87, 160.85, 142.71, 137.37, 136.96, 136.79, 130.54, 130.47, 129.65, 129.61, 129.36, 129.28, 128.85, 128.75, 128.59, 128.55, 128.46, 128.11, 127.88, 127.00, 126.61, 126.59, 126.55, 125.34, 125.26, 123.49,

109.87, 109.82, 71.76, 71.67, 56.53, 56.51, 55.82, 55.77, 55.70, 53.00, 52.93, 52.55, 52.50, 52.18, 32.54, 32.33, 32.02, 28.47, 28.38, 18.98, 18.94, 18.25, 18.17, 14.27.

Macrocycle 94:

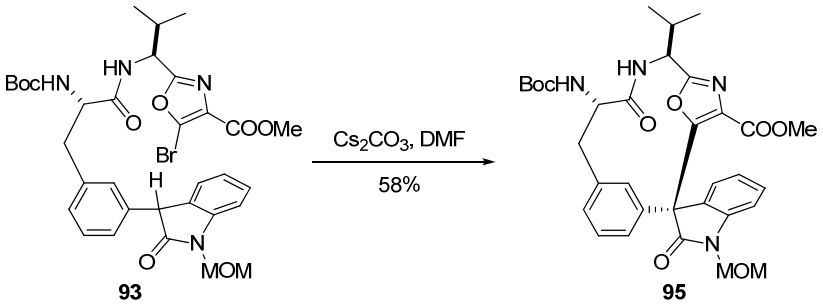


Amide **92** (52.0 mg, 0.078 mmol, 1.0 equiv) and Cs_2CO_3 (28.0 mg, 0.086 mmol, 1.1 equiv) were combined in a 25 mL round bottom flask, which was capped and purged with N_2. Anhydrous DMF (8 mL, degassed by three freeze-pump-thaw cycles) was then cannulated into the flask. The needle was removed from the septum, which was then sealed with electrical tape. The suspension was placed in a 65 °C oil bath and stirred for 8 h. The reaction was then cooled to ambient temperature, diluted with EtOAc (20 mL), and quenched by addition of 1 M HCl (20 mL). The aqueous layer was extracted with 1:1 hexanes:EtOAc (20 mL×3), and the combined organic layers were washed with H_2O (20 mL×4), brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure. Purification by flash chromatography (6:1 $CHCl_3$:EtOAc) provided the desired cyclized product **94** as a white solid (32 mg, 70%). No isomeric material was identified in the crude ^{1}H NMR spectrum.

R_f = 0.12 in 6:1 $CHCl_3$:EtOAc. **$[\alpha]_D^{26}$** = –495.6 (*c* 0.503, MeOH). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.48 – 7.34 (m, 2H), 7.26 (t, *J* = 6.0 Hz, 1H), 7.19 (m, 3H), 6.99 (d, *J* =

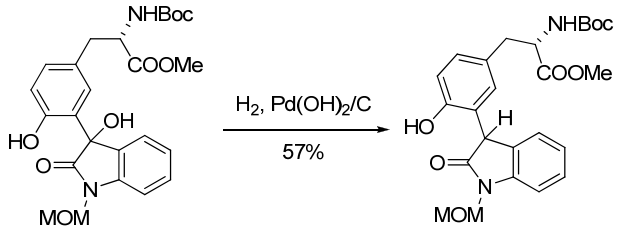
7.5 Hz, 1H), 6.72 (s, 1H), 6.10 (d, J = 5.8 Hz, 1H), 5.27 (AB, J = 10.8 Hz, ν_{ab} = 17.8 Hz, 2H), 5.13 (d, J = 8.9 Hz, 1H), 4.59 (t, J = 7.1 Hz, 1H), 4.00 (t, J = 9.0 Hz, 1H), 3.42 (s, 3H), 3.28 (t, J = 12.0 Hz, 1H), 2.77 (d, J = 10.5 Hz, 1H), 2.05 (m, 1H), 1.44 (s, 9H), 1.03 (d, J = 6.6 Hz, 3H), 0.96 (d, J = 6.6 Hz, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 172.8, 172.4, 164.9, 158.2, 155.1, 141.4, 139.7, 136.8, 131.4, 130.8, 129.4, 129.0, 126.9, 125.7, 124.9, 124.5, 113.3, 110.9, 110.6, 80.6, 72.3, 58.0, 57.1, 56.8, 56.2, 38.1, 30.0, 28.4, 19.4, 19.2. **m.p.**: 170 – 172 °C. **IR** (cm^{-1}): 3318, 2966, 2925, 2242, 1728, 1711, 1674, 1507, 1495. **HRMS** m/z calcd for $C_{32}H_{35}N_5O_6Na^+$: 608.2489; found: 608.2480.

Macrocycle 95:



Compound **95** was prepared in 58% yield via a similar procedure as the preparation of amide **94**. $\mathbf{R_f}$ = 0.25 in 1:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.27 (m, 2H), 7.21 (m, 2H), 7.12 (m, 2H), 7.04 (m, 2H), 5.95 (d, J = 6.0 Hz, 1H), 5.29 (AB, 2H), 5.23 (d, J = 8.7 Hz, 1H), 5.16 – 5.05 (br s, rotamer), 4.74 (t, J = 6.6 Hz, 1H), 4.10 (t, J = 9.4 Hz, 1H), 3.44 (s, 3H), 3.42 (s, 3H), 3.24 (t, J = 12.1 Hz, 1H), 2.84 (d, J = 11.0 Hz, 1H), 2.25 – 2.05 (m, 1H), 1.44 (s, 9H), 0.96 (dd, J = 11.8, 6.7 Hz, 6H).

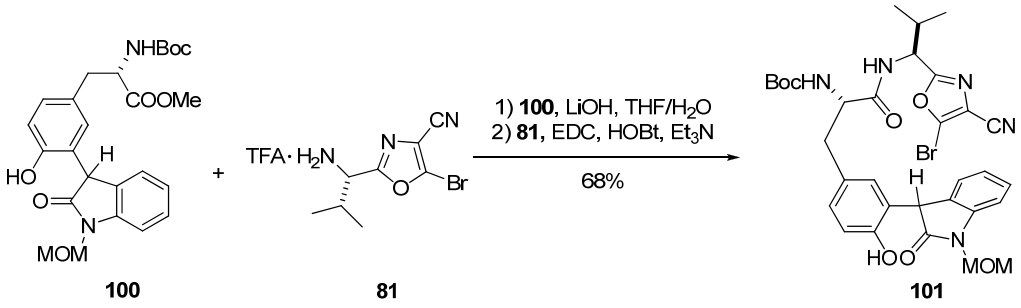
3-Aryloxindole 100:



Tertiary alcohol **87** (205 mg, 0.421 mmol, 1.0 equiv) was dissolved in MeOH (8 mL) in a 500 mL Parr flask, and Pearlman's catalyst (20 wt. %, 29.6 mg, 0.042 mmol, 0.1 equiv) was added. The reaction mixture was then subjected to H_2 (45 psi) with shaking for 64 h. The reaction was then filtered through a short pad of celite, washed with EtOAc, and concentrated under reduced pressure to provide a yellow oil. Purification by flash chromatography (2:1 hexanes:EtOAc) provided compound **100** (112 mg, 57%) as a colorless oil and recovered starting material **87** (64 mg, 31%) as a yellowish foam.

^{1}H NMR (500 MHz, CD_3CN; obtained as an approximately 1:1 mixture of diastereomers) δ 7.39 (br s, 1H), 7.32 – 7.25 (m, 1H), 7.10 – 6.94 (m, 5H), 6.91 (two br s, 1H), 6.78 (s, 0.5 H), 6.76 (s, 0.5H), 5.52 (dd, *J* = 16.3, 8.8 Hz, 1H), 5.13 (AB, 2H), 4.83 (s, 1H), 4.28 (m, 1H), 3.59 (s, 1.5 H, 1/2 Me), 3.58 (s, 1.5 H, 1/2 Me), 3.31 (s, 3H), 3.04 – 2.89 (m, 1H), 2.82 (m, 1H), 1.36 (s, 4.5H, 1/2 *t*-Bu), 1.35 (s, 4.5 H, 1/2 *t*-Bu). **^{13}C NMR** (75 MHz, CD_3CN; obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 178.18, 178.16, 173.8, 173.4, 156.3, 154.7, 143.9, 132.3, 130.6, 129.8, 129.5, 128.9, 125.2, 125.1, 124.94, 124.93, 123.7, 116.7, 110.2, 80.0, 72.2, 56.6, 56.0, 52.65, 52.62, 49.4, 37.4, 28.5. **IR** (cm^{-1}): 3334 (br), 2987, 2933, 1720, 1609, 1511, 1356, 1168. **HRMS** m/z calcd for $C_{25}H_{30}N_2O_7Na^+$: 493.1945; found: 493.1955.

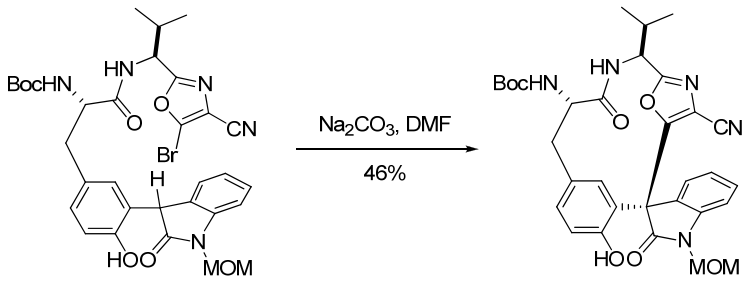
Amide 101:



3-Aryloxindole **100** (76.5 mg, 0.163 mmol, 1.0 equiv) was dissolved in anhydrous THF (4 mL), and the solution was degassed by three freeze-pump-thaw cycles. Degassed LiOH solution (4.0 mL of a 0.4 M aqueous solution, 1.6 mmol, 10.0 equiv, sparged with N_2 for 1 h prior to use) was then cannulated. The resulting mixture was stirred at ambient temperature for 1 h, and quenched by addition of 1 M HCl (5 mL). CH_2Cl_2 (30 mL) was added, and the layers were separated. The aqueous layer was extracted with CH_2Cl_2 (10 mL×2), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude acid as a white solid. The crude acid was dissolved in anhydrous CH_2Cl_2 (8 mL), and oxazole salt **81** (111 mg, 0.325 mmol, 2.0 equiv), Et_3N (46 μL, 0.325 mmol, 2.0 equiv), HOBt·H_2O (49.8 mg, 0.325 mmol, 2.0 equiv) and EDC (62.3 mg, 0.325 mmol, 2.0 equiv) were added sequentially. The resulting yellow solution was stirred at room temperature for 1 h, diluted with CH_2Cl_2 (100 mL), washed with 1 M HCl (aq, 20 mL), H_2O (25 mL), brine (25 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified by flash chromatography (2:1 hexanes:EtOAc) to provide amide **101** as a white solid (75 mg, 68%) as an approximately 1:1 mixture of diastereomers.

^{1}H NMR (500 MHz, CD_3CN; obtained as an approximately 1:1 mixture of diastereomers) δ 7.38 – 7.24 (m, 2H), 7.19 – 7.09 (br m, 1H), 7.09 – 6.99 (m, 3H), 6.99 (s, 1H), 6.97 (s, 1H), 6.72 (t, *J* = 7.5 Hz, 1H), 5.58 (d, *J* = 8.0 Hz, 0.5 H), 5.53 (d, *J* = 7.8 Hz, 0.5H), 5.18 – 5.07 (AB, 2H), 4.93 – 4.86 (m, 1H), 4.79 (s, 0.5 H), 4.77 (s, 0.5 H), 4.28 – 4.14 (m, 1H), 3.30 (s, 3H), 3.04 – 2.87 (m, 1H), 2.74 (m, 1H), 2.28 – 2.13 (m, 1H), 1.36 (s, 4.5H, 1/2 *t*Bu), 1.35 (s, 4.5 H, 1/2 *t*Bu), 0.93 (m, 3H), 0.91 – 0.84 (m, 3H). **^{13}C NMR** (75 MHz, CD_3CN; obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 178.11, 178.08, 172.8, 167.1, 156.4, 154.6, 143.9, 132.9, 132.7, 132.5, 130.7, 130.6, 129.8, 129.7, 128.9, 125.2, 125.1, 124.8, 123.7, 116.5, 116.2, 112.2, 110.2, 80.1, 72.2, 56.8, 56.7, 56.6, 53.8, 49.7, 49.5, 37.4, 32.3, 28.5, 19.2, 18.3. **m.p.**: >120 °C (dec). **IR** (cm^{-1}): 3326, 32556, 2970, 2929, 2239, 1683, 1650, 1519, 1368, 1356. **HRMS** m/z calcd for $C_{32}H_{36}BrN_5O_7Na^+$: 704.1690; found: 704.1693.

Macrocycle 99:



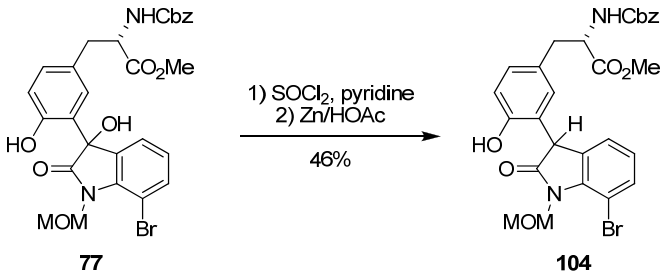
98 **99**

Amide **98** (38.2 mg, 0.056 mmol, 1.0 equiv) and Na_2CO_3 (29.7 mg, 0.280 mmol, 5.0 equiv, dried in the oven overnight before use) were combined in a 25 mL round bottom

flask, which was capped and purged with N_2. Anhydrous DMF (10 mL, degassed by three freeze-pump-thaw cycles) was then cannulated into the flask. The needle was removed from the septum, which was then sealed with electrical tape. The suspension was placed in a 65 °C oil bath and stirred for 2 h. The reaction was cooled to ambient temperature, and H_2O (10 mL) and Et_2O (100 mL) were added. The mixture was acidified by addition of 1 M HCl (20 mL). The layers were separated, and the aqueous layer was extracted with Et_2O (30 mL×3). The combined organic layers were washed with H_2O (20 mL×4), brine (20 mL), dried over Na_2SO_4, filtered, and concentrated under reduced pressure to provide a yellow solid. Purification by flash chromatography (1:1 hexanes:EtOAc) provided macrocycle **99** (15.6 mg, 46 %) as a white solid. No isomeric material was identified in the crude ^{1}H NMR spectrum.

R_f = 0.2 in 1:1 hexanes:EtOAc. **$[\alpha]_D^{26}$** = –338.8 (*c* 0.333, MeOH). **^{1}H NMR** (500 MHz, [D_6]acetone) δ 8.78 (s, 1H), 8.20 (d, *J* = 6.3 Hz, 1H), 7.42 (td, *J* = 7.8, 1.2 Hz, 1H), 7.34 (t, *J* = 9.8 Hz, 1H), 7.21 (d, *J* = 7.9 Hz, 1H), 7.11 (td, *J* = 7.6, 0.8 Hz, 1H), 7.06 (dd, *J* = 8.1, 2.1 Hz, 1H), 6.74 (d, *J* = 8.1 Hz, 1H), 6.33 (s, 1H), 6.26 (d, *J* = 8.5 Hz, 1H), 5.19 (AB, *J* = 11.0 Hz, v_{ab} = 11.9 Hz, 2H), 4.58 – 4.50 (m, 1H), 4.18 – 4.08 (m, 1H), 3.38 – 3.32 (m, 3H), 3.18 (t, *J* = 12.6 Hz, 1H), 2.60 (d, *J* = 12.8 Hz, 1H), 2.19 – 2.08 (m, 1H), 1.43 (s, *J* = 7.2 Hz, 9H), 1.14 (d, *J* = 6.5 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H). **^{13}C NMR** (75 MHz, [D_6]acetone) δ 173.9, 173.3, 167.0, 158.6, 155.6, 153.5, 153.4, 144.0, 133.1, 131.0, 130.8, 129.0, 127.1, 126.9, 126.2, 124.0, 116.6, 116.4, 113.4, 111.6, 110.7, 79.3, 72.8, 57.4, 57.2, 56.5, 38.2, 28.6, 19.9, 19.4. **m.p.**: >185 °C (dec). **IR** (cm^{-1}): 3309 (br), 2966, 2929, 2243, 1707, 1679, 1613, 1511, 1495. **HRMS** m/z calcd for $C_{32}H_{35}N_5O_7HNa^+$: 624.2428; found: 624.2443.

3-Aryloxindole 104:

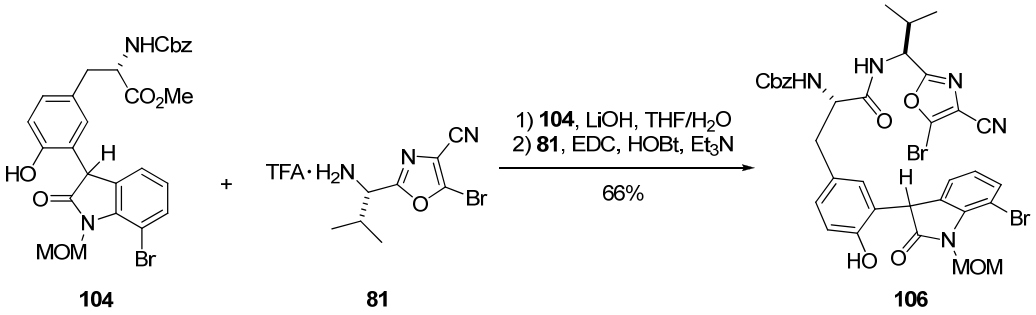


$SOCl_2$ (227 μL, 3.11 mmol, 2.5 equiv) was added dropwise via syringe to a solution of tertiary alcohol **77** (745 mg, 1.24 mmol, 1.0 equiv) and pyridine (503 μL, 6.22 mmol, 5.0 equiv) in dry Et_2O (25 mmol) at 0 °C under nitrogen. The yellow solution became dark brown upon the addition of $SOCl_2$, and turned into a white suspension immediately. After stirring at 0 °C for 10 min, the reaction was quenched with H_2O (5 mL), and diluted with Et_2O (50 mL) and sat. $NaHCO_3$ (50 mL). The aqueous layer was extracted with Et_2O (30 mL×3), and the combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated to provide a tertiary chloride as a light pink sticky oil, which was used immediately into the next step without purification.

The crude tertiary chloride was dissolved in dry THF (25 mL), and zinc dust (813 mg, 12.4 mmol, 10 equiv) and HOAc (1.4 mL, 24.9 mmol, 20 equiv) were added. The suspension was stirred at room temperature for 1 h, and filtered through a short pad of celite, washed with Et_2O (50 mL). The reaction mixture was washed with water (20 mL), sat. $NaHCO_3$ (20 mL×2), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellow solid. Purification by flash chromatography (3:2 hexanes:EtOAc)

provided compound **104** (334 mg, 46%) as a colorless oil. $\mathbf{R}_f$ = 0.25 in 3:2 hexanes:EtOAc.

Amide 106:

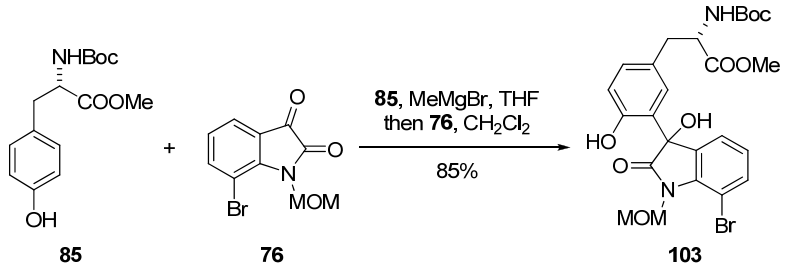


3-Aryloxindole **104** (330 mg, 0.566 mmol, 1.0 equiv) was dissolved in anhydrous THF (11 mL), and the solution degassed by three freeze-pump-thaw cycles. Degassed LiOH solution (238 mg in 11 ml H_2O, 5.66 mmol, 10.0 equiv, sparged with N_2 for 15 min prior to use) was then cannulated. The resulting mixture was stirred at ambient temperature for 1 h, and quenched by addition of 1 M HCl (10 mL). Et_2O (30 mL) was added, and the layers were separated. The aqueous layer was extracted with Et_2O (20 mL×2), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude acid as a greenish foam. The crude acid was dissolved in anhydrous CH_2Cl_2 (11 mL), and oxazole salt **81** (232 mg, 0.679 mmol, 1.2 equiv), Et_3N (60 μL, 0.427 mmol, 1.2 equiv), HOBt·H_2O (130 mg, 0.848 mmol, 1.5 equiv), and EDC (163 mg, 0.848 mmol, 1.5 equiv) were added sequentially. The resulting yellow solution was stirred at room temperature for 2 h, diluted with Et_2O (150 mL), washed with H_2O (30 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a yellow foam. The

crude product was purified by flash chromatography (3:2 hexanes:EtOAc) to provide amide **106** as a yellowish foam (296 mg, 66%) as an approximately 1:1 mixture of diastereomers.

$\mathbf{R_f}$ = 0.20 in 3:2 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers) δ 8.11 (br s, one diastereomer, 0.5H), 7.93 (br s, one diastereomer, 0.5H), 7.43 (d, *J* = 8.1 Hz, one diastereomer, 0.5 H), 7.40 (J = 8.1 Hz, one diastereomer, 0.5 H), 7.28 (m, 4H), 7.20 – 7.05 (m, 1H), 7.02 (t, *J* = 8.3 Hz, 1H), 6.92 – 6.81 (two t, 1H), 6.74 (s, 1 H), 6.69 (d, *J* = 7.3 Hz, 0.5H), 6.53 (s and d, *J* = 8.8 Hz, 1.5H), 5.55 – 5.38 (m, 2.5H), 5.35 (d, *J* = 8.0 Hz, one diastereomer, 0.5H), 5.09 – 4.98 (m, 2.5H), 4.96 – 4.89 (m, 1H), 4.83 (s, one diastereomer, 0.5H), 4.39 (m, 1H), 3.36 (s, one diastereomer, 1/2Me), 3.30 (s, one diastereomer, 1/2Me), 2.86 (two dd, *J* = 18.8, 12.9 Hz, 1H), 2.78 – 2.68 (m, 0.5H), 2.65 -2.55 (m, 0.5H), 2.11 (m, 1H), 0.90 – 0.82 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 179.28, 179.26, 171.83, 165.97, 156.55, 154.38, 140.16, 135.89, 135.78, 134.40, 134.32, 134.21, 131.32, 131.30, 130.79, 130.69, 129.96, 129.63, 129.59, 129.27, 128.84, 128.81, 128.78, 128.71, 128.70, 128.53, 128.49, 128.46, 128.32, 128.12, 124.94, 124.49, 124.44, 122.92, 122.73, 117.58, 117.47, 115.92, 110.95, 103.57, 103.48, 71.52, 67.50, 67.44, 56.50, 56.44, 56.32, 56.29, 53.23, 37.34, 37.28, 36.74, 31.98, 31.94, 28.81, 18.79, 18.21, 18.09.

Tertiary Alcohol 103:

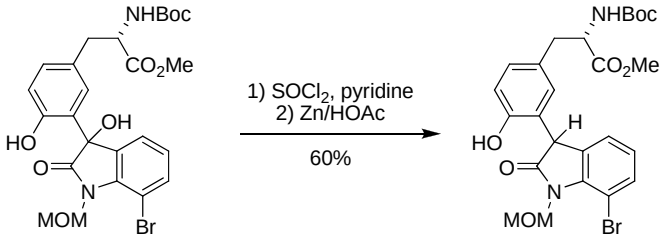


To a 0 °C solution of *N*-Boc-L-tyrosine methyl ester[5] (**85**, 3.61 g, 12.2 mmol, 1.1 equiv) in THF (110 mL) was added MeMgBr (4.07 mL of a 3.0 M solution in Et_2O, 12.2 mmol, 1.1 equiv) dropwise. After addition was completed, the ice bath was removed. The mixture was warmed to ambient temperature, stirred for an additional 30 min, and concentrated to yield a white solid. Residual solvent was removed under high vacuum. *N*-MOM-isatin (**76**, 3.0 g, 11.1 mmol, 1.0 equiv) was added to the white solid followed by anhydrous CH_2Cl_2 (110 mL). The flask was fitted with a condenser and a drying tube, and the heterogeneous dark brown mixture was heated to reflux for 48 h. The reaction was quenched by addition of 1 M HCl (50 mL), and the layers were separated. The aqueous layer was extracted with EtOAc (80 mL×3), and the combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a greenish foam. Purification by flash chromatography (2:1 then 1:2 hexanes:EtOAc) provided tertiary alcohol **103** (5.36 g, 85%) as a yellowish foam as an approximately 1:1 mixture of diastereomers.

R_f = 0.15 in 2:1 hexanes:EtOAc. **^{1}H NMR** (400 MHz, $CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers) δ 8.39 (br s, 1H), 7.45 (d, *J* = 8.1 Hz, 1H), 7.30 – 7.20 (m, 1H), 6.94 (dd, *J* = 9.8, 5.6 Hz, 1H), 6.86 (d, *J* = 8.2 Hz, 1H), 6.73 (d, *J* = 8.2 Hz, 1H), 6.61 (s, 1H), 5.37 (s, 2H), 4.97 (t, *J* = 8.5 Hz, 1H), 4.93 – 4.83 (br s, 20% rotamer peaks), 4.37 (s, 1H), 4.24 – 4.04 (br s, 20% rotamer peaks), 3.61 (br, s, 1H), 3.56

(two s, 3H), 3.27 (s, 3H), 2.85 (m, 2H), 1.31 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 179.31, 172.36, 172.31, 155.37, 155.27, 154.49, 139.57, 135.86, 135.78, 133.19, 133.15, 131.32, 131.21, 127.90, 127.72, 127.51, 125.36, 124.82, 124.76, 124.44, 124.35, 118.15, 118.06, 103.64, 80.31, 77.96, 77.91, 71.56, 56.39, 56.36, 54.42, 54.32, 52.39, 52.31, 52.29, 37.33, 37.25, 28.34, 28.19.

3-Aryloxindole 105:



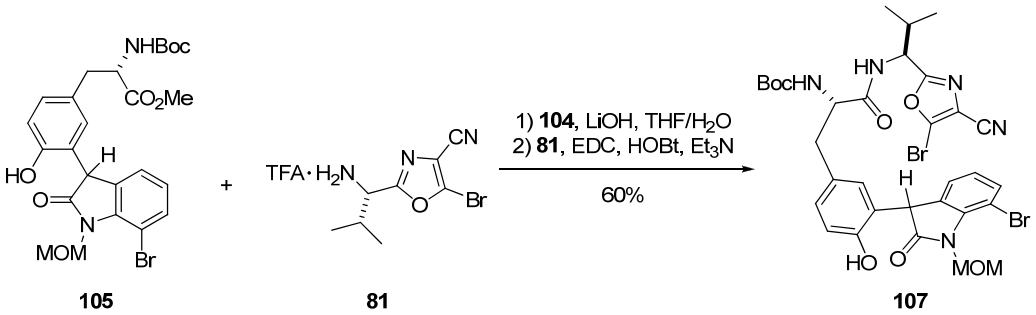
103 **105**

Compound **105** was prepared via a similar procedure as the preparation of compound **104** as a colorless oil (310 mg) in 60% yield.

R_f = 0.35 in 3:2 hexanes:EtOAc. **^{1}H NMR** (400 MHz, $CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers) δ 8.09 (br s, one diastereomer, 0.5H), 8.04 (br s, one diastereomer, 0.5H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.08 (d, *J* = 6.1 Hz, 1H), 6.93 (t, *J* = 7.8 Hz, 1H), 6.88 – 6.77 (m, 1H), 6.72 (t, *J* = 7.4 Hz, 1H), 6.60 (s, one diastereomer, 0.5H), 6.55 (s, one diastereomer, 0.5H), 5.55 – 5.38 (m, two AB, 2H), 5.02 (s, one diastereomer 0.5H), 4.99 – 4.88 (m, 1.5H), 4.88 – 4.72 (br s, 15% rotamer peaks), 4.41 (m, 1H), 4.28 – 4.14 (br s, 15% rotamer peaks), 3.58 (s, 1/2Me), 3.55 (s, 1/2Me), 3.35 (two s, 3H), 2.88 (m, 2H), 1.36 (s, 1/2*t*-Bu), 1.34 (s, 1/2*t*-Bu). **^{13}C NMR** (101 MHz,

$CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 179.30, 179.23, 172.44, 172.38, 155.28, 155.20, 154.33, 154.30, 140.13, 140.10, 134.19, 130.86, 130.77, 130.31, 130.26, 129.46, 129.34, 128.00, 127.89, 124.71, 124.48, 124.37, 123.08, 123.04, 117.54, 103.47, 80.15, 80.11, 71.48, 71.46, 56.45, 54.49, 54.34, 52.29, 52.19, 47.76, 47.42, 37.39, 37.19, 28.51, 28.34.

Tertiary Amide 107:

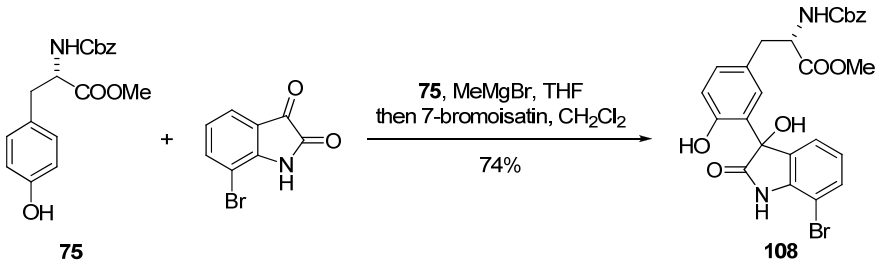


Compound **107** was prepared via the same procedure as compound **106** as a colorless foam (188 mg) in 60% yield.

R_f = 0.30 in 3:2 hexanes:EtOAc. **^{1}H NMR** (400 MHz, $CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers) δ 8.19 (br s, one diastereomer, 1.5H), 7.95 (br s, one diastereomer, 0.5H), 7.45 (d, *J* = 8.1 Hz, one diastereomer, 0.5H), 7.40 (d, *J* = 8.1 Hz, one diastereomer, 0.5H), 7.25 (br s, 1H), 7.05 (m, 1H), 6.93 (t, *J* = 7.8 Hz, one diastereomer, 0.5H), 6.89 (t, *J* = 7.9 Hz, one diastereomer, 0.5H), 6.65 – 6.93 (m, 1.5H), 6.60 – 6.30 (s, 1.5H), 5.64 – 5.36 (m, two AB, 2H), 5.14 (d, *J* = 7.6 Hz, one diastereomer, 0.5H), 5.10 (br s, one diastereomer, 0.5H), 5.02 (d, *J* = 7.6 Hz, one diastereomer, 0.5H), 4.95 (m, 1H), 4.82 (br s, one diastereomer, 0.5H), 4.31 (br s, 1H), 3.38 (s, 1/2Me), 3.36 (s,

1/2Me), 2.88 (m, 1H), 2.71 (m, 0.5H), 2.54 (m, 0.5H), 2.15 (m, 1H), 1.37 (s, 1/2*t*-Bu), 1.36 (s, 1/2*t*-Bu), 0.98 – 0.74 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 179.37, 172.35, 172.27, 166.02, 166.00, 156.20, 156.11, 154.37, 154.01, 140.13, 139.96, 134.26, 134.12, 131.21, 130.99, 129.88, 129.49, 129.24, 128.21, 128.10, 124.93, 124.66, 124.39, 123.97, 122.73, 117.28, 117.13, 115.89, 115.86, 110.93, 103.54, 103.41, 80.81, 71.49, 56.45, 56.43, 56.06, 55.90, 53.14, 46.94, 37.01, 32.01, 31.98, 28.79, 28.77, 28.34, 18.98, 18.81, 18.29, 18.17.

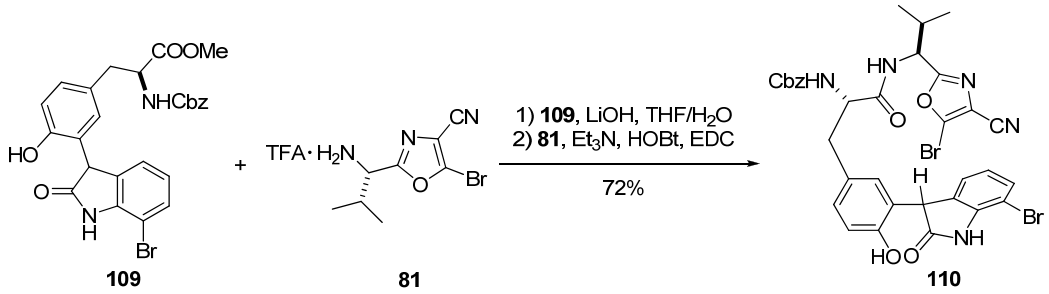
Tertiary alcohol 108:



To a cold (0 °C) solution of *N*-Cbz-L-tyrosine methyl ester[1] (**75**, 12.82 g, 38.9 mmol, 1.1 equiv) in dry THF (350 mL) was added MeMgBr (14.2 mL of a 3.0 M solution in Et_2O, 42.5 mmol, 1.2 equiv) dropwise via syringe. The ice bath was removed, and the solution was warmed to ambient temperature. Stirring was continued for 30 min, and the reaction was concentrated under reduced pressure to provide the phenoxide as a white solid, which was dried under high vacuum to remove the residual THF. 7-Bromoisatin (8.0 g, 35.4 mmol, 1.0 equiv) was added to the white solid, and anhydrous CH_2Cl_2 (500 mL) was added. The flask was fitted with a condenser and a drying tube. The

heterogeneous dark brown mixture was heated to reflux for 48 h. The reaction was quenched by addition of 1 M HCl (aq, 100 mL) and stirred until it became a clear yellow solution. The layers were separated, and the aqueous layer was extracted with EtOAc (80 mL×3). The combined organic layers were washed with brine (50 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellow foam. Purification by flash chromatography (2:1 then 1:1 hexaens:EtOAc) provided compound **108** (14.55 g, 74%) as a yellowish foam. Spectral data of **108** were consistent with that reported in the literature.[14]

Amide 110:

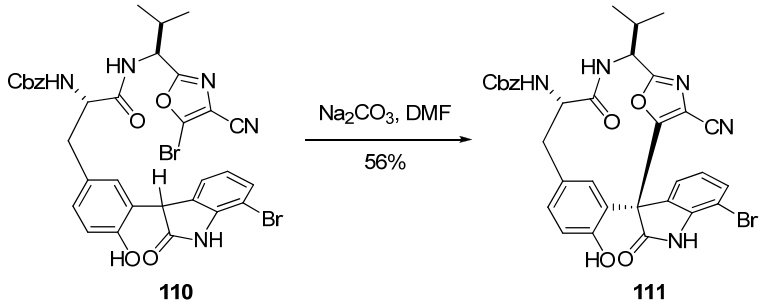


3-Aryloxindole **109** (270 mg, 0.501 mmol, 1.0 equiv) was dissolved in THF (5 mL), and the resulting solution was degassed by three freeze-pump-thaw cycles. Degassed LiOH solution (5.0 mL of a 1 M aqueous solution, 5.0 mmol, 10.0 equiv, sparged with N_2 for 1 h prior to use) was then cannulated into the THF solution. The resulting mixture was stirred at room temperature for 3 h, and quenched by addition of 1 M HCl (aq, 20 mL). The aqueous layer was extracted with CH_2Cl_2 (20 mL×3), and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide the crude acid as a white solid. The crude acid was dissolved in CH_2Cl_2 (10 mL), and oxazole salt **81** (256 mg, 0.751 mmol, 1.5 equiv), Et_3N (140 μL, 1.001 mmol,

2.0 equiv), HOBt·H_2O (153 mg, 1.001 mmol, 2.0 equiv), and EDC (192 mg, 1.001 mmol, 2.0 equiv) were added sequentially. After 1 hour of stirring at room temperature, the reaction mixture was diluted with EtOAc (25 mL) and 1 M HCl (25 mL). The aqueous layer was extracted with EtOAc (25 mL×3), and the combined organic layers were washed with 1 M HCl (20 mL), H_2O (20 mL), and brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (1:1 hexanes:EtOAc) provided amide **110** (271 mg, 72%) as a white solid as an approximately 1:1 mixture of diastereomers.

^{1}H NMR (500 MHz, CD_3CN; obtained as an approximately 1:1 mixture of diastereomers) δ 8.81 (s, 0.5H), 8.78 (s, 0.5 H), 7.40 (s, 0.5H), 7.37 (s, 0.5H), 7.36 – 7.17 (m, 8H), 7.01 – 6.86 (m, 3H), 6.86 – 6.76 (m, 1H), 6.72 (d, *J* = 8.0 Hz, 0.5 H), 6.69 (d, *J* = 8.2 Hz, 0.5 H), 6.04 (d, *J* = 8.2 Hz, 0.5 H), 5.98 (d, *J* = 8.3 Hz, 0.5 H), 5.07 – 4.95 (m, 2H), 4.95 – 4.85 (m, 1H), 4.79 (s, 0.5 H), 4.75 (s, 0.5 H), 4.41 – 4.25 (m, 1H), 3.16 – 2.84 (m, 1H), 2.72 (m, 1H), 2.23 – 2.10 (m, 1H), 0.93 (m, 3H), 0.87 (m, 3H). **^{13}C NMR** (75 MHz, CD_3CN; obtained as an approximately 1:1 mixture of diastereomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 178.34, 178.31, 172.6, 166.99, 166.97, 157.0, 154.65, 154.60, 142.6, 138.0, 133.0, 132.6, 132.4, 131.5, 130.81, 130.76, 129.65, 129.57, 129.4, 128.9, 128.62, 128.56, 124.39, 124.33, 116.6, 116.5, 116.2, 112.2, 102.7, 67.2, 57.1, 53.9, 50.9, 50.6, 37.6, 32.2, 19.2, 18.4, 18.3. **m.p.**: >110 °C (dec). **IR** (cm^{-1}): 3297 (br), 3068 (br), 2970, 2978, 2868, 2239, 1707, 1618, 1516. **HRMS** m/z calcd for $C_{33}H_{29}Br_2N_5O_6H^+$: 750.0557; found: 750.0584.

Macrocycle 111:

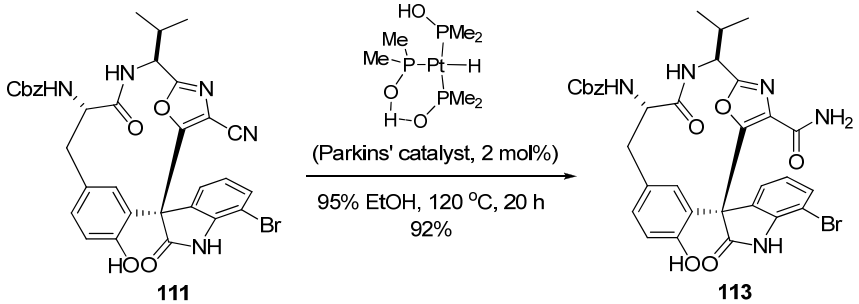


Amide **110** (868.5 mg, 1.156 mmol, 1.0 equiv) and Na_2CO_3 (306 mg, 2.89 mmol, 2.5 equiv, dried in the oven overnight prior to use) were combined in a 100 mL round bottom flask, which was capped and purged with N_2. Anhydrous DMF (50 mL, degassed by three freeze-pump-thaw cycles) was then cannulated into the flask. The needle was removed from the septum, which was then sealed with electrical tape. The suspension was placed in a 65 °C oil bath and stirred for 20 h. The reaction mixture was diluted with EtOAc (50 mL), and quenched by addition of 1 M HCl (50 mL). The layers were separated, and the aqueous layer was extracted with 1:1 hexanes:EtOAc (50 mL×3). The combined organic layers were washed with H_2O (30 mL×4), brine (20 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by flash chromatography (1:1 $CHCl_3$:EtOAc) provided macrocycle **111** as a white solid (432 mg, 56%). No isomeric material was identified in the crude ^{1}H NMR spectrum. A single crystal of **111** was obtained by slow evaporation from its solution of acetone, and the structure was determined by X-ray crystallography.

$\mathbf{R_f}$ = 0.22 in 1:1 $CHCl_3$:EtOAc. $\mathbf{[\alpha]_D^{26}}$ = –357.5 (*c* 0.640, MeOH). **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.56 (br s, 1H), 7.52 (d, *J* = 8.2 Hz, 1H), 7.41 (br s, 1 H), 7.49 – 7.30 (m, 6H), 7.16 (d, *J* = 7.6 Hz, 1H), 7.09 (dd, *J* = 8.0 Hz, 2.0 Hz, 1H), 7.02 (t, *J* = 8.2 Hz, 1H),

6.82 (d, J = 8.1 Hz, 1H), 6.17 (s, 1H), 5.47 (d, J = 9.0 Hz, 1H), 5.23 – 5.08 (AB, J = 12.1 Hz, ν_{ab} = 11.2 Hz, 2H), 4.67 (dd, J = 6.9, 10.3 Hz, 1H), 3.86 (ddd, J = 11.6, 8.6, 2.0 Hz, 1H), 3.28 (t, J = 12.2 Hz, 1H), 2.67 (dd, J = 13.5, 3.0 Hz, 1H), 2.07 – 1.94 (m, 1H), 1.07 (d, J = 6.6 Hz, 3H), 0.81 (d, J = 6.7 Hz, 3H). **^{1}H NMR** (500 MHz, CD_3CN) δ 8.96 (br s, 1H), 7.52 (dd, J = 8.2, 0.8 Hz, 1H), 7.46 (br d, J = 6.5 Hz, 1H), 7.42 – 7.30 (m, 7H), 7.23 (dd, J = 7.5, 0.8 Hz, 1H), 7.07 (br d, J = 7.9 Hz, 1H), 6.95 (t, J = 8.6 Hz, 1H), 6.73 (d, J = 8.2 Hz, 1H), 6.18 (br s, 1H), 5.07 (AB, J = 12.6 Hz, ν_{ab} = 13.1 Hz, 2H), 4.49 (dd, J = 6.9, 10.3 Hz, 1H), 4.13 (ddd, J = 11.6, 8.6, 2.0 Hz, 1H), 3.11 (t, J = 12.4 Hz, 1H), 2.62 (d, J = 12.9 Hz, 1H), 2.08 – 1.97 (m, 1H), 1.02 (d, J = 6.4 Hz, 3H), 0.91 (d, J = 6.3 Hz, 3H). **^{13}C NMR** (75 MHz, CD_3CN) δ 173.9, 173.3, 166.9, 158.0, 156.4, 153.2, 142.7, 138.1, 134.0, 133.2, 131.4, 129.5, 129.1, 128.9, 128.7, 128.3, 126.6, 126.5, 124.8, 116.6, 113.6, 112.0, 103.1, 67.2, 57.6, 57.2, 38.1, 30.6, 19.7, 19.2. **m.p.**: > 235 °C (dec). **IR** (cm^{-1}): 3289 (br), 2966, 2929, 2243, 1724, 1691, 1516. **HRMS** m/z calcd for $C_{33}H_{28}BrN_5O_6H^+$: 670.1296; found: 670.1314.

Carboxamide 113:

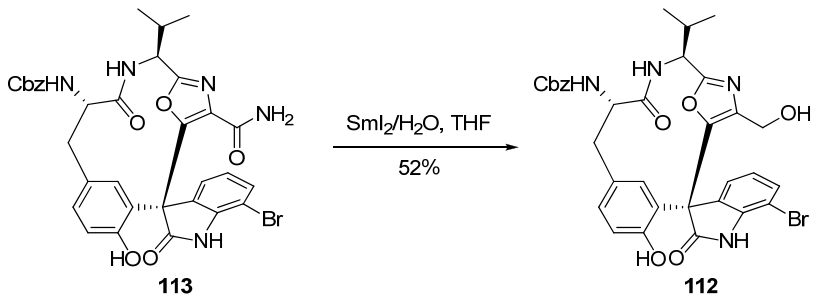


Nitrile **111** (132 mg, 0.197 mmol, 1.0 equiv) was dissolved in 95% EtOH (10 mL) in a 50 mL pressure vessel with a stir bar, and Parkins' catalyst (1.7 mg, 3.94 μmol, 0.02

equiv) was added. The vessel was sealed, and heated in a 120 °C oil bath for 20 h. After cooling to RT, the reaction was diluted with EtOAc (100 mL), transferred to a round bottom flask, and concentrated under reduced pressure to provide a yellowish solid. Purification by flash chromatography (15:1 $CHCl_3$:MeOH) provided the desired carboxamide (**113**, 126 mg, 92%) as a white solid.

R_f = 0.45 in EtOAc. **$[\alpha]_D^{28}$** = –356.7 (*c* 0.502, MeOH). **^{1}H NMR** (500 MHz, CD_3CN) δ 8.66 (s, 1H), 7.54 – 7.22 (m, 7H), 7.18 (br s, 1H), 7.02 (d, *J* = 7.2 Hz, 1H 1H), 6.91 (d, *J* = 7.4 Hz, 1H), 6.77 (t, *J* = 7.9 Hz, 1H), 6.70 (d, *J* = 8.2 Hz, 1H), 6.69 (br s, 1H), 6.38 (s, 1H), 6.06 (d, *J* = 6.2 Hz, 1H), 5.72 (s, 1H), 5.09 (AB, *J* = 12.7 Hz, ν_{ab} = 16.1 Hz, 2H), 4.46 (t, *J* = 7.8 Hz, 1H), 4.14 (t, *J* = 8.6 Hz, 1H), 3.07 (t, *J* =12.6 Hz, 1H), 2.68 (d, *J* =12.6 Hz, 1H), 1.97 (m, 1H), 1.01 (d, *J* = 6.1 Hz, 3H), 0.92 (d, *J* = 6.2 Hz, 3H). **^{13}C NMR** (75 MHz, CD_3OD) δ 177.5, 175.4, 165.0, 164.9, 157.7, 154.2, 151.6, 143.6, 138.2, 135.0, 133.2, 132.8, 131.9, 130.8, 129.5, 129.0, 128.8, 128.3, 124.6, 124.3, 116.8, 103.4, 67.6, 58.4, 58.11, 58.09, 57.9, 38.6, 30.9, 20.3, 19.7. **m.p.**: > 220 °C (dec). **IR** (cm^{-1}): 3395 (br), 2958, 2929, 1720, 1691, 1654, 1601. **HRMS** m/z calcd for $C_{33}H_{30}BrN_5O_7H^+$: 688.1407; found: 688.1413.

Alcohol 112:



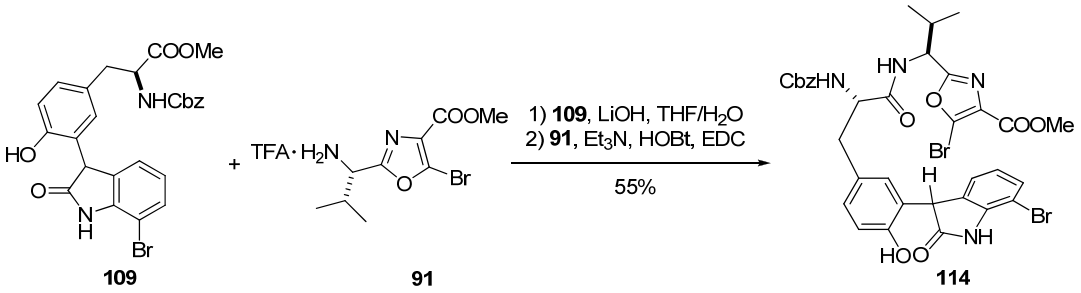
113 **112**

Amide **113** (16.5 mg, 0.024 mmol, 1.0 equiv) was dissolved in dry THF (2.2 mL) and SmI_2 (0.1 M in THF, 1.1 mL, 0.108 mmol, 4.5 equiv, purchased from Aldrich chemical company) was added via syringe, followed quickly (< 5 seconds) by addition of degassed H_2O (43 μL, 2.396 mmol, 100 equiv, sparging with Ar for 30 min prior to use). The dark blue color disappeared immediately and the solution became clear. Saturated $NaHCO_3$ (2 mL) was then added, and the mixture was stirred for an additional 10 min. The reaction mixture was extracted with EtOAc (20 mL×4), and the combined organic extracts were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated under reduced pressure to provide a white solid. Purification by flash chromatography (15:1 $CHCl_3$:MeOH) provided the desired primary alcohol (**112**, 8.4 mg, 52%) as a white solid. Further purification was accomplished by HPLC (silica gel column, 32:64:4 hexanes/EtOAc/MeOH). ^{1}H and ^{13}C NMR spectra were consistent with that reported by Nicolaou.[19] The structure of this material was further confirmed by gradient HMBC and HSQC experiments.

^{1}H NMR (500 MHz, CD_3CN) δ 8.69 (s, 1H), 7.48 (d, J = 8.2 Hz, 1H), 7.42 – 7.30 (m, 5H), 7.27 (br d, J = 7.0 Hz, 1H), 7.25 (br s, 1H), 7.07 (d, J = 7.4 Hz, 1H), 7.02 (d, J = 7.6 Hz, 1H), 6.90 (t, J = 7.6 Hz, 1H), 6.71 (d, J = 8.0 Hz, 1H), 6.23 (s, 1H), 6.03 (br d, J = 6.2 Hz, 1H), 5.07 (AB, J = 12.6 Hz, ν_{ab} = 16.0 Hz, 2H), 4.45 (t, J = 7.9 Hz, 1H), 4.11 (t, J = 8.6 Hz, 1H), 3.63 (ABX, J = 10.5, 5.8 Hz, 2H), 3.06 (t, J = 12.2 Hz, 1H), 2.75 (t, J = 5.7 Hz, 1H), 2.62 (d, J = 13.0 Hz, 1H), 2.00 (m, 1H), 1.01 (d, J = 6.5 Hz, 3H), 0.91 (d, J = 6.5 Hz, 3H). **^{13}C NMR** (150 MHz, CD_3CN) δ 173.4, 164.7, 156.2, 153.1, 144.8, 142.5, 139.2, 138.2, 133.7, 133.0, 130.7, 130.1, 129.4, 129.1, 128.7, 128.6, 127.8, 125.5, 124.3,

116.4, 103.0, 67.0, 57.6, 57.1, 55.9, 38.5, 30.7, 19.7, 19.3. **HRMS** m/z calcd for $C_{33}H_{31}BrN_4O_7Na^+$: 697.1268; found: 697.1276.

Ester 114:



Compound **114** was prepared via a similar procedure as the preparation of compound **110**. Purification by flash chromatography (2:3 hexanes:EtOAc) provided the title product (882 mg, 53%) as a white solid as an approximately 1:1 mixture of diastereomers.

$\mathbf{R_f}$ = 0.45 in 2:3 hexanes:EtOAc, **^{1}H NMR** (500 MHz, $CDCl_3$; obtained as an approximately 1:1 mixture of diastereomers) δ 8.30 (s, 0.5H), 8.15 (s, 0.5H), 7.80 (s, 0.5H), 7.68 (s, 0.5H), 7.41 (d, *J* = 8.3 Hz, 0.5H), 7.37 (d, *J* = 8.4 Hz, 0.5H), 7.35 – 7.25 (m, 5H), 7.10 (d, *J* = 7.3 Hz, 1H), 6.98 (t, *J* = 10.4 Hz, 0.5H), 6.94 – 6.80 (m, 2H), 6.75 (s, 0.5H), 6.67 (s, 0.5H), 6.52 (d, *J* = 7.7 Hz, 0.5H), 5.13 (s, 0.5H), 5.10 (s, 0.5H), 5.03 (two AB, 2H), 4.93 (s, 1.5H), 4.38 – 4.22 (m, 1H), 3.89 (s, 3H), 2.22 – 2.12 (m, 0.5H), 2.12 – 2.04 (m, 0.5H), 0.96 – 0.70 (two dd, 6H).

3.10 Refercences and Notes

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4 Cascade α-Arylation / Direct Arylation Approach

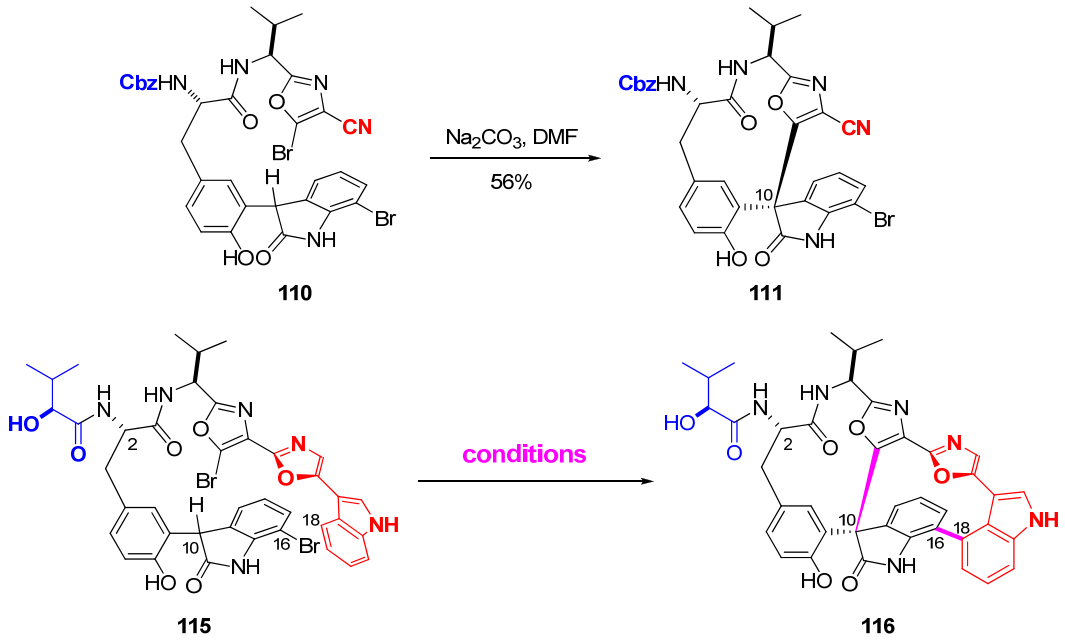
4.1 Introduction

After successfully completing a formal synthesis of diazonamide A, I anticipated that I could obtain the natural product via Nicolaou's eleven-step sequence (Scheme 1.2) from compound **112**.[1,2] Although Nicolaou's first synthesis confirmed that Harran's revised structure was the correct structure of diazonamide A, there was a lot of room to be improved in the eleven-step sequence, including the yields of some of the key reactions and the ease of processing. For example, Witkop-type photocyclization of compound **9** only provided 30% yield; reductive cyclization of **11** utilized 100 equivalent of DIBAL, which is obviously impractical on large scale. With the successful application of α-arylation of 3-aryloxindole in the formal synthesis of diazonamide A, I planned to apply this methodology to the total synthesis.

4.2 Retrosynthetic Analysis

The success of the macrocyclization of compound **110** via an S_NAr mechanism under very mild basic conditions (Na_2CO_3 in DMF) depends on the reactivity of the oxindole enolate and the highly electron-deficient bromooxazole ring. In compound **110**, this is due to a strong electron-withdrawing cyano group. Extension of the α-arylation of 3-aryloxindole to substrate **115**, which bears the complete heterocyclic rings, and a 2-hydroxyisovaleric acid side chain may be possible (Scheme 4.1). In addition, the mild

basic conditions should not interfere with the 2-hydroxyisovaleric acid side chain, thereby avoiding protection of the primary amine on C2. However, the oxazole attached to the bromooxazole ring is significantly less electron-withdrawing than a cyano group, and may not be able to induce an S_NAr reaction. As such, I was also interested in looking for other conditions to facilitate the macrocyclization of compound **115** to construct the quaternary C10.

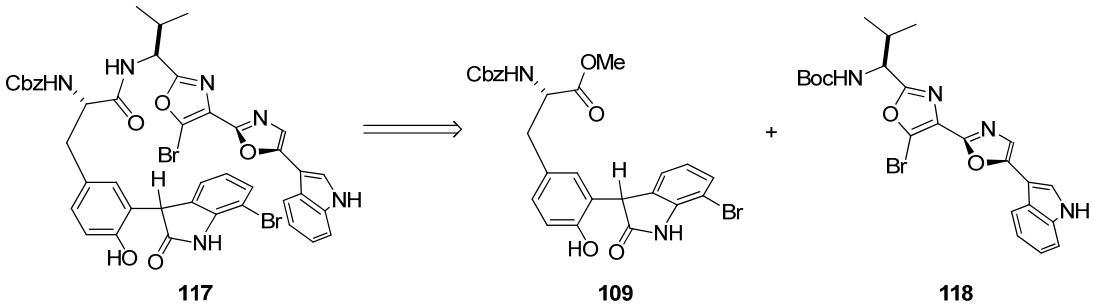


Scheme 4.1 Proposed Cascade α-Arylation/Direct Arylation Reactions

Recently, transition-metal-catalyzed α-arylation of carbonyl compounds[3,4,5] and direct arylation via C-H activation[6,7,8] have been hot topics among organic synthetic chemistry. I envisioned that the whole heterocyclic scaffold of diazonamide A could be constructed via a single cascade reaction consisting of a transition-metal-catalyzed α-arylation to form the C10 quaternary carbon and a direct arylation to form C16-C18 bond. There are two bromine atoms in compound **115**. Because the oxazole is known to be

more electron-deficient than the phenyl ring, the C-Br bond on the oxazole ring is expected to more readily undergo transition metal oxidative addition, which may facilitate the formation of the quaternary C10 to furnish the left hand macrocycle of diazonamide A. Further, in the product of the α-arylation, the oxindole and the indole are in close proximity, and this is expected to promote a transition-metal-catalyzed direct arylation to complete the whole framework. In prior work, Sainsbury has shown that the 4-position of indoles can react with aryl triflate intramolecularly to form biaryls via direct arylation. [9] Sainsbury also reported that oxidative coupling with unmodified phenyl groups could occur on the 4-position of indoles.[10,11] With the successful completion of this cascade reaction, completion of the total synthesis could occur via operations known from the previous total syntheses to provide the natural product in a more efficient way.

Model studies using cyclization precursor **117** (lacking the 2-hydroxyisovaleric acid side chain) were conducted (Scheme 4.2). Compound **117** was prepared in a highly convergent manner by an amide bond formation between compounds **109** and compound **118** as described below. Compound **115** with the 2-hydroxyisovaleric acid side chain is expected to retain the same reactivity for macrocyclization as **117**, and can be used in the total synthesis of diazonamide A. Because the synthesis of ester **109** is known from our formal synthesis (see Chapter 3), preparation of Boc-protected amine **118** was first pursued.

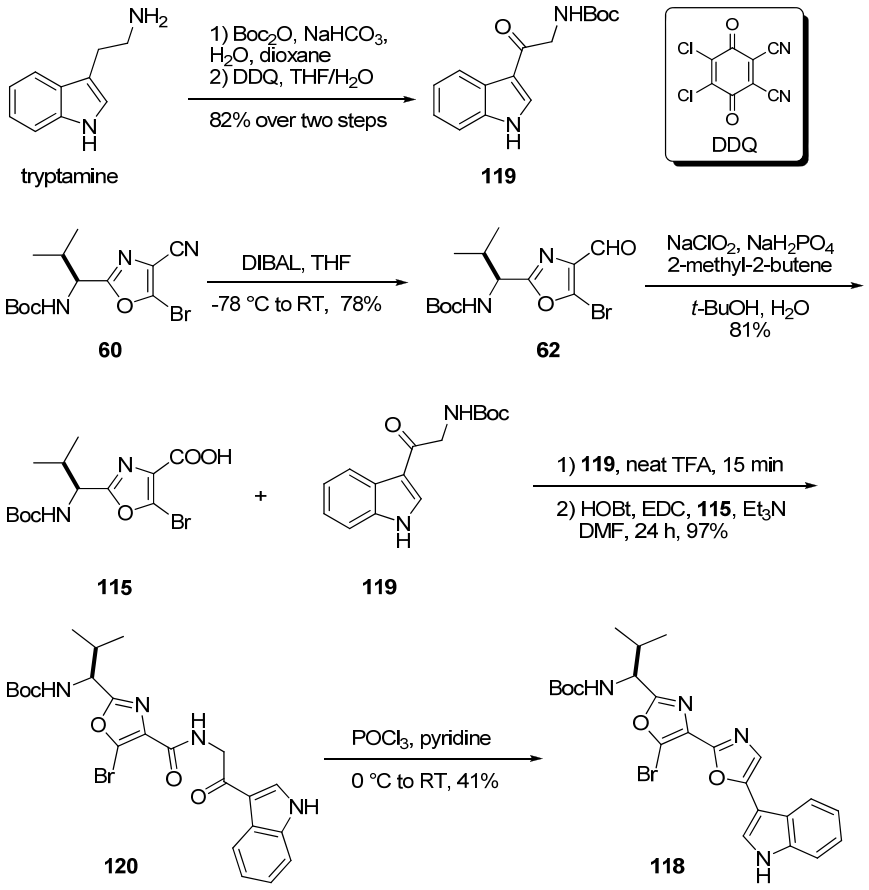


Scheme 4.2 Retrosynthesis of Cyclization Precursor **117**

4.3 Synthesis of Cyclization Precursor and Attempted S_NAr reactions

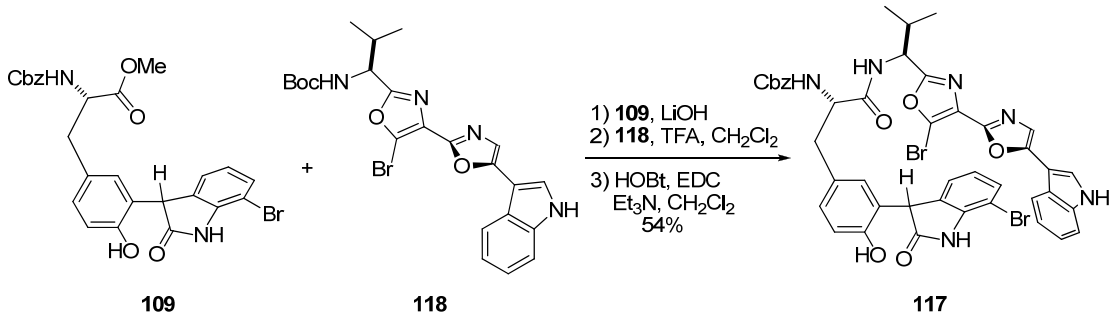
Synthesis of the Boc-protected amine, **118**, began with the functionalization of commercially available tryptamine (Scheme 4.3). Boc-protection of the free amine of tryptamine, followed by oxidation of the benzyl position with DDQ, afforded ketone **119** in 82% yield over two steps.[2] The other fragment, carboxylic acid **115**, was synthesized from nitrile **60** as described in Chapter 3. In the hands of Dr, Matthew Sammons, attempted hydrolysis of the nitrile of **60** failed under acidic or basic conditions likely due to competing S_NAr processes. This compound was instead subjected to reduction using DIBAL-H and Pinnick-Lindgren oxidation to provide carboxylic acid **115**.[12] Treatment of Boc-protected amine **119** with neat TFA released the free amine to generate the amine TFA salt, which was coupled with carboxylic acid **115** under common amide bond formation conditions (EDC/HOBt) to provide keto amide **120**. Interestingly, Wipf oxazole formation (PPh_3, Et_3N, and C_2Cl_6 of I_2)[13,14] did not provide oxazole **120**, possibly due to the steric hindrance of the bulky bromine atom on the oxazole. However,

Nicolaou's conditions[2] using $POCl_3$ in pyridine afforded oxazole **120** in a moderate yield of 41%.



Scheme 4.3 Synthesis of Bis-Oxazole Indole **118**

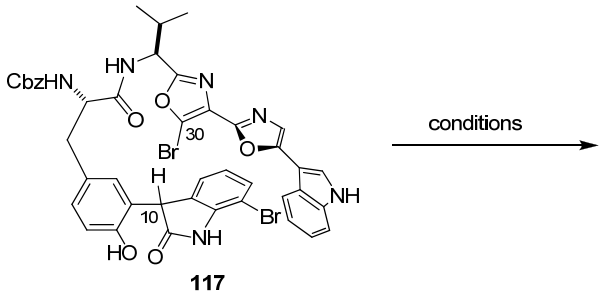
Treating bis-oxazole indole **118** with neat TFA provided an amine TFA salt, which was coupled with the carboxylic acid generated from saponification of ester **109** using standard peptide coupling conditions (EDC/HOBt), to provide cyclization precursor **117** as a 1:1 mixture of diastereomers (Scheme 4.4).



Scheme 4.4 Synthesis of Cyclization Precursor **117**

With cyclization precursor **117** in hand, screening of cyclization conditions was conducted. First, I subjected **117** to our S_NAr cyclization conditions (Table 4.1, entry 1), and I observed no cyclization product and recovered starting material. Surprisingly, even changing the base to a stronger one, such as LiHMDS (entry 2), still did not provide any cyclization product, and starting material was recovered. Attempted Pd-catalyzed α-arylations using the conditions we developed for intermolecular α-arylations of 3-diaryloxindoles, using either Cs_2CO_3 or LiHMDS as the base (entries 3 and 4), did not provide any cyclization product. It is likely that the unprotected oxindole nitrogen is detrimental for such α-arylations, as in our previous work, we found that protection of the oxindole nitrogen facilitates the reaction using Cs_2CO_3. I studied another approach wherein Lewis acid additives were anticipated to bind to the two nitrogen atoms in bis-oxaozole moiety to activate the bromooxazole for nucleophilic attack. Unfortunately, all conditions (entries 5-11) with different Lewis acid additives provided either recovered starting material, or complex mixtures. Some Lewis acid, for example, $AuCl_3$, decomposed the starting material prior to the addition of base or heating.

Table 4.1 Attempted Cyclization of Precursor **117**



117

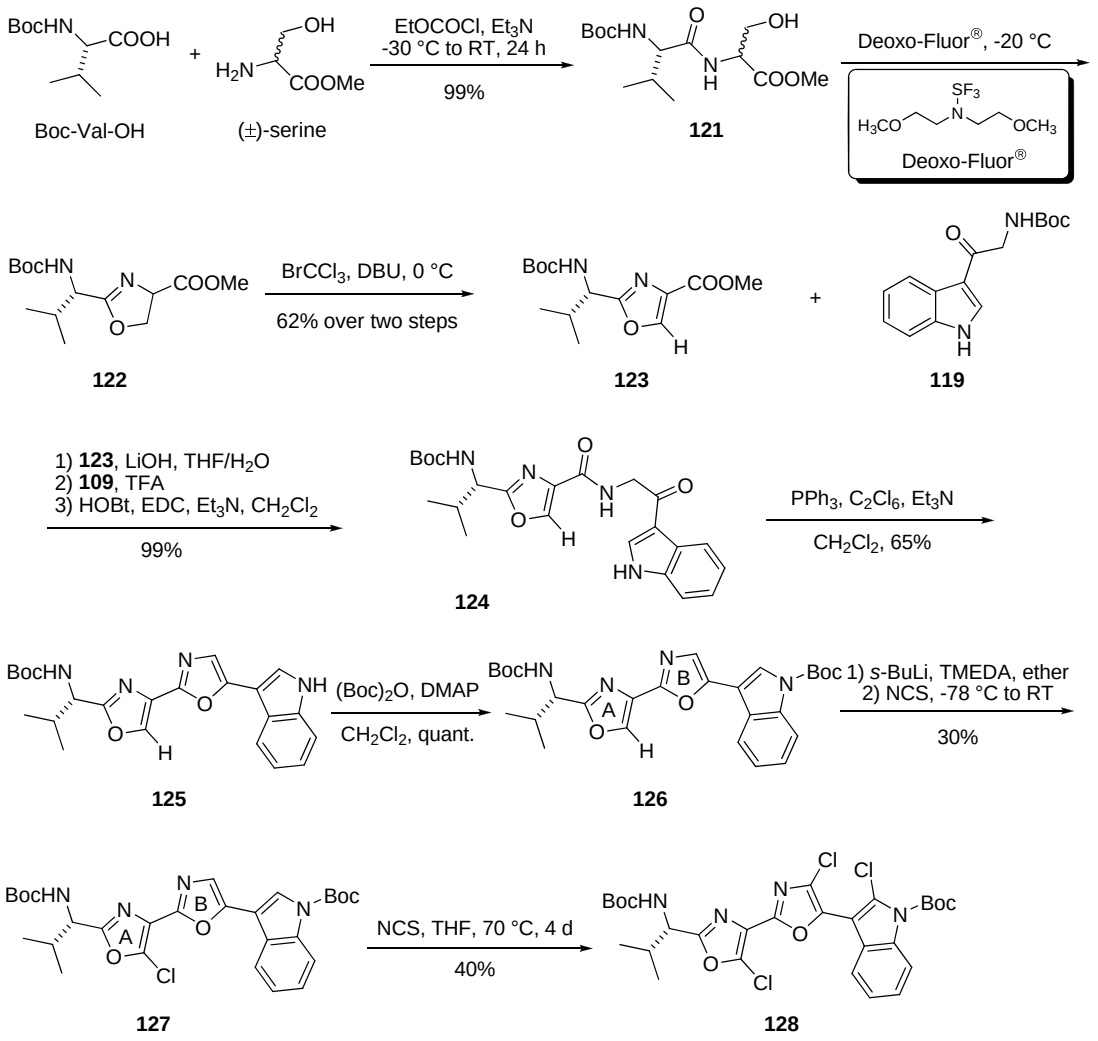
Entry	Conditions	Results
1	Na_2CO_3 (5 equiv), DMF, 65 °C, 24 h	recovered **117**
2	LiHMDS (5 equiv), DMF, 0 °C to 65 °C, 15 h	recovered **117**
3	$Pd(dba)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3 (3.5 equiv), toluene, reflux, 3 h	recovered **117**
4	$Pd(dba)_2$, *t*-Bu_3PHBF_4, LiHMDS (3.5 equiv), toluene, reflux, 3 h	recovered **117**
5	$Zn(OTf)_2$ (5 equiv), Na_2CO_3 (10 equiv), DMF, 65 °C, 20 h	recovered **117**
6	$Bi(OTf)_3$ (5 equiv), Na_2CO_3 (10 equiv), DMF, 65 °C, 20 h	recovered **117**
7	$Sc(OTf)_2$ (5 equiv), Na_2CO_3 (10 equiv), DMF, 65 °C, 20 h	recovered **117**
8	CuOTf (1.1 equiv), Na_2CO_3 (10 equiv), DMF, 65 °C, 20 h	complex mixtures
9	$Cu(OTf)_2$ (1.1 equiv), Na_2CO_3 (10 equiv), DMF, 65 °C, 20 h	complex mixtures
10	$Cu(OTf)_2$ (5 equiv), DCE, RT, 20 h	recovered most **117**
11	$AuCl_3$ (1.1 equiv), DCE, RT, 20 h	complex mixtures

For the S_NAr reaction of compound **117**, we hypothesized that steric repulsion between the indole and the bromooxindole hinders the reaction in the transition state and prevents the formations of C10-C30 bond. In addition, we have shown that the unprotected oxindole is detrimental to Pd-catalyzed α-arylation. Protection of the oxindole nitrogen with a group smaller than a MOM group is preferred as we have found that MOM-protection can be problematic in arylation reactions of oxindoles (See Scheme 3.7). As such, a methyl group might be an ideal protecting group and may be able to facilitate the formation of the C10 quaternary carbon. Further, the methyl group can be possibly removed via a radical oxidative mechanism.[15]

4.4 Synthesis of Chlorinated Cyclization Precursors

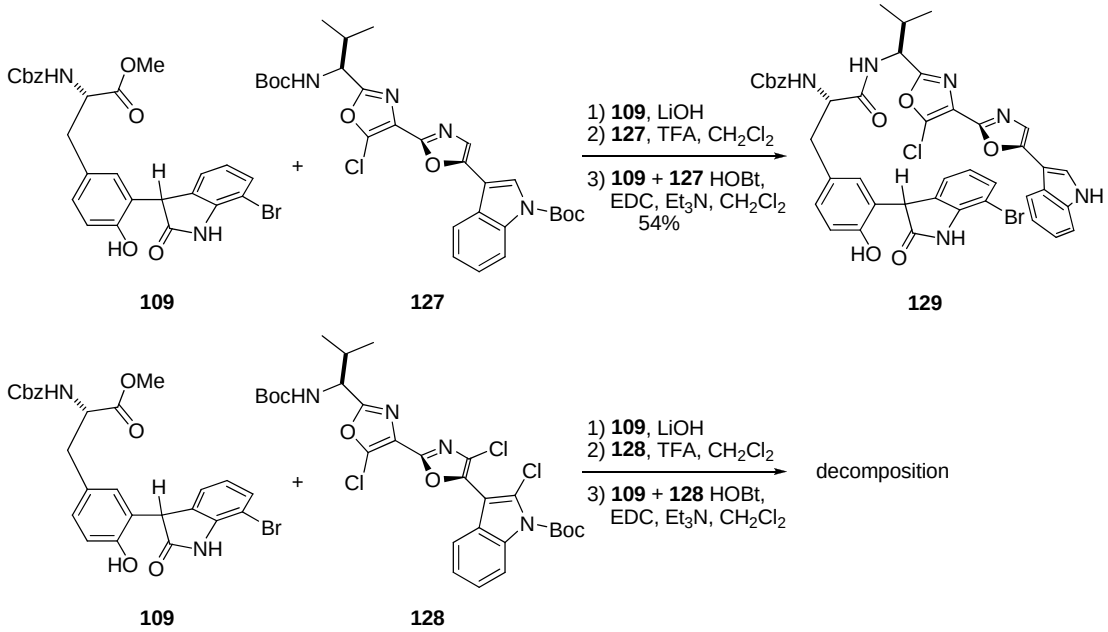
For typical S_NAr reactions, electron-deficient chloro-arenes are more reactive than their bromo counterparts. In order to render the S_NAr reaction successful for the construction of the C10 quaternary center of diazonamide A, synthesis of the chlorooxazole analogue of compound **117** is desired. Decreasing the electron density of the bromooxazole is also helpful for S_NAr reactions. Because diazonamide A has two peripheral chlorine atoms, introducing these two chlorine atoms on the cyclization precursor also shortens the synthetic route. Therefore, chlorinated bis-oxazole indole **127** and **128** were synthesized as described below.

Condensation of Boc-Val-OH and racemic serine using standard peptide coupling methods (EtOCOCl, Et_3N) provided amide **121** (Scheme 4.5).[16] Application of the Wipf Deoxo-Fluor mediated dehydrative cyclization to compound **121** provided oxazoline **122**, which was oxidized under Williams' condition ($BrCCl_3$ and DBU) to form oxazole **123**.[17] Amide **124** was prepared via condensation of the carboxylic acid generated from saponification of ester **123** and the amine TFA salt produced by treating **119** with neat TFA. Wipf oxazole formation (PPh_3, C_2Cl_6, and Et_3N)[13,14] was used to convert keto amide **124** to bis-oxazole **125**.[18] Because chlorination of compound **125** with NCS was low-yielding, I decided to protect the indole of **125** as the *tert*-butyl carbamate (**126**),[19] which was then treated with *s*-BuLi (2.2 equiv) and TMEDA to provide chlorooxazole **127** after trapping with NCS.[20] In this reaction, the nitrogen atom of oxazole **B** directed the lithium to selectively deprotonate the hydrogen on oxazole **A**. Compound **127** was further chlorinated on oxazole ring **B** and the indole to provide tri-chlorinated **128** in modest yield (40%) with NCS at higher temperature.



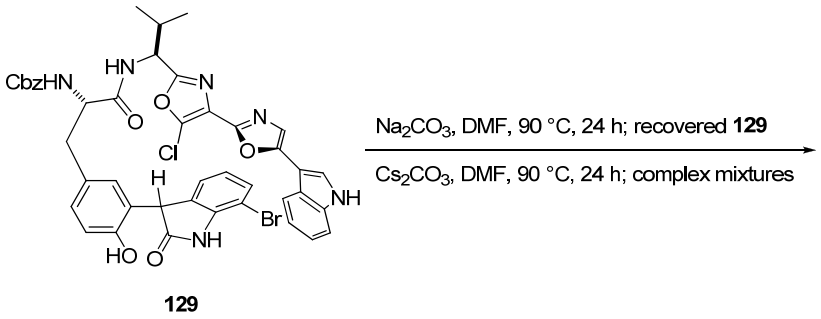
Scheme 4.5 Synthesis of Chlorinated Bis-Oxazole Indole **127** and **128**

Treating chlorinated bis-oxazole indole **127** and 3-aryloxindole **109** under the same amide bond formation conditions as in the preparation of cyclization precursor **117** provided **129** in modest yield (54%, Scheme 4.6). However, under the same conditions, the reaction of **109** and bis-oxazole indole **128** did not provide any coupled product, possibly because tri-chlorinated **128** was not stable under strong acidic conditions (TFA).



Scheme 4.6 Couplings of Bis-Oxazole Indole **127** and **128**

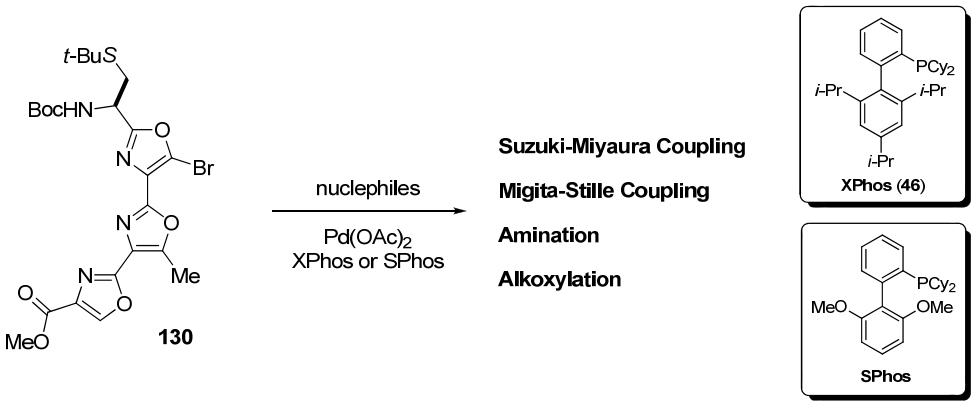
With cyclization precursor **129** in hand, S_NAr reactions were studied (Scheme 4.7). Unfortunately, treating compound **129** with week base (Na_2CO_3 in DMF) only provided recovered starting material; stronger base (Cs_2CO_3 in DMF) lead to complex mixtures.



Scheme 4.7 Attempted S_NAr reactions of **129**

4.5 Intermolecular Pd-Catalyzed α-Arylation of Bis-Oxazole Indoles

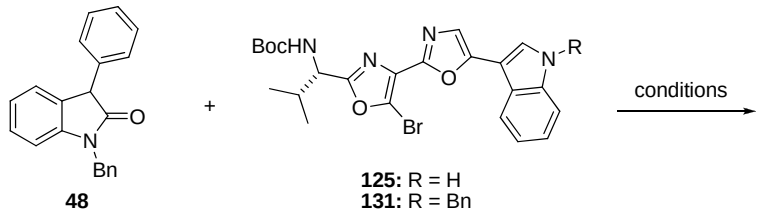
Takahashi and coworkers reported that tri-oxazole **130** could undergo several cross-coupling reactions, such as Suzuki-Miyaura couplings, Migita-Stille Couplings, and Buchwald-Hartwig's aminations and alkoxylations, to functionalize the bromooxazole using $Pd(OAc)_2$ with XPhos or SPhos as ligands.[21] These reactions indicate that Pd-catalyzed cross-coupling reactions with compound **130** are viable. As such, even though Pd-catalyzed α-arylations reactions using compound **130** were not studied, we felt that they are viable, too.



Scheme 4.8 Cross-Coupling Reactions of Tri-Oxazole **130**

In order to confirm the viability of our Pd-catalyzed α-arylation reactions to construct the C10 quaternary center in a system related to the synthesis of diazonamide A, I also studied the intermolecular *a*-arylations of *N*-benzyl-3-phenyloxindole (**48**) and aryl bromide **125** and **131** (Table 4.2). Compound **131** was used, because compound **125** with a Boc protecting group on the indole was sensitive to basic conditions (i.e., carbonate base in protic solvent), while the benzyl protecting group on **131** survives. Unfortunately, all the conditions I had tried only provided recovered starting materials, debromination of aryl bromide **131**, or complex mixtures.

Table 4.2 Attempted Intermolecular Pd-Catalyzed *a*-Arylations



48

125: R = H
131: R = Bn

entry	conditions	results
1	**125**, $Pd(dba)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, toluene, reflux, 3 h	recovered **48** and **131**
2	**125**, $Pd(dba)_2$, RuPhos, Cs_2CO_3, toluene, reflux, 3 h	oxidation of **48**
3	**125**, $Pd(dba)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, Ag_2CO_3, toluene, reflux, 3 h	complex mixtures
4	**131**, $Pd(OAc)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, toluene, reflux, 3 h	debromination of **131**
5	**131**, $Pd(OAc)_2$, *t*-Bu_3PHBF_4, LiHMDS, toluene, reflux, 3 h	debromination of **131**
6	**131**, $Pd(dba)_2$, no ligand, LiHMDS, toluene, reflux, 20 h	debromination of **131**
7	**131**, $Pd(PPh_3)_4$, Cs_2CO_3, 1 h	complex mixtures
8	**131**, $Pd(OAc)_2$, SPhos, Cs_2CO_3, toluene, 1 h	complex mixtures
9	**131**, $FeCl_3$, Cs_2CO_3, DMF, 90 °C, 15 h	recovered **48** and **131**
10	**131**, $Pd(OAc)_2$, RuPhos, Cs_2CO_3, toluene, 3 h	complex mixtures

4.6 Conclusion

An attempted cascade α-arylation/direct arylation approach to the total synthesis of diazonamide A was described. Cyclization precursor **117** was successfully prepared, and subjected to a variety of conditions. Although no desired cyclization was observed, this approach provides a novel disconnection for the synthesis of diazonamide A. Some modifications are needed to furnish the desired α-arylation product and the following direct arylation.

4.7 Abbreviations

Cbz	Carboxybenzyl

DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DIBAL	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
Deoxo-Fluor®	Bis(2-methoxyethyl)aminosulfur trifluoride
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
HOBt	Hydroxybenzotriazole
LiHMDS	Lithium bis(trimethylsilyl)amide
NCS	*N*-Chlorosuccinimide
RuPhos	2-Dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TFA	Trifluoroacetic acid
TMEDA	Tetramethylethylenediamine
XPhos	2-Dicyclohexylphosphino-2′,4′,6′-triisopropylbiphenyl

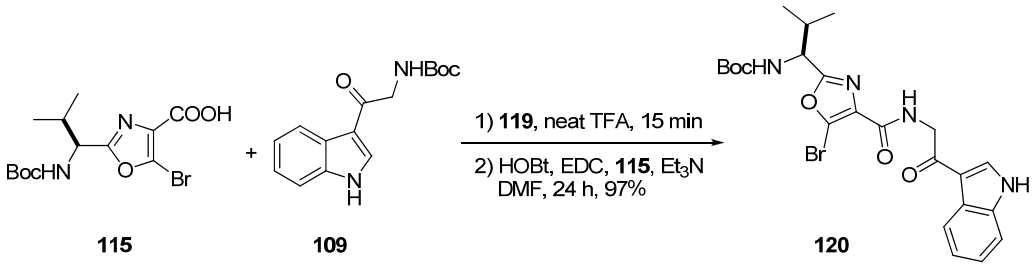
4.8 Experimental Details

General Information

All glassware was oven-dried or flame-dried. DMF were freshly distilled over CaH_2 under reduced pressure prior to use; THF and Et_2O were distilled from sodium benzophenone ketyl under N_2; DME was distilled over Na under N_2. CH_2Cl_2, hexanes and toluene were distilled over CaH_2 under N_2; TMEDA was distilled from Na under reduced pressure. Unless specifically mentioned, all chemicals are commercially available and were used as received. Thin layer chromatography (TLC) was performed using EM Science Silica Gel 60 F254 glass plates. Flash chromatography was performed using 60 Å silica gel (37-75 μm). ^{1}H NMR spectra were recorded at either 400 MHz or 500 MHz, and ^{13}C NMR spectra were recorded at either 75 MHz or 100 MHz in $CDCl_3$, CD_3CN, [D6]acetone, or [D6]DMSO as indicated. Chemical shifts are reported in ppm referenced to residual solvent peaks as follows: $CDCl_3$, 7.24 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR; CD_3CN (1.94 ppm for ^{1}H NMR; 1.32 ppm for ^{13}C NMR.); [D6]acetone, 2.05 ppm for ^{1}H NMR, 29.84 ppm for ^{13}C NMR; and [D6]DMSO, 2.50

ppm for ^{1}H NMR, 39.52 ppm for ^{13}C NMR. Infrared (FT-IR) spectra were obtained as thin films on NaCl plates. Exact mass was determined using electrospray ionization (M+H, M+Na, or M+K as indicated).

Keto Amide 120:

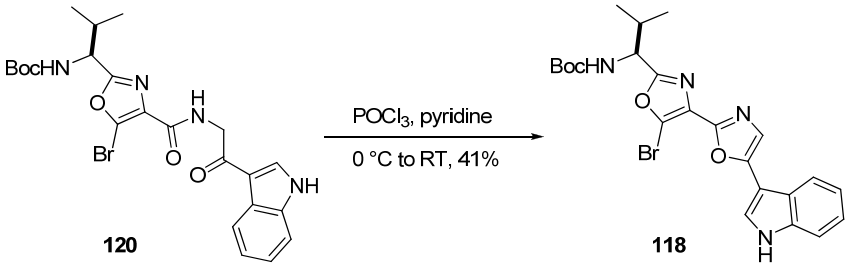


115 **109** **120**

Boc-protected amine **109** (76 mg, 0.275 mmol, 2.0 equiv) was treated with neat TFA (5 mL). After stirring at room temperature for 10 min, the reaction was concentrated, and solvent exchanged with toluene three times to provide the amine TFA salt as a white solid. This amide TFA salt should be prepared right before the coupling. The crude TFA salt and carboxylic acid **115** (50 mg, 0.138 mmol, 1.0 equiv) were dissolved in DMF (3 mL), and Et_3N (58 μL, 0.413 mmol, 3.0 equiv), HOBt (32 mg, 0.206 mmol, 1.5 equiv), and EDC (40 mg, 0.206 mmol, 1.5 equiv) were added sequentially. The resultant yellow solution was stirred at room temperature for 15 h, and diluted with ether (50 mL) and 1 M HCl (10 mL). The organic layer was washed with H_2O (15 mL×3), sat. $NaHCO_3$ (15 mL), brine (15 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. Purification by flash chromatography (2:1 $CHCl_3$:EtOAc) provided keto amide **120** (70 mg, 97%) as a yellowish solid.

R_f = 0.15 in 1:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.83 (s, 1H), 8.30 (dd, *J* = 6.4, 2.5 Hz, 1H), 7.94 (d, *J* = 3.2 Hz, overlapping with a singlet, 2H), 7.45 – 7.36 (m, 1H), 7.31 – 7.24 (m, 2H), 5.18 (d, *J* = 9.3 Hz, 1H), 4.88 (s, 15 % rotamer peaks), 4.75 (dd, *J* = 9.1, 6.1 Hz, 1H), 4.71 (d, *J* = 4.7 Hz, 2H), 4.57 (s, 15% rotamer peaks), 2.27 – 2.11 (m, *J* = 13.3, 6.6 Hz, 1H), 1.47 (s, 9H), 0.94 (dd, *J* = 6.7, 3.2 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 188.49, 164.55, 159.97, 155.60, 136.54, 131.86, 131.58, 125.44, 124.96, 124.10, 123.13, 122.08, 115.21, 112.00, 80.68, 54.60, 46.01, 32.64, 28.48, 18.96, 18.08. **IR** (cm^{-1}) 3285, 2966, 2929, 1699, 1642, 1585.

Bis-Oxazole Indole 118:

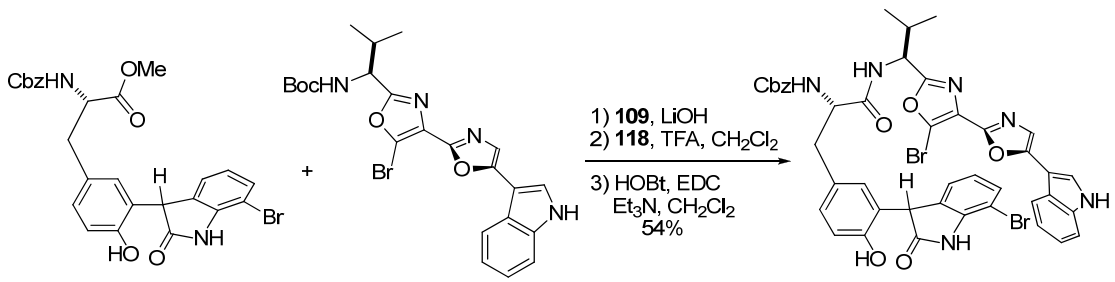


$POCl_3$ (3.0 mL, 32.3 mmol, 20 equiv) was added dropwise via syringe to a solution of keto amide **120** (838 mg, 1.62 mmol, 1.0 equvi) in dry pyridine (3 mL) at 0 °C. The clear solution became a white suspension upon the addition of $POCl_3$. The reaction was allowed to warm up to room temperature and stirred overnight (20 h). The reaction was diluted with EtOAc (50 mL), and poured slowly into sat. $NaHCO_3$ (50 mL) in an ice bath. The aqueous layer was extracted with EtOAc (50 mL×3), and the combined organic layers were washed with H_2O (30 mL), brine (30 mL), dried over $MgSO_4$, filtered, and

concentrated to provide a dark brown solid. Purification by flash chromatography (4:1 $CHCl_3$:EtOAc) provide bis-oxazole indole **118** (329 mg, 41%) as a yellow solid.

R_f = 0.45 in 4:1 $CHCl_3$:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.41 (s, 1H), 7.89 (d, *J* = 7.4 Hz, 1H), 7.58 (d, *J* = 1.9 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.38 (s, 1H), 7.28 – 7.14 (m, 2H), 5.32 (d, *J* = 9.2 Hz, 1H), 5.04 (s, 12 % rotamer peaks), 4.81 (dd, *J* = 9.0, 6.1 Hz, 1H), 4.62 (s, 12% rotamer peaks), 2.28 – 2.09 (m, 1H), 1.43 (s, 9H), 0.94 (d, *J* = 6.8 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.72, 155.62, 151.69, 148.76, 136.44, 128.93, 124.07, 123.02, 121.06, 120.99, 120.77, 119.98, 111.90, 104.91, 80.41, 54.61, 32.79, 28.39, 18.89, 18.01. **IR** (cm^{-1}) 3403, 3318, 2970, 3060, 2929, 2872, 1704, 1630, 1605.

Cyclization Precursor 117:

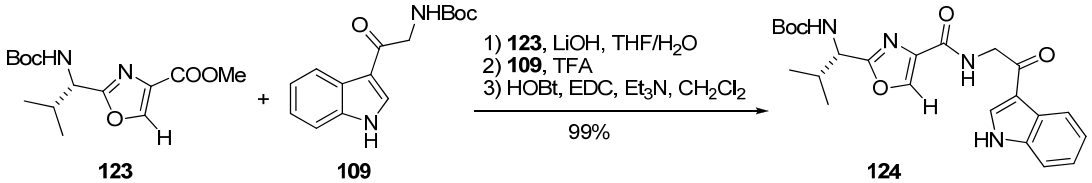


Saponification of compound **109** was conducted as in the preparation of compound **110** (see Chapter 3) to provide a carboxylic acid as a white solid. Bis-oxazole indole **118** (49 mg, 0.098 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (5 mL), and TFA (380 µL, 4.89 mmol, 50 equiv) was added. The yellow solution was stirred at room temperature for 2 h, and concentrated, solvent exchanged with toluene three times to provide an amine

TFA salt as a yellowish solid. The crude TFA salt, the carboxylic acid (51 mg, 0.098 mmol, 1.0 equiv) generated from **109**, and HOBt (30 mg, 0.195 mmol, 2.0 equiv) were combined in a 25 mL round bottom flask, and dry CH_2Cl_2 (5 mL), Et_3N (27 μL, 0.195 mmol, 2.0 equiv), and EDC (21 mg, 0.108 mmol, 1.1 equiv) were added. The resultant yellow solution was stirred at room temperature for 3 h, diluted with EtOAc (50 mL), washed with 1 M HCl (10 mL), H_2O (10 mL), sat. $NaHCO_3$ (10 mL), brine (10 mL), and dried over $MgSO_4$, filtered, and concentrated to provide a yellowish solid. Purification by flash chromatography (1:1 $CHCl_3$:EtOAc) provided cyclizatioin precursor **117** (48 mg, 54%) as a yellowish solid.

R_f = 0.15 in 1:1 $CHCl_3$:EtOAc. **^{1}H NMR** (500 MHz, CD_3CN; obtained as an approximately 1:1 mixture of diastereomers) δ 9.85 (s, 0.5H), 9.83 (s, 0.5H), 8.75 (s, 1H), 7.91 (d, *J* = 3.9 Hz, 0.5H), 7.89 (d, *J* = 3.9 Hz, 0.5H), 7.59 (s, 1H), 7.58 (d, *J* = 2.7 Hz, 0.5H), 7.56 (d, *J* = 2.6 Hz, 0.5H), 7.50 (d, *J* = 7.4 Hz, 1H), 7.40 (s, 1H), 7.36 – 7.20 (m, 8H), 7.17 (t, *J* = 7.1 Hz, 1H), 6.97 (d, *J* = 2.3 Hz, 0.5H), 6.96 (overlapping s and d, 1.5H), 6.84 (d, *J* = 7.3 Hz, 0.5H), 6.80 (d, *J* = 7.1 Hz, 0.5H), 6.73 (m, 1H), 6.68 (m, 1H), 5.98 (d, *J* = 8.1 Hz, 0.5H), 5.94 (d, *J* = 8.3 Hz, 0.5H), 5.09 – 4.88 (m, 3H), 4.73 (s, 0.5H), 4.69 (s, 0.5H), 4.50 – 4.29 (m, 1H), 3.15 – 2.95 (m, 1H), 2.89 – 2.66 (m, 1H), 2.30-2.17 (m, 1 H), 1.04 – 0.81 (m, 6H).

Keto Amide 124:



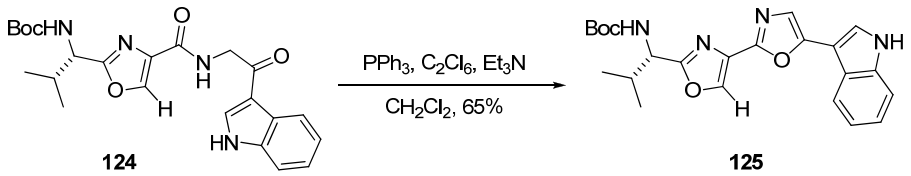
Ester **123** (298 mg, 1.0 mmol, 1.0 equiv) was dissolved in dry THF (5 mL), and a solution of LiOH monohydrate (420 mg, 10.0 mmol, 10.0 equiv) in H_2O (5 mL) was added. The white suspension was stirred at room temperature for 3 h, and diluted with EtOAc (50 mL). The aqueous layer was extracted with EtOAc (10 mL×3), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to provide yellowish solid, which was used as the crude without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 12.10 (br s, 1H), 8.26 (s, 1H), 6.55 (br s, 15% rotamer peaks), 6.45 (d, *J* = 8.4 Hz, 1H), 4.80 (dd, *J* = 9.7, 6.7 Hz, 1H), 4.69 (br s, 15% rotamer peaks), 2.17 (m, 1H), 1.35 (s, 9H), 0.90 (dd, *J* = 34.1, 6.8 Hz, 6H).

Boc-protected amine **109** (411 mg, 1.50 mmol, 1.5 equiv) was treated with neat TFA (6 mL). After stirring at room temperature for 10 min, the reaction was concentrated, and solvent exchanged with toluene three times to provide the amine TFA salt as a white solid. This amide TFA salt should be prepared right before the coupling.

The crude carboxylic acid and the crude TFA salt were combined in a 50 mL round bottom flask, and dry DCM (20 mL) was added. Et_3N (420 μL, 3.0 mmol, 3.0 equiv), HOBt (229 mg, 1.50 mmol, 1.5 equiv), and EDC (287 mg, 1.50 mmol, 1.5 equiv) were added sequentially. The reaction was stirred at room temperature for 24 h, and diluted with EtOAc (50 mL) and 1 M HCl (30 mL). The aqueous layer was extracted with EtOAc (30 mL×3), and the combined organic layers were washed with H_2O (30 mL×2), sat. $NaHCO_3$ (20 mL), brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. Purification by flash chromatography (1:1 hexanes:EtOAc, then 1:2 hexanes:EtOAc) provided keto amide **124** (434 mg, 99%) as a colorless sticky oil.

R_f = 0.15 in 1:2 hexanes:EtOAc. **^{1}H NMR** (500 MHz, CD_3CN) δ 10.06 (s, 1H), 8.28 – 8.23 (m, 1H), 8.22 (s, 1H), 8.17 (d, *J* = 3.2 Hz, 1H), 7.77 (s, 1H), 7.59 – 7.45 (m, 1H), 7.33 – 7.16 (m, 2H), 5.92 (d, *J* = 8.5 Hz, 1H), 4.72 (d, *J* = 5.2 Hz, 2H), 4.64 (t, *J* = 8.0 Hz, 1H), 2.29 – 2.11 (m, 2H), 1.39 (s, 9H), 0.97 (d, *J* = 6.8 Hz, 3H), 0.89 (d, *J* = 6.8 Hz, 3H). **^{13}C NMR** (75 MHz, CD_3CN) δ 190.24, 165.35, 161.28, 156.59, 141.98, 137.48, 136.89, 133.86, 126.42, 124.38, 123.33, 122.41, 115.31, 113.09, 80.08, 55.63, 46.47, 32.81, 28.53, 19.27, 18.65. **IR** (cm^{-1}) 3289, 2966, 2929, 2872, 1699, 1638, 1605.

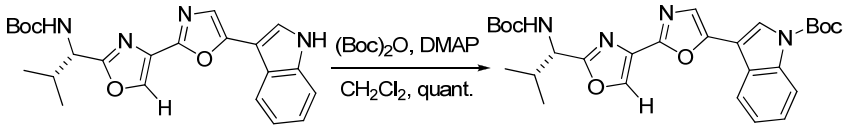
Bis-Oxazole Indole 125:



Et_3N (270 µL, 1.93 mmol, 5.0 equiv), followed by a solution of keto amide **124** (170 mg, 0.386 mmol, 1.0 equiv) in dry CH_2Cl_2 (6 mL), were added dropwise over 10 min to a stirred solution of PPh_3 (253 mg, 0.965 mmol, 2.5 equiv) and C_2Cl_6 (228 mg, 0.965 mmol, 2.5 equiv) in dry CH_2Cl_2 (2 mL) at 0 °C. The reaction was allowed to warm up to room temperature and stirred overnight (24 h). The yellow solution became dark brown. The reaction was diluted with CH_2Cl_2 (30 mL) and H_2O (20 mL), and the aqueous layer was extracted with CH_2Cl_2 (10 mL×3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to provide a bloody brown oil. Purification by flash chromatography (2:1 hexanes:EtOAc) provided bis-oxazole indole **125** (106 mg, 65%) as a yellowish solid.

R_f = 0.35 in 1:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.07 (br s, 1H), 8.00 (s, 1H), 7.73 (d, *J* = 7.3 Hz, 1H), 7.47 (d, *J* = 2.1 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.18 – 7.07 (m, 2H), 5.30 (d, *J* = 9.2 Hz, 1H), 4.91 (s, 12% rotamer peaks), 4.73 (dd, *J* = 9.1, 6.0 Hz, 1H), 4.57 (s, 12% rotamer peaks), 2.24 – 2.01 (m, *J* = 13.1, 6.5 Hz, 1H), 1.32 (s, 9H), 0.83 (t, *J* = 6.5 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 165.26, 155.69, 152.81, 148.30, 137.56, 136.45, 130.78, 124.14, 123.04, 122.87, 121.05, 120.99, 119.87, 111.91, 105.04, 80.21, 54.54, 33.06, 28.42, 18.82, 18.15. **IR** (cm^{-1}) 3375, 3199, 2953, 2925, 1699.

Boc-Protected Bis-Oxazole Indole 126:



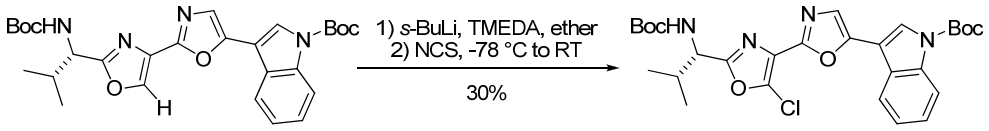
125 **126**

Bis-oxazole indole **125** (82 mg, 0.194 mmol, 1.0 equiv) and catalytic amount of DMAP (4.7 mg, 0.039 mmol, 2 mol%) were dissolved in dry CH_2Cl_2 (2 mL), and Boc_2O (47 mg, 0.214 mmol, 1.1 equiv) was added. After stirring at room temperature for 1 h, the reaction was concentrated to provide a yellow oil. Purification by flash chromatography (5:1 hexanes:EtOAc) provided Boc-protected bis-oxazole indole **126** (101 mg, quantative) as a colorless sticky oil.

R_f = 0.15 in 5:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.21 (s, 2H), 7.98 (s, 1H), 7.81 (d, *J* = 7.6 Hz, 1H), 7.47 (s, 1H), 7.40 (td, *J* = 7.7, 1.1 Hz, 1H), 7.35 (td, *J* = 7.7, 1.1 Hz, 1H), 5.37 (d, *J* = 9.2 Hz, 1H), 4.85 (dd, *J* = 9.2, 5.9 Hz, 1H), 4.74 – 4.63 (br s, 10% rotamer peaks), 2.24 (m, 1H), 1.69 (s, 9H), 1.44 (s, 9H), 1.03 – 0.91 (m, 6H). **^{13}C NMR**

(75 MHz, $CDCl_3$) δ 165.46, 155.50, 153.85, 149.37, 146.35, 138.09, 135.65, 130.59, 126.63, 125.32, 123.58, 123.56, 123.19, 120.08, 115.67, 109.08, 84.63, 80.02, 54.41, 33.13, 28.39, 28.26, 18.81, 18.08. **IR** (cm^{-1}) 3354 (br), 2958, 2921, 2872, 1740, 1703.

Chlorooxazole 127:



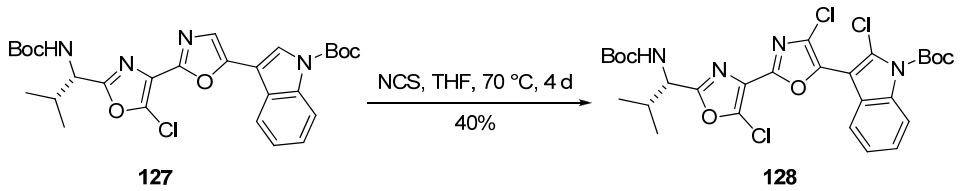
126 **127**

Boc-protected bis-oxazole indole **126** (90 mg, 0.172 mmol, 1.0 equiv) was charged in a 25 mL round bottom flask, and dry Et_2O (9 mL) and fresh distilled TMEDA (103 μL, 0.689 mmol, 4.0 equiv) were added via syringe. The colorless solution was cooled in a dry ice / acetone bath, and *s*-BuLi (424 μL of 1.3 M solution in hexanes, 0.551 mmol, 3.2 equiv) was added dropwise, and the resultant dark brown solution was stirred at -78 °C for 1 h. NCS (23 mg, 0.689 mmol, 4.0 equiv) in dry THF (2 mL) was cannulated into the reaction, and the resultant yellow solution was stirred at -78 °C for an additional 1 h, before quenched with sat. NH_4Cl (5 mL). The reaction was diluted with Et_2O (30 mL), and the organic layer was washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. Purification by flash chromatography (5:1 hexanes:EtOAc) provided chlorooxazole **127** (29 mg, 30%) as a yellowish oil.

$\mathbf{R_f}$ = 0.24 in 5:1 hexanes:EtAOc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.20 (d, *J* = 7.6 Hz, 1H), 7.99 (s, 1H), 7.86 (d, *J* = 7.7 Hz, 1H), 7.50 (s, 1H), 7.39 (td, *J* = 7.2, 1.2 Hz, 1H), 7.34 (td, *J* = 7.5, 1.0, 1H), 5.29 (d, *J* = 9.4, 1H), 4.94 – 4.85 (br s, 4% rotamer peaks),

4.81 (dd, J = 9.3, 5.9 Hz, 1H), 4.67 – 4.52 (br s, 4% rotamer peaks), 2.23 (m, 1H), 1.69 (s, 9H), 1.44 (s, 9H), 0.97 (dd, J = 6.6, 3.8 Hz, 6H). **IR** (cm^{-1}) 3427, 3346, 3138, 2970, 2933, 1724, 1634, 1450.

Tri-Chlorinated Bis-Oxazole Indole 128:

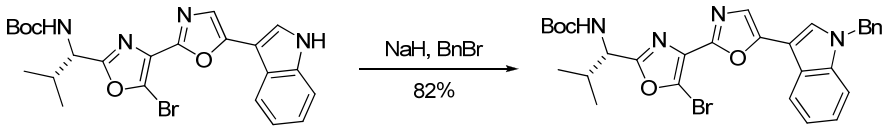


127 **128**

Chlorooxazole **127** (20 mg, 0.036 mmol, 1.0 equiv) and NCS (19 mg, 0.14 mmol, 4.0 equiv) were charged in a 10 mL sealable test tube, which was evacuated and refilled with Ar three times, and dry THF (2 mL) was added. The test tube was sealed with the screw cap, and place into a 70 °C oil bath overnight (48 h). The reaction was diluted with Et_2O (30 mL), washed with H_2O (5 mL×3), brine (5 mL), dried over Na_2SO_4, filtered, and concentrated to provide a yellow oil. Purification by flash chromatography (10:1 hexanes:EtOAc) provided tri-chlorinated bis-oxazole indole **128** (9 mg, 40%) as a colorless oil.

$\mathbf{R_f}$ = 0.25 in 10:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.12 (d, J = 8.4 Hz, 1H), 7.55 (d, J = 7.7 Hz, 1H), 7.36(td, J = 7.2, 1.24, 1H), 7.29 (td, J = 7.6, 0.8, 1H), 5.27 (t, J = 7.3, 1H), 4.79 (dd, J = 9.2, 5.8, 1H), 2.21 (m, 1H), 1.70 (s, 9H), 1.43 (s, 9H), 0.96 (two d, J = 5.9 Hz, 7H).

Bis-Oxazole Indole 126:



118 **131**

Bis-oxazole indole **126** (35 mg, 0.07 mmol, 1.0 equiv) and NaH (7.0 mg, 60% suspension in mineral oil, 0.175 mmol, 2.5 equiv) were charged in a 10 mL round bottom flask, and dry THF (2 mL) was added. The mixture was stirred at room temperature for 10 min, before the addition of BnBr (9 μL, 0.077 mmol, 1.1 equiv) via syringe. The reaction was quenched with sat. NH_4Cl (5 mL), diluted with Et_2O (20 mL), and the aqueous layer was extracted with Et_2O (10 mL×2). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to provide a yellow oil. Purification by flash chromatography (2:1 hexanes:EtOAc) provided bis-oxazole indole **126** (34 mg, 82%) as a colorless oil.

$\mathbf{R_f}$ = 0.22 in 3:1 hexanes:EtOAc; ^{1}**H NMR** (500 MHz, $CDCl_3$) δ 7.97 – 7.88 (m, 1H), 7.57 (s, 1H), 7.39 (s, 1H), 7.35 – 7.24 (m, 6H), 7.17 – 7.10 (m, 2H), 5.37 (s, 2H), 5.30 (d, *J* = 9.4 Hz, 1H), 4.82 (dd, *J* = 9.4, 5.9 Hz, 1H), 2.28 – 2.15 (m, 1H), 1.43 (s, 9H), 0.95 (dd, *J* = 6.7, 4.1 Hz, 6H). ^{13}**C NMR** (75 MHz, $CDCl_3$) δ 165.84, 155.47, 151.79, 148.40, 136.90, 136.69, 129.05, 128.08, 126.95, 126.50, 124.93, 123.08, 121.41, 121.12, 120.74, 120.41, 110.48, 104.54, 80.23, 54.51, 50.54, 33.01, 28.44, 18.93, 18.01. **IR** (cm^{-1}) 3424, 3318, 2978, 2925, 2876, 1704.

4.9 References and Notes

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5 Synthesis of the Aromatic Core of Diazonamide A

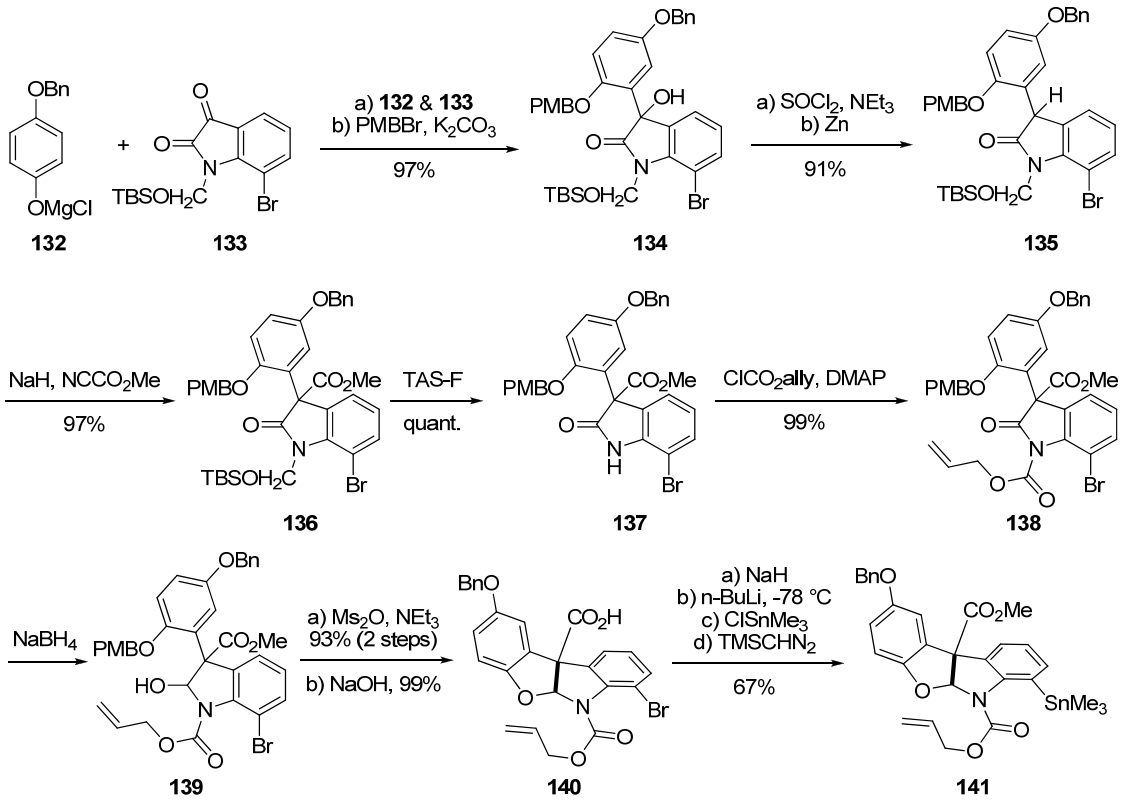
5.1 Introduction

The right hand macrocycle of diazonamide A consists of a highly rigid heterocyclic ring system, and is also difficult to construct. Numerous research groups have contributed synthetic efforts to the formations of the bis-oxazole-indole moiety, but, besides the four reported total syntheses, only a few successful syntheses of the complete right hand macrocycle were reported.

5.2 Vedjes's Synthesis of Right Hand Macrocycle

Vedjes reported the synthesis of the heteroaromatic core of the incorrect, initially proposed Fenical and Clardy structure of diazonamide A using a Dieckmann-type cyclization in 2001.[1] Later, he found that this method is also viable for the synthesis of the correct structure (Scheme 5.1).[2] This synthesis proceeded by nucleophilic addition of chloromagnesium phenolate **132** to bromoisatin **133** followed by protection of the phenol as the PMB ether to afford tertiary alcohol **134**. The tertiary alcohol of **134** was chlorinated ($SOCl_2$) and reduced (Zn dust) to provide compound **135**. This compound was deprotonated with NaH, and the enolate was trapped with Mander's regent (NCCOOMe) to provide ester **136**. The siloxymethyl protecting group of **136** was then removed with TAS-F, and the oxindole nitrogen was reprotected using *N*-allyl chloroformate to provide **138**. Reduction of the carbonyl group of oxindole **138** with

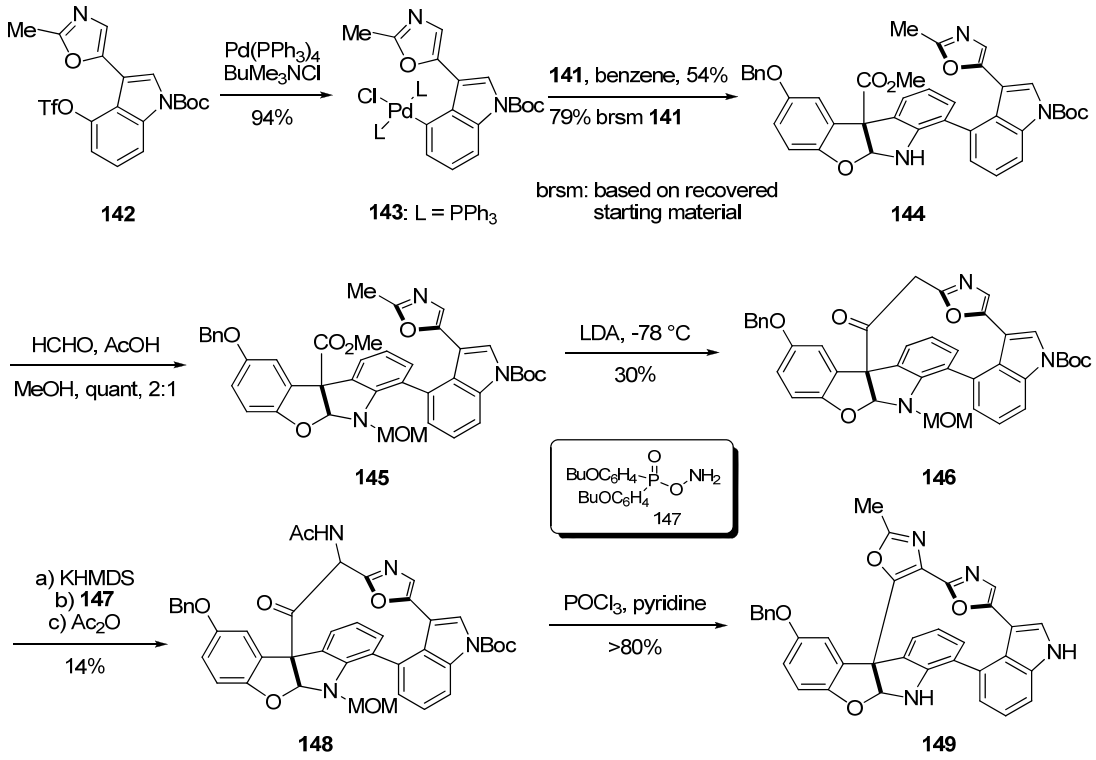
$NaBH_4$ provided alcohol **139**, which was treated with Ms_2O to activate the hemiaminal with concomitant loss of the PMB group and cyclization to form the cyclized hemiaminal. Saponification of the methyl ester (NaOH) provided carboxylic acid **140**, which was temporarily protected as a sodium carboxylate, and treated with *n*-BuLi to facilitate lithium-halogen exchange. The resulting aryl lithium species was trapped with $ClSnMe_3$ and methylated with $TMSCHN_2$ to provide stannane **141**.



Scheme 5.1 Vedjes's Synthesis of Hemiaminal **141**

Stille coupling of stannane **141** using stoichiometric amounts of Pd complex **143**, which was generated from oxidative addition of $Pd(Ph_3P)_4$ to triflate **142**, provided biaryl **144** with the loss of the allyl carbamate protecting group (Scheme 5.2). The remaining conditions in the synthesis are incompatible with the hemiaminal moiety, and as such, the

free amine was protected with a MOM group. Dieckmann-type condensation using LDA provided macrocycle **146** in 30% yield. Enolate amination using diarylphosphinyl-hydroxylamine **147** and KHMDS as the base, followed by protection with Ac_2O, afforded acetamide **148**. This compound was then cyclized using Nicolaou's oxazole synthesis ($POCl_3$, pyridine)[3] to provide bis-oxazole indole **149** bearing the complete heterocyclic core and the hemiaminal moiety as a 1:1 mixture of diastereomers.

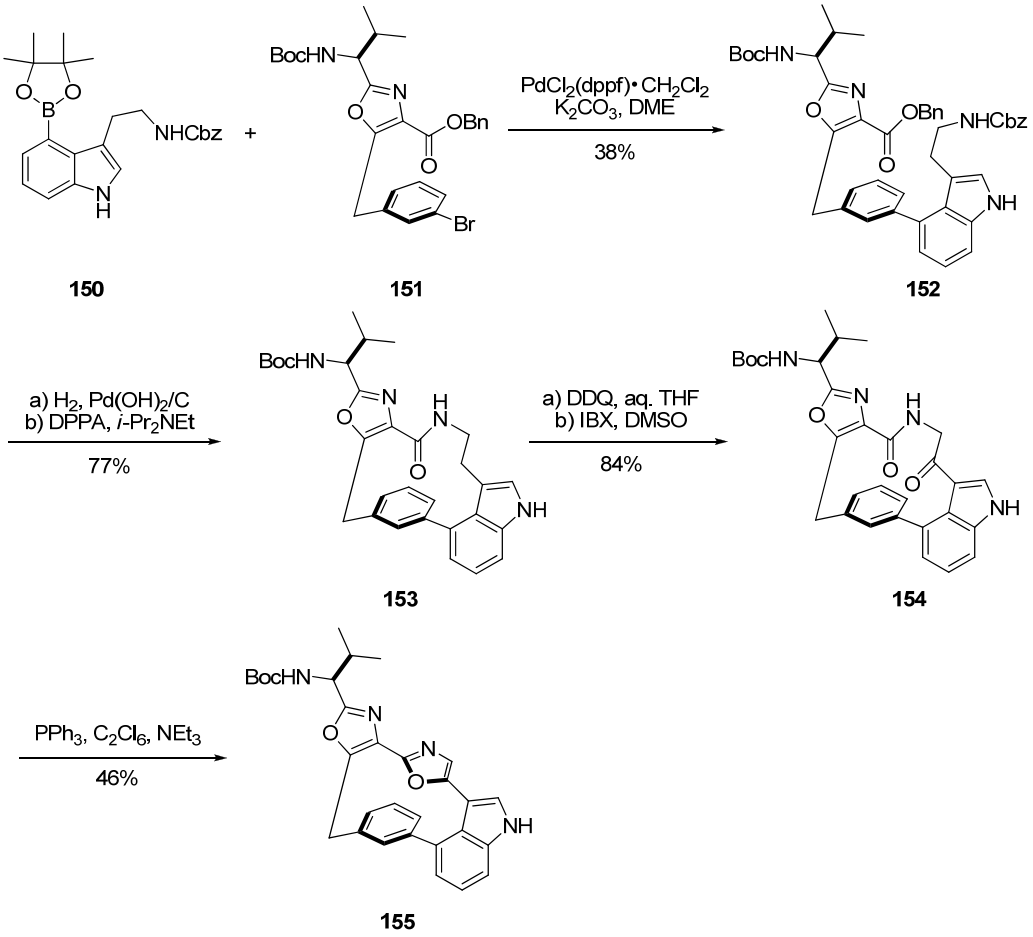


Scheme 5.2 Vedjes's Synthesis of Heterocyclic Core of Diazonamide A

5.3 Moody's Synthesis of Right Hand Macrocycle

In 2005, Moody reported his efforts towards the synthesis of the right hand macrocycle of diazonamide A (Scheme 5.3).[4] His synthesis began with a Suzuki coupling

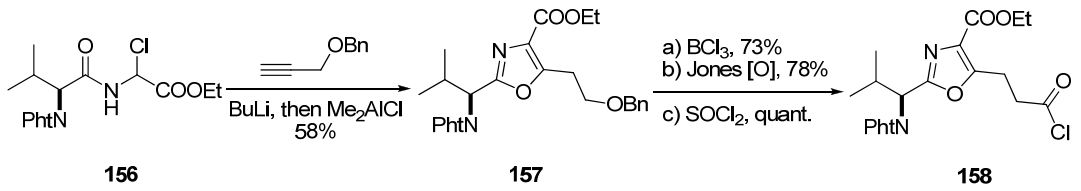
of pinacolato boronic ester **150** and aryl bromide **151** to provide biaryl **152**. Both the terminal protecting groups, Cbz and Bn, were removed via hydrogenolysis using Pearlman's catalyst ($Pd(OH)_2$), and the resulting amino acid was cyclized (DPPA, Hunig's base) to afford macrolactam **153**.[5] Yonemitsu benzylic oxidation of **153** with DDQ to a benzylic alcohol, followed by further oxidation with IBX furnished keto amide **154**, which was cyclized to form oxazole **155** via Wipf's oxazole synthesis (PPh_3, C_2Cl_6, and Et_3N).[6,7] Moody's synthesis of bis-oxazole indole macrocycle **155** did not incorporate the formation of the challenging C10 quaternary center of diazonamide A.



Scheme 5.3 Moody's Synthesis of Bis-Oxazole Indole Macrocycle **155**

5.4 Ciufolini's Synthesis of Right Hand Macrocycle

In 2011, Ciufolini reported another approach to the bis-oxazole indole macrocycle of the diazonamides.[8] The synthesis relied on an oxazole formation (Scheme 5.4) developed in his group. [9] Condensation of valine-derived chloroglycinate **156** with the dimethylaluminum acetylide prepared from benzyl propargyl ether, provided enantiopure oxazole **157** (Scheme 5.4). This compound was debenzylated (BCl_3), oxidized (Jones reagent), and chlorinated ($SOCl_2$) to afford acid chloride **158** ready for coupling with other fragments.

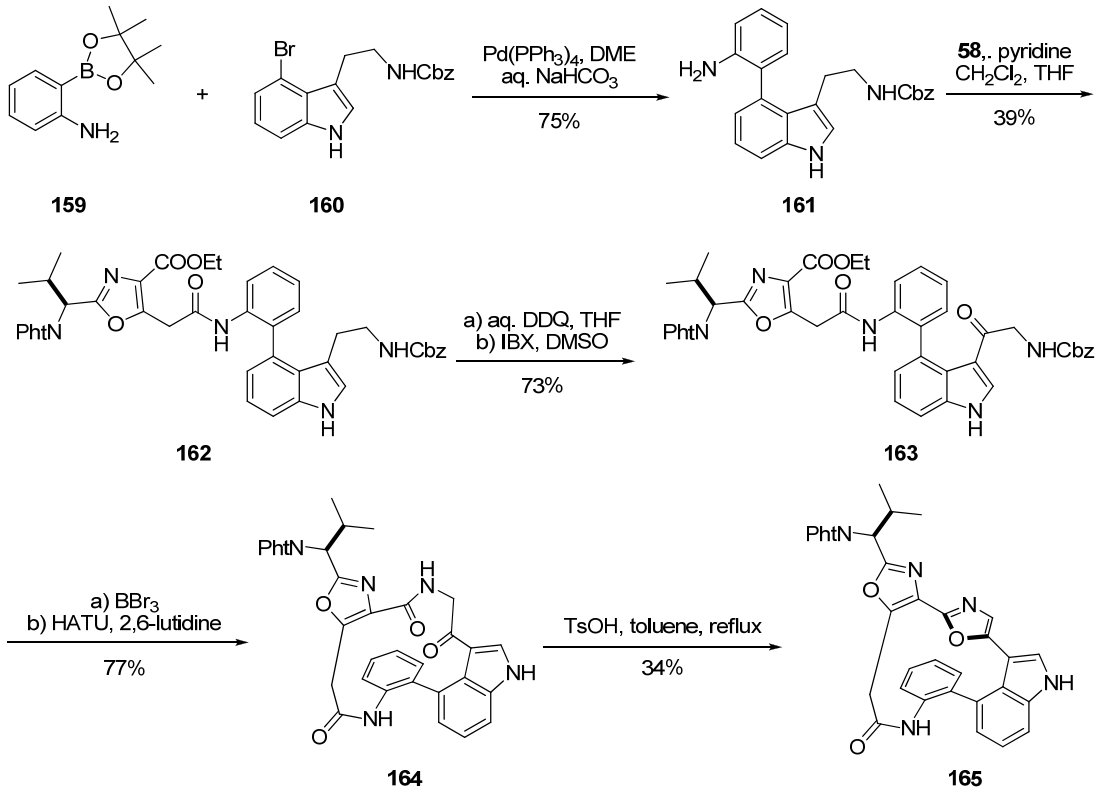


156 **157** **158**

Scheme 5.4 Ciufolini Oxazole Synthesis

Suzuki coupling of commercially available boronic ester **159** and 4-bromo tryptamine derivative **160** provided biaryl amine **161** as a 1:1 mixture of atropisomers (Scheme 5.5). This was coupled with acid chloride **158** to furnish amide **162**. A two-step Yonemitsu benzylic oxidation similar to that of Moody (DDQ, and then IBX) converted indole **162** to ketone **163**. After deprotection of the Cbz protecting group of **163** with BBr_3, intramolecular amide bond formation under peptide coupling conditions (HATU in 2,6-lutidine) afforded macrolactam **164**. Finally, a *p*-TsOH mediated Robinson-Gabriel oxazole formation provided macrocycle **165** as a 1:1 mixture of atropisomers bearing the

complete bis-oxazole indole moiety. As above, this synthesis did not include the formation of the highly hindered quaternary C10 of diazonamide A.

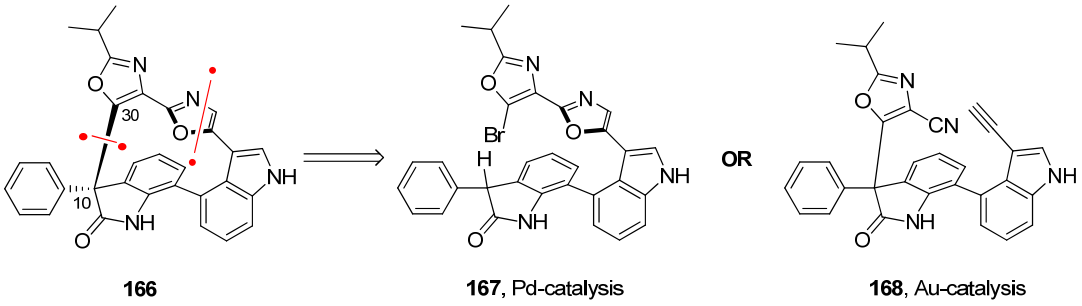


Scheme 5.5 Ciufolini's Synthesis of Bis-Oxazole Indole Macrocycle **165**

5.5 Our Approach to Right Hand Macrocycle

After completing the formal synthesis of diazonamide A via a diastereoselective α-arylation to build the left hand macrocycle, I planned to develop a versatile method to construct the right-hand aromatic core including the C10 quaternary center and the complete right hand heterocyclic ring system on a model. We can then apply this method to the total synthesis of diazonamide A using the intermediate I previously prepared in our formal synthesis.

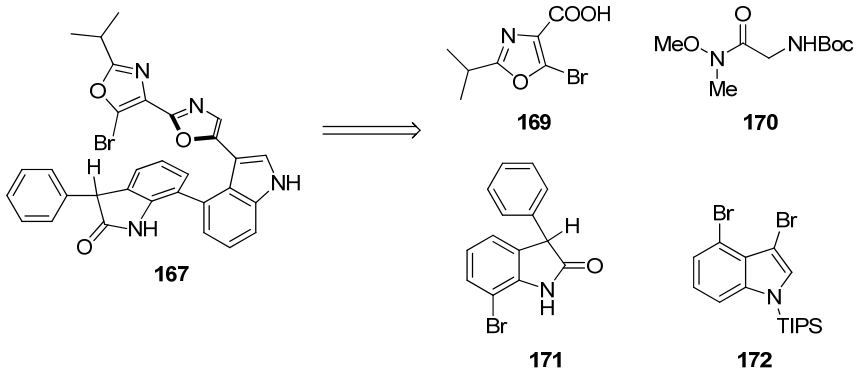
We targeted the synthesis of compound **166** as a model (Scheme 5.6). I envisioned that this macrocycle could be constructed either via an intramolecular Pd-catalyzed α-arylation of compound **167**, or via an intramolecular Au-catalyzed [2+2+1] oxazole formation on compound **168** using the chemistry first described by Professor Liming Zhang and coworkers.[10]



Scheme 5.6 Proposed Syntheses of the Right Hand Macrocycle **166**

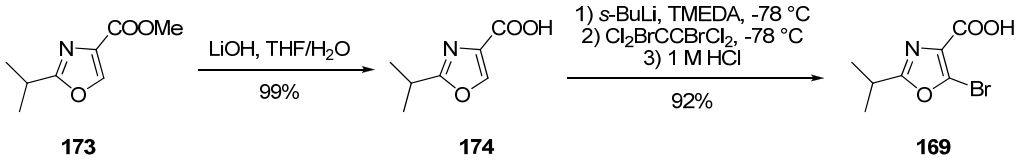
5.5.1 Pd-Catalyzed α-Arylation Approach

We have successfully developed intermolecular Pd-catalyzed α-arylations of 3-aryloxindoles and various aryl bromides, and applying intramolecular version of this method to the synthesis of our model system seems promising. In our retrosynthetic analysis, cyclization precursor **167** can be synthesized from four fragments of almost equivalent complexity as showed in Scheme 5.7.



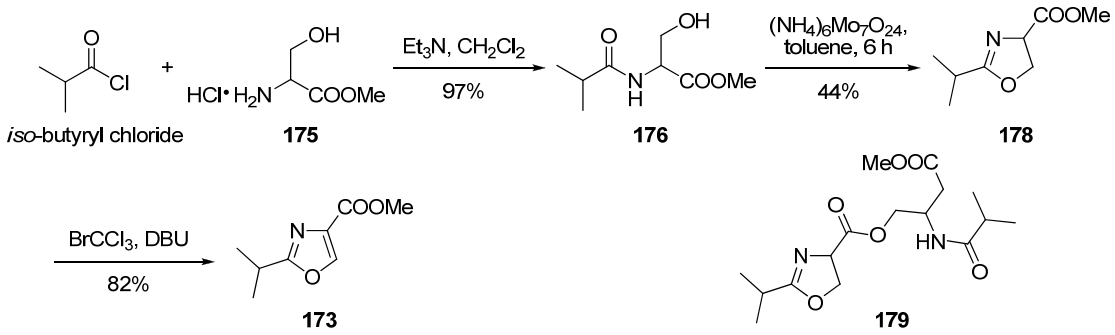
Scheme 5.7 Retrosynthetic Analysis of Pd-Catalyzed Cyclization Precursor **167**

Carboxylic acid **169** was prepared from an oxazolyl nitrile via reduction (DIBAL-H), followed by Pinnick-Lindgren oxidation, similar to the preparation of carboxylic acid **115** (Scheme 4.3). Introduction of a bromine atom to an oxazole has been accomplished by a Sandmeyer-type reaction on an amino oxazole; however, this reaction was proved to be low-yielding in our hands. I, therefore, synthesized carboxylic acid **169** from a known compound **173** as described in Scheme 5.8.[11] Saponification of **173** using LiOH provided carboxylic acid **174**, which directed *s*-BuLi to selectively deprotonate the *ortho* position of the carboxylic acid. Trapping the resulting lithiated oxazole with $C_2Br_2Cl_4$ provided bromooxazole **169** in good yield, after acidic work-up. Attempts to introducing a chlorine atom by trapping the lithiated oxazole with NCS or trichloroisocyanuric acid (TCA) provided complex mixtures. Pd-catalyzed carboxylic acid directed halogenation methods developed by Jin-Quan Yu and coworkers (cat. $Pd(OAc)_2$, IOAc, *n*-Bu_4NBr, DCE, 100 °C, 24 h) failed to provide bromooxazole **169**.[12] This carboxylic acid directed *ortho* metalation (DoM) method[13] to introduce a bromine atom was more efficacious than the low-yielding Sandermeyer-type reactions previously used. Further this provided the desired oxazolyl carboxylic acids ready for peptide coupling without the need to hydrolyze a nitrile, sometimes problematic, as in our previous synthesis.



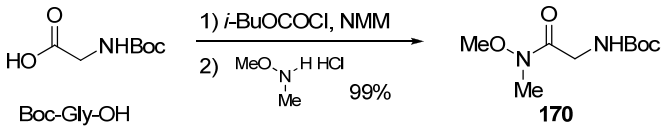
Scheme 5.8 Synthesis of Carboxylic Acid **169**

Compound **173** was prepared as showed in Scheme 5.9. Condensation of *iso*-butylryl chloride and (±)-serine methyl ester HCl salt (**175**) provided amide **176**, which was cyclized to form the oxazoline using DAST or Deoxo-Fluor®.[14] While these reagents are commercially available, they are very expensive. Ishihara has developed a much more economical method using a catalytic amount of ammonium molybdate with azeotropic removal of water in refluxing toluene.[15] Compound **176** was cyclized to form oxazoline **178** along with some dimerized side product **179** using Ishihara's conditions. Although this reaction only provided the desired product in moderate yield (44%), it was more economical compared to the use of the expensive reagents, DAST and Deoxo-Fluor®. Later, oxazole **173** was obtained after oxidation of oxazoline **178** using Williams' conditions.[16]



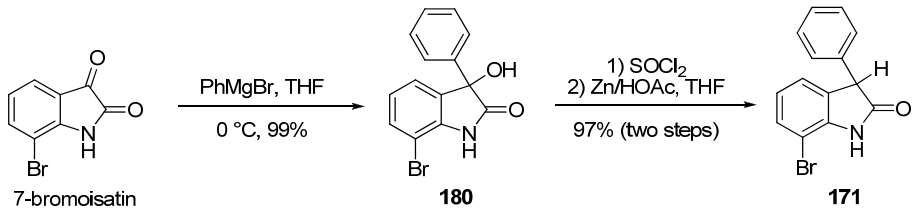
Scheme 5.9 Synthesis of Ester **173**

Weinreb amide **170** was synthesized from commercially available Boc-protected glycine with methyl methoxy amine HCl salt in near quantitative yield (*i*-BuOCOCl and *N*-methyl morpholine (NMM)).[17]



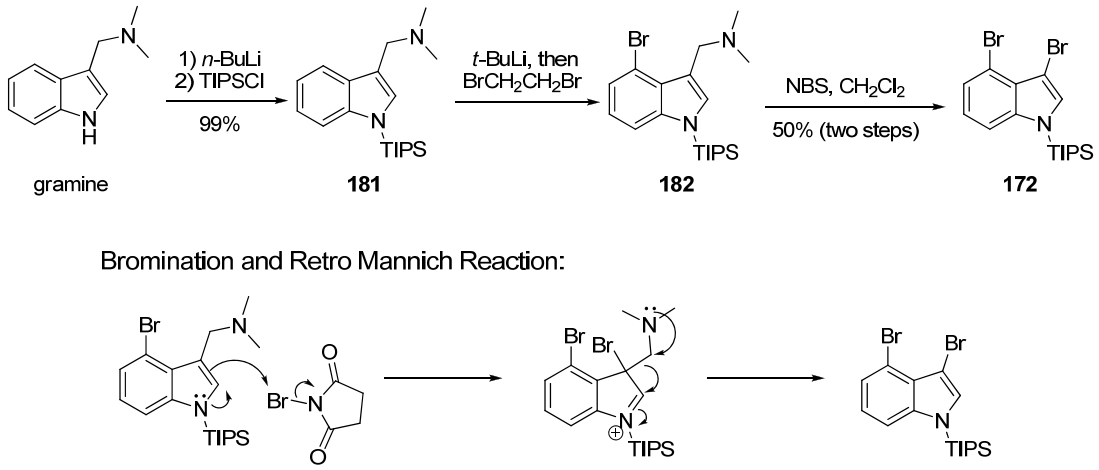
Scheme 5.10 Synthesis of Weinreb Amide **170**

The addition of PhMgBr to 7-bromoisatin provided alcohol **180** after acidic work up (Scheme 5.11). 3-Phenyloxindole **171** was then obtained in good yield by chlorination (neat $SOCl_2$) of alcohol **180**, and reduction (Zn/HOAc) of the resultant tertiary chloride.



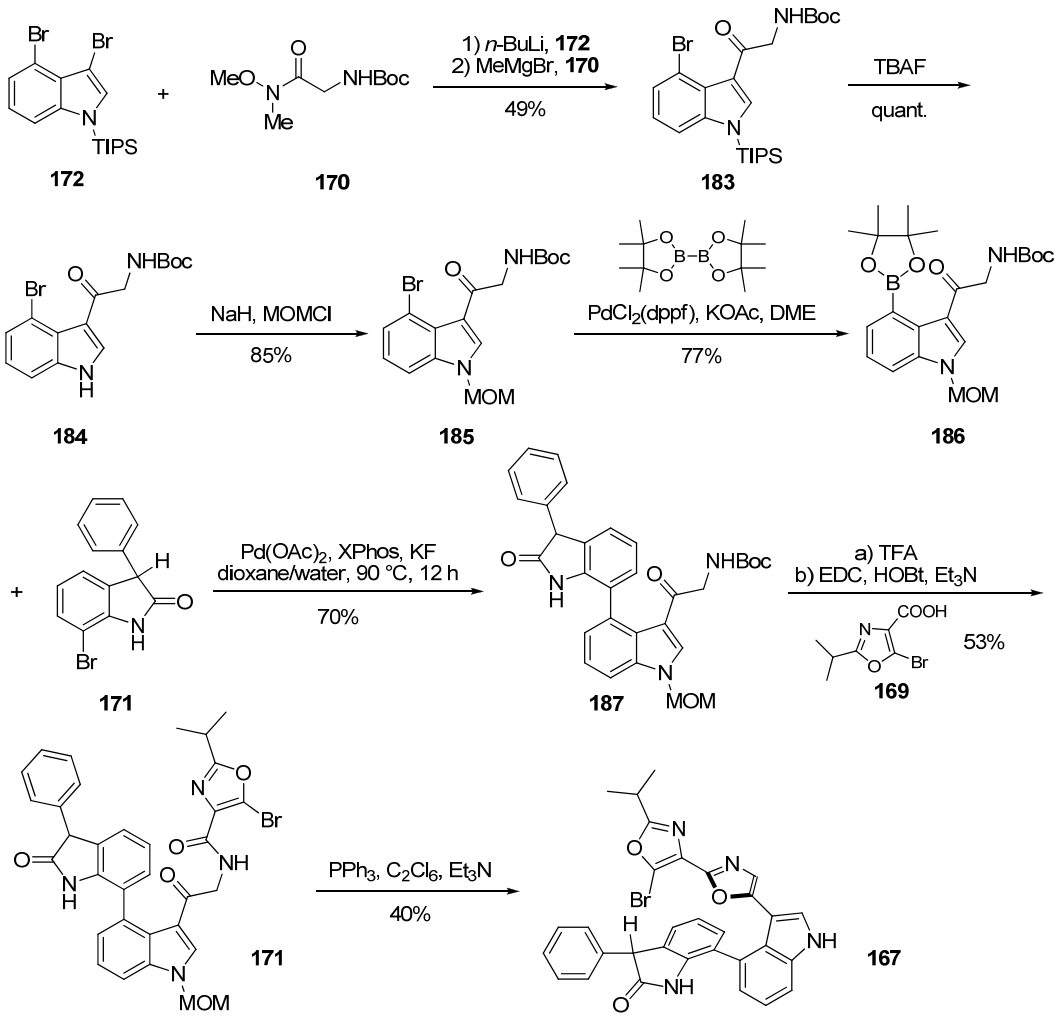
Scheme 5.11 Synthesis of 3-Aryloxindole **171**

Synthesis of dibromoindole **172** relied on the directed *ortho* metalation (DoM) and retro Mannich reaction sequence of gramine and its derivatives developed by Iwao and Snieckus (Scheme 5.12).[18] The indole nitrogen of gramine was first protected with a bulky TIPS group in order to block the 2-position of gramine and allow directed metalation at the 4-position. Compound **181** was then treated with *t*-BuLi to metalate the 4-position, and trapped using1,2-dibromoethane to afford bromo gramine derivative **182**. Upon exposure to NBS, compound **182** underwent a rapid retro Mannich reaction to provide dibromoindole **172**. The mechanism of this transformation is shown in Scheme 5.12.



Scheme 5.12 Synthesis of Dibromoindole **172**

With these four fragments in hand, synthesis of cyclization precursor **167** was conducted in a convergent fashion (Scheme 5.13). Selective metalation at the 3-position of dibromoindole **172**,[19,20] followed by trapping with the magnesium salt of Weinreb amide **170**,[21] provided ketone **183**. It is likely that treatment of dibromoindole **172** with 1 equivalent of *n*-BuLi results in an initial unselective lithium halogen exchange to yield a mixture of 3- and 4-lithated indoles. This mixture can then be converted to the more thermodynamically stable 3-lithiated indole via a rapid halogen dance reaction.[22] The TIPS group was found to be labile to the subsequent transformations, and as such was removed and the nitrogen was reprotected as the MOM aminal. The Miyaura borylation reaction was then used to convert bromide **185** to pinacolato boronic ester **186**, which was coupled with bromooxindole **171** via Suzuki coupling to afford biaryl **187**. After removing the Boc protecting group of **187** with neat TFA, the resultant amine TFA salt was coupled with carboxylic acid **169** under typical amide formation conditions (EDC/HOBt) to provide keto amide **171**. This compound was cyclized via the Wipf oxazole synthesis6,[7] to provide cyclization precursor **167** in moderate yield (40%).

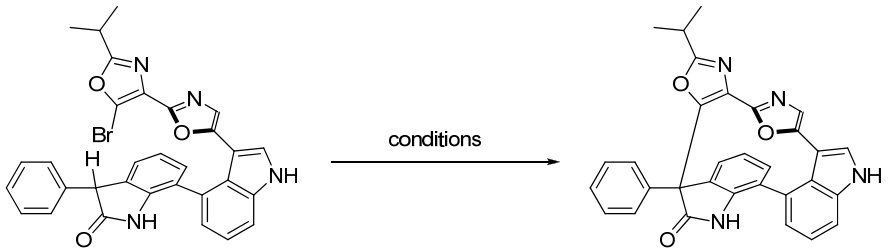


Scheme 5.13 Convergent Synthesis of Cyclization Precursor **167**

With cyclization precursor **167** in hand, I set out to study Pd-catalyzed α-arylations under a variety of conditions. Our typical intermolecular Pd-catalyzed α-arylation conditions provided complex mixtures (Table 5.1, entry 1). S_NAr conditions without Pd-catalyst only provided recovered starting material (entry 2). Pd-catalysis with a stronger base, LiHMDS (entry 3), in order to increase the concentration of the enolate, also provided complex mixtures; while a weaker base, Na_2CO_3 (entry 4), only provided recovered starting material. Furthermore, changing the palladium pre-catalyst and the ligands did not prove to be promising, which either just provided recovered starting

material (entries 5 & 6) or some debromination by-product of starting material (entry 7). Similar Pd-catalyzed conditions were also applied to keto amide **171**; however, no desired α-arylation was observed.

Table 5.1 Attempted Cyclizations of Compound **167**

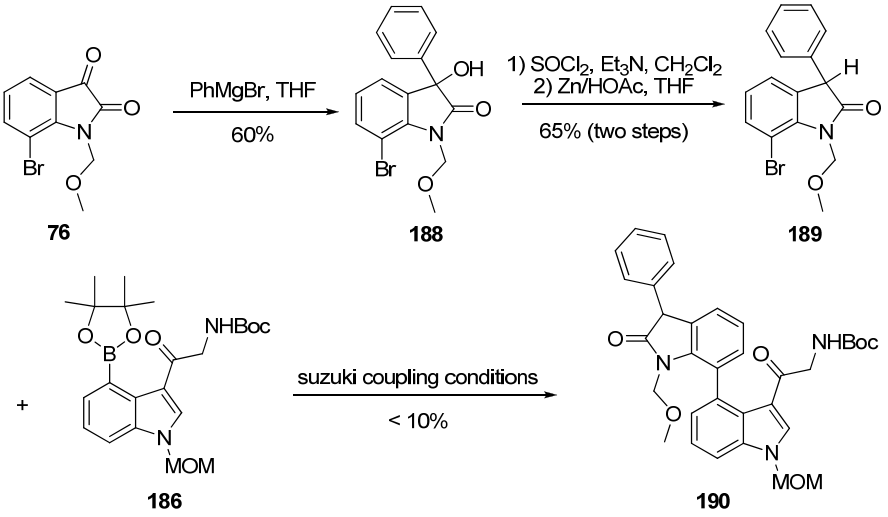


Entry	Conditions	Results[a]
1	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, Cs_2CO_3, toluene, 90 °C, 3 h	complex mixtures
2	LiHMDS (5 equiv), DMF, 0 °C to 65 °C, 15 h	recovered **167**
3	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, LiHMDS, toluene, 90 °C, 20 h	complex mixtures
4	$Pd(OAc)_2$, *t*-Bu_3PHBF_4, Na_2CO_3, toluene, 90 °C, 20 h	recovered **167**
5	$Pd(OAc)_2$, RuPhos, Na_2CO_3, toluene, 90 °C, 20 h	recovered **167**
6	$Pd(dba)_2$, *t*-Bu_3PHBF_4, Na_2CO_3, toluene, 90 °C, 20 h	recovered **167**
7	$PdMe_2$(TMEDA), *t*-Bu_3PHBF_4, Na_2CO_3, toluene, 90 °C, 20 h	recovered **167**[b]

[a] Determined by the crude NMR. [b] Some debromination of **167** was observed.

The failure of the Pd-catalyzed α-arylations of cyclization precursor **167** indicated that the unprotected oxindole nitrogen might be detrimental to the cyclizations. Protecting the oxindole nitrogen with an appropriate group might be a way to solve this problem. Protection of the oxindole nitrogen at late stage (protecting compound **167** lead to complex mixtures) was unsuccessful due to the acidic C3-H on the oxindole. Therefore, I had to use the protected oxindole from the beginning of the synthesis. *N*-MOM-7-Bromoisatin (**76**) was arylated with PhMgBr and the resulting tertiary alcohol was converted to **189** by chlorination ($SOCl_2$, Et_3N) and reduction (Zn/HOAc, Scheme 5.14). Unfortunately, Suzuki coupling of **189** with **186** only provided the desired biaryl product (**190**) in very low yield under a variety of Pd-catalyzed conditions, possibly due to steric

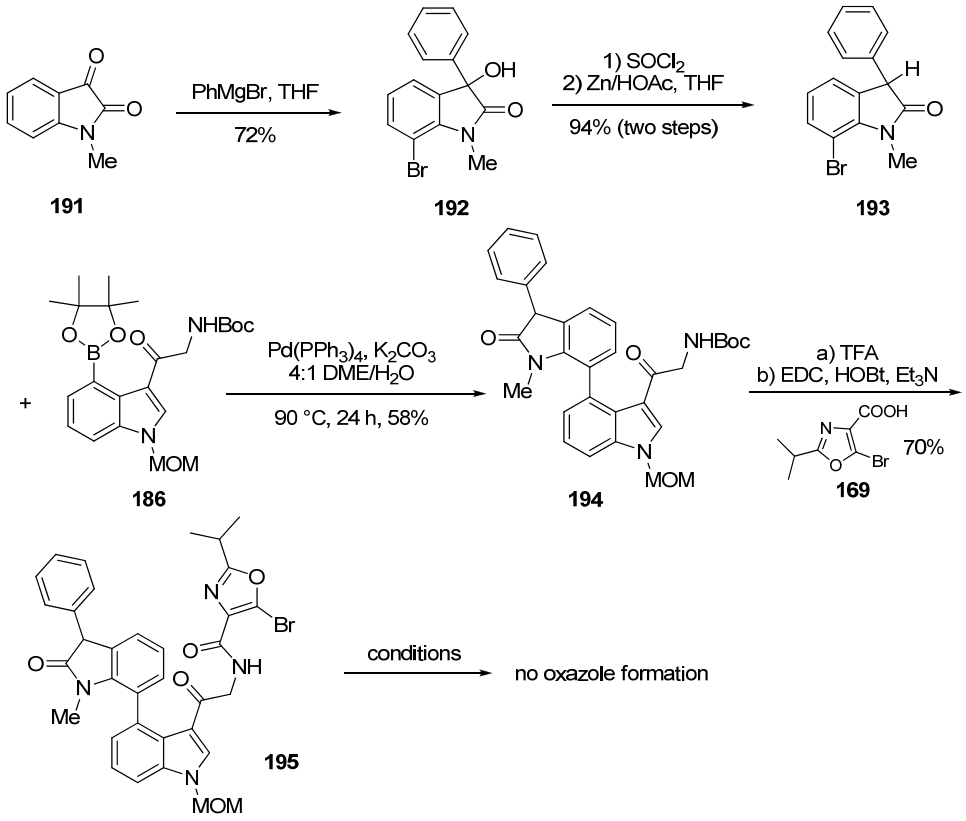
hinderance of the formation of the biaryl C-C bond. Therefore, I sought a protecting group smaller than a MOM group and settled on the use of a methyl group.



Scheme 5.14 Synthesis of MOM-Protected Biaryl **190**

A methyl group is not typically considered as a protecting group; however, Nakatsuka has developed a useful method to remove the methyl group from an indole nitrogen via radical oxidation followed by hydrolysis.[23] I, therefore, synthesized *N*-methyl keto amide **195** (Scheme 5.15) starting from *N*-methyl isatin (**191**), which was subjected to PhMgBr to provide tertiary alcohol **192** after acidic work up. The alcohol was converted to 3-aryloxindole **193** via a two-step sequence, chlorination ($SOCl_2$) and reduction (Zn/HOAc). Suzuki coupling of bromide **193** and boronic ester **186** provided biaryl **194** in 58% yield using 10 mol% $Pd(PPh_3)_4$ and K_2CO_3 in 4:1 DME/H_2O. Different catalytic systems, e.g., $Pd(dppf)Cl_2$, K_2CO_3 in DME at reflux, only provided biaryl **194** in 35% yield. Interestingly, the same reaction conditions ($Pd(OAc)_2$, XPhos, KF, 10:1 dioxane/H_2O) used to couple compounds **171** and **186** only provided complex mixtures with trace amount of biaryl **194** (<5%). Coupling of the amine generated after

deprotection of compound **194** and carboxylic acid **169** using HOBt and EDC provided keto amide **195**. Surprisingly, keto amide **195** could not be cyclized to form the oxazole under a variety of conditions. It is likely that the methyl group on the oxindole nitrogen of compound **195** induced a conformation change, which raised the reaction barrier of the oxazole formation.



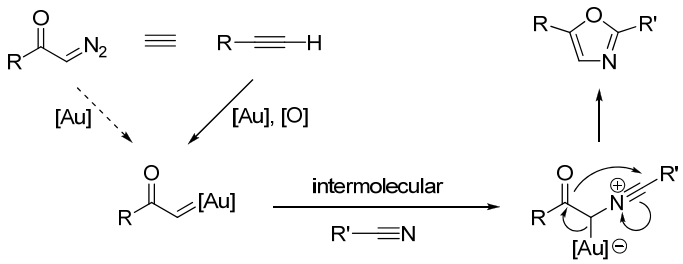
Scheme 5.15 Synthesis of *N*-Methyl Oxindole **195**

In summary, cyclization precursor **167** for Pd-catalyzed α-arylations was synthesized, and attempted cyclization under various conditions to form the right hand macrocycle of diazonamide A were studied. Unfortunately, no desired arylation was observed. Protecting the oxindole nitrogen of **167** with a MOM or methyl group was

unsuccessful for the preparation of the cyclization precursors. Attempted cyclization of the mono-oxzole substrates **171** and **195** were also unsuccessful.

5.5.2 Au-Catalyzed Oxazole Formation Approach

Recently, Liming Zhang and coworkers at UCSB reported a novel Au-catalyzed [2+2+1] oxazole synthesis employing a terminal alkyne, a nitrile, and an external oxidant. They only reported the intermolecular version of this reaction with either a large excess of a nitrile or the nitrile as the solvent.[10] They proposed the mechanism shown in Scheme 5.16 wherein the alkyne-gold catalyst complex is oxidized by an external oxidant to generate an α-keto gold carbenoid. This is a Fisher-type gold carbenoid that can be attacked by a weakly nucleophilic species such as a nitrile to produce a nitrilium. The ketone can then attack the nitrilium to form an oxazole and regenerated the gold catalyst. This carbenoid can also, in principle, be generated directly from a α-diazo ketone and a gold catalyst; however, generating the carbenoid from an alkyne renders this more convenient and somewhat safer than handling the potentially explosive α-diazo ketones.

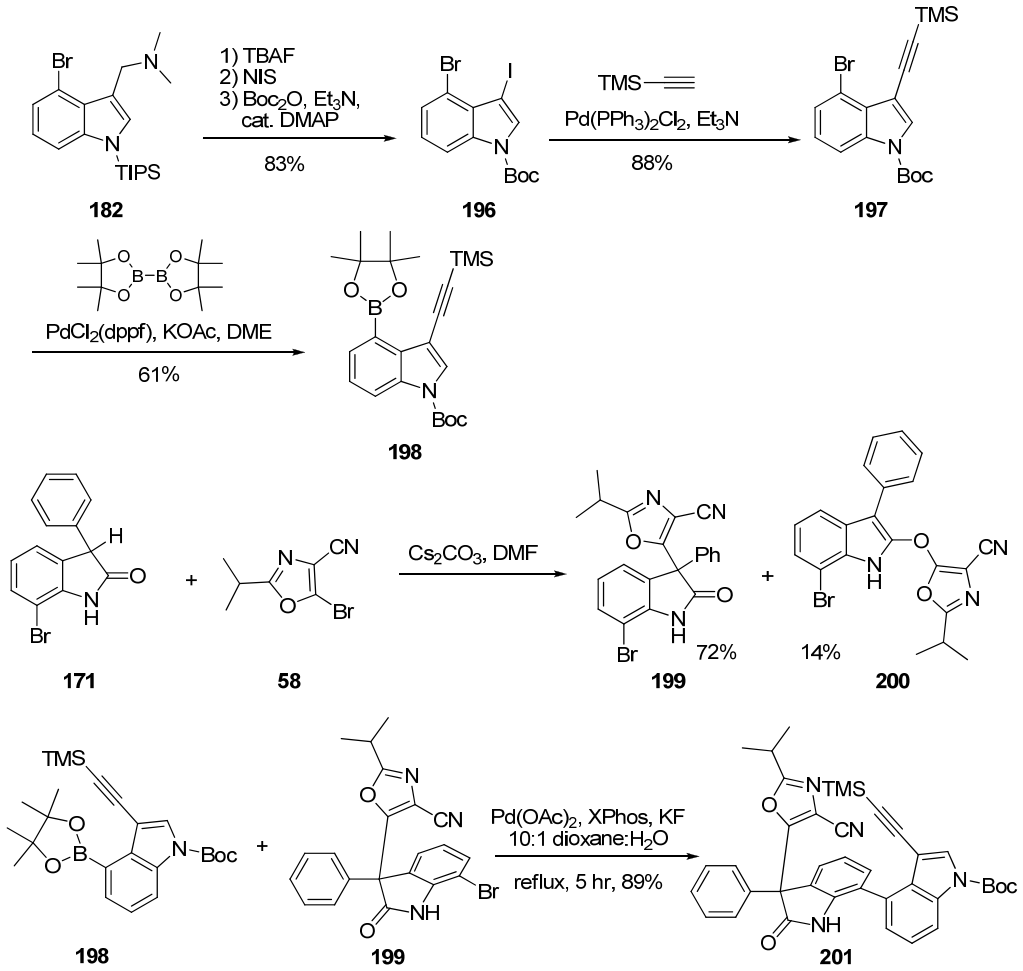


Scheme 5.16 Zhang Au-Catalyzed [2+2+1] Oxazole Synthesis

Because the S_NAr substrate (**111**) in our formal synthesis of diazonamide A bears a nitrile, I anticipated that this nitrile could be used to form an oxazole via an

intramolecular reaction with a pendant alkyne and an external oxidant under Au-catalysis. I, therefore, planned to study the oxazole synthesis of compound **168** as a model, and can further develop this strategy as a general method for macrocyclization of natural products bearing oxazole rings.[24]

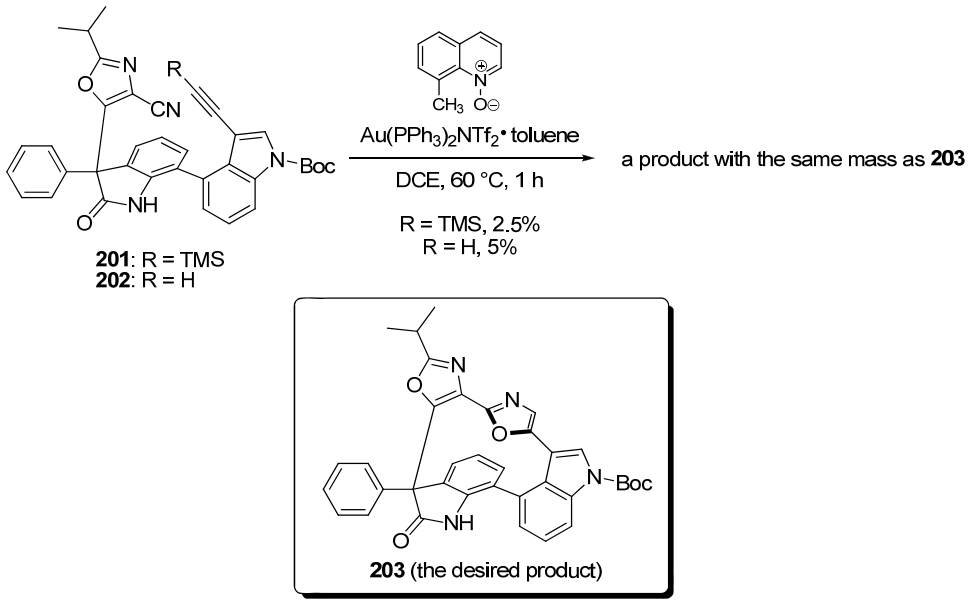
Synthesis of cyclization precursor **201** relied on the preparation of both alkynyl boronic ester **198** and bromooxindole **199** (Scheme 5.17). Removal of the TIPS protecting group of compound **182** with TBAF, followed by a rapid retro-Mannich reaction using NIS introduced an iodine atom at the C3 position of indole **182**. Immediate protection of the nitrogen of this indole with $(Boc)_2O$ provided iodo indole **196**.[18] This compound was subjected to Sonigashira reaction with trimethylsilylacetylene to introduce a TMS-protected alkyne onto the C3 position of the indole (**197**). Miyaura borylation was used to convert bromide **197** to pinacolato boronic ester **198**. Bromooxindole **199** was simultaneously prepared via an S_NAr reaction between oxindole **171** and bromooxazole **58**. This reaction provided the desired *C*-arylation product **199** in 72% yield, along with the undesired *O*-arylation product **200** in 14% yield. With fragments **198** and **199** in hand, cyclization precursor **201** was prepared via Suzuki coupling wherein KF was found to be the most suitable base to promote the reaction in very good yield (89%). Other bases, such as Na_2CO_3 or K_2CO_3, provided complex mixtures, probably due to the instability of TMS and Boc protecting groups of compound **198**. These protecting groups have been reported to be labile to K_2CO_3 in MeOH.[25]



Scheme 5.17 Synthesis of Cyclization Precursor **201**

With cyclization precursor **201** in hand, Au-catalyzed [2+2+1] oxazole formation (Scheme 5.18) was attempted using a modification of Zhang's general conditions ($Au(PPh_3)_2NTf_2$ toluene complex, 8-methylquinoline oxide) [26] but using 1,2-dichloroethane at reflux as solvent (Zhang typically runs his reactions either neat or using excess nitriles as solvents). Interestingly, this reaction provided a product in 2.5% yield with the same mass as the desired compound **203** as identified by mass spectrometry. We hypothesized that the TMS group is cleaved before cyclization under the reaction conditions as reported by the Zhang group. Removing the TMS group with TBAF

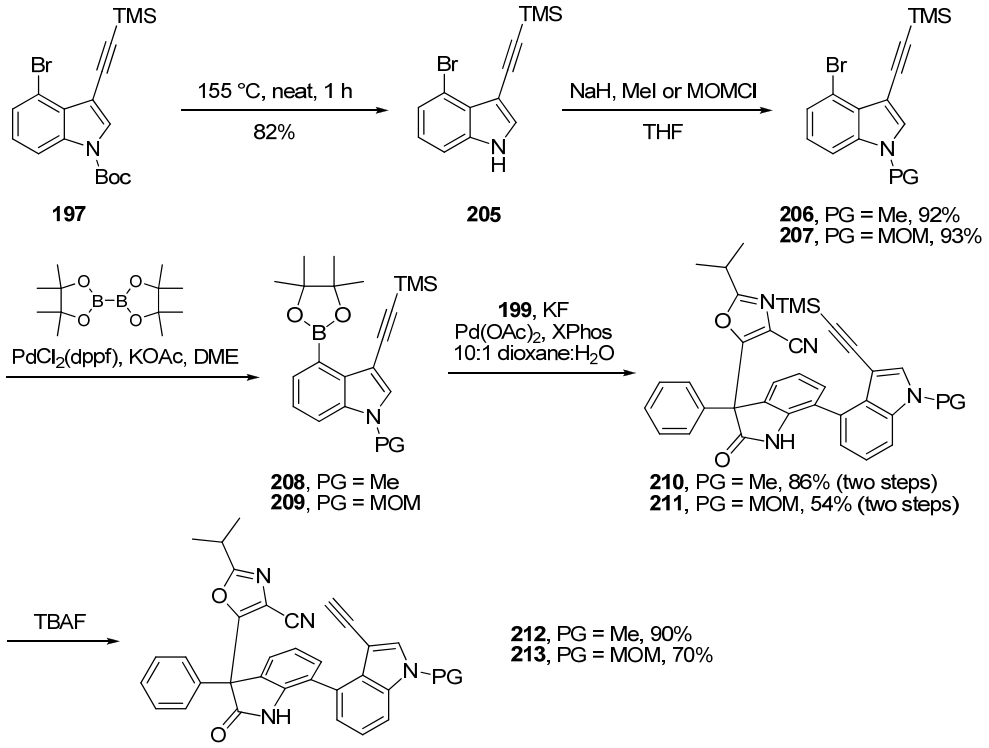
provided terminal alkyne **202**, which cyclized using the same conditions as **201** to provide the same product in better yield (5%).



Scheme 5.18 Au-Catalyzed Oxazole Formation of **201** and **202**

We suspected that the Boc protecting group is too labile under the reaction conditions, leading to decomposition and diminished yields. I, therefore, synthesized the *N*-methyl indole **211** as described in Scheme 5.19. Removing the Boc protecting group of compound **201** or **202** proved difficult as attempted removal provided complex mixtures under acidic or basic conditions. As such, the Boc group was removed on a precursor, compound **197**, by heating it neat at 155 °C under reduced pressure. Reprotecting the indole with a methyl group using NaH / MeI afforded compound **206**, which was converted to boronic ester **208** via Miyaura borylation. Because boronic ester **208** was not amenable to purification by flash chromatography, I used the crude **208** directly in the next step without further purification. Suzuki coupling of boronic ester **208** and bromooxindole **199** provided biaryl **210** in 86% yield over two steps. Removing the TMS

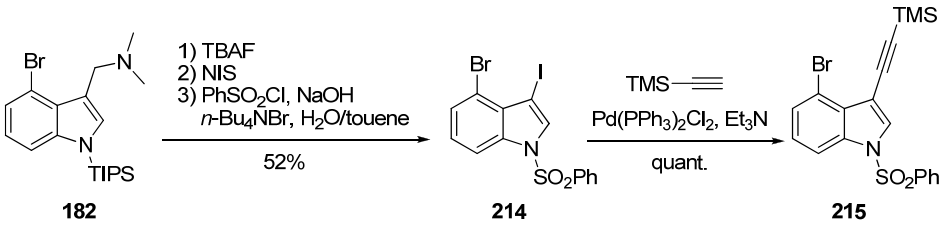
group of **210** with TBAF provided cyclization precursor **212**. Compound **213** with a MOM-protected indole was also prepared from unprotected indole **215** via similar procedures as shown in Scheme 5.19.



Scheme 5.19 Synthesis of *N*-Protected Indoles **212** and **213**

In addition to methyl and MOM protected indole cyclization precursors **212** and **213**, both of which bear electron-rich indoles, I also prepared indole **218**, bearing a strong electron-withdrawing group ($PhSO_2$-), as showed in Scheme 5.20. A method developed by Snieckus was used to convert gramine derivative **208** to protected iodo indole **214** via a three-step sequence consisting of removal of the TIPS protecting group with TBAF, introducing an iodo atom on C3-position of indole via a rapid retro-mannich reaction with NIS, and immediate protection the indole with $PhSO_2Cl$ under biphasic conditions. Sonigashira coupling of iodide **214** and TMS-acetylene provided alkyne **215**, which

could be converted to the cyclization precursor via a procedure similar to that shown in Scheme 5.19.



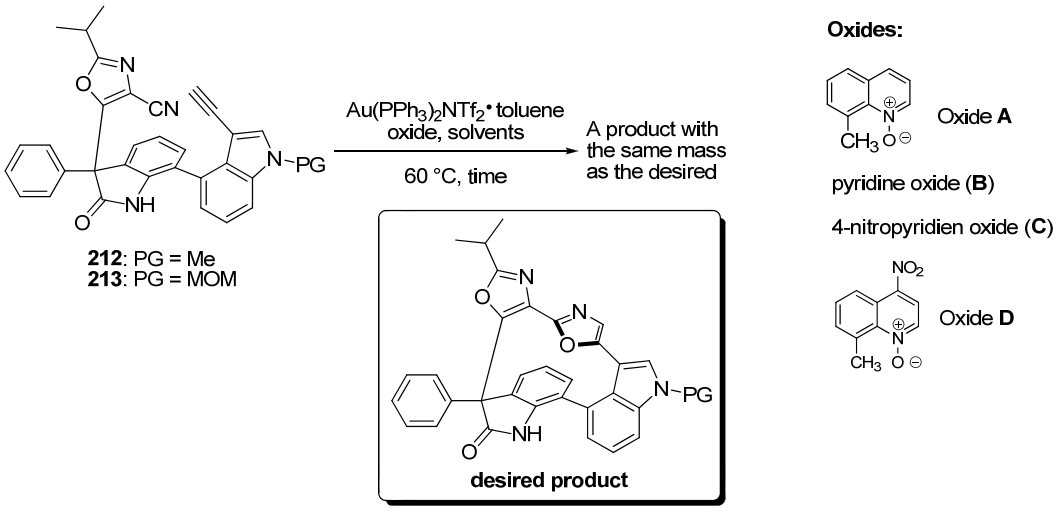
182 **214** **215**

Scheme 5.20 Preparation of Indole **215**

With all cyclization precursors in hand, I first conducted a solvent survey (Table 5.2) using *N*-methyl protected indole **212** in a variety of common solvents for Au-catalyzed oxazole synthesis. Reactions were typically run at 0.01 M concentration in various solvents with compound **212** (1.0 equiv, ~10 mg), $Au(PPh_3)_2NTf_2$ toluene complex (10 mol%), and 8-methylquinoline oxide (1.2 equiv). I found that common solvents used in other Au-catalyzed reactions, for example, DCE, $PhCF_3$, and toluene only provided complex mixtures. Only ethereal solvents (DME, dioxane, and THF) provided some product in detectable amounts observed in the crude NMR. Among these three solvents, the most polar solvent, THF, provided the best yield, and I, therefore, decided to investigate other aprotic polar solvents. Acetone provided a comparable yield as THF, while acetonitrile provided a slightly diminished yield. DMF provided a lower yield, probably due to deactivation of the gold catalyst by coordination. The highly polar, but non-chelating solvent, CH_3NO_2, also provided a comparable yield as THF. Interestingly, neat reaction also provided some product, albeit in low yield (~19%). With THF identified as the best solvent, I continued studying the effect of concentration, and found that both high (0.02 M) and low (slow addition via syringe pump) concentrations were

harmful to the reaction. 0.01 M was found to be an optimal concentration. Different oxides were also screened. Pyridine oxide provided complex mixtures, while 4-nitropyridine oxide provided the product in good yield. This indicated that a strong electron-withdrawing group (-NO_2) on the pyridine ring could significantly minimize the binding of pyridine-byproduct to the Au-catalyst, which is likely harmful to catalyst turnover. Therefore, I synthesized oxide **D** by subjecting oxide **A** to KNO_3 in concentrated H_2SO_4. Reaction with oxide **D** provided the same product with a slightly higher yield, and the product was easier to be purified by flash chromatography. Cyclization precursor **213** with a MOM protecting group also provided a product in a very good yield under these optimal conditions.

Table 5.2 Optimization for Au-Catalyzed Oxazole Formation



entry	PG	solvent[a]	oxide	time[b]	yield (%)[c]
1	Me	DCE	A	1 h	complex mixtures
2	Me	$PhCF_3$	A	15 min	complex mixtures
3	Me	toluene	A	15min	complex mixture
4	Me	DME	A	1 h	28
5	Me	dioxane	A	1 h	18
6	Me	THF (0.005 M)	A	1 h	39
7	Me	THF (0.01 M)	A	1 h	40 (32)[e]
8	Me	THF (0.02 M)	A	1 h	25

9	Me	THF (0.1 M)	A	1 h	8
10	Me	THF (slow addition) [d]	A	1 h	16
11	Me	neat	A	1 h	18
12	Me	acetone	A	1 h	38
13	Me	DMF	A	1 h	20
14	Me	CH_3CN	A	1 h	31
15	Me	CH_3NO_2	A	1 h	37
16	Me	THF (0.01 M)	B	24 h	complex mixtures[f]
17	Me	THF (0.01 M)	C	1 h	34
18	Me	THF (0.01 M)	D	1 h	36 [e]
19	MOM	THF (0.01 M)	D	1 h	51 [e]

[a] reactions conditions (1.0 equiv cyclization precursor, 1.2 equiv of 8-methylquinoline oxide, and 10 mol% Au-catalyst, 0.01 M in various solvents). [b] reaction time was determined based on the cyclization precursors were all consumed by TLC. [c] yields were estimated on the integral ratio of 8-methylquinoline oxide and 8-methylquinoline verse the desired products or using vanillin as internal standards. [d] the final concentration was 0.01 M. [e] isolated yield. [f] a lot of starting material left by TLC.

With optimal conditions in hand, I can isolate sufficient amount of the product for full characterization. The ^{1}H NMR displays dynamic behavior and a very broad peak that integrates to two protons around 3.8 ppm is always observed. Upon heating to 60 °C in THF-*d*8, this broad peak sharpens and appears as an AB pattern (Figure 5.1). In addition, the new formed oxazole should appear as a singlet, but this was not observed in various deuterated solvents. This was initially attributed to dynamic processes broadening this peak, but this signal was not observed even at elevated temperature. Furthermore, the products from the reactions of compound **212** and **213** both showed a signal at 190 ppm in ^{13}C NMR, which suggested the presence of a conjugated ketone. In addition, an extra alkyl carbon peak in ^{13}C NMR as compared to the desired oxazole product, is observed. All these indicated that the products of these reactions are not the desired, but instead are ketones **216** and **217**. They appear to be generated by the nucleophilic addition of the phenyl ring of the oxindole to the α-ketone gold carbenoid. The structures of **216** and **217** were further supported by observations of nitrile stretches in the IR. Moody has also observed such a C-H insertion product in a related approach.[27] Very recently, the Zhang group applied similar reactions to prepare chroman-3-ones. [28]

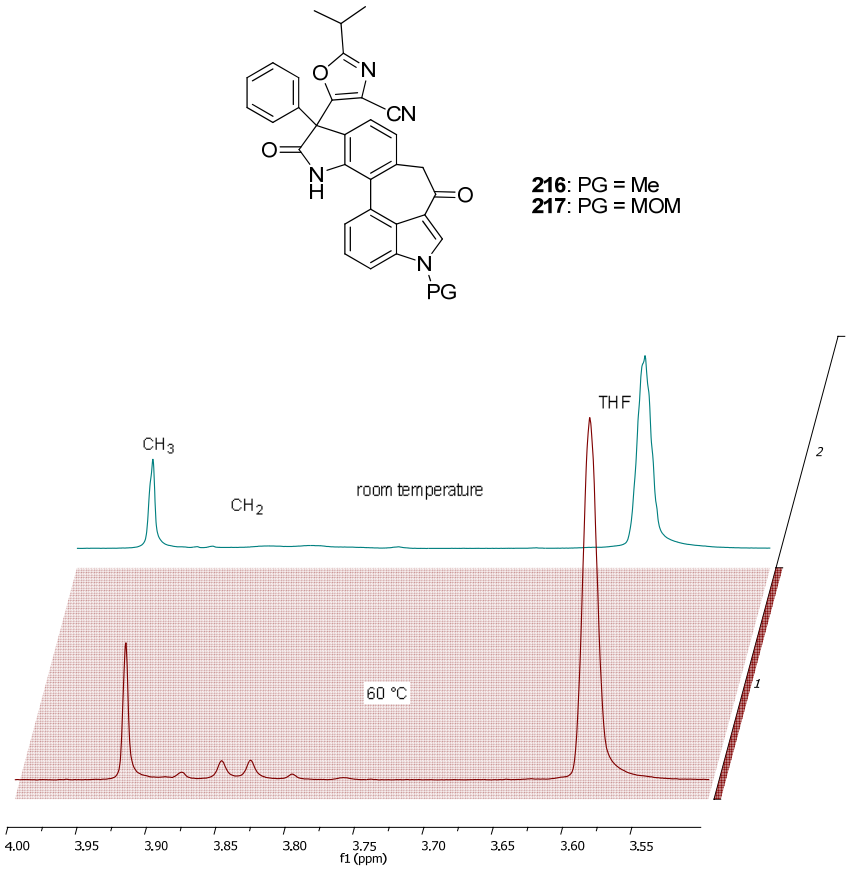


Figure 5.1 Structures of **216** and **217** and Partial ^{1}H NMR of **217**

5.6 Conclusion

Synthesis of the right hand macrocycle of diazonamide A was attempted, both via Pd-catalyzed α-arylation and Au-catalyzed oxazole formation. Unfortunately, neither of these two methods provided the desired heterocyclic macrocycle. Further modifications of cyclization precursors and conditions for both cyclization methods are required. In order to render the Au-catalyzed oxazole formation reaction viable for the synthesis of diazonamide A, deactivation of the oxindole phenyl ring is required. In one approach, a

bromine atom could be introduced at the 5-position of the oxindole to prevent the nucleophilic attack by the 6-position of the oxindole in compound **212** and **213**.

5.7 Abbriviations

Cbz	Carboxybenzyl
DCE	Dichloroethane
DME	1,2-Dimethoxyethane
DMF	*N*,*N*-Dimethylformamide
DDQ	2,3-Dichloro-5,6-dicyanobenzoquinone
DIBAL	Diisobutylaluminium hydride
DMAP	4-Dimethylaminopyridine
Deoxo-Fluor®	Bis(2-methoxyethyl)aminosulfur trifluoride
DPPA	Diphenylphosphoryl Azide
EDC	1-Ethyl-3-(3-dimethylaminopropyl) carbodiimide
HOBt	Hydroxybenzotriazole
LiHMDS	Lithium bis(trimethylsilyl)amide
NCS	*N*-Chlorosuccinimide
NIS	*N*-Iodosuccinimide
Pht	Phthalimido
RuPhos	2-Dicyclohexylphosphino-2',6'-di-i-propoxy-1,1'-biphenyl
SPhos	2-Dicyclohexylphosphino-2',6'-dimethoxybiphenyl
TAS-F	Tris(dimethylamino)sulfonium difluorotrimethylsilicate
TFA	Trifluoroacetic acid
TMEDA	Tetramethylethylenediamine

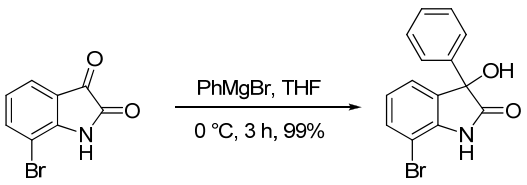
5.8 Experimental Details

General Information

All glassware was oven-dried or flame-dried. DMF were freshly distilled over CaH_2 under reduced pressure prior to use; THF and Et_2O were distilled from sodium benzophenone ketyl under N_2; DME was distilled over Na under N_2. CH_2Cl_2, hexanes

and toluene were distilled over CaH_2 under N_2; TMEDA was distilled from Na under reduced pressure. Unless specifically mentioned, all chemicals are commercially available and were used as received. Thin layer chromatography (TLC) was performed using EM Science Silica Gel 60 F254 glass plates. Flash chromatography was performed using 60 Å silica gel (37-75 μm). ^{1}H NMR spectra were recorded at either 400 MHz or 500 MHz, and ^{13}C NMR spectra were recorded at either 75 MHz or 100 MHz in $CDCl_3$, [D6]acetone, or [D6]DMSO as indicated. Chemical shifts are reported in ppm referenced to residual solvent peaks as follows: $CDCl_3$, 7.24 ppm for ^{1}H NMR, 77.16 ppm for ^{13}C NMR; [D6]acetone, 2.05 ppm for ^{1}H NMR, 29.84 ppm for ^{13}C NMR; and [D6]DMSO, 2.50 ppm for ^{1}H NMR, 39.52 ppm for ^{13}C NMR; [D8]THF, 3.58 ppm for ^{1}H NMR. Infrared (FT-IR) spectra were obtained as thin films on NaCl plates. Exact mass was determined using electrospray ionization (M+H, M+Na, or M+K as indicated).

Tertiary Alcohol 180:



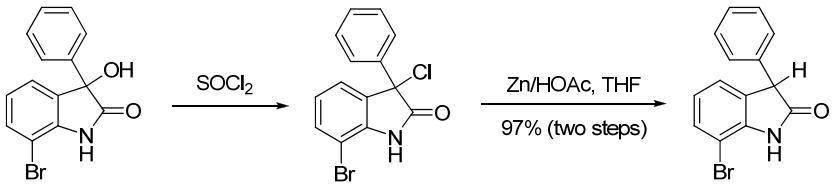
7-bromoisatin **180**

Magnesium turning (968 mg, 39.8 mmol, 3.0 equiv) was charged in a 100 mL three neck round bottom flask, and dry THF (50 mL) and bromobenzene (3.07 mL, 29.2 mmol, 2.2 equiv) were added. After the reaction was initiated, and the reaction was allowed to stir until no bubbling was observed on the magnesium surface, and cooled to room temperature. 7-Bromoisatin (3.0 g, 13.27 mmol, 1.0 equiv) was charged in another 250

mL round bottom flask, and dry THF (80 mL) was added. The solution was cooled in an ice bath, and the prepared Grignard reagent was cannulated into the flask containing 7-bromoisatin. The resulting dark brown solution was stirred in the ice bath for 3 h. The reaction was quenched with sat. NH_4Cl (30 mL), 1 M HCl (20 mL), and diluted with EtOAc (150 mL). The aqueous layer was extracted with EtOAc (50 mL×3) three times, and the combined organic layers were dried over $MgSO_4$, filtered, and concentrated to provide a brown oil. Flash chromatography with 5:1 CH_2Cl_2:EtOAc provided alcohol **180** (3.75 g, 93%) as a yellow solid.

$\mathbf{R_f}$ = 0.52 in 5:1 CH_2Cl_2:EtOAc. **^{1}H NMR** (500 MHz, [D6]acetone) δ 9.64 (s, 1H), 8.00 (s, 1H), 7.52 – 7.39 (m, 3H), 7.39 – 7.24 (m, 3H), 7.19 (d, *J* = 7.4 Hz, 1H), 6.99 (dd, *J* = 8.1, 7.4 Hz, 1H), 5.80 (s, 1H). **^{13}C NMR** (75 MHz, [D6]acetone) δ 178.49, 142.14, 141.62, 135.96, 133.01, 129.02, 128.65, 126.32, 124.83, 103.27, 79.52, 79.12. **IR** (cm^{-1}) 3403, 1642.

3-Aryloxidole 171:



Tertiary alcohol **180** (3.30 g, 10.85 mmol, 1.0 equiv) was charged into a 200 mL round bottom flask, and neat $SOCl_2$ (15.84 mL, 217.0 mmol, 20.0 equiv) was added. The resulting brown solution was stirred for 15 h and concentrated under reduced pressure. The crude tertiary chloride was dissolved in dry THF (55 mL), and zinc dust (3,55 g, 54.3

mmol, 5.0 equiv) and acetic acid (6.21 mL, 109.0 mmol, 10.0 equiv) were added. The suspension was allowed to stir at RT for 3 h. The reaction was diluted with ether (250 mL), washed with brine (30 mL), sat. $NaHCO_3$ (30 mL×2), brine (30 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellowish solid (purity > 95%), which was used directly in the next step without any purification.

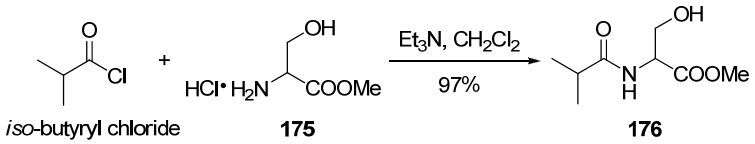
Tertiary chloride:

An analytical sample was prepared by flash chromatography with 5:1 hexanes:EtOAc as a white solild. $\mathbf{R_f}$ = 0.48 in 5:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.40 (s, 1H), 7.58 – 7.49 (m, 2H), 7.45 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.39 – 7.33 (m, 3H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.55 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 173.98, 139.53, 135.89, 133.15, 132.02, 129.32, 128.78, 127.50, 125.15, 124.92, 103.77, 67.32.

3-Phenyloxindole 171:

$\mathbf{R_f}$ = 0.25 in 5:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.44 – 7.26 (m, 4H), 7.21 (dd, *J* = 5.3, 3.1 Hz, 2H), 7.05 (d, *J* = 7.4 Hz, 1H), 6.91 (t, *J* = 7.4 Hz, 1H), 4.73 (s, 1H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 176.84, 141.17, 135.89, 131.24, 130.80, 129.12, 128.52, 127.97, 124.25, 124.04, 102.96, 53.76. **IR** (cm^{-1}) 3424 (br), 1642.

Amide 176:

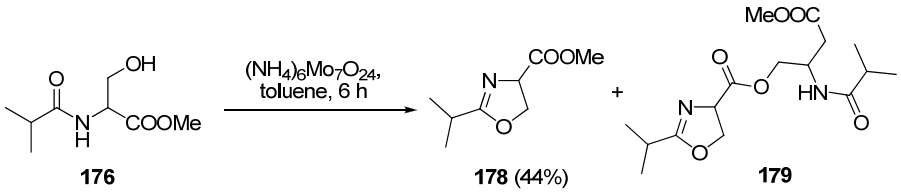


iso-butyryl chloride **175** **176**

To a suspension of (±)-serine methyl ester hydrochloride (2.02 g, 13.0 mmol, 1.0 equiv) and dry Et_3N (5.5 mL, 39.0 mmol, 3.0 equiv) in CH_2Cl_2 (50 mL) in an ice bath was added isobutyryl chloride (1.45 mL, 13.7 mmol, 1.05 equiv) dropwise. The reaction was allowed to warm up to RT and stirred overnight (20 h). The solvent was removed under reduced pressure and the reaction was diluted with EtOAc (100 mL). The suspension was filtered to remove the white salt, and the filtrate was concentrated to provide a colorless oil. Purification by flash chromatography (10% MeOH in 5:1 hexanes:EtOAc) provided amide **176** (2.39 g, 97%) as a colorless oil.

R_f = 0.18 in 10% MeOH in 5:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.62 (d, *J* = 7.4 Hz, 1H), 4.60 (dt, *J* = 7.5, 3.6 Hz, 1H), 3.93 (dd, *J* = 11.2, 3.9 Hz, 1H), 3.83 (dd, *J* = 11.2, 3.3 Hz, 1H), 3.73 (s, 3H), 3.49 (s, 1H), 2.43 (hept, *J* = 6.9 Hz, 1H), 1.13 (dd, *J* = 6.9, 3.7 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 177.88, 171.26, 63.32, 54.60, 52.77, 35.49, 19.51, 19.48. **IR** (cm^{-1}) 3342 (br), 2966, 2933, 2872, 1744, 1654.

Oxazoline 178 and Ester 179:



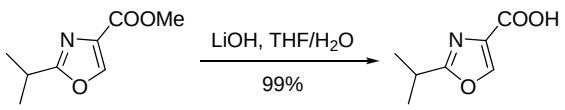
176 **178** (44%) **179**

Amide **176** (1.60 g, 8.46 mmol, 1.0 equiv) was dissolved in dry toluene (45 mL) in a 100 mL round bottom flask, and $(NH_4)_6Mo_7O_{24}$ tetrahydrate (1.045 g, 0.846 mmol, 10 mol%) was added, and the reaction was heated to reflux with a Dean-Stark apparatus for 6 h. The reaction was diluted with EtOAc (200 mL), washed with sat. $NaHCO_3$ (30 mL), brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. Purification by flash chromatography (10% MeOH in 5:1 hexanes:EtOAc) provided oxazoline **178** (640 mg, 44%) as a colorless oil, along with ester **179** (430 mg, 30%) as a white solid. Spectral data for **178** are consistent with that reported in the literature.[29]

Ester 179:

R_f = 0.25 in 10% MeOH in 5:1 hexanes:EtAOc; **^{1}H NMR** (500 MHz, $CDCl_3$) δ 6.33 (d, *J* = 7.7 Hz, 1H), 4.81 (dt, *J* = 7.9, 4.0 Hz, 1H), 4.60 (ddd, *J* = 10.5, 7.5, 0.9 Hz, 1H), 4.44 (s, 1H), 4.44 (d, *J* = 0.7 Hz, 1H), 4.39 – 4.24 (m, 2H), 3.69 (s, 3H), 2.60 – 2.48 (m, 1H), 2.41 – 2.28 (m, 1H), 1.13 (dt, *J* = 6.7, 2.2 Hz, 6H), 1.09 (d, *J* = 6.9 Hz, 6H). **IR** (cm^{-1}) 3328 (br), 2966, 2933, 2872, 1660, 1516.

Carboxylic Acid 174:

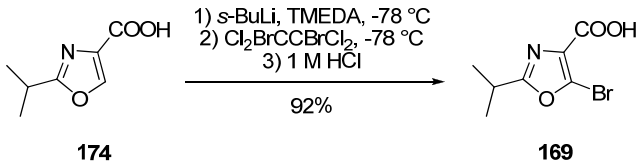


173 **174**

Ester **173** (860 mg, 5.08 mmol, 1.0 equiv) was dissolved in 50 mL THF in a 250 mL round bottom flask, which was cooled in an ice bath. LiOH (2.135 g, 50.8 mmol, 10.0 equiv) was dissolved in 50 mL water, and the solution was added to the THF solution of

ester **173**. The resulting colorless solution was stirred in the ice bath for 1 h, and the reaction was diluted with ether (150 mL), acidified with 1 M HCl (55 mL). The aqueous layer was extracted with ether (50 mL×3), and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide carboxylic acid **174** (785 mg, 99%) as a colorless crystalline solid, which was used directly in the next step without further purification. Spectral data for **174** are consistent with that reported in the literature.[30]

Bromooxazole 169:



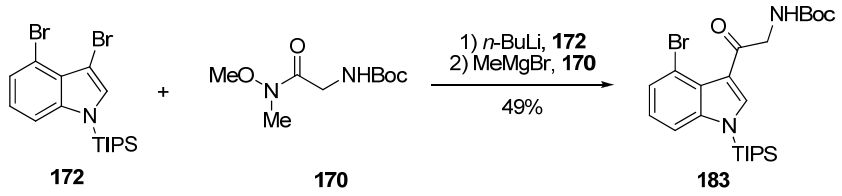
174 **169**

s-BuLi (1.25 mL of a 1.3 mol/L solution in cyclohexane, 1.63 mmol, 2.2 equiv) was added to a -78 °C solution of carboxylic acid **174** (115 mg, 0.74 mmol, 1.0 equiv) and TMEDA (276 μL, 1.85 mmol, 2.5 equiv) in dry THF (7 mL), and the resulting orange solution was stirred at - 78 °C for 1 h. A solution of $Cl_2BrCCBrCl_2$ (724 mg, 2.22 mmol, 3.0 equiv) in dry THF (3.5 mL), and the reaction was allowed to warm up to RT. The reaction was quenched with H_2O, and diluted with Et_2O. The organic layer was extracted with 0.1 M NaOH (15 mL×3), and the combined aqueous layers were acidified with 1 M HCl (10 mL), and extracted with Et_2O (20 mL×3). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to provide

bromooxazole **169** (159 mg, 92%) a colorless sticky oil. The crude acid was used directly into the next step without any further purification.

^{1}H NMR (500 MHz, $CDCl_3$) δ 11.56 (s, 1H), 3.24 – 3.01 (m, 1H), 1.31 (d, J = 7.0, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 170.66, 164.83, 129.74, 129.10, 28.76, 20.07. **IR** (cm^{-1}) 3085, 2974, 2929, 2976, 1699, 1585.

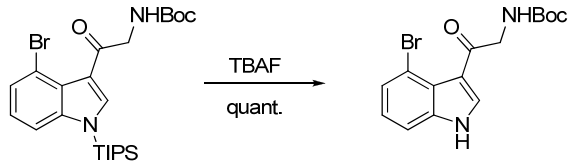
Ketone 183:



To a cold (-78 °C) solution of dibromoindole **172** (1.94 g, 4.50 mmol, 1.0 equiv) in dry THF (20 mL) was added *n*-BuLi (3.26 mL of a 1.38 mol/L solution in hexanes, 4.50 mmol, 1.0 equiv) dropwise, and the solution was stirred at -78 °C for 1 h. In another flask, MeMgBr (3.37 mL of a 2.8 mol/L solution in Et_2O, 9.45 mmol, 2.1 equiv) was added slowly to a solution of Weinreb amdie **170** (1.963 g, 9.0 mmol, 2.0 equiv) in dry THF (25 mL) in an ice bath, and the solution was stirred in the ice bath for 1 h before cannulating into the lithiated indole solution. The resultant yellow solution was allowed to warm up to RT, and stirred overnight (24 h). The reaction was quenched with 1 M HCl (5 mL), and the mixture was stirred at RT for 10 min, before diluting with Et_2O (100 mL). The organic layer was washed with sat. $NaHCO_3$ (20 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. Purification by flash chromatography (5:1 hexanes:EtOAc) provided ketone **183** (1.12 g, 49%) as a colorless oil.

R_f = 0.42 in 5:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.83 (s, 1H), 7.45 (d, *J* = 1.2 Hz, 1H), 7.43 (s, 1H), 7.05 (t, *J* = 8.0 Hz, 1H), 5.68 (s, 1H), 4.48 (t, *J* = 21.7 Hz, 2H), 1.76 – 1.56 (m, 3H), 1.43 (s, 9H), 1.10 (d, *J* = 7.6 Hz, 17H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.69, 156.09, 143.25, 138.48, 127.99, 127.81, 124.33, 118.61, 114.70, 113.51, 79.83, 49.63, 28.59, 18.13, 12.88. **IR** (cm^{-1}) 3423, 1711, 1679, 1169, 990. **HRMS** m/z calcd for $C_{24}H_{37}BrN_2O_3SiNa^+$: 531.1649; found: 531.1632.

Indole 184:



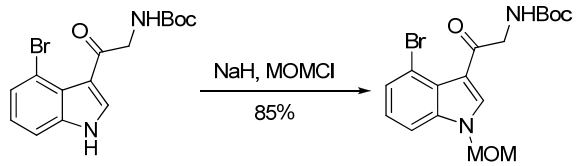
183 **184**

A solution of TBAF (2.4 mL of a 1.0 mol/L solution, 2.41 mmol, 1.1 equiv) in THF was added via syringe to a solution of ketone **183** (1.12 g, 2.20 mmol, 1.0 equiv) in THF (20 mL), and the resultant yellow solution was stirred at RT for 10 min. The reaction was diluted with sat. NH_4Cl (20 mL) and Et_2O (100 mL). The aqueous layer was extracted with Et_2O (20 mL×3), and the combined organic layers were washed with brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. Trituration with hexanes provided indole **184** (776 mg, quantitative) as a white solid, which was suitable for further use. An analytical sample was prepared by recrystallization from CH_2Cl_2/hexanes.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm 9.71 (br s, 1H), 7.79 (d, *J* = 3.16 Hz, 1H), 7.45

(dd, J = 7.67, 0.8 Hz 1H), 7.36 (dd, J = 8.15, 0.8 Hz 1H), 7.12-7.06 (m, 1H), 5.67 (br s, 1H), 4.45 (d, J = 4.81 Hz, 2H), 1.48 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.11, 156.54, 138.44, 131.91, 128.15, 125.00, 124.81, 116.31, 114.71, 111.36, 80.31, 49.16, 28.62. **IR** (cm^{-1}) 3271, 1667, 1515, 1163. **HRMS** m/z calcd for $C_{15}H_{17}BrN_2O_3Na^+$: 375.0314; found: 375.0294.

***N*-MOM indole 185:**



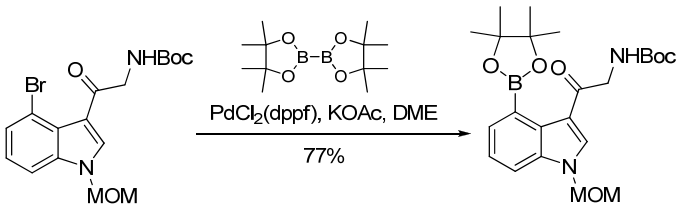
184 **185**

A dry THF (17 mL) solution of indole **184** (818 mg, 2.316 mmol, 1.0 equiv) was cannulated into a flask charged with NaH (60% suspension in mineral oil, prewashed with dry hexanes three times) in dry THF (5 mL). The resultant suspension was stirred at RT for 1 h, MOMCl (185 µL, 2.432 mmol, 1.05 equiv) was added via syringe. After stirring at RT for 18 h, the reaction was quenched with water (25 mL), diluted with ether (50 mL). The aqueous layer was extracted with ether (20 mL×2), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. Purification by flash chromatography (10:1 CH_2Cl_2:EtOAc) provided *N*-MOM indole **185** (780 mg, 85%) as a colorless oil.

R_f = 0.35 in 10:1 CH_2Cl_2:EtOAc. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.41 (dd, J = 7.7, 0.8, 1H), 7.38 (dd, J = 8.3, 0.8, 1H), 7.07 (J = 7.95 Hz, 1H), 5.66 (s, 1H), 5.37 (s, 2H), 4.42 (d, J = 4.9, 2H), 3.17 (s, 3H), 1,41 (s, 9 H). **^{13}C NMR** (75 MHz, $CDCl_3$)

δ 189.34, 155.79, 137.93, 135.19, 127.74, 125.32, 124.38, 115.19, 114.11, 109.78, 79.19, 78.00, 55.93, 48.95, 28.12. **IR** (cm^{-1}) 3357, 1707, 1679, 1524, 1167. **HRMS** m/z calcd for $C_{17}H_{21}BrN_2O_4Na^+$: 419.0577; found: 419.0568.

Boronic Ester 186:



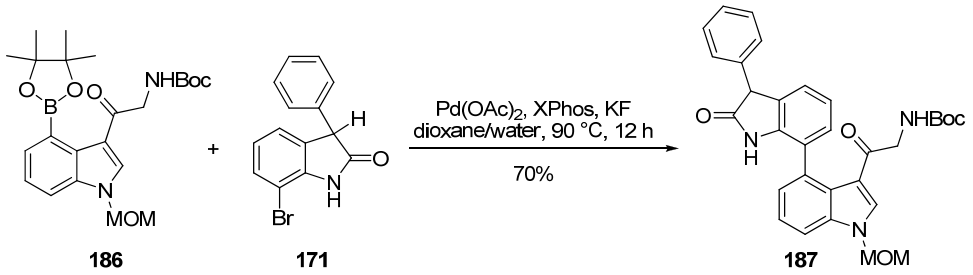
185 **186**

Bromide **185** (350 mg, 0.881 mmoml, 1.0 equiv), $PdCl_2$(dppf) CH_2Cl_2 complex (72 mg, 0.088 mmol, 10 mol%), bispinacolatodiboron (447 mg, 1.762 mmol, 2.0 equiv), and KOAc (259 mg, 2.64 mmol, 3.0 equiv) were combined in a 25 mL long neck flask with a cold finger. Fresh distilled DME (8 mL) was degassed by sparging with N_2 for 15 min, and cannulated into the flask. The resulting orange solution was stirred in a 90 °C oil bath for 20 h. The reaction was filtered through celite, washed with EtOAc, concentrated to provide a brown oil. Flash chromatography with 20:1 hexanes:EtOAc provided boronic ester **186** (300.5 mg, 77%) as a white solid.

$\mathbf{R_f}$ = 0.25 in 10:1 CH_2Cl_2:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ ppm 7.82 (s, 1H), 7.49 (dd, *J* = 8.25, 1.0 Hz, 1H), 7.42 (dd, *J* = 7.08, 1.0 Hz 1H), 7.30 (dd, *J* = 7.16, 8.16 Hz, 1H), 5.48 (s, 1H), 5.45 (s, 2H), 4.48 (d, *J* = 4.50 Hz, 2H), 3.20 (s, 3H), 1.47 (s, 12H), 1.46 (s, 9H). **^{13}C NMR** (100 MHz, $CDCl_3$) δ 189.23, 156.03, 136.09, 133.78, 128.24, 127.88, 123.83, 115.54, 111.50, 84.09, 79.80, 78.39, 56.29, 47.06, 28.58, 25.72. **IR** (cm^{-1})

3359, 1712, 1659, 1534, 1096. **HRMS** m/z calcd for $C_{23}H_{33}BN_2O_6H^+$: 445.2508; found: 445.2491.

Biaryl 187:



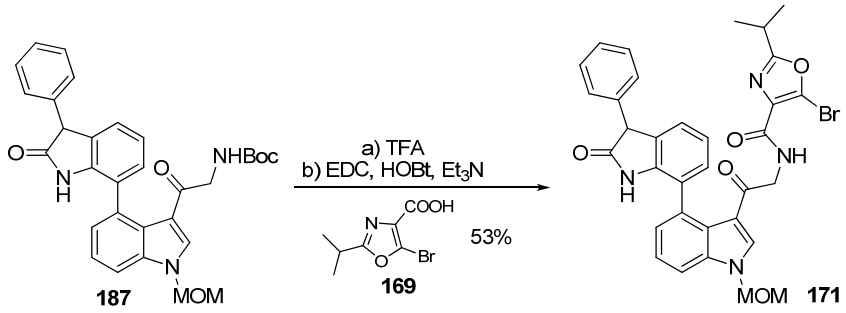
186 171 187

Boronic ester **186** (85 mg, 0.191 mmol, 1.1 equiv), bromide **171** (50 mg, 0.174 mmol, 1.0 eqiuv), $Pd(OAc)_2$ (1.9 mg, 8.7 μmol, 5 mol%), XPhos (8.3 mg, 17 μmol, 10 mol%), and KF (30.2 mg, 0.521mmol, 3.0 equiv) were combined in a 25 mL long neck flask with a cold finger. 10:1 dioxane:H_2O (4 mL) were degassed by sparging with N_2 for 15 min, and cannulated into the flask with all the reagents. The resultant yellow solution was placed in a 90 °C oil bath for 12 h, and diluted with EtOAc (25 mL) and sat. NH_4Cl (25 mL). The aqueous layer was extracted with EtOAc (20 mL×3), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to provide a white solid. Purification by flash chromatography (1:2 hexanes:EtOAc) provided biaryl **187** (64 mg, 70%, about 8:3 ratio of atropisomers) as a white solid.

$\mathbf{R_f}$ = 0.25 in 1:2 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$, 8:3 ratio of atropisomers) δ 8.05 (s, 1H), 7.62 (d, *J* = 8.2 Hz, minor,1H), 7.58 (d, *J* = 8.2 Hz, major, 1H), 7.52 - 7,27 (m, 9H), 7.24 - 7.20 (m, 3H), 7.09 (s, minor, 1H), 5.61 – 5.40 (minor's

CH_2 overlap with one of major's CH_2), 5.36 (t, J = 4.0 Hz, 1H), 5.17 (d, J = 10.9 Hz, 1H), 4.75 (s, minor, 1H), 4.68 – 4.53 (major's CH_2 overlap with oxindole C3-H, 2H), 4.47 (dd, J = 18.1, 4.5 Hz, minor 1H), 4.32 (dd, J = 18.1, 4.5 Hz, minor 1H), 4.14 (dd, J = 18.3, 3.8 Hz, major, 1H), 3.35 (s, minor, 3H), 3.29 (s, major, 3H), 1.42 (s, minor, 9H), 1.37 (s, major , 9H). **^{13}C NMR** (75 MHz, CDCl3, 8:3 ratio of atropisomers. The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 188.52, 187.79, 178.35, 177.69, 155.47, 140.80, 139.80, 137.84, 137.71, 136.83, 136.70, 136.10, 131.53, 131.50, 129.20, 129.12, 129.01, 128.64, 128.57, 128.48, 128.40, 127.68, 125.93, 125.82, 125.63, 125.22, 124.62, 124.37, 124.01, 123.95, 123.87, 123.26, 122.75, 122.50, 116.08, 116.00, 110.98, 110.87, 79.71, 79.50, 78.56, 78.29, 56.59, 56.31, 53.15, 52.87, 48.06, 29.82, 29.78, 28.50, 28.47. **IR** (cm^{-1}) 3321, 3252, 1708, 1658.

Keto Amide 171:

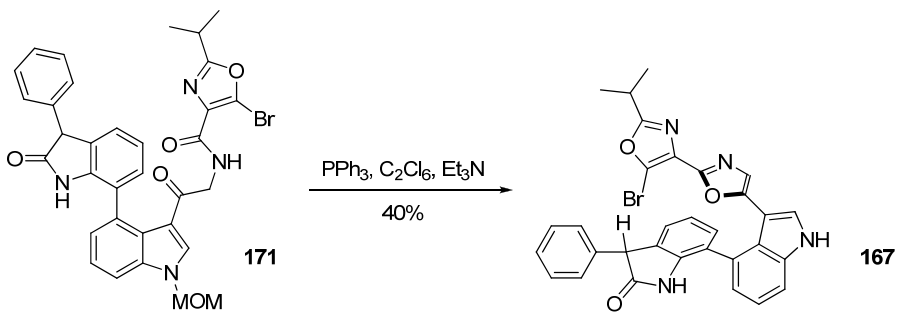


Boc-protected amine **187** (217 mg, 0.413 mmol, 1.0 equiv) was dissolved in dry CH_2Cl_2 (3.2 mL), and TFA (1.6 mL, 20.65 mmol, 50 equiv) was added. The reaction was stirred at RT for 30 min, and concentrated to provide the crude amine TFA salt as a yellowish solid. To the flask containing the crude amine TFA salt were added carboxylic acid **169** (116 mg, 0.496 mmol, 1.2 equiv), dry CH_2Cl_2 (3.8 mL), and Et_3N (174 µL,

1.239 mmol, 3.0 equiv). The HOBt monohydrate (126 mg, 0.826 mmol, 2.0 equiv) and EDC (158 mg, 0.826 mmol, 2.0 equiv) were added subsequently. The resultant yellow solution was stirred at RT for 15 h, and diluted with EtOAc (50 mL), washed with 1 M HCl (10 mL), water (10 mL), brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellow solid. Flash chromatography with 1:1 $CHCl_3$:EtOAc provided keto amide **171** (141 mg, 10:3 ratio of inseparable atropisomers, 53% combined yield) as a white solid.

R_f = 0.12 in 1:1 CH_2Cl_2:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$; 10:3 ratio of atropisomers) δ 8.26 (two s, 2H), 8.17 (s, 0.3H), 7.62 – 7.49 (m, 2H), 7.49 – 7.25 (m, 10H), 7.24 – 7.19 (m, 3H), 7.17 (d, *J* = 4.8 Hz, 0.3H), 7.11 (d, *J* = 7.4 Hz, 1H), 5.45 (d, *J* = 10.9 Hz, 0.3H), 5.31 (d, *J* = 11.0 Hz, 0.3H), 5.13 (d, *J* = 11.0 Hz, 1H), 5.06 (dd, *J* = 18.8, 5.0 Hz, 1H), 4.75 (dd and s, *J* = 16.5, 6.9 Hz, 0.6H), 4.59 (d, *J* = 10.9 Hz, 1H), 4.54 (s, 1H), 4.42 (dd, *J* = 17.9, 4.8 Hz, 0.3H), 4.22 (dd, *J* = 18.8, 4.1 Hz, 1H), 3.29 (s, minor CH_3), 3.14 (s, major CH_3), 3.10 (sept, 1H), 3.03 (sept, 0.3 H), 1.37 (dd, *J* = 7.0, 3.3 Hz, 6H), 1.32 (dd, *J* = 7.0, 1.9 Hz, 2H).

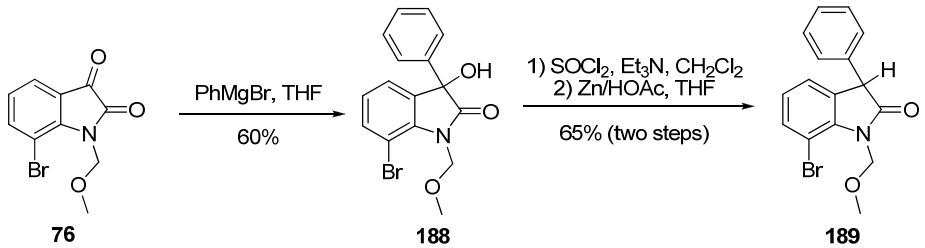
Bis-Oxazole Indole 167:



To a solution of PPh_3 (37mg, 0.14 mmol, 5.0 equiv) in dry CH_2Cl_2 (4 mL) was added C_2Cl_6 (33 mg, 0.14 mmol, 5.0 equiv), and the solution was stirred at RT for 10 min, at which time dry Et_3N (39 μL, 0.28 mmol, 10.0 equiv) was added dropwise. After stirring at RT for 10 min, the solution was cannulated to a solution of keto amide **171** (18 mg, 0.028 mmol, 1.0 equiv) in dry CH_2Cl_2 (1 mL) in an ice bath. The reaction was stirred in the ice bath for 1.5 h, and diluted with EtOAc (50 mL), washed with sat. $NaHCO_3$ (10 mL), brine (5 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellow solid. Purification by flash chromatography (2:1 hexanes:EtOAc) provided oxazole **167** (7 mg, 40%) as a yellow oil.

R_f = 0.55 in 2:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 9.11 (br s, 1H), 8.15 (s, 1H), 8.10 (d, *J* = 8.4 Hz, 1H), 7.75 (s, 1H), 7.73 (d, *J* = 7.7 Hz, 1H), 7.43 (d, *J* = 8.1 Hz, 1H), 7.36 – 7.23 (m, 6H), 7.17 (dd, *J* = 8.2, 7.2 Hz, 1H), 7.05 (dt, *J* = 7.2, 1.1 Hz, 1H), 5.54 – 5.46 (AB, 2H), 4.80 (s, 1H), 3.30 (s, 3H), 3.17 – 3.03 (m, 1H), 1.35 (d, *J* = 7.0, 6H).

***N*-MOM-Oxindole 188 and 189:**



Compound **188** was prepared in 60% yield from *N*-MOM-isatin **76** via a similar procedure as the preparation of tertiary alcohol **180**, and recrystallized from hot MeOH

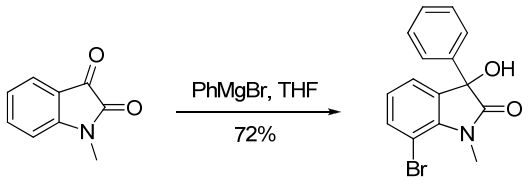
and H_2O after flash chromatography (5:1 hexanes:EtOAc) to provide a yellowish solid. $\mathbf{R_f}$ = 0.55 in 2:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.49 (dd, *J* = 8.2, 1.1 Hz, 1H), 7.38 – 7.27 (m, 5H), 7.21 (dd, *J* = 7.4, 1.1 Hz, 1H), 6.96 (dd, *J* = 8.0, 7.6 Hz, 1H), 5.56 – 5.43 (AB, 2H), 3.38 (s, 3H), 3.12 (br s, 1H).

Tertiary chloride:

To a solution of tertiary alcohol **188** (398 mg, 1.14 mmol, 1.0 equiv) and Et_3N (805 µL, 5.72 mmol, 5.0 equiv) in dry CH_2Cl_2 (22 mL) in an ice bath was added $SOCl_2$ (210 µL, 2.86 mmol, 2.5 equiv), and the resultant dark brown solution was stirred in the ice bath for 30 min. The reaction was washed with sat. $NaHCO_3$ (10 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. Purification by flash chromatography (10:1 hexanes:EtOAc) provide the tertiary chloride (285 mg, 68%) as a yellow oil. $\mathbf{R_f}$ = 0.35 in 10:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.2 Hz, 1H), 7.51 – 7.46 (m, 2H), 7.40 – 7.29 (m, 4H), 7.03 (t, *J* = 7.8 Hz, 1H), 5.50 (AB, 2H), 3.35 (s, 3H).

Compound **189** was prepared in 96% yield from the above tertiary chloride via a similar procedure as the preparation of compound **171**, and used without purification. $\mathbf{R_f}$ = 0.45 in 5:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.44 (dt, *J* = 8.2, 0.9 Hz, 1H), 7.35 – 7.21 (m, 3H), 7.14 (dt, *J* = 3.8, 2.2 Hz, 2H), 7.05 (dt, *J* = 7.3, 1.1 Hz, 1H), 6.90 (dd, *J* = 8.1, 7.4 Hz, 1H), 5.48 (AB, 2H), 4.65 (s, 1H), 3.35 (s, 3H).

Tertiary Alcohol 192:

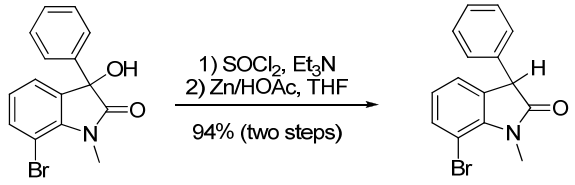


191 **192**

Compound **192** was prepared in 72% yield (4.59 g, a yellow solid) from *N*-methyl isatin **191** via a similar procedure as the preparation of compound **180**.

R_f = 0.26 in 5:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.42 (dd, *J* = 8.2, 1.2 Hz, 1H), 7.35 – 7.25 (m, 5H), 7.16 (dd, *J* = 7.3, 1.2 Hz, 1H), 6.89 (dd, *J* = 8.2, 7.4 Hz, 1H), 4.00 (br s, 1H), 3.58 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 178.21, 140.91, 139.84, 135.52, 134.82, 128.82, 128.63, 125.31, 124.91, 124.29, 102.98, 30.34. **IR** (cm^{-1}) 3387 (br), 1712, 1605, 1577, 1454.

3-Aryloxindole 193:



192 **193**

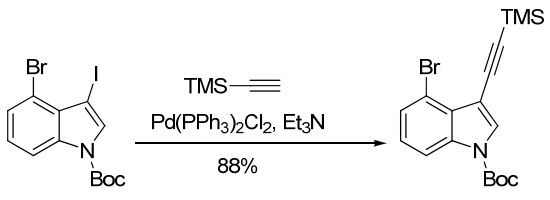
Tertiary alcohol **192** (1.12 g, 3.51 mmol, 1.0 equiv) was dissolved in neat $SOCl_2$ (5.12 mL, 70.2 mmol, 20 equiv), and the yellow solution was stirred overnight (15 h). The solvent was removed under reduced pressure, and the residue was dissolved in toluene (10 mL×3) and concentrated three times to provide the tertiary chloride a yellow oil, which was used without further purification. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.51 –

7.43 (m, 3H), 7.37 – 7.32 (m, 3H), 7.31 (dd, *J* = 7.4, 1.1 Hz, 1H), 6.99 (dd, *J* = 8.1, 7.6 Hz, 1H), 3.61 (s, 3H).

The crude chloride was dissolved in dry THF (30 mL), and zinc dust (1.15 g, 17.5 mmol, 5.0 equiv) and HOAc (2.0 mL, 35.1 mmol, 10.0 equiv) were added. The suspension was stirred at RT for 5 h, diluted with Et_2O (200 mL) and brine (25 mL). The organic layer was washed with sat. $NaHCO_3$ (20 mL×2), brine (20 mL), dried over $MgSO_4$, filtered, and concentrated to provide a colorless oil. Purification by flash chromatography (10:1 hexanes:EtOAc) provided 3-aryloxindole **193** (1.0 g, 94%) as a colorless crystalline solid.

R_f = 0.28 in 10:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.41 (dt, *J* = 8.2, 1.1 Hz, 1H), 7.35 – 7.25 (m, 3H), 7.18 – 7.10 (m, 2H), 7.04 (dt, *J* = 7.3, 1.2 Hz, 1H), 6.87 (dd, *J* = 8.1, 7.4 Hz, 1H), 4.57 (s, 1H), 3.62 (s, 3H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 175.72, 141.27, 135.97, 133.56, 131.58, 128.57, 128.08, 127.36, 123.85, 123.49, 101.97, 51.40, 29.72. **IR** (cm^{-1}) 3085, 3056, 3023, 2942, 2909, 1716.

Alkyne 197:

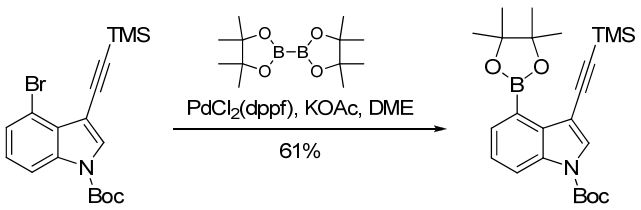


Iodide **196** (345 mg, 0.817 mmol, 1.0 equiv), $Pd(PPh_3)_2Cl_2$ (28.7 mg, 0.041 mmol, 5 mol%), CuI (15.6 mg, 0.082 mmol, 10 mol%), TMSA (170 μL, 1.226 mmol, 1.5 equiv)

were charged in a 25 mL round bottom flask with a condenser. Dry triethylamine (5.7 mL, 40.9 mmol, 50.0 equiv) was degassed by sparging with N_2 for 15 min, and cannulated into the flask. The reaction was stirred in a 60 °C oil bath under N_2 atmosphere for 3 h, and concentrated to provide a brown oil. Flash chromatography with 20:1 hexanes:EtOAc provided alkyne **197** (282 mg, 88%) as a yellow oil.

$\mathbf{R_f}$ = 0.32 in 40:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.14 (br d, *J* = 8.3 Hz, 1H), 7.82 (s, 1H), 7.39 (dd, *J* = 7.8, 0.8 Hz, 1H), 7.13 (t, *J* = 8.1 Hz, 1H), 1.63 (s, 9H), 0.25 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 148.54, 135.81, 131.92, 128.18, 128.00, 126.04, 115.49, 114.66, 103.73, 99.61, 97.66, 85.03, 28.23, -0.21. **IR** (cm^{-1}) 2958, 2157, 1748.

Boronic Ester 198:



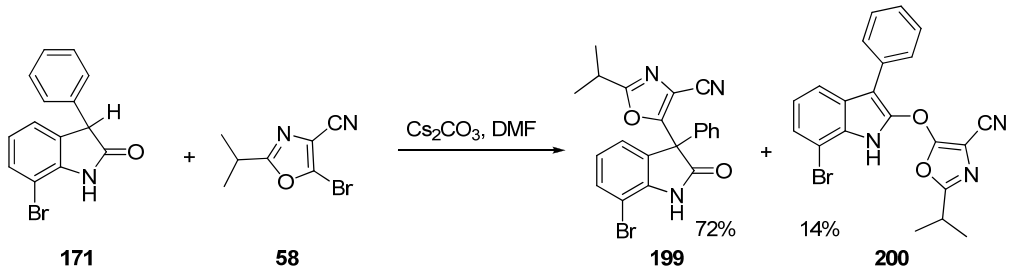
197 **198**

Bromide **197** (282 mg, 0.719 mmol, 1.0 equiv), $PdCl_2$(dppf) CH_2Cl_2 complex (58.7 mg, 0.072 mmol, 10 mol%), bispinacolatodiboron (365 mg, 1.437 mmol, 2.0 equiv), and KOAc (212 mg, 2.156 mmol, 3.0 equiv) were combined in a 25 mL long neck flask with a cold finger. Fresh distilled DME (7 mL) was degassed by sparging with N_2 for 15 min, and cannulated into the flask. The resulting orange solution was stirred in a 90 °C oil bath for 5 h. The reaction was filtered through celite, washed with EtOAc, concentrated to

provide a brown oil. Flash chromatography with 20:1 hexanes:EtOAc provided boronic ester **198** (191.5 mg, 61%) as a yellow oil.

R_f = 0.36 in 20:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.25 (br d, *J* = 8.3 Hz, 1H), 7.87 (s, 1H), 7.59 (dd, *J* = 7.2, 1.1 Hz, 1H), 7.29 (dd, *J* = 8.3, 7.2 Hz, 1H), 1.64 (s, 9H), 1.41 (s, 12H), 0.25 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 148.86, 134.61, 133.68, 131.74, 130.36, 124.27, 117.34, 104.51, 99.43, 96.85, 84.47, 84.27, 28.32, 28.24, 25.08, 0.45. **IR** (cm^{-1}) 2974, 2153, 1744.

C-Arylation Oxindole 199 and O-Arylation Oxindole 200:



Oxindole **171** (75 mg, 0.26 mmol, 1.1 equiv), bromooxazole **58** (50 mg, 0.23 mmol, 1.0 equiv), and Cs_2CO_3 (167 mg, 0.51 mmol, 2.2 equiv) were charged in a Schlenk tube. Fresh distilled dry DMF was degassed by sparging with N_2 for 15 min, and cannulated into the Schlenk tube, which was then sealed and placed in a 65 °C oil bath. After stirring at 65 °C for 15 h, the reaction was diluted with Et_2O (50 mL) and EtOAc (10 mL), washed with water (10 mL×4), brine, dried over $MgSO_4$, filtered, and concentrated to provide a yellow sticky oil. Flash chromatograph with 5:1 hexanes:EtOAc provided C-arylation oxindole **199** (72 mg, 73%) and O-arylation product **200** (13.5 mg, 14%) as white solids.

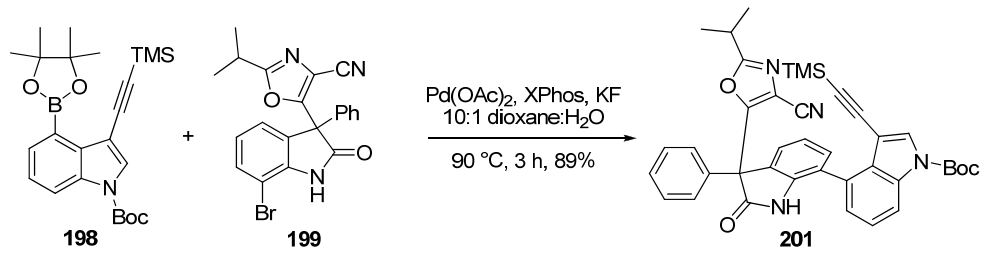
***C*-arylation oxindole 199:**

R_f = 0.25 in 5:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.36 (s, 1H), 7.48 (dd, *J* = 8.2, 0.9 Hz, 1H), 7.42 – 7.30 (m, 5H), 7.27 (d, *J* = 7.5 Hz, 1H), 7.04 (t, *J* = 7.76 Hz, 1H), 3.01 (hept, *J* = 7.0 Hz, 1H), 1.28 (dd, *J* = 7.0, 4.9 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.35, 160.06, 139.94, 130.87, 129.73, 129.01, 128.77, 127.49, 126.86, 125.82, 122.67, 119.30, 110.73, 104.80, 104.03, 92.16, 29.85, 28.57, 19.74. **m.p**. = 208 – 209 °C. **IR** (cm^{-1}) 3199, 3092, 2974, 2242, 1728, 1617.

***O*-arylation oxindole 200:**

R_f = 0.45 in 5:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.55 – 7.47 (m, 2H), 7.46 – 7.36 (m, 3H), 7.35 – 7.26 (m, 1H), 7.08 (t, *J* = 7.9 Hz, 1H), 2.79 (hept, *J* = 7.0 Hz, 1H), 1.14 (d, *J* = 7.0 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 161.35, 160.06, 139.94, 130.87, 129.73, 129.01, 128.77, 127.49, 126.86, 125.82, 122.67, 119.30, 110.73, 104.80, 104.03, 92.16, 28.57, 19.74. **IR** (cm^{-1}) 3395, 3272, 2978, 2239, 1646, 1621, 1580.

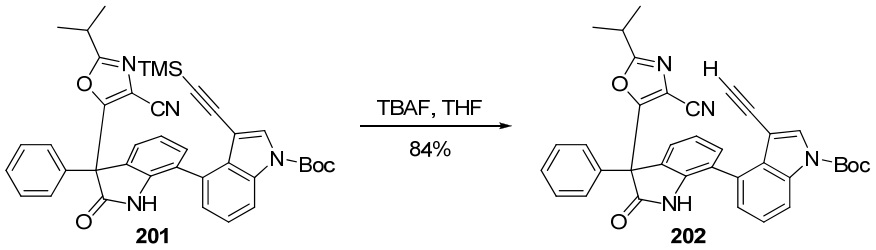
Cyclization Precursor 201:



Oxindole **199** (115 mg, 0.272 mmol, 1.0 equiv), boronic ester **198** (144 mg, 0.3237 mmol, 1.2 equiv), $Pd(OAc)_2$ (6.1 mg, 0.027 mmol, 10 mol%), XPhos (26.0 mg, 0.054 mmol, 20 mol%), and KF (47.5 mg, 0.817 mmol, 3.0 equiv) were charged in a long neck round bottom flask with a cold finger. A mixture of 10:1 dioxane:H_2O (6 mL) was degassed by sparging with N_2 for 15 min, and cannulated into the flask with all the materials. The resultant brown solution was stirred in a 90 °C oil bath for 3 h, and concentrated to provide a brown oil. Flash chromatograph with 5:1 hexanes:EtOAc provided biaryl **201** (149 mg, 84%, about 4:3 ratio of atropisomers) as a yellow oil.

$\mathbf{R_f}$ = 0.25 in 5:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.27 (d, *J* = 8.3 Hz, 1H), 7.88 (s, 1H), 7.65 (br s, major, 1H), 7.62 (br s, minor, 1H), 7.50 – 7.43 (m, 1H), 7.43 (s, 7H), 7.24 – 7.07 (m, 2H), 3.12 – 2.86 (two hept, 1H), 1.67 (two s, 9H), 1.36 – 1.21 (two dd, 6H), -0.03 (s, major, 9H), -0.17 (s, minor, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$; The number of signals observed is not exactly twice that of a single atropisomer due to overlapping signals.) δ 173.29, 169.87, 169.38, 158.15, 157.76, 148.72, 139.02, 138.98, 135.92, 135.89, 135.76, 135.61, 133.28, 133.18, 132.81, 132.52, 131.16, 129.71, 129.68, 129.17, 129.10, 128.97, 128.89, 128.81, 128.11, 127.98, 127.93, 127.83, 127.25, 127.14, 126.88, 125.49, 125.45, 125.35, 124.94, 124.77, 124.70, 123.80, 123.67, 123.10, 122.49, 122.36, 122.19, 115.68, 115.51, 112.47, 112.30, 111.63, 111.50, 105.92, 102.69, 102.60, 98.88, 98.81, 97.40, 97.21, 84.99, 57.76, 57.48, 57.33, 28.53, 28.46, 28.31, 28.25, 20.32, 20.19, 19.99, 19.90, 0.04, -0.15. **IR** (cm^{-1}): 3300, 2977, 2926, 2239, 2110, 1736, 1723. **HRMS** m/z calcd for $C_{39}H_{38}N_4O_4SiNa^+$: 677.2560; found: 677.2557.

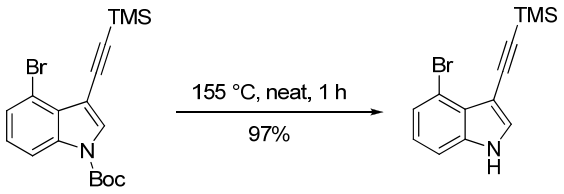
Alkyne 202:



TMS-protected alkyne **201** (32 mg, 0.049 mmol, 1.0 equiv) was dissolved in THF (1 ml), and a solution of TBAF trihydrate (31 mg, 0.098 mg, 2.0 equiv) in THF (3.2 mL) was added. The yellow solution was stirred at RT for 1 h, and the reaction was diluted with ether (30 mL), washed with brine, dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. Purification by flash chromatography (5:1 hexanes:EtOAc) provided alkyne **202** (24 mg, 84%, about 3:2 ratio of atropisomers) as a colorless oil.

$\mathbf{R_f}$ = 0.15 in 5:1 hexanes:EtAOc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.29 (d, J = 8.4 Hz, 1H), 7.89 (s, minor, 1H), 7.84 (s, major, 1H), 7.53 – 7.34 (m, 8H), 7.30 – 7.14 (m, 3H), 3.03 (two hept, 1H), 2.51 (s, minor, 1H), 2.26 (s, major, 1H), 1.69 (two s, 9H), 1.31 (two dd, 6H). ^{13}C NMR (75 MHz, $CDCl_3$, The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 173.34, 173.29, 169.88, 169.77, 157.84, 157.66, 148.73, 148.70, 139.87, 139.81, 135.85, 135.35, 135.27, 135.08, 132.48, 132.28, 131.91, 131.66, 129.66, 129.62, 129.21, 129.16, 129.14, 129.10, 128.94, 128.29, 127.92, 127.85, 127.48, 127.20, 126.96, 125.95, 125.83, 125.80, 125.65, 125.42, 125.02, 122.86, 122.81, 122.58, 115.90, 115.86, 112.83, 112.72, 111.78, 111.45, 75.67, 75.46, 57.52, 57.42, 28.56, 28.51, 28.25, 20.20, 20.18, 20.06, 19.97. **IR** (cm^{-1}): 2971, 2240, 2151, 1742, 1727. **HRMS** m/z calcd for $C_{36}H_{30}N_4O_4Na^+$: 605.2165; found: 605.2166.

Indole 205:

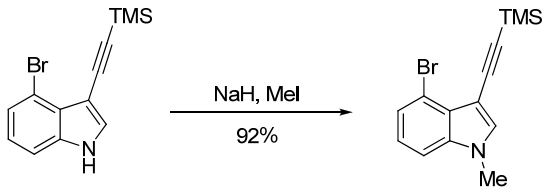


197 **205**

Boc-protected indole **197** (1.08 g, 2.75 mmol) was charged in a 100 mL round bottom flask, which was attached to vacuum, and the flask was placed into a 155 °C oil bath for 1 h. After gas evolving was ceased, the residual brown oil was purified by flash chromatography (5:1 hexanes:EtOAc) to provide indole **205** (780 mg, 97%) as a colorless oil.

R_f = 0.25 in 5:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.28 (br s, 1H), 7.44 (d, *J* = 2.7 Hz, 1H), 7.29 (dd, *J* = 7.6, 0.6 Hz, 1H), 7.26 (dd, *J* = 8.2, 0.6 Hz, 1H), 7.01 (t, *J* = 7.9 Hz, 1H), 0.25 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 136.03, 130.71, 126.42, 125.47, 124.07, 115.55, 110.96, 99.78, 99.32, 97.32, -0.04. **IR** (cm^{-1}) 3407, 2958, 2892, 2149, 1613, 1560, 1417.

***N*-Methyl Indole 206:**

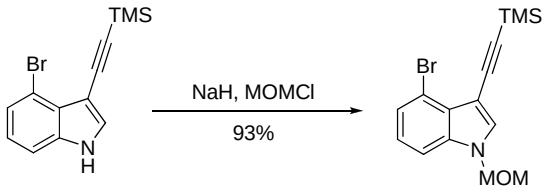


205 **206**

Indole **205** (56.5 mg, 0.193 mmol) and NaH (60% in mineral oil, 9.3 mg, 0.232 mmol, 1.2 equiv) were combined in a 10 mL round bottom flask, which was cooled in an ice bath, and dry THF (3.6 mL) was added via syringe. The yellow solution was stirred in the ice bath for 30 min, and MeI (24 μL, 0.387 mmol, 2.0 equiv) was added via syringe. After stirring in the ice bath for 1 h, the reaction was diluted with Et_2O (20 mL), washed with brine (5 mL), dried over $MgSO_4$, filtered, and concentrated to provide a yellow oil. Purification by flash chromatography (10:1 hexanes:EtOAc) provided *N*-methyl indole **206** (54.5 mg, 92%) as a white solid.

R_f = 0.25 in 10:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.28 (dd and s, *J* = 7.6, 0.6 Hz, 2H), 7.18 (dd, *J* = 8.2, 0.5 Hz, 1H), 7.02 (t, *J* = 7.9 Hz, 1H), 3.70 (s, 3H), 0.25 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.00, 135.05, 127.00, 125.00, 123.47, 115.64, 109.08, 99.35, 97.96, 96.94, 33.42, 0.01.

***N*-MOM indole 207:**

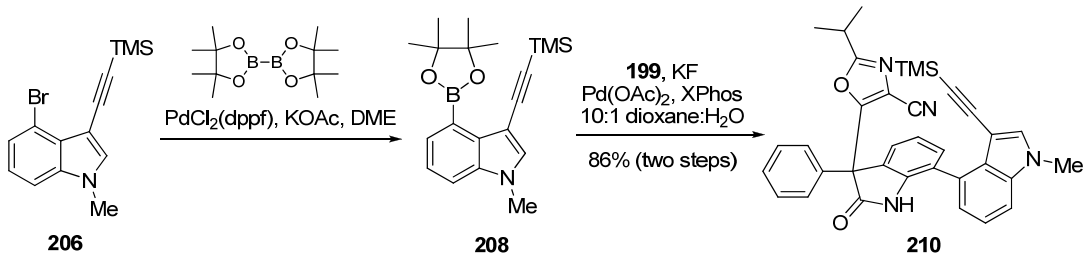


205 **207**

Compound **207** was prepared in 93% yield (285 mg) via a similar procedure as the preparation of *N*-methyl indole **206**. **R_f** = 0.25 in 10:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.34 (d, *J* = 8.2 Hz, 1H), 7.31 (d, *J* = 7.6 Hz, 1H), 7.03 (t, *J* = 7.9 Hz, 1H), 5.30 (s, 2H), 3.14 (s, 3H), 0.28 (s, *J* = 9.9 Hz, 9H). **^{13}C NMR** (75 MHz,

$CDCl_3$) δ 136.39, 134.15, 127.34, 125.79, 124.10, 115.53, 109.86, 99.29, 98.81, 97.60, 77.86, 56.07, -0.09.

Biaryl 210:



Bromide **206** (55 mg, 0.18 mmol, 1.0 equiv), $PdCl_2$(dppf) CH_2Cl_2 complex (14.6 mg, 0.018 mmol, 10 mol%), bispinacolatodiboron (50 mg, 0.20 mmol, 1.1 equiv), and KOAc (53 mg, 0.539 mmol, 3.0 equiv) were combined in a 25 mL long neck flask with a cold finger. Fresh distilled DME (3.5 mL) was degassed by sparging with N_2 for 15 min, and cannulated into the flask. The resulting orange solution was stirred in a 90 °C oil bath for 20 h. The reaction was cooled down to room temperature, diluted with Et_2O (20 mL) and H_2O (20 mL). The aqueous layer was extracted with Et_2O (20 mL×3), and the combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, filtered, and concentrated to provide compound **208** as a dark brown oil, which was used directly in the next step withour purification. An analytical sample of **208** was prepared by flash chromatography (1:2 hexanes:CH_2Cl_2) as an orange oil. **Caution**: Compound **208** partially decomposed on the silica column.

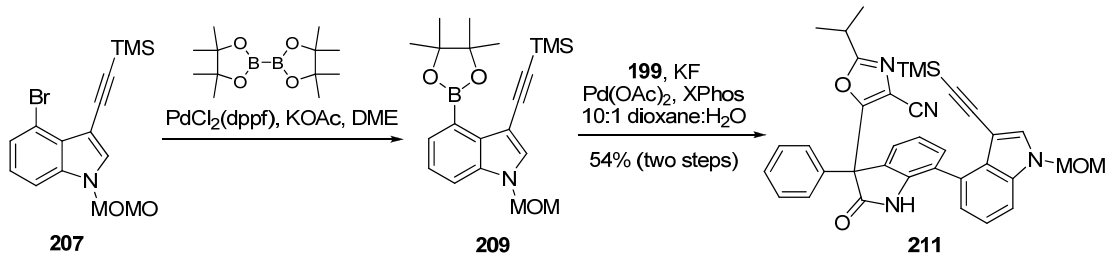
Boronic ester **208**: $\mathbf{R_f}$ = 0.45 in 1:2 hexanes:CH_2Cl_2. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 7.0 Hz, 1H), 7.39 (s, 1H), 7.33 (d, *J* = 8.2 Hz, 1H), 7.21 (dd, *J* = 8.0, 7.3 Hz,

1H), 3.70 (s, 3H), 1.41 (s, 12H), 0.25 (s, 9H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 137.16, 135.85, 130.27, 128.09, 121.67, 111.92, 101.38, 98.19, 94.33, 84.02, 33.11, 29.82, 25.08, 0.68. **IR** (cm^{-1}) 2970, 2137.

The crude boronic ester **208** (63.5 mg, theoretically yield, 0.18 mmol, 1.2 equiv), bromooxindole **199** (63 mg, 0.15 mmol, 1.0 equiv), $Pd(OAc)_2$ (3.4 mg, 0.015 mmol, 10 mol%), XPhos (14.5 mg, 0.030 mmol, 20 mol%), and KF (26.0 mg, 0.45 mmol, 3.0 equiv) were charged in a long neck round bottom flask with a cold finger. A mixture of 10:1 dioxane:H_2O (3 mL) was degassed by sparging with N_2 for 15 min, and cannulated into the flask with all the materials. The resultant brown solution was stirred in a 90 °C oil bath for 3 h, and concentrated to provide a brown oil. Purification by Flash chromatography (10% CH_2Cl_2 in 5:1 hexanes:EtOAc) provided biaryl **210** (73 mg, 86% over two steps, about 4:3 ratio of atropisomers) as a white solid.

Biaryl **210**: $\mathbf{R_f}$ = 0.25 in 10% CH_2Cl_2 in 5:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, J = 14.6 Hz, 2H), 7.49 – 7.26 (m, 9H), 7.19 (t, J = 7.7 Hz, 1H), 7.12 (d, J = 6.7 Hz, major, 1H), 7.05 (s, J = 6.8 Hz, minor, 1H), 3.81 (s, 3H), 3.05 (m, 1H), 1.32 – 1.19 (m, 6H), -0.02 (s, major, $SiMe_3$), -0.17 (s, minor, $SiMe_3$). **^{13}C NMR** (101 MHz, $CDCl_3$; The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 173.31, 173.24, 169.80, 157.94, 138.81, 137.21, 136.08, 136.01, 135.82, 135.73, 135.62, 133.23, 129.92, 129.60, 129.29, 129.22, 129.08, 128.89, 128.41, 128.24, 128.19, 128.13, 127.98, 125.53, 125.14, 123.08, 123.03, 122.96, 122.83, 122.38, 122.23, 121.85, 112.38, 111.67, 111.60, 110.13, 99.16, 96.81, 96.71, 96.53, 33.45, 28.51, 20.21, 19.98, 0.23, 0.05.

Biaryl 211:

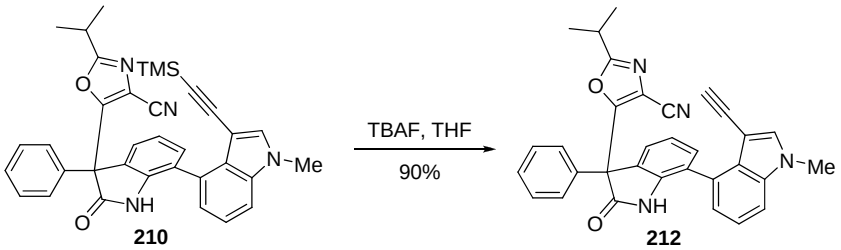


207 209 211

Compound **211** was prepared as a white solid in 54% yield (about 4:3 ratio of atropisomers) via a similar procedure as the preparation of alkyne **210**.

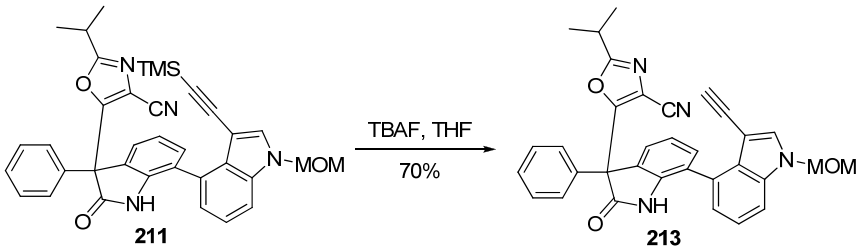
R_f = 0.25 in 2:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.59 – 7.44 (m, 4H), 7.43 – 7.26 (m, 8H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.16 (d, *J* = 7.2 Hz, major, 1H), 7.08 (d, *J* = 7.2 Hz, minor, 1H), 5.45 (s, 2H), 3.26 (s, minor, Me), 3.25 (s, major, Me), 3.05 (hept, *J* = 6.9 Hz, major, 1 H), 2.99 (hept, *J* = 6.9 Hz, minor, 1 H), 1.31 (d, *J* = 6.9 Hz, major, 6 H), 1.28 (d, *J* = 6.8 Hz, minor, 6H), -0.00 (s, major, $SiMe_3$), -0.16 (s, minor, $SiMe_3$). **^{13}C NMR** (101 MHz, $CDCl_3$; The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 173.22, 169.83, 157.86, 138.83, 136.73, 135.78, 135.63, 135.22, 134.91, 133.27, 129.81, 129.27, 129.24, 129.11, 128.91, 128.02, 127.95, 127.84, 127.79, 127.75, 126.36, 126.06, 125.28, 125.24, 123.62, 123.55, 123.46, 122.88, 122.78, 122.73, 122.67, 122.39, 122.29, 122.22, 112.44, 112.33, 111.67, 111.59, 110.95, 98.62, 98.47, 98.34, 98.22, 97.14, 77.95, 56.33, 28.54, 28.48, 20.35, 20.23, 20.00, 19.90, 0.18, -0.01. **IR** (cm^{-1}) 3220, 2240 (nitrile), 2149 (alkyne), 1711.

Alkyne 212:



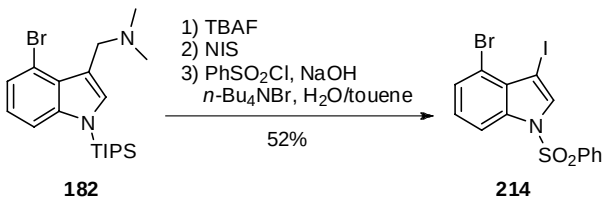
Alkyne **212** was prepared in 90% yield (about 3:2 ratio of atropisomers) via a similar procedure as the preparation of alkyne **202**. $\mathbf{R_f}$ = 0.25 in 2:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.55 – 7.47 (m, 1H), 7.43 (d, *J* = 7.7 Hz, 1H), 7.41 – 7.27 (m, 9H), 7.21 (m, 1H), 7.13 (d, *J* = 6.2 Hz, major, 1H), 7.07 (d, J = 7.0 Hz, minor, 1H), 3.82 (s, minor, Me), 3.80 (s, major, Me), 3.11 – 2.95 (m, 1H), 2.51 (s, minor, 1H), 2.22 (s, major, 1H), 1.36 – 1.17 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$; The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 173.41, 173.22, 169.74, 158.09, 157.70, 139.88, 139.77, 136.62, 136.58, 136.01, 135.50, 135.32, 135.02, 131.67, 131.33, 129.59, 129.10, 129.07, 129.00, 128.95, 128.83, 128.40, 127.81, 127.36, 127.13, 125.85, 125.47, 125.42, 123.66, 123.56, 123.20, 123.07, 122.81, 122.76, 122.58, 122.34, 112.54, 111.81, 111.48, 110.22, 95.46, 95.30, 78.80, 78.67, 57.34, 33.46, 28.51, 28.45, 20.18, 20.03, 19.93. **IR** (cm^{-1}) 3301, 2970, 2933, 2238, 2096, 1728, 1618, 1597.

Alkyne 213:



Alkyne **213** was prepared in 70% yield (about 2:1 ratio of atropisomers) via a similar procedure as the preparation of alkyne **202**. $\mathbf{R_f}$ = 0.15 in 2:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.3 Hz, 1H), 7.53 – 7.46 (m, 2H), 7.45 – 7.30 (m, 8H), 7.22 (t, *J* = 7.8 Hz, 1H), 7.17 (d, *J* = 7.2 Hz, major, 1H), 7.11 (d, *J* = 7.2 Hz, minor, 1H), 5.43 (d, *J* = 7.3 Hz, 2H), 3.26 (s, CH_3, major), 3.24 (s, CH_3, minor), 3.11 – 2.93 (m, 1H), 2.51 (s, alkyne C-H, minor, 1H), 2.23 (s, alkyne C-H, major, 1H), 1.35 – 1.25 (m, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$; The number of signals observed is not exactly twice that of a single diastereomer due to overlapping signals.) δ 173.50, 173.36, 169.88, 169.83, 158.09, 157.73, 139.95, 139.84, 136.25, 136.19, 136.09, 135.12, 134.78, 134.59, 131.92, 131.55, 129.86, 129.84, 129.22, 129.19, 129.12, 128.95, 128.46, 127.90, 127.50, 127.26, 126.50, 126.10, 125.68, 125.64, 123.96, 123.82, 123.65, 123.51, 123.40, 123.23, 122.92, 122.84, 122.67, 112.91, 112.67, 111.90, 111.57, 111.12, 97.13, 96.95, 79.43, 79.26, 78.02, 76.79, 76.62, 57.45, 56.49, 28.62, 28.56, 20.28, 20.14, 20.03. **IR** (cm^{-1}) 3301, 2974, 2925, 2242 (nitrile), 2108 (alkyne), 1728.

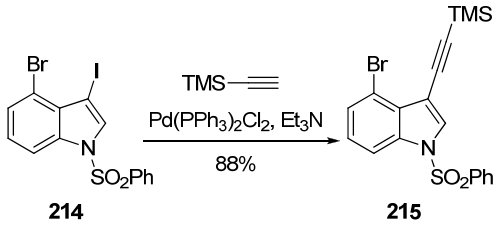
Iodo Indole 214:



To a solution of gramine derivative **182** (942 mg, 2.30 mmol, 1.0 equiv) in THF (10 mL) was added a solution of TBAF trihydrate (763 mg, 2.42 mmol, 1.05 equiv) in THF (12 mL), and the mixture was stirred for 15 min. After concentrating under reduced pressure, H_2O (20 mL) and CH_2Cl_2 (20 mL) were added, and the phases were separated. The organic layer was cooled in an ice bath, and NIS (569 mg, 2.53 mmol, 1.1 equiv) was added in one portion. The resulting orange solution was stirred in the ice bath for 5 min, and poured into H_2O (20 mL) in a separatory funnel. The phases were separated, and the organic layer was washed with H_2O (10 mL) and brine (10 mL), concentrated to provide a brown oil. The brown residue was dissolved in toluene (20 mL), a mixture of H_2O (20 mL), *n*-Bu_4NBr (74 mg, 0.23 mmol, 0.1 equiv), $PhSO_2Cl$ (356 μL, 2.76 mmol, 1.2 equiv), and NaOH (1.33 g, 23.0 mmol, 10.0 equiv) was added. The biphasic mixture was vigorously stirred at room temperature for 2 h, and the phases were separated, and the organic phase was washed with H_2O (10 mL×3), brine (10 mL), dried over Na_2SO_4, filtered, and concentrated to provide a yellow oil. Purification by flash chromatography (5:1 hexanes:EtOAc) provided iodo indole **214** (555 mg, 52%) as a yellowish solid.

$\mathbf{R_f}$ = 0.45 in 5:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, $CDCl_3$) δ 8.00 (d, *J* = 8.3 Hz, 1H), 7.86 (d, *J* = 7.7 Hz, 2H), 7.81 (s, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.43 (t, *J* = 7.8 Hz, 2H), 7.39 (d, *J* = 7.7 Hz, 1H), 7.13 (t, *J* = 8.1 Hz, 1H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.40, 134.80, 134.52, 132.79, 129.61, 129.01, 126.98, 126.87, 126.15, 115.77, 112.95, 62.99. No significant absorptions in IR.

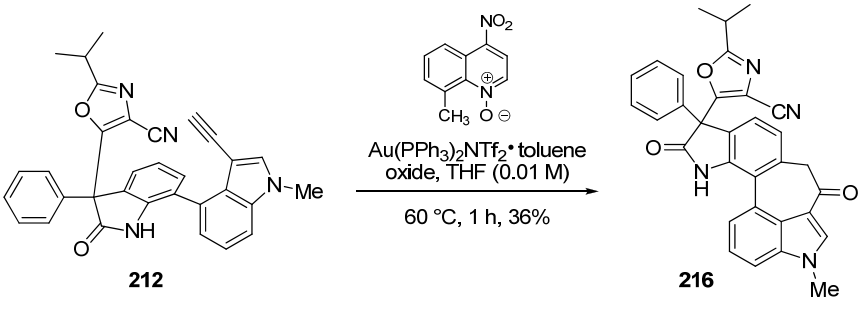
Alkyne 215:



214 **215**

Compound **215** was prepared as a yellowish oil in a quantitative yield (378 mg) from iodo indole **214** (400 mg) via a similar procedure as the preparation of alkyne **197**. $\mathbf{R_f}$ = 0.45 in 5:1 hexanes:EtOAc. **^{1}H NMR** (400 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 8.4, 0.7 Hz, 1H), 7.88 – 7.81 (m, 3H), 7.55 – 7.47 (m, 1H), 7.44 – 7.33 (m, 3H), 7.12 (t, *J* = 8.1 Hz, 1H), 0.25 (s, 9H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 137.40, 134.93, 134.48, 131.66, 129.55, 128.55, 128.37, 126.94, 126.33, 115.78, 112.80, 105.57, 100.84, 96.48, -0.35. **IR** (cm^{-1}) 3134, 3060, 2950, 2892, 2157, 1597, 1556.

Ketone 216:



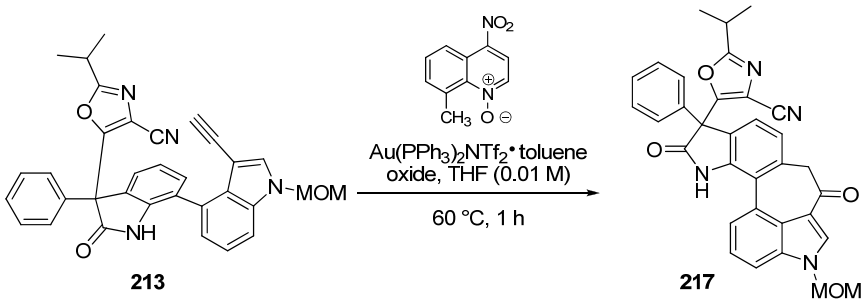
212 **216**

Alkyne **212** (125 mg, 0.252 mmol, 1.0 equiv), $Au(PPh_3)NTf_2$ toluene complex (20 mg, 0.013 mmol, 5 mol%), and 8-methyl-4-nitro quinolone oxide (57 mg, 0.28 mmol, 1.1 equiv) were charged in a 100 mL round bottom flask, and dry THF (25 mL) was added. The reaction was placed in a 60 °C oil bath, and stirred for 1 h. The reaction was

concentrated, and purified by flash chromatography (5% $CHCl_3$ in 2:1 hexanes:acetone) provided ketone **216** (47 mg, 36%) as a yellowish solid.

R_f = 0.25 in 5% $CHCl_3$ in 2:1 hexanes:acetone. **^{1}H NMR** (500 MHz, $CDCl_3$, peaks are broad due to slow rotation along the biaryl C-C bond.) δ 8.21 (s, 1H, exchagable by D_2O shake), 7.80 (s, 1H), 7.56 (s, 1H), 7.46 (br s, 3H), 7.38 (br s, 4H), 7.29 (d, *J* = 7.5, 1H), 7.21 (d, *J* = 7.6, 1 H), 3.92 (s + br s, 3H + 2H), 2.99 (s, 1H), 1.26 (s, 6H). **^{1}H NMR** (500 MHz, [D8]THF) δ 9.74 (s, 1H), 7.87 (s, 1H), 7.67 (d, *J* = 7.4 Hz, 1H), 7.56 (d, *J* = 8.1 Hz, 1H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.50 – 7.26 (m, 6H), 7.16 (d, *J* = 7.7 Hz, 1H), 3.93 (s, 3H), 3.81 (very br s, 2H), 3.00 (m, 1H), 1.24 (d, *J* = 6.9 Hz, 6H). **^{13}C NMR** (75 MHz, $CDCl_3$) δ 189.77, 170.02, 139.13, 138.23, 135.16, 133.55, 129.36, 129.32, 128.56, 128.46, 128.08, 126.60, 126.46, 126.21, 123.83, 121.61, 121.08, 118.15, 112.90, 111.64, 110.65, 57.38, 53.38, 34.11, 28.61, 20.29, 20.07. **IR** (cm^{-1}) 2962, 2921, 2848, 2243 (nitrile), 1728 (amide), 1663 (α,β-unsaturated ketone), 1467.

Ketone 217:



Ketone **217** was prepared in a 52% yield (36 mg) from alkyne **213** via a similar procedure as the preparation of ketone **216**. **R_f** = 0.15 in 1:1 hexanes:EtOAc. **^{1}H NMR** (500 MHz, CDCl3) δ 8.16 (s, 1H), 7.89 (s, 1H), 7.62 (d, J = 8.1 Hz, 1H), 7.58 (d, *J* = 4.0

Hz, 1H), 7.51 – 7.45 (m, 2H), 7.38 (br s, 4H), 7.30 (d, *J* = 7.7 Hz, 1H), 7.21 (d, *J* = 7.7 Hz, 1H), 5.54 (s, 2H), 4.30 – 3.57 (very broad, CH_2), 3.31 (s, 3H), 2.99 (m, 1H), 1.27 (br d, *J* = 4.2 Hz, 6H). **^{1}H NMR** (500 MHz, [D8]THF) δ 9.74 (s, 1H), 8.02 (s, 1H), 7.69 (two d, 2H), 7.48 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 7.6 Hz, 5H), 7.17 (d, *J* = 7.7 Hz, 1H), 5.62 (s, 2H), 4.02 – 3.74 (very broad, CH_2), 3.25 (s, 3H), 3.11 – 2.84 (m, 1H), 1.24 (d, J = 6.9 Hz, 6H). **^{13}C NMR** (101 MHz, $CDCl_3$) δ 190.18, 170.04, 139.16, 137.54, 134.82, 132.40, 129.33, 128.68, 128.55, 128.16, 128.05, 126.89, 126.59, 126.22, 124.43, 121.62, 121.46, 119.04, 111.64, 111.52, 78.88, 56.78, 53.33, 29.95, 28.62, 20.30, 20.08. **IR** (cm^{-1}) 3252, 2970, 2925, 2235, 1736, 1667, 1605.

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