Chapter 3

Direct and Selective Copper-Catalyzed Arylation of Tryptamines and Tryptophans: Total Synthesis of (+)-Naseseazines A and B[†]

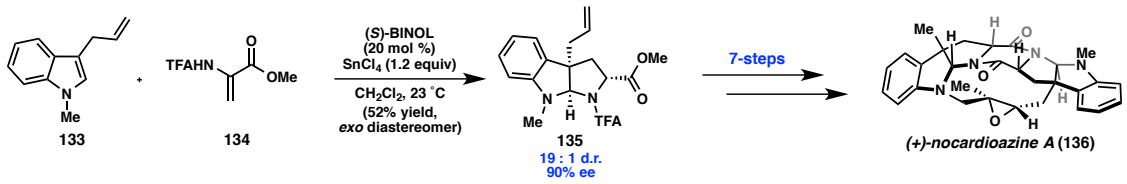
3.1 INTRODUCTION

3.1.1 Limitation of the Formal (3+2) Methodology

The pyrroloindoline is a common structural motif that unites several biosynthetically distinct families of alkaloids.[1] As discussed in **Chapters 1** and **2**, our lab has developed an enantioselective method to access this scaffold through the formal (3+2) cycloaddition of 3-substituted indoles and 2-amido acrylates. This strategy has been subsequently applied in the synthesis of several distinct natural products.[2] For example, 3-allyl pyrroloindoline **135,** prepared in 52% yield and 90% ee from 3-allylindole, can be advanced in only seven-steps to the macrocyclic natural product, (+)-nocardioazine A (**136**), a p-glycoprotein inhibitor.[3]

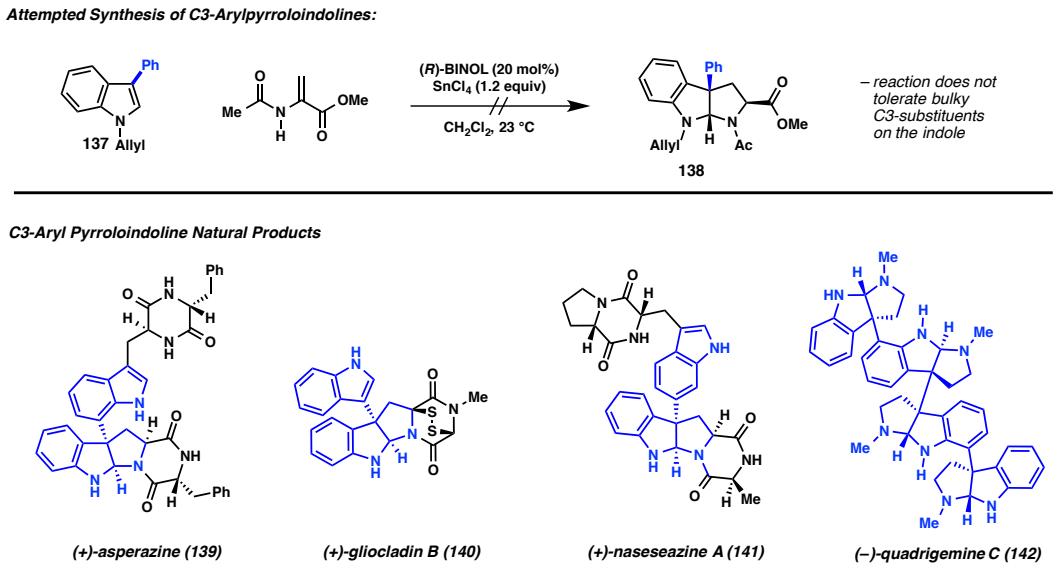
[†] Portions of this chapter have been reproduced from published studies (Kieffer, M. E.; Chuang, K. V.; Reisman, S. E. *Chem. Sci.* **2012**, *3*, 3170 – and – Kieffer, M. E.[★]; Chuang, K. V.[★]; Reisman, S. E. *J. Am. Chem. Soc.* **2013**, *135*, 5557) and the supporting information found therein. Work was conducted in collaboration with Kangway V. Chuang.

Scheme 3.1. *Total synthesis of (+)-nocardioazine A*



One major limitation of this convergent methodology is the inability to utilize indoles bearing bulky C3 substituents. For instance, *N*-allyl-3-phenylindole (**137**) fails to react under the optimized conditions, even after prolonged reaction times and more forcing conditions. This finding proved to be particularly unfortunate due to the prevalence of an important subclass of pyrroloindoline natural products characterized by a C3-quaternary center bearing an *aryl* substituent (**Figure 3.1**). These compounds, including quadrigemine C (**142**) and gliocladine B (**140**), exhibit potent biological activity, yet methods for their efficient preparation have remained a challenge in modern synthetic chemistry.[4,5] This chapter describes our efforts towards the development of a complementary and direct arylation reaction in order to gain convergent access to this subclass of natural products.

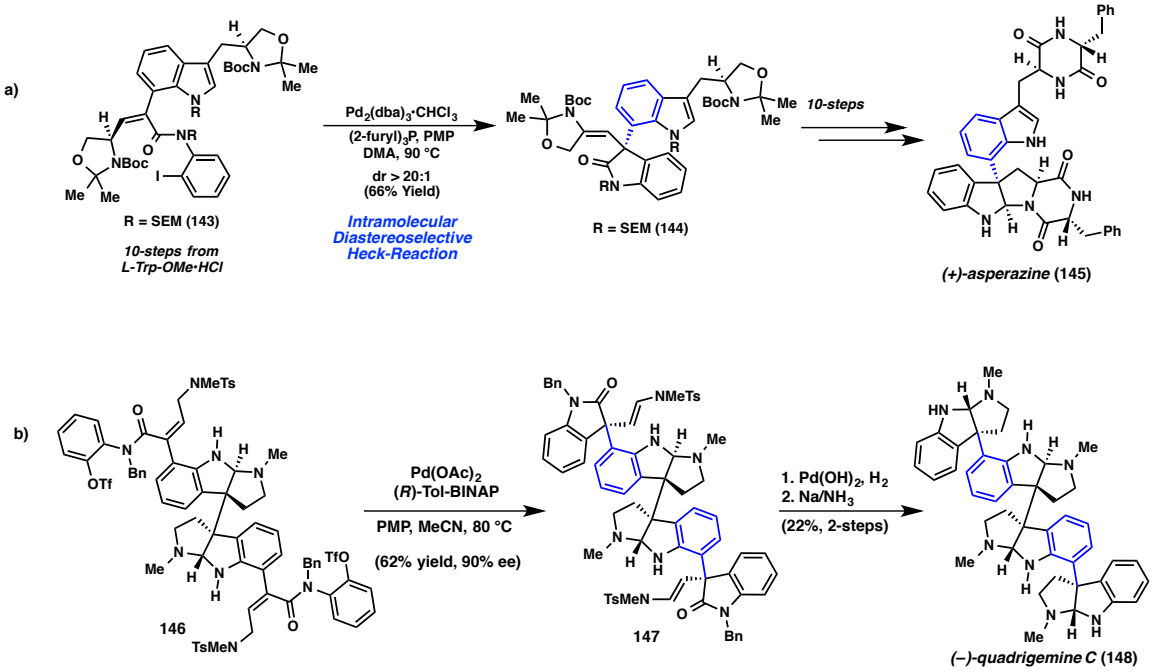
Figure 3.1. *C3-Aryl pyrroloindoline natural products*



3.1.2 Previous Syntheses of C3-arylated Pyrroloindolines

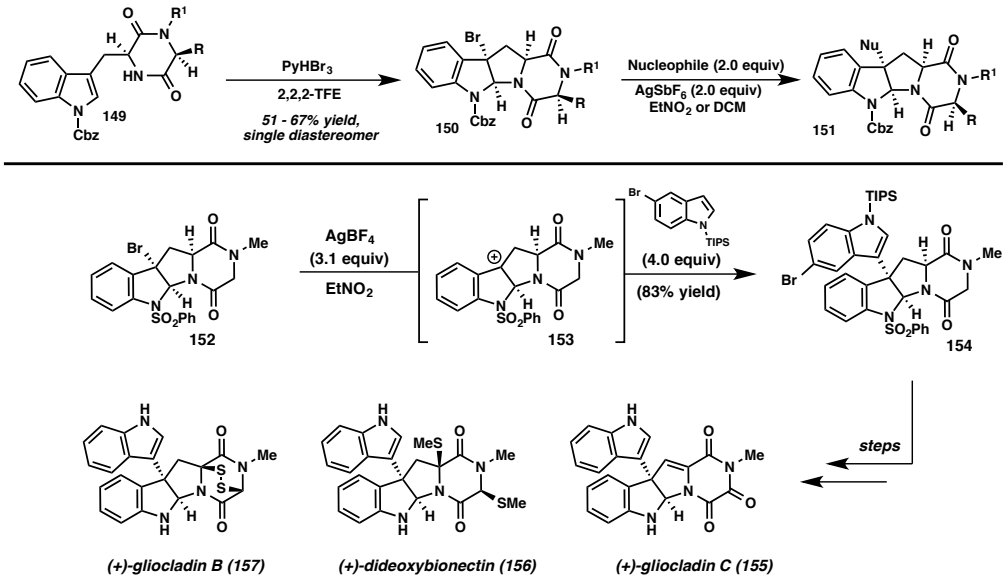
In a seminal 2001 report, Overman and Govek reported the successful implementation of an intramolecular Heck strategy in the synthesis of (+)-asperazine, a bisindole alkaloid containing a unique C3-C7 aryl linkage.[6] In 10-steps (*L*)-tryptophan methylester hyrdrochloride was advanced to iodoanilide **143** that, in a key step, was subjected to $Pd_2(dba)_3$, $(2\text{-furyl})_3P$, and PMP to effect a highly diastereoselective, intramolecular Heck reaction to form the C3-arylated quaternary center found in the natural product. Oxindole **144** was further advanced to (+)-asperazine in another 10-steps. The following year, Overman reported the total synthesis of the polypyrroloindoline alkaloid (–)-quadrigemine C, now utilizing a key, *enantioselective* Heck desymmetrization of a meso compound (**Scheme 3.2**, **b**).[7] Treatment of meso-**146** with $Pd(OAc)_2$ and *(R)*-tol-BINAP with pentamethylpiperidine affords bisoxindole **147**, which is efficiently cyclized under reductive conditions to the natural product.

Scheme 3.2. *Overman's approach to C3-aryl pyrroloindolines*



A decade later, Movassaghi and co-workers reported a general strategy towards this class of compounds using a bromocyclization/Friedel–Crafts approach (**Scheme 1.16, Chapter 1**).[5c] A subsequent publication details the extension of this strategy towards the completion of indole-bearing natural products **155**–**157** (**Scheme 3.3**). Again, starting with tryptophan-derived bromo tetracycle **152**, subjection to superstoichiometric $AgBF_4$ to generate the benzylic tertiary carbocation followed by the addition of four equivalents of an indole nucleophile, provides C3-aryl pyrroloindoline **154**. This common intermediate can be further functionalized to access (+)-gliocladins B and C and (+)-dideoxybionectin, demonstrating the power and versatility of this approach.[5d]

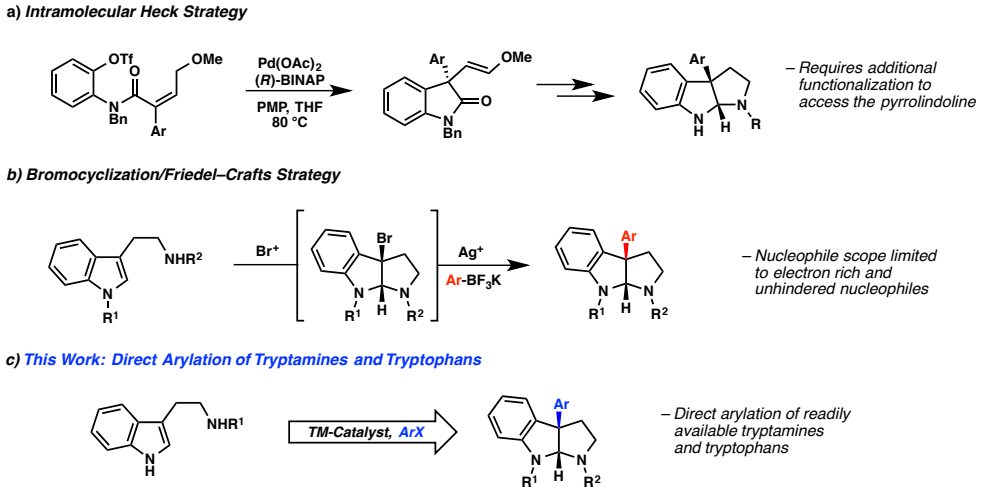
Scheme 3.3. *Movassaghi's approach to C3-aryl pyrroloindolines*



At the outset of our studies, the strategies presented by Overman and Movassaghi represented the state-of-the-art in the preparation of C3-aryl pyrroloindolines. Despite the ability of these elegant approaches to provide access to the desired scaffold, we believed there might be room for improvement (**Scheme 3.4**). For example, while the Heck reaction is a powerful tool for the generation of quaternary centers, the preparation of the cyclization precursor is lengthy, and additional steps are required for advancement to pyrroloindolines. In contrast, Movassaghi's approach is potentially more general and allows for late-stage aryl group installation, yet the reported conditions only provide moderate yields and require superstoichiometric amounts of silver salts and precious nucleophiles. Furthermore, only electron-rich and sterically unencumbered nucleophiles are tolerated with this approach. In considering various strategies, we recognized that there existed *no direct method* for the preparation of C3-arylpyrroloindolines, and therefore anticipated that the development of a direct arylation/cyclization cascade of tryptamines and tryptophans would significantly streamline the assembly and preparation

of a diverse array of C3-arylpyrroloindolines and enable the concise preparation of related natural products.

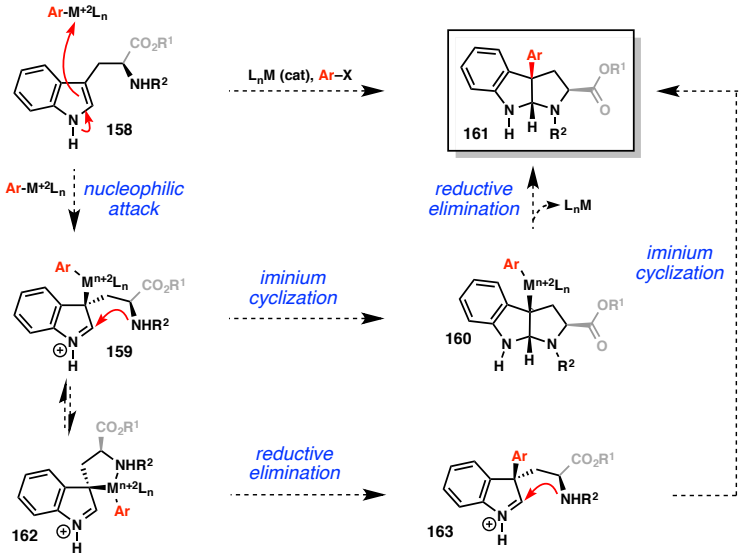
Scheme 3.4. *Strategies to access C3-aryl pyrroloindolines*



3.2 REACTION DESIGN

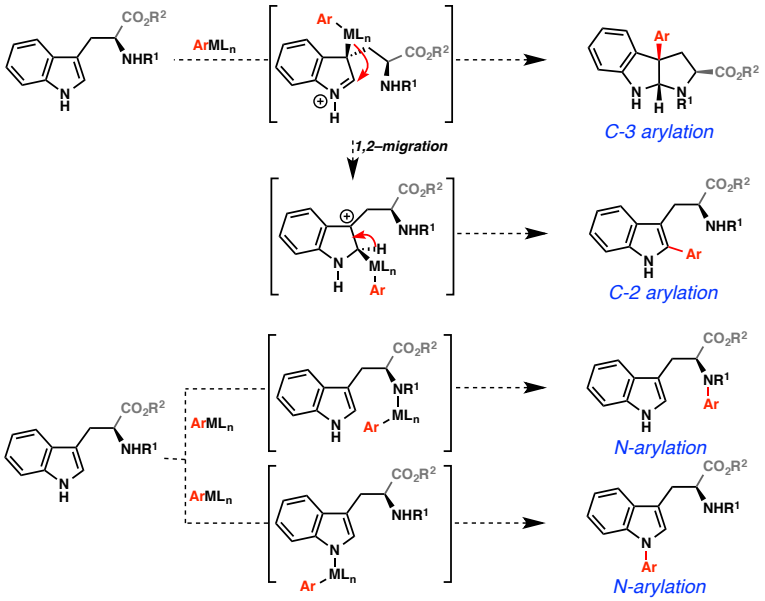
One possible strategy to effect this transformation is through transition metal catalysis. Although C3-functionalization/cyclization has been a widely employed approach for pyrroloindoline synthesis, and furthermore has been utilized successfully in the context of Pd-mediated C3-allylation and benzylation reactions, at the outset of our studies no equivalent *arylation* reaction had been reported.[8,9,10] Mechanistically, we hypothesized such a transformation could proceed through initial nucleophilic attack of a tryptamine or tryptophan onto an electrophilic metal center to form C3-metallated intermediate **159** (**Scheme 3.5**). Iminium cyclization to form the pyrrolidine ring, followed by reductive elimination to furnish the all carbon quaternary center, would provide the desired product (**161**). Alternatively, we imagined that the pendant amine might stabilize C3-metallated **159**. Reductive elimination from a spirocyclic intermediate (**162**) and subsequent iminium cyclization could also provide the pyrroloindoline product.

Scheme 3.5. *Proposed transition metal mechanism*



Although a transformation proceeding *via* indole C3-metallation seemed attractive, we recognized from the outset that this design was not without inherent challenges in chemoselectivity. Specifically, key to the success of this transformation is the generation of C3-metallated species **159**, which must undergo reductive elimination and cyclization to provide the desired product (**Scheme 3.6**). One major concern was the relative stability of such an intermediate, which is known to undergo facile migration to the C2 position of the indole.[11] Reductive elimination and rearomatization could then furnish 2-aryl indoles. Additionally, one could imagine coordination of the transition metal catalyst to either the indole nitrogen or the pendant amine to yield Buchwald-Hartwig type products.

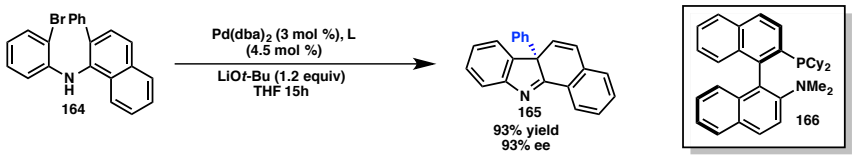
Scheme 3.6. *Possible indole reactivity*



3.2.1 Initial Investigation into Palladium Catalysis

Our initial strategy was inspired by 2009 work from Buchwald and co-workers in which they utilized a Pd(0-II) cycle in the asymmetric dearomatization of naphthalenes (**Scheme 3.7**).[12] Using chiral Davephos **166**, a variety of substituted arenes served as competent substrates in the generation of sterically demanding, arylated quaternary centers.

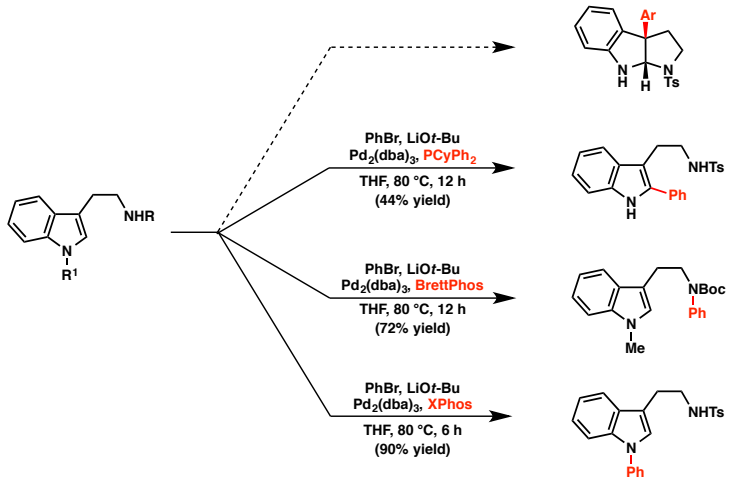
Scheme 3.7. *Buchwald's Pd-catalyzed intramolecular arylation*



Drawing an analogous mechanism, we wondered if Pd(0)/(II) catalysis could be applied to the direct arylation of tryptamine derivatives. A systematic screen of substrates, palladium sources, and ligands revealed the ability to selectivity access each of the predicted product isomers, except for the desired pyrroloindoline (**Scheme 3.8**).

Employing slightly smaller ligands, C2-arylation was observed while the use of bulky ligands, perhaps unsurprisingly, resulted in the formation of C–N bonds. With these negative results, a change in strategy was deemed necessary.

Scheme 3.8. *Pd-catalyzed arylation*



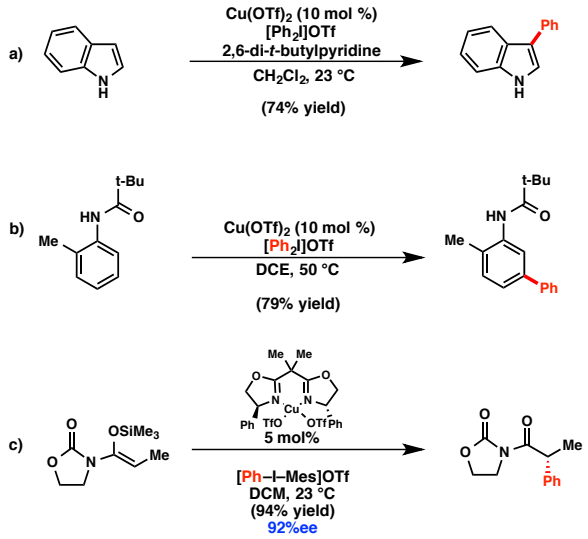
3.2.2 Investigation into Copper Catalysis

In our previous palladium approach, a variety of strong bases were used deprotonate the indole in order to increase its reactivity and nucleophilicity. Given the undesired reactivity observed, we decided to employ an alternative tactic to modify the reactivity. We reasoned that, rather than increasing substrate nucleophilicity, increasing metal electrophilicity might facilitate the rate of reductive elimination over 1,2-migration, thereby enabling the preparation of C3-arylated products.

To this end, we were encouraged by several reports from the Gaunt group, in which mild arylation of nucleophiles with diaryliodonium salts could be effected through Cu-catalysis (**Scheme 3.9**).[13] Specifically, Gaunt invokes a highly electrophilic Cu(III)-aryl intermediate, which is generated under mild conditions due to the ease of oxidative addition to diaryliodonium salts. We hypothesized that it may be possible to harness the

reactivity of this Cu/iodonium system to effect the direct arylation of tryptamines to form pyrroloindolines, but recognized from the outset that the generation of a sterically-demanding, aryl quaternary center may test the limits of this technology. Specifically, at the outset of our exploratory efforts, *no examples* of quaternary-center formation using Cu/ArI_2X had been reported in the literature.

Scheme 3.9. *Gaunt's Cu-catalyzed arylation*



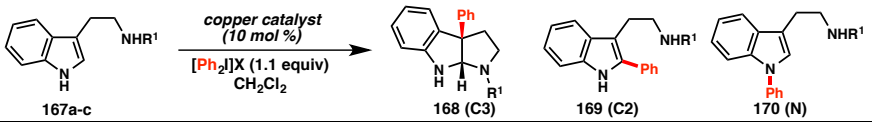
3.3 SCREENING AND OPTIMIZATION

Excited about the application of this new catalyst system, tosyl tryptamine **167a** was easily prepared and treated with Ph_2IBF_4, di-*tert*-butylpyridine, and 10 mol % $Cu(OTf)_2$, identical conditions to those reported by Gaunt and co-workers. Disappointingly, these efforts were met with extremely low conversion of starting material; however, trace masses corresponding to arylated products were detected by UHPLCMS. In considering the reaction conditions, we wondered whether di-*tert*-butylpyridine was potentially acting as a ligand and coordinating the copper catalyst, thereby mitigating its reactivity. Closer inspection of Gaunt's reported conditions

revealed that stoichiometric base was employed to suppress acid-catalyzed dimerization of the 2,3-unsubstituted indoles. As 3-substituted indoles have a significantly lower propensity to dimerize, the reaction was repeated in the absence of base. To our delight, 3-aryl pyrroloindoline **168a** was isolated in 60% yield along with 27% yield of migratory side product **169a** (**Table 3.1**).

Our optimization efforts began with a screen of Cu(I) and Cu(II) sources (**Table 3.1**). Whereas copper catalysts with highly coordinating ligands such as halides and acetonitrile (entries **6**–**7**) showed no reactivity, $Cu(OAc)_2$ exhibited an incredibly clean reaction profile (entry **8**) and moderate yields. Surprisingly, a low yield of side product **169a** did not necessarily correspond to a higher yield of product. In fact, it appears that 2-aryl indole **169a** converts to an unknown oxidative dimer as the reaction proceeds. In terms of the iodonium salts, the best results were obtained using the non-coordinating tetrafluoroborate counterion. Interestingly, use of a TFA counterion results in chemoselective *N*-arylation of the indole nitrogen (**170a**). The non-symmetric iodonium salt [Ph-I-Mes]BF_4, for which the mesityl group serves as a non-transferable ligand, is also a competent coupling partner, although longer reaction times are required.

Table 3.1. *Optimization of Cu-source and protecting group*



167a-c 168 (C3) 169 (C2) 170 (N)

entry	R^1	Cu source	X	additive	C3 : C2 : N	pdt	yield[a] (%)
1	Ts	$Cu(OTf)_2$	BF_4	–	2.3 : 1 : 0	168a	62[b]
2	Ts	–	BF_4	–	–	168a	0
3	Boc	$Cu(OTf)_2$	BF_4	–	–	168b	<5
4	Ac	$Cu(OTf)_2$	BF_4	–	–	168c	<5
5	Ts	$(CuOTf)_2$•PhMe	BF_4	–	3.4 : 1 : 0	168a	64
6	Ts	CuI	BF_4	–	–	168a	0
7	Ts	$Cu(MeCN)_4PF_6$	BF_4	–	–	168a	0
8	Ts	$Cu(OAc)_2$	BF_4	–	2.9 : 1	168a	64
9	Ts	$Cu(OTf)_2$	PF_6	–	2.5 : 1	168a	28
10	Ts	$Cu(OTf)_2$	OTf	–	2.9 : 1	168a	32
11	Ts	$Cu(OTf)_2$	Cl	–	–	168a	0
12	Ts	$Cu(OTf)_2$	TFA	–	0 : 0 : 1	170a	nd
13	Ts	$Cu(OTf)_2$	BF_4	dtbpy	–	168a	<5
14	Ts	$Cu(OTf)_2$	BF_4	–	2.6 : 1	168a	65[b]

[a] Determined by HPLC *versus* an internal standard. [b] Isolated yield. [c] $[Ph\text{-}I\text{-}Mes]BF_4$ was employed as the electrophile.

Although both $Cu(OTf)_2$ and $Cu(OAc)_2$ furnished comparable yields of pyrroloindoline **168a** when using $[Ph_2I]BF_4$ as the electrophile, the $Cu(OAc)_2$-catalyzed reaction profile was cleaner overall, thereby simplifying purification. As a result, $Cu(OAc)_2$ was the catalyst of choice for arylation reactions employing $[Ph_2I]BF_4$ or other symmetric iodonium salts. On the other hand, $Cu(OTf)_2$ proved superior for arylation reactions that employed less reactive, mesityl-substituted iodonium salts.

3.4 SUBSTRATE SCOPE OF RACEMIC ARYLATION

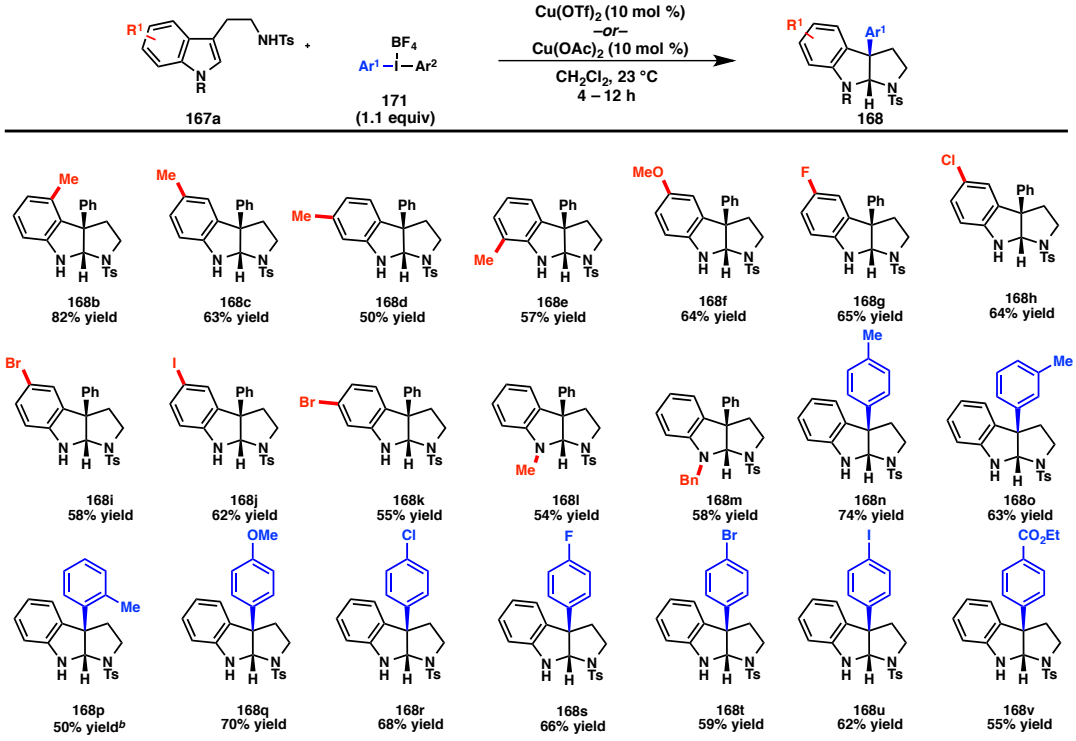
3.4.1 Tryptamine and Iodonium Scope

Using this method, a variety of arylated pyrroloindolines can be prepared in a single step from the corresponding *N*-tosyl tryptamines at ambient temperatures (**Table 3.2**). We were pleased to find that tryptamine substrates bearing alkyl substitution at C4, C5, C6, and C7 are accommodated, providing the corresponding pyrroloindolines in good

yields (**168b–168e**). Additionally, a variety of electron-donating and electron-withdrawing substituents are tolerated at C5. Although comparable yields are obtained, slower rates are observed in the reactions of indoles substituted with electron-withdrawing groups. *N*-tosyltryptamines bearing alkyl substitution on the indole nitrogen are also competent reaction partners (**168l–168m**).

We next investigated the scope of the aryl coupling partner. We were pleased to find that a range of electron-donating and withdrawing substituents were well tolerated at the *para*- and *meta*- positions, utilizing both symmetric and non-symmetric iodoniums. Unfortunately, *ortho*-substitution was poorly tolerated, providing the product in low yield (**168p**, 15% yield). Fortunately, reactivity could be restored by switching to the symmetric iodonium salt (**168p**, 50% yield).

Table 3.2. *Substrate Scope*

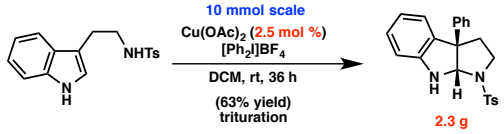


[a] Reactions were conducted on 0.30 mmol scale. Isolated yields are reported. [b] The symmetric iodonium was utilized.

3.4.2 Scale-up Procedure

Our screening protocol was conducted using 10–20 mol% catalyst loading to ensure uniformly good yields over a range of substrates. However, to demonstrate the scalability and efficiency of this transformation, the reaction has been carried out on a 3 g scale using N-tosyltryptamine and $[Ph_2I]BF_4$ with only 2.5 mol % catalyst loading. Purification by filtration followed by trituration provides analytically pure pyrroloindoline in 63% yield, without the need for column chromatography. Notably, the reaction proceeds at ambient temperature with nearly equimolar ratios of indole and $[Ph_2I]BF_4$.

Scheme 3.10. *Scale-up reaction*

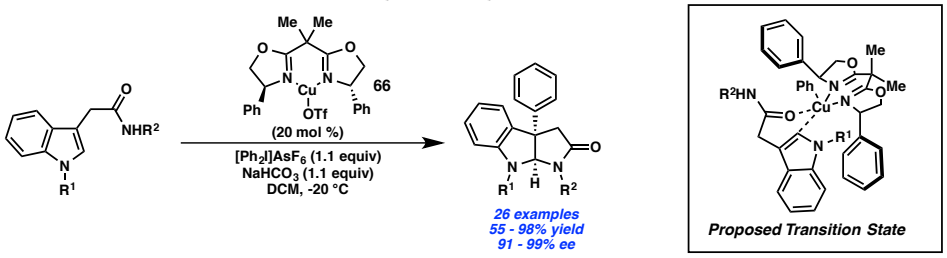


3.5 DIASTEREOSELECTIVE ARYLATION REACTION DESIGN

3.5.1 Macmillan's Enantioselective Method

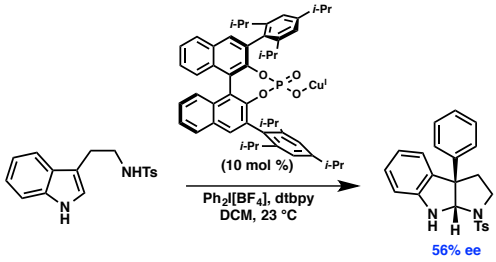
As the manuscript for this methodology was being prepared, a similar enantioselective transformation was reported by MacMillan and co-workers.[14] Utilizing chiral copper box complexes, they were able to effect both a chemoselective and enantioselective arylation of indole carboxamides. Their method proved general for a variety of substituted indoles and diaryliodonium salts (**Scheme 3.11**).

Scheme 3.11. *MacMillan's Cu-catalyzed arylation*



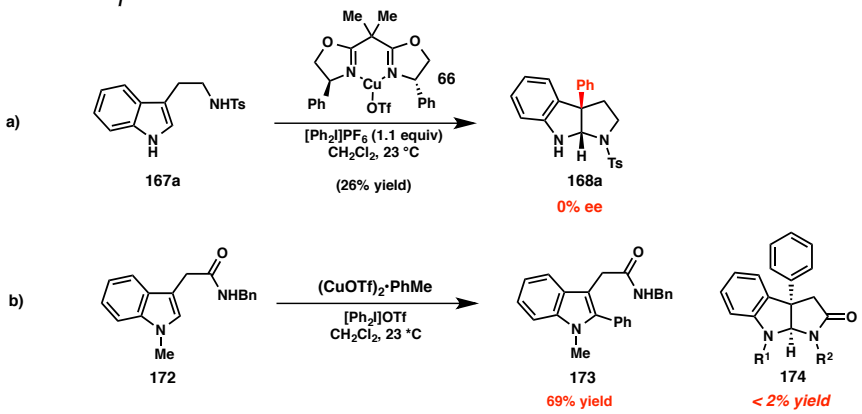
This report was particularly disappointing as we had already gathered preliminary data on an enantioselective variant of our arylation reaction. Employing catalytic copper and chiral copper phosphates, C3-aryl pyrroloindoline **168a** was recovered in moderate but promising enantioselectivities (**Scheme 3.12**).

Scheme 3.12. *Enantioselective result.*



Regardless, we resolved to investigate the differences and similarities between our conditions and MacMillan's conditions to gain a better understanding of the reactivity of these types of systems. Based on MacMillan's work, it has been established that indole carboxamides in conjunction with copper catalysis and diaryliodonium salts provide pyrroloindoline products in a chemoselective and enantioselective fashion. Interestingly, subjection of our substrate (**167a**) to MacMillan's conditions, provides low yields of arylated product and in racemic form. Similarly, subjection of MacMillan's substrate (**172**) to our ligandless copper conditions, provided almost exclusive C2-arylation (**173**).

Scheme 3.13. *Comparison Studies*



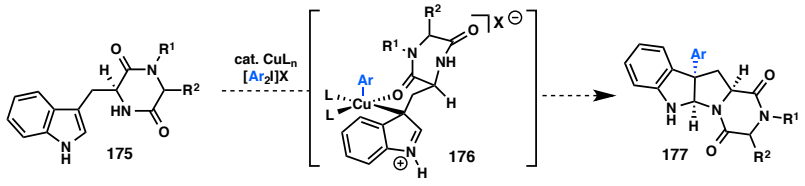
3.5.2 New Reaction Design

We rationalized that a careful matching of the directing group (Lewis-basicity) and catalyst stereoelectronics likely determined product ratios. Specifically, it appeared that MacMillan's more Lewis-basic directing group may compensate for the diminished electrophilicity of the ligated copper complex, allowing for the complex to still coordinate strongly to the substrate. Similarly, the diminished electrophilicity of the ligated copperbox complex may prevent meaningful coordination of *N*-tosyltryptamine, resulting in poor reactivity, yield, and no enantioinduction.

Acknowledging that our ultimate goal was to develop methodology useful in the application of natural product total synthesis, we recognized that neither our arylation method, nor that of MacMillan and co-workers, provides products with the functionality necessary for advancement to natural products. Instead, perhaps the most straightforward and useful approach was the direct and *diastereoselective* arylation of tryptophan derivatives. Starting with tryptophan-derived diketopiperazines **175**, we hoped to use the inherent Lewis basicity of the amide to selectively direct a copper catalyst to a single face of the indole to provide pyrroloindoline products in a diastereoselective fashion (**177**).

Successful execution would represent the most convergent route to this class of compounds reported to date.

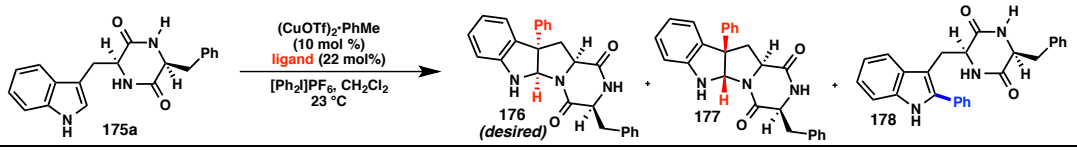
Scheme 3.14. *Proposed diastereoselective arylation*



3.6 OPTIMIZATION OF DIASTEREOSELECTIVE ARYLATION

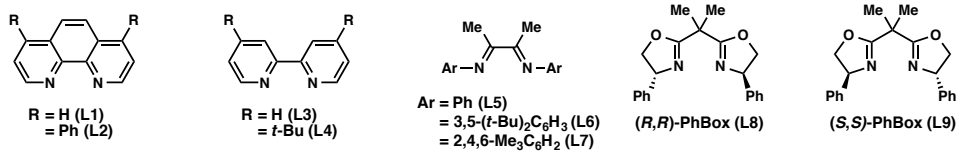
Our efforts to effect this diastereoselective transformation began with subjection of tryptophan-derived diketopiperazine **175a**, to our previously optimized conditions of ligandless copper (**Table 3.3**, **entry 1**). We were encouraged to recover the desired isomer in 22% yield. However, pyrroloindoline **176** was also formed in a 1:1 C3:C2 mixture (**178**), as well as a 3:1 diastereomeric ratio (**177**). In an effort to test our hypothesis on the necessary matching of directing group ability and the catalyst electronics, we conducted a screen of bidentate ligands. While more conventional bipy and phenanthroline based ligands provided minimal increases in yield, we were pleased to find that they were able to modulate the selectivities. We were delighted to find that use of the sterically congested bis(mesityl)-α-diimine ligand (**L7**) furnished the product in 70% yield. Further investigation into the sterics of the diimine ligand revealed that the precise substitution around the adjacent arene exerts a significant effect on the reactivity and selectivity of the reaction. The yield of pyrroloindoline was further improved through the use of a triflate counterion, providing the product in 85% isolated yield as a single diastereomer (**entry 14**).

Table 3.3. *Diastereoselective optimization*



entry	ligand	[Ph$_2$I]X	C3:C2[a]	dr[a]	yield (%)[a]
1	–[b]	[Ph$_2$I]PF$_6$	–	–	0
2	–	[Ph$_2$I]PF$_6$	1:1	3:1	22
3	L1	[Ph$_2$I]PF$_6$	1:1	3:1	15
4	L2	[Ph$_2$I]PF$_6$	1:2	2:1	<5
5	L3	[Ph$_2$I]PF$_6$	6:1	10:1	20
6	L4	[Ph$_2$I]PF$_6$	12:1	12:1	38
7	L5	[Ph$_2$I]PF$_6$	2:1	5:1	26
8	L6	[Ph$_2$I]PF$_6$	1:1	4:1	24
9	L7	[Ph$_2$I]PF$_6$	>20:1	>20:1	70
10	L8	[Ph$_2$I]PF$_6$	1:1	4:1	15
11	L9	[Ph$_2$I]PF$_6$	2:1	20:1	35
12	L7	[Ph$_2$I]BF$_4$	>20:1	>20:1	76
13	L7	[Ph$_2$I]AsF$_6$	>20:1	>20:1	81
14	L7	[Ph$_2$I]OTf	>20:1	>20:1	83 (85)[c]

[a]Yield of major diastereomer as determined by ^{1}H NMR analysis of the crude reaction mixture. [b] No (CuOTf)$_2$•PhMe was used. [c] Isolated yield.

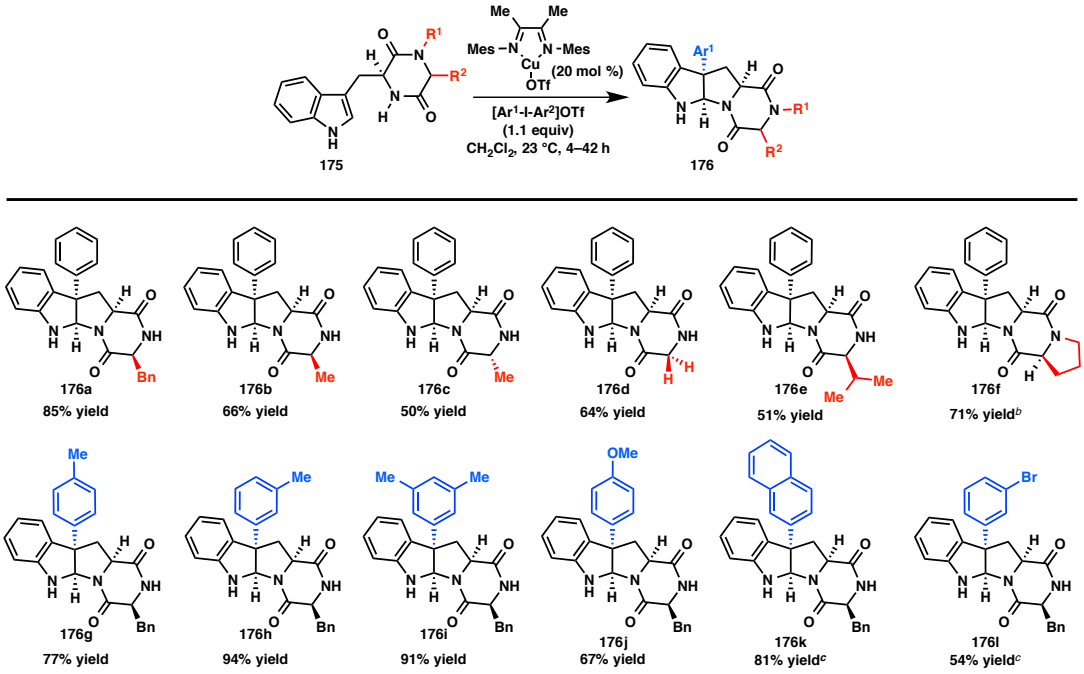


3.7 SCOPE OF DIASTEREOSELECTIVE ARYLATION

With optimized conditions in hand, the substrate scope of this diastereoselective reaction was examined (**Table 3.4**). A variety of arylated pyrroloindolines (**176**) can be prepared in one step from the corresponding diketopiperazines (**175**). Interestingly, the diketopiperazines derived from either L- or D-alanine react to deliver diastereomeric pyrroloindolines **176b** and **176c**, respectively, which possess the same configuration at the newly formed quaternary center. This observation indicates that the configuration at the tryptophan-derived stereogenic center is the dominant stereocontrolling factor. The scope of the aryl coupling partner was also investigated and was found to be tolerant of both electron-rich and electron-poor arenes (**176j–176l**).

In contrast, diketopiperazine **175f**, derived from *L*-Pro, proved to be a challenging substrate and provided **176f** in low yield as a result of poor C3:C2 selectivity under our standard conditions. We hypothesized that the increased substitution at nitrogen may result in a destabilizing interaction with the bulky Cu^{I}(**L7**) catalyst. A screen of more sterically-accessible ligands revealed that the use 40 mol % **L6** in conjunction with [Ph-$_2$I]PF_6 restores the C3:C2 selectivity and delivers pyrroloindoline **176f** in 71% yield. At this time, we believe that the need for increased ligand loading with **L6** is likely due to the formation of bridging Cu-catalyst dimers. This hypothesis is further supported by the fact that reaction rates utilizing **L6** are considerably accelerated at higher dilutions.

Table 3.4. *Substrate scope of diastereoselective arylation*

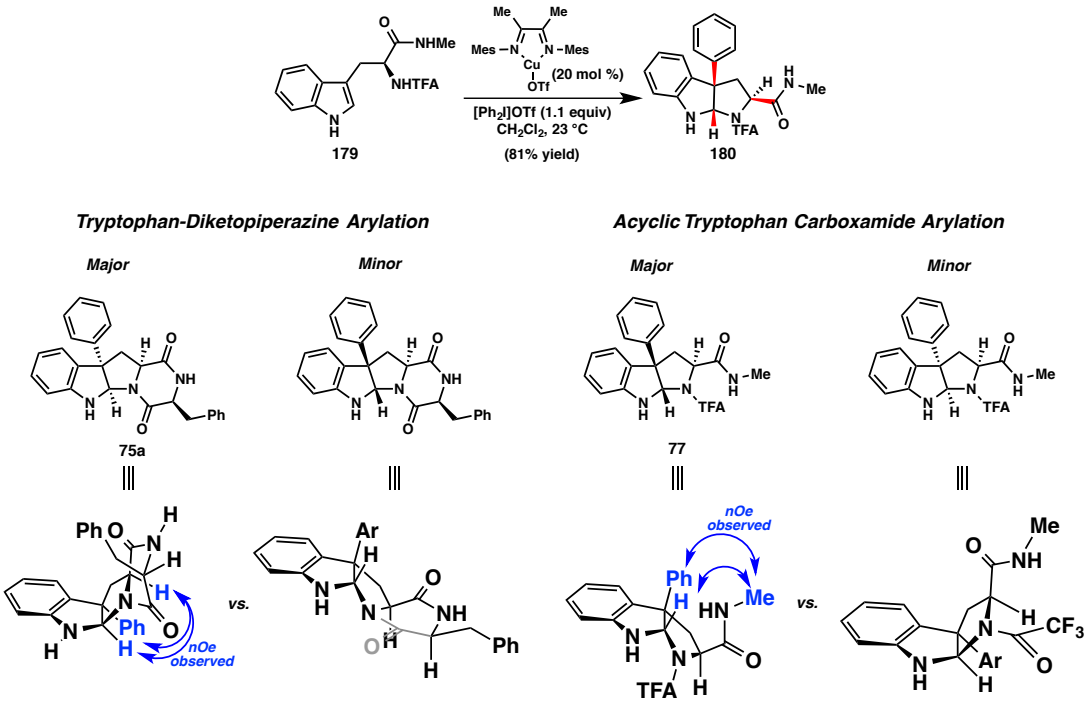


[a] Reactions conducted on 0.3 mmol scale using symmetric diaryliodonium triflate unless otherwise noted. Isoltaed yields are reported. [b] 40 mol % ligand **L6** was used with diphenyliodonium hexfluorophosphate. [c] Non-symmetric aryl[*p*-xylyl]iodonium triflate was used.

Given the success of a range of diketopiperazine-containing substrates, we next turned our attention to a more flexible system. Specifically, we wondered if an acyclic

tryptophan-derived carboxamide would behave similarly under our reaction conditions. Remarkably, subjection of *acyclic* **179** to our optimized conditions provided pyrroloindoline products in which arylation occurred with opposite facial selectivity at the quaternary center to that seen with diketopiperazine substrates (**180**). From a synthetic standpoint, this presents the exciting opportunity to access either enantiomeric series of pyrroloindoline products from naturally occurring (*L*)-tryptophan.

Figure 3.2. *Reversal in diastereoselectivity*

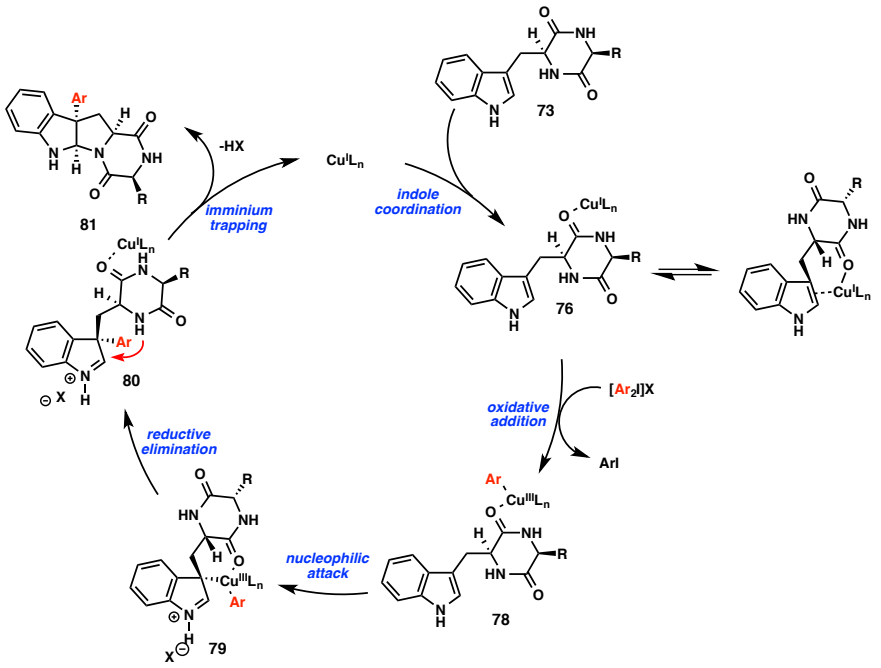


3.8 MECHANISTIC HYPOTHESIS

The mechanism of this reaction is still under investigation and our attempted studies have been complicated by the presence of paramagnetic species in ^{1}H NMR experiments as well as the heterogeneous nature of this reaction. Currently, we can only speculate on the possible mechanisms based on circumstantial evidence. However, in analogy to that proposed by Gaunt for the Cu-catalyzed C3-arylation of unsubstituted

indoles, we currently favor a Cu(I–III) catalytic cycle (**Scheme 3.15**). Although Gaunt proposes oxidative addition prior to indole coordination, our studies suggest indole coordination is likely necessary for oxidation to a Cu(III) species.

Scheme 3.15. *Possible arylation mechanism*



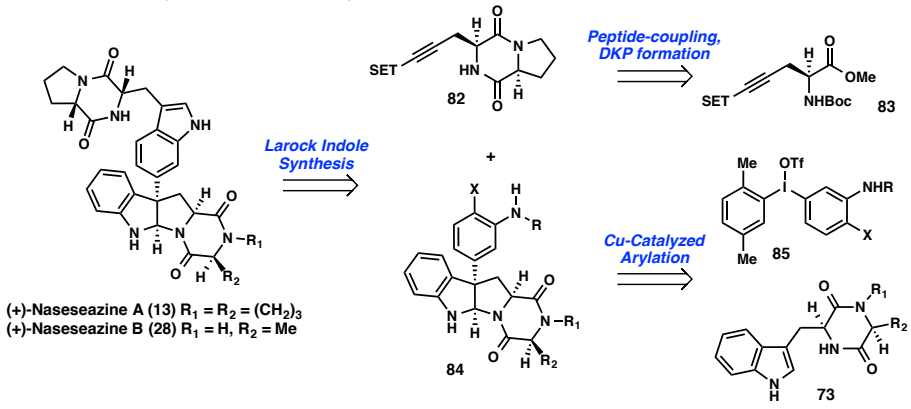
3.9 TOTAL SYNTHESIS OF (+)-NASESEAZINES A AND B

3.9.1 Retrosynthetic Analysis

Having successfully optimized this diastereoselective transformation, we set out to demonstrate the versatility and efficiency of this transformation through the total synthesis of C3-arylpyrroloindoline-containing natural products (+)-naseseazines A and B. Retrosynthetically, we imagined a disconnection through the tryptophan indole *via* a late stage Larock indole synthesis between an appropriate haloaniline and alkynyl diketopiperazine. We hoped to synthesize the necessary haloaniline from our newly developed diastereoselective arylation of a tryptophan-derived diketopiperazine and a

functionalized iodoniun. Alkynyl diketopiperazine **82** was expected to be available *via* a peptide coupling followed by cyclocondensation of the corresponding propargylglycine derivative.

Scheme 3.16. *Retrosynthetic Analysis*

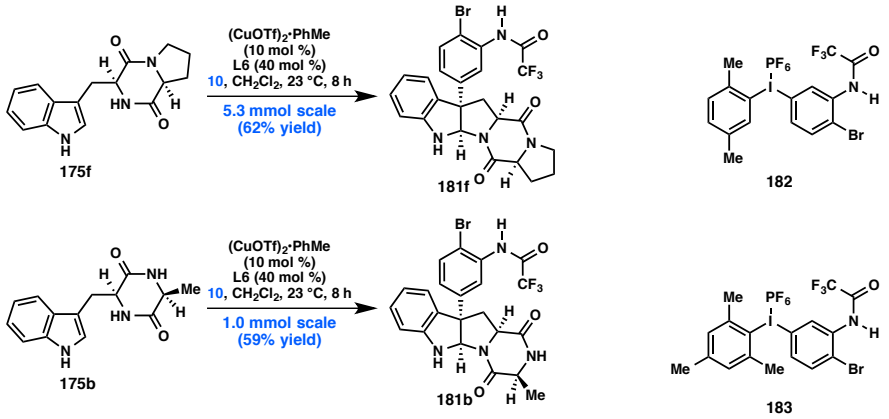


3.9.2 Forward Synthesis

In the forward sense, we began by investigating the arylation reaction of cyclo-L-Trp-L-Pro (**175f**) with diaryliodonium salt **182**, readily prepared in 80% yield over two-steps from commercially available 2-bromo-5-iodoaniline. We were pleased to find that subjecting these two coupling partners to a prestirred solution of 10 mol% (CuOTf)$_2$•PhMe and 40 mol% $^{t\text{-Bu}}$DAB$_{Me}$ (**L6**), conditions previously optimized for (L)-proline-derived diketopiperazine **175f**, provided **181f** in modest yield. Unfortunately competitive *p*-xylyl transfer was also observed, resulting in an inseparable mixture of arylation products. Although our previous studies had indicated that Cu(**L7**)OTf was incapable of transferring ortho-substituted arenes, this new observation led us to believe that the active Cu(**L6**) species was significantly more sterically accessible, and may tolerate a bulkier, nontransferable ligand. As a result, mesityl iodonium **183** was readily prepared and subjected to the reaction conditions. Gratifyingly, pyrroloindoline **181f** was cleanly isolated in 62% yield with good selectivity. This direct and efficient procedure is easily

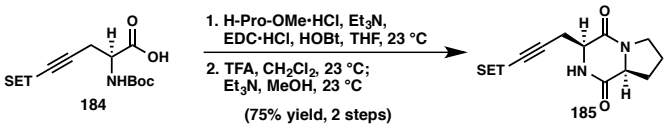
performed on large scale and provides the desired pyrroloindoline with excellent levels of diastereocontrol. Moreover, the same conditions could be applied to alanine-derived **175b** to give pyrroloindoline **181b** in 59% yield.

Scheme 3.17. *Arylation using a functionalized iodonium*



To prepare the other coupling fragment for a Larock indolization, alkynyl diketopiperazine **185** was synthesized on gram scale via initial peptide coupling of amino acid **184** with (*L*)-proline methyl ester hydrochloride. One-pot Boc deprotection and base-mediated cyclocondensation provide the desired coupling partner.

Scheme 3.18. *Preparation of a propargyl diketopiperazine*

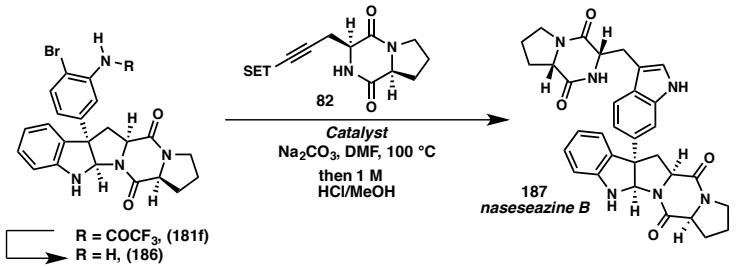


With these coupling partners in hand, all that remained in the synthesis was a late-stage Larock indolization to access the natural product. Although Larock indole syntheses between iodoanilines and alkynes are commonplace in the literature, the corresponding reaction of bromoanilines has been considerably less developed.[15,16] We were encouraged that this reaction could be viable based on reports by Boger and co-workers on an intramolecular Larock macrocyclization of a bromoaniline en route to the total synthesis

of the complestatin natural products.[16] Despite the use of superstoichiometric $Pd(OAc)_2$ and ditertbutylferrocenylphosphine as a ligand, this precedent demonstrated the viability of such a reaction in the context of advanced stage total synthesis and in the presence of numerous peptide bonds.

We were therefore encouraged to find that the use of stoichiometric palladium with 1,1'-bis(di-*tert*-butylphosphino)ferrocene (dtbpf) gave traces of the natural product (**Table 3.5**, **entry 2**). Unfortunately, a closer analysis of the reaction mixture showed that the major products of this reaction consisted of hydrodebrominated starting material, *epi*-naseseazine B, and *iso*-naseseazine B. Furthermore, subsequent attempts to optimize this reaction based on the conditions identified by Boger and co-workers proved completely unfruitful, and we therefore embarked on an extensive screen of less conventional ligands. Interestingly, treatment of stoichiometric amounts of the *N*-heterocyclic carbene-based catalyst PEPPSI-IPr greatly reduced debromination, although **187** was recovered in low yield. Subjecting the free aniline to identical conditions improved the recovery, providing a 39% isolated yield (entry 7). Additional screening revealed that the bulky preformed catalyst $Pd[P(o\text{-tol})_3]_2$ was highly active, reaching full conversion in only 15 minutes and providing 27% yield of the product. Intrigued by the reactivity, we wondered whether catalysis might be achieved under these conditions. Gratifyingly, treatment with only 25 mol % $Pd[P(o\text{-tol})_3]_2$ afforded **187** in 51% yield, constituting the first catalytic Larock indolization on a bromoaniline in total synthesis.

Table 3.5. *Optimization of the Larock indole synthesis*



entry	R	catalyst	time	product:debromo	yield (%)
1	TFA	$Pd(OAc)_2$ (1.1 equiv), LiCl	8 h	–	–
2	TFA	$Pd(OAc)_2$ (1.1 equiv), dtbpf (1.2 equiv)	2 h	1 : 1	<10
3	TFA	$Pd_2(dba)_3$ (0.5 equiv), dtbpf (1.2 equiv)	2 h	1 : 1	<10
4	TFA	$Pd(OAc)_2$ (1.1 equiv), DavePhos (1.2 equiv)	2 h	1 : 1	<10
5	TFA	$Pd(OAc)_2$ (1.1 equiv), PCy_3 (1.2 equiv)	8 h	0 : 1	–
6	TFA	PEPPSI-IPr (1.1 equiv)	8 h	>20 :1	<20
7	H	PEPPSI-IPr (1.1 equiv)	8 h	>20 :1	39
8	H	$Pd[P(o\text{-tol})_3]_2$ (1.1 equiv)	15 min	10 :1	27
9	H	$Pd[P(o\text{-tol})_3]_2$ (25 mol %)	90 min	>20 : 1	51

An analogous sequence was applied to furnish the related natural product (+)-naseseazine A by utilizing alanine-derived diketopiperazine **181b**. Through this Cu-catalyzed arylation chemistry, these complex polycyclic alkaloids are available in only five steps (longest linear sequence) from commercially available starting materials in 19% and 25% overall yield respectively, highlighting the ability to generate structurally diverse pyrroloindolines in an extremely convergent manner.

3.10 CONCLUSION

In conclusion, this report describes the discovery and development of new, Cu-catalyzed arylation reactions of tryptamine and tryptophan-derivatives to form 3-arylpyrroloindolines. Direct and selective C3-arylation is achieved through the use of copper catalysts in conjunction with hypervalent iodine(III) salts as the aryl source. *N*-sulfonyltryptamines were found to react uniquely using copper(I) or (II) salts and

diaryliodonium tetrafluoroborates to afford racemic C3-aryl pyrroloindolines in good yields. Furthermore, the addition of α-diimine ligands to the system has enabled the development of an efficient and highly diastereoselective tryptophan arylation reaction. Using this transformation to assemble the pyrroloindoline core enables the concise, stereoselective syntheses of the bisindole alkaloids (+)-naseseazines A and B in overall yields of 25 and 19%, respectively.

3.11 EXPERIMENTAL SECTION

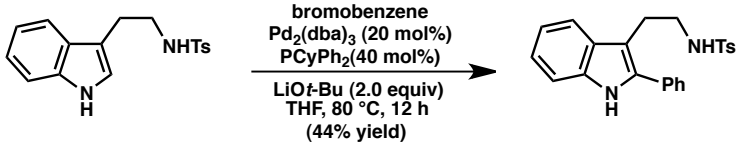
3.11.1 Materials and Methods

Unless otherwise stated, reactions were performed under a nitrogen atmosphere using freshly dried solvents. Tetrahydrofuran (THF), methylene chloride (CH_2Cl_2), acetonitrile (MeCN), dimethylformamide (DMF), and toluene (PhMe) were dried by passing through activated alumina columns. Triethylamine (Et_3N) was distilled over calcium hydride prior to use. Unless otherwise stated, chemicals and reagents were used as received. All reactions were monitored by thin-layer chromatography using EMD/Merck silica gel 60 F254 pre-coated plates (0.25 mm) and were visualized by UV, *p*-anisaldehyde, or $KMnO_4$ staining. Reaction samples were analyzed on an Agilent 1290 Series LC/MS using an Eclipse Plus C18 column (RRHD 1.8 μm, 2.1 x 50 mm, 11,072 plates). Flash column chromatography was performed either as described by Still et al. using silica gel (particle size 0.032-0.063) purchased from Silicycle or using pre-packaged RediSep®Rf columns on a CombiFlash Rf system (Teledyne ISCO Inc.). Alumina was purchased from Sigma-Aldrich (Aluminum oxide, ~150 mesh, 58Å pore size, activated, basic, Brockmann I) and deactivated with 3% v/w H2O (30.0 mL / 970 g). ^{1}H and ^{13}C NMR

spectra were recorded on a Varian 400 MR (at 400 MHz and 101 MHz, respectively), a Varian Inova 500 (at 500 MHz and 126 MHz, respectively), or a Varian Inova 600 (at 600 MHz and 150 MHz, respectively), and are reported relative to internal $CHCl_3$ (^1H, δ = 7.26) or DMSO (^1H, δ = 2.50), and $CDCl_3$ (^{13}C, δ = 77.0), or DMSO (^{13}C, δ = 40.0). Data for ^1H NMR spectra are reported as follows: chemical shift (δ ppm) (multiplicity, coupling constant (Hz), integration). Multiplicity and qualifier abbreviations are as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin Elmer Paragon 1000 spectrometer and are reported in frequency of absorption (cm^{-1}). HRMS were acquired using an Agilent 6200 Series TOF with an Agilent G1978A Multimode source in electrospray ionization (ESI), atmospheric pressure chemical ionization (APCI), or mixed (MM) ionization mode.

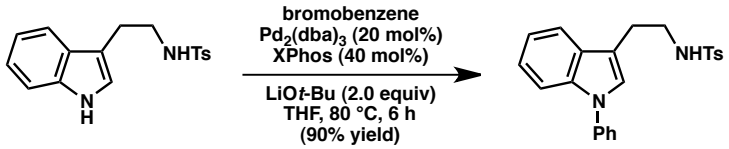
3.11.2 Optimization of Racemic Arylation

A. Palladium-Catalyzed Reaction Screens

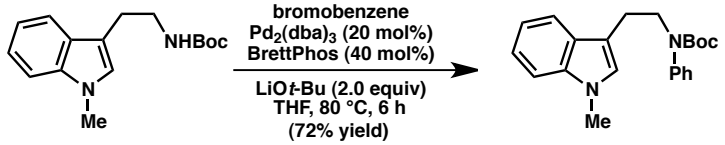


To a flame-dried vial in the glove box was charged $PCyPh_2$ (11 mg, 0.04 mmol), $Pd_2(dba)_3$ (11 mg, 0.02 mmol), N-tosyltryptamine (31 mg, 0.1 mmol), bromobenzene (51 μL, 0.5 mmol), LiOtBu (16 mg, 0.2 mmol) and THF (1 mL). The vial was sealed and heated to 80 ^oC for 12 hours. The reaction mixture was filtered through a plug of silica and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (20% EtoAc in hexanes) to afford 2-phenyl tryptamine **17** (16.9 mg, 0.04 mmol, 44%). ^1H NMR ($CDCl_3$, 500 MHz) δ 8.11 (s, 1H), 7.58 (d, *J* = 8.2 Hz, 2H), 7.52 – 7.42 (m, 5H), 7.40 (ddd, *J* = 4.1, 1.5, 1.5 Hz, 1H), 7.37 (d, *J* = 8.1 Hz, 1H), 7.20

(dd, J = 16.1, 7.8 Hz, 3H), 7.09 (dd, J = 7.8, 7.2 Hz, 1H), 4.35 (t, J = 5.8 Hz, 1H), 3.28 (dd, J = 13.3, 6.8 Hz, 2H), 3.08 (dd, J = 7.1, 7.1 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.2, 136.7, 135.8, 132.5, 129.6, 129.0, 128.5, 128.10, 128.09, 127.0, 122.6, 120.0, 118.8, 110.9, 108.3, 43.2, 25.0, 21.5;HRMS (MM) calc'd for $[M+H]^+$ 391.1475, found 391.1491.



To a flame-dried vial in the glove box was charged XPhos (19 mg, 0.04 mmol), $Pd_2(dba)_3$ (11 mg, 0.02 mmol), N-tosyltryptamine (31 mg, 0.1 mmol), bromobenzene (51 μL, 0.5 mmol), LiOtBu (16 mg, 0.2 mmol) and THF (1 mL). The vial was sealed and heated to 80 ^{o}C for 6 hours. The reaction mixture was filtered through a plug of silica and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (20% EtoAc in hexanes) to afford N-phenyl tryptamine (35.2 mg, 0.09 mmol, 90%). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.70 – 7.65 (m, 2H), 7.57 – 7.43 (m, 6H), 7.39 – 7.32 (m, 1H), 7.23 (dd, J = 11.6, 4.5 Hz, 3H), 7.16 – 7.10 (m, 1H), 7.09 (s, 1H), 4.54 (t, J = 6.1 Hz, 1H), 3.34 (q, J = 6.6 Hz, 2H), 2.99 (t, J = 6.7 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.3, 139.4, 136.8, 136.1, 129.6, 128.3, 127.0, 126.4, 126.2, 124.1, 122.7, 120.1, 118.8, 112.7, 110.7, 43.1, 25.4, 21.5. HRMS (MM) calc'd for $[M+H]^+$ 391.1475, found 391.1470.



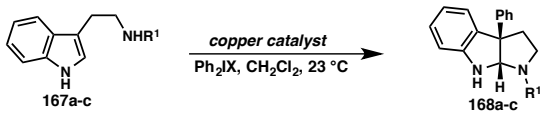
To a flame-dried vial in the glove box was charged BrettPhos (6.4 mg, 0.012 mmol), $Pd_2(dba)_3$ (3.5 mg, 0.006 mmol), *N*-Boc-*N'*-methyltryptamine (8 mg, 0.1 mmol), bromobenzene (16 μL, 0.15 mmol), LiOtBu (4.8 mg, 0.06 mmol) and THF (1 mL). The vial was sealed and heated to 80 ^oC for 6 hours. The reaction mixture was filtered through a plug of silica and concentrated *in vacuo*. The crude residue was purified by silica gel flash chromatography (20% EtoAc in hexanes) to afford N-phenyl tryptamine (28.0 mg, 0.02 mmol, 72%). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.54 (d, *J* = 7.9 Hz, 1H), 7.34 (dd, *J* = 10.7, 4.9 Hz, 2H), 7.28 (d, *J* = 8.2 Hz, 1H), 7.24 – 7.18 (m, 4H), 7.07 (ddd, *J* = 7.9, 7.0, 1.0 Hz, 1H), 6.85 (s, 1H), 3.97 – 3.87 (m, 2H), 3.72 (s, 3H), 3.06 – 2.95 (m, 2H), 1.42 (s, 10H). ^{13}C NMR ($CDCl_3$, 126 MHz) 148.4, 143.5, 139.4, 136.4, 135.6, 132.6, 131.9, 129.6, 128.5, 127.2, 127.1, 127.0, 125.7, 124.3, 119.2, 109.4, 84.4, 62.1, 47.4, 37.9, 21.4, 20.8. FTIR (NaCl, thin film): 3056, 3027, 2949, 2891, 2827, 1762, 1605, 1491, 1347, 1160, 1092, 1022. HRMS (MM) calc'd for $[M+H]^+$ 409.1381, found 409.1363.

B. Copper-Catalyzed Reaction Screen

General Procedure – To a flame-dried, 1-dram vial was charged the appropriate tryptamine (0.10 mmol), 4,4'-di-*tert*-butylbiphenyl, diaryl iodonium salt (0.11 mmol), copper catalyst (0.010 mmol), and additive (0.10 mmol, if applicable). Anhydrous CH_2Cl_2 (1.0 mL) was then added and the reaction stirred under inert atmosphere and monitored by UHPLC-MS for optimal yield.

The following response factors relative to an internal standard of 4,4'-di-*tert*-butylbiphenyl were measured and calculated based on three runs of varied concentration at λ = 254 nm:

N-Tosyltryptamine **167a** (Starting Material): Response Factor = 0.117
N-Tosylpyrroloindoline **168a** (Product): Response Factor = 0.253
UHPLC samples were analyzed at λ = 254 nm and yields calculated based on the above factors.



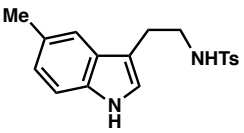
entry	R	Cu source	X	additive	pdt	yield (%)[a]
1	Ts	$Cu(OTf)_2$	BF_4	–	**19a**	62[b]
2	Ts	–	BF_4	–	**19a**	0
3	Boc	$Cu(OTf)_2$	BF_4	–	**19b**	<5
4	Ac	$Cu(OTf)_2$	BF_4	–	**19c**	<5
5	Ts	$(CuOTf)_2$•PhMe	BF_4	–	**19a**	64
6	Ts	CuI	BF_4	–	**19a**	0
7	Ts	$Cu(MeCN)PF_6$	BF_4	–	**19a**	0
8	Ts	$Cu(OAc)_2$	BF_4	–	**19a**	64
9	Ts	$Cu(OTf)_2$	PF_6	–	**19a**	28
10	Ts	$Cu(OTf)_2$	OTf	–	**19a**	32
11	Ts	$Cu(OTf)_2$	Cl	–	**19a**	0
12	Ts	$Cu(OTf)_2$	BF_4	dtbpy	**19a**	<5
13	Ts	$Cu(OTf)_2$	BF_4	$NaHCO_3$	**19a**	55
14	Ts	$Cu(OTf)_2$	BF_4	AcOH	**19a**	62
15	Ts	$Cu(OTf)_2$	BF_4	–[c]	**19a**	65

[a] Determined by HPLC versus an internal standard. [b] Isolated yield. [c] [Ph-I-Mes]BF_4 was employed as the electrophile

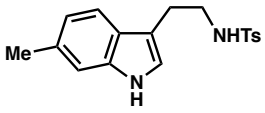
3.11.3 Preparation of N-tosyl tryptamine derivatives

General Procedure A – To a solution of tryptamine (1.00 equiv) in CH_2Cl_2 (0.1 M) was added Et_3N (1.50 equiv). The solution was cooled to 0 °C in an ice bath and *p*-toluenesulfonyl chloride (1.01 equiv) added in one portion as solid against a positive steam of nitrogen. The solution was stirred for 15 minutes, then the ice bath removed and allowed to warm up to ambient temperature (20 to 25 °C) and stirred for an additional 4

hours. The reaction was then quenched with 1 N aq. HCl (equal volume to CH_2Cl_2 used) and the organic layer separated and washed with another portion of 1N aq. HCl. The combined aqueous layers were then combined and back extracted with CH_2Cl_2 (20 mL), then the organic layers combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting crude residue was purified by flash chromatography (SiO_2) to afford *N*-tosyltryptamine as a white or off-white solid.



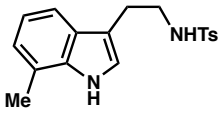
***N*-Tosyltryptamine 167b**: Prepared according to General Procedure A. Reaction run on 6.40 mmol (1.30 g) scale. The crude material was purified by silica gel chromatography (gradient elution, 10-60% EtOAc in Hexane) to afford **167b** as a white, amorphous solid (1.58 g, 4.81 mmol, 75 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (s, 1H), 7.67 – 7.60 (m, 2H), 7.25 – 7.19 (m, 3H), 7.17 (dd, *J* = 1.5, 0.7 Hz, 1H), 7.01 (dd, *J* = 8.3, 1.6 Hz, 1H), 6.92 (d, *J* = 2.3 Hz, 1H), 4.46 (t, *J* = 6.0 Hz, 1H), 3.26 (q, *J* = 6.5 Hz, 2H), 2.89 (dd, *J* = 6.9, 6.3 Hz, 2H), 2.41 (s, 3H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) 143.2, 136.7, 134.7, 129.6, 128.7, 127.0, 127.0, 123.8, 122.7, 118.1, 110.9, 110.9, 42.9, 25.4, 21.5, 21.4; FTIR (NaCl, thin film): 3401, 3290, 3042, 2919, 2864, 1597, 1423, 1320, 1303, 1157, 1093. HRMS (MM) calc'd for $[M+H]^+$ 329.1318, found 329.1316.



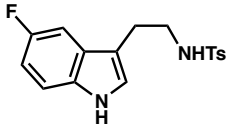
***N*-Tosyltryptamine 167c**: Prepared according to General Procedure A. Reaction run on 3.68 mmol (641 mg) scale. The

crude material was purified by silica gel chromatography (gradient elution, 10-60% EtOAc in Hexane) to afford **167c** as a white, amorphous solid (940 mg, 2.87 mmol, 78 % yield).

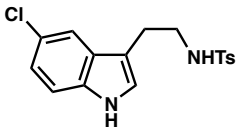
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.94 (s, 1H), 7.67 – 7.59 (m, 2H), 7.29 (d, *J* = 8.1 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 2H), 7.14 (s, 1H), 6.92 – 6.86 (m, 2H), 4.46 (t, *J* = 6.1 Hz, 1H), 3.25 (q, *J* = 6.5 Hz, 2H), 2.90 (t, *J* = 6.6 Hz, 2H), 2.45 (s, 3H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.2, 136.8, 136.7, 132.1, 129.6, 127.0, 124.7, 121.9, 121.3, 118.1, 111.3, 111.2, 43.0, 25.5, 21.6, 21.5. FTIR (NaCl, thin film): 3401, 3280, 2913, 2859, 1456, 1404, 1320, 1301, 1157, 1093. HRMS (MM) calc'd for $[M+H]^+$ 329.1318, found 329.1307.



***N*-Tosyltryptamine 167d**: Prepared according to General Procedure A. Reaction run on 3.84 mmol (669 mg) scale. The crude material was purified by silica gel chromatography (gradient elution, 10-60% EtOAc in Hexane) to afford **167d** as a white, amorphous solid (1.02g, 3.11 mmol, 81 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.27 (s, 1H), 7.90 (d, *J* = 8.2 Hz, 2H), 7.57 – 7.50 (m, 1H), 7.48 (d, *J* = 8.5 Hz, 2H), 7.24 (dd, *J* = 9.7, 2.0 Hz, 3H), 4.75 (t, *J* = 6.1 Hz, 1H), 3.53 (q, *J* = 6.5 Hz, 2H), 3.18 (t, *J* = 6.6 Hz, 2H), 2.73 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (126 MHz, $cdcl_3$) δ 143.3, 136.7, 136.0, 129.6, 127.0, 126.3, 122.7, 122.3, 120.5, 119.7, 116.2, 112.0, 43.0, 25.6, 21.5, 16.6l FTIR (NaCl, thin film): 3400, 3275, 3047, 2908, 2849, 1436, 1320, 1303, 1157, 1093, 1063. HRMS (MM) calc'd for $[M+H]^+$ 329.1318, found 329.1307.

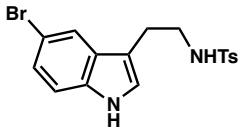


***N*-Tosyltryptamine 167e:** Prepared according to General Procedure A. Reaction run on 3.43 mmol (610 mg) scale. The crude material was purified by silica gel chromatography (gradient elution, 10-60% EtOAc in Hexane) to afford **167e** as an off-white, amorphous solid (940 mg, 2.83 mmol, 82 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.12 (s, 1H), 7.64 – 7.60 (m, 2H), 7.28 – 7.24 (m, 1H), 7.22 (dd, J = 8.5, 0.6 Hz, 2H), 7.02 (d, J = 2.4 Hz, 1H), 6.99 – 6.89 (m, 2H), 4.45 (t, J = 6.0 Hz, 1H), 3.24 (q, J = 6.6 Hz, 2H), 2.87 (dd, J = 6.8, 6.4 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.6 (d, $J_{C\text{-}F}$ = 233.8 Hz), 143.5, 136.4, 132.8, 129.6, 127.1 (d, $J_{C\text{-}F}$ = 10.0 Hz), 127.0, 124.4, 111.9 (d, $J_{C\text{-}F}$ = 8.8 Hz), 111.6 (d, $J_{C\text{-}F}$ = 5.0 Hz), 110.6 (d, $J_{C\text{-}F}$ = 26.3 Hz), 103.4 (d, $J_{C\text{-}F}$ = 22.5 Hz), 42.71, 25.32, 21.47; FTIR (NaCl, thin film): 3392, 3275, 2933, 2864, 1486, 1457, 1319, 1301, 1157, 1093 cm^{-1}. HRMS (MM) calc'd for $[M+H]^+$ 333.1068, found 333.1058.

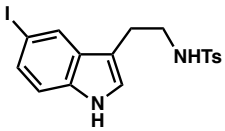


***N*-Tosyltryptamine 167f**: Prepared according to General Procedure A. Reaction run on 3.34 mmol (650 mg) scale. The crude material was purified by silica gel chromatography (gradient elution, 10-60% EtOAc in Hexane) to afford **167f** as an off-white, amorphous solid (1.08 g, 3.10 mmol, 92 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.18 (s, 1H), 7.65 – 7.57 (m, 2H), 7.28 (d, J = 2.0 Hz, 1H), 7.24 (d, J = 0.5 Hz, 1H), 7.21 (dd, J = 8.5, 0.6 Hz, 2H), 7.11 (dd, J = 8.7, 1.9 Hz, 1H), 7.00 (d, J = 2.3 Hz, 1H), 4.49 (t, J = 6.0 Hz, 1H), 3.23 (q, J = 6.6 Hz, 2H), 2.86 (td, J = 6.7, 0.6 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.5, 136.4, 134.7, 129.7, 127.9, 126.9, 125.2, 124.1, 122.5, 117.9, 112.3, 111.2, 42.7, 25.2, 21.5; FTIR

(NaCl, thin film): 3385, 3275, 2913, 2859, 1464, 1422, 1319, 1156, 1093 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 349.0772, found 349.0766.

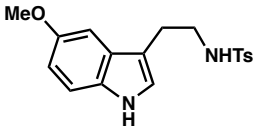


5-Bromo-*N*-Tosyltryptamine 167g: Reaction run on 7.99 mmol (1.91 g) scale. The crude material was purified by silica gel chromatography (gradient elution, 10-60% EtOAc in Hexane) to afford **167g** as a white amorphous solid (2.63g, 6.69 mmol, 84% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.17 (s, 1H), 7.68 – 7.65 (m, 1H), 7.63 – 7.59 (m, 2H), 7.41 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.23 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.12 (dd, *J* = 8.5, 0.4 Hz, 1H), 6.95 (d, *J* = 2.3 Hz, 1H), 4.48 (t, *J* = 6.0 Hz, 1H), 3.23 (q, *J* = 6.5 Hz, 2H), 2.85 (t, *J* = 6.6 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.5, 136.4, 135.4, 130.5, 129.7, 129.4, 127.3, 126.9, 123.5, 113.3, 110.9, 82.9, 42.8, 25.2, 21.6; FTIR (NaCl, thin film): 3376, 3290, 2922, 2864, 1598, 1460, 1420, 1320, 1157, 1093 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 393.0267, found 393.0260.

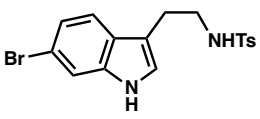


5-Iodo-*N*-tosyltryptamine 167h: To a 50-mL Schlenk tube was charged 5-bromo-*N*-tosyltryptamine **167g** (858 mg, 2.18 mmol, 1.00 equiv), CuI (42.0 mg, 0.220 mmol, 0.10 equiv), and NaI (654 mg, 4.36 mmol, 2.00 equiv). The vessel was then evacuated and backfilled with N_2 three times, and *N,N'*-dimethylethylene diamine (47 μL, 0.44 mmol, 0.20 equiv) and 1,4-dioxane (2.2 mL) added. The vessel was then sealed and heated to 100 °C for 23 hours, then cooled to room temperature, and quenched with concentrated aqueous NH_4OH (10 mL), then diluted with H_2O (30 mL). The mixture was then extracted with CH_2Cl_2 (3 x 30 mL), the organic layers combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in*

vacuo. Flash chromatography (gradient elution, 10-60% EtOAc in Hexanes) afforded 5-iodo-N-tosyltryptamine as a white solid (900 mg, 2.04 mmol, 94% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.27 (s, 1H), 7.63 – 7.57 (m, 2H), 7.44 (d, *J* = 1.8 Hz, 1H), 7.24 – 7.17 (m, 4H), 6.96 (d, *J* = 2.4 Hz, 1H), 4.62 (t, *J* = 6.0 Hz, 1H), 3.22 (q, *J* = 6.6 Hz, 2H), 2.83 (t, *J* = 6.6 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.5, 136.3, 134.9, 129.7, 128.5, 126.9, 124.9, 124.0, 120.9, 112.8, 112.6, 111.0, 42.7, 25.1, 21.5; FTIR (NaCl, thin film): 3391, 3290, 2928, 2854, 1598, 1456, 1417, 1319, 1288, 1157, 1093 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 441.0128, found 441.0130.



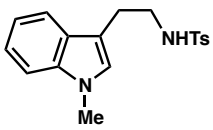
5-Methoxy-*N*-Tosyltryptamine 167i: Prepared according to General Procedure A. Reaction run on 5.94 mmol (1.13 g) scale. The crude material was purified by silica gel chromatography (gradient elution, 10-60% EtOAc in Hexane) to afford **167i** as a white amorphous solid (1.68g, 4.88 mmol, 82 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.98 (s, 1H), 7.64 – 7.58 (m, 2H), 7.24 (dd, *J* = 8.7, 0.5 Hz, 1H), 7.20 (d, *J* = 7.9 Hz, 2H), 6.95 (d, *J* = 2.3 Hz, 1H), 6.87 – 6.81 (m, 2H), 4.45 (t, *J* = 6.0 Hz, 1H), 3.80 (s, 3H), 3.25 (q, *J* = 6.5 Hz, 2H), 2.91 (t, *J* = 6.6 Hz, 2H), 2.40 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 154.0, 143.3, 136.6, 131.6, 129.6, 127.2, 127.0, 123.3, 112.5, 112.0, 111.2, 100.2, 55.8, 42.8, 25.4, 21.5; FTIR (NaCl, thin film): 3390, 3285, 2928, 2824, 1486, 1459, 1437, 1319, 1215, 1156, 1092 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 345.1267, found 345.1266.



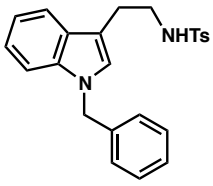
***N*-Tosyltryptamine 167j**: Prepared according to General

Procedure A. Reaction run on 10.90 mmol (2.61 g) scale. The crude material was purified by silica gel chromatography (gradient elution, 10-60% EtOAc in Hexane) to afford **167j** as a white, amorphous solid (3.42g, 8.70 mmol, 80 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 8.11 (s, 1H), 7.63 – 7.56 (m, 2H), 7.49 (dd, *J* = 1.7, 0.5 Hz, 1H), 7.23 (d, *J* = 8.4 Hz, 1H), 7.21 – 7.18 (m, 2H), 7.13 (dd, *J* = 8.4, 1.7 Hz, 1H), 6.95 (d, *J* = 2.4 Hz, 1H), 4.44 (t, *J* = 6.1 Hz, 1H), 3.24 (q, *J* = 6.5 Hz, 2H), 2.89 (t, *J* = 6.4 Hz, 2H), 2.40 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.4, 137.1, 36.5, 129.6, 126.9, 125.8, 123.2, 122.8, 119.7, 115.8, 114.2, 111.8, 42.9, 25.3, 21.5; FTIR (NaCl, thin film): 3368, 3270, 2933, 2864, 1457, 1399, 1319, 1156, 1092. HRMS (MM) calc'd for $[M+H]^+$ 393.0267, found 393.0252.

General procedure B – To a solution of *N*-tosyltryptamine (1.57 g, 5.00 mmol, 1.00 equiv) in DMF (17 mL) at 20 °C was added NaH (60% dispersion in mineral oil, 0.700 g, 17.5 mmol, 3.5 equiv) slowly, with vigorous stirring, and stirring continued at 20 °C. After 30 minutes, the solution was cooled to 0 °C in an ice bath, and the appropriate alkyl halide (5.00 mmol, 1.00 equiv) was added dropwise by syringe over three minutes. Stirring was continued at 0 °C for two hours, and the reaction allowed to warm to 20 °C and stirring continued for 13 hours. The reaction was then carefully quenched by the dropwise addition of saturated, aqueous ammonium chloride (10 mL), and the mixture diluted with EtOAc (100 mL), and washed with brine (2 x 50 mL). The organic layer was then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. Flash chromatography (SiO_2) afforded *N'*-alkylated tryptamines as a white solid.



***N*-tosyl-*N'*-methyltryptamines 167k**: Prepared according to General Procedure B. Reaction run on 5.00 mmol (1.57 g) scale. The crude material was purified by silica gel chromatography (gradient elution, 20-40% EtOAc in Hexane) to afford **20k** as a white, amorphous solid (1.18 g, 3.59 mmol, 72 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 (d, *J* = 8.3 Hz, 2H), 7.40 (d, *J* = 7.9 Hz, 1H), 7.29 (d, *J* = 8.2 Hz, 1H), 7.25 – 7.19 (m, 3H), 7.05 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.82 (s, 1H), 4.41 (t, *J* = 6.0 Hz, 1H), 3.73 (s, 3H), 3.26 (q, *J* = 6.5 Hz, 2H), 2.92 (t, *J* = 6.6 Hz, 2H), 2.41 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.1, 143.1, 137.0, 136.8, 129.6, 129.5, 129.5, 129.5, 129.5, 129.5, 127.3, 127.2, 126.9, 121.7, 118.9, 118.9, 118.5, 109.9, 109.9, 109.3, 109.3, 43.2, 43.2, 32.6, 32.5, 25.3, 25.3, 21.5, 21.4, 14.1; FTIR (NaCl, thin film):3292, 3051, 2929, 1616, 1473, 1325, 1158, 1093 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 329.1318, found 329.1314.



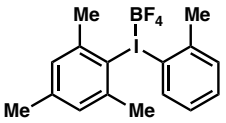
***N*-tosyl-*N'*-benzyltryptamines**: Prepared according to General Procedure B. Reaction run on 5.00 mmol (1.57 g) scale. The crude material was purified by silica gel chromatography (gradient elution, 20-30% EtOAc in Hexane) to afford **167l** as a white, amorphous solid (1.52 g, 3.76 mmol, 75 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.62 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 7.9 Hz, 1H), 7.33 – 7.22 (m, 4H), 7.21 – 7.13 (m, 3H), 7.12 – 7.07 (m, 2H), 7.06 – 7.01 (m, 1H), 6.85 (s, 1H), 5.23 (s, 2H), 4.44 (t, *J* = 6.1 Hz, 1H), 3.27 (q, *J* = 6.6 Hz, 2H), 2.91 (t, *J* = 6.7 Hz, 2H), 2.38 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 143.2, 137.3, 136.8, 136.8, 129.6, 128.8, 127.7, 127.5, 127.0, 126.8, 126.5, 122.0, 119.3, 118.7, 110.7, 109.8,

49.9, 43.1, 25.5, 21.5; FTIR (NaCl, thin film): 3284, 3057, 3029, 2922, 1597, 1466, 1326, 1159, 1094, 1076 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 405.1557, found 405.1630.

3.11.4 Preparation of Diaryliodonium Tetrafluoroborates

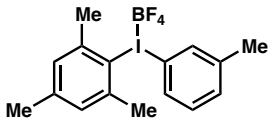
General Procedure C – To a solution of aryl iodide (1.00 equiv) in Ac_2O (0.5 M) was added *m*CPBA (1.50 equiv). After stirring 1 hour at 23 °C, the mixture was cooled to 0 °C and mesitylene (1.10 equiv) was added followed by dropwise addition of HBF_4 (50% *aq* solution, 2.00 equiv). The reaction continued stirring at 0 °C for 30 minutes, followed by 6 hours at 23 °C. The mixture was diluted with water, extracted with CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Crude reaction mixtures were dissolved in minimal CH_2Cl_2 and precipated with Et_2O to yield fine, white powders. The precipitate was filtered and dried overnight under high vacuum at 100 °C.

(2-Methylphenyl)(2,4,6-trimethylphenyl)iodonium tetrafluoroborate: Prepared



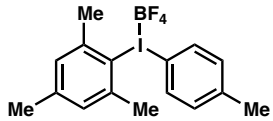
according to General Procedure C. Reaction run on 10.0 mmol (2.18 g) scale. Trituration afforded the product as a white powder (3.0 g, 7.1 mmol, 71 % yield). ^1H NMR (500 MHz, DMSO) δ 7.96 (d, J = 7.8 Hz, 1H), 7.56 – 7.54 (m, 2H), 7.29 – 7.23 (m, 1H), 7.21 (s, 2H), 2.56 (s, 6H), 2.56 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (DMSO, 125 MHz) δ 143.5, 142.1, 141.2, 137.2, 132.9, 132.4, 130.4, 129.8, 122.3, 119.1, 26.6, 24.9, 21.0. FTIR (NaCl, thin film): 1587, 1558, 1457, 1382, 1301, 1064, 1024. HRMS (MM) calc'd for $[M]^+$ 337.0448, found 337.0443.

(3-Methylphenyl)(2,4,6-trimethylphenyl)iodonium tetrafluoroborate: Prepared according to General Procedure C. Reaction run on 10.0 mmol (2.18 g) scale. Trituration afforded the product as a white powder (3.9 g, 9.2 mmol, 92 % yield).



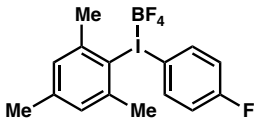
^{1}H NMR (500 MHz, DMSO) δ 7.85 (s, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.45 (d, *J* = 7.6 Hz, 1H), 7.38 (t, *J* = 7.8 Hz, 1H), 7.22 (s, 2H), 2.60 (s, 6H), 2.32 (s, 3H), 2.29 (s, 3H); ^{13}C NMR (DMSO, 126 MHz) δ 143.5, 142.45, 142.1, 135.1, 133.0, 132.2, 132.0, 130.3, 122.9, 114.8, 26.8, 21.2, 21.0. FTIR (NaCl, thin film): 2913, 1595, 1558, 1452, 1301, 1063, 1024 cm^{-1}; HRMS (MM) calc'd for $[M]^+$ 337.0448, found 337.0443.

(4-Methylphenyl)(2,4,6-trimethylphenyl)iodonium tetrafluoroborate: Prepared according to General Procedure C. Reaction run on 10.0 mmol (2.18 g) scale. Trituration afforded the product as a white powder (3.4 g, 8.2 mmol, 80 % yield).



^{1}H NMR (500 MHz, DMSO) δ 7.90 – 7.84 (m, 2H), 7.31 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.20 (s, 2H), 2.60 (s, 6H), 2.33 (s, 3H), 2.29 (s, 3H). ^{13}C NMR (DMSO, 125 MHz) δ 143.5, 142.7, 141.9, 135.0, 133.0, 130.2, 123.2, 111.4, 26.8, 21.7, 21.0. FTIR (NaCl, thin film): 1586, 1451, 1381, 1064, 1024. HRMS (MM) calc'd for $[M]^+$ 337.0448, found 447.0446.

(4-Fluorophenyl)(2,4,6-trimethylphenyl)iodonium tetrafluoroborate: Prepared according to General Procedure C. Reaction run on 10.0 mmol (2.22 g) scale. Trituration afforded the product as a white powder (1.7 g, 4.1 mmol, 40 % yield). ^{1}H NMR (500 MHz, DMSO) δ 8.08 – 8.01 (m, 2H), 7.40 –

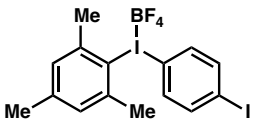


7.34 (m, 2H), 7.22 (s, 2H), 2.60 (s, 6H), 2.30 (s, 3H). ^{13}C NMR (DMSO, 125 MHz) δ 164.2 (d, $J_{C\text{-}F}$ = 250.0 Hz), 143.7, 142.00, 137.8 (d, $J_{C\text{-}F}$ = 8.75 Hz), 130.3, 123.4, 119.7 (d, $J_{C\text{-}F}$ = 22.5 Hz), 109.1, 26.8, 21.0; FTIR (NaCl, thin film): 1576, 1482, 1301, 1237, 1165, 1064, 1024 cm^{-1}; HRMS (MM) calc'd for $[M–BF_4]^+$ 341.0197, found 341.0188.

(4-Chlorophenyl)(2,4,6-trimethylphenyl)iodonium tetrafluoroborate: Prepared according to General Procedure C. Reaction run on 10.0 mmol (2.39 g) scale. Trituration afforded the product as a white powder (1.92 g, 4.3 mmol, 44 % yield). ^{1}H NMR (500 MHz, DMSO) δ 7.99 – 7.93 (m, 2H), 7.60 – 7.55 (m, 2H), 7.23 (d, J = 0.5 Hz, 2H), 2.59 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (DMSO, 125 MHz) δ 143.7, 142.1, 137.5, 136.7, 132.3, 130.3, 123.3, 112.8, 26.77, 21.02; FTIR (NaCl, thin film): 1469, 1380, 1301, 1064, 1027 cm^{-1}; HRMS (MM) calc'd for $[M–BF_4]^+$ 356.9901, found 356.9895.

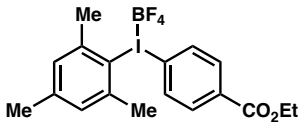
(4-Bromophenyl)(2,4,6-trimethylphenyl)iodonium tetrafluoroborate: Prepared according to General Procedure C. Reaction run on 10.0 mmol (2.83 g) scale. Trituration afforded the producct as a white powder (2.67 g, 5.5 mmol, 55 % yield). ^{1}H NMR (500 MHz, DMSO) δ 7.91 – 7.86 (m, 2H), 7.73 – 7.68 (m, 2H), 7.23 (d, J = 0.5 Hz, 2H), 2.59 (s, 6H), 2.30 (s, 3H). ^{13}C NMR (DMSO, 126 MHz) δ 143.8, 142.1, 136.8, 135.2, 130.3, 126.3, 123.2, 113.5, 26.8, 21.0; FTIR (NaCl, thin film): 1085, 1469, 1388, 1303, 1064 1024 cm^{-1}; HRMS (MM) calc'd for $[M–BF_4]^+$ 400.9396, found 400.9392.

(4-iodophenyl)(2,4,6-trimethylphenyl)iodonium tetrafluoroborate: Prepared



according to General Procedure C. Reaction run on 5.0 mmol (1.24 g) scale. Trituration afforded the product as a white powder (1.59 g, 3.0 mmol, 30 % yield). ^{1}H NMR (500 MHz, DMSO) δ 7.88 – 7.82 (m, 2H), 7.73 – 7.69 (m, 2H), 7.22 (s, 2H), 2.58 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (DMSO, 125 MHz) δ 143.71, 142.06, 140.93, 136.50, 130.31, 123.13, 114.38, 100.25, 26.77, 21.02; FTIR (NaCl, thin film): 1464, 1380, 1303, 1064, 1024, 984 cm^{-1}; HRMS (MM) calc'd for $[M–BF_4]^+$ 448.9258, found 448.9248.

(4-ethoxycarbonyl)(2,4,6-trimethylphenyl)iodonium tetrafluoroborate: Prepared



according to General Procedure C. Reaction run on 10.0 mmol (2.76 g) scale. Trituration afforded the product as a white powder (2.20 g, 4.6 mmol, 46 % yield).

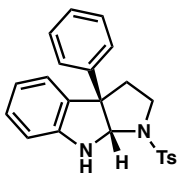
^{1}H NMR (500 MHz, DMSO) δ 8.11 – 8.05 (m, 2H), 8.02 – 7.96 (m, 2H), 7.24 (d, J = 0.5 Hz, 2H), 4.32 (q, J = 7.1 Hz, 2H), 2.59 (s, 6H), 2.30 (s, 3H), 1.30 (t, J = 7.1 Hz, 3H); ^{13}C NMR (DMSO, 125 MHz) δ 165.03, 143.8, 142.2, 135.2, 133.1, 132.4, 130.4, 123.2, 119.8, 62.0, 26.8, 21.0, 14.5; FTIR (NaCl, thin film): 2984, 1719, 1583, 1449, 1395, 1365, 1277, 1064, 1024 cm^{-1}; HRMS (MM) calc'd for $[M–BF_4]^+$ 395.0502, found 395.0493.

3.11.5 Preparation of N-Tosylpyrroloindolines

General Procedure D – To a flame-dried flask was charged the appropriate *N*-tosyltryptamine derivative (0.300 mmol, 1.0 equiv), the appropriate iodonium (0.330 mmol, 1.1 equiv), $Cu(OAc)_2$ or $Cu(OTf)_2$ (0.030 mmol or 0.060 mmol, 0.10 equiv or 0.20

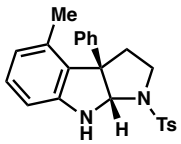
mmol) and CH_2Cl_2 (3.0 mL). The reaction was stirred for the time indicated, at which point the reaction was diluted with CH_2Cl_2 (10 mL), and quenched with saturated aq. $NaHCO_3$ (15 mL). The organic layer was separated and washed with additional $NaHCO_3$ (2 x 15 mL) and the resulting aqueous layers were then combined and back extracted with CH_2Cl_2 (15 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The crude residue was purified by flash chromatography (SiO_2 or basic alumina) to afford the *N*-tosylpyrroloindoline as a white or off-white solid.

Pyrroloindoline 168a: Prepared according to General Procedure D using 10 mol% $Cu(OAc)_2$ for 4 hours. Reaction run on 0.30 mmol (94 mg) scale. The crude material was purified on basic alumina (gradient elution, 40% THF in hexanes) to afford **168a** as a white, amorphous solid (72.6 mg, 0.19 mmol, 62 % yield).



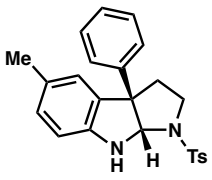
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 – 7.71 (m, 2H), 7.30 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.25 – 7.15 (m, 3H), 7.14 – 7.09 (m, 3H), 7.00 (ddd, *J* = 7.4, 1.1, 0.5 Hz, 1H), 6.80 – 6.74 (m, 1H), 6.70 (dd, *J* = 7.8, 0.6 Hz, 1H), 5.43 (s, 1H), 4.91 (s, 1H), 3.65 (ddd, *J* = 10.6, 7.8, 1.4 Hz, 1H), 3.25 (td, *J* = 11.0, 5.6 Hz, 1H), 2.48 (ddd, *J* = 12.4, 5.6, 1.0 Hz, 1H), 2.44 (s, 3H), 2.34 (ddd, *J* = 12.4, 11.3, 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.8, 143.6, 143.0, 136.3, 131.4, 129.8, 128.8, 128.6, 127.0, 127.0, 125.7, 123.9, 119.6, 110.1, 85.6, 61.8, 48.1, 37.3, 21.5. FTIR (NaCl, thin film): 3366, 2978, 2878, 1610, 1595, 1491, 1466, 1332, 1318, 1303, 1159, 1094. HRMS (MM) calc'd for $[M+H]^+$ 391.1475, found 391.1473.

Pyrroloindoline 168a: Prepared according to General Procedure D using 10 mol% $Cu(OAc)_2$ for 6 hours. Reaction run on 0.30 mmol (98.5 mg) scale. The crude material was purified on basic alumina (gradient elution, 40% THF in Hexane) to afford **168a** as a white foam (99.4 mg, 0.25 mmol, 82 % yield).



^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.78 – 7.70 (m, 2H), 7.30 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.24 – 7.15 (m, 3H), 7.12 – 7.08 (m, 2H), 6.95 (dd, *J* = 6.5, 0.8 Hz, 1H), 6.89 – 6.82 (m, 1H), 6.72 (dd, *J* = 7.4, 7.4 Hz, 1H), 5.47 (s, 1H), 4.70 (s, 1H), 3.67 (ddd, *J* = 10.5, 7.8, 1.5 Hz, 1H), 3.24 (ddd, *J* = 10.9, 10.9, 5.6 Hz, 1H), 2.47 (ddd, *J* = 12.4, 5.6, 1.1 Hz, 1H), 2.44 (s, 3H), 2.35 (ddd, *J* = 12.4, 11.2, 7.8 Hz, 1H), 2.16 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ147.4, 143.6, 143.1, 136.5, 130.8, 129.8, 129.7, 128.6, 126.98, 126.94, 125.7, 121.4, 119.7, 119.5, 85.5, 62.2, 48.2, 37.6, 21.5, 16.7. FTIR (NaCl, thin film): 3351, 3059, 2892, 1595, 1447, 1332, 1153, 1089. HRMS (MM) calc'd for $[M+H]^+$ 405.1631, found 405.1629.

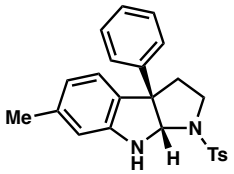
Pyrroloindoline 168b: Prepared according to General Procedure D using 10 mol% $Cu(OAc)_2$ for 6 hours. Reaction run on 0.30 mmol (98.5 mg) scale. The crude material was purified on basic alumina (gradient elution, 40% THF in Hexane) to afford **168b** as a white, amorphous solid (76.6 mg, 0.19 mmol, 63 % yield).



^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.29 (d, *J* = 8.0 Hz, 2H), 7.25 – 7.16 (m, 3H), 7.15 – 7.10 (m, 2H), 6.91 (dd, *J* = 7.9, 1.0 Hz, 1H), 6.79 (d, *J* = 0.4 Hz,

1H), 6.61 (d, *J* = 7.9 Hz, 1H), 5.41 (s, 1H), 3.64 (ddd, *J* = 10.5, 7.8, 1.3 Hz, 1H), 3.25 (ddd, *J* = 11.0, 11.0, 5.6 Hz, 1H), 2.50 – 2.38 (m, 1H), 2.43 (s, 3H), 2.32 (ddd, *J* = 12.3, 11.3, 7.9 Hz, 1H), 2.22 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 146.4, 143.5, 143.1, 136.3, 131.7, 129.8, 129.2, 129.0, 128.6, 126.97, 126.95, 125.7, 124.4, 110.1, 85.9, 61.8, 48.1, 37.1, 21.5, 20.9. FTIR (NaCl, thin film): 3385, 2922, 1617, 1597, 1496, 1448, 1340, 1159, 1093. HRMS (MM) calc'd for $[M+H]^+$ 405.1631, found 405.1644.

Pyrroloindoline 168c: Prepared according to General Procedure D using 10 mol% $Cu(OAc)_2$ for 6 hours. Reaction run on 0.30 mmol (98.5 mg) scale. The crude material was purified on basic alumina (gradient elution, 40% THF in Hexane) to afford **168c** as a white foam (61.0 mg, 0.15 mmol, 50 % yield).

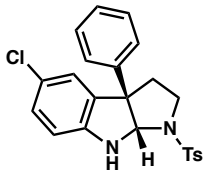


^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 – 7.70 (m, 2H), 7.30 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.25 – 7.14 (m, 3H), 7.13 – 7.07 (m, 2H), 6.88 (d, *J* = 7.6 Hz, 1H), 6.59 (ddd, *J* = 7.6, 1.4, 0.7 Hz, 1H), 6.55 – 6.51 (m, 1H), 5.41 (s, 1H), 4.83 (s, 1H), 3.64 (ddd, *J* = 10.6, 7.8, 1.4 Hz, 1H), 3.27 (ddd, *J* = 11.0, 11.0, 5.6 Hz, 1H), 2.49 – 2.41 (m, 1H), 2.44 (s, 3H), 2.31 (ddd, *J* = 7.9, 6.9, 5.7 Hz, 1H), 2.28 (s, 3H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.0, 143.6, 143.2, 138.8, 136.4, 129.8, 128.6, 128.6, 127.0, 126.9, 125.7, 123.6, 120.4, 111.0, 85.9, 61.6, 48.2, 37.3, 21.5, 21.5. FTIR (NaCl, thin film): 3353, 2889, 1595, 1490, 1448, 1331, 1307, 1159, 1119, 1092. HRMS (MM) calc'd for $[M+H]^+$ 405.1631, found 405.1609.

Pyrroloindoline 168d: Prepared according to General Procedure D using 10 mol% $Cu(OAc)_2$ for 6 hours. Reaction run on 0.30 mmol (98.5 mg) scale. The crude material was purified on basic alumina (gradient elution, 40% THF in Hexane) to afford **168d** as a white, crystalline solid (69.2 mg, 0.17 mmol, 57% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.81 – 7.70 (m, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.25 – 7.15 (m, 3H), 7.13 – 7.07 (m, 2H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.86 (d, *J* = 7.1 Hz, 1H), 6.72 (dd, *J* = 7.4, 7.4 Hz, 1H), 5.47 (s, 1H), 4.70 (s, 1H), 3.67 (ddd, *J* = 10.5, 7.8, 1.4 Hz, 1H), 3.24 (ddd, *J* = 10.9, 10.9, 5.6 Hz, 1H), 2.47 (ddd, *J* = 12.4, 5.6, 1.1 Hz, 1H), 2.44 (s, 3H), 2.35 (ddd, *J* = 12.4, 11.2, 7.8 Hz, 1H), 2.16 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.4, 143.6, 143.1, 136.5, 130.8, 129.8, 129.7, 128.6, 127.0, 126.9, 125.7, 121.4, 119.7, 119.5, 85.5, 62.2, 48.2, 37.6, 21.5, 16.7; FTIR (NaCl, thin film): 3350, 2892, 1594, 1490, 1465, 1448, 1331, 1319, 1305, 1243, 1151, 1109, 1089 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 405.1631, found 405.1590.

Pyrroloindoline 168e: Prepared according to General Procedure D using 10 mol% $Cu(OAc)_2$ for 24 hours. Reaction run on 0.30 mmol (99.7 mg) scale. The crude material was purified on basic alumina (gradient elution, 40% THF in Hexane) to afford **168e** as a white, crystalline solid (80.1 mg, 0.20 mmol, 65 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.73 (d, *J* = 8.3 Hz, 2H), 7.30 (d, *J* = 8.0 Hz, 2H), 7.26 – 7.17 (m, 3H), 7.15 – 7.08 (m, 2H), 6.82 (ddd, *J* = 8.9, 8.9, 2.6 Hz, 1H), 6.71 (dd, *J* = 8.2, 2.6 Hz, 1H), 6.63 (dd, *J* = 8.5, 4.2 Hz, 1H), 5.43 (s, 1H), 3.65 (ddd, *J* = 10.5, 7.8, 1.4 Hz, 1H), 3.27 (ddd, *J* = 10.9, 10.9, 5.7 Hz, 1H), 2.48 – 2.39 (m, 1H), 2.44 (s, 3H), 2.33 (ddd, *J* = 12.5, 11.2, 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ

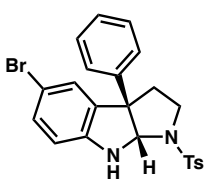
157.4 (d, $J_{C\text{-}F}$ = 235.0 Hz), 144.7, 143.7, 142.3, 136.1, 133.3 (d, $J_{C\text{-}F}$ = 7.5 Hz), 129.9, 128.7, 127.3, 127.0, 125.6, 115.2 (d, $J_{C\text{-}F}$ = 22.5 Hz), 111.2 (d, $J_{C\text{-}F}$ = 23.8 Hz), 110.8 (d, $J_{C\text{-}F}$ = 7.5 Hz), 86.2, 62.0, 48.0, 37.0, 21.5. FTIR (NaCl, thin film): 3365, 2891, 1996, 1593, 1488, 1448, 1329, 1306, 1154, 1091. HRMS (MM) calc'd for $[M+H]^+$ 409.1381, found 409.1375.



Pyrroloindoline 168f: Prepared according to General Procedure D using 10 mol% $Cu(OAc)_2$ for 24 hours. Reaction run on 0.30 mmol (105 mg) scale. The crude material was purified on basic alumina (gradient elution, 40% THF in Hexane) to afford **168f** as a white, crystalline solid (81.7 mg, 0.19 mmol, 64 % yield).

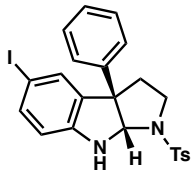
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.74 – 7.69 (m, 2H), 7.29 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.27 – 7.19 (m, 3H), 7.13 – 7.09 (m, 2H), 7.06 (dd, *J* = 8.3, 2.1 Hz, 1H), 6.93 (d, *J* = 2.1 Hz, 1H), 6.62 (d, *J* = 8.3 Hz, 1H), 5.44 (s, 1H), 4.95 (s, 1H), 3.64 (ddd, *J* = 10.6, 7.8, 1.5 Hz, 1H), 3.27 (ddd, *J* = 11.0, 11.0, 5.6 Hz, 1H), 2.50 – 2.40 (m, 1H), 2.43 (s, 3H), 2.33 (ddd, *J* = 12.5, 11.2, 7.9 Hz, 1H). ^{13}C NMR ($CDCl_3$, 126 MHz) δ 147.3, 143.8, 142.3, 136.1, 133.6, 129.9, 128.8, 128.7, 127.3, 126.9, 125.5, 124.1, 111.0, 85.8, 61.8, 48.0, 37.0, 21.5. FTIR (NaCl, thin film): 3386, 3059, 2971, 1598, 1481, 1447, 1336, 1258, 1158, 1090 1037. HRMS (MM) calc'd for $[M+H]^+$ 425.1085, found 425.1083.

Pyrroloindoline 168g: Prepared according to General Procedure D using 10 mol% $Cu(OAc)_2$ for 24 hours. Reaction run on 0.30 mmol (118.0 g) scale. The crude material was purified on basic alumina (gradient elution,



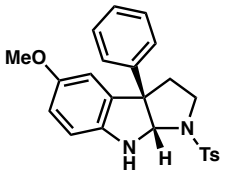
40% THF in Hexane) to afford **168g** as a white, crystalline solid (82.1 mg, 0.18 mmol, 58 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 – 7.69 (m, 2H), 7.29 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.27 – 7.18 (m, 4H), 7.10 (dd, *J* = 8.1, 1.5 Hz, 2H), 7.06 (d, *J* = 2.0 Hz, 1H), 6.58 (d, *J* = 8.3 Hz, 1H), 5.43 (s, 1H), 4.96 (s, 1H), 3.64 (ddd, *J* = 10.7, 7.8, 1.5 Hz, 1H), 3.27 (ddd, *J* = 11.0, 11.0, 5.6 Hz, 1H), 2.48 – 2.44 (m, 1H), 2.43 (s, 3H), 2.33 (ddd, *J* = 8.2, 6.4, 4.8 Hz, 1H). ^{13}C NMR ($CDCl_3$, 126 MHz) 147.8, 143.8, 142.3, 136.1, 134.1, 131.5, 129.9, 128.7, 127.3, 126.9, 126.9, 125.5, 111.5, 111.1, 85.7, 61.8, 48.0, 37.0, 21.5. FTIR (NaCl, thin film): 3386, 3059, 2971, 1598, 1477, 1336, 1258, 1093, 1037. HRMS (MM) calc'd for $[M+H]^+$ 469.0580, found 469.0578.

Pyrroloindoline 168h: Prepared according to General Procedure D using 10 mol% $Cu(OAc)_2$ for 24 hours. Reaction run on 0.30 mmol (132.1 mg) scale. The crude material was purified on basic alumina (gradient elution, 40% THF in Hexane) to afford **168h** as a white, amorphous solid (92.6 mg, 0.19 mmol, 62 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.67 (d, *J* = 8.3 Hz, 2H), 7.33 (dd, *J* = 8.2, 1.8 Hz, 1H), 7.25 (d, *J* = 7.9 Hz, 2H), 7.23 – 7.15 (m, 4H), 7.08 – 7.03 (m, 2H), 6.45 (d, *J* = 8.3 Hz, 1H), 5.38 (d, *J* = 6.8 Hz, 1H), 4.93 (s, 1H), 3.59 (ddd, *J* = 10.6, 7.8, 1.5 Hz, 1H), 3.23 (ddd, *J* = 10.9, 10.9, 5.6 Hz, 1H), 2.45 – 2.35 (m, 1H), 2.39 (s, 3H), 2.28 (ddd, *J* = 12.5, 11.2, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.4, 143.6, 142.4, 137.4, 136.1, 134.6, 132.6, 129.9, 128.7, 127.3, 126.9, 125.5, 112.2, 85.5, 80.3, 61.6, 48.0, 37.0, 21.5. FTIR (NaCl, thin film): 3385, 3057, 2968, 1597, 1476, 1446,

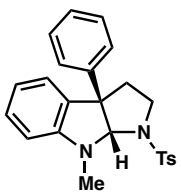


1420, 1334, 1260, 1159, 1093 cm $^{-1}$; HRMS (MM) calc'd for $[M+H]^+$ 517.0441, found 517.0436.

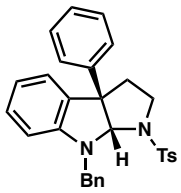
Pyrroloindoline 168i: Prepared according to General Procedure D using 10 mol% $Cu(OAc)_2$ for 6 hours. Reaction run on 0.30 mmol (103.3 mg) scale. The crude material was purified on basic alumina (gradient elution, 40% THF in Hexane) to afford **168i** as a white, amorphous solid (72.6 mg, 0.19 mmol, 62 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 – 7.70 (m, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.25 – 7.15 (m, 3H), 7.15 – 7.08 (m, 2H), 6.69 (dd, *J* = 8.5, 2.5 Hz, 1H), 6.64 (d, *J* = 8.4 Hz, 1H), 6.60 (d, *J* = 2.5 Hz, 1H), 5.40 (s, 1H), 4.71 (s, 1H), 3.71 (s, 3H), 3.65 (ddd, *J* = 10.5, 7.8, 1.3 Hz, 1H), 3.25 (ddd, *J* = 11.0, 11.0, 5.6 Hz, 1H), 2.49 – 2.44 (m, 1H), 2.43 (s, 3H), 2.32 (ddd, *J* = 12.4, 11.3, 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) 153.9, 143.6, 142.7, 142.6, 136.3, 133.0, 129.8, 128.6, 127.1, 127.0, 125.7, 113.6, 110.8, 110.6, 86.3, 62.1, 55.8, 48.1, 37.0, 21.5; FTIR (NaCl, thin film): 3380, 3057, 3025, 2947, 2832, 1598, 1492, 1336, 1159, 1093, 1035; HRMS (MM) calc'd for $[M+H]^+$ 421.1580, found 421.1577.



Pyrroloindoline 168k: Prepared according to General Procedure D using 10 mol% $Cu(OAc)_2$ for 24 hours. Reaction run on 0.30 mmol (98.5 mg) scale. The crude material was purified on basic alumina (gradient elution, 20 – 25% THF in Hexane) to afford **168k** as a white, solid (65.1 mg, 0.16 mmol, 54% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.71 – 7.65 (m, 2H), 7.23 (d, *J* = 8.0 Hz, 2H), 7.20 – 7.17 (m, 3H), 7.17 – 7.13 (m, 1H), 6.96 – 6.89 (m, 2H), 6.85 (dd, *J* = 7.3, 1.1 Hz,

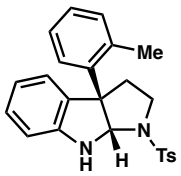


1H), 6.67 (ddd, *J* = 7.4, 7.4, 0.8 Hz, 1H), 6.50 (d, *J* = 7.9 Hz, 1H), 5.53 (s, 1H), 3.76 (ddd, *J* = 12.1, 7.0, 1.0 Hz, 1H), 3.13 (ddd, *J* = 11.9, 11.9, 5.2 Hz, 1H), 3.06 (s, 3H), 2.44 (s, 3H), 2.21 (ddd, *J* = 12.2, 5.0, 1.2 Hz, 1H), 2.05 (ddd, *J* = 12.0, 12.0, 7.1 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) 150.5, 143.6, 143.0, 136.5, 132.2, 129.7, 128.8, 128.4, 127.2, 126.7, 125.9, 123.62, 117.8, 106.2, 91.9, 61.1, 48.8, 38.0, 31.2, 21.5; FTIR (NaCl, thin film): 3056, 3027, 2949, 2891, 2827, 1762, 1605, 1491, 1347, 1160, 1092, 1022 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 405.1631, found 405.1600.

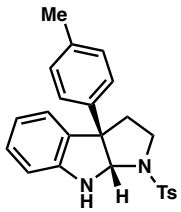


Pyrroloindoline 168l: Prepared according to General Procedure D using 10 mol% $Cu(OAc)_2$ for 24 hours. Reaction run on 0.30 mmol (121 mg) scale. The crude material was purified on basic alumina (gradient elution, 20 – 25% THF in Hexane) to afford **168l** as a white foam (83.4 mg, 0.17 mmol, 58% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.64 – 7.52 (m, 2H), 7.41 – 7.36 (m, 2H), 7.36 – 7.30 (m, 2H), 7.29 – 7.24 (m, 1H), 7.19 – 7.12 (m, 5H), 7.09 – 7.02 (m, 1H), 6.89 – 6.81 (m, 3H), 6.64 (ddd, *J* = 7.4, 7.4, 0.9 Hz, 1H), 6.42 (d, *J* = 7.8 Hz, 1H), 5.69 (s, 1H), 4.89 (d, *J* = 16.4 Hz, 1H), 4.63 (d, *J* = 16.4 Hz, 1H), 3.82 (dd, *J* = 12.5, 6.8 Hz, 1H), 3.25 (ddd, *J* = 12.2, 12.2, 5.1 Hz, 1H), 2.41 (s, 3H), 2.24 (dd, *J* = 11.9, 4.7 Hz, 1H), 2.06 (ddd, *J* = 12.1, 12.1, 7.2 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 149.7, 143.6, 143.5, 138.5, 136.4, 132.2, 129.7, 128.7, 128.4, 128.4, 127.3, 127.2, 126.9, 126.7, 125.8, 123.9, 117.9, 106.5, 90.7, 61.3, 48.5, 48.1, 38.2, 21.5; FTIR (NaCl, thin film): 3062, 3027, 2898, 1604, 1493, 1346, 1158, 1089 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 481.1944, found 481.1947.

Pyrroloindoline 168a: Prepared according to General Procedure D using 20 mol% $Cu(OTf)_2$ for 12 hours. Reaction run on 0.30 mmol (94 mg) scale with the symmetric di-*o*-tolyliodonium tetrafluoroborate. The crude material was purified by silica gel chromatography (gradient elution, 20% EtOAc in Hexane) to afford **168a** as a white, amorphous solid (60.6 mg, 0.15 mmol, 50 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.69 – 7.63 (m, 2H), 7.20 (d, *J* = 7.9 Hz, 2H), 7.14 – 7.04 (m, 4H), 7.03 – 6.98 (m, 1H), 6.92 (dd, *J* = 7.4, 0.8 Hz, 1H), 6.76 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.67 (s, 1H), 4.94 (s, 1H), 3.59 (ddd, *J* = 10.1, 7.7, 4.0 Hz, 1H), 3.36 (ddd, *J* = 10.1, 8.6, 6.6 Hz, 1H), 2.69 (ddd, *J* = 12.9, 7.9, 7.9 Hz, 1H), 2.40 (s, 3H), 2.39 – 2.34 (m, 1H), 2.03 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.4, 143.5, 139.4, 136.4, 135.6, 132.6, 131.9, 129.6, 128.5, 127.2, 127.1, 127.0, 125.7, 124.3, 119.2, 109.4, 84.4, 62.1, 47.4, 37.9, 21.4, 20.8; FTIR (NaCl, thin film): 3390, 3057, 2975, 2883, 1606, 1485, 1338, 1158 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 405.1631, found 405.1633.

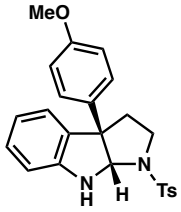


Pyrroloindoline 168b: Prepared according to General Procedure D using 20 mol % $Cu(OTf)_2$ for 12 hours. Reaction run on 0.30 mmol (94 mg) scale. The crude material was purified by silica gel chromatography (gradient elution, 20% EtOAc in Hexane) to afford **168b** as a white, amorphous solid (90.0 mg, 0.22 mmol, 74 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 – 7.71 (m, 2H), 7.30 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.11 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 7.04 (dd, *J* = 4.7, 4.0 Hz, 2H), 6.99 (ddd, *J* = 3.8, 3.8, 1.6 Hz, 3H), 6.77 (ddd, *J* = 7.4, 1.0 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.39 (s, 1H), 3.64 (ddd, *J* = 10.6, 7.8, 1.4 Hz, 1H), 3.25

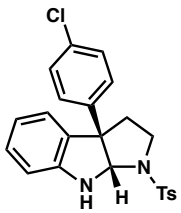


(ddd, *J* = 10.9, 10.9, 5.6 Hz, 1H), 2.51 – 2.40 (m, 1H), 2.44 (s, 3H), 2.37 – 2.29 (m, 1H), 2.28 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.7, 143.6, 140.0, 136.7, 136.31, 131.6, 129.8, 129.2, 128.7, 127.0, 125.6, 123.8, 120.0, 110.1, 85.7, 61.5, 48.1, 37.3, 21.5, 20.9; FTIR (NaCl, thin film): 3395, 3052, 3022, 2913, 1607, 1465, 1336, 1159, 1094, 1035 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 405.1631, found 405.1624.

Pyrroloindoline 168c: Prepared according to General Procedure D using 20 mol % $Cu(OTf)_2$ for 4 hours. Reaction run on 0.30 mmol (94 mg) scale. The crude material was purified by silica gel chromatography (gradient elution, 6:3:1 Hexanes:CH_2Cl_2:Acetone) to afford **168c** as a white foam (88.1 mg, 0.21 mmol, 70 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 – 7.70 (m, 2H), 7.30 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.11 (ddd, *J* = 7.9, 7.4, 1.3 Hz, 1H), 7.04 – 6.96 (m, 3H), 6.80 – 6.72 (m, 3H), 6.71 – 6.67 (m, 1H), 5.36 (s, 1H), 4.89 (br s, 1H), 3.74 (s, 3H), 3.63 (ddd, *J* = 10.6, 7.8, 1.5 Hz, 1H), 3.23 (td, *J* = 10.9, 5.6 Hz, 1H), 2.47 – 2.40 (m, 1H), 3.2.44 (s, 3H) 2.32 (ddd, *J* = 12.4, 11.2, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 158.5, 148.77, 143.6, 136.3, 135.0, 131.7, 129.8, 128.7, 127.0, 126.8, 123.8, 119.6, 113.9, 110.1, 85.8, 61.2, 55.2, 48.2, 37.3, 21.5; FTIR (NaCl, thin film): 3390, 3047, 2953, 2834, 1608, 1512, 1483, 1466, 1336, 1251, 1183, 1159, 1094 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 421.1580, found 421.1580.

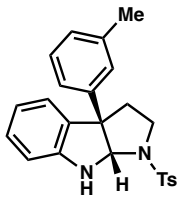


Pyrroloindoline 168d: Prepared according to General Procedure D using 20 mol % $Cu(OTf)_2$ for 12 hours. Reaction run on 0.30 mmol (94 mg) scale. The crude material was purified on basic alumina (gradient elution, 40% THF



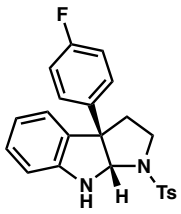
in Hexane) to afford **168d** as a white, amorphous solid (86.5 mg, 0.20 mmol, 68 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 – 7.69 (m, 2H), 7.30 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.21 – 7.15 (m, 2H), 7.15 – 7.09 (m, 1H), 7.06 – 7.00 (m, 2H), 6.95 (ddd, *J* = 7.4, 1.2, 0.5 Hz, 1H), 6.77 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H), 6.70 (dd, *J* = 4.5, 4.0 Hz, 1H), 5.37 (s, 1H), 4.91 (br s, 1H), 3.65 (ddd, *J* = 10.7, 7.8, 1.5 Hz, 1H), 3.24 (ddd, *J* = 11.0, 11.0, 5.6 Hz, 1H), 2.51 – 2.40 (m, 1H), 2.44 (s, 3H), 2.28 (ddd, *J* = 12.4, 11.2, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.7, 143.7, 141.5, 136.2, 132.9, 131.0, 129.9, 129.0, 128.7, 127.1, 126.9, 123.7, 119.7, 110.2, 85.6, 61.3, 48.1, 37.1, 21.5; FTIR (NaCl, thin film): 3386, 3051, 2970, 2893, 1607, 1493, 1466, 1483, 1399, 1336, 1159, 1093 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 425.1085, found 425.1077.

Pyrroloindoline 168e: Prepared according to General Procedure D using 20 mol % $Cu(OTf)_2$ for 12 hours. Reaction run on 0.30 mmol (94 mg) scale. The crude material was purified by silica gel chromatography (gradient elution, 20% EtOAc in Hexane) to afford **168e** as a white, amorphous solid (75.2 mg, 0.19 mmol, 63% yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.77 – 7.72 (m, 2H), 7.31 (d, *J* = 7.9 Hz, 2H), 7.14 – 7.08 (m, 2H), 7.02 – 6.97 (m, 2H), 6.92 – 6.86 (m, 2H), 6.77 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.42 (s, 1H), 3.66 (ddd, *J* = 10.6, 7.8, 1.4 Hz, 1H), 3.25 (ddd, *J* = 11.0, 11.0, 5.6 Hz, 1H), 2.49 – 2.45 (m, 1H), 2.44 (s, 3H), 2.32 (ddd, *J* = 12.5, 11.4, 7.9 Hz, 1H), 2.25 (s, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.8, 143.6, 143.0, 138.2, 136.4, 131.4, 129.9, 128.7, 128.4, 127.8, 127.0, 126.3, 124.0, 122.8, 119.6, 110.1, 85.7, 61.8, 48.2, 37.6, 21.5, 21.5; FTIR (NaCl, thin

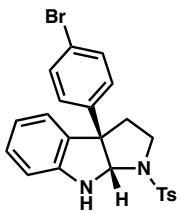


film): 3390, 2047, 2970, 1607, 1483, 1466, 1340, 1159, 1094 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 405.1631, found 405.1626.

Pyrroloindoline 168f: Prepared according to General Procedure D using 20 mol % $Cu(OTf)_2$ for 12 hours. Reaction run on 0.30 mmol (94 mg) scale. The crude material was purified on basic alumina (gradient elution, 40% THF in Hexane) to afford **168f** as a white, amorphous solid (80.3 mg, 0.20 mmol, 66 % yield). ^1H NMR ($CDCl_3$, 500 MHz) δ 7.77 – 7.70 (m, 2H), 7.30 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.16 – 7.09 (m, 1H), 7.09 – 7.04 (m, 2H), 6.97 (ddd, *J* = 7.4, 1.2, 0.5 Hz, 1H), 6.93 – 6.86 (m, 2H), 6.78 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.38 (s, 1H), 3.66 (ddd, *J* = 10.6, 7.8, 1.4 Hz, 1H), 3.24 (ddd, *J* = 11.0, 11.0, 5.6 Hz, 1H), 2.49 – 2.42 (m, 1H), 2.44 (s, 3H), 2.30 (ddd, *J* = 12.4, 11.2, 7.8 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 161.6 (d, J_{C-F} = 245.0 Hz), 148.7, 143.7, 138.7, 138.7, 136.2, 131.3, 129.8, 128.9, 127.3 (d, J_{C-F} = 7.5 Hz), 126.9, 123.7, 119.7, 115.3 (d, J_{C-F} = 20.0 Hz), 110.2, 109.9, 85.7, 61.2, 48.1, 37.3, 21.5; FTIR (NaCl, thin film): 3391, 3051, 2970, 2892, 1607, 1510, 1483, 1466, 1400, 1336, 1233, 1160, 1095 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 409.1381, found 409.1363.



Pyrroloindoline 168g: Prepared according to General Procedure D using 20 mol % $Cu(OTf)_2$ for 12 hours. Reaction run on 0.30 mmol (94 mg) scale. Reaction run on 0.30 mmol (94 mg) scale. The crude material was purified on basic alumina (gradient elution, 40% THF in Hexane) to afford **168g** as a white, amorphous solid (83.4 mg, 0.19 mmol, 59 %

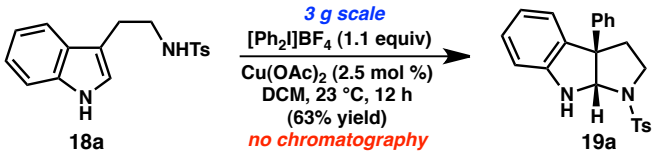


yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.76 – 7.69 (m, 2H), 7.36 – 7.28 (m, 4H), 7.12 (ddd, *J* = 7.7, 7.7, 1.2 Hz, 1H), 7.00 – 6.92 (m, 3H), 6.77 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.37 (s, 1H), 4.91 (s, 1H), 3.65 (ddd, *J* = 10.7, 7.8, 1.4 Hz, 1H), 3.24 (ddd, *J* = 10.9, 10.9, 5.6 Hz, 1H), 2.49 – 2.40 (m, 1H), 2.44 (s, 3H), 2.27 (ddd, *J* = 12.4, 11.2, 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.6, 143.7, 142.0, 136.1, 131.6, 130.9, 129.9, 129.0, 127.5, 126.9, 123.71, 121.0, 119.7, 110.2, 85.5, 61.4, 48.1, 37.0, 21.5; FTIR (NaCl, thin film): 3391, 3051, 2970, 2892, 1608, 1597, 1484, 1466, 1396, 1336, 1159, 1095 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 469.0580, found 469.0553.

Pyrroloindoline 168h: Prepared according to General Procedure D using 20 mol % $Cu(OTf)_2$ for 12 hours. Reaction run on 0.30 mmol (94 mg) scale. The crude material was purified on basic alumina (gradient elution, 40% THF in Hexanes) to afford **168h** as a white, amorphous solid (95.8 mg, 0.19 mmol, 62 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.75 – 7.69 (m, 2H), 7.55 – 7.51 (m, 2H), 7.30 (d, *J* = 7.9 Hz, 2H), 7.12 (ddd, *J* = 7.7, 7.7, 1.2 Hz, 1H), 6.96 – 6.92 (m, 1H), 6.88 – 6.83 (m, 2H), 6.76 (ddd, *J* = 7.4, 7.4, 1.0 Hz, 1H), 6.70 (d, *J* = 7.8 Hz, 1H), 5.35 (s, 1H), 3.64 (ddd, *J* = 10.7, 7.8, 1.4 Hz, 1H), 3.24 (ddd, *J* = 11.0, 11.0, 5.6 Hz, 1H), 2.49 – 2.39 (m, 1H), 2.44 (s, 3H), 2.26 (ddd, *J* = 12.4, 11.2, 7.9 Hz, 1H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 148.7, 143.8, 142.8, 137.6, 136.2, 130.9, 129.9, 129.0, 127.7, 126.9, 123.7, 119.8, 110.3, 92.5, 85.5, 61.5, 48.1, 36.9, 21.6; FTIR (NaCl, thin film): 3390, 3047, 2948, 2878, 1612, 1486, 1336, 1158, 1005 cm^{-1}; HRMS (MM) calc'd for $[M+H]^+$ 517.0441, found 517.0424.

Pyrroloindoline 168i: Prepared according to General Procedure D using 20 mol % $Cu(OTf)_2$ for 12 hours. Reaction run on 0.30 mmol (94.0 mg) scale. The crude material was purified by silica gel chromatography (gradient elution, 6:3:1 Hexanes:DCM:Acetone) to afford **168i** as a colorless oil (78.2 mg, 0.17 mmol, 56 % yield). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.91 – 7.85 (m, 2H), 7.75 – 7.69 (m, 2H), 7.29 (dd, *J* = 8.5, 0.6 Hz, 2H), 7.21 – 7.15 (m, 2H), 7.14 – 7.08 (m, 1H), 6.96 (ddd, *J* = 7.4, 1.2, 0.5 Hz, 1H), 6.76 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.71 (dd, *J* = 7.2, 0.7 Hz, 1H), 5.43 (s, 1H), 4.92 (s, 1H), 4.34 (q, *J* = 7.1 Hz, 2H), 3.66 (ddd, *J* = 10.7, 7.8, 1.4 Hz, 1H), 3.26 (ddd, *J* = 11.0, 11.0, 5.6 Hz, 1H), 2.49 (ddd, *J* = 12.3, 5.5, 1.0 Hz, 1H), 2.43 (s, 3H), 2.31 (ddd, *J* = 12.4, 11.3, 7.9 Hz, 1H), 1.36 (t, *J* = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 126 MHz) δ 166.1, 148.7, 148.0, 143.8, 136.2, 130.9, 129.9, 129.9, 129.7, 129.0, 126.9, 125.63, 123.8, 119.7, 110.2, 85.4, 61.8, 60.9, 48.1, 37.1, 21.5, 14.3; FTIR (NaCl, thin film): 3387, 3052, 2979, 2895, 1713, 1610, 1483, 1467, 1343, 1278, 1160, 1110 cm^{-1}. HRMS (MM) calc'd for $[M+H]^+$ 463.1686, found 463.1666.

3.11.6 Catalyst Efficiency and Scalability



To a flame-dried, 100 mL flask was charged *N*-tosyltryptamine (3.15 g, 10.0 mmol, 1.0 equiv), Ph_2IBF_4 (4.04 g, 11.0 mmol, 1.1 equiv) and $Cu(OAc)_2$ (45.4 mg, 0.25 mmol, 0.025 equiv). The dissolved in 50 mL CH_2Cl_2 and allowed to stir at room temperature

for 12 hours at which point the reaction was diluted with CH_2Cl_2 (100 mL), washed with saturated aqueous $NaHCO_3$ (2 x 50 mL) and the resulting aqueous layers were then combined and back extracted with CH_2Cl_2 (50 mL). The organic layers were combined, dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The resultant yellow solid was dissolved in 50 mL CH_2Cl_2, 100 mL Et_2O and 200 mL hexanes to afford a light yellow powder. The powder was filtered and dried under vacuum to give **168a** (2.55g, 6.5 mmol, 65% yield).

3.11.7 Preparation of Diimine Ligands

α-Diimine ligands were prepared following literature precedent by Bercaw et al. $^{Mes}DAB_{Me}$ (**L7**) and $^{t\text{Bu}}DAB_{Me}$ (**L6**) were readily prepared on greater than 40 gram scale in comparable yields to those reported in the literature. Ligands were thoroughly dried under high-vacuum (< 1.0 mTorr) at 50 °C for 4 hours prior to use and stored in a glovebox under inert atmosphere.

3.11.8 Preparation of Diketopiperazine Substrates

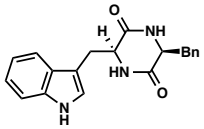
The preparation of diketopiperazines **175a-f** have been previously prepared in the literature. Diketopiperazine substrates **175d** and **175e** were prepared according to known literature procedures. Improved yields were obtained for substrates **175a-175c** using an analogous procedure as reported by Movassaghi et al.

General Procedure (I) *for the Synthesis of Diketopiperazine Substrates:*

To a solution of L-tryptophan methyl ester hydrochloride (1.0 equiv) in CH_2Cl_2 (0.1 M) at 0 °C was added Et_3N (4.5 equiv) dropwise. HOBt•H_2O (1.5 equiv) and Boc-

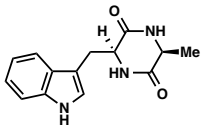
amino acid (2.0 equiv) were sequentially added and stirred vigorously. Once homogenous, EDC•HCl (1.5 equiv) was added in a single portion and the solution allowed to warm to 23 °C. The reaction was stirred for 15 hours, at which time it was quenched by the addition of 1N HCl, and the aqueous layer extracted with CH_2Cl_2 (2 x). The combined organics were then washed with saturated aqueous $NaHCO_3$, and the aqueous layer back extracted with CH_2Cl_2 (2 x). The organics were pooled, then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The resulting oil/foam was subsequently dissolved in CH_2Cl_2 (0.2 M), and cooled to 0 °C. TFA (1.5 mL/5 mL CH_2Cl_2) was added dropwise, then the solution was warmed to 23 °C and stirred for 2 h. The mixture was concentrated *in vacuo* and the resulting viscous residue dissolved in methanol (0.25 M), and cooled to 0°C. Ammonium hydroxide (28–30% in H_2O, 1 mL/ 6 mL MeOH) was then added dropwise and the reaction mixture allowed to warm to 23 °C and stirred for 24 h. The resulting suspension was cooled to 0 °C, and the fine white precipitate was filtered and rinsed with cold methanol. The white solid is then crushed and dried under high vacuum (< 1 mTorr) at 50 °C for a minimum of 2 h.

Cyclo-(L)-Trp-(L)-Phe (175a)



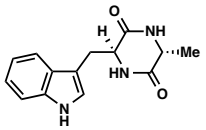
Prepared from L-tryptophan methyl ester hydrochloride following *General Procedure I* on 19.6 mmol scale. The crude reaction mixture was filtered to yield 5.8 g (89% yield) of **175a** as a white solid. Spectral data matches that reported in the literature.

Cyclo-(L)-Trp-(L)-Ala (175b)



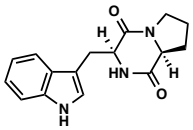
Prepared from L-tryptophan methyl ester hydrochloride following *General Procedure I* on 9.8 mmol scale. The crude reaction mixture was filtered to yield 2.3 g (92% yield) of **175b** as a white solid. Spectral data matches that reported in the literature.

Cyclo-(L)-Trp-(D)-Ala (175c)



Prepared from L-tryptophan methyl ester hydrochloride following *General Procedure I* on 7.9 mmol scale. The crude reaction mixture was filtered to yield 1.8 g (89% yield) of **175c** as a white solid. Spectral data matches that reported in the literature.

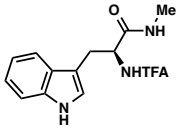
Large Scale Preparation of Cyclo-(L)-Trp-(L)-Pro (175f):



To a solution of L-proline methyl ester hydrochloride (11.0 g, 66.6 mmol, 1.00 equiv) in CH_2Cl_2 (700 mL) at 0 °C was added triethylamine (32.5 mL, 233 mmol, 3.50 equiv) dropwise by addition funnel. *N*-hydroxybenzotriazole monohydrate (15.3, 100 mmol, 1.50 equiv) and Boc-(L)-tryptophan (31.8 g, 100 mmol, 1.50 equiv) were then added successively. After 10 minutes, EDC•HCl (19.2 g, 100 mmol, 1.50 equiv) was added in a single portion and the mixture allowed to warm to 23 °C over 2.0 hours. After 20 hours, the solution was quenched by the addition of 1N HCl (1.0 L), and the aqueous layer extracted with CH_2Cl_2 (2 x 150 mL). The combined organics were then washed with saturated aqueous $NaHCO_3$ (1.0 L), and the aqueous layer back extracted with CH_2Cl_2 (200 mL). The combined organics were then dried over anhydrous sodium sulfate, filtered, and concentrated in

vacuo. The resulting white foam was then dissolved in CH_2Cl_2 (200 mL), and trifluoroacetic acid (60 mL) added dropwise by addition funnel. After 2 h, the solution was concentrated in vacuo and the viscous residue dissolved in methanol (900 mL) and cooled to 0 °C. Ammonium hydroxide (28 to 30% in H_2O, 35.0 mL) was added dropwise by addition funnel. The solution was then stirred for 14 hours, concentrated in vacuo, and redissolved in CH_2Cl_2 (1.0 L). The solution was next washed with H_2O (3 x 500 mL), and the aqueous layer back extracted with CH_2Cl_2 (250 mL). The organic layers were then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was dissolved in MeOH (200 mL) and the solution cooled to 0 °C. After 20 minutes, the resulting white precipitate was collected. The filtrate was then concentrated to 100 mL and recooled to 0 °C, and a second crop of precipitate collected. The process was repeated a third time to collect a third crop of product. The resulting precipitates were combined, powdered, and dried under high vacuum at 50 °C for 12 hours to afford analytically pure cyclo-L-Pro-L-Trp as a white solid (12.4 g, 43.8 mmol, 66% yield). Spectral data matches that reported in the literature.

Preparation of Trifluoroacetyltryptophan methyl carboxamide (7):



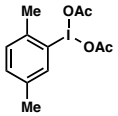
To (L)-Tryptophan methyl ester hydrochloride (5.84 g, 22.9 mmol) was added methylamine (33% solution in EtOH, 50 mL). The mixture was stirred for 48 h at 20 °C, then concentrated *in vacuo*, and the mixture co-evaporated with CH_2Cl_2 (50 mL), then Et_2O (3 x 100 mL), sequentially to afford a white solid. The solid was then suspended in anhydrous CH_2Cl_2 (250 mL), and Et_3N (9.6 mL, 68.7 mmol, 3.0 equiv) added dropwise by syringe at 20 °C. The resulting mixture was then cooled to 0

°C, and TFAA (3.23 mL, 22.9 mmol, 1.00 equiv) added dropwise by syringe. After 24 hours, the reaction was quenched with 1N HCl (200 mL), extracted with CH_2Cl_2 (200 mL), dried over Na_2SO_4, filtered and concentrated. The residue was then dissolved in EtOAc (250 mL), and filtered through a short plug of silica gel, and the filter cake washed with additional EtOAc (250 mL). The filtrate was then concentrated, and the resulting yellow solid was treated with Et_2O/pentane to afford **7** as a white, amorphous powder (2.97 g, 42% yield). ^{1}H NMR (500 MHz, DMSO-d_6) 10.82 (d, J = 0.9 Hz, 1H), 9.61 (d, J = 8.2 Hz, 1H), 8.21 (q, J = 4.3 Hz, 1H), 7.65 (d, J = 7.9 Hz, 1H), 7.33 (d, J = 8.1 Hz, 1H), 7.13 (d, J = 2.3 Hz, 1H), 7.10 – 7.04 (m, 1H), 6.99 (ddd, J = 7.9, 7.1, 1.0 Hz, 1H), 4.52 (ddd, J = 9.9, 8.5, 4.8 Hz, 1H), 3.20 (dd, J = 14.6, 4.6 Hz, 1H), 3.08 (dd, J = 14.6, 10.0 Hz, 1H), 2.62 (d, J = 4.6 Hz, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) 170.3, 156.2 (q, $J_{C\text{-}F}$ = 36.4 Hz), 136.1, 127.1, 123.7, 121.0, 118.4, 118.3, 115.8 (q, $J_{C\text{-}F}$ = 288.2 Hz), 111.4, 109.7, 54.3, 27.2, 25.7; FTIR (NaCl, thin film): 3277, 1700, 1696, 1653, 1636, 1560, 1347, 1185; $[\alpha]_D^{25}$ = +8.53 (c = 0.44, $CHCl_3$); LRMS (EI+) calc'd $[M+H]^+$ 314.1, found 314.1.

3.11.9 Preparation of Diaryliodonium Triflate Salts

The following diaryliodonium salts were prepared following known procedures: diphenyliodonium tetrafluoroborate, diphenyliodonium hexafluoroarsentate, diphenyliodonium triflate, bis-*p*-tolyliodonium triflate, and bis-*p*-methoxyiodonium triflate. Diphenyliodonium hexafluorophosphate was purchased from Alfa-Aesar. *m*-CPBA (Sigma-Aldrich, <77%) was dried under high vacuum (< 1 mTorr) at 23 °C for 4 hours as reported by Oloffson and coworkers.

Preparation of 2-iodo-*p*-xylene diacetate (SI-1):



To a solution of 2-iodo-1,4-dimethylbenzene (11.6 g, 50.0 mmol, 1.00 equiv) in AcOH (1.0 L) at 50 °C was added $NaBO_3$•$4H_2O$ (84.7 mmol, 0.55 mmol, 11.0 equiv) portion wise over 30 minutes. The solution was vigorously stirred at 50 °C for 5 hours, then cooled to ambient temperature and diluted with H_2O (500 mL) and extracted with CH_2Cl_2 (3 x 500 mL). The combined organics were then washed with water (3 x 500 mL), dried over anhydrous sodium sulfate, filtered, and concentrated *in vacuo*. The crude residue was suspended in a minimum of Et_2O, then triturated with hexanes and the precipitate collected by vacuum filtration. 2-Iodo-*p*-xylene diacetate was obtained as a white, crystalline solid (14.0 g, 40.0 mmol, 80% yield). Spectral data obtained match that previously reported, ^{1}H and ^{13}C NMR data is reported for convenience. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.97 (d, *J* = 1.2 Hz, 1H), 7.37 (d, *J* = 7.8 Hz, 1H), 7.30 (dd, *J* = 7.8, 1.2 Hz, 1H), 2.65 (s, 3H), 2.36 (s, 3H), 1.97 (s, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 176.3, 138.5, 137.3, 137.3, 133.5, 130.4, 126.8, 24.9, 20.6, 20.2.

General Procedure II

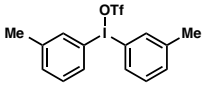
To a solution of iodoarene in CH_2Cl_2 (0.25 M) was added *m*CPBA (1.1 equiv), and BF_3•OEt_2 (2.5 equiv). The solution was stirred for 45 minutes, then the solution cooled to 0 °C in a dry ice corresponding aryl boronic acid (1.00 equiv) added a solid in a single portion. The solution was stirred for 15 minutes, then warmed to room temperature and stirring continued for 45 minutes. The solution was then recooled to 0 °C and TfOH (2.00

equiv) added dropwise via syringe. The solution was stirred for 5 minutes at 0 °C, then warmed to room temperature and concentrated under reduced pressure. The resulting solution was then filtered through a plug of silica gel, eluting with 5% MeOH/CH_2Cl_2, the filtrate concentrated, and the residue triturated from Et_2O to afford pure diaryliodonium triflate, typically as a white, crystalline solid.

General Procedure III

To a solution of aryl boronic acid (1.00 equiv) in CH_2Cl_2 (0.25 M) at 0 °C was added BF_3•OEt_2 (1.1 equiv) dropwise by syringe. The solution was stirred for 15 minutes, then a solution of iodoxylene diacetate (1.00 equiv) in CH_2Cl_2 (0.5 M) added dropwise by cannula transfer over 15 minutes. The solution was slowly warmed to 23 °C over 1 h, then recooled to 0 °C and TfOH (2.00 equiv) added dropwise via syringe. The solution was stirred for 5 minutes at 0 °C, then warmed to room temperature and concentrated under reduced pressure. The resulting solution was then filtered through a plug of silica gel, eluting with 5 % MeOH/CH_2Cl_2, the filtrate concentrated, and the residue triturated from Et_2O to afford pure diaryliodonium triflate salt, typically as a white, crystalline solid.

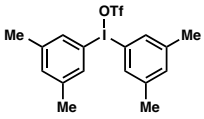
Di-(3-tolyl)iodonium triflate (SI-2)



Prepared by *General Procedure II* from 3-methylphenyl boronic acid and 3-methyliodobenzene on 5.00 mmol scale. Trituration from Et_2O afforded the product as a white, crystalline solid (1.54 g, 3.36 mmol, 67% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.10 (td, J = 1.8, 0.9 Hz, 2H), 8.04 (ddt, J = 7.9, 1.8, 0.9

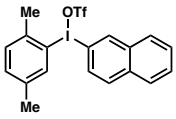
Hz, 2H), 7.48 (ddt, *J* = 7.7, 1.8, 1.0 Hz, 2H), 7.41 (t, *J* = 7.8 Hz, 2H), 2.34 (d, *J* = 0.8 Hz, 6H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 142.3, 135.78, 133.2, 132.7, 131.9, 116.6, 21.2; FTIR (NaCl, thin film): 3744, 3675, 1596, 1259, 1172, 1036, 1026 cm^{-1}; LRMS (EI+) calc'd $[M–OTf]^+$ 309.1, found 309.0.

Di-(3,5-dimethylphenyl)iodonium triflate (SI-3)



Prepared by *General Procedure II* from 3,5-dimethyliodobenzene and 3,5-dimethylphenylboronic acid on 10.0 mmol scale. Trituration from Et_2O afforded the product as a white, crystalline solid (3.72 g, 7.65 mmol, 77% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 7.88 (dt, *J* = 1.5, 0.8 Hz, 4H), 7.30 (tt, *J* = 1.5, 0.8 Hz, 2H), 2.30 (d, *J* = 0.9 Hz, 12H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 141.9, 133.9, 132.9, 116.2, 21.1; FTIR (NaCl, thin film): 1599, 1558, 1451, 1381, 1243, 1221, 1171, 1154, 1026 cm^{-1}; LRMS (EI+) calc'd $[M–OTf]^+$ 337.2, found 337.2.

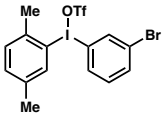
(2-naphthyl)(*p*-xylyl)iodonium triflate (SI-4)



Prepared by *General Procedure III* from 2-naphthyl boronic acid on 5.00 mmol scale. Trituration from Et_2O afforded the product as a white, crystalline solid (2.15 g, 4.23 mmol, 85% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.93 (d, *J* = 1.9 Hz, 1H), 8.29 (dd, *J* = 1.7, 0.9 Hz, 1H), 8.18 (dd, *J* = 8.8, 1.9 Hz, 1H), 8.10 – 7.99 (m, 4H), 7.73 – 7.66 (m, 2H), 7.43 (d, *J* = 7.8 Hz, 1H), 7.38 (ddd, *J* = 7.7, 1.7, 0.8 Hz, 1H), 2.61 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 139.6, 137.9, 137.6, 136.5, 134.4, 133.9, 133.8, 132.00, 131.5, 130.6, 129.4, 128.6, 128.6, 128.4, 121.6,

113.0, 25.0, 20.5; FTIR (NaCl, thin film): 3670, 3588, 1653, 1635, 1490, 1347, 1259, 1172, 1036, 1024 cm^{-1}; LRMS (EI+) calc'd $[M–OTf]^+$ 359.0, found 359.0.

(3-bromophenyl)(*p*-xylyl)iodonium triflate (SI-5)



Prepared by *General Procedure III* from 3-bromophenyl boronic acid on 5.00 mmol scale. Trituration from Et_2O afforded the product as a white, crystalline solid (1.33 g, 2.48 mmol, 50% yield). ^1H NMR (500 MHz, DMSO-d_6) δ 8.53 (dd, J = 1.8, 1.8 Hz, 1H), 8.28 (dd, J = 1.8, 0.9 Hz, 1H), 8.18 (ddd, J = 8.0, 1.8, 0.9 Hz, 1H), 7.85 (ddd, J = 8.1, 1.9, 0.9 Hz, 1H), 7.51 - 7.42 (m, 2H), 7.44 - 7.38 (m, 1H), 2.57 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (500 MHz, DMSO-d_6): δ 139.2, 137.5, 137.1, 136.7, 134.9, 133.9, 133.6, 133.5, 131.1, 123.3, 121.2, 116.1, 24.5, 20.0; FTIR (NaCl, thin film): 3074, 1569, 1554, 1490, 1456, 1275, 1242, 1170, 1025 cm^{-1}; LRMS (EI+) calc'd $[M–OTf]^+$ 388.1, found 388.9.

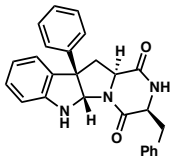
3.11.10 Optimization of Reaction Parameters for Diastereoselective Arylation

Optimization Procedure – In a glovebox, $(CuOTf)_2$•PhMe (20.7 mg, 0.040 mmol), and ligand (0.088 mmol) were dissolved in anhydrous CH_2Cl_2 (4.0 mL). The solution was stirred vigorously for 1.0 hr, filtered through a plug of cotton and removed from the glovebox. A portion of the solution (1.00 mL, 0.020 mmol, 20 mol % in Cu) was added to an oven-dried, 1-dram vial containing diketopiperazine (0.100 mmol) and diaryliodonium salt (0.110 mmol). The solution was stirred at 23 °C (care was taken not to exceed 25 °C) for 24 hrs, then quenched by the addition of concentrated ammonia (28–30% in H_2O, 1.0 mL). After 5 minutes, the mixture was diluted with EtOAc (30 mL) and

washed with a mixture water (20 mL) and brine (20 mL). The aqueous layer was then back extracted with EtOAc (2 x 10 mL) and the combined organics dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo* to afford a solid residue.

The residue was then dissolved in a standard solution of maleic acid in DMSO-d_6, and the solution analyzed for yield, C3:C2 ratio, and dr. NMR yields were obtained via careful integration against the standard.

Preparation of minor diastereomer 177



To an oven dried vial was added diketopiperazine **175a** (33 mgs, 0.1 mmol), diaryliodonium hexafluorophosphate (47 mgs, 0.11 mmol) and $(CuOTf)_2$•PhMe (5.2 mgs, 0.01 mmol). The solids were dissolved in 1 mL CH_2Cl_2 and the reaction was allowed to stir for 24 hours, then quenched by the addition of 1 mL NH_4OH. The mixture was diluted with EtOAc and extracted with EtOAc (2 X 10 mL). The organic layers were combined, dried over Na_2SO_4, filtered and concentrated. The minor diastereomer was purified from the crude residue by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **177** as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) 7.30 – 7.27 (m, 2H), 7.26 – 7.22 (m, 3H), 7.22 – 7.16 (m, 3H), 7.15 – 7.09 (m, 2H), 7.04 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 6.88 – 6.83 (m, 1H), 6.67 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.61 (d, *J* = 7.8 Hz, 1H), 5.77 (s, 1H), 5.69 (d, *J* = 9.3 Hz, 1H), 4.40 – 4.32 (m, 1H), 4.16 (ddd, *J* = 10.5, 3.8, 1.3 Hz, 1H), 3.51 (dd, *J* = 14.5, 3.8 Hz, 1H), 3.15 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.69 (ddd, *J* = 16.6, 14.1, 10.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) 168.8, 166.8, 147.2, 142.3, 135.6, 133.3, 129.2, 128.9, 128.8, 128.6, 127.5, 127.3, 126.5, 124.1, 119.6, 109.6, 85.5, 59.2, 58.6, 56.1, 38.6, 36.2;

FTIR (NaCl, thin film): 3306, 3058, 2929, 1674, 1607, 1482, 1447, 1318, 1223, 1071 cm^{-1}; $[\alpha]_D^{25} = -329$ ($c = 0.31$, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 410.2, found 410.2.

3.11.11 Substrate Scope for Diastereoselective Arylation – Characterization Data

General Procedure IV: Tryptophan Arylation

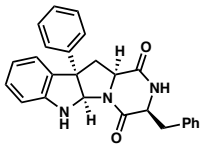
Catalyst Preparation – In a glovebox, copper(I)trifluoromethanesulfonate toluene complex (0.10 equiv) and alpha-diimine-ligand (0.22 equiv) were dissolved in anhydrous CH_2Cl_2 (0.1 M in Cu). The solution was vigorously stirred for 1.0 hour, and then filtered through a plug of cotton.[1] The solution was then removed from the glovebox for immediate use.

Arylation Reaction – A flame-dried flask containing a magnetic stirbar was charged with tryptophan substrate (0.300 mmol, 1.00 equiv) and diaryliodonium salt (0.330 mmol, 1.1 equiv), then equipped with a rubber septum. To the solids was added the freshly-prepared Cu-catalyst solution prepared above (3.00 mL, 0.030 mmol, 20 mol %) and the solution vigorously stirred at 20 °C. After the time indicated below, the solution was quenched with aqueous ammonia (3.00 mL of a 27-33% solution in H_2O) and stirred for 5 minutes. The reaction was then diluted with EtOAc (30 mL) and washed with a mixture of H_2O (30 mL) and brine (30 mL). The aqueous portion was back extracted with EtOAc (2 x 10 mL) and the combined organics dried over anhydrous $MgSO_4$, filtered, and concentrated *in vacuo*. The crude residue was purified by column chromatography on silica gel to

[1] Filtering the catalyst solution was found to improve the overall selectivity, reactivity, and reproducibility of the reaction.

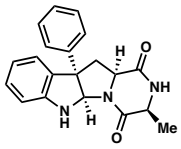
afford pure arylpyrroloindoline product, typically as either a white, amorphous powder or a white foam.

Pyrroloindoline 176a



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and diphenyliodonium triflate. The crude residue was purified by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **176a** as a white solid (104.0 mg, 0.254 mmol, 85% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 – 7.31 (m, 6H), 7.28 (ddd, *J* = 5.1, 2.3, 2.3 Hz, 2H), 7.20 (d, *J* = 7.0 Hz, 2H), 7.12 (ddd, *J* = 7.7, 7.7, 1.2 Hz, 1H), 6.97 – 6.89 (m, 1H), 6.75 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.69 (d, *J* = 7.9 Hz, 1H), 5.85 (s, 1H), 5.60 (s, 1H), 4.44 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.24 (ddd, *J* = 10.7, 3.7, 1.1 Hz, 1H), 3.61 (dd, *J* = 14.5, 3.7 Hz, 1H), 3.23 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.77 (ddd, *J* = 13.6, 10.2, 2.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 166.8, 147.1, 142.3, 135.6, 133.3, 129.3, 128.9, 128.9, 128.7, 127.6, 127.6, 126.5, 124.2, 119.7, 109.7, 85.5, 59.3, 58.7, 56.2, 38.6, 36.3; FTIR (NaCl, thin film): 3315, 3087, 3052, 3027, 2928, 2849, 1676, 1605, 1498, 1407, 1348, 1306, 1261, 1221 cm^{-1}; $[\alpha]_D^{25}$ = +113 (*c* = 1.8, $CHCl_3$); LRMS (EI+) calc'd $[M+H]^+$ 410.2, found 410.2.

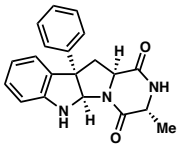
Pyrroloindoline 176b



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and diphenyliodonium triflate for 24 h. Reaction was run with additional CH_2Cl_2 (3.00 mL) for solubility. The crude residue was purified by silica gel chromatography (20% hexanes : 77.5% ethyl acetate: 2.5% methanol) to afford **176b**

as a white solid (66.2 mg, 0.199 mmol, 66% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 4H), 7.32 – 7.26 (m, 1H), 7.09 (dd, *J* = 7.7, 7.7 Hz, 1H), 6.94 (d, *J* = 7.5 Hz, 1H), 6.74 (d, *J* = 7.5, 7.5 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.82 (d, *J* = 8.3 Hz, 1H), 5.79 (s, 1H), 4.48 (dd, *J* = 8.3, 8.3 Hz, 1H), 4.15 – 4.05 (m, 1H), 3.21 (dd, *J* = 13.8, 7.6 Hz, 1H), 2.84 (dd, *J* = 13.8, 9.3 Hz, 1H), 1.46 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.3, 167.9, 147.2, 142.3, 133.2, 128.9, 128.7, 127.4, 126.5, 124.2, 119.7, 109.8, 85.5, 59.4, 59.0, 51.3, 38.3, 15.7; FTIR (NaCl, thin film): 3255, 2928, 2849, 1669, 1653, 1486, 1419, 1219 cm^{-1}; $[\alpha]_D^{25}$ = +158 (*c* = 0.85, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 334.2, found 334.1.

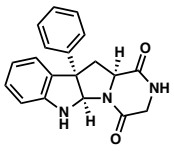
Pyrroloindoline 176c



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and diphenyliodonium triflate for 24 h. Reaction was run with additional CH_2Cl_2 (3.00 mL) for solubility. The crude residue was purified by silica gel chromatography (77.5% ethyl acetate, 20% hexanes, 2.5% methanol) to afford **5c** as a white solid (49.5 mg, 0.149 mmol, 50% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.32 (m, 4H), 7.31 – 7.26 (m, 1H), 7.09 (ddd, *J* = 7.6, 7.6, 1.0 Hz, 1H), 7.01 (d, *J* = 3.8 Hz, 1H), 6.88 (dd, *J* = 7.4, 0.5 Hz, 1H), 6.72 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.65 (d, *J* = 7.9 Hz, 1H), 5.84 (d, *J* = 3.0 Hz, 1H), 5.54 (d, *J* = 3.0 Hz, 1H), 4.43 (dd, *J* = 10.6, 7.0 Hz, 1H), 4.01 (qd, *J* = 7.2, 4.2 Hz, 1H), 3.29 (dd, *J* = 13.7, 7.0 Hz, 1H), 2.65 (dd, *J* = 13.7, 10.7 Hz, 1H), 1.46 (d, *J* = 7.2 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 167.9, 147.1, 142.2, 133.6, 128.9, 128.7, 127.3, 126.7, 124.0, 119.5, 109.6, 86.0, 58.8, 57.2, 53.6, 39.4,

19.8; FTIR (NaCl, thin film): 3275, 3042, 2913, 1684, 1652, 1437, 1308, 1266, 1221 cm^{-1}; $[\alpha]_D^{25}$ = +119 (*c* = 1.1, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 334.2, found 334.1

Pyrroloindoline 176d



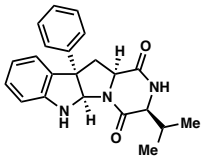
Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and diphenyliodonium triflate for 24 h. Reaction was run with additional CH_2Cl_2 (3.00 mL) for solubility. The crude residue was purified by silica gel chromatography (77.5% ethyl acetate, 20% hexane, 2.5% methanol) to afford **176d** as a white solid (61.5 mg, 0.193 mmol, 64% yield).

^1H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.30 (m, 4H), 7.29 – 7.26 (m, 1H), 7.09 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 6.96 – 6.90 (m, 1H), 6.86 (d, *J* = 4.2 Hz, 1H), 6.73 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.65 (d, *J* = 7.8 Hz, 1H), 5.81 (s, 1H), 4.43 (dd, *J* = 8.5, 8.5 Hz, 1H), 4.02 (dd, *J* = 17.0, 1.6 Hz, 1H), 3.85 (dd, *J* = 17.0, 4.6 Hz, 1H), 3.23 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.77 (dd, *J* = 13.8, 9.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 165.2, 147.1, 142.3, 133.3, 128.9, 128.7, 127.3, 126.5, 124.2, 119.7, 109.8, 85.4, 59.2, 58.0, 46.7, 38.7; FTIR (NaCl, thin film): 3280, 3047, 2928, 2854, 1674, 1602, 1483, 1441, 1310, 1263, 1219, 1155 cm^{-1}; $[\alpha]_D^{25}$ = +80.2 (*c* = 0.59, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 320.1, found 320.1.

Pyrroloindoline 176e

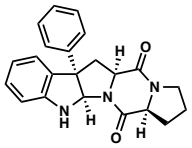
Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and diphenyliodonium triflate for 24 h. The crude residue was purified by silica gel chromatography (20% hexanes,

77.5% ethyl acetate, 2.5% methanol) to afford **176e** as a white solid (55.5 mg, 0b.154 mmol, 51% yield).



^{1}H NMR (500 MHz, $CDCl_3$) δ 7.39 – 7.31 (m, 4H), 7.30 – 7.26 (m, 1H), 7.11 – 7.06 (m, 1H), 6.96 – 6.92 (m, 1H), 6.73 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.66 – 6.62 (m, 1H), 5.87 (s, 1H), 5.80 (d, *J* = 2.6 Hz, 1H), 5.44 (d, *J* = 2.4 Hz, 1H), 4.47 – 4.39 (m, 1H), 3.91 – 3.87 (m, 1H), 3.23 (dd, *J* = 13.7, 7.4 Hz, 1H), 2.79 (dd, *J* = 13.7, 9.7 Hz, 1H), 2.60 (heptd, *J* = 7.1, 2.6 Hz, 1H), 1.05 (d, *J* = 7.2 Hz, 3H), 0.87 (d, *J* = 6.8 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.4, 166.7, 147.3, 142.4, 133.3, 128.9, 128.6, 127.3, 126.5, 124.3, 119.6, 109.5, 85.5, 60.4, 59.1, 58.2, 38.8, 28.4, 19.3, 16.0; FTIR (NaCl, thin film): 3292, 2964, 1669, 1609, 1483, 1465, 1419, 1347, 1291, 1222 cm^{-1}; $[\alpha]_D^{25}$ = +107 (*c* = 0.52, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 362.2, found 362.2.

Pyrroloindoline 176f

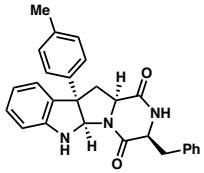


Prepared following *General Procedure IV* using 40 mol % $^{t\text{-}Bu}DAB_{Me}$ and diphenyliodonium hexafluorophosphate for 4 h. The crude residue was purified by silica gel chromatography (77.5% ethyl acetate, 20% hexanes, 2.5% methanol) to afford **176f** as a white solid (76.6 mg, 0.213 mmol, 71% yield).

^{1}H NMR (500 MHz, $CDCl_3$) δ 7.38 - 7.34 (m, 4H), 7.31 - 7.27 (m, 1H), 7.08 (ddd, *J* = 7.9, 7.5, 1.3 Hz, 1H), 6.91 (ddd, *J* = 7.5, 1.3, 0.6 Hz, 1H), 6.73 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.67 - 6.61 (m, 1H), 5.83 (s, 1H), 5.36 (s, 1H), 4.55 - 4.48 (m, 1H), 4.14 (ddd, *J* = 9.1, 7.3, 1.6 Hz, 1H), 3.54 - 3.46 (m, 2H), 3.21 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.81 (dd, *J* =

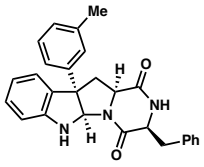
13.9, 9.8 Hz, 1H), 2.31 (dddd, *J* = 12.8, 7.0, 7.0, 3.4 Hz, 1H), 2.17 (dddd, *J* = 12.9, 10.7, 9.2, 7.2 Hz, 1H), 2.07 - 1.96 (m, 1H), 1.90 (dddd, *J* = 14.9, 6.8, 4.0, 1.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 167.9, 165.7, 147.0, 142.3, 133.6, 128.8, 128.8, 128.6, 127.3, 126.7, 124.1, 119.7, 109.7, 85.3, 60.5, 60.3, 59.9, 45.2, 38.1, 27.6, 23.2; FTIR (NaCl, thin film): 3330, 2952, 2878, 1665, 1607, 1484, 1467, 1423, 1340, 1313, 1219, 1154, 1068 cm^{-1}; $[\alpha]_D^{25}$ = +108 (*c* = 0.63, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 360.2, found 360.2.

Pyrroloindoline 176g



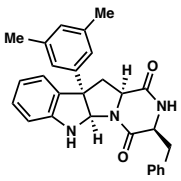
Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and di(*p*-tolyl)iodonium triflate for 32 h. The crude residue was purified by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **176g** as a white solid (98.2 mg, 0.232 mmol, 77% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.31 (m, 2H), 7.28 (ddd, *J* = 4.7, 1.9, 1.9 Hz, 1H), 7.24 – 7.18 (m, 4H), 7.16 (d, *J* = 8.0 Hz, 2H), 7.11 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 6.93 – 6.89 (m, 1H), 6.74 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 5.84 (d, *J* = 2.9 Hz, 1H), 5.56 (s, 1H), 5.43 (d, *J* = 2.8 Hz, 1H), 4.48 – 4.38 (m, 1H), 4.23 (ddd, *J* = 10.8, 3.7, 1.3 Hz, 1H), 3.61 (dd, *J* = 14.5, 3.7 Hz, 1H), 3.21 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.74 (ddd, *J* = 18.4, 14.1, 10.4 Hz, 2H), 2.33 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 166.8, 147.1, 139.3, 137.1, 135.6, 133.5, 129.5, 129.3, 128.9, 128.6, 127.6, 126.4, 124.1, 119.7, 109.6, 85.6, 59.0, 58.7, 56.2, 38.7, 36.3, 20.9; FTIR (NaCl, thin film): 3315, 3027, 2923, 2859, 1686, 1602, 1412, 1343, 1308, 1219 cm^{-1}; $[\alpha]_D^{25}$ = +208 (*c* = 0.61, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 424.2, found 424.2.

Pyrroloindoline 176h



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and di(*m*-tolyl)iodonium triflate for 4 h. The crude residue was purified by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **176h** as a white solid (119.0 mg, 0.280 mmol, 94% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.33 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.28 (d, *J* = 7.3 Hz, 1H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.20 (d, *J* = 7.1 Hz, 2H), 7.16 – 7.07 (m, 4H), 6.93 (d, *J* = 7.4 Hz, 1H), 6.74 (dd, *J* = 13.8, 6.3 Hz, 1H), 6.68 (d, *J* = 7.8 Hz, 1H), 5.87 (d, *J* = 2.9 Hz, 1H), 5.60 (s, 1H), 5.46 (d, *J* = 2.7 Hz, 1H), 4.49 – 4.39 (m, 1H), 4.24 (dd, *J* = 10.8, 2.7 Hz, 1H), 3.61 (dd, *J* = 14.5, 3.7 Hz, 1H), 3.23 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.81 – 2.68 (m, 2H), 2.34 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 166.8, 147.1, 142.2, 138.6, 135.6, 133.4, 129.3, 128.9, 128.7, 128.6, 128.1, 127.6, 127.2, 124.1, 123.6, 119.6, 109.6, 85.5, 59.2, 58.7, 56.2, 38.7, 36.3, 21.6; FTIR (NaCl, thin film): 3385, 3270, 3032, 2918, 2839, 1676, 1602, 1409, 1350, 1313, 1234, 1197 cm^{-1}; $[\alpha]_D^{25}$ = +169 (*c* = 0.81, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 424.2, found 424.2.

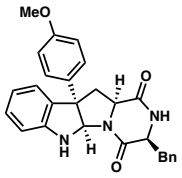
Pyrroloindoline 176i



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and bis(3,5-dimethylphenyl)iodonium triflate for 4 h. The crude residue was purified by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **176i** as a white solid (119.4 mg, 0.273 mmol, 91% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.37 – 7.31 (m, 2H), 7.30 – 7.26 (m, 1H), 7.23 – 7.18 (m, 2H), 7.14 –

7.09 (m, 1H), 6.97 – 6.94 (m, 2H), 6.94 – 6.90 (m, 2H), 6.74 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.71 – 6.65 (m, 1H), 5.88 (d, *J* = 2.9 Hz, 1H), 5.61 (s, 1H), 5.44 (d, *J* = 2.8 Hz, 1H), 4.43 (ddd, *J* = 9.8, 7.1, 1.0 Hz, 1H), 4.24 (ddd, *J* = 10.8, 3.7, 1.4 Hz, 1H), 3.62 (dd, *J* = 14.5, 3.7 Hz, 1H), 3.23 (dd, *J* = 13.7, 7.1 Hz, 1H), 2.77 (dd, *J* = 14.5, 10.8 Hz, 1H), 2.68 (dd, *J* = 13.7, 10.1 Hz, 1H), 2.30 (d, *J* = 0.4 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) 168.9, 166.7, 147.1, 142.1, 138.4, 135.7, 133.5, 129.3, 129.0, 128.9, 128.5, 127.6, 124.4, 124.1, 119.6, 109.6, 85.5, 59.1, 58.7, 56.2, 38.8, 36.3, 21.4; FTIR (NaCl, thin film): 3288, 3051, 2919, 2854, 1684, 1604, 1484, 1455, 1418, 1346, 1312, 1255, 1204, 1156, 1109 cm^{-1}; $[\alpha]_D^{25}$ = +101 (*c* = 2.0, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 438.2, found 438.2.

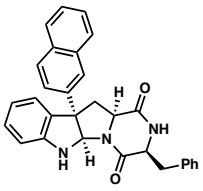
Pyrroloindoline 176j



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ using di(*p*-methoxyphenyl)iodonium triflate for 42 h. The crude residue was purified by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **176j** as a white solid (88.1 mg, 0.200 mmol, 67% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.36 – 7.30 (m, 2H), 7.28 (d, *J* = 7.2 Hz, 1H), 7.27 – 7.23 (m, 2H), 7.20 (d, *J* = 7.0 Hz, 2H), 7.11 (ddd, *J* = 7.7, 7.7, 1.2 Hz, 1H), 6.91 (dd, *J* = 7.4, 0.7 Hz, 1H), 6.89 – 6.86 (m, 2H), 6.74 (ddd, *J* = 7.5, 7.5, 0.9 Hz, 1H), 6.67 (d, *J* = 7.8 Hz, 1H), 5.81 (s, 1H), 5.57 (s, 1H), 4.48 – 4.40 (m, 1H), 4.24 (ddd, *J* = 10.8, 3.7, 1.2 Hz, 1H), 3.79 (s, 3H), 3.61 (dd, *J* = 14.5, 3.5 Hz, 1H), 3.18 (dd, *J* = 13.7, 7.3 Hz, 1H), 2.74 (ddd, *J* = 20.3, 14.1, 10.4 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) 168.9, 166.8, 158.7, 147.1, 135.6, 134.2, 133.5, 129.3, 128.9, 128.6, 127.7, 127.6, 124.1, 119.7, 114.2, 109.7, 85.7, 58.8, 58.7, 56.2, 55.3, 38.7, 36.3; FTIR (NaCl, thin film): 3309, 3052, 2938, 2839, 1684,

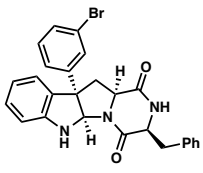
1653, 1609, 1513, 1457, 1419, 1312, 1251, 1183, 1032 cm^{-1}; $[\alpha]_D^{25}$ = +70 (*c* = 0.80, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 440.2, found 440.2.

Pyrroloindoline 176k



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and (2-naphthyl)(*p*-xylyl)iodonium triflate for 42 h. The crude residue was purified by silica gel chromatography (50% hexanes, 47.5% ethyl acetate, 2.5% methanol) to afford **176k** as a white solid (113.0 mg, 0.246 mmol, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.85 – 7.78 (m, 4H), 7.54 – 7.45 (m, 2H), 7.38 (ddd, *J* = 11.4, 3.9, 3.9 Hz, 1H), 7.36 – 7.31 (m, 2H), 7.31 – 7.26 (m, 1H), 7.23 – 7.18 (m, 2H), 7.14 (ddd, *J* = 7.7, 7.7, 1.2 Hz, 1H), 6.93 (dd, *J* = 7.4, 0.9 Hz, 1H), 6.78 – 6.68 (m, 2H), 5.98 (s, 1H), 5.59 (s, 1H), 5.50 (s, 1H), 4.57 – 4.49 (m, 1H), 4.25 (ddd, *J* = 10.8, 3.7, 1.3 Hz, 1H), 3.62 (dd, *J* = 14.5, 3.7 Hz, 1H), 3.39 (ddd, *J* = 16.0, 8.0, 8.0 Hz, 1H), 2.80 (ddd, *J* = 14.4, 12.1, 10.5 Hz, 2H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.8, 166.7, 147.2, 139.2, 135.6, 133.3, 133.0, 132.4, 129.3, 129.0, 128.9, 128.8, 128.0, 127.6, 127.5, 126.6, 126.4, 125.5, 124.3, 124.2, 119.7, 109.7, 85.4, 59.5, 58.8, 56.2, 38.5, 36.3; FTIR (NaCl, thin film): 3330, 3052, 2918, 1676, 1605, 1483, 1409, 1343, 1303 cm^{-1}; $[\alpha]_D^{25}$ = +237 (*c* = 0.57, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 460.2, found 460.2.

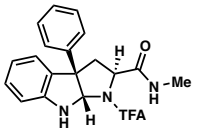
Pyrroloindoline 176l



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and (3-bromophenyl)(*p*-xylyl)iodonium triflate for 42 h. The crude residue was purified by silica gel chromatography (50% hexanes, 47.5% ethyl

acetate, 2.5% methanol) to afford **176l** as a white solid (79.3 mg, 0.163 mmol, 54% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.48 (dd, *J* = 1.8, 1.8 Hz, 1H), 7.44 – 7.39 (m, 1H), 7.33 (dd, *J* = 7.3, 7.3 Hz, 2H), 7.30 – 7.25 (m, 2H), 7.24 – 7.18 (m, 3H), 7.13 (dd, *J* = 7.4, 7.4 Hz, 1H), 6.93 (d, *J* = 7.5 Hz, 1H), 6.76 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.69 (d, *J* = 7.8 Hz, 1H), 5.79 (d, *J* = 1.3 Hz, 1H), 5.59 (s, 1H), 5.50 (s, 1H), 4.42 (dd, *J* = 8.4, 8.4 Hz, 1H), 4.25 (dd, *J* = 10.8, 3.0 Hz, 1H), 3.60 (dd, *J* = 14.5, 3.7 Hz, 1H), 3.15 (dd, *J* = 13.8, 7.5 Hz, 1H), 2.78 (ddd, *J* = 18.5, 14.2, 10.1 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$) 168.6, 166.9, 147.1, 144.8, 135.5, 132.5, 130.6, 130.4, 129.6, 129.3, 129.0, 128.9, 127.6, 125.3, 124.2, 123.1, 119.9, 109.9, 85.4, 59.1, 58.5, 56.2, 38.5, 36.2; FTIR (NaCl, thin film): 3315, 3057, 2933, 2864, 1679, 1612, 1560, 1482, 1412, 1343, 1313, 1221 cm^{-1}; $[\alpha]_D^{25}$ = -+91.4 (*c* = 2.8, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 488.1, found 488.1.

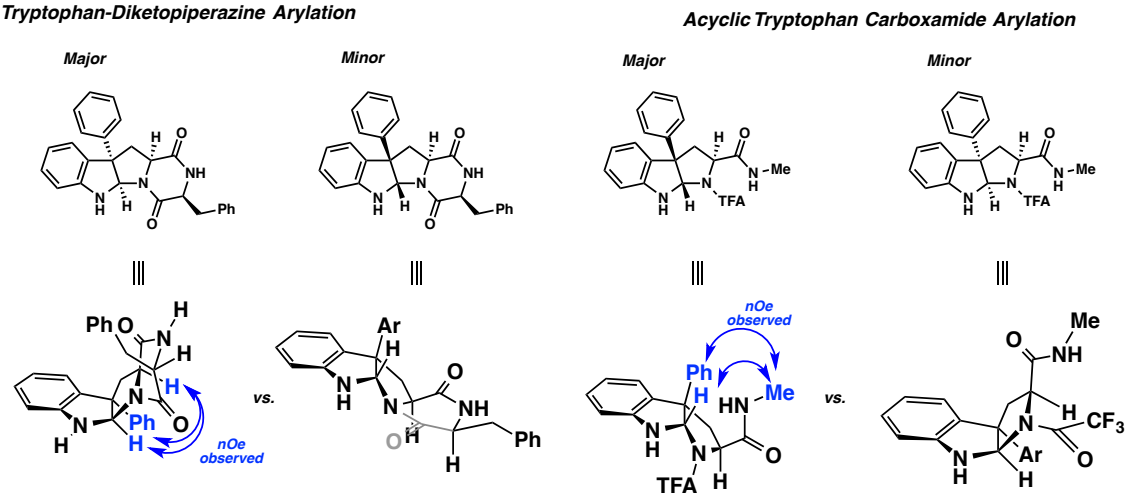
Pyrroloindoline 180



Prepared following *General Procedure IV* using $^{Mes}DAB_{Me}$ and diphenyliodonium triflate for 3 h. The crude residue was purified by silica gel chromatography (60% hexanes, 37.5% ethyl acetate, 2.5% methanol) to afford 1**80** as a white solid (94.6 mg, 0.243 mmol, 81% yield). ^{1}H NMR (500 MHz, $CDCl_3$) 7.55 (d, *J* = 2.9 Hz, 1H), 7.34 – 7.30 (m, 2H), 7.30 – 7.27 (m, 1H), 7.27 – 7.23 (m, 1H), 7.23 – 7.18 (m, 3H), 6.96 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.73 (d, *J* = 7.8 Hz, 1H), 5.17 (d, *J* = 2.8 Hz, 1H), 4.63 (d, *J* = 2.3 Hz, 1H), 4.25 (ddd, *J* = 12.6, 4.2, 4.2 Hz, 1H), 3.24 (dd, *J* = 12.6, 4.1 Hz, 1H), 3.07 (s, 3H), 2.48 (dd, *J* = 12.6, 12.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) 169.0, 156.9 (q, J_{C-F} = 37.6 Hz), 148.0, 144.9, 130.1, 129.4, 128.9, 127.5, 125.9, 125.3, 120.9, 115.5 (q, J_{C-F} = 287.7 Hz), 110.3, 83.8, 53.4, 49.1, 35.9, 33.3; FTIR

(NaCl, thin film): 3361, 3057, 2937, 1718, 1653, 1608, 1559, 1487, 1469, 1320, 1268, 1216, 1187, 1163, 1058, 1034 cm^{-1}; $[\alpha]_D^{25}$ = +215 (*c* = 1.3, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 390.1, found 390.1.

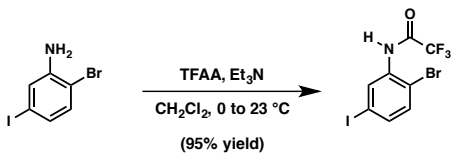
3.11.12 Stereochemical Assignment of Tryptophan Arylation



The stereochemical assignment of the pyrroloindole products was assigned by ^1H, ^{13}C, COSY, HSQC, HMBC, and NOESY 2D experiments on L-Trp-L-Phe derived pyrroloindoline and assigned by spectroscopic analogy for pyrroloindoles 1**76b-f**. Acyclic tryptophan-derived carboxamide **180** was independently analyzed by ^1H, ^{13}C, COSY, HSQC, HMBC, and NOESY 2D experiments and found to arylate from the opposite face of the prochiral indole moiety. Selected NOESY 2D data is included in the spectral data

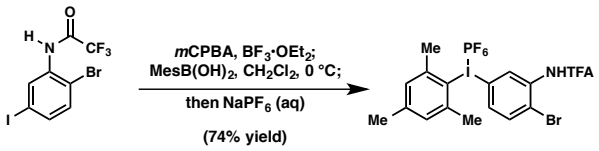
3.11.13 Total Synthesis of (+)-Naseseazines A and B

Preparation of *N*-**(2-bromo-5-iodophenyl)-2,2,2-trifluoroacetamide**



To a solution of 2-bromo-5-iodoaniline (14.9 g, 50.0 mmol, 1.0 equiv) in CH_2Cl_2 (250 mL) was added Et_3N (10.4 mL, 75.0 mmol, 1.50 equiv). The solution was cooled to 0 °C and trifluoroacetic anhydride (7.8 mL, 55.0 mmol, 1.10 equiv) added dropwise by syringe. The solution was stirred for 30 minutes and slowly warmed to 23 °C and stirring continued for 4 hours. The reaction was then quenched by the addition of 0.5 N HCl (150 mL), and the reaction washed with 0.5 N HCl (2 x 100 mL). The combined organics were then back extracted with Et_2O (100 mL), and the organics dried over Na_2SO_4, filtered, and concentrated in vacuo to afford pure 2-bromo-5-iodotrifluoroacetanilide as a white fluffy solid (18.8 g, 47.7 mmol, 95% yield). ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.63 (d, J = 2.0 Hz, 1H), 8.37 (s, 1H), 7.42 (dd, J = 8.4, 2.1 Hz, 1H), 7.29 (d, J = 8.4 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.58 (q, J = 38.0 Hz), 136.2, 134.0, 133.7, 130.5, 115.3 (q, J = 288.7 Hz), 113.8, 93.0; IR (NaCl, thin film): 3267, 3081, 1709, 1574, 1529, 1459, 1395, 1260, 1186, 1165, 1034 cm^{-1}; LRMS (EI+) calc'd for $[M+H]^+$ 393.9, found 393.9.

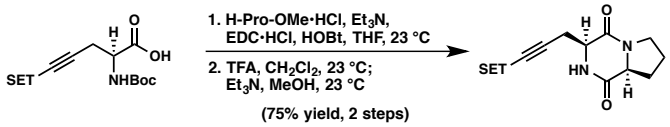
Preparation of (3-trifluoroacetamido-4-bromophenyl)(mesityl)iodonium hexafluorophosphate



To a solution of 2-bromo-5-iodotrifluoroacetanilide (11.8 g, 30.0 mmol, 1.00 equiv) in CH_2Cl_2 (120 mL) was added *m*CPBA (80%, 7.15 g, 33.0 mmol, 1.10 equiv). The solution was stirred for 5 minutes, then BF_3•OEt_2 (9.26 mL, 75.0 mmol, 2.50 equiv) was added dropwise by syringe to afford a bright orange solution. After 45 minutes, the solution was cooled to 0 °C and 2,4,6-trimethylphenylboronic acid (5.41 g, 33.0 mmol, 1.10 equiv)

added in a single portion. The mixture was stirred for an additional 15 minutes, warmed to 23 °C over 15 minutes, then stirred for an additional 20 minutes at room temperature. Saturated aqueous $NaPF_6$ (150 mL) was added to the solution, and the heterogeneous mixture stirred vigorously for 1 hr. The solution was diluted with CH_2Cl_2 (100 mL) and H_2O (150 mL), the layers separated, and the aqueous layer extracted with CH_2Cl_2 (2 x 100 mL). The combined organics were then dried over anhydrous Na_2SO_4, filtered, and concentrated *in vacuo* to afford a thick oil. The oil was co-evaporated once from Et_2O (100 mL), and diluted with Et_2O (500 mL). The clear supernatant was decanted and the residual oil co-evaporated from Et_2O (200 mL), resulting in precipitation. The resulting solid was suspended in Et_2O (500 mL) and cooled in an ice-bath for 20 minutes, then collected by vacuum filtration and dried under high vacuum (<1 mTorr) for 15 h to afford diaryliodonium hexafluorophosphate **183** as an off-white, powdery solid (14.6 g, 22.2 mmol, 74 % yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ 11.53 (s, 1H), 8.24 (d, J = 1.8 Hz, 1H), 7.91 (dd, J = 8.6, 1.9 Hz, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.27 – 7.21 (m, 2H), 2.62 (s, 6H), 2.30 (s, 3H); ^{13}C NMR (126 MHz, DMSO-d_6) δ 155.9 (q, J = 37.6 Hz), 143.8, 142.1, 136.5 (d, J = 13.8 Hz), 135.7 (d, J = 35.8 Hz), 130.4, 126.0, 123.4, 116.3 (q, J = 288.2 Hz), 113.2 , 26.8, 21.0; FTIR (NaCl, thin film): 3365, 3092, 2926, 1735, 1582, 1523, 1457, 1405, 1267, 1204, 1157, 1031 cm^{-1}; LRMS (EI+) calc'd $[M–PF_6]^+$ 511.9, found 511.9.

Preparation of Diketopiperazine 185

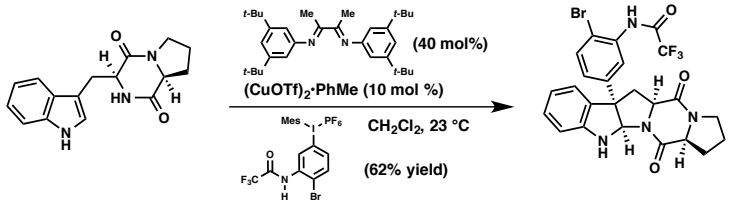


To a solution of freshly prepared amino acid (4.75 g, 14.5 mmol, 1.00 equiv) in THF (0.4 M, 240 mL) at 0 °C was added EDC•HCl (3.34 g, 17.4 mmol, 1.20 equiv), anhydrous HOBt (2.74 g, 20.3 mmol, 1.40 equiv) and Et_3N (4.5 mL, 32 mmol, 2.2 equiv). The mixture was then stirred for 5 minutes, and *L*- proline methyl ester hydrochloride (2.89 g, 17.4 mmol, 1.20 equiv) was added. The reaction was slowly warmed to 23 °C over 2 hours and stirring continued for 20 hours. The reaction was then quenched with 1 N HCl (500 mL) and extracted with EtOAc (3 x 250 mL), then the combined organics washed with saturated aqueous $NaHCO_3$ (500 mL), and aqueous layer back extracted with EtOAc (200 mL). The combined organic layers were then dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo to afford crude dipeptide as a viscous oil.

The residue was then dissolved in CH_2Cl_2 (100 mL), and trifluoroacetic acid (30 mL) was added dropwise by addition funnel at room temperature over 10 minutes. Stirring was continued for 20 minutes, then the solution diluted with toluene (100 mL) and the mixture concentrated in vacuo to afford a thick oil. The residue was then redissolved in MeOH (75 mL) and the mixture cooled to 0 °C. Et_3N (55 mL) was then added dropwise the stirring solution over 10 minutes by addition funnel. Upon completion of the addition, the cooling bath was removed and the reaction was warmed to 23 °C over 1 hr. After an additional 3 hrs at room temperature, the solution was concentrated, the crude residue dissolved in Et_2O (500 mL), and the solution washed with water (2 x 500 mL). The organic layers were back extracted with Et_2O (250 mL), and the combined organic layers washed with brine (200 mL), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo to afford a yellow oil. The residue was purified by silica gel flash chromatography (5% MeOH in EtOAc) to afford diketopiperazine **185** as a white solid (3.32 g, 10.8

mmol, 75% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.15 (s, 1H), 4.17 – 4.10 (m, 2H), 3.65 – 3.57 (m, 1H), 3.53 (ddd, *J* = 12.0, 8.9, 3.2 Hz, 1H), 3.10 (dd, *J* = 17.5, 3.6 Hz, 1H), 2.58 (dd, *J* = 17.5, 10.5 Hz, 1H), 2.43 – 2.32 (m, 1H), 2.14 – 1.97 (m, 2H), 1.97 – 1.83 (m, 1H), 0.97 (t, *J* = 7.9 Hz, 9H), 0.59 (q, *J* = 7.9 Hz, 6H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.0, 163.9, 101.9, 86.6, 59.3, 53.9, 45.4, 28.4, 22.6, 22.5, 7.4, 4.3; FTIR (NaCl, thin film): 3233, 2954, 2908, 2873, 2176, 1675, 1457, 1417, 1338, 1306, 1018 cm^{-1}; $[\alpha]_D^{25}$ = -–108 (*c* = 0.93, $CHCl_3$); HRMS (MM) calc'd for $[M+H]^+$ 307.1836, found 307.1839.

Preparation of Pyrroloindoline 181f



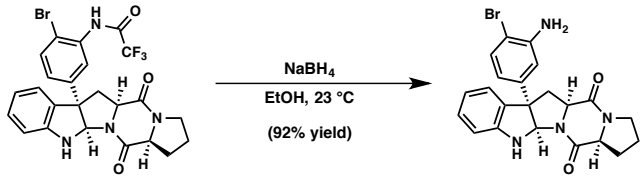
In a glovebox, $Cu(OTf)_2$•PhMe (310 mg, 0.600 mmol) and $^{t\text{Bu}}DAB_{Me}$ (1.10 g, 2.40 mmol) were added to an oven-dried, 200 mL round-bottomed flask. Anhydrous CH_2Cl_2 (60.0 mL) was then added by syringe, and the resulting deep-purple solution was stirred for 1 hr at 25 °C in the glovebox. The solution was then filtered through a tight plug of cotton, and the resulting solution removed from the glovebox.

To a flame-dried, 1-liter round-bottomed flask was charged cyclo-L-Pro-L-Trp **175f** (1.50 g, 5.30 mmol, 1.00 equiv), (4-bromo-3-trifluoroacetamidophenyl)mesityliodonium hexafluorophosphate (4.19 g, 6.36 mmol, 1.20 equiv) in anhydrous CH_2Cl_2 (480 mL). The solution was stirred at 23 °C for 10 minutes, then cooled to 15 °C in a cold water bath. To the flask was then added the freshly prepared catalyst solution of $Cu^I(^{t\text{Bu}}DAB_{Me})$ (53.0 mL, 1.06 mmol, 0.20 equiv) dropwise over 20 minutes. The deep-purple solution

was allowed to warm to 23 °C over 2 hours, then stirred for 20 hours at 23 °C by which time the solution had turned to a deep red. The solution was then quenched by the addition of aqueous ammonium hydroxide (1.8 M, 500 mL). The mixture was transferred to a separatory funnel, vigorously shaken, and the layers partitioned. The aqueous layer was then back extracted with EtOAc (2 x 100 mL), and the combined organic layers dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Repeated silica gel chromatography (5% MeOH, 25% Hexanes, 70% EtOAc) afforded aryl pyrrolodine **181f** as an amorphous white solid (1.79 g, 3.26 mmol, 62% yield).

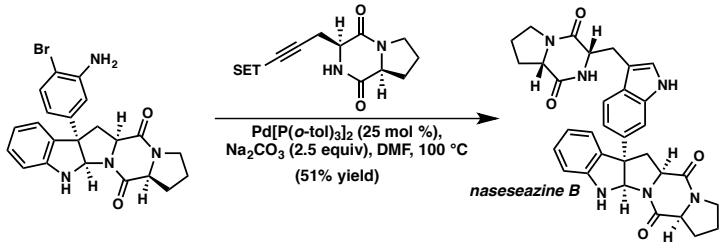
^{1}H NMR (500 MHz, $CDCl_3$) δ 8.47 (s, 1H), 8.42 (d, *J* = 2.3 Hz, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.10 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 7.04 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.97 (ddd, *J* = 7.6, 1.2, 0.5 Hz, 1H), 6.76 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.64 (ddd, *J* = 7.8, 0.8, 0.8 Hz, 1H), 5.73 (s, 1H), 4.59 - 4.51 (m, 1H), 4.20 - 4.11 (m, 1H), 3.51 - 3.40 (m, 2H), 3.09 (dd, *J* = 14.0, 7.9 Hz, 1H), 2.96 (dd, *J* = 14.0, 8.9 Hz, 1H), 2.30 (dddd, *J* = 12.9, 7.0, 7.0, 3.5 Hz, 1H), 2.15 (dddd, *J* = 13.0, 10.5, 9.0, 7.2 Hz, 1H), 2.02 - 1.93 (m, 1H), 1.88 (ddddd, *J* = 17.2, 10.5, 8.6, 4.3, 4.3 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 168.2, 165.4, 154.8 (q, $J_{C\text{-}F}$ = 38.0 Hz), 147.2, 144.1, 133.5, 132.8, 132.0, 129.0, 125.9, 124.2, 120.0, 119.9, 115.46 (q, $J_{C\text{-}F}$ = 288.7 Hz), 112.8, 110.0, 85.0, 60.5, 60.1, 59.8, 45.2, 38.1, 27.5, 23.3; FTIR (NaCl, thin film): 3270, 1733, 1683, 1586, 1539, 1485, 1467, 1418, 1312, 1245, 1198, 1162 cm^{-1}; $[\alpha]_D^{25}$ = +67.8 (*c* = 1.8, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 549.1, found 549.1.

Preparation of Aniline 186:



To a solution of pyrroloindoline **181f** (150 mg, 0.273 mmol, 1.00 equiv) in EtOH at 23 °C was added $NaBH_4$ (77.0 mg, 2.02 mmol, 7.4 equiv). The solution was stirred vigorously for 1 h, then cooled to 0 °C and slowly quenched with saturated aqueous ammonium chloride (5 mL). The mixture was then diluted with H_2O (50 mL) and extracted with EtOAc (3 x 25 mL). The combined organics were then dried over sodium sulfate, filtered, and concentrated under reduced pressure. Purification of the crude residue by flash silica gel chromatography (75% EtOAc, 20% Hexanes, 5% MeOH) afforded bromoaniline **186** as a white, amorphous solid (114 mg, 0.252 mmol, 92% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (d, *J* = 8.3 Hz, 1H), 7.08 (ddd, *J* = 7.7, 7.7, 1.3 Hz, 1H), 6.93 - 6.89 (m, 1H), 6.72 (ddd, *J* = 7.5, 7.5, 1.0 Hz, 1H), 6.70 (d, *J* = 2.3 Hz, 1H), 6.65 - 6.58 (m, 2H), 5.76 (d, *J* = 2.8 Hz, 1H), 5.35 (d, *J* = 3.0 Hz, 1H), 4.52 - 4.44 (m, 1H), 4.18 - 4.07 (m, 3H), 3.48 (ddd, *J* = 8.6, 5.2, 5.2 Hz, 2H), 3.11 (dd, *J* = 13.9, 7.4 Hz, 1H), 2.76 (dd, *J* = 13.9, 9.7 Hz, 1H), 2.31 (dddd, *J* = 12.8, 7.0, 7.0, 3.3 Hz, 1H), 2.15 (dddd, *J* = 12.9, 10.6, 9.2, 7.2 Hz, 1H), 2.05 - 1.96 (m, 1H), 1.95 - 1.86 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ167.9, 165.6, 147.1, 144.3, 143.0, 133.1, 132.8, 128.7, 124.1, 119.7, 117.4, 114.0, 109.6, 108.0, 85.1, 60.5, 60.2, 59.5, 45.2, 38.0, 27.6, 23.3; FTIR (NaCl, thin film): 3457, 3341, 3003, 2953, 2881, 1661, 1612, 1572, 1484, 1466, 1422, 1341, 1293, 1252, 1214, 1152 cm^{-1}; $[\alpha]_D^{25}$ = +118 (*c* = 0.80, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 453.1, found 453.1.

Preparation of (+)-Naseseazine B (187)



In a glovebox, a 1-dram vial was charged with bromoaniline **186** (74.6 mg, 0.165 mmol, 1.00 equiv), alkyne **10** (127 mg, 0.412 mmol, 2.50 equiv), Na_2CO_3 (43.7 mg, 0.412 mmol, 2.50 equiv), and $Pd[P(o\text{-tol})_3]_2$ (29.5 mg, 0.0412 mmol, 25 mol %). DMF (1.70 mL) was then added and the solution stirred vigorously for 3 minutes at 25 °C. The solution was then heated to 100 °C for 1.5 h, cooled, and concentrated under reduced pressure and dried under high vacuum to ensure complete removal of residual DMF. The residue was then dissolved in CH_2Cl_2 (3 mL) and filtered through a plug of silica gel (50 g) to remove residual catalyst and base, then the filter cake rinsed (5% MeOH in CH_2Cl_2, 200 mL). The filtrate was then concentrated, and the crude residue dissolved in 1M methanolic HCl (10 mL), and stirred for 2 h at 23 °C. The solution was then concentrated and the residue was quenched by the addition of methanolic NH_3 (1 N, 5 mL) and reconcentrated. The residue was purified by flash chromatography on silica gel (2 to 7% MeOH in CH_2Cl_2) afforded Naseseazine B (**187)** as a white, powdery solid (47.3 mg, 0.837 mmol, 51% yield). Excess TES-alkyne **185** could be recovered during chromatography.

Spectroscopic and physical data, including ^1H, ^{13}C NMR in CD_3OD, DMSO-*d6,* IR, MS, and $[\alpha]_D^{25}$, obtained for Naseseazine B matched that as reported during isolation by Raju

et. al and data obtained by Movassaghi and Kim. See below for ^{1}H and ^{13}C comparison table. The use of natural amino acids in this report to synthesize (+)-naseseazine B is in agreement with Movassaghi and Kim's structural reassignment of the natural product.[2] During the course of this study, we determined that the exact chemical shifts (δ) of Naseseazine B observed in CD_3OD had a slight concentration dependence.

^{1}H NMR (600 MHz, CD_3OD) δ 7.56 (d, *J* = 8.5 Hz, 1H), 7.40 (d, *J* = 0.6 Hz, 1H), 7.12 (s, 1H), 7.04 (td, *J* = 7.6, 1.1 Hz, 1H), 7.00 (dd, *J* = 8.5, 1.1 Hz, 1H), 6.82 (dd, *J* = 7.2, 1.0 Hz, 1H), 6.69 – 6.64 (m, 2H), 5.82 (s, 1H), 4.71 – 4.61 (m, 1H), 4.38 (app t, *J* = 4.4 Hz, 1H), 4.24 (app t, *J* = 8.1, 1H), 3.96 (dd, *J* = 9.6, 6.6 Hz, 1H), 3.51 – 3.36 (m, 3H), 3.30 – 3.27 (m, 2H), 3.26 – 3.21 (m, 2H), 2.57 (dd, *J* = 13.7, 10.1 Hz, 1H), 2.24 (dddd, *J* = 10.0, 6.9, 6.9, 3.1 Hz, 1H), 2.13 – 2.03 (m, 1H), 2.00 – 1.93 (m, 2H), 1.93 – 1.84 (m, 1H), 1.72 – 1.60 (m, 1H), 1.49 – 1.40 (m, 1H), 1.01 – 0.92 (m, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 170.8, 170.1, 168.4, 167.3, 149.1, 137.9, 137.0, 136.0, 129.4, 127.7, 126.4, 124.9, 120.5, 119.6, 111.1, 110.4, 109.7, 86.9, 61.8, 61.7, 61.5, 60.0, 57.1, 46.2, 45.9, 39.5, 29.2, 29.0, 28.5, 24.2, 22.6.

^{1}H NMR (600 MHz, DMSO-d_6) δ 10.80 (d, *J* = 2.4 Hz, 1H), 7.68 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.31 (d, *J* = 1.6 Hz, 1H), 7.19 (d, *J* = 2.4 Hz, 1H), 7.03 – 6.96 (m, 2H), 6.80 (dd, *J* = 7.5, 1.2 Hz, 1H), 6.75 (s, 1H), 6.61 (d, *J* = 6.6, 1 H), 6.58 (dd, *J* = 6.6, 1H), 5.68 (s, 1H), 4.72 (ddd, *J* = 9.3, 7.7, 1.3 Hz, 1H), 4.34 (ddd, *J* = 8.9, 7.4, 1.4 Hz, 1H), 4.29 (app t *J* = 5.3 Hz, 1H), 4.06 (ddd, *J* = 9.9, 6.8, 1.4 Hz, 1H), 3.37 – 3.33 (m, 2H), 3.25 (ddd, *J* = 12.1, 9.0, 3.9 Hz, 1H), 3.22 (dd, *J* = 14.9, 4.8 Hz, 1H), 3.13 (dd, *J* = 13.7, 7.4

Hz, 1H), 3.05 (dd, *J* = 14.9, 5.8 Hz, 1H), 2.37 (dd, *J* = 13.7, 10.4 Hz, 1H), 2.16 (dddd, *J* = 12.4, 7.0, 7.0, 3.6 Hz, 1H), 2.03 - 1.91 (m, 2H), 1.90 - 1.78 (m, 2H), 1.69 (dddd, *J* = 10.7, 8.7, 5.8, 2.5 Hz, 1H), 1.67 - 1.57 (m, 1H), 1.46 - 1.38 (m, 1H). ^{13}C NMR (126 MHz, DMSO-d_6) δ 169.1, 167.9, 165.9, 165.5, 148.1, 135.9, 135.6, 134.6, 127.9, 126.1, 125.1, 123.4, 119.2, 118.0, 117.9, 109.3, 109.2, 84.9, 60.0, 59.8, 59.5, 58.4, 55.2, 44.6, 38.7, 27.7, 27.1, 25.7, 23.0, 21.9. IR: 3270, 2943, 2859, 1653, 1559, 1419, 1340 cm^{-1}; $[\alpha]_D^{25}$ = +97 (*c* = 0.45, MeOH) LRMS (EI+) calc'd for $[M+H]^+$ 565.3, found 565.3.

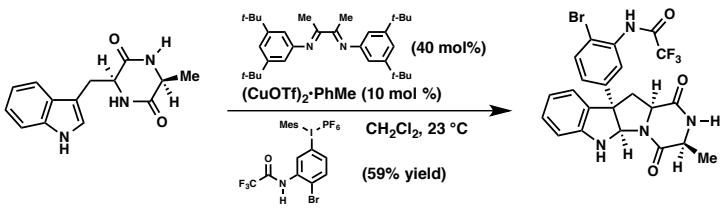
Comparison of ^{1}H NMR data for Natural vs. Synthetic (+)-Naseseazine B

Raju et al. Report, Natural (+)–Naseseazine B ^{1}H NMR, 600 MHz, CD_3OD	This Work, Synthetic (+)–Naseseazine B ^{1}H NMR, 600 MHz, CD_3OD
δ 7.58 (d, *J* = 8.4 Hz, 1H)	δ 7.56 (d, *J* = 8.5 Hz, 1H)
7.41 (d, *J* = 1.4 Hz, 1H)	7.40 (d, *J* = 0.6 Hz, 1H)
7.12 (s, 1H)	7.12 (s, 1H)
7.06 (td, *J* =7.6, 1.3 Hz)	7.04 (td, *J* = 7.6, 1.1 Hz, 1H)
7.03 (dd, *J* = 8.4, 1.8 Hz, 1H)	7.00 (dd, *J* = 8.5, 1.1 Hz, 1H)
6.84 (dt, *J* =7.2, 0.9 Hz, 1H)	6.82 (dt, *J* = 7.2 Hz, 1.0 Hz, 1H),
6.69 (t, *J* = 7.6 Hz, 1H)	6.69 – 6.64 (m, 2H)
6.68 (t, *J* = 7.6 Hz, 1H)	–
5.85 (s, 1H)	5.82 (s, 1H)
4.75 (dd, *J* = 10.2, 8.7 Hz, 1H)	4.71 – 4.61 (m, 1H)
4.40 (br t, *J* =4.7 Hz, 1H)	4.38 (app t, *J* = 4.4, 1H)
4.33 (dd, *J* = 9.5, 7.1 Hz, 1H)	4.24 (app t, *J* = 8.1, 1H)
3.99 (ddd, *J* = 11.4, 6.6 , 1.6 Hz, 1H)	3.96 (dd, *J* = 9.6, 6.6 Hz, 1H)
3.49 (m, 1H)	3.51 – 3.36 (m, 3H)
3.44 (m, 1H)	–
3.44 (m, 1H)	–
3.32 (m, 1H)	3.30 – 3.27 (m, 2H)
3.28 (m, 1H)	–
3.27 (m, 1H)	3.26 – 3.21 (m, 2H)
3.24 (m, 1H)	–
2.59 (dd, *J* = 13.8, 10.2 Hz, 1H)	2.57 (dd, *J* = 13.7, 10.1 Hz, 1H)
2.28 (m, 1H)	2.24 (dddd, *J* = 10.0, 6.9, 6.9, 3.1 Hz, 1H)
2.11 (m, 1H)	2.13 – 2.03 (m, 1H)
2.00 (m, 1H)	2.00 – 1.93 (m, 2H)
1.97 (m, 1H)	–
1.95 (m, 1H)	1.93 – 1.84 (m, 1H)
1.67 (m, 1H)	1.72 – 1.60 (m, 1H)
1.44 (m, 1H)	1.49 – 1.40 (m, 1H)
0.92 (m, 1H)	1.01 – 0.92 (m, 1H)

Comparison of ^{13}C NMR data for Natural vs. Synthetic (+)-Naseseazine B

Raju et al. Report, Natural (+)–Naseseazine B ^{13}C NMR, 151 MHz, CD_3OD	This Work, Synthetic (+)–Naseseazine B ^{13}C NMR, 126 MHz, CD_3OD	Chemical Shift Difference, Δδ
δ 170.7	δ 170.8	0.1
170.2	170.1	0.1
168.4	168.4	0.0
167.3	167.3	0.0
149.0	149.1	0.1
137.9	137.9	0.0
136.9	137.0	0.1
136.0	136.0	0.0
129.1	129.4	0.3
127.6	127.7	0.1
126.1	126.4	0.3
124.8	124.9	0.1
120.3	120.5	0.2
120.3	–	–
119.4	119.6	0.2
111.0	111.1	0.1
110.3	110.4	0.1
109.5	109.4	0.1
86.8	86.9	0.1
61.8	61.8	0.0
61.7	61.7	0.0
61.3	61.5	0.2
59.9	60.0	0.1
57	57.1	0.1
45.9	46.2	0.3
45.8	45.9	0.1
39.5	39.5	0.0
29.2	29.2	0.0
29.1	29.0	0.1
28.3	28.5	0.2
24.1	24.2	0.1
22.4	22.6	0.2

Preparation of Pyrroloindoline 181b

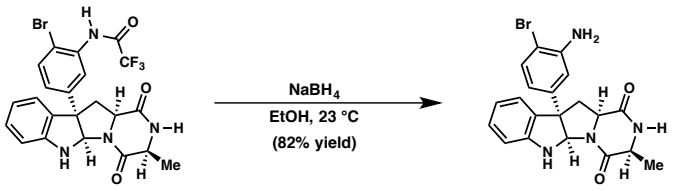


In a glovebox, $Cu(OTf)_2$•PhMe (77.6 mg 0.150 mmol) and $^{t\text{Bu}}DAB_{Me}$ (277 mg, 0.600 mmol, 2.40 mmol) were added to an oven-dried, 50 mL round-bottomed flask. Anhydrous CH_2Cl_2 (27.0 mL) was then added by syringe, and the resulting deep-purple solution was stirred for 1 hr at 25 °C in the glovebox. The solution was then filtered through a tight plug of cotton, and the resulting solution removed from the glovebox.

To a flame-dried, 100-mL round-bottomed flask was charged cyclo-L-Ala-L-Trp **175b** (334 mg, 1.30 mmol, 1.00 equiv) and (4-bromo-3-trifluoroacetamidophenyl)mesityliodonium hexafluorophosphate (940 mg, 1.43 mmol, 1.10 equiv)). To the flask was then added the freshly prepared catalyst solution of $Cu^{I}(^{tBu}DAB_{Me})$ (26.0 mL, 0.260 mmol, 0.20 equiv) dropwise over 20 minutes. The deep-purple solution was allowed to warm to 23 °C over 2 hours, then stirred for 8 hours at 23 °C. The solution was then quenched by the addition of aqueous ammonium hydroxide (1.8 M, 20 mL). The mixture was then diluted with EtOAc (100 mL), transferred to a separatory funnel, vigorously shaken, and the layers partitioned. The aqueous layer was then back-extracted with EtOAc (2 x 100 mL), and the combined organic layers dried over anhydrous Na_2SO_4, filtered, and concentrated in vacuo. Repeated silica gel chromatography (78% EtOAc, 20% hexanes, 2 % MeOH) afford aryl pyrrolodine **181b** as a white solid (402.0 mg, 0.767 mmol, 59% yield). ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.51 (s, 1H), 8.39 (d, *J* = 2.3 Hz, 1H), 7.53 (d, *J* = 8.5 Hz, 1H), 7.20 (s, 1H), 7.09 (ddd, *J* = 7.7, 7.7, 1.0 Hz, 1H), 7.03 (dd, *J* = 8.5, 2.3 Hz, 1H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.73 (dd, *J* = 7.5, 7.5 Hz, 1H), 6.64 (d, *J* = 7.9 Hz, 1H), 5.73 (s, 1H), 5.68 (br s, 1H), 4.47 (dd, *J* = 8.3, 8.3 Hz, 1H), 4.10 – 4.03 (m, 1H), 3.09 (dd, *J* = 13.9, 7.9 Hz, 1H), 2.89 (dd, *J* = 13.9, 8.9 Hz, 1H), 1.41 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 169.8, 168.4, 154.8

(q, $J_{C\text{-}F}$ = 38.0 Hz) 147.3, 144.0, 133.4, 132.8, 131.9, 129.0, 125.9, 124.0, 120.0, 119.7, 115.4 (q, $J_{C\text{-}F}$ = 288.6 Hz) 113.0, 110.1, 85.1, 59.3, 58.7, 51.2, 38.2, 15.2; FTIR (NaCl, thin film): 3270, 1733, 1683, 1586, 1539, 1485, 1467, 1418, 1312, 1245, 1198, 1162 cm^{-1}; $[\alpha]_D^{25}$ = +84 (*c* = 0.42, $CHCl_3$); LRMS (EI+) calc'd for $[M+H]^+$ 523.1, found 523.1.

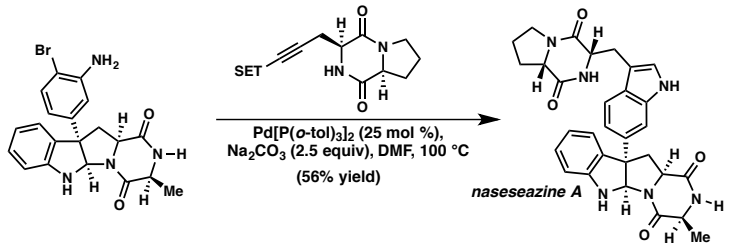
Preparation of Aniline 186b



To a solution of pyrroloindoline **181b** (140 mg, 0.268 mmol, 1.00 equiv) in EtOH (5.4 mL) at 23 °C was added $NaBH_4$ (76.3 mg, 2.00 mmol, 7.5 equiv). The solution was stirred vigorously for 1 h, then cooled to 0 °C and slowly quenched with saturated aqueous ammonium chloride (5 mL). The mixture was then diluted with H_2O (50 mL) and extracted with EtOAc (3 x 45 mL). The combined organics were then dried over sodium sulfate, filtered, and concentrated in vacuo. Purification of the crude residue by flash silica gel chromatography (75% EtOAc, 20% Hexanes, 5% MeOH) afforded bromoaniline **186b** as a white, amorphous solid (94.0 mg, 0.220 mmol, 82% yield). ^1H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8.4 Hz, 1H), 7.04 (ddd, *J* = 7.6, 7.6, 1.3 Hz, 1H), 6.91 - 6.85 (m, 1H), 6.85 (d, *J* = 2.3 Hz, 1H), 6.67 (ddd, *J* = 19.2, 7.7, 1.0 Hz, 2H), 6.56 (dd, *J* = 8.4, 2.4 Hz, 1H), 5.72 (s, 1H), 4.56 (ddd, *J* = 10.0, 7.4, 1.6 Hz, 1H), 4.14 (qd, *J* = 6.8, 1.5 Hz, 1H), 3.10 (ddd, *J* = 14.0, 7.5, 1.7 Hz, 1H), 2.52 (dd, *J* = 13.6, 9.9 Hz, 1H), 1.37 (d, *J* = 6.9 Hz, 2H); FTIR (NaCl, thin film): 3345, 2919, 1668, 1605, 1483, 1418,

1300, 1209 cm^{-1}; $[\alpha]_D^{25}$ = +156 (*c* = 0.38, MeOH); LRMS (EI+) calc'd for $[M+H]^+$ 427.1, found 427.1.

Preparation of (+)-Naseseazine A



In a glovebox, a 1-dram vial was charged with bromoaniline **186b** (79.8 mg, 0.187 mmol, 1.00 equiv), alkyne **185** (143 mg, 0.467 mmol, 2.50 equiv), Na_2CO_3 (49.5 mg, 0.467 mmol, 2.50 equiv), and $Pd[P(o\text{-tol})_3]_2$ (33.4 mg, 0.0467 mmol, 25 mol %). DMF (1.90 mL) was then added and the solution stirred vigorously for 3 minutes at 25 °C. The solution was then heated to 100 °C for 1 h, cooled, and concentrated under reduced pressure and dried under high vacuum to ensure complete removal of residual DMF. The residue was then dissolved in CH_2Cl_2 (3 mL) and filtered through a plug of silica gel (50 g) to remove residual catalyst and base, then the filter cake rinsed (6% MeOH in CH_2Cl_2, 260 mL). The filtrate was then concentrated, and the crude residue dissolved in 1M methanolic HCl (12 mL), and stirred for 2 h at 23 °C. The solution was then concentrated and the residue was quenched by the addition of methanolic NH_3 (1 N, 12 mL) and reconcentrated. The residue was purified by flash chromatography on silica gel (2 to 10% MeOH in CH_2Cl_2) afforded Naseseazine A as a white, powdery solid (56.5 mg, 0.105 mmol, 56% yield). Excess TES-alkyne **185** could be recovered during chromatography.

Spectroscopic and physical data, including ^{1}H, ^{13}C NMR in CD_3OD, DMSO-*d6,* IR, MS, and $[\alpha]_D^{25}$, obtained for Naseseazine A matched that as reported during isolation by Raju et. al[15] and data obtained by Movassaghi and Kim.[2] See below for ^{1}H and ^{13}C comparison table. The use of natural amino acids in this report to synthesize (+)-naseseazine A is in agreement with Movassaghi and Kim's structural reassignment of the natural product.[2] During the course of this study, we determined that the exact chemical shifts (δ) of Naseseazine A observed in CD_3OD had a slight concentration dependence.

^{1}H NMR (600 MHz, CD_3OD) δ 7.55 (d, *J* = 8.4 Hz, 1H), 7.38 (s, 1H), 7.11 (s, 1H), 7.04 (app t, *J* = 7.6 Hz, 1H), 7.00 (d, *J* = 8.4 Hz, 1H), 6.83 (d, *J* = 7.4 Hz, 1H), 6.70 – 6.62 (m, 2H), 5.80 (s, 1H), 4.58 (app t, *J* = 8.6 Hz, 1H), 4.37 (dd, *J* = 4.7, 4.7 Hz, 1H), 4.10 (q, *J* = 6.8 Hz, 1H), 3.95 (dd, *J* = 10.7, 6.5 Hz, 1H), 3.41 (dt, *J* = 11.8, 8.3 Hz, 1H), 3.29 – 3.25 (m, 3H), 3.23 (dd, *J* = 13.2, 7.8 Hz, 2H), 2.58 (dd, *J* = 13.5, 10.0 Hz, 1H), 2.00 – 1.91 (m, 1H), 1.71 – 1.60 (m, 1H), 1.48 – 1.40 (m, 1H), 1.36 (d, *J* = 6.8 Hz, 3H), 1.01 – 0.91 (m, 1H); ^{13}C NMR (126 MHz, CD_3OD) δ 172.5, 170.8, 170.7, 167.3, 149.1, 137.9, 137.2, 135.9, 129.4, 127.6, 126.4, 125.0, 120.5, 120.4, 119.6, 111.1, 110.3, 109.7, 87.1, 61.2, 60.3, 60.0, 57.1, 52.2, 45.9, 39.7, 29.2, 29.0, 22.6, 15.3.

^{1}H NMR (600 MHz, DMSO-*d6*) δ 10.80 (s, 1H), 8.18 (s, 1H), 7.68 (s, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.29 (s, 1H), 7.19 (s, 1H), 7.01 – 6.96 (m, 2H), 6.83 (d, *J* = 7.3 Hz, 1H), 6.73 (s, 1H), 6.65 – 6.54 (m, 2H), 5.66 (s, 1H), 4.61 (dd, *J* = 8.6, 8.6 Hz, 1H), 4.28 (dd, *J* = 4.6, 4.6 Hz, 1H), 4.14 (q, *J* = 6.7 Hz, 1H), 4.10 – 4.03 (m, 1H), 3.40 – 3.35 (m, 1H), 3.28 – 3.18 (m, 2H), 3.07 (ddd, *J* = 26.8, 14.2, 6.7 Hz, 2H), 2.42 (dd, *J* = 13.1, 10.3 Hz,

1H), 2.02 – 1.93 (m, 1H), 1.70 (ddd, *J* = 27.0, 9.2, 9.2 Hz, 1H), 1.65 – 1.56 (m, 1H), 1.48 – 1.37 (m, 1H), 1.23 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR (126 MHz, DMSO-*d6*) δ 170.0, 169.1, 168.6, 165.5, 148.1, 135.9, 135.7, 134.4, 127.9, 126.1, 125.0, 123.6, 119.1, 117.9, 117.8, 109.3, 109.2, 109.1, 85.0, 59.3, 58.4, 58.4, 55.2, 50.3, 44.6, 38.8, 27.7, 25.7, 21.9, 14.8. FTIR: 3306, 2913, 2859, 1668, 1449, 1418, 1343, 1308 cm^{-1}; $[\alpha]_D^{25}$ = +121 (*c* = 0.30, MeOH); LRMS (EI+) calc'd for $[M+H]^+$ 539.2, found 539.2.

Comparison of ^{1}H NMR data for Natural vs. Synthetic (+)-Naseseazine A

Raju et al. Report, (+)–Naseseazine A ^{1}H NMR, 600 MHz, CD_3OD	**This Work (+)–Naseseazine A ^{1}H NMR, 600 MHz, CD_3OD**
δ 7.57 (d, *J* = 8.4 Hz, 1H)	δ 7.55 (d, *J* = 8.4 Hz, 1H)
7.40 (s, 1H)	7.38 (s, 1H)
7.11 (s, 1H)	7.11 (s, 1H)
7.05 (t, 7.2 Hz, 1H)	7.04 (app t, *J* = 7.6 Hz, 1H)
7.02 (d, *J* = 8.4 Hz, 1H)	7.00 (d, *J* = 8.4 Hz, 1H)
6.85 (d, *J* = 7.4 Hz, 1H)	6.83 (d, *J* = 7.4 Hz, 1H)
6.69 (d, *J* = 7.6 Hz, 1H)	6.70 – 6.62 (m, 2H)
6.67 (t, *J* = 8.5 Hz, 1H)	–
5.83 (s, 1H)	5.80 (s, 1H)
4.64 (dd, *J* = 8.4, 7.4 Hz, 1H)	4.58 (app t, *J* = 8.6 Hz, 1H)
4.39 (br t, *J* = 4.5 Hz, 1H)	4.37 (dd, *J* = 4.7, 4.7 Hz, 1H)
4.15 (q, *J* = 6.9 Hz, 1H)	4.10 (q, *J* = 6.8 Hz, 1H)
3.97 (dd, *J* = 10.8, 6.6 Hz, 1H)	3.95 (dd, *J* = 10.7, 6.5 Hz, 1H
3.42 (dt, *J* = 11.8, 8.1 Hz, 1H)	3.41 (dt, *J* = 11.8, 8.3 Hz, 1H)
3.30 (m, 1H)	3.29 – 3.25 (m, 3H)
3.29 (m, 1H)	–
3.26 (m, 1H)	–
3.24 (m, 1H)	3.23 (dd, *J* = 13.2, 7.8 Hz, 2H)
2.59 (dd, *J* = 13.7, 10.2 Hz, 1H)	2.58 (dd, *J* = 13.5, 10.0 Hz, 1H)
1.97 (m, 1H)	2.00 – 1.91 (m, 1H)
1.66 (m, 1H)	1.71 – 1.60 (m, 1H)
1.43 (m, 1H)	1.48 – 1.40 (m, 1H)
1.38 (d, *J* = 6.9 Hz, 1H)	1.36 (d, *J* = 6.8 Hz, 3H)
0.93 (m, 1H)	1.01 – 0.91 (m, 1H)

Comparison of ^{13}C NMR data for Natural vs. Synthetic (+)-Naseseazine A

Raju et al. Report, (+)–Naseseazine A ^{13}C NMR, 151 MHz, CD_3OD	This Work (+)–Naseseazine A ^{13}C NMR, 126 MHz, CD_3OD	Chemical Shift Difference, Δδ
172.6	172.5	0.1
170.6	170.8	0.2
170.6	170.7	0.1
167.3	167.3	0.0
149.1	149.1	0.0
137.9	137.9	0.0
137.2	137.2	0.0
135.8	135.9	0.1
129.2	129.4	0.2
127.6	127.6	0.0
126.2	126.4	0.2
124.9	125.0	0.1
120.3	120.5	0.2
120.2	120.4	0.2
119.5	119.6	0.1
110.9	111.1	0.2
110.1	110.3	0.2
109.5	109.7	0.2
87.1	87.1	0.0
61.2	61.2	0.0
60.2	60.3	0.1
60.0	60.0	0.0
57.2	57.1	0.1
52.1	52.2	0.1
45.8	45.9	0.1
39.7	39.7	0.0
29.0	29.2	0.2
29.0	29.0	0.0
22.5	22.6	0.1
15.2	15.3	0.1

3.12 NOTES AND REFERENCES

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(2) L. M. Repka, J. Ni and S. E. Reisman, J. Am. Chem. Soc., 2010, 132, 14418.

(3) Wang, H.; Reisman, S. E. *Angew. Chem. Int. Ed.* **2014**, *53*, 6206.

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