Transition Metal-Catalyzed Intramolecular C-H Amination Reactions and Applications in Drug Discovery

BY

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THESIS

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I've got to start with Tom G. Driver, whose astute guidance, endless support, and good humor, have seen me through seven of my nine years at UIC. He is the reason I am on the path I am today, and I cannot thank him enough for the opportunities he has made possible during my Ph.D. studies. Since the moment I walked through his door as an undergraduate, Professor Driver has had a faith in my abilities that has been truly inspirational over the years. It is an honor to have been trained by Professor Driver himself, and I am forever indebted to him for the inspiration for this career path.

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Nichole, my lifelong best friend, was always my source for comic relief. Nate, one of the good ones, thank you for all the love, trust and support. My parents, George and Pamela, my siblings Shannon and Brad, and the rest of my extended family have given more loving and unconditional support throughout this process than a girl could ask for.

CONTRIBUTION OF AUTHORS

Chapter 1 discusses material from a previously published manuscript ("Rh_2(II)-Catalyzed Synthesis of α-, β- or δ-Carbolines from Aryl Azides." Pumphrey, A. L.; Dong, H.; Driver, T. G. *Angew. Chem., Int. Ed.* **2012**, *51*, 5920.) for which I was the primary author. Dr. Huijun Dong contributed to the initial discovery of this reactivity and also to the formation of the β-carboline isomers. My advisor Dr. Tom G. Driver contributed to the writing of the manuscript.

Chapter 2 represents unpublished work involving the discovery of new anti-Schistosomiasis targets. My contribution was to the identity of the active targets through assay screening. Dr. Ke Sun synthesized the compounds used in this study and this research is ongoing in the laboratory. Ultimately this work will be published as part of a co-authored manuscript in collaboration with Dr. David Williams of RUSH University.

Chapter 3 represents unpublished work involving the development of novel NAMPT inhibitors. I was the major driver of the synthesis of these inhibitors and Dr. Roberto Machado in UIC's College of Medicine is continuing the evaluation of these targets. Brittney Mikelle (undergraduate), Cody Lee (undergraduate) and Rebecca Ranay (undergraduate) assisted in the synthesis of some of the starting intermediates in the inhibitor synthesis. This work will ultimatly be published as a co-authored manuscript and patent.

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LIST OF ABBREVIATIONS

Ac	acetyl
Alk	alkyl
aq	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	*tert*-butoxycarbonyl
BOM	benzyloxymethyl
BQ	1,4-benzoquinone
Bz	benzoyl
n-Bu	butyl
t-Bu	*tert*-butyl
Calcd	calculated
cat.	catalytic amount
COD	1,5-cyclooctadiene
Cy	cyclohexyl
δ	chemical shifts in parts per million downfield from tetramethylsilane (NMR)
2D	two-dimensional (NMR)
d	doublet
dba	dibenzylidene acetone
DCM	dichloromethane

LIST OF ABBREVIATIONS (continued)

DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyanobenzoquinone
DEPT	distortionless enhancement by polarization transfer
DFT	Density Functional Theory
DMA	dimethylacetamide
DMB	2,4-dimethoxybenzyl
DMF	dimethylformamide
DMSO	dimethylsulfoxide
dppm	1,1'-bis(diphenylphosphino)methane
EB	3-ethylbutyryl
EDG	electron-donating group
EE	ethoxyethyl
EI	electron impact ionization (in mass spectrometry)
Et	ethyl
equiv.	molar equivalent
EWG	electron withdrawing group
G	group, Gibbs free energy
g	gram
GC	gas chromatography
h, hrs	hour(s)
HIV	human immunodeficiency virus

LIST OF ABBREVIATIONS (continued)

HMBC	heteronuclear multiple-bond correclation spectroscopy (NMR)
HMG-CoA	3-hydroxy-methyl glutaryl coenzyme A
HMQC	heteronuclear multiple-quantum coherence spectroscopy (NMR)
HR	high resolution (mass spectrometry)
Hz	Hertz
J	spin-spin coupling constant (NMR)
L	ligand
LDA	lithium diisopropyl amide
m	multiplet (NMR)
mp	melting point
μ	micro
[M]	metal
M	molar
MS	mass spectrometry
MS	molecular sieves
Me	methyl
Mes	Mesityl
mg	milligram
min	minute
mL	milliliter
mm	millimeter

LIST OF ABBREVIATIONS (continued)

mmol	millimole
mol	mole
MOM	methoxymethyl
MHz	megahertz
m/z	mass to charge ratio
NMP	*N*-methyl-2-pyrrolidinone
NMR	nuclear magnetic resonance
Ns	*p*-nitrobenzenesulfonyl
pfb	perfluorobutyrate, heptafluorobutyrate
Ph	phenyl
Phth	phthalyl
Piv	pivalyl, trimethylacetyl
PMB	*p*-methoxybenzyl
ppm	parts per million
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl
Py	pyridine
q	quartet (NMR)
quint	quintet (NMR)
rt	room temperature

LIST OF ABBREVIATIONS (continued)

s	singlet (NMR)
sept	septet (NMR)
sPLA2	human secreted phospholipase A2
t	triplet (NMR)
TBS	*tert*-butyldimethylsilyl
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
THP	tetrahydropyranyl
TLC	thin layer chromatography
TMS	trimethylsilyl
Tol, tol	tolyl
Ts	*p*-toluenesulfonyl
TTBP	2,4,6-tris-*tert*-butylpyrimidine

SUMMARY

This thesis describes the development of methodology towards the formation of complex N-heterocycles via transition metal-mediated C-H amination of aryl azides. These novel reactions lead to the formation of α-, β-, γ-, and δ-carbolinium ions and the corresponding carbolines. These complex heterocylces are then used in the synthesis of new antischistosomal and pulmonary arterial hypertension therapeutic targets. Assay development is also carried out to test the potency of these novel inhibitors.

In chapter one, the biological significance of carbolines is described as well as the importance of new synthetic routes to achieve them. After that, the developed methodologies for the construction of α-, β-, and δ-carbolines and tetrahydro-carbolines are described. This new method for building the carboline scaffold is then integrated into the synthesis of a variety of natural and non-natural products with biological importance.

Chapter two briefly describes the Neglected Tropical Disease (NTD) Schistosomiasis and highlights the importance of developing new treatments for this third world disease. The synthesis of a novel series of antischistosomal targets is then discribed and an assay for the screening of their inhibition is developed in the lab of Dr. David Williams of RUSH University.

Finally, chapter three describes the causes and classifications of pulmonary arterial hypertension (PAH) and explains the importance of developing new therapeutic targets that address the primary cause of cellular

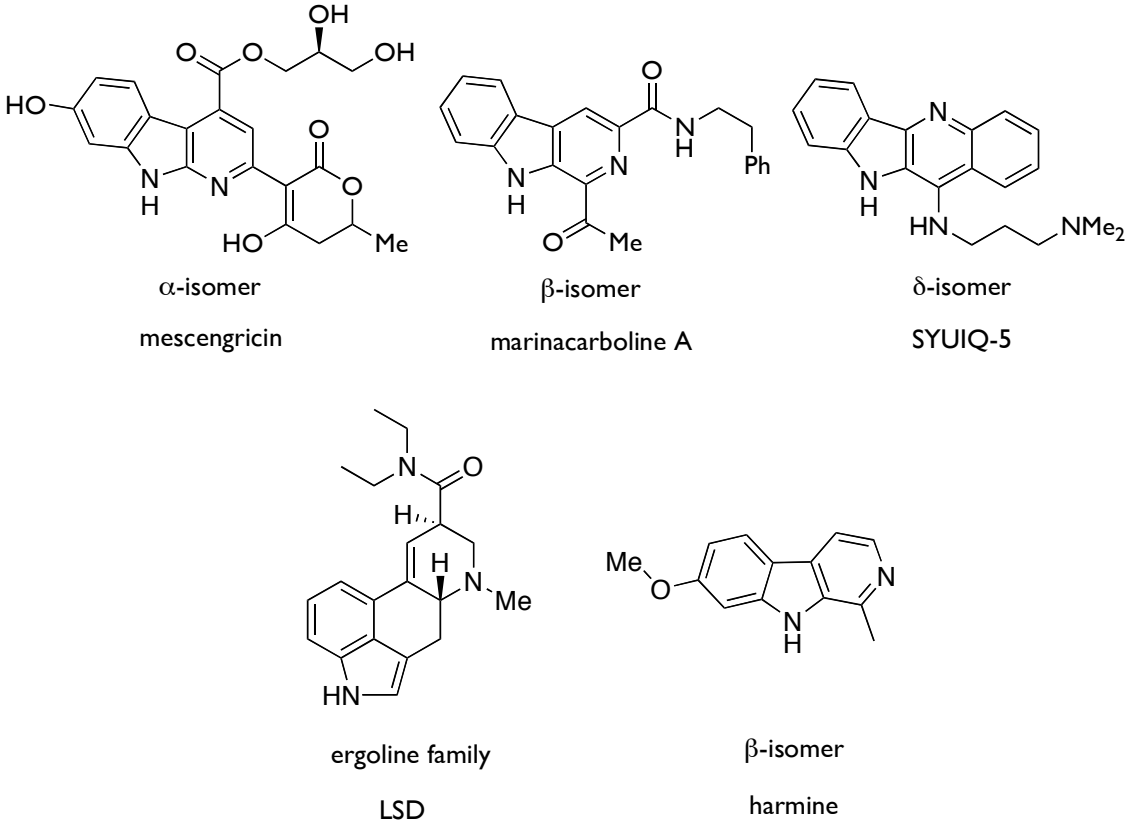
disfuction. This work highlights a collaboration across mulitple fields within UIC, and my expertise in the synthesis of complex heterocycles is utilized towards the development of a new PAH target. Validation of the new inhibitor is then carried out in the lab of Dr. Roberto Machado in UIC's College of Medicine.

CHAPTER 1

Rh(II)-Mediated C-H Amination of Aryl Azides Towards Carbolines

Carbolines and the saturated analogs tetrahydrocarbolines are common moieties in many biologically active pharmaceuticals and natural products.[1-3] This is most likely due to their facile biosynthetic route, the condensation reaction of tryptophan and aryl alkylamines with aldehydes, which can be enzymatically catalyzed.[4] The first isolation of carbolines, for example harmine, dates back to the 1840's from the seeds of *Peganum harmala*, an herb also known as Syrian Rue, which is traditionally used as both an emmenagogue and an abortifacient in North Africa and the Middle East.[5] Carbolines are part of the alkaloid family, which notoriously includes many illegal drugs and hallucinogens, including LSD.[6] The β-Carbolines from *Peganum harmala* have also been identified as monoamine oxidase (MAO) inhibitors[7-10] and occur as minor components in tobacco.[11] In mammals, carbolines occur naturally in platelets, plasma and urine.[12] More recently this alkaloid family has shown interesting antitumor,[13] antiviral,[14] antimicrobial[15] and antiparasitic[16,17] activity. Because of these interesting biological effects, there is no question as to why the carboline alkaloids have become important targets for synthetic chemists. Figure 1.1 shows a representative example of various biologically active alkaloids.

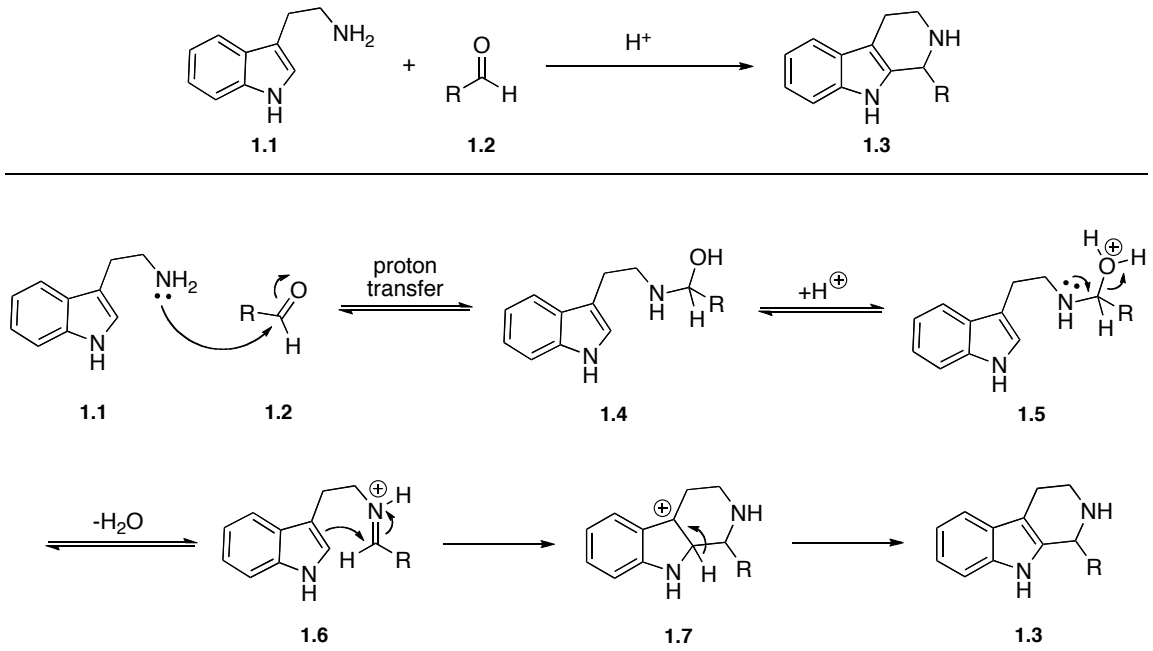
Figure 1.1 Examples of biologically active carboline alkaloids



Among the carboline isomers, the β-carboline is the most prevalent naturally and has inspired significant synthetic efforts. There are two classic pathways to access the β-carboline scaffold, the Pictet–Spengler reaction and the Bischler–Napieralski reaction.[18-20] The Pictet–Spenger reaction was discovered by Amé Pictet and Theodore Spengler in 1911, and to this day still remains an important synthetic route to access alkaloids and other pharmaceuticals. Initially, the reaction led to the formation of tetrahydroisoquinolines. Shortly after this reactivity was discovered, Tatsui and coworkers extended the reactivity towards the formation of tetrahydro-β-

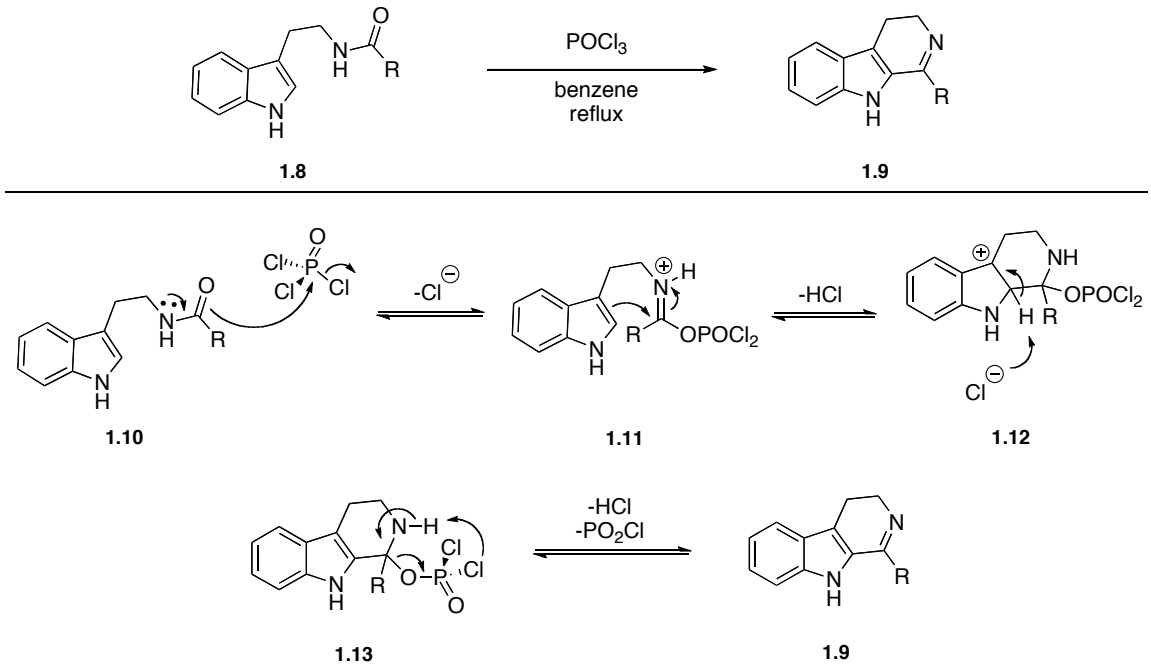
carbolines.[21] With a large variety of tryptamine and aryl aldehyde derivatives available this reaction provides the most modular approach to synthesizing the β-isomer.

Scheme 1.1 The Pictet–Spengler reaction



The Bischler–Napieralski reaction is another intramolecular electrophilic aromatic substitution reaction that allows for β-carboline formation from β-arylethylamides. This reaction was discovered in 1893 by August Bischler and Bernard Napieralski, and provided a new route to the partially saturated β-carbolines more commonly known as dihydroisoquinolines.[20] Both the Pictet–Spenger and Bischler–Napieralski synthetic routes involve attack of an iminium ion as the key step.

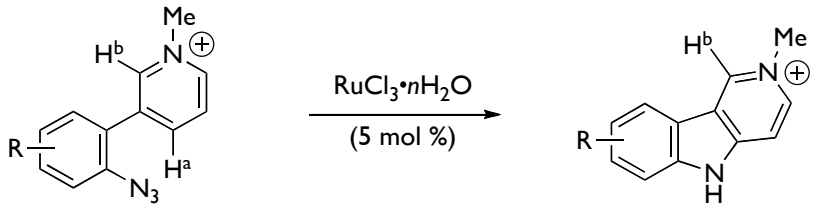
Scheme 1.2 The Bischler-Napieralski reaction



While there are a large variety of methods to access β-carbolines, methods to access the δ- or α-isomer are not prevalent despite their important biological activities. Two examples of these structural motifs include the δ-carboline SYUIQ-5, shown in Figure 1.1, is a known telomerase inhibitor[22] and has recently demonstrated antitumor activity.[23-25] Also depicted is mescengricin, a potential neural protectant,[26,27] contains the α-carboline scaffold. With an obvious need for new synthetic routes to access these various carboline isomers we decided to find optimal conditions for their construction from aryl azides. This work stemmed from the previous discovery by Dr. Huijun Dong in our group, that ruthenium trichloride-hydrate selectively transformed aryl azides **1.14** into γ-

carbolinium ions **1.15** (Scheme 1.3).[28] Upon trying to use these conditions for the synthesis of the α-, β-, and δ-carboline isomers we found they were not successful.

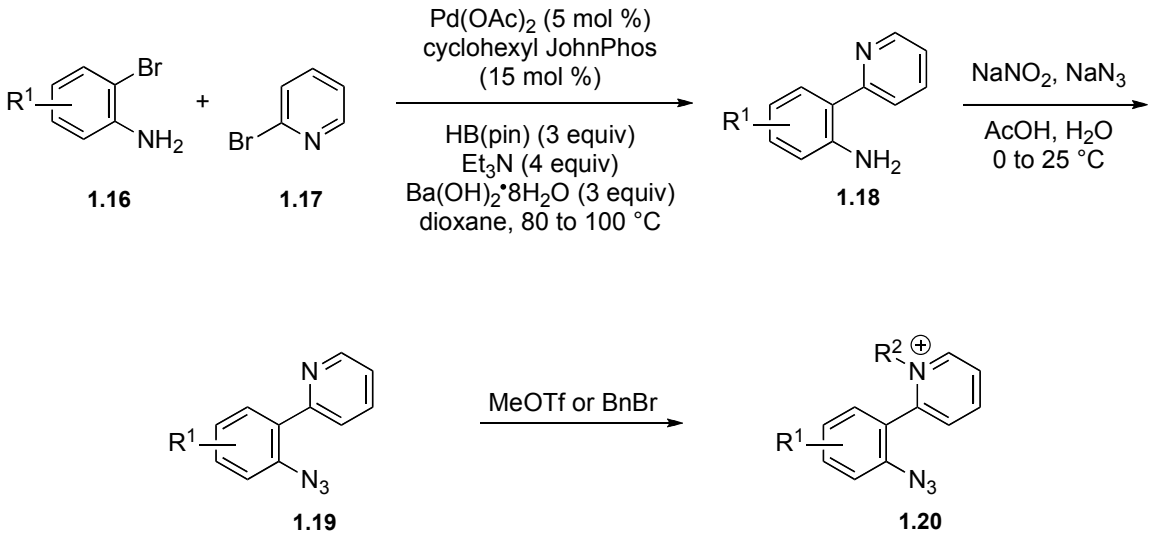
Scheme 1.3 Ruthenium-catalyzed γ-carbolinium ion formation



1.14 **1.15**

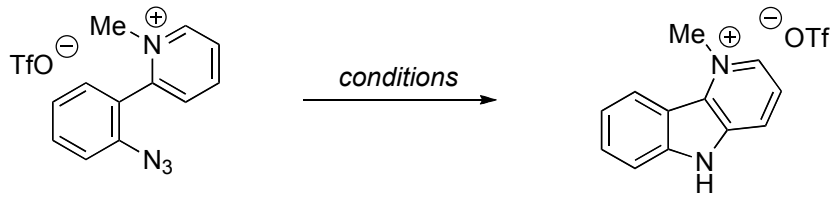
The aryl azides for this study were synthesized in a three-step sequence from the appropriate, commercially available 2-bromoanilines **1.16** (Scheme 1.4). The first step in the sequence was the Suzuki cross coupling of the 2-bromoaniline with the appropriate pyridineboronic acid **1.17**. Azidation of the subsequent biaryl amines **1.18** followed by alkylation of the pyridine nitrogen afforded the pyridinium ions **1.20**. The crystalline nature of the aryl azides made them extremely facile to synthesize and isolate. The final alkylation step was also a very clean, quantitative reaction that required no purification.

Scheme 1.4 *ortho*-Substituted pyridinium biaryl azide synthetic route



To examine the possibility of accessing δ- or α-carbolines from aryl azides, we exposed aryl azide 1.21 to a series of transition metal salts and complexes (Table 1.1). Reaction conversions were quantitated by 1H NMR spectroscopy using CH_2Br_2 as an internal standard. In the presence of no catalyst, at temperatures as high as 170 °C, no thermal decomposition of the aryl azide was seen (entries 1 and 2). As previously stated, $RuCl_3•nH_2O$ (entry 16) did not lead to carbolinium ion formation as well as $Cu(OTf)_2$ (entry 13), ZnI_2 (entry 14), and $FeBr_2$ (entry 15). Upon trying complexes with rhodium and iridium, the formation of carbolinium ion was finally seen although in trace amounts (entries 3 an 8-12). $Rh_2(esp)_2$ was selected for further optimization.

Table 1.1 Optimization of rhodium-catalyzed δ-carbolinium ion formation



1.21 **1.22**

entry	metal salt	mol %	solvent	wt %, 4 Å MS	T (°C)	yield, %[c]
1	none	n.a.	decalin	0	160	0
2	none	n.a.	decalin	0	170	0
3	$Rh_2(esp)_2$	1.0	DCE	0	80	trace
4	$Rh_2(esp)_2$	5.0	toluene	100	80	73
5	$Rh_2(esp)_2$	5.0	1M DCE	0	80	85
6	$Rh_2(esp)_2$	5.0	DCE	0	80	trace
7	**$Rh_2(esp)_2$**	**5.0**	**DCE**	**100**	**80**	**100**
8	$Rh_2(O_2CC_7F_{15})_4$	5.0	DCE	100	80	trace
9	$Rh_2(O_2CCF_3)_4$	5.0	DCE	100	80	n.r.
10	$Rh_2(O_2CC_3F_7)_4$	5.0	DCE	100	80	trace
11	$[(cod)IrCl]_2$	5.0	DCE	100	80	trace
12	$[(cod)Ir(OMe)]_2$	5.0	DCE	100	80	trace
13	$Cu(OTf)_2$	5.0	DCM	100	40	n.r.
14	ZnI_2	5.0	DCM	100	40	n.r.
15	$FeBr_2$	5.0	DCM	100	40	n.r.
16	$RuCl_3 \bullet nH_2O$	5.0	IPAC	100	80	n.r.

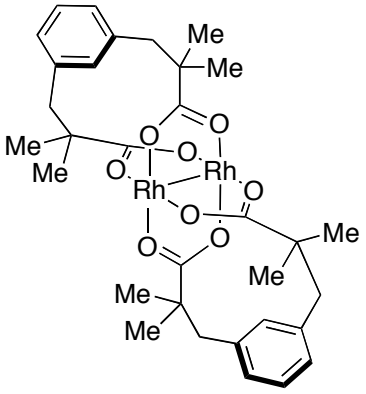
[a] Reaction performed in conical vial. [b] 16 hour reaction time.

[c] As determined with ^1H NMR spectroscopy using CH_2Br_2 as an internal standard.

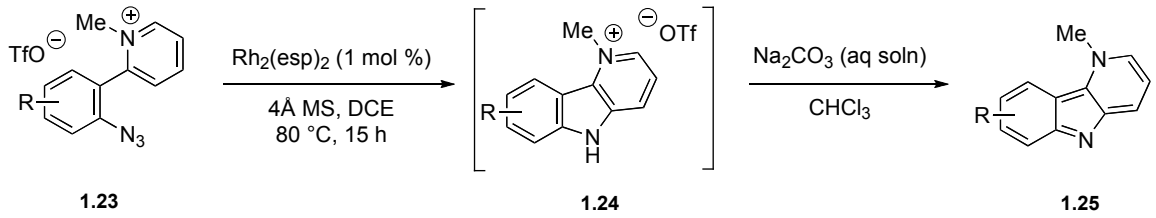
Upon optimization Du Bois's rhodium(II) carboxylate catalyst[29] was found to be the most efficient, with the optimal conditions being 5 mol % [$Rh_2(esp)_2$] complex in DCE at 80 °C (Scheme 1.4). We attribute the efficiency of this catalyst to it's thermal stability imbued by the tetradentate carboxylate ligands on each rhodium atom (Figure 1.2). Deprotonation of the δ-isomers using aqueous

Na_2CO_3 produced the free base, which could easily be purified using MPLC on silica.

Figure 1.2 Structure of $Rh_2(esp)_2$ catalyst



Scheme 1.5 Rhodium(II)$_2$-catalyzed δ-carboline formation

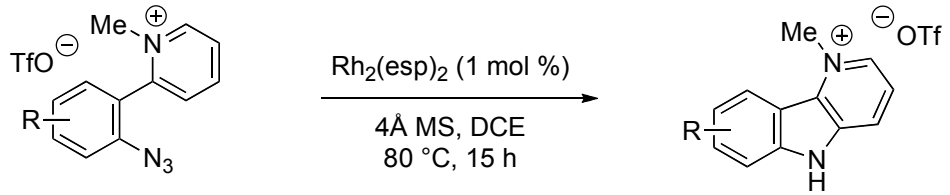


1.23 **1.24** **1.25**

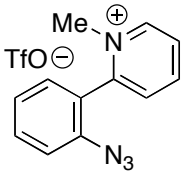
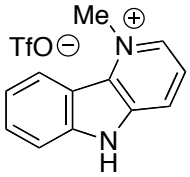
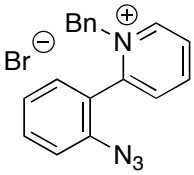
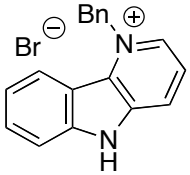
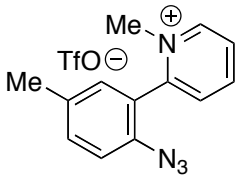
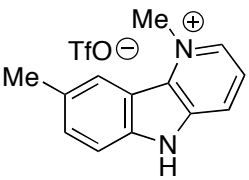
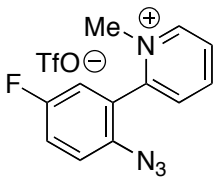
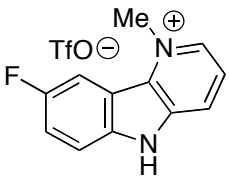
The scope and limitations were investigated for the δ-carbolinium ion formation by submitting a variety of aryl azides **1.23** to the optimized reaction conditions. The amination reaction was found to tolerate a wide variety of substituents on the aryl azide portion of the starting material. Both electron-donating alkyl groups and electron-withdrawing halo- and trifluoromethyl groups

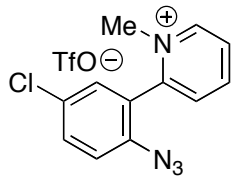
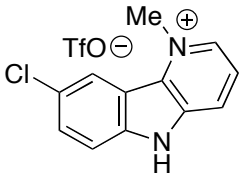
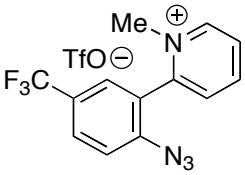
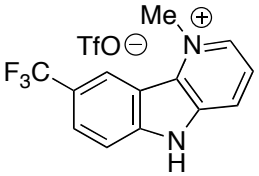
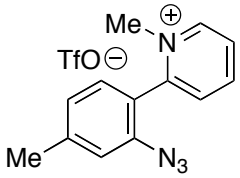
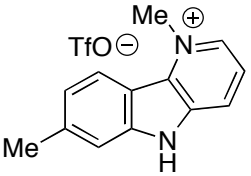
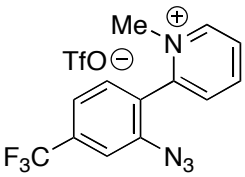
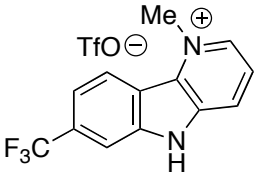
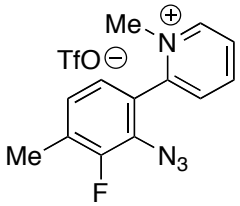
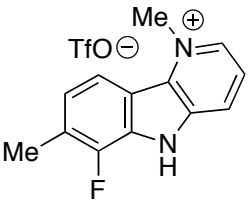
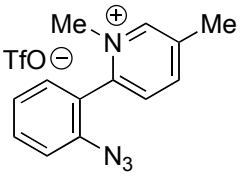
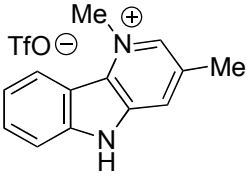
were efficiently transformed into the corresponding δ-carbolines. Surprisingly the reaction was also tolerant of an additional *ortho*-substituent to the azide portion of the substrate (entry 9)**.** While substitution on the azide portion of the starting substrate was tolerated, a significant decrease in the reaction yield was seen when substituents were placed on the pyridinium ring (entry 10).

Table 1.2 Scope and limitations of Rh(II)-catalyzed δ-carbolinium formation



1.23 **1.24**

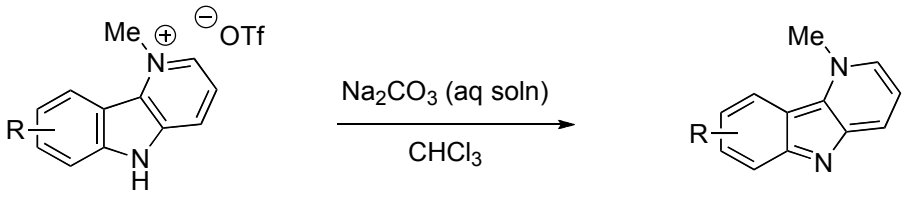
entry	substrate	##	product	##	yield, %[a]
1		**1.21**		**1.22**	quant.
2		**1.26**		**1.35**	66
3		**1.27**		**1.36**	85
4		**1.28**		**1.37**	quant.

5		**1.29**		**1.38**	97
6		**1.30**		**1.39**	97
7		**1.31**		**1.40**	85
8		**1.32**		**1.41**	98
9		**1.33**		**1.42**	quant.
10		**1.34**		**1.43**	60

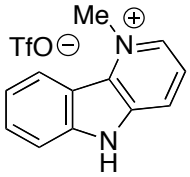
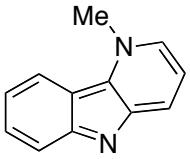
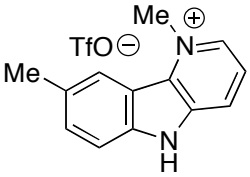
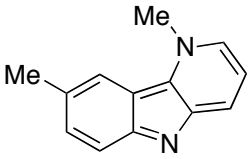
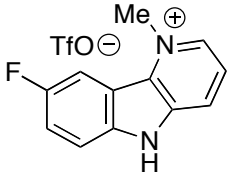
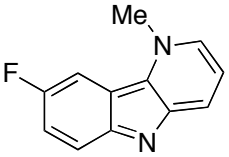
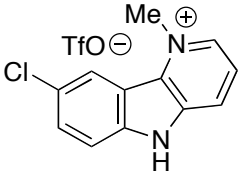
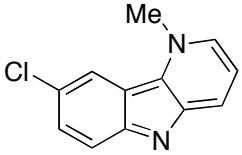
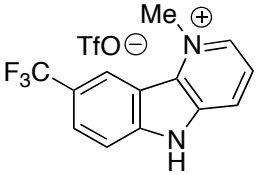
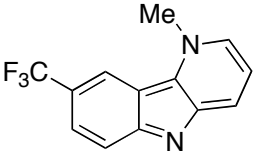
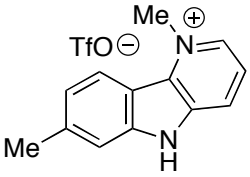
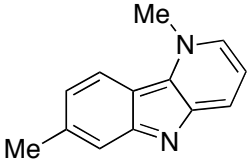
[a] As determined with ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard.

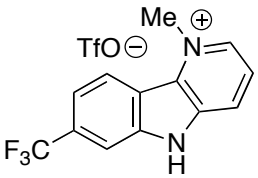
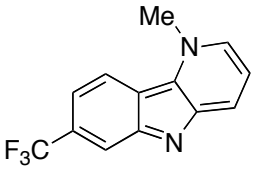
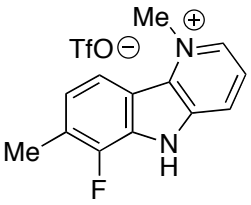
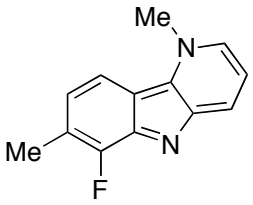
The resulting δ-carbolinium ion mixtures were exposed to a basic workup, which lead to deprotonation of the pyridinium ions to the free base **1.25.** This allowed us to obtain isolated yields by silica MPLC (Table 1.3). The yields range from 66% - 96%.

Table 1.3 Scope of 1*H*-pyrido indole formation



1.24 **1.25**

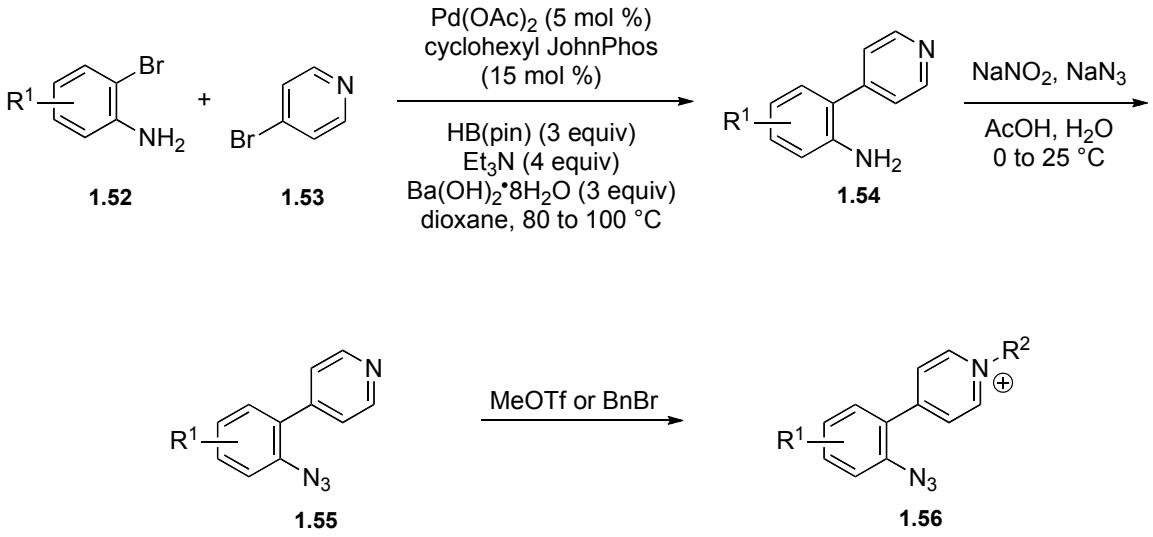
entry	substrate	##	product	##	yield, %[a]
1		**1.22**		**1.44**	74
2		**1.36**		**1.45**	71
3		**1.37**		**1.46**	96
4		**1.38**		**1.47**	77
5		**1.39**		**1.48**	78
6		**1.40**		**1.49**	75

7		**1.41**		**1.50**	86
8		**1.42**		**1.51**	66

[a] Yield after silica gel chromatography.

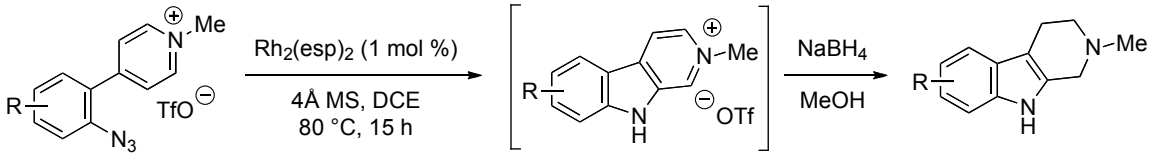
After the success of synthesizing a variety of δ-carbolinium triflates **1.24**, we set out to attempt the amination reaction with 4-substituted pyridinium ions to afford β-carbolinium ions. The aryl azide substrates were synthesized in the same three-step, Suzuki-Azidation-Alkylation sequence starting from 4-bromopyridine **1.53** (Scheme 1.6).

Scheme 1.6 *para*-Substituted pyridinium biaryl azide synthetic route



Excitingly, the optimal $Rh(II)_2$-catalyzed conditions efficiently converted the aryl azides **1.56** to the β-isomers (Scheme 1.7). Furthermore, the reduction of the β-carbolinium ion with $NaBH_4$ readily produced the saturated tetrahydro-β-carbolines (tryptolines). The reduction allowed for access to the biologically relevant tryptolines as well as easy purification of the final products on silica gel MPLC.

Scheme 1.7 Rhodium(II)$_2$-catalyzed β-carboline formation

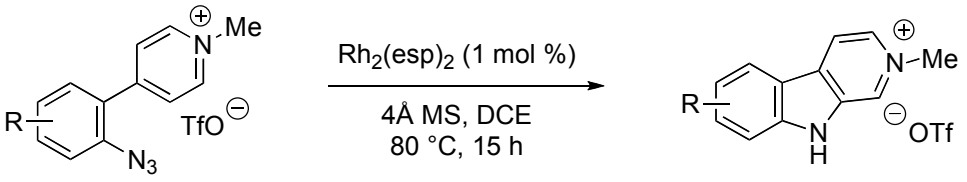


1.56 **1.57** **1.58**

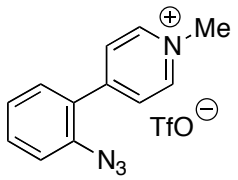
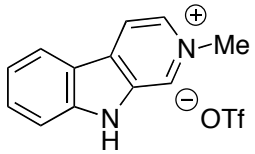
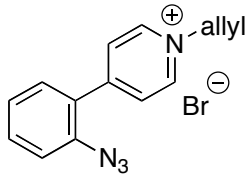
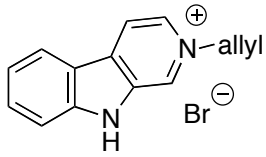
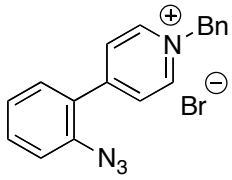
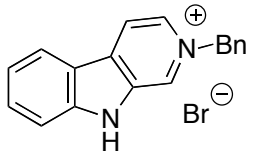
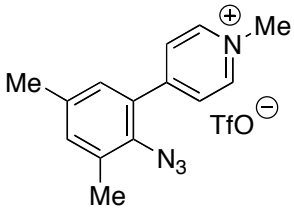
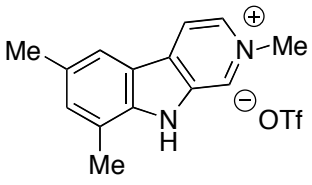
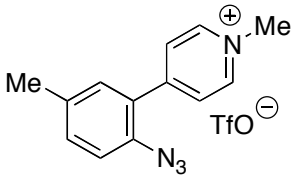
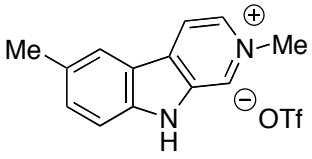
To examine the scope and limitations of tryptoline formation, a range of aryl azides was examined (Table 1.4). First, we demonstrated a variety of different N-alkyl groups were tolerated in our reaction as long as a stoichiometric amount of the silver salt was added (entries 2 and 3). We felt that both the N-allyl and N-Bn substituents improved the synthetic impact of our transformation by providing another synthetic handle on the carboline product that could be easily removed. As previously seen with the δ-isomers, an additional *ortho*-substituent could be added to the azide without perturbing the reaction yield (entry 4). In this case, the *ortho*-methyl subsituent increases the steric environment around the azide portion. The electronic nature of the azide ring

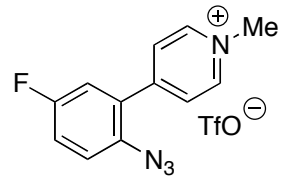
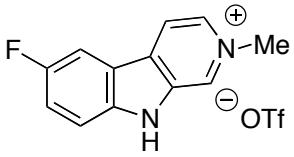
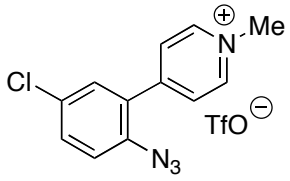
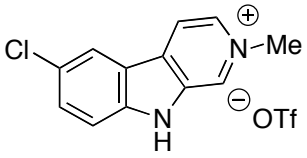
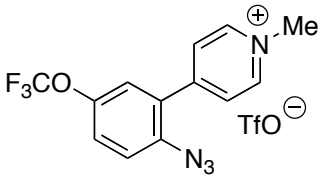
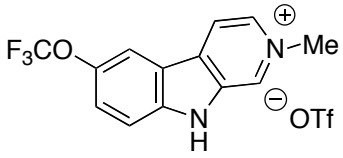
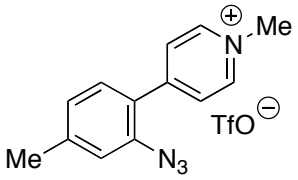
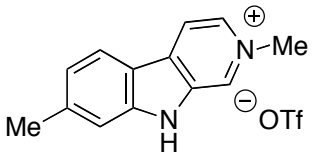
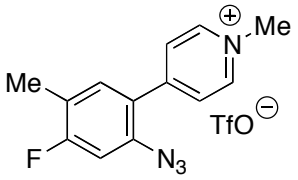
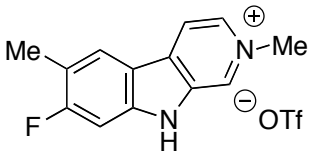
could also be varied and the reaction was shown to tolerate both electron-withdrawing as well as electron-donating substituents without attenuating the yield of the amination reaction (entries 5 – 10).

Table 1.4 Scope and limitations of Rh(II)-catalyzed β-carbolinium formation



1.56 **1.57**

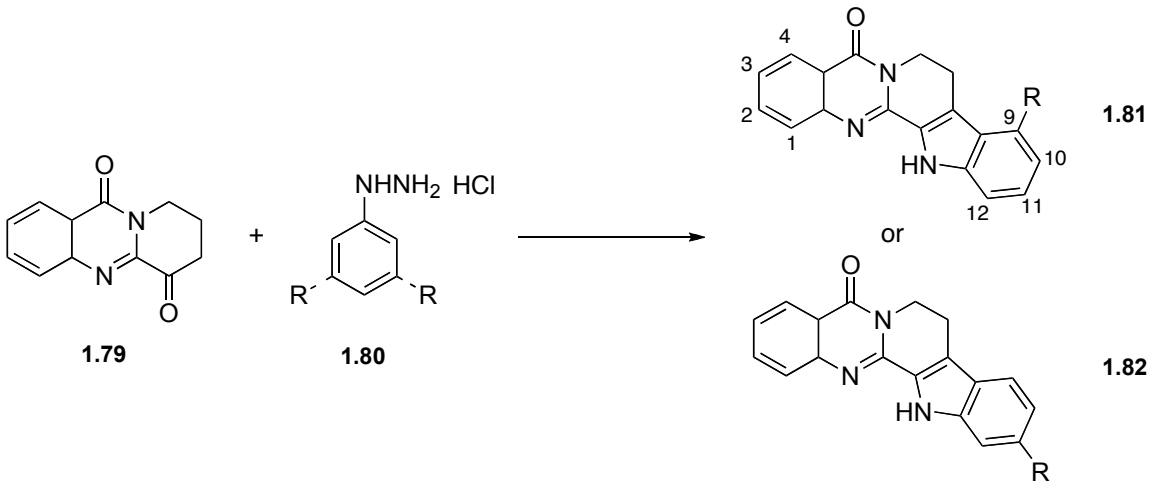
entry	substrate	##	product	##	yield, %[a]
1		**1.59**		**1.69**	quant.
2[b]		**1.60**		**1.70**	90
3[b]		**1.61**		**1.71**	89
4		**1.62**		**1.72**	94
5		**1.63**		**1.73**	quant.

6		**1.64**		**1.74**	quant.
7		**1.65**		**1.75**	91
8		**1.66**		**1.76**	quant.
9		**1.67**		**1.77**	quant.
10		**1.68**		**1.78**	quant.

[a] As determined with ^{1}H NMR spectroscopy using CH_2Br_2 as an internal standard. [b] 1.1 equiv AgOTf added.

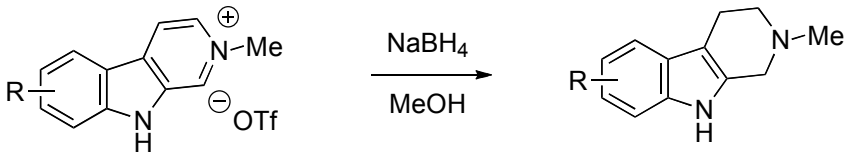
Notably, this method allows for *meta*-substitution on the aryl ring (entries 9 and 10) while still leading to a single carboline isomer. This starkly contrasts the classic Fischer indole synthesis where a mixture of products is normally obtained with *meta* substitution on the phenylhydrazine precursor. For example Eung Seok Lee et. al mentioned the drawback of having to separate the two regioisomers formed from 3-substituted phenylhydrazines **1.80** in their synthesis of biologically active Rutaecarpine derivatives[30] **1.81** and **1.82** (Scheme 1.8).

Scheme 1.8 Non-selective carboline formation via Fisher Indole synthesis

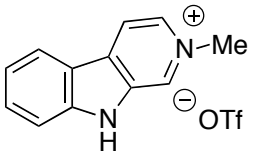
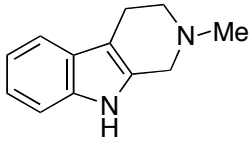
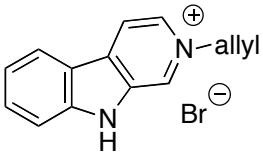
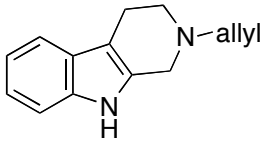
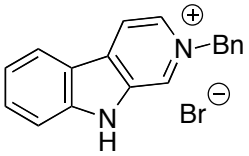
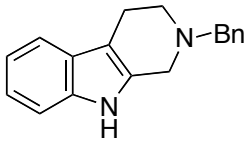
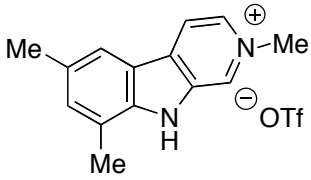
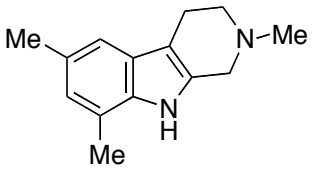
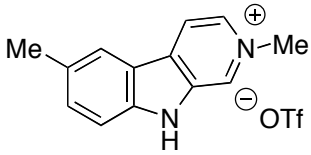
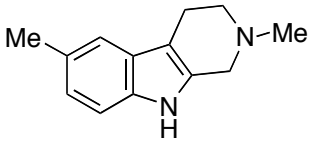
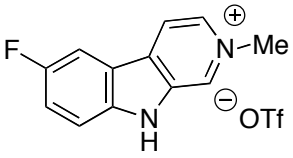
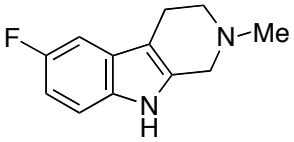
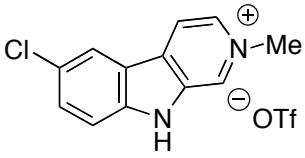
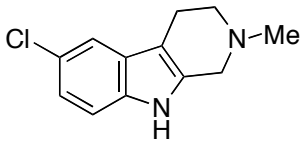


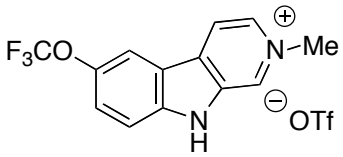
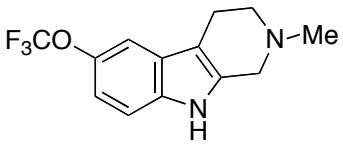
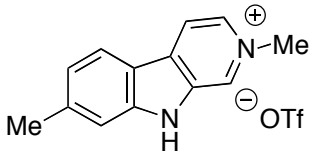
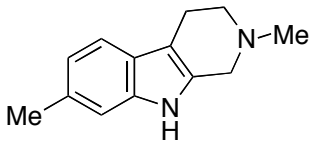
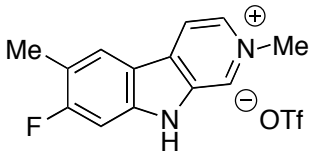
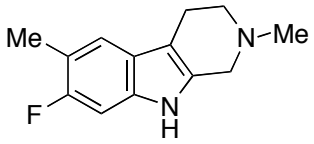
Following formation of the β-carbolinium ions, reduction of the carbolinium ions with $NaBH_4$ not only allowed for easy isolation by MPLC of the final products, but also demonstrated an efficient route to access the most prevalent tetrahydro-β-carbolines. Carbolines containing a variety of different alkyl groups on the pyridine nitrogen were easily reduced (entries 1 – 3), and the electronic nature of the azide ring could also be varied with both electron-withdrawing as well as electron-donating substituents without attenuating the yield of the reduction (entries 4 – 10).

Table 1.5 Scope of tryptoline formation



1.83 **1.84**

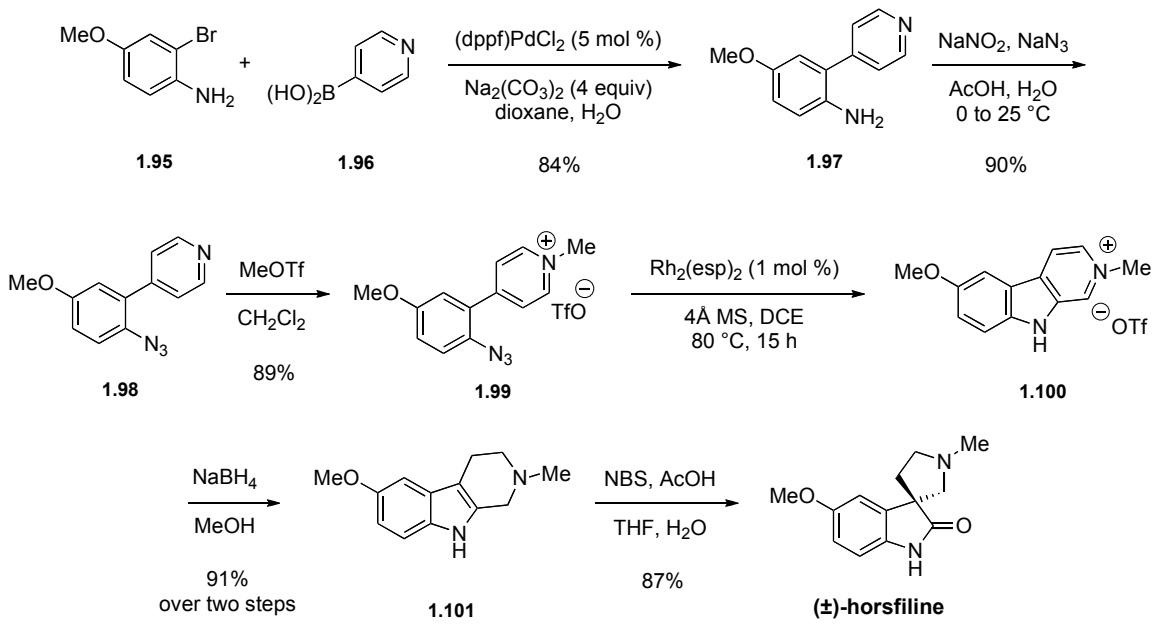
entry	substrate	##	product	##	yield, %[a]
1		**1.69**		**1.85**	99
2		**1.70**		**1.86**	60
3		**1.71**		**1.87**	71
4		**1.72**		**1.88**	83
5		**1.73**		**1.89**	94
6		**1.74**		**1.90**	71
7		**1.75**		**1.91**	70

8		**1.76**		**1.92**	88
9		**1.77**		**1.93**	90
10		**1.78**		**1.94**	> 95

[a] Yield after silica gel chromatography.

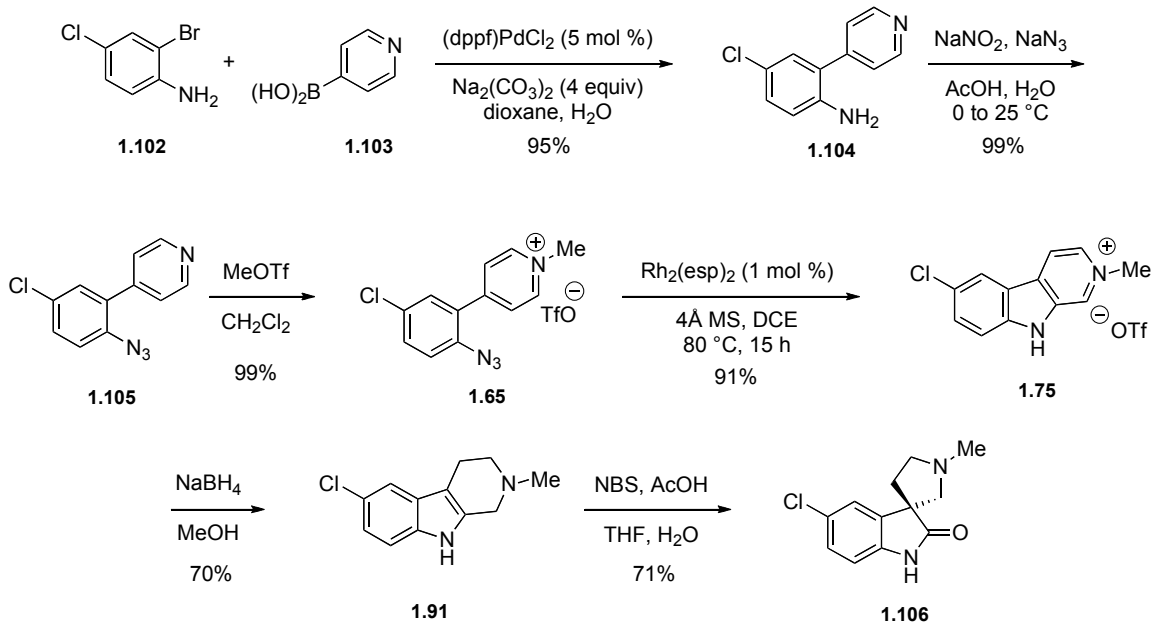
To further illustrate the utility of this new methodology (±)-horsfiline was synthesized (Scheme 1.9).[31-42] (±)-Horsfiline is a naturally occurring oxindole alkaloid, which is utilized for its analgesic properties. Starting from commercially available 2-bromo-4-methoxy-aniline **1.95** the 4-substituted pyridine ring **1.96** was added via a Suzuki cross-coupling. Azidation of the resulting aryl amine **1.97** followed by alkylation of the pyridine nitrogen afforded pyridinium ion **1.99** which could then undergo C-H amination. The resulting carbolinium ion **1.100** was reduced to tryptoline **1.101** and oxidation with NBS[43,44] lead to formation of the final oxindole. The total synthesis was demonstrated in six-steps with an overall yield of 53%.

Scheme 1.9 Synthesis of (±)-Horsfiline



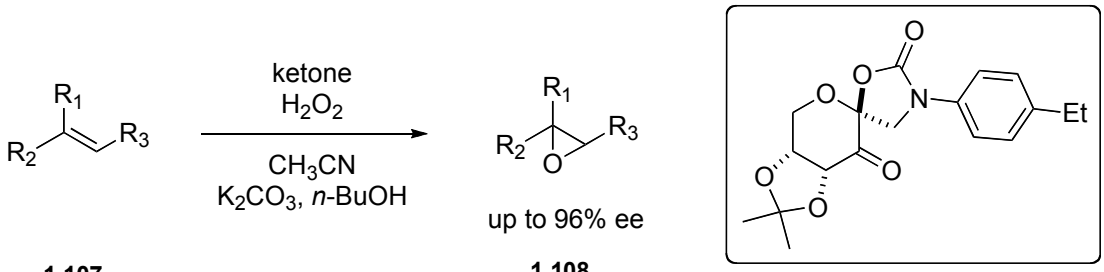
To demonstrate the modular nature of this synthetic route, a non-natural analog of (±)-horsfiline was also synthesized (Scheme 1.10). Starting from the 2-bromo-4-chloroaniline **1.102** the chlorinated analog **1.106** was synthesized in an overall yield of 42%.

Scheme 1.10 Synthesis of a non-natural (±)-horsfiline derivative



After the development of an efficient total synthesis of (±)-horsfiline we attempted to design an asymmetric approach, which had not been previously demonstrated. To our knowledge there were no chiral, electrophilic bromine sources for the initial oxidation of the indole, however we hypothesized that the oxidative rearrangement might be triggered by asymmetric epoxidation. Yian Shi and coworkers had previously demonstrated the use of chiral dioxiranes as efficient reagents for the asymmetric epoxidation of olefins.[45-48] Shi's approach involves using various fructose-derived ketones **1.109** as precursors for chiral dioxirane (Scheme 1.11).

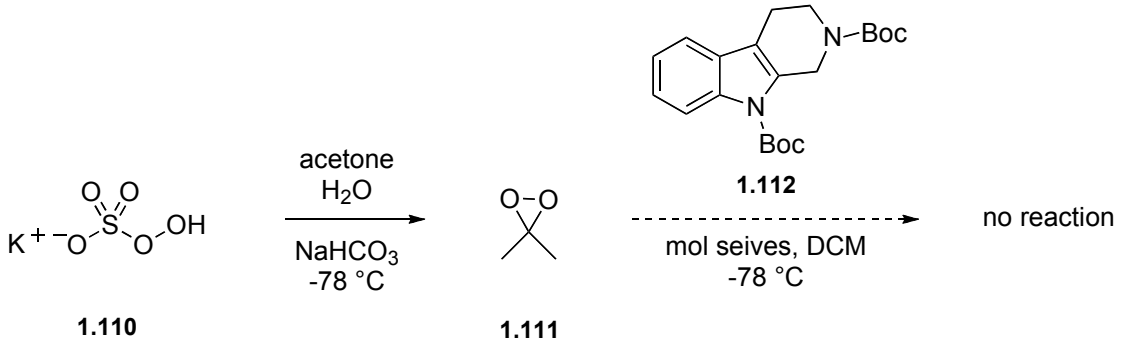
Scheme 1.11 Asymmetric epoxidation by Shi and coworkers



1.107 **1.108** **1.109**

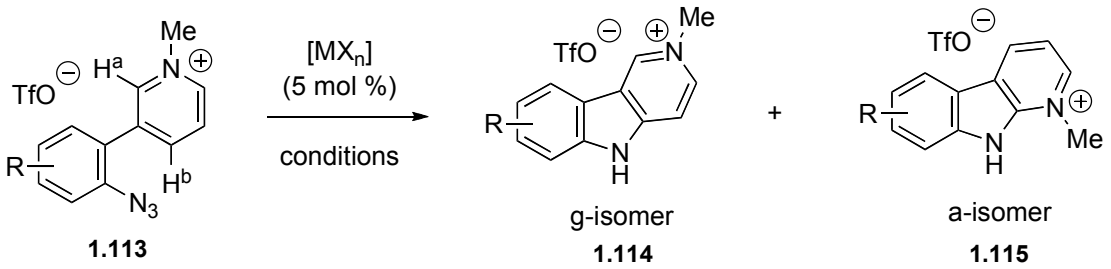
Initially, we subjected commercially available, BOC-protected β-carboline **1.112** to non-selective epoxidation conditions (Scheme 1.12). Dimethyl dioxirane (DMDO) **1.111** was synthesized from oxone **1.110** in acetone and added immediately to a cooled, -78 °C, solution of the protected β-carboline. After multiple attempts only starting material was recovered from the reaction. This reaction obviously needs to undergo further screening, but the lack of reactivity may be due to the tetra-substitution of the indole olefin. Shi and coworkers have never demonstrated oxidation of a tetra-substituted olefin.[45-48]

Scheme 1.12 Investigation of asymmetric oxindole formation



Lastly, *ortho*-substituted aryl azides with *meta*-substituted pyridinium ions were examined as substrates in our Rh(II)-catalyzed amination sequence (Scheme 1.13). Unlike the previous sets of biaryl azides, this class of subtrates contained two active C–H bonds that could potentially undergo C–H amination. This class of substrates was previously used in the $RuCl_3$ hydrate-catalyzed method reported by Dr. Huijun Dong. Under her reaction conditions amination occurred solely at the C-H^b to produce the γ-carboline isomer **1.114** as the sole product. Surprisingly, upon exposing this class of substrates to $[Rh_2(esp)_2]$ only the α-isomer **1.115** was formed. Further investigation needs to be carried out to probe mechanistic implications to this difference in selectivity.

Scheme 1.13 Two active C-H bonds in *meta*-pyridinium ions; $Rh_2(esp)_2$ vs. $RuCl_3$ selectivity trend

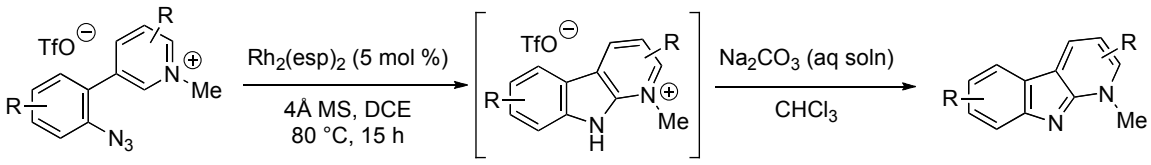


1.113 g-isomer **1.114** a-isomer **1.115**

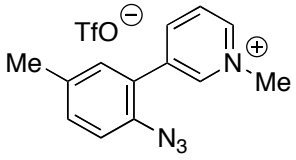
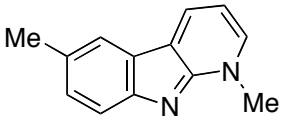
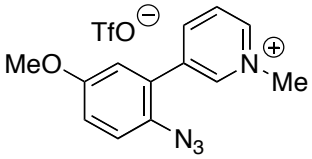
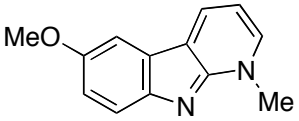
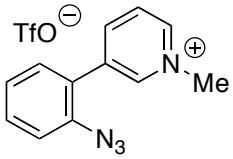
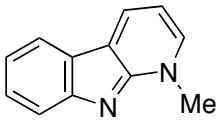
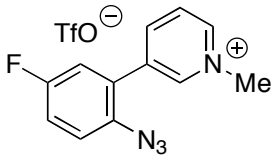
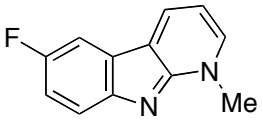
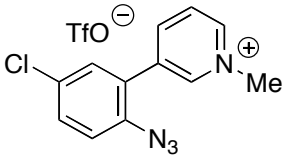
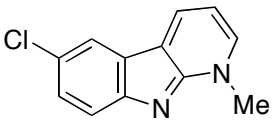
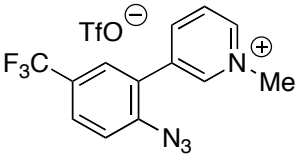
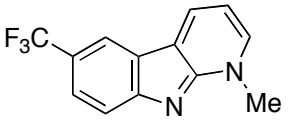
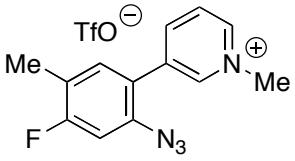
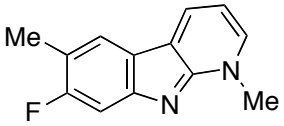
[MX_n]	conditions	yield [%]	g : a
$RuCl_3 \cdot H_2O$	$MeCO_2iPr$, 80 °C	>95%	100 : 0
$[Rh_2(esp)_2]$	DCE, 80 °C	90%	0 : 90

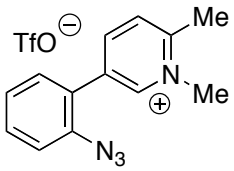
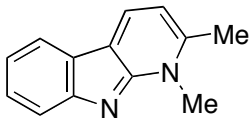
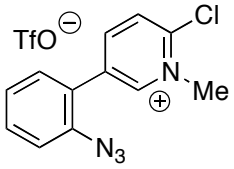
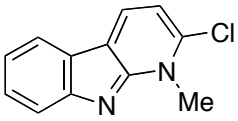
The scope and limitations for formation of the α-isomers was then carried out (Table 1.6). In order to quantify the reaction, the carbolinium ions **1.115** were deprotonated using an aqueous sodium carbonate wash, which allowed easy purification on silica gel. Similar to the other carboline isomers this method tolerated a variety of electron-withdrawing as well as electron-donating subtituents on the aryl azide moiety, although the yield was notably decreased upon the presence of a *para*-methoxy group (entry 2). In contrast to our other methods, this class of substrates was also found to tolerate substitution on the pyridinium moiety of the starting aryl azides (entries 8 and 9).

Table 1.6 Scope and limitations of Rh(II)-catalyzed α-carboline formation



1.113 **1.115** **1.116**

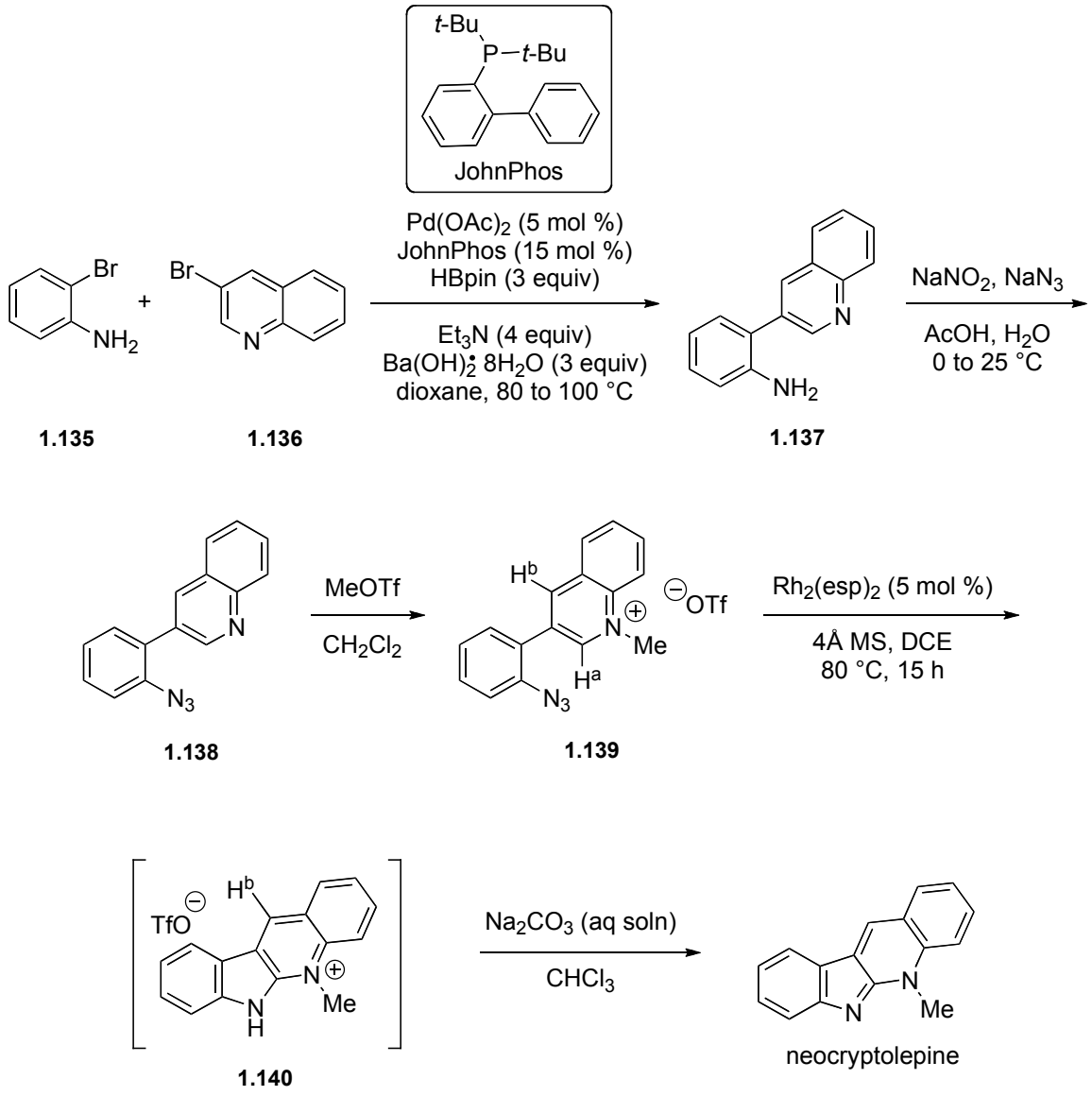
entry	substrate	##	product	##	yield, %[a]
1		**1.117**		**1.126**	83
2		**1.118**		**1.127**	63
3		**1.119**		**1.128**	80
4		**1.120**		**1.129**	83
5		**1.121**		**1.130**	67
6		**1.122**		**1.131**	78
7		**1.123**		**1.132**	64

8		**1.124**		**1.133**	77
9		**1.125**		**1.134**	77

[a] Yield after silica gel chromatography.

Since this methodology allowed substitution on the pyridinium ring, we anticipated that we would showcase its synthetic utility by synthesizing the indoloquinoline alkaloid neocryptolepine (Scheme 1.14). This alkaloid has demonstrated promising cytotoxicity toward cancer cells as well as antiplasmoidial activity towards chloroquinine-resistant strains of bacteria.[49-67] Starting from commercially available 2-bromoaniline **1.135** the 3-substituted quinoline **1.136** was added via a Suzuki cross-coupling. Azidation of the resulting aryl amine **1.137** followed by alkylation of the pyridine nitrogen afforded pyridinium ion **1.139** which could then undergo C-H amination. Basic workup afforded the final product neocryptolepine. The synthesis was carried out in 4-steps with an overall yield of 68%.

Scheme 1.14 Synthesis of Neocryptolepine



In conclusion, we demonstrated that aryl azides are important precursors for a diverse range of α-, β-, or δ-carbolinium ions from *ortho*-pyridinium ion aryl azides. These selective C–H bond amination reactions were achieved using 1-5 mol % of [$Rh_2(esp)_2$]. This work combined with the previous γ-carbonlinium ion

formation, reported by Dr. Huijun Dong in our group, provides an efficient and facile strategy to every isomer of the carolinium ion. The easy accessibility of the starting aryl azides also makes this a very practical route to carbolines. We have also further demonstrated the utility of this method by including it in the natural product syntheses of (±)-horsfiline and neocryptolepine. The modular nature of our method was demonstrated by synthesizing a chlorinated analog of (±)-horsfiline and shows that our method is an efficient way to access alkaloids that were not previously accessible synthetically.

Experimental

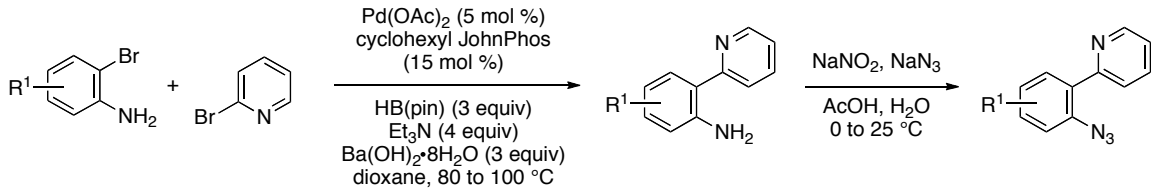
A. General. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High resolution mass spectra were acquired on a JEOL CGMate II- or Thermo Finnigan brand LTQ FT spectrometer, and were obtained by peak matching. Infared spectroscopy was obtained using a diamond attenuated total reflectance (ATR) accessory. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 μm) mesh silica gel (SiO_2). Medium pressure liquid

chromatography (MPLC) was performed to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60 μm) mesh silica gel (SiO_2). All reactions were carried out under an atmosphere of nitrogen in glassware, which had been oven-dried. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Acetonitrile, Methanol, Toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs.[68] Metal salts were stored in a nitrogen atmosphere dry box.

B. Preparation of *ortho*-Subsituted Pyridinium Biaryl Azides

B1. Preparation of *ortho*-Substituted Pyridyl Biaryl Azides

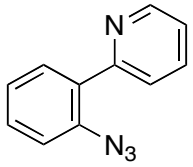
General procedure for Azidation of *ortho*-Substituted Pyridyl Biaryl Azides. Unless otherwise noted, the biaryl azides were synthesized from the substituted 2-bromoanilines and 2-bromopyridine using Suzuki reactions.[69] The resulting biaryl amines were converted to the biaryl azides without purification using traditional diazotization reaction conditions. Yields were not optimized.



In a dry 3-neck, 100 mL round bottom flask, 2-bromoaniline (1.0 equiv), $Pd(OAc)_2$ (5 mol %) and [1,1'-biphenyl]-2-yldicyclohexylphosphine (15.0 mol %) were dissolved in anhydrous dioxane (0.5 M) at 23 °C. Et_3N (4.00 equiv) followed by

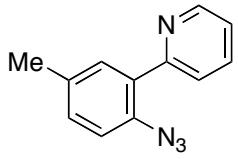
pinacolborane (3.00 equiv) was then added slowly, and the resulting mixture was heated at 80 °C for 1.0 hour. Then $Ba(OH)_2 \cdot 8H_2O$ (3.00 equiv), 2-bromopyridine (1.00 equiv) and water (2.3 M) were subsequently added. The suspension is heated at 100 °C for 4.0 h. After cooling, the reaction mixture was filtered through celite, and 1.5 N NaOH solution and 30 mL of CH_2Cl_2 were added to the filtrate. The phases are separated and the aqueous phase was extracted with an additional 3 × 30 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford a brown oil. This crude mixture was used for the next step without any further purification.

In a 100 mL of round bottom flask, the crude biaryl amine (1.0 equiv) was dissolved in HOAc and H_2O (2:1 v/v, 0.25M) and chilled in an ice bath. $NaNO_2$ (1.4 equiv) was added slowly, then the resulting mixture was stirred at 0 °C for 1.5 hour. NaN_3 (1.5 equiv) was then added slowly, the resulting mixture was warmed up to ambient temperature, and stirred for 30 minutes. The solution was then diluted with 20 mL of water and 20 mL of CH_2Cl_2, and basified by slow addition of K_2CO_3 until the pH of the mixture was 8. The phases were separated and the aqueous phase was extracted with an additional 2 × 20 mL of CH_2Cl_2. The combined organic phase were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford oil. Purification by MPLC afforded the product.



1.141

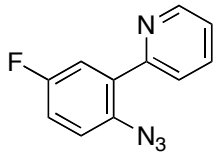
2-(2-Azidophenyl)pyridine (**1.141**).[70] The general procedure was followed using 1.72 g of 2-bromoaniline (10.0 mmol). Purification of the reaction mixture using MPLC afforded the product as yellow liquid (1.80 g, 91%), R_f = 0.48 (2:8 EtOAc:hexane). Azide **1.141** was previously reported by Smith and Boyer.[70] ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.72-8.71 (m, 1H), 7.75 (td, *J* = 7.7, 1.8 Hz, 1H), 7.68 (dq, *J* = 7.8, 1.2 Hz, 2H), 7.47-7.43 (m, 1H), 7.28 (d, *J* = 3.4 Hz, 1H), 7.27-7.24 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.9 (C), 149.6 (CH), 137.3 (C), 135.9 (CH), 132.3 (C), 131.5 (CH), 129.9 (CH), 125.1 (CH), 124.9 (CH), 122.2 (CH), 118.9 (CH); IR: 2118, 1584, 1462, 1284 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{11}H_8N_4$ $(M)^+$: 196.07489, found: 196.07403.



1.142

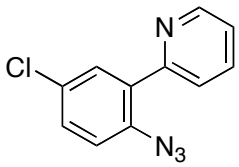
2-(2-Azido-5-methylphenyl)pyridine (**1.142**). The general procedure was followed using 0.930 g of 2-bromo-4-methylaniline (5.0 mmol). Purification of the reaction mixture using MPLC afforded the product as yellow liquid (0.330 g, 31 %), R_f = 0.47 (2:8 EtOAc:hexane): ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.71-8.70 (m, 1H), 7.73 (td, *J* = 7.6, 1.8 Hz, 1H), 7.68 (d, *J* = 7.9 Hz, 1H), 7.51 (dd, *J* = 1.5, 0.5 Hz, 1H), 7.26-7.24 (m, 2H), 7.16 (d, *J* = 8.1 Hz, 1H), 2.38 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.9 (C), 149.6 (CH), 135.8 (CH), 135.0 (2C), 134.5 (C), 132.0 (CH), 130.6 (CH), 124.9 (CH), 122.2 (CH), 118.8 (CH), 20.8 (CH_3); IR: 2114,

1584, 1460, 1283, 793 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_{10}N_4$ $(M)^+$: 210.09054, found: 210.09130.



1.143

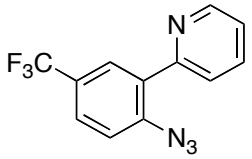
2-(2-Azido-5-fluorophenyl)pyridine (**1.143**). The general procedure was followed using 0.950 g of 2-bromo-4-fluoroaniline (5.0 mmol). Purification of the reaction mixture using MPLC afforded the product as yellow liquid (0.270 g, 25%), R_f = 0.54 (2:8 EtOAc:hexane): ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.69-8.68 (m, 1H), 7.72-7.70 (m, 2H), 7.46 (dd, *J* = 9.2, 2.9 Hz, 1H), 7.24 (ddd, *J* = 6.7, 4.8, 1.9 Hz, 1H), 7.18 (dd, *J* = 8.8, 4.7 Hz, 1H), 7.11 (ddd, *J* = 8.8, 7.5, 3.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.8 (d, *J* = 244.3 Hz, C), 154.4 (C), 149.7 (CH), 136.0 (CH), 133.8 (d, *J* = 7.5 Hz, C), 133.0 (C), 124.8 (CH), 122.7 (CH), 120.3 (d, *J* = 9.1 Hz, CH), 118.2 (d, *J* = 24.0 Hz, CH), 116.7 (d, *J* = 22.4 Hz, CH); ^{19}F NMR (471 MHz, CD_3OD) δ –118.4; IR: 2120, 1566, 1462, 1290, 1187 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{11}H_7FN_4$ $(M)^+$: 214.06547, found: 214.06459.



1.144

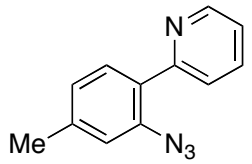
2-(2-Azido-5-chlorophenyl)pyridine (**1.144**). The general procedure was followed using 1.45 g of 2-bromo-4-chloroaniline (7.0 mmol). Purification of the reaction mixture using MPLC afforded the product as yellow liquid (0.500 g,

31%), R_f = 0.50 (2:8 EtOAc:hexane): ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.69-8.68 (m, 1H), 7.74-7.70 (m, 2H), 7.68-7.66 (m, 1H), 7.36 (dd, *J* = 8.6, 2.5 Hz, 1H), 7.26-7.23 (m, 1H), 7.15 (d, *J* = 8.6 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.3 (C), 149.7 (CH), 136.05 (CH), 135.86 (C), 133.5 (C), 131.4 (CH), 130.5 (C), 129.7 (CH), 124.9 (CH), 122.7 (CH), 120.2 (CH); IR: 2108, 1489, 1286, 1096, 805 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{11}H_7ClN_4$ $(M–N_2)^+$: 202.02978, found: 202.03088.



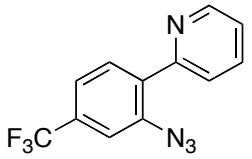
1.145

2-(2-Azido-5-trifluoromethylphenyl)pyridine (**1.145**). The general procedure was followed using 1.68 g of 2-bromo-4-trifluoromethylaniline (7.0 mmol). Purification of the reaction mixture using MPLC afforded the product as yellow liquid (0.510 g, 25%), R_f = 0.54 (2:8 EtOAc:hexane): ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.71 (dd, *J* = 2.8, 1.9 Hz, 1H), 8.01 (d, *J* = 0.7 Hz, 1H), 7.74-7.69 (m, 2H), 7.65-7.63 (m, 1H), 7.31 (dd, *J* = 8.2, 4.2 Hz, 1H), 7.27-7.26 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.2 (C), 149.8 (CH), 140.8 (C), 136.1 (CH), 132.5 (C), 128.9 (d, *J* = 3.3 Hz, CH), 127.2 (q, *J* = 33.2 Hz, C), 126.6 (CH), 124.96 (q, *J* = 272 Hz, CF_3), 124.88 (CH), 122.8 (CH), 119.2 (CH); ^{19}F NMR (471 MHz, CD_3OD) δ –63.7; IR: 2115, 1333, 1263, 11115, 1075, 819 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_7F_3N_4$ $(M–N_2)^+$: 236.05614, found: 236.05543.



1.146

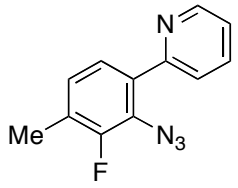
2-(2-Azido-4-methylphenyl)pyridine (**1.146**). The general procedure was followed using 1.68 g of 2-bromo-4-trifluoromethylaniline (7.0 mmol). Purification of the reaction mixture using MPLC afforded the product as yellow liquid (0.510 g, 25 %), R_f = 0.54 (2:8 EtOAc:hexane): ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.71-8.69 (m, 1H), 7.73 (td, *J* = 7.7, 1.8 Hz, 1H), 7.68-7.66 (m, 1H), 7.59 (d, *J* = 8.2 Hz, 1H), 7.25-7.22 (m, 1H), 7.07 (ddd, *J* = 4.0, 2.5, 0.7 Hz, 2H), 2.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 155.9 (C), 149.5 (CH), 140.2 (C), 136.9 (C), 135.8 (CH), 131.4 (CH), 129.6 (C), 126.1 (CH), 124.8 (CH), 122.0 (CH), 119.3 (CH), 21.3 (CH_3); IR: 2105, 1586, 1462, 1288, 783 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_{10}N_4$ $(M–N_2)^+$: 182.08440, found: 182.08534.



1.147

2-(2-Azido-4-trifluoromethylphenyl)pyridine (**1.147**). The general procedure was followed using 1.68 g of 2-bromo-5-trifluoromethylaniline (7.0 mmol). Purification of the reaction mixture using MPLC afforded the product as yellow liquid (0.516 g, 28%), R_f = 0.47 (2:8 EtOAc:hexane): ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.73-8.72 (m, 1H), 7.83 (d, *J* = 7.9 Hz, 1H), 7.77 (td, *J* = 7.7, 1.8 Hz, 1H), 7.72-7.70 (m, 1H), 7.50-7.48 (m, 2H), 7.30 (ddd, *J* = 7.4, 4.9, 1.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 154.4 (C), 149.8 (CH), 138.2 (C), 136.1 (CH), 135.4 (C), 132.3 (CH), 132.0 (q, *J* = 33.3 Hz, C), 124.9 (CH), 123.5 (q, *J* = 270 Hz, CF_3), 122.9 (CH), 121.7 (CH), 115.9 (CH); ^{19}F NMR (471 MHz, CD_3OD) δ –64.4; IR:

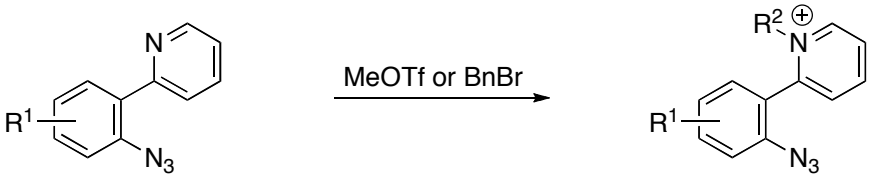
2101, 1330, 1145, 1084, 873 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_7F_3N_4$ $(M–N_2)^+$: 236.05614, found: 236.05522.



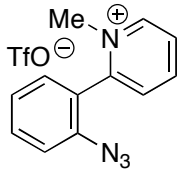
1.148

2-(2-Azido-3-fluoro-4-methylphenyl)pyridine (**1.148**). The general procedure was followed using 1.43 g of 2-bromo-4-fluoro-6-methylaniline (7.0 mmol). Purification of the reaction mixture using MPLC afforded the product as yellow liquid (0.468 g, 29%), R_f = 0.52 (2:8 EtOAc:hexane): ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.70-8.69 (m, 1H), 7.75-7.72 (m, 1H), 7.66 (dd, *J* = 7.9, 1.0 Hz, 1H), 7.55 (d, *J* = 8.3 Hz, 1H), 7.25-7.23 (m, 1H), 6.93 (dd, *J* = 9.9, 0.3 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.5 (d, *J* = 249.9 Hz, C), 155.0 (C), 149.6 (CH), 136.08 (C), 135.93 (CH), 134.3 (d, *J* = 5.8 Hz, CH), 128.1 (d, *J* = 3.5 Hz, C), 124.8 (CH), 122.15 (d, *J* = 5.5 Hz, CH), 121.98 (C), 105.8 (d, *J* = 25.9 Hz, CH), 14.1 (CH_3); ^{19}F NMR (470 MHz, CD_3OD) δ –115.9; IR: 2108, 1584, 1462, 1324, 1109, 834 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_9FN_4$ $(M)^+$: 228.08112, found: 228.08034.

B2. Preparation of *ortho*-Substituted Pyridinium Ions

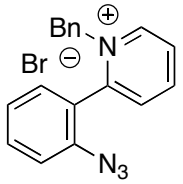


General procefure for preparation of *ortho*-substituted pyridinium ions. In a dry 25 mL round bottom flask, biaryl azide was dissolved in dry CH_2Cl_2 (0.5 M). MeOTf (1.1 equiv) or BnBr (1.0 equiv) was then added dropwise via syringe over 10 min, and the resulting solution was allowed to stir at ambient temperature overnight. The volatiles were removed *in vacuo* to afford the product, which was used directly without further purification.



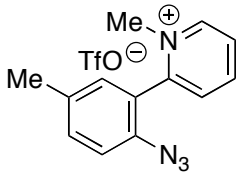
1.21

1-Methyl-2-(2-azidophenyl)pyridinium triflate (**1.21**). The general procedure was followed using 0.224 g of biaryl azide **1.141** (1.14 mmol) and 0.140 mL of MeOTf (1.26 mmol) in 5 mL of CH_2Cl_2 afforded the product as gray solid (0.410 g, 99%): ^{1}H NMR (500 MHz; CD_3OD): δ 9.05 (d, *J* = 6.1 Hz, 1H), 8.63 (t, *J* = 7.7 Hz, 1H), 8.12 (t, *J* = 6.7 Hz, 1H), 8.00 (d, *J* = 7.8 Hz, 1H), 7.78 (t, *J* = 7.8 Hz, 1H), 7.54 (dd, *J* = 10.9, 8.1 Hz, 2H), 7.45 (t, *J* = 7.5 Hz, 1H), 4.15 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 146.5 (CH), 145.5 (CH), 139.0 (C), 133.1 (CH), 130.6 (CH), 130.3 (CH), 127.1 (CH), 125.4 (CH), 122.5 (C), 121.7 (C), 119.0 (CH), 45.9 (CH_3); IR: 2143, 1276, 1151, 1029, 757 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{12}H_{11}N_4$ $(M–OTf)^+$: 211.0984, found: 211.0986.



1.26

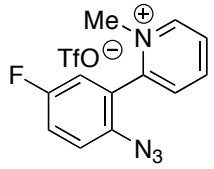
1-Benzyl-2-(2-azidophenyl)pyridinium triflate (**1.26**). The same procedure as pyridinium **1a** was followed using 0.392 g of biaryl azide **1.141** (2 mmol) and 0.240 mL of benzyl bromide (2.0 mmol) in 10 mL of CH_3CN afforded the product as light brown solid (0.242 g, 66%): ^{1}H NMR (500 MHz; CD_3OD): δ 9.30 (d, *J* = 6.2 Hz, 1H), 8.70 (td, *J* = 7.9, 1.3 Hz, 1H), 8.23 (t, *J* = 7.0 Hz, 1H), 8.01 (d, *J* = 7.9 Hz, 1H), 7.72 (ddd, *J* = 8.2, 7.4, 1.6 Hz, 1H), 7.43-7.36 (m, 3H), 7.35-7.32 (m, 1H), 7.30-7.27 (m, 2H), 6.93-6.91 (m, 2H), 5.75 (q, *J* = 13.4 Hz, 2H); ^{13}C NMR (126 MHz; CD_3OD): δ 153.0 (C), 146.5 (CH), 146.2 (CH), 139.1 (C), 133.1 (CH), 132.6 (C), 131.7 (CH), 130.2 (CH), 129.0 (CH), 128.7 (CH), 128.0 (CH), 127.6 (CH), 125.2 (CH), 122.4 (C), 119.0 (CH), 62.6 (CH_2); IR: 2125, 1624, 1485, 1288, 1151 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{18}H_{15}N_4$ $(M–OTf)^+$: 287.1297, found: 287.1299.



1.27

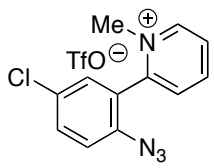
1-Methyl-2-(2-azido-5-methylphenyl)pyridinium triflate (**1.27**). The general procedure was followed using 0.330 g of biaryl azide **1.142** (1.57 mmol) and 0.190 mL of MeOTf (1.73 mmol) in 6 mL of CH_2Cl_2 afforded the product as yellow solid (0.545 g, 93%): ^{1}H NMR (500 MHz; CD_3OD): δ 9.04 (dd, *J* = 2.0, 0.6 Hz, 1H), 8.62 (t, *J* = 0.3 Hz, 1H), 8.11 (t, *J* = 0.4 Hz, 1H), 7.99-7.98 (m, 1H), 7.60-7.59 (m, 1H), 7.43-7.42 (m, 1H), 7.36 (d, *J* = 0.4 Hz, 1H), 4.15 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 153.4 (C), 146.5 (CH), 145.5 (CH), 136.1

(C), 136.0 (C), 133.7 (CH), 130.5 (2CH), 127.1 (CH), 122.3 (C), 118.8 (CH), 45.9 (CH_3), 19.4 (CH_3); IR: 2135, 1261, 1148, 1029 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{13}N_4$ $(M–OTf)^+$: 225.1140, found: 225.1139.



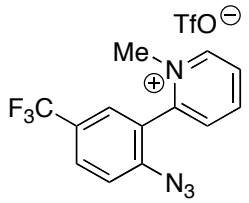
1.28

1-Methyl-2-(2-azido-5-fluorophenyl)pyridinium triflate (**1.28**). The general procedure was followed using 0.230 g of biaryl azide **1.143** (0.98 mmol) and 0.120 mL of MeOTf (1.08 mmol) in 6 mL of CH_2Cl_2 afforded the product as light brown solid (0.484 g, 100%): ^{1}H NMR (500 MHz; CD_3OD): δ 9.07 (d, *J* = 6.0 Hz, 1H), 8.64 (t, *J* = 7.7 Hz, 1H), 8.16-8.13 (m, 1H), 8.03 (d, *J* = 7.7 Hz, 1H), 7.56 (dd, *J* = 10.2, 3.2 Hz, 2H), 7.39 (dd, *J* = 7.8, 1.7 Hz, 1H), 4.17 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 159.5 (d, *J* = 247.2 Hz, CF), 151.7 (C), 146.7 (CH), 145.7 (CH), 135.2 (d, *J* = 3.7 Hz, C), 130.5 (CH), 127.5 (CH), 123.5 (d, *J* = 7.7 Hz, C), 121.1 (d, *J* = 8.8 Hz, CH), 120.01 (d, *J* = 24.0 Hz, CH), 117.31 (d, *J* = 25.9 Hz, CH), 46.0 (CH_3); ^{19}F NMR (470 MHz, CD_3OD) δ –81.6, –119.2; IR: 2139, 1489, 1261, 1151, 1027, 822 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{12}H_{10}FN_4$ $(M–OTf)^+$: 229.0889, found: 229.0892.



1.29

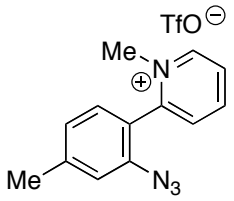
1-Methyl-2-(2-azido-5-chlorophenyl)pyridinium triflate (**1.29**). The general procedure was followed using 0.380 g of biaryl azide **1.144** (1.65 mmol) and 0.200 mL of MeOTf (1.81 mmol) in 6 mL of CH_2Cl_2 afforded the product as light yellow solid (0.530 g, 81%): ^{1}H NMR (500 MHz; CD_3OD): δ 9.07-9.06 (m, 1H), 8.66-8.63 (m, 1H), 8.16-8.13 (m, 1H), 8.04-8.02 (m, 1H), 7.78-7.76 (m, 1H), 7.61 (d, *J* = 1.3 Hz, 1H), 7.56-7.54 (m, 1H), 4.16 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 151.7 (C), 146.8 (CH), 145.7 (CH), 138.0 (C), 133.0 (CH), 130.54 (CH), 130.47 (C), 130.0 (CH), 127.5 (CH), 123.7 (C), 120.7 (CH), 46.0 (CH_3); IR: 2127, 1255, 1151, 1028 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{12}H_{10}ClN_4$ $(M–OTf)^+$: 245.0594, found: 245.0596.



1.30

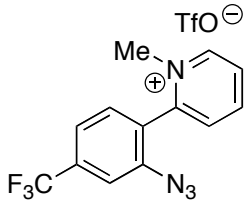
1-Methyl-2-(2-azido-5-trifluoromethylphenyl)pyridinium triflate (**1.30**). The general procedure was followed using 0.495 g of biaryl azide **1.145** (1.87 mmol) and 0.230 mL of MeOTf (2.06 mmol) in 6 mL of CH_2Cl_2 afforded the product as light yellow solid (0.780 g, 97%): ^{1}H NMR (500 MHz; CD_3OD): δ 9.09 (d, *J* = 6.2 Hz, 1H), 8.66 (t, *J* = 7.8 Hz, 1H), 8.17 (t, *J* = 7.0 Hz, 1H), 8.06 (dt, *J* = 5.2, 2.6 Hz, 2H), 7.92 (s, 1H), 7.74 (d, *J* = 8.6 Hz, 1H), 4.16 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 151.6 (C), 146.9 (CH), 145.8 (CH), 143.2 (C), 130.7 (CH), 129.9 (d, *J* = 3.10 Hz, CH), 127.7 (CH), 127.6 (CH), 127.1 (d, *J* = 34 Hz, C), 123.5 (q, *J* = 272 Hz, CF_3), 122.8 (C), 120.1 (CH), 46.0 (CH_3); ^{19}F NMR (470 MHz, CD_3OD) δ

–65.3, –81.7; IR: 2134, 1258, 1153, 1027 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{10}F_3N_4$ $(M–OTf)^+$: 279.0858, found: 279.0857.



1.31

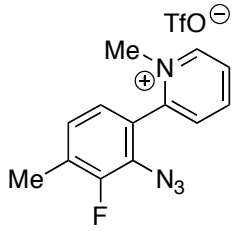
1-Methyl-2-(2-azido-4-methylphenyl)pyridinium triflate (**1.31**). The general procedure was followed using 0.577 g of biaryl azide **1.146** (2.75 mmol) and 0.340 mL of MeOTf (3.02 mmol) in 8 mL of CH_2Cl_2 afforded the product as off-white solid (1.28 g, 100%): ^1H NMR (500 MHz; CD_3OD): δ 9.02 (d, *J* = 6.1 Hz, 1H), 8.60 (t, *J* = 7.8 Hz, 1H), 8.10 (t, *J* = 7.0 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H), 7.39 (d, *J* = 7.8 Hz, 1H), 7.36 (s, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 4.14 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 153.5 (C), 146.5 (CH), 145.4 (CH), 144.5 (C), 138.7 (C), 130.7 (CH), 130.0 (CH), 128.7 (C), 127.0 (CH), 126.3 (CH), 119.3 (CH), 45.9 (CH_3), 20.1 (CH_3); IR: 2130, 1262, 1153, 1026, 778 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{13}N_4$ $(M–OTf)^+$: 225.1140, found: 225.1141



1.32

1-Methyl-2-(2-azido-4-trifluoromethylphenyl)pyridinium triflate (**1.32**). The general procedure was followed using 0.353 g of biaryl azide **1.147** (1.34 mmol) and 0.164 mL of MeOTf (1.47 mmol) in 6 mL of CH_2Cl_2 afforded the product as

light yellow solid (0.586 g, 100%): ^{1}H NMR (500 MHz; CD_3OD): δ 9.09 (d, *J* = 5.8 Hz, 1H), 8.67 (t, *J* = 7.7 Hz, 1H), 8.17 (t, *J* = 6.5 Hz, 1H), 8.05 (d, *J* = 7.8 Hz, 1H), 7.81 (s, 1H), 7.74 (s, 2H), 4.16 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 151.8 (C), 146.9 (CH), 145.8 (CH), 140.5 (C), 134.6 (q, *J* = 33.1 Hz, C), 131.5 (CH), 130.5 (CH), 127.6 (CH) 125.7 (C), 123.2 (q, *J* = 273 Hz, CF_3), 121.8 (CH), 116.2 (d, *J* = 2.93 Hz, CH), 46.0 (CH_3); ^{19}F NMR (471 MHz, CD_3OD) δ –66.2, –81.7; IR: 2122, 1258, 1147, 1031, 779 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{10}F_3N_4$ (M–OTf)$^{+}$: 279.0858, found: 279.0858.



1.33

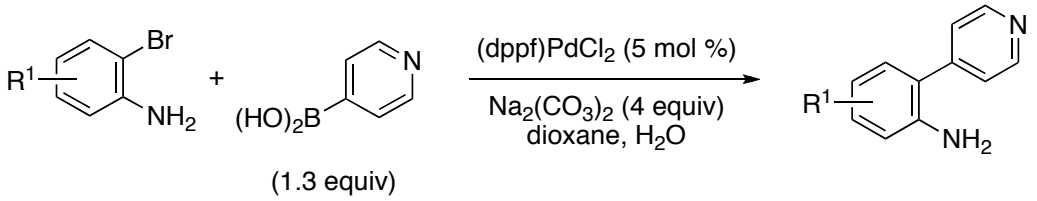
1-Methyl-2-(2-azido-3-fluoro-4-methylphenyl)pyridinium triflate (**1.33**). The general procedure was followed using 0.448 g of biaryl azide **1.148** (1.96 mmol) and 0.240 mL of MeOTf (2.16 mmol) in 6 mL of CH_2Cl_2 afforded the product as yellow solid (0.720 g, 94%): ^{1}H NMR (500 MHz; CD_3OD): δ 9.04 (d, *J* = 6.1 Hz, 1H), 8.61 (t, *J* = 7.8 Hz, 1H), 8.11 (t, *J* = 7.0 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.42 (d, *J* = 7.7 Hz, 1H), 7.32 (d, *J* = 10.0 Hz, 1H), 4.15 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 163.4 (d, *J* = 252.9 Hz, CF), 152.6 (C), 146.6 (CH), 145.5 (CH), 138.62 (C), 133.2 (d, *J* = 6.0 Hz, CH), 130.8 (CH), 127.2 (CH), 123.0 (d, *J* = 18.6 Hz, C), 118.4 (C), 106.3 (d, *J* = 27.4 Hz, CH), 45.9 (CH_3), 12.6 (d, *J* = 3.3 Hz, CH_3); ^{19}F NMR (470 MHz, CD_3OD) δ –81.7, –112.4; IR: 2120, 1492, 1225

1106, 1011 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{12}FN_4$ $(M–OTf)^+$: 243.1046, found: 243.1043.

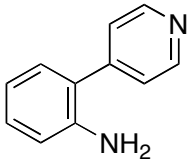
C. Preparation of *para*-Subsituted Pyridinium Biaryl Azides

C1. Preparation of *para*-Substituted Pyridyl Biaryl Amines

General procedure for Suzuki reaction using 4-Pyridineboronic acid. Unless otherwise noted, the biaryl amines were synthesized from substituted 2-bromoanilines and pyridineboronic acid using Suzuki reactions. Yields were not optimized.

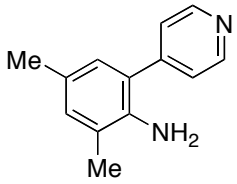


In a dry 100 mL round bottom flask, 4-pyridineboronic acid (1.3 equiv), Na_2CO_3 (4 equiv), and $PdCl_2$(dppf) were dissolved in dioxane (0.2 M), and H_2O (0.5 M). Bromoaniline (1.0 equiv) was then added, and the resulting mixture was heated at 80 °C for 2.5 hours. After cooling, the reaction mixture was diluted with a 1.5 N NaOH aqueous solution and 30 mL of CH_2Cl_2. The aqueous phase was extracted with 3 × 30 mL of CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford brown oil. Purification by MPLC afforded the product.



1.149

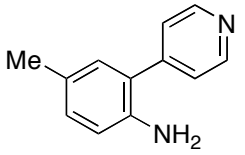
4-(2-Aminophenyl)pyridine (1.149).[71] The general procedure was followed using 1.21 g of 2-bromoaniline (7 mmol), 1.12 g of 4-pyridylboronic acid (9.1 mmol), 2.97 g of Na_2CO_3 (28 mmol), and 0.256 g of $PdCl_2$(dppf) in 35 mL of dioxane and 14 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (1.07 g, 90%). R_f = 0.38 (15:15:70 EtOAc:MeOH:hexane), m.p. = 75-78 °C. Biaryl amine **1.149** has been previously reported by Itoh and Mase:[71] ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.65-8.64 (m, 2H), 7.40 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.19 (t, *J* = 7.7 Hz, 1H), 7.11 (d, *J* = 7.6 Hz, 1H), 6.83 (t, *J* = 7.5 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 3.84 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.3 (CH), 147.6 (C), 143.4 (C), 130.1 (CH), 129.8 (CH), 124.4 (C), 123.9 (CH), 118.9 (CH), 116.1 (CH); IR: 3213, 1593, 1408, 1291, 749 cm^{-1}.



1.150

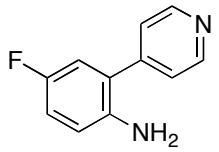
4-(2-Amino-3,5-dimethylphenyl)pyridine (**1.150**). The general procedure was followed using 1.00 g of 2-bromo-4,6-methylaniline (5 mmol), 0.799 g of 4-pyridylboronic acid (6.5 mmol), 2.12 g of Na_2CO_3 (20 mmol), and 0.204 g of $PdCl_2$(dppf) in 25 mL of dioxane and 10 mL of H_2O. Purification of the reaction

mixture using MPLC afforded the product as brown solid (0.560 g, 56%). R_f = 0.35 (15:15:70 EtOAc:MeOH:hexane), m.p. = 102-105 °C. ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.66 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.40 (dd, *J* = 4.4, 1.6 Hz, 2H), 6.95 (s, 1H), 6.82 (s, 1H), 3.61 (s, 2H), 2.26 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.3 (CH), 148.2 (C), 138.9 (C), 131.6 (CH), 128.2 (CH), 127.6 (C), 124.5 (C), 124.1 (CH), 123.1 (C), 20.3 (CH_3), 17.8 (CH_3); IR: 3317, 3212, 1631, 1595, 1473, 1246, 987, 825 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{13}H_{14}N_2$: 198.11570, found: 198.11511.



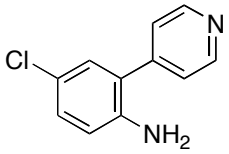
1.151

4-(2-Amino-5-methylphenyl)pyridine (**1.151**). The general procedure was followed using 1.12 g of 2-bromo-4-methylaniline (6 mmol), 0.959 g of 4-pyridylboronic acid (7.8 mmol), 2.54 g of Na_2CO_3 (24 mmol), and 0.220 g of $PdCl_2$(dppf) in 30 mL of dioxane and 12 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as brown solid (1.02 g, 95%). R_f = 0.38 (15:15:70 EtOAc:MeOH:hexane), m.p. = 156-159 °C. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.65 (d, *J* = 4.7 Hz, 2H), 7.41 (d, *J* = 5.0 Hz, 2H), 7.02 (d, *J* = 7.9 Hz, 1H), 6.94 (s, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 3.68 (s, 2H), 2.28 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.3 (CH), 147.7 (C), 140.9 (C), 130.5 (CH), 130.4 (CH), 128.3 (C), 124.5 (C), 123.9 (CH), 116.3 (CH), 20.4 (CH_3); IR: 3214, 1594, 1504, 1300, 1158 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_{12}N_2$: 184.10005, found: 184.09946.



1.152

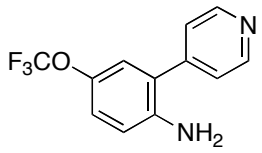
4-(2-Amino-5-fluorophenyl)pyridine (**1.152**). The general procedure was followed using 0.950 g of 2-bromo-4-fluoroaniline (5 mmol), 0.799 g of 4-pyridylboronic acid (6.5 mmol), 2.12 g of Na_2CO_3 (20 mmol), and 0.204 g of $PdCl_2$(dppf) in 25 mL of dioxane and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as brown solid (0.857 g, 91%). R_f = 0.37 (15:15:70 EtOAc:MeOH:hexane), m.p. = 134-137 °C. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.68 (d, *J* = 5.9 Hz, 2H), 7.40 (dd, *J* = 4.7, 1.3 Hz, 2H), 6.92 (td, *J* = 8.4, 2.9 Hz, 1H), 6.86 (dd, *J* = 9.0, 2.9 Hz, 1H), 6.71 (dd, *J* = 8.8, 4.7 Hz, 1H), 3.66 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 156.4 (d, *J* = 238.3 Hz, C), 150.5 (CH), 146.6 (C), 139.5 (C), 125.3 (d, *J* = 7.3 Hz, C), 123.7 (CH), 117.1 (d, *J* = 7.7 Hz, CH), 116.4 (d, *J* = 13.6 Hz, CH), 116.2 (d, *J* = 15.0 Hz, CH); ^{19}F NMR (471 MHz, $CDCl_3$) δ –128.0; IR: 3460, 3316, 1587, 1398, 1176, 894 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{11}H_9FN_2$: 188.07498, found:188.07469.



1.104

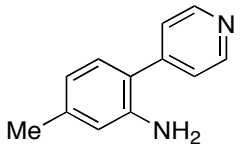
4-(2-Amino-5-chlorophenyl)pyridine (**1.104**). The general procedure was followed using 1.45 g of 2-bromo-4-chloroaniline (7 mmol), 1.12 g of 4-pyridylboronic acid (9.1 mmol), 2.97 g of Na_2CO_3 (28 mmol), and 0.256 g of

$PdCl_2$(dppf) in 35 mL of dioxane and 14 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (1.37 g, 95%). R_f = 0.36 (15:15:70 EtOAc:MeOH:hexane), m.p. = 140-144 °C. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.71 (d, *J* = 6.0 Hz, 2H), 7.40 (d, *J* = 6.0 Hz, 2H), 7.17 (dd, *J* = 8.6, 2.4 Hz, 1H), 7.12 (d, *J* = 2.4 Hz, 1H), 6.72 (d, *J* = 8.6 Hz, 1H), 3.79 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.5 (CH), 146.3 (C), 142.0 (C), 129.54 (CH), 129.48 (CH), 123.7 (CH), 123.5 (C), 121.4 (C), 117.2 (CH); IR: 3197, 1597, 1483, 1400 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{11}H_9ClN_2$: 204.04543, found: 204.04484.



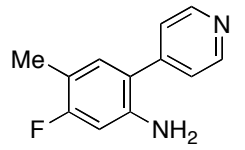
1.153

4-(2-Amino-5-trifluoromethoxyphenyl)pyridine (**1.153**). The general procedure was followed using 1.28 g of 2-bromo-4-trifluoromethoxyaniline (5 mmol), 0.799 g of 4-pyridylboronic acid (6.5 mmol), 2.12 g of Na_2CO_3 (20.0 mmol), and 0.204 g of $PdCl_2$(dppf) in 25 mL of dioxane and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as brown solid (1.18 g, 93%). R_f = 0.37 (15:15:70 EtOAc:MeOH:hexane), m.p. = 95-98 °C. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.70 (d, *J* = 5.9 Hz, 2H), 7.40 (d, *J* = 5.9 Hz, 2H), 7.07 (d, *J* = 8.7 Hz, 1H), 7.00 (s, 1H), 6.75 (d, *J* = 8.7 Hz, 1H), 3.84 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.6 (CH), 146.2 (C), 142.2 (C), 141.4 (C), 124.9 (C), 123.7 (CH), 122.9 (CH), 122.8 (CH), 120.5 (q, *J* = 255 Hz, CF_3), 116.6 (CH); ^{19}F NMR (471 MHz, $CDCl_3$) δ –60.0; IR: 3307, 1597, 1481, 1211, 1141, 831 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_9F_3N_2O$: 254.06671, found: 254.06734.



1.154

4-(2-Amino-4-methylphenyl)pyridine (**1.154**).[72] The general procedure was followed using 0.930 g of 2-bromo-5-methylaniline (5 mmol), 0.799 g of 4-pyridylboronic acid (6.5 mmol), 2.12 g of Na_2CO_3 (20 mmol), and 0.204 g of $PdCl_2$(dppf) in 25 mL of dioxane and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as white solid (0.793 g, 86%). Pyridine **1.155** was previously reported by Shigyo *et al*:[72] R_f = 0.35 (15:15:70 EtOAc:MeOH:hexane), m.p. = 109-111 °C. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.65 (dd, *J* = 4.4, 1.7 Hz, 2H), 7.41 (dd, *J* = 4.4, 1.7 Hz, 2H), 7.03 (d, *J* = 7.7 Hz, 1H), 6.68 (dd, *J* = 7.7, 0.5 Hz, 1H), 6.61 (s, 1H), 3.75 (s, 2H), 2.31 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.3 (CH), 147.7 (C), 143.2 (C), 139.9 (C), 130.0 (CH), 123.9 (CH), 121.8 (C), 120.0 (CH), 116.7 (CH), 21.3 (CH_3); IR: 3322, 1626, 1410, 989, 800 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_{12}N_2$: 184.10005, found: 184.10028.



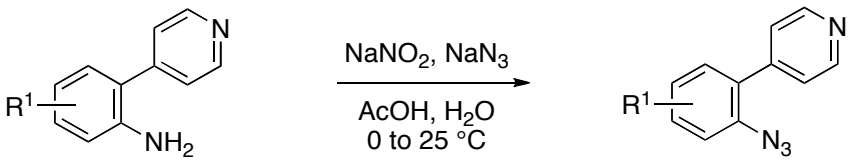
1.155

4-(2-Amino-4-fluoro-5-methylphenyl)pyridine (**1.155**). The general procedure was followed using 1.02 g of 2-bromo-5-fluoro-4-methylaniline (5 mmol), 0.799 g of 4-pyridylboronic acid (6.5 mmol), 2.12 g of Na_2CO_3 (20 mmol), and 0.204 g of

$PdCl_2$(dppf) in 25 mL of dioxane and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as brown solid (0.911 g, 90%). R_f = 0.37 (15:15:70 EtOAc:MeOH:hexane), m.p. = 135-138 °C. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.65 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.37 (dd, *J* = 4.4, 1.6 Hz, 2H), 6.92 (d, *J* = 8.4 Hz, 1H), 6.46 (d, *J* = 11.1 Hz, 1H), 3.75 (s, 2H), 2.19 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.9 (d, *J* = 245.8 Hz, C), 150.4 (CH), 147.0 (C), 142.8 (d, *J* = 11.1 Hz, C), 132.7 (d, *J* = 7.3 Hz, CH), 123.9 (CH), 120.4 (C), 115.0 (d, *J* = 18.8 Hz, C), 102.7 (d, *J* = 25.8 Hz, CH), 13.6 (CH_3); ^{19}F NMR (471 MHz, $CDCl_3$) δ –118.1; IR: 3400, 3174, 1595, 1398, 1255, 1136, 835 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_{11}FN_2$: 202.09063, found: 202.08971.

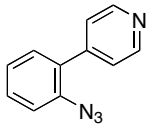
C2. Preparation of *para*-Substituted Pyridyl Biaryl Azides

General procedure for azidation of biaryl amines. Unless otherwise noted, the biaryl azides were synthesized from the corresponding biaryl amines using traditional diazotization/azidation conditions (sodium nitrite and sodium azide). Yields were not optimized.



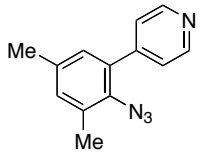
In a 100 mL of round bottom flask, biaryl amine (1.0 equiv) was dissolved in HOAc and H_2O (2:1 v/v, 0.25M) and chilled in an ice bath. $NaNO_2$ (1.4 equiv) was added slowly, then the resulting mixture was stirred at 0 °C for 1.5 hour. NaN_3 (1.5 equiv) was then added slowly, the resulting mixture was warmed up to

ambient temperature, and stirred for 30 minutes. The solution was then diluted with 20 mL of water and 20 mL of CH_2Cl_2, and basified by slow addition of K_2CO_3 until the pH of the reaction mixture was 8. The phases were separated and the aqueous phase was extracted with an additional 2 × 20 mL of CH_2Cl_2. The combined organic phase were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford oil. Purification by MPLC (EtOAc:MeOH:hexane) afforded the product.



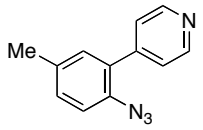
1.156

4-(2-Azidophenyl)pyridine (**1.156**). The general procedure was followed using 0.851 g of biaryl amine **1.149** (5.0 mmol), 0.488 g of $NaNO_2$ (7.5 mmol), and 0.483 g of NaN_3 (7.0 mmol) in 20 mL of AcOH and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (0.903 g, 92%), R_f = 0.23 (3:7 EtOAc:hexane), m.p. = 108-111 °C: ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.63 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.42 (ddd, *J* = 8.0, 7.4, 1.6 Hz, 1H), 7.36 (dd, *J* = 4.4, 1.7 Hz, 2H), 7.31 (dd, *J* = 7.6, 1.6 Hz, 1H), 7.25 (dd, *J* = 8.1, 1.1 Hz, 1H), 7.21 (td, *J* = 7.5, 1.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.7 (CH), 145.8 (C), 137.2 (C), 130.9 (CH), 130.7 (C), 130.1 (CH), 125.2 (CH), 124.2 (CH), 119.0 (CH); IR: 2119, 1591, 1405, 1284, 752 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{11}H_8N_4$ $(M)^+$: 196.0749, found 196.0756.



1.157

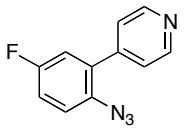
4-(2-Azido-3,5-dimethylphenyl)pyridine (**1.157**). The general procedure was followed using 0.548 g of biaryl amine **1.150** (2.8 mmol), 0.269 g of $NaNO_2$ (3.9 mmol), and 0.274 g of NaN_3 (4.2 mmol) in 12 mL of AcOH and 6 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (0.556 g, 88%), R_f = 0.52 (3:7 EtOAc:hexane), m.p. = 133-136 °C: ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.67 (d, *J* = 6.0 Hz, 2H), 7.38-7.37 (m, 2H), 7.06 (d, *J* = 0.6 Hz, 1H), 6.95 (s, 1H), 2.38 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.9 (CH), 146.6 (C), 135.8 (C), 133.3 (C), 132.9 (C), 132.8 (C), 132.3 (CH), 129.1 (CH), 124.0 (CH), 20.8 (CH_3), 18.1 (CH_3); IR: 2119, 1595, 1402, 1308, 842 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{13}H_{12}N_4$ $(M)^+$: 224.10619, found: 224.10653.



1.158

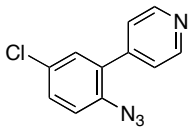
4-(2-Azido-5-methylphenyl)pyridine (**1.158**). The general procedure was followed using 0.986 g of biaryl amine **1.151** (5.4 mmol), 0.524 g of $NaNO_2$ (7.6 mmol), and 0.527 g of NaN_3 (8.1 mmol) in 22 mL of AcOH and 11 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (1.04 g, 92%), R_f = 0.50 (3:7 EtOAc:hexane), m.p. = 130-135 °C: ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.64 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.37 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.25 (dt, *J* = 8.3, 1.0 Hz, 1H), 7.17-7.14 (m, 2H), 2.38 (s, 3H); ^{13}C NMR (126

MHz, $CDCl_3$): δ 149.6 (CH), 146.0 (C), 135.1 (C), 134.5 (C), 131.4 (CH), 130.7 (CH), 130.5 (C), 124.2 (CH), 118.9 (CH), 20.8 (CH_3); IR: 2118, 1597, 1482, 1284, 1157 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_{10}N_4$ $(M)^+$: 210.09054, found: 210.09111.



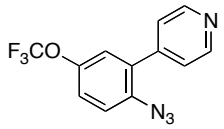
1.159

4-(2-Azido-5-fluorophenyl)pyridine (**1.159**). The general procedure was followed using 0.840 g of biaryl amine **1.152** (4.5 mmol), 0.435 g of $NaNO_2$ (6.3 mmol), and 0.442 g of NaN_3 (6.8 mmol) in 20 mL of AcOH and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (0.370 g, 38%), R_f = 0.53 (3:7 EtOAc:hexane): ^{1}H NMR (500 MHz; $CDCl_3$), m.p. = 130-133 °C: δ 8.67 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.37 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.24 (dt, *J* = 9.4, 5.0 Hz, 1H), 7.16 (ddd, *J* = 8.8, 7.6, 2.9 Hz, 1H), 7.07 (dd, *J* = 8.7, 2.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.7 (d, *J* = 246.0 Hz, C), 149.8 (CH), 144.7 (C), 133.2 (C), 132.3 (d, *J* = 7.8 Hz, C), 124.0 (CH), 120.4 (d, *J* = 7.5 Hz, CH), 117.6 (d, *J* = 24.0 Hz, CH), 116.8 (d, *J* = 22.7 Hz, CH); ^{19}F NMR (471 MHz, $CDCl_3$) δ –118.6; IR: 2120, 1596, 1480, 1194 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{11}H_7FN_4$ $(M)^+$: 214.06547, found: 214.06556.



1.105

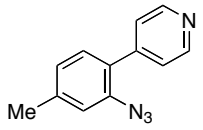
4-(2-Azido-5-fluorophenyl)pyridine (**1.105**). The general procedure was followed using 1.023 g of biaryl amine **1.104** (5.0 mmol), 0.488 g of $NaNO_2$ (7.5 mmol), and 0.483 g of NaN_3 (7.0 mmol) in 20 mL of AcOH and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (1.21 g, 99%), R_f = 0.57 (3:7 EtOAc:hexane), m.p. = 157-160 °C: ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.65 (dq, *J* = 4.4, 1.4 Hz, 2H), 7.39 (ddd, *J* = 8.6, 3.2, 2.5 Hz, 1H), 7.33 (dq, *J* = 4.5, 1.5 Hz, 2H), 7.30 (t, *J* = 2.7 Hz, 1H), 7.18 (dd, *J* = 8.6, 3.2 Hz, 1H).; ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.8 (CH), 144.5 (C), 135.9 (C), 132.1 (C), 130.7 (CH), 130.5 (C), 129.9 (CH), 124.0 (CH), 120.2 (CH); IR: 2114, 1473, 1302, 1095 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{11}H_7ClN_4$: 230.03592, found: 230.03663.



1.160

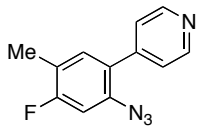
4-(2-Azido-5-trifluoromethoxyphenyl)pyridine (**1.160**). The general procedure was followed using 1.16 g of biaryl amine **1.153** (4.6 mmol), 0.442 g of $NaNO_2$ (6.4 mmol), and 0.449 g of NaN_3 (6.9 mmol) in 20 mL of AcOH and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (1.07 g, 83%), R_f = 0.53 (3:7 EtOAc:hexane), m.p. = 85-90 °C: ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.69 (dd, *J* = 4.9, 1.1 Hz, 2H), 7.38-7.37 (m, 2H), 7.34-7.28 (m, 2H), 7.22 (d, *J* = 1.8 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.9 (CH), 146.0 (C), 144.4 (C), 136.1 (C), 132.1 (C), 124.0 (CH), 123.5 (CH), 122.6 (CH), 120.4 (q, *J* = 255 Hz, CF_3), 120.2 (CH); ^{19}F NMR (471 MHz, $CDCl_3$) δ –

59.7; IR: 2125, 1597, 1482, 1255, 1144 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_7F_3N_4O$ $(M)^+$: 280.05720, found: 280.05632.



1.161

4-(2-Azido-4-methylphenyl)pyridine (**1.161**). The general procedure was followed using 0.793 g of biaryl amine **1.154** (4.3 mmol), 0.414 g of $NaNO_2$ (6.0 mmol), and 0.423 g of NaN_3 (6.5 mmol) in 20 mL of AcOH and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (1.07 g, 83%), R_f = 0.55 (3:7 EtOAc:hexane), m.p. = 111-115 °C: ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.63 (dd, *J* = 4.6, 1.5 Hz, 2H), 7.38 (dd, *J* = 4.5, 1.6 Hz, 2H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.08 (s, 1H), 7.05 (dt, *J* = 7.8, 0.7 Hz, 1H), 2.43 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.6 (CH), 145.8 (C), 140.5 (C), 137.0 (C), 130.7 (CH), 127.9 (C), 126.2 (CH), 124.2 (CH), 119.5 (CH), 21.3 (CH_3); IR: 2096, 1600, 1398, 1284, 810 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_{10}N_4$ $(M)^+$: 210.09054, found: 210.08982.



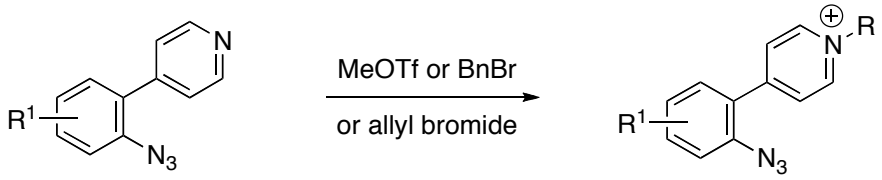
1.162

4-(2-Azido-4-fluoro-5-methylphenyl)pyridine (**1.162**). The general procedure was followed using 0.898 g of biaryl amine **1.155** (4.4 mmol), 0.428 g of $NaNO_2$ (6.2 mmol), and 0.429 g of NaN_3 (6.6 mmol) in 20 mL of AcOH and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as

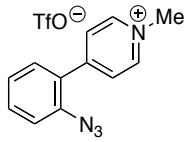
yellow solid (0.890 g, 89%), R_f = 0.50 (3:7 EtOAc:hexane), m.p. = 131-134 °C: ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.64 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.34 (dd, *J* = 4.4, 1.6 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.95 (d, *J* = 9.8 Hz, 1H), 2.30 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.6 (d, *J* = 249.7 Hz, C), 149.7 (CH), 145.1 (C), 136.2 (C), 133.6 (d, *J* = 5.5 Hz, CH), 126.5 (d, *J* = 3.6 Hz, C), 124.2 (CH), 122.2 (d, *J* = 18.4 Hz, C), 106.1 (d, *J* = 25.9 Hz, CH), 14.1 (CH_3); ^{19}F NMR (471 MHz, $CDCl_3$) δ –115.3; IR: 2105, 1595, 1324, 1259, 989, 816 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_9FN_4$ $(M)^+$: 228.08112, found: 228.08115.

C3. Preparation of *para*-Substituted Pyridinium Ions

General procedure for alkylation of *para*-substituted pyridinium ions. Unless otherwise noted, the pyridinium ions were synthesis from the corresponding substituted biaryl azide. Yields were not optimized.

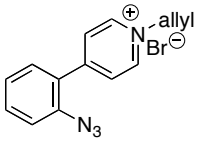


In a dry 25 mL round bottom flask, biaryl azide was dissolved in dry CH_2Cl_2 (0.5 M), MeOTf (1.1 equiv) or allyl bromide (1.1 equiv) or benzyl bromide (1.0 equiv) was then added dropwise via syringe over 10 min, and the resulting solution was allowed to stir at ambient temperature overnight. The volatile was removed *in vacuo* to afford the product that was used directly without further purification.



1.59

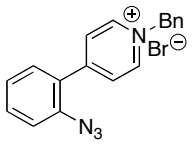
1-Methyl-4-(2-azidophenyl)pyridinium triflate (**1.59**). The general procedure was followed using 0.883 g of biaryl azide **1.156** (4.5 mmol) and 0.543 mL of methyl triflate (4.95 mmol) in 9 mL of CH_2Cl_2 afforded the product as pale yellow solid (1.59 g, 98%): ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.89 (s, 2H), 8.08 (s, 2H), 7.58-7.55 (m, 1H), 7.47-7.45 (m, 1H), 7.30-7.27 (m, 2H), 4.45 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 154.5 (C), 144.9 (CH), 138.1 (C), 133.0 (CH), 131.2 (CH), 128.2 (CH), 126.1 (C), 125.9 (CH), 119.4 (CH), 48.1 (CH_3); IR: 2138, 1637, 1255, 1148, 1026, 781, 634 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{13}N_4$ $(M - OTf)^+$: 225.1140, found: 225.1145.



1.60

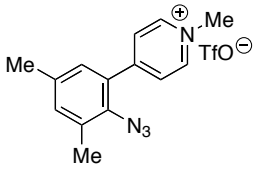
1-Allyl-4-(2-azidophenyl)pyridinium bromide (**1.60**). The same procedure as pyridinium **1b** was followed using 0.490 g of biaryl azide **1.156** (2.5 mmol) and 0.238 mL of allyl bromide (2.75 mmol) in 10 mL of CH_3CN (0.5 M) afforded the product as yellow solid (0.685 g, 86%): ^{1}H NMR (500 MHz; CD_3OD): δ 8.97 (d, *J* = 6.6 Hz, 2H), 8.32 (d, *J* = 6.6 Hz, 2H), 7.70-7.66 (m, 2H), 7.51 (d, *J* = 8.1 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 6.27-6.19 (m, 1H), 5.60-5.57 (m, 2H), 5.30 (d, *J* = 6.4 Hz, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 155.3 (C), 143.9 (CH), 138.3 (C), 132.8 (CH), 131.0 (CH), 130.5 (CH), 128.2 (CH), 126.4 (C), 125.5 (CH), 122.3

(CH_2), 119.4 (CH), 62.6 (CH_2); IR: 2119, 1630, 1483, 1291, 1154, 772 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{14}H_{13}N_4$ $(M - Br)^+$: 237.1140, found: 237.1138.



1.61

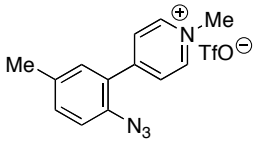
1-Benzyl-4-(2-azidophenyl)pyridinium bromide (**1.61**). The same procedure as pyridinium **1b** was followed using 0.490 g of biaryl azide **1.156** (2.5 mmol) and 0.297 mL of benzyl bromide (2.5 mmol) in 10 mL of CH_3CN (0.5 M) afforded the product as gray solid (0.828 g, 90%): ^1H NMR (500 MHz; CD_3OD): δ 9.07 (d, *J* = 6.5 Hz, 2H), 8.30 (d, *J* = 6.4 Hz, 2H), 7.69-7.64 (m, 2H), 7.58-7.57 (m, 2H), 7.50-7.48 (m, 4H), 7.39 (t, *J* = 7.6 Hz, 1H), 5.88 (s, 2H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 155.3 (C), 143.8 (CH), 138.3 (C), 133.4 (C), 132.8 (CH), 131.1 (CH), 129.7 (CH), 129.4 (CH), 128.8 (CH), 128.3 (CH), 126.4 (C), 125.5 (CH), 119.4 (CH), 63.7 (CH_2); IR: 2122, 1633, 1437, 1288, 1160 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{18}H_{15}N_4$ $(M - Br)^+$: 287.1297, found: 287.1300.



1.62

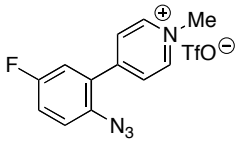
1-Methyl-4-(2-azido-3,5-dimethylphenyl)pyridinium triflate (**1.62**). The general procedure was followed using 0.538 g of biaryl azide **1.157** (2.4 mmol) and 0.427 mL of methyl triflate (2.6 mmol) in 10 mL of CH_2Cl_2 afforded the

product as yellow solid (0.857 g, 92%): ^{1}H NMR (500 MHz; CD_3OD): δ 8.89 (d, *J* = 6.1 Hz, 2H), 8.20 (d, *J* = 6.0 Hz, 2H), 7.30 (s, 1H), 7.26 (s, 1H), 4.43 (s, 3H), 2.47 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 155.7 (C), 144.8 (CH), 137.0 (C), 134.9 (CH), 133.8 (C), 133.1 (C), 129.4 (C), 129.0 (CH), 127.8 (CH), 47.0 (CH_3), 19.3 (CH_3), 16.7 (CH_3); IR: 2134, 1637, 1257, 1152, 1027 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{14}H_{15}N_4$ $(M - OTf)^+$: 239.1297, found: 239.1293.



1.63

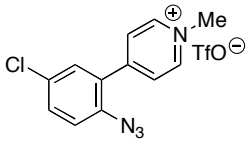
1-Methyl-4-(2-azido-5-methylphenyl)pyridinium triflate (**1.63**). The general procedure was followed using 1.06 g of biaryl azide **1.158** (5.0 mmol) and 0.963 mL of methyl triflate (5.5 mmol) in 10 mL of CH_2Cl_2 afforded the product as yellow solid (1.67 g, 89%): ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.89 (d, *J* = 6.8 Hz, 2H), 8.08 (d, *J* = 6.8 Hz, 2H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.27-7.26 (m, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 4.46 (s, 3H), 2.37 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 154.7 (C), 144.8 (CH), 136.0 (C), 135.3 (C), 133.7 (CH), 131.6 (CH), 128.1 (CH), 125.9 (C), 119.3 (CH), 48.0 (CH_3), 20.7 (CH_3); IR: 2118, 1643, 1252, 1151, 1026 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{13}N_4$ $(M - OTf)^+$: 225.1140, found: 225.1142.



1.64

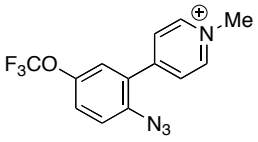
1-Methyl-4-(2-azido-5-fluorophenyl)pyridinium triflate (**1.64**). The general procedure was followed using 0.352 g of biaryl azide **1.159** (1.6 mmol) and 0.295

mL of methyl triflate (1.8 mmol) in 10 mL of CH_2Cl_2 afforded the product as beige solid (0.538 g, 89%): ^{1}H NMR (500 MHz; CD_3OD): δ 8.90 (d, *J* = 5.7 Hz, 2H), 8.26 (d, *J* = 5.5 Hz, 2H), 7.52 (dd, *J* = 8.4, 4.6 Hz, 1H), 7.48-7.43 (m, 2H), 4.43 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 159.9 (d, *J* = 245.0 Hz, C), 153.3 (C), 144.9 (CH), 134.3 (C), 127.96 (CH), 127.86 (d, *J* = 8.4 Hz, C), 121.4 (d, *J* = 8.6 Hz, CH), 119.3 (d, *J* = 22.6 Hz, CH), 117.4 (d, *J* = 25.3 Hz, CH), 47.1 (CH_3); ^{19}F NMR (471 MHz, $CDCl_3$) δ –89.3, –127.6; IR: 2134, 1642, 1255, 1135, 1028 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{12}H_{10}FN_4$ $(M - OTf)^+$: 229.0889, found: 229.0893.



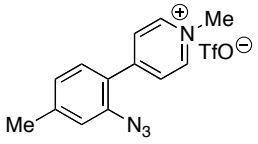
1.65

1-Methyl-4-(2-azido-5-chlorophenyl)pyridinium triflate (**1.65**). The general procedure was followed using 0.988 g of biaryl azide **1.105** (4.4 mmol) and 0.531 mL of methyl triflate (4.84 mmol) in 9 mL of CH_2Cl_2 afforded the product as yellow solid (1.70 g, 99%): ^{1}H NMR (500 MHz; CD_3OD) δ 8.91-8.90 (m, 2H), 8.26 (d, *J* = 2.9 Hz, 2H), 7.69-7.67 (m, 2H), 7.52-7.50 (m, 1H), 4.44 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD) δ 153.2 (C), 144.9 (CH), 137.1 (C), 132.2 (CH), 130.59 (C), 130.42 (CH), 127.97 (CH), 127.90 (C), 121.1 (CH), 47.3 (CH_3); IR: 2130, 1643, 1254, 1143 1028 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{12}H_{10}ClN_4$ (M-OTf): 245.0594, found: 245.0593.



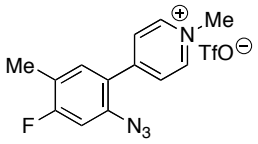
1.66

1-Methyl-4-(2-azido-5-trifluoromethoxyphenyl)pyridinium triflate (**1.66**). The general procedure was followed using 1.06 g of biaryl azide **1.160** (3.8 mmol) and 0.690 mL of methyl triflate (4.2 mmol) in 10 mL of CH_2Cl_2 afforded the product as beige solid (1.39 g, 82%): ^{1}H NMR (500 MHz; CD_3OD): δ 8.92 (d, *J* = 5.4 Hz, 2H), 8.26 (d, *J* = 5.5 Hz, 2H), 7.60 (s, 3H), 4.45 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 153.0 (C), 145.9 (C), 145.0 (CH), 137.4 (C), 128.05 (CH), 127.87 (C), 125.0 (CH), 123.6 (CH), 121.2 (CH), 120.5 (q, *J* = 256 Hz, CF_3), 47.1 (CH_3); ^{19}F NMR (471 MHz, $CDCl_3$) δ –61.4, –81.7; IR: 2140, 1641, 1247, 1146, 1027 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{10}F_3N_4O$ (M-OTf)$^+$: 295.0807, found: 295.0813.



1.67

1-Methyl-4-(2-azido-4-methylphenyl)pyridinium triflate (**1.67**). The general procedure was followed using 0.827g of biaryl azide **1.161** (3.9 mmol) and 0.706 mL of methyl triflate (4.3 mmol) in 10 mL of CH_2Cl_2 afforded the product as orange solid (1.45 g, 99%): ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.83 (d, *J* = 6.8 Hz, 2H), 8.24 (d, *J* = 6.8 Hz, 2H), 7.54 (d, *J* = 7.9 Hz, 1H), 7.30 (s, 1H), 7.22 (d, *J* = 7.8 Hz, 1H), 4.40 (s, 3H), 2.47 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 154.6 (C), 144.6 (CH), 144.1 (C), 138.1 (C), 130.9 (CH), 127.5 (CH), 126.5 (CH), 123.7 (C), 119.8 (CH), 46.8 (CH_3), 20.0 (CH_3); IR: 2112, 1641, 1255, 1146, 1024, 823 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{13}N_4$ (M – OTf)$^+$: 225.1140, found: 225.1135.



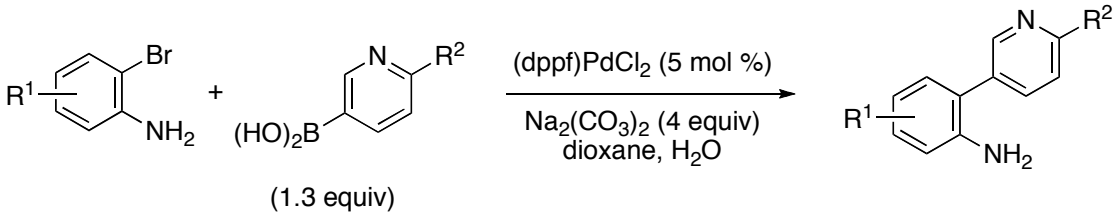
1.68

1-Methyl-4-(2-azido-4-fluoro-5-methylphenyl)pyridinium triflate (**1.68**). The general procedure was followed using 0.879 g of biaryl azide **1.162** (3.9 mmol) and 0.706 mL of methyl triflate (4.3 mmol) in 10 mL of CH_2Cl_2 afforded the product as beige solid (1.34 g, 88%): ^{1}H NMR (500 MHz; CD_3OD): δ 8.85 (d, *J* = 6.7 Hz, 2H), 8.23 (d, *J* = 6.8 Hz, 2H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.25 (d, *J* = 10.0 Hz, 1H), 4.41 (s, 3H), 2.34 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 163.2 (d, *J* = 253.1 Hz, C), 153.8 (C), 144.7 (CH), 137.9 (d, *J* = 9.4 Hz, C), 134.0 (d, *J* = 6.8 Hz, CH), 127.7 (CH), 122.9 (d, *J* = 17.7 Hz, C), 122.5 (d, *J* = 3.4 Hz, C), 106.5 (d, *J* = 26.8 Hz, CH), 46.9 (CH_3), 12.5 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –79.2, –110.8; IR: 2125, 1635, 1261, 1147, 1018, 845 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{12}FN_4$ $(M - OTf)^+$: 243.1046, found: 243.1046.

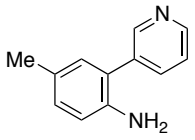
D. Preparation of *meta*-Subsituted Pyridinium Biaryl Azides

D1. Preparation of *meta*-Substituted Pyridyl Biaryl Amines

General procedure for preparation of biaryl amines. Unless otherwise noted, the biaryl amines were synthesized from substituted 2-bromoanilines and pyridineboronic acid using Suzuki reactions. Yields were not optimized.



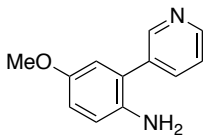
In a dry 100 mL round bottom flask, pyridineboronic acid (1.3 equiv), Na_2CO_3 (4 equiv), and $PdCl_2$(dppf) were dissolved in dioxane (0.2 M) and H_2O (0.5 M). Bromoaniline (1.0 equiv) was then added, and the resulting mixture was heated at 80 °C for 2.5 hours. After cooling, the reaction mixture was diluted with a 1.5 N aqueous solution of NaOH and 30 mL of CH_2Cl_2. The phases were separated, and the aqueous phase was extracted with an additional 3 × 30 mL of CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford brown oil. Purification by MPLC afforded the product. The syntheses of pyridines **1.163** – **1.170** were previously reported us.[28]



1.163

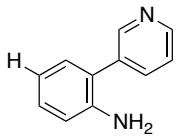
3-(2-Amino-5-methylphenyl)pyridine (**1.163**).[28] The general procedure was followed using 0.930 g of 2-bromo-4-methylaniline (5 mmol), 0.799 g of 3-pyridylboronic acid (6.5 mmol), 2.12 g of Na_2CO_3 (20 mmol), and 0.183 g of $PdCl_2$(dppf) in 25 mL of dioxane and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as brown oil (0.907 g, 99%), R_f = 0.37 (15:15:70 EtOAc:MeOH:hexane). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.71 (d, *J* = 0.8 Hz, 1H), 8.59-8.58 (m, 1H), 7.80 (dd, *J* = 7.8, 1.7 Hz, 1H), 7.37-7.35 (m, 1H),

7.02 (d, *J* = 8.1 Hz, 1H), 6.93 (s, 1H), 6.71 (d, *J* = 8.1 Hz, 1H), 3.61 (s, 2H), 2.29 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 150.1 (CH), 148.4 (CH), 141.3 (C), 136.5 (CH), 135.4 (C), 131.0 (CH), 129.9 (CH), 128.2 (C), 123.8 (C), 123.5 (CH), 116.1 (CH), 20.4 (CH_3); IR (thin film) 3420, 1630, 1479, 865, 713, 625 cm^{-1}.



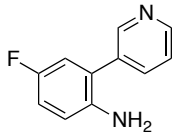
1.164

3-(2-Amino-5-methoxyphenyl)pyridine (**1.164**).[28] The general procedure was followed using 1.01 g of 2-bromo-4-methoxyaniline (5 mmol), 0.799 g of 3-pyridylboronic acid (6.5 mmol), 2.12 g of Na_2CO_3 (20 mmol), and 0.183 g of $PdCl_2$(dppf) in 25 mL of dioxane and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as brown solid (1.00 g, 100%) R_f = 0.39 (15:15:70 EtOAc:MeOH:hexane), m.p. = 90-94 °C: ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.72 (s, 1H), 8.60 (d, *J* = 3.9 Hz, 1H), 7.82-7.80 (m, 1H), 7.37 (t, *J* = 6.1 Hz, 1H), 6.81 (dd, *J* = 8.5, 2.1 Hz, 1H), 6.74 (d, *J* = 8.7 Hz, 1H), 6.70 (d, *J* = 2.1 Hz, 1H), 3.77 (s, 3H), 3.46 (s, 2H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 152.9 (C), 150.1 (CH), 148.6 (CH), 137.4 (C), 136.5 (CH), 135.2 (C), 124.9 (C), 123.5 (CH), 117.3 (CH), 115.8 (CH), 115.3 (CH), 55.9 (CH_3). IR: 3401, 1642, 1493, 1409, 1281, 1037, 815, 710 cm^{-1}.



1.165

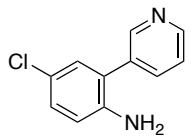
3-(2-Aminophenyl)pyridine (**1.165**).[28] The general procedure was followed using 1.49 g of 2-bromoaniline (8 mmol), 1.28 g of 3-pyridylboronic acid (10.4 mmol), 3.39 g of Na_2CO_3 (32 mmol), and 0.293 g of $PdCl_2$(dppf) in 40 mL of dioxane and 16 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as brown solid (1.38 g, 99 %) R_f = 0.26 (10:5:85 EtOAc:MeOH:hexane): ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.70 (d, *J* = 1.2 Hz, 1H), 8.57 (d, *J* = 4.8 Hz, 1H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.34 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.18 (t, *J* = 7.7 Hz, 1H), 7.08 (d, *J* = 7.5 Hz, 1H), 6.83 (t, *J* = 7.4 Hz, 1H), 6.76 (d, *J* = 8.0 Hz, 1H), 3.77 (s, 2H). ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.1 (CH), 148.5 (CH), 143.9 (C), 136.6 (CH), 135.3 (C), 130.6 (CH), 129.4 (CH), 123.7 (C), 123.6 (CH), 118.9 (CH), 115.9 (CH). IR 3213, 1593, 1291, 749, 616 cm^{-1}.



1.166

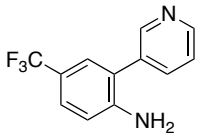
3-(2-Amino-5-fluorophenyl)pyridine (**1.166**).[28] The general procedure was followed using 0.950 g of 2-bromo-4-fluoroaniline (5 mmol), 0.799 g of 3-pyridylboronic acid (6.5 mmol), 2.12 g of Na_2CO_3 (20 mmol), and 0.183 g of $PdCl_2$(dppf) in 25 mL of dioxane and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (0.898 g, 95%) R_f = 0.40 (15:15:70 EtOAc:MeOH:hexane), m.p. = 93-96 °C. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.70 (d, *J* = 1.4, 1H), 8.62-8.61 (m, 1H), 7.79 (dd, *J* = 7.8, 2.1, 1H), 7.40-7.37 (m, 1H), 6.94-6.90 (m, 1H), 6.85 (dt, *J* = 9.0, 2.2, 1H), 6.72 (dd, *J* = 8.7, 4.8, 1H), 3.59 (s, 2H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 156.3 (d, *J* = 237 Hz, C),

149.9 (CH), 148.9 (CH), 140.0 (C), 136.4 (CH), 134.4 (C), 124.7 (d, *J* = 7.1 Hz, C), 123.7 (CH), 116.8 (CH), 116.76 (d, *J* = 33.4, CH), 115.9 (d, *J* = 22.2Hz, CH); ^{19}F NMR (282 MHz, $CDCl_3$) δ –126.7; IR (thin film) 3314, 1639, 1496, 1405, 1168, 888, 706 cm^{-1}.



1.167

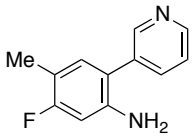
3-(2-Amino-5-chlorophenyl)pyridine (**1.167**).[28] The general procedure was followed using 1.45 g of 2-bromo-4-chloroaniline (7 mmol), 1.12 g of 3-pyridylboronic acid (9.1 mmol), 2.97 g of Na_2CO_3 (28 mmol), and 0.256 g of $PdCl_2$(dppf) in 35 mL of dioxane and 14 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (1.37 g, 95%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.68 (d, *J* = 1.5 Hz, 1H), 8.61 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.77 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.38 (ddd, *J* = 8.0, 5.0, 0.5 Hz, 1H), 7.14 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.08 (d, *J* = 2.0 Hz, 1H), 6.71 (d, *J* = 8.5 Hz, 1H), 3.72 (s, 2H); ^{13}C NMR (125 MHz; $CDCl_3$): δ 149.9 (CH), 149.0 (CH), 142.4 (C), 136.5 (CH), 134.1 (C), 130.0 (CH), 129.1 (CH), 125.0 (C), 123.7 (CH), 123.5 (C), 117.0 (CH).



1.168

3-(2-Amino-5-trifluoromethylphenyl)pyridine (**1.168**).[28] The general procedure was followed using 0.720 g of 2-bromo-4-trifluoromethylaniline (3 mmol), 0.479 g of 3-pyridylboronic acid (3.9 mmol), 1.27 g of Na_2CO_3 (12 mmol), and 0.10 g of

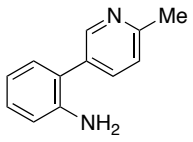
$PdCl_2$(dppf) in 15 mL of dioxane and 6 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as brown oil (0.695 g, 97%). ^{1}H NMR (500 MHz; CDCl3): δ 8.70 (s, 1H), 8.65-8.63 (m, 1H), 7.79-7.76 (m, 1H), 7.43-7.40 (m, 2H), 7.34 (s, 1H), 6.81 (dd, *J* = 8.1, 4.8 Hz, 1H), 4.05 (s, 2H); ^{13}C NMR (125 MHz, CDCl3): δ 150.0 (CH), 149.2 (CH), 146.8 (C), 136.6 (CH), 133.9 (C), 127.8 (t, J_{CF} = 3.5 Hz, CH), 126.5 (d, J_{CF} = 3.2 Hz, CH), 124.6 (q, J_{CF} = 271.9 Hz, CF_3), 123.8 (CH), 123.1 (C), 120.7-120.2 (m, C), 115.2 (CH); ^{19}F NMR (282 MHz, $CDCl_3$) δ –61.8; IR (thin film) 3156, 1323, 1264, 1094, 712, 617 cm^{-1}.



1.169

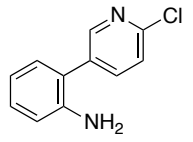
3-(2-Amino-4-fluoro-5-methylphenyl)pyridine (**1.169**).[28] The general procedure was followed using 1.22 g of 2-bromo-5-fluoro-4-methylaniline (6 mmol), 0.959 g of 3-pyridylboronic acid (7.8 mmol), 2.54 g of Na_2CO_3 (24 mmol), and 0.219 g of $PdCl_2$(dppf) in 30 mL of dioxane and 12 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as brown solid (1.15 g, 95%) R_f = 0.44 (15:15:70 EtOAc:MeOH:hexane), m.p. = 86-90 °C. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.65 (d, *J* = 1.5 Hz, 1H), 8.57 (dd, *J* = 4.7, 1.4 Hz, 1H), 7.74 (dt, *J* = 7.8, 1.8 Hz, 1H), 7.34 (dd, *J* = 7.6, 4.9 Hz, 1H), 6.88 (d, *J* = 8.4 Hz, 1H), 6.45 (d, *J* = 11.1 Hz, 1H), 3.70 (s, 2H), 2.14 (d, *J* = 14.4 Hz, 3H). ^{13}C NMR (125 MHz; $CDCl_3$): δ 161.8 (d, J_{CF} = 244.1 Hz, C), 150.2 (CH), 148.5 (CH), 143.1 (d, J_{CF} = 11.1 Hz, C), 136.6 (CH), 134.6 (C), 133.1 (d, *J* = 6.2 Hz, CH), 123.6 (CH), 119.7 (C), 114.7 (d, *J* = 18.3 Hz, C), 102.6 (d, *J* = 25.7 Hz, CH), 13.6 (CH_3); ^{19}F NMR

(282 MHz, $CDCl_3$) δ –117.6; IR (thin film) 3428, 1626, 1398, 1125, 829, 709, 559 cm^{-1}, HRMS (EI) *m / z* calcd for $C_{12}H_{11}FN_2$ $(M)^+$: 202.0906, found 202.0913.



1.170

3-(2-Aminophenyl)-6-methylpyridine (**1.170**).[28] The general procedure was followed using 0.860 g of 2-bromoaniline (5 mmol), 0.890 g of 3-pyridyl-6-methylboronic acid (6.5 mmol), 2.12 g of Na_2CO_3 (20 mmol), and 0.183 g of $PdCl_2$(dppf) in 25 mL of dioxane and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (0.767 g, 83%) R_f = 0.40 (15:15:70 EtOAc:MeOH:hexane). ^1H NMR (500 MHz; $CDCl_3$): δ 8.59-8.59 (m, 1H), 7.69 (dd, *J* = 7.9, 2.3 Hz, 1H), 7.23 (d, *J* = 7.9 Hz, 1H), 7.18 (td, *J* = 7.7, 1.5 Hz, 1H), 7.09 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.84 (td, *J* = 7.4, 1.1 Hz, 1H), 6.77 (d, *J* = 8.0 Hz, 1H), 3.71 (s, 2H), 2.60 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.2 (C), 149.3 (CH), 143.9 (C), 136.9 (CH), 132.2 (C), 130.6 (CH), 129.1 (CH), 123.9 (C), 123.2 (CH), 118.9 (CH), 115.8 (CH), 24.3(CH_3); IR: 3320, 1626, 1479, 1296, 1002, 753 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_{12}N_2$ $(M)^+$: 184.1000, found: 184.0987.



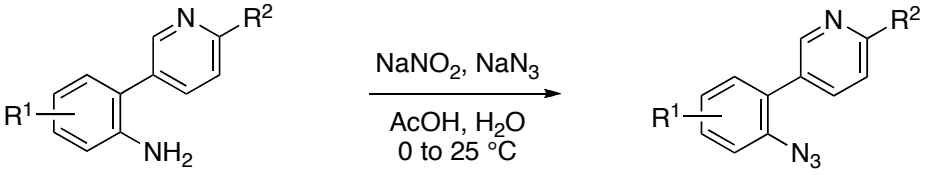
1.171

3-(2-Aminophenyl)-6-chloropyridine (**1.171**). The general procedure was followed using 1.032 g of 2-bromoaniline (6 mmol), 1.227 g of 6-chloro-3-

pyridinylboronic acid (7.8 mmol), 2.54 g of Na_2CO_3 (24 mmol), and 0.220 g of $PdCl_2$(dppf) in 30 mL of dioxane and 12 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (0.291 g, 24%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.49 (d, *J* = 2.5 Hz, 1H), 7.79 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.40 (dd, *J* = 8.0, 0.5 Hz, 1H), 7.21 (td, *J* = 8.0, 1.5 Hz, 1H), 7.08 (dd, *J* = 8.0, 1.5 Hz, 1H), 6.85 (td, *J* = 7.5, 1.0 Hz, 1H), 6.79 (dd, *J* = 8.0, 1.0 Hz, 1H), 3.70 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.2 (C), 149.9 (CH), 143.7 (C), 139.4 (CH), 134.2 (C), 130.5 (CH), 129.8 (CH), 124.3 (CH), 122.4 (C), 119.1 (CH), 116.1 (CH).

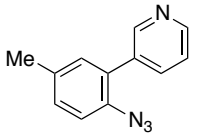
D2. Preparation of *meta*-Substituted Pyridyl Biaryl Azides

General procedure for azidation of biaryl azides. Unless otherwise noted, the biaryl azides were synthesized from the corresponding biaryl amines using traditional diazotization/azidation conditions (sodium nitrite and sodium azide). Yields were not optimized.



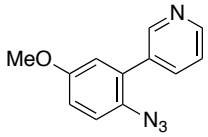
In a 100 mL of round bottom flask, biaryl amine (1.0 equiv) was dissolved in HOAc and H_2O (2:1 v/v, 0.25 M) and chilled in an ice bath. $NaNO_2$ (1.4 equiv) was added slowly, then the resulting mixture was stirred at 0 °C for 1.5 hour. NaN_3 (1.5 equiv) was then added slowly, the resulting mixture was warmed up to ambient temperature, and stirred for 30 minutes. The solution was then diluted

with 20 mL of water and 20 mL of CH_2Cl_2, and basified by slow addition of K_2CO_3 until the mixture reached a pH of 8. The phases were separated and the aqueous phase was extracted with an additional 2 × 20 mL of CH_2Cl_2. The combined organic phase were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford oil. Purification by MPLC (EtOAc:MeOH:hexanes) afforded the product. We have previously reported the syntheses of **1.172** – **1.179**.[28]



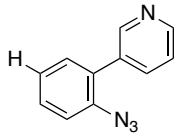
1.172

3-(2-Azido-5-methylphenyl)pyridine (**1.172**).[28] The general procedure was followed using 0.907 g of biaryl amine **1.163** (5 mmol), 0.483 g of $NaNO_2$ (7 mmol), and 0.488 g of NaN_3 in 20 mL of AcOH and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (0.752 g, 72%). R_f = 0.45 (15:15:70 EtOAc:MeOH:hexane), m.p. = 36 – 39 °C: ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.68 (d, *J* = 2.1 Hz, 1H), 8.59 (dd, *J* = 3.4, 1.4 Hz, 1H), 7.78 (ddd, *J* = 7.8, 1.7, 0.7 Hz, 1H), 7.36-7.33 (m, 1H), 7.26-7.24 (m, 1H), 7.18 (d, *J* = 8.1 Hz, 1H), 7.15 (s, 1H), 2.39 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 150.1 (CH), 148.6 (CH), 136.8 (CH), 135.0 (C), 134.7 (C), 134.0 (C), 131.7 (CH), 130.2 (CH), 129.8 (C), 122.9 (CH), 118.8 (CH), 20.9 (CH_3); IR: 2060, 1493, 1259, 748, 529 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_{10}N_4$ $(M)^+$: 210.0905, found: 210.0896.



1.173

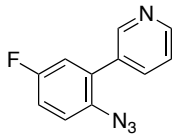
3-(2-Azido-5-methoxyphenyl)pyridine (**1.173**).[28] The general procedure was followed using 1.00 g of biaryl amine **1.164** (5 mmol), 0.483 g of $NaNO_2$ (7 mmol), and 0.488 g of NaN_3 (7.5 mmol) in 20 mL of AcOH and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (0.889 g, 79 %), m.p. = 65 – 67 °C. ^{1}H NMR (500 MHz; $CDCl_3$): 8.68 (td, *J* = 2.5, 0.8 Hz, 1H), 8.59 (dt, *J* = 4.8, 2.0 Hz, 1H), 7.78-7.76 (m, 1H), 7.33 (ddd, *J* = 7.9, 4.8, 0.9 Hz, 1H), 7.18 (dd, *J* = 8.8, 1.9 Hz, 1H), 6.97 (ddd, *J* = 8.8, 2.9, 2.2 Hz, 1H), 6.86 (t, *J* = 2.7 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 157.0 (C), 150.0 (CH), 148.7 (CH), 136.7 (CH), 133.8 (C), 131.0 (C), 129.8 (C), 122.9 (CH), 120.0 (CH), 116.4 (CH), 115.0 (CH), 55.7 (CH_3) ; IR: 2117, 1602, 1484, 1227, 1030, 877, 805, 705 cm^{-1}.



1.174

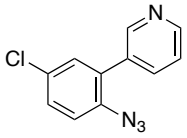
3-(2-Azidophenyl)pyridine (**1.174**).[28] The general procedure was followed using 1.38 g of biaryl amine **1.165** (8 mmol), 0.773 g of $NaNO_2$ (11.2 mmol), and 0.780 g of NaN_3(12 mmol) in 32 mL of AcOH and 16 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as brown oil (1.42 g, 90%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.69 (s, 1H), 8.60 (dd, *J* = 4.8, 1.5 Hz, 1H), 7.79 (ddd, *J* = 7.9, 2.2, 1.8 Hz, 1H), 7.45 (td, *J* = 7.7, 1.3 Hz, 1H), 7.36-7.33 (m, 2H), 7.29 (dd, *J* = 8.1, 0.6 Hz, 1H), 7.24 (dd, *J* = 7.5, 1.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 150.1 (CH), 148.6 (CH), 137.5 (C), 136.8 (CH), 133.9 (C), 131.1 (CH),

130.1 (C), 129.6 (CH), 125.2 (CH), 122.9 (CH), 118.9 (CH); IR: 2087, 1468, 1282, 1001, 710 cm^{-1}.



1.175

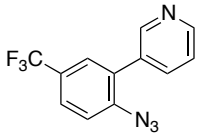
3-(2-Azido-5-fluorophenyl)pyridine (**1.175**).[28] The general procedure was followed using 0.898 g of biaryl amine **1.166** (4.8 mmol), 0.462 g of $NaNO_2$ (6.7 mmol), and 0.468 g of NaN_3 (7.2 mmol) in 20 mL of AcOH and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (0.565 g, 55%), m.p. = 75-77 °C: ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.66-8.65 (m, 1H), 8.59 (dd, *J* = 4.9, 1.6 Hz, 1H), 7.75 (ddd, *J* = 7.9, 2.3, 1.7 Hz, 1H), 7.33 (ddd, *J* = 7.9, 4.8, 0.8 Hz, 1H), 7.20 (dd, *J* = 8.8, 4.7 Hz, 1H), 7.13-7.10 (m, 1H), 7.04 (dd, *J* = 8.8, 2.9 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 159.8 (d, *J* = 245 Hz, C), 149.9 (CH), 149.1(CH), 136.7 (CH), 133.3 (C), 132.8 (C), 131.6 (d, *J* = 7.8 Hz, C), 123.0 (CH), 120.3 (d, *J* = 9.3 Hz, CH), 117.8 (d, *J* = 22.6 Hz, CH), 116.3 (d, *J* = 23.8 Hz, CH); ^{19}F NMR (282 MHz, $CDCl_3$) δ –117.4; IR 2120, 1590, 1395, 1200, 891, 706, 640 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{11}H_7FN_4$ $(M)^+$: 214.0655, found 214.0649.



1.176

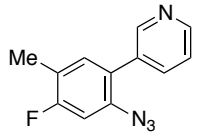
3-(2-Azido-5-chlorophenyl)pyridine (**1.176**).[28] The general procedure was followed using 1.242 g of biaryl amine **1.167** (6.1 mmol), 0.587 g of $NaNO_2$ (8.5

mmol), and 0.598 g of NaN_3 (9.2 mmol) in 26 mL of AcOH and 13 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (1.16 g, 82%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.67 (m, 1H), 8.62 (m, 1H), 7.76 (m, 1H), 7.42 - 7.33 (m, 3H), 7.21 (m, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 149.9 (CH), 149.1 (CH), 136.7 (CH), 136.2 (C), 132.7 (C), 131.5 (C), 130.9 (CH), 130.5 (C), 129.4 (CH), 123.0 (CH), 120.1 (CH).



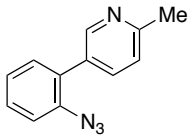
1.177

3-(2-Azido-5-trifluoromethylphenyl)pyridine (**1.177**).[28] The general procedure was followed using 0.695 g of biaryl amine **1.168** (3 mmol), 0.299 g of $NaNO_2$ (4.2 mmol), and 0.292 g of NaN_3 (4.5 mmol) in 12 mL of AcOH and 6 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as white solid (0.476 g, 60%), mp = 68 – 70 °C: ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.70 (s, 1H), 8.65-8.63 (m, 1H), 7.80-7.77 (m, 1H), 7.70-7.68 (m, 1H), 7.59 (s, 1H), 7.39-7.36 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.0 (CH), 149.3 (CH), 141.2 (C), 136.7 (CH), 132.6 (C), 130.5 (C), 128.2 (CH), 127.4 (q, J_{CF} = 33.3 Hz, C), 126.5 (CH), 123.7 (q, J_{CF} = 271.9 Hz, CF_3), 123.1 (CH), 119.2 (CH); ^{19}F NMR (282 MHz, $CDCl_3$) δ -62.8; IR (thin film) 2111, 1334, 1109, 820, 708 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_7F_3N_4$: 264.06228, found 264.06295.



1.178

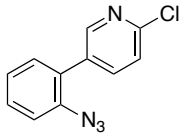
3-(2-Azido-4-fluoro-5-methylphenyl)pyridine (**1.178**).[28] The general procedure was followed using 1.15 g of biaryl amine **1.169** (5.69 mmol), 0.550 g of $NaNO_2$ (8.0 mmol), and 0.555 g of NaN_3 (8.5 mmol) in 20 mL of AcOH and 10 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow solid (1.02 g, 78%), R_f = 0.51 (15:15:70 EtOAc:MeOH:hexane), mp = 62 – 66 °C: ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.60 (d, *J* = 2.2 Hz, 1H), 8.54 (dd, *J* = 4.8, 1.6 Hz, 1H), 7.69-7.67 (m, 1H), 7.28 (dd, *J* = 7.9, 4.9 Hz, 1H), 7.10 (d, *J* = 8.1 Hz, 1H), 6.89 (d, *J* = 9.8 Hz, 1H), 2.25 (d, *J* = 1.6 Hz, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 161.4 (d, J_{CF} = 248.0 Hz, C), 150.0 (CH), 148.6 (CH), 136.7 (CH), 136.3 (d, J_{CF} = 7.8 Hz, C), 133.7 (d, J_{CF} = 7.2 Hz, CH), 133.1 (C), 125.8 (d, J_{CF} = 3.7 Hz, C), 122.8 (CH), 122.0 (d, J_{CF} = 18.4 Hz, C), 105.9 (d, J_{CF} = 25.9 Hz, CH), 14.0 (d, J_{CF} = 3.0 Hz, CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –114.8 ; IR (thin film) 2107, 1511, 1388, 1262, 829, 706 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_9FN_4$ $(M)^+$: 228.0811, found 228.0817.



1.179

3-(2-Azidophenyl)-6-methylpyridine (**1.179**).[28] The general procedure was followed using 0.745 g of biaryl amine **1.170** (4.04 mmol), 0.390 g of $NaNO_2$ (5.66 mmol), and 0.394 g of NaN_3 (6.07 mmol) in 18 mL of AcOH and 9 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as yellow oil (0.673 g, 79%), R_f = 0.59 (3:7 EtOAc:hexane): ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.55 (d, *J* = 1.8 Hz, 1H), 7.65 (dd, *J* = 8.0, 2.3 Hz, 1H), 7.38 (t, *J* = 7.7

Hz, 1H), 7.29 (d, *J* = 7.6 Hz, 1H), 7.22 (d, *J* = 8.0 Hz, 1H), 7.20-7.17 (m, 2H), 2.58 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 157.4 (C), 149.3 (CH), 137.4 (C), 137.1 (CH), 131.0 (CH), 130.9 (C), 130.2 (C), 129.3 (CH), 125.2 (CH), 122.5 (CH), 118.8 (CH), 24.3 (CH_3); IR: 2082, 1476, 1298, 1150, 833, 739 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_{11}N_4$ $(M)^+$: 210.0905, found 210.0896.

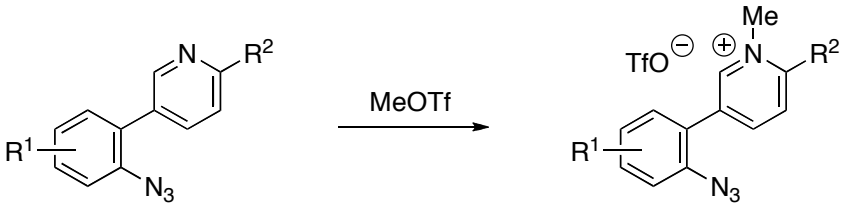


1.180

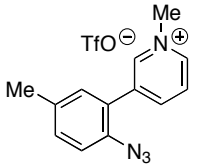
3-(2-Azidophenyl)-6-chloropyridine (**1.180**). The general procedure was followed using 0.290 g of biaryl amine **1.171** (1.42 mmol), 0.137 g of $NaNO_2$ (1.98 mmol), and 0.138 g of NaN_3 (2.13 mmol) in 10 mL of AcOH and 5 mL of H_2O. Purification of the reaction mixture using MPLC afforded the product as a white powder (0.230 g, 70%). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.45 (d, *J* = 2.5 Hz, 1H), 7.77 (dd, *J* = 8.0, 2.5 Hz, 1H), 7.46 (td, *J* = 7.0, 1.5 Hz, 1H), 7.38 (d, *J* = 8.5 Hz, 1H), 7.33-7.23 (m, 3H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 150.5 (C), 149.8 (CH), 139.7 (CH), 137.5 (C), 132.8 (C), 130.9 (CH), 130.0 (CH), 128.6 (C), 125.3 (CH), 123.6 (C), 118.9 (CH).

D3. Preparation of *meta*-Substituted Pyridinium Ions

General procedure for the synthesis of *meta*-substituted pyridinium ions. Unless otherwise noted, the pyridinium ions were synthesis from the corresponding substituted biaryl azide. Yields were not optimized.

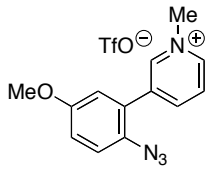


In a dry 25 mL round bottom flask, the biaryl azide was dissolved in dry CH_2Cl_2 (0.5 M), MeOTf (1.1 equiv) was then added dropwise via syringe over 10 min, and the resulting solution was allowed to stir at ambient temperature overnight. The volatiles were removed *in vacuo* to afford the product, which can be used directly without further purification. We previously reported the synthesis of pyridinium triflates **1.117** – **1.124**.[28]



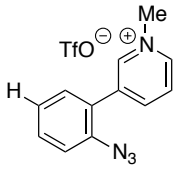
1.117

1-Methyl-3-(2-azido-5-methylphenyl)pyridinium triflate (**1.117**).[28] The general procedure was followed using 0.883 g of biaryl azide **1.172** (4.5 mmol) and 0.543 mL of MeOTf (4.95 mmol) in 9 mL of CH_2Cl_2 afforded the product as yellow solid (1.59 g, 98%), mp = 125 – 127 °C: ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.10 (s, 1H), 8.85 (d, *J* = 5.6 Hz, 1H), 8.69 (d, *J* = 8.0 Hz, 1H), 8.12-8.09 (m, 1H), 7.46-7.45 (m, 1H), 7.41 (s, 1H), 7.35 (dd, *J* = 8.2, 3.2 Hz, 1H), 4.47 (s, 3H), 2.42 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 145.4 (CH), 143.5 (CH), 138.6 (C), 135.8 (C), 134.9 (C), 132.2 (2CH), 131.3 (CH), 127.1 (CH), 124.9 (C), 118.9 (CH), 47.6 (CH_3), 19.4 (CH_3); IR: 2127, 1251, 1152, 1028, 816, 634 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{13}N_4$ $(M–OTf)^+$: 225.1140, found 225.1133.



1.118

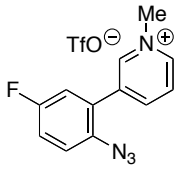
1-Methyl-3-(2-azido-5-methoxyphenyl)pyridinium triflate (**1.118**).[28] The general procedure was followed using 0.888 g of biaryl azide **1.173** (3.9 mmol) and 0.470 mL of methyl triflate (4.29 mmol) in 8 mL of CH_2Cl_2 afforded the product as purple solid (1.02 g, 67%), mp = 128 – 130 °C: ^{1}H NMR (500 MHz; CD_3OD) δ 9.13 (s, 1H), 8.87 (d, *J* = 6.1 Hz, 1H), 8.71 (d, *J* = 8.2 Hz, 1H), 8.12 (dd, *J* = 7.7, 6.4 Hz, 1H), 7.40 (d, *J* = 8.9 Hz, 1H), 7.22 (dd, *J* = 8.9, 2.9 Hz, 1H), 7.14 (d, *J* = 2.9 Hz, 1H), 4.47 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$): δ 157.5 (C), 145.6 (CH), 145.0 (CH), 143.8 (CH), 138.6 (C), 129.6 (C), 127.5 (CH), 125.3 (C), 120.2 (CH), 118.5 (CH), 115.6 (CH), 56.1 (CH_3), 49.0 (CH_3). IR: 2121, 1491, 1250, 1029, 817, 636 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{13}N_4O$ $(M–OTf)^+$: 241.1089, found 241.1085.



1.119

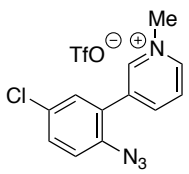
1-Methyl-3-(2-azidophenyl)pyridinium triflate (**1.119**).[28] The general procedure was followed using 1.42 g of biaryl azide **1.174** (7.21 mmol) and 0.870 mL of methyl triflate (7.93 mmol) in 15 mL of CH_2Cl_2 afforded the product as gray solid (2.60 g, 99%), mp = 90 – 96 °C: ^{1}H NMR (500 MHz; CD_3OD) δ 9.12 (s, 1H), 8.87 (d, *J* = 6.0 Hz, 1H), 8.71 (d, *J* = 8.2 Hz, 1H), 8.12 (t, *J* = 7.1 Hz, 1H), 7.64 (td, *J* =

7.9, 1.4 Hz, 1H), 7.57 (dd, *J* = 7.7, 1.0 Hz, 1H), 7.48 (dd, *J* = 8.2, 0.7 Hz, 1H), 7.38 (td, *J* = 7.6, 1.0 Hz, 1H), 4.48 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD) δ 145.5 (CH), 143.6 (CH), 138.4 (C), 137.8 (CH), 131.7 (CH), 130.9 (CH), 127.1 (CH), 125.5 (CH), 125.2 (C), 121.7 (C), 119.0 (CH), 47.8 (CH_3); IR: 2132, 1255, 1142, 1029, 763, 634 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{12}H_{11}N_4$ (M–OTf)$^+$: 211.0984, found 211.0984.



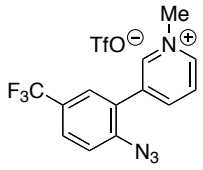
1.120

1-Methyl-3-(2-azido-5-fluorophenyl)pyridinium triflate (**1.120**).[28] The general procedure was followed using 0.565 g of biaryl azide **1.175** (2.64 mmol) and 0.320 mL of methyl triflate (2.90 mmol) in 6 mL of CH_2Cl_2 afforded the product as pink solid (1.00 g, 100%), mp = 148 – 153 °C: ^{1}H NMR (500 MHz; CD_3OD) δ 9.15 (s, 1H), 8.90 (d, *J* = 6.1 Hz, 1H), 8.73 (d, *J* = 8.2 Hz, 1H), 8.14 (t, *J* = 7.1 Hz, 1H), 7.52-7.49 (m, 1H), 7.43-7.40 (m, 2H), 4.48 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD) δ 159.9 (d, J_{CF} = 244.1 Hz, C), 145.6 (CH), 144.0 (CH), 137.3 (C), 133.9 (d, *J* = 3.0 Hz, C), 127.2 (2CH), 126.5 (C), 121.0 (d, *J* = 9.1 Hz, CH), 118.3 (d, *J* = 23.6 Hz, CH), 117.5 (d, *J* = 25.4 Hz, CH), 47.7 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –78.3, –117.3; IR (thin film) 2200, 1252, 1021, 813, 624 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{12}H_{10}FN_4$ (M–OTf)$^+$: 229.0889, found 229.0884.



1.121

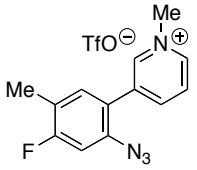
1-Methyl-3-(2-azido-5-chlorophenyl)pyridinium triflate (**1.121**).[28] The general procedure was followed using 1.141 g of biaryl azide **1.176** (4.90 mmol) and 0.592 mL of methyl triflate (5.40 mmol) in 10 mL of CH_2Cl_2 afforded the product as brown solid (1.76 g, 91%). ^{1}H NMR (500 MHz; CD_3OD): δ 9.14 (s, 1H), 8.90 (d, *J* = 6.0, 1H), 8.72 (d, *J* = 8.5, 1H), 8.13 (t, *J* = 7.5, 1H), 7.64 (m, 2H), 7.48 (m, 1H), 4.48 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 145.6 (CH), 144.1 (CH), 137.1 (C), 136.8 (C), 131.3 (CH), 130.5 (CH), 127.2 (CH), 126.6 (C), 121.7 (C), 120.7 (CH), 119.2 (CH), 47.2 (CH_3); IR (thin film) 2144, 1256, 1143, 1030, 634 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{12}H_{10}FN_4$ $(M–OTf)^+$: 245.0589, found 245.0592.



1.122

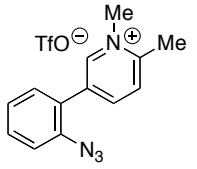
1-Methyl-3-(2-azido-5-trifluoromethylphenyl)pyridinium triflate (**1.122**).[28] The general procedure was followed using 0.476 g of biaryl azide **1.177** (1.80 mmol) and 0.217 mL of methyl triflate (1.98 mmol) in 5 mL of CH_2Cl_2 afforded the product as white solid (0.795 g, 99%): ^{1}H NMR (500 MHz; CD_3OD) δ 9.17 (s, 1H), 8.92 (d, *J* = 6.0 Hz, 1H), 8.75 (d, *J* = 8.0 Hz, 1H), 8.15 (t, *J* = 7.1 Hz, 1H), 7.92 (d, *J* = 9.6 Hz, 2H), 7.68 (d, *J* = 8.3 Hz, 1H), 4.49 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD) δ 145.8 (CH), 145.7 (CH), 144.2 (CH), 142.0 (C), 137.1 (C), 128.3 (d, J_{CF} = 3.43 Hz, CH), 128.0 (CH), 127.2 (CH), 127.1 (q, J_{CF} = 33.3 Hz, C), 125.7 (C), 123.8 (q, J_{CF} = 271.8 Hz, C), 119.96 (CH), 47.7 (CH_3); ^{19}F NMR (282

MHz, $CDCl_3$) δ –61.2, –78.3; IR (thin film) 2143, 1249, 1122, 1028, 689, 517 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{10}F_3N_4$ $(M–OTf)^+$: 279.0858, found 279.0850.



1.123

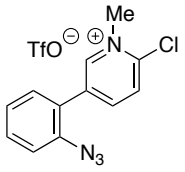
1-Methyl-3-(2-azido-4-fluoro-5-methylphenyl)pyridinium triflate (**1.123**).[28] The general procedure was followed using 1.00 g of biaryl azide **1.178** (4.38 mmol) and 0.538 mL of methyl triflate (4.82 mmol) in 9 mL of CH_2Cl_2 afforded the product as yellow solid (1.62 g, 94%), m.p. = 149-153 °C: ^1H NMR (500 MHz; CD_3OD): δ 9.08 (s, 1H), 8.85 (d, *J* = 6.0 Hz, 1H), 8.68 (d, *J* = 8.2 Hz, 1H), 8.10 (t, *J* = 7.1 Hz, 1H), 7.49 (d, *J* = 7.9 Hz, 1H), 7.21 (dd, *J* = 10.0, 4.1 Hz, 1H), 4.47 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD): δ 162.5 (d, *J* = 251 Hz, C), 145.4 (d, *J* = 4.1 Hz, CH), 143.5 (CH), 137.7 (C), 137.2 (d, *J* = 9.2 Hz, C), 133.8 (d, *J* = 6.8 Hz, CH), 127.1 (CH), 122.7 (d, *J* = 18.5 Hz, C), 121.2 (d, *J* = 3.3 Hz, C), 106.2 (CH), 106.0 (CH), 47.7 (CH_3), 12.6 (CH_3); ^{19}F NMR (282 MHz, $CDCl_3$) δ –78.9, –103.8 ; IR (thin film) 2117, 1492, 1258, 1138, 1031, 630 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{12}FN_4$ $(M–OTf)^+$: 243.1046, found 243.1042.



1.124

1-Methyl-3-(2-azidophenyl)-6-methylpyridinium triflate (**1.124**).[28] The general procedure was followed using 0.650 g of biaryl azide **1.179** (3.10 mmol) and 380

mL of methyl triflate (3.40 mmol) in 7 mL of CH_2Cl_2 afforded the product as white solid (1.15 g, 99%): ^{1}H NMR (500 MHz; CD_3OD) δ 9.04 (s, 1H), 8.56 (dd, *J* = 8.2, 1.2 Hz, 1H), 8.01 (d, *J* = 8.3 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.7 Hz, 1H), 7.46 (d, *J* = 8.1 Hz, 1H), 7.36 (t, *J* = 7.6 Hz, 1H), 4.34 (s, 3H), 2.87 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD) δ 154.6 (C), 145.8 (CH), 145.5 (CH), 137.8 (C), 136.0 (C), 131.4 (CH), 130.8 (CH), 128.6 (CH), 125.42 (CH), 125.24 (C), 119.0 (CH), 45.1 (CH_3), 18.8 (CH_3); IR (thin film): 2132, 1256, 1143, 1029, 763, 634 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{12}H_{11}N_4$ $(M–OTf)^+$: 211.0984, found: 211.0984.

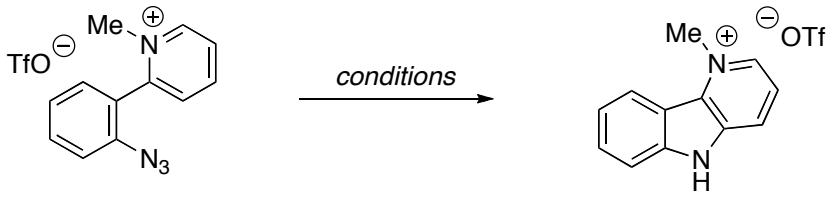


1.125

1-Methyl-3-(2-azidophenyl)-6-chloropyridinium triflate (**1.125**). The general procedure was followed using 0.230 g of biaryl azide **1.180** (1.00 mmol) and 0.123 mL of methyl triflate (1.10 mmol) in 5 mL of CH_2Cl_2 afforded the product as white solid (0.393 g, 99%): ^{1}H NMR (500 MHz; CD_3OD) δ 9.27 (d, *J* = 2.5, 1H), 8.71 (dd, *J* = 8.5, 2.0 Hz, 1H), 8.29 (d, *J* = 8.5 Hz, 1H), 7.65 (td, *J* = 7.5, 1.5 Hz, 1H), 7.57 (dd, *J* = 7.5, 1.0 Hz, 1H), 7.48 (d, *J* = 8.0 Hz, 1H), 7.38 (td, *J* = 7.5, 1.0 Hz, 1H), 4.48 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD) δ 147.8 (CH), 147.3 (CH), 146.1 (C), 137.8 (C), 136.8 (C), 131.8 (CH), 130.8 (CH), 128.8 (CH), 125.5 (CH), 124.4 (C), 119.1 (CH), 47.0 (CH_3); IR: 2133, 1489, 1256, 1143, 1030, 634 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{12}H_{10}N_4$ $(M–OTf)^+$: 245.0589, found: 245.0601.

E. Development of Rh_2(II)-Catalyzed δ-Carbolinium Ion Formation

E1. General Procedure for Screening of Catalysts



1.21 **1.22**

To a mixture of 1-methyl-2-(2-azidophenyl)pyridinium triflate **1.21** (0.020 g, 0.05 mmol, 1.0 equiv) and metal salt (5 mol %) in a capped conical vial with Teflon-lined spetum was added solvent. The resulting mixture was heated and after 15 h, the heterogenous mixture was filtered through celite. The filtrate was concentrated *in vacuo*. The areas of the C-H peak on the 2-position in **1.21** and **1.22** were compared to derive a ^{1}H NMR yield.

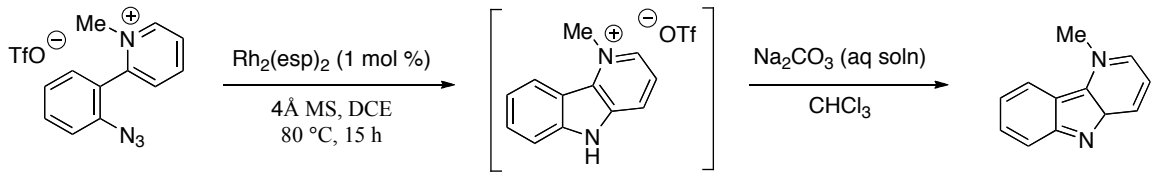
Optimization of δ-Carbolinium Triflate Formation.[a,b]

entry	metal salt	mol %	solvent	wt %, 4 Å MS	T (°C)	yield, %[c]
1	none	n.a.	decalin	0	160	0
2	none	n.a.	decalin	0	170	0
3	$Rh_2(esp)_2$	1.0	DCE	0	80	trace
4	$Rh_2(esp)_2$	5.0	toluene	100	80	73
5	$Rh_2(esp)_2$	5.0	1M DCE	0	80	85
6	$Rh_2(esp)_2$	5.0	DCE	0	80	trace
7	**$Rh_2(esp)_2$**	**5.0**	**DCE**	**100**	**80**	**100**
8	$Rh_2(O_2CC_7F_{15})_4$	5.0	DCE	100	80	trace
9	$Rh_2(O_2CCF_3)_4$	5.0	DCE	100	80	n.r.
10	$Rh_2(O_2CC_3F_7)_4$	5.0	DCE	100	80	trace
11	$[(cod)IrCl]_2$	5.0	DCE	100	80	trace
12	$[(cod)Ir(OMe)]_2$	5.0	DCE	100	80	trace
13	$Cu(OTf)_2$	5.0	DCM	100	40	n.r.

14	ZnI2	5.0	DCM	100	40	n.r.
15	FeBr2	5.0	DCM	100	40	n.r.
16	$RhCl_3•nH_2O$	5.0	IPAC	100	80	n.r.

[a] Reaction performed in conical vial. [b] 16 hour reaction time. [c] As determined using ^1H NMR spectroscopy.

E2. Preparation of δ-Carbolines

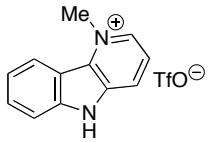


Optimized general procedure for the synthesis of 1*H*-pyrido[2,3-b]indoles. To a mixture of 1-methyl-2-(2-azidophenyl)pyridinium triflate **1.21** (0.144 g, 0.4 mmol, 1.0 equiv), 100% w/w of crushed 4 Å mol sieves, and $Rh_2(esp)_2$ (0.003 g, 0.004 mmol, 0.01 equiv) was added 4 mL of DCE (0.1 M). The resulting mixture was stirred at 80 °C. After 15 h, the heterogenous mixture was filtered through celite, and the filtrate was concentrated *in vacuo* to afford 1-methyl-5*H*-pyrido[3,2-*b*]indolium triflate **1.22**.

While **1.22** could be characterized at this point, it was deprotonated to simplify isolation and manipulation. In a separatory funnel, the reaction mixture was diluted with 20 mL of a 5% aqueous solution of Na_2CO_3. The mixture was vigorously shaken, and the resulting mixture was extracted with 3 × 10 mL of $CHCl_3$. Solid Na_2CO_3 was added to the combined organic phases. The mixture

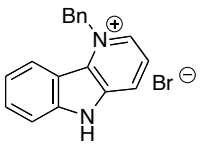
was filtered, and the filtrate was concentrated *in vacuo* to afford analytically pure 1-methyl-1*H*-pyrido[3,2-*b*]indole **1.44**.

E3. Preparation of 1-Methyl-δ-Carbolinium Triflates



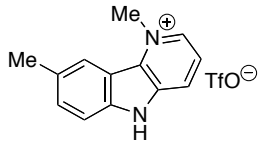
1.22

1-Methyl-5*H*-pyrido[3,2-*b*]indolium triflate (**1.22**).[73] The general procedure was followed using 0.054 g of pyridinium triflate **1.21** (0.15 mmol) and 0.001 g of $Rh_2(esp)_2$ (0.0015 mmol) in 1.5 mL of DCE afforded the product as off-white solid (0.050 g, 100%). 1-Methyl-δ-carbolinium iodide was previously reported by Rocca and co-workers.[73] ^{1}H NMR (500 MHz; DMSO-d_6) δ 12.86 (br s, 1H), 8.86 (d, *J* = 5.9 Hz, 1H), 8.68 (d, *J* = 8.3 Hz, 1H), 8.50 (d, *J* = 8.3 Hz, 1H), 7.99 (dd, *J* = 8.3, 6.0 Hz, 1H), 7.84-7.80 (m, 2H), 7.49 (ddd, *J* = 8.1, 6.3, 1.7 Hz, 1H), 4.81 (s, 3H); ^{13}C NMR (126 MHz; DMSO-d_6) δ 142.2 (C), 138.2 (CH), 136.2 (C), 132.5 (C), 131.8 (CH), 126.9 (CH), 124.4 (CH), 122.1 (CH), 121.8 (CH), 114.8 (C), 113.6 (CH), 46.6 (CH_3); IR: 3096, 1253, 1156, 1025 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{12}H_{11}N_2$ $(M–OTf)^+$: 183.0922, found: 183.0919.



1.35

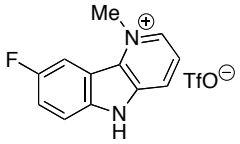
1-Benzyl-5*H*-pyrido[3,2-*b*]indolium triflate (**1.35**). The general procedure was followed using 0.055 g of pyridinium **1.26** (0.15 mmol), 0.001 g of $Rh_2(esp)_2$ (0.0015 mmol) and 0.113 g of AgOTf (0.44 mmol, 1.1 equiv) in 1.5 mL of DCE afforded the product as brown gel (0.050 g, 98%): ^{1}H NMR (500 MHz; CD_3OD) δ 9.25 (d, *J* = 6.2 Hz, 1H), 8.68 (t, *J* = 7.9 Hz, 1H), 8.21 (t, *J* = 7.0 Hz, 1H), 8.00 (d, *J* = 7.9 Hz, 1H), 7.72 (t, *J* = 7.8 Hz, 1H), 7.40-7.37 (m, 2H), 7.35-7.32 (m, 1H), 7.28 (t, *J* = 7.4 Hz, 2H), 6.91 (d, *J* = 7.4 Hz, 2H), 5.73 (q, *J* = 13.9 Hz, 2H); ^{13}C NMR (126 MHz; CD_3OD) δ 153.0 (C), 146.5 (C), 146.1 (CH), 139.1 (C), 133.1 (CH), 132.6 (C), 131.7 (CH), 130.2 (CH), 129.0 (CH), 128.7 (CH), 127.9 (CH), 127.6 (CH), 125.2 (CH), 122.4 (C), 118.9 (CH), 62.6 (CH_2); IR: 3063, 1255, 1148, 1029 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{18}H_{15}N_2$ $(M–OTf)^+$: 259.1235, found: 259.1235.



1.36

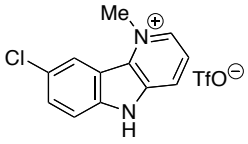
1,8-Dimethyl-5*H*-pyrido[3,2-*b*]indolium triflate (**1.36**). The general procedure was followed using 0.056 g of pyridinium triflate **1.27** (0.15 mmol) and 0.001 g of $Rh_2(esp)_2$ (0.0015 mmol) in 1.5 mL of DCE afforded the product as dark yellow solid (0.044 g, 85%): ^{1}H NMR (500 MHz; DMSO-d_6) δ 12.73 (br s, 1H), 8.82 (d, *J* = 6.0 Hz, 1H), 8.65 (d, *J* = 8.4 Hz, 1H), 8.32 (s, 1H), 7.96 (dd, *J* = 8.3, 6.0 Hz, 1H), 7.75 (d, *J* = 8.5 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 1H), 4.81 (s, 3H), 2.55 (s, 3H); ^{13}C NMR (126 MHz; DMSO-d_6) δ 140.6 (C), 138.0 (CH), 136.3 (C), 133.5 (CH),

132.2 (C), 131.3 (C), 126.8 (CH), 123.5 (CH), 121.5 (CH), 114.9 (C), 113.3 (CH), 46.6 (CH_3), 21.6 (CH_3); IR: 3102, 1251, 1139, 1026 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{13}N_2$ $(M–OTf)^+$: 197.1079, found: 197.1072.



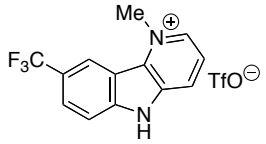
1.37

1-Methyl-8-fluoro-5*H*-pyrido[3,2-*b*]indolium triflate (**1.37**). The general procedure was followed using 0.057 g of pyridinium trilate **1.28** (0.15 mmol) and 0.001 g of $Rh_2(esp)_2$ (0.0015 mmol) in 1.5 mL of DCE afforded the product as yellow solid (0.054 g, 100%): ^{1}H NMR (500 MHz; DMSO-d_6) δ 12.93 (br s, 1H), 8.88 (d, *J* = 5.9 Hz, 1H), 8.72 (d, *J* = 8.4 Hz, 1H), 8.36 (dd, *J* = 9.6, 2.4 Hz, 1H), 8.02 (dd, *J* = 8.4, 5.9 Hz, 1H), 7.88 (dd, *J* = 9.1, 4.5 Hz, 1H), 7.73 (td, *J* = 9.1, 2.4 Hz, 1H), 4.80 (s, 3H); ^{13}C NMR (126 MHz; DMSO-d_6) 157.8 (d, *J* = 236.5 Hz, CF), 138.7 (CH), 137.0 (C), 132.0 (C), 127.7 (CH), 122.2 (CH), 120.4 (d, *J* = 26.0 Hz, CH), 119.9 (C), 115.3 (d, *J* = 9.3 Hz, CH), 114.7 (d, *J* = 11.2 Hz, C), 109.5 (d, *J* = 26.0 Hz, CH), 46.5 (CH_3); ^{19}F NMR (471 MHz, CD_3OD) δ –81.7, –123.2; IR: 3176, 1505, 1214, 1028 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{12}H_{10}FN_2$ $(M–OTf)^+$: 201.0828, found: 201.0825.



1.38

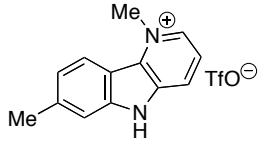
1-Methyl-8-chloro-5*H*-pyrido[3,2-*b*]indolium triflate (**1.38**). The general procedure was followed using 0.064 g of pyridinium triflate **1.29** (0.15 mmol) and 0.001 g of $Rh_2(esp)_2$ (0.0015 mmol) in 1.5 mL of DCE afforded the product as yellow solid (0.058 g, 97%): ^{1}H NMR (500 MHz; DMSO-d_6) δ 13.00 (br s, 1H), 8.90 (d, *J* = 5.8 Hz, 1H), 8.73 (d, *J* = 8.4 Hz, 1H), 8.57 (s, 1H), 8.04 (dd, *J* = 8.3, 6.0 Hz, 1H), 7.87 (d, *J* = 8.8 Hz, 1H), 7.83 (dd, *J* = 8.9, 1.5 Hz, 1H), 4.82 (s, 3H); ^{13}C NMR (126 MHz; DMSO-d_6) δ 140.5 (C), 139.0 (CH), 136.7 (C), 131.6 (CH), 131.5 (C), 127.8 (CH), 126.5 (C), 123.5 (CH), 122.5 (CH), 115.7 (C), 115.4 (CH), 46.7 (CH_3); IR: 3083, 1258, 1150, 1025, 829 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{12}H_{10}ClN_2$ $(M–OTf)^+$: 217.0533, found: 217.0530.



1.39

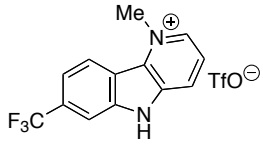
1-Methyl-8-trifluoromethyl-5*H*-pyrido[3,2-*b*]indolium triflate (**1.39**). The general procedure was followed using 0.064 g of pyridinium triflate **1.30** (0.15 mmol) and 0.001 g of $Rh_2(esp)_2$ (0.0015 mmol) in 1.5 mL of DCE afforded the product as yellow solid (0.058 g, 97%): ^{1}H NMR (500 MHz; DMSO-d_6) δ 8.97 (d, *J* = 5.9 Hz, 1H), 8.80 (d, *J* = 7.8 Hz, 2H), 8.11-8.08 (m, 2H), 8.03 (d, *J* = 8.8 Hz, 1H), 4.90 (s, 3H), NH peak lays beyond the viewable region; ^{13}C NMR (126 MHz; DMSO-d_6) δ 142.9 (C), 139.0 (CH), 136.6 (C), 131.8 (C), 127.6 (CH), 127.1 (d, *J* = 3.2 Hz, CH), 124.6 (d, *J* = 272.0 Hz, C), 122.4 (CH), 121.9 (d, *J* = 5.6 Hz, C), 121.7 (CH), 114.3 (CH), 113.9, 46.2 (CH_3); ^{19}F NMR (471 MHz, CD_3OD) δ –63.6,

–81.7; IR: 3109, 1279, 1027 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{10}F_3N_2$ $(M–OTf)^+$: 251.0796, found: 251.0797.



1.40

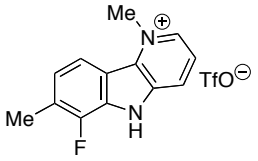
1,7-Dimethyl-5*H*-pyrido[3,2-*b*]indolium triflate (**1.40**). The general procedure was followed using 0.056 g of pyridinium triflate **1.31** (0.15 mmol) and 0.001 g of $Rh_2(esp)_2$ (0.0015 mmol) in 1.5 mL of DCE afforded the product as yellow solid (0.044 g, 85%): ^{1}H NMR (500 MHz; DMSO-d_6) δ 12.73 (br s, 1H), 8.80 (d, *J* = 6.1 Hz, 1H), 8.61 (d, *J* = 8.2 Hz, 1H), 8.38 (d, *J* = 8.5 Hz, 1H), 7.93 (dd, *J* = 8.3, 6.0 Hz, 1H), 7.62 (d, *J* = 0.4 Hz, 1H), 7.34 (d, *J* = 8.4 Hz, 1H), 4.77 (s, 3H), 2.58 (s, 3H); ^{13}C NMR (126 MHz; DMSO-d_6) 142.87 (C), 142.80 (C), 137.7 (CH), 136.2 (C), 132.8 (C), 126.4 (CH), 124.08 (CH), 124.01 (CH), 121.2 (CH), 113.1 (CH), 112.7 (C), 46.5 (CH_3), 22.4 (CH_3); IR: 3316, 1265, 1142, 1027, 804 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{13}N_2$ $(M–OTf)^+$: 197.1079, found: 197.1076.



1.41

1-Methyl-7-trifluoromethyl-5*H*-pyrido[3,2-*b*]indolium triflate (**1.41**). The general procedure was followed using 0.064 g of pyridinium triflate **1.32** (0.15 mmol) and 0.001 g of $Rh_2(esp)_2$ (0.0015 mmol) in 1.5 mL of DCE afforded the product as yellow solid (0.059 g, 98%): ^{1}H NMR (500 MHz; DMSO-d_6) δ 13.15 (br s, 1H), 8.99 (d, *J* = 5.9 Hz, 1H), 8.83 (d, *J* = 8.4 Hz, 1H), 8.74 (d, *J* = 8.6 Hz, 1H),

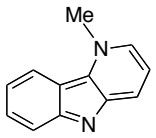
8.23 (s, 1H), 8.11 (dd, *J* = 8.4, 5.9 Hz, 1H), 7.78 (d, *J* = 8.6 Hz, 1H), 4.87 (s, 3H); ^{13}C NMR (126 MHz; DMSO-d_6) 141.0 (C), 139.6 (CH), 137.4 (C), 131.5 (C), 130.7 (q, *J* = 31.6 Hz, C), 128.5 (CH), 125.8 (CH), 124.7 (q, *J* = 272 Hz, CF_3), 123.2 (CH), 117.8 (d, *J* = 3.4 Hz, CH), 117.4 (C), 111.2 (d, *J* = 3.8 Hz, CH), 46.8 (CH_3); ^{19}F NMR (471 MHz, CD_3OD) δ –65.2, –81.7; IR: 3278, 1258, 1118, 1029 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{10}F_3N_2$ $(M–OTf)^+$: 251.0796, found: 251.0799.



1.42

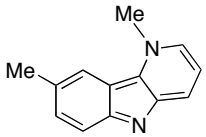
1,7-Dimethyl-6-fluoro-5*H*-pyrido[3,2-*b*]indolium triflate (**1.42**). The general procedure was followed using 0.059 g of pyridinium triflate **1.33** (0.15 mmol) and 0.001 g of $Rh_2(esp)_2$ (0.0015 mmol) in 1.5 mL of DCE afforded the product as yellow solid (0.053 g, 100%): ^{1}H NMR (500 MHz; DMSO-d_6) δ 12.84 (br s, 1H), 8.82 (d, *J* = 5.9 Hz, 1H), 8.63 (d, *J* = 8.3 Hz, 1H), 8.46 (d, *J* = 7.2 Hz, 1H), 7.95 (dd, *J* = 8.2, 6.0 Hz, 1H), 7.63 (d, *J* = 10.1 Hz, 1H), 4.78 (s, 3H), 2.45 (s, 3H); ^{13}C NMR (126 MHz; DMSO-d_6) δ 163.3 (d, *J* = 249.6 Hz, C), 141.9 (C), 138.2 (CH), 136.7 (C), 132.2 (C), 126.6 (CH), 126.5 (d, *J* = 7.5 Hz, CH), 121.4 (CH), 120.3 (d, *J* = 20.3 Hz, C), 111.6 (C), 99.5 (d, *J* = 27.6 Hz, CH), 46.5 (CH_3), 15.2 (CH_3); ^{19}F NMR (471 MHz, CD_3OD) δ –81.7, –110.9; IR: 3048, 1470, 1259, 1131, 1030, 992 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{12}FN_2$ $(M–OTf)^+$: 215.0985, found: 215.0980.

E4. Preparation of 1*H*-Pyrido[2,3-*b*]indoles



1.44

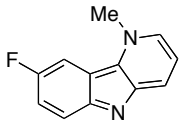
1-Methyl-1*H*-pyrido[3,2-*b*]indole (**1.44**).[74] Starting from 0.030 g of pyridinium triflate **1.21**, the general procedure was followed to afford **1.44** as an orange solid (0.011 g, 74% from **1.21**). 1-Methyl-1*H*-pyrido[3,2-*b*]indole **1.44** was previously reported by Abramovitch and co-workers.[74] ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.32 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.92 (d, J = 8.5 Hz, 1H), 7.58 (d, J = 6.0 Hz, 1H), 7.55 (t, J_1 = 7.0 Hz, 1H), 7.28 (dd, J_1 = 8.0 Hz, J_2 = 6.0 Hz, 1H), 7.11 (t, J_1 = 8.0 Hz, 1H), 4.45 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 156.6 (C), 147.3 (C), 133.7 (C), 128.4 (CH), 128.0 (CH), 127.9 (CH), 121.7 (CH), 120.0 (CH), 117.7 (CH), 115.6 (CH), 114.9 (C), 45.0 (CH_3); ATR-FTIR (thin film): 1621, 1476, 1330, 1255, 721 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{12}H_{10}N_2$: 182.0844, found: 182.0835.



1.45

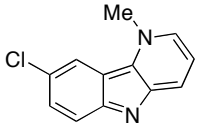
1,8-Dimethyl-1*H*-pyrido[3,2-*b*]indole (**1.45**). Starting from 0.030 g of pyridinium triflate **1.27**, the general procedure was followed to afford **1.45** as an orange solid (0.011 g, 71% from **1.27**): ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.29 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 8.5 Hz, 1H), 7.74 (s, 1H), 7.57 (d, J = 5.5 Hz, 1H), 7.39 (dd, J_1 = 8.5

Hz, J_2 = 1.5 Hz, 1H), 7.24 (dd, J_1 = 8.5 Hz, J_2 = 6.0 Hz, 1H), 4.44 (s, 3H), 2.51 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 154.8 (C), 147.0 (C), 133.1 (C), 130.9 (CH), 128.1(CH), 127.7 (CH), 126.9 (C), 120.7 (CH), 119.4 (CH), 115.3 (CH), 114.8 (C), 45.0 (CH_3), 21.8 (CH_3); ATR-FTIR (thin film): 2914, 1478, 1260, 774, 718 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{13}H_{12}N_2$: 196.1000, found: 196.0996.



1.46

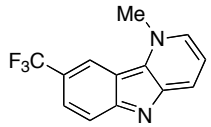
1-Methyl-8-fluoro-1*H*-pyrido[3,2-*b*]indole (**1.46**). Starting from 0.030 g of pyridinium triflate **1.28**, the general procedure was followed to afford **1.46** as an orange solid (0.016 g, 96% from **1.28**): ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.34 (d, J = 8.5 Hz, 1H), 7.86 (m, 1H), 7.60 (m, 2H), 7.32 (m, 2H), 4.45 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 157.1 (d, J_{CF} = 233 Hz, C), 153.0 (C), 147.7 (C), 133.2 (C), 129.0 (CH), 128.7 (CH), 120.9 (d, J_{CF} = 9.0 Hz, CH), 118.0 (d, J_{CF} = 25.8 Hz, CH), 115.7 (CH), 113.4 (d, J_{CF} = 10.6 Hz, C), 105.4 (d, J_{CF} = 23.8 Hz, CH), 44.9 (CH_3); ATR-FTIR (thin film): 1593, 1470, 1317, 1152, 778 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_9FN_2$: 200.0750, found: 200.0759.



1.47

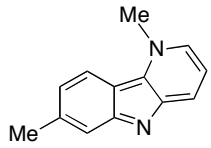
1-Methyl-8-fluoro-1*H*-pyrido[3,2-*b*]indole (**1.47**). Starting from 0.030 g of pyridinium triflate **1.29**, the general procedure was followed to afford **1.47** as an orange solid (0.013 g, 77% from **1.29**): ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.31 (d, J =

8.0 Hz, 1H), 7.81 (m, 2H), 7.56 (d, J = 5.5 Hz, 1H), 7.44 (dd, J_1 = 9.0 Hz, J_2 = 2.0 Hz, 1H), 7.28 (dd, J_1 = 8.0 Hz, J_2 = 6.0 Hz, 1H), 4.35 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 154.5 (C), 147.7 (C), 132.5 (C), 129.0 (CH), 128.9 (CH), 128.8 (CH), 122.8 (C), 121.0 (CH), 120.5 (CH), 116.0 (CH), 115.1 (C), 45.0 (CH_3); ATR-FTIR (thin film): 1586, 1365, 1317, 1257, 785 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_9ClN_2$: 216.0454, found: 216.0459.



1.48

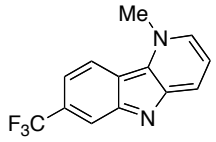
1-Methyl-8-trifluoromethyl-1*H*-pyrido[3,2-*b*]indole (**1.48**). Starting from 0.030 g of pyridinium triflate **1.30**, the general procedure was followed to afford **1.48** as an yellow solid (0.014 g, 78% from **1.30**): ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.41 (d, J = 8.5 Hz, 1H), 8.28 (s, 1H), 7.95 (d, J = 8.5 Hz, 1H), 7.71 (m, 2H), 7.39 (dd, J_1 = 8.5 Hz, J_2 = 6.0 Hz, 1H), 4.56 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 157.2 (C), 148.5 (C), 133.9 (C), 129.5 (CH), 129.3 (CH), 125.4 (q, J = 269 Hz, CF_3), 124.3 (CH), 120.4 (CH), 119.7 (d, J = 5.2 Hz, CH), 119.4 (d, J = 31.1 Hz, C), 116.8 (CH), 113.8 (C), 45.2 (CH_3); ATR-FTIR (thin film): 1623, 1323, 1287, 1092, 796 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{13}H_9F_3N_2$: 250.0718, found: 250.0716.



1.49

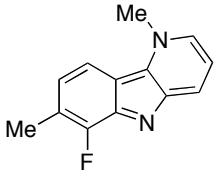
1,7-Dimethyl-1*H*-pyrido[3,2-*b*]indole (**1.49**). Starting from 0.030 g of pyridinium triflate **1.31**, the general procedure was followed to afford **1.49** as an yellow solid

(0.012 g, 75% from **1.31**): ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.29 (d, *J* = 8.0 Hz, 1H), 7.92 (d, *J* = 8.5 Hz, 1H), 7.69 (s, 1H), 7.58 (d, *J* = 5.5 Hz, 1H), 7.27 (dd, J_1 = 8.0 Hz, J_2 = 6.0 Hz, 1H), 6.96 (d, *J* = 8.0 Hz, 1H), 4.49 (s, 3H), 2.57 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 157.4 (C), 147.6 (C), 139.1 (C), 127.5 (CH), 127.2 (CH), 121.3 (CH), 120.2 (CH), 119.2 (CH), 115.3 (CH), 112.9 (C), 110.0 (C), 44.9 (CH_3), 22.6 (CH_3); ATR-FTIR (thin film): 1619, 1417, 1301, 1257, 792 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{13}H_{12}N_2$: 196.1000, found: 196.1007.



1.50

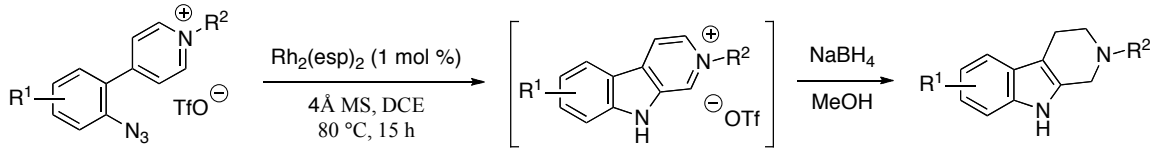
1-Methyl-7-trifluoromethyl-1*H*-pyrido[3,2-*b*]indole (**1.50**). Starting from 0.030 g of pyridinium triflate **1.32**, the general procedure was followed to afford **1.50** as an yellow solid (0.015 g, 86% from **1.32**): ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.46 (d, *J* = 8.5 Hz, 1H), 8.20 (s, 1H), 8.10 (d, *J* = 9.0 Hz, 1H), 7.76 (d, *J* = 5.5 Hz, 1H), 7.43 (dd, J_1 = 8.0 Hz, J_2 = 5.5 Hz, 1H), 7.28 (d, *J* = 8.5 Hz, 1H), 4.60 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 154.9 (C), 147.2 (C), 129.9 (CH), 129.6 (C), 129.4 (CH), 124.9 (d, *J* = 270 Hz, CF_3), 122.2 (CH), 117.5 (d, *J* = 4.75 Hz, CH), 116.8 (C), 116.6 (CH), 116.5 (C), 113.4 (d, *J* = 3.63 Hz, CH), 45.3 (CH_3); ATR-FTIR (thin film): 1477, 1337, 1223, 1052, 794 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{13}H_9F_3N_2$: 250.0718, found: 250.0716.



1.51

1-Methyl-6-fluoro-7-methyl-1*H*-pyrido[3,2-*b*]indole (**1.51**). Starting from 0.030 g of pyridinium triflate **1.33**, the general procedure was to afford **1.51** as an yellow solid (0.011 g, 66% from **1.33**): ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.26 (d, J = 8.0 Hz, 1H), 7.75 (d, J = 8.0 Hz, 1H), 7.60 (d, J = 6.0 Hz, 1H), 7.47 (d, J = 11.5 Hz, 1H), 7.28 (dd, J_1 = 8.0 Hz, J_2 = 6.0 Hz, 1H), 4.49 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 163.9 (C), 161.9 (C), 147.8 (C), 133.4 (C), 128.0 (CH), 127.0 (CH), 122.8 (d, J_{CF} = 7.4 Hz, CH), 117.0 (d, J_{CF} = 22.1 Hz, C), 115.3 (CH), 111.8 (C), 103.5 (d, J_{CF} = 23.4 Hz, CH), 45.0 (CH_3), 15.6 (CH_3); ATR-FTIR (thin film): 2918, 1631, 1451, 1114, 788 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{13}H_{11}FN_2$: 214.0906, found: 214.0909.

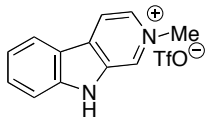
F. Rh_2(II)-Catalyzed β-Carbolinium Ion Formation and Reduction



General procedure for the synthesis of tryptolines. To a mixture of pyridinium **1.59** (0.144 g, 0.4 mmol, 1.0 equiv), 100% w/w of crushed 4 Å mol sieves, and $Rh_2(esp)_2$ (0.003 g, 0.004 mmol, 0.01 equiv) were added 4 mL of DCE (0.1 M). The resulting mixture was stirred at 80 °C for 15 h. The heterogenous mixture was then filtered through celite, and the filtrate was concentrated *in vacuo*. The resulting 1-methyl-β-carbolonium triflate **1.69** was used directly in the subsequent reduction reaction without further purification.

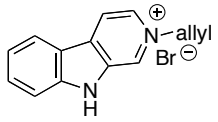
Following the procedure developed by Elliot,[75] 1-methyl-β-carbolonium triflate **1.69** and $NaBH_4$ (4 equiv) were added to a 50 mL round bottom flask. A 1:1 v/v of methanol and water (0.03 M) was then slowly added. The resulting mixture was stirred at room temperature for 15 min, then heated to 100 °C for 10 min. After cooling to room temperature, the reaction mixture was diluted with 10 mL of CH_2Cl_2 and 10 mL of water and separated. The aqueous phase was extracted with additional 2 × 20 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the crude product **1.85**. Purification by MPLC (EtOAc: hexanes) afforded the product.

F1. Preparation of 1Methyl-β-Carbolinium Triflates



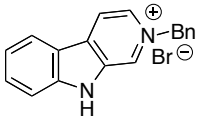
1.69

2-Methyl-9*H*-pyrido[3,4-*b*]indolium triflate (**1.69**).[73] The general procedure was followed using 0.144 g of pyridinium triflate **1.59** (0.4 mmol) and 0.003 g of $Rh_2(esp)_2$ (0.004 mmol) in 4 mL of DCE. 2-Methyl-9*H*-pyrido[3,4-*b*]indolium **1.69** was previously reported by Rocca and co-workers.[73] Selected spectral data: ^{1}H NMR (500 MHz; CD_3OD) δ 9.10 (s, 1H), 8.59 (d, *J* = 6.4 Hz, 1H), 8.44 (d, *J* = 6.3 Hz, 1H), 8.36 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.45 (t, *J* = 7.5 Hz, 1H), 4.50 (s, 3H).



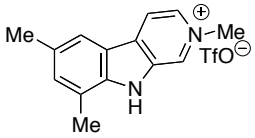
1.70

2-Allyl-9*H*-pyrido[3,4-*b*]indolium triflate (**1.70**). The general procedure was followed using 0.127 g of pyridinium triflate **1.60** (0.4 mmol), 0.003 g of $Rh_2(esp)_2$ (0.004 mmol) and 0.113 g of AgOTf (0.44 mmol, 1.1 equiv) in 4 mL of DCE. Selected spectral data: ^{1}H NMR (500 MHz; CD_3OD) δ 9.20 (s, 1H), 8.68 (d, *J* = 6.1 Hz, 1H), 8.53 (d, *J* = 6.2 Hz, 1H), 8.41 (d, *J* = 8.0 Hz, 1H), 7.82 (d, *J* = 7.7 Hz, 1H), 7.77 (s, 1H), 7.49-7.46 (m, 1H), 6.26 (dq, *J* = 16.7, 8.3 Hz, 1H), 5.53-5.50 (m, 2H), 5.36 (d, *J* = 5.9 Hz, 2H), 3.35 (s, 3H).



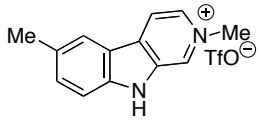
1.71

2-Phenylmethyl-9*H*-pyrido[3,4-*b*]indolium triflate (**1.71**). **Amendola et al., 2005, #40219**}[76] The general procedure was followed using 0.147 g of pyridinium triflate **1.61** (0.4 mmol), 0.003 g of $Rh_2(esp)_2$ (0.004 mmol) and 0.113 g of AgOTf (0.44 mmol, 1.1 equiv) in 4 mL of DCE. 2-Phenylmethyl-9*H*-pyrido[3,4-*b*]indolium triflate **1.71** was previously reported by Fabbrizzi and co-workers.[76] Selected spectral data: ^{1}H NMR (500 MHz; CD_3OD) δ 9.28 (s, 1H), 8.63 (d, *J* = 8.2 Hz, 2H), 8.37 (d, *J* = 8.1 Hz, 1H), 7.79-7.75 (m, 1H), 7.74 (s, 1H), 7.53 (d, *J* = 7.0 Hz, 1H), 7.47-7.43 (m, 5H), 5.91 (s, 2H).



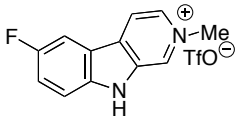
1.72

2,6,8-Trimethyl-9*H*-pyrido[3,4-*b*]indolium triflate (**1.72**). The general procedure was followed using 0.155 g of pyridinium **1.62** (0.4 mmol) and 0.003 g of $Rh_2(esp)_2$ (0.004 mmol) in 5 mL of DCE. Selected spectral data: ^{1}H NMR (500 MHz; CD_3OD) δ 9.01 (s, 1H), 8.51 (d, *J* = 5.8 Hz, 1H), 8.40 (d, *J* = 5.3 Hz, 1H), 7.94 (s, 1H), 7.43 (s, 1H), 4.50 (s, 3H), 2.60 (s, 3H), 2.51 (s, 3H).



1.73

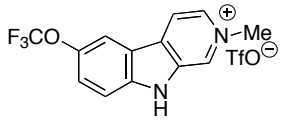
2,6-Dimethyl-9*H*-pyrido[3,4-*b*]indolium triflate (**1.73**).[77] The general procedure was followed using 0.112 g of pyridinium triflate **1.63** (0.3 mmol) and 0.0023 g of $Rh_2(esp)_2$ (0.003 mmol) in 4 mL of DCE. 2,6-Dimethyl-9*H*-pyrido[3,4-*b*]indolium **5f** was previously reported by Gademan and co-workers.[77] Selected spectral data: ^{1}H NMR (500 MHz; CD_3OD): δ 9.10 (s, 1H), 8.58 (d, *J* = 6.4 Hz, 1H), 8.43 (d, *J* = 6.5 Hz, 1H), 8.18 (s, 1H), 7.65 (s, 2H), 4.50 (s, 3H), 2.56 (s, 3H).



1.74

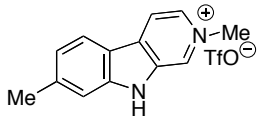
2-Methyl-6-fluoro-9*H*-pyrido[3,4-*b*]indolium triflate (**1.74**)[77] The general procedure was followed using 0.151 g of pyridinium triflate **1.64** (0.4 mmol) and 0.003 g of $Rh_2(esp)_2$ (0.004 mmol) in 5 mL of DCE. 2-Methyl-6-fluoro-9*H*-pyrido[3,4-*b*]indolium **1.74** was previously reported by Gademan and co-workers.[77] Selected spectral data: ^{1}H NMR (500 MHz; CD_3OD) δ 9.19 (s, 1H),

8.63 (dd, *J* = 7.8, 4.2 Hz, 1H), 8.48 (d, *J* = 6.3 Hz, 1H), 8.13-8.09 (m, 1H), 7.75 (dt, *J* = 6.7, 3.4 Hz, 1H), 7.61 (tdd, *J* = 6.2, 5.1, 2.1 Hz, 1H), 4.53 (s, 3H).



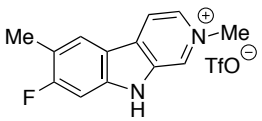
1.76

2-Methyl-6-trifluoromethyl-9*H*-pyrido[3,4-*b*]indolium triflate (**1.76**). The general procedure was followed using 0.178 g of pyridinium triflate **1.66** (0.4 mmol) and 0.003 g of $Rh_2(esp)_2$ (0.004 mmol) in 5 mL of DCE. Selected spectral data: ^{1}H NMR (500 MHz; CD_3OD): δ 9.24 (s, 1H), 8.71 (d, *J* = 6.4 Hz, 1H), 8.53 (d, *J* = 6.4 Hz, 1H), 8.39 (s, 1H), 7.84 (d, *J* = 9.0 Hz, 1H), 7.72 (d, *J* = 8.9 Hz, 1H), 4.55 (s, 3H).



1.77

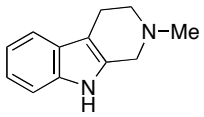
2,7-Dimethyl-9*H*-pyrido[3,4-*b*]indolium triflate (**1.77**).[77] The general procedure was followed using 0.150 g of pyridinium triflate **1.67** (0.4 mmol) and 0.003 g of $Rh_2(esp)_2$ (0.004 mmol) in 5 mL of DCE. 2,7-Dimethyl-9*H*-pyrido[3,4-*b*]indolium **1.77** was previously reported by Gademan and co-workers.[77] Selected spectral data: ^{1}H NMR (500 MHz; CD_3OD) δ 8.99 (d, *J* = 0.2 Hz, 1H), 8.46 (d, *J* = 6.3 Hz, 1H), 8.37-8.36 (m, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 7.48 (s, 1H), 7.26 (d, *J* = 8.1 Hz, 1H), 4.45 (s, 3H), 2.57 (s, 3H).



1.78

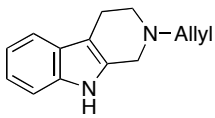
2,6-Dimethyl-7-fluoro-9*H*-pyrido[3,4-*b*]indolium triflate (**1.78**). The general procedure was followed using 0.157 g of pyridinium triflate **1.68** (0.4 mmol) and 0.003 g of $Rh_2(esp)_2$ (0.004 mmol) in 5 mL of DCE. Selected spectral data: ^{1}H NMR (500 MHz; CD_3OD) δ 9.09 (s, 1H), 8.53 (d, *J* = 6.4 Hz, 1H), 8.45 (d, *J* = 6.3 Hz, 1H), 8.25 (d, *J* = 7.3 Hz, 1H), 7.39 (d, *J* = 10.0 Hz, 1H), 4.49 (s, 3H), 2.45 (s, 3H).

F2. Preparation of Tryptolines



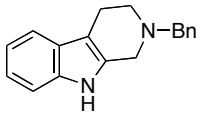
1.85

Tryptoline (**1.85**).[28] The general procedure was followed using 0.050 g of indolium triflate **1.69** (0.15 mmol) and 0.023 g of $NaBH_4$ (0.6 mmol) in 5 mL of MeOH and 5 mL of H_2O to afford the product as white solid (0.035 g, 99%). Tryptoline **1.85** was previously reported by us.[28] ^{1}H NMR (500 MHz; $CDCl_3$) δ 7.81 (s, 1H), 7.48 (d, *J* = 7.7 Hz, 1H), 7.29 (d, *J* = 8.0 Hz, 1H), 7.15-7.07 (m, 2H), 3.61 (s, 2H), 2.85-2.84 (m, 2H), 2.82-2.80 (m, 2H), 2.52 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 136.1 (C), 131.8 (C), 127.3 (C), 121.3 (CH), 119.3 (CH), 118.0 (CH), 110.7 (CH), 108.1 (C), 53.0 (CH_2), 52.4 (CH_2), 45.7 (CH_3), 21.5 (CH_2); IR: 2934, 1445, 1236, 968, 737 cm^{-1}.



1.86

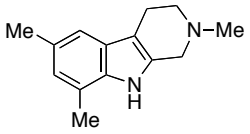
Tryptoline (**1.86**). The general procedure was followed using 0.4 mmol of indolium **1.70** and 0.061 g of $NaBH_4$ (1.6 mmol) in 10.5 mL of MeOH and 4.5 mL of H_2O to afford the product as white solid (0.060 g, 60%), R_f = 0.45 (1.5:1.5:7 EtOAc:MeOH:hexane). ^1H NMR (500 MHz; CD_3OD) δ 7.39-7.38 (m, 1H), 7.27 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.04 (t, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 7.4 Hz, 1H), 6.03-5.95 (m, 1H), 5.33 (dd, *J* = 17.1, 1.5 Hz, 1H), 5.28 (d, *J* = 10.1 Hz, 1H), 3.75 (s, 2H), 2.94 (d, *J* = 5.3 Hz, 2H), 2.86-2.85 (m, 2H), 3.33 (d, *J* = 6.6 Hz, 2H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 136.6 (C), 133.6 (CH), 130.7 (C), 126.8 (C), 120.6 (CH), 118.6 (CH_2), 118.4 (CH), 117.1 (CH), 110.5 (CH), 106.5 (C), 60.3 (CH_2), 50.5 (CH_2), 49.7 (CH_2), 20.5 (CH_2); IR: 2929, 1451, 1309, 1162, 910, 732 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{14}H_{16}N_2$ $(M)^+$: 212.1313, found: 212.13079.



1.87

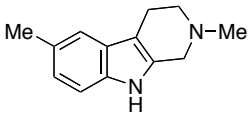
Tryptoline (**1.87**).[78] The general procedure was followed using 0.4 mmol of indolium **1.71** and 0.061 g of $NaBH_4$ (1.6 mmol) in 10.5 mL of MeOH and 4.5 mL of H_2O to afford the product as yellow solid (0.074 g, 71%), R_f = 0.47 (1.5:1.5:7 EtOAc:MeOH:hexane). Tryptoline **1.87** was previously reported by Kuehne and co-workers.[78] ^1H NMR (500 MHz; CD_3OD) δ 7.40-7.33 (m, 5H), 7.30-7.28 (m, 1H), 7.25 (dd, *J* = 8.0, 0.7 Hz, 1H), 7.03 (dd, *J* = 8.0, 7.1 Hz, 1H), 6.96 (dd, *J* = 7.7, 7.1 Hz, 1H), 3.74 (s, 2H), 3.63 (s, 2H), 2.86 (t, *J* = 5.6 Hz, 2H), 2.80 (d, *J* = 5.9 Hz, 2H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 137.0 (C), 136.6 (C), 131.3 (C), 129.5 (CH), 128.1 (CH), 127.2 (CH), 127.0 (C), 120.5 (CH), 118.3 (CH), 117.1 (CH),

110.4 (CH), 106.6 (C), 61.8 (CH_2), 50.6 (CH_2), 49.9 (CH_2), 20.7 (CH_2); IR: 2929, 1453, 1020, 739 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{18}H_{18}N_2$ $(M)^+$: 262.1470, found: 262.14560.



1.88

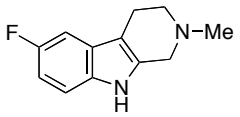
Tryptoline (**1.88**). The general procedure was followed using 0.4 mmol of indolium triflate **1.72** and 0.061 g of $NaBH_4$ (1.6 mmol) in 10.5 mL of MeOH and 4.5 mL of H_2O to afford the product as white solid (0.071 g, 83%), R_f = 0.30 (3:7 MeOH:CH_2Cl_2). ^1H NMR (500 MHz; CD_3OD) δ 7.00 (s, 1H), 6.68 (s, 1H), 3.63 (s, 2H), 2.79 (s, 4H), 2.49 (s, 3H), 2.39 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 134.2 (C), 131.0 (C), 127.5 (C), 126.7 (C), 122.9 (CH), 119.5 (C), 114.6 (CH), 106.1 (C), 52.8 (CH_2), 52.0 (CH_2), 44.3 (CH_3), 21.0 (CH_2), 20.2 (CH_3), 15.5 (CH_3); IR: 2910, 1444, 1373, 1319, 1119, 838 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{14}H_{18}N_2$ $(M)^+$: 214.14700, found: 214.14607.



1.89

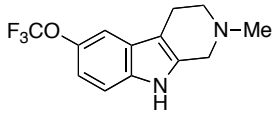
Tryptoline (**1.89**).[79] The general procedure was followed using 0.4 mmol of indolium triflate **1.73** and 0.061 g of $NaBH_4$ (1.6 mmol) in 10.5 mL of MeOH and 4.5 mL of H_2O to afford the product as white solid (0.056 g, 94%), R_f = 0.41 (1.5:1.5:7 EtOAc:MeOH:hexane). Tryptoline **1.89** was previously reported by Lehmann and Pohl.[79] ^1H NMR (500 MHz; CD_3OD) δ 7.17 (s, 1H), 7.15 (d, *J* = 8.2

Hz, 1H), 6.88 (d, *J* = 8.3 Hz, 1H), 3.70 (s, 2H), 2.88 (d, *J* = 5.3 Hz, 2H), 2.84 (d, *J* = 5.4 Hz, 2H), 2.55 (s, 3H), 2.38 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 134.9 (C), 133.0 (C), 128.0 (C), 124.1 (C), 120.6 (CH), 116.6 (CH), 111.6 (CH), 106.2 (C), 52.6 (CH_2), 51.7 (CH_2), 44.2 (CH_3), 20.6 (CH_2); IR: 2852, 1454, 1246, 1149, 784 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{13}H_{16}N_2$ $(M)^+$: 200.13135, found: 200.13210.



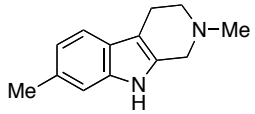
1.90

Tryptoline (**1.90**).[79] The general procedure was followed using 0.4 mmol of indolium triflate **1.74** and 0.061 g of $NaBH_4$ (1.6 mmol) in 10.5 mL of MeOH and 4.5 mL of H_2O to afford the product as white solid (0.058 g, 71%), R_f = 0.50 (3:7 MeOH:CH_2Cl_2). Tryptoline **1.90** was previously reported by Lehmann and Pohl.[79] ^{1}H NMR (500 MHz; CD_3OD) δ 7.20 (dd, *J* = 8.7, 4.4 Hz, 1H), 7.04 (dd, *J* = 9.7, 2.5 Hz, 1H), 6.79 (td, *J* = 9.1, 2.5 Hz, 1H), 3.64 (s, 2H), 2.83 (dd, *J* = 6.3, 3.3 Hz, 2H), 2.80 (d, *J* = 4.8 Hz, 2H), 2.51 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 157.6 (d, *J* = 233.2 Hz, C), 133.3 (C), 133.1 (C), 127.2 (d, *J* = 9.5 Hz, C), 111.0 (d, *J* = 9.2 Hz, CH), 108.3 (d, *J* = 26.0 Hz, CH), 106.5 (d, *J* = 5.1 Hz, C), 101.9 (d, *J* = 22.4 Hz, CH), 52.6 (CH_2), 51.76 (CH_2), 44.2 (CH_3), 20.70 (CH_2); ^{19}F NMR (471 MHz, CD_3OD) δ –118.1; IR: 2807, 1442, 1146, 849, 780, 596 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_{13}N_2F$ $(M)^+$: 204.10628, found: 204.10558.



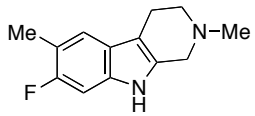
1.92

Tryptoline (**1.92**). The general procedure was followed using 0.4 mmol of indolium triflate **1.76** and 0.061 g of $NaBH_4$ (1.6 mmol) in 10.5 mL of MeOH and 4.5 mL of H_2O to afford the product as white solid (0.096 g, 88%), R_f = 0.45 (3:7 MeOH:CH_2Cl_2). ^1H NMR (500 MHz; CD_3OD) δ 7.28 (d, *J* = 8.7 Hz, 1H), 7.26 (s, 1H), 6.94 (d, *J* = 8.7 Hz, 1H), 3.62 (s, 2H), 2.80 (s, 4H), 2.49-2.48 (m, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 142.4 (C), 134.9 (C), 133.7 (C), 127.0 (C), 120.9 (q, *J* = 253 Hz, CF_3), 114.1 (CH), 111.1 (CH), 109.6 (CH), 106.9 (C), 52.5 (CH_2), 51.6 (CH_2), 44.2 (CH_3), 20.6 (CH_2); ^{19}F NMR (471 MHz, CD_3OD) δ –61.2; IR: 2797, 1454, 1244, 1127, 788 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{13}H_{13}N_2OF_3$ $(M)^+$: 270.09801, found: 270.09897.



1.93

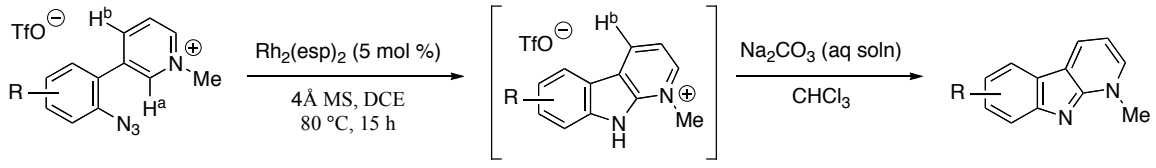
Tryptoline (**1.93**). The general procedure was followed using 0.4 mmol of indolium triflate **1.77** and 0.061 g of $NaBH_4$ (1.6 mmol) in 10.5 mL of MeOH and 4.5 mL of H_2O to afford the product as white solid (0.072 g, 90%), R_f = 0.47 (3:7 MeOH:CH_2Cl_2). ^1H NMR (500 MHz; CD_3OD) δ 7.25 (d, *J* = 8.0 Hz, 1H), 7.06 (s, 1H), 6.81 (d, *J* = 8.0 Hz, 1H), 3.62 (s, 2H), 2.81 (s, 4H), 2.50 (s, 3H), 2.39 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) 137.0 (C), 130.29 (C), 130.16 (C), 124.8 (C), 120.0 (CH), 116.8 (CH), 110.5 (CH), 106.0 (C), 52.7 (CH_2), 51.8 (CH_2), 44.2 (CH_3), 20.9 (CH_2), 20.5 (CH_3); IR: 2782, 1446, 1165, 804 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{13}H_{16}N_2$ $(M)^+$: 200.13135, found: 200.13063.



1.94

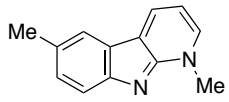
Tryptoline (**1.94**). The general procedure was followed using 0.4 mmol of indolium triflate **1.78** and 0.061 g of $NaBH_4$ (1.6 mmol) in 10.5 mL of MeOH and 4.5 mL of H_2O to afford the product as white solid (0.087 g, 100%), R_f = 0.37 (3:7 MeOH:CH_2Cl_2). ^{1}H NMR (500 MHz; CD_3OD) δ 7.17 (d, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 10.7 Hz, 1H), 3.65 (s, 2H), 2.86 (t, *J* = 5.3 Hz, 2H), 2.81 (t, *J* = 5.2 Hz, 2H), 2.53 (s, 3H), 2.30-2.29 (m, 3H).; ^{13}C NMR (126 MHz; $CDCl_3$) δ 157.9 (d, *J* = 233.9 Hz, C), 135.0 (d, *J* = 12.7 Hz, C), 131.0 (C), 123.4 (C), 118.4 (d, *J* = 6.8 Hz, CH), 115.4 (d, *J* = 18.8 Hz, C), 105.8 (C), 96.3 (d, *J* = 27.6 Hz, CH), 52.6 (CH_2), 51.7 (CH_2), 44.1 (CH_3), 20.6 (CH_2), 13.6 (CH_3); ^{19}F NMR (470 MHz, CD_3OD) δ –118.1; IR: 2910, 1454, 1322, 1130, 860 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{13}H_{15}N_2F$ $(M)^+$: 218.12193, found: 218.12113.

G. Rh_2(II)-Catalyzed α-Carboline Formation



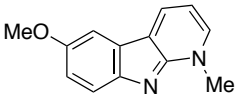
General procedure for the synthesis of 1*H*-Pyrido[2,3-*b*]indoles. To a mixture of pyridinium triflate **1.117** (0.030 g, 0.08 mmol, 1.0 equiv), 100% w/w of crushed 4 Å mol sieves, and $Rh_2(esp)_2$ (0.003 g, 0.004 mmol, 0.05 equiv) were added 0.83 mL of DCE (0.1 M), the resulting mixture was stirred at 80 °C for 15

h. The heterogenous mixture was then filtered through celite and the filtrate was concentrated *in vacuo*. In a separatory funnel, the reaction mixture was diluted with 20 mL of a 5% aqueous solution of Na_2CO_3. The mixture was vigorously shaken, and the resulting mixture was extracted with 3 × 10 mL of $CHCl_3$. Solid Na_2CO_3 was added to the combined organic phases. The mixture was filtered, and the filtrate was concentrated *in vacuo* to afford analytically pure 1-methyl-1*H*-pyrido[2,3-*b*]indole **1.126**.



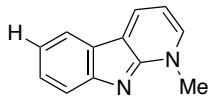
1.126

1,6-Dimethyl-1*H*-pyrido[2,3-*b*]indole (**1.126**).[80] The general procedure was followed using 0.030 g of pyridinium triflate **1.117**. Purification of the reaction mixture using MPLC afforded the product as a yellow solid (0.013 g, 83% from **1.117**). 1-Methyl-α-carboline **1.126** was previously reported by Peczynska-Czoch and co-workers.[80] ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.28 (dd, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 1H), 7.85 (s, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.62 (d, J = 6.5 Hz, 1H), 7.37 (dd, J_1 = 8.5 Hz, J_2 = 1.5 Hz, 1H), 6.76 (t, J = 6.5 Hz, 1H), 4.25 (s, 3H), 2.53 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 153.6 (C), 151.8 (C), 133.2 (CH), 129.7 (CH), 128.5 (CH), 128.4 (C), 127.0 (C), 123.1 (C), 120.7 (CH), 117.7 (CH), 106.6 (CH), 40.2 (CH_3), 21.5 (CH_3); ATR-FTIR (thin film): 1489, 1302, 1183, 809, 753 cm^{-1}.



1.127

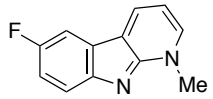
6-Methoxy-1-methyl-1*H*-pyrido[2,3-*b*]indole (**1.127**).[80] The general procedure was followed using 0.030 g of pyridinium triflate **1.118**. Purification of the reaction mixture using MPLC afforded the product as a yellow solid (0.010 g, 63% from **1.118**). 1-Methyl-α-carboline **1.127** was previously reported by Peczynska-Czoch and co-workers.[80] ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.31 (dd, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 1H), 7.74 (d, J = 9.0 Hz, 1H), 7.65 (d, J = 6.5 Hz, 1H), 7.54 (d, J = 2.5 Hz, 1H), 7.20 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 6.78 (t, J = 7.0 Hz, 1H), 4.27 (s, 3H), 3.92 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 154.4 (C), 153.8 (C), 153.1 (C), 133.5 (CH), 128.9 (CH), 127.1 (C),123.0 (C), 118.6 (CH), 117.5 (CH), 106.4 (CH), 103.7 (CH), 56.1 (CH_3), 40.3 (CH_3); ATR-FTIR (thin film): 1467, 1309, 1195, 1050, 750 cm^{-1}.



1.128

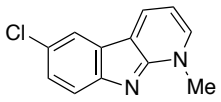
1-Methyl-1*H*-pyrido[2,3-*b*]indole (**1.128**).[80] The general procedure was followed using 0.030 g of pyridinium triflate **1.119**. Purification of the reaction mixture using MPLC afforded the product as a yellow solid (0.012 g, 80% from **1.119**. 1-Methyl-α-carboline **1.128** was previously reported by Peczynska-Czoch and co-workers.[80] ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.33 (dd, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 1H), 8.06 (d, J = 7.5 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 6.5 Hz, 1H), 7.54 (td, J_1 = 7.5 Hz, J_2 = 1.5 Hz, 1H), 7.23 (td, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H), 6.80 (t, J = 6.5 Hz, 1H), 4.27 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 153.8 (C), 153.7 (C), 133.3 (CH), 128.7 (CH), 128.2 (CH), 127.1 (C), 123.1 (C), 120.8 (CH), 119.1

(CH), 118.1 (CH), 106.9 (CH), 40.3 (CH_3); ATR-FTIR (thin film): 1489, 1306, 1201, 753, 730 cm^{-1}.



1.129

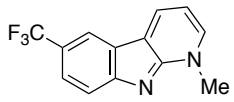
6-Fluoro-1-methyl-1*H*-pyrido[2,3-*b*]indole (**1.129**).[80] The general procedure was followed using the crude reaction using 0.030 of pyridinium triflate **1.120**. Purification of the reaction mixture using MPLC afforded the product as a yellow solid (0.013 g, 83% from **1.120**). 1-Methyl-α-carboline **1.129** was previously reported by Peczynska-Czoch and co-workers.[80] ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.31 (dd, J_1 = 7.0 Hz, J_2 = 0.5 Hz, 1H), 7.74 (dd, J_1 = 8.5 Hz, J_2 = 4.5 Hz, 1H), 7.68 (m, 2H), 7.27 (td, J_1 = 9.0 Hz, J_2 = 2.5 Hz, 1H), 6.80 (t, J = 6.5 Hz, 1H), 4.26 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 156.4 (C), 153.8 (C), 149.9 (C), 134.0 (CH), 129.7 (CH), 126.8 (d, J = 5.4 Hz, C), 122.9 (C), 118.6 (d, J = 9.4 Hz, CH), 116.1 (d, J = 24.1 Hz, CH), 106.7 (CH), 106.3 (d, J = 23.9 Hz, CH), 40.3 (CH_3); ATR-FTIR (thin film): 1452, 1328, 1166, 803, 755 cm^{-1}.



1.130

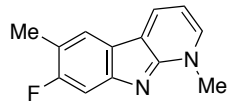
6-Chloro-1-methyl-1*H*-pyrido[2,3-*b*]indole (**1.130**).[81] The general procedure was followed using 0.030 g of pyridinium triflate **1.121**. Purification of the reaction mixture using MPLC afforded the product as a yellow solid (0.011 g, 67% from **1.121**). 1-Methyl-α-carboline **1.130** was previously reported by Maes and co-workers.[81] ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.31 (dd, J_1 = 7.0 Hz, J_2 = 1.0

Hz, 1H), 7.99 (d, *J* = 2.5 Hz, 1H), 7.73 (d, *J* = 8.5 Hz, 1H), 7.70 (d, *J* = 6.0 Hz, 1H), 7.47 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 6.83 (t, *J* = 6.5 Hz, 1H), 4.27 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 153.8 (C), 151.9 (C), 134.1 (CH), 129.8 (CH), 128.3 (CH), 126.2 (C), 124.4 (C), 123.9 (C), 120.5 (CH), 119.1 (CH), 107.3 (CH), 40.4 (CH_3); ATR-FTIR (thin film): 1438, 1198, 1040, 819, 736 cm^{-1}.



1.131

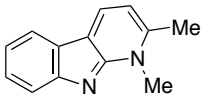
1-Methyl-6-trifluoromethyl-1*H*-pyrido[2,3-*b*]indole (**1.131**). The general procedure was followed using 0.030 g of pyridinium triflate **1.122** Purification of the reaction mixture using MPLC afforded the product as a yellow solid (0.014 g, 78% from **1.122**). ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.42 (d, *J* = 7.0 Hz, 1H), 8.32 (s, 1H), 7.87 (d, *J* = 8.5 Hz, 1H), 7.76 (m, 2H), 6.91 (t, *J* = 7.0 Hz, 1H), 4.31 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 155.4 (C), 154.7 (C), 134.4 (CH), 130.1 (CH), 126.5 (C), 124.7 (d, *J* = 3.5 Hz, CH), 124.3 (d, *J* = 27.4 Hz, CF_3), 122.4 (C), 121.0 (d, *J* = 31.1 Hz, C), 118.5 (d, *J* = 3.9 Hz, CH), 118.1 (CH), 108.0 (CH), 40.5 (CH_3); ATR-FTIR (thin film): 1324, 1265, 1097, 825, 743 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{13}H_9F_3N_2$: 250.0718, found: 250.0716.



1.132

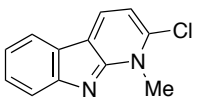
6-Fluoro-1-methyl-1*H*-pyrido[2,3-*b*]indole (**1.132**). The general procedure was followed using 0.030 g of pyridinium triflate **1.123** Purification of the reaction mixture using MPLC afforded the product as a yellow solid (0.011 g, 64% from

1.123). ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.23 (dd, J_1 = 7.5 Hz, J_2 = 1.0 Hz, 1H), 7.82 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 6.5 Hz, 1H), 7.43 (d, J = 11.0 Hz, 1H), 6.80 (t, J = 6.5 Hz, 1H), 4.25 (s, 3H), 2.42 (d, J = 1.5 Hz, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 162.2 (d, J_F = 242.5 Hz, C), 154.1 (C), 153.2 (d, J_F = 12.6 Hz, C), 132.6 (CH), 128.0 (CH), 126.6 (C), 122.4 (d, J_{CF} = 7.25 Hz, CH), 119.2 (C), 116.7 (d, J_{CF} = 20.0 Hz, C), 107.2 (CH), 103.6 (CH), 40.2 (CH_3), 15.1 (CH_3); ATR-FTIR (thin film): 1442, 1324, 1097, 908, 743 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{13}H_{11}FN_2$: 214.0906, found: 214.0899.



1.133

1,2-Dimethyl-1*H*-pyrido[2,3-*b*]indole (**1.133**).[80] The general procedure was followed using 0.030 g of pyridinium triflate **1.124**. Purification of the reaction mixture using MPLC afforded the product as a yellow solid (0.011 g, 69% from **1.124**). 1-Methyl-α-carboline **1.133** was previously reported by Pecnynska-Czoch and co-workers.[80] ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.19 (d, J = 7.5 Hz, 1H), 8.01 (d, J = 7.5 Hz, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.50 (t, J = 8.0 Hz, 1H), 7.20 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 7.0 Hz, 1H), 4.23 (s, 3H), 2.66 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 155.2 (C), 153.3 (C), 142.0 (C), 128.7 (CH), 127.4 (CH), 124.4 (C), 123.6 (C), 120.4 (CH), 118.8 (CH), 117.9 (CH), 108.2 (CH), 34.7 (CH_3), 20.3 (CH_3); ATR-FTIR (thin film): 1631, 1559, 1299, 755, 727 cm^{-1}.

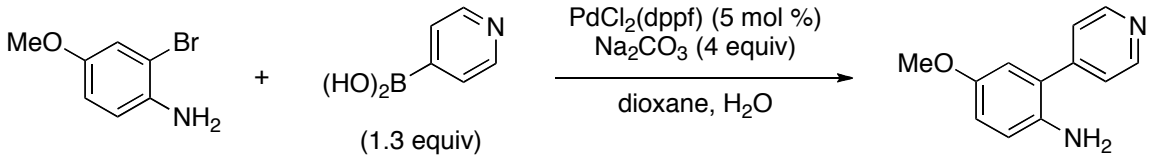


1.134

2-Chloro-1-methyl-1H-pyrido[2,3-*b*]indole (**1.134**).[80] The general procedure was followed using 0.030 g of pyridinium triflate **1.125**. Purification of the reaction mixture using MPLC afforded the product as a yellow solid (0.013 g, 77% from **1.125**). 1-Methyl-α-carboline **1.134** was previously reported by Peczynska-Czoch and co-workers.[80] ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.17 (d, *J* = 7.5 Hz, 1H), 8.01 (d, *J* = 7.5 Hz, 1H), 7.80 (d, *J* = 8.0 Hz, 1H), 7.54 (t, *J* = 8.0 Hz, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 6.91 (d, *J* = 7.5 Hz, 1H), 4.38 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 155.3 (C), 155.9 (C), 134.5 (C), 128.3 (CH), 128.2 (CH), 125.4 (C), 123.3 (C), 120.7 (CH), 119.7 (CH), 118.3 (CH), 107.6 (CH), 36.4 (CH_3); ATR-FTIR (thin film): 1600, 1482, 1188, 815, 724 cm^{-1}.

H. Synthesis of (±)-Horsfiline and Non-natural Analog

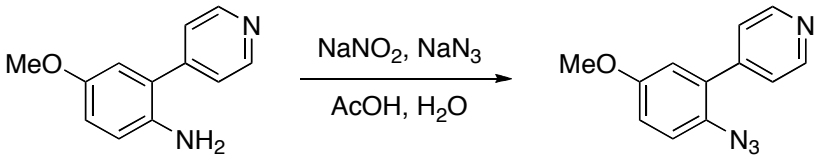
H1. Preparation of Biaryl Amine



General procedure for the formation of 4-(2-Amino-5-methoxyphenyl)pyridine (**1.97**). In a dry 100 mL round bottom flask, 0.320 g of 4-pyridineboronic acid (2.6 mmol), 0.848 g of Na_2CO_3 (8 mmol), and 0.073 g of $PdCl_2$(dppf) were dissolved in 10 mL of dioxane and 4 mL of H_2O. 2-Bromo-4-methoxyaniline (0.404 g, 2.0 mmol) was then added, and the resulting mixture was heated at 80 °C for 2.5 hours. After cooling, the reaction mixture was diluted

with a 1.5 N NaOH aqueous solution and 30 mL of CH_2Cl_2. The aqueous phase was extracted with 3 × 30 mL of CH_2Cl_2. The combined organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford brown oil. Purification of the reaction mixture using MPLC afforded the product as brown solid (0.335 g, 84%). R_f = 0.39 (15:15:70 EtOAc:MeOH:hexane). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.67 (d, *J* = 4.7 Hz, 2H), 7.42 (d, *J* = 4.7 Hz, 2H), 6.83-6.81 (m, 1H), 6.75-6.71 (m, 2H), 3.77 (s, 3H), 3.52 (s, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 152.9 (C), 150.4 (CH), 147.5 (C), 137.0 (C), 125.5 (C), 123.8 (CH), 117.5 (CH), 115.8 (CH), 115.2 (CH), 55.9 (CH_3); IR: 3384, 1598, 1488, 1407, 1281, 1173, 1041, 821 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_{12}N_2O$: 200.09497, found: 200.09415.

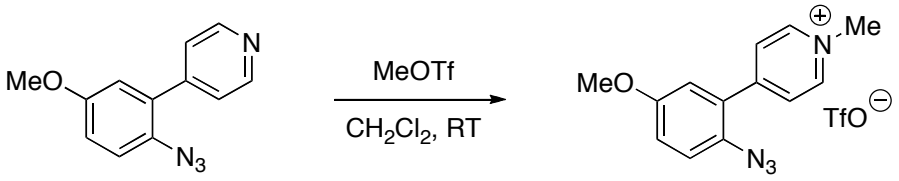
H2. Preparation of Pyridil Biaryl Azide



General procedure for the preparation of 4-(2-Azido-5-methoxyphenyl)pyridine (**1.98**). In a 100 mL of round bottom flask, 0.557 g of 4-(2-amino-5-methoxyphenyl)pyridine **1.97** (2.8 mmol) was dissolved in 12 mL of HOAc and 6 mL of H_2O and chilled in an ice bath. $NaNO_2$ (0.269 g, 3.9 mmol) was added slowly, then the resulting mixture was stirred at 0 °C for 1.5 hour. NaN_3 (0.274 g, 4.2 mmol) was then added slowly, the resulting mixture was

warmed up to ambient temperature, and stirred for 30 minutes. The solution was then diluted with 20 mL of water and 20 mL of CH_2Cl_2, and basified by slow addition of K_2CO_3 until the pH of the reaction mixture was 8. The phases were separated and the aqueous phase was extracted with an additional 2 × 20 mL of CH_2Cl_2. The combined organic phase were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford oil. Purification by MPLC (EtOAc:MeOH:hexane) afforded the product as yellow solid (0.566 g, 90%), R_f = 0.45 (2:8 EtOAc:hexane), m.p. = 95-100 °C: ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.62 (d, *J* = 6.0 Hz, 2H), 7.34 (dd, *J* = 4.5, 1.5 Hz, 2H), 7.15 (d, *J* = 8.8 Hz, 1H), 6.96 (dd, *J* = 8.8, 2.9 Hz, 1H), 6.84 (d, *J* = 2.9 Hz, 1H), 3.79 (s, 3H); ^{13}C NMR (126 MHz, $CDCl_3$) δ 157.0 (C), 149.7 (CH), 145.7 (C), 131.7 (C), 129.6 (C), 124.1 (CH), 120.1 (CH), 116.1 (CH), 115.5 (CH), 55.7 (CH_3); IR: 2119, 1597, 1483, 1406, 1290, 1217, 1039 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_{19}N_4O$ $(M)^+$: 226.08546, found: 226.08461.

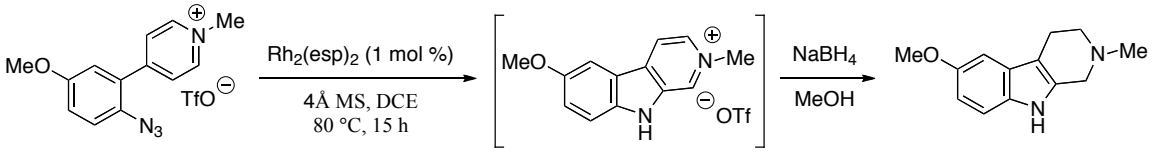
H3. Preparation of Pyridinium Biaryl Azide



General prodecure for the preparation of 1-Methyl-4-(2-azido-5-methoxyphenyl)pyridinium triflate (**1.99**). In a dry 25 mL round bottom flask, 0.556 g of biaryl azide **1.98** (2.5 mmol) was dissolved in 10 mL of dry CH_2Cl_2 (0.5

M) and MeOTf (1.1 equiv) (1.0 equiv) was then added dropwise via syringe over 10 min,and the resulting solution was allowed to stir at ambient temperature overnight. The reaction mixture was concentrated *in vacuo* to afford the product as dark yellow solid (0.860 g, 89%): ^{1}H NMR (500 MHz; CD_3OD) δ 8.87 (d, *J* = 6.6 Hz, 2H), 8.25 (d, *J* = 6.6 Hz, 2H), 7.41 (d, *J* = 8.9 Hz, 1H), 7.25 (dd, *J* = 8.9, 2.9 Hz, 1H), 7.17 (d, *J* = 2.9 Hz, 1H), 4.42 (s, 3H), 3.87 (s, 3H); ^{13}C NMR (126 MHz; CD_3OD) δ 157.4 (C), 154.2 (C), 144.7 (CH), 130.2 (C), 127.9 (C), 127.2 (C), 120.7 (CH), 118.5 (CH), 115.6 (CH), 55.2 (CH_3), 47.1 (CH_3); IR: 2125, 1638, 1261, 1025, 843 cm^{-1}; HRMS (ESI) *m / z* calcd for $C_{13}H_{13}N_4O$ $(M - OTf)^+$: 241.1089, found: 241.1083.

H4. Preparation of Methoxy Substituted Tryptoline

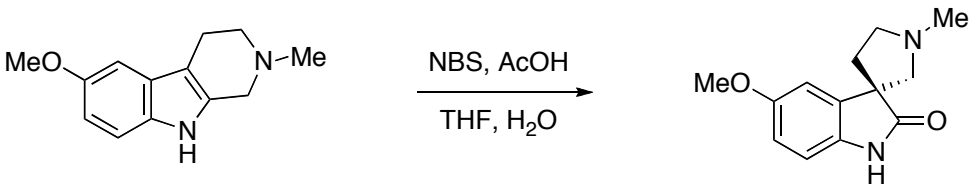


General procedure for the synthesis of 2-Methyl-6-methoxy-9*H*-pyrido[3,4-*b*]indolium triflate (**1.100**).[82] To a mixture of pyridinium triflate **1.99** (0.156 g, 0.4 mmol), 0.156 g of crushed 4 Å mol sieves, and 0.003 g of $Rh_2(esp)_2$ (0.004 mmol) were added 4 mL of DCE. The resulting mixture was stirred at 80 °C for 15 h. The heterogenous mixture was then filtered through celite, and the filtrate was concentrated *in vacuo*. The resulting 1-methyl-β-carbolonium triflate **1.100** was used directly in the subsequent reduction reaction without further purification. 2-Methyl-6-methoxy-9*H*-pyrido[3,4-*b*]indolium **1.100** was isolated

from *Desmodium gangeticum* by Ghosal and Mukherjee.[82] Selected spectral data for **1.100**: ^{1}H NMR (500 MHz; CD_3OD) δ 9.08 (s, 1H), 8.58 (d, *J* = 6.3 Hz, 1H), 8.39 (d, *J* = 6.1 Hz, 1H), 7.82 (s, 1H), 7.64 (d, *J* = 9.0 Hz, 1H), 7.43 (d, *J* = 7.9 Hz, 1H), 4.49 (s, 3H), 3.94 (s, 3H).

General prodecure for the synthesis of Triptoline (**1.101**).[83] 1-Methyl-β-carbolinium triflate **1.100** (0.4 mmol) and 0.061 g of $NaBH_4$ (1.6 mmol) were added to a 50 mL round bottom flask. Methanol (10.5 mL) and 4.5 mL of water were then slowly added. The resulting mixture was stirred at room temperature for 15 min, then heated to 100 °C for 10 min. After cooling to room temperature, the reaction mixture was diluted with 10 mL of CH_2Cl_2 and 10 mL of water and separated. The aqueous phase was extracted with additional 2 × 20 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford the product as white solid (0.079 g, 91%), R_f = 0.46 (5:5 MeOH:CH_2Cl_2). The spectral data matched that reported by White and co-workers:[83] ^{1}H NMR (500 MHz; DMSO-d_6) δ 10.55 (br, 1H), 7.13 (dd, *J* = 8.7, 0.4 Hz, 1H), 6.84 (d, *J* = 2.4 Hz, 1H), 6.62 (dd, *J* = 8.7, 2.5 Hz, 1H), 3.72 (s, 3H), 3.53 (s, 2H), 2.69 (d, *J* = 4.9 Hz, 2H), 2.66 (d, *J* = 4.8 Hz, 2H), 2.41 (s, 3H); ^{13}C NMR (126 MHz; $CDCl_3$) δ 153.5 (C), 133.7 (C), 131.4 (C), 127.4 (C), 111.9 (CH), 110.4 (CH), 106.3 (C), 100.2 (CH), 55.8 (CH_3), 53.1 (CH_2), 52.5 (CH_2), 45.7 (CH_3), 21.6 (CH_2); IR: 2741, 1485, 1214, 1150, 1034, 826 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{13}H_{16}N_2O$ $(M)^+$: 216.1263, found: 216.12548.

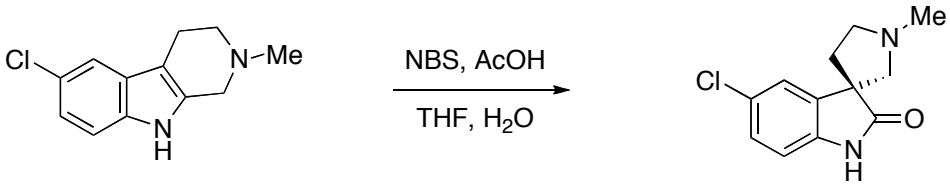
H5. Preparation of (±)-Horsfiline



(±)-horsfiline

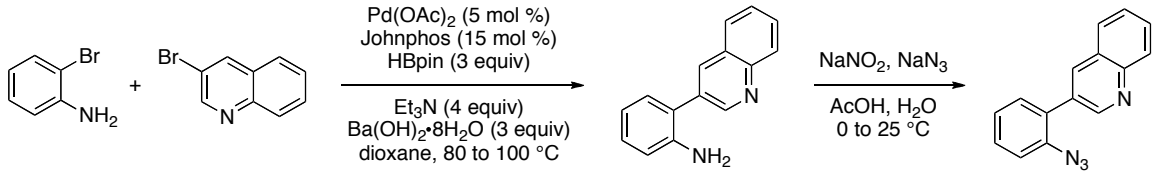
General procedure for the formation of (±)-Horsfiline. To a solution of tryptoline **1.101** (0.095 g, 0.44 mmol) in 5.98 mL of a 1:1:1.5 v/v/v mixture of THF/H_2O/AcOH was added 0.083 g of *N*-bromosuccimide (0.47 mmol, 1.07 equiv). After stirring the mixture at 25 °C for 15 min, 20 mL of a saturated aqueous solution of $NaHCO_3$ was added. The resulting solution was extracted with 3 × 10 mL of a 6:1 mixture of EtOAc and Et_3N. The combined organic phases were dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was purified using MPLC to afford (±)-horsfiline as a colorless solid (0.089 g, 87%). The spectral data matched that reported by White and co-workers:[83] ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.42 (s, 1H), 7.02 (s, 1H), 6.79 (d, J = 8.5 Hz, 1H), 6.72 (dd, J_1 = 8.5 Hz, J_2 = 2.5 Hz, 1H), 3.79 (s, 3H), 3.01 (m, 1H), 2.86 (s, 2H), 2.76 (m, 1H), 2.46 (s, 3H), 2.41 (m 1H), 2.09 (m, 1H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 182.8 (C), 156.2 (C), 137.7 (C), 133.4 (C), 112.4 (CH), 110.4 (CH), 109.8 (CH), 66.4 (CH_2), 56.7 (CH_2), 55.9 (CH_3), 54.2 (C), 41.8 (CH_3), 38.1 (CH_2); ATR-FTIR (thin film): 2940, 1701, 1477, 1030, 727 cm^{-1}.

H6. Preparation of Chloro-Substituted Analog



General procedure for the synthesis of Oxindole 1.106. To a solution of tryptoline **1.91** (0.071 g, 0.32 mmol) in 4.38 mL of a 1:1:1.5 v/v/v mixture of THF/H_2O/AcOH was added 0.061 g of *N*-bromosuccimide (0.34 mmol, 1.07 equiv). After stirring the mixture at 25 °C for 15 min, 20 mL of a saturated aqueous solution of $NaHCO_3$ was added slowly. The resulting solution was extracted with 3 × 10 mL of a 6:1 mixture of EtOAc and Et_3N. The combined organic phases were dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. The resulting residue was purified using MPLC to afford oxindole **7** as a colorless solid (0.054 g, 71%). ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.28 (s, 1H), 7.41 (d, J = 2.0 Hz, 1H), 7.16 (dd, J_1 = 8.5 Hz, J_2 = 2.0 Hz, 1H), 6.81 (d, J = 8.5 Hz, 1H), 3.04 (m, 1H), 2.83 (m, 2H), 2.71 (q, J = 8.5 Hz, 1H), 2.45 (s, 3H), 2.41 (m, 1H), 2.07 (m, 1H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 182.0 (C), 138.4 (C), 138.2 (C), 128.2 (C), 127.7 (CH), 123.9 (CH), 110.4 (CH), 66.3 (CH_2), 56.5 (CH_2), 53.9 (C), 41.7 (CH_3), 37.8 (CH_2); ATR-FTIR (thin film): 2849, 1701, 1477, 1316, 547 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{12}H_{13}ClN_2O$: 236.0716, found: 236.0723.

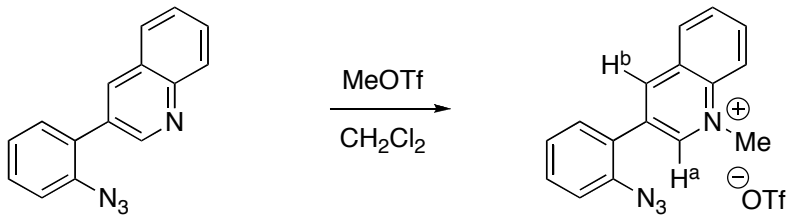
I. Synthesis of Neocryptolepine



General procedure for the synthesis of Neocryptolepine. In a dry 3-neck, 100 mL round bottom flask, 2-bromoaniline (1.0 equiv), $Pd(OAc)_2$ (5 mol %) and [1,1'-biphenyl]-2-yldicyclohexylphosphine (15.0 mol %) were dissolved in anhydrous dioxane (0.5 M) at 23 °C. Et_3N (4.00 equiv) followed by pinacolborane (3.00 equiv) was then added slowly, and the resulting mixture was heated at 80 °C for 1.0 hour. Then $Ba(OH)_2 \cdot 8H_2O$ (3.00 equiv), 2-bromopyridine (1.00 equiv) and water (2.3 M) were subsequently added. The suspension is heated at 100 °C for 4.0 h. After cooling, the reaction mixture was filtered through celite, and 1.5 N NaOH solution and 30 mL of CH_2Cl_2 were added to the filtrate. The phases are separated and the aqueous phase was extracted with an additional 3 × 30 mL of CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford a brown oil. This crude mixture was used for the next step without any further purification.

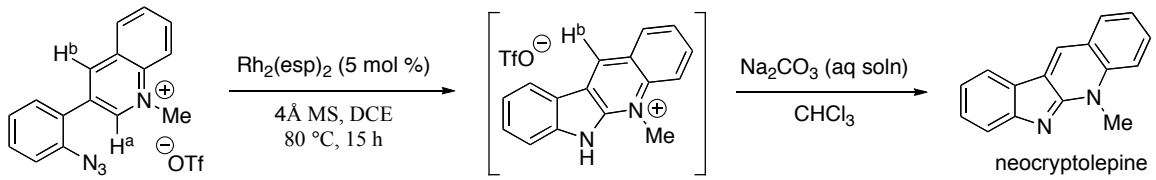
In a 100 mL of round bottom flask, the crude biaryl amine **1.137** (1.0 equiv) was dissolved in HOAc and H_2O (2:1 v/v, 0.25M) and chilled in an ice bath. $NaNO_2$ (1.4 equiv) was added slowly, then the resulting mixture was stirred at 0 °C for 1.5 hour. NaN_3 (1.5 equiv) was then added slowly, the resulting mixture was warmed up to ambient temperature, and stirred for 30 minutes. The solution was

then diluted with 20 mL of water and 20 mL of CH_2Cl_2, and basified by slow addition of K_2CO_3 until the pH of the mixture was 8. The phases were separated and the aqueous phase was extracted with an additional 2 × 20 mL of CH_2Cl_2. The combined organic phase were dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo* to afford oil. Purification by MPLC afforded the product as a yellow solid (1.932 g, 78% over two steps). The spectral data of 3-(2-azidophenyl)-quinoline **1.138** matched that reported by Timári and co-workers.[84] ^{1}H NMR (500 MHz; $CDCl_3$) δ 9.03 (d, J = 2.0 Hz, 1H), 8.21 (d, J = 1.5 Hz, 1H), 8.15 (d, J = 8.0 Hz, 1H), 7.86 (d, J = 8.0 Hz, 1H), 7.74 (td, J_1 = 7.0 Hz, J_2 = 1.5 Hz, 1H), 7.57 (td, J_1 = 7.0 Hz, J_2 = 1.0 Hz, 1H), 7.46 (m, 2H), 7.29 (m, 2H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 151.4 (CH), 147.2 (C), 137.8 (C), 135.9 (CH), 131.4 (CH), 131.2 (C), 130.1 (C), 129.6 (2CH), 129.3 (CH), 128.1 (CH), 127.6 (C), 126.9 (CH), 125.3 (CH), 118.9 (CH); ATR-FTIR (thin film): 2118, 2077, 1568, 1492, 711 cm^{-1}.



In a dry 25 mL round bottom flask, the biaryl azide **1.138** was dissolved in dry CH_2Cl_2 (0.5 M), MeOTf (1.1 equiv) was then added dropwise via syringe over 10 min, and the resulting solution was allowed to stir at ambient temperature

overnight. The volatiles were removed *in vacuo* to afford the product, which can be used directly without further purification.



To a mixture of pyridinium triflate **1.139** (0.030 g, 0.07 mmol, 1.0 equiv), 100 % w/w of crushed 4 Å mol sieves, and $Rh_2(esp)_2$ (0.003 g, 0.004 mmol, 0.05 equiv) were added 0.7 mL of DCE (0.1 M), the resulting mixture was stirred at 80 °C for 15 h. The heterogenous mixture was then filtered through celite and the filtrate was concentrated *in vacuo*. In a separatory funnel, the reaction mixture was diluted with 20 mL of a 5% aqueous solution of Na_2CO_3. The mixture was vigorously shaken, and the resulting mixture was extracted with 3 × 10 mL of $CHCl_3$. Solid Na_2CO_3 was added to the combined organic phases. The mixture was filtered, and the filtrate was concentrated *in vacuo.* Purification by MPLC afforded analytically pure neocryptolepine as an orange oil (0.012 g, 68% from **1.139**). The spectral data of neocryptolepine matched that reported by Haddadin and co-workers.[85] ^{1}H NMR (500 MHz; $CDCl_3$) δ 8.54 (s, 1H), 8.06 (d, *J* = 7.5 Hz, 1H), 8.00 (d, *J* = 7.5 Hz, 1H), 7.77 (m, 3H), 7.55 (t, *J* = 7.5 Hz, 1H), 7.45 (m, 1H), 7.24 (t, *J* = 7.5 Hz, 1H), 4.37 (s, 3H); ^{13}C NMR (125 MHz; $CDCl_3$) δ 156.3 (C), 155.4 (C), 137.0 (C), 130.4 (CH), 130.0 (CH), 129.3 (CH), 128.2 (CH), 128.1 (C),

124.0 (C), 121.9 (CH), 121.0 (CH), 120.9 (C), 119.9 (CH), 117.7 (CH), 114.2 (CH), 33.1 (CH_3); ATR-FTIR (thin film): 1644, 1562, 1492, 1201, 740 cm^{-1}.

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CHAPTER 2

Synthetic Targets Towards Schistosomiasis Drug Discovery

The World Heath Organization (WHO) has identified 17 neglected tropical diseases among the worlds most underpriviliged people. These common, chronic infections kill approximately 500,000 every year.[1] The lack of attention to these diseases only causes more long-term poverty in these struggling countries, due to their illnesses causing lower productivity.[2-5] This project is focused on developing new treatments for schistosomiasis, which belongs to the section of these diseases caused by eukaryotic parasites.

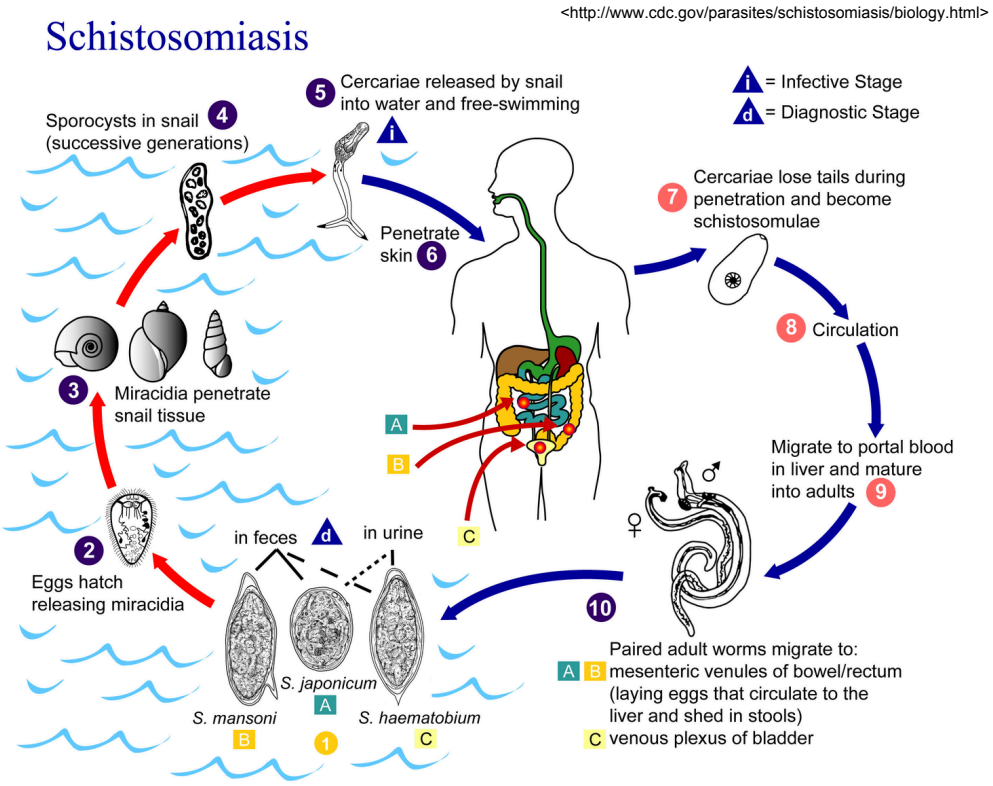
Schistosomiasis, also known as bilharzia, is a debilitating disease caused by parasitic trematodes in tropical areas.[6,7] There are several species infectious to humans: *Schistosoma haematobium, Schistosoma intercalatum, Schistosoma japonicum, Schistosoma mansoni, and Schistosoma mekongi.* This work has focused specifically on the genus *S. mansoni* (Figure 2.1).[8]

Figure 2.1 *Schistosomiasis mansoni* male-female pair

Schistosomiasis mansoni

The larval form of the parasite, cercariae, is the infectious stage to humans and uses freshwater snails as intermediate hosts.[9] Infection occurs when the cercariae (5 in Figure 2.2)[10] penetrate the skin during contact with infected water sources. In communities that rely on these water sources for farming, fishing, and daily chores infection is inevitable and is most common in children who play in the infected water sources.

Figure 2.2 Life cycle of the Schistosomiasis parasite

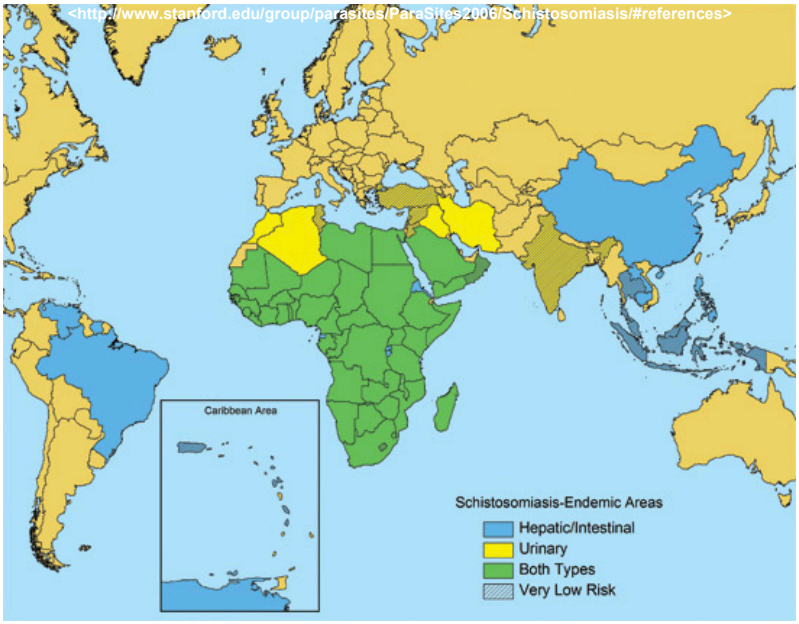


These parasitic trematodes lead a very complicated life cycle and alternate between the invertebrate snail host and the definitive human host. Once the cercariae enter a human host they shed their mobility tails and transform into

schistosomulae (7 in Figure 2.2). They then travel to the liver and eventually settle in the portal blood where they mature into adult worms (10 in Figure 2.2). Adult worms pair up to mate and travel to mesenteric venules of the bowels. The eggs laid by the worms are then passed through the host's stool and hatch into miracidia (2 in Figure 2.2) upon contact with water. These miracidia then penetrate the soft tissue of the aquatic snails and mature into cercariae, which continue the life cycle. This extremely complex life cycle makes identifying antischistosomiasis targets difficult.[11-17] Since infection occurs in humans from cercariae, our research has mostly targeted inhibition of this larval stage and also the adult worms which reside in the portal veins after infection.

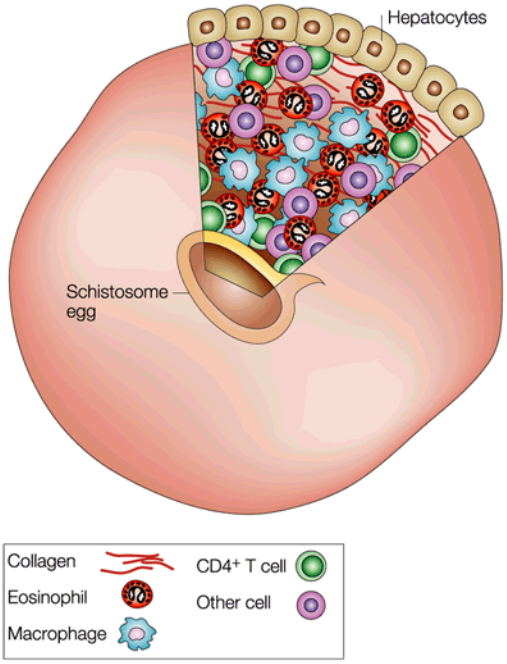
Schistosomiasis is considered one of the Neglected Tropical Diseases (NTDs) by the Centers for Disease Control and Prevention (CDC). Although it is not found in the United States, the disease affects more than 200 million people worldwide (Figure 2.3)[18], and is second only to malaria in morbidity and mortality of parasitic diseases.[7,19] Antischistosome drug research is severely limited due to the challenges involved in working with an infectious parasite and the low priority that the pharmaceutical industry gives tropical diseases.

Figure 2.3 Map of Schistosomiasis-endemic areas



Although the schistosomiasis parasites do not kill the host directly, the extreme host defenses that the laying of eggs in the liver and bowel tissues triggers leads to detrimental sequelae.[20] Extreme inflammation[21] and granulomatous reactions[22,23] arise in the human host (Figure 2.4)[20], and can be fatal if not treated. Chronic infection from *Schistosoma mansoni* can result in periprotal fibrosis of the liver[24], bladder calcification and other abnormalities.

Figure 2.4 Granulomatous lesions around individual eggs



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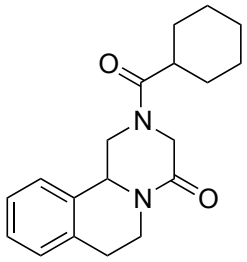
<http://www.nature.com/nri/journal/v2/n7/box/nri843_BX2.html>

Currently, there is only one antischistosomal drug commercially available for treatment. Praziquantel (PZQ), commercialy known as Biltricide, was developed in the mid 1970's by the laboratories of Bayer AG and Merck KGaA in Germany (Figure 2.5).[25,26] PZQ is active against all five species of Schistosomiasis that infect humans and can be administered orally, which has made it a mainstay for the control of schistosomiasis.[27]

Figure 2.5 Structure of Praziquantel



Praziquantel

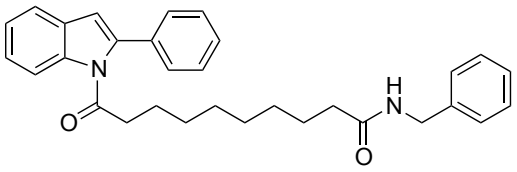
Surprisingly, PZQ has remained the drug of choice for over 40 years and there is little evidence of developed resistance. However, with the growing problem of drug resitance it is urgent that new antischistosomal targets are identified. If resistant strains of schistosomes develop for the only drug availiable, PZQ, treatment will truly be in a state of crisis.

Studies have also been done that show the activity of PZQ is dependent on the developmental stage of the schistosome.[28,29] The drug is most active against the mature adult worm, and at these levels will not treat immature schistosomes effectively to avoid reinfection. Therefore, we believe activity against both mature and immature developmental stages needs to be an aspect identified in any successful, future therapeutic target.

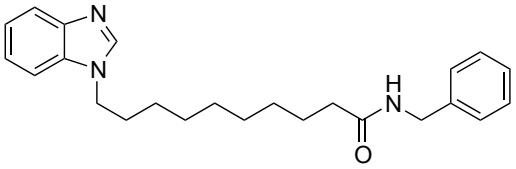
Initially, Dr. Ke Sun of the Driver group had synthesized a small library of myosin light-chain kinase (MLCK) inhibitors (Figure 2.6). With the hypothesis that these molecules might be targets for schistosomiasis we started collaboration with Dr. David Williams of RUSH University, to test for activity. The goal of this

research was to develop an *in vitro* drug screening assay for *S. mansoni* in the schistosomula stage and eventually test the active compounds against adult worms.

Figure 2.6 Dr. Ke Sun's MLCK inhibitor library



2.1



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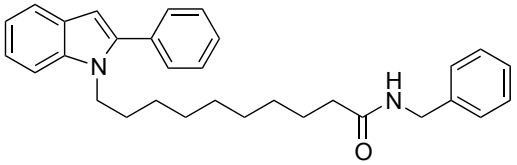
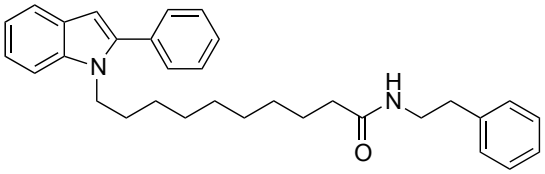


2.2



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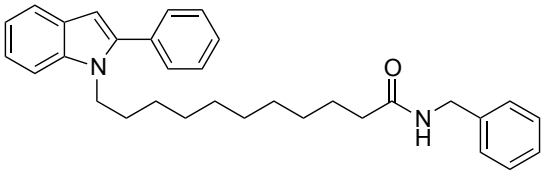

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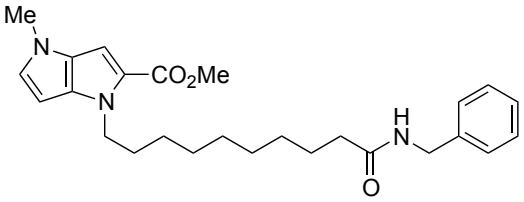

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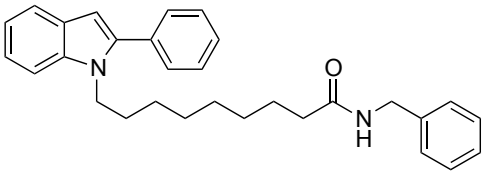

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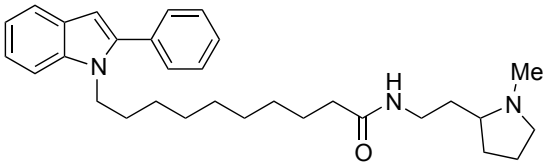

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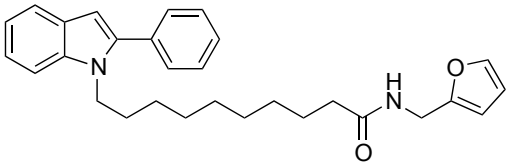
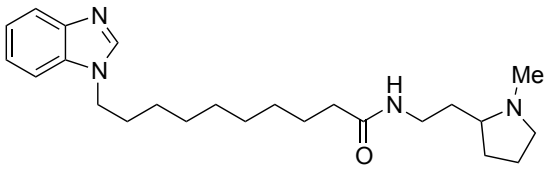


2.5



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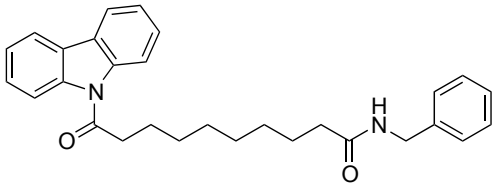

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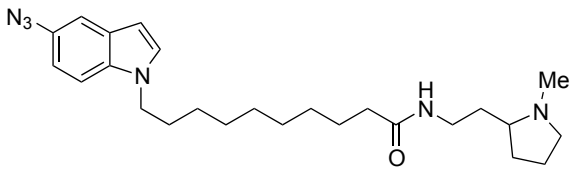

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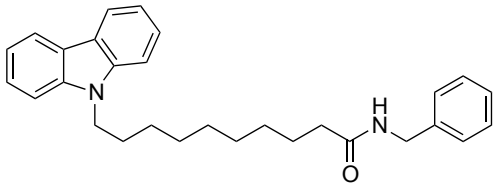


2.7

The *S. mansoni* cercariae used in this study were isolated from infected *Biomphalaria glabrata* snails (Figure 2.7).[30,31] Naturally in field conditions, cercariae are shed from the snails during the day upon exposure to light. To simulate this exposure in the lab, the snails are placed in a glass beaker and exposed to a strong lamp.

Figure 2.7 *Biomphalaria glabrata* snail

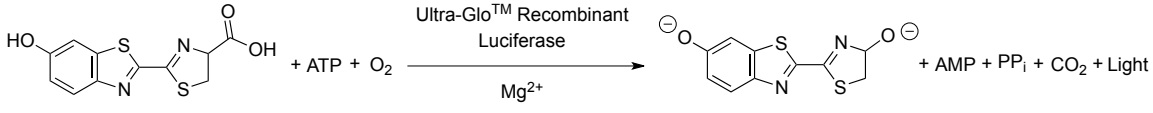
<http://en.wikipedia.org/wiki/File:Biomphalaria_glabrata.jpg>

Biompharlaria glabrata

Separating the bodies of the cercariae from the tails is necessary in order to obtain simulation of the infectious stage inside the human body, somula. In this process the cercariae undergo a vortex transformation in Basch's media followed by purifictation on a Percoll® gradient. Somula are then organized in a 96 well plate with approximately 100 somules per well. After a 24-hour incubation period at 37 °C the somula were exposed to the target compounds and incubated for another 24-hour period.

Evaluation of the somule was carried out using a cell viability assay, which allowed for quantitation of the ATP levels in each individual well. Specifically the CellTiter-Glo® Cell Viability Assay was used from Promega. This assay generates a "glow-type" luminescent signal that can allow for high throughput readings on a luminometer. Mono-oxidation of luceferin catalyzed by luciferase in the presence of ATP, Mg^{2+}, and oxygen produces a signal that can last up to 5 hours (Scheme 2.1).

Scheme 2.1 CellTiter-Glo® luminescent reaction

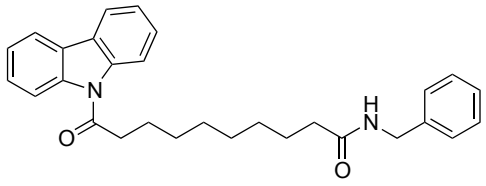


Beetle Luciferin Oxyluciferin

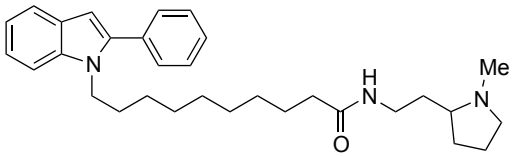
With a quantitative and reliable assay in hand Dr. Ke Sun's MLCK library of compounds was screened for reactivity. We were delighted to see that of the

thirteen compounds Dr. Sun synthesized, three were active against schistosomes. Compounds **2.6**, **2.7** and **2.11** were selected as the lead compounds for this project, along with compound **2.14** submitted by Márton Siklós of the Thatcher group in UIC's College of Pharmacy (Figure 2.8).

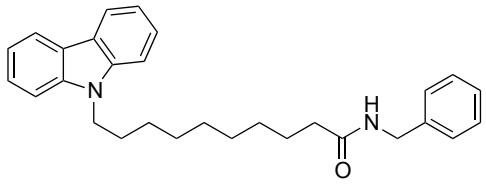
Figure 2.8 Lead antischistosomiasis compounds



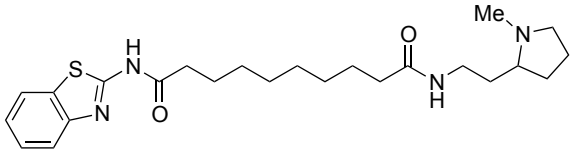
2.6



2.11



2.7



2.14

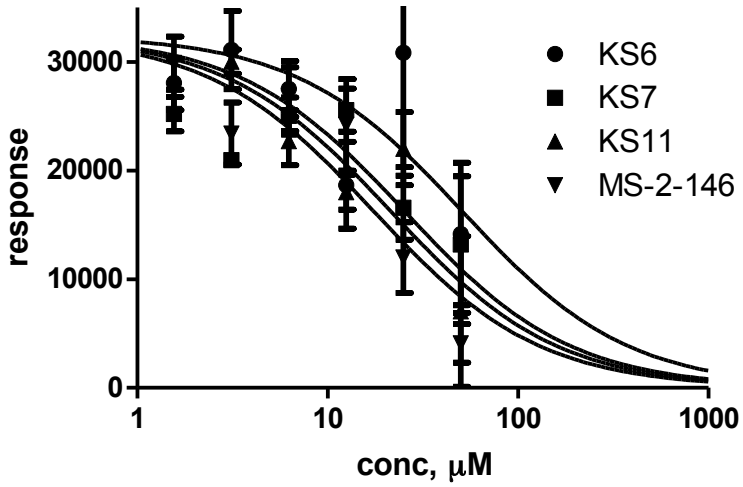
After identification of the lead compounds they were diluted into a series of concentrations that allowed for calculation of their IC_{50} values when incubated for a 24-hour period on somulae (Figure 2.9). Utilizing Graphpad Prism we could also show the error involed in the data set.

Structure reactivity analaysis suggests that the length of the central, aliphatic chain needs to be specific. Our data shows that a 10-carbon chain linker between the nitrogen atoms is necessary for inhibition. The identity of the N-heterocyle used on the left end cap does not need to be specific, although the tail cap seems to favor the use of the N-methyl pyrolidine. Obviously many more N-

heterocycles need to be investigated for this library of compounds and would be a good place to start in developing a new generation of compounds. Also the use of linkers besides amides needs to be investigated. Ureas and guanidines would be a great place to start.

Figure 2.9 Graph of response vs. concentration for lead compounds: IC_{50} values

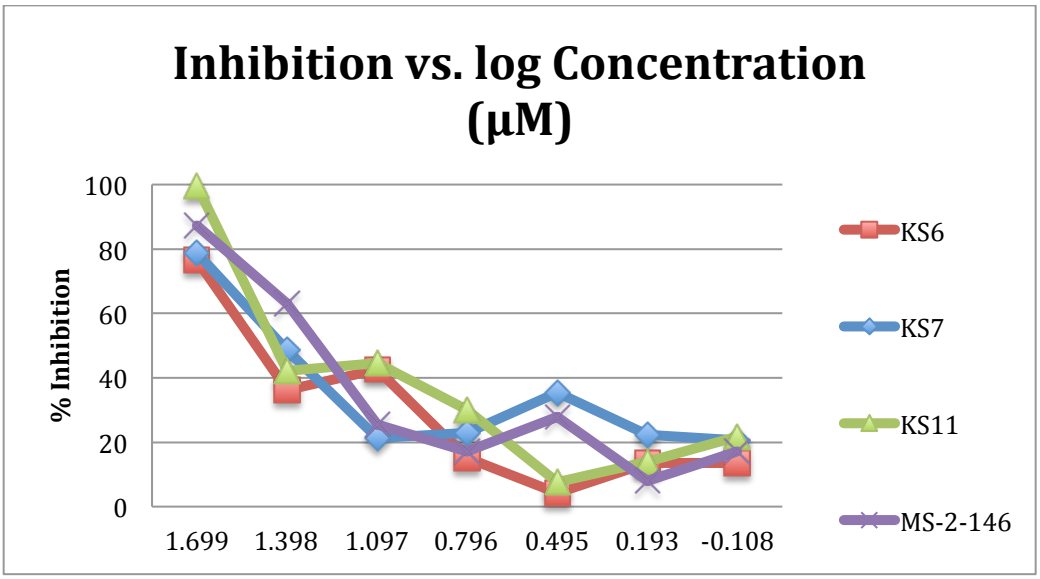
KS6	KS7	KS11	MS-2-146
51.01	25.42	21.49	17.49



The source of the errors involed in the Glo assay have not been determined yet, but microscopic techniques are being used to find a trend in unusually high or low readings from the luminometer. Changing the type of culture plate that the reading takes place in is also being investigated. The

CellTiter-Glo protocol calls for opaque, white plates, however plates with translucent bottoms allows for secondary verification of total somule inhibition.

Figure 2.10 Graph of inhibition vs. log concentration for CellTiter-Glo assay



Looking at the graph of inhibition versus concentration we saw that about 50 µM concentrations were needed for 100% inhibition of schistosomula with the lead target KS11 which corresponds to structure **2.11** (Figure 2.10). Optimal incubation periods on somula, with the compounds are still under investigation in the Williams' lab.

In conclusion, it is urgent that new antischistosomal targets are identified, as drug resistance for the schistosomiasis species is inevitable. The Driver group's work to identify such targets will be ongoing with the William's lab. Future directions include the identification of the protein within *Schistosoma mansoni* that our lead compound is interacting with. Identifying the exact target of

inhibition will allow for optimal synthetic design apart from normal structure reactivity relationships (SAR). We hypothesize that KS13 (structure **2.13)**, containing an azide moiety, might provide a synthetic handle to covalently bind our compounds to the protein. This would allow for identification, via Western blot techniques, of the protein.

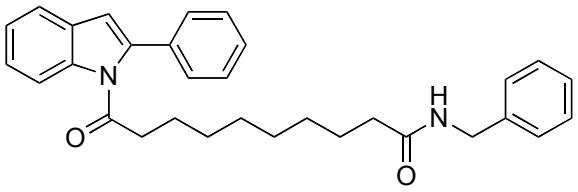
Designing a versatile drug that is active against multiple species of schistosomes as well as multiple developmental stages is still another major goal of this project. Testing of the lead compounds on adult worms is the next step for this project in the Williams' lab.

Experimental

A. General. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High resolution mass spectra were acquired on a JEOL CGMate II- or Thermo Finnigan brand LTQ FT spectrometer, and were obtained by peak matching. Infared spectroscopy was obtained using a diamond attenuated total reflectance (ATR) accessory. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent

system on 60Å (40 – 60 μm) mesh silica gel (SiO_2). Medium pressure liquid chromatography (MPLC) was performed to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60 μm) mesh silica gel (SiO_2). All reactions were carried out under an atmosphere of nitrogen in glassware, which had been oven-dried. Unless otherwise noted, all reagents were commercially obtained and, where appropriate, purified prior to use. Acetonitrile, Methanol, Toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs.[32] Metal salts were stored in a nitrogen atmosphere dry box.

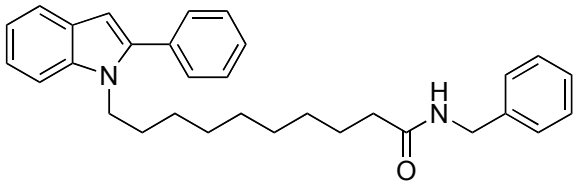
B. Spectral Data for Myosin Light-Chain Kinase Inhibitors



2.1

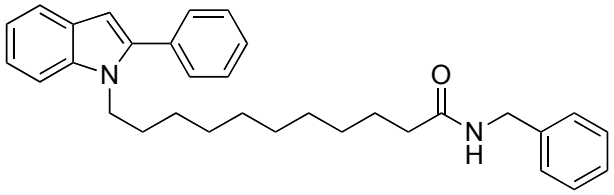
***N*-benzyl-10-oxo-10-(2-phenyl-1*H*-indol-1-yl)decanamide** (**2.1**). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.64 (dd, *J* = 7.5, 1.0 Hz 1H), 7.49-7.45 (m, 6H), 7.35-7.31 (m, 2H), 7.29-7.25 (m, 3H), 7.23 (tt, *J* = 8.0, 1.0 Hz, 1H), 7.13 (td, *J* = 8.0, 1.0 Hz, 1H), 6.52 (s, 1H), 5.75 (s, 1H), 4.44 (d, *J* = 5.5 Hz, 4H), 4.15 (t, *J* = 7.5 Hz, 2H), 2.27 (t, *J* = 7.5 Hz, 2H), 2.17 (q, *J* = 8.0 Hz, 2H), 1.71-1.65 (m, 2H), 1.63-1.57 (m, 4H), 1.54-1.49 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 141.4 (C), 139.5 (C), 138.4 (C), 137.3 (C), 134.2 (C), 133.3 (C), 129.4 (C), 129.9 (CH), 129.2 (CH),

129.1 (CH), 128.8 (CH), 128.3 (CH), 128.2 (CH), 127.9 (CH), 123.9 (CH), 121.9 (CH), 120.9 (CH), 120.8 (CH), 120.1 (CH), 110.5 (CH), 110.0 (CH), 102.4 (CH), 44.4 (CH_2), 44.0 (CH_2), 37.2 (CH_2), 30.3 (CH_2), 29.7 (CH_2), 29.6 (CH_2), 29.4 (CH_2), 27.1 (CH_2), 26.1 (CH_2).



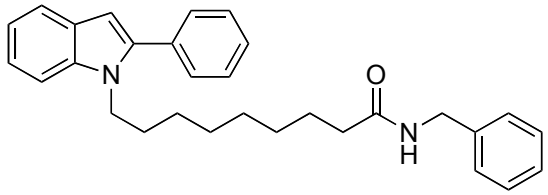
2.2

***N*-benzyl-10-(2-phenyl-1*H*-indol-1-yl)decanamide** (**2.2**). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.51-7.46 (m, 4H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.35-7.32 (m, 2H), 7.24 (td, *J* = 7.0, 1.0 Hz, 1H), 7.14 (td, *J* = 8.0, 0.5 Hz, 1H), 6.53 (s, 1H), 5.76 (s, 1H), 4.44 (d, *J* = 5.5 Hz, 2H), 4.15 (t, *J* = 8.0 Hz, 2H), 2.18 (t, *J* = 7.5 Hz, 2H), 1.69 (m, 2H), 1.62 (quintet, *J* = 8.0 Hz, 2H), 1.23-1.15 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.9 (C), 141.4 (C), 138.4 (C), 137.3 (C), 133.3 (C), 129.8 (CH), 129.4 (CH), 128.8 (CH), 128.7 (C), 128.5 (2CH), 128.2 (CH), 127.9 (CH), 127.8 (CH), 127.5 (CH), 121.5 (CH), 120.6 (CH), 119.7 (CH), 110.5 (CH), 110.1 (CH), 102.0 (CH), 43.9 (CH_2), 43.6 (CH_2), 36.8 (CH_2), 29.9 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 26.7 (CH_2), 25.7 (CH_2).



2.3

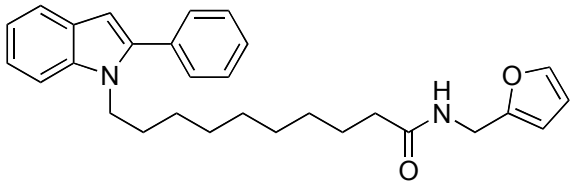
***N*-benzyl-11-(2-phenyl-1*H*-indol-1-yl)undecanamide** (**2.3**). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.52-7.47 (m, 4H), 7.43 (dt, *J* = 7.0, 2.0 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.36-7.33 (m, 2H), 7.29-7.24 (m, 4H), 7.16 (td, *J* = 8.0, 1.0 Hz, 1H), 6.55 (s, 1H), 5.85 (s, 1H), 4.43 (d, *J* = 5.5 Hz, 2H), 4.16 (t, *J* = 7.5 Hz, 2H), 2.18 (t, *J* = 7.5 Hz, 2H), 1.70 (quintet, *J* = 7.0 Hz, 2H), 1.63 (quintet, *J* = 7.5 Hz, 2H), 1.32-1.17 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.9 (C), 141.4 (C), 138.5 (C), 137.4 (C), 133.3 (C), 129.4 (2CH), 128.7 (CH), 128.5 (2CH), 128.2 (C), 127.9 (CH), 127.8 (2CH), 127.5 (CH), 121.5 (CH), 120.6 (CH), 119.7 (CH), 110.5 (CH), 110.1 (CH), 102.1 (CH), 43.9 (CH_2), 43.6 (CH_2), 36.7 (CH_2), 29.9 (CH_2), 29.3 ($2CH_2$), 29.2 ($2CH_2$), 29.0 (CH_2), 26.7 (CH_2), 25.7 (CH_2).



2.4

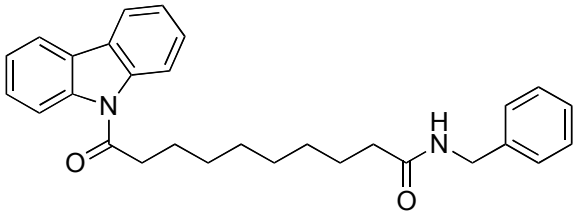
***N*-benzyl-9-(2-phenyl-1*H*-indol-1-yl)nonanamide** (**2.4**). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.66 (d, *J* = 8.0 Hz, 1H), 7.52-7.47 (m, 4H), 7.43 (dt, *J* = 7.0, 1.5 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 1H), 7.35-7.32 (m, 2H), 7.30-7.24 (m, 4H), 7.15 (td, *J* = 7.0, 1.0 Hz, 1H), 6.54 (s, 1H), 5.79 (s, 1H), 4.42 (d, *J* = 5.5 Hz, 2H), 4.16 (t, *J* = 7.5 Hz, 2H), 2.12 (t, *J* = 8.0 Hz, 2H), 1.69 (quintet, *J* = 7.5 Hz, 2H), 1.57 (quintet, *J* = 6.5 Hz, 2H), 1.17 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.8 (C), 141.4 (C), 138.4 (C), 137.4 (C), 133.3 (C), 129.4 (2CH), 128.7 (2CH), 128.5 (2CH), 128.2 (C), 127.9 (CH), 127.8 (2CH), 127.5 (CH), 121.5 (CH), 120.6 (CH), 119.8

(CH), 110.1 (CH), 102.1 (CH), 43.9 (CH_2), 43.6 (CH_2), 36.6 (CH_2), 29.8 (CH_2), 29.0 ($2CH_2$), 28.7 (CH_2), 26.5 (CH_2), 25.5 (CH_2).



2.5

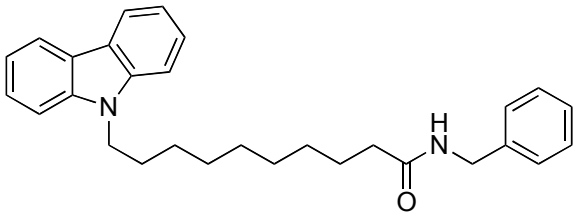
***N*-(furan-2-ylmethyl)-10-(2-phenyl-1*H*-indol-1-yl)decanamide** (**2.5**). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.64 (d, *J* = 7.5 Hz, 1H), 7.51-7.45 (m, 4H), 7.42 (dt, *J* = 6.5, 1.5 Hz, 1H), 7.39 (d, *J* = 8.0 Hz, 1H), 7.35-7.30 (m, 2H), 7.14 (td, *J* = 7.0, 0.5 Hz, 1H), 6.53 (s, 1H), 6.32 (dd, *J* = 3.5, 2.0 Hz, 1H), 6.22 (d, *J* = 3.5 Hz, 1H), 5.75 (s, 1H), 4.44 (d, *J* = 5.5 Hz, 2H), 4.14 (t, *J* = 7.5 Hz, 2H), 2.15 (t, *J* = 8.0 Hz, 2H), 1.69 (m, 2H), 1.60 (quintet, *J* = 7.0 Hz, 2H), 1.26-1.19 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.1 (C), 141.4 (C), 138.9 (C), 137.3 (C), 133.3 (C), 129.4 (CH), 128.7 (CH), 128.6 (C), 128.5 (CH), 127.9 (CH), 126.5 (CH), 121.4 (CH), 120.5 (CH), 119.7 (CH), 110.5 (CH), 110.0 (CH), 109.6 (CH), 107.4 (CH), 102.0 (CH), 43.9 (CH_2), 40.5 (CH_2), 36.6 (CH_2), 29.9 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.1 (CH_2), 29.0 (CH_2), 26.7 (CH_2), 25.7 (CH_2).



2.6

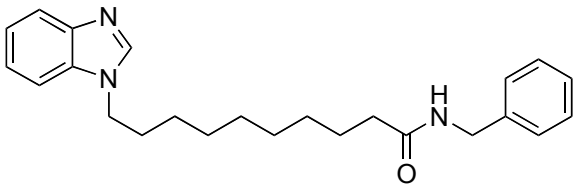
***N*-benzyl-10-(9*H*-carbazol-9-yl)-10-oxodecanamide** (**2.6**). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.21 (d, *J* = 8.5 Hz, 2H), 7.99 (d, *J* = 7.5 Hz, 2H), 7.47 (td, *J* = 8.5, 1.0

Hz, 2H), 7.38 (t, *J* = 7.5 Hz, 2H), 7.33-7.30 (m, 2H), 7.27-7.24 (m, 3H), 5.87 (s, 1H), 4.43 (d, *J* = 5.5 Hz, 2H), 3.10 (t, *J* = 7.5 Hz, 2H), 2.21 (t, *J* = 7.5 Hz, 2H), 1.91 (quintet, *J* = 7.5 Hz, 2H), 1.67 (quintet, *J* = 7.5 Hz, 2H), 1.48 (quintet, *J* = 7.5 Hz, 2H), 1.41-1.34 (m, 6H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.4 (C), 172.9 (C), 138.5 (2C), 138.4 (C), 128.7 (2CH), 127.8 (CH), 127.4 (2CH), 127.3 (C), 126.4 (C), 123.5 (2CH), 119.8 (2CH), 116.4 (2CH), 110.0 (2CH), 43.9 (CH_2), 39.6 (CH_2), 37.2 (CH_2), 29.8 (CH_2), 29.7 (CH_2), 29.6 ($2CH_2$), 26.2 (CH_2), 25.1 (CH_2).



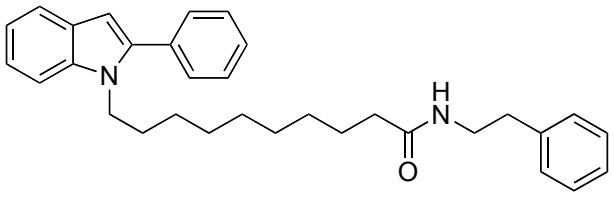
2.7

***N*-benzyl-10-(9*H*-carbazol-9-yl)decanamide** (**2.7**). ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.12 (d, *J* = 7.5 Hz, 2H), 7.48 (t, *J* = 7.5 Hz, 2H), 7.42 (d, *J* = 8.0 Hz, 2H), 7.35-7.32 (m, 2H), 7.29-7.23 (m, 5H), 5.79 (s, 1H), 4.42 (d, *J* = 5.5 Hz, 2H), 4.30 (t, *J* = 7.5 Hz, 2H), 2.16 (t, *J* = 7.5 Hz, 2H), 1.88 (quintet, *J* = 7.5 Hz, 2H), 1.63 (quintet, *J* = 6.5 Hz, 2H), 1.40-1.30 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.9 (C), 140.4 (2C), 138.5 (C), 128.7 (2CH), 127.8 (2CH), 127.5 (CH), 125.6 (2CH), 122.8 (2C), 120.3 (2CH), 118.7 (2CH), 110.0 (CH), 109.1 (CH).



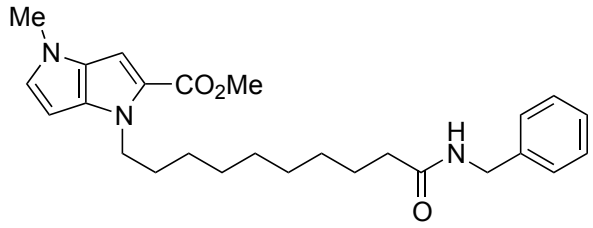
2.8

10-(1*H*-benzo[*d*]imidazol-1-yl)-*N*-benzyldecanamide (**2.8**). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.73 (d, *J* = 7.0 Hz, 2H), 7.35 (d, *J* = 7.5 Hz, 1H), 7.28-7.21 (m, 7H), 6.71 (s, 1H), 4.37 (d, *J* = 5.5 Hz, 2H), 4.07 (t, *J* = 7.0 Hz, 2H), 2.16 (t, *J* = 7.5 Hz, 2H), 1.79 (quintet, *J* = 7.0 Hz, 2H), 1.59 (quintet, *J* = 7.0 Hz, 2H), 1.24-1.21 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.2 (C), 143.7 (C), 142.9 (CH), 138.7 (C), 133.8 (C), 128.6 (2CH), 127.7 (2CH), 127.3 (CH), 122.8 (CH), 122.0 (CH), 120.2 (CH), 109.8 (CH), 45.0 (CH_2), 43.4 (CH_2), 36.6 (CH_2), 29.7 (CH_2), 29.1 (CH_2), 28.9 (CH_2), 26.7 (CH_2), 25.7 (CH_2).



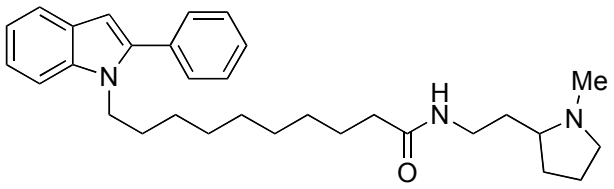
2.9

***N*-phenethyl-10-(2-phenyl-1*H*-indol-1-yl)decanamide** (**2.9**). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.66 (d, *J* = 7.5 Hz, 1H), 7.52-7.47 (m, 4H), 7.43 (dt, *J* = 7.0, 2.0 Hz, 1H), 7.41 (d, *J* = 8.5 Hz, 1H), 7.36-7.31 (m, 2H), 7.27-7.23 (m, 4H), 7.15 (t, *J* = 7.5 Hz, 1H), 6.54 (s, 1H), 5.87 (s, 1H), 4.43 (d, *J* = 5.5 Hz, 2H), 4.16 (t, *J* = 7.5 Hz, 2H), 2.17 (t, *J* = 7.5 Hz, 2H), 2.10 (t, *J* = 7.5 Hz, 2H), 1.71 (quintet, *J* = 6.5 Hz, 2H), 1.61 (quintet, *J* = 6.5 Hz, 2H), 1.20 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.1 (C), 141.4 (C), 138.9 (C), 137.4 (C), 133.3 (C), 129.4 (2CH), 128.8 (2CH), 128.6 (2CH), 128.5 (CH), 128.2 (C), 127.9 (2CH), 126.5 (CH), 121.5 (CH), 120.6 (CH), 119.7 (CH), 110.1 (CH), 102.1 (CH), 43.9 (CH_2), 40.5 (CH_2), 36.8 (CH_2), 35.7 (CH_2), 29.9 (CH_2), 29.3 (CH_2), 29.2 ($2CH_2$), 28.9 (CH_2), 26.7 (CH_2), 25.7 (CH_2).



2.10

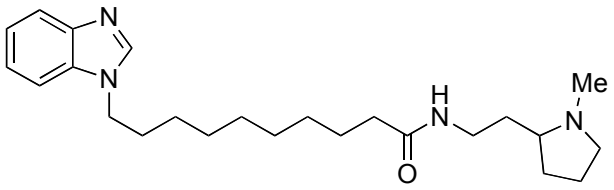
methyl 1-(10-(benzylamino)-10-oxodecyl)-4-methyl-1,4-dihydrocyclopenta-[*b*]pyrrole-2-carboxylate (**2.10**). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.34-7.26 (m, 6H), 6.77 (d, *J* = 3.0 Hz, 1H), 6.76 (s, 1H), 5.90-5.89 (m, 2H), 4.42 (d, *J* = 6.0 Hz, 2H), 4.37 (t, *J* = 7.0 Hz, 2H), 4.28 (q, *J* = 7.0 Hz, 2H), 3.65 (s, 3H), 2.18 (t, *J* = 7.5 Hz, 2H), 1.78 (quintet, *J* = 7.0 Hz, 2H), 1.63 (quintet, *J* = 7.5 Hz, 2H), 1.36 (t, *J* = 7.0 Hz, 3H), 1.32-1.25 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 173.0 (C), 162.3 (C), 138.5 (C), 135.6 (C), 129.5 (CH), 128.7 (2CH), 128.1 (C), 127.8 (2CH), 127.4 (2CH), 122.9 (C), 97.4 (CH), 89.2 (CH), 59.5 (CH_2), 47.0 (CH_2), 43.5 (CH_2), 36.7 (CH_2), 34.4 (CH_3), 30.8 (CH_2), 29.3 (CH_2), 29.2 (CH_2), 29.2 (CH_2), 26.9 (CH_2), 25.7 (CH_2), 14.6 (CH_3).



2.11

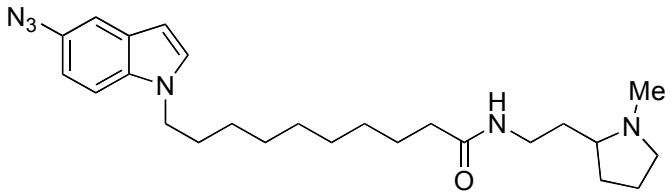
***N*-(2-(1-methylpyrrolidin-2-yl)ethyl)-10-(2-phenyl-1*H*-indol-1-yl)decanamide** (**2.11**). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.63 (d, *J* = 8.0 Hz, 1H), 7.50-7.45 (m, 4H), 7.41 (dt, *J* = 7.0, 2.0 Hz, 1H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.23 (td, *J* = 7.0, 1.0 Hz, 1H), 7.13 (td, *J* = 8.0, 1.0 Hz, 1H), 6.74 (s, 1H), 6.52 (s, 1H), 4.14 (t, *J* = 7.5 Hz

2H), 3.44 (sextet, *J* = 6.5 Hz, 1H), 3.25-3.18 (m, 1H), 3.07-3.03 (m, 1H), 2.31 (s, 3H), 2.27-2.21 (m, 1H), 2.11 (t, *J* = 7.5 Hz, 2H), 1.96-1.88 (m, 1H), 1.77-1.67 (m, 6H), 1.62-1.53 (m, 4H), 1.29-1.18 (m, 8H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.9 (C), 141.4 (C), 137.3 (C), 133.3 (C), 129.4 (2CH), 128.5 (2CH), 127.9 (CH), 121.4 (CH), 120.5 (CH), 119.7 (CH), 110.1 (CH), 102.0 (CH), 64.7 (CH), 57.1 (CH_2), 43.9 (CH_2), 40.6 (CH_3), 36.9 (CH_2), 36.7 ($2CH_2$), 31.0 (CH_2), 29.9 (CH_2), 29.2 ($2CH_2$), 29.0 ($2CH_2$), 26.7 (CH_2), 25.7 (CH_2), 22.3 (CH_2).



2.12

10-(1*H*-benzo[*d*]imidazole-1-yl)-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)-decanamide (**2.12**). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.29-7.26 (m, 2H), 7.10 (d, *J* = 3.0 Hz, 1H), 6.86 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.71 (s, 1H), 6.41 (d, *J* = 3.0 Hz, 1H), 4.07 (t, *J* = 7.0 Hz, 2H), 3.43 (sextet, *J* = 6.0 Hz, 1H), 3.24-3.17 (m, 1H), 3.05-3.01 (m, 1H), 2.29 (s, 3H), 2.25-2.19 (m, 1H), 2.16-2.09 (m, 3H), 1.93-1.86 (m, 1H), 1.82-1.77 (m, 2H), 1.75-1.68 (m, 3H), 1.62-1.53 (m, 4H), 1.28-1.25 (m, 10H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.9 (C), 133.8 (C), 131.5 (C), 129.3 (CH), 113.4 (CH), 110.5 (CH), 110.4 (CH), 100.6 (CH), 64.7 (CH_3), 57.1 (CH_2), 46.6 (CH_2), 40.6 (CH), 36.9 (CH_2), 36.7 (CH_2), 31.1 (CH_2), 30.2 (CH_2), 29.4 (CH_2), 29.3 ($2CH_2$), 29.2 (CH_2), 29.1 (CH_2), 26.9 (CH_2), 25.7 (CH_2), 22.4 (CH_2).



2.13

10-(5-azido-1*H*-indol-1-yl)-*N*-(2-(1-methylpyrrolidin-2-yl)ethyl)decanamide (**2.13**). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.29-7.26 (m, 2H), 7.10 (d, *J* = 3.0 Hz, 1H), 7.86 (dd, *J* = 8.6, 2.0 Hz, 1H), 6.71 (s, 1H), 6.41 (d, *J* = 3.0 Hz, 1H), 4.07 (t, *J* = 7.0 Hz, 2H), 3.43 (sextet, *J* = 6.0 Hz, 1H), 3.20 (m, 1H), 3.03 (m, 1H), 2.29 (s, 3H), 2.22 (m, 1H), 2.10 (t, *J* = 8.0 Hz, 2H), 1.93-1.86 (m, 1H), 1.79 (m, 2H), 1.71 (m, 2H), 1.57 (m, 4H), 1.28-1.25 (m, 12H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 172.9 (C), 133.8 (C), 131.5 (C), 129.3 (C), 129.2 (CH), 113.4 (CH), 110.5 (CH), 110.4 (CH), 100.6 (CH), 64.7 (CH_3), 57.1 (CH_2), 46.6 (CH_2), 40.6 (CH), 36.9 (CH_2), 36.7 (CH_2), 31.1 (CH_2), 30.2 (CH_2), 29.28 (CH_2), 29.25 (CH_2), 29.2 (CH_2), 26.9 (CH_2), 25.7 (CH_2), 22.4 (CH_2).

C. Protocol for isolation and culture of schistosomulae

General procedure for the isolation of cercariae from infected *Biomphalaria glabrata* snails. Preparation of schistosomula from cercariae were as described.[33,34] *Biomphalaria glabrata* infected with S. *mansoni* were obtained from the Biomedical Research Insititute (BRI). The snails were maintained in tanks with “pond water” (0.25 g/L $FeCl_3$•$6H_2O$, 12.9 g/L $CaCl_2$•$2H_2O$, 10.0 g/L $MgSO_4$•$7H_2O$, and phosphate buffer). Tanks were kept in a room close to

windows so a 12 hour day and night cycle could be simulated. The first shedding after obtaining the snails took place 4-6 weeks after the date of infection. Approximately 80-100 snails were collected in the morning and placed in a beaker with about 50 mL pond water. The beaker was then placed under a strong desk lamp for approximately 1 hour to allow the snails to shed the cercariae. The water in the beaker was then strained into a 50 mL plastic conical tube and the snails were returned to their tank. The filtrate was then placed on ice for 30 minutes to reduce parasite motility and was centrifuged for 2 minutes at 100xg and 4 °C. In a laminar flow hood most of the tank water above the cercariae was removed with an electrip pipette gun. Dulbecco's Modified Eagle's Medium (DMEM) (Life Technologies) was then added until the parasite solution was about 5 mL. To induce cercariae tail shedding the 50 mL tube was vortexed for three 1 minute periods with 1 minute of rest between each vortex cycle. (DMEM) was then added until the total volume of solution was 10 mL. The separation of somula bodies from the tails was carried out by centrifugation on a Percoll® (polyvinylpyrolidone-coated colloidal silica particles) gradient. Percoll gradient suspension: 24 mL Percoll®, 4 mL 10 x Eagle's Minimum Essential Medium (Life Technologies), 1.5 mL penicillin-streptomycin (10,000 µg per mL penicillin/ 10,000 µg per mL streptomycin, Life Technologies), 1 mL 1.0M HEPES in 0.85% (w/v) NaCl, 9.5 mL distilled H_2O, Store up to 5 days at 4° C. The gradient was topped with the 10mL somula suspension in DMEM and the gradient was centrifuged for 15 minutes at 500xg and 4 °C. The media above the somula pellet was removed leaving the bottom 10 mL in the tube and then filled

again to 50 mL with fresh DMEM. This was repeated three times and after the third series all of the media was removed and the somula were supspended in 10 mL of Basch Medium (Life Technologies). Somulae per μL solution were counted under a microscope and the suspension was concentrated to yield 10 somulae per μL solution in Basch` Medium. Somules were then distributed into 96 well, white tissue culture plates at approximately 100 somula per well in Basch Medium. These were incubated at 37 °C for 24 hours.

D. Protocol for treatment of somula with Dr. Ke Sun's compounds

General prodecure for the treatment of somula with compounds. Starting from 4 mM stock solutions of the compounds in DMSO, the compounds were diluted with Basch Medium to the desired concentration. The tissue culture plate wells were set up to test triplicates of every concentration. To the 50 μL somula solution with Basch Medium was added 50 μL of the compound solution with DMSO. Auranofin was used as the positive control and pure DMSO as the negative. The somula were then incubated at 37 °C for 24 hours with the compounds.

E. CellTiter-Glo® Luminescent Cell Viability Assay protocol

General procedure for determining compound inhibition via the CellTiter-Glo® assay. The CellTiter-Glo® buffer solution was thawed to room

temperature prior to use and was added to the CellTiter-Glo® substrate with minimal agitation to avoid bubbles. To the 96 well tissue culture plate containing the somula in Basch Medium, 100 μL of glo solution was added with a multichannel pipette to each cell. The plate was then shaken via Fluorskan Ascent software for 2 minutes. After the shake step, the plate was incubated at room temperature for 10 minutes. The plate was then read in the luminometer using Gen5 software. The raw data was analyzed via Microsoft Excel.

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CHAPTER 3

Exploring a New Series of NAMPT Inhibitors for the Treatment of Pulmonary Arterial Hypertension

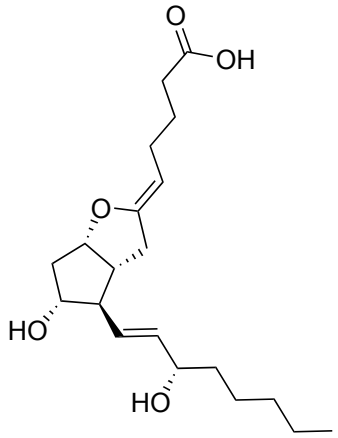
Pulmonary arterial hypertension (PAH) is a debilitating disease that involves vasoconstriction of the lung vasculature.[1-3] This remodeling of the blood vessels leads to dangerously high blood pressure in the arteries of the lungs. Normally the mean pressure in the pulmonary arteries is 9-18 mmHg,[4] but in patients with PAH these levels can reach up to 49 (± 13) mmHg.[5] Tightening in the arteries makes it hard for blood to be carried from the heart to the lungs, and this backup causes a rise in blood pressure. Consequently, the heart starts to work overtime to force blood through the narrowed arteries and this stress on the heart will eventually lead to heart failure.

Several types of PAH currently exist and include: idiopathic PAH[6] in which the cause is unknown, familial PAH[7,8] which has been linked to genetic defects, and associated PAH[9] which is most common and occurs simultaneously with other medical conditions. In every case the result is the same: the affected blood vessels begin to form excess tissue in a reparative process known as fibrosis.[10] This excess tissue leads to further thickening of the arteries making it even harder for the right side of the heart to get blood to the lungs and therefore oxygen to the rest of the body.

Symptoms commonly seen in patients with PAH include fatigue[11], shortness of breath with little physical activity, coughing, dizziness, swelling, and occasionally coughing up blood.[12] Currently there is no cure for pulmonary arterial hypertension and treatments target the vasoconstriction.[13] These drugs are commonly prostanoids, phosphodiesterase inhibitors, or endothelin antagonists. Epoprostenol[14] (commercially marketed as Flolan®) is considered

the most affective treatment for PAH currently although other prostanoids have been developed (Figure 3.1).

Figure 3.1 Structure of Flolan®



Flolan®

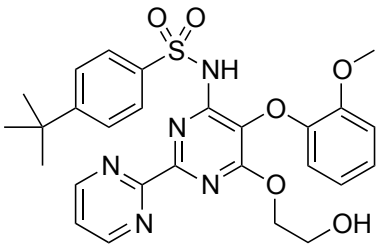
(Epoprostenol)

Current treatments for PAH may help relieve symptoms but are associcated with significant deficiencies. The effects of Flolan, for example, are extremely fleeting due to the instablility of the molecule and it requires continuous infusion through a venous catheter. The drug's half-life is about 5 minutes, which means it has to be continuously administered and interruption of treatment can be fatal for the patient. This intravenous delivery method can also lead to sepsis[15] and thrombosis[16] creating futher complications.

Bosentan[17] (commercially known as Tracleer®) is one of the only endothelin receptor antagonists available in the United States (Figure 3.2). This

drug works by blocking the interaction of endothelin-1 with ET-A or ET-B receptors, which causes constriction of the pulmonary blood vessels. A major side effect of this drug is liver damage.[18] Therefore, monthly liver function tests are required by the FDA while taking Bosentan.

Figure 3.2 Structure of Tracleer®



Tracleer®

(Bosentan)

Since PAH progressively worsens over time[19] and eventually leads to heart failure[20] it is vital that new treatments are developed. Within one year approximately 15% of patients[21] with idiopathic PAH face mortality and the numbers are even higher for patients with associated PAH and scleroderma.[22] With PAH worsening over time the numbers increase to 40% mortality within three years for idiopathic PAH. Treatments that target the underlying cellular disfunction are the main goal of this project.

Preliminary data for this project was gathered by the research groups of Roberto F. Machado, M.D.[23-39] and Gregory R. J. Thatcher of UIC. Utilizing a genomic approach the Machado group examined differential gene expression in

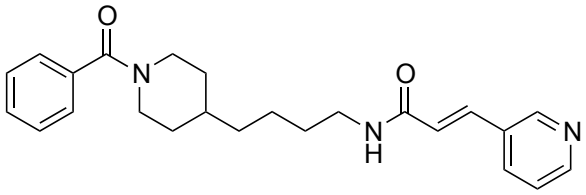
PAH patients and identified the cytozyme pre-B cell colony enhancing factor (PBEF) as a novel target gene and biomarker.

Cytozyme PBEF, also known as nicotinamide phosphoribosyl transferase (NAMPT)[40] or visfatin, is a key enzyme in the mammalian NAD biosynthesis pathway.[41] NAMPT catalyzes the first, rate-limiting step of the cycle which involves the synthesis of nicotinamide mononucleotide from nicotinamide. This pathway regulates ATP levels and studies have show that NAMPT may have pro-angiogenic activity which supports the growth of some types of tumours.[42] We hypothesize that this catalysis of cellular disfunction by NAMPT is also relevant in the reconstruction of the pulmonary arteries in PAH patients.

This hypothesis was supported by Machado's preliminary data showing that patients with idiopathic PAH have a significant increase in plasma PBEF compared to a control volunteer. Furthermore, histological staining of lung tissues with PBEF antibodies revealed significant increase in PBEF in PAH patients. With these initial discoveries they hypothesized that PBEF is upregulated in PAH patients and is a potent contributor to pulmonary vascular remodeling that could be targeted therapeutically.

To initially test this hypothesis a known PBEF/NAMPT/visfatin inhibitor, FK866,[43] was chosen to screen for prevention as well as reversal of monocrotaline (MCT) induce PAH in a rat-model (Figure 3.3). FK866, an NAMPT inhibitor, has demonstrated that it can induce apoptosis, programmed cell death, in cancer[44] and immune[45] cells.

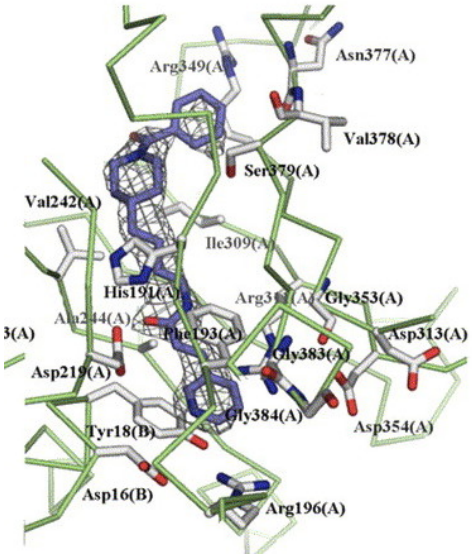
Figure 3.3 Structure of FK866



FK866

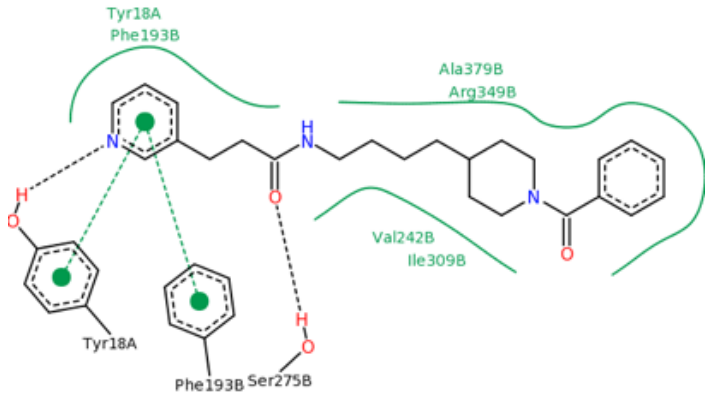
The visfatin gene was originally isolated from a human peripheral blood lymphocyte cDNA library in 1994 by Samal et al.,[46] and more recently in 2006 the first crystal structure[47] of NAMPT complexed with FK866 was obtained which allowed for more detailed analysis of it's inhibition. The crystal structure showed that the enzymatic active site of NAMPT is optimized for nicotinamide binding and that this binding site is important for inhibition (Figure 3.4).

Figure 3.4 Binding of FK866 with NAMPT taken from Kim et al., *JMB,* 2006



To determine the important structural moieties in FK866 and illucidate the significant interactions in our designed library, Emma Mendonca of the Thatcher group utilized this crystal structure for docking of Thatcher's and Driver's lead compounds. The active site of NAMPT is a dimer interface in which both sides of the dimer interacts with the inhibitor. Docking showed that the pyridyl ring of the inhibitor is sandwiched between the side chains of Phe193 of chain B and Tyr18 of chain A. There is also a significant hydrogen bonding interaction between the amide carbonyl oxygen and a fixed water molecule in the active site (Figure 3.5).

Figure 3.5 Binding mode of FK866 in active site



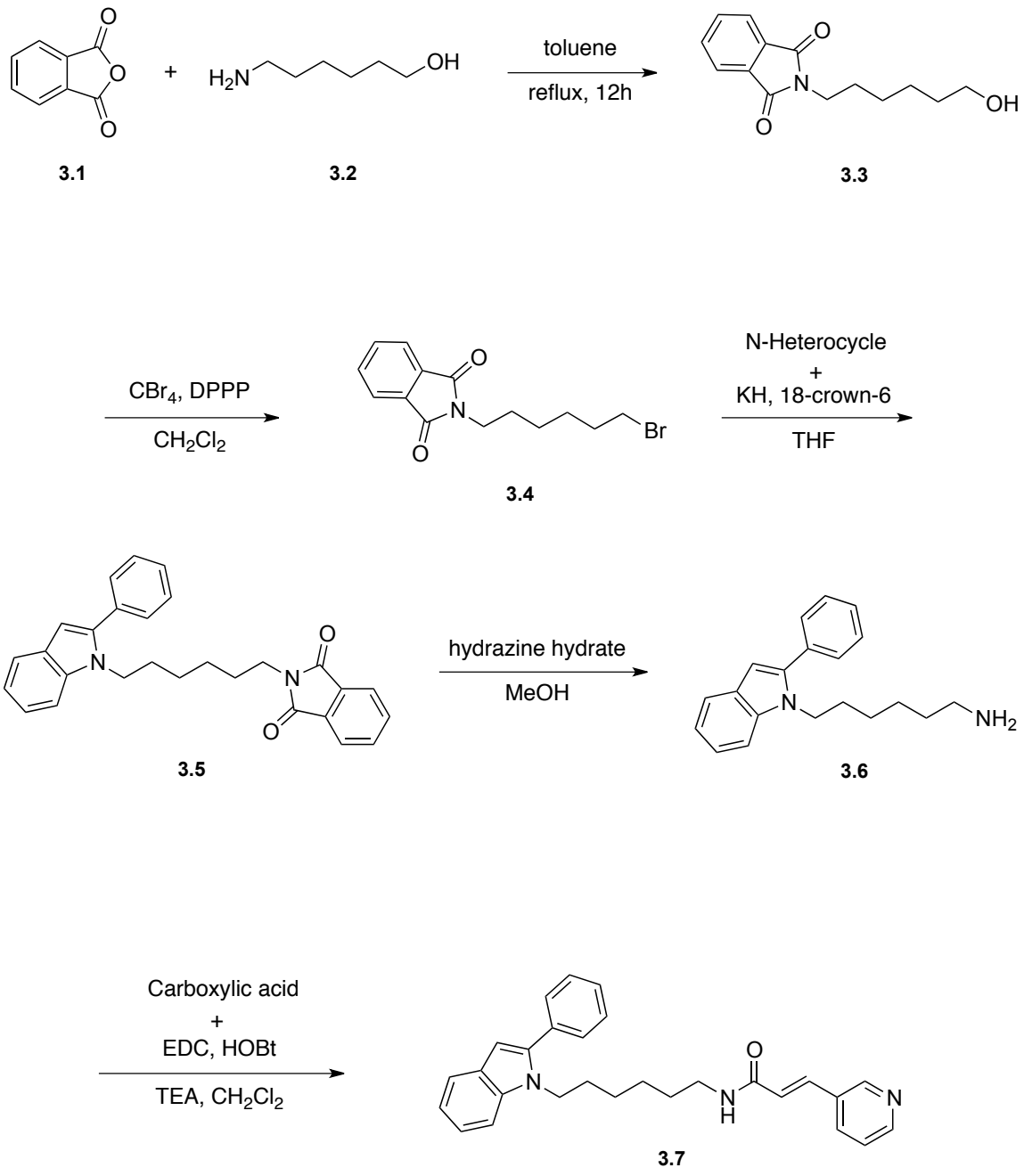
With a model therapeutic target identified by the Machado group, FK866, and the significant structural aspects understood, the Driver group focused its collaborative efforts on the development of a new inhibitor. Utilizing our expertise

in transition-metal-catalyzed formation of N-heterocycles we hoped to design a modular synthesis that would quickly lead to a library of inhibitors. The ultimate goal was to develop a patentable, novel, PBEF inhibitor that provides a new treatment for patients with PAH.

The synthetic approach for these compounds was to create a modular synthesis that could be tailored to each molecule in the library by simple addition of a variety of N-Heterocycles as the head group, keeping the majority of the synthesis linear. The alternate head and tail groups were to be added at the very end of the synthesis.

To start, a long alkyl chain containing different functionality at each end was chosen. This allowed for manipulation of each end of the molecule individually. Amino alcohol **3.2** was found to work the best for the initial substrate and the free amine portion was selectively protected with phthalic anhydride **3.1**. The bromide-leaving group was then generated at the other end of the chain **3.4**, which allowed for introduction of our nucleophilic N-heterocycle. Deprotection of the phthalamide **3.5** unveiled the synthetic handle in **3.6**, an amine, for addition of the final tail group. An EDC-mediated coupling reaction between a carboxylic acid and amine **3.6** afforded the final product **3.7**.

Scheme 3.1 NAMPT inhibitor synthetic route

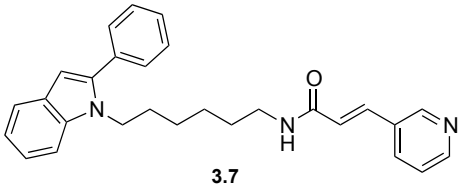


3.1 **3.2** **3.3** **3.4** **3.5** **3.6** **3.7**

A variety of inhibitors were quickly generated using this synthetic scheme (Figure 3.6). For the N-heterocycle substituted indoles and carbazoles were

utilized. The pyridyl tails were mostly composed of acrylic acid derivatives as well as N-methyl and N-hydrogen pyrolidines. The length of the spacer between the pyridyl cap and the amide was also varied, and the identity of the carbonyl was also replaced with a urea or guanidine. With these changes, the focused library in Figure 3.6 was created.

Figure 3.6 Driver lab scope of novel NAMPT inhibitors



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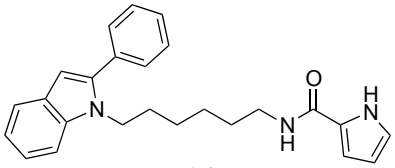

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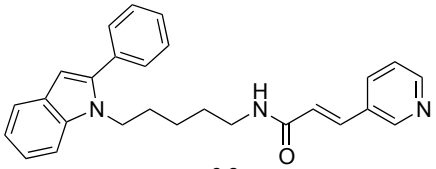

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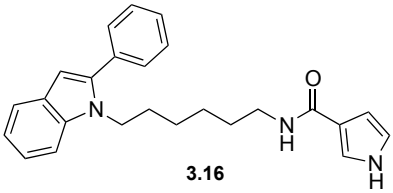

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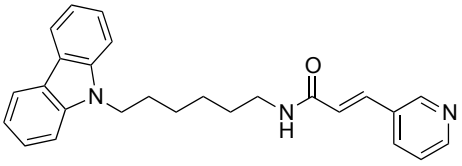

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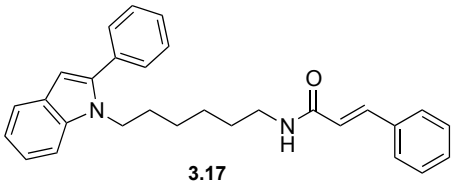

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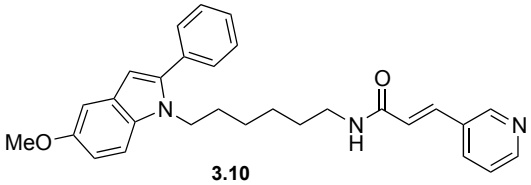

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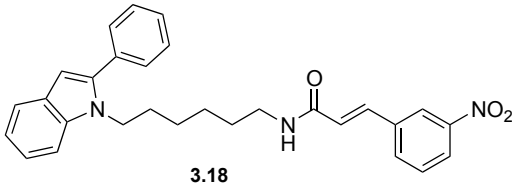

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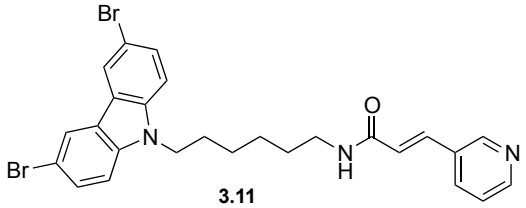

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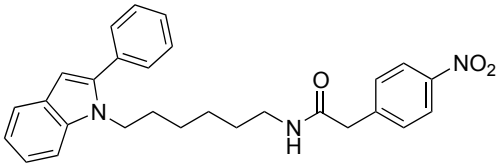

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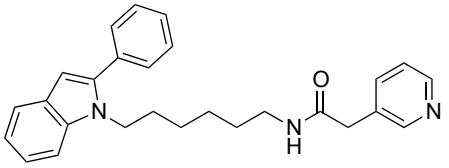

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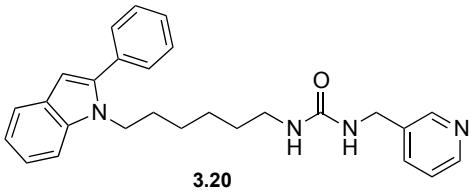

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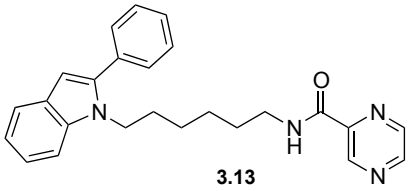

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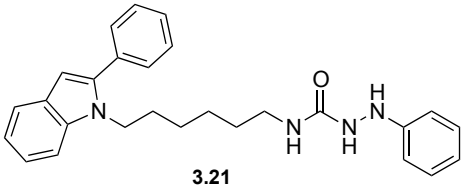
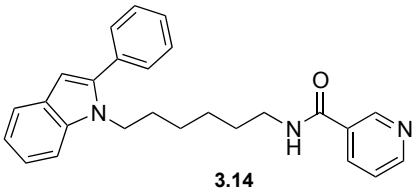


3.21



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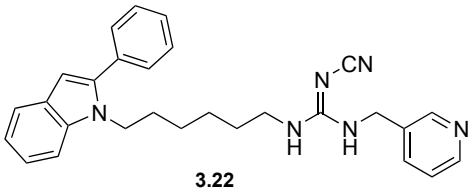

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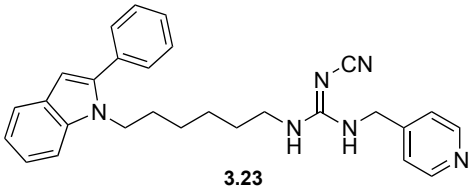
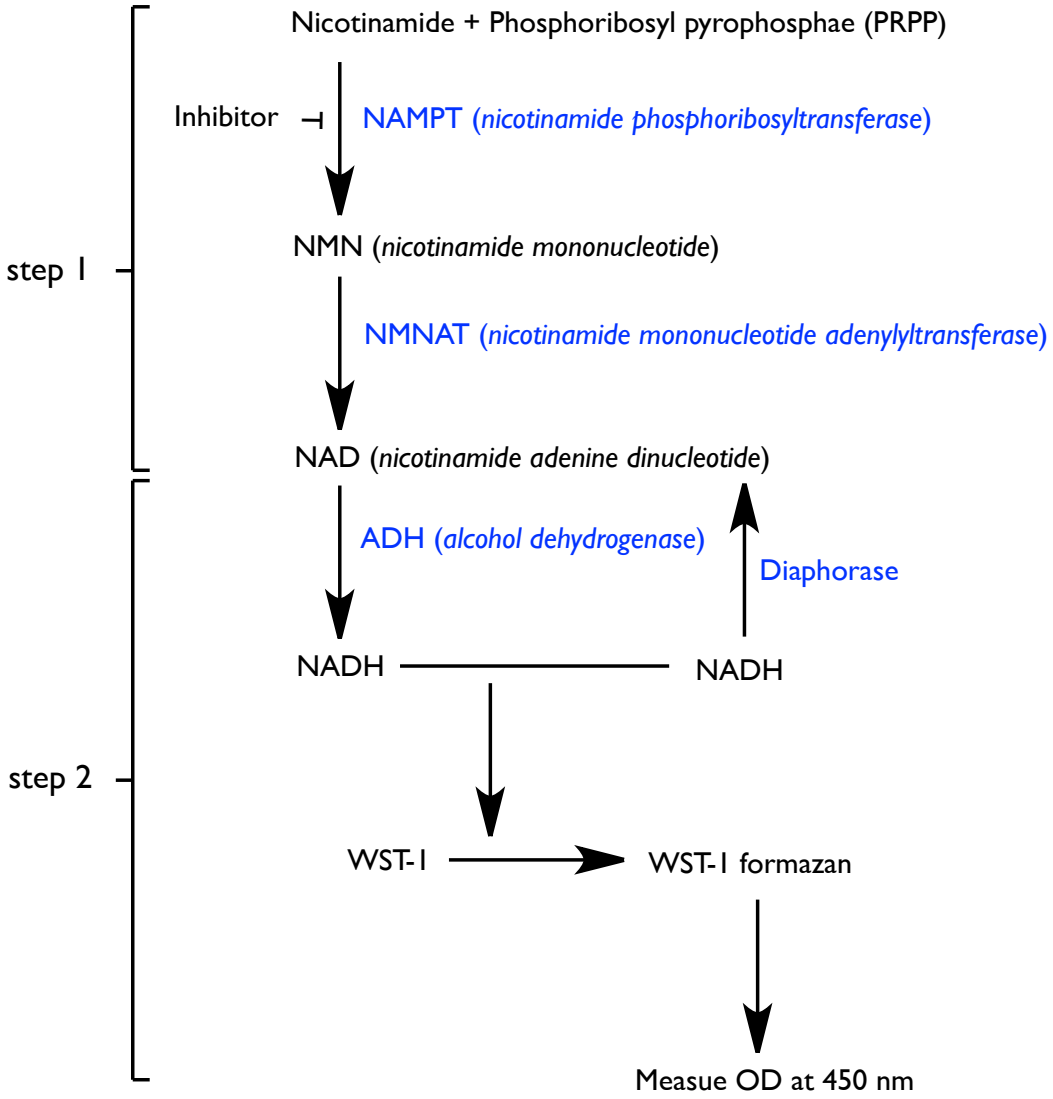


3.23

After synthesizing a variety of compounds containing different N-heterocyle head groups as well as alternative pyridyl tail groups, these compounds were combined with the Thatcher group library and screened for inhibition of NAMPT by Márton Siklós using a colormetric assay (Figure 3.7). This nicotinamide nucleotide assay provides a tool for the quantification of NAD and NADH. The reaction cycle is specific for the detection of the NAD and NADH and

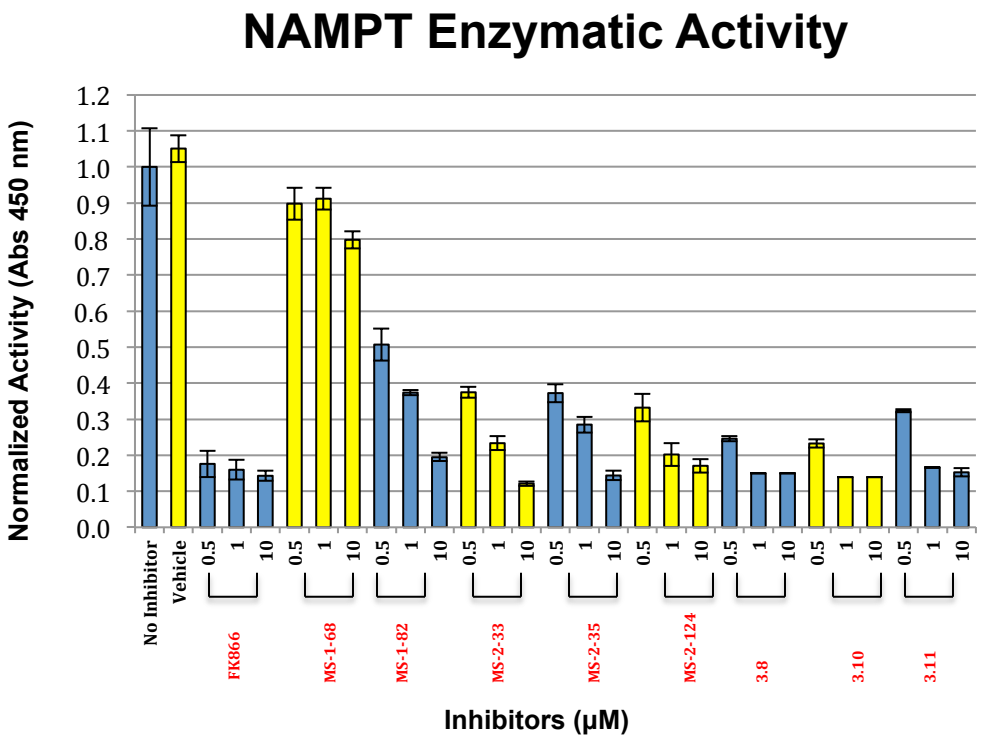
requires no purification of these nucleotides from the tested samples. Since NAMPT catalyzes the first step in this cycle, the formation of nicotinamide mononucleotide (NMN), no NAD or NADH will be produced if inhibition occurs. Therefore, higher output readings, at 450 nm from the colorimeter, corresponded to lower inhibition of NAMPT.

Figure 3.7 Assay Screening of NAMPT inhibitors



Outputs from this assay were plotted versus concentration and compared to the established inhibitor FK866 (Figure 3.8). The goal was to obtain an inhibitor that was as effective if not more potent than FK866 to use in the phase 3 rat-model. After analyzing the data we found that structures **3.7**, **3.9**, **3.10** and **3.20** showed excellent inhibition of NAMPT when compared to FK866.

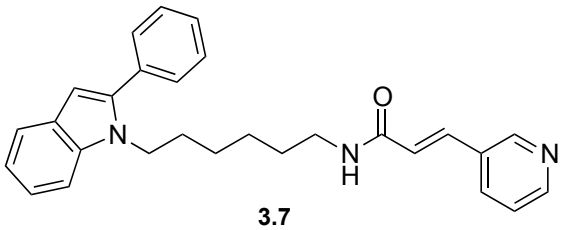
Figure 3.8 Sample data analysis of colormetric assay



Due to ease of synthesis and overall assay results **3.7** (Figure 3.9) was chosen as our lead inhibitor to carry on into phase 3 of the study. The synthetic route was scaled up to gram quantities to provide enough material for the

Machado lab to carry out phase three of the study. This phase will include gathering toxicology data on the lead inhibitors as well as validation of the candidate inhibitors in *vivo* using a MCT-induced PAH model in rats. This part of the project is currently ongoing in the Machado lab.

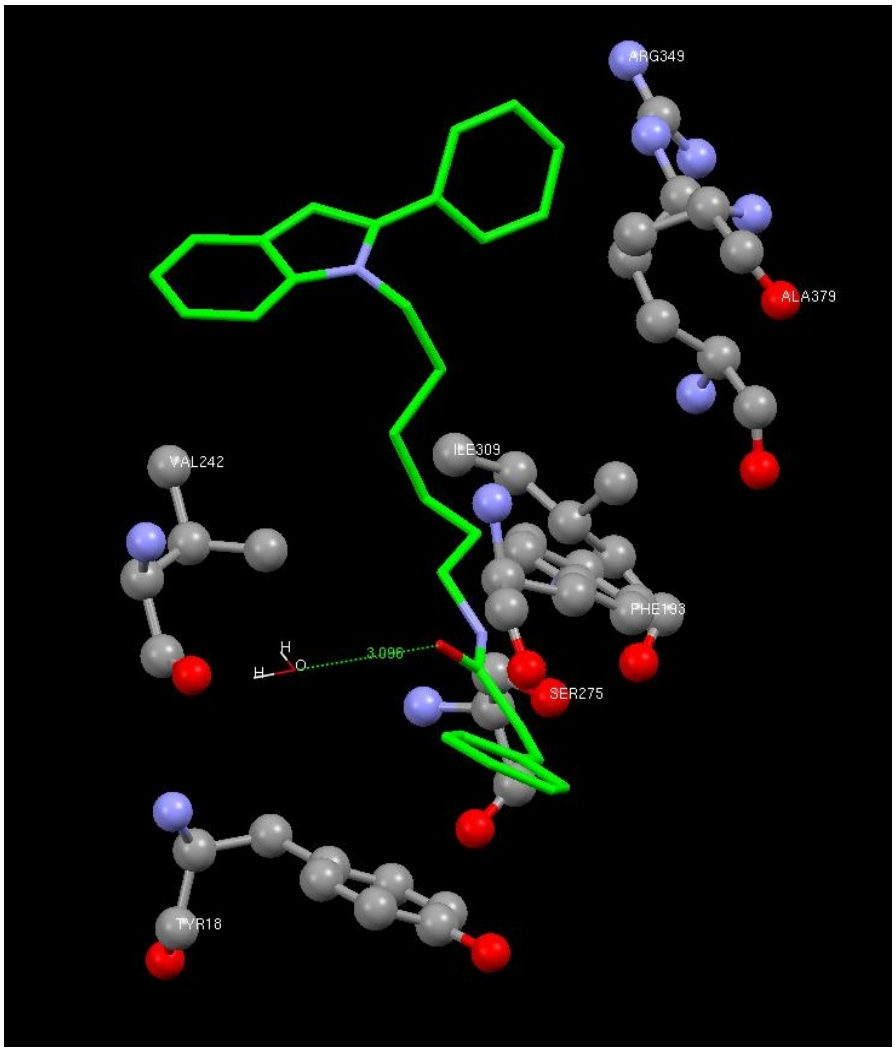
Figure 3.9 Lead pulmonary arterial hypertension inhibitor



3.7

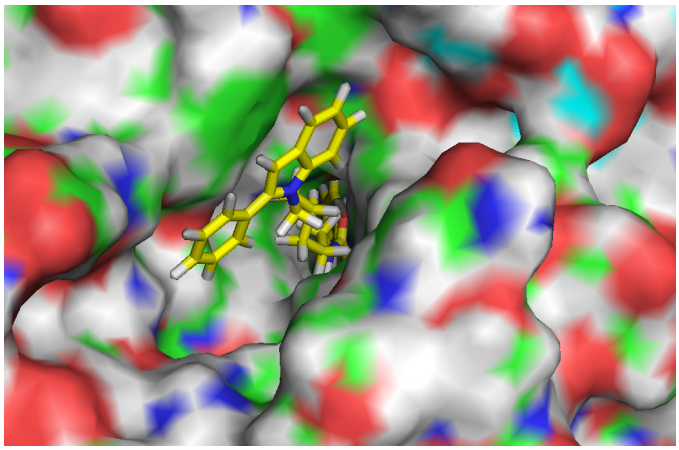
Identification of our lead chemical probe validates Emma's *in silica* modeling approach. Compound **3.7** scored high in Emma's GOLD settings and satisfied the known pharmocophoric requirements such as terminal aromatic ring π-π stacking and a long aliphatic linker for the 15 Å tunnel. Using this software the Thatcher lab was able to predict binding modes of **3.7** (Figure 3.10). It is evident that the terminal aromatic ring forms a pi-pi stacking interaction between Tyr18 and Phe193 similar to FK866. In the surface view (Figure 3.11) the rigid surface-binding group sits at the opening of the enzyme channel and blocks the mouth of the active site.

Figure 3.10 Predicted binding mode of lead inhibitor



GOLD: Predicted binding mode

Figure 3.11 Surface view of the predicted binding mode



GOLD: Surface binding mode

Currently, preliminary data obtained from Jiwang Chen, of the Machado lab, has been promising for the rat model. Male Sprague-Dawley rats (200-220g) were injected with one dose of MCT (60mg/kg) to induce PAH. In the prevention experiments rats were simultaneously administered subcutaneously with **3.7** (5mg/kg) every two days over a two-week period. Subsequent measurement of the right ventricular systolic pressure (RVSP) was conducted with a pressure transducer catheter. The right ventricle to left ventrical plus septum (RV/LV+S) weith ratio was calculated. Upon analysis **3.7** was shown to significantly prevent MCT-induced PAH in rats, which is demonstrated by significantly lower RVSP and right ventricular hypertrophy.

At this point in the study optimization of the drug dosage and administration vehicle is being carried out due to significant weight loss in the model rats upon treatment. After this optimization and cell toxicity studies this collaborative effort will hopefully provide a new treatment for patients with PAH by targeting the enzyme that triggers vascular remodeling.

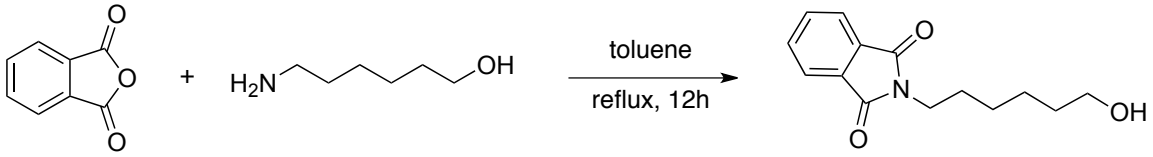
Experimental

A. General. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane on the δ scale, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz) and integration. High-resolution mass spectra were acquired on a JEOL CGMate II- or Thermo Finnigan brand LTQ FT spectrometer, and were obtained by peak matching. Infared spectroscopy was obtained using a diamond attenuated total reflectance (ATR) accessory. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 μm) mesh silica gel (SiO_2). Medium pressure liquid chromatography (MPLC) was performed to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60 μm) mesh silica gel (SiO_2). All reactions were carried out under an atmosphere of nitrogen in glassware, which had been oven-dried. Unless otherwise noted, all reagents

were commercially obtained and, where appropriate, purified prior to use. Acetonitrile, Methanol, Toluene, THF, Et_2O, and CH_2Cl_2 were dried by filtration through alumina according to the procedure of Grubbs.[48] Metal salts were stored in a nitrogen atmosphere dry box.

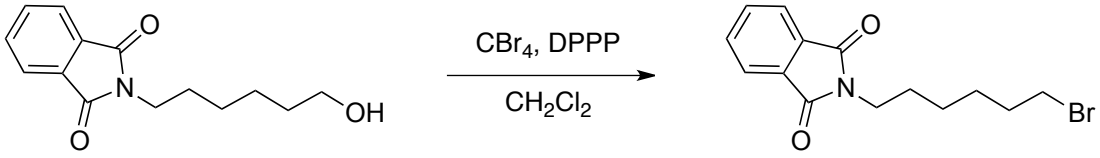
B. Synthesis of Amide Series of Compounds

B1. Preparation of Phthalamide



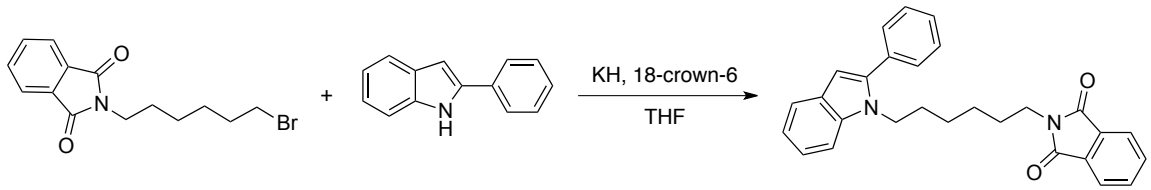
General procedure for the formation of 2-(6-hydroxyhexyl)isoindoline-1,3-dione. (**3.3**) Phthalic anhydride (2.53 g, 17.07 mmol) and 6-Amino-1-hexanol (2.0 g, 17.07 mmol) were suspended in toluene (20 mL) and heated to reflux for 16 h. After warming to room temperature the mixture was concentrated in *vacuo* to afford yellow oil. The crude product was used in the next step without further purification. Yields were not optimized. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.87 (dd, *J* = 5.5, 1.5 Hz, 2H), 7.74 (dd, *J* = 5.0, 3.0 Hz, 2H), 3.72 (t, *J* = 7.5 Hz, 2H), 3.67 (t, *J* = 6.5 Hz, 2H), 1.90 (br s, 1H), 1.73 (quintet, *J* = 7.0 Hz, 2H), 1.61 (quintet, *J* = 7.5 Hz, 2H), 1.49–1.38 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.5 (C), 133.9 (CH), 132.2 (C), 123.2 (CH), 62.8 (CH_2), 37.9 (CH_2), 32.6 (CH_2), 28.6 (CH_2), 26.6 (CH_2), 25.3 (CH_2).

B2. Preparation of Alkyl Bromide



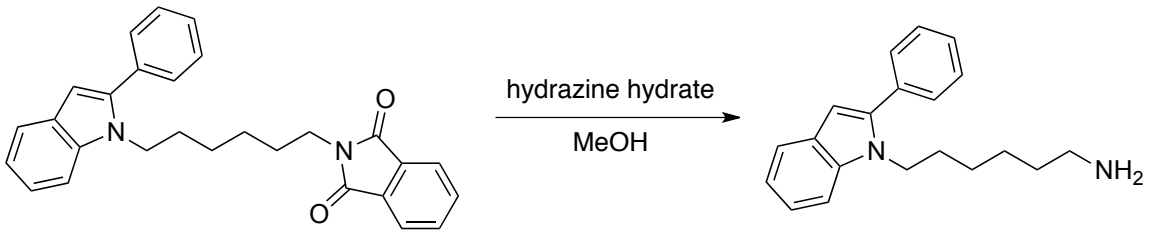
General procedure for the formation of 2-(6-bromohexyl)isoindoline-1,3-dione. (**3.4**) To a stirred solution of **3.3** (4.45g, 17.86 mmol) in CH_2Cl_2 (127 mL) was added DPPP (5.89 g, 14.29 mmol). The mixture was cooled to 0°C and CBr_4 (7.70 g, 23.22 mmol) was added in one portion. After warming to ambient temperature the reaction was stirred for 16 h. The mixture was poured into 200 mL Et_20 and filtered through celite. The filtrate was concentrated in *vacuo* and purified by MPLC on silica (20% EtOAc/Hexanes). Yields were not optimized. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.82 (dd, *J* = 5.5, 3.5 Hz, 2H), 7.73 (dd, *J* = 5.5, 3.0 Hz, 2H), 3.67 (t, *J* = 7.0 Hz, 2H), 3.38 (t, *J* = 7.0 Hz, 2H), 1.84 (quintet, *J* = 7.5 Hz, 2H), 1.68 (quintet, *J* = 7.5 Hz, 2H), 1.47 (quintet, *J* = 7.5 Hz, 2H), 1.36 (quintet, *J* = 7.5 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.4 (C), 133.9 (CH), 132.1 (C), 123.2 (CH), 37.8 (CH_2), 33.7 (CH_2), 32.6 (CH_2), 28.4 (CH_2), 27.7 (CH_2), 26.0 (CH_2).

B3. Preparation of Alkylated Indole



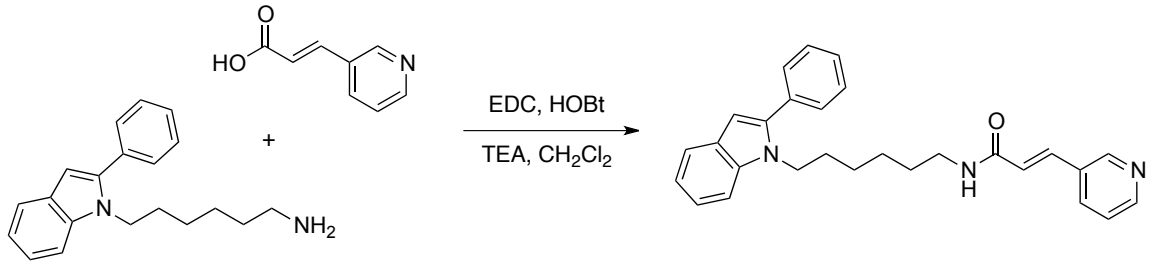
General procedure for the formation of 2-(6-(2-phenyl-1*H*-indol-1-yl)hexyl)isoindoline-1,3-dione. (**3.5**) In a flame dried flask 18-crown-6 (0.64 g, 2.40 mmol) and KH (0.10 g, 2.40 mmol) were weight out and suspended in solution with THF. 2-Phenyl indole (0.31 g, 1.60 mmol) was then added in one portion and this was stirred for 30 min. The mixture was then cooled to 0°C and **3.4** (0.50 g, 1.60 mmol) was added in one portion. The mixture was warmed to ambient temperature and stirred for 16h. The red solution was diluted with H_2O and extracted with 3 x 30 mL Et_2O. The combined organic phases were washed with brine and dried over Na_2SO_4. Concentration in *vacuo* afforded a yellow oil which was purified by MPLC on silica (0:100 – 20:80, EtOAc/Hexanes). Yields were not optimized. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.84 (m, 2H), 7.69 (m, 3H), 7.52 (m, 4H), 7.42 (m, 2H), 7.27 (t, *J* = 6.5 Hz, 1H), 7.17 (t, *J* = 6.0 Hz, 1H), 6.56 (d, *J* = 1.5 Hz, 1H), 4.19 (t, *J* = 5.5 Hz, 2H), 3.62 (t, *J* = 5.5 Hz, 2H), 1.73 (quintet, *J* = 6.0 Hz, 2H), 1.59 (quintet, *J* = 6.0 Hz, 2H), 1.23 (m, 4H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 168.4 (C), 141.4 (C), 137.4 (C), 133.9 (CH), 133.3 (C), 132.2 (C), 129.5 (CH), 128.6 (CH), 128.3 (C), 128.0 (CH), 123.2 (CH), 121.6 (CH), 120.6 (CH), 119.8 (CH), 110.1 (CH), 102.2 (CH), 43.8 (CH_2), 37.9 (CH_2), 29.8 (CH_2), 28.5 (CH_2), 26.4 (CH_2), 26.3 (CH_2).

B3. Preparation of Free Amine



General procedure for the formation of 6-(2-phenyl-1*H*-indol-1-yl)hexan-1-amine. (**3.6**) In a flame dried flask 2 (0.20 g, 0.48 mmol) was suspended in MeOH (0.33 mL) and hydrazine hydrate was added (0.04 mL, 0.72 mmol). This stirred at ambient temperature for 10 min before another portion of MeOH (0.24 mL) was added. This stirred for 16h at ambient temperature. The solution was diluted with 1M NaOH and extracted with 3 x 30 mL CH_2Cl_2. The combined organic phases were washed with brine and dried over Na_2SO_4. Concentration in vacuo afforded a yellow oil which was purified by MPLC on silica (0:100 – 20:80, EtOAc/Hexanes). ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.64 (d, *J* = 8.0 Hz, 1H), 7.51-7.38 (m, 6H), 7.27-7.22 (m, 1H), 7.17-7.13 (m, 1H), 6.53 (s, 1H), 4.16 (t, *J* = 7.5 Hz, 2H), 3.23 (q, *J* = 7.0 Hz, 2H), 2.57 (s, 2H), 1.69 (quintet, *J* = 7.0 Hz, 2H), 1.41 (quintet, *J* = 7.0 Hz, 2H), 1.30 (quintet, *J* = 7.0 Hz, 2H), 1.17 (m, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 137.4 (C), 134.6 (C), 133.3 (C), 130.1 (CH), 129.5 (CH), 128.4 (CH), 128.3 (C), 127.9 (CH), 121.6 (CH), 120.6 (CH), 119.8 (CH), 119.7 (CH), 110.1 (CH), 102.2 (CH), 43.8 (CH_2), 40.0 (CH_2), 29.8 (CH_2), 29.2 (CH_2), 26.6 (CH_2), 26.4 (CH_2).

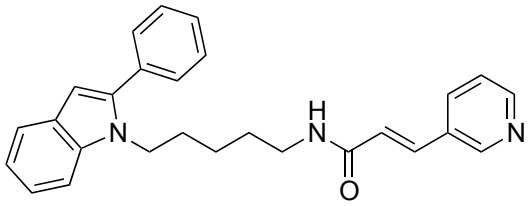
B4. Preparation of Amide Through EDC Coupling



General procedure for the formation of (E)-*N*-(6-(2-phenyl-1*H*-indol-1-yl)hexyl)-3-(pyridine-3-yl) acrylamide. (**3.7**) To a stirred solution of *trans*-3-(3-Pyridyl)acrylic acid (0.17 g, 1.15 mmol) in CH_2Cl_2 (18 mL) was added N-(3-Dimethylaminopropyl)-N'-ethylcarbodiimide (EDC) (0.41 mL, 2.30 mmol), 1-Hydroxybenzotriazole hydrate (HOBt) (0.28 g, 1.73 mmol), and Triethylamine (TEA) (0.24 mL, 1.73 mmol). To this mixture **3.6** (0.39 g, 1.39 mmol) was added as a solution in CH_2Cl_2 (5 mL). After stirring at ambient temperature for 16h, the reaction mixture was diluted with sat. $NaHCO_3$ and extracted with 3 x 30 mL CH_2Cl_2. The combined organic phases were dried over Na_2SO_4 and filtered. The filtrate was concentrated in *vacuo* to afford a yellow oil. Purification was carried out on silica (0:100 – 20:80, EtOAc/Hexanes). Yields were not optimized. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.72 (d, *J* = 2.0 Hz, 1H), 8.55 (dd, *J* = 5.0, 1.5 Hz, 1H), 7.74 (dt, *J* = 8.0, 2.0 Hz, 1H), 7.64 (d, *J* = 8.0 Hz, 1H), 7.58 (d, *J* = 16.0 Hz, 1H), 7.49-7.44 (m, 4H), 7.42-7.36 (m, 2H), 7.27 (dd, *J* = 8.0, 5.0 Hz, 1H), 7.23 (td, *J* = 7.0, 1.0 Hz, 1H), 7.13 (td, *J* = 8.0, 1.0 Hz, 1H), 6.52 (s, 1H), 6.41 (d, *J* = 15.5 Hz,

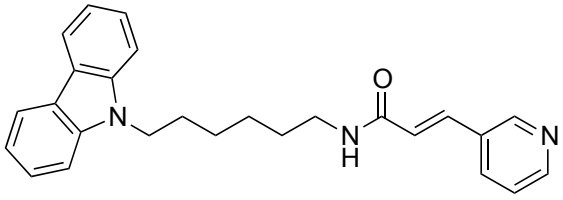
1H), 5.83 (t, *J* = 5.5 Hz, 1H), 4.16 (t, *J* = 7.5 Hz, 2H), 3.26 (q, *J* = 7.0 Hz, 2H), 1.67 (quintet, *J* = 7.0 Hz, 2H), 1.41 (quintet, *J* = 7.0 Hz, 2H), 1.16 (m, 4H).

B5. Preparation of Amides



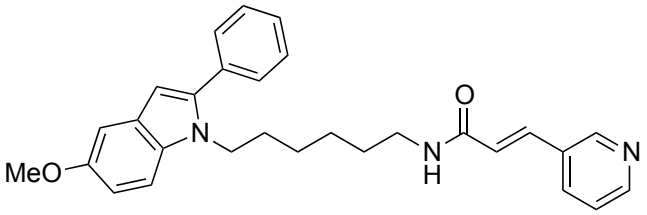
3.9

(E)-*N*-(5-(2-phenyl-1*H*-indol-1-yl)pentyl)-3-(pyridine-3-yl) acrylamide (**3.9**). Yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.65 (d, *J* = 1.5 Hz, 1H), 8.45 (d, *J* = 4.0 Hz, 1H), 7.61 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 16.0 Hz, 1H), 7.44-7.38 (m, 4H), 7.35-7.32 (m, 2H), 7.19 (t, *J* = 7.5 Hz, 1H), 7.14-7.09 (m, 2H), 6.88 (t, *J* = 5.5 Hz, 1H), 6.48 (d, *J* = 14.5 Hz, 2H), 4.09 (t, *J* = 7.0 Hz, 2H), 3.19 (q, *J* = 7.0 Hz, 2H), 1.62 (quintet, *J* = 1.5 Hz, 2H), 1.35 (quintet, *J* = 7.5 Hz, 2H), 1.11 (quintet, *J* = 8.0 Hz, 2H).



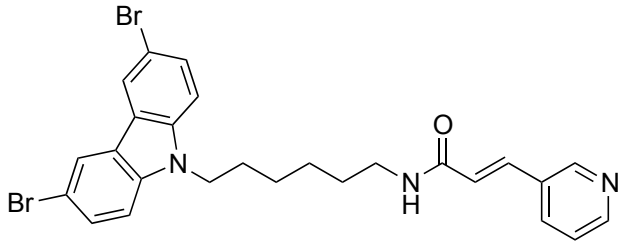
3.10

(E)-*N*-(6-(9*H*-carbazol-9-yl)hexyl)-3-(pyridine-3-yl) acrylamide. (**3.10**) Yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.69 (d, *J* = 2.0 Hz, 1H), 8.51 (dd, *J* = 5.0, 1.5 Hz, 1H), 8.10 (d, *J* = 7.5 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.55 (d, *J* = 16.0 Hz, 1H), 7.45 (dd, *J* = 8.0, 1.0 Hz, 2H), 7.37 (d, *J* = 8.5 Hz, 2H), 7.22 (m, 3H), 6.36 (d, *J* = 15.5 Hz, 1H), 6.09 (m, 1H), 4.25 (t, *J* = 7.0 Hz, 2H), 3.25 (q, *J* = 7.0 Hz, 2H), 1.82 (quintet, *J* = 7.0 Hz, 2H), 1.43 (quintet, *J* = 7.0 Hz, 2H), 1.31 (m, 4H).



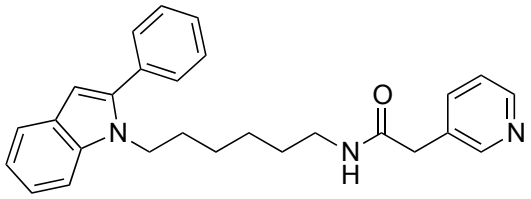
3.11

(*E*)-*N*-(6-(5-methoxy-2-phenyl-1*H*-indol-1-yl)hexyl)-3-(pyridin-3-yl) acrylamide. (**3.11**) Yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.69 (s, 1H), 8.52 (dd, *J* = 4.5, 1.5 Hz, 1H), 7.70 (d, *J* = 7.5, 1.2 Hz, 1H), 7.56 (d, *J* = 16.0 Hz, 1H), 7.45 (m, 4H), 7.40-7.38 (m, 1H), 7.25 (d, *J* = 8.5 Hz, 2H), 7.09 (d, *J* = 2.5 Hz, 1H), 6.88 (dd, *J* = 8.5, 2.0 Hz, 1H), 6.43 (m, 2H), 6.08 (m, 1H), 4.10 (m, 2H), 3.85 (s, 3H), 3.24 (q, *J* = 7.0 Hz, 2H), 1.63 (quintet, *J* = 7.0 Hz, 2H), 1.40 (quintet, *J* = 7.0 Hz, 2H), 1.14 (m, 4H).



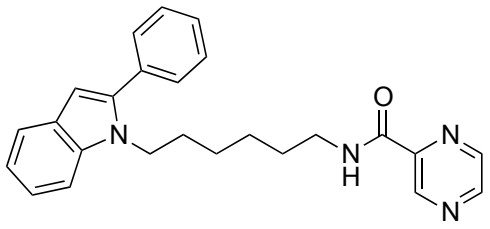
3.12

(*E*)-*N*-(6-(3,6-dibromo-9*H*-carbazol-9-yl)hexyl)-3-(pyridin-3-yl) acrylamide. (**3.12**) Yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.67 (s, 1H), 8.49 (d, *J* = 3.5 Hz, 1H), 8.06 (s, 2H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.54 (d, *J* = 16.0 Hz, 1H), 7.49 (dd, *J* = 8.5, 1.5 Hz, 2H), 7.22 (dd, *J* = 7.5, 5.0 Hz, 1H), 7.18 (d, *J* = 8.5 Hz, 2H), 6.42 (d, *J* = 15.5 Hz, 1H), 6.17 (m, 1H), 4.15 (t, *J* = 7.0 Hz, 2H), 3.29 (q, *J* = 7.0 Hz, 2H), 1.76 (quintet, *J* = 7.0 Hz, 2H), 1.46 (quintet, *J* = 7.0 Hz, 2H), 1.30 (m, 4H).



3.13

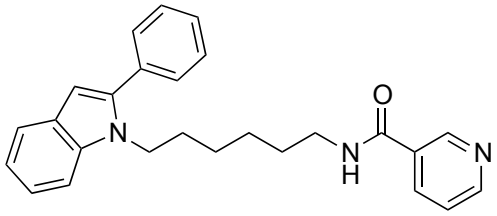
***N*-(6-(2-phenyl-1H-indol-1-yl)hexyl)-2-(pyridin-3-yl) acetamide.** (**3.13**) Yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.69 (dd, *J* = 7.0, 2.5 Hz, 1H), 7.63 (m, 2H), 7.58 (d, *J* = 8.0 Hz, 1H), 7.46-7.44 (m, 4H), 7.42-7.39 (m, 2H), 7.23 (td, *J* = 7.0, 1.0 Hz, 2H), 7.14 (m, 1H), 6.52 (s, 1H), 5.52 (m, 1H), 4.14 (t, *J* = 7.5 Hz, 2H), 3.41 (s, 2H), 3.05 (q, *J* = 7.0 Hz, 2H), 1.63 (quintet, *J* = 7.5 Hz, 2H), 1.30 (m, 4H), 1.04 (quintet, *J* = 7.5, Hz, 2H).



3.14

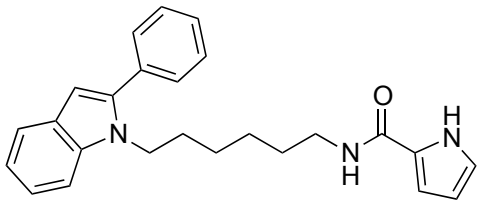
***N*-(6-(2-phenyl-1*H*-indol-1-yl)hexyl)pyrazine-2-carboxamide**. (**3.14**) Yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.39 (d, *J* = 1.5 Hz, 1H), 8.74 (d, *J* = 2.5 Hz, 1H),

8.50 (dd, *J* = 2.5, 1.5 Hz, 1H), 7.69 (m, 1H), 7.62 (t, *J* = 8.0 Hz, 1H), 7.49-7.43 (m, 4H), 7.39-7.35 (m, 2H), 7.22 (td, *J* = 7.5, 1.5 Hz, 1H), 7.12 (td, *J* = 7.0, 1.0 Hz, 1H), 6.52 (s, 1H), 4.18 (t, *J* = 7.5 Hz, 2H), 3.35 (q, *J* = 7.0 Hz, 2H), 1.73 (quintet, *J* = 7.0 Hz, 2H), 1.48 (quintet, *J* = 7.0 Hz, 2H), 1.22 (m, 4H).



3.15

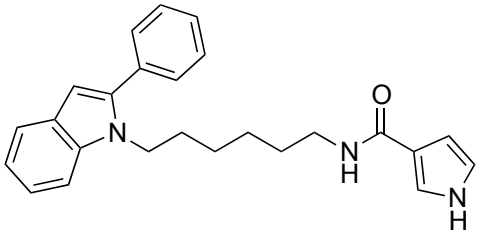
***N*-(6-(2-phenyl-1*H*-indol-1-yl)hexyl) nicotinamide**. (**3.15**) Yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.61 (d, *J* = 8.0 Hz, 1H), 7.50-7.41 (m, 7H), 7.38-7.35 (m, 3H), 7.17 (td, *J* = 7.0, 1.0 Hz, 1H), 7.10 (td, *J* = 8.0, 0.5 Hz, 1H), 6.50 (s, 1H), 6.41 (t, *J* = 5.5 Hz, 1H), 4.15 (t, *J* = 7.5 Hz, 2H), 3.18 (q, *J* = 7.0 Hz, 2H), 1.68 (quintet, *J* = 7.0 Hz, 2H), 1.36 (quintet, *J* = 7.0 Hz, 2H), 1.26 (m, 2H), 1.14 (m, 2H).



3.16

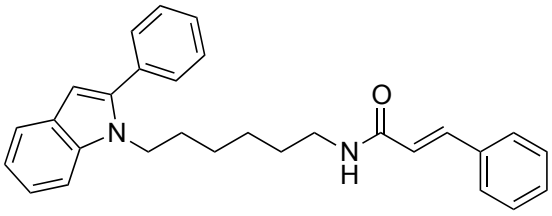
***N*-(6-(2-phenyl-1*H*-indol-1-yl)hexyl)-1*H*-pyrrole-2-carboxamide**. (**3.16**) Yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.61 (s, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.49-7.43 (m, 5H), 7.39 (m, 1H), 7.23 (td, *J* = 7.0, 1.0 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.89 (m, 1H), 6.53 (s, 1H), 6.47 (m, 1H), 6.22 (q, *J* = 3.5 Hz, 1H), 5.74 (t, *J* = 5.0 Hz,

1H), 4.18 (t, *J* = 7.5 Hz, 2H), 3.26 (q, *J* = 7.0 Hz, 2H), 1.71 (quintet, *J* = 7.5 Hz, 2H), 1.41 (quintet, *J* = 7.5 Hz, 2H), 1.28 (m, 2H), 1.18 (quintet, *J* = 7.5 Hz, 2H).



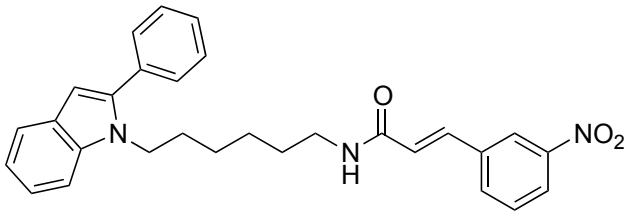
3.17

***N*-(6-(2-phenyl-1*H*-indol-1-yl)hexyl)-1*H*-pyrrole-3-carboxamide**. (**3.17**) Yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 9.55 (s, 1H), 7.65 (d, *J* = 7.5 Hz, 1H), 7.54-7.45 (m, 7H), 7.42-7.39 (m, 2H), 7.21 (t, *J* = 7.5 Hz, 1H), 7.14 (t, *J* = 7.0 Hz, 1H), 6.54 (s, 1H), 6.52 (t, *J* = 5.5 Hz, 1H), 4.19 (t, *J* = 7.0 Hz, 2H), 3.22 (q, *J* = 7.0 Hz, 2H), 1.72 (quintet, *J* = 7.0 Hz, 2H), 1.41 (quintet, *J* = 7.0 Hz, 2H), 1.30 (m, 2H), 1.18 (quintet, *J* = 7.0 Hz, 2H).



3.18

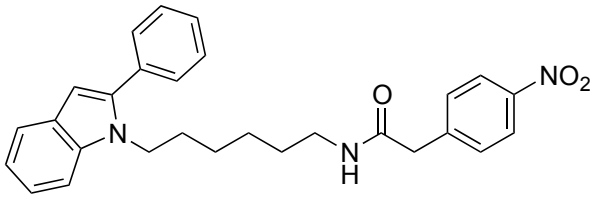
***N*-(6-(2-phenyl-1*H*-indol-1-yl)hexyl) cinnamamide**. (**3.18**) Yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 7.65 (d, *J* = 8.0 Hz, 1H), 7.62 (d, *J* = 15.5 Hz, 1H), 7.49-7.45 (m, 6H), 7.42-7.39 (m, 2H), 7.37-7.34 (m, 3H), 7.24 (td, *J* = 7.5, 1.0 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.53 (s, 1H), 6.35 (d, *J* = 15.5 Hz, 1H), 5.63 (m, 1H), 4.16 (t, *J* = 7.5 Hz, 2H), 3.26 (q, *J* = 6.0 Hz, 2H) 1.68 (quintet, *J* = 7.0 Hz, 2H), 1.41 (quintet, *J* = 7.0 Hz, 2H), 1.17 (m, 4H).



3.19

(*E*)-3-(3-nitrophenyl)-*N*-(6-(2-phenyl-1*H*-indol-1-yl)hexyl) acrylamide. (**3.19**)

Yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.35 (s, 1H), 8.17 (d, *J* = 8.0 Hz, 1H), 7.73 (d, *J* = 7.5 Hz, 1H), 7.64 (m, 2H), 7.53 (t, *J* = 8.0 Hz, 1H), 7.48-7.45 (m, 4H), 7.42-7.35 (m, 2H), 7.23 (t, *J* = 8.0 Hz, 1H), 7.13 (t, *J* = 7.5 Hz, 1H), 6.52 (s, 1H), 6.48 (d, *J* = 15.5 Hz, 1H), 5.75 (m, 1H), 4.17 (t, *J* = 7.5 Hz, 2H), 3.28 (q, *J* = 6.5 Hz, 2H), 1.68 (quintet, *J* = 7.0 Hz, 2H), 1.44 (quintet, *J* = 7.0 Hz, 2H), 1.17, (m, 4H).

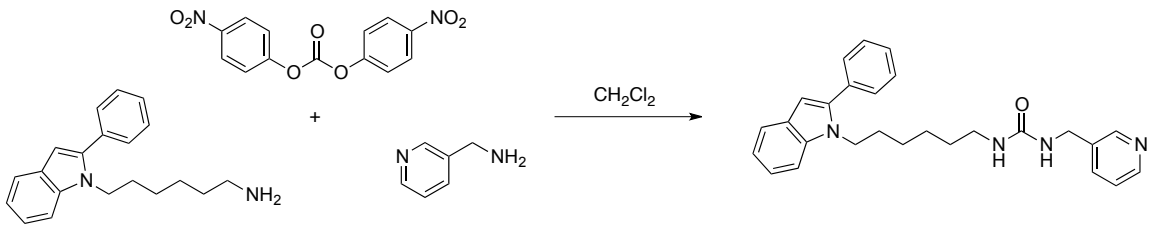


3.20

2-(4-nitrophenyl)-*N*-(6-(2-phenyl-1*H*-indol-1-yl)hexyl) acetamide. (**3.20**)

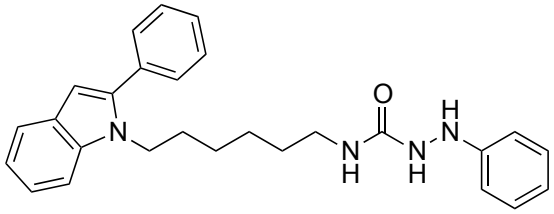
Yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.26 (d, *J* = 9.5 Hz, 2H), 7.67 (d, *J* = 9.5 Hz, 1H), 7.53-7.48 (m, 4H), 7.46-7.40 (m, 2H), 7.32 (d, *J* = 9.0 Hz, 2H), 7.26 (td, *J* = 8.0, 1.0 Hz, 1H), 7.17 (td, *J* = 7.0, 1.0 Hz, 1H), 6.56 (s, 1H), 5.03 (m, 1H), 4.22 (t, *J* = 7.5 Hz, 2H), 3.19 (q, *J* = 7.0 Hz, 2H), 1.72 (quintet, *J* = 7.0 Hz, 2H), 1.47 (quintet, *J* = 7.0 Hz, 2H), 1.21 (m, 4H).

C. Preparation of Ureas



General procedure for the formation of 1-(6-(2-phenyl-1*H*-indol-1-yl)hexyl)-3-(pyridin-3-ylmethyl) urea. (**3.21**) To a stirred solution of **3.6** (0.056 g, 0.19 mmol) in CH_2Cl_2 (1.15 mL) was added Bis(4-nitrophenyl) carbonate (0.058 g, 0.19 mmol). This was stirred for 12 h at room temperature and then 3-Pyridinemethanamine (18 µL, 0.18 mmol) was added and stirred at room temperature for another 12 h. The reaction mixture was concentrated in *vacuo* to afford a yellow oil. Yields were not optimized. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.46 (s, 1H), 8.43-8.34 (m, 2H), 7.74 (d, *J* = 7.0 Hz, 1H), 7.53 (d, *J* = 8.0 Hz, 1H), 7.45-7.43 (m, 4H), 7.38-7.33 (m, 3H), 7.31-7.28 (m, 1H), 7.15 (m, 1H), 7.03 (m, 1H), 6.43 (d, *J* = 3.0 Hz, 1H), 4.91 (s, 2H), 4.15 (t, *J* = 7.0 Hz, 2H), 2.98-2.91 (m, 2H), 1.55 (m, 2H), 1.26 (m, 2H), 1.05 (m, 2H).

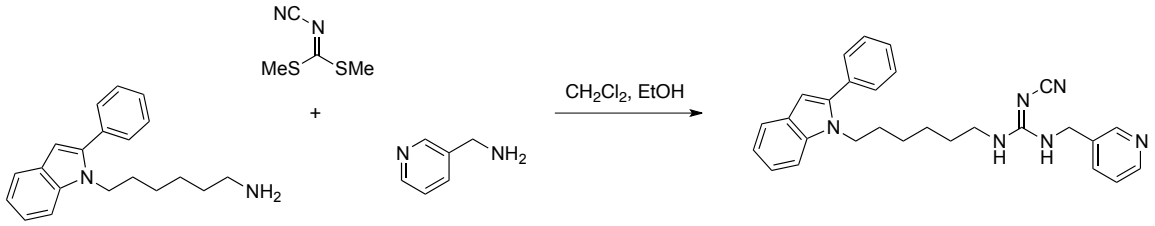
C1. Formation of Ureas



3.22

2-phenyl-*N*-(6-(2-phenyl-1*H*-indol-1-yl)hexyl) hydrazinecarboxamide. (**3.22**) Yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.25 (m, 1H), 8.16 (m, 1H), 7.67 (d, *J* = 7.5 Hz, 1H), 7.51-7.40 (m, 6H), 7.31 (d, *J* = 9.0 Hz, 2H), 7.26 (t, *J* = 7.0 Hz, 1H), 7.17 (t, *J* = 8.0 Hz, 1H), 6.88 (m, 1H), 6.56 (s, 1H), 5.18 (m, 1H), 4.21 (t, *J* = 7.5 Hz, 2H), 3.83 (m, 2H), 3.19 (q, *J* = 7.5 Hz, 2H), 1.70 (quintet, *J* = 7.0 Hz, 2H), 1.46 (quintet, *J* = 7.0 Hz, 2H), 1.19 (m, 4H).

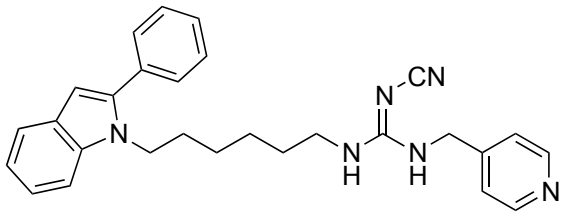
D. Preparation of Guanidines



General procedure for the formation of 2-cyano-1-(6-(2-phenyl-1*H*-indol-1-yl)hexyl)-3-(pyridin-3-ylmethyl) guanidine. (**3.23**) To a stirred solution of *N*-Cyanoimido-S,S-dimethyl-dithiocarbonate (0.055 g, 0.38 mmol) in EtOH (1 mL) was added **3.6** (0.10 g, 0.34 mmol) in CH_2Cl_2 (1.00 mL). This was stirred for 12 h at room temperature and then 3-Pyridinemethanamine (21 µL, 0.21 mmol)

was added and stirred at room temperature for another 12 h. The reaction mixture was concentrated in *vacuo* to afford a yellow oil. Yields were not optimized. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.49 (s, 1H), 8.43 (dd, *J* = 4.5, 1.0 Hz, 1H), 7.62 (m, 2H), 7.43 (m, 4H), 7.39-7.33 (m, 2H), 7.25-7.08 (m, 5H), 6.48 (s, 1H), 4.12 (m, 2H), 3.85 (s, 2H), 3.21-3.13 (m, 2H), 1.63 (m, 2H), 1.40 (m, 2H), 1.09 (m, 4H).

D1. Formation of Guanidines



3.24

2-cyano-1-(6-(2-phenyl-1*H*-indol-1-yl)hexyl)-3-(pyridin-4-ylmethyl)guanidine. (**3.24**) Yellow oil. ^{1}H NMR (500 MHz; $CDCl_3$): δ 8.45-8.40 (m, 2H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.42-7.31 (m, 6H), 7.21-7.14 (m, 5H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.46 (s, 1H), 4.09 (m, 2H), 3.83 (s, 2H), 3.14 (m, 2H), 1.60 (m, 2H), 1.38 (m, 2H), 1.07 (m, 4H).

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CONCLUSION

I have deloped new intramolecular transition metal-catalyzed C-H amination reactions of readily-synthesized aryl azides. The resulting C-N bond forming reactions allow access to a variety of biologically significant scaffolds with only nitrogen gas as the byproduct. I have then demonstrated the utility of these reactions by using them in the synthesis of medically relevant therapeutic inhibitors. Through assay development and inhibitor screening we have begun to illucidate new therapeutic targets and will hopefully provide new treatments for Schistosomiasis and pulmonary arterial hypertension.

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Ashley LeAnn Pumphrey

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Education

2009 – May 2014 Ph. D., Organic Chemistry (Tom G. Driver – Advisor)
University of Illinois at Chicago

2005 – 2009 B.Sc. Chemistry
University of Illinois at Chicago

Research Experience

2009 – current UNIVERSITY OF ILLINOIS AT CHICAGO

Graduate Research Associate
with T. G. Driver

Reactions for the synthesis of aromatic N-heterocycles:

-Rh_2^{II}-catalyzed decompositions of sp^2 azides in aromatic C-N bond-forming C-H functionalization reactions for the synthesis of indoles and pyroles.

-Rh_2^{II}-catalyzed decompositions of pyridinium ions in aromatic C-N bond-forming C-H functionalization reactions for the synthesis of δ-carbolines.

-Fluorescent assay screening of N-Heterocycles for Schistosomiasis Drug Discovery.

2006 – 2009 UNIVERSITY OF ILLINOIS AT CHICAGO

Undergraduate Research Assistant
with T. G. Driver

-Method development towards new complex molecules via transition metal-mediated reactions.

Teaching Experience

2013 – 2014 Chemistry Lecturer – Chemistry 101: Preparatory Chemistry
University of Illinois at Chicago

-Served as the primary instructor of three 1 hr lectures per week for ca. 155 students. Supervised two teaching assistants who provided weekly discussion sections.

2009 – 2013 Graduate Teaching Assistant – General and Organic Chemistry
University of Illinois at Chicago

-Supervised weekly laboratory and discussion sections for ca. 40 students.

Awards and Honors

2012-2014 Chancellor's Graduate Research Fellowship

2007	-2008	Herbert E. Paaren Academic Year Research Scholarship
2008		Herbert E. Paaren Summer Research Scholarship
2008		University of Illinois at Chicago Honors Council Award
2007		UIC Scholarship Association Award

Peer-Reviewed Publications

"Development of Novel Compounds towards Schistosomiasis Drug Discovery." Pumphrey, A. L.; Siklós, M.; Thatcher, G.; Williams, D.; Driver, T. G. *manuscript in preparation.*

"Synthesis, Quantitative Structure-Activity Relationship Analysis and Docking Studies of a Novel Series of Nicotinamide Phosphoribosyltransferase (NAMPT) Inhibitors." Pumphrey, A. L.; Siklós, M.; Mendonca, E.; Chen, J.; Thatcher, G.; Driver, T. G. *manuscript in preparation.*

"RhII2-Catalyzed Synthesis of α-, β-, or δ-Carbolines from Aryl Azides." Pumphrey, A. L.; Dong, H.; Driver, T. G. *Angew. Chem. Int. Ed.* **2012**, 51, 5920-5923.

"Transition Metal-Catalyzed Synthesis of Pyrroles from Dienyl Azides." Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey A. L.; Driver, T. G. *Org. Lett.* **2007**, *9* (25), 5191-5194.

"Intramolecular C–H Amination Reactions: Exploitation of the Rh_2(II)-Catalyzed Decomposition of Azidoacrylates." Stokes, B. J.; Dong. H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. *J. Am. Chem. Soc.* **2007**, *129* (24), 7500-7501.

Poster Presentations

1. Chicago Organic Symposium. April 30, 2012. "Transition Metal-Catalyzed Synthesis of Carbolinium Ions from Aryl Azides."