University of Illinois at Chicago

Transition-Metal Catalyzed C-H Bond Amination from Aryl Azide

By

Ke Sun

B.S., Dalian University of Technology, 2003
M.S., Nankai University, Tianjin, 2007

THESIS

Submitted as partial fulfillment of the requirements
for the degree of Doctor of Philosophy in Chemistry
in the Graduate College of the
University of Illinois at Chicago, 2014
Chicago, Illinois

Defense Committee:

Tom Driver, Chair and Advisor
Chad Eichman, Loyola University
Laura Anderson, Chemistry Department
Duncan Wardrop, Chemistry Deparment
Donald Wink, Chemistry Department

Acknowledgements

I would like to thank Professor Tom Driver, for his guidance, instruction and support during my PhD study. His enthusiasm for the knowledge of science has impressed me since the first day of my graduate school and continues inspiring me. His encouragement and belief in my abilities and potential have meant much to me over the past years, and undoubtedly, will continue serving me in my future pursuits. It's my great honor to be Professor Driver's one of the graduate students and have spent much more time working with him in the lab. I have truly enjoyed discussing chemistry and working with him over the years. He is a fantastic advisor and mentor.

I would also like to thank the members of my thesis committee, Professor Chad Eichman, Professor Duncan Wardrop, Professor Laura Anderson, and Professor Scott Shippy for their help and insightful comments on this thesis. Especially Professor Laura Anderson provides me lots of valuable suggestions during the group meetings.

I would also like to thank all current and former members of Professor Driver's research group for their friendship and help. Among them, I must mention Dr. Meihua Shen, who is a great chemist, helped me starting research here and show me how to work on the first Iridium project. Our group's first PhD, Ben Stoke, who is in charge of all the lab work and help Prof. Drive to set up the lab at the beginning. Special thanks to Dr. Huijun Dong, who help me a lot when I first arrive in Chicago and start a new foreign life. I was my absolute pleasure to work with these wonderful people.

I would like to thank Dr. Dan McElheny (UIC) for assistance with NMR Spectroscopy, and Dr. Furong Sun (UIUC) for mass spectrometry data. I also thank Ms. Pat Ratajczyk, Dr. Randall Puchalski, Ms. Silvia Solis, Mr. Brian Schwandt, and Mr. Don Rippon, as well as all the staff of the Chemistry Department, for their help.

Special thank to my wife Xiaoru Zhu for her unwavering support in every way over the years. Also I thank my Mom and Dad and all my family for their love and support. Without them, I could not be where I am.

TABLE OF CONTENTS

LIST OF FIGURES

LIST OF SCHEMES

LIST OF SCHEMES (continued)

LIST OF TABLES

LIST OF ABBREVIATIONS

Ac	acetyl
Alk	alkyl
aq	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	*tert*-butoxycarbonyl
Bpin	pinacolborane
Bz	benzoyl
n-Bu	butyl
t-Bu	*tert*-butyl
Calcd	calculated
cat.	catalytic amount
COD	1,5-cyclooctadiene
COE	cyclooctene
COT	cyclooctatetraene
Cp	cyclopentadienyl
Cy	cyclohexyl
δ	chemical shifts in parts per million downfield from tetramethylsilane (NMR)
d	doublet
dba	dibenzylidene acetone
dppf	1, 1′-Bis(diphenylphosphino)ferrocene
DCM	dichloromethane
DCE	1,2-dichloroethane
DEPT	distortionless enhancement by polarization transfer
DFT	Density Functional Theory
DMA	dimethylacetamide
DMF	dimethylformamide
DMSO	dimethylsulfoxide
DTBMP	di-*tert*-butyl-4-methlypyridine
dtbpy	4,4'-di-*tert*-butylbipyridine
EI	electron impact ionization (in mass spectrometry)
Et	ethyl
eq, equiv.	molar equivalent
$Rh_2(esp)_2$	Bis[rhodium(α, α, α′, α′-tetramethyl-1,3-benzenedipropionic acid)]
FePc	iron phthalocyanine
FT	Fourier transform
g	gram
GC	gas chromatography
h, hrs	hour(s)
HMDS	hexamethyldisilizane
HR	high resolution (mass spectrometry)
Hz	Hertz
J	spin-spin coupling constant (NMR)
L	ligand

LIST OF ABBREVIATIONS (continued)

LDA	lithium diisopropyl amide
m	multiplet (NMR)
mp	melting point
MPLC	medium pressure liquid chromatograph
Ns	*p*-nitrobenzenesulfonyl
μ	micro
[M]	metal
M	molar
MS	mass spectrometry
MS	molecular sieves
Me	methyl
mg	milligram
min	minute
mL	milliliter
mm	millimeter
mmol	millimole
mol	mole
MHz	megahertz
m/z	mass to charge ratio
p-cymene	*para*-isopropyltoluene
pfb	perflurobutyrate, heptafluorobutyrate
Ph	phenyl
Piv	pivalyl, trimethylacetyl
ppm	parts per million
Pr	propyl
i-Pr	isopropyl
n-Pr	propyl
Py	pyridine
q	quartet (NMR)
quint	quintet (NMR)
rt	room temperature
s	singlet (NMR)
sept	septet (NMR)
t	triplet (NMR)
Tf	trifluoromethanesulfonyl
THF	tetrahydrofuran
TLC	thin layer chromatography
TMS	trimethylsilyl
TMTU	tetramethylthiourea
Tol, tol	tolyl
tpa	triphenylacetate
TPP	tetraphenylporphinato
Troc	trichloroethoxycarbonyl
Ts	p-toluenesulfonyl

LIST OF ABBREVIATIONS (continued)

TTX	tetradotoxin
UV	ultraviolet

SUMMARY

This thesis describes transition metal catalyzed benzylic and aliphatic C–H amination reaction by employing aryl azides as the nitrogen source, with the generation of indoline. Additionly, Rh(II) carboxylate promoting disubtituted indole formation from β, β-disubstituted styryl azide is discussed afterwards.

Chapter one briefly introduce a variety of C–H bond functionalization including borylation, silylation and amination. Among them, amination has been widely discussed: intermolecular and intramolecular C–H bond amination are described respectively. Subsequently, Iridium complexes and Rh(II) carboxylate used to promote C–H bond functionalization are well studied. Finally, two examples are shown to demonstrate the application of transition metal catalyzed C–H bond amination.

Chapter two discloses benzylic C–H bond amination catalyzed by iridium complex, producing 2-arylindoline. This reaction features low catalyst loading and mild condition. However, the methodology is limited on benzylic C–H bond and lead to no reaction if electron donationg group attached on the aryl azide. Mechanism study implies that an electrophilic iridium nitrenoid (14) is generated in the reaction.

Chapter three discribes thermally robust $Rh_2(esp)_2$ could catalyze the aliphatic amination transformation without requiring electron poor environment on the aryl azide. Due to the decomposition of other metal catalysts at high temperature, no reaction was observed by using other rhodium carboxylate, and iridium, iron, copper catalysts. To improve the isolated yield of the amination, Boc_2O was added to the reaction mixture to protect the resulting indoline. N-atom transfer mechanism was proposed to explained the reaction activities.

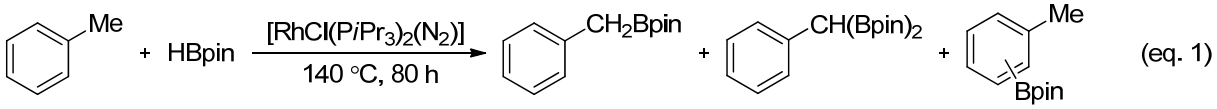
Chapter four investigates Rhodium-catalyzed synthesis of 2,3-disubstituted indoles from β,β-disubstituted styryl azide with controlling the selectivity of migration of one of the β-substituents. We discovers that aryl group migrates faster than alkyl group and more electron rich group prefers participate in migration. The migratorial aptitude suggests that a phenonium ion is reactive intermediate.

Chapter 1. Transition Metal-Catalyzed Aliphatic C–H Bond Functionalization

The functionalization of sp^3-C–H bonds is an important transformation because they are ubiquitous in organic molecules and direct functionalization of them rapidly increases the molecular complexity of the starting material. In this chapter, recent advances in benzylic C–H bond functionalization are discussed.

1.1 Aliphatic C–H Bond Borylation

One of the first examples of benzylic C–H bond functionalization was reported in 2001 by Marder and co-workers[1]. They reported that benzylic C–H bond borylation of alkylbenzenes could be achieved using transition metal complexes with pinacolborane as the boron source. (eq. 1). The regioselectivity of the C–H bond functionalization depended on the identity of the Rh(I)-complex's ligands. The authors reported that use of $[Cp^*RhCl_2]_2$[2] resulted in 62% of aromatic C–H bond functionalization products were formed without the formation of benzylic C–H bond activation products. In contrast, $[RhCl(P\textit{i}\text{-}Pr_3)_2(N_2)]$ was identified to catalyze benzylic sp^3 C–H bond borylation. The optimal conditions for benzylic monoborylation were determined to be exposure of toluene to 10 mol % $[RhCl(P\textit{i}\text{-}Pr_3)_2(N_2)]$, after 80 h at 140 ºC resulted in formation of **1.2** in 69%. While monoborylated **1.2** was the main product, the formation of diborylated **1.3** indicated that the Bpin substituent activated the secondary benzylic C–H bond in **1.2** to further functionalization.



(eq. 1)

1.1 **1.2** **1.3** **1.4**

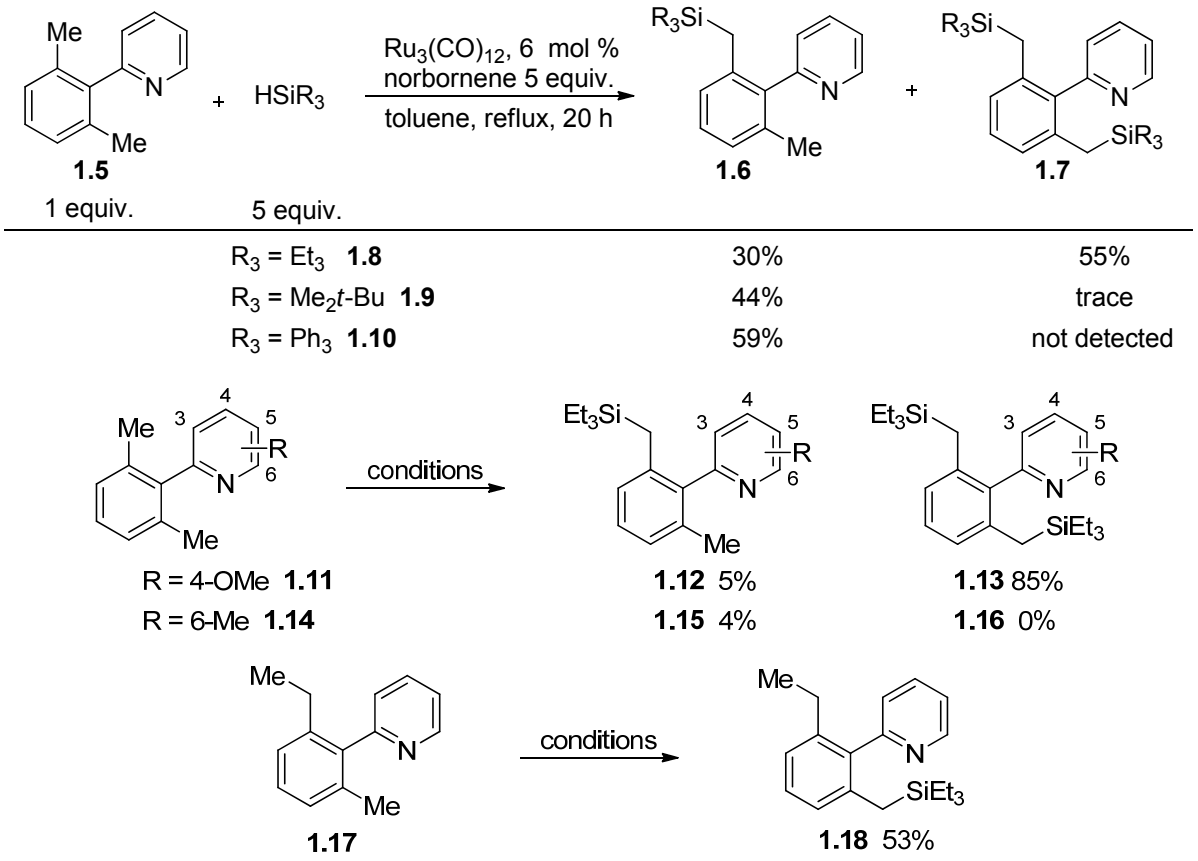
yield % 69 : 7 : 19

1.2 Aliphatic C–H Bond Silylation

In addition to benzylic C–H bond borylation, silylation of these C–H bonds has also been achieved. In 2004, Kakiuchi, Chatani and co-workers[3] demonstrated a new type of transition metal-catalyzed functionalization of benzylic sp^3 C–H bonds with hydrosilanes (Scheme 1.1). Critical to the success of their reaction was the presence of *ortho*-directing groups, such as a pyridyl-, pyrazoyl- or imino- group in hydrozones chelation-assisted C–H bond cleavage. Among various of rhodium complexes screened, such as $Ru_3(CO)_{12}$, $[Rh(OH)(cod)]_2$, $RuH_2(CO)(PPh_3)_3$, Ru(cod)(cot), $RuCl_3{\cdot}3H_2O$, $[RuCl_2(p\text{-cymene})]_2$, and $[Ir(OMe)(cod)]_2$, $Rh_3(CO)_{12}$ showed the highest activity. In the presence of norbornene as a hydrogen acceptor, 2-(2,6-dimethylphenyl)-pyridine could react with triethylsilane generating mono- (**1.6**) and disilylation (**1.7**) products in 30% and 55% yields, respectively. The coupling reaction using sterically hindered hydrosilanes (**1.9** and **1.10**) selectively gave the exclusive monosilylation coupling product **1.6**. Since triethylsilane **1.8** could provide the best conversion, the author determined to choose it as silicon source for further substrate screening.

Entensive screening of different substrates indicated that electron-rich group on pyridine ring **1.11** could improve the reactivity of arylpyridines, presumably due to their enhanced chelating ability to induce cleavage of the proximal C–H bond. Additionally, the yield was also affected by the steric environment: because coordination to the pyridyl nitrogen is inhibited, the reactivity of 6-substituted methyl pyridine **1.14** was found to be dramatically decreased.

Scheme 1.1. Benzylic C–H bond silylation catalyzed by $Rh_3(CO)_{12}$ complex.



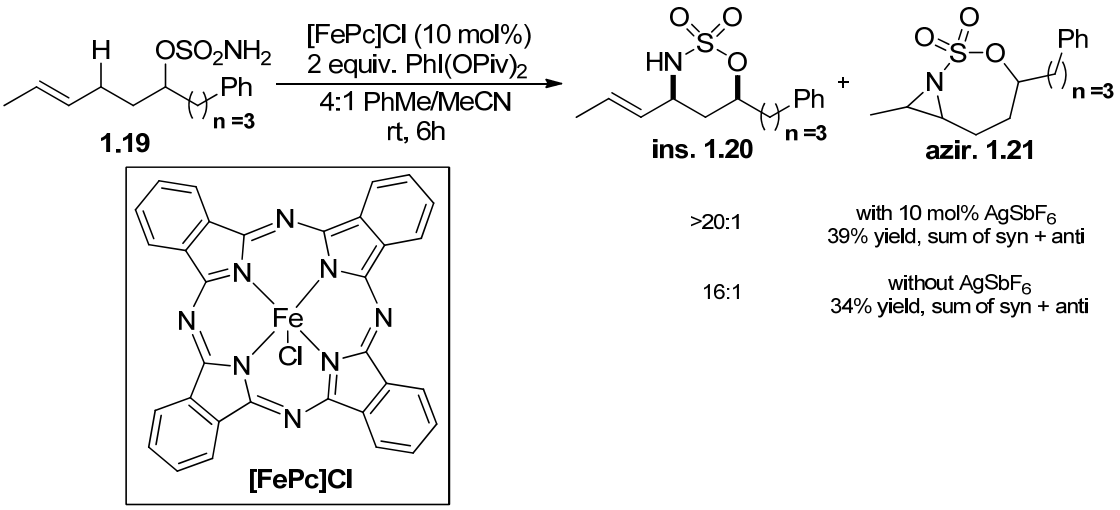
1.3 Aliphatic C–H Bond Amination

1.3.1 Intramolecular C–H Bond Amination

In addition to silylation or borylation of benzylic C–H bonds, metal-catalyzed C–H amination processes have also been widely studied. Metal-nitrenoid-based C–H aminations has attracted extensive attention with rhodium catalysts. The intramolecular reactivity trends observed using rhodium(II) carboxylate catalysts indicate that C–H amination preferentially occurs at electron-rich C–H bonds, and the alkene aziridination dominates the reaction when competing with allylic C–H bond amination. After Breslow and Gellman[4] published their seminal paper about Fe(TPP)Cl- and $Rh_2(OAc)_4$ catalyzed amination of aliphatic and benzylic

C–H bonds, very few approaches employing nontoxic[5] iron catalysts have been reported[6,7,8]. Recently, White and co-workers reported that commercial available [FePc]Cl could be used to catalyzed selectively allylic C–H amination.[9] Optimization of reaction conditions revealed that use of mixed solvent system (4:1 PhMe: MeCN) and more soluble $PhI(OPiv)_2$ led to significantly improved reactivity. Additionally, removal of $AgSbF_6$ from reaction mixture only cause slightly decrease in reactivity. The silver-free environment is particular beneficial in large-scale application.

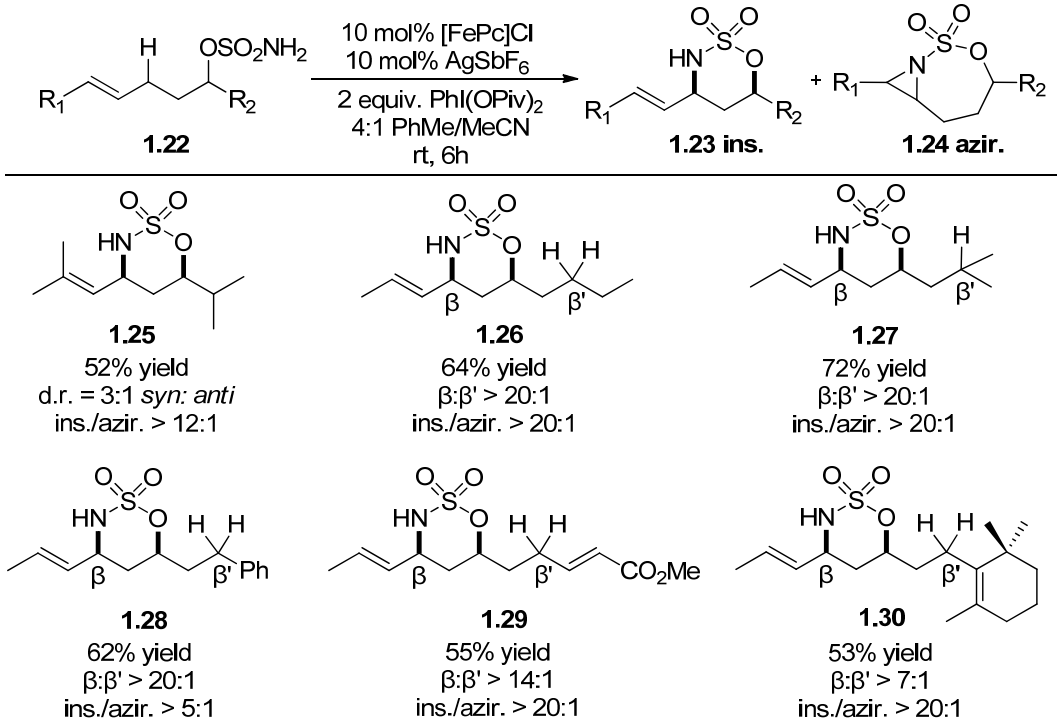
Scheme 1.2. Iron-catalyzed intromolecular allylic C–H amination.



The steric- and electronic constraints of substrates were evaluated. (Scheme 1.3). White's system displays highly chemoselectivities for allylic C–H amination over aziridination, including aliphatic (*E*)-olefins and styryl- and trisubstituted olefins. Their methods distinguishes itself from previous reports in the area because aziridination is preferred for terminal aliphatic olefins for rhodium- and ruthenium-catalyzed systems[10]. Analysis of the substrate scope reveals that the trend of allylic C–H bond reactivity is in agreement with dissociation energies of C–H bond: allylic > benzylic > 3° > 2° >> 1°. The electronic indentity of allylic C–H bond also plays an important role on reactivities: electron-withdrawing groups, like α, β-unsaturated ester **1.29** was

found to reduce the reaction yield substantially. Allylic amination was also found to depend on the steric environment: the less hindered allylic C–H bond of **1.30** was functionalized with selectivity over 7:1.

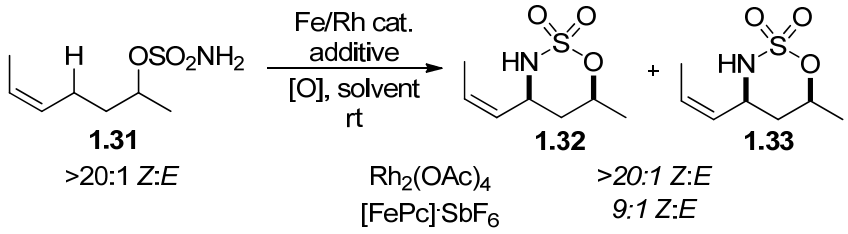
Scheme 1.3. Substrate scope of iron-catalyzed intromolecular allylic C–H amination.



[a]Determined by ^{1}H NMR analysis of the crude reaction mixture (d.r. ≈ 3). bIsolated yield (syn + anti; *E*/*Z* > 20:1 in all cases).

The mechanism of iron catalyzed allyic C–H amination was probed by comparision with $Rh_2(OAc)_4$. When sulfamate ester **1.31** was subjected to [Fe^{III}Pc]-catalyzed C–H amination, the allylic functionalization was obtained as a 9:1 Z/E mixture, suggesting that the reaction process through the intermediacy of a stabilized carbon-centered radical. While no isomerization was observed under $Rh_2(OAc)_4$ catalysts environment, different mechanisms maybe operating in these two cases.

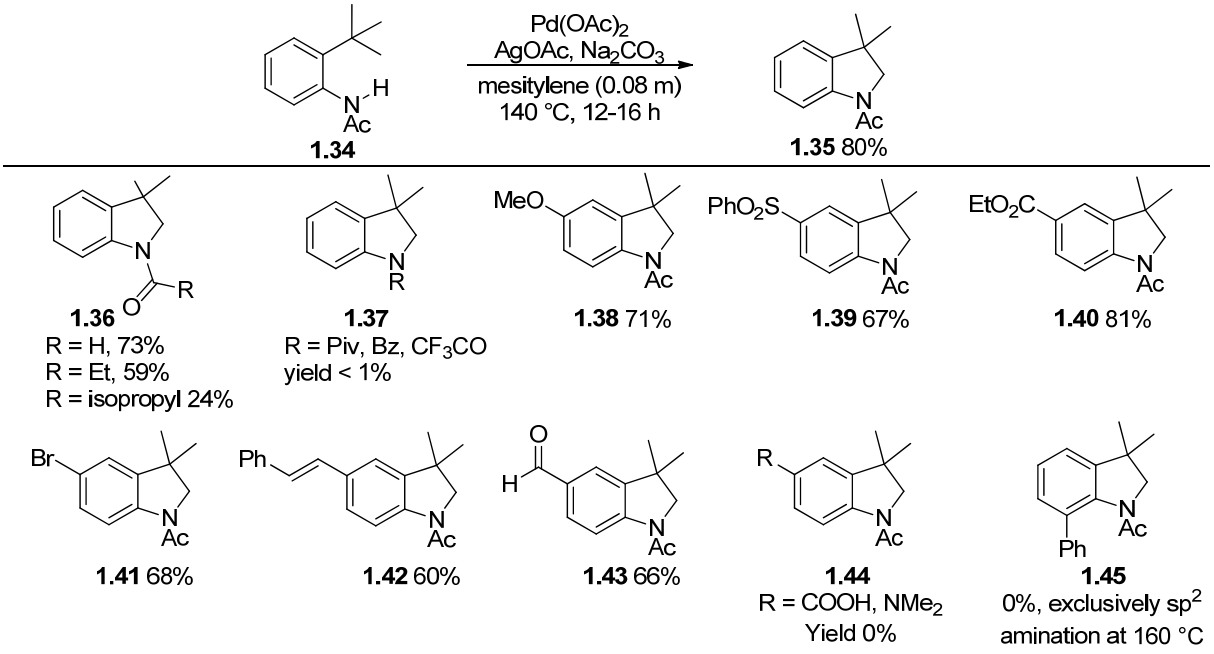
Scheme 1.4. Mechanism study of iron-catalyzed intromolecular allylic C–H amination.



The amination of an unactivated sp^3-C–H bond was reported by the Glorious group not to involve a metal nitrene intermediate.[11] After extensive screening, they identified that $Pd(OAc)_2$ could catalyzed **1.34** to **1.35** in 88% yield if AgOAc was added as an oxidant. The best results were obtained using an N-acetyl group. Reduced yields were observed when switching protection group (**1.36**) to formyl-, propioyl-, or isobutyryl group. No reaction was observed if pivaloyl, benzoyl, or trifloroacetyl groups (**1.37**) were used. The authors concluded that the success of this amination reaction depended on a delicate balance between the electronic- and steric properties of the nitrogen substituent.

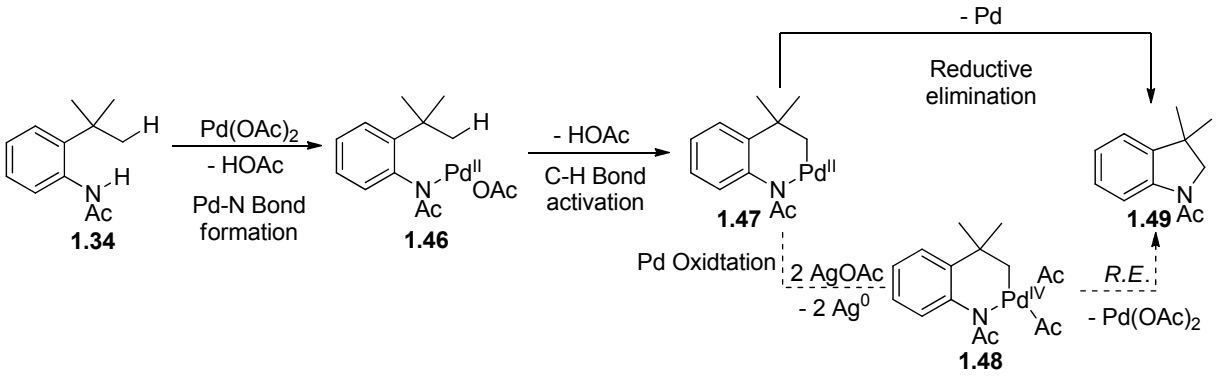
Substrate screening was performed by the Glorious group using the optimized conditions. (Scheme 1.5) They reported that their reaction could tolerate a broad range of functional groups on the arene. The reaction works well with both electron-donating and electron-withdrawing substituents including ether **1.38**, sulfones **1.39**, and ester **1.40**, as well as reactive substituents, such as bromo **1.41**, olefin **1.42**, aldehyde **1.43** groups. These latter groups provide opportunities for further functional group manipulation. Substituents that contain acidic protons or basic substituents **1.44** led to no formation of corresponding indoline. Phenyl group on *ortho*-position of acetamide results in significantly intramolecular competition reaction **1.45**: exclusive sp^2-C–H bond activation at the phenyl group was observed leading the production of carbazole.

Scheme 1.5. Palladium-catalyzed amidation of unactivated C(sp^3)–H bond.



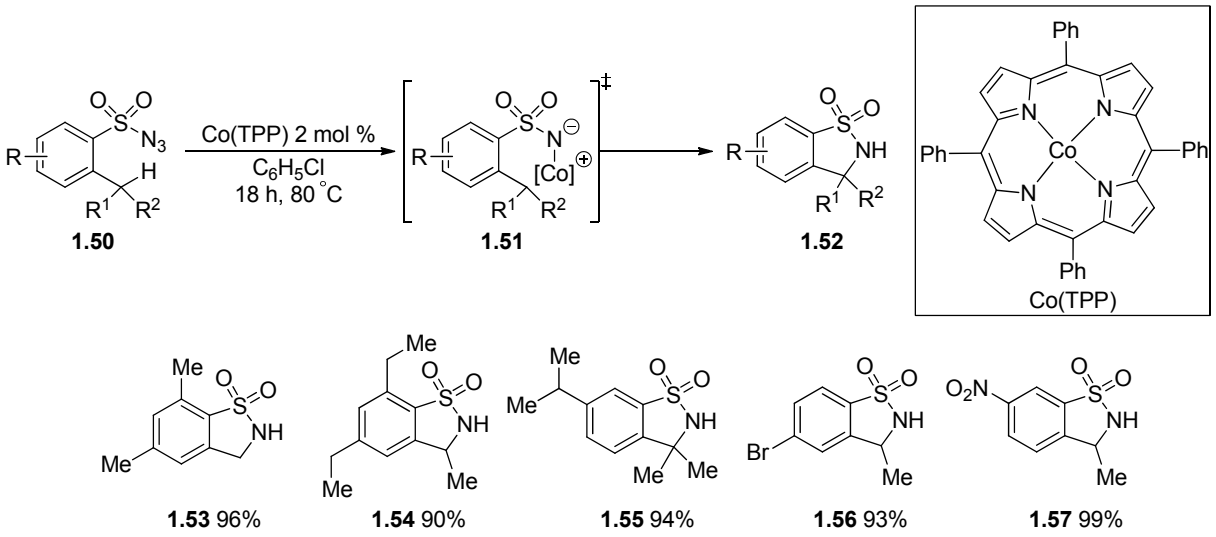
The authors proposed several possible mechanisms for the formation of *N*-(2-*tert*-butylphenyl)acetamide (Scheme 1.6). Initially, ligand substitution of one acetate with the directing group acetanilide moiety produces **1.46**. Then, activation proximal sp^3 C–H bond by palladium(II) takes place to give intermediate **1.47**. Subsequent reductive elimination of palladium(0) results in the formation of indoline product **1.49**. Palladium would be reoxidized to palladium(II) by the silver salt in the system. Alternatively, the reaction could proceed through a more highly oxidized palladium(IV) species **1.48**, which is formed from silver(I)-oxidation of **1.47** silver(I).[12]

Scheme 1.6. Mechanism palladium-catalyzed amidation of unactivated C(sp^3)–H bond.



Another transition metal widely used for C-H amination is cobalt. In 2007, the Zhang group[13] reported that commercial available cobalt(II) tetraphenylporphyrin complexes, Co(TPP), catalyzed the intramolecular amination of benzylic C–H bonds using arylsulfonyl azides as nitrogen source **1.50** (Scheme 1.7). This cobalt-catalyzed process proceeds efficiently using mild conditions: requiring low catalyst loading without the need of other reagents or additives, generating environmentally benign nitrogen gas as the only by-product. The author proposed that the process via cobalt-nitrene intermediate **1.51**.

Scheme 1.7. Colbalt(II) complex catalyze intramolecular amination using arylsulfonyl aizde as nitrogen source.



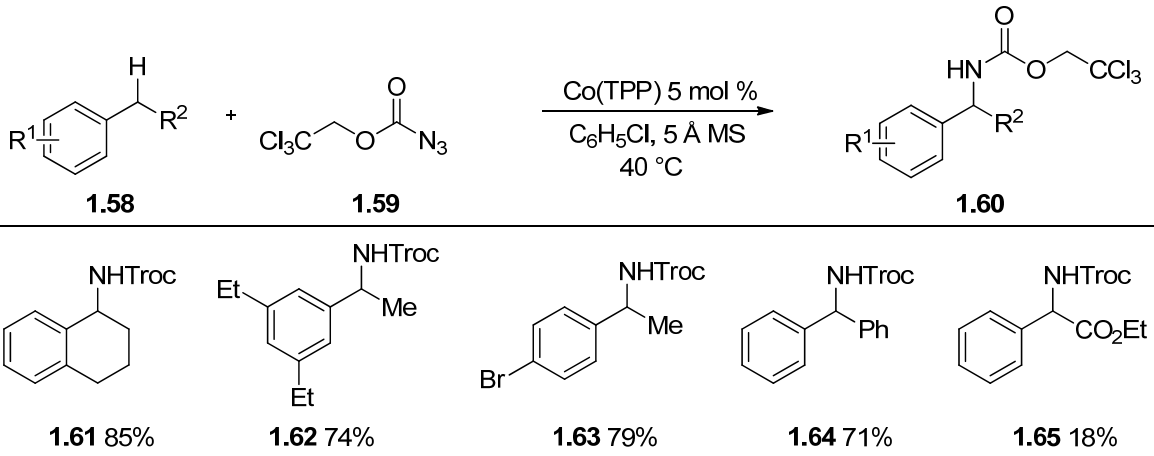
The scope of the cobalt-catalyzed benzylic C–H bond amination reaction was reported by Zhang and co-workers to be broad. Good yields were obtained with intramolecular nitrene insertion into tertiary C–H bonds (**1.55**), secondary (**1.54**), and even primary C–H bonds (**1.53**). When the reaction was conducted at a lower temperature, the reactivity pattern of the C–H bonds followed the order of 3° > 2° > 1°. The functional group tolerance of the reaction was reported to be relatively broad with substrates bearing either nitro- (**1.57**) or bromo- (**1.56**) substituents on aromatic ring formed the corresponding five-membered heterocycles in good yields.

1.3.2 Intermolecular C–H Bond Amination

In the subsequent research, the Zhang group[14] also found that cobalt tetraphenylporphyrin complex could also catalyze intermolecular C–H bond functionalization using 2,2,2-trichloroethoxycarbonyl azide **1.59** ($TrocN_3$) as the N-atom source (Scheme 1.8). The scope of the Co(TPP)/$TrocN_3$-based catalytic system toward nitrene insertion of other benzylic C–H

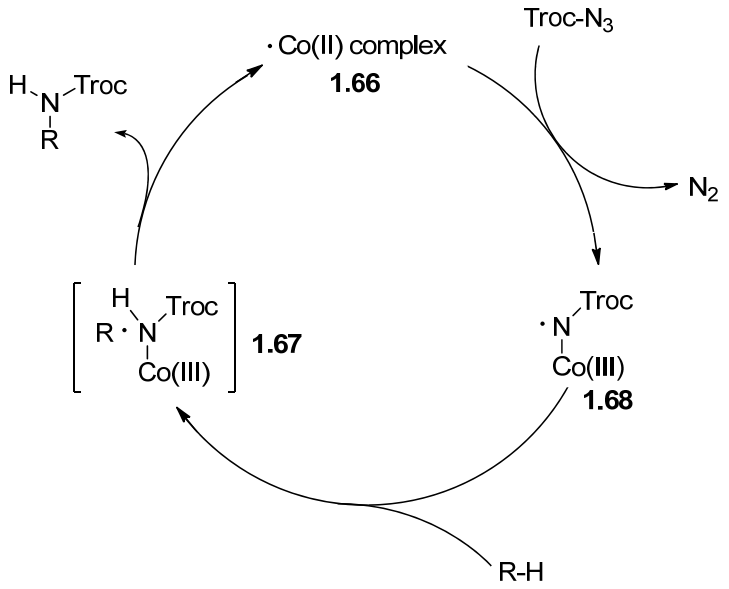
bonds was investigated using different substrates. Like the **1.61**, the benzylic C–H bonds of diethyl substituted ethyl benzene and *para*-brominated ethyl benzene could be selectively aminated to provide the corresponding amine products **1.62** and **1.63** in 74% and 79% yields, respectively. Diphenylmethane **1.64** was reported to be a good substrate for the catalytic amination with its yield 71%. Some challenging substrates such as ethyl phenylacetate **1.65** could be aminated, which provides an alternative way to synthesize α-amino acids directly from corresponding carboxylic acid, but the reaction yield was modest. It was noteworthy that the corresponding $TrocNH_2$ of $TrocN_3$ was the common side product.

Scheme 1.8. Cobalt(II) complex catalyze intermolecular amination using $TrocN_3$.



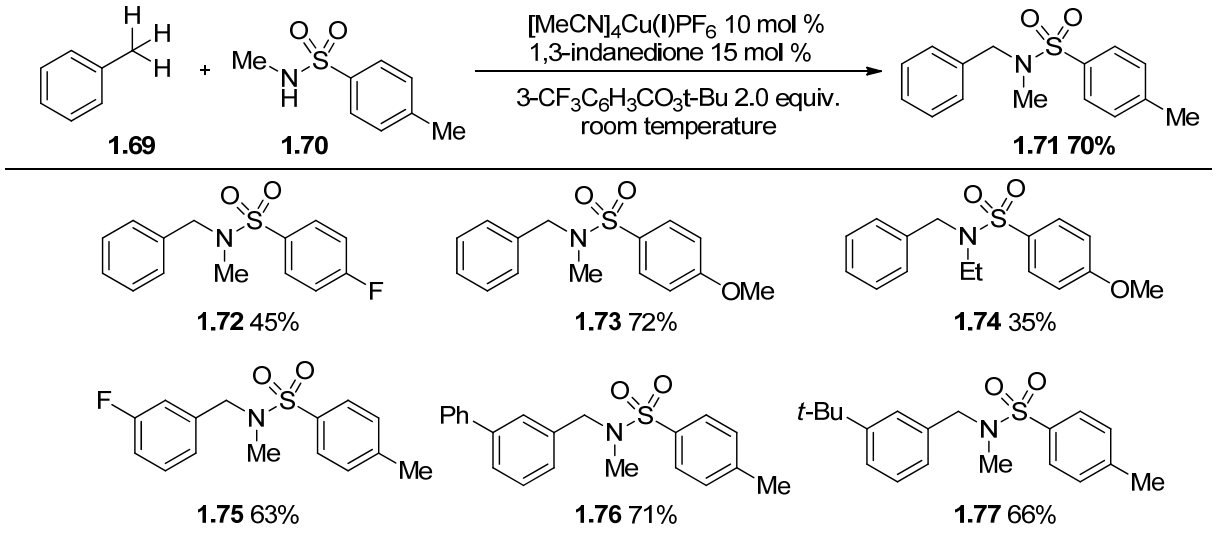
The author also proposed possible mechanism to explain the reaction (Scheme 1.9).[14] Initially, the Co(II) complex **1.66** reacts with $TrocN_3$ to generate Co(III) intermediate **1.67** with simultaneous extrusion of N_2 gas. Nitrogen-based radical of the newly formed Co(III)-N **1.67** abstracts the hydrogen from R–H to produce the complex **1.68** with a caged R• radical nearby. Radical recombination then produces the new C–N bond and release of the cobalt complex regenerates the active catalyst. Byproduct $TrocNH_2$ is produced from homolysis of weak Co-N bond in aminyl free radical **1.68**.

Scheme 1.9. Mechanism of Co(II) catalyzed intermolecular amination.



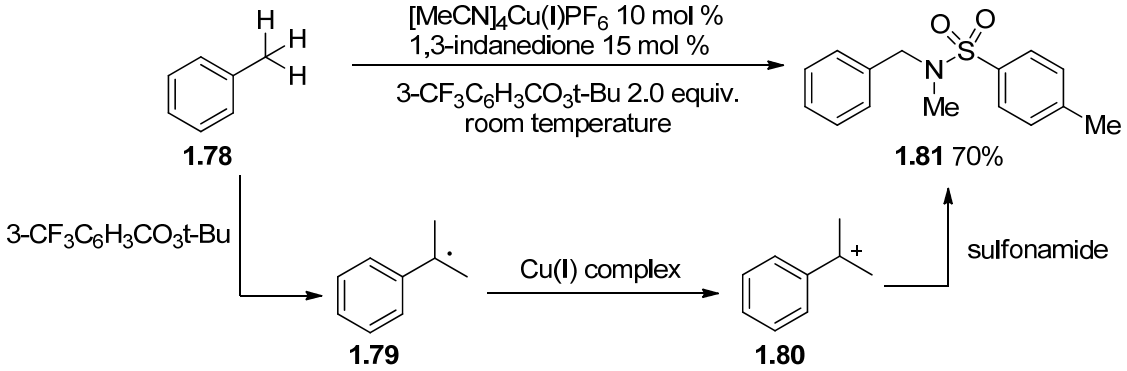
In addition to Co(II)-catalyzed benzylic C–H bond amination, promotion of this reaction by other metals has been reported as well. In 2010, Powell and Fan[15] described a room-temperature, copper-catalyzed amination of primary benzylic C−H bonds with primary and secondary sulfonamides (Scheme 1.10). The reaction is applicable to the coupling of a range of primary- or secondary benzylic hydrocarbons with a variety of sulfonamides and is tolerant of substitution on both coupling partners. Compared to electron-rich sulfonamides (**1.70, 1.73**), lower yields were obtained with aryl sulfonamides substituted with electron-withdrawing groups (**1.72**). In addition to sulfonamide nucleophilicity, steric factors influence the reaction, with the corresponding N-ethyl (**1.74**), 4-toluene sulfonamides affording lower yields in comparison to the N-methyl analogue (**1.71**). Comparable yields were obtained with a variety of primary benzylic hydrocarbon coupling partners, including those containing electron-donating (**1.76**) or modestly electron-withdrawing substituents (**1.75**).

Scheme 1.10. Intermolecular amination of benzylic C–H bond with sulfonamide.



In contrast to the aforementioned metal-nitrene-based amidation reactions, the authors proposed a mechanism on the basis of the established Kharasch-Sosnovsky reaction that involves initial formation of a benzylic radical[16] **1.79** (Scheme 1.11) generated from oxidation of toluene. Formation of a C–N bond may then proceed via a transient carbocation **1.80** which was formed by oxidation of **1.79** with a Cu(I) complex. The author mentioned that further investigation is required to confirm the assumed mechanism.

Scheme 1.11. Mechanism of Cu(I) catalyzed intermolecular amidation.

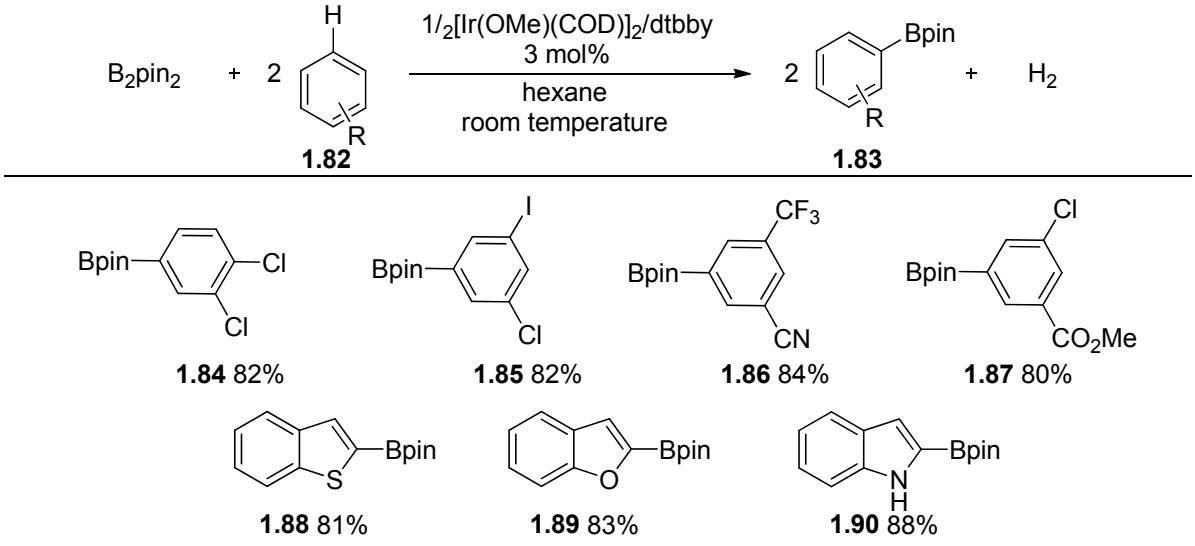


1.4 Iridium Catalysts Promote C–H Bond Functionalization

1.4.1 Iridium Complexes Catalyzed C–H Bond Borylation

Iridium complexes are also widely used for aromatic C–H bond activation processes. Harwig and co-workers[17, 18] developed iridium-catalyzed C–H bond borylation (Scheme 1.12). After examination of a range of iridium precursors and ligands, they identified the combination of $[Ir(COD)(OMe)]_2$ and dtbby (4,4'-di-*tert*-butyl-2,2'-bipyridine) as the ideal system and rationalized that the better yields were achieved using $[Ir(COD)(OMe)]_2$ instead of $[Ir(COD)Cl]_2$, because the more electron-rich iridium complex facilitated the oxidative addition of aromatic C–H bond. They also proposed that the use of dtbby increased the solubility of the catalyst and prevented the borylation of the ligand's C–H bonds. Using this optimal catalyst system, they found the process could be performed with a 1:1 ratio of boron to arene at room temperature.

Scheme 1.12. Iridium-catalyzed aromatic C–H bond borylation.

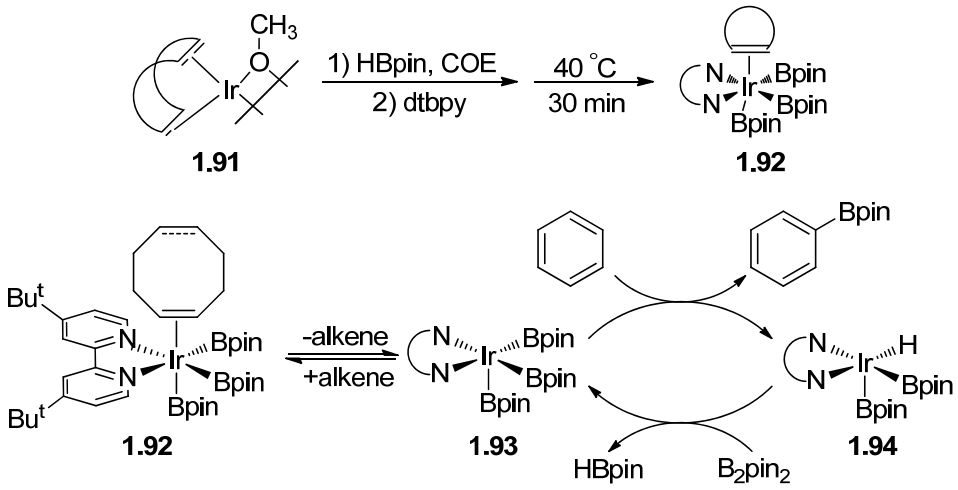


With the optimal catalyst system, the authors reported that the regioselectivity of aromatic C–H bond borylation was controlled by steric effects. Reactions of symmetrically substituted 1,2- (**1.84**) and 1,3-substituted (**1.85**) arenes formed a single product, since a single

C–H bond is more sterically accessible than the others. The authors also found that their iridium catalyst preferred borylation of an aromatic C–H bond instead of oxidative addition of carbon-halogen bond. The reaction also tolerated typical organic functional group like nitriles (**1.86**) and esters (**1.87**). In contrast to the site-selectivity for the borylation of arenes, the regioselectivity for the borylation of heteroarenes is largely controlled by electronic effects[18,19,20], Furans **1.89**, pyrroles **1.90**, and thiophenes **1.88** undergo reaction at the C–H bond alpha to the heteroatom.

Studies of the mechanism of the Ir-catalyzed borylation reaction revealed insight into the identity of several catalytic intermediates (Scheme 1.13).[21, 22] The alkene adduct Ir(dtbpy)(Bpin)$_3$(COE) **1.92** was isolated from the stoichiometric reaction was found to be an active catalyst. This complex was prepared in high yield by the reaction of [Ir(COD)(OMe)]$_2$ **1.91** with HBpin and an excess of cyclooctene, followed by the addition of di-tert-butyl-bipyridine and slight warming. To accommodate the activity of **1.92**, the authors propose that the catalyst cycle for C–H bond borylation starts from dissociation of alkene from iridium alkene complex to form 16 electron iridium complex **1.93**, which reacts with arene by oxidative addition or sigma bond metathesis to produce arylboronate ester and an iridium hydride product **1.94**. The iridium hydride product then reacts with B_2pin_2 to form HBpin and regenerate the trisboryl complex.

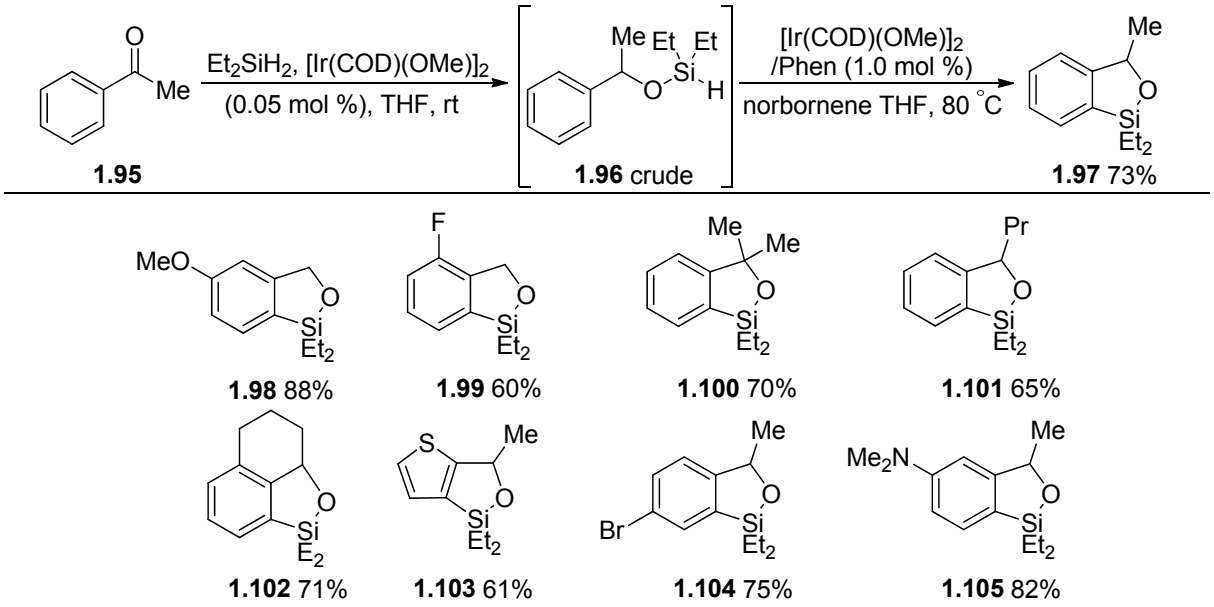
Scheme 1.13. Iridium catalyzed aromatic C–H bond borylation.



1.4.2 Iridium Complexes Catalyzed Aromatic C–H Bond Silylation

In addition to aromatic C–H bond activation, iridium-catalyzed arene *ortho*-silylation by formal hydroxyl-directed C−H activation (Scheme 1.14) was also reported by Hartwig group.[23] They reported that ketones **1.95** could be easily transformed in two steps into benzoxasiloles **1.97**. Initially, formation of a (hydrido)silyl ether **1.96** from the reaction of the carbonyl compound or alcohol catalyzed by $[Ir(COD)(OMe)]_2$. Then, subsequent dehydrogenative cyclization at 80 − 100 °C in the presence of norbornene as a hydrogen acceptor and the combination of 1 mol % $[Ir(COD)(OMe)]_2$ and 1,10-phenanthroline as a catalyst to form benzoxasiloles.

Scheme 1.14. Iridium catalyzed aromatic C–H bond silylation.

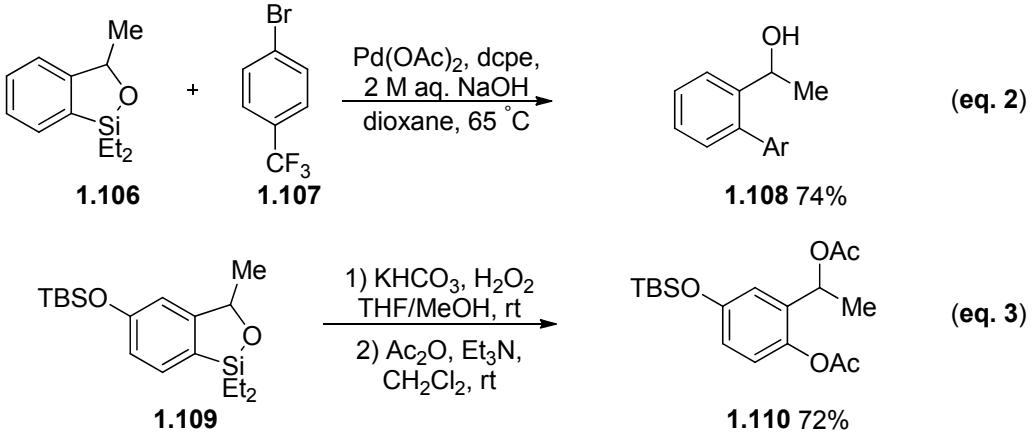


The scope of the silylation reaction was investigated by Hartwig and co-workers. Similarly to the borylation reaction, the authors found that the regioselectivity of this reaction was controlled by steric interactions. The presence of a substituent at the *meta*-position of the aryl ring leads to reaction at the 6-position of **1.98**. The silylation could occur with benzylic silyl ethers derived from secondary alcohols **1.101** or tertiary alcohols **1.100**. It even occurs to generate tricyclic benzoxasiloles **1.102** and its heteroaromatic analogue **1.103**. In addition, substrates bearing bromo- **1.104**, and dialkylamino **1.105** groups underwent cyclization in good yields.

The synthetic utility of resulting benzoxasilole product was investigated by the Hartwig group. They demonstrated that aryl-aryl bond **1.108** could be obtained from Aryl-Si bond via Hiyama type coupling[24] of the benzoxasiloles **1.106** with aryl halides **1.107** (eq 2). Tamao-Fleming oxidation[25] was also developed to transform Aryl-Si linkage in to Aryl-O bond **1.110** by

treatment of benzoxasiloles **1.109** with H_2O_2 and $KHCO_3$ in THF/MeOH at room temperature (eq 3).

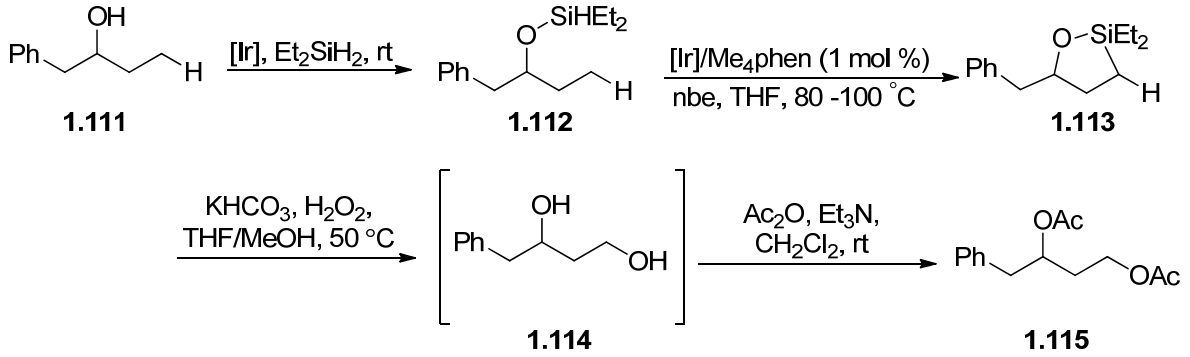
Scheme 1.15. Synthetic utility of resulting benzoxasilole product.



1.4.3 Iridium Complexes Catalyzed Aliphatic C–H Bond Silylation

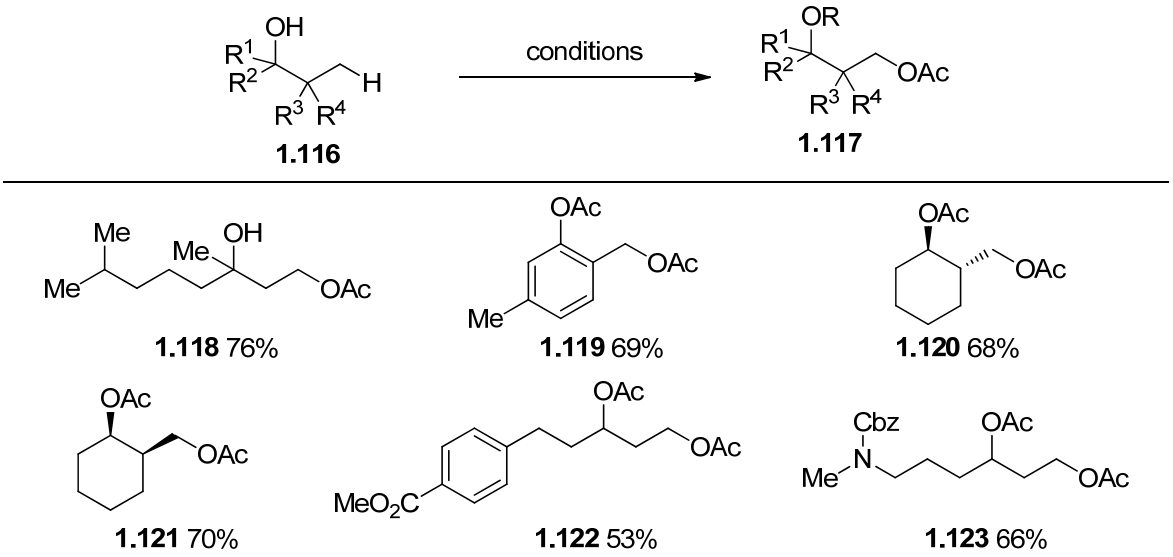
In contrast to aromatic C–H bond activation, instances of aliphatic C–H bond functionalization catalyzed by iridium complexes are rare. Recently, Simmons and Hartwig reported that aliphatic hydroxyl groups direct a highly selective iridium-catalyzed sp^3 C–H bond functionalization reaction (Scheme 1.16). Starting from their aromatic C–H bond silylation, the Hartwig group[26] found if 3,4,7,8-tetramethyl-1,10-phenanthroline[27] was used in place of 4,4'-di-*tert*-butylpyridine the silylation of aliphatic C–H bonds could be achieved.[28] In this procedure, a single dihydridosilane Et_2SiH_2 not only attaches to the oxygen atom to direct the C–H bond functionalization but also provide the second hydride for resulting (dihydrido)silyl ether to conduct dehydrogenative functionalization of a primary C–H bond without isolation of the intermediate (hydrido)silyl ether. Following the iridium-catalyzed aliphatic C–H bond silylation, the diol **1.114** was unmasked by treating **1.114** with MeOH, $KHCO_3$ and aqueous H_2O_2. For purification purposes, the diol was acylated.

Scheme 1.16. Iridium complex catalyzed aliphatic C–H bond silylation.



The scope of the aliphatic silylation reaction was investigated (Scheme 1.17). The authors reported that both tertiary **1.118** and secondary **1.120** acyclic alcohols underwent silylation in good yield. Silylation occurred with phenols **1.119** and cyclic aliphatic alcohols **1.120** in moderate yield. The reaction was reported to be insensitive to the stereochemistry of the ring fusion in the bicyclic oxasilolane intermediate: trans- **1.120** and cis-2-methylcyclohexanol **1.121** underwent this process in similar yields. A variety of functional groups like ester **1.122** and Cbz-protected amine **1.123** were also tolerated in the process.

Scheme 1.17. Scope of aliphatic C–H bond silylation catalyzed by iridium complexes.

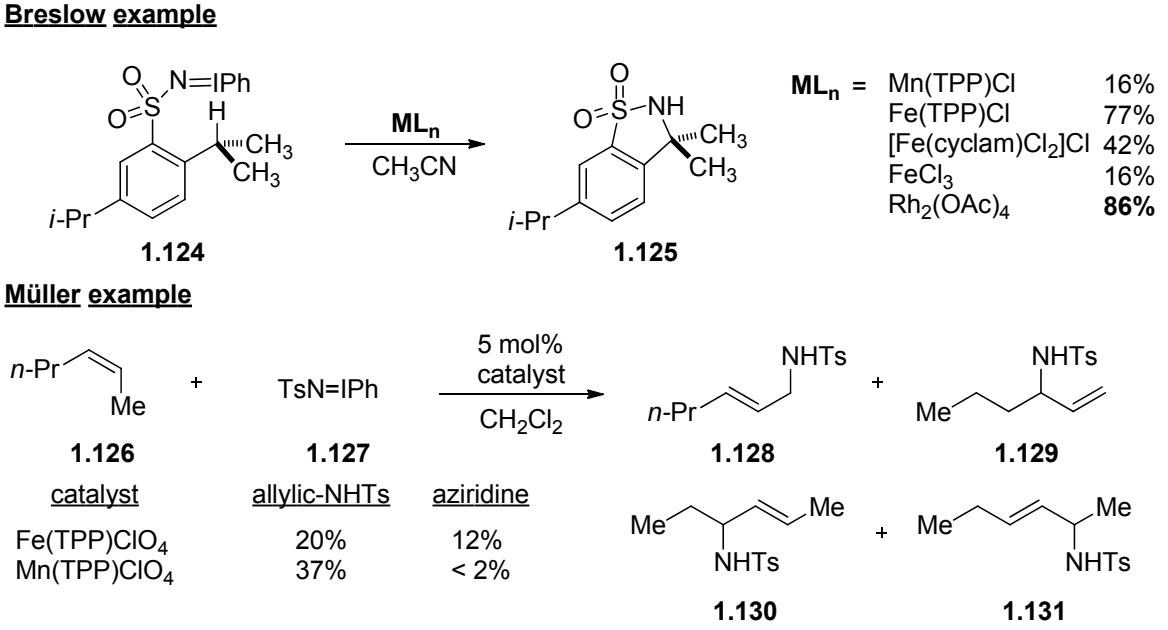


1.5 Rhodium(II) Carboxylate Catalyzed C–H Bond Amination

1.5.1 Seminal Study of Rhodium(II) Carboxylate Catalyzed C–H Bond Amination

Dirhodium(II) carboxylate species are widely used metal catalysts for C–H bond amination. These complexes were originally noted by Breslow,[4] and later developed by Müller,[29] to promote C–H amination using hypervalent iminoiodinanes as nitrenoid precursors. (Scheme 1.18) However, the preparation of iminoiodinanes has been limited to a small subset of sulfonamide derivatives, thus restricting the synthetic utility of this technology.

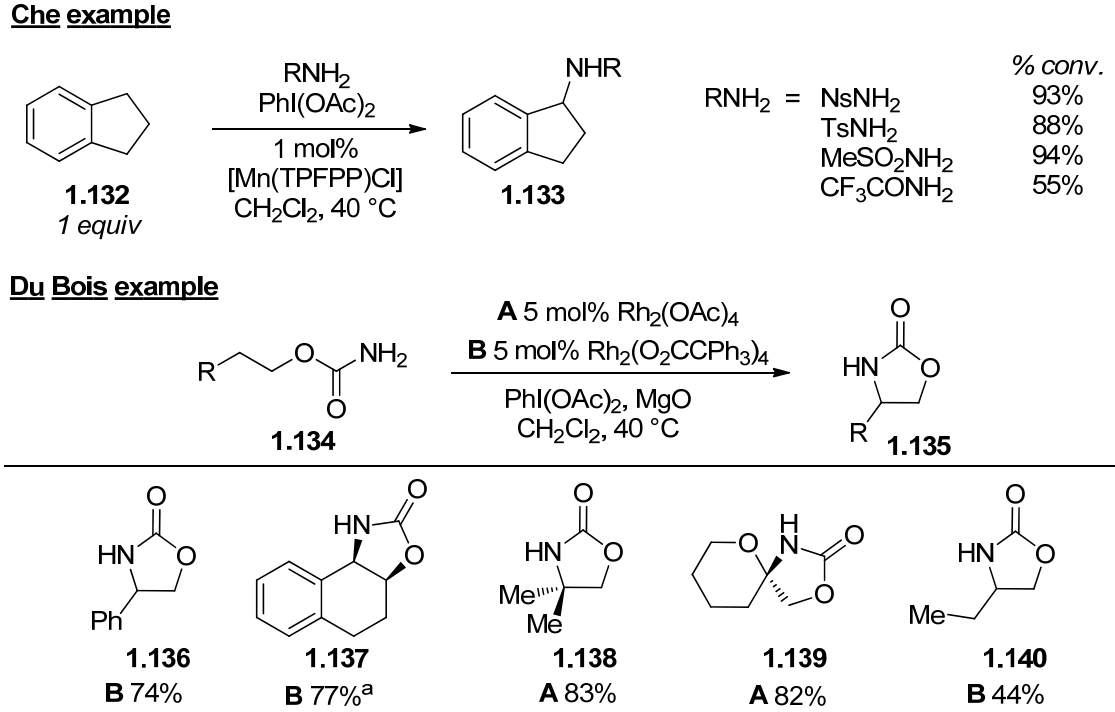
Scheme 1.18. Original study of C–H amination via iminoiodinanes.



1.5.2 Rhodium(II) Carboxylate Catalyzed Formation of Carbamate and Sulfamate

Che and co-workers first reported that the iminoiodinane species could be prepared directly with commercial available $PhI(OAc)_2$ and NH_2R (R = Ts, Ns, SO_2Me, Scheme 1.19).[30] Shortly thereafter, Du Bois and co-workers reported that this *in situ* preparation of iminoiodinanes could be used in Rh_2(II)-catalyzed C–H bond amination for the oxidative conversion of carbamates **1.134** to oxazolidinones **1.135**. Intramolecular amination at the β-carbon is preferred with carbamates.[31] Rhodium(II) tetracetate can be used as the catalyst with certain substrate; in some cases, however, the readily prepared triphenylacetate (tpa) complex $[Rh_2(tpa)_4]$, with greater resistance towards oxidation, is a more effective promoter at a 5 mol% loading. Good yields were reported for benzylic (**1.136**, **1.137**), tertiary (**1.138**) and ethereal C–H (**1.139**) bond.

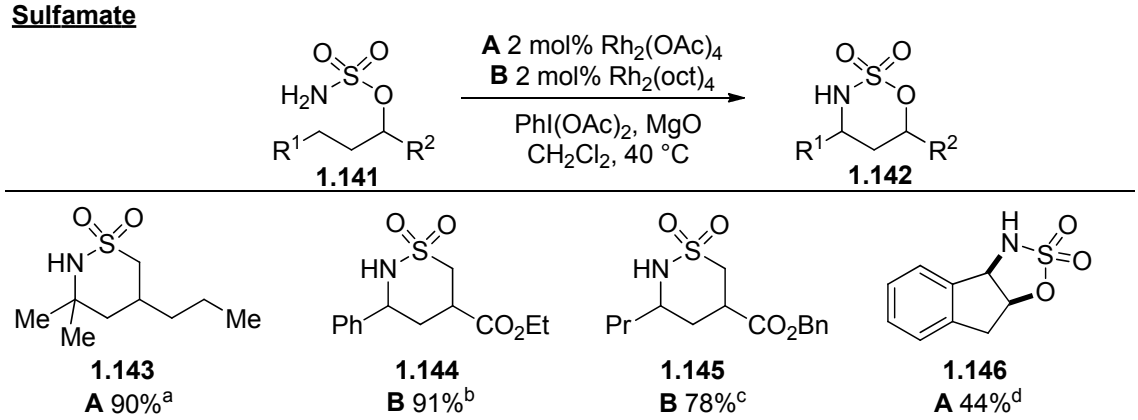
Scheme 1.19. C–H amination via in situ generation of iminoiodinanes.



[a] Exclusive product as determined by 1H NMR spectroscopy of the unpurified reaction mixture; *cis* stereochemistry assigned based on 1H coupling constants.

Further explorations of Rh(II) carboxylate catalyzed amination from primary carbamate in Du Bois group have led to amination using sulfamate esters **1.141**.[32] (Scheme 1.20) This uniquely reactive class of compounds affords six-membered ring insertion products **1.142** through exclusive γ-C–H bond amination.[33] Such findings contrast distinctly the reactions of carbamates, which the authors ascribe to the elongated S–O and S–N bonds (1.58 Å) and the more obtuse N–S–O angle (103°) of the sulfamate. Together these attributes more closely match the metrical parameters of the heterocyclic product.[34] If the γ-position is blocked, the five-membered sulfamidate **1.146** was obtained. The authors reported good yields for sulfamates bearing tertiary **1.143** and benzylic C–H center **1.144**. In comparison to carbamate formation, better yields were reported with sulfamate **1.145**, although tertiary C–H bonds react in preference to secondary C–H bond **1.143**.

Scheme 1.20. Rhodium catalyzed C–H amination with sulfamate as nitrogen source.



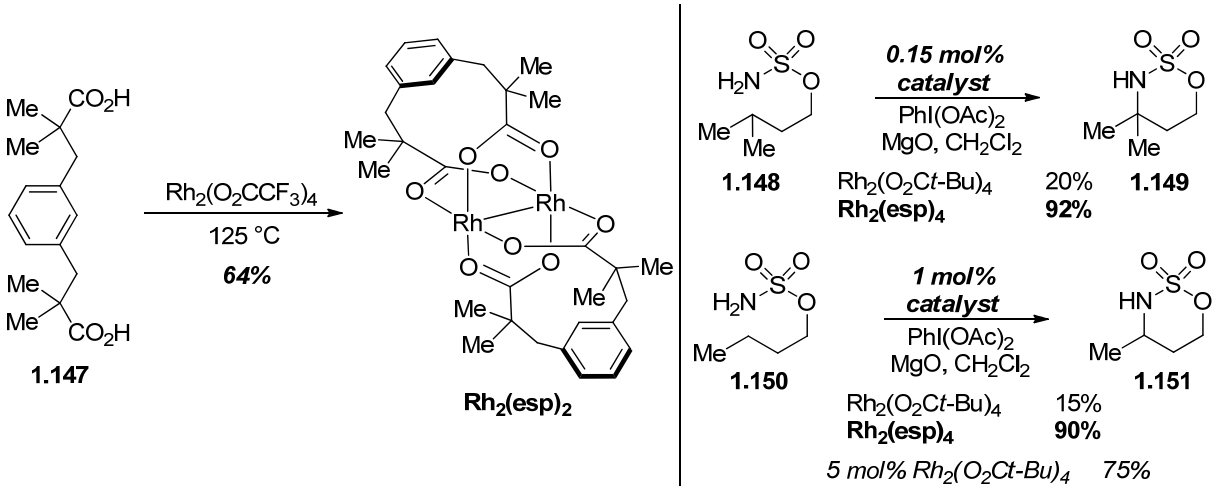
[a] Exclusive product as determined by 1H NMR spectroscopy of the unpurified reaction mixture. [b] 13:1 syn/anti by ^{1}H NMR. [c] 4:1 syn/anti by ^{1}H NMR. [d] Product isolated by crystallization; conversion is >97% from 1H NMR of the unpurified reaction mixture

1.5.3 Efficient and Versatile $Rh_2(esp)_2$ Catalysts

To enhance the versatility and efficiency of Rh(II) catalyzed C–H amination, a novel Rh(II) carboxylate catalyst was designed and synthesized by Du Bois group.[35] The authors built on results reported by Taber[36] and Davies[37] for Rh-meditated diazodecomposition reactions using tetradentate-ligated Rh(II) complexes because they hypothesized that carboxylate detachment from the dinuclear Rh core accounts for the degradation of catalyst.[38] Consequently, connection of two carboxylate ligands through an appropriate linker would provide additional stability to the metal complexes. The chelate effect would prevent complete ligand dissociation from the rhodium center. $Rh_2(esp)_2$ can be readily prepared by substitution of tetramethylated *m*-benzenedipropionic acid **1.147** with the trifluoroacetate ligands present on $Rh_2(O_2CCF_3)_4$ (Scheme 1.21). This catalyst has proven to be an exceptionally effective and universal catalyst for C–H bond amination. For example, quantitative conversion of **1.149** was reported by Du Bois and co-workers when **1.148** was treated with 0.15 mol % of $Rh_2(esp)_2$. In contrast, reaction **1.150** with $Rh_2(O_2C$*t*-Bu$)_4$ afforded a complex mixture of products that contained only 20% of

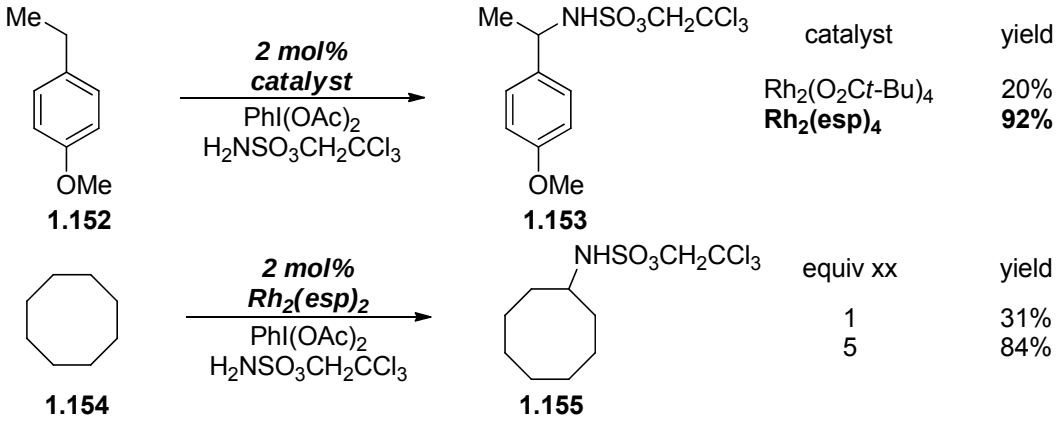
oxathiazinane **1.151**. In general, lower catalyst loading of $Rh_2(esp)_2$ is sufficient to catalyzed unactive C–H bond amination: only 1 mol % of $Rh_2(esp)_2$ is required for formation of **1.151** whereas 5 mol% of $Rh_2(O_2Ct\text{-}Bu)_4$ was necessary to provide the oxathiazinane.

Scheme 1.21. Systhesis of $Rh_2(esp)_2$ and application in C–H amination



Du Bois and co-workers also disclosed that $Rh_2(esp)_2$ can promote intermolecular C–H bond amination.(Scheme 1.22) They reported that exposure of **1.152**, which has been proven to be robust to Mn, Fe, Ru, Rh and Cu complexes,[38,39] to 2 mol % of $Rh_2(esp)_2$ generated benzyl amine **1.153**. Similar findings were reported for C–H bond amination of cyclooctane **1.154**. These results are in contrast to the intermolecular experiments performed with 2 mol % $Rh_2(O_2Ct\text{-}Bu)_4$, which provides a 20% yield only when 5 equiv of cyclooctane **1.154** was employed.

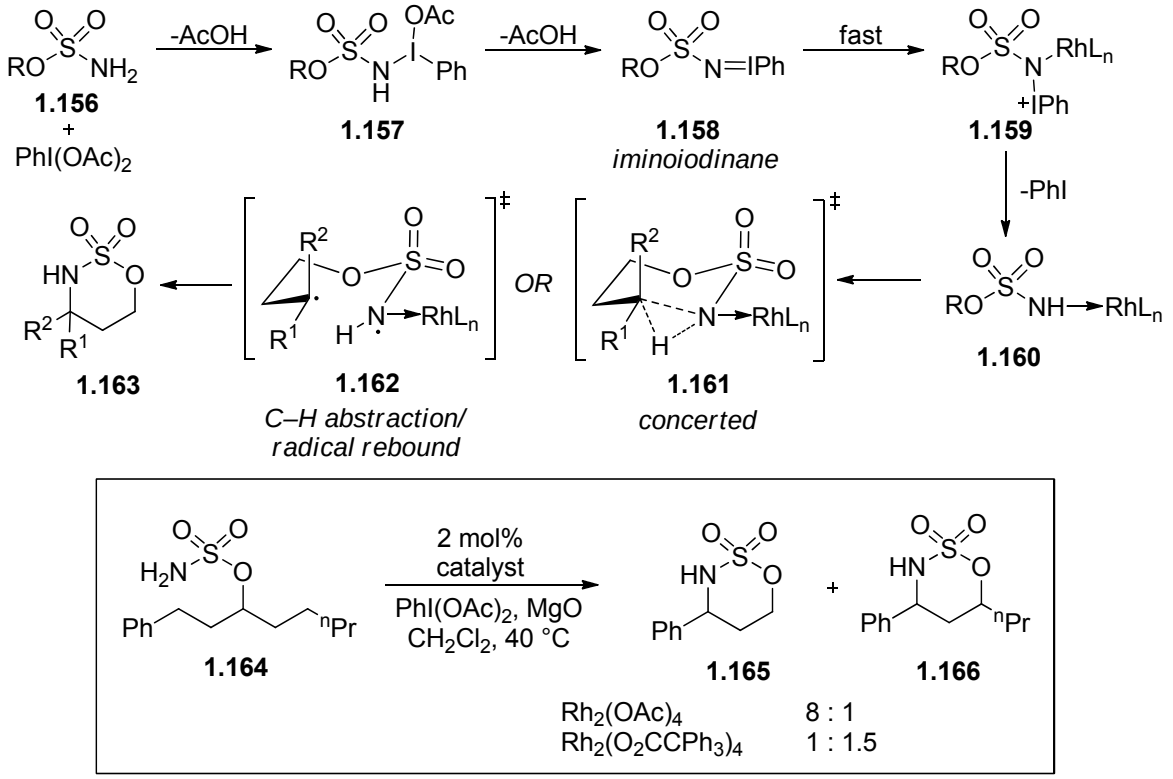
Scheme 1.22. $Rh_2(esp)_2$ catalyzed intermolecular C–H amination.



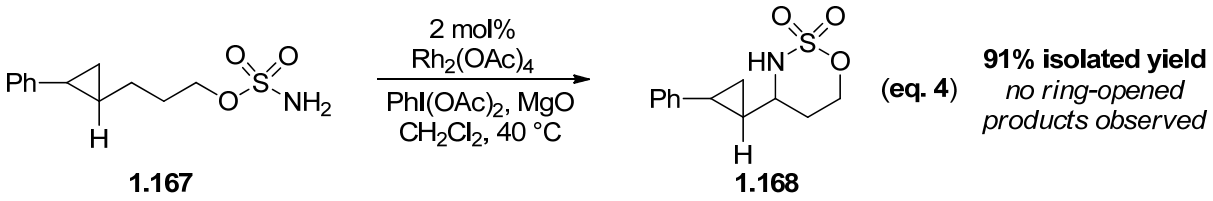
1.5.4 Mechanism Study of Rh(II) Carboxylate Catalyzed C–H Bond Amination

The authors reported a possible mechanism to explain the C–H amination process (Scheme 1.23).[40] Reaction of sulfamate with $PhI(OAc)_2$ gives iminoiodinane **1.158**, which reacts with Rh(II)-carboxylate to yield rhodium nitrenoid **1.160**. Subsequent C–N bond formation could occur by two different pathways: a concerted insertion of the singlet nitrenoid **1.161** or hydrogen-atom abstraction with triplet nitrenoid **1.162** followed by radical recombination. Since treating same substrate with difference rhodium catalysts resulted in different products, Du Bois and co-workers suggested that the active oxidant is rhodium-bounded nitrenoid **1.160**. To account for why C–H amination at benzylic position **1.164** is disfavored in the reactions promoted by $Rh_2(O_2CCPh_3)_4$, the authors hypothesized that the remote steric effects between the substrate and catalyst framework dictates the chemoselectivity of the reaction.

Scheme 1.23. Mechanism of rhodium-catalyzed C–H amination.



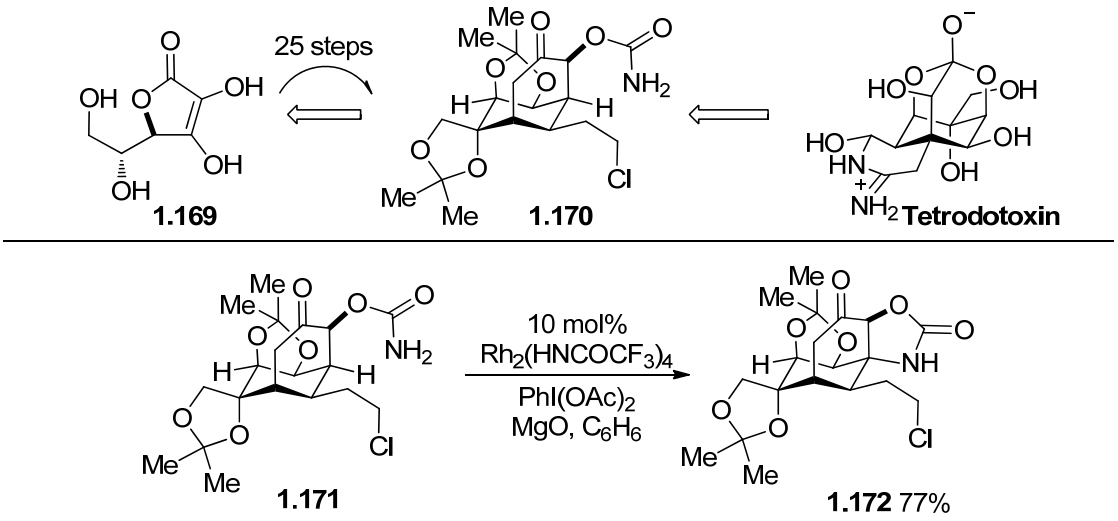
Phenyl-substituted cyclopropane **1.167** was prepared to provide insight into the identity of the reactive intermediates in the C–H bond amination step of the catalytic cycle (Scheme 1.24).[41] The authors reported that exposure of **1.167** to reaction conditions produced the amination product **1.168** in nearly quantitative yield. The absence of cyclopropane ring-opening and olefin-containing products,[42] expected from cyclopropane fragmentation provides evidence for a concerted C–H insertion pathway. Although it is possible to employ radical clocks that fragment/rearrange at faster rates, Du Bois and co-workers concluded that this radical clock data together with the Hammett ρ-value and KIE strongly suggest that Rh(II)-catalyzed C–H bond amination occurs through a concerted insertion pathway.



1.6 Application of Aliphatic C–H Bond Amination

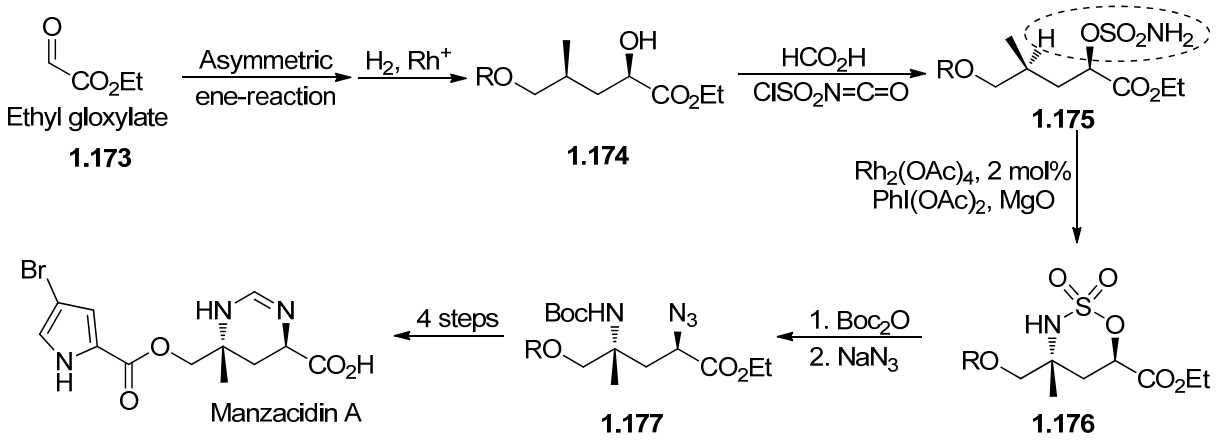
Nitrogen-containing heterocycles are ubiquitous motifs of biologically active compounds and nature product. In the previous sections, several methodologies that form the C–N bond directly from a C–H bond were presented. To conclude this introductorily chapter, two examples of the use of C–H bond amination reactions to streamline the synthesis of natural products are discussed. First, Du Bois and co-workers demonstrated the synthetic utility of their Rh(II)-amination technology in the synthesis of tetrodotoxin (TTX), the guanidium poison synonymous with Japanses *fugu*. Its complex structure consists of a densely oxygenated cyclohexane framework and bearing unique ortho-acid and guanidine aminal functionalities (Scheme 1.25).[43] The application of selective C–H bond amination employing carbamate **1.171** occurs at step 25 in the synthetic sequence with a good yield of 77%. Notably, the insertion is exclusive for the bridgehead tertiary C–H bond and clearly tolerates several reactive functionality.

Scheme 1.24. Synthesis of tetrodotoxin.



Another illustrative example (Scheme 1.26) was reported by Du Bois and co-workers in their enantioselective synthesis of manzacidin A and C.[44] This bromopyrrole alkaloid was isolated as bioactive constituents of the Okinawan sponge, which possess potentially useful pharmacological activities as serotonin antagonists and actomyosin ATPase activators. The key optically pure intermediate **1.175** was prepared by sulfamoylation of the alcohol **1.174**, obtained by application of an asymmetric ene reaction from ethyl glyoxylate followed by a diastereoselective alkene hydrogenation. C–H bond amination proceeded smoothly and stereospecifically with 2 mol % of $Rh_2(OAc)_4$ and 1.1 equiv of $PhI(OAc)_2$ to generate the crystalline oxathiazinane product **1.176** in 85% yield with retention of configuration. The heterocycle **1.176** can be activated for facile nucleophilic ring opening to give 1,3-difunctionalized amine product **1.177**. Manzacidin A was obtained after four additional steps.

Scheme 1.25. Synthesis of manzacidin A.



1.7 Conclusion

We have described a variety of transition metal-catalyzed C–H bond functionalization reactions. Among those methods, C–H bond amination reactions are significantly important, since *N*-heterocycles are ubiquitous in biologically active nature occurring products, pharmaceuticals and materials. We have found that, by using azides to transfer N-atoms, we can avoid adding additives and generate environmentally benign byproduct without pre-activated C–H bond. In the following chapters, we show that aliphatic azides can be activated by transition metals and decomposed intramolecularly under mild conditions, to afford indoline. Additionaly, we also demonstrated that Rhodium carboxylate could promote 2,3-Disubstituted Indoles formation from β, β-Disubstituted Stryryl Azides.

1.8 Reference

1 Shimada, S. Batsanov, A. S. Howard, J. K. Marder, T. B. "Formation of aryl- and benzylboronate sster by rhodium-catalyzed C–H bond functionalization with pinacolborane" *Angew. Chem*. **2001**, *113*, Nr. 11

2 (a) Chen, H. Y. Schlecht, S. Semple, T. C. Hartwig, J. F. "Thermal, catalytic, regiospecific functionalization of alkanes" *Science*. **2000**, *287*, 1995 (b) Cho, J. Iverson, C. N Smith III, M. R. "Steric and chelate directing effects in aromatic borylation" *J. Am. Chem. Soc*. **2000**, *122*, 12868

3 Kakiuchi, F. Tsuchiya, K. Matsumoto, M. Mizushima, E. Chatani, N. "$Ru_3(CO)_3$-catalyzed silylation of benzylic C–H bonds in arylpyridines and arylpyrazoles with hyrdrogsilanes via C–H bond cleavage" *J. Am. Chem. Soc*. **2004**, *126*, 12792

4 Breslow, R. Gellman, S. H. "Intramolecular nitrene carbon-hydrogen insertions mediated by transition-metal complexes as nitrogen analogs of cytochrome P-450 reactions." *J. Am. Chem. Soc*. **1983**, *105*, 6728. (b) Breslow, R. Gellman, S. H. "Tosylamidation of cyclohexane by a cytochrome P-450 model." *J. Chem. Soc.,Chem.Comm*. **1982**, 1400.

5 Enthaler, S. Junge, K. Beller, M. "Sustainable metal catalysis with iron: from rust to a rising star?"*Angew. Chem., Int. Ed*. **2008**, *47*, 3317.

6: (a) Suzuki, K. Oldenberg, P. D. Que, L. Jr. "Iron-catalyzed asymmetric olefin cis-dihydroxylation with 97 % enantiomeric excess." *Angew. Chem., Int. Ed*. **2008**, *47*, 1887. (b) Legros, J. Bolm, C. "Iron-catalyzed asymmetric sulfide oxidation with aqueous hydrogen peroxide." *Angew. Chem., Int. Ed*. **2003**, *42*, 5487. (c) White, M. C. Doyle, A. G. Jacobsen, E. N. "A synthetically useful, self-assembling MMO mimic system for catalytic alkene epoxidation with aqueous H_2O_2."*J. Am. Chem. Soc*. **2001**, *123*, 7194.

7 (a) Sapountzis, I. Lin, W. Kofink, C. C. Despotopoulou, C. Knochel, P. "Iron-catalyzed aryl–aryl cross-couplings with magnesium-derived copper reagents."*Angew. Chem., Int. Ed*. **2005**, *44*, 1654. (b) Nakamura, M. Matsuo, K. Ito, S. Nakamura, E. "Iron-catalyzed cross-coupling of primary and secondary alkyl halides with aryl grignard reagents." *J. Am. Chem. Soc*. **2004**, *126*, 3686. (c) Enthaler, S. Erre, G. Tse, M. K. Junge, K. Beller, M. "Biomimetic transfer hydrogenation of ketones with iron porphyrin catalysts." *Tetrahedron Lett*. **2006**, *47*, 8095.

8 (a) Barton, D. H. R. Hay-Motherwell, R. S. Motherwell, W. B. "Functionalisation of saturated hydrocarbons. Part 1. Some reactions of a ferrous chloride–chloramine-T complex with hydrocarbons." *J. Chem. Soc., Perkin Trans*. **1983**, 445. (b) King, E. R. Hennessy, E. T. Betley, T. A. "Catalytic C−H bond amination from high-spin Iron imido complexes." *J. Am. Chem. Soc*. **2011**, *133*, 4917. For stoichiometric ligand C−H amination, see: (d) King, E. R. Betley, T. A. "C−H bond amination from a ferrous dipyrromethene complex." *Inorg. Chem*. **2009**, *48*, 2361. For catalytic C−H amination, see: (e) Wang, Z. Zhang, Y. Fu, H. Jiang, Y. Zhao, Y. "Efficient intermolecular iron-catalyzed amidation of C−H bonds in the presence of N-bromosuccinimide." *Org. Lett*. **2008**, *10*, 1863.

9 Paradine, S. M. White, M. C. "Iron-catalyzed intramolecular allylic C–H amination." *J. Am. Chem. Soc*. **2012**, *134*, 2036.

10 (a) Harvey, M. E. Musaev, D. G. Du Bois, J. "A diruthenium catalyst for selective, intramolecular allylic C–H amination: reaction development and mechanistic insight gained through experiment and theory." *J. Am. Chem. Soc*. **2011**, *133*, 17207.

11 Glorius, F. Dröge, T. Rakshit, S. Neumann, J. J. "Palladium-catalyzed amidation of unactivated $C(sp^3)$ –bonds: from anilines to indolines." *Angew. Chem. Int. Ed*. **2009**, *48*, 6892.

12 (a) Tsou, T. T. Kochi, J. K. "Mechanism of biaryl synthesis with nickel complexes." *J. Am. Chem. Soc*. **1979,** *101*, 7547. (b) Canty, A. J. "Development of organopalladium(IV) chemistry: fundamental aspects and systems for studies of mechanism in organometallic chemistry and catalysis." *Acc. Chem. Res*. **1992**, *25*, 83.

13 Ruppel, J. V. Kamble, R. M. Zhang, X. P. "Colbalt-catalyzed intramolecular C–H amination with arylsulfonyl azides." Org. Lett. **2007**, *9*, 4889

14 Lu, H. Subbarayan, V. Tao, J. Zhang, X. P. "Cobalt(II)-catalyzed intermolecular benzylic C–H bond amination with 2,2,2-trichloroethoxycarbonyl azide($TrocN_3$)." *Organometallic*, **2010**, *29*, 389.

15 Vadola, P. A. Carrera, I. Sames, D. "C−H bond functionalization via hydride transfer: formation of α-arylated piperidines and 1,2,3,4-tetrahydroisoquinolines via stereoselective intramolecular amination of benzylic C−H bonds." *J. Org, Chem*. **2012**, *77*, 6689.

16 (a) Eames, J. Watkinson, M. "Catalytic allylic oxidation of alkenes using an asymmetric Kharasch–Sosnovsky reaction." *Angew. Chem. Int. Ed.* **2001**, *40*, 3567. (b) Borduas, N. Powell, D. A. "Copper-catalyzed oxidative coupling of benzylic C−H bonds with 1,3-dicarbonyl compounds." *J. Org. Chem*. **2008**, *73*, 7822.

17 Ishiyama, T. Takagi, J. Hartwig, J. F. Miyaura, N. "A stoichiometric aromatic C–H borylation catalyzed by iridium(I)/2,2'-bipyridine complexes at room temperature." *Angew. Chem., Int. Ed*. **2002**, *41*, 3056.
18 Ishiyama, T. Nobuta, Y. Hartwig, J. F. Miyaura, N. "Room temperature borylation of arenes and heteroarenes using stoichiometric amounts of pinacolborane catalyzed by iridium complexes in an inert solvent." *Chem. Commun*. **2003**, *39*, 2924.
19 Ishiyama, T. Takagi, J. Yonekawa, Y. Hartwig, J. F. Miyaura, N. "Iridium-catalyzed directborylation of five-membered heteroarenes by bis(pinacolato)diboron: regioselective, stoichiometric and room temperature reactions." *Adv. Synth. Catal*. **2003**, *345*, 1103.
20 Vanchura, I. I. B. A. Preshlock, S. M. Roosen, P. C. Kallepalli, V. A. Staples, R. J. Maleczka, J. R. E. Singleton, D. A. Smith, M. R. "Electronic effects in iridium C–H borylations: insights from unencumbered substrates and variation of boryl ligand substituents." *Chem. Commun*. **2010**, *46*, 7724.
21 Ishiyama, T. Takagi, J. Ishida, K. Miyaura, N. Anastasi, N. Hartwig, J. F. "Mild iridiumcatalyzed borylation of arenes. High turnover numbers, room temperature reactions, and isolation of a potential intermediate." *J. Am. Chem. Soc.* **2002**, *124*, 390.
22 Boller, T.M. Murphy, J. M. Hapke, M. Ishiyama, T. Miyaura, N. Hartwig, J. F. "Mechanism of the mild functionalization of arenes by diboron reagents catalyzed by iridium complexes. intermediacy and chemistry of bipyridine-ligated iridium tris boryl complexes." *J. Am. Chem. Soc*. **2005**, *127*, 14263.
23 Simmons, E.M. Hartwig, J. F. "Iridium-catalyzed arene ortho-silylation by formal hydroxyl-directed C–H activation." *J. Am. Chem. Soc.* **2010**, *132*, 17092.
24 Denmark, S. E. Sweis, R. F. "Design and implementation of new, silicon-based, cross coupling reactions: importance of silicon-oxygen bonds." *Acc. Chem. Res.* **2002**, *35*, 835.
25 Jones, G. R. Landais, Y. "The oxidation of the carbon-silicon bond." *Tetrahedron*, **1996**, *52*, 7599.
26 Simmons, E. M. Hartwig, J. F. "Catalytic functionalization of unactivated primary C–H bonds directed by an alcohol." *Nature*. **2012**, *483*, 70.
27 Crotti, C. Farnetti, E. Filipuzzi, S. Stener, M. Zangrando, E. Moras, P. "Evaluation of the donor ability of phenanthrolines in iridium complexes by means of synchrotron radiation photoemission spectroscopy and DFT calculations." *Dalton Trans*, **2007**, 133.
28 Mkhalid, I. A. I. Barnard, J. H. Marder, T. B. Murphy, J. M. Hartwig, J. F. "C–H activation for the construction of C–B bonds." *Chem. Rev*, **2010**, *110,* 890.
29 (a) Nägeli, I. Baud, C. Bernardinelli, G. Jacquier, Y. Moran, M. Müller, P. "Rhodium(II)-catalyzed C–H insertions with {[(4-Nitrophenyl)sulfonyl]imino} phenyl-λ^3-iodane." *Helv. Chim. Acta.* **1997**, *80*, 1087.
30 Yu, X.-Q. Huang, J.-S. Zhou, X.-G. Che, C.-M. "Amidation of saturated C−H bonds catalyzed by electron-deficient ruthenium and manganese porphyrins. a highly catalytic nitrogen atom transfer process." *Org. Lett*. **2000**, *2*, 2233.
31 Espino, C. G. Du Bois, J. "A Rh-catalyzed C−H insertion reaction for the oxidative conversion of carbamates to oxazolidinones. "*J. Angew. Chem., Int. Ed.* **2001**, *40*, 598.
32 Espino, C. Wehn, P. Chow, J. Du Bois, J. "Synthesis of 1,3-difunctionalized amine derivatives through selective C−H bond oxidation." *J. Am. Chem. Soc*, **2001**, *123*, 6935.
33 Riddell, F. G. Royles, B. J. L. "In comprehensive heterocyclic chemistry II" *Boulton, A. J., Ed*.; Pergamon Press: Oxford, **1996**; *Vol. 6*, 825.
34 Gritsonie, P. Pilkington, M. Wallis, J. D. Provey, D. C. "Methyl DL-3-benzyl-2,2-dioxo-1,2,3-oxathiazolidine-4-carboxylate - an intermediate for amino acid synthesis." *Acta Crystallogr*. **1994**. *C50*, 763.
35 (a) Espino, C. D. Fiori, K. W. Kim, M. Du Bois, J. "Expanding the scope of C–H amination through catalyst design." *J. Am. Chem. Soc*. **2004**, *126*, 15379. (b) Du Bois, J. Zalatan, D. N. "Understanding the differential performance of $Rh_2(esp)_2$ as a catalyst for C–H amaination." *J. Am. Chem. Soc*. **2009**. *131*. 7558.
36 Taber, D. F. Meagley, R. P. Louey, J. P. Rheingold, A. L. "Molecular complex design: bridging the tetrakiscarboxylatodirhodium core." *Inorg. Chim. Acta*. **1995**, *239*, 25.
37 (a) Davies, H. M. L. "Catalytic enantioselective synthesis of β^2-amino acids." *Eur. J. Org. Chem*. **1999**, 2459. (b) Davies, H. M. L. Venkataramani, C. "Dirhodium tetraprolinate-catalyzed asymmetric cyclopropanations with high turnover numbers." *Org. Lett*. **2003**, *5*, 1403.
38 (a) Bickley, J. Bonar-Law, R. McGrath, T. Singh, N. Steiner, A. "Dirhodium (II) carboxylate complexes as building blocks. *cis*-Chelating dicarboxylic acids designed to bridge the dinuclear core." *New J. Chem*. **2004**, *28*, 425. (b) Bonar-Law, R. P. McGrath, T. D. Singh, N. Bickley, J. F. Femoni, C. Steiner, A. "Dirhodium(II) carboxylates as building blocks. Synthesis and structures of cis-chelate complexes." *J. Chem. Soc., Dalton Trans*. **2000**, 4343.

39 (a) Au, S.-M. Huang, J.-S. Che, C.-M. Yu, W.-Y. "Amidation of unfunctionalized hydrocarbons catalyzed by ruthenium cyclic amine or bipyridine complexes." *J. Org.Chem*. **2000**, *65*, 7858. (b) Liang, J.-L. Huang, J.-S. Yu, X.-Q. Zhu, N. Che, C.-M. "Metalloporphyrin-mediated asymmetric nitrogen-atom transfer to hydrocarbons: aziridination of alkenes and amidation of saturated C-H bonds catalyzed by chiral ruthenium and manganese porphyrins." *Chem. sEur. J*. **2002**, *8*, 1563.

40 Williams Fiori, K. Espino, C. G. Brodsky, B. H. Du Bois, J. "A mechanism analysis of the Rh-catalyzed intramolecular C–H amination reaction." *Tetrahedron*. **2009**, *65*, 3042.

41 (a) Groves, J. T. "High-valent iron in chemical and biological oxidations." *J. Inorg. Biochem*. **2006**, *100*, 434. (b) Newcomb, M. Toy, P. H. "Hypersensitive radical probes and the mechanisms of cytochrome P450-catalyzed hydroxylation reactions." *Acc. Chem. Res*. **2000**, *33*, 449.

42 Fiori, K. W. Du Bois, J. "Rh(II)-catalyzed intermolecular oxidative sulfamidation of aldehydes: a mild efficient synthesis of N-sulfonylcarboxamides." *J. Am. Chem. Soc*. **2007**, *129*, 562.

43 Du Bois, J. Hinman, A. "A stereoslective synthesis of (–)-Tetrodotoxin." *J. Am. Chem. Soc*. **2003**. *125*. 11510.

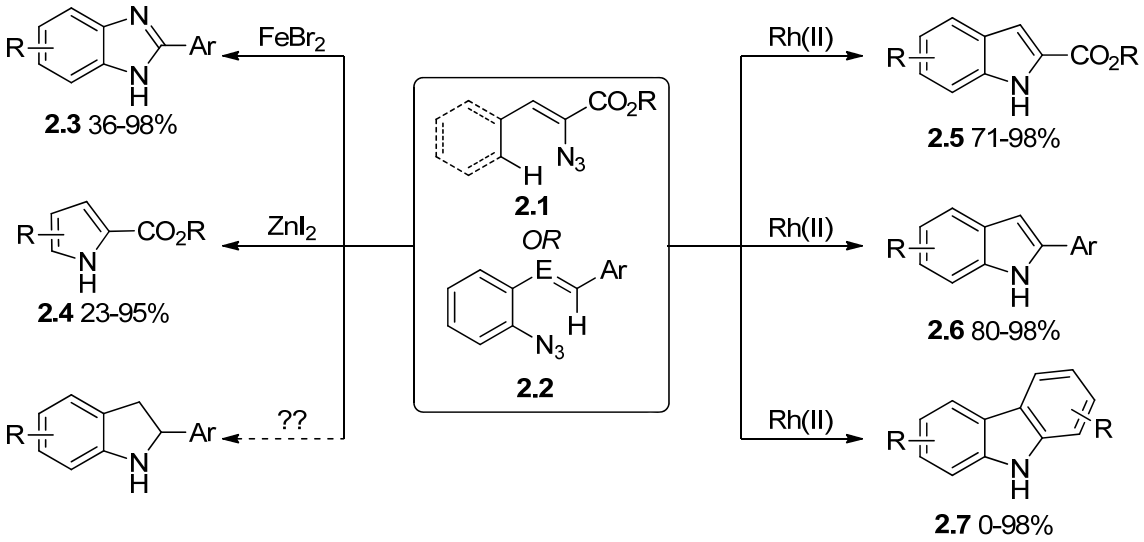
44 Wehn. P. M. Du Bois, J. "Enantioselective synthesis of the bromopyrrole alkaloids manzacidin A and C by stereospecific C−H bond oxidation."*J. Am. Chem. Soc.* **2002**, *124*, 12950.

Chapter 2. [Ir(COD)(OMe)]$_2$ Catalyze Benzylic C–H Bond Amination with Aryl Azide

2.1 Introdouction

Research in the Driver group was focused on transforming sp^2 C–H bonds into C–N bonds through the development of transition metal-catalyzed amination reactions of vinyl- or aryl azides (Scheme 2.1). In 2006, they reported[1] that rhodium(II) carboxylate complexes catalyzed the transformation of vinyl azides **2.1** into 2-carboxylate-substituted indoles **2.5**. Formation of benzimidazoles[2] **2.3** and pyrroles[3] **2.4** catalyzed by Lewis acid $FeBr_2$ as well as ZnI_2 respectively; Rh_2(II)-carboxylate catalyze formation of indole[4] **2.6**, carbazole[5] **2.7** using aryl azide **2.2** as nitrogen source. Unfortunately, these catalysts were unable to accomplish aliphatic C–H bond amination with aryl azide as nitrogen source.

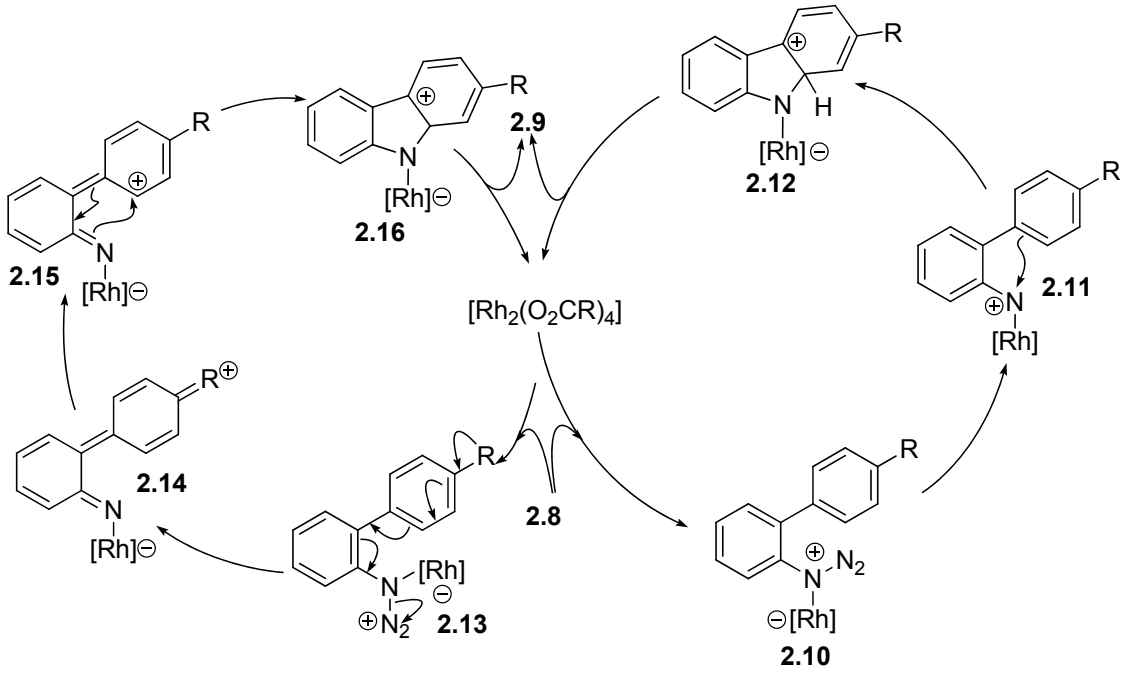
Scheme 2.1. Vinyl- Aromatic C–H bond amination from Driver group.



A mechanistic study on Rh(II) carboxylate catalyzed carbazole formation provided insight into how sp^2-C–H bond amination occurred and the challenges for sp^3-C–H bond functionaliztion. One plausible mechanism involved electrophilic aromatic substitution as shown in the right hand portion of Scheme 13. After coordination of aryl azide **2.8** to rhodium

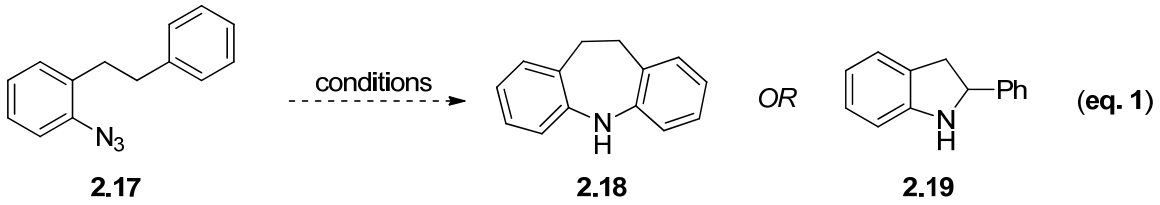
complexes, rhodium nitrenoid **2.10** is formed with the release of N_2. Carbazole **2.9** is formed through subsequent electrophilic substitution and rearomatization. While possible a Hammett study implicated that C–N bond formation occurred through an electrocyclization mechanism (left hand portion of Scheme 2.2). With the assistance of an R group, intermediate quinoid **2.13** could be formed. C–N bond formation could then occur through a 4-electron-5-atom electrocyclization via **2.14.** A 1,5-hydride shift from **2.15** then afforded the **2.16**. Both mechanisms required conjugated system or aromatic C–H bond, and no amination of sp^3 C–H bond was observed at the corresponding conditions.

Scheme 2.2. Plausible mechanisms for the carbazole formation.



To address this deficiency, we designed an aryl azide in order to identify a transition metal complex to catalyze benzylic C–H bond amination, aryl azide **2.17** contains two possible reaction sites (eq. 4): aromatic C–H bond amination produces 7-membered ring diphenylazepine **2.18** or aliphatic C–H bond amination to afford 2-phenyl indoline **2.19**. If neither C–H bond

reacted, we expected to observe decomposition of the aryl azide to afford either the aniline or oligomerization to produce tar.[6] Based on our mechanistic study, we expected the aryl C–H bond to be more reactive than benzylic C–H bond, although 7-membered ring formation is considerably more difficult than five-membered ring formation.

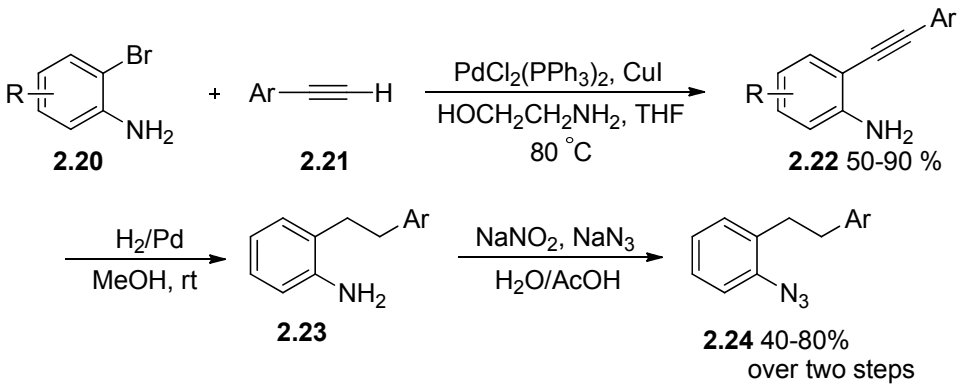


2.17 **2.18** **2.19** **(eq. 1)**

2.2 Synthesis of Starting Aryl Azides

The requisite aryl azides **2.24** for our study are readily accessible in three steps (Scheme 14) from the commercially available 2-bromoanilines **2.20**. The three-step synthesis began with Sonogashira cross-coupling of 2-bromoaniline **2.20** and acetylene **2.21**. Hydrogenation of the resulting arylacetylene **2.22** produced the corresponding 2-phenylethylarene **2.23**. Subsequent azidation of **2.23** transformed the aniline into aryl azide **2.24**.

Scheme 2.3. Preparation of starting aryl azide.



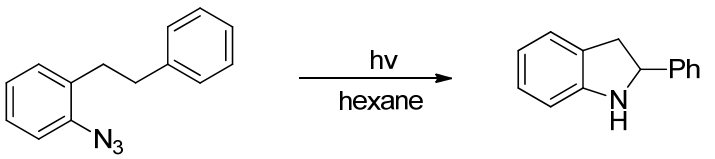
2.20 **2.21** **2.22** 50-90 %

2.23

2.24 40-80% over two steps

2.3 Optimization

The amination chemistry of aryl azide **2.17** C–H was studied by Murata and co-workers to elucidate the identity of nitrene during the reaction process.[6] They reported that the photolysis of 2-(2-phenylethyl)phenyl azide in cyclohexane exclusively afforded 31% 2-phenylindoline **2.19** with 2% 2-(2-phenylethyl)indole as a by-product. The author proposed that **2.19** was produced by intramolecular insertion of the nitrene into a β-C–H bond of the 2-phenylethyl group. They also concluded from stereochemical probes that C–H insertion of the nitrenes proceeds primarily by a hydrogen abstraction–recombination process. Although, they did not have enough evidence to identify the spin state of the nitrenes involved in the hydrogen abstraction.



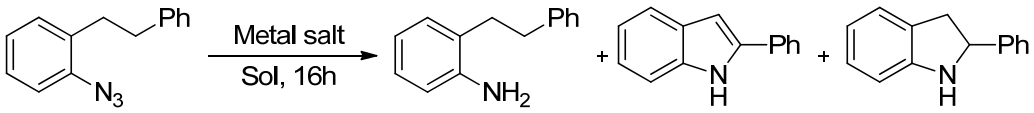
2.17 **2.19** **(eq. 2)**

2.3.1 Optimization of Catalysts

To address the poor reaction outcome of the photolysis, we performed experiments aimed at determining the optimal conditions for transition metal-catalyzed benzylic C–H bond amination (Table 2.1). Initially, thermolysis of the aryl azide **2.17** at 120 ºC provided 20% indole **2.16** as well as 70% indoline **2.19**. To lower the temperature of the amination reaction, a series of metal complexes were screened. A variety of metal complexes (Ru[7], Zn[8], Fe[9], Cu[10], Co[11] complexes), which were known to catalyze nitrenoid chemistry, were not able to provide any of the desired product. In contrast to our earlier studies—though no surprise based on our mechanistic experiments—exposure of **2.17** to rhodium(II) complexes resulted in no reaction. Rhodium(I) complexes, for example, $[Rh(COD)(OMe)]_2$, were also found to be incompetent

catalysts. After extensive screening of metal complexes and conditions, we found that exposure of **2.17** to $[Ir(COD)(OMe)]_2$, at 100 ºC temperature, could yield 30% corresponding aniline **2.25**, 40% indole **2.26** without observance of any indoline. Surprisingly, only iridium complexes worked: employment of $[Ir(COE)_2Cl]_2$, $Ir(COD)(C_5H_7O_2)$, $Ir(COD)(C_5HF_6O_2)$, $[Ir(COD)Cl]_2$ catalysts could yield indole product. Control experiments established that aniline retarded the reaction suggesting that coordination of aniline to catalyst would deactivate the catalyst.

Table 2.1. Optimization of indoline formation.



2.17 **2.25** **2.26** **2.19**

entry	metal salt	mol %	solvent	wt %, 4 Å MS	T (°C)	yield, %[c] (**2.25** : **2.26** : **2.19**)
1	none	n.a.	Mesitylene	0	120	90 (0:20:70)
2	none	n.a.	Mesitylene	0	reflux	90 (0:20:70)
3	none	n.a.	Mesitylene	0	80	0
4	$Rh_2(O_2CC_3F_7)_4$	5	PhMe	100	80	n.r
5	$Rh_2(O_2CCF_3)_4$	5	PhMe	100	80	n.r
6	$Rh_2(O_2CC_7H_{15})_4$	5	PhMe	100	80	n.r
7	$RhCl_3$	5	PhMe	100	80	n.r
8	$[Rh(COD)Cl]_2$	5	PhMe	100	80	n.r
9	$[Rh(COD)(OMe)]_2$	5	PhMe	100	80	n.r
10	$Pd(O_2CCF_3)_2$	5	PhMe	100	80	n.r
11	$PdCl_2(PPh_3)_2$	5	PhMe	100	80	n.r
12	$Fe(O_2CCH_3)_2$	5	PhMe	100	80	n.r
13	$FeBr_2$	5	PhMe	100	80	n.r
14	$Fe(C_5H_7O_2)_3$	5	PhMe	100	80	n.r
15	FeF_2	5	PhMe	100	80	n.r
16	ZnI_2	5	PhMe	100	80	n.r
17	$Cu(OTf)_2$	5	PhMe	100	80	n.r

18	$AuCl_3$	5	PhMe	100	80	n.r
19	Co(Salen)	5	PhMe	100	80	n.r
20	$Ag(O_2CCH_3)$	5	PhMe	100	80	n.r
21	$IrCl(CO)(PPh_3)_2$	5	PhMe	100	100	n.r
22	$IrClH_2(C_{16}H_{37}NP_2)$	5	PhMe	100	100	44 (44:trace:0)
23	$Ir(COD)_2^+[B(C_8H_3F_6)_4]^-$	5	PhMe	100	100	30 (30:0:0)
24	(COD)IrCp*	5	PhMe	100	100	34 (34:0:0)
25	Indenyl(COD)iridium	5	PhMe	100	100	35 (35:0:0)
26	$[(COE)_2IrCl]_2$	5	PhMe	100	100	69 (45:24:0)
27	$(COD)Ir(C_5H_7O_2)$	5	PhMe	100	100	57 (35:22:0)
28	$(COD)Ir(C_5HF_6O_2)$	5	PhMe	100	100	42 (28:14:0)
29	$[(COD)IrCl]_2$	5	PhMe	100	100	72 (48:24:0)
30	$[(COD)Ir(OMe)]_2$	5	PhMe	100	100	70 (30:40:0)

2.3.2 Optimization of Solvents

Optimization was continued by examining the amination reaction in different solvents (Table 2.2). We found that benzene (entry 8) and toluene gave comparable yields. Lower yields were obtained with anisole (entry 6) and chlorobenzene (entry 7) as solvents. Employment of non-aromatic solvent DMF could promote the catalytic reaction as well, although the reaction conversion was not as good as toluene. Using THF, $CHCl_3$ or acetone as solvents resulted in no reaction with starting aryl azide recovered. We attributed these results to the poor solubility of the catalysts in these solvents.

Table 2.2. Optimization of reaction solvent.[a,b]

entry	metal salt	mol %	solvent	T (°C)	yield, %[c] (**2.25** : **2.26** : **2.19**)

1	$[(cod)Ir(OMe)]_2$	2	THF	60	71 (41:20:10)
2	$[(cod)Ir(OMe)]_2$	2	$CHCl_3$	60	n.r
3	$[(cod)Ir(OMe)]_2$	2	Acetone	60	45 (28:17:0)
4	$[(cod)Ir(OMe)]_2$	2	$(ClCH_2)_2$	40	10 (10:0:0)
5	$[(cod)Ir(OMe)]_2$	2	DMF	40	77 (50:27:0)
6	$[(cod)Ir(OMe)]_2$	2	$MeOC_6H_5$	rt	74 (22:9:43)
7	$[(cod)Ir(OMe)]_2$	2	ClC_6H_5	rt	77 (15:10:52)
8	$[(cod)Ir(OMe)]_2$	2	C_6H_6	rt	84 (15:6:63)

[a] Reactions performed using Schlenk techniques. [b] 16 h reaction time. [c] As determined using ^1H NMR spectroscopy.

Additionally, the effect of temperature on the reaction was also examined. Table 2.3 shows that formation of the indoline was maximized at room temperature and decreased at higher temperature. These observations suggest that indoline is rapidly converted to indole via dehydrogenation at elevated temperatures. Since other iridium complexes such as Ir(COD)Cl, Ir(COD)($C_5H_7O_2$), Ir(COD)($C_5HF_6O_2$) exhibited no reactivity at ambient temperature we concluded that $[Ir(COD)(OMe)]_2$ was the optimal catalyst and 25 °C was the optimal reaction temperature to selectively achieve benzylic C–H bond amination and the preparation of indolines.

2.3.3 Optimization of Temperature

Table 2.3. Optimization of catalysts and temperature.

entry	metal salt	mol %	Solvent	T	yield, %[a,b]

				(°C)	(**2.25** : **2.26** : **2.19**)
1	$[(cod)Ir(OMe)]_2$	5	PhMe	100	75 (25:50:0)
2	$[(cod)Ir(OMe)]_2$	5	PhMe	80	91 (31:19:41)
3	$[(cod)Ir(OMe)]_2$	5	PhMe	60	82 (19:20:43)
4	$[(cod)Ir(OMe)]_2$	5	PhMe	40	85 (16:16:53)
5	$[(cod)Ir(OMe)]_2$	5	PhMe	rt	90 (19:13:58)
6	$[(cod)IrCl]_2$	5	PhMe	rt	18 (10:8:0)
7	$Ir(cod)_2^+[B(C_8H_3F_6)_4]^-$	5	PhMe	rt	n.r
8	$(cod)Ir(C_5H_7O_2)$	5	PhMe	rt	n.r
9	$(cod)Ir(C_5HF_6O_2)$	5	PhMe	rt	n.r

[a] Reactions performed using Schlenk techniques. [b] As determined using ^{1}H NMR spectroscopy.

2.3.4 Optimization of Catalysts Loading

Subsequent examination of catalyst loading showed that 2 mol % $[Ir(COD)(OMe)]_2$ was equally as effective as 5 mol % $[Ir(COD)(OMe)]_2$ (entry 2) (Table 2.4).

Table 2.4. Optimization of catalyst loading

entry	metal salt	mol %	solvent	wt %, 4 Å MS	T (°C)	yield, %[a] (**5** : **6** : **7**)
1	$[(cod)Ir(OMe)]_2$	2	PhMe	100	60	81 (18:22:41)
2	$[(cod)Ir(OMe)]_2$	5	PhMe	100	60	82 (19:20:43)
3	$[(cod)Ir(OMe)]_2$	10	PhMe	100	40	75 (13:17:45)

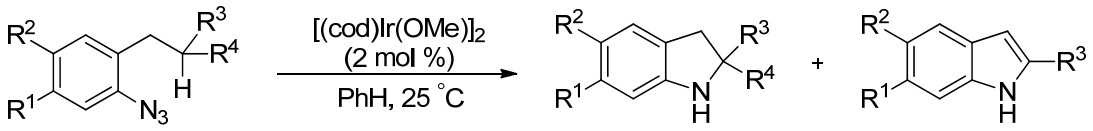
[a] As determined using ^{1}H NMR spectroscopy

2.4 Substrate Scope and Limitations

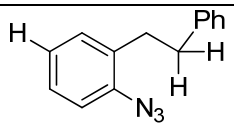
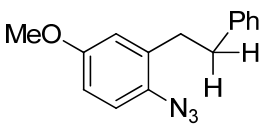
After determination of the optimal conditions to achieve C–H amination (2 mol % of $[Ir(COD)(OMe)]_2$, toluene, 25 °C), the scope and limitations of the transformation were investigated (Table 2.5). Examination of scope revealed that the amination is sensitive to the

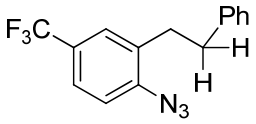
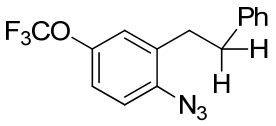
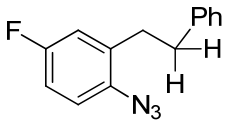
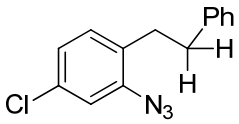
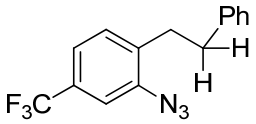
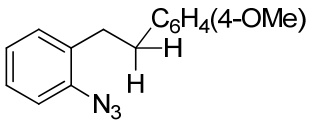
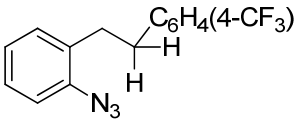
electronic nature of aryl azide: indoline formation was arrested when an electron-rich group are attached (entry 2). Attachment of an electron-withdrawing substituent, such as CF_3, however, to aryl azide provided only the indoline product in high yield (entry 3). Varying the strength of the electron-withdrawing group affected the yield of indoline, which increased as stronger electron-withdrawing R^1- and R^2-groups were added to aryl azide **2.17** (Table 2.2, entries 1-7). In contrast, the electronic identity of the homobenzylic aryl group did not influence the yield of reaction (entries 8-11). Changing the electronic identity of the homobenzylic aryl group provided indolines in similar yields (entry, 7-9). Comparable yields were also observed for these groups on electron deficient aryl azides (entries 10 and 11). Presently, our Ir(I)-catalyzed reaction is limited to the amination of secondary benzylic C–H bonds. Substrates with either a secondary aliphatic C–H bond or a tertiary benzylic C–H bond did not react (entries 12 and 13).

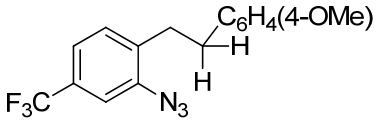
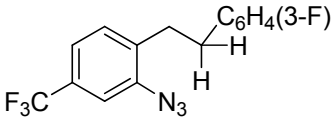
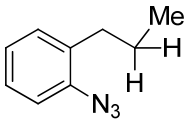
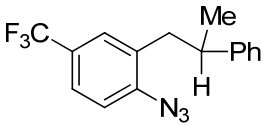
Table 2.5. Scope and limitations of Ir(I)-catalyzed benzylic C–H bond amination.



2.28 **2.29** **2.30**

entry	substrate	indoline yield, %	indole yield,%	isolated yield, %
1	 **2.17**	58	11	52
2			no reaction	

	2.31			
3		91	2	81
	2.32			
4		75	13	72
	2.33			
5		72	21	66
	2.34			
6		81	13	71
	2.35			
7		93	4	82
	2.36			
8		53	15	59
	2.37			
9		59	39	60
	2.38			

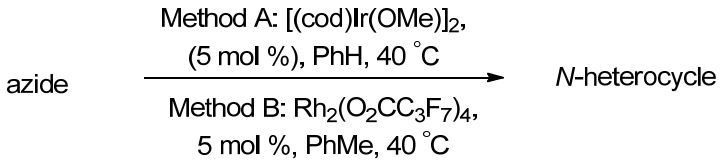
10	 **2.39**	81	4	75
11	 **2.40**	85	8	80
12	 **2.41**		no reaction	
13	 **2.42**		no reaction	

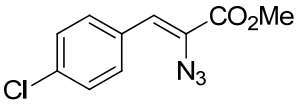
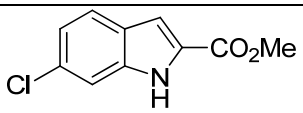
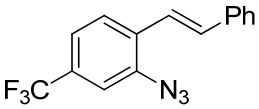
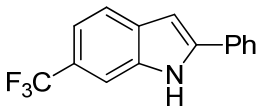
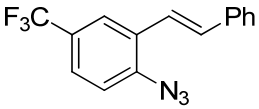
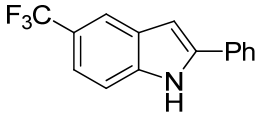
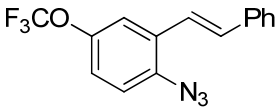
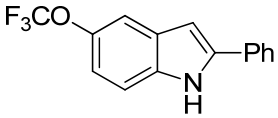
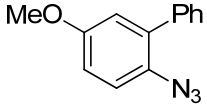
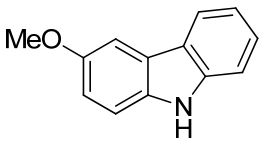
2.5 [Ir(COD)(OMe)]$_2$-Catalyzed Aromatic and Vinyl C–H Bond Amination

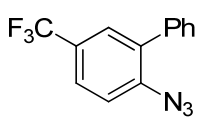
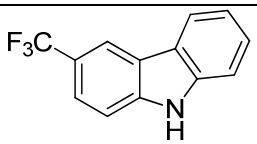
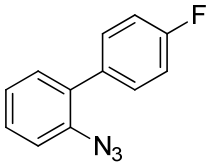
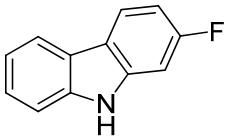
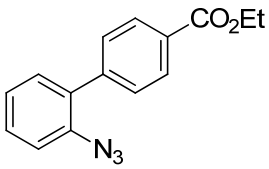
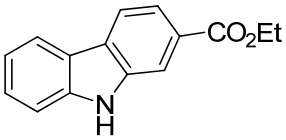
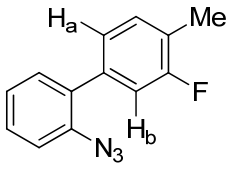
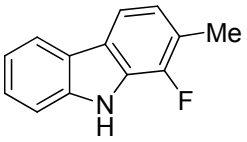
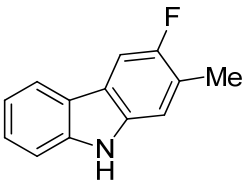
A variety of vinyl and aryl azides were examined to determine if [Ir(COD)(OMe)]$_2$ could catalyze the amination of aryl- or vinyl C–H bonds (Table 2.6). These reactions were set up at 40 °C to compare the reactivity of [Ir(COD)(OMe)]$_2$ with $Rh_2(O_2CC_3F_7)_4$. While all azidoacrylates **2.1** were unreactive towards [Ir(COD)(OMe)]$_2$, indoles or carbazoles are accessible from the corresponding aryl azide in comparable yields to $Rh_2(O_2CC_3F_7)_4$. Examination of biaryl azides (**2.52**–**2.58**) enabled comparison of the selectivity of C–H bond amination. Enhanced regioselectivity was observed in the reaction of with [Ir(COD)(OMe)]$_2$ as compared to $Rh_2(O_2CC_3F_7)_4$. Surprisingly in comparison to *ortho*-phenylethyl-substituted aryl

azides **2.51**, the reactivity of aryl azides **2.51** was not dependent on the electronic nature of their substituents: substrates bearing strong electron-donating group produced carbazole in decent yield. The difference implies that a different mechanism (or rate-determining step) is operating for aromatic *N*-heterocycle formation than for indoline formation.

Table 2.6. Comparison of catalytic efficiency of Ir(I) versus Rh(II) for aromatic N-heterocycle formation.



entry	substrate	##	product	##	yield, % method A : B
1		**2.43**		**2.44**	n.r. : 85
2		**2.45**		**2.46**	83 : 89
3		**2.47**		**2.48**	91 : 82
4		**2.49**		**2.50**	92 : 95
5		**2.51**		**2.52**	73 : 71

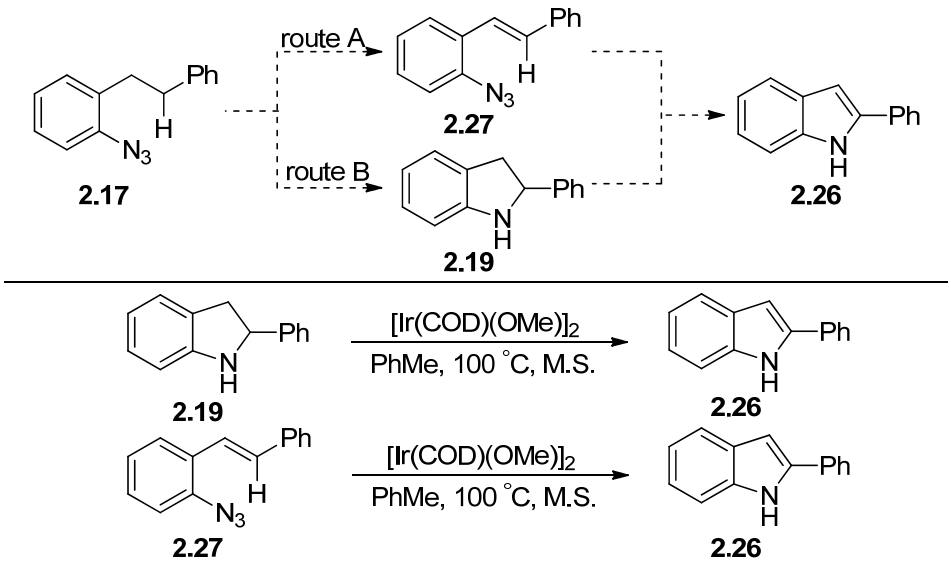
6		**2.53**		**2.54**	79 : 83
7		**2.55**		**2.56**	79 : 83
8		**2.57**		**2.58**	77 : 91
9		**2.59**		**2.60**	**2.60 : 2.61** method A 59% (61:39)
				**2.61**	Method B 98% (8:92)

2.6 Mechanistic Study

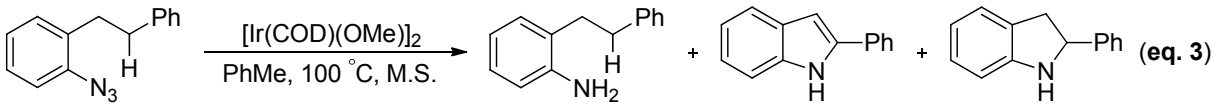
We theorized that the formation of the indole could occur by one of two pathways (Scheme 2.4). We anticipated that dehydrogenation of **2.17** followed by iridium-catalyzed vinyl C–H bond amination would form 2-phenylindole. Alternatively, indole **2.26** could result from iridium-catalyzed benzylic C–H bond functionalization to generate indoline, followed by subsequent dehydrogenation. Further examination showed that indole could be accessed from either route: submission of vinyl azide **2.27** or indoline **2.19** to reaction conditions afforded 2-phenylindole. Reduction of the reaction time, however, suggested that dehydrogenation of

indoline accounted for indole **2.26** formation: if reaction was set up for 4 hours, 32% of indoline **2.19** was generated. After 8 hours, only indole was observed. We interpreted this result to indicate that the reaction may not require as harsh conditions, and we anticipated that shorter reaction times or lower temperatures might provide a higher yield of the desired indoline.

Scheme 2.4. Potential pathway to generate indoline.



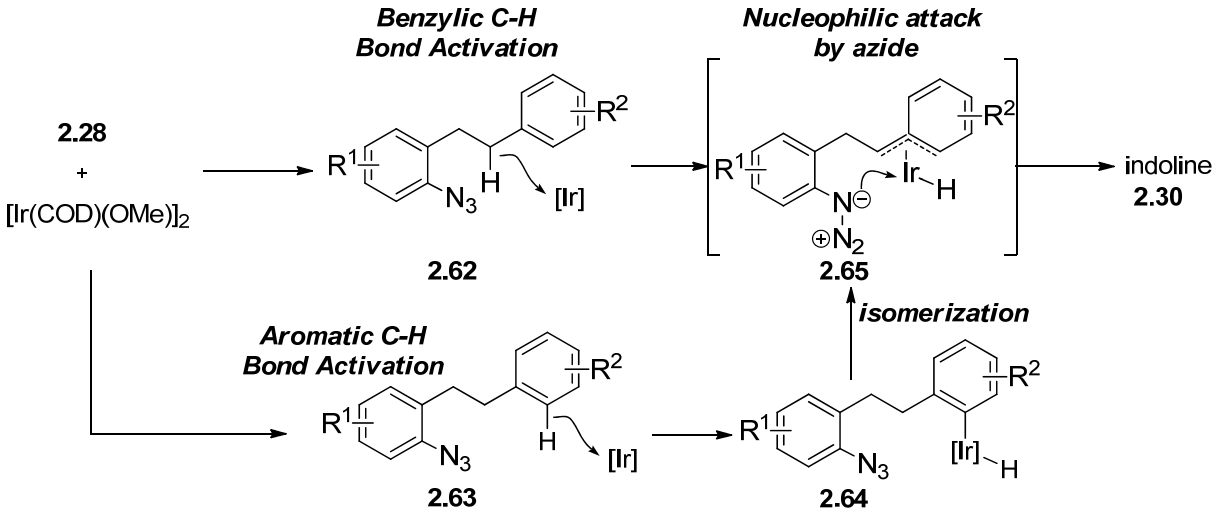
To test the hypothesis of the idea above, the reaction of aryl azide **2.109** in the presence of $[Ir(COD)(OMe)]_2$ at room temperature was examined (eq 6). Gratifyingly, 13% indole, 58% indoline plus 19% aniline were generated. Changing of ligand COD to COE, norbornene, or norbornadiene turned off the reaction. Other alkoxy groups were also examined, such as OH-, EtO- and bulky *t*BuO-, however, all of the modifications shut down amination and all of the starting aryl azide was recovered. These results emphasize the importance of the metal ligand combination present in $[Ir(COD)(OMe)]_2$ to trigger the decomposition of *ortho*-homobenzyl-substituted aryl azides at room temperature.



2.6.1 Possible Mechanism via Benzylic C–H Bond Activation

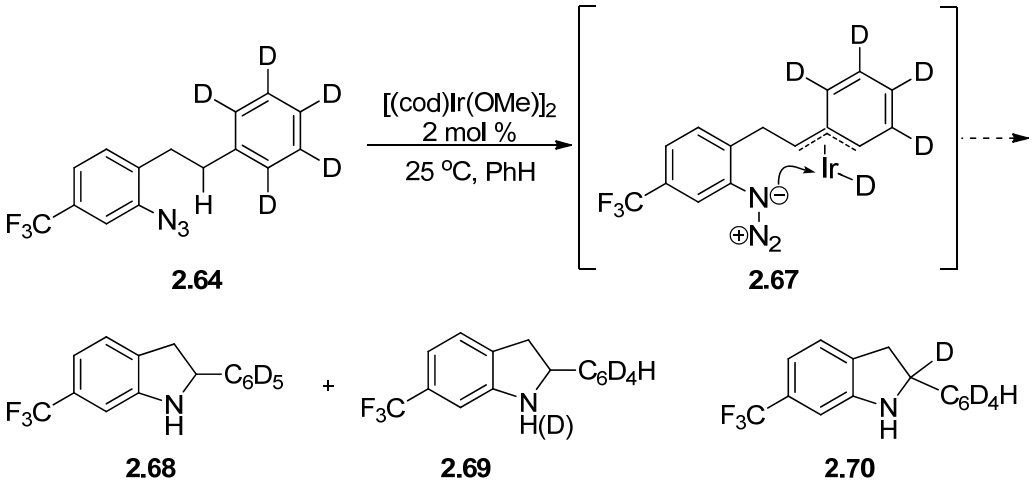
An alternative mechanism than Ir-catalyzed N-atom transfer could account for heterocycle formation. Because our Ir(I)-catalyzed reaction is limited to the amination of secondary benzylic C–H bonds, the β-aryl group is necessary for the reaction. One possible explanation (Scheme 2.5) for this reactivity is that the reaction involves the formation of the η^3-benzyl complex **2.65** in the catalytic cycle. This intermediate could be formed through the activation of a benzylic C–H bond[12] or more likely through aromatic C–H bond activation **2.63** followed by isomerization to the η^3-complex **2.65.**[13] In either case, carbon-nitrogen bond formation could occur through nucleophilic attack by the proximal azide.

Scheme 2.5. Mechanism through C–H bond activation.



Aryl azide **2.64** bearing α β-deuterated phenyl group was chosen to test the validity of η^3 benzyl complex in the catalytic cycle (Scheme 2.6). If the mechanism went through this catalytic intermediate we anticipated that indolines **2.68**, **2.69** and **2.70** would be observed since H/D exchange occurs readily in electrophilic C–H bond activation.[14] In contrast to this expectation, only **2.68** was detected. This result suggests that a benzylic C–H bond activation/nucleophilic addition mechanism does not account for N-heterocycle formation.

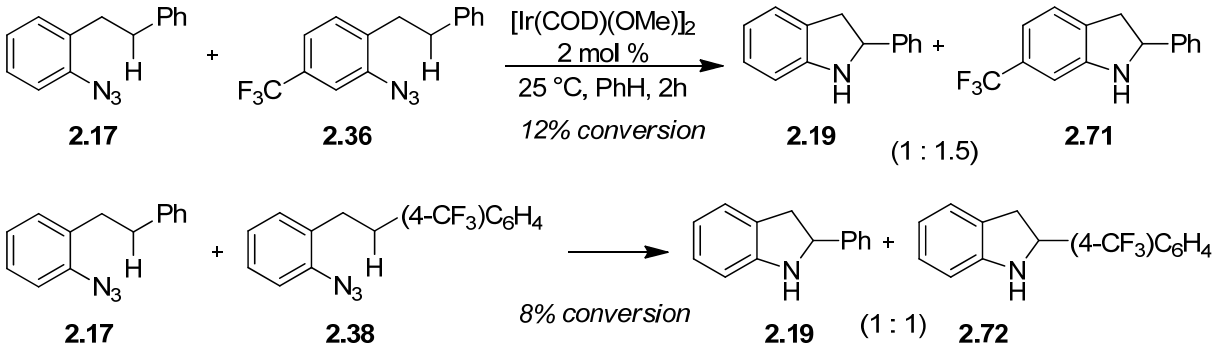
Scheme 2.6. H/D scrambling study to prove η^3- benzyl complex intermediate.



Besides the previous hydrogen-scrambling reaction, two intermolecular competition reactions were performed to determine if η^3-benzylic complex **2.65** was a potential reactive intermediate (Scheme 2.7). In the first experiment, the rates of reaction between unsubstituted aryl azide **2.17** and electron-poor aryl azide **2.36** were investigated. If this mechanism was occurring, less indoline **2.71** was anticipated in the presence of electron-withdrawing CF_3 substituents **2.36** since the rate of nucleophilic addition of azide should be attenuated by the electron-deficient substituent. The second experiment investigated the effect of the electronic nature of the β-aryl substituent (**2.17** versus **2.38**). The rate of benzylic C–H bond activation by iridium complex was expected to be attenuated in **2.38**, due to electron deficiency of benzylic C–

H bond. In contrast to these expectations, aryl azides **2.17** and **2.38** exhibited nearly equal reactivity toward $[(cod)Ir(OMe)]_2$ and the more electron deficient **2.36** reacted faster than **2.17**. The two competition reactions indicate that the process of catalytic proceeds through a different pathway.

Scheme 2.7. Intermolecular competition reaction.



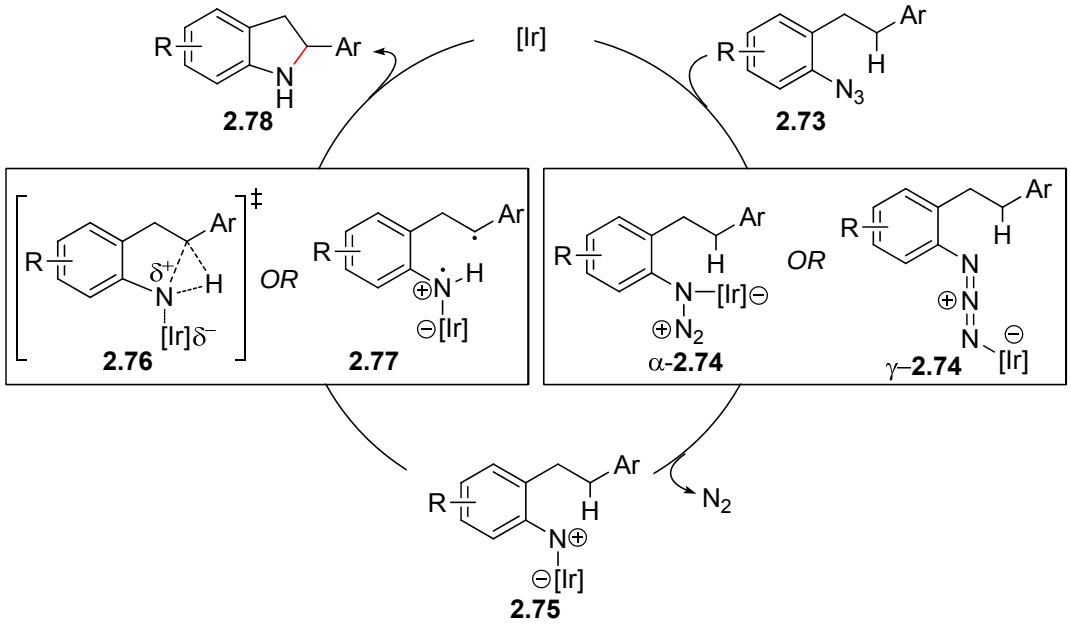
2.17 **2.36** **2.19** **2.71**

2.17 **2.38** **2.19** **2.72**

2.6.2 Possible Pathway via Iridium Nitrenoid Intermidiate

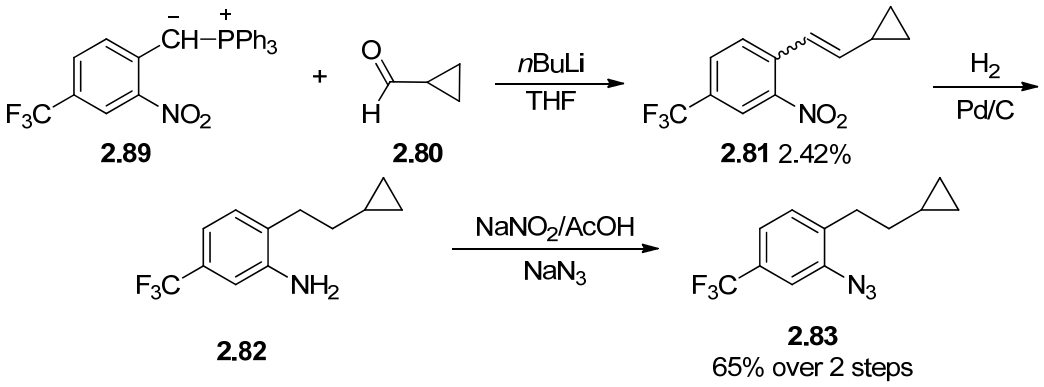
Besides the η^3-benzyl complex, an alternative reaction intermediate is iridium nitrenoid (Scheme 2.8). The appearance of aniline, a common nitrene decomposition product, also suggests that mechanism involving an electrophilic iridium nitrenoid is operating. This nitrenoid **2.75** could be produced after coordination of aryl azide (to form α-**2.74** or γ-**2.74**) with the $[(cod)Ir(OMe)]_2$ and followed by extrusion of N_2. Subsequent C–N bond formation could occur by two different pathways: a concerted insertion of the singlet nitrenoid **2.76** or hydrogen-atom abstraction with triplet nitrenoid **2.77** followed by radical recombination.

Scheme 2.8. Proposed mechanism via iridium nitrenoid.

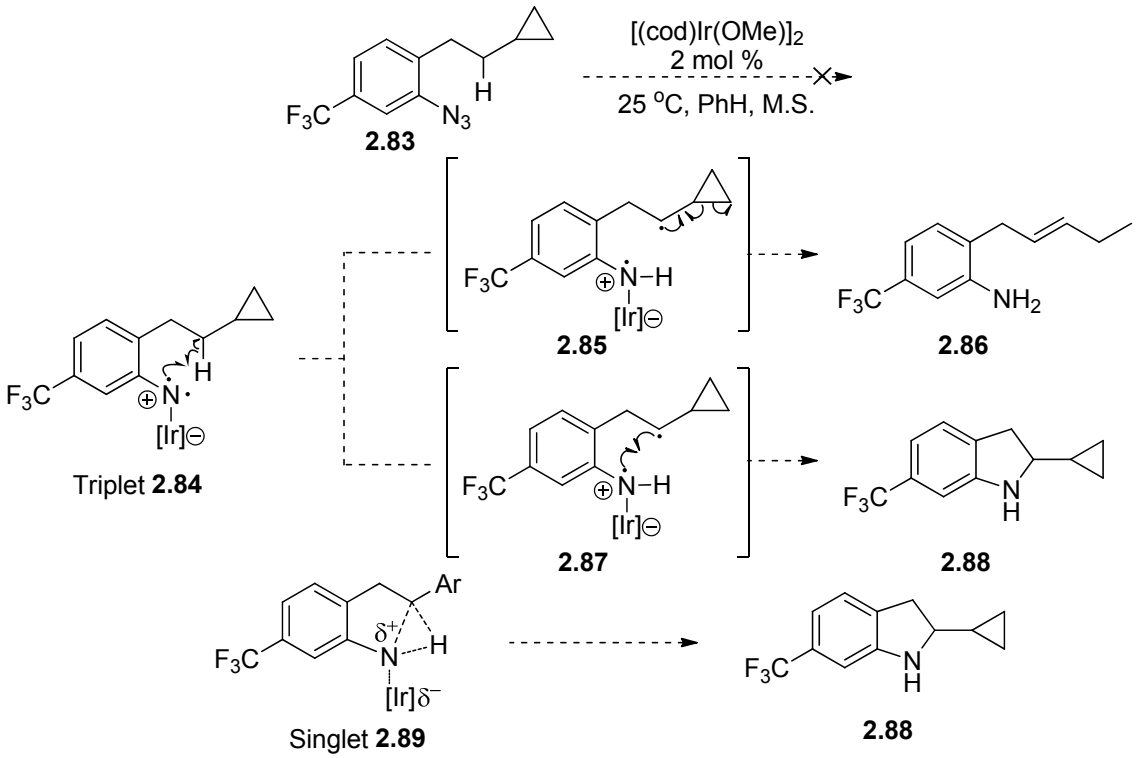


To determine what kind of iridium nitrenoid existed during the course of C–N bond formation, a substrate bearing β-cyclopropyl substituent **2.83** was synthesized starting from phosphonium ylide **2.79** through a Wittig reaction followed by a hydrogenation and subsequent azidation reaction. (Scheme 2.9). Unfortunately, submission of aryl azide **2.83** to the reaction conditions (Scheme 2.10) generates a number of products—none of which corresponded to **2.86** or **2.88**. Therefore, we cannot obtain any mechanistic information based on this specific reaction. If triplet nitrenoid **2.84** was involved, cyclopropyl substituent might undergo hydrogen abstraction, ring opening, and radical recombination to provide olefin aniline and 2-cyclopropyl indoline. In contrast, only 2-cyclopropyl indoline would be produced if single iridium nitrenoid **2.89** existed.

Scheme 2.9. Synthesis of β-cyclopropyl substituted aryl azide.



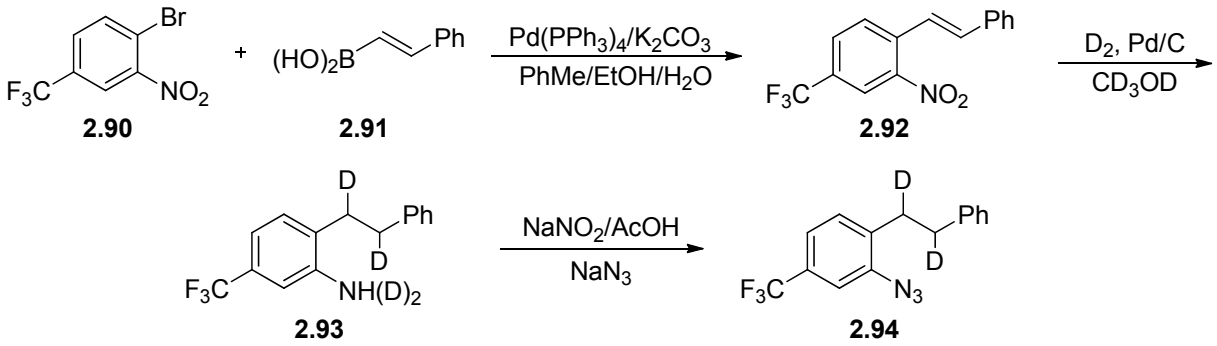
Scheme 2.10. Study to determine nitrenoid type.



2.6.3 Isotope Effect Study

With the failure of the cyclopropyl-substituted aryl azide, we anticipated that mechanistic insight into the identity of the catalytic intermediates would be available from an intramolecular kinetic isotope study. The required aryl azide-d_2 **2.94** was synthesized (Scheme 2.11) from nitroarene **2.90** through a Suzuki cross-coupling reaction followed by reduction with D_2 using CD_3OD as solvent. Azidation was conducted with sodium nitrite and sodium azide.

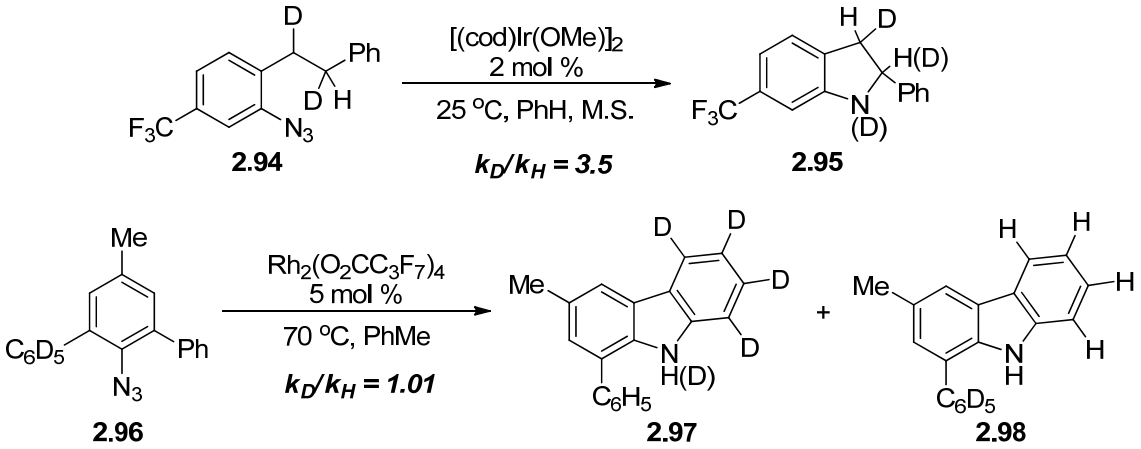
Scheme 2.11. Synthesis of substrate for intramolecular isotope effect study.



To examine the mechanism of C–H bond cleavage, two isotope effect study experiments were performed (Scheme 2.12). When **2.94** and **2.96**[5] were exposed to reaction conditions, intramolecular kinetic isotope effects (KIE) of 5.06 and 1.04 were observed to suggest that different mechanisms or change in the rate-determining step are applied for aryl azides **2.94**. Our measured value for (5.06) is smaller than the intramolecular KIE of the photochemical reaction of **2.17** (14.7) and is comparable to the KIE measured for the reaction of a rhodium nitrenoid with cyclohexane. While the photochemical KIE was usually considered as evidence for a triplet nitrene intermediate, the combination of radical clock studies, Hammett correlation studies with isotope experiments indicate that the electronic state of the rhodium nitrenoid is a singlet. The magnitude of our KIE (5.06) is similar to those observed for the Rh_2(II)-nitrenoid insertion

mechanism, but further experiments are necessary to rule out alternative mechanisms, including one involving a triplet nitrene.

Scheme 2.12. Isotope effect study.



2.7 Conclusion

Indoline moities are a significantly important class of molecules that constitutes a variety of biologically active nature products. We have demonstrated that iridium(I)-complexes can catalyze the functionalization of benzylic C–H bonds to produce indolines from aryl azides at room temperature. The reaction, however, was largely dependent on the electronic nature of the reactive intermediates. The mechanism study indicated that the indoline formation could occur through the nitrenoid intermediate. The resulting mechanistic insight will be exploited in the development of new asymmetric methods to form *N*-heterocycles from azides by metal-mediated nitrogen atom transfer.

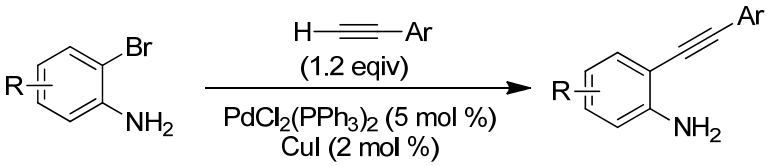
2.8 Experimental

General. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using Bruker DRX 500 or Varian DRX 300 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 GCMate II or Thermo Finnigan LTQ FT spectrometer, and were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on Sorbent Technologies 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 Sorbent Technologies 60Å (40 – 60 μm) mesh silica gel (SiO_2). Medium pressure liquid chromatography (MPLC) was performed using Thomson SINGLE StEP pumps to force flow the indicated solvent system down columns that had been packed with Sorbent Technologies 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[15]. Metal salts were stored in an MBraun labmaster nitrogen atmosphere dry box.

2.8.1 Preparation of 2-Alkyl-Substituted Anilines

General Procedure for the Preparation of 2-Alkynyl-Substituted Anilines.

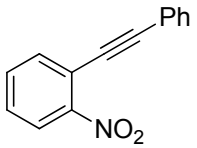
Unless otherwise noted, the 2-alkynyl-substituted anilines were synthesized from substituted 2-bromoanilines using a Sonagashira reaction (eq. 4).[23] Yields were not optimized.



(eq. 4)

To a mixture of $PdCl_2(PPh_3)_3$ (5 mol %), CuI (2 mol %), and 1-bromo-2-nitrobenzene (1.0 equiv) in THF was added phenylacetylene (1.2 equiv) at room temperature. After bubbling argon through the mixture for 30 minutes, a 3.0 M solution of ethanolamine in H_2O was added dropwise. The resulting mixture was heated to reflux for 19 hours and then cooled to room temperature. The resulting mixture was extracted with 3 × 5 mL of CH_2Cl_2. The organic extracts were washed with 1 × 10 mL of brine. The resulting organic phase was dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. Purification by MPLC (1:50 – 10:90 EtOAc:hexanes) afforded the product.

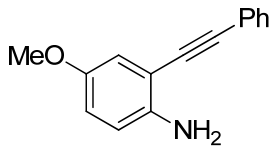
Syntheses of 2-Alkynyl-Substituted Arenes



2.99

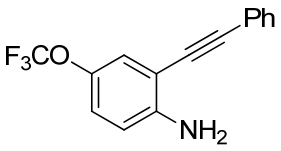
1-Nitro-2-(phenylethynyl)benzene (2.99). The representative procedure was followed using 0.035 g of $PdCl_2(PPh_3)_2$ (0.05 mmol), 0.004 g of CuI (0.02 mmol), 0.202 g of 1-bromo-2-nitrobenzene (1.0 mmol), 0.13 mL of phenylacetylene (1.2 mmol), 6.0 mL THF and 4.0 mL of a

3.0 M solution of ethanolamine (12.0 mmol) in water. Purification by MPLC (0:100 – 2:98 EtOAc: hexanes) afforded the product as a yellow solid (0.177 g, 76%): R_f= 0.68 (14:86 EtOAc: hexane); mp 37-40 °C; The spectral data matched that reported by Driver and co-workers:[1] ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.04 (d, *J* = 8.5, 1H), δ 7.74 (d, *J* = 8.0, 1H), 7.54 –7.60 (m, 3H), 7.35-7.43 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.5, 134.6, 133.0, 132.1 (2C), 129.3 128.7, 128.5, 124.7, 122.4, 118.7, 97.2, 84.9; IR (thin film): 2219, 1608, 1522, 1342, 748, 757, 689 cm^{-1}.



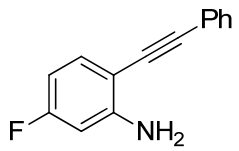
2.100

Aniline 2.100. The representative procedure was followed using 0.350 g of $PdCl_2(PPh_3)_2$ (0.5 mmol), 0.038 g of CuI (0.2 mmol), 2.01 g of 2-bromo-4-methoxybenzenamine (10.0 mmol), 1.32 mL of phenylacetylene (12.0 mmol), 60.0 mL THF and 40.0 mL of a 3.0 M solution of ethanolamine (120.0 mmol) in water. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the product as a brown oil (1.81 g, 81%): R_f= 0.44 (14:86 EtOAc: hexane). ^{1}H NMR (500 MHz, $CDCl_3$): 7.54 – 7.56 (m, 2H), 7.36 – 7.37 (m, 3H), 6.95 (d, *J* = 3 Hz, 1H), 6.80 (dd, *J* = 3 Hz, 9 Hz, 1H), 6.69 (d, *J* = 9 Hz, 1H), 4.44 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.9, 142.1, 131.5 (2C), 128.5 (2C), 128.4, 123.2, 117.5, 116.0, 115.8, 108.6, 94.7 86.1, 55.9; IR (thin film): 3456, 3365, 1601, 1500, 1421, 1336, 1284, 1227, 1146, 1038, 816, 756, 690 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{13}ON$ $(M)^+$ 223.09972, found 233.09961.



2.101

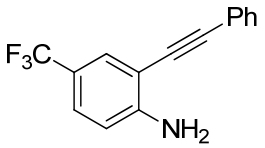
Aniline 2.101. The representative procedure was followed using 0.350 g of $PdCl_2(PPh_3)_2$ (0.5 mmol), 0.038 g of CuI (0.2 mmol), 2.56 g of 2-bromo-4-(trifluoromethoxy)benzenamine (10.0 mmol), 1.32 mL of phenylacetylene (12.0 mmol), 60.0 mL THF and 40.0 mL of a 3.0 M solution of ethanolamine (120.0 mmol) in water. Purification by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded the product as a light yellow powder (2.31 g, 83%): R_f = 0.52 (14:86 EtOAc: hexane); mp 84-86 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.57 – 7.59 (m, *2*H), δ 7.38 – 7.39 (m, 3H), 7.28 (s, 1H), 7.04 (d, *J* = 9 Hz, 1H), 6.68 (d, *J* = 8.5 Hz, 1H), 4.34 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.8, 140.4, 131.6 (2C), 128.8, 128.6 (2C), 124.8, 123.3, 122.7, 120.0 (q, J_{CF} = 297.5 Hz), 114.9, 108.5, 95.7, 84.7; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –59.0; IR (thin film): 3459, 3340, 1619, 1497, 1255, 1144, 879, 756, 691 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{10}ONF_3$ $(M)^+$ 277.0715, found 277.0713.



2.102

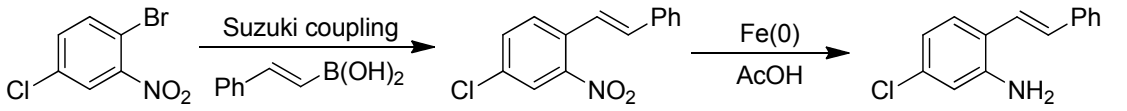
Aniline 2.102.[16] The representative procedue was followed using 0.350 g of $PdCl_2(PPh_3)_2$ (0.5 mmol), 0.038 g of CuI (0.2 mmol), 1.902 g of 2-bromo-4-fluorobenzenamine (10.0 mmol), 1.32 mL of phenylacetylene (12.0 mmol), 60.0 mL THF and 40.0 mL of a 3.0 M solution of ethanolamine (120.0 mmol) in water. Purification by MPLC (1:100 – 5:95 EtOAc: hexanes) afforded the product as a yellow solid (1.734 g, 81%): R_f = 0.67 (14:86 EtOAc: hexane); mp 66-68 °C; The spectral data matched that reported by Sakai and co-workers:[3] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 – 7.54 (m, *2*H), δ 7.36 – 7.39 (m, 3H), 7.08 (m, 1H), 6.88 (m, 1H), 6.67 (m, 1H), 4.15 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.2 (d, J_{CF} = 235.1 Hz), 114.2, 131.6, 128.6, 128.5, 122.8, 117.8 (d, J_{CF} = 22.1Hz), 116.9 (d, J_{CF} = 23.5 Hz), 115.3 (d, J_{CF} = 7.9 Hz), 118.7 (d,

J_{CF} = 8.0Hz), 95.4, 85.0; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –127.24; IR (thin film): 3462, 3374, 2362, 1616, 1498, 1429, 1196, 1138, 881, 812, 756, 690 cm^{-1}.



2.103

Aniline 2.103. [17] The representative procedure was followed using 0.350 g of $PdCl_2(PPh_3)_2$ (0.5 mmol), 0.038 g of CuI (0.2 mmol), 2.38 g of 2-bromo-4-(trifluoromethyl)benzenamine (10.0 mmol), 1.32 mL of phenylacetylene (12.0 mmol), 60.0 mL THF and 40.0 mL of an 3.0 M solution of ethanolamine (120.0 mmol) in water. Purification by MPLC (1:100 – 5:95 EtOAc: hexanes) afforded the product as a yellow powder (2.28 g, 88%): R_f= 0.72 (14:86 EtOAc: hexane). mp 81-82 °C. The spectral data matched that reported by Ye and co-workers:[4] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.65 (s, 1H), 7.54 –7.56 (m, 2H), 7.38 –7.40 (m, 4H), 7.74 (d, 8.5Hz, 1H), 4.59 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.2, 131.6 (2C), 129.5 (q, J_{CF} = 3.4 Hz), 128.7, 128.5, 126.6 (q, J_{CF} = 3.4 Hz), 124.4 (q, J_{CF} = 268.0 Hz), 122.7, 119.8 (q, J_{CF} = 32.1 Hz), 113.7, 107.5, 95.7, 84.4; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –62.0; IR (thin film): 3458, 3361, 1623, 1575, 1507, 1428, 1336, 1276, 1107, 909, 827, 760, 691, 644 cm^{-1}.

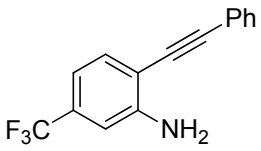


2.104 **2.105** (eq. 5)

***E*-4-chloro-2-nitro-1-styrylbenzene 2.104.** To a mixture of 1.043 g of trans-2-phenylvinylboronic acid (7.0 mmol), 0.571 g of $Pd(PPh_3)_4$ (0.5 mmol) and 3.2 g of K_2CO_3 (4.0 equiv) in a 30 mL PhMe, 12 mL EtOH, and 6 mL H_2O was added 1.18 g of 1-bromo-4-chloro-2-nitrobenzene (5.0 mmol). The resultant mixture was then purged with N_2 and refluxed. After 24 h, the mixture was cooled to room temperature and diluted with 50 mL of NH_4Cl and 20 mL of

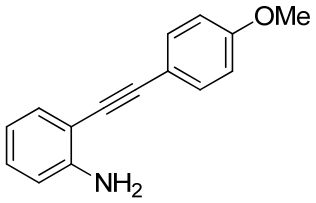
CH_2Cl_2. The phases were separated and the resulting aqueous phase was extracted with an additional 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, and was concentrated *in vacuo*. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded the **s6** as a yellow oil (1.14 g, 89%): R_f = 0.71 (14:86 EtOAc: hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.95 (d, *J* = 2.5 Hz, 1H), 7.71 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 2.5 Hz, 1H), 7.52 – 7.55 (m, 3H), 7.38 – 7.41 (m, 2H), 7.32 – 7.35 (m, 1H), 7.08 (d, *J* = 16 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 148.0, 136.2, 134.5, 133.5, 133.3, 131.6, 129.3, 128.9 (2C), 127.2, 124.9, 122.3; IR (thin film): 1628, 1526, 1449, 1346, 1256, 1151, 1110, 962, 891, 819, 764, 694, 533 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{14}H_{10}O_2NCl$ $(M)^+$ 259.0400, found 259.0399.

Aniline 2.105 was obtained by reduction of nitro group following the method reported by Driver and co-workers.[1] To a solution of 1.07 g **2.104** (4.00 mmol) in 12 mL of absolute ethanol was added 12 mL of glacial acetic acid and 0.44 g of iron powder (16.0 mmol). The mixture was heated to reflux. After 3 h, the crude mixture was cooled and filtered through a pad of Celite. The filtrate was concentrated *in vacuo*. Purification via MPLC (0:100 – 5:95 EtOAc:hexanes) afforded **s7** as a light yellow solid (0.60 g, 65%): R_f = 0.56 (14:86 EtOAc: hexane); mp 92 – 94 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.56 (d, *J* = 8.0 Hz, 2H), 7.42 – 7.45 (m, 2H), 7.36 (d, *J* = 7.5 Hz, 2H), 7.11 (d, *J* = 16 Hz, 1H), 7.01 (d, *J* = 16 Hz, 1H), 6.83 (d, *J* = 8.5 Hz, 1H), 6.73 (s, 1H), 3.88 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.1, 137.4, 134.0, 130.8, 128.9, 128.4, 127.9, 126.6, 123.2, 122.4, 119.2, 115.9; IR (thin film): 3358, 1633, 1560, 1458, 1421, 1254, 967, 856, 805, 757, 691, 511 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{14}H_{12}NCl$ $(M)^+$ 229.06582, found 229.06563.



2.106

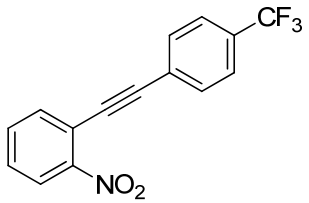
Aniline 2.106. The representative procedure was followed using 0.350 g of $PdCl_2(PPh_3)_2$ (0.5 mmol), 0.038 g of CuI (0.2 mmol), 2.386 g of 2-bromo-5-(trifluoromethyl)benzenamine (10.0 mmol), 1.32 mL of phenylacetylene (12.0 mmol), 60.0 mL THF and 40.0 mL of an 3.0 M solution of ethanolamine (120.0 mmol) in water. Purification by MPLC (1:100 – 5:95 EtOAc: hexanes) afforded the product as a yellow powder (2.37 g, 91%): R_f = 0.69 (14:86 EtOAc: hexane); mp 79 – 80 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.54 – 7.56 (m, 2H), 7.45 (d, J = 8.5 Hz, 1H), 7.38 – 7.39 (m, 3H), 6.95 – 6.96 (m, 2H) 4.46 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.8, 132.6, 131.6 (2C), 131.5 (q, J_{CF} = 31.1 Hz), 128.8, 128.5, 124.0 (q, J_{CF} = 270.0 Hz), 122.7, 114.3 (q, J_{CF} = 3.5 Hz), 111.2, 110.7 (q, J_{CF} = 4.6 Hz), 96.5, 84.6; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –62.0; IR (thin film): 3459, 3366, 1621, 1331, 1346, 1250, 1169, 1108, 873, 822, 759, 692 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{10}NF_3$ $(M)^+$ 261.0765, found 261.0765.



2.107

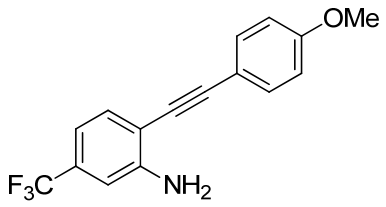
Aniline 2.107. [18] The representative procedure was followed using 0.350 g of $PdCl_2(PPh_3)_2$ (0.5 mmol), 0.038 g of CuI (0.2 mmol), 2.65 g of 2-bromobenzenamine (10.0 mmol), 1.58 g of 1-ethynyl-4-methoxybenzene (12.0 mmol), 60.0 mL THF and 40.0 mL of an 3.0 M solution of ethanolamine (120.0 mmol) in water. Purification by MPLC (1:100 – 5:95 EtOAc: hexanes) afforded the product as a yellow solid (1.48 g, 67%): R_f= 0.42 (14:86 EtOAc: hexane); mp 104 – 105 °C. The spectral data matched that reported by Fujioka and co-workers:[5]

^{1}H NMR (500 MHz, $CDCl_3$): δ 7.47 (d, J = 9.0 Hz, 2H), 7.35 – 7.37 (m, 1H), 7.12 – 7.15 (m, 1H), 6.89 (d, J = 9.0 Hz, 2H), 6.73 (d, J = 8.0 Hz, 2H), 4.26 (s, 2H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.6, 147.7, 133.0 (2C), 132.0, 129.5, 118.0, 115.5, 114.3, 114.1, 108.4, 94.7, 84.5, 55.4; IR (thin film): 3483, 3384, 1611, 1566, 1508, 1489, 1454, 1313, 1287, 1246, 1174, 1106, 1025, 833, 751 cm^{-1}.



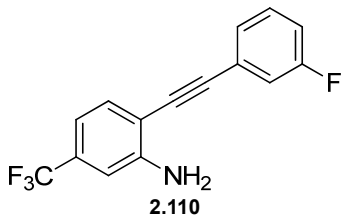
2.108

1-nitro-2-((4-(trifluoromethyl)phenyl)ethynyl)benzene 2.108. [19] The representative procedure was followed using 0.362 g of $PdCl_2(PPh_3)_2$ (0.05 mmol), 0.041 g of CuI (0.02 mmol), 2.23 g of 1-bromo-2-nitrobenzene (1.0 mmol), 2.04 g of 1-ethynyl-4-(trifluoromethyl)benzene (12.0 mmol), 60.0 mL THF and 40.0 mL of an 3.0 M solution of ethanolamine (12.0 mmol) in water. Purification by MPLC (0:100 – 2:98 EtOAc: hexanes) afforded the product as a yellow solid (2.45 g, 92%): R_f = 0.65 (14:86 EtOAc: hexane); mp 46 – 48 °C; The spectral data matched that reported by Yoakim and co-workers: ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.03 (d, J = 8.0 Hz, 1H), 7.61 – 7.64 (m, 3H), 7.53 – 7.57 (m, 3H), 7.42 – 7.45 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.5, 134.7, 133.0, 132.2 (2C), 130.6 (q, J_{CF} = 32.9 Hz), 129.2, 126.2, 125.3 (q, J_{CF} = 3.3 Hz), 124.8, 123.9 (q, J_{CF} = 270.1 Hz), 117.9, 95.1, 87.0; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –63.5; IR (thin film): 1611, 1568, 1532, 1321, 1172, 1128, 1064, 1017, 841, 786, 745, 688, 662, 596 cm^{-1}.



2.109

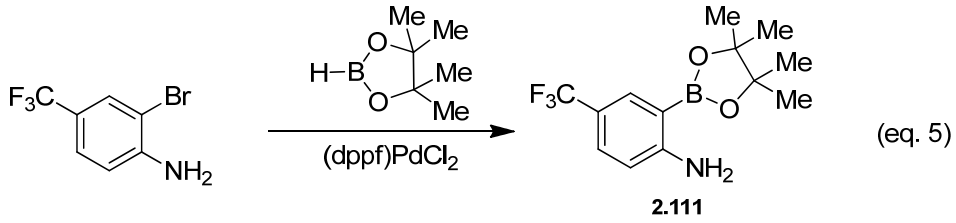
Aniline 2.109. The representative procedure was followed using 0.350 g of $PdCl_2(PPh_3)_2$ (0.5 mmol), 0.038 g of CuI (0.2 mmol), 2.65 g of 2-bromo-5-(trifluoromethyl)benzenamine (10.0 mmol), 1.58 g of 1-ethynyl-4-methoxybenzene (12.0 mmol), 60.0 mL THF, and 40.0 mL of a 3.0 M solution of ethanolamine (120.0 mmol) in water. Purification by MPLC (1:100 – 5:95 EtOAc: hexanes) afforded the product as a yellow solid (1.95 g, 67%): R_f = 0.52 (14:86 EtOAc: hexane); mp 128 – 131 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 –7.49 (m, 2H), 7.42 (d, J = 8.5 Hz, 1H), 6.93 – 6.94 (m, 2H), 6.89 – 6.91 (m, 2H), 4.44 (s, 2H), 3.84 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 160.0, 147.6, 133.1 (2C), 132.4, 131.0 (q, J_{CF} = 32.8 Hz), 124.0, (q, J_{CF} = 270.1 Hz), 114.7, 114.3 (q, J_{CF} = 3.6 Hz), 114.2 (2C), 111.6, 110.6 (q, J_{CF} = 3.5 Hz), 96.6, 83.3, 55.4; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –63.6; IR (thin film): 3465, 3371, 1616, 1500, 1439, 1336, 1246, 1167, 1026, 876, 843, 739, 665 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{16}H_{12}ONF_3$ $(M)^+$ 291.0871, found 291.0870.



2.110

Aniline 2.110. The representative procedure was followed using 0.350 g of $PdCl_2(PPh_3)_2$ (0.5 mmol), 0.038 g of CuI (0.2 mmol), 2.42 g of 2-bromo-5-(trifluoromethyl)benzenamine (10.0 mmol), 1.46 g of 1-ethynyl-3-fluorobenzene (12.0 mmol), 60.0 mL THF and 40.0 mL of a 3.0 M solution of ethanolamine (120.0 mmol) in water. Purification by MPLC (1:100 – 5:95 EtOAc : hexanes) afforded the product as a light yellow powder (2.16 g, 77%): R_f = 0.73 (14:86 EtOAc :

hexane); mp 46 – 48 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.46 (d, J = 8.0 Hz, 1H), 7.34 -7.37 (m, 2H), 7.25 – 7.27 (d, J = 9.0 Hz, 1H), 7.09 – 7.11 (m, 1H), 6.97 – 6.99 (m, 2H), 4.48 (s, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 162.4 (d, J_{CF} = 244.3 Hz), 148.0, 132.7, 131.7 (q, J_{CF} = 32.6 Hz), 130.1 (d, J_{CF} = 8.0 Hz), 127.5, 124.5 (d, J_{CF} = 9.4 Hz), 124.0 (q, J_{CF} = 270.1 Hz), 118.4 (d, J_{CF} = 22.4 Hz), 116.1 (d, J_{CF} = 21 Hz), 114.3 (q, J_{CF} = 3.5 Hz), 110.8 (q, J_{CF} = 3.4 Hz), 110.6, 95.2, 85.5; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –63.8, –112.9; IR (thin film): 3479, 3399, 1620, 1578, 1441, 1341, 1170, 1118, 915, 868, 813, 784, 679 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_9NF_4$ $(M)^+$ 279.0671, found 279.0671.

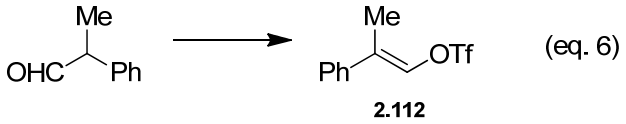


2.111

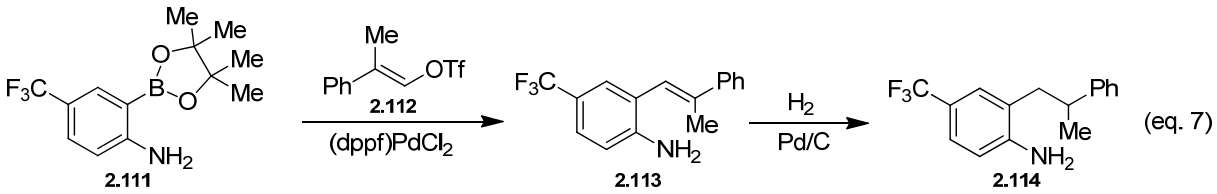
(eq. 5)

Aniline 2.111. To a mixture of 1.19 g of 2-bromo-5-(trifluoromethyl)benzenamine (5.0 mmol), 2.09 mL Et_3N (20.0 mmol), 0.185 g $(dppf)PdCl_2$ (0.25 mmol) in 15 mL 1,4-dioxane, was added dropwise 2.20 mL 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.0 mmol). The resultant mixture was heated to 100 °C. After 5h, the mixture was cooled to room temperature and diluted with 20 mL NH_4Cl. The resulting aqueous phase was extracted with an additional 2 × 20 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, and was concentrated *in vacuo*. Purification via MPLC (0:100 – 2:100 EtOAc:hexanes) afforded the product as a light yellow powder (0.98 g, 66%): R_f = 0.61 (14:86 EtOAc: hexane); mp 46 – 48 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.87 (s, 1H), 7.42 (d, J = 8.5 Hz, 1H), 6.59 (d, J = 8.5 Hz, 1H), 5.11 (s, 2H), 1.36 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.2, 134.2 (q, J_{CF} = 3.6 Hz), 129.5 (q, J_{CF} = 3.1 Hz), 125.1 (q, J_{CF} = 268.3 Hz),

118.4 (q, J_{CF} = 31.3 Hz), 114.2, 84.0, 24.9 (4C); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –61.6; IR (thin film): 3473, 3396, 2979, 2936, 1624, 1570, 1438, 1372, 1246, 1168, 1146, 1084, 962, 854, 817, 747, 679 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{13}H_{17}NO_2BF_3$ $(M)^+$ 287.1304, found 287.1304.



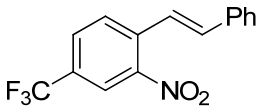
(*E*)-2-phenylprop-1-enyl trifluoromethanesulfonate 2.112. To a mixture of 1.32 mL 2-phenylpropanal (10.0 mmol) and 2.65 mL 2,6-di-*tert*-butylpyridine (12.0 mmol) in 40 mL 1,2-dichloroethane was added 1.85 mL triflatic anhydride (11.0 mmol). The resultant mixture was heated to 70 °C. After 2h, the mixture was cooled to room temperature and diluted with 40 mL CH_2Cl_2. The resulting aqueous phase was extracted with an additional 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, and was concentrated *in vacuo* to afford 2.53 g of crude triflate **2.112**.



Aniline 2.113. To a mixture of 0.919 g of boronic ether **2.111** (3.2 mmol), 0.261 g (dppf)$PdCl_2$ (0.32 mmol) in 40 mL 1,4-dioxane was added 8 mL of a 3M solution of NaOH in water followed by 1.36 g of crude triflate **2.112** (5.12 mmol). The resultant mixture was heated to 80 °C. After 12 h, the mixture was cooled to room temperature and filtrated through a pad of Celite. The filtrate was diluted with 20 mL saturated NH_4Cl and extracted with an additional 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, and was concentrated *in vacuo* to afford 1.32 g

of aniline **2.113**, which was submitted to the subsequent hydrogenation step without further purification.

To a mixture of 1.32 g of aniline **2.113** and 0.540 g of Pd/C (Pd, 10 wt % on carbon powder) in 40 mL of THF was added a balloon of H_2. After 16 h, the reaction mixture was filtered and the resulting filtrate was concentrated *in vacuo*. Purification by MPLC (0:100 – 5:95 EtOAc:hexane) afforded 0.530 g of aniline **2.114** as a yellow oil (1.76 mmol, 59% over two steps). R_f = 0.57 (14:86 EtOAc: hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.19 – 7.31 (m, 7H), 6.64 (d, J = 8.5 Hz, 1H), 3.67 (s, 2H), 3.05 – 3.09 (m, 1H), 2.73 – 2.82 (m, 2H), 1.34 – 1.36 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6, 146.4, 128.6, 128.0 (q, J_{CF} = 2.2 Hz), 126.9, 126.5, 124.9 (q, J_{CF} = 268.3 Hz), 124.6, 124.4 (q, J_{CF} = 3.8 Hz), 120.2 (q, J_{CF} = 32.5 Hz), 115.0, 40.6, 39.4, 21.3; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –61.7. IR (thin film): 3487, 3398, 1628, 1513, 1330, 1146, 1109, 908, 823, 762, 701, 627 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{16}H_{16}NF_3$ $(M)^+$ 279.1235, found 279.1231.



2.115

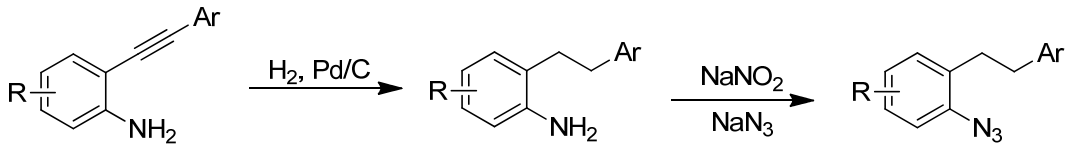
(E)-2-nitro-1-styryl-4-(trifluoromethyl)benzene 2.115. To a mixture of 1.06 g of trans-2-phenylvinylboronic acid (7.0 mmol), 0.582 g of $Pd(PPh_3)_4$ (0.5 mmol) and 3.2 g of K_2CO_3 (4.0 equiv) in 30 mL of PhMe, 12 mL of EtOH, and 6 mL H_2O was added 1.38 g of 1-bromo-2-nitro-4-(trifluoromethyl)benzene (5.0 mmol). The resultant mixture was then purged with N_2 and refluxed. After 24 h, the mixture was cooled to room temperature and diluted with 50 mL of NH_4Cl and 20 mL of CH_2Cl_2. The phases were separated and the resulting aqueous phase was extracted with an additional 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed

with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, and was concentrated *in vacuo*. Purification via MPLC (0:100 – 15:85 EtOAc:hexanes) afforded the product as a yellow oil (1.13 g, 77%): R_f = 0.73 (14:86 EtOAc:hexane); mp 72 – 73 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 8.23 (s, 1H), 7.90 (d, J = 8.0 Hz, 1H), 7.82 (d, J = 9.0 Hz, 1H), 7.46 (d, J = 16 Hz, 1H), 7.55 – 7.57 (m, 2H), 7.35 – 7.42 (m, 3H), 7.18 (d, J = 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.6, 136.4, 136.3, 135.9, 130.1 (q, J_{CF} = 34.8 Hz), 129.4 (q, J_{CF} = 2,8 Hz), 129.3, 129.0, 128.9, 127.4 (2C), 123.0 (q, J_{CF} = 270.8 Hz), 122.3 (q, J_{CF} = 4.5 Hz), 119.7; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –63.3; IR (thin film): 1623, 1566, 1530, 1490, 1328, 1122, 961, 902, 827, 764, 689, 525 cm^{-1}, HRMS (EI) *m / z* calcd for $C_{15}H_{10}O_2NF_3$ $(M)^+$ 293.06636, found 293.06684.

2.8.2 Preparation of 2-Alkyl-Substituted Aryl Azides.

General Procedure for the Preparation of 2-Alkyl-Substituted Aryl Azides.

Unless otherwise noted, the 2-alkyl-substituted aryl azides were synthesized from substituted 2-bromoanilines through a two-step procedure of hydrogenation followed by a diazotization-azidation sequence.[1] (s4). Yields were not optimized.



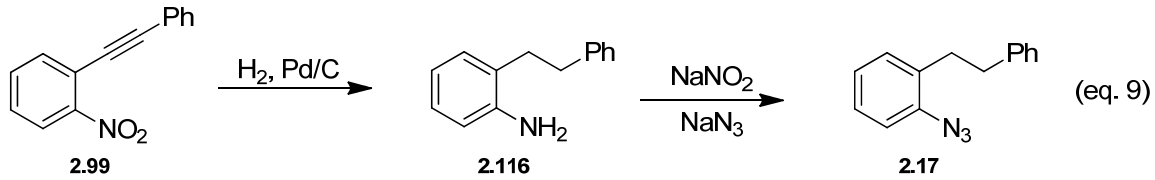
(eq. 8)

A mixture of aniline and Pd/C (Pd, 10 wt % on carbon powder) in THF were vigorously stirred at room temperature under a hydrogen atmosphere. After 20 h, visualization of the

reaction progress using thin layer chromatography indicated consumption of the starting material. The mixture was then filtered through a pad of Celite to afford crude 2-phenethylbenzenamine.

To a cooled mixture (0 °C) of the crude aniline (1.0 equiv) in a 50:50 mixture of AcOH and H_2O (by volume) was added $NaNO_2$ (1.2 equiv). After 2h, NaN_3 (1.4 equiv) was added portionwise to the reaction mixture. The resulting mixture was warmed to room temperature. After 0.5 h, the reaction mixture was diluted with 30 mL of water and 30 mL of CH_2Cl_2. To the resulting biphasic mixture was slowly added Na_2CO_3 until the pH of the solution was seven. The phases were separated, and the resulting aqueous phase was extracted with an additional 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 20 mL of distilled water and 1 × 20 mL of brine. The resulting organic phase was dried over Na_2SO_4 and the heterogeneous mixture was filtered. The filtrate was concentrated *in vacuo*. Purification by MPLC (0:100 – 5:95 EtOAc:hexane) afforded azide.

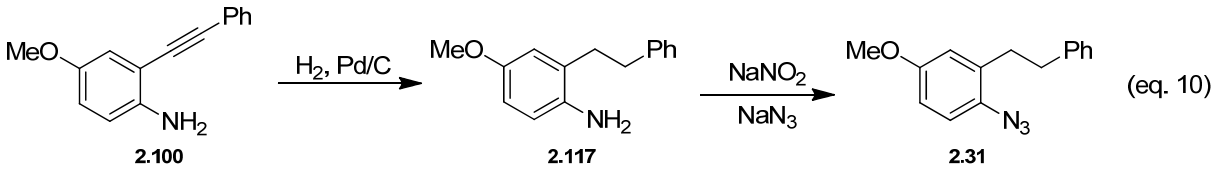
Syntheses of 2-Alkyl-Substituted Aryl Azides.



2.99 **2.116** **2.17**

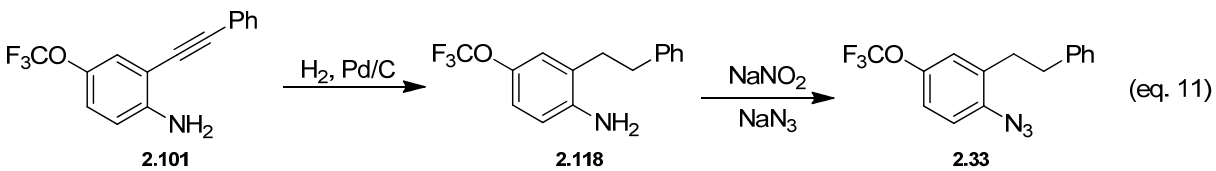
Azide 2.17 [20] The representative hydrogenation procedure was followed using 0.652 g of **2.99** (2.90 mmol) and 0.200 g of Pd/C in 20 mL of THF to afford 0.660 g of aniline **2.116**. The representative procedure for the diazotization-azidation sequence was followed using 0.660 g of the crude aniline (**2.116**, 2.9 mmol), 20.0 mL of acetic acid, 20.0 mL of H_2O, 0.240 g of sodium nitrite (3.48 mmol, 1.2 equiv), and 0.266 g of sodium azide (4.09 mmol, 1.41 equiv). Purification by MPLC (0:100 – 5:95 EtOAc:hexane) afforded azide **2.17** as a yellow liquid (0.414 g, 63%,

two steps): R_f = 0.68 (hexane). The spectral data matched that reported by Murata and co-workers:[7] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.39 (m, 2H), 7.27 – 7.33 (m, 4H), 7.19 – 7.23 (m, 2H), 7.11 – 7.14 (m, 1H), 2.96 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.8, 138.1, 133.3, 130.7, 128.6, 128.4, 127.6, 126.1, 124.8, 118.2, 36.8, 33.9; IR (thin film): 2120, 1580, 1489, 1451, 1285, 750, 698, 653 cm^{-1}.



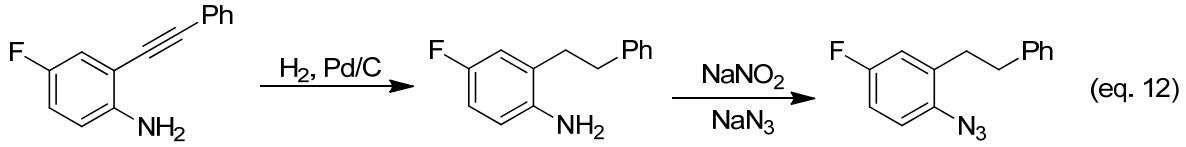
2.100 2.117 2.31 (eq. 10)

Azide 2.31. The representative hydrogenation procedure was followed using 1.291 g of aniline **2.100** (5.79 mmol) and 0.467 g of Pd/C in 40 mL of THF to afford 1.178 g of aniline **2.117**. The representative procedure for the diazotization-azidation sequence was followed using 1.178 g of aniline **2.117** (5.18 mmol), 50 mL of acetic acid, 50 mL of H_2O, 0.454 g of sodium nitrite (6.57 mmol, 1.27 equiv), and 0.498 g of sodium azide (7.67 mmol, 1.48 equiv). Purification via MPLC (0:100 – 5:95 EtOAc:hexane) afforded azide **2.31** as a light yellow liquid (0.981 g, 67%, two steps): R_f = 0.59 (hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.34 (m, 2H), 7.23 – 7.25 (m, 3H), 7.09 (d, J = 9 Hz, 1H), 6.82 (dd, J = 3 Hz, 9 Hz, 1H), 6.69 (d, J = 3 Hz, 1H), 3.77 (s, 3H), 2.88 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.7, 141.7, 134.5, 130.5, 128.5, 128.4, 126.0, 119.1, 116.1, 112.8, 55.5, 36.6, 33.7; IR (thin film): 2119, 1603, 1493, 1452, 1290, 1242, 1157, 1038, 874, 800, 741, 700, 623 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{15}ON_3$ $(M)^+$ 253.1215, found 253.1211.



2.101 2.118 2.33 (eq. 11)

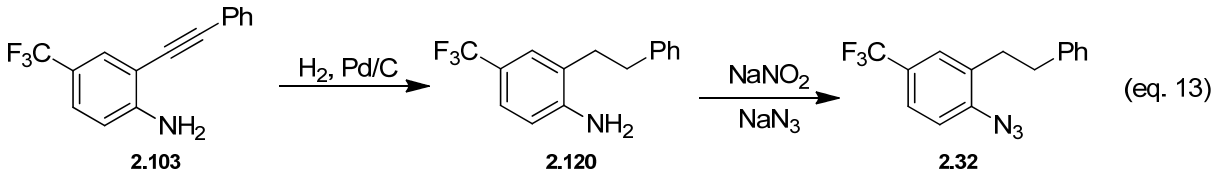
Azide 2.33. The representative hydrogenation procedure was followed using 1.82 g of acetylene **2.101** (6.58 mmol) and 0.620 g of Pd/C in 50 mL of THF to afford 1.760 g of aniline **2.118** (6.26 mmol). The representative procedure for the diazotization-azidation sequence was followed using 1.76 g of aniline **2.101** (6.26 mmol), 50.0 mL of acetic acid, 50.0 mL of H_2O, 0.518 g of sodium nitrite (7.51 mmol, 1.2 equiv), and 0.610 g of sodium azide (9.39 mmol, 1.5 equiv). Purification by MPLC (0:100 – 5:95 EtOAc:hexane) afforded azide **2.33** as a light yellow powder (1.540 g, 76%, two steps): R_f = 0.68 (hexane); mp 65 – 67 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.26 – 7.31 (m, 2H), 7.20 – 7.23 (m, 1H), 7.16 – 7.18 (m, 2H), 7.11 – 7.15 (m, 2H), 6.95 (s, 1H), 2.87 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.6, 141.0, 136.8, 134.9, 128.47, 128.41, 26.2, 123.3, 120.5 (q, J_{CF} = 302.5 Hz), 120.1, 119.1, 36.2, 33.4; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –58.7; IR (thin film): 2128, 2087, 1601, 1493, 1212, 1167, 882, 742, 702 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{12}F_3N_3O$ $(M)^+$ 307.0933, found 307.0933.



2.102 **2.119** **2.34**

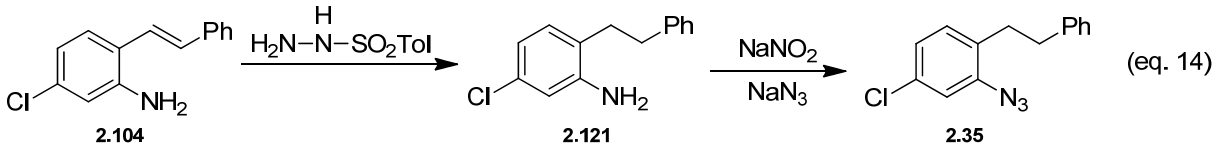
Azide 2.34. The representative hydrogenation procedure was followed using 1.64 g of aniline **2.102** (7.80 mmol) and 0.500 g of Pd/C in 40 mL of THF to afford 1.63 g of aniline **2.119** (7.59 mmol). The representative procedure for the diazotization-azidation sequence was followed using 1.63 g of aniline **2.119** (7.60 mmol), 50.0 mL of acetic acid, 50.0 mL of H_2O, 0.652 g of sodium nitrite (9.12 mmol, 1.20 equiv), and 0.765 g of sodium azide (11.6 mmol, 1.53 equiv). Purification by MPLC (0:100 – 5:95 EtOAc:hexane) afforded azide **2.34** as a yellow oil (1.398 g, 73%, two steps): R_f = 0.70 (hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.24 – 7.27 (m, 2H), 7.12 – 7.18 (m, 3H), 6.99 (dd, *J* = 5 Hz, 9.5 Hz, 1H), 6.88 (dd, *J* = 3 Hz, 8.5 Hz, 1H), 6.78

(dd, J = 3 Hz, 8 Hz, 1H), 2.81 (s, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.8 (d, J_{CF} = 242.4 Hz), 141.3, 135.3 (d, J_{CF} = 7.3 Hz), 133.9, 128.6, 128.5, 126.3, 119.3 (d, J_{CF} = 9.1 Hz), 117.3 (d, J_{CF} = 22.1 Hz), 114.2 (d, J_{CF} = 23.9 Hz), 36.4, 33.5; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –118.4; IR (thin film): 2124, 2085, 1491, 1455, 1300, 1276, 1235, 1156, 1276, 1235, 1156, 873, 807, 751, 699 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{14}H_{12}FN_3$ $(M)^+$ 241.1015, found 241.1016.



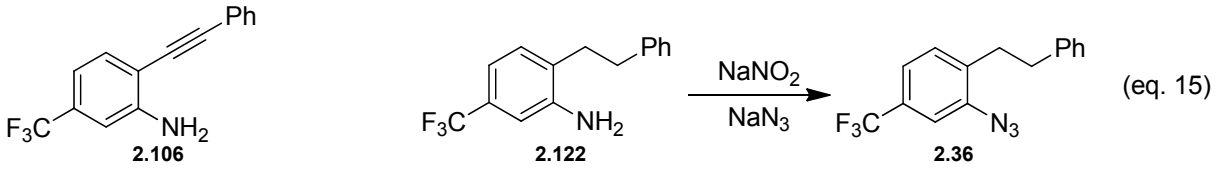
2.103 2.120 2.32 (eq. 13)

Azide 2.32. The representative hydrogenation procedure was followed using 0.987 g of aniline **2.103** (3.78 mmol) and 0.330 g of Pd/C in 40 mL of THF to afford 0.862 g of aniline **2.120**. The representative procedure for the diazotization-azidation sequence was followed using 0.862 g of aniline **2.120** (3.25 mmol), 35.0 mL of acetic acid, 35.0 mL of H_2O, 0.258 g of sodium nitrite (3.96 mmol, 1.22 equiv), and 0.313 g of sodium azide (4.78 mmol, 1.47 equiv). Purification by MPLC (0:100 – 5:95 EtOAc:hexane) afforded azide **2.32** as a light yellow oil (0.836 g, 76%, two steps): R_f = 0.67 (10:90 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (dd, J = 1.5 Hz, 6 Hz, 1H), 7.37 (d, J = 1.5 Hz, 1H), 7.30 – 7.33 (m, 2H), 7.20 – 7.25 (m, 4H), 2.87 – 2.95 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.9, 141.2, 133.9, 128.6, 128.5, 127.6 (q, J_{CF} = 3.4 Hz), 126.8 (q, J_{CF} = 33.0 Hz), 126.3, 124.6 (q, J_{CF} = 3.5 Hz), 124.2 (q, J_{CF} = 259.9 Hz), 118.2, 36.3, 33.4; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –62.7; IR (thin film): 2123, 2080, 1613, 1499, 1331, 1123, 896, 820, 749, 699 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{12}F_3N_3$ $(M)^+$ 291.0983, found 291.0987.



(eq. 14)

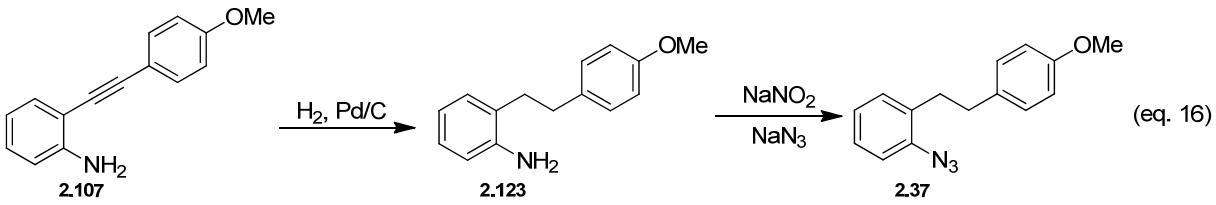
Azide 2.35. The reduction of aniline **2.104** was accomplished using diimide. To a mixture of 0.580 g of aniline **2.104** (2.53 mmol) in 12 mL of ethoxylethanol was added 1.90 g of 4-methylbenzenesulfonohydrazine (10.2 mmol). The mixture was heated to reflux. After 12h, the mixture was cooled to room temperature and concentrated *in vacuo* to afford 0.986 g of crude **2.121**. The representative procedure for the diazotization-azidation sequence was followed using, 0.986 g of crude **2.121,** 20 mL of acetic acid, 20 mL of H_2O, 0.613 g of sodium nitrite (8.88 mmol), and 0.632 g of sodium azide (9.72 mmol) to afford 0.24 g of **2.35** (0.94 mmol, 37%, two steps) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39-7.42 (m, 2H), 7.28-7.34 (m, 3H), 7.21(s, 1H), 7.08 – 7.12 (m, 2H), 2.947 – 2.95 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.4, 139.4, 132.8, 131.7, 131.6, 128.6, 128.5, 126.2, 124.9, 118.3, 36.5, 33.0; IR (thin film): 3377, 1607, 1483, 1452, 1258, 1068, 930, 905, 841, 759, 700, 627 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{14}H_{12}N_3Cl$ $(M)^+$ 257.0720, found 257.0722.



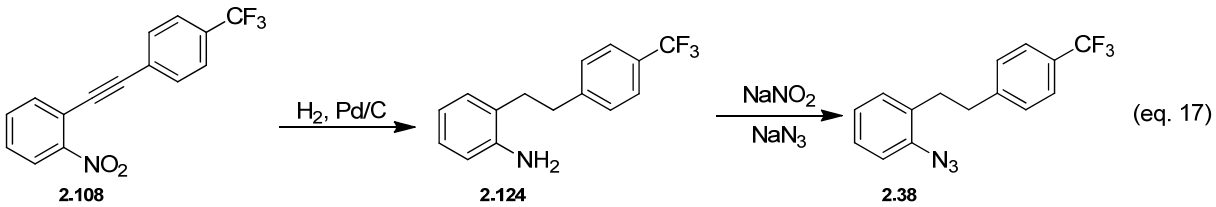
(eq. 15)

Azide 2.36. The representative hydrogenation procedure was followed using 1.37 g of aniline **2.106** (5.24 mmol) and 0.560 g of Pd/C in 40 mL of THF to afford 1.356 g of aniline **2.122** (5.11 mmol). The representative procedure for the diazotization-azidation sequence was followed using 1.36 g of aniline **2.122** (5.11 mmol), 45 mL of acetic acid, 45 mL of H_2O, 0.431 g of sodium nitrite (6.23 mmol, 1.22 equiv), and 0.488 g of sodium azide (7.51 mmol, 1.47 equiv).

Purification via MPLC (0:100 – 2:98 EtOAc:hexane) afforded azide **2.36** as a light yellow oil (1.13 g, 78%, two steps): R_f = 0.75 (hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.37 (s, 1H), 7.29 – 7.32 (m, 3H), 7.18 – 7.24 (m, 4H), 2.92 – 2.95 (m, 2H), 2.86 – 2.89 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 141.1, 139.0, 137.0, 131.1, 130.0 (q, J_{CF} = 31.3 Hz), 128.5, 128.4, 126.2, 123.7 (q, J_{CF} = 269.8 Hz), 121.4 (q, J_{CF} = 3.4 Hz), 114.9 (q, J_{CF} = 3.4 Hz), 36.2, 33.3; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –63.1; IR (thin film): 2176, 2115, 1419, 1330, 1289, 1171, 1079, 899, 824, 749, 699, 656 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{12}F_3N_3$ $(M)^+$ 291.09833, found 291.09817.

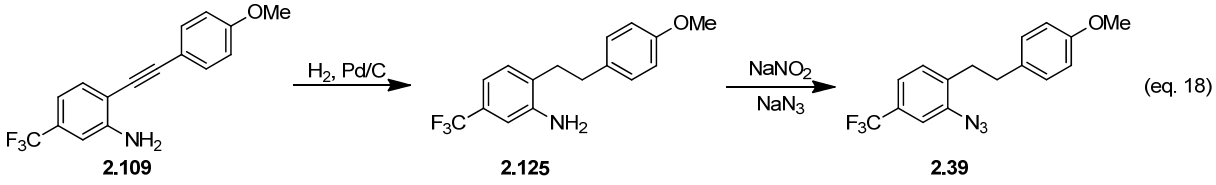


Azide 2.37. The representative hydrogenation procedure was followed using 1.014 g of aniline **2.107** (4.55 mmol) and 0.480 g of Pd/C in 40 mL of THF to afford 0.899 g of aniline **2.123**. The representative procedure for the diazotization-azidation sequence was followed using 0.899 g of aniline **2.123** (3.96 mmol), 40 mL of acetic acid, 40 mL of H_2O, 0.330 g of sodium nitrite (4.79 mmol, 1.21 equiv), and 0.372 g of sodium azide (5.70 mmol, 1.44 equiv). Purification via MPLC (0:100 – 2:98 EtOAc:hexane) afforded azide **2.37** as a yellow solid (0.552 g, 48%, two steps): R_f = 0.50 (14:86 EtOAc:hexane); mp 76 – 77 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 – 7.33 (m, 1H), 7.17 – 7.21 (m, 4H), 7.10 – 7.13 (m, 1H), 6.92 (d, *J* = 8.0 Hz, 2H), 3.85 (s, 3H), 2.90 – 2.91 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.0, 138.1, 133.9, 133.3, 130.7, 129.5, 127.5, 124.8, 118.2, 113.8, 55.3, 35.8, 33.8; IR (thin film): 2125, 1611, 1581, 1512, 1487, 1453, 1285, 1247, 1175, 1085, 1036, 818, 753, 652 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{15}ON_3$ $(M)^+$ 253.12152, found 253.12134



2.108 2.124 2.38

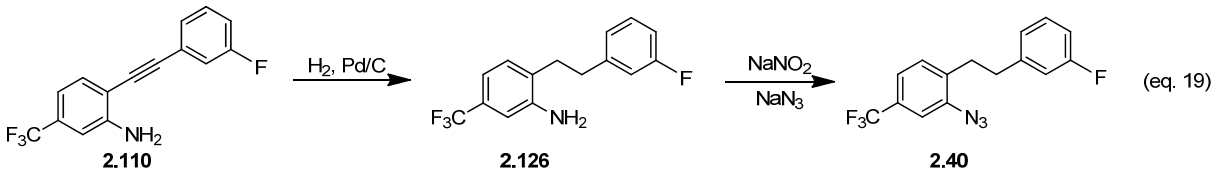
Azide 2.38. The representative hydrogenation procedure was followed using 2.205 g of **2.108** (7.58 mmol) and 0.890 g of Pd/C in 50 mL of THF to afford 2.18 g of aniline **2.124**. The representative procedure for the diazotization-azidation sequence was followed using 1.88 g of aniline **2.124** (7.09 mmol), 50 mL of acetic acid, 50 mL of H_2O, 0.623 g of sodium nitrite (9.03 mmol, 1.29 equiv), and 0.707 g of sodium azide (10.8 mmol, 1.53 equiv). Purification via MPLC (0:100 – 2:98 EtOAc:hexane) afforded azide **2.38** as a yellow liquid (1.70, 77%, two steps): R_f= 0.76 (hexane);^{1}H NMR (500 MHz, $CDCl_3$): δ 7.52 (d, J= 8.5 Hz, 2H),7.25 – 7.28 (m, 3H), 7.14 – 7.15(m, 1H), 7.04 – 7.07 (m, 2H), 2.87 – 2.92 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 145.7, 138.1, 132.4, 130.6, 128.8, 128.3 (q, J_{CF}= 33.8 Hz), 127.8, 125.2 (q, J_{CF}= 3.5 Hz), 124.8, 124.4 (q, J_{CF}= 270.0 Hz), 118.2, 36.4, 33.2; IR (thin film): 2124, 1618, 1582, 1417, 1327, 1287, 1164, 1123, 1068, 1019, 939, 829, 752, 656 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{15}H_{12}N_3F_3$ $(M)^+$ 291.09833, found 291.09794



2.109 2.125 2.39

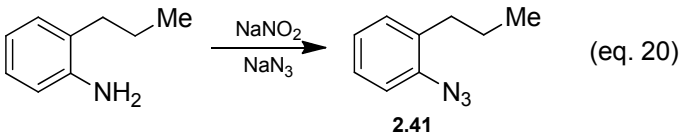
Azide 2.39. The representative hydrogenation procedure was followed using 1.230 g of **2.109** (4.23 mmol) and 0.340 g of Pd/C in 40 mL of THF to afford 1.087 g of aniline **2.125**. The representative procedure for the diazotization-azidation sequence was followed using 1.087 g of aniline **2.125** (3.68 mmol), 35 mL of acetic acid, 35 mL of H_2O, 0.317 g of sodium nitrite (4.6

mmol, 1.25 equiv), and 0.356 g of sodium azide (5.48 mmol, 1.49 equiv). Purification via MPLC (0:100 – 2:98 EtOAc:hexane) afforded azide **2.39** as a light yellow powder (0.747, 55%): R_f = 0.54 (hexane); mp 39 – 41 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.40 (s, 1H), 7.32 (d, J = 8 Hz, 1H), 7.22 (d, J = 8 Hz, 1H), 7.13 (d, J = 8.5 Hz, 2H), 6.88 (d, J = 8.5 Hz, 2H), 3.83 (s, 3H), 2.85 – 2.93 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.1, 139.0, 137.2, 133.1, 131.1, 129.9 (q, J_{CF} = 33.0 Hz), 129.4, 126.0 (q, J_{CF} = 270.0 Hz), 121.4 (q, J_{CF} = 3.3 Hz), 114.9 (q, J_{CF} = 3.4 Hz), 113.8, 55.2, 35.3, 33.6; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –63.0; IR (thin film): 2117, 1612, 1583, 1512, 1419, 1329, 1256, 1173, 1128, 901, 874, 831, 739 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{16}H_{14}F_3ON_3$ $(M)^+$ 321.1089, found 321.1087.



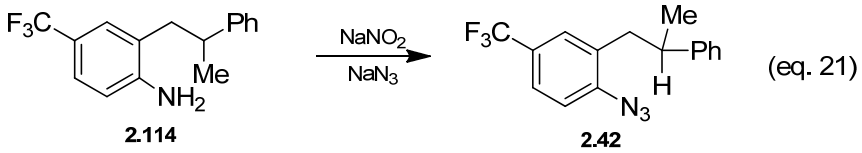
Azide 2.40. The representative hydrogenation procedure was followed using 1.90 g of aniline **2.110** (6.81 mmol) and 0.590 g of Pd/C in 40 mL of THF to afford 1.68 g of aniline **2.126**. The representative procedure for the diazotization-azidation sequence was followed using 1.68 g of aniline **2.126** (5.92 mmol), 60 mL of acetic acid, 60 mL of H_2O, 0.510 g of sodium nitrite (7.40 mmol, 1.25 equiv), and 0.566 g of sodium azide (8.70 mmol, 1.47 equiv). Purification via MPLC (0:100 – 2:98 EtOAc:hexane) afforded azide **2.40** as a light yellow oil (1.33 g, 63%, two steps): R_f = 0.65 (hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (s, 1H), 7.40 – 7.42 (d, J = 8 Hz, 1H), 7.30 – 7.38 (m, 2H), 7.07 (d, J = 7.5 Hz, 1H), 7.00 – 7.03 (m, 2H), 2.97 – 3.05 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.0 (d, J_{CF} = 243 Hz), 143.7 (d, J_{CF} = 7.3 Hz), 139.1, 136.6, 131.0, 130.2 (q, J_{CF} = 33 Hz), 129.9 (d, J_{CF} = 7.6 Hz), 124.2, 123.4 (q, J_{CF} = 270 Hz), 121.4 (q, J_{CF} = 3.4 Hz), 115.3 (d, J_{CF} = 21.4 Hz), 115.0 (q, J_{CF} = 3.5 Hz), 113.1 (d, J_{CF} = 20 Hz), 35.8, 33.0; ^{19}F

NMR ($CDCl_3$, 282 MHz) δ –63.1, –113.8; IR (thin film): 2117, 1616, 1587, 1489, 1419, 1329, 1267, 1173, 1128, 899, 783, 739, 658 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{11}N_3F_4$ $(M)^+$ 309.0889, found 309.0891.



2.41 (eq. 20)

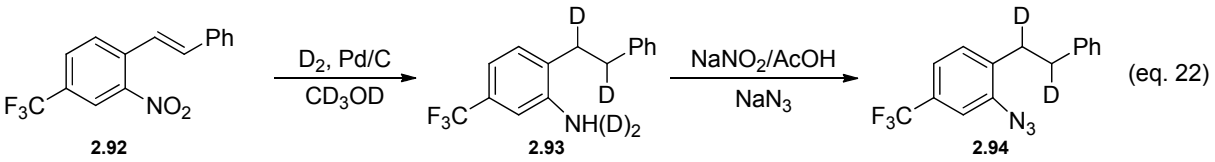
Azide 2.41.[21] The representative procedure for the diazotization-azidation sequence was followed using 1.351 g of 2-*n*-propyl-aniline (10 mmol), 40 mL of acetic acid, 40 mL of H_2O, 0.845 g of sodium nitrite (12.2 mmol, 1.22 equiv), and 0.955 g of sodium azide (14.7 mmol, 1.47 equiv). Purification via MPLC (0:100 – 2:98 EtOAc:hexane) afforded azide **2.41** as a brown liquid (1.143 g, 71%): R_f= 0.89 (hexane); Azide **2.41** was previously reported by Sundberg and co-workers:[8] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.25 – 7.28 (m, 1H), 7.15 – 7.20 (m, 2H), 7.08 – 7.11(m, 1H), 2.59 (t, *J*= 7.5 Hz, 2H), 1.64 (td, *J*= 10.Hz, *J*= 7.5 Hz, 2H), 0.99 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 138.0, 134.2, 130.5, 127.2, 124.6, 118.1, 33.3, 23.5, 14.0; IR (thin film): 2122, 1582, 1489, 1450, 1285, 1450, 1107, 750, 653 cm^{-1}.



2.114 2.42 (eq. 21)

Azide 2.42. The representative procedure for the diazotization-azidation sequence was followed using 0.589 g of aniline **2.114** (2.1 mmol), 25 mL of acetic acid, 25 mL of H_2O, 0.192 g of sodium nitrite (2.78 mmol, 1.32 equiv), and 0.196 g of sodium azide (3.06 mmol, 1.45 equiv). Purification via MPLC (0:100 – 2:98 EtOAc:hexane) afforded azide **2.42** as a yellow liquid (0.381 g, 59%): R_f= 0.89 (hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 – 7.50 (m, 1H), 7.29 –

7.32 (m, 2H), 7.18 – 7.23 (m, 5H), 3.03 – 3.10 (m, 1H), 2.84 – 2.92 (m, 2H), 1.29 – 1.30 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 146.0, 141.8, 132.9, 128.3 (2C), 127.2, 127.0 (2C), 126.4 (q, J_{CF} = 33.0 Hz) 126.3, 124.4, 123.9 (q, J_{CF} = 267.0 Hz), 118.1, 40.3, 40.2, 20.9; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –62.9. IR (thin film): 2123, 1616, 1500, 1421, 1335, 1294, 1167, 1122, 1082, 906, 773, 750, 700 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{16}H_{14}N_3F_3$ $(M)^+$ 305.11398, found 305.11363.



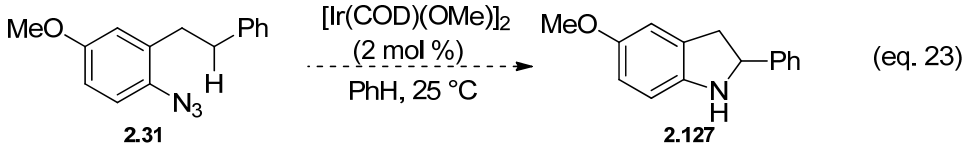
2.92 2.93 2.94 (eq. 22)

Azide 2.94. The hydrogenation procedure was followed using 0.345 g of aniline **2.92** (1.18 mmol) and 0.120 g of Pd/C in 20 mL of THF. The mixture was vigorously stirred at room temperature under a D_2 for 12h. Purification via MPLC (0:100 – 2:98 EtOAc:hexane) afforded aniline **2.93** as a light yellow oil (0.246 g, 79%): R_f = 0.64 (14:86 EtOAc:hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35-7.38 (m, 2H), 7.24-7.31 (m, 3H), 7.16(d, *J* = 8.0 Hz, 1H), 7.03 (d, *J* = 8.0 Hz, 1H), 6.92 (s, 1H), 3.69 (s, 1.74), 2.96 – 2.99 (m, 1.27H), 2.83 – 2.86 (m, 1.26H); ^{13}C NMR (125 MHz, CDCl3): δ 144.6, 131.3, 129.9, 129.4 (q, J_{CF} = 32.6 Hz), 128.7, 128.5, 126.4, 124.5 (q, J_{CF} = 269.9 Hz), 115.3 (q, J_{CF} = 4.5 Hz), 112.0 (q, J_{CF} = 4.8 Hz), 34.5 (J_{CD} = 19.1 Hz), 32.8 (J_{CD} = 19.3 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –62.9.

The representative procedure for the diazotization-azidation sequence was followed using 0.246 g of aniline **2.93** (0.94 mmol), 10 mL of acetic acid, 10 mL of H_2O, 0.071 g of sodium nitrite (1.2 mmol, 1.25 equiv), and 0.092 g of sodium azide (1.42 mmol, 1.51 equiv). Purification via MPLC (0:100 – 2:98 EtOAc:hexane) afforded azide **2.94** as a light yellow oil (0.176 g, 65%): R_f = 0.74 (hexane); ^{1}H NMR (500 MHz, $CDCl_3$):^{1}H NMR (500 MHz, $CDCl_3$): δ

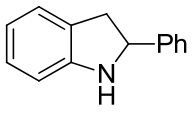
7.37 (s, 1H), 7.29 – 7.32 (m, 3H), 7.18 – 7.24 (m, 4H), 2.86 – 2.93 (m, 2.58H); ^{13}C NMR (125 MHz, CDCl3): δ 141.0, 139.0, 137.0, 131.1, 130.0 (q, J_{CF} = 32.8 Hz), 128.5, 128.4, 126.2, 125.9 (q, J_{CF} = 270.2 Hz), 121.4 (q, J_{CF} = 3.6 Hz), 114.9 (q, J_{CF} = 3.5 Hz), 35.7 (J_{CD} = 18.9 Hz), 32.9 (J_{CD} = 20.0 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –63.0.

2.8.3 Scope and Limitations of Ir(I)-Catalyzed Indoline Formation.



2.31 2.127 (eq. 23)

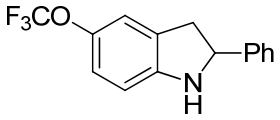
Indoline 2.97. The general procedure was followed with 0.078 g of azide **2.31** (4.0 mmol) and 0.005 g of $[(cod)IrOMe]_2$ (0.08 mmol) in 0.51 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, analysis of the resulting oil using ^{1}H NMR spectroscopy showed only azide **2.123**.



2.19

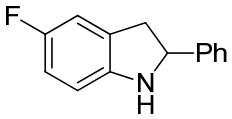
Indoline 2.19. The general procedure was followed with 0.062 g of azide **2.17** (0.278 mmol) and 0.004 g of $[(cod)IrOMe]_2$ (0.006 mmol) in 0.52 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, analysis of the resulting oil using ^{1}H NMR spectroscopy showed 58% formation of **2.19**. Purification by MPLC (0:100 – 1:100 EtOAc:hexanes) afforded indoline (0.017 g, 31%) and indole (0.011 g, 21%). Characterization data for indoline **2.19**: R_f = 0.62 (14:86 EtOAc: hexane); mp 45 – 46 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.48 (d, J = 7.0 Hz, 2H), 7.39 – 7.42 (m, 2H), 7.32 – 7.35 (m, 1H), 7.12 – 7.16 (m, 2H), 6.79 – 6.82 (m, 1H), 6.72 (d, J = 8.0 Hz, 1H), 4.99 (t, J = 9.0 Hz, 1H), 4.16 (s, 1H), 3.49 (dd, J = 9.0 Hz, 15.5 Hz, 1H), 3.04 (dd, J = 9.0 Hz, 15.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$):

δ 151.1, 144.7, 128.7, 128.2, 127.7, 127.5, 126.4, 124.7, 118.9, 108.9, 63.6, 39.7; IR (thin film): 3369, 3028, 1609, 1483, 1466, 1400, 1360, 1321, 1248, 748, 700, 634, 544 cm^{-1}.



2.128

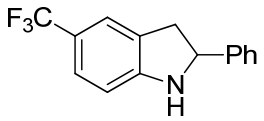
Indoline 2.128. The general procedure was followed with 0.092 g of azide **2.33** (0.30 mmol) and 0.004 g of $[(cod)IrOMe]_2$ (0.006 mmol) in 0.50 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, analysis of the resulting oil using ^1H NMR spectroscopy showed 75% formation of **2.128**. Purification by MPLC (0:100 – 1:100 EtOAc:hexanes) afforded indoline (0.043 g, 51%) and indole (0.016 g, 21%). Characterization data for indoline **2.128**: R_f = 0.66 (14:86 EtOAc: hexane); mp 65 – 67 °C; ^1H NMR (500 MHz, $CDCl_3$): δ 7.44 – 7.46 (m, 2H), 7.38 – 7.42 (m, 2H), 7.33 – 7.36 (m, 1H), 6.98 (m, 2H), 6.61 (d, J = 8.0 Hz, 1H), 5.02 (t, J = 9.0 Hz, 1H), 4.17 (s, 1H), 3.47 (dd, J = 9.0 Hz, 16.0 Hz, 1H), 3.02 (dd, J = 9.0 Hz, 16.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 149.8, 144.1, 141.8, 129.5, 128.8, 127.7, 126.3, 120.8 (q, J_{CF} = 253.4 Hz), 120.7, 118.4, 108.5, 64.1, 39.5; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –58.9; IR (thin film): 3381, 1615, 1490, 1453, 1271, 1162, 1046, 961, 817, 759, 701, 669 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{12}ONF_3$ $(M)^+$ 279.08710, found 279.08759.



2.129

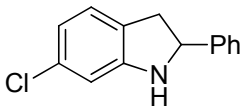
Indoline 2.129. The general procedure was followed with 0.109 g of azide **2.34** (0.452 mmol) and 0.006 g of $[(cod)IrOMe]_2$ (0.009 mmol) in 0.50 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, analysis of the resulting oil using ^1H NMR spectroscopy showed 72% formation of **2.99**. Purification by MPLC (0:100 – 1:100

EtOAc:hexanes) afforded indoline (0.046 g, 48%) and indole (0.017 g, 18%). Characterization data for indoline **2.129**: R_f = 0.66 (14:86 EtOAc: hexane); mp 49 – 50 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.42 – 7.44 (m, 2H), 7.35 – 7.38 (m, 2H), 7.29 – 7.32 (m, 1H), 6.76 – 6.85 (m, 2H), 6.56 – 6.59 (m, 1H), 4.97 (t, *J* = 9.0 Hz, 1H), 4.04 (s, 1H), 3.43 (dd, *J* = 9.5 Hz, 16.5 Hz, 1H), 2.99 (dd, *J* = 8.5 Hz, 16.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 157.1 (d, J_{CF} = 234.1 Hz), 147.0, 144.3, 129.8 (d, J_{CF} = 7.8 Hz), 128.7, 127.6, 126.3, 113.4 (d, J_{CF} = 23.4 Hz), 112.2 (d, J_{CF} = 23.4 Hz), 109.0 (d, J_{CF} = 7.8 Hz), 64.2, 39.7; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –126.6; IR (thin film): 3370, 1488, 1449, 1227, 1207, 1124, 861, 807, 760, 701, 556 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{14}H_{12}NF$ $(M)^+$ 213.0954, found 213.0953.



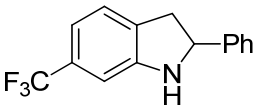
2.130

Indoline 2.130. The general procedure was followed with 0.075 g of azide **2.32** (0.258 mmol) and 0.004 g of $[(cod)IrOMe]_2$ (0.005 mmol) in 0.50 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, analysis of the resulting oil using ^{1}H NMR spectroscopy showed 91% formation of **2.130**. Purification by MPLC (0:100 – 1:100 EtOAc:hexanes) afforded indoline (0.041 g, 60%) and indole (0.015 g, 21%). Characterization data for indoline **2.130**: R_f = 0.68 (14:86 EtOAc: hexane); mp 81 – 82 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.42 (m, 7H), 6.65 (d, *J* = 8.0 Hz, 1H), 5.04 (t, 9.0 Hz, 1H), 4.40 (s, 1H), 3.50 (dd, *J* = 9.5 Hz, 16.0 Hz, 1H), 3.02 (dd, 8.5 Hz, 16.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.8, 144.0, 128.8, 128.2, 127.9, 126.2, 125.6 (q, J_{CF} = 3.6 Hz), 124.0, 121.7 (q, J_{CF} = 3.5 Hz), 120.4 (q, J_{CF} = 31.6 Hz), 107.4, 63.5, 39.0; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –61.2; IR (thin film): 3383, 1622, 1502, 1416, 1327, 1294, 1263, 1149, 1107, 1059, 889, 822, 762, 702, 644, 613, 573 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{12}NF_3$ $(M)^+$ 263.0922, found 263.0921.



2.131

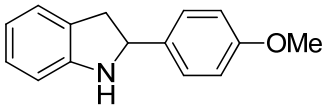
Indoline 2.131. The general procedure was followed with 0.091 g of azide **2.35** (0.35 mmol) and 0.005 g of $[(cod)IrOMe]_2$ (0.007 mmol) in 0.52 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, analysis of the resulting oil using ^{1}H NMR spectroscopy showed 81% formation of **2.131**. Purification by MPLC (0:100 – 1:100 EtOAc:hexanes) afforded indoline (0.042 g, 52%) and indole (0.015 g, 19%). Characterization data for indoline **2.131**: R_f = 0.66 (14:86 EtOAc: hexane); mp 62 – 64°C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.34 – 7.41 (m, 4H), 7.29 – 7.31 (m, 1H), 6.97 (d, *J* = 7.5 Hz, 1H), 6.69 (d, 8.0 Hz, 1H), 6.63 (s, 1H), 4.98 (t, *J* = 9.0 Hz, 1H), 4.19 (s, 1H), 3.42 (dd, *J* = 9.5 Hz, 16.0 Hz, 1H), 2.94 (dd, *J* = 8.5 Hz, 15.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 152.2, 144.2, 128.7, 127.6, 126.5, 126.2, 125.3, 118.4, 108.8, 63.9, 38.9; IR (thin film): 3377, 1607, 1483, 1452, 1258, 1068, 1045, 930, 841, 795, 700, 627, 541 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{14}H_{12}NCl$ $(M)^+$ 229.06582, found 229.06537.



2.71

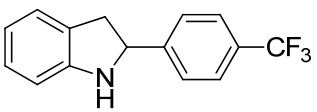
Indoline 2.71. The general procedure was followed with 0.087 g of azide **2.36** (0.299 mmol) and 0.004 g of $[(cod)IrOMe]_2$ (0.006 mmol) in 0.50 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, analysis of the resulting oil using ^{1}H NMR spectroscopy showed 93% formation of **2.71**. Purification by MPLC (0:100 – 1:100 EtOAc:hexanes) afforded indoline (0.053 g, 60%) and indole (0.017 g, 22%). Characterization data for indoline **2.71**: R_f = 0.67 (14:86 EtOAc: hexane); mp 75 – 76 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.41 – 7.43 (m, 2H), 7.36 – 7.39 (m, 2H), 7.30 – 7.33 (m, 1H), 7.15 (d, *J* = 7.5 Hz,

1H), 7.00 (d, J = 7.5 Hz, 1H), 6.85 (s, 1H), 5.02 (t, J = 9.0 Hz, 1H), 4.30 (s, 1H), 3.50 (dd, J = 9.0 Hz, 16.0 Hz, 1H), 3.04 (dd, J = 8.5 Hz, 16.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.3, 144.0, 132.0, 130.0 (q, J_{CF} = 31.5 Hz), 128.8, 127.7, 126.2, 124.6 (q, J_{CF} = 270.5 Hz), 124.5, 115.7 (q, J_{CF} = 3.6 Hz), 104.8 (q, J_{CF} = 3.5 Hz), 63.6, 39.3; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –62.8; IR (thin film): 3381, 1618, 1454, 1338, 1321, 1267, 1161, 1115, 1045, 930, 860, 816, 762, 700 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{12}NF_3$ $(M)^+$ 263.09218, found 263.09216.



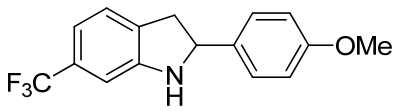
2.132

Indoline 2.132. The general procedure was followed with 0.098 g of azide **2.37** (0.387 mmol) and 0.005 g of $[(cod)IrOMe]_2$ (0.008 mmol) in 0.50 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, analysis of the resulting oil using ^{1}H NMR spectroscopy showed 53% formation of **2.132**. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded indoline (0.036 g, 41%) and indole (0.016 g, 18%). Characterization data for indoline **2.132**: R_f = 0.68 (14:86 EtOAc: hexane); mp 48 – 49 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.35 (d, J = 8.5 Hz, 2H), 7.06 – 7.11 (m, 2H), 6.88 (d, J = 8.5 Hz, 2H), 6.73 – 6.76 (m, 1H), 6.67 (d, J = 7.5 Hz, 1H), 4.91 (t, J = 9.0 Hz, 1H), 4.11 (s, 1H), 3.81 (s, 3H), 3.41 (dd, J = 9.0 Hz, 15.5 Hz, 1H), 2.97 (dd, J = 9.0 Hz, 15.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.0, 151.0, 136.7, 128.2, 127.55, 127.47, 124.6, 118.8, 114.0, 108.8, 63.1, 55.4, 39.7; IR (thin film): 3364, 3010, 2834, 1609, 1152, 1485, 1291, 1246, 1175, 1035, 830, 748, 699, 605 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{15}H_{15}NO$ $(M)^+$ 225.1154, found 225.1152.



2.72

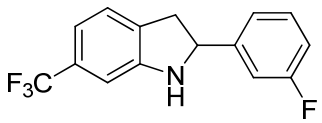
Indoline 2.72. The general procedure was followed with 0.077 g of azide **2.38** (0.265 mmol) and 0.004 g of $[(cod)IrOMe]_2$ (0.005 mmol) in 0.50 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, analysis of the resulting oil using ^{1}H NMR spectroscopy showed 29% formation of **2.72**. Purification by MPLC (0:100 – 1:100 EtOAc:hexanes) afforded indoline (0.013 g, 19%) and indole (0.028 g, 41%). Characterization data for indoline **2.72**: R_f = 0.63 (14:86 EtOAc: hexane); mp 63 – 65 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.63 (d, J = 8.0 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.11 – 7.14 (m, 2H), 6.79 – 6.82 (m, 1H), 6.73 (d, J = 8.0 Hz, 1H), 5.04 (t, J = 9.0 Hz, 1H), 4.19 (s, 1H), 3.51 (dd, J = 9.5 Hz, 15.5 Hz, 1H), 2.97 (dd, J = 9.0 Hz, 15.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 150.8, 148.7, 129.6 (q, J_{CF} = 32.9 Hz), 127.8, 127.6, 126.7, 125.6 (q, J_{CF} = 3.0 Hz), 124.7, 124.3(q, J_{CF} = 270.0 Hz), 119.2, 109.1, 63.1, 39.7; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –62.9; IR (thin film): 3364, 3051, 1609, 1485, 1465, 1418, 1235, 1164, 1123, 1067, 929, 836, 749, 697 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{12}NF_3$ $(M)^+$ 263.0922, found 263.0921.



2.133

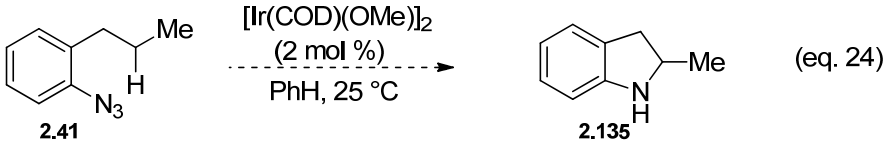
Indoline 2.133. The general procedure was followed with 0.087 g of azide **2.39** (0.271 mmol) and 0.004 g of $[(cod)IrOMe]_2$ (0.005 mmol) in 0.50 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, analysis of the resulting oil using ^{1}H NMR spectroscopy showed 81 % formation of **2.133**. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded indoline (0.044 g, 55%) and indole (0.016 g, 20%). Characterization data for indoline **2.133**: R_f = 0.68 (14:86 EtOAc: hexane); mp 62 – 63 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 (d, J = 9.0 Hz, 2H), 7.13 (d, J = 7.5 Hz, 1H), 6.96 (d, J = 7.5 Hz, 1H), 6.87 (d, J = 8.5 Hz, 2H), 6.81 (s, 1H), 4.96 (t, J = 9.0 Hz, 1H), 4.24 (s, 1H), 3.80 (s, 3H), 3.43 (dd, J = 9.5 Hz,

16.0 Hz, 1H), 2.97 (dd, J = 8.5 Hz, 16.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 159.2, 151.2, 136.0, 132.1, 130.0 (q, J_{CF} = 31.4 Hz), 127.4, 124.6 (q, J_{CF} = 271.3 Hz), 124.5, 115.7 (q, J_{CF} = 3.5 Hz), 114.1, 104.8 (q, J_{CF} = 3.5 Hz), 63.2, 55.4, 39.3; ^{19}F NMR ($CDCl_3$, 282 MHz) δ -62.8; IR (thin film): 3377, 1614, 1513, 1457, 1323, 1249, 1161, 1117, 1036, 930, 830, 737, 700 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{16}H_{14}NOF_3$ $(M)^+$ 293.10275, found 293.10279.



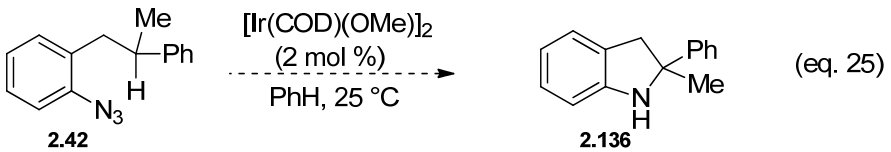
2.134

Indoline 2.134. The general procedure was followed with 0.088 g of azide **2.40** (0.285 mmol) and 0.004 g of $[(cod)IrOMe]_2$ (0.006 mmol) in 0.50 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, analysis of the resulting oil using ^{1}H NMR spectroscopy showed 85% formation of **2.134**. Purification by MPLC (0:100 – 1:100 EtOAc:hexanes) afforded indoline (0.048 g, 60%) and indole (0.016 g, 20%). Characterization data for indoline **2.134**: R_f = 0.63 (14:86 EtOAc: hexane). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31 – 7.35 (m, 1H), 7.14 – 7.19 (m, 3H), 6.98 – 7.01 (m, 2H), 6.86 (s, 1H), 5.02 (t, J_{CF} = 9.0 Hz, 1H), 4.31 (s, 1H), 3.50 (dd, J = 9.5 Hz, 16.0 Hz, 1H), 2.98 (dd, J = 8.5 Hz, 16.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.1 (d, J_{CF} = 245.8Hz), 151.1, 146.7 (d, J_{CF} = 7.3Hz), 131.7, 130.3 (d, J_{CF} = 7.3 Hz), 130.2 (q, J_{CF} = 31.3Hz), 124.6, 124.5 (q, J_{CF} = 269.9 Hz), 121.8, 116.0 (q, J_{CF} = 3.4 Hz), 114.5 (d, J_{CF} = 22.0 Hz), 113.1 (d, J_{CF} = 22.0 Hz), 105.0 (q, J_{CF} = 2.8 Hz), 63.1, 39.3; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –62.8, –112.7; IR (thin film): 3403, 3063, 1617, 1592, 1489, 1455, 1337, 1323, 1268, 1163, 1053, 922, 866, 822, 786, 738, 694, 660 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{11}NF_4$ $(M)^+$ 281.08276, found 281.08266.



2.41 2.135 (eq. 24)

Indoline 2.135. The general procedure was followed with 0.122 g of azide **2.41** (0.757 mmol) and 0.010 g of $[(cod)IrOMe]_2$ (0.015 mmol) in 0.54 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, analysis of the resulting oil using ^1H NMR spectroscopy showed only starting material.

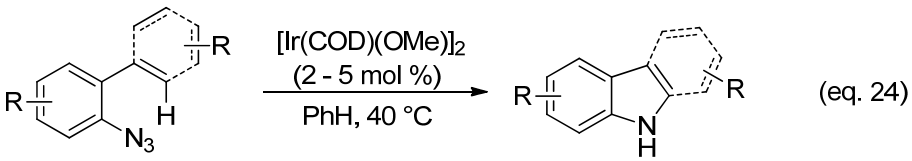


2.42 2.136 (eq. 25)

Indoline 2.136. The general procedure was followed with 0.077 g of azide **2.42** (0.324 mmol) and 0.004 g of $[(cod)IrOMe]_2$ (0.004 mmol) in 0.50 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, analysis of the resulting oil using ^1H NMR spectroscopy showed only starting material.

2.8.4 Comparison of Reactivity Between Rh_2(II)-Complexes and Ir(I) for the Synthesis of Aromatic *N*-Heterocycles

General Procedure for Ir(I)-Mediated Aromatic *N*-Heterocycle Formation.

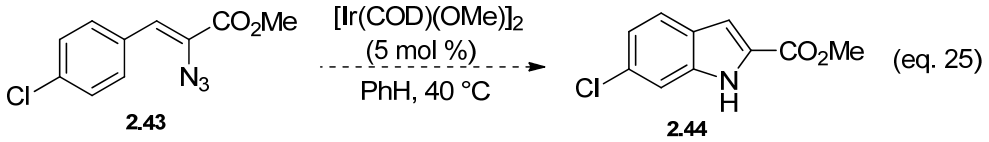


2.137 2.138 (eq. 24)

To 0.090 g of the aryl azide **2.137** (0.311 mmol) in a Schlenk tube inside a glove box was added 0.003 g of $[(cod)Ir(OMe)]_2$ (2 mol %) followed by the addition of 0.34 mL of benzene. The resulting mixture was heated to 40 °C. After 12 h, the reaction mixture was cooled to room temperature, and the heterogenous mixture was filtered through SiO_2. The filtrate was

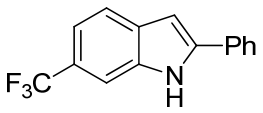
concentrated *in vacuo*. Purification via MPLC (0:100 – 10:90 EtOAc:hexanes) provided indole **2.138** as a white solid.

Scope and Limitations of Ir(I)-Mediated Aromatic N-Heterocycle Formation.



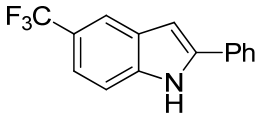
2.43 **2.44**

Indole 2.44. The general procedure was followed with 0.030 g of azide **2.43** (0.127 mmol) and 0.004 g of $[(cod)IrOMe]_2$ (0.006 mmol) in 0.42 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, ^{1}H NMR spectroscopy showed only starting material.



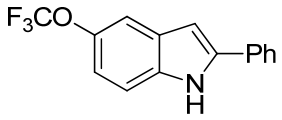
2.46

Indole 2.46[22]**.** The general procedure was followed with 0.090 g of azide **2.45** (0.311 mmol), 0.004 g of $[(cod)Ir(OMe)]_2$ (2 mol %) in 1.04 mL of benzene. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded indole **2.46** as a white solid (0.067 g, 83%). The spectral data matched that reported by Buchwald and co-workers:[10] ^{1}H NMR (DMSO-d_6, 500 MHz) δ 12.00 (br s, 1H), 7.89 (d, J = 7.3 Hz, 2H), 7.71 (d, J = 8.3 Hz, 1H), 7.68 (s, 1H), 7.49 (t, J = 7.7 Hz, 2H), 7.36 (t, J = 7.4 Hz, 1H), 7.27 (d, J = 8.3 Hz, 1H), 7.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 140.9, 135.8, 131.4, 131.2, 129.1, 128.3, 125.5, 125.4 (q, J_{CF} = 269.4 Hz), 121.7 (q, J_{CF} = 31.1 Hz), 120.8, 115.7 (q, J_{CF} = 2.3 Hz), 108.4 (q, J_{CF} = 5.0 Hz), 99.0; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –59.5; IR (thin film): 3442, 1456, 1344, 1167, 1155, 1281, 1105, 829, 766, 742, 690 cm^{-1}.



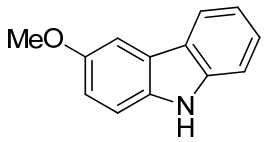
2.48

Indole 2.48[22]. The general procedure was followed with 0.087 g of azide **2.47** (0.301 mmol), 0.004 g of $[(cod)Ir(OMe)]_2$ (2 mol %) in 1 mL of benzene. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded indole **2.48** as a white solid (0.072 g, 91%). The spectral data matched that reported by Buchwald and co-workers:[10] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 12.04 (br s, 1H), 7.94 – 7.91 (m, 3H), 7.61 (d, J = 8.4 Hz, 1H), 7.51 (t, J = 7.8 Hz, 2H), 7.42 – 7.38 (m, 2H), 7.08 (s, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.9, 139.4, 138.6, 131.5, 129.0, 128.1, 127.9, 125.6 (q, J_{CF} = 269.4 Hz), 125.3, 120.3 (q, J_{CF} = 31.1 Hz), 118.0 (q, J_{CF} = 3.5 Hz), 117.6 (q, J_{CF} = 3.3 Hz), 112.0, 99.5; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –59.2; IR (thin film): 3431, 1448, 1340, 1168, 1103, 1057, 895, 820, 767, 747, 688 cm^{-1}.



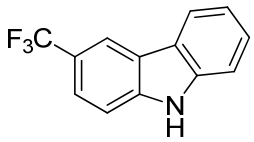
2.50

Indole 2.50. The general procedure was followed with 0.075 g of azide **2.49** (0.245 mmol), 0.003 g of $[(cod)Ir(OMe)]_2$ (2 mol %) in 0.82 mL of benzene. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded indole **2.50** as a white solid (0.064 g, 95%). The spectral data matched that reported by Driver and co-workers:[2] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.83 (br s, 1H), 7.85 (dd, J = 8.3 Hz, 1.1 Hz, 2H), 7.46 (td, J = 8.1 Hz, 3.9 Hz, 4H), 7.34 (t, J = 7.4 Hz, 1H), 7.05 (dd, J = 8.7 Hz, 1.3 Hz, 1H), 6.95 (d, J = 1.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 142.5, 140.4, 136.0, 132.1, 129.5, 129.2, 128.4, 125.7, 121.0 (q, J_{CF} = 253.8 Hz), 115.6, 112.8, 112.6, 99.6; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –57.5; IR (thin film): 3428, 1456, 1306, 1213, 1151, 879, 764, 739, 688 cm^{-1}.



2.52

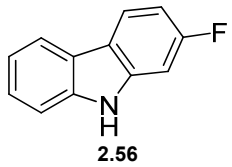
Carbazole 2.52[23]**.** The general procedure was followed with 0.077 g of azide **2.51** (0.342 mmol), 0.011 g of $[(cod)Ir(OMe)]_2$ (5 mol%) in 1.14 mL of benzene. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded carbazole **2.52** as a white solid (0.049 g, 73%). The spectral data matched that reported by Bedford and co-workers:[11] ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.01 (br s, 1H), 8.07 (dd, J = 7.8 Hz, 0.5 Hz, 1H), 7.65 (d, J = 2.5 Hz, 1H), 7.41 (dt, J = 8.1 Hz, 0.8 Hz, 1H), 7.37-7.31 (m, 2H), 7.09 (ddd, J = 7.9 Hz, 7.0 Hz, 0.9 Hz, 1H), 7.00 (dd, J = 8.7 Hz, 2.5 Hz, 1H), 3.82 (s, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 153.4, 140.8, 135.0, 125.8, 123.2, 122.9, 120.7, 118.4, 115.2, 112.1, 111.4, 103.4, 56.1; IR (thin film): 3424, 2248, 1650, 1485, 1209, 1057, 1028, 1007, 822, 760, 623 cm^{-1}.



2.54

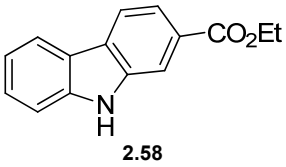
Carbazole 2.54[24]**.** The general procedure was followed with was followed with 0.078 g of azide **2.53** (0.297 mmol), 0.004 g of $[(cod)Ir(OMe)]_2$ (2 mol%) in 0.99 mL of benzene. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded carbazole **2.54** as a white solid (0.055 g, 79%). This compound was previously reported by Forbes and co-workers[24]. ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.73 (br s, 1H), 8.57 (s, 1H), 8.29 (d, J = 7.8 Hz, 1H), 7.69 (dd, J = 8.6 Hz, 1.5, 1H), 7.66 (d, J = 8.6 Hz, 1H), 7.57 (dd, J = 8.1 Hz, 0.7 Hz, 1H), 7.47 (td, J = 7.6 Hz, 1.0 Hz, 1H), 7.24 (d, J = 0.7 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 141.4, 140.4, 126.6, 125.6 (q, J_{CF} = 269.8 Hz), 124.5, 122.5, 122.1, 122.0 (q, J_{CF} = 3.4 Hz), 120.9, 119.4, 119.1 (q, J_{CF} =

31.3 Hz), 117.9 (q, J_{CF} = 3.6 Hz), 111.4; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –58.7; IR (thin film): 3431, 1346, 1165, 1101, 1057, 825, 756, 650, 569 cm^{-1}.



2.56

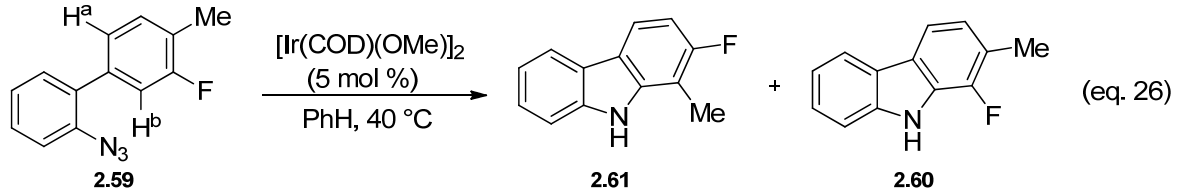
Carbazole 2.56. The representative procedure was followed with 0.048 g of azide **2.55** (0.296 mmol), 0.010 g of [(cod)Ir(OMe)]$_2$ (5 mol%) in 0.98 mL of benzene. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded carbazole **2.56** as a white solid (0.048 g, 87%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.37 (br s, 1H), 8.11 – 8.06 (m, 2H), 7.47 (dd, J = 8.1 Hz, 0.7 Hz, 1H), 7.35 (ddd, J = 8.1 Hz, 7.1 Hz, 1.1 Hz, 1H), 7.24 (dd, J = 10.1 Hz, 2.3 Hz, 1H), 7.14 (td, J = 7.5 Hz, 0.8 Hz, 1H), 6.97 (ddd, J = 9.8 Hz, 8.6 Hz, 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 161.5 (d, J_{CF} = 236.7 Hz), 140.7, 140.6 (d, J_{CF} = 11.1 Hz), 125.6, 122.4, 121.8 (d, J_{CF} = 11 Hz), 120.3, 119.5, 119.3, 111.3, 106.8 (d, J_{CF} = 23.9 Hz), 97.6 (d, J_{CF} = 26.4 Hz); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –116.3; IR (thin film): 3411, 1624, 1585, 14578, 1441, 1366, 845, 810, 746, 725, 571 cm^{-1}.



2.58

Carbazole 2.58. The general procedure was followed with 0.081 g of azide **2.57** (0.303 mmol), 0.010 g of [(cod)Ir(OMe)]$_2$ (5 mol%) in 1.01 mL of benzene. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded indole **2.58** as a pale brown solid (0.056 g, 77%). ^{1}H NMR (DMSO-d_6, 500 MHz): δ 11.55 (br s, 1H), 8.23 (dd, J = 14.6 Hz, 8.0 Hz, 2H), 8.14 (d, J = 0.8 Hz, 1H), 7.80 (dd, J = 8.2 Hz, 1.5 Hz, 1H), 7.58 (d, J = 8.2 Hz, 1H), 7.51-7.48 (m, 1H), 7.25-

7.22 (m, 1H), 4.38 (q, J = 7.1 Hz, 2H), 1.39 (t, J = 7.1 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 166.9, 141.5, 139.5, 127.5, 127.0, 126.6, 122.1, 121.6, 119.7, 119.6, 112.7, 111.8, 61.1, 14.8; IR (thin film): 3500, 1706, 1631, 1446, 1300, 1267, 1216, 1056, 1028, 1009, 822, 760 cm^{-1}.

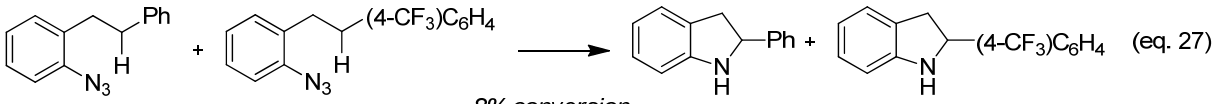


2.59 **2.61** **2.60**

Carbazole 2.60/2.61. The general procedure was followed with 0.072 g of azide **2.59** (0.317 mmol), 0.011 g of $[(cod)Ir(OMe)]_2$ (5 mol%) in 1.06 mL of benzene. Analysis of the crude reaction mixture using ^{1}H NMR spectroscopy indicated that a 61:39 mixture of carbazoles **2.60** and **2.61** were formed. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded indole **2.60/2.61** as a white solid (0.062 g, 92%): (DMSO-d_6, 500 MHz): δ 11.22 (br s, 1H), 8.03 (d, J = 7.7 Hz, 1H), 7.98 (d, J = 7.7 Hz, 1H), 7.45 (d, J = 8.1 Hz, 1H), 7.36 (t, J = 7.5 Hz 1H), 7.22 (d, J = 10.7 Hz, 1H), 7.16 (t, J = 7.5 Hz, 1H), 2.37 (d, J = 1.7 Hz, 3H); ^{13}C NMR ($CDCl_3$, 125 MHz): δ 160.2 (d, J_{CF} = 236.1 Hz), 140.7, 139.1, 125.5, 122.4 (d, J_{CF} = 6.9 Hz), 120.3, 119.3 (d, J_{CF} = 19.8 Hz), 115.4, 115.3, 111.2 (d, J_{CF} = 27.6 Hz), 109.7, 97.6 (d, J_{CF} = 26.4 Hz), 15.1; ^{19}F NMR ($CDCl_3$, 282 MHz) δ –119.4; IR (thin film): 3390, 2370, 1544, 1456, 1344, 883, 845, 754, 723 cm^{-1}.

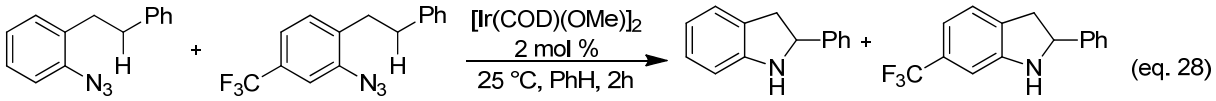
2.8.5 Mechanism Study

Competition Experiments



2.17 **2.38** **2.19** (1 : 1) **2.72**

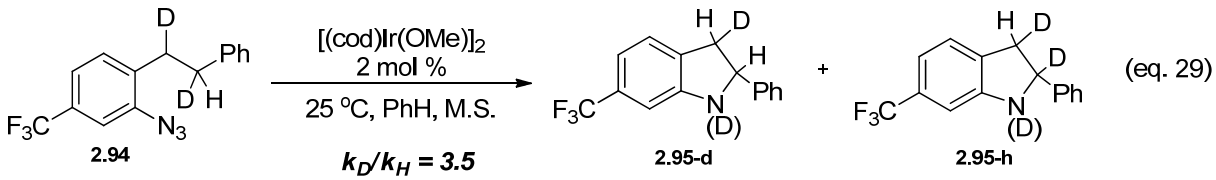
0.023 g of azide **2.17** (0.1 mmol), 0.030 g of azide **2.38** (0. 1 mmol) and 0.001 g of $[(cod)IrOMe]_2$ (0.002 mmol) were dissolved in 0.50 mL of benzene. After 2h, the reaction mixture was filtered through Celite, and the filtrate was concentrated *in vacuo*. Analysis of the resulting mixture using ^1H NMR spectroscopy revealed an 8.0 % conversion of azides **2.17** and **2.38** into a 1:1 mixture of indolines **2.19** and **2.72**.



2.17 **2.36** **2.19** (1 : 1.5) **2.71**

0.023 g of azide **2.17** (0.1 mmol), 0.029 g of azide **2.36** (0.1 mmol) and 0.001 g of $[(cod)IrOMe]_2$ (0.002 mmol) were dissolved in 0.50 mL of benzene. After 2h, the reaction mixture was filtered through Celite, and the filtrate was concentrated *in vacuo*. Analysis of the resulting mixture using ^1H NMR spectroscopy revealed an 12% conversion of azides **2.17** and **2.36** into a 1:1.5 mixture of indolines **2.19** and **2.71**.

Intramolecular Kinetic Isotope Experiment for Indoline Formation.



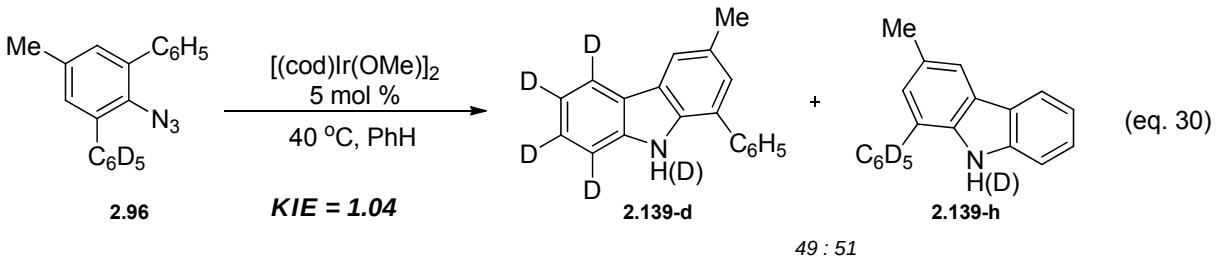
2.94 **2.95-d** **2.95-h**

16.5 : 83.5

Indoline 2.95. The general procedure was followed with 0.023 g of azide **2.94** (0.078 mmol) and 0.002 g of $[(cod)IrOMe]_2$ (0.002 mmol) in 0.52 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, the product mixture was analyzed using ^1H NMR spectroscopy. Analysis of the spectral data revealed that **2.95-d** and **2.95-h** were formed

in a 16.5 : 83.5 ratio. Purification by MPLC (0:100 – 1:100 EtOAc:hexanes) afforded indoline **2.95-h**. Characterization data for indoline **2.95-h**: R_f = 0.62 (14:86 EtOAc: hexane); ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.39 – 7.41 (m, 2H), 7.34 – 7.37 (m, 2H), 7.28 – 7.32 (m, 2H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.98 (d, *J* = 8.5 Hz, 1H), 6.842 (s, 1H), 5.00 -5.02 (m, 1H), 4.29 (s, 1H), 3.46 – 3.48 (m, 1H), 3.00 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 151.3, 143.9, 131.9, 130.1 (q, J_{CF} = 31.3 Hz), 128.8, 127.7, 126.2, 124.6, 124.5 (q, J_{CF} = 270.1 Hz), 115.7, 104.8, 63.5, 38.8 (J_{CD} = 20.4 Hz); the yield was not quantified.

Intramolecular Kinetic Isotope Experiment for Carbazole Formation.



Carbazole 2.110. The general procedure was followed with 0.036 g of azide **2.96** (0.124 mmol) and 0.002 g of $[(cod)IrOMe]_2$ (0.003 mmol) in 0.50 mL of benzene. After filtration through Celite and removal of solvent *in vacuo*, the product mixture was analyzed using ^{1}H NMR spectroscopy. Analysis of the spectral data revealed that **2.139-d** and **2.139-h** were formed in a 49 : 51 ratio. Purification by MPLC (0:100 – 1:100 EtOAc:hexanes) afforded carbazole **2.139-h**. Characterization data for carbazole **2.139-h**: ^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.22 (br s, 1H), 8.14 (d, *J* = 7.8 Hz, 1H), 7.94 (s, 1H), 7.45 (m, 1H), 7.41 (dd, *J* = 8.0, 0.9 Hz, 1H), 7.35 (d, *J* = 1.0 Hz, 1H), 7.29 (m, 1H), 2.65 (s, 3H) ^{13}C NMR ($CDCl_3$, 125 MHz): δ 139.9 (C), 139.1 (C), 135.6 (C), 129.3 (C), 128.8 (J_{CD} = 24.6 Hz, CD), 128.0 (J_{CD} = 24.0 Hz, CD), 127.2 (CH), 127.1 (J_{CD} = 25.9 Hz, CD), 125.9 (CH), 124.7 (C), 124.0 (C), 123.5 (C), 120.5 (CH), 119.6 (CH), 119.4 (CH), 110.8 (CH), 21.57 (CH_3); IR (thin film): 3448, 3053, 2919, 2860,

2270, 1608, 1493, 1453, 1418, 1382, 1331, 1301, 1264, 1233, 861, 748, 756 cm^{-1}. HRMS (EI) *m / z* calculated for $C_{19}H_{10}N_2H_5$ (M^+): 262.1518, found: 262.1520.

---

1 Stokes, B. Dong, H. Leslie, B. Pumphrey, A. Driver, T. "Intramolecular C–H amination reactions: exploitation of the Rh_2(II)-Catalyzed decomposition of azidoacrylates." *J. Am. Chem. Soc*. **2007**, *129*, 7500.

2 Shen, M. Driver, T. "Iron(II) bromide-catalyzed synthesis of benzimidazoles from aryl azides." *Org. Lett.* **2008**, *10*, 3367.

3 Dong, H. Shen, M. Redford, J. Stokes, B. Pumphrey, A. Driver, T. "Transition metal-mediated synthesis of pyrroles from dienyl azides." *Org. Lett*. **2007**, *9*, 5191.

4 Shen, M. Leslie, B. Driver, T. "Rh_2(II)-Catalyzed intramolecular C–H amination of aryl azides." *Angew. Chem., Int. Ed*. **2008**, *47*, 5056.

5 (a) Stokes, B. Jovanovic, B. Dong, H. Richert, K. Riell, R. Driver, T. "Rh_2(II)-Catalyzed synthesis of carbazoles from biaryl azides." *J. Org. Chem*. **2009**, *74*, 3225. (b) Stokes, B. Richert, K. "Examination of the mechanism of Rh_2(II)-catalyzed carbazole formation using intramolecular competition experiments." *J. Org. Chem*. **2009**, *74*, 6442.

6 Murata, S. Tsubone, Y. Kawai, R. Eguchi, D. Tomioka, H. "Mechanistic studies of intramolecular C–H insertion reaction of arylnitrenes: isotope effect, configurational purity and radical clock studies." *J. Phys. Org. Chem*, **2005**, *18*, 9.

7 (a) Harvey, M. E. Musaev, D. G. Du Bois, J. "A diruthenium catalyst for selective, intramolecular allylic C-H amination: reaction development and mechanistic insight gained through experiment and theory." *J. Am. Chem. Soc*. **2011**, *133*, 17207. (b) Caselli, A. Gallo, E. Ragaini, F. Ricatto, F. Abbiati, G. Cenini, S. "Chiral porphyrin complexes of cobalt(II) and ruthenium(II) in catalytic cyclopropanation and amination reactions." *Inorg. Chim. Acta*. **2006**, *359*, 2924. (c) Ragaini, F. Penoni, A. Gallo, E. Tollari, S. Gotti, C. L. Lapadula, M. Mangioni, E. Cenini, S. "Amination of benzylic C-H bonds by arylazides catalysed by CoII(porphyrin) complexes. A synthetic and mechanistic study." *Chem. Eur. J*. **2003**, *9*, 249. (d) Shou, W. G. Li, J.; Guo, T. Lin, Z. Jia, G. "Ruthenium-catalyzed intramolecular amination reactions of aryl- and vinylazides." *Organometallics*. **2009**, *28*, 6847.

8 Dong, H. Shen, M. Redford, J. E. Stokes, B. J. Pumphrey, A. L. Driver, T. G. " Transition metal-mediated synthesis of pyrroles from dienyl azides." *Org. Lett*. **2007**, *9*, 5191.

9 (a) King, E. R. Hennessy, E. T. Betley, T. A. "Catalytic C−H bond amination from high-spin iron imido complexes." *J. Am. Chem. Soc*. **2011**, *133*, 4917. (b) King, E. R. Betley, T. A. "C−H bond amination from a ferrous dipyrromethene complex." *Inorg. Chem*. **2009**, *48*, 2361. (c) Shen, M. Driver, T. G. "Iron(II) bromide-catalyzed synthesis of benzimidazoles from aryl azides." *Org. Lett*. **2008**, *10*, 3367.

10 (a) Badiei, Y. M. Dinescu, A. Dai, X. Palomino, R. M. Heinemann, F. W. Cundari, T. R. Warren, T. H. "Copper-nitrene complexes in catalytic C−H amination." *Angew. Chem., Int. Ed*. **2008**, *47*, 9961. (b) Badiei, Y. M. Krishnaswamy, A. Melzer, M. M. Warren, T. H. "Transient terminal Cu-nitrene intermediates from discrete dicopper nitrenes." *J. Am. Chem. Soc*. **2006**, *128*, 15056. (c) Zang, Y. Hsung, R. P. Trscey, M. R. Kurtz, K. C. M. Vera, E. L. "Copper sulfate-pentahydrate-1,10-phenanthroline catalyzed amidations of alkynyl bromides. Synthesis of heteroaromatic amine substituted ynamides." *Org. Lett*. **2004**, *6*, 1151. (d) Dong, H. Shen, M. Redford, J. E. Stokes, B. J. Pumphrey, A. L. Driver T. G., "Transition metal-catalyzed synthesis of pyrroles from dienyl azides." *Org. Lett*., **2007**, *9*, 5191. (e) Chiba, S. Zhang, L. Ang, G. Y. Hui, B. W.-Q. "Generation of iminyl copper species from alpha-azido carbonyl compounds and their catalytic C−C bond cleavage under an oxygen atmosphere." *Org. Lett*. **2010**, *12*, 2052.

11 (a) Lu, H. Tao, J. Jones, J. E. Wojtas, L. Zhang, X. P. "Cobalt(II)-catalyzed intramolecular C−H amination with phosphoryl azides: formation of 6- and 7-membered cyclophosphoramidates." *Org. Lett*. **2010**, *12*, 1248. (b) Subbarayan, V. Ruppel, J. V. Zhu, S. Perman, J. A. Zhang, X. P. "Highly asymmetric cobalt-catalyzed aziridination of alkenes with trichloroethoxysulfonyl azide ($TcesN_3$)." *Chem. Commun*. **2009**, *4266*. (c) Gao, G.-Y. Lu, H. Subbarayan, V. Tao, J. Zhang, X. P. "Cobalt(II)-catalyzed intermolecular benzylic C−H amination with 2,2,2-Trichloroethoxycarbonyl Azide ($TrocN_3$)" *Organometallics*, **2009**, *29*, 389. (d) Ruppel, J. V. Jones, J. E. Huff, C. A. Kamble, R. M. Chen, Y. Zhang, X. P. "A highly effective cobalt catalyst for olefin aziridination with azides: hydrogen bonding guided catalyst design." *Org. Lett*. **2008**, *10*, 1995. (e) Caselli, A. Gallo, E. Fantauzzi, S. Morlacchi, S. Ragaini, F. Cenini, S. "Allylic amination and aziridination of olefins by aryl azides catalyzed by CoII(tpp): A synthetic and mechanistic study" *Eur. J. Inorg. Chem*. **2008**, 3009.

12 (a) Yung, C. M. Skaddan, M. B. Bergman, R. G. "Stoichiometric and catalytic H/D incorporation by cationic iridium complexes: a common monohydrido-iridium intermediate." *J. Am. Chem. Soc*. **2004**, *126*, 13033. (b) Boller,

T. M. Murphy, J. M. Hapke, M. Ishiyama, T. Miyaura, N. Hartwig, J. F. J. "Mechanism of the mild functionalization of arenes by diboron reagents catalyzed by iridium complexes. intermediacy and chemistry of bipyridine-ligated iridium trisboryl complexes." *J. Am. Chem. Soc.* **2005**, *127*, 14263. (c) Tenn, W. J. Young, K. J. H. Oxgaard, J. Nielsen, R. J. Goddard, W. A. Periana, R. A. "Heterolytic C–H activation and catalysis by an O-donor iridium−hydroxo complex." *Organometallics*, **2006**, *25*, 5173. (d) Zhu, Y. Fan, L. Chen, C.-H. Finnell, S. R. Foxman, B. M. Ozerov, O. V. "C−H Oxidative addition to a (PNP)Ir center and ligand-induced reversal of benzyl/aryl selectivity." *Organometallics*, **2007**, *26*, 6701.

13 For related iridium η^3 complexes, see: Fryzuk, M. D. McConville, D. H. Rettig, S. J. J. "Synthesis, structure and hydrogenation of η^3-benzyl diphosphine complexes of rhodium and iridium." *Organomet. Chem*. **1993**, *445*, 245.

14 Belozerskaya, L. Denisov, G. Tupitsyn, I. "Kinetics of deuteron exchange in the groups of pyrole, indole, and carbazole." Scientific-Research Institute of Physics, Leningrad State University, **1970**, *6*, 408.

15 Pangborn, A. Giardello, M. Grubbs, R. Rosen, R. Timmers, F. "Safe and convenient procedure for solvent purification." *Organometallics*, **1996**, *15*, 1518。

16 Sakai, N. Annaka, K. Fujita, A. Sato, A. Konakahara, T. "$InBr_3$-Promoted divergent approach to polysubstituted indoles and quinolines from 2-ethynylanilines: switch from an intramolecular cyclization to an intermolecular dimerization by a type of terminal substituent group." *J. Org. Chem*. **2008**, *73*, 4160.

17 Ye, S. Ding, Q. Wang, Z. Zhou, H. Wu, J. "Tandem addition-cyclization reactions of 2-alkynylbenzenamines with isocyanates catalyzed by $PdCl_2$" *J. Org. Biomol. Chem*. **2008**, *6*, 4406.

18 Murai, K. Hayashi, S. Takaichi, N. Kita, Y. Fujioka, H. "Tandem β-enamino ester formation and cyclization with o-alkynyl anilines catalyzed by $InBr_3$:efficient synthesis of β-(N-Indolyl)-α, β-unsaturated esters." *J. Org. Chem.* **2009**, *74*, 1418.

19 DeRoy, P. L. Surprenant, S. Bertrand-Laperle, M. Yoakim, C. "Efficient nucleophilic aromatic substitution between aryl nitrofluorides and alkynes." *Org. Lett*. **2007**, *9*, 2741.

20 Murata, S. Yoshidome, R. Satoh, Y. Kato, N. Tomioka, H. "Reactivities of nitrenes generated by photolysis of 2-(.omega.-phenylalkyl)phenyl azides." *J. Org. Chem.* **1995**, *60*, 1428.

21 Sundberg, R. "A study of the deoxygenation of some *o*-alkylnitro- and *o*-alkylnitrosobenzenes in triethyl phosphite." *J. Am. Chem. Soc*. **1966**, *88*, 3781.

22 Rutherford, J. L. Rainka, M. P. Buchwald, S. L. "An annulative approach to highly substituted indoles: unusual effect of phenolic additives on the success of the arylation of ketone enolates." *J. Am. Chem. Soc.* **2002**, *124*, 15168.

23 Bedford, R. Betham, M. "N−H carbazole synthesis from 2-chloroanilines via consecutive amination and C–H activation." *J. Org. Chem.* **2006**, *71*, 9403.

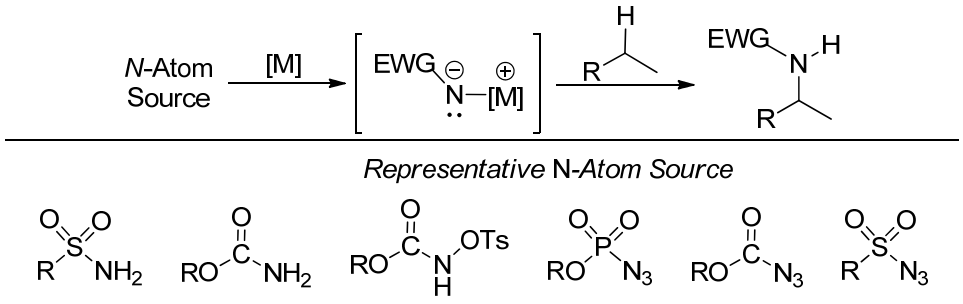
24 Forbes, E. Stacey, M. Tatlow, J. C. Wragg, R. "Diaryliodonium salts—XII: The phenylation of dimedone, dibenzoylmethane and tribenzoylmethane." *Tetrahedron* **1960**, *8*, 67.

Chapter 3. Rh_2(II)-Catalyzed Intramolecular Aliphatic C-H bond Amination Reactions Using Aryl Azides as the *N*-Atom Source

3.1 Introduction

In Chapter 2 the development of $[Ir(COD)(OMe)]_2$ catalyzed intramolecular benzylic C–H bond amination of *ortho*-substituted aryl azides was described. One of the limitations of this method was non-benzylic C–H bonds were found to be unreactive. At the conclusion of this study, our goal was to figure out a method to achieve aliphatic C–H bond amination using aryl azides as nitrogen source. However, a number of publications[1] on sp^2 C–H bond amination from our group suggest that C–N bond formation occurs via a 4π-electron-5-atom electrocyclization.[1b] In contrast, lack of conjugation system requires aliphatic C–H bond amination process through metal-catalyzed C–H insertion or H-atom abstraction mechanisms, mechanisms that have remained elusive to control.[2] Further, nearly every current N-atom-transfer reactions that proceed through a metal nitrene require require strong electron-withdrawing groups on the nitrene (Scheme 3.1).

Scheme 3.1. Electron-withdrawing nitrogen substituent requirement for aliphatic C–H bond amination.



3.2 Optimization

In corporation with my labamte Nguyen, Quyen, we successfully developed aliphatic C–H bond amination using aryl azides as the nitrene source which would complement previous methods and provide a new method to form ArN–C bonds from C–H bonds. In search of the optimal conditions to achieve intramolecular aliphatic C–H bond amination using ayl azide, the *o-tert*-butylaryl azide was chosen to examine reactivity towards transition metal complexes (Table 3.1)[3]. This aryl azide is relatively thermally robust, with no reaction observed at 120 ºC (entry 1)[4]. Aryl azide **3.1** was exposed to commercially available transition metal complexes known to catalyze N-atom-transfer reactions to determine if any would the metal complexes would induce aliphatic C–H bond amination. In presence of iron,[5] copper,[6] cobalt,[7] ruthenium,[8] or iridium complexes,[9] no desired C–H bond amination product was observed (entries 2 – 6). When aryl azide **3.1** was treated with $Rh_2(O_2CC_7H_{15})_4$ at 120 °C—a significantly higher temperature than our previous processes— partial conversion was observed, which was attributed to decomposition of catalyst at high temperature (entry 8). By switching to the more thermally robust $Rh_2(esp)_2$,[10] both yield and conversion of the process were improved (entry 9).

Table 3.1. Development of optimal catalysts.

3.1 **3.2**

entry	metal salt	conv, %[a]	yield, %[b]
1	none	0	0
2	$FeBr_2$	0	decop[c]
3	CuBr	0	0
4	CoTPP	0	0
5	$RuCl_3 \cdot nH_2O$	0	0

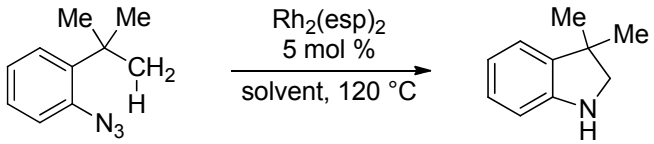
6	$[Ir(COD)(OMe)]_2$	0	0
7	$[Rh(COD)(OMe)]_2$	10	0[c]
8	$Rh_2(O_2CC_7H_{15})_4$	35	35
9	$Rh_2(esp)_2$	99	75

[a]As determined using 1H NMR spectroscopy. [b]Isolated after silica gel chromatography. [c]Aniline formed.

3.2.1 Optimization of Additives

To prevent oxidation of indoline during chromatography purification and improve the isolated yield, in situ protection of indoline-nitrogen was attempted (Table 3.2). We found that the reaction yield was improved with indoline protected with either a Boc or Ac group (entry 2 and 3). The reaction outcome appeared to correlate with pK_a of the acid byproduct of the pretection reaction: aniline was produced when stronger benzoic and triflic acids were produced (entry 4 and 5).[11]

Table 3.2. Optimization of additive.



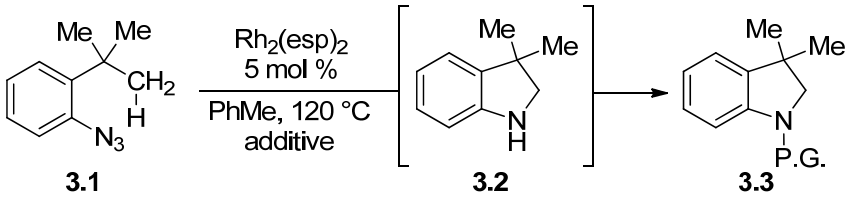
entry	solvent	yield, %[a]
1	PhMe	75
2	PhH	73
3	PhBr	56
4	PhCl	47
5	1,3-$C_6H_4Cl_2$	61
6	$PhCF_3$	31
7	DCE	47

[a]As determined using ^{1}H NMR spectroscopy

3.2.2 Optimization of Solvents

Our optimization experiments were continued by examining different solvents (Table 3.3). We found that benzene (entry 2) would provide comparable yield as toluene. Chlorinated aromatic solvents (entries 4 and 5) gave lower yield than non-chlorinated solvents. 1,2-dichloroethane, (entry 7) a previously reported[2d] superior solvent for dirhodium complexes catalyzed C–H amination reaction. Other aromatic solvents like trifluorobenzene (entry 6) and bromobenzene (entry 3), both gave worse conversion than PhMe or PhH. Consequently, we concluded that PhMe is best solvent for this C–H amination reaction.

Table 3.3. Development of optimal solvents.



3.1 3.2 3.3

entry[a]	additive	conv, %[b]	yield, %[c]
1	n.a.	99	75
2	Boc_2O	99	90
3	Ac_2O	99	83
4	Bz_2O	99	aniline
5	Tf_2O	99	aniline

[a]One equivalent additive was added. [b]As determined using 1H NMR spectroscopy. [c]Isolated after silica gel chromatography.

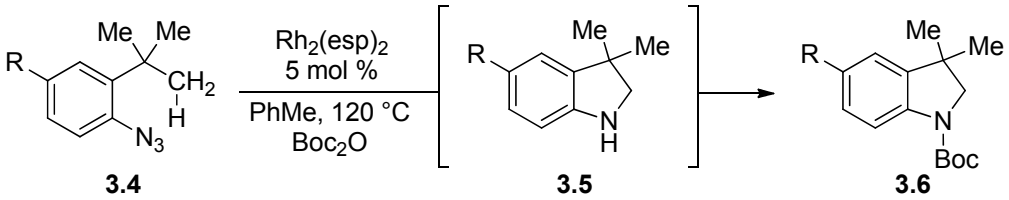
3.3 Substrate Scope and Limitation

3.3.1 Investigation of Electronic Nature of Azide Arene

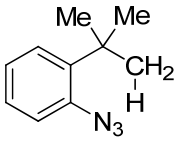
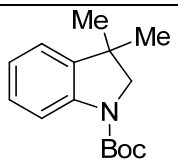
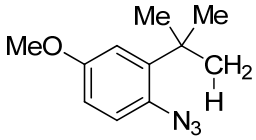
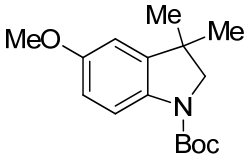
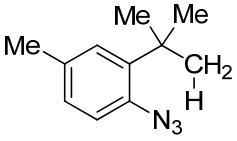
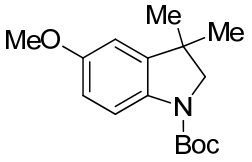
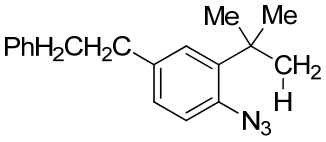
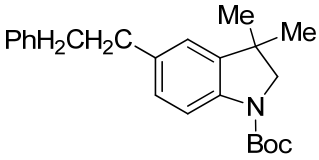
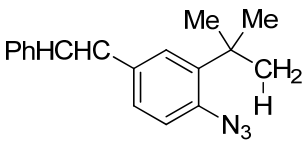
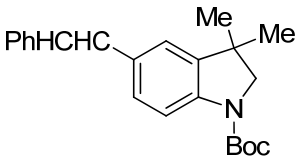
The electronic and steric constraints of the intramolecular aliphatic C–H bond amination reactions were investigated using optimized conditions (Table 3.4). Other substituents on arene

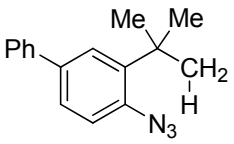
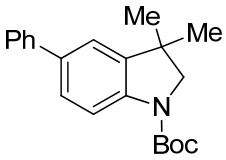
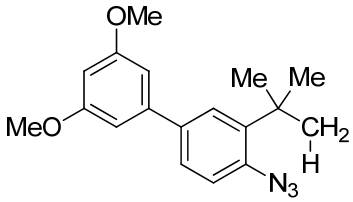
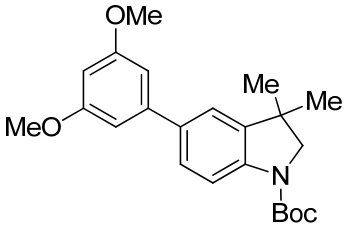
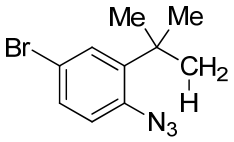
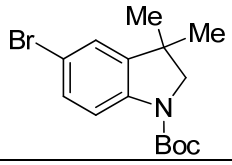
were examined subsequently. Active bromo- group (entry 8) was tolerated in the reaction as well, which could be used for subsequent cross-coupling reactions to install various functional groups. Illustrating the chemoselectivity of our process, styrene (entry 5) was tolerated as substituents with no intermolecular C–H bond amination products observed. In contrast to existing amination processes from azides,[12,13] our method does not require an electron-withdrawing group on the nitrogen: aryl azides bearing *para*-electron-donating, -neutral, or –withdrawing groups were converted to indolines efficiently.

Table 3.2. Scope and limitation of indoline formation.



3.4 **3.5** **3.6**

Entry	aryl azide	#.#	indoline	#.#	yield, %[a]
1		**3.1**		**3.7**	84
2		**3.8**		**3.9**	63
3		**3.10**		**3.11**	54
4		**3.12**		**3.13**	64
5		**3.14**		**3.15**	70

6		**3.16**		**3.17**	54
7		**3.18**		**3.19**	58
8		**3.20**		**3.21**	73

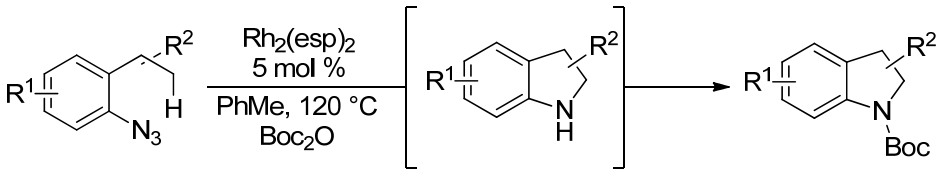
[a] Isolated after silica gel chromatography

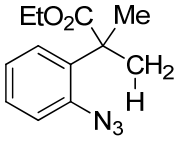
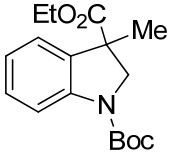
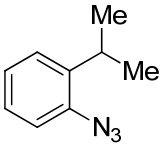
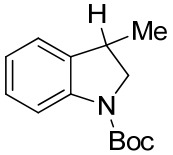
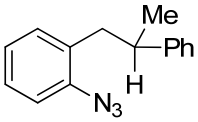
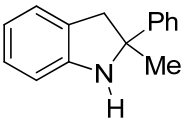
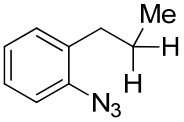
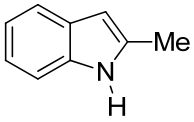
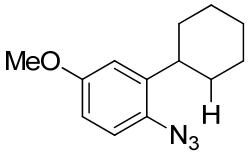
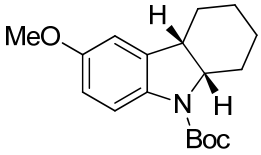
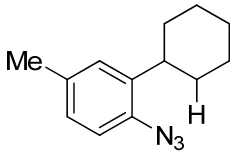
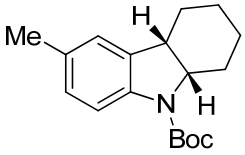
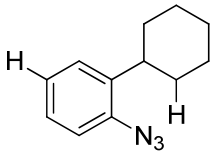
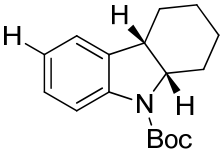
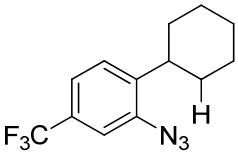
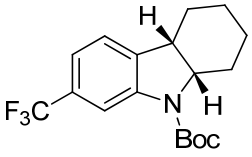
3.3.2 Examination of *ortho*-Alkyl Substituents Identity

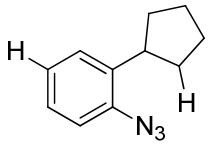
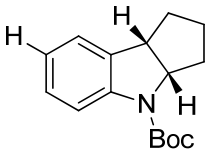
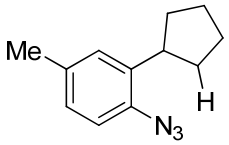
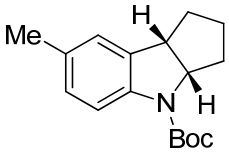
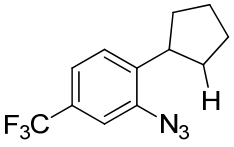
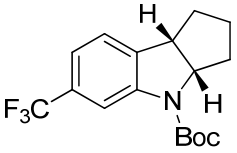
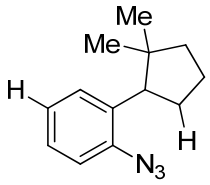
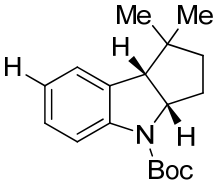
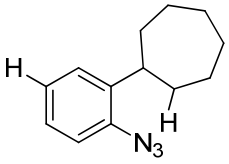
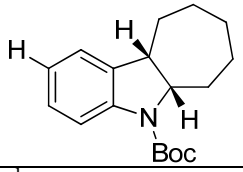
To further examine the scope of the transformation, the identity of the *ortho*-alkyl substituent was varied (Table 3.5). Replacing one of the methyl groups with an ethyl ester did not reduce the yield (entry 1), while substitution with hydrogen instead of methyl group attenuated the reaction efficiency (entry 2). In addition, substitution at the C–H reaction center was examined as well: amination can be achieved at secondary C–H bond, although dehydrogenation occurred to afford indole **3.29** (entry 4); dehydrogenation could be circumvented if amination occurred at tertiary C–H bond by introduction of an additional phenyl substituent at the reaction center (entry 3). Submission of aryl azides bearing cyclopentyl- or cyclohexyl *ortho*-substituents to reaction conditions produced indolines as single diastereomers (entries 5-11). The diastereoselectivity observed from these substrates can be compared to the pyrolysis of aryl azide **3.34**, which was reported by Smolinsky to produce a 1:1 mixture of diastereomers.[14] The chemoselectivity of our process was demonstrated with aryl azide **3.44**, which afforded indoline **3.45** as sole product with no observance of methyl C–H bond amination product (entry 12). While single diastereomers were obtained from substrates bearing *o*-

cyclopentyl or *o*-cyclohexyl groups, diminished stereoselectitity was observed with *o*-cycloheptyl-substituted aryl azide **3.46**.

Table 3.3. Examination of indentity of the *ortho*-alkyl substituents.



entry	aryl azide	#.#	indoline	#.#	yield, %[a]
1		**3.22**		**3.23**	70
2		**3.24**		**3.25**	20
3		**3.26**		**3.27**	55[b]
4		**3.28**		**3.29**	30[c]
5		**3.30**		**3.31**	80
6		**3.32**		**3.33**	73
7		**3.34**		**3.35**	70
8		**3.36**		**3.37**	63

9		**3.38**		**3.39**	85
10		**3.40**		**3.41**	73
11		**3.42**		**3.43**	82
12		**3.44**		**3.45**	86
13		**3.46**		**3.47**	63 d.r. 82:18

[a]Isolated after silica gel chromatography. [b]20% aniline observed. [c]30% aniline observed

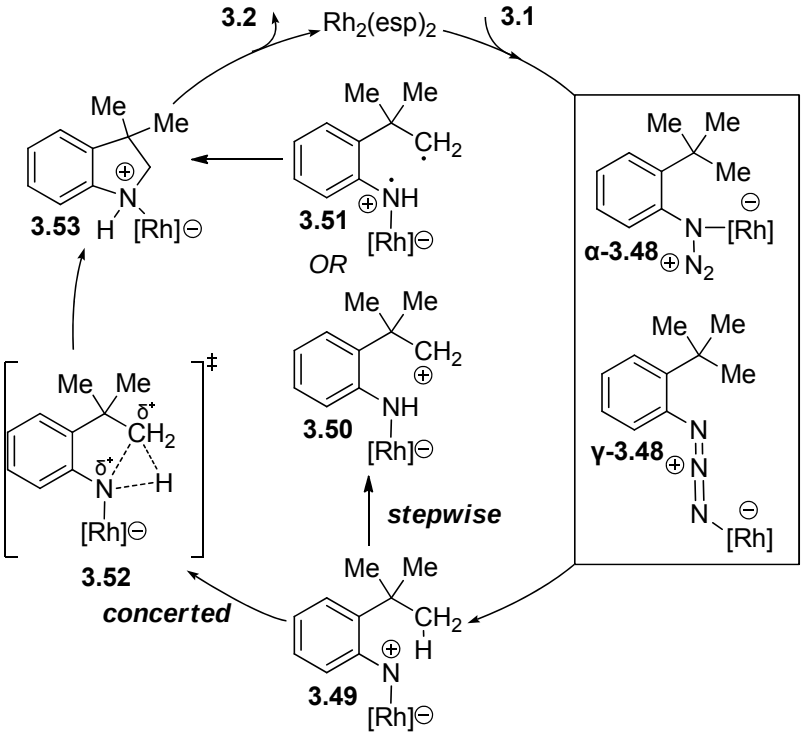
3.4 Mechanism Study

While several mechanisms could account for indoline formation, the reactivity trends suggest that C–N bond formation occurs through the reaction of a rhodium nitrene with the pendant C–H bond (Scheme 3.2).[15] This catalytic intermediate is formed from coordination of rhodium(II) carboxylate to either the α- or γ-nitrogen of the azide produces **3.48**.[16] Subsequent extrusion of N_2 forms the rhodium nitrene **3.49**.[17] While the role of the rhodium(II) carboxylate could be to generate a free nitrene,[18] our current mechanistic hypothesize that the nitrene remains metal bound for the C–H bond amination step since pyrolysis involving free nitrene is not diastereoselective.[14] This amination step could be stepwise or concerted: hydride[19] or H-atom abstraction[20] (to form **3.50** or **3.51**) followed by recombination produces the carbon–nitrogen bond **3.53**. Alternatively, this bond could be formed through the concerted insertion[21] of the

metal nitrene into the proximal C–H bond via transition state **3.52**. Finally, the indoline **3.2** is produced upon dissociation of the rhodium complex.

3.4.1 Possible Mechanism Pathway

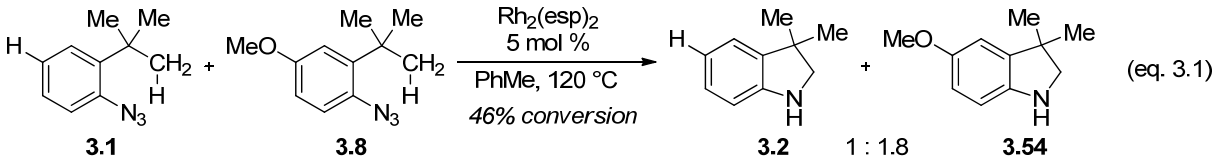
Scheme 3.2. Possible mechanism for intramolecular apliphatic C–H bond amination.



3.4.2 Intermolecular Competition Reaction

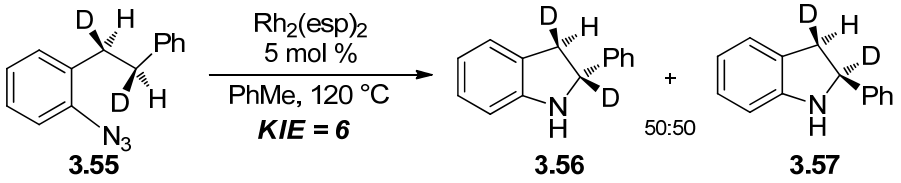
To provide insight into the mechanism, intermolecular competition reactions were performed. First, the effect of changing the electronic nature of the aryl azide on the reaction was examined by comparing the reactivity of **3.1** to *para*-methoxy substituted **3.8** (eq. 3.1). Underscoring the difference between our method for aliphatic C–H bond amination and others, we found that more electron-rich aryl azides were more active towards the reaction conditions. The enhanced reactivity of **3.8** as compared to **3.1** was attributed to either the preferred

coordination of **3.8** to $Rh_2(esp)_2$ or the accelerated N_2 extrusion from the resulting azide-metal complex.



3.4.3 Examination of Labeled Aryl Azide

To probe the mechanism of the C–H bond amination step, two stereospecifically labeled aryl azide were examined (eq. 3.2). We anticipated that the number of indoline diastereomers from **3.55** would be reveal if the amination step of catalytic cycle was stepwise or concerted. Only two products would be produced via insertion into either the the β-C–H or β-C–D bond, If the reaction was concerted. In contrast, if stepwise insertion was operating from through either a radical- or cation reactive intermediate, then scrambling of the C2-stereocenter could occur before recombination to form both **3.56**-d_2 and **3.57**-d_2. In support of stepwise the β-C–H or β-C–D bond amination, two diastereomers of 2-phenylindoline (dr 50:50) and an intramolecular kinetic effect (KIE) of 6.7[22] were observed. The magnitude of this isotope effect is significantly smaller than for the reaction involving an H-atom abstraction by an aryl nitrene or an aryl metal nitene[2c] (k_H/k_D = 12 – 14), but larger than hydride shift reaction ($k_H/k_D \approx 2$ for Cannizzaro reaction and Meerwein–Ponndorf–Verley reduction).[23,24,25] In addition, smaller KIEs were observed at lower reaction temperatures (Table 3.6) revealing that our amination reaction occurs above the isokinetic temperature and, as a consequence, is under entropic control.[26,27] We found, however, that spatial constraints of this reaction override these isotope effects: cyclopentanone-derived aryl azide **3.58** reacted preferentially with the *syn*-C–D bond to form **3.59** exclusively (eq 3.3).[28]

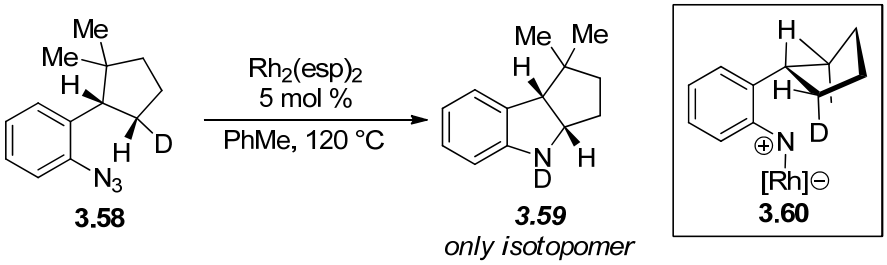


(eq. 3.2)

Table 3.4. Observed kinetic isotope effects.

entry	T (ºC)	k_H/k_D[a]
1	80	3.7
2	100	5.7
3	120	6.7

[a] As determined using ^{1}H NMR spectroscopy



(eq. 3.3)

3.5 Conclustion

In conclusion, we have developed an efficient and diastereoselective rhodium(II)-catalyzed aliphatic C−H bond amination reaction with an aryl azide as the N-atom source. Our method is different from previously reported aliphatic C−H bond amination reactions which requiring a strong electron-withdrawing group on the nitrogen atom. The reactivity of stereospecific labeled aryl azides revealed that the amination reaction occurred stepwise with the *syn*-C−H bond. The mechanistic insight will be exploited to develop this reactivity of aryl azides to the stereoselective synthesis of complex, functionalized N-heterocycles.

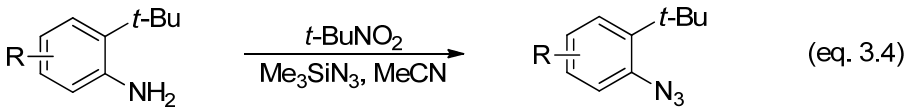
3.6 Experimental

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 obtained by peak matching. Melting points are reported uncorrected. Infrared 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.[1] Metal salts were stored in a nitrogen atmosphere dry box.

3.6.1 Preparation of Substituted *ortho-tert*-Butyl-Substituted Aryl Azides

General Procedure for the Azidation Reaction

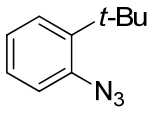
Following the procedure of Zhang and Moses,[2] the 2-*tert*-butyl aryl azides were prepared. Yields were not optimized.



$$ **3.61** (eq. 3.4)

To a cooled solution of aniline in MeCN (0.2 M) was added dropwise *t*-$BuNO_2$ (4 equiv) and Me_3SiN_3 (3 equiv) dropwise. The resulting solution was warmed to room temperature. After 1h, visualization of the reaction progress using TLC indicated the consumption of the starting material. De–ionized water was added to the reaction mixture. The mixture then was extracted with 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 20 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded azide.

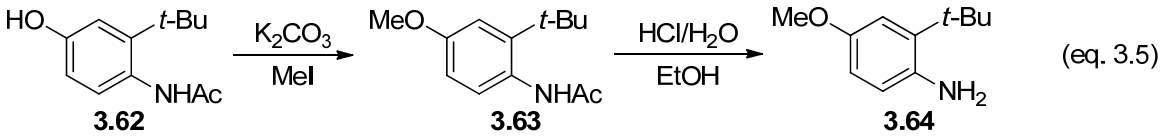
Synthesis of *ortho-tert*-Butyl-Substituted Aryl Azides.



3.1

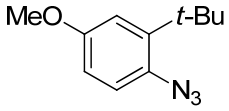
1-Azido-2-*tert*-butylbenzene 3.1.[3] The general procedure was followed using 0.298 g of 2-*tert*-butylaniline (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-$BuNO_2$ and 0.842 mL of Me_3SiN_3. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow red oil (0.287 g, 84%). This azide was previously reported by Smith and co-workers.[3] ^{1}H NMR (500MHz, $CDCl_3$) δ 7.36 (d, J = 8.0 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.18 (d, J = 8.0 Hz,

1H), 7.09 (t, J = 8.0 Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0 (C), 137.9 (C), 127.3 (CH), 127.2 (CH), 124.7 (CH), 119.5 (CH), 35.1 (C), 29.9 (CH_3). ATR-FTIR (thin film): 3067, 2995, 2956, 2118, 2081, 1575, 1484, 1439, 1283, 1150, 1056, 747, 646 cm^{-1}.



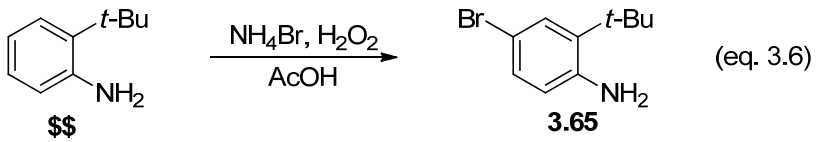
3.62 **3.63** **3.64** (eq. 3.5)

2-*tert*-Butyl-4-methoxyaniline 3.64.[4] To a solution of 2.07 g of acetamide **3.62** (10.0 mmol) and 6.9 g K_2CO_3 (50.0 mmol) in 40 mL of acetone was added 5.3 mL of MeI (80.0 mmol), after refluxing for 6 hours, the mixture was cooled to room temperature and diluted with 20 mL of H_2O. The resulting aqueous phase was extracted with additional 3 × 20 mL of Et_2O. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Without further purification, to the crude product **s2** in 100 mL of H_2O was added 30 mL of EtOH and 30 mL of HCl. After stirring at 100 °C overnight, the resulting mixture was neutralized with Na_2CO_3, and extract with 3 × 30 mL of CH_2Cl_2. The organic phase was concentrated *in vacuo*. Purification by MPLC (5:95 – 20:80 EtOAc:hexanes) afford aniline **s3** as brown solid (0.587 g, 33%). The spectral data matched that reported by Glorius and co-workers.[4] ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.88 (d, J = 2.5 Hz, 1H), 6.63 (dd, J = 6.0 Hz, 2.5 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 3.76 (s, 3H), 3.57 (s, 2H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.8 (C), 138.3 (C), 136.0 (C), 118.8 (CH), 113.9 (CH), 111.1 (CH), 55.7 (CH_3), 34.5 (C), 29.6 (CH_3); ATR-FTIR (thin film): 2998, 2955, 2912, 2105, 1602, 1483, 1416, 1260, 1225, 1048, 876, 799, 637 cm^{-1}.



3.8

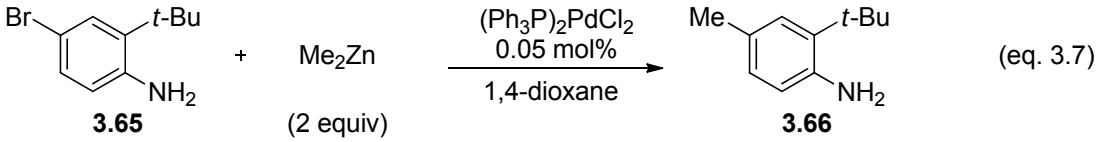
1-Azido-2-*tert*-butyl-4-methoxybenzene 3.8. The general procedure was followed using 0.358 g of 2-*tert*-butyl-4-methoxyaniline **3.64** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-$BuNO_2$ and 0.842 mL of Me_3SiN_3. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a brown oil (352 mg, 86%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.10 (d, J = 8.5 Hz, 1H), 6.94 (d, J = 1.5 Hz, 1H), 6.79 (dd, J = 1.5, 8.5 Hz, 1H), 3.81 (s, 3H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.6 (C), 142.6 (C), 130.4 (C), 120.4 (CH), 114.5 (CH), 111.0 (CH), 55.5 (CH_3), 35.2 (C), 29.9 (CH_3); ATR-FTIR (thin film): 2998, 2955, 2912, 2105, 1602, 1483, 1416, 1260, 1225, 1048, 876, 799, 637cm^{-1}; HRMS (EI) *m/z* calculated for $C_{11}H_{15}N_3O$ $(M)^+$: 205.1215, found: 205.1207.



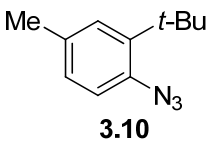
$$ **3.65** (eq. 3.6)

4-Bromo-2-*tert*-butylaniline 3.65. In the round-bottom flask were placed 1.79 g of 2-*tert*-butylaniline (12.03 mmol), 1.29 g of NH_4Br (13.23 mmol, 1.1 equiv) and 24 mL of glacial acetic acid. 1.36 mL of H_2O_2 was added dropwise via a syringe pump and the reaction mixture was left to stir for 48 hours. The reaction mixture then was neutralized with $NaHCO_3$ and extracted with with an additional 3 × 20.0 mL of CH_2Cl_2. The combined organic phases were washed with 30.0 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification using MPLC (0:100 – 50:50 EtOAc: hexanes) afforded the product as a brown red oil (1.64 g, 60%). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.31 (d, J = 2.5 Hz, 1H), 7.12 (dd, J = 6.5 Hz, 2.0 Hz, 1H), 6.51 (d, J = 8.5 Hz, 1H), 3.82 (s, 2H), 1.40 (s,

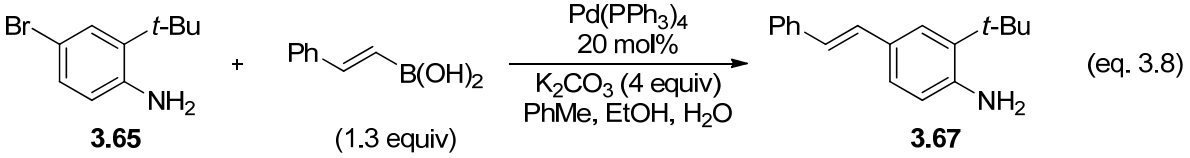
9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7 (C), 135.9 (C), 129.6 (C), 129.5 (CH), 119.2 (CH), 110.7 (CH), 34.4 (C), 29.4 (CH_3). ATR-FTIR (thin film): 3493, 3392, 2963, 2909, 2871, 1619, 1486, 1400, 1249, 1151, 1101, 867, 809 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{10}H_{14}BrN$ $(M)^+$: 227.0310, found: 227.0300.



2-*tert*-Butyl-4-methylaniline 3.66.[5] Following the procedure by Herbert, Aniline **s5** was prepared.[6] To the solution of 1.1 g of 2-*tert*-butyl-4-bromo-phenylamine **3.65** (5.0 mmol), 0.17 g of $PdCl_2(PPh_3)_2$ (0.25 mmol) in 20 mL of 1,4-dioxane under argon was added 5 mL of Me_2Zn (2M in toluene). After refluxing for 3 hours, the mixture was cooled to room temperature. Then the resulting solution was diluted with 20 mL of MeOH, washed with 20 mL of 1M HCl, and extracted with 3 × 20 mL of Et_2O. The organic phase was collected and concentrated. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded aniline **s5** as a pale solid (0.530 g, 65%). This aniline was reported recently by Dixon and Burgoyne.[5] ^{1}H NMR (500MHz, $CDCl_3$ + DMSO) δ 6.75 (m, 2H), 6.53 (dd, *J* = 5.5 Hz, 3.0 Hz, 1H), 3.47 (s, 2H), 1.97 (s, 3H), 1.25 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO) δ 156.3 (C), 148.1 (C), 133.0 (CH), 127.5 (C), 113.7 (CH), 113.2 (CH), 35.0 (C), 31.1 (CH_3), 23.5 (CH_3). ATR-FTIR (thin film): 3287, 2967, 1679, 1601, 1531, 1427, 1365, 1291, 1204, 1141, 1078, 804, 618 cm^{-1}.

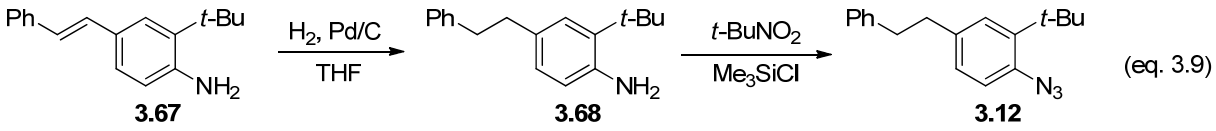


1-Azido-2-*tert*-butyl-4-methoxybenzene 3.10. The general procedure was followed using 0.326 g of 2-*tert*-butyl-4-methylaniline (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-$BuNO_2$ and 0.842 mL of Me_3SiN_3. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow oil (318 mg, 84%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 (s, 1H), 7.13 (m, 2H), 2.41 (s, 3H), 1.50 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.8 (C), 135.1 (C), 134.2 (C), 128.2 (CH), 127.8 (CH), 119.5 (CH), 35.0 (C), 30.1 (CH_3), 21.2 (CH_3). ATR-FTIR (thin film): 2995, 2956, 2912, 2871, 2109, 1574, 1493, 1439, 1361, 1282, 1213, 807, 750 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{11}H_{15}N_3$ $(M)^+$: 189.1266, found: 189.1270.



(*E*)-2-*tert*-Butyl-4-styrylaniline 3.67. To a dry 100 mL round bottom flask equipped with a stir bar were added 2-0.456 g of 2-tert-butyl-4-bromoaniline (2 mmol), 0.429 g of (*E*)-2-phenylvinylboronic acid (2.9 mmol), K_2CO_3 (1.1 g) and 0.105 g of $Pd(PPh_3)_4$ (0.2 equiv). The mixture of toluene:H_2O:EtOH (3:2:1) was added to reaction flask. The resultant mixture was heated to 100 °C. After 16 hours, the mixture was cooled to room temperature and diluted with 20 mL of NH_4Cl. The resulting aqueous phase was extracted with an additional 3 × 20 mL of CH_2Cl_2. The combined organic phases were washed with 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification by MPLC (0:100 – 50:50 EtOAc: hexanes) afforded the product as a brown oil (0.366 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 7.5 Hz, 2H), 7.41 (d, J = 1.5 Hz, 1H), 7.34 – 7.37 (m, 2H), 7.28 (dd, J = 1.5, 8.0 Hz, 1H), 7.22 – 7.25 (m, 1H), 7.08 (d, J = 16.5 Hz, 1H), 6.95 (d, J = 16.5 Hz, 1H), 6.66 (d, J = 8.5 Hz, 1H), 3.93 (br, 2H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$)

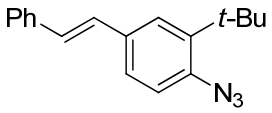
δ 144.5 (C), 138.2 (C), 133.6 (C), 129.4 (CH), 128.6 (CH), 127.9 (C), 126.8 (CH), 126.1 (CH), 125.8 (CH), 125.0 (CH), 124.8 (CH), 118.1 (CH), 34.3 (C), 29.6 (CH_3); ATR-FTIR (thin film): 3498, 3388, 3020, 2955, 2871, 1709, 1617, 1592, 1497, 1410, 1277, 1192, 958, 813, 751, 691 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{18}H_{21}N$ $(M)^+$: 251.1674, found: 251.1671.



(eq. 3.9)

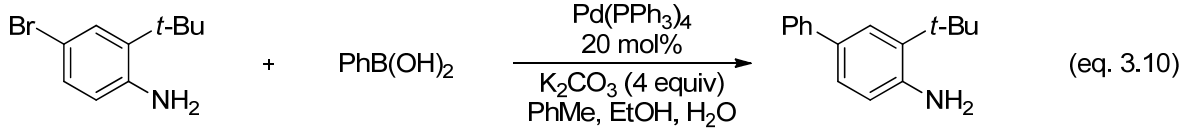
1-Azido-2-*tert*-butyl-4-phenethylbenzene 3.12. A mixture of (*E*)-2-*tert*-butyl-4-styrylaniline **3.67** and Pd/C (Pd, 10 wt % on carbon powder) in THF were vigorous stirred at room temperature under hydrogen atmosphere. After 20h, visualization of the reaction progress using TLC indicated consumption of the starting material. The mixture then was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* to afford crude product, which was subjected to the *t*-$BuNO_2$-mediated azidation reaction without purification.

The general azidation procedure was followed using 0.506 g of 2-*tert*-butyl-4-phenethylaniline **3.68** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-$BuNO_2$ and 0.842 mL of $(CH_3)_3SiN_3$. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow oil (0.497 g, 89%).^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 (dt, *J* = 6.5, Hz, 1.0 Hz, 2H), 7.24 (m, 1H), 7.19 (d, *J* = 8.0 Hz, 2H), 7.11 (m, 2H), 7.09 (s, 1H), 2.94 (s, 4H), 1.41 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.6 (C), 140.7 (C), 138.1 (C), 135.6 (C), 128.6 (CH), 128.4 (CH), 127.8 (CH), 127.1 (CH), 126.0 (CH), 119.5 (CH), 38.1 (CH_2), 37.6(CH_2), 35.0 (C), 30.0 (CH_3); ATR-FTIR (thin film): 3027, 2953, 2863, 2102, 2061, 1602, 1489, 1291, 1076, 809, 745, 697 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{18}H_{21}N_3$ $(M)^+$: 279.1735, found: 279.1742.



3.14

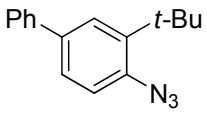
(*E*)-1-Azido-2-*tert*-butyl-4-styrylbenzene 3.14. The general azidation procedure was followed using 0.502 g of (*E*)-2-*tert*-butyl-4-styrylaniline **3.67** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-$BuNO_2$ and 0.842 mL of $(CH_3)_3SiN_3$. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow solid (0.432 g, 78%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.60 (d, *J* = 8.0 Hz, 2H), 7.57 (s, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.45 (t, *J* = 7.0 Hz, 2H), 7.35 (t, *J* = 7.5 Hz, 1H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.15 (d, *J* = 4.5 Hz, 2H), 1.53 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2 (C), 137.4 (C), 137.1 (C), 133.9 (C), 128.8 (CH), 128.35 (CH), 128.3 (CH), 127.7 (CH), 126.6 (CH), 126.0 (CH), 125.1 (CH), 120.0 (CH), 35.2 (C), 30.0 (CH_3); ATR-FTIR (thin film): 2999, 2957, 2863, 2104, 2070, 1591, 1480, 1357, 1289, 1073, 957, 891. 799, 690 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{18}H_{19}N_3$ $(M)^+$: 277.1579, found: 277.1568.



3.65 (1.3 equiv) **3.69** (eq. 3.10)

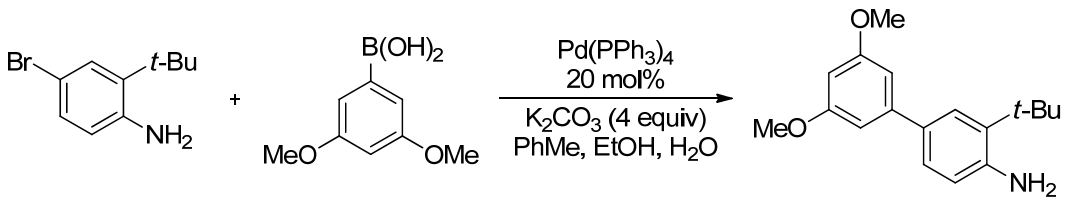
2-*tert*-Butyl-4-phenylaniline 3.69. To a dry 100 mL round bottom flask equipped with a stir bar were 0.456 g of 2-*tert*-butyl-4-bromoaniline (2 mmol), 0.354 g of phenylboronic acid (2.9 mmol), 1.1 g of K_2CO_3 (4 equiv) and 0.105 g of $Pd(PPh_3)_4$ (0.2 equiv). A mixture of toluene:H_2O:EtOH (3:2:1) was added to reaction flask. The resultant mixture was heated to 100 °C. After 16 hours, the mixture was cooled to room temperature and diluted with 20 mL of NH_4Cl. The resulting aqueous phase was extracted with an additional 3 × 20 mL of CH_2Cl_2. The combined organic phases were washed with 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification using MPLC

(0:100 – 50:50 EtOAc: hexanes) afforded aniline **3.69** as a brown oil (0.283 g, 63%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.66 (d, J = 1.0 Hz, 1H), 7.64 (d, J = 1.0 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 7.50 (t, J = 8.5 Hz, 2H), 7.40 – 7.35 (m, 2H), 6.79 (d, J = 8.0 Hz, 1H), 3.94 (s, 2H), 1.57 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2 (C), 141.9 (C), 133.9 (C), 131.6 (C), 128.8 (CH), 126.7 (CH), 126.3 (CH), 125.7 (CH), 118.3 (CH), 34.5 (C), 29.8 (CH_3) only visible signals; ATR-FTIR (thin film): 3497, 3385, 3028, 2955, 1617, 1483, 1402, 1292, 1240, 1157, 1024, 890, 762, 696 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{16}H_{19}N$ $(M)^{+}$: 225.1517, found: 225.1521.



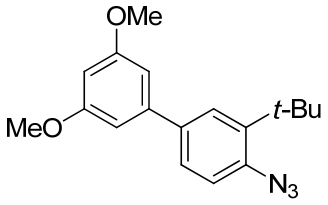
3.16

1-Azido-2-*tert*-butyl-4-phenylbenzene 3.16. The general azidation procedure was followed using 0.450 g of 2-*tert*-butyl-4-phenylaniline **3.69** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-$BuNO_2$ and 0.842 mL of $(CH_3)_3SiN_3$. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow solid (0.412 g, 82%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 – 7.59 (m, 3H), 7.45 – 7.50 (m, 3H), 7.35 -7.38 (m, 1H), 7.24 (s, 1H), 1.48 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.3 (C), 140.9 (C), 137.7 (C), 137.1 (C), 128.8 (CH), 127.2 (CH), 127.0 (CH), 126.3 (CH), 125.9 (CH), 120.0 (CH), 35.3 (C), 30.0 (CH_3); ATR-FTIR (thin film): 3004, 2948, 2903, 2116, 2089, 1600, 1475, 1394, 1290, 1240, 1075, 1023, 894, 811, 756 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{16}H_{17}N_3$ $(M)^{+}$: 251.1244, found: 251.1431.



3.65 (1.3 equiv) **3.70** (eq. 3.11)

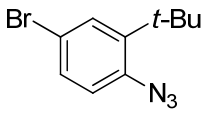
3-*tert*-Butyl-3',5'-dimethoxybiphenyl-4-amine 3.70. To a dry 100 mL round bottom flask equipped with a stir bar were added 0.456 g of 2-*tert*-butyl-4-bromoaniline (2 mmol), 0.548 g of 3,5-dimethoxyphenylboronic acid (2.9 mmol), 1.1 g of K_2CO_3 (4 equiv) and 0.105 g of $Pd(PPh_3)_4$ (0.2 equiv). A mixture of toluene:H_2O:EtOH (3:2:1) was added to reaction flask. The resultant mixture was heated to 100 °C. After 16 hours, the mixture was cooled to room temperature and diluted with 20 mL of NH_4Cl. The resulting aqueous phase was extracted with an additional 3 × 20.0 mL of CH_2Cl_2. The combined organic phases were washed with 30.0 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification by MPLC (0:100 – 50:50 EtOAc: hexanes) afforded aniline **3.70** as a light brown solid (0.416 g, 73%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 2.0 Hz, 1H), 7.33 (dd, *J* = 6.0 Hz, 2.0 Hz, 1H), 6.76 (d, *J* = 2.0 Hz, 2H), 6.74 (d, *J* = 8.0 Hz, 1H), 6.48 (t, *J* = 2.0 Hz, 1H), 3.96 (s, 2H), 3.89 (s, 6H), 1.52 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1 (C), 157.9 (C), 144.5 (C), 144.2 (C), 133.8 (C), 131.5 (C), 125.7 (CH), 118.1 (CH), 105.1 (CH), 98.2 (CH), 94.3 (CH), 93.1 (CH), 55.4 (CH_3), 34.5 (C), 29.7 (CH_3); ATR-FTIR (thin film): 2975, 2925, 2855, 1685, 1600, 1480, 1455, 1386, 1290, 1245, 1163, 908, 724 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{18}H_{23}NO_2$ $(M)^+$: 285.1729, found: 285.1712.



3.18

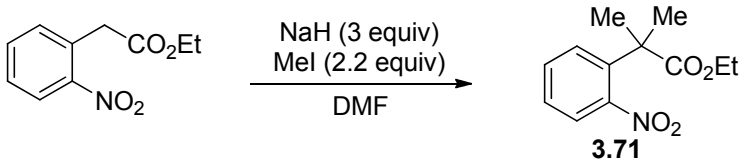
4-Azido-3-*tert*-butyl-3, 5'-dimethoxybiphenyl 3.18. The general azidation procedure was followed using 0.570 g of 3-*tert*-butyl-3',5'-dimethoxybiphenyl-4-amine **3.70** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-$BuNO_2$ and 0.842 mL of $(CH_3)_3SiN_3$. Purification by MPLC (0:100

– 10:90 EtOAc:hexanes) afforded the product as a brown yellow solid (0.566 g, 91%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 8.5 Hz, 1H), 6.83 (s, 2H), 6.58 (s, 1H), 3.92 (s, 6H), 1.58 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.3 (C), 143.1 (C), 141.3 (C), 137.7 (C), 137.4 (C), 126.4 (CH), 126.0 (CH), 120.0 (CH), 105.5 (CH), 99.1 (CH), 55.4 (CH_3), 35.3 (C), 30.1 (CH_3); ATR-FTIR (thin film): 2995, 2955, 2838, 2117, 2079, 1592, 1495, 1456, 1386, 1285, 1202, 1151, 929, 812 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{18}H_{21}N_3O_2$ $(M)^+$: 311.1634, found: 311.1620.



3.20

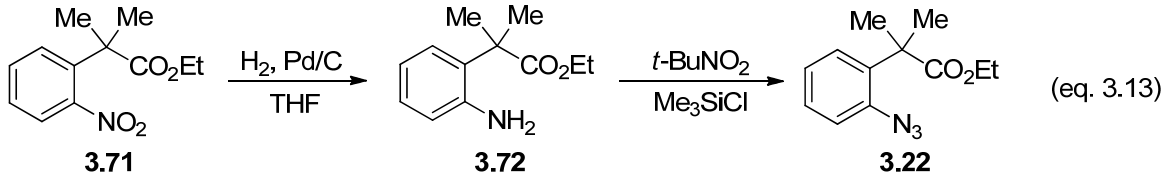
1-Azido-4-bromo-2-*tert*-butylbenzene 3.20. The general procedure was followed using 0.454 g of 4-bromo-2-*tert*-butylaniline **3.65** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-$BuNO_2$ and 0.842 mL of $(CH_3)_3SiN_3$. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a brown yellow oil (0.409 g, 81%). ^{1}H NMR (500MHz, $CDCl_3$) δ 7.53 (d, J = 2.0 Hz, 1H), 7.37 (dd, J = 6.5 Hz, 2.0 Hz, 1H), 7.03 (d, J = 8.5 Hz, 1H), 1.46 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.2 (C), 137.2 (C), 130.6 (CH), 130.0 (CH), 121.0 (CH), 117.9 (C), 35.3 (C), 29.7 (CH_3). ATR-FTIR (thin film): 2991, 2956, 2909, 2118, 2088, 1585, 1565, 1481, 1362, 1289, 1077, 805, 583 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{10}H_{12}BrN_3$ $(M)^+$: 253.0215, found: 253.0220.



3.71 (eq. 3.12)

2-Methyl-2-(2-nitrophenyl)proponic acid ethyl ester 3.71. Following the procedure reported by Glorius and co-workers, methyl ester **3.71** was prepared.[4] To a 2.1 g of (2-nitro-

phenyl)-acetic acid methyl ester (10.0 mmol), and 2 mL of MeI (22.0 mmol) in 20 mL of DMF at 0 °C was added small amount of NaH (60% in mineral oil) until the mixture turn blue. The rest NaH (total 1.2 g, 30.0 mmol) was added gradually during 30 minutes while the temperature was kept at 0 °C. Then the reaction was warmed to room temperature. After 6 hours, the mixture was diluted with 60 mL of H_2O and extracted with 4 × 30 mL of Et_2O. The organic phase was concentrated. Purification by MPLC (2:98 – 10:90 EtOAc:hexanes) afforded the product as a light yellow solid (1.9 g, 80%). The spectral data matched that reported by Glorius and co-workers [4]. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, J = 8.0 Hz, 1H), 7.57 – 7.58 (m, 2H), 7.35 – 7.38 (m, 1H), 4.06 (q, J = 7.0 Hz, 2H), 1.63 (s, 6H), 1.14 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 175.1 (C), 148.7 (C), 139.4 (C), 133.2 (CH), 128.1 (CH), 127.7 (CH), 125.5 (CH), 61.0 (CH_2), 46.4 (C), 27.5 (CH_3), 13.9 (CH_3); ATR-FTIR (thin film): 2985, 1722, 1526, 1351, 1227, 1111, 911, 729 cm^{-1}.

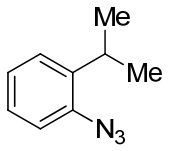


(eq. 3.13)

Ethyl 2-(2-azidophenyl)-2-methylpropanoate 3.22. Reduction of the nitro group was accomplished by mixing 0.47 g of ethyl ester **3.71** and 0.1 g of Pd on activated carbon in 10 mL of MeOH. A balloon of hydrogen was attached. After 4 hours, the balloon was removed, and the reaction mixture was filtered. The resulting filtrate was concentrated *in vacuo* to afford aniline **3.72**, which was used in the azidation reaction without further purification.

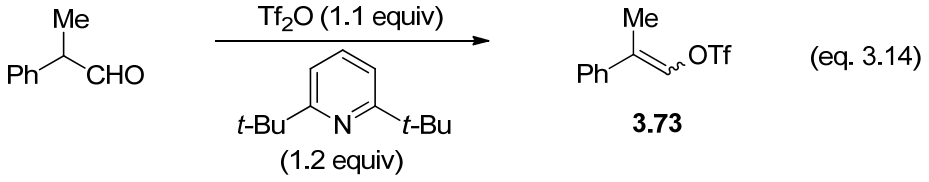
The general procedure for azidation was followed using 0.41 g of ethyl 2-(2-aminophenyl)-2-methylpropanoate **3.72** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-$BuNO_2$ and 0.842 mL of $(CH_3)_3SiN_3$. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the

product as a yellow oil (0.16 g, 34%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.36 – 7.34 (m, 1H), 7.33 – 7.29 (m, 1H), 7.17 – 7.14 (m, 2H), 4.16 (q, *J* = 7.0 Hz, 2H), 1.54 (s, 6H), 1.19 (t, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.1 (C), 137.5 (C), 136.4 (C), 128.0 (CH), 126.4 (CH), 124.9 (CH), 118.6 (CH), 60.8 (CH_2), 45.1 (C), 26.1 (CH_3), 14.1 (CH_3); ATR-FTIR (thin film): 2987, 2931, 2122, 2092, 1729, 1578, 1487, 1445, 1382, 1285, 1140, 858, 748, 672 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{12}H_{15}N_3O_2$ $(M)^+$: 233.1164, found: 233.1166.



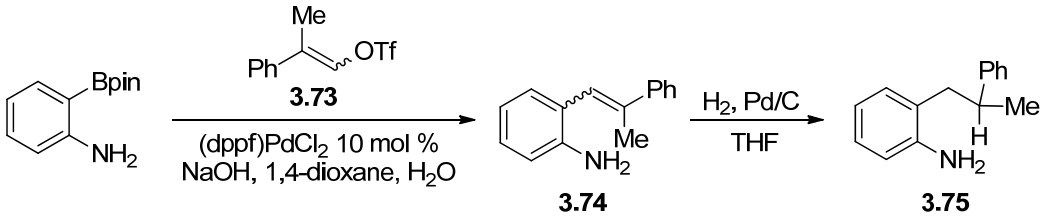
3.24

1-Azido-2-isopropylbenzene 3.24. [7] The general procedure was followed using 0.270 g of 2-isopropylaniline (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-$BuNO_2$ and 0.842 mL of $(CH_3)_3SiN_3$. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow solid (0.258 g, 80%). The spectral data matched that reported by Fokin and co-workers.[7] ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30 (d, *J* = 7.5 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 7.17 – 7.13 (m, 2H), 3.26 (m, *J* = 7.0 Hz, 1H), 1.25 (d, *J* = 7.0 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 140.0 (C), 137.2 (C), 126.9 (CH), 126.6 (CH), 125.0 (CH), 118.1 (CH), 28.0 (CH), 22.9 (CH_3); ATR-FTIR (thin film): 3067, 2963, 2121, 2091, 1580, 1487, 1445, 1290, 1077, 907, 748 cm^{-1}.



(E)-2-phenylprop-1-enyl trifluoromethanesulfonate 3.73. To a mixture of 1.32 mL of 2-phenylpropanal (10.0 mmol) and 2.65 mL of 2,6-di-*tert*-butylpyridine (12.0 mmol) in 40 mL

of 1,2-dichloroethane was added 1.85 mL of triflic anhydride (11.0 mmol). The resultant mixture was heated to 70 °C. After 2h, the mixture was cooled to room temperature and diluted with 40 mL of CH_2Cl_2. The phases were separated, and the resulting aqueous phase was extracted with an additional 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, and was concentrated *in vacuo* to afford 2.53 g of triflate **3.73**, which was used in the subsequent Suzuki cross-coupling reaction without further purification.

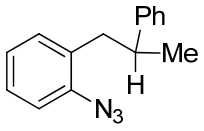


(eq. 3.15)

Aniline 3.74. To a mixture of 0.7 g of 2-aniline boronic pinacol ester (3.2 mmol), 0.261 g of (dppf)$PdCl_2$ (0.32 mmol) in 40 mL of 1,4-dioxane was added 8 mL of a 3 M solution of NaOH in water followed by 1.36 g of triflate **3.73** (5.12 mmol). The resultant mixture was heated to 80 °C. After 12 h, the mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was diluted with 20 mL of a saturated aqueous solution of NH_4Cl. The phases were separated and the resulting aqueous phase was extracted with an additional 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, and was concentrated *in vacuo* to afford 0.627 g of aniline **3.74**, which was submitted to the subsequent hydrogenation step without further purification.

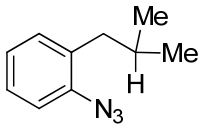
To a mixture of 0.627 g of aniline **3.74** and 0.540 g of Pd/C (Pd, 10 wt % on carbon powder) in 40 mL of THF was added a balloon of H_2. After 16 h the balloon was removed, and the reaction mixture was filtered. The resulting filtrate was concentrated *in vacuo*. Purification

by MPLC (0:100 – 5:95 EtOAc:hexane) afforded 0.397 g of aniline **3.75** as a yellow oil (1.76 mmol, 59% over two steps).). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.32 – 7.35 (m, 2H), 7.23 – 7.26 (m, 3H), 7.05 – 7.08 (m, 1H), 7.0 (d, *J* = 8.0 Hz, 1H), 6.74 (t, *J* = 8.0 Hz, 1H) 6.67 (d, *J* = 8.0 Hz, 1H), 3.44 (br, 2H), 3.09 – 3.15 (m, 1H), 2.85 (dd, *J* = 6.5 Hz, 14.0 Hz, 1H), 2.74 (dd, *J* = 8.0 Hz, 14.0 Hz, 1H), 1.36 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1 (C), 144.5 (C), 131.0 (CH), 128.5 (CH), 127.2 (CH), 127.0 (CH), 126.3 (CH), 125.3 (C), 118.7 (CH), 115.9 (CH), 40.8 (CH_2), 39.5 (CH), 21.4 (CH_3); ATR-FTIR (thin film): 3451, 3371, 1621, 1490, 1449, 1268, 907 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{15}H_{17}N$ $(M)^+$: 211.1361, found: 211.1380.



3.26

Azide 3.26. The general azidation procedure was followed using 0.422 g of 2-(2-phenylpropyl)aniline **3.75** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-$BuNO_2$ and 0.842 mL of $(CH_3)_3SiN_3$. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow oil (0.356 g, 75%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (t, *J* = 7.5 Hz, 2H), 7.23 – 7.29 (m, 4H), 7.17 (d, *J* = 8.0 Hz, 1H), 7.04 (m, 2H), 3.08 – 3.15 (m, 1H), 2.93 (dd, *J* = 7.0 Hz, 13.0 Hz, 1H), 2.84 (dd, *J* = 7.0 Hz, 13.0 Hz, 1H), 1.31 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.9 (C), 138.3 (C), 132.4 (C), 131.5 (CH), 128.3 (CH), 127.5 (CH), 127.1 (CH), 126.1 (CH), 124.4 (CH), 118.1 (CH), 40.5 (CH_2), 40.3 (CH), 21.0 (CH_3); IR (thin film): 2113, 1578, 1490, 1448, 1281, 1148, 902, 731 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{15}H_{15}N_3$ $(M)^+$: 237.1266, found: 237.1276.



3.28

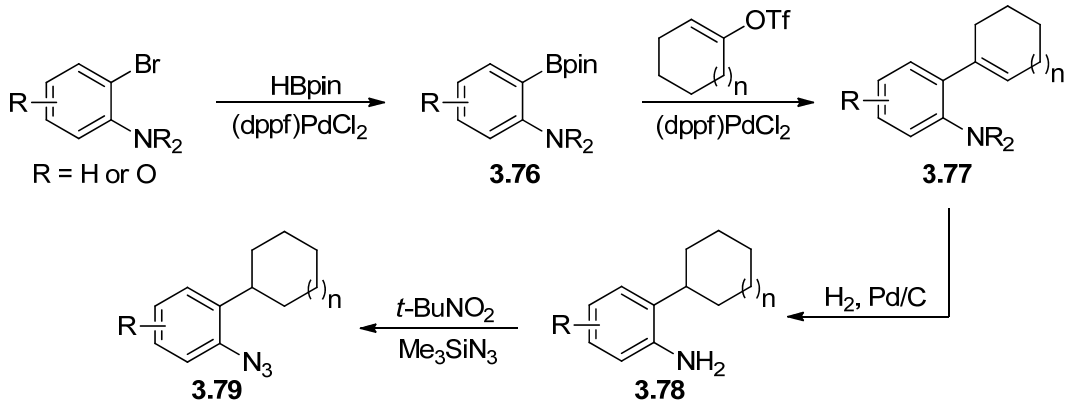
1-Azido-2-*n*-propylbenzene 3.28.[8] The general procedure was followed using 0.270 mg of 2-*n*-butylaniline (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-$BuNO_2$ and 0.842 mL of $(CH_3)_3SiN_3$. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow oil (0.264 g, 82%). The spectral data matched that reported by Driver and co-workers.[8] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.25 – 7.28 (m, 1H), 7.15 – 7.20 (m, 2H), 7.08 – 7.11 (m, 1H), 2.59 (t, *J*= 7.5 Hz, 2H), 1.64 (td, *J*= 10.Hz, *J*= 7.5 Hz, 2H), 0.99 (t, *J*= 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.0, 134.2, 130.5, 127.2, 124.6, 118.1, 33.3, 23.5, 14.0; IR (thin film): 2122, 1582, 1489, 1450, 1285, 1450, 1107, 750, 653 cm^{-1}.

3.6.2 Preparation of Substituted *ortho*-cycloalkyl-Substituted Aryl Azides

Route to Substrates.

Substituted *ortho*-azido-cycloalkylbenzenes were synthesized using the route outlined in Scheme s1. Arylboronic pinacol esters **3.76** were prepared from corresponding 2-bromoaniline or 2-bromo-1-nitrobenzene. A subsequent Suzuki cross-coupling reaction with a vinyl triflate afforded substituted 2-cycloalkenylanilines **3.77**. Hydrogenation of **3.77** using the combination of Pd/C and H_2 afforded 2-cycloalkylanilines **3.78**. Treatment of the anilines with *tert*-butyl nitrite and azidotrimethylsilane provided the requisite aryl azides **3.79**.

Scheme 3.3. Synthetic route to *ortho*-cyclosubstituted aryl azides.



Synthesis of Aryl Boronic Pinacol Esters

A. General Procedure

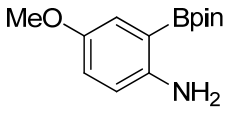
The requisite arylboronic pinacol esters were prepared in one-step from commercially available *ortho*-bromoanilines and HBPin using (dppf)$PdCl_2$ as catalyst. Yields were not optimized.

(eq. 3.16)

To a mixture of 2-bromo-aniline (5.00 mmol), 0.185 g of (dppf)$PdCl_2$ (0.250 mmol), 2.78 mL of Et_3N (20.0 mmol) in 20.0 mL of 1,4-dioxane, was added dropwise 2.17 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.0 mmol). The resultant mixture was heated to 100 °C. After 16h, the mixture was cooled to room temperature and diluted with 20.0 mL of NH_4Cl. The resulting aqueous phase was extracted with an additional 3 × 20.0 mL of CH_2Cl_2. The combined organic phases were washed with 30.0 mL of brine. The resulting organic phase was dried over

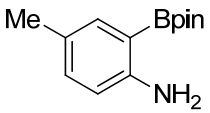
Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification using MPLC afforded the product.

B. Syntheses



3.80

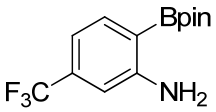
Aryl boronicpinacol ester 3.80.[9] The general procedure was following using 2.02 g of 2-bromo-4-methoxylaniline (10.0 mmol), 0.401 mg of (dppf)$PdCl_2$ (0.500 mmol), 4.40 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30.0 mmol) and 5.70 mL of Et_3N (40.0 mmol) in 50.0 mL of 1,4-dioxane. Purification by MPLC (5:100 – 10:90 EtOAc: hexanes) afforded the product as a brown liquid (1.53 g, 62%). The spectral data matched that reported by Driver and co-workers.[9] ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.15 (s, 1H), 6.85 (dd, J = 8.5, 3.0 Hz, 1H), 6.57 (d, J = 8.5 Hz, 1H), 4.47 (s, 2H), 3.76 (s, 3H), 1.34 (s, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.4 (C), 148.0 (C), 120.6 (CH), 119.6 (CH), 116.5 (CH), 83.6 (C), 56.0 (CH_3), 25.0 (CH_3) only signals visible; ATR-FTIR (thin film): 3456, 3366, 1494, 1421, 1359, 1304, 1226, 1037, 855, 829, 750 cm^{-1}.



3.81

Aryl boronicpinacol ester 3.81. The general procedure was following using 1.86 g of 2-bromo-4-methylaniline (10.0 mmol), 0.401 g of (dppf)$PdCl_2$ (0.500 mmol), 4.40 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30.0 mmol) and 5.70 mL of Et_3N (40.0 mmol) in 50.0 mL of 1,4-dioxane. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the product as a dark gold solid (0.840 g, 36%), mp 60 °C, R_f = 0.45 (15:75 EtOAc:hexanes, visualized by 254

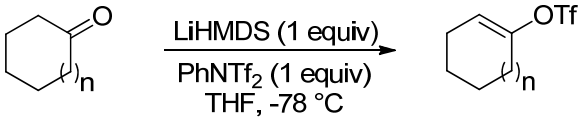
nm UV light). ^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.48 (s, 1H), 7.08 (d, J = 8.0 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 4.65 (s, 2H), 2.26 (s, 3H), 1.38 (s, 12H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ 151.5 (C), 136.8 (CH), 133.7 (CH), 125.8 (C), 115.1 (CH), 83.5 (C), 25.0 (CH_3), 20.3 (CH_3) only signals visible; ATR-FTIR (thin film): 3500, 2980, 2244, 1618, 1576, 1496 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{13}H_{20}BNO_2$ $(M)^+$: 233.1587, found: 233.1583.



3.82

Aryl boronicpinacol ester 3.82. The general procedure was following using 2.40 g of 2-bromo-5-(trifluoromethyl)aniline (10.0 mmol), 0.401 g of (dppf)$PdCl_2$ (0.500 mmol), 4.40 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30.0 mmol) and 5.7 mL of Et_3N (40.0 mmol) in 50.0 mL of 1,4-dioxane. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow solid (1.83 g, 64%): mp 63-65 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (d, J = 7.5 Hz, 1H), 6.93 (d, J = 7.5 Hz, 1H), 6.83 (s, 1H), 5.03 (s, 2H), 1.38 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9 (C), 137.6 (CH), 134.3 (q, J_{CF} = 32 Hz, C), 124.3 (q, J_{CF} = 272 Hz, CF_3), 112.6 (q, J_{CF} = 3.4 Hz, CH), 110.9 (q, J_{CF} = 4.5 Hz, CH), 84.0 (C), 24.8 (CH_3) only signals visible; ^{19}F NMR (282 MHz, $CDCl_3$) δ –63.948. ATR-FTIR (thin film): 3499, 3397, 2980, 2958, 2929, 1622, 1508, 1437, 1333, 1245 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{13}H_{17}BFNO_2$ $(M)^+$: 287.1304, found: 287.1310.

General Procedure for the Synthesis of Vinyl Trifles



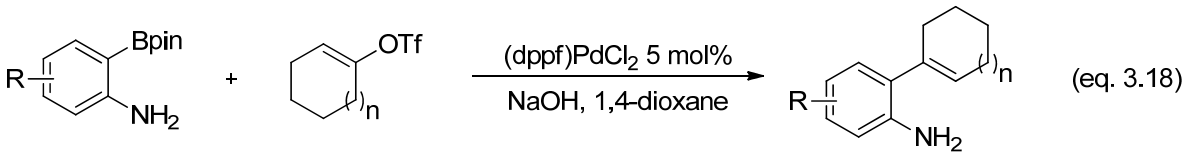
(eq. 3.17)

To a stirring solution of 1.67 g of LiHMDS (10.0 mmol) in THF (30.0 mL) at –78 °C was added 10.0 mmol of cyclic ketone. The resultant mixture was warmed to room temperature for 1h, then cooled to –78 °C. A solution of 3.57 g of $PhNTf_2$ (10.0 mmol) in THF was added to reaction mixture in one portion, and then the mixture was maintained at –78 °C for 1h. The cooling bath was removed, and the reaction mixture was allowed to warm to room temperature. After 18h at room temperature, the mixture was diluted with 40.0 mL of CH_2Cl_2. The resulting aqueous phase was extracted with an additional 2 × 30.0 mL of CH_2Cl_2. The combined organic phases were washed with 30.0 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo* to afford crude triflate..

Suzuki Reaction of *ortho*-Bromoanilines

A. General Procedure.

Following the procedure of Driver and co-workers,[9] a series of aryl boronicpinacol esters were treated with cyclic triflates in the presence of $(dppf)PdCl_2$ to produce the desire aniline. Yields were not optimized.

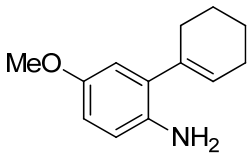


3.76 **3.77** (eq. 3.18)

To a mixture of 1.00 mmol of boronic ester **3.76**, and 0.037g of $(dppf)PdCl_2$ (0.050 mmol) in 15 mL of 1,4-dioxane was added 3.00 mL of a 3M solution of NaOH in water followed by 1.20 mmol of cycloalkyltriflate. The resultant mixture was heated to 100 °C. After 12 h, the mixture was cooled to room temperature and diluted with 10 mL of a saturated aqueous solution of NH_4Cl. The resulting mixture was separated, and the aqueous phase was extracted with an additional 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 30 mL of

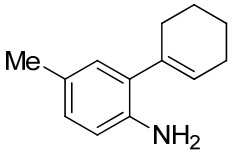
brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification of the oily residue using MPLC afforded the product.

B. Syntheses



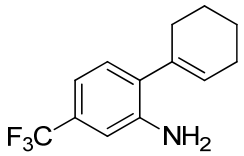
3.83

Aniline 3.83. The general procedure was following using 1.24 g of boronic ester **3.80** (5.00 mmol), crude cyclohexyltriflate (derived from 10.0 mmol of cyclohexanone), 0.183 g of (dppf)$PdCl_2$, and 1.80 g of NaOH (45.0 mmol) in 75.0 mL of 1,4-dioxane and 15.0 mL of water. Purification by MPLC (10:90 – 50:50 EtOAc: hexanes) afforded the product as a brown yellow oil (0.741 g, 73%), R_f = 0.78 (50:50 EtOAc:hexanes, visualized by 254 nm UV light): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.65 (d, *J* = 1.5 Hz, 2H), 6.60 (d, *J* = 1.5 Hz, 1H), 5.76 (t, *J* = 9.0 Hz, 1H), 3.75 (s, 3H), 3.54 (s, 2H), 2.27 (d, *J* = 2.0 Hz, 2H), 2.20 (d, *J* = 3.5 Hz, 2H), 1.79 (d, *J* = 6.0 Hz, 2H), 1.71 (d, *J* = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5 (C), 136.9 (C), 136.6 (C), 131.7 (C), 126.9 (CH), 116.6 (CH), 114.3 (CH), 113.2 (CH), 55.7 (CH_3), 29.3 (CH_2), 25.5 (CH_2), 23.2 (CH_2), 22.2(CH_2). ATR-FTIR (thin film): 3420, 3009, 2929, 2227, 1623, 1521, 1462, 987, 758 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{13}H_{17}NO$ $(M)^+$: 203.1310, found: 203.1296.



3.84

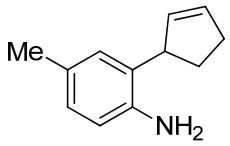
Aniline 3.84. The general procedure was following using 1.16 g of boronic ester **3.81** (5.00 mmol), crude cyclohexyltriflate (derived from 10.0 mmol of cyclohexanone), 0.183 g of (dppf)$PdCl_2$, and 1.80 g of NaOH (45.0 mmol) in 75.0 mL of 1,4-dioxane and 15.0 mL of water. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the product as a dark red oil (0.842 g, 90%), R_f = 0.47 (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.96 (dd, *J* = 7.0 Hz, 1.0 Hz, 1H), 6.93 (s, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 5.86 (t, *J* = 2.0 Hz, 1H), 3.73 (s, 2H), 2.36 (m, 2H), 2.35 (s, 3H), 2.28 (m, 2H), 1.9 (m, 2H), 1.8 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.7 (C), 136.8 (C), 130.6 (C), 129.3 (CH), 128.1 (CH), 127.4 (C), 126.7 (CH), 115.7 (CH), 29.6 (CH_2), 25.6 (CH_2), 23.4 (CH_2), 22.4(CH_2), 20.6 (CH_3). ATR-FTIR (thin film): 3444, 2927, 2224, 1618, 1500, 1461, 815 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{13}H_{17}N$ $(M)^+$: 187.1361, found: 187.1365.



3.85

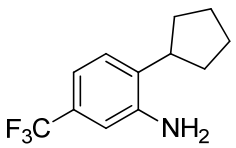
Aniline 3.85. The general procedure was following using 1.43 g of boronic ester **3.82** (5.00 mmol), crude cyclohexyltriflate (derived from 10.0 mmol of cyclohexanone), 0.183 g of (dppf)$PdCl_2$, and 1.80 g of NaOH (45.0 mmol) in 75.0 mL of 1,4-dioxane and 15.0 mL of water. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.961 g, 80%), R_f = 0.45 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (d, *J* = 8.0 Hz, 1H), 6.97 (d, *J* = 8.0 Hz, 1H), 6.92 (s, 1H), 5.8 (s, 1H), 3.94 (s, 2H), 2.21 (m, 4H), 1.75 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.7 (C), 135.6 (C), 133.5 (C), 129.7 (q, J_{CF} = 31 Hz, C), 129.1 (CH), 127.9 (CH), 124.5 (q, J_{CF} = 270 Hz, CF_3), 114.7 (q, J_{CF} = 3 Hz, C), 111.7 (q, J_{CF} = 3.5 Hz, C), 29.2 (CH_2), 25.4 (CH_2), 23.1 (CH_2), 22.1(CH_2); ^{19}F

NMR (282 MHz, $CDCl_3$) δ –61.06. ATR-FTIR (thin film): 2936, 2240, 1619, 1512, 1433, 1333 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{13}H_{14}NF_3$ $(M)^+$: 241.1078, found: 241.1081.



3.86

2-(cyclopent-2-enyl)-4-methyl-1-nitrobenzene 3.86. Following the procedure of Larock and co-workers,[10] nitrobenzene **3.86** was synthesized using 0.71 mL of 2-iodo-4-methyl-1-nitrobenzene (5 mmol), 1.7 g of cyclopentene (5 equiv), 0.028 g of $Pd(OAc)_2$ (2.5 mol %), 1.39 g of *n*-Bu_4NCl (1 equiv), 0.735 g of KOAc (3 equiv), 0.0328 g of PPh_3 (2.5 mol %) in 10 mL of DMF. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.457 g, 45%). ^1H NMR (500 MHz, $CDCl_3$) δ 7.74 (d, *J* = 7.5 Hz, 1H), 7.13 (s, 1H), 7.10 (d, *J* = 9.0 Hz, 1H), 6.03 (m, 1H), 5.68 (m, 1H), 4.38 (m, 1H), 2.65 – 2.60 (m, 1H), 2.52 – 2.43 (m, 2H), 2.39 (s, 3H), 1.73 – 1.66 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.1 (C), 143.9 (C), 141.1 (C), 133.6 (CH), 132.6 (CH), 129.4 (CH), 127.4 (CH), 124.3 (CH), 46.4 (CH), 33.5 (CH_2), 32.3 (CH_2), 21.5 (CH_3). ATR-FTIR (thin film): 3004, 2933, 1614, 1531, 1467, 1331, 1195, 845, 735, 679 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{12}H_{13}NO_2$ $(M)^+$: 203.0946, found: 203.0934.



3.87

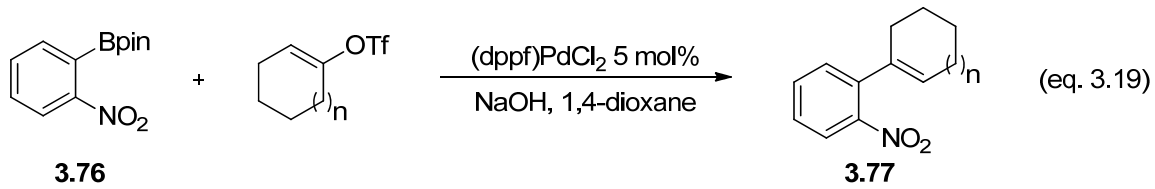
Aniline 3.87. The general Suzuki cross-coupling procedure was following using 1.43 g of boronic ester **3.82** (5.00 mmol), crude cyclopentyltriflate (derived from 10.0 mmol of

cyclopentanone), 0.183 g of (dppf)$PdCl_2$, and 1.80 g of NaOH (45.0 mmol) in 75.0 mL of 1,4-dioxane and 15.0 mL of water. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the aniline as a red oil which was submitted to the subsequent hydrogenation step. To a mixture of 0.829 g of aniline and 0.273 g of Pd/C (Pd, 10 wt % on carbon powder) in 20 mL of THF was added a balloon of H_2. After 16 h the balloon was removed, and the reaction mixture was filtered. The resulting filtrate was concentrated *in vacuo*. Purification by MPLC (0:100 – 5:95 EtOAc:hexane) afforded 0.652 g of aniline **3.87** as a yellow oil (2.85 mmol, 57% over two steps). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 (d, J = 8.0 Hz, 1H), 6.98 (d, J = 8.0 Hz, 1H), 6.89 (s, 1H), 3.84 (s, 2H), 2.98 (m, 1H), 2.09 – 2.05 (m, 2H), 1.84 – 1.80 (m, 2H), 1.74 – 1.71 (m, 2H), 1.67 – 1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4 (C), 133.9 (C), 128.8 (q, J_{CF} = 31 Hz, C), 126.3 (CH), 124.4 (q, J_{CF} = 270 Hz, CF_3), 115.2 (q, J_{CF} = 4.3 Hz, C), 111.9 (q, J_{CF} = 3.6 Hz, C), 39.9 (CH), 32.0 (CH_2), 25.2 (CH_2); ^{19}F NMR (282 MHz, $CDCl_3$) δ –62.94. ATR-FTIR (thin film): 3485, 3403, 2956, 2870, 1624, 1513, 1433, 1335, 1256, 1116, 927, 814 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{12}H_{14}NF_3$ $(M)^+$: 229.1078, found: 229.1075.

Suzuki Reaction of 2-Bromo-1-Nitrobenzenes

A. General Procedure

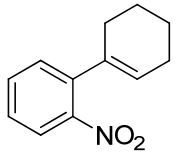
Following the procedure of Driver and co-workers,[9] 2-nitrophenylboronic acid was treated with a cyclic triflate in the presence of (dppf)$PdCl_2$ to produce the desire 2-cycloalkenylnitrobenzenes. Yields were not optimized.



3.76 **3.77** (eq. 3.19)

To a mixture of 0.165 g of 2-nitrophenylboronic acid (1.00 mmol), 0.037g of (dppf)$PdCl_2$ (0.050 mmol) in 15 mL of 1,4-dioxane was added 3 mL of a 3M solution of NaOH in water followed by 1.20 mmol of cycloalkenyltriflate. The resultant mixture was heated to 100 °C. After 12 h, the mixture was cooled to room temperature and diluted with 10 mL of saturated aqueous solution of NH_4Cl. The phases were separated, and the aqueous phase was extracted with an additional 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification of the oily residue using MPLC afforded the product.

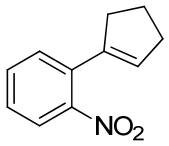
B. Syntheses



3.88

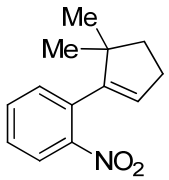
Nitrobenzene 3.88. The general procedure was following using 0.825 g of boronic acid (5.00 mmol), crude cyclohexenyl triflate (derived from 10.0 mmol of cyclohexanone), 0.183 g of (dppf)$PdCl_2$, 1.80 g of NaOH (45.0 mmol) in 75.0 mL of 1,4-dioxane and 15.0 mL of water. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the product as a brown yellow oil (0.995 g, 98%), R_f = 0.5 (15:75 EtOAc:hexanes, visualized by 254 nm UV light):^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 9.0 Hz, 1H), 7.30 (t, *J* = 7.0 Hz, 1H), 7.23 (d, *J* = 7.5 Hz, 1H), 5.57 (t, *J* = 2.0 Hz, 1H), 2.18 (q, *J* = 2.5 Hz, 2H), 2.09 (q, *J* = 2.5 Hz, 2H), 1.71 (q, *J* = 3.5 Hz, 2H), 1.62 (q, *J* = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.7 (C), 139.4 (C), 135.9 (C), 132.4 (CH), 130.8 (CH), 127.4 (CH), 126.6 (CH), 123.8 (CH), 29.3 (CH_2), 25.4 (CH_2), 22.8 (CH_2), 21.7 (CH_2). ATR-FTIR (thin film): 2956, 2928, 2859, 2249, 1606, 1571,

1526, 1457, 1264 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{12}H_{13}NO_2$ $(M)^+$: 203.0946, found: 203.0953.



3.89

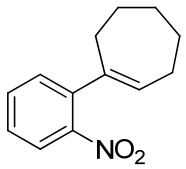
Nitrobenzene 3.89. The general procedure was following using 0.825 g of boronic acid (5.00 mmol), crude cyclohexyltriflate (derived from 10.0 mmol of cyclohexanone), 0.183 g of (dppf)$PdCl_2$, and 1.80 g of NaOH (45.0 mmol) in 75.0 mL of 1,4-dioxane and 15.0 mL of water. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the product as a brown yellow oil (0.995 g, 98%), R_f = 0.5 (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (d, *J* = 7.0 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.35 – 7.31 (m, 2H), 5.81 (t, *J* = 2.0 Hz, 1H), 2.57 (t, *J* = 7.0 Hz, 2H), 2.47 (t, *J* = 6.5 Hz, 2H), 2.00 (m, *J* = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.8 (C), 140.0 (C), 133.5 (C), 132.1 (CH), 130.8 (CH), 127.6 (CH), 123.6 (CH), 35.3 (CH_2), 33.5 (CH_2), 24.1 (CH_2) only visible signals. ATR-FTIR (thin film): 2964, 2934, 2849, 2229, 1623, 1573, 1526, 1459, 1265, 987, 783 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{11}H_{11}NO_2$ $(M)^+$: 189.0790, found: 189.0799.



3.90

Nitrobenzene 3.90. The general procedure was following using 0.825 g of boronic acid (5.00 mmol), crude cyclopentyltriflate (derived from 10.0 mmol of 2,2-dimethylcyclopentanone),

0.183 g of (dppf)$PdCl_2$, and 1.80 g of NaOH (45.0 mmol) in 75.0 mL of 1,4-dioxane and 15.0 mL of water. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the impure product as a yellow oil. This product was carried on to the next step without any characterization.

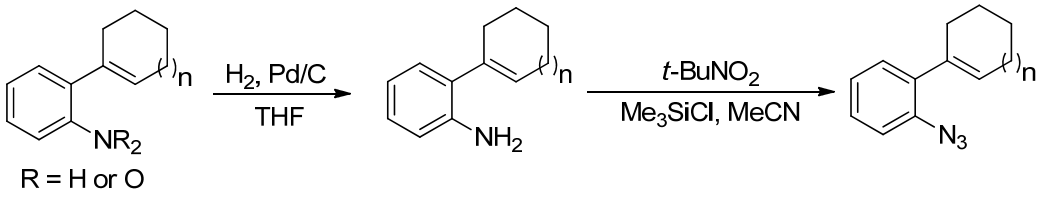


3.91

Nitrobenzene 3.91. The general procedure was following using 0.825 g of boronic acid (5.00 mmol), crude cycloheptyltriflate (derived from 10.0 mmol of cycloheptanone), 0.183 g of (dppf)$PdCl_2$, and 1.80 g of NaOH (45.0 mmol) in 75.0 mL of 1,4-dioxane and 15.0 mL of water. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.998 g, 92%), R_f = 0.5 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 (d, *J* = 8.0 Hz, 1H), 7.46 (t, *J* = 8 Hz, 1H), 7.30 (t, *J* = 7.5 Hz, 1H), 7.25 (d, *J* = 7.5 Hz, 1H), 5.79 (t, *J* = 6.5 Hz, 1H), 2.40 (t, *J* = 5.5 Hz, 2H), 2.23 (q, *J* = 6.0 Hz, 2H), 1.78 (m, *J* = 6 Hz, 2H), 1.61 (m, *J* = 6 Hz, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.0 (C), 142.4 (C), 141.3 (C), 132.5 (CH), 132.0 (CH), 130.9 (CH), 127.2 (CH), 123.9 (CH), 34.6 (CH_2), 32.3 (CH_2), 29.1 (CH_2), 26.8 (CH_2), 26.7 (CH_2). ATR-FTIR (thin film): 2923, 2848, 1713, 1606, 1524, 1350, 904, 783, 725 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{13}H_{15}NO_2$ $(M)^+$: 217.1103, found: 217.1115.

Preparation of the Aryl Azide Substrates through Hydrogenation/Azidation Sequence

A. General Procedure

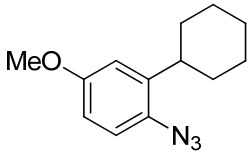


(eq. 3.20)

A mixture of aniline and Pd/C (Pd, 10 wt % on carbon powder) in THF were vigorous stirred at room temperature under hydrogen atmosphere. After 20h, visualization of the reaction progress using TLC indicated consumption of the starting material. The mixture then was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* to afford crude 2-cycloalkylaniline, which was subjected to the *t*-$BuNO_2$-mediated azidation reaction without further purification.

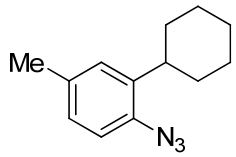
To a cooled solution of aniline in MeCN (0.2 M) was added dropwise *t*-$BuNO_2$ (4 equiv) and Me_3SiN_3 (3 equiv) dropwise. The resulting solution was warmed to room temperature. After 1h, visualization of the reaction progress using TLC indicated the consumption of the starting material. De-ionized H_2O was then added to the reaction mixture. The mixture then was extracted with 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 20 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded azide **4**.

B. Syntheses



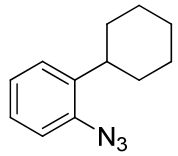
3.30

1-Azido-2-cyclohexyl-4-methoxybenzene 3.30. The general procedure was following using crude aniline (derived from 2 mmol of aniline **3.83**), 0.95 mL of *t*-$BuNO_2$, and 0.84 mL of Me_3SiN_3. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a brown yellow oil (0.296 g, 64%), R_f = 0.7 (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.06 (d, *J* = 9 Hz, 1H), 6.83 (s, 1H), 6.78 (d, *J* = 8.5 Hz, 1H), 3.81 (s, 3H), 2.85 (t, *J* = 11.5 Hz, 1H), 1.84 (m, 5H), 1.40 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 157.1 (C), 140.6 (C), 129.7 (C), 118.9 (CH), 113.4 (CH), 111.6 (CH), 55.4 (CH_3), 38.5 (CH), 33.3 (CH_2), 26.9 (CH_2), 26.3 (CH_2). ATR-FTIR (thin film): 2923, 2855, 2110, 1717, 1605, 1493, 1448, 1355, 1287, 1242, 1220, 1036, 796 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{13}H_{17}N_3O$ $(M)^+$: 231.1372, found: 231.1366.



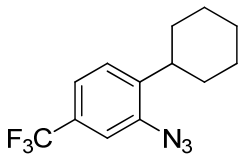
3.32

1-Azido-2-cyclohexyl-4-methylbenzene 3.32. The general procedure was following using crude aniline (derived from 2 mmol of aniline **3.84**), in 10 mL of MeCN, 0.951 mL of *t*-$BuNO_2$ and 0.842 mL of $TMSN_3$. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a brown red oil (0.378 g, 88%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.08 (s, 1H) , 7.05 (s, 2H), 2.84 (t, *J* = 11.5 Hz, 1H), 2.36 (s, 3H), 1.86 (m, 5H), 1.44 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.9 (C), 134.5 (C), 134.4 (C), 127.9 (CH), 127.5 (CH), 118.0 (CH), 38.3 (CH), 33.4 (CH_3), 27.0 (CH_2), 26.4 (CH_2), 21.1 (CH_2). ATR-FTIR (thin film): 3002, 2971, 2934, 1738, 1567, 1494, 1378, 1288, 1211, 967, 754 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{13}H_{17}N_3$ $(M)^+$: 215.1422, found: 215.1413.



3.34

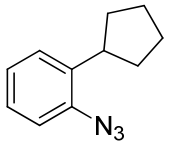
1-Azido-2-cyclohexylbenzene 3.34.[11] The general procedure was following using crude aniline (derived from 2 mmol of nitro **3.88**), 0.95 mL of*t*-$BuNO_2$, and 0.84 mL of Me_3SiN_3. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a light brown oil (0.209 g, 52%), R_f = 0.8 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). Azide **4g** was originally reported by Smolinsky. [11] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.48 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 8 Hz, 1H), 7.34 (d, *J* = 9 Hz, 1H), 7.32 (d, *J* = 8 Hz, 1H), 3.15 (t, *J* = 6.5 Hz, 1H), 2.05 (m, 5H), 1.66 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3 (C), 137.4 (C), 127.2 (CH), 127.0 (CH), 125.0 (CH), 118.1 (CH), 38.4 (CH), 33.5 (CH_2), 27.2 (CH_2), 26.5 (CH_2). ATR-FTIR (thin film): 2924, 2852, 2114, 2082, 1577, 1486, 1447, 1281, 898, 732 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{12}H_{15}N_3$ $(M)^+$: 201.1266, found: 201.1275.



3.36

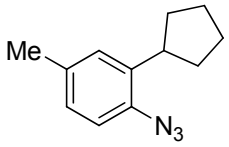
1-Azido-3-triflouromethyl-5-cyclohexylbenzene 3.36. The general procedure was following using crude aniline (derived from 2 mmol of **3.85**), 0.95 mL of *t*-$BuNO_2$, and 0.84 mL of Me_3SiN_3. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow oil (0.479 g, 89%), R_f = 0.8 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 (s, 1H), 7.36 (s, 1H), 7.34 (s, 1H), 2.89 (t, *J* = 12 Hz, 1H), 1.84 (m, 5H), 1.41 (m, 5H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.0 (C), 138.1 (C), 129.3 (q, J_{CF} =

33 Hz, C), 127.7 (CH), 123.8 (q, J_{CF} = 271 Hz, CF_3), 121.6 (q, J_{CF} = 3.5 Hz, CH), 114.8 (q, J_{CF} = 3.6 Hz, CH), 38.3 (CH), 33.1 (CH_2), 26.7 (CH_2), 26.1 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ – 63.06. ATR-FTIR (thin film): 2929, 2859, 2103, 1606, 1500, 1448, 1417, 1324, 1272, 1119, 1085, 872 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{13}H_{14}N_3F_3$ $(M)^+$: 269.1140, found: 269.1131.



3.38

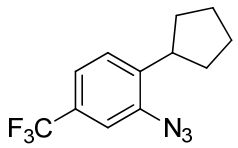
1-Azido-2-cyclopentylbenzene 3.38. The general procedure was following using crude aniline (derived from 2 mmol of nitrobenzene **3.89**, 0.95 mL of *t*-$BuNO_2$, and 0.84 mL of Me_3SiN_3. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a red oil (0.161g, 43%), R_f = 0.8 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.31 (d, *J* = 8 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 7 Hz, 1H), 7.13 (d, *J* = 7.5 Hz, 1H), 3.29 (m, 1H), 2.08 (m, 2H), 1.86 (m, 2H), 1.74 (m, 2H), 1.60 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.9 (C), 137.7 (C), 127.3 (CH), 126.9 (CH), 124.9 (CH), 118.1 (CH), 40.1 (CH), 33.6 (CH_2), 25.6 (CH_2). ATR-FTIR (thin film): 2957, 2870, 2123, 2089, 1580, 1489, 1451, 1292, 903, 725 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{11}H_{13}N_3$ $(M)^+$: 187.1109, found: 187.1105.



3.40

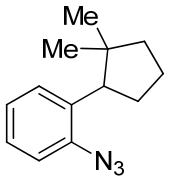
1-Azido-2-cyclopentyl-4-methylbenzene 3.40. The general procedure was following using crude aniline (derived from 2 mmol of **3.86**), 0.95 mL of *t*-$BuNO_2$, and 0.84 mL of Me_3SiN_3. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a

brown oil (0.346 g, 86%), R_f = 0.8 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 (s, 1H), 7.14 (s, 2H), 3.38 (m, 1H), 2.47 (s, 3H), 2.19 (m, 2H), 1.98 (m, 2H); 1.86 (m, 2H), 1.72 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5 (C), 135.2 (C), 134.5 (C), 128.0 (CH), 127.6 (CH), 118.0 (CH), 40.3 (CH), 33.7 (CH_2), 25.7 (CH_2), 21.1 (CH_3). ATR-FTIR (thin film): 2952, 2867, 2114, 1715, 1608, 1578, 1493, 1452, 1359, 1290, 1218, 881, 804 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{12}H_{15}N_3$ $(M)^+$: 201.1266, found: 201.1262.



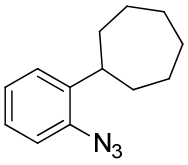
3.42

1-Azido-3-trifluoromethyl-5-cyclopentylbenzene 3.42. The general procedure was following using 0.458 g of aniline **3.87** (2.0 mmol) in 10 mL of MeCN, 0.95 mL of *t*-$BuNO_2$, and 0.84 mL of Me_3SiN_3. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.398 g, 78%), R_f = 0.8 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.44 – 7.39 (m, 3H), 3.36 (m, 1H), 2.13 (q, J = 6.5 Hz, 2H), 1.89 (m, 2H); 1.79 (q, J = 5 Hz, 2H), 1.62 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.8 (C), 138.8 (C), 129.5 (q, J_{CF} = 32 Hz, C), 127.6 (CH), 123.9 (q, J_{CF} = 271 Hz, CF_3), 121.5 (q, J_{CF} = 3 Hz, CH), 114.7 (q, J_{CF} = 3.5 Hz, CH), 40.2 (CH), 33.3 (CH_2), 25.5 (CH_2). ^{19}F NMR (282 MHz, $CDCl_3$) δ – 63.06. ATR-FTIR (thin film): 2956, 2873, 2107, 1713, 1612, 1578, 1505, 1417, 1328, 1276, 1122, 872, 826 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{12}H_{12}N_3F_3$ $(M)^+$: 255.0983, found: 255.0969.



3.44

1-Azido-2-(2,2-dimethylcyclopentyl)benzene 3.44. The general procedure was following using impure aniline **s25**(derived from 0.96 g of nitrobenzene **3.90** containing some impurity), 0.95 mL of *t*-$BuNO_2$, and 0.84 mL of Me_3SiN_3. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.370 g, 35% over 3 steps, calculation based on corresponding boronic acid), R_f = 0.8 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.30 (m, 2H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 3.27 (dt, *J* = 1.5 Hz, *J* = 8.5 Hz, 1H), 2.00 – 2.05 (m, 2H), 1.77 – 1.91 (m, 2H), 1.63 – 1.66 (m, 2H), 1.08 (s, 3H), 0.73 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6 (C), 134.6 (C), 129.3 (CH), 127.0 (CH), 124.1 (CH), 118.0 (CH), 48.0 (CH), 43.2 (C), 41.6 (CH_2), 30.9 (CH_2), 28.8 (CH_3), 23.6 (CH_3), 22.0 (CH_2) ATR-FTIR (thin film): 2953, 2118, 2084, 1578, 1445, 1294, 908, 734 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{13}H_{17}N_3$ $(M)^+$: 215.1422, found: 215.1441.



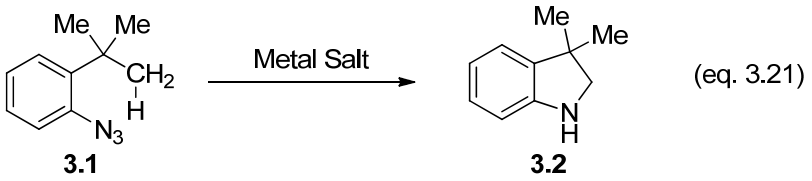
3.46

1-Azido-2-cycloheptylbenzene 3.46. The general procedure was following using crude aniline (derived from 2 mmol of nitrobenzene **3.91**), 0.95 mL of *t*-$BuNO_2$, and 0.84 mL of Me_3SiN_3. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.288 g, 67%), R_f = 0.8 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.28 (d, *J* = 8 Hz, 1H), 7.24 (d, *J* = 7.5 Hz, 1H), 7.16 (d, *J* = 8 Hz,

1H), 7.13 (d, J = 7.5 Hz, 1H), 3.07 (m, 1H), 1.88 (m, 4H), 1.79 (m, 2H), 1.66 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.2 (C), 136.6 (C), 127.5 (CH), 126.7 (CH), 124.9 (CH), 118.0 (CH), 40.3 (CH), 35.8 (CH_2), 28.0 (CH_2), 27.5 (CH_2). ATR-FTIR (thin film): 2925, 2854, 2118, 1579, 1487, 1446, 1288, 1084, 904, 727 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{13}H_{17}N_3$ $(M)^+$: 215.1423, found: 215.1428.

3.6.3 Rhodium-Catalyzed Formation of Indolines from Aryl Azides

General Procedure for the Screening of Catalysts to Promote the Decomposition of Aryl Azides



3.1 **3.2** (eq. 3.21)

To a mixture of 0.0175 g of 1-azido-2-*tert*-butylbenzene **3.1** (0.1 mmol), and a metal salt (0-5 mol %) in Schlenk tube was added 0.50 mL of solvent. The resulting mixture was heated, and after 16 h, the heterogenous mixture was filtered through a short pad of Al_2O_3. The filtrate was concentrated *in vacuo*. The resulting oil was dissolved in 1.5 mL of $CDCl_3$ and 0.007 mL of dibromomethane (0.1 mmol) was added. The area of the C6–H peak in **3.2** was compared to the area of CH_2Br_2 to derive a yield.

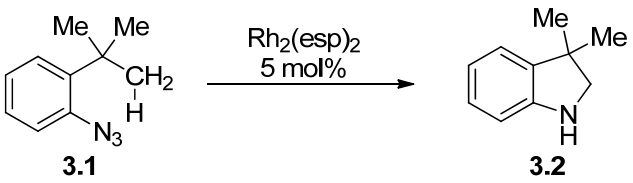
Table 3.5. Survey of transition metal complexes

entry	metal salt	mol %	solvent	T (°C)	**3.2** yield, %[a]
1	none	n.a.	mesitylene	220	No rxn
2	none	n.a.	PhMe	120	No rxn
3	[(cod)Ir(OMe)]$_2$	5	PhMe	120	No rxn

4	$Ru(cod)Cl_2$	5	PhMe	120	No rxn
5	$[Ru(p\text{-cymene})Cl_2]_2$	5	PhMe	120	No rxn
6	$Ru_3(CO)_{12}$	5	PhMe	120	No rxn
7	$RuBr_3$	5	PhMe	120	No rxn
8	$RuCl_3$	5	PhMe	120	No rxn
9	Ir(cod)(cp')	5	PhMe	120	No rxn
10	$[(cod)Rh(OMe)]_2$	5	PhMe	120	No rxn
11	$RhCl_4$	5	PhMe	120	No rxn
12	$[Rh(cod)_2]SO_3CF_3$	5	PhMe	120	No rxn
13	$[Rh(PPh_3)_3]Cl$	5	PhMe	120	No rxn
14	$[(HO)Rh(cod)]_2$	5	PhMe	120	Aniline formed (10)
15	$Rh(OAc)_4$	5	PhMe	120	No rxn
16	$Rh_2(O_2CC_7H_{15})_4$	5	PhMe	120	35
17	$Rh_2(O_2CC_3F_7)_4$	5	PhMe	120	20
18	$Rh_2(esp)_2$	5	PhMe	120	75
19	$Rh_2(esp)_2$	2	PhMe	120	45
20	$Rh_2(S\text{-PTAD})_4$	5	PhMe	120	No rxn
21	ZnI_2	5	PhMe	120	No rxn
22	AgOTf	5	PhMe	120	No rxn
23	$Ag(O_2CCF_3)$	5	PhMe	120	No rxn
24	AgOAc	5	PhMe	120	No rxn
25	$CoTTP^b$	5	PhMe	120	No rxn

[a]As determined using ^1H NMR spectroscopy.[b]TTP = tetraphenylporphyrin.

Table 3.6. Survey of solvents.

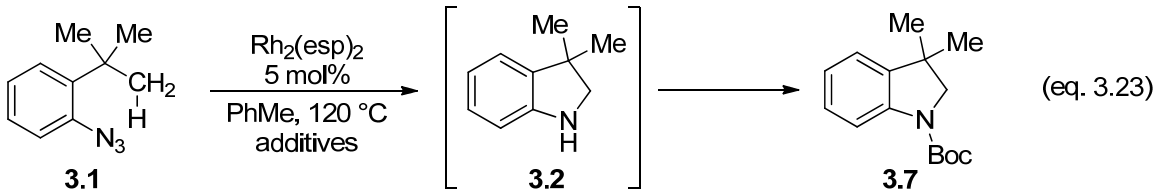


3.1 3.2 (eq. 3.22)

Entry	metal salt	solvent	**2a** yield, %[a]
1	$Rh_2(esp)_2$	PhMe	75
2	$Rh_2(esp)_2$	PhH	73
3	$Rh_2(esp)_2$	PhBr	56
4	$Rh_2(esp)_2$	PhCl	47
5	$Rh_2(esp)_2$	1,3-$C_6H_4Cl_2$	61
6	$Rh_2(esp)_2$	$PhCF_3$	31
7	$Rh_2(esp)_2$	DCE	47

[a]As determined using ^{1}H NMR spectroscopy.

Table 3.7. Survey of additives.



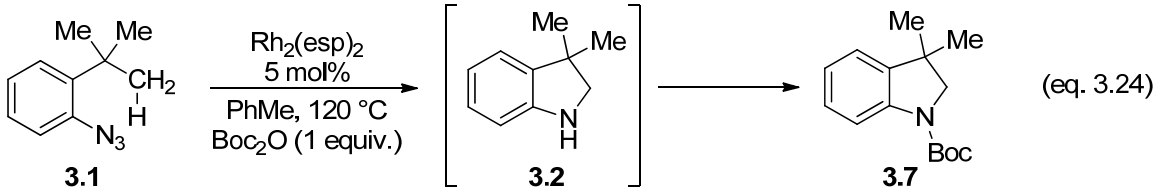
3.1 3.2 3.7 (eq. 3.23)

entry	additives	**2a** yield, %[a]
1	TsCl (1 equiv)	20
2	TsCl (1 equiv) Et_3N (3 equiv)	No rxn

3[b]	TsCl (1 equiv) DTBMP (1 equiv)	No rxn
4	TsCl (1 equiv) Cs_2CO_3 (1 equiv)	20
5	Boc_2O (1 equiv)	83
6	Moc_2O (1 equiv)	45
7	Ac_2O (1 equiv)	73
8	Bz_2O (1 equiv)	aniline
9	$(CF_3CO)_2O$ (1 equiv)	35
10	Tf_2O (1 equiv)	20

[a]As determined using ^{1}H NMR spectroscopy.[b]DTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

Optimized General Procedure

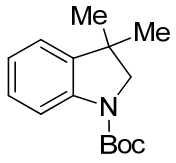


(eq. 3.24)

To a mixture of 0.070 g of aryl azide **3.1** (0.40 mmol), 0.0870 g of Boc_2O, and 0.0153 g of $Rh_2(esp)_2$ (5 mol%) in Schlenk tube was added 0.80 mL of PhMe. The resulting mixture was heated at 120 °C. After 16 h, the mixture was cooled to room temperature and diluted with 5 mL of a saturated aqueous solution of Na_2CO_3. The phases were separated, and the aqueous phase was extracted with an additional 2 × 5 mL of CH_2Cl_2. The combined organic phases were washed with 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography (0:100

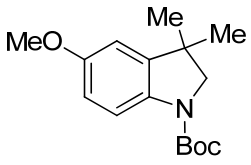
– 10:90 EtOAc: hexanes) with Al_2O_3 afforded the product as 66:34 mixture of amide rotamers (0.082 g, 84%).

Scope and Limitations of Indoline Formation



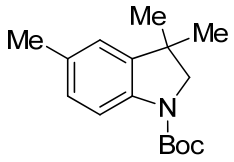
3.7

Indoline 3.7. [12] The general procedure was followed with 0.0700 g of aryl azide **3.1** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded a orange red oil product as 66:34 mixture of amide rotamers (0.082 g, 84%), R_f = 0.65 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). Indoline **3.7** was previously reported by Faul and co-workers.[12] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (br, 1H), 7.18 (t, *J* = 7.5 Hz, 1H), 7.14 (d, *J* = 7.5 Hz, 1H), 6.97 (t, *J* = 7.5 Hz, 1H), 3.72 (s, 2H), 1.58 (s, 9H), 1.33 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7 (C), 141.7 (C), 140.1 (C), 127.6 (CH), 122.4 (CH), 121.9 (CH), 114.7 (CH), 80.3 (C), 62.3 (CH_2), 39.5 (C), 28.8 (CH_3), 28.5 (CH_3). ATR-FTIR (thin film): 3004, 2963, 2925, 1697, 1602, 1484, 1455, 1381, 1335, 1290, 1159, 1016, 857, 747 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{15}H_{21}NO_2$ $(M)^+$: 247.1572, found: 247.1581.



3.9

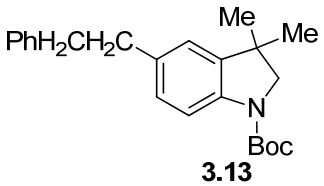
Indoline 3.9. The general procedure was followed with 0.0820 g of aryl azide **3.8** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded a peach solid product as 66:34 mixture of amide rotamers (0.0698 g, 63%), R_f = 0.38 (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (br, 1H), 6.69 (dd, *J* = 8.5 Hz, 2.5 Hz, 1H), 6.67 (d, *J* = 2.5 Hz, 1H), 3.78 (s, 3H), 3.68 (s, 2H), 1.54 (s, 9H), 1.31 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 155.7 (C), 152.6 (C), 141.7 (C), 135.4 (C), 115.1 (CH), 111.8 (CH), 108.8 (CH), 80.1 (C), 62.6 (CH_3), 62.2 (C), 55.7 (CH_3), 39.7 (C), 28.5 (CH_3). ATR-FTIR (thin film): 3026, 2960, 2934, 1685, 1598, 1493, 1394, 1274, 1221, 1143, 1082, 1015, 807, 763 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{16}H_{23}NO_3$ $(M)^+$: 277.1678, found: 277.1689.



3.11

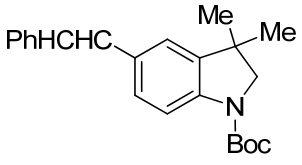
Indoline 3.11. The general procedure was followed with 0.0756 g of aryl azide **3.10** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded a yellow oil product as 66:34 mixture of amide rotamers (0.0564 g, 54%), R_f = 0.55 (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (br, 1H), 7.00 (d, *J* = 7.5 Hz, 1H), 6.94 (s, 1H), 3.72 (s, 2H), 2.34 (s, 3H), 1.59 (s, 9H), 1.34 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7 (C), 140.2 (C), 139.4 (C), 131.8 (C), 128.0 (CH), 122.6 (CH), 114.4 (CH), 80.2 (C), 62.5 (CH_2), 39.5 (C), 28.7 (CH_3), 28.5 (CH_3), 21.0 (CH_3). ATR-

FTIR (thin film): 2977, 2929, 2871, 1689, 1613, 1491, 1470, 1432, 1392, 1338, 1282, 1146, 1021, 860, 817 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{16}H_{23}NO_2$ $(M)^+$: 261.1729, found: 261.1724.



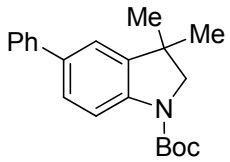
3.13

Indoline 3.13. The general procedure was followed with 0.1116 g of aryl azide **3.12** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded a yellow oil product as 68:32 mixture of amide rotamers (0.0899 g, 64%), R_f = 0.52 (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.79 (br, 1H), 7.3 (t, *J* = 7.5 Hz, 2H), 7.23 – 7.18 (m, 3H), 7.04 (d, *J* = 8 Hz, 1H), 6.85 (s, 1H), 3.72 (s, 2H), 2.91 (s, 4H), 1.60 (s, 9H), 1.32 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.7 (C), 141.9 (C), 140.0 (C), 139.9 (C), 135.9 (CH), 128.6 (CH), 128.3 (CH), 127.6 (CH), 125.9 (CH), 122.2 (C), 114.5 (CH), 80.3 (C), 62.6 (CH_2), 39.5 (C), 38.4 (CH_2), 37.7 (CH_2), 28.7 (CH_3), 28.6 (CH_3). ATR-FTIR (thin film): 3022, 2975, 2927, 1683, 1489, 1336, 1144, 1021, 907, 818, 728 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{23}H_{29}NO_2$ $(M)^+$: 351.2198, found: 351.2187.



3.15

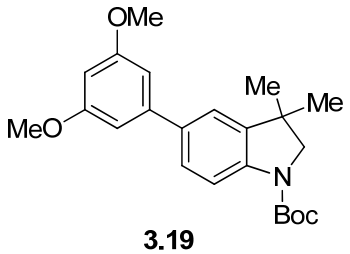
Indoline 3.15. The general procedure was followed with 0.1108 g of aryl azide **3.14** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded a yellow oil product as 67:33 mixture of amide rotamers (0.0977 g, 70%), R_f = 0.47 (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.84 (s, 1H), 7.51 (d, *J* = 7.5 Hz, 2H), 7.36 (t, *J* = 7.5 Hz, 3H), 7.29 (s, 1H), 7.25 (t, *J* = 8 Hz, 1H), 7.10 (d, *J* = 16.5 Hz, 1H), 7.02 (d, *J* = 16.5 Hz, 1H), 3.74 (s, 2H), 1.58 (s, 9H), 1.37 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.9 (C), 152.6 (C), 141.5 (C), 140.8 (C), 137.7 (CH), 131.9 (CH), 128.7 (CH), 127.2 (CH), 126.7 (CH), 126.6 (CH), 126.3 (CH), 119.8 (C), 114.7 (CH), 80.6 (C), 62.6 (CH_2), 39.4 (C), 28.8 (CH_3), 28.5 (CH_3). ATR-FTIR (thin film): 3026, 2974, 2931, 1692, 1596, 1488, 1438, 1378, 1335, 1244, 1145, 1019, 960, 816 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{23}H_{27}NO_2$ $(M)^+$: 349.2042, found: 349.2030.



3.17

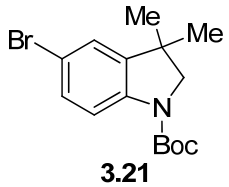
Indoline 3.17. The general procedure was followed with 0.1005g of aryl azide **3.16** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded a yellow oil product as 65:35 mixture of amide rotamers (0.0564 g, 54%), R_f = 0.55 (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (br, 1H), 7.59 (d, *J* = 8.5 Hz, 2H), 7.44 (t, *J* = 8.0 Hz, 3H), 7.35 (s, 1H), 7.32 (m, 1H), 3.77 (s, 2H), 1.60 (s, 9H), 1.39 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6 (C), 141.3 (C), 135.7 (CH), 128.8 (CH), 126.9 (CH), 126.8 (CH), 126.6 (C), 121.1 (C), 120.9 (C), 120.8

(CH), 114.9 (CH), 80.6 (C), 62.7 (CH_2), 39.6 (C), 28.8 (CH_3), 28.5 (CH_3). ATR-FTIR (thin film): 2977, 2929, 2871, 1689, 1613, 1491, 1470, 1432, 1392, 1338, 1282, 1146, 1021, 860, 817 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{21}H_{25}NO_2$ $(M)^+$: 323.1885, found: 323.1896.



3.19

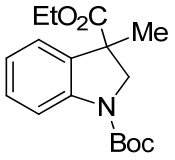
Indoline 3.19. The general procedure was followed with 0.1244g of aryl azide **3.18** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded a yellow oil product as 64:36 mixture of amide rotamers (0.0889 g, 58%), R_f = 0.48 (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ^1H NMR (500 MHz, $CDCl_3$) δ 7.90 (br, 1H), 7.41 (d, *J* = 7.5 Hz, 1H), 7.31 (s, 1H), 6.72 (s, 2H), 6.45 (s, 1H), 3.86 (s, 6H), 3.76 (s, 2H), 1.59 (s, 9H), 1.38 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 161.1 (C), 152.6 (C), 143.5 (C), 141.5 (C), 140.8 (C), 135.6 (CH), 126.6 (CH), 120.8 (C), 114.8 (CH), 105.2 (CH), 98.7 (CH), 80.6 (C), 62.7 (CH_2), 55.5 (CH_3), 39.5 (C), 28.8 (CH_3), 28.5 (CH_3). ATR-FTIR (thin film): 3007, 2962, 2931, 1685, 1594, 1469, 1389, 1369, 1333, 1203, 1146, 1065, 826, 647 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{23}H_{29}NO_4$ $(M)^+$: 383.2097, found: 383.2114.



3.21

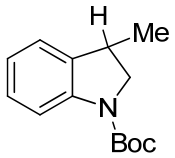
Indoline 3.21. The general procedure was followed with 0.1010g of aryl azide **3.20** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of

toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded a gray solid product as 65:35 mixture of amide rotamers (0.0950 g, 73%), R_f = 0.59 (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.26 (s, 1H), 7.17 (s, 1H), 3.69 (s, 2H), 1.55 (s, 9H), 1.30 (s, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4 (C), 142.6 (C), 140.9 (C), 130.4 (CH), 125.3 (CH), 116.2 (CH), 114.7 (C), 80.8 (C). 62.4 (CH_2), 39.5 (C), 28.6 (CH_3), 28.5 (CH_3). ATR-FTIR (thin film): 2970, 1694, 1594, 1482, 1378, 1337, 1247, 1147, 1021, 819 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{15}H_{20}BrNO_2$ $(M)^+$: 325.0677, found: 325.0669.



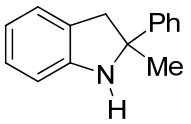
3.23

Indoline 3.23. The general procedure was followed with 0.0932 g of aryl azide **3.22** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded a yellow oil product as 66:34 mixture of amide rotamers (0.0854g, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (br, 1H), 7.31 (d, *J* = 7.5 Hz, 1H), 7.22 (t, *J* = 8 Hz, 1H), 6.96 (t, *J* = 7.5 Hz, 1H), 4.57 (d, *J* = 11 Hz, 1H), 4.17 (m, 2H), 3.71 (s, 1H), 1.58 (s, 9H), 1.56 (s, 3H), 1.24 (t, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 173.8 (C), 152.2 (C), 142.1 (C), 133.5 (C), 128.8 (CH), 123.9 (CH), 122.4 (CH), 114.8 (CH), 80.8 (C), 65.9 (C), 61.5 (CH_2), 57.9 (CH_2), 28.5 (CH_3), 25.7 (CH_3), 14.1 (CH_3). ATR-FTIR (thin film): 2976, 2928, 1730, 1702, 1599, 1484, 1389, 1336, 1143, 1016, 858, 750 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{17}H_{23}NO_4$ $(M)^+$: 305.1627, found: 305.1636.



3.25

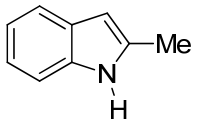
Indoline 3.25. The general procedure was followed with 0.0644 g of aryl azide **3.24** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded a brown yellow oil product as 67:33 mixture of amide rotamers (0.0187 mg, 20%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.17 (d, *J* = 8.5 Hz, 1H), 7.14 (t, *J* = 7.5 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 4.15 (t, *J* = 8 Hz, 1H), 3.49 (t, *J* = 7 Hz, 1H), 3.39 (m, 1H), 1.57 (s, 9H), 1.32 (d, *J* = 7 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.6 (C), 135.9 (C), 127.5 (CH), 123.5 (CH), 122.2 (CH), 116.6 (C), 114.6 (CH), 80.3 (C), 55.7 (CH_2), 34.1 (C), 28.5 (CH_3), 20.3 (CH_3). ATR-FTIR (thin film): 2978, 2931, 1690, 1602, 1484, 1452, 1391, 1171, 1145, 1045, 905, 648 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{14}H_{19}NO_2$ $(M)^+$: 233.1416, found: 233.1411.



3.27

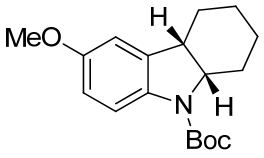
Indoline 3.27. The general procedure was followed (without the presence of Boc_2O) with 0.0948g of aryl azide **3.26** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded the product as a yellow oil (0.070 g, 55%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.53 (d, *J* = 7.0 Hz, 2H), 7.36 (t, *J* = 8.0 Hz, 2H), 7.24 – 7.27 (m, 1H), 7.07 – 7.10 (m, 2H), 6.70 – 6.76 (m, 2H), 4.02 (br, 1H), 4.23 (dd, *J* = 15.5 Hz, *J* = 18.0 Hz, 2H), 1.67 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.0 (C), 148.8 (C), 128.4 (CH), 127.5 (CH),

126.6 (CH), 125.2 (CH), 124.9 (CH), 118.7 (CH), 109.2 (CH), 66.3 (C), 46.0 (CH_2), 29.4 (CH_3); ATR-FTIR (thin film): 3358, 3030, 1609, 1483, 1253, 904, 693 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{15}H_{15}N$ $(M)^+$: 209.2863, found: 209.1218.



3.29

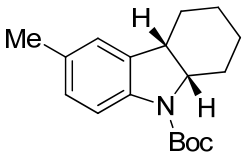
Indoline 3.29. The general procedure was followed (without the presence of Boc_2O) with 0.0644 g of aryl azide **3.28** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded the product as a brown yellow oil. ^1H NMR (500MHz, $CDCl_3$) δ 7.82 (br, 1H), 7.52 (d, J = 7.5 Hz, 1H), 7.28 – 7.30 (m, 1H), 7.06 – 7.13 (m, 2H), 6.23 (s, 1H), 2.45 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 136.1 (C), 135.0 (C), 129.1 (C), 121.0 (CH), 119.6 (CH), 110.2 (CH), 100.4 (CH), 13.8 (CH_3) only signals visible; ATR-FTIR (thin film): 3411, 2928, 1727, 1455, 1284, 1047, 904, 721 cm^{-1}.



3.31

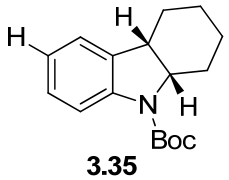
Indoline 3.31. The general procedure was followed with 0.0924g of aryl azide **3.30** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded the product as a yellow oil (0.0970 g, 80%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.63 (s, 1H), 6.71 (s, 1H), 6.68 (d, J = 9.5 Hz, 1H), 4.33 (s, 1H), 3.78 (s, 3H), 3.39 (t, J = 5 Hz, 1H), 2.18 (t, J = 14 Hz, 1H), 2.06 (s, 1H), 1.78 (s, 1H), 1.55 (m, 11H), 1.2 (m, 3H);^{13}C NMR (125 MHz, $CDCl_3$)

δ 155.8 (C), 152.2 (C), 115.9 (C), 115.4 (C), 111.3 (CH), 109.7 (CH), 108.3 (CH), 80.8 (C), 60.5 (CH), 55.7 (CH_3), 48.4 (CH), 39.5 (CH_2), 28.5 (CH_3), 24.2 (CH_2), 22.4 (CH_2), 21.1 (CH_2). ATR-FTIR (thin film): 3016, 2915, 2923, 1657, 1604, 1489, 1334, 1291, 1153, 1023, 877, 775 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{18}H_{25}NO_3$ $(M)^+$: 303.1834, found: 303.1821.



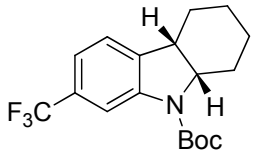
3.33

Indoline 3.33. The general procedure was followed with 0.0861g of aryl azide **3.32** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded the product as a light orange solid (0.0838 g, 73%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8 Hz, 1H), 6.97 (d, *J* = 8 Hz, 1H), 6.94 (s, 1H), 4.33 (s, 1H), 3.39 (t, *J* = 6.5 Hz, 1H), 2.32 (s, 3H), 2.24 (m, 1H), 2.10 (m, 2H), 1.57 (m, 11H), 1.48 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3 (C), 131.8 (CH), 127.6 (CH), 123.4 (C), 122.1 (C), 115.3 (CH), 114.6 (C), 80.8 (C), 60.5 (CH), 39.3 (CH), 28.5 (CH_3), 27.9 (CH_3), 24.2 (CH_2), 22.4 (CH_2), 21.1 (CH_2) only visible signals. ATR-FTIR (thin film): 3013, 2945, 2956, 1667, 1656, 1434, 1323, 1245, 1023, 845, 767 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{18}H_{25}NO_2$ $(M)^+$: 287.1885, found: 287.1880.



3.35

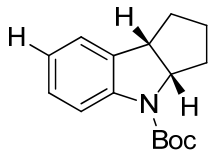
Indoline 3.35. [13] The general procedure was followed with 0.0804g of aryl azide **3.34** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded the product as a yellow oil (0.0765 mg, 70%). Indoline **6g** was previously reported by Gilchrist and co-workers.[13] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.17 (t, J = 7.5 Hz, 1H), 7.12 (d, J = 7 Hz, 1H), 6.98 (t, J = 7 Hz, 1H), 4.34 (s, 1H), 3.42 (t, J = 5.5 Hz, 1H), 2.27 (d, J = 14.5 Hz, 1H), 2.08 (s, 1H), 1.80 (m, 1H), 1.57 (m, 11H), 1.21 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3 (C), 127.3 (CH), 122.6 (CH), 122.4 (CH), 121.4 (C), 115.5 (CH), 114.8 (C), 81.0 (C), 60.5 (CH), 39.3 (CH), 28.5 (CH_3), 24.1 (CH_2), 22.4 (CH_2), 21.1 (CH_2) only visible signals. ATR-FTIR (thin film): 2969, 2929, 2859, 1691, 1603, 1477, 1460, 1389, 1365, 1168, 1141, 909, 647 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{17}H_{23}NO_2$ $(M)^+$: 273.1729, found: 273.1734.



3.37

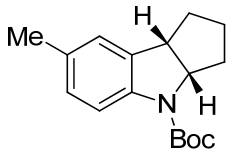
Indoline 3.37. The general procedure was followed with 0.1076g of aryl azide **3.36** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded the product as a light yellow solid (0.0859 g, 63%): ^{1}H NMR (500MHz, $CDCl_3$) δ δ 7.99 (s, 1H), 7.24 (d, J = 8 Hz, 1H), 7.19 (d, J = 7.5 Hz, 1H), 4.38 (s, 2H), 3.44 (s, 1H), 2.26 (d, J = 14 Hz, 1H), 2.10 (d, J =11 Hz, 1H), 1.85 – 1.80 (m, 1H), 1.57 (m, 11H), 1.20 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.1 (C), 142.6 (C), 137.7 (C), 129.8 (q, J_{CF} = 31.4 Hz, C), 124.4 (q, J_{CF} = 271 Hz, CF_3), 122.7 (CH), 119.5 (q, J_{CF} = 3.3 Hz, CH), 112.3 (q, J_{CF} = 4.1 Hz, CH), 81.2 (C), 60.7 (CH), 39.4 (CH), 28.4 (CH3), 27.2 (CH_2), 23.9 (CH_2), 22.1 (CH_2), 21.0 (CH_2); ^{19}F

NMR (282 MHz, $CDCl_3$) δ –62.43. ATR-FTIR (thin film): 3004, 2963, 2929, 1696, 1602, 1484, 1335, 1290, 1159, 1016, 857, 747 cm^{-1}. HRMS (EI) *m/z* calculated for $C_{18}H_{22}F_3NO_2$ $(M)^+$: 341.1603, found: 341.1619.



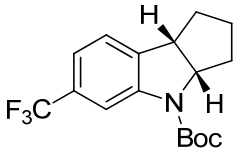
3.39

Indoline 3.39. The general procedure was followed with 0.0748 g of aryl azide **3.38** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3afforded the product, a dark brown oil, as a 66:34 mixture of amide rotamers (0.0881 g, 85%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (br s, 0.59H), 7.50 (br s, 0.30H), 7.15 (s, 1H), 7.10 (d, J = 6.5 Hz, 1H), 6.94 (t, J = 7 Hz, 1H), 4.75 – 4.55 (br s, 1H), 3.78 (t, J = 8.5 Hz, 1H), 1.96 (m, 3H), 1.84 (m, 1H), 1.58 (m, 10H), 1.39 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ152.5 (C), 143.3 (C), 134.6 (C), 127.5 (CH), 124.1 (CH), 122.4 (CH), 114.4 (CH), 80.2 (C), 64.9 (CH), 44.9 (CH), 35.6 (CH_2), 34.9 (CH_2), 28.5 (CH_3), 23.9 (CH_2). ATR-FTIR (thin film): 2974, 2934, 2869, 1690, 1601, 1482, 1387, 1256, 1147, 1046, 859, 647 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{16}H_{21}NO_2$ $(M)^+$: 259.1575, found: 259.1564. See page SI2 *s*-116 for a ^1H NMR spectrum of the crude reaction mixture of indoline **5i**. Diagnostic data for disastereoselectivity determination: ^1H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, J = 7.0 Hz, 1H), 6.99 (t, J = 7.5 Hz, 1H), 6.67 (t, J = 7.5 Hz, 1H), 6.53 (d, J = 7.5 Hz, 1H), 4.36 (t, J = 8.0 Hz, 1H), 3.781 (t, J = 7.5 Hz, 1H), 3.9 – 3.7 (br s, 1H), 1.96 (m, 1H), 1.81 – 1.56 (m, 5H).



3.41

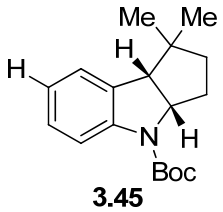
Indoline 3.41. The general procedure was followed with 0.0804 g of aryl azide **3.40** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded the product, a yellow oil, as a 65:35 mixture of amide rotamers (0.0798 g, 73%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (br, 1H), 6.95 (s, 1H), 6.92 (s, 1H), 4.65 (br, 1H), 3.74 (t, J = 8 Hz, 1H), 2.29 (s, 3H), 1.97 (m, 4H), 1.56 (s, 9H), 1.40 (br, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4 (C), 141.0 (C), 134.7 (C), 131.8 (CH), 127.9 (CH), 124.8 (C), 114.1 (CH), 80.0 (C), 65.1 (CH), 44.9 (CH), 35.6 (CH_2), 34.8 (CH_2), 28.6 (CH_3), 23.9 (CH_3), 20.9 (CH_2). ATR-FTIR (thin film): 2975, 2930, 2845, 1691, 1609, 1585, 1420, 1387, 1257, 1137, 1034, 885, 649 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{17}H_{23}NO_2$ $(M)^+$: 273.1729, found: 273.1734 . See page SI2 *s*-124 for a ^{1}H NMR spectrum of the crude reaction mixture of indoline **5j**. Diagnostic data for disastereoselectivity determination: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (t, J = 6.0 Hz, 1H), 3.79 (t, J = 8.0 Hz, 1H),



3.43

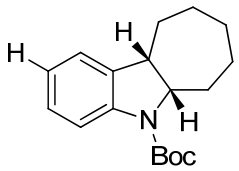
Indoline 3.43. The general procedure was followed with 0.1020 g of aryl azide **3.42** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded the product, a yellow solid, as a 68:32 mixture of amide rotamers (0.107 g, 82%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.11 (s, 1H), 7.19 (m, 2H), 4.71 (s, 1H), 3.79 (t, J = 8.5 Hz, 1H), 2.02 (m,

3H), 1.98 (m, 1H), 1. 83 (m, 1H), 1.56 (s, 9H), 1.38 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3 (C), 143.8 (C), 138.6 (C), 129.9 (q, J_{CF} = 30.6 Hz, C), 124.4 (q, J_{CF} = 270 Hz, CF_3), 124.2 (q, J_{CF} = 4.5 Hz, CH), 119.4 (CH), 111.3 (q, J_{CF} = 2.8 Hz, CH), 80.9 (C), 65.4 (CH), 44.9 (CH), 35.6 (C), 34.8 (CH_2), 28.4 (CH_3), 23.9 (CH_2). ATR-FTIR (thin film): 2974, 2932, 2867, 1689, 1674, 1580, 1521, 1469, 1345, 1233, 1145, 970, 750 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{17}H_{20}F_3NO_2$ $(M)^+$: 327.1446, found: 327.1456. See page SI2 *s*-126 for a ^{1}H NMR spectrum of the crude reaction mixture of indoline **3.43**. Diagnostic data for disastereoselectivity determination: ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.45 (t, *J* = 7.5 Hz, 1H), 3.81 (t, *J* = 7.0 Hz, 1H).



3.45

Indoline 3.45. The general procedure was followed with 0.0860 g of aryl azide **3.44** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded the product, a yellow oil, as a 67:33 mixture of amide rotamers (0.101 g, 88%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.88 (br, 1H), 7.18 (t, *J* = 8.0 Hz, 1H), 7.13 (d, *J* = 7.0 Hz, 1H), 6.92 (t, *J* = 7.0 Hz, 1H), 4.70 (s, 1H), 3.31 (d, *J* = 9.5 Hz, 1H), 2.33 (s, 1H), 1.90 (s, 1H), 1.56 (s, 9H), 1.45 (t, *J* = 7.5 Hz, 2H), 1.20 (s, 3H), 0.79 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.5 (C), 143.7 (C), 131.3 (C), 127.6 (CH), 125.2 (CH), 121.6 (CH), 114.4 (CH), 80.2 (C), 65.9 (CH), 55.5 (CH), 43.5 (CH_2), 40.0 (CH_2), 33.8 (C), 29.8 (CH_3), 28.5 (CH_3), 24.5 (CH_3). ATR-FTIR (thin film): 2963, 2931, 2864, 1688, 1596, 1483, 1458, 1386, 1344, 1271, 1166, 1141, 908, 724 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{18}H_{25}NO_2$ $(M)^+$: 287.1885, found: 287.1899.

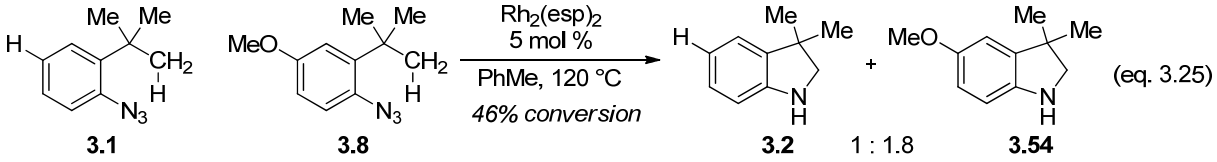


3.47

Indoline 3.47. The general procedure was followed with 0.0860 g of aryl azide **3.46** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $Rh_2(esp)_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded the product as an 82:18 mixture of diastereomers (0.0724 g, 63%). Major diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.67 (s, 1H), 7.15 (t, *J* = 8 Hz, 1H), 7.06 (d, *J* = 7 Hz, 1H), 6.95 (t, *J* = 7.5 Hz, 1H), 4.46 (s, 1H), 3.66 (m, 1H), 2.32 (m, 1H), 1.77 (m, 3H), 1.64 (m, 2H), 1.61 (m, 2H), 1.52 (s, 9H), 1.32 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.3 (C), 143.4 (C), 133.7 (C), 127.3 (CH), 122.4 (CH), 122.2 (CH), 114.9 (CH), 81.0 (C), 65.9 (CH), 46.0 (CH), 31.1 (CH_2), 30.5 (CH_2), 28.5 (CH_3), 27.8 (CH_2), 27.3 (CH_2), 26.9 (CH_2); Selected data for the minor diastereomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.99 (m, 1H), 3.21 (m, 1H), 2.81 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7 (C), 135.6 (C), 133.1 (C), 127.7 (CH), 127.4 (CH), 123.6 (CH), 122.7 (CH), 77.3 (C), 66.6 (CH), 43.9 (CH), 33.5 (CH_2), 30.3 (CH_2), 29.9 (CH_2), 28.4 (CH_3), 26.8 (CH_2), 25.2 (CH_2). Mixture: ATR-FTIR (thin film): 3004, 2966, 2934, 1591, 1505, 1455, 1201, 1151, 901, 819, 724, 648 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{18}H_{25}NO_2$ $(M)^+$: 287.1885, found: 287.1898.

3.6.4 Mechanistic Experiments

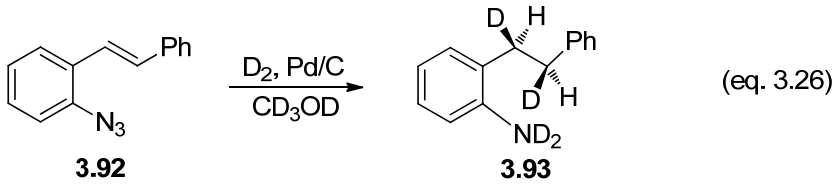
Intermolecular Competition Experiment



To a mixture of 0.070 g of 1-azido-2-*tert*-butylbenzene **3.1** (0.4 mmol), 0.0820 g of 1-azido-2-*tert*-butyl-4-methoxybenzene **3.8** (0.4 mmol) and 0.0155 g of $Rh_2(esp)_2$ (5 mol %) in a Schlenk tube was added 0.80 mL of PhMe. The resulting mixture was heated to 120 °C. After 3 h, the mixture was cooled to room temperature and diluted with 5 mL of a saturated aqueous solution of Na_2CO_3. The phases were separated, and the aqueous phase was extracted with an additional 2 × 5 mL of CH_2Cl_2. The combined organic phases were washed with 10 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography (0:100 – 10:90 EtOAc: hexanes) recovered 6% azide **3.54** and 48% azide **3.2**.

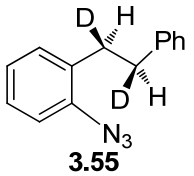
Isotope Labeling Studies

A. Synthesis of Aryl Azide Substrates



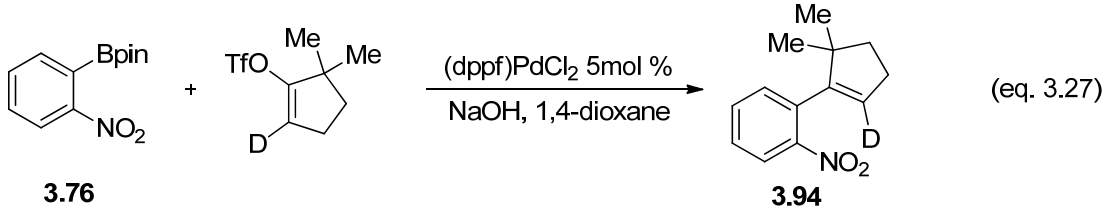
Aniline **3.93.** A mixture of azide **3.92** and Pd/C (Pd, 10 wt % on carbon powder) in CD_3OD were vigorous stirred at room temperature under deuterium atmosphere. After 3h, visualization of the reaction progress using TLC indicated consumption of the starting material.

The balloon of D_2 was removed, and the mixture then was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* to afford aniline **3.93**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.72 (t, J = 7.5 Hz, 2H), 7.66 – 7.60 (m, 3H), 7.49 (q, J = 8.0 Hz, 2H), 7.21 (t, J = 7.5 Hz, 1H), 7.00 (d, J = 8.0 Hz, 1H), 3.75 (s, 0.5 H), 3.32 (m, 1H), 3.14 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8 (C), 142.3 (C), 129.8 (CH), 127.6 (CH), 126.5 (CH), 126.3 (CH), 119.1 (CH), 116.0 (C), 35.2 (q, J_{CD} = 25.9 Hz, CD), 33.3 (q, J_{CD} = 25.6 Hz, CD) only signals visible.



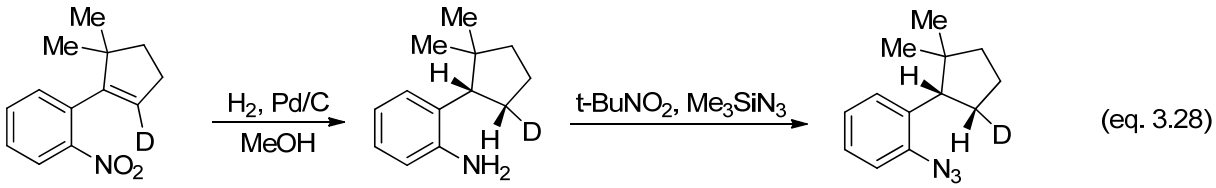
3.55

1-Azido-2-phenylethylbenzene 3.55. To a cooled solution of aniline in MeCN (0.2 M) was added dropwise *t*-$BuNO_2$ (4 equiv) and Me_3SiN_3 (3 equiv). The resulting solution was warmed to room temperature. After 1h, visualization of the reaction progress using TLC indicated the consumption of the starting material. Deionized H_2O was added to the reaction mixture. The mixture then was extracted with 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 20 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded azide **3.55**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 – 7.27 (m 3H), 7.23 (d, J = 8.0 Hz, 3H), 7.19 – 7.14 (m, 2H), 7.08 (t, J = 7.5 Hz, 1H), 2.88 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 130.6 (CH), 128.5 (CH), 128.4 (CH), 127.5 (CH), 126.0 (CH), 124.7 (CH), 118.1 (CH), 36.3 (q, J_{CD} = 25.8 Hz, CD), 33.1 (q, J_{CD} = 23.8 Hz, CD) only visible signals.



3.76 **3.94** (eq. 3.27)

1-Nitro-2-dimethylcyclopentylbenzene-d_1 3.94. To a mixture of 0.825 g of boronic ester **3.76** (5.00 mmol), 1.80 g of NaOH (45.0 mmol) and 0.183 g of (dppf)$PdCl_2$ (0.224 mmol) was added 75 mL of 1,4-dioxane and 15.0 mL of water followed by 1.20 mmol of 2,2-dimethylcyclopentyltriflate-d_1 (prepared from 10.0 mmol of 2,2-dimethylcyclopentanone-d_2, which was prepared following the procedure reported by Shiner and Imhoff.) The resultant mixture was heated to 100 °C. After 12 h, the mixture was cooled to room temperature and diluted with 10 mL of a saturated aqueous solution of NH_4Cl. The resulting mixture was separated, and the aqueous phase was extracted with an additional 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification of the oily residue using MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the 0.96 g of the impure nitrobenzene **s30**, which was submitted to the hydrogenation reaction without further purification.



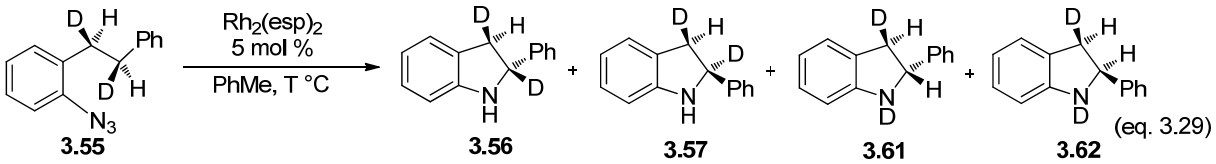
3.94 **3.95** **3.58** (eq. 3.28)

Aryl Azide 3.58. A mixture of nitrobenzene **3.94** (0.96 g) and Pd/C (Pd, 10 wt % on carbon powder) in MeOH were vigorous stirred at room temperature under hydrogen atmosphere. After 3h, visualization of the reaction progress using TLC indicated consumption of the starting material. The mixture then was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* to afford crude aniline **3.95**, which was subjected to the *t*-$BuNO_2$-mediated azidation reaction without further purification.

To a cooled solution of aniline in MeCN (0.2 M) was added dropwise 0.95 mL of *t*-$BuNO_2$ (4 equiv) and 0.84 mL of Me_3SiN_3 (3 equiv). The resulting solution was warmed to

room temperature. After 1h, visualization of the reaction progress using TLC indicated the consumption of the starting material. De – ionized H_2O was then added to the reaction mixture. The mixture then was extracted with 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 20 mL of brine. The resulting organic phase was dried over Na_2SO_4, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded azide **3.58** as a single diastereomer (0.370 g, 35% from boronic acid **3.94**), R_f = 0.8 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.24 – 7.27 (m, 2H), 7.16 – 7.18 (m, 1H), 7.10 – 7.13 (m, 1H), 3.23 (d, J = 8.0 Hz, 1H), 1.95 – 2.00 (m, 1H), 1.74 – 1.87 (m, 2H), 1.59 – 1.65 (m, 2H), 1.95 (s, 3H), 0.70 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.6 (C), 134.5 (C), 129.3 (CH), 127.0 (CH), 124.1 (CH), 118.0 (CH), 47.9 (CH), 43.2, 41.5 (CH_2), 30.5 (t, J_{CD} = 18.9 Hz, CH), 28.8 (CH_3), 23.6 (CH_3), 21.9 (CH_2); ATR-FTIR (thin film): 2951, 2118, 2084, 1487, 1281, 1151, 746 cm^{-1}; HRMS (EI) *m/z* calculated for $C_{13}H_{16}DN_3$ $(M)^+$: 216.1500, found: 216.1499.

B. C–H Bond Amination Experiments



(eq. 3.29)

To a mixture of 0.0225 g of azide **3.55** (0.1 mmol) and 0.0038 g of $Rh_2(esp)_2$ (5 mol %) in a Schlenk tube was added 0.50 mL of toluene. The resulting mixture was heated to three different temperatures (120 °C, 100 °C and 80 °C) and after 16 h, the heterogenous mixture was filtered through a short pad of Al_2O_3. The filtrate was concentrated *in vacuo*, and the reaction progress was analyzed using ^{1}H NMR spectroscopy. Analysis of the spectral data based on the ratio of **3.61 (3.62)** and **3.56 (3.57)** revealed the kinetic isotope effect at each temperature.

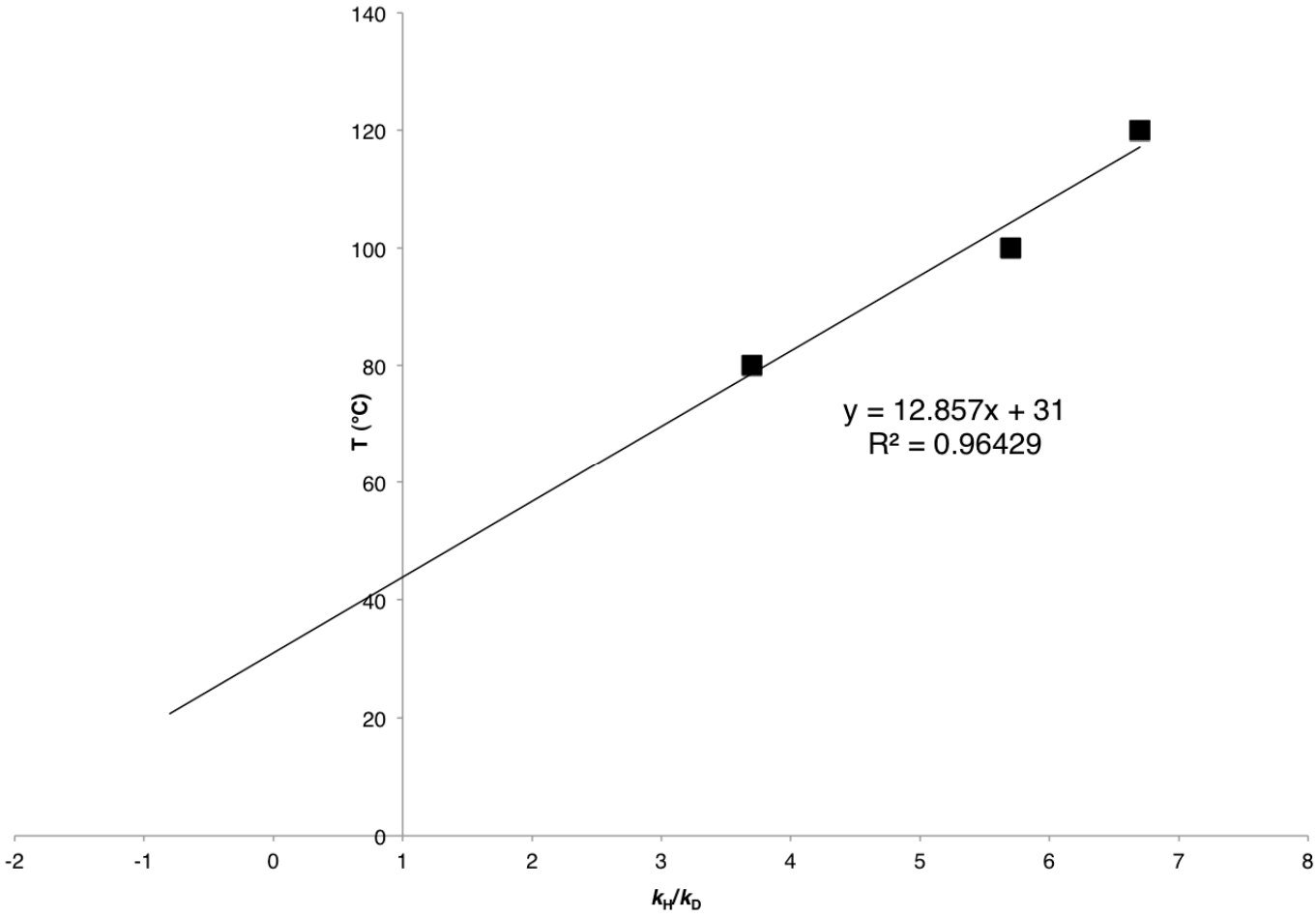
Table 3.8. Observed kinetic isotope effects

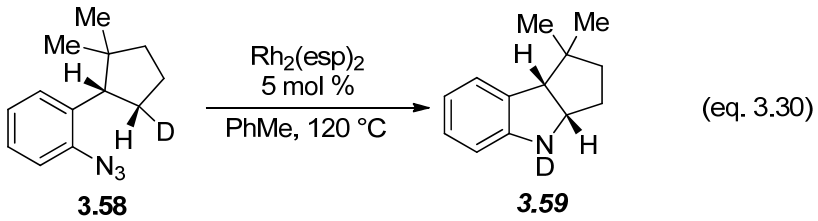
entry	T (°C)	k_H/k_D[a]
1	80	3.7
2	100	5.7
3	120	6.7

[a] As determined using ^{1}H NMR spectroscopy.

From these data, the isokinetic temperature was calculated to be approximately 43 °C (Figure 3.1), indicating that the reaction is under entropic control.

Figure 3.1. Temperature dependence of k_H/k_D.





3.58 ***3.59*** (eq. 3.30)

To a mixture of 0.0215 g of azide **3.58** (0.1 mmol) and 0.0038 g of $Rh_2(esp)_2$ (5 mol %) in a Schlenk tube was added 0.50 mL of toluene-d_8. The resulting mixture was heated to 120 °C and after 16 h, the reaction progress was analyzed using ^{1}H NMR spectroscopy. The reaction conversion was determined to be 64.6% by comparison the pick C5 – H of azide **3.58** with the

C5 – H pick of indoline **3.59**. Only the formation of a single diastereomer of **3.59** was observed.

No change in the diastereomeric ratio of **3.59** was observed.

3.7 References

1 (a) Dong, H. Latka, R. T. Driver, T. G. "Ruthenium-catalyzed γ-carbolinium ion formation from aryl azides; synthesis of dimebolin." *Org. Lett*. **2011**, *13*, 2726. (b) Stokes, B. J. Richert, K. J. Driver, T. G. "Examination of the mechanism of Rh_2(II)-catalyzed carbazole formation using intramolecular competition experiments." *J. Org. Chem*. **2009**, *74*, 6442. (c) Dong, H. Shen, M. Redford, J. E. Stokes, B. J. Pumphrey, A. L. Driver, T. G. "Transition metal-catalyzed synthesis of pyrroles from dienyl azides." *Org. Lett*. **2007**, *9*, 5191. (d) Shen, M. Leslie, B. E. Driver, T. G. "Dirhodium(II)-catalyzed intramolecular C−H amination of aryl azides." *Angew. Chem., Int. Ed*. **2008**, *47*, 5056. (e) Stokes, B. J. Dong, H. Leslie, B. E. Pumphrey, A. L. Driver, T. G. "Intramolecular C−H amination reactions: exploitation of the Rh_2(II)-catalyzed decomposition of azidoacrylates." *J. Am. Chem. Soc*. **2007**, *129*, 7500.

2 For descriptions of the competing reactions, see: (a) Caselli, A. Gallo, E. Ragaini, F. Ricatto, F. Abbiati, G. Cenini, S. "Chiral porphyrin complexes of cobalt(II) and ruthenium(II) in catalytic cyclopropanation and amination reactions." *Inorg. Chim. Acta*. **2006**, *359*, 2924. (b) Ragaini, F. Penoni, A. Gallo, E. Tollari, S. Gotti, C. L. Lapadula, M. Mangioni, E. Cenini, S. "Amination of benzylic C-H bonds by aryl azides catalyzed by CoII–porphyrin complexes: a synthetic and mechanistic study." *Chem.-Eur. J*. **2003**, *9*, 249. (c) Cenini, S. Tollari, S. Penoni, A. Cereda, C. "Catalytic amination of unsaturated hydrocarbons: reactions of p-nitrophenylazide with alkenes catalysed by metallo-porphyrins." *J. Mol. Catal. A*. **1999**, *137*, 135.

3 Refer to the supporting information for a comprehensive description of the reaction conditions examined.

4 Photolysis or pyrolysis of aryl azides with *ortho*-alkyl substituents affords a variety of products, including tar, anilines, azepines, indoles, and indolines. For leading reports, see: (a) Murata, S. Yoshidome, R. Satoh, Y. Kato, N. Tomioka, H. "Reactivities of nitrenes generated by photolysis of 2-(.omega.-phenylalkyl)phenyl azides." *J. Org. Chem*. **1995**, *60*, 1428. (b) Smolinsky, G. Feuer, B. I. "Nitrene chemistry. An analysis of the products from the pyrolysis of 2-butylazidobenzene." *J. Org. Chem*. **1964**, *29*, 3097.

5 For recent reports of iron-catalyzed aliphatic C−H bond amination from azides, see: (a) King, E. R. Hennessy, E. T. Betley, T. A. "Catalytic C−H bond amination from high-spin iron imido complexes." *J. Am. Chem. Soc*. **2011**, *133*, 4917. (b) King, E. R. Betley, T. A. "C−H bond amination from a ferrous dipyrromethene complex." *Inorg. Chem*. **2009**, *48*, 2361.

6 For recent reports of copper-catalyzed aliphatic C−H bond amination from azides, see: (a) Badiei, Y. M. Dinescu, A. Dai, X. Palomino, R. M. Heinemann, F. W. Cundari, T. R. Warren, T. H. "Copper–nitrene complexes in catalytic C−H amination." *Angew. Chem., Int. Ed*. **2008**, *47*, 9961. (b) Badiei, Y. M. Krishnaswamy, A. Melzer, M. M. Warren, T. H. "Transient terminal Cu−nitrene intermediates from discrete dicopper nitrenes." *J. Am. Chem. Soc*. **2006**, *128*, 15056.

7 Cf.: (a) Subbarayan, V.; Ruppel, J. V. Zhu, S. Perman, J. A. Zhang, X. P. "Highly asymmetric cobalt-catalyzed aziridination of alkenes with trichloroethoxysulfonyl azide ($TcesN_3$)." *Chem. Commun*. **2009**, 4266. (b) Gao, G.-Y. Lu, H. Subbarayan, V. Tao, J. Zhang, X. P. "A highly effective cobalt catalyst for olefin aziridination with azides: hydrogen bonding guided catalyst design." *Organometallics*. **2009**, *29*, 389. (c) Ruppel, J. V. Jones, J. E. Huff, C. A. Kamble, R. M. Chen, Y. Zhang, X. P. "Cobalt-catalyzed asymmetric olefin aziridination with diphenylphosphoryl azide." *Org. Lett*. **2008**, *10*, 1995.

8 For reports of Ru-catalyzed amination, see: (a) Milczek, E. Boudet, N. Blakey, S. "Enantioselective C−H amination using cationic ruthenium(II)–pybox catalysts." *Angew. Chem., Int. Ed*. **2008**, *47*, 6825. (b) Shou, W. G. Li, J. Guo, T. Lin, Z. Jia, G. "Ruthenium-catalyzed intramolecular amination reactions of aryl- and vinylazides." *Organometallics*. **2009**, *28*, 6847.

9 Sun, K. Sachwani, R. Richert, K. J. Driver, T. G. "Intramolecular Ir(I)-catalyzed benzylic C−H bond amination of *ortho*-substituted aryl azides." *Org. Lett*. **2009**, *11*, 3598.

10 Espino, C. G. Fiori, K. W. Kim, M. Du Bois, J. "Expanding the scope of C−H amination through catalyst design." *J. Am. Chem. Soc*. **2004**, *126*, 15378.

11 Azepines, common aryl nitrene byproducts, were never observed for any of the substrates investigated. In general, the only byproduct observed in our Rh_2(II)-catalyzed amination reaction was aniline.

12 (a) Harvey, M. E. Musaev, D. G. Du Bois, J. "A diruthenium catalyst for selective, intramolecular allylic C–H amination: reaction development and mechanistic insight gained through experiment and theory." *J. Am. Chem. Soc*. **2011**, *133*, 17207. (b) Lu, H. Tao, J. Jones, J. E. Wojtas, L. Zhang, X. P. "Cobalt(II)-catalyzed intramolecular C−H amination with phosphoryl azides: formation of 6- and 7-membered cyclophosphoramidates." *Org. Lett*. **2010**, *12*, 1248. (c) Kurokawa, T. Kim, M. Bois, J. D. "Synthesis of 1,3-diamines through rhodium-catalyzed C−H insertion." *Angew. Chem., Int. Ed*. **2009**, *48*, 2777. (d) Wasa, M. Yu, J.- Q. "Synthesis of β-, γ-, and δ-lactams via Pd(II)-catalyzed C−H activation reactions." *J. Am. Chem. Soc*. **2008**, *130*, 14058. (e) Huard, K. Lebel, H. "N-tosyloxycarbamates as reagents in rhodium-catalyzed C−H amination reactions." *Chem.−Eur. J*. **2008**, *14*, 6222. (f) Liang, C. Collet, F. Robert-Peillard, F. Muller, P. Dodd, R. H. Dauban, P. "Toward a synthetically useful stereoselective C−H amination of hydrocarbons." *J. Am. Chem. Soc*. **2008**, *130*, 343. (g) Li, Z. Capretto, D. A. Rahaman, R. He, C. "Silver-catalyzed intermolecular amination of C−H groups." *Angew. Chem., Int. Ed*. **2007**, *46*, 5184.

13 (a) Gao, G.-Y. Lu, H. Subbarayan, V. Tao, J. Zhang, X. P. "A highly effective cobalt catalyst for olefin aziridination with azides: hydrogen bonding guided catalyst design." *Organometallics*. **2009**, *29*, 389. (b) Ruppel, J. V. Jones, J. E. Huff, C. A. Kamble, R. M. Chen, Y. Zhang, X. P. "Cobalt-catalyzed asymmetric olefin aziridination with diphenylphosphoryl azide." *Org. Lett*. **2008**, *10*, 1995. (c) Jones, J. E. Ruppel, J. V. Gao, G.-Y. Moore, T. M. Zhang, X. P. "Construction of robust ruthenium(salen)(CO) complexes and asymmetric aziridination with nitrene precursors in the form of azide compounds that bear easily removable N-sulfonyl groups." *J. Org. Chem*. **2008**, 73, 7260. (d) Kawabata, H. Omura, K. Katsuki, T. "Asymmetric aziridination: a new entry to optically active non-N-protected aziridines." *Tetrahedron Lett*. **2006**, *47*, 1571.

14 Smolinsky, G. "Thermal reactions of substituted aryl azides: the nature of the azene intermediate." *J. Am. Chem. Soc*. **1961**, *83*, 2489.

15 For leading reports on the mechanism of related metal-mediated C−H bond amination reactions, see: (a) Lyaskovskyy, V. Suarez, A. I. O. Lu, H. Jiang, H. Zhang, X. P. de Bruin, B. "Mechanism of cobalt(II) porphyrin-catalyzed C–H amination with organic azides: radical nature and H-atom abstraction ability of the key cobalt(III)–nitrene intermediates." *J. Am. Chem. Soc*. **2011**, *133*, 12264. (b) Fiori, K. W. Espino, C. G. Brodsky, B. H. Du Bois, J. "A mechanistic analysis of the Rh-catalyzed intramolecular C–H amination reaction." *Tetrahedron*. **2009**, *65*, 3042. (c) Fiori, K. W. Du Bois, J. "Catalytic intermolecular amination of C−H bonds: method development and mechanistic insights." *J. Am. Chem. Soc*. **2007**, *129*, 562.

16 For crystal structures of metal−azide complexes, see: (a) Water-man, R. Hillhouse, G. L. "η^2-Organoazide complexes of nickel and their conversion to terminal imido complexes via dinitrogen extrusion." *J. Am. Chem. Soc*. **2008**, *130*, 12628. (b) Dias, H. V. R. Polach, S. A. Goh, S.-K. Archibong, E. F. Marynick, D. S. "Copper and silver complexes containing organic azide ligands: syntheses, structures, and theoretical investigation of [HB(3,5-$(CF_3)2Pz)_3$]CuNNN(1-Ad) and [HB(3,5-$(CF_3)2Pz)_3$]AgN(1-Ad)NN (Where Pz = Pyrazolyl and 1-Ad = 1-Adamantyl)." *Inorg. Chem*. **2000**, *39*, 3894. (c) Fickes, M. G. Davis, W. M. Cummins, C. C. "Isolation and structural characterization of the terminal mesityl azide complex V(N_3Mes)(I)$(NRArF)_2$ and its conversion to a vanadium(V) imido complex." *J. Am. Chem. Soc*. **1995**, *117*, 6384. (d) Proulx, G. Bergman, R. G. "Synthesis and structure of a terminal metal azide complex: an isolated intermediate in the formation of imidometal complexes from organic azides." *J. Am. Chem. Soc*. **1995**, *117*, 6382.

17 For computational studies on the mechanism of metal nitrenoid formation from azides, see: (a) References 10a and 16a. (b) Cundari, T. R. Dinescu, A. Kazi, A. B. "Bonding and structure of copper nitrenes." *Inorg. Chem*. **2008**, *47*, 10067.

18 Kornecki, K. P. Berry, J. F. "Evidence for a one-electron mechanistic regime in dirhodium-catalyzed intermolecular C−H amination." *Chem-Eur. J*. **2011**, *17*, 5827.

19 (a) Vadola, P. A. Sames, D. "C−H bond functionalization via hydride transfer: direct coupling of unactivated alkynes and sp^3 bonds catalyzed by platinum tetraiodide." *J. Am. Chem. Soc*. **2009**, *131*, 16525. (b) Murarka, S. Deb, I. Zhang, C. Seidel, D. "Catalytic enantioselective intramolecular redox reactions: ring-fused tetrahydroquinolines." *J. Am. Chem. Soc*. **2009**, *131*, 13226.

20 Murata, S. Tsubone, Y. Kawai, R. Eguchi, D. Tomioka, H. "Mechanistic studies of intramolecular CH insertion reaction of arylnitrenes: isotope effect, configurational purity and radical clock studies." *J. Phys. Org. Chem*. **2005**, *18*, 9.

21 (a) Lin, X. Zhao, C. Che, C.-M. Ke, Z. Phillips, D. L. "A DFT study on the mechanism of Rh_2(II)-catalyzed intramolecular amidation of carbamates." *Chem.-Asian J*. **2007**, *2*, 1101. (b) Nageli, I. Baud, C. Bernardinelli, G.

Jacquier, Y. Moraon, M. Muller, P. "Rhodium(II)-catalyzed C−H insertions with {[(4-Nitrophenyl)sulfonyl]imino}phenyl-λ^3-iodane." *Helv. Chim. Acta*. **1997**, *80*, 1087.

22 The observed KIE is composed of both a primary and an assumed small secondary isotope effect. We thank a reviewer for pointing out that this secondary effect is not necessarily the same forthe two diastereomeric transition states that lead to 15-d_2 and 16-d_2.

23 (a) Wiberg, K. B. "The deuterium isotope effect of some ionic reactions of benzaldehyde." *J. Am. Chem. Soc*. **1954**, *76*, 5371. (b) Cohen, R. Graves, C. R. Nguyen, S. T. Martin, J. M. L. Ratner, M. A. "The mechanism of aluminum-catalyzed Meerwein−Schmidt−Ponndorf−Verley reduction of carbonyls to alcohols." *J. Am. Chem. Soc*. **2004**, *126*, 14796.

24 k_H/k_D = 5 was reported by Lebel and Huard for the Rh_2(II)- catalyzed C−H bond amination of cyclohexane using N-tosylox- ycarbamate as the N-atom source.

25 If C−H bond cleavage did occur via a hydride shift, formation of carbocation 9 would be expected to trigger the migration of one of the methyl groups. For alkyl group migrations in Rh_2(II)-catalyzed reactions of aryl azides, see: Sun, K. Liu, S. Bec, P. M. Driver, T. G. "Rhodium-catalyzed synthesis of 2,3-disubstituted indoles from β,β-disubstituted stryryl azides." *Angew. Chem., Int. Ed*. **2011**, *50*, 1702.

26 At 100 and 80 °C, the KIE was determined to be 5.7 and 3.7. The linear correlation of these data with temperature revealed the isokinetic temperature to be 43 °C.

27 For leading discussions on the isokinetic temperature, see: (a) Carpenter, B. K. Determination of Organic Reaction Mechanisms; Wiley: New York, 1984; pp 149−150. (b) Leffler, J. E. "The enthalpy-entropy relationship and its implications for organic chemistry." *J. Org. Chem*. **1955**, *20*, 1202.

28 In contrast, other aliphatic C−H bond functionalization reactions show a preference for equatorial C−H bonds: (a) Chen, K. Eschenmoser, A. Baran, P. S. "Strain release in C−H bond activation?" *Angew. Chem., Int. Ed*. **2009**, *48*, 9705. (b) Chen, M. S. White, M. C. "A predictably selective aliphatic C–H oxidation reaction for complex molecule synthesis." *Science*. **2007**, *318*, 783. (c) Wehn, P. M. Lee, J. Du Bois, J. "Stereochemical models for Rh-catalyzed amination reactions of chiral sulfamates." *Org. Lett*. **2003**, *5*, 4823.

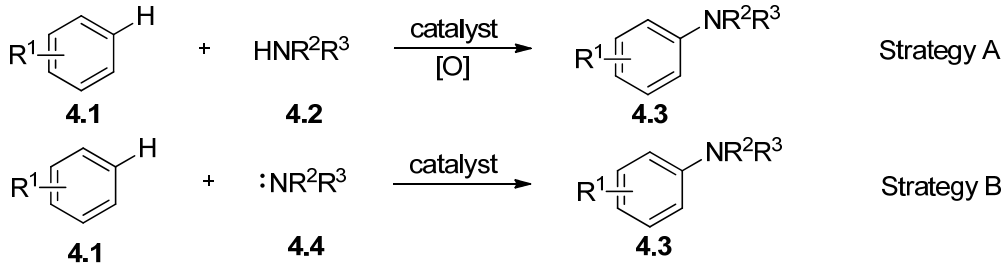
Chapter 4. Rhodium-Catalyzed Synthesis of 2,3-Disubstituted Indoles from β, β-Disubstituted Stryryl Azides

4.1 Introduction

Nitrogen-containing heterocycles are important subclass of organic compounds, found in novel pharmaceuticals[1] and natural products[2] ranging from chemotherapeutic compounds to bioactive plant materials. The ubiquity of aromatic C–N bonds in organic molecules has made the development of novel amination methodologies an important objective for chemists. Among these synthetic methods, transition metal catalyzed sp^2 C–H bond amination has attracted great attention recently. This chapter will present a brief introduction on C–N bond formation as well as our work on Rh(II) carboxylate catalyzed synthesis of 2,3-disubstitued indole from β,β-disubstitued styryl azide. The results from these experiments suggested that rhodium-nitrene formation from azides could be exploited to achieve tandem- or cascade bond forming reactions.

C–H bond amination plays an important role in the transition-metal catalyzed C–N formation. In general, two strategies are used to aminate the sp^2 C-H bond (Scheme 4.1); strategy A is oxidative amination, which requires the addition of an oxidant to regenerate catalyst. strategy B involves formation of nitrene **4.4** followed by insertion to C–H bond of **4.1**.

Scheme 4.1. Two C–N bond formation strategies.



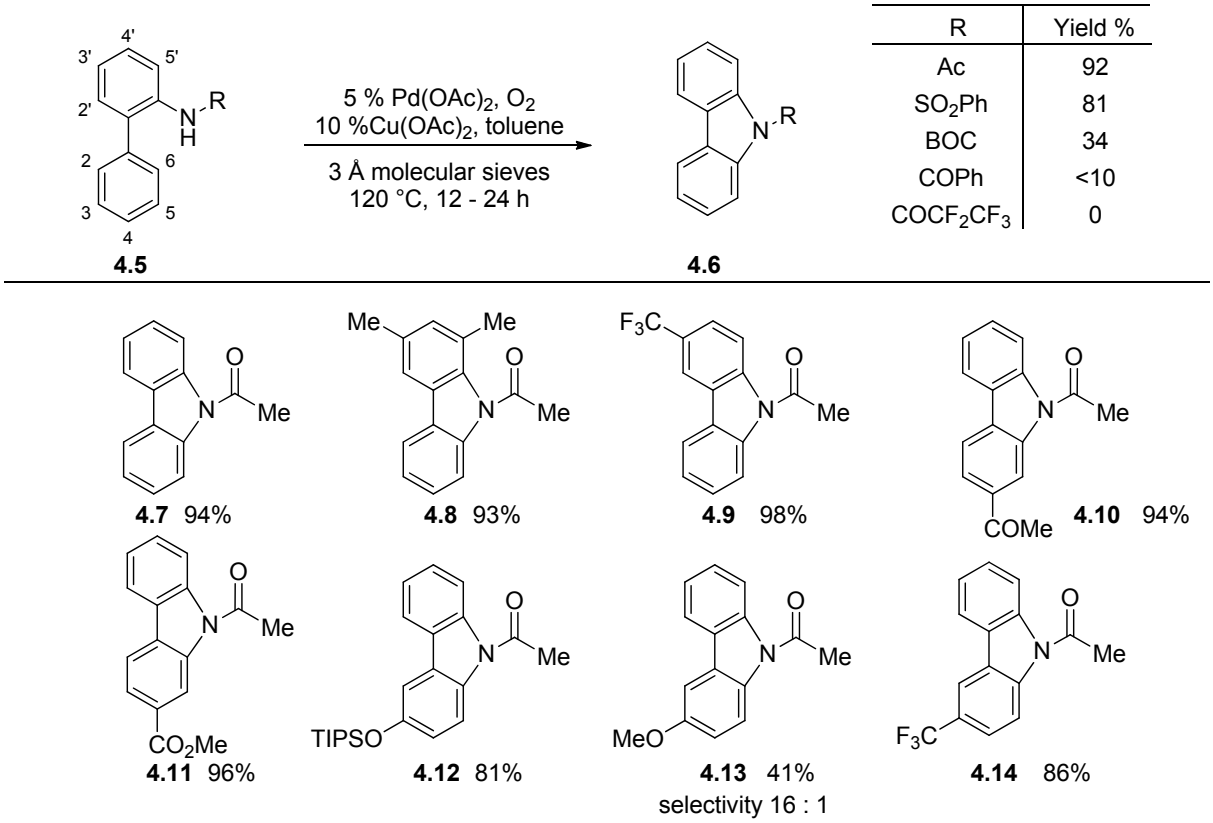
4.2 Initial Study on Transition-Metal Catalyzed C–N Bond Formation

Among C–N bond formation reactions of the first type (oxidative amination, Scheme 4.1, strategy A), employment of amine with acidic hydrogen as N-atom source was widely studied.[3] Buchwald first reported that 2-acetaminobiphenyl could be successfully converted to *N*-acetyl carbazole quantitatively with 5% $Pd(OAc)_2$ and stoichiometric amount of $Cu(OAc)_2$ under atmosphere of air.[4] Later on, they found that the decrease in $Cu(OAc)_2$ loading to catalytic amount 10% in the presence of oxygen had no effect on the yield.

The $Pd(OAc)_2$-based catalytic system was found to be suitable for a broad range of 2-acetaminobiphenyl (Scheme 4.2). In addition to tolerating a range of different electronic substituents (**4.9**, **4.13**, **4.14**) on both arenes, the cyclization process was compatible with a variety of sensitive functional groups, including ketone (**4.10**), ester (**4.11**), and triisoproylsilane (**4.12**). The excellent regioselectivity (**4.13**) observed was attributed to the minimization of steric interactions during the C–N bond formation. The author also investigated the identity of substituents on *N*-atom on the process: while comparable yields were obtained using sulfonyl group protected biphenyl amine as the acetyl group, much lower yields were obtained using amines protected with Boc, benzamide and pentafluoropropionyl group. These results demonstrate that moderate acidic amine hydrogen is required. Enhanced acidity would lead to

premature deprotonation: if it occurred prior to the coordination of $Pd(OAc)_2$ to amide, the catalytic efficiency could be significantly diminished.

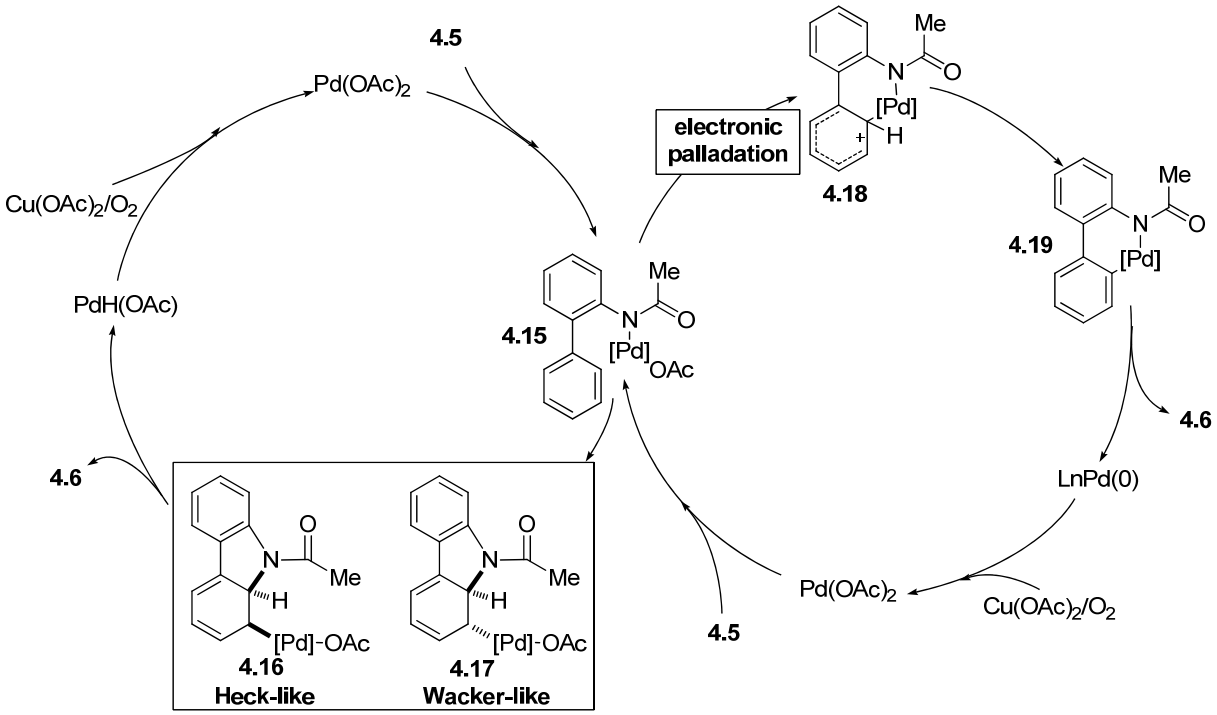
Scheme 4.2. Substrate scope of $Pd(OAc)_2$ catalyzed C–N bond formation from amide.



From their extensive substrate study, the Buchwald group proposed two mechanisms for carbazole formation (Scheme 4.3). Initially, they believed that the cyclization process (the right part of Scheme 4.3) involved the formation of palladacyle (**4.19**) and followed by reductive elimination to afford carbazole (**4.6**). The conversion of **4.13** and **4.14**, however, is inconsistent with this proposed mechanism. If palladacycle intermediate existed, the authors expected higher yields to be obtained for electron-rich **4.13** compared to **4.14** bearing strong electron-withdrawing CF_3 substituent. A couple of pathways were proposed to better explain the different reactivity of substrates (the left part of Scheme 4.3). After formation of palladium amide (**4.15**),

cyclization might occur either through a Heck-like[5] insertion mechanism to form **4.16**, which will undergo rearomatization through reductive elimination to form carbazole (**4.6**). Alternatively, Wacker-like[6] mechanism maybe operating. Palladium amide (**4.15**) would be attacked by arene to complete cyclization via **4.17** followed by rearomatization. Reoxidation of newly formed Pd(0) with $Cu(OAc)_2$ and oxygen would complete the catalytic cycle.

Scheme 4.3. Potential mechanisms of $Pd(OAc)_2$-catalyzed C–N bond formation from amides.

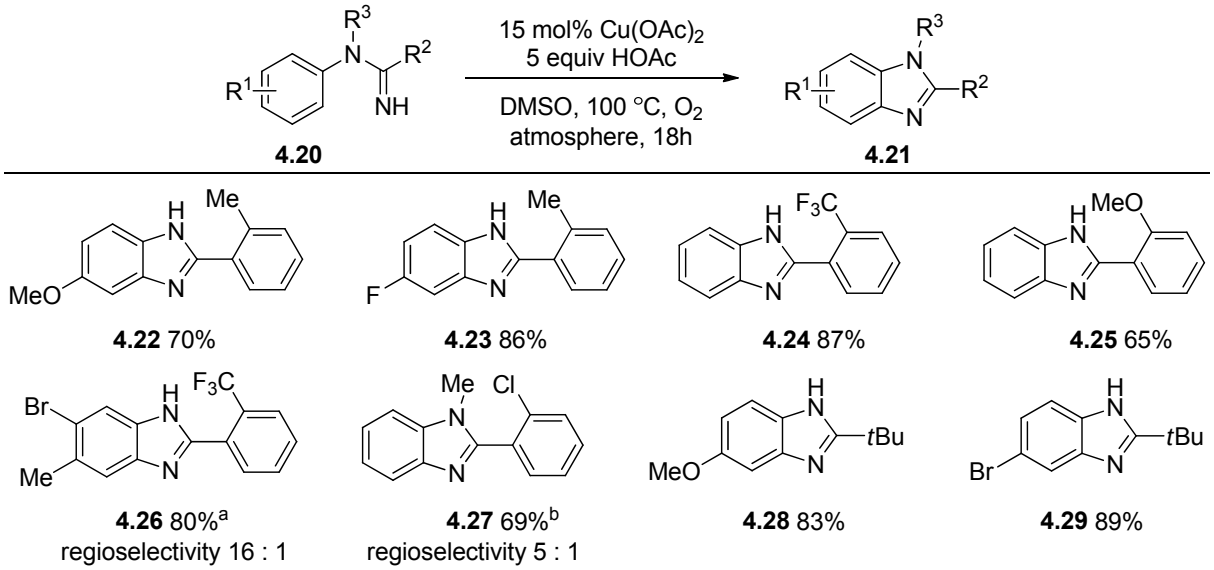


4.3 $Cu(OAc)_2$ Catalyzed Benzimidazole Formation from Imines

Besides amides, the Buchwald group demonstrated that imines are potential nitrogen sources. Brasche and Buchwald found that $Cu(OAc)_2$ facilitated benzimidazole formation from the corresponding amidine.[7] The optimized condition used $Cu(OAc)_2$ as the catalyst in presence of O_2 at 100 °C (Scheme 4.4). Using these conditions, the generality of reaction was investigated. The authors reported that a *ortho*-substituted R^2-aryl group or an R^2-*tert*-butyl group was

required. Unfortunately, the authors did not provide any further explanation for their requirement. Only decomposition of starting amidines was reported in the absence of these groups. Besides this limitation, their transformation tolerated a range of electronically different R^2- and R^3 groups. The bromide functionality present in **4.26** and **4.29** also survived the reaction, which enables ready functionalization of benzimidazole product. High regioselectivity (16:1) was observed if unsymmetrical amidines (**4.26**) were used. Further examination revealed that N-methylated amidines can also be employed as substrates to give benzimidazoles such as **4.27.**

Scheme 4.4. Substrate scope of benzimidazole formation.

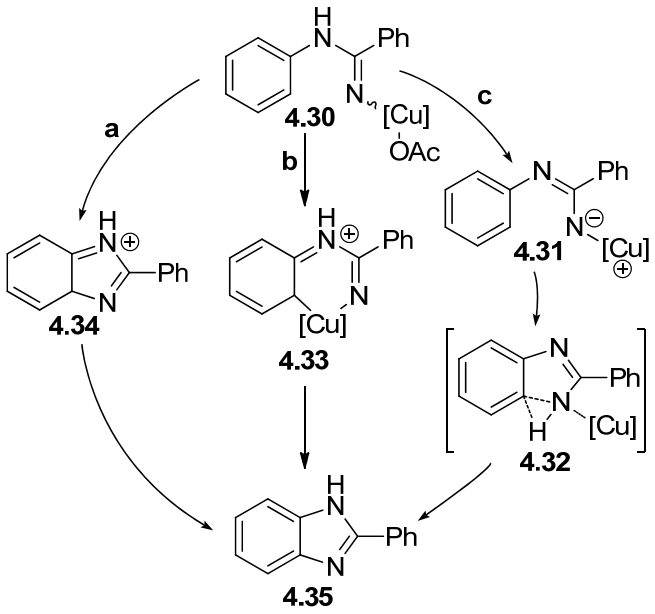


[a] 16:1 regioselectivity was observed by HPLC. [b] 2 equiv. HOAc, and 48 h required for conversion.

Plausible pathways were outlined by authors to explain benzimidazole formation (Scheme 4.5). Coordination of copper complex to imine nitrogen (**4.30**) initiates the catalytic cycle with copper either in oxidation state II or III. In pathway a, aromatic electrophilic attack the coordinated nitrogen with simultaneous release of copper species to affords **4.34**. Benzimidazole **4.35** is obtained after subsequent deprotonation and rearomatization. Pathway b involves oxidative addition of copper center to *ortho*-aromatic C–H bond. Reductive elimination from

metallocycle **4.33** directly provides benzimidazole **4.35** and a reduced copper catalyst, which could be regenerated by oxidant. In contrast to stepwise C–H bond amination, benzimidazole formation could occur via copper nitrenoid **4.31** (pathway c). Concerted C–H bond insertion of this copper nitrenoid into the adjacent C–H bond (transition state **4.32**) generates the benzimidazole product after dissociation of the copper complex.

Scheme 4.5. Proposed mechanism of benzimidazole formation.

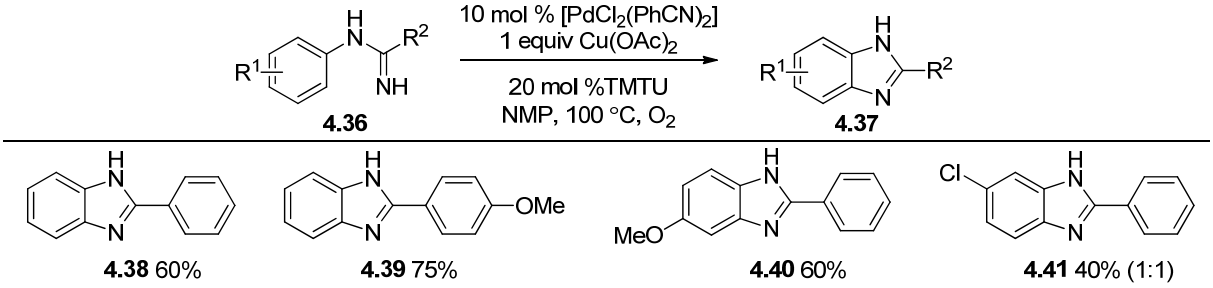


4.4 Modification of Benzimidazole Formation Promoted by Pd(II) Complexes

An extension of Buchwald's copper-catalyzed benzimidazole formation from amidine was reported by Xiao and Shi.[8] They discovered that amidines can be smoothly transformed to benzimidazoles using $PdCl_2(PhCN)_2$ in combination with stoichiometric $Cu(OAc)_2$, acetic acid and NMP as solvent (Scheme 4.6). Unlike Buchwald method, this system could tolerate substrates lacking *ortho*-substituted R^2-aryl groups. Their method, however, is limited to substrates bearing electron-rich or electron-neutral R^2-groups. Electron-deficient substrates

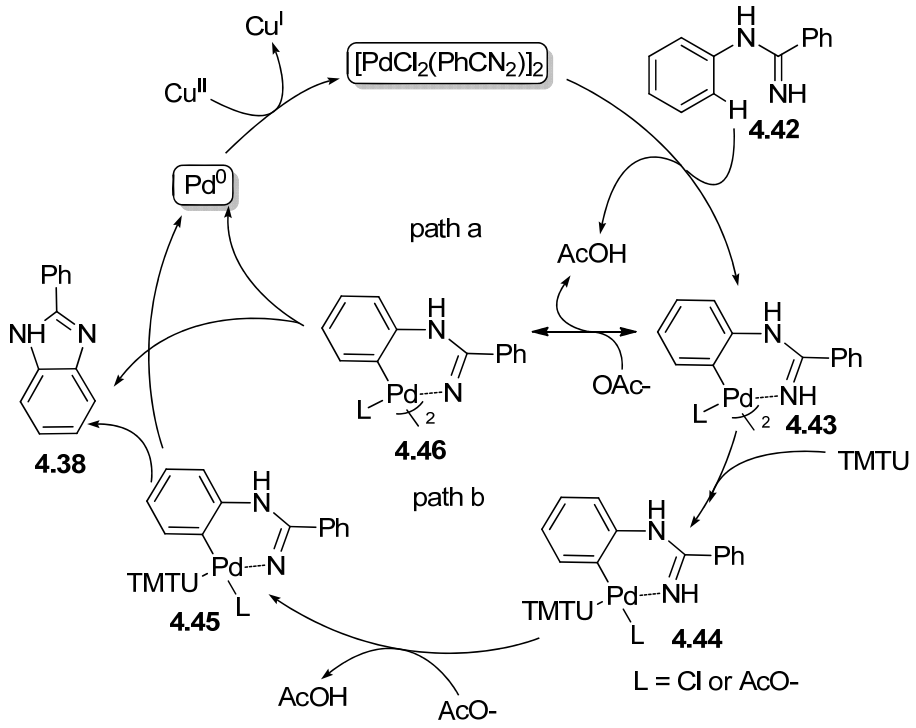
afforded extremely low yields. In addition, any extra substituent on nitrogen shut down the reaction, implying that the free N–H group is necessary for the reaction. No obvious regioselectivity was observed for the process: benzimidazole **4.41** was formed as a 1:1 mixture of regioisomers from the corresponding 3-substituted aniline starting material.

Scheme 4.6. Scope of Shi's Pd-catalyzed benzimidazole formation.



Based on optimization and their preliminary mechanism study, Shi proposed that the mechanism for this transformation proceed through a Pd(0)/Pd(II) redox cycle (Scheme 4.7). After formation of palladacycle **4.43** via oxidative addition, deprotonation with base NaOAc and reductive elimination from dimer **4.46** leads to benzimidazole and Pd(0). Oxidation of Pd(0) with Cu(II) regenerates the catalyst. Shi and co-workers observed that tetramethylthiourea (TMTU) dramatically improves the yield of the transformation, and their preliminary study indicated that treatment of the dimer with TMTU facilitated monomer formation. Hence, an alternative mechanism was suggested, where TMTU assisted dissociation of the dimer to monomer **4.44**, which was characterized by X-ray crystallography. Deprotonation of palladacycle **4.44** afforded **4.45**. Reductive elimination from **4.45** gives benzimidazole **4.38**.

Scheme 4.7. Mechanistic study of benzimidazle based on Shi's method.

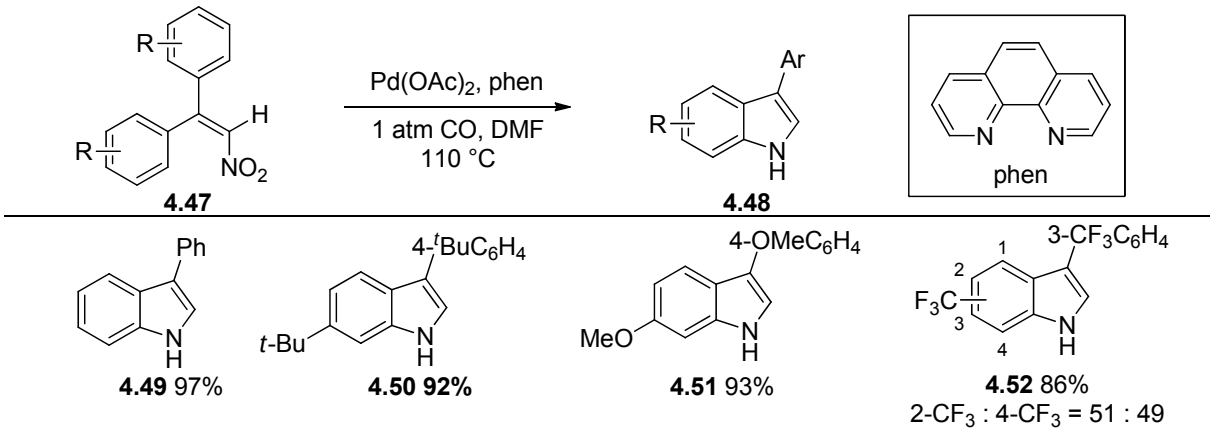


4.5 C–H Bond Amination Using Nitro Group as Nitrogen Source.

The nitro group has also proven to be an important nitrogen precursor for C–N bond formation as well. Initial work on trivalent phosphorus-mediated deoxygenation of nitro group was conducted in Sundberg laboratories.[9] Subsequently in 1994,[10] the Watanabe group reported that palladium complex catalyzed reductive *N*-heterocyclization of nitroarenes to access indole. Building on their results, Dong and co-workers reported that a wide range of metal salts could catalyze the C–H bond amination reaction from nitro-groups (Scheme 4.8).[11] Their studies revealed that $Pd(OAc)_2$ provided the best result, with the optimal conditions found to be 2 mol % of $Pd(OAc)_2$, 4 mol % of 1,10-phenanthroline (phen), DMF, 110 ºC, and 1 atm of CO. Palladium-catalyzed indole from nitro-substituted styrene is compatible with both electron-rich (**4.51**) and electron-deficient (**4.52**) substrates. One weakness of this catalytic system is that no

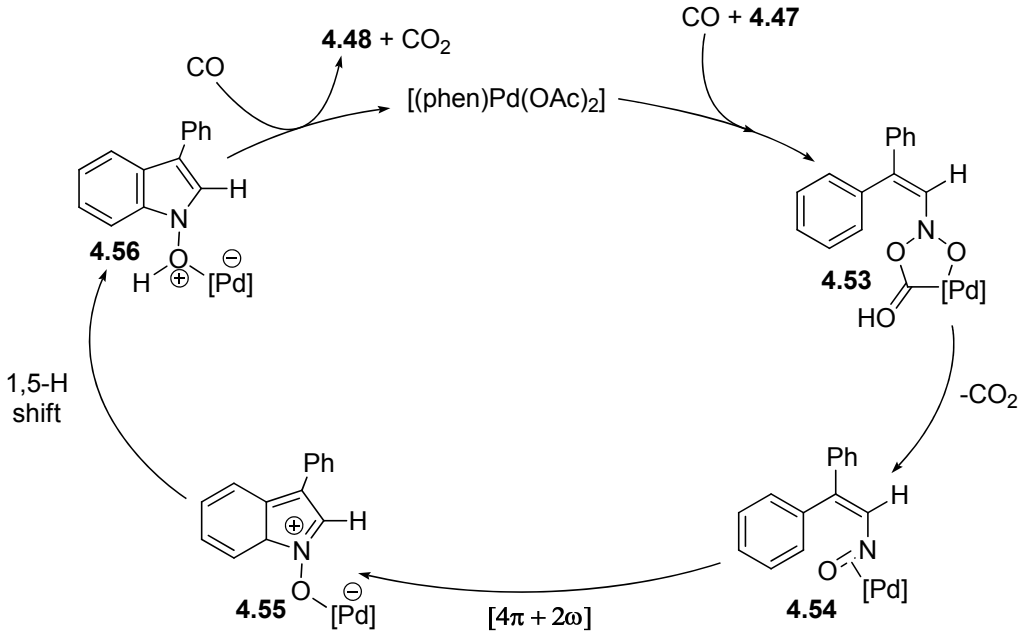
regioselectivity was observed: exposure of 3-substituted styrenes afforded a 1:1 mixture of indole isomers (**4.52**).

Scheme 4.8. $Pd(OAc)_2$ catalyzed indole formation using the nitro group as nitrogen source.



Although a variety of mechanisms could be operating, the authors proposed the catalytic cycle in Scheme 4.9. Reaction of the β-nitrostyrene with the palladium(II) catalyst and CO produces palladacycle **4.53**. Extrusion of CO_2 affords nitrosostyrene **4.54** with coordination of palladium complex to N–O bond, which undergoes electrocyclization with the pendant arene to give nitronate **4.55**. Subsequent 1,5-H shift affords *N*-hydroxyindole **4.56**, which is reduced by a second molecule of CO to afford indole **4.48** and regenerate palladium catalyst with release of CO_2.

Scheme 4.9. Possible mechanism of indole formation with nitro group.



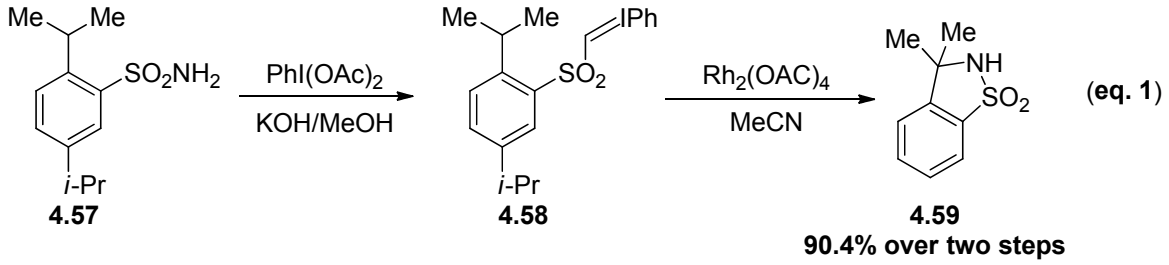
4.6 Amination of C–H Bond Employed Nitrenoid as Nitrogen Source

A more common reactive intermediate for C–H bond amination reactions is the divalent nitrene. Nitrene is considered as a good source to trigger electrophilic C-H bond amination because it lacks a full octet of electrons. The high reactivity of uncoordinated nitrene, however, leads to decomposition as well as poor regioselectivity. To lower the reactivity, modern amination reactions employ nitrenoids: transition metal cooridinated nitrenes. The nitrenoids can be generated from different nitrogen sources, including iminoiodinanes, and azides.

4.6.1 Iminoiodinane as Nitrenoid Precusor

Employment of iminoiodinane as a nitrenoid precursor in intramolecular C–H bond amination reactions was initially reported by Breslow and Gellman.[12] This method (eq. 1) is limited to the requirement of isolation of intermediate sulfonyliminoiodinane **4.58** prepared by reaction of sulfonylamide **4.57** with phenyliododiacetate and isolation of explosive

iminoiodinane. This process is believed to proceed through intramolecular metal-nitrene insertion into an isopropyl methyl C–H bond, though no mechanistic data was offered at the time in support of this claim.



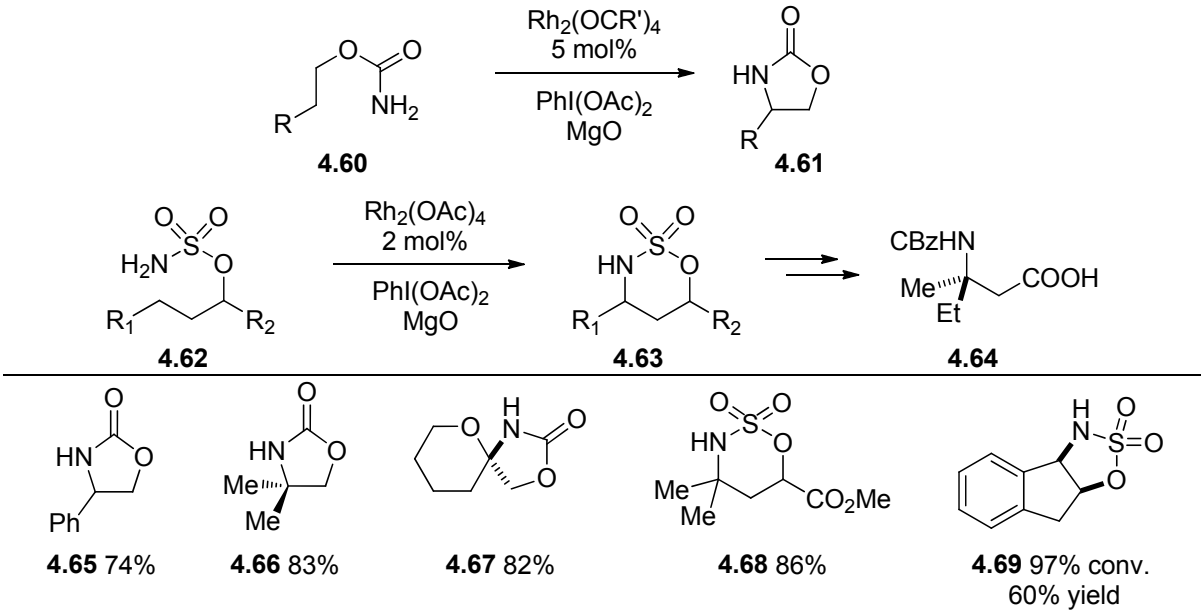
4.57 **4.58** **4.59**

90.4% over two steps

4.6.2 C–N Bond Formation Using Carbamates and Sulfamates as Nitrenoid Source

Recently, the Du Bois group achieved rhodium carboxylate-catalyzed amination of intramolecular aliphatic C-H bonds through formation of iminoiodinane in situ from carbamates or sulfamate esters (Scheme 4.10). Five-membered heterocycle oxazolidinones **4.61** could be accessed from carbamate **4.60** with MgO as base.[13] In addition, the reaction of sulfamate ester **4.62** when the Rh(II)-carboxylate was used to transfer the nitrene from the iminoiodinane. Substrates containing both benzylic **4.65** and tertiary C-H **4.66, 4.67** centers are cyclized to oxazolidinone products. Oxidation of sulfamate ester **4.62** in the presence of $Rh_2(OAc)_4$ enables the formation 6-membered oxathiazinane **4.63.**[14] The Du Bois group showed that the resulting heterocyclic products could be easily transformed into chiral amino acid **4.64** through nucleophilic ring-opening of oxathiazinane. Successful formation of **4.64** indicated a potential method to furnish optical pure quaternary center. Screen of substrates scope shows that unreactive tertiary C–H **4.68** works well under optimized conditons. It is possible to generate efficiently the five-membered sulfamidate **4.69** in systems as well.

Scheme 4.10. Intramolecular amination from carbamates or sulfamate esters.

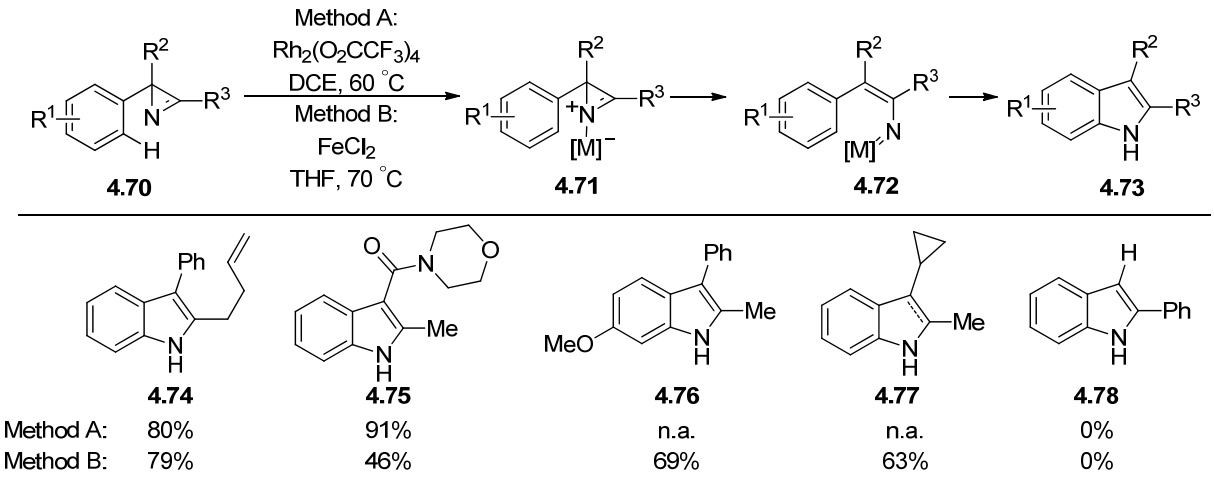


4.6.3 Nitrenoid Fromation from Azirines

Non-oxidative nitrenoid formation from azirines is also possible. Rearrangement of azirine promoted by transition metal is applied to access vinyl nitrene-metal complexes[15]. Recently, Narasaka and co-workers reported (Scheme 4.11) that $Rh_2(O_2CCF_3)_4$ could trigger the isomerization of azirine to a metal nitrene, which reacts with a proximal C–H bond.[16] Their catalyst system tolerates a variety of functional groups including strong electron-withdrawing trifluoromethyl, cyano, as well as potentially reactive allyl and alkynes. After Narasaka group publication, Jana and Zheng disclosed an alternative way to activate azirine.[17] Comparable yields could be obtained using the cheaper $FeCl_2$ instead using expensive rhodium complexes. They also observed that the metal nitrene could activate electron-rich aromatic C–H bond exclusively to yield single regioselective product **4.76**. The cyclopropyl-substituted azirine provided insight into the electronic nature of the transform. Formation of indole **4.73** indicated that the metal nitrene was singlet in nature. If triplet nitrene formed, the ring-opening of cyclopropane

substituent would be observed. Both Narasaka's and Zheng's methods, however, share a common limitation in the substrate scope (**4.78**): an R^2-substituent is required which could be alkyl (**4.77**), aryl (**4.74**), or amide (**4.75**).

Scheme 4.11. Indole formation from azirine.



4.6.4 Generation of Nitrenoid from Azides

Although C–N bond formation process employing $PhI(OAc)_2$ to generate nitrene has been widely studied, this process requires *in situ* generation of iminoiodinane and formation of byproducts. While using azirines as the nitrogen-atom precursor eliminates the need for an oxidant in the amination reaction, it suffers from difficult substrate preparation and limited scope. Using easily accessible azide as nitrogen source could avoid these drawbacks, and environmentally friendly nitrogen gas would be produced as only by-product. Azides has attracted considerable attention since it was recognized as nitrene precursor.[18] Initial reports mostly focused on thermolysis or photolysis of azide. While these reactions could access a variety of N-heterocycles, they are limited by the requirement of harsh condition and hyperactivity of the free nitrene intermediate, which led to poor selectivity and low yields due to intervening decomposition pathways. Development of transition-metal mediated nitrene

formation would overcome these limitations by attenuating the reactivity of the nitrene through coordination to a transition metal catalyst.

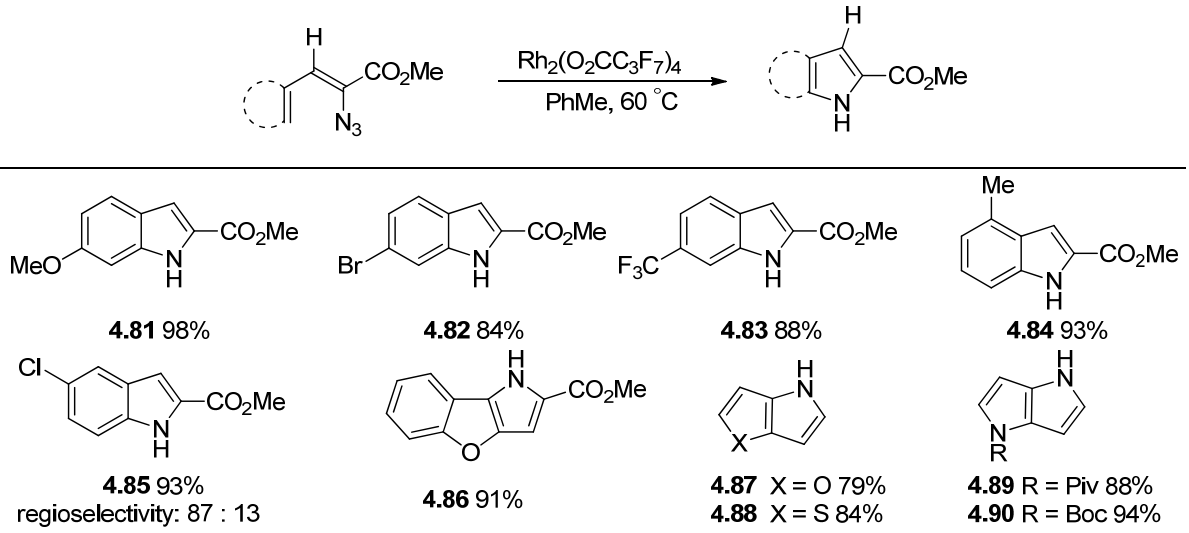
Not too surprisingly, metal-catalyzed decomposition of azides has been pursued by synthetic chemists to achieve intermolecular aziridine formation catalyzed by ruthenium-[19] or copper complexes;[20] as well as cobalt-promoted benzylic C–H bonding amination using sulfonyl azide[21] and Troc-azide;[22] and $RuCl_3$ catalyzed N-hetercycle formation from aryl azides was also reported by Jia, Lin and co-workers.[23]

Rh(II) Carboxylate Promoted Indole Fromation using Vinyl Aizdes as Nitrogen Source

Our group has published a series of papers[24] on the C–N bond formation from vinyl- and aryl azides. In 2007, our group found that rhodium carboxylates triggered the formation of indoles from vinyl azides at room temperature. After screening a variety of transition metal complexes, such as Fe[25], Zn[26], Cu[27], Ru[28], only rhodium(II) carboxylate complexes were found to catalyze the amination reaction with decent yields. Among these rhodium complexes surveyed, the best result was obtained using rhodium(II) perflurobutyrate.

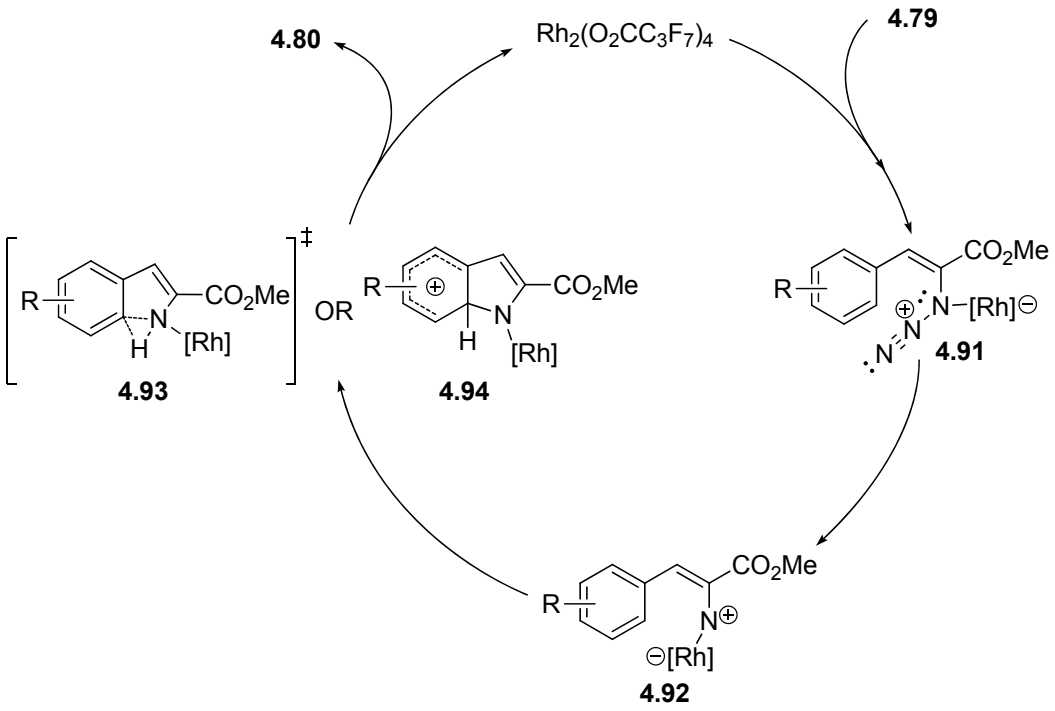
The optimized conditions could enable a large range of vinly azide to be transformed to corresponding indoles (Scheme 4.12). Substrates screening revealed that modulation of electronic nature on arene had little effect on the yield of reaction (**4.81**, **4.83**). Regioselectivity was also observed where the new C–N bond was formed from the sterically less hindered C–H bond (**4.85**). Besides indole formation, 2-substituted benzofurans (**4.86**), furans (**4.87**) and thiophenes (**4.88**) can be efficiently converted as well to the corresponding indolo-heterocycle. While the pyrrole-functionality is compatible with the reaction condition, protection of nitrogen atom with Piv (**4.89**) or Boc (**4.90**) is necessary. Our group assumed that coordination of nitrogen to rhodium(II) attenuated the activity of catalyst without protection.

Scheme 4.12. Rhodium(II) catalyzed indole formation from vinyl azide.



The proposed mechanism (Scheme 4.13) was based on the formation of nitrenoid **4.92** which came from **4.91** after extrusion of N_2 gas. C–N bond formation could occur either from concerted insertion of nitrenoid to *ortho* C-H bond **4.93** or from a stepwise pathway, which we first believed was an electrophilic aromatic substitution via arenium ion **4.94**.

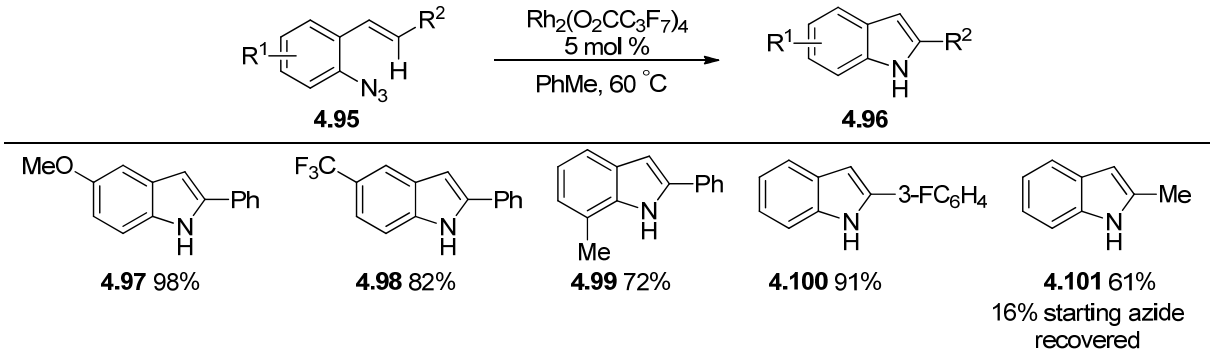
Scheme 4.13. Plausible catalytic cycle for indole formation catalyzed by Rh(II) carboxylate.



Indole Formation with Aryl Azide as Nitrogen Source

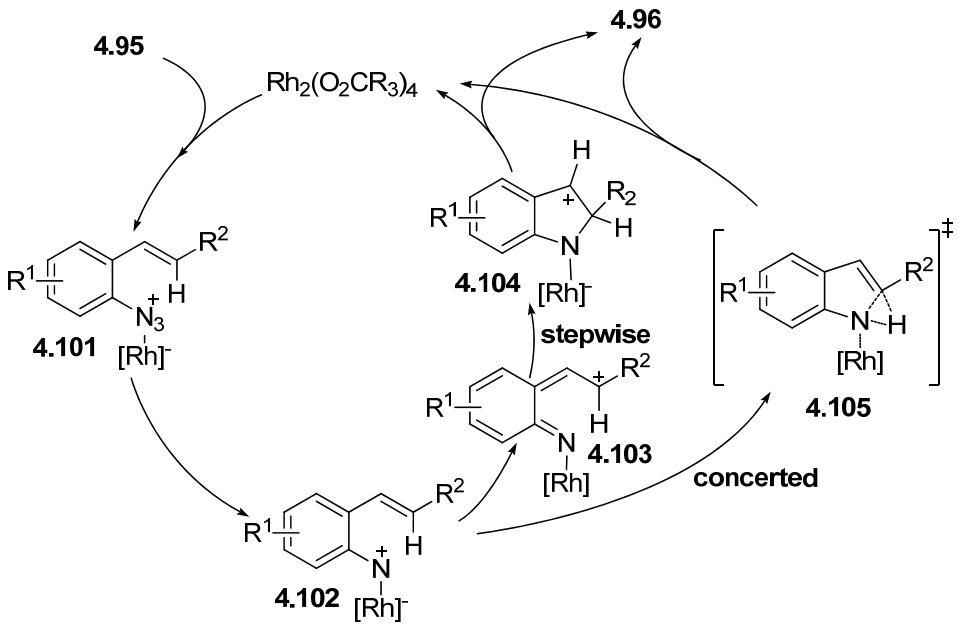
In addition to forming indoles from vinyl azides, our group has shown that rhodium(II) carboxylate complexes catalyze the conversion of styryl azides into 2-substituted indoles (Scheme 4.14). Our group demonstrated that using rhodium octanoate or perfluorobutyrate, a wide range of indoles could be formed from azides **4.95** at 60 ºC. A screen of different substrates showed that both electron-donating- and electron-withdrawing groups could be tolerated (cf. **4.97** and **4.98**). In addition, even alkyl R^2-substituents were tolerated on the styryl azide without any intervening benzylic C–H bond amination.

Scheme 4.14. Rh(II) carboxylate catalyze indole formation from aryl azide.



While indole formation could occur through several different mechanisms, our reactivity trends suggest that C–N bond formation through rhodium-mediated N-atom transfer (Scheme 4.15). The catalytic cycle begins by coordination of rhodium(II) carboxylate to α- or γ- nitrogen to produce **4.101**. Extrusion of nitrogen gas then forms the rhodium nitrene **4.102**. Three different pathways could potentially operate to functionalize the proximal aromatic C–H bond. First, C–N bond formation could occur through a stepwise mechanism: 4-π-electron-5-atom electrocyclization from **4.103** affords **4.104** followed by a 1,5 hydride shift produces the indole product. Alternatively, concerted insertion of nitrene into C-H bond via **4.105** could occur to produce indole.

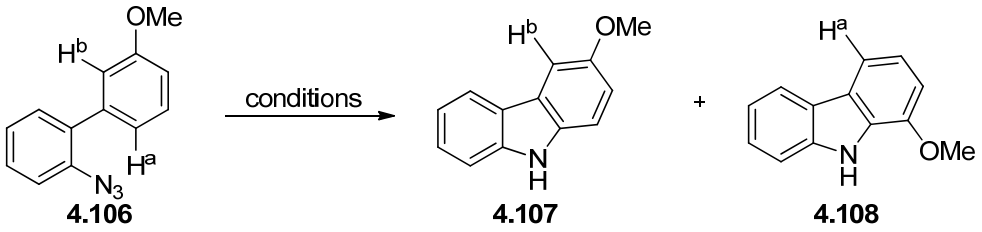
Scheme 4.15. Plausible mechanism for indole formation from aryl azide.



Rh(II) Caboxylate Catalyzed Cabazoles Formation from Aryl Azide.

Our group has extended this methodology to the synthesis of carbazoles from biaryl azides. We found that with rhodium(II) carboxylate catalyst, biaryl azides could be transformed to carbazoles at 60 ºC. Further study revealed that regioselectivity exhibits when employing rhodium(II) carboxylate as catalyst (Scheme 4.16). Themolysis or photolysis of biaryl azide **4.106** only provides 50:50 mixture of **4.107**:**4.108** [29]. In contrast, rhodium(II) carboxylate afforded **4.107** as the major product, which was attributed to involvement of the sterically bulky rhodium nitrenoid in the C–N bond formation step.

Scheme 4.16. Regioselectivity of carbazole formation.



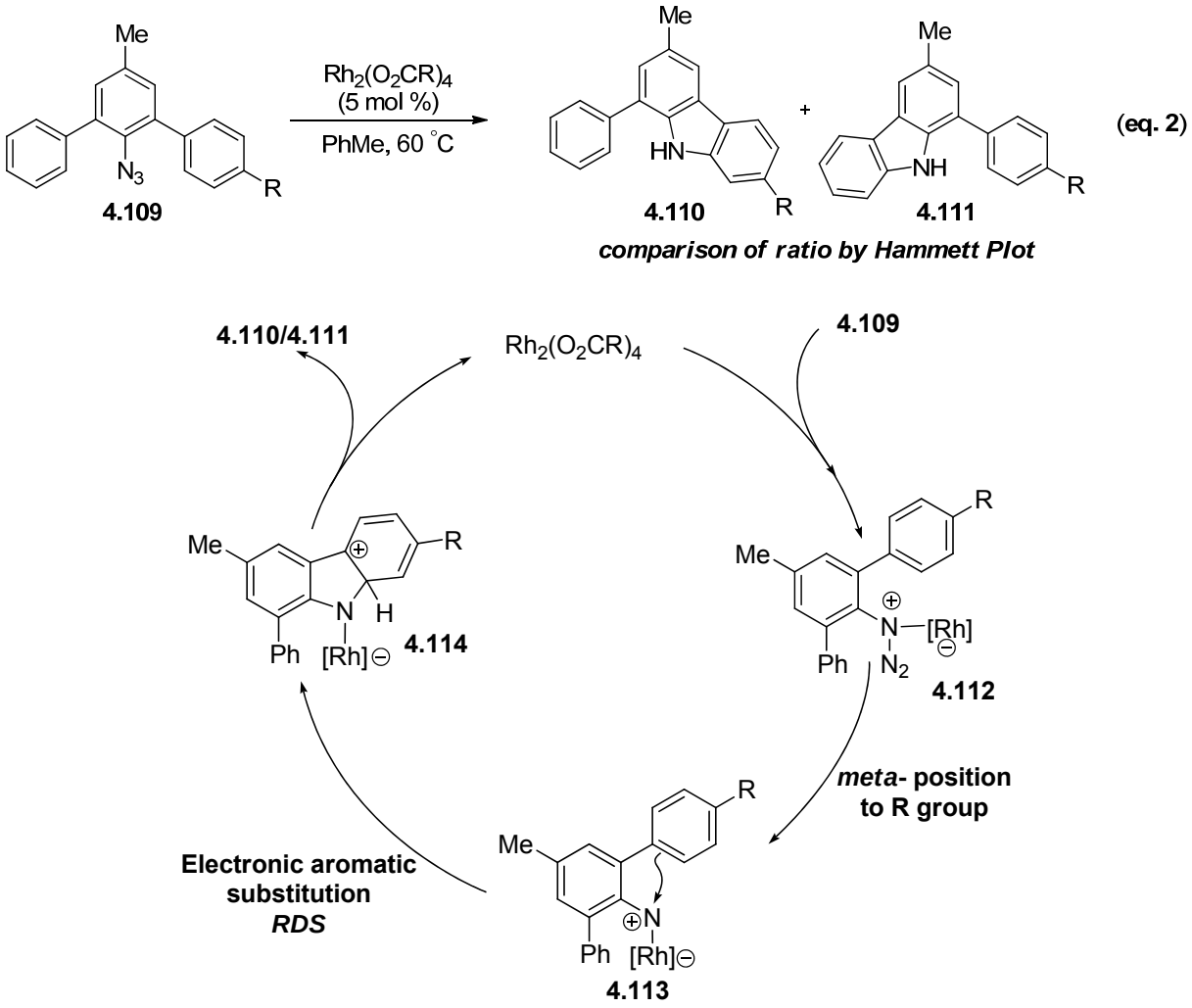
4.106 **4.107** **4.108**

conditions	yield %	**4.107** : **4.108**
150 °C or hν	40 - 70	50 : 50
$[Rh_2(O_2CC_7H_{15})_4]$ (5 mol %, 60 °C)	71	94 : 6

Mechanism Study on Carbazole Formation.

To provide insight into the mechanism of our sp^2 C–H bond amination reactions, a series of intramolecular competition experiments were performed using triaryl azides (**eq 2**). The product ratio was analyzed using the Hammett equation and a v-shaped curve was obtained when σ^+-values were used. The initial mechanism assumption (Scheme 4.17) involves nitrenoid formation (**4.113**) followed by C–N bond formation via electrophilic aromatic substitution. Since the reaction site located on the meta-position to the R-group, a linear correlation to σ_{meta}-constants would be expected if this proposed mechanism was operating. In contrast to the expectation, based on the data obtained, no linear correlation with σ_{meta}-constants was observed. Consequently, the explanation of catalytic cycle through electrophilic aromatic substitution was abandoned.

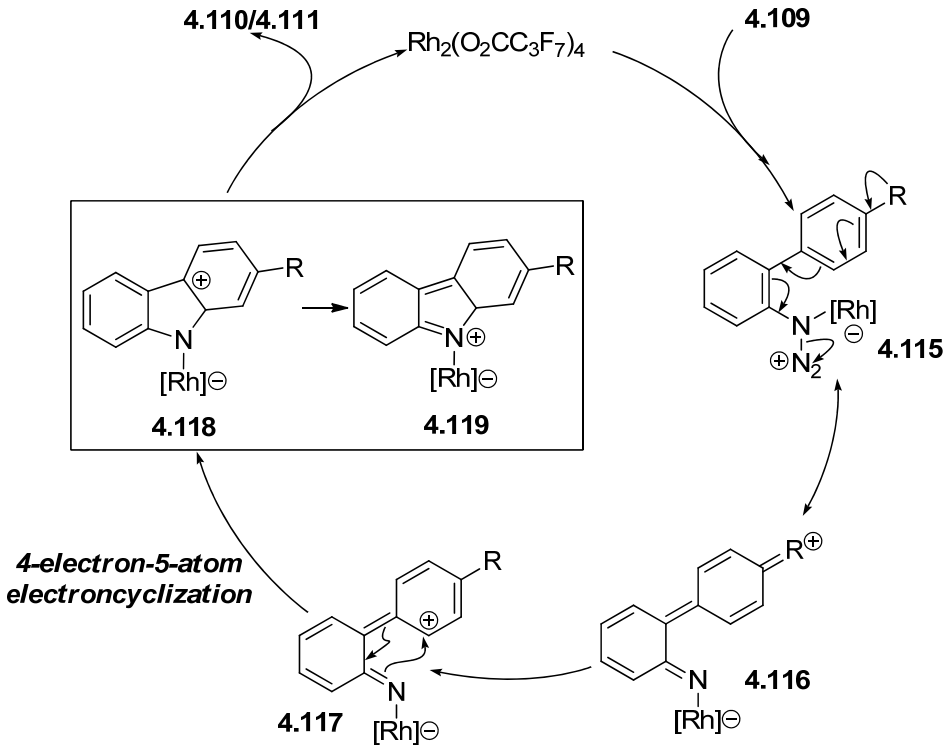
Scheme 4.17. Initial explanation for the carbazole formation.



The best linear correlation with the Hammett equation occurred when the data was plotted using σ^{+}-constants. The v-shaped nature of the plot was rationalized to mean that change in rate-determining step or mechanism leads to changes the sign of the slope. We concluded from the data that rhodium nitrenoid formation would be facilitated if electron-rich R-group attached to the arene and as a consequence that significant charge delocalization of the nitrene into the π-system was occurring. To account for the observed results, the mechanism pictured in Scheme 4.18 was suggested. With the assistance of R group, intermediate quinoid **4.116** could be formed.

C–N bond formation could then occur through a 4-electron-5-atom electrocyclization via **4.117**. A 1,5-hydride shift from **4.119** then affords the **4.110/4.111**. Implicit in this mechanism is that C–H bond is not required for the C–N bond formation.

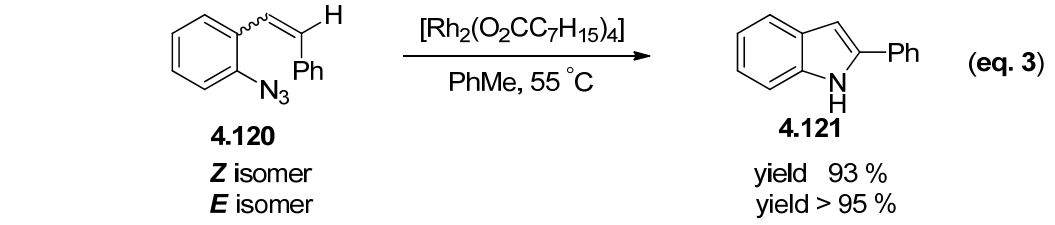
Scheme 4.18. Proposed mechanism based on Hammett studies.



4.7 Introduction on Rhodium Carboxyalte Catalyzed Disubstituted Indole Formation

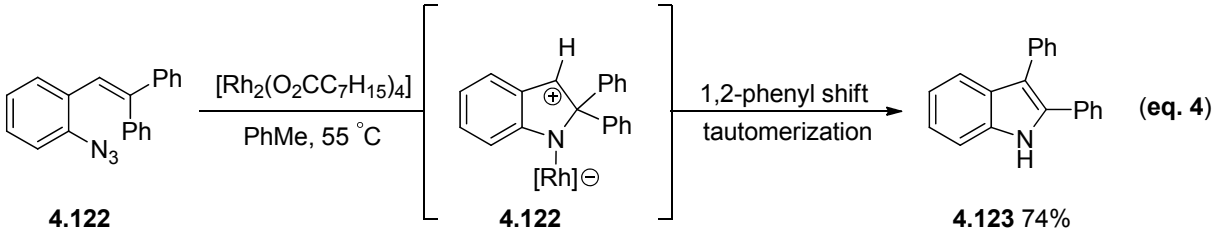
Support of this stepwise C–H bond amination reaction came from reactivity studies of both the *E*- and *Z*-styryl azides (eq. 3).[24c] Submission of either isomer **4.120** to reaction conditions produced 2-phenyindole **4.121** in comparable conversion and yield. In the process of reaction, no *E*/*Z* azide isomerization was observed. This result rules out the possibility of concerted insertion of nitrene to C-H bond and demonstrates that C–N bond formation precedes C-H bond cleavage. To support this assumption, gem-biphenyl-substituted styrene azide **4.122** was tested with rhodium octanoate (eq. 4). Formation of 2,3-diphenyl indole **4.123** strongly

suggested that carbon cation **4.122** is generated during the course of reaction and C–N bond was established prior to N-H bond formation.



4.120
Z isomer
E isomer

4.121
yield 93 %
yield > 95 %



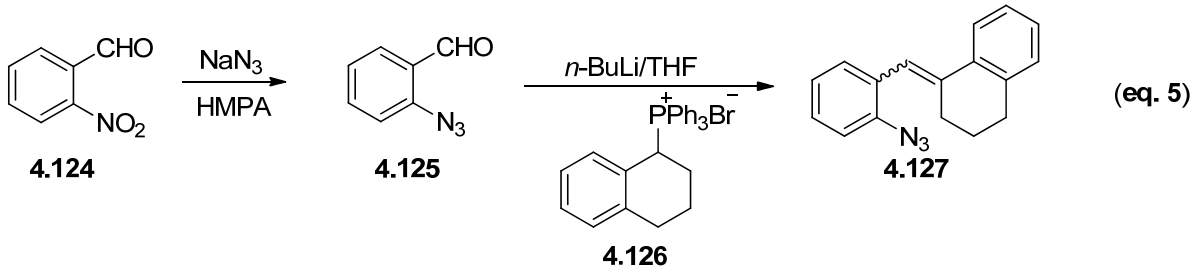
4.122 **4.122** **4.123** 74%

Mechanistic study (Scheme 4.18) of rhodium(II)-catalyzed carbazole formation from biaryl azides suggested that C–N bond formation preceded C–H bond cleavage through a 4-electron–5-atom electrocyclization. Consequently, we anticipated that substrates lacking functionalizable C–H bonds might participate in a migratorial process where a new C–C bond is formed in addition to the C–N bond. In support of this hypothesis, migratorial conversion of β,β-diphenyl stryryl azide **4.122** to 2,3-diphenylindole **4.123**[24c] demonstrated that metal nitrene enable reaction with olefins not only with C–H bond (eq. 4).This result, however, does not indicate whether this process can be rendered selectively for styryl azides that contain two different β-substituents to form 2,3-disubstituted indoles.

4.8 Synthesis of β, β-Disubstituted Styryl Azide

To address this migratorial aptitude issues, my project was to design styryl azides to determine the proper metal complexes to achieve selectivity in the migration process. The requisite styryl azide **4.127** could be readily furnished in two steps (Scheme 4.14) from the commercially available 2-nitrobenzaldehyde **4.124**.[30] The synthesis began with azidation of

4.124 to produce 2-azidobenzaldehyde **2.125**. Subsequent Wittig reaction of the resulting aryl azide **4.125** with triphenyl phosphonium ylide afforded the corresponding styryl azide **4.127**.

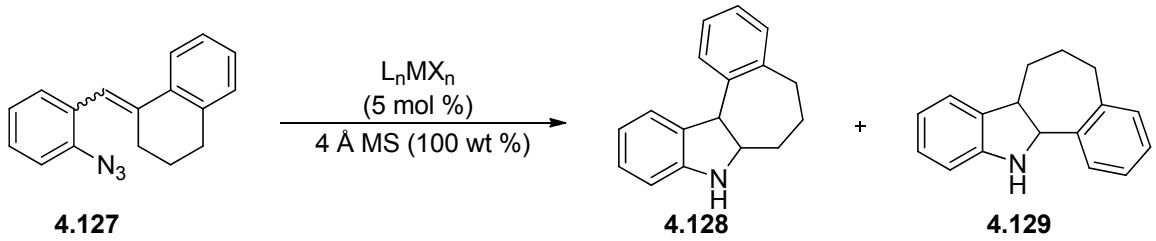


4.124 **4.125** **4.126** **4.127** **(eq. 5)**

4.9 Optimization

Optimization was performed to find an operating condition (Table 4.1). A variety of dirhodium(II) complexes were examined to catalyze the selective formation of disubstituted indole from azide **4.127**. To our delight, predominated formation of indole **4.128** was obtained with exposure of **4.127** to $Rh_2(O_2CC_3F_7)_4$ (entries 4-6),[31] $Rh_2(O_2CC_7H_{15})_4$ (entry 2), or $Rh_2(esp)_2$ (entry 3).[32] Other transition metal complexes known to decompose azides or π-Lewis acids,[33] including $(COD)Ir(OMe)]_2$ (entry 7),[34] Co(tpp) (entry 8),[21] $RuCl_3$ (entry 9),[23] or a copper salt (entry 10),[35] did not promote indole formation. Importantly, both the *E*- and *Z*-isomer of **4.127** were converted to indole **4.128** revealing that the selectivity of the reaction did not depend on the stereochemistry of the starting styryl azide. Consequently, the reaction conditions were further optimized using rhodium hexaflourobutyrate. Incomplete conversions were observed when either the catalyst loading or the reaction temperature was lowered (<5 mol % or <70 ºC). The optimal solvent was found to be either toluene or dichloroethane. Analytically pure indole was readily purified by filtering the reaction mixture through a pipette of alumina.

Table 4.1. Determination of optimal conditions



4.127 **4.128** **4.129**

entry	metal salt[a]	T (°C)	Yield, %[b]	(**4.128** : **4.129**)[c]
1	$Rh_2(O_2CCH_3)_4$	70	8	-
2	$Rh_2(O_2CC_7H_{15})_4$	70	93	96:4
3	$Rh_2(esp)_2$	70	98	98:2
4	$Rh_2(O_2CCF_3)_4$	70	86	99:1
5	$Rh_2(O_2CC_3F_7)_4$	70	95	100:0
6[d]	$Rh_2(O_2CC_3F_7)_4$	70	80[e]	100:0
7	$[(COD)Ir(OMe)]_2$	70	0	-
8	Co(tpp)	80	0	-
9[f]	$RuCl_3 \cdot nH_2O$	65	trace	-
10	$Cu(OTf)_2$	70	0	-
11	AgOTf	65	0	-
12	AuCl	65	0	-

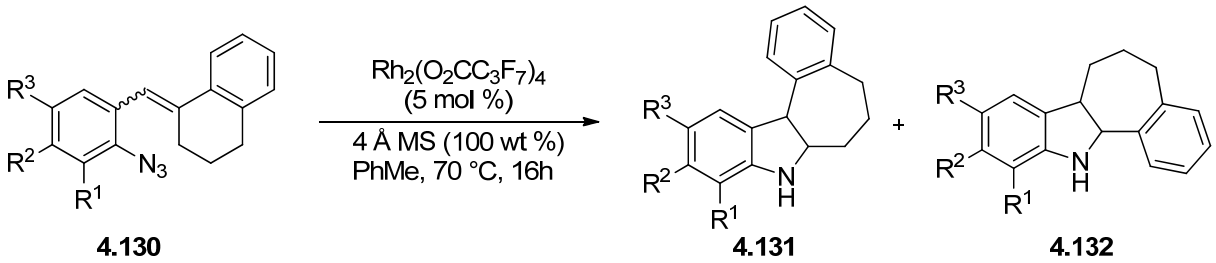
[a] esp = α, α, α′, α′-tetramethyl-1,3-benzenedipropionate; cod = cyclooctadiene; tpp = tetraphenylporphyrin. [b] Yield after Al_2O_3 chromatography. [c] As determined by using ^1H NMR sepectroscopy. [d] 3 mol % catalyst. [e] 10% aryl azide remained. [f] No molecular sieves added.

4.10 Examiantion of Scope and Limitation

Using our optimized conditions, the scope and limitations of the rhodium(II)-catalyzed formation of 2,3-disubstituted indoles from β,β-disubstituted stryryl azides was examined (Table 4.2). In every example, only aryl group selectively migrated even if the functional group with different electronic nature attached to the aryl azide moiety. Substrate with electron-donating substituents such as methoxide promoted migratorial reaction efficiently (entries 1 and 2).

Similar reaction yields and selective aryl migration was observed with electron-withdrawing groups (entries 3 – 8). In addition, azides bearing potentially reactive bromides, esters, or sulfones were competent substrates in our process. The reaction was not also sensitive to the steric nature around the azide: nearly quantitative yield was observed in entry 1, which contained *ortho*-substituents. Purification of every 2,3-disubstituted indole was also completed by simple filtration through alumina, emphasizing the synthetic utility of our reaction.

Table 4.2. Scope of Rh(II)-catalyzed tandem reaction.



4.130 **4.131** **4.132**

entry	R^1	R^2	R^3	Yield [%][a]	(**4.131** : **4.132**)[b]
1	MeO	H	H	96	>95:5
2	H	MeO	H	97	>95:5
3	H	Cl	H	99	>95:5
4[c]	H	MeO_2C	H	94	>95:5
5	H	F_3C	H	90	>95:5
6[d]	H	MeO_2S	H	95	>95:5
7	H	H	H	95	>95:5
8[d]	H	H	MeO_2C	95	>95:5

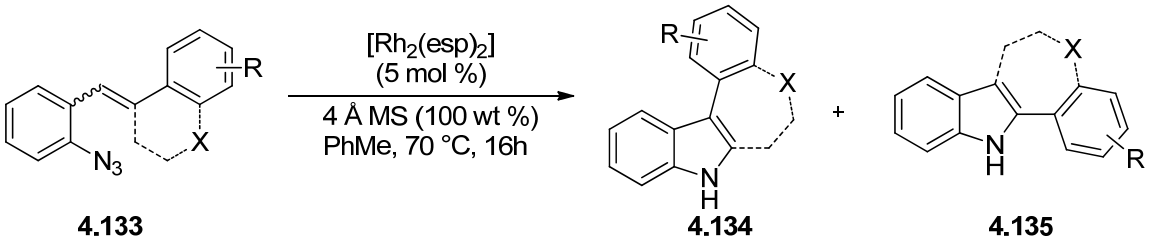
[a] Yield after Al_2O_3 chromatography. [b] As determined by using ^1H NMR spectroscopy. [c] X-ray structure of product indole obtained. [d] 5 mol % of $[Rh_2(esp)_2]$ used

4.11 Investigation of Nature of Migration Group on the Aryl Azide

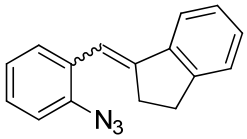
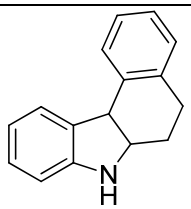
The nature of the migrating group on the aryl azide was investigated as well. Similar to the substrates above, only aryl group migration was observed for the styryl azides listed in Table 4.3. While rhodium perfluorobutyrate was a competent catalyst, $Rh_2(esp)_2$ provided the highest

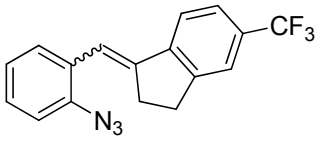
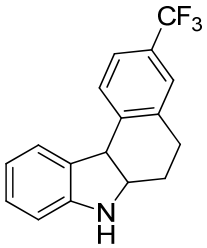
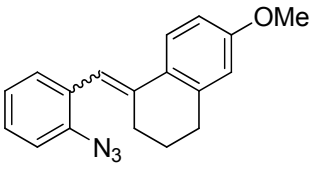
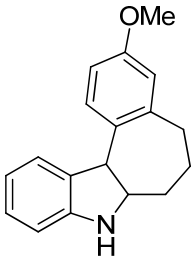
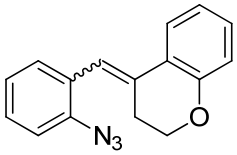
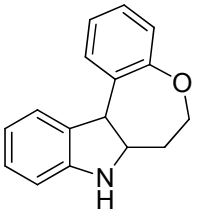
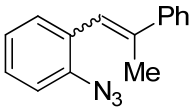
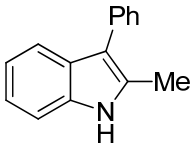
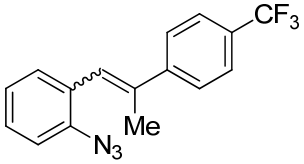
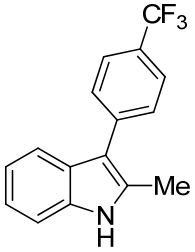
yields of the reaction of these substrates. Even if tether was shortened, only 3-aryl-indole **4.137** was observed. Attachment of either electron-withdrawing trifluoromethyl group (**4.138**) or an electron-donating methoxy group (**4.140**) to the migrating arene also did not affect reaction yield or the migration selectivity. Tether containing an oxygen atom **4.142** was also tolerated under the optimized conditions. The reaction was not limited to ring expansion: despite appending of strong electron-withdrawing group to the migrating aryl group, only indoles **4.145** and **4.147** were formed from azides **4.144** and **4.146**. For every styryl azide investigated, only aryl group migration was observed.

Table 4.3. Impact of the varying the β-aryl substituent on the tandem reaction.



4.133 **4.134** **4.135**

Entry	Substrate	Indole product	Yield [%][a]
1	 **4.136**	 **4.137**	88

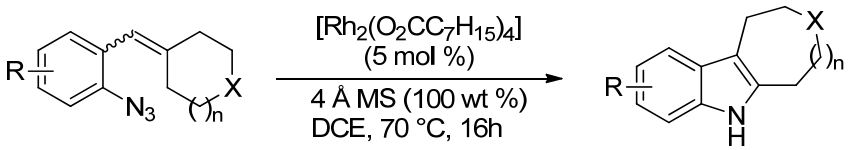
2	 **4.138**	 **4.139**	78
3	 **4.140**	 **4.141**	92
4	 **4.142**	 **4.143**	94
5	 **4.144**	 **4.145**	91
6	 **4.146**	 **4.147**	93

[a] Yield after filtration through a pad of neutral alumina.

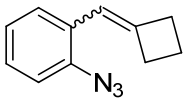
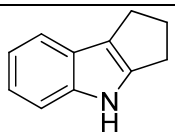
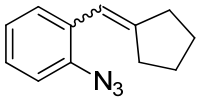
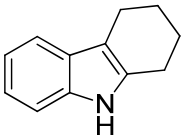
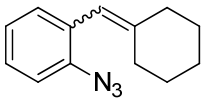
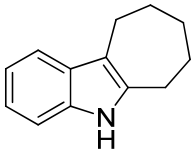
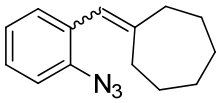
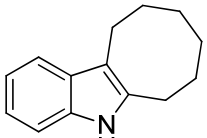
The nature of ring size on the reaction activities was subsequently examined using styryl azides **4.148** (Table 4.4). For this series of substrates, rhodium octanoate exhibit the most

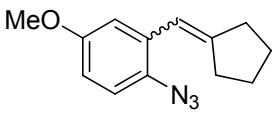
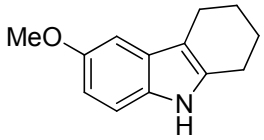
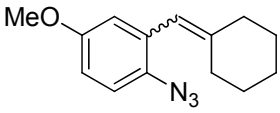
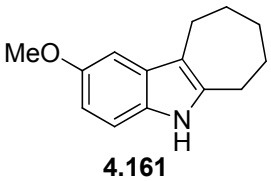
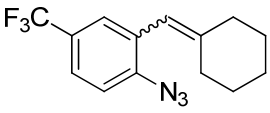
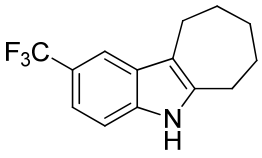
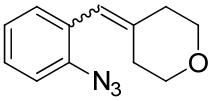
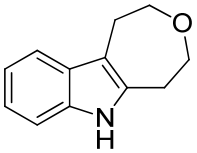
powerful catalytic ability. While ring expanded products were formed from 4- (**4.151**), 5- (**4.153**), and 6- (**4.155**) membered substrates, poor conversion was observed for 7-membered azide **4.156** (entries 1 – 4). As we previously observed, changing the electronic nature of the aryl azide did not affect the yield of the reaction (entries 5 – 7). Oxygen atoms **4.164** were tolerated (cf. **4.142**) in the tether without lowering the yield of the ring expansion (entry 8).

Table 4.4. Effect of varying the length of the tether between the β-substituents.



4.148 **4.149**

Entry	Substrate	Indole product	Yield [%][a]
1	 **4.150**	 **4.151**	98
2	 **4.152**	 **4.153**	93
3	 **4.154**	 **4.155**	93
4	 **4.156**	 **4.157**	18[b,c]

5	 **4.158**	 **4.159**	quant.
6	 **4.160**	 **4.161**	quant.
7	 **4.162**	 **4.163**	88
8	 **4.164**	 **4.165**	97

[a] Yield after Al_2O_3 chromatography. [b] As determined by using ^1H NMR spectroscopy. [c] 35% remaining azide, DCE = dichloroethane.

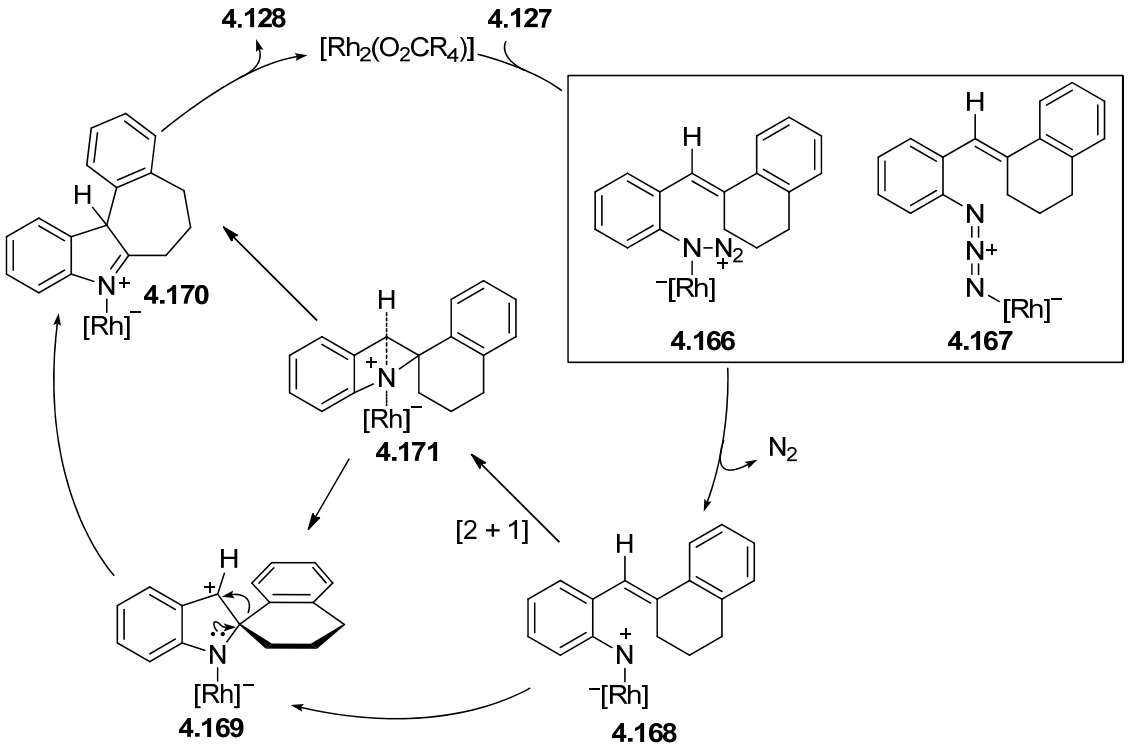
4.12 Mechanism Study

4.12.1 Possible Indole Formation Pathway.

Although many operating mechanisms might explain the reaction route, our study indicates that an electrocyclization-1,2-migration tandem reaction is occurring (Scheme 4.19). Initially, coordination of the Rh(II) carboxylate complexe to the aryl azides produces either **4.166** or **4.167**[36]. Extrusion of N_2 afforded rhodium nitrene **4.178**[37] which engages in a 4-electron-5-atom electrocyclization to establish the carbon-nitrogen bond in **4.169**. Generation of this benzylic carbon cation **4.169** triggers the 1,2 migration to form the more stable tertiary

iminium ion **4.170**, which tautermizes to produce disubstituted indole **4.128**. Alternatively, the *ortho*-alkenyl group could assist in N_2 extrusion to form the intermediate **4.171**, or this intermediate could be formed from a [2+1] cycloaddition of the pendant double bond with the electrophilic metallonitrene **4.168**. While **4.171** is strained,[38] its intermediacy may explain the increased activity of aryl azide with unsaturated *ortho*-substituents.

Scheme 4.19. Potential mechanisms for 1,2-disubstituted indole formation.

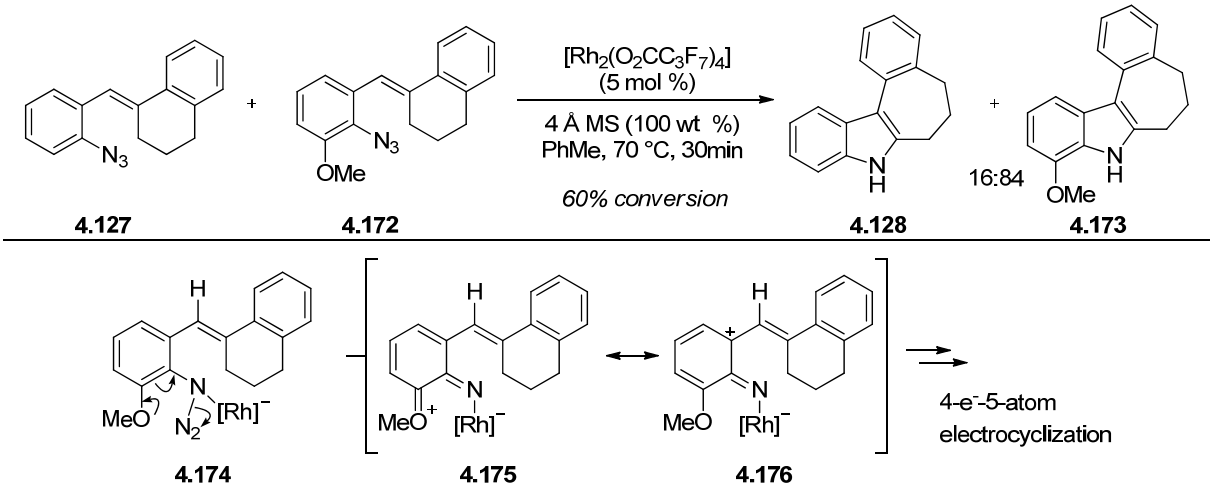


4.12.2 Examination of Mechanism with Intermolecular Competition Reactions

To test the validity of proposed mechanism, several experiments were conducted. Intermolecular competition reactions (Scheme 4.20) were performed to examine whether the loss of N_2 preceded formation of carbon-nitrogen bond. Previous research[31] of our group suggested that N_2 extrusion occurred faster with electron-rich aryl azide based on Hammett correlation study. Since electron-donating group could facilitate the N_2 loss, accelerating the formation of

metallonitrene. In contrast, if extrusion of N_2 occurred simultaneously with carbon-nitrogen bond formation, we expected that the more electron-deficient aryl azide **4.172** would react faster. To test these assumptions, a 1:1 mixture of styryl azides **4.127** and **4.172** were exposed to the reaction conditions. Despite the increased steric environment around the azide **4.172**, the more electron-rich substrate reacted faster to produce indole **4.173** as the major product to support our proposed electrocyclization mechanism.

Scheme 4.20. Intermolecular competition experiments to examine the mechanism of our reaction.

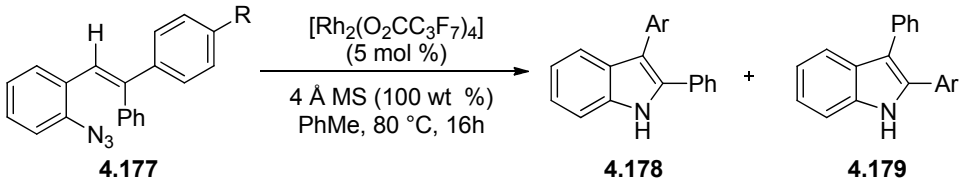


4.12.3 Hammett Equation Study to Support Existence of Phenonium Ion Intermediate

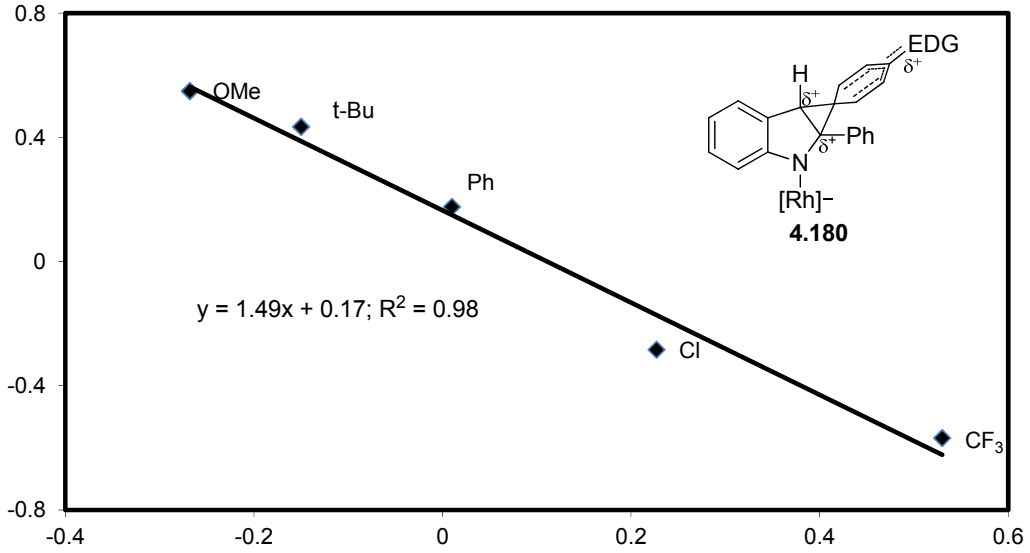
To gain insight into the mechanistic details of the aryl migration step of the catalytic cycle, a series of intramolecular competition experiments were performed using β,β-diaryl-substituted styryl azides **4.177** (Scheme 4.21). If the migration involved the formation of phenonium ion **4.180**, we anticipated that electron-rich aryl groups would migrate faster. To prove the formation of partial positive charge during the reaction, a series of styryl azides **4.177**, which varied the identity of the *para*-substituent, were exposed to reaction conditions.

Comparison of the results with the Hammett equation revealed that the best linear correlation was obtained with σ_{para}-values to give a ρ value of –1.49. The sign and magnitude of this value indicates the build up of positive charge in the migrating aryl group and supports the phenonium reactive intermediate. [39,40]

Scheme 4.21. Intramolecular competition experiments and correlation to the Hammett equation.



4.177 **4.178** **4.179**



4.180

4.13 Conclusion

In conclusion, we have demonstrated that rhodium carboxylate complexes catalyze cascade reactions of β, β-disubstituted styryl azides to selectively produce 2,3-disubstituted indoles. Our mechanism study suggests that the selectivity of the migratorial process is controlled by the formation of a phenonium ion. Future experiments will be conducted to further illustrate the mechanism of this reaction as well as determining if the benzylic cation can be

intercepted with additional nucleophiles to produce complex, functionalized N-heterocycles from simple, readily available styryl azides.

4.14 Experimental

General. ^{1}H NMR and ^{13}C NMR spectra were recorded at ambient temperature using Bruker DRX 500 or Varian DRX 300 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 GCMate II or Thermo Finnigan LTQ FT spectrometer, and were obtained by peak matching. Melting points are reported uncorrected. Analytical thin layer chromatography was performed on Sorbent Technologies 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 Sorbent Technologies 60Å (40 – 60 μm) mesh silica gel (SiO_2). Medium pressure liquid chromatography (MPLC) was performed using Thomson SINGLE StEP pumps to force flow the indicated solvent system down columns that had been packed with Sorbent Technologies 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[41]. Metal salts were stored in an MBraun labmaster nitrogen atmosphere dry box.

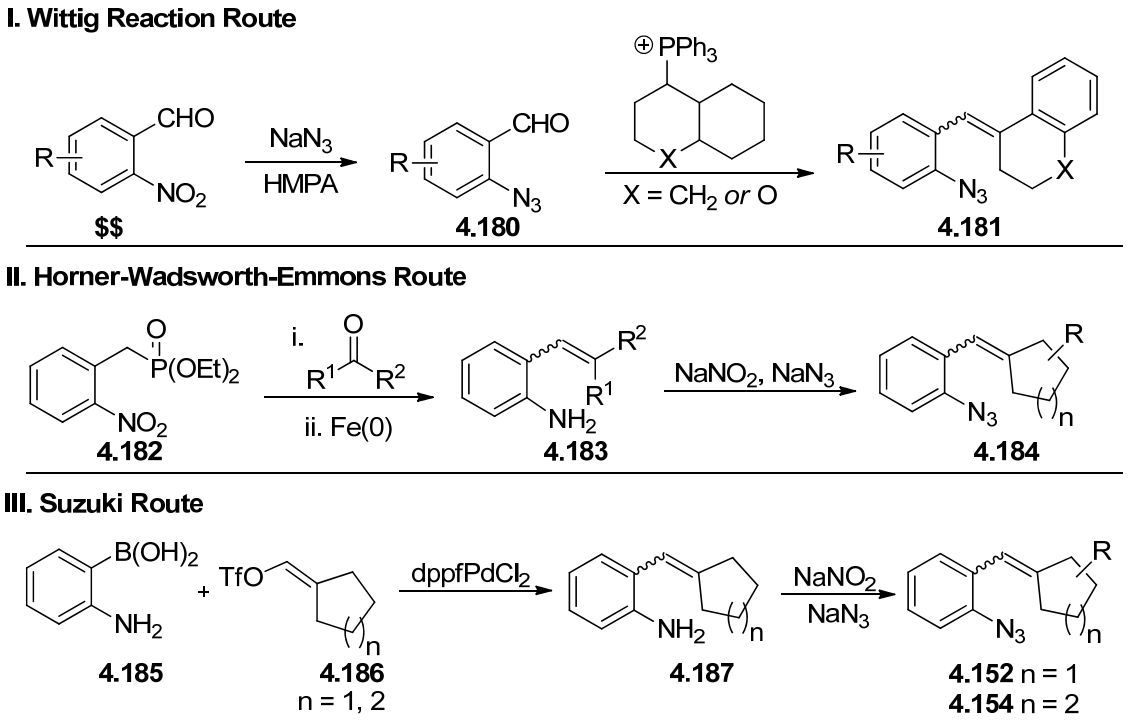
4.14.1 Preparation of Substrates Using Wittig Reaction

Routes to Substrates

The stryryl azides investigated in this study were synthesized by one three different routes (Scheme 4.22). The majority of the substrates were formed in two steps from

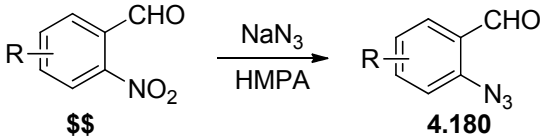
commercially available *ortho*-nitro-substituted benzaldehydes starting by a nucleophilic aromatic substitution using NaN_3 followed by a Wittig reaction. Alternatively the styryl azides were constructed from phosphonate **4.182** using a Horner–Wadworth–Emmons reaction of phosphonate **4.182**, followed by an iron-mediated reduction to form aniline **4.183**. Azidation then provided the required styryl azide. Finally styryl azides, **4.152** and **4.154**, were accessed from boronic acid **4.185** and the corresponding vinyl triflate **4.186**.

Scheme 4.22. Routes to styryl azides.



General Procedure for the Nucleophilic Substitution of 2-Nitrobenzaldehydes

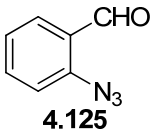
Following the procedure of Driver and co-workers,[42] the 2-azidobenzaldehydes were prepared. Yields were not optimized.



(eq. 6)

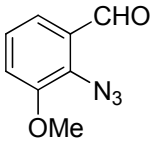
To a dry, stir bar-equipped scintillation vial were added 0.453 g of 2-nitro-benzaldehyde (3.0 mmol), 0.585 g of NaN_3 (9.0 mmol), and 9.0 mL of HMPA. The reaction was stirred overnight at room temperature, then was taken up in diethyl ether (100 mL) and washed with water (5 × 50 mL). The organic layer was dried over Na_2SO_4 and filtered. The filtrate was concentrated *in vacuo*. Purification with MPLC afford the 2-azido-benzaldehyde.

Synthesis of 2-Azidobenzaldehydes



4.125

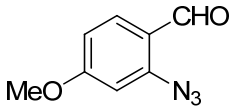
Benzaldehyde 4.125.[42] The general procedure was followed using 2.10 g of 2-nitrobenzaldehyde (13.9 mmol) and 2.92 g of NaN_3 (45.0 mmol, 3.3 eq) in 40 mL of HMPA. Purification by MPLC (1:100 EtOAc: hexanes) afforded the product as a light yellow solid (1.70 g, 83%); mp 33 - 36 °C; The spectral data matched that reported by Driver and co-workers: ^{1}H NMR (500 MHz, $CDCl_3$) 10.25 (s, 1H), 7.79 (dd, J = 1.5 Hz, 7.5 Hz, 1H), 7.54 (dt, J = 1.5 Hz, 8.0 Hz, 1H) 7.14 – 7.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.4 (CH), 142.8 (C), 135.4 (CH), 128.9 (CH), 126.9 (C), 124.8 (C), 119.1 (CH); IR (thin film): 2971, 2121, 1690, 1594, 1477, 1290, 1274 cm^{-1}.



4.188

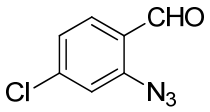
Benzaldehyde 4.188. The general procedure was followed using 1.81 g of 2-nitro-3-methoxybenzaldehyde (10 mmol) and 1.31 g of NaN_3 (20 mmol) in 50 mL of HMPA at 50 °C. Purification of the reaction mixture using MPLC (1:30 EtOAc:hexanes) afforded the product as a white solid (1.61 g, 91%); mp 54 – 56 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ 10.15 (s, 1H), 7.82 (d,

J = 8.5 Hz, 1H), 6.72 (dd, *J* = 2.5 Hz, 8.5 Hz, 1H), 6.67 (d, *J* = 2.5 Hz, 1H), 3.88 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.2 (CH), 165.3 (C), 144.9 (C), 131.1 (CH), 121.0 (C), 111.1 (CH), 103.9 (CH), 55.8 (CH_3); IR (thin film): 2359, 2341, 2110, 1723, 1264, 730, 703 cm^{-1}. HRMS (EI) *m / z* calcd for $C_8H_7O_2N_3$ $(M)^+$ 177.05383, found 177.05529.



4.189

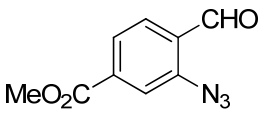
Benzaldehyde 4.189. The general procedure was followed using 1.81 g of 2-nitro-4-methoxybenzaldehyde (10 mmol) and 1.31 g of NaN_3 (20 mmol) in 50 mL of HMPA at 50 °C. Purification of the reaction mixture using MPLC (1:30 EtOAc: hexanes) afforded the product as a white solid (1.62 g, 92%); mp 73 – 75 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ 10.17 (s, 1H), 7.84 (d, *J* = 9.0 Hz, 1H), 6.74 (dd, *J* = 2.5 Hz, 9.0 Hz, 1H), 6.68 (d, *J* = 2.5 Hz, 1H), 3.90 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.2 (CH), 165.3 (C), 144.9 (C), 131.1 (CH), 121.1 (C), 111.1 (CH), 104.0 (CH), 55.8 (CH_3); IR (thin film): 3457, 3015, 2970, 2116, 1744, 1367, 1229, 750, 528 cm^{-1}. HRMS (EI) *m / z* calcd for $C_8H_7O_2N_3$ $(M)^+$ 177.05383, found 177.05520.



4.190

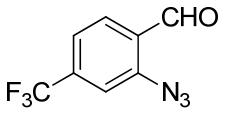
Benzaldehyde 4.190. The general procedure was followed using 1.85 g of 2-nitro-4-chlorobenzaldehyde (10 mmol) and 0.98 g of NaN_3 (15 mmol) in 50 mL of HMPA. Purification of the reaction mixture using MPLC (1:100 EtOAc:hexanes) afforded the product as a white solid (1.45 g, 80%); mp 91 – 93 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ 10.28 (s, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.26 (d, *J* = 2.0 Hz, 1H), 7.21 (dd, *J* = 1.5 Hz, 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.4 (CH), 144.0 (C), 141.7 (C), 130.2 (CH), 125.6 (CH), 125.4 (C), 119.2 (CH); IR

(thin film): 3455, 3016, 2969, 2123, 1739, 1366, 1216, 750, 528 cm^{-1}. HRMS (EI) *m / z* calcd for $C_7H_4ON_3Cl$ $(M)^+$ 183.00134, found 183.00217.



4.191

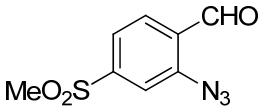
Benzaldehyde 4.191. The general procedure was followed using 2.09 g of methyl 4-formyl-3-nitrobenzoate (10 mmol) and 1.31 g of NaN_3 (20 mmol) in 50 mL of HMPA. Purification of the reaction mixture using MPLC (1:30 EtOAc: hexanes) afforded the product as a white solid (1.95 g, 95 %); mp 112 – 114 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ 10.38 (s, 1H), 7.94 – 7.92 (m, 2H), 7.85 – 7.83 (m, 1H), 3.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 188.1 (CH), 165.3 (C), 143.1 (C), 136.2 (C), 129.4 (C), 129.1 (CH), 125.6 (CH), 120.3 (C), 52.8 (CH_3); IR (thin film): 3458, 3015, 2970, 2122, 1738, 1366, 1216, 762, 527 cm^{-1}. HRMS (EI) *m / z* calcd for $C_9H_7O_3N_3$ $(M)^+$ 205.04875, found 205.04990.



4.192

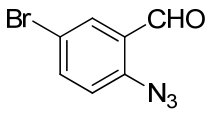
Benzaldehyde 4.192. [43] The general procedure was followed using 2.69 g of 2-nitro-4-trifluoromethylbenzaldehyde (12.3 mmol) and 2.21 g of NaN_3 (34.0 mmol) in 50 mL of HMPA. Purification by MPLC (1:100 EtOAc: hexanes) afforded the product as a yellow solid (2.49 g, 94%): mp 89 -91 °C; The spectral data matched that reported by Driver and co-workers:[42] ^{1}H NMR (500 MHz, $CDCl_3$) 10.38 (s, 1H), 8.00 (d, J = 8.0 Hz, 1H), 7.50 (s, 1H) 7.48 (d, J = 8.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 187.5 (CH), 143.5 (C), 136.8 (q, J_{CF} = 31.4 Hz, C), 129.8 (CH), 126.1 (C), 122.9 (q, J_{CF} = 270.9 Hz, C), 121.6 (q, J_{CF} = 3.5 Hz, CH) 116.3 (q, J_{CF} =

36.3 Hz, CH); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –61.10; IR (thin film): 2980, 2901, 2122, 1689, 1414, 1392, 1328, 1072. 750 cm^{-1}.



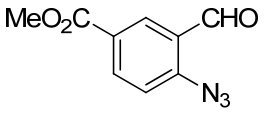
4.193

Benzaldehyde 4.193. The general procedure was followed using 2.29 g of 4-(methylsulfonyl)-2-nitrobenzaldehyde (10 mmol) and 1.31 g of NaN_3 (20 mmol) in 50 mL of HMPA. Purification of the reaction mixture using MPLC (1:10 EtOAc: hexanes) afforded the product as a white solid (1.96 g, 87%); mp 125 – 127 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ 10.40 (s, 1H), 8.05 (d, *J* = 8.0 Hz, 1H), 7.85 (s, 1H), 7.5 (d, *J* = 8.0 Hz, 1H), 3.12 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.3 (CH), 146.5 (C), 144.1 (C), 130.3 (CH), 129.8 (C), 132.3 (CH), 118.4 (CH), 44.2 (CH_3); IR (thin film): 3023, 2925, 2852, 2115, 1681, 1398, 1279, 1159, 1135 cm^{-1}.



4.194

Benzaldehyde 4.194. [44] The general procedure was followed using 2.03 g of 2-nitro-5-bromobenzaldehyde (10 mmol) and 1.3 g of NaN_3 (20 mmol) in 40 mL of DMSO at 50 °C. Purification of the reaction mixture using MPLC (1:100 EtOAc:hexanes) afforded the product as a white solid (2.19 g, 97%); mp 94 – 96 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ 10.27 (s, 1H), 7.98 (d, *J* = 2.5 Hz, 1H), 7.70 (dd, *J* = 2.5 Hz, 8.5 Hz, 1H), 7.16 (d, *J* = 8.5 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.1 (CH), 141.9 (C), 138.0 (CH), 131.7 (CH), 128.0 (C), 120.8 (CH), 118.3 (C); IR (thin film): 3457, 3005, 2970, 2130, 1725, 1368, 1214, 750, 527 cm^{-1}. HRMS (EI) *m / z* calcd for $C_7H_4ON_3Br$ $(M)^+$ 224.95377, found 224.95459.

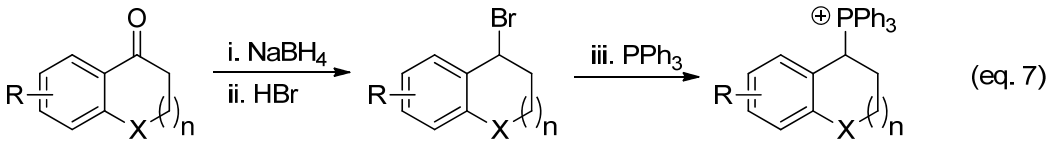


4.195

Benzaldehyde 4.195. The general procedure was followed using 2.09 g of methyl 3-formyl-4-nitrobenzoate (10 mmol) and 1.31 g of NaN_3 (20 mmol) in 50 mL of HMPA. Purification of the reaction mixture using MPLC (1:30 EtOAc:hexanes) afforded the product as a white solid (1.97 g, 96%); mp 118 –120 °C; ^{1}H NMR (500 MHz; $CDCl_3$) δ 10.31 (s, 1H), 8.49 (d, J = 2.0 Hz, 1H), 8.23 (dd, J = 2.0 Hz, 8.5 Hz, 1H), 7.31 (d, J = 8.5 Hz, 1H), 3.97 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 187.7 (CH), 165.4 (C), 146.8 (C), 136.0 (CH), 130.8 (CH), 127.0 (C), 127.6 (C), 119.2 (CH), 52.4 (CH_3); IR (thin film): 3458, 3015, 2970, 2122, 1738, 1366, 1216, 762, 527 cm^{-1}. HRMS (EI) m/z calcd for $C_9H_7O_3N_3$ $(M)^+$ 205.04875, found 205.04980.

General Procedure for the Phosphonium Salt Synthesis

Unless otherwise noted, the phosphonium salt was synthesized from the corresponding cycloketone. Yields were not optimized.



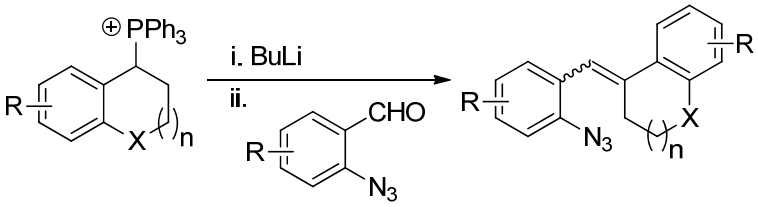
(eq. 7)

To a solution of 2.92 g of α-tetralone (20 mmol) in 30 mL of EtOH was added 1.52 g of $NaBH_4$ (40 mmol). The mixture was monitored by thin layer chromatography. Once the starting material spot had disappeared, the mixture was concentrated *in vacuo*, and the resulting material was diluted with 50 mL of water. The resulting aqueous mixture was extracted with dichloromethane (3 × 10 mL). The organic phase (containing the alcohol) was treated with proportional HBr. The progress of the reaction was monitored by thin layer chromatography.

Once the alcohol completely consumed, the mixture was diluted with 100 mL of water, then extracted with dichloromethane (3 × 20 mL). The resulting organic phase was dried over Na_2SO_4. The mixture was filtered and the filtrate was concentrated *in vacuo* to afford bromide. To a solution of the bromide in 60 mL of PhMe was added 5.76 g of PPh_3. The reaction mixture was heated to reflux. After 16h, the mixture was cooled down to room temperature, then filtrated. The solid was washed with diethyl ether (3 × 30 mL), and dried under high vacuum to afford phosphonium salt.

General Procedure for the Wittig Reaction of 2-Azidobenzaldehydes

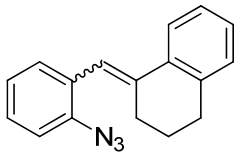
Following the procedure of Scott and co-workers,[45] the 2-azidobenzaldehydes were prepared. Yields were not optimized.



(eq. 8)

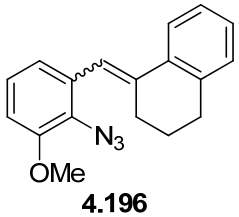
To a solution of 4.0 mmol of the phosphonium salt in 12 mL of THF at –78 °C, was added 1.6 mL of *n*-BuLi (2.5 M in hexanes, 4.0 mmol) dropwise. After stirring 1h at –78 °C, the mixture was warmed to room temperature and stirred additional one hour. Then 0.647 g of 2-azidobenzaldehyde (4.4 mmol) was added and the mixture was stirred for 1 h at ambient temperature. The resulting mixture was diluted with 15 mL of water and extracted with CH_2Cl_2 (3 × 10 mL). The resulting organic phase was washed with 20 mL of brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. Purification of the reaction mixture using MPLC afforded the product.

Synthesis of Styryl Azides



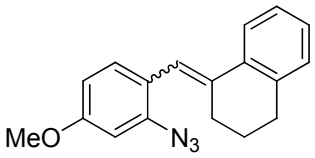
4.127

Styryl Azide 4.127. The general procedure was followed using 1.94 g of 2-azidobenzaldehyde **s9** (13.2 mmol), 6.85 g of the phosphonium salt (14.5 mmol), 5.8 mL of a 2.5 M solution of BuLi in hexanes in 50 mL of THF. Purification by MPLC (pure hexanes) afforded the product as a white powder, as an 84:16 mixture of *E*- and *Z*-isomers (2.24 g, 65%): R_f= 0.45 (18:82 EtOAc: hexane). Selected spectral data for the major (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.80 - 7.99 (m, 1H), 7.33 – 7.37 (m, 2H), 7.13 – 7.26 (m, 5H), 7.07 (s, 1H), 2.91 (t, *J* = 6.5 Hz, 2H), 2.71 (t, *J* = 6.0 Hz, 2H), 1.87 – 1.92 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 138.7 (C), 138.6 (C), 137.9 (C), 135.9 (C), 130.9 (CH), 130.1 (C), 129.2 (CH), 128.1 (CH), 127.6 (CH), 126.2 (CH), 124.7 (CH), 124.3 (CH), 118.7 (CH), 118.4 (CH); 30.4 (CH_2), 28.2 (CH_2), 23.8 (CH_2); Selected spectral data for the minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.13 – 7.26 (m, 5H), 7.07 – 7.08 (m, 1H), 6.95 – 6.98 (m, 1H), 6.85 – 6.88 (m, 1H), 6.47 (s, 1H), 2.95 (t, *J* = 6.5 Hz, 2H), 2.63 (t, *J* = 6.5 Hz, 2H), 2.05 – 2.10 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8 (C), 138.7 (C), 138.0 (C), 134.7 (C), 131.3 (CH), 130.1 (C), 128.9 (CH), 128.0 (CH), 127.6 (CH), 124.7 (CH), 124.5 (CH), 119.9 (CH), 118.5 (CH), 35.0 (CH_2), 29.7 (CH_2), 24.2 (CH_2); Selected spectral data for the mixture: δ IR (thin film): 2117, 2083, 1486, 1445, 756, 745 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{17}H_{15}N_3$ $(M - N_2)^+$ 261.12660, found 261.12679.



4.196

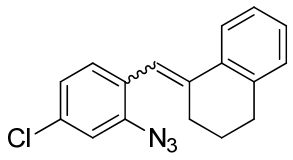
Styryl Azide 4.196. The general procedure was followed using 0.58 g of 2-azido-3-methoxybenzaldehyde **4.188** (3.3 mmol), 1.42 g of the phosphonium salt (3.0 mmol), 1.2 mL of a 2.5 M solution of BuLi in hexanes in 25 mL of THF. Purification by MPLC (1:50 EtOAc:hexanes) afforded the product as a white powder, as a 76:24 mixture of *E*- and *Z*-isomers (0.63 g, 72%). Selected spectral data for the major (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.76 – 7.74 (m, 1H), 7.23 – 7.21 (m, 2H), 7.14 – 7.04 (m, 3H), 6.93 – 6.90 (m, 1H), 6.84 – 6.82 (m, 1H), 3.93 (s, 3H), 2.88 (t, *J* = 6.5 Hz, 2H), 2.66 (dt, *J* = 1.5 Hz, 6.0 Hz, 2H), 1.86 (pent, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9 (C), 138.5 (C), 137.8 (C), 135.9 (C), 131.8 (C), 129.2 (CH), 127.6 (CH), 126.9 (C), 126.2 (CH), 124.6 (CH), 124.6 (CH), 122.8 (CH), 119.4 (CH), 110.2 (CH), 56.1 (CH_3), 30.3 (CH_2), 28.2 (CH_2), 23.7 (CH_2); Selected spectral data for the minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.25 (m, 1H), 7.14 – 7.04 (m, 3H), 6.88 – 6.85 (m, 1H), 6.75 – 6.71 (m, 2H), 6.41 (s, 1H), 3.91 (s, 3H), 2.92 (t, *J* = 6.5 Hz, 2H), 2.60 (dt, *J* = 1.5 Hz, 6.0 Hz, 2H), 2.04 (pent, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9 (C), 139.5 (C), 138.8 (C), 134.8 (C), 132.5 (C), 129.0 (CH), 128.8 (CH), 127.5 (CH), 125.7 (CH), 125.0 (C), 124.8 (CH), 123.1 (CH), 120.5 (CH), 109.9 (CH), 56.0 (CH_3), 34.9 (CH_2), 29.7 (CH_2), 24.2 (CH_2); Selected spectral data for the mixture: δ IR (thin film): 2933, 2103, 1756, 1450, 1262, 1087, 737 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{18}H_{17}ON$ $(M\text{-}N_2)^+$ 263.13102, found 163.132000.



4.197

Styryl Azide 4.197. The general procedure was followed using 0.58 g of 2-azido-4-methoxybenzaldehyde **4.189** (3.3 mmol), 1.42 g of the phosphonium salt (3.0 mmol), 1.2 mL of

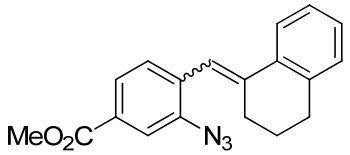
a 2.5 M solution of BuLi in hexanes in 25 mL of THF. Purification by MPLC (1:50 EtOAc: hexanes) afforded the product as a white powder, as an 83:17 mixture of *E*- and *Z*-isomers (0.37 g, 43%). Selected spectral data for the major (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 – 7.72 (m, 1H), 7.26 (d, *J* = 8.5 Hz, 1H), 7.23 – 7.19 (m, 2H), 7.14 – 7.12 (m, 1H), 6.97 (s, 1H), 6.74 – 6.71 (m, 2H), 3.87 (s, 3H), 2.87 (t, *J* = 6.5 Hz, 2H), 2.67 (dt, *J* = 1.5 Hz, 6.0 Hz, 2H), 1.87 (pent, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5 (C), 139.6 (C), 137.7 (C), 137.5 (C), 136.1 (C), 131.7 (CH), 129.1 (CH), 127.4 (CH), 126.2 (CH), 124.5 (CH), 122.8 (C), 118.3 (CH), 110.0 (CH), 104.2 (CH), 55.5 (CH_3), 30.3 (CH_2), 28.1 (CH_2), 23.7 (CH_2); Selected spectral data for the minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.19 (m, 1H), 7.10 – 7.05 (m, 3H), 6.86 (t, *J* = 6.5 Hz, 1H), 6.69 (d, *J* = 2.5 Hz, 1H), 6.51 (dd, *J* = 2.5 Hz, 8.5 Hz, 1H), 6.33 (s, 1H), 3.83 (s, 3H), 2.91 (t, *J* = 6.5 Hz, 2H), 2.57 (dt, *J* = 1.5 Hz, 6.0 Hz, 2H), 2.03 (pent, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5 (C), 138.7 (C), 134.9 (C), 132.7 (C), 132.0 (CH), 128.9 (CH), 128.7 (CH), 128.6 (CH), 128.5 (C), 124.7 (CH), 123.1 (C), 119.4 (CH), 110.6 (CH), 104.0 (CH), 55.4 (CH_3), 34.9 (CH_2), 29.7 (CH_2), 24.2 (CH_2); Selected spectral data for the mixture: δ IR (thin film): 2935, 2101, 1753, 1436, 1266, 1084, 739 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{18}H_{17}ON_3$ $(M)^+$ 291.13717, found 291.13649.



4.198

Styryl Azide 4.198. The general procedure was followed using 0.60 g of 2-azido-4-chlorobenzaldehyde **4.190** (3.3 mmol), 1.42 g of the phosphonium salt (3.0 mmol), 1.2 mL of a 2.5 M solution of BuLi in hexanes in 25 mL of THF. Purification by MPLC (1:100 EtOAc: hexanes) afforded the product as a white powder, as an 82:18 mixture of *E*- and *Z*-isomers (0.49

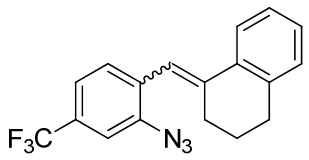
g, 55%). Selected spectral data for the major (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 – 7.70 (m, 1H), 7.26 – 7.20 (m, 3H), 7.16 (d, *J* = 2.0 Hz, 1H), 7.13 – 7.12 (m, 2H), 6.91 (s, 1H), 2.86 (t, *J* = 6.5 Hz, 2H), 2.62 (dt, *J* = 1.5 Hz, 6.5 Hz, 2H), 1.85 (pent, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.8 (C), 139.3 (C), 137.9 (C), 135.6 (C), 133.3 (C), 131.8 (CH), 129.2 (CH), 128.6 (C), 127.8 (CH), 126.3 (CH), 124.6 (CH), 124.6 (CH), 118.6 (CH), 117.6 (CH), 30.3 (CH_2), 28.2 (CH_2), 23.7 (CH_2); Selected spectral data for the minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.19 (m, 1H), 7.11 – 7.09 (m, 1H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.98 (d, *J* = 8.0 Hz, 1H), 6.88 (dd, *J* = 2.0 Hz, 8.5 Hz, 1H), 6.84 (t, *J* = 6.0 Hz, 1H), 6.27 (s, 1H), 2.89 (t, *J* = 6.5 Hz, 2H), 2.56 (dt, *J* = 1.5 Hz, 6.5 Hz, 2H), 2.03 (pent, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.6 (C), 139.2 (C), 139.0 (C), 134.4 (C), 133.2 (C), 132.3 (CH), 129.1 (C), 129.0 (CH), 128.8 (CH), 124.8 (CH), 124.8 (CH), 124.6 (CH), 118.7 (CH), 118.6 (CH), 34.9 (CH_2), 29.7 (CH_2), 24.1 (CH_2); Selected spectral data for the mixture: δ IR (thin film): 2931, 2109, 1738, 1486, 1286, 756 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{17}H_{14}N_3Cl$ $(M)^+$ 295.08762, found 295.08889.



4.199

Styryl Azide 4.199. The general procedure was followed using 0.68 g of methyl 3-azido-4-formylbenzoate **4.191** (3.3 mmol), 1.42 g of the phosphonium salt (3.0 mmol), 1.2 mL of a 2.5 M solution of BuLi in hexanes in 25 mL of THF. Purification by MPLC (1:50 EtOAc: hexanes) afforded the product as a white powder, as an 83:17 mixture of *E*- and *Z*-isomers (0.39 g, 41%). Selected spectral data for the major (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 (d, *J* = 1.5 Hz, 1H), 7.80 (dd, *J* = 1.5 Hz, 8.0 Hz, 1H), 7.73 (dd, *J* = 3.5 Hz, 5.5 Hz, 1H), 7.39 (d, *J* = 3.0 Hz,

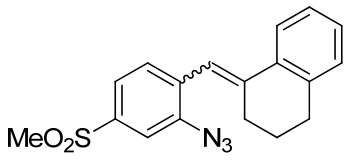
1H), 7.22 (dd, *J* = 3.5 Hz, 5.5 Hz, 2H), 7.14 – 7.12 (m, 1H), 7.00 (s, 1H), 3.95 (s, 3H), 2.87 (t, *J* = 6.5 Hz, 2H), 2.67 (dt, *J* = 1.5 Hz, 6.5 Hz, 2H), 1.86 (pent, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2 (C), 140.4 (C), 139.1 (C), 138.1 (C), 135.5 (C), 134.6 (C), 130.7 (CH), 129.6 (C), 129.2 (CH), 128.0 (CH), 126.3 (CH), 125.4 (CH), 124.7 (CH), 119.4 (CH), 117.9 (CH), 52.4 (CH_3), 30.2 (CH_2), 28.3 (CH_2), 23.7 (CH_2); Selected spectral data for the minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, *J* = 1.5 Hz, 1H), 7.55 (dd, *J* = 3.0 Hz, 8.0 Hz, 1H), 7.23 – 7.18 (m, 1H), 7.14 – 7.12 (m, 2H), 6.94 (d, *J* = 8.5 Hz, 1H), 6.80 (t, *J* = 8.5 Hz, 1H), 6.35 (s, 1H), 3.92 (s, 3H), 2.90 (t, *J* = 6.5 Hz, 2H), 2.59 (dt, *J* = 1.5 Hz, 6.5 Hz, 2H), 2.03 (pent, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.2 (C), 141.1 (C), 139.0 (C), 138.3 (C), 135.5 (C), 134.2 (C), 131.2 (CH), 129.2 (CH), 129.0 (CH), 128.8 (CH), 128.8 (C), 125.4 (CH), 124.8 (CH), 119.6 (CH), 119.0 (CH), 52.3 (CH_3), 34.9 (CH_2), 29.6 (CH_2), 24.0 (CH_2); Selected spectral data for the mixture: δ IR (thin film): 3456, 3015, 2970, 2116, 1739, 1436, 1367, 1228, 1092, 748, 527 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{19}H_{17}O_2N_3$ $(M)^+$ 319.13208, found 319.13140.



4.200

Styryl Azide 4.200. The general procedure was followed using 0.95 g of 2-azidobenzaldehyde **4.192** (4.4 mmol), 1.89 g of thephosphonium salt (4.0 mmol), 1.8 mL of a 2.5 M solution of BuLi in hexanes in 20 mL of THF. Purification by MPLC (1:100 EtOAc: hexanes) afforded the product as a light yellow powder, as a 87:13 mixture of *E*- and *Z*-isomers (1.81 g, 81%): Selected spectral data for the major (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 – 7.77 (m, 1H), 7.40 – 7.46 (m, 3H), 7.24 – 7.28 (m, 2H), 7.14 – 7.18 (m, 1H), 7.02 (s, 1H), 2.91 (m, *J* = 6.5 Hz, 2H),

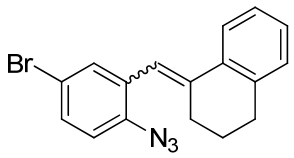
2.67 – 2.69 (m, 2H), 1.89 (pent, J = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.5 (C), 139.4 (C), 133.6 (C), 131.3 (CH), 130.1 (q, J_{CF} = 32.6 Hz, C), 129.3 (CH), 129.0 (C), 128.1 (CH), 126.3 (CH), 124.7 (CH), 123.8 (q, J_{CF} = 270.8 Hz, C), 121.0 (q, J_{CF} = 3.5 Hz, CH), 117.4 (CH), 115.3 (q, J_{CF} = 3.8 Hz, CH), 30.2 (CH_2), 28.2 (CH_2), 23.7 (CH_2) one overlapping aromatic carbon signal; Selected spectral data for the minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.40 – 7.46 (m, 1H), 7.24 – 7.28 (m, 1H), 7.14 – 7.18 (m, 3H), 6.99 (d, J = 8.0 Hz, 1H), 6.86 – 6.89 (m, 1H), 6.37 (s, 1H), 2.95 (t, J = 6.5 Hz, 2H), 2.62 – 2.64 (m, 2H), 2.01 (pent, J = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.9 (C), 139.1 (C), 138.8 (C), 134.3 (C), 134.1 (C), 138.1 (CH), 135.3 (CH), 131.8 (CH), 129.0 (CH), 128.8 (CH), 124.9 (CH), 118.5 (CH), 115.5 (q, J_{CF} = 3.8 Hz, CH), 34.9 (CH_2), 29.6 (CH_2), 24.0 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –63.12; Selected spectral data for the mixture: IR (thin film): 2111, 1739, 1328, 1273, 1123, 913, 745 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{18}H_{14}N_3F_3$ $(M)^+$ 329.11398, found 329.11303.



4.201

Styryl Azide 4.201. The general procedure was followed using 0.74 g of 2-azido-4-(methylsulfonyl)benzaldehyde **4.193** (3.3 mmol), 1.42 g of the phosphonium salt (3.0 mmol), 1.2 mL of a 2.5 M solution of BuLi in hexanes in 25 mL of THF. Purification by MPLC (1:20 EtOAc: hexanes) afforded the product as a white powder as one isomer (0.47 g, 46%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 (d, J = 1.5 Hz, 2H), 7.68 (dd, J = 1.5 Hz, 8.0 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.25 – 7.22 (m, 2H), 7.15 – 7.13 (m, 1H), 6.98 (s, 1H), 3.11 (s, 3H), 2.88 (t, J = 6.5 Hz, 2H), 2.66 (dt, J = 1.5 Hz, 6.5 Hz, 2H), 1.87 (pent, J = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$)

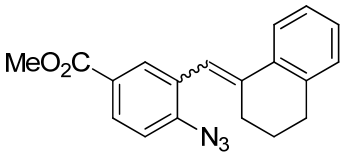
δ 141.5 (C), 140.1 (C), 139.7 (C), 138.2 (C), 135.5 (C), 135.1 (C), 131.7 (CH), 129.3 (CH), 128.3 (CH), 126.3 (CH), 124.7 (CH), 123.0 (CH), 117.2 (CH), 117.1 (CH), 44.6 (CH_3), 30.1 (CH_2), 28.3 (CH_2), 23.7 (CH_2); IR (thin film): 3454, 3026, 2969, 2116, 1738, 1366, 1206, 738, 536 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{18}H_{17}O_2NS$ $(M\text{-}N_2)^+$ 311.09800, found 311.09698.



4.202

Styryl Azide 4.202. The general procedure was followed using 0.75 g of 2-azido-5-bromobenzaldehyde **4.194** (3.3 mmol), 1.42 g of the phosphonium salt (3.0 mmol), 1.2 mL of a 2.5 M solution of BuLi in hexanes in 25 mL of THF. Purification by MPLC (1:100 EtOAc: hexanes) afforded the product as a white powder, as an 83:17 mixture of *E*- and *Z*-isomers (0.62 g, 61%). Selected spectral data for the major (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.73 – 7.71 (m, 1H), 7.45 (d, *J* = 2.5 Hz, 1H), 7.42 (dd, *J* = 2.5 Hz, 8.5 Hz, 1H), 7.25 – 7.21 (m, 2H), 7.17 – 7.14 (m, 1H), 7.05 (d, *J* = 8.5 Hz, 1H), 6.92 (s, 1H), 2.88 (t, *J* = 6.5 Hz, 2H), 2.66 (dt, *J* = 1.5 Hz, 6.5 Hz, 2H), 1.87 (pent, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.9 (C), 138.0 (C), 137.8 (C), 135.4 (C), 133.4 (CH), 131.9 (C), 130.7 (CH), 129.2 (CH), 128.0 (C), 127.9 (CH), 126.2 (CH), 124.8 (CH), 120.0 (CH), 117.4 (CH), 30.3 (CH_2), 28.1 (CH_2), 23.7 (CH_2); Selected spectral data for the minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.34 (dd, *J* = 2.0 Hz, 8.5 Hz, 1H), 7.27 (d, *J* = 2.0 Hz, 1H), 7.17 – 7.14 (m, 2H), 7.01 (d, *J* = 8.0 Hz, 2H), 6.90 – 6.87 (m, 1H), 6.28 (s, 1H), 2.92 (t, *J* = 6.5 Hz, 2H), 2.59 (dt, *J* = 1.5 Hz, 6.5 Hz, 2H), 2.04 (pent, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1 (C), 138.9 (C), 137.2 (C), 134.0 (C), 133.7 (CH), 132.6 (C), 129.0 (CH), 128.6 (CH), 128.0 (C), 124.8 (CH), 124.8 (CH), 120.1 (CH), 118.3 (CH), 117.2 (CH), 35.0 (CH_2), 29.7 (CH_2), 24.1 (CH_2); Selected spectral data for the

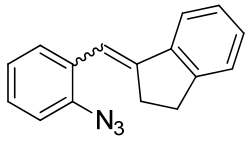
mixture: δ IR (thin film): 3457, 3015, 2970, 2122, 1755, 1369, 1215, 747, 516 cm^{-1}; HRMS (EI) *m / z* calcd for $C_{17}H_{14}N_3Br$ $(M)^+$ 339.03710, found 339.03776.



4.203

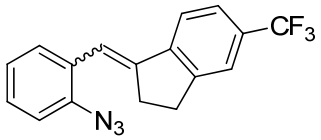
Styryl Azide 4.203. The general procedure was followed using 0.68 g of methyl 3-azido-4-formylbenzoate **4.195** (3.3 mmol), 1.42 g of the phosphonium salt (3.0 mmol), 1.2 mL of a 2.5 M solution of BuLi in hexanes in 25 mL of THF. Purification by MPLC (1:50 EtOAc: hexanes) afforded the product as a white powder, as an 87:13 mixture of *E*- and *Z*-isomers (0.38 g, 40%). Selected spectral data for the major (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 1.5 Hz, 1H), 7.98 (dd, *J* = 1.5 Hz, 8.0 Hz, 1H), 7.74 (dd, *J* = 3.5 Hz, 5.5 Hz, 1H), 7.23 – 7.20 (m, 3H), 7.15 – 7.14 (m, 1H), 6.98 (s, 1H), 3.94 (s, 3H), 2.87 (t, *J* = 6.5 Hz, 2H), 2.69 (dt, *J* = 1.5 Hz, 6.5 Hz, 2H), 1.86 (pent, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.5 (C), 143.2 (C), 139.6 (C), 138.0 (C), 135.6 (C), 132.2 (CH), 129.9 (C), 129.3 (CH), 129.2 (CH), 127.8 (CH), 126.2 (CH), 126.1 (C), 124.6 (CH), 118.2 (CH), 117.7 (CH), 52.1 (CH_3), 30.3 (CH_2), 28.2 (CH_2), 23.7 (CH_2); Selected spectral data for the minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (dd, *J* = 3.0, 8.5 Hz, 1H), 7.83 (d, *J* = 3.0 Hz, 1H), 7.23 – 7.20 (m, 1H), 7.13 – 7.10 (m, 1H), 6.95 (d, *J* = 8.5 Hz, 1H), 6.80 (t, *J* = 6.5 Hz, 1H), 6.33 (s, 1H), 3.82 (s, 3H), 2.92 (t, *J* = 6.5 Hz, 2H), 2.60 (dt, *J* = 1.5 Hz, 6.5 Hz, 2H), 2.05 (pent, *J* = 6.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3 (C), 142.6 (C), 140.9 (C), 138.9 (C), 135.5 (C), 134.2 (C), 132.7 (CH), 130.8 (CH), 129.0 (CH), 128.4 (CH), 126.4 (CH), 126.1 (C), 124.8 (CH), 118.7 (CH), 118.4 (CH), 52.0 (CH_3), 35.0 (CH_2), 29.7 (CH_2), 24.1 (CH_2); Selected spectral data for the mixture: δ IR (thin film): 3024,

2969, 2121, 1753, 1372, 1292, 762, 528 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{19}H_{17}ON$ $(M)^+$ 291.12593, found 291.12443.



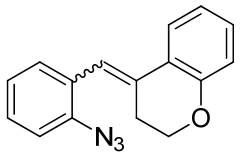
4.136

Styryl Azide 4.136. The general procedure was followed using 0.92 g of 2-azidobenzaldehyde **s9** (6.54 mmol), 2.40 g of the phosphonium salt (5.24 mmol), 2.3 mL of a 2.5 M solution of BuLi in hexanes in 15 mL of THF. Purification by MPLC (1:100 EtOAc: hexanes) afforded the product as a light yellow powder, as an 82:18 mixture of *E*- and *Z*-isomers (0.24 g, 19%): R_f = 0.45 (18:82 EtOAc: hexane). Selected spectral data for the major (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.65 – 7.67 (m, 1H), 7.54 (dd, *J* = 1.5 Hz, 7.5 Hz, 1H), 7.10 – 7.35 (m, 7H), 3.00 – 3.08 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.0 (C), 145.6 (C), 142.4 (C), 137.8 (C), 130.0 (C), 128.9 (CH), 128.5 (CH), 127.6 (CH), 126.8 (CH), 125.3 (CH), 124.5 (CH), 120.7 (CH), 118.4 (CH), 113.4 (CH), 30.8 (CH_2), 30.7 (CH_2); Selected spectral data for the minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 8.0 Hz, 1H), 7.10 – 7.35 (m, 5H), 7.04 (d, *J* = 8.0 Hz, 1H), 6.92 – 6.95 (m, 1H) 6.47 (s, 1H), 3.00 – 3.08 (m, 2H), 2.94 – 2.97 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0 (C), 145.0 (C), 139.4 (C), 138.0 (C), 130.8 (CH), 130.1 (C), 129.0 (CH), 128.5 (CH), 125.9 (CH), 125.4 (CH), 124.7 (CH), 124.2 (CH), 118.7 (CH), 116.8 (CH), 33.9 (CH_2), 30.2 (CH_2); Selected spectral data for the mixture: IR (thin film): 2117, 2084, 1570, 1483, 1277, 1264, 749 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{16}H_{13}N_3$ $(M)^+$ 247.11095, found 247.11013.



4.138

Styryl Azide 4.138. The general procedure was followed using 0.76 g of 2-azidobenzaldehyde **s9** (5.18 mmol), 2.48 g of the phosphonium salt (4.70 mmol), 2.1 mL of a 2.5 M solution of BuLi in hexanes in 15 mL of THF. Purification by MPLC (1:100 EtOAc: hexanes) afforded the product as a light yellow oil, as a 72:28 mixture of *E*- and *Z*-isomers (0.52 g, 35%): R_f = 0.45 (18:82 EtOAc: hexane). Selected spectral data for the major (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.81 (d, J = 7.5 Hz, 1H), 7.51 – 7.54 (m, 2H), 7.30 -7.39 (m, 2H), 7.11 – 7.23 (m, 3H), 3.18 – 3.24 (m, 2H), 3.05 – 3.08 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.3 (C), 143.7 (C), 143.5 (C), 143.3 (C), 138.0 (C), 129.4 (C), 128.9 (CH), 128.1 (CH), 127.1 (CH), 125.1 (q, J_{CF} = 4.0 Hz, CH), 124.6 (CH), 124.2 (q, J_{CF} = 271.9, C), 123.9 (CH), 118.4 (CH), 115.0 (CH), 30.4 (CH_2), 29.6 (CH_2); Selected spectral data for the minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.43 (d, *J* = 7.5 Hz, 1H), 7.30 – 7.39 (m, 2H), 7.11 – 7.23 (m, 2H), 7.13 (dd, *J* = 0.5 Hz, 7.5 Hz, 1H), 7.05 (t, *J* = 7.5 Hz, 1H), 6.57 (s, 1H), 3.18 – 3.24 (m, 2H), 2.99 – 3.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5 (C), 141.3 (C), 138.1 (C), 130.5 (CH), 129.5 (C), 128.8 (CH), 127.5 (C), 127.4 (CH), 127.2 (C), 126.3 (CH), 125.1 (q, J_{CF} = 4.0 Hz, CH), 124.8 (CH), 118.8 (CH), 118.5 (CH), 33.5 (CH_2), 28.8 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –63.12; Selected spectral data for the mixture: IR (thin film): 2124, 2083, 1595, 1318, 1160, 1118, 750 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{17}H_{12}N_3F_3$ $(M)^+$ 315.09833, found 315.09885.



4.142

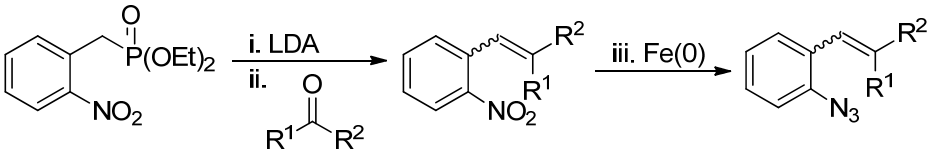
Styryl Azide 4.142. The general procedure was followed using 0.65 g of 2-azidobenzaldehyde **s9** (4.42 mmol), 1.87 g of the phosphonium salt (3.95 mmol), 1.73 mL of a 2.5 M solution of BuLi in hexanes in 20 mL of THF. Purification by MPLC (1:100 EtOAc: hexanes) afforded the

product as a white powder, as an 83:17 mixture of *E*- and *Z*-isomers (0.28 g, 27%): R_f = 0.45 (18:82 EtOAc: hexane). Selected spectral data for the major (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (dd, *J* = 1.5 Hz, 8.0 Hz, 1H), 7.32 – 7.35 (m, 1H), 7.27 (d, *J* = 8.0 Hz, 1H), 7.19 – 7.22 (m, 2H), 7.14 – 7.17 (m, 1H), 7.08 (s, 1H), 6.95 – 6.98 (m, 1H), 6.83 – 6.85 (m, 1H), 4.20 (t, *J* = 6.0 Hz, 2H), 2.80 – 2.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.9 (C), 138.7 (C), 132.1 (C), 130.9 (CH), 129.5 (CH), 128.8 (C), 128.3 (CH), 124.8 (CH), 124.3 (CH), 122.4 (C), 120.9 (CH), 118.4 (CH), 117.5 (CH), 117.0 (CH), 66.2 (CH_2), 26.9 (CH_2); Selected spectral data for the minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.38 (d, *J* = 7.5 Hz, 1H), 7.29 – 7.30 (m, 1H), 7.09 – 7.11 (m, 1H), 7.00 – 7.04 (m, 2H), 6.84 (dd, *J* = 1.0 Hz, 8.0 Hz, 1H), 6.65 – 6.58 (m, 1H), 6.29 (s, 1H), 4.38 (t, 5.5 Hz, 2H), 2.71- 2.73 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) 154.9 (C) 138.1 (C), 132.5 (C), 131.1 (CH), 129.7 (CH), 128.53 (CH), 128.50 (CH), 124.7 (CH), 120.6 (C), 120.0 (CH), 119.3 (CH), 118.6 (CH), 117.1 (CH), 67.4 (CH_2), 33.3 (CH_2); Selected spectral data for the mixture: δ IR (thin film): 2117, 2091, 1603, 1572, 1468, 1450, 1281, 1049, 749 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{16}H_{13}ON_3$ $(M)^+$ 263.10587, found 263.10672.

4.14.2 Preparation of Substrates using a Horner–Wadsworth–Emmons Reaction

General Procedure for the Horner–Wadsworth–Emmons Reaction and Fe-Mediated Nitro-Group Reduction

2-Amino substituted styrenes were synthesized via a two-step procedure of Horner-Wadsworth-Emmons reaction followed by nitro-group reduction. Yields were not optimized.



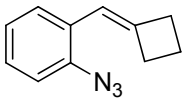
(eq. 9)

To a -78 °C solution of LDA (4.4 mmol) in 10 mL of THF was added dropwise *ortho*-nitrobenzylphosphonate in 3 mL of THF. After an additional hour, a solution of the ketone in 5

mL of THF was added slowly to the mixture at -78 °C. The reaction mixture was allowed to warm to ambient temperature slowly. After 1h, 10 mL water was added to quench the reaction. The resulting mixture was taken up by dichloromethane and separated. The aqueous phase was washed with 3 × 5 mL dichloromethane. The resulting organic phase was washed with 20 mL of brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo* to produce 2-nitro-styrene, which was submitted to the subsequent Fe-mediated nitro-group reduction without further purification.

To a solution of nitro-substituted styrene (prepared from 4.0 mmol of ortho-nitrobenzylphophonate) in 20 mL of AcOH and 20 mL of EtOH was added 1.8 g of Fe powder (32 mmol). The resultant mixture was allowd to reflux at 80 °C overnight. After cooled down to ambient temperature, the resulting mixture was filtrated with a pad of Celite. The filtrate was diluted with 50 mL of water and washed with 3 × 10 mL dichloromethane. The resulting organic phase was washed with 40 mL of brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated in *vacuo*. Purification of the reaction mixture using MPLC afforded the product

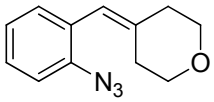
Synthesis of Nitro-Substituted Styrenes.



4.150

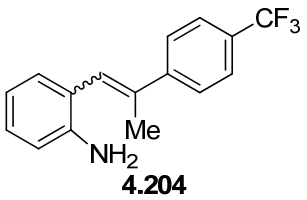
Styrene 4.150. The general procedure of Horner–Wadsworth–Emmons reaction was followed using 1.09 g of *ortho*-nitrobenzylphosphonate[46] (4.0 mmol), 0.45 mL of cyclobutanone (6.0 mmol) and LDA (4.4 mmol) in 6 mL of THF. After work-up, the representative pathway of nitro-group reduction was followed by using 1.79 g of Fe (32.0 mmol), in 20.0 mL of AcOH and 20.0 mL of EtOH. Purification by MPLC (1:100 – 20:80 EtOAc: hexanes) afforded the product

as a light yellow oil (0.25 g, 39% two steps): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 – 7.19 (m, 1H), 7.07 – 7.11 (m, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.79 – 6.83 (m, 1H), 6.11 (s, 1H), 3.71 (s, 2H), 2.92 – 2.99 (m, 4H), 2.10 – 2.16 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.2 (C), 143.5 (C), 128.2 (CH), 127.3 (CH), 123.4 (C), 118.5 (CH), 115.8 (CH), 115.7 (CH), 32.6 (CH_2), 32.3 (CH_2), 18.2 (CH_2); IR (thin film): 3451, 3366, 2948, 1614, 1488 1297, 1263, 744cm^{-1}. HRMS (EI) *m / z* calcd for $C_{11}H_{13}N$ $(M)^+$ 159.10480, found 159.10560.



4.164

Styrene 4.164. The general procedure of Horner–Wadsworth–Emmons reaction was followed using 1.09 g of *ortho*-nitrobenzylphosphonate[46] (4.0 mmol), 0.55 mL of tetrahydro-4*H*-pyran-4-one (6.0 mmol) and LDA (4.4 mmol) in 6 mL of THF. After work-up, the representative pathway of nitro-group reduction was followed by using 1.79 g of Fe (32.0 mmol), in 20.0 mL of AcOH and 20.0 mL of EtOH. Purification by MPLC (1:100 – 20:80 EtOAc: hexanes) afforded the product as a light yellow oil (0.50 g, 66% two steps): ^{1}H NMR (500 MHz, $CDCl_3$) 7.07 (t, *J* = 8.0 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 6.69 – 6.75 (m, 2H), 6.14 (s, 1H), 3.80 (t, *J* = 5.5 Hz, 2H), 3.69 (s, 2H), 3.66 (t, *J* = 5.5 Hz, 2H), 2.43 (t, *J* = 5.5 Hz, 2H), 2.36 (t, *J* = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.2 (C), 139.8 (C), 130.1 (CH), 127.9 (CH), 122.9 (C), 119.6 (CH), 118.1 (CH), 115.1 (CH), 69.7 (CH_2), 69.0 (CH_2), 37.0 (CH_2), 31.0 (CH_2); IR (thin film): 3459, 3355, 1613, 1489, 1452, 1229, 1093, 995, 746 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{12}H_{15}ON$ $(M)^+$ 189.11537, found 189.11613.

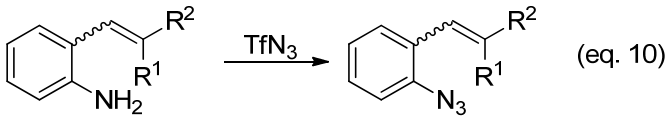


4.204

Styrene 4.204. The general procedure of Horner–Wadsworth–Emmons reaction was followed using 1.09 g of *ortho*-nitrobenzylphosphonate[46] (4.0 mmol), 0.83 g of 4-acetylbenzotrifluoride (4.4 mmol) and LDA (4.4 mmol) in 6 mL of THF. After work-up, the representative pathway of nitro-group reduction was followed by using 1.79 g of Fe (32.0 mmol), in 20.0 mL of AcOH and 20.0 mL of EtOH. Purification by MPLC (1:100 – 20:80 EtOAc: hexanes) afforded the crude product as a brown oil (0.34 g, 31% two steps). The aniline was carried on to the azidation reaction without further purification.

General Procedure for the Azidation Reaction

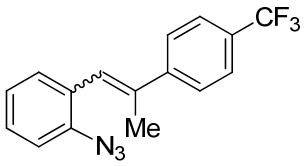
Following the procedure of Tor and co-workers,[47] the aniline group was transformed into an azide (**eq. 10**). Yields were not optimized.



(eq. 10)

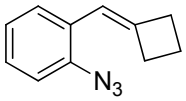
To a solution of aniline (3 mmol) in 5 mL of CH_2Cl_2 was added subsequently 24 mg of $CuSO_4$, 1.2 mL of Et_3N, freshly prepared triflyl azide (9 mmol) in 15 mL of CH_2Cl_2, 1 mL of water and 2 mL of MeOH. The resulting mixture was allowed to react at room temperature overnight. Then, the reaction mixture was taken up by 15 mL dichloromethane, neutralized with a saturated aq. soln. of $NaHCO_3$ and washed with 3 × 10 mL of CH_2Cl_2. The resulting organic phase was washed with 20 mL of brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. Purification of the reaction mixture using MPLC afforded the product.

Synthesis of Styryl Azides



4.146

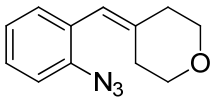
Styryl Azide 4.146. The general procedure for azidation was followed using 0.31 g of aniline **s20** (1.1 mmol), 0.01 g of $CuSO_4$, freshly prepared dichloromethane solution of TfN_3 (from 3.0 mmol of Tf_2O), and 0.4 mL of Et_3N (3.0 mmol) in 4 mL CH_2Cl_2, 2 mL of MeOH and 1 mL of H_2O. Purification by MPLC (1:100 EtOAc: hexanes) afforded the product as a light yellow solid (0.22 g, 66%): mp 62 - 65 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.51 (d, J = 8.0 Hz, 2H), 7.28 (d, J = 8.0 Hz, 2H), 7.17 – 7.20 (m, 1H), 7.12 (dd, J = 1.0 Hz, 8.0 Hz, 1H), 6.80 – 6.83 (m, 1H), 6.74 (d, J = 7.5 Hz, 1H), 6.65 (s, 1H), 2.29 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145. 3 (C), 138.6 (C), 138.1 (C), 131.1 (CH), 129.076 (q, J_{CF} = 32.6 Hz, C), 129.075 (C), 128.7 (CH), 128.1 (CH), 125.2 (q, J_{CF} = 3.5 Hz, CH), 124.3 (CH), 124.2 (q, J_{CF} = 271 Hz, C), 123.5 (CH), 118.2 (CH), 23.0 (CH_3); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –63.04; IR (thin film): 2122, 1615, 1482, 1323, 1123, 738 cm^{-1}. HRMS (EI) m/z calcd for $C_{16}H_{12}N_3F_3$ $(M)^+$ 303.09833, found 303.09697.



4.150

Styryl Azide 4.150. The general procedure for azidation was followed using 0.23 g of aniline **s18** (1.44 mmol), 0.02 g of $CuSO_4$, freshly prepared dichloromethane solution of TfN_3 (from 4.5 mmol of Tf_2O), and 0.6 mL of Et_3N (4.5 mmol) in 6 mL CH_2Cl_2, 3 mL of MeOH and 2 mL of H_2O. Purification by MPLC (100% hexanes) afforded the product as a light yellow oil (0.14 g, 54%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 8.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.11 (t, J = 7.5 Hz, 1H), 6.35 (s, 1H), 3.01 – 3.04 (m, 2H), 2.92 – 2.95 (m, 2H),

2.12 – 2.16 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.5 (C), 136.5 (C), 129.5 (C), 127.9 (CH), 127.1 (CH), 124.5 (CH), 118.3 (CH), 115.1 (CH), 32.9 (CH_2), 32.7 (CH_2), 18.4 (CH_2); IR (thin film): 2951, 2113, 1482, 1285, 1099, 743, 665 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{11}H_{11}N_3$ $(M)^+$ 185.09530, found 185.09451.

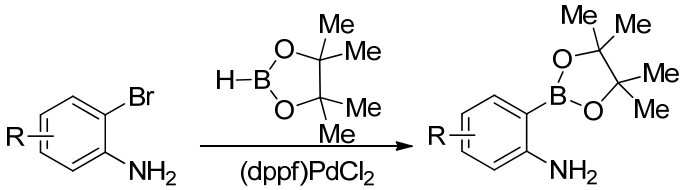


4.164

Styryl Azide 4.164. The general procedure for azidation was followed using 0.43 g of aniline **s19** (2.28 mmol), 0.02 g of $CuSO_4$, freshly prepared dichloromethane solution of TfN_3 (from 9.0 mmol of Tf_2O), and 1.3 mL of Et_3N (9.0 mmol) in 6 mL CH_2Cl_2, 3 mL of MeOH and 2 mL of H_2O. Purification by MPLC (1:100 EtOAc: hexanes) afforded the product as a light yellow oil (0.31 g, 63%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.22 – 7.25 (m, 1H), 7.10 – 7.15 (m, 2H), 7.07 (t, *J* = 7.5 Hz, 1H), 6.24 (s, 1H), 3.77 (t, *J* = 5.5 Hz, 2H), 3.64 (t, *J* = 5.5 Hz, 2H), 2.37 – 2.41 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3 (C), 138.1 (C), 130.8 (CH), 129.1 (C), 128.0 (CH), 124.3 (CH), 119.3 (CH), 118.4 (CH), 69.4 (CH_2), 68.6 (CH_2), 37.2 (CH_2), 30.9 (CH_2); IR (thin film): 2115, 2082, 1482, 1279, 1230, 1097, 997, 748, 665 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{12}H_{13}ON_3$ $(M)^+$ 215.10587, found 215.10709.

4.14.3 Preparation of Substrates using a Suzuki Reaction

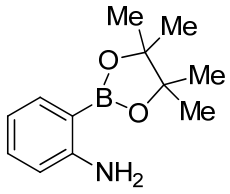
General Procedure for the Arylboronic Acid Pinacol Ester Syntheses



(eq. 11)

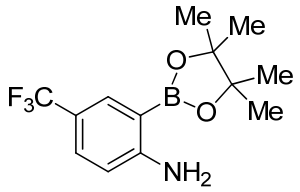
To a mixture of 0.85 g of 2-bromo-aniline (5.0 mmol), 2.09 mL of Et_3N (20.0 mmol), 0.185 g of (dppf)$PdCl_2$ (0.25 mmol) in 15 mL 1,4-dioxane, was added dropwise 2.20 mL 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.0 mmol). The resultant mixture was heated to 100 °C. After 12h, the mixture was cooled to room temperature and diluted with 20 mL of NH_4Cl. The resulting aqueous phase was extracted with an additional 2 × 20 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, and was concentrated *in vacuo*. Purification via MPLC afforded the product.

Syntheses of Arylboronic Acid Pinacol Esters



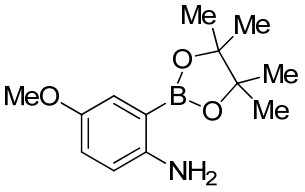
4.205

Aniline 4.205.[48] The general procedure was followed using 3.4 g of 2-bromo-aniline (20.0 mmol), 8.7 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (60.0 mmol), 0.82 g of (dppf)$PdCl_2$ (1.0 mmol), and 8.4 mL of Et_3N (80.0 mmol) in 100 mL of 1, 4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow solid (3.02 g, 69%): mp 62 -64 °C; The spectral data matched that reported by Driver and co-workers:[48] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (d, J = 7.5 Hz, 1H), 7.24 (t, J = 7.0 Hz, 1H), 6.70 (t, J = 7.0 Hz, 1H), 6.61 (d, J = 8.5 Hz, 1H), 4.76 (s, 2H), 1.36 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.7 (C), 136.8 (CH), 132.8 (CH), 116.9 (CH), 114.8 (CH), 83.5 (C), 25.0 (CH_3); IR (thin film): 3486, 3380, 1624, 1605, 1352, 1311, 1244, 1135, 1086, 847, 758, 654 cm^{-1}.



4.206

Aniline 4.206.[48] The general procedure was followed using 2.65 g of 2-bromo-4-(trifluoromethyl)aniline (10.0 mmol), 4.4 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30.0 mmol), 0.41 g of (dppf)PdCl2 (0.5 mmol), and 4.2 mL of Et_3N (40.0 mmol) in 50 mL of 1, 4-dioxane. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a brown solid (1.81 g, 63%): mp 107 -109 °C. The spectral data matched that reported by Driver and co-workers:[48] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.86 (s, 1H), 7.41 (d, J = 8.5 Hz, 1H), 6.59 (d, J = 8.5 Hz, 1H), 5.08 (s, 2H), 1.35 (s, 12H); 13C NMR (125 MHz, $CDCl_3$) δ 156.1 (C), 134.3 (q, J_{CF} = 3.8 Hz, CH), 129.5 (q, J_{CF} = 3.8 Hz, CH), 125.0 4 (q, J_{CF} = 268.8 Hz, C), 118.5 (q, J_{CF} = 32.5 Hz, C), 84.0 (C) 114.2 (CH), 24.9 (CH3); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –61.64; IR (thin film): 3472, 3375, 1625, 1370, 1304, 1256, 1140, 1097, 1072, 832.9 cm^{-1}.

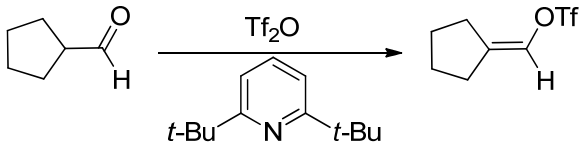


4.207

Aniline 4.207.[48] The general procedure was followed using 2.02 g of 2-bromo-4-methoxyaniline (10.0 mmol), 4.4 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30.0 mmol), 0.41 g of (dppf)$PdCl_2$ (0.5 mmol), and 4.2 mL of Et_3N (40.0 mmol) in 50 mL of 1, 4-dioxane. Purification by MPLC (5:100 – 10:90 EtOAc: hexanes) afforded the product as a brown liquid (1.52 g, 61%). The spectral data matched that reported by Driver and co-workers:[48] ^{1}H NMR (500 MHz, $CDCl_3$) 7.15 (d, J = 3.5 Hz, 1H), 6.85 (dd, J = 3.0 Hz, 8.5 Hz, 1H), 6.58 (d, J = 8.5 Hz, 1H), 4.48

(s, 2H), 3.76 (s, 3H), 1.34 (s, 12H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.3 (C), 147.9 (C), 120.7 (CH), 119.5 (CH), 116.5 (CH), 83.6 (C), 56.0 (CH_3), 25.0 (CH_3); IR (thin film): 3456, 3366, 1494, 1421, 1359, 1304, 1226, 1037, 855, 829, 750 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{13}H_{20}O_3NB$ $(M)^+$ 249.1536, found 249.1540.

General Procedure for the Triflate Formation

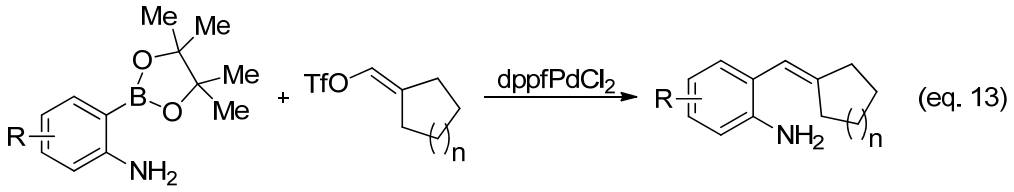


(eq. 12)

To a mixture of 10.0 mmol of cyclopentanecarboxaldehyde and 2.65 mL 2,6-di-*tert*-butylpyridine (12.0 mmol) in 40 mL of 1,2-dichloroethane was added 1.85 mL of triflic anhydride (11.0 mmol). The resultant mixture was heated to 70 °C. After 2h, the mixture was cooled to room temperature and diluted with 40 mL CH_2Cl_2. The resulting aqueous phase was extracted with an additional 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, and was concentrated *in vacuo* to afford crude triflate.

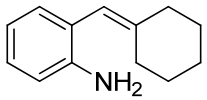
General Procedure for the Suzuki Reaction

Following the procedure of Driver and co-workers,[48] was aniline **s6** treated with vinyl triflate **s7** in the presence of (dppf)$PdCl_2$ to produce the desired aniline (s8). Yields were not optimized.



To a mixture of 0.919 g of boronic ether (3.2 mmol), 0.261 g of (dppf)$PdCl_2$ (0.32 mmol) in 40 mL 1,4-dioxane was added 8 mL of a 3M solution of NaOH in water followed by 1.36 g of crude triflate (5.12 mmol). The resultant mixture was heated to 80 °C. After 12 h, the mixture was cooled to room temperature and filtrated through a pad of Celite. The filtrate was diluted with 20 mL saturated NH_4Cl and extracted with an additional 2 × 30 mL of CH_2Cl_2. The combined organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na_2SO_4, and was concentrated *in vacuo*. Purification via MPLC afforded the product.

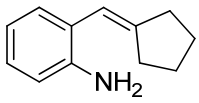
Synthesis of Anilines



4.208

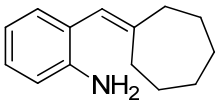
Aniline 4.208. The general procedure was followed using 1.10 g of boronic ester **4.205** (5.0 mmol), crude vinyl triflate (derived from 10.0 mmol of cyclohexanecarboxaldehyde), 0.82 g of (dppf)$PdCl_2$ (1.0 mmol), and 1.8 g of NaOH (45.0 mmol) in 75 mL of 1,4-dioxane and 15 mL of water. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow oil (0.74 g, 79%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.09 (t, *J* = 6.0 Hz, 1H), 7.04 (d, *J* = 7.5 Hz, 1H), 6.77 (t, *J* = 7.5 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 6.05 (s, 1H), 3.70 (s, 2H), 2.33 (t, *J* = 6.0 Hz, 2H), 2.24 (t, *J* = 6.0 Hz, 2H), 1.56 – 1.70 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.4 (C), 144.3 (C), 130.3 (CH), 127.5 (CH), 124.0 (C), 118.0 (CH), 117.8 (CH), 115.0 (CH), 37.2 (CH_2), 30.0 (CH_2), 28.9 (CH_2), 28.1 (CH_2), 26.8 (CH_2); IR (thin film): 3466, 3368, 1161, 1489,

1448, 1297, 1265, 745 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{13}H_{17}N$ $(M)^+$ 187.13610, found 187.13596.



4.209

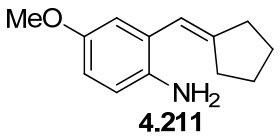
Aniline 4.209. The general procedure was followed using 2.19 g of boronic ester **4.205** (10.0 mmol), crude vinyl triflate (derived from 15.0 mmol of cyclopentenanecarboxaldehyde), 0.82 g of (dppf)$PdCl_2$ (1.0 mmol), and 3.6 g of NaOH (90.0 mmol) in 100 mL of 1, 4-dioxane and 30 mL of water. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow oil (1.54 g, 89%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.16 (d, *J* = 7.5 Hz, 1H), 7.05 (dt, *J* = 1.5 Hz, 7.5 Hz, 1H), 6.76 (t, *J* = 7.5 Hz, 1H), 6.70 (d, *J* = 7.5 Hz, 1H), 6.23 (s, 1H), 3.67 (s, 2H), 2.49 (s, 2H), 2.39 (s, 2H), 1.70 – 1.73 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 148.6 (C), 143.7 (C), 129.1 (CH), 127.3 (CH), 124.9 (C), 118.2 (CH), 115.7 (CH), 115.2 (CH), 34.6 (CH_2), 30.7 (CH_2), 26.7 (CH_2), 25.8 (CH_2); IR (thin film): 3452, 3368, 1613, 1488, 1453, 1295, 1263, 1155, 871, 744 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{12}H_{15}N$ $(M)^+$ 173.1164, found 173.1204.



4.210

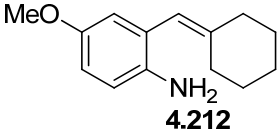
Aniline 4.210. The general procedure was followed using 0.76 g of boronic ester **4.205** (3.5 mmol), crude vinyl triflate (derived from 10.0 mmol of cycloheptanecarboxaldehyde), 0.25 g of (dppf)$PdCl_2$ (0.3 mmol), and 1.2 g of NaOH (30.0 mmol) in 40 mL of 1, 4-dioxane and 10 mL of water. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow oil (0.25 g, 35%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.07 (dt, *J* = 1.5 Hz, 7.5 Hz, 1H), 7.03

(d, J = 7.5 Hz, 1H), 6.74 (dt, J = 1.0 Hz, 7.5 Hz, 1H), 6.71 (dd, J = 1.5 Hz, 7.5 Hz, 1H), 6.10 (s, 1H), 3.68 (s, 2H), 2.43 – 2.45 (m, 2H), 2.31 – 2.33 (m, 2H) 1.68 – 1.72 (m, 2H), 1.52 – 1.62 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.5 (C), 144.0 (C), 130.0 (CH), 127.4 (CH), 124.5 (C), 121.0 (CH), 118.0 (CH), 114.9 (CH), 37.8 (CH_2), 31.2 (CH_2), 29.9 (CH_2), 29.5 (CH_2), 29.37 (CH_2), 27.3 (CH_2); IR (thin film): 3464, 3372, 2918, 2849, 1611, 1489, 1451, 745 cm^{-1}. HRMS (EI) m / z calcd for $C_{14}H_{19}N$ $(M)^+$ 201.15175 found 201.15198



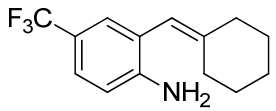
4.211

Aniline 4.211. The general procedure was followed using 1.69 g of boronic ester **4.207** (6.8 mmol), crude vinyl triflate (derived from 10.0 mmol of cyclopentanecarboxaldehyde), 0.57 g of (dppf)$PdCl_2$ (0.68 mmol), and 1.44 g of NaOH (36.0 mmol) in 40 mL of 1, 4-dioxane and 12 mL of water. Purification by MPLC (2:100 – 20:80 EtOAc: hexanes) afforded the product as a brown oil (0.97 g, 70%): ^{1}H NMR (500 MHz, $CDCl_3$) δ (500 MHz, $CDCl_3$): δ 6.77 (d, J = 1.8 Hz, 1H), 6.64 – 6.64 (m, 2H), 6.23 (t, J = 2.3 Hz, 1H), 3.75 (s, 3H), 3.44 (s, 2H), 2.48 (ddd, J = 7.7, 5.5, 1.9 Hz, 2H), 2.42-2.40 (m, 2H), 1.71 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.4 (C), 148.8 (C), 137.5 (C), 126.2 (C), 116.4 (CH), 115.9 (CH), 114.6 (CH), 112.9 (CH), 55.8 (CH_3), 34.7 (CH_2), 30.8 (CH_2), 26.7 (CH_2), 25.8 (CH_2); IR (thin film): 3437, 3357, 2947, 1604, 1494, 1281, 1040, 904, 813 cm^{-1}. HRMS (EI) m / z calcd for $C_{13}H_{17}ON$ $(M)^+$ 203.13102, found 203.13075.



4.212

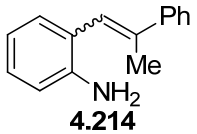
Aniline 4.212. The general procedure was followed using 1.44 g of boronic ester **4.207** (5.8 mmol), crude vinyl triflate (derived from 9.0 mmol of cyclohexanecarboxaldehyde), 0.57 g of (dppf)$PdCl_2$ (0.68 mmol), and 1.20 g of NaOH (30.0 mmol) in 40 mL of 1, 4-dioxane and 10 mL of water. Purification by MPLC (2:100 – 20:80 EtOAc: hexanes) afforded the product as a brown oil (0.21 g, 17%): ^{1}H NMR (500 MHz, $CDCl_3$): 6.60 – 6.68 (m, 3H), 6.01 (s, 1H), 3.74 (s, 3H), 3.13 (s, 2H), 2.29 (t, J = 6.0 Hz, 2H), 2.21 (t, J = 6.5 Hz, 2H), 1.52 – 1.66 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 152.2 (C), 145.6 (C), 138.0 (C), 125.3 (C), 117.7 (CH), 116.1 (CH), 115.7 (CH), 113.1 (CH), 55.8 (CH_3), 37.2 (CH_2), 30.0 (CH_2), 28.8 (CH_2), 28.0 (CH_2), 26.7 (CH_2); IR (thin film): 3438, 3358, 1494, 1276, 1216, 1159, 1039, 811 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{14}H_{19}ON$ $(M)^+$ 217.1467, found 217.1466.



4.213

Aniline 4.213. The general procedure was followed using 3.01 g of boronic ester **4.206** (10.5 mmol), crude vinyl triflate (derived from 15.0 mmol corresponding aldehyde), 0.87 g of (dppf)$PdCl_2$ (1.05 mmol), and 3.60 g of NaOH (90.0 mmol) in 110 mL of 1, 4-dioxane and 30 mL of water. Purification by MPLC (2:100 – 10:90 EtOAc: hexanes) afforded the product as a brown liquid (1.82 g, 62%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.30 (d, J = 8.5 Hz, 1H), 7.26 (s, 1H), 6.69 (d, J = 8.5 Hz, 1H), 5.98 (s, 1H), 4.01 (s, 2H), 2.32 (t, J = 5.5 Hz, 2H), 2.18 (t, J = 6.5 Hz, 2H), 1.54 – 1.71 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 147.3 (C), 147.1 (C), 127.3 (q, J_{CF} = 3.8 Hz, CH), 125.1 (q, J_{CF} = 268.8 Hz, C), 124.6 (q, J_{CF} = 3.8 Hz, CH), 123.3 (C), 119.5 (q, J_{CF} = 31.3 Hz, C), 116.4 (CH), 114.1 (CH), 37.1 (CH_2), 30.0 (CH_2), 28.8 (CH_2), 28.0 (CH_2), 26.6

(CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –61.47; IR (thin film): 3492, 3398, 1620, 1323, 1142, 1103, 1071, 820 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{14}H_{16}NF_3$ $(M)^+$ 255.1235, found 255.1239.

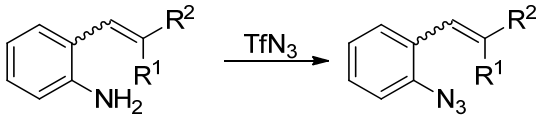


4.214

Aniline 4.214. The general procedure was followed using 1.75 g of boronic ester **4.205** (8.0 mmol), crude vinyl triflate (derived from 15.0 mmol corresponding aldehyde), 0.66 g (dppf)$PdCl_2$ (0.8 mmol), and 3.60 g of NaOH (90.0 mmol) in 110 mL of 1,4-dioxane and 30 mL of water. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the product as a light yellow oil, as a 69:31 mixture of *Z*- and *E*-isomers (1.41 g, 84%): R_f = 0.45 (18:82 EtOAc: hexane). Selected spectral data for the major (*Z*) isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.11 – 7.23 (m, 5H), 6.97 (t, *J* = 8.0 Hz, 1H), 6.72 – 6.76 (m, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 6.52 (t, *J* = 7.5 Hz, 1H), 6.41 (s, 1H), 3.70 (br, 2H), 2.28 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.0 (C), 141.2 (C), 139.5 (C), 130.0 (CH), 128.1 (CH), 127.5 (CH), 127.0 (CH), 123.98 (C), 123.1 (CH), 118.3 (CH), 115.3 (CH), 25.7 (CH_3) one overlapping aromatic C not distinguishable; Selected spectral data for the minor (*E*) isomer: ^1H NMR (500 MHz, $CDCl_3$) δ 7.57 – 7.58 (m, 2H), 7.38 – 7.41 (m, 2H), 7.31 – 7.34 (m, 1H), 7.11- 7.23 (m, 2H), 6.81 (t, *J* = 7.5 Hz, 1H), 6.72 – 6.76 (m, 2H), 3.70 (br s, 2H), 2.17 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.4 (C), 142.9 (C), 139.1 (C), 130.5 (CH), 128.4 (CH), 128.1 (CH), 127.4 (CH), 124.01 (C), 123.9 (CH), 123.5 (CH), 118.2 (CH), 115.2 (CH), 17.2 (CH_3); Selected spectral data for the mixture: δ IR (thin film): 3464, 3374, 1613, 1489, 1454, 1275, 1264 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{15}N$ $(M)^+$ 209.12045, found 209.12206.

General procedure of Styryl Azides Syntheses

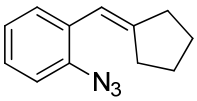
Following the procedure of Tor and co-workers,[47] the aniline group was transformed into an azide (s5). Yields were not optimized.



(eq. 10)

To a solution of aniline (3 mmol) in 5 mL of CH_2Cl_2 was added subsequently 24 mg of $CuSO_4$, 1.2 mL of Et_3N, freshly prepared triflyl azide (9 mmol) in 15 mL of CH_2Cl_2, 1 mL of water and 2 mL of MeOH. The resulting mixture was allowed to react at room temperature overnight. Then, the reaction mixture was taken up by 15 mL dichloromethane, neutralized with a saturated aq. soln. of $NaHCO_3$ and washed with 3 × 10 mL of CH_2Cl_2. The resulting organic phase was washed with 20 mL of brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. Purification of the reaction mixture using MPLC afforded the product.

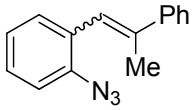
Synthesis of Styryl Azide



4.152

Styryl Azide 4.152. The general procedure for azidation was followed using 0.95 g of aniline **4.209** (5.5 mmol), 0.05 g of $CuSO_4$, freshly prepared dichloromethane solution of TfN_3 (from 18.0 mmol of Tf_2O), and 2.5 mL of Et_3N (18.0 mmol) in 6 mL of CH_2Cl_2, 4 mL of MeOH and 2 mL of H_2O. Purification by MPLC (1:100 EtOAc: hexanes) afforded the product as a light yellow oil, as a 72:28 mixture of *Z*- and *E*-isomers (0.68 g, 62%): Selected spectral data for the major (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.32 (m, 6H), 7.13 – 7.15 (d, J = 8.5 Hz, 1H), 6.80 – 6.84 (m, 2H), 6.62 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5 (C), 140.3 (C), 137.9 (C), 131.2 (CH), 129.8 (C), 128.4 (CH), 127.7 (CH), 127.1 (CH), 124.2 (CH),

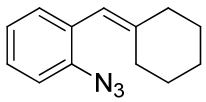
121.9 (CH), 118.1 (CH), 26.5 (CH_3); Selected spectral data for the minor (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 1.0 Hz, 8.5 Hz, 2H), 7.36 – 7.47 (m, 5H), 7.18 (dd, *J* = 2.0 Hz, 6.0 Hz, 2H), 6.92 (s, 1H), 2.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3 (C), 138.7 (C), 138.5 (C), 130.8 (CH), 130.2 (C), 128.5 (CH), 128.2 (CH), 127.5 (CH), 126.1 (CH), 124.4 (CH), 123.1 (CH), 118.5 (CH), 17.5 (CH_3); Selected spectral data for the mixture: δ IR (thin film): 2116, 2083, 1479, 1443, 1278, 759 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{12}H_{13}N_3$ $(M)^+$ 199.1109, found 119.1112.



4.144

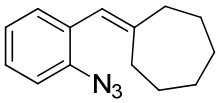
Styryl Azide 4.144.[49] The general procedure for azidation was followed using 0.65 g of aniline **4.214** (3.1 mmol), 0.02 g of $CuSO_4$, freshly prepared dichloromethane solution of TfN_3 (from 9.0 mmol of Tf_2O), and 1.3 mL of Et_3N (9.0 mmol) in 4 mL of CH_2Cl_2, 2 mL of MeOH and 1 mL of H_2O. Purification by MPLC (1:100 – 20:80 EtOAc: hexanes) afforded the product as a light yellow oil, as a 72:28 mixture of *Z*- and *E*-isomers (0.59 g, 81%): Selected spectral data for the major (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.21 – 7.32 (m, 6H), 7.13 – 7.15 (d, *J* = 8.5 Hz, 1H), 6.80 – 6.84 (m, 2H), 6.62 (s, 1H), 2.33 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.5 (C), 140.3 (C), 137.9 (C), 131.2 (CH), 129.8 (C), 128.4 (CH), 127.7 (CH), 127.1 (CH), 124.2 (CH), 121.9 (CH), 118.1 (CH), 26.5 (CH_3) one overlapping aromatic C not distinguishable; Selected spectral data for the minor (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.64 (dd, *J* = 1.0 Hz, 8.5 Hz, 2H), 7.36 – 7.47 (m, 5H), 7.18 (dd, *J* = 2.0 Hz, 6.0 Hz, 2H), 6.92 (s, 1H), 2.72 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.3 (C), 138.7 (C), 138.5 (C), 130.8 (CH), 130.2 (C), 128.5 (CH), 128.2 (CH), 127.5 (CH), 126.1 (CH), 124.4 (CH), 123.1 (CH), 118.5 (CH), 17.5 (CH_3); Selected

spectral data for the mixture: δ IR (thin film): 2116, 2083, 1479, 1443, 1278, 759 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{15}H_{13}N_3$ $(M)^+$ 235.11095, found 235.11230.



4.154

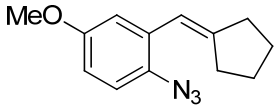
Styryl Azide 4.154. The general procedure for azidation was followed using 1.42 g of aniline **4.208** (7.6 mmol), 0.06 g of $CuSO_4$, freshly prepared dichloromethane solution of TfN_3 (from 22.8 mmol of Tf_2O), and 3.2 mL of Et_3N (22.8 mmol) in 10 mL of CH_2Cl_2, 5 mL of MeOH and 3 mL of H_2O. Purification by MPLC (100% hexane) afforded the product as a light yellow oil (1.36 g, 84%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.23 – 7.27 (m, 1H), 7.17 (d, *J* = 7.5 Hz, 1H), 7.13 (dd, *J* = 1.0 Hz, 8.0 Hz, 1H), 7.07 – 7.10 (m, 1H), 6.14 (s, 1H), 2.30 (t, *J* = 5.5 Hz, 2H), 2.25 (t, *J* = 5.5 Hz, 2H), 1.55 – 1.68 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 145.0 (C), 138.0 (C), 131.0 (CH), 130.2 (C), 127.5 (CH), 124.3 (CH), 118.3 (CH), 117.3 (CH), 37.5 (CH_2), 29.8 (CH_2), 28.6 (CH_2), 27.9 (CH_2), 26.7 (CH_2); IR (thin film): 2112, 2080, 1482, 1444, 1281, 836, 746, 836, 746, 725, 671 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{13}H_{15}N_3$ $(M)^+$ 213.12660, found 213.12686.



4.156

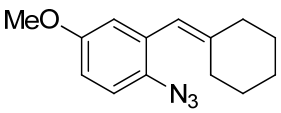
Styryl Azide 4.156. The general procedure for azidation was followed using 0.21 g of aniline **4.210** (1.1 mmol), 0.01 g of $CuSO_4$, freshly prepared dichloromethane solution of TfN_3 (from 3.0 mmol of Tf_2O), and 0.4 mL of Et_3N (3.0 mmol) in 4 mL of CH_2Cl_2, 2 mL of MeOH and 1 mL of H_2O. Purification by MPLC (100% hexane) afforded the product as a light yellow oil (0.18 g, 76%): ^1H NMR (500 MHz, $CDCl_3$) δ 7.19 – 7.26 (m, 2H), 7.08 – 7.14 (m, 2H), 6.25 (s, 1H),

2.45 (t, J = 6.0 Hz, 2H), 2.37 (t, J = 6.0 Hz, 2H), 1.58 – 1.70 (m, 8H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.8 (C), 137.8 (C), 130.6 (CH), 127.4 (CH), 124.3 (CH), 120.6 (CH), 118.3 (CH), 38.3 (CH_2), 31.3 (CH_2), 29.8 (CH_2), 29.3 (CH_2), 29.1 (CH_2), 27.3 (CH_2) one overlapping aromatic C not distinguishable; IR (thin film): 2919, 2113, 2079, 1572, 1480, 1443, 1281, 1085, 746 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{14}H_{17}N_3$ $(M)^+$ 227.14225 found 227.14169.



4.158

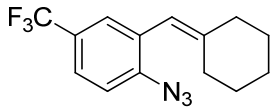
Styryl Azide 4.158. The general procedure for azidation was followed using 0.97 g of aniline **4.211** (4.8 mmol), 0.02 g of $CuSO_4$, freshly prepared dichloromethane solution of TfN_3 (from 14.4 mmol of Tf_2O), and 2.0 mL of Et_3N (14.4 mmol) in 6 mL CH_2Cl_2, 3 mL of MeOH and 2 mL of H_2O. Purification by MPLC (100% hexane) afforded the product as a light yellow oil (0.80 g, 73%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, J = 8.7 Hz, 1H), 6.93 (d, J = 2.8 Hz, 1H), 6.77 (dd, J = 8.7, 2.9 Hz, 1H), 6.43 (s, 1H), 3.80 (s, 3H), 2.46 – 2.52 (m, 4H), 1.71 – 1.78 (m, 2H), 1.71 – 1.66 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.4 (C), 149.3 (C), 131.6 (C), 129.8 (C), 119.1 (CH), 115.3 (CH), 114.6 (CH), 112.5 (CH), 55.5 (CH_3), 35.5 (CH_2), 31.2 (CH_2), 27.0 (CH_2), 25.6 (CH_2); IR (thin film): 2953, 2115, 2080, 1480, 1446, 744 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{13}H_{15}ON_3$ $(M)^+$ 229.12152, found 229.12192.



4.160

Styryl Azide 4.160. The general procedure for azidation was followed using 0.21 g of aniline **4.212** (1.0 mmol), 0.01 g of $CuSO_4$, freshly prepared dichloromethane solution of TfN_3 (from 3.0 mmol of Tf_2O), and 1.3 mL of Et_3N (3.0 mmol) in 3 mL of CH_2Cl_2, 2 mL of MeOH and 1 mL of

H_2O. Purification by MPLC (100% hexane) afforded the product as a light yellow oil (0.41 g, 43%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.04 (d, J = 9.0 Hz, 1H), 6.80 (dd, J = 3.0 Hz, 8.5 Hz, 1H), 6.72 (d, J = 3.0Hz, 1H), 6.12 (s, 1H), 3.79 (s, 3H), 2.26 – 2.31 (m, 4H), 1.56 – 1.67 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.3 (C), 145.3 (C), 131.3 (C), 130.6 (C), 119.3 (CH), 117.4 (CH), 116.4 (CH), 112.8 (CH), 55.5 (CH_3), 37.4 (CH_2), 29.9 (CH_2), 28.6 (CH_2), 27.8 (CH_2), 26.6 (CH_2); IR (thin film): 2106, 2084, 1486, 1284, 1239, 1165, 1035, 798, 732 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{14}H_{17}ON_3$ $(M)^+$ 243.1372, found 243.1372.

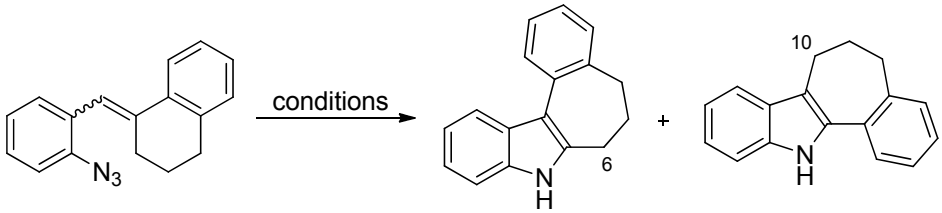


4.162

Styryl Azide 4.162. The general procedure for azidation was followed using 1.60 g of aniline **4.213** (6.3 mmol), 0.04 g of $CuSO_4$, freshly prepared dichloromethane solution of TfN_3 (from 18.8 mmol of Tf_2O), and 2.6 mL of Et_3N (18.8 mmol) in 8 mL of CH_2Cl_2, 4 mL of MeOH and 3 mL of H_2O. Purification by MPLC (100% hexane) afforded the product as a light yellow oil (0.04 g, 3%): ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.49 (dd, J = 8.5 Hz, 2.0 Hz, 1H), 7.40 (s, 1H), 7.20 (d, J = 7.0 Hz, 1H), 6.11 (s, 1H), 2.30 (t, J = 5.5 Hz, 2H), 2.22 (t, J = 5.5 Hz, 2H), 1.54 – 1.70 (m, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 146.7 (C), 141.5 (C), 130.6 (C), 128.2 (q, J_{CF} = 3.6 Hz, CH), 126.4 (q, J_{CF} = 31.4 Hz, C), 124.4 (q, J_{CF} = 3.4 Hz, CH), 124.0 (q, J_{CF} = 270.1 Hz, C), 118.5 (CH), 116.3 (CH), 37.4 (CH_2), 29.8 (CH_2), 28.5 (CH_2), 27.8 (CH_2), 26.5 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –61.62; IR (thin film): 2929, 2120, 2088, 1329, 1289, 1106, 817 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{14}H_{14}NF_3$ $(M - N_2)^+$ 255.1000, found 255.1000.

4.14.4 Development of Rhodium-Catalyzed Migration Reaction

General Procedure for the Screening of Catalysts to Promote the Migration



4.127 **4.128** **4.129** (eq. 14)

To a mixture of 0.026 g of aryl azide **4.127** (0.1 mmol), 0-100 % w/w of crushed 4 Å mol sieves, and metal salt (0 – 5 mol %) in Schlenk tube was added 0.50 mL of solvent. The resulting mixture was heated and, after 16 h, the heterogenous mixture was filtered through a short pad of Al_2O_3. The filtrate was concentrated *in vacuo*. The resulting solid (oil) was dissolved in 1.5 mL of $CDCl_3$ and 0.007 mL of dibromomethane (0.1 mmol) was added. The areas of the C–H peak on the carbon 6 position in **4.128** and carbon 10 in **4.129** were compared to the area of CH_2Br_2 to derive a yield.

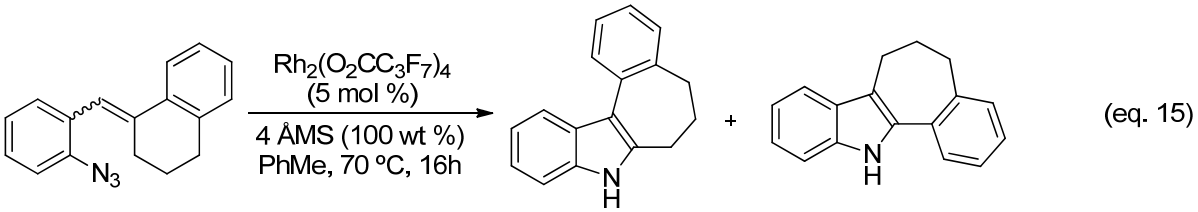
Table 4.5. Optimization of Migration Process[a,b]

Entry	metal salt	Mol %	solvent	wt %, 4 Å MS	T (°C)	yield, %[c]	**6** : **7**
1	none	n.a.	xylenes	0	170		xx:xx
2	$Rh_2(O_2CCH_3)_4$	5	PhMe	100	70	8	n.a.
3	$Rh_2(O_2CCF_3)_4$	5	PhMe	100	70	86	100:0
4	$Rh_2(O_2CC_3F_7)_4$	5	PhMe	100	70	95	100:0
5	$Rh_2(O_2CC_7H_{15})_4$	5	PhMe	100	70	93	96:4
6	$Rh_2(O_2CC_7H_{15})_4$	3	PhMe	100	70	80[d]	96:4
7	$Rh_2(O_2CC_7H_{15})_4$	3	PhMe	100	60	88[e]	96:4
8	$Rh_2(O_2CC_7H_{15})_4$	5	PhMe	100	80	95	96:4
9	$Rh_2(O_2CC_7H_{15})_4$	5	DCE	100	60	74[f]	96:4
10	$Rh_2(O_2CC_7H_{15})_4$	5	DCE	100	70	94	98:2
11	$Rh_2(O_2CC_7H_{15})_4$	5	DCE	100	80	88	96:4
12	$Rh_2(esp)_2$	5	PhMe	100	70	98	>98:2
13	$RhCl_3$	5	PhMe	100	70	0	n.a.

14	$(Ph_3P)_3RuCl$	5	PhMe	100	70	trace	n.a.
15	$Cu(OTf)_2$	5	PhMe	100	70	0	n.a.
16	Ru(TPFPP)CO	5	IPAC	0		48	100:0

[a] Reaction performed in conical vial. [b] 16 hour reaction time. [c] As determined using ^{1}H NMR spectroscopy. [d] xx % of **5** remained (*E* : *Z* = xx : xx). [e] 10 % of **5** remained (*E* : *Z* = 74 : 26). [f] 23% of **5** remained (*E* : *Z* = 80 : 20)

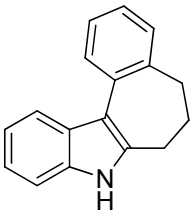
Optimized General Procedure



4.127 **4.128** **4.129** (eq. 15)

To a mixture of 0.026 g of aryl azide **4.127** (0.1 mmol), 100 % w/w of crushed 4 Å mol sieves, and metal salt ($Rh_2(esp)_4$ or $Rh_2(hpfb)_4$, 5 mol %) in Schlenk tube was added 0.50 mL of PhMe. The resulting mixture was heated at 70 °C for 16 h, then, the heterogenous mixture was filtered through a short pad of Al_2O_3. The filtrate was concentrated *in vacuo* to afford analytically pure indole. In some cases, purification by MPLC is required.

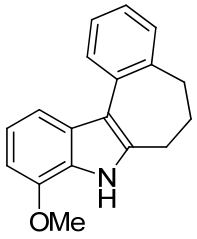
Effect of Aryl Azide Substitution on Rhodium-Catalyzed Migration Selectivity



4.128

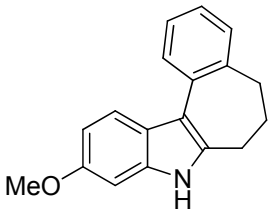
Indole 4.128. The general procedure was followed using 0.027 g of styryl azide **4.127** (0.102 mmol) and 0.005 g of $Rh_2(hpfb)_4$ (0.005 mmol) in 0.5 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.128** (0.025, 95%). mp 125 – 127 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.94 – 7.96 (m, 2H), 7.87 (d, *J* = 7.5 Hz, 1H), 7.34 – 7.40 (m, 2H), 7.30 (d, *J* = 7.5 Hz, 1H), 7.18 – 7.24 (m, 3H), 2.94 (t, *J* = 7.5 Hz, 2H), 2.76 – 2.78 (m, 2H), 2.23 – 2.29 (m, 2H); ^{13}C NMR

(125 MHz, $CDCl_3$) δ 141.0 (C), 136.9 (C), 135.7 (C), 135.1 (C), 129.3 (CH), 127.9 (CH), 127.3 (C), 126.3 (CH), 125.3 (CH), 121.6 (CH), 120.1 (CH), 119.2 (CH), 112.8 (C), 110.6 (CH), 33.5 (CH_2), 30.1 (CH_2), 26.5 (CH_2); IR (thin film): 3396, 1599, 1492, 1459, 1275, 906, 745 cm^{-1}. HRMS (EI) *m* / *z* calcd for $C_{17}H_{15}N$ $(M)^+$ 233.12054, found 233.11957.



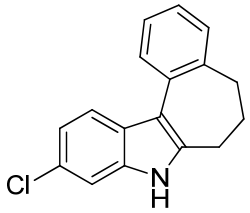
4.215

Indoles 4.215 The general procedure was followed using 0.0291 g of styryl azide **4.196** (0.100 mmol) and 0.0053 g of $Rh_2(hpfb)_4$ (0.005 mmol) in 0.5 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.215** (0.0252 g, 96%) as a colorless oil. ^1H NMR (500 MHz, $CDCl_3$) δ 8.31 (br, 1H), 7.88 (dd, *J* = 1.0 Hz, 7.5 Hz, 1H), 7.57 (d, *J* = 8.0 Hz, 1H), 7.38 (dt, *J* = 1.5 Hz, 7.5 Hz, 1H), 7.30 (dd, *J* = 1.0 Hz, 7.5 Hz, 1H), 7.21 (dt, *J* = 1.5 Hz, 7.5 Hz, 1H), 7.13 (t, *J* = 8.0 Hz, 1H), 6.71 (d, *J* = 8.0 Hz, 1H), 4.02 (s, 3H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.79 – 2.76 (m, 2H), 2.30 – 2.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 164.0 (C), 145.8 (C), 141.0 (C), 136.5 (C), 135.4 (C), 129.3 (CH), 128.6 (C), 128.0 (CH), 126.3 (CH), 125.2 (CH), 120.5 (CH), 113.3 (C), 112.2 (CH), 101.8 (CH), 55.4 (CH_3), 33.6 (CH_2), 30.2 (CH_2), 26.4 (CH_2); IR (thin film): 3443, 2941, 1497, 1264, 733 cm^{-1}. HRMS (EI) *m* / *z* calcd for $C_{18}H_{17}ON$ $(M)^+$ 263.13102, found 263.13028.



4.216

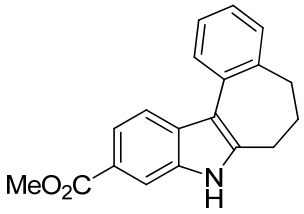
Indoles 4.216. The general procedure was followed using 0.0291 g of styryl azide **4.197** (0.100 mmol) and 0.0053 g of $Rh_2(hpfb)_4$ (0.005 mmol) in 0.5 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.216** (0.0254 g, 97%) as a white solid; mp 164 – 166 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.85 – 7.83 (m, 2H), 7.81 (d, *J* = 7.5 Hz, 1H), 7.35 (dt, *J* = 1.5 Hz, 7.5 Hz, 1H), 7.27 (dd, *J* = 1.0 Hz, 7.5 Hz, 1H), 7.21 (dt, *J* = 1.0 Hz, 7.5 Hz, 1H), 6.85 (dd, *J* = 2.5 Hz, 8.5 Hz, 1H), 6.82 (d, *J* = 1.5 Hz, 1H), 3.85 (s, 3H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.77 – 2.75 (m, 2H), 2.23 – 2.17 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 156.0 (C), 141.1 (C), 136.6 (C), 135.6 (C), 135.0 (C), 129.3 (CH), 127.8 (CH), 126.3 (CH), 125.2 (CH), 121.7 (C), 120.0 (CH), 112.5 (C), 109.3 (CH), 94.7 (CH), 55.8 (CH_3), 33.7 (CH_2), 29.5 (CH_2), 26.8 (CH_2); IR (thin film): 3399, 2937, 1461, 1264, 738 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{18}H_{17}ON$ $(M)^+$ 263.13102, found 263.13140.



4.217

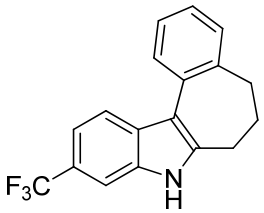
Indoles 4.217. The general procedure was followed using 0.0295 g of styryl azide **4.198** (0.100 mmol) and 0.0053 g of $Rh_2(hpfb)_4$ (0.005 mmol) in 0.5 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.217** (0.0264 g, 99%) as a colorless oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.92 (br, 1H), 7.82 (d, *J* = 8.5 Hz, 1H), 7.79 (dd, *J* = 1.5 Hz, 7.5 Hz, 1H), 7.37 (dt, *J* = 1.5 Hz, 7.5 Hz, 1H), 7.32 – 7.28 (m, 2H), 7.21 (dt, *J* = 1.5 Hz, 6.5 Hz, 1H), 7.14 (dd, *J* = 2.0 Hz, 6.5 Hz, 1H), 2.91 (t, *J* = 7.5 Hz, 2H), 2.78 – 2.74 (m, 2H), 2.26 – 2.21 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.1 (C), 137.5 (C), 136.1 (C), 134.5 (C), 129.4 (CH), 127.8 (CH), 127.3 (C), 126.4 (CH), 126.0 (C), 125.6 (CH), 120.7 (CH), 120.1 (CH), 112.9 (C), 110.5 (CH), 33.5

(CH_2), 29.8 (CH_2), 26.6 (CH_2); IR (thin film): 3401, 2929, 1462, 1275, 749 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{17}H_{14}NCl$ $(M)^+$ 267.08147, found 267.08182.



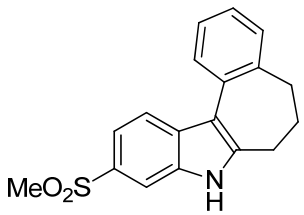
4.218

Indoles 4.218. The general procedure was followed using 0.0319 g of styryl azide **4.199** (0.100 mmol) and 0.0038 g of $Rh_2(esp)_2$ (0.005 mmol) in 0.5 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.218** (0.0274 g, 94%) as a white solid; mp 203 – 205 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.55 (br, 1H), 8.11 (d, *J* = 1.5 Hz, 1H), 7.91 (d, *J* = 8.5 Hz, 1H), 7.85 (dd, *J* = 1.5 Hz, 8.5 Hz, 1H), 7.79 (dd, *J* = 1.0 Hz, 8.0 Hz, 1H), 7.37 (dt, *J* = 1.5 Hz, 7.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.20 (dt, *J* = 1.5 Hz, 7.5 Hz, 1H), 3.96 (s, 3H), 2.97 (t, *J* = 7.5 Hz, 2H), 2.75 – 2.72 (m, 2H), 2.30 – 2.25 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.4 (C), 140.9 (C), 140.8 (C), 135.0 (C), 134.5 (C), 130.9 (C), 129.4 (CH), 127.9 (CH), 126.4 (CH), 125.7 (CH), 122.9 (C), 121.3 (CH), 118.6 (CH), 113.5 (C), 112.9 (CH), 52.0 (CH_3), 33.3 (CH_2), 30.2 (CH_2), 26.4 (CH_2); IR (thin film): 3656, 2950, 1690, 1503, 1217, 1062, 911 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{19}H_{17}O_2N$ $(M)^+$ 291.12593, found 291.12553.



4.219

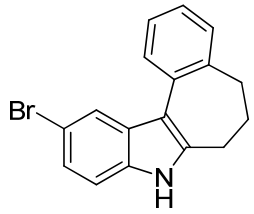
Indole 4.219. The general procedure was followed using 0.046 g of styryl azide **4.200** (0.140 mmol) and 0.007 g of $Rh_2(hpfb)_4$ (0.007 mmol) in 0.6 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.219** (0.038 g, 90%). ^{1}H NMR (500 MHz, $CDCl_3$): 8.18 (s, 1H), 7.98 (d, *J* = 8.5 Hz, 1H), 7.80 (d, *J* = 7.5 Hz, 1H), 7.06 (s, 1H), 7.38 – 7.42 (m, 2H), 7.31 -7.32 (m, 1H), 7.22 – 7.26 (m, 1H), 2.95 (t, 7.5 Hz, 2H), 2.73 – 2.76 (m, 2H), 2.24 – 2.30 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): 141.0 (C), 139.7 (C), 134.6 (C), 134.3 (C), 129.6 (C), 129.5 (CH), 127.9 (CH), 126.5 (CH), 125.8 (CH), 125.3 (q, *J* = 269.9 Hz, C), 123.5 (q, *J* = 31.8 Hz, C), 119.4 (CH), 116.8 (q, *J* = 3.5 Hz, CH), 113.2 (C), 108.1 (q, *J* = 4.8 Hz, CH), 33.3 (CH_2), 30.1 (CH_2), 26.4 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) ; IR (thin film): 3401, 2940, 1740, 1728, 1333, 1217, 1111, 1057 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{18}H_{14}NF_3$ $(M)^+$ 301.10783, found 301.10748.



4.220

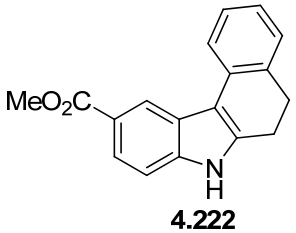
Indoles 4.220. The general procedure was followed using 0.0339 g of styryl azide **4.201** (0.100 mmol) and 0.0053 g of $Rh_2(hpfb)_4$ (0.005 mmol) in 0.5 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.220** (0.0295 g, 95%) as a white solid; mp 159 – 161 °C. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.23 (br, 1H), 8.11 (d, *J* = 1.0 Hz, 1H), 7.97 (d, *J* = 8.5 Hz, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.65 (dd, *J* = 1.0 Hz, 8.5 Hz, 1H), 7.36 (dt, *J* = 1.0 Hz, 7.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.21 (dt, *J* = 1.0 Hz, 7.5 Hz, 1H), 3.13 (s, 3H), 2.99 (t, *J* = 7.5 Hz, 2H), 2.71(t, *J* = 6.0 Hz, 2H), 2.29 – 2.24 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 142.4 (C), 140.9 (C), 134.5 (C), 134.1 (C), 132.0 (C), 131.0 (C), 129.1 (CH), 127.8 (CH), 126.5 (CH), 126.0 (CH), 119.6 (CH), 118.2 (CH), 113.4 (C), 111.0 (CH), 45.3 (CH_3), 33.2 (CH_2), 30.2 (CH_2), 26.2

(CH_2); IR (thin film): 3351, 2928, 1498, 1265, 1141, 740 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{18}H_{17}O_2NS$ $(M)^+$ 311.09800, found 311.09821.



4.221

Indoles 4.221. The general procedure was followed using 0.0340 g of styryl azide **4.202** (0.100 mmol) and 0.0053 g of $Rh_2(hpfb)_4$ (0.005 mmol) in 0.5 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.221** (0.0295 g, 95%) as a white solid; mp 146 – 148 °C. ^1H NMR (500 MHz, $CDCl_3$) δ 8.03 (d, *J* = 1.5 Hz, 1H), 8.00 (br, 1H), 7.76 (d, *J* = 7.5 Hz, 1H), 7.37 (dt, *J* = 1.5 Hz, 7.5 Hz, 1H), 7.29 – 7.26 (m, 2H), 7.21 (dt, *J* = 1.0 Hz, 6.5 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 1H), 2.92 (t, *J* = 7.5 Hz, 2H), 2.74 – 2.72 (m, 2H), 2.27 – 2.22 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 140.9 (C), 138.2 (C), 134.4 (C), 134.3 (C), 129.4 (CH), 129.0 (C), 127.8 (CH), 126.5 (CH), 125.7 (CH), 124.3 (CH), 121.6 (CH), 113.5 (C), 112.6 (C), 111.9 (CH), 33.4 (CH_2), 30.1 (CH_2), 26.4 (CH_2); IR (thin film): 3411, 2936, 1469, 1264, 740 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{17}H_{14}NBr$ $(M)^+$ 313.02891, found 313.03030.

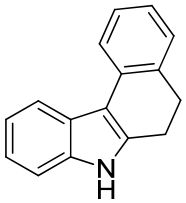


4.222

Indole 4.222. The general procedure was followed using 0.0319 g of styryl azide **4.203** (0.100 mmol) and 0.0038 g of $Rh_2(esp)_2$ (0.005 mmol) in 0.5 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.222** (0.0276 g, 95%) as a white solid; mp 244 – 246 °C. ^1H NMR (500 MHz, acetone-d_6) δ 10.65 (br, 1H), 8.57 (s, 1H), 7.82 (dd, *J* = 1.0 Hz, 8.5 Hz, 1H), 7.79 (d,

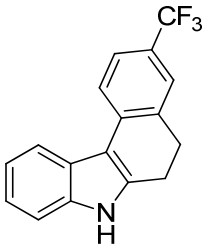
J = 7.5 Hz, 1H), 7.46 (d, J = 8.5 Hz, 1H), 7.37 (dt, J = 1.5 Hz, 7.5 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 7.17 (dt, J = 1.5 Hz, 7.5 Hz, 1H), 3.87 (s, 3H), 3.04 (t, J = 7.5 Hz, 2H), 2.74 – 2.72 (m, 2H), 2.24 – 2.19 (m, 2H); ^{13}C NMR (125 MHz, acetone-d_6) δ 167.5 (C), 141.2 (C), 139.3 (C), 139.0 (C), 134.6 (C), 129.3 (CH), 127.7 (CH), 126.8 (C), 126.3 (CH), 125.4 (CH), 122.4 (CH), 121.6 (C), 121.2 (CH), 112.9 (C), 110.6 (CH), 51.0 (CH_3), 33.3 (CH_2), 29.6 (CH_2), 26.1 (CH_2); IR (thin film): 3643, 2951, 1737, 1231, 1062, 913, 857 cm^{-1}. HRMS (EI) m / z calcd for $C_{19}H_{17}O_2N$ $(M)^+$ 291.12593, found 291.12504.

Effect of Migrating Group Identity on Rhodium-Catalyzed Migration Selectivity



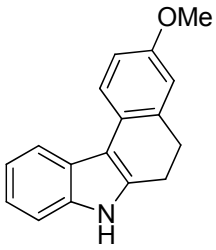
4.137

Indole 4.137.[50] The general procedure was followed using 0.041 g of styryl azide **4.136** (0.17 mmol) and 0.006 g of $Rh_2(esp)_4$ (0.008 mmol) in 0.7 mL of PhMe. Filtration by Al_2O_3 afforded a 98:2 mixture; Purification by MPLC (10:100 EtOAc: hexanes) afforded compound **4.137** as a white powder (0.032 g, 88%); Indole **12a** was previously reported by Katritzky and Wang:[50] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.05 (d, J = 7.5 Hz, 1H), 7.95 (s, 1H), 7.88 (d, J = 7.5 Hz, 1H), 7.31 – 7.36 (m, 2H), 7.19 – 7.27 (m, 3H), 7.09 – 7.12 (m, 1H), 3.05 – 3.08 (t, J = 7.5 Hz, 2H), 2.93 – 2.96 (t, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$): δ 137.2 (C), 136.2 (C), 133.9 (C), 133.3 (C), 128.0 (CH), 127.0 (CH), 125.0 (C), 124.3 (CH), 122.3 (CH), 121.5 (CH), 120.6 (CH), 119.5 (CH), 111.1 (CH), 110.8 (C), 29.5 (CH_2), 22.5 (CH_2); IR (thin film): 3396, 1601, 1497, 1456, 1255, 908, 767, 731 cm^{-1}.



4.139

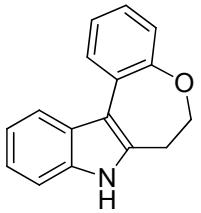
Indole 4.139. The general procedure was followed using 0.050 g of styryl azide **4.138** (0.16 mmol) and 0.006 g of $Rh_2(esp)_4$ (0.008 mmol) in 0.6 mL of PhMe. Filtration by Al_2O_3 afforded a 95:5; Purification by MPLC (10:100 EtOAc: hexanes) afforded compound **4.139** as a light yellow powder (0.031 g, 78%); mp 227 -230 °C; ^{1}H NMR (500 MHz, DMSO) δ 8.03 (d, J = 7.5 Hz, 1H), 7.93 – 7.95 (m, 1H), 7.37 – 7.45 (m, 3H), 7.11 – 7.13 (m, 2H), 3.10 (t, J = 7.5 Hz, 2H), 2.98 (t, J = 8.0 Hz, 2H), *N-H peak not available*; ^{13}C NMR (125 MHz, DMSO) δ 139.2 (C), 136.9 (C), 136.4 (C), 131.6 (C), 127.53 (CH), 127.49 (q, J_{CF} = 27.8 Hz, C), 126.0 (CH), 125.3 (q, J_{CF} = 272.0 Hz, C), 124.6, 121.5 (CH), 120.9 (q, J_{CF} = 5.5 Hz, CH), 120.6 (CH), 119.1 (CH), 112.2 (CH), 108.3 (C), 25.5 (CH_2), 21.5 (CH_2); IR (thin film): 3406, 1601, 1557, 1452, 1311, 1162, 1108, 749 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{17}H_{12}NF_3$ $(M)^+$ 287.09218, found 287.09182.



4.141

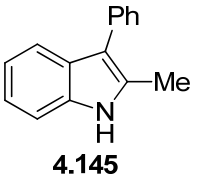
Indole 4.141. The general procedure was followed using 0.041 g of styryl azide **4.140** (0.141 mmol) and 0.005 g of $Rh_2(esp)_4$ (0.007 mmol) in 0.5 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.141** (0.034 g, 92%). ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.99 (s, 1H), 7.56 (d, J = 7.5 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.15 (t, J = 7.5 Hz, 1H), 6.82 – 6.85 (m, 2H), 3.86 (s, 3H), 3.11 (t, J = 7.0 Hz, 2H), 2.89 –

2.91 (m, 2H), 2.15 – 2.19 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7 (C), 144.0 (C), 136.1 (C), 132.7 (C), 130.2 (C), 126.4 (CH), 124.6 (C), 122.4 (CH), 119.5 (CH), 118.4 (CH), 115.5 (CH), 113.1 (C), 111.5 (CH), 110.5 (CH), 55.3 (CH_3), 35.6 (CH_2), 26.7 (CH_2), 26.0 (CH_2); IR (thin film): 3414, 2926, 2834, 1605, 1461, 1433, 1260, 1243, 1033, 810, 735 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{18}H_{17}ON$ $(M)^+$ 263.13102, found 263.13192.



4.143

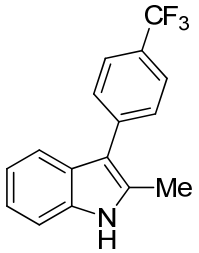
Indole 4.143. The general procedure was followed using 0.052 g of styryl azide **4.142** (0.198 mmol) and 0.008 g of $Rh_2(esp)_4$ (0.010 mmol) in 0.7 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.143** (0.044 g, 94%). mp 175 -177 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.14 (d, *J* = 7.5 Hz, 1H), 8.10 (d, *J* = 7.5 Hz, 1H), 8.04 (s, 1H), 7.31 – 7.32 (m, 1H), 7.12 – 7.26 (m, 5H), 4.39 (t, *J* = 6.0 Hz, 2H), 3.32 (t, *J* = 6.0 Hz, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 158.7 (C), 136.5 (C), 134.8 (C), 128.4 (CH), 127.3 (C), 127.0 (C), 125.9 (CH), 123.8 (CH), 122.1 (CH), 121.1 (CH), 120.3 (CH), 120.2 (CH), 110.6 (CH), 109.7 (C), 70.0 (CH_2), 31.0 (CH_2); IR (thin film): 3348, 1492, 1459, 1441, 1196, 905, 748 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{16}H_{13}ON$ $(M)^+$ 235.09972, found 235.10055.



4.145

Indole 4.145.[51] The general procedure was followed using 0.044 g of styryl azide **4.144** (0.187 mmol) and 0.007 g of $Rh_2(esp)_4$ (0.009 mmol) in 0.6 mL of PhMe (reaction is set up at 80 °C). Filtration by Al_2O_3 afforded analytically pure compound **4.145** (0.035 g, 91%). Spectral data for

4.145 matched that reported by Tan and Hartwig:[51] ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.93 (s, 1H), 7.69 (d, J = 8.0 Hz, 1H), 7.53 – 7.55 (m, 2H), 7.47 – 7.50 (m, 2H), 7.31 – 7.35 (m, 2H), 7.17 – 7.20 (m, 1H), 7.12 – 7.15 (m, 1H), 2.52 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5 (C), 135.3 (C), 131.4 (C), 129.5 (CH), 128.5 (CH), 127.9 (C), 125.8 (CH), 121.6 (CH), 120.0 (CH), 118.8 (CH), 114.6 (C), 110.3 (CH), 12.6 (CH_3); IR (thin film): 3401, 1603, 1496, 1459, 1258, 908, 748, 702 cm^{-1}.

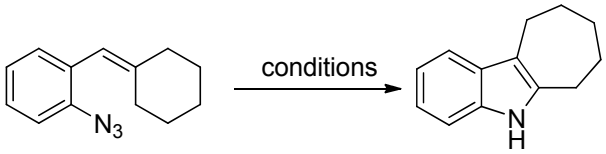


4.147

Indole 4.147.[52] The general procedure was followed using 0.036 g of styryl azide **4.146** (0.117 mmol) and 0.005 g of $Rh_2(esp)_4$ (0.006 mmol) in 0.5 mL of PhMe (reaction is set up at 80 °C). Filtration by Al_2O_3 afforded analytically pure compound **4.147** (0.030 g, 93%). Indole **4.147** was previously reported by Chiba and co-workers.[52] Spectral data for **4.147**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.02 (s, 1H), 7.73 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 7.5 Hz, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.22 (dt, J = 1.0 Hz, 8.0 Hz, 1H), 7.16 (dt, J = 1.0 Hz, 7.5 Hz, 1H), 2.53 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.4 (C), 135.3 (C), 132.2 (C), 129.4 (CH), 127.7 (q, J_{CF} = 32.8 Hz, C), 127.5 (C), 125.5 (q, J_{CF} = 3.5 Hz, CH), 124.5 (q, J_{CF} = 269.9 Hz, C), 122.0 (CH), 120.4 (CH), 118.5 (CH), 113.4 (C), 110.5 (CH), 12.6 (CH_3); IR (thin film): 3397, 1615, 1459, 1234, 1163, 1109, 1068, 747 cm^{-1}.

Effect of Ring Size on Rhodium-Catalyzed Migration

A. General Procedure for the Optimization of Conditions to Promote the Migration



4.154 **4.155** (eq. 16)

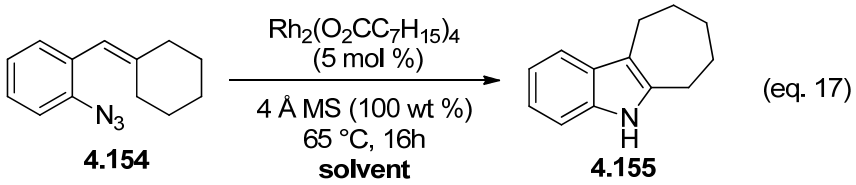
To a mixture of 0.1 mmol of aryl azide **4.154** (0.1 mmol), 0-100 % w/w of crushed 4 Å mol sieves, and metal salt (0 – 5 mol %) in Schlenk tube was added 0.50 mL of solvent. The resulting mixture was heated and, after 16 h, the heterogenous mixture was filtered through a short pad of Al_2O_3. The filtrate was concentrated *in vacuo*. The resulting solid (oil) was dissolved in 1.5 mL of $CDCl_3$ and 0.007 mL of dibromomethane (0.1 mmol) was added.

Table 4.6. Optimization of migration process.

entry	metal salt	mol %	wt %, 4 Å MS	temp (°C)	yield, %[a]
1	None	n.a.	0	150	>95
2	$Rh_2(O_2CC_7H_{15})_4$	5	100	55	33
3	$Rh_2(O_2CC_7H_{15})_4$	5	100	65	63
4	$Rh_2(O_2CC_7H_{15})_4$	5	0	65	53
5	$Rh_2(O_2CC_7H_{15})_4$	3	100	65	39
6	$Rh_2(O_2CC_7H_{15})_4$	5	100	80	90
7	$[Ir(cod)OMe]_2$	5	100	80	0
8	$Rh_2(esp)_2$	5	100	80	20
9	$RhCl(PPh_3)_3$	5	100	80	0
10	$Rh_2(O_2CC_3F_7)_4$	5	100	80	66
11	$RhCl_3$	5	100	80	0
12	$Rh_2(O_2CCH_3)_4$	5	100	80	0
13	$Rh_2(O_2CCF_3)_4$	5	100	80	34
14	$RuCl_3.xH_2O$	5	100	65	trace
15	$RuCl_3.xH_2O$	5	0	65	trace
16	$Rh_2(O_2CC_7H_{15})_4$	5	100	65(40)	90
17	Co TPP	5	100	65	0
18	Ag(OTf)	5	100	65	0
19	$Cu(OTf)_2$	5	100	65	0
20	$Rh_2(O_2CC_7H_{15})_4$	5	100	75	59
21	ZnI_2	10	100	65	0
22	$FeBr_2$	20	100	65	0
23	AuCl	10	100	65	0

[a] Isolated yield after Al_2O_3 chromatography.

B. Optimization of Solvent

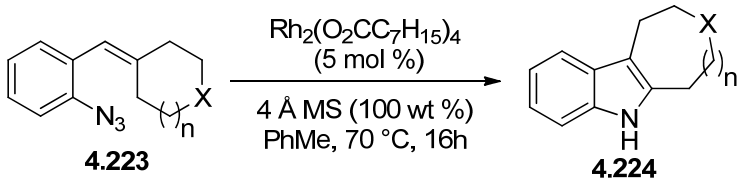


4.154 **4.155** (eq. 17)

solvent	PhMe	1,2-DCE	1,4-dioxane	DME	DMF
yield, %[a]	63%	66%	0	0	0

[a] Isolated yield after Al_2O_3 chromatography.

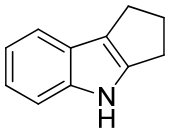
C. Optimized Procedure for Ring Expansion



4.223 **4.224** (eq. 18)

To a mixture of 0.026 g of aryl azide **4.223** (0.1 mmol), 100 % w/w of crushed 4 Å mol sieves, and metal salt ($Rh_2(O_2CC_7H_{15})_4$, 5 mol %) in Schlenk tube was added 0.50 mL of PhMe. The resulting mixture was heated at 80 °C for 16 h, then, the heterogenous mixture was filtered through a short pad of Al_2O_3. The filtrate was concentrated *in vacuo* to afford analytically pure indole.

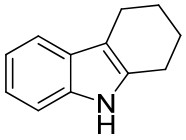
D. Scope and Limitations of Ring Expansion



4.151

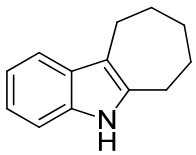
Indole 4.151.[51] The general procedure was followed using 0.035 g of styryl azide **4.150** (0.189 mmol) and 0.007 g of $Rh_2(O_2CC_7H_{15})_4$ (0.009 mmol) in 0.6 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.151** (0.029 g, 98%). Indole **4.151** was previously reported by Tan and Hartwig.[51] mp 58 - 61 °C; ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.74 (s, 1H), 7.47 – 7.49 (m, 1H), 7.29 – 7.31 (m, 1H), 7.12 – 7.14 (m, 2H), 2.86 -2.89 (m, 4H), 2.56 – 2.59 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 143.8 (C), 141.0 (C), 124.8 (C), 120.5 (CH), 119.8 (C), 119.5 (CH),

118.5 (CH), 111.4 (CH), 28.7 (CH_2), 25.9 (CH_2), 24.5 (CH_2); IR (thin film): 3400, 2951, 2853, 1467, 1313, 913, 736 cm^{-1}.



4.153

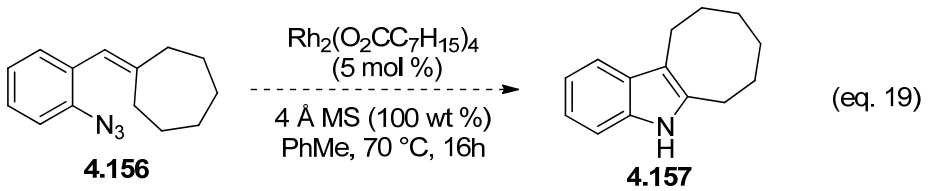
Indole 4.153.[53] The general procedure was followed using 0.055 g of styryl azide **4.152** (0.276 mmol) and 0.011 g of $Rh_2(O_2CC_7H_{15})_4$ (0.014 mmol) in 0.7 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.153** (0.044 g, 93%). The spectral data for **4.153** matched that reported by Leogane and Lebel[1]H NMR:[53] (500 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.48 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.08 – 7.15 (m, 2H), 2.73 (t, *J* = 6.0 Hz, 4H), 1.87 – 1.96 (m, 4H); [13]C NMR (125 MHz, $CDCl_3$) δ 135.7 (C), 134.1 (C), 127.9 (C), 121.0 (CH), 119.1 (CH), 117.7 (CH), 110.4 (CH), 110.2 (C), 23.34 (CH_2), 23.26 (CH_2), 21.0 (CH_2) one overlapping aliphatic C not distinguishible; IR (thin film): 3397, 1667, 1603, 1497, 1456, 1276, 911, 749 cm^{-1}.



4.155

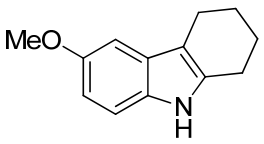
Indole 4.155[54] The general procedure was followed using 0.051 g of styryl azide **4.154** (0.239 mmol) and 0.009 g of $Rh_2(O_2CC_7H_{15})_4$ (0.012 mmol) in 0.6 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.155** (0.041 g, 93%). The spectral data for **4.155** matched that reported by Banwell and co-workers:[54] mp 140 - 142 °C; [1]H NMR (500 MHz, $CDCl_3$) δ 7.61 (s, 1H), 7.15 – 7.53 (m, 1H), 7.26 – 7.27 (m, 1H), 7.11 – 7.15 (m, 2H), 2.82 -2.87 (m, 4H), 1.91

– 1.94 (m, 2H), 1.81 – 1.83 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 137.5 (C), 134.3 (C), 129.3 (C), 120.6 (CH), 119.1 (CH), 117.7 (CH), 113.8 (C), 110.3 (CH), 31.9 (CH_2), 29.6 (CH_2), 28.8 (CH_2), 27.6 (CH_2), 24.7 (CH_2); IR (thin film): 3391, 2914, 2844, 1465, 1438, 913, 743 cm^{-1}.



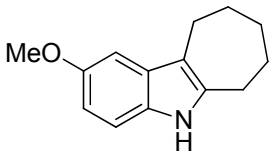
4.156 **4.157** (eq. 19)

Indole 4.157. The general procedure was followed using 0.046 g of styryl azide **4.156** (0.203 mmol) and 0.008 g of $Rh_2(O_2CC_7H_{15})_4$ (0.010 mmol) in 0.6 mL of PhMe. Analysis of the reaction progress using ^{1}H NMR spectroscopy revealed that 18% of indole **4.157** formed and 35% starting of aryl azide **4.156** remained.



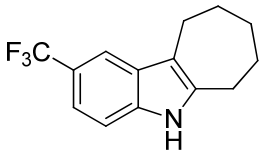
4.159

Indole 4.159. The general procedure was followed using 0.061 g of styryl azide **4.158** (0.266 mmol) and 0.010 g of $Rh_2(O_2CC_7H_{15})_4$ (0.013 mmol) in 0.7 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.159** (0.054 g, 100%). Spectral data for **4.159**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.56 (s, 1H), 7.16 (d, J = 9.0 Hz, 1H), 6.97(d, J = 2.5 Hz, 1H), 6.81 (dd, J = 2.5 Hz, 9.0 Hz, 1H), 3.89 (s, 3H), 2.70 – 2.72 (m, 4H), 1.89 – 1.95 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9 (C), 135.2 (C), 130.8 (C), 128.2 (C), 111.0 (CH), 110.5 (CH), 110.0 (C), 100.4 (CH), 56.0 (CH_3), 23.38 (CH_2), 23.27 (CH_2), 21.0 (CH_2) one overlapping aliphatic carbon signal not distinguishable; IR (thin film): 3281, 2936, 1659, 1492, 1274, 1214, 1030, 732 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{13}H_{15}ON$ $(M)^+$ 201.11537, found 201.11616.



4.161

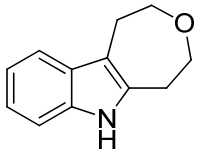
Indole 4.161. The general procedure was followed using 0.045 g of styryl azide **4.160** (0.201 mmol) and 0.008 g of $Rh_2(O_2CC_7H_{15})_4$ (0.010 mmol) in 0.5 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.161** (0.039 g, 100%). mp 42 - 46 °C; Spectral data for **4.161**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.58 (s, 1H), 7.14 (d, J = 8.5 Hz, 1H), 6.97(d, J = 2.5 Hz, 1H), 6.79 (dd, J = 2.5 Hz, 8.5 Hz, 1H), 3.89 (s, 3H), 2.79 – 2.81(m, 4H), 1.90 – 1.92 (m, 2H), 1.79 – 1.81 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.9 (C), 138.6 (C), 129.6 (C), 129.4 (C), 113.6 (C), 110.9 (CH), 110.4 (CH), 100.1 (CH), 56.0 (CH_3), 31.9 (CH_2), 29.7 (CH_2), 28.8 (CH_2), 27.6 (CH_2), 24.8 (CH_2); IR (thin film): 3401, 2916, 1625, 1483, 1452, 913, 745 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{14}H_{17}ON$ $(M)^+$ 215.13102, found 215.13248.



4.163

Indole 4.163. The general procedure was followed using 0.027 g of styryl azide **4.162** (0.009 mmol) and 0.004 g of $Rh_2(O_2CC_7H_{15})_4$ (0.005 mmol) in 0.5 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.163** (0.021 g, 88%). Spectral data for **4.163**: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.89 (s, 1H), 7.76 (s, 1H), 7.29 – 7.34 (m, 2H), 2.82 – 2.86 (m, 4H), 1.90 – 1.94 (m, 2H), 1.76 – 1.82 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.3 (C), 135.6 (C), 128.7 (C), 125.6 (q, J_{CF} = 270.1 Hz, C), 121.4 (q, J_{CF} = 31.3 Hz, C), 117.4 (q, J_{CF} = 3.6 Hz, CH), 115.4 (q, J_{CF} = 3.5 Hz, CH), 114.7 (C), 110.2 (CH), 31.6 (CH_2), 29.6 (CH_2), 28.5 (CH_2), 27.4 (CH_2), 24.6 (CH_2); ^{19}F NMR ($CDCl_3$, 282 MHz) δ –60.66; IR (thin film): 3474, 3419, 2921, 1626, 1463,

1327, 1108, 1050, 763 cm^{-1}. HRMS (EI) *m* / *z* calcd for $C_{14}H_{14}F_3N$ $(M)^+$ 253.10783, found 253.10944.

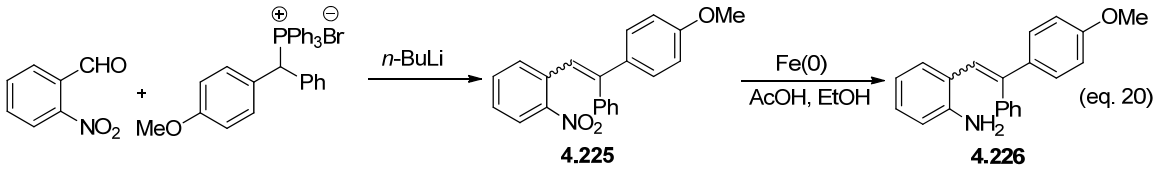


4.165

Indole 4.165. The general procedure was followed using 0.057 g of styryl azide **4.164** (0.265 mmol) and 0.010 g of $Rh_2(O_2CC_7H_{15})_4$ (0.013 mmol) in 0.6 mL of PhMe. Filtration by Al_2O_3 afforded analytically pure compound **4.165** (0.048 g, 97%). mp 116 - 119 °C; Spectral data for **4.**: ^1H NMR (500 MHz, $CDCl_3$) δ 7.85 (s, 1H), 7.49 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.12 – 7.18 (m, 2H), 3.97 – 4.02 (m, 4H), 3.00 – 3.03 (m, 4H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.5 (C), 134.8 (C), 128.9 (C), 121.2 (CH), 119.4 (CH), 117.8 (CH), 112.4 (C), 110.4 (CH), 73.1 (CH_2), 70.7 (CH_2), 32.2 (CH_2), 27.6 (CH_2); IR (thin film): 3400, 3294, 2936, 1464, 1113, 913 cm^{-1}. HRMS (EI) *m* / *z* calcd for $C_{12}H_{13}ON$ $(M)^+$ 187.09972, found 187.10060.

4.14.5 Mechanistic Experiments

Synthesis of Aryl Azides

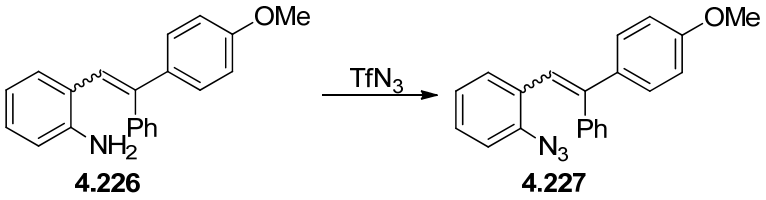


Styrene 4.225. To a solution of 10.4 g of the phosphonium salt (19.3 mmol) in 100 mL of THF at –78 °C, was added 8.5 mL of *n*-BuLi (2.5 M in hexanes, 21.2 mmol) dropwise. After stirring for 1h at –78 °C, the mixture was warmed to room temperature and stirred additional half an hour. Then 2.65 g of 2-nitrobenzaldehyde (17.5 mmol) was added, and the mixture was heated

to reflux. After 16 h, the reaction mixture was diluted with 50 mL of water and extracted with CH_2Cl_2 (3 × 30 mL). The resulting organic phase was washed with 60 mL of brine and dried over Na_2SO_4. The mixture was filtered and the filtrate was concentrated *in vacuo* to afford styrene **s31**, which was carried on to the subsequent Fe-mediated reduction without any additional purification.

Aniline 4.226. To a solution of nitro-substituted styrene **4.225** in 40 mL of AcOH and 40 mL of EtOH was added 8.6 g of Fe powder (154.4 mmol). The resultant mixture was heated to reflux at 80 °C. After 16 h, the reaction mixture was cooled down to ambient temperature. Once cool, the resulting mixture was filtered through a pad of Celite. The filtrate was diluted with 80 mL of water and washed with 3 × 30 mL of dichloromethane. The resulting organic phase was washed with 50 mL of brine and dried over Na_2SO_4. The resulting mixture was filtered, and the filtrate was concentrated in *vacuo*. Purification by MPLC (10:1 hexanes:EtOAc) afforded the product as a yellow viscous oil as an 67:33 mixture of *E*- and *Z*-isomers (1.37 g, 24%, two steps): Spectral data for the major (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.39 (m, 4H), 7.17 – 7.19 (m, 1H), 7.10 (d, J = 8.5 Hz, 2H), 6.89 (d, J = 8.5 Hz, 1H), 6.84 (d, J = 7.5 Hz, 1H), 6.74 – 6.80 (m, 4H), 6.53 (t, J = 7.5 Hz, 1H), 3.80 (s, 3H), *N-H peak not observed:* ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.5 (C), 143.8 (C), 143.6 (C), 132.3 (C), 131.7 (CH), 130.4 (CH), 128.25 (CH), 128.19 (CH), 127.9 (CH), 127.6 (CH), 123.93 (C), 123.90 (C), 123.8 (CH), 118.3 (CH), 115.5 (CH), 113.6 (CH), 55.2 (CH_3); Selected spectral data for the minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.29 – 7.39 (m, 4H), 7.24 – 7.26 (m, 3H), 6.96 – 7.02 (m, 3H), 6.64 -6.66 (m, 3H), 6.50 (t, J = 7.5 Hz, 1H), 3.84 (s, 3H), *N-H peak not available*; ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.6 (C), 140.3 (C), 136.0 (C), 130.51 (CH), 130.43 (CH), 129.3 (CH), 127.8 (CH), 127.4 (CH), 122.8 (CH), 118.2 (CH), 115.4 (CH), 55.4 (CH_3) *these are the only visible peaks*; Selected

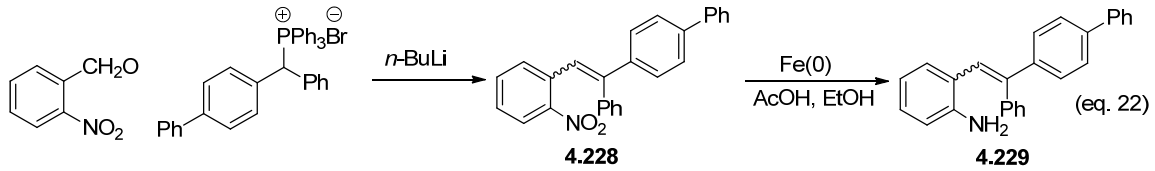
spectral data for the mixture: IR (thin film): 3462, 3375, 1739, 1605, 1508, 1242, 1176, 1031, 749 cm^{-1}.



4.226 **4.227** (eq. 21)

Aryl Azide 4.227. To a solution of 0.82 g of aniline **4.226** (2.7 mmol) in 5 mL of CH_2Cl_2 was added subsequently 24 mg of $CuSO_4$, 1.2 mL of Et_3N, freshly prepared triflyl azide (9 mmol) in 15 mL of CH_2Cl_2, 1 mL of water and 2 mL of MeOH. The resulting mixture was stirred at room temperature. After 16 h,, the reaction mixture was diluted with 15 mL of CH_2Cl_2, and the resulting mixture was neutralized by the addition of a saturated aq. soln. of $NaHCO_3$. Once pH 7 was reached, the resulting mixture was washed with 3 × 10 mL of CH_2Cl_2. The resulting organic phase was washed with 20 mL of brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. Purification by MPLC (10:1 hexane:EtOAc) afforded the product as a yellow viscous oil as an 69:31 mixture of *E*- and *Z*-isomers (0.42 g, 48%): Selected spectral data for the major (*E*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.36 (m, 4H), 7.12 – 7.17 (m, 2H), 7.08 (d, *J* = 9.0 Hz, 2H), 6.87 – 6.88 (m, 2H), 6.80 – 6.83 (m, 3H), 3.82 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.0 (C), 143.8 (C), 143.5 (C), 138.6 (C), 132.2 (C), 129.8 (C), 131.8 (CH), 130.7 (CH), 129.2 (CH), 128.37 (CH), 128.18 (CH), 128.11 (CH), 127.7 (CH), 124.1 (CH), 118.2 (CH), 113.8 (CH), 55.2 (CH_3); Selected spectral data for the minor (*Z*) isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.27 – 7.36 (m, 5H), 7.12 – 7.17 (m, 4H), 6.95 – 6.96 (m, 3H), 6.77 – 6.78 (m, 2H), 3.83 (s, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 159.5 (C), 143.7 (C), 140.2 (C), 138.5 (C), 135.8 (C), 129.7 (C), 130.72 (CH), 130.58 (CH), 127.94 (CH), 127.82 (CH), 127.4 (CH),

124.0 (CH), 122.5 (CH), 121.3 (CH), 118.1 (CH), 113.6 (CH), 55.4 (CH_3); Selected spectral data for the mixture: IR (thin film): 2117, 2085, 1738, 1604, 1509, 1289, 1246, 1176, 1034, 751 cm^{-1}.

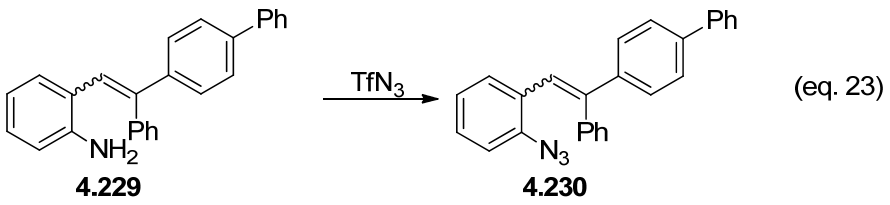


4.228 **4.229**

Styrene 4.228. To a solution of 9.6 g of the phosphonium salt (16.4 mmol) in 60 mL of THF at –78 °C, was added 7.2 mL of *n*-BuLi (2.5 M in hexanes, 18.1 mmol) dropwise. After stirring for 1 h at –78 °C, the mixture was warmed to room temperature and stirred additional half an hour. Then 2.48 g of 2-nitrobenzaldehyde (16.4 mmol) was added, and the mixture was heated to reflux. After 16 h, the reaction mixture was diluted with 50 mL of water and extracted with CH_2Cl_2 (3 × 30 mL). The resulting organic phase was washed with 60 mL of brine and dried over Na_2SO_4. The mixture was filtered and the filtrate was concentrated *in vacuo* to afford styrene **4.228**, which was carried on to the subsequent Fe-mediated reduction without any additional purification.

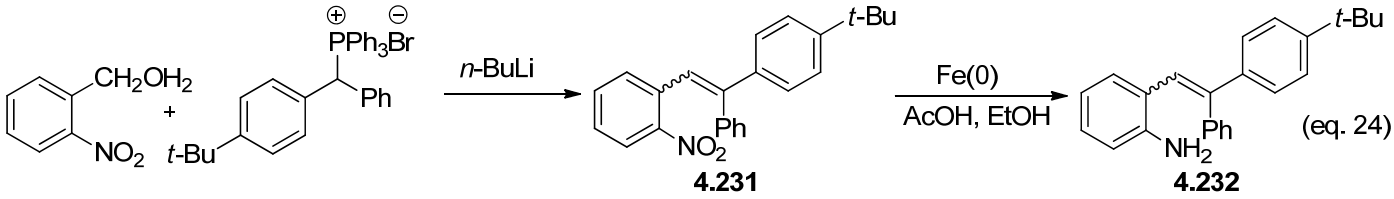
Aniline 4.229. To a solution of nitro-substituted styrene **4.228** in 30 mL of AcOH and 30 mL of EtOH was added 7.3 g of Fe powder (131.2 mmol). The resultant mixture was heated to reflux at 80 °C. After 16 h, the reaction mixture was cooled down to ambient temperature. Once cool, the resulting mixture was filtered through a pad of Celite. The filtrate was diluted with 70 mL of water and washed with 3 × 30 mL of dichloromethane. The resulting organic phase was washed with 50 mL of brine and dried over Na_2SO_4. The resulting mixture was filtered, and the filtrate was concentrated in *vacuo*. Purification by MPLC (10:1 hexanes:EtOAc) afforded the product as

a yellow solid (602 mg, 11%, two steps); Spectral data for the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.63- 7.70 (m, 4H), 7.47 – 7.56 (m, 5H), 7.41 – 7.43 (m, 1H), 7.27 – 7.34 (m, 4H), 7.03 – 7.07 (m, 1H), 6.95 (s, 1H), 6.86 (d, J = 7.5 Hz, 1H), 6.70 – 6.71 (m, 1H), 6.56 -6.60 (m, 1H), 3.92 (br, 2H): ^{13}C NMR (125 MHz, $CDCl_3$) δ 144.8 (C), 143.7 (C), 142.4 (C), 140.8 (C), 140.5 (C), 131.1 (CH), 130.63 (CH), 130.48 (CH), 128.9 (CH), 128.6 (CH), 128.38 (CH), 128.20 (CH), 127.6 (CH), 127.12 (CH), 127.01 (CH), 124.4 (CH), 123.7 (C), 118.3 (CH), 115.6 (CH); Selected spectral data for the mixture: IR (thin film): 3457, 1739, 1486, 1454, 1366, 1216, 905 cm^{-1}.



4.229 **4.230**

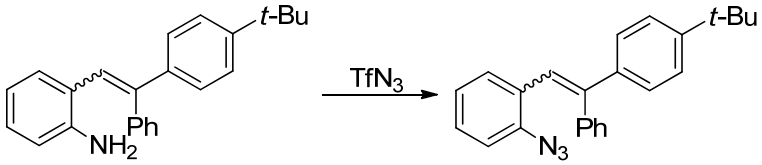
Aryl Azide 4.230. To a solution of 0.55 g of aniline **4.229** (1.6 mmol) in 5 mL of CH_2Cl_2 was added subsequently 16 mg of $CuSO_4$, 0.8 mL of Et_3N, freshly prepared triflyl azide (6 mmol) in 15 mL of CH_2Cl_2, 1 mL of water and 2 mL of MeOH. The resulting mixture was stirred at room temperature. After 16 h, the reaction mixture was diluted with 15 mL of CH_2Cl_2, and the resulting mixture was neutralized by the addition of a saturated aq. soln. of $NaHCO_3$. Once pH 7 was reached, the resulting mixture was washed with 3 × 10 mL of CH_2Cl_2. The resulting organic phase was washed with 20 mL of brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. Purification by MPLC (10:1 hexane:EtOAc) afforded the product as a pale solid (0.26 g, 43%): The peaks which belongs to E or Z isomer cannot be distinguished. Selected spectral data for the mixture: IR (thin film): 2117, 2085, 1738, 1604, 1509, 1289, 1246, 1176, 1034, 751 cm^{-1}. HRMS (EI) *m* / *z* calcd for $C_{26}H_{19}N_3$ $(M)^+$ 373.15790, found 373.15891.



Styrene 4.231. To a solution of 10.8 g of the phosphonium salt (19.1 mmol) in 60 mL of THF at –78 °C, was added 8.4 mL of *n*-BuLi (2.5 M in hexanes, 21.01 mmol) dropwise. After stirring for 1h at –78 °C, the mixture was warmed to room temperature and stirred additional half an hour. Then 2.69 g of 2-nitrobenzaldehyde (19.1 mmol) was added, and the mixture was heated to reflux. After 16 h, the reaction mixture was diluted with 50 mL of water and extracted with CH_2Cl_2 (3 × 30 mL). The resulting organic phase was washed with 60 mL of brine and dried over Na_2SO_4. The mixture was filtered and the filtrate was concentrated *in vacuo* to afford styrene **4.231**, which was carried on to the subsequent Fe-mediated reduction without any additional purification.

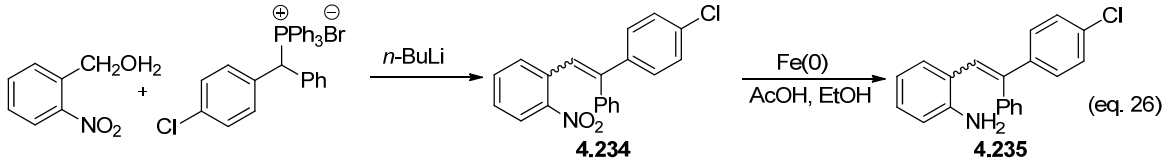
Aniline 4.232. To a solution of nitro-substituted styrene **4.231** in 40 mL of AcOH and 40 mL of EtOH was added 8.6 g of Fe powder (152.8 mmol). The resultant mixture was heated to reflux at 80 °C. After 16 h, the reaction mixture was cooled down to ambient temperature. Once cool, the resulting mixture was filtered through a pad of Celite. The filtrate was diluted with 80 mL of water and washed with 3 × 30 mL of dichloromethane. The resulting organic phase was washed with 50 mL of brine and dried over Na_2SO_4. The resulting mixture was filtered, and the filtrate was concentrated in *vacuo*. Purification by MPLC (10:1 hexanes:EtOAc) afforded the product as a yellow solid (1.5 g, 24%, two steps); Spectral data for the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.37 – 7.39 (m, 2H), 7.31 – 7.33 (m, 2H), 7.25 – 7.27 (m, 3H), 7.19 – 7.21 (m, 2H),

6.97 – 7.00 (m, 1H), 6.84 (s, 1H), 6.77 (d, J = 8.0 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 6.51 (t, J = 7.5 Hz, 1H), 3.74 (br, 2H), 1.37 (s, 9 H): ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.8 (C), 144.7 (C), 143.9 (C), 140.4 (C), 140.2 (C), 130.53 (CH), 130.43 (CH), 128.2 (CH), 127.9 (CH), 127.7 (CH), 127.3 (CH), 125.2 (CH), 123.7 (CH), 118.2 (CH), 115.4 (CH), 34.6 (C), 31.4 (CH_3); Selected spectral data for the mixture: IR (thin film): 3379, 1617, 1246, 905, 726, 701, 649 cm^{-1}.



4.232 **4.233** (eq. 25)

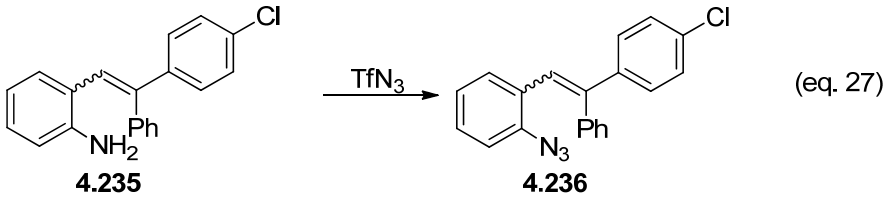
Aryl Azide 4.233. To a solution of 1.2 g of aniline **4.232** (3.8 mmol) in 5 mL of CH_2Cl_2 was added subsequently 32 mg of $CuSO_4$, 1.6 mL of Et_3N, freshly prepared triflyl azide (12 mmol) in 15 mL of CH_2Cl_2, 1 mL of water and 2 mL of MeOH. The resulting mixture was stirred at room temperature. After 16 h, the reaction mixture was diluted with 15 mL of CH_2Cl_2, and the resulting mixture was neutralized by the addition of a saturated aq. soln. of $NaHCO_3$. Once pH 7 was reached, the resulting mixture was washed with 3 × 10 mL of CH_2Cl_2. The resulting organic phase was washed with 20 mL of brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. Purification by MPLC (10:1 hexane:EtOAc) afforded the product as a yellow solid as an 1:1 mixture of *E*- and *Z*-isomers (0.88 g, 66%): *The peaks which belong to E- or Z-isomer cannot be distinguished*. Selected spectral data for the mixture: IR (thin film): 2117, 2085, 1796, 1730, 1287, 908, 733 cm^{-1}. HRMS (EI) m / z calcd for $C_{24}H_{23}N_3$ $(M)^+$ 353.18920, found 353.19017.



Styrene 4.234. To a solution of 8.5 g of the phosphonium salt (15.7 mmol) in 50 mL of THF at –78 °C, was added 6.9 mL of *n*-BuLi (2.5 M in hexanes, 17.3 mmol) dropwise. After stirring for 1h at –78 °C, the mixture was warmed to room temperature and stirred additional half an hour. Then 2.4 g of 2-nitrobenzaldehyde (15.7 mmol) was added, and the mixture was heated to reflux. After 16 h, the reaction mixture was diluted with 50 mL of water and extracted with CH_2Cl_2 (3 × 30 mL). The resulting organic phase was washed with 60 mL of brine and dried over Na_2SO_4. The mixture was filtered and the filtrate was concentrated *in vacuo* to afford styrene **4.234**, which was carried on to the subsequent Fe-mediated reduction without any additional purification.

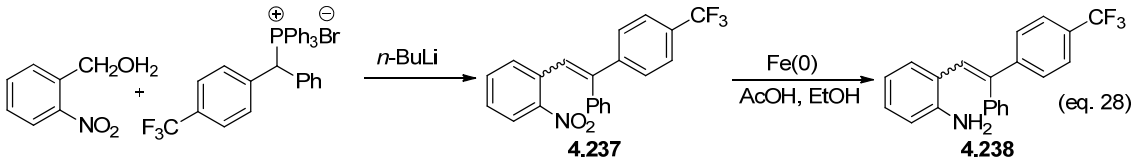
Aniline 4.235. To a solution of nitro-substituted styrene **4.234** in 40 mL of AcOH and 40 mL of EtOH was added 7.1 g of Fe powder (125.6 mmol). The resultant mixture was heated to reflux at 80 °C. After 16 h, the reaction mixture was cooled down to ambient temperature. Once cool, the resulting mixture was filtered through a pad of Celite. The filtrate was diluted with 80 mL of water and washed with 3 × 30 mL of dichloromethane. The resulting organic phase was washed with 50 mL of brine and dried over Na_2SO_4. The resulting mixture was filtered, and the filtrate was concentrated in *vacuo*. Purification by MPLC (10:1 hexanes:EtOAc) afforded the product as a pale solid (1024 mg, 21%, two steps); Spectral data for the major isomer: ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.52 – 7.34 (m, 14H), 3.76 (br, 2H): The peaks which belong to *E* or *Z* isomer cannot

be distinguished; Selected spectral data for the mixture: IR (thin film): 3463, 3378, 1614, 1485, 1089, 728 cm^{-1}.



4.235 **4.236** (eq. 27)

Aryl Azide 4.236. To a solution of 0.90 g of aniline **4.235** (3.0 mmol) in 5 mL of CH_2Cl_2 was added subsequently 24 mg of $CuSO_4$, 1.2 mL of Et_3N, freshly prepared triflyl azide (9 mmol) in 15 mL of CH_2Cl_2, 1 mL of water and 2 mL of MeOH. The resulting mixture was stirred at room temperature. After 16 h, the reaction mixture was diluted with 15 mL of CH_2Cl_2, and the resulting mixture was neutralized by the addition of a saturated aq. soln. of $NaHCO_3$. Once pH 7 was reached, the resulting mixture was washed with 3 × 10 mL of CH_2Cl_2. The resulting organic phase was washed with 20 mL of brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. Purification by MPLC (10:1 hexane:EtOAc) afforded the product as a yellow viscous oil (0.44 g, 45%): The peaks which belong to *E* or *Z* isomer cannot be distinguished. Selected spectral data for the mixture: IR (thin film): 2117, 2085, 1738, 1604, 1509, 1289, 1246, 1176, 1034, 751 cm^{-1}. HRMS (EI) *m* / *z* calcd for $C_{20}H_{14}N_3Cl$ $(M)^+$ 331.08762, found 331.08665.

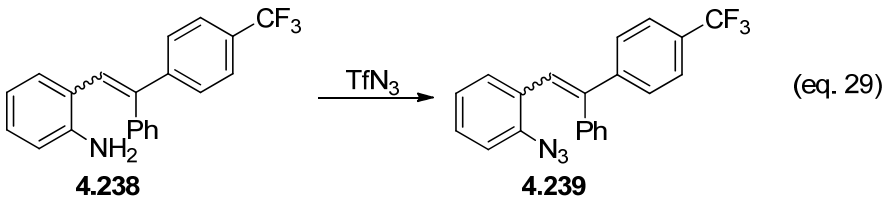


4.237 **4.238** (eq. 28)

Styrene 4.237. To a solution of 3.46 g of the phosphonium salt (6 mmol) in 60 mL of THF at –78 °C, was added 2.4 mL of *n*-BuLi (2.5 M in hexanes, 6 mmol) dropwise. After stirring for 1h

at –78 °C, the mixture was warmed to room temperature and stirred additional half an hour. Then 0.91 g of 2-nitrobenzaldehyde (6 mmol) was added, and the mixture was heated to reflux. After 16 h, the reaction mixture was diluted with 50 mL of water and extracted with CH_2Cl_2 (3 × 30 mL). The resulting organic phase was washed with 60 mL of brine and dried over Na_2SO_4. The mixture was filtered and the filtrate was concentrated *in vacuo* to afford styrene **4.237**, which was carried on to the subsequent Fe-mediated reduction without any additional purification.

Aniline 4.238. To a solution of nitro-substituted styrene **4.237** in 15 mL of AcOH and 15 mL of EtOH was added 2.7 g of Fe powder (48 mmol). The resultant mixture was heated to reflux at 80 °C. After 16 h, the reaction mixture was cooled down to ambient temperature. Once cool, the resulting mixture was filtered through a pad of Celite. The filtrate was diluted with 20 mL of water and washed with 3 × 10 mL of dichloromethane. The resulting organic phase was washed with 20 mL of brine and dried over Na_2SO_4. The resulting mixture was filtered, and the filtrate was concentrated in *vacuo*. Purification by MPLC (10:1 hexanes:EtOAc) afforded the product as a yellow solid (190 mg, 12%, two steps); The peaks which belong to *E* or *Z* isomer cannot be distinguished; HRMS (EI) *m* / *z* calcd for $C_{21}H_{16}F_3N$ $(M)^+$ 339.12348, found 339.12435.

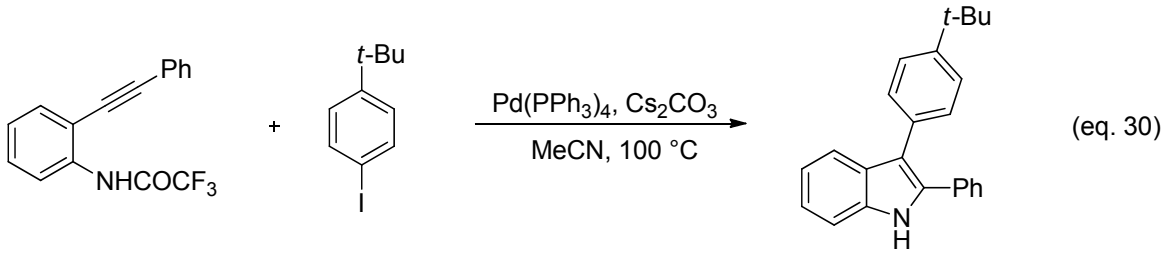


4.238 **4.239** (eq. 29)

Aryl Azide 4.239. To a solution of 0.17 g of aniline **4.238** (0.5 mmol) in 5 mL of CH_2Cl_2 was added subsequently 6 mg of $CuSO_4$, 0.3 mL of Et_3N, freshly prepared triflyl azide (2 mmol) in 5 mL of CH_2Cl_2, 1 mL of water and 2 mL of MeOH. The resulting mixture was stirred at room temperature. After 16 h, the reaction mixture was diluted with 10 mL of CH_2Cl_2, and the resulting mixture was neutralized by the addition of a saturated aq. soln. of $NaHCO_3$. Once pH 7 was reached, the resulting mixture was washed with 3 × 10 mL of CH_2Cl_2. The resulting organic phase was washed with 20 mL of brine and dried over Na_2SO_4. After filtration, the filtrate was concentrated *in vacuo*. Purification by MPLC (10:1 hexane:EtOAc) afforded the product as a yellow viscous oil (0.076 g, 42%): The peaks which belong to *E* or *Z* isomer cannot be distinguished. Selected spectral data for the mixture: IR (thin film): 1752, 1727, 1368, 1228, 1216, 750 cm^{-1}.

Syntheses of 2,3-Diarylindoles

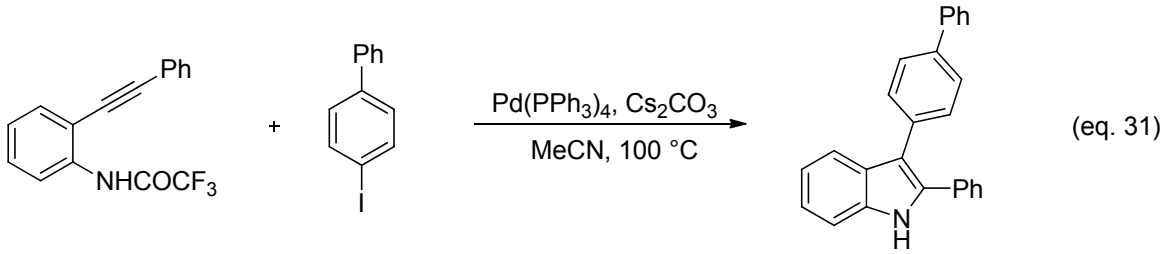
2-Phenyl-3-arylindoles were synthesized from alkynyltrifluoroacetanilide **4.240** following the method reported by Cacchi and co-workers.[15]



4.240 **4.241** (eq. 30)

Indole 4.241.[15] To a solution of 0.59 g of acetylene (2.0 mmol) in 15 mL of MeCN was added subsequently 1.43 g of Cs_2CO_3, 0.1 mol of $Pd(PPh_3)_4$ (5 mol %), 1.14 g of 4-*tert*-butyliodobenzene (4.4 mmol). The resulting mixture was stirred at 100 °C until complete conversion (2h). After this time, the reaction mixture was cooled to room temperature, diluted

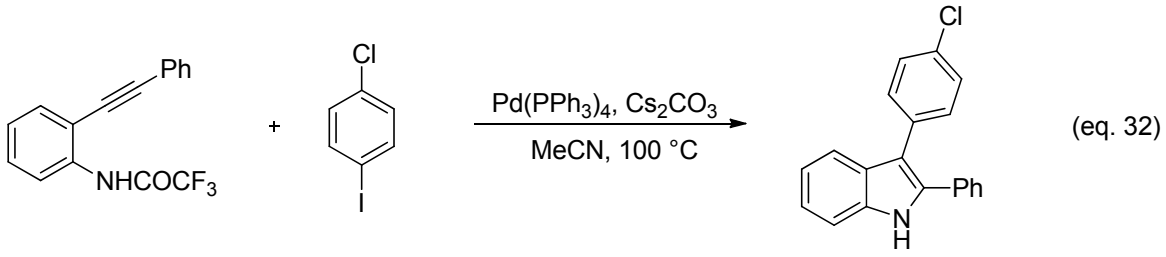
with 30 mL of water and extracted with CH_2Cl_2 (3 × 20 mL). The resulting organic phase was washed with 60 mL of brine and dried over Na_2SO_4. Purification by MPLC (30:1 hexane:EtOAc) afforded the product **4.241** as a yellow solid (0.59 g, 91%). The spectral data matched that reported by Cacchi and co-workers:[15] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (br, 1H), 7.76 (d, *J* = 8.0 Hz, 1H), 7.40 -7.48 (m, 7H), 7.26 - 7.36 (m, 4H), 7.17 - 7.20 (m, 1H) 1.49 (s, 9H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 149.0 (C), 136.0 (C), 134.0 (C), 133.0 (C), 132.0 (C), 129.7 (CH), 129.0 (C), 128.7 (CH), 128.3 (CH), 127.6 (CH), 125.5 (CH), 122.7 (CH), 120.3 (CH), 120.0 (CH), 115.0 (C), 110.9 (CH), 34.6 (C), 31.5 (CH3); IR (thin film): 3457, 1761, 1442, 1378, 1223, 732 cm^{-1}. HRMS (EI) *m* / *z* calcd for $C_{24}H_{23}N$ $(M)^+$ 325.18404, found 325.18305.



4.240 **4.242** (eq. 31)

Indole 4.242.[15] To a solution of 0.59 g of acetylene (2.0 mmol) in 15 mL of MeCN was added subsequently 1.43 g of Cs_2CO_3, 0.1 mol of $Pd(PPh_3)_4$ (5 mol %), 1.03 g of 4-bromobiphenyl (4.4 mmol). The resulting mixture was stirred at 100 °C until complete conversion (2h). After this time, the reaction mixture was cooled to room temperature, diluted with 30 mL of water and extracted with CH_2Cl_2(3 × 20 mL). The resulting organic phase was washed with 60 mL of brine and dried over Na2SO4. Purification by MPLC (30:1 hexane:EtOAc) afforded the product **4.242** as a yellow solid (0.54 g, 78%). Spectral data matched that reported by Cacchi and coworkers:[15] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.25 (br, 1H), 7.78 (d, *J* = 7.5 Hz, 1H), 7.69 (d, *J* = 8.0 Hz, 2H), 7.65 (d, *J* = 8.0 Hz, 2H), 7.55 (d, *J* = 7.5 Hz, 2H), 7.45 – 7.55 (m, 5H), 7.22 – 7.39 (m, 5H), 7.19

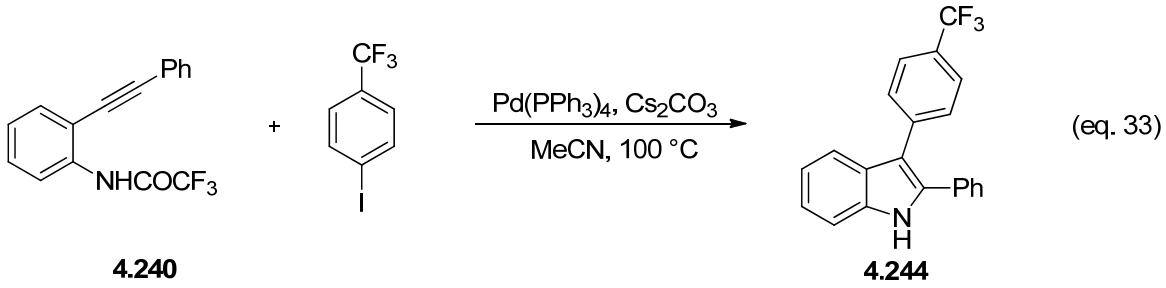
– 7.22 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 141.0 (C), 138.8 (C), 136.0 (C), 134.29 (C), 134.20 (C), 132.8 (C), 130.5 (CH), 128.81 (CH), 128.76 (CH), 128.3 (CH), 127.8 (CH), 127.23 (CH), 127.18 (CH), 126.99 (CH), 122.8 (CH), 120.6 (CH), 119.8 (CH), 114.6 (C), 111.0 (CH); IR (thin film): 3415, 1770, 1455, 1248, 903, 725, 698, 649 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{26}H_{19}N$ $(M)^+$ 345.15175, found 345.25258.



4.240 **4.243** (eq. 32)

Indole 4.243.[15] To a solution of 0.59 g of acetylene (2.0 mmol) in 15 mL of MeCN was added subsequently 1.43 g of Cs_2CO_3, 0.1 mol of $Pd(PPh_3)_4$ (5 mol %), 1.05 g of 1-chloro-4-iodobenzene (4.4 mmol). The resulting mixture was stirred at 100 °C until complete conversion (2h). After this time, the reaction mixture was cooled to

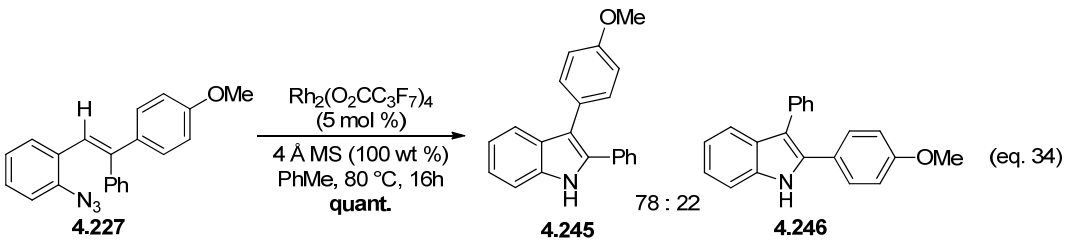
room temperature, diluted with 30 mL of water and extracted with CH_2Cl_2 (3 × 20 mL). The resulting organic phase was washed with 60 mL of brine and dried over Na_2SO_4. Purification by MPLC (30:1 hexane:EtOAc) afforded the product **4.243** as a yellow solid (0.53 g, 88%). The spectral data matched that reported by Cacchi and co-workers:[15] 1H NMR (500 MHz, $CDCl_3$) δ 8.23 (br, 1H), 7.68 (d, *J* = 8.0 Hz, 1H), 7.34 -7.45 (m, 10H), 7.29 (t, *J* = 7.5 Hz, 1H), 7.20 – 7.23 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 135.9 (C), 134.4 (C), 133.7 (C), 132.4 (C), 132.1 (C), 131.4 (CH), 128.88 (CH), 128.84 (CH), 128.5 (C), 128.3 (CH), 128.0 (CH), 122.9 (CH), 120.7 (CH), 119.5 (CH), 113.8 (C), 111.1 (CH); IR (thin film): 3411, 1770, 1601, 1500, 1248, 1091, 1014, 905, 728 cm^{-1}. HRMS (EI) *m / z* calcd for $C_{20}H_{14}NCl$ $(M)^+$ 303.08147, found 303.08070.



4.240 4.244 (eq. 33)

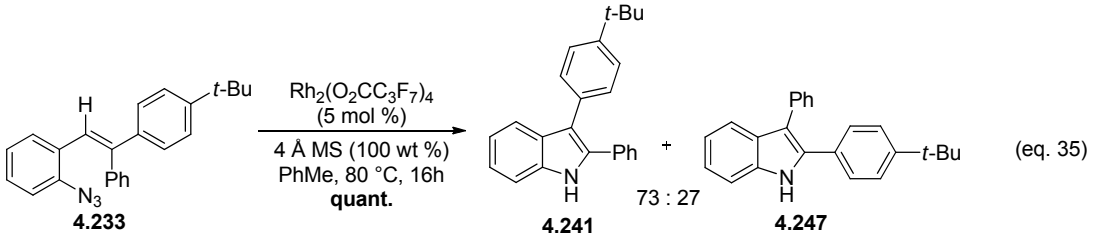
Indole 4.244.[16] To a solution of 0.59 g of acetylene (2.0 mmol) in 15 mL of MeCN was added subsequently 1.43 g of Cs_2CO_3, 0.1 mol of $Pd(PPh_3)_4$ (5 mol %), 0.97 g of 4-trifluromethyliodobenzene (4.4 mmol). The resulting mixture was stirred at 100 °C until complete conversion (2h). After this time, the reaction mixture was cooled to room temperature, diluted with 30 mL of water and extracted with CH_2Cl_2 (3 × 20 mL). The resulting organic phase was washed with 60 mL of brine and dried over Na_2SO_4. Purification by MPLC (30:1 hexane:EtOAc) afforded the product **4.244** as a yellow solid (0.63 g, 94%). The spectral data matched that reported by Wang and co-workers:[16] ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.29 (br, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 2H), 7.57 (d, J = 8.0 Hz, 2H), 7.36 – 7.47 (m, 6H), 7.29 – 7.32 (m, 1H), 7.20 – 7.24 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 139.1 (C), 136.0 (C), 135.0 (C), 132.2 (C), 130.2 (CH), 129.0 (CH), 128.4 (CH), 128.2 (CH), 128.1 (d, J_{CF} = 38.5 Hz, CH), 125.5 (d, J_{CF} = 3.6 Hz, CH), 124.5 (d, J_{CF} = 270.0 Hz, C), 123.1 (C), 121.3 (C), 120.9 (CH), 119.3 (CH), 113.6 (C), 111.2 (CH); IR (thin film): 3405, 1614, 1448, 1321, 1108, 1065, 905, 850 cm^{-1}. HRMS (EI) m / z calcd for $C_{20}H_{14}NF_3$ $(M)^+$ 337.10783, found 337.10868.

Intramolecular Competition Experiments

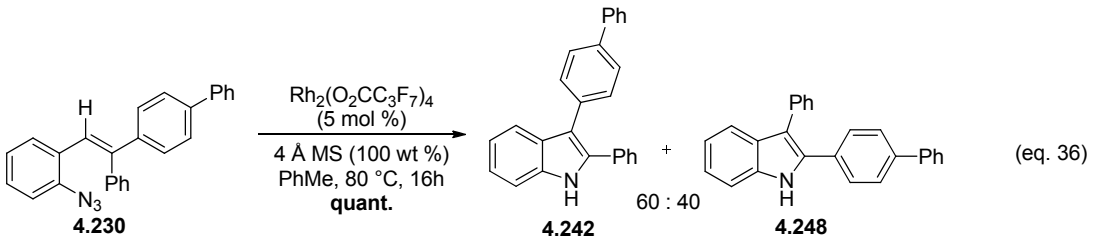


4.227 4.245 4.246 (eq. 34)

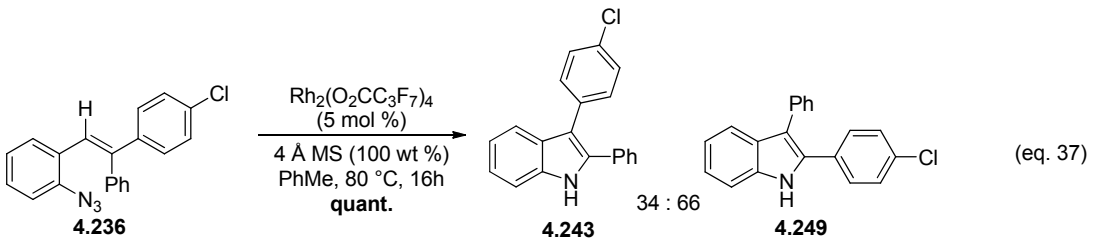
To a mixture of 0.023 g of aryl azide **4.227** (0.07 mmol), 0.023 g of crushed 4 Å mol sieves, and 0.004 g of $Rh_2(O_2CC_3F_7)_4$ (0.004 mol) in Schlenk tube was added 0.50 mL of PhMe. The resulting mixture was heated at 80 °C, after 16 h, the heterogenous mixture was filtered through a short pad of Al_2O_3. The filtrate was concentrated *in vacuo* to afford 0.021 g of a mixture of **4.245** and **4.246** (78:22). The resulting solid was dissolved in 1.5 mL of $CDCl_3$. The areas of the C–H peak on the methoxy position were compared to derive a ratio (78:22). The products were identified by comparison with published ^{1}H NMR spectra of **4.245**[55] and **4.207**.[56]



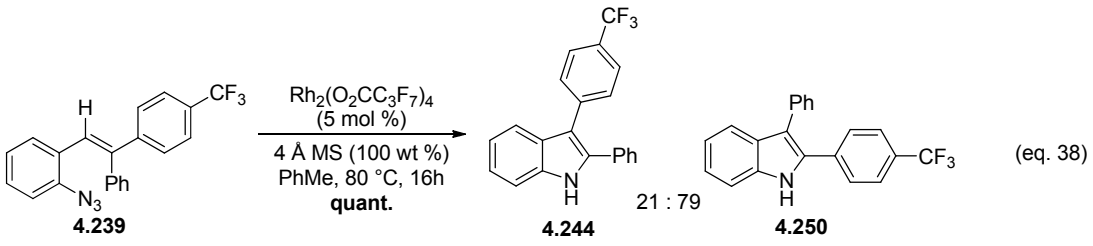
To a mixture of 0.058 g of aryl azide **4.233** (0.16 mmol), 0.058 g of crushed 4 Å mol sieves, and 0.009 g of $Rh_2(O_2CC_3F_7)_4$ (0.008 mol) in Schlenk tube was added 0.50 mL of PhMe. The resulting mixture was heated at 80 °C, after 16 h, the heterogenous mixture was filtered through a short pad of Al_2O_3. The filtrate was concentrated *in vacuo* to afford 0.053 g of a mixture of **4.241** and **4.247** (73:27). The resulting solid was dissolved in 1.5 mL of $CDCl_3$. The areas of the C–H peak on the aromatic region were compared to derive a ratio (73:27). The products were identified by comparison with ^{1}H NMR spectra of **4.241**.



To a mixture of 0.060 g of aryl azide **4.230** (0.16 mmol), 0.060 g of crushed 4 Å mol sieves, and 0.009 g of $Rh_2(O_2CC_3F_7)_4$ (0.008 mol) in Schlenk tube was added 0.50 mL of PhMe. The resulting mixture was heated at 80 °C, after 16 h, the heterogenous mixture was filtered through a short pad of Al_2O_3. The filtrate was concentrated *in vacuo* to afford 0.054 g of a mixture of **4.242** and **4.248** (60:40). The resulting solid was dissolved in 1.5 mL of $CDCl_3$. The areas of the C–H peak on the aromatic region were compared to derive a ratio (60:40). The products were identified by comparison with ^{1}H NMR spectra of **4.242**.



To a mixture of 0.043 g of aryl azide **4.236** (0.13 mmol), 0.043 g of crushed 4 Å mol sieves, and 0.007 g of $Rh_2(O_2CC_3F_7)_4$ (0.006 mol) in Schlenk tube was added 0.50 mL of PhMe. The resulting mixture was heated at 80 °C, after 16 h, the heterogenous mixture was filtered through a short pad of Al_2O_3. The filtrate was concentrated *in vacuo* to afford 0.039 g of a mixture of **4.243** and **4.249** (34:66). The resulting solid was dissolved in 1.5 mL of $CDCl_3$. The areas of the C–H peak on the aromatic region were compared to derive a ratio (34:66). The products were identified by comparison with ^{1}H NMR spectra of **4.243**.

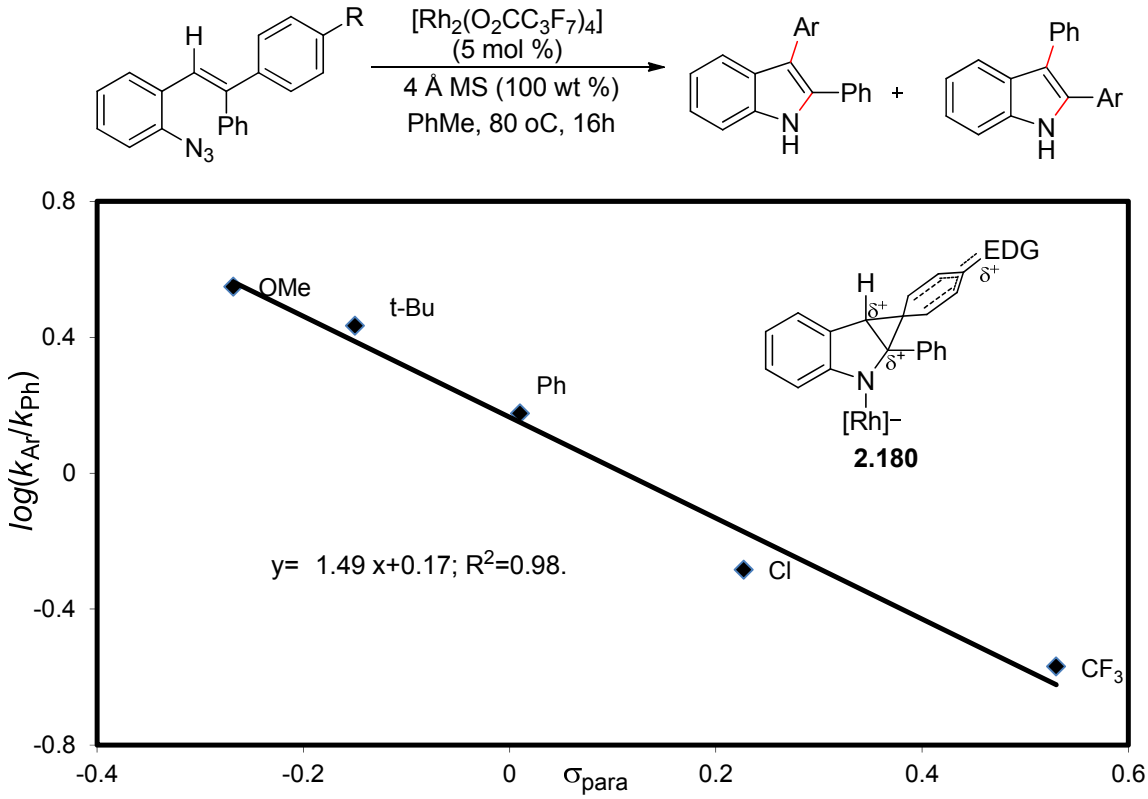


To a mixture of 0.040 g of aryl azide **4.239** (0.11 mmol), 0.040 g of crushed 4 Å mol sieves, and 0.006 g of $Rh_2(O_2CC_3F_7)_4$ (0.005 mol) in Schlenk tube was added 0.50 mL of PhMe. The resulting mixture was heated at 80 °C, after 16 h, the heterogenous mixture was filtered through a short pad of Al_2O_3. The filtrate was concentrated *in vacuo* to afford 0.032 g of a mixture of **4.244** and **4.250** (21:79). The resulting solid was dissolved in 1.5 mL of $CDCl_3$. The areas of the C–H peak on the aromatic region were compared to derive a ratio (21:79). The products were identified by comparison with ^{1}H NMR spectra of **4.244**.

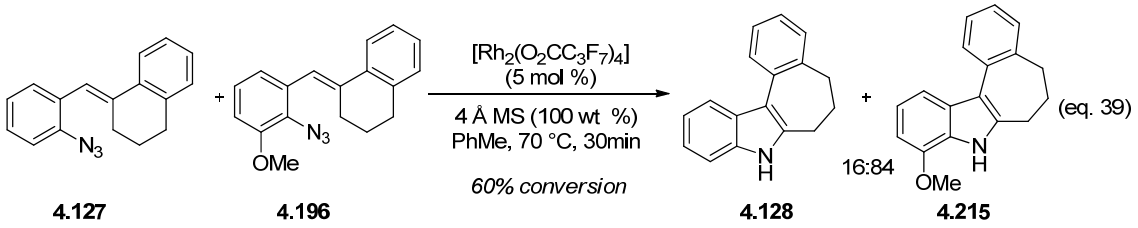
Correlation of Product Ratio with Hammett Plot

The log of the product ratios was correlated with Hammett σ-values to ascertain the existence of any linear free energy relationships.

Figure 4.1. Correlation of Product Ratios with Hammett σ_{para}-Values.



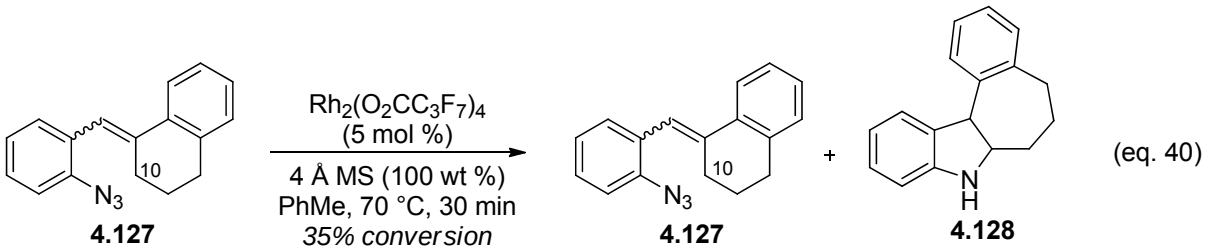
Intermolecular Competition Experiment



To a mixture of 0.013 g of styryl azide **4.127** (0.05 mmol) and 0.0145 g of styryl azide **4.196** (0.05 mmol), 100 % w/w of crushed 4 Å mol sieves, and $Rh_2(hpfb)_4$ (5 mol %) in Schlenk tube was added 0.50 mL of PhMe. The resulting mixture was heated at 70 °C. After 30 min, the heterogenous mixture was filtered through a short pad of Al_2O_3. The filtrate was concentrated *in vacuo* to afford analytically pure indoles. Analysis of the ^{1}H NMR spectrum showed 98%

conversion of the styryl azide **4.196** into **4.215** and 60% conversion of the styryl azide **4.127** into indole **4.128**. ^{1}H NMR (500 MHz, $CDCl_3$) δ 4.02 (s, 3 H) vs 3.94 (s, 0.0734 H) vs 7.07 – 7.08 (m, 0.774 H) = **4.215** vs **4.196** vs **4.127**.

Examination of Rates of Reaction of *E*- and *Z*- Isomers



4.127 (5.3:1 *E*:*Z*) → **4.127** (5.4:1 *E*:*Z*) + **4.128** (eq. 40)

To a mixture of 0.043 g of aryl azide **4.127** (0.16 mmol), 0.043 g of crushed 4 Å mol sieves, and 0.009 g of $Rh_2(O_2CC_3F_7)_4$ (0.008 mol) in Schlenk tube was added 0.60 mL of PhMe. The resulting mixture was heated at 70 °C, after 30 min, the heterogenous mixture was filtered through a short pad of Al_2O_3. The filtrate was concentrated *in vacuo*. The resulting solid (oil) was dissolved in 1.5 mL of $CDCl_3$. The areas of the C–H peak on the carbon **9** in starting material aryl azide **4.127** was compared to derive a *E:Z* ratio.

4.15 Reference

1 (a) Fürstner, A.; Szillat, H.; Gabor, B.; Mynott, R. "Platinum- and acid-catalyzed enyne metathesis reactions: mechanistic studies and applications to the syntheses of streptorubin B and metacycloprodigiosin" J. Am. Chem. Soc. 1998, 120, 8305. (b) Thompson, R. B. "Foundations for blockbuster drugs in federally sponsored research" FASEB J. 2001, 15, 1671.

2 (a) Butler, M. S. "The role of natural product chemistry in drug discovery" J. Nat. Prod. 2004, 67, 2141 (b) O'Hagan, D. "Pyrrole, pyrrolidine pyridine, piperidine, azepine and tropane alkaloids" Nat. Prod. Rep. 1997, 14, 637. (c) Fan, H.; Peng, J.; Hamann, M. T.; Hu, J.-F. "Lamellarins and related pyrrole-derived alkaloids from marine organisms" Chem. Rev. 2008, 108, 264.

3 (a) Tremont, S. J. "*Ortho*-alkylation of acetanilides using alkyl halides and palladium acetate" *J. Am. Chem. Soc*. **1984**, *106*, 5759. (b) Daugulis, O.; Zaitsev, V. G. " Catalytic coupling of haloolefins with anilides" *J. Am. Chem. Soc*. **2005**, *127*, 4156. (c) Inamoto, K.; Saito, T.; Hiroya, K.; Doi, T. "A new approach to 3-substituted indoles through palladium-catalyzed C-H activation followed by intramolecular amination reaction of enamines" *Synlett* **2008**, *20*, 3157. (d) Inamoto, K.; Saito, T.; Hiroya, K.; Doi, T. "Palladium-catalyzed intramolecular amidation of C(sp2)−H bonds: synthesis of 4-aryl-2-quinolinones" *J. Org. Chem*. **2010**, *75*, 3900.

4 (a) Tsang, W. C. P.; Zheng, N.; Buchwald, S. L. "Combined C-H functionalization/C-N bond formation route to carbazoles" J. Am. Chem. Soc, 2005, 127, 14560. (b) Tsang, W. C. P.; Munday, R.; Gordon, B.; Zheng, N.;

Buchwald, S. L. “A palladium-catalyzed method for the synthesis of carbazoles via tandem C-H functionalization and C-N bond formation” J. Org. Chem. 2008, 73, 7603
5 Lautens, M. Fang, Y.-Q. “Synthesis of novel tetracycles via an intramolecular Heck reaction with anti-hydride elimination” *Org. Lett.* **2003**, *5*, 3679
6 Jira, R. In Applied Homogeneous Catalysis with Organometallic Compounds; Cornils, B. Herrmann, W. A. Eds. Wiley-VCH: New York, **2002**; *Vol. 1*, 386.
7 Brasche, G. Buchwald, S. L. “C-H functionalization/C-N bond formation: copper-catalyzed synthesis of benzimidazoles from amidines" Angew. Chem. Int. Ed. 2008, 47, 1932
8 Xiao, Q.; W.-H. Wang, W.-H.; Liu, G.; Meng, F.-K.; Chen, J.-H. Yang Z.; Shi, Z.-J. *Chem. Eur. J*. **2009**, *15*, 7292
9 Sundberg, R. J.“Deoxygenation of nitro Groups by Trivalent Phosphorus. Indoles from o-Nitrostyrenes” *J. Org. Chem.* **1965**, *30*, 3604–3610
10 Akazome, M.; Kondo, T.; Watanabe, Y. “Palladium complex-catalyzed reductive N-heterocyclization of nitroarenes: novel synthesis of indole and 2H-indazole derivatives” *J. Org. Chem.* **1994**, *59*, 3375
11 Hsieh, T. H. H.; Dong, V. M. “Indole synthesis: palladium-catalyzed C–H bond amination via reduction of nitroalkenes with carbon monoxide” *Tetrahedron* **2009**, *65*, 3062
12 (a) Breslow, R.; Gellman, S. H. “Tosylamidation of cyclohexane by a cytochrome P-450 model” *J. Chem. Soc., Chem. Commun*, **1982**, 1400. (b) Breslow, R.; Gellman, S. H. “Intramolecular nitrene carbon-hydrogen insertions mediated by transition-metal complexes as nitrogen analogs of cytochrome P-450 reactions” *J. Am. Chem. Soc*, **1983**, *105*, 6728
13 Espino, C. G.; Du Bois, J. “A Rh-catalyzed C−H insertion reaction for the oxidative conversion of carbamates to oxazolidinones” *Angew. Chem., Int. Ed*, **2001**, *40*, 598
14 Espino, C. Wehn, P. Chow, J. Du Bois, J. “Synthesis of 1,3-difunctionalized amine derivatives through selective C−H bond oxidation” *J. Am. Chem. Soc*, **2001**, *123*, 6935
15 (a) Hawkins, D. G.; Meth-Cohn, O. “An in-depth study of the azidobenzophenone–anthranil–acridone transformation” *J. Chem. Soc. Perkin. Trans. 1*. **1983**, 2077. (b) Isomura, K.; Uto, K.; Taniguchi, H. “Palladium(II)-catalysed formation of indoles from 2,2-diphenyl-2H-azirines” *J. Chem. Soc., Chem. Commun*. **1977**, 664.
16 Chiba, S.; Hattori, G.; Narasaka, K. “Rh(II)-catalyzed isomerization of 2-Aryl-2H-azirines to 2,3-disubstituted indoles” Chem. Lett. 2007, 36, 52
17 Jana, S.; Clements, M. D.; Sharp, B. K.; Zheng, N. “Fe(II)-catalyzed amination of aromatic C−H bonds via ring opening of 2H-azirines: synthesis of 2,3-disubstituted indoles” Org. Lett. 2010, 12, 3736
18 (a) Cenini, S. Gallo, E. Caselli, A. Ragaini, F. Fantauzzi, S. Piangiolino, C. “Coordination chemistry of organic azides and amination reactions catalyzed by transition metal complexes” *Coord. Chem. Rev*. **2006**, *250*, 1234. (b) T. Katsuki, T. “Azide Compounds: Nitrogen sources for atom-efficient and ecologically benign nitrogen-atom-transfer reactions” *Chem. Lett*. **2005**, *34*, 1304. (c) Driver, T. “Recent advances in transition metal-catalyzed N-atom transfer reactions of azides.” *Org. Biomol. Chem*. **2010**, *8*, 3831
19 (a) Murakami, M. Uchida T. Katsuki, T. “Ru(salen)-catalyzed asymmetric sulfimidation using arylsulfonyl azide” *Tetrahedron Lett*, **2001**, *42*, 7071 (b) Fujita, H. Uchida, T. Lrie, R. Katsuki, T. “Asymmetric sulfimidation with cis-β Ru(salalen)$(CO)_2$ complexes as catalyst” *Chem. Lett*, **2007**, *36*, 1092
20 (a) Kwart, H. Khan, A. “Copper-catalyzed decomposition of benzenesulfonyl azide in cyclohexene solution ”*J. Am. Chem. Soc*, **1967**, *89*, 1951 (b) Evans, D. Faul, M. Bilodeau, M. “Copper-catalyzed aziridination of olefins by (N-(p-toluenesulfonyl)imino)phenyliodinane”*J. Org. Chem*, **1991**, *56*, 6744
21 Ruppel, J. Kamble, R. Zhang, X. “Cobalt-catalyzed intramolecular C−H amination with arylsulfonyl azides” *Org. Lett*, **2007**, *9*, 4889
22 Lu, H. Tao, J. Jones, J. Wojtas, L. Zhang, X. “Cobalt(II)-catalyzed intramolecular C−H amination with phosphoryl azides: formation of 6- and 7-membered cyclophosphoramidates” *Org. Lett*, **2010**, *12*, 1248.
23 W. G. Shou, J. Li, T. Guo, Z. Lin and G. Jia, Organometallics, 2009, 28, 6847
24 (a) Stokes, B. J.; Dong, H.; Leslie, B. E.; Pumphrey, A. L.; Driver, T. G. “Intramolecular C–H amination reactions: exploitation of the Rh(II)-catalyzed decomposition of azidoacrylates.” *J. Am. Chem. Soc*. **2007**, *129*, 7500. (b) Dong, H.; Shen, M.; Redford, J. E.; Stokes, B. J.; Pumphrey, A. L.; Driver, T. G. “Transition metal-mediated synthesis of pyrroles from dienyl azides.” *Org. Lett*. **2007**, *9*, 5191. (c) Shen, M.; Leslie, B. E.; Driver, T. G. “Rh(II)-catalyzed intramolecular C–H amination of aryl azides.” *Angew. Chem., Int. Ed*. **2008**, *47*, 5056.
25 (a) King, E. R. Hennessy, E. T. Betley, T. A. “Catalytic C−H bond amination from high-spin iron imido complexes.” *J. Am. Chem. Soc*. **2011**, *133*, 4917. (b) King, E. R. Betley, T. A. “C−H bond amination from a ferrous

dipyrromethene complex." *Inorg. Chem*. **2009**, *48*, 2361. (c) Shen, M. Driver, T. G. "Iron(II) bromide-catalyzed synthesis of benzimidazoles from aryl azides." *Org. Lett*. **2008**, *10*, 3367.

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

27 (a) Badiei, Y. M. Dinescu, A. Dai, X. Palomino, R. M. Heinemann, F. W. Cundari, T. R. Warren, T. H. "Copper-nitrene complexes in catalytic C−H amination." *Angew. Chem., Int. Ed*. **2008**, *47*, 9961. (b) Badiei, Y. M. Krishnaswamy, A. Melzer, M. M. Warren, T. H. "Transient terminal Cu-nitrene intermediates from discrete dicopper nitrenes." *J. Am. Chem. Soc*. **2006**, *128*, 15056. (c) Zang, Y. Hsung, R. P. Trscey, M. R. Kurtz, K. C. M. Vera, E. L. "Copper sulfate-pentahydrate-1,10-phenanthroline catalyzed amidations of alkynyl bromides. Synthesis of heteroaromatic amine substituted ynamides." *Org. Lett*. **2004**, *6*, 1151. (d) Dong, H. Shen, M. Redford, J. E. Stokes, B. J. Pumphrey, A. L. Driver T. G., "Transition metal-catalyzed synthesis of pyrroles from dienyl azides." *Org. Lett*., **2007**, *9*, 5191. (e) Chiba, S. Zhang, L. Ang, G. Y. Hui, B. W.-Q. "Generation of iminyl copper species from alpha-azido carbonyl compounds and their catalytic C−C bond cleavage under an oxygen atmosphere." *Org. Lett*. **2010**, *12*, 2052.

28 (a) Harvey, M. E. Musaev, D. G. Du Bois, J. "A diruthenium catalyst for selective, intramolecular allylic C-H amination: reaction development and mechanistic insight gained through experiment and theory." *J. Am. Chem. Soc*. **2011**, *133*, 17207. (b) Caselli, A. Gallo, E. Ragaini, F. Ricatto, F. Abbiati, G. Cenini, S. "Chiral porphyrin complexes of cobalt(II) and ruthenium(II) in catalytic cyclopropanation and amination reactions." *Inorg. Chim. Acta*. **2006**, *359*, 2924. (c) Ragaini, F. Penoni, A. Gallo, E. Tollari, S. Gotti, C. L. Lapadula, M. Mangioni, E. Cenini, S. "Amination of benzylic C-H bonds by arylazides catalysed by CoII(porphyrin) complexes. A synthetic and mechanistic study." *Chem. Eur. J*. **2003**, *9*, 249. (d) Shou, W. G. Li, J.; Guo, T. Lin, Z. Jia, G. "Ruthenium-catalyzed intramolecular amination reactions of aryl- and vinylazides." *Organometallics*. **2009**, *28*, 6847.

29 Swenton, J. S. Ikeler, T. J. Williams, B. H. "Photochemistry of singlet and triplet azide excited states." *J. Am. Chem.Soc*. **1970**, *92*, 3103.

30 For more information, refer to the Supporting Information part.

31 Stokes, B. J.; Jovanović, B.; Dong, H.; Richert, K. J.; Riell, R. D.; Driver, T. G. "Rh_2(II)-Catalyzed synthesis of carbazoles from biaryl azides." *J. Org. Chem*. **2009**, *74*, 3225.

32 Espino, C. G.; Fiori, K. W.; Kim, M.; Du Bois, J. "Expanding the scope of C−H amination through catalyst design." *J. Am. Chem. Soc*. **2004**, *126*, 15378.

33 Gorin, D. J.; Davis, N. R.; Toste, F. D. "Gold(I)-catalyzed intramolecular acetylenic schmidt reaction." *J. Am. Chem. Soc*. **2005**, *127*, 11260

34 Sun, K.; Sachwani, R.; Richert, K. J. "Intramolecular Ir(I)-catalyzed benzylic C–H bond amination of ortho-substituted aryl azides." *Org, Lett*. **2009**, *11*, 3598.

35 (a) Chiba, S.; Zhang, L.; Lee, J.-Y. "Copper-catalyzed synthesis of azaspirocyclohexadienones from α-azido-N-arylamides under an oxygen atmosphere" *J. Am, Chem. Soc*. **2010**, *132*, 7266. (b) Chiba, S.; Zhang, L.; Ang, G. Y.; Hui, W.-Q. "Generation of iminyl copper species from α-azido carbonyl compounds and their catalytic C−C bond cleavage under an oxygen atmosphere" *Org. Lett*. **2010**, *12*, 2052.

36 (a) Waterman, R.; Hillhouse, G. L. "η^2-Organoazide complexes of nickel and their conversion to terminal imido complexes via dinitrogen extrusion" *J. Am. Chem. Soc*. **2008**, *130*, 12628.; (b) Albertin, G.; Antoniutti, S.; Baldan, D.; Castro, J.; Garcia-Fontan, S. "Preparation of benzyl azide complexes of iridium(III)." *Inorg. Chem*. **2008**, *47*, 742.; N_α and N_γ coordination: (c) Dias, H. V. R.; Polach, S. A.; Goh, S.-K.; Archibong, E. F.; Marynick, D. S.; "Copper and silver complexes containing organic azide ligands: syntheses, structures, and theoretical investigation of $[HB(3,5\text{-}(CF_3)_2Pz)_3]CuNNN(1\text{-}Ad)$ and $[HB(3,5\text{-}(CF_3)_2Pz)_3]AgN(1\text{-}Ad)NN$ (where Pz = Pyrazolyl and 1-Ad = 1-Adamantyl)." *Inorg. Chem*. **2000**, *39*, 3894; N_γ coordination: (d) Fickes, M. G.; Davis, W. M.; Cummins, C. C. "Isolation and structural characterization of the terminal mesityl azide complex $V(N_3Mes)(I)(NRArF)_2$ and its conversion to a vanadium(V) imido complex." *J. Am. Chem. Soc*. **1995**, *117*, 6384

37 For computional studies on the mechanism of copper nitrenoid formation from azides, see: (a) Badiei, Y. M.; Dinescu, A.; Dai, X.; Palomino, R. M.; Heinemann, F. W.; Cundari, T. R. Warren, T. H. "Copper–nitrene complexes in catalytic C-H amination" *Angew. Chem*. **2008**, *120*, 10109; *Angew, Chem, Int, Ed*. **2008**, *47*, 9961. (b). Cundari, T. R.; Dinescu, A; Kazi, A. B. "Bonding and structure of copper nitrenes." *Inorg. Chem*. **2008**, *47*, 10067.

38 For report of related bicycle[4.2.0] nonadienes, see: Scholes, G.; Graham, G. R.; Brookhart, M. *J. Am, Chem, Soc*. **1974**, *96*, 5665.; Paquette, L. A.; Photis, J. M.; "Reactions of the K-region oxides of carcinogenic and related polycyclic hydrocarbons with nucleophiles: stereochemistry and regioselectivity" *J. Am. Chem. Soc*. **1976**, *98*, 4936.

39 (a) Cram, D. J.; *J. Am. Chem. Soc*. **1949**, *71*, 3863. (b) Cram, D. J. "Phenonium ions as discrete intermediates in certain Wagner-Meerwein rearrangements." *J. Am. Chem. Soc*. **1964**, *86*, 3767.
40 (a) Olah, G. A.; Head, N. J.; Rasul, G.; Prakash, G. K. S. "Protonation of benzocyclobutene with superacid: Cram's phenonium ion (spiro[5.2]octa-5,7-dien-4-yl cation) revisited." *J. Am. Chem. Soc*. **1995**, *117*, 875. (b) Manet, I.; Monti, S.; Grabner, G.; Protti, S.; Dondi, D.; Dichiarante, V.; Fagnoni, M.; Albini, A. "Revealing phenylium, phenonium, vinylenephenonium and benzenium ions in solution." *Chem. Eur. J*. **2008**, *14*, 1029.
41 Pangborn, A. B.; Giardello, M. A.; Grubbs, R. H.; Rosen, R. K.; Timmers, F. J. "Safe and convenient procedure for solvent purification." *Organometallics*, **1996**, 15, 1518.
42 Stokes, B. J.; Vogel, C. V.; Urnezis, L. K.; Pan, M.; Driver, T. G. "Intramolecular Fe(II)-catalyzed N-O or N-N bond formation from aryl azides." *Org. Lett*. **2010**, *12*, 2884.
43 Brawn, R. A.; Welzel, M.; Lowe, J. T.; Panek, J. S. "Regioselective intramolecular dipolar cycloaddition of azides and unsymmetrical alkynes." *Org. Lett*. **2010**, *12*, 336
44 Main, C. A.; Petersson, H. M.; Rahman, S. S.; Hartley, R. C. "High throughput synthesis of diverse 2,5-disubstituted indoles using titanium carbenoids bearing boronate functionality". *Tetrahedron* **2008**, *64*, 901
45 Hill, T. J.; Hughes, R. K.; Scott, L. T. "Steps toward the synthesis of a geodesic $C_{60}H_{12}$ end cap for a C_{3v} carbon [6,6] nanotube." *Tetrahedron* **2008**, *64*, 11360
46 Chong, P. Y.; Janicki, S. Z.; Petillo, P. A. "Multilevel selectivity in the mild and high-yielding chlorosilane-induced cleavage of carbamates to isocyanates." *J. Org. Chem.* **1998**, *63*, 8515
47 Liu, Q.; Tor, Y. "Simple conversion of aromatic amines into azides" *Org. Lett.* **2003**, *5*, 2571
48 Sun, K.; Sachwani, R.; Richert, K. J.; Driver, T. G. "Intramolecular Ir(I)-catalyzed benzylic C-H bond amination of *ortho*-substituted aryl azides" *Org. Lett.* **2009**, *11*, 3598
49 Smith, P. A. S.; Rowe, C. D.; Hansen, D. W. "Stereochemistry in the cyclization of *o*-azidophenylalkenes to indoles" *Tetrahedron Lett.* **1983**, *24*, 5169
50 Katritzky, A. R.; Wang, Z. "The synthesis of some alkylbenzocarbazoles" *J. Heterocycl. Chem.* **1988**, *25*, 671
51 Tan, Y.; Hartwig, J. F. "Palladium-catalyzed amination of aromatic C−H bonds with oxime esters" *J. Am. Chem. Soc.* **2010**, *132*, 3676
52 Chiba, S.; Hattori, G.; Narasaka, K. "Rh (II)-Catalyzed isomerization of 2-aryl-2H-azirines to 2, 3-disubstituted indoles" *Chem. Lett.* **2007**, *36*, 52
53 Leogane, O.; Lebel, H. "One-pot multicomponent synthesis of indoles from 2-iodobenzoic acid" *Angew. Chem., Int. Ed.* **2008**, *47*, 350
54 Banwell, M. G.; Kelly, B. D.; Kokas, O. J.; Lupton, D. W. "Synthesis of indoles via palladium[0]-mediated ullmann cross-coupling of α-halonitroarenes with α-halo-enones or –enals" *Org. Lett.* **2003**, *5*, 2497
55 Cacchi, S.; Fabrizi, G.; Lamba, D.; Marinelli, F.; Parisi, L. M. "2-Substituted 3-aryl- and 3-heteroarylindoles by the palladium-catalyzed reaction of *o*-trifluoroacetanilides with aryl bromides and triflates" *Synthesis* **2003**, *5,* 728
56 Wang, X.; Gribkov, D. V.; Sames, D. "Phosphine-free palladium-catalyzed C-H bond arylation of free (N-H)-indoles and pyrroles" *J. Org. Chem.* **2007**, *72*, 1476

Curriculum vitae

Education and Honors

University of Illinois at Chicago, Chicago, IL

2007 – Current Ph.D., Organic Chemistry, expected 2012
Travel Award, 42nd National Organic Symposium (NOS), 2011 Summer

Nankai University, Tianjin, China

2004 – 2007 M.S., organic Chemistry
Graduate Registration Scholoarship 2004 – 2006

Dalian University of Technology, Dalian, China

1999 – 2003 B.E., Chemical Engineering and Technology
2nd Tier Dalian University of Technology Scholarship, 2000-2001
Network course won the Award of Excellence by the Ministry of Education

Research and Teaching Experience

2007 – Present **PhD candidate; Graduate Research Associate** *with* ***Dr. Tom Driver***
Intramolecular Ir(I)-catalyzed benzylic C-H bond amination of aryl azide.
Rhodium-catalyzed Synthesis of 2,3-disubstituted indoles from migration of β,β -disubstituted styryl azide.
Rh_2(II)-catalyzed intramolecular aliphatic C-H bond amination.
Teaching Assistant in Organic Chem, Organic Chem Lab and General Chem

2004 – 2007 **Graduate Research Associate** *with* ***Dr. Yuanyuan Qiao***
Using statistical method to determine what kind of ligand fragments are more likely to fit binding site of protein in drug discovery.
Research Assistant for Prof. Yuanyuan Qiao.
Maintained the facilities and supervised the lab.

2000 – 2002 **Undergraduate Research Assistant** *with* ***Dr. Zhanxian Gao***
Design and development of network couse of organic chemistry
Supervised Prof. Zhanxian Gao's lab and organized lab work
Participated in Prof. Zhanxian Gao's academic activities

Peer-Reviewed Publications

1. Qiao, Y.; **Sun, K.;** Liu, C., Chemoinformatics and the openness of drug discovery research. *Computers and Applied Chemistry*, **2006**, *23*, 1283-1286

2. **Sun, K.**; Sachwani, R.; Richert, K. J.; Driver, T. G., Intramolecular Ir(I)-catalyzed benzylic C-H bond amination of *ortho*-substituted aryl azides, *Organic Letters* **2009**, *11*, 3598-3601.

3. **Sun, K.**; Liu, S.; Bec, P. M.; Driver, T. G., Rhodium-catalyzed synthesis of 2,3-disubstituted indoles from β,β-disubstituted styryl azides, *Angew. Chem., Int. Ed.* **2011**, *50*, 1702-1706

4. Nguyen, Q.; **Sun, K.**; Driver, T. G., Rh_2(II)-catalyzed intramolecular aliphatic C-H bond amination reactions using aryl azides as the N-atom source, *J. Am. Chem. Soc.* **2012**, *134*, 7262-7265

Poster Presentation

1. **Sun, K.**; Driver, T. G., Formation of 2,3-disubstituted indoles via a Rh_2(II)-catalyzed Tandem reactions from aryl azides, 2nd Chicago Organic Symposium, Evanston, IL, United States, February, 2010

1. **Sun, K.**; Liu, S.; Bec, P. M.; Driver, T. G., Rh_2(II)-catalyzed cascade reactions of styryl azides produce 2,3-disubstituted indoles, 3rd Chicago Organic Symposium, Evanston, IL, United States, February, 2011

3. **Sun, K.**; Liu, S.; Bec, P. M.; Driver, T. G., Rh_2(II)-catalyzed cascade reactions of styryl azides produce 2,3-disubstituted indoles, 42nd National Organic Symposium, Princeton, NJ, June 5 – 9, 2011.