

Transition-Metal Catalyzed $\text{sp}^3\text{-C-H}$ Bond Amination from Aryl Azides

BY

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THESIS

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This thesis is dedicated to my husband and my son, without whom it would never have been accomplished

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A lot of love and appreciation go for my family. It is my hope that completing this work will be a cause of pride for all of them. And last but not least, special thank to Huy Vuong, my husband. Your endless love and care have helped me through all ups and downs of graduate school. Being amazing husband and friend, you deserve my deepest respect. More importantly, you brought to me a piece of you, our little son Sam, whose smiles just made our lives brighter. I find no words to describe my feelings for making me a mom. And you must know, this is not an acknowledgement that will be forgotten in a while, but it is something that I want it to remain forever to remind you that you will always be my beloved soul mate.

Chapter 1 is a literature review on a variety of C–H bond amination in both intermolecular and intramolecular fashion in which I introduced my dissertation question in the context of larger field. Chapter two described my published work on $\text{Rh}_2(\text{esp})_2$ catalyzed aliphatic C–H bond amination reactions of aryl azides (*J. Am. Chem. Soc.* **2012**, *134*, 7262) for which I the primary author and major driver of the research. To finish this work, I have received assistant from Dr. Ke Sun in the experiments shown in section 2.6. Chapter three disclosed the tandem ethereal C–H bond amination–elimination–[1,2]–migration reaction catalyzed by inexpensive, nontoxic FeBr_2 (*J. Am. Chem. Soc.* **2013**, *135*, 620). My undergraduate student Tuyen Nguyen assisted me in the experiments shown in section 3.6. Chapter 4 represents a published manuscript (*Angew. Chem., Int. Ed.* **2014**, *53*, 785) for which I was the second author. I performed a part of experiments described in section 4.6. and contributed to writing of the supporting information along with the first author Dr. Crystalann Jones. My research advisor, Dr. Tom Driver contributed to the writing of all published work.

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LIST OF ABBREVIATIONS

Ac	acetyl
Alk	alkyl
aq	aqueous
Ar	aryl
atm	atmosphere
Bn	benzyl
Boc	<i>tert</i> -butoxycarbonyl
Bpin	pinacolborane
Bz	benzoyl
<i>n</i> -Bu	butyl
<i>t</i> -Bu	<i>tert</i> -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- <i>tert</i> -butyl-4-methylpyridine
dtbpy	4,4'-di- <i>tert</i> -butylbipyridine
EI	electron impact ionization (in mass spectrometry)
Et	ethyl
eq, equiv.	molar equivalent
Rh ₂ (esp) ₂	Bis[rhodium($\alpha,\alpha,\alpha',\alpha'$ -tetramethyl-1,3-benzenedipropionic acid)]
FePc	iron phthalocyanine
FT	Fourier transform
g	gram
GC	gas chromatography
h, hrs	hour(s)
HMDS	hexamethyldisilazane
HR	high resolution (mass spectrometry)
Hz	Hertz
<i>J</i>	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	<i>p</i> -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
<i>p</i> -cymene	<i>para</i> -isopropyltoluene
pfb	perfluorobutyrate, heptafluorobutyrate
Ph	phenyl
Piv	pivalyl, trimethylacetyl
ppm	parts per million
Pr	propyl
<i>i</i> -Pr	isopropyl
<i>n</i> -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

LIST OF ABBREVIATIONS (continued)

Ts	p-toluenesulfonyl		
TTX	tetradotoxin	UV	ultraviolet

SUMMARY

This thesis studied transition metal catalyzed sp^3 -C–H amination reaction using aryl azides as the nitrogen source to produce N-heterocyclic compounds including indole and indoline. Additionally, dirhodium(II) carboxylate promoting the formation of 1,2,3-trisubstituted Indoles from styryl azides was discussed afterwards.

Chapter one briefly introduced a variety of C–H bond amination in both intermolecular and intramolecular fashion. Subsequently, iron complexes and dirhodium(II) carboxylate promoting C–H bond amination was well studied, and $Rh_2(esp)_2$ has been widely discussed. To demonstrate the application of transition metal catalyzed C–H bond amination, at the end of this chapter, examples on total synthesis of natural product tetrodotoxin and manzacidin A were presented.

Chapter two described $Rh_2(esp)_2$ catalyzed aliphatic C–H bond amination reactions of aryl azides without requiring a strong electron-withdrawing group on the nitrogen atom. When other metal catalysts such as iridium, iron, copper complexes led to no reaction at high temperature, thermally robust $Rh_2(esp)_2$ was found to effectively generate corresponding indolines from aryl azides. To improve the isolated yield of the reaction, Boc_2O was added to the reaction mixture to protect the resulting indoline. The mechanistic study carried out on the reactivity of stereospecific labeled aryl azides supports for the formation of the nitrenoid followed by stepwise pathway with the *syn*-C–H bond through radical species.

Chapter three disclosed the tandem ethereal C–H bond amination–elimination-[1,2]-migration reaction catalyzed by inexpensive, nontoxic $FeBr_2$. The electronic nature of the aryl azide was found not to affect the reaction yield and the migratorial preference for the 1,2-shift step of the catalytic cycle was established to be $Me \ll 1^\circ \ll 2^\circ \ll Ph$. With the successful

isolation of some intermediates, mechanistic experiments revealed FeBr₂ to be essential for both the C–H bond amination as well as the iminium ion generation.

Chapter four investigated Rh₂(II)-catalyzed formation of 1,2,3-trisubstituted indoles from trisubstituted styryl azides with exclusive carbonyl migration. The requisite styryl azides were readily available in three steps from cyclobutanone and 2-iodoaniline. We discovered that a range of different substituents at the α -position as well as on aryl azide was tolerated in this reaction. The proposed mechanism involved 4 π -electron-5-atom electrocyclization and formation of spirocyclic cation that triggers the migration process.

Chapter 1. Transition Metal-Catalyzed $\text{sp}^3\text{-C-H}$ Bond Amination

The catalytic functionalization of $\text{sp}^3\text{-C-H}$ bonds is a highly sought methodology because it could rapidly enable the conversion of simple starting materials into highly functionalized organic compounds and the efficient structural editing of already complex molecules by eliminating functional group manipulation and minimizing waste. Therefore, the interest of the research community in developing these sustainable methodologies is strongly increasing. To date, several notable results of selective functionalization of $\text{sp}^3\text{-C-H}$ bond have been reported, such as the intramolecular arylation of an $\text{sp}^3\text{-C-H}$ bond,¹ the alkylation² and carbonylation³ of an $\text{sp}^3\text{-C-H}$ bond adjacent to a heteroatom, the borylation⁴ and silylation⁵ of a benzylic C-H bond with hydroboranes and hydrosilanes, the introduction of a heteroatom at an $\text{sp}^3\text{-C-H}$ bond,⁶ and so on. Among them, the direct transformation of a C-H bond into a C-N bond represents a research area of high impact because nitrogen-containing heterocyclic compounds are biologically active and are scaffolds for many pharmaceuticals. In this chapter, recent advances in $\text{sp}^3\text{-C-H}$ bond amination and their applications are discussed.

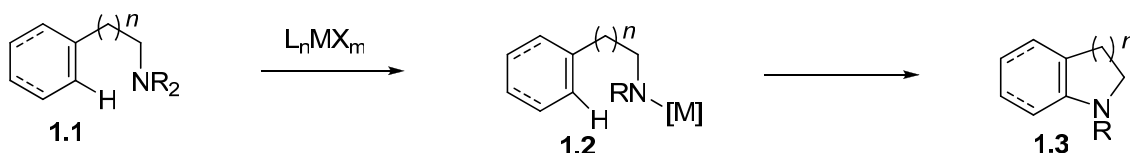
1.1 Intramolecular C-H Bond Amination

As aforementioned, metal-catalyzed C-H amination processes have been widely pursued. In general, there are two different strategies to promote the C-H bond amination (Scheme 1.1).⁸ The first one is to access a metal nitrene through the activation of the N-atom. When the N-atom is inserted into a proximal C-H bond in either a concerted or stepwise fashion, the requisite C-N bond can be formed. The second strategy is to use transition metal complexes that selectively activate the C-H bond to create a carbon-metal bond as in **1.4**. The desired C-N bond would then be generated through the functionalization of this reactive carbon-metal bond using an

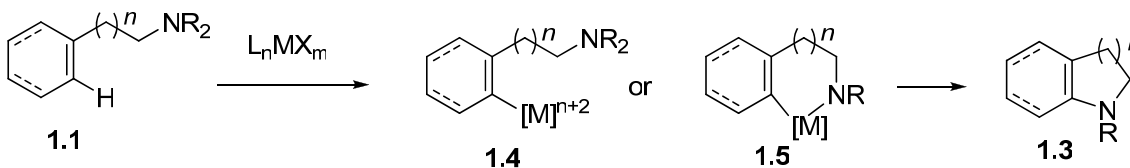
amine or an amine surrogate. The tactic that has been used most successfully has been to incorporate the amine into the substrate to enable access of metallocycles, such as **1.5**, from which reductive elimination can occur to establish the C–N bond. Since the amine can direct C–H bond activation, this latter approach exhibits good regioselectivity.

Scheme 1.1. Strategies for transition metal-catalyzed C–H bond functionalization.

N-atom activation



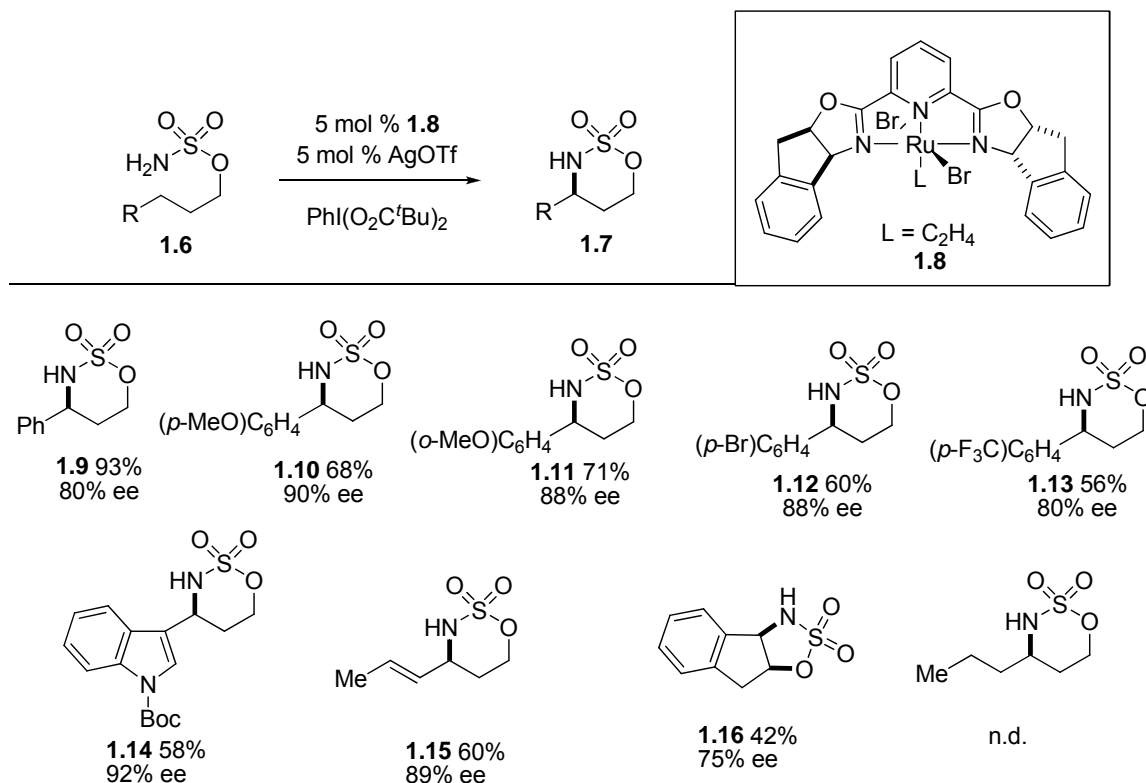
C - H bond activation



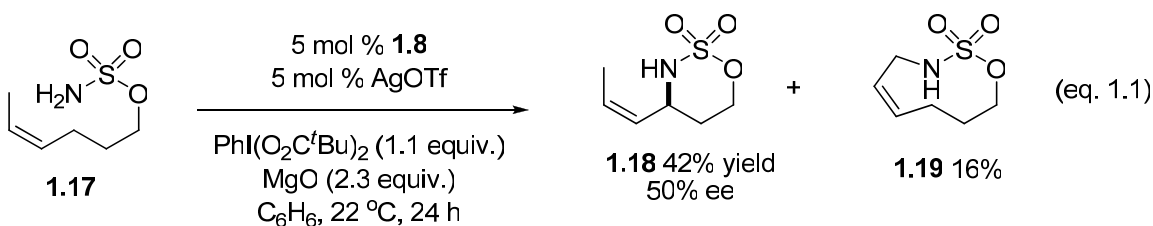
1.1.1 Intramolecular processes via nitrene insertions

While the reactivities of nitrenes and nitrenoids make them valuable tools for C–H aminations, it is also a challenge to control their reactivity so that other competing processes such as aziridination cannot interfere. Blakey and co-workers have reported that high enantioselectivity can be obtained using cationic Ru(II)-pybox catalyst, such as in the reaction of **1.6** (Scheme 1.2).⁸ The anionic ligands provided the flexibility to achieve catalytic asymmetric amination of both benzylic and allylic C–H bonds. Under optimized conditions, substrates bearing either electron-donating or electron-withdrawing substituents on the aryl ring were tolerated, and the products were obtained with good yields and excellent enantioselectivities.

Scheme 1.2. Asymmetric amination of benzylic and allylic C–H bonds



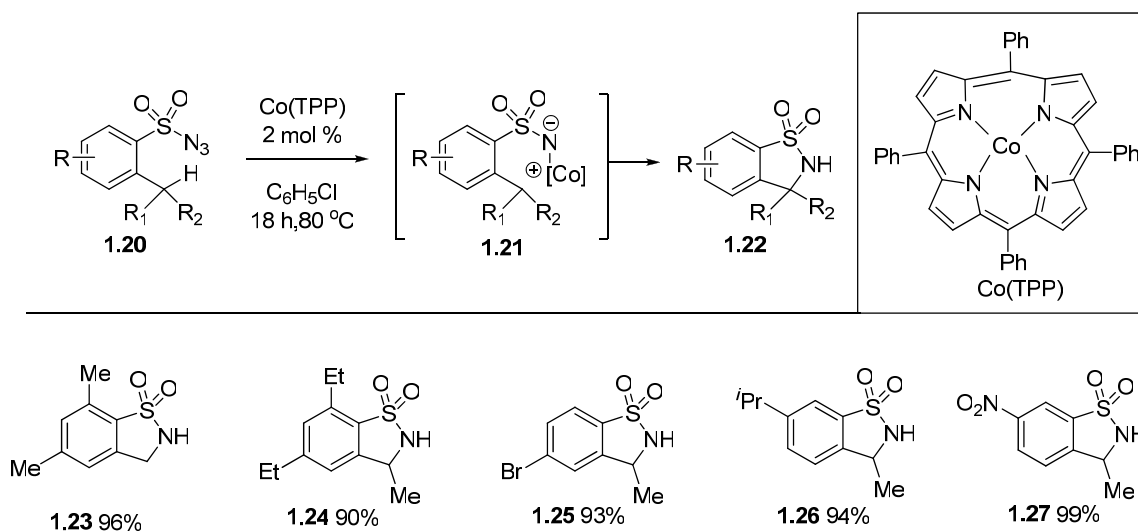
The preference for C–H insertion exhibited by the cationic Ru(II)-pybox system was further highlighted in the reaction of *cis*-olefin **1.17** (equation 1.1) producing only six- or nine-membered ring products: no arizidation product was observed. However, this method is limited to the ineffective amination of straight-chain aliphatic substrates.



Azides are considered one of the better potential nitrenoid precursor because they are readily available from sodium azide, no additives are required besides catalyst to form nitrenoid reactive intermediate, and the sole byproduct is the environmentally benign N_2 gas. Although

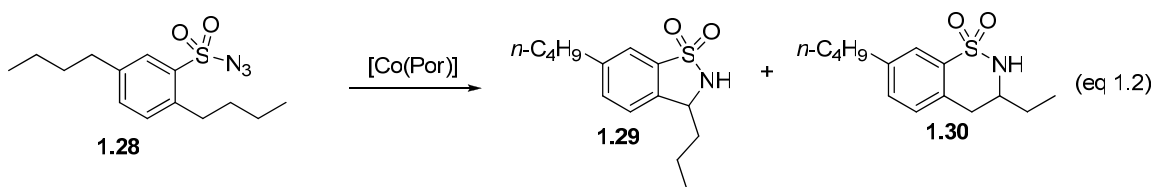
difficulty in controlling azide reactivity has limited their usage as a viable C–H amination reagent, recent strides have been made. In 2007, the Zhang group reported that commercially available cobalt(II) tetraphenylporphyrin complexes, Co(TPP), to be an effective catalyst for intramolecular amination reaction of benzylic C–H bonds using arylsulfonylazides **1.20** as nitrogen source (Scheme 1.3).⁹ Under mild conditions in low catalyst loading without the need of other reagents or additives, this cobalt-catalyzed process provides an efficient methodology to synthesize corresponding benzosultam derivatives **1.22**, which are presented in various important natural products. The authors proposed the mechanism involved cobalt-nitrene intermediate **1.21**.

Scheme 1.3. Cobalt(II) complex catalyzes intramolecular amination using arylsulfonyl azide as nitrogen source.



The scope of this cobalt-mediated benzylic C–H bond amination reaction was found to be broad. Selective formation of the corresponding five-membered heterocycles can be obtained from intramolecular nitrene insertion into tertiary (**1.26**), secondary (**1.24**), and even primary C–H bonds (**1.23**) of various arylsulfonyl azides having multiple aromatic substituents.

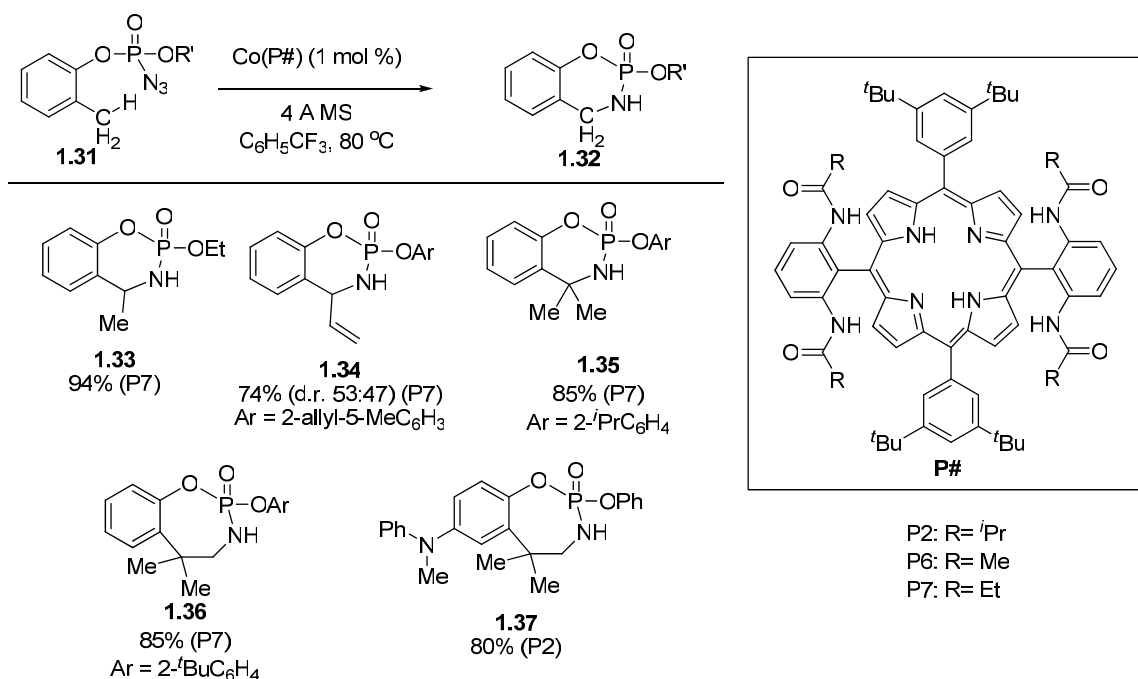
Interestingly, they noticed that higher yields could be obtained by increasing substitution on the aromatic ring, which suggested a positive buttressing effect of *meta*- and *para* groups on the nitrene insertion of *ortho* C–H bonds. Evaluating the reaction at three different temperatures (80 °C, 40 °C, and room temperature), they found that at lower temperature the reactivity pattern of the C–H bonds followed the order of 3° > 2° > 1°. In addition, azides containing two different 2° C–H bonds such as benzylic and aliphatic types in **1.28** led to formation of both five- and six-membered ring products (equation 1.2). Their preliminary results indicated that the use of different porphyrin ligands affected the ratio of **1.29** and **1.30**.



Three years later, the Zhang group reported another intramolecular benzylic C–H bond amination reaction which could be accomplished from aryl phosphorylazide (Scheme 1.4).¹⁰ In contrast to their previous sulfonylazide study, the lower productivity of Co(TPP) indicated that phosphorylazides are less reactive than sulfonyl- and carbonyl azides. They also found that the identity of the porphyrin ligand strongly affected reaction efficiency. Porphyrins **P2**, **P6** and **P7** were showed to be effective ligands for Co(II)-based catalyzed 1,6- or 1,7- C–H nitrene insertion processes to form phosphoramidite **1.32**, presumably due to their participation in hydrogen bonding of the amide N–H with the oxide of the phosphoryl group on the nitrenoid. Under the optimized conditions, a range of phosphorylazides could be employed in the reaction to generate either a six- or a seven-membered ring. The latter is noteworthy for C–H bond aminations because it is rarely observed. In addition to secondary and tertiary C–H bonds, both benzylic and non-benzylic primary C–H bonds could be intramolecularly aminated in excellent yields using

this catalytic system. The authors also noticed that arizidination was not a competitive reaction when **1.34** can be obtained successfully. The cyclic phosphoramidite amination products can be reduced with LiAlH_4 or methanolized to produce value-added amine-containing products.

Scheme 1.4. Co-catalyzed intramolecular $\text{sp}^3\text{-C-H}$ amination of arylphosphorylazides

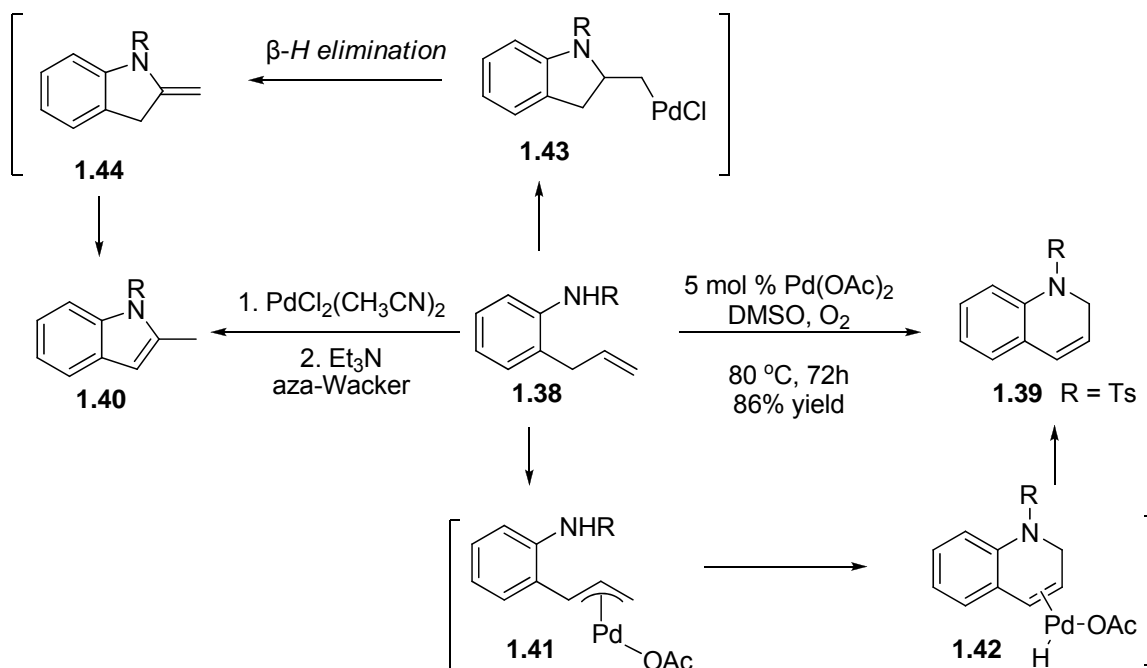


1.1.2 Intramolecular process via non-nitrene species

In 1996, Larock and coworkers reported a Pd(II) -catalyzed intramolecular amination/cyclization of olefinic tosylamides.¹¹ When 2-allyl-aniline **1.38** was exposed under Pd(II) catalyst system, the corresponding 6-membered ring 1,2-dihydroquinoline derivatives **1.39** were obtained exclusively in 86% yield instead of the expected product of a Markonikov-aza-Wacker addition, 2-methylindole **1.40**. This finding greatly simplified the synthesis of this ring system (Scheme 1.5). From their observation, the nature of cyclization remarkably depended on the identity of the group attached to nitrogen and the counterion presented in Pd catalyst. In

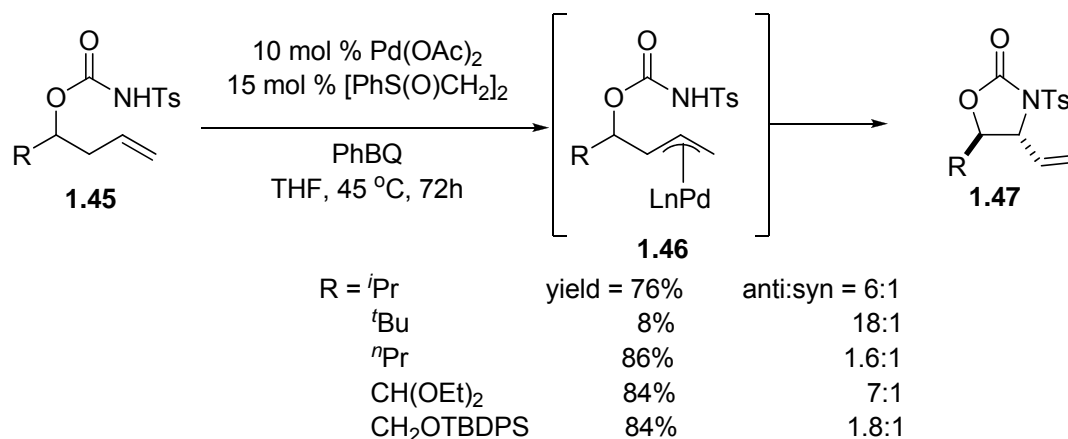
addition, the authors suggested that their catalyst system can either alter the regioselectivity of ring closure during electrophilic aminopalladation or proceed through an entirely different mechanism involving the formation of a π -allyl Pd intermediate **1.41**.

Scheme 1.5. Pd(II)-catalyzed C – H amination/cyclization



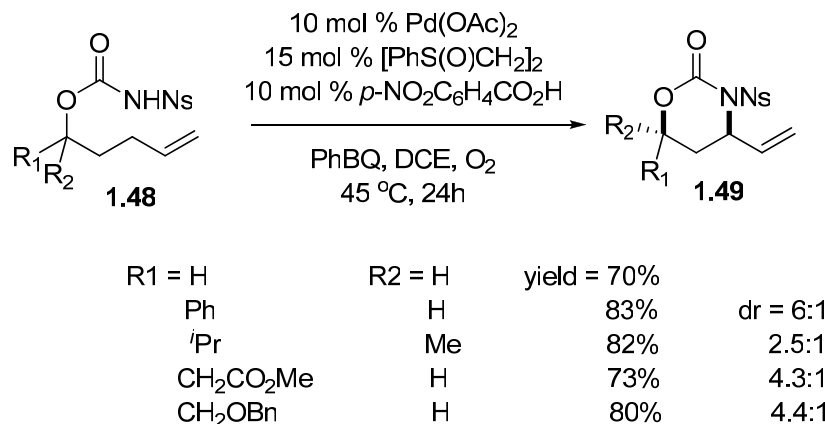
As a part of their ongoing work in Pd-catalyzed oxidation, White and coworkers utilized catalytic $\text{Pd}(\text{OAc})_2$ and a bis-sulfoxide ligand to streamline the synthesis of a diverse collection of syn-1,2-amino alcohols via diastereoselective allylic C–H amination (Scheme 1.6).¹² When examining the generality of their method, they found that increased branching on the R-group of **1.45** results in decreased yields, but increased diastereoselectivity in favor of the anti-product **1.47**. Data from their mechanistic studies revealed that a Pd(II)/bis-sulfoxide mediated C–H bond cleavage and formed a π -allyl Pd intermediate. Pd carboxylate counterion then acted as a base to deprotonate N-tosylcarbamate nucleophile and achieved functionalization. This was considered the first example of a general and stereoselective, catalytic allylic C–H amination.

Scheme 1.6. Pd(II)-catalyzed intramoleculardiastereoselective C–H amination



Two years later, a further report came from the White group when they discovered that by changing the N-protecting group from tosyl to 4-nosyl, the acidity of the NH group was increased, resulted in accelerating the reaction and improving yields of the formation of 1,3-amino alcohol motifs (Scheme 1.7).¹³ In terms of reactivity, chemo- and diastereo-selectivity, this reaction proved to be more generally effective for the formation of 6-membered oxazinanes **1.49**. The reactivity greatly favored the position adjacent to terminal double bonds over that of internal double bonds. In all cases, they were able to obtain dr's greater than 20:1 in good yield after standard column chromatography. The utility of this method was displayed in the synthesis of (+)-allosedrine in six steps, 27% overall yields, and >99% ee.¹⁴

Scheme 1.7. Synthesis of *syn*-1,3-amino alcohols from *N*-nosylcarbamates

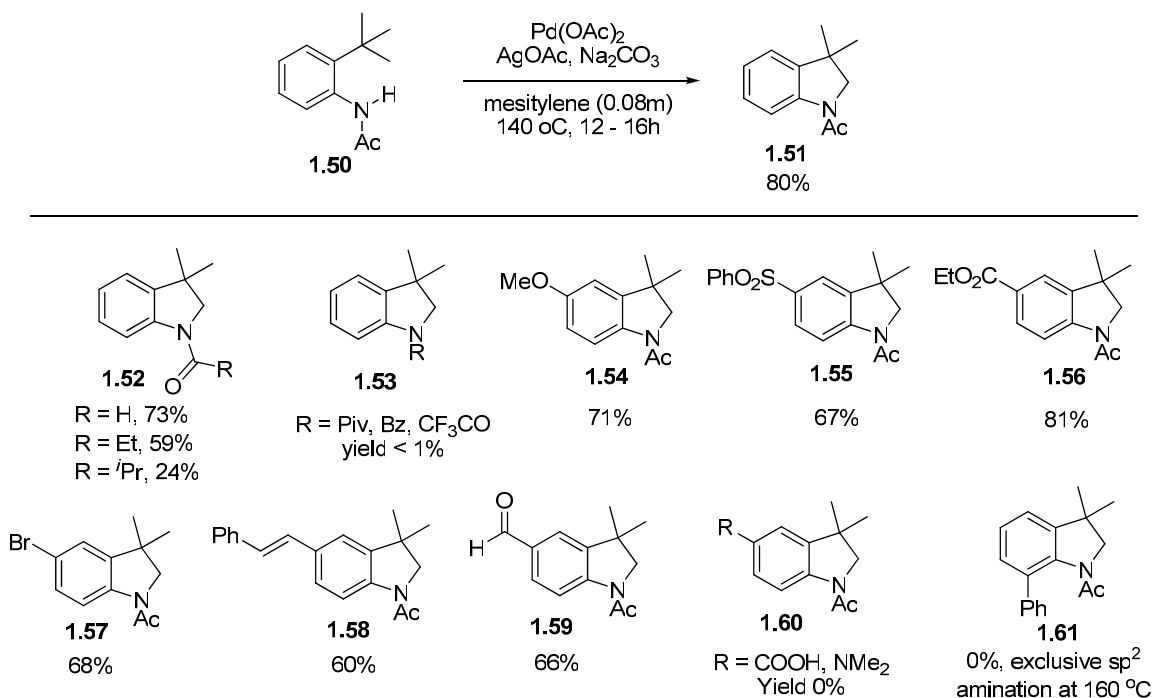


While transition metal-catalyzed activated $\text{sp}^3\text{-C-H}$ bond amination is common and well-developed, the amination of an unactivated $\text{sp}^3\text{-C-H}$ bond has been less studied. In 2009, the Glorius group reported the first unactivated $\text{sp}^3\text{-C-H}$ bond activation/C–N bond forming process mediated by Pd catalyst system that does not involve a metal nitrene intermediate (Scheme 1.8).¹⁵ After extensive screening, $\text{Pd}(\text{OAc})_2$ was identified to facilitate the transformation from **1.34** to **1.35** in 89% yield with an oxidant AgOAc . Under the optimized condition, an acetyl group on nitrogen gave the best result compared to formyl, propionyl, or isobutyryl group, and even no reaction was observed if pivaloyl, benzoyl, or trifluoroacetyl groups (**1.37**) were used. This observation indicated that this process strongly depended on a delicate balance between the electronic- and steric properties of the nitrogen substituent.

When the scope of this reaction was further examined using the optimized conditions (Scheme 1.8), it showed that a broad range of functional groups on the arene are tolerated. Both electron-donating and electron-withdrawing substituents, including ether, sulfones, and ester, as well as reactive substituents, such as bromo, olefin, and aldehyde groups, provided good to

excellent yields. However, when acidic protons (-OH, -COOH) or basic amines (-NH₂) were present in starting material anilines, the corresponding indolines were not observed, thus illustrating some of the limitations of this method. In addition, to test the competition in activity between sp²- vs sp³-C-H bond, a substrate having phenyl substituent in the 6-position was subjected to reaction condition. Only product generated from the exclusive sp²-C-H activation at the phenyl group was observed, demonstrating the challenge of sp³-C-H bond functionalization. Overall, the reaction was exceptionally successful in amination of unactivated sp³-C-H bonds.

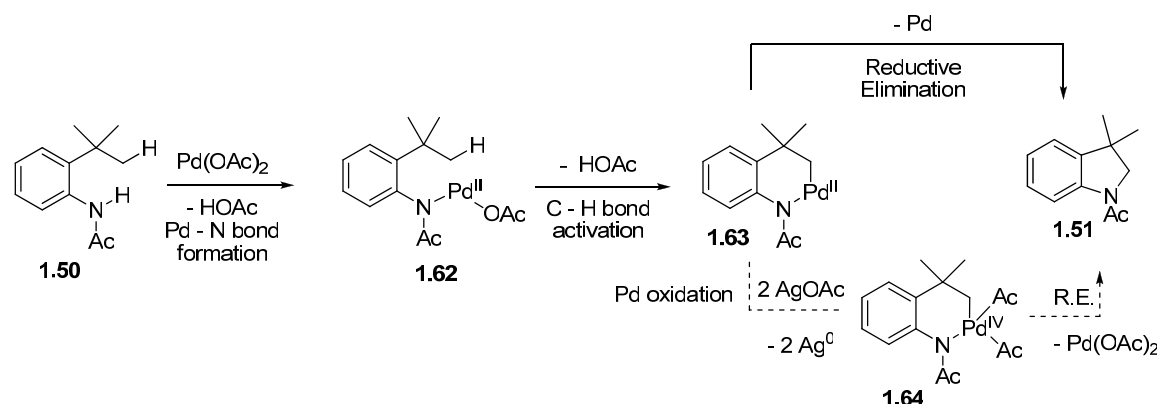
Scheme 1.8. Palladium-catalyzed amidation of unactivated sp³-C-H bond.



To account for the formation of *N*-(2-*tert*-butylphenyl) acetamide, a possible mechanism was proposed (Scheme 1.9). Initially, Pd(II) catalyst coordinates to nitrogen atom through ligand substitution of one acetate with the directing group acetanilide to produce **1.62**. When the Pd is close to proximal sp³-C-H bond of alkyl group, C-H bond activation can occur to yield intermediate **1.63**. Indoline **1.51** is the product of subsequent reductive elimination of Pd(0).

Alternatively, the reaction can proceed through a more highly oxidized Pd(IV) species **1.64**, which is formed from silver(I)-promoted oxidation of **1.63**.¹⁶

Scheme 1.9. Mechanism palladium-catalyzed amidation of unactivated sp^3 -C–H bond.



The concept of non-nitrene amination was further developed by both Chen and Daugulis when they succeeded in using the picoliamide group to direct intramolecular sp^3 -C–H activation. In 2005, Daugulis showed examples of the picoliamide (PA) group enabling a wide range of transformations including arylation and alkenylation of sp^3 - γ -C–H bonds with aryl and vinyl iodides.¹⁷ Inspired from his work, Chen and co-workers further expanded the synthetic utility of this PA-direct C–H functionalization strategy in synthesizing azetidines, pyrrolidines, and indolines via Pd catalyzed intramolecular amination of unactivated sp^3 -C–H bonds.¹⁸

An investigation was conducted in functionalizing sp^3 - γ -C–H bonds to C–N bonds under certain oxidative conditions through a Pd(II)/Pd(IV) catalytic cycle. The optimal condition for azetidine formation was found to be 5 mol % of Pd(OAc)₂ and two equivalents of AcOH in the presence of PhI(OAc)₂ as an oxidant. The scope of reaction was examined with a range of substrates bearing primary sp^3 - γ -C–H bonds with varying α - and β -substituents (Table 1.1). When both α - and β -substituents are present, reaction proceeded in good yields and high diastereoselectivity. In contrast, substrates lacking β -substitution produced poor yields.

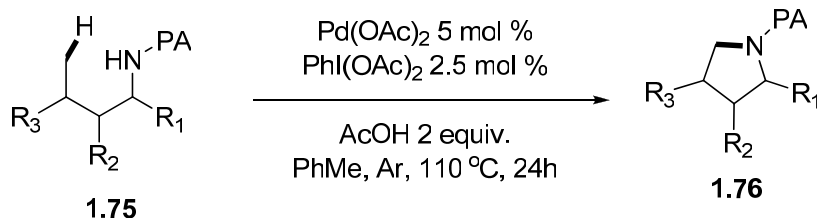
Table 1.1. Synthesis of Azetidines via intramolecular amination

<div style="display: flex; align-items: center; justify-content: space-around;"> <div style="text-align: center;"> <p>1.65 1.66</p> </div> <div style="border: 1px solid black; padding: 5px; text-align: center;"> <p>PA:</p> </div> </div>			
Substrate	Product	Substrate	Product
<p>1.67</p>	<p>1.68 (82%, dr > 20:1)</p>	<p>1.71</p>	<p>1.72 (68%)</p>
<p>1.69</p>	<p>1.70 (79%)</p>	<p>1.73</p>	<p>1.74 (25%)</p>

Formation of a five-membered pyrrolidine and indoline product from a six-membered Pd-intermediate is considered more favorable compared with the ring contraction to yield a four-membered azetidine, therefore, the possibility of the sp^3 - γ -C–H activation was later tested under these oxidative conditions. Similar to the azetidine synthesis, good yields and good diastereoselectivities could be achieved with the exception of substrates bearing no γ -substituents (Table 1.2). Through deuteration experiments, the order of relative reactivities of different sp^3 -C–H bonds under reaction conditions was established to be primary γ -C–H > primary δ -C–H > secondary and tertiary γ -C–H bonds. Overall, this new method features a relatively low catalyst loading and use of inexpensive reagents and allows the access of substitution at both γ and δ -

positions of amine substrates.

Table 1.2. Synthesis of pyrrolidines via intramolecular amination



Substrate	Product	Substrate	Product
<p>1.77</p>	<p>1.78 (82%, dr ~ 7:1)</p>	<p>1.81</p>	<p>1.82 (72%, dr > 20:1)</p>
<p>1.79</p>	<p>1.80 (17%)</p>	<p>1.83</p>	<p>1.84 (61%)</p>

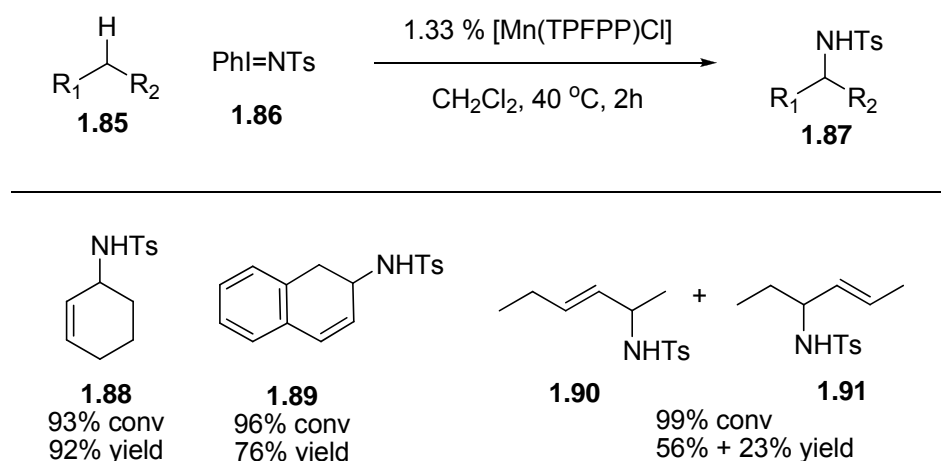
1.2 Intermolecular C–H Bond Amination

1.2.1 Intermolecular processes via nitrene insertions

Intermolecular amination using nitrene chemistry is considered more challenging due to the instability of metallonitrene intermediate; however, new methods have been able to evade these problems. In 1982, Breslow and Gellman successfully amidated cyclohexane with $\text{PhI}=\text{NTs}$ in the presence of Fe- and Mn porphyrins as the pioneering work on metal-mediated amidation of saturated C–H bonds with a nitrene source.¹⁹ Later, Muller²⁰ reported $\text{Rh}_2(\text{II})$ complexes catalyzed amidation of a series of hydrocarbon with $\text{PhI}=\text{NR}$. All methods

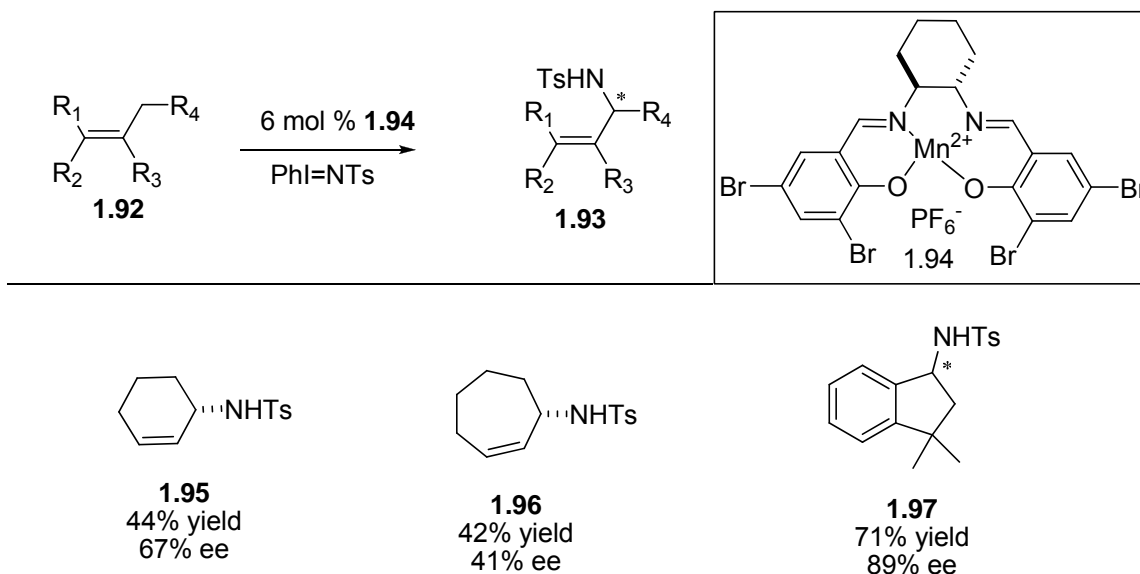
shared the same limitation, as the pre-synthesis of the explosive iminoiodinane from $\text{PhI}(\text{OAc})_2$ and NH_2R was required. A breakthrough occurred when Che and coworkers reported that hydrocarbons can be C–H aminated at various sites including allylic and benzylic carbons by directly using $\text{PhI}(\text{OAc})_2/\text{NH}_2\text{R}$ as amidating reagents in the presence of Mn complex (Scheme 1.10).²¹ The selectivity, however, was not excellent (**1.90** and **1.91**) and aziridination was competing process in case of allyl benzene and cyclooctene.

Scheme 1.10. Mn-porphrin catalyzed allylic C–H amination

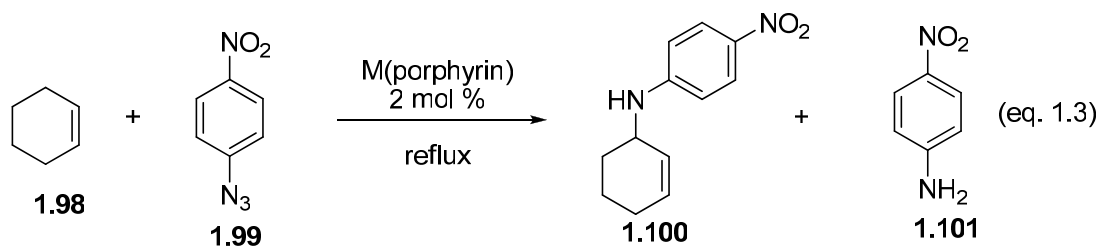


To overcome this limitation, chiral cationic $\text{Mn}(\text{salen})$ complexes bearing electron-withdrawing substituents with higher catalytic activity were synthesized by the Katsuki group and successfully employed to mediate asymmetric C–H amination enantioselectively (Scheme 1.11).²² Under optimized conditions, good yield and high ee were obtained in the reaction of various substrates bearing allylic and benzylic C–H bonds.

Scheme 1.11. Mn(III) salen-catalyzed enantioselective amination



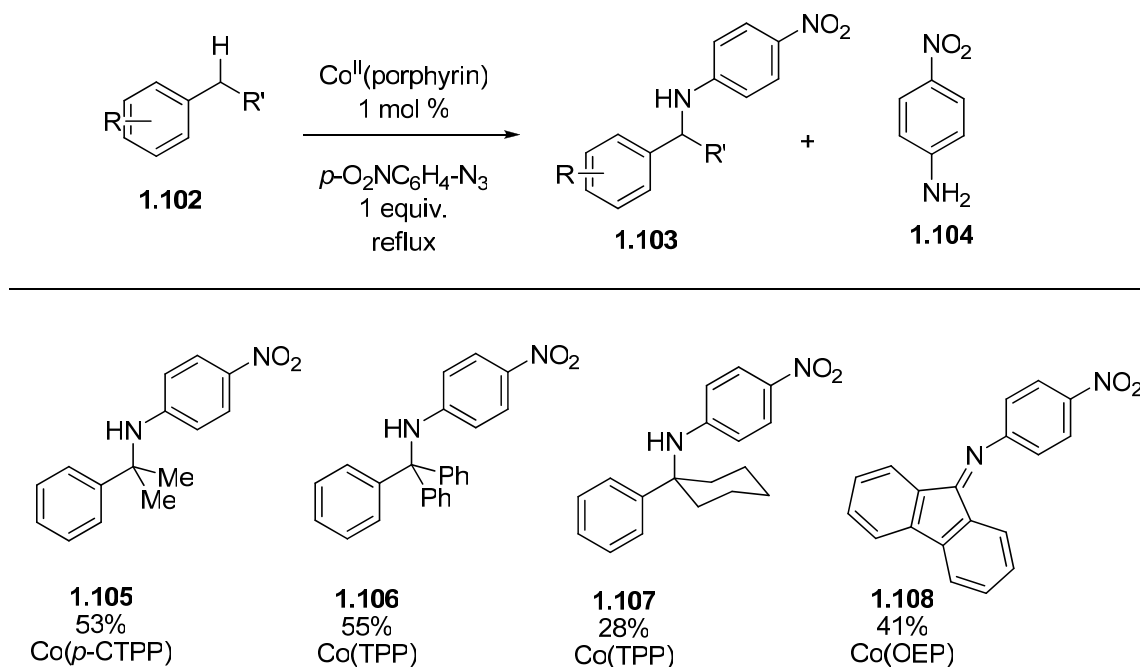
Azides have been studied extensively with respect to their utility in intermolecular C–H amination. In 1999, Cenini and coworkers reported ruthenium- and cobalt porphyrin complexes catalyzed allylic C–H bond amination reaction using *p*-nitrophenylazide as the source of the nitrogen-atom.²³ The authors observed the formation of allyl amine **1.100** when cyclohexene was exposed to either catalyst, while cycloheptene and cyclooctene, in contrast, were effectively converted to the corresponding aziridine (equation 1.3) and *p*-nitroaniline was formed as a major by-product from reduction of azide. They also noted that the yield of allylic C–H bond amination was significantly reduced when an electron-rich azide was used. In addition, only the allylic C–H bond of an olefin could be functionalized. The mechanistic studies suggested that the reaction proceeds through reversible coordination of the aryl azide to the Co^{II} -porphyrin complex.



	% yield	
M(porphyrin)	1.100	aniline
Co(TPP)	53	17
Co(OEP)	61	10
Ru(TPP)(CO)	62	16
Ru(OEP)(CO)	45	9

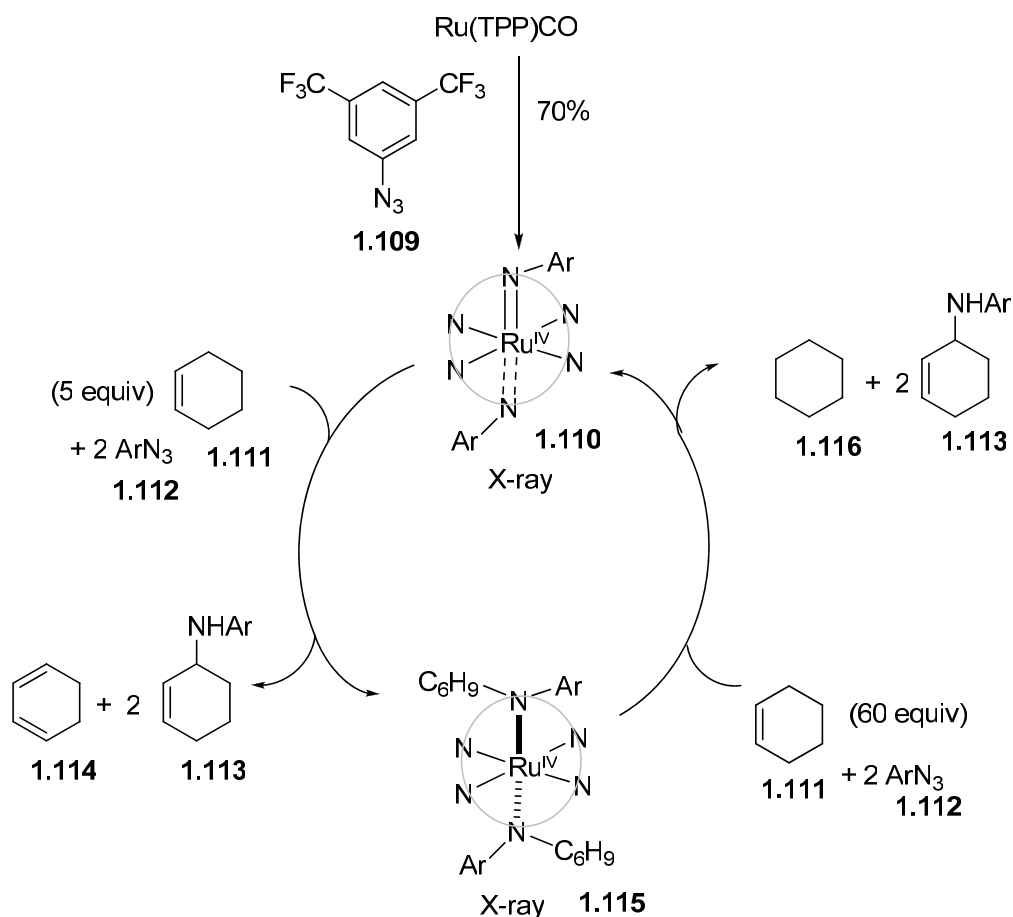
Co(II)-catalyzed benzylic C–H bond amination was also investigated using p-nitrophenylazide to achieve corresponding amines (Scheme 1.12).²⁴ The reaction, however, is sensitive to the nature of starting material azides: when toluene is substrate and Co(TPP) is catalyst, the presence of electron-withdrawing group in the *para*-position increases the yield of the imine and accelerated the reaction. The empirical evidence revealed that different hydrocarbon substrate required a screen of different porphyrin ligands to achieve the highest yield.

Scheme 1.12. Cobalt-catalyzed $\text{sp}^3\text{-C-H}$ bond amination

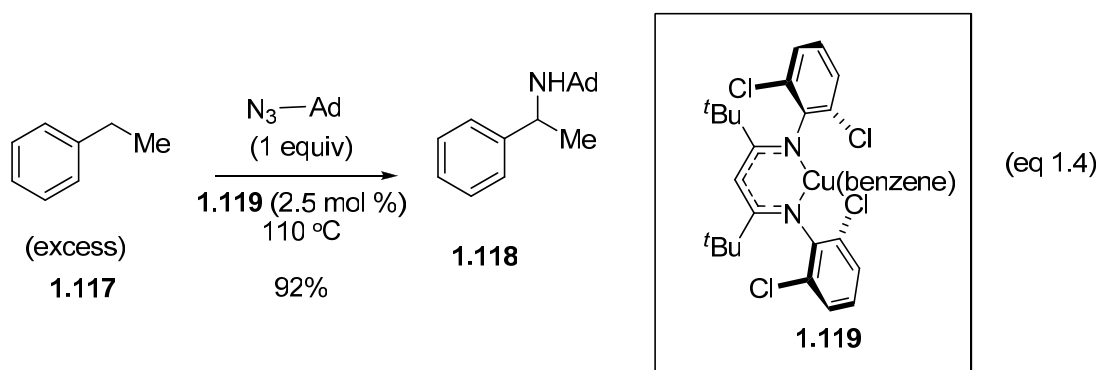


Further insight into the mechanism of allylic C–H bond amination was gained from the isolation of a diimido key intermediate ruthenium diimido complex **1.110** and **1.115** (Scheme 1.13).²⁵ When aryl azide **1.109** was exposed to ruthenium tetraphenylporphyrin, complex **1.110** was generated, and its structure was determined by X-ray crystallography. This complex then mediated the reduction of a stoichiometric amount of cyclohexene to cyclohexane and formed second complex **1.115**. Their experimental data indicated that in amination process “NR” insertion into C–H bond proceeds via radical intermediate. **1.110** could be regenerated from **1.115** through hydrogen transfer reaction, in which cyclohexene was oxidized to 1,3-cyclohexadiene, and the catalytic cycle was complete.

Scheme 1.13. Characterization and reactivity of ruthenium porphyrin reactive intermediates

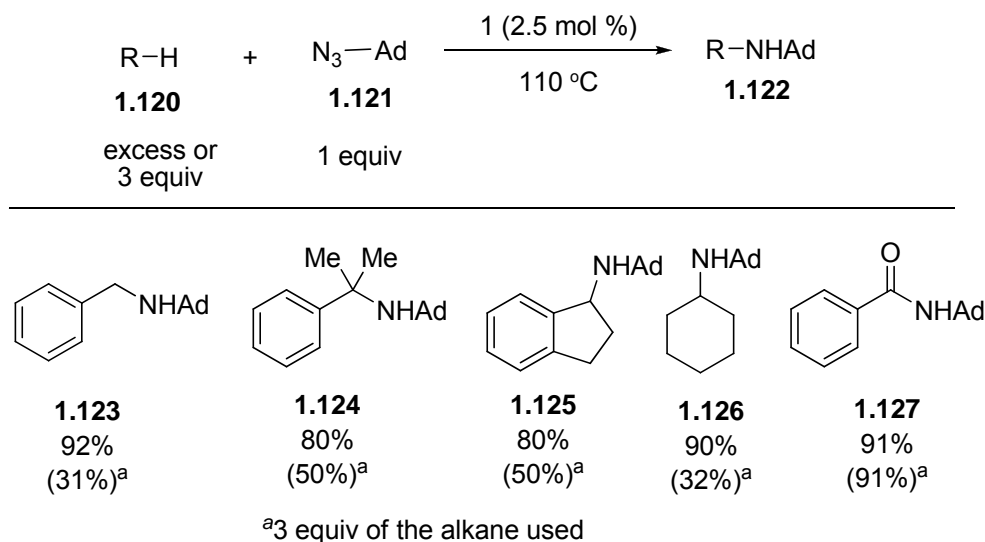


In the field of catalytic design, the Warren group gave their contribution in synthesizing copper ketimine complexes to mediate intermolecular $\text{sp}^3\text{-C-H}$ amination reaction (equation 1.4).²⁶ The complex **1.119** can be prepared in 94% yield from the reaction of free diimine and CuO^tBu in benzene, and its structure was confirmed by X-ray crystallographic analysis. Initial investigation proved the reactivity of this catalyst when exposure of ethylbenzene and adamantyl azide to **1.119** selectively produced benzyl amine **1.118**.



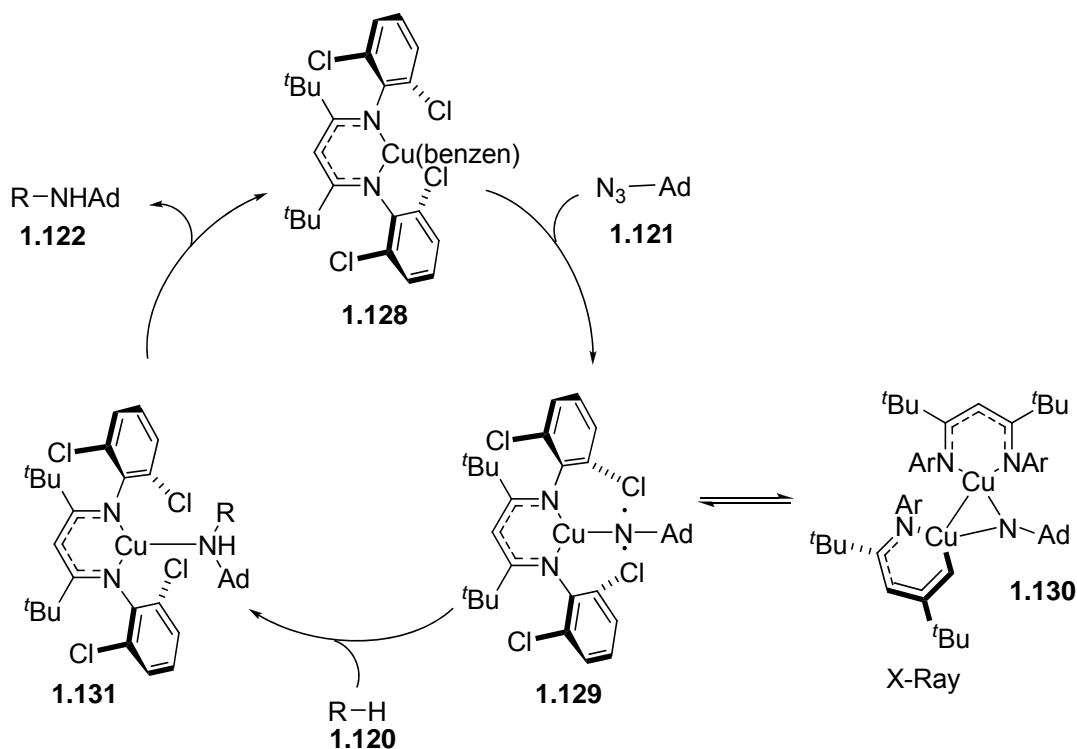
The scope of this reaction was quite broad as a variety of hydrocarbons was tolerated to form the corresponding amine (Scheme 1.14). In general, higher isolated yields were achieved with secondary benzylic C–H bond than primary or tertiary C–H bond. The authors also observed the decreased yield for the toluene amination, presumably due to further oxidation of primary product PhCH_2NHAd to adamantyl aldimine $\text{PhCH}=\text{NAd}$, which enabled the direct conversion of toluene into benzylic imine. In addition to benzylic C–H bonds, aliphatic C–H bond in cyclohexane could be aminated to afford cyclohexyl amine but it required slightly longer reaction times. While excellent yields were observed if the reaction was performed neat in hydrocarbon, lowering the amount of the substrate to one equivalent resulted in diminished yields for toluene and cyclohexane. The yield of products obtained from more reactive C–H bonds amination such as secondary benzylic C–H bonds, however, was not affected.

Scheme 1.14. Scope of Cu-catalyzed intermolecular $\text{sp}^3\text{-C-H}$ bond amination using adamantyl azide.



The isolation of several copper species provided valuable information about the nature of amination process in catalytic cycle (Scheme 1.15). Their proposed mechanism for the catalytic C–H amination started with reaction of copper ketiminate with adamantyl azide to form copper nitrenoid **1.129**. This species can react irreversibly with an additional copper ketiminate to produce the isolable **1.130**. On the other hand, it can also undergo C–H insertion to yield the copper amine **1.131**. In the last step, amine **1.131** dissociates to regenerate the copper ketiminate complex and form product **1.122**. The data from density functional theory calculations revealed the nature of copper nitrenoid **1.129**. The ground state of **1.129** was determined to be a singlet biradical and to exist $18\text{ kcal}\cdot\text{mol}^{-1}$ below the triplet state.

Scheme 1.15. Potential mechanism for Cu-catalyzed C–H bond amination of hydrocarbons.



1.2.2 Intermolecular processes via non-nitrene intermediates

Because of the bias that the reactivity of nitrene complexes was difficult to control, development of transition metal catalyzed intermolecular C–H bond amination via a non-nitrene intermediate was pursued. While great achievements have been made on transition metal catalyzed amination of activated $\text{sp}^3\text{—C—H}$ bond for installing nitrogen functional group, the activation of simple $\text{sp}^3\text{—C—H}$ bonds followed by C–N bond formation remains a challenge, especially in an intermolecular fashion. A breakthrough occurred in 2011 when Buchwald and coworkers developed the first method for Pd(0) -catalyzed intermolecular unactivated $\text{sp}^3\text{—C—H}$ bonds amination through non-nitrene based intermediates.²⁸ Significantly, the utilization of an N-heterocyclic carbene ligand (SIPr.HBF_4) in this reaction resulted in excellent yield. Under

optimized conditions, the scope of this reaction was found to be broad: variations of the aryl amine (Table 1.3) and substitution of the aryl group (Table 1.4) were tolerated. However, this chemistry is quite limited to aryl amines and the requirement of sterically bulky groups on the aryl bromide.

Table 1.3. C–H amination with Aryl Amines

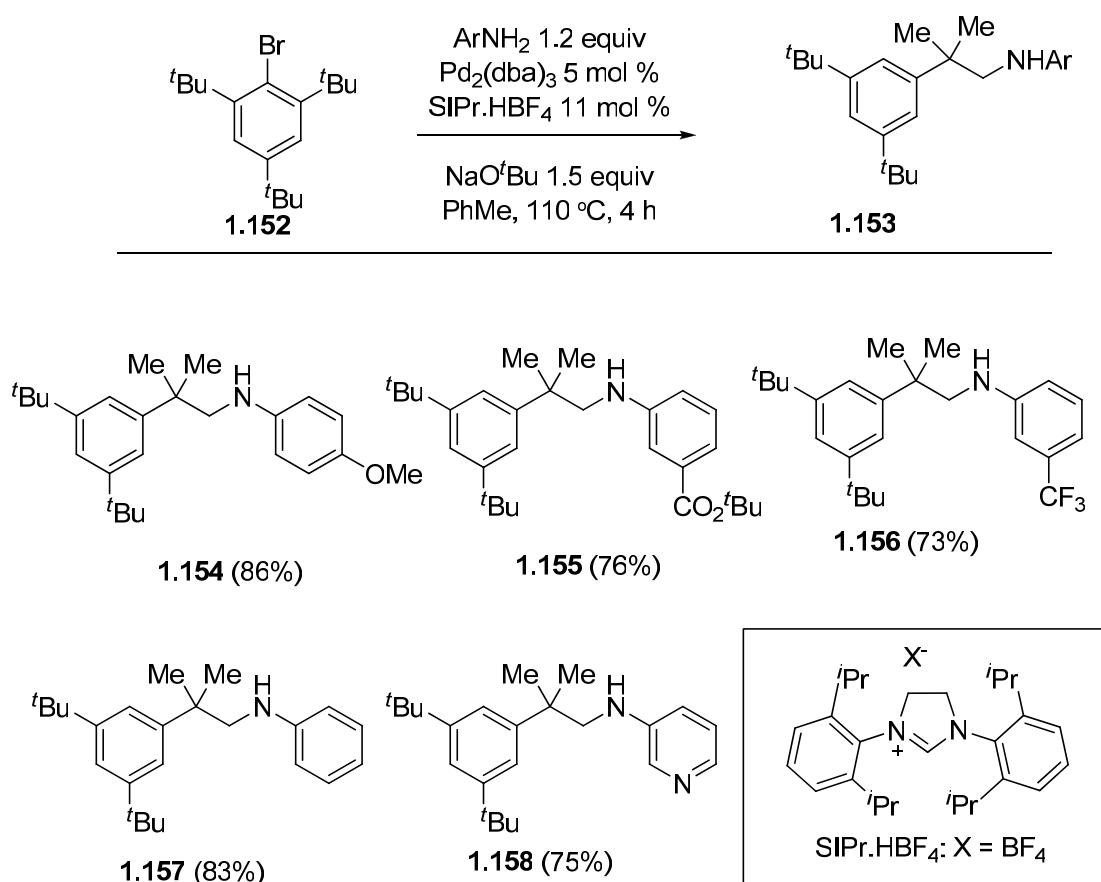
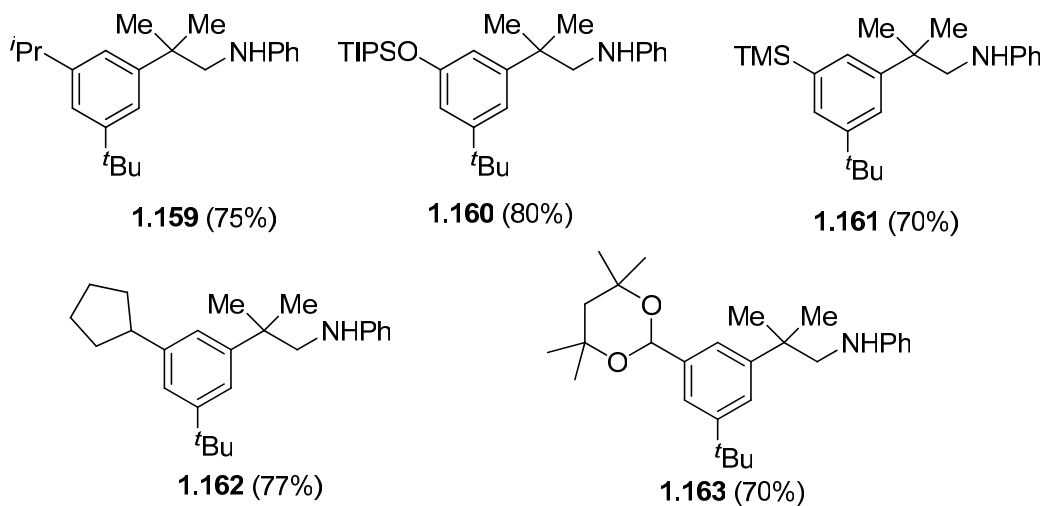
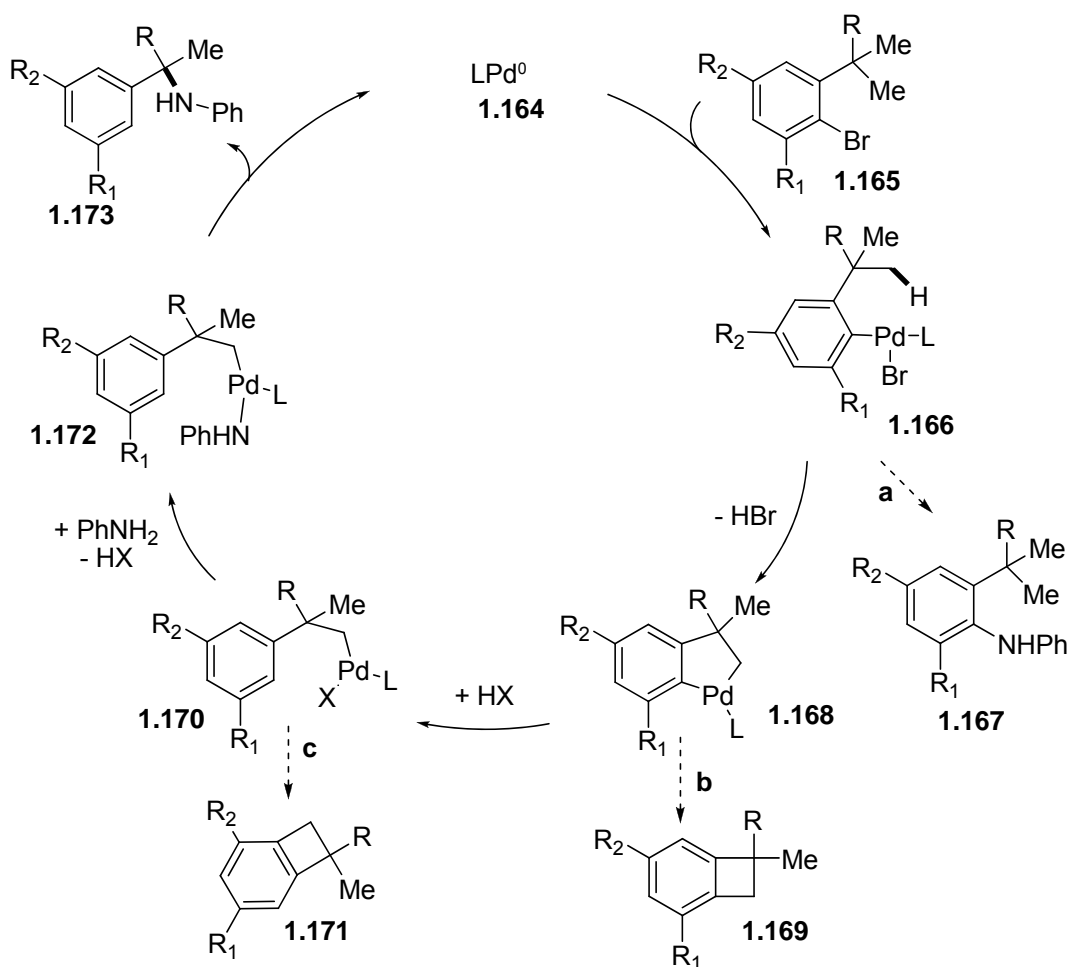


Table 1.4. Amination of unactivated $\text{sp}^3\text{-C-H}$ bonds with aniline



In the proposed mechanism, the catalytic cycle started with an initial oxidative addition of $\text{Pd}(0)$ to the aryl bromide to yield intermediate **1.166** which would undergo C–H activation of at an $\text{sp}^3\text{-C-H}$ bond to generate the palladacycle **1.168** (Scheme 1.16). Protonation follows, producing the alkyl $\text{Pd}(\text{II})$ species **1.170** which then undergoes transmetalation with the aniline. Finally, reductive elimination of **1.172** yields final product **1.173**. There were possible multiple side reactions that can happen, but a presence of sterically hindered R_1 group plays an important role in suppressing both direct C–N cross-coupling (side reaction a) and benzocyclobutene formation (side reaction b). Additionally, a bulky group R_2 minimizes the possibility of $\text{sp}^2\text{-C-H}$ activation followed by reductive elimination to yield by-product **1.171** (side reaction c).

Scheme 1.16. Proposed mechanism of C–H/C–N coupling.



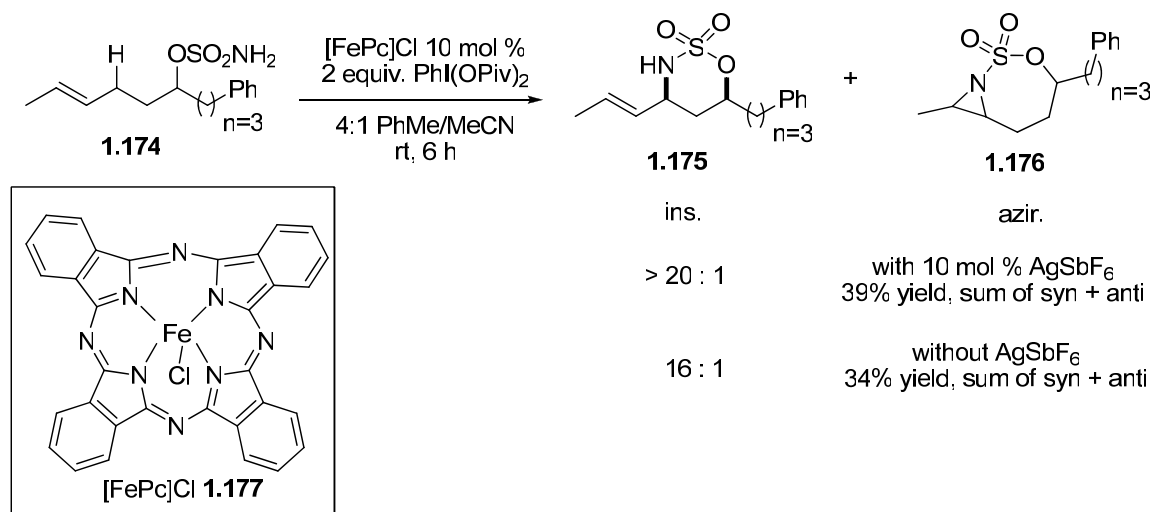
(a) Side reaction A (b) Side reaction B (c) Side reaction C

1.3 Iron Complexes Catalyzed Aliphatic C–H Bond amination

Breslow and Gellman¹⁹ were considered pioneers in the field of metal-nitrenoid-based C–H amination when they published their seminal paper on $Fe(TPP)Cl$ - and $Rh_2(OAc)_4$ catalyzed amination of aliphatic and benzylic C–H bonds. However, after their initial disclosure, very few approaches employing nontoxic²⁹ iron catalysts were reported³⁰. Recently, White and co-workers reported that commercial available $[FePc]Cl$ could promote selective allylic C–H amination (Scheme 1.17).³¹ After extensive screening, mixed solvent system (4:1 PhMe: MeCN) and more

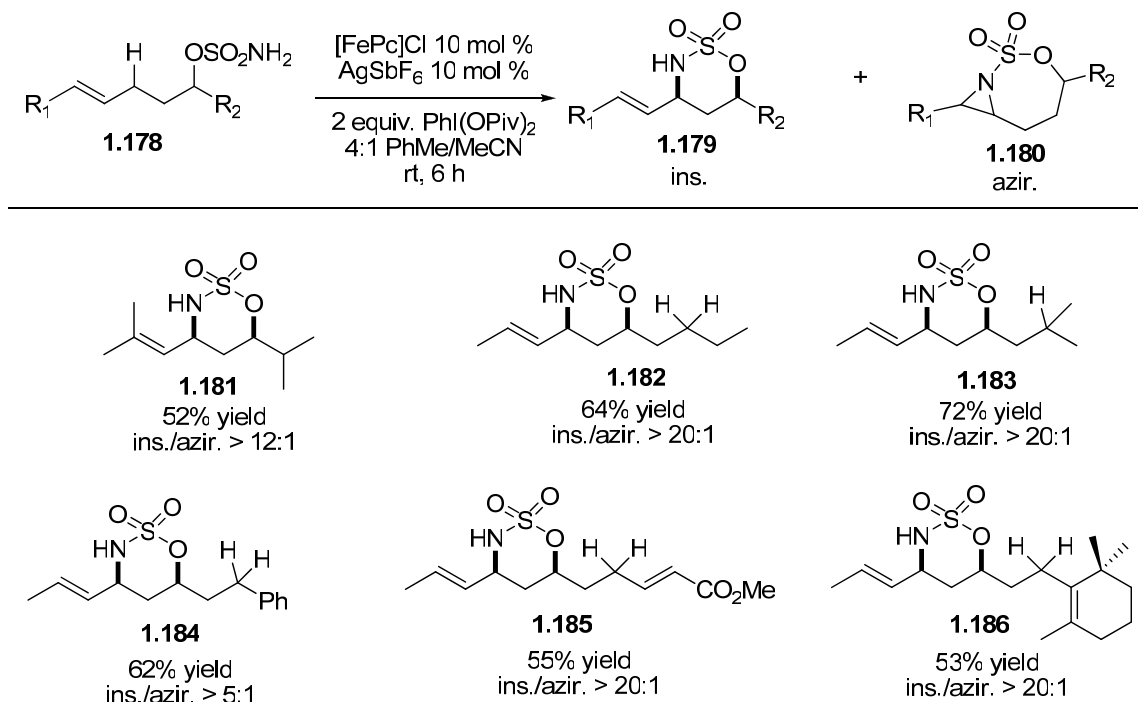
soluble $\text{PhI}(\text{OPiv})_2$ were found to significantly improve reactivity of the system. To show that their reaction could be used in a large-scale application, the authors demonstrated that removal of AgSbF_6 from reaction mixture only caused as light decrease in reactivity.

Scheme 1.17. Iron-catalyzed intramolecular allylic C–H amination.



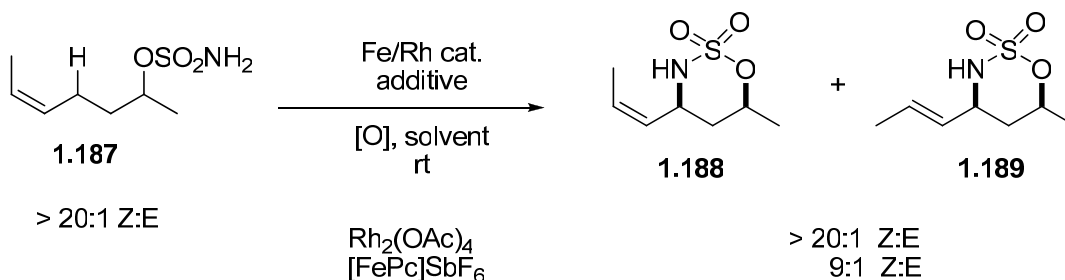
The steric- and electronic constraints of substrates were examined (Scheme 1.18). Their catalytic system displays a strong preference for allylic C–H amination over aziridination, including aliphatic (*E*)-olefins and styryl- and trisubstituted olefins. While aziridination is preferred for terminal aliphatic olefins for rhodium- and ruthenium-catalyzed systems,³² their method distinguishes itself from previous reports in this area. When the scope of substrate was examined, the trend of C–H bond reactivity appeared to be allylic > benzylic > 3° > 2° >> 1° which is in agreement with dissociation energies of C–H bond. In addition, the reaction depends on the electronic nature of allylic C–H bond: the presence of electron-withdrawing substituents such as α,β -unsaturated ester **1.185** led to a significantly diminished yield. The steric environment also plays an important role in allylic C–H amination when the less hindered allylic C–H bond of **1.186** was functionalized with selectivity over 7:1.

Scheme 1.18. Substrate scope of iron-catalyzed intramolecular allylic C–H amination.



To gain insight into the nature of allylic C–H amination process, mechanistic studies were conducted. The measured kinetic isotope effect of 2.5 ± 0.2 under Fe-based catalysis is higher than that measured for the same substrate under Rh-based catalysis (1.8 ± 0.2) but much lower than the measured value of reaction proceeded via a C–H abstraction/rebound amination, therefore, no firm conclusion can be drawn. In further experiments, sulfamate ester **1.187** was subjected to $[\text{Fe}^{\text{III}}\text{Pc}]$ -catalyzed C–H amination, the allylic functionalized product 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 $\text{Rh}_2(\text{OAc})_4$ catalysts environment, different mechanisms may be operating in these two cases (Scheme 1.19).

Scheme 1.19. Mechanistic study of iron-catalyzed intramolecular allylic C–H amination.



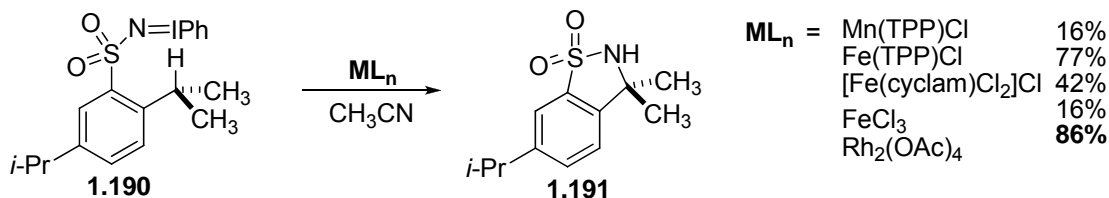
1.4 Rhodium(II) Carboxylate-Catalyzed C–H Bond Amination

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

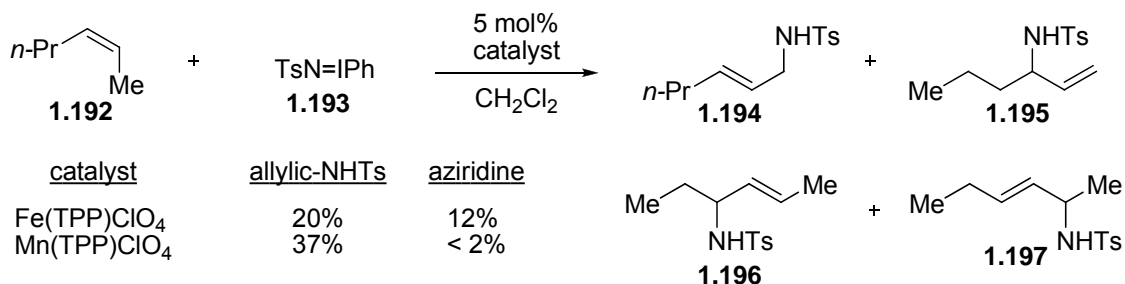
In the field of transition metal catalyzed C–H amination, dirhodium(II) carboxylate species are well-known for their reactivities in both inter- and intramolecular fashion. As aforementioned, these complexes were originally developed by Breslow, and later elaborated by Müller, to perform analogous C–H amination reactions using hypervalent iminoiodinanes as nitrenoid precursors such as $\text{TsN}=\text{IPh}$ (Scheme 1.20). The preparation of iminoiodinanes, however, has been limited to a small subset of sulfonamide derivatives, along with the need to often employ large excess of hydrocarbon substrates, thus restricting the ability to expand further synthetic utility of this class of iodine oxidants.

Scheme 1.20. Original study of C–H amination via iminoiodinanes.

Breslow example



Müller example



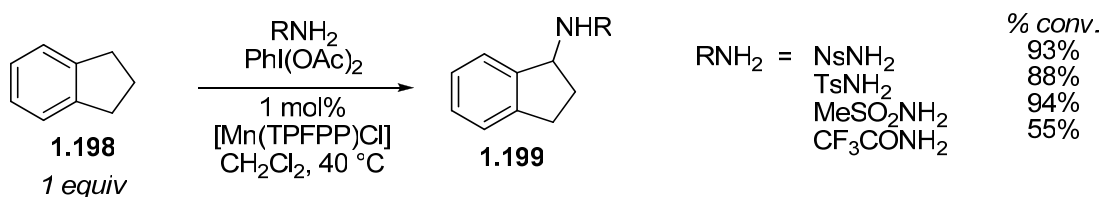
1.4.2 Rhodium(II) Carboxylate Catalyzed Formation of Carbamate and Sulfamate

To overcome the limitation of Breslow and Muller's methods, Che and co-workers reported that the iminoiodinane species could be simply prepared *in situ* from commercially available $PhI(OAc)_2$ or $PhI=O$ and amine NH_2R ($R = Ts, Ns, SO_2Me$) (Scheme 1.23). With this novel strategy, they successfully enabled the application of carbamate, alkylsulfonamide, sulfamate and phosphoramidate starting materials in electrophilic N-atom transfer reactions. 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 insertion for the oxidative conversion of carbamates **1.200** to oxazolidinones **1.201** (Scheme 1.21).³³ To illustrate the potential value of this reaction, various substrates containing both benzylic and tertiary C–H centers were exposed under optimized conditions with either $Rh_2(OAc)_4$ or $Rh_2(tpa)_4$ catalyst. As all of them were cyclized to oxazolidinone products in good yields, the authors noted that when $Rh_2(OAc)_4$ can be

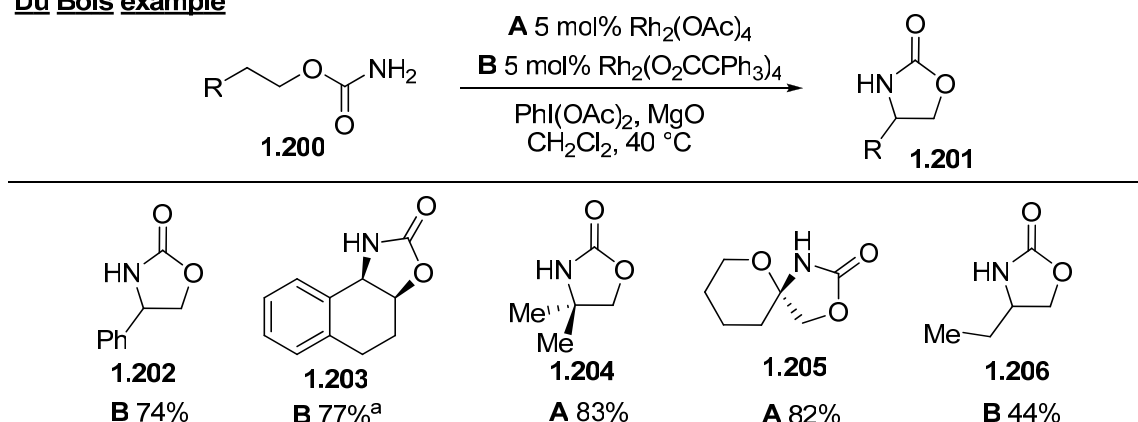
used as the catalyst with certain substrates; in some cases, the readily prepared triphenylacetate (*tpa*) complex $\text{Rh}_2(\text{tpa})_4$ is a more effective promoter at a 5 mol% loading, presumably due to its greater resistance towards oxidation under reaction conditions. Good yields were reported for benzylic (**1.202**, **1.203**), tertiary (**1.204**) and ethereal C–H (**1.205**) bond. Their observations on the reactivity of chiral substrates suggested that Rh catalyst is in some way mediating stereospecific C–N bond formation, and a free nitrene is not the active oxidant.

Scheme 1.21. C–H amination via in situ generation of iminoiodinanes.

Che example



Du Bois example



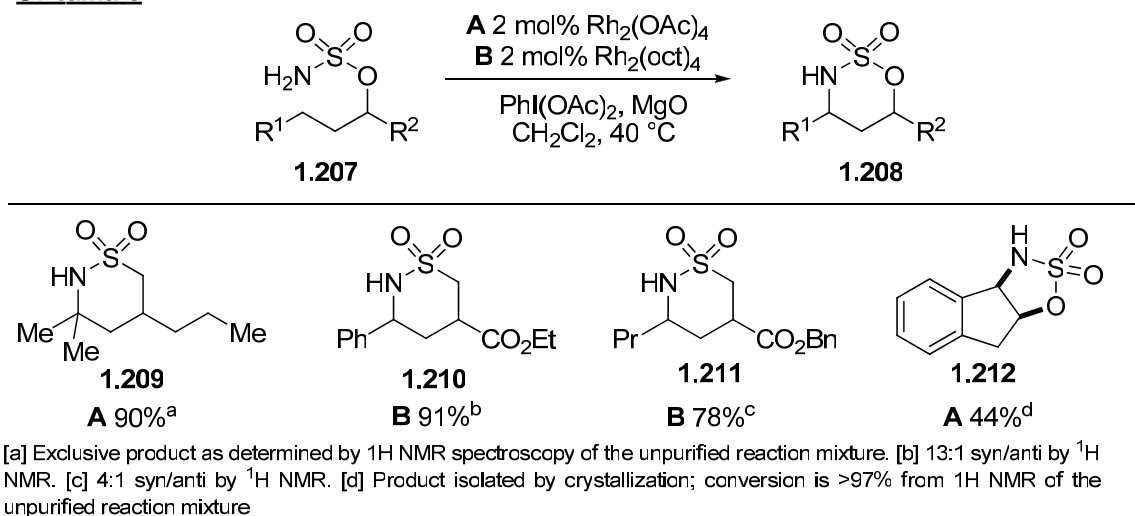
[a] Exclusive product as determined by ¹H NMR spectroscopy of the unpurified reaction mixture; *cis* stereochemistry assigned based on ¹H coupling constants.

Further studies on Rh(II) carboxylate catalyzed amination from primary carbamate in the Du Bois group have guided them to sulfamate esters **1.207** (Scheme 1.22).³⁴ Through exclusive γ -C–H bond amination, six-membered ring insertion products oxathiazinane **1.208** could be afforded.³⁵ 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. If the γ -C–H bond is unavailable, the five-membered sulfamidate **1.212** could be generated. Good yields are obtained for sulfamates bearing tertiary **1.209** and benzylic C–H center **1.210** without exception. Although tertiary C–H bonds react in preference to secondary C–H bond unit to yield **1.209**, better yields were reported with sulfamate **1.211** in comparison to carbamate formation.

Scheme 1.22. Rhodium catalyzed C–H amination with sulfamate as nitrogen source.

Sulfamate

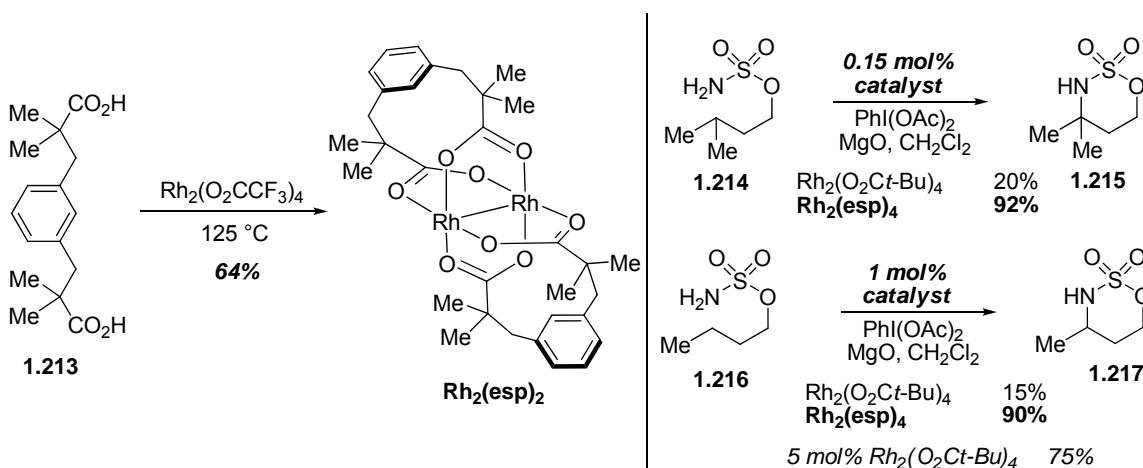


1.4.3 Efficient and Versatile Rh₂(esp)₂ Catalysts

When studying the mechanism of Rh(II) carboxylate complex catalyzed C–H amination, Du Bois and coworkers hypothesized that carboxylate detachment from the dinuclear Rh core is responsible for catalyst degradation; therefore, the connection of two carboxylate ligands through an appropriate spaced linker would provide more stability to these catalysts.³⁶ Mechanistic postulates and inventive work of Taber and Davies³⁷ guided them to design and synthesize a

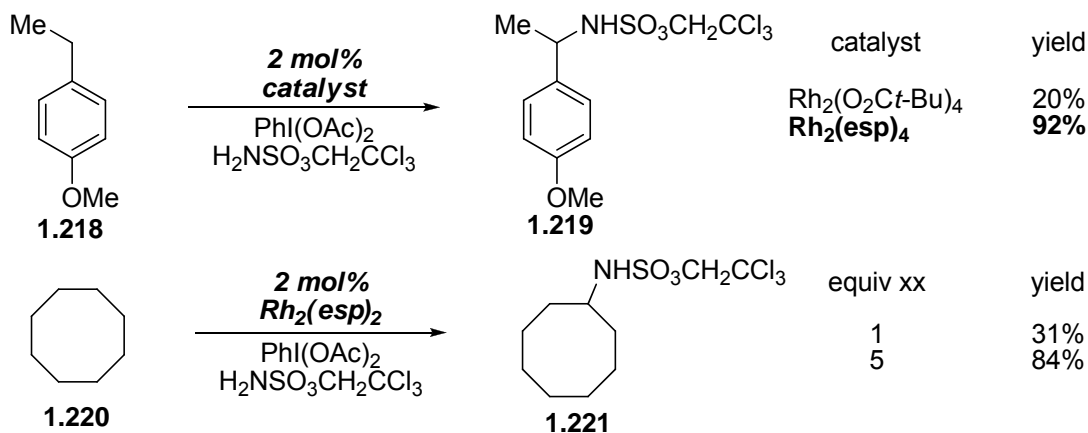
novel Rh(II) carboxylate catalyst: $\text{Rh}_2(\text{esp})_2$. Substitution of tetramethylated *m*-benzenedipropionic acid **1.213** onto $\text{Rh}_2(\text{O}_2\text{CCF}_3)_4$ proceeded with remarkable facility and afforded the desired $\text{Rh}_2(\text{esp})_2$ in 64% yield (Scheme 1.22). The activity of $\text{Rh}_2(\text{esp})_2$ was examined towards C–H bond amination and has proven to be exceptionally effective in both the inter- and intramolecular fashion. For instance, 0.15 mol% of $\text{Rh}_2(\text{esp})_2$ assembles the reaction of substrate **1.214** bearing tertiary C–H bond in quantitative conversion while in contrast, only 20% of oxathiazinane **1.215** is obtained when $\text{Rh}_2(\text{O}_2\text{Ct-Bu})_4$ was employed. In general, lower catalyst loading of $\text{Rh}_2(\text{esp})_2$ is sufficient to catalyze unactive methylene unit: 1 mol % of $\text{Rh}_2(\text{esp})_2$ is required for formation of **1.217** in 90% whereas five times as much of $\text{Rh}_2(\text{O}_2\text{Ct-Bu})_4$ only affords 75% of this desired heterocyclic product.

Scheme 1.23. Synthesis of $\text{Rh}_2(\text{esp})_2$ and application in intramolecular C–H amination



The examples of $\text{Rh}_2(\text{esp})_2$ aminated intermolecular C–H bonds also were reported (Scheme 1.23). Substrate **1.218** has been proven to be inactive to Mn, Fe, Ru, Rh and Cu complexes,^{38,39} while its exposure to 2 mol% of $\text{Rh}_2(\text{esp})_2$ generated benzyl amine **1.219** in excellent yield. Similar finding recorded for C–H insertion of cyclooctane **1.220** also exhibited the better performance of $\text{Rh}_2(\text{esp})_2$ over $\text{Rh}_2(\text{O}_2\text{Ct-Bu})_4$.

Scheme 1.24. Rh₂(esp)₂ catalyzed intermolecular C–H amination.

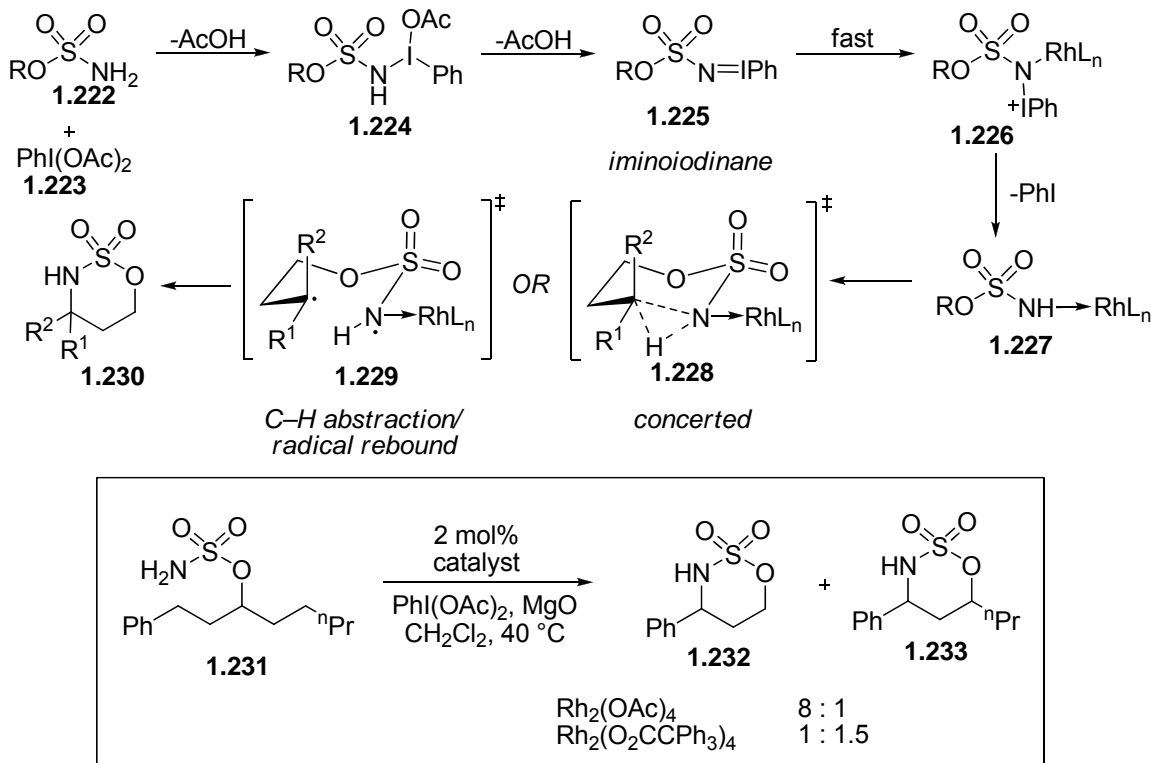


1.4.4 Mechanism Study of Rh(II) Carboxylate Catalyzed C–H Bond Amination

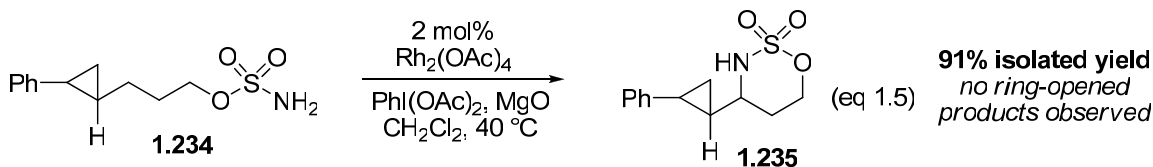
To further understand the nature of the active oxidant and identify the steps in the catalytic cycle of Rh₂(esp)₂ aminated C–H bond insertion, the Du Bois group performed a series of mechanistic experiments (Scheme 1.24).⁴⁰ Their proposed mechanism included reduction of sulfamate substrate **1.222** by oxidant PhI(OAc)₂ to yield iminoiodinane **1.225**, which further reacts with Rh(II)-carboxylate to generate rhodium nitrenoid **1.227**. Subsequent C–N bond formation could occur by two different pathways: hydrogen-atom abstraction via triplet nitrenoid **1.229** followed by radical recombination or a concerted insertion of the singlet nitrenoid **1.228**. Their experiments showed that catalyst structure can influence product selectivity when different products were afforded when treating the same substrate with different rhodium catalysts. It provides the most compelling evidence that rhodium-bounded nitrenoid **1.227** is the active oxidant. The reactivity of **1.213** towards Rh₂(esp)₂ and Rh₂(O₂CCPh₃)₄ showed that C–H insertion at benzylic position in the reaction promoted by Rh₂(O₂CCPh₃)₄ is strongly disfavored, presumably due to the remote steric effects between the substrate and catalyst framework direct

the chemoselectivity of the reaction.

Scheme 1.25. Mechanism of rhodium-catalyzed C–H amination.



To gain insight into the nature of C–H amination step whether it follows concerted- or stepwise pathway, radical-clock study was carried out with phenyl-substituted cyclopropane **1.234** (equation 1.5).⁴¹ Exposure of **1.234** to reaction conditions produced only amination product **1.235** without any cyclopropane ring-opening and olefin-containing products formed from cyclopropane fragmentation. Even though it is possible to employ radical clocks that fragment/rearrange at faster rates, the authors believed that this data together with the Hammett ρ -value and KIE strongly suggest a concerted, asynchronous insertion pathway for $\text{Rh}(\text{II})$ -catalyzed C–H bond amination.

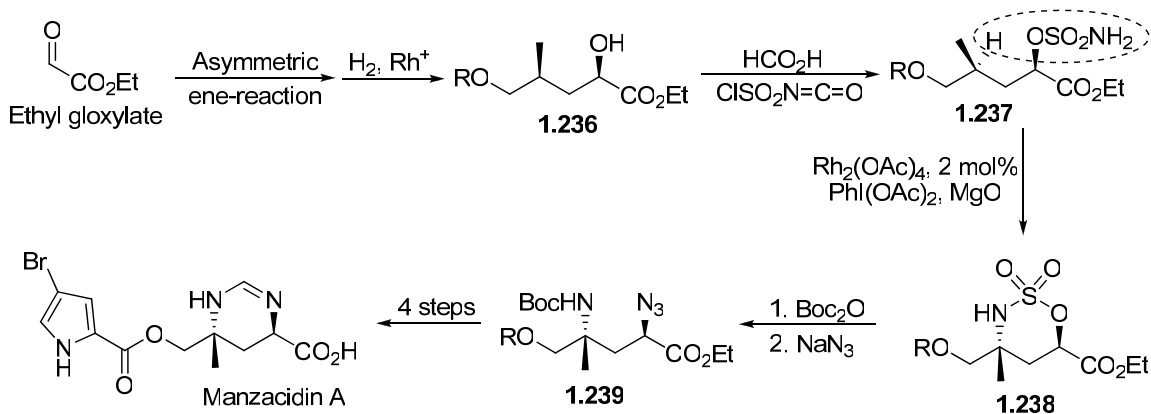


1.5 Application of Aliphatic C–H Bond Amination

Amination reactions of $\text{sp}^3\text{-C-H}$ bonds hold great potential as methods for the synthesis of amines and amine derivatives, especially nitrogen-containing heterocycles presented in many biologically active compounds and nature products. In the previous sections, several methodologies that directly convert C–H bond into C–N bonds were discussed. This introductory chapter will be concluded with two examples representing the use of C–H bond amination reactions to streamline the synthesis of natural products.

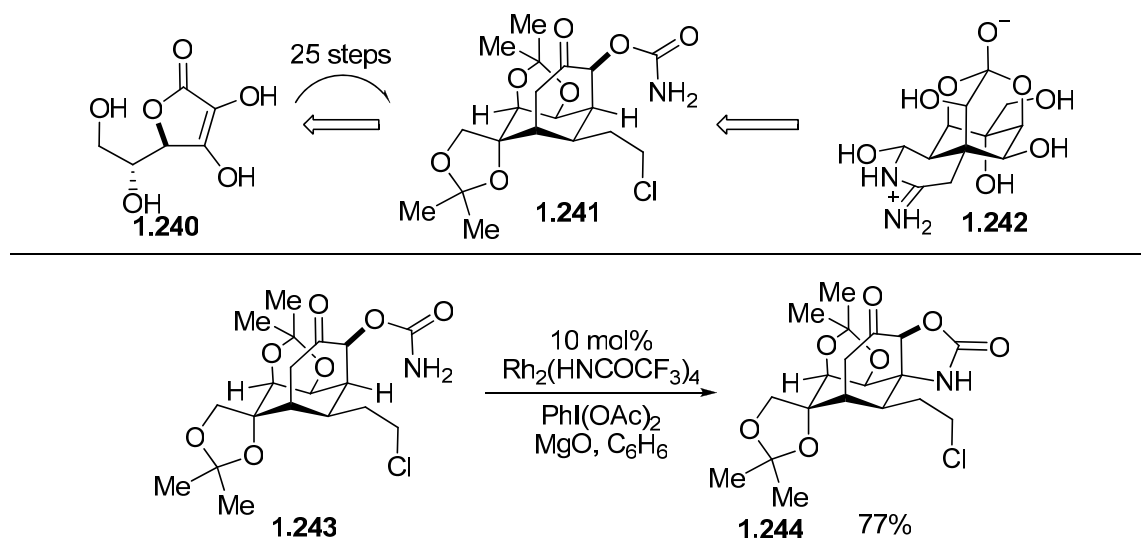
In 2002, the Du Bois group demonstrated the synthetic utility of their Rh(II)-amination method in enantioselective synthesis of manzacidin A and C (Scheme 1.25).⁴² These compounds were isolated as bioactive constituents of the Okinawan sponge and represent one small family of bromopyrrole alkaloids which possess potentially useful pharmacological activities as serotonin antagonists and actomyosin ATPase activators. The alcohol **1.236** obtained from an asymmetric ene reaction of ethyl glyoxylate followed by a diastereoselective alkene hydrogenation was subjected to sulfamoylation to synthesize **1.237**. When optically pure sulfamate **1.237** was prepared, it underwent C–H bond amination smoothly and stereospecifically with 2 mol % of $\text{Rh}_2(\text{OAc})_4$ and 1.1 equiv of $\text{PhI}(\text{OAc})_2$ to yield oxathiazinane **1.238** in 85% yield with retention of configuration. Synthesis of manzacidin A was completed after nucleophilic ring opening and four additional steps.

Scheme 1.26. Synthesis of manzacidin A.



To further validate Rh-nitrene insertion as a powerful new tool in the synthesis of nitrogen-containing heterocycles, Du Bois and co-workers one more time applied their method in the asymmetric synthesis of tetrodotoxin (TTX), the guanidium poison synonymous with the Japanese *fugu* (Scheme 1.26).⁴³ Construction of this highly oxygenated cyclohexylamine derivatives is challenging, most notably because of two tetra substituted stereocenters at C6 and C8a. To solve this problem, the authors decided to install the amine unit into C8 in the late stages of the synthesis through a stereospecific Rh-mediated nitrene C–H insertion reaction. After 25 steps, selective C–H bond amination of carbamate **1.243** was performed in the synthetic sequence with 10 mol % $\text{Rh}_2(\text{HNCOCF}_3)_4$ and gave **1.244** in a good yield of 77%. Notably, the insertion is exclusive for the bridgehead tertiary C–H bond and clearly tolerates several reactive functionalities. This finished work underscored C–H amination as a unique strategy for assembling complex N-heterocyclic compounds.

Scheme 1.27 Synthesis of tetrodotoxin.



1.6 Conclusion

A variety of transition metal-catalyzed C–H bond amination reactions that are important in preparation of *N*-heterocycles present in biologically active natural products, pharmaceuticals and materials have been described in this chapter. From literature, reactions utilizing azides as a source of N-atom feature avoiding the use of additives and generating environmentally benign byproduct N_2 gas without pre-activated C–H bond. In the following chapters, we demonstrate that sp^3 -C–H bonds in aryl azides can be aminated by various transition metals to afford indoles and indolines. Additionally, we also illustrate that rhodium carboxylate could promote formation of 1,2,3-trisubstituted indoles from styrylazides.

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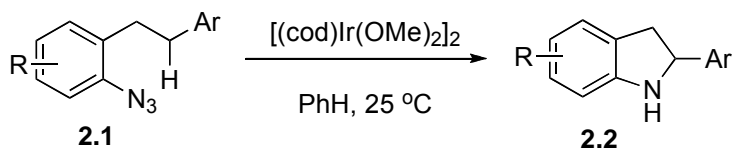
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Chapter 2. Rh₂(II)-Catalyzed Intramolecular Aliphatic C–H Bond Amination Reactions Using Aryl Azide as the N-Atom Source.

2.1 Introduction

Research in Driver's group has focused on the transition-metal catalyzed C–H amination to achieve the wide range of valuable biological N-heterocyclic compounds. To overcome the limitations of current methods, they utilized the azides as the N-atom precursor. The advantages of their method included no oxidants or additives required, and the reaction generated environmentally benign N₂-gas as the only by-product.¹ While a number of sp² C–H bond amination has been reported,² their initial studies into extending the reactivity of azides toward the amination of sp³-C–H bond were limited to benzylic C–H bonds. In their example, an iridium(I)-complex was demonstrated to enable the functionalization of benzylic C–H bonds in aryl azides to produce indolines at room temperature (Scheme 2.1).³ However, primary and tertiary benzylic C–H bonds were found to be unreactive, and no reaction was observed with substrate containing an electron- rich substituent on the aryl azide portion.

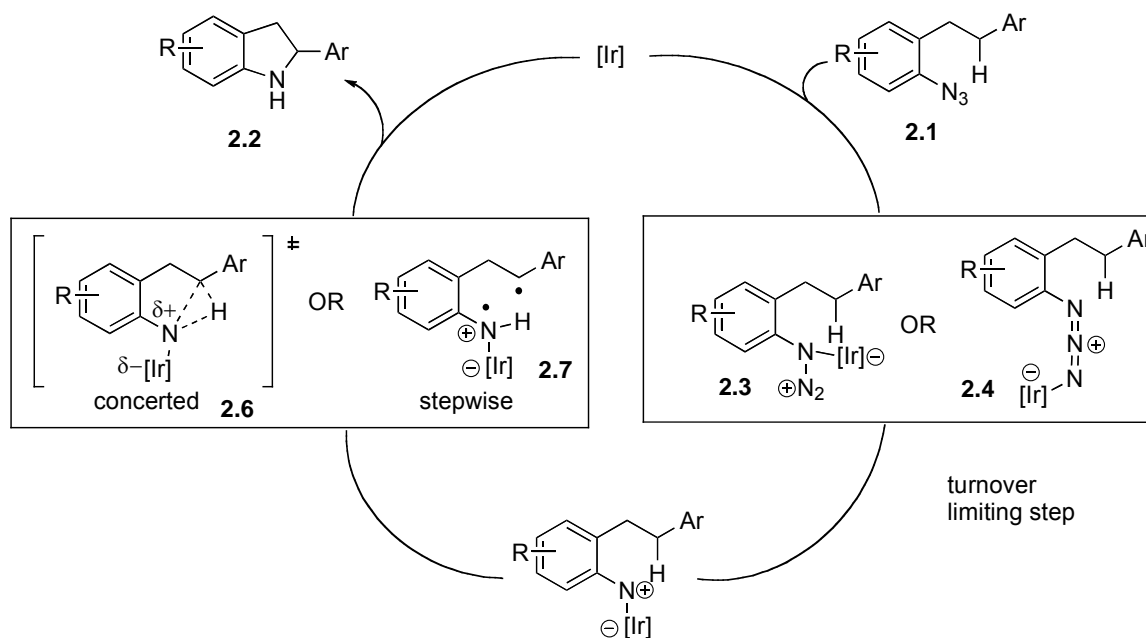
Scheme 2.1. Previous work on benzylic C–H bond amination.



Studying mechanism of this reaction, they proposed that the formation of the nitrenoid reactive intermediate from N₂ extrusion of **2.3** or **2.4** could be the rate-determining step. Subsequent C–N bond formation could occur by two different pathways: a concerted insertion of

the singlet nitrenoid **2.6** or H-atom abstraction with triplet nitrenoid **2.7** followed by radical recombination (Scheme 2.2).

Scheme 2.2. Proposed mechanism for benzylic C–H bond amination.



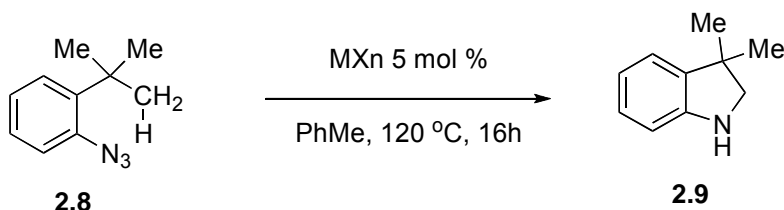
The aforementioned limitations prompted our interest in developing a more general method to achieve aliphatic C–H bond amination using aryl azides as the N-atom source. We anticipated that the aliphatic C–H bond would be more inert than aryl- or vinyl C–H bonds because the C–N formation in these situations can occur via 4π -electron-5-atom electrocyclization.^{1b} The lack of conjugated system in aliphatic C–H bond suggests that this process requires either metal-catalyzed C–H insertion or H-atom abstraction which remained elusive to control using aryl azides as the N-atom precursor.⁴

2.2 Optimization experiments

2.2.1 Optimization of transition-metal complexes

In the course of searching for aliphatic C–H bond amination reactions, *o*-*tert*-butylaryl azide was chosen to expose under commercially available transition-metal complexes. We found that at 120 °C, no reaction was observed with this relatively thermally robust substrate,⁵ and the indoline was not formed in the presence of iron,⁶ copper,⁷ cobalt,⁸ ruthenium^{4,9} or iridium³ complexes which were known to catalyzed N-atom-transfer reactions (entry 2-6). The rhodium octanoate was determined to partially convert aryl azide **2.8** into desired product (entry 8), which may result from the decomposition of catalyst at high temperature. Further examination of Rh₂(II)-complexes, a more robust catalyst Rh₂(esp)₂¹⁰ was found to increase both conversion and yield of the process.

Table 2.1. Development of optimal catalysts.



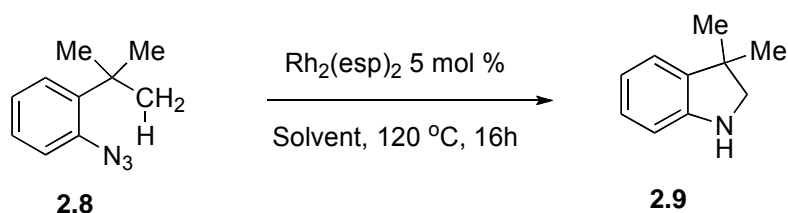
entry	metal salt	conv, % ^a	yield, % ^b
1	none	0	0
2	FeBr ₂	0	dec ^c
3	CuBr	0	0
4	CoTPP	0	0
5	RuCl ₃ · <i>n</i> H ₂ O	0	0
6	[Ir(COD)(OMe)] ₂	0	0
7	[Rh(COD)(OMe)] ₂	10	0 ^c
8	Rh ₂ (O ₂ CC ₇ H ₁₅) ₄	35	35
9	Rh ₂ (esp) ₂	99	75

^aAs determined using ¹H NMR spectroscopy. ^bIsolated after silica gel chromatography. ^cAniline formed.

2.2.2 Optimization of solvent

Our optimization experiments of solvent showed that toluene and benzene would give comparable yield (entries 1 and 2) when in general halogenated aromatic solvents would significantly decrease the reaction yield (Table 2.2). Both trifluorobenzene (entry 6) and bromobenzene (entry 3) were not efficient in the reaction condition. Consequently, we chose toluene as the best solvent for this C–H bond amination reaction. A brief survey of alternative concentrations or reaction temperatures did not produce a higher yield.

Table 2.2. Optimization of solvent.



entry	solvent	yield, % ^a
1	PhMe	75
2	PhH	73
3	PhBr	56
4	PhCl	47
5	1,3-C ₆ H ₄ Cl ₂	61
6	PhCF ₃	31
7	DCE	47

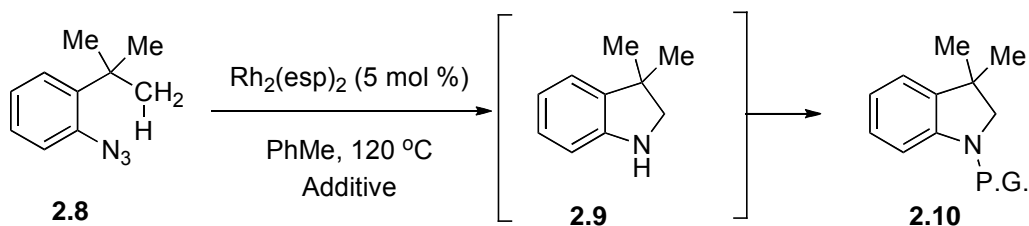
^aAs determined using ¹H NMR spectroscopy

2.2.3 Optimization of Additive

We anticipated that the decomposition of indoline product may occur under reaction condition or during purification with silica gel, therefore, the protection of nitrogen atom in situ is necessary to improve the yield. Isolated yield was increased with either Boc or Ac group

protection (entry 2, 3). Aniline formation was observed when the stronger benzoic and triflic acids were produced in the protection reaction as by product (entry 4, 5).

Table 2.3. Optimization of additive.



entry ^a	additive	conv, % ^b	yield, % ^c
1	n.a.	99	75
2	Boc ₂ O	99	90
3	Ac ₂ O	99	83
4	Bz ₂ O	99	aniline
5	Tf ₂ O	99	aniline

^aOne equivalent additive was added. ^bAs determined using ¹H NMR spectroscopy. ^cIsolated after silica gel chromatography.

2.3 Scope and limitation of indoline formation

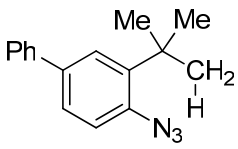
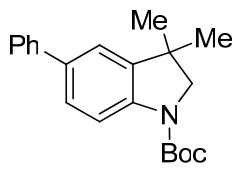
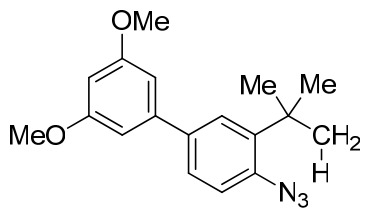
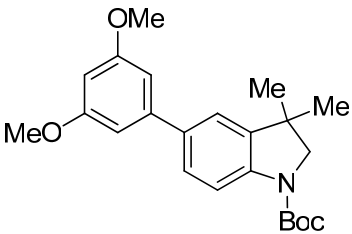
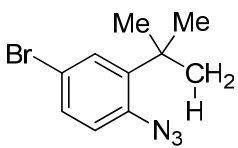
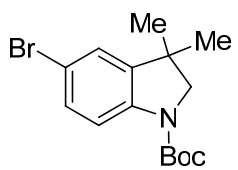
2.3.1 Investigation of Electronic Nature of Azide Arenes

To examine the electronic and steric constraints of this aliphatic C–H bond amination reaction, the substituted *o*-*tert*-butyl azide arenes were submitted towards the above optimal condition. The scope of our reaction was found to be broader than the Ir(I)-catalyzed amination of benzylic C–H bonds: both electron-rich and electron-poor aryl azides gave the good to

excellent isolated yield of the indoline. In addition, our reaction exhibited good chemoselectivity produce only indoline **2.22** without any reaction at the alkenyl substituent (entry 5). Furthermore, the preparation of **2.28** bearing active bromo-group in this process provided an efficient method to access various valuable compounds through further cross-coupling reaction (entry 8).

Table 2.4. Scope and limitation of indoline formation.

Entry	aryl azide ^a	##	indoline	##	yield, % ^b
1		2.8		2.14	84
2		2.15		2.16	63
3		2.17		2.18	54
4		2.19		2.20	64
5		2.21		2.22	70

6		2.23		2.24	54
7		2.25		2.26	58
8		2.27		2.28	73

^a Some starting materials were prepared by Ke Sun. ^b Isolated after silica gel chromatography.

2.3.2 Examination of *ortho*-Alkyl Substituents Identity

We further examined the scope of this C–H bond amination by varying the identity of *ortho*-alkyl substituted group. The yield is comparable when one of the methyl group was replaced by an ester group (entry 1) but significantly diminished if the replacement is with hydrogen, presumably due to the presence of less number of C–H bonds and the smaller bond angle which increases the distance between methyl group and azide center (entry 2). By tolerating both primary and tertiary C–H reaction sites, our reaction condition was found to be significantly more broad than our previous report on benzylic C–H bond amination. The yield of **2.38**, however, was low due to competitive dehydrogenation (entry 4).

The α -substituted cycloalkyl aryl azides of different ring sizes (5-, 6- and 7-) were submitted to the reaction conditions to afford the N-heterocyclic products as single diastereoisomer. While the pyrolysis of **2.44** led to a 1:1 mixture of diastereoisomers,¹¹ only **2.45**

cis-product was produced selectively in the presence of $\text{Rh}_2(\text{esp})_2$ (entry 7). Although both *o*-cyclopentyl and *o*-cyclohexyl aryl azide produced only single diastereoisomer, the stereoselectivity was diminished with *o*-cycloheptyl-substituted substrate (entry 13). The indoline structure of product was preferred over the naphthalene ring since only amination of C–H methylene occurred in **2.54** when two methyl groups were retained (entry 12).

Table 2.5. Examination of identity of the *ortho*-alkyl substituents.

Entry	aryl azide	##	indoline	##	yield, % ^a
1		2.32		2.33	70
2		2.34		2.35	20
3		2.36		2.37	55 ^b
4		2.38		2.39	30 ^c
5		2.40		2.41	80

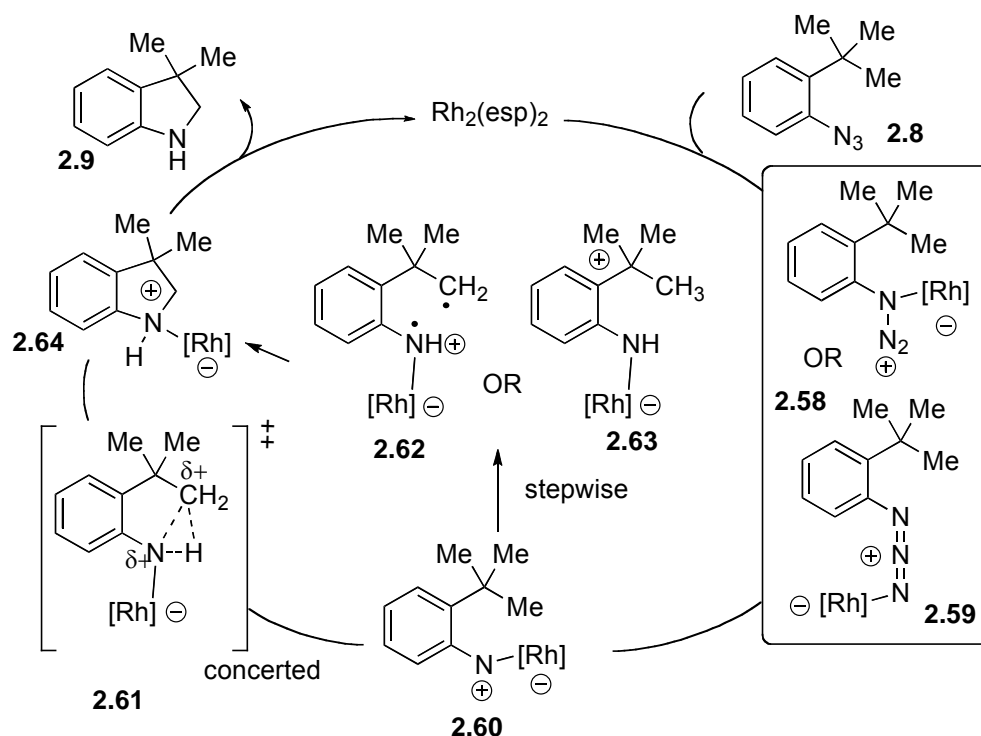
6		2.42		2.43	73
7		2.44		2.45	70
8		2.46		2.47	63
9		2.48		2.49	85
10		2.50		2.51	73
11		2.52		2.53	82
12		2.54		2.55	86
13		2.56		2.57	63 d.r. 82:18

^aIsolated after silica gel chromatography. ^b20% aniline observed. ^c30% aniline observed

2.4 Mechanism Study

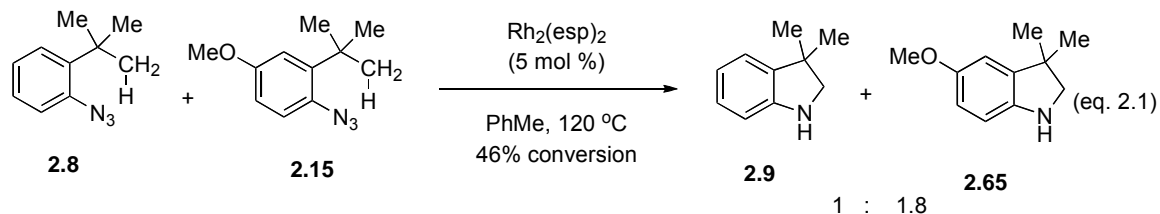
While several mechanisms could account for the formation of indoline product,^{7a,12} our previous works on C–H amination suggested that the rhodium nitrene would be the reactive intermediate for constructing C–N bond through N-atom transfer (Scheme 2.3). Our proposed catalytic cycle starts with the coordination of Rh₂(esp)₂ to either the α - or γ -nitrogen of aryl azide¹³ to produce **2.58** or **2.59** respectively, followed by the extrusion of N₂ gas to generate rhodium nitrene **2.60**.¹⁴ Since pyrolysis involves free nitrene is not diastereoselective, we believed that a reversible one-electron oxidation¹⁵ does not happened in our mechanism. Two mechanistic pathways are possible to account for the C–H amination process: concerted insertion^{12c,17} of the metal nitrene into the proximal C–H bond via transition state **2.61**; or hydride¹⁶ or H-atom abstraction^{12a,18} followed by recombination to produce the C–N bond in stepwise process. In the last step, the dissociation of rhodium complex affords the indoline product.

Scheme 2.3. Possible mechanism for intramolecular aliphatic C–H bond amination.



2.4.1 Intermolecular Competition Reaction

Intermolecular competition reactions were carried out to gain insight into the mechanism. The reactivity of **2.8** to *para*-methoxy substituted **2.15** was compared to examine the effect of different electronic nature of the aryl azide (eq. 2.1). We found that substrate bearing more electron-releasing is more active towards the reaction condition which distinguishes our method itself from previously reported aliphatic C–H bond amination. This finding was attributed to either the accelerated N_2 extrusion from the resulting azide-metal complex or the preferred coordination of **2.8** to $\text{Rh}_2(\text{esp})_2$.



2.4.2 Isotope Labeling Study

The stereospecific labeled aryl azide **2.66** was prepared to gain more information on the nature of the C–H bond amination step to reveal whether it was concerted or stepwise. If the process was concerted, the insertion of nitrenoid into either the $\beta\text{-C-H}$ or $\beta\text{-C-D}$ bond would produce only two indoline products. In contrast, stepwise pathway involving recombination of a radical- or cation intermediate would lead to the scrambling of the C2-stereocenter and generated four products. The mechanistic study carried out on the reactivity of **2.66** supported for stepwise pathway and provided the intramolecular kinetic effect (KIE) to be 6.7. When the KIE involves H-atom abstraction by an aryl nitrene¹⁸ or an aryl metal nitrene^{4c} ($k_{\text{H}}/k_{\text{D}}$) was reported about 12 – 14, and around 2 in hydride shift reaction (as example of Cannizzaro reaction and Meerwein–Ponndorf–Verley reduction),¹⁹ we cannot suggest the intermediate of this C–H amination related to radical or cation intermediate. In addition, the smaller KIEs were observed at lower temperature (Table 2.6) revealing that our amination reaction occurs above the isokinetic temperature and, as a consequence, is under entropic control.²⁰ However, submission of cyclopentanone-derived aryl azide **2.69** to reaction condition exclusively produced only **2.70** via the *syn*-C–H bond amination suggested that the spatial constraints of this reaction overpowered these isotope effects.²¹

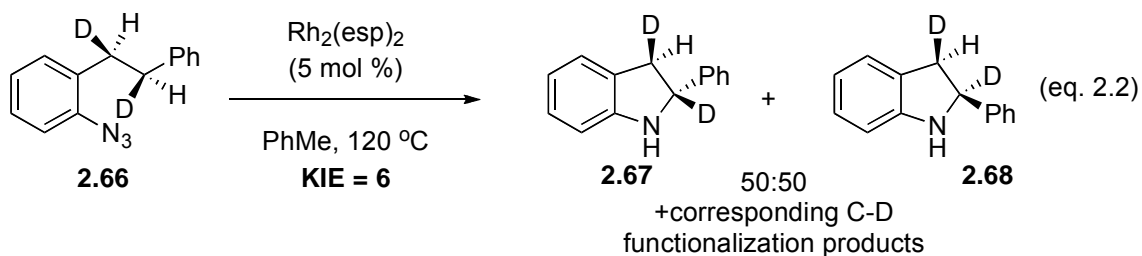
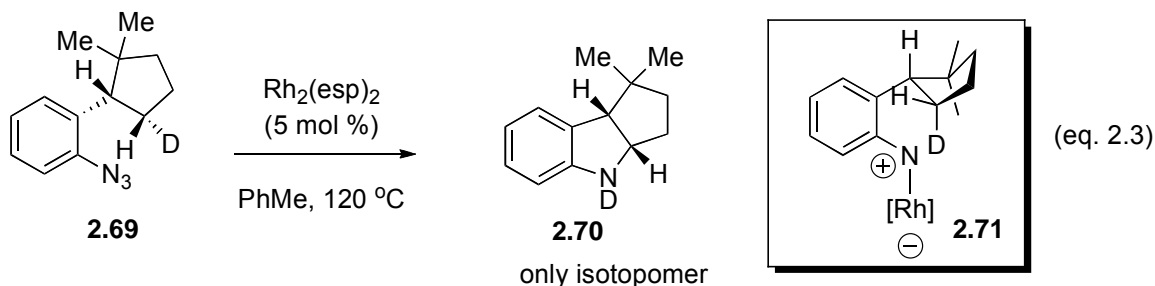


Table 2.6. Observed kinetic isotope effects.

entry	T (°C)	$k_{\text{H}}/k_{\text{D}}^{\text{a}}$
1	80	3.7
2	100	5.7
3	120	6.7

^aAs determined using ¹H NMR spectroscopy



2.5 Conclusion

In conclusion, rhodium (II)-catalyzed unactivated aliphatic C–H bond amination using aryl azides as N-atom source has been developed efficiently. The scope of our reaction was found to be broader than previously reported aliphatic C–H bond amination by not requiring a strong electron-withdrawing group on the nitrogen atom. The mechanistic experiments suggested that the amination reaction occurred through stepwise pathway with the *syn*-C–H bond. Our future research aims to examine the nature of catalytic species in this C–H bond amination and further

develop the synthetic method for preparation of complex, functionalized N-heterocycles.

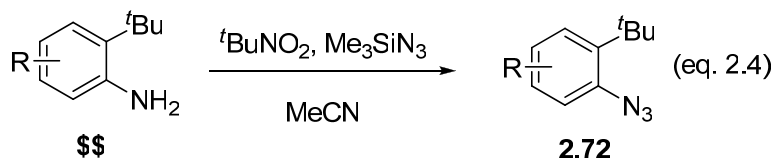
2.6 Experiments

General. The general experiments were performed as described in Jana et al. *J. Org. Chem.* **2014**, 79, 2781. “¹H NMR and ¹³C 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 μ m) mesh silica gel (SiO₂). Medium pressure liquid chromatography (MPLC) was performed to force flow the indicated solvent system down columns that had been packed with 60Å (40 – 60 μ m) mesh silica gel (SiO₂). 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, Et₂O, and CH₂Cl₂ were dried by filtration through alumina according to the procedure of Grubbs.²² Metal salts were stored in a nitrogen atmosphere dry box.”

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

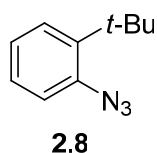
2.6.1.1 General Procedure for the Azidation Reaction

Following the procedure of Zhang and Moses,²³ the 2-*tert*-butyl aryl azides were prepared. Yields were not optimized.



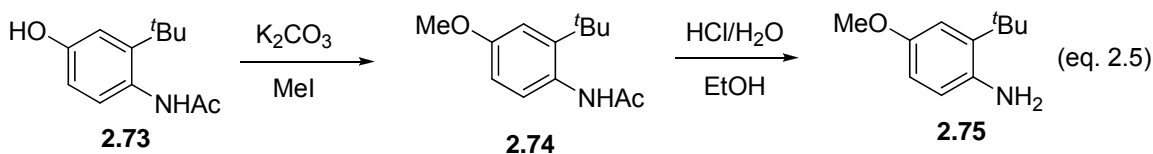
To a cooled solution of aniline in MeCN (0.2 M) was added dropwise *t*-BuNO₂ (4 equiv) and Me₃SiN₃ (3 equiv) dropwise. The resulting solution was warmed to room temperature. After 1h, visualization of the reaction progress using TLC indicated the consumption of the starting material. De-ionized water was added to the reaction mixture. The mixture then was extracted with 2 × 30 mL of CH₂Cl₂. The combined organic phases were washed with 20 mL of brine. The resulting organic phase was dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded azide.

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

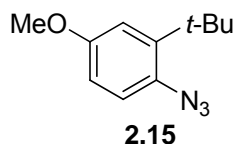


1-Azido-2-*tert*-butylbenzene 2.8.²⁴ The general procedure was followed using 0.298 g of 2-*tert*-butylaniline (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-BuNO₂ and 0.842 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow red oil (0.287 g, 84%). This azide was previously reported by Smith and co-workers.³¹ ¹H NMR (500MHz, CDCl₃) δ 7.36 (d, *J* = 8.0 Hz, 1H), 7.26 (t, *J* = 8.0 Hz, 1H), 7.18 (d, *J* = 8.0 Hz,

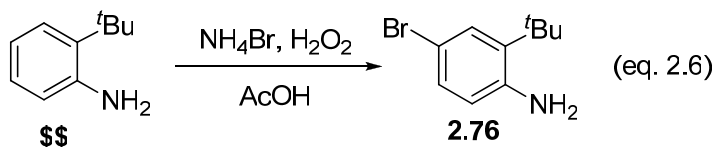
1H), 7.09 (t, $J = 8.0$ Hz, 1H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 141.0 (C), 137.9 (C), 127.3 (CH), 127.2 (CH), 124.7 (CH), 119.5 (CH), 35.1 (C), 29.9 (CH_3). ATR-FTIR (thin film): 3067, 2995, 2956, 2118, 2081, 1575, 1484, 1439, 1283, 1150, 1056, 747, 646 cm^{-1} .



2-tert-Butyl-4-methoxyaniline 2.75.²⁵ To a solution of 2.07 g of acetamide **2.73** (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 **2.74** 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 **2.75** as brown solid (0.587 g, 33%). The spectral data matched that reported by Glorius and co-workers.⁴¹ ^1H 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} .

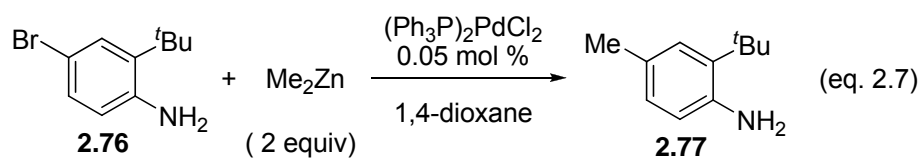


1-Azido-2-*tert*-butyl-4-methoxybenzene 2.15. The general procedure was followed using 0.358 g of 2-*tert*-butyl-4-methoxyaniline **2.75** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-BuNO₂ and 0.842 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a brown oil (352 mg, 86%). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 156.6 (C), 142.6 (C), 130.4 (C), 120.4 (CH), 114.5 (CH), 111.0 (CH), 55.5 (CH₃), 35.2 (C), 29.9 (CH₃); ATR-FTIR (thin film): 2998, 2955, 2912, 2105, 1602, 1483, 1416, 1260, 1225, 1048, 876, 799, 637cm⁻¹; HRMS (EI) *m/z* calculated for C₁₁H₁₅N₃O (M)⁺: 205.1215, found: 205.1207.

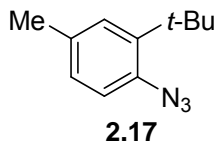


4-Bromo-2-*tert*-butylaniline 2.76. In the round-bottom flask were placed 1.79 g of 2-*tert*-butylaniline (12.03 mmol), 1.29 g of NH₄Br (13.23 mmol, 1.1 equiv) and 24 mL of glacial acetic acid. 1.36 mL of H₂O₂ was added dropwise via a syringe pump and the reaction mixture was left to stir for 48 hours. The reaction mixture then was neutralized with NaHCO₃ and extracted with an additional 3 × 20.0 mL of CH₂Cl₂. The combined organic phases were washed with 30.0 mL of brine. The resulting organic phase was dried over Na₂SO₄, 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%). ¹H NMR (500MHz, CDCl₃)

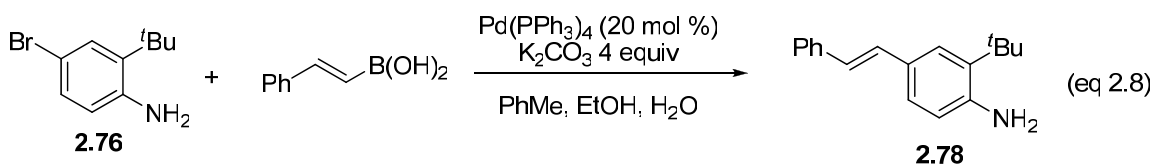
δ 7.31 (d, J = 2.5 Hz, 1H), 7.12 (dd, J = 6.5 Hz, 2.0 Hz, 1H), 6.51 (d, J = 8.5 Hz, 1H), 3.82 (s, 2H), 1.40 (s, 9H); ^{13}C NMR (125 MHz, CDCl_3) δ 143.7 (C), 135.9 (C), 129.6 (C), 129.5 (CH), 119.2 (CH), 110.7 (CH), 34.4 (C), 29.4 (CH_3). ATR-FTIR (thin film): 3493, 3392, 2963, 2909, 2871, 1619, 1486, 1400, 1249, 1151, 1101, 867, 809 cm^{-1} ; HRMS (EI) m/z calculated for $\text{C}_{10}\text{H}_{14}\text{BrN}$ (M) $^{+}$: 227.0310, found: 227.0300.



2-tert-Butyl-4-methylaniline 2.77.²⁶ Following the procedure by Herbert, Aniline **2.77** was prepared.²⁷ To the solution of 1.1 g of 2-tert-butyl-4-bromo-phenylamine **2.76** (5.0 mmol), 0.17 g of $\text{PdCl}_2(\text{PPh}_3)_2$ (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 **2.77** as a pale solid (0.530 g, 65%). This aniline was reported recently by Dixon and Burgoyne.⁵¹ ^1H 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} .

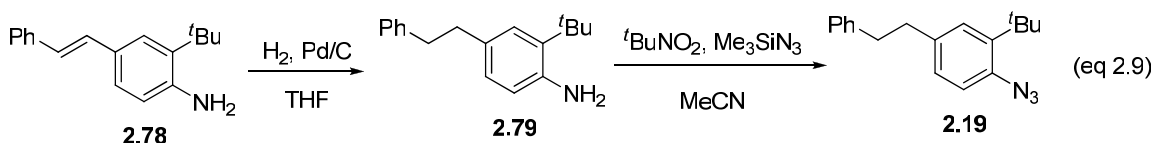


1-Azido-2-*tert*-butyl-4-methoxybenzene 2.17. The general procedure was followed using 0.326 g of 2-*tert*-butyl-4-methylaniline (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-BuNO₂ and 0.842 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow oil (318 mg, 84%). ¹H NMR (500 MHz, CDCl₃) δ 7.24 (s, 1H), 7.13 (m, 2H), 2.41 (s, 3H), 1.50 (s, 9H); ¹³C NMR (125 MHz, CDCl₃) δ 140.8 (C), 135.1 (C), 134.2 (C), 128.2 (CH), 127.8 (CH), 119.5 (CH), 35.0 (C), 30.1 (CH₃), 21.2 (CH₃). 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 C₁₁H₁₅N₃ (M)⁺: 189.1266, found: 189.1270.



(*E*)-2-*tert*-Butyl-4-styrylaniline 2.78. 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), K₂CO₃ (1.1 g) and 0.105 g of Pd(PPh₃)₄ (0.2 equiv). The mixture of toluene:H₂O: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 NH₄Cl. The resulting aqueous phase was extracted with an additional 3 × 20 mL of CH₂Cl₂. The combined organic phases were washed with 30 mL of brine. The resulting organic phase was dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification

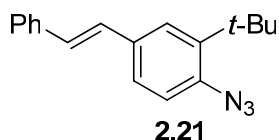
by MPLC (0:100 – 50:50 EtOAc: hexanes) afforded the product as a brown oil (0.366 g, 73%). ^1H NMR (500 MHz, CDCl_3) δ 7.51 (d, J = 7.5 Hz, 2H), 7.41 (d, J = 1.5 Hz, 1H), 7.34 – 7.37 (m, 2H), 7.28 (dd, J = 1.5, 8.0 Hz, 1H), 7.22 – 7.25 (m, 1H), 7.08 (d, J = 16.5 Hz, 1H), 6.95 (d, J = 16.5 Hz, 1H), 6.66 (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 $\text{C}_{18}\text{H}_{21}\text{N}$ (M) $^+$: 251.1674, found: 251.1671.



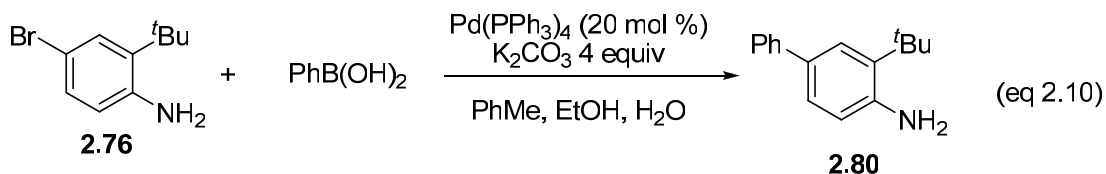
1-Azido-2-*tert*-butyl-4-phenethylbenzene 2.19. A mixture of (*E*)-2-*tert*-butyl-4-phenethylaniline **2.78** and Pd/C (Pd, 10 wt % on carbon powder) in THF were vigorously stirred at room temperature under hydrogen atmosphere. After 20h, visualization of the reaction progress using TLC indicated consumption 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*-BuNO₂-mediated azidation reaction without purification.

The general azidation procedure was followed using 0.506 g of 2-*tert*-butyl-4-phenethylaniline **2.79** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-BuNO₂ and 0.842 mL of (CH₃)₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow oil (0.497 g, 89%). ^1H NMR (500 MHz, CDCl_3) δ 7.32 (dt, J = 6.5, 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, CDCl₃) 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 (CH₂), 37.6 (CH₂), 35.0 (C), 30.0 (CH₃); ATR-FTIR (thin film): 3027, 2953, 2863, 2102, 2061, 1602, 1489, 1291, 1076, 809, 745, 697 cm⁻¹; HRMS (EI) m/z calculated for C₁₈H₂₁N₃ (M)⁺: 279.1735, found: 279.1742.

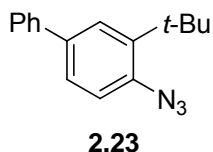


(E)-1-Azido-2-tert-butyl-4-styrylbenzene 2.21. The general azidation procedure was followed using 0.502 g of (*E*)-2-tert-butyl-4-styrylaniline **2.78** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-BuNO₂ and 0.842 mL of (CH₃)₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow solid (0.432 g, 78%). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₃); 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 C₁₈H₁₉N₃ (M)⁺: 277.1579, found: 277.1568.



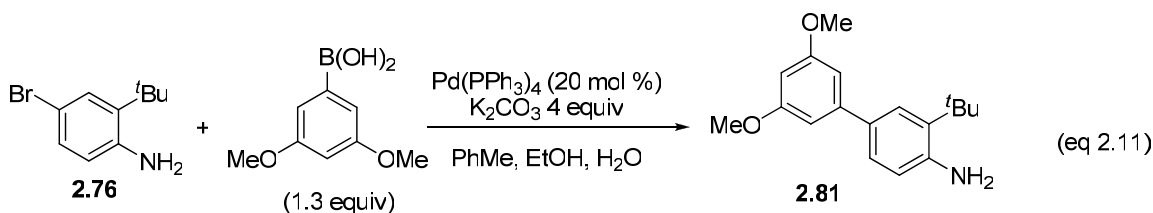
2-tert-Butyl-4-phenylaniline 2.80. To a dry 100 mL round bottom flask equipped with a stir bar were 0.456 g of 2-tert-butyl-4-bromoaniline (2 mmol), 0.354 g of phenylboronic acid

(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:H₂O: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 **2.80** as a brown oil (0.283 g, 63%). 1H 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.



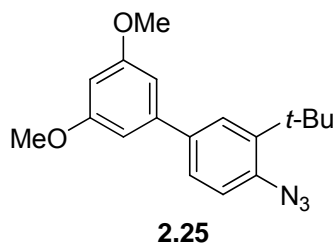
1-Azido-2-tert-butyl-4-phenylbenzene 2.23. The general azidation procedure was followed using 0.450 g of 2-tert-butyl-4-phenylaniline **2.80** (2 mmol) in 10 mL of MeCN, 0.951 mL of $t\text{-BuNO}_2$ and 0.842 mL of $(CH_3)_3SiN_3$. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow solid (0.412 g, 82%). 1H 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 $\text{C}_{16}\text{H}_{17}\text{N}_3$ (M^+): 251.1244, found: 251.1431.

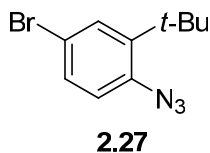


3-tert-Butyl-3',5'-dimethoxybiphenyl-4-amine 2.81. To a dry 100 mL round bottom flask equipped with a stir bar were added 0.456 g of 2-tert-butyl-4-bromoaniline (2 mmol), 0.548 g of 3,5-dimethoxyphenylboronic acid (2.9 mmol), 1.1 g of K_2CO_3 (4 equiv) and 0.105 g of $\text{Pd(PPh}_3)_4$ (0.2 equiv). A mixture of toluene: H_2O :EtOH (3:2:1) was added to reaction flask. The resultant mixture was heated to $100\text{ }^\circ\text{C}$. 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 $3 \times 20.0\text{ mL}$ 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 **2.81** as a light brown solid (0.416 g, 73%). ^1H NMR (500 MHz, CDCl_3) δ 7.53 (d, $J = 2.0\text{ Hz}$, 1H), 7.33 (dd, $J = 6.0\text{ Hz}$, 2.0 Hz , 1H), 6.76 (d, $J = 2.0\text{ Hz}$, 2H), 6.74 (d, $J = 8.0\text{ Hz}$, 1H), 6.48 (t, $J = 2.0\text{ Hz}$, 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.

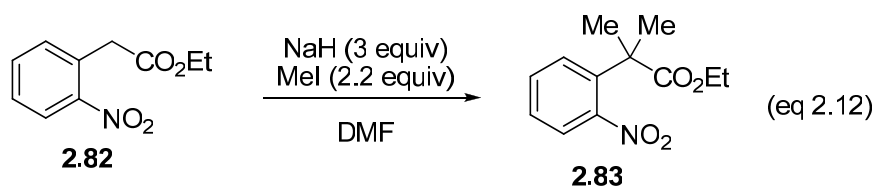


4-Azido-3-tert-butyl-3',5'-dimethoxybiphenyl 2.25. The general azidation procedure was followed using 0.570 g of 3-tert-butyl-3',5'-dimethoxybiphenyl-4-amine **2.81** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-BuNO₂ and 0.842 mL of (CH₃)₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a brown yellow solid (0.566 g, 91%). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₃), 35.3 (C), 30.1 (CH₃); 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.

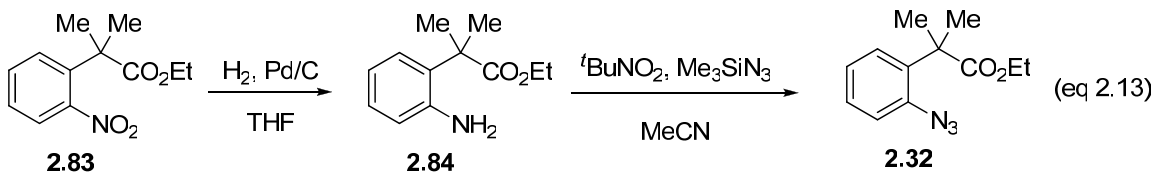


1-Azido-4-bromo-2-tert-butylbenzene 2.27. The general procedure was followed using 0.454 g of 4-bromo-2-tert-butylaniline **2.76** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-BuNO₂ and 0.842 mL of (CH₃)₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a brown yellow oil (0.409 g, 81%). ¹H NMR (500MHz, CDCl₃) 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 $\text{C}_{10}\text{H}_{12}\text{BrN}_3$ (M^+): 253.0215, found: 253.0220.

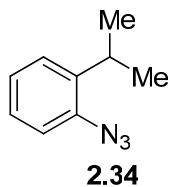


2-Methyl-2-(2-nitrophenyl)propanoic acid ethyl ester 2.83. Following the procedure reported by Glorius and co-workers, methyl ester **2.83** was prepared.⁴ To a 2.1 g of (2-nitrophenyl)-acetic acid methyl ester (10.0 mmol), and 2 mL of MeI (22.0 mmol) in 20 mL of DMF at 0 °C was added small amount of 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-workers²⁵. ^1H 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} .



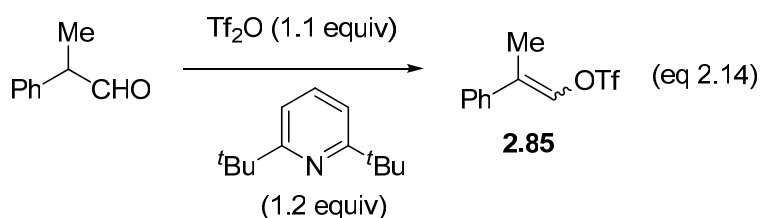
Ethyl 2-(2-azidophenyl)-2-methylpropanoate 2.32. Reduction of the nitro group was accomplished by mixing 0.47 g of ethyl ester **2.83** and 0.1 g of Pd on activated carbon in 10 mL of MeOH. A balloon of hydrogen was attached. After 4 hours, the balloon was removed, and the reaction mixture was filtered. The resulting filtrate was concentrated *in vacuo* to afford aniline **2.84**, 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 **2.84** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-BuNO₂ and 0.842 mL of (CH₃)₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow oil (0.16 g, 34%). ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (125 MHz, CDCl₃): δ 177.1 (C), 137.5 (C), 136.4 (C), 128.0 (CH), 126.4 (CH), 124.9 (CH), 118.6 (CH), 60.8 (CH₂), 45.1 (C), 26.1 (CH₃), 14.1 (CH₃); 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 C₁₂H₁₅N₃O₂ (M)⁺: 233.1164, found: 233.1166.

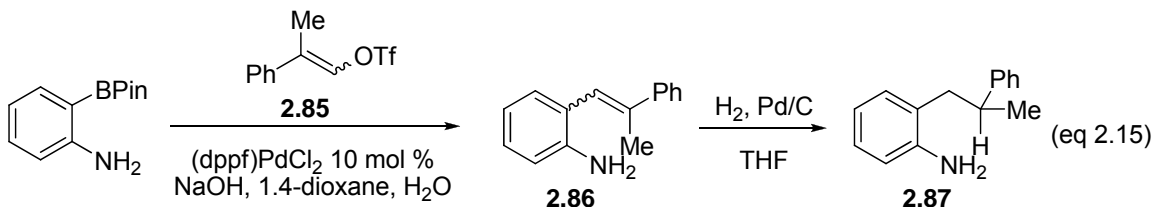


1-Azido-2-isopropylbenzene 2.34.²⁸ The general procedure was followed using 0.270 g

of 2-isopropylaniline (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-BuNO₂ and 0.842 mL of (CH₃)₃SiN₃. 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. ¹H NMR (500 MHz, CDCl₃): 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); ¹³C NMR (125 MHz, CDCl₃): δ 140.0 (C), 137.2 (C), 126.9 (CH), 126.6 (CH), 125.0 (CH), 118.1 (CH), 28.0 (CH), 22.9 (CH₃); ATR-FTIR (thin film): 3067, 2963, 2121, 2091, 1580, 1487, 1445, 1290, 1077, 907, 748 cm⁻¹.



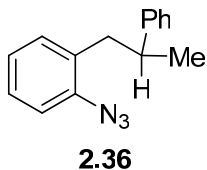
(E)-2-phenylprop-1-enyl trifluoromethanesulfonate 2.85. To a mixture of 1.32 mL of 2-phenylpropanal (10.0 mmol) and 2.65 mL of 2,6-di-*tert*-butylpyridine (12.0 mmol) in 40 mL of 1,2-dichloroethane was added 1.85 mL of triflic anhydride (11.0 mmol). The resultant mixture was heated to 70 °C. After 2h, the mixture was cooled to room temperature and diluted with 40 mL of CH₂Cl₂. The phases were separated, and the resulting aqueous phase was extracted with an additional 2 × 30 mL of CH₂Cl₂. The combined organic phases were washed with 1 × 30 mL of brine. The resulting organic phase was dried over Na₂SO₄, and was concentrated *in vacuo* to afford 2.53 g of triflate **2.85**, which was used in the subsequent Suzuki cross-coupling reaction without further purification.



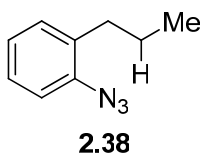
Aniline 2.86. To a mixture of 0.7 g of 2-aniline boronic pinacol ester (3.2 mmol), 0.261 g of $(\text{dppf})\text{PdCl}_2$ (0.32 mmol) in 40 mL of 1,4-dioxane was added 8 mL of a 3 M solution of NaOH in water followed by 1.36 g of triflate **2.85** (5.12 mmol). The resultant mixture was heated to 80 °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 **2.86** which was submitted to the subsequent hydrogenation step without further purification.

To a mixture of 0.627 g of aniline **2.86** 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 **2.87** as a yellow oil (1.76 mmol, 59% over two steps). ^1H 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 (CH₂), 39.5 (CH), 21.4 (CH₃); ATR-FTIR (thin film): 3451, 3371, 1621, 1490, 1449, 1268, 907 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₅H₁₇N(M)⁺: 211.1361, found: 211.1380.



Azide 2.36. The general azidation procedure was followed using 0.422 g of 2-(2-phenylpropyl)aniline **2.87** (2 mmol) in 10 mL of MeCN, 0.951 mL of *t*-BuNO₂ and 0.842 mL of (CH₃)₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow oil (0.356 g, 75%). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 40.3 (CH), 21.0 (CH₃); IR (thin film): 2113, 1578, 1490, 1448, 1281, 1148, 902, 731 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₅H₁₅N₃ (M)⁺: 237.1266, found: 237.1276.



1-Azido-2-*n*-propylbenzene 2.38.²⁹ 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*-BuNO₂ and 0.842 mL of (CH₃)₃SiN₃. 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-

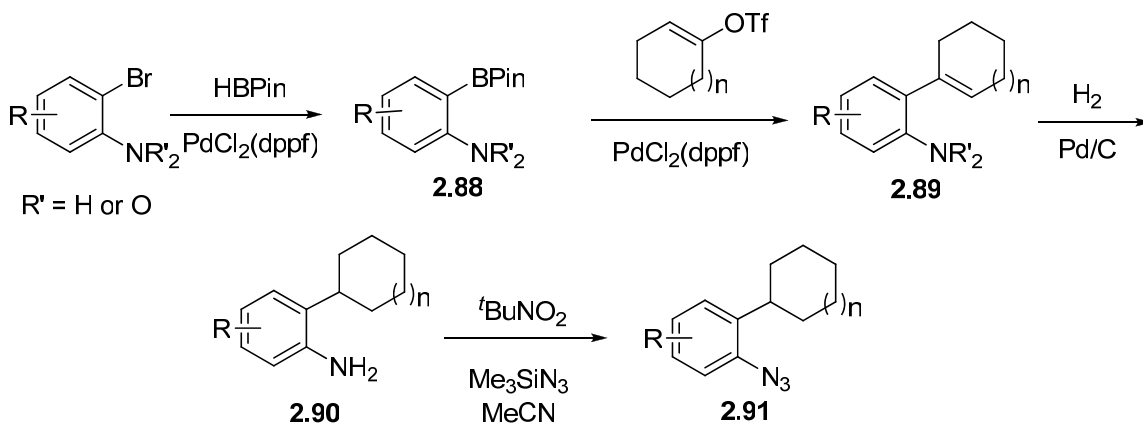
workers.⁸¹H NMR (500 MHz, CDCl₃) δ 7.25 – 7.28 (m, 1H), 7.15 – 7.20 (m, 2H), 7.08 – 7.11 (m, 1H), 2.59 (t, J = 7.5 Hz, 2H), 1.64 (td, J = 10.0 Hz, J = 7.5 Hz, 2H), 0.99 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 138.0, 134.2, 130.5, 127.2, 124.6, 118.1, 33.3, 23.5, 14.0; IR (thin film): 2122, 1582, 1489, 1450, 1285, 1450, 1107, 750, 653 cm⁻¹.

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

2.6.2.1 Route to Substrates.

Substituted *ortho*-azido-cycloalkylbenzenes were synthesized using the route outlined in Scheme s1. Arylboronic pinacol esters **2.88** 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 **2.89**. Hydrogenation of **2.89** using the combination of Pd/C and H₂ afforded 2-cycloalkylanilines **2.90**. Treatment of the anilines with *tert*-butyl nitrite and azidotrimethylsilane provided the requisite aryl azides **2.91**.

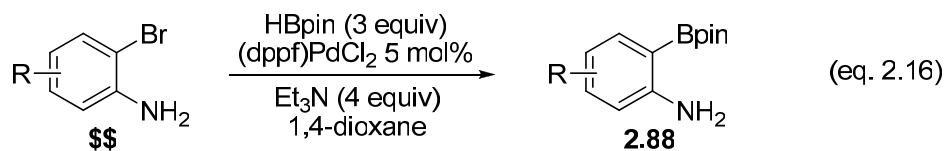
Scheme 2.4. Synthetic route to *ortho*-cyclosubstituted aryl azides.



2.6.2.2 Synthesis of Aryl Boronic Pinacol Esters

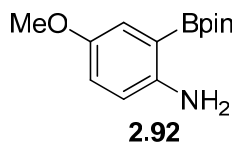
General Procedure

The requisite arylboronic pinacol esters were prepared in one-step from commercially available *ortho*-bromoanilines and HBPin using (dppf)PdCl₂ as catalyst. Yields were not optimized.



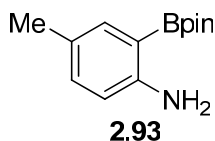
To a mixture of 2-bromo-aniline (5.00 mmol), 0.185 g of (dppf)PdCl₂ (0.250 mmol), 2.78 mL of Et₃N (20.0 mmol) in 20.0 mL of 1,4-dioxane, was added dropwise 2.17 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (15.0 mmol). The resultant mixture was heated to 100 °C. After 16h, the mixture was cooled to room temperature and diluted with 20.0 mL of NH₄Cl. The resulting aqueous phase was extracted with an additional 3 × 20.0 mL of CH₂Cl₂. The combined organic phases were washed with 30.0 mL of brine. The resulting organic phase was dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification using MPLC afforded the product.

Syntheses

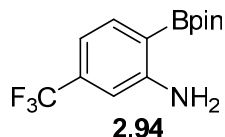


Aryl boronic pinacol ester 2.92.³⁰ The general procedure was following using 2.02 g of 2-bromo-4-methoxyaniline (10.0 mmol), 0.401 mg of (dppf)PdCl₂ (0.500 mmol), 4.40 mL of

4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30.0 mmol) and 5.70 mL of Et₃N (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 ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 125 MHz) δ 151.4 (C), 148.0 (C), 120.6 (CH), 119.6 (CH), 116.5 (CH), 83.6 (C), 56.0 (CH₃), 25.0 (CH₃) only signals visible; ATR-FTIR (thin film): 3456, 3366, 1494, 1421, 1359, 1304, 1226, 1037, 855, 829, 750 cm⁻¹.

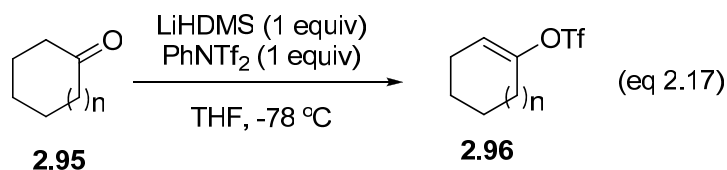


Aryl boronicpinacol ester 2.93. The general procedure was following using 1.86 g of 2-bromo-4-methylaniline (10.0 mmol), 0.401 g of (dppf)PdCl₂ (0.500 mmol), 4.40 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30.0 mmol) and 5.70 mL of Et₃N (40.0 mmol) in 50.0 mL of 1,4-dioxane. Purification by MPLC (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). ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 125 MHz) δ 151.5 (C), 136.8 (CH), 133.7 (CH), 125.8 (C), 115.1 (CH), 83.5 (C), 25.0 (CH₃), 20.3 (CH₃) only signals visible; ATR-FTIR (thin film): 3500, 2980, 2244, 1618, 1576, 1496 cm⁻¹; HRMS (EI) m/z calculated for C₁₃H₂₀BNO₂ (M)⁺: 233.1587, found: 233.1583.



Aryl boronicpinacol ester 2.94. The general procedure was following using 2.40 g of 2-bromo-5-(trifluoromethyl)aniline (10.0 mmol), 0.401 g of (dppf)PdCl₂ (0.500 mmol), 4.40 mL of 4,4,5,5-tetramethyl-1,3,2-dioxaborolane (30.0 mmol) and 5.7 mL of Et₃N (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. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 153.9 (C), 137.6 (CH), 134.3 (q, *J*_{CF} = 32 Hz, C), 124.3 (q, *J*_{CF} = 272 Hz, CF₃), 112.6 (q, *J*_{CF} = 3.4 Hz, CH), 110.9 (q, *J*_{CF} = 4.5 Hz, CH), 84.0 (C), 24.8 (CH₃) only signals visible; ¹⁹F NMR (282 MHz, CDCl₃) 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 C₁₃H₁₇BFNO₂ (M)⁺: 287.1304, found: 287.1310.

2.6.2.3 General Procedure for the Synthesis of Vinyl Trifles



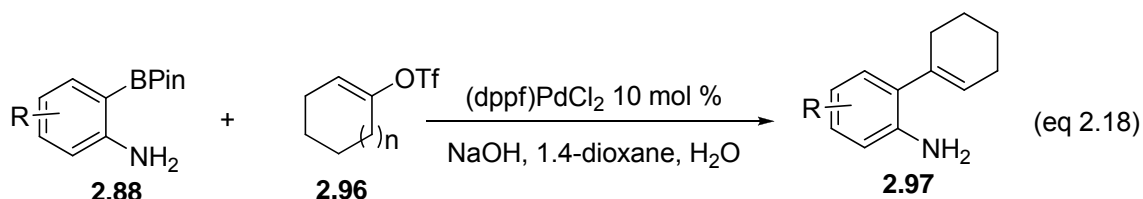
To a stirring solution of 1.67 g of LiHMDS (10.0 mmol) in THF (30.0 mL) at –78 °C was added 10.0 mmol of cyclic ketone. The resultant mixture was warmed to room temperature for 1h, then cooled to –78 °C. A solution of 3.57 g of PhNTf₂ (10.0 mmol) in THF was added to reaction mixture in one portion, and 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 CH₂Cl₂. The resulting aqueous phase was extracted with an additional 2 × 30.0 mL of CH₂Cl₂. The combined organic phases were washed with 30.0 mL of brine. The resulting organic phase was dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo* to afford crude triflate..

2.6.2.4 Suzuki Reaction of *ortho*-Bromoanilines

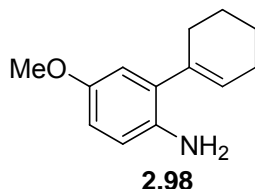
General Procedure.

Following the procedure of Driver and co-workers,³⁰ a series of aryl boronicpinacol esters were treated with cyclic triflates in the presence of (dppf)PdCl₂ to produce the desire aniline. Yields were not optimized.

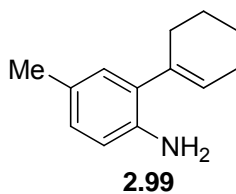


To a mixture of 1.00 mmol of boronic ester **2.88**, and 0.037g of (dppf)PdCl₂ (0.050 mmol) in 15 mL of 1,4-dioxane was added 3.00 mL of a 3M solution of NaOH in water followed by 1.20 mmol of cycloalkyltriflate. The resultant mixture was heated to 100 °C. After 12 h, the mixture was cooled to room temperature and diluted with 10 mL of a saturated aqueous solution of NH₄Cl. The resulting mixture was separated, and the aqueous phase was extracted with an additional 2 × 30 mL of CH₂Cl₂. The combined organic phases were washed with 30 mL of brine. The resulting organic phase was dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification of the oily residue using MPLC afforded the product.

Syntheses

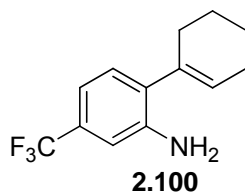


Aniline 2.98. The general procedure was following using 1.24 g of boronic ester **2.92** (5.00 mmol), crude cyclohexyltriflate (derived from 10.0 mmol of cyclohexanone), 0.183 g of (dppf)PdCl₂, and 1.80 g of NaOH (45.0 mmol) in 75.0 mL of 1,4-dioxane and 15.0 mL of water. Purification by MPLC (10:90 – 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): ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₃), 29.3 (CH₂), 25.5 (CH₂), 23.2 (CH₂), 22.2 (CH₂). ATR-FTIR (thin film): 3420, 3009, 2929, 2227, 1623, 1521, 1462, 987, 758 cm⁻¹; HRMS (EI) m/z calculated for C₁₃H₁₇NO (M)⁺: 203.1310, found: 203.1296.

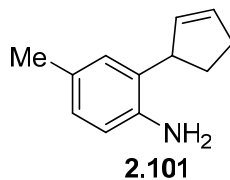


Aniline 2.99. The general procedure was following using 1.16 g of boronic ester **2.93** (5.00 mmol), crude cyclohexyltriflate (derived from 10.0 mmol of cyclohexanone), 0.183 g of (dppf)PdCl₂, and 1.80 g of NaOH (45.0 mmol) in 75.0 mL of 1,4-dioxane and 15.0 mL of water.

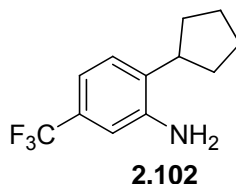
Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the product as a dark red oil (0.842 g, 90%), R_f = 0.47 (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ^1H NMR (500 MHz, CDCl_3) δ 6.96 (dd, J = 7.0 Hz, 1.0 Hz, 1H), 6.93 (s, 1H), 6.70 (d, J = 8.0 Hz, 1H), 5.86 (t, J = 2.0 Hz, 1H), 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 $\text{C}_{13}\text{H}_{17}\text{N}$ (M) $^+$: 187.1361, found: 187.1365.



Aniline 2.100. The general procedure was following using 1.43 g of boronic ester **2.94** (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). ^1H 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 $\text{C}_{13}\text{H}_{14}\text{NF}_3$ (M) $^+$: 241.1078, found: 241.1081.



2-(cyclopent-2-enyl)-4-methyl-1-nitrobenzene 2.101. Following the procedure of Larock and co-workers,³¹ nitrobenzene **2.101** 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*-Bu₄NCl (1 equiv), 0.735 g of KOAc (3 equiv), 0.0328 g of PPh₃ (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, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 32.3 (CH₂), 21.5 (CH₃). ATR-FTIR (thin film): 3004, 2933, 1614, 1531, 1467, 1331, 1195, 845, 735, 679 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₂H₁₃NO₂ (M)⁺: 203.0946, found: 203.0934.



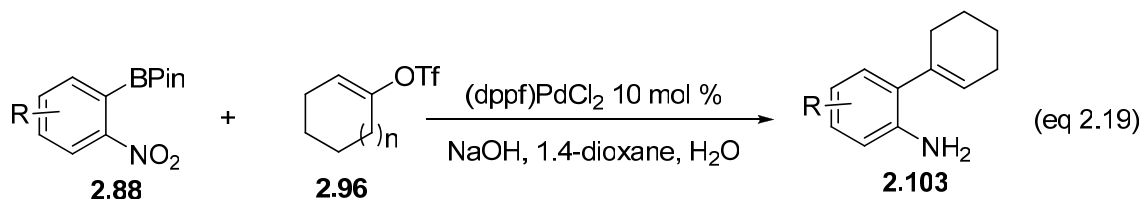
Aniline 2.102. The general Suzuki cross-coupling procedure was following using 1.43 g of boronic ester **2.94** (5.00 mmol), crude cyclopentyltriflate (derived from 10.0 mmol of cyclopentanone), 0.183 g of (dppf)PdCl₂, and 1.80 g of NaOH (45.0 mmol) in 75.0 mL of 1,4-dioxane and 15.0 mL of water. Purification 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 H₂. 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 **2.102** as a yellow oil (2.85 mmol, 57% over two steps). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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, CF₃), 115.2 (q, *J*_{CF} = 4.3 Hz, C), 111.9 (q, *J*_{CF} = 3.6 Hz, C), 39.9 (CH), 32.0 (CH₂), 25.2 (CH₂); ¹⁹F NMR (282 MHz, CDCl₃) 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 C₁₂H₁₄NF₃ (M)⁺: 229.1078, found: 229.1075.

2.6.2.5 Suzuki Reaction of 2-Bromo-1-Nitrobenzenes

General Procedure

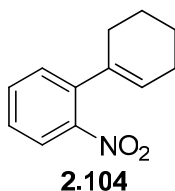
Following the procedure of Driver and co-workers,³⁰ 2-nitrophenylboronic acid was treated with a cyclic triflate in the presence of (dppf)PdCl₂ to produce the desired 2-cycloalkenyl nitrobenzenes. Yields were not optimized.



To a mixture of 0.165 g of 2-nitrophenylboronic acid (1.00 mmol), 0.037 g of (dppf)PdCl₂

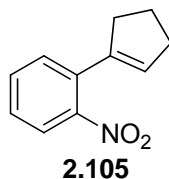
(0.050 mmol) in 15 mL of 1,4-dioxane was added 3 mL of a 3M solution of NaOH in water followed by 1.20 mmol of cycloalkenyltriflate. The resultant mixture was heated to 100 °C. After 12 h, the mixture was cooled to room temperature and diluted with 10 mL of saturated aqueous solution of NH₄Cl. The phases were separated, and the aqueous phase was extracted with an additional 2 × 30 mL of CH₂Cl₂. The combined organic phases were washed with 30 mL of brine. The resulting organic phase was dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification of the oily residue using MPLC afforded the product.

Syntheses

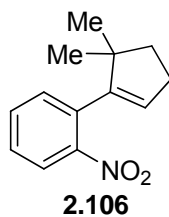


Nitrobenzene 2.104. The general procedure was following using 0.825 g of boronic acid (5.00 mmol), crude cyclohexenyl triflate (derived from 10.0 mmol of cyclohexanone), 0.183 g of (dppf)PdCl₂, 1.80 g of NaOH (45.0 mmol) in 75.0 mL of 1,4-dioxane and 15.0 mL of water. Purification by MPLC (1:100 – 10:90 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): ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 25.4 (CH₂), 22.8 (CH₂), 21.7 (CH₂). ATR-FTIR (thin film): 2956, 2928, 2859, 2249, 1606, 1571, 1526, 1457, 1264 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₂H₁₃NO₂ (M)⁺: 203.0946,

found: 203.0953.

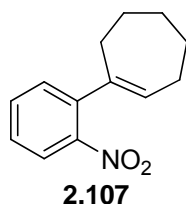


Nitrobenzene 2.105. The general procedure was following using 0.825 g of boronic acid (5.00 mmol), crude cyclohexyltriflate (derived from 10.0 mmol of cyclohexanone), 0.183 g of (dppf)PdCl₂, and 1.80 g of NaOH (45.0 mmol) in 75.0 mL of 1,4-dioxane and 15.0 mL of water. Purification by MPLC (1:100 – 10:90 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): ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 148.8 (C), 140.0 (C), 133.5 (C), 132.1 (CH), 130.8 (CH), 127.6 (CH), 123.6 (CH), 35.3 (CH₂), 33.5 (CH₂), 24.1 (CH₂) 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 C₁₁H₁₁NO₂ (M)⁺: 189.0790, found: 189.0799.



Nitrobenzene 2.106. 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)PdCl₂, and 1.80 g of NaOH (45.0 mmol) in 75.0 mL of 1,4-dioxane and 15.0

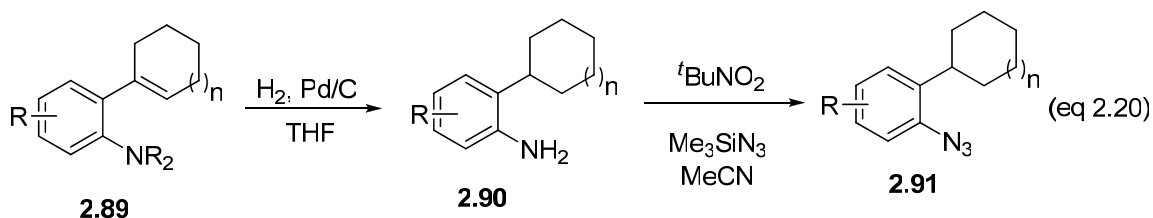
mL of water. Purification by MPLC (1:100 – 10:90 EtOAc: hexanes) afforded the impure product as a yellow oil. This product was carried on to the next step without any characterization.



Nitrobenzene 2.107. 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)PdCl₂, 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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 32.3 (CH₂), 29.1 (CH₂), 26.8 (CH₂), 26.7 (CH₂). ATR-FTIR (thin film): 2923, 2848, 1713, 1606, 1524, 1350, 904, 783, 725 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₃H₁₅NO₂ (M)⁺: 217.1103, found: 217.1115.

2.6.2.6 Preparation of the Aryl Azide Substrates through Hydrogenation/Azidation Sequence

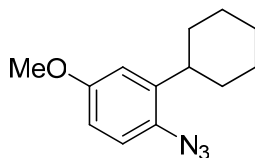
General Procedure



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*-BuNO₂-mediated azidation reaction without further purification.

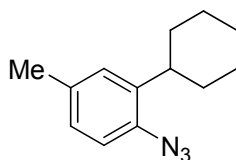
To a cooled solution of aniline in MeCN (0.2 M) was added dropwise *t*-BuNO₂ (4 equiv) and Me₃SiN₃ (3 equiv) dropwise. The resulting solution was warmed to room temperature. After 1h, visualization of the reaction progress using TLC indicated the consumption of the starting material. De-ionized H₂O was then added to the reaction mixture. The mixture then was extracted with 2 × 30 mL of CH₂Cl₂. The combined organic phases were washed with 20 mL of brine. The resulting organic phase was dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded azide **2.91**.

Syntheses



2.40

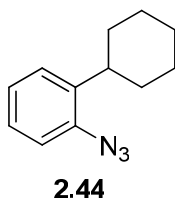
1-Azido-2-cyclohexyl-4-methoxybenzene 2.40. The general procedure was following using crude aniline (derived from 2 mmol of aniline **2.98**), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a brown yellow oil (0.296 g, 64%), *R*_f = 0.7 (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 157.1 (C), 140.6 (C), 129.7 (C), 118.9 (CH), 113.4 (CH), 111.6 (CH), 55.4 (CH₃), 38.5 (CH), 33.3 (CH₂), 26.9 (CH₂), 26.3 (CH₂). 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 C₁₃H₁₇N₃O (M)⁺: 231.1372, found: 231.1366.



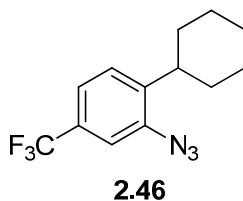
2.42

1-Azido-2-cyclohexyl-4-methylbenzene 2.42. The general procedure was following using crude aniline (derived from 2 mmol of aniline **2.99**), in 10 mL of MeCN, 0.951 mL of *t*-BuNO₂ and 0.842 mL of TMSN₃. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a brown red oil (0.378 g, 88%). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR

(125 MHz, CDCl₃) δ 138.9 (C), 134.5 (C), 134.4 (C), 127.9 (CH), 127.5 (CH), 118.0 (CH), 38.3 (CH), 33.4 (CH₃), 27.0 (CH₂), 26.4 (CH₂), 21.1 (CH₂). ATR-FTIR (thin film): 3002, 2971, 2934, 1738, 1567, 1494, 1378, 1288, 1211, 967, 754 cm⁻¹; HRMS (EI) m/z calculated for C₁₃H₁₇N₃ (M)⁺: 215.1422, found: 215.1413.

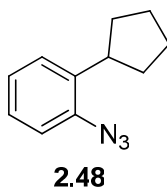


1-Azido-2-cyclohexylbenzene 2.44.³²The general procedure was following using crude aniline (derived from 2 mmol of nitro **2.104**), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a light brown oil (0.209 g, 52%), R_f = 0.8 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). Azide **2.44** was originally reported by Smolinsky. ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 139.3 (C), 137.4 (C), 127.2 (CH), 127.0 (CH), 125.0 (CH), 118.1 (CH), 38.4 (CH), 33.5 (CH₂), 27.2 (CH₂), 26.5 (CH₂). ATR-FTIR (thin film): 2924, 2852, 2114, 2082, 1577, 1486, 1447, 1281, 898, 732 cm⁻¹; HRMS (EI) m/z calculated for C₁₂H₁₅N₃ (M)⁺: 201.1266, found: 201.1275.

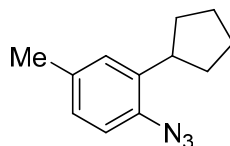


1-Azido-3-trifluoromethyl-5-cyclohexylbenzene 2.46.The general procedure was

following using crude aniline (derived from 2 mmol of **2.100**), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. 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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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, CF₃), 121.6 (q, *J*_{CF} = 3.5 Hz, CH), 114.8 (q, *J*_{CF} = 3.6 Hz, CH), 38.3 (CH), 33.1 (CH₂), 26.7 (CH₂), 26.1 (CH₂). ¹⁹F NMR (282 MHz, CDCl₃) 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 C₁₃H₁₄N₃F₃ (M)⁺: 269.1140, found: 269.1131.

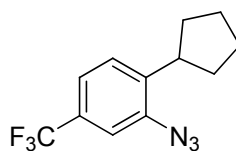


1-Azido-2-cyclopentylbenzene 2.48. The general procedure was following using crude aniline (derived from 2 mmol of nitrobenzene **2.105**, 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a red oil (0.161g, 43%), *R*_f = 0.8 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 137.9 (C), 137.7 (C), 127.3 (CH), 126.9 (CH), 124.9 (CH), 118.1 (CH), 40.1 (CH), 33.6 (CH₂), 25.6 (CH₂). ATR-FTIR (thin film): 2957, 2870, 2123, 2089, 1580, 1489, 1451, 1292, 903, 725 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₁H₁₃N₃ (M)⁺: 187.1109, found: 187.1105.



2.50

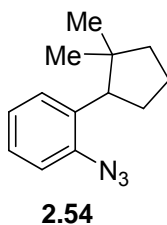
1-Azido-2-cyclopentyl-4-methylbenzene 2.50. The general procedure was following using crude aniline (derived from 2 mmol of **2.101**), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a brown oil (0.346 g, 86%), *R_f* = 0.8 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 137.5 (C), 135.2 (C), 134.5 (C), 128.0 (CH), 127.6 (CH), 118.0 (CH), 40.3 (CH), 33.7 (CH₂), 25.7 (CH₂), 21.1 (CH₃). 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 C₁₂H₁₅N₃ (M)⁺: 201.1266, found: 201.1262.



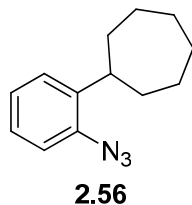
2.52

1-Azido-3-trifluoromethyl-5-cyclopentylbenzene 2.52. The general procedure was following using 0.458 g of aniline **2.102** (2.0 mmol) in 10 mL of MeCN, 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. 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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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, CF₃), 121.5 (q, *J_{CF}*

= 3 Hz, CH), 114.7 (q, J_{CF} = 3.5 Hz, CH), 40.2 (CH), 33.3 (CH₂), 25.5 (CH₂). ¹⁹F NMR (282 MHz, CDCl₃) 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 C₁₂H₁₂N₃F₃ (M)⁺: 255.0983, found: 255.0969.



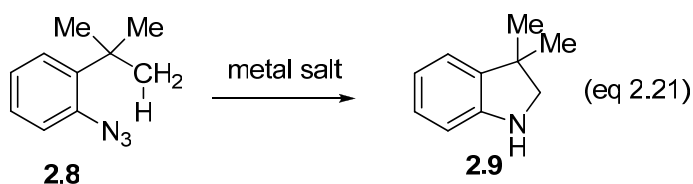
1-Azido-2-(2,2-dimethylcyclopentyl)benzene 2.54. The general procedure was following using impure aniline **s25**(derived from 0.96 g of nitrobenzene **2.106** containing some impurity), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product 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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 30.9 (CH₂), 28.8 (CH₃), 23.6 (CH₃), 22.0 (CH₂) ATR-FTIR (thin film): 2953, 2118, 2084, 1578, 1445, 1294, 908, 734 cm⁻¹; HRMS (EI) m/z calculated for C₁₃H₁₇N₃ (M)⁺: 215.1422, found: 215.1441.



1-Azido-2-cycloheptylbenzene 2.56. The general procedure was following using crude aniline (derived from 2 mmol of nitrobenzene **2.107**), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. 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). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 141.2 (C), 136.6 (C), 127.5 (CH), 126.7 (CH), 124.9 (CH), 118.0 (CH), 40.3 (CH), 35.8 (CH₂), 28.0 (CH₂), 27.5 (CH₂). ATR-FTIR (thin film): 2925, 2854, 2118, 1579, 1487, 1446, 1288, 1084, 904, 727 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₃H₁₇N₃ (M)⁺: 215.1423, found: 215.1428.

2.6.3 Rhodium-Catalyzed Formation of Indolines from Aryl Azides

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



To a mixture of 0.0175 g of 1-azido-2-*tert*-butylbenzene **2.8** (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 Al₂O₃. The filtrate was concentrated *in vacuo*. The resulting oil was dissolved in 1.5 mL of CDCl₃ and 0.007 mL of dibromomethane (0.1 mmol) was added. The area of the C6-H peak in **2.9** was compared to the

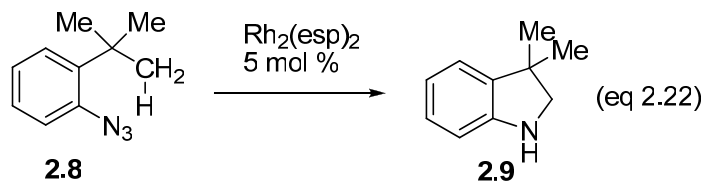
area of CH₂Br₂ to derive a yield.

Table 2.7. Survey of transition metal complexes

entry	metal salt	mol %	solvent	T (°C)	2.9 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(<i>p</i> -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 ₃ CF 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 ₂ CC ₇ H ₁₅) ₄	5	PhMe	120	35
17	Rh ₂ (O ₂ CC ₃ F 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 (<i>S</i> -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 ₂ CCF ₃)	5	PhMe	120	No rxn
24	AgOAc	5	PhMe	120	No rxn
25	CoTTP ^b	5	PhMe	120	No rxn

^aAs determined using ¹H NMR spectroscopy. ^bTTP = tetraphenylporphyrin.

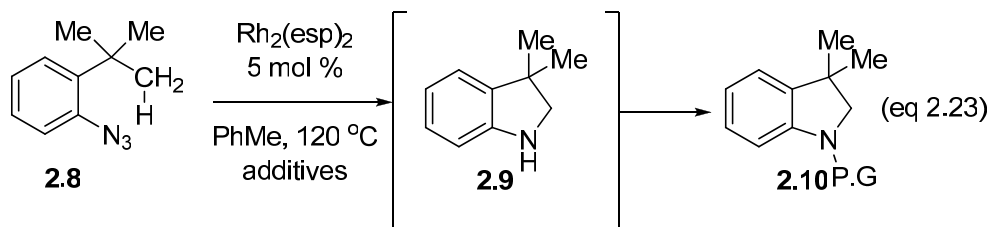
Table 2.8. Survey of solvents.



Entry	metal salt	solvent	2.9 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 ₆ H ₄ Cl ₂	61
6	Rh ₂ (esp) ₂	PhCF ₃	31
7	Rh ₂ (esp) ₂	DCE	47

^aAs determined using ¹H NMR spectroscopy.

Table 2.9. Survey of additives.

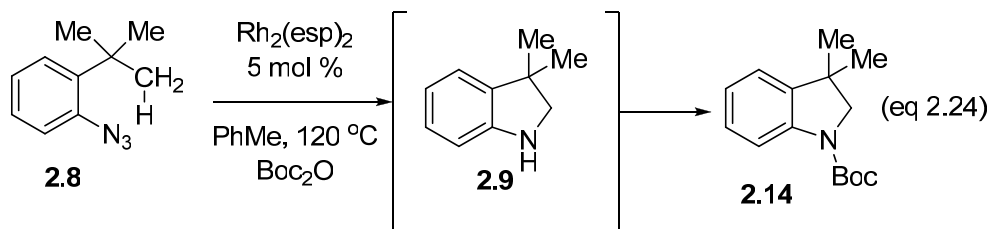


entry	additives	2a yield, % ^a
1	TsCl (1 equiv)	20
2	TsCl (1 equiv)	No rxn
	Et ₃ N (3 equiv)	
3 ^b	TsCl (1 equiv)	No rxn
	DTBMP (1 equiv)	

	TsCl (1 equiv)	
4	Cs ₂ CO ₃ (1 equiv)	20
5	Boc ₂ O (1 equiv)	83
6	Moc ₂ O (1 equiv)	45
7	Ac ₂ O (1 equiv)	73
8	Bz ₂ O (1 equiv)	aniline
9	(CF ₃ CO) ₂ O (1 equiv)	35
10	Tf ₂ O (1 equiv)	20

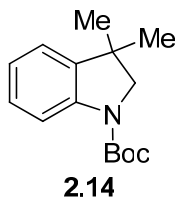
^aAs determined using ¹H NMR spectroscopy. ^bDTBMP = 2,6-di-*tert*-butyl-4-methylpyridine.

2.6.3.2 Optimized General Procedure

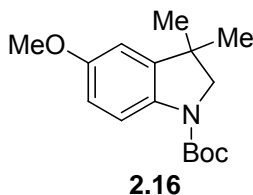


To a mixture of 0.070 g of aryl azide **2.8** (0.40 mmol), 0.0870 g of Boc₂O, and 0.0153 g of Rh₂(esp)₂ (5 mol%) in Schlenk tube was added 0.80 mL of PhMe. The resulting mixture was heated at 120 °C. After 16 h, the mixture was cooled to room temperature and diluted with 5 mL of a saturated aqueous solution of Na₂CO₃. The phases were separated, and the aqueous phase was extracted with an additional 2 × 5 mL of CH₂Cl₂. The combined organic phases were washed with 10 mL of brine. The resulting organic phase was dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by flash chromatography (0:100 – 10:90 EtOAc: hexanes) with Al₂O₃ afforded the product as 66:34 mixture of amide rotamers (0.082 g, 84%).

2.6.3.3 Scope and Limitations of Indoline Formation

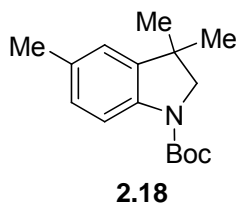


Indoline 2.14.³³ The general procedure was followed with 0.0700 g of aryl azide **2.8** (0.40 mmol), 0.0872 g of Boc₂O (0.40 mmol) and 0.0153 g of Rh₂(esp)₂ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al₂O₃ afforded a orange red oil product 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 **2.14** was previously reported by Faul and co-workers.¹²¹ ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 39.5 (C), 28.8 (CH₃), 28.5 (CH₃). 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 C₁₅H₂₁NO₂ (M)⁺: 247.1572, found: 247.1581.



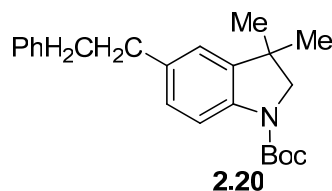
Indoline 2.16. The general procedure was followed with 0.0820 g of aryl azide **2.15** (0.40 mmol), 0.0872 g of Boc₂O (0.40 mmol) and 0.0153 g of Rh₂(esp)₂ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al₂O₃

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): ^1H 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 $\text{C}_{16}\text{H}_{23}\text{NO}_3$ (M) $^+$: 277.1678, found: 277.1689.

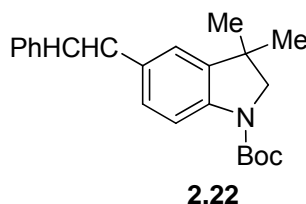


Indoline 2.18. The general procedure was followed with 0.0756 g of aryl azide **2.17** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $\text{Rh}_2(\text{esp})_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded a 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): ^1H 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 C₁₆H₂₃NO₂ (M)⁺: 261.1729, found: 261.1724.

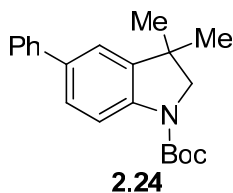


Indoline 2.20. The general procedure was followed with 0.1116 g of aryl azide **2.19** (0.40 mmol), 0.0872 g of Boc₂O (0.40 mmol) and 0.0153 g of Rh₂(esp)₂ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al₂O₃ afforded a yellow oil product as 68:32 mixture of amide rotamers (0.0899 g, 64%), *R_f* = 0.52 (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 39.5 (C), 38.4 (CH₂), 37.7 (CH₂), 28.7 (CH₃), 28.6 (CH₃). ATR-FTIR (thin film): 3022, 2975, 2927, 1683, 1489, 1336, 1144, 1021, 907, 818, 728 cm⁻¹; HRMS (EI) *m/z* calculated for C₂₃H₂₉NO₂ (M)⁺: 351.2198, found: 351.2187.



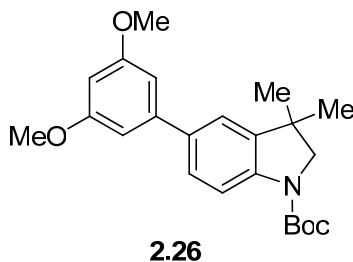
Indoline 2.22. The general procedure was followed with 0.1108 g of aryl azide **2.21** (0.40 mmol), 0.0872 g of Boc₂O (0.40 mmol) and 0.0153 g of Rh₂(esp)₂ (0.02 mmol) in 0.8 mL of

toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al₂O₃ 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): ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 39.4 (C), 28.8 (CH₃), 28.5 (CH₃). 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 C₂₃H₂₇NO₂ (M)⁺: 349.2042, found: 349.2030.

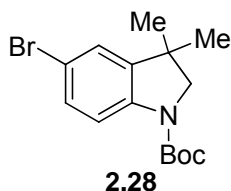


Indoline 2.24. The general procedure was followed with 0.1005g of aryl azide **2.23** (0.40 mmol), 0.0872 g of Boc₂O (0.40 mmol) and 0.0153 g of Rh₂(esp)₂ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al₂O₃ afforded a yellow oil product as 65:35 mixture of amide rotamers (0.0564 g, 54%), R_f = 0.55 (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 39.6 (C), 28.8 (CH₃), 28.5 (CH₃). 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 $\text{C}_{21}\text{H}_{25}\text{NO}_2$ (M) $^{+}$: 323.1885, found: 323.1896.

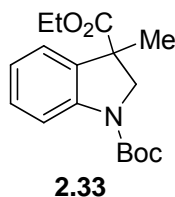


Indoline 2.26. The general procedure was followed with 0.1244 g of aryl azide **2.25** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $\text{Rh}_2(\text{esp})_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded a 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 $\text{C}_{23}\text{H}_{29}\text{NO}_4$ (M) $^{+}$: 383.2097, found: 383.2114.

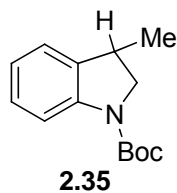


Indoline 2.28. The general procedure was followed with 0.1010 g of aryl azide **2.27** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $\text{Rh}_2(\text{esp})_2$ (0.02 mmol) in 0.8 mL of

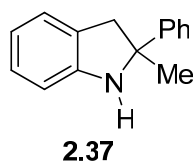
toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al₂O₃ afforded a gray solid product as 65:35 mixture of amide rotamers (0.0950 g, 73%), $R_f = 0.59$ (15:75 EtOAc:hexanes, visualized by 254 nm UV light): ¹H NMR (500 MHz, CDCl₃) δ 7.72 (s, 1H), 7.26 (s, 1H), 7.17 (s, 1H), 3.69 (s, 2H), 1.55 (s, 9H), 1.30 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 39.5 (C), 28.6 (CH₃), 28.5 (CH₃). ATR-FTIR (thin film): 2970, 1694, 1594, 1482, 1378, 1337, 1247, 1147, 1021, 819 cm⁻¹; HRMS (EI) m/z calculated for C₁₅H₂₀BrNO₂ (M)⁺: 325.0677, found: 325.0669.



Indoline 2.33. The general procedure was followed with 0.0932 g of aryl azide **2.32** (0.40 mmol), 0.0872 g of Boc₂O (0.40 mmol) and 0.0153 g of Rh₂(esp)₂ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al₂O₃ afforded a yellow oil product as 66:34 mixture of amide rotamers (0.0854g, 70%): ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 57.9 (CH₂), 28.5 (CH₃), 25.7 (CH₃), 14.1 (CH₃). ATR-FTIR (thin film): 2976, 2928, 1730, 1702, 1599, 1484, 1389, 1336, 1143, 1016, 858, 750 cm⁻¹; HRMS (EI) m/z calculated for C₁₇H₂₃NO₄ (M)⁺: 305.1627, found: 305.1636.

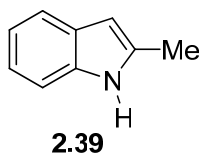


Indoline 2.35. The general procedure was followed with 0.0644 g of aryl azide **2.34** (0.40 mmol), 0.0872 g of Boc₂O (0.40 mmol) and 0.0153 g of Rh₂(esp)₂ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al₂O₃ afforded a brown yellow oil product as 67:33 mixture of amide rotamers (0.0187 mg, 20%): ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 34.1 (C), 28.5 (CH₃), 20.3 (CH₃). ATR-FTIR (thin film): 2978, 2931, 1690, 1602, 1484, 1452, 1391, 1171, 1145, 1045, 905, 648 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₄H₁₉NO₂ (M)⁺: 233.1416, found: 233.1411.

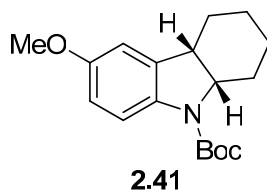


Indoline 2.37. The general procedure was followed (without the presence of Boc₂O) with 0.0948g of aryl azide **2.36** (0.40 mmol), 0.0872 g of Boc₂O (0.40 mmol) and 0.0153 g of Rh₂(esp)₂ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al₂O₃ afforded the product as a yellow oil (0.070 g, 55%). ¹H NMR (500 MHz, CDCl₃) 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, 693cm^{-1} ; HRMS (EI) m/z calculated for $\text{C}_{15}\text{H}_{15}\text{N}$ (M) $^+$: 209.2863, found: 209.1218.

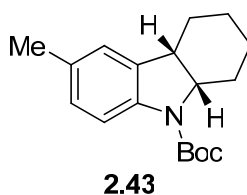


Indoline 2.39. The general procedure was followed (without the presence of Boc_2O) with 0.0644 g of aryl azide **2.38** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $\text{Rh}_2(\text{esp})_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: 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, 721cm^{-1} .

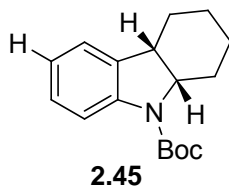


Indoline 2.41. The general procedure was followed with 0.0924g of aryl azide **2.40** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $\text{Rh}_2(\text{esp})_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded the product as a yellow oil (0.0970 g, 80%): ^1H NMR (500 MHz, CDCl_3) δ 7.63 (s, 1H),

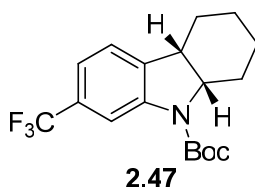
6.71 (s, 1H), 6.68 (d, $J = 9.5$ Hz, 1H), 4.33 (s, 1H), 3.78 (s, 3H), 3.39 (t, $J = 5$ Hz, 1H), 2.18 (t, $J = 14$ Hz, 1H), 2.06 (s, 1H), 1.78 (s, 1H), 1.55 (m, 11H), 1.2 (m, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 155.8 (C), 152.2 (C), 115.9 (C), 115.4 (C), 111.3 (CH), 109.7 (CH), 108.3 (CH), 80.8 (C), 60.5 (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 $\text{C}_{18}\text{H}_{25}\text{NO}_3$ (M) $^+$: 303.1834, found: 303.1821.



Indoline 2.43. The general procedure was followed with 0.0861 g of aryl azide **2.42** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $\text{Rh}_2(\text{esp})_2$ (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%): ^1H 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 $\text{C}_{18}\text{H}_{25}\text{NO}_2$ (M) $^+$: 287.1885, found: 287.1880.

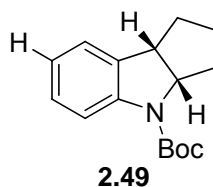


Indoline 2.45.³⁴ The general procedure was followed with 0.0804g of aryl azide **2.44** (0.40 mmol), 0.0872 g of Boc₂O (0.40 mmol) and 0.0153 g of Rh₂(esp)₂ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al₂O₃ afforded the product as a yellow oil (0.0765 mg, 70%). Indoline **2.45** was previously reported by Gilchrist and co-workers.³⁴ ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₃), 24.1 (CH₂), 22.4 (CH₂), 21.1 (CH₂) 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 C₁₇H₂₃NO₂ (M)⁺: 273.1729, found: 273.1734.

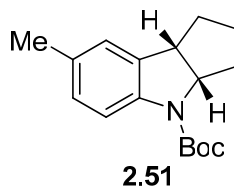


Indoline 2.47. The general procedure was followed with 0.1076g of aryl azide **2.46** (0.40 mmol), 0.0872 g of Boc₂O (0.40 mmol) and 0.0153 g of Rh₂(esp)₂ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al₂O₃ afforded the product as a light yellow solid (0.0859 g, 63%): ¹H NMR (500MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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, CF₃), 122.7 (CH), 119.5 (q, *J*_{CF} = 3.3 Hz, CH), 112.3 (q, *J*_{CF} = 4.1 Hz, CH), 81.2 (C),

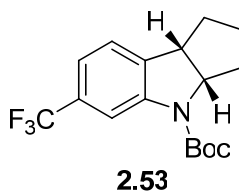
60.7 (CH), 39.4 (CH), 28.4 (CH₃), 27.2 (CH₂), 23.9 (CH₂), 22.1 (CH₂), 21.0 (CH₂); ¹⁹F NMR (282 MHz, CDCl₃) δ –62.43. ATR-FTIR (thin film): 3004, 2963, 2929, 1696, 1602, 1484, 1335, 1290, 1159, 1016, 857, 747 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₈H₂₂F₃NO₂ (M)⁺: 341.1603, found: 341.1619.



Indoline 2.49. The general procedure was followed with 0.0748 g of aryl azide **2.48** (0.40 mmol), 0.0872 g of Boc₂O (0.40 mmol) and 0.0153 g of Rh₂(esp)₂ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al₂O₃ afforded the product, a dark brown oil, as a 66:34 mixture of amide rotamers (0.0881 g, 85%): ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) δ 152.5 (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 (CH₂), 34.9 (CH₂), 28.5 (CH₃), 23.9 (CH₂). ATR-FTIR (thin film): 2974, 2934, 2869, 1690, 1601, 1482, 1387, 1256, 1147, 1046, 859, 647 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₆H₂₁NO₂ (M)⁺: 259.1575, found: 259.1564. See page SI2 s-116 for a ¹H NMR spectrum of the crude reaction mixture of indoline **2.49**. Diagnostic data for diastereoselectivity determination: ¹H NMR (500 MHz, CDCl₃) 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).

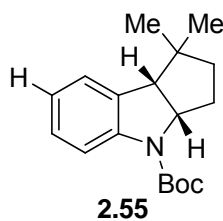


Indoline 2.51. The general procedure was followed with 0.0804 g of aryl azide **2.50** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $\text{Rh}_2(\text{esp})_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded the product, a yellow oil, as a 65:35 mixture of amide rotamers (0.0798 g, 73%): ^1H 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 $\text{C}_{17}\text{H}_{23}\text{NO}_2$ (M) $^+$: 273.1729, found: 273.1734. See page SI2 s-124 for a ^1H NMR spectrum of the crude reaction mixture of indoline **2.51**. Diagnostic data for diastereoselectivity determination: ^1H NMR (500 MHz, CDCl_3) δ 4.45 (t, $J = 6.0$ Hz, 1H), 3.79 (t, $J = 8.0$ Hz, 1H),



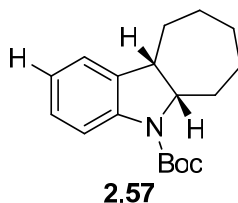
Indoline 2.53. The general procedure was followed with 0.1020 g of aryl azide **2.52** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $\text{Rh}_2(\text{esp})_2$ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al_2O_3 afforded the product, a yellow solid, as a 68:32 mixture of amide rotamers (0.107 g, 82%): ^1H NMR

(500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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, CF₃), 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 (CH₂), 28.4 (CH₃), 23.9 (CH₂). 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 C₁₇H₂₀F₃NO₂ (M)⁺: 327.1446, found: 327.1456. See page SI2 s-126 for a ¹H NMR spectrum of the crude reaction mixture of indoline **2.53**. Diagnostic data for diastereoselectivity determination: ¹H NMR (500 MHz, CDCl₃) δ 4.45 (t, J = 7.5 Hz, 1H), 3.81 (t, J = 7.0 Hz, 1H).



Indoline 2.55. The general procedure was followed with 0.0860 g of aryl azide **2.54** (0.40 mmol), 0.0872 g of Boc₂O (0.40 mmol) and 0.0153 g of Rh₂(esp)₂ (0.02 mmol) in 0.8 mL of toluene. Purification by flash chromatography (0:100 – 10:90 EtOAc: hexanes) using Al₂O₃ afforded the product, a yellow oil, as a 67:33 mixture of amide rotamers (0.101 g, 88%): ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 40.0 (CH₂), 33.8 (C), 29.8 (CH₃), 28.5 (CH₃), 24.5 (CH₃). ATR-FTIR (thin

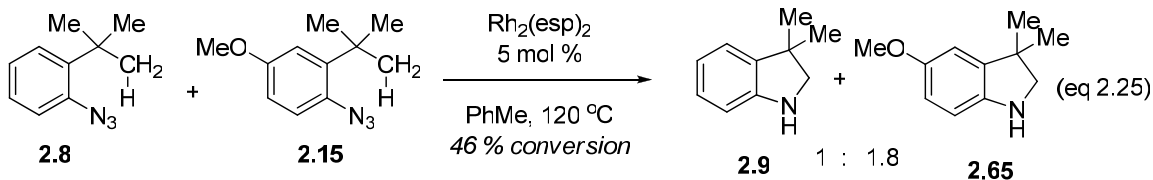
film): 2963, 2931, 2864, 1688, 1596, 1483, 1458, 1386, 1344, 1271, 1166, 1141, 908, 724 cm^{-1} ;
HRMS (EI) m/z calculated for $\text{C}_{18}\text{H}_{25}\text{NO}_2$ (M) $^{+}$: 287.1885, found: 287.1899.



Indoline 2.57. The general procedure was followed with 0.0860 g of aryl azide **2.56** (0.40 mmol), 0.0872 g of Boc_2O (0.40 mmol) and 0.0153 g of $\text{Rh}_2(\text{esp})_2$ (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: ^1H 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: ^1H 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 $\text{C}_{18}\text{H}_{25}\text{NO}_2$ (M) $^{+}$: 287.1885, found: 287.1898.

2.6.4 Mechanistic Experiments

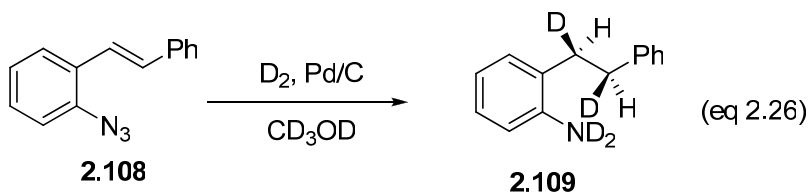
2.6.4.1 Intermolecular Competition Experiment



To a mixture of 0.070 g of 1-azido-2-*tert*-butylbenzene **2.8** (0.4 mmol), 0.0820 g of 1-azido-2-*tert*-butyl-4-methoxybenzene **2.15** (0.4 mmol) and 0.0155 g of $\text{Rh}_2(\text{esp})_2$ (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 **2.8** and 48% azide **2.15**.

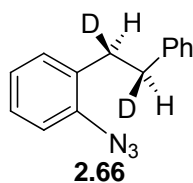
2.6.4.2 Isotope Labeling Studies

Synthesis of Aryl Azide Substrates

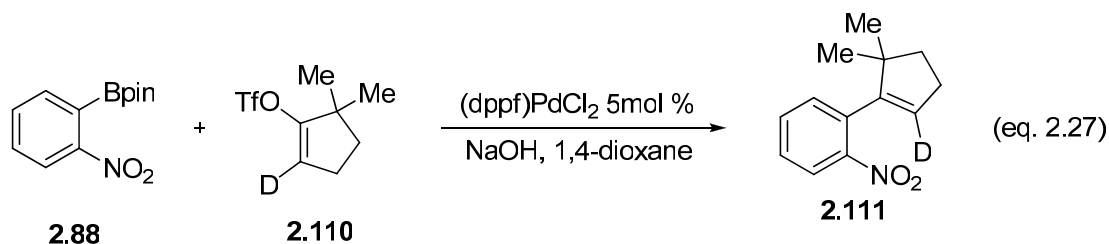


Aniline **2.109**. A mixture of azide **2.108** and Pd/C (Pd, 10 wt % on carbon powder) in CD_3OD were vigorously stirred at room temperature under deuterium atmosphere. After 3 h,

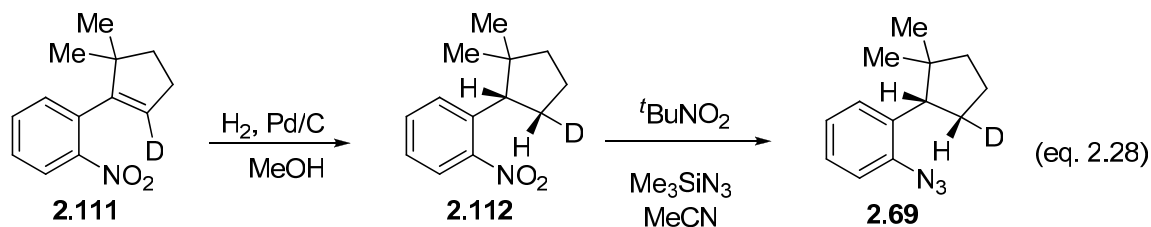
visualization of the reaction progress using TLC indicated consumption of the starting material. The balloon of D₂ was removed, and the mixture then was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* to afford aniline **2.109**. ¹H NMR (500 MHz, CDCl₃) δ 7.72 (t, *J* = 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); ¹³C NMR (125 MHz, CDCl₃) 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.



1-Azido-2-phenylethylbenzene 2.66. To a cooled solution of aniline in MeCN (0.2 M) was added dropwise *t*-BuNO₂ (4 equiv) and Me₃SiN₃ (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 H₂O was added to the reaction mixture. The mixture then was extracted with 2 × 30 mL of CH₂Cl₂. The combined organic phases were washed with 20 mL of brine. The resulting organic phase was dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded azide **2.66**: ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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.



1-Nitro-2-dimethylcyclopentylbenzene-*d*₁ 2.111. To a mixture of 0.825 g of boronic ester **2.88** (5.00 mmol), 1.80 g of NaOH (45.0 mmol) and 0.183 g of (dppf)PdCl₂ (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 NH₄Cl. The resulting mixture was separated, and the aqueous phase was extracted with an additional 2 × 30 mL of CH₂Cl₂. The combined organic phases were washed with 30 mL of brine. The resulting organic phase was dried over Na₂SO₄, 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 **2.111**, which was submitted to the hydrogenation reaction without further purification.

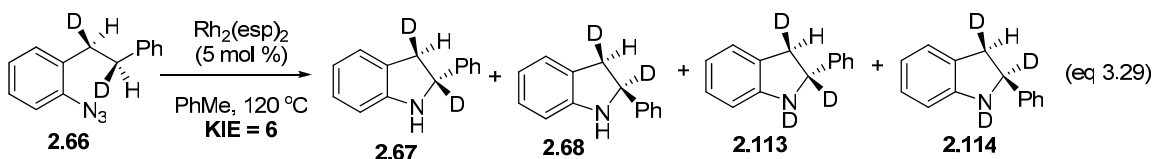


Aryl Azide 2.69. A mixture of nitrobenzene **2.111** (0.96 g) and Pd/C (Pd, 10 wt % on carbon powder) in MeOH were vigorously stirred at room temperature under hydrogen

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 **2.112**, which was subjected to the *t*-BuNO₂-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*-BuNO₂ (4 equiv) and 0.84 mL of Me₃SiN₃ (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 H₂O was then added to the reaction mixture. The mixture then was extracted with 2 × 30 mL of CH₂Cl₂. The combined organic phases were washed with 20 mL of brine. The resulting organic phase was dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded azide **2.69** as a single diastereomer (0.370 g, 35% from boronic acid **2.111**), *R_f* = 0.8 (15:75 EtOAc:hexanes, visualized by 254 nm UV light). ¹H NMR (500 MHz, CDCl₃) 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); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 30.5 (t, *J_{CD}* = 18.9 Hz, CH), 28.8 (CH₃), 23.6 (CH₃), 21.9 (CH₂); ATR-FTIR (thin film): 2951, 2118, 2084, 1487, 1281, 1151, 746 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₃H₁₆DN₃ (M)⁺: 216.1500, found: 216.1499.

C–H Bond Amination Experiments



To a mixture of 0.0225 g of azide **2.66** (0.1 mmol) and 0.0038 g of $\text{Rh}_2(\text{esp})_2$ (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 ^1H NMR spectroscopy. Analysis of the spectral data based on the ratio of **2.113** (**2.114**) and **2.67** (**2.68**) revealed the kinetic isotope effect at each temperature.

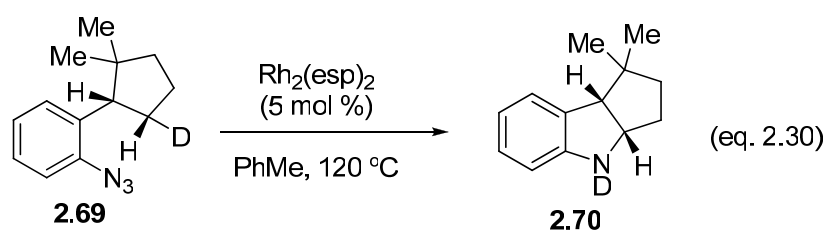
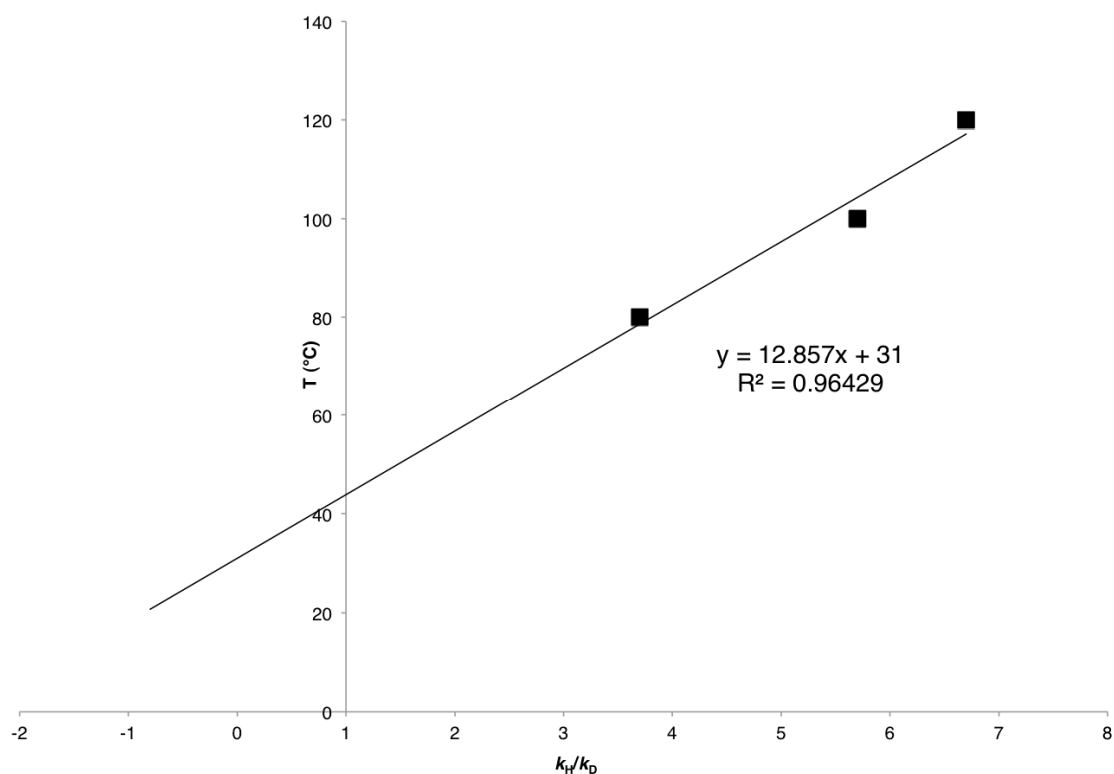
Table 2.10. Observed kinetic isotope effects

entry	T (°C)	$k_{\text{H}}/k_{\text{D}}^a$
1	80	3.7
2	100	5.7
3	120	6.7

^aAs determined using ^1H NMR spectroscopy.

From these data, the isokinetic temperature was calculated to be approximately 43 °C (Figure 2.1), indicating that the reaction is under entropic control.

Figure 2.1. Temperature dependence of $k_{\text{H}}/k_{\text{D}}$.



To a mixture of 0.0215 g of azide **2.69** (0.1 mmol) and 0.0038 g of $\text{Rh}_2(\text{esp})_2$ (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 ^1H NMR spectroscopy. The reaction conversion was determined to be 64.6% by comparison the pick C5 – H of azide **2.69** with the C5 – H pick of indoline **2.70**. Only the formation of a single diastereomer of **2.70** was observed. No change in the diastereomeric ratio of **2.70** was observed.

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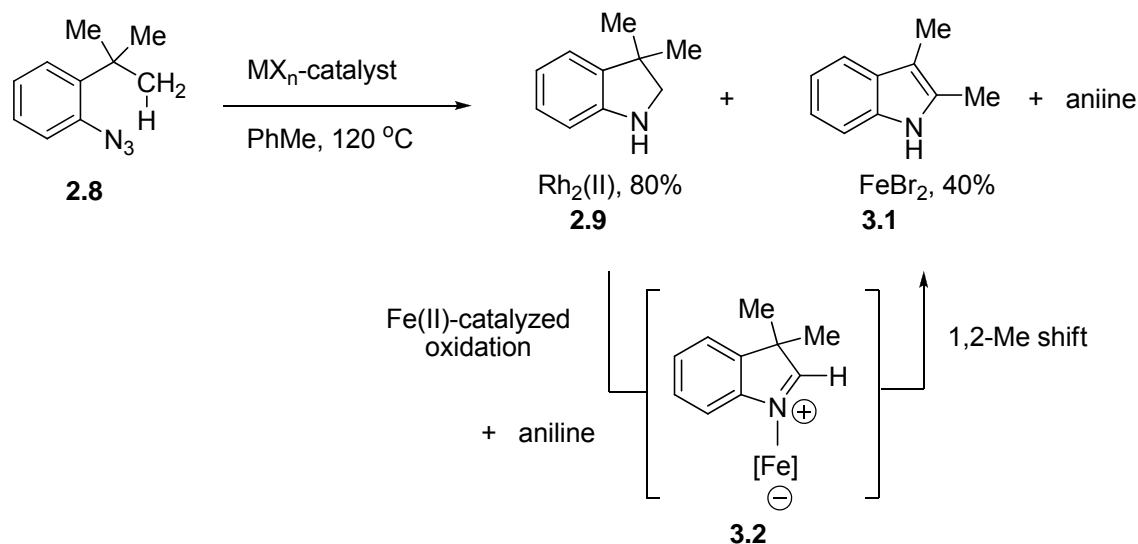
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Chapter 3. Iron(II) Bromide-Catalyzed Intramolecular C–H Bond Amination [1,2]-Shift Tandem Reactions of Aryl Azides.

3.1 Introduction

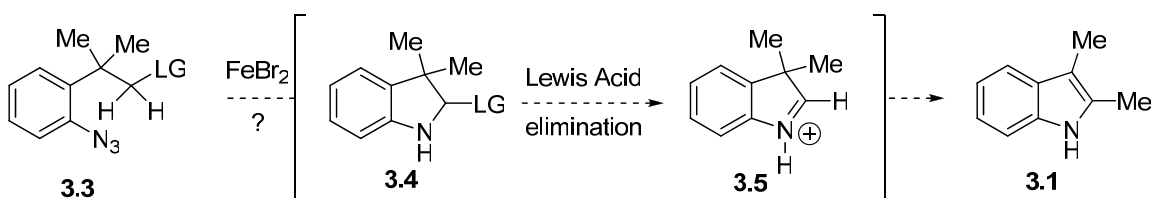
In chapter 2, the reactivity of Rh(II)-carboxylate salts in catalyzing the aliphatic C–H bond amination reaction has been discussed. During our optimization study when various transition-metal complexes were tested toward the formation of indoline from *tert*-butyl aryl azide, we unexpectedly observed the presence of aniline and indole **3.1** instead of indoline **2.9** in the reaction mixture when FeBr₂ was used (Scheme 3.1). To account for the formation of these products, we hypothesized that Fe-catalyst mediated oxidation reaction of the indoline **2.9** produced from C–H bond amination process¹ and aryl azide **2.8** acts as oxidant to generate aniline and iminium ion **3.2**² followed by [1,2]-methyl shift to form indole **3.1**. If the formation of indole **3.1** can be optimized, this methodology would provide the efficient synthetic way to prepare N-heterocyclic compounds by rapidly increasing the molecular complexity of simple substrate through the incorporation of transition-metal-catalyzed C–H bond amination and migratorial process into one cascade sequence, ideally utilizing inexpensive, nontoxic first-row transition-metal salt.

Scheme 3.1. Observation of a Fe(II)-Promoted Tandem Reaction.



To minimize the formation of aniline and increase the yield of indole **3.1**, our strategy was to replace one of the β -H atoms in **2.8** by a leaving group to change the mechanism of iminium ion formation from oxidation process which requires azide as an oxidant into elimination process (Scheme 3.2). The order of cascade reaction toward formation of indole **3.1**, therefore, would start with transition-metal-catalyzed ethereal C–H bond amination reaction of **3.3**³, followed by Lewis acid-catalyzed elimination of indoline **3.4**, and then desired 1,2-migratorial process of iminium ion **3.5**.

Scheme 3.2. Our Strategy on Optimizing Indole Formation.

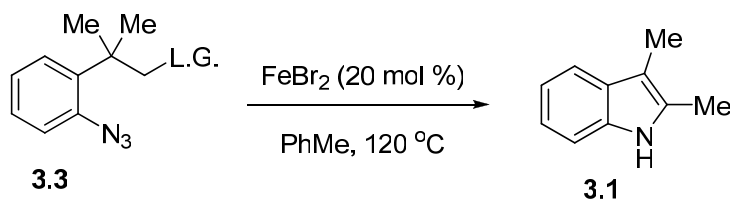
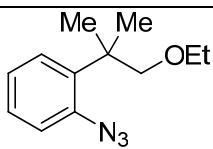
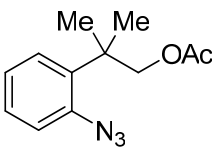


3.2 Optimization experiments

3.2.1 Optimization of substrates

In the course of searching for the good leaving group to promote elimination process, ethoxyl and acetate substrates were explored under FeBr_2 (Table 3.1)³⁻⁵. When the decomposition of acetate substrate mainly led to formation of aniline (entry 2), the promising result was obtained when ethoxyl was leaving group with 75% isolated yield. Aryl azide **3.6**, therefore, was chosen to be the optimal substrate for further study.

Table 3.1. Survey of Substrates.

		
entry	Substrate	10a yield, % ^a
1	 3.6	75
2	 3.7	10

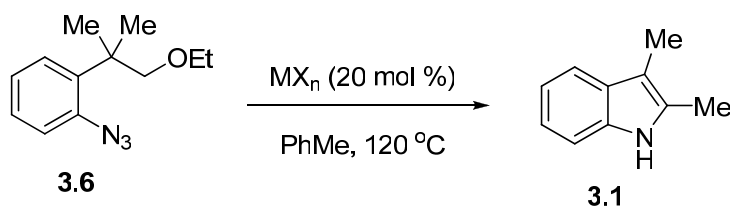
^aAs determined using ^1H NMR spectroscopy.

3.2.2 Optimization of transition-metal catalysts

In the next step of optimization study, the reactivity of a range of commercial transition-

metal complexes was investigated to determine if there is any catalyst more efficient than FeBr₂ for our tandem reaction. From our observation, no better result was found even though Rh₂(II)⁶, Ir(I)⁷, Co(I)⁸, Ru(III)⁹ or Cu(I)¹⁰ were known for their ability to catalyze N-atom transfer reactions from aryl azides (entry 3-7). Iron chloride which was reported to enable the nitrene formation does not proceed our cascade reaction, could be explained by its inappropriate Lewis acidity (entry 8). FeBr₂ also showed to be unique when attenuation of indole formation was observed with the alternative oxidation state of Fe in FeBr₃ salts (entry 9).¹¹ In the limit of our research, these results proved the ability of FeBr₂ to be the best catalyst for our tandem reaction including C–H bond amination, elimination and 1,2-shift.

Table 3.2. Development of Optimal catalysts.



entry	metal salt	yield, % ^a
1	none	0
2	FeBr ₂	75
3	CuI	0
4	CoTPP	0
5	RuCl ₃ · <i>n</i> H ₂ O	0
6	Rh ₂ (esp) ₂	0
7	ZnI ₂	0
8	FeCl ₂	0
9	FeBr ₃	20

^aAs determined using ¹H NMR spectroscopy.

3.2.3 Optimization of temperature and catalyst loading

Our optimization experiments continued with the examination on temperature and different loading of FeBr₂ to improve isolated yield. We observed the severe attenuation of indole formation when temperature was dropped to 100 °C or catalyst loading was reduced to 10 mol %. When reaction mixture was heated up to 140 °C, we achieved 85% isolated yield of indole **3.1**. The final optimal condition was chosen to be 20 mol % FeBr₂ in toluene at 140 °C.

Table 3.3. Optimization of Temperature and Catalyst Loading.

CC(C)(OCC)c1ccccc1[N+]=[N-]
 $\xrightarrow[\text{PhMe, 16h, T}]{\text{FeBr}_2 \text{ (xx mol \%)}}$
CC1=C(C)c2ccccc2N1

3.6 **3.1**

entry	Catalyst loading (mol %)	T (°C)	yield, % ^a
1	20	100	37
2	20	120	75
3	20	140	85
4	10	140	16

^aIsolated after silica gel chromatography.

3.3 Scope and limitation of indole formation

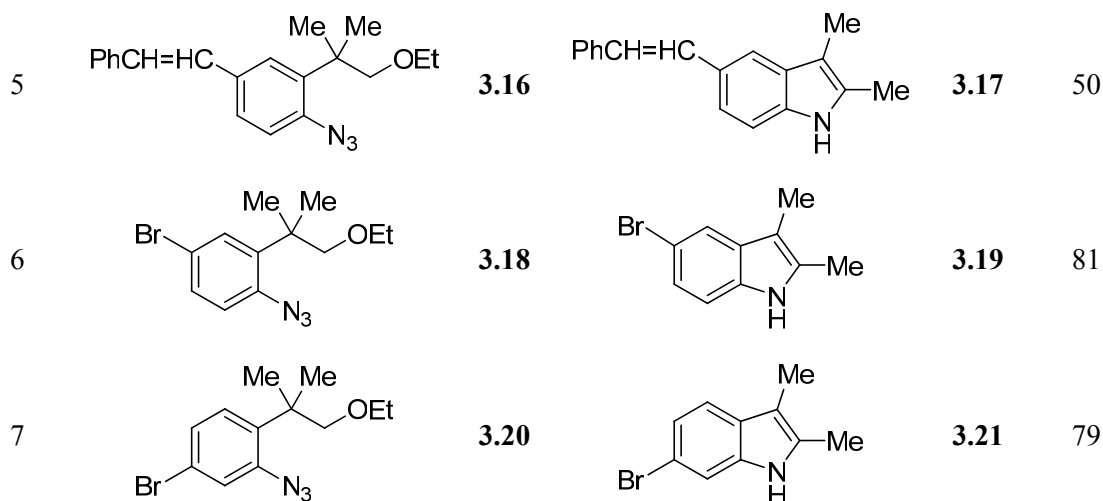
3.3.1 Investigation of Electronic Nature of Azide Arenes

The electronic constraints of this tandem C–H bond amination-elimination-migration reaction was examined by exploring substituted azide arenes under the above optimal condition. The scope of our reaction was found to be quite broad when both electron-releasing and electron-withdrawing aryl azides gave the good to excellent isolated yield. With a diminished

yield, the desired indole was obtained in the example of styryl azide **3.16** even though the olefin was known for their reactivity with iron nitrene (entry 5).^{1c} In addition, the preparation of 6-substituted indole **3.21** in this process provided an efficient method to access various valuable compounds that cannot be synthesized regioselectively through Fisher-indole reaction (entry 7).¹² The steric factor does not have significant effect on the reaction when the substituted on para or meta position to azide group gave the similar results (entry 6, 7).

Table 3.4. Scope and limitation of indole formation.

Entry	aryl azide	##	indoline	##	yield, % ^a
1		3.6		3.1	85
2		3.10		3.11	70
3		3.12		3.13	98
4		3.14		3.15	85



^a Isolated after silica gel chromatography.

3.3.2 Examination of Migrating group Identity

We further examined the scope of this tandem C–H bond amination 1,2 migration reaction by varying the identity of migrating group. Not only 1,2-methyl shift but also ethyl migration were observed with good isolated yield (entry 1). Ring expansion products were obtained with cyclobutyl, –pentyl and –hexyl aryl azides with moderate to good yields with the increasing yields from four to six member ring (entry 2, 3, 4). Even higher energy was released from ring strain, the cyclobutyl-substituted aryl azide gave lower yield than cyclopentyl and cyclohexyl-substituted azide, presumably due to the smaller C – C bond angle and further distance between C – H bond and azide group which would raise difficulties for C – H amination reaction.

When two migration components were presented in starting material azide, the high selectivity was observed (entry 5-11). In the example of azide **3.33**, under our reaction condition, aryl group migration occurred exclusively over methyl group, leading to the formation of 2-aryl-3-methylindoles which we assumed that it proceed through the phenonium ion. However, the

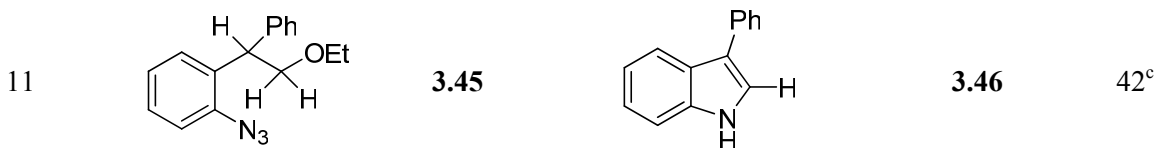
electronic nature of the aryl group plays an important role in this migration process when the presence of electron-poor substituent group stopped the reaction. The high selectivity was observed between sp^2 and sp^3 carbons, and between different sp^3 -substituted migrating groups (entry 8, 9). To our surprise, we observed ethyl group migration dominated in the example of **3.39**, afforded 2-ethyl-3-methylindole as the only product. This observation seems to be a trend when submission of azide **3.41** having both isopropyl and ethyl groups to reaction condition led to the formation of the only product indole **3.42**.

Examining the aryl and alkyl migration of azide **3.43** and **3.45** bearing an α -H atom, we found that only 3-substituted indoles were obtained with diminished yield, presumably these groups did not migrate when α -H atom is presented (entry 10, 11).¹³ By comparing migration aptitude of different groups in various starting azides, we established the scale of our reaction to be $\text{Me} < 1^\circ < 2^\circ < \text{Ph}$.

Table 3.5. Examination of identity of the *ortho*-alkyl substituents.

entry	aryl azide	##	indoline	##	yield, % ^a
1		3.25		3.26	83
2		3.27		3.28	65 ^b

3		3.29		3.30	69
4		3.31		3.32	78
5		3.33		3.34	95
6		3.35		3.36	58
7		3.37		3.38	Dec
8		3.39		3.40	83
9		3.41		3.42	60 ^b
10		3.43		3.44	50

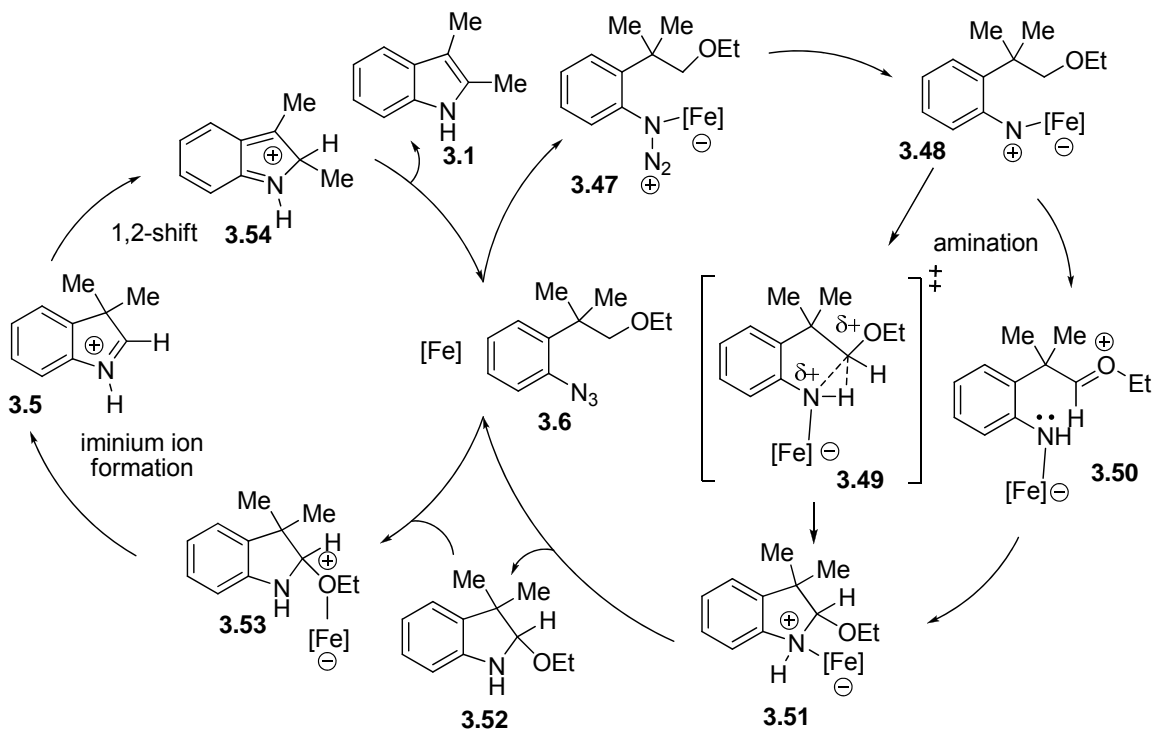


^aIsolated after silica gel chromatography. ^bAniline obtained as byproduct. ^c Determined using ¹H-NMR spectroscopy with CH₂Br₂ as internal standard.

3.4 Mechanism Study

When a number of mechanisms can account for the formation of indole **3.1**,¹⁴ our result reveals that the function of FeBr₂ in this tandem reaction is both an N-atom transfer catalyst and Lewis acid in two catalytic cycles in proposed mechanism (Scheme 3.3). The first catalytic cycle starts with the coordination of Fe(II) catalyst to nitrogen atom of azide to form **3.47**,¹⁵ followed by the extrusion of N₂ gas to produce the nitrene intermediate **3.51**. Two mechanistic pathways are possible to account for the C–H amination process: C–N bond formation could be concerted insertion of ethereal C–H bond to nitrene via transition state **3.49**; or stepwise through an H-atom abstraction-radical combination reaction which leads to oxocarbenium ion **3.50** that is attached by the proximal amine later.¹⁶ When indoline **3.52** is generated, iron salt acts as the Lewis acid to coordinate with ethyl ether group, cleave this leaving group and form iminium ion **3.5** then trigger the 1,2-shift in the second catalytic cycle.¹⁷ In the last step, subsequent deprotonation of **3.54** by iron ethoxide affords the indole product.

Scheme 3.3. Possible Mechanism for our Tandem Reaction.



3.4.1 Isolation of intermediates

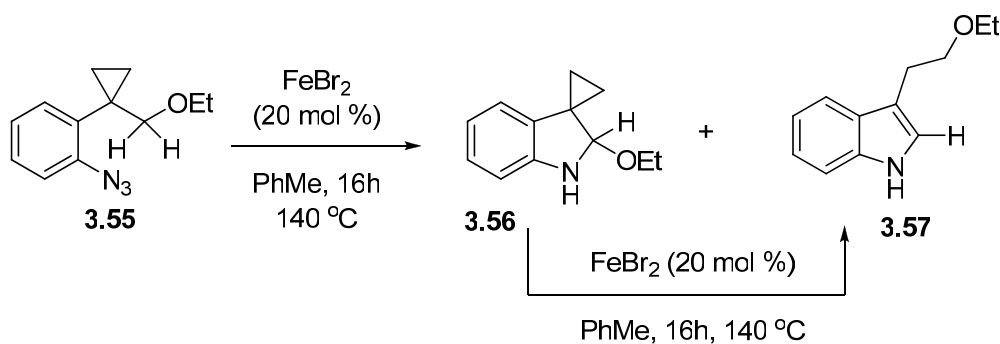
In our optimization study, two potential intermediates were isolated, whose reactivity toward reaction conditions provided the evidences to support our proposed mechanism.

3.4.1.1 Cyclopropyl Substrate Experiment

The cyclopropyl-substituted aryl azide **3.55** was prepared and submitted to reaction condition. In the reaction mixture after 16 hours, indoline **3.56** and indole **3.57** were observed and isolated. The isolation of indoline **3.56** consists with our mechanistic hypothesis that the formation of C–N bond occurs through an ethereal C–H bond amination. The nature of amination reaction is considered to be stepwise through hydride transfer since no fragmentation of cyclopropane was observed.^{14e,h,18} To gain more information about the function of FeBr₂, **3.56**

intermediate was resubmitted to reaction condition, and indole **3.57** was obtained. On the other hand, without FeBr₂, indoline **3.56** remained after thermolysis reaction.

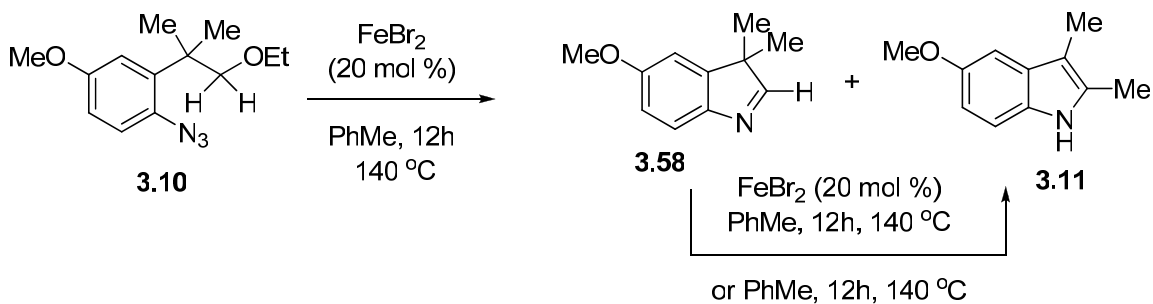
Scheme 3.4. The Isolation of Indoline Intermediate.



3.4.1.2 Methoxyl Substrate Experiment

The other isolated potential intermediate was 3-H indole **3.58** after the methoxyl-substituted **3.10** was explored under reaction condition for 12 hours. The isolation of indole **3.58** suggests that the 1,2-methyl shift occurs after elimination of the ethoxyl group, and iminium ion is probably generated as intermediate in the mechanism of our tandem reaction. In addition, the formation of 2,3-dimethylindole through thermolysis of **3.58** independent from the presence of FeBr₂ indicates that catalyst is not required for migration process. The iron salt, therefore, is considered to be essential for both C–H amination and elimination steps, but not for 1,2-alkyl migration.

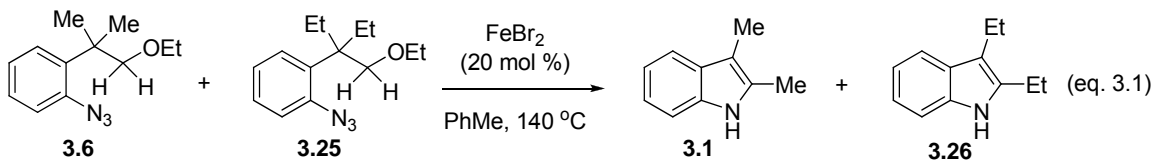
Scheme 3.5. The Isolation of 3-H Indole Intermediate.



3.4.2 Double Crossover Experiment

To probe the 1,2-shift reaction mechanism, dimethyl and diethyl substrates were prepared and submitted to the double cross-over experiment (Scheme 3.6). If the mechanism is stepwise and double cross-over happens, we would expect to observe the formation of more than 2 indoles when the ethyl carbocation can combine with either 3-methyl indoline intermediate or 3-ethyl indoline intermediate. On the other hand, the concerted pathway would generate only two corresponding products from two azide reactants. From what we noted, only two indoles were formed in the ratio 1:1 of **3.1** and **3.26** when no exchange was observed between two azides indicated the similar reactivity of methyl and ethyl substrates. The mechanism of 1,2-shift could be concerted, or if it occurred through stepwise way, the rate of shift and recombination would be significant faster than the rate of diffusion of migrating group.

Scheme 3.6. The Double Crossover Experiment.



3.5 Conclusion

In conclusion, iron (II) bromide catalyzed tandem ethereal C–H bond amination 1,2-migration reactions using *ortho*-substituted aryl azides as N-atom source to synthesize 2,3-disubstituted indoles has been discovered. In our report, the selectivity of migrating group in 1,2-shift is remarkable, and we were able to establish the migration aptitude to be Me < 1° < 2° < Ph. The information from isolated intermediates in the mechanistic experiments suggested that the C–H bond amination reaction occurred through concerted pathway, followed by elimination of leaving group to generate iminium ion and trigger the 1,2-shift; and FeBr₂ is necessary catalyst and Lewis acid for both amination and iminium ion formation, but not for 1,2-shift. Our future research aims to gain better understanding on the nature of our tandem reaction and further develop the synthetic method for preparation of complex, functionalized N-heterocycles utilized iron-catalyzed C–H bond amination reactions.

3.6 Experiments

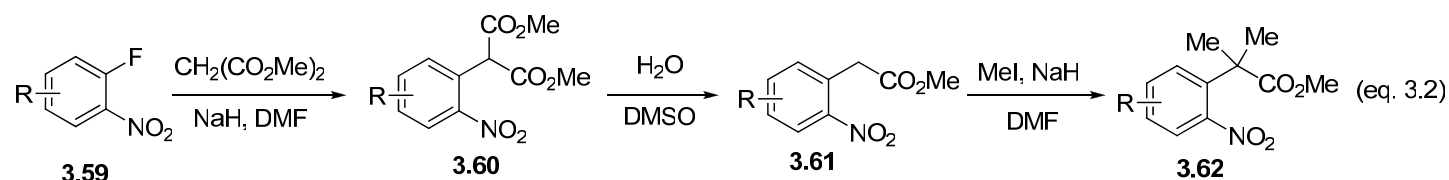
General. The general experiments were performed as described in Jana et al. *J. Org. Chem.* **2014**, 79, 2781. ¹H NMR and ¹³C NMR spectra were recorded at ambient temperature using 500 MHz or 300 MHz spectrometers. The data are reported as follows: chemical shift in ppm from internal tetramethylsilane 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 (SiO₂). 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 (SiO₂). 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, Et₂O, and CH₂Cl₂ were dried by filtration through alumina according to the procedure of Grubbs.¹⁹ Metal salts were stored in a nitrogen atmosphere dry box.

3.6.1. Preparation of Substituted Methyl 2-Methyl-2-(2-Nitroaryl)propanoate

3.6.1.1 Route to Substrates.

Substituted *ortho*-(1-ethoxy-2-methylpropan-2-yl)-aryl azides were synthesized using the route outlined in equation 3.2. Yields were not optimized.

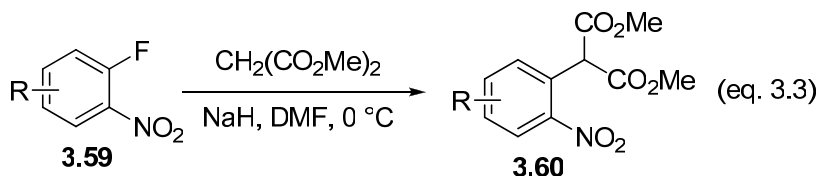


Dimethyl 2-(nitroaryl)malonate esters **3.60** were prepared from corresponding *ortho*-fluoro nitroarenes through a nucleophilic substitution reaction, followed by hydrolysis in DMSO to generate methyl 2-nitroaryl acetate **3.61**. Methylation reaction with methyl iodide afforded substituted methyl 2-methyl-2-(2-nitroaryl)propanoate **3.62**.

3.6.1.2 Synthesis of Arylmalonate Esters.

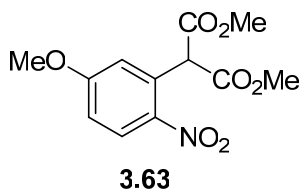
General Procedure.

The arylmalonate esters were prepared in one-step from commercially available *ortho*-fluoronitrobenzenes and dimethyl malonate in DMF using NaH as base as in the equation 3.3. Yields were not optimized.



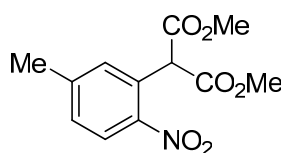
To a cooled solution (0 °C) of *ortho*-fluoronitrobenzene (50.00 mmol) and 6.30 mL of dimethyl malonate (55.00 mmol, 1.1 equiv) in 60 mL of DMF was slowly added 2.6 g of NaH (65 mmol, 1.3 equiv). The resultant mixture then was stirring at room temperature. After 4 hours, the mixture was diluted with water and the resulting aqueous phase was extracted with an additional 3 × 30.0 mL of diethyl ether. The combined organic phases were washed with 30.0 mL of brine. The resulting organic phase was dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification using MPLC afforded the product.

Synthesis



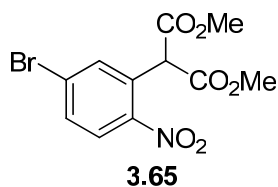
Dimethyl 2-(5-methoxy-2-nitrophenyl)malonate 3.63.²⁰ The general procedure was followed using 8.55 g of 2-fluoro-4-methoxy-1-nitrobenzene (50.00 mmol), 6.30 mL of dimethyl

malonate (55.00 mmol) and 2.6 g of NaH. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a yellow solid (6.08 g, 43%). Malonate **3.63** was previously reported Knölker and co-workers.² ¹H NMR (500 MHz, CDCl₃) δ 8.12 (d, *J* = 9.0 Hz, 1H), 6.92 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.89 (d, *J* = 3.0 Hz, 1H), 5.40 (s, 1H), 3.85 (s, 3H), 3.76 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 167.7 (C), 163.5 (C), 141.5 (C), 130.7 (C), 128.2 (CH), 117.0 (CH), 113.4 (CH), 56.0 (CH₃), 54.6 (CH), 53.1 (CH₃). ATR-FTIR (thin film): 2954, 2846, 1733, 1613, 1581, 1514, 1435, 1337, 1296, 1246, 1150, 1084, 1021, 854, 745 cm⁻¹.

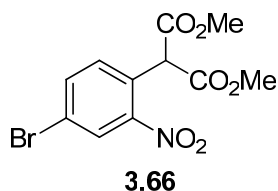


3.64

Dimethyl 2-(5-methyl-2-nitrophenyl)malonate 3.64. The general procedure was followed using 7.75 g of 2-fluoro-4-methyl-1-nitrobenzene (50.00 mmol), 6.30 mL of dimethyl malonate (55.00 mmol) and 2.6 g of NaH. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a yellow solid (4.67 g, 35%). Malonate **3.64** was previously reported by Atkinson and co-workers:³ ¹H NMR (500 MHz, CDCl₃) δ 7.94 (d, *J* = 8.0 Hz, 1H), 7.26 (d, *J* = 7.5 Hz, 1H), 7.21 (s, 1H), 5.29 (s, 1H), 3.75 (s, 6H), 2.40 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 167.8 (C), 146.4 (C), 145.1 (C), 131.8 (CH), 129.9 (CH), 127.9 (C), 125.5 (CH), 54.3 (CH), 53.1 (CH₃), 21.5 (CH₃). ATR-FTIR (thin film): 2955, 1737, 1611, 1591, 1519, 1435, 1343, 1306, 1245, 1151, 1031, 908, 735 cm⁻¹.



Dimethyl 2-(5-bromo-2-nitrophenyl)malonate 3.65. The general procedure was followed using 11.0 g of 4-bromo-2-fluoro-1-nitrobenzene (50.00 mmol), 6.30 mL of dimethyl malonate (55.00 mmol) and 2.6 g of NaH. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a yellow solid (8.28 g, 50%). ^1H NMR (500 MHz, CDCl_3) δ 7.93 (d, J = 9.5 Hz, 1H), 7.65 – 7.64 (m, 2H), 5.29 (s, 1H), 3.80 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.1 (C), 147.5 (C), 134.5 (CH), 132.6 (CH), 129.7 (C), 128.6 (C), 126.7 (CH), 53.8 (CH), 53.4 (CH_3). ATR-FTIR (thin film): 3009, 2957, 1733, 1530, 1437, 1339, 1274, 1201, 1147, 1023, 849, 685 cm^{-1} .



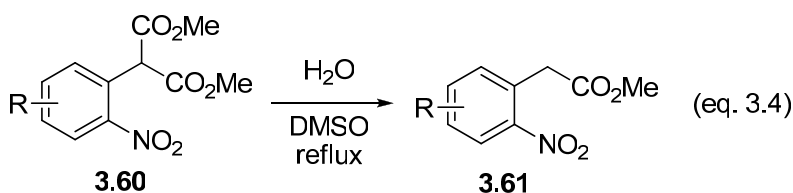
Dimethyl 2-(4-bromo-2-nitrophenyl)malonate 3.66.²¹ The general procedure was followed using 11.0 g of 4-bromo-1-fluoro-2-nitrobenzene (50.00 mmol), 6.30 mL of dimethyl malonate (55.00 mmol) and 2.6 g of NaH. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a yellow solid (8.61 g, 52%). Malonate **3.66** was previously reported by Quallich and Morrissey.⁴ ^1H NMR (500 MHz, CDCl_3) δ 8.16 (d, J = 2.0 Hz, 1H), 7.74 (dd, J = 8.5, 1.5 Hz, 1H), 7.39 (d, J = 8.5 Hz, 1H), 5.25 (s, 1H), 3.77 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 167.2 (C), 149.1 (C), 136.6 (CH), 132.9 (CH), 128.2 (CH), 126.9

(C), 122.7 (C), 53.6 (CH), 53.3 (CH₃). ATR-FTIR (thin film): 2955, 1735, 1532, 1435, 1346, 1225, 1150, 1097, 1016, 876, 740 cm⁻¹.

3.6.1.3 Synthesis of Methyl 2-Nitroaryl Acetate.

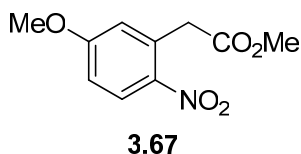
General Procedure.

The methyl 2-nitroaryl acetates were prepared in one-step from malonate esters through hydrolysis and decarboxylation sequence as described in equation 3.4. Yields were not optimized.



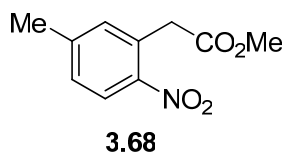
To the solution of 30.0 mmol of malonate ester in 20.0 mL of DMSO was added 1.08 mL of H₂O (2 equiv). The resulting mixture was heated to reflux (163 °C). After 3 hours, the reaction mixture was cooled to room temperature and diluted with water. The resulting mixture was extracted with 3 × 20 mL of methylene chloride. The combined organic phases were dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification using MPLC afforded the product.

Synthesis

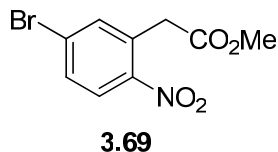


Methyl 2-(5-methyl-2-nitrophenyl)acetate 3.67.²² The general procedure was followed

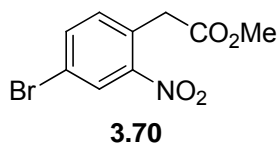
using 8.49 g of ester **3.63** (3.0 mmol), 20.0 mL of DMSO and 1.08 mL of H₂O. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a yellow solid (5.94 g, 88%). The spectral data of **3.67** matched that reported by Palmisano and co-workers.⁵ ¹H NMR (500 MHz, CDCl₃) δ 8.17 (d, *J* = 9.5 Hz, 1H), 6.90 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.78 (d, *J* = 3.0, 1H), 3.99 (s, 2H), 3.88 (s, 3H), 3.70 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.4 (C), 163.5 (C), 141.6 (C), 132.7 (C), 128.1 (CH), 118.6 (CH), 113.0 (CH), 55.9 (CH₃), 52.2 (CH₃), 40.4 (CH₂). ATR-FTIR (thin film): 2951, 2846, 1736, 1609, 1581, 1509, 1434, 1333, 1292, 1258, 1206, 1160, 1003, 837, 749 cm⁻¹.



Methyl 2-(5-methyl-2-nitrophenyl)acetate 3.68.²³ The general procedure was followed using 8.01 g of ester **3.64** (30.0 mmol), 20.0 mL of DMSO and 1.08 mL of H₂O. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a yellow solid (4.70 g, 75%). ¹H NMR (500 MHz, CDCl₃) δ 8.00 (d, *J* = 8.0 Hz, 1H), 7.23 (d, *J* = 8.5 Hz, 1H), 7.17 (s, 1H), 3.96 (s, 2H), 3.68 (s, 3H), 2.40 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 170.5 (C), 146.3 (C), 145.0 (C), 134.0 (CH), 129.8 (C), 129.1 (CH), 125.3 (CH), 52.0 (CH₃), 39.6 (CH₂), 21.2 (CH₃). ATR-FTIR (thin film): 2955, 1738, 1613, 1592, 1518, 1342, 1246, 1203, 906, 837, 725 cm⁻¹.



Methyl 2-(5-bromo-2-nitrophenyl)acetate 3.69.²⁴ The general procedure was followed using 9.90 g of ester **3.65** (30.0 mmol), 20.0 mL of DMSO and 1.08 mL of H₂O. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a yellow solid (5.73 g, 70%). Acetate **3.69** was previously reported by Madar and co-workers.⁷ ¹H NMR (500 MHz, CDCl₃) δ 7.91 (d, *J* = 8.5 Hz, 1H), 7.54 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.48 (d, *J* = 2.0 Hz, 1H), 3.94 (s, 2H), 3.65 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 169.8 (C), 147.6 (C), 136.2 (CH), 131.8 (CH), 131.7 (C), 128.3 (C), 126.7 (CH), 52.4 (CH₂), 39.2 (CH₃). ATR-FTIR (thin film): 2955, 2849, 1734, 1604, 1565, 1522, 1436, 1339, 1213, 1167, 1099, 884, 833 cm⁻¹.



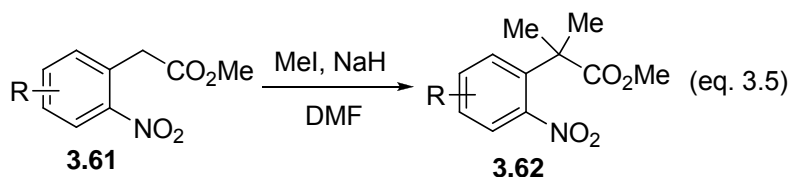
Methyl 2-(4-bromo-2-nitrophenyl)acetate 3.70.²² The general procedure was followed using 9.90 g of ester **3.66** (30.0 mmol), 20.0 mL of DMSO and 1.08 mL of H₂O. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a yellow solid (5.98 g, 73%). Acetate **3.70** was previously reported by Quallich and Morrissey.⁴ ¹H NMR (500MHz, CDCl₃) δ 8.14 (d, *J* = 1.5 Hz, 1H), 7.65 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.20 (d, *J* = 8.0 Hz, 1H), 3.93 (s, 2H), 3.64 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 169.9 (C), 149.1 (C), 136.5 (CH), 134.7 (CH), 128.8 (C), 128.1 (CH), 121.6 (C), 52.3 (CH₂), 39.0 (CH₃). ATR-FTIR (thin film): 2953, 1736,

1526, 1435, 1344, 1246, 1215, 1167, 1095, 999, 879, 812 cm⁻¹.

3.6.1.4 Synthesis of Methyl 2-Methyl-2-(2-Nitroaryl)propanoate

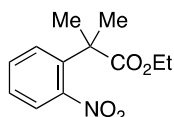
General Procedure.

Following the procedure reported by Glorius and co-workers,²⁵ dimethyl substituted ester **3.62** was prepared as described in the equation 3.5. Yields were not optimized.

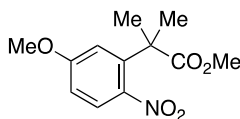


To a solution of (2-nitro-aryl)-acetic acid methyl ester (10.0 mmol) and 2 mL of MeI (22.0 mmol) in 20 mL of DMF at 0 °C was added small amounts of NaH (60% in mineral oil) until the mixture turn blue. The rest NaH (total 1.20 g, 30.0 mmol) was added gradually during 30 minutes while the temperature was kept at 0 °C. Then the reaction was warmed to room temperature. After 6 hours, the mixture was diluted with 60 mL of H₂O and extracted with 4 × 30 mL of Et₂O. The combined organic phases were dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded ester **3.62**.

Synthesis.



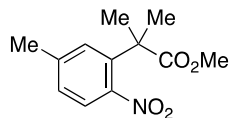
2-Methyl-2-(2-nitrophenyl)propanoic acid ethyl ester 3.71.²⁶ The general procedure was followed using 2.09 g of ester ethyl 2-(2-nitrophenyl)acetate (10.0 mmol), 2.0 mL of MeI (22.0 mmol), 20.0 mL of DMF, and 1.20 g of NaH. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow oil (1.9 g, 80%). The spectral data of **3.71** matched that reported by Driver and co-workers:⁹ ¹H NMR (500 MHz, CDCl₃) δ 7.83 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 3.0 Hz, 2H), 7.37 – 7.34 (m, 1H), 4.05 (q, *J* = 7.0 Hz, 2H), 1.62 (s, 6H), 1.12 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 175.1 (C), 148.7 (C), 139.4 (C), 133.2 (CH), 128.1 (CH), 127.7 (CH), 125.5 (CH), 61.0 (CH₂), 46.4 (C), 27.5 (CH₃), 13.9 (CH₃); ATR-FTIR (thin film): 2985, 1722, 1526, 1351, 1227, 1111, 911, 729 cm⁻¹.



3.72

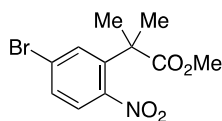
Methyl 2-(5-methoxy-2-nitrophenyl)-2-methylpropanoate 3.72.²⁷ The general procedure was followed using 2.25 g of ester **3.67** (10.0 mmol), 2 mL of MeI (22.0 mmol), 20.0 mL of DMF, and 1.20 g of NaH. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow oil (1.77 g, 70%). Acetate **3.72** was reported by Hanna, Noland and co-workers.¹⁰ ¹H NMR (500 MHz, CDCl₃) δ 7.99 (d, *J* = 9.0 Hz, 1H), 7.00 (d, *J* = 2.5 Hz, 1H), 6.80 (dd, *J* = 9.0, 2.5 Hz, 1H), 3.84 (s, 3H), 3.55 (s, 3H), 1.57 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 175.6 (C), 163.4 (C), 142.4 (C), 141.4 (C), 128.7 (CH), 114.9 (CH), 110.8 (CH), 55.9 (CH₃), 51.9 (CH₃), 46.6 (C), 27.2 (CH₃); ATR-FTIR (thin film): 2985, 2949, 1738, 1673, 1677,

1514, 1342, 1249, 1146, 1061, 924, 757 cm^{-1} .



3.73

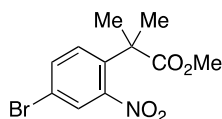
Methyl 2-methyl-2-(5-methyl-2-nitrophenyl)propanoate 3.73. The general procedure was followed using 2.09 g of ester **3.68** (10.0 mmol), 2 mL of MeI (22.0 mmol), 20.0 mL of DMF, and 1.20 g of NaH. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow oil (1.99 g, 84%). ^1H NMR (500 MHz, CDCl_3) δ 7.81 (d, $J = 8.0$ Hz, 1H), 7.35 (s, 1H), 7.16 (s, 1H), 3.60 (s, 3H), 2.42 (s, 3H), 1.62 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.8 (C), 146.4 (C), 144.4 (C), 139.3 (C), 128.7 (CH), 128.2 (CH), 125.8 (CH), 59.1 (CH₃), 46.3 (C), 27.4 (CH₃), 21.7 (CH₃); ATR-FTIR (thin film): 2985, 2948, 1732, 1586, 1519, 1349, 1147, 907, 726 cm^{-1} .



3.74

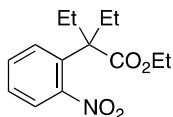
Methyl 2-(5-bromo-2-nitrophenyl)-2-methylpropanoate 3.74. The general procedure was followed using 2.73 g of ester **3.69** (10.0 mmol), 2 mL of MeI (22.0 mmol), 20.0 mL of DMF, and 1.20 g of NaH. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow oil (2.80 g, 93%). ^1H NMR (500 MHz, CDCl_3) δ 7.80 (d, $J = 8.5$ Hz,

1H), 7.70 (d, $J = 2.0$ Hz, 1H), 7.55 (dd, $J = 8.5, 2.0$ Hz, 1H), 3.64 (s, 3H), 1.65 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.1 (C), 147.6 (C), 141.4 (C), 131.4 (C), 130.9 (CH), 128.1 (CH), 127.2 (CH), 52.2 (CH_3), 46.5 (C), 27.3 (CH_3); ATR-FTIR (thin film): 2982, 2950, 1729, 1560, 1523, 1351, 1221, 1144, 987, 886 cm^{-1} .



3.75

Methyl 2-(4-bromo-2-nitrophenyl)-2-methylpropanoate 3.75.²⁸ The general procedure was followed using 2.73 g of ester **3.70** (10.0 mmol), 2 mL of MeI (22.0 mmol), 20.0 mL of DMF, and 1.20 g of NaH. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow oil (2.59 g, 86%). Ester **3.75** was reported by Ashimori and co-workers.¹⁰ ^1H NMR (500 MHz, CDCl_3) δ 7.94 (s, 1H), 7.66 (d, $J = 8.5$ Hz, 1H), 7.45 (d, $J = 8.5$ Hz, 1H), 3.57 (s, 3H), 1.59 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.2 (C), 149.2 (C), 138.3 (C), 136.1 (CH), 129.8 (CH), 128.3 (CH), 120.7 (C), 52.1 (CH_3), 46.3 (C), 27.3 (CH_3); ATR-FTIR (thin film): 2996, 2948, 1739, 1529, 1354, 1244, 1145, 1060, 875, 756 cm^{-1} .



3.76

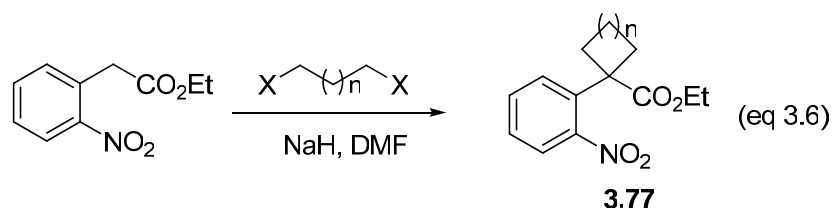
Ethyl 2-ethyl-2-(2-nitrophenyl)butanoate 3.76. The general procedure was followed

using 2.09 g of ester ethyl 2-(2-nitrophenyl)acetate (10.0 mmol), 1.78 mL of EtI (22.0 mmol), and 20.0 mL of DMF, 1.20 g of NaH. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow oil (1.86 g, 70%). ^1H NMR (500 MHz, CDCl_3) δ 7.78 (dd, $J = 7.0, 1.0$ Hz, 1H), 7.53 (dt, $J = 8.0, 1.5$ Hz, 1H), 7.42 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.35 (dt, $J = 8.5, 1.5$ Hz, 1H), 4.05 (q, $J = 7.0$ Hz, 2H), 2.12 (q, $J = 7.5$ Hz, 4H), 1.13 (t, $J = 7.0$ Hz, 3H), 0.71 (t, $J = 7.5$ Hz, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 173.6 (C), 150.2 (C), 135.5 (C), 131.9 (CH), 129.9 (CH), 127.5 (CH), 125.6 (CH), 60.6 (CH_2), 54.0 (C), 28.5 (CH_2), 14.0 (CH_3), 8.8 (CH_3); ATR-FTIR (thin film): 2977, 2940, 2874, 1728, 1527, 1356, 1219, 851, 735 cm^{-1} .

3.6.2 Preparation of cycloalkyl 2-(2-nitrophenyl)ester

3.6.2.1 General Procedure

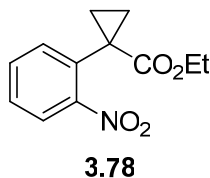
Cycloalkyl esters were prepared from ethyl 2-(2-nitrophenyl)acetate and dihaloalkane as in the equation 3.6. Yields were not optimized.



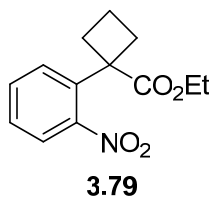
To a cooled solution (0 °C) of ethyl 2-(2-nitrophenyl)acetate (1 equiv) and dihalogenalkane (1.1 equiv) in DMF was slowly added NaH (4 equiv). The reaction then was warmed to room temperature. After 10 hours, the mixture was diluted with 30 mL of H_2O and extracted with 3×30 mL of Et_2O . The combined organic phases were dried over Na_2SO_4 ,

filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC afforded cycloalkyl ester **3.77**.

3.6.2.2 Synthesis

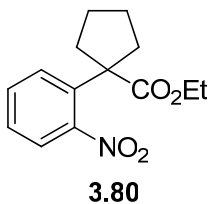


Ethyl 1-(2-nitrophenyl)cyclopropanecarboxylate 3.78. The general procedure was followed using 6.27 g of ethyl 2-(2-nitrophenyl)acetate (30.0 mmol), 2.84 mL of 1,2-dibromoethane (33.0 mmol), 60 mL of DMF and 4.80 g of NaH. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow oil (2.12 g, 30%). ¹H NMR (500 MHz, CDCl₃) δ 7.96 (d, *J* = 7.5 Hz, 1H), 7.56 (t, *J* = 7.5 Hz, 1H), 7.47 (d, *J* = 7.5 Hz, 1H), 7.42 (t, *J* = 7.5 Hz, 1H), 4.07 (q, *J* = 7.0 Hz, 2H), 1.70 (s, 2H), 1.14 (s, 2H), 1.10 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.8 (C), 150.3 (C), 134.9 (C), 133.1 (CH), 132.8 (CH), 128.4 (CH), 124.7 (CH), 61.3 (CH₂), 27.7 (C), 17.1 (CH₂), 14.0 (CH₃); ATR-FTIR (thin film): 2982, 1719, 1611, 1522, 1367, 1346, 1294, 1116, 1108, 851 cm⁻¹.



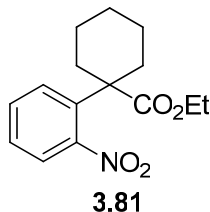
Ethyl 1-(2-nitrophenyl)cyclobutanecarboxylate 3.79. The general procedure was followed using 6.27 g of ethyl 2-(2-nitrophenyl)acetate (30.0 mmol), 3.79 mL of 1,3-

diiodopropane (33.0 mmol), 60 mL of DMF and 4.80 g of NaH. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow oil (3.14 g, 42%). ^1H NMR (500 MHz, CDCl_3) δ 7.86 (d, J = 8.0 Hz, 1H), 7.60 (t, J = 7.5 Hz, 1H), 7.46 (d, J = 8.0 Hz, 1H), 7.37 (t, J = 8.0 Hz, 1H), 4.16 (q, J = 7.0 Hz, 2H), 2.81 – 2.76 (m, 2H), 2.44 – 2.38 (m, 2H), 2.34 – 2.28 (m, 1H), 1.85 – 1.79 (m, 1H), 1.18 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.4 (C), 147.6 (C), 139.6 (C), 132.8 (CH), 130.0 (CH), 127.5 (CH), 124.6 (CH), 61.2 (CH_2), 51.2 (C), 31.8 (CH_2), 16.4 (CH_2), 14.1 (CH_3); ATR-FTIR (thin film): 2980, 2953, 1723, 1523, 1351, 1296, 1228, 1202, 1120, 852, 737 cm^{-1} .



Ethyl 1-(2-nitrophenyl)cyclopentanecarboxylate 3.80. The general procedure was followed using 6.27 g of ethyl 2-(2-nitrophenyl)acetate (30.0 mmol), 4.35 mL of 1,4-diiodobutane (33.0 mmol), 60 mL of DMF and 4.80 g of NaH. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow oil (7.10 g, 90%). ^1H NMR (500 MHz, CDCl_3) δ 7.76 (d, J = 8.0 Hz, 1H), 7.55 – 7.51 (m, 2H), 7.35 – 7.32 (m, 1H), 4.06 (q, J = 7.0 Hz, 2H), 2.49 (m, J = 6.0 Hz, 2H), 1.97 (m, J = 7.0 Hz, 2H), 1.86 – 1.82 (m, 2H), 1.70 – 1.64 (m, 2H), 1.11 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 175.1 (C), 149.0 (C), 139.1 (C), 132.7 (CH), 129.0 (CH), 127.5 (CH), 125.0 (CH), 61.0 (CH_2), 57.0 (C), 37.7 (CH_2), 25.1 (CH_2), 14.0 (CH_3); ATR-FTIR (thin film): 2959, 2874, 1726, 1525, 1354, 1298, 1159, 1094,

1026, 909, 851, 737 cm^{-1} .

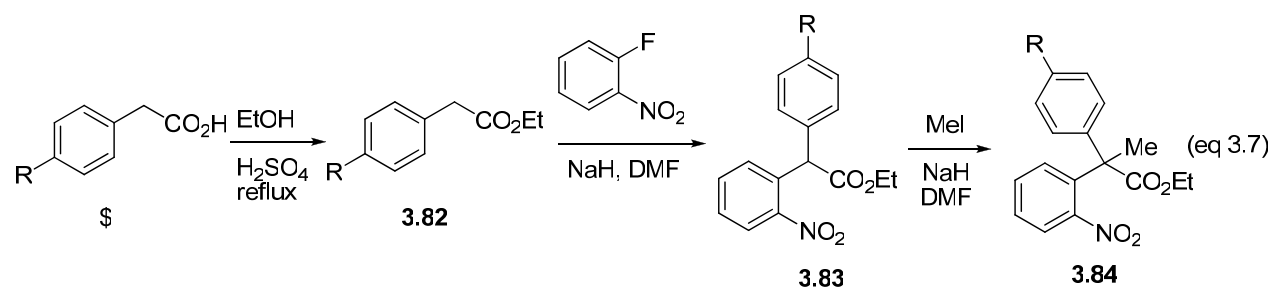


Ethyl 1-(2-nitrophenyl)cyclohexanecarboxylate 3.81. The general procedure was followed using 6.27 g of ethyl 2-(2-nitrophenyl)acetate (30.0 mmol), 4.91 mL of 1,5-diiodopentane (33.0 mmol), 60 mL of DMF and 4.80 g of NaH. Purification by MPLC (0:100 – 1:99 EtOAc:hexanes) afforded the product as a light yellow oil (3.99 g, 48%). ^1H NMR (500 MHz, CDCl_3) δ 7.66 – 7.63 (m, 2H), 7.55 (t, m, $J = 7.5$ Hz, 1H), 7.35 (t, $J = 7.5$ Hz, 1H), 4.11 (q, $J = 7.0$ Hz, 2H), 2.19 – 2.15 (m, 2H), 1.98 – 1.94 (m, 2H), 1.70 – 1.66 (m, 2H), 1.50 – 1.36 (m, 4H), 1.15 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 174.8 (C), 149.8 (C), 136.4 (C), 132.1 (CH), 130.2 (CH), 127.6 (CH), 125.2 (CH), 60.8 (CH_2), 49.9 (C), 33.9 (CH_2), 25.7 (CH_2), 22.4 (CH_2), 14.0 (CH_3); ATR-FTIR (thin film): 2933, 2862, 1729, 1525, 1452, 1358, 1302, 1215, 1129, 1024, 853, 732 cm^{-1} .

3.6.3 Preparation of Para-Substituted Ethyl 2-aryl-2-(2-nitrophenyl)propanoate

3.6.3.1 Route to Substrates.

Ethyl 2-(4-substituted phenyl)-2-(2-nitrophenyl)propanoate were synthesized using the route outlined in equation 3.7. Yields were not optimized.

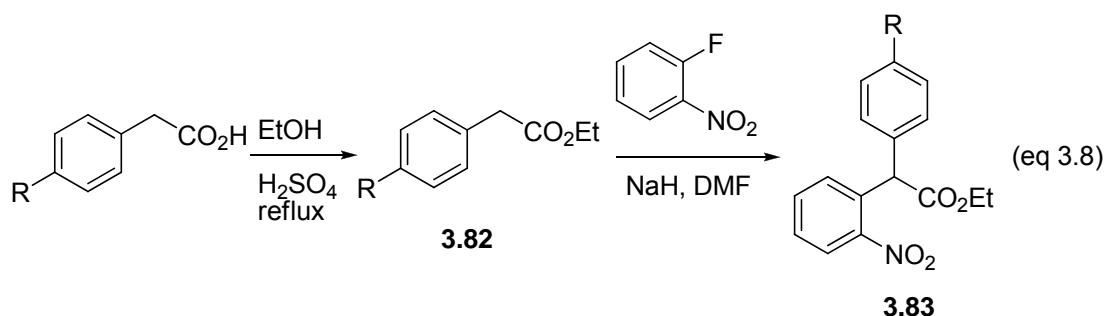


Para-substituted phenyl esters **3.82** were prepared from corresponding acid by esterification reaction, followed by nucleophilic aromatic substitution of 1-fluoro-2-nitrobenzene using NaH as base in DMF to generate ester **3.83**. Methylation of **3.83** afforded substituted propanoates **3.84**.

3.6.3.2 Synthesis of ethyl 2-(4-substitutedphenyl)-2-(2-nitrophenyl)acetate

General Procedure

The ethyl 2-(4-substituted phenyl)-2-(2-nitrophenyl)acetates were prepared through the esterification reaction of carboxylic acid followed by nucleophilic substitution reaction as the route outlined in equation 3.8. Yields were not optimized.

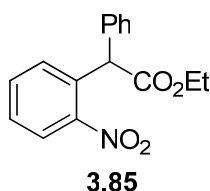


A mixture of carboxylic acid, concentrated sulfuric acid and ethanol was refluxed at 80 °C. After 3 hours, the mixture was cooled down to room temperature, diluted with H₂O and

extracted with 3×30 mL of CH_2Cl_2 . The combined organic phases were dried over Na_2SO_4 , filtered, and the filtrate was concentrated *in vacuo* to obtain the crude ester, which was subjected to the nucleophilic aromatic substitution reaction without further purification.

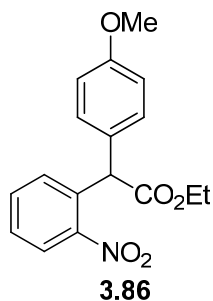
To a cooled solution ($0\text{ }^\circ\text{C}$) of acetate ester **3.82** (1 equiv), 1-fluoro-2-nitrobenzene (1 equiv) in DMF was slowly added NaH (1.1 equiv). The resulting solution was warmed to room temperature. After 12 hours, the reaction mixture was diluted with H_2O and extracted with 3×30 mL of diethyl ether. The combined organic phases were dried over Na_2SO_4 , filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC afforded ester **3.83**.

Synthesis

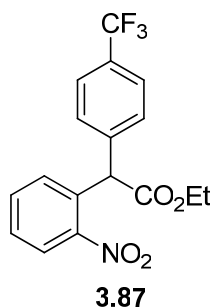


Ethyl 2-(2-nitrophenyl)-2-phenylacetate 3.85.²⁹ The general procedure was followed using 8.20 g of ethyl 2-phenylacetate (50.0 mmol), 5.27 mL of 1-fluoro-2-nitrobenzene, 80.0 mL of DMF, and 2.20 g of NaH. Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded the product as a yellow oil (5.70 g, 40%). The spectral data matched that reported by Noguchi and co-workers:¹² ^1H NMR (500 MHz, CDCl_3) δ 8.01 (d, $J = 7.0$ Hz, 1H), 7.48 (t, $J = 7.0$ Hz, 1H), 7.41 – 7.34 (m, 4H), 7.29 (d, $J = 7.0$ Hz, 2H), 7.15 (d, $J = 7.5$ Hz, 1H), 5.69 (s, 1H), 4.29 – 4.17 (m, 2H), 1.25 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.4 (C), 150.0 (C), 136.7 (C), 134.0 (C), 133.2 (CH), 131.6 (CH), 129.3 (CH), 129.2 (CH), 129.1 (CH), 128.4 (CH), 128.3

(CH), 127.9 (CH), 124.9 (CH), 61.6 (CH₂), 53.3 (CH), 14.1 (CH₃); ATR-FTIR (thin film): 2981, 1729, 1605, 1523, 1348, 1301, 1186, 1156, 1024, 849, 735 cm⁻¹.



Ethyl 2-(4-methoxyphenyl)-2-(2-nitrophenyl)acetate 3.86. The general procedure was followed using 9.70 g of ethyl 2-(4-methoxyphenyl)acetate (50.0 mmol), 5.27 mL of 1-fluoro-2-nitrobenzene, 80.0 mL of DMF, and 2.20 g of NaH. Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded the product as a light yellow oil (5.36 g, 34%). ¹H NMR (500 MHz, CDCl₃) δ 7.98 (d, *J* = 8.0 Hz, 1H), 7.47 (t, *J* = 7.5 Hz, 1H), 7.38 (t, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.5 Hz, 2H), 7.16 (d, *J* = 8.0 Hz, 1H), 6.91 (d, *J* = 8.5 Hz, 2H), 5.62 (s, 1H), 4.28 – 4.22 (m, 1H), 4.19 – 4.13 (m, 1H), 3.79 (s, 3H), 1.23 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.6 (C), 159.3 (C), 148.9 (C), 134.4 (C), 133.1 (CH), 131.5 (CH), 130.4 (CH), 128.6 (C), 128.2 (CH), 124.8 (CH), 114.5 (CH), 61.5 (CH₂), 55.3 (CH₃), 52.6 (CH), 14.1 (CH₃); ATR-FTIR (thin film): 2938, 2839, 1730, 1629, 1510, 1448, 1348, 1250, 1161, 1028, 929, 841 cm⁻¹.

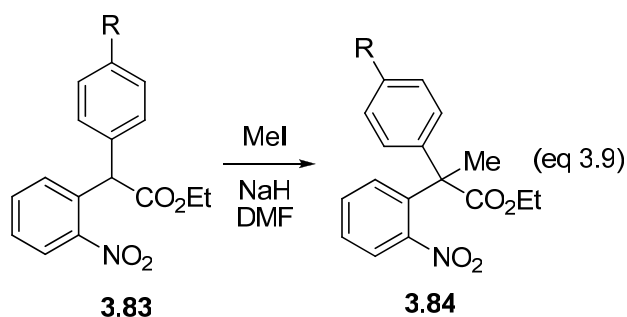


Ethyl 2-(2-nitrophenyl)-2-(4-(trifluoromethyl)phenyl)acetate 3.87. The general procedure was followed using 11.6 g of ethyl 2-(4-(trifluoromethyl)phenyl)acetate (50.0 mmol), 5.27 mL of 1-fluoro-2-nitrobenzene, 80.0 mL of DMF, and 2.20 g of NaH. Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded the product as a light yellow oil (6.53 g, 37%). ¹H NMR (500 MHz, CDCl₃) δ 7.86 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.75 (d, *J* = 8.0 Hz, 2H), 7.68 (d, *J* = 8.0 Hz, 2H), 7.48 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.43 (dt, *J* = 7.5, 1.5 Hz, 1H), 6.85 (dd, *J* = 8.0, 1.5 Hz, 1H), 4.45 (s, 1H), 4.38 – 4.27 (m, 2H), 1.28 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 171.9 (C), 148.9 (C), 143.8 (C), 136.1 (C), 132.4 (CH), 131.3 (CH), 130.9 (q, *J*_{CF} = 33 Hz, C), 129.5 (CH), 127.5 (CH), 125.5 (q, *J*_{CF} = 3.4 Hz, CH), 125.0 (CH), 123.9 (q, *J*_{CF} = 270 Hz, CF₃), 79.7 (CH), 63.2 (CH₂), 13.9 (CH₃); ¹⁹F NMR (282 MHz, CDCl₃) δ –63.32; ATR-FTIR (thin film): 2982, 1732, 1532, 1412, 1323, 1245, 1163, 1120, 1067, 1017, 845, 750 cm^{–1}.

3.6.3.3 Synthesis of ethyl 2-(4-substitutedphenyl)-2-(2-nitrophenyl)propanoate

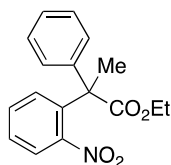
General Procedure

Methylation of the nucleophilic aromatic substitution product provided ester **3.84** as described in the equation 3.9. Yields were not optimized.



To a cooled solution (0 °C) of ethyl 2-(4-substitutedphenyl)-2-(2-nitrophenyl)acetate **3.83** (10.0 mmol) and 3 mL of MeI (33.0 mmol) in 60.0 mL of DMF was slowly added NaH (1.20 g, 30.0 mmol). After addition, the reaction was warmed to room temperature. After 5 hours, the mixture was diluted with 30 mL of H₂O and extracted with 3 × 20 mL of Et₂O. The combined organic phases were dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC afforded ester **3.84**.

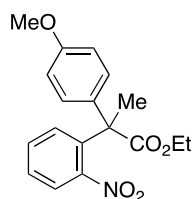
Synthesis



3.88

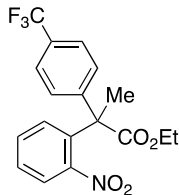
Ethyl 2-(2-nitrophenyl)-2-phenylpropanoate 3.88. The general procedure was followed using 2.85 g of ester **3.85** (10.0 mmol), 3 mL of MeI, 60.0 mL of DMF and 1.20 g of NaH. Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded the product as a light yellow oil (2.21 g, 74%). ¹H NMR (500 MHz, CDCl₃) δ 7.89 – 7.87 (m, 1H), 7.47 (d, *J* = 7.0 Hz, 2H), 7.38

– 7.31 (m, 5H), 6.89 – 6.87 (m, 1H), 4.16 – 4.10 (m, 1H), 4.03 – 3.97 (m, 1H), 2.18 (s, 3H), 1.15 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.3 (C), 149.5 (C), 142.1 (C), 141.0 (C), 132.4 (CH), 131.9 (CH), 128.5 (CH), 128.4 (CH), 127.8 (CH), 127.6 (CH), 124.9 (CH), 61.4 (CH_2), 55.6 (C), 25.3 (CH_3), 13.8 (CH_3); ATR-FTIR (thin film): 2989, 1726, 1525, 1487, 1447, 1356, 1299, 1183, 1163, 1106, 1015, 849, 788 cm^{-1} .



3.89

Ethyl 2-(4-methoxyphenyl)-2-(2-nitrophenyl)propanoate 3.89. The general procedure was followed using 3.15 g of ester **3.86** (10.0 mmol), 3 mL of MeI, 60.0 mL of DMF and 1.20 g of NaH. Purification by MPLC (0:100 – 5:95 EtOAc:hexanes) afforded the product as a light yellow oil (2.07 g, 63%). ^1H NMR (500 MHz, CDCl_3) δ 7.86 (dd, $J = 7.5, 2.0$ Hz, 1H), 7.39 – 7.34 (m, 4H), 6.91 (dd, $J = 7.5, 2.0$ Hz, 1H), 6.85 (d, $J = 9.0$ Hz, 2H), 4.15 – 4.09 (m, 1H), 4.02 – 3.97 (m, 1H), 3.81 (s, 3H), 2.14 (s, 3H), 1.15 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.4 (C), 159.1 (C), 149.4 (C), 141.3 (C), 134.0 (C), 132.4 (CH), 131.8 (CH), 129.5 (CH), 127.5 (C), 124.9 (CH), 113.7 (CH), 61.3 (CH_2), 55.3 (CH_3), 54.9 (C), 25.3 (CH_3), 13.8 (CH_3); ATR-FTIR (thin film): 2985, 2836, 1732, 1606, 1527, 1510, 1357, 1252, 1180, 1094, 1030, 831, 735 cm^{-1} .



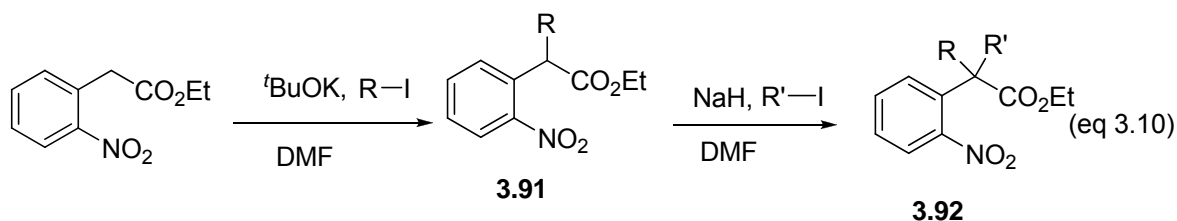
3.90

Ethyl 2-(2-nitrophenyl)-2-(4-(trifluoromethyl)phenyl)propanoate 3.90. The general procedure was followed using 3.53 g of ester **3.87** (10.0 mmol), 3 mL of MeI, 60.0 mL of DMF and 1.20 g of NaH. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow oil (2.35 g, 64%). ^1H NMR (500 MHz, CDCl_3) δ 7.82 (d, $J = 8.0, 1.0$ Hz, 1H), 7.64 (d, $J = 8.5$ Hz, 2H), 7.58 (d, $J = 8.5$ Hz, 2H), 7.55 (d, $J = 7.0$ Hz, 1H), 7.50 – 7.45 (m, 2H), 4.30 – 4.17 (m, 2H), 3.32 (s, 3H), 1.21 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 168.3 (C), 149.1 (C), 142.9 (C), 135.5 (C), 132.4 (CH), 130.6 (CH), 130.4 (q, $J_{\text{CF}} = 33$ Hz, CH), 129.3 (CH), 129.2 (C), 124.8 (q, $J_{\text{CF}} = 3.3$ Hz, CH), 124.7 (CH), 123.9 (q, $J_{\text{CF}} = 270$ Hz, CF_3), 84.7 (C), 61.9 (CH_2), 54.0 (CH_3), 13.8 (CH_3); ^{19}F NMR (282 MHz, CDCl_3) δ -63.37; ATR-FTIR (thin film): 2985, 2945, 1735, 1532, 1325, 1252, 1166, 1118, 1068, 1018, 909, 838 cm^{-1} .

3.6.4 Preparation of ethyl alkyl-alkyl'-2-(2-nitrophenyl)acetate

3.6.4.1 Route to Substrates.

Ethyl alkyl-alkyl'-2-(2-nitrophenyl)acetate was prepared by alkylation of each alkyl group one after the other into ester as the route outlined in equation 3.10. Yields were not optimized.

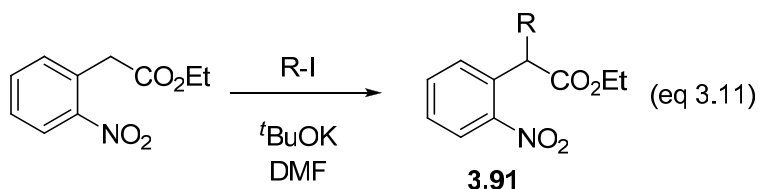


Ethyl 2-(2-nitrophenyl) esters **3.91** were prepared from ethyl 2-(2-nitrophenyl)acetate by an alkylation reaction with alkyl iodide using $t\text{BuOK}$ as base. The second alkylation reaction with NaH base installed the second alkyl group to afford esters **3.92**.

3.6.4.2 Synthesis of alkyl 2-(2-nitrophenyl)ester

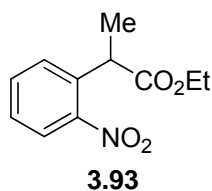
General procedure

Alkylation of ethyl 2-(2-nitrophenyl)acetate provided ester **3.91** as described in equation 3.11. Yields were not optimized.

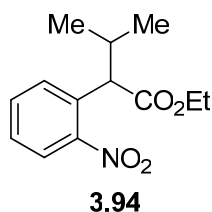


To a cooled solution of ethyl 2-(2-nitrophenyl)acetate in DMF was added a 1 M solution of $t\text{BuOK}$ in THF (1 equiv), followed by the alkyl iodide (0.95 equiv). The reaction mixture was allowed to warm up to room temperature. After 5 hours, the mixture was diluted with 20 mL of H_2O and extracted with 3×20 mL of Et_2O . The combined organic phases were dried over Na_2SO_4 , filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC afforded ester **3.91**.

Synthesis



Ethyl 2-(2-nitrophenyl)propanoate 3.93.³⁰ The general procedure was followed using 1.05 g of ethyl 2-(2-nitrophenyl)acetate (5.00 mmol), 0.30 mL of iodomethane, 20 mL of DMF and 5 mL of a 1M solution of ^tBuOK in THF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow oil (0.93 g, 84%). Ester **3.93** was reported earlier by Lesiak.¹³ ¹H NMR (500 MHz, CDCl₃) δ 7.82 (d, *J* = 7.0 Hz, 1H), 7.52 (t, *J* = 7.5 Hz, 1H), 7.42 (d, *J* = 7.5 Hz, 1H), 7.33 (t, *J* = 8.0 Hz, 1H), 4.21 (q, *J* = 7.0 Hz, 1H), 4.06 – 4.01 (m, 2H), 1.51 (d, *J* = 7.5 Hz, 3H), 1.11 – 1.08 (m, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 172.9 (C), 145.0 (C), 135.2 (C), 133.2 (CH), 129.8 (CH), 128.0 (CH), 124.7 (C), 61.0 (CH₂), 41.4 (CH), 17.7 (CH₃), 13.9 (CH₃); ATR-FTIR (thin film): 2983, 2945, 1730, 1609, 1523, 1349, 1201, 1179, 1078, 1022, 854, 786 cm⁻¹.



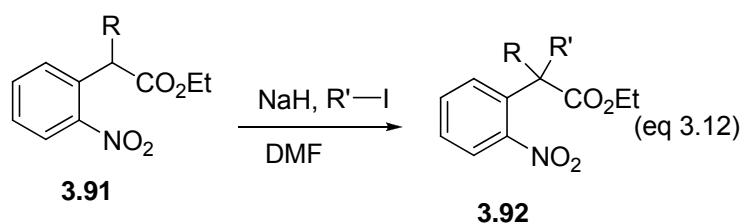
Ethyl 3-methyl-2-(2-nitrophenyl)butanoate 3.94. The general procedure was followed using 1.05 g of ethyl 2-(2-nitrophenyl)acetate, 0.55 mL of 1-iodo-2-methylpropane, 20 mL of DMF and 5 mL of a 1M solution of ^tBuOK in THF. Purification by MPLC (0:100 – 2:98

EtOAc:hexanes) afforded the product as a yellow oil (0.75 g, 60%). ^1H NMR (500 MHz, CDCl_3) δ 7.68 (d, $J = 8.0$ Hz, 1H), 7.65 (d, $J = 8.0$ Hz, 1H), 7.50 (t, $J = 7.0$ Hz, 1H), 7.31 (dd, $J = 8.0$, 1.5 Hz, 1H), 4.11 – 3.96 (m, 2H), 3.79 (d, $J = 10$ Hz, 1H), 2.36 – 2.29 (m, 1H), 1.11 (t, $J = 7.0$ Hz, 3H), 1.00 (d, $J = 6.5$ Hz, 3H), 0.66 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 172.6 (C), 150.8 (C), 132.4 (CH), 132.2 (C), 129.6 (CH), 127.9 (CH), 123.8 (C), 60.9 (CH_2), 52.2 (CH), 32.4 (CH), 21.2 (CH_3), 19.9 (CH_3), 14.0 (CH_3); ATR-FTIR (thin film): 2968, 2934, 2873, 1729, 1526, 1354, 1282, 1177, 1113, 1024, 851, 780 cm^{-1} .

3.6.4.3 Synthesis of alkyl alkyl' 2-(2-nitrophenyl)ester

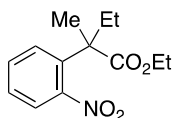
General Procedure

The second nucleophilic substitution was carried out to obtain disubstituted ester **3.92** as described in equation 3.12. Yields were not optimized.



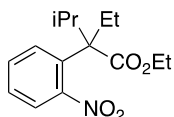
To a cooled solution (0 °C) of alkyl 2-(2-nitrophenyl)ester **3.91** (1 equiv) and alkyl iodide (3 equiv) in DMF at was slowly added NaH (3 equiv). Then the reaction was warmed to room temperature. After 12 hours, the mixture was diluted with 30 mL of H_2O and extracted with 3×30 mL of Et_2O . The combined organic phases were dried over Na_2SO_4 , filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC afforded ester **3.92**.

Synthesis



3.95

Ethyl 2-methyl-2-(2-nitrophenyl)butanoate 3.95. The general procedure was followed using 1.12 g of ester **3.93** (5.00 mmol), 20 mL of DMF, 1.21 mL of ethyl iodide (15.0 mmol), and 0.60 g of NaH. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a yellow oil (0.84 g, 67%). ¹H NMR (500 MHz, CDCl₃) δ 7.82 (d, *J* = 8.0 Hz, 1H), 7.56 (t, *J* = 7.0 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.36 (t, *J* = 8.0 Hz, 1H), 4.08 – 4.03 (m, 2H), 2.11 (q, *J* = 7.5 Hz, 2H), 1.62 (s, 3H), 1.15 (t, *J* = 7.0 Hz, 3H), 0.74 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 174.3 (C), 149.5 (C), 137.5 (C), 132.6 (CH), 128.9 (CH), 127.5 (CH), 125.6 (CH), 60.8 (CH₂), 50.3 (C), 31.5 (CH₂), 25.6 (CH₃), 14.0 (CH₃), 9.1 (CH₃); ATR-FTIR (thin film): 2980, 2931, 1726, 1527, 1356, 1230, 1137, 1109, 1024, 908, 730 cm⁻¹.



3.96

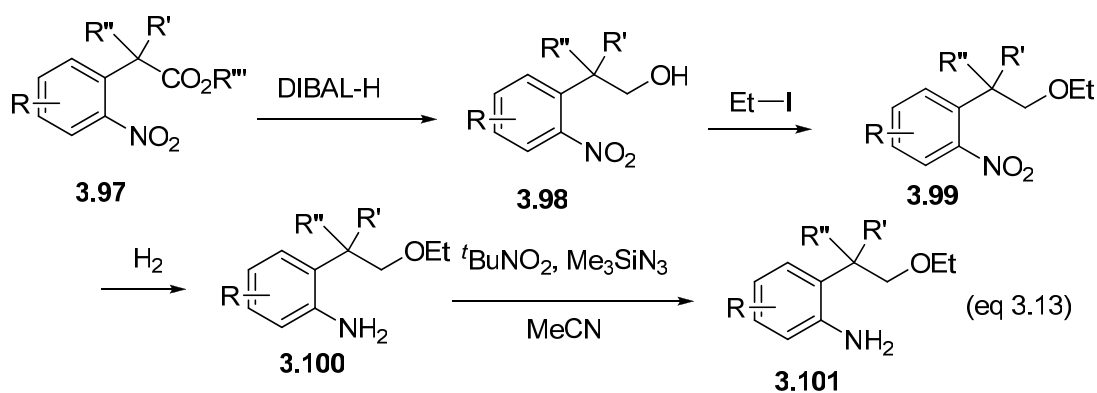
Ethyl 2-ethyl-3-methyl-2-(2-nitrophenyl)butanoate 3.96. The general procedure was followed using 1.26 g of ester **3.94** (5.00 mmol), 20 mL of DMF, 1.21 mL of ethyl iodide (15.0 mmol), and 0.60 g of NaH. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the

product as a yellow oil (0.87 g, 62%). ^1H NMR (500 MHz, CDCl_3) δ 7.78 (d, $J = 8.0$ Hz, 1H), 7.54 (t, $J = 7.0$ Hz, 1H), 7.46 (d, $J = 7.5$ Hz, 1H), 7.36 (t, $J = 7.5$ Hz, 1H), 4.19 – 4.12 (m, 1H), 4.01 – 3.95 (m, 1H), 2.66 (m, $J = 7.0$ Hz, 1H), 2.38 – 2.20 (m, 2H), 1.19 (t, $J = 8.0$ Hz, 3H), 0.98 (d, $J = 7.0$ Hz, 3H), 0.81 (d, $J = 7.0$ Hz, 3H), 0.74 (t, $J = 7.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 171.3 (C), 151.0 (C), 135.5 (C), 131.4 (CH), 130.3 (CH), 127.2 (CH), 125.7 (CH), 60.3 (CH_2), 57.3 (C), 32.0 (CH), 28.4 (CH_2), 19.0 (CH_3), 18.1 (CH_3), 14.1 (CH_3), 8.6 (CH_3); ATR-FTIR (thin film): 2978, 2938, 1729, 1530, 1353, 1204, 1102, 1021, 844, 782 cm^{-1} .

3.6.5 Preparation of Aryl Azides

3.6.5.1 Route to Substrates.

The aryl azides were prepared as the route outlined in equation 3.13. Yields were not optimized.



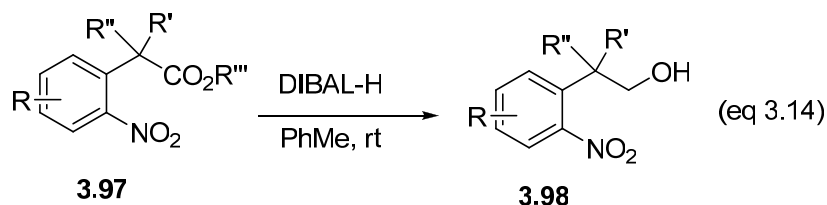
Reduction of ester group using DIBAL-H formed primary alcohol **3.98**. Etherification reaction converted the alcohol to ethyl ether **3.99**. Hydrogenation of **3.99** yielded aniline **3.100**.

Treatment of the anilines **3.100** with *tert*-butyl nitrite and azidotrimethylsilane provided the requisite aryl azides **3.101**.

3.6.5.2 Synthesis of Primary Alcohols.

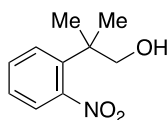
General procedure

The ester was reduced to primary alcohol using DIBAL-H as described in equation s13. Yields were not optimized.

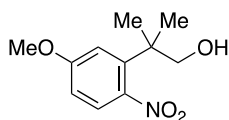


To a solution of ester (5 mmol) in 20 mL of toluene was added drop wise 11.0 mL of a 1M solution of DIBAL-H (2.2 equiv) in toluene. After addition, the reaction mixture was diluted with 20 mL of diethyl ether. The mixture was cooled to 0 °C and 0.44 mL of H₂O, 0.44 mL of a 25% aqueous solution of NaOH and 1.1 mL of H₂O were sequentially added. The ice bath was then removed and the reaction was allowed to warm up to room temperature and stirred for 15 minutes. The mixture was filtered, and the filtrate was diluted with 30 mL of H₂O and extracted with 3 × 30 mL of Et₂O. The combined organic phases were dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC afforded alcohol **3.98**.

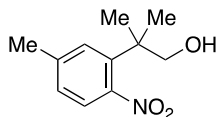
Synthesis



2-Methyl-2-(2-nitrophenyl)propan-1-ol 3.102.³¹ The general procedure was followed using 1.19 g of ester **3.71** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H in toluene (11.0 mmol) and 20.0 mL of toluene. Purification by MPLC (0:100 – 20:80 EtOAc:hexanes) afforded the product as a yellow liquid (0.90 g, 92%). Alcohol **3.102** was previously reported by Terauchi and Curran.¹⁴ ¹H NMR (500 MHz, CDCl₃) δ 7.51 (d, J = 7.5 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.26 – 7.25 (m, 2H), 3.64 (s, 2H), 2.76 (s, 1H), 1.29 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 151.7 (C), 137.3 (C), 130.8 (CH), 130.2 (CH), 127.4 (CH), 123.9 (CH), 71.3 (CH₂), 41.1 (C), 25.2 (CH₃); ATR-FTIR (thin film): 3389, 2971, 2884, 1523, 1370, 1037, 858, 840 cm⁻¹.

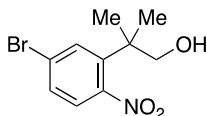


2-(5-Methoxy-2-nitrophenyl)-2-methylpropan-1-ol 3.103. The general procedure was followed using 1.27 g of ester **3.72** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H in toluene (11.0 mmol) and 20.0 mL of toluene. Purification by MPLC (0:100 – 20:80 EtOAc:hexanes) afforded the product as a light yellow liquid (0.79 g, 70%). ¹H NMR (500 MHz, CDCl₃) δ 7.40 (d, J = 8.5 Hz, 1H), 7.04 (s, 1H), 6.77 (d, J = 8.5 Hz, 1H), 3.85 (s, 3H), 3.79 (d, J = 6.0 Hz, 2H), 1.63 (s, 1H), 1.37 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 161.0 (C), 145.6 (C), 140.1 (C), 126.4 (CH), 116.6 (CH), 110.8 (CH), 71.5 (CH₂), 55.7 (CH₃), 41.4 (C), 25.5 (CH₃); ATR-FTIR (thin film): 3396, 2968, 2934, 1601, 1517, 1482, 1360, 1289, 1248, 1041 cm⁻¹.



3.104

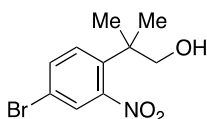
2-Methyl-2-(5-methyl-2-nitrophenyl)propan-1-ol 3.104. The general procedure was followed using 1.19 g of ester **3.73** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H (11.0 mmol) in toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 20:80 EtOAc:hexanes) afforded the product as a light yellow liquid (0.86 g, 82%). ^1H NMR (500 MHz, CDCl_3) δ 7.32 (s, 1H), 7.23 (d, $J = 8.5$ Hz, 1H), 7.10 (d, $J = 8.5$ Hz, 1H), 3.73 (d, $J = 5.5$ Hz, 2H), 2.39 (s, 3H), 1.84 (s, 1H), 1.35 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 149.8 (C), 141.3 (C), 137.1 (C), 130.6 (CH), 127.8 (CH), 124.2 (CH), 71.6 (CH_2), 41.1 (C), 25.4 (CH_3), 21.5 (CH_3); ATR-FTIR (thin film): 3389, 2965, 1608, 1521, 1364, 1041, 907, 729 cm^{-1} .



3.105

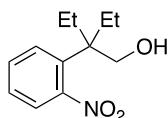
2-(5-Bromo-2-nitrophenyl)-2-methylpropan-1-ol 3.105. The general procedure was followed using 1.5 g of ester **3.74** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H (11.0 mmol) in toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 20:80 EtOAc:hexanes) afforded the product as a light yellow liquid (0.96 g, 70%). ^1H NMR (500 MHz, CDCl_3) 7.71 (d, $J = 2.0$ Hz, 1H), 7.47 (dd, $J = 8.5, 2.0$ Hz, 1H), 7.24 (d, $J = 8.0$ Hz, 1H), 3.74 (s, 2H), 2.05 (s,

¹H), 1.36 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 150.6 (C), 139.8 (C), 133.4 (CH), 130.5 (CH), 125.5 (CH), 125.1 (C), 71.2 (CH₂), 41.4 (C), 25.3 (CH₃); ATR-FTIR (thin film): 3399, 2978, 2880, 1560, 1517, 1468, 1363, 1285, 1099, 1044, 909, 820, 728 cm⁻¹.



3.106

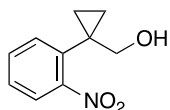
2-(4-Bromo-2-nitrophenyl)-2-methylpropan-1-ol 3.106. The general procedure was followed using 1.5 g of ester **3.75** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H (11.0 mmol) in toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 20:80 EtOAc:hexanes) afforded the product as a light yellow liquid (1.00 g, 73%). ¹H NMR (500 MHz, CDCl₃) 7.57 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.47 (d, *J* = 2.5 Hz, 1H), 7.43 (d, *J* = 9.0 Hz, 1H), 3.69 (s, 2H), 1.92 (s, 1H), 1.33 (s, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 151.9 (C), 136.7 (C), 133.7 (CH), 132.0 (CH), 126.6 (CH), 120.0 (C), 70.8 (CH₂), 40.9 (C), 25.0 (CH₃); ATR-FTIR (thin film): 3378, 2971, 2880, 1526, 1475, 1367, 1044, 974, 871, 817, 746 cm⁻¹.



3.107

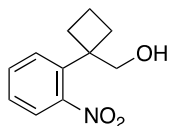
2-Ethyl-2-(2-nitrophenyl)butan-1-ol 3.107. The general procedure was followed using 1.26 g of ester **3.76** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H (11.0 mmol) in

toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 20:80 EtOAc:hexanes) afforded the product as a light yellow liquid (0.87 g, 78%). ^1H NMR (500 MHz, CDCl_3) δ 7.48 – 7.44 (m, 2H), 7.34 – 7.30 (m, 2H), 3.84 (s, 2), 1.76 (m J = 7.5 Hz, 4H), 1.61 (s, 1H), 0.76 (t, J = 7.5 Hz, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 152.1 (C), 135.0 (C), 130.8 (CH), 130.4 (CH), 127.3 (CH), 124.2 (CH), 65.4 (CH_2), 47.8 (C), 26.4 (CH_2), 8.5 (CH_3); ATR-FTIR (thin film): 3511, 2931, 2857, 1658, 1438, 1384, 1258, 1092, 654 cm^{-1} .

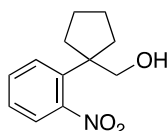


3.108

(1-(2-Nitrophenyl)cyclopropyl)methanol 3.108.³² The general procedure was followed using 1.18 g of ester **3.78** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H (11.0 mmol) in toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a light yellow liquid (0.64 g, 66%). ^1H NMR (500 MHz, CDCl_3) δ 7.73 (d, J = 8.0 Hz, 1H), 7.61 (d, J = 7.5 Hz, 1H), 7.53 (t, J = 8.0 Hz, 1H), 7.38 (t, J = 8.0 Hz, 1H), 3.67 (s, 2H), 2.20 (s, 1H), 0.94 (t, J = 6.0 Hz, 2H), 0.75 (t, J = 5.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.5 (C), 137.0 (C), 134.6 (CH), 132.4 (C), 127.9 (CH), 124.0 (CH), 70.6 (CH_2), 26.4 (C), 11.3 (CH_2); ATR-FTIR (thin film): 3358, 2998, 2873, 1553, 1357, 1034, 864, 782, 753 cm^{-1} .

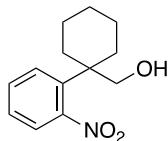


(1-(2-Nitrophenyl)cyclobutyl)methanol 3.109. The general procedure was followed using 1.25 g of ester **3.79** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H (11.0 mmol) in toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a light yellow liquid (0.72 g, 70%). ^1H NMR (500 MHz, CDCl_3) δ 7.58 (d, J = 8.0 Hz, 1H), 7.47 (t, J = 7.5 Hz, 1H), 7.28 (t, J = 7.5 Hz, 1H), 7.21 (d, J = 8.0 Hz, 1H), 4.00 (d, J = 5.5 Hz, 2H), 2.40 (t, J = 6.0 Hz, 1H), 2.28 – 2.24 (m, 2H), 2.19 – 2.12 (m, 2H), 2.05 – 1.97 (m, 1H), 1.78 – 1.72 (m, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 149.2 (C), 141.9 (C), 131.9 (CH), 130.7 (CH), 126.9 (CH), 124.0 (CH), 68.6 (CH_2), 47.3 (C), 30.2 (CH_2), 15.8 (CH_2); ATR-FTIR (thin film): 3382, 2985, 2938, 2870, 1523, 1357, 1238, 1021, 909, 712 cm^{-1} .



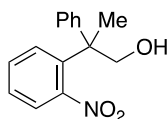
(1-(2-Nitrophenyl)cyclopentyl)methanol 3.110. The general procedure was followed using 1.32 g of ester **3.80** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H (11.0 mmol) in toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a light yellow liquid (0.70 g, 63%). ^1H NMR (500 MHz, CDCl_3) δ 7.49 – 7.45 (m, 2H), 7.43 – 7.41 (m, 1H), 7.33 – 7.31 (m, 1H), 3.74 (d, J = 6.0 Hz, 2H), 2.18 (t, J = 5.5 Hz, 1H), 2.17 (m, 1H), 1.69 (m, 7H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.4 (C), 139.4 (C), 132.2 (CH), 130.8 (CH), 127.2 (CH), 123.8 (CH), 67.5 (CH_2), 53.3 (C), 34.0 (CH_2), 23.4 (CH_2); ATR-FTIR

(thin film): 3394, 2956, 2874, 1506, 1363, 1298, 1047, 1008, 960, 847, 776, 722 cm^{-1} .



3.111

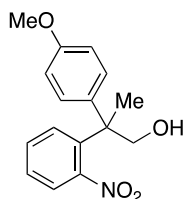
(1-(2-Nitrophenyl)cyclohexyl)methanol 3.111. The general procedure was followed using 1.39 g of ester **3.81** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H (11.0 mmol) in toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a light yellow liquid (1.08 g, 92%). ^1H NMR (500 MHz, CDCl_3) δ 7.49 – 7.45 (m, 2H), 7.43 – 7.41 (m, 1H), 7.33 – 7.31 (m, 1H), 3.74 (d, J = 6.0 Hz, 2H), 2.18 (t, J = 5.5 Hz, 1H), 2.17 (m, 1H), 1.69 (m, 7H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.4 (C), 139.4 (C), 132.2 (CH), 130.8 (CH), 127.2 (CH), 123.8 (CH), 71.0 (CH_2), 46.2 (C), 32.7 (CH_2), 26.5 (CH_2), 22.4 (CH_2); ATR-FTIR (thin film): 3487, 2931, 2859, 1658, 1438, 1388, 1252, 1092, 1061, 675 cm^{-1} .



3.112

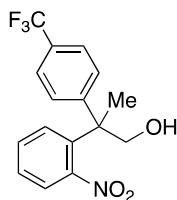
2-(2-Nitrophenyl)-2-phenylpropan-1-ol 3.112. The general procedure was followed using 1.50 g of ester **3.88** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H (11.0 mmol) in toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a light yellow liquid (0.96 g, 75%). ^1H NMR (500 MHz, CDCl_3) δ 7.74 (dd, J =

8.0, 1.0 Hz, 1H), 7.57 (dt, $J = 8.5, 1.5$ Hz, 1H), 7.43 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.38 (dt, $J = 8.0, 1.0$ Hz, 1H), 7.28 (t, $J = 7.0$ Hz, 2H), 7.24 (t, $J = 7.0$ Hz, 1H), 7.12 (d, $J = 8.5$ Hz, 2H), 4.13 – 4.07 (m, 2H), 1.84 (s, 3H), 1.69 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 163.9 (C), 151.7 (C), 143.4 (C), 138.9 (C), 131.4 (CH), 129.9 (CH), 128.4 (CH), 127.7 (CH), 126.9 (CH), 125.0 (CH), 70.9 (CH_2), 48.7 (C), 25.2 (CH_3); ATR-FTIR (thin film): 3402, 2971, 2938, 2884, 1526, 1492, 1448, 1360, 1021, 943, 854, 773, 695 cm^{-1} .



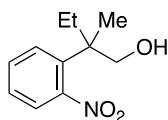
3.113

2-(4-Methoxyphenyl)-2-(2-nitrophenyl)propan-1-ol 3.113. The general procedure was followed using 1.65 g of ester **3.89** (5.00 mmol), 11.0 mL of a 1 M solution of DIBAL-H (11.0 mmol) in toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a light yellow liquid (1.00 g, 73%). ^1H NMR (500 MHz, CDCl_3) δ 7.71 (d, $J = 8.0$ Hz, 1H), 7.53 (dt, $J = 8.0, 1.5$ Hz, 1H), 7.39 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.34 (t, $J = 8.0$ Hz, 1H), 7.01 (d, $J = 9.0$ Hz, 2H), 6.78 (d, $J = 8.5$ Hz, 2H), 4.04 (d, $J = 6.5$ Hz, 2H), 3.75 (s, 3H), 1.85 (t, $J = 6.5$ Hz, 1H), 1.80 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 158.3 (C), 151.8 (C), 139.2 (C), 135.4 (C), 131.2 (CH), 129.7 (CH), 128.1 (CH), 127.6 (CH), 124.8 (CH), 113.7 (CH), 71.0 (CH_2), 55.2 (CH_3), 48.0 (C), 25.2 (CH_3); ATR-FTIR (thin film): 3443, 2944, 2886, 2833, 1608, 1526, 1461, 1363, 1249, 1184, 1031, 912, 827 cm^{-1} .



3.114

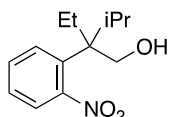
2-(2-Nitrophenyl)-2-(4-(trifluoromethyl)phenyl)propan-1-ol 3.114. The general procedure was followed using 1.84 g of ester **3.90** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H (11.0 mmol) in toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a light yellow liquid (1.25 g, 77%). ^1H NMR (500 MHz, CDCl_3) δ 7.58 (d, $J = 8.0$ Hz, 2H), 7.50 (t, $J = 8.5$ Hz, 1H), 7.46 – 7.40 (m, 5H), 4.38 (dq, $J = 34.0, 5.5$ Hz, 2H), 3.12 (s, 3H), 2.26 (t, $J = 6.0$ Hz, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 150.2 (C), 144.9 (C), 133.8 (C), 130.7 (C), 130.1 (q, $J_{\text{CF}} = 33$ Hz, C), 129.7 (CH), 129.1 (CH), 127.6 (CH), 125.2 (q, $J_{\text{CF}} = 3.5$ Hz, CH), 124.1 (CH), 124.0 (q, $J_{\text{CF}} = 285$ Hz, CF_3), 84.6 (C), 65.2 (CH_2), 51.3 (CH_3); ^{19}F NMR (282 MHz, CDCl_3) δ -63.22; ATR-FTIR (thin film): 2985, 2945, 1735, 1532, 1325, 1252, 1166, 1118, 1068, 1018, 909, 838 cm^{-1} .



3.115

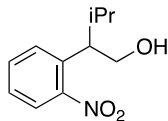
2-Methyl-2-(2-nitrophenyl)butan-1-ol 3.115. The general procedure was followed using 1.26 g of ester **3.95** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H (11.0 mmol) in

toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a light yellow liquid (0.85 g, 81%). ¹H NMR (500 MHz, CDCl₃) δ 7.45 (d, *J* = 7.5 Hz, 1H), 7.44 – 7.40 (m, 1H), 7.30 – 7.26 (m, 2H), 3.66 (dd, *J* = 12.5, 11 Hz, 2H), 2.26 (s, 1H), 1.82 (m, *J* = 7.5 Hz, 1H), 1.47 (m, *J* = 7.5 Hz, 1H), 1.32 (s, 3H), 0.69 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 152.1 (C), 135.2 (C), 131.1 (CH), 130.5 (CH), 127.4 (CH), 124.0 (CH), 70.9 (CH₂), 45.2 (C), 30.4 (CH₂), 21.9 (CH₃), 8.6 (CH₃); ATR-FTIR (thin film): 3382, 2975, 2938, 2880, 1523, 1479, 1370, 1041, 997, 943, 854 cm⁻¹.



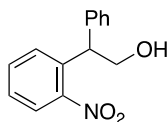
3.116

2-Ethyl-3-methyl-2-(2-nitrophenyl)butan-1-ol 3.116. The general procedure was followed using 1.40 g of ester **3.96** (5.00 mmol), 11.0 mL of 1 M solution of DIBAL-H (11.0 mmol) in toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a light yellow liquid (0.97 g, 82%). ¹H NMR (500 MHz, CDCl₃) δ 7.55 (d, *J* = 8.0 Hz, 1H), 7.46 – 7.44 (m, 1H), 7.33 – 7.31 (m, 2H), 3.98 (s, 2H), 2.24 (m, *J* = 7.0 Hz, 1H), 1.82 (t, *J* = 7.5 Hz, 2H), 1.79 (s, 1H), 0.89 (d, *J* = 7.0 Hz, 3H), 0.85 (d, *J* = 7.0 Hz, 3H), 0.80 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 152.3 (C), 135.0 (C), 131.6 (CH), 130.2 (CH), 127.1 (CH), 124.5 (CH), 66.2 (CH₂), 50.8 (C), 35.4 (CH), 26.9 (CH₂), 19.1 (CH₃), 18.2 (CH₃), 9.9 (CH₃); ATR-FTIR (thin film): 3450, 2965, 2880, 1526, 1465, 1367, 1167, 1037, 851, 766, 742 cm⁻¹.



3.117

3-Methyl-2-(2-nitrophenyl)butan-1-ol 3.117. The general procedure was followed using 1.26 g of ester **3.94** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H (11.0 mmol) in toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a light yellow liquid (0.90 g, 86%). ^1H NMR (500 MHz, CDCl_3) δ 7.64 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.52 (dt, $J = 7.5, 1.0$ Hz, 1H), 7.47 (dd, $J = 8.0, 1.0$ Hz, 1H), 7.31 (dt, $J = 7.5, 1.5$ Hz, 1H), 3.93 (dd, $J = 6.0, 4.5$ Hz, 1H), 3.78 (dd, $J = 11.0, 3.0$ Hz, 1H), 2.95 (m, $J = 4.5$ Hz, 1H), 2.03 – 1.97 (m, 1H), 1.94 (s, 1H), 1.01 (d, $J = 7.0$ Hz, 3H), 0.68 (d, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 152.0 (C), 136.9 (C), 132.2 (CH), 128.8 (CH), 127.0 (C), 123.6 (CH), 64.5 (CH_2), 48.8 (CH), 30.1 (CH), 21.3 (CH_3), 20.8 (CH_3); ATR-FTIR (thin film): 3389, 2962, 2873, 1608, 1526, 1461, 1354, 1295, 1062, 1001, 854, 780 cm^{-1} .



3.118

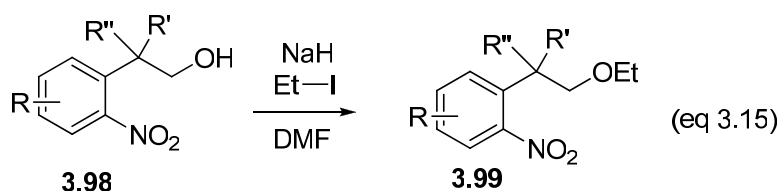
2-(2-Nitrophenyl)-2-phenylethanol 3.118. The general procedure was followed using 1.43 g of ester **3.85** (5.00 mmol), 11.0 mL of the 1 M solution of DIBAL-H (11.0 mmol) in toluene and 20.0 mL of toluene. Purification by MPLC (0:100 – 30:70 EtOAc:hexanes) afforded the product as a light yellow liquid (1.08 g, 89%). ^1H NMR (500 MHz, CDCl_3) δ 7.79 (dd, $J =$

8.0, 1.0 Hz, 1H), 7.56 – 7.51 (m, 2H), 7.36 (dt, $J = 7.5, 2.0$ Hz, 1H), 7.31 (t, $J = 7.5$ Hz, 2H), 7.25 – 7.23 (m, 3H), 4.86 (t, $J = 7.0$ Hz, 1H), 4.20 – 4.18 (m, 2H), 2.09 (s, 1H); ^{13}C NMR (125 MHz, CDCl_3) δ 150.5 (C), 139.8 (C), 136.0 (C), 132.7 (CH), 129.9 (CH), 128.8 (CH), 128.5 (CH), 127.6 (CH), 127.2 (CH), 124.6 (CH), 65.5 (CH_2), 47.4 (CH); ATR-FTIR (thin film): 3380, 3062, 3027, 2949, 2881, 1521, 1494, 1354, 1056, 736, 700 cm^{-1} .

3.6.5.3 Synthesis of Ethyl Ether

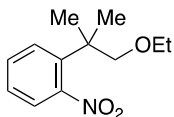
General Procedure

O-Alkylation of alcohol **3.98** with ethyl iodide was achieved as described in equation 3.15. Yields were not optimized.



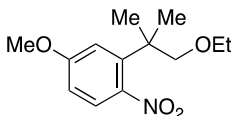
To a cooled solution (0 °C) of alcohol **3.98** (1 equiv) in DMF at was slowly added NaH (6 equiv). The reaction mixture was warmed up to room temperature and ethyl iodide (6 equiv) was added. After 3 hours, visualization of the reaction progress using TLC indicated the consumption of the starting material. De-ionized water was added to the reaction mixture. The mixture then was extracted with 2 × 30 mL of diethyl ether. The combined organic phases were 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 ether **3.99**.

Synthesis



3.119

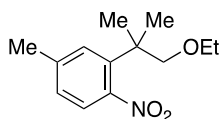
1-(1-Ethoxy-2-methylpropan-2-yl)-2-nitrobenzene 3.119. The general procedure was followed using 0.98 g of alcohol **3.102** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a yellow oil (0.72 g, 65%). ^1H NMR (500 MHz, CDCl_3) δ 7.54 (dd, $J = 8.5, 1.0$ Hz, 1H), 7.40 (dt, $J = 7.5, 2.0$ Hz, 1H), 7.28 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.24 (dt, $J = 7.5, 1.5$ Hz, 1H), 3.54 (s, 2H), 3.41 (q, $J = 7.0$ Hz, 2H), 1.38 (s, 6H), 1.09 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.6 (C), 138.3 (C), 130.6 (CH), 130.1 (CH), 127.0 (CH), 123.9 (CH), 78.8 (CH_2), 66.7 (CH_2), 40.2 (C), 26.2 (CH_3), 14.9 (CH_3); ATR-FTIR (thin film): 2978, 2927, 2867, 1530, 1482, 1367, 1289, 1109, 840, 776 cm^{-1} .



3.120

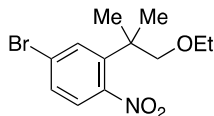
2-(1-Ethoxy-2-methylpropan-2-yl)-4-methoxy-1-nitrobenzene 3.120. The general procedure was followed using 1.13 g of alcohol **3.103** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a yellow oil (1.16 g, 92%). ^1H NMR (500 MHz, CDCl_3)

δ 7.38 (d, J = 8.5 Hz, 1H), 7.05 (d, J = 2.5 Hz, 1H), 6.74 (dd, J = 8.5, 2.5 Hz, 1H), 3.83 (s, 3H), 3.55 (s, 2H), 3.43 (q, J = 7.0 Hz, 2H), 1.38 (s, 6H), 1.12 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 160.9 (C), 145.5 (C), 141.3 (C), 126.2 (CH), 116.3 (CH), 110.6 (CH), 78.7 (CH_2), 66.7 (CH_2), 55.6 (CH_3), 40.4 (C), 26.2 (CH_3), 14.9 (CH_3); ATR-FTIR (thin film): 2976, 2931, 2867, 1570, 1523, 1489, 1357, 1289, 1248, 1109, 1065, 844, 755, 614 cm^{-1} .



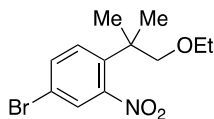
3.121

2-(1-Ethoxy-2-methylpropan-2-yl)-4-methyl-1-nitrobenzene 3.121. The general procedure was followed using 1.05 g of alcohol **3.104** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow oil (0.95 g, 80%). ^1H NMR (500 MHz, CDCl_3) δ 7.33 (s, 1H), 7.25 (d, J = 8.0 Hz, 1H), 7.07 (d, J = 9.0 Hz, 1H), 3.54 (s, 2H), 3.43 (q, J = 7.0 Hz, 2H), 2.39 (s, 3H), 1.38 (s, 6H), 1.12 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 149.6 (C), 140.9 (C), 138.2 (C), 130.5 (CH), 127.4 (CH), 124.1 (CH), 78.8 (CH_2), 66.7 (CH_2), 40.1 (C), 26.3 (CH_3), 21.6 (CH_3), 14.9 (CH_3); ATR-FTIR (thin film): 2968, 2877, 1601, 1523, 1492, 1363, 1296, 1106, 1075, 912, 820, 755 cm^{-1} .



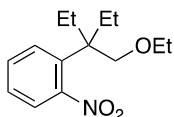
3.122

4-Bromo-2-(1-ethoxy-2-methylpropan-2-yl)-1-nitrobenzene 3.122. The general procedure was followed using 1.37 g of alcohol **3.105** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow oil (1.14 g, 76%). ^1H NMR (500 MHz, CDCl_3) δ 7.69 (d, $J = 7.0$ Hz, 1H), 7.42 (dd, $J = 8.0, 2.0$ Hz, 1H), 7.21 (d, $J = 8.5$ Hz, 1H), 3.50 (s, 2H), 3.42 (q, $J = 7.0$ Hz, 2H), 1.38 (s, 6H), 1.12 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 150.4 (C), 140.6 (C), 133.3 (CH), 130.1 (CH), 125.4 (CH), 124.8 (C), 78.4 (CH_2), 66.7 (CH_2), 40.3 (C), 26.1 (CH_3), 14.9 (CH_3); ATR-FTIR (thin film): 2976, 2931, 2870, 1530, 1468, 1360, 1289, 1109, 905, 728 cm^{-1} .



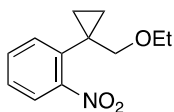
4-Bromo-1-(1-ethoxy-2-methylpropan-2-yl)-2-nitrobenzene 3.123. The general procedure was followed using 1.37 g of alcohol **3.106** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow oil (1.17 g, 78%). ^1H NMR (500 MHz, CDCl_3) δ 7.51 (dd, $J = 8.5, 2.0$ Hz, 1H), 7.45 (d, $J = 2.0$ Hz, 1H), 7.42 (d, $J = 8.5$ Hz, 1H), 3.48

(s, 2H), 3.39 (q, $J = 7.0$ Hz, 2H), 1.34 (s, 6H), 1.08 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.9 (C), 137.5 (C), 133.6 (CH), 131.9 (CH), 126.6 (CH), 119.8 (C), 78.6 (CH_2), 66.7 (CH_2), 40.1 (C), 26.1 (CH_3), 14.9 (CH_3); ATR-FTIR (thin film): 2975, 2931, 2866, 1590, 1533, 1475, 1367, 1106, 1061, 871, 820 cm^{-1} .



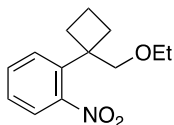
3.124

1-(3-(Ethoxymethyl)pentan-3-yl)-2-nitrobenzene 3.124. The general procedure was followed using 1.12 g of alcohol **3.107** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a yellow oil (0.75 g, 60%). ^1H NMR (500 MHz, CDCl_3) δ 7.45 – 7.41 (m, 2H), 7.33 – 7.26 (m, 2H), 3.61 (s, 2H), 3.43 (q, $J = 7.0$ Hz, 2H), 1.79 (dq, $J = 7.5, 1.5$ Hz, 4H), 1.14 (t, $J = 7.0$ Hz, 3H), 0.75 (t, $J = 7.5$ Hz, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 152.0 (C), 135.9 (C), 130.7 (CH), 130.2 (CH), 126.8 (CH), 124.2 (CH), 73.0 (CH_2), 66.5 (CH_2), 47.0 (C), 28.7 (CH_2), 15.0 (CH_3), 8.8 (CH_3); ATR-FTIR (thin film): 2971, 2934, 2880, 1523, 1455, 1367, 1109, 1068, 844, 746 cm^{-1} .



3.125

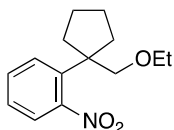
1-(1-(Ethoxymethyl)cyclopropyl)-2-nitrobenzene 3.125. The general procedure was followed using 0.97 g of alcohol **3.108** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow liquid (0.82 g, 74%). ^1H NMR (500 MHz, CDCl_3) δ 7.67 (d, $J = 8.0$ Hz, 1H), 7.59 (d, $J = 8.0$ Hz, 1H), 7.46 (t, $J = 7.5$ Hz, 1H), 7.31 (t, $J = 8.0$ Hz, 1H), 3.56 (s, 2H), 3.38 (q, $J = 7.0$ Hz, 2H), 1.07 (t, $J = 7.0$ Hz, 3H), 0.91 (t, $J = 5.5$ Hz, 2H), 0.69 (t, $J = 5.5$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.4 (C), 137.4 (C), 135.0 (CH), 131.9 (CH), 127.6 (CH), 123.6 (CH), 77.3 (CH_2), 66.4 (CH_2), 24.6 (C), 15.0 (CH_3), 11.2 (CH_2); ATR-FTIR (thin film): 2975, 2864, 1523, 1354, 1101, 1068, 1027, 866, 782, 752 cm^{-1} .



3.126

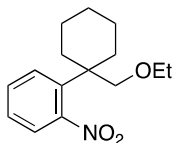
1-(1-(Ethoxymethyl)cyclobutyl)-2-nitrobenzene 3.126. The general procedure was followed using 1.04 g of alcohol **3.109** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a yellow oil (0.94 g, 80%). ^1H NMR (500 MHz, CDCl_3) δ 7.53 (d, $J = 8.0$ Hz, 1H), 7.40 (t, $J = 8.0$ Hz, 1H), 7.24 – 7.20 (m, 2H), 3.84 (s, 2H), 3.38 (q, $J = 7.0$ Hz, 2H), 2.31 (t, $J = 9.5$ Hz, 2H), 2.16 (t, $J = 10.0$ Hz, 2H), 2.02 (m, $J = 10$ Hz, 1H), 1.69 (m, $J = 10$ Hz, 1H), 1.06 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 149.0 (C), 142.4 (C), 131.3 (CH), 131.2 (CH), 126.5 (CH), 123.5 (CH), 75.7 (CH_2), 66.8 (CH_2), 46.3 (C), 30.7 (CH_2), 15.9 (CH_2),

14.9 (CH₃); ATR-FTIR (thin film): 2974, 2934, 2869, 1523, 1365, 1108, 909, 781, 753, 730 cm⁻¹.



3.127

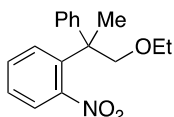
1-(1-(Ethoxymethyl)cyclopentyl)-2-nitrobenzene 3.127. The general procedure was followed using 1.11 g of alcohol **3.110** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a yellow oil (1.01 g, 81%). ¹H NMR (500 MHz, CDCl₃) δ 7.50 (d, *J* = 8.0 Hz, 1H), 7.43 – 7.39 (m, 2H), 7.28 (t, *J* = 8.5 Hz, 1H), 3.59 (s, 2H), 3.32 (q, *J* = 7.0 Hz, 2H), 2.20 (m, 2H), 1.68 (m, 6H), 1.04 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 151.2 (C), 140.3 (C), 132.5 (CH), 130.3 (CH), 126.7 (CH), 123.4 (CH), 74.6 (CH₂), 66.7 (CH₂), 52.0 (C), 34.5 (CH₂), 23.6 (CH₂), 14.9 (CH₃); ATR-FTIR (thin film): 2969, 2872, 2362, 1523, 1365, 1108, 1028, 847, 776 cm⁻¹.



3.128

1-(1-(Ethoxymethyl)cyclohexyl)-2-nitrobenzene 3.128. The general procedure was

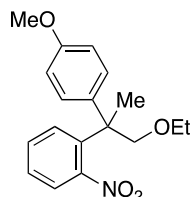
followed using 1.18 g of alcohol **3.111** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a yellow liquid (0.89 g, 68%). ^1H NMR (500 MHz, CDCl_3) δ 7.55 (d, J = 8.0 Hz, 1H), 7.42 – 7.39 (m, 1H), 7.25 (d, J = 8.0 Hz, 2H), 3.55 (s, 2H), 3.31 (q, J = 7.0 Hz, 2H), 2.13 (d, J = 14 Hz, 2H), 1.58 (t, J = 7.0 Hz, 2H), 1.53 – 1.43 (m, 3H), 1.30 – 1.20 (m, 3H), 1.01 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 152.2 (C), 134.6 (C), 132.2 (CH), 130.2 (CH), 127.1 (CH), 123.9 (CH), 78.1 (CH_2), 66.7 (CH_2), 53.5 (C), 32.9 (CH_2), 26.5 (CH_2), 22.5 (CH_2), 14.9 (CH_3); ATR-FTIR (thin film): 3009, 2972, 2873, 2819, 2362, 2335, 1529, 1418, 1369, 1113, 751 cm^{-1} .



3.129

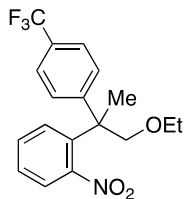
1-(1-Ethoxy-2-phenylpropan-2-yl)-2-nitrobenzene 3.129. The general procedure was followed using 1.29 g of alcohol **3.112** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow liquid (1.05 g, 74%). ^1H NMR (500 MHz, CDCl_3) δ 7.79 (d, J = 8.0 Hz, 1H), 7.51 (t, J = 7.5 Hz, 1H), 7.39 (d, J = 6.5 Hz, 1H), 7.35 – 7.31 (m, 2H), 7.27 – 7.22 (m, 3H), 7.13 (d, J = 7.0 Hz, 1H), 3.93 (d, J = 9.5 Hz, 1H), 3.78 (d, J = 10 Hz, 1H), 3.46 (q, J = 7.0 Hz, 2H), 1.85 (s, 3H), 1.15 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.6 (C), 144.9 (C), 139.6 (C), 130.9 (CH), 130.8 (CH), 128.0 (CH), 127.3 (CH), 126.9 (CH), 126.6

(CH), 124.5 (CH), 78.5 (CH₂), 66.9 (CH₂), 48.0 (C), 25.6 (CH₃), 15.0 (CH₃); ATR-FTIR (thin film): 3062, 2975, 2873, 1529, 1365, 1297, 1105, 1071, 906, 854, 770, 729 cm⁻¹.



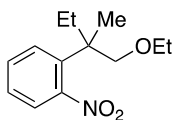
3.130

1-(1-Ethoxy-2-(4-methoxyphenyl)propan-2-yl)-2-nitrobenzene 3.130. The general procedure was followed using 1.44 g of alcohol **3.113** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a yellow liquid (1.32 g, 84%). ¹H NMR (500 MHz, CDCl₃) δ 7.78 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.50 (dt, *J* = 9.5, 1.5 Hz, 1H), 7.37 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.33 (dt, *J* = 7.5, 1.0 Hz, 1H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.79 (d, *J* = 9.0 Hz, 2H), 3.89 (d, *J* = 9.5 Hz, 1H), 3.79 (s, 3H), 3.76 (d, *J* = 9.5 Hz, 1H), 3.49 – 3.44 (m, 2H), 1.83 (s, 3H), 1.16 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 158.1 (C), 151.7 (C), 139.8 (C), 137.0 (C), 130.8 (CH), 130.7 (CH), 128.0 (CH), 127.2 (CH), 124.4 (CH), 113.2 (CH), 78.7 (CH₂), 66.8 (CH₂), 55.1 (CH₃), 47.3 (C), 25.6 (CH₃), 15.0 (CH₃); ATR-FTIR (thin film): 2974, 2900, 2873, 1609, 1529, 1512, 1365, 1294, 1249, 1184, 1105, 831, 777 cm⁻¹.



3.131

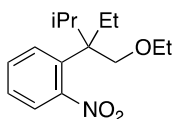
2-(2-Nitrophenyl)-2-(4-(trifluoromethyl)phenyl)propan-1-ol 3.131. The general procedure was followed using 1.63 g of alcohol **3.114** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a yellow liquid (1.05 g, 74%). ^1H NMR (500 MHz, CDCl_3) δ 7.59 (d, $J = 8.5$ Hz, 2H), 7.52 – 7.44 (m, 6H), 4.20 (q, $J = 5.5$ Hz, 2H), 3.47 (q, $J = 7.0$ Hz, 2H), 3.24 (s, 3H), 1.13 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 150.4 (C), 146.1 (C), 134.3 (C), 131.0 (CH), 130.2 (CH), 129.7 (q, $J_{\text{CF}} = 33$ Hz, C), 128.8 (CH), 127.9 (CH), 124.8 (q, $J_{\text{CF}} = 3.5$ Hz, CH), 124.1 (q, $J_{\text{CF}} = 271$ Hz, CF_3), 123.8 (CH), 82.3 (C), 73.9 (CH_2), 67.1 (CH_2), 52.4 (CH_3), 14.9 (CH_3); ^{19}F NMR (282 MHz, CDCl_3) δ –63.13; ATR-FTIR (thin film): 2973, 2933, 2871, 2364, 1532, 1375, 1329, 1158, 1122, 1073, 1018 cm^{-1} .



3.132

1-(1-Ethoxy-2-methylbutan-2-yl)-2-nitrobenzene 3.132: The general procedure was followed using 1.05 g of alcohol **3.115** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes)

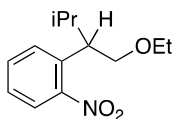
afforded the product as a yellow liquid (0.99 g, 83%). ^1H NMR (500 MHz, CDCl_3) δ 7.50 (d, J = 8.0 Hz, 1H), 7.42 (t, J = 6.0 Hz, 1H), 7.31 – 7.26 (m, 2H), 3.55 (dd, J = 10.0, 9.0 Hz, 2H), 3.40 (q, J = 7.0 Hz, 2H), 1.89 (m, J = 7.5 Hz, 1H), 1.65 (m, J = 7.5 Hz, 1H), 1.39 (s, 3H), 1.10 (t, J = 7.0 Hz, 3H), 0.75 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 152.0 (C), 136.4 (C), 130.9 (CH), 130.3 (CH), 127.0 (CH), 123.9 (CH), 78.0 (CH_2), 66.7 (CH_2), 44.0 (C), 31.2 (CH_2), 23.2 (CH_3), 14.9 (CH_3), 8.7 (CH_3); ATR-FTIR (thin film): 2974, 2933, 2877, 1527, 1484, 1460, 1369, 1109, 907, 700 cm^{-1} .



3.133

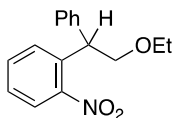
1-(3-(Ethoxymethyl)-2-methylpentan-3-yl)-2-nitrobenzene 3.133: The general procedure was followed using 1.19 g of alcohol **3.116** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow liquid (0.81 g, 61%). ^1H NMR (500 MHz, CDCl_3) δ 7.51 (d, J = 8.0 Hz, 1H), 7.43 (t, J = 7.0 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.27 (t, J = 7.5 Hz, 1H), 3.65 (t, J = 5.0 Hz, 2H), 3.37 (t, J = 7.0 Hz, 2H), 2.32 – 2.27 (m, 1H), 1.82 (q, J = 7.5 Hz, 2H), 1.14 (t, J = 7.0 Hz, 3H), 0.93 (d, J = 7.0 Hz, 3H), 0.84 (d, J = 7.0 Hz, 3H), 0.73 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 152.5 (C), 136.1 (C), 131.6 (CH), 130.1 (CH), 126.6 (CH), 124.5 (CH), 74.0 (CH_2), 66.2 (CH_2), 50.0 (C), 36.4 (CH), 28.6 (CH_2), 19.3 (CH_3), 18.0 (CH_3), 15.0 (CH_3), 9.7 (CH_3); ATR-FTIR (thin film): 2972, 2934, 2877, 1527, 1363, 1171,

1114, 1072, 852, 742 cm^{-1} .



3.134

1-(1-Ethoxy-3-methylbutan-2-yl)-2-nitrobenzene 3.134. The general procedure was followed using 1.05 g of alcohol **3.117** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow liquid (1.03 g, 87%). ^1H NMR (500 MHz, CDCl_3) δ 7.64 (d, $J = 8.0$ Hz, 1H), 7.54 (d, $J = 8.0$ Hz, 1H), 7.50 (t, $J = 7.5$ Hz, 1H), 7.30 (t, $J = 6.5$ Hz, 1H), 3.66 (ddd, $J = 28, 7.0, 4.0$ Hz, 2H), 3.41 – 3.34 (m, 2H), 3.09 – 3.05 (m, 1H), 2.11 – 2.07 (m, 1H), 1.09 (t, $J = 7.0$ Hz, 3H), 1.04 (d, $J = 6.5$ Hz, 3H), 0.74 (d, $J = 6.5$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 151.6 (C), 137.7 (C), 131.7 (CH), 129.5 (CH), 126.6 (CH), 123.4 (CH), 71.7 (CH₂), 66.4 (CH₂), 46.2 (CH), 30.1 (CH), 21.3 (CH₃), 20.6 (CH₃), 15.0 (CH₃); ATR-FTIR (thin film): 2960, 2925, 2871, 1607, 1525, 1464, 1355, 1112, 856, 781 cm^{-1} .



3.135

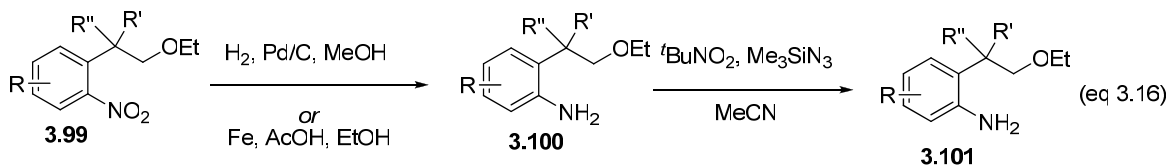
1-(2-Ethoxy-1-phenylethyl)-2-nitrobenzene 3.135. The general procedure was followed

using 1.21 g of alcohol **3.118** (5.00 mmol), 2.42 mL of ethyl iodide, 1.20 g of NaH (30.0 mmol) and 25.0 mL of DMF. Purification by MPLC (0:100 – 2:98 EtOAc:hexanes) afforded the product as a light yellow liquid (1.08 g, 80%). ^1H NMR (500 MHz, CDCl_3) δ 7.78 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.53 (dt, $J = 8.0, 1.5$ Hz, 1H), 7.46 (dd, $J = 7.5, 1.0$ Hz, 1H), 7.35 (dt, $J = 8.0, 1.0$ Hz, 1H), 7.33 – 7.32 (m, 2H), 7.24 (d, $J = 8.0$ Hz, 2H), 5.04 (t, $J = 7.0$ Hz, 1H), 3.96 (d, $J = 7.5$ Hz, 2H), 3.55 – 3.48 (m, 2H), 1.16 (t, $J = 7.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 150.5 (C), 140.4 (C), 136.5 (C), 132.3 (CH), 130.1 (CH), 128.53 (CH), 128.51 (CH), 127.2 (CH), 126.9 (CH), 124.3 (CH), 72.9 (CH_2), 66.5 (CH_2), 44.8 (CH), 15.0 (CH_3); ATR-FTIR (thin film): 3064, 2975, 2869, 1577, 1522, 1451, 1354, 1298, 1108, 1077, 856, 741, 699 cm^{-1} .

3.6.5.4 Preparation of the Aryl Azide Substrates through Hydrogenation/Azidation Sequence

General Procedure.

Following the procedure of Zhang and Moses,³³ the azides were prepared as the route outlined in equation 3.16. Yields were not optimized.



The hydrogenation reaction was carried out followed either way:

Procedure A: A mixture of nitroarene **3.99** and Pd/C (Pd, 10 wt % on carbon powder) in MeOH was vigorously stirred at room temperature under a hydrogen atmosphere. After 3 hours, visualization of the reaction progress using TLC indicated consumption of the starting material.

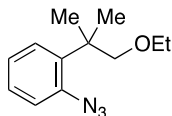
The mixture then was filtered through a pad of Celite, and the filtrate was concentrated *in vacuo* to afford crude aniline, which was subjected to the *t*-BuNO₂-mediated azidation reaction without further purification.

Procedure B: A mixture of nitroarene **3.99** and Fe powder (5 equiv) in a 1:1 v/v of acetic acid and ethanol was refluxed at 80 °C. After 2 hours, visualization of the reaction progress using TLC indicated consumption of the starting material. The mixture then was neutralized with Na₂CO₃ and extracted with 3 × 20 mL of diethyl ether. The combined organic phases were dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo* to afford crude aniline, which was subjected to the *t*-BuNO₂-mediated azidation reaction without further purification.

Preparation of aryl azide from aniline:³⁴

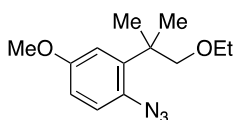
To a cooled solution of aniline in MeCN (0.2 M) was added dropwise *t*-BuNO₂ (4 equiv) and Me₃SiN₃ (3 equiv). The resulting solution was warmed to room temperature. After 2 hours, visualization of the reaction progress using TLC indicated the consumption of the starting material. De-ionized H₂O was then added to the reaction mixture. The mixture then was extracted with 2 × 30 mL of CH₂Cl₂. The combined organic phases were washed with 20 mL of brine. The resulting organic phase was dried over Na₂SO₄, filtered, and the filtrate was concentrated *in vacuo*. Purification of the residue by MPLC afforded azide.

Synthesis



3.6

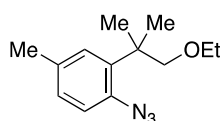
1-Azido-2-(1-ethoxy-2-methylpropan-2-yl)benzene 3.6. The general procedure was following using crude aniline (derived from 2 mmol of nitro **3.119** through procedure A), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.39 g, 90% from **3.119**). ¹H NMR (500 MHz, CDCl₃) δ 7.39 (dd, *J* = 8.0, 1.5 Hz, 1H), 7.28 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.17 (dd, *J* = 8.0, 1.0 Hz, 1H), 7.12 (dt, *J* = 7.5, 1.5 Hz, 1H), 3.70 (s, 2H), 3.48 (q, *J* = 7.0 Hz, 2H), 1.43 (s, 6H), 1.16 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 138.0 (C), 137.7 (C), 128.8 (CH), 127.5 (CH), 124.8 (CH), 119.4 (CH), 78.1 (CH₂), 66.7 (CH₂), 39.8 (C), 25.4 (CH₃), 15.1 (CH₃). ATR-FTIR (thin film): 2964, 2929, 2861, 2122, 2083, 1707, 1602, 1455, 1387, 1206, 742 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₂H₁₇N₃O (M)⁺: 219.1372, found: 219.1365.



3.10

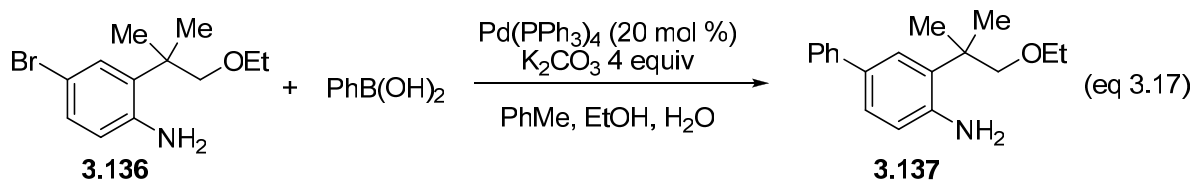
1-Azido-2-(1-ethoxy-2-methylpropan-2-yl)-4-methoxybenzene 3.10. The general procedure was following using crude aniline (derived from 2 mmol of nitro **3.120** through procedure A), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.40 g, 81% from **3.120**). ¹H NMR

(500 MHz, CDCl₃) δ 7.07 (d, J = 8.5 Hz, 1H), 6.96 (d, J = 3.0 Hz, 1H), 6.79 (dd, J = 8.5, 3.0 Hz, 1H), 3.79 (s, 2H), 3.67 (s, 2H), 3.47 (q, J = 7.0 Hz, 2H), 1.39 (s, 6H), 1.15 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 156.7 (C), 139.5 (C), 130.2 (C), 120.2 (CH), 115.7 (CH), 111.6 (CH), 78.0 (CH₂), 66.7 (CH₂), 55.4 (CH₂), 39.9 (C), 25.3 (CH₃), 15.1 (CH₃). ATR-FTIR (thin film): 2968, 2934, 2867, 2109, 1603, 1577, 1484, 1291, 1243, 1107, 1044 cm⁻¹; HRMS (EI) m/z calculated for C₁₃H₁₉N₃O₂ (M)⁺: 249.1477, found: 249.1482.

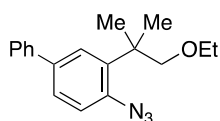


3.12

1-Azido-2-(1-ethoxy-2-methylpropan-2-yl)-4-methylbenzene 3.12. The general procedure was following using crude aniline (derived from 2 mmol of nitroarene **3.121** through procedure A), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.33 g, 71% from **3.121**). ¹H NMR (500 MHz, CDCl₃) δ 7.16 (s, 1H), 7.05 (dd, J = 4.0, 2.5 Hz, 2H), 3.67 (s, 2H), 3.47 (q, J = 7.0 Hz, 2H), 2.33 (s, 3H), 1.39 (s, 6H), 1.15 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 137.6 (C), 134.2 (C), 129.6 (CH), 128.0 (CH), 122.9 (C), 119.3 (CH), 78.0 (CH₂), 66.7 (CH₂), 39.7 (C), 27.5 (CH₃), 25.4 (CH₃), 21.1 (CH₃). ATR-FTIR (thin film): 2968, 2866, 2110, 1492, 1382, 1299, 1282, 1106, 1072, 990, 806, 645 cm⁻¹; HRMS (EI) m/z calculated for C₁₃H₁₉N₃O (M)⁺: 233.1528, found: 233.1533.



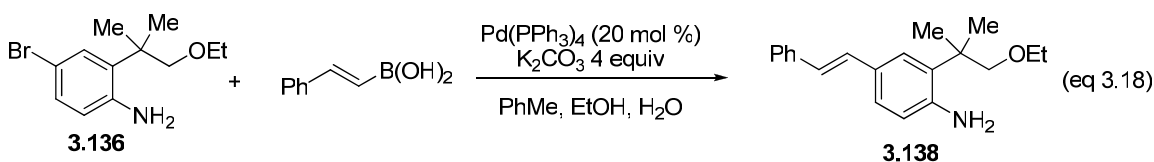
3-(1-Ethoxy-2-methylpropan-2-yl)biphenyl-4-amine 3.137. The coupling reaction procedure of Driver and co-workers³⁴ was followed using 0.542 g of aniline **3.136** (2 mmol), 0.354 g of phenylboronic acid (2.9 mmol), K₂CO₃ (1.1 g) and 0.105 g of Pd(PPh₃)₄ (0.2 equiv). Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product aniline **3.137** as a brown oil (0.43 g, 80%). ¹H NMR (500 MHz, CDCl₃) δ 7.74 (d, *J* = 7.0 Hz, 2H), 7.68 (d, *J* = 2.0 Hz, 1H), 7.57 (t, *J* = 7.5 Hz, 2H), 7.47 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.43 (t, *J* = 7.0, 1H), 6.85 (d, *J* = 8.0 Hz, 1H), 4.85 (s, 2H), 3.72 (s, 2H), 3.65 (q, *J* = 7.0 Hz, 2H), 1.69 (s, 6H), 1.38 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 146.1 (C), 142.1 (C), 132.2 (CH), 128.9 (CH), 126.8 (CH), 126.7 (CH), 126.3 (CH), 126.1 (CH), 118.7 (CH), 115.7 (C), 81.5 (CH₂), 67.1 (CH₂), 39.4 (C), 25.8 (CH₃), 15.3 (CH₃); ATR-FTIR (thin film): 3337 3236, 3013, 2934, 2877, 1563, 1521, 1423, 1245, 1108, 978, 956, 826, 729 cm⁻¹.



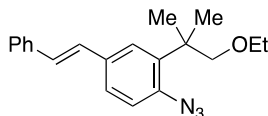
3.14

4-Azido-3-(1-ethoxy-2-methylpropan-2-yl)biphenyl 3.14. The general procedure was following using 2 mmol of aniline **3.137**, 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.48 g, 82%). ¹H NMR (500 MHz, CDCl₃) δ 7.71 (d, *J* = 2.0 Hz, 1H), 7.66 (d, *J* = 8.5 Hz, 2H), 7.55 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.52 (t, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.0 Hz,

1H), 3.81 (s, 2H), 3.58 (q, $J = 7.0$ Hz, 2H), 1.56 (s, 6H), 1.26 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.9 (C), 138.3 (C), 137.7 (C), 137.1 (C), 128.9 (CH), 128.0 (CH), 127.3 (CH), 127.1 (CH), 126.2 (CH), 120.0 (CH), 78.2 (CH_2), 66.9 (CH_2), 40.1 (C), 25.6 (CH_3), 15.3 (CH_3). ATR-FTIR (thin film): 2970, 2929, 2867, 2119, 2100, 1481, 1288, 1106, 1072, 890, 818, 759 cm^{-1} ; HRMS (EI) m/z calculated for $\text{C}_{18}\text{H}_{21}\text{N}_3\text{O}$ (M^+): 295.1685, found 295.1691.

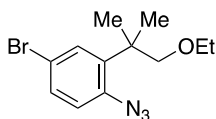


(E)-2-(1-Ethoxy-2-methylpropan-2-yl)-4-styrylaniline 3.138. The coupling reaction procedure of Driver and co-workers¹⁷ was followed using 0.542 g of aniline **3.136** (2 mmol), 0.429 g of styrylboronic acid (2.9 mmol), K_2CO_3 (1.1 g) and 0.105 g of $\text{Pd}(\text{PPh}_3)_4$ (0.2 equiv). Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product aniline **3.138** as a brown oil (0.42 g, 78%). ^1H NMR (500 MHz, CDCl_3) δ 7.53 (d, $J = 7.0$ Hz, 2H), 7.41 (d, $J = 1.5$ Hz, 1H), 7.38 (t, $J = 7.5$ Hz, 2H), 7.30 (dd, $J = 8.0, 1.5$ Hz, 1H), 7.25 (t, $J = 7.5$, 1H), 7.10 (d, $J = 16.0$ Hz, 1H), 6.95 (d, $J = 16.5$ Hz, 1H), 6.66 (d, $J = 8.5$ Hz, 1H), 4.73 (s, 2H), 3.58 (s, 2H), 3.54 (q, $J = 7.0$ Hz, 2H), 1.54 (s, 6H), 1.26 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 146.5 (C), 138.2 (C), 131.8 (C), 129.4 (CH), 128.6 (CH), 127.4 (C), 126.8 (CH), 126.7 (CH), 126.1 (CH), 125.2 (CH), 124.5 (CH), 118.3 (CH), 81.4 (CH_2), 66.9 (CH_2), 39.1 (C), 25.6 (CH_3), 15.1 (CH_3); ATR-FTIR (thin film): 3336, 3299, 3023, 2973, 2873, 1593, 1500, 1411, 1271, 1103, 959, 906, 815, 729 cm^{-1} .



3.16

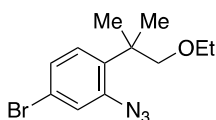
(E)-1-Azido-2-(1-ethoxy-2-methylpropan-2-yl)-4-styrylbenzene 3.16. The general procedure was following using 2 mmol of aniline **3.12-3**, 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow solid (0.52 g, 83%). ¹H NMR (500 MHz, CDCl₃) δ 7.54 (d, *J* = 7.0 Hz, 3H), 7.45 (dd, *J* = 8.0, 2.0 Hz, 1H), 7.39 (t, *J* = 7.5 Hz, 2H), 7.28 (dd, *J* = 15.0, 7.5 Hz, 1H), 7.16 (d, *J* = 8.0 Hz, 1H), 7.09 (dd, *J* = 21.5, 16.0 Hz, 2H), 3.74 (s, 2H), 3.53 (q, *J* = 7.0 Hz, 2H), 1.48 (s, 6H), 1.20 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 138.1 (C), 137.5 (C), 136.9 (C), 134.0 (C), 128.8 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 127.6 (CH), 126.6 (CH), 125.4 (CH), 119.9 (CH), 78.1 (CH₂), 66.8 (CH₂), 39.9 (C), 25.5 (CH₃), 15.3 (CH₃). ATR-FTIR (thin film): 3025, 2969, 2866, 2112, 2073, 1595, 1487, 1381, 1291, 1105, 1070, 958, 808, 690 cm⁻¹; HRMS (EI) *m/z* calculated for C₂₀H₂₃N₃O (M)⁺: 321.1841, found: 321.1835.



3.18

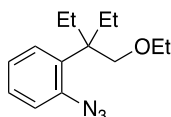
1-Azido-4-bromo-2-(1-ethoxy-2-methylpropan-2-yl)benzene 3.18. The general procedure was following using crude aniline (derived from 2 mmol of nitroarene **3.122** through procedure B), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.36 g, 61% from **3.122**). ¹H NMR (500 MHz, CDCl₃) δ 7.46 (d, *J* = 2.5 Hz, 1H), 7.36 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.00 (d, *J* = 8.5 Hz,

1H), 3.64 (s, 2H), 3.46 (q, $J = 7.0$ Hz, 2H), 1.37 (s, 6H), 1.14 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 140.1 (C), 137.0 (C), 132.2 (CH), 130.3 (CH), 120.8 (CH), 118.1 (C), 77.7 (CH_2), 66.8 (CH_2), 40.0 (C), 25.3 (CH_3), 15.0 (CH_3). ATR-FTIR (thin film): 2972, 2867, 2122, 2094, 1482, 1382, 1293, 1109, 1074, 880, 806 cm^{-1} ; HRMS (EI) m/z calculated for $\text{C}_{12}\text{H}_{16}\text{BrN}_3\text{O}$ (M^+): 297.0477, found: 297.0472.



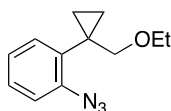
3.20

2-Azido-4-bromo-1-(1-ethoxy-2-methylpropan-2-yl)benzene 3.20. The general procedure was following using crude aniline (derived from 2 mmol of nitroarene **3.123** through procedure B), 0.95 mL of $t\text{-BuNO}_2$, and 0.84 mL of Me_3SiN_3 . Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.34 g, 57% from **3.123**). ^1H NMR (500 MHz, CDCl_3) δ 7.27 (d, $J = 2.0$ Hz, 1H), 7.23 (d, $J = 8.0$ Hz, 1H), 7.20 (dd, $J = 8.5, 2.0$ Hz, 1H), 3.65 (s, 2H), 3.46 (q, $J = 7.0$ Hz, 2H), 1.39 (s, 6H), 1.14 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 139.2 (C), 137.1 (C), 130.4 (CH), 127.8 (CH), 122.2 (CH), 120.6 (C), 77.8 (CH_2), 66.8 (CH_2), 39.7 (C), 25.3 (CH_3), 15.1 (CH_3). ATR-FTIR (thin film): 2973, 2929, 2866, 2093, 1584, 1559, 1482, 1382, 1282, 1107, 867, 810, 739 cm^{-1} ; HRMS (EI) m/z calculated for $\text{C}_{12}\text{H}_{16}\text{BrN}_3\text{O}$ (M^+): 297.0477, found: 297.0482.



3.25

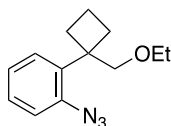
1-Azido-2-(3-(ethoxymethyl)pentan-3-yl)benzene. The general procedure was following using crude aniline (derived from 2 mmol of nitroarene **3.124** through procedure A), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.41 g, 82% from **3.124**). ¹H NMR (500 MHz, CDCl₃) δ 7.28 – 7.23 (m, 2H), 7.17 (dd, *J* = 7.5, 1.5 Hz, 1H), 7.10 (dt, *J* = 7.5, 1.5 Hz, 1H), 3.74 (s, 2H), 3.52 (q, *J* = 7.0 Hz, 2H), 2.06 (m, *J* = 7.5 Hz, 2H), 1.89 (m, *J* = 7.5 Hz, 2H), 1.21 (t, *J* = 8.0 Hz, 3H), 0.68 (t, *J* = 7.0 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 137.7 (C), 135.8 (C), 130.0 (CH), 127.3 (CH), 124.6 (CH), 119.4 (CH), 72.5 (CH₂), 66.7 (CH₂), 46.1 (C), 26.9 (CH₂), 15.2 (CH₃), 8.8 (CH₃). ATR-FTIR (thin film): 2967, 2933, 2875, 2119, 2083, 1574, 1468, 1441, 1283, 1109, 1073 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₄H₂₁N₃O (M)⁺: 247.1685, found: 247.1676.



3.55

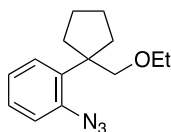
1-Azido-2-(1-(ethoxymethyl)cyclopropyl)benzene 3.55. The general procedure was following using crude aniline (derived from 2 mmol of nitro **3.125** through procedure A), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.30 g, 69% from **3.125**). ¹H NMR (500 MHz, CDCl₃) δ 7.36 (d, *J* = 7.5 Hz, 1H), 7.28 (t, *J* = 7.5 Hz, 1H), 7.13 (d, *J* = 8.0 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 3.52 (s, 2H), 3.43 (q, *J* = 7.0 Hz, 2H), 1.10 (t, *J* = 7.0 Hz, 3H), 0.89 (s, 2H), 0.80 (s, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 139.7 (C), 134.4 (C), 132.7 (CH), 128.0 (CH), 124.5 (CH), 118.3 (CH), 76.7 (CH₂), 66.2 (CH₂), 23.6 (C), 15.1 (CH₂), 10.9 (CH₂). ATR-FTIR (thin film): 3075, 3007, 2974, 2861, 2120, 2083, 1575, 1489, 1443, 1290, 1104, 750 cm⁻¹; HRMS (EI) *m/z*

calculated for $C_{12}H_{15}N_3O$ (M)⁺: 217.1215, found: 217.1211.



3.27

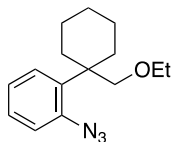
1-Azido-2-(1-(ethoxymethyl)cyclobutyl)benzene 3.27. The general procedure was following using crude aniline (derived from 2 mmol of nitroarene **3.126** through procedure A), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.31 g, 67% from **3.126**). ¹H NMR (500 MHz, CDCl₃) δ 7.26 – 7.22 (m, 1H), 7.13 – 7.07 (m, 3H), 3.67 (s, 2H), 3.37 (q, *J* = 7.0 Hz, 2H), 2.40 – 2.32 (m, 4H), 2.12 – 2.02 (m, 1H), 1.83 – 1.67 (m, 1H), 1.08 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 139.0 (C), 136.8 (C), 129.2 (CH), 127.2 (CH), 124.3 (CH), 118.4 (CH), 75.9 (CH₂), 66.9 (CH₂), 46.5 (C), 30.9 (CH₂), 16.7 (CH₂), 15.0 (CH₃). ATR-FTIR (thin film): 2974, 2953, 2866, 2117, 2080, 1577, 1486, 1442, 1290, 1106, 749 cm⁻¹; HRMS (EI) *m/z* calculated for $C_{13}H_{17}N_3O$ (M)⁺: 231.1372, found: 231.1363.



3.29

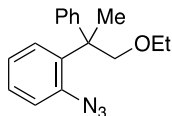
1-Azido-2-(1-(ethoxymethyl)cyclopentyl)benzene 3.29. The general procedure was following using crude aniline (derived from 2 mmol of nitroarene **3.127** through procedure A), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.26 g, 54% from **3.127**). ¹H NMR (500 MHz,

CDCl₃) δ 7.33 (dd, J = 8.0, 1.5 Hz, 1H), 7.24 (dd, J = 7.0, 1.5 Hz, 1H), 7.14 (dd, J = 8.0, 1.5 Hz, 1H), 7.08 (dt, J = 7.5, 1.5 Hz, 1H), 3.54 (s, 2H), 3.30 (q, J = 7.0 Hz, 2H), 2.16 – 2.14 (m, 2H), 1.90 – 1.86 (m, 2H), 1.69 (m, 4H), 1.02 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 138.6 (C), 137.6 (C), 129.8 (CH), 127.3 (CH), 124.4 (CH), 119.0 (CH), 74.7 (CH₂), 66.7 (CH₂), 51.5 (C), 35.0 (CH₂), 24.1 (CH₂), 15.0 (CH₃). ATR-FTIR (thin film): 2951, 2870, 2119, 2083, 1480, 1288, 1106, 906 cm⁻¹; HRMS (EI) m/z calculated for C₁₄H₁₉N₃O (M)⁺: 245.1528, found: 245.1525.



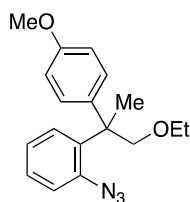
3.31

1-Azido-2-(1-(ethoxymethyl)cyclohexyl)benzene 3.31. The general procedure was following using crude aniline (derived from 2 mmol of nitroarene **3.128** through procedure A), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.37 g, 72% from **3.128**). ¹H NMR (500 MHz, CDCl₃) δ 7.41 (d, J = 8.0, 1H), 7.26 (t, J = 7.5 Hz, 1H), 7.16 (d, J = 8.0 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 3.65 (s, 2H), 3.35 (q, J = 7.0 Hz, 2H), 2.41 – 2.38 (m, 2H), 1.79 – 1.74 (m, 2H), 1.59 – 1.37 (m, 6H), 1.06 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 137.8 (C), 135.8 (C), 131.1 (CH), 127.3 (CH), 124.6 (CH), 119.7 (CH), 76.3 (CH₂), 66.8 (CH₂), 44.0 (C), 32.6 (CH₂), 26.5 (CH₂), 22.5 (CH₂), 15.0 (CH₃). ATR-FTIR (thin film): 2974, 2926, 2856, 2119, 2080, 1485, 1444, 1284, 1101, 977, 907, 749 cm⁻¹; HRMS (EI) m/z calculated for C₁₅H₂₁N₃O (M)⁺: 259.1685, found: 259.1691.



3.33

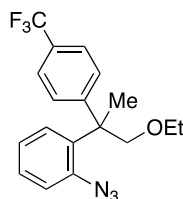
1-Azido-2-(1-ethoxy-2-phenylpropan-2-yl)benzene 3.33. The general procedure was following using crude aniline (derived from 2 mmol of nitroarene **3.129** through procedure A), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.36 g, 64% from **3.129**). ¹H NMR (500 MHz, CDCl₃) δ 7.60 (d, *J* = 8.0 Hz, 1H), 7.32 – 7.27 (m, 2H), 7.24 (s, 1H), 7.20 – 7.17 (m, 2H), 7.13 (d, *J* = 7.0 Hz, 2H), 7.08 (d, *J* = 8.0 Hz, 1H), 3.94 (d, *J* = 9.5 Hz, 1H), 3.72 (d, *J* = 9.5 Hz, 1H), 3.50 – 3.46 (m, 2H), 1.80 (s, 3H), 1.17 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 147.3 (C), 138.2 (C), 138.0 (C), 129.2 (CH), 127.9 (CH), 127.8 (CH), 126.6 (CH), 125.7 (CH), 124.6 (CH), 119.7 (CH), 78.3 (CH₂), 66.8 (CH₂), 47.3 (C), 23.9 (CH₃), 15.0 (CH₃). ATR-FTIR (thin film): 3058, 2974, 2866, 2119, 2086, 1575, 1484, 1443, 1283, 1071, 697 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₇H₁₉N₃O (M)⁺: 281.1528, found: 281.1533.



3.35

1-Azido-2-(1-ethoxy-2-(4-methoxyphenyl)propan-2-yl)benzene 3.35. The general procedure was following using crude aniline (derived from 2 mmol of nitroarene **3.130** through procedure B), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.48 g, 77% from **3.130**). ¹H NMR

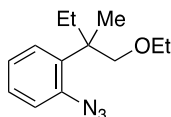
(500 MHz, CDCl₃) δ 7.63 (d, J = 7.0 Hz, 1H), 7.32 (t, J = 7.0 Hz, 1H), 7.21 (t, J = 7.0 Hz, 1H), 7.13 – 7.09 (m, 3H), 6.84 (d, J = 8.5 Hz, 2H), 3.96 (d, J = 9.5 Hz, 1H), 3.82 (s, 3H), 3.74 (d, J = 9.5 Hz, 1H), 3.53 (q, J = 7.0 Hz, 2H), 1.84 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 157.5 (C), 139.4 (C), 138.2 (C), 138.1 (C), 129.2 (CH), 127.7 (CH), 127.6 (CH), 124.6 (CH), 119.6 (CH), 113.2 (CH), 78.6 (CH₂), 66.8 (CH₂), 55.2 (CH₃), 46.7 (C), 24.0 (CH₃), 15.1 (CH₃). ATR-FTIR (thin film): 2973, 2868, 2119, 2086, 1609, 1510, 1441, 1284, 1246, 1105, 1034, 827, 751 cm⁻¹; HRMS (EI) m/z calculated for C₁₈H₂₁N₃O₂ (M)⁺: 311.1634, found: 311.1636.



3.37

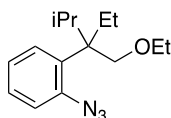
1-Azido-2-(1-ethoxy-2-(4-(trifluoromethyl)phenyl)propan-2-yl)benzene 3.37. The general procedure was following using crude aniline (derived from 2 mmol of nitroarene **3.131** through procedure A), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.36 g, 51% from **3.131**). ¹H NMR (500 MHz, CDCl₃) δ 7.84 (d, J = 8.0 Hz, 1H), 7.54 (d, J = 8.0 Hz, 2H), 7.43 (d, J = 8.5 Hz, 2H), 7.37 (t, J = 7.5 Hz, 1H), 7.23 (t, J = 7.5 Hz, 1H), 7.11 (d, J = 8.0 Hz, 1H), 4.27 (q, J = 10.5 Hz, 2H), 3.55 – 3.42 (m, 2H), 3.22 (s, 3H), 1.11 (t, J = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 146.9 (C), 137.4 (C), 132.7 (C), 129.7 (CH), 129.2 (CH), 129.0 (C), 127.6 (CH), 124.6 (CH), 124.5 (q, J_{CF} = 3.5 Hz, CH), 124.3 (q, J_{CF} = 270 Hz, CF₃), 119.3 (CH), 81.3 (C), 72.3 (CH₂), 67.2 (CH₂), 51.6 (CH₃), 14.9 (CH₃); ¹⁹F NMR (282 MHz, CDCl₃) δ -63.01. ATR-FTIR

(thin film): 2976, 2934, 2872, 2122, 2086, 1578, 1482, 1298, 1162, 1084, 1017 cm^{-1} ; HRMS (EI) m/z calculated for $\text{C}_{17}\text{H}_{15}\text{F}_3\text{NO}$ $[\text{M}-\text{N}_2-\text{CH}_3]^+$: 306.1106, found: 306.0845.



3.39

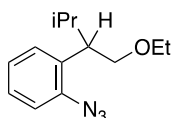
1-Azido-2-(1-ethoxy-2-methylbutan-2-yl)benzene 3.39. The general procedure was following using crude aniline (derived from 2 mmol of nitroarene **3.132** through procedure A), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.35 g, 76% from **3.132**). ¹H NMR (500 MHz, CDCl₃) δ 7.40 (dd, J = 8.0, 1.5 Hz, 1H), 7.31 (dt, J = 7.5, 1.5 Hz, 1H), 7.21 (dd, J = 8.0, 1.0 Hz, 1H), 7.16 (dt, J = 7.5, 1.5 Hz, 1H), 3.93 (d, J = 9.0 Hz, 1H), 3.65 (d, J = 9.0 Hz, 1H), 3.54 (m, J = 7.0 Hz, 2H), 2.25 (m, J = 7.5 Hz, 1H), 1.82 (m, J = 7.5 Hz, 1H), 1.52 (s, 3H), 1.22 (t, J = 7.0 Hz, 3H), 0.75 (t, J = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 137.7 (C), 136.4 (C), 130.0 (CH), 127.5 (CH), 124.8 (CH), 119.3 (CH), 77.4 (CH₂), 66.8 (CH₂), 43.6 (C), 29.1 (CH₂), 23.1 (CH₃), 15.2 (CH₃), 8.8 (CH₃). ATR-FTIR (thin film): 2971, 2932, 2868, 2119, 2082, 1486, 1283, 1108, 908, 749 cm^{-1} ; HRMS (EI) m/z calculated for $\text{C}_{13}\text{H}_{19}\text{N}_3\text{O}$ (M)⁺: 233.1528, found: 233.1523.



3.41

1-Azido-2-(3-(ethoxymethyl)-2-methylpentan-3-yl)benzene 3.41. The general

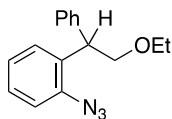
procedure was following using crude aniline (derived from 1 mmol of nitroarene **3.133** through procedure A), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃ at room temperature. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.18 g, 68% from **3.133**). ¹H NMR (500 MHz, CDCl₃) δ 7.36 (d, *J* = 8.0 Hz, 1H), 7.27 (t, *J* = 7.5 Hz, 1H), 7.18 (d, *J* = 7.5 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 3.86 (d, *J* = 9.5 Hz, 1H), 3.74 (d, *J* = 9.5 Hz, 1H), 3.56 – 3.48 (m, 2H), 2.58 (m, *J* = 7.0 Hz, 1H), 2.28 (m, *J* = 7.0 Hz, 1H), 1.79 (m, *J* = 7.5 Hz, 1H), 1.24 (t, *J* = 7.0 Hz, 3H), 1.00 (d, *J* = 7.0 Hz, 3H), 0.78 (d, *J* = 7.0 Hz, 3H), 0.68 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 137.7 (C), 136.0 (C), 130.9 (CH), 127.1 (CH), 124.4 (CH), 119.3 (CH), 74.0 (CH₂), 66.5 (CH₂), 49.1 (C), 34.6 (CH), 27.0 (CH₂), 19.6 (CH₃), 17.9 (CH₃), 15.3 (CH₃), 10.0 (CH₃). ATR-FTIR (thin film): 2967, 2875, 2119, 2085, 1483, 1286, 1112, 1071, 907, 731 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₅H₂₃N₃O (M)⁺: 261.1841, found: 261.1849.



3.43

1-Azido-2-(1-ethoxy-3-methylbutan-2-yl)benzene 3.43. The general procedure was following using crude aniline (derived from 2 mmol of nitroarene **3.134** through procedure A), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.38 g, 81% from **3.134**). ¹H NMR (500 MHz, CDCl₃) δ 7.30 – 7.24 (m, 2H), 7.16 – 7.10 (m, 2H), 3.70 – 3.66 (m, 2H), 3.47 – 3.40 (m, 2H), 2.07 – 2.00 (m, 1H), 1.14 (dt, *J* = 7.0, 2.0 Hz, 3H), 1.03 (dd, *J* = 7.0, 2.5 Hz, 3H), 0.78 (dd, *J* = 6.5, 2.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 138.3 (C), 135.1 (C), 129.0 (CH), 127.1 (CH),

124.5 (CH), 118.0 (CH), 72.1 (CH₂), 66.3 (CH₂), 45.7 (C), 30.4 (CH), 20.9 (CH₃), 20.8 (CH₃), 15.1 (CH₃). ATR-FTIR (thin film): 2961, 2869, 2118, 1579, 1488, 1283, 1108, 908, 749 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₃H₁₉N₃O (M)⁺: 233.1528, found: 233.1530.

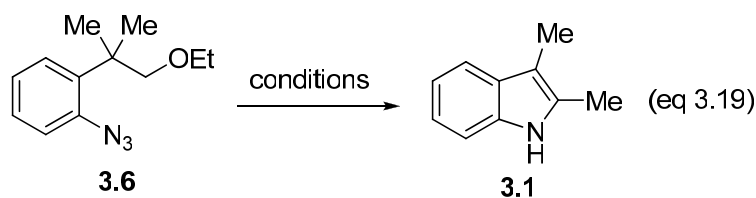


3.45

1-Azido-2-(2-ethoxy-1-phenylethyl)benzene 3.45. The general procedure was following using crude aniline (derived from 2 mmol of nitroarene **3.135** through procedure A), 0.95 mL of *t*-BuNO₂, and 0.84 mL of Me₃SiN₃. Purification by MPLC (0:100 – 10:90 EtOAc: hexanes) afforded the product as a yellow oil (0.35 g, 66% from **3.135**). ¹H NMR (500 MHz, CDCl₃) δ 7.33 – 7.26 (m, 6H), 7.22 (t, *J* = 7.5 Hz, 1H), 7.14 (dd, *J* = 15, 7.5 Hz, 2H), 4.66 (t, *J* = 7.5 Hz, 1H), 3.97 – 3.90 (m, 2H), 3.55 (q, *J* = 7.0 Hz, 2H), 1.19 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 141.6 (C), 138.2 (C), 133.4 (C), 128.9 (CH), 128.4 (CH), 128.3 (CH), 127.7 (CH), 126.4 (CH), 124.7 (CH), 118.3 (CH), 72.8 (CH₂), 66.4 (CH₂), 44.8 (CH), 15.1 (CH₃). ATR-FTIR (thin film): 3061, 3027, 2974, 2863, 2118, 1580, 1487, 1449, 1281, 1109, 748, 697 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₆H₁₇N₃O (M)⁺: 267.1372, found: 267.1365.

3.6.6 Iron-Catalyzed Formation of Indoles from Aryl Azides.

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



To a mixture of 0.0219 g of aryl azide **3.6** (0.1 mmol), and a metal salt (0 – 100 mol %) in a Schlenk tube was added solvent. The resulting mixture was heated, and after 16 h, the heterogenous mixture was filtered through a short pad of Al₂O₃. The filtrate was concentrated *in vacuo*. The resulting oil was dissolved in 1.5 mL of CDCl₃ and 0.007 mL of dibromomethane (0.1 mmol) was added. The area of C–H peak of methyl at C-3 in **3.1** was compared to the area of CH₂Br₂ to derive a yield.

Table 3.6. Survey of Substrates.

entry	Substrate	metal salt	T (°C)	3.1 yield, % ^a
1		FeBr ₂	120	75
2		FeBr ₂	120	10

^aAs determined using ¹H NMR spectroscopy.

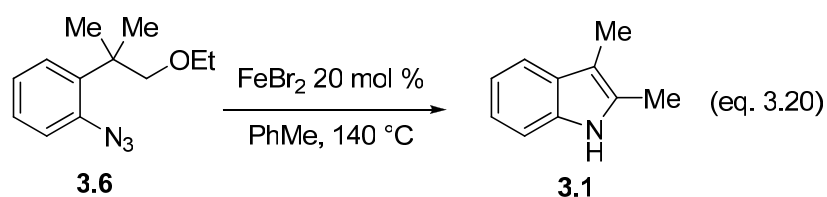
Table 3.7. Survey of Transition Metal Salts and Complexes.

entry	metal salt	mol %	solvent	T (°C)	3.1 yield, % ^a
1	none	n.a.	PhMe	120	0
2	none	n.a.	Mesitylene	220	0
3	FeBr ₂	20	PhMe (1.2 mL)	120	75
4	FeCl ₂	20	PhMe (1.2 mL)	120	0
5	FeBr ₃	20	PhMe (1.2 mL)	120	20

6	ZnI ₂	20	PhMe (1.2 mL)	120	trace
7	CuI	20	PhMe (1.2 mL)	120	0
8	RuCl ₃ · nH ₂ O	20	PhMe (1.2 mL)	120	0
9	CoTTP ^b	20	PhMe (1.2 mL)	120	0
10	Rh ₂ (esp) ₂	20	PhMe (1.2 mL)	120	0
11	FeBr ₂ + ZnI ₂	20 + 100	PhMe (1.2 mL)	120	76
12	FeBr ₂	100	PhMe (1.2 mL)	100	37
13	FeBr ₂	100	PhMe (1.2 mL)	120	72
14	FeBr ₂	100	PhMe (1.2 mL)	140	90
15	FeBr ₂	50	PhMe (1.2 mL)	140	87
16	FeBr ₂	20	PhMe (1.2 mL)	140	85
17	FeBr ₂	10	PhMe (1.2 mL)	140	16
18	FeBr ₂	20	PhMe (0.4 mL)	140	67
19	FeBr ₂	20	PhMe (0.8 mL)	140	76

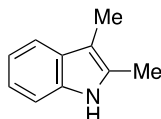
^aAs determined using ¹H NMR spectroscopy. ^bTTP = tetraphenylporphyrin.

3.6.6.2 Optimized General Procedure.



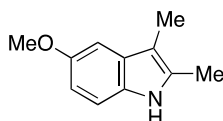
To a mixture of 0.0219 g of aryl azide **3.6** (0.10 mmol), 0.0022 g of FeBr₂ (20 mol%) in a Schlenk tube was added 1.20 mL of PhMe. The resulting mixture was heated to 140 °C. After 16 h, the heterogenous mixture was cooled to room temperature. Purification of the reaction mixture by MPLC with a pad of Al₂O₃ afforded indole (0.0132 g, 85%).

3.6.6.3 Scope and Limitations of Indoline Formation.



3.1

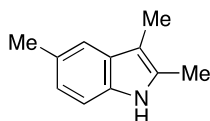
Indole 3.1.³⁵ The general procedure was followed with 0.0219 g of aryl azide **3.6** (0.10 mmol) and 0.0022 g of FeBr₂ (0.02 mmol) in 1.2 mL of toluene. Purification by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded a yellow solid product (0.0132 g, 85%). The spectral data matched that reported by Raucher and Koolpe:¹⁸ ¹H NMR (500 MHz, CDCl₃) δ 7.62 (br, 1H), 7.50 (d, *J* = 7.0 Hz, 1H), 7.26 (d, *J* = 7.0 Hz, 1H), 7.15 – 7.10 (m, 2H), 2.37 (s, 3H), 2.26 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 135.2 (C), 130.7 (C), 129.5 (C), 120.9 (CH), 119.0 (CH), 118.0 (CH), 110.0 (CH), 107.1 (C), 11.5 (CH₃), 8.5 (CH₃). ATR-FTIR (thin film): 3304, 2965, 2923, 1611, 1529, 1482, 1291, 1154, 1109, 1067, 741 cm⁻¹.



3.11

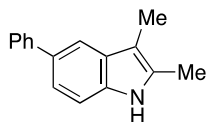
Indole 3.11.³⁶ The general procedure was followed with 0.0249 g of aryl azide **3.10** (0.10 mmol) and 0.0022 g of FeBr₂ (0.02 mmol) in 1.2 mL of toluene. Purification by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded a yellow oil product (0.0123 g, 70%). The spectral data matched that reported by Chou and co-workers:¹⁹ ¹H NMR (500 MHz, CDCl₃) δ 7.56 (br, 1H), 7.14 (d, *J* = 8.5 Hz, 1H), 6.92 (d, *J* = 2.5 Hz, 1H), 6.76 (dd, *J* = 8.5, 2.0 Hz, 1H), 3.86 (s, 3H), 2.35 (s, 3H),

2.19 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 131.6 (C), 130.3 (C), 129.9 (C), 121.5 (C), 110.6 (CH), 110.5 (CH), 107.0 (C), 100.5 (CH), 56.0 (CH_3), 11.7 (CH_3), 8.5 (CH_3). ATR-FTIR (thin film): 3274, 2933, 2836, 1684, 1654, 1520, 1463, 1415, 1361, 1285, 1210, 1044, 908 cm^{-1} .



3.13

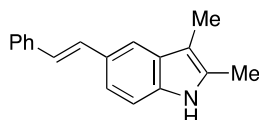
Indole 3.13.³⁷ The general procedure was followed with 0.0233 g of aryl azide **3.12** (0.10 mmol) and 0.0022 g of FeBr_2 (0.02 mmol) in 1.2 mL of toluene. Purification by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded a yellow solid product (0.0156 g, 98%). The spectral data matched that reported by Madsen and co-workers:²⁰ ^1H NMR (500 MHz, CDCl_3) δ 7.55 (br, 1H), 7.26 (s, 1H), 7.14 (d, $J = 8.5\text{ Hz}$, 1H), 6.94 (d, $J = 8.0\text{ Hz}$, 1H), 2.46 (s, 3H), 2.34 (s, 3H), 2.21 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 130.8 (C), 130.4 (C), 129.7 (C), 128.1 (C), 122.3 (CH), 117.8 (CH), 109.6 (CH), 106.7 (C), 21.5 (CH_3), 11.6 (CH_3), 8.4 (CH_3). ATR-FTIR (thin film): 3386, 2974, 2923, 2865, 1691, 1649, 1586, 1518, 1493, 1360, 1258, 1201, 1154 cm^{-1} .



3.15

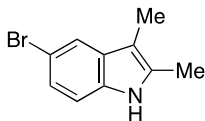
Indole 3.15. The general procedure was followed with 0.0295 g of aryl azide **3.14** (0.10

mmol) and 0.0022 g of FeBr₂ (0.02 mmol) in 1.2 mL of toluene. Purification by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded a yellow solid product (0.0188 g, 85%). ¹H NMR (500 MHz, CDCl₃) δ 7.69 – 7.68 (br m, 4H), 7.45 (t, *J* = 7.5 Hz, 2H), 7.38 (d, *J* = 8.0 Hz, 1H), 7.33 – 7.30 (m, 2H), 2.38 (s, 3H), 2.28 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 143.0 (C), 134.8 (C), 132.7 (C), 131.4 (C), 130.0 (C), 129.1 (C), 128.3 (CH), 127.4 (C), 126.1 (CH₂), 120.7 (C), 116.6 (CH), 110.2 (CH), 11.6 (CH₃), 8.5 (CH₃). ATR-FTIR (thin film): 3380, 3053, 2976, 2859, 1617, 1597, 1478, 1378, 1264, 1109, 879, 732 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₆H₁₅N (M)⁺: 221.1204, found: 221.1208.



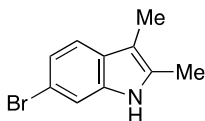
3.17

Indole 3.17. The general procedure was followed with 0.032 g of aryl azide **3.16** (0.10 mmol) and 0.0022 g of FeBr₂ (0.02 mmol) in 1.2 mL of toluene. Purification by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded a yellow solid product (0.0124 g, 50%). ¹H NMR (500 MHz, CDCl₃) δ 7.67 (br, 1H), 7.61 (s, 1H), 7.54 (d, *J* = 7.5 Hz, 2H), 7.37 (t, *J* = 7.0 Hz, 3H), 7.38 – 7.22 (m, 3H), 7.09 (d, *J* = 16.5 Hz, 1H), 2.36 (s, 3H), 2.26 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 138.2 (C), 135.1 (C), 131.4 (C), 130.5 (CH), 129.8 (C), 128.7 (C), 128.6 (CH), 126.8 (CH), 126.2 (CH), 125.5 (CH), 119.8 (CH), 116.7 (CH), 110.3 (CH), 107.6 (C), 11.6 (CH₃), 8.5 (CH₃). ATR-FTIR (thin film): 3381, 3033, 3023, 2966, 2847, 1606, 1597, 1456, 1314, 1264, 1108, 845, 790 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₈H₁₇N (M)⁺: 247.1361, found: 247.1360.



3.19

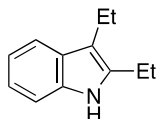
Indole 3.19.³⁸ The general procedure was followed with 0.0297 g of aryl azide **3.18** (0.10 mmol) and 0.0022 g of FeBr₂ (0.02 mmol) in 1.2 mL of toluene. Purification by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded a yellow solid product (0.0181 g, 81%). The spectral data matched that reported by De Brabander, Ready and co-workers.²¹ ¹H NMR (500 MHz, CDCl₃) δ 7.71 (br, 1H), 7.58 (d, *J* = 2.0 Hz, 1H), 7.17 (dd, *J* = 8.5, 2.0 Hz, 1H), 7.11 (d, *J* = 8.5 Hz, 1H), 2.35 (s, 3H), 2.18 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 133.8 (C), 132.1 (C), 131.3 (C), 123.6 (CH), 120.6 (CH), 112.3 (C), 111.4 (CH), 107.0 (C), 11.6 (CH₃), 8.4 (CH₃). ATR-FTIR (thin film): 3398, 2962, 2915, 1613, 1485, 1468, 1416, 1323, 1238, 1151, 1102, 905, 807 cm⁻¹.



3.21

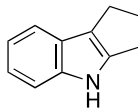
Indole 3.21.³⁹ The general procedure was followed with 0.0297 g of aryl azide **3.20** (0.10 mmol) and 2.20 mg of FeBr₂ (0.05 mmol) in 1.2 mL of toluene. Purification by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded a yellow solid product (0.0176 g, 79%). The spectral data matched that reported by Zheng and co-workers.²² ¹H NMR (500 MHz, CDCl₃) δ 7.69 (br, 1H), 7.38 (d, *J* = 2.0 Hz, 1H), 7.31 (d, *J* = 8.0 Hz, 1H), 7.17 (dd, *J* = 8.5, 1.5 Hz, 1H), 2.34 (s, 3H),

2.19 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 135.9 (C), 131.4 (C), 128.4 (C), 122.2 (CH), 119.2 (CH), 114.3 (C), 112.9 (CH), 107.4 (C), 11.6 (CH_3), 8.4 (CH_3). ATR-FTIR (thin film): 3399, 2916, 2857, 1577, 1468, 1429, 1304, 1238, 864, 798 cm^{-1} .



3.26

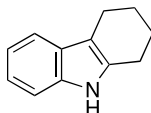
Indole 3.26.⁴⁰ The general procedure was followed with 0.0247 g of aryl azide **3.25** (0.10 mmol) and 2.20 mg of FeBr_2 (0.05 mmol) in 1.2 mL of toluene. Purification by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded a yellow solid product (0.0144 g, 83%). The spectral data matched that reported by Cabrera and co-workers:²³ ^1H NMR (500 MHz, CDCl_3) δ 7.69 (br, 1H), 7.55 (d, J = 8.0 Hz, 1H), 7.29 (d, J = 7.5 Hz, 1H), 7.14 – 7.08 (m, 2H), 2.78 (m, J = 7.5 Hz, 2H), 2.73 (m, J = 7.5 Hz, 2H), 1.30 (t, J = 7.5 Hz, 3H), 1.26 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 136.0 (C), 135.3 (C), 128.5 (C), 120.9 (CH), 119.0 (CH), 118.3 (CH), 113.2 (C), 110.3 (CH), 19.4 (CH_2), 17.3 (CH_2), 15.8 (CH_3), 14.5 (CH_3). ATR-FTIR (thin film): 3357, 2966, 2933, 2873, 1697, 1524, 1453, 1207, 907 cm^{-1} .



3.28

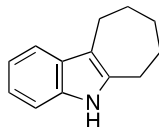
Indole 3.28.⁴¹ The general procedure was followed with 0.0231 g of aryl azide **3.27** (0.10

mmol) and 2.20 mg of FeBr₂ (0.05 mmol) in 1.2 mL of toluene. Purification by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded a yellow solid product (0.0102 g, 65%). The spectral data matched that reported by Driver and co-workers.²⁴ ¹H NMR (500 MHz, CDCl₃) δ 7.68 (br, 1H), 7.42 (d, *J* = 9.0 Hz, 1H), 7.24 (d, *J* = 8.0 Hz, 1H), 7.10 – 7.05 (m, 2H), 2.83 – 2.80 (m, 4H), 2.55 – 2.49 (m, 2H); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 25.9 (CH₂), 24.5 (CH₂). ATR-FTIR (thin film): 3404, 2955, 2927, 2854, 1577, 1535, 1468, 1450, 1366, 1313, 1089, 907, 735 cm⁻¹.



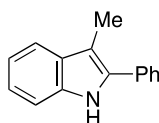
3.20

Indole 3.20.⁴² The general procedure was followed with 0.0245 g of aryl azide **3.29** (0.10 mmol) and 2.20 mg of FeBr₂ (0.05 mmol) in 1.2 mL of toluene. Purification by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded a yellow solid product (0.0118 g, 69%). The spectral data matched that reported by Driver and co-workers.²⁴ ¹H NMR (500 MHz, CDCl₃) δ 7.58 (br, 1H), 7.52 (d, *J* = 7.5 Hz, 1H), 7.28 (d, *J* = 7.5 Hz, 1H), 7.19 – 7.12 (m, 2H), 2.78 – 2.72 (m, 4H), 1.97 – 1.92 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) 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), 23.3 (CH₂), 21.0 (CH₂) only signals visible. ATR-FTIR (thin film): 3400, 2965, 2915, 1668, 1602, 1496, 1455, 1387, 1285, 1276, 1059, 1026, 921, 747 cm⁻¹.



3.32

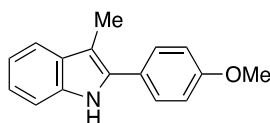
Indole 3.32.⁴² The general procedure was followed with 0.0259 g of aryl azide **3.31** (0.10 mmol) and 2.20 mg of FeBr₂ (0.05 mmol) in 1.2 mL of toluene. Purification by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded a light yellow solid product (0.0144 g, 78%). The spectral data matched that reported by Driver and co-workers.²⁴ ¹H NMR (500 MHz, CDCl₃) δ 7.63 (br, 1H), 7.53 – 7.51 (m, 1H), 7.27 – 7.25 (m, 1H), 7.15 – 7.11 (m, 2H), 2.87 – 2.82 (m, 4H), 1.96 – 1.91 (m, 2H), 1.83 – 1.80 (m, 4H); ¹³C NMR (125 MHz, CDCl₃) 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 (CH₂), 29.6 (CH₂), 28.8 (CH₂), 27.6 (CH₂), 24.7 (CH₂). ATR-FTIR (thin film): 3391, 3054, 2916, 2845, 1717, 1617, 1465, 1234, 1183, 1007, 906, 738 cm⁻¹.



3.34

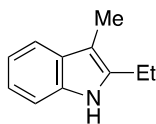
Indole 3.34.⁴² The general procedure was followed with 0.0281 g of aryl azide **3.33** (0.10 mmol) and 2.20 mg of FeBr₂ (0.05 mmol) in 1.2 mL of toluene. Purification by MPLC (0:100 – 5:95 EtOAc: hexanes) afforded a yellow solid product (0.0197 g, 95%). The spectral data matched that reported by Li and co-workers:²⁵ ¹H NMR (500 MHz, CDCl₃) δ 8.02 (br, 1H), 7.63 (d, *J* = 8.0 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 2H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.38 (d, *J* = 8.5 Hz, 2H),

7.23 (t, $J = 7.5$ Hz, 1H), 7.17 (t, $J = 7.0$ Hz, 1H), 2.49 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 135.9 (C), 134.1 (C), 133.4 (C), 130.1 (C), 128.9 (CH), 127.8 (CH), 127.4 (CH), 122.3 (CH), 119.6 (CH), 119.0 (CH), 110.7 (CH), 108.7 (C), 9.7 (CH_3). ATR-FTIR (thin film): 3356, 3058, 2976, 2924, 1649, 1582, 1532, 1449, 1359, 1247, 1095, 752, 700 cm^{-1} .

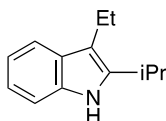


3.36

Indole 3.36.⁴³ The general procedure was followed with 0.0311 g of aryl azide **3.35** (0.10 mmol) and 2.20 mg of FeBr_2 (0.05 mmol) in 1.2 mL of toluene. Filtration using Al_2O_3 afforded a yellow solid product (0.0154 g, 65%). The spectral data matched that reported by Jeong and co-workers:²⁶ ^1H NMR (500 MHz, CDCl_3) δ 7.95 (br, 1H), 7.59 (d, $J = 7.5$ Hz, 1H), 7.51 (d, $J = 9.0$ Hz, 2H), 7.35 (d, $J = 8.0$ Hz, 1H), 7.20 (t, $J = 8.0$ Hz, 1H), 7.15 (t, $J = 8.0$ Hz, 1H), 7.02 (d, $J = 8.5$ Hz, 2H), 3.88 (s, 3H), 2.44 (s, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 159.0 (C), 135.7 (C), 134.0 (C), 130.1 (C), 129.0 (CH), 125.9 (C), 122.0 (CH), 119.4 (CH), 118.8 (CH), 114.3 (CH), 110.5 (C), 107.8 (C), 55.4 (CH_3), 9.6 (CH_3). ATR-FTIR (thin film): 3408, 2959, 2913, 2861, 1603, 1509, 1460, 1252, 1180, 1034, 901, 725 cm^{-1} .



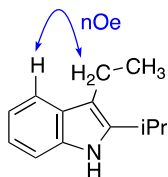
Indole 3.40.²³ The general procedure was followed with 0.0233 g of aryl azide **3.39** (0.10 mmol) and 2.20 mg of FeBr₂ (0.05 mmol) in 1.2 mL of toluene. Filtration using Al₂O₃ afforded a yellow solid product (0.0132 g, 83%). The spectral data matched that reported by Cabrera and co-workers.²³ ¹H NMR (500 MHz, CDCl₃) δ 7.69 (br, 1H), 7.53 (d, *J* = 7.5 Hz, 1H), 7.29 (d, *J* = 7.5 Hz, 1H), 7.18 – 7.12 (m, 2H), 2.77 (q, *J* = 7.5 Hz, 2H), 2.28 (s, 3H), 1.30 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 136.5 (C), 135.1 (C), 129.5 (C), 120.9 (CH), 119.0 (CH), 118.1 (CH), 110.2 (C), 106.2 (CH), 19.4 (CH₂), 14.1 (CH₃), 8.4 (CH₃). ATR-FTIR (thin film): 3308, 2969, 2930, 1721, 1691, 1581, 1524, 1359, 1248, 1201, 910, 734 cm⁻¹.



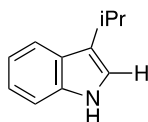
3.42

Indole 3.42. The general procedure was followed with 0.0261 g of aryl azide **3.41** (0.10 mmol) and 2.20 mg of FeBr₂ (0.05 mmol) in 1.2 mL of toluene. Filtration using Al₂O₃ afforded a yellow solid product (0.0112 g, 60%). ¹H NMR (500 MHz, CDCl₃) δ 7.72 (br, 1H), 7.54 (d, *J* = 8.5 Hz, 1H), 7.30 (d, *J* = 8.0 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 3.28 (m, *J* = 7.0 Hz, 1H), 2.75 (q, *J* = 7.5 Hz, 2H), 1.33 (d, *J* = 7.0 Hz, 6H), 1.25 (t, *J* = 7.5 Hz, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 139.9 (C), 135.1 (C), 128.5 (C), 120.9 (CH), 119.0 (CH), 118.3 (CH), 112.3 (C), 110.4 (CH), 25.5 (CH), 22.9 (CH₃), 17.3 (CH₂), 15.9 (CH₃). ATR-FTIR (thin film): 3416, 2963, 2928, 2868, 1459, 1297, 1229, 1059, 909, 740 cm⁻¹. HRMS (EI) *m/z*

calculated for $C_{13}H_{17}N$ (M)⁺: 187.1361, found: 187.1369.

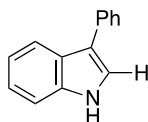


To distinguish **3.42** from 2-ethyl-3-isopropyl-1H-indole, the nOe experiments were carried out and confirmed our hypothesis (see spectrum).



3.44

Indole 3.44.⁴⁴ The general procedure was followed with 0.0233 g of aryl azide **3.43** (0.10 mmol) and 2.20 mg of FeBr₂ (0.05 mmol) in 1.2 mL of toluene. Filtration using Al₂O₃ afforded a yellow solid product (0.008 g, 50%). The spectral data matched that reported by Shim and co-workers:²⁷ ¹H NMR (500 MHz, CDCl₃) δ 7.91 (br, 1H), 7.66 (d, *J* = 7.5 Hz, 1H), 7.35 (d, *J* = 8.0 Hz, 1H), 7.18 (t, *J* = 7.0 Hz, 1H), 7.11 (t, *J* = 7.0 Hz, 1H), 6.96 (s, 1H), 3.22 (m, *J* = 7.0 Hz, 1H), 1.37 (d, *J* = 6.5 Hz, 6H); ¹³C NMR (125 MHz, CDCl₃) δ 136.6 (C), 126.8 (C), 124.1 (C), 121.8 (CH), 119.4 (CH), 119.2 (CH), 119.0 (CH), 111.1 (CH), 25.5 (CH), 23.3 (CH₃). ATR-FTIR (thin film): 3410, 2957, 2867, 1457, 1419, 1338, 1227, 1098, 1028, 1010, 739 cm⁻¹.

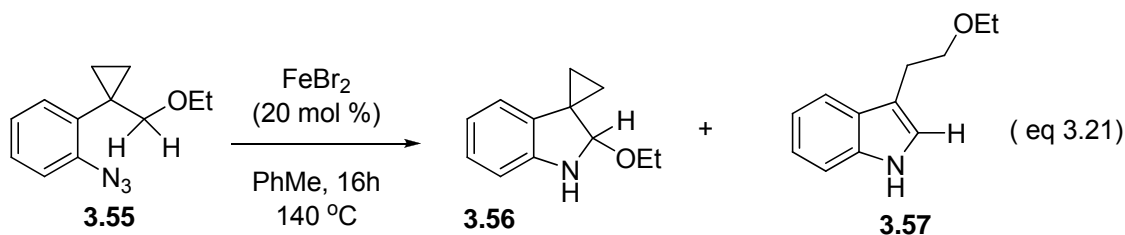


3.46

Indole 3.46.⁴⁵ The general procedure was followed with 0.0267 g of aryl azide **3.45** (0.10 mmol) and 2.20 mg of FeBr₂ (0.05 mmol) in 1.2 mL of toluene. Filtration using Al₂O₃ afforded inseparable mixture 1:2 of corresponding aniline and indole **3.46** (0.008 g, 42%). The spectral data of **3.46** matched that reported by Driver and co-workers:²⁸ ¹H NMR (500 MHz, CDCl₃) δ 8.25 (br, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.68 (d, J = 7.5 Hz, 2H), 7.49 – 7.44 (m, 3H), 7.38 (d, J = 2.5 Hz, 1H), 7.30 – 7.20 (m, 3H).

3.6.7 Mechanistic Experiments.

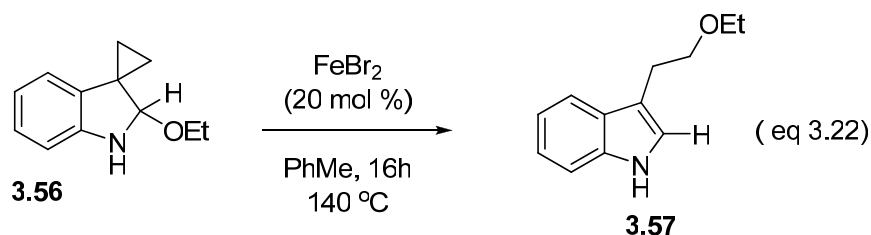
3.6.7.1 Cyclopropyl Substrate Experiment.



To a mixture of aryl azide **3.55** (0.2 mmol) and 0.0087 g of FeBr₂ (20 mol %) in a Schlenk tube was added 2.40 mL of PhMe. The resulting mixture was heated to 140 °C. After 16 h, the mixture was cooled to room temperature and filter through a short pad of Al₂O₃. The filtrate then was concentrated *in vacuo*. Purification of the residue by flash chromatography (0:100 – 10:90 EtOAc: hexanes) afforded indoline **3.56** and indole **3.57**. Spectral data of indole **3.57**: ¹H NMR (500 MHz, CDCl₃) δ 7.97 (br, 1H), 7.63 (d, J = 8.0 Hz, 1H), 7.35 (d, J = 8.0 Hz, 1H), 7.19 (t, J = 8.0 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.06 (s, 1H), 3.73 (t, J = 7.5 Hz, 2H),

3.55 (q, $J = 7.0$ Hz, 2H), 3.06 (t, $J = 7.5$ Hz, 2H), 1.24 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 136.2 (C), 127.6 (C), 122.0 (CH), 121.9 (CH), 119.3 (CH), 118.9 (CH), 111.1 (CH), 70.9 (CH_2), 66.2 (CH_2), 25.9 (CH_2), 15.3 (CH_3) only signals visible. Diagnostic data of indoline **3.56**: ^1H NMR (500 MHz, CDCl_3) δ 7.16 – 7.11 (m, 2H), 6.63 (m, $J = 7.5$ Hz, 2H), 4.90 (s, 1H), 3.50 – 3.15 (m, 3H), 1.07 (t, $J = 7.0$ Hz, 3H), 0.72 (s, 2H), 0.61 (s, 2H).

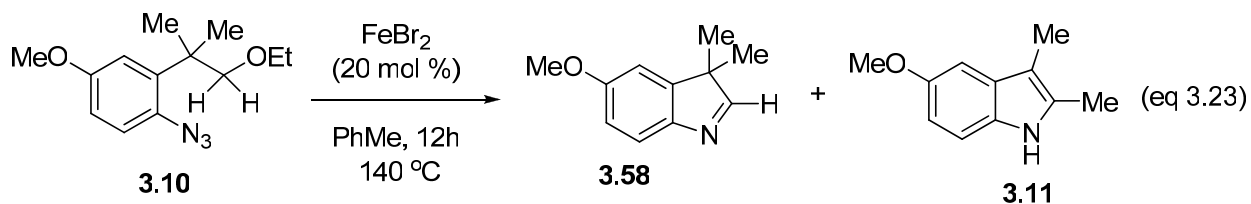
Further exposure of **3.56** under reaction condition without catalyst shows that there was no decomposition or change in reaction mixture.



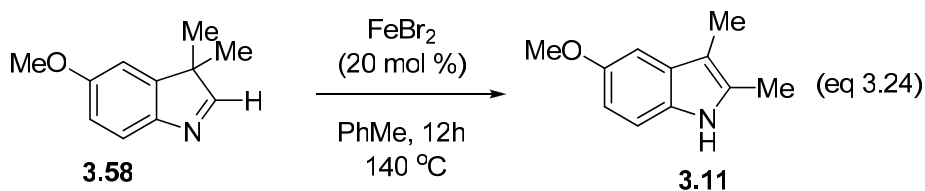
To a mixture of indoline **3.56** (0.02 mmol) and 0.0009 g of FeBr_2 (20 mol %) in a Schlenk tube was added 1.20 mL of PhMe. The resulting mixture was heated to 140 $^\circ\text{C}$. After 16 h, the mixture was cooled to room temperature and filter through a short pad of Al_2O_3 . The filtrate then was concentrated *in vacuo*. Crude NMR showed the formation of indole **3.57**.

The control experiment was carried out: A solution of indoline **3.56** (0.02 mmol) in 0.6 mL of PhMe in a Schlenk tube was heated to 140 $^\circ\text{C}$. After 16 h, the mixture was cooled to room temperature and filter through a short pad of Al_2O_3 . The filtrate then was concentrated *in vacuo*. Crude NMR only showed the presence of starting material indoline **3.56**.

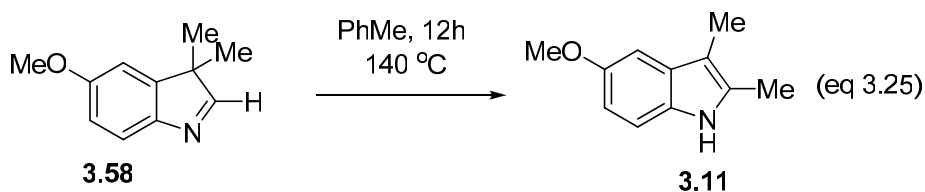
3.6.7.2 Methoxyl Substrate Experiment.



To a mixture of 0.050 g of azide **3.10** (0.2 mmol) and 0.0087 g of FeBr_2 (20 mol %) in a Schlenk tube was added 2.40 mL of PhMe. The resulting mixture was heated to 140°C . After 24 h, the mixture was cooled to room temperature and filter through a short pad of Al_2O_3 . The filtrate then was concentrated *in vacuo*. Purification of the residue by flash chromatography (0:100 – 10:90 EtOAc: hexanes) afforded **3.58** and **3.11**. Spectral data of **3.58**: ^1H NMR (500 MHz, CDCl_3) δ 7.90 (br, 1H), 7.51 (d, $J = 8.5$ Hz, 1H), 6.86 (d, $J = 2.0$ Hz, 1H), 6.84 (dd, $J = 8.0, 2.5$ Hz, 1H), 3.84 (s, 3H), 1.33 (s, 6H); ^{13}C NMR (125 MHz, CDCl_3) δ 178.1 (CH), 158.7 (C), 148.0 (C), 146.7 (C), 121.5 (CH), 112.2 (CH), 107.8 (CH), 55.7 (CH_3), 53.7 (C), 21.8 (CH_3).



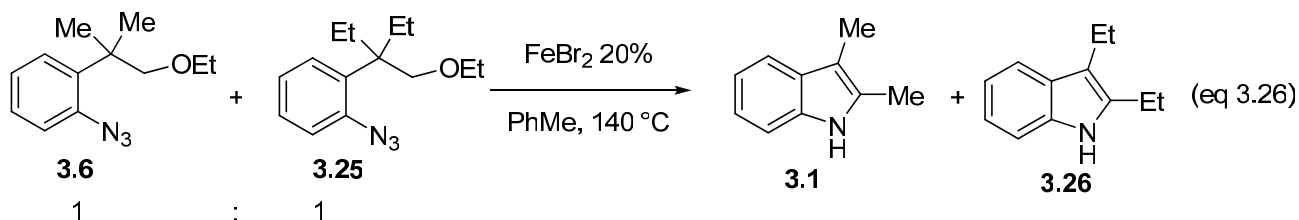
To a mixture of 0.0035 g of **3.58** (0.02 mmol) and 0.0009 g of FeBr_2 (20 mol %) in a Schlenk tube was added 0.6 mL of PhMe. The resulting mixture was heated to 140°C . After 12 h, the crude NMR of reaction mixture showed only formation of desired product **3.11**.



The control experiment was carried out: A solution of 0.0035 g of **3.58** (0.02 mmol) in

0.6 mL of PhMe in a Schlenk tube was heated to 140 °C. After 12 h, the crude NMR of reaction mixture showed only formation of desired product **3.11**.

3.6.7.3 Double Cross-over Experiment.



To a mixture of 0.022 g of azide **3.6** (0.1 mmol), 0.025 g of azide **3.25** and 0.0087 g of FeBr₂ (20 mol %) in a Schlenk tube was added 2.40 mL of PhMe. The resulting mixture was heated to 140 °C. After 16 h, the mixture was cooled to room temperature and filter through a short pad of Al₂O₃. The filtrate then was concentrated *in vacuo*. The crude NMR shows the formation of 2 indole **3.1** and **3.26** with the ratio 1:1 indicated that no double cross-over occurred.

3.7 References

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Chapter 4. Dirhodium(II) Carboxylate Catalyzed Formation of 1,2,3-Trisubstituted Indoles from Styryl Azides.

4.1 Introduction

Among synthetic methods for C–N bond formation to prepare pharmaceuticals and natural products containing N-heterocycles, transition metal-catalyzed tandem reaction has attracted great attention due to its capability of constructing polysubstituted complex blocks efficiently. As the continuing study of chapter III on Rh(II)-catalyzed C–H bond amination-[1,2]-migration tandem reaction, this chapter will present a brief introduction on electrocyclization/migration cascade reactions as well as our work on dirhodium(II) carboxylates catalyzed synthesis of 1,2,3-trisubstituted indole from styryl azide.

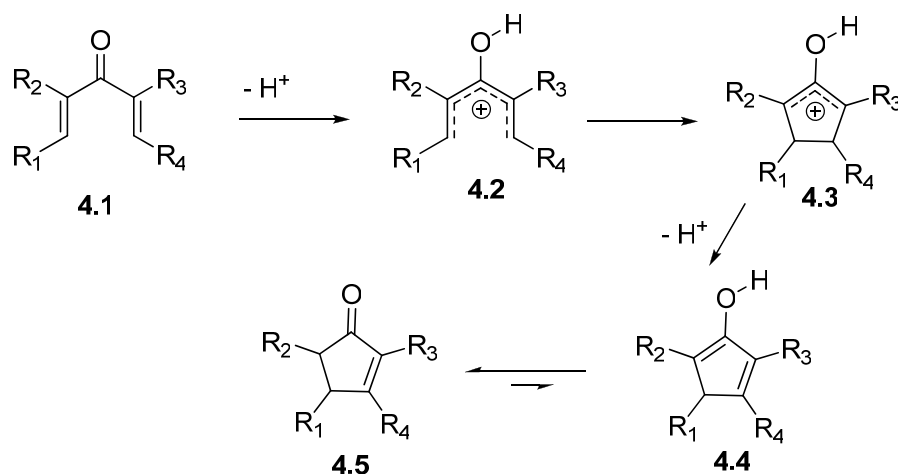
In the midst of cyclization reactions, Nazarov reaction that enables the synthesis of five-membered rings such as 2-cyclopentenone has been very attractive to organic chemists. Recent modifications to the Nazarov cyclization have made this reaction a powerful tool for the construction of important structural five-member carbocycles.¹ The following section will briefly describe some recent development and application of Nazarov cyclization reaction.

4.1.1 Classical Nazarov reaction and proposed mechanism

Nazarov reaction was discovered by Nazarov in 1942 when he observed the isomerism of divinyl ketones to vinyl allyl ketones followed by spontaneous cyclization under acidic condition to yield 2-cyclopentenone.² The pericyclic nature of Nazarov reaction, however, was not revealed until 1967 when Woodward, assisted with new orbital symmetric rules and the

suspicion that the cyclization might be a 4π -electrocyclic ring closure of a pentadienyl cation, proposed the mechanism through careful examination of the stereochemical outcomes.³ In accepted mechanism, coordination of the divinyl ketone to a Lewis or Brønsted acid yields pentadienyl cation **4.2**, then ring closure of this cation generates oxalyl cation **4.3**, which subsequently undergoes E1 elimination to form enone **4.4**. This enone tautomerizes to give cyclopentenone **4.5**.

Scheme 4.1. Proposed mechanism for Nazarov reaction.



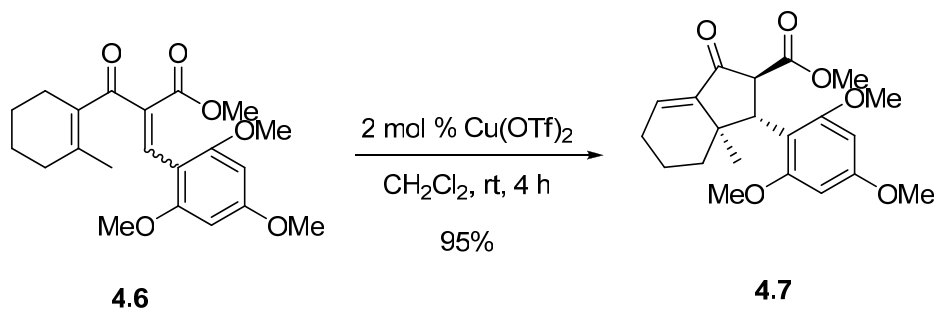
The traditional conditions of Nazarov cyclization have been somewhat harsh. Typically, reactions are conducted at room temperature or below, however, the elevated temperature is not uncommon. To promote the reaction, usually one or more equivalent of a strong Lewis acid (AlCl_3 , $\text{BF}_3\cdot\text{OEt}_2$, TiCl_4) or Brønsted acid (HCl , H_2SO_4 , H_3PO_4) is required. In addition, site selectivity and stereoselectivity are common issues.

4.1.2 Recent development on reactivity

There have been a number of approaches to combat the requirement of a full equivalent

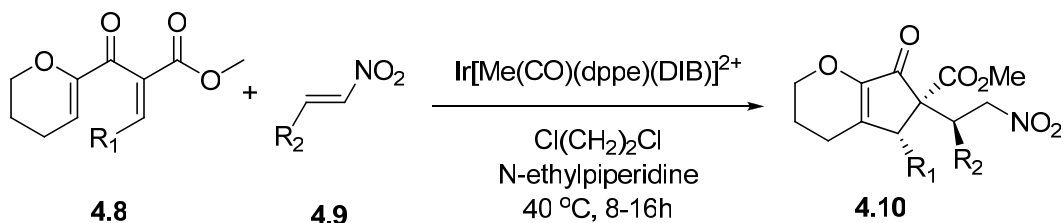
of acid to promote the Nazarov cyclization and to solve the issue of site selectivity. In 1982, the report of Denmark group on silicon-directed Nazarov reaction in 1982 was considered a pioneered work they presented a method for elimination site selectivity.⁴ Denmark theorized that through β -silicon effect, carbocation can be stabilized, and a series of β -silyl divinyl ketones could be cyclized to afford the less thermodynamically stable product cyclopentenone. Later, the Frontier group reported a method of substrate control wherein the divinyl ketone is substituted with an electron-donating group and an electron-withdrawing group.⁵ It is proposed that the electronic difference creates a “vinyl nucleophile” and a “vinyl electrophile” which allows the reaction to proceed with 2 mol % copper triflate (Scheme 4.2). The major drawback to this method is that it demands product substitution that may be undesirable.

Scheme 4.2. Copper triflate promotes Nazarov cyclization



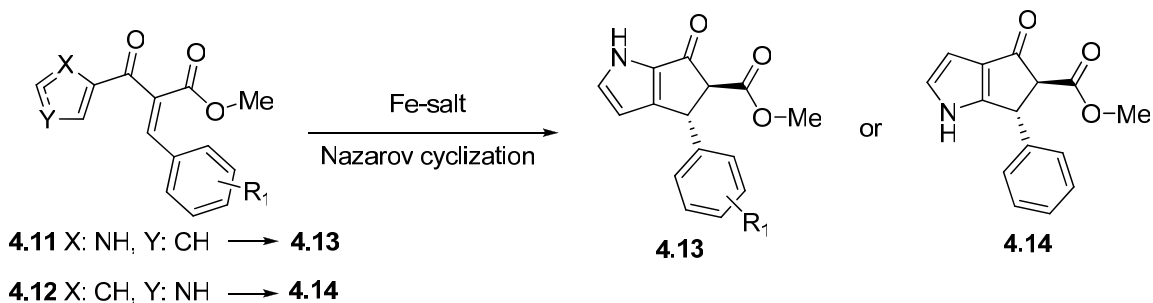
The Frontier group also reported the catalysis of a tandem Nazarov cyclization-Michael addition of β -ketoesters with nitroalkenes.⁶ The reaction proceeds with 4 mol % of an iridium catalyst. This system was shown to catalyze a simple Nazarov cyclization in the Frontier group's total synthesis of (\pm)-merrilactone.⁷

Scheme 4.3. [Ir]-catalyzed Nazarov cyclization-Michael addition reaction



The other development in this area is report of Itoh group on using Fe complex to promote Nazarov reaction of pyrrole substituted β -ketoesters (Scheme 4.4).⁸ The Nazarov cyclization of pyrrole derivatives **4.11** or **4.12** took place in the presence of 3~5 mol% of $\text{Fe}(\text{ClO}_4)_3 \cdot \text{Al}_2\text{O}_3$ to give cyclized product, and the compound further reacted with vinyl ketone to afford the Michael product **4.13** and **4.14**, respectively, with perfect stereoselectivity. Unfortunately, the scope is so far limited to these highly specific substrates.

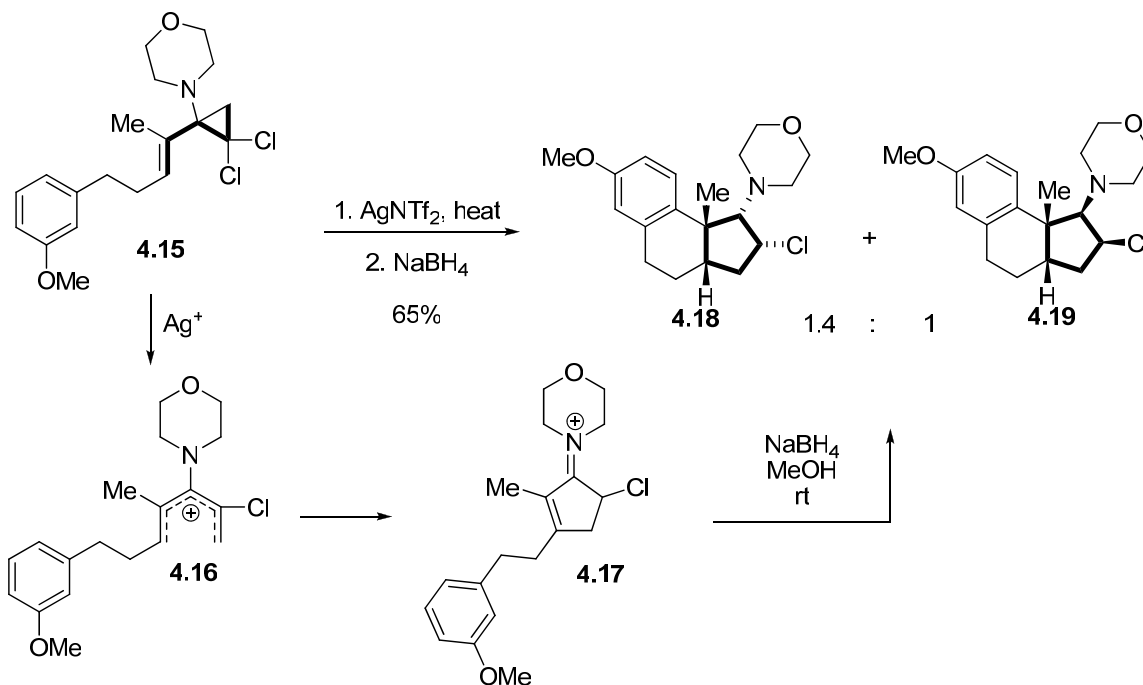
Scheme 4.4. Itoh's work on Nazarov reaction



Recently, the West group reported a new approach to the Nazarov problem when they enabled the Ag-assisted electrocyclic opening of 1-amino-1-alkenyl-2,2-dichlorocyclopropanes to provide a convenient route to the 3-aminopentadienyl cations which is required for imino-Nazarov cyclization.⁹ Despite concerns about the unfavorability of this electrocyclization due to preferential stabilization of the open pentadienyl form, their substrates underwent cyclization to

give unsaturated iminium salts, which could then be stereoselectively reduced with borohydride.

Scheme 4.5. Ag-promoted Imino-Nazarov reaction of vinyl cyclopropylamines

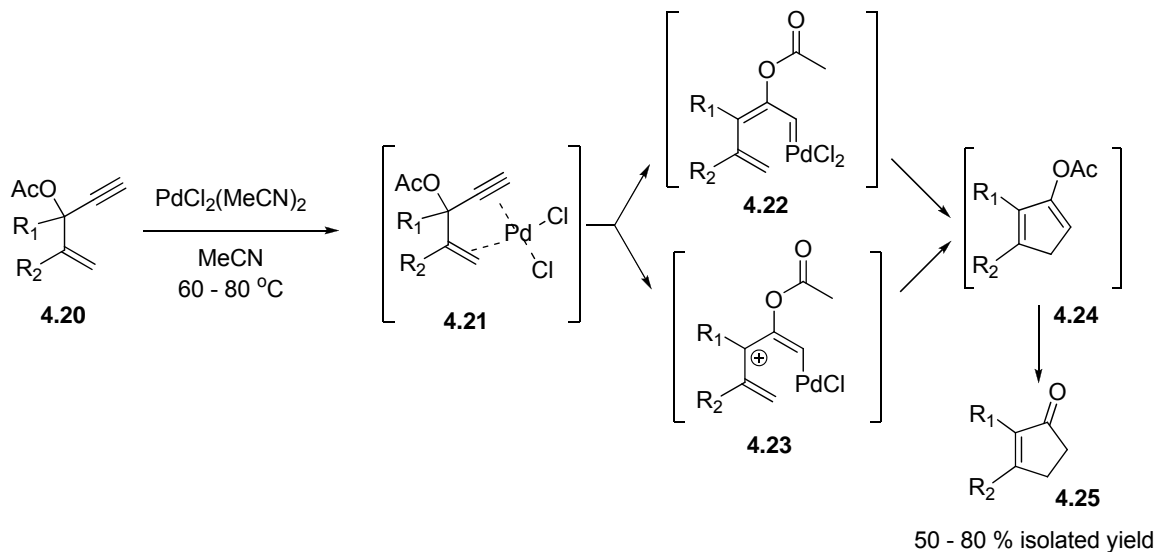


4.1.3 Development on rearrangement/ Nazarov cyclization tandem reaction

Quite early in 1984, Rautenstrauch reported a unique Pd(II)-mediated rearrangement of 1-ethynyl-2-propenyl acetates **4.20** to give 1,4-cyclopentadienyl acetates **4.24**, which were cleaved in situ to 2-cyclopentenones **4.25**, as a new approach to Pd-catalyzed variant of the Nazarov electrocycloization.¹⁰ In his paper, the optimization of reaction conditions and the rearrangement results for five different substrates were described. He also proposed mechanism in which the cyclization started with formation of chelate **4.21** via the coordination of the Pd(II) catalyst to the alkyne that triggers 1,2-acetoxy migration and leads to the generation of a metal carbene species **4.22**. When this carbene is in equilibrium with a pentadienyl cation **4.23**, they

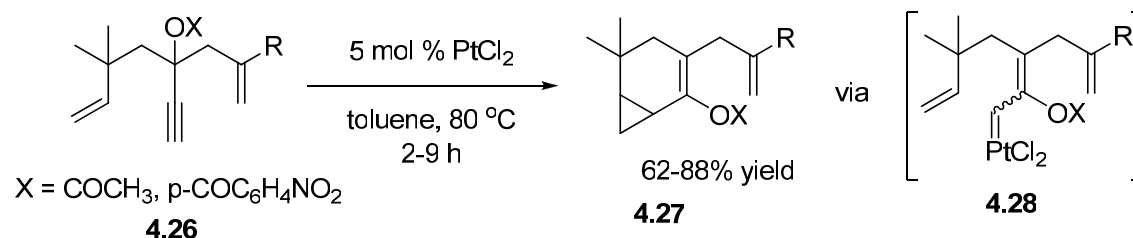
both can undergo cyclization and ester cleavage to afford the cyclopentenone ring.

Scheme 4.6. Rautenstrauch's work on [1,2]-migration/Nazarov cyclization



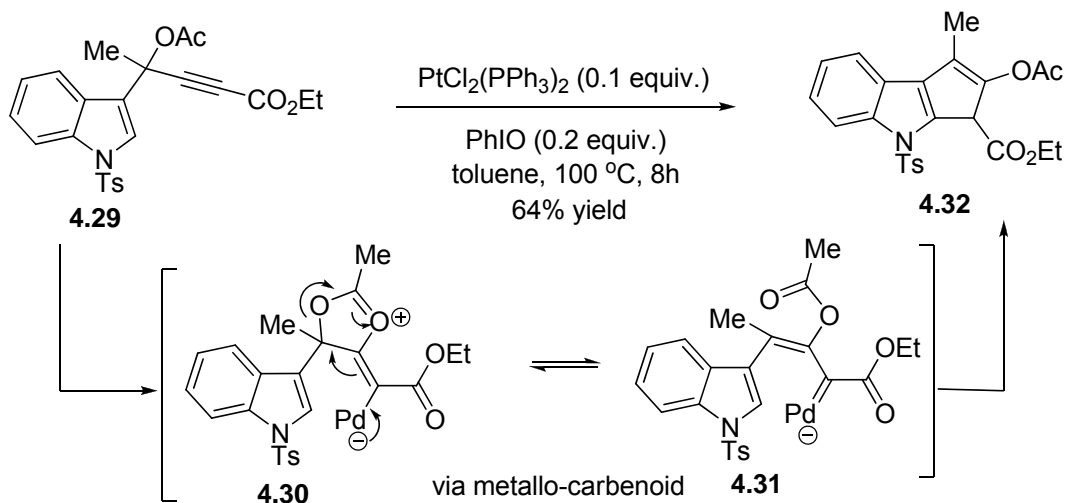
While the Rautenstrauch rearrangement provided an efficient route to cyclopentenones, it was limited to the preparation of achiral cyclopentenones substituted at C2 and C3-position. The scope of this reaction was expanded when Fensterbank and his co-workers reported the PdCl_2 -catalyzed tandem rearrangement/cyclopropanation of dienynes to give fused bicyclic cyclopropanes in 2002 (Scheme 4.7).¹¹ The proposed mechanism involved a metal carbene intermediate **4.28** generated through [1,2]-acetoxymigration, similar to the reaction pathway proposed by Rautenstrauch in 1984 for $\text{Pd}(\text{II})$.

Scheme 4.7. Fensterbank's work on rearrangement/cyclopropanation reaction



Similarly, Sarpong and co-workers have also reported Pt(II)-catalyzed pentannulation reactions of propargylic esters involving the putative formation of metal carbene intermediate and [1,2]-acetoxy migration (Scheme 4.8).¹² By developing this methodology, they enabled the preparation of 2-indanone derivatives which are indeed one of the most useful families presented in many biologically active compounds such as taiwaniaquinoids and other medicinally important products.

Scheme 4.8. Sarpong's indene synthesis

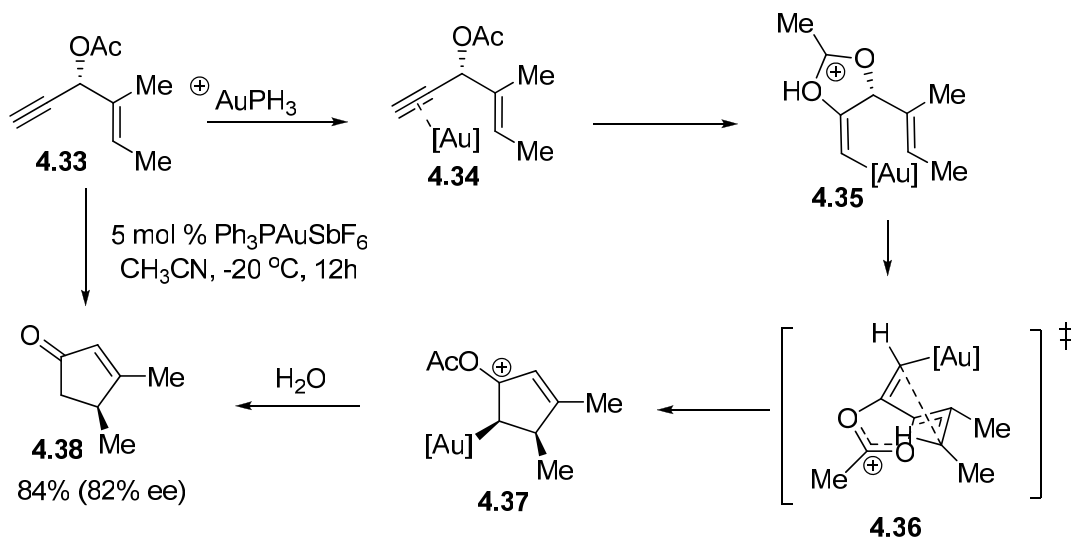


To allow the preparation of chiral cyclopentenones, in 2005, Toste and co-workers reported a gold(I)-catalyzed rearrangement of 1-ethynyl-2-propenyl acetates to 2-

cyclopentenones (Scheme 4.9).¹³ To account for a high degree of chirality transfer observed for reactions of chiral substrates, they proposed the mechanism started with the intramolecular [1,2]-addition of the ester onto the alkyne, induced by coordination of the alkyne to a cationic gold(I) complex, afforded vinyl gold species. The intramolecular cyclization proceeded through a transition state **4.36** in which the leaving group occupies a position orthogonal to the plane of the olefin. The cyclization produced cationic intermediate **4.37**, which upon elimination of cationic gold (I) and hydrolyzation afforded cyclopentenone **4.38**.

Following computational studies of Lera group on Rautenstrauch rearrangement reported by Toste group also indicate that reactions occur with chirality transfer proceed through helical, pentadienyl cationic intermediates.¹⁴

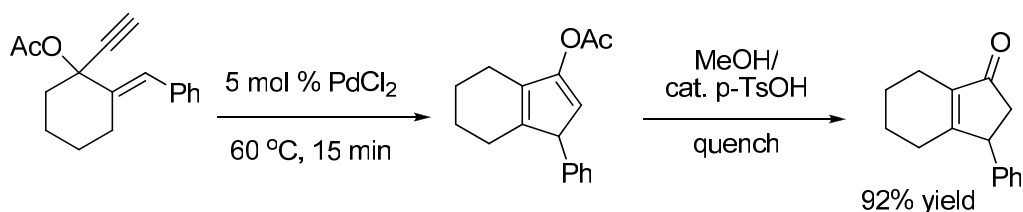
Scheme 4.9. Gold-catalyzed Rautenstrauch rearrangement



Inspired by Rautenstrauch's pioneering work wherein an unusual cyclopentenone fused to a macrocycle was generated, Frontier's group was seeking for much milder conditions to carry out unconventional Nazarov reaction and reported a Pd(II)- and Hg(II)-catalyzed rearrangements

of propargyl acetates.¹⁵ Treatment of a series of appropriate acetate substrate with PdCl₂ afforded synthetically useful fused 5,6-bicyclic-1,4-cyclopentadienyl acetates and 2-cyclopentenones. They found that the substituents at the alkynyl and alkenyl positions of the acetate substrate had a significant impact on the outcome of the reaction.

Scheme 4.10. Frontier's work on rearrangement/ electrocyclization reaction

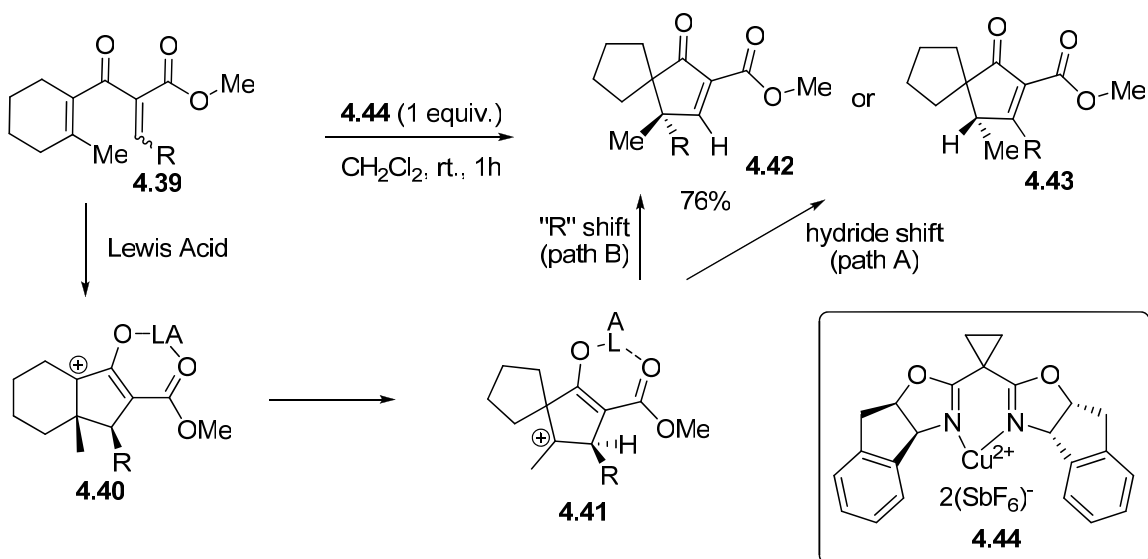


4.1.4 Development on Nazarov cyclization/rearrangement tandem reaction

When the sequence of tandem reaction changes to Nazarov cyclization followed by rearrangement, the mechanism usually involves the formation of cyclopentyl cation, which triggers [1,2]-shift. In the same year, another report came from Frontier's group on development of a Nazarov cyclization/Wagner–Meerwein rearrangement sequence for the stereoselective synthesis of spirocycles.¹⁶ These transformations are highly stereoselective, efficient for a range of substrate types, and capable of creating adjacent quaternary centers. Different from abovementioned methodologies, they were able to perform smooth cyclization/ring contraction to afford spirocycles **4.42** or **4.43**. In the proposed mechanism, 4π conrotatory electrocyclic process occurs first to generate oxyallyl cation **4.40**, followed by ring contraction led to spirocyclic cation **4.41**. Then, depending on the migratory ability of the substituents R, either hydride shift (part A) or "R" shift (part B) occurs. Their results indicate that the alkyl shift is favored when the R group is electron-rich and can stabilize the adjacent tertiary cation. If R

groups cannot provide strong stabilization for the cation **4.41**, for either steric or electronic reasons, the hydride shift will be favored.

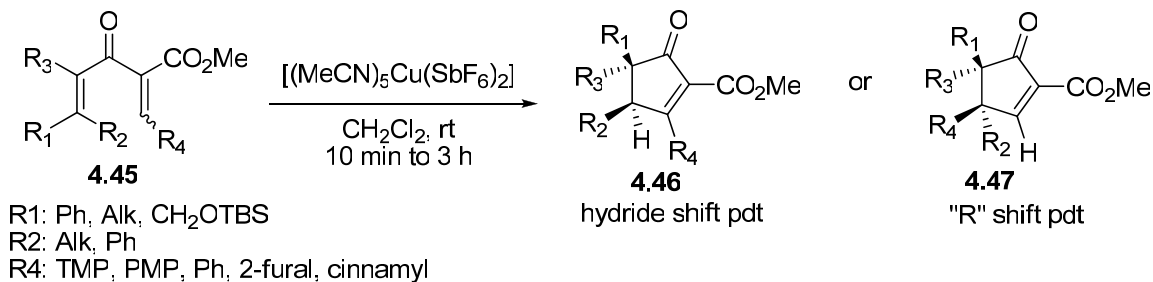
Scheme 4.11. Nazarov cyclization/Wagner-Meerwein rearrangement for spirocycles formation



Recently, Frontier group continued to extend the reactivity of compounds with different substituents at C1, C2 and C5 when they have developed an efficient, chemoselective method for the preparation of highly functionalized cyclopentenones based on a stereospecific, Cu(II)-mediated Nazarov cyclization/Wagner-Meerwein rearrangement sequence (Scheme 4.12).¹⁷ Their original experiments indicated that both migratory ability and steric demand of the substituents at C1 and C5 influenced which group underwent [1,2]-Wagner-Meerwein shift, and the chemoselectivity of the reactions is remarkable. In general, the migration aptitude was followed: aromatic group underwent [1,2]-migration in preference to an alkyl or hydride, unless steric factors prevent migration of aromatic ring. They also found that selective cyclization/rearrangement could be achieved with a catalytic amount of the copper promoter in

combination with a weakly Lewis acidic sodium salt.

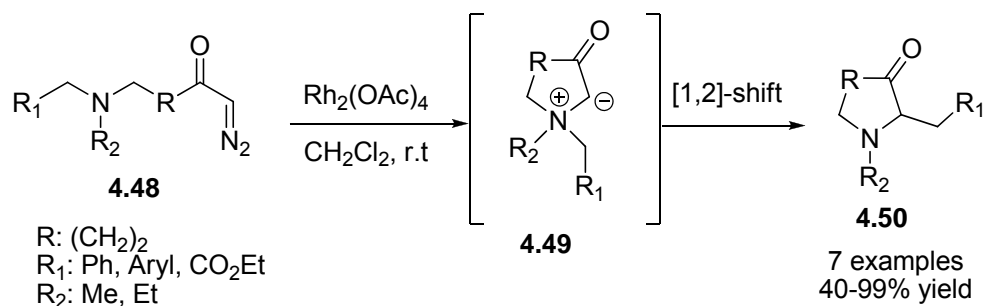
Scheme 4.12. Nazarov cyclization/Wagner–Meerwein rearrangement for highly substituted cyclopentanone formation



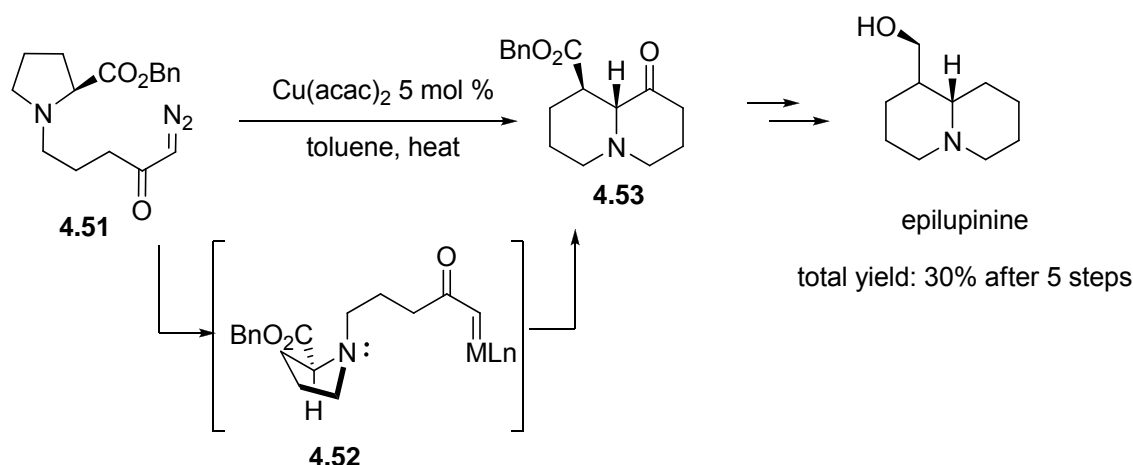
4.1.5 Cyclization/rearrangement for C – N bonds formation

The metal carbene intermediate inducing cyclization and [1,2]-shift were well utilized to make new C–C bonds and C–N bonds. West group have reported numbers of methodologies related to formation of ammonium ylides through metal carbene, which triggered Stevens [1,2]-rearrangement. Early in 1993, they developed the sequence of Rh-catalyzed carbenoid generation/ammonium ylide formation/Stevens [1,2]-shift utilizing acyclic dialkylamino diazo carbonyl substrates that can be applied to the synthesis of six- membered nitrogen heterocycles in good to excellent yields (Scheme 4.13).¹⁸ Complete migrating group selectivity was seen in all cases, consistent with the expectation that the carbon with the best radical stabilizing substituent will migrate. Their strategy enabled the total synthesis of epilupinine in which the key rearrangement step is to generate the quinolizidine skeleton proceeding with high levels of diastereoselectivity and moderate enantiospecificity (Scheme 4.14).¹⁹ However, the limitation of this method is the requirement of conjugating group on the migration carbon, typically aryl or carbonyl, presumably to stabilize the intermediate radical center.

Scheme 4.13. West's work on cyclization/Stevens [1,2]-rearrangement

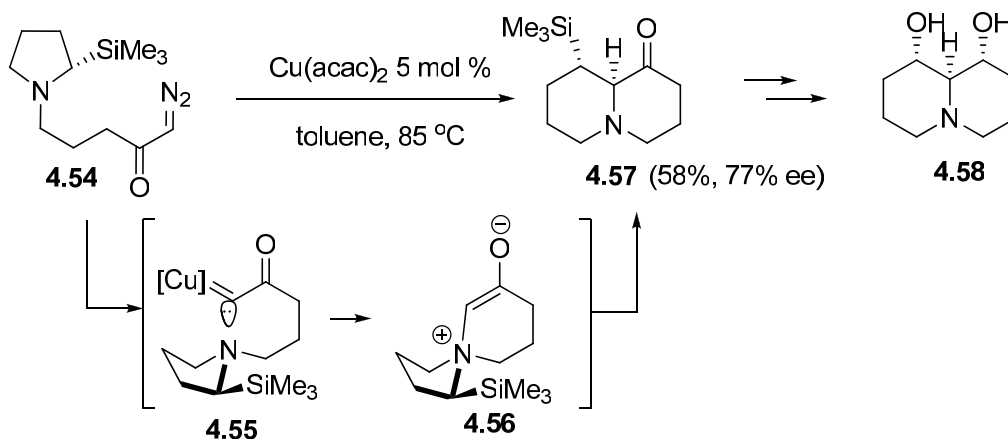


Scheme 4.14. Their application on total synthesis of epilupinine



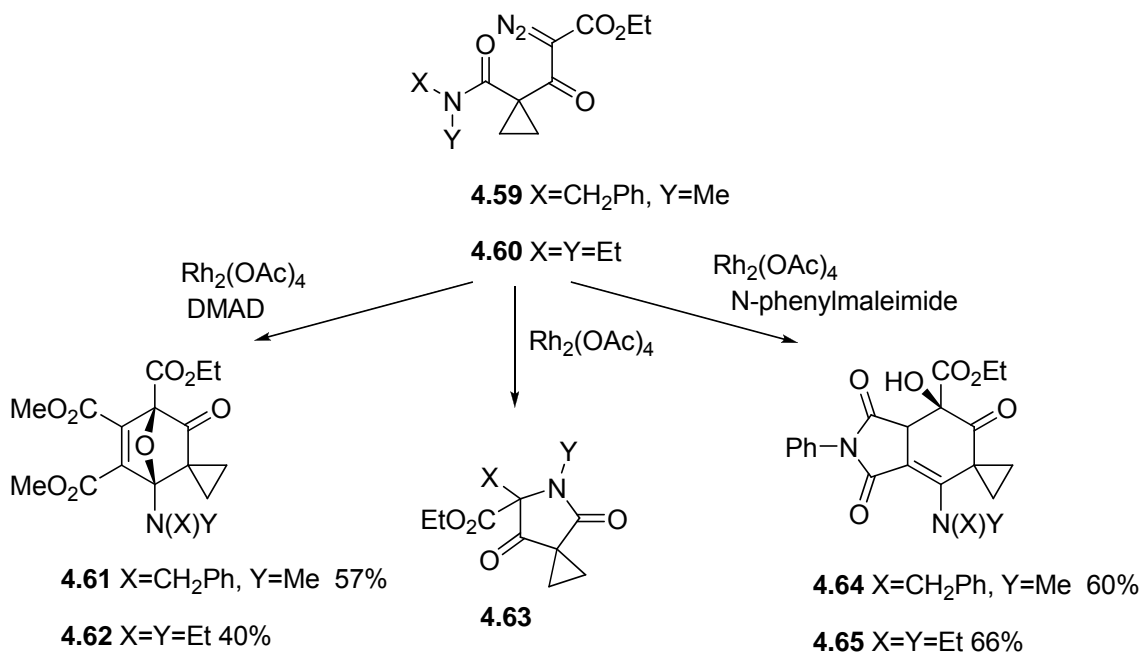
The scope of this type of reaction has been expanded later in 2002 when West group reported another novel, stereoselective silyl-directed Stevens [1,2]-shift of ammonium ylides.²⁰ The silyl group presented in **4.54** plays several critical roles: a stereochemical control element in a facially selective carbenoid addition to the ring nitrogen, a stereochemical “place holder” during regioselective 1,2-migration with the retention by resulting the spirocyclic ammonium ylide **4.56**, and a hydroxyl surrogate for an eventual stereoselective Tamao–Fleming oxidation. It furnished dihydroxyquinolizidines **4.58** in six steps from commercial available starting material Boc-pyrrolidine.

Scheme 4.15. Silyl-directed Stevens [1,2]-shift of ammonium ylides



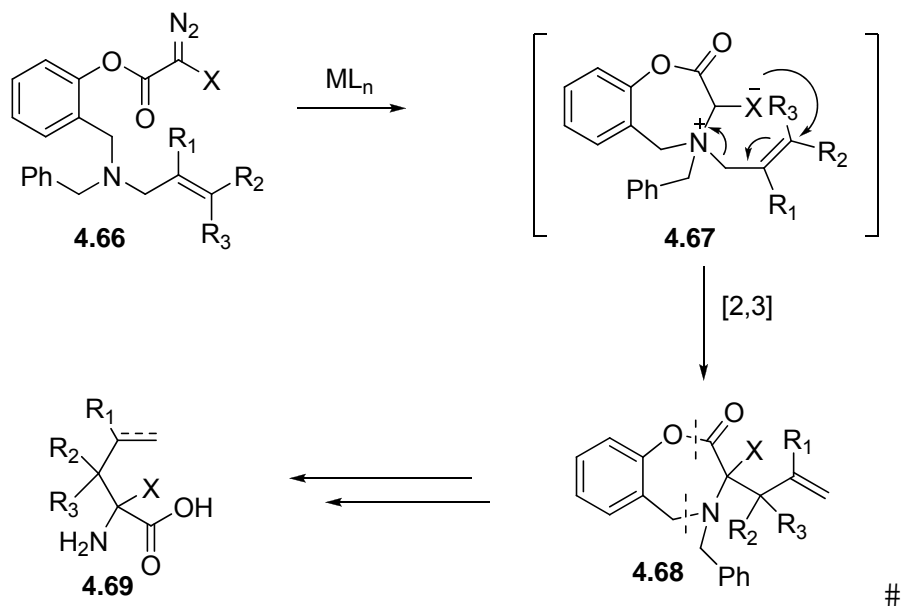
To compare product distribution arising from ammonium vs carbonyl ylide formation, in 1997, Padwa and coworkers investigated the cyclization of Rh carbenoid using ester and amino carbonyl groups (Scheme 4.16).²¹ When product **4.61** was expected to achieve from preferential carbonyl ylide formation followed by reaction with dimethyl acetylenedicarboxylate (DMAD), the formation of both **4.61** and **4.63** in reaction mixture was observed. They also noted that without DMAD, the lactam **4.63** is the only product, presumably arising from α',β -fragmentation of ammonium ylide with consequent generation of ethylene. In a further extension, diazo compounds **4.59** and **4.60** were exposed to $\text{Rh}_2(\text{OAc})_4$ in the presence of *N*-phenylmaleimide to afford the mixture of **4.64** and **4.65** along with [1,2]-rearrangement product **4.63** when exclusion of *N*-phenylmaleimide only led to **4.63** in high yield. These data strongly suggested that the formation of both ammonium and carbonyl ylide is a common feature with their compounds **4.59** and **4.60**.

Scheme 4.16. Competing ammonium and carbonyl ylide formation.



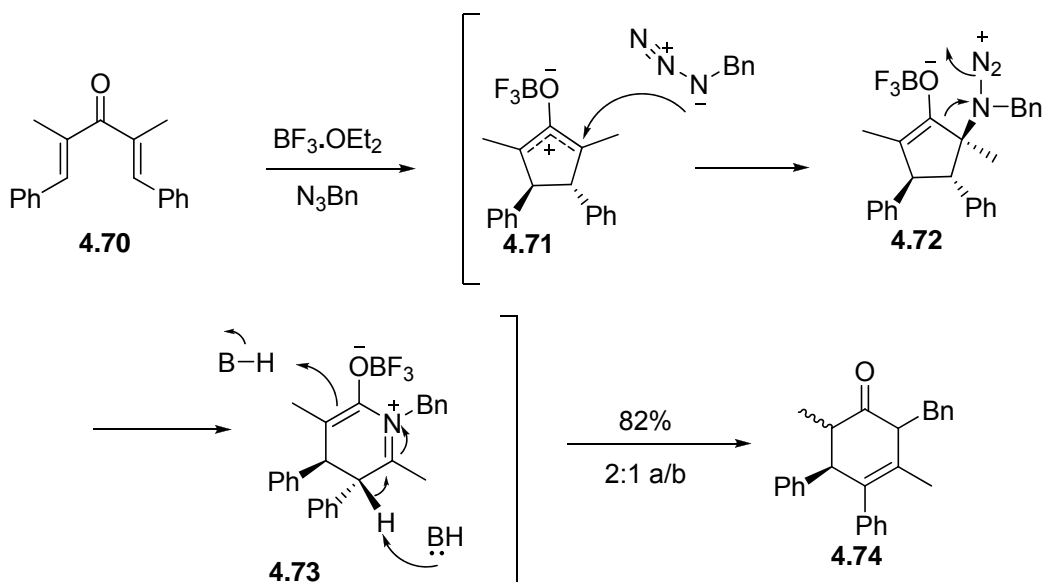
Similar study involving carbenoid precursor with concomitant [2,3]-rearrangement was reported by Clark and co-workers in 2002 (Scheme 4.17).²² Intramolecular trapping of a metal carbenoid by an allylic amine generated an ammonium ylide **4.67**, followed by subsequent rearrangement to deliver an azalactone **4.68**, which could be converted into amino acid **4.69** through lactone cleavage and hydrolysis of the benzylic group. In optimization experiments, the reactivity of $Cu(acac)_2$, $Cu(hfacac)_2$ and $Rh_2(OAc)_4$ were investigated, and $Cu(hfacac)_2$ appeared to be the best. Overall, this tandem reaction offers a highly flexible route to synthesizing amino acids containing various unusual groups (X) at the R position. Stereoselective substitution at the α position is also possible when R2 and/or R3 group in allylic amine precursor is different from H.

Scheme 4.17. General strategy for amino acid synthesis

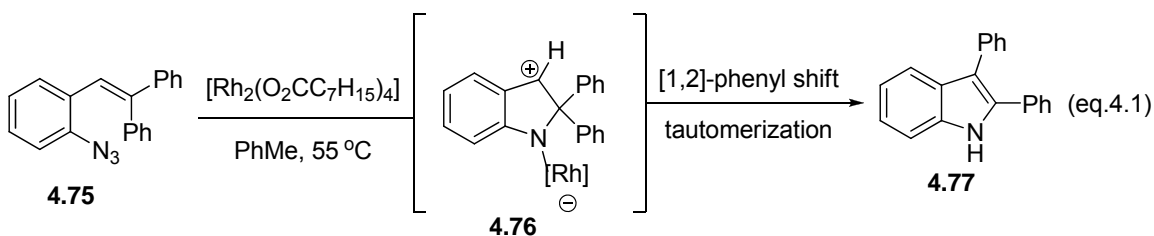


In 2007, West group continued to report other way to interrupt the Nazarov reaction when they performed azide trapping of the cationic species in intermolecular fashion, followed by Schmidt rearrangement to afford dihydropyridones **4.74** (Scheme 4.18).²³ By going through intermolecular way, this method features the advantage of utilizing very simple, readily available dienone **4.70** and organic azide, also avoiding the preparation of intramolecular substrates before crucial Nazarov reaction could be implemented. In these cases, cationic intermediate **4.71** yielded from electrocyclization, was attacked by benzyl azide at the least substituted terminus. Schmidt rearrangement of **4.72** provided zwitterionic species that further rearranged to generate product **4.74**. The formation of trans-dihydropyridone **4.74** was occurred predominantly or exclusively in all reactions.

Scheme 4.18. Intermolecular azide capture.



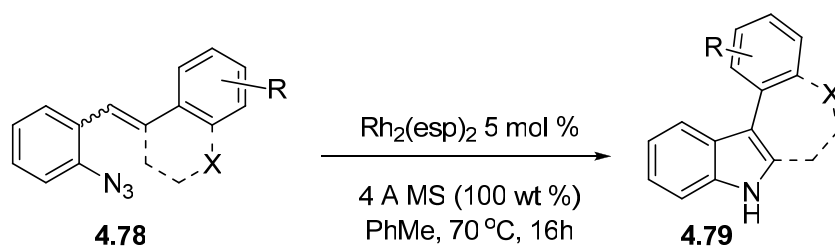
The example of transition metal-catalyzed cyclization/migration tandem reaction through N-atom transfer, however, remains underdeveloped. In 2008, Driver group has reported Rh(II) octanoate-catalyzed migration of a phenyl group to transform β,β -diphenylstyryl azide into 2,3-diphenylindole,²⁴ and our mechanistic experiments suggested that C–N bond formation occurred through a 4π -electron-5-atom electrocyclicization and cation intermediate **4.76** was produced and triggered [1,2]-phenyl shift (equation 4.1).



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. Three

years later, we have demonstrated that rhodiumcarboxylate complexes catalyze cascade reactions of β , β -disubstitutedstyryl azides to selectively produce 2,3-disubstitutedindoles.²⁵ Our investigation revealed that only aryl group preferentially migrated over alkyl group. Attachment of either electron-withdrawing or an electron-donating group to the migrating arene did not affect the migration selectivity. We also found that while ring expanded products were formed from 4-, 5-, and 6- membered substrates, poor conversion was observed for 7-membered azide. The mechanistic study suggests that the selectivity of the migratorial process is controlled by the formation of a phenonium ion.

Scheme 4.19. Rh(II)- catalyzed synthesis of 2,3-disubstituted indoles



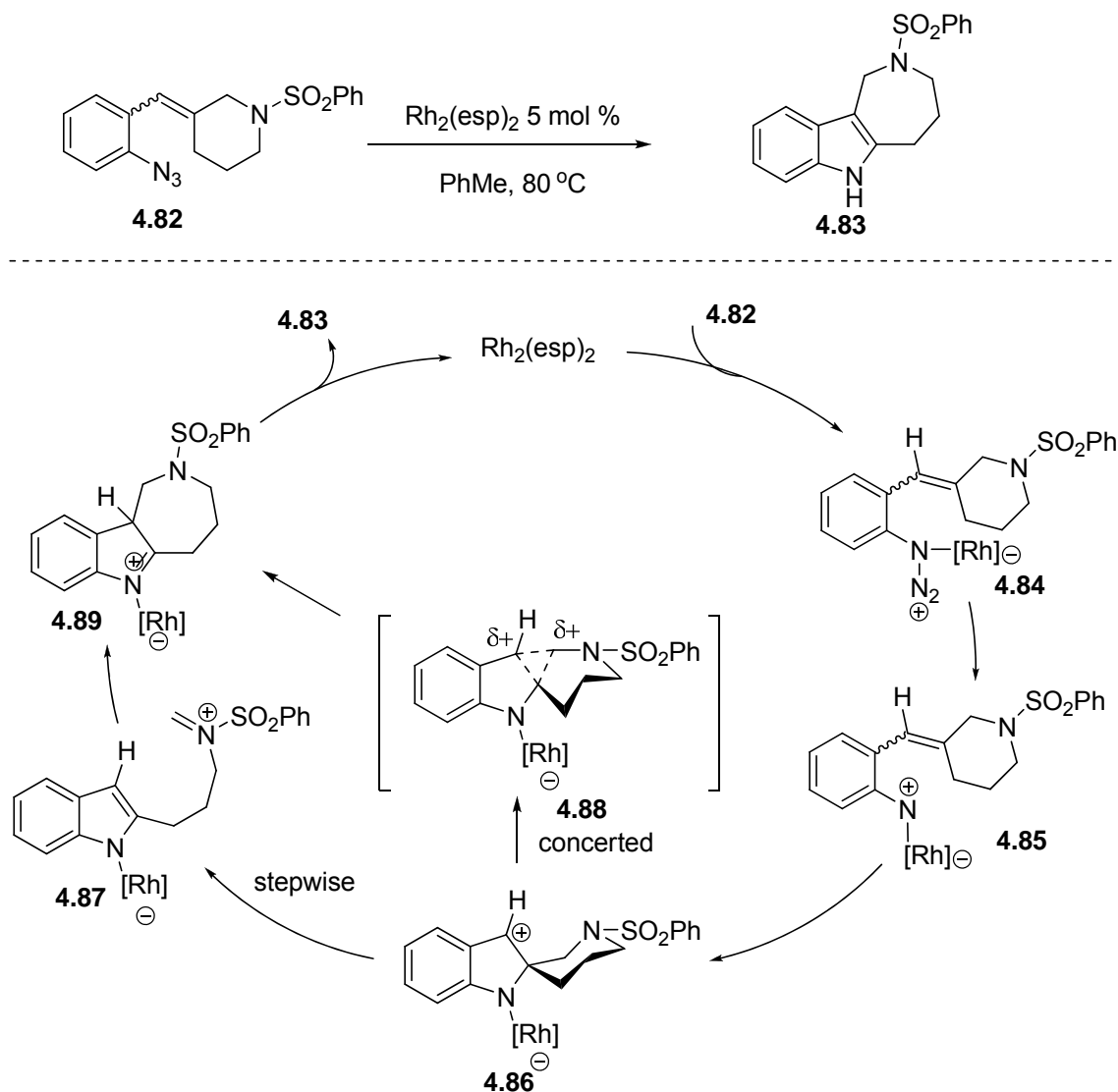
To expand the scope of this electrocyclization/migration tandem reaction, we recently investigated on the migratorial process that can distinguish between two β -methylene units when one was substituted with an amine (Scheme 4.20).²⁶ From our observation, Rh(II) complexes can catalyze aminomethylene shift reaction that transform β,β -disubstituted styryl azides into tetrahydrocarbolines or indoloazepines.

Scheme 4.20. Rh(II)-catalyzed selective aminomethylene migration



To account for aminomethylene migration process, we proposed the catalytic cycle involving rhodium nitrene **4.85** underwent 4π -electron-5-atom electrocyclization to generate benzyl cation **4.86** (Scheme 4.21). Formation of **4.86** triggers the concerted or stepwise migration of the aminomethylene via iminium ion **4.89**. Indole **4.83** is afforded through tautomerization.

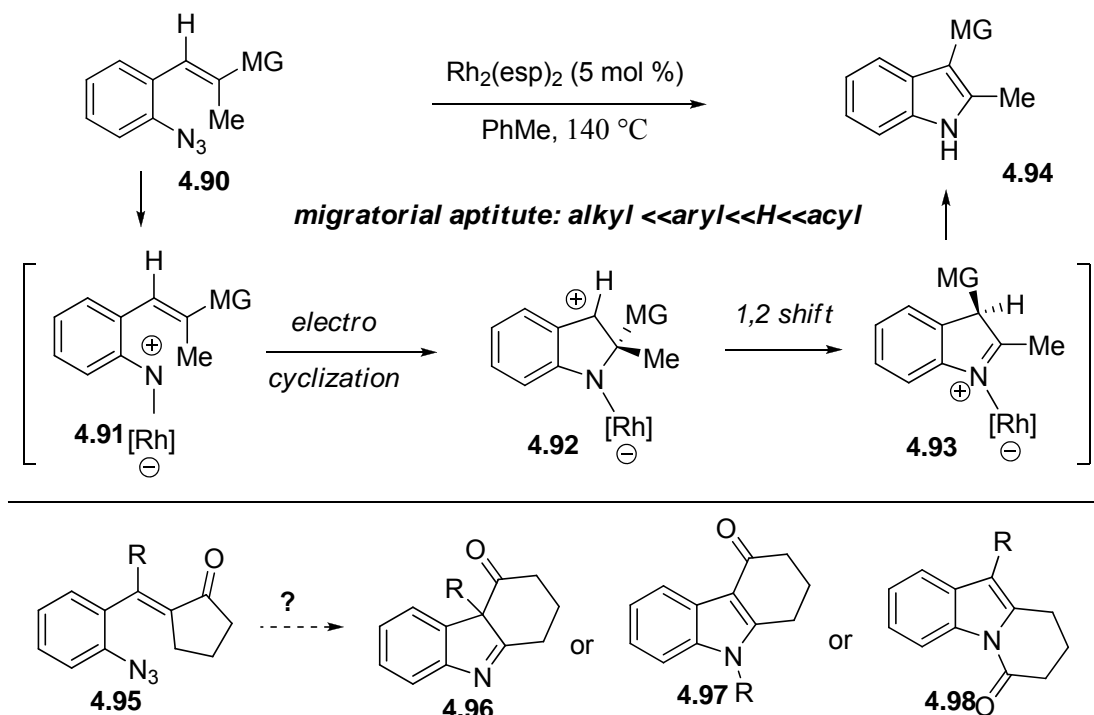
Scheme 4.21. Potential catalytic cycle for selective aminomethylene migration



In this chapter, the reactivity of $\text{Rh}_2(\text{II})$ -carboxylate salts in catalyzing the electrocyclization and an exclusive carbonyl migration to produce 1,2,3-trisubstituted indoles that present in a variety of natural products including the Strychnos and Kopsia alkaloid families^{27,28} will be discussed. From our mechanistic investigations, we anticipated that [1,2]-migrations could be triggered upon electrocyclization of the rhodium nitrene complexes to form 2,3-disubstituted indoles from β,β -disubstituted styryl azides (Scheme 4.22).^{25,26,29} Since our

previous studies on migratorial aptitude suggested the preferential shift of the carbonyl group,²⁹ we were curious whether indole **4.96**, **4.97** or **4.98** would be formed when the α -hydrogen was replaced with an aryl- or alkyl group. If the reactivity of **4.95** was found to be similar to the β,β -disubstituted styryl azides **4.90**, either **4.96** or **4.97** would be major product in this reaction. Unexpectedly, we observed 1,2,3-trisubstituted indoles **4.98** as the only isomer formed in the presence of $\text{Rh}_2(\text{II})$ -carboxylate catalyst.³⁰

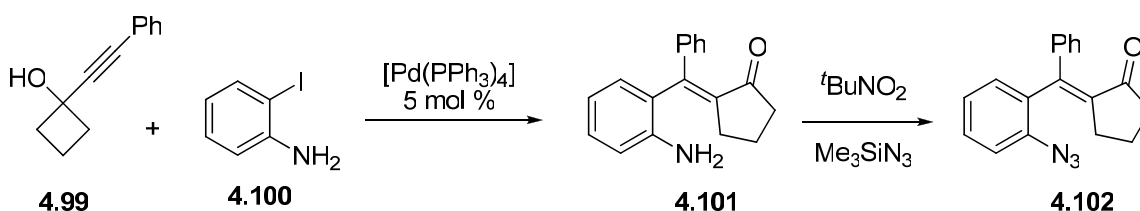
Scheme 4.22. Development of a new metal-catalyzed electrocyclization/migration tandem reactions of substituted styryl azides.



In corporation with my labmate Crystalann Jones, we successfully developed electrocyclization/migration tandem reaction that efficiently transforming styryl azide into trisubstituted indoles. In the search of the operating condition for this carbonyl [1,2]-shift reaction, trisubstituted styryl azide **4.102** herein was synthesized in two steps (Scheme

4.23). First, the Heck cross-coupling ring-expansion reaction between 2-iodoaniline and the cyclobutanol **4.99** was performed to achieve carbonyl substituted styryl aniline **4.101**. Aniline **4.101** then was easily converted to azide through subsequent azidation.^{31,32} With the requisite azide **4.102** in hand, Crystalann Jones examined its reactivity towards a range of transition-metal complexes in different reaction conditions.

Scheme 4.23. Preparation of trisubstituted styryl azide

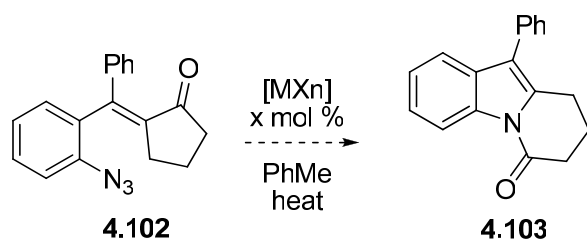


4.2 Optimization experiments

Our initial investigation on the reactivity of substituted aryl azide revealed that trisubstituted styryl azide **4.102** is more inert than the β,β -disubstituted styryl azide **4.75** since $Rh_2(esp)_2$ was found to transfer β,β -disubstituted styryl azide into desired indole but no reaction was observed at 80 °C when **4.102** was employed (entry 1, 7). If we increase temperature to 100 °C, indole **4.103** then will be afforded as the only product (entry 3-6).³³ While a variety of metal complexes were examined to convert aryl azide **4.102** into indole **4.103**, $Rh_2(II)$ -carboxylate salts were found to be more competent than other nitrogen-atom-transfer catalyst including copper,³⁴ iron,³⁵ ruthenium,³⁶ cobalt³⁷ or iridium³⁸. Among the rhodium complexes surveyed, $Rh_2(OAc)_4$ and $Rh_2(esp)_2$ appeared to be the most efficient candidates. Our previous study suggested that $Rh_2(esp)_2$ could promote indole formation presumably due to its thermal robust tetradentate ligands³⁹ when limited success was achieved with $Rh_2(OAc)_4$ because of its insolubility^{25,26,29,40}.

Interestingly, in this reaction at elevated temperature, Rh₂(OAc)₄ was quite compete to Rh₂(esp)₂ (entry 4). However, when we performed the reaction on larger scale, the higher yield and greater reproducibility were obtained when Rh₂(esp)₂ was employed (entry 9). Finally, Rh₂(esp)₂ was chosen to be optimal catalyst with 5 mol % loading at 130 °C.

Table 4.1. Development of optimal catalysts and temperature.



entry	metal salt	mol %	T [°C]	yield, % ^a
1	none	n.a.	130	n.r.
2	Rh ₂ (O ₂ CCF ₃) ₄	5	100	60
3	Rh ₂ (O ₂ CC ₃ F ₇) ₄	5	100	76
4	Rh ₂ (O ₂ CCH ₃) ₄	5	100	90
5	Rh ₂ (O ₂ CC ₇ H ₁₅) ₄	5	100	89
6	Rh ₂ (esp) ₂	5	100	70
7	Rh ₂ (esp) ₂	5	80	n.r.
8	Rh ₂ (esp) ₂	5	130	90
9	Rh ₂ (esp) ₂	1	100	75
10	CuI	10	100	n.r.
11	FeBr ₂	10	100	42
12	RuBr ₃ .nH ₂ O	10	100	35
13	CoTTP	5	100	38
14	[Ir(cod)(OMe)] ₂	10	100	54

^aAs determined using ¹H NMR spectroscopy.

Additionally, we examined the effect of media on our carbonyl [1,2]-shift reaction. After extensive screening different types including ethereal, chlorinated and aromatic solvents, the highest isolated yield of indole was obtained when the reaction performed in toluene. From our

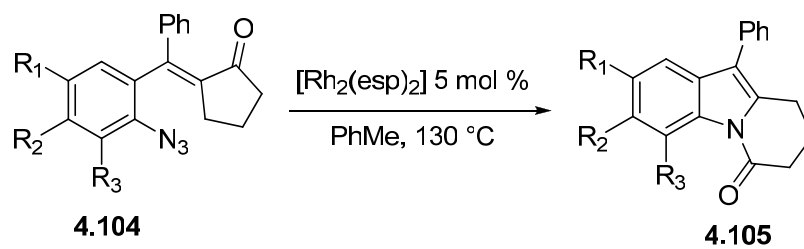
observation, we concluded that the optimal condition to maximize the formation of indole in our tandem reaction is $\text{Rh}_2(\text{esp})_2$ at 5 mol %, at 130 °C in toluene environment. To our delight, analytically pure indole was readily purified by filtering the reaction mixture through a pipette of silica gel.

4.3 Scope and limitation of indole formation

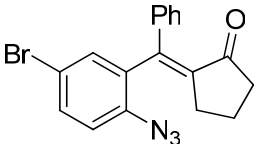
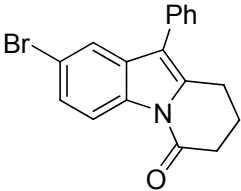
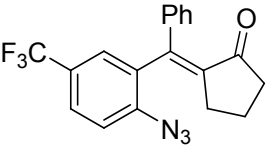
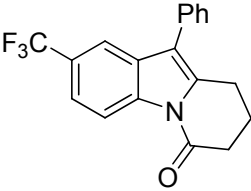
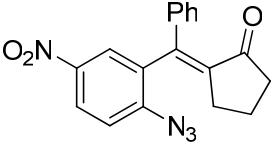
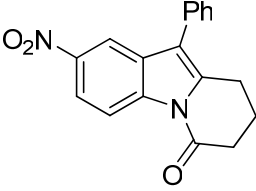
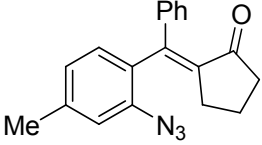
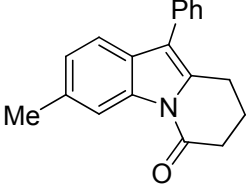
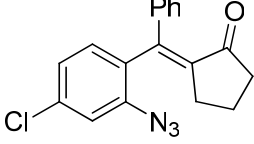
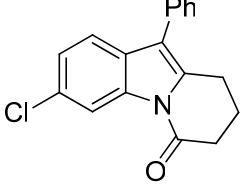
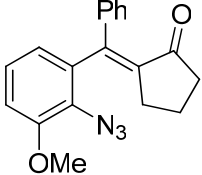
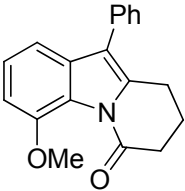
4.3.1 Investigation of Electronic Nature of Azide Arenes

After determination of the optimal conditions to achieve carbonyl [1,2]-shift reaction, the scope and limitations of this transformation were investigated (Table 4.2). Examination of scope revealed that the migration reaction is not sensitive to the electronic nature of aryl azide: both electron-donating and electron-withdrawing R1 substituents were giving good to excellent isolated yield of 1,2,3,5-substituted indoles **4.107-4.119**. Attachment of a strong electron-withdrawing group, such as NO_2 , to aryl azide successfully led to the indole formation (entry 8). To test the ability of our method in preparing 6-substituted indoles that are difficult to synthesize regioselectively via Fischer-Indole reaction⁴¹, azide **4.120** and **4.122** were exposed to reaction condition. To our delight, **4.121** and **4.123** were achieved at 97% and 87 %, respectively. When the steric hinder was introduced into substrate **4.124**, the reaction still proceeded smoothly with slightly diminished yield of indole **4.125** (entry 11).

Table 4.2. Scope and limitation of indole formation.



Entry	aryl azide	##	indole	##	yield, % ^a
1		4.102		4.103	87
2		4.106		4.107	93
3		4.108		4.109	96
4		4.110		4.111	93
5		4.112		4.113	95

6		4.114		4.115	95
7		4.116		4.117	81
8		4.118		4.119	90
9		4.120		4.121	97
10		4.122		4.123	87
11		4.124		4.125	70

^a Isolated after filtration through silica gel.

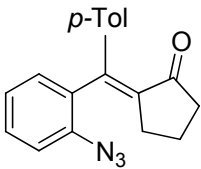
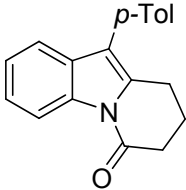
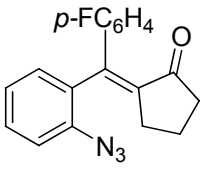
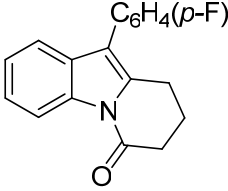
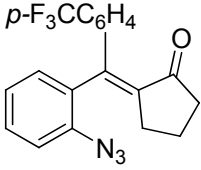
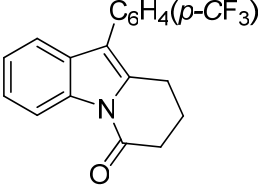
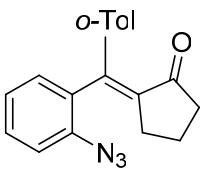
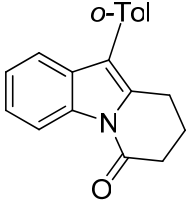
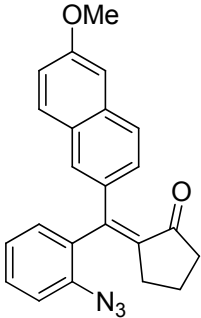
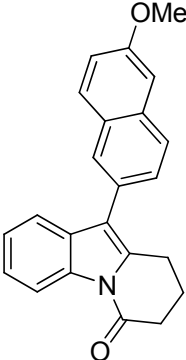
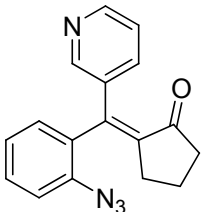
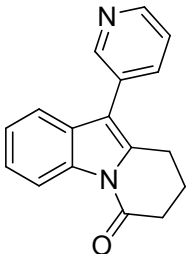
4.3.2 Examination of α -substituent group Identity

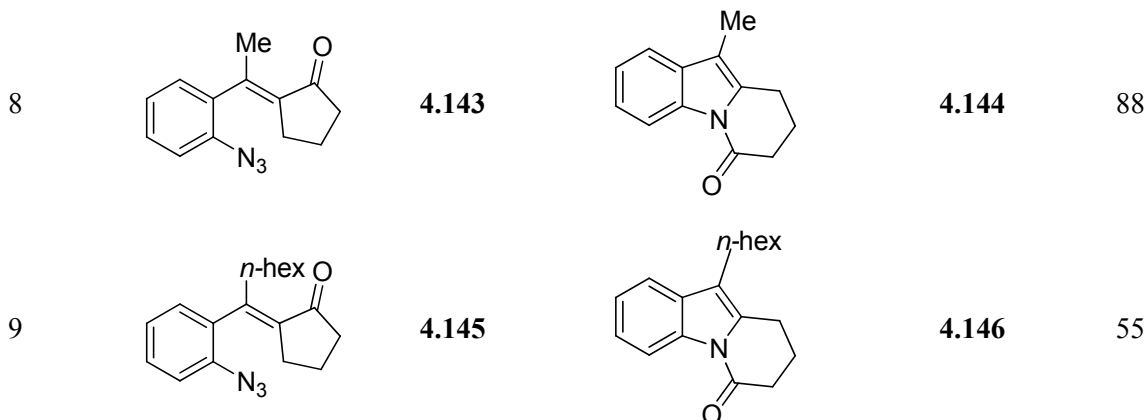
We further examined the scope and limitation of this tandem carbonyl [1,2]-migration reaction by varying the identity of α -substituent group. In every example, only β -carbonyl group

selectively migrated to the indole nitrogen atom even if the functional group with different electronic and steric nature attached to the aryl moiety (entry 1 – 5) or alkyl groups were installed in α -position (entry 8, 9). Considering all experiments of α -aryl group substrates, we found that the scope of our reaction was broader than our earlier studies when substrates bearing Lewis-basic substituents were tolerated (entry 7). However, the pink color of reaction mixture appeared when azide **4.141** was explored under our optimal condition suggested that this quite Lewis basic substrate sequestered the rhodium catalyst. This limitation can be overcome by increasing catalyst loading and reaction temperature, led to 59% isolated yield of desired indole **4.142**. When the employment of methyl and *n*-hexyl group as α -substituent group in azide **4.143** and **4.145** did not change the outcome of the reaction with slightly diminished isolated yield in latter case, it indicated the generality of our process. Exclusive migration of carbonyl group to afford 1,2,3-trisubstituted indole **4.128** in every reaction illustrated the selectivity and generality of our method.

Table 4.3. Examination of identity of the *ortho*-alkyl substituents.

entry	aryl azide	##	indoline	##	yield, % ^a
1		4.129		4.130	77

2		4.131		4.132	89
3		4.133		4.134	75
4		4.135		4.136	85
5		4.137		4.138	72
6		4.139		4.140	96
7		4.141		4.142	20(59) ^[b]



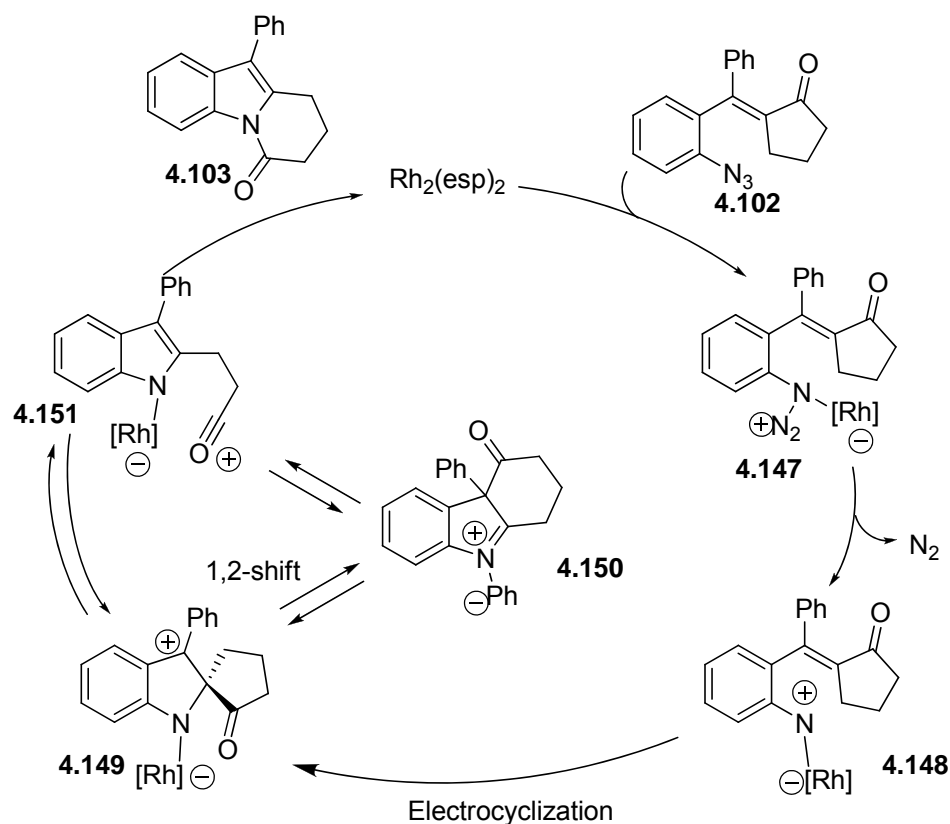
^aIsolated after silica gel chromatography. ^bObtained using 10 mol % of [Rh₂(esp)₂] at 140 °C.

4.4 Mechanism Study

4.4.1 Proposed mechanism for cyclization/migration tandem reaction

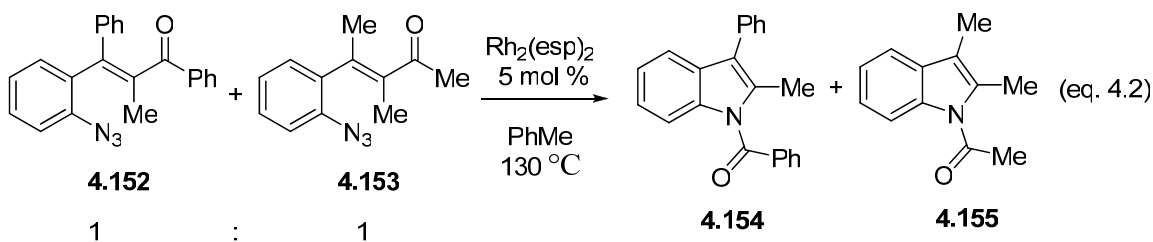
When a number of mechanisms can account for the exclusive formation of 1,2,3-trisubstituted indoles, we proposed that the rhodium nitrenoid is key intermediate participated in this catalytic cycle (Scheme 4.24). Our previous studies on transition-metal related to nitrene reveals that in the first step, the coordination of styryl azide to the rhodium complex produces **4.147**,⁴² followed by extrusion of N₂ gas to form nitrene **4.148**. The 4 π -electron-5-atom electrocyclization of nitrene **4.148** would generate spirocyclic cation **4.149**. In the next step, this spirocyclic cation could undergo [1,2]-shift to afford the 2H-indole **4.150**. However, Ban and co-workers reported that **4.150** is likely to be unstable and prone to fragmentation upon exposure to Lewis or Brønsted acid.⁴³ Next, acylium ion **4.151** could be produced through Lewis acid rhodium (II) carboxylate-promote fragmentation of either **4.149** or **4.150** in reversible manner. If the acylium ion **4.151** was attacked at C3-position, kinetic favor⁴⁴ but unstable⁴⁵ **4.150** would be reformed. On the other hand, the attachment at anionic nitrogen atom would lead to thermodynamic indole **4.93** and regenerate the rhodium (II) carboxylate catalyst to finish the catalytic cycle.

Scheme 4.24. Potential catalytic cycle.



4.4.2 Double Crossover Experiment

To probe the [1,2]-acyl shift mechanism, methyl and phenyl substituted substrates **4.152** and **4.153** were prepared and submitted to the double cross-over experiment (equation 4.2). If in the mechanism, N-acylation step was slow and the acylium ion may diffuse, we would expect to observe the double cross phenomena with the formation of four indoles. On the other hand, when the N-acylation occurred faster than diffusion or the [1,2]-shift followed concerted pathway, only two corresponding products from two azide reactants would be generated. From what we noted, after **4.152** and **4.153** were exposed to the reaction condition, only two indoles were formed indicated the mechanism of [1,2]-acylation shift is concerted, or if it followed stepwise manner, that N-acylation occurs faster than diffusion.



4.5 Conclusion

In conclusion, the reactivity of rhodium(II) carboxylate-catalyzed tandem electrocyclization [1,2]-acetyl migration reactions using α,β,β -trisubstituted styryl azides as N-atom source to synthesize 1,2,3-trisubstituted indoles has been reported. In our discovery, the migration of β -carbonyl group to N-atom is exclusive. The requisite styryl azides are readily available in two steps from commercial 2-iodoaniline, and a wide range of different substituents at the α -position as well as on the aryl azides are tolerated in our reaction. This methodology also enables the efficient preparation of polysubstituted indoles, which cannot be accessed selectively using Fischer-Indole-type processes. The information from mechanism study suggested that the [1,2]-shift is either concerted or N-acylation occurs faster than diffusion. Our future research aims to further explore this new reactivity in the design of new methods to access complex, functionalized *N*-heterocycles from readily available trisubstituted styryl azides.

4.6 Experiments

General. The general experiments were performed as described in Jana et al. *J. Org. Chem.* **2014**, 79, 2781. ^1H 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

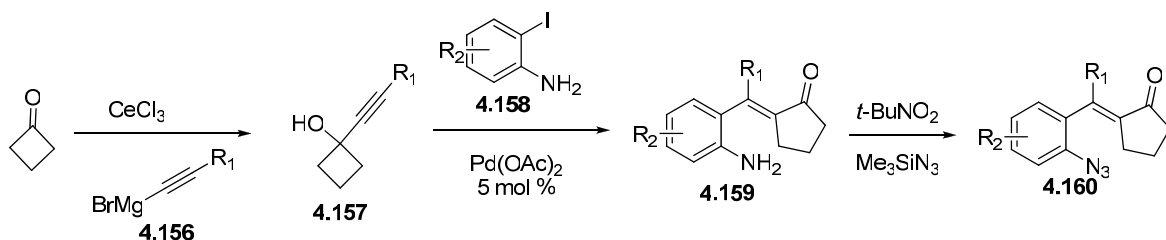
resolution mass spectra were obtained by peak matching. Melting points are reported uncorrected. Infrared spectroscopy was obtained using a diamond attenuated total reflectance (ATR) accessory. Analytical thin layer chromatography was performed on 0.25 mm extra hard silica gel plates with UV254 fluorescent indicator. Liquid chromatography was performed using forced flow (flash chromatography) of the indicated solvent system on 60Å (40 – 60 µm) mesh silica gel (SiO₂). 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 (SiO₂). 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, Et₂O, and CH₂Cl₂ were dried by filtration through alumina according to the procedure of Grubbs.⁴⁶ Metal salts were stored in a nitrogen atmosphere dry box.

4.6.1 Synthesis of Trisubstituted Styryl Azides.

4.6.1.1 Substrate Synthesis Overview.

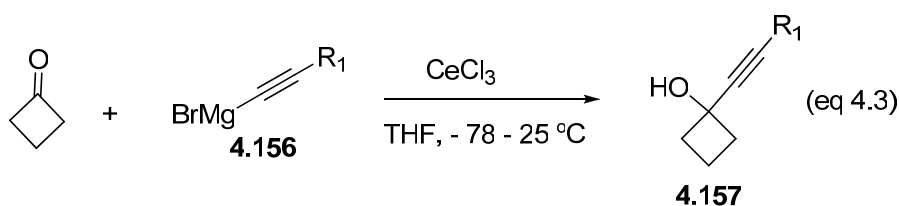
The trisubstituted styryl azides were constructed from cyclobutanone and 2-iodoaniline following the process outlined in Scheme s1. Addition of the appropriate Grignardacetylide to cyclobutanone afforded cyclobutanol **4.157**, which was subjected to the Heck reaction conditions reported by Larock and Reddy to furnish the trisubstituted styrene **4.159**.⁴⁷ Azidation of **4.159** using trimethylsilyl azide following the conditions reported by Zhang and Moses produced the requisite styryl azide for our method development.⁴⁸

Scheme 4.25. Synthesis of trisubstituted aryl azide substrates.



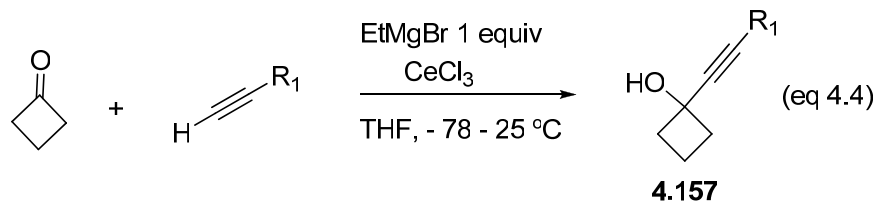
4.6.1.2 Synthesis of Cyclobutanols.

General Procedure A.



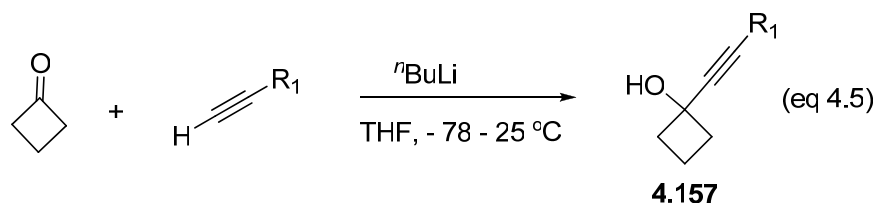
In a 100 mL Schlenk flask, 3.03 g of anhydrous cerium (III) chloride (12.3mmol) was suspended in 24 mL of THF. After cooling to $-78\text{ }^{\circ}\text{C}$, 12.3 mL of a 1.0 M solution of phenylethynylmagnesium bromide in THF (12.3mmol) was added dropwise. After 1 h, a solution of cyclobutanone (0.662 g, 9.45mmol) in 7.0 mL of THF was added. The resulting reaction mixture was allowed to warm to room temperature. After 6 h, the reactives in the heterogeneous mixture were quenched with water, and the resulting mixture was extracted with $3 \times 25\text{ mL}$ of Et_2O . The combined organic phases were washed with $1 \times 50\text{ mL}$ of NH_4Cl , $1 \times 50\text{ mL}$ of distilled water and $1 \times 50\text{ mL}$ of brine. The organic phase was dried over MgSO_4 , and the heterogeneous mixture was filtered. The filtrate was concentrated *in vacuo* to afford a yellow oil, which was purified by flash chromatography (10:90 EtOAc :hexanes) to afford the product (0.800 g, 55%).

General Procedure B.



A 25 mL flamed dried round bottom flask was evacuated, back filled with N₂ and charged with 1.57 mL of a 1.0 M solution of ethyl magnesiumbromide in THF (1.57 mmol). 4-Ethynyltoluene (1.57 mmol) was then added dropwise at room temperature. After 2 h, the crude reaction mixture was then added slowly to a 25 mL Schlenk flask charged with 0.387 g of cerium chloride (1.57 mmol) in 3.14 mL of THF at -78 °C. After 1 h, a solution of cyclobutanone (0.095 g, 1.20 mmol) in 0.90 mL of THF was added dropwise. The resulting reaction mixture was allowed to warm to room temperature. After 6 h, the reactives in the heterogeneous mixture were quenched with water, and the resulting mixture was extracted with 3 × 25 mL of Et₂O. The combined organic phases were washed with 1 × 50 mL of NH₄Cl, 1 × 50 mL of distilled water and 1 × 50 mL of brine. The organic phase was dried over MgSO₄, and the heterogeneous mixture was filtered. The filtrate was concentrated *in vacuo* to afford an orange oil, which was purified by flash chromatography (10:90 EtOAc:hexanes) to afford the product (0.790 g, 64%).

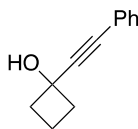
General Procedure C.



A 50 mL flamed dried round bottom flask was charged with 0.726 g (5.00 mmol) of 4-

ethynyl-*N,N*-dimethylaniline, evacuated and back filled with argon. The acetylene was dissolved in 25 mL of THF, and the solution was cooled to $-78\text{ }^{\circ}\text{C}$. A solution of *n*-butyllithium (2.5 M in hexane, 2.0 mL, 5.0 mmol) was added dropwise by syringe. After 30 min, a solution of cyclobutanone (0.292 g, 4.16 mmol) in 4 mL of THF was then added dropwise. After 1 h, the solution was allowed to warm to room temperature and the reactives in the heterogeneous mixture were quenched with NH_4Cl , and the resulting mixture was extracted with $3 \times 50\text{ mL}$ of Et_2O . The combined organic phases were washed with $1 \times 50\text{ mL}$ of brine and the organic phase was dried over MgSO_4 . The crude product was concentrated *in vacuo* to afford a brown oil, which was purified by flash chromatography (10:90 EtOAc:hexanes) to afford the product (0.788 g, 88%).

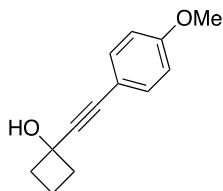
Characterization data for Cyclobutanols.



4.99

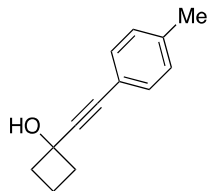
Cyclobutanol 4.99.^[2] General procedure A for cyclobutanol formation was followed using 3.03 g of cerium chloride (12.3 mmol), 12.3 mL of a 1.0 M solution of phenylethynylmagnesium bromide and 0.662 g cyclobutanone (9.45 mmol) in 7 mL of THF. The product was purified by flash chromatography (10:90 EtOAc:hexanes) to afford the product (0.882 g, 55%). The spectral data of cyclobutanol **4.99** matched that reported by Larock and Reddy:^[2] ^1H NMR (CDCl_3 , 500 MHz) δ 7.45 (dd, $J = 6.6, 3.0\text{ Hz}$, 2H), 7.29 (dd, $J = 5.0, 1.7\text{ Hz}$, 3H), 3.49 (s, 1H), 2.55 (ddd, $J = 13.3, 7.1, 3.6\text{ Hz}$, 2H), 2.39 (qd, $J = 9.4, 2.7\text{ Hz}$, 2H), 1.90-1.84 (m, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 131.7 (CH), 128.3 (CH), 122.9 (C), 92.8 (C), 83.4 (C),

68.2 (C), 38.7 (CH₂), 13.1 (CH₂) only signals visible; IR (thin film): 3316, 2988, 2943, 1600, 1489, 1445, 1489, 1242, 1154, 1104, 914, 753, 689cm⁻¹.



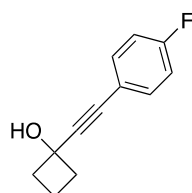
4.158

Cyclobutanol 4.158.⁴⁹General procedure B for cyclobutanol formation was followed using 1.90 mL of a 1.0 M solution of ethyl magnesium bromide in THF (1.90 mmol), 0.25 mL of 4-ethynylanisole(1.90 mmol), 0.468 g of cerium chloride (1.90 mmol), and 0.094 g cyclobutanone (1.46 mmol) in 1.1 mL of THF. The product was purified by flash chromatography (10:90EtOAc:hexanes) to afford the product (0.218 g, 74%). The spectral data of cyclobutanol **4.158** matched that reported by Hashmi and co-workers:^[4]¹H NMR (CDCl₃, 500 MHz) δ7.34 (dd, *J* = 9.2, 2.4 Hz, 2H), 6.80 (dd, *J* = 9.2, 2.3 Hz, 2H), 3.76 (s, 3H), 3.19 (s, 1H), 2.52-2.47 (m, 2H), 2.34 (qd, *J* = 9.4, 2.7 Hz, 2H), 1.87-1.81 (m, 2H);¹³C NMR (CDCl₃, 125 MHz) δ159.5 (C), 133.1 (CH), 114.9 (C), 113.9 (CH), 91.3 (C), 83.2 (C), 68.2 (C), 55.2 (CH₃), 38.7 (CH₂), 13.0 (CH₂).



4.159

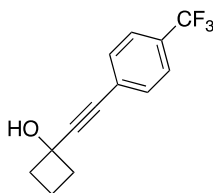
Cyclobutanol 4.159.^[4]General procedure B for cyclobutanol formation was followed using 1.57 mL of a 1.0 M solution of ethyl magnesium bromide in THF (1.57 mmol), 0.20 mL of 4-ethynyltoluene (1.57 mmol), 0.387 g of cerium chloride (1.57 mmol), and 0.095 g cyclobutanone (1.2 mmol) in 0.90 mL of THF. The product was purified by flash chromatography (10:90EtOAc:hexanes) to afford the product (0.115 g, 51%). The spectral data of cyclobutanol **4.159** matched that reported by Hashmi and co-workers:^[4]¹H NMR (CDCl₃, 500 MHz) δ 7.34 (d, J = 8.1 Hz, 2H), 7.10 (d, J = 7.8 Hz, 2H), 2.99 (s, 1H), 2.56-2.51 (m, 2H), 2.38 (td, J = 9.4, 2.7 Hz, 2H), 2.34 (s, 3H), 1.90-1.84 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 138.3 (C), 131.6 (CH), 129.0 (CH), 119.7 (C), 92.0 (C), 83.5 (C), 68.3 (C), 38.7 (CH₂), 21.4 (CH₃), 13.0 (CH₂); IR (thin film): 3319, 3029, 2994, 2943, 2871, 1509, 1448, 1378, 1290, 1242, 1151, 1104, 961, 819, 736cm⁻¹.



4.160

Cyclobutanol 4.160.^[4]General procedure B for cyclobutanol formation was followed

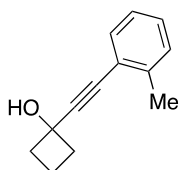
using 4.16 mL of a 1.0 M solution of ethyl magnesium bromide in THF (14.16 mmol), 0.48 mL of 4-fluorophenylacetylene (4.16 mmol), 1.03 g of cerium chloride (4.16 mmol), and 0.224 g cyclobutanone (3.20 mmol) in 2.3 mL of THF. The product was purified by flash chromatography (10:90EtOAc:hexanes) to afford the product (0.403 g, 51%). The spectral data of cyclobutanol **4.160** matched that reported by Hashmi and co-workers:^[4]¹H NMR (CDCl₃, 500 MHz) δ 7.36 (dd, J = 8.0, 5.9 Hz, 2H), 6.93 (t, J = 8.6 Hz, 2H), 3.91 (s, 1H), 2.51-2.46 (m, 2H), 2.36 (q, J = 10.5 Hz, 2H), 1.82 (quintet, J = 7.7 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 163.5 (C), 133.6 (d, J = 8.9 Hz, CH), 118.8 (d, J = 3.2 Hz, C), 115.6 (d, J = 22.1 Hz, CH), 92.2 (C), 82.4 (C), 68.3 (C), 38.6 (CH₂), 13.0 (CH₂); IR (thin film): 3326, 2988, 2940, 1596, 1502, 1223, 1151, 1091, 958, 835 cm⁻¹.



4.161

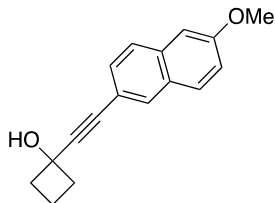
Cyclobutanol 4.161. General procedure B for cyclobutanol formation was followed using 2.0 mL of a 1.0 M solution of ethyl magnesium bromide in THF (2.0 mmol), 0.33 mL of 4-(trifluoromethyl)phenylacetylene (2.0 mmol), 0.493 g of cerium chloride (2.0 mmol), and 0.103 g cyclobutanone (1.54 mmol) in 1.15 mL of THF. The product was purified by flash chromatography (10:90EtOAc:hexanes) to afford the product (0.273 g, 74%): ¹H NMR (CDCl₃, 500 MHz) δ 7.54 (q, J = 8.2 Hz, 4H), 2.58 (d, J = 12.4 Hz, 1H), 2.55 (dt, J = 9.9, 4.9 Hz, 2H), 2.39-2.33 (m, 2H), 1.89 (quintet, J = 8.0 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 131.9 (CH),

130.2 (q, $J_{\text{CF}} = 131.5$ Hz, CF_3), 129.0 (CH), 126.6 (CH), 125.2 (q, $J_{\text{CF}} = 3.5$ Hz, CH), 95.0 (C), 82.2 (C), 68.2 (C), 38.5 (CH_2), 13.0 (CH_2); IR (thin film): 3316, 2991, 2946, 1616, 1410, 1321, 1245, 1262, 1163, 1126, 1065, 1015, 841 cm^{-1} . HRMS (EI) m/z calculated for $\text{C}_{13}\text{H}_{10}\text{OF}_3$ (M^+): 239.0683, found 239.0685.



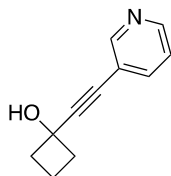
4.162

Cyclobutanol 4.162. General procedure B for cyclobutanol formation was followed using 2.58 mL of a 1.0 M solution of ethyl magnesium bromide in THF (2.58 mmol), 0.33 mL of 2-ethynyltoluene (2.58 mmol), 0.636 g of cerium chloride (2.58 mmol), and 0.139 g cyclobutanone (1.98 mmol) in 1.45 mL of THF. The product was purified by flash chromatography (10:90EtOAc:hexanes) to afford the product (0.246 g, 67%): ^1H NMR (CDCl_3 , 500 MHz) δ 7.44 (d, $J = 7.8$ Hz, 1H), 7.24-7.19 (m, 2H), 7.15-7.12 (m, 1H), 3.62 (s, 1H), 2.60-2.55 (m, 2H), 2.47 (s, 3H), 2.44 (td, $J = 9.4, 2.6$ Hz, 2H), 1.95-1.87 (m, 2H); (CDCl_3 , 125 MHz) δ 140.2 (C), 131.9 (CH), 129.4 (CH), 128.3 (CH), 125.5 (CH), 122.6 (C), 96.9 (C), 82.3 (C), 68.4 (C), 39.0 (CH_2), 20.7 (CH_3), 13.1 (CH_2); IR (thin film): 3326, 3067, 2988, 2943, 2871, 1482, 1242, 1158, 1097, 958, 753 cm^{-1} . HRMS (EI) m/z calculated for $\text{C}_{13}\text{H}_{13}\text{O}$ (M^+): 185.0966, found 185.0969.



4.163

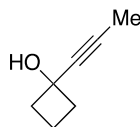
Cyclobutanol 4.163. General procedure C for cyclobutanol formation was followed using 1.00 g (5.50 mmol) of 2-ethynyl-6-methoxynaphthalene, 2.2 mL of a 2.5 M solution of *n*-butyllithium in hexane (5.5 mmol), and 0.321 g cyclobutanone (4.58 mmol) in 4.5 mL of THF. The product was purified by flash chromatography (10:90 EtOAc:hexanes) to afford the product (1.12 g, 97%): ^1H NMR (CDCl_3 , 500 MHz) δ 7.88 (s, 1H), 7.65 (t, $J = 7.7$ Hz, 2H), 7.45 (d, $J = 8.4$ Hz, 1H), 7.15 (dd, $J = 8.9, 2.5$ Hz, 1H), 7.08 (s, 1H), 3.91 (s, 3H), 2.67 (s, 1H), 2.61 – 2.56 (m, 2H), 2.39 (qd, $J = 9.3, 2.8$ Hz, 2H), 1.91 (dt, $J = 14.5, 7.0$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 158.2 (C), 134.1 (C), 131.4 (CH), 129.3 (C), 129.1 (CH), 128.5 (C), 126.8 (CH), 119.4 (C), 117.8 (C), 105.9 (CH), 92.5 (C), 84.0 (C), 68.4 (C), 55.3 (CH_3), 38.8 (CH_2), 13.2 (CH_2); IR (thin film): 3297, 2994, 2940, 1622, 1596, 1385, 1022, 854 cm^{-1} . HRMS (EI) m/z calculated for $\text{C}_{17}\text{H}_{16}\text{O}_2(\text{M}^+)$: 252.1150, found 252.1148.



4.164

Cyclobutanol 4.164.⁵⁰ General procedure C for cyclobutanol formation was followed

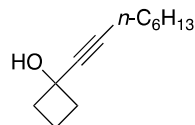
using 0.567 g (5.50 mmol) of 3-ethynylpyridine, 2.2 mL of a 2.5 M solution of *n*-butyllithium in hexane (5.5 mmol), and 0.321 g cyclobutanone (4.58 mmol) in 4.5 mL of THF. The product was purified by flash chromatography (10:90 EtOAc:hexanes) to afford the product (0.774 g, 97%). The spectral data for cyclobutanol **4.164** matched that reported by Andrieux and co-workers:^[5] ¹H NMR (CDCl₃, 500 MHz) δ 8.61 (d, *J* = 1.9 Hz, 1H), 8.37 (dd, *J* = 4.9, 1.4 Hz, 1H), 7.61 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.15 (dd, *J* = 7.9, 4.9 Hz, 1H), 5.98 (s, 1H), 2.43 – 2.39 (m, 2H), 2.33 – 2.27 (m, 2H), 1.84 – 1.74 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 151.7 (CH), 147.7 (CH), 139.0 (CH), 123.2 (CH), 120.5 (C), 97.7 (C), 79.1 (C), 67.4 (C), 38.1 (CH₂), 13.2 (CH₂) only signals visible; IR (thin film): 3206, 3051, 2991, 2940, 1568, 1477, 1262, 1158, 1113, 911, 730 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₁H₁₁ON (M⁺): 172.0762, found 172.0759.



4.165

Cyclobutanol 4.165.⁴⁷ General procedure A for cyclobutanol formation was followed using 2.46 g of cerium chloride (10.0 mmol), 20.0 mL of a 0.5 M solution of 1-propynylmagnesium bromide and 0.560 g cyclobutanone (8.00 mmol) in 20 mL of THF. The product was purified by flash chromatography (10:90EtOAc:hexanes) to afford the product (0.800 g, 91%): The spectral data of cyclobutanol **4.165** matched that reported by Larock and Reddy:^[2] ¹H NMR (CDCl₃, 500 MHz) δ 3.20 (s, 1H), 2.30-2.25 (m, 2H), 2.15 (qd, *J* = 9.4, 2.5 Hz, 2H), 1.72-1.65 (m, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 83.0 (C), 79.2 (C), 67.8 (C), 38.5

(CH₂), 12.7 (CH₃), 3.5 (CH₂).



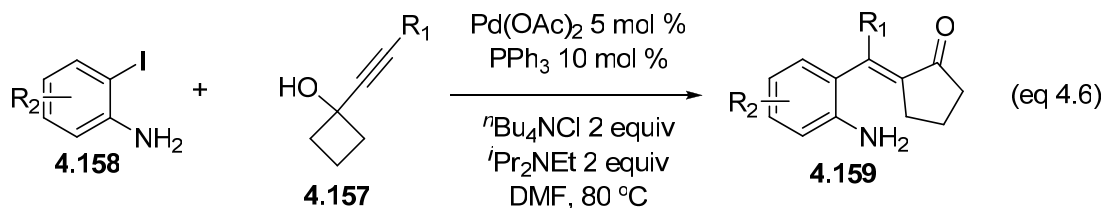
4.166

Cyclobutanol 4.166. General procedure B for cyclobutanol formation was followed using 9.07 mL of a 1.0 M solution of ethyl magnesium bromide in THF (9.07 mmol), 1.33 mL of 1-octyne (9.07 mmol), 2.24 g of cerium chloride (9.07 mmol), and 0.489 g cyclobutanone (6.98 mmol) in 5 mL of THF. The product was purified by flash chromatography (10:90EtOAc:hexanes) to afford the product (0.790 g, 64%): ¹H NMR (CDCl₃, 500 MHz) δ2.37 (dddd, *J* = 9.6, 7.3, 4.7, 2.5 Hz, 2H), 2.26 – 2.20 (m, 4H), 2.12 (s, 1H), 1.82 – 1.74 (m, 2H), 1.51 (quintet, *J* = 7.4 Hz, 2H), 1.39 (dq, *J* = 14.5, 7.4 Hz, 2H), 1.33-1.27 (m, 4H), 0.89 (t, *J* = 7.0 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ84.1 (C), 83.7 (C), 68.1 (C), 38.8 (CH₂), 31.3 (CH₂), 28.6 (CH₂), 28.5 (CH₂), 22.5 (CH₂), 18.7 (CH₃), 14.0 (CH₂). HRMS (EI) *m/z* calculated for C₁₂H₂₀O (M⁺): 179.1436, found 179.1439.

4.6.1.3 Heck Reaction to Produce Alkylidenecyclopentanones.

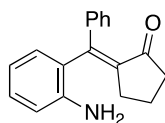
General procedure.

Cyclobutanols were converted to 2-alkylidenecyclopentanones without optimization following the Larock and Reddy's report (eq 4.6).^[2]



In a flame dried 100 mL round bottom flask was dissolved 1.00 g of 1-(1-propynyl)cyclobutanol **4.157** (5.80 mmol), 1.27 g of 2-iodoaniline (5.80 mmol), 3.22 g of *n*-Bu₄NCl (11.6mmol), 2.00 mL of *i*Pr₂EtN (11.6mmol), 0.304 g of PPh₃ (1.16mmol) and 0.132 g of Pd(OAc)₂ (0.580mmol) in 58 mL of DMF. The flask was then de-gassed, flushed with nitrogen, placed in an 80 °C oil bath. After 12 hours, the heterogeneous mixture was diluted with 1 × 50 mL of water, and the mixture was extracted with 3 × 50 mL of CH₂Cl₂. The combined organic phases were washed with 2 × 50 mL of distilled water and 1 × 50 mL of brine. The resulting organic phase was dried over Na₂SO₄, and the heterogeneous mixture was filtered. The filtrate was concentrated *in vacuo* yielding a dark red oil. The product was purified by flash chromatography (10:90EtOAc:hexanes) affording the product as an orange oil (1.64 g, 55%).

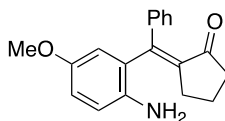
Characterization data for 2-alkylidenecyclopentanones.



4.101

2-Alkylidenecyclopentanone 4.101.^[2b] The general procedure was followed using 1.00 g of 1-(1-phenylethynyl)cyclobutanol **4.99** (5.80 mmol), 1.27 g of 2-iodoaniline (5.80 mmol), 3.22 g of *n*-Bu₄NCl (11.6mmol), 2.00 mL of *i*Pr₂EtN (11.6mmol), 0.304 g of PPh₃ (1.16 mmol) and 0.132 g of Pd(OAc)₂ (0.58 mmol) in 58 mL of DMF. The reaction mixture was purified by flash

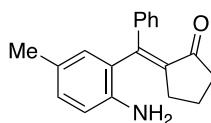
chromatography (10:90 EtOAc:hexanes) affording the product as a dark orange oil (1.64 g, 55%). The spectral data for the product matched that reported by Reddy and Larock:^[2b] ¹H NMR (500 MHz, CDCl₃) δ 7.28 – 7.26 (m, 5H), 7.11 (t, *J* = 7.5 Hz, 1H), 6.92 (d, *J* = 7.5 Hz, 1H), 6.73 – 6.67 (m, 2H), 3.69 (s, 2H), 2.62 (t, *J* = 6.7 Hz, 2H), 2.41 (t, *J* = 7.7 Hz, 2H), 1.92 (q, *J* = 7.4 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 206.4 (C), 146.0 (C), 143.5 (C), 138.5 (C), 135.6 (C), 129.8 (CH), 129.4 (CH), 129.3 (CH), 128.4 (CH), 127.9 (CH), 127.5 (C), 118.1 (CH), 116.0 (CH), 40.4 (CH₂), 32.3 (CH₂), 19.8 (CH₂); IR(thin film): 3459, 3364, 3054, 2953, 1704, 1616, 1489, 1173, 750 cm⁻¹.



4.167

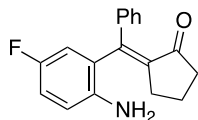
2-Alkylidenecyclopentanone 4.167. The general procedure was followed using 0.860 g of 1-(1-phenylethynyl)cyclobutanol **4.99** (5.00 mmol), 1.50 g of 2-iodo-4-methoxyaniline (6.00 mmol), 2.78 g of *n*-Bu₄NCl (10.0 mmol), 1.75 mL of *i*Pr₂EtN (10.0 mmol), 0.26 g of PPh₃ (1.00 mmol) and 0.125 g of Pd(OAc)₂ (0.50 mmol) in 50 mL of DMF. The reaction mixture was purified by flash chromatography (30:70 EtOAc:hexanes) affording the product as an orange oil. The product contained some inseparable impurities that were removed after the subsequent azidation step. ¹H NMR (500 MHz, CDCl₃) δ 7.30 – 7.27 (m, 5H), 6.74 (dd, *J* = 9.0, 3.0 Hz, 1H), 6.65 (d, *J* = 8.5 Hz, 1H), 6.53 (d, *J* = 3.0 Hz, 1H), 3.70 (s, 3H), 3.39 (s, 2H), 2.64 (t, *J* = 7.0 Hz, 2H), 2.42 (t, *J* = 8.0 Hz, 2H), 1.93 (m, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 206.2

(C), 152.3 (C), 145.8 (C), 138.1 (C), 137.2 (C), 135.7 (C), 129.4 (CH), 128.7 (C), 128.5 (CH), 127.9 (CH), 117.5 (CH), 115.3 (CH), 114.7 (CH), 55.7 (CH₂), 40.4 (CH₂), 32.3 (CH₂), 19.8 (CH₂); ATR-FTIR(thin film): 3450, 3355, 3054, 2952, 2831, 1706, 1591, 1496, 1268, 1037, 818, 732 cm⁻¹.



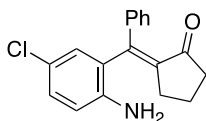
4.168

2-Alkylidenecyclopentanone 4.168. The general procedure was followed using 0.860 g of 1-(1-phenylethynyl)cyclobutanol **4.99** (5.00 mmol), 1.40 g of 2-iodo-4-methylaniline (6.00 mmol), 2.78 g of *n*-Bu₄NCl (10.0 mmol), 1.75 mL of *i*Pr₂EtN (10.0 mmol), 0.26 g of PPh₃ (1.00 mmol) and 0.125 g of Pd(OAc)₂ (0.50 mmol) in 50 mL of DMF. The reaction mixture was purified by flash chromatography (10:90EtOAc:hexanes) affording the product as an orange oil (0.92 g, 60%): ¹H NMR (500 MHz, CDCl₃) δ 7.34 (m, 5H), 6.98 (d, *J* = 7.0 Hz, 1H), 6.78 (s, 1H), 6.63 (d, *J* = 8.5 Hz, 1H), 3.63 (s, 2H), 2.68 (t, *J* = 7.0 Hz, 2H), 2.45 (t, *J* = 8.0 Hz, 2H), 2.25 (s, 3H), 1.95 (m, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 206.3 (C), 146.2 (C), 141.2 (C), 138.8 (C), 135.5 (C), 130.0 (CH), 129.9 (CH), 129.6 (CH), 128.4 (CH), 127.9 (CH), 127.7 (C), 127.1 (CH), 116.3 (CH), 40.5 (CH₂), 32.3 (CH₂), 20.6 (CH₃), 19.9 (CH₂). ATR-FTIR(thin film): 3450, 3363, 3050, 2960, 2880, 1705, 1589, 1500, 1265, 1172, 814, 732 cm⁻¹.



4.169

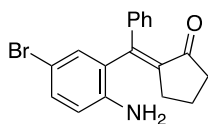
2-Alkylidenecyclopentanone 4.169. The general procedure was followed using 0.860 g of 1-(1-phenylethynyl)cyclobutanol **4.99** (5.00 mmol), 1.42 g of 4-fluoro-2-iodoaniline (6.00 mmol), 2.78 g of *n*-Bu₄NCl (10.0 mmol), 1.75 mL of *i*Pr₂EtN (10.0 mmol), 0.26 g of PPh₃ (1.00 mmol) and 0.125 g of Pd(OAc)₂ (0.50 mmol) in 50 mL of DMF. The reaction mixture was purified by flash chromatography (30:70EtOAc:hexanes) affording the product as an orange oil. The product contained some inseparable impurities that were removed after the subsequent azidation step. ¹H NMR (500 MHz, CDCl₃) δ 7.31 – 7.30 (m, 3H), 7.26 – 7.24 (m, 2H), 6.84 (dt, *J* = 8.5, 3.0 Hz, 1H), 6.67 (dd, *J* = 9.0, 2.5 Hz, 1H), 6.63 (dd, *J* = 9.0, 5.0 Hz, 1H), 3.55 (s, 2H), 2.63 (t, *J* = 7.0 Hz, 2H), 2.42 (t, *J* = 8.0 Hz, 2H), 1.94 (m, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 206.1 (C), 154.8 (C), 144.7 (C), 139.6 (C), 137.8 (C), 136.1 (C), 135.2 (C), 129.4 (CH), 128.7 (CH), 128.0 (CH), 117.1 (d, *J*_{CF} = 7.5 Hz, CH), 115.9 (d, *J*_{CF} = 22.0 Hz, CH), 115.7 (CH), 40.4 (CH₂), 32.2 (CH₂), 19.8 (CH₂); ¹⁹F NMR (282 MHz, CDCl₃) δ –111.35. ATR-FTIR(thin film): 3464, 3353, 3055, 2959, 2889, 1710, 1593, 1494, 1265, 1179, 731, 698 cm^{–1}.



4.170

2-Alkylidenecyclopentanone 4.170. The general procedure was followed using 0.860 g

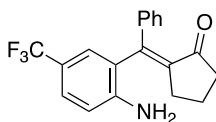
of 1-(1-phenylethynyl)cyclobutanol **4.99** (5.00 mmol), 1.52 g of 4-chloro-2-iodoaniline (6.00 mmol), 2.78 g of *n*-Bu₄NCl (10.0 mmol), 1.75 mL of *i*Pr₂EtN (10.0 mmol), 0.26 g of PPh₃ (1.00 mmol) and 0.125 g of Pd(OAc)₂ (0.50 mmol) in 50 mL of DMF. The reaction mixture was purified by flash chromatography (10:90EtOAc:hexanes) affording the product as an orange oil. The product contained some inseparable impurities that were removed after the subsequent azidation step. ¹H NMR (500 MHz, CDCl₃) δ 7.29 – 7.30 (m, 3H), 7.24 – 7.22 (m, 2H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.70 – 6.68 (m, 2H), 3.75 (s, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.42 (t, *J* = 7.5 Hz, 2H), 1.93 (m, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 206.3 (C), 144.9 (C), 144.7 (C), 138.1 (C), 136.1 (C), 134.8 (C), 131.1 (CH), 129.4 (C), 128.7 (CH), 128.0 (CH), 125.8 (C), 118.2 (CH), 115.6 (CH), 40.4 (CH₂), 32.3 (CH₂), 19.8 (CH₂). ATR-FTIR (thin film): 3464, 3359, 3053, 2942, 2879, 1707, 1666, 1484, 1265, 1094, 816, 732 cm⁻¹.



4.171

2-Alkylidenecyclopentanone 4.171. The general procedure was followed using 0.860 g of 1-(1-phenylethynyl)cyclobutanol **4.99** (5.00 mmol), 1.80 g of 4-bromo-2-iodoaniline (6.00 mmol), 2.78 g of *n*-Bu₄NCl (10.0 mmol), 1.75 mL of *i*Pr₂EtN (10.0 mmol), 0.26 g of PPh₃ (1.00 mmol) and 0.125 g of Pd(OAc)₂ (0.50 mmol) in 50 mL of DMF. The reaction mixture was purified by flash chromatography (10:90EtOAc:hexanes) affording the product as an orange oil. The product contained some inseparable impurities that were removed after the subsequent

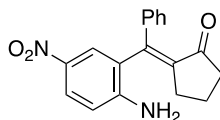
azidation step. ^1H NMR (500 MHz, CDCl_3) δ 7.29 – 7.30 (m, 3H), 7.24 – 7.22 (m, 2H), 7.18 (dd, J = 9.0, 2.5 Hz, 1H), 7.03 (d, J = 2.5 Hz, 1H), 6.57 (d, J = 8.5 Hz, 1H), 3.72 (s, 2H), 2.61 (t, J = 7.0 Hz, 2H), 2.41 (t, J = 7.5 Hz, 2H), 1.93 (m, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 206.3 (C), 144.4 (C), 141.8 (C), 137.7 (C), 136.2 (C), 135.0 (C), 131.9 (CH), 129.4 (CH), 128.7 (CH), 128.0 (CH), 127.7 (CH), 127.6 (C), 117.6 (CH), 40.4 (CH_2), 32.2 (CH_2), 19.7 (CH_2).ATR-FTIR(thin film): 3474, 3360, 3054, 2951, 2879, 1707, 1611, 1482, 1264, 1174, 732 cm^{-1} .



4.172

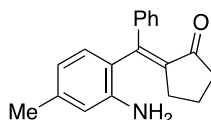
2-Alkylidenecyclopentanone 4.172. The general procedure was followed using 0.860 g of 1-(1-phenylethynyl)cyclobutanol **4.99** (5.00 mmol), 1.72 g of 2-iodo-4-trifluoromethylaniline (6.00 mmol), 2.78 g of $n\text{-Bu}_4\text{NCl}$ (10.0 mmol), 1.75 mL of $i\text{Pr}_2\text{EtN}$ (10.0 mmol), 0.26 g of PPh_3 (1.00 mmol) and 0.125 g of $\text{Pd}(\text{OAc})_2$ (0.50 mmol) in 50 mL of DMF. The reaction mixture was purified by flash chromatography (30:70EtOAc:hexanes) affording the product as an orange oil. The product contained some inseparable impurities that were removed after the subsequent azidation step. ^1H NMR (500 MHz, CDCl_3) δ 7.35 – 7.30 (m, 5H), 7.25 (m, 1H), 7.19 (m, 1H), 6.71 (d, J = 8.5 Hz, 1H), 4.00 (s, 2H), 2.60 (t, J = 7.0 Hz, 2H), 2.43 (t, J = 8.0 Hz, 2H), 1.94 (m, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 206.0 (C), 146.3 (C), 144.4 (C), 137.5 (C), 136.5 (C), 136.1 (C), 130.2 (q, J_{CF} = 23 Hz, C), 129.4 (CH), 128.8 (CH), 128.4 (CH), 128.3 (CH), 128.1 (q, J_{CF} = 3.0 Hz, CH), 126.7 (q, J_{CF} = 270 Hz, CF_3), 115.5 (q, J_{CF} = 3.0 Hz, CH),

40.4 (CH₂), 32.2 (CH₂), 19.7 (CH₂); ¹⁹F NMR (282 MHz, CDCl₃) δ –62.42. ATR-FTIR(thin film): 3448, 3357, 3054, 2959, 2887, 1709, 1670, 1622, 1319, 1263, 1108, 825, 734 cm⁻¹.



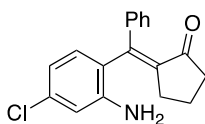
4.173

2-Alkylidenecyclopentanone 4.173. The general procedure was followed using 0.860 g of 1-(1-phenylethynyl)cyclobutanol **4.99** (5.00 mmol), 1.59 g of 2-iodo-4-nitroaniline (6.00 mmol), 2.78 g of *n*-Bu₄NCl (10.0 mmol), 1.75 mL of *i*Pr₂EtN (10.0 mmol), 0.26 g of PPh₃ (1.00 mmol) and 0.125 g of Pd(OAc)₂ (0.50 mmol) in 50 mL of DMF. The reaction mixture was purified by flash chromatography (10:90 EtOAc:hexanes) affording the product as an orange oil (1.02 g, 66%): ¹H NMR (500 MHz, CDCl₃) δ 7.97 (dd, *J* = 9.0, 2.0 Hz, 1H), 7.83 (d, *J* = 2.0 Hz, 1H), 7.29 – 7.28 (m, 3H), 7.23 – 7.22 (m, 2H), 6.62 (d, *J* = 8.0 Hz, 1H), 4.66 (s, 2H), 2.57 (t, *J* = 7.0 Hz, 2H), 2.39 (t, *J* = 8.0 Hz, 2H), 1.92 (m, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 206.2 (C), 149.8 (C), 143.1 (C), 138.3 (C), 137.4 (C), 137.1 (C), 129.4 (CH), 128.9 (CH), 128.2 (CH), 126.6 (CH), 125.8 (C), 125.7 (CH), 114.7 (CH), 40.3 (CH₂), 32.1 (CH₂), 19.6 (CH₂). ATR-FTIR(thin film): 3477, 3357, 3221, 3055, 2959, 1709, 1621, 1486, 1262, 1101, 827, 732 cm⁻¹.



4.174

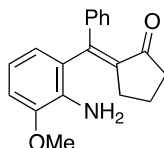
2-Alkylidenecyclopentanone 4.174. The general procedure was followed using 0.860 g of 1-(1-phenylethynyl)cyclobutanol **4.99** (5.00 mmol), 1.40 g of 2-iodo-5-methylaniline (6.00 mmol), 2.78 g of *n*-Bu₄NCl (10.0 mmol), 1.75 mL of *i*Pr₂EtN (10.0 mmol), 0.26 g of PPh₃ (1.00 mmol) and 0.125 g of Pd(OAc)₂ (0.50 mmol) in 50 mL of DMF. The reaction mixture was purified by flash chromatography (10:90EtOAc:hexanes) affording the product as an orange oil. The product contained some inseparable impurities that were removed after the subsequent azidation step. ¹H NMR (500 MHz, CDCl₃) δ 7.32 – 7.30 (m, 5H), 6.84 (d, *J* = 8.0 Hz, 1H), 6.56 (d, *J* = 8.0 Hz, 1H), 6.52 (m, 1H), 3.65 (s, 3H), 2.66 (t, *J* = 7.0 Hz, 2H), 2.43 (t, *J* = 7.5 Hz, 2H), 1.94 (m, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 206.4 (C), 146.3 (C), 143.6 (C), 139.4(C), 138.9 (C), 135.5 (C), 129.9 (CH), 129.6 (CH), 128.4 (CH), 127.9 (CH), 119.1 (CH), 116.6 (CH), 40.5 (CH₂), 32.5 (CH₂), 21.4 (CH₃), 19.9 (CH₂) only visible signals. ATR-FTIR(thin film): 3467, 3368, 3054, 2956, 1704, 1613, 1588, 1435, 1200, 1172, 834, 732 cm⁻¹.



4.175

2-Alkylidenecyclopentanone 4.175. The general procedure was followed using 0.860 g of 1-(1-phenylethynyl)cyclobutanol **4.99** (5.00 mmol), 1.52 g of 5-chloro-2-iodoaniline (6.00

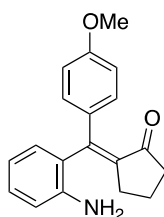
mmol), 2.78 g of *n*-Bu₄NCl (10.0 mmol), 1.75 mL of *i*Pr₂EtN (10.0 mmol), 0.26 g of PPh₃ (1.00 mmol) and 0.125 g of Pd(OAc)₂ (0.50 mmol) in 50 mL of DMF. The reaction mixture was purified by flash chromatography (10:90EtOAc:hexanes) affording the product as an orange oil. The product contained some inseparable impurities that were removed after the subsequent azidation step. ¹H NMR (500 MHz, CDCl₃) δ 7.31 – 7.29 (m, 5H), 7.05 (d, *J* = 2.5 Hz, 1H), 6.90 (d, *J* = 2.5 Hz, 1H), 6.61 (d, *J* = 8.5 Hz, 1H), 3.71 (s, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.41 (t, *J* = 7.5 Hz, 2H), 1.93 (m, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 206.1 (C), 144.5 (C), 142.1 (C), 137.8 (C), 136.2 (C), 135.7 (C), 129.4 (CH), 129.1 (CH), 129.0 (CH), 128.7 (CH), 128.0 (CH), 122.7 (C), 117.2 (CH), 40.4 (CH₂), 32.2 (CH₂), 19.7 (CH₂).ATR-FTIR(thin film): 3445, 3365, 3055, 2958, 2879, 1704, 1593, 1486, 1416, 1195, 914, 735 cm⁻¹.



4.176

2-Alkylidenecyclopentanone 4.176. The general procedure was followed using 0.860 g of 1-(1- phenylethynyl)cyclobutanol **4.99** (5.00 mmol), 1.50 g of 2-iodo-6-methoxyaniline (6.00 mmol), 2.78 g of *n*-Bu₄NCl (10.0 mmol), 1.75 mL of *i*Pr₂EtN (10.0 mmol), 0.260 g of PPh₃ (1.00 mmol) and 0.125 g of Pd(OAc)₂ (0.500mmol) in 50 mL of DMF. The reaction mixture was purified by flash chromatography (30:70EtOAc:hexanes) affording the product as an orange oil (0.59 g, 40%). ¹H NMR (500 MHz, CDCl₃) δ 7.30 (m, 5H), 6.77 (d, *J* = 7.0 Hz, 1H), 6.70 (t, *J* = 7.5 Hz, 1H), 6.59 (dd, *J* = 7.5, 1.0 Hz, 1H), 3.90 (s, 2H), 3.86 (s, 3H), 2.65 (t, *J* = 7.0 Hz, 2H),

2.43 (t, $J = 8.0$ Hz, 2H), 1.93 (m, $J = 7.5$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 206.3 (C), 147.4 (C), 145.8 (C), 138.6 (C), 135.6 (C), 133.6 (C), 129.4 (CH), 128.4 (CH), 127.8 (CH), 127.5 (C), 121.7 (CH), 117.3 (CH), 109.5 (CH), 55.6 (CH_2), 40.5 (CH_2), 32.3 (CH_2), 19.8 (CH_2); ATR-FTIR(thin film): 3451, 3376, 3034, 2934, 2823, 1706, 1582, 1489, 1245, 1134, 818, 732 cm^{-1} .

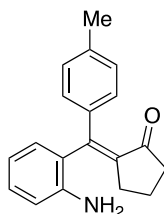


4.177

2-Alkylidenecyclopentanone 4.177. The general procedure was followed using 0.178 g of 1-((4-methoxyphenyl)ethynyl)cyclobutanol (0.880 mmol), 0.385 g of 2-iodoaniline (1.76 mmol), 0.489 g of *n*-Bu₄NCl (1.76 mmol), 0.300 mL of *i*Pr₂EtN (1.76 mmol), 0.0460 g of PPh₃ (0.176 mmol) and 0.0190 g of Pd(OAc)₂ (0.0880 mmol) in 10 mL of DMF. The reaction mixture was purified by flash chromatography (10:90 EtOAc:hexanes) affording the product as an orange oil (0.113 g, 44%). The product contained some inseparable impurities that were removed after the subsequent electrocyclization. ^1H NMR (500 MHz, CDCl_3) δ 7.21 (d, $J = 8.5$ Hz, 2H), 7.09 (t, $J = 7.4$ Hz, 1H), 6.90 (d, $J = 7.3$ Hz, 1H), 6.78 (d, $J = 8.5$ Hz, 2H), 6.70 (t, $J = 7.3$ Hz, 1H), 6.65 (d, $J = 7.9$ Hz, 1H), 3.83 (s, 3H), 3.63 (s, 2H), 2.58 (t, $J = 6.7$ Hz, 2H), 2.39 (t, $J = 7.6$ Hz, 2H), 1.87 (quintet, $J = 7.3$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 206.3 (C), 159.9 (C), 146.1 (C), 143.6 (C), 134.3 (C), 131.3 (CH), 130.4 (s, C), 129.8 (CH), 129.2 (CH), 127.8

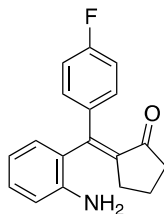
(C), 118.0 (CH), 116.0 (CH), 113.2 (CH), 55.2 (CH₃), 40.7 (CH₂), 32.5 (CH₂), 19.8 (CH₂).

HRMS (EI) m/z calculated for C₁₉H₁₉O₂N(M⁺): 293.1415, found 293.1410.



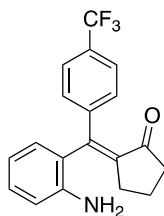
4.178

2-Alkylidenecyclopentanone 4.178. The general procedure was followed using 0.200 g of 1-((4-methylphenyl)ethynyl)cyclobutanol (1.07 mmol),⁴ 0.472 g of 2-iodoaniline (2.15 mmol), 0.596 g of *n*-Bu₄NCl (2.15 mmol), 0.36 mL of *i*Pr₂EtN (2.15 mmol), 0.060 g of PPh₃ (0.215 mmol) and 0.024 g of Pd(OAc)₂ (0.11 mmol) in 10.7 mL of DMF. The reaction mixture was purified by flash chromatography (10:90 EtOAc:hexanes) affording the product as an orange oil (0.062 g, 21%). The product contained some inseparable impurities that were removed after the subsequent azidation step. ¹H NMR (500 MHz, CDCl₃) δ 7.18 – 7.09 (m, 5H), 6.95 (d, *J* = 7.4 Hz, 1H), 6.74 (t, *J* = 7.0 Hz, 1H), 6.68 (d, *J* = 7.9 Hz, 1H), 3.64 (s, 2H), 2.62 (t, *J* = 6.9 Hz, 2H), 2.43 (t, *J* = 7.7 Hz, 2H), 2.34 (s, 3H), 1.92 (t, *J* = 7.3 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 206.3 (C), 146.3 (C), 143.4 (C), 138.5 (C), 135.3 (C), 135.1 (C), 129.8 (CH), 129.5 (CH), 129.2 (CH), 128.6 (CH), 127.6 (C), 118.2 (CH), 116.0 (CH), 40.5 (CH₂), 32.4 (CH₂), 21.4 (CH₃), 19.9 (CH₂); IR (thin film): 3462, 3368, 3051, 3019, 2956, 2925, 2871, 1707, 1609, 1486, 1452, 1170, 822, 750 cm⁻¹. HRMS (EI) m/z calculated for C₁₉H₁₉ON (M⁺): 277.1466, found 277.1470.



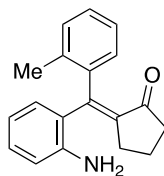
4.179

2-Alkylidenecyclopentanone 4.179. The general procedure was followed using 0.100 g of 1-((4-fluorophenyl)ethynyl)cyclobutanol (0.520mmol),⁴ 0.228 g of 2-iodoaniline (1.04 mmol), 0.292 g of *n*-Bu₄NCl (1.04 mmol), 0.180 mL of *i*Pr₂EtN (1.04 mmol), 0.0280 g of PPh₃ (0.104 mmol) and 0.0120 g of Pd(OAc)₂ (0.0520mmol) in 5.2 mL of DMF. The reaction mixture was purified by flash chromatography (10:90 EtOAc:hexanes) affording the product as an orange oil (0.082 g, 56%). The product contained some inseparable impurities that were removed after the subsequent azidation step. ¹H NMR (500 MHz, CDCl₃) δ 7.38 (d, *J* = 4.4 Hz, 1H), 7.24 (d, *J* = 1.4 Hz, 1H), 7.13 (t, *J* = 7.6 Hz, 1H), 6.97 (t, *J* = 7.8 Hz, 2H), 6.91 (d, *J* = 7.6 Hz, 1H), 6.75 (d, *J* = 7.3 Hz, 1H), 6.71 (t, *J* = 7.1 Hz, 1H), 3.64 (s, 2H), 2.62 (t, *J* = 6.8 Hz, 2H), 2.43 (t, *J* = 7.7 Hz, 2H), 1.93 (quintet, *J* = 7.4 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 206.3 (C), 162.8 (d, *J*_{CF} = 249.7 Hz, CF), 144.9 (C), 143.2 (C), 135.6 (C), 135.2 (C), 131.5 (d, *J*_{CF} = 8.8 Hz, CH), 129.7 (CH), 129.4 (CH), 127.7 (C), 118.3 (CH), 116.1 (CH), 114.9 (d, *J*_{CF} = 21.9 Hz, CH), 40.5 (CH₂), 32.3 (CH₂), 19.8 (CH₂); ¹⁹F NMR (282 MHz, CDCl₃) δ -113.07; IR (thin film): 3472, 3373, 3061, 2956, 2925, 1704, 1596, 1502, 1223, 1154, 837 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₈H₁₆ONF (M⁺): 281.1215, found 281.1219.



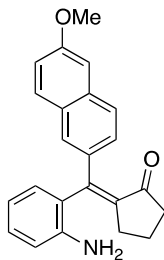
4.180

2-Alkylidenecyclopentanone 4.180. The general procedure was followed using 0.250 g of 1-((4-trifluoromethylphenyl)ethynyl)cyclobutanol (1.04 mmol), 0.455 g of 2-iodoaniline (2.07 mmol), 0.580 g of *n*-Bu₄NCl (2.07 mmol), 0.350 mL of *i*Pr₂EtN (2.07 mmol), 0.0590 g of PPh₃ (0.210mmol) and 0.0250 g of Pd(OAc)₂ (0.104 mmol) in 11 mL of DMF. The reaction mixture was purified by flash chromatography (10:90 EtOAc:hexanes) affording the product as an orange oil (0.172 g, 50%). The product contained some inseparable impurities that were removed after the subsequent azidation step. ¹H NMR (500 MHz, CDCl₃) δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.36 (d, *J* = 8.1 Hz, 2H), 7.14 (td, *J* = 7.7, 1.3 Hz, 1H), 6.89 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.74 (dd, *J* = 7.5, 0.6 Hz, 1H), 6.72 (d, *J* = 8.0 Hz, 1H), 3.68 (s, 2H), 2.65 (t, *J* = 7.0 Hz, 2H), 2.44 (t, *J* = 7.8 Hz, 2H), 1.96 (quintet, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 206.3 (C), 144.1 (C), 143.1 (C), 142.4 (C), 137.0 (C), 129.8 (C), 129.6 (d, *J* = 8.9 Hz, CH), 127.9 (CH), 127.7 (q, *J* = 241.3 Hz, CF), 127.8 (CH), 126.7 (C), 124.8 (CH), 118.4 (CH), 116.1 (CH), 40.3 (CH₂), 32.1 (CH₂), 19.7 (CH₂); ¹⁹F NMR (282 MHz, CDCl₃) δ -62.92; IR (thin film): 3472, 3368, 3212, 3054, 2960, 2853, 1707, 1609, 1492, 1407, 1321, 1163, 1116, 1069, 844, 740 cm⁻¹; HRMS (EI) *m/z* calculated for C₁₉H₁₆ONF₃(M⁺): 332.1262, found 332.1248.



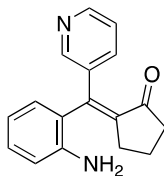
4.181

2-Alkylidenecyclopentanone 4.181. The general procedure was followed using 0.0500 g of 1-((2-methylphenyl)ethynyl)cyclobutanol (0.270mmol), 0.117 g of 2-iodoaniline (0.540mmol), 0.150 g of *n*-Bu₄NCl (0.54 mmol), 0.090 mL of iPr₂EtN (0.54 mmol), 0.014 g of PPh₃ (0.054 mmol) and 0.0060 g of Pd(OAc)₂ (0.027 mmol) in 2.5 mL of DMF. The reaction mixture was purified by flash chromatography (10:90 EtOAc:hexanes) affording the product as an orange oil (0.0200 g, 27%). The product contained some inseparable impurities that were removed after the subsequent azidation step. ¹H NMR (500 MHz, CDCl₃) δ 7.18 (tt, *J* = 15.8, 7.9 Hz, 3H), 7.09 (q, *J* = 8.5 Hz, 2H), 6.90 (d, *J* = 7.6 Hz, 1H), 6.68 (dt, *J* = 13.7, 7.1 Hz, 2H), 3.86 (s, 2H), 2.70 (d, *J* = 31.9 Hz, 2H), 2.37 (t, *J* = 7.6 Hz, 2H), 2.14 (s, 3H), 1.96 (ddd, *J* = 2.0, 1.1, 0.6 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 206.5 (C), 164.0 (C), 144.6 (C), 143.4 (C), 140.0 (C), 135.5 (C), 130.3 (CH), 130.0 (CH), 129.3 (CH), 129.1 (CH), 127.8 (CH), 126.1 (CH), 125.6 (CH), 118.0 (CH), 115.9 (CH), 39.8 (CH₂), 31.8 (CH₂), 20.2 (CH₃), 19.8 (CH₂); IR(thin film): 3370, 3061, 2956, 2921, 2855, 1710, 1606, 1448, 1265, 1015, 736 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₉H₁₉ON (M⁺): 277.1466, found 277.1461.



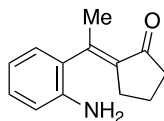
4.182

2-Alkylidenecyclopentanone 4.182. The general procedure was followed using 0.500 g of 1-((1-naphthenyl)ethynyl)cyclobutanol (1.98 mmol), 0.565 g of 2-iodoaniline (2.58 mmol), 1.10 g of *n*-Bu₄NCl (3.96 mmol), 0.700 mL of *i*Pr₂EtN (3.96 mmol), 0.104 g of PPh₃ (0.396 mmol) and 0.0440 g of Pd(OAc)₂ (0.198 mmol) in 20 mL of DMF. The reaction mixture was purified by flash chromatography (10:90 EtOAc:hexanes) affording the product as a yellow solid (0.342 g, 50%). The product contained some inseparable impurities that were removed after the subsequent azidation step. ¹H NMR (500 MHz, CDCl₃) δ 7.63 (dd, *J* = 14.7, 6.6 Hz, 3H), 7.39 (dd, *J* = 8.5, 1.6 Hz, 1H), 7.14 (t, *J* = 8.3 Hz, 1H), 7.10 (d, *J* = 2.2 Hz, 1H), 7.08 (dd, *J* = 8.8, 2.5 Hz, 1H), 6.99 (dd, *J* = 7.6, 1.3 Hz, 1H), 6.75 (t, *J* = 7.4 Hz, 1H), 6.70 (d, *J* = 8.1 Hz, 1H), 3.91 (s, 3H), 3.68 (s, 2H), 2.67 (t, *J* = 7.1 Hz, 2H), 2.45 (t, *J* = 7.8 Hz, 2H), 1.96 (quintet, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 206.3 (C), 158.3 (C), 146.3 (C), 143.6 (C), 135.3 (C), 134.7 (C), 133.6 (C), 130.0 (CH), 129.3 (CH), 128.9 (CH), 128.5 (C), 128.3 (CH), 127.9 (C), 126.0 (CH), 118.8 (CH), 118.3 (CH), 116.1 (CH), 105.8 (CH), 55.4 (CH₃), 40.5 (CH₂), 32.6 (CH₂), 19.9 (CH₂) only signals visible; IR (thin film): 3472, 3364, 3215, 3054, 2956, 2893, 2836, 1698, 1603, 1408, 1259, 1160, 1027, 851, 736 cm⁻¹. HRMS (EI) *m/z* calculated for C₂₃H₂₁O₂N (M⁺): 343.1472, found 343.1576.

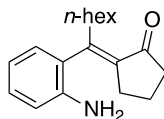


4.183

2-Alkylidenecyclopentanone 4.183. The general procedure was followed using 0.500 g of 1-((3-pyridyl)ethynyl)cyclobutanol **4.165** (2.89 mmol), 0.822 g of 2-iodoaniline (3.75 mmol), 1.61 g of *n*-Bu₄NCl (5.78 mmol), 1.00 mL of *i*Pr₂EtN (5.78 mmol), 0.152 g of PPh₃ (0.578 mmol) and 0.0650 g of Pd(OAc)₂ (0.289 mmol) in 29 mL of DMF. The reaction mixture was purified by flash chromatography (10:90 EtOAc:hexanes) affording the product as an orange oil (0.218 g, 29%). The product contained some inseparable impurities that were removed after the subsequent azidation step. ¹H NMR (500 MHz, CDCl₃) δ 8.44 (s, 2H), 7.51 (dt, *J* = 7.9, 1.8 Hz, 1H), 7.16 (dd, *J* = 7.8, 4.9 Hz, 1H), 7.08 (t, *J* = 8.4 Hz, 1H), 6.81 (d, *J* = 7.9 Hz, 1H), 6.66 (t, *J* = 7.2 Hz, 2H), 3.76 (s, 2H), 2.60 (t, *J* = 6.5 Hz, 2H), 2.37 (t, *J* = 7.8 Hz, 2H), 1.89 (quintet, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 206.2 (C), 150.0 (CH), 148.9 (CH), 143.2 (C), 142.0 (C), 137.2 (C), 136.7 (CH), 134.6 (C), 129.5 (CH), 126.4 (C), 122.7 (CH), 118.2 (CH), 116.0 (CH), 40.3 (CH₂), 32.0 (CH₂), 19.6 (CH₂) only signals visible; IR (thin film): 3418, 3326, 3215, 1698, 1638, 1588, 1407, 1306, 1192, 1027, 819, 743 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₇H₁₆ON₂(M⁺): 264.1262, found 264.1261.



2-Alkylidenecyclopentanone 4.184.^{2b} The general procedure was followed using 0.200 g of 1-(1-propynyl)cyclobutanol (1.82 mmol), 0.790 g of 2-iodoaniline (3.63 mmol), 1.00 g of *n*-Bu₄NCl (3.63 mmol), 0.630 mL of *i*Pr₂EtN (3.63 mmol), 0.0950 g of PPh₃ (0.360mmol) and 0.410 g of Pd(OAc)₂ (0.180mmol) in 18 mL of DMF. The reaction mixture was purified by flash chromatography (10:90 EtOAc:hexanes) affording the product as an orange oil (0.256 g, 70%). The product contained some inseparable impurities that were removed after the subsequent azidation step. The spectral data for the product matched that reported by Larock and Reddy:^{2b} ¹H NMR (500 MHz, CDCl₃) δ 7.09 (td, *J* = 7.7, 1.1 Hz, 1H), 6.91 (dd, *J* = 7.6, 1.4 Hz, 1H), 6.75 (td, *J* = 7.4, 0.8 Hz, 1H), 6.70 (d, *J* = 8.0 Hz, 1H), 3.64 (s, 2H), 2.45 (s, 4H), 2.38 (t, *J* = 7.8 Hz, 3H), 1.81 (quintet, *J* = 7.3 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 208.7 (C), 145.5 (C), 141.7 (C), 134.4 (C), 129.1 (C), 128.5 (CH), 127.2 (CH), 118.4 (CH), 115.5 (CH), 40.7 (CH₂), 30.5 (CH₂), 19.8 (CH₂), 19.7(CH₃). IR(thin film): 3465, 3368, 3218, 3054, 2963, 2881, 2839, 1698, 1613, 1588, 1492, 1448, 1302, 1195, 996, 829, 746 cm⁻¹.



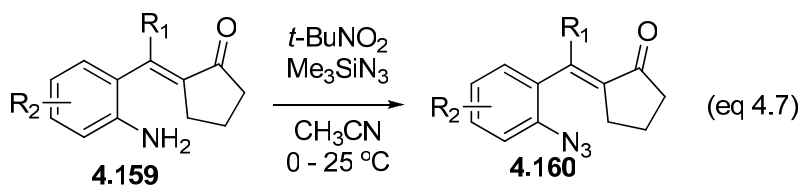
2-Alkylidenecyclopentanone 4.185. The general procedure was followed using 0.200 g of 1-(1-octynyl)cyclobutanol (1.10 mmol), 0.488 g of 2-iodoaniline (2.23 mmol), 0.616 g of *n*-Bu₄NCl (2.23 mmol), 0.4 mL of *i*Pr₂EtN (2.23 mmol), 0.0640 g of PPh₃ (0.220mmol) and 0.0240 g of Pd(OAc)₂ (0.110mmol) in 18 mL of DMF. The reaction mixture was purified by flash

chromatography (10:90 EtOAc:hexanes) affording the product as an orange oil (0.098 g, 33%). The product contained some inseparable impurities that were removed after the subsequent azidation step. ^1H NMR (500 MHz, CDCl_3) δ 7.09 (td, $J = 7.7, 1.1$ Hz, 1H), 6.89 (dd, $J = 7.5, 1.1$ Hz, 1H), 6.75 (t, $J = 7.4$ Hz, 1H), 6.70 (d, $J = 8.0$ Hz, 1H), 3.62 (s, 2H), 3.17–3.10 (m, 1H), 2.77 (dt, $J = 12.0, 7.6$ Hz, 1H), 2.47 (dt, $J = 16.2, 7.9$ Hz, 1H), 2.37 (t, $J = 7.9$ Hz, 2H), 2.31 (dd, $J = 16.5, 6.8$ Hz, 1H), 1.80 (s, $J = 7.1$ Hz, 2H), 1.36–1.29 (m, 4H), 1.23 (t, $J = 3.3$ Hz, 4H), 0.84 (t, $J = 6.8$ Hz, 3H); ^{13}C NMR (125 MHz, CDCl_3) δ 208.1 (C), 150.6 (C), 142.2 (C), 134.2 (C), 128.4 (C), 127.9 (CH), 127.5 (CH), 118.2 (CH), 115.4 (CH), 40.7 (CH_2), 32.8 (CH_2), 31.7 (CH_2), 30.7 (CH_2), 29.6 (CH_2), 28.4 (CH_2), 22.6 (CH_2), 19.9 (CH_2), 14.1 (CH_3); IR (thin film): 3469, 3368, 3219, 2956, 2925, 2852, 1698, 1616, 1492, 1448, 1299, 1195, 829, 746 cm^{-1} . HRMS (EI) m/z calculated for $\text{C}_{18}\text{H}_{25}\text{ON}$ (M^+): 271.1936 found 271.1931.

4.6.1.4 Synthesis of Styryl Azides.

General procedure.

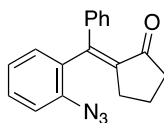
The 2-alkylidenecyclopentanones were converted to styryl azides following the diazotization reported by Zhang and Moses (eq s3).^[3]



In a 10 mL round bottom flask was dissolved 0.200 g of 2-alkylidenecyclopentanone (0.92 mmol) in 4 mL of CH_3CN . The resulting solution was cooled to 0°C and 0.360 mL of t -

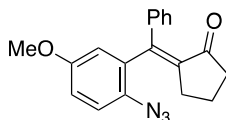
BuNO₂ (2.98mmol) was added followed by the dropwise addition of 0.520 mL of Me₃SiN₃ (3.96mmol). After 1 h, the reaction mixture was concentrated *in vacuo* and the resulting residue was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.20 g, 90%).

Characterization data for styryl azides.



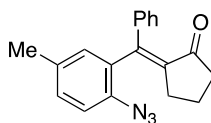
4.102

Styryl Azide 4.102. The general procedure was followed using 0.220 g of 2-alkyldienecyclopentanone **4.101** (0.84 mmol), 0.300 mL of *t*-BuNO₂ (2.50 mmol) and 0.79 mL of Me₃SiN₃ in 15 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.200 g, 83%): ¹H NMR (500 MHz, CDCl₃) δ 7.36 (td, *J* = 7.6, 1.6 Hz, 1H), 7.30 (d, *J* = 1.6 Hz, 1H), 7.29 (d, *J* = 2.0 Hz, 2H), 7.23 (dd, *J* = 6.6, 3.0 Hz, 2H), 7.20 (d, *J* = 8.0 Hz, 1H), 7.14 (td, *J* = 7.4, 0.6 Hz, 1H), 7.11 (dd, *J* = 7.6, 1.8 Hz, 1H), 2.52 (t, *J* = 0.4 Hz, 2H), 2.42 (t, *J* = 7.8 Hz, 2H), 1.92 (quintet, *J* = 7.2 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 205.7 (C), 144.7 (C), 138.7 (C), 137.1 (C), 135.6 (C), 133.9 (C), 130.1 (CH), 129.3 (CH), 129.1 (CH), 128.0 (CH), 127.7 (CH), 124.9 (CH), 118.8 (CH), 40.4 (CH₂), 31.9 (CH₂), 19.7 (CH₂); IR (thin film): 3050, 2958, 2364, 2333, 2121, 1708, 1589, 1446, 1361, 1295, 1176, 746 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₈H₁₅ON₃(M⁺): 290.1293 found 290.1295.



4.106

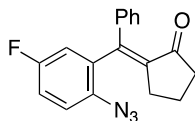
Styryl Azide 4.106. The general procedure was followed using 0.293 g of 2-alkyldenecyclopentanone **4.167** (1.00 mmol), 0.47 mL of *t*-BuNO₂ (4.00 mmol) and 0.42 mL of Me₃SiN₃ in 5 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.271 g, 85%): ¹H NMR (500 MHz, CDCl₃) δ 7.31 – 7.30 (m, 3H), 7.27 – 7.26 (m, 2H), 7.12 (d, *J* = 8.5 Hz, 1H), 6.90 (dd, *J* = 8.5, 3.0 Hz, 1H), 6.66 (d, *J* = 3.0 Hz, 1H), 3.76 (s, 3H), 2.56 (s, 2H), 2.42 (t, *J* = 8.0 Hz, 2H), 1.94 (m, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 205.6 (C), 156.9 (C), 144.4 (C), 138.5 (C), 135.6 (C), 135.0 (C), 129.5 (C), 129.0 (CH), 128.1 (CH), 127.7 (CH), 120.0 (CH), 115.3 (CH), 114.7 (CH), 55.7 (CH₃), 40.4 (CH₂), 31.9 (CH₂), 19.7 (CH₂). ATR-FTIR (thin film): 3055, 2960, 2119, 1711, 1597, 1489, 1285, 1265, 1234, 1179, 732, 700 cm⁻¹. HRMS (ES pos.) *m/z* calculated for C₁₉H₁₈N₃O₂ [M+H]⁺: 320.1399, found: 320.1400.



4.108

Styryl Azide 4.108. The general procedure was followed using 0.277 g of 2-alkyldenecyclopentanone **4.168** (1.00 mmol), 0.47 mL of *t*-BuNO₂ (4.00 mmol) and 0.42 mL of Me₃SiN₃ in 5 mL of CH₃CN. The reaction mixture was purified by flash chromatography

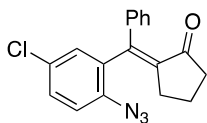
(5:95EtOAc:hexanes) to afford the styryl azide as a brown oil (0.297 g, 98%): ^1H NMR (500 MHz, CDCl_3) δ 7.34 – 7.30 (m, 5H), 7.18 (d, J = 8.0 Hz, 1H), 7.12 (d, J = 8.0 Hz, 1H), 6.96 (s, 1H), 2.58 (s, 2H), 2.45 (t, J = 8.0 Hz, 2H), 2.34 (s, 3H), 1.95 (m, J = 7.0 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 205.6 (C), 144.8 (C), 138.9 (C), 135.5 (C), 134.9 (C), 134.3 (C), 133.9 (C), 130.5 (CH), 130.1 (CH), 129.1 (CH), 128.0 (CH), 127.7 (CH), 118.8 (CH), 40.4 (CH_2), 31.9 (CH_2), 20.9 (CH_3), 19.7 (CH_2). ATR-FTIR(thin film): 3054, 2963, 2118, 1710, 1596, 1490, 1293, 1184, 907, 808 cm^{-1} . HRMS (ES pos.) m/z calculated for $\text{C}_{19}\text{H}_{18}\text{N}_3\text{O}$ $[\text{M}+\text{H}]^+$: 304.1450, found: 304.1445.



4.110

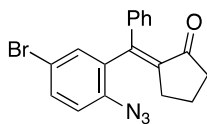
Styryl Azide 4.110. The general procedure was followed using 0.281 g of 2-alkylidenecyclopentanone **4.169** (1.00 mmol), 0.47 mL of *t*-BuNO₂ (4.00 mmol) and 0.42 mL of Me₃SiN₃ in 5 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95EtOAc:hexanes) to afford the styryl azide as a brown oil (0.225 g, 80%). ^1H NMR (500 MHz, CDCl_3) δ 7.31 – 7.30 (m, 3H), 7.23 – 7.22 (m, 2H), 7.15 (dd, J = 8.5, 5.0 Hz, 1H), 6.71 (dt, J = 8.5, 3.0 Hz, 1H), 6.85 (dd, J = 8.5, 3.0 Hz, 1H), 2.53 (s, 2H), 2.42 (t, J = 8.0 Hz, 2H), 1.94 (m, J = 7.5 Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 205.4 (C), 159.6 (d, J_{CF} = 245 Hz, C), 143.2 (C), 138.1 (C), 136.0 (C), 135.4 (d, J_{CF} = 7.3 Hz, C), 133.0 (C), 129.0 (CH), 128.3 (CH), 127.8 (CH), 120.3 (d, J_{CF} = 9.0 Hz, CH), 116.8 (d, J_{CF} = 22.1 Hz, CH), 116.2 (d, J_{CF} = 23.8 Hz, CH), 40.3 (CH_2), 31.8 (CH_2), 19.6 (CH_2); ^{19}F NMR (282 MHz, CDCl_3) δ -15.46. ATR-FTIR(thin

film): 3056, 2964, 2885, 2119, 1713, 1599, 1484, 1267, 1179, 1104, 814 cm^{-1} . HRMS (EI) m/z calculated for $\text{C}_{18}\text{H}_{14}\text{FN}_3\text{O}$ (M^+): 307.3217, found: 307.1198.



4.112

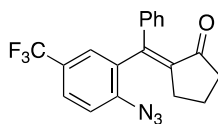
Styryl Azide 4.112. The general procedure was followed using 0.297 g of 2-alkylidenecyclopentanone **4.170** (1.00 mmol), 0.47 mL of *t*-BuNO₂ (4.00 mmol) and 0.42 mL of Me₃SiN₃ in 5 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.244 g, 82%). ¹H NMR (500 MHz, CDCl₃) δ 7.33 – 7.31 (m, 4H), 7.23 – 7.22 (m, 2H), 7.13 (d, J = 8.5 Hz, 1H), 7.11 (d, J = 2.5 Hz, 1H), 2.53 (s, 2H), 2.42 (t, J = 8.0 Hz, 2H), 1.94 (m, J = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 205.3 (C), 143.1 (C), 138.1 (C), 136.1 (C), 135.9 (C), 135.3 (C), 130.3 (C), 129.9 (CH), 129.3 (CH), 129.1 (CH), 128.3 (CH), 127.8 (CH), 120.2 (C), 40.3 (CH₂), 31.8 (CH₂), 19.6 (CH₂). ATR-FTIR (thin film): 3055, 2965, 2882, 2122, 2092, 1713, 1610, 1475, 1297, 1174, 907 cm^{-1} . HRMS (ES pos.) m/z calculated for $\text{C}_{18}\text{H}_{15}\text{ClN}_3\text{O}$ [$\text{M}+\text{H}$]⁺: 324.0904, found: 324.0905.



4.114

Styryl Azide 4.114. The general procedure was followed using 0.341 g of 2-

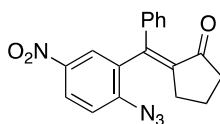
alkylidenecyclopentanone **4.171** (1.00 mmol), 0.47 mL of *t*-BuNO₂ (4.00 mmol) and 0.42 mL of Me₃SiN₃ in 5 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95EtOAc:hexanes) to afford the styryl azide as a brown oil (0.301 g, 82%). ¹H NMR (500 MHz, CDCl₃) δ 7.45 (dd, *J* = 8.5, 2.5 Hz, 1H), 7.32 – 7.30 (m, 3H), 7.24 (d, *J* = 2.5 Hz, 1H), 7.23 – 7.21 (m, 2H), 7.07 (d, *J* = 8.5 Hz, 1H), 2.52 (s, 2H), 2.42 (t, *J* = 8.0 Hz, 2H), 1.94 (m, *J* = 7.0 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 205.4 (C), 143.0 (C), 138.0 (C), 136.4 (C), 136.1 (C), 135.6 (C), 132.7 (CH), 132.2 (CH), 129.0 (CH), 128.3 (CH), 127.8 (CH), 120.5 (CH), 117.8 (C), 40.3(CH₂), 31.8 (CH₂), 19.6 (CH₂). ATR-FTIR(thin film): 3055, 2963, 2883, 2120, 2088, 1712, 1609, 1474, 1294, 1174,808 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₈H₁₄BrN₃O (M⁺): 368.2273, found: 368.0398.



4.116

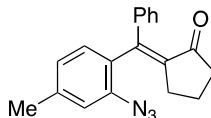
Styryl Azide 4.116. The general procedure was followed using 0.331 g of 2-alkylidenecyclopentanone **4.172** (1.00 mmol), 0.47 mL of *t*-BuNO₂ (4.00 mmol) and 0.42 mL of Me₃SiN₃ in 5 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95EtOAc:hexanes) to afford the styryl azide as a brown oil (0.343 g, 96%): ¹H NMR (500 MHz, CDCl₃) δ 7.61 (d, *J* = 8.5 Hz, 1H), 7.39 (s, 1H), 7.32 – 7.29 (m, 4H), 7.24 – 7.22 (m, 2H), 2.50 (s, 2H), 2.43 (t, *J* = 8.0 Hz, 2H), 1.95 (m, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 205.3 (C), 143.0 (C), 140.9 (C), 137.9 (C), 136.4 (C), 134.3 (C), 129.1 (CH), 128.4 (CH), 127.9 (CH), 127.2 (q, *J*_{CF} = 33 Hz, C), 127.1 (q, *J*_{CF} = 3.3 Hz, CH), 126.3 (q, *J*_{CF} = 3.3 Hz, CH), 121.6

(q, $J_{CF} = 270$, CF₃), 119.3 (CH), 40.3 (CH₂), 31.8 (CH₂), 19.6 (CH₂); ¹⁹F NMR (282 MHz, CDCl₃) – 62.43. ATR-FTIR(thin film): 3057, 2960, 2124, 2098, 1714, 1607, 1492, 1333, 1263, 1153, 1075, 823 cm⁻¹. HRMS (ES pos.) m/z calculated for C₁₉H₁₅F₃N₃O [M+H]⁺: 358.1167, found: 358.1169.



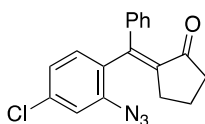
4.118

Styryl Azide 4.118. The general procedure was followed using 0.308 g of 2-alkylidenecyclopentanone **4.173** (1.00 mmol), 0.47 mL of *t*-BuNO₂ (4.00 mmol) and 0.42 mL of Me₃SiN₃ in 5 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.244 g, 73%). ¹H NMR (500 MHz, CDCl₃) δ 8.19 (dd, $J = 8.5, 2.5$ Hz, 1H), 8.02 (d, $J = 3.0$ Hz, 1H), 7.32 – 7.29 (m, 4H), 7.25 – 7.23 (m, 2H), 2.52 (t, $J = 6.5$ Hz, 2H), 2.43 (t, $J = 8.0$ Hz, 2H), 1.95 (m, $J = 7.5$ Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 205.1 (C), 144.5 (C), 144.0 (C), 142.0 (C), 137.6 (C), 136.8 (C), 134.5 (C), 129.1 (CH), 128.5 (CH), 127.9 (CH), 125.6 (CH), 124.6 (CH), 119.5 (CH), 40.2 (CH₂), 31.8 (CH₂), 19.6 (CH₂). ATR-FTIR(thin film): 3081, 2959, 2122, 2090, 1713, 1608, 1574, 1517, 1340, 1287, 1192, 826 cm⁻¹. HRMS (ES pos.) m/z calculated for C₁₈H₁₅N₄O₃ [M+H]⁺: 335.1144, found: 335.1138.



4.120

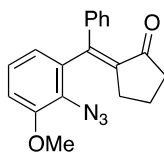
Styryl Azide 4.120. The general procedure was followed using 0.277 g of 2-alkylidenecyclopentanone **4.174** (1.00 mmol), 0.47 mL of *t*-BuNO₂ (4.00 mmol) and 0.42 mL of Me₃SiN₃ in 5 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.288 g, 95%): ¹H NMR (500 MHz, CDCl₃) δ 7.31 – 7.29 (m, 3H), 7.25 – 7.23 (m, 2H), 7.02 – 7.00 (m, 2H), 6.96 (d, *J* = 7.5 Hz, 1H), 2.55 (s, 2H), 2.43 (t, *J* = 8.0 Hz, 2H), 2.39 (s, 3H), 1.93 (m, *J* = 7.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 205.7 (C), 144.8 (C), 139.6 (C), 139.0 (C), 136.9 (C), 135.6 (C), 131.3 (C), 130.0 (CH), 129.1 (CH), 128.0 (CH), 127.6 (CH), 125.9 (CH), 119.3 (CH), 40.4 (CH₂), 32.0 (CH₂), 21.3 (CH₂), 19.7 (CH₂). ATR-FTIR (thin film): 3055, 2958, 2102, 1710, 1607, 1499, 1294, 1194, 1171, 808, 733, 696 cm⁻¹. HRMS (ES pos.) *m/z* calculated for C₁₉H₁₈N₃O [M+H]⁺: 304.1450, found: 304.1458.



4.122

Styryl Azide 4.122. The general procedure was followed using 0.298 g of 2-alkylidenecyclopentanone **4.175** (1.00 mmol), 0.47 mL of *t*-BuNO₂ (4.00 mmol) and 0.42 mL of Me₃SiN₃ in 5 mL of CH₃CN. The reaction mixture was purified by flash chromatography

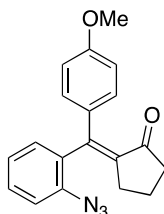
(5:95EtOAc:hexanes) to afford the styryl azide as a brown oil (0.221 g, 68%): ^1H NMR (500 MHz, CDCl_3) δ 7.29 (m, 3H), 7.18 (m, 3H), 7.11 (d, $J = 8.0$ Hz, 1H), 7.03 (d, $J = 8.0$ Hz, 1H), 2.51 (m, 2H), 2.42 (t, $J = 7.5$ Hz, 2H), 1.93 (m, $J = 7.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 205.5 (C), 143.4 (C), 138.5 (C), 138.3 (C), 136.0 (C), 134.8 (C), 132.4 (C), 131.2 (CH), 129.0 (CH), 128.2 (CH), 127.7 (CH), 125.3 (CH), 119.0 (CH), 40.3 (CH_2), 31.9(CH_2), 19.6 (CH_2). ATR-FTIR(thin film): 3082, 2962, 2102, 1712, 1562, 1481, 1392, 1285, 1193, 903 cm^{-1} . HRMS (ES pos.) m/z calculated for $\text{C}_{18}\text{H}_{15}\text{ClN}_3\text{O}$ $[\text{M}+\text{H}]^+$: 324.0904, found: 324.0905.



4.124

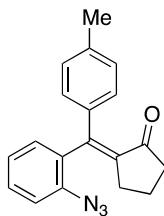
Styryl Azide 4.124. The general procedure was followed using 0.293 g of 2-alkylidenecyclopentanone **4.176** (1.00 mmol), 0.470 mL of *t*-BuNO₂ (4.00 mmol) and 0.420 mL of Me₃SiN₃ in 5 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95EtOAc:hexanes) to afford the styryl azide as a brown oil (0.252 g, 79%). ^1H NMR (500 MHz, CDCl_3) δ 7.31 – 7.26 (m, 5H), 7.09 (t, $J = 8.0$ Hz, 1H), 6.84 (dd, $J = 8.0, 1.0$ Hz, 1H), 6.70 (dd, $J = 7.5, 1.0$ Hz, 1H), 3.90 (s, 3H), 2.55 (s, 2H), 2.42 (t, $J = 8.0$ Hz, 2H), 1.93 (m, $J = 7.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 205.7 (C), 154.2 (C), 145.1 (C), 138.8 (C), 135.7 (C), 135.3 (C), 129.0 (CH), 128.0 (CH), 127.6 (CH), 125.6 (CH), 125.4 (C), 121.4 (CH), 111.1 (CH), 56.0 (CH_3), 40.4 (CH_2), 31.8 (CH_2), 19.7 (CH_2). ATR-FTIR(thin film): 3052, 2960, 2118, 1721, 1586, 1499, 1205, 1125, 1014, 819, 732, 700 cm^{-1} . HRMS (ES pos.) m/z calculated for $\text{C}_{19}\text{H}_{18}\text{N}_3\text{O}_2$

$[M+H]^+$: 320.1399, found: 320.1401.



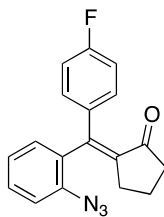
4.129

Styryl Azide 4.129. The general procedure was followed using 0.0780 g of 2-alkylidenecyclopentanone **4.177** (0.27 mmol), 0.097 mL of *t*-BuNO₂ (0.80 mmol) and 0.095 mL of Me₃SiN₃ in 5.5 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.0630 g, 73%). The product contained some inseparable impurities that were removed after the subsequent electrocyclization. ¹H NMR (CDCl₃, 500 MHz) δ 7.35 (td, *J* = 7.7, 1.5 Hz, 1H), 7.19 (d, *J* = 8.2 Hz, 1H), 7.17 (d, *J* = 1.8 Hz, 1H), 7.16 (t, *J* = 2.3 Hz, 1H), 7.13 (dd, *J* = 7.4, 0.9 Hz, 1H), 7.08 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.80 (d, *J* = 8.8 Hz, 2H), 3.80 (s, 3H), 2.48 (s, 2H), 2.42 (t, *J* = 7.8 Hz, 2H), 1.90 (dt, *J* = 14.4, 7.2 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 205.7 (C), 159.6 (C), 144.8 (C), 137.2 (C), 134.5 (C), 134.4 (C), 130.9 (CH), 130.6 (C), 130.2 (CH), 129.2 (CH), 124.9 (CH), 118.8 (CH), 112.9 (CH), 55.2 (CH₃), 40.6 (CH₂), 32.2 (CH₂), 19.7 (CH₂); IR (thin film): 3057, 2960, 2921, 2842, 2118, 1707, 1596, 1505, 1482, 1442, 1290, 1245, 1173, 1027, 825, 730 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₉H₁₇N₃O₂ (M⁺): 319.1321, found 319.1419.



4.131

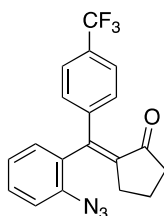
Styryl Azide 4.131. The general procedure was followed using 0.0610 g of 2-alkylidenecyclopentanone **4.177** (0.220 mmol), 0.080 mL of *t*-BuNO₂ (0.66 mmol) and 0.12 mL of Me₃SiN₃ in 4 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.0470 g, 70%): ¹H NMR (CDCl₃, 500 MHz) δ 7.35 (td, *J* = 7.6, 1.4 Hz, 1H), 7.19 (d, *J* = 8.0 Hz, 1H), 7.14 (dt, *J* = 7.4, 3.6 Hz, 2H), 7.10 (q, *J* = 5.5 Hz, 4H), 2.50 (dd, *J* = 1.3, 0.8 Hz, 2H), 2.41 (t, *J* = 7.8 Hz, 2H), 2.34 (s, 3H), 1.91 (dt, *J* = 14.6, 7.4 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 205.6 (C), 144.8 (C), 138.0 (C), 137.1 (C), 135.6 (C), 135.1 (C), 134.2 (C), 130.1 (CH), 129.2 (CH), 129.1 (CH), 128.4 (CH), 124.9 (CH), 118.8 (CH), 40.4 (CH₂), 31.9 (CH₂), 21.4 (CH₂), 19.6 (CH₃); IR (thin film): 2956, 2925, 2855, 2118, 1710, 1606, 1486, 1442, 1294, 1173, 1059, 819, 753 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₉H₁₇N₃O (M⁺): 304.1450, found 304.1447.



4.133

Styryl Azide 4.133. The general procedure was followed using 0.0400 g of 2-

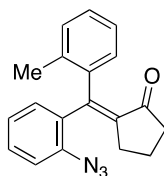
alkylidenecyclopentanone **4.178** (0.140 mmol), 0.0500 mL of *t*-BuNO₂ (0.430 mmol) and 0.070 mL of Me₃SiN₃ in 3 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.0380 g, 88%): ¹H NMR (CDCl₃, 500 MHz) δ 7.37 (td, *J* = 7.7, 1.3 Hz, 1H), 7.21 (s, 1H), 7.19 (dd, *J* = 6.0, 2.6 Hz, 2H), 7.15 (td, *J* = 7.5, 0.5 Hz, 1H), 7.09 (dd, *J* = 7.6, 1.5 Hz, 1H), 6.96 (t, *J* = 8.7 Hz, 2H), 2.51 (t, *J* = 7.3 Hz, 2H), 2.42 (t, *J* = 7.8 Hz, 2H), 1.91 (quintet, *J* = 7.4 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 205.7 (C), 162.7 (d, *J*_{CF} = 247.7 Hz, CF), 143.7 (C), 137.2 (C), 135.6 (C), 134.4 (d, *J*_{CF} = 3.7 Hz, C), 133.7 (C), 131.1 (d, *J*_{CF} = 8.6 Hz, CH), 129.9 (CH), 129.4 (CH), 125.0 (CH), 118.9 (CH), 114.6 (d, *J*_{CF} = 21.8 Hz, CH), 40.4 (CH₂), 31.9 (CH₂), 19.6 (CH₂); ¹⁹F NMR (282 MHz, CDCl₃) δ -113.89; IR (thin film): 2972, 2884, 2118, 1714, 1603, 1505, 1486, 1442, 1294, 1223, 1097, 825, 753 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₈H₁₄FN₃O (M⁺): 308.1199 found 308.1186.



4.135

Styryl Azide 4.135. The general procedure was followed using 0.0750 g of 2-alkylidenecyclopentanone **4.179** (0.230 mmol), 0.0700 mL of *t*-BuNO₂ (0.680 mmol) and 0.10 mL of Me₃SiN₃ in 6 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.0570 g, 71%): ¹H NMR (CDCl₃, 500 MHz) δ 7.53 (d, *J* = 8.2 Hz, 2H), 7.38 (td, *J* = 7.7, 1.4 Hz, 1H), 7.33 (d, *J* = 8.1 Hz, 2H), 7.21 (d, *J* = 8.0 Hz, 1H), 7.15 (td, *J* = 7.5, 0.9 Hz, 1H), 7.11 (dd, *J* = 7.6, 1.5 Hz, 1H), 2.54

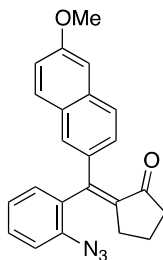
(t, $J = 6.7$ Hz, 2H), 2.42 (t, $J = 7.8$ Hz, 2H), 1.94 (quintet, $J = 7.5$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 205.7 (C), 142.9 (C), 142.5 (C), 137.2 (C), 136.8 (C), 133.0 (C), 129.9 (CH), 129.6 (CH), 129.3 (CH), 125.1 (CH), 124.7 (q, $J_{\text{CF}} = 3.4$ Hz, CH), 124.2 (q, $J_{\text{CF}} = 269.8$ Hz, C), 123.1 (C), 118.9 (CH), 40.2 (CH_2), 31.7 (CH_2), 19.6 (CH_2); ^{19}F NMR (282 MHz, CDCl_3) δ -62.93; IR (thin film): 2965, 2925, 2855, 2128, 1717, 1613, 1574, 1482, 1407, 1324, 1294, 1223, 1163, 1123, 1069, 851, 753cm^{-1} . HRMS (EI) m/z calculated for $\text{C}_{19}\text{H}_{14}\text{F}_3\text{N}_3\text{O}$ (M^+): 358.1167 found 358.1163.



4.137

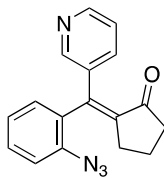
Styryl Azide 4.137. The general procedure was followed using 0.0650 g of 2-alkyldienecyclopentanone **4.181** (0.23 mmol), 0.080 mL of $t\text{-BuNO}_2$ (0.703 mmol) and 0.125 mL of Me_3SiN_3 in 4.6 mL of CH_3CN . The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.0530 g, 76%); ^1H NMR (CDCl_3 , 500 MHz) δ 7.33 (ddd, $J = 8.3, 5.8, 2.7$ Hz, 1H), 7.21 – 7.11 (m, 4H), 7.10–7.06 (m, 3H), 2.60 (d, $J = 51.0$ Hz, 2H), 2.36 (t, $J = 7.7$ Hz, 2H), 2.18 (s, 3H), 1.92 (d, $J = 4.2$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 205.9 (C), 139.5 (C), 137.2 (C), 130.4 (CH), 130.1 (CH), 129.3 (CH), 128.7 (CH), 127.6 (CH), 125.3 (CH), 124.7 (CH), 118.6 (CH), 39.8 (CH_2), 31.5 (CH_2), 19.9 (CH_2), 19.8 (CH_3) only signals visible; IR (thin film): 2963, 2921, 2852, 2128, 1714, 1613, 1574, 1486, 1442, 1296, 1195, 1173, 1097, 1069, 1059, 750cm^{-1} ; HRMS (EI) m/z

calculated for $C_{19}H_{17}N_3O$ (M^+): 304.1450 found 304.1439.



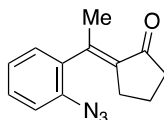
4.139

Styryl Azide 4.139. The general procedure was followed using 0.100 g of 2-alkylidenecyclopentanone **4.182** (0.290 mmol), 0.100 mL of *t*-BuNO₂ (0.870 mmol) and 0.15 mL of Me₃SiN₃ in 6 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.0920 g, 85%): ¹H NMR (CDCl₃, 500 MHz) δ 7.64 (t, *J* = 8.4 Hz, 2H), 7.52 (s, 1H), 7.39-7.35 (m, 2H), 7.21 (d, *J* = 7.7 Hz, 1H), 7.15 (d, *J* = 3.7 Hz, 2H), 7.11 (d, *J* = 2.0 Hz, 1H), 7.08 (dd, *J* = 8.8, 2.5 Hz, 1H), 3.90 (s, 3H), 2.56 (s, 2H), 2.45 (t, *J* = 7.7 Hz, 2H), 1.95 (quintet, *J* = 7.4 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 205.6 (C), 158.2 (C), 145.0 (C), 137.9 (C), 137.3 (C), 135.4 (C), 134.5 (C), 134.3 (C), 134.1 (C), 130.4 (CH), 129.9 (CH), 129.4 (CH), 129.1 (CH), 128.4 (CH), 125.7 (CH), 124.9 (CH), 118.9 (CH), 118.7 (CH), 105.8 (CH), 55.4 (CH₃), 40.5 (CH₂), 32.2 (CH₂), 19.8 (CH₂); IR (thin film): 3061, 2960, 2934, 2849, 2122, 1710, 1628, 1600, 1482, 1445, 1391, 1296, 1267, 1214, 1166, 1030, 854, 809, 736 cm⁻¹. HRMS (EI) *m/z* calculated for C₂₃H₁₉N₃O₂ (M^+): 370.1555, found 370.1561.



4.141

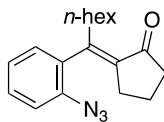
Styryl Azide 4.141. The general procedure was followed using 0.100 g of 2-alkylidenecyclopentanone **4.183** (0.380 mmol), 0.140 mL of *t*-BuNO₂ (1.13 mmol) and 0.20 mL of Me₃SiN₃ in 6 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.070 g, 64%): ¹H NMR (CDCl₃, 500 MHz) δ 8.45 (d, *J* = 26.7 Hz, 2H), 7.53 (s, 1H), 7.37 (s, 1H), 7.15 (td, *J* = 15.4, 7.1 Hz, 4H), 2.55 (t, *J* = 7.2 Hz, 2H), 2.42 (t, *J* = 7.8 Hz, 2H), 1.93 (quintet, *J* = 7.5 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 205.6 (C), 149.7 (CH), 148.7 (CH), 141.0 (C), 137.3 (C), 137.1 (C), 136.5 (CH), 134.5 (C), 132.8 (C), 129.9 (CH), 129.7 (CH), 125.1 (CH), 122.5 (CH), 118.9 (CH), 40.2 (CH₂), 31.7 (CH₂), 19.6 (CH₂); IR (thin film): 3061, 2963, 2886, 2122, 1714, 1609, 1578, 1486, 1442, 1410, 1296, 1192, 755 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₇H₁₅N₄O (M⁺): 291.1245, found 291.1241.



4.143

Styryl Azide 4.143. The general procedure was followed using 0.150 g of 2-alkylidenecyclopentanone **4.184** (0.75 mmol), 0.27 mL of *t*-BuNO₂ (2.24 mmol) and 0.39 mL of Me₃SiN₃ in 15 mL of CH₃CN. The reaction mixture was purified by flash chromatography

(5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.135 g, 80%): ^1H NMR (CDCl_3 , 500 MHz) δ 7.33 (td, $J = 7.7, 1.5$ Hz, 1H), 7.18 (d, $J = 8.0$ Hz, 1H), 7.14 (td, $J = 7.5, 0.7$ Hz, 1H), 7.05 (dd, $J = 7.6, 1.3$ Hz, 1H), 2.41 (s, 3H), 2.38 (t, $J = 7.8$ Hz, 2H), 2.33 (t, $J = 7.6$ Hz, 2H), 1.80 (quintet, $J = 7.5$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 208.4 (C), 144.7 (C), 136.2 (C), 135.4 (C), 133.9 (C), 128.8 (CH), 128.4 (CH), 125.0 (CH), 118.7 (CH), 40.7 (CH_2), 30.7 (CH_2), 20.0 (CH_2), 19.8 (CH_3); IR (thin film): 3057, 2963, 2884, 2842, 2118, 1707, 1625, 1574, 1486, 1438, 1369, 1290, 1198, 999, 755cm^{-1} ; HRMS (EI) m/z calculated for $\text{C}_{17}\text{H}_{15}\text{N}_4\text{O}$ (M^+): 227.1058, found 227.1055.



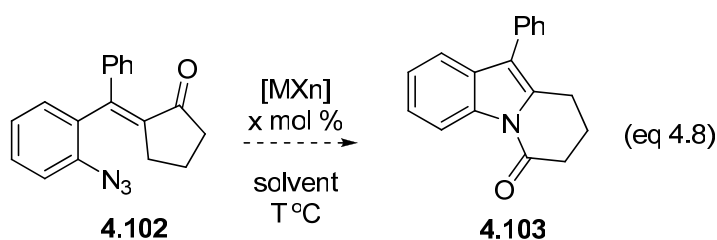
4.145

Styryl Azide 4.145. The general procedure was followed using 0.0900 g of 2-alkylidenecyclopentanone **4.185** (0.330 mmol), 0.112 mL of *t*-BuNO₂ (0.990 mmol) and 0.176 mL of Me₃SiN₃ in 4 mL of CH₃CN. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the styryl azide as a brown oil (0.0696 g, 71%): ^1H NMR (CDCl_3 , 500 MHz) δ 7.34 (ddd, $J = 8.0, 7.4, 1.5$ Hz, 1H), 7.19 (dd, $J = 8.1, 0.8$ Hz, 1H), 7.14 (td, $J = 7.5, 1.1$ Hz, 1H), 7.03 (dd, $J = 7.6, 1.4$ Hz, 1H), 2.94 (t, $J = 6.1$ Hz, 2H), 2.37 (td, $J = 7.7, 5.0$ Hz, 2H), 2.32 (t, $J = 7.2$ Hz, 1H), 2.27 (t, $J = 6.6$ Hz, 1H), 1.81 (t, $J = 6.8$ Hz, 1H), 1.77 (t, $J = 7.2$ Hz, 1H), 1.29-1.22 (m, 8H), 0.84 (t, $J = 7.0$ Hz, 3H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 207.8 (C), 149.7 (C), 136.6 (C), 134.2 (C), 133.7 (C), 128.9 (CH), 128.78 (CH), 124.8 (CH), 118.5

(CH), 40.8 (CH₂), 32.5 (CH₂), 31.7 (CH₂), 30.9(CH₂), 29.4 (CH₂), 28.1 (CH₂), 22.6 (CH₂), 19.8 (CH₂), 14.1 (CH₃).IR(thin film): 2956, 2925, 2855, 2118, 1704, 1625, 1571, 1482, 1442, 1375, 1290, 1195, 999, 822, 753cm⁻¹. HRMS (EI) *m/z* calculated for C₁₈H₂₃N₃O (M⁺): 298.1919, found 298.1920.

4.6.2 Development of Optimal Conditions for Indole Formation.

Screening of Reaction Conditions.



To a mixture of styryl azide and metal catalyst was added solvent. The resulting mixture was heated for 16 h. The mixture was cooled to room temperature, diluted with CH₂Cl₂ and concentrated *in vacuo*. 7 μL CH₂Br₂ (0.1 mmol) was added to the mixture and the yield of the product was determined using ¹H NMR spectroscopy.

Table 4.4. Survey of reaction conditions for indole formation.

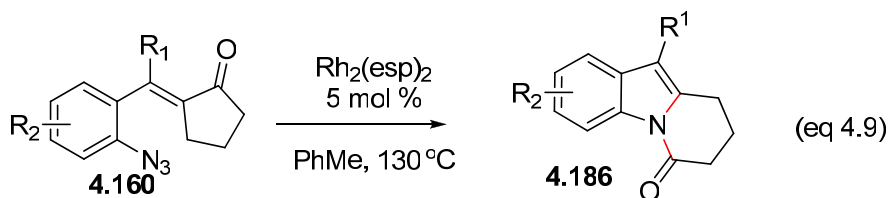
entry	catalyst	mol %	T (°C)	solvent	%, yield ^a
1	none	...	100	Toluene	n.r.
2	none	...	130	Toluene	n.r.
3	Rh ₂ (O ₂ CCF ₃) ₄	5	100	Toluene	60
4	Rh ₂ (O ₂ C ₃ F ₇) ₄	5	100	Toluene	76
5	Rh ₂ (O ₂ CCH ₃) ₄	5	100	Toluene	90
6	Rh ₂ (O ₂ CC ₇ H ₁₅) ₄	5	100	Toluene	89
7	Rh ₂ (esp) ₂	5	100	Toluene	70

8	$\text{Rh}_2(\text{esp})_2$	5	80	Toluene	n.r.
9	$\text{Rh}_2(\text{esp})_2$	5	130	Toluene	90
10	$\text{Rh}_2(\text{esp})_2$	1	100	Toluene	75
11	CuI	10	100	Toluene	n.r.
12	FeBr_2	10	100	Toluene	42
13	$\text{RuBr}_3 \cdot n\text{H}_2\text{O}$	10	100	Toluene	35
14	CoTPP	5	100	Toluene	38
15	$[\text{Ir}(\text{COD})(\text{OMe})]_2$	10	80	Toluene	54
16	$\text{Ru}(\text{TPP})\text{CO}$	5	80	Toluene	0

^aas determined using ^1H NMR spectroscopy using CH_2Br_2 as the internal standard.

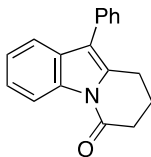
4.6.3 Synthesis of 1,2,3-Trisubstituted Indoles.

4.6.3.1 Optimized Procedure.



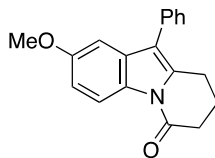
To an oven dried 3 mL conical vial was suspended 0.0500 g of styryl azide **4.160** (0.220mmol) and 0.0080 g of $\text{Rh}_2(\text{esp})_2$ (0.011 mmol) in 0.50 mL of toluene. The resulting mixture was then heated to 130 °C. After 16 hours, the reaction mixture was concentrated *in vacuo*, and the reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) to afford the product as an off-white solid (0.0393 g, 88%).

4.6.3.2 Characterization Data.



4.103

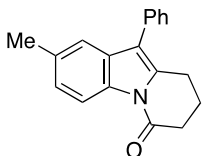
Indole 4.103.⁵¹The optimized procedure was followed using 0.0500 g of styryl azide **4.102** (0.173 mmol) and 0.0065 g of Rh₂(esp)₂ (0.0090 mmol) in 0.40 mL of toluene. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) affording the product as an off white solid (0.0393g, 70%). The spectral data of indole **4.103** matched that reported by Fürstner and Junbam:^[6]¹H NMR (CDCl₃, 500 MHz) δ 8.56 (d, *J* = 8.1 Hz, 1H), 7.60 (d, *J* = 7.5 Hz, 1H), 7.49 (d, *J* = 8.9 Hz, 4H), 7.40 – 7.34 (m, 2H), 7.31 – 7.28 (m, 1H), 3.07 (t, *J* = 6.2 Hz, 2H), 2.85 (t, *J* = 6.3 Hz, 2H), 2.09 (quintet, *J* = 6.3 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 169.6 (C), 134.8 (C), 134.1 (C), 133.3 (C), 129.5 (C), 129.4 (CH), 128.7 (CH), 127.1 (CH), 124.6 (CH), 124.1 (CH), 118.8 (CH), 118.6 (C), 116.6 (CH), 34.7 (CH₂), 22.9 (CH₂), 21.4 (CH₂). IR (thin film): 3057, 2953, 2842, 1704, 1613, 1574, 1499, 1455, 1366, 1334, 1309, 1265, 1166, 1148, 750, 705, 569 cm⁻¹.



4.107

Indole 4.107.The optimized procedure was followed using 0.0320 g of styryl azide **4.106**

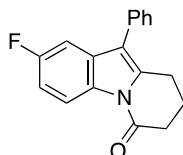
(0.100mmol) and 0.0040 g of $\text{Rh}_2(\text{esp})_2$ (0.0050 mmol) in 1.00 mL of toluene. The reaction mixture was filtered through a short pad of silica gel affording the product as an off white solid (0.0270 g, 93%). ^1H NMR (CDCl_3 , 500 MHz) δ 8.43 (d, J = 9.0 Hz, 1H), 7.50 – 7.48 (m, 4H), 7.38 (m, J = 6.5 Hz, 1H), 7.05 (d, J = 2.5 Hz, 1H), 6.94 (dd, J = 9.0, 2.5 Hz, 1H), 3.83(s, 3H), 3.03 (t, J = 6.0 Hz, 2H), 2.82 (t, J = 6.5 Hz, 2H), 2.07 (m, J = 6.5 Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 169.2 (C), 157.0 (C), 134.9 (C), 133.3 (C), 130.6 (C), 129.4 (C), 129.3 (CH), 128.8 (CH), 127.2 (CH), 118.5 (C), 117.3 (CH), 112.4 (CH), 102.2 (CH), 55.8 (CH_3), 34.5 (CH_2), 22.9 (CH_2), 21.5 (CH_2). ATR-FTIR (thin film): 3052, 2960, 2118, 1721, 1586, 1499, 1205, 1125, 1014, 819, 732, 700 cm^{-1} . HRMS (ES pos.) m/z calculated for $\text{C}_{19}\text{H}_{18}\text{NO}_2$ $[\text{M}+\text{H}]^+$: 292.1338, found: 292.1333.



4.109

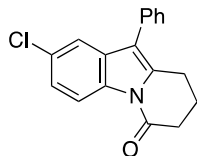
Indole 4.109. The optimized procedure was followed using 0.0300 g of styryl azide **4.108** (0.100mmol) and 0.0040 g of $\text{Rh}_2(\text{esp})_2$ (0.0050 mmol) in 1.00 mL of toluene. The reaction mixture was filtered through a short pad of silica gel affording the product as an off white solid (0.0260 g, 96%). ^1H NMR (CDCl_3 , 500 MHz) δ 8.41 (d, J = 8.0 Hz, 1H), 7.50 – 7.49 (m, 4H), 7.37 (m, 2H), 7.16 (d, J = 8.5 Hz, 1H), 3.04 (t, J = 6.0 Hz, 2H), 2.83 (t, J = 6.5 Hz, 2H), 2.44 (s, 3H), 2.08 (m, J = 6.5 Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 169.4 (C), 134.2 (C), 133.8 (C), 133.4 (C), 133.0 (C), 129.7 (C), 129.4 (CH), 128.7 (CH), 127.1 (CH), 125.8 (CH), 118.8 (CH),

118.4 (C), 116.2 (CH), 34.6 (CH₂), 22.9 (CH₂), 21.6 (CH₃), 21.4 (CH₂). ATR-FTIR(thin film): 3054, 2949, 2873, 1697, 1608, 1472, 1359, 1175, 1134, 810, 702 cm⁻¹. HRMS (ES pos.) *m/z* calculated for C₁₉H₁₈NO [M+H]⁺: 276.1388, found: 276.1379.



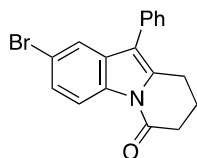
4.111

Indole 4.111. The optimized procedure was followed using 0.0310 g of styryl azide **4.110** (0.100mmol) and 0.0040 g of Rh₂(esp)₂ (0.0050 mmol) in 1.00 mL of toluene. The reaction mixture was filtered through a short pad of silica gel affording the product as an off white solid (0.0260 g, 93%). ¹H NMR (500 MHz, CDCl₃) δ 8.49 (dd, *J* = 9.0, 5.0 Hz, 1H), 7.50 (t, *J* = 7.5 Hz, 2H), 7.45 (d, *J* = 6.5 Hz, 2H), 7.39 (t, *J* = 7.0 Hz, 1H), 7.23 (dd, *J* = 9.0, 2.5 Hz, 1H), 7.04 (dt, *J* = 9.0, 3.0 Hz, 1H), 3.06 (t, *J* = 6.5 Hz, 2H), 2.84 (t, *J* = 6.5 Hz, 2H), 2.10 (m, *J* = 6.5 Hz, 2H); ¹³C NMR (125 MHz, CDCl₃) δ 169.3 (C), 161.2 (C), 159.3 (C), 135.8 (C), 132.8 (C), 131.1 (CH), 130.8 (CH), 129.2 (CH), 128.8 (CH), 127.4 (CH), 117.5 (d, *J*_{CF} = 9.1 Hz, CH), 111.9(d, *J*_{CF} = 24 Hz, CH), 104.7 (d, *J*_{CF} = 24 Hz, CH), 34.5 (CH₂), 22.9 (CH₂), 21.4 (CH₂); ¹⁹F NMR (282 MHz, CDCl₃) δ -109.46. ATR-FTIR(thin film): 3057, 2952, 2879, 1711, 1615, 1471, 1345, 1178, 1031, 1009, 812 cm⁻¹. HRMS (ES pos.) *m/z* calculated for C₁₈H₁₅FNO [M+H]⁺: 280.1138, found: 280.1138.



4.113

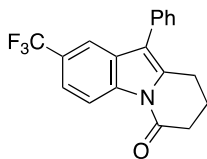
Indole 4.113. The optimized procedure was followed using 0.0320 g of styryl azide **4.112** (0.100mmol) and 0.0040 g of $\text{Rh}_2(\text{esp})_2$ (0.0050 mmol) in 1.00 mL of toluene. The reaction mixture was filtered through a short pad of silica gel affording the product as an off white solid (0.0280 g, 95%). ^1H NMR (CDCl_3 , 500 MHz) δ 8.45 (d, $J = 9.0$ Hz, 1H), 7.53 (d, $J = 2.0$ Hz, 1H), 7.50 (t, $J = 7.5$ Hz, 2H), 7.45 (d, $J = 6.5$ Hz, 2H), 7.39 (t, $J = 7.0$ Hz, 1H), 7.28 (dd, $J = 8.5$, 2.0 Hz, 1H), 3.05 (t, $J = 6.0$ Hz, 2H), 2.84 (t, $J = 6.5$ Hz, 2H), 2.10 (m, $J = 6.0$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 169.4 (C), 135.5 (C), 133.1 (C), 132.6 (C), 130.9 (C), 129.8 (C), 129.3 (CH), 128.9 (CH), 127.4 (CH), 124.6 (CH), 118.6 (CH), 118.0 (C), 117.5 (CH), 34.5 (CH_2), 22.9 (CH_2), 21.4 (CH_2). ATR-FTIR (thin film): 3055, 2951, 2876, 1704, 1609, 1447, 1357, 1162, 1009, 954, 810, 702 cm^{-1} . HRMS (ES pos.) m/z calculated for $\text{C}_{18}\text{H}_{15}\text{ClNO}$ $[\text{M}+\text{H}]^+$: 296.0842, found: 296.0843.



4.115

Indole 4.115. The optimized procedure was followed using 0.0370 g of styryl azide **4.114** (0.100mmol) and 0.0040 g of $\text{Rh}_2(\text{esp})_2$ (0.0050 mmol) in 1.00 mL of toluene. The

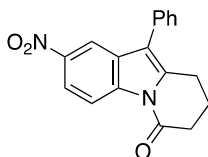
reaction mixture was filtered through a short pad of silica gel affording the product as an off white solid (0.0320 g, 95%). ^1H NMR (CDCl_3 , 500 MHz) δ 8.40 (d, $J = 8.5$ Hz, 1H), 7.69 (d, $J = 2.0$ Hz, 1H), 7.50 (t, $J = 7.5$ Hz, 2H), 7.45 – 7.38 (m, 4H), 3.04 (t, $J = 6.0$ Hz, 2H), 2.84 (t, $J = 6.5$ Hz, 2H), 2.08 (m, $J = 6.0$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 169.5 (C), 135.4 (C), 133.5 (C), 132.5 (C), 131.3 (C), 129.3 (CH), 128.9 (CH), 127.5 (CH), 127.3 (CH), 121.6 (CH), 117.9 (CH), 117.8 (C), 117.6 (C), 34.5 (CH_2), 22.8 (CH_2), 21.3 (CH_2). ATR-FTIR (thin film): 3054, 2952, 2897, 1706, 1609, 1445, 1429, 1308, 1161, 964, 811, 768 cm^{-1} . HRMS (EI) m/z calculated for $\text{C}_{18}\text{H}_{14}\text{BrNO}$ (M^+): 339.0259, found: 338.0181.



4.117

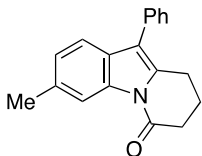
Indole 4.117. The optimized procedure was followed using 0.0360 g of styryl azide **4.116** (0.100 mmol) and 0.0040 g of $\text{Rh}_2(\text{esp})_2$ (0.0050 mmol) in 1.00 mL of toluene. The reaction mixture was filtered through a short pad of silica gel affording the product as an off white solid (0.0270 g, 81%). ^1H NMR (500 MHz, CDCl_3) δ 8.64 (d, $J = 8.5$ Hz, 1H), 7.83 (s, 1H), 7.58 (d, $J = 8.5$ Hz, 1H), 7.53 (t, $J = 7.5$ Hz, 2H), 7.47 (d, $J = 7.0$ Hz, 2H), 7.42 (t, $J = 7.5$ Hz, 1H), 3.09 (t, $J = 6.5$ Hz, 2H), 2.88 (t, $J = 6.5$ Hz, 2H), 2.12 (m, $J = 6.0$ Hz, 2H); ^{13}C NMR (125 MHz, CDCl_3) δ 169.6 (C), 136.3 (C), 135.9 (C), 132.4 (C), 129.4 (C), 129.3 (CH), 129.0 (CH), 127.6 (CH), 126.5 (C), 126.3 (C), 121.4 (q, $J_{\text{CF}} = 3.5$ Hz, CH), 118.6 (C), 116.7 (CH), 116.1 (q, $J_{\text{CF}} = 3.5$ Hz, CH), 34.6 (CH_2), 22.9 (CH_2), 21.3 (CH_2); ^{19}F NMR (282 MHz, CDCl_3) δ

–62.42. ATR-FTIR(thin film): 3058, 2958, 2926, 1712, 1618, 1440, 1350, 1281, 1163, 1114, 958 cm^{-1} . HRMS (ES pos.) m/z calculated for $\text{C}_{19}\text{H}_{15}\text{F}_3\text{NO}$ $[\text{M}+\text{H}]^+$: 330.1106, found: 330.1102.



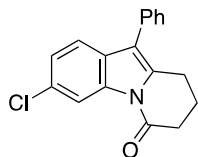
4.119

Indole 4.119. The optimized procedure was followed using 0.0330 g of styryl azide **4.118** (0.100 mmol) and 0.0040 g of $\text{Rh}_2(\text{esp})_2$ (0.0050 mmol) in 1.00 mL of toluene. The reaction mixture was filtered through a short pad of silica gel affording the product as an off white solid (0.0280 g, 90%). ^1H NMR (CDCl_3 , 500 MHz) δ 8.60 (d, $J = 9.0$ Hz, 1H), 8.41 (d, $J = 2.0$ Hz, 1H), 8.18 (dd, $J = 9.0, 2.0$ Hz, 1H), 7.53 (t, $J = 7.0$ Hz, 2H), 7.45 (d, $J = 7.5$ Hz, 2H), 7.42 (d, $J = 7.5$ Hz, 1H), 3.11 (t, $J = 6.0$ Hz, 2H), 2.90 (t, $J = 6.5$ Hz, 2H), 2.14 (m, $J = 6.0$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 169.6 (C), 144.7 (C), 137.8 (C), 137.2 (C), 131.7 (C), 129.7 (C), 129.2 (CH), 129.1 (CH), 127.9 (CH), 119.8 (CH), 119.0 (C), 116.6 (CH), 115.0 (CH), 34.5 (CH_2), 22.9 (CH_2), 21.1 (CH_2). ATR-FTIR(thin film): 3076, 2971, 2869, 1723, 1580, 1511, 1334, 1159, 1010, 890, 833, 773 cm^{-1} . HRMS (EI) m/z calculated for $\text{C}_{18}\text{H}_{14}\text{N}_2\text{O}_3$ (ES pos.) m/z calculated for $\text{C}_{18}\text{H}_{15}\text{N}_2\text{O}_3$ $[\text{M}+\text{H}]^+$: 307.1083, found: 307.1085.



4.121

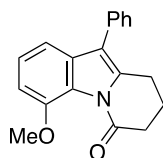
Indole 4.121.⁵²The optimized procedure was followed using 0.0300 g of styryl azide **4.120** (0.100 mmol) and 0.0040 g of $\text{Rh}_2(\text{esp})_2$ (0.0050mmol) in 1.00 mL of toluene. The reaction mixture was filtered through a short pad of silica gel affording the product as an off white solid (0.0270 g, 97%). The spectral data for indole **4.121** matched that reported by Lu and co-workers:^[6]¹H NMR (CDCl_3 , 500 MHz) δ 8.40 (s, 1H), 7.50 – 7.46 (m, 5H), 7.39 – 7.36 (m, 1H), 7.12 (d, J = 8.0 Hz, 1H), 3.05 (t, J = 6.0 Hz, 2H), 2.84 (t, J = 6.5 Hz, 2H), 2.51 (s, 3H), 2.07 (m, J = 6.0 Hz, 2H); ¹³C NMR (CDCl_3 , 125 MHz) δ 169.7 (C), 135.2 (C), 134.7 (C), 133.5 (C), 133.3 (C), 129.3 (CH), 128.7 (CH), 127.2 (C), 127.1 (CH), 125.4 (CH), 118.5 (C), 118.4 (CH), 116.9 (CH), 34.7 (CH_2), 22.9 (CH_2), 21.8 (CH_3), 21.4 (CH_2).ATR-FTIR(thin film): 3054, 3030, 2950, 1703, 1610, 1362, 1310, 1176, 1120, 939, 810, 703 cm^{-1} .



4.123

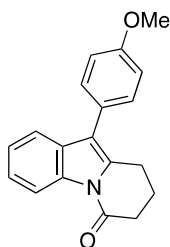
Indole 4.123.The optimized procedure was followed using 0.0320 g of styryl azide **4.122** (0.100 mmol) and 0.0040 g of $\text{Rh}_2(\text{esp})_2$ (0.0050mmol) in 1.00 mL of toluene. The reaction mixture was filtered through a short pad of silica gel affording the product as an off white solid

(0.0260 g, 87%). ^1H NMR (CDCl_3 , 500 MHz) δ 8.58 (d, $J = 1.5$ Hz, 1H), 7.49 (t, $J = 7.5$ Hz, 2H), 7.45 (t, $J = 8.0$ Hz, 3H), 7.39 (t, $J = 7.5$ Hz, 1H), 7.24 (dt, $J = 8.5$, 1.5 Hz, 1H), 3.03 (t, $J = 7.0$ Hz, 2H), 2.83 (t, $J = 6.5$ Hz, 2H), 2.07 (m, $J = 6.0$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 169.5 (C), 135.0 (C), 134.7 (C), 132.7 (C), 130.3 (C), 129.3 (CH), 128.8 (CH), 128.0 (C), 127.4 (CH), 124.5 (CH), 119.5 (CH), 118.2 (C), 116.7 (CH), 34.5 (CH_2), 22.9 (CH_2), 21.3 (CH_2). ATR-FTIR (thin film): 2963, 2925, 2878, 1714, 1606, 1456, 1428, 1352, 1306, 909, 812, 703 cm^{-1} . HRMS (ES pos.) m/z calculated for $\text{C}_{18}\text{H}_{15}\text{ClNO}$ [$\text{M}+\text{H}^+$]: 296.0842, found: 296.0839.



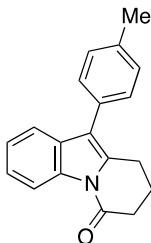
4.125

Indole 4.125. The optimized procedure was followed using 0.0320 g of styryl azide **4.124** (0.100 mmol) and 0.0040 g of $\text{Rh}_2(\text{esp})_2$ (0.0050 mmol) in 1.00 mL of toluene. The reaction mixture was filtered through a short pad of silica gel affording the product as an off white solid (0.0190 g, 67%). ^1H NMR (CDCl_3 , 500 MHz) δ 7.50 – 7.45 (m, 4H), 7.39 – 7.36 (m, 1H), 7.23 (d, $J = 7.5$ Hz, 1H), 7.16 (d, $J = 7.0$ Hz, 1H), 6.91 (d, $J = 7.5$ Hz, 1H), 4.01 (s, 3H), 3.03 (t, $J = 6.0$ Hz, 2H), 2.89 (t, $J = 6.5$ Hz, 2H), 2.09 (m, $J = 6.5$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 167.6 (C), 149.1 (C), 136.5 (C), 133.4 (C), 133.1 (C), 129.5 (CH), 128.6 (CH), 127.1 (CH), 125.3 (CH), 124.3 (C), 118.8 (C), 111.8 (CH), 108.6 (CH), 56.8 (CH_3), 35.3 (CH_2), 23.3 (CH_2), 21.6 (CH_2). ATR-FTIR (thin film): 3054, 2935, 2836, 1720, 1609, 1487, 1429, 1267, 1095, 984, 786, 731 cm^{-1} . HRMS (ES pos.) m/z calculated for $\text{C}_{19}\text{H}_{18}\text{NO}_2$ [$\text{M}+\text{H}^+$]: 292.1338, found: 292.1333.



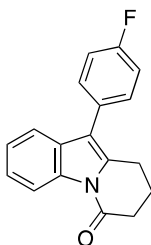
4.130

Indole 4.130. The optimized procedure was followed using 0.0500 g of styryl azide **4.129** (0.173 mmol) and 0.0065 g of $\text{Rh}_2(\text{esp})_2$ (0.0090 mmol) in 0.40 mL of toluene. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) affording the product as an off white solid (0.0351 g, 77%). ^1H NMR (CDCl_3 , 500 MHz) δ 8.54 (d, $J = 8.2$ Hz, 1H), 7.56 (d, $J = 7.6$ Hz, 1H), 7.42 (d, $J = 8.8$ Hz, 2H), 7.34 (td, $J = 7.6, 0.9$ Hz, 2H), 7.03 (d, $J = 8.8$ Hz, 2H), 3.88 (s, 3H), 3.04 (t, $J = 6.1$ Hz, 2H), 2.84 (t, $J = 6.2$ Hz, 2H), 2.09 (dt, $J = 11.8, 5.8$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 169.6 (C), 158.8 (C), 134.7 (C), 133.6 (C), 130.5 (CH), 129.7 (C), 125.5 (C), 124.5 (CH), 124.1 (CH), 118.8 (CH), 118.2 (C), 116.6 (CH), 114.2 (CH), 55.4 (CH₃), 34.7 (CH₂), 22.9 (CH₂), 21.4 (CH₂); IR (thin film): 2956, 2918, 2849, 1704, 1603, 1511, 1457, 1366, 1249, 1173, 1034, 750 cm^{-1} ; HRMS (EI) m/z calculated for $\text{C}_{19}\text{H}_{17}\text{NO}_2$ (M^+): 291.1259, found 291.1258.



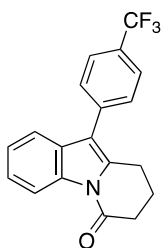
4.132

Indole 4.132.⁵³The optimized procedure was followed using 0.0500 g of styryl azide **4.131** (0.165 mmol) and 0.0065 g of $\text{Rh}_2(\text{esp})_2$ (0.0090 mmol) in 0.40 mL of toluene. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) affording the product as an off white solid (0.0424 g, 89%). The spectral data of indole **4.132** matched that reported by Lu and co-workers:^[7]¹H NMR (CDCl_3 , 500 MHz) δ 8.56 (d, $J = 8.1$ Hz, 1H), 7.59 (d, $J = 7.4$ Hz, 1H), 7.40 (d, $J = 7.9$ Hz, 2H), 7.36 – 7.28 (m, 4H), 3.05 (t, $J = 6.2$ Hz, 2H), 2.84 (t, $J = 6.3$ Hz, 2H), 2.48 (s, 3H), 2.08 (quintet, $J = 6.3$ Hz, 2H); ¹³C NMR (CDCl_3 , 125 MHz) δ 169.6 (C), 136.9 (C), 134.8 (C), 133.8 (C), 130.2 (C), 129.6 (C), 129.4 (CH), 129.2 (CH), 124.5 (CH), 124.1 (CH), 118.9 (CH), 118.5 (C), 116.6 (CH), 34.7 (CH_2), 22.9 (CH_2), 21.4 (CH_2), 21.3 (CH_3); IR(thin film): 3024, 2956, 2874, 1703, 1603, 1509, 1456, 1362, 1310, 1163, 1157, 840, 755 cm^{-1} .



4.134

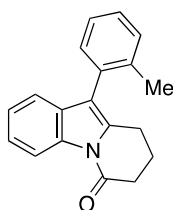
Indole 4.134. The optimized procedure was followed using 0.0500 g of styryl azide **4.133** (0.163 mmol) and 0.0060 g of $\text{Rh}_2(\text{esp})_2$ (0.0080mmol) in 1.6 mL of toluene. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) affording the product as an off white solid (0.0341 g, 75%): ^1H NMR (CDCl_3 , 500 MHz) δ 8.54 (d, $J = 7.5$ Hz, 1H), 7.52 (d, $J = 7.4$ Hz, 1H), 7.45 (dd, $J = 8.3, 5.8$ Hz, 2H), 7.35 (t, $J = 7.6$ Hz, 1H), 7.29 (t, $J = 7.5$ Hz, 1H), 7.18 (t, $J = 8.7$ Hz, 2H), 3.03 (t, $J = 6.2$ Hz, 2H), 2.85 (t, $J = 6.4$ Hz, 2H), 2.09 (dt, $J = 12.4, 6.3$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 169.5 (C), 162.9 (C), 134.7 (C), 134.1 (C), 130.9 (d, $J_{\text{CF}} = 8.5$ Hz, CH), 129.4 (C), 129.2 (C), 125.3 (C), 124.7 (CH), 124.2 (CH), 118.5 (CH), 117.6 (C), 116.62 (CH), 115.73 (d, $J_{\text{CF}} = 20.8$ Hz, CH), 34.6 (CH_2), 22.8 (CH_2), 21.4 (CH_2); ^{19}F NMR (282 MHz, CDCl_3) δ -115.19; IR (thin film): 3051, 2953, 2931, 1704, 1603, 1509, 1457, 1363, 1312, 1223, 1170, 750, 560cm^{-1} ; HRMS (EI) m/z calculated for $\text{C}_{18}\text{H}_{14}\text{NO}_2\text{F}$ (M^+): 279.1059, found 279.1058.



4.136

Indole 4.136. The optimized procedure was followed using 0.0500 g of styryl azide **4.135** (0.140 mmol) and 0.0053 g of $\text{Rh}_2(\text{esp})_2$ (0.0070 mmol) in 0.40 mL of toluene. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) affording the product as an off white solid (0.0392 g, 85%): ^1H NMR (CDCl_3 , 500 MHz) δ 8.48 (d, $J = 8.1$ Hz, 1H), 7.67 (d, $J = 7.9$ Hz, 2H), 7.53 (d, $J = 7.9$ Hz, 2H), 7.47 (d, $J = 7.6$ Hz, 1H), 7.29 (t, $J = 7.6$

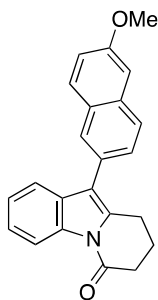
Hz, 1H), 7.23 (t, $J = 7.5$ Hz, 1H), 2.98 (t, $J = 6.1$ Hz, 2H), 2.78 (t, $J = 6.2$ Hz, 2H), 2.03 (quintet, $J = 6.1$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 169.5 (C), 137.2 (C), 134.9 (C), 134.8 (C), 129.6 (CH), 129.0 (C) 128.9 (CH), 125.7 (q, $J_{\text{CF}} = 2.8$ Hz, CH), 125.0 (CH), 124.4 (CH), 124.2 (q, $J_{\text{CF}} = 270.1$ Hz, CF) 118.4 (CH), 117.3 (C), 116.7 (CH), 34.6 (CH_2), 22.9 (CH_2), 21.3 (CH_2) only signals visible; ^{19}F NMR (282 MHz, CDCl_3) δ -62.86; IR (thin film): 3051, 2953, 2931, 1704, 1603, 1509, 1457, 1363, 1312, 1223, 1170, 750, 560cm^{-1} . HRMS (EI) m/z calculated for $\text{C}_{19}\text{H}_{14}\text{NOF}_3$ (M^+): 329.1027, found 329.1022.



4.138

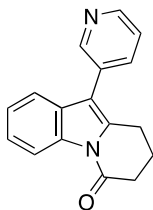
Indole 4.138. The optimized procedure was followed using 0.0480 g of styryl azide **4.137** (0.158 mmol) and 0.0060 g of $\text{Rh}_2(\text{esp})_2$ (0.0079 mmol) in 1.50 mL of toluene. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) affording the product as an off white solid (0.0313 g, 72%): ^1H NMR (CDCl_3 , 500 MHz) δ 8.52 (d, $J = 8.1$ Hz, 1H), 7.35 – 7.31 (m, 3H), 7.28 – 7.22 (m, 3H), 7.18 (d, $J = 7.7$ Hz, 1H), 2.89 – 2.72 (m, 4H), 2.18 (s, 3H), 2.08 (dt, $J = 12.6, 6.3$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 169.6 (C), 137.6 (C), 134.5 (C), 134.3 (C), 132.3 (C), 130.8 (CH), 130.3 (CH), 130.2 (C), 127.9 (CH), 125.8 (CH), 124.4 (CH), 124.0 (CH), 119.1 (CH), 118.5 (C), 116.4 (CH), 34.7 (CH_2), 22.6 (CH_2), 21.4 (CH_2), 20.1 (CH_3); IR (thin film): 3026, 2956, 2877, 1704, 1607, 1511, 1456, 1362, 1309, 1163, 1159,

847, 755 cm^{-1} . HRMS (EI) m/z calculated for $\text{C}_{19}\text{H}_{17}\text{NO}$ (M^+): 275.1310, found 275.1309.



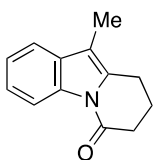
4.140

Indole 4.140. The optimized procedure was followed using 0.0300 g of styryl azide **4.139** (0.0810mmol) and 0.0030 g of $\text{Rh}_2(\text{esp})_2$ (0.0040mmol) in 0.80 mL of toluene. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) affording the product as an off white solid (0.026 g, 96%): ^1H NMR (CDCl_3 , 500 MHz) δ 8.58 (d, J = 8.1 Hz, 1H), 7.85 (t, J = 3.8 Hz, 2H), 7.78 (d, J = 9.6 Hz, 1H), 7.63 (d, J = 7.6 Hz, 1H), 7.59 (d, J = 8.5 Hz, 1H), 7.37 (t, J = 7.5 Hz, 1H), 7.31 (t, J = 7.4 Hz, 1H), 7.21 (t, J = 2.7 Hz, 2H), 3.96 (s, 3H), 3.10 (t, J = 6.1 Hz, 2H), 2.86 (t, J = 6.3 Hz, 2H), 2.10 (quintet, J = 6.2 Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 169.6 (C), 157.9 (C), 134.8 (C), 134.2 (C), 133.6 (C), 129.7 (C), 129.4 (CH), 129.1 (C), 128.4 (C), 128.0 (CH), 127.9 (CH), 127.1 (CH), 124.6 (CH), 124.2 (CH), 119.3 (CH), 118.9 (CH), 118.6 (C), 116.6 (CH), 105.8 (C), 55.4 (CH_3), 34.7 (CH_2), 23.0 (CH_2), 21.4 (CH_2); IR(thin film): 3054, 2953, 2934, 2846, 1704, 1616, 1489, 1455, 1366, 1333, 1265, 1214, 1176, 1027, 854, 736, 569 cm^{-1} ; HRMS (EI) m/z calculated for $\text{C}_{23}\text{H}_{19}\text{NO}_2$ (M^+): 341.1416, found 341.1414.



4.142

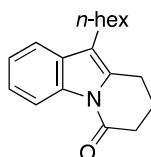
Indole 4.142. The optimized procedure was followed using 0.0500 g of styryl azide **4.141** (0.172 mmol) and 0.0070 g of $\text{Rh}_2(\text{esp})_2$ (0.0086 mmol) in 1.0 mL of toluene. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) affording the product as an off white solid (0.0257 g, 57%): ^1H NMR (CDCl_3 , 500 MHz) δ 8.75 (s, 1H), 8.62 (d, $J = 4.1$ Hz, 1H), 8.55 (d, $J = 8.1$ Hz, 1H), 7.82 (dd, $J = 7.8, 1.5$ Hz, 1H), 7.53 (d, $J = 7.8$ Hz, 1H), 7.43 (dd, $J = 7.7, 4.9$ Hz, 1H), 7.37 (t, $J = 7.7$ Hz, 1H), 7.31 (t, $J = 7.5$ Hz, 1H), 3.06 (t, $J = 6.2$ Hz, 2H), 2.87 (t, $J = 6.3$ Hz, 2H), 2.12 (quintet, $J = 6.3$ Hz, 2H); ^{13}C NMR (CDCl_3 , 125 MHz) δ 169.5 (C), 150.2 (CH), 148.3 (CH), 136.5 (CH), 135.0 (C), 134.8 (C), 129.4 (C), 128.9 (C), 125.0 (CH), 124.4 (CH), 123.6 (CH), 118.3 (CH), 116.7 (CH), 115.1 (C), 34.6 (CH_2), 22.8 (CH_2), 21.3 (CH_2); IR(thin film): 3051, 2956, 2973, 2846, 1704, 1609, 1457, 1363, 1309, 1267, 1166, 1144, 1024, 753, 569cm^{-1} . HRMS (EI) m/z calculated for $\text{C}_{17}\text{H}_{14}\text{N}_2\text{O}$ (M^+): 262.1106, found 262.1107.



4.144

Indole 4.144.⁵⁴ The optimized procedure was followed using 0.0500 g of styryl azide **4.143** (0.220 mmol) and 0.0080 g of $\text{Rh}_2(\text{esp})_2$ (0.011 mmol) in 0.50 mL of toluene. The

reaction mixture was purified by flash chromatography (5:95EtOAc:hexanes) affording the product as an off white solid (0.0385 g, 88%). Indole **4.144** was previously reported by Ban and co-workers.^[9] ¹H NMR (CDCl₃, 500 MHz) δ 8.44 (dt, J = 5.1, 2.0 Hz, 1H), 7.42 (dt, J = 4.4, 2.2 Hz, 1H), 7.28 (dd, J = 6.6, 2.9 Hz, 2H), 2.91 (t, J = 6.1 Hz, 2H), 2.77 (t, J = 6.4 Hz, 2H), 2.18 (s, 3H), 2.08 (quintet, J = 6.15 Hz, 2H); ¹³C NMR (CDCl₃, 125 MHz) δ 169.2 (C), 134.5 (C), 133.2 (C), 131.1 (C), 124.2 (CH), 123.7 (CH), 117.8 (CH), 116.3 (CH), 112.2 (C), 34.5 (CH₂), 21.8 (CH₂), 21.3 (CH₂), 8.5 (CH₃); IR(thin film): 2952, 2923, 2868, 1700, 1625, 1456, 1369, 1333, 1265, 1174, 907, 727cm⁻¹.



4.146

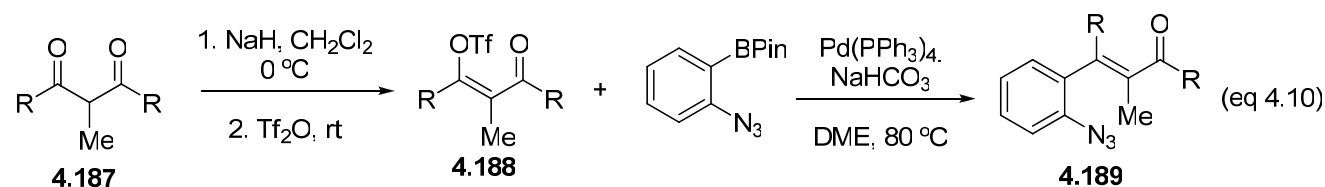
Indole 4.146. The optimized procedure was followed using 0.0500 g of styryl azide **4.145** (0.168mmol) and 0.0060 g of Rh₂(esp)₂ (0.0080 mmol) in 0.80 mL of toluene. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) affording the product as an off white solid (0.0250 g, 55%): ¹H NMR (CDCl₃, 500 MHz) δ 8.46 (dd, J = 6.6, 2.4 Hz, 1H), 7.45 (dd, J = 6.2, 2.5 Hz, 1H), 7.30 – 7.24 (m, 2H), 2.91 (t, J = 6.3 Hz, 2H), 2.77 (t, J = 6.4 Hz, 2H), 2.63 (t, J = 7.5 Hz, 2H), 2.08 (quintet, J = 6.3 Hz, 2H), 1.64 – 1.59 (m, 2H), 1.38 – 1.26 (m, 6H), 0.88 (t, J = 6.9 Hz, 3H); ¹³C NMR (CDCl₃, 125 MHz) δ 169.3 (C), 134.7 (C), 133.2 (C), 130.5 (C), 124.1 (CH), 123.6 (CH), 118.1 (CH), 117.2 (C), 116.4 (CH), 34.5 (CH₂), 31.7 (CH₂), 29.7 (CH₂), 29.3 (CH₂), 23.9 (CH₂), 22.7 (CH₂), 21.9 (CH₂), 21.3 (CH₂), 14.1 (CH₃); IR(thin film): 3047, 2953, 2928, 2855, 1706, 1616, 1457, 1373, 1331, 1262, 1176, 1097, 750, 563cm⁻¹.

¹;HRMS (EI) *m/z* calculated for C₁₈H₂₃NO (M⁺): 269.1780, found 269.1779.

4.6.4 Double Crossover Experiment.

4.6.4.1 Preparation of Aryl Azide Substrates.

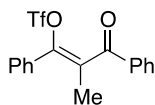
The substrates for the double crossover experiment were synthesized following the two-step procedure below:



To a cooled solution (0 °C) of diketone **4.187** (1 equiv) in dichloromethane was added NaH (1.2 equiv). After 2 hours, anhydrous triflic anhydride (1.1 equiv) then was slowly added to the reaction flask, and the color of enolate immediately faded away. The reaction was warmed to room temperature. After 2 hours, the mixture was diluted with 30 mL of H₂O and extracted with 3 × 30 mL of dichloromethane. The combined organic phases were dried over Na₂SO₄, filtered, and the filtrate was concentrated in vacuo. Purification of the residue by MPLC afforded triflate **4.188**.

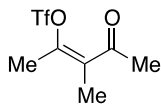
To a mixture of 2-azidophenyl boronate (1.1 equiv) and triflate **4.188** (1.0 equiv) was added Pd(PPh₃)₄ (10mol%) in an inert atmosphere box. The mixture was removed from the glovebox, and DME and saturated solution of NaHCO₃ then was added. The resulting mixture was heated to 80 °C. Once visualization of the reaction progress using TLC indicated consumption of the starting material, the mixture then was cooled to r.t. and diluted with H₂O and extracted with Et₂O. The combined organic phases were dried over Na₂SO₄,

filtered, and the filtrate was concentrated in vacuo. Purification of the residue by MPLC afforded azides **4.189**.



4.190

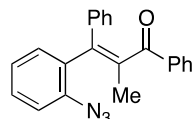
Triflate 4.190. The general procedure was followed using 1.19 g of 2-methyl-1,3-diphenylpropane-1,3-dione (5.00 mmol) in 20 mL of dichloromethane, 0.24 g of NaH and 0.931 mL of Tf₂O. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a colorless oil (0.39 g, 21%): ¹H NMR (500 MHz, CDCl₃) δ 8.00 (d, *J* = 7.5 Hz, 2H), 7.65 (t, *J* = 7.5 Hz, 1H), 7.57 – 7.53 (m, 4H), 7.49 (t, *J* = 3.0 Hz, 3H), 2.06 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 194.7 (C), 143.3 (C), 134.8 (C), 134.3 (CH), 130.9 (C), 130.6 (CH), 130.0 (C), 129.5 (CH), 129.4 (CH), 129.0 (CH), 128.8 (CH), 118.0 (q, *J*_{CF} = 318 Hz), 16.9 (CH₃); ATR-FTIR (thin film): 2999, 2957, 2863, 1701, 1602, 1558, 1480, 1357, 1287, 1071, 891 cm⁻¹.



4.191

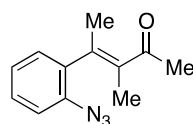
Triflate 4.191. The general procedure was followed using 0.57 g of 3-methylpentane-2,4-dione (5.00 mmol) in 20 mL of dichloromethane, 0.24 g of NaH and 0.931 mL of Tf₂O. No purification was needed to afford the product as a colorless oil (1.03 g, 84%): ¹H NMR (500

MHz, CDCl₃) δ 2.35 (s, 3H), 2.14 (s, 3H), 1.90 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 199.6 (C), 144.8 (C), 129.6 (C), 118.2 (q, J_{CF} = 318 Hz), 29.7 (CH₃), 17.3 (CH₃), 14.9 (CH₃); ATR-FTIR (thin film): 2968, 2898, 1702, 1632, 1576, 1481, 1334, 1271, 1071, 892 cm⁻¹.



4.152

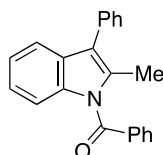
Styryl Azide 4.152. The general procedure was followed using 0.054 g of 2-azidophenyl boronate (0.22 mmol), 0.074 g of triflate **4.190** (0.2 mmol), 0.023 g of Pd(PPh₃)₄, 0.50 mL of NaHCO₃ and 2.00 mL of DME. Reaction was finished after 15 minutes. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow solid (0.053 g, 78%): ¹H NMR (500 MHz, CDCl₃) δ 7.78 (d, J = 7.0 Hz, 2H), 7.41 – 7.36 (m, 3H), 7.32 – 7.27 (m, 5H), 7.15 (dd, J = 7.5, 1.5 Hz, 1H), 7.06 (dt, J = 7.5, 1.5 Hz, 1H), 6.91 (t, J = 7.5 Hz, 1H), 6.72 (d, J = 8.0 Hz, 1H), 2.20 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 200.6 (C), 140.6 (C), 139.6 (C), 138.0 (C), 137.2 (C), 137.0 (C), 132.7 (C), 132.6 (CH), 132.4 (CH), 129.4 (CH), 129.3 (CH), 128.8 (CH), 128.0 (CH), 127.9 (CH), 127.6 (C), 124.3 (CH), 118.3 (CH), 18.7 (CH₃); ATR-FTIR (thin film): 3051, 2961, 2932, 2844, 2116, 1706, 1596, 1525, 1467, 1421, 1391, 1241, 1172, 825, 730 cm⁻¹. HRMS (EI) m/z calculated for C₂₂H₁₇N₃O(M⁺): 339.3899, found 339.3898.



4.153

Styryl Azide 4.153. The general procedure was followed using 0.270 g of 2-azidophenyl boronates**36** (1.1 mmol), 0.246 g of triflate**4.191** (1.0 mmol), 0.121 g of Pd(PPh₃)₄, 2.00 mL of NaHCO₃ and 10.0 mL of DME. Reaction was finished after 15 minutes. Purification by MPLC (0:100 – 10:90 EtOAc:hexanes) afforded the product as a yellow solid (0.101 g, 47%): ¹H NMR (500 MHz, CDCl₃) δ 7.33 (dt, *J* = 7.5, 1.5 Hz, 1H), 7.16 (d, *J* = 7.5 Hz, 1H), 7.08 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.5 Hz, 1H), 2.04 (s, 3H), 1.97 (s, 3H), 1.73 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 204.8 (C), 138.9 (C), 137.0 (C), 136.9 (C), 135.5 (C), 130.2 (CH), 129.1 (CH), 125.1 (CH), 118.6 (CH), 29.8 (CH₃), 21.6 (CH₃), 15.8 (CH₃); ATR-FTIR (thin film): 3032, 2962, 2943, 2843, 2115, 1707, 1591, 1523, 1445, 1423, 1312, 1298, 1122, 827, 731 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₂H₁₃N₃O(M⁺): 215.2511, found 215.2512.

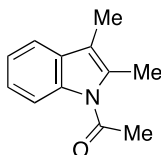
4.6.4.2 Preparation of Trisubstituted Indoles



4.154

Indole 4.154. The optimized procedure for indole formation was followed using 0.0240 g of styryl azide **4.152** (0.070 mmol) and 0.0030 g of Rh₂(esp)₂ (0.0040 mmol) in 1.50 mL of toluene. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) affording the product as an off white solid (0.0190 g, 87%): ¹H NMR (500 MHz, CDCl₃) δ 8.18 (d, *J* = 8.5 Hz, 1H), 7.67 – 7.64 (m, 1H), 7.62 (d, *J* = 6.5 Hz, 2H), 7.55 (t, *J* = 7.5 Hz, 2H), 7.50 (t, *J* = 6.5 Hz, 3H), 7.44 (d, *J* = 7.0 Hz, 1H), 7.40 (d, *J* = 8.5 Hz, 2H), 7.32 (d, *J* = 6.5 Hz, 2H), 2.16 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 160.9 (C), 147.8 (C), 146.3 (C), 141.6 (C), 137.8 (C), 129.5 (CH),

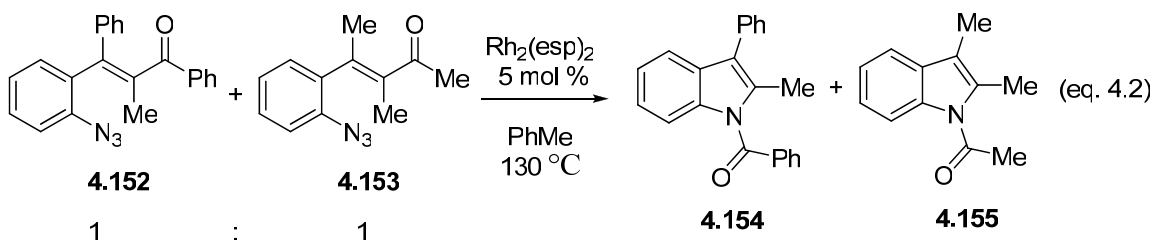
129.4 (CH), 129.0 (CH), 128.7 (CH), 128.6 (CH), 128.3 (CH), 128.1 (CH), 127.9 (CH), 127.1 (C), 126.8 (C), 126.3 (CH), 126.0 (CH), 18.6 (CH₃); ATR-FTIR (thin film): 3012, 2963, 2912, 2893, 1712, 1592, 1563, 1435, 1413, 1334, 1218, 1102, 826, 732 cm⁻¹. HRMS (EI) *m/z* calculated for C₂₂H₁₇NO(M⁺): 311.3765, found 311.3766



4.155

Indole 4.155. The optimized procedure for indole formation was followed using 0.015 g of styryl azide **4.153** (0.070 mmol) and 0.0030 g of Rh₂(esp)₂ (0.0040 mmol) in 1.50 mL of toluene. The reaction mixture was purified by flash chromatography (5:95 EtOAc:hexanes) affording the product as an off white solid (0.0080 g, 60%): ¹H NMR (500 MHz, CDCl₃) δ 7.98 (d, *J* = 8.0 Hz, 1H), 7.94 (d, *J* = 8.5 Hz, 1H), 7.59 (dt, *J* = 8.0, 1.5 Hz, 1H), 7.46 (dt, *J* = 8.0, 1.0 Hz, 1H), 2.70 (s, 3H), 2.59 (s, 3H), 2.39 (s, 3H); ¹³C NMR (125 MHz, CDCl₃) δ 158.4 (C), 145.8 (C), 140.6 (C), 129.0 (CH), 127.9 (CH), 127.8 (C), 127.1 (C), 125.4 (CH), 123.5 (CH), 24.8 (CH₃), 15.8 (CH₃), 14.4 (CH₃); ATR-FTIR (thin film): 3002, 2991, 2923, 2873, 1713, 1592, 1536, 1425, 1409, 1322, 1218, 1132, 825, 738 cm⁻¹. HRMS (EI) *m/z* calculated for C₁₂H₁₃NO(M⁺): 187.2377, found 187.2377.

4.6.4.3 Double Crossover Experiment



To the solution of 0.024 g of azide **4.152** (0.07 mmol) and 0.015 g of azide **4.153** (0.07 mmol) in 2.00 mL of PhMe was added 0.006 g of $\text{Rh}_2(\text{esp})_2$ (5 mol %) and the reaction mixture was heated up to 130 °C. After 16 hours, the reaction mixture was cooled to room temperature and filtered through a short pad of silica gel with dichloromethane. The filtrate was concentrated in vacuo, and analysis of the residue using NMR spectroscopy revealed the presence of only two indoles, **4.154** and **4.155**. Purification by MPLC afforded indole **4.154** (0.0174 mg, 80%) and indole **4.155** (0.00733 mg, 56%).

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Reactions of Aryl Azides.” Nguyen, Q.; Nguyen, T.; Driver, T. G. *J. Am. Chem. Soc.* **2012**, *135*, 620.

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4. “Development of Suzuki Cross-Coupling Reaction between 2-Azidoarylboronic Pinacolate Esters and Vinyl Triflates to Enable the Synthesis of [2,3]-Fused Indoles.” Jana, N.; Nguyen, Q.; Driver, T. G. *J. Org. Chem.* **2014**, *79*, 2781.

Poster

1. Quyen Nguyen, Ke Sun and Tom Driver* “Rh₂(II)-Catalyzed Intramolecular Aliphatic C–H Bond Amination Reactions Using Aryl Azides as the N– Atom Source”. Presented at the 4th Chicago Organic Symposium, Chicago, Illinois, April 2012.
2. Crystalann Jones, Quyen Nguyen and Tom Driver* “Rh₂(II)-Catalyzed Formation of 1,2,3-Trisubstituted Indoles from Styryl Azides”. Presented at the 5th Chicago Organic Symposium, Notre Dame, Indiana, July 2013.
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